Long-term waning of vaccine-induced immunity to measles in England: a mathematical modelling study

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Summary

Background Among people infected with measles in England between 2010 and 2019, the proportion of cases who had previously received two doses of vaccine has increased, especially among young adults. Possible explanations include rare infections in vaccinated individuals who did not gain immunity upon vaccination, made more common because fewer individuals in the population were born in the endemic era, before vaccination was introduced, and exposed as part of endemic transmission, or the waning of vaccine-induced immunity, which would present new challenges for measles control in near-elimination settings. We aimed to evaluate whether measles dynamics observed in England between 2010 and 2019 were in line with a waning of vaccine-induced immunity.

Methods We used a compartmental mathematical model stratified by age group, region, and vaccine status, fitted to individual-level case data reported in England from 2010 to 2019 and collected by the UK Health Security Agency. The deterministic model was fitted using Monte Carlo Markov Chains under three scenarios: without the waning of vaccine-induced immunity, with waning depending on time since vaccination, and with waning depending on time since vaccination, starting in 2000. We generated stochastic simulations from the fitted parameter sets to evaluate which scenarios could replicate the transmission dynamics observed in vaccinated cases in England.

Findings The scenario without waning overestimated the number of one-dose recipients among measles cases, and underestimated the number of two-dose recipients among cases older than 15 years (median 75 cases [95% simulation interval (SI) 44–124] in simulations without waning, 196 [95% SI 122–315] in simulations when waning was included, 188 [95% SI 118–301] in simulations when waning started in 2000, and 202 observed cases). The number of onward transmissions from vaccinated cases was 83% (95% credible interval 72–91%) of the number of transmissions from unvaccinated cases. The estimated waning rate was slow (0·039% per year of age; 95% credible interval 0·034–0·044% per year in the best-fitting scenario with waning starting in 2000), but sufficient to increase measles burden.

Interpretation Measles case dynamics in England are consistent with scenarios assuming the waning of vaccine-induced immunity. Since measles is highly infectious, slow waning leads to a heightened burden in outbreaks, increasing the number of measles cases in people who are both vaccinated and unvaccinated. Our findings show that although the vaccine remains highly protective against measles infections for decades and most transmission is connected to people who are unvaccinated, breakthrough infections are increasingly frequent for individuals aged 15 years and older who have been vaccinated twice.

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Introduction

Measles vaccines are highly protective against infection,[1] and led to a great decrease in the global burden of measles after the start of immunisation programmes in the 1970s and 1980s. The probability of primary vaccine failure, whereby individuals do not respond immunologically to the vaccine, is less than 5%.[1,2] The risk of secondary vaccine failure—namely, the loss of immunity over time after vaccination, or waning of vaccine-induced immunity—was first reported after the initiation of routine immunisation programmes in individuals who had received one dose of the vaccine.[3,4]

After successful routine immunisation programmes, some countries in Europe, the Americas, and Asia have become eligible for an elimination status since 2000. However, Europe and the Americas have reported a resurgence of measles between 2015 and 2020,[5] with young adults being increasingly affected in Europe.[6] This resurgence was mostly reported in under-immunised communities and linked to past variations in vaccine coverage.[7]

Occasional outbreaks were also reported in highly vaccinated groups in Portugal and Japan,[8,9] leading to concerns over the waning of measles immunity among adults who had received two doses of measles vaccine during their childhood.[10] Immunological studies from Canada,[11] Japan,[12] and Czechia[13] point towards the waning of antibodies in young adults who had received two doses of vaccine more than 20 years earlier, whereas no decrease was observed in previously infected

Research in context

Evidence before this study

We searched PubMed from database inception up to Feb 29, 2024, with no language restrictions, using the following search terms: ("measles") AND ("secondary vaccine failure" OR "waning") AND ("antibody" OR "vaccine effectiveness"), and excluded studies that focused on waning of maternal antibodies in infants. We found evidence of a waning of antibody concentration in young adults from laboratory data, but this finding might not translate into a loss of protection against infection. We also found estimates of vaccine effectiveness per age group from statistical analysis that used the total number of cases across various outbreaks rather than transmission dynamics. We did not identify any study estimating the waning rate of measles vaccine from recent measles case dynamics.

Added value of this study

Our study uses measles case data from England, reported between 2010 and 2019 and collected by the UK Health Security Agency. Using a modelling approach of three scenarios, one considering no waning, and two scenarios considering waning and comparing these to the observed data, we found that the transmission dynamics in that period were consistent with a waning of vaccine-induced immunity. On average, the number of onward transmissions from individuals who had previously been vaccinated was 72–91% of the number of transmissions from individuals who were unvaccinated, indicating that individuals with vaccination could be associated with onward transmission. Waning of vaccine-induced immunity has increased the burden caused by measles in England since 2010.

Implications of all the available evidence

The available evidence suggests that waning of immunity could result in an increased number of measles cases in vaccinated individuals. Some adults vaccinated during their childhood might be at a risk of infection, and increase the burden caused by measles outbreaks in near-elimination settings. Because vaccine coverage dropped in many countries that were near elimination between 2020 and 2022, more areas are at risk of measles outbreaks, and waning would increase the size of future outbreaks. Investigations into measles cases among vaccinated individuals are needed to evaluate whether waning happens across all near-elimination settings, and what factors affect the waning rate. Future work on an individual-level history of transmission should focus on estimating how often there is onward transmission from vaccinated individuals infected with measles.

individuals.[14] Young vaccinated adults had little exposure to measles in near-elimination settings, suggesting that the waning of vaccine-induced immunity might be related to the time since the end of endemic transmission.[15] However, low levels of antibody concentrations might not result in a complete absence of protection against infection.

Analyses from outbreak data suggest a drop in vaccine effectiveness among young adults who had received two doses of vaccine in France (from 99·6% immediately after vaccination to 96·7% 16 years after after receiving a second vaccine dose) and in Berlin (from 99% immediately after vaccination to 90·9% in individuals aged 31–40 years, 25–30 years after receiving a second vaccine dose).[16,17] Both studies computed the age-stratified vaccine effectiveness using the screening method, a statistical calculation of vaccine effectiveness similar to a case–control study where the vaccine coverage in the whole population is considered as the control. Franconeri and colleagues[16] showed that the vaccine effectiveness estimates were sensitive to assumptions on infection-induced immunity: the estimates of vaccine effectiveness in older age groups increased in scenarios where the proportion of the population with infection-induced immunity was higher. The method implemented in both studies relied on total case numbers per age group and did not take into account outbreak dynamics.

It is crucial to understand whether measles case dynamics observed in settings with high vaccine coverage result from a waning of vaccine-induced immunity, or whether changes in the distribution of immunity in the population are driving the distribution of vaccine status among cases, because fewer adults were born in an era of endemic transmission before vaccination had been widely introduced. Using a mathematical transmission model stratified by age, region, and vaccine status we aimed to evaluate whether measles dynamics observed in England between 2010 and 2019 were in line with a waning of vaccine-induced immunity. Such dynamic models are able to capture the non-linear interplay between vaccination and infection-induced immunity, and disentangle its effect on historical case data. We applied this model to measles case data by region and age group reported between 2010 and 2019 in England. Measles in England follows typical near-elimination transmission dynamics, with sporadic localised outbreaks and high national vaccine coverage. After large outbreaks between 2011 and 2013, England reached measles elimination status after there were low levels of transmission until 2017. A resurgence of measles was observed from 2017 onwards.[18]

We modelled three possible scenarios: (1) vaccinated individuals might only become infected because of primary vaccine failure; (2) vaccinated individuals might become infected because of primary or secondary vaccine failure, with the risk of secondary vaccine failure depending on age; and (3) vaccinated individuals might become infected because of primary or secondary vaccine

failure, with the risk of secondary vaccine failure depending on age and time since measles stopped being endemic (ie, waning of vaccine-induced protection started in 2000).[15] We fitted each scenario to measles case data reported in England between 2010 and 2019, and compared the resulting performance to assess the most plausible scenario.

Methods

Data sources

Data on all confirmed measles cases in England between 2010 and 2019 were collected by Public Health England (now the UK Health Security Agency). This dataset included the date of symptom onset, region of residence, age, and vaccine status of each individual. Only cases reported in England with no missing information on age and onset date were considered. When the region of residency was not reported (996 cases), we used the region of the general practitioner who reported the case, because 95% of individuals resided in the same region as the general practitioner when both were reported. The final case dataset contained 7504 cases.

Vaccine status was labelled no for individuals who had not been vaccinated, v1 for individuals who had received one dose of the vaccine before being infected, or v2 for individuals who had received two doses of the vaccine. Between 2014 and 2019, the vaccine status of 143 individuals was reported as yes. We classified these individuals as one-dose recipients since no other individual was classified as v1 between 2014 to 2019 (whereas 152 were classified as v2). Furthermore, 19 of the individuals classified as yes were 3 years or younger, which is younger than the recommended age for the second dose of vaccine in the UK (current recommended age of vaccination: 1 year for the first dose, and 3 years and 4 months for the second dose). Vaccine status was unknown for 105 patients (1·4% of all cases) from all age groups, regions, and outbreak years, and these cases were set as unvaccinated.

General framework of the compartmental model

We use a compartmental Susceptible-Exposed-Infectious-Recovered-type model to fit the number of daily cases per age group, region, and vaccine status in England between 2010 and 2019 (figure 1). Upon infection, individuals moved from "susceptible" to "exposed", from "exposed" to "infectious" at the end of the latent period, and moved to the "recovered" compartment when the infectious period ended.

We implemented the model using the R package odin.dust. The model was stratified by age, region, and vaccine status. For each stratum, the likelihood was computed by comparing the daily case data to the number of cases moving from exposed to infectious compartments each day. The log likelihoods in each stratum were then added to compute the overall log likelihood (appendix p 11). The model estimated how quickly measles spread (infection rate, seasonality, and contact matrix between age groups and regions), how often measles was imported from other countries (number and seasonality of importations), and how protective and effective the vaccine was (rate of primary vaccine failure, protection against onward transmission, and rate of waning in scenarios with waning). Using a mix of data and parameters, the model estimated the distribution of immunity in each age group and region at the start date (Jan 1, 2010). The duration of latent and infectious periods were exponentially distributed, with a fixed mean. The timing and duration of outbreaks were affected by the seasonality of transmission (estimated), the seasonality of importations (estimated), and the number of importations by region (fixed, with an estimated report rate). All parameters are summarised in the appendix (pp 2–7). The infection rate, infectious period, and contact between age groups and regions was used to compute the basic reproduction number (R_0), defined here as the mean number of secondary cases generated by a typical infectious individual in a fully susceptible population. Measles is highly infectious, with an R_0 typically ranging between 12 and 18, although it can vary outside this range.[19]

We implemented a linear waning of vaccine-induced immunity. The risk of becoming infected increased with each year of age. Because individuals were classified in age groups (figure 2B), the waning followed a stepwise function, with the risk of infection being the same for all individuals in a given age group (appendix p 4).

The parameters were estimated by fitting a deterministic version of the model to the case data. The parameter

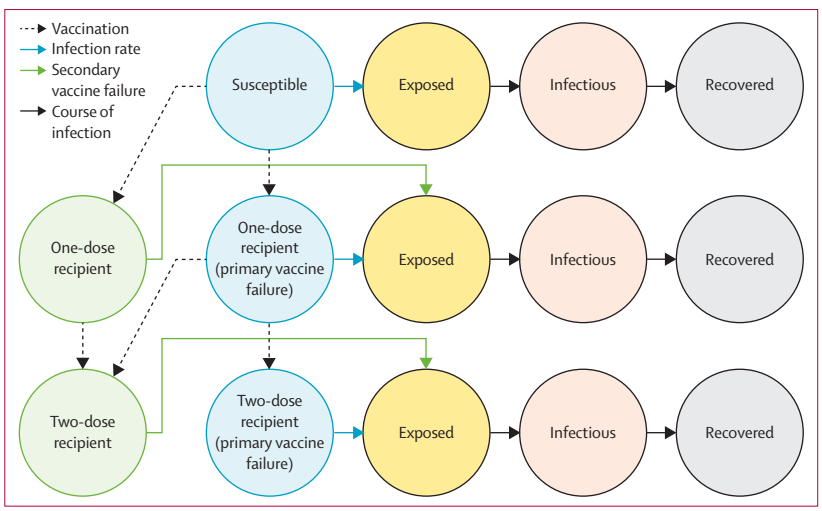

Figure 1: **Schematics of the compartmental transmission model**
The model is stratified by age and region, which means that the compartmental structure is repeated in each age group and region stratum. In the <1 year age group, individuals are placed in the maternal immunity compartment (not pictured) when they are born, and move into the susceptible compartment at a rate defined by the duration of maternal immunity. In the 40 years and older age group, individuals exit the recovered compartment at a rate corresponding to the number of deaths per day. In the scenario without waning, the two grey vaccinated compartments are not connected to the exposed compartments.

See Online for appendix

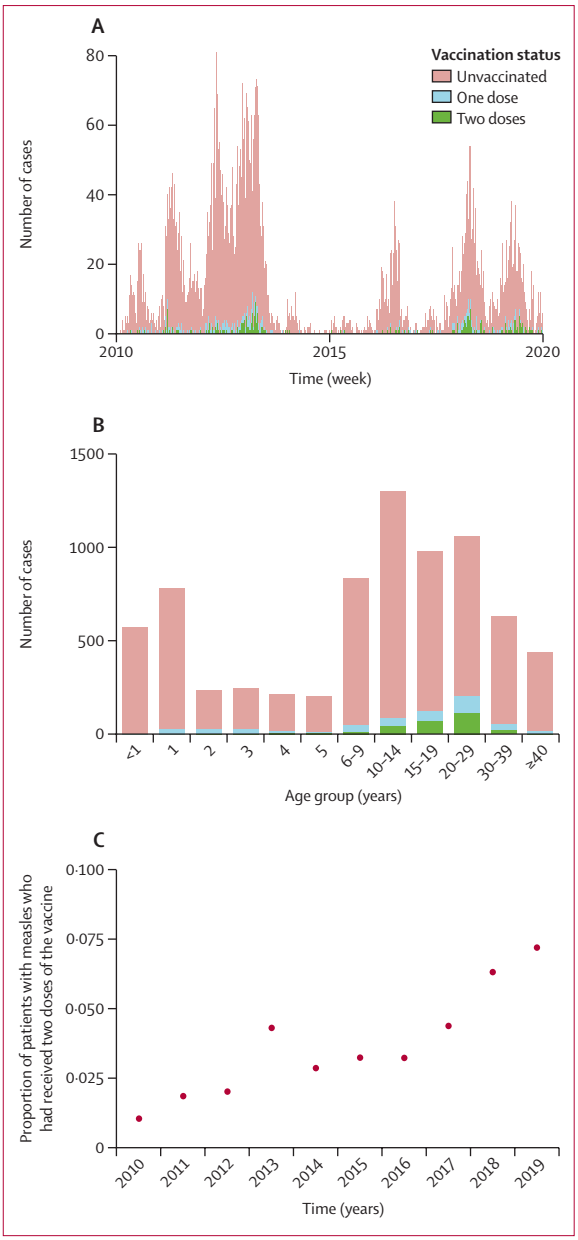

Figure 2: **Description of measles case data reported in England between 2010 and 2019**

(A) Number of weekly measles cases reported in England between 2010 and 2019, stratified by vaccine status. (B) Number of cases reported between 2010 and 2019 by age group and vaccine status. (C) Proportion of individuals with measles who had received two doses of the vaccine per year.

sets were used to generate stochastic simulations between Jan 1, 2010, and Dec 31, 2019, using a version of the model where transitions between compartments were treated as a stochastic process. The stochastic simulations showed the set of dynamics the parameter estimates could generate, with a higher variance than the deterministic fits. Fitting a stochastic version of the model was not computationally feasible given the number of compartments and stratum.

Vaccination data

The model required the proportion of vaccinated individuals for each age group and region, over time. Two sources of vaccination data were used: Cover of Vaccination Evaluated Rapidly (COVER), a dataset published by NHS Digital summarising UK vaccination coverage at the age of 2 years and 5 years per region for the measles, mumps, and rubella (MMR) vaccine;[20] and Clinical Practice Research Datalink (CPRD) Aurum, a primary care dataset from general practitioner practices containing patient-level information on immunisations.[21] The appendix (pp 11–15) shows a comparison between COVER data and CPRD data. CPRD coverage tended to be higher than raw COVER data. Data for years not covered by CPRD data (children born before 2006 or after 2015) were supplemented with estimated values by region based on COVER data adjusted for 50% under-ascertainment. These corrected values were consistent with estimates from previous studies.[22] Region-stratified coverage data were not available for children born before 2004, so we used the first and second dose coverage from the UK Health Security Agency's risk assessment for measles resurgence in the UK (based on COVER data), which gives the national coverage in all of England and in London specifically.[23]

The first MMR vaccine dose is given from the age of 1 year, so most children get vaccinated between the age of 1 year and 2 years. Because the model was stratified in age groups, all children would have been unvaccinated until they reached 2 years if the model used MMR coverage at 1 year and 2 years. This would not be an accurate representation of reality and could introduce biases. Thus, first-dose coverage at 1 year was set to 75% of the first-dose coverage at 2 years in the model. Similarly, the second MMR dose is given from the age of 3 years and 4 months, so most children would have received their second dose between 3 and 4 years. We set the second-dose coverage at 3 years to 50% of the second-dose coverage at 4 years.

England introduced a one-dose MMR routine schedule in 1988, and moved to a two-dose schedule in 1996. Before 1988, individuals received one dose of a measles-containing vaccine. In the reference analysis, we assumed that no individual in the 30–39 year age group (born in the 1970s) and 40 years and older age group (born before 1970) in 2010 had been vaccinated against measles. In England, routine vaccination against measles started in 1968, so individuals born in the 1970s did receive one dose of the vaccine. However, because measles was still endemic at that time, infection before vaccination was more common, and a substantial proportion of individuals vaccinated in the 1970s might have been vaccinated in catchup campaigns, making assumptions about age at second dose and coverage challenging. Hence, the reference analysis assumed that only infection-induced immunity (ie, providing full non-waning protection) was possible in this age group.

Scenarios and sensitivity analysis

We assessed whether the waning of vaccine-induced immunity affected measles dynamics by comparing three scenarios: without the waning of immunity (ie, transmission between the vaccinated and the exposed compartments is only possible in the case of primary vaccine failure), with the waning of immunity increasing with each year of age from 5 years, and with the waning of immunity increasing with each year of age from 5 years and from the year 2000. In the third scenario, individuals vaccinated before 2000 had full protection until 2000, when the waning of immunity is then linked to the low rates of transmission observed since 2000 in England.[24] All scenarios included primary vaccine failure. Waning starts at the age of 5 years because most vaccinated individuals have received their second dose by then (appendix pp 13–14). We compared the posterior distributions to find the best performing scenario, and used stochastic simulations to show which scenarios captured the transmission dynamics observed in vaccinated cases. If measles dynamics had been affected by the waning of immunity, then the scenarios with waning should better capture the transmission dynamics. Additional figures describing the reference scenario fits and simulations are shown in the appendix (pp 15–20).

We used sensitivity analyses to assess whether the effect of waning of immunity was robust to changes in assumptions, including: (1) the addition of a constant risk of secondary vaccine failure estimated by the model—namely, that the protection against infection is not perfect, but is not waning over time (appendix pp 21–23); (2) using the COVER data without adjustment for under-ascertainment, and using the CPRD data to compute the proportion of newly vaccinated individuals at the age of 3 years and 4 years (appendix pp 24–29); (3) estimating the proportion of individuals aged 30–39 years in 2010 who received one dose of the vaccine (appendix pp 29–32); (4) fixing the cross-regional transmission rate to test different transmission patterns between regions (appendix pp 32–36); and (5) setting the start of waning to 1995 in a scenario where waning depends on both age and time since end of endemicity (appendix pp 36–39).

In each scenario, the model was fit using Monte Carlo Markov Chains, with 20 000 iterations and a burning period of 1000 iterations. Samples from the posterior distribution were used to compute the 95% credible interval for each parameter of each scenario. We compared the performance of each scenario using the posterior density distribution. We then generated stochastic simulations from the parameter samples (5000 simulations per scenario), and compared the simulations with the transmission dynamics observed in the data among vaccinated and unvaccinated cases. The simulations were described using the 95% and 50% simulation intervals (ie, the 95% and 50% percentile of the number of recipients across the simulations for this scenario). All analyses were generated in R (version 4.4.0).

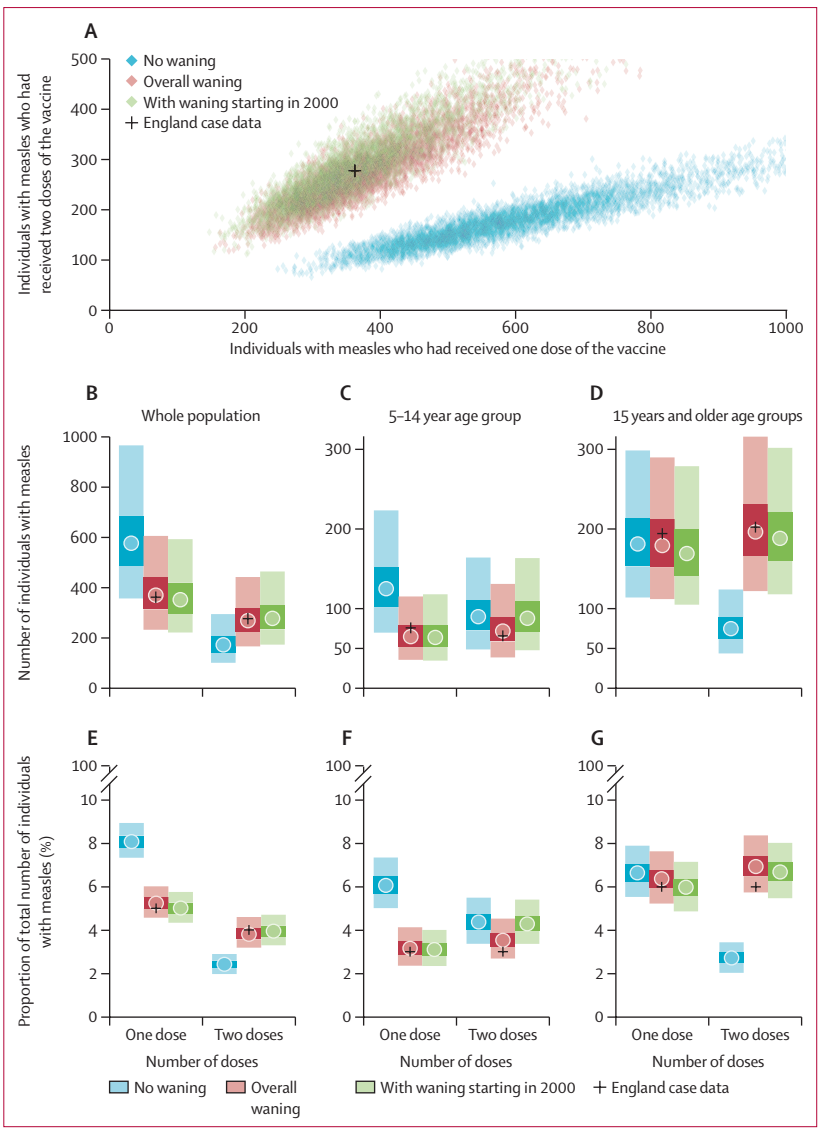

Figure 3: **Comparison of the age distribution of vaccinated cases in each scenario and in the data**
(A) Comparison of the number of individuals with measles who received one and two doses of the vaccine (orange and red dots cover the same area, and so might be masking each other). (B) Overall number of individuals with measles vaccinated in each scenario and in observed data. (C) Number of individuals aged 5–15 years who were vaccinated. (D) Number of individuals with measles older than 15 years who were vaccinated. All plots show the number of cases across all regions and years. (E) Percentage of total number of individuals vaccinated in each scenario and in observed data. (F) Percentage of individuals with measles aged 5–15 years who were vaccinated. (G) Percentage of individuals with measles 15 years and older who were vaccinated. In panels B–G, the black cross represents the value observed in the data, the dark area shows the 95% simulation interval, the light area shows the 50% simulation interval, and the dot shows the median value in each scenario.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The annual proportion of individuals who had been infected with measles who had received two doses of the vaccine out of the overall number of individuals

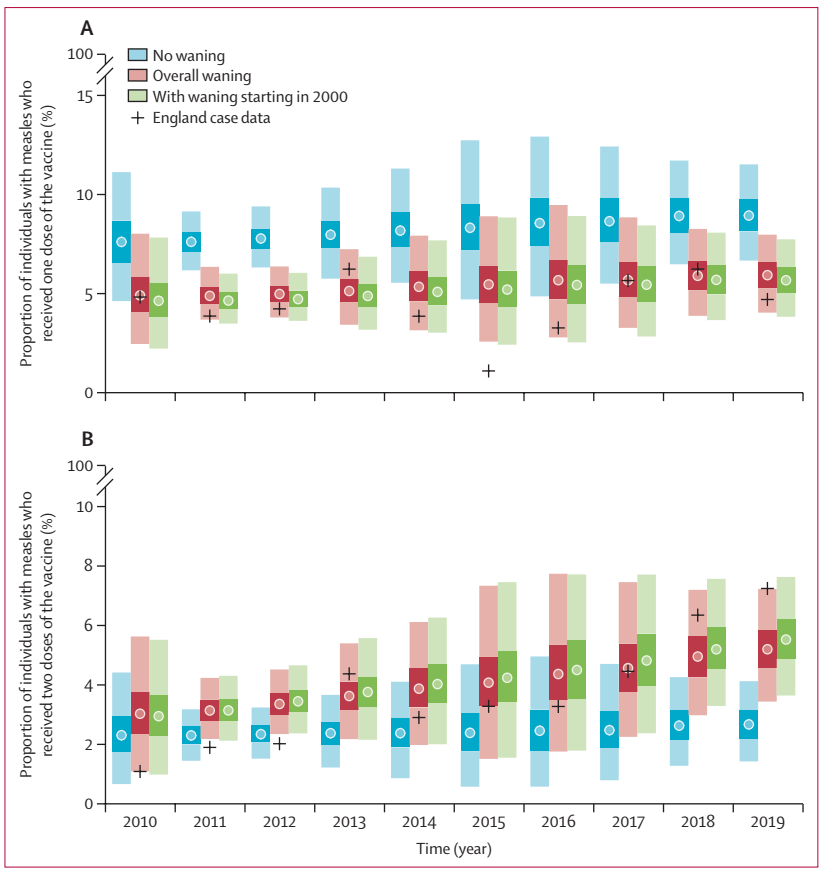

Figure 4: **Percentage of individuals with measles who had been vaccinated each year across all regions and age groups in each scenario and in the data**

(A) One dose. (B) Two doses. Black crosses represent the value observed in the data, the dark area shows the 95% simulation interval, the light area shows the 50% simulation interval, and the dot shows the median value in each scenario.

with measles was three times higher in 2019 than in 2011 (figure 2A, C). The median age of individuals with measles was 12·5 years, with 2280 (30·4%) of 7504 individuals aged 10–19 years, and 1059 (14·1%) individuals aged 20–29 years (figure 2B).

The posterior density distribution of each scenario showed that scenarios integrating waning of vaccine-induced immunity better captured measles case dynamics than the scenario without waning (appendix p 15). In particular, only scenarios with waning captured the distribution of vaccinated cases by age group and over time; when waning of immunity was not included in the model, the simulations could not reproduce the number of cases among those who had received one dose and two doses of the vaccine observed in the data (figure 3A), the number of one-dose recipients among cases was overestimated (median 561 cases; 95% simulation interval [SI] 354–939; 362 cases in the data), and the number of two-dose recipients was underestimated (median 168 cases; 95% SI 102–287; 277 cases in the data; figure 3). Similarly, the scenario without waning overestimated the number of one-dose recipients among children infected with measles (5–15 years: median 125 cases; 95% SI 70–233; 76 cases in the data), and underestimated the number of two-dose recipients among teenagers and adults (median 75 cases; 95% SI 44–124; 202 cases in the data; figure 3B–G). When incorporating a constant risk of secondary vaccine failure, the overall number of vaccinated cases in the scenario without waning was similar to the data (one-dose recipients among cases: median 351 cases [95% SI 222–572], 362 in the data; two-dose recipients among cases: median 296 cases [95% SI 180–498], 277 in the data; appendix pp 21–24), but the age distribution of two-dose recipients did not correspond with the observed data: there were 150 estimated two-dose recipients among individuals aged 5–15 years (95% SI 85–265) and 66 in the data; and 135 estimated two-dose recipients among individuals older than 15 years (95% SI 84–219) and 202 in the data (appendix p 21). Only simulations including waning of vaccine-induced immunity captured the age distribution of vaccinated cases (estimated number of one-dose recipients among cases in the scenario with waning, 370 cases [95% SI 233–605], with waning starting in 2000: 352 cases [222–592]; 362 cases in the data; estimated number of two-dose recipients among cases for the scenario with waning: median 269 cases [167–442]; and with waning starting in 2000: 278 cases [174–464]; 277 cases in the data; estimated number of two-dose recipients among teenagers and adults for the scenario with waning: 196 cases [122–315], with waning starting in 2000: 188 cases [118–301], 202 in the data; figure 3).

The annual proportion of vaccinated cases was better captured by scenarios incorporating the waning of immunity (figure 4). The scenario without waning overestimated the annual proportion of one-dose recipients among measles cases (2010: 7·3% [95% SI 4·2–11·2%], data: 4·8%; 2014: 8·0% [4·8–11·7%], data: 3·8%; 2018: 8·7% [5·9–11·7%], data: 6·2%). In both scenarios, when waning of vaccine-induced immunity was included, the proportion of one-dose recipients who were infected with measles was similar to the data every year except in 2015, where case numbers were low (there were 92 cases in 2015, only one of which was a one-dose recipient; scenarios with waning: 2010: 5·0% [95% SI: 2·5–8·3%]; 2014: 5·3% [3·1–8·0%]; and 2018: 5·9% [3·8–8·4%]; scenarios with waning starting in 2000: 2010: 4·8% [2·2–8·0%]; 2014: 5·1% [2·8–8·2%]; and 2018: 5·7% [3·6–8·3%]). The observed proportion of two-dose recipients within measles cases increased over time. The scenarios with waning also showed an increase; when waning started in 2000, the increase was slightly faster (scenarios without waning: 2010: 2·1% [95% SI 0·4–4·4%], data: 1·1%; 2014: 2·2% [0·5–4·2%], data: 2·9%; 2018: 2·5% [1·0–4·2%], data: 6·3%; with waning: 2010: 2·8% [0·9–5·3%]; 2014: 3·6% [1·7–5·9%]; 2018: 4·6% [2·7–6·8%]; with waning starting in 2000: 2010: 2·9% [0·9–5·5%]; 2014: 3·9% [1·7–6·4%]; 2018: 5·0% [2·9–7·3%]; figure 4B).

In all modelled scenarios, the R_0 was estimated between 16 and 18 (scenarios without waning: 16·6 [95% credible interval (CrI): 16·2–17·0]; scenarios with waning: 17·2 [16·9–17·6]; scenarios with waning starting in 2000: 17·1 [16·8–17·4]; figure 5A; appendix p 18), which is within the typical range for measles (between 12 and 18). Scenarios incorporating the waning of immunity estimated a decrease in vaccine effectiveness over time, although vaccine effectiveness was still high after several decades (figure 5D). The waning rate was 0·039% per year (95% CrI 0·034–0·044%) in the scenario with waning starting in 2000 and 0·028% per year of age (95% CrI 0·025–0·033%) in the scenario with consistent waning. The rate of primary vaccine failure was higher in the scenario without waning (median estimate, 5·1% [95% CrI 4·8–5·4%]), than with waning (2·4% [2·1–2·7]) or with waning starting in 2000 (2·3% [2·0–2·6]; figure 5C; appendix p 18). The number of onward transmission from vaccinated cases compared with unvaccinated cases was estimated to be 83% (95% CrI 72–91%; figure 5B) when waning started in 2000, and more than 80% in all scenarios (without waning: 84% [95% CrI 73–92%], with waning 82% [71–90%]). Therefore, in the reference analysis, the risk of onward transmissions from vaccinated cases were similar to that from unvaccinated cases. The risk of onward transmission was lower when using the COVER vaccine data compared with the CPRD data (between 10% and 45%; appendix p 28).

We estimated the effect of waning on case numbers by setting the waning rate to 0 in scenarios that incorporated waning, and comparing case numbers with the reference simulations (appendix p 20). Removing waning substantially decreased the number of cases in the simulations, especially in 2018 and 2019 (from 524 [95% SI 266–962] to 408 [216–728] cases in the simulations in 2018 compared with 963 in the data; and from 654 [346–1154] to 478 [260–806] cases in the simulations in 2019 compared with 790 in the data). Removing waning had less effect on case numbers in the sensitivity analysis using COVER data compared with the CPRD data (appendix p 29).

The overall distribution of cases by age group, year, or region was the same in all scenarios (appendix p 19). The simulated number of cases by age groups were similar to the data, although the number of cases in infants were underestimated. The number of cases reported in northwest and northeast England were underestimated, and the burden in east Midlands and west Midlands was higher than the data (appendix p 19). Discrepancies in the spatial distribution of cases were expected because R_0 was not stratified by region, and spatial heterogeneity in transmission risk only depended on region-stratified vaccine coverage, available for cases vaccinated from 2004 onwards (appendix p 5).

We implemented a sensitivity analysis allowing for vaccination in individuals aged 30–39 years in 2010 (ie, born between 1970 and 1980). As in the reference scenario, we found that only scenarios with waning were able to capture the age distribution of vaccinated cases (appendix pp 29–32). All scenarios estimated that the proportion of people aged 30–39 years who were vaccinated was less than 50% (without waning: 36% [95% CrI 23–48%], with waning: 9% [5–14%], with waning starting in 2000: 19% [11–30%]), and the waning rate was similar to the reference analysis (with waning: 0·026% per year of age [0·022–0·029%], with waning starting in 2000: 0·037% per year of age [0·032–0·042%]). We implemented a sensitivity analysis to assess the effect of changing the spatial kernel between regions of England (appendix pp 32–36). The fixed spatial kernel did not change the dynamics in vaccinated cases in each scenario: only scenarios with waning could reproduce the number and age distribution of cases in individuals who had received one or two doses of the vaccine. Finally, we implemented a sensitivity analysis setting the start of waning to 1995 (instead of 2000), which slightly decreased the waning rate (0·033% per year of age [0·029–0·037%]), but did not change the transmission dynamics among vaccinated cases in the scenario with waning (appendix pp 36–39).

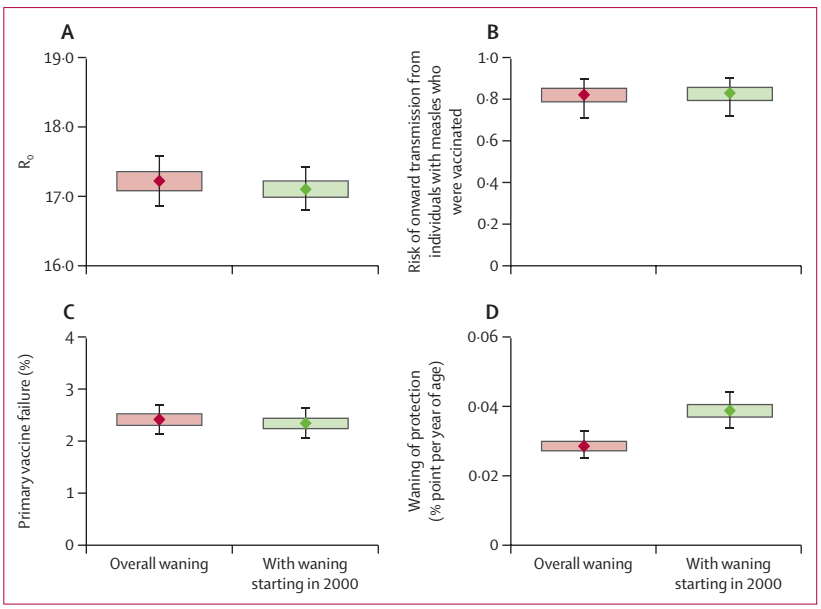

Figure 5: **Key parameter estimates in the two scenarios including waning of vaccine-induced immunity (using Clinical Practice Research Datalink vaccine data)**
(A) Basic reproduction number R_0. (B) Risk of onward infection from individuals with measles who were vaccinated compared with those who were not vaccinated. (C) Proportion of primary vaccine failure (ie, proportion of vaccinated individuals who do not gain immunity after vaccination). (D) Rate of waning of vaccine-induced immunity (in percentage point per year of age). Rectangles represent the 50% credible intervals, bars represent the 95% credible intervals, and dots represent the median estimates.

Discussion

We found that the waning of vaccine-induced immunity best explained observed measles transmission dynamics among vaccinated cases in England. In the scenario

where waning started in 2000, the estimated waning rate was 0·039% per year (95% CrI 0·034–0·044%). Although slow, waning was associated with an increased burden over time; setting the waning variable in this scenario to 0 led to a substantial decrease in cases (appendix p 20). The overall vaccine effectiveness was estimated to stay high over the decades despite this waning, but our estimation suggests that the increasing number of breakthrough infections has contributed to the measles burden in England.

The additional disease burden brought by waning is directly related to the risk of transmission from vaccinated cases, since individuals infected by people who had been vaccinated would not have been infected without waning. In the reference scenario, vaccinated and unvaccinated cases had similar rates of onward transmission (figure 5B). Onward transmission from vaccinated cases was rarer in sensitivity analyses using COVER data (appendix p 28). So far, epidemiological reports have shown rare but existing onward transmission events from vaccinated cases,[9,25,26] potentially because unvaccinated cases cluster in groups with lower vaccine coverage (eg, related to religious beliefs or inequal access to health care) so opportunities of transmission are rarer for vaccinated individuals.[27,28] Contact tracing investigations or transmission tree reconstruction methods[29] with better spatial resolution should be used to quantify how often vaccinated cases are associated with onward transmission.

Early signs of waning-linked transmissions have been observed through outbreaks in other near-elimination settings (Europe[8] and Japan[9]). Future analyses should assess whether other near-elimination countries show similar waning rates and identify population-level factors influencing the waning rate. Such estimates will be crucial to evaluate the current ability to eliminate measles in high-coverage settings. The proportion of measles cases that are two-dose recipients is increasing faster in the data than in all simulated scenarios, so waning dynamics might be more complex than what we tested. Our model integrates linear waning (ie, an absolute reduction in vaccine effectiveness for each year of age). Because individuals are classified in age groups, waning follows a stepwise function, where vaccinated individuals in a given age group all have the same waning rate. Age-specific variations in the waning rate might better explain the data.[14] We considered that the waning of vaccine-induced immunity starts at the age of 5 years, which does not account for individuals vaccinated later in life. Allowing for disparities would have required adding multiple compartments and parameters to the model, thereby creating identification issues. However, local vaccine coverage data show that the second dose of MMR coverage at 5 years usually exceeds 90%, so most individuals would have been vaccinated before waning started in our model.

Epidemiological reports have highlighted that symptoms in vaccinated cases are milder (less likely to develop conjunctivitis, fever, or coryza), thereby increasing the risk of under-reporting.[9,25] National measles guidelines in the UK state that the number of vaccinated cases is expected to increase with the higher availability of testing and a better reporting rate.[30] If the testing rate similarly increases among unvaccinated groups, the proportion of vaccinated cases would be unchanged. However, improvements in testing patterns specific to some settings or subpopulations (eg, in health-care settings) would lead to an increase in case numbers specific to vaccinated cases, especially because unvaccinated cases are more likely to be part of marginalised communities with less access to health care and vaccination. This might partly explain the increase in proportion of vaccinated cases. However, only the proportion of two-dose recipients increased, whereas the proportion of one-dose recipients was constant (figure 4), indicating changes in dynamics specific to adults and teenagers vaccinated twice. We did not have access to data on testing, so it could not be integrated into the model.

The estimates of vaccine coverage relied on data up to the age of 5 years, which might not consider the teenage and adult population moving between regions, migration into each region, and late vaccination. To account for these limitations and test their effect on the conclusions, we estimated the effect of catchup campaigns before 2010, and used several vaccine datasets (appendix pp 24–29). We also tested whether adding a proportion of one-dose recipients in individuals aged 30–39 years in 2010 affected the parameter estimates (appendix pp 29–32). We found that scenarios with waning still performed better than the scenario without waning.

Within a given age group, region, and vaccine status, the model was homogeneous, so it did not account for variations in transmission risk within regions. Measles outbreaks in near-elimination settings are triggered by importations in pockets of susceptibility where vaccine coverage is low. The spatial granularity of the model was too coarse to identify these pockets. Compartmental models are therefore inappropriate to estimate the future risk of outbreaks or identify pockets of susceptibility in near-elimination settings. We do not anticipate that it would affect the vaccine distribution of the cases or affect the estimates of the waning rate from historical outbreaks.

To ensure that the parameters can be statistically identified, the infection rate does not depend on the region or age group. Region-specific and age-specific outbreak risks only depend on the spatial kernel, contact matrix, and vaccine coverage, all of which are only captured by estimations. This assumption leads to discrepancies between the spatial distribution of cases in the data and simulations. We implemented a sensitivity analysis where the parameters of the gravity model were fixed, in

which scenarios with waning still better captured measles dynamics in vaccinated cases (appendix pp 32–36).

Our results suggest that the waning of vaccine-induced immunity likely explains the observed dynamics and age distribution of vaccinated measles cases in England between 2010 and 2019. Many near-elimination countries have reported decreased vaccine coverage since 2020,[31] leading to an increase in measles incidence in Europe in 2023.[32] Accounting for the effect of waning, as well as declining coverage, on future measles dynamics will be paramount to anticipating and responding to the burden of measles in countries where incidence has been low for decades.

Contributors

AR, AMS, and AJK developed the analysis plan. AR implemented the analysis, wrote the code, and ran the model. AMS computed and collated the coverage data. AJK and AR accessed and verified the data. AR and AMS interpreted the results, with contributions from AJK. AR wrote the first draft and the additional file. AR, AMS, and AJK contributed to the manuscript, and read and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

The individual-level case data were collected by UK Health Security Agency (UKHSA) and cannot be shared publicly. The code used to generate the fits, simulations, and figures presented in the paper is shared in a Github repository (https://github.com/alxsrobert/measles_england_sir). This repository contains the model fits generated using the case data, the stochastic simulations, and all population and coverage data used in the analysis. To make this study as reproducible as possible, we generated a simulated linelist and included it in the Github repository, so readers can generate model fits on the simulated datasets.

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