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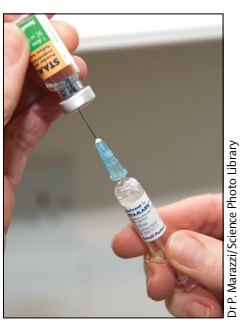
Yellow fever vaccination: estimating coverage

Recent decades have witnessed an unprecedented emergence of epidemic arbovirus diseases, including yellow fever.[1] The yellow fever outbreak that started in Angola in 2016 developed into the largest and most widespread outbreak of yellow fever reported in Africa in more than 20 years, leading to depletion of all yellow fever vaccine stocks.[2] The outbreak also resulted in the first documented importation of yellow fever into Asia.[3] Furthermore, since late 2016, yellow fever has caused outbreaks in southeastern Brazil close to the most populated areas of South America, with Rio de Janeiro state hosting nearly 16 million people.[4] Relying on reactive vaccination campaigns will inevitably result in preventable deaths[5] and hence, the mainstay for yellow fever control remains adequate vaccine coverage. To achieve high vaccination coverage on a long-term basis, the best strategy is to incorporate yellow fever vaccination into routine infant immunisations and to perform catch-up campaigns in the remaining population. According to WHO, a vaccine coverage of at least 80% would be necessary to prevent and control such outbreaks.[6] As such, I welcome the analysis by Freya Shearer and colleagues[7] in *The Lancet Infectious Diseases* that attempted to estimate vaccine coverage from 1970 to 2016 and calculate the number of individuals to be vaccinated to achieve the 80% population coverage required for each region to support WHO's Global Strategy to Eliminate Yellow Fever Epidemics.

Shearer and colleagues tracked each age cohort (from ages 0 to 99 years) in every district in countries with yellow fever transmission from their birth year through to 2016, updating the coverage level whenever a routine, preventive, or outbreak response campaign was done. The proportion vaccinated for each age cohort was calculated under three vaccination-targeting scenarios. To estimate population-wide vaccination under each scenario, the weighted mean proportion vaccinated across all age cohorts was calculated, weighted by population size and taking into account a bias correction for each country and year based on ratios derived from estimates of mean coverage for the diphtheria-tetanus-pertussis–containing vaccine from the Global Burden of Disease Study and administratively reported estimates from WHO/UNICEF. Because the estimates were not derived from a statistical model, estimates of uncertainty were not provided; instead, the three scenarios provide some indication of the uncertainty around those data.

Shearer and colleagues report overall substantial increases in yellow fever vaccine coverage since 1970, with vaccination coverage higher in Latin America than in Africa. However, notable gaps in vaccination coverage within yellow fever risk zones remain. Population vaccination coverage in countries within risk zones ranged from a maximum of 100% in parts of Amazonas State, Brazil, to 0% coverage in parts of central and east Africa (where routine infant immunisation programmes have not yet been introduced). Increased coverage was recently achieved overall in west and central Africa because large preventive campaigns supported by the Yellow Fever Initiative and the GAVI Alliance were implemented in 2006. Important gaps were apparent within the risk zones of Africa, including large areas of central and east Africa and parts of Nigeria, Niger, Sierra Leone, Liberia, and Guinea-Bissau. In Latin America, low coverage was estimated for Guyana, Suriname, French Guiana, and Colombia. Coverage was particularly high in Brazil during the 1970s and 1980s, decreased slightly in the 1990s,



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and was again very high in most parts of the country by 2016. However, the authors estimated lower levels of vaccination coverage at the eastern edge of the risk zone in Brazil for 2016, including within the state of Minas Gerais, where a yellow fever outbreak arose in December, 2016. Country-level estimates of yellow fever vaccination coverage by age group in 2016 highlight the progress of routine infant immunisation programmes in protecting children and young adults on both continents, but they also revealed coverage gaps in adult populations for most countries. Angola, Cameroon, Guinea, Senegal, Togo, Paraguay, Bolivia, and Brazil were exceptions to this, with moderate-to-high coverage estimated across all age groups.

This study provides an unprecedented wealth of data, which includes sets of coverage maps, detailed tables, and estimates of the number of individuals requiring vaccination. Using the estimates of the proportion of individuals vaccinated for each district, other researchers can recalculate the number of individuals requiring vaccination to reach any new threshold. The data provided on coverage by age groups is of particular additional interest for policy makers and epidemiologists. The actual risk based on population immune and non-immune estimates combined with published criteria on transmission risk[8] will determine where action is needed, and how to prioritise countries on the basis of the level of risk. Documentation of yellow fever vaccine coverage over the past decades to the present time has many benefits: (1) to document the quality of national vaccination programmes over time, (2) to provide data to study why some areas had yellow fever outbreaks in the past and anticipate outbreaks in the future, (3) to set targets for countries to achieve higher coverage rates, and (4) to guide planning of future vaccination strategies, emergency stockpiling, and manufacturing surge capacity.

From the 2016 outputs, Shearer and colleagues estimate that 383·6–461·4 million individuals still require supplementary vaccination within at-risk districts globally to achieve the 80% population coverage threshold recommended by WHO to prevent outbreaks; the vast majority of those individuals reside in Africa. However, these figures are far higher than the annual production of yellow fever vaccines. The present annual yellow fever vaccine production from all six of the world's manufacturers is only about 80 million doses per year, and the global supply of immediately available yellow fever vaccine is only about 5–6 million doses.[9] The small number of producers, and the manufacturing process requiring embryonated chicken eggs limit the amount of vaccine available.[10] Over the coming decade, vaccine manufacturers are expected to scale up production to meet the global demand. WHO estimates the global demand to be as high as 1·38 billion doses over the next decade—an amount needed to cover childhood immunisation programmes, catch-up and supplementary programmes, and stockpiling.[6] Meeting this demand will require increases in vaccine production, particularly in the next 5 years.

The total population living in countries with *Aedes* mosquitoes is estimated to be more than 3 billion people. Although highly populated Asia has not witnessed a yellow fever outbreak so far, despite the wide distribution of receptive *Aedes* mosquitoes, the increasing travel volume between yellow fever endemic areas and Asia[11] and the first documented importation of yellow fever from Angola to China underpins the potential threat.[3] Therefore stockpiling and contingency plans need to be developed for Asia. Furthermore, during the African outbreak in 2016, more unvaccinated travellers with yellow fever have been reported than in the past 50 years, showing that a substantial number of travellers are still able to circumvent the International Health Regulations. Absent or erratic control of proof of yellow fever vaccination at entry,[12] falsified vaccine certificates, flawed risk assessments in travel medicine clinics,[13] changing travel patterns and attitudes of travellers,[14,15] and inadequate information by travel medicine providers[16] have led to preventable cases of yellow fever in travellers, which contributes to the spread into new areas. Although the pre-emptive protection of endemic populations should be the main thrust, efforts should also be enhanced to contain outbreaks rapidly and to stop international spread.[6]

For decades we have had the tools at hand to control yellow fever, and with Shearer and colleagues' study we now also have well researched data to inform policy makers where to scale up vaccine coverage and to instruct vaccine manufacturers how much to scale up supply. The onus is on the world to avoid vaccine shortfalls in the future. To this end, a new effort led by WHO, the Global Strategy for Eliminating Yellow Fever Epidemics, will roll out over the next 5 years.

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I declare no competing interests.

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Recovery from serious fungal infections should be realisable for everyone

Fungal infections are neglected by social and political communities. However, they affect more than a billion people, resulting in approximately 11·5 million life-threatening infections and more than 1·5 million deaths annually.[1,2] There have been enormous advances in fungal diagnostics and antifungal drug development over the past 20 years, but most of the world's population has not yet benefited from these advances. *The Lancet Infectious Diseases* Fungal Infections Series brings readers up to date on fungal infections and addresses how fungal infection management can be integrated into health systems in low-income and middle-income countries (LMICs).

Many medical specialties see patients with fungal infections, including general practitioners (eg, cutaneous, thrush), paediatricians (almost all infections), dermatologists (eg, cutaneous, sporotrichosis), ophthalmologists (fungal keratitis), oncologists and haematologists (candidiasis and invasive mould infections), intensive-care-unit practitioners (candidiasis and aspergillosis), internal medicine and AIDS physicians (eg, cryptococcosis, histoplasmosis, pneumocystis pneumonia), ear, nose, and throat surgeons (external otitis, fungal rhinosinusitis), and respiratory physicians (all forms of aspergillosis and fungal asthma), which complicates provision of holistic education about fungal infections. In countries with developed health systems, fungal infections are diagnosed and treated, although many are still missed and only identified at autopsy.[3-5] However, in LMICs the absence of diagnostic tools and antifungal drugs, plus insufficient training of health-care staff, ensures that the mortality and morbidity of fungal infections remains unacceptably high. Kneale and colleagues[6] highlighted many country differences in antifungal drug availability and price in 2015. Amphotericin B is not available to a population of 481 million, and where it is available the price varies from less than US$1 per day to $171 per day. Flucytosine is unavailable to more than 2·9 billion people in more than 70% of the countries investigated. Conversely, the situation was better for azole drugs. Fluconazole was licensed in 88·6% of the countries surveyed, with a daily price variation (750–800 mg) of less than $1 to $31. Itraconazole was unavailable to more than 78 million

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