Addressing Gaps in Data and Methods in Measles Burden Estimation

Alyssa Nicole Sbarra

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Centre for Mathematical Modelling of Infectious Diseases

Department of Infectious Disease Epidemiology

Faculty of Epidemiology and Population Health

London School of Hygiene & Tropical Medicine

Declaration

Statement of Own Work

I, Alyssa Sbarra, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, this has been indicated in the thesis. I have read and understood the School's definition of plagiarism and cheating given in the Research Degrees Handbook.

Alyssa Sbarra

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Abstract

Vaccination against measles has been available for decades, although still a substantial number of global cases and deaths persist. Strategies to reach measles elimination goals require a more comprehensive understanding of the patterns of immunity and burden across locations, time, and age in local contexts throughout the world, particularly in low- and middle-income countries (LMICs). These challenges, in part, can be addressed via a thorough examination of all available data on measles immunity, cases, and deaths and synthesizing these data streams through the development of novel mathematical and statistical models. The overall aims of this thesis are to (A) improve upon and better understand the data available for modellers interested in estimating measles susceptibility, incidence, or mortality in LMICs, and (B) develop improved methodology for generating more robust estimates using these data, including by dimensions of age, space, and time.

To accomplish these aims, this thesis first identified all data on measles seroprevalence and characterized bias within each primary study. Next, this thesis explored subnational measles case notifications in Ethiopia and tested multiple methodologic strategies for fitting dynamic transmission models with these data while accounting for various case ascertainment rates. Then, to aid in developing more robust models of measles mortality, this thesis outlined activities following an expert consultation to establish a conceptual framework of population-level factors related to measles case fatality and a literature review of evidence of an

association between related indicators and case fatality. Finally, to quantify the heterogeneity in measles case fatality temporally, in different locations and across the lifespan, this thesis estimated country-, year-, and age-specific case-fatality via a meta-regression model using all available literature and identified indicators as covariates. Altogether, this thesis addressed gaps across challenges related to measles burden estimation.

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List of abbreviations

AIC	Akaike information criterion
AMR	Region of the Americas
ART	Antiretroviral therapy
CFR	Case fatality ratio
CI	Confidence interval
EIA	Enzyme immunoassays
ELISA	Enzyme-linked immunosorbent assays
EPI	Expanded Programme on Immunizations
FOI	Force of infection
GBD	Global Burden of Disease study
GMRLN	Global Measles and Rubella Laboratory Network
GVAP	Global Vaccine Action Plan
HI/HAI	Hemagglutination inhibition
HIV	Human immunodeficiency virus
IA2030	Immunization Agenda 2030
IDSR	Integrated Disease Surveillance and Response
IQR	Interquartile range
LMIC	Low- and middle-income country
MBA	Multiplex bead assays
MCMC	Markov chain Monte Carlo
MCV	Measles-containing vaccine
MCV1	First dose of any measles-containing vaccine
MCV2	Second dose of any measles-containing vaccine
MMR	Measles-mumps-rubella
MMR-V	Measles-mumps-rubella-varicella
MR	Measles-rubella
NIAID	National Institute of Allergy and Infectious Disease
OR	Odds ratio
PAHO	Pan American Health Organization
PRN	Plaque reaction neutralization

RR	Relative risk
RT-PCR	Reverse transcription polymerase chain reaction
SD	Standard deviation
SIA	Supplemental immunization activity
SSPE	Subacute sclerosing panencephalitis
U5M	Under-5 mortality
UI	Uncertainty interval
Unicef	United Nations Children's Fund
VR	Vital registration
WHO	World Health Organization
WUENIC	WHO/Unicef estimates of national immunization coverage

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1. Introduction

1.1 Measles

1.1.1 Measles virus

Measles is caused by an infection from a non-segmented, negative-sense RNA virus that is in the *Paramyxoviridae* family of the *Morbillivius* genus[1]. Measles is transmitted from infected humans, the only known host reservoir[2], via respiratory droplets often before symptom onset. While small differences in measles strains exist from deviations in the hemagglutinin membrane protein[3], there is only one antigenic type (i.e., serotype) of measles virus[4,5].

Once viral particles enter a host, the innate immune system mounts a response, particularly among lymphocytes, dendritic cells, and alveolar macrophages[6,7], and the virus begins replicating in the lungs. After approximately two days, the viral incubation period begins. Once in this incubation period, the measles virus reaches lymphatic tissue and is transported via blood circulation throughout the host by infected lymphocytes[7]. These infected cells then infect epithelial and endothelial cells across host organ systems after five to seven days. Measles virus particles are released via the surface of respiratory epithelial cells or damaged tissue, allowing for transmission via the respiratory pathway[8]. Following the innate immune response, the adaptive immune system produces cellular and humoral responses. To clear infection, the cellular immune system first uses Th1 CD4+ T cells to increase levels of plasma interferon-γ[9]. Further in recovery, Th2 CD4+ T cells are then used to increase production of interleukin 4, 10 and 13[10]. As such, children with T cell deficiencies, such as those with a human immunodeficiency virus (HIV) infection, often have worse clinical manifestations and outcomes[11,12].

The humoral immune system first produces IgM antibodies, typically around the time of clinical rash onset, which can be found for six to eight weeks[1]. Later, IgG antibodies are produced, mainly against the nucleoprotein[13].

Clinical manifestations

As measles is not known to have asymptomatic carriers, persons with measles infections develop clinical symptoms[1,5]. The incubation period of measles, i.e., from exposure to prodrome, is approximately 11 to 12 days[14]. The prodromal period, ranging from one to seven days but averaging two to four days, is marked by an increasing fever, cough, coryza, and conjunctivitis. One to two days prior to rash onset, Koplik spots appear on oral mucosa. Following the prodrome, a maculopapular rash emerges and last for five to six days. The rash first appears on the head and then moves towards the hands and feet by the third day. Persons suffering from measles also often experience weight loss and lymph node swelling.

Diagnosis

The World Health Organization (WHO) provides multiple case definitions for measles[15]. Suspected cases are those defined by a fever and maculopapular rash or if healthcare personnel suspect measles. A laboratory-confirmed measles case is a suspected measles case that was confirmed to be positive via testing in a WHO-accredited laboratory. Common confirmatory tests include an immunoassay to confirm the presence of IgM antibody in a collected blood specimen or real-time reverse transcription polymerase chain reaction (RT-PCR) from a specimen collected via throat or nasopharyngeal swab or urine to detect viral RNA. Despite a much shorter infectious period, lasting for a few days before and after rash onset, RNA can be found for up to three months[16]. IgM antibodies might not be detectable in early disease phases until after a rash has been present for some time[17]. Epidemiologically-linked cases are suspected cases that do not have laboratory confirmation but are geographically and temporally related to a laboratory-confirmed or an additional epidemiologically-linked case. Finally, clinically compatible cases are other suspected cases without laboratory confirmation or an epidemiological link but had a fever, maculopapular rash, and at least one of cough, coryza, or conjunctivitis.

Sequalae and Outcomes

Common complications of measles infection include diarrhoea, otitis media, pneumonia, and encephalitis[14]. Other, less common sequalae include subacute sclerosing panencephalitis (SSPE) and acute death. Most complications occur in children aged less than 5 years[14]. Immunocompromised persons with measles infections experience relatively more complications[18,19].

SSPE, a progressive neurological disorder, affects the central nervous system among a small proportion of children with a history of a measles infection[20]. Most cases of SSPE have a history of measles before their second birthday which follows by a latent period lasting six to eight years before symptom onset. Symptoms of SSPE include cognitive decline, seizures, blindness, and behaviour changes, and in later advanced stages, loss of motor function, loss of control of autonomic nervous system, and heart failure. Life expectancy of patients with SSPE is only one to three years. There is no cure for SSPE.

First observed in the 1960s, persons with a history of measles infection have been known to experience long-term immunosuppressive effects of measles virus, which influences ability to respond to additional infections and vaccinations[1]. Specific immunomodulatory consequences include: (1) a depletion of immune cells[21] (e.g., T cells) which has consequences for fighting secondary infections, (2) selectively targeting memory T cells[21] which allows for reinfection, (3) disrupting cytokine responses[22] which yields a dampened overall immune response, and (4) impaired antigen-presenting cells[22,23], such as dendritic cells and macrophages, which slows adaptive immune responses. The loss of previous immune memory, called "immune amnesia", has also been shown as a long-term immunomodulated effect of measles[24-26]; in an experiment testing sera both pre- and post-measles infection in 77 unvaccinated children, approximately 20% of overall antibody repertoire diversity was lost and approximately 16% of children lost over 40% of their antibody repertoire diversity[24]. Associated

immunosuppressive effects have been shown to last from several weeks[27,28] to years[29] following a measles infection. Mortality attributable to infectious diseases besides measles has been shown to lag behind increases in measles incidence for up to 3 years[29]. The immunosuppressive effects of measles have substantially larger implications for disease beyond acute burden associated with recent infection and should be considered a critical public health challenge.

Treatment

As there is no specific treatment or antiviral therapies available for measles, treatment mainly includes supportive care, management of symptoms, and addressing complications as they arise. Supportive care efforts focus on supplying fluids to avoid dehydration, managing nutritional deficiencies, and supplying vitamin A treatment. Non-specific antiviral medications, such as interferon alfa and ribavirin, have been used to treat severe measles[30]. Post-exposure prophylactic administration of immunoglobulins to certain high-risk individuals (e.g., infants younger than 6 months, pregnant persons with no evidence of immunity, those who are immunocompromised) has also been shown to prevent subsequent measles infection and hence complications[31].

Vitamin A is an essential micronutrient critical to the normal function of epithelial cells and persons deficient in vitamin A have damaged epithelial tissue and depressed immune function[32]. As such, persons with vitamin A deficiency are at increased risk of severe complications of measles as the infection will only continue to additionally damage epithelial cells. Dosing with vitamin A has been shown to reduce measles mortality-related outcomes[33-37], as well as prevent eye damage and blindness, and is recommended for immediate delivery to all severe or hospitalized measles cases. The WHO recommends[38] two doses of vitamin A on successive days with specific dosing amount dependent on patient age (i.e., 200000 IU for children aged older than 1 year, 100000 IU for children aged 6 months to 1 year, and 50000 IU for children aged younger than 6 months).

Common complications arising from a measles infection include bacterial co-infections, such as diarrhoeal and bacterial pneumonia infections. Prophylactic antibiotic use is not recommended[39], however prescribed for persons who develop a bacterial infection. Oral rehydration therapy is recommended[40] for management of measles-related diarrhoea and for diarrhoeal co-infections.

Prevention and immunity

Immunity to measles infection can be conferred through either maternal antibody, via natural infection, or through vaccination. Previous measles history has shown to yield life-long, sustained antibody titres above a clinically protective threshold. Measles maternal antibodies, transferred placentally to the fetus, provide temporary protection from measles infection following birth. The duration for which antibody levels remain high enough for clinical protection vary by mother or infant immune status, mother measles infection or vaccination history, and underlying measles dynamics within a community. On average, maternal antibody titres remain above clinically protective thresholds until an infant is approximately four months old[41]. As recommended and assuming subsequent seroconversion, measles vaccination yields lifelong measles immunity.

1.1.2 Measles vaccination

Vaccination against measles has been widely available and recommended for use globally for multiple decades. Measles vaccines rely on live-attenuated viruses that have been derived from various viral strains[14]. The first measles vaccines were licensed in 1963. Various strains of measles virus, including the Edmonston, Schwarz, Edmonston-Zagreb or Moraten strains, have been used over time, and some of which are still used currently[42]. Measles vaccines are stored as powder in a single multi-dose vial to be injected once combined with diluent.

Progress in vaccine technology over multiple decades have afforded the opportunity for advancement in measles-containing vaccines (MCV). Various combination vaccines, such as measles-rubella (MR), measles-mumps-rubella

(MMR) and measles-mumps-rubella-varicella (MMR-V), have been developed in the 1970s (MR and MMR) and 2005 (MMR-V) and since introduced in countries that contain the additional antigens in their immunization schedule[43]. Additionally, in the early 2000s, development began to expand vaccination delivery mechanisms and technology, including MCV micro-array patches[44,45]. Ongoing research suggests the use of micro-array patches are effective, can be cost-effective[46], and could increase vaccine access in remote locations, but have yet to be implemented or licensed.

Dosing schedule

The WHO recommends the first dose of measles vaccine to be delivered between ages 9 and 12 months and a second dose between ages 15 and 18 months. The second dose must be given no less than four weeks after the first dose. As recommended, a single dose of measles vaccine has an estimated 93% efficacy from clinical trials, yielding an estimated 97% efficacy from a two-dose regimen[14]. Specific schedules by country are chosen to maximize vaccine efficacy given the particular setting and context of measles epidemiology. It has been shown that seroconversion increases between infants aged 4 to 11 months old[47,48], and early age upon the first vaccine dose administered has increased rates of failure to seroconvert following a two-dose schedule[49]. However, in some settings with high transmission, recommending doses at age 12 months (versus earlier in the 9 to 12 months age window) poses too great a risk of acquiring an infection after maternal antibodies wane. In these instances, a first dose is recommended within a shorter time interval as the decreased efficacy is not seen as a strong enough benefit to outweigh the risk of infection from delayed vaccination.

In select circumstances, vaccine doses are permitted to be administered to children between ages 6 to 9 months in specific scenarios of high infection risk or epidemiologic need, such as in populations experiencing epidemics, high malnutrition prevalence, those occupying overcrowded areas, and those born to mothers with HIV infections. If one or both recommended doses have been

missed, WHO recommends that all children and adults should be offered catch-up doses from clinical personnel[50]. Measles vaccines are contraindicated for severely immunocompromised persons, pregnant or breastfeeding people, those with allergic reactions to previous doses, or anyone with an acute severe febrile illness.

Beyond age at vaccination, setting specific contexts, such as among communities with recent outbreaks of other diseases[51], high rates of malnutrition[52,53] or HIV prevalence[54], suggest lower observed vaccine effectiveness. Additionally, while typically measles immunity is presumed to be lifelong, there is some indication that vaccine-induced immunity does wane over time in near-elimination or low transmission settings[55]. Both possible lower vaccine effectiveness and waning of immunity overtime have implications for long-term vaccine delivery and programming, as it will be even more challenging to achieve herd immunity by obtaining immunity among a critical portion of the population in local communities (i.e., 95%)[56,57].

Supplemental immunization activities

Outside the routine immunization system, doses of measles vaccine are frequently administered through supplemental immunization activities (SIAs), or campaigns, targeting different specific populations[58]. "Catch-up" SIAs are a single event that target all eligible children, typically aged under 5 or 15 years, with the goal of dramatically reducing the number of susceptible persons most likely to acquire measles within a population. "Follow-up" SIAs are planned, based on routine immunization coverage levels, to occur every two to four years and are aimed to reduce susceptible build up across children born since any previous SIA. Other SIAs can be used during outbreak response to mitigate any ongoing transmission to persons remaining susceptible. While SIAs are useful for reducing the proportion of susceptible persons in a community, measles and vaccination experts recommend that strong and sustainable immunization programs rely primarily on delivering doses through routine vaccination[59].

1.2 Measles in low- and middle-income countries

1.2.1 Trends in measles vaccination coverage

Following licensure of a measles vaccine, individual countries implemented national-level measles vaccination campaigns and introductions to routine services throughout the 1960s and early 1970s[60]. In 1966, a measles immunization program was introduced in Africa with the aim of vaccinating against measles, as well as eradicating smallpox, with partners including WHO, CDC, USAID, and governments of over 20 African countries[60]. Initial vaccine roll out was proven to be successful at stopping ongoing measles transmission in various locations, such as in The Gambia during a 1967 outbreak[60].

Introduction of Expanded Programme on Immunizations

Immunization programs within countries experienced complications related to governmental and public motivation to vaccinate, ineffective program management, and insufficient resources for vaccine monitoring. In 1974, less than 5% of children had been vaccinated with three doses of diphtheria-tetanus-pertussis and poliomyelitis recommended childhood vaccines before their first birthday[61]. Immunization programs within countries experienced complications related to governmental and public motivation to vaccinate. To combat these concerns and further expand the reach of vaccine programmes globally, the Expanded Programme on Immunizations (EPI) was developed in 1974[61].

The initial goal of EPI, in 1977, was to make vaccinations against measles, along with diphtheria, tetanus, pertussis, poliomyelitis and tuberculosis available to every child before 1990[61]. In 1984, the WHO established a standardized schedule for these EPI vaccines[61]. Later the EPI added additional vaccines to their recommended list (e.g., Hepatitis B, yellow fever in endemic countries). From 1980 to 1990, estimates of MCV1 coverage increased from approximately 38% to approximately 66% globally, which is largely attributable to the implementation of EPI within countries around the world[62].

Gavi, the Vaccine Alliance

After immediate increases following EPI introduction, MCV1 coverage, along with coverage for vaccines against other diseases, was stagnating as barriers to achieving universal vaccine delivery were unaffordable to surpass in low- and middle-income countries (LMICs). To counter these emerging challenges, a partnership between the Bill & Melinda Gates Foundation, WHO, the United Nations Children's Fund (Unicef), the World Bank, and other organizations was formed to create the Global Alliance for Vaccines and Immunization, now called Gavi, the Vaccine Alliance[63] (hereafter "Gavi"). Gavi leverages an agreement with vaccine manufacturers to provide vaccine doses at a lower price in qualifying countries in exchange for consistent, predicable, large scale and long-term demand commitments[63] as well as provide resources for health system strengthening, such as for expanding cold chain capacity and vaccination campaigns. From inception in 2000 to 2021, Gavi has contributed to the delivery of vaccines to over 981 million children, over 185.3 billion USD in estimated economic benefits, and the prevention of over 16.2 million estimated deaths from vaccine preventable diseases[64].

Through collaboration with the Measles & Rubella Initiative[65], Gavi has four different types of support available for countries to combat measles: MR routine immunization for first- and second-dose, measles follow-up campaigns, MR catch-up and follow-up campaigns, and measles outbreak response. Gavi, the Vaccine Alliance supports MR combination vaccinations to also prevent avoidable rubella and congenital rubella syndrome. Gavi has consequently indirectly contributed to global routine MCV1 coverage increases from approximately 72% to approximately 83% from 2000 to 2010[62] and additionally vaccinating over 524 million children via SIAs from 2000 to 2018[64].

Planning for the last decade

In 2010, the WHO, Unicef, US National Institute of Allergy and Infectious Disease (NIAID) and the Bill & Melinda Gates Foundation joined efforts to

devise the Global Vaccine Action Plan (GVAP)[66], a strategy to increase international coordination to increase vaccine coverage estimates during the oncoming decade. With accompanying goals to increase country ownership, equity, integration, sustainability, and innovation, the GVAP set a target of achieving 90% vaccine coverage in each country by 2020.

Along with setting national-level coverage targets, GVAP additionally set a goal of reaching at least 80% routine MCV1 coverage in each subnational district (i.e., second-administrative level unit). In order to monitor progress towards this objective, the WHO and Unicef have asked member states to report subnational administrative coverage metrics[67]. However, these data are currently subject due to substantial bias and quality-related concerns that limit their utility[68,69]. In response to these limitations, numerous model-based efforts[70-74] have identified subnational MCV1 coverage and geographic coverage heterogeneity by using data from household-based surveys, such as the Demographic and Health Survey[75] and Multiple Indicator Cluster Survey[76] series.

Besides subnational targeting, additional priorities for immunization programmes have been outlined by the Equity Reference Group for Immunization[77], which calls for particular attention to be paid to children living in urban poor or remote rural settings, in conflict-affected areas, and across genders to eliminate preventable disease burden and deaths including from measles infection. Understanding the distribution of unvaccinated persons across these particularly vulnerable communities is critical for targeting planned interventions. The distribution of unvaccinated children across communities affected by conflict and in urban and remote rural locations varies by country[78], suggesting a better understanding of these trends within specific settings is critical when planning targeted interventions[59].

Monitoring routine immunization

While household-based survey data in specific country-years as well as country reported administrative coverage data could be used to monitor national-level coverage, estimates synthesizing various data sources are often alternatively used. There are two predominant estimates of national vaccine coverage at a global scale: WHO/Unicef estimates of national immunization coverage (WUENIC)[79] and the Global Burden of Disease study (GBD)[62,80]. The WUENIC coverage estimates[79] are generated via a rule-based system that first prioritizes information reported by countries from administrative data while including information also from household-based surveys and grey literature reports. When administrative estimates are similar to those from surveys, WUENIC accepts the reported administrative coverage estimate from the specific year as the official coverage value. If they are discrepant, WUENIC uses the reported survey coverage value for that given country-year.

Alternatively, national coverage estimates have also been produced by the GBD[62]. The GBD uses a space-time Gaussian process model to estimate coverage along with uncertainty. While input data is similar to WUENIC (i.e., administrative data and microdata from household-based surveys), the GBD estimation process prioritizes information from household-based surveys to perform a bias correction on the administrative data in a model using country-years with paired observations from both sources. After this adjustment, both survey and adjusted administrative data are used in the modelling framework to estimate coverage. Estimates between GBD and WUENIC are usually comparable[62].

Based on GBD coverage estimates, in 2010, 58% of all countries globally had a high probability of reaching the GVAP target and in 2019, 61% of countries had the same probability of reaching this coverage target, far off from the GVAP goal[62]. This overall lack of change is likely attributable to stagnations and declines in many individual countries over the decade[62,79]. By the end of 2019, global MCV1 coverage was approximately 84%, similar to what it was in 2010.

Estimated global MCV2 coverage increased from 32% in 2000, to 45% in 2010, and to 67% in 2019[62]. In 2010, MCV2 coverage was not introduced into national immunization schedules in 58 countries. Over the following decade, mainly through the support of Gavi, MCV2 has been implemented into routine schedules in additional 41 countries[79]. In 2021, 12 countries still had not introduced MCV2 into their recommended routine immunization schedule[79].

In order to monitor progress towards subnational coverage targets, the WHO and Unicef have asked member states to report subnational administrative coverage metrics[67]. However, these data are currently subject to substantial bias and quality-related concerns that limit their utility[68,69]. In response to these limitations, numerous model-based efforts[70-74] have quantified subnational MCV1 coverage and geographic coverage heterogeneity by using data from household-based surveys, such as the Demographic and Health Survey[75] and Multiple Indicator Cluster Survey[76] series. Substantial inequality persists between LMICs as well as within the countries themselves. From 2000 to 2019, MCV1 coverage was estimated to have increased in 57% of second-administrative level units (e.g., districts, counties, zones, which are one administrative boundary more granular than first-administrative units, such as states, regions, or provinces) across LMICs[70]. Similar to national-level coverage though, the period from 2000 to 2010 showed greater coverage gains across subnational areas (i.e., 71% of second-administrative units had estimated increases in coverage), while the period from 2010 to 2019 suggested stalls and decreases in coverage (i.e., 40% of second-administrative level units had estimated increases in coverage). 38% of second-administrative level units had a high probability of reaching 80% GVAP targets in 2000, and 33% of units had a high probability of reaching the same target in 2019.

Monitoring supplemental immunization activities
From 2000 to 2019, over 2.7 billion children across multiple WHO regions have received additional doses of MCV through supplemental immunization programs[59,81]. SIAs have contributed to overall increases in population-level

immunity and decreased ongoing transmission, and as such, it is critical to monitor their contributions to overall vaccine-induced immunity metrics (i.e., combined routine and supplemental immunization coverage). This can be technically challenging, though, as some proportion of children vaccinated during an SIA will already have vaccine-induced immunity from either previous routine or supplemental immunization.

Increases in overall coverage following SIAs, or other metrics of campaign efficiency, can be computed through an understanding of individual-level vaccination status before and after the SIA took place along with an understanding of campaign participation[82], if these data are available. Overall, SIAs have been shown to yield higher combined MCV coverage across various geographies than from routine immunization alone[73,83].

Current status of routine immunization programs
While the global immunization community transitioned from the strategy set by GVAP to the updated strategy outlined by the Immunization Agenda 2030 (IA2030)[84], the onset of the SARS-CoV-2 pandemic began to unfold[85]. Despite WHO recommending continuing vaccination programs during the pandemic due to its favourable risk-benefit[86], measles vaccination experienced substantial global disruptions following widescale disturbances to health services[87]. In 2020, MCV1 coverage was estimated to be almost 8% lower than what it may have reached in the absence of the pandemic[88]. In 2022, estimated global MCV1 coverage reached only 83%, which is still below levels observed in 2019, and almost 22 million eligible children were estimated to missed their first dose. In low-income countries specifically, coverage continued to decline by decreasing an additional percentage since 2021[89]. MCV2 introduction to national schedules continued to boost estimated global MCV2 coverage to 74% in 2022.

In addition to pandemic-related disruptions, growing concerns regarding diminishing vaccine confidence levels globally[90,91] threaten coverage progress,

particularly among communities with low science education and low trust in health care personnel[92].

1.2.2 Trends in measles burden

Incidence

Measles epidemiology was presumed to be similar in LMICs as was observed in high-income countries prior to vaccine introduction. This assumption has been made as scant data exists from LMICs in the pre-vaccine era, but could introduce limitations related to generalizability across heterogeneous settings. Regardless, in high income countries before vaccination, most children acquired measles before turning10 years-old[93,94]; prior to EPI introduction, trends related to measles incidence were mainly attributable to outbreaks and occurred in an approximately biennial cyclic pattern dependent on the birth rate and accumulating size of the susceptible population. After vaccine introduction and largescale coverage increases in these high-income settings, estimated measles incidence decreased substantially[95], average age of measles infection increased[96-98], and the average infection reproductive number decreased[96]. Similarly to what was observed in high-income settings, following the implementation of Gavi-funding programming in 2000, measles cases continued to fall across supported countries and regions[99,100]. While global progress has been established, over 99% of measles cases are estimated occur in LMICs[80].

Because of large improvements in vaccination programs and subsequent decreases in measles cases, in 2012, global measles programmes were able to set a new ultimate goal of measles eradication through regional elimination[101]. The WHO defines elimination as "the absence of endemic measles virus transmission in a defined geographical area (e.g., region or country) for at least 12 months in the presence of a surveillance system that has been verified to be performing well"[102]. All WHO regions have committed to measles elimination[103].

However, despite many improvements across countries and regions, measles elimination had only been reached in the Region of the Americas (AMR). This effort in the AMR was certified as achieved in September 2016[104] and included sustained high routine immunization coverage, mass SIAs with high coverage, and case-based surveillance programs planned over multiple decades across all member countries and harmonized by the Pan American Health Organization (PAHO)[105]. However, endemic measles has re-emerged in both Venezuela and Brazil, revoking elimination status in the AMR[106]. Eight other countries, including 4 LMICs (i.e., Albania, Cambodia, Mongolia, and Uzbekistan), who had achieved elimination status have experienced restored endemic transmission[99]. At the start of 2022, 76 countries have achieved and sustained measles elimination[99]. By 2100, less than 40% of LMICs have been estimated to be able to achieve conditions necessary for elimination, mainly due to the dependence on SIAs as a result of low routine immunization coverage[107].

These countries with low immunization rates are unable or not expected to achieve reduction of endemic transmission and additionally are likely to experience large outbreaks. The number of reported measles cases was higher in 2018 than in previous recent years[108], due to persisting numbers of unvaccinated children[109] and the cyclical nature of measles incidence globally. There was an initial decrease in measles cases over the start of the COVID-19 pandemic period[110] likely resulting from pandemic-related non-pharmaceutical interventions (e.g., lockdowns, school closures). However, in 2022, 22 countries experienced disruptive measles outbreaks[99]. These outbreaks are likely attributable to drops in vaccination coverage sustained as a result of pandemic-related disruptions as well as additional build up in susceptible persons following decreased transmission in the early pandemic period.

Mortality
Participating in measles vaccination campaigns overall has been shown to reduce all-cause mortality among children under-five-years-old by increasing the

probability of survival to age five by 2.4 percentage points[111]. Population-level measles vaccination also contributes towards decreased measles incidence, as well as less severe measles cases among vaccinated individuals[112]. Therefore, along with substantial decreases in overall measles cases, vaccination programmes have resulted in less severe infections, which afford faster recovery and less opportunity for secondary infection[70,113-124]. Due mainly to reductions in cases, measles vaccination introduction in LMICs has averted an estimated 56 million deaths between 2000 and 2021 alone[99].

In 2000, over 760,000 measles-attributable deaths were estimated globally; in 2019, there were an estimated 207,500 measles deaths[125]. Following the onset of the COVID-19 pandemic, the number of global measles deaths in 2021 fell to less than 130,000[99], which was likely attributable to overall reductions in incidence during the pandemic period. Advances in development, such as in living conditions, as well as the widespread use of antibiotic treatment for secondary infections, have also led to decreases in measles mortality[126,127]. Additionally, decreases in malnutrition prevalence[128] also likely contributed towards decreasing measles mortality[129]. Overall, reductions in measles mortality have led to marked decreases in mortality among children under 5-years-old[130].

1.3 Gaps and challenges in burden estimation
1.3.1 Gaps in data to understand measles immunity
Challenges in estimating measles susceptibility
Understanding measles immunity and susceptibility profiles across locations and age groups underpins surveillance priorities set by WHO and is critical for planning targeted interventions, such as vaccine campaigns or routine immunization strengthening, and becomes increasingly critical as countries or regions approach conditions necessary to achieve elimination. Susceptibility to measles can be approximated through both vaccination coverage estimates and evidence of natural infection history; however, using these sources to generate comprehensive immunity estimates can be challenging. The coverage estimates

from both WUENIC and GBD primarily rely on survey-derived data sources, with varying degrees of quality, completeness, accuracy and representativeness, or administrative in nature, which come with additional biases and limitations[62,131,132]. Additionally, previous vaccination status is also an imperfect metric of immunity acquired via vaccination. While measles vaccination is generally highly immunogenic and effective, factors such as cold chain disruptions and age at vaccination may result in no or suboptimal immunity following a vaccine dose[133]. Challenges of effective coverage also impact doses administered through SIAs. In addition, despite the number of doses administered through each SIA being reported to WHO and available publicly[81], these administrative data often implausibly suggest coverage greater than 100%.

Immunity to measles can also result from natural infection; however, assessing immunity though prior infection is also complex. Often, especially in endemic settings, suspected measles cases are not confirmed via laboratory diagnosis[134]. Also, case reporting or ascertainment rates vary substantially across locations and time and thus are challenging to estimate.

Serologic assays to estimate measles immunity

Instead of relying on previous vaccination or infection status, serosurveys can provide a snapshot of the current immunity gaps that remain in the population. Serologic assays can be used to determine an individual's level of serum antibody but cannot determine whether the subsequent antibody titres were provided via vaccination or natural infection. While serosurveillance can be used as a stand-alone product to assess immunity gaps among a population, they are most often used with additional data sources on vaccine coverage and case notifications or disease surveillance. As such, serology data are often used as an input to dynamic models of disease transmission and have potential to be informative in the assessment of case under-ascertainment in settings with endemic measles transmission. In settings that have reached or are approaching elimination where

antibody titres have likely declined, using seroprevalence data to estimate similar dynamics or characteristics of transmission may be more complex[135].

Serologic assays to determine the presence of various individual antibodies have been developed for many infections, including measles, and implemented globally. WHO provides programmatic and technical guidance for countries on the use of serologic assays in both routine disease surveillance and to track outbreaks and symptomatic suspected measles cases[136]. While serosurveillance and laboratory confirmation of measles cases tests individuals for short-lasting IgM antibodies, assessing overall immunity patterns in a population requires a seroassay to detect IgG antibodies against measles.

In a previous systematic review by Thompson and Odahowski[137], available serological data on immunizing antibody (i.e., IgG) against measles and rubella were presented through June 2014. The systematic review found 72 countries that contained data from at least one study. An additional review by Dimech and Mulders[138] included studies from 1998 to 2014. 68 articles containing measles seroprevalence data were included. The review contained information on measles seroprevalence along with some details on study population, sample size, and measurement assay. Both reviews, however, only contained data from a limited time window, did not provide critical information required from a systematic review, and did not go on to assess each study by underlying characteristics.

Types of seroassays
Major classes of seroassays that have been frequently used to detect measles antibodies include hemagglutination inhibition (HI/HAI) assays, enzyme immunoassays (EIA), enzyme-linked immunosorbent assays (ELISA), plaque reaction neutralization (PRN) assays, and multiplex bead assays (MBA). HI/HAI assays[139] identify measles antibodies by measuring virus' ability to agglutinate red blood cells in the presence of sera. This assay has a simple protocol and is inexpensive to conduct, however is also time consuming[138] and has generally

lower sensitivity[140]. EIA/ELISAs rely on microplates that allow antibodies from samples to be bound to antigens along with other enzyme-conjugated antibodies that change colour. EIA/ELISAs are commonly used for antibody detection, but require individual tests for each antigen of interest, are expensive, and require a sizable amount of sample volume[141]; additionally, available commercial kits have variable levels of accuracy[140,142].

Being highly sensitive, PRN assays are considered the "gold standard" immunoassay for detecting measles antibodies[143]. PRN assays test the ability of serum mixed with virus isolates to prevent virus-made plaques from forming on infected cells. PRN assays are very time consuming, require experienced technical laboratory personnel, and are difficult to scale to analyse many samples[144]. More newly developed[145], MBAs examine binding of serum samples to antigen-coated beads to detect measles antibodies. MBAs can test for antibodies against many antigens simultaneously across many samples, which allows for high throughput analyses to be conducted[141,144,145].

Possible biases among population-based serosurveillance data
Noting these differences in underlying seroassays and as well as the importance of survey design and laboratory standardization[146], the proceeding systematic reviews are not sufficient to contribute towards effective modelling efforts to estimate population-level measles immunity or susceptibility. The review by Thompson and Odahowski[137] includes data across a variety of years and locations, but makes no note of study design, population-representativeness, seroassay, or other factors than may influence assay sensitivity. The review by Dimech and Mulders[138] starts to note some of these factors, but only contains data published from 1998 to 2014, which leaves out many years of important data collection that might be critical for use in calibrating models to understand susceptibility and immunity.

Assay sensitivity and specificity, as well as associated sensitivity and specificity of various specimen types (e.g., blood, oral fluid), can affect the interpretation of population-level seroprevalence estimates. For example, in the case of studies using HI/HAI assays, which have known lower sensitivity in a population with much vaccine-derived immunity (i.e., lower antibody titres following a single MCV dose than from natural infection[147]), seroprevalence estimates might be an underestimate of true population-level immunity. Despite the increasing number of carefully planned and strategized serosurveys that are underway and the utility of these high-quality study results[148], the majority of existing data have uncategorized limitations that likely should influence their interpretation.

1.3.2 Understanding utility of subnational case notification data

Overview of case notifications and surveillance systems

Surveillance programs for infectious diseases, including measles, need to be able to share data quickly, access laboratory resources adequately, and prioritize communication with other countries and international organizations, such as WHO[149]. In 2021, all WHO member states conduced measles surveillance, however 65% of all countries that reported the number of suspected cases determined to neither be measles or rubella did not meet set sensitivity targets (i.e., two or more discarded cases per 100,000 people)[99]. This suggests measles surveillance programs broadly are not performing to their potential.

When approaching elimination, case-based surveillance is required in order to sufficiently identify, explore, and validate every suspected measles case[149]. However, most LMICs are not yet approaching elimination and are still trying to decrease the number of measles deaths. For countries in the mortality reduction phase of measles control, WHO suggests that surveillance programs should prioritize the following: (1) monitoring coverage and incidence, (2) determining areas with poor performance or high risk, (3) articulating epidemiologic trends across age, vaccination status and time, and (4) early detection of and investigating outbreaks[150].

Broadly across vaccine-preventable diseases, surveillance robustness has fallen behind in progress compared to success of immunization programs. The promise of increases to vaccine coverage, in part, is the short-term benefit of case reductions, while improvements to surveillance systems are challenging and do not see immediate benefits in population-level measles control[150]. Surveillance systems, however, are underperforming. These data on reported cases are often unstable over time, having varying degrees of laboratory confirmation, and are often incomplete. For example, over the last few decades, temporal trends in measles surveillance systems suggest improvements afforded through contributions to overall health system strengthening from Gavi and the adaptation of the Integrated Disease Surveillance and Response (IDSR) framework from WHO. While surveillance system improvements are valuable, it can make comparing case notifications across years challenging when the underlying reporting mechanism or identification system changes.

Laboratory specimens, such as blood, respiratory samples or urine, from suspected measles cases are recommended to be tested for confirmatory diagnosis[151]. Standard rapid diagnostics include an EIA or chemiluminescent immunoassay[152,153]. Breakthrough infections may not yield a substantial IgM accumulation and require RT-PCR for testing[153]. Other molecular detection and virus isolation, including for genotyping, leverage RT-PCR among other techniques. WHO's Global Measles and Rubella Laboratory Network (GMRLN) assists in analysing samples; in 2021, GMRLN received over 122,000 specimens from suspected measles cases for testing[99]. The proportion of suspected cases that are lab-confirmed varies substantially between ages, locations, and years[154-156], which causes great challenges for interpreting suspected case notifications.

Active surveillance for measles consists of healthcare personnel actively seeking out ongoing disease and following-up on infections and related contacts, which both requires significant person time and financial resources. Alternatively

passive surveillance systems, such as notifiable disease surveillance, capture cases that are reported from clinics or local governments to more centralized entities. For a measles case to be captured via passive surveillance systems, persons with symptoms need to first seek medical care, be given a diagnosis (e.g., suspected or laboratory confirmed case) by a health care professional, and then the facility or clinic needs to report the diagnosis to the Ministry of Health or some other entity depending on the country. There are multiple places along this cascade for measles cases to not be captured (i.e., persons could not seek care, they could be misdiagnosed or not seen at the clinic, or the health care facility could have mishandled the case reporting). High-income settings (such as the United States and the Netherlands), which now have robust health care and surveillance systems, historically had low case reporting rates through the 1990s estimated given known measles incidence[70,157,158]. Similar trends across LMICs are hypothesized, but infrequently quantified.

Utility of case notifications in measles modelling

To understand measles susceptibility, especially temporally, there are limited data sources available to investigators. For example, data from serosurveys are expensive to collect and do not provide a complete picture of the underlying dynamics of measles in a community, especially temporally. Alternatively, relying on primarily vaccine coverage estimates, which only provide a partial perspective on immunity patterns, is also unfavourable. As such, policy-makers often leverage work of mathematical and statistical modelers that approximate the underlying transmission dynamics of measles to synthesize data sources and estimate subsequent incidence and immunity patterns to inform decision-making and planning[159]. Calibrating these models requires researchers to use additional data often from counts of reported measles cases from routine surveillance systems, serosurveys, vaccine coverage, or some combination of these.

Multiple efforts to generate modelled estimates of measles incidence and susceptibility have been under-taken by researchers on national scales, which

include estimates from WHO, GBD, the Vaccine Impact Modelling Consortium and many individual country-specific investigations. For example, WHO has used a methodologic framework for estimating measles incidence originally published by Chen, Fricks and Ferrari[160]. In this state-space modelling approach, national incidence and deaths are estimated from a time-series Susceptible-Infected-Recovered (TSIR) dynamic model. The model includes inputs of case notifications and administrative vaccination coverage. While providing a global comparison framework using routinely collected data, these estimates do not consider subnational dynamics of disease transmission, geographic heterogeneity in vaccine coverage, or pockets of susceptibility by age.

Other researchers have also estimated national and regional measles incidence in various settings, with different applications and limitations. For example, Verguet *et al*[57] used a dynamic transmission model (DynaMICE) to generate estimates of measles susceptibility to inform optimal timing of SIAs in nine selected countries with highest measles mortality burden. This model, while age-structured and accounting for differential vaccine efficacy by age, is deterministic (i.e., not accounting for stochastic transmissions or case importations), does not leverage information from case notifications, and does not make inference. Instead, transmission parameters were computed from an assumed R_0 value (i.e., the basic reproduction number; the average number of cases arising following transmission from a single infected individual) and assumed SIA scenarios were the only variability in model outputs. This overall model is used as part of the Vaccine Impact Modelling Consortium[161] to generate estimates of measles burden averted attributable to vaccination.

The GBD[80] also estimates measles incidence by country on a global scale. For countries with robust surveillance systems (e.g., high-income countries, countries in Central and Eastern Europe, Central Asia, Latin America, and the Caribbean), the GBD uses reported counts of measles cases to derive incidence estimates. For other countries without trust-worthy surveillance, the GBD leverages a linear

mixed-effects model that uses information on MCV1 and MCV2 coverage, reported coverage from SIAs, and location-level random effects to fit to reported national case notifications. When predicting from this model, a random effect is substituted such that the attack rate for measles in the absence of vaccination is 95%. While this model may be sufficient to accurately predict long-term trends in measles incidence, it does not account for the underlying dynamics of measles within a community that result in outbreaks, nor does it capture population-level effects of herd immunity.

Other modelling efforts have estimated national measles incidence on the scale of individual countries. For example, Dong and Wakefield[162] estimated measles incidence in Benin from 2012 to 2018 using a TSIR framework that allowed for testing various reporting rates. They use a two-step modelling approach: estimate reporting rate using an ordinary least squares regression, and then use Markov chain Monte Carlo (MCMC) to fit a Bayesian hierarchical model to estimate other model parameters and latent variables. Their model assumed homogenous population mixing, which limits the ability to use this framework in settings with large geographies or with substantial heterogeneity in transmission or risk of transmission (i.e., coverage). Additionally, the authors describe the reporting rate identified from modelling to be over-estimated when shorter time series of cases are used for fitting (which they attribute to small sample sizes) and under-estimated when longer time series of cases are used for fitting (which they attribute to a correlation between cumulative reported incidence and deviance of the susceptible population across the time series from the mean).

From the previously mentioned estimates of subnational measles vaccine coverage, it is known that there are dramatic inequalities in vaccine coverage both between and within countries. As measles transmission can be maintained if herd immunity has not been reached, assessing the underlying gaps of measles susceptibility within a population is essential for vaccination programs and infectious disease control efforts as countries move towards elimination. While

useful for global benchmarking and tracking progress towards national and regional elimination goals, national estimates are of limited utility when planning local decisions. National estimates do not identify local pockets of low immunity that leave individuals and communities at risk for measles[56]. Along with assessing gaps in subnational immunity by geography, identifying gaps in age group susceptibility is critical for planning targeted interventions to halt transmission.

Researchers also have begun to explore subnational measles modelling in specific contexts and scenarios with unique datasets. Objectives and methods for estimating spatial measles dynamics varied widely. The following studies are set of examples across the published literature:

- Estimating the critical vaccination threshold and effective reproductive number (R_E) in Tanzania by accounting for spatial susceptibility clustering (Truelove *et al*[163]);
- Replicating measles dynamics in London boroughs using a Kriged Kalman Filter method (Chiogna and Gaetan[164]);
- Replicate spatial measles dynamics using power law models that incorporate estimates of subnational vaccination coverage and reported measles cases in Cameroon (Parpia *et al*[165]);
- Estimating the role of spatial movement in measles outbreaks via a gravity model incorporating case notification data, cell phone mobility data, and estimates of vaccine coverage (Wesolowski *et al*[166]);
- Testing the impact of SIA timing on measles transmission in subnational units in Pakistan implemented a TSIR model (Thakkar *et al*[167]); and
- Estimating relative measles risk using various analyses (Kundrick *et al*[71], Ntirampeba *et al*[168], Tang *et al*[169] and Zhu *et al*[170]).

Most of these models make substantial assumptions or use methods that limit their broad applicability to answer specific questions regarding measles susceptibility by age and space. For example, most studies did not construct age-structured models or stratify susceptibility results by age. Also, many published models make simplifying assumptions about vaccination such as not accounting for

vaccine doses that have been administered through SIAs (e.g., Parpia *et al*[165]), only accounting for one vaccine dose (e.g., Truelove *et al*[163]), assumed constant vaccination coverage across the time period investigated (e.g., Thakkar *et al*[167]), or assumed perfect vaccine efficacy (e.g., Truelove *et al*[163]). Other studies (e.g., Chiogna and Gaetan[164]) only investigated measles in the pre-vaccination era and therefore did not incorporate vaccination into models.

Many models also assumed complete case ascertainment (e.g., Chiogna and Gaetan[164], Parpia *et al*[165], Wesolowski *et al*[166]). The study authors of Wesolowski *et al*[166], however, note possible concerns about quality of case data, including incomplete reporting and possible varying reporting rates by subnational unit (neither of which they accounted for), and the possible subsequent limitations when interpreting their results. Others, such as Thakkar *et al*[167], accounted for lab confirmation of cases.

Finally, some investigations computed overall measles risk profiles within a country or other subnational location. For example, Tang *et al*[169] and Zhu *et al*[170], used spatial scan statistics to estimate historical seasonal peaks and high-risk spatial clusters of measles cases based of reported laboratory-confirmed measles cases. Other studies (e.g., Ntirampeba *et al*[168]) used reported case notifications along with covariates, such as population size, education level, malnutrition prevalence, vaccine coverage and previous measles incidence rates, to estimate measles risk. Alternatively, other studies (e.g., Kundrick *et al*[71]) based risk estimates off the proportion of reported cases with history of vaccination and assumed vaccine efficacy using methods described by Orenstein *et al*[171]. However, analyses that only assess underlying relative risks within the location of interest do not provide the ability to estimate current measles susceptibility quantitatively nor by age or space.

All in all, studies investigating subnational patterns of measles burden have noted various data challenges related to the importance of considering person movement

in considering disease dynamics, the critical relationship between subnational vaccine coverage and measles transmission, and interpreting case notifications that have been largely unsolved. However, to date, no published models to estimate subnational measles susceptibility have considered case ascertainment rates and vaccine effectiveness along with both subnational case notification and routine and supplemental vaccination coverage data.

1.3.3 Methods for case fatality estimation

Utility of case fatality ratio estimates

In many countries where measles is common, there is a lack of sustainable or robust vital registration (VR) systems[172] to systematically capture measles-related deaths. As there is a lack of reliable data on measles mortality from most LMICs, estimating mortality from combining information or estimates of measles incidence and measles case fatality ratios (CFRs) is a common approach to determining estimates of measles deaths[173]. Estimates of CFR are insightful when identifying opportunities for health system strengthening, as well as are critical inputs for the estimation of measles mortality[110] and the impact of vaccination programs in calculations of number of averted deaths attributable to vaccination[100,174].

Data available for estimating CFR

Primary data, collected via retrospective or prospective cohort studies and outbreak investigations, published in the literature are the main source of information on measles case fatality. These data also consist of few reports of routine surveillance systems that capture both cases and deaths for measles, among other vaccine-preventable and notifiable diseases. However, all these data available are limited to specific locations, years, and settings.

Two previous systematic reviews have attempted to synthesize these individual studies. The first review, by Wolfson *et al*[175], was published in 2009. It used 58 community-based studies in 29 countries to provide global evidence of measles

CFR. Using descriptive methods, the Wolfson analysis published results suggesting an overall CFR of 3.29%, with a median of 3.91%, mean of 7.40%, and range from 0 – 40.15%. For outbreak investigations, results suggested a median CFR of 5.18% (95% CI: 2.56 – 11.55%). These results were the first to produce figures of measles CFR beyond single country-year studies, reports, and investigations, however had several limitations as it only included community-based studies. The later review, by Portnoy *et al*[176] published in 2019, included data until 2016 from LMICs; studies were included from both community- (n=85) and hospital-based settings (n=39).

Advantages of modelling for CFR estimation

The original Wolfson *et al* study did not predict estimates for other locations or years or further stratify by other underlying determinants of mortality, such as development status of each country. Instead, the review presented one overall metric of CFR across all locations and years. However, given changes in health system infrastructure and vaccination coverage, among other factors, using a static estimate of CFR across time and locations is likely not sufficient to understand measles mortality historically or make policy-relevant projections to the current or future years.

Instead of estimating a single CFR across all studies, the study by Portnoy *el al* used a log-linear prediction model with a select set of covariates, hypothesized to be causally (previous vaccination history [first dose MCV coverage used as a proxy], estimated measles incidence, measles attack rate, and HIV prevalence) and indirectly associated with measles CFR (national income per capita, under-5 mortality [U5M], total fertility rate, proportion of population living in urban areas, population density, and educational attainment). The study reported predicted CFR stratified by year, country-development status, under-5 mortality rate, community- versus hospital-settings, and for age under- or over-5 years, as well as to year 2030. Results predicted a mean CFR of 2.2% (95% CI: 0.7 – 4.5%) for

years 1989-2015, with stratification for community (CFR: 1.5, 95% CI: 0.5 –
3.1%) and hospital-based studies (CFR: 2.9, 95% CI: 0.9 – 6.0%).

It has been shown that time- varying CFR estimates have an impact on measles
mortality estimates[177]. Since time-varying CFR estimates are higher in most
historical years when measles incidence estimates are also higher and lower in
more recent years when measles incidence estimates are also lower, overall
historic estimates of measles deaths increase when using time-varying CFR
estimates compared to using a static CFR estimate. Additionally, estimating
historic vaccine impact via deaths averted due to vaccination, the number of
deaths averted also increases. However, contemporary projections yield decreases
in estimated deaths averted as CFR was projected to continue to decrease in future
years.

Limitations in existing CFR estimates
Advances in CFR estimation have been widely accepted as improvements to the
overall measles mortality estimation process, as long as data included models and
estimates are continually updated[178]. However, the most recent review of measles
CFR estimates only includes data published through 2016. These data also do not
include studies that were published in languages other than English.

Additionally, there are multiple population-level characteristics and individual-
level factors that are hypothesized to be relevant when estimating measles CFR,
such as nutritional status, prevalence of other infections such as HIV or malaria,
communities living in refugee settings or temporary settlements, and if there is an
ongoing measles outbreak, among others[175,176,179]. To date, however, there has not
been an established causal framework on factors contributing to measles CFR.
Also, given the underlying clinical significance of vitamin A deficiency and
current best treatment practices, considering possible covariates related to vitamin
A therapy is recommended[178].

Another clinically significant consideration that has largely been neglected by previous estimates of CFR is the hypothesized variation in case fatality by age. Both previous systematic reviews characterized CFR to be higher among children under 5-years-old compared to children aged 5-years and older[175,176], but did not explore in finer detail. Given that there is likely to be variation in immune response to measles (e.g., attributable to maternal antibody presence, immune system maturation, previous vaccination) and that most measles cases occur in younger, unvaccinated children[98], there is an unmet critical need to understand and quantify variation in CFR across young children. However, since measles is likely to occur in younger ages in settings with low vaccine coverage, the possible confounding of this relationship with additional development-related factors requires any future investigation to leverage a meta-regression framework.

1.4 Aims and objectives

Given these current gaps and challenges across various areas related to measles burden and susceptibility estimation, the aims of this thesis are to:

A) Improve upon and better understand the data available for modellers interested in estimating measles susceptibility, incidence, or mortality in LMICs, and

B) Develop improved methodology for generating more robust estimates using these data, including by dimensions of age and space.

To address these aims, I have four objectives:

1. To review available data on measles seroprevalence and examine the underlying biases inherent in each conducted serosurvey.

2. To investigate how best to consider subnational case notifications when fitting a dynamic transmission model to estimate subnational susceptibility.

3. To outline a conceptual framework of population-level indicators related to measles CFR.

4. To develop methodology to generate measles CFR estimates that are specific by age, space, and time.

1.5 Thesis structure

This thesis is presented across six chapters. Most chapters forming the body of the PhD work follow 'research-paper style', and some have been published in peer-reviewed academic journals. These chapters follow an introduction and proceed an overall discussion. The chapters are as follows:

- **Chapter 1: Introduction**

- **Chapter 2: Evaluating scope and bias of population-level measles serosurveys: a systematic review and bias assessment**
  This chapter addresses Objective 1. The corresponding manuscript has been uploaded as a pre-print to *medRxiv* and is currently under review at *BMC Infectious Diseases*. In this chapter, I conduct a systematic review of measles seroprevalence data in LMICs and review bias across multiple categories in each serostudy.

- **Chapter 3: Exploring the utility of subnational case notifications in fitting dynamic measles model in Ethiopia**
  This chapter addresses Objective 2 and is in the process of preparation to submit to a peer reviewed journal. In this chapter, I examine subnational case notifications from Ethiopia from 2013 to 2019 and fit a subnational, age-specific transmission model using these data while accounting for differential case ascertainment.

- **Chapter 4: Population-Level Risk Factors Related to Measles Case Fatality: A Conceptual Framework Based on Expert Consultation and Literature Review**

This chapter addresses Objectives 3 and is a research paper that has been published in *Vaccines*. In this chapter, I construct a conceptual framework of mechanisms related to systematic increases or decreases in measles CFR and identify evidence of an association between CFR and population-level related factors related to these underlying mechanisms.

- **Chapter 5: Estimating national-level measles case–fatality ratios in low-income and middle-income countries: an updated systematic review and modelling study**
  This chapter addresses Objective 4 and is published in *Lancet Global Health*. Across this chapter, I identify covariate sets for identified population-level factors in Chapter 4 and fit a meta-regression model to predict CFR by location, year, and age.

- **Chapter 6: Discussion**

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2. Evaluating scope and bias of population-level measles serosurveys: a systematic review and bias assessment

Alyssa N. Sbarra[1,2], Felicity T. Cutts[1], Han Fu[1], Ishu Poudyal[2], Dale Rhoda[3], Jonathan F. Mosser[2,4†], Mark Jit[1†]

[1] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

[2] Institute of Health Metrics and Evaluation, University of Washington, Seattle, WA, USA

[3] Biostat Global Consulting, Worthington, OH, USA

[4] Department of Health Metrics Sciences, University of Washington, Seattle, WA, USA

† Authors contributed equally

Objective: To review available data on measles seroprevalence and examine the underlying biases inherent in each conducted serosurvey.

2.1 Overview

This chapter has been uploaded as a pre-print to *medRxiv* and is under review at *BMC Infectious Diseases*. It outlines a systematic review of measles seroprevalence data in LMICs and describes an assessment to characterize bias across serosurveys included in the review.

Data on measles incidence or cases and vaccination coverage are uncertain. As such, estimates from measles seroprevalence surveys can be useful in estimating measles susceptibility, such as for inputs to dynamic transmission models.

However, underlying factors related to study design (e.g., population representativeness) or serologic assay (e.g., factors affecting test sensitivity) used in these studies can influence accurate interpretation of these results. A previous systematic review identified over 200 studies containing data published through mid-2014 on measles or rubella seroprevalence. This review noted limitations related to variation in underlying methods across studies; however, study authors did not include tabular extracted data per study for future use, include specific information on study design, seroassay, or any other relevant indicators that could impact the interpretation of these results.

To fill these gaps, in this chapter, I designed and conducted a systematic review across primary sources from measles serosurveys that presented measles seroprevalence estimates from LMICs. Following the review, I developed a pilot bias assessment tool that considered bias across three categories: study selection of participants, measurement tool and classification of immunity, and reporting of results. I characterized bias across serostudies in each category and compared both seroprevalence estimates regionally and by time and assessed trends in bias characterizations.

I developed the search string used in the systematic review and performed the review search. I screened titles and abstracts and reviewed full text for all studies, and along with assistance from two colleagues (H.F. extracted 14 studies in Mandarin and I.P. extracted 85 studies based on the template I provided with my supervision and confirmation), extracted indicators of interest from each study. I worked alongside co-authors (F.T.C., D.R., M.J., J.F.M.) to develop our bias assessment tool and I classified bias in each study. I also wrote the first draft of the paper, created all figures, and was responsible for all revisions. The manuscript version in this chapter is the submitted version to the *BMC Infectious Diseases*.

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SECTION E

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Supervisor Signature	██████████
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2.3 Abstract

Background: Measles seroprevalence data has potential to be a useful tool for understanding transmission dynamics and for decision making efforts to strengthen immunization programs. In this study, we conducted a systematic review and bias assessment of all primary data on measles seroprevalence in low- and middle-income countries published from 1962 to 2021.

Methods: On March 9, 2022, we searched PubMed for all available data. We included studies containing primary data on measles seroprevalence and excluded studies if they were clinical trials or brief reports, from only health care workers, suspected measles cases, or only vaccinated persons. We extracted all available information on measles seroprevalence, study design, and seroassay protocol. We conducted a bias assessment based on multiple categories and classified each study as having low, moderate, severe, or critical bias. This review was registered with PROSPERO (CRD42022326075).

Results: We identified 221 relevant studies across all World Health Organization regions, decades and unique age ranges. The overall crude mean seroprevalence across all studies was 78.00% (SD: 19.29%) and median seroprevalence was 84.00% (IQR: 72.75 – 91.66%). We classified 80 (36.2%) studies to have severe or critical overall bias. Studies from country-years with lower measles vaccine coverage or higher measles incidence had higher overall bias.

Conclusions: While many studies have underlying bias, many studies provide data that can be used to inform modelling efforts to examine measles dynamics and programmatic decisions to reduce measles susceptibility.

2.4 Introduction

Measles remains a substantial cause of global morbidity and mortality[1], especially in low- and middle-income settings where over 99% of measles cases and deaths occur[2], despite the availability of a safe and effective vaccine[3]. Because ongoing

measles transmission can be maintained if herd immunity (i.e., when the proportion of the population immune is sufficient to limit disease spread) has not been reached and sustained, estimating the proportion of people susceptible within a community is essential to plan immunization programs and assess future risk of measles outbreaks and deaths. However, due to factors such as timeliness of and age at vaccination[4], disruptions to cold chains[5], a lack of seroconversion in specific subpopulations (e.g., among persons living with human immunodeficiency virus (HIV)[6]), and variable surveillance systems across locations and time, inferring population-level measles immunity from a combination of vaccination coverage and case notifications can be challenging[7]. Alternatively, serosurveys can provide a snapshot of immunity gaps that remain in a community by determining population-level prevalence of IgG antibody levels above specific thresholds that suggest clinical protection against disease.

As such, seroprevalence data can be used as tools to guide decisions to and strengthen immunization programs, as inputs to dynamic models of disease transmission, and additionally to provide insights into vaccine field effectiveness and assessment of case ascertainment rates[7,8]. The interpretation of seroprevalence data is complicated, however, because of the potential for bias. Some of this bias can be due to inadequate sensitivity of laboratory assays[9] and/or specimen types[10] used for measuring antibody levels. Additionally, bias from assay procedures can be suspected when protocols or commercial details are not reported or if no quality control was performed. Furthermore, population-based surveys have the potential for additional bias to be introduced in the selection of participants or from lack of representativeness of the selected sample from the community.

Beyond understanding the selection processes and laboratory assays used, it is critical to also consider how results of the serosurveys are reported. Considerations include what threshold of antibody titer was used as a correlate of clinical protection and how some tests report indeterminate results. In order to responsibly use and accurately interpret seroprevalence data for decision making

or for modelling exercises, these issues need to be transparently acknowledged and discussed.

A more in-depth understanding of available seroprevalence data across locations and time, as well as the related implications, is critical for using these historic data to calibrate models used to inform decision making for immunization program strengthening, especially in low- and middle-income countries (LMICs) that face the highest ongoing measles burden. To fill these gaps, we first conducted a systematic review of literature reporting measles seroprevalence data published through 2021 and extracted information on key study and assay information. Then, we developed a pilot bias assessment tool to assess the risk of bias in each study across the following categories: study selection of participants, measurement tool and classification of immunity, and results reporting.

2.5 Methods

Search strategy and selection criteria

This study follows PRISMA guidelines (Appendix A Tables 1-2) and was registered with PROSPERO (CRD42022326075). We performed a systematic review of published literature in any language containing information on population-level measles seroprevalence in LMICs. We searched PubMed on March 9, 2022 for primary data published through December 31, 2021 using the following search string:

> (((Measles) AND (seroprevalence OR sero-prevalence OR seropositive OR sero-positive OR seronegative OR sero-negative OR seroepidemiology OR sero-epidemiology OR seroprofile OR seroimmunity OR sero-immunity))
> OR ("Measles/epidemiology"[MeSH] AND (antibod* OR serolog*)))
> AND ("1900"[Date - Publication] : "2021"[Date - Publication])

One individual (A.N.S.) screened titles and abstracts for each study in the search results. For relevant studies, one of multiple individuals (A.N.S., H.F., I.P.) reviewed the full-text of each to determine their inclusion or exclusion. We included studies that contained original data on measles antibody prevalence and excluded studies if they only contained data from high-income locations (as based on WorldBank 2021 income classifications[11]), did not contain data on measles IgG antibody, were based on non-original data or from non-human subjects, contained only results from laboratory assay development or clinical trials (including studies only containing information on vaccinated persons), studied a target population of only health-care workers or active measles cases, or were a review, abstract, letter, editorial or brief report.

Following full text review, for each study that met our inclusion and exclusion criteria, we extracted the following data: study setting, study design and type (including information on planned, achieved (i.e., how many persons were reached via sampling), and reported (i.e., how many persons were represented in final study metrics) sample sizes), population demographics (including income and representativeness), type of specimen collected, serologic assay details (including type, name, and inclusion of a reference preparation), antibody threshold used for seropositivity and/or seroprotection (if relevant), and measures of proportion seropositive, seronegative, or indeterminate with accompanying uncertainty. We extracted data into a Microsoft Excel workbook and for seroprevalence measure, we recorded the most granular levels for relevant strata (i.e., by age, subnational geography, vaccination status, infection history, etc.) presented in each study.

Bias assessment
Following extraction of all available data, we developed a comprehensive bias assessment tool and applied the tool to characterize the level of bias across each study. Our tool, modified from the ROBINS-I tool[12], considers bias across the following categories, with associated indicators: study selection of participants,

measurement tool and classification of immunity, and reporting of results (Appendix A Figures 1-3). We classified the level of bias across each category to be either low, moderate, severe, or critical. We then finally assessed the overall level of bias as low, moderate, severe, or critical for each study by taking the mean score of the category-specific classifications.

To assess bias among study selection of participants, we considered whether the study design used a random process for sample selection, if a study relied on a convenience sample, was restricted only to a subset of the population (e.g., only included pregnant women or cancer survivors), and reporting of planned, achieved, specimen, and final sample sizes. To assess the level of bias among the measurement tool and classification of immunity, we considered whether assay protocol, name, or references were provided, if internal or external validation or quality control was performed, and if there were other known factors known to decrease sensitivity or specificity. These factors included using oral fluid as specimens[13], using a hemagglutination inhibition (HI/HAI) assay[13], or using the Whittaker enzyme-linked immunosorbent assay (ELISA)[14]. Last, for bias among reporting of results, we considered whether a known threshold was used for determining protective titer levels, including metrics of uncertainty with seroprevalence estimates, and, if an enzyme immunoassay (EIA) or ELISA was used, whether and how equivocal results were handled and reported.

We characterized the overall level of bias in each study using the following criteria. For each category of bias studies were given a numeric score: low bias was assigned a score of 1, moderate a score of 2, severe a score of 3, and critical a score of 4. We took the sum of scores across all three categories. Studies with a score sum of 3 to 4 were characterized to have low overall bias, 5 to 7 to have moderate overall bias, 8 to 9 to have severe bias, and 10 to 12 to have critical bias.

We converted all metrics reported to proportion seropositive and then used R version 5.4.0 to compute summary metrics and make figures. For studies

reporting seropositive and indeterminate/equivocal results independently, we did not include indeterminate results in the numerator of our overall seroprevalence calculation. We compared data availability by decade and bias level.

We additionally investigated bias levels across time and region and assessed bias levels across locations with higher and lower first-dose measles-containing vaccine (MCV1) coverage (as reported by WUENIC[15]) and higher and lower estimated annual measles incidence (as estimated by a state-space model and described elsewhere[16]) in the year from which study data was collected. To examine the relationship between MCV1 coverage and overall bias as well as annual measles incidence and overall bias, we used separate proportional odds logistic regression models for each coverage and incidence and assessed the coefficient significance.

Role of the funding source
The Bill & Melinda Gates Foundation, Gavi, the Vaccine Alliance and the US National Institutes of Health had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. All authors had access to the data and the corresponding author had final responsibility to decide to submit for publication.

2.6 Results
Systematic review
From our search, we identified 2032 studies for screening (Figure 1). Following screening, we excluded 1116 studies that did not meet our search criteria. For the remaining 916 studies, we assessed the full-text articles for inclusion. We identified 221 studies for inclusion and extracted information on measles seroprevalence, study design, and seroassay (extracted data by age, geography, vaccination or infection status as available) can be downloaded from: https://github.com/alyssasbarra/measles_serology/tree/main). Studies were

published between 1962 to 2021, including seroprevalence surveys conducted between 1953 and 2019.

Figure 1. PRISMA diagram.

Identification of studies via databases and registers

Identification

Records identified from:
PubMed (n = 2032)

Records removed *before screening*:
Duplicate records removed (n = 0)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)

Screening

Records screened
(n = 2032)

Records excluded
(n = 1116)

Reports sought for retrieval
(n = 916)

Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n = 916)

Reports excluded:
High-income country (n = 447)
No measles data or serology data (n = 26)
Research, vaccine efficacy study, trial (n = 92)
Literature review (n = 7)
Non-original data (n = 28)
Outbreak or case-testing (n = 53)
Abstract, editorial, brief report (n = 32)
Only included health-care workers (n = 10)

Included

Studies included in review
(n = 221)

Among 182,789 persons sampled across all studies, age groups, and years, the crude mean measles seroprevalence was 78.00% (SD: 19.29%) and median seroprevalence was 84.00% (IQR: 72.75 – 91.66%). Across regions of the World Health Organization (WHO), there were 43 studies containing data from the African Region, 47 from the Eastern Mediterranean Region, 35 from the European Region, 25 from the Region of the Americas, 20 from the South-East Asia Region, and 73 from the Western Pacific Region (Figure 2). There were 24 studies that represented data collected before 1980, 32 studies from 1980 to 1989,

29 studies from 1990 to 1999, 55 studies from 2000 to 2009, and 83 studies from 2010 to 2019. 178 studies (80.5%) contained age stratified results across 531 unique age ranges.

Figure 2. Number of serosurveys with data included per country.
Map of number of studies per country with available data identified by systematic review.
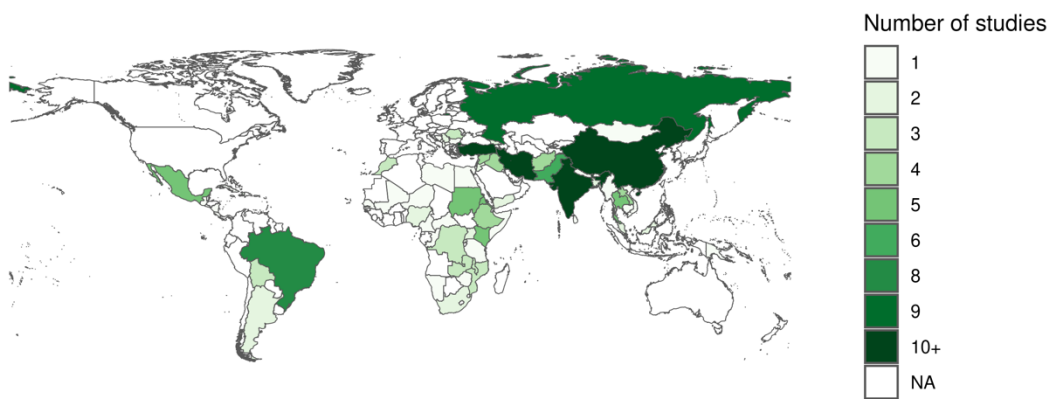
Bias assessment

Table 1 shows results of our bias assessment for each included study. For overall bias, we classified bias as low in 12 (5.4%) studies moderate in 129 (58.3%), severe in 58 (26.2%) and critical in 22 (10.0%). No studies had low or critical bias across all the categories of study selection of participants, measurement tool and classification of immunity, and reporting of results (Table 1).

Table 1. Overall and categorical bias classifications.
Results of bias assessment in each of three categories (study selection of participants, measurement tool and classification of immunity, and reporting of results), and overall level of bias per study.

Level of bias	Study selection of participants	Measurement tool and classification of immunity	Reporting of results	Overall
Low	15	19	20	12
Moderate	181	130	63	129
Severe	23	46	70	58
Critical	2	26	18	22

For study selection of participants, we identified 15 studies with low bias, 181 with moderate bias, 23 with severe bias, and 2 with critical bias. 81 studies used a random sample selection method. 117 studies with convenience samples used a restricted, non-representative sample (i.e., only among a specific subgroup of the population, such as persons living with HIV). 2 studies did not report the final sample size, and of the 81 samples that used a random sample selection method, 45 reported the planned sample size, and 15 additionally reported the planned, achieved, and specimen sample sizes.

In measurement assay and classification of immunity, we identified 19 studies with low bias, 130 with moderate bias, 46 with severe bias, and 26 with critical bias. Across the three categories of bias assessment, measurement assay and classification of immunity had the highest number of studies classified as having critical bias, largely due to absence of information on assay protocol details, commercial kit name or other appropriate citation describing the underlying methods. 195 studies provided details on the assay protocol or commercial kit name, and 25 studies conducted internal or external validation or quality control.

6 studies specified that samples were oral fluid specimens and 30 studies specified that samples collected were dried blood spots.

54 studies used an HI/HAI assay, 139 used an EIA or ELISA, 13 used a plaque reduction neutralization test (PRNT), 6 used a multiplex bead assay, and 11 used other or undescribed assay types. We noted changing temporal trends of types of seroassays used. While EIA, ELISA and PRNT assays were used in even distribution across all studies examined, there was no study published after 2001 that utilized an HI/HAI assay, and all studies using a multiplex immunofluorescent assay were conducted in 2013 or later.

We identified 20 studies with low bias, 63 with moderate bias, 70 with severe bias, and 18 with critical bias in reporting of results. 155 studies reported a threshold to define seroprevalence. Among the 139 studies that used an EIA or ELISA, 30 studies reported equivocal results separately or included with seropositivity results and 1 study excluded equivocal results and they were less than 5% of the overall sample. Finally, 59 studies reported metrics of seropositivity or seronegativity with any accompanying uncertainty.

Seroprevalence trends

The crude median seroprevalence estimates from studies in the Western Pacific Region was 88.3% (IQR: 79.2 – 93.4%), in the Eastern Mediterranean Region was 87.2% (IQR: 81.3 – 93.2%), the European Region was 82.0% (IQR: 77.8 – 89.0%), in the Region of the Americas was 78.4% (IQR: 60.7 – 93.0%), in the African Region was 77.6% (IQR: 60.7 – 89.9%), and in the South-East Asia Region was 66.8% (IQR: 47.4 – 88.4%). Trends in seroprevalence and bias vary by decade (Figure 3). The median seroprevalence was lower in studies from 2010 to 2019 than those conducted before 1980 (i.e., the pre-vaccination era). Crude seroprevalence from studies conducted before 1980 was 90.5% (IQR: 67.8 – 93.3%), from 1980 to 1989 was 78.6% (IQR: 57.8 – 90.7%), from 1990 to 1999 was 88.3% (IQR: 60.7 – 92.6%), from 2000 to 2010 was 80.4% (IQR: 65.6 –

88.2%), and from 2010 to 2019 was 84.6% (IQR: 78.3 – 92.9%). Among 31 country-years with studies containing critical bias, 23 (74%) occurred in earlier time periods (i.e., before 1980 and between 1980 and 1989). In the 159 country-years with studies containing low or moderate bias, 96 (60%) have occurred between 2010 and 2019.

Figure 3. Measles seroprevalence by time period and overall bias level. Beeswarm plot of measles seroprevalence by time period. Each point represents one country-year of data per study and are coloured by overall bias level. Black lines represent the median observation across each decade.
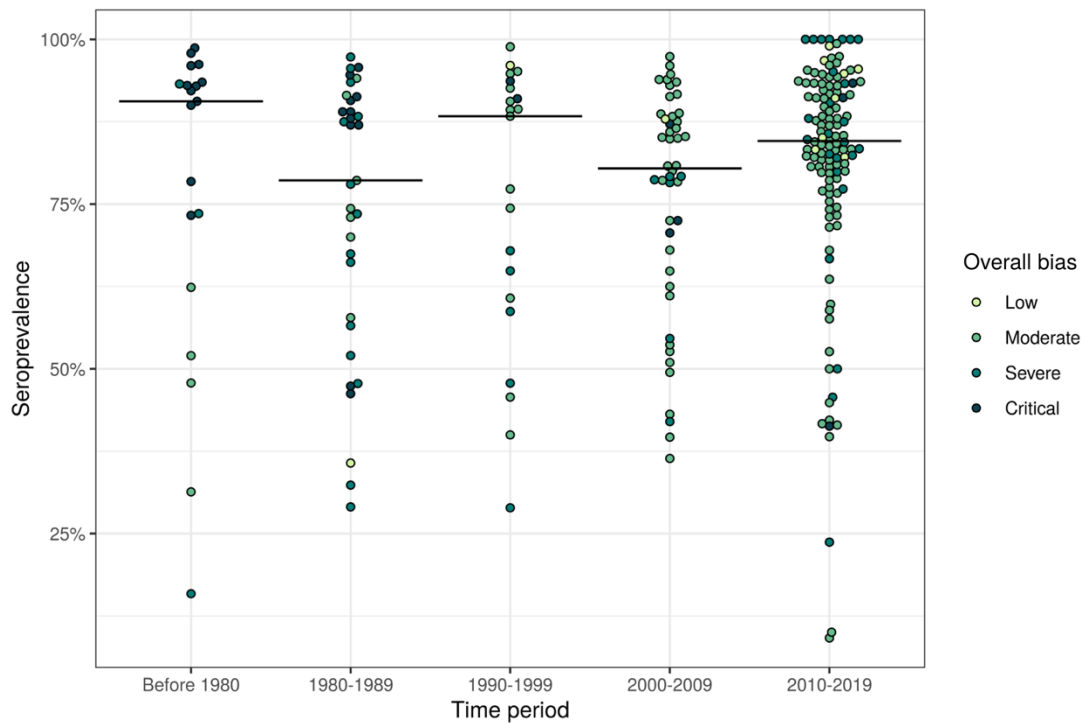
We additionally compared the overall bias levels for each country-year of the studies to the MCV1 coverage and measles incidence from the same country-year (Figure 4). Generally, studies in countries and years in 1980 or later with lower MCV1 coverage and higher measles incidence had more bias compared to studies from countries and years with higher MCV1 coverage and lower measles

incidence (p < 0.001, in proportional odds logistic regression models for both MCV1 coverage and incidence). Among 109 studies from countries and years with MCV1 coverage greater than 80%, 93 (85%) had low or moderate overall bias, and from the 58 studies from countries and years with MCV1 coverage of 80% or lower, 34 (58%) had low or moderate overall bias. A similar trend persisted across studies in countries and years with high incidence – 103 of 122 (84%) studies in countries and years with average annual reported measles incidence less than 5 per 1000 persons had low or moderate overall bias, and 24 of 49 (49%) of studies in countries with annual measles incidence of 5 per 1000 persons or greater had low or moderate overall bias.

Figure 4. Overall bias level by MCV1 coverage and annual measles incidence. Each point represents each country-year represented across all studies, overall bias level by MCV1 coverage (top) and annual estimated measles incidence (bottom).
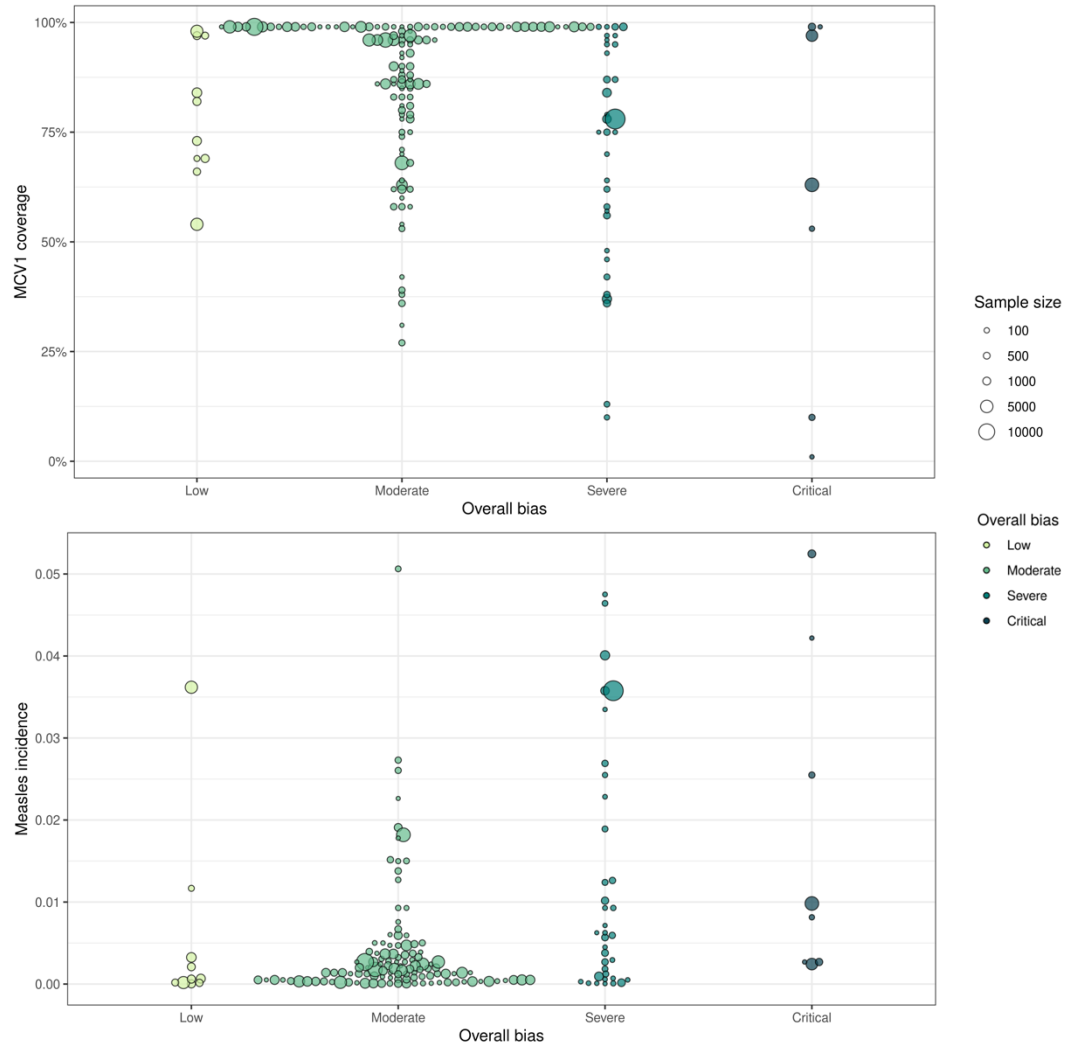
2.7 Discussion

To identify the scope of measles seroprevalence data, we conducted an updated systematic review of serosurveys to identify primary data sources and characterized underlying bias across these studies. The resulting data repository from our investigation along with information on factors related to underlying bias per study could contribute to analyses of measles dynamics among low- and middle-income countries. We identified serosurveys available in each decade, WHO region, and across a wide variety of ages, which could be useful when modelling location-, time-, and age-specific estimates of measles transmission and susceptibility. Despite this variation, there were locations for which very few or no serosurveys have been conducted – mainly in the African Region – which contribute to knowledge and data gaps to inform high-quality modelling and analyses.

Additionally, our study provides insight to issues to consider when designing and reporting a seroprevalence study to ensure that the highest quality surveys are conducted and that complete, accurate and transparent reports are generated. The number of available measles seroprevalence studies has increased in the last few decades compared to periods before the introduction of national measles vaccination programmes in LMICS. This trend provides the opportunity for researchers to examine the impact of vaccination programs on ongoing susceptibility within the population represented in each study. However, we found that locations with high annual measles incidence and lower MCV1 coverage tend to have not only less studies conducted, but also higher bias – this is understandable given that coverage tends to be lower in the most difficult settings such as remote and/or conflict-affected regions, where surveys are especially challenging to conduct. Research and programmatic teams planning seroprevalence studies, especially among persons living in these vulnerable communities, could use the framework presented in this study as a starting point to determining the feasibility and cost of conducting a high-quality seroprevalence

survey and consider alternative ways to invest the funds (e.g., in strengthening ongoing surveillance of coverage and disease incidence).

More recently, there have been examples of high-quality serosurveys, such as a nationally representative survey in Zambia[17], that have been conducted and used for informative modelling. Given the complexity, time, and expense of these surveys, it is worthwhile to make the most of high-quality surveys that are being conducted for different infections and funded through a variety of different programs. This serosurvey in Zambia, for example, leveraged residual sera from the Zambia Population-Based HIV Impact Assessment (ZAMPHIA) study[18] originally collected to estimate HIV incidence and viral load. Applications of such data extend to innovative modelling efforts to estimate subnational and age-specific seroprevalence estimates as well as national level outbreak risk[17]. That study serves as an example of the potential to leverage other major population surveys and to use high quality seroprevalence estimates to inform evidence for decision making.

More studies had low or moderate bias compared to severe or critical bias among the categories of selection of study participants and measurement tool and classification of immunity. For the category of reporting of results, more studies had severe or critical bias levels than low or moderate bias levels. Overall, we found that less than 10% of studies had low overall bias, suggesting that the quality of conduct and reporting of seroprevalence studies has substantial potential for improvement.

While interpreting seroprevalence estimates identified by our review, it is essential to also consider the associated sensitivity and specificity of the seroassays used in studies along with the route of induced immunity (i.e., from vaccination or natural infection). For example, HI/HAI assays are often less sensitive than other types[13]. If HI/HAI assays are used in a population with mainly vaccine-induced immunity, seroprevalence results may be underestimated.

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However, since HI/HAI assays were historically used more frequently, during an era with less vaccine-derived immunity and subsequently higher natural immunity affording higher antibody levels, assay sensitivity might not be as important to consider. In our bias assessment in the category of measurement tool and classification of immunity, we defined factors that influence assay specificity and sensitivity as either (1) using an HI/HAI assay, (2) using the Whittaker commercial ELISA kit, or (3) using oral fluid samples. However, the utility of this specific contribution to our bias assessment might be subject to the specific study setting, vaccination program implementation and success, and underlying measles epidemiology.

In this study, we developed a framework to categorise risk for bias (i.e., a systematic deviation) among seroprevalence estimates. Characterising bias is important because it can impact estimate interpretability. However, this study does not attempt to directly quantify or characterize uncertainty (i.e., the degree to which a result is known) in seroprevalence estimates. While sources of uncertainty can be challenging to characterise overall, similar factors that contributed to our assessment of bias could also impact the underlying uncertainty of seroprevalence estimates identified in this study. These include uncertainty resulting from the test results themselves (e.g., measurement uncertainty from the assays) as well as uncertainty resulting from the sampling process or survey design. While studies that are highly biased might also have high uncertainty, there are other factors not considered in this review that might change this relationship. For example, a well-designed study with a small sample size may have low risk of bias yet high uncertainty. In data extraction and when assessing the bias in the reporting of results category, we did note whether studies reported metrics of uncertainty along with seroprevalence measures. We did not, however, consider the width of these ranges in assessing bias levels.

Our study has several limitations. First, we were unable to fully synthesize results of our systematic review in a meta-analysis or other stratified analysis by age,

location, or year. This was due to the differing study populations, regions, time periods, and age groups presented in studies identified in this review as well as the varying degrees of bias characterized to be present across studies. These results can serve as the basis for future models that synthesize the data while also accounting for underlying measles infection dynamics, vaccination coverage and population structures for each individual study setting, which was out of the scope of our analysis.

Secondly, we were constrained by the information reported in each publication. Without adequate reporting, we assumed the highest level of associated bias whenever appropriate. For example, if a study did not specifically note if they used an international reference preparation, we assumed they did not use one. This may have led us to classify studies as having higher bias in relevant categories than might have been the case if all available information had been included in the publication – it possible that some details were omitted to meet restrictions on word counts, for example. As such, there might be great utility in the widespread use of standardized reporting expectations for ongoing and future seroprevalence studies.

Next, we did not consider sample size in our assessment of bias. Since the impact of sample size on the reliability of point estimates from seroprevalence studies should be reflected in the provided uncertainty interval, we considered the inclusion of such in our bias assessment. We did not however further assess the implications of smaller or wide interval spans if they were presented or whether point estimates or uncertainty intervals were adjusted or standardized for population demographics or other factors. Finally, there are likely additional sources of bias that are more difficult to ascertain objectively, such as potential issues with specimen storage and laboratory capacity, practices, and quality.

Our study strengthens the understanding of the availability and bias among measles seroprevalence studies in low- and middle-income countries by

identifying primary sources of measles seroprevalence studies and conducting a bias assessment of the associated data. Our framework for assessing bias could provide a foundation for further work by relevant agencies and interested partners to develop a tool for use in planning and reporting future surveys. This work can be a vital tool to be used during modelling exercises, planning immunization-based interventions, and ultimately, to make informed decisions to reduce preventable measles morbidity and mortality.

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3. Exploring the utility of subnational case notifications in fitting dynamic measles models in Ethiopia

Alyssa N. Sbarra[1,2], Mark Jit[1†], Jonathan F. Mosser[2,3†]

[1] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

[2] Institute of Health Metrics and Evaluation, University of Washington, Seattle, WA, USA

[3] Department of Health Metrics Sciences, University of Washington, Seattle, WA, USA

† Authors contributed equally

Objective: To investigate how best to consider subnational case notifications when fitting a dynamic transmission model to estimate subnational susceptibility.

3.1 Overview

This chapter describes an investigation of subnational case notification data from Ethiopia and outlines an exploration of model parameterizations and fitting algorithms to use these case notifications. It is written as a research paper that will be submitted to a peer review journal for publication.

As previously discussed in Chapter 1, identifying measles susceptibility is critical for programmatic planning of interventions, such as vaccination campaigns. Previous investigations to estimate subnational measles susceptibility[1-9] note

substantial limitations, including substantial simplifying assumptions about vaccination coverage or effectiveness and complete case ascertainment, which likely biases estimates of both incidence and susceptibility. Also, many of these studies do not attempt to quantify absolute susceptibility but rather estimate some relative metric or pattern of risk. No previously published effort has attempted to use subnational case notifications and vaccine coverage data to quantify measles susceptibility via a dynamic transmission model that accounts for case ascertainment along with considerations of vaccine effectiveness.

Subnational, age-specific case notifications collected in Ethiopia, a low-income country located in east Africa, provide a unique opportunity to explore the utility of these types of data in fitting dynamic transmission models. Subnational heterogeneity in measles vaccination coverage has been identified in Ethiopia[10-12], which suggests a high probability of susceptibility heterogeneity that is critical to quantify. Ethiopia has received numerous investments from Gavi, the Vaccine Alliance across multiple disease areas and additionally for broader health system strengthening. Following one of these investments in 2012 with specific intent to train healthcare workers and implement electronic medical recording systems[13] and roughly coinciding with newly formed African regional measles elimination goals[14], Ethiopia's measles surveillance program updated their integrated disease surveillance and response (IDSR) programme[15] to try to capture more measles cases through notifiable reporting systems and encourage more case-based follow-up. While still a passive surveillance system, the robustness of the program was increased and yielded new reports of cases by second-administrative units (i.e., zones) starting in 2013. These data, which I obtained from the World Health Organization Headquarters, have yet to be used within the published literature to estimate subnational measles susceptibility in Ethiopia.

To fill methodologic gaps related to fitting models of subnational susceptibility and leverage the opportunity to explore these Ethiopian data, in this chapter, I conducted analyses to understand features of and potential biases within these

case notification data from 2013 to 2019. I then developed a subnational, measles dynamic transmission model that accounts for heterogeneous mixing and mobility along with routine and supplemental measles vaccine coverage. I investigated various model parameterizations and fitting algorithms, along with different structures to capture incomplete case ascertainment, to determine the utility of these case data in informing estimates of measles susceptibility. My explorations showed that only highly tailored fitting algorithms and model specifications were able to adequately fit the case notification data due to its biased and variable nature.

I conducted all analyses of measles case notification data. I worked alongside co-authors (M.J., J.F.M.) to develop the transmission model. I wrote and implemented all computer code and ran all model experiments and analyses. I planned, organized, and held multiple sessions with collaborators from Ethiopia with expertise on measles to consult with them on the data and our findings. Following ongoing discussions with collaborators, I expect contributors listed in the Acknowledgements section of this chapter to be added as co-authors on this manuscript, if they are willing, prior to submission to a peer reviewed journal. I also created all figures, wrote the first draft of this paper, and was responsible for all subsequent revisions. This manuscript will be submitted to a peer reviewed journal following final discussions with collaborators.

3.2 Research Paper Coversheet

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First Name(s)	Alyssa		
Surname/Family Name	Sbarra		
Thesis Title	Addressing Gaps and Challenges in Measles Burden Estimation		
Primary Supervisor	Prof. Mark Jit		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	N/A		
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was responsible for developing the model, conducting all analyses and generating all code. I planned and organized sessions with collaborators from Ethiopia to review this work and gather their feedback. I wrote the manuscript and was responsible for all revisions.

SECTION E

Student Signature	
Date	6 October 2023

Supervisor Signature	
Date	6 October 2023

3.3 Abstract

Assessing the underlying gaps of measles susceptibility within a population is essential for vaccination programs and infectious disease control efforts. Recently, there have been increased efforts to use geospatial and small area methods to estimate subnational measles vaccination coverage in high burden settings, such as in Ethiopia. However, the distribution of remaining susceptible persons, either unvaccinated or having never previously been infected, across age groups and subnational geographies is unknown. In this study, we explored subnational, age-specific case notification data from Ethiopia and developed a dynamic transmission model that incorporates spatial estimates of routine measles vaccination coverage, available data on supplemental immunization activities, and reported cases to estimate measles incidence and susceptibility across time, age, and space to consider how best to use these subnational case notifications during model fitting. We developed a time-varying compartmental model to estimate age-specific measles incidence and susceptibility. We use gridded population estimates and subnational estimates of measles routine and supplemental vaccination coverage. To account for mixing between age-groups, we used a synthetic contact matrix. Travel times via a friction surface were used in a modified gravity model to account for spatial movement. The following parameters were estimated: transmission probabilities and first-administrative level reporting rates, and age-group specific reporting rates. Following extensive investigations of model parameterization and possible fitting algorithms, this model was fit to case notifications adjusted for case ascertainment in using maximum likelihood estimation with block coordinate descent. This strategy was chosen because the many data observations (and likely presence of unquantified uncertainty) yielded a steep likelihood surface, which was challenging to fit using Bayesian approaches. We ran sensitivity analyses to best determine vaccine effectiveness and compared patterns of susceptibility across space, time, and age. Overall, substantial heterogeneity in reported measles cases as well as susceptibility persists across ages and second-administrative units. We found that estimates generated from methods that account for variable case data reporting

and quality could contribute towards tailored subnational and local planning to reduce preventable measles burden. However, computational and data challenges would prohibit these methods to be applied on a large scale.

3.4 Introduction

Recently, there have been increased efforts to map geographic variation in vaccination coverage across low- and middle-income countries, including Ethiopia[10-12]. In 2019, Ethiopia reached 56% coverage[16] for the first-dose of any measles-containing vaccine (MCV1) nationally, albeit with substantial subnational coverage heterogeneity[10]. From 2000 to 2019, Ethiopia experienced increased national MCV1 coverage but also increases in geographic inequality, suggesting emerging specific geographies with increased relative vulnerability to ongoing measles transmission. Ethiopia introduced a second dose of MCV (MCV2) into the national immunization schedule in 2019[17]. Within the first year of introduction, routine MCV2 coverage reached 41% nationally[16]. In 2017, Ethiopia executed two subnationally targeted measles campaigns, or supplemental immunization activities (SIAs), in March and August which combined delivered over 23,750,000 vaccine doses[17].

Broadly, there is interest in conducting more targeted SIAs by either age or geography in various low- and middle-income countries (LMICs), including Ethiopia. These targeted interventions would be most useful in settings with moderate vaccine coverage, as targeting approaches by age or geography might not be as relevant in settings with low coverage. Alternatively, high coverage settings with pockets of persistent transmission among communities without explicit geographic division (e.g., among networks in the United States), might need different strategies to increase coverage beyond the use of campaigns. A similar motivation in moderate coverage settings could also exist for implementing routine immunization strengthening efforts by location.

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To inform targeted intervention approaches, it would be ideal to have an understanding of who is susceptible within a population. Subnational routine MCV coverage estimates, along with information on vaccine doses delivered via SIAs, afford the opportunity to begin to understand local subnational patterns of measles susceptibility. However, making policy decisions based on vaccination coverage estimates alone would provide an incomplete picture in places where there are large amounts of natural immunity. This could yield inefficient delivery strategies if persons who were already immune due to previous infection were targeted. Additionally, serosurveys could also provide useful insight, but are costly, have biases[18], and are limited to data availability.

Nevertheless, locations with vulnerable persons with neither vaccine nor natural immunity need to be identified in short- and medium-term efforts to plan targeted interventions and prevent avoidable measles infections. Instead of relying on the coverage estimates alone, mathematical models incorporating transmission dynamics can potentially be used to incorporate not only information on vaccine coverage, but also demography, contact patterns, person mobility, and case notifications, to estimate the dynamics of measles within a community and quantify measles susceptibility.

Likely due to low coverage and geographic heterogeneities, in 2019, Ethiopia reported almost 4,000 measles cases nationally[19]. However, case notifications in Ethiopia, like many LMICs, are captured via passive surveillance, and as such likely have substantial under-reporting. Given these limitations of case notifications, it is unclear to what extent this information can readily be used in models. To use case notifications to calibrate a model, it would be critical to account for case ascertainment to estimate historical measles dynamics and overall susceptibility. Reporting rates are likely to vary by location or across other factors that influence the underlying reporting mechanism or available resources.

Previous investigations have explored subnational measles susceptibility[1-9], however all have made broad assumptions that limit the interpretation of their findings. Of these previous investigations, few[2,3,5,9] attempted to quantify measles susceptibility instead of just estimating risk or relative patterns that could be used for prioritization exercises. Many of the remaining investigations[1,4,6,7] made simplifying assumptions about vaccination, such as only considering MCV1 coverage, neglecting to account for doses administered through campaigns, or assuming perfect vaccine efficacy. For investigations that leveraged the use of case notifications, all but one study[6] assumed complete case reporting, which likely greatly biases estimates of incidence and susceptibility. To quantify measles susceptibility, no published model has utilized subnational case notifications and subnational MCV1 and MCV2 vaccination coverage from both routine and supplemental immunization, while also systematically considering case ascertainment rates and vaccine effectiveness.

To address these methodologic gaps, research exploring new applications to traditional modelling approaches that incorporate information from case notifications is needed. In this work, we investigated subnational case notifications from Ethiopia, explored methodologic considerations that would be necessary when using these data in transmission models to understand measles dynamics and estimate susceptibility by age, location, and time, and examined limits of data quality and implied underreporting rates.

3.5 Methods

Case notifications

We obtained subnational case notifications from across Ethiopia from 2013 (the first year that they were available) to 2019 in 5-year age bins (e.g., 0-4-year-olds, 5-9-year-olds, etc.). We identified the most appropriate corresponding zone (i.e., second-administrative division level; represented by z or d in equations to follow) based on GADM administrative boundaries[20]. We compared the distribution of reported incidence by region (i.e., first-administrative division level; represented

by *R* in equations to follow) and age bin. We additionally aggregated subnational, age-specific case notifications nationally and across all ages to compute a suggested national reported incidence and compared to the actual national, age-aggregated reported incidence. We also compared MCV1 coverage across zones by year to the reported number of cases across all ages by year in each zone and computed their corresponding correlation. To examine stochasticity in reporting, we assessed the number of zones reporting 0, less than 10, and less than 100 cases across available years and additionally computed the number of times zones reported cases with a single week gap.

We used vaccine coverage estimates for the first- and second-dose of any measles containing vaccine (MCV1 and MCV2) from either a routine or supplementary immunization program. These estimates rely on spatial estimates of MCV1 and MCV2 coverage, as well as a computed metric of campaign efficiency used to allocate doses of administered during campaigns to either previously vaccinated or unvaccinated children. These coverage estimates are age-, epiweek-, and zone-specific and are generated using a cohorting model to track coverage across ages groups over time and space. These estimates are based of previously published work[10] and additional details can be found in Appendix B Section 1.

Dynamic model structure

We then used these subnational case notifications to fit a dynamic, zone-level, transmission model across weeks from 1980 to 2019 in 24 age groups, with smaller intervals for ages with high measles incidence (12 for monthly bins for 0-11-month-olds, 4 for yearly bins for 1-4-year-olds, 1 bin for 5-9-year-olds, 1 bin for 10-14-year-olds, and 5 10-year-bins for 15-64-year-olds, and 1 bin for 65-year-olds and older). Flowcharts of our modelling structure can be found in Appendix B Figures 1-2. We used demographic information from WorldPop gridded population surfaces[21] calibrated to population sizes from the Global Burden of Disease study[22] as age-specific population and live birth counts by zone. We linearly interpolated annual population sizes to epiweeks and assumed a

constant weekly birth rate for each year. For each country, we used a synthetic contact matrix[23] that has been standardized for zone population size in each epiweek.

To estimate transmission between zones, we used a gridded friction surface of travel time by motorized vehicle[24] to compute the travel time in minutes between every combination of population-weighted centroids from all zones. We used these values to construct a modified gravity matrix (G) for each pair of zones (z and d), such that:

$$G_{z,d} = \frac{P_z P_d}{D_{z,d}}$$

, where P_z and P_d are population sizes and $D_{z,d}$ is the distance in minutes computed from the friction surface. We used our modified gravity matrix G to compute a mobility matrix (M), such that:

$$M_{z,d} = \frac{G_{z,d}}{G_D} * (1 - \theta), \text{ when } z \neq d$$

$$M_{z,d} = \theta, \text{ when } z = d$$

, where G_D are the sums of the columns of G and θ is the probability of persons staying in their home zone in a given epiweek. We assume θ to be 0.99.

We used a time-varying compartmental model to track the proportion of persons in each age group and zone that were maternally immune, susceptible, infected, and recovered across epiweeks from 1980 to 2019. For each compartment, we maintained information on the proportion of persons who were unvaccinated, vaccinated with 1 dose of MCV, and those who were vaccinated with 2 or more doses of MCV. We defined a constant starting state based on assumptions of population-level immunity in a pre-vaccine era[25,26], such that 25% of infants

under 6-months-old, 60% of 6-to-8-months, and 98% of all other persons were recovered, as well as 40% of infants aged under 6-months and 10% of infants aged 6-to-8-months were maternally immune. All other persons were considered susceptible at our starting state. We tested the sensitivity of these assumptions and they yielded little to no difference in final results, likely as the model had ample time to equilibrate since it was run for 33 years (i.e., 1749 epiweeks) before fitting to the first available data in 2013.

For each time step or epiweek (i), we computed the transmission probability (β_i) such that:

$$\beta_i = A * sin\left(2\pi * \frac{i}{53} + 2\right) + D$$

$$D = \frac{\beta_{max} + \beta_{min}}{2}$$

$$A = \frac{\beta_{max} - \beta_{min}}{2}$$

$$\beta_{max} > \beta_{min}$$

, where β_{max} is the maximum transmission probability bounded between 0.1 and 1, β_{min} is the minimum transmission probability bounded between 0 and 1, a is the amplitude, and D is the vertical displacement. The seasonal displacement was calculated from reported case notifications and was determined to be approximately 2 (i.e., at the 13 week of each year). We then computed the force of infection (FOI) for each time step (i), zone (d), and age group (a) using the following equation:

$$FOI_{a,d,i} = \beta_i * \sum_{c=1}^{C} \sum_{z=1}^{Z} (W_{a,c,i,d} * M_{z,d} * I_{i-1,c,z}^{\alpha})$$

, where $W_{a,c,i,d}$ is the contact rate from our synthetic contact matrix between age groups a and c standardized to the population size in time i and zone d, $M_{z,d}$ is the proportion of persons from zone z travelling to zone d in a given time step, and $I_{i-1,c,z}$ is the proportion of persons in age group c from zone z who were infected in the previous time step. α is a parameter, assumed to be 0.99, to account for mixing parameters of the contact process or the discretization of a continuous process[27,28].

In each time step, we use the FOI to estimate the newly infected persons in each age group and zone. We assume the serial interval to be 2 epiweeks and that maternal immunity wanes exponentially starting at 4-months-old[29]. Finally, based off already discussed MCV1 and MCV2 coverage values from routine and supplemental immunization, we re-calibrate to weekly population-level vaccination prevalence.

We started testing model fitting algorithms by estimating the following parameters: maximum and minimum transmission parameters over a season (β_{max} and β_{min}) and a reporting rate (ρ). We assumed the following distribution of cases:

$$C_{a,d,i} \sim NegativeBinomial\left(I_{a,d,i} * \rho, 5\right)$$

, where $C_{a,d,i}$ is the reported number of cases in zone d, age group a and time step i, $I_{a,d,i}$ is the down-adjusted number of estimated cases in zone d, age group a and time step i, and ρ is a reporting rate. We used R version 5.4.0[30] for this analysis and package Rcpp[31] to build our transmission model.

Model fitting: sporadic case reporting

As evidenced at the regional level, data artefacts (e.g., many zones only reported cases every other week) in time series of case notifications by individual zones suggest very sporadic cases that are likely not epidemiologically plausible. However, it was difficult to tell from the data whether the zones that reported alternating weeks with zero cases represent the total sum of cases across two weeks or whether these are missing other values that were not reported. Based off discussions with collaborators in Ethiopia, we hypothesized it was most likely that cases were being aggregated across weeks prior to reporting such that the alternating weeks were the sum of cases from every two weeks.

We explored a range of ways of handling cases before their inclusion in model fitting. We first explored aggregating cases by month or annual quarter. However, this approach led to poor model fits as the model, which is run at the epiweek level, would sometimes have marginally different peak transmission which would happen to miss the aggregation window in the specific month or quarter (Appendix B Figure 3). Despite likely small differences in specific weekly timing between major transmission events, in these instances, likelihood calculations suggested poor model fits. Instead, we chose to smooth cases by zone and age group using a loess function with a span of 0.2. We tested loess functions with multiple spans for sensitivity, but ultimately chose 0.2 to maintain underlying variation across the time series and avoid over-smoothing. This process yielded a smooth time series of cases in each zone and age group, which allowed for the model to interpret an average of cases across a time period which is more likely to temporally represent true measles case reporting.

Model fitting considerations: vaccine effectiveness
We initially assumed that vaccine efficacy was 93% for each dose given (for either first- or second-dose) and independent of the number of doses previously received. However, this assumption yielded little to no transmission in more recent years (Appendix B Figure 4) even with complete reporting due to high recorded vaccine coverage, which are both implausible as they do not match

recent case reports. Therefore, we added a parameter in our model to represent vaccine effectiveness, which ultimately increased the proportions of susceptible persons in our dynamic system to foster transmission events occurring in later years. This vaccine effectiveness term was capped at 93% to account for known vaccine efficacy[32].

Model fitting considerations: variation in reporting rates

Based on previous studies of subnational measles susceptibility in the literature that noted possible geographic differences in reporting along with observed trends in the subnational case data from Ethiopia, we suspected that there were likely differential rates of case ascertainment by geography. To further explore structures for reporting rates, we tested the implications of applying different reporting rates during model fitting. We assumed that cases followed a negative binomial distribution and fit cases to incidence adjusted for reporting rates ($\rho_{a,d,i}$) from our modelling output. We first tested a single reporting rate ρ across all age groups, regions, and years, such that:

$$logit(\rho_{a,d,i}) = logit(\rho)$$

To explore variations in reporting, we tested a model with region-specific reporting rates, ρ_R, for each region R, such that:

$$logit(\rho_{a,d,i}) = logit(\rho_R)$$

Model fitting considerations: steep likelihood surface

We were fitting a high-dimensional model with over 260,000 likelihood contributions from data observations that overall have unmeasured biases and uncertainty. Despite these data limitations, having so many observations yields a very steep likelihood surface (regardless of underlying statistical distribution assumed), and as such Bayesian methods using any kind of sampler had a very challenging time accepting proposed samples. For illustration, if the input data

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were perfectly replicated in our model results, our model would yield a log-likelihood value of -57603 (i.e., the highest possible log-likelihood given the sheer volume of likelihood contributions). Adding just 0.1 case to each observation – a trivial difference, in practical terms – would yield a log-likelihood of -75607, or a log-space difference of -18004, which is far too great to be accepted by MCMC samplers. This example demonstrates the steepness of the likelihood surface, which limits the ability of most conventional MCMC approaches to explore the surface appropriately and provide a reasonable quantification of uncertainty.

These challenging statistical considerations stemming from including many data observations suggested a steep likelihood surface despite likely being subject to varied and unmeasurable surveillance biases, which also led to computational limitations related to the complexity of our underlying model. We tested various algorithms for model fitting including the following: Markov chain Monte Carlo (MCMC), MCMC with parallel tempering, adaptive MCMC, rejection sampling, rejection sampling of Sobol hypercube samples, and a deterministic optimization algorithm.

In subsequent models using MCMC, samplers have very limited ability to explore the full parameter surface and often accept very few samples. In attempt to combat these issues, we explored alternative forms of MCMC including implementing MCMC with parallel tempering[33] (Appendix B Figure 5) and adaptive MCMC samplers[34]. Ultimately, neither alternative approach substantially accepted more samples and both approaches failed to overcome the fundamental steepness of this surface. Additionally, because we were fitting a high-dimensional model with a relatively slow likelihood calculation (approximately 20 seconds), allowing the model to run over many hundreds of thousands of iterations in hopes of eventual convergence would be computationally expensive and unfeasible.

We then explored generating proposed samples without using a Bayesian framework, by externally generating parameter samples through the use of a Sobol hypercube to select a quasi-random set of parameter values to use in a rejection sampler. However, the root of the problem (i.e., steep likelihood surface) remained, with very few samples being accepted (i.e., various runs yielded between 1 and 6 samples of 10000 selected).

As such, we addressed this issue using a deterministic optimization of a derivative-free maximum likelihood estimator (via the dftoptim package[35]) via block coordinate descent, as described below. Models were able to successfully run and converge while using a fraction of the computational resources. Since deterministic MLE optimization algorithms do not inherently yield metrics of uncertainty as we would have obtained from Bayesian methods, we ran 100 bootstrapped samples, holding out 75% and using 25% of zone-weeks.

Model fitting considerations: collinear parameters

Transmission parameters, vaccine effectiveness, and reporting rates all interact relative to one another when estimating the underlying dynamics of measles within a community. For example, when transmission parameters are low, reporting rates are likely to be higher. Additionally, another layer of vaccine effectiveness can also influence this relationship. Lower vaccine effectiveness typically corresponds to lower transmission parameters as well as lower reporting rates, as there are more susceptible persons within a population.

Given the collinearities among our parameters being estimated (i.e., transmission parameters, vaccine effectiveness, and reporting rate) we needed to make additional modifications to our model fitting algorithm. The first was to remove vaccine effectiveness as a parameter that was directly estimated in our modelling framework. Instead, we decided to run sensitivity analyses using different vaccine effectiveness parameters and to select the model with the best fit as determined by statistical criteria (i.e., Akaike Information Criterion [AIC] score).

This left us with transmission parameters and reporting rate to fit, which are still collinear (i.e., low transmission rates suggest a high reporting rate, and high transmission rates suggest a low reporting rate). When fitting models that estimated both transmission rates and reporting rates, we additionally noted sensitivities to starting state of using a single deterministic MLE algorithm (Appendix B Tables 1a and 1b). As an alternative to fitting a single model to estimate both sets of parameters, we instead used block coordinate descent. In this approach, we first fit a reporting rate using an MLE given an initial starting state of transmission parameters in an accepted range of R_0 values for measles (i.e., $9 - 19$)[36-38]. Then we fit another MLE to estimate the transmission parameters using the fitted values for a reporting rate estimated from our first step. We repeat this two-step process in total ten times and then take final fitted values as our parameter estimates for each bootstrapped sample.

Final model fitting algorithm

We ultimately used maximum likelihood estimation via block coordinate descent to first fit our reporting rate parameters (i.e., either ρ, or ρ_R by region depending on the reporting structure for the model) while holding β_{max} and β_{min} constant, and then subsequently to fit β_{max} and β_{min} while holding our reporting rate parameter value(s) constant. This sequence (i.e., fit reporting rate parameter(s), then transmission parameters) was repeated iteratively 10 times, as typically by iteration 6 to 7 the algorithm yielded negligible changes (i.e., less than 0.001) in parameter values. We selected initial values for β_{max} and β_{min} of 0.25 and 0.12 respectively based off a plausible range of corresponding R_0 values (i.e., $9 - 19$).

We fit 100 bootstrapped samples of parameter values and likelihoods. Zone-weeks were selected for inclusion randomly such that 25% of zone-weeks were included per bootstrapped sample (among all age groups). Across various reporting structures and among a sensitivity analysis of vaccine effectiveness values, we selected the model with the lowest AIC score based on the median

likelihood value across bootstraps. We tested four values of overall vaccine effectiveness (47%, 70%, 82%, and 88%) to account for both estimated 93% vaccine efficacy from prior studies, as well as faults in cold chain or other reasons biologically associated with lack of seroconversion (e.g., malnutrition). We used our posterior bootstrapped samples to make predictions of measles incidence and susceptibility across age, location, and time. We calculated R_0 values using a next generation matrix approach (Appendix B Figure 6) such that for each zone d across age groups a and c, we computed the following:

$$\psi_{a,c} = \beta * W_{a,c,2,d}$$

$$\tau_d = \max(eigen(\psi))$$

, such that β is a transmission probability and τ_d is the zone-specific R_0 value. We took the mean τ_d across all zones to calculate the expected R_0 from each possible β value. All data processing, model, and diagnostic code can be found here: https://github.com/alyssasbarra/ethiopia_case_fitting.

3.6 Results

Case notifications

Cases were reported across zones and regions in Ethiopia from 2013 to 2019 with varying seasonal patterns and annual magnitudes (Figure 1a). 21 of 79 zones reported fewer than 100 cases across the entire seven-year period, nine of which reported fewer than ten cases, and six of which reported no cases. Per zone, on average a one-week gap in reported cases occurred 46 times (sd = 27.2). One zone reported cases with a one-week gap 105 times. There were no zones that reported at least one case every week. The sum of available cases reported subnationally were aggregated to annual, national, all-age values of reported cases to compare to cases reported via the Joint Reporting Form. Temporal patterns of cases were not consistent between both sources (Figure 1b), with the aggregated subnational cases having relatively little temporal variation nor matching the large outbreak reported within national case notifications in 2015.

Figure 1a. Reported suspected measles case notifications nationally and by region (i.e., first-administrative unit) in Ethiopia from 2013 to 2019.

Figure 1b. Reported suspected measles case notifications nationally (blue) from 2000 to 2019 via Joint Reporting Form and aggregated subnational case notifications to national scale (red) from 2013 to 2019.
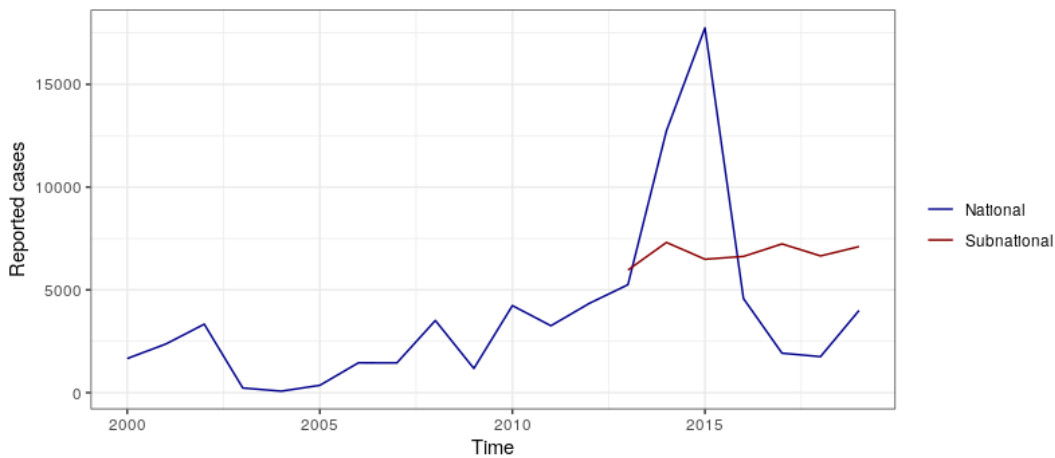
The age distribution of reported cases across most years stayed consistent over years and yielded approximately half the number of cases reported among 5-to-9-year-olds than among 0-to-4-year-olds (Figure 2).
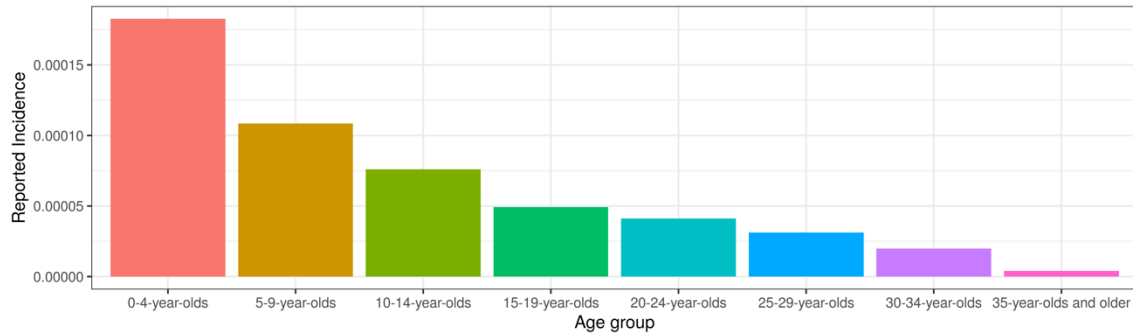
The number of reported cases among 10-to-14-year-olds were approximately two-thirds of those reported among 5-to-9-year-olds. The age pattern of reported cases is that typically seen from countries or locations approaching measles elimination[39], not endemic transmission with relatively moderate vaccine coverage (as expected in Ethiopia). Additionally, we aggregated cases across zones by year and compared to MCV1 coverage from RI or SIA among 0-to-4-year-olds (Figure 3). Reported case notifications by zone-year are not correlated with coverage among 0-to-4-year-olds in the same zone year (Pearson's product-moment correlation, t = -1.705, p = 0.089). This suggests variable case reporting as cases and coverage would otherwise likely be negatively correlated.

Model fitting

We fit bootstrapped samples using block coordinate descent across two different reporting structures (i.e., a single reporting rate and region-specific reporting rates). For each reporting structure, we tested in a sensitivity analysis four different vaccine effectiveness values (i.e., 47%, 70%, 82%, and 88%). We selected the model with the best AIC score. For all models, see Appendix B Tables 2 and 3 for fitted parameter values and log-likelihood values. Additionally, Appendix B Figure 6 contains information on corresponding R0 values per β value.

The model with the lowest AIC score was with both region-specific reporting and a vaccine effectiveness of approximately 47%. A comparison of susceptibility results across 0-to-4-year olds from models with 47% and 70% vaccine effectiveness values can be found in Appendix B Figure 8. The relative geographic patterns appear similar across model versions, however, the overall susceptibility estimates from the model with lower vaccine effectiveness are higher (as might be expected). In this model, the maximum and minimum transmission parameters were 0.135 (95% uncertainty interval (UI): 0.134 – 0.137) and 0.102 (95% UI: 0.102 – 0.102) respectively, which corresponds to a range of R_0 values from 7.5 to 9.8 (Appendix B Figure 6). Block coordinate descent iterations for all parameter values are in Appendix B Figure 7. Reporting ranged from 0.26% (95% UI: 0.24 – 0.27%) in Tigray to 2.93% (95% UI: 2.53 – 3.35%) in Gambela Peoples' Region. Incidence and case predictions across weeks and zones by age groups (0-to-4-year-olds, 5-to-9-year-olds, and 10-to-14-year-olds) are available in Appendix B Figures 9 – 14.

Figure 3. Reported suspected measles incidence across regions in Ethiopia against first-dose measles-containing vaccine (MCV1) coverage among 0-to-4-year-olds in 2019.
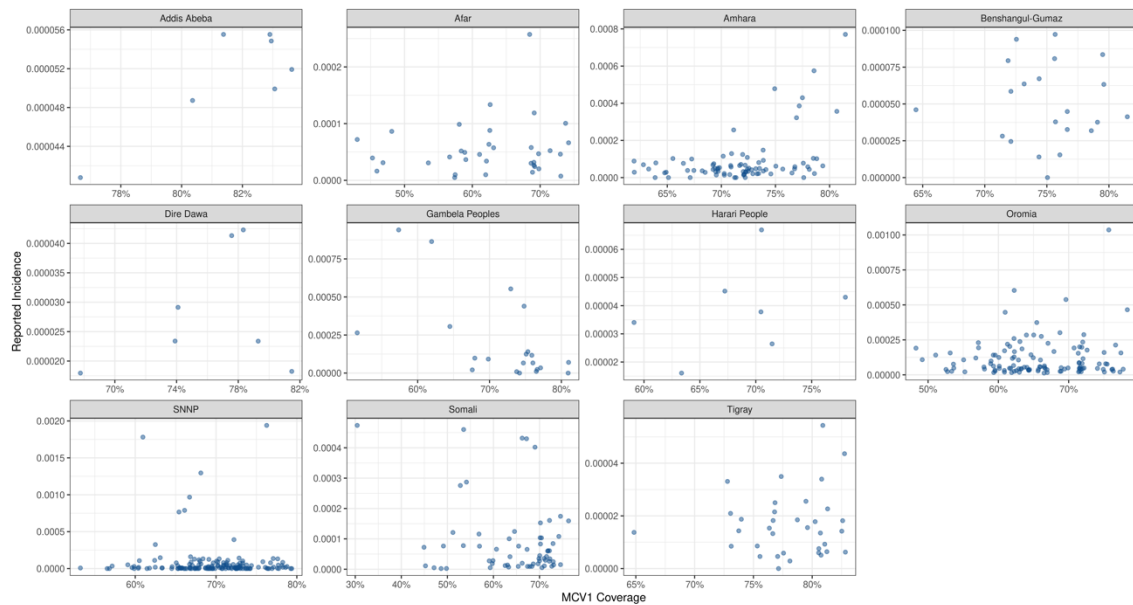
Subnational susceptibility patterns

We compared subnational patterns of susceptibility (i.e., among persons without immunity from vaccination, natural infection, or maternal immunity) in 2019 suggested from the median of our modelled, bootstrapped results from both models with a single and regional reporting rates. Among 0-to-4-year-olds, susceptibility results from models with regional reporting rates were correlated with coverage estimates (Figure 4, among 0-to-4-year-olds via Pearson's product-moment correlation $p < 0.001$). When using a model with a single reporting rate compared to a regional reporting rate, there were negligible differences in susceptibility patterns across 0-to-4-year-olds, as approximately the same transmission parameters were estimated. The three zones with the highest proportion of susceptibility based on median predictions among 0-to-4-year-olds are Doolo (35.3%), Jarar (38.4%), and Fafan (38.8%).

Figure 4. Proportion susceptible in 2019 in Ethiopia among 0-to-4-year-olds, top panel unvaccinated (i.e., 1 – MCV1 coverage from routine or supplemental immunization) and bottom panel from modelled outputs (i.e., not maternally immune, immunity from vaccination, or immunity from previous infection).
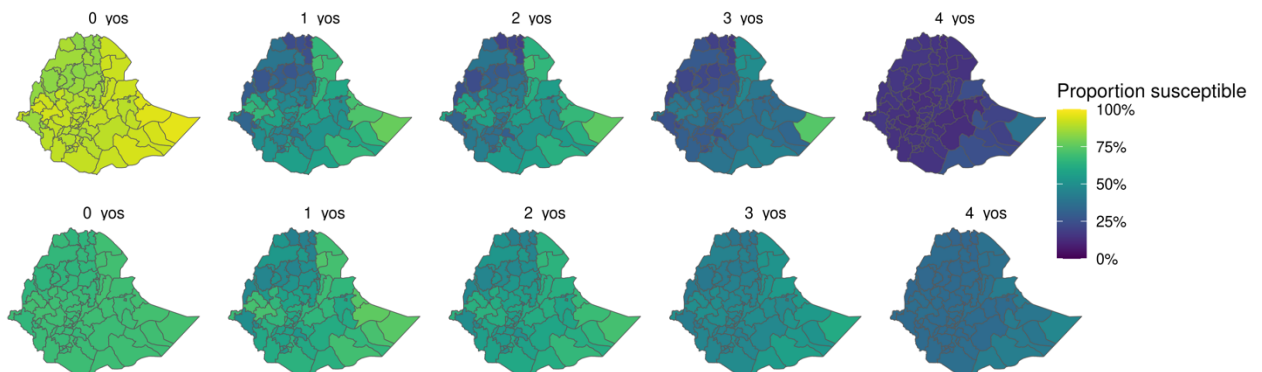
3.7 Discussion

Considering subnational measles dynamics and heterogeneity are critical for identifying areas for planning targeted interventions, as local pockets of

susceptibility are responsible for driving ongoing measles transmission. However, there is currently no "gold-standard" data set available to fit models that reflect these heterogeneities. Seroprevalence data are sparse and present biases related to test sensitivity, vaccine coverage data do not present the full picture of susceptibility and also require assumptions about doses administered through SIAs, and, finally, case notifications are often under-reported. We explored subnational case notifications from Ethiopia and considerations necessary to make these case notifications useful when fitting subnational transmission models. During this process, we faced challenges related to data quality and statistical and computational complexity that we need to solve in order to use these data for this purpose.

Overall, our experience suggests there are several modelling considerations that are critical when fitting models to estimate subnational susceptibility. First, underlying trends in reported case data are likely biased in multiple ways (e.g., sporadic reporting, incomplete ascertainment). Without accounting for these biases, estimates of susceptibility are likely to be themselves biased. Additionally, with many data contributions, high-dimensional models are challenging to fit using traditional Bayesian methods. It should be ensured that models either converge using Bayesian methods with many iterations or other means are used. Finally, assuming vaccine efficacy equal to vaccine effectiveness is likely to skew epidemiologic conclusions and results that do not account for underlying mechanisms to lower efficacy should be interpreted with caution.

We faced substantial challenges fitting our model via statistical algorithms. Traditional Bayesian methods (i.e., MCMC and other samplers) were unable to handle capturing uncertainty from many data observations that suggested a very steep likelihood surface. If our dataset were smaller, we ran our model for fewer years, locations or age groups, or explored substantial adaptations to our sampling algorithm[40], we may have been able to use Bayesian methods for model fitting. However, these modifications were out of the scope of the motivation for this

project and we moved forward with a deterministic optimization approach via block coordinate descent. Not only did this approach yield models with consistent convergence, our computational demand substantially decreased as we no longer needed to generate many hundreds of thousands of posterior samples for fitting.

Understanding the mechanism for case reporting is critical for understanding how best these case data could be incorporated into fitting dynamic transmission models. Epidemiologists in Ethiopia reported that these mechanisms are very varied, but suffer from location-, and time-dependent biases, which reduces their information content. Therefore, we had to make various assumptions. For example, due to frequent one-week gaps in case reporting as well as well as otherwise sporadic reporting, we assumed that cases were inconsistently reported temporally so chose to smooth cases before including them in model fits.

We estimated case ascertainment rates of less than 3% across many regions. Robust surveillance systems are the backbone to understanding measles dynamics and as countries approach elimination are even more essential to understanding remaining gaps in vaccination programs. In Ethiopia, future investigations should continue to explore case ascertainment rates for notifiable diseases, like measles, and interventions that promote enhanced surveillance.

Our sensitivity analysis on vaccine effectiveness suggested lower values than expected (i.e., 47%) yielded better model fits (via AIC score), as well as R_0 values that were lower than often-cited ranges for measles[37,38] but suggested as plausible by other sources[36]. While these lower vaccine effectiveness metrics could reflect true low effectiveness stemming from disrupted cold chains or lack of seroconversion due to individual biological factors, such as malnutrition or compromised immune function due to human immunodeficiency virus (HIV) infection, this metric could also be reflecting other uncertainties in our model. One alternative option is that coverage estimates from both routine immunization or SIAs might not be as high as originally estimated or that there are limitations in

the current available data, which are aggregated to zones, to capture true coverage heterogeneity. If this is occurring, the lower vaccine effectiveness measure might be adjusting coverage to reflect these potential inaccuracies.

In addition to vaccine effectiveness, the concurrent estimation of under-reporting and force of infection is similarly challenging. For example, policymakers could exhibit caution regarding a potential measles outbreak. Consequently, they may choose to plan a large-scale SIA, which would could significantly increase coverage, and simultaneously could intensify surveillance efforts. These developments, if implemented together, could subsequently complicate the correlation between coverage and reported cases. Additionally, there may be either geographic or social clustering of measles vaccine coverage within zones so that there are large pockets of highly connected unvaccinated persons. Any one or multiple of these could be occurring in these dynamics, and without a way to stay with confidence which is occurring, this vaccine effectiveness metric, in combination with other parameter values, should be interpreted with caution.

Ultimately, models, such as the one we developed, that estimate subnational susceptibility could be used to plan targeted interventions. These could include subnational vaccination campaigns across zones or regions that target age ranges with estimated susceptibility gaps. Extensions of this work could be used to determine the optimal timing of immunization-based interventions to reduce predicted disease burden through the use of short-term forecasts[6] or the cost-benefit of conducting national versus subnationally targeted immunization system strengthen efforts or campaigns[41].

There are several limitations to our analysis. First, we did not have access to stratified cases beyond five-year age bins nor were we able to distinguish between cases that reported zero cases as true zeros or a lack of reporting. We only considered suspected measles cases and did not consider lab-confirmed measles cases or adjust for test positivity rates. More exploration should be done in this

area to see if there is any additional information that can be learned about reporting rates and possibly increased usability of case notifications. We did not have stratified contact patterns among age groups smaller than 5-year bins, which limits our understanding particularly among contact patterns in 0-to-4-year-olds. This age group is likely to have substantial heterogeneity across the age group (i.e., infants versus 4-year-olds) as well as the age group in which we would expect the most measles transmission to occur. We did not have access to mobility data so assumed the proportion of persons staying home (θ), although this parameter ideally would be generated from inference. There are two serosurveys available in Ethiopia[18], however we did not use these in our model fitting as their relative contribution to the overall magnitude of our likelihood was likely to be negligible.

We were unable to effectively estimate vaccine effectiveness outside a sensitivity analysis as the collinearity of all three sets of parameters (i.e., also maximum and minimum transmission parameters, and reporting parameters) was challenging for model fitting; additional analyses could further explore a more precise range for the vaccine effectiveness measure. The uncertainty in our estimates was obtained from our bootstrapped samples, which only reflect uncertainty from the data alone. Finally, our exploration of cases was of those reported through the end of 2019, which does not consider changing epidemiology, reporting patterns, or demographic, contact or mobility changes associated with the COVID-19 pandemic[42], ongoing conflict and insecurity[43], and famine[44] in Ethiopia. Additional future work is needed to further explore plausible methods to elucidate subnational measles susceptibility given these evolving transmission dynamics and available data landscape.

Understanding subnational susceptibility is essential for targeted intervention planning and will be critical for countries working towards measles elimination goals. Using case notifications is challenging but necessary to guide this understanding to ultimately prevent avoidable measles morbidity and mortality.

3.8 Acknowledgements

3.9 References

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4. Population-Level Risk Factors Related to Measles Case Fatality: A Conceptual Framework Based on Expert Consultation and Literature Review

Alyssa N. Sbarra[1,2], Mark Jit[1], Jonathan F. Mosser[2,3], Matthew Ferrari[4], Felicity Cutts[1], Mark Papania[5], Katrina Kretsinger[5], Kevin A. McCarthy[6], Niket Thakkar[6], Katy A. M. Gaythorpe[7], Deepa Gamage[8], L. Kendall Krause[9], Emily Dansereau[9], Natasha Crowcroft[10], Allison Portnoy[11,12]

[1] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

[2] Institute of Health Metrics and Evaluation, University of Washington, Seattle, WA, USA

[3] Department of Health Metrics Sciences, University of Washington, Seattle, WA, USA

[4] Department of Biology, Pennsylvania State University, State College, PA, USA

[5] Global Immunization Division, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, GA, USA

[6] Institute for Disease Modeling, Global Health Division, Bill & Melinda Gates Foundation, Seattle, WA, USA

[7] MRC Centre for Global Infectious Disease Analysis, Jameel Institute, School of Public Health, Imperial College London, London, UK

[8] Epidemiology Unit, Ministry of Health, Colombo, Sri Lanka

[9] Global Development Division, Bill & Melinda Gates Foundation, Seattle, WA, USA

[10] Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland

[11] Department of Global Health, Boston University School of Public Health, Boston, MA, USA

[12] Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, MA, USA

Objective: To outline a conceptual framework of population-level indicators related to measles CFR.

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4.1 Overview

This chapter has been published as a manuscript in *Vaccines* in August 2023. It describes activities by a working group of experts and a subsequent literature review to outline available evidence of underlying mechanisms contributing to systematic increases or decreases in measles case fatality and related population-level indicators.

Understanding population-level factors related to measles case fatality is critical for population health interventions and to also estimate measles mortality. Since measles deaths are often not accurately captured in routine surveillance systems among LMICs, mortality estimates are often generated via combining estimates of measles incidence and case fatality ratios (CFRs). CFR most recently has been estimated via a predictive model and has been shown to vary across settings, time, and subpopulations. Models to estimate case fatality, though, need to use population-level covariates (i.e., not estimates of an individual-level fatality risk given a set of underlying risk factors) during fitting and prediction stages that ultimately reflect underlying mechanisms that contribute towards increases or decreases in measles case fatality. However, to date, there have been no established causal or conceptual framework of population-level factors related to measles case fatality that could be used as modelling covariates, or a comprehensive literature review of related factors, which limited previous modelling choices to subjective covariate selections.

In this chapter, I fill this gap by orchestrating, chairing, and holding meetings for a working group of experts (who are co-authors on this work) from various institutions with background in global measles epidemiology. Along with the working group, I developed a comprehensive conceptual framework of factors related to measles CFR and generated a list of all population-level indicators that were related to these underlying mechanisms. I designed and conducted a literature review to assess the evidence of a relationship between each of these indicators and CFR. Then, I characterized each indicator by the level of available evidence found within the literature (i.e., published literature supports a causal relationship, published literature supports an observational relationship, published literature supports a qualitative relationship, and no evidence was found).

I contributed to the overall study design of this project. I organized, coordinated, and chaired the expert group formed as part of this work. I developed the search strategy used for the literature review and performed the search. I screened titles and abstracts, reviewed the full text of articles, and recorded findings along with a colleague (A.P.). I also wrote the first draft of the manuscript, generated all tables and figures, and was responsible for making any revisions. The manuscript version in this chapter is the published version appearing in *Vaccines*.

4.2 Research Paper Coversheet

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
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SECTION E

Student Signature	
Date	31 August 2023

Supervisor Signature	
Date	2 Sept 2023

4.3 Abstract

A better understanding of population-level factors related to measles case fatality is needed to estimate measles mortality burden and impact of interventions such as vaccination. This study aimed to develop a conceptual framework of mechanisms associated with measles case fatality ratios (CFRs) and assess the scope of evidence available for related indicators. Using expert consultation, we developed a conceptual framework of mechanisms associated with measles CFR and identified population-level indicators potentially associated with each mechanism. We conducted a literature review by searching PubMed on 31 October 2021 to determine the scope of evidence for the expert-identified indicators. Studies were included if they contained evidence of an association between an indicator and CFR and were excluded if they were from non-human studies or reported non-original data. Included studies were assessed for study quality. Expert consultation identified five mechanisms in a conceptual framework of factors related to measles CFR. We identified 3772 studies for review and found 49 studies showing at least one significant association with CFR for 15 indicators (average household size, educational attainment, first- and second-dose coverage of measles-containing vaccine, human immunodeficiency virus prevalence, level of health care available, stunting prevalence, surrounding conflict, travel time to major city or settlement, travel time to nearest health care facility, under-five mortality rate, underweight prevalence, vitamin A deficiency prevalence, vitamin A treatment, and general malnutrition) and only non-significant associations for five indicators (antibiotic use for measles-related pneumonia, malaria prevalence, percent living in urban settings, pneumococcal conjugate vaccination coverage, vitamin A supplementation). Our study used expert consultation and a literature review to provide additional insights and a summary of the available evidence of these underlying mechanisms and indicators that could inform future measles CFR estimations.

4.4 Introduction

While measles mortality has decreased over the last several decades, an estimated 60,700 people died from measles in 2020[1]. However, in many settings, mortality is difficult to estimate through traditional measles case surveillance approaches alone due to challenges in cause-of-death attribution, weaknesses in vital registration systems, and variability in data completeness and quality in reporting cases and deaths[2]. Instead, global stakeholders use models of measles mortality that require robust and dynamic estimates of measles case fatality ratios (CFR, i.e., proportion of cases with fatal outcome)[3] to track progress towards eliminating measles deaths[4] and to evaluate the impact of vaccination programs[5]. Recently, an updated modelling approach has provided estimates of measles CFR by region, age group, and income level for the years 1990 through 2030[6]. This foundation for producing dynamic CFR estimates is a critical advancement in estimating context- and intervention-specific measles mortality[7].

There is evidence that various plausible risk factors contribute to systematically higher individual-level measles case fatality, such as nutritional or vaccination status, overcrowding at home, and overall health system access or quality[8-10]. However, current surveillance systems do not systematically capture data on all possible risk factors for mortality. In places where accurate vital registration systems are not available, an improved estimation of measles mortality burden, including the previously mentioned modelling approach, requires an understanding of case fatality risk factors. One approach is to evaluate evidence on potential CFR risk factors for which population-level data are consistently available, so that the most relevant population-level risk factors can be applied to estimates of population-level CFR.

A clear framework of possible mechanisms related to CFR provides a means to organize the compiled evidence on risk factors associated with measles case fatality. Improved CFR estimates could help to assess health gains achieved through vaccination and other interventions such as nutrition supplementation,

identify remaining gaps, understand likely drivers behind increased CFR, and support targeted efforts to reduce the disease burden in particularly vulnerable communities. Therefore, we used expert consultation to develop a conceptual framework of mechanisms related to measles CFR and identify population-level indicators related to these underlying mechanisms. We used expert consultation because the underlying mechanisms related to measles case fatality are multifactorial, complex, and challenging to establish casual pathways of to describe systematic changes in CFR. Then, we conducted a literature review to assess the evidence of association between these indicators and case fatality.

4.5 Methods

4.5.1 Expert Consultation

We consulted with a group of experts who are co-authors on this paper (Appendix C Section 1) to determine associative pathways that lead to either systematic increases or decreases in measles CFR. These pathways, referred to as "mechanisms" represent possible ways in which specific risk factors could be associated with measles CFR. We developed a conceptual framework relating each mechanism to measles case fatality.

To adequately represent these underlying mechanisms via population-level factors, we identified a list of 58 indicators typically available at the population level (Appendix C Section 2) that could be related to measles case fatality and together would be representative of these mechanisms. Following discussion, the group determined 42 of these possible indicators (Appendix C Section 3) to be most plausibly related to measles case fatality. From those, the group determined a list of indicators for further investigation with at least one vote for their inclusion (Appendix C Section 4); through this process, exclusive breastfeeding and sanitation quality indicators were removed. Age, measles incidence/attack rate, and outbreak settings have complex interactions with each other and other indicators as well, and as such, they were determined to be fundamental in any consideration of measles mortality without requiring further investigation in the

literature[6,10]. This yielded 37 indicators for additional investigation. Each indicator was then assigned to represent an underlying mechanism following discussion of the expert group.

4.5.2 Literature Review

To assess the level of evidence of association between measles case fatality and the final list of identified indicators, we conducted a review of the available literature (Appendix C Section 5). We searched the PubMed database from 1 January 1980 to 31 October 2021 for any article with the following search terms:

(indicator-specific search terms)
AND "measles"
AND ("case fatality" OR "CFR" OR "fatality" OR "mortality" OR "morbid*" OR "comorbid*" OR
"sever*" OR "complicat*" OR "risk" OR "secondary outcome" OR "death")

A full list of indicator-specific search terms can be found in Appendix C Section 6. A single investigator screened the Title and Abstract for each study for inclusion and exclusion criteria; for passing studies, a single investigator reviewed the full text for the same criteria. Articles were included if they contained information on an association between our outcome (i.e., measles case fatality or acute mortality) and the indicator of interest among any age or setting among our population of interest (i.e., persons with an acute measles infection). Articles were excluded if they were from non-human studies or reporting on non-original data.

Following the search, each indicator was assigned to one of the following categories: indicator has at least one published randomized controlled trial supporting a significant relationship with CFR, indicator has at least one published quantitative observational study supporting a significant association with CFR, indicator has at least one published qualitative study supporting an association with CFR, indicator has published evidence of a non-significant

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relationship between indicator and CFR, and indicator had no published evidence investigating the relationship with CFR, depending on the highest category of evidence found.

For each study presenting any evidence of an association between an indicator and CFR, we assessed the overall quality of evidence presented in each study using the GRADE working group framework as a model[11]. Each study received a quality score from 1 to 5, with 5 representing studies of the highest quality. Each of the following attributes contributed to a one-point deduction in quality score: having a sample size less than 100, not being a randomized clinical trial or adjusting measures of association for confounding, not indicating a laboratory confirmation of measles cases, and not providing a definition of death being attributable to acute measles.

4.6 Results

4.6.1 Conceptual Framework

Five underlying mechanisms were identified by the expert group: health system access and care-seeking behaviours, health system quality, measles control and epidemiology, nutritional status, and risk of secondary infection. Each mechanism was hypothesized by the expert group to have a direct association to either systematic increases or decreases in measles CFR, as well as interdependently with one another (Figure 1). For example, the risk of secondary infection would be directly associated with measles CFR, but would also be associated with nutritional status, which would also be directly associated with measles CFR. Each indicator outlined above was assigned a primary mechanism (Table 1) to ensure each mechanism was adequately represented by the grouping of indicators assigned to it (e.g., human immunodeficiency virus (HIV) prevalence was assigned to the "risk of secondary infection" mechanism).

Figure 1. Conceptual framework of mechanisms related to measles case fatality rates.

Each mechanism is represented by a coloured circle. Dark grey arrows show direct relationship with measles CFR and light grey arrows show relationships between the mechanisms.
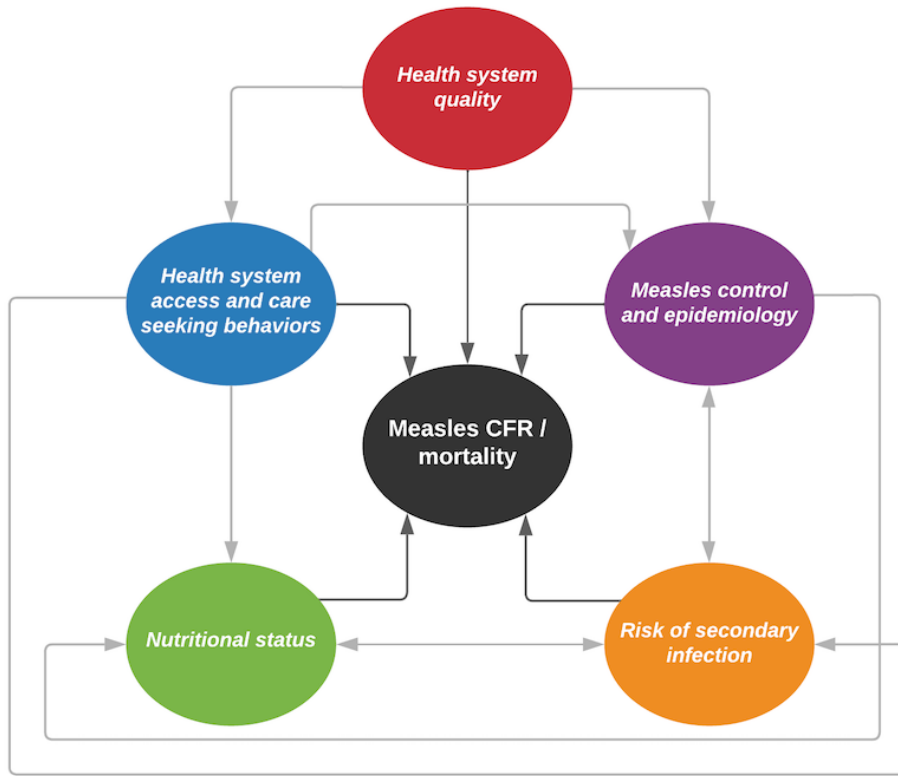
Table 1. Mechanisms impacting measles CFR with related hypothesized indicators.

Mechanisms	Indicators
Health system access and care-seeking behaviours	- Educational attainment - Percent living in urban settings - Surrounding conflict - Time to care seeking - Travel time to major city or settlement - Travel time to nearest health care facility

Health system quality	• Access to intensive care unit • Health expenditure per capita • Level of health care available • Under-five mortality rate
Measles control and epidemiology	• First-dose coverage of measles-containing vaccine (MCV1) • Maternal antibody dynamics • Maternal measles vaccination coverage • Second-dose coverage of measles-containing vaccine (MCV2) • Vaccine coverage equity • Vaccination efficacy • Vaccination schedule • Vitamin A treatment
Nutritional status	• Stunting prevalence • Underweight prevalence • Vitamin A deficiency prevalence • Vitamin A supplementation • Wasting prevalence
Risk of secondary infection	• Ambient air pollution • Antibiotic use for measles-related pneumonia • Average household size • De-worming frequency • Diarrheal disease prevalence • Human immunodeficiency virus (HIV) prevalence • Human immunodeficiency virus (HIV) treatment / antiretroviral therapy (ART) prevalence • Malaria prevalence • Lower respiratory infection prevalence • Oral rehydration solution for measles-related diarrhoea • Pneumococcal conjugate vaccination coverage • Population density

	• Pre-term birth prevalence			
	• Total fertility rate			

4.6.2 Literature Review

The search yielded 3772 articles; the full text was reviewed for 857 of these articles meeting inclusion and exclusion criteria (Figure 2). Each indicator was classified depending on availability of evidence (Table 2). There was 1 indicator with at least one published randomized controlled trial supporting a significant relationship with CFR, 13 indicators with at least one published quantitative observational study supporting a significant association with CFR, 1 indicator with at least one published qualitative study supporting an association with CFR, 5 indicators with published evidence of a non-significant relationship between indicator and CFR, and 17 indicators with no published evidence investigating a relationship with CFR. For the 49 studies in which there was evidence of an association for an indicator with measles case fatality, the findings are outlined below.

Table 2. Available evidence of relationship between indicators and measles CFR.

Published literature includes randomized controlled trial with significant relationship	Published literature supports significant observational association	Published literature supports qualitative association	Published literature with non-significant evidence	No evidence found in published literature
• Vitamin A treatment	• Average household size • Educational attainment • First-dose coverage of	• Level of health care available	• Antibiotic use for measles-related pneumonia • Malaria prevalence	• Access to intensive care unit • Ambient air pollution

	measles-containing vaccine (MCV1) • Human immunodeficiency virus (HIV) prevalence • Second-dose coverage of measles-containing vaccine (MCV2) • Stunting prevalence • Surrounding conflict • Travel time to major city or settlement • Travel time to nearest health care facility • Under-five mortality rate • Underweight prevalence		• Percent living in urban settings • Pneumococcal conjugate vaccination coverage • Vitamin A supplementation	• De-worming frequency • Diarrheal disease prevalence • Health expenditure per capita • Human immunodeficiency virus (HIV) treatment / antiretroviral therapy (ART) prevalence • Lower respiratory infection prevalence • Maternal antibody dynamics • Maternal measles vaccination coverage • Oral rehydratio

	- Vitamin A deficiency prevalence - General malnutrition (surrogate for wasting prevalence)			n solution for measles-related diarrheal - Population density - Pre-term birth prevalence * - Time to care seeking - Total fertility rate - Vaccine coverage equity - Vaccination efficacy - Vaccination schedule

Among these 49 studies, the following 26 countries were represented: Afghanistan, Bangladesh, Chad, Costa Rica, Democratic Republic of the Congo, Ethiopia, France, Ghana, Guinea-Bissau, India, Indonesia, Kenya, Malawi, Mexico, Mongolia, Nepal, Niger, Nigeria, Pakistan, Papua New Guinea, Senegal, South Africa, Sweden, Tanzania, Turkey, and Zambia. There were 9 studies published in the period 1980–1989, 14 in the period 1990–1999, 14 in the period 2000–2009, 7 in the period 2010–2019, and 5 in the period 2020–2021. All studies with significant and non-significant evidence of an association between an

indicator and measles CFR, along with their quality scores, are presented in
Appendix C Sections 7–9.

Figure 2. PRISMA diagram of literature review sources.
For the completed literature review, number of studies at each stage of the review
is shown. Studies included in review were those to have contained significant
evidence of an association with an indicator and measles CFR.
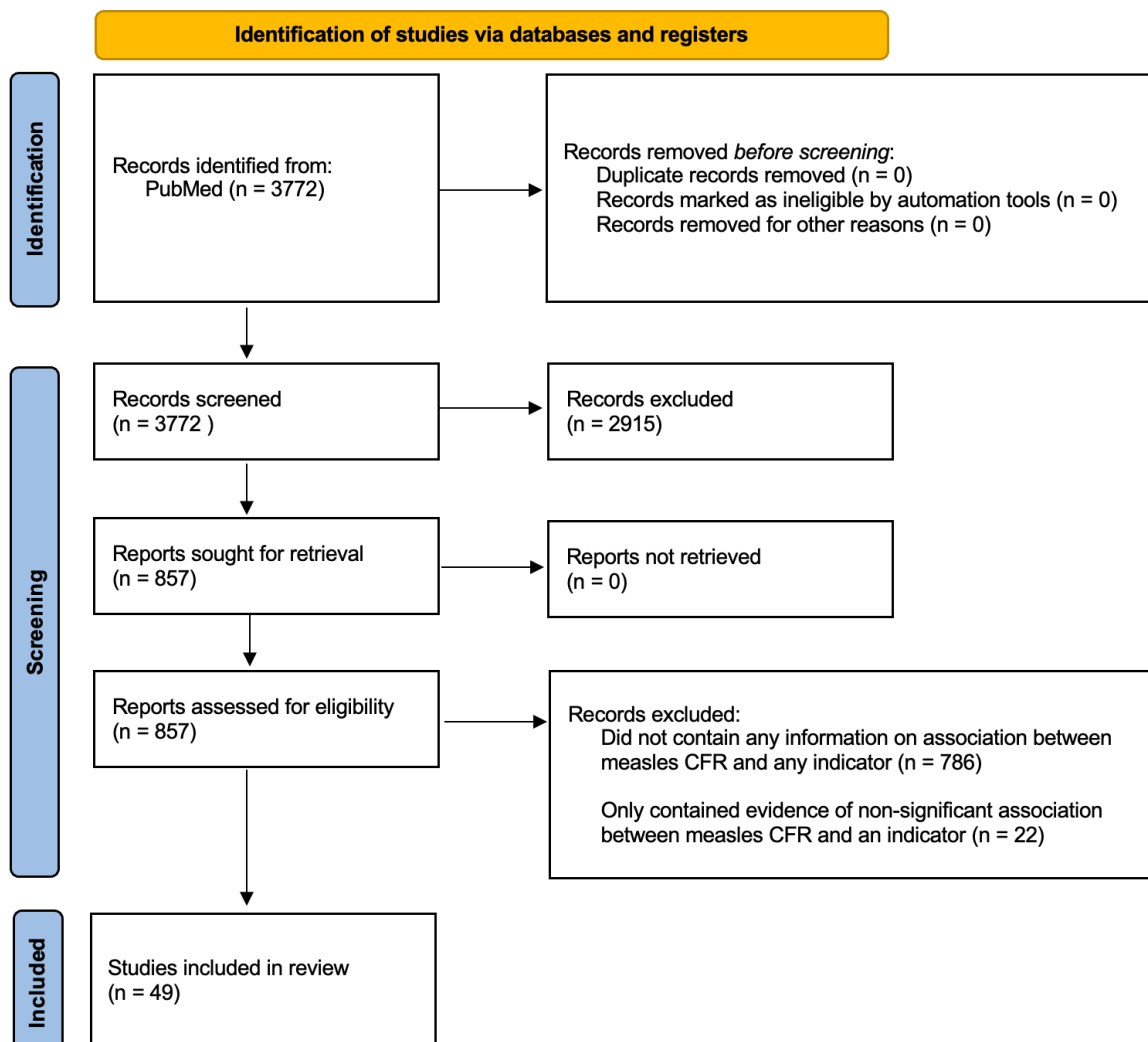
4.6.2.1 Health System Access and Care-Seeking Behaviours

Educational Attainment

In 1980, Bhuiya and colleagues[12] showed that Bangladeshi children with measles whose mothers had no education had an increased odds of death (odds ratio (OR): 2.11 [95% confidence interval (CI): 1.06–4.19]) compared to those with mothers having "some" education. In a case–control study among deaths and non-fatal cases in Bangladesh from 1982 to 1984, Clemens and colleagues[13] estimated the increased odds (OR: 1.32 [1.07–1.63]) of death when the head of household had no (versus any) education. Similarly, they found an increased odds (OR: 1.72 [1.36–2.19]) of death when mothers had no (versus any) education. Ndikuyeze and colleagues[14] noted there were higher CFRs among children living in Chad from 1988 to 1992 with mothers who were "less well educated"; no data were shown. In Zambia, from 1998 to 2003, Moss and colleagues[15] showed children hospitalized with measles whose maternal education was less than or equal to eight years had an increased relative risk of death (relative risk (RR): 2.15 [1.11–4.17]) compared to children whose mothers had more than eight years of education. Murhekar and colleagues[16] showed that children with measles with illiterate heads of households living in India in 2012 had an increased relative risk (RR: 6.23 [1.48–26.21]) of death compared to those having a parent with primary education or above.

Surrounding Conflict

Salama and colleagues[17] noted that in Ethiopia in 2000, famine, exacerbated by conflict, was associated with many deaths related to measles, and without relief interventions, measles mortality would have been greater. Joshi and colleagues[18] showed that in Nepal in 2004, children with measles living in locations with critical insecurity levels had an increased odds of death (OR: 15.8 [3.4–73.4]) compared to children living in locations with moderate insecurity levels. Additionally, Meteke and colleagues[19] noted that conflict settings can lead to infectious disease outbreaks; no data were shown. Moss and colleagues[20] noted that measles is a major cause of death among internally displaced and refugee

persons as well as very high rates of CFRs among various emergency situations; no data were shown.

Travel Time to Nearest Health Facility/Major City or Settlement

In 2013, in the Democratic Republic of the Congo, Gignoux and colleagues[21] showed children with measles who lived more than 30 km from a hospital had an increased relative risk (RR: 2.2 [1.0–4.7]) of death compared to children with measles who lived 30 or fewer kilometres away from a hospital. In Mongolia, from 2015 to 2016, Lee and colleagues[22] noted that children with measles who lived outside of Ulaanbaatar City had an increased relative risk (RR: 1.9 [1.3–2.8]) of death compared to children with measles who lived within Ulaanbaatar City.

Indicators without Supporting Evidence

With regard to the percent living in urban settings, published evidence of a non-significant relationship with CFR was found. There was no published evidence examining the association between CFR and time to care seeking.

4.6.2.2 Health System Quality

Level of Health Care Available

Rey and colleagues[23] noted that among measles cases in France from 1970 to 1979, there was a significant decrease in mortality throughout the study period, which the authors suggested was most likely attributable to general improvements in health care availability; no data were shown.

Under-Five Mortality Rate

Multiple studies[17,24-27] noted the temporal correlation and overall trend between decreasing under-five mortality and measles mortality in various years and settings.

Indicators without Supporting Evidence

There was no published evidence examining the association between CFR and access to intensive care units or health expenditure per capita.

4.6.2.3 Nutritional Status

<u>Malnutrition</u>

Joshi and colleagues[18] showed that in Nepal in 2004, persons with measles who were stunted had an increased relative risk (RR: 5.34 [2.31–12.36]) of death compared with persons who were not stunted. Among persons hospitalized with measles in Pakistan from 2013 to 2017, Aurangzeb and colleagues[28] estimated that there was an increased odds (OR: 6.8 [3.24–14.26]) of death among those who were stunted compared to those who were not stunted.

Barclay and colleagues[29] showed that among persons with measles in Tanzania from 1982 to 1983, there was an increased relative risk (RR: 3.94 [1.69–9.21]) of death among persons with a weight for age less than 60%. In Ghana, from 1989 to 1991, Dollimore and colleagues[30] described an increased odds (OR: 2.5 [1.3–5.1], adjusted for age, sex, vaccination status, paternal education, and wet versus dry season) of death among children with measles who were two or more standard deviations below their weight-for-age z-score compared to those that were not. Among patients hospitalized with measles in Nigeria from 2000 to 2004, Lagunju and colleagues[31] showed that underweight persons had an increased relative risk (RR: 2.23 [1.17–4.26]) of death compared to those who were not underweight. Additionally, Ahmed and colleagues[32] estimated that in Nigeria from 2002 to 2005, being underweight was associated with increased measles case fatality (chi-squared p = 0.01). In South Africa from 2009 to 2010, le Roux and colleagues[33] showed that there was an association between overall weight-for-age and measles case fatality. Also, among persons hospitalized with measles in Pakistan from 2013 to 2017, Aurangzeb and colleagues[28] noted that there was an increased odds (OR: 2.93 [1.44–5.93]) of death among measles cases who were underweight compared to those who were not underweight. Coetzee and colleagues[34] showed that among paediatric hospitalized measles patients in an intensive care unit in

South Africa in 2014, underweight persons had an increased relative risk (RR: 2.77 [1.38–5.55]) of death compared to persons who were not underweight.

In addition to the biometric indicators of stunting and underweight identified by the expert group, multiple studies reported on the association between non-specific malnutrition and measles case-fatality; as such, the evidence associating non-specific malnutrition with measles case fatality are presented here. In Ghana, from 1973 to 1982, Commey and colleagues[35] showed that among measles hospitalizations for malnourished children, there was an increased relative risk (RR: 2.02 [1.63–2.51]) of death compared to measles hospitalizations among children who were not malnourished. Avila-Figueroa and colleagues[36] showed that children hospitalized with measles in Mexico from 1976 to 1989 had an increased relative risk (RR: 2.47 [1.1–5.52]) of death if they were malnourished compared to those who were not malnourished. Samsi and colleagues[37] showed that hospitalized measles patients in Indonesia from 1982 to 1986 who were malnourished had an increased relative risk of death (RR: 2.48 [1.4–4.39]) compared to hospitalized measles patients who were not malnourished. Among hospitalized measles patients in Kenya from 1982 to 1985, Alwar and colleagues[38] showed that those who were malnourished had an increased relative risk (RR: 3.77 [1.85–7.66]) of death compared to those who were not malnourished. Choudhry and colleagues[39] noted that in Afghanistan from 1983 to 1985, hospitalized measles cases with malnutrition had an increased relative risk (RR: 14.66 [5.46–39.36]) of death compared to patients without malnutrition. Madhulika and colleagues[40] noted that in India in 1991, measles cases that were malnourished experienced increased case fatality compared to those that were not malnourished (Chi-squared p = 0.0156). In hospitalized measles patients from 1994 to 2004 in Nigeria, Fetuga and colleagues[41] estimated that cases who were malnourished had an increased relative risk (RR: 7.33 [1.62–33.16]) of death compared to patients who were not malnourished. Moss and colleagues[20,42] also noted an association between malnutrition and case fatality; no data were shown. The expert group identified wasting as a potential biometric indicator related to

CFR, However, no evidence directly examining this relationship was found. However, because of the strong preponderance of evidence supporting an association between general malnutrition and CFR, wasting was included having observational-level associative evidence.

Vitamin A Deficiency Prevalence

Among hospitalized measles patients in Malawi from 1992 to 1993, Courtright and colleagues[43] showed that there was an increased relative risk (RR: 4.00 [1.21–13.33]) of death for patients with vitamin A abnormalities compared to patients without vitamin A abnormalities. Moss and colleagues[20] noted that there is a high risk of measles case fatality for those with underlying vitamin A deficiencies; no data were shown. Additionally, Nojilana and colleagues[44] reported on the increased relative risk (RR: 1.86 [1.32–2.59]) of vitamin A deficiency on measles case fatality.

Vitamin A Supplementation

While evidence was collected from various studies on vitamin A supplementation, a recent meta-analysis[45] pooling data from 43 trials in 18 settings in the period 1976–2010 found no effect of vitamin A supplementation on measles case fatality. We, therefore, chose to exclude this indicator.

4.6.2.4 Risk of Secondary Infection

Average Household Size

Burström and colleagues[46] showed that in Sweden from 1885 to 1910, there was an increased relative risk of death among children with measles who had siblings (RR: 2.9 [1.6–5.4]) compared to those who did not, as well as for children with measles with a household size of more than four persons (RR: 1.9 [1.3–2.8]) compared to those with household sizes with three or less people; they also showed other significant univariate associations. Aaby and colleagues[47] noted that among children in Guinea-Bissau in 1979 there was an association between increased case fatality among "other" types of households relative to those that

were monogamous (Chi-squared p < 0.01). Also, Aaby and colleagues[48] showed that among children with measles in Guinea-Bissau in 1979, those living in homes with more than four children had an increased relative risk (RR: 1.9 [1.2–3.0]) of death compared to those living in homes with four or fewer children. Nandy and colleagues[49] noted that among persons with measles in Niger in 2003, those living in a household with eight or more persons had an increased relative risk (RR: 1.82 [1.22–2.71]) of death compared to those living with fewer than eight persons.

HIV Prevalence

Among hospitalized measles patients in Zambia from 1993 to 1995, Oshitani and colleagues[50] found that patients with HIV had an increased relative risk (RR: 3.35 [1.95–5.76]) of death compared to patients without HIV. Jeena and colleagues[51] showed that hospitalized measles patients in South Africa from 1994 to 1996 who were HIV positive had a substantially increased relative risk (RR: 129.62 [40.12–412.64]) of death compared to patients who were HIV negative. Moss and colleagues[15] demonstrated that in Zambia during the period 1998–2003, hospitalized measles patients with HIV had an increased relative risk (RR: 2.95 [1.83–4.74]) of death when compared to other hospitalized measles patients without HIV. Also, in an outbreak with 552 cases in South Africa from 2009 to 2010, le Roux and colleagues[33] estimated that after adjusting for age and weight for age, persons with HIV had an increased odds (OR: 7.55 [2.27–25.12]) of death compared to persons without HIV. Coetzee and colleagues[34] also showed that among paediatric hospitalized measles patients in an intensive care unit in South Africa in 2014, persons with HIV had an increased relative risk (RR: 2.29 [1.24–4.20]) of death compared to persons without HIV.

Indicators without Supporting Evidence

Published evidence of non-significant relationships between each indicator and CFR were found for the following indicators: antibiotic use for measles-related pneumonia, malaria prevalence, and pneumococcal conjugate vaccination coverage. There was no published evidence examining the association with CFR

and the following indicators: ambient air pollution, human immunodeficiency virus (HIV) treatment/antiretroviral therapy (ART) prevalence, de-worming frequency, oral rehydration solution for measles-related diarrhoea, population density, and total fertility rate. For the association between pre-term birth prevalence and increased measles case fatality, evidence of an association[52] was found but excluded for only having one study with significant evidence which had a small sample size (N = 57). Several studies suggested a significant relationship between measles case fatality and diarrheal disease or lower respiratory infection. In these studies, however, it was not possible to distinguish whether these data reflected secondary infections or measles-virus related symptoms. After discussions with the expert group, we excluded these studies and these indicators.

4.6.2.5 Measles Control and Epidemiology

First-Dose Coverage of Measles-Containing Vaccine (MCV1)

Nayir and colleagues[53] noted a temporal trend relating measles vaccination and declining measles mortality rates in Turkey from 1970 to 2017. In Bangladesh from 1982 to 1985, Aaby and colleagues[54] showed a protective effect of measles vaccination on measles deaths (vaccine efficacy against measles death: 95% [79–99%]). Samb and colleagues[55] estimated that vaccinated measles cases in Senegal from 1983 to 1990 had lower case fatality rates than unvaccinated cases (p = 0.038). Oshitani and colleagues[56] showed that in Zambia from 1992 to 1993, children with measles who had at least one dose of any measles-containing vaccine (MCV) had a decreased relative risk (RR: 0.4 [0.19–0.83]) of death compared to unvaccinated children with measles. Fetuga and colleagues[41] noted an association between measles vaccination and case fatality in Nigeria from 1994 to 2004 (Fisher's exact p = 0.033). Dollimore and colleagues[30] noted that among measles cases in Ghana from 1998 to 1999, those who were unvaccinated had an increased relative risk (RR: 1.72 [1.04–2.84]) of death compared to those who were previously vaccinated with at least one dose of any MCV. Mgone and colleagues[57] noted an inverse association between measles vaccination and case

fatality in Papua New Guinea in 1999 (chi-squared p = 0.0423) among patients hospitalized with measles.

Among hospitalized measles patients in Pakistan from 2003 to 2004, Aurangzeb and colleagues[58] showed that there were increased odds (OR: 8.40 [1.00–71.84]) of death among children who were previously unvaccinated compared to those with at least one dose of MCV. Among persons with measles in Nepal in 2004, Joshi and colleagues[18] showed that there was an increased relative risk (RR: 3.7 [2.0–6.7]) of death among unvaccinated cases compared to those who had at least one dose of any MCV. In Ethiopia, from 2007 to 2016, Gutu and colleagues[59] [59] showed that unvaccinated measles cases had an increased odds (OR: 1.55 [1.14–2.11]) of death compared to cases with a previous vaccination history with at least one dose of any MCV. Gignoux and colleagues[21], in a 2013 outbreak in the Democratic Republic of the Congo, noted a decreased relative risk (RR: 0.3 [0.1–0.9]) of death among children previously vaccinated with only one dose of MCV compared to those that were previously unvaccinated. Moss and colleagues[20,42] have also noted an association between measles vaccination status and case fatality; no data were shown.

Second-Dose Coverage of Measles-Containing Vaccine (MCV2)

During an outbreak in the Democratic Republic of the Congo in 2013, Gignoux and colleagues[21] noted a decreased relative risk (RR: 0.2 [0.1–0.3]) of death among children with measles who were previously vaccinated with at least two doses of MCV (compared to those that were previously unvaccinated or had only received one dose). Aurangzeb and colleagues[28] showed that in Pakistan from 2013 to 2017, children with measles that were previously unvaccinated had an increased relative risk (RR: 7.0 [2.03–24.01]) of death compared to those who had received at least two doses of any MCV; additionally, children with measles that had previously only had one dose had an increased relative risk (RR: 5.73 [1.49–22.07]) of death compared to those who had received at least two doses of any MCV.

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<u>Vitamin A Treatment</u>

In a randomized trial in South Africa in 1987, Hussey and colleagues[60] showed there were decreased odds (OR: 0.21 [0.05–0.94]) of death among hospitalized measles patients who had received vitamin A treatment compared to those who had not. In another randomized trial in South Africa in the period 1989–1990, Hussey and colleagues[61] concluded there were decreased odds (OR: 0.36 [0.18–0.70]) of death among hospitalized measles patients who were treated with vitamin A therapy compared to those who were not. Joshi and colleagues[18] showed that in Nepal in 2004, measles cases that did not receive vitamin A treatment had an increased relative risk (RR: 3.09 [1.69–5.67]) of death compared to cases that did receive vitamin A treatment. Murhekar and colleagues[16] showed that in India in 2012, among measles cases who received vitamin A treatment, there was a decreased relative risk (RR: 0.14 [0.03–0.61]) of death compared to those who did not receive treatment. In a measles outbreak in 2017 in India, Dzeyie and colleagues[62] showed vitamin A treatment was associated with decreased measles case fatality (chi-squared p = 0.0351).

<u>Indicators without Supporting Evidence</u>

We did not find any studies examining the relationship between CFR and the following indicators: maternal measles vaccination coverage, maternal antibody dynamics, vaccination efficacy, vaccination schedule, and vaccine coverage equity.

4.7 Discussion

Our conceptual framework of mechanisms related to measles CFR, based on expert consultation, and a literature review of indicators associated with these mechanisms strengthen the understanding of measles CFR and mortality estimation. We categorized potential risk factors for measles CFR into five mechanisms related to either systematic increases or decreases in measles CFR and searched for evidence of an association with measles CFR across 37

population-level indicators that are representative of these mechanisms. Among indicators included in our search, 15 indicators had evidence of an association with measles CFR.

Overall, 26 countries were represented in 49 studies published from 1983 to 2021 that included quantitative or qualitative evidence of an association with CFR. Most locations were from low- or middle-income countries. Relative to other mechanisms, nutritional status had the greatest number of studies available across its group indicators. Only one indicator, vitamin A supplementation, had a previously conducted systematic review with meta-analysis pooling results across studies. For multiple indicators, results of various studies showed both statistically significant and non-significant associations with CFR. In the absence of a meta-analysis, we considered indicators with studies presenting evidence of a statistically significant association with CFR and studies presenting evidence of a non-significant association to be plausibly associated with CFR if there was at least one study with significant evidence.

Most indicators could likely be classified under multiple underlying mechanisms. For example, MCV1 coverage could be related to measles control and epidemiology, but also to general health system access, health system quality, and risk of secondary infection. However, because indicators were used to represent mechanisms at large, the assignment of each indicator to a single mechanism for illustrative purposes did not influence the determination as to whether an association with CFR existed. These classifications, though, might have implications for future use cases of this work, such as for mathematical or statistical modelling, and users will need to consider these assumptions in the specific context in which they are working.

While they may be associated with measles CFR, we identified 17 indicators for which no evidence had any significant association. For some indicators, the type of data available did not allow us to reliably assess the association with CFR,

despite the availability of published evidence. For lower respiratory infection and diarrheal disease prevalence, high rates of community prevalence of related pathogens may theoretically increase the risk of secondary infection in measles cases and subsequently increase case fatality. There was substantial evidence to suggest that the development of pneumonia or diarrhoea following acute measles infection was associated with increased case fatality. However, it was not possible to distinguish whether the development of pneumonia or diarrhoea represented the progression of primary measles or reflected secondary infection with an additional pathogen. Without routine specimen testing when additional clinical symptoms arise, we are unable to distinguish whether these are population-level factors related to increased measles CFR or markers of disease severity. Thus, it was not possible to determine the nature of these specific associations.

Given the heterogeneity of underlying studies and their varying quality scores, we were unable to perform any quantitative synthesis to combine the evidence found in the published literature. Additionally, the objective of our review was to generate supportive evidence for the conceptual framework and related indicators via identifying any evidence suggesting an association with measles CFR rather than generating a single effect size per indicator.

We assessed only associations with acute measles case fatality as our end point. However, it is known that since health facilities experience higher patient loads[63] and secondary measles cases present with increased severity compared to primary cases[48,64], increases in measles incidence are associated with increased measles CFR (such as in an outbreak setting[10]). If this association is causal, then anything that increases measles incidence could also plausibly increase measles CFR, but we did not examine these relationships in this work.

We did not explicitly re-examine the relationship between age or measles incidence, given their known importance regarding case fatality. It has been shown previously that as age increases, CFR decreases[6,10]. These patterns likely

reflect a variety of complex relationships between age, maturation of immune responses to infection, and age-dependencies in other risk factors for CFR. In young infants, maternal antibodies are likely to provide some protection both against infection and case fatality, though the presence and duration of this protection depends on maternal immunity rates, gestational age, and underlying nutritional status, among other additional factors[65]. As maternal immunity wanes, young children may be particularly vulnerable to measles infection and case fatality, until they receive measles vaccination (typically between 9 and 12 months). The complex interplay between maternal immunity, measles epidemiology, and vaccination (as well as possible age-related confounders) complicates the interpretation of reported CFRs—especially among age groups representing these youngest children—and warrants particular attention when developing measles control strategies. Complex relationships between other risk factors for measles CFR—such as those between MCV1 coverage and HIV prevalence—can also contribute to differences in measles CFR by age and may vary from setting to setting.

Children born to HIV-positive mothers are likely to have fewer maternal antibodies[66] as well as a lower probability of sustained seroconversion following measles vaccination[67]. Persons living with HIV are more likely to both acquire and subsequently die from measles, making them a particularly important community to consider when estimating measles CFR[68]. More robust data needs to be collected to better understand and account for these interdependent relationships between age, measles incidence, MCV coverage, and HIV prevalence. Additionally, since the relationship between age and measles CFR is so strong, modelling efforts to understand measles mortality should ideally account for the underlying age pattern in both measles cases and CFRs.

This work has several limitations. First, the evidence presented in this study is heterogeneous and includes both population-level and individual-level relationships. Next, we did not identify the reasons for studies showing non-

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significant associations, such as having an underpowered sample size to assess significance. We only used one database during our literature search. Additionally, due to limitations in available data, we were unable to assess causality of associations between indicators and CFR. For example, as with nutritional status, few studies had information on anthropometry prior to measles onset, and since measles infection commonly leads to weight loss, reverse causality cannot always be excluded. Nonetheless, some large prospective studies confirmed increased CFR in malnourished children. Additionally, we did not consider evidence specific to populations that are at particularly high risk of measles infection and mortality, such as refugees or internally displaced persons. While these subgroups of the overall population are likely at higher risk of both measles infection and mortality given underlying concerns related to access to health services and other increased risk of infection, there is a scarcity of population-specific indicators and underlying data regarding measles CFR. Although data in these populations are likely challenging to collect, we support the investigation of these critical questions to better understand how to assess burden among these high-risk groups. Additionally, we considered only acute fatality from a measles case (i.e., within the first 28 days). Additional consideration should be given to which indicators and mechanisms contribute to longer-term impacts of measles on overall mortality[69]. Finally, several studies did not provide information on either the proportion of cases with laboratory confirmation or the underlying definition for a measles case, which reduces the overall quality of evidence presented in these particular studies.

Overall, this study addresses some of the knowledge gaps around factors influencing measles CFR and, moreover, may be valuable for decision making and programmatic targeting among disease control programs. More work as well as primary data collection is needed to continue expanding what is known about these associations, to close important knowledge gaps, and to better estimate measles CFR across settings and populations.

4.8 Acknowledgements

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5. Estimating national-level measles case–fatality ratios in low-income and middle-income countries: an updated systematic review and modelling study

Alyssa N. Sbarra[1,2], Jonathan F. Mosser[2,3], Mark Jit[1], Matthew Ferrari[4], Rebecca E. Ramshaw[1], Patrick O'Connor[5], L. Kendall Krause[6], Emma L. B. Rogowski[1], Allison Portnoy[7]

[1] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

[2] Institute of Health Metrics and Evaluation, University of Washington, Seattle, WA, USA

[3] Department of Health Metrics Sciences, University of Washington, Seattle, WA, USA

[4] Department of Biology, The Pennsylvania State University, University Park, PA USA

[5] Department of Immunization, Vaccines, and Biologicals, WHO, Geneva, Switzerland

[6] Global Development Division, Bill & Melinda Gates Foundation, Seattle, WA, USA

[7] Center for Health Decision Science, Harvard T. H. Chan School of Public Health, Boston, MA, USA

Objective: To develop methodology to generate measles CFR estimates that are specific by age, space, and time.

5.1 Overview

This chapter has been published as a manuscript in the *Lancet Global Health* in March 2023. It describes an updated systematic review of available data on measles case fatality, a data analysis to select covariates to use for modelling, and the fitting of and prediction from a location-, age-, and year-specific model of measles CFR in low- and middle-income countries.

As previously discussed, measles mortality estimates in LMICs rely on estimates of measles case fatality ratios (CFRs). In Chapter 4, I identified population-level factors related to measles CFR, which can be used in a model to predict CFR estimates across location and time. Findings in Chapter 4 highlight the critical need to consider age heterogeneity in CFR, especially since youngest children (who are more likely to experience higher rates of case fatality) are also not yet old enough to be vaccinated, further increasing their vulnerability. A previous model estimates CFR by location and year, as well as for under-five-year-olds and for five-and-older. However, this model fails to fully capture the critical importance of estimating age variation in case fatality, does not reflect the updated understanding of potential population-level covariates developed in Chapter 4, and only includes data published through 2016.

Therefore, this chapter builds upon Chapter 4 to address these gaps in measles mortality estimation more comprehensively. In this chapter, I used the identified population-level indicators in Chapter 4 as covariate sets to fit predictive models of measles CFR. Finally, I fit a predictive meta-regression model to estimates measles CFR by age, location, and year in LMICs and compared trends across age groups, regions, and decades.

I contributed to the screening and data extraction associated with the updated systematic review along with co-authors (R.E.R., E.L.B.R.). I identified and conducted the data analyses of covariate sets. I tested various modelling frameworks and selected the most statistically appropriate. I additionally fit the

final model version and made subsequent predictions of CFR by age, location, and year. I wrote the first draft of the manuscript, developed all tables and figures, and made any revisions. The manuscript version in this chapter has been published in the *Lancet Global Health* in March 2023.

5.2 Research Paper Coversheet

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

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SECTION A – Student Details

Student ID Number	1903678	**Title**	Ms.
First Name(s)	Alyssa		
Surname/Family Name	Sbarra		
Thesis Title	Addressing Gaps and Challenges in Measles Burden Estimation		
Primary Supervisor	Prof. Mark Jit		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Lancet Global Health		
When was the work published?	Available online March 2023		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I contributed to designing the research questions, was responsible for screening and extracting updated data in the systematic review, conducing data analyses for covariate seelction, designing and selecting the updated model and making predictions.

SECTION E

Student Signature	███████████
Date	31 August 2023

Supervisor Signature	███████████
Date	2 Sept 2023

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5.3 Abstract

Background: To understand the current measles mortality burden, and to mitigate the future burden, it is crucial to have robust estimates of measles case fatalities. Estimates of measles case–fatality ratios (CFRs) that are specific to age, location, and time are essential to capture variations in underlying population-level factors, such as vaccination coverage and measles incidence, which contribute to increases or decreases in CFRs. In this study, we updated estimates of measles CFRs by expanding upon previous systematic reviews and implementing a meta-regression model. Our objective was to use all information available to estimate measles CFRs in low-income and middle-income countries (LMICs) by country, age, and year.

Methods: For this systematic review and meta-regression modelling study, we searched PubMed on Dec 31, 2020 for all available primary data published from Jan 1, 1980 to Dec 31, 2020, on measles cases and fatalities occurring up to Dec 31, 2019 in LMICs. We included studies that previous systematic reviews had included or which contained primary data on measles cases and deaths from hospital-based, community-based, or surveillance-based reports, including outbreak investigations. We excluded studies that were not in humans, or reported only data that were only non-primary, or on restricted populations (e.g., people living with HIV), or on long-term measles mortality (e.g., death from subacute sclerosing panencephalitis), and studies that did not include country-level data or relevant information on measles cases and deaths, or were for a high-income country. We extracted summary data on measles cases and measles deaths from studies that fitted our inclusion and exclusion criteria. Using these data and a suite of covariates related to measles CFRs, we implemented a Bayesian meta-regression model to produce estimates of measles CFRs from 1990 to 2019 by location and age group. This study was not registered with PROSPERO or otherwise.

Findings: We identified 2705 records, of which 208 sources contained information on both measles cases and measles deaths in LMICS and were included in the review. Between 1990 and 2019, CFRs substantially decreased in both community-based and hospital-based settings, with consistent patterns across age groups. For people aged 0–34 years, we estimated a mean CFR for 2019 of 1.32% (95% uncertainty interval [UI] 1.28–1.36) among community-based settings and 5.35% (5.08–5.64) among hospital-based settings. We estimated the 2019 CFR in community-based settings to be 3.03% (UI 2.89–3.16) for those younger than 1 year, 1.63% (1.58–1.68) for age 1–4 years, 0.84% (0.80–0.87) for age 5–9 years, and 0.67% (0.64–0.70) for age 10–14 years.

Interpretation: Although CFRs have declined between 1990 and 2019, there are still large heterogeneities across locations and ages. One limitation of this systematic review is that we were unable to assess measles CFR among particular populations, such as refugees and internally displaced people. Our updated methodological framework and estimates could be used to evaluate the effect of measles control and vaccination programmes on reducing the preventable measles mortality burden.

5.4 Research in Context

Evidence before this study

We searched PubMed on Dec 6, 2022, for systematic reviews published from Jan 1, 1980, to Dec 6, 2022, using the search terms "measles" AND "case fatality". We included studies if they were a systematic review of measles case–fatality ratios (CFRs). We excluded studies that were not systematic reviews or did not contain information about measles or CFRs. We identified two previous systematic reviews that have synthesised individual studies of measles CFRs. The first of these reviews, by Wolfson and colleagues, was published in 2009 and used 58 community-based studies in 29 countries to provide global estimates of measles CFR. Wolfson and colleagues published a descriptive analysis suggesting global estimates of CFR with a mean of 3.3%, a median of 3.9%, and range from 0 to 40.1%. For outbreak investigations, results suggested a median CFR of 5.2% (95% CI 2.6–11.6). These results were the first figures of measles CFRs beyond single country–year studies, reports, and investigations; however, this review only included community- based studies, did not produce estimates for other locations or years, and did not stratify by other underlying determinants of mortality, such as the income level of each country.

The second review, by Portnoy and colleagues, was published in 2019 and included data from 1980 to 2016 from low- income and middle-income countries; studies included reports from both community-based (n=85) and hospital- based (n=39) settings. Following the review, the authors used a log-linear prediction model with a select set of covariates, generally understood to be related to measles CFR (e.g., previous vaccination history [with first dose of measles-containing vaccine coverage used as a proxy] and estimated measles attack rate) and indirectly associated with measles CFR (e.g., mortality in children younger than 5 years [hereafter referred to as under-5 mortality], total fertility rate, proportion of population living in urban areas, and population density). The authors reported predicted CFR stratified by year, World Bank country-development status, under-5 mortality, care setting (community vs hospital), age

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(younger than 5 years vs 5 years or older), and calendar year from 1990 to 2030. Results predicted a mean CFR of 2.2% (95% CI 0.7–4.5) for years 1990–2015, with stratification for studies based in the community (CFR 1.5% [0.5–3.1]) and hospitals (CFR 2.9% [0.9–6.0]).

Added value of this study

Our study produced estimates specific to age, geographical location, and year of measles CFR (from 1990 to 2019) by building on previous estimates in three ways. Our study updated the existing body of evidence to include data published up to Dec 31, 2020, cases occurring up to Dec 31, 2019, and from non-English language studies. Our study incorporated an explicit conceptual framework based on a literature review and expert consultation to identify a suite of covariates shown to be related to measles CFR at the population level. We used a Bayesian meta-regression model with a flexible spline component, to improve capture of variation in CFR by age.

Implications of all the available evidence

This model, along with the corresponding estimates, can contribute to a deeper understanding of measles CFR and allow for an increasingly robust assessment of vaccination programmes and other interventions to reduce measles mortality burden.

5.5 Introduction

In 2019, more than 207,500 deaths were estimated to be attributable to measles[1]. However, the exact figure cannot be measured directly because of an absence of reliable data on measles mortality from most high-burden settings. Instead, measles mortality is usually estimated by combining incidence and case–fatality ratio (CFR) estimates[2]. Therefore, an accurate understanding of CFRs across different times and geographies is essential for the estimation of measles mortality burden. Additionally, a robust understanding of country-level CFRs can help to identify opportunities to strengthen health systems and to inform assessments of

the effectiveness of vaccination programmes. Cohort-based and cross-sectional studies and outbreak investigations provide literature reports of CFRs but are often limited to specific settings and years[3].

Previous work has reviewed the available published data on measles CFRs[3]. An additional study[4] also modelled estimates of measles CFRs for low-income and middle-income countries (LMICs) among children younger than 5 years (hereafter referred to as children under 5) and those aged 5 years or older, in both community-based and hospital-based settings. Time- varying estimates of CFRs are crucial for understanding patterns of measles mortality across time and location and have been instrumental in understanding acute measles deaths and the effect of various vaccination scenarios[5]. Despite being a major advancement, these previously published estimates do not include CFR data from after 2016 or an underlying conceptual model for the relation between the CFR and associated covariates[6].

Additionally, CFR estimates stratified by broad age categories might obscure important variation within age groups, particularly for young children. Both previous systematic review studies[3,4] showed higher CFRs in children under 5 compared with those aged 5 years or older. However, there are likely to be crucial age-specific variations between infants (aged ≤1 year) and young children (aged 1–4 years), related to maternal antibody presence[7], immune-system maturation, and vaccination status, among other factors, which go uncaptured in a composite estimate of CFR among all children under 5. Given that measles incidence tends to be highest among young, unvaccinated children[8], an accurate understanding of CFRs among these ages is crucial for understanding the measles mortality burden and developing targeted interventions, such as vaccination campaigns.

Our objective was to use all information available to estimate measles CFRs in LMICs by country, age, and year. As such, we did a full literature review of

measles CFR data representing both community and hospital cases in LMICs. We expanded on previous reviews by including data from non-English studies, examining all studies for granular age data, and extending the scope to include data published up to 2020 (representing cases occurring up to Dec 31, 2019). Additionally, we developed a Bayesian meta-regression model to produce location-specific, year-specific, and age- specific estimates of CFR from 1990 to 2019.

5.6 Methods

Search strategy and selection criteria

We did a systematic review to extend previously published systematic literature reviews[3,4] on measles CFRs in LMICs to include cases occurring up to Dec 31, 2019, and studies not published in English. To do so, we searched PubMed on Dec 31, 2020, for primary data published from Jan 1, 1980, to Dec 31, 2020, using the search string: (measles[MeSH Terms] OR measles) AND (mortality[MeSH Terms] OR mortality OR "case fatality rate" OR "case fatality ratio" OR "case fatality"). In addition to the literature search, we added studies from previous systematic reviews[3,4] and the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD)[9] before deduplicating and screening studies. We screened the study titles and abstracts from the search results and then reviewed the full-text versions of, and extracted summary data from, each study that passed application of our inclusion and exclusion criteria. We included studies in any language if they were included in previous systematic reviews or if, upon screening, they contained primary data on measles cases and deaths from hospital-based, community-based, or surveillance-based reports, including outbreak investigations. We excluded studies if they were not in humans, contained only non-original or non-primary data (i.e., reported on the outcomes of another study), reported on data from global or regional surveillance (rather than country-level data), or did not contain relevant information on measles cases and deaths. Additionally, as with the previous reviews, we excluded studies that: reported measles cases and deaths among only restricted populations (e.g., communities of

internally displaced people or people living with HIV); reported on only long-term measles mortality (e.g., death from subacute sclerosing panencephalitis); or were for a high-income country, as defined by the World Bank country income classification in 2017.

We extracted the following data from each study: number of measles cases, number of measles deaths, study year, age, geographical location, and setting (hospital vs community; outbreak vs non-outbreak). If reported in the study, we also extracted laboratory confirmation of cases and the length of time required after onset of rash for a death to be considered attributable to measles. Data were extracted in a Microsoft Excel 2016 workbook. For each study, we computed annual age-specific CFRs; we included all suspected measles cases and considered all deaths within 30 days of rash onset, unless cases or acute deaths were defined otherwise in individual studies.

On Nov 29, 2022, to determine the evidence available to assess CFRs during the COVID-19 pandemic, we ran our search again, for publications from Jan 1, 2020, to Nov 28, 2022, using the same search string and inclusion and exclusion criteria for screening articles.

Data analysis

An overview of our entire covariate selection and modelling process can be found in Appendix D Section 1. Previous work identified measles incidence and age to be crucial covariates when assessing measles CFR[3,4,6]. We also selected additional covariates to analyse on the basis of a literature review and expert consultation[6] that identified five possible underlying mechanisms that contribute to systematic increases or decreases in measles CFR (i.e., health-system access and care-seeking behaviours, health-system quality, nutritional status, measles control and epidemiology, and risk of secondary infection) and related population-level indicators with evidence of an association with CFR (i.e., mean household size, educational attainment, coverage of measles- containing vaccine first dose

[MCV1] and second dose [MCV2], HIV prevalence, extent of health-care availability, stunting prevalence, surrounding conflict, travel time to nearest health-care facility, under-5 mortality, under- weight prevalence, vitamin A deficiency prevalence, vitamin A treatment prevalence, and wasting prevalence). We used previous estimates of country-specific annual incidences of measles that were generated using a semi- mechanistic, stochastic model fitted to observed annual case data[10]. For remaining covariates, we searched databases of health-related indicators (from WHO, the UN, World Bank, and GBD[9]) to identify possible covariate sets that could be used to represent each indicator. For the following indicators, we were able to find an appropriate covariate set available for nearly all (≥90%) countries and years from 1980 to 2019: HIV prevalence[9], MCV1 coverage[11], under-5 mortality rate[12], vitamin A deficiency prevalence[9], and wasting prevalence[9]. If a covariate set was not available, we identified a proxy covariate set if an appropriate alternative existed on the basis of expert group review. Proxy covariate sets, identified by expert consultation, include the following (Appendix D Section 1): gross domestic product per person[12] (for level of health care available), maternal education9 (for educational attainment), proportion living in an urban setting[12] and total fertility rate[12] (for mean household size), and mortality rate due to war and terrorism[9] (for surrounding conflict). For vitamin A treatment, we were unable to identify an appropriate proxy covariate set; therefore, vitamin A treatment was excluded as a covariate in our model.

If country-level data for specific years were missing in covariate sets, we either computed an interpolated or projected value if there were fewer than 20% of years missing per country for the covariate, or used the GBD regional mean of covariate values for a country if there was at least 20% missingness. For covariates with less than 20% missingness per country, we linearly interpolated missing years using values from adjacent available years of covariate values. If missing covariate values were at the beginning or end of the covariate time series, to complete the full time series we used an annualised rate of change, weighted

exponentially, to compute the projected covariate values either forwards or backwards in time, such that weights were more representative of years in the time series that were closer to either the most recent year for forwards projections or the earliest year for backwards projections. For wasting prevalence specifically, which was available from only 1990 onwards, we held the 1990 value constant from 1980 to 1990. We assumed that all covariates took their values in 1980 for pre-1980 years.

We did a two-step data analysis of the covariate sets to determine the strength of relationship and predictive capability of each covariate in describing underlying trends in CFR. Covariates were grouped into five mechanisms, as described previously[6]. To examine the correlation of covariates, we calculated the pairwise correlation of each of the covariates in each mechanistic group. If there was a correlation greater than 0.8 for any pairwise comparison, covariates were removed sequentially on the basis of the mean highest collinearity between all other covariates in the mechanistic group. As the second step, we did a simple linear regression of the remaining covariates per mechanistic group with the CFR dataset. Covariates were removed as uninformative if they had a p value greater than twice the mean p value across all covariates (i.e., > 0.33). The final list of covariates selected for inclusion were: age, a categorical indicator for community versus hospital studies, measles incidence, mortality rate due to war and terrorism, maternal education, gross domestic product per person, HIV prevalence, MCV1 coverage, total fertility rate, under-5 mortality, proportion living in urban settings, vitamin A deficiency, and wasting prevalence (Appendix D Section 1).

Finally, we selected a transformation (log, logit, or untransformed) for each covariate by fitting separate linear regressions with each version of the transformed covariate as a predictor and an outcome of logit CFR. Transformation was selected on the basis of the corresponding model with the lowest Akaike information criterion score[13]. Then, to improve model stability, we standardised

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each transformed covariate by subtracting the mean of the transformed covariate and dividing by the standard deviation.

Some included studies reported deaths aggregated into large age bands, which could bias results if mortality is higher in the lower end of the age band. To reduce this bias, we fitted the model to the data in two stages. First, we fitted a model to only the data for which there was age granularity representing groupings that were 5 years wide or narrower; data used in this model included ages 0–34 years. This model used the granular data for age and transformed and standardised covariate values for each study midpoint year and fit a Bayesian fixed-effects meta-regression model[14] with the outcome variable as the logit CFR (for details on model selection see Appendix D Section 2). We computed SE in logit space per study using the delta method transformation[15-17] and used these values as weights in the meta-regression. To represent the relationship between logit CFR and age, we used a quadratic spline with five knots, with three internal knots, placed uniformly on the basis of data density (i.e., equal proportions of input data represented between each knot) resulting in internal knots placed at ages 0.68, 1.31, and 3.83 years. Next, we split cases and deaths from each input data source reporting age bins wider than 1 year differentially on the basis of estimates of country-specific and age-specific incidence[10] and the overall relative age pattern of CFR estimated in the first stage model. We then recalculated logit of CFR and SE per the newly adjusted number of deaths and cases per new granular age group.

In a second-stage model, we used the same general model formula described earlier, maintaining the spline knot locations identified in the first stage model, and fit our outcome of logit CFR to all data after age splitting (Appendix D Section 3). To ensure the correct direction of association between each covariate and CFR, defined as the direction described in a previous publication[6], we placed priors on each regression coefficient. We generated 1000 samples of the regression coefficients from their fitted joint posterior distribution and predicted

country-specific and age- specific CFRs in LMICs from 1990 to 2019. We assumed CFRs varied up to age 34 years (the maximum age for which we had age-specific data) and held the CFR constant for older ages.

To understand the effect of modelling changes, adding new covariates, and updating our dataset on our estimates of CFR relative to those produced by Portnoy and colleagues[4], we did a decomposition analysis that compared the statistical performance of this new modelling framework to that of Portnoy and colleagues (Appendix D Section 4). Additionally, we computed in-sample and 5-fold out-of-sample cross-validation metrics to assess model performance. The mean error was 0.0035 from in-sample validation and 0.0011 from the out-of-sample validation (Appendix D Table 12). We produced mean estimates of CFR at the level of age, region, or year by using the case-weighted mean of CFR estimates specific to age, location, or year.

We ran sensitivity analyses that excluded studies without information on laboratory confirmation of cases and also without a death definition (Appendix D, Section 5). Finally, in an illustrative example of an application of our model, we additionally predicted results for a scenario in which there had been no vaccine introduction (i.e., MCV1 coverage was 0% in all countries and years, and incidence values also reflect an absence of vaccination). Methods for estimating incidence in a no-vaccination scenario have been described at length elsewhere[18]. We performed all analyses and produced all figures within the R computing environment (version 5.4).

This study was exempt from institutional ethics approval as only publicly available data were used.

This study was not registered with PROSPERO or otherwise. This systematic review follows PRISMA guidelines.

Role of the funding source

An author of this study (L.K.K.) was an employee of the Bill & Melinda Gates Foundation and had a role in the writing of this report and the decision to submit the paper for publication. Gavi, the Vaccine Alliance and the US National Institutes of Health had no role in study design, data collection, data analysis, data interpretation, the writing of the report, or the decision to submit the paper for publication.

5.7 Results

Our search identified 2705 records, of which 2130 records were excluded after screening, because they were duplicates or did not meet our inclusion criteria (Figure 1). We assessed 575 full-text reports and, after applying inclusion and exclusion criteria, excluded 367 records. We extracted information on measles cases and deaths from 208 studies (Appendix D Table 4). 175 of these studies contained observations from community-based settings and 66 contained observations from hospital-based settings. 126 studies contained granular information on age (i.e., at least one age group that was no wider than 5 years), 67 studies presented information without any age granularity, and 15 studies reported age by groups that were wider than 5 years. Overall, 57 unique age groups were represented among the included sources. 88 sources provided information on laboratory confirmation of cases and 84 sources provided information on a definition for a measles-related death.

Information on cases and deaths from before 1980 was available in 44 studies, for 1980–89 in 119 studies, for 1990–99 in 84 studies, for 2000–09 in 67 studies, and for 2010–19 in 71 studies. 75 countries were represented among sources. Among 1,817,931 cases included among the sources, the crude mean CFR was 5.70% (SD 7.03) and the median CFR was 2.73% (IQR 0.86–7.99). The crude mean CFR was 8.50% (SD 8.35) among hospital-based studies and 4.42% (5.94) among community-based studies.

Figure 1. Study selection.
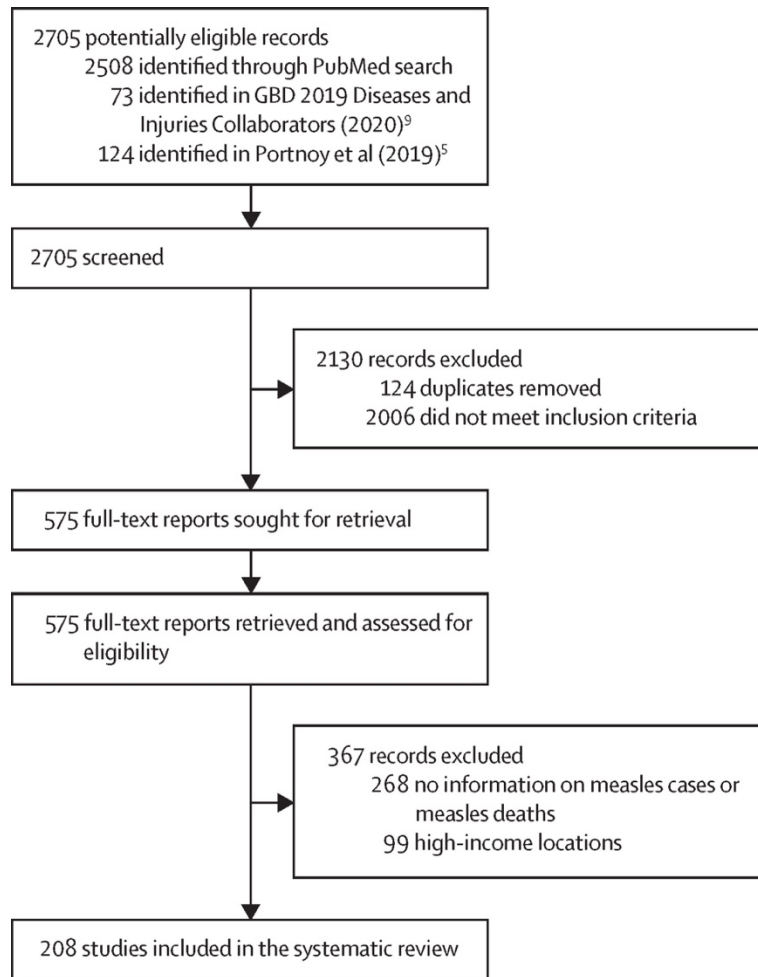
The mean estimated community-based CFR among people aged 0–34 years for 1990 was 2.60% (95% uncertainty interval [UI] 2.52–2.69) and was 1.32% (1.28–1.36) for 2019. Among hospital-based settings, the mean estimated CFR across all locations was 10.13% (95% UI 9.67–10.60) in 1990 and 5.35% (5.08–5.64) in 2019. In all regions, estimated CFRs decreased from 1990 to 2019 in both community-based and hospital-based settings (Table 1). Across all regions, CFRs were estimated to be highest in the sub-Saharan Africa region in 2019 in both community-based and hospital-based settings.

Table 1. Mean estimated case-weighted measles case–fatality ratio by year, setting, and region

	1990		2000		2010		2019	
	Community-based	Hospital-based	Community-based	Hospital-based	Community-based	Hospital-based	Community-based	Hospital-based
All locations	2.60% (2.52 – 2.69%)	10.13% (9.67 – 10.60%)	2.16% (2.10 – 2.22%)	8.48% (8.12 – 8.85%)	1.39% (1.33 – 1.44%)	5.64% (5.33 – 5.98%)	1.32% (1.28 – 1.36%)	5.35% (5.08 – 5.64%)
North Africa and Middle East	3.33% (3.14 – 3.53%)	12.53% (11.75 – 13.33%)	3.28% (3.08 – 3.49%)	12.32% (11.56 – 13.13%)	2.23% (2.08 – 2.38%)	8.78% (8.18 – 9.42%)	0.83% (0.79 – 0.86%)	3.42% (3.19 – 3.65%)
Sub-Saharan Africa	3.63% (3.50 – 3.75%)	13.63% (13.09 – 14.19%)	3.05% (2.97 – 3.15%)	11.75% (11.30 – 12.23%)	2.10% (2.04 – 2.17%)	8.34% (7.92 – 8.75%)	1.92% (1.86 – 1.97%)	7.67% (7.31 – 8.07%)
Central Europe, Eastern Europe, and Central Asia	0.66% (0.60 – 0.71%)	2.79% (2.52 – 3.09%)	0.28% (0.26 – 0.31%)	1.22% (1.10 – 1.35%)	0.15% (0.14 – 0.16%)	0.64% (0.58 – 0.71%)	0.18% (0.16 – 0.20%)	0.79% (0.70 – 0.89%)
South Asia	3.16% (3.03 – 3.29%)	12.34% (11.72 – 12.99%)	2.23% (2.08 – 2.27%)	8.79% (8.32 – 9.27%)	1.51% (1.44 – 1.57%)	6.18% (5.82 – 6.57%)	0.82% (0.78 – 0.86%)	3.45% (3.24 – 3.69%)
Latin America and Caribbean	1.81% (1.69 – 1.92%)	7.34% (6.76 – 7.94%)	0.87% (0.82 – 0.93%)	3.66% (3.34 – 3.98%)	0.52% (0.48 – 0.56%)	2.21% (1.99 – 2.43%)	0.35% (0.32 – 0.39%)	1.50% (1.34 – 1.67%)
Southeast Asia, East Asia, and Oceania	0.92% (0.88 – 0.97%)	3.83% (3.58 – 4.09%)	0.65% (0.61 – 0.67%)	2.73% (2.54 – 2.93%)	0.40% (0.38 – 0.42%)	1.71% (1.59 – 1.85%)	0.37% (0.34 – 0.39%)	1.56% (1.45 – 1.68%)

The median country-specific case-weighted CFR estimates and range by country decreased across the study period (Figure 2). All estimated LMIC CFRs decreased from 1990 to 2019. Because mean CFR estimates had been case-weighted, country-specific and year-specific mean values were influenced by the underlying distribution of the ages of people with measles within that specific country and year; a relative distribution of these ages is shown in Appendix D Figure 7. Age-standardised CFR estimates, which showed that declining CFR trends persisted after age standardisation, can be found in Appendix D Figure 8, as can country-specific CFR results and validation metrics.

We conducted sensitivity analyses using data from only studies including information on laboratory confirmation of measles cases as well as also on studies providing a definition for a death attributable to measles to investigate the implications of using all studies in our model. Results from models that excluded data without indication of laboratory confirmation of measles were systematically lower than models that contained all available data and results from models that excluded data without reporting a death definition were also estimated to be

systematically lower than those using all available data. Additional results and description of these analyses can be found in Appendix D Section 5.2.

Figure 2. Box plots of estimated country-specific, community-based measles case–fatality rates, by year

Horizontal lines represent the median case–fatality ratio, boxes represent the interquartile range, and the whiskers (thin lines) represent adjacent values that are (by convention) within 1·5 times the interquartile range. Dots represent patients outside of the adjacent values, known as outliers. The red line shows the case-weighted mean case–fatality ratio for low-income and middle-income countries, by year.
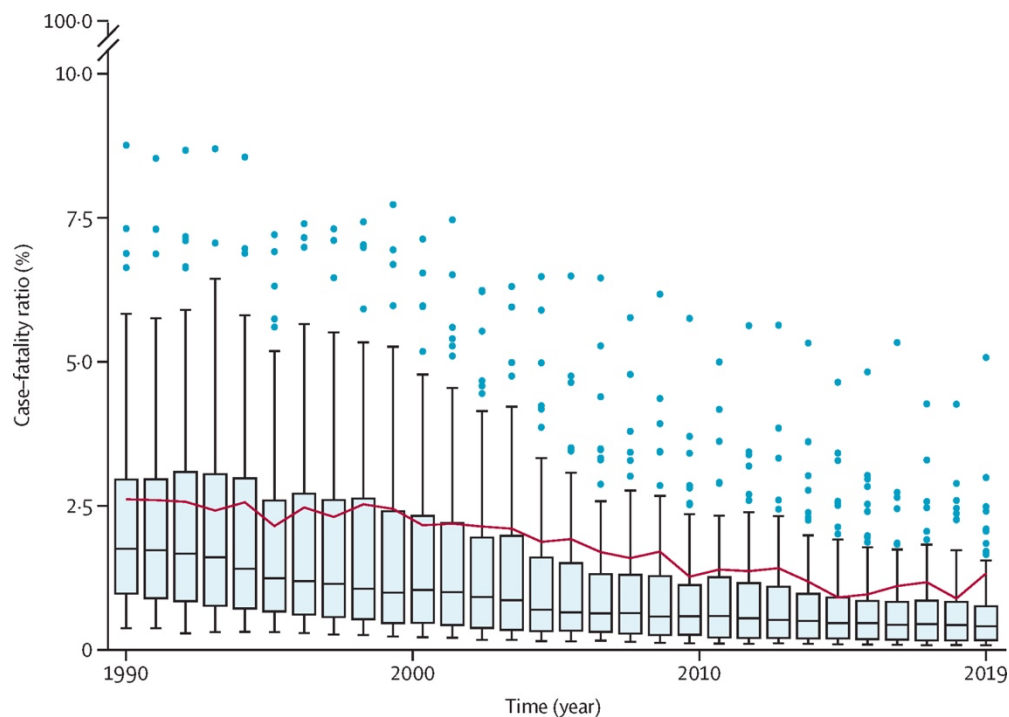
We estimated CFR to be highest among children younger than 1 year and to decline monotonically as age increased (Figure 3A). This general trend was consistent across regions and time (Figure 3B). For 2019 across LMICs in community-based settings, we estimated that the CFR among children younger than 1 year was 3.03% (95% UI 2.89–3.16), was 1.63% (1.58–1.68) for ages 1–4 years, 0.84% (0.80–0.87) for ages 5–9 years, and was 0.67% (0.64–0.70) for ages

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10–14 years. Among LMIC hospital-based settings in 2019, the estimated CFR was 5.33% (95% UI 5.06–5.59) for children younger than 1 year, 2.80% (2.70–2.90) for ages 1–4 years, 1.50% (1.44–1.57) for ages 5–9 years, and 0.87% (0.83–0.91) for ages 10–14 years.

When we projected CFR in a no-vaccination scenario, estimates by region, year, and care setting were larger than the baseline vaccination scenario (Table 2). As a result of these differences in CFR and incidence, we estimated that from years 1990 to 2019, there have been approximately 71 million deaths averted attributable to measles vaccination in these LMICs. In 2019, there were 46.3 deaths averted per 100 000 people.

Table 2. Mean estimated case-weighted measles case–fatality ratio for a no-vaccination scenario, by year, setting, and region.

	1990		2000		2010		2019	
	Community-based	Hospital-based	Community-based	Hospital-based	Community-based	Hospital-based	Community-based	Hospital-based
All locations	4.06% (3.84 – 4.29%)	15.15% (14.43 – 15.94%)	3.17% (2.99 – 3.36%)	12.05% (11.45 – 12.77%)	2.34% (2.19 – 2.51%)	9.20% (8.65 – 9.84%)	2.08% (1.94 – 2.23%)	8.24% (7.75 – 8.86%)
North Africa and Middle East	5.04% (4.66 – 5.48%)	18.26% (17.03 – 19.65%)	4.51% (4.19 – 4.90%)	16.45% (15.39 – 17.67%)	3.52% (3.25 – 3.82%)	13.25% (12.33 – 14.29%)	1.83% (1.68 – 1.99%)	7.19% (6.65 – 7.79%)
Sub-Saharan Africa	5.32% (5.04 – 5.62%)	19.03% (18.30 – 19.87%)	4.15% (3.93 – 4.41%)	15.41% (14.73 – 16.17%)	3.67% (3.46 – 3.92%)	13.79% (13.07 – 14.65%)	2.77% (2.59 – 2.96%)	10.77% (10.16 – 11.51%)
Central Europe, Eastern Europe, and Central Asia	1.97% (1.78 – 2.14%)	7.97% (7.31 – 8.61%)	0.56% (0.50 – 0.63%)	2.39% (2.14 – 2.67%)	0.37% (0.33 – 0.42%)	1.57% (1.39 – 1.77%)	0.33% (0.29 – 0.38%)	1.42% (1.25 – 1.62%)
South Asia	4.50% (4.25 – 4.76%)	16.88% (16.03 – 17.79%)	3.42% (3.20 – 3.65%)	13.21% (12.46 – 14.05%)	2.49% (2.31 – 2.67%)	9.89% (9.25 – 10.63%)	1.61% (1.49 – 1.74%)	6.57% (6.11 – 7.11%)
Latin America and Caribbean	2.75% (2.48 – 3.01%)	10.80% (9.84 – 11.84%)	1.88% (1.68 – 2.07%)	7.58% (6.81 – 8.41%)	1.24% (1.08 – 1.40%)	5.12% (4.50 – 5.75%)	0.88% (0.77 – 1.01%)	3.66% (3.18 – 4.16%)
Southeast Asia, East Asia, and Oceania	1.64% (1.52 – 1.78%)	6.68% (6.21 – 7.21%)	1.16% (1.06 – 1.26%)	4.79% (4.40 – 5.21%)	0.83% (0.75 – 0.91%)	3.45% (3.13 – 3.79%)	0.75% (0.68 – 0.83%)	3.15% (2.86 – 3.47%)

On re-running our search on Nov 29, 2022, we identified 308 studies published from Jan 1, 2020, to Nov 28, 2022. After screening using the same criteria as before, we found 27 studies for full-text review, of which only two were published studies on measles CFRs during the pandemic period: one in South

Sudan (CFR 1.16%)[19] and another in Ethiopia (7.14%)[20]. Authors of both studies noted various factors that were likely to have affected CFR estimates, including the under-reporting of deaths in the community studied in South Sudan and a high prevalence of malnutrition in the community in Ethiopia. Neither study quantified directly CFR changes caused by the COVID-19 pandemic or mentioned specifically any effect of the pandemic on the country reporting system or surveillance capacity.

5.8 Discussion

Until 2019, there was only one systematic review of measles CFR, which was limited to community-based settings and did not examine temporal changes in CFR[3]. In 2019, an updated systematic review[4] expanded the literature by including CFRs among hospital-based settings, and used a time-varying model to estimate CFR by location and year. Although more comprehensive than the first review, this updated review did not include age- specificity beyond variation among ages under 5 years versus 5 years or older, and the covariates included were not selected via a transparent, systematic process. Our new study addresses these shortcomings by: updating the former literature searches; basing covariate selection on widespread expert consultation, a literature review, and selection through a statistical process; and accounting for the distribution of age in the modelling process. Our study included 40 new sources from 21 new countries. We statistically tested for the inclusion of new covariates with a known relation to measles CFR, such as vitamin A deficiency prevalence. Community-based settings had lower CFRs than hospital-based settings. Higher measles incidence, under-5 mortality, the proportion of people living in urban settings, and vitamin A deficiency prevalence were associated with higher CFRs, whereas higher levels of maternal education and MCV1 coverage were associated with lower CFRs.

Figure 3. Estimated age-specific, community-based, case-weighted measles case–fatality ratio, by age, year, and location

Shaded areas indicate the 95% CI. (A) Estimated age-specific, community-based, case-weighted measles case–fatality ratio for people aged 0–34 years, living in low-income and middle-income countries, for 1990, 2000, 2010, and 2019. (B) Estimated age-specific, community-based, case-weighted measles case–fatality ratio for people aged 0–34 years, for 1990, 2000, 2010, and 2019, by region.
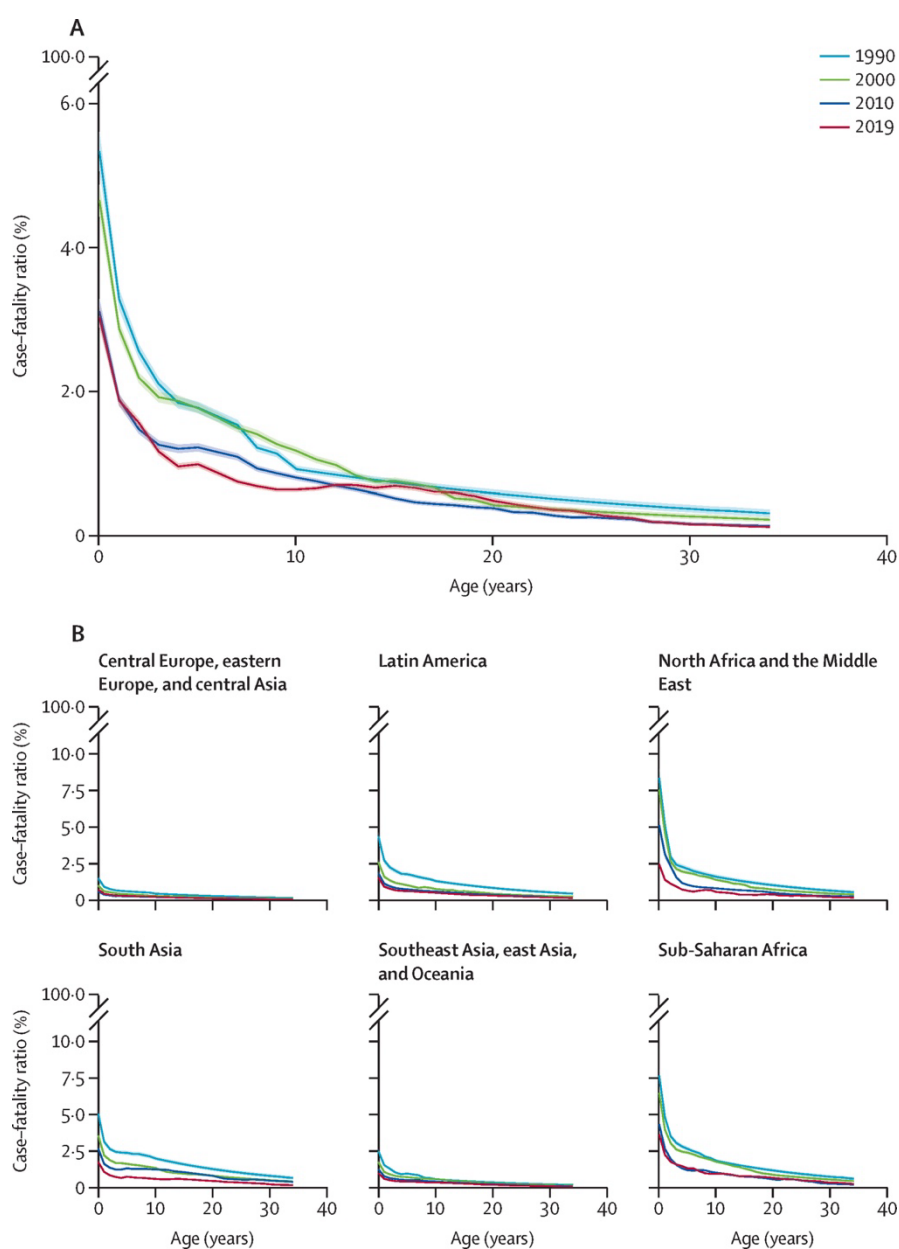
We estimated CFRs in people aged 0–34 years in community-based settings to be 2.60% (95% UI 2.52–2.69) and to have declined to 1.32% (95% UI 1.28–1.36) by 2019. We estimated higher CFRs in hospital- based settings relative to community-based settings, which was consistent with previous findings4 that probably observed the most severe cases, which required hospitalisation. We estimated infants to have the highest CFRs. In this age group, the risk of infection is influenced by the persistence of maternal antibodies, which in turn depend on gestational age and underlying maternal immunity rates[7]. On an individual level, the presence of maternal antibodies might also mitigate the severity of infection, potentially leading to lower CFRs than in absence of these antibodies. In our analysis, after controlling for study-level covariates, our model suggested population-level CFR decreases monotonically with age, consistent with previous studies[21], which might be because infants who acquire measles do not have sufficient maternal antibodies to prevent infection. Increasingly detailed and robust data collection in these youngest ages will be crucial for assessing this relationship further.

In an illustrative example of an application of our findings, we also estimated CFRs for a no-vaccination scenario that reflected both 0% MCV coverage and the corresponding measles incidence values if there was no vaccination. We used these CFR estimates to estimate a metric of the number of deaths averted owing to vaccination, which is similar to indicators that are used to assess the effectiveness of vaccination programmes and, through this example, we show our model can be used for such evaluations.

The COVID-19 pandemic probably affected measles CFRs. Reported measles incidence in most countries decreased, beginning in 2020, following lockdowns and physical-distancing measures. Reduced incidence is generally associated with reduced CFRs; however, this relationship might have been countered by important changes in other underlying drivers of case fatality, such as nutritional status[22] and health-system quality and access[23].

Limitations in data availability currently prevent reliable CFR estimation during the pandemic period. Additional data (on both the initial pandemic period and on the period afterwards, as health systems continue to rebound from long-lasting pandemic effects) will be published in the coming months and years. It will be important to monitor this evidence to assess the effects of the pandemic on health-system capacity, nutrition, and other factors related to case fatality, especially as the risk of widespread outbreaks could increase with ongoing disruptions to vaccination systems and increased numbers of susceptible people globally.

This study has several limitations. We did not include studies representing particular populations that might be especially susceptible to both measles infection and increased case fatality, such as refugees and internally displaced people; unfortunately, there are too few data on these subpopulations to accurately assess their current situation. We assumed that the CFRs presented in each study were nationally representative, which might have biased the relationship between CFR and national-level covariates. Furthermore, the included studies were heterogeneous in design and setting and, despite the inclusion of UIs, additional uncertainty owing to heterogeneity in the original data might have remained. Also, we assumed that the age distribution of people with measles in those studies that did not report age specificity followed the same relative age distribution of cases estimated nationally in that country and year during our age-splitting process.

We were constrained by the small number of studies that both reported laboratory confirmed cases and defined death attributable to measles. We therefore included all available studies in our analysis, regardless of whether they did either, to avoid compositional bias stemming from differences in study-level demographics in our estimates. Also, owing to data limitations, we were unable to estimate CFR differentially by sex or gender and race or ethnicity.

We were not able to incorporate uncertainty from our covariates and model specification. As such, our uncertainty estimates only reflect uncertainty in the CFR modelling process itself, without any additional factors. Also, for all covariates that passed our analysis checks, we included each in our modelling framework with priors to govern the direction of association estimated by the model. In this process, four covariates (mortality rate due to war and terrorism, wasting prevalence, HIV prevalence, and gross domestic product per person) no longer contributed statistically significantly to our model, so were removed. We emphasise that these covariates might still be related to measles CFR; their exclusion was a result of the underlying collinearity of our covariates that suggested little added predictive benefit to their inclusion in the final model. We developed our model for projection rather than for inference. We did not test for interactions between covariates. Also, we did not examine individual-level relationships between CFR and the covariates included in our modelling framework, but instead assessed population-level trends for use in population-level modelling, so the presented associations between covariates and CFR should not be considered causal.

Our study improved upon previous estimates of measles CFR by incorporating new data sources, systematically identifying covariates, and including improved age-specific variation. These estimates might aid in future assessments of measles mortality and vaccination programmes by decision makers at the global and country level.

5.9 Data sharing

This study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting[24]. The results of this study are supported by extracted publicly available data; for sources see Appendix D Table 4 and https://zenodo.org/record/7633577#.Y-kbkuzMIV8. Covariate sets are available from their original sources.9–12 Estimates of measles CFR by country, year, and age can be found at https://zenodo.org/ record/7633577#.Y-kbkuzMIV8, and the

R computer code can be found at https://zenodo.org/record/7633577#.Y-kbkuzMIV8.

5.10 Acknowledgments

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6. Discussion

6.1 Summary of Findings

Vaccination against measles has been available for decades[1], although still a substantial number of global cases and deaths persist[2,3]. Strategies to reach measles elimination goals require a more comprehensive understanding of the patterns of immunity and burden across locations, time, and age in local contexts throughout the world, particularly in low- and middle-income countries (LMICs). These challenges, in part, can be addressed via a thorough examination of all available data on measles immunity, cases, and deaths and synthesizing these data streams through the development of novel mathematical and statistical models.

In this thesis, I improved upon and developed a better understanding of the data available for modellers interested in estimating measles susceptibility, incidence, or mortality in LMICs by conducting a systematic review of available measles seroprevalence data and assessing associated bias[4], exploring a model framework for using subnational case notification data to understand susceptibility gaps, improving upon the knowledge base for population-level risk factors of measles case fatality[5], and constructing an updated database of available primary data on measles case fatality including specific information by age[6]. Additionally, in this thesis, I developed improved methodology for generating more robust estimates using these data, including by dimensions of age, space, and time. I leveraged subnational case notifications to explore how to estimate subnational age-specific incidence and susceptibility in Ethiopia, while discussing key considerations that modellers working with real data to try to produce such estimates may face. I additionally used information gathered in this thesis to estimate measles case fatality by age, country, and year. These contributions have larger implications for understanding measles burden which can inform targeted interventions and immunization planning efforts.

I will first give a summary of the principal findings of Chapters 2 – 5 and then provide a discussion on strengths, limitations, and possible future directions.

6.1.1 Evaluating scope and bias of population-level measles serosurveys
In Chapter 2, I conducted a systematic review of primary literature containing information on measles seroprevalence and extracted relevant indicators related to measles seroprevalence, study design, and serologic assay protocol. I then assessed bias (as low, moderate, severe, or critical) within each serosurvey across multiple categories: study selection of participants, measurement tool and classification of immunity, and reporting of results. Following classifying bias by category, I assessed the overall bias level per study and compared against first-dose measles-containing vaccine coverage (MCV1) and annual measles incidence.

I identified 221 studies containing primary data on measles seroprevalence in LMICs for inclusion and extracted relevant information from these studies. I identified data sparsity both geographically as well as temporally, which limits the utility of these data to provide a complete narrative of measles seroprevalence in a majority of LMICs. Among categories of study selection of participants and measurement tool and classification of immunity, most studies had moderate bias. In the reporting of results category, studies were more varied across bias classifications. Overall, studies from country-years with lower MCV1 coverage or higher annual measles incidence had higher bias than studies from country-years with higher MCV1 coverage or lower annual measles incidence.

6.1.2 Exploring the utility of subnational case notifications in fitting dynamic measles model in Ethiopia
In Chapter 3, I examined subnational case notifications available from Ethiopia from 2013 to 2019 among five-year age bins (e.g., 0-to-4-year-olds, 5-to-9-year-olds, etc.). I explored temporal patterns of reported suspected measles cases by first-administrative units (i.e., regions) as well as reporting consistencies between

second-administrative units (i.e., zones). I additionally investigated age patterns of reported suspected measles cases and observed many cases reported in older age groups. I used these reported cases to fit dynamic transmission models of measles with various reporting structures to explore how best to capture case ascertainment. Then, I used these subnational case data to inform estimates of subnational measles susceptibly.

I explored many different model fitting approaches and ultimately used a deterministic optimization algorithm via block coordinate descent to fit models with different reporting structures (i.e., single reporting rate and region-specific reporting rates) and conducted a sensitivity analysis across multiple vaccine effectiveness values. I also generated a bootstrapped set of posterior parameter sets and used these parameter sets to make 100 predictions of age-, zone-, and week-specific measles incidence and susceptibility from 2013 to 2019. I identified similar geographic patterns of across comparisons of susceptibility estimates from modelled outputs (i.e., from maternal immunity, infection history or successful vaccination) and unvaccinated persons.

In this chapter, I also discussed various considerations that need to be made when fitting dynamic transmission models to subnational case notification data based on their inherent biases. These include:
- accounting for sporadic temporal case reporting,
- fitting models to biased and variable case notifications despite their certainty based on statistical calculations,
- considering how best to estimate parameters that may be collinear (i.e., transmission probabilities and reporting rates),
- accounting for various reporting mechanisms and how they may contribute to under-reporting, and
- exploring implications related to assumptions on vaccine effectiveness.

Throughout the data exploration and model fitting process, I consulted with collaborators in Ethiopia, identified through the Global Burden of Disease study collaborator network, to discuss patterns of inconsistency within case notification data, underlying case reporting mechanisms, appropriateness of other input data (e.g., coverage estimates, contact and mobility patterns), and overall measles epidemiology. I will review my final results with them in coming weeks.

6.1.3 Population-level risk factors related to measles case fatality

In Chapter 4, I developed a conceptual framework of mechanisms related to measles case fatality and identified associated population-level risk factors that could be used in predictive models of measles case fatality ratios (CFR). I organized and chaired a series of sessions with a working group of experts with expertise in global measles epidemiology. The objectives of the working group were to develop a conceptual framework of factors or mechanisms related to measles CFR (i.e., health care access and care seeking behaviours, health care quality, nutritional status, risk of secondary infection, and general measles control and epidemiology) and to generate a comprehensive list of population-level indicators related to these mechanisms. Following these sessions with the working group of experts, I designed and conducted a review of primary literature to assess the level of evidence suggesting an association between measles CFR and these identified population-level indicators. I classified evidence available into one of the following categories: published literature supports a causal relationship, published literature supports an observational relationship, published literature supports a qualitative relationship, and no evidence found.

I identified evidence supporting a causal relationship between measles CFR and vitamin A treatment. I additionally identified primary literature supporting an observational relationship between measles CFR and the following indicators: average household size, educational attainment, MCV1 coverage, human immunodeficiency virus (HIV) prevalence, second-dose MCV (MCV2) coverage, stunting prevalence, surrounding conflict, travel time to major city or settlement,

travel time to nearest health care facility, under-five mortality rate, underweight prevalence, vitamin A deficiency prevalence, and general malnutrition (as a surrogate for wasting prevalence). I also observed primary literature supporting a qualitative relationship between measles CFR and level of healthcare available.

6.1.4 Estimating national-level measles case–fatality ratios in low-income and middle-income countries

In Chapter 5, I leveraged findings from Chapter 4 to identify covariate sets for indicators with an established association with measles CFR and then conducted data analyses to remove collinear and likely uninformative covariate sets. I updated a previous systematic review[7] of primary data on measles CFR to include data published through 2020 and from non-English studies. I used these updated data and covariate sets to fit a country-, year-, and age-specific Bayesian meta-regression model and used this model to predict country-specific CFRs among single-year age groups across 0-to-34-olds from 1990 to 2019 for both community- and hospital-based settings.

Investigations with the working group of experts and the literature review from Chapter 4 emphasized the necessity of exploring age variation in CFR, especially among young children who are most likely to not yet be eligible for vaccination as well as experience higher rates of case fatality. I found that CFR monotonically decreases as age increases.

6.2 Strengths and Limitations

Because each individual research chapter of this thesis contains its own specific discussion section that include strengths and limitations of each study, here I will provide a discussion on the strengths and limitations of this thesis overall.

6.2.1 Strengths

Expanding scope and depth of available data

Estimating measles morbidity and mortality burden largely relies on the results of statistical and mathematical models of measles susceptibility[8-11], transmission[12,13], and case fatality[7]. To estimate measles burden, accurate estimates of measles seroprevalence, incidence, and case fatality (in the absence of quality vital registration data) are required. However, data and estimates available for each of these are subject to substantial limitations.

This thesis was able to address multiple of these existing gaps. First, as reporting is incomplete and vaccination coverage estimates may not be perfect, seroprevalence data has the potential to be useful as a direct measure of measles susceptibility as well as possibility to quantify under-reporting of cases in transmission models. However, there was no comprehensive review of measles seroprevalence in LMICs. Not only does this thesis include a complete set of available primary serosurveys containing data on measles serostatus, but also a detailed set of data extractions including information on study design, represented population, seroassay used and protocol details, specimen type, and how titre results were classified as seropositive or seronegative and reported.

Next, as vital registration systems do not accurately capture measles deaths, estimates of measles mortality rely on estimates of CFR, which are likely to vary between countries, over time, and across age groups. To strengthen and expand the evidence available for measles CFR estimation, this thesis updated a systematic review[7] of primary literature containing information on measles CFR by including data published through 2020 and from non-English studies, as well as providing detailed age stratifications among data extractions.

Finally, as reliable estimates of CFR are a crucial requirement for current modelling strategies to accurately estimate measles mortality[14], this thesis provided additional data on age-, country-, and year-specific predictions of measles CFR from 1990 to 2019 among community- and hospital-based settings. This thesis additionally identified key and salient questions about real-world data

(i.e., subnational case notifications) that could be used in models of incidence and susceptibility and explored various approaches to account for these issues.

Explore methods to quantify heterogeneity

Quantifying heterogeneity is a critical precursor to accurate estimation of burden and for improving equity, as it provides evidence for and motivation to subsequently address disparities and inequalities between geographies, ages, or subpopulations. In this thesis, I explored how in models of subnational measles susceptibility we can best capture heterogeneity by subnational location and age from information provided from subnational vaccination coverage estimates and subnational case notifications. Planning targeted interventions[15], such as vaccination campaigns, requires understanding of subnational measles susceptibility. As vaccine coverage estimates provide an incomplete picture of susceptibility and there is a lack of representative serosurveys, case notification data are critical inputs for methods to estimate subnational measles susceptibility in endemic settings. These case notifications, however, are obtained through passive surveillance and as such are often under-reported.

While these data have limitations, they are, and will likely continue to be, the primary data source to understand subnational patterns of transmission on a short- to medium-term basis. Therefore, it is important to explore innovative models and approaches to extract as much useful information from them as possible in attempt to quantify spatial and age-specific heterogeneity. In this thesis, I built a high-dimensional, subnational transmission model accounting for age-specific contact patterns and person mobility and tested various methods of model fitting (e.g., Markov chain Monte Carlo and maximum likelihood estimation) and reporting structures (i.e., single reporting and regional reporting) in order to leverage these case notification data. Models that fit to these kinds of data should consider the underlying data generating processes (i.e., reporting mechanisms) and related inherent biases (i.e., case ascertainment, sporadic reporting).

Additionally, in this thesis, I explored and applied methods to estimate measles CFR not only by year, region, or country, but among an additional dimension of age. Understanding age patterns of measles CFR is essential for estimating age-specific measles mortality burden. Among infants and young children, there is an increased risk of acquiring measles infection as maternal antibodies wane prior to eligibility for vaccination[16]. I identified age-stratified data on measles CFR and explored methods for fitting models to these age-specific data. I implemented a meta-regression model that included a spline covariate for age[17], which allowed for data to be included in fitting from a varying range of age bins. This spline feature allows for then any specified age range to be predicted from the model also, further expanding our knowledge on the heterogeneity of measles CFR by age in various country- and year-specific settings.

Providing evidence to strengthen immunization systems

Policy makers rely on robust evidence to guide decisions and make progress towards strengthening immunization systems and vaccination programmes. This thesis provides overall support and evidence for decision makers across various aspects of immunization programmes and planning. While investigating the bias and availability of measles seroprevalence data in LMICs, I have provided evidence for where additional serosurvey collection efforts would be useful. Additionally, I have outlined a tool for decision makers interpreting serosurveys, to inform routine or supplemental immunization programming and to use when assessing biases among seroprevalence metrics. I identified salient issues and considerations for measles modelling in Ethiopia that might be relevant across other LMICs and settings, including key areas of data quality weakness, the importance of understanding subnational patterns of case ascertainment, and the potential role that additional serosurveys might have in informing susceptibility patterns. I will continue to engage with stakeholders from Ethiopia to share findings and determine how results might be applicable while forming local policy. Additionally, improved estimates of measles CFR stemming from this thesis provide critical inputs for estimating measles mortality[2] and subsequent

impact of vaccination programmes on averting measles deaths, which also can be used to inform immunization system planning.

Transparent data and code

Transparent research is critical for sustainable and rigorous scientific research. Data collected and generated in this thesis as well as computer code are publicly available online. For Chapter 2, seroprevalence data by geography, age and vaccination status where available extracted per study during the measles seroprevalence systematic review is publicly available on GitHub along with the bias assessment overall and across assessed categories per serosurvey. For Chapter 3, computer code for data processing, modelling and diagnostics are also publicly available on GitHub. For Chapter 4, data extracted from the literature review of population-level factors related to measles CFR are publicly available. For Chapter 5, data from the updated systematic review of primary sources with data on measles CFR, all computer code, and model generated age-, location-, and year-specific predictions are available on Zenodo. The open availability of the code and data extractions adds value by allowing researchers to use these data for additional investigations and to adapt code for future analyses and models, as well as promoting collaboration and transparency among the larger scientific community.

6.2.2 Limitations

Implications of data-related limitations on model fitting

All models are simplifications of complex real-world scenarios and require use of both assumptions as well as input data. These input data often have associated limitations and biases, which was true for all data used in models included in this thesis. In Chapter 3, I used over 260,000 observations of reported suspected measles cases from 9 age groups, 79 second-administrative units (i.e., zones) and over 370 weeks. Feedback from stakeholders in Ethiopia, as well as findings from exploratory analyses of the data (e.g., temporal fluctuations in reporting, inconsistencies between reported cases and coverage), suggest variable reporting

and low ascertainment rates. Additionally, these subnational case data, when aggregated nationally, do not match national case notifications. Incorporating the sheer quantity of data observations available for this model presents additional challenges. When these data are incorporated into a maximum likelihood estimation framework, under usual statistical distribution assumptions (e.g., Poisson, negative binomial, or others), the data imply a high degree of certainty about true patterns of transmission, and do not account for what is likely to be a substantial amount of unmeasured uncertainty inherent in the reporting process. I aimed to address this through smoothing the reported case data and developing techniques for accounting for case ascertainment. However, new innovations are needed, such as those by Jewell *et al*[18], to incorporate more robustly the difficult-to-quantify uncertainty from large, granular yet noisy surveillance data like these.

The data I used in Chapter 5 to estimate age-, country-, and year-specific measles CFRs also present limitations. First, data contained within the published literature likely are subject to publication bias, such that CFRs in locations in the published literature may be systematically different than those in locations without published data. This is because those sites may have more resources and personnel to allow for publication, serve different populations, or capture more severe measles cases.

Additionally, most of the primary literature on measles case fatality did not provide indication on lab-confirmation of cases nor a specific definition of which deaths were classified as attributable to measles. Laboratory confirmation of suspected measles cases requires resources and skilled lab personnel. Locations with passive surveillance, where measles is endemic, often do not lab-confirm most measles cases. However, locations approaching measles elimination are required to meet specific criteria related to showing high performing surveillance systems. Therefore, in countries or regions approaching elimination, many more cases may be lab-confirmed compared to measles cases for countries not yet close to elimination targets.

Also, defining a measles "death" can be challenging. Measles is often a contributory cause in a sequence of events that can lead to death, and frequently children with co-infections (e.g., diarrhoea, pneumonia) are at risk for the most severe outcomes. Disentangling cause of death from multiple infections or complications is often not possible. Additionally, measles can additionally present long-term sequalae (e.g., SSPE, immunosuppression) that are not traditionally considered in estimates of acute measles mortality. However, among studies that do not specifically define what is considered an acute death, it is not possible to determine if all deaths are occurring within 28 days of measles infection.

Without knowing whether true measles cases were captured in the underlying data, I may have under-estimated CFR. On the other hand, without knowing if the deaths included in numerators of CFR were true acute measles deaths occurring within approximately 28 days of measles onset or also were true measles cases in the denominator, I might have over-estimated CFR. As such, models are only as accurate and robust as the data they are able to leverage.

Burden estimation among vulnerable communities
There are specific subpopulations that likely experience enhanced vulnerability to measles morbidity and mortality. Those communities include refugees and internally displaced persons (IDPs)[19,20], those living in conflict-affected areas, persons living with HIV[21], and other immunocompromised persons[21]. Largely, I was unable to improve upon the representativeness of these subpopulations while addressing gaps and challenges in measles burden estimation in this thesis. While in Chapter 2 I extracted all available information on measles seroprevalence including among immunocompromised subpopulations, such as persons living with HIV, largely these data do not exist for other subgroups, especially among refugees and IDPs.

Understanding measles burden in these communities is critical, as low MCV coverage is frequently documented in refugee camps and temporary settlements[20,22]. However, estimating measles morbidity and mortality in these higher-risk subpopulations is challenging and comes with its own set of biases and limitations, as there is often not an understanding of the distribution of measles incidence by subpopulation. While this is a critical area for future work and investigation, this thesis is limited in its representativeness of these vulnerable communities.

Measles and COVID-19

The COVID-19 pandemic caused widescale disruptions to measles immunization programmes globally[23,24]. Beyond impacts to vaccination systems, there were other disruptions observed in health system delivery and capacity[25], malnutrition prevalence[26], and many other factors possibly contributing to both short- and long-term impacts on overall measles morbidity and mortality. Measles incidence decreased substantially during initial pandemic-era years[2], which is likely attributable to reduced transmission due to non-pharmaceutical interventions (e.g., social distancing, lockdowns). However, considering wide-scale immunization system disruptions and an increased build of susceptible persons from reduced transmission, it will be imperative to revisit analyses contained in this thesis once more data are available to assess measles seroprevalence, national and subnational susceptibility, and case fatality. The analyses in this thesis, though, are limited to the current scope of available data to describe the pandemic-period, which are either very limited or not yet available. For example, any available data published[27,28] on measles case fatality that describe measles cases and associated deaths after the start of 2020 do not explicitly quantify the impact of the pandemic on measles CFR and were limited to specific country contexts and settings.

Additionally, I ended my exploration of subnational case notifications and susceptibility in Ethiopia in 2019. This was due to data limitations from the pandemic period and additional challenges related to capturing complex dynamics

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in the country unrelated to the pandemic, which were outside the scope of my objective (i.e., considering the utility of subnational case data in model fitting), such as conflict and famine. Therefore, I did not explore how to incorporate pandemic-related effects, including from NPIs, into input data (e.g., contact patterns) or methods (e.g., temporal changes in reporting systems following the pandemic).

6.3 Reflection on funding sources

I received funding for work contained within this thesis from the US National Institutes of Health, as well as from both Gavi, the Vaccine Alliance (hereafter Gavi) and the Bill & Melinda Gates Foundation (hereafter BMGF). This thesis, particularly in Chapter 1, provide insight and commentary on the work and contributions of both organizations.

Despite these improvements to vaccine and health services access afforded by these organizations detailed in Chapter 1, it should be noted that both Gavi and BMGF have been subject to critique. For example, Gavi relies on market-pricing agreements that are inaccessible to countries once they are no longer receiving Gavi-support which could make vaccines unaffordable for these countries[29]. Gavi and has also been criticised for an overall lack of accountability and transparency in overall funding and decision-making processes[30,31]. Additionally, BMGF has also been critiqued for contributing to colonialism in the global health field by setting agendas for LMICs[32-34].

Readers of this work should consider the funding sources that supported it, including the accomplishments and critiques of these organisations, in order to fully contextualise and interpret the results and discussion presented here.

6.4 Implications and future work

The research I presented in this thesis has the following four main implications:

Chapter 2 highlights locations for which few or low quality historical serosurveys have been conducted across LMICs and identifies key considerations for the conduct and reporting high quality serosurveys. These results can be used to support the development of new, targeted serosurveys to better understand immunity patterns in places where a more detailed contemporary understanding of residual measles susceptibility is needed.

Chapters 3 and 5 underscore the limitations and biases of current measles incidence and mortality surveillance systems and their resulting implications for understanding measles burden and susceptibility. While results in these chapters highlight methods that can be used to partially address these limitations, there is no substitute for robust surveillance programmes.

Chapter 3 advances methodologic innovation for subnational, age-specific susceptibility estimation by directly testing various modelling approaches to account for case ascertainment. Methodologic considerations discussed in this chapter can and should be used by other researchers using case notification data to estimate subnational measles transmission and susceptibility.

Chapters 4 and 5 provide the ability to capture heterogeneity in measles CFR estimates more precisely by identifying and incorporating associated population-level covariates during modelling as well as developing methods for accurately capturing age-variation. These results can be used to support measles mortality burden estimation and evaluation of vaccination programmes.

This thesis overall also has identified several areas for future work for measles and infectious disease modelling. First, many data repositories that could be used across areas of measles burden estimation were updated as part of this thesis, including systematic reviews of primary literature containing information on measles seroprevalence and CFR. In order for these resources to remain relevant in future years for modellers and researchers, these data repositories should be

updated with the latest information available, especially if considering estimating the impact of the COVID-19 pandemic on measles burden.

In settings with poor quality data, subnational and age-specific susceptibility gaps still need to be identified. Beyond additional data collection or surveillance system strengthening efforts, innovative modelling approaches that build upon this work can and should be identified and explored to overcome these limitations. These could include:

- estimating susceptibility by age cohorts over time through integrating and extrapolating results from seroprevalence metrics collected by serosurveys;
- exploring how to extract and use temporal, age, or spatial patterns from case notifications to fit transmission models, along with coverage and seroprevalence metrics, rather than the absolute values of cases; and
- developing meaningful and transferable risk assessment frameworks across measles endemic locations that do not require complete quantification of susceptibility or replication of underlying dynamics.

If simpler models identified through additional explorations were able to fit efficiently to the available vaccine coverage, serology, or case notification data to predict similar subnational units and age groups to prioritize for targeted interventions compared to findings in Chapter 3, there may be little additional benefit from fitting more complex and computationally expensive models. Streamlining and simplifying methods, when and as appropriate, would allow for ease in interpretation and communication when translating results for policy to decision makers.

Finally, the methods used for transparently and systematically identifying population-level factors related to measles CFR and developing a framework to estimate variation in CFR by location, time, and age should be adapted for other infectious diseases. Many vaccine-preventable disease related deaths, such as for

typhoid, pertussis and tetanus, lack complete surveillance via vital registration systems and could benefit from more rigorous methods to estimate CFRs by country, age, and year to inform estimates of mortality burden.

6.5 Concluding Remarks

This thesis addressed data and methodologic gaps related to measles burden and susceptibility estimation, particularly in LMICs. Despite ongoing challenges in measles surveillance systems, this thesis underscores the potential of innovative modelling and data-based efforts to enhance understanding and guide informed vaccination policy decisions.

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Appendix A. Supplementary Information for Chapter 2

Section 1. Tables
Table 1. PRISMA abstract checklist.

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	N/A
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Declarations of Interest
Registration	12	Provide the register name and registration number.	This review was not registered.

Table 2. PRISMA checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Appendix A Table 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods (Systematic Review subsection)
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods (Systematic Review subsection)
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods (Systematic Review subsection)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods (Systematic Review subsection)
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods (Systematic Review subsection); Contributions
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods (Systematic Review subsection)
	10b	List and define all other variables for which data	Methods

Section and Topic	Item #	Checklist item	Location where item is reported
		were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	(Systematic Review subsection)
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Contributions
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Results
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Results
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Results
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A, no sensitivity analyses were conducted
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods (Bias Assessment subsection)
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods (Bias Assessment subsection)
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results; Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why	N/A; no studies met

Section and Topic	Item #	Checklist item	Location where item is reported
		they were excluded.	this criteria
Study characteristics	17	Cite each included study and present its characteristics.	Results (see link to Zenodo file)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results, also see link to Zenodo file
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A, no sensitivity analyses were conducted
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Abstract, Methods
	24b	Indicate where the review protocol can be accessed,	Methods, see

Section and Topic	Item #	Checklist item	Location where item is reported
		or state that a protocol was not prepared.	PROSPERO registration for protocol
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Declarations of Interest; Contributions
Competing interests	26	Declare any competing interests of review authors.	Declarations of Interest
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Results

Section 2. Figures

Figure 1. Bias of selection of study participants flowchart.
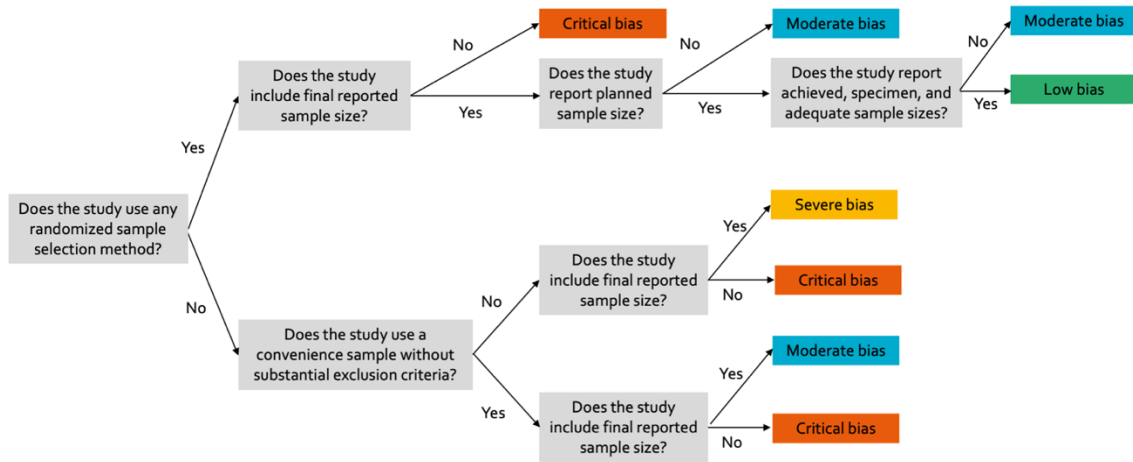
Figure 2. Bias of measurement tool and classification of immunity flowchart.
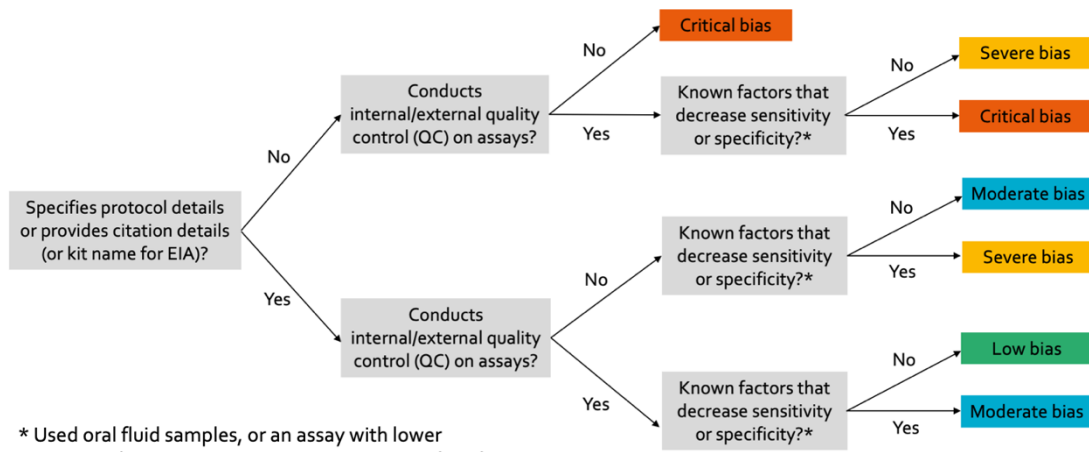
Figure 3. Bias of reporting of results flowchart.
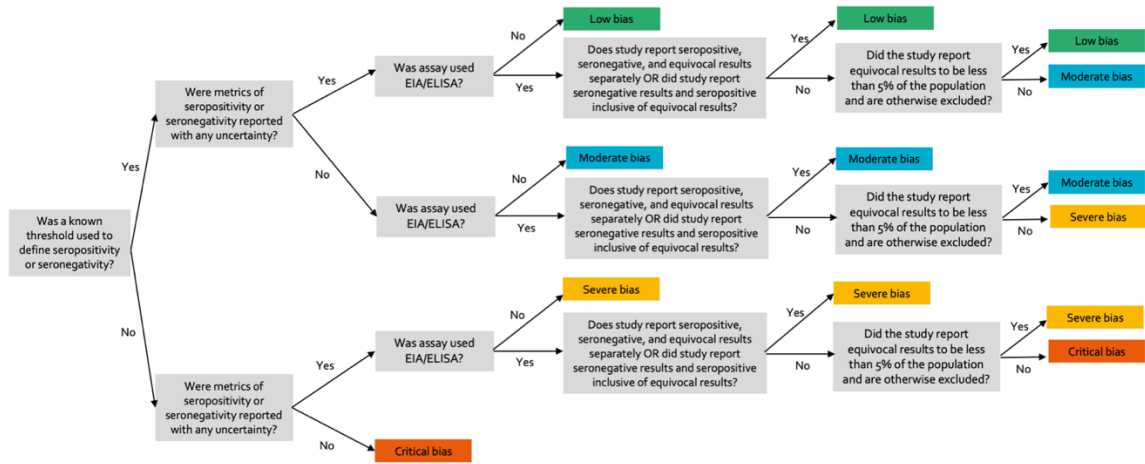
Appendix B. Supplementary Information for Chapter 3

Section 1. First- and second-dose coverage of measles-containing vaccines

Routine immunization

Estimates of routine first-dose measles containing vaccine (MCV1) coverage were obtained using methods similar to those described previously[1]. These models leverage household-based survey data, a suite of geospatial covariates, and model-based geostatistical techniques to predict coverage at the 5-x-5 km level. Updated estimates include age-specificity via a space-time-age error term and an age-specific Gaussian process using the following equations:

$$C_{s,t,a} \sim \text{Binomial}\left(N_{s,t,a}, p_{s,t,a}\right)$$

$$\text{logit}\left(p_{s,t,a}\right) = \beta_0 + \boldsymbol{\beta_1} \boldsymbol{X_{s,t}} + \epsilon_{GP_{s,t,a}} + \epsilon_{ctry_{[s]}} + \epsilon_{s,t,a} + \epsilon_{GP_a}$$

, where p is coverage among 5-x-5-km pixel s, year t from 2000 to 2019, and age-group a (i.e., 9-11 months, 1 year, 2 years, 3 years, and 4 years). $\boldsymbol{X_{s,t}}$ are the predicted surfaces from generalized additive models, Lasso, and boosted regression tree models. $\epsilon_{GP_{s,t,a}}$ is a correlated space-time-age error term, where the spatial covariance modeled using a Matérn function, temporal covariance modeled as an autoregressive process of order 1 and the age group covariance is also modeled as an autoregressive process of order 1. $\epsilon_{ctry_{[s]}}$ is a country-level random effect, $\epsilon_{s,t,a}$ is a nugget effect to represent observation-specific irreducible error, and ϵ_{GP_a} is a correlated age-only error term. 5-x-5 km level estimates are aggregated to the second administrative units using population-weighted averages across administrative boundaries. Models are fit using Template Model Builder in R version 5.4.0.

Estimates of second-dose measles containing vaccine (MCV2) coverage were obtained by using hierarchical models at the second-administrative level. MCV2

coverage is completely correlated with MCV1 coverage as persons cannot receive a second dose of measles prior to receipt of a first dose. These models to estimate MCV2 coverage leverage global, regional, and country priors on parameter values to fit second-administrative unit trends in MCV2 coverage across time using the following equations:

$$C_{t,g} \sim Binomial(N_{t,g}, p_{t,g})$$
$$logit(p_{t,g}) = \beta_{0,g} + \boldsymbol{\beta}_{1,g}\boldsymbol{X}_t + \boldsymbol{\beta}_{2,g} * Spline(t)$$
$$C_{t,c} \sim Binomial(N_{t,c}, p_{t,c})$$
$$logit(p_{t,c}) = \beta_{0,c} + \boldsymbol{\beta}_{1,c}\boldsymbol{X}_t + \boldsymbol{\beta}_{2,c} * Spline(t)$$
$$\boldsymbol{\beta}_{(x),c} \sim N(\boldsymbol{\beta}_{(x),g}, (\sigma * \theta)^2)$$
$$C_{t,a1} \sim Binomial(N_{t,a1}, p_{t,a1})$$
$$logit(p_{t,a1}) = \beta_{0,a1} + \boldsymbol{\beta}_{1,a1}\boldsymbol{X}_t + \boldsymbol{\beta}_{2,a1} * Spline(t)$$
$$\boldsymbol{\beta}_{(x),a1} \sim N(\boldsymbol{\beta}_{(x),a1}, (\sigma * \theta)^2)$$

, where p is coverage across time t at various geographic levels (i.e., global (g), country-specific (c), or first-administrative unit-specific ($a1$). $\boldsymbol{\beta}$ values are normally-distributed priors informed by parameters in either previous global or country-specific hierarchical fits. θ was an additional parameter used to increase or reduce the influence of the priors on modelled estimates. θ in the country-specific models was 30 and was 3 in the first-administrative unit level models. Models were fit using a Bayesian meta-regression in R version 5.4.0. Model predictions were made at the second-administrative unit level following fitted values at the first-administrative unit level.

Supplementary immunization activities
Estimates of routine immunization (RI) coverage do not include doses administered via campaigns or supplemental immunization activities (SIAs). In order to also account for doses administered through SIAs, we developed a cohort model that estimates "RI + SIA" coverage for MCV1 and MCV2 by age, space

and time from 1980 to 2019. This model leverages RI coverage estimates, the number of doses reported to be administered through the SIA[2], and the relative risk of being vaccinated during a campaign given previous vaccination status. We compute the relative risk or risk ratio (RR) via a meta-analysis of data from children with vaccine cards with parents interviewed during household-based surveys or post-campaign coverage surveys asking information about campaign participation, with similar results to those previously shown[3]. We used a RR value of 1.44 derived from our meta-analysis. Then, we compute a metric of "campaign-efficiency", p, which is computed at the most geographically granular resolution possible such that:

$$p = \frac{\# \ of \ doses \ administered}{(RR * \# \ previously \ vaccinated) + \# \ previously \ unvaccinated}$$

Then, we compute RI + SIA coverage by week, age, and second-administrative unit such that:

$$RI + SIA \ coverage =$$

$$\frac{((\# \ previously \ vaccinated) + p * (\# \ previously \ unvaccinated))}{total \ pop}$$

The cohorting model is run for each subnational unit through 2019 while also accounting for demographic changes (i.e., aging, births, mortality, and migration) using similar inputs to those described for our transmission model (e.g., population surfaces from WorldPop[4] calibrated to the Global Burden of Disease study[5]).

Section 2. Tables

Table 1a. Testing various starting values for model with regional reporting including fitting vaccine effectiveness. Starting states yielded inconsistent identified parameters.

	Starting value 1		Starting value 2		Starting value 3		Starting value 4	
	Start	End	Start	End	Start	End	Start	End
β_{max}	0.7	0.51	0.6	0.57	0.9	0.59	0.51	0.50
β_{min}	0.6	0.43	0.5	0.39	0.8	0.56	0.43	0.42
$logit(\rho_{Addis\ Abeba})$	-3	-5.80	-5	-4.36	-4	-4.70	-5.8	-4.26
$logit(\rho_{Afar})$	-3	-5.26	-5	-5.28	-4	-5.58	-5.3	-5.32
$logit(\rho_{Amhara})$	-3	-5.02	-5	-4.84	-4	-5.07	-5	-4.81
$logit(\rho_{Benshangul-Gumaz})$	-3	-4.26	-5	-5.63	-4	-5.74	-4.3	-5.47
$logit(\rho_{Dire\ Dawa})$	-3	-3.03	-5	-5.91	-4	-6.05	-3	-5.66
$logit(\rho_{Gambela\ Peoples})$	-3	-3.13	-5	-3.15	-4	-3.47	-3.1	-3.19
$logit(\rho_{Harari\ People})$	-3	-3.98	-5	-6.8	-4	-6.01	-4	-5.72
$logit(\rho_{Oromia})$	-3	-4.62	-5	-4.45	-4	-4.68	-4.6	-4.51
$logit(\rho_{Somali})$	-3	-4.99	-5	-5.00	-4	-5.30	-5	-4.98
$logit(\rho_{SNNP})$	-3	-5.00	-5	-5.12	-4	-5.39	-5	-5.10

$logit(\rho_{Tigray})$	-3	-5.57	-5	-5.67	-4	-6.20	-5.6	-5.73
$logit(vaccine\ effectiveness)$	0.5	0.63	0.8	0.53	0.6	0.00	0.6	0.62

Table 1b. Testing various starting values for model with regional reporting without fitting vaccine effectiveness with inconsistent results still observed.

	Starting value 1		Starting value 2		Starting value 3		Starting value 4	
	Start	End	Start	End	Start	End	Start	End
β_{max}	0.7	0.65	0.6	0.81	0.9	0.81	0.51	0.51
β_{min}	0.6	0.5	0.5	0.74	0.8	0.74	0.43	0.34
$logit(\rho_{Addis\ Abeba})$	-3	-4.42	-5	-4.49	-4	-4.49	-5.8	-3.77
$logit(\rho_{Afar})$	-3	-5.43	-5	-5.58	-4	-5.58	-5.3	-5.26
$logit(\rho_{Amhara})$	-3	-4.83	-5	-4.86	-4	-4.86	-5	-4.68
$logit(\rho_{Benshangul-Gumaz})$	-3	-5.58	-5	-5.57	-4	-5.57	-4.3	-4.75
$logit(\rho_{Dire\ Dawa})$	-3	-5.86	-5	-5.97	-4	-5.97	-3	-3.48
$logit(\rho_{Gambela\ Peoples})$	-3	-3.34	-5	-3.47	-4	-3.47	-3.1	-2.71
$logit(\rho_{Harari\ People})$	-3	-5.90	-5	-6.01	-4	-6.02	-4	-5.35
$logit(\rho_{Oromia})$	-3	-4.48	-5	-4.61	-4	-4.61	-4.6	-4.74
$logit(\rho_{Somali})$	-3	-5.11	-5	-5.33	-4	-5.33	-5	-5.13
$logit(\rho_{SNNP})$	-3	-5.21	-5	-5.31	-4	-5.31	-5	-4.85
$logit(\rho_{Tigray})$	-3	-5.95	-5	-6.09	-4	-6.09	-5.6	-5.32

Table 2. Models with single reporting rates, with different vaccine effectiveness values with 95% uncertainty interval from bootstrapped samples.

Vaccine effectiveness	47%	70%	82%	88%
LL	-24260.2 (-24617.4, -23693.4)	-27538.6 (-28058.0, -26884.6)	-48654.4 (-53637.5, -36397.1)	-48555.4 (-53289.0, -44474.3)
β_{max}	0.135 (0.133, 0.138)	0.224 (0.219, 0.247)	0.597 (0.277, 0.712)	0.632 (0.400, 0.830)
β_{min}	0.102 (0.102, 0.103)	0.138 (0.135, 0.146)	0.066 (0.010, 0.256)	0.219 (0.073, 0.368)
ρ	0.007 (0.007, 0.008)	0.054 (0.037, 0.058)	1 (1, 1)	1 (1, 1)

Table 3. Models with regional reporting rates, with different vaccine effectiveness values with 95% uncertainty interval from bootstrapped samples.

Vaccine effectiveness	47%	70%	82%	88%
Log-likelihood	-23865.3 (-24249.8, -23373.5)	-26218.7 (-26793.5, -25739.2)	-48416.0 (-53724.5, -36172.8)	-49346.6 (-53712.6, -45012.9)
β_{max}	0.1349 (0.1336, 0.1374)	0.2198 (0.2176, 0.2250)	0.5966 (0.2773, 0.7123)	0.7116 (0.3990, 0.8332)
β_{min}	0.1021 (0.1019, 0.1024)	0.1385 (0.1366, 0.1400)	0.0671 (0.0101, 0.2559)	0.1559 (0.0673, 0.3725)
$\rho_{Addis\ Abeba}$	0.0132 (0.0123, 0.0144)	0.3881 (0.3363, 0.4493)	1 (1, 1)	1 (1, 1)
ρ_{Afar}	0.0045 (0.0041, 0.0049)	0.0303 (0.0242, 0.0368)	1 (1, 1)	1 (1, 1)
ρ_{Amhara}	0.0069 (0.0065, 0.0072)	0.1284 (0.1170, 0.1377)	1 (1, 1)	1 (1, 1)
$\rho_{Benshangul-Gumaz}$	0.0055 (0.0051, 0.0060)	0.0484 (0.0411, 0.0538)	1 (1, 1)	1 (1, 1)
$\rho_{Dire\ Dawa}$	0.0042 (0.0036, 0.0046)	0.1238 (0.0996, 0.1546)	1 (1, 1)	1 (1, 1)
$\rho_{Gambela\ Peoples}$	0.0293 (0.0253, 0.0335)	0.4827 (0.4010, 0.5626)	1 (1, 1)	1 (1, 1)

$\rho_{Harari\ People}$	0.0045 (0.0039, 0.0052)	0.0315 (0.0225, 0.0431)	1 (1, 1)	1 (1, 1)
ρ_{Oromia}	0.0087 (0.0083, 0.0092)	0.0432 (0.0404, 0.0458)	1 (1, 1)	1 (1, 1)
ρ_{Somali}	0.0065 (0.0060, 0.0070)	0.0381 (0.0341, 0.0415)	1 (1, 1)	1 (1, 1)
ρ_{SNNP}	0.0063 (0.0060, 0.0066)	0.0639 (0.0588, 0.0694)	1 (1, 1)	1 (1, 1)
ρ_{Tigray}	0.0026 (0.0024, 0.0027)	0.0818 (0.0742, 0.0911)	1 (1, 1)	1 (1, 1)

Section 3. Figures

Figure 1. Transmission modelling functional block diagram.
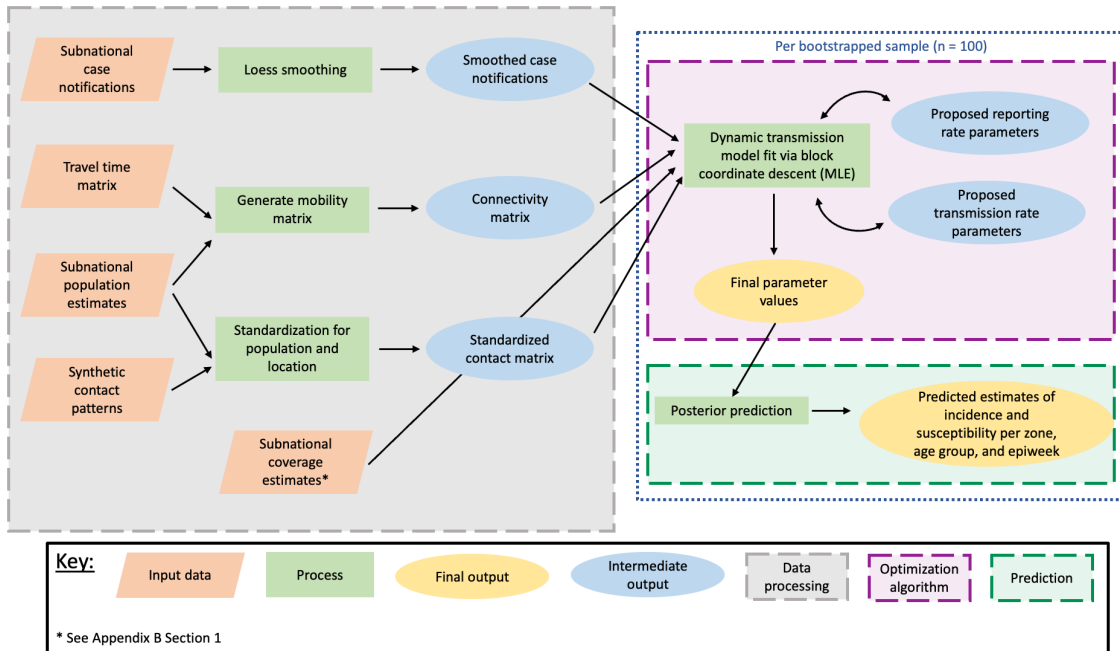
Figure 2. Transmission modelling flowchart.

Compartmental flowchart of transmission model. M represents the maternally immune class, S represents the susceptible class, I the infected class, and R the recovered class. Solid lines represent transitions following infection, small dashed lines represent transitions following loss of maternal immunity, and large dashed lines represent transitions following either successful or unsuccessful vaccination events. Unvax compartments are with unvaccinated persons, vax1 vaccinated with 1 dose of MCV, and vax2 with 2 or more doses.
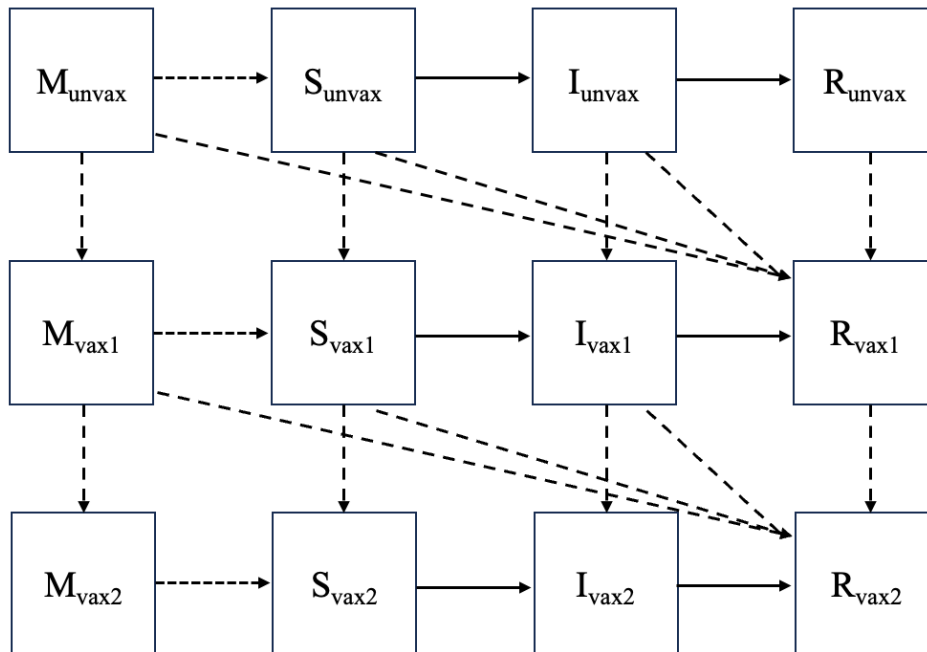
Figure 3. Model fit (blue) compared to aggregated quarterly measles cases (pink) in Bale, Ethiopia among 0-to-4-month-olds by quarters.

Models suggested poor fit as misaligned aggregated peaks yielded large penalties to likelihood during evaluations.
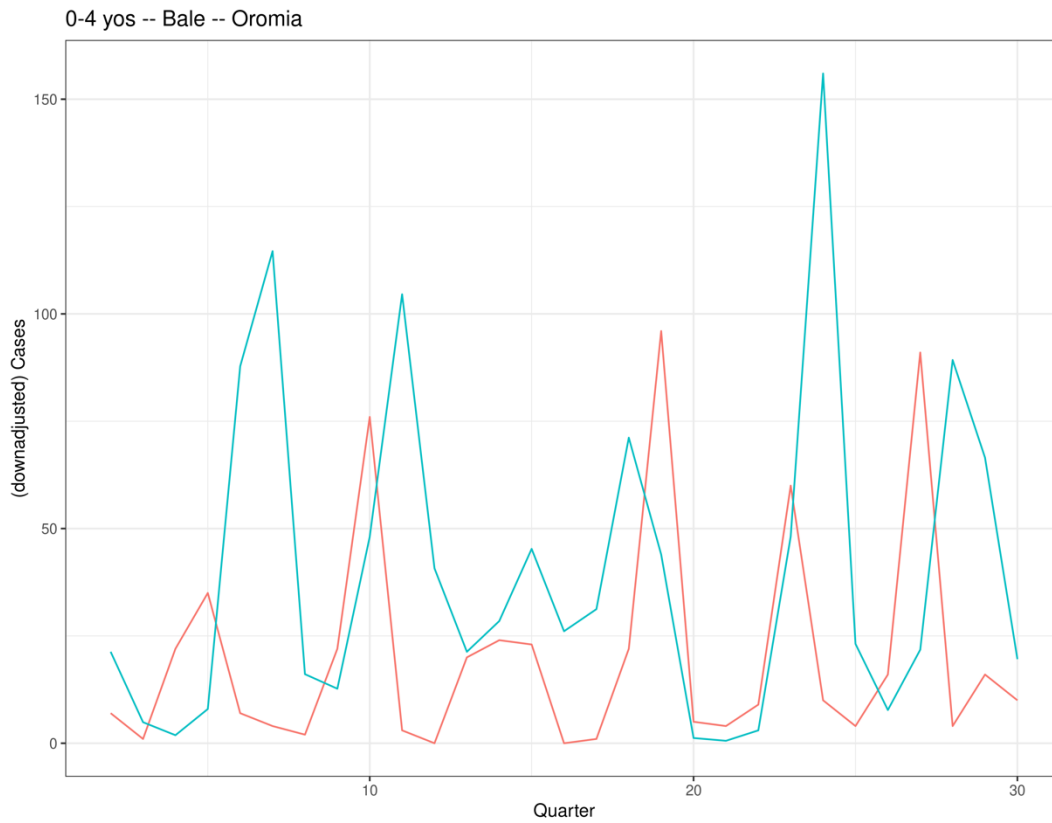
Figure 4. National-level proportion of the population in each compartment by age group in model with assumed 93% vaccine efficacy.

Models with assumed 93% vaccine efficacy, without any other assumptions or information on vaccine effectiveness, yielded little to no transmission in later years as seen in the bottom left panel of the Infected compartment.
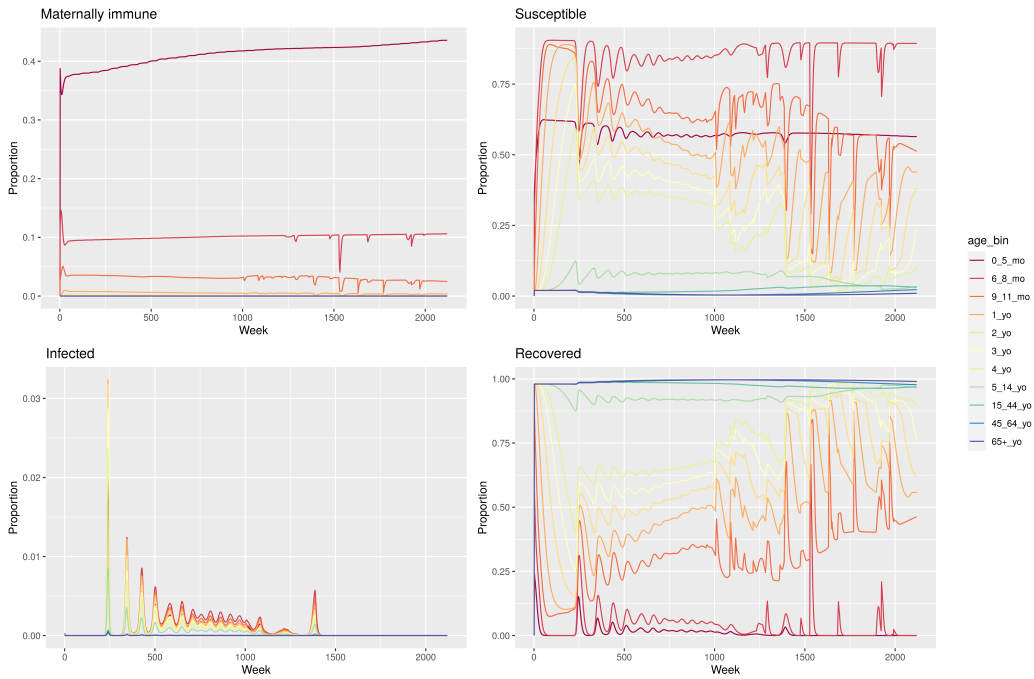
Figure 5. Trace plots from MCMC model using parallel tempering.
Trace plots of over 12000 samples accepted less than 1% of proposed samples, in lowest temperature chain of parallel tempering.
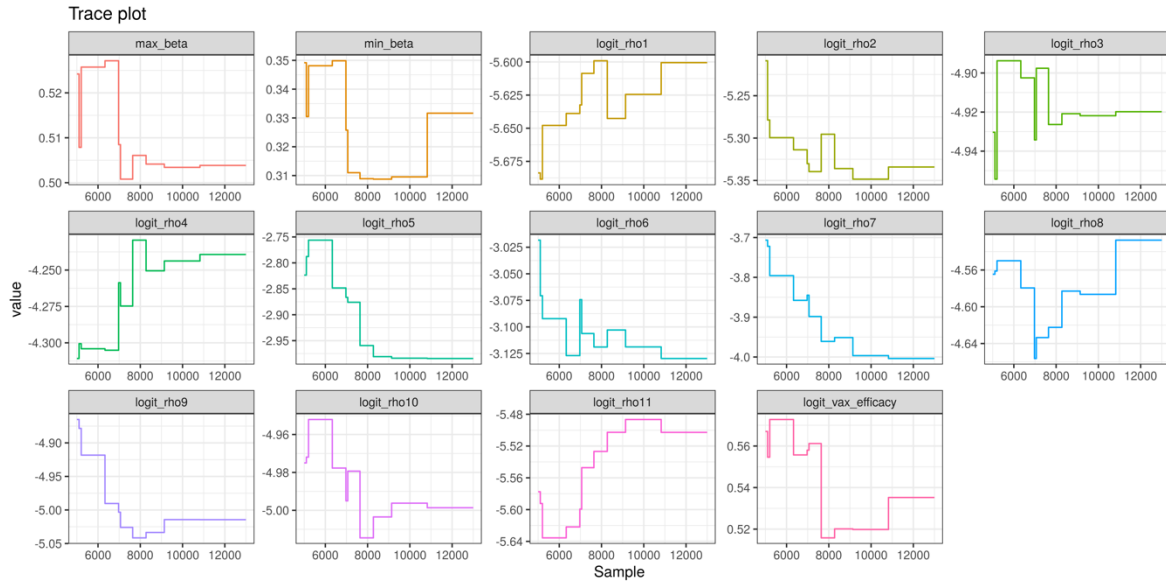
Figure 6. R_0 value by transmission probability parameters (β).

R_0 values were computed via a next-generation matrix approach
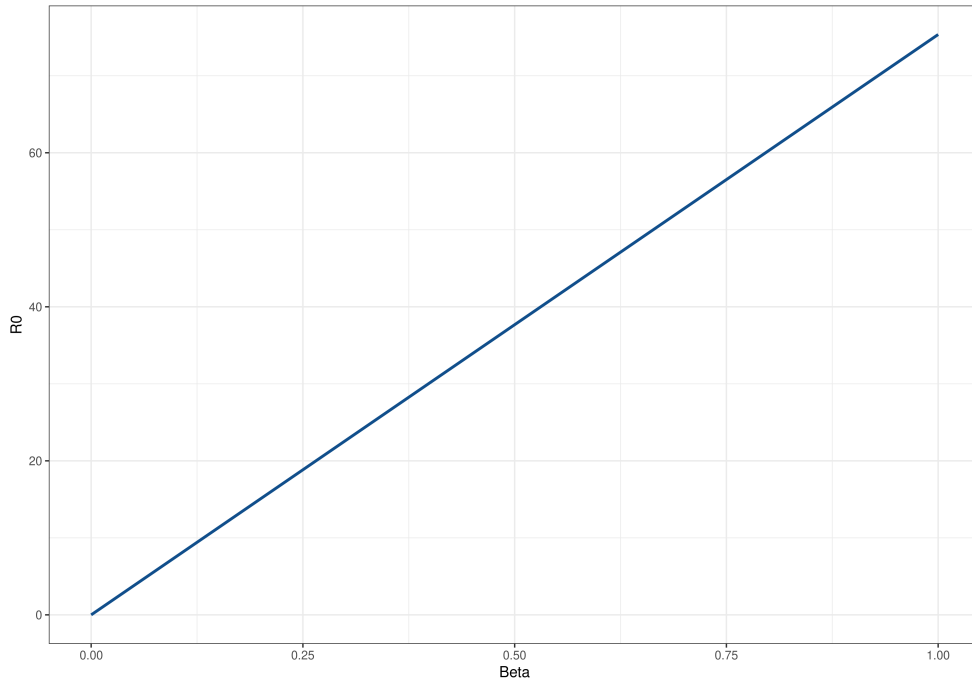
Figure 7. Block coordinate descent iterations for each parameter from model selected with best fit. Each line represents one bootstrapped sample (n = 100 per parameter).
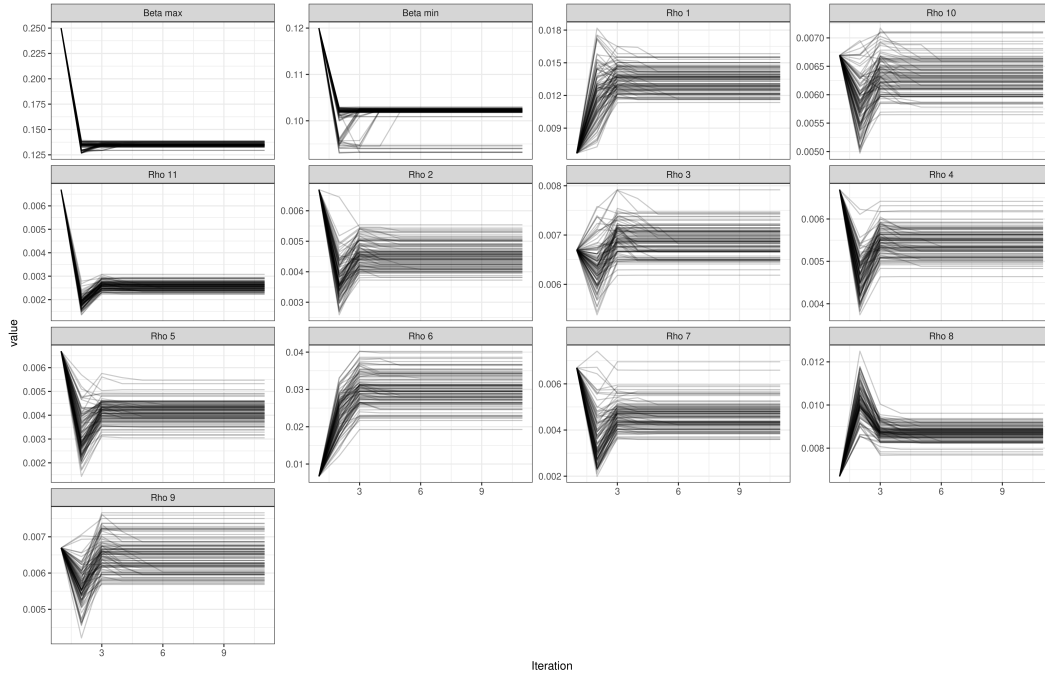
Figure 8. Proportion susceptible in each zone in 2019 across 0-to-4-year olds from best model fit with 47% vaccine effectiveness and sensitivity analysis model fit with 70% vaccine effectiveness.
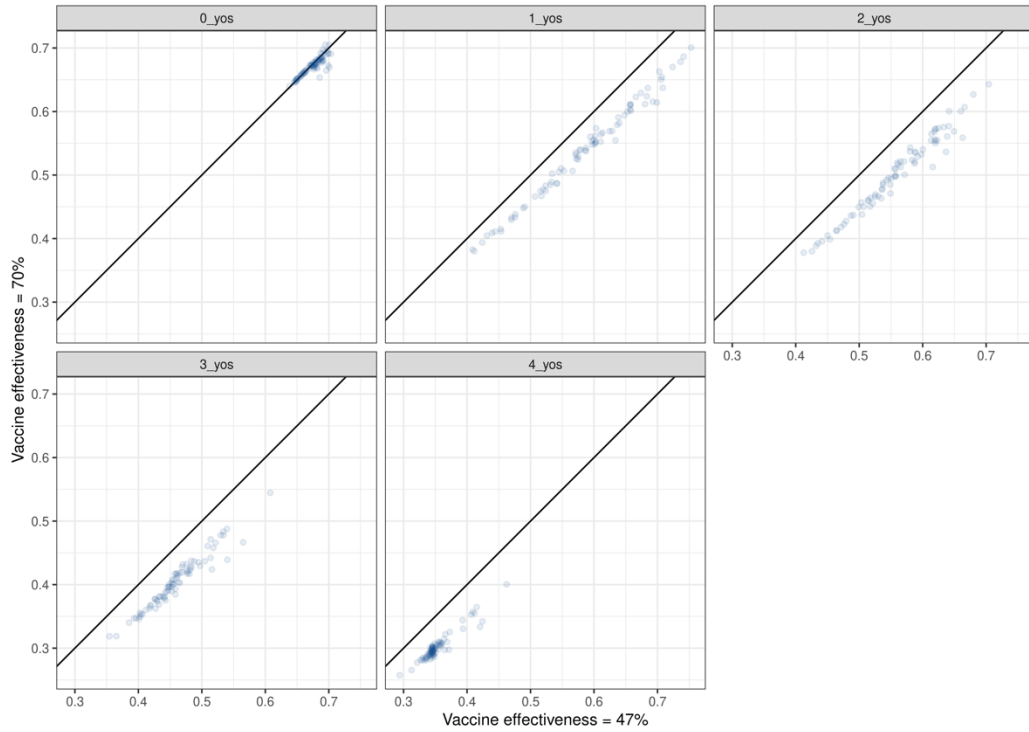
Figure 9. Smoothed reported suspected measles incidence among 0-to-4-year-olds (light blue) compared to estimated incidence adjusted for reporting (black) from best model fit.

Figure 10. Smoothed reported suspected measles incidence among 5-to-9-year-olds (green) compared to estimated incidence adjusted for reporting (black) from best model fit.

Figure 11. Smoothed reported suspected measles incidence among 10-to-14-year-olds (orange) compared to estimated incidence adjusted for reporting (black) from best model fit.
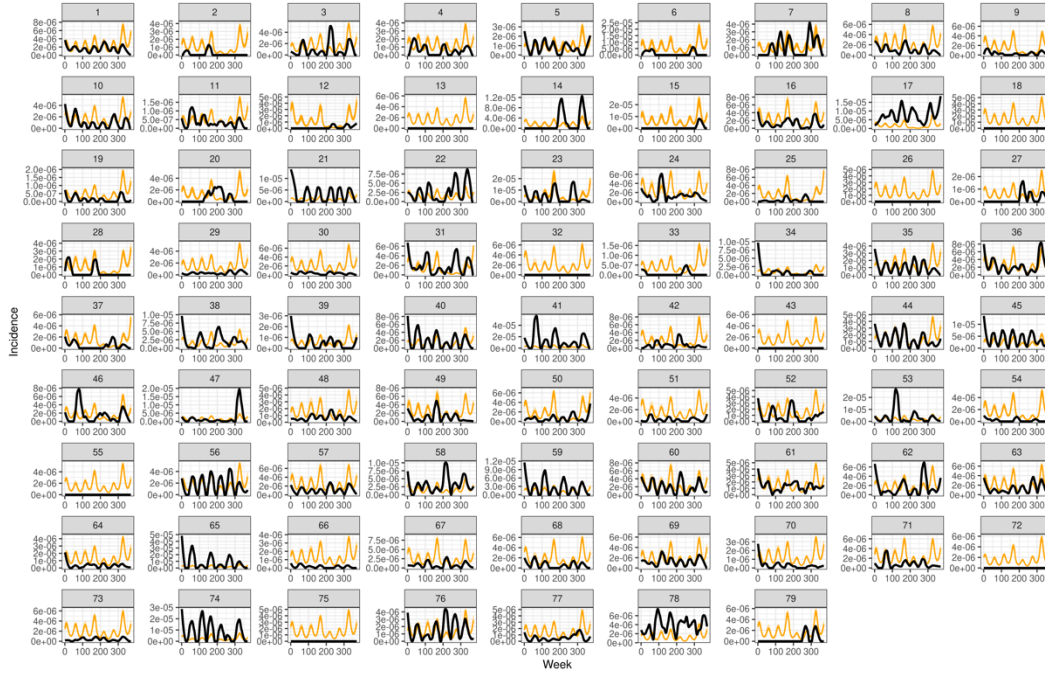
Figure 12. Smoothed reported suspected measles cases among 0-to-4-year-olds (dark blue) compared to estimated incidence adjusted for reporting (black) from best model fit.

Figure 13. Smoothed reported suspected measles cases among 5-to-9-year-olds (green) compared to estimated incidence adjusted for reporting (black) from best model fit.
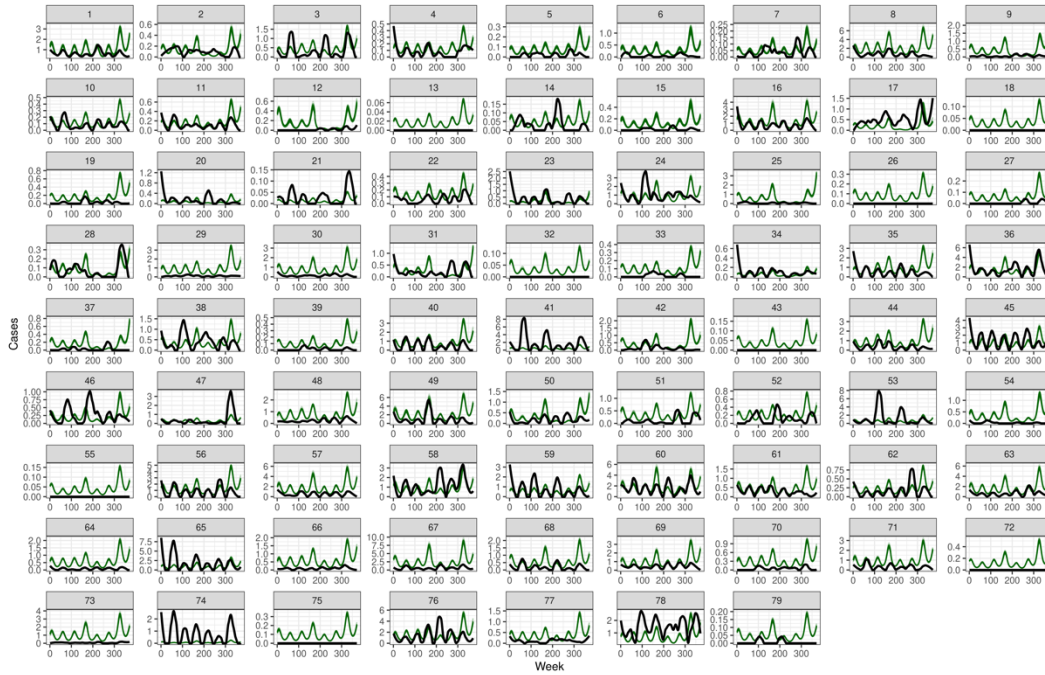
Figure 14. Smoothed reported suspected measles cases among 10-to-14-year-olds (orange) compared to estimated incidence adjusted for reporting (black) from best model fit.
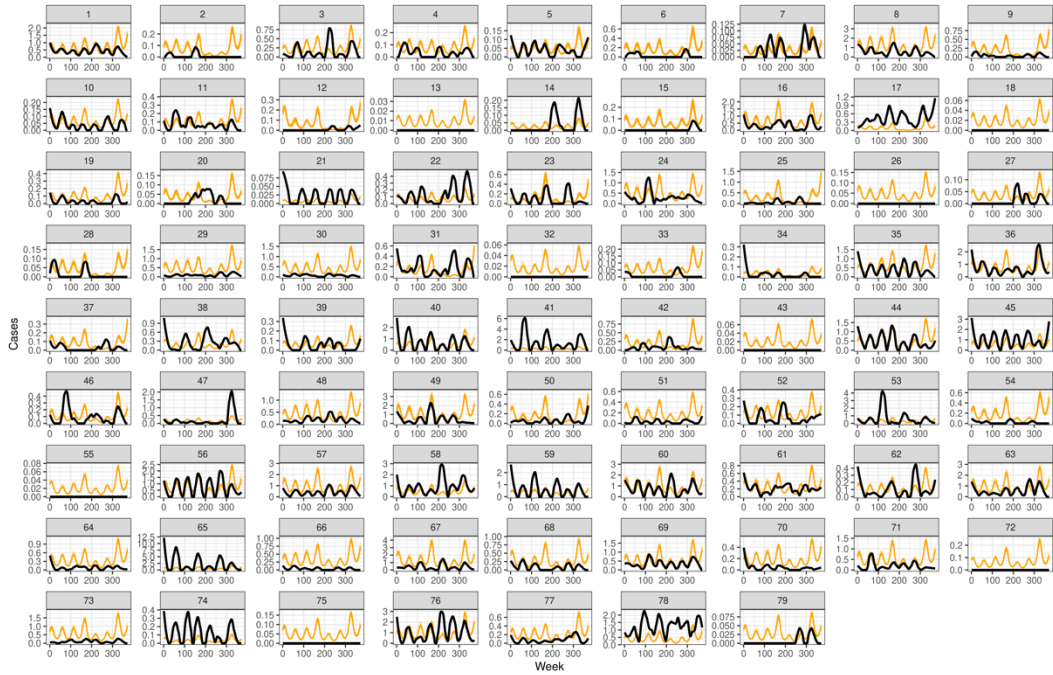
Section 4. References

1   Mapping routine measles vaccination in low- and middle-income countries. *Nature* **589**, 415-419 (2021). https://doi.org:10.1038/s41586-020-03043-4

2   World Health Organization. *Immunization data*, <https://immunizationdata.who.int/listing.html> (2023).

3   Portnoy, A., Jit, M., Helleringer, S. & Verguet, S. Impact of measles supplementary immunization activities on reaching children missed by routine programs. *Vaccine* **36**, 170-178 (2018). https://doi.org:10.1016/j.vaccine.2017.10.080

4   Tatem, A. J. WorldPop, open data for spatial demography. *Sci Data* **4**, 170004 (2017). https://doi.org:10.1038/sdata.2017.4

5   Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **396**, 1204-1222 (2020). https://doi.org:10.1016/s0140-6736(20)30925-9

Appendix C. Supplementary Information for Chapter 4

Section 1. Activities of the Expert Working Group

The Working Group was established with the intent to gain feedback throughout the development of a conceptual framework as related to measles CFR. Members of the Working Group included:

- Natasha Crowcroft (WHO)
- Felicity Cutts (LSHTM)
- Emily Dansereau (BMGF)
- Matthew Ferrari (Penn State)
- Deepa Gamage (WHO)
- Katy Gaythorpe (VIMC)

- Kendall Krause (BMGF)
- Katrina Kretsinger (WHO / CDC)
- Kevin McCarthy (IDM / BMGF)
- Mark Papania (CDC)
- Niket Thakkar (IDM / BMGF)

The overall objectives for convening this Working Group, related to indicator investigation, were as follows:

1. Determine all possible indicators (and proxy metrics, as needed) as related to measles CFR
2. Determine relative order and group of available indicator importance
3. Provide guidance and recommendation on targeted literature reviews
4. Approve final indicator list and conceptual framework

Each session of the Working Group was conducted online, via Zoom. Activities for each Session are outlined below.

Session 1

Objectives

1. *Discuss a full list of possible covariates to explore, including proxies*
2. *Determine overall importance of each covariate candidate*

Working Group members brainstormed a comprehensive, full list of possible population-level indicators related to measles CFR. These were not to include those describing special populations, such as internally displaced persons and refugees, as the underlying available CFR data does not include adequate information on these groups. The full list of indicators generated by the Working Group are defined in Appendix C Section 2. Working Group members voted for each indicator that they thought had an important relationship with measles CFR; members could "up-vote" or "down-vote" for each. Indicators with no more than 2 down-votes were considered for further inclusion. This list can be found in Appendix C Section 3.

<u>Session 2</u>

Objectives:

1. *Anonymously rank indicators to determine relative importance*
2. *Determine indicator candidates further worth investigation*

Working Group members ranked indicators in order of importance to consider relative to one another. Each ranked position from 1 to 42 was assigned each corresponding weight. Age was removed from this process. Overall indicator rank was determined by average weight across responses, shown in Appendix C Section 4.

Members asserted, with at least one verbal yes, their desire for the inclusion of all indicators for further analysis. Members suggested considering mechanisms that might impact measles mortality or case fatality so it could be ensured that remaining indicators adequately captured the underlying components of these possible mechanisms.

<u>Session 3</u>

Objectives

1. *Review mechanistic groups and indicators per group*
2. *Review protocol for literature review and dataset investigation*

Members reviewed the following mechanistic groups and indicators corresponding with each group. The groups and related covariates are described in Table 1 (Chapter 4).

Members confirmed the inclusion of all indicators other than sanitation quality and the following protocol for literature review and data analysis:

1. Search for and review any available literature (systematic literature review)
2. Search for and review any available population level data (database search)
3. Categorize into following groups:
   a. Published literature supporting causal relationship and population-level data
   b. Published literature supporting observational relationship and population-level data
   c. Published literature with supporting qualitative evidence and population-level data
   d. No literature published, but population-level data available
   e. No literature published and population-level data is untrustworthy, contains missingness, or is otherwise unsuitable

4. Follow-up with Working Group to share indicator categories
5. Framework development

<u>Session 4</u>

Objectives

1. *Provide feedback on proposed conceptual framework of mechanistic groups*
2. *Review results from literature review and dataset investigation*
3. *Provide specific recommendation for areas in literature with ambiguous results*

From a systematic review of the literature, each covariate was classified in Table 2 (Chapter 4).

Section 2. Full list of identified indicators potentially related to measles case fatality identified by Expert Working Group

- Access to intensive care unit (ICU)
- Age
- Ambient air pollution
- Antibiotic use for measles-related pneumonia
- Asthma prevalence
- Autoimmune condition prevalence
- Average household size
- Bacille Calmette-Guérin vaccination coverage
- Breastfeeding prevalence
- Cancer prevalence
- De-worming frequency
- Diarrheal disease prevalence
- Diphtheria- tetanus- pertussis (DTP) vaccination coverage
- Educational attainment
- First-dose coverage of measles-containing vaccine (MCV1)
- Health expenditure per capita
- *Haemophilus influenzae* type B (Hib) vaccination coverage
- Human immunodeficiency virus (HIV) prevalence
- Human immunodeficiency virus (HIV) treatment / antiretroviral therapy (ART) prevalence
- Household air pollution
- Level of health care available
- Lower respiratory infection (LRI) prevalence
- Malaria prevalence
- Maternal antibody dynamics
- Maternal measles vaccination coverage
- Maternal smoking prevalence
- Measles attack rate / incidence
- Meningococcal serogroup A vaccination coverage
- Oral rehydration treatment or solution (ORT/S) for measles-related diarrhoea
- Outbreak susceptibility
- Overweight prevalence
- Pneumococcal conjugate vaccination (PCV) coverage
- Polio vaccination coverage
- Pre-term birth prevalence
- Rotavirus vaccine coverage
- Rubella vaccine coverage

- Sanitation quality
- Second-dose coverage of measles-containing vaccine (MCV2)
- Sex
- Stunting prevalence
- Surrounding conflict
- Time
- Time to care seeking
- Total fertility rate
- Travel time to major city or settlement
- Travel time to nearest health care facility
- Tuberculosis prevalence
- Under-five mortality rate
- Underweight prevalence
- Vaccination efficacy
- Vaccination schedule
- Vaccine coverage equity
- Vitamin A deficiency prevalence
- Vitamin A supplementation prevalence
- Vitamin A treatment prevalence
- Wasting prevalence
- Water quality
- Yellow fever vaccination coverage

Section 3. Post-discussion list of identified indicators related to measles case fatality

- Access to ICU
- Age
- Ambient air pollution
- Antibiotic use for measles-related pneumonia
- Average household size
- Breastfeeding prevalence
- De-worming frequency
- Diarrheal disease prevalence
- Educational attainment
- Health expenditure per capita
- HIV prevalence
- HIV treatment prevalence / ART prevalence
- Level of health care available
- LRI prevalence
- Malaria prevalence
- Maternal antibody dynamics
- Maternal measles vaccination coverage
- Measles attack rate / incidence
- MCV1 coverage
- MCV2 coverage
- ORT/S for measles-related diarrhoea
- Outbreak setting indicator
- PCV vaccine coverage
- Percent living in urban setting
- Population density
- Pre-term birth prevalence
- Sanitation quality
- Surrounding conflict
- Stunting prevalence
- Time to care seeking
- Total fertility rate
- Travel time to major city or settlement
- Travel time to nearest health care facility
- Under-five mortality rate
- Underweight prevalence
- Vaccine coverage equity
- Vaccination efficacy
- Vaccination schedule
- Vitamin A deficiency prevalence
- Vitamin A supplementation
- Vitamin A treatment
- Wasting prevalence

Section 4. Ranked list of indicators related to measles case fatality, with average rank

1. Age (1.86)
2. MCV1 coverage (8.43)
3. Underweight prevalence (9.71)
4. Wasting prevalence (9.71)
5. Vitamin A treatment (13.29)
6. Travel time to nearest health facility (13.86)
7. MCV2 coverage (14.00)
8. Level of health care available (14.57)
9. ORT/S for measles-related diarrhoea (14.86)
10. Antibiotic use for measles-related pneumonia (15.14)
11. Time to care seeking (15.71)
12. Vitamin A deficiency prevalence (15.71)
13. Stunting prevalence (18.00)
14. Measles incidence (19.57)
15. Surrounding conflict (20.00)
16. Health expenditure per capita (20.14)
17. Access to ICU (20.29)
18. Measles attack rate (20.43)
19. Under-5 mortality (20.71)
20. LRI prevalence (21.00)
21. Diarrheal disease prevalence (21.29)
22. Average household size (21.71)
23. Outbreak setting indicator (23.00)
24. Vitamin A supplementation (23.29)
25. HIV prevalence (23.71)
26. Travel time to nearest city or settlement (23.71)
27. Population density (25.43)
28. Sanitation quality (25.43)
29. HIV treatment prevalence / ART prevalence (25.86)
30. Maternal (measles) vaccination coverage (26.00)
31. Preterm birth prevalence (26.00)
32. TFR / average children per woman (26.86)
33. Percent living in urban setting (27.00)
34. Proxy for maternal antibody dynamics (27.71)
35. Proxy for vaccine coverage equity (28.71)
36. PCV vaccine coverage (30.29)
37. Educational attainment (30.71)
38. Vaccination efficacy (32.14)
39. Ambient air pollution (32.71)

40. Malaria prevalence (33.71)

41. De-worming frequency (34.43)

42. Vaccination schedule (36.71)

Section 5. PRISMA checklists

Section 5a. PRISMA compliance checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title; identified as literature review
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Appendix C Section 5b
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods (Literature Review subsection)
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods (Literature Review subsection)
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods (Literature Review subsection); Appendix C Section 6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each	Methods (Literature Review

Section and Topic	Item #	Checklist item	Location where item is reported
		record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	subsection); Contributions
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods (Literature Review subsection); Contributions
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods (Literature Review subsection)
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods (Literature Review subsection)
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Contributions
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Results
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A as no synthesis was performed

Section and Topic	Item #	Checklist item	Location where item is reported
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A as no synthesis was performed
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A as no synthesis was performed
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A as no synthesis was performed
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A as no synthesis was performed
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A as no sensitivity analyses were conducted
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods (Literature Review subsection)
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A as no synthesis was performed
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results; Figure 2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A; no studies met this criteria

Section and Topic	Item #	Checklist item	Location where item is reported
Study characteristics	17	Cite each included study and present its characteristics.	Results; Appendix C Sections 7-8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results; Appendix C Sections 7-8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A as no synthesis was performed
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A as no statistical analysis was conducted
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A as no synthesis was performed
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A as no sensitivity analyses were conducted
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A as no synthesis was performed
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A as no synthesis was performed
DISCUSSION			

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	This review was not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	A protocol was not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Declarations of Interest; Contributions
Competing interests	26	Declare any competing interests of review authors.	Declarations of Interest
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Results; Appendix C Sections 7-8

Section 5b. PRISMA compliance abstract checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	N/A
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes

Section and Topic	Item #	Checklist item	Reported (Yes/No)
OTHER			
Funding	11	Specify the primary source of funding for the review.	Declarations of Interest
Registration	12	Provide the register name and registration number.	This review was not registered.

Section 6. Full list of indicator-specific search terms for systematic review

("educational attainment" OR "education" OR "educat*" OR "school"

OR "urban" OR "crowding" OR "dens*"

OR "conflict" OR "unrest" OR "war" OR "disobedience" OR "state of emergency" OR "pariah state"

OR "travel to health facility" OR "distance to health facility"

OR "care seeking" OR "care-seeking"

OR "proximity to city" OR "travel time to city" OR "distance to city"

OR "stunting" OR "malnourished" OR "malnutrition"

OR "underweight"

OR "vitamin A supplementation"

OR "vitamin A deficien*"

OR "wasting"

OR "ICU" OR "intensive care"

OR "health expenditure" OR "health spending" OR "spending" OR "healthcare per capita"

OR "health care quality" OR "healthcare quality" OR "health care access" OR "healthcare access"

OR "under 5 mortality" OR "under-5 mortality" OR "under five mortality" OR "under-five mortality" OR "infant mortality" OR "child mortality" OR "under 5 death" OR "under-5 death" OR "under five death" OR "under-five death"

OR "air pollution" OR "smog"

OR "antibiotic" OR "pneumonia"

OR "household"

OR "de-worming" OR "deworming"

OR "diarrhoea" OR "rotavirus"

OR "HIV" OR "human immunodeficiency virus" OR "acquired immunodeficiency syndrome" OR "AIDS"

OR "antiretroviral therapy" OR "ART"

OR "malaria" OR "plasmodium falciparum" OR "plasmodium vivax"

OR "lower respiratory infection" OR "LRI"

OR "oral rehydration"

OR "pneumococcal vaccine" OR "pneumococcal conjugate vaccine"

OR "pre-term birth" OR "preterm birth" OR "low birthweight" OR "low birth weight"

OR "total fertility rate" OR "average children per women" OR "average number of children per woman" OR "births per woman" OR "parity"

OR "measles attack rate" OR "measles transmission"

OR "measles incidence"

OR "maternal antibody"

OR "maternal measles vaccination" OR "maternal measles immunity" OR "maternal measles vaccine"

OR (("second dose" OR "MCV2" OR "first dose" OR "MCV1" OR "vaccination" OR "vaccine" OR "immunization") AND "coverage")

OR "equity"

OR "vaccination efficacy" OR "immunization efficacy"

OR "vaccination schedule" OR "immunization schedule" OR "recommended age of vaccination" OR "recommended age of immunization" OR "dosing schedule"

OR "vitamin A treatment"

)

AND "measles"

AND ("case fatality" OR "CFR" OR "fatality" OR "mortality" OR "morbid*" OR "comorbid*" OR "sever*" OR "complicat*" OR "risk" OR "secondary outcome" OR "death")

Section 7. Studies containing evidence of an association between measles CFR and specified indicator

Lead Author	Title	Country	Publication Year	Indicator(s)	Measurement of association	Has sample size > 100?	Clinical trial?	Indicates lab confirmation of measles cases?	Provides definition of acute death attributable to measles?	Measure of association adjusted for confounding?	Quality score
Aaby, P.	Overcrowding and intensive exposure as determinants of measles mortality	Guinea-Bissau	1984	Average household size	RR: 1.9 [1.2 – 3.0]	X	--	--	X	--	3
Aaby, P.	Measles mortality, state of nutrition, and family structure: a community study from Guinea-Bissau	Guinea-Bissau	1983	Average household size	Chi-squared p<0.01	--	--	--	X	--	2
Aaby, P.	The survival benefit of measles immunization may not be explained entirely by the prevention of	Bangladesh	2003	MCV1 coverage	vaccine efficacy against measles death: 95% [79% - 99%]	--	--	--	X	--	2

	measles disease: a community study from rural Bangladesh										
Ahmed, P. A.	Review of childhood measles admissions at the National Hospital, Abuja	Nigeria	2010	Underweight prevalence	chi-squared p=0.01	--	--	--	--	--	1
Alwar, A. J.	The effect of protein energy malnutrition on morbidity and mortality due to measles at Kenyatta National Hospital, Nairobi (Kenya)	Kenya	1992	Malnutrition	RR: 3.77 [1.85–7.66]	X	--	--	--	--	2
Aurangzeb, B.	Clinical outcome in children hospitalized with complicated measles	Pakistan	2005	MCV1 coverage	OR: 8.40 [1.00–71.84]	X	--	--	--	--	2

Aurangzeb, B.	Risk factors for mortality among admitted children with complications of measles in Pakistan: An observational study	Pakistan	2021	Stunting prevalence	OR: 6.8 [3.24–14.26]	X	--	--	X	--	3
				Underweight prevalence	OR: 2.93 [1.44–5.93]						
				MCV2 coverage	RR (against unvaccinated): 7.0 [2.03–24.01] and RR (against only receiving one dose): 5.73 [1.49–22.07])						
Avila-Figueroa, C.	Complications in children with measles	Mexico	1990	Malnutrition	RR: 2.47 [1.1–5.52]	X	--	X	X	--	4
Barclay, A. J.	Vitamin A supplements and mortality related to measles: a randomised clinical trial	Tanzania	1987	Underweight prevalence	RR: 3.94 [1.69–9.21]	X	--	--	X	--	3
Bhuiya, A.	Measles case fatality among the under-fives: a multivariate analysis of risk factors in a rural area of Bangladesh	Bangladesh	1987	Educational attainment	OR: 2.11 [1.06–4.19]	X	--	--	X	--	3

Burström, B.	Child mortality in Stockholm during 1885-1910: the impact of household size and number of children in the family on the risk of death from measles	Sweden	1999	Average household size	RR (siblings): 2.9 [1.6–5.4] and RR (households with more than four persons): 1.9 [1.3–2.8]	X	--	--	--	--	2
Choudhry, V. P.	Effect of protein energy malnutrition on the immediate outcome of measles	Afghanistan	1987	Malnutrition	RR: 14.66 [5.46–39.36]	X	--	--	--	--	2
Clemens, J. D.	Measles vaccination and childhood mortality in rural Bangladesh	Bangladesh	1988	Educational attainment	OR (head of household): 1.32 [1.07–1.63] and OR (mothers): 1.72 [1.36–2.19]	X	--	--	--	--	2
Coetzee, S.	Measles in a South African paediatric intensive care unit: again!	South Africa	2014	Underweight prevalence	RR: 2.77 [1.38–5.55]	--	--	X	--	--	2
				HIV prevalence	RR: 2.29 [1.24–4.20]						

Commey, J. O.	Measles in Ghana--1973-1982	Ghana	1984	Malnutrition	RR: 2.02 [1.63–2.51]	X	--	--	--	--	2
Courtright, P.	Abnormal vitamin A cytology and mortality in infants aged 9 months and less with measles	Malawi	2002	Vitamin A deficiency prevalence	RR: 4.00 [1.21–13.33]	X	--	--	--	--	2
Dollimore, N.	Measles incidence, case fatality, and delayed mortality in children with or without vitamin A supplementation in rural Ghana	Ghana	1997	Underweight prevalence MCV1 coverage	OR: 2.5 [1.3–5.1] RR: 1.72 [1.04–2.84]	X	--	--	--	X	3
Dzeyie, K. A.	Measles outbreak investigation at Indo-Myanmar border, Longding District, Arunachal Pradesh, India, 2017	India	2021	Vitamin A treatment	chi-squared p=0.0351	--	--	X	X	--	3

Fetuga, M. B.	A ten-year study of measles admissions in a Nigerian teaching hospital	Nigeria	2007	Malnutrition	RR: 7.33 [1.62–33.16]	X	--	--	--	--	2
				MCV1 coverage	Association noted (p=0.033)						
Gignoux, E.	Risk factors for measles mortality and the importance of decentralized case management during an unusually large measles epidemic in eastern Democratic Republic of Congo in 2013	Democratic Republic of the Congo	2018	Travel time to nearest health care facility	RR: 2.2 [1.0–4.7]	X	--	X	X	--	4
				MCV1 coverage	RR: 0.3 [0.1–0.9]						
				MCV2 coverage	RR: 0.2 [0.1–0.3]						
Gutu, M. A.	Epidemiology of measles in Oromia region, Ethiopia, 2007-2016	Ethiopia	2020	MCV1 coverage	OR: 1.55 [1.14–2.11]	X	--	X	--	--	3
Hussey, G. D.	A randomized, controlled	South Africa	1990	Vitamin A treatment	OR: 0.21 [0.05–0.94]	X	X	--	--	--	3

	trial of vitamin A in children with severe measles										
Hussey, G. D.	Routine high-dose vitamin A therapy for children hospitalized with measles	South Africa	1993	Vitamin A treatment	OR: 0.36 [0.18–0.70]	X	X	--	--	--	3
Jeena, P. M.	Infectious diseases at the paediatric isolation units of Clairwood and King Edward VIII Hospitals, Durban. Trends in admission and mortality rates (1985-1996) and the early impact of HIV (1994-1996)	South Africa	1998	HIV prevalence	RR: 129.62 [40.12–412.64]	X	--	X	--	--	3
Joshi, A. B.	Measles deaths in Nepal: estimating the national case-fatality ratio	Nepal	2009	Surrounding conflict	OR: 15.8 [3.4–73.4]	X	--	X	X	--	4
				Stunting prevalence	RR: 5.34 [2.31–12.36]						
				MCV1 coverage	RR: 3.7 [2.0–6.7]						

				Vitamin A treatment	RR: 3.09 [1.69–5.67]						
Lagunju, I. A.	Measles in Ibadan: a continuous scourge	Nigeria	2005	Underweight prevalence	RR: 2.23 [1.17–4.26]	X	--	--	--	--	2
le Roux, D. M.	South African measles outbreak 2009 - 2010 as experienced by a paediatric hospital	South Africa	2012	Malnutrition HIV prevalence	Association noted OR: 7.55 [2.27–25.12]	X	--	X	--	X	4
Lee, C. T.	Increase in Infant Measles Deaths During a Nationwide Measles Outbreak- Mongolia, 2015-2016	Mongolia	2019	Travel time to nearest city or settlement	RR: 1.9 [1.3–2.8]	X	--	X	X	--	4
Madhulika	Vitamin A supplementation in post-measles complications	India	1994	Malnutrition	Chi-squared p=0.0156	X	--	--	--	--	2
Malina, R. M.	Epidemiologic transition in an isolated indigenous	Mexico	2008	Under-5 mortality rate	Correlation noted	--	--	--	--	--	1

	community in the Valley of Oaxaca, Mexico										
Meteke, S.	Delivering infectious disease interventions to women and children in conflict settings: a systematic review	Various	2020	Surrounding conflict	Qualitative	--	--	--	--	--	1
Mgone, J. M.	Control measures and the outcome of the measles epidemic of 1999 in the Eastern Highlands Province	Papua New Guinea	2000	MCV1 coverage	chi-squared p=0.0423	X	--	--	--	--	2
Moss, W. J.	Measles still has a devastating impact in unvaccinated populations	Various	2007	Surrounding conflict	Qualitative	--	--	--	--	--	1
				Malnutrition	Qualitative						
				Vitamin A deficiency	Qualitative						
				MCV1 coverage	Qualitative						
Moss, W. J.	HIV type 1 infection is a risk factor for mortality in	Zambia	2008	Educational attainment	RR: 2.15 [1.11–4.17]	X	--	X	--	--	3
				HIV prevalence	RR: 2.95 [1.83–4.74]						

	hospitalized Zambian children with measles										
Moss, W. J.	Measles	Various	2017	Malnutrition	Qualitative	--	--	--	--	--	1
				MCV1 coverage	Qualitative						
Murhekar, M. V.	Measles case fatality rate in Bihar, India, 2011-12	India	2014	Educational attainment	RR: 6.23 [1.48–26.21]	X	--	X	X	--	4
				Vitamin A treatment	RR: 0.14 [0.03–0.61]						
Nandy, R.	Case-fatality rate during a measles outbreak in eastern Niger in 2003	Niger	2006	Average household size	RR: 1.82 [1.22 – 2.71]	X	--	X	X	--	4
Nayir, T.	Effects of immunization program on morbidity and mortality rates of vaccine-preventable diseases in Turkey	Turkey	2020	MCV coverage	Association noted	--	--	--	--	--	1
Ndikuyeze, A.	Priorities in global measles control: report of an outbreak in N'Djamena, Chad	Chad	1995	Educational attainment	Qualitative	--	--	--	X	--	2

Author	Title	Country	Year	Variable	Result						
Nojilana, B.	Estimating the burden of disease attributable to vitamin A deficiency in South Africa in 2000	South Africa	2007	Vitamin A deficiency prevalence	RR: 1.86 [1.32–2.59]	--	--	--	--	--	1
Oshitani, H.	Measles infection in hospitalized children in Lusaka, Zambia	Zambia	1995	MCV coverage/vaccination status	RR: 0.4 [0.19–0.83]	X	--	--	--	--	2
Oshitani, H.	Measles case fatality by sex, vaccination status, and HIV-1 antibody in Zambian children	Zambia	1996	HIV prevalence	RR: 3.35 [1.95–5.76]	X	--	--	X	--	3
Rey, M.	Impact of measles in France	France	1983	Level of health care available	Qualitative	--	--	--	--	--	1
Rosero-Bixby, L.	Socioeconomic development, health interventions and mortality	Costa Rica	1991	Under-5 mortality rate	Correlation noted	--	--	--	--	--	1

	decline in Costa Rica										
Salama, P.	Malnutrition, measles, mortality, and the humanitarian response during a famine in Ethiopia	Ethiopia	2001	Surrounding conflict	Qualitative	X	--	--	--	--	2
				Under-5 mortality rate	Correlation noted						
Samb, B.	Decline in measles case fatality ratio after the introduction of measles immunization in rural Senegal	Senegal	1997	MCV1 coverage	Association noted (p=0.038)	--	--	--	X	--	2
Samsi, T. K.	Risk factors for severe measles	Indonesia	1992	Malnutrition	RR: 2.48 [1.4–4.39]	X	--	--	--	--	2
Sepúlveda, J.	Improvement of child survival in Mexico: the diagonal approach	Mexico	2006	Under-5 mortality rate	Correlation noted	--	--	--	--	--	1
Spencer, H. C.	Impact on mortality and fertility of a community-	Kenya	1987	Under-5 mortality rate	Correlation noted	--	--	--	--	--	1

	based malaria control programme in Saradidi, Kenya									

Section 8. Studies containing non-significance evidence of an association between measles CFR and specified indicator

Lead Author	Title	Country	Publication Year	Indicator(s)	Has sample size > 100?	Clinical trial?	Indicates lab confirmation of measles cases?	Provides definition of acute death attributable to measles?	Measure of association adjusted for confounding?	Quality score
Aaby, P.	Vaccinated children get milder measles infection: a community study from Guinea-Bissau	Guinea-Bissau	1986	MCV1 coverage	X	--	--	--	--	2
Aaby, P.	Measles mortality, state of nutrition, and family structure: a community study from Guinea-Bissau	Guinea-Bissau	1983	Malnutrition, educational attainment	--	--	--	X	--	2
Aaby, P.	Measles incidence, vaccine efficacy, and mortality in two urban African areas with high vaccination coverage	Guinea-Bissau	1990	MCV1 coverage	--	--	--	--	--	1
Aaby, P.	Overcrowding and intensive exposure as determinants of measles mortality	Guinea-Bissau	1984	Average household size, malnutrition	X	--	--	X	--	3
Adu, F. D.	Measles outbreak in Ibadan: clinical, serological and virological identification of affected children in selected hospitals	Nigeria	1997	MCV1 coverage	--	--	X	--	--	2
Ahmed, P. A.	Review of childhood measles admissions at the National Hospital, Abuja	Nigeria	2010	MCV1 coverage	--	--	--	--	--	1
Ananthakrishnan, S.	Vitamin A and post measles complications	India	1993	Vitamin A deficiency prevalence	X	--	--	--	--	2

Ariyasriwatana, C.	Severity of measles: a study at the Queen Sirikit National Institute of Child Health	Thailand	2004	HIV prevalence	X	--	--	--	--	2
Arya, L. S.	Spectrum of complications of measles in Afghanistan: a study of 784 cases	Afghanistan	1987	Malnutrition	X	--	--	--	--	2
Aurangzeb, B.	Clinical outcome in children hospitalized with complicated measles	Pakistan	2005	Malnutrition, proportion living in urban setting	X	--	--	--	--	2
Barclay, A. J.	Vitamin A supplements and mortality related to measles: a randomised clinical trial	Tanzania	1987	Vitamin A treatment	X	--	--	X	--	3
Coakley, K. J.	A review of measles admissions and deaths in the paediatric ward of Goroka Base Hospital during 1989	Papua New Guinea	1991	Preterm birth, vitamin A treatment	--	--	--	--	--	1
Coetzee, S.	Measles in a South African paediatric intensive care unit: again!	South Africa	2014	Antibiotic use, vitamin A treatment, PCV coverage	--	--	X	--	--	2
Courtright, P.	Abnormal vitamin A cytology and mortality in infants aged 9 months and less with measles	Malawi	2002	MCV1 coverage	X	--	--	--	--	2
Coutsoudis, A.	Vitamin A supplementation reduces measles morbidity in young African children: a randomized, placebo-controlled, double-blind trial	South Africa	1991	Vitamin A treatment	--	X	--	--	--	2
Dollimore, N.	Measles incidence, case fatality, and delayed mortality in children with or without vitamin A supplementation in rural Ghana	Ghana	1997	Average household size, educational attainment	X	--	--	--	X	3
Donadel, M.	Risk factors for measles deaths among children during a	Romania	2021	Antibiotic use, PCV coverage, preterm birth, vitamin A treatment,	X	--	X	X	X	5

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	Nationwide measles outbreak - Romania, 2016-2018			MCV1 coverage, malnutrition						
Fischer, P. R.	Measles in Zaire: 1987	Democratic Republic of the Congo	1988	Malnutrition, MCV1 coverage	X	--	--	--	--	2
Gignoux, E.	Risk factors for measles mortality and the importance of decentralized case management during an unusually large measles epidemic in eastern Democratic Republic of Congo in 2013	Democratic Republic of the Congo	2018	HH size	X	--	X	X	--	4
Gutu, M. A.	Epidemiology of measles in Oromia region, Ethiopia, 2007-2016	Ethiopia	2020	Proportion living in urban setting	X	--	X	--	--	3
Hull, H. F.	Increased measles mortality in households with multiple cases in the Gambia, 1981	Gambia	1988	Average household size	X	--	--	--	--	2
Joshi, A. B.	Measles deaths in Nepal: estimating the national case-fatality ratio	Nepal	2009	Average household size	X	--	X	X	--	4
Julien, M.	Changing patterns in paediatric mortality, Maputo Central Hospital, Mozambique, 1980-1990	Mozambique	1995	Malaria prevalence	X	--	--	--	--	2
Khoo, A.	Measles--an experience in Sandakan Hospital, Sabah, 1990	Malaysia	1994	Malnutrition	X	--	--	--	--	2
Koster, F. T.	Mortality among primary and secondary cases of measles in Bangladesh	Bangladesh	1988	Malnutrition	X	--	X	--	--	3
Lagunju, I. A.	Measles in Ibadan: a continuous scourge	Nigeria	2005	MCV1 coverage	X	--	--	--	--	2
le Roux, D. M.	South African measles outbreak 2009 - 2010 as experienced by a paediatric hospital	South Africa	2012	MCV1 coverage	X	--	X	--	X	4

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Author	Title	Country	Year	Factors						
Lee, C. T.	Increase in Infant Measles Deaths During a Nationwide Measles Outbreak-Mongolia, 2015-2016	Mongolia	2019	Antibiotic use, malnutrition, MCV1 coverage, vitamin A treatment	X	--	X	X	--	4
Mafigiri, R.	Risk factors for measles death: Kyegegwa District, western Uganda, February-September, 2015	Uganda	2017	Malnutrition	--	--	X	--	--	2
Markowitz, L. E.	Vitamin A levels and mortality among hospitalized measles patients, Kinshasa, Zaire	Democratic Republic of the Congo	1989	Wasting prevalence	X	--	--	--	--	1
Moss, W. J.	Prospective study of measles in hospitalized, human immunodeficiency virus (HIV)-infected and HIV-uninfected children in Zambia	Zambia	2002	HIV prevalence	X	--	X	--	--	3
Munir, M.	Measles and its problems. A clinical analysis of hospitalized patients under 5 years of age	Indonesia	1982	Malnutrition	X	--	--	--	--	2
Nandy, R.	Case-fatality rate during a measles outbreak in eastern Niger in 2003	Niger	2006	Vitamin A treatment, travel time to nearest health care facility	X	--	X	X	X	5
Ogaro, F. O.	Effect of vitamin A on diarrhoeal and respiratory complications of measles	Kenya	1993	Vitamin A treatment	X	X	--	--	--	3
Sension, M. G.	Measles in hospitalized African children with human immunodeficiency virus	Democratic Republic of the Congo	1988	HIV prevalence	X	--	X	--	--	3
Smedman, L.	Nutritional status and measles: a community study in Guinea-Bissau	Guinea-Bissau	1983	Malnutrition	X	--	--	X	--	3

Section 9. Indicators with significant evidence of an association with highest quality score from contributing studies

Mechanism	Indicator	Highest quality score
Health system access and care-seeking behaviours	Educational attainment	4
	Percent living in urban settings	2
	Surrounding conflict	4
	Travel time to major city or settlement	4
	Travel time to nearest health care facility	4
Health system quality	Level of health care available	1
	Under-five mortality rate	2
Measles control and epidemiology	First-dose coverage of measles-containing vaccine (MCV1)	4
	Second-dose coverage of measles-containing vaccine (MCV2)	4
	Vitamin A treatment	4
Nutritional status	Stunting prevalence	4
	Underweight prevalence	3
	Vitamin A deficiency prevalence	2
	Wasting prevalence	4
Risk of secondary infection	Average household size	4
	Human immunodeficiency virus (HIV) prevalence	4

Appendix D. Supplementary Information for Chapter 5

Section 1. Covariate selection via statistical analysis

Section 1.1. Rationale for covariate inclusion

We selected covariates for the remainder of this analysis based on a previous publication that used expert consultation to develop a conceptual framework of mechanisms related to measles CFR and literature review to assess the body of evidence related to population-level factors associated with these mechanisms.

Covariates associated with the underlying mechanism of health care access and care seeking were maternal education, mortality rate due to war and terrorism, and proportion living in urban settings. Each of these individual covariates contribute to the ability for persons to access health care as well as might influence behaviour contributing to the decision to seek care, ultimately leading to higher CFR if care is not sought or accessed.

Covariates associated with the underlying mechanism of health care quality were under-5 mortality rate and GDP per capita. Higher under-5 mortality rates or lower GDP per capita might be associated with lower health care quality which might be related to higher CFR.

Covariates associated with the underlying mechanism of risk of secondary infection were HIV prevalence and total fertility rate (TFR). Based on the risk of secondary infection associated with higher HIV prevalence or TFR, CFR might be higher.

Covariates associated with the underlying mechanism of nutritional status were vitamin A deficiency prevalence and wasting prevalence. Higher vitamin A deficiency prevalence or wasting prevalence could be associated with higher CFR.

Covariates associated with the underlying mechanism of general measles control and epidemiology were MCV1 and MCV2 coverage. Lower MCV1 or MCV2 coverage values could be associated with higher CFR.

Section 1.2. Additional details on covariate interpolation

The following covariate sets did not require interpolation or use of regional values: education, maternal education, war rate due to mortality and terrorism, health access and quality index, universal health coverage, sociodemographic index, stunting prevalence, wasting prevalence, underweight prevalence, vitamin A deficiency prevalence, HIV prevalence, and MCV2 coverage. For 12 countries, we interpolated covariate values for GDP per capita; we also used regional values in 23 countries. For 7 countries, we interpolated covariate values for under-5 mortality rate; we also used regional values in 2 countries. We used regional covariate values in 6 countries for total fertility rate. We used regional covariate values in 14 countries for MCV1 coverage. For 1 country, we interpolated covariate values for proportion living in urban settings; we also used regional values in 2 countries.

Section 1.3. Test for collinearity per underlying mechanism

For the underlying mechanism of "health care access and care seeking", we tested covariate sets for education, maternal education, proportion living in an urban setting, and mortality rate due to war and terrorism. Education was correlated with maternal education; correlation coefficients shown below. As education was more correlated with the other covariates relative to maternal education, it was removed from further analysis. Covariates moving on to the second step of data analysis for the "health care access and care seeking" mechanism were: maternal education, proportion living in an urban setting, and mortality rate due to war and terrorism.

	Education	Maternal education	Prop. living in urban setting	War mortality rate
Education	1.0	0.9965	0.6539	-0.0648
Maternal education		1.0	0.6523	-0.0645
Prop. living in urban setting			1.0	-0.537
War mortality rate				1.0

For the underlying mechanism of "health care quality", we tested covariate sets for under-5 mortality rate, health access and quality index, universal health coverage, GDP per capita, and sociodemographic index. Under-5 mortality rate, health access and quality index, universal health coverage and sociodemographic index were all correlated with each other; correlation coefficients shown below. Health access and quality index, universal health coverage, and sociodemographic index were more correlated with the other covariates relative to under-5 mortality rate, and so they were removed from further analysis. Covariates moving on to the second step of data analysis for the "health care quality" mechanism were: under-5 mortality rate, and GDP per capita.

	Under-5 mortality rate	Health access and quality index	Universal health coverage	GDP per capita	Sociodemographic Index
Under-5 mortality rate	1.0	-0.8027	-0.8346	-0.3920	-0.8525

Heath access and quality index		1.0	0.9916	0.6428	0.9365
Universal health coverage			1.0	0.6311	0.9417
GDP per capita				1.0	0.6159
Sociodemographic Index					1.0

For the underlying mechanism of "nutritional status", we tested covariate sets for stunting prevalence, wasting prevalence, underweight prevalence, and vitamin A deficiency prevalence. Stunting prevalence, underweight prevalence, and wasting prevalence were correlated with each other; correlation coefficients shown below. Stunting prevalence, and underweight prevalence were more correlated with the other covariates relative to wasting prevalence, and so they were removed from further analysis. Covariates moving on to the second step of data analysis for the "nutritional status" mechanism were: wasting prevalence and vitamin A deficiency prevalence.

	Stunting	Wasting	Underweight	Vitamin A deficiency
Stunting	1.0	0.7597	0.8970	0.6965
Wasting		1.0	0.8927	0.5687
Underweight			1.0	0.6509
Vitamin A deficiency				1.0

For the underlying mechanism of "risk of secondary infection", we tested covariate sets for HIV prevalence and total fertility rate. The covariates were not correlated with each other; correlation coefficient shown below. Both covariates moved on to the second step of data analysis for the "risk of secondary infection" mechanism.

	HIV prevalence	TFR
HIV prevalence	1.0	0.2279
TFR		1.0

For the underlying mechanism of "measles control and epidemiology", we tested covariate sets for MCV1 and MCV2 coverage. The covariates were not correlated with each other; correlation coefficient shown below. Both covariates moved on to the second step of data analysis for the "measles control and epidemiology" mechanism.

	MCV1 coverage	MCV2 coverage
MCV1 coverage	1.0	0.4713

MCV2 coverage		1.0

Section 1.4. *Test for predictive capacity per underlying mechanism*

For the mechanism of "health care access and care seeking", no covariates tested had p-values greater than 0.3 (see below). Therefore, all remaining covariates (maternal education, proportion living in urban setting, and mortality rate due to war and terrorism) were kept as covariate sets for the remainder of the analysis.

	Estimate	P-value
Intercept	0.0876	< 0.0001
Maternal education	-0.0039	0.019
Prop urban	-0.0435	0.12
War mortality rate	13.15116	0.12

For the mechanism of "health care quality", no covariates tested had p-values greater than 0.3 (see below). Therefore, all remaining covariates (under-5 mortality rate and GDP per capita) were kept as covariate sets for the remainder of the analysis.

	Estimate	P-value
Intercept	-0.0001441	0.99
Under-5 mortality rate	0.0004097	<0.0001
GDP per capita	0.0000007766	0.039

For the mechanism of "nutritional status", no covariates tested had p-values greater than 0.3 (see below). Therefore, all remaining covariates (wasting prevalence and vitamin A deficiency prevalence) were kept as covariate sets for the remainder of the analysis.

	Estimate	P-value
Intercept	0.0097	0.19
Wasting	0.0901	0.27
Vitamin A deficiency	0.0767	0.13

For the mechanism of "risk of secondary infection", no covariates tested had p-values greater than 0.3 (see below). Therefore, all remaining covariates (HIV prevalence and total fertility rate) were kept as covariate sets for the remainder of the analysis.

	Estimate	P-value
Intercept	-0.01540	0.17
HIV prevalence	0.2675	0.25
TFR	0.008409	0.0003

For the mechanism of "measles control and epidemiology", MCV2 coverage had a p-value greater than 0.3 (see below). Therefore, MCV1 coverage was the only covariate sets kept for the remainder of the analysis.

	Estimate	P-value
Intercept	0.1160	<0.0001
MCV1 coverage	-0.1078	<0.0001
MCV2 coverage	0.0021	0.86

Section 2. Model selection

Section 2.1. First stage model with age granular data

We analysed the relationship between age and CFR in reported studies with age-specific data both with and without controlling for other covariates. There was a consistent relationship between covariate values and CFR values, particularly for measles incidence and MCV1 coverage (Appendix D Figures 5-6). Taken together, these suggested that the relationship between age and CFR was confounded by these other covariates, and therefore we elected to adjust for other covariates in our first-stage model.

Section 2.2. Knot selection

We ran both first and second stage models with both 4 knots (with 2 internal) and 5 knots (with 3 internal) placed uniformly on data density and selected the best performing model based on the lowest Akaike information criterion (AIC) score among results from the second stage model. This process selected the model with 5 knots (AIC: 174907) instead of 4 knots (AIC: 175086).

Section 2.3. Inclusion of random effects

We additionally tested the inclusion of random effects in our second stage model, by testing a random effect placed on each study. This approach caused the coefficient for the community versus hospital-setting indicator to become 0, with a non-significant p-value (p-value=1). Because we know these sets of studies (i.e. those from community-based settings and those from hospital-based settings) were collected from different underlying populations with known difference in measles severity, we elected to use a model without the inclusion of random effects.

Section 3. Final covariate processing and model structure

For covariates requiring interpolation, we used the following formula:

$$y = y_1 + \frac{(x - x_1)(y_2 - y_1)}{(x_2 - x_1)}$$

Following transformation, covariates were standardized as follows such that μ represents the mean transformed covariate value and σ represents the standard deviation of the transformed covariate value:

$$standardized\ covariate = \frac{transformed\ covariate - \mu}{\sigma}$$

Our final first stage CFR model (that only uses age specific input data) follows the following structure. Using transformed and standardized covariate values for each study midpoint year, we fit a Bayesian fixed-effects meta-regression model[1] with the outcome variable of the logit of CFR. We computed standard error in logit space per study using the delta transformation and used these values as weights in the meta-regression. Before transforming to logit space, CFR ratios equalling 0 were offset to 0.0002202378 and ratios equal to 1 were offset to 0.9999999999999.

Our regression equation is as follows:

$$y_i = X_i(\beta) + \epsilon_i$$

$$\epsilon_i \sim N(0, \Lambda)$$

where y_i is the vector of observations of logit of CFR from the ith study, X_i is a vector of covariates paired with each data observation, β are regression coefficients ($\beta_{community\ indicator}$, $\beta_{incidence}$, $\beta_{mortality\ rate\ due\ to\ war\ and\ terrorism}$, $\beta_{maternal\ education}$, $\beta_{GDP\ per\ capita}$, $\beta_{HIV\ prevalence}$, $\beta_{MCV1\ coverage}$, $\beta_{total\ fertility\ rate}$, $\beta_{under\ 5\ mortality\ rate}$, $\beta_{proportion\ living\ in\ urban\ setting}$,

$\beta_{vitamin\ A\ deficiency\ prevalence}$, $\beta_{wasting\ prevalence}$, β_{age}), and ϵ_i are measurement errors with a given covariance Λ. For age, our β coefficient is represented as a function f representing a quadratic spline with 5 knots (3 internal) placed uniformly based on data density at locations 0, 0.68, 1.31, 3.83 and 34 years. This can be represented via the following generalized equation for each data interval i:

$$s_i(x) = a_i x^2 + b_i x + c_i$$

For $x \in [x_i, x_{i+1}]$ and $i = 1, 2, \dots, n - 1$. Data intervals are based on knot locations. Additionally, we included a prior to ensure a right linear tail on our quadratic spline function.

Our final second stage model (that uses all data) is as follows. Model specifications are identical to the first stage as previously defined, except with the following additional priors:

$$\beta_{community\ indicator} \sim Uniform(-\infty, 0)$$
$$\beta_{incidence} \sim Uniform(0, \infty)$$
$$\beta_{mortality\ rate\ due\ to\ war\ and\ terrorism} \sim Uniform(0, \infty)$$
$$\beta_{maternal\ education} \sim Uniform(-\infty, 0)$$
$$\beta_{GDP\ per\ capita} \sim Uniform(-\infty, 0)$$
$$\beta_{HIV\ prevalence} \sim Uniform(0, \infty)$$
$$\beta_{MCV1\ coverage} \sim Uniform(-\infty, 0)$$
$$\beta_{total\ fertility\ rate} \sim Uniform(0, \infty)$$
$$\beta_{under\ 5\ mortality\ rate} \sim Uniform(0, \infty)$$
$$\beta_{proportion\ living\ in\ urban\ setting} \sim Uniform(0, \infty)$$
$$\beta_{vitamin\ A\ deficiency\ prevalence} \sim Uniform(0, \infty)$$
$$\beta_{wasting\ prevalence} \sim Uniform(0, \infty)$$

Priors in this work were only used to impose directionality on covariates, such that the direction of association estimated was consistent with the observed relationship in the literature identified by previous literature review.[2] Therefore, we did not update the priors at any point in this analysis as these directions of association are fixed.

Following our first-stage model, we used the following method to age-split our input data that was reported from sources in age groups wider than 1 year. For the given age range, we computed the proportion of cases for each single age year within the age range given overall age incidence. We then split the number of reported cases per study based on those proportions to generate single age year specific case counts.

Using the total number of deaths reported in the study for the entire age range, we then used the following algorithm:

$$X = \frac{D}{\sum_{a=b}^{B}(C_a * R_a)}$$

, where D was the total number of deaths reported for the age range per study, was the total number of C_a is the number of age-split cases per age a, and R_a was the reference proportion which was calculated taking the ratio of predicted age specific CFR from our first stage-model relative to the CFR among 0-year-olds CFR_a/C_0. Then, we use the following to compute our adjusted CFR ($aCFR$) and adjusted number of deaths (aD_a) per single age year a to use as input data in our model:

$$aCFR_a = X * R_a$$
$$aD_{a=} aCFR_a * C_a$$

We then use our second stage model (similar in specifications) to produce final estimates of age-, year-, and location-specific CFR using our age-split input data. In model fitting, we use linear point optimization via cyipopt[3] described in detail in the technical documentation[1] to the methods used in this paper. Therefore, as MCMC or another sampling algorithm was not used, a burn-in period was not

applicable to our analysis. Since we used a numerical optimization technique[1] to fit our model, we do not need to perform replication tests as would be needed to assess stability from a model fit using MCMC. We generated 1000 posterior samples to allow for robust calculations for various uncertainty intervals. We calculated 95% uncertainty intervals (UI) for all estimates.

Section 4. Decomposition analysis for validating changes to model structure, covariates, and input data

To increase the robustness and rigor of measles CFR modelling, we considered various updates to the model structure, covariates, and input data sources relative to the model previously published by Portnoy et al.[4] With updates to each component (model structure, covariates, and input data), we tracked the overall change in model performance to ensure updates were statistically beneficial in the estimation of measles CFR. Specific steps and validation at each step are described in each subsequent section.

Section 4.1. First stage, updates to model structure

We made the following sequential adaptations to the log-linear model published previously:

Model 0: Generalized linear model, with log link and cases as weights

Model 1.A: Generalized linear model, with log(CFR) as outcome and cases as weights

Model 1.B: Generalized linear model, with logit(CFR) as outcome and cases as weights

Model 1.C: Bayesian meta-regression, with logit(CFR) as outcome and standard error as weights

The structure of Model 0 is identical to the model previously published[4], and serves as our baseline. In order to more accurately represent CFR as a ratio bounded between 0 and 1, we first removed the log link from the model and instead log (Model 1.A) then logit (Model 1.B) transformed CFR as our outcome.

In order to best capture the underlying uncertainty from the data, we then implemented a Bayesian meta-regression framework using standard errors as weights (Model 1.C). We compared both in- and out-of-sample validation for each model iteration. Model 1.C performed best among both in- and out-of-sample validation exercises across metrics (Appendix D Tables 8-9) yielding generally lower root mean squared error (RMSE), mean error and man absolute error and higher correlation.

Section 4.2. Second stage, updates to covariates

We made the following sequential adaptations to the best model (previously referred to as Model 1.C) from our first decomposition step:

Model 1: Previously described Model 1.C with original covariates and original data inputs

Model 2: Previously described Model 1.C with updated covariates and original data inputs

We compared the best model using original covariates and data inputs to a new model fit using the updated covariate set. We compared the performance of these two models to the original model version (Model 0) in Appendix D Tables 10-11. Model 2 performed best across most in- and out-of-sample validation metrics yielding generally lower root mean squared error (RMSE), mean error and mean absolute error and higher correlation.

Section 4.3. Third stage, updates to input data sources

We made the following sequential adaptations to the best model from our second decomposition step updates:

Model 2: Previously described Model 1.C with updated covariates and original data inputs

Model 3: Previously described Model 1.C with updated covariates and updated data inputs

There were 40 additional new studies added across 21 additional countries. Because the input data sources were changing, we did not compare validation metrics to previous decomposition steps. Full model validation can be found in Appendix D Tables 12-13.

The mean predicted CFR from 1990 to 2015 in the previously published model was 1.5% (95% confidence interval (CI): 0.5 – 3.1%) in community-based settings and 2.9% (95% CI: 0.9 – 6.0%) in hospital-based settings. Our findings had a mean case-weighted CFR from 1990 to 2015 of 2.2% (95% uncertainty interval (UI): 2.1 – 2.2%) in community-based settings and in 8.4% (95% uncertainty interval (UI): 8.1 – 8.8%) in hospital-based settings.

Section 5. Supplementary Results

Section 5.1. Age-standardized results

Because the age distribution of cases within a country impacts the ability to compare trends across locations, we also computed country-specific age-standardized CFRs using a reference population of the global age pattern of cases from 1990 as well as the general population age distribution from the UN in 1990 (Appendix D Figure 8). Age-standardized estimates of CFR allow users to more directly compare estimates across locations and years.

Section 5.2. Sensitivity analyses

We ran sensitivity analyses to investigate the implications of using all studies regardless of if they provided information on laboratory confirmation of cases or a definition of a death attributable to measles. Generally, studies that reported information on laboratory confirmation of cases were from countries and years with lower measles incidence, higher MCV1 coverage, and lower CFRs relative to studies that did not report information on laboratory confirmation (Appendix D Figures 11-13). In a sensitivity analysis excluding first studies without information on laboratory confirmation of cases, we were estimated

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systematically lower CFRs than when including all studies in our model (Appendix D Figure 14).

Additionally, studies reporting definitions of deaths attributable to measles were most often from hospital-based settings rather than community-based settings (Chi-squared p-value < 0.0001). When excluding studies without information on a death definition, we also estimated systematically lower CFRs than when including all studies in our model (Appendix D Figure 15).

Section 5. Tables

Table 1. GATHER compliance checklist.

Item number	Checklist item	Reported in Chapter 5 section(s):
Objectives and funding		
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Introduction
2	List the funding sources for the work.	Acknowledgements
Data inputs		
For all data inputs from multiple sources that are synthesised as part of the study:		
3	Describe how the data were identified and how the data were accessed.	Methods
4	Specify the inclusion and exclusion criteria. Identify all ad hoc exclusions.	Methods
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	Appendix D Table 4
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	Methods; Discussion
For data inputs that contribute to the analysis but were not synthesised as part of the study:		
7	Describe and give sources for any other data inputs.	Methods
For all data inputs:		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or	Data sharing statement

	legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	
Data analysis		
9	Provide a conceptual overview of the data analysis method. A diagram might be helpful.	Appendix D Figure 1
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Methods; Appendix D Section 3
11	Describe how candidate models were evaluated and how the final model(s) were selected.	Appendix D Section 2
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	Methods
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Methods
14	State how analytic or statistical source used to generate estimates can be accessed.	Data sharing statement
Results and discussion		
15	Provide published estimates in a file format from which data can be efficiently extracted.	Data sharing statement
16	Report a quantitative measure of uncertainty of the estimates (e.g., uncertainty intervals).	Results
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Discussion
18	Discuss limitations that affect interpretation of the estimates.	Discussion

Table 2. PRISMA compliance checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Appendix D Table 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Research in context
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if	Contributors

Section and Topic	Item #	Checklist item	Location where item is reported
		applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods

Section and Topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	Appendix D Table 4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Data sharing statement
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Data sharing statement

Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results; Data sharing statement
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results; Appendix D Section 5.2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Appendix D Section 5.2
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Data sharing statement
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	This review was not registered.

Section and Topic	Item #	Checklist item	Location where item is reported
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	No protocol was prepared for this review.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	No protocol was prepared for this review.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements
Competing interests	26	Declare any competing interests of review authors.	Declaration of interest
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data sharing statement

Table 3. PRISMA abstract compliance checklist.

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Title
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Background subsection
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Methods subsection
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Methods subsection
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Methods subsection
Synthesis of results	6	Specify the methods used to present and synthesise results.	Methods subsection
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Results subsection
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Results subsection
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Interpretation
Interpretation	10	Provide a general interpretation of the results and important implications.	Interpretation

Section and Topic	Item #	Checklist item	Reported (Yes/No)
OTHER			
Funding	11	Specify the primary source of funding for the review.	Funding subsection
Registration	12	Provide the register name and registration number.	This review was not registered.

Table 4. Input data sources for final model.

Citation	ISO3	Midpoint Year	Community indicator	Minimum age (years)	Maximum age (years)
Arya LS, Azamy S, Ghani AR, Singh M. Outcome of measles in Afghanistan. Indian pediatrics. 1981 Feb;18(2):112-6.	AFG	1978	0	0.4167	12
Arya LS, Taana I, Tahiri C, Saidali A, Singh M. Spectrum of complications of measles in Afghanistan: a study of 784 cases. The Journal of tropical medicine and hygiene. 1987 Jun 1;90(3):117-22.	AFG	1981	0	0.3333	12
Choudhry VP, Atmar M, Amin I, Aram GN, Ghani R. Effect of protein energy malnutrition on the immediate outcome of measles. The Indian Journal of Pediatrics. 1987 Sep;54(5):717-22.	AFG	1984	0	0	17
Wakeham PF. Severe measles in Afghanistan. Journal of Tropical Pediatrics and Environmental Child Health. 1978;24(2):87-8.	AFG	1971	1	0	99
Chen RT, Weierbach R, Bisoffi Z, Cutts F, Rhodes P, Ramaroson S, Ntembagara C, Bizimana F. A 'post-honeymoon period' measles outbreak in Muyinga sector, Burundi. International journal of epidemiology. 1994 Feb 1;23(1):185-93.	BDI	1988	1	0	5

Kambiré C, Konde MK, Yaméogo A, Tiendrébéogo SR, Ouédraogo RT, Otten Jr MW, Cairns KL, Zuber PL. Measles incidence before and after mass vaccination campaigns in Burkina Faso. Journal of Infectious Diseases. 2003 May 15;187(Supplement_1):S80-5.	BFA	2000	1	0	99
Kidd S, Ouedraogo B, Kambire C, Kambou JL, McLean H, Kutty PK, Ndiaye S, Fall A, Alleman M, Wannemuehler K, Masresha B. Measles outbreak in Burkina Faso, 2009: a case–control study to determine risk factors and estimate vaccine effectiveness. Vaccine. 2012 Jul 13;30(33):5000-8.	BFA	2009	1	0	99
Sahuguède P, Roisin A, Sanou I, Nacro B, Tall F. Epidémie de rougeole au Burkina Faso: 714 cas hospitalisés à l'hôpital de Bobo-Dioulasso: étude des facteurs de risque. InAnnales de pédiatrie (Paris) 1989 (Vol. 36, No. 4, pp. 244-251).	BFA	1986	0	0	18
World Health Organization. Measles mortality reduction in West Africa, 1996-2002. Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire. 2003;78(45):390-2.	BFA	2002	1	0	99
Bhuiya A, Wojtyniak B, D'Souza S, Nahar L, Shaikh K.	BGD	1980	1	0	4

Measles case fatality among the under-fives: a multivariate analysis of risk factors in a rural area of Bangladesh. Social science & medicine. 1987 Jan 1;24(5):439-43.					
Francisco AD, Fauveau V, Sarder AM, Chowdhury HR, Chakraborty J, Yunus MD. Measles in rural Bangladesh: issues of validation and age distribution. International journal of epidemiology. 1994 Apr 1;23(2):393-9.	BGD	1989	1	0	5
Fauveau V, Chakraborty J, Sarder AM, Khan MA, Koenig MA. Measles among under-9-month-olds in rural Bangladesh: its significance for age at immunization. Bulletin of the World Health organization. 1991;69(1):67.	BGD	1980	1	0.5	99
Koster FT, Curlin GC, Aziz KM, Haque A. Synergistic impact of measles and diarrhoea on nutrition and mortality in Bangladesh. Bulletin of the World Health Organization. 1981;59(6):901.	BGD	1975	1	0	10
Shahid NS, Clauquin P, Shaikh K, Zimicki S. Long-term complication of measles in rural Bangladesh. The Journal of Tropical Medicine and Hygiene. 1983 Apr 1;86(2):77-80.	BGD	1980	1	0	1

World Health Organization. Expanded Programme on Immunization: Public health importance of measles. Weekly Epidemiological Record. 1986;61(12):89-90.	BGD	1984	1	0	99
Tricou V, Pagonendji M, Manengu C, Mutombo J, Mabo RO, Gouandjika-Vasilache I. Measles outbreak in Northern Central African Republic 3 years after the last national immunization campaign. BMC Infectious Diseases. 2013 Dec;13(1):1-6.	CAF	2011	1	0	99
Aiqiang X, Zijian F, Wenbo X, Lixia W, Wanshen G, Qing X, Haijun S, Lee LA, Xiaofeng L. Active Case-Based Surveillance for Measles in China: Lessons Learned from Shandong and Henan Provinces. Journal of Infectious Diseases. 2003 May 15;187(Supplement_1):S258-63.	CHN	2001	1	0	53
Ji Y, Zhang Y, Xu S, Zhu Z, Zuo S, Jiang X, Lu P, Wang C, Liang Y, Zheng H, Liu Y. Measles resurgence associated with continued circulation of genotype H1 viruses in China, 2005. Virology Journal. 2009 Dec;6(1):1-8.	CHN	2005	1	0	99
Ma C, Rodewald L, Hao L, Su Q, Zhang Y, Wen N, Fan C, Yang H, Luo H, Wang H,	CHN	2013	1	0	99
	CHN	2014	1	0	99
	CHN	2015	1	0	99

Goodson JL. Progress Toward Measles Elimination—China, January 2013-June 2019. China CDC Weekly. 2019 Dec;1(2):21.	CHN	2016	1	0	99
	CHN	2017	1	0	99
	CHN	2018	1	0	99
	CHN	2019	1	0	99
World Health Organization. Expanded Programme on Immunization: Measles outbreak= PROGRAMME ÉLARGI DE VACCINATION: Flambée de rougeole. 1990; 65(49): 379-81.	CHN	1988	1	0	99
Ye Y, Wang W, Wang X, Yu H. The clinical epidemiology of paediatric patients with measles from 2000 to 2009 in Shanghai, China. Clinical Pediatrics. 2011 Oct;50(10):916-22.	CHN	2002	0	0	18
	CHN	2007	0	0	18
Yu X, Wang S, Guan J, Gou A, Liu Q, Jin X, Ghildyal R. Analysis of the cause of increased measles incidence in Xinjiang, China in 2004. The Pediatric infectious disease journal. 2007 Jun 1;26(6):513-8.	CHN	2004	1	0	35
Zhang RQ, Li HB, Li FY, Han LX, Xiong YM. Epidemiological characteristics of measles from 2000 to 2014: Results of a measles catch-up vaccination campaign in xianyang, china. Journal of Infection and Public Health. 2017 Sep 1;10(5):624-9.	CHN	2009	1	0	99

Njim T, Agyingi K, Aminde LN, Atunji EF. Trend in mortality from a recent measles outbreak in Cameroon: a retrospective analysis of 223 measles cases in the Benakuma Health District. The Pan African Medical Journal. 2016;23.	CMR	2015	1	0	99
Fischer PR. Measles in Zaire: 1987. Clinical pediatrics. 1988 May;27(5):234-5.	COD	1986	0	0	15
Gignoux E, Polonsky J, Ciglenecki I, Bichet M, Coldiron M, Thuambe Lwiyo E, Akonda I, Serafini M, Porten K. Risk factors for measles mortality and the importance of decentralized case management during an unusually large measles epidemic in eastern Democratic Republic of Congo in 2013. PloS one. 2018 Mar 14;13(3):e0194276.	COD	2012	1	0	99
Grout L, Minetti A, Hurtado N, François G, Fermon F, Chatelain A, Harczi G, de Dieu Ilunga Ngoie J, N'Goran A, Luquero FJ, Grais RF. Measles in Democratic Republic of Congo: an outbreak description from Katanga, 2010–2011. BMC infectious diseases. 2013 Dec;13(1):1-8.	COD	2010	1	0	30
Kasongo Project Team. Influence of measles	COD	1976	1	0	5

vaccination on survival pattern of 7-35-month-old children in Kasongo, Zaire. The Lancet. 1981 Apr 4;317(8223):764-7.					
Mancini S, Coldiron ME, Ronsse A, Ilunga BK, Porten K, Grais RF. Description of a large measles epidemic in Democratic Republic of Congo, 2010–2013. Conflict and health. 2014 Dec;8(1):1-8.	COD	2010	1	0	99
	COD	2011	1	0	99
	COD	2012	1	0	99
	COD	2013	1	0	99
N'Goran AA, Ilunga N, Coldiron ME, Grais RF, Porten K. Community-based measles mortality surveillance in two districts of Katanga Province, Democratic Republic of Congo. BMC Research Notes. 2013 Dec;6(1):1-3.	COD	2011	1	0	99
	COD	2011	1	0	14
Pan American Health Organization / World Health Organization. Epidemiological Update: Measles. 18 January 2019, Washington, D.C.: PAHO/WHO; 2019	COL	2018	1	0	99
El Shazly MK, Atta HY, Kishk NA. Poliomyelitis, measles and neonatal tetanus: a hospital based epidemiological study. The Journal of the Egyptian Public Health Association. 1997 Jan 1;72(5-6):527-48.	EGY	1994	0	0	60
Belda K, Tegegne AA, Mersha AM, Bayenessagne MG, Hussein I, Bezabeh B. Measles outbreak investigation in Guji zone of Oromia Region,	ETH	2015	1	0.25	30

Ethiopia. The Pan African Medical Journal. 2017;27(Suppl 2).					
Gutu MA, Bekele A, Seid Y, Woyessa AB. Epidemiology of measles in Oromia region, Ethiopia, 2007-2016. The Pan African Medical Journal. 2020;37.	ETH	2011	1	0	99
Kalil FS, Gemeda DH, Bedaso MH, Wario SK. Measles outbreak investigation in Ginnir district of Bale zone, Oromia region, Southeast Ethiopia, May 2019. Pan African Medical Journal. 2020 May 14;36(1).	ETH	2018	1	0	99
Lindtjørn B. Severe measles in the Gardulla area of southwest Ethiopia. Journal of tropical pediatrics. 1986;32(5):234-9.	ETH	1981	0	0	25
	ETH	1981	1	0	4
Mitiku K, Bedada T, Masresha BG, Kegne W, Nafo-Traoré F, Tesfaye N, Yigzaw A. Progress in measles mortality reduction in Ethiopia, 2002–2009. The Journal of infectious diseases. 2011 Jul 1;204(suppl_1):S232-8.	ETH	2006	1	0.0833	65
Navarro-Colorado C, Mahamud A, Burton A, Haskew C, Maina GK, Wagacha JB, Ahmed JA, Shetty S, Cookson S, Goodson JL, Schilperoord M. Measles outbreak response among adolescent and adult Somali	ETH	2011	0	0	99

refugees displaced by famine in Kenya and Ethiopia, 2011. The Journal of infectious diseases. 2014 Dec 15;210(12):1863-70.					
Poletti P, Parlamento S, Fayyisaa T, Feyyiss R, Lusiani M, Tsegaye A, Segafredo G, Putoto G, Manenti F, Merler S. The hidden burden of measles in Ethiopia: how distance to hospital shapes the disease mortality rate. BMC medicine. 2018 Dec;16(1):1-2.	ETH	2015	0	0	65
Tariku MK, Misikir SW. Measles outbreak investigation in Artuma Fursi Woreda, Oromia zone, Amhara region, Ethiopia, 2018: a case control study. BMC Research Notes. 2019 Dec;12(1):1-6.	ETH	2018	1	0	99
Güris D, Auerbach SB, Vitek C, Maes E, McCready J, Durand M, Cruz K, Iohp K, Haddock R, Rota J, Rota P. Measles outbreaks in Micronesia, 1991 to 1994. The Pediatric infectious disease journal. 1998 Jan 1;17(1):33-9.	FSM	1992	1	0	19
Bosu WK, Odoom S, Deiter P, Essel-Ahun M. Epidemiology of measles in the Central Region of Ghana: a five-year case review in three district hospitals. East African medical journal. 2003;80(6):312-7.	GHA	1998	0	0	60
Commey JO, Dekyem P. Measles in southern Ghana:	GHA	1989	0	0.25	12

1985-1993. West African Journal of Medicine. 1994 Oct 1;13(4):223-6.					
Commey JO, Richardson JE. Measles in Ghana—1973–1982. Annals of tropical paediatrics. 1984 Sep 1;4(3):189-94.	GHA	1977	0	0.3333	14
Dollimore N, Cutts F, Binka FN, Ross DA, Morris SS, George Smith P. Measles incidence, case fatality, and delayed mortality in children with or without vitamin A supplementation in rural Ghana. American journal of epidemiology. 1997 Oct 15;146(8):646-54.	GHA	1990	1	0	7
Hull H, Williams PJ, Oldfield F. Measles mortality and vaccine efficacy in rural West Africa. The Lancet. 1983 Apr 30;321(8331):972-5.	GMB	1981	1	0.25	10
Hull HF. Increased measles mortality in households with multiple cases in the Gambia, 1981. Clinical Infectious Diseases. 1988 Mar 1;10(2):463-7.	GMB	1981	1	0	10
Lamb WH. Epidemic measles in a highly immunized rural West African (Gambian) village. Clinical Infectious Diseases. 1988 Mar 1;10(2):457-62.	GMB	1984	1	0	99
Williams PJ. Effect of measles immunization on child	GMB	1984	1	0	15

mortality in rural Gambia. Journal of Biosocial Science. 1989;21(S10):95-104.					
Williams PJ, Hull HF. Status of measles in the Gambia, 1981. Reviews of infectious diseases. 1983 May 1;5(3):391-4.	GMB	1981	1	0.25	10
Aaby P, Bukh J, Lisse IM, da Silva MC. Further community studies on the role of overcrowding and intensive exposure on measles mortality. Clinical Infectious Diseases. 1988 Mar 1;10(2):474-7.	GNB	1981	1	0.42	18
Aaby P, Bukh J, Lisse IM, Smits AJ. Introduction of measles into a highly immunised West African community: the role of health care institutions. Journal of Epidemiology & Community Health. 1985 Jun 1;39(2):113-6.	GNB	1981	1	0	99
Aaby P, Bukh J, Lisse IM, Smits AJ. Measles mortality, state of nutrition, and family structure: a community study from Guinea-Bissau. Journal of infectious diseases. 1983 Apr 1;147(4):693-701.	GNB	1979	1	0	18
Aaby P, Knudsen K, Jensen TG, Thirup J, Poulsen A, Sodemann M, da Silva MC, Whittle H. Measles incidence, vaccine efficacy, and mortality in two urban African areas with high vaccination coverage.	GNB	1983	1	0	1
	GNB	1986	1	0	1

Journal of infectious diseases. 1990 Nov 1;162(5):1043-8.					
Aaby P, Martins C, Bale C, Garly ML, Rodrigues A, Biai S, Lisse IM, Whittle H, Benn CS. Sex differences in the effect of vaccines on the risk of hospitalization due to measles in Guinea-bissau. The Pediatric infectious disease journal. 2010 Apr 1;29(4):324-8.	GNB	2003	0	0.5	5
Aaby P, Bukh J, Lisse IM, da Silva MC. Decline in measles mortality: nutrition, age at infection, or exposure?. Br Med J (Clin Res Ed). 1988 Apr 30;296(6631):1225-8.	GNB	1979	1	0	17
	GNB	1982	1	0	17
Aaby P, Bukh J, Lisse IM, Smits AJ, Gomes J, Fernandes MA, Indi F, Soares M. Determinants of measles mortality in a rural area of Guinea-Bissau: crowding, age, and malnutrition. Journal of tropical pediatrics. 1984 Jun 1;30(3):164-8.	GNB	1980	1	0	20
Martins CL, Garly ML, Balé C, Rodrigues A, Ravn H, Whittle HC, Lisse IM, Aaby P. Protective efficacy of standard Edmonston-Zagreb measles vaccination in infants aged 4.5 months: interim analysis of a randomised clinical trial. Bmj. 2008 Jul 24;337.	GNB	2003	1	0.375	0.375
Aaby P, Bukh J, Lisse IM, Smits AJ. Overcrowding and	GNB	1979	1	0	5

intensive exposure as determinants of measles mortality. American journal of epidemiology. 1984 Jul 1;120(1):49-63.					
Tollefson JE, Hospedales CJ, White FM. Epidemiological indicators and the epidemiology of measles in the English-speaking Caribbean and Suriname. The West Indian Medical Journal. 1992 Mar 1;41(1):2-7.	GUY	1988	1	0	99
World Health Organization. Measles surveillance: Measles in the Caribbean prior to the elimination campaign. Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire. 1991;66(40):291-4.	GUY	1988	1	0	99
Lubis CP, Pasaribu S, Lubis MM. Morbidity and mortality of tetanus, diphtheria and morbilli (measles) cases (a 1982-1985 study at the Child Health Department, Dr. Pirngadi Hospital, Medan). The Journal of the Singapore Paediatric Society. 1987 Jan 1;29:66-72.	IDN	1982	0	0	15
	IDN	1983	0	0	15
	IDN	1984	0	0	15
	IDN	1985	0	0	15
	IDN	1986	0	0	15
Munir M, Mustadjab I, Wulur FH. Measles and its problems. A clinical analysis of hospitalized patients under 5 years of age. Paediatrica	IDN	1980	0	0	5

Indonesiana. 1982 Apr 30;22(3-4):49-64.					
Rangkuti SM, Nazir N, Sutanto AH, Lubis A, Siregar H. Measles morbidity and mortality in the Department of Child Health, Dr Pirngadi General Hospital, Medan, in 1973-1977. Paediatrica Indonesiana. 1980;20(7/8):139-44.	IDN	1975	0	0	12
Samsi TK, Ruspandji T, Susanto I, Gunawan K. Risk factors for severe measles. The Southeast Asian Journal of Tropical Medicine and Public Health. 1992 Sep 1;23(3):497-503.	IDN	1984	0	0.5	18
Agarwal DK, Dutta A, Arora RR, Nair MR. Natural history of measles in rural and urban community of Varanasi. Journal of Communicable Diseases. 1976;8(4):289-98.	IND	1974	1	0	18
Ananthakrishnan S, Srinivasan S, Mahadevan S. Vitamin A and post measles complications. Indian pediatrics. 1993;30(4):520-2.	IND	1989	0	0.5	18
Basa S, Das RR, Khan JA. Root-Cause Analytical Survey for Measles Outbreak: Vaccination or Vaccine?-A Study From Madhepura District, Bihar, India. Journal of Clinical and Diagnostic	IND	2008	1	0	12

Research: JCDR. 2015 Jun;9(6):SC04.					
Basu RN. Measles vaccine—feasiblity, efficacy and complication rates in a multicentric study. The Indian Journal of Pediatrics. 1984 Mar;51(2):139-43.	IND	1982	1	0.75	2
Bhatia R. Measles outbreak in village Tophema in Nagaland. Journal of communicable diseases. 1985;17(2):185-9.	IND	1983	1	1	12
Bose AS, Jafari H, Sosler S, Narula AP, Kulkarni VM, Ramamurty N, Oommen J, Jadi RS, Banpel RV, Henao-Restrepo AM. Case based measles surveillance in Pune: evidence to guide current and future measles control and elimination efforts in India. PLoS One. 2014 Oct 7;9(10):e108786.	IND	2010	1	0	99
Chand P, Rai RN, Chawla U, Tripathi KC, Datta KK. Epidemiology of measles--a thirteen years prospective study in a village. The Journal of Communicable Diseases. 1989 Sep 1;21(3):190-9.	IND	1980	1	0	14
Cherian T, Joseph A, John TJ. Low antibody response in infants with measles and children with subclinical measles virus infection. The Journal of Tropical Medicine	IND	1979	1	0	5

and Hygiene. 1984 Feb 1;87(1):27-31.					
Dhanoa JA, Cowan BE. Measles in the community-a study in non-hospitalised young children in Punjab. Journal of Tropical Pediatrics. 1982;28(2):59-61.	IND	1980	1	0	2
Gupta BP, Sharma S. Measles outbreak in a rural area near Shimla. Indian Journal of Community Medicine. 2006 Apr 1;31(2):106.	IND	2004	1	0	14
Gupta BP, Swami HM, Bhardwaj AK, Vaidya NK, Sharma CD, Kaushal RK. An outbreak of measles in a remote tribal area of Himachal Pradesh. Indian J Comm Health. 1989;5:25-8.	IND	1986	1	0	14
Jajoo UN, Chhabra S, Gupta OP, Jain AP. Measles epidemic in a rural community near Sevagram (Vidarbha). Indian journal of public health. 1984;28(4):204-7.	IND	1982	1	0	10
John S, Sanghi S, Prasad S, Bose A, George K. Two doses of measles vaccine: are some states in India ready for it?. Journal of tropical pediatrics. 2009 Aug 1;55(4):253-6.	IND	1999	1	0	9
	IND	2006	1	0	18
John TJ, Joseph A, George TI, Radhakrishnan J, Singh RP, George K. Epidemiology and prevention of measles in rural south India. Indian Journal of	IND	1977	1	0	9

Medical Research. 1980;72(August):153-8.					
Kalita J, Mani VE, Bhoi SK, Misra UK. Spectrum and outcome of acute infectious encephalitis/encephalopathy in an intensive care unit from India. QJM: An International Journal of Medicine. 2017 Mar 1;110(3):141-8.	IND	2013	0	2	85
Lakhanpal U, Rathore MS. Epidemiology of measles in rural area of Punjab. Journal of communicable diseases. 1986;18(3):185-8.	IND	1983	1	0	14
Lobo J, Reddaiah VP, Kapoor SK, Nath LM. Epidemiology of measles in a rural community. The Indian Journal of Pediatrics. 1987 Mar;54(2):261-5.	IND	1984	1	0	9
Mangal N, Shah K, Sitaraman S. Epidemiological study of measles in urban (slum) area of Jaipur. Indian pediatrics. 1990;27(11):1216-7.	IND	1985	1	0	9
Mishra A, Mishra S, Jain P, Bhadoriya RS, Mishra R, Lahariya C. Measles related complications and the role of vitamin A supplementation. The Indian Journal of Pediatrics. 2008 Sep;75(9):887-90.	IND	2004	1	0	18
Murhekar MV, Ahmad M, Shukla H, Abhishek K, Perry RT, Bose AS, Shimpi R,	IND	2011	1	0	99

Kumar A, Kaliaperumal K, Sethi R, Selvaraj V. Measles case fatality rate in Bihar, India, 2011–12. Plos one. 2014 May 13;9(5):e96668.					
Murhekar MV, Hutin YJ, Ramakrishnan R, Ramachandran V, Biswas AK, Das PK, Gupta SN, Maji D, Martolia HC, Mohan A, Gupte MD. The heterogeneity of measles epidemiology in India: implications for improving control measures. The Journal of infectious diseases. 2011 Jul 1;204(suppl_1):S421-6.	IND	2004	1	0	14
	IND	2005	1	0	14
	IND	2006	1	0	14
NARAIN JP, KHARE S, Rana SR, Banerjee KB. Epidemic measles in an isolated unvaccinated population, India. International journal of epidemiology. 1989 Dec 1;18(4):952-8.	IND	1986	0	0	99
	IND	1986	1	0	99
Phaneendra Rao RS, Kumari J, RAO K, Narasimham VL. Measles in a rural Community. Journal of communicable diseases. 1988;20(2):131-5.	IND	1983	1	0	5
Raoot A, Dewan DK, Dubey AP, Batra RK, Seth S. Measles outbreak in high risk areas of Delhi: epidemiological investigation and laboratory confirmation. The Indian Journal of Pediatrics. 2016 Mar;83(3):200-8.	IND	2014	1	0	99

Ratho RK, Mishra B, Singh T, Rao P, Kumar R. Measles outbreak in a migrant population. Indian J Pediatr. 2005;72(10):893-4.	IND	2003	1	1	25
Ray SK, Mallik S, Munsi AK, Mitra SP, Baur B, Kumar S. Epidemiological study of measles in slum areas of Kolkata. The Indian Journal of Pediatrics. 2004 Jul;71(7):583-6.	IND	1999	1	0	17
Risbud AR, Prasad SR, Mehendale SM, Mawar N, Shaikh N, Umrani UB, Bedekar SS, Banerjee K. Measles outbreak in a tribal population of Thane district, Maharashtra. Indian pediatrics. 1994 May 1;31(5):543-51.	IND	1991	1	0	10
	IND	1992	1	0	10
Satpathy SK, Chakraborty AK. Epidemiological study of measles in Singur, West Bengal. The Journal of Communicable Diseases. 1990 Mar 1;22(1):23-6.	IND	1986	1	0	99
Sharma MK, Bhatia V, Swami H. Outbreak of measles amongst vaccinated children in a slum of Chandigarh. Indian Journal of Medical Sciences. 2004;58(2):47.	IND	2003	1	0	14
Sharma RS. An epidemiological study of measles epidemic in district Bhilwara, Rajasthan. Journal of	IND	1984	1	0	13

communicable diseases. 1988;20(4):301-11.					
Sharma RS, Kaushic VK, Johri SP, Ray SN. An epidemiological investigation of measles outbreak in Alwar-Rajasthan. Journal of communicable diseases. 1984;16(4):299-303.	IND	1982	1	0	5
Singh J, Kumar A, Rai RN, Khare S, Jain DC, Bhatia R, Datta KK. Widespread outbreaks of measles in rural Uttar Pradesh, India, 1996: high risk areas and groups. Indian pediatrics. 1999 Mar 1;36(3):249-56.	IND	1996	1	0	99
Singh J, Sharma RS, Verghese T. Measles mortality in India: a review of community based studies. The Journal of Communicable Diseases. 1994 Dec 1;26(4):203-14.	IND	1980	1	0	99
	IND	1985	1	0	99
	IND	1992	1	0	14
Swami SS, Chandra S, Dudani IU, Sharma R, Mathur MM. Epidemiology of measles in Western Rajasthan. Journal of communicable diseases. 1987;19(4):370-2.	IND	1980	1	0	14
Thakur JS, Ratho RK, Bhatia SP, Grover R, Issaivanan M, Ahmed B, Parmar V, Swami HM. Measles outbreak in a Periurban area of Chandigarh: need for improving vaccine coverage and strengthening surveillance. The Indian	IND	1998	1	0	99

Journal of Pediatrics. 2002 Jan;69(1):33-7.					
Vasudev JP, Nandan D, Chandra R, Srivastava BC. Post measles complications in a rural population. Journal of communicable diseases. 1983;15(4):249-52.	IND	1980	1	0	17
Janghorbani M, Parizi MH, Ghorbani K. Measles epidemics in Kerman city, Iran. Public Health. 1993 Mar 1;107(2):79-87.	IRN	1990	1	0.4167	35
Tollefson JE, Hospedales CJ, White FM. Epidemiological indicators and the epidemiology of measles in the English-speaking Caribbean and Suriname. The West Indian Medical Journal. 1992 Mar 1;41(1):2-7.	JAM	1989	1	0	99
World Health Organization. Measles surveillance: Measles in the Caribbean prior to the elimination campaign. Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire. 1991;66(40):291-4.	JAM	1989	1	0	99
Alwar AJ. The effect of protein energy malnutrition on morbidity and mortality due to measles at Kenyatta National Hospital, Nairobi (Kenya). East African medical journal. 1992 Aug 1;69(8):415-8.	KEN	1983	0	0.0385	20

Borus PK, Cumberland P, Sonoiya S, Kombich J, Tukei PM, Cutts FT. Measles trends and vaccine effectiveness in Nairobi, Kenya. East African medical journal. 2003;80(7):361-4.	KEN	1998	0	0	99
Burström B, Abby P, Mutie DM. Validity of measles mortality data using hospital registers and community surveys. International journal of epidemiology. 1995 Jun 1;24(3):625-9.	KEN	1986	0	0	17
	KEN	1986	1	0	17
	KEN	1988	0	0	17
	KEN	1988	1	0	17
Burström B, Aaby P, Mutie DM. Child mortality impact of a measles outbreak in a partially vaccinated rural African community. Scandinavian journal of infectious diseases. 1993 Jan 1;25(6):763-9.	KEN	1987	1	0	99
Burström B, Aaby P, Mutie DM, Kimani G, Bjerregaard P. Severe measles outbreak in western Kenya. East African medical journal. 1992 Aug 1;69(8):419-23.	KEN	1985	1	0	17
Kisangau N, Sergon K, Ibrahim Y, Yonga F, Langat D, Nzunza R, Borus P, Galgalo T, Lowther SA. Progress towards elimination of measles in Kenya, 2003-2016. Pan African Medical Journal. 2018 Sep 28;31(1).	KEN	2009	1	0	99

Mahamud A, Burton A, Hassan M, Ahmed JA, Wagacha JB, Spiegel P, Haskew C, Eidex RB, Shetty S, Cookson S, Navarro-Colorado C. Risk factors for measles mortality among hospitalized Somali refugees displaced by famine, Kenya, 2011. Clinical Infectious Diseases. 2013 Oct 15;57(8):e160-6.	KEN	2011	0	0	99
Menge I, Esamai F, Van Reken D, Anabwani G. Paediatric morbidity and mortality at the Eldoret District Hospital, Kenya. East African medical journal. 1995;72(3):165-9.	KEN	1993	0	0	17
Muller AS, Voorhoeve AM, T'mannetje W, Schulpen TW. The impact of measles in a rural area of Kenya. East African medical journal. 1977;54(7):364-72.	KEN	1975	1	0	14
	KEN	1976	1	0	14
Navarro-Colorado C, Mahamud A, Burton A, Haskew C, Maina GK, Wagacha JB, Ahmed JA, Shetty S, Cookson S, Goodson JL, Schilperoord M. Measles outbreak response among adolescent and adult Somali refugees displaced by famine in Kenya and Ethiopia, 2011. The Journal of infectious diseases. 2014 Dec 15;210(12):1863-70.	KEN	2011	0	0	99
Centers for Disease Control and Prevention (CDC.	KHM	1999	1	0	99

Accelerated measles control--Cambodia, 1999-2002. MMWR. Morbidity and mortality weekly report. 2003 Jan 10;52(1):4-6.					
Oum S, Chandramohan D, Cairncross S. Community-based surveillance: a pilot study from rural Cambodia. Tropical medicine & international health. 2005 Jul;10(7):689-97.	KHM	2001	1	0	14
Kuroiwa C, Vongphrachanh P, Xayyavong P, Southalack K, Hashizume M, Nakamura S. Measles epidemiology and outbreak investigation using IgM test in Laos. Journal of Epidemiology. 2001;11(6):255-62.	LAO	1994	1	0	99
	LAO	1995	1	0	99
	LAO	1996	1	0	99
	LAO	1997	1	0	99
	LAO	1998	1	0	99
	LAO	1999	1	0	99
	LAO	2000	1	0	99
Nagbe T, Williams GS, Rude JM, Flomo S, Yeabah T, Fallah M, Skrip L, Agbo C, Mahmoud N, Okeibunor JC, Yealue K. Lessons learned from detecting and responding to recurrent measles outbreak in Liberia post Ebola-Epidemic 2016-2017. The Pan African Medical Journal. 2019;33(Suppl 2).	LBR	2016	1	0	99
Lamabadusuriya SP, Jayantha UK. An outbreak of measles in the Southern Province. The Ceylon Medical Journal. 1992 Jun 1;37(2):46-8.	LKA	1989	0	0	17
Premaratna R, Luke N, Perera H, Gunathilake M, Amarasena	LKA	2015	0	18	99

P, Chandrasena TG. Sporadic cases of adult measles: a research article. BMC research notes. 2017 Dec;10(1):1-6.					
Puvimanasinghe JP, Arambepola CK, Abeysinghe NM, Rajapaksa LC, Kulatilaka TA. Measles outbreak in Sri Lanka, 1999–2000. Journal of Infectious Diseases. 2003 May 15;187(Supplement_1):S241-5.	LKA	1999	1	0	99
World Health Organization (WHO). Expanded programme on immunization. Public health importance of measles: Sri Lanka. Wkly Epidemiol Rec. 1985;60(13): 95-7.	LKA	1983	1	0	99
Nimpa MM, Andrianirinarison JC, Sodjinou VD, Douba A, Masembe YV, Randriatsarafara F, Ramamonjisoa CB, Rafalimanantsoa AS, Razafindratsimandresy R, Ndiaye CF, Rakotonirina J. Measles outbreak in 2018-2019, Madagascar: epidemiology and public health implications. The Pan African Medical Journal. 2020;35.	MDG	2018	1	0	99
Hyde TB, Dayan GH, Langidrik JR, Nandy R, Edwards R, Briand K, Konelios M, Marin M, Nguyen HQ, Khalifah AP, O'leary MJ. Measles outbreak in the Republic of the Marshall Islands, 2003. International	MHL	2003	1	0	49

journal of epidemiology. 2006 Apr 1;35(2):299-306.					
McIntyre RC, Preblud SR, Polloi AN, Korean MA. Measles and measles vaccine efficacy in a remote island population. Bulletin of the World Health Organization. 1982;60(5):767.	MHL	1977	1	0	30
World Health Organization. Measles mortality reduction in West Africa, 1996-2002. Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire. 2003;78(45):390-2.	MLI	2002	1	0	99
Chin J, Thaung UM. The unchanging epidemiology and toll of measles in Burma. Bulletin of the World Health Organization. 1985;63(3):551.	MMR	1983	0	0	9
	MMR	1983	1	0	9
Khin M, Win S, Aye SS. The impact of national measles immunization programme on measles admissions to the major children's hospital in Yangon. Tropical doctor. 1994 Jul;24(3):141-3.	MMR	1985	0	0	12
	MMR	1989	0	0	12
Lee CT, Hagan JE, Jantsansengee B, Tumurbaatar OE, Altanchimeg S, Yadamsuren B, Demberelsuren S, Tserendorj C, Munkhtogoo O, Badarch D, Gunregjav N. Increase in infant measles deaths during a nationwide	MNG	2015	1	0	0.9999
	MNG	2015	1	0	99

measles outbreak—Mongolia, 2015–2016. The Journal of infectious diseases. 2019 Oct 22;220(11):1771-9.					
Orsoo O, Saw YM, Sereenen E, Yadamsuren B, Byambaa A, Kariya T, Yamamoto E, Hamajima N. Epidemiological characteristics and trends of a Nationwide measles outbreak in Mongolia, 2015–2016. BMC Public Health. 2019 Dec;19(1):1-0.	MNG	2015	1	0	99
Cliff J, Simango A, Augusto O, Van der Paal L, Biellik R. Failure of targeted urban supplemental measles vaccination campaigns (1997–1999) to prevent measles epidemics in Mozambique (1998–2001). Journal of Infectious Diseases. 2003 May 15;187(Supplement_1):S51-7.	MOZ	1993	1	0	99
	MOZ	1998	1	0	99
Mandomando I, Naniche D, Pasetti MF, Cuberos L, Sanz S, Vallès X, Sigauque B, Macete E, Nhalungo D, Kotloff KL, Levine MM. Assessment of the epidemiology and burden of measles in Southern Mozambique. The American journal of tropical medicine and hygiene. 2011 Jul 7;85(1):146.	MOZ	2002	0	0	18
Boushab BM, Savadogo M, Sow MS, Dao S. Epidemiological, clinical, and	MRT	2011	0	1	33

prognostic study of the measles in the Aioun regional hospital in Mauritania. Médecine et Santé Tropicales. 2015 Apr 1;25(2):180-3.					
Minetti A, Kagoli M, Katsulukuta A, Huerga H, Featherstone A, Chiotcha H, Noel D, Bopp C, Sury L, Fricke R, Iscla M. Lessons and challenges for measles control from unexpected large outbreak, Malawi. Emerging infectious diseases. 2013 Feb;19(2):202.	MWI	2010	1	0	99
Courtright P, Fine D, Broadhead RL, Misoya L, Vagh M. Abnormal vitamin A cytology and mortality in infants aged 9 months and less with measles. Annals of tropical paediatrics. 2002 Sep 1;22(3):239-43.	MWI	1992	0	0.25	0.8333
Yamaguchi S, Dunga A, Broadhead RL, Brabin BJ. Epidemiology of measles in Blantyre, Malawi: analyses of passive surveillance data from 1996 to 1998. Epidemiology & Infection. 2002 Oct;129(2):361-9.	MWI	1997	1	0	99
Grais RF, Dubray C, Gerstl S, Guthmann JP, Djibo A, Nargaye KD, Coker J, Alberti KP, Cochet A, Ihekweazu C, Nathan N. Unacceptably high mortality related to measles	NER	2003	1	0	99

epidemics in Niger, Nigeria, and Chad. PLoS medicine. 2007 Jan;4(1):e16.					
Kaninda AV, Legros D, Jataou IM, Malfait P, Maisonneuve M, Paquet C, Moren A. Measles vaccine effectiveness in standard and early immunization strategies, Niger, 1995. The Pediatric infectious disease journal. 1998 Nov 1;17(11):1034-9.	NER	1995	1	0	4
Malfait P, Jataou IM, Jollet MC, Margot A, DE BENOIST AC, Moren A. Measles epidemic in the urban community of Niamey: transmission patterns, vaccine efficacy and immunization strategies, Niger, 1990 to 1991. The Pediatric infectious disease journal. 1994 Jan 1;13(1):38-44.	NER	1990	0	0.5	4.9167
Nandy R, Handzel T, Zaneidou M, Biey J, Coddy RZ, Perry R, Strebel P, Cairns L. Case-fatality rate during a measles outbreak in eastern Niger in 2003. Clinical infectious diseases. 2006 Feb 1;42(3):322-8.	NER	2003	1	0	99
World Health Organization. Expanded Programme on Immunization: High measles case-fatality rates during an outbreak in a rural area.	NER	1991	1	0	99

Weekly Epidemiological Record. 1993;68(20):142-5.					
Adedoyin MA. The pattern of measles in Ilorin. West African Journal of Medicine. 1990 Apr 1;9(2):103-7.	NGA	1982	0	0	5
	NGA	1983	0	0	5
	NGA	1984	0	0	5
Ahmed PA, Babaniyi IB, Otuneye AT. Review of childhood measles admissions at the National Hospital, Abuja. Nigerian Journal of Clinical Practice. 2010;13(4).	NGA	2003	0	0.5833	10
Babalola OJ, Ibrahim IN, Kusfa IU, Gidado S, Nguku P, Olayinka A, Abubakar A. Measles outbreak investigation in an urban slum of Kaduna Metropolis, Kaduna State, Nigeria, March 2015. Pan African Medical Journal. 2019 Mar 28;32(1).	NGA	2015	1	0	99
Bamgboye EA, Familusi JB. Mortality pattern at a children's emergency ward, University College Hospital, Ibadan, Nigeria. African journal of medicine and medical sciences. 1990 Jun 1;19(2):127-32.	NGA	1982	0	0	17
Byass P, Adedeji MD, Mongdem JG, Zwandor AC, Brew-Graves SH, Clements CJ. Assessment and possible control of endemic measles in urban Nigeria. Journal of Public Health. 1995 Jun 1;17(2):140-5.	NGA	1992	1	0	4

Ekanem EE, Ochigbo SO, Kwagtsule JU. Unprecedented decline in measles morbidity and mortality in Calabar, south-eastern Nigeria. Tropical doctor. 2000 Oct;30(4):207-9.	NGA	1994	0	0	11
Fagbule D, Orifunmishe F. Measles and childhood mortality in semi-urban Nigeria. African journal of medicine and medical sciences. 1988 Sep 1;17(3):181-5.	NGA	1984	0	0.25	7
Faruk AS, Adebowale AS, Balogun MS, Taiwo L, Adeoye O, Mamuda S, Waziri NE. Temporal trend of measles cases and impact of vaccination on mortality in Jigawa State, Nigeria, 2013-2017: a secondary data analysis. The Pan African Medical Journal. 2020;35(Suppl 1).	NGA	2015	1	0	99
Fatiregun AA, Adebowale AS, Fagbamigbe AF. Epidemiology of measles in Southwest Nigeria: an analysis of measles case-based surveillance data from 2007 to 2012. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2014 Mar 1;108(3):133-40.	NGA	2009	1	0	99
Fatiregun AA, Olowookere SA, Abubakar O, Aderibigbe A. Small-scale outbreak of measles in the Irewole local government area of Osun State	NGA	2008	1	0.6667	14

in Nigeria. Asian Pacific Journal of Tropical Medicine. 2009;2(6):33-6.					
Fetuga MB, Njakanna OF, Ongunfowora OB. A ten-year study of measles admissions in a Nigerian teaching hospital. Nigerian Journal of Clinical Practice. 2007 Sep 14;10(1):41-6.	NGA	1999	0	0.3333	12
Grais RF, Dubray C, Gerstl S, Guthmann JP, Djibo A, Nargaye KD, Coker J, Alberti KP, Cochet A, Ihekweazu C, Nathan N. Unacceptably high mortality related to measles epidemics in Niger, Nigeria, and Chad. PLoS medicine. 2007 Jan;4(1):e16.	NGA	2004	1	0	99
Ibia EO, Asindi AA. Measles in Nigerian children in Calabar during the era of expanded programme on immunization. Tropical and geographical medicine. 1990 Jul 1;42(3):226-32.	NGA	1985	0	0.375	11
Ibrahim BS, Usman R, Mohammed Y, Datti Z, Okunromade O, Abubakar AA, Nguku PM. Burden of measles in Nigeria: a five-year review of casebased surveillance data, 2012-2016. The Pan African Medical Journal. 2019;32(Suppl 1).	NGA	2012	1	0	99
	NGA	2013	1	0	99
	NGA	2014	1	0	99
	NGA	2015	1	0	99
	NGA	2016	1	0	99
Lagunju IA, Orimadegun AE, Oyedemi DG. Measles in	NGA	2002	0	0.3333	10

Ibadan: a continuous scourge. African journal of medicine and medical sciences. 2005 Dec 1;34(4):383-7.					
Olugbade OT, Adeyemi AS, Adeoti AH, Ilesanmi OS, Gidado SO, Waziri NE, Aworh MK. Measles outbreaks and Supplemental Immunization Activities (SIAs): the Gwagwalada experience, Abuja 2015. The Pan African Medical Journal. 2019;32(Suppl 1).	NGA	2015	1	0	33
Weldegebriel GG, Gasasira A, Harvey P, Masresha B, Goodson JL, Pate MA, Abanida E, Chevez A. Measles resurgence following a nationwide measles vaccination campaign in Nigeria, 2005–2008. The Journal of infectious diseases. 2011 Jul 1;204(suppl_1):S226-31.	NGA	2008	1	0	99
Joshi AB, Luman ET, Nandy R, Subedi BK, Liyanage JB, Wierzba TF. Measles deaths in Nepal: estimating the national case-fatality ratio. Bulletin of the World Health Organization. 2009;87:456-65.	NPL	2004	1	0	99
Sitaula S, Awasthi GR, Thapa JB, Ramaiya A. Measles outbreak among unvaccinated children in Bajura. Journal of Nepal Medical Association. 2010 Oct 1;50(180).	NPL	2010	1	0.75	25

Aurangzeb B, Fatmee A, Waris R, Haider N, Berjees A, Raza SH. Risk factors for mortality among admitted children with complications of measles in Pakistan–an observational. Journal of the Pakistan Medical Association. 2020 Nov 3:1-4.	PAK	2015	0	0.75	18
Aurangzeb B, Nisar YB, Hazir T, Burki F, Hassan M. Clinical outcome in children hospitalized with complicated measles. J Coll Physicians Surg Pak. 2005 Sep 1;15(9):547-1.	PAK	2003	0	0.5	12
Murray M, Rasmussen Z. Measles outbreak in a northern Pakistani village: epidemiology and vaccine effectiveness. American journal of epidemiology. 2000 Apr 15;151(8):811-9.	PAK	1990	1	0	13
Anis-ur-Rehman ST, Idris M. Clinical outcome in measles patients hospitalized with complications. J Ayub Med Coll Abbottabad. 2008;20(2):14-6.	PAK	2004	0	0.5	12
Rehman IU, Bukhsh A, Khan TM. Measles in Pakistan: time to make steps towards eradication. Travel medicine and infectious disease. 2017 Jul 1;18:67-9.	PAK	2012	1	0	18
	PAK	2013	1	0	18
Saeed A, Butt ZA, Malik T. Investigation of measles outbreak in a district of Balochistan province, Pakistan.	PAK	2014	1	0	11

Journal of Ayub Medical College Abbottabad. 2015 Dec 15;27(4):900-3.					
Sniadack DH, Moscoso B, Aguilar R, Heath J, Bellini W, Chiu MC. Measles epidemiology and outbreak response immunization in a rural community in Peru. Bulletin of the World Health Organization. 1999;77(7):545.	PER	1993	1	0	40
Almoradie-Javonillo I, Javonillo T. Profile of a measles epidemic in a remote Philippine barrio. Journal of the Philippine Medical Association. 1984 Apr 30;60(3).	PHL	1983	1	0	14
Bronzwaer SL, De Groot CJ. Risk factors for a complicated disease course in children with measles admitted to a Philippine university hospital. Nederlands Tijdschrift Voor Geneeskunde. 1997 Dec 1;141(51):2492-5.	PHL	1994	0	0	15
Benjamin AL, Dramoi V. Outbreak of measles in the National Capital District, Papua New Guinea in 2001. Papua and New Guinea Medical Journal. 2002 Sep 1;45(3-4):178-84.	PNG	2001	0	0	17
Coakley KJ, Coakley CA, Spooner V, Smith TA, Javati A, Kajoi M. A review of measles admissions and deaths	PNG	1989	0	0	17

in the paediatric ward of Goroka Base Hospital during 1989. Papua and New Guinea Medical Journal. 1991 Mar 1;34(1):6-12.					
Mgone JM, Mgone CS, Duke TR, Frank DA, Yeka WI. Control measures and the outcome of the measles epidemic of 1999 in the Eastern Highlands Province. Papua and New Guinea medical journal. 2000 Mar 1;43(1-2):91-7.	PNG	1999	0	0	13
Centers for Disease Control and Prevention (CDC. Emergency measles control activities--Darfur, Sudan, 2004. MMWR. Morbidity and mortality weekly report. 2004 Oct 1;53(38):897-9.	SDN	2004	1	0	99
Coronado F, Musa N, Ahmed El Tayeb ES, Haithami S, Dabbagh A, Mahoney F, Nandy R, Cairns L. Retrospective measles outbreak investigation: Sudan, 2004. Journal of tropical pediatrics. 2006 Oct 1;52(5):329-34.	SDN	2003	1	0	99
El Karim O, Salih MA. Morbidity and mortality from measles in an urban community of the Sudan. Annals of Tropical Medicine & Parasitology. 1981 Apr 1;75(2):227-30.	SDN	1975	0	0	18
Ibrahim SA, Mustafa O, Mukhtar MM, Saleh EA, El	SDN	1998	1	0.4167	14

Mubarak HS, Abdallah A, El-Hassan AM, Osterhaus AD, Groen J, De Swart RL, Zijlstra EE. Measles in suburban Khartoum: an epidemiological and clinical study. Tropical Medicine & International Health. 2002 May;7(5):442-9.					
Sulaiman AA, Elmadhoun WM, Noor SK, Almobarak AO, Bushara SO, Osman MM, Awadalla H, Ahmed MH. An outbreak of measles in gold miners in River Nile State, Sudan, 2011. Eastern Mediterranean Health Journal. 2020 Feb 1;26(2).	SDN	2011	1	0	99
Aaby P, Whittle H, Cisse B, Samb B, Jensen H, Simondon F. The frailty hypothesis revisited: mainly weak children die of measles. Vaccine. 2001 Dec 12;20(5-6):949-53.	SEN	1984	1	0	99
	SEN	1988	1	0	99
	SEN	1992	1	0	99
Aaby P. Influence of cross-sex transmission on measles mortality in rural Senegal. The Lancet. 1992 Aug 15;340(8816):388-91.	SEN	1984	1	0	18
Cisse B, Aaby P, Simondon F, Samb B, Soumare M, Whittle H. Role of schools in the transmission of measles in rural Senegal: implications for measles control in developing countries. American journal of epidemiology. 1999 Feb 15;149(4):295-301.	SEN	1994	1	0.4167	30

Pison G, Bonneuil N. Increased risk of measles mortality for children with siblings among the Fula Bande, Senegal. Clinical Infectious Diseases. 1988 Mar 1;10(2):468-70.	SEN	1985	1	0	11
Pison G. Dynamique d'une population traditionelle: les Peul Bande (Senegal oriental). Institut national d'etudes demographiques. Cahier no. 99. Paris: Presses Universitaires de France, 1982. 1982.	SEN	1977	1	0	19
Samb B, Aaby P, Whittle H, Seck AM, Simondon F. Decline in measles case fatality ratio after the introduction of measles immunization in rural Senegal. American journal of epidemiology. 1997 Jan 1;145(1):51-7.	SEN	1984	1	0	99
	SEN	1988	1	0	99
Sesay T, Denisiuk O, Zachariah R. Paediatric morbidity and mortality in Sierra Leone. Have things changed after the 2014/2015 Ebola outbreak?. F1000Research. 2019;8.	SLE	2013	0	0	5
	SLE	2014	0	0	5
	SLE	2016	0	0	5
Sugerman DE, Fall A, Guigui MT, N'dolie M, Balogun T, Wurie A, Goodson JL. Preplanned national measles vaccination campaign at the beginning of a measles outbreak—Sierra Leone, 2009–2010. The Journal of infectious diseases. 2011 Jul 1;204(suppl_1):S260-9.	SLE	2009	1	0	99

World Health Organization (WHO). Expanded Programme on Immunization: Epidemiology of Measles in a Rural Community. Wkly Epidemiol Rec. 1980;55(12): 85-7.	SOM	1978	1	0	99
Grais RF, Dubray C, Gerstl S, Guthmann JP, Djibo A, Nargaye KD, Coker J, Alberti KP, Cochet A, Ihekweazu C, Nathan N. Unacceptably high mortality related to measles epidemics in Niger, Nigeria, and Chad. PLoS medicine. 2007 Jan;4(1):e16.	TCD	2003	1	0	99
Ndikuyeze A, Cook A, Cutts FT, Bennett S. Priorities in global measles control: report of an outbreak in N'Djamena, Chad. Epidemiology & Infection. 1995 Oct;115(2):309-14.	TCD	1990	1	0	5
World Health Organization. Measles mortality reduction in West Africa, 1996-2002. Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire. 2003;78(45):390-2.	TGO	2002	1	0	99
Ariyasriwatana C, Kalayanarooj S. Severity of measles: a study at the Queen Sirikit National Institute of Child Health. Journal of the Medical Association of	THA	2000	0	0	14

Thailand. 2004 Jun 1;87(6):581.					
World Health Organization (WHO). Expanded programme on immunization. Measles outbreak among the hill tribes. Wkly Epidemiol Rec. 1985; 60(11): 79.	THA	1984	1	0.5833	25
Burgess W, Mduma B, Josephson GV. Measles in Mbeya, Tanzania-1981-1983. Journal of tropical pediatrics. 1986;32(4):148-53.	TZA	1982	0	0	99
Mafigiri R, Nsubuga F, Ario AR. Risk factors for measles death: Kyegegwa District, western Uganda, February–September, 2015. BMC Infectious Diseases. 2017 Dec;17(1):1-7.	UGA	2015	1	0.3	36
Weeks RM, Barenzi JF, Wayira JR. A low-cost, community-based measles outbreak investigation with follow-up action. Bulletin of the World Health Organization. 1992;70(3):317.	UGA	1990	1	0.4167	12
Espinosa L, Mirinaviciute G. Health crisis in Venezuela: status of communicable diseases and implications for the European Union and European Economic Area, May 2019. Eurosurveillance. 2019 May 30;24(22):1900308.	VEN	2017	1	0	99
	VEN	2018	1	0	99
Pan American Health Organization / World Health	VEN	2017	1	0	99

Organization. Epidemiological Update: Measles. 18 January 2019, Washington, D.C.: PAHO/WHO; 2019					
Karim SA, Karim QA, Dilraj A, Chamane M. Unsustainability of a measles immunisation campaign-rise in measles incidence within 2 years of the campaign. South African Medical Journal. 1993;83(5).	ZAF	1989	0	0	99
	ZAF	1990	0	0	99
	ZAF	1991	0	0	99
Coetzee S, Morrow BM, Argent AC. Measles in a S outh A frican paediatric intensive care unit: Again!. Journal of Paediatrics and Child Health. 2014 May;50(5):379-85.	ZAF	2010	0	0.42	0.75
Dramowski A, Aucamp M, Bekker A, Mehtar S. Infectious disease exposures and outbreaks at a South African neonatal unit with review of neonatal outbreak epidemiology in Africa. International Journal of Infectious Diseases. 2017 Apr 1;57:79-85.	ZAF	2010	0	0	0.9999
Gibson, IHN, Carmichael, TR & Kustner HG. Measles notifications-the first year. South African Medical Journal. 1982 Jan 1;61(3):84-8.	ZAF	1979	1	0	99
Hussey GD, Klein M. Routine high-dose vitamin A therapy for children hospitalized with measles. Journal of tropical	ZAF	1985	0	0	18

pediatrics. 1993 Dec 1;39(6):342-5.					
Jeena PM, Wesley AG, Coovadia HM. Infectious diseases at the paediatric isolation units of Clairwood and King Edward VIII hospitals, Durban. South African Medical Journal. 1998;88(7).	ZAF	1985	0	0	18
	ZAF	1986	0	0	18
	ZAF	1987	0	0	18
	ZAF	1988	0	0	18
	ZAF	1989	0	0	18
	ZAF	1990	0	0	18
	ZAF	1991	0	0	18
	ZAF	1992	0	0	18
	ZAF	1993	0	0	18
	ZAF	1994	0	0	18
	ZAF	1995	0	0	18
	ZAF	1996	0	0	18
Le Roux DM, Le Roux SM, Nuttall JJ, Eley BS. South African measles outbreak 2009-2010 as experienced by a paediatric hospital. South African Medical Journal. 2012;102(9):760-4.	ZAF	2009	0	0	18
Loening WE, Coovadia HM. Age-specific occurrence rates of measles in urban, peri-urban, and rural environments: implications for time of vaccination. The Lancet. 1983 Aug 6;322(8345):324-6.	ZAF	1980	0	0	17
McMorrow ML, Gebremedhin G, Van den Heever J, Kezaala R, Harris BN, Nandy R. Measles outbreak in South Africa, 2003-2005. South African Medical Journal. 2009;99(5).	ZAF	2004	1	0	99
	ZAF	2005	1	0	99
Uzicanin A, Eggers R, Webb E, Harris B, Durrheim D,	ZAF	1989	1	0	99

Ogunbanjo G, Isaacs V, Hawkridge A, Biellik R, Strebel P. Impact of the 1996–1997 supplementary measles vaccination campaigns in South Africa. International journal of epidemiology. 2002 Oct 1;31(5):968-76.					
Centers for Disease Control and Prevention (CDC. Measles incidence before and after supplementary vaccination activities--Lusaka, Zambia, 1996-2000. MMWR. Morbidity and mortality weekly report. 2001 Jun 22;50(24):513-6.	ZMB	1996	0	0	99
	ZMB	1997	0	0	99
	ZMB	1998	0	0	99
	ZMB	1999	0	0	99
Moss WJ, Monze M, Ryon JJ, Quinn TC, Griffin DE, Cutts F. Prospective Study of Measles in Hospitalized, Human Immunodeficiency Virus (HIV)—Infected and HIV—Uninfected Children in Zambia. Clinical infectious diseases. 2002 Jul 15;35(2):189-96.	ZMB	1999	0	0	18
Oshitani H, Mpabalwani M, Kasolo F, Mizuta K, Luo NP, Bhat GJ, Suzuki H, Numazaki Y. Measles infection in hospitalized children in Lusaka, Zambia. Annals of tropical paediatrics. 1995 Jun 1;15(2):167-72.	ZMB	1992	0	0	15
Rolfe M. Measles immunization in the Zambian Copperbelt: cause for concern.	ZMB	1980	1	0	4

Transactions of the Royal Society of Tropical Medicine and Hygiene. 1982 Jan 1;76(4):529-30.					
Kambarami RA, Nathoo KJ, Nkrumah FK, Pirie DJ. Measles epidemic in Harare, Zimbabwe, despite high measles immunization coverage rates. Bulletin of the World Health Organization. 1991;69(2):213.	ZWE	1988	1	0.1154	30
Marufu T, Siziya S, Tshimanga M, Murugasampillay S, Mason E, Manyume B. Factors associated with measles complications in Gweru, Zimbabwe. East African medical journal. 2001;78(3):135-8.	ZWE	1984	1	0	99
Nsungu M. Measles vaccination status, delay in recognizing measles outbreaks and outbreak outcome. The Central African journal of medicine. 1995 Nov 1;41(11):336-9.	ZWE	1994	0	0	24
Uyirwoth GP. Measles in Mashonaland Central Province: Zimbabwe. East African medical journal. 1993 Jul 1;70(7):455-9.	ZWE	1987	0	0	99
	ZWE	1988	0	0	99
	ZWE	1989	0	0	99

Table 5. Proxy covariate sets used for analysis.

Original covariate	Proxy covariate used
Level of health care available	Gross domestic product per capita
Educational attainment	Maternal educations
Mean household size	Proportion living in urban setting
	Total fertility rate
Surrounding conflict	Mortality rate due to war and terrorism

Table 6. Covariate set values by country in 2019.

ISO3	Vitamin A deficiency prevalence	Mortality rate due to war and terrorism	HIV prevalence	Maternal education	Total fertility rate	GDP per capita	Under-5 mortality rate	MCV1 coverage	Proportion living in urban setting	Wasting prevalence	Measles incidence
AFG	0.1404	0.0006	0.0003	3.1116	4.3210	9992.3903	60.1000	0.6400	0.2575	0.0638	0.0018
AGO	0.1336	0.0000	0.0133	6.4430	5.4420	2612.3470	74.2000	0.5100	0.6618	0.0528	0.0002
ALB	0.1462	0.0000	0.0000	10.5183	1.5970	4543.3865	9.7000	0.9500	0.6123	0.0391	0.0008
ARM	0.0042	0.0000	0.0004	12.3754	1.7580	4758.5575	11.5000	0.9500	0.6322	0.0337	0.0011
AZE	0.0598	0.0000	0.0002	11.6242	1.8100	4758.5575	20.4000	0.9500	0.5603	0.0498	0.0000
BDI	0.1587	0.0000	0.0077	4.1233	5.3210	278.2026	56.6000	0.9200	0.1337	0.0553	0.0107
BEN	0.2289	0.0000	0.0061	3.9160	4.7670	1201.5614	88.4000	0.6800	0.4786	0.0739	0.0043
BFA	0.2216	0.0000	0.0045	1.9187	5.1090	738.2189	87.8000	0.8800	0.2998	0.1257	0.0012
BGD	0.0824	0.0000	0.0002	6.5529	2.0110	1581.5675	30.7000	0.9700	0.3741	0.1159	0.0012
BIH	0.1323	0.0000	0.0000	11.4522	1.2540	4758.5575	5.9000	0.9500	0.4863	0.0244	0.0021
BLR	0.0092	0.0000	0.0017	13.3724	1.3820	4758.5575	3.1000	0.9500	0.7904	0.0139	0.0008
BLZ	0.0366	0.0000	0.0045	9.0432	2.2740	4712.8401	12.3000	0.9600	0.4587	0.0321	0.0009
BOL	0.0469	0.0000	0.0023	9.3314	2.6880	3317.3709	26.3000	0.7900	0.6977	0.0155	0.0017
BTN	0.1027	0.0000	0.0023	3.9344	1.9540	3238.0605	28.6000	0.9700	0.4161	0.0395	0.0009
CAF	0.2080	0.0001	0.0244	4.2122	4.6450	418.7217	106.6000	0.4100	0.4177	0.0958	0.0286
CHN	0.0501	0.0000	0.0004	10.3300	1.6960	10155.4929	7.9000	0.9900	0.6031	0.0164	0.0002
CIV	0.1888	0.0000	0.0194	4.4157	4.5930	2327.7454	80.3000	0.7300	0.5124	0.0606	0.0006
CMR	0.2070	0.0000	0.0230	7.8759	4.5060	1449.2775	74.7000	0.6000	0.5697	0.0485	0.0068
COD	0.2071	0.0000	0.0046	8.0764	5.8190	512.5863	83.8000	0.6500	0.4505	0.0850	0.0549
COG	0.2218	0.0000	0.0197	9.7790	4.3740	1793.0281	52.5000	0.7300	0.6737	0.0581	0.0026
COL	0.0449	0.0000	0.0028	9.6068	1.7890	6384.5358	13.6000	0.9500	0.8110	0.0102	0.0001
COM	0.1889	0.0000	0.0000	7.4271	4.1380	1284.3523	63.5000	0.9000	0.2916	0.0928	0.0044
CPV	0.0069	0.0000	0.0057	6.6588	2.2420	3482.4485	14.9000	0.9800	0.6620	0.0197	0.0021

CUB	0.0205	0.0000	0.0021	11.8680	1.6020	8031.0354	5.2000	0.9900	0.7711	0.0141	0.0004
DJI	0.0541	0.0000	0.0125	4.9588	2.6760	1898.1839	57.8000	0.8300	0.7792	0.1899	0.0006
DZA	0.0428	0.0000	0.0007	8.9292	2.9880	4115.3955	23.3000	0.8000	0.7319	0.0446	0.0004
ECU	0.0802	0.0000	0.0023	10.7738	2.4030	5853.8131	13.4000	0.8300	0.6399	0.0196	0.0000
EGY	0.0344	0.0000	0.0001	11.3261	3.2800	3964.9871	20.1000	0.9500	0.4273	0.0477	0.0001
ERI	0.1807	0.0000	0.0039	4.8723	3.9970	1898.1839	40.6000	0.7580	0.4473	0.1201	0.0008
ETH	0.2584	0.0000	0.0069	3.7181	4.1460	799.7951	50.8000	0.5800	0.2123	0.0968	0.0177
FJI	0.0773	0.0000	0.0005	11.6860	2.7540	5869.0211	26.9000	0.9600	0.5675	0.0470	0.0010
FSM	0.1739	0.0000	0.0011	9.6625	3.0100	2921.1456	25.4000	0.7800	0.2281	0.0452	0.0055
GEO	0.0614	0.0000	0.0012	13.2363	2.0550	4773.4233	9.5000	0.9500	0.5904	0.0091	0.0013
GHA	0.2136	0.0000	0.0119	8.6681	3.8160	2053.5867	46.4000	0.9200	0.5671	0.0649	0.0028
GIN	0.1931	0.0000	0.0093	3.3759	4.6250	945.5074	98.0000	0.4700	0.3650	0.0873	0.0016
GMB	0.2132	0.0000	0.0134	5.1083	5.1540	714.5421	51.2000	0.8500	0.6193	0.0806	0.0001
GNB	0.2644	0.0000	0.0217	3.6300	4.4020	650.0694	79.6000	0.7900	0.4378	0.0628	0.0002
GTM	0.0625	0.0000	0.0009	6.3516	2.8220	4254.0352	24.5000	0.9000	0.5144	0.0105	0.0005
GUY	0.0576	0.0000	0.0075	10.6060	2.4400	6478.2877	29.3000	0.9800	0.2669	0.0595	0.0004
HND	0.0527	0.0000	0.0004	6.8878	2.4270	2499.4928	16.8000	0.8900	0.5773	0.0128	0.0003
HTI	0.1300	0.0000	0.0164	6.3011	2.8870	1373.8831	62.2000	0.6500	0.5619	0.0598	0.0000
IDN	0.1468	0.0000	0.0004	9.8638	2.2880	3877.4246	23.8000	0.8800	0.5599	0.1031	0.0014
IND	0.1941	0.0000	0.0014	7.5065	2.2020	1965.5393	34.4000	0.9500	0.3447	0.1679	0.0026
IRN	0.0233	0.0000	0.0002	10.0437	2.1460	5308.9199	13.4000	0.9900	0.7539	0.0359	0.0001
IRQ	0.0777	0.0000	0.0000	10.1375	3.5970	5132.7011	26.1000	0.8200	0.7068	0.0477	0.0004
JAM	0.0320	0.0000	0.0044	12.1379	1.9650	5065.3749	13.7000	0.9400	0.5599	0.0264	0.0002
JOR	0.0838	0.0000	0.0000	13.1249	2.6910	4133.5498	15.5000	0.8700	0.9120	0.0213	0.0001
KEN	0.2275	0.0000	0.0322	8.8740	3.4230	1602.7884	43.0000	0.8900	0.2751	0.0404	0.0003
KGZ	0.0682	0.0000	0.0009	12.2232	3.3000	1226.8245	18.3000	0.9500	0.3659	0.0244	0.0006
KHM	0.0858	0.0000	0.0045	5.5688	2.4780	5300.9050	26.6000	0.8400	0.2381	0.0830	0.0052
KIR	0.1922	0.0000	0.0001	10.1285	3.5300	1505.1552	51.2000	0.9400	0.5484	0.0360	0.0063

LAO	0.1423	0.0000	0.0015	5.5657	2.6260	2579.2537	45.7000	0.8300	0.3565	0.0681	0.0003
LBR	0.1736	0.0000	0.0088	6.3476	4.2470	1898.1839	80.4000	0.7580	0.5162	0.0478	0.0041
LKA	0.0873	0.0000	0.0001	10.8837	2.1880	4228.1492	7.2000	0.9900	0.1859	0.1363	0.0007
LSO	0.2039	0.0000	0.1844	9.1413	3.1080	1126.8438	90.9000	0.9000	0.2859	0.0317	0.0019
MAR	0.1116	0.0000	0.0010	5.9305	2.3820	3044.9063	19.5000	0.9900	0.6299	0.0282	0.0012
MDA	0.0139	0.0000	0.0019	13.6890	1.2690	4758.5575	14.8000	0.9500	0.4273	0.0217	0.0009
MDG	0.1778	0.0000	0.0019	7.7934	4.0260	488.9137	51.9000	0.5500	0.3786	0.1056	0.0014
MHL	0.1666	0.0000	0.0011	9.6251	2.6453	3612.6023	31.6000	0.8500	0.7742	0.0013	0.0014
MKD	0.1158	0.0000	0.0000	11.9490	1.3400	4758.5575	6.8000	0.9500	0.5821	0.0299	0.0013
MLI	0.2093	0.0001	0.0062	2.4365	5.7850	815.3791	94.2000	0.7000	0.4314	0.0949	0.0026
MMR	0.0891	0.0000	0.0041	6.7895	2.1380	1548.4566	45.2000	0.8400	0.3085	0.0597	0.0016
MNG	0.1118	0.0000	0.0001	9.9933	2.8670	4394.9881	16.0000	0.9800	0.6854	0.0122	0.0001
MOZ	0.1973	0.0000	0.0691	4.6535	4.7830	598.8137	72.9000	0.8700	0.3653	0.0419	0.0001
MRT	0.1653	0.0000	0.0001	6.8802	4.5030	1620.9967	73.0000	0.7500	0.5451	0.1034	0.0001
MWI	0.1935	0.0000	0.0623	7.2392	4.1270	401.3927	40.6000	0.9200	0.1717	0.0412	0.0001
NAM	0.0746	0.0000	0.0850	9.3781	3.3440	4504.6174	41.9000	0.7580	0.5104	0.0636	0.0011
NER	0.2241	0.0000	0.0016	1.5164	6.8240	523.8842	80.3000	0.7900	0.1652	0.1421	0.0167
NGA	0.1805	0.0000	0.0102	7.6417	5.3170	2502.6523	116.9000	0.5700	0.5116	0.1068	0.0110
NIC	0.0282	0.0000	0.0010	7.6677	2.3770	1982.6286	16.6000	0.9900	0.5876	0.0125	0.0007
NPL	0.1110	0.0000	0.0017	5.1189	1.8760	1069.7891	29.3000	0.9200	0.2015	0.0820	0.0035
PAK	0.1313	0.0000	0.0012	5.6196	3.4540	1497.9868	67.3000	0.8100	0.3691	0.1305	0.0115
PER	0.0722	0.0000	0.0020	9.9372	2.2330	6613.8764	13.3000	0.8500	0.7810	0.0050	0.0005
PHL	0.1621	0.0000	0.0024	11.4090	2.5260	3664.7907	27.1000	0.7500	0.4715	0.0702	0.0050
PNG	0.0627	0.0000	0.0051	3.9336	3.5200	2816.7188	45.3000	0.3700	0.1325	0.1173	0.0003
PRK	0.0868	0.0000	0.0008	11.5175	1.8960	5300.9050	17.3000	0.9800	0.6213	0.0377	0.0004
PRY	0.1386	0.0000	0.0011	10.0671	2.4050	5774.1662	19.5000	0.8700	0.6188	0.0118	0.0001
RWA	0.1339	0.0000	0.0197	5.5620	3.9900	885.6381	41.9000	0.9600	0.1731	0.0256	0.0157
SDN	0.0854	0.0000	0.0026	7.9076	4.3470	1969.1201	58.4000	0.9000	0.3494	0.1290	0.0027

SEN	0.2062	0.0000	0.0037	3.7067	4.5560	1384.3970	39.7000	0.8900	0.4765	0.0664	0.0005
SLB	0.1085	0.0000	0.0010	5.8482	4.3610	2289.5289	20.0000	0.8100	0.2421	0.0775	0.0007
SLE	0.1814	0.0000	0.0088	4.3162	4.1690	649.7603	111.9000	0.7580	0.4248	0.0684	0.0021
SLV	0.0942	0.0000	0.0019	7.9788	2.0210	3993.5291	13.3000	0.8200	0.7275	0.0145	0.0005
SOM	0.2289	0.0001	0.0021	3.7816	5.9780	1898.1839	118.3000	0.4600	0.4555	0.1367	0.0481
SRB	0.1402	0.0000	0.0001	13.4823	1.8695	4758.5575	5.7000	0.9500	0.5626	0.0297	0.0009
STP	0.2164	0.0000	0.0001	7.6839	4.2670	1898.1839	17.0000	0.9500	0.7360	0.0452	0.0037
SWZ	0.1338	0.0000	0.1904	9.0000	2.9580	3833.2468	48.0000	0.8100	0.2398	0.0157	0.0001
SYR	0.0688	0.0005	0.0000	11.3038	2.7710	969.2613	22.2000	0.6500	0.5482	0.1087	0.0006
TCD	0.2270	0.0000	0.0075	2.3917	5.6490	660.0699	113.5000	0.4100	0.2328	0.1458	0.0092
TGO	0.2067	0.0000	0.0138	5.5127	4.2590	630.7905	66.5000	0.7500	0.4225	0.0561	0.0004
THA	0.0729	0.0000	0.0069	10.6705	1.5140	6612.2274	9.0000	0.9600	0.5069	0.0543	0.0007
TJK	0.1168	0.0000	0.0005	10.5055	3.5560	1174.0817	33.3000	0.9500	0.2731	0.0691	0.0001
TKM	0.0613	0.0000	0.0006	10.1778	2.7400	7692.5787	42.4000	0.9500	0.5205	0.0445	0.0002
TLS	0.1079	0.0000	0.0020	7.1972	3.9430	5300.9050	43.7000	0.9007	0.3095	0.1996	0.0003
TON	0.1027	0.0000	0.0012	10.9248	3.5180	4652.5886	11.7000	0.9900	0.2311	0.0465	0.0011
TUN	0.0131	0.0000	0.0004	9.6807	2.1740	4208.0662	16.9000	0.9800	0.6925	0.0232	0.0002
TUV	0.1023	0.0000	0.0011	9.9877	2.6453	5300.9050	22.7000	0.9600	0.6322	0.0284	0.0029
TZA	0.1373	0.0000	0.0332	7.1880	4.8320	1071.3501	50.5000	0.8800	0.3450	0.0389	0.0001
UGA	0.1485	0.0000	0.0366	7.6903	4.8240	894.5204	45.3000	0.8700	0.2436	0.0411	0.0028
UKR	0.0129	0.0000	0.0059	13.9316	1.2280	2425.6345	8.4000	0.9500	0.6947	0.0777	0.0072
UZB	0.0532	0.0000	0.0006	12.6813	2.7850	3161.4154	14.8000	0.9500	0.5043	0.0315	0.0003
VEN	0.0702	0.0000	0.0033	9.5810	2.2500	13111.5940	24.2000	0.9300	0.8824	0.0341	0.0001
VNM	0.0708	0.0000	0.0023	10.0258	2.0500	3250.5675	21.1000	0.9500	0.3663	0.0567	0.0007
VUT	0.1474	0.0000	0.0010	7.6942	3.7440	2881.7490	25.6000	0.8000	0.2539	0.0459	0.0003
WSM	0.1119	0.0000	0.0010	10.8043	3.8300	4504.9193	17.4000	0.9600	0.1806	0.0414	0.0043
YEM	0.1624	0.0004	0.0006	4.7560	3.7000	9992.3903	61.5000	0.6700	0.3727	0.1579	0.0008
ZAF	0.1268	0.0000	0.0639	10.9565	2.3810	6125.7353	33.0000	0.8300	0.6686	0.0333	0.0000

ZMB	0.1795	0.0000	0.0724	8.9401	4.5590	1348.7384	64.1000	0.9300	0.4407	0.0451	0.0001
ZWE	0.1489	0.0000	0.0876	9.7120	3.5310	1414.8291	54.2000	0.8500	0.3221	0.0356	0.0001

Table 7. Second step model fitted meta-regression coefficients.

Variable	Coefficient values	p-values
Intercept	-2.1084	<0.0001
Community indicator	-1.4597	<0.0001
Incidence	0.2513	<0.0001
Mortality rate due to war and terrorism	0	1.0
Maternal education	-0.6915	<0.0001
GDP per capita	0	1.0
HIV prevalence	0	1.0
MCV1 coverage	-0.1581	<0.0001
Total fertility	0	1.0
Under 5 mortality rate	0.1140	<0.0001
Proportion living in urban setting	0.4161	<0.0001
Vitamin A deficiency prevalence	0.0652	<0.0001
Wasting prevalence	0	1.0

Table 8. In-sample validation metrics from first stage decomposition analysis.

IS	Model 0	Model 1.A	Model 1.B	Model 1.C
Correlation	0.29	0.2785	0.2776	0.3415
RMSE	0.0616	0.0629	0.0631	0.0598
Mean Error	0.0104	0.0218	0.0202	0.0075
Mean Abs. Error	0.0356	0.0354	0.0358	0.0354

Table 9. Out-of-sample validation metrics from first stage decomposition analysis.

OOS	Model 0	Model 1.A	Model 1.B	Model 1.C
Correlation	0.2897	0.2783	0.2775	0.3376
RMSE	0.0624	0.0635	0.0641	0.0608
Mean Error	0.0100	0.0200	0.0182	0.0052
Mean Abs. Error	0.0357	0.0357	0.0362	0.0364

Table 10. In-sample validation metrics from second stage decomposition analysis.

IS	Model 0	Model 1	Model 2
Correlation	0.29	0.3415	0.3929
RMSE	0.0616	0.0598	0.0591
Mean Error	0.0104	0.0075	-0.0010

Mean Abs. Error	0.0356	0.0354	0.0349

Table 11. Out-of-sample validation metrics from first and second stage decomposition analysis.

OOS	Model 0	Model 1	Model 2
Correlation	0.2897	0.3376	0.3833
RMSE	0.0624	0.0608	0.0616
Mean Error	0.0100	0.0052	-0.0022
Mean Abs. Error	0.0357	0.0364	0.0362

Table 12. In-sample (IS) and out-of-sample (OOS) validation metrics from final model using age split input data for comparison.

	IS	OOS
Correlation	0.5002	0.4517
RMSE	0.0451	0.0270
Mean Error	0.0035	0.0011
Mean Abs. Error	0.0175	0.0110

Table 13. In-sample (IS) and out-of-sample (OOS) validation metrics from final model using original (pre-age split) data for comparison.

	IS	OOS
Correlation	0.4667	0.2754
RMSE	0.0934	0.0820

Mean Error	0.0156	0.0027
Mean Abs. Error	0.0343	0.0325

Table 14. Age-specific CFR by region in 2019.

Region	Age Group	Setting	CFR	Lower 95% UI	Upper 95% UI
Central Europe, Eastern Europe, and Central Asia	under 1-year-olds	Hospital	3.06%	2.71%	3.41%
		Community	0.72%	0.65%	0.79%
	1- to 4-year-olds	Hospital	1.51%	1.34%	1.68%
		Community	0.35%	0.32%	0.39%
	5- to 9-year-olds	Hospital	1.18%	1.04%	1.32%
		Community	0.27%	0.25%	0.30%
	10- to 14-year-olds	Hospital	0.97%	0.86%	1.09%
		Community	0.22%	0.20%	0.25%
	15-year-olds and older	Hospital	0.39%	0.33%	0.46%
		Community	0.09%	0.08%	0.10%
Latin America and Caribbean	under 1-year-olds	Hospital	6.35%	5.72%	7.01%
		Community	1.54%	1.40%	1.67%
	1- to 4-year-olds	Hospital	3.46%	3.11%	3.80%
		Community	0.82%	0.75%	0.89%
	5- to 9-year-olds	Hospital	2.49%	2.25%	2.74%
		Community	0.58%	0.53%	0.63%
	10- to 14-year-olds	Hospital	1.95%	1.75%	2.15%
		Community	0.46%	0.41%	0.50%
	15-year-olds and older	Hospital	0.99%	0.85%	1.13%
		Community	0.23%	0.20%	0.26%
North Africa and Middle East	under 1-year-olds	Hospital	9.76%	9.00%	10.55%
		Community	2.45%	2.27%	2.61%
	1- to 4-year-olds	Hospital	4.84%	4.53%	5.19%
		Community	1.17%	1.10%	1.23%
	5- to 9-year-olds	Hospital	2.75%	2.55%	2.95%
		Community	0.65%	0.62%	0.68%
	10- to 14-year-olds	Hospital	2.12%	1.97%	2.29%
		Community	0.50%	0.47%	0.52%
	15-year-olds and older	Hospital	1.10%	0.97%	1.24%
		Community	0.26%	0.23%	0.29%
South Asia	under 1-year-olds	Hospital	7.20%	6.67%	7.81%
		Community	1.77%	1.66%	1.88%

	1- to 4-year-olds	Hospital	3.91%	3.67%	4.19%
		Community	0.93%	0.88%	0.97%
	5- to 9-year-olds	Hospital	3.01%	2.82%	3.22%
		Community	0.71%	0.68%	0.75%
	10- to 14-year-olds	Hospital	2.57%	2.39%	2.76%
		Community	0.60%	0.57%	0.64%
	15-year-olds and older	Hospital	2.05%	1.86%	2.25%
		Community	0.48%	0.44%	0.52%
Southeast Asia, East Asia, and Oceania	under 1-year-olds	Hospital	4.22%	3.87%	4.61%
		Community	1.01%	0.93%	1.08%
	1- to 4-year-olds	Hospital	2.41%	2.23%	2.60%
		Community	0.57%	0.53%	0.60%
	5- to 9-year-olds	Hospital	1.78%	1.66%	1.92%
		Community	0.42%	0.39%	0.44%
	10- to 14-year-olds	Hospital	1.49%	1.38%	1.60%
		Community	0.35%	0.33%	0.37%
	15-year-olds and older	Hospital	0.70%	0.63%	0.79%
		Community	0.16%	0.15%	0.18%
Sub-Saharan Africa	under 1-year-olds	Hospital	13.91%	13.06%	14.72%
		Community	3.65%	3.49%	3.81%
	1- to 4-year-olds	Hospital	8.18%	7.79%	8.62%
		Community	2.03%	1.97%	2.10%
	5- to 9-year-olds	Hospital	5.30%	5.04%	5.59%
		Community	1.28%	1.23%	1.33%
	10- to 14-year-olds	Hospital	3.82%	3.58%	4.06%
		Community	0.91%	0.87%	0.95%
	15-year-olds and older	Hospital	2.88%	2.65%	3.12%
		Community	0.68%	0.63%	0.73%

Section 7. Figures

Figure 1. Overview of modelling process.
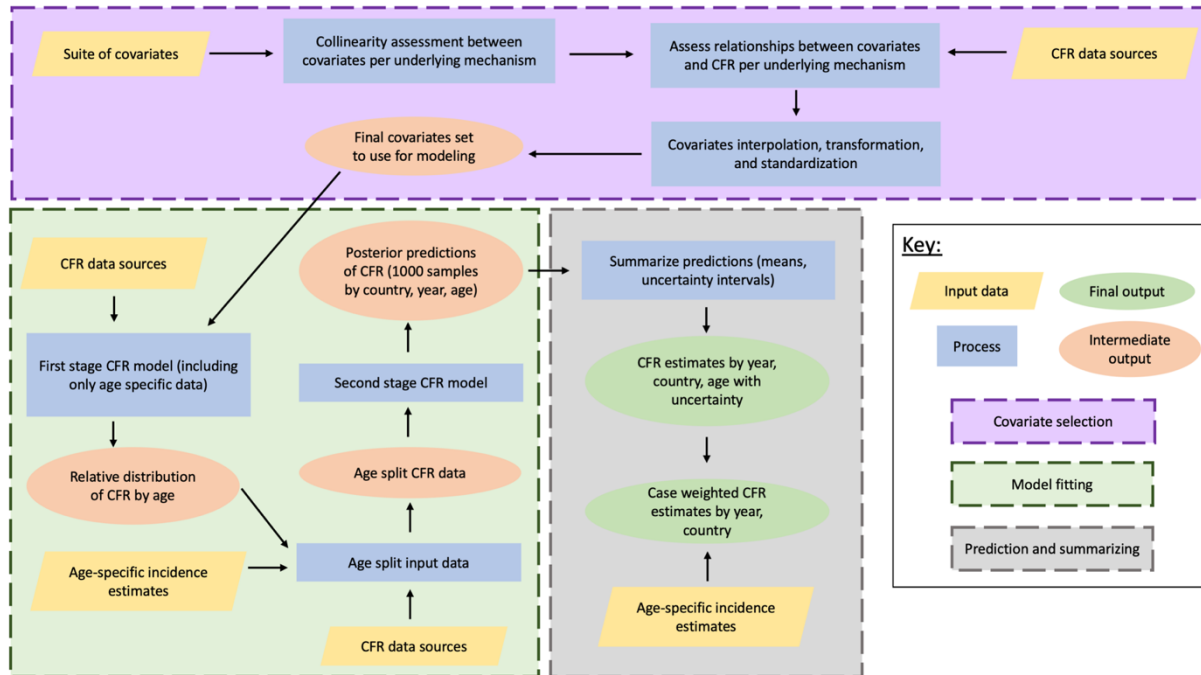
Figure 2. Recent data available by country.

For countries with data available, year of most recent data available by country shown in map.
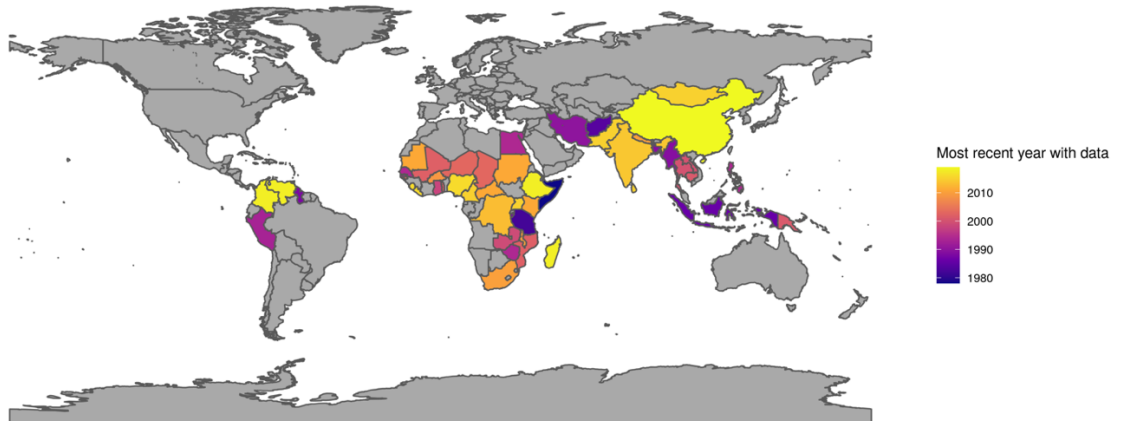
Figure 3. Relative age pattern from first-stage model with 4 knots (with 2 internal).
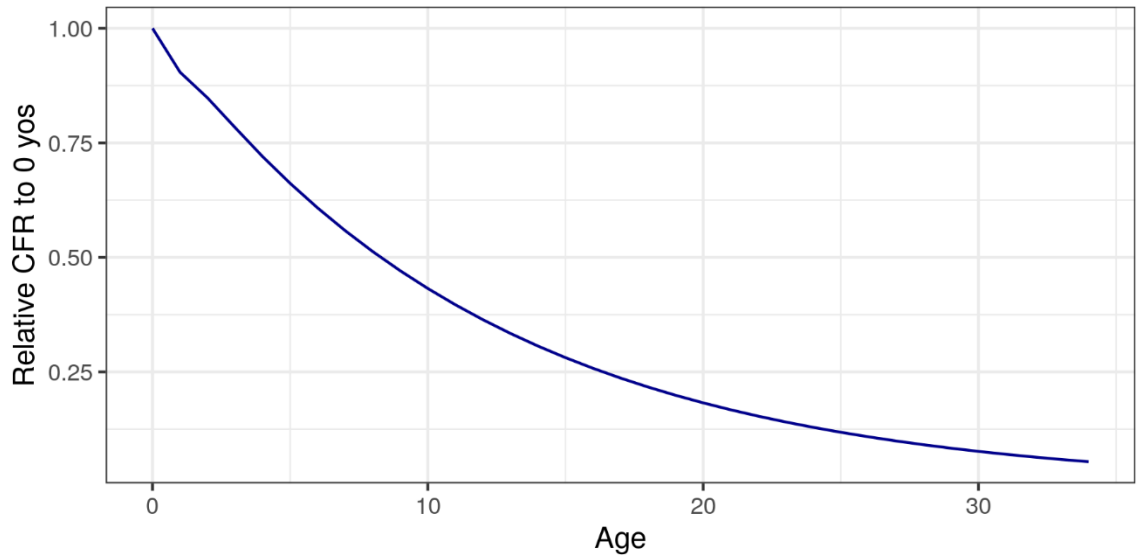
Figure 4. Relative age pattern from first-stage model with 5 knots (with 3 internal).
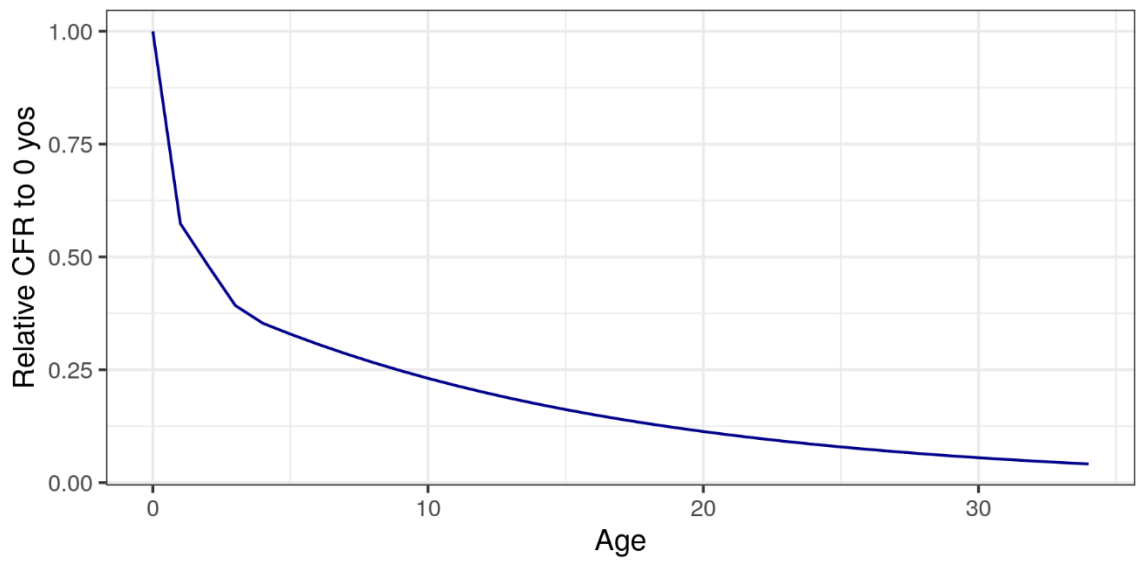
Figure 5. Relationship between age of input data and standardized measles incidence from country-year input data was collected.

Grey lines represent a smooth loess curve, and black lines represent a loess curve weighted on standard error of each input data.
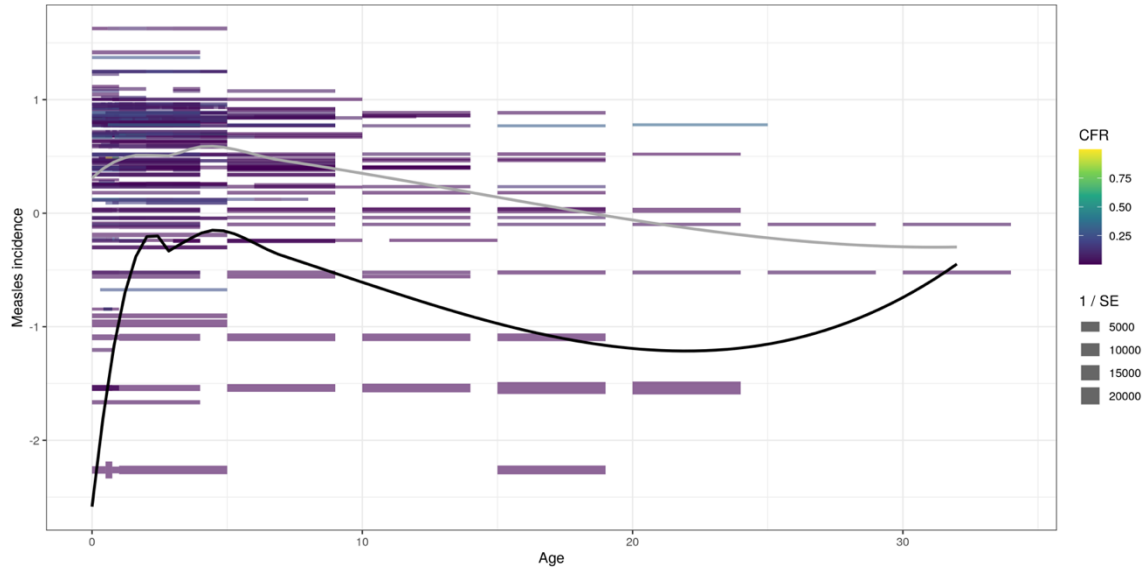
Figure 6. Relationship between age of input data and standardized first-dose measles-containing vaccine (MCV1) coverage from country-year input data was collected.

Grey lines represent a smooth loess curve, and black lines represent a loess curve weighted on standard error of each input data.
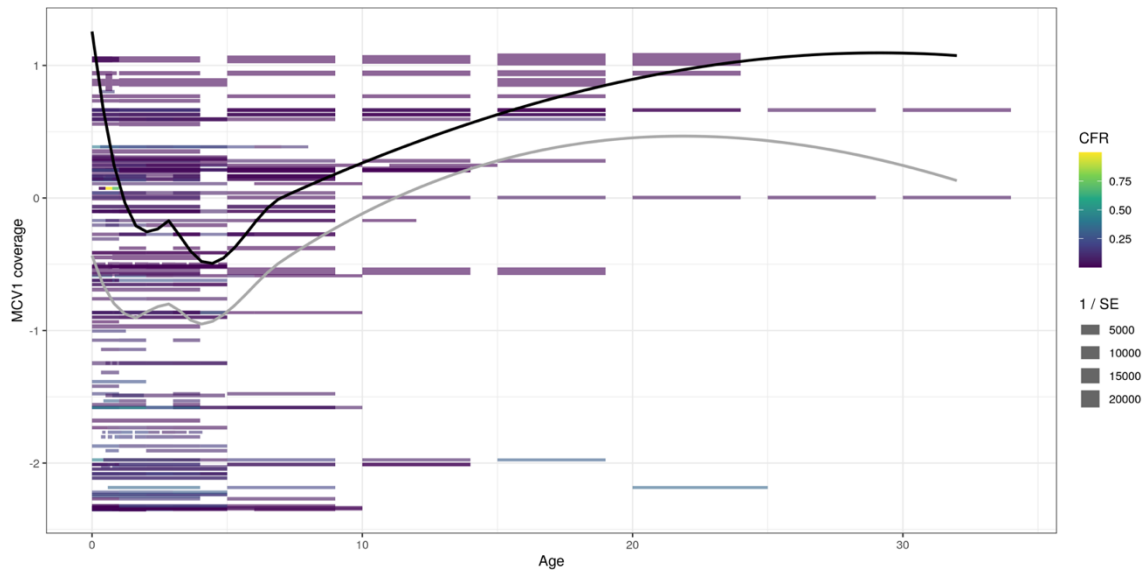
Figure 7. Mean age of measles cases by country and year.

Grey lines represent the mean age of cases by year for each country included in analysis, and the red line is a smoothed LOESS curve through individual country lines.
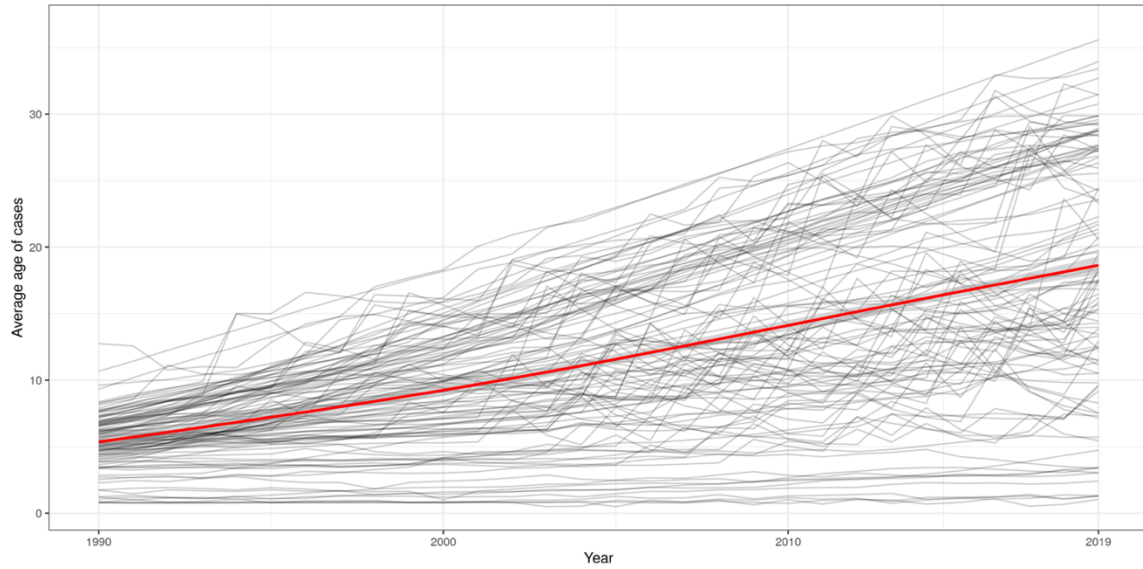
Figure 8. Standardized and unstandardized estimates of case-weighted measles CFR across all countries from 1990 to 2019.

Case-weighted mean CFR across LMICs is presented in yellow, by year. Using the UN standard population from 2019, we age-standardized case-weighted mean CFR estimates for LMICs (shown in red). In blue, we additionally age-standardized case-weighted mean CFR estimates using the age distribution across cases in LMICs in 1990 as our "standard population".
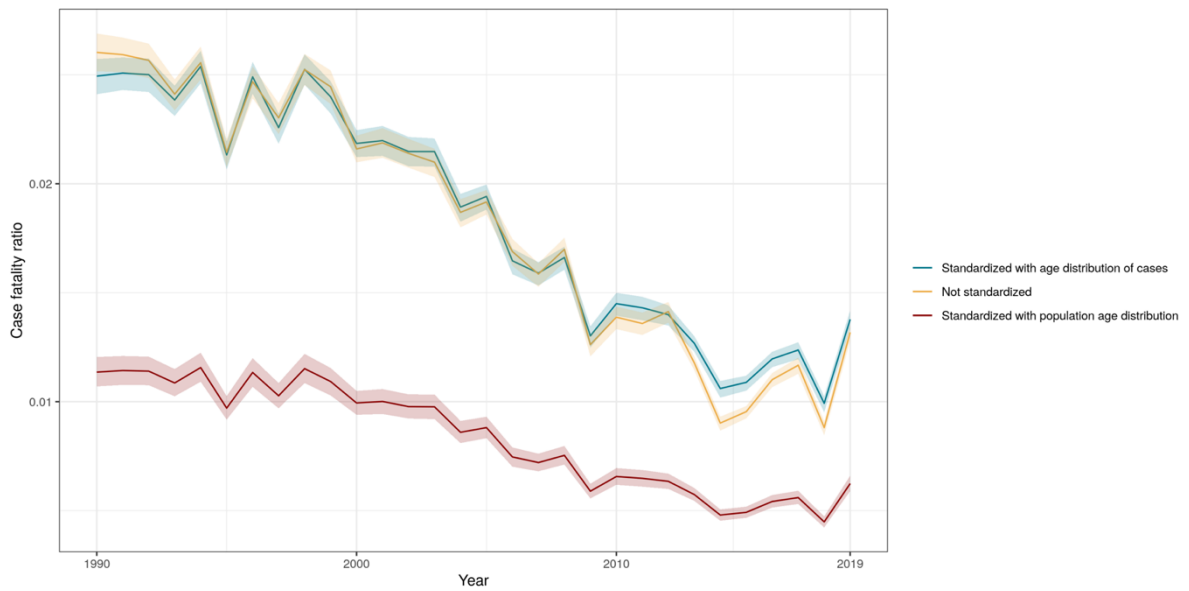
Figure 9a-d. Age-specific, community-based, case-weighted case fatality ratio (CFR) estimates among 0–14-year-olds for low- and middle-income countries – for single years 1990, 2000, 2010, and 2019.
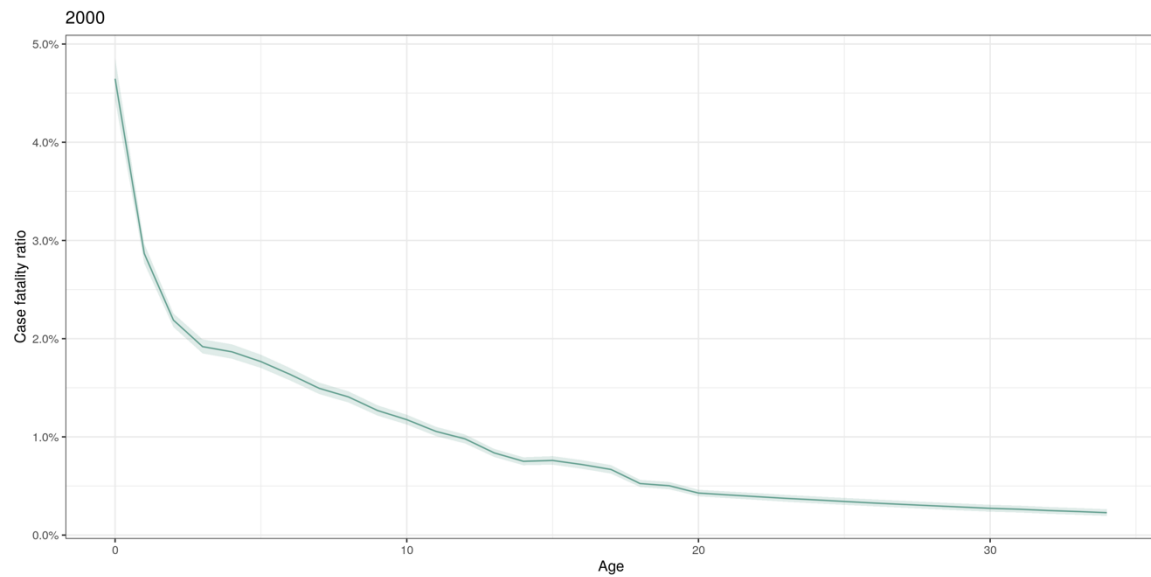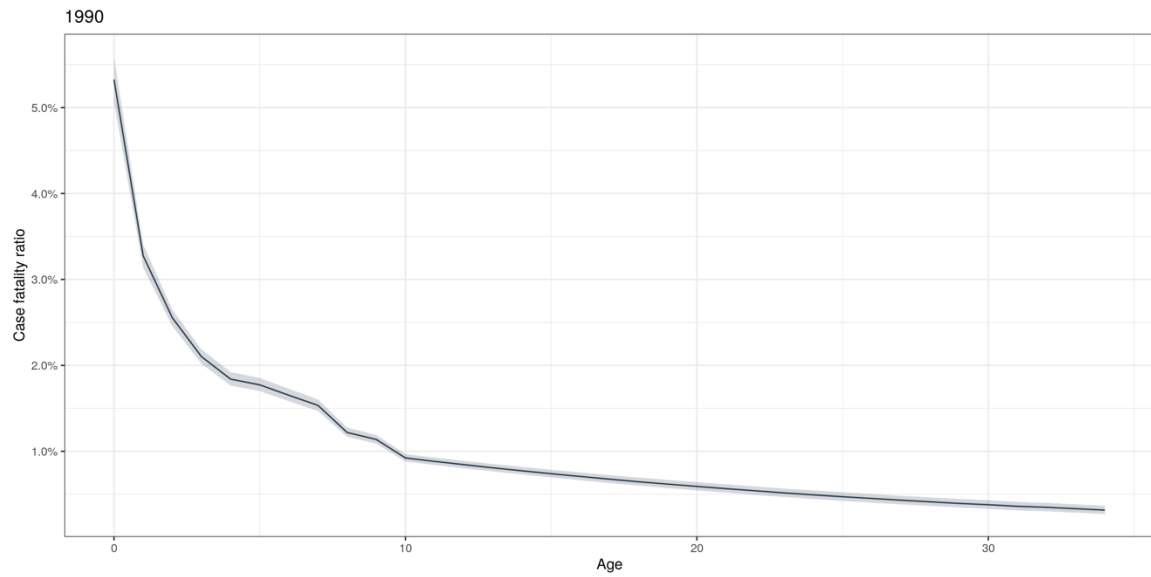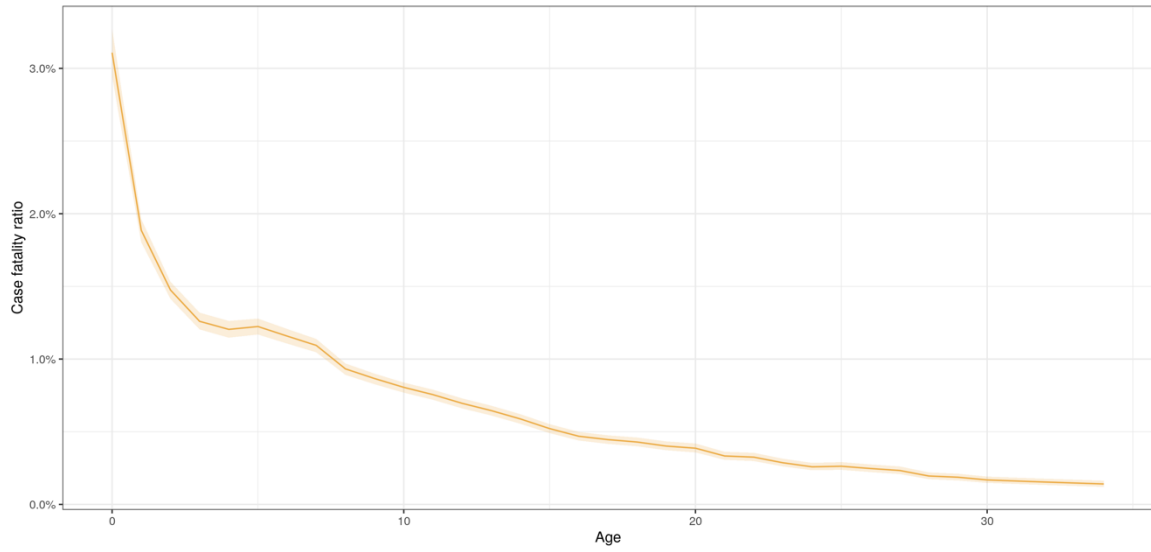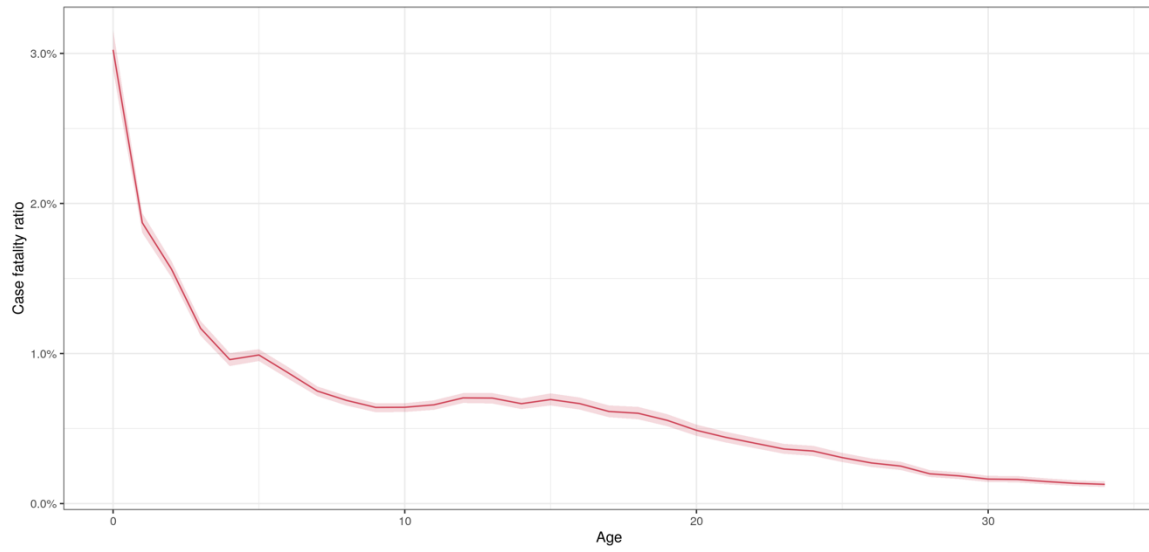
2010

2019

Figure 10a-d. Age-specific, community-based, case-weighted case fatality ratio (CFR) (CFR) estimates among 0–14-year-olds, by region – for single years 1990, 2000, 2010, and 2019.
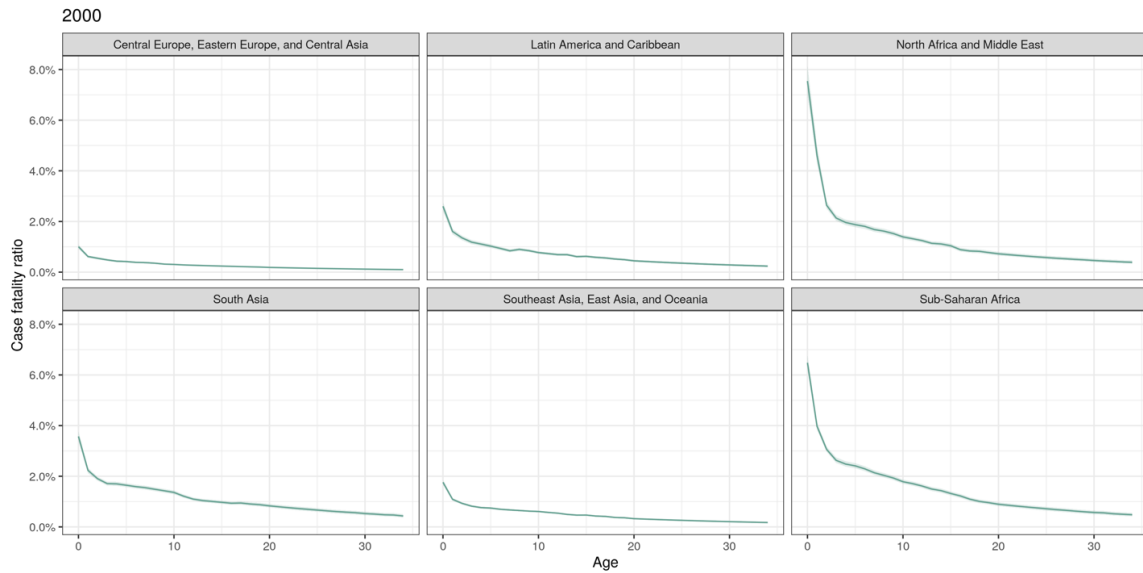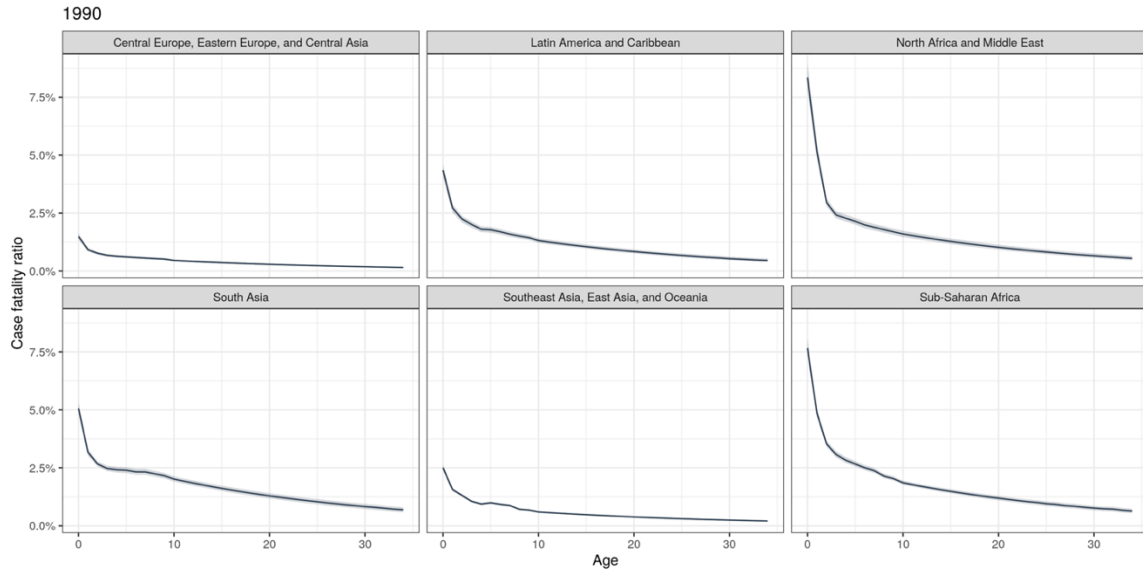
2010
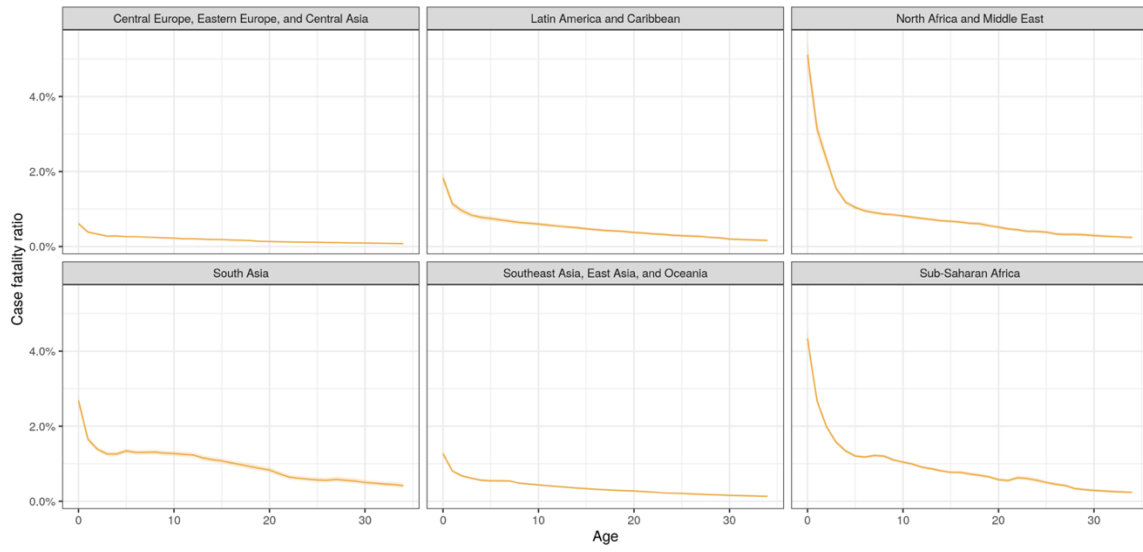
2019
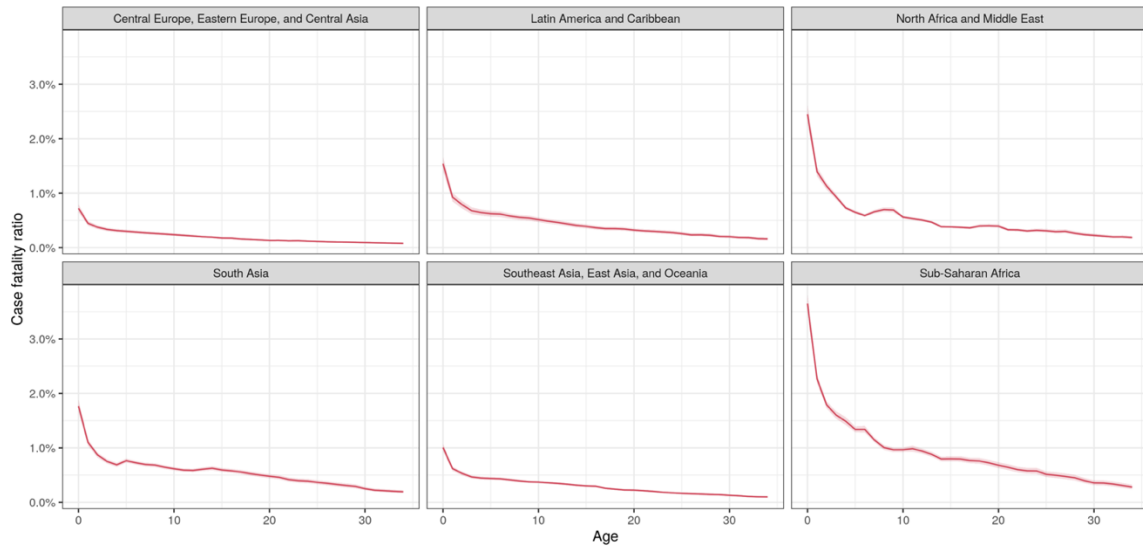
Figure 11. Distribution of CFR values for studies providing information on laboratory confirmation of cases (1) versus not providing information on laboratory confirmation of cases (0).
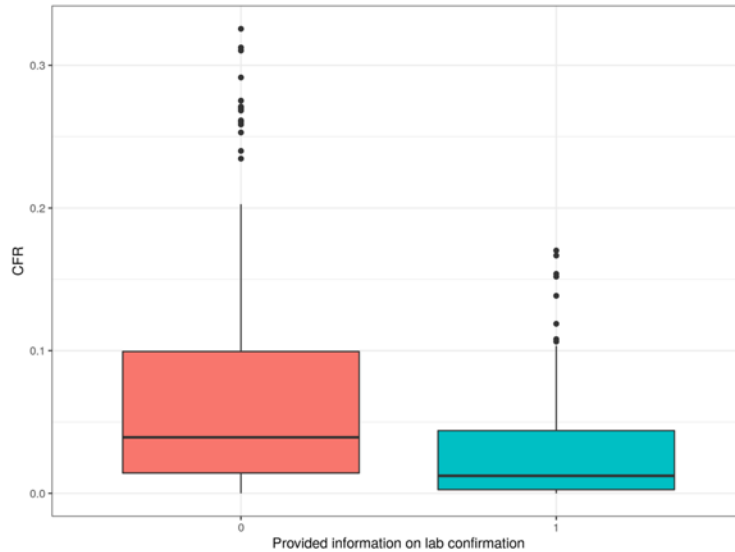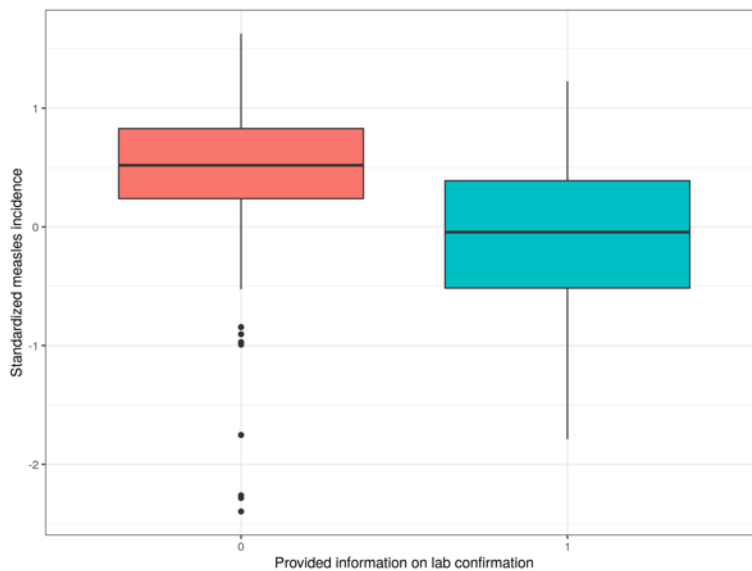

Figure 12. Distribution measles incidence values used for covariates of country-years for studies providing information on laboratory confirmation of cases (1) versus not providing information on laboratory confirmation of cases (0).
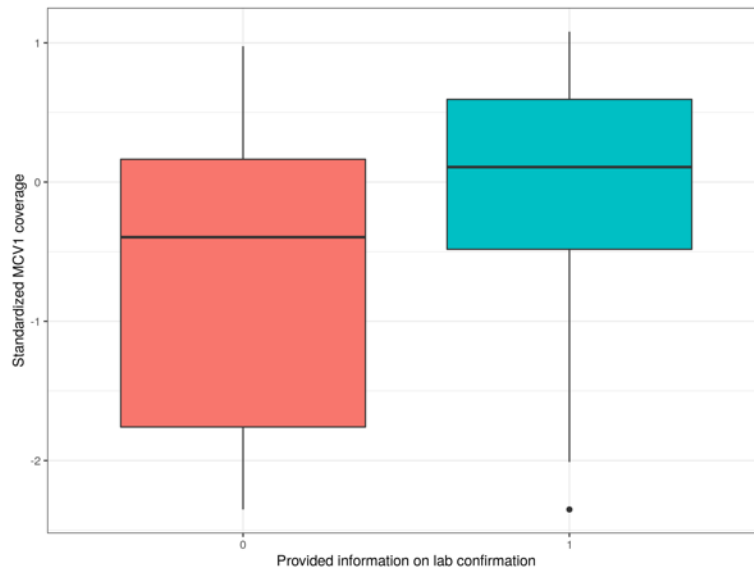
Figure 13. Distribution MCV1 coverage values used for covariates of country-years for studies providing information on laboratory confirmation of cases (1) versus not providing information on laboratory confirmation of cases (0).

Figure 14. CFR estimates from framework using all studies versus only studies providing information on laboratory confirmation of cases, for select years.
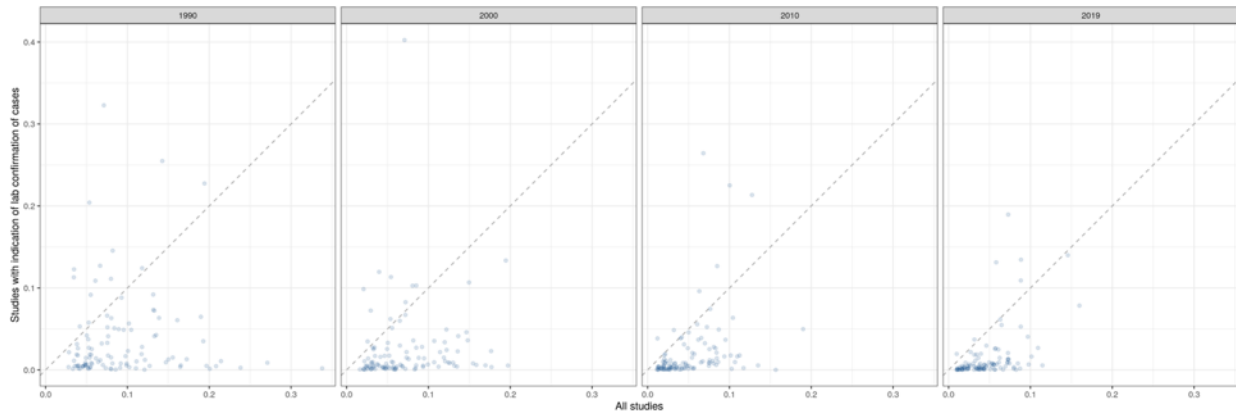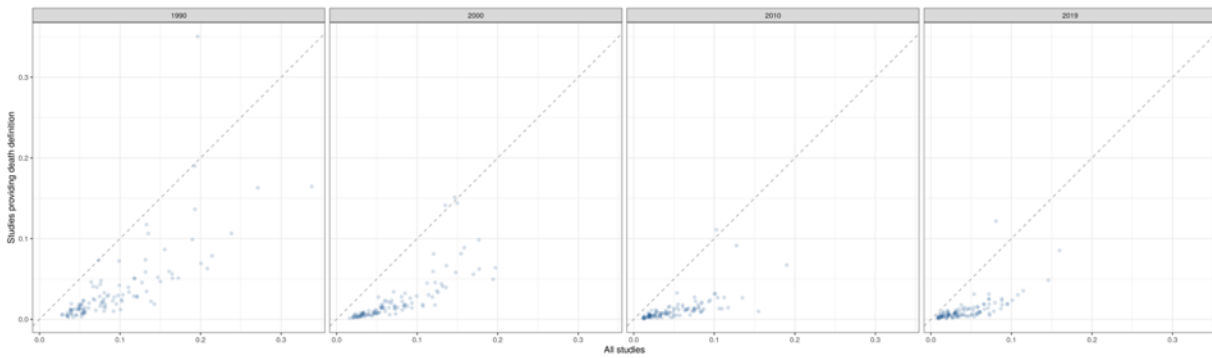

Figure 15. CFR estimates from framework using all studies versus only studies providing definition of death attributable to measles, for select years.

Section 8. References

1   Zheng, P., Barber, R., Sorensen, R. J. & Murray, C. J. Trimmed constrained mixed effects models: formulations and algorithms. *Journal of Computational and Graphical Statistics* **30**, 1-13 (2021).

2   Sbarra, A. N. *et al.* Population-level risk factors related to measles case fatality: a conceptual framework and systematic review of evidence. *medRxiv* (2022). https://doi.org:https://doi.org/10.1101/2022.09.30.22280585

3   *cyipopt*, <https://cyipopt.readthedocs.io/en/stable/> (2022).

4   Portnoy, A. *et al.* Estimates of case-fatality ratios of measles in low-income and middle-income countries: a systematic review and modelling analysis. *Lancet Glob Health* **7**, e472-e481 (2019). https://doi.org:10.1016/s2214-109x(18)30537-0

Appendix E. Ethics

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Ms Alyssa Sbarra

LSHTM

5 January 2022

Dear Alyssa

Submission Title: Development and application of subnational measles incidence and mortality estimates in high burden and incidence settings

LSHTM Ethics Ref: 25262

Thank you for responding to the Observational Committee Chair's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Investigator CV	cv - MOST RECENT	01/04/2021	april2021
Other	Research_Ethics_online_training_certificate	04/05/2021	Sbarra
Investigator CV	cv_oct2021	13/10/2021	13 oct 2021
Protocol / Proposal	leo_ethics_submission_protocol_v1	14/10/2021	14 oct 2021
Covering Letter	ethics_sbarra_coverletter	23/11/2021	23 nov 2021
Protocol / Proposal	MR_non_disclosure _agreement_IHME_revised_Y2020D08M03_CJLM	23/11/2021	23 nov 2021

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor Jimmy Whitworth
Chair

Page 1 of 2

Improving health worldwide

London School of Hygiene & Tropical Medicine

Keppel Street, London WC1E 7HT

United Kingdom

Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Ms Alyssa Sbarra
LSHTM

3 January 2023

Dear Ms Alyssa Sbarra,

Project Title: Development and application of subnational measles incidence and mortality estimates in high burden and incidence settings

Project ID: 25262

Thank you for your annual report application for the continuation of your research dated 17/12/2022 01:05 , which has now been considered by the Chair on behalf of the Ethics Committee.

Confirmation of ethical opinion

This application is approved by the committee for a further year from the date of this letter.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

After ethical review

Any changes to the application must be submitted to the committee via an Amendment form.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reaction (SUSARs) which occur during the project by submitting a SUSAR and Protocol Violation form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at http://leo.lshtm.ac.uk.

Additional information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

Professor David Leon and Professor Clare Gilbert
Co-Chairs

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

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