The global landscape of smallpox vaccination history and implications for current and future orthopoxvirus susceptibility: a modelling study

Juliana C Taube, Eva C Rest*, James O Lloyd-Smith, Shweta Bansal*

Summary

Background More than four decades after the eradication of smallpox, the ongoing 2022 monkeypox outbreak and increasing transmission events of other orthopoxviruses necessitate a greater understanding of the global distribution of susceptibility to orthopoxviruses. We aimed to characterise the current global landscape of smallpox vaccination history and orthopoxvirus susceptibility.

Methods We characterised the global landscape of smallpox vaccination at a subnational scale by integrating data on current demography with historical smallpox vaccination programme features (coverage and cessation dates) from eradication documents and published literature. We analysed this landscape to identify the factors that were most associated with geographical heterogeneity in current vaccination coverage. We considered how smallpox vaccination history might translate into age-specific susceptibility profiles for orthopoxviruses under different vaccination effectiveness scenarios.

Findings We found substantial global spatial heterogeneity in the landscape of smallpox vaccination, with vaccination coverage estimated to range from 7% to 60% within admin-1 regions (ie, regions one administrative level below country) globally, with negligible uncertainty (99·6% of regions have an SD less than 5%). We identified that geographical variation in vaccination coverage was driven mostly by differences in subnational demography. Additionally, we found that susceptibility for orthopoxviruses was highly age specific based on age at cessation and age-specific coverage; however, the age profile was consistent across vaccine effectiveness values.

Interpretation The legacy of smallpox eradication can be observed in the current landscape of smallpox vaccine protection. The strength and longevity of smallpox vaccination campaigns globally, combined with current demographic heterogeneity, have shaped the epidemiological landscape today, revealing substantial geographical variation in orthopoxvirus susceptibility. This study alerts public health decision makers to non-endemic regions that might be at greatest risk in the case of widespread and sustained transmission in the 2022 monkeypox outbreak and highlights the importance of demography and fine-scale spatial dynamics in predicting future public health risks from orthopoxviruses.

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*Contributed equally

Department of Biology, Georgetown University, Washington, DC, USA (J C Taube AB, E C Rest MS, S Bansal PhD); **Department of Ecology and Evolutionary Biology, University of California Los Angeles, Los Angeles, CA, USA** (Prof J O Lloyd-Smith PhD)

Correspondence to: Dr Shweta Bansal, Department of Biology, Georgetown University, Washington, DC 20057, USA **shweta.bansal@georgetown.edu**

Introduction

More than four decades after the landmark eradication of smallpox, the ongoing 2022 outbreak of monkeypox in more than 100 non-endemic countries threatens global health. If the monkeypox outbreak is not contained and widespread transmission ensues, the spatial distribution of infections could be influenced by the immune landscape of smallpox due to cross-protection conferred by the *Vaccinia*-based smallpox vaccine.[1–3] Multiple factors influence this immune landscape, including country-specific timelines of smallpox endemicity and elimination, protocols for routine smallpox vaccination, and demographic and migration patterns after eradication. However, global estimates of the proportion of the current population immunised against smallpox are unavailable, limiting the prediction of large-scale transmission dynamics in the current monkeypox outbreak or of potential future outbreaks of other *Orthopoxvirus* genus viruses.

Smallpox is the only endemic human disease to be successfully eradicated. WHO committed to an intensified global smallpox eradication campaign in 1967, particularly focusing on countries with high rates of endemic smallpox across Africa, Asia, and South America.[1] Although WHO initially set a target vaccination rate of 80% worldwide, novel vaccination strategies helped eliminate smallpox country by country. Variation in vaccination strategies introduced spatial heterogeneity in vaccination coverage. The jet injector enabled mass vaccination efforts, the bifurcated needle stretched vaccine stocks further, and the use of targeted ring vaccination allowed for the successful elimination of smallpox at lower vaccination rates.[1] Progress towards elimination in each country was tracked via scar surveys

Research in context

Evidence before this study

Before this work, smallpox vaccination cessation dates and vaccination coverage pre-eradication were distributed in WHO documents and in the landmark book, *Smallpox and its Eradication*. However, no single source provided this historical data for all countries. Additionally, there have been no publications since smallpox eradication that provide current fine-scale global estimates of residual smallpox vaccination coverage.

Added value of this study

We characterised the current fine-scale spatial landscape of smallpox vaccination based on geographical heterogeneity in demography and past smallpox vaccination programme features, including vaccination coverage and cessation dates. We found substantial spatial heterogeneity in current smallpox vaccination coverage, influenced in part by the proportion of the population in a region who were born before smallpox vaccination cessation. We contribute an open (and living) database of all current subnational vaccination estimates and uncertainties as an immediate resource for the global health community working on the monkeypox outbreak.

Implications of all the available evidence

Our findings highlight the need to consider spatial clustering of individuals who are unvaccinated and the importance of fine-scale spatial analysis in light of the increased risk of orthopoxvirus emergence. If transmission becomes widespread during the 2022 global monkeypox outbreak, our vulnerability map can inform public health efforts on identifying non-endemic regions and age cohorts at greatest risk, allocating scarce vaccine supplies, and predicting transmission dynamics in concert with data on contact patterns, mobility, and real-time prevalence.

for vaccination and pockmark surveys for infection (both considered validated measures of immunity).[1,4] In 1977, just 10 years into the intensified eradication campaign, the final naturally occurring case of smallpox occurred in Somalia. WHO declared smallpox eradicated in 1980.[5] There have been no naturally occurring smallpox cases since, but the use of smallpox as a biological weapon remains a risk.

Monkeypox is an orthopoxvirus closely related to but less severe than smallpox. Unlike smallpox, monkeypox was historically limited to central and west Africa, with small outbreaks of zoonotic origin.[6] Studies during a period of intensified WHO monkeypox surveillance in the 1980s found that previous smallpox vaccination led to reduced secondary attack rates and reduced symptom severity during monkeypox infection, estimating that the *Vaccinia*-based smallpox vaccine was 85% effective in preventing monkeypox infection and disease.[2,7,8] More recent studies support these findings, reporting continued evidence that past smallpox vaccination prevented clinical monkeypox infection with more than 80% effectiveness and reduced infection severity in cases that did arise.[3,9,10]

Monkeypox outbreaks have risen in frequency and size since routine smallpox vaccination ended and reports of zoonotic transmission of cowpox and buffalopox, two other members of the *Orthopoxvirus* genus, have also increased.[3,11–13] Since the *Vaccinia*-based smallpox vaccine confers some immunity against almost all human orthopoxviruses, we expect that infections from other orthopoxviruses will become more common as the proportion of the population that is unvaccinated increases.[14,15] Therefore, mapping global heterogeneity in smallpox vaccination coverage and cessation is important to accurately understand the populations most susceptible to sustained transmission arising from the 2022 monkeypox outbreak, a smallpox biological attack, or future emerging orthopoxvirus outbreaks. However, considering these processes at large spatial scales can obscure important geographical heterogeneity (eg, potentially high-risk areas where targeted interventions might be needed), necessitating a fine-scale approach to characterising the orthopoxvirus susceptibility landscape.[16–18]

In this Article, we characterised the current global spatial landscape of smallpox vaccination history and orthopoxvirus susceptibility based on geographical heterogeneity in demography and past smallpox vaccination efforts. We considered subnational age distributions of populations and national smallpox vaccination coverage (by age where available) and cessation date. We characterised uncertainties in these estimates and analysed the role of each demographic and vaccination campaign characteristic. Although other factors (eg, contact patterns) remain crucial to predicting monkeypox transmission, our work maps the current global landscape of susceptibility to monkeypox and other orthopoxviruses, providing key information to guide public health decision making for the evolving 2022 outbreak and beyond.

Methods

Data collection

We generated a database of routine smallpox vaccination campaign cessation dates, estimates of smallpox vaccination coverage before cessation, and age compositions for each region one administrative level below country (admin-1; eg, a state in the USA) globally. From this database, we estimated the proportion of each current-day population that was expected to have been vaccinated against smallpox. Additionally, we estimated how this vaccination history could translate to susceptibility to orthopoxviruses (eg, monkeypox) under different scenarios of cross-protection.

For data on smallpox vaccination near eradication, we used Fenner and colleagues' book,[1] which documented

the WHO smallpox eradication campaign and country-specific data during the intensified eradication period from 1967 to 1977 in Africa, Asia, and South America. For countries in Europe, central America, the Middle East, and Oceania, where intensified eradication efforts were not concentrated, information was sparse and scattered. Available information for these areas was supplemented via searches of WHO eradication documents, *Bulletin of the World Health Organization* and *Morbidity and Mortality Weekly Report* digital archives, and published literature and reports via Google Scholar and PubMed for data on smallpox vaccination coverage rates and cessation dates for each country. We used the search terms: "smallpox vaccination cessation", "end of smallpox vaccination", "stop smallpox vaccination", "smallpox vaccination coverage", "smallpox scar surveys", and "smallpox serum surveys", combined with each country name for articles, abstracts, or reports published in English between database inception and July 28, 2022.

Vaccination cessation

Cessation dates reflect the end of routine smallpox vaccination programmes after country-specific smallpox elimination or global smallpox eradication. Global vaccine cessation date information was obtained through a literature review for each country (appendix p 8). If direct evidence of the year of cessation was not available, we used approximate dates or ranges provided in the literature. For overseas territories, we used the cessation date of the governing country at the time. If no information on the vaccine cessation date was available, we assumed the cessation date to be 1980 on the basis of WHO recommendations to discontinue vaccination that year and the lowest data quality grade was recorded (appendix p 8).[1]

Vaccination coverage

Vaccination coverage data were obtained, whenever possible, via surveys of vaccination scars in each country (appendix p 8). Scar surveys are based on take, vaccinations that form a small and visible scar, and represent efficacious vaccine coverage but were mostly conducted during the WHO intensified eradication campaign starting in 1967 and are thus unavailable for most countries that achieved elimination before then.[1,4] Scar survey information was first obtained from Fenner and colleagues[1] or WHO,[5] and we then searched WHO eradication documents and general literature. If multiple within-country coverages were given in a scar survey, the population-weighted average was taken as the national coverage. If age-specific coverage rates were available, the 5–14 years age group coverage was used for all individuals of that age or younger at the time of the scar survey (or born between the scar survey date and the cessation date), whereas the 15 years or older age group coverage (if available) or the overall coverage was used for all individuals aged 15 years or older during the scar survey (appendix p 2). If no age-stratified data were available, the overall population coverage was used if available, and if country-specific coverage data were not available, we did spatial imputation of coverage based on countries that were spatially proximate with a comparable sociopolitical profile. If such imputation was not possible, coverage was assumed to be 80% based on the WHO target vaccination coverage for the eradication campaign,[1] and the lowest data quality grade was recorded (appendix p 8).

Demography

To estimate global demography at the admin-1 level, we used the most recent admin-1 level age distribution data from the Gridded Population of the World (GPW) dataset[19] in 5-year age groups from 2010, as well as total admin-1 population sizes from GPW from 2020. We validated our assumption of constant age distributions from 2010 to 2020 at the national scale (appendix p 10).

Population vaccination coverage estimates

To estimate expected smallpox vaccination coverage for current populations of each admin-1 level region in all countries, we used the smallpox vaccination cessation dates and historical vaccination coverages from our global database for each country and information on demography at the admin-1 level.

See Online for appendix

We first estimated the proportion of each 5-year age group that was vaccinated with the *Vaccinia*-based smallpox vaccine on the basis of their age at cessation and coverage before cessation within that country. To estimate the current overall admin-1 smallpox vaccination coverage, we took an age-specific population-weighted mean across historical vaccination coverage estimates.

To validate our estimates, we compared our estimated age-specific smallpox vaccination coverage (projected to the appropriate year) with more recent age-specific smallpox scar survey data[3,20–22] and antibody study data[23] from five countries (see appendix pp 4–5).

We did not include the effect of natural immunity to smallpox in our estimates of protection because incidence levels were low during the 1970s for individuals alive today, even in the last countries to have endemic smallpox (appendix pp 20–21).

Estimating uncertainty in population vaccination estimates

To quantify the robustness of our population vaccination estimates under varying data quality, we characterised the uncertainty in smallpox vaccination cessation dates, vaccination coverage levels, and admin-1-level age distributions. We derived uncertainty intervals (UIs) for coverage and cessation date for each country by placing bounds on plausible values for those inputs, characterising the part of the interval with the highest likelihood, and parameterising probability distributions based on these bounds and skew. UIs for cessation dates

were defined based on known information about each country's smallpox vaccination campaign, and aggregate regional data available from source literature. Intervals for vaccination coverage were derived from within-country or regional spatial variability in coverage from scar surveys. For locations without uncertainty information, wide default UIs were assumed (appendix pp 2–3). Additionally, we included variability in age distributions due to noise in demography data sources and the unavailability of current fine-scale demography data (appendix pp 2–3). To integrate these sources of uncertainty, we used parametric bootstrapping to estimate population vaccination history with uncertainty.

To estimate the effect of data resolution on our estimates, we also did a more detailed analysis of the USA using finer-scale age distribution data, additional information on immigration, and subnational spatial heterogeneity in vaccination coverage (appendix pp 6–7).

Estimating the role of demography and vaccination campaigns

To assess the role of each factor in our vaccination history estimates, we homogenised data in a given demographic or vaccination factor and compared the resulting population vaccination estimates against the original estimates. The three scenarios we considered were: all countries ceased routine smallpox vaccination in 1984, removing heterogeneity in cessation date; all countries had 100% vaccination coverage before cessation, removing heterogeneity in historical vaccination coverage; and all administrative regions have the same global average age distribution, removing admin-1 level heterogeneity in age distribution.

Population susceptibility estimates

To demonstrate how smallpox vaccination history might translate to orthopoxvirus susceptibility, we considered a range of scenarios given the sparse information available on vaccine effectiveness. We defined orthopoxvirus susceptibility as the complement of vaccine protection towards orthopoxviruses, which is the product of age-specific smallpox vaccination coverage and vaccine effectiveness of the smallpox vaccine against orthopoxviruses. We used five hypothetical levels of vaccine effectiveness arising from past smallpox vaccination (90%, 80%, 70%, 50%, and 30%), reflecting cross-immunity against different orthopoxviruses and overall immune waning over time since cessation. As an alternative scenario, we considered age-specific waning by assuming that all eligible individuals were vaccinated once as a young child, with an initial vaccine effectiveness of 85%, which then waned exponentially by 1·4% per year[24] from time of vaccination (assumed to be by age 5 years or by 1980, whichever was earlier). We illustrated the effects of these assumptions about waning and susceptibility through case studies in four countries with high-quality vaccination coverage and cessation date information (Brazil, Chad, China, and France).

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

We developed a high-resolution global map of contemporary smallpox vaccination coverage based on subnational and age-specific estimates of demography and historical vaccination efforts and we found substantial variation across countries, with vaccination coverage ranging from 7% to 47% (appendix pp 22–23). For 72 (31%) of 230 countries (comprising 49% of the global population), we found direct evidence of the year of cessation. For 102 (44%) of 230 countries (comprising 49% of the global population), we assumed the cessation date to be 1980 on the basis of WHO recommendations to discontinue vaccination that year. We estimated the cessation year for 56 (24%) countries (comprising 2% of the global population), as the exact year was unavailable. Country-specific coverage data were not available for 89 (39%) countries (comprising 16% of the world population); thus, we spatially imputed coverage based on similar, spatially proximate countries. Spatial imputation of coverage was not possible for 85 (37%) countries (comprising 14% of the global population), for which we assumed coverage to be 80%. Our database containing information on smallpox vaccination, our sources, and the quality of evidence for each country can be accessed, see the appendix (p 8). We show the spatial distribution in the appendix (p 9).

We characterised the robustness of our estimates to uncertainty in the inputs and found that coverage estimates had an SD of less than 5% in 3232 (99·6%) of 3245 admin-1 regions (appendix pp 24–25). To validate our projected estimates of population vaccine immunity, we compared them to field data from 2003–16 smallpox scar surveys or antibody studies from five countries and found that our model estimates were quantitatively consistent (ie, model estimates were contained within the UIs of empirical estimates) with empirical estimates from larger surveys, and qualitatively consistent with surveys with smaller sample sizes in large countries (appendix p 25).

We found high spatial heterogeneity in the contemporary landscape of smallpox vaccination, with admin-1 level population vaccination coverage ranging from 7% to 60% globally, and varying by up to 9% within countries (figure 1A). We found that parts of Finland, Bulgaria, Japan, and Sweden had the highest coverage of vaccination, whereas some of the regions with the lowest coverage were in Yemen, Colombia, Guinea-Bissau, and Ethiopia. There was substantial subnational heterogeneity in many areas, but it was particularly evident in large

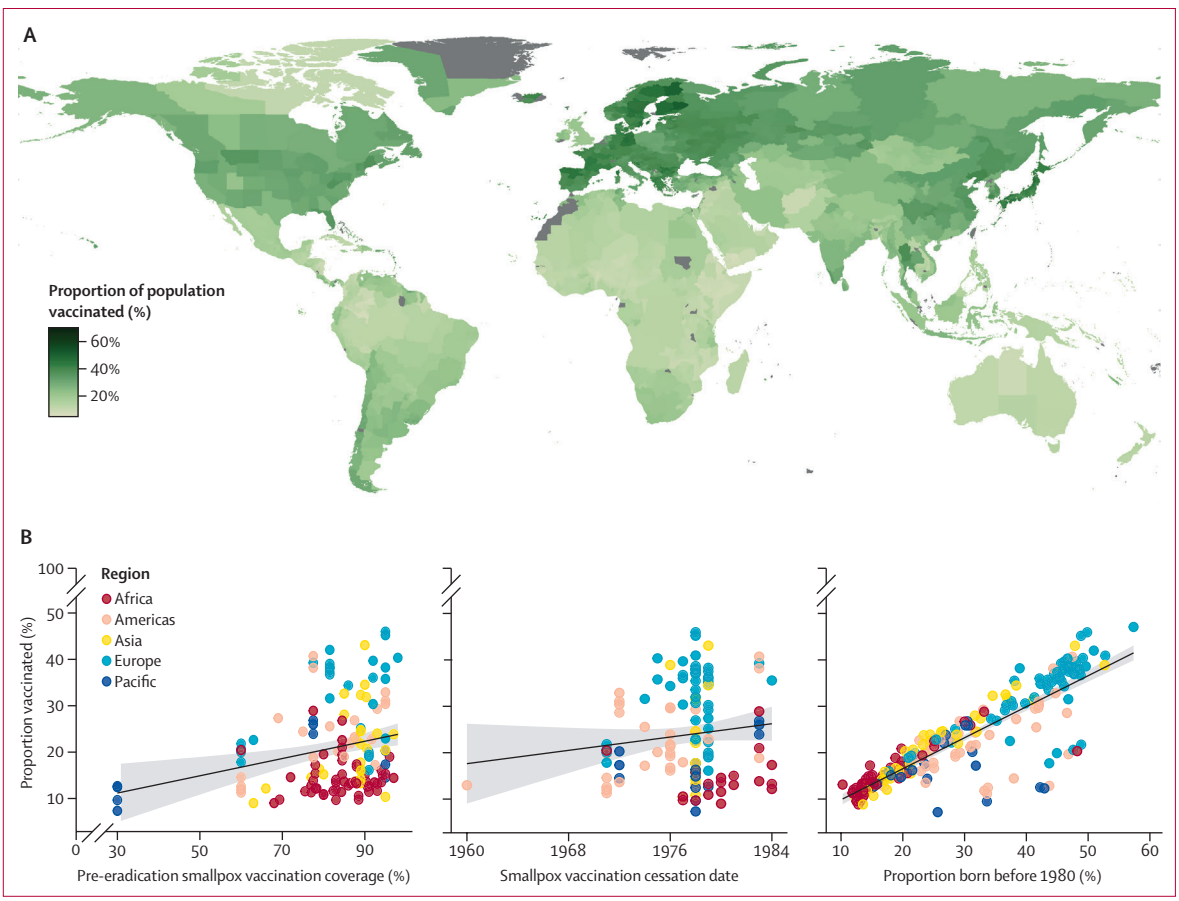

Figure 1: **The global landscape of smallpox vaccination**
Grey colours show no available data. (A) Population smallpox vaccination coverage at the administrative level below country (admin-1 scale) globally. (B) Relationship between the current mean national population smallpox vaccination coverage and mean national smallpox vaccination coverage coverage pre-eradication (left), the year that routine smallpox vaccination ceased within the country (middle), and the proportion of the country's current population that was born before 1980 (right). The black lines are based on linear regressions of the data and are meant to guide the eye, rather than assert a linear relationship. Outlier countries are Australia and New Zealand (low coverage), Cuba (early cessation), and the UK (low coverage). Countries with default coverage are excluded from the left plot and countries with default cessation date are excluded from the middle plot.

countries such as India, China, Brazil, and the USA. There were low levels of contemporary vaccination coverage in central and western Africa, despite the high frequency of monkeypox spillover in these areas. Overall, we found a high degree of spatial clustering in current vaccination coverage at the admin-1 level (Moran's I 0·94).

We assessed the role of demography and historical vaccination factors in shaping the current landscape of vaccination (figure 1B). We found that a nation's current demography (as measured by the proportion of the population born before smallpox eradication in 1980) was highly predictive of current vaccination coverages (Pearson's correlation of linear association 0·86 [95% CI 0·83–0·89]), whereas pre-eradication vaccination coverage was only moderately predictive of current coverage (0·26 [0·10–0·41]). Although historical smallpox vaccination coverage was not predictive on its own, it was correlated with current smallpox vaccine protection in countries with older populations (eg, in Europe and Asia).

To identify factors influencing the observed spatial heterogeneity in the smallpox vaccination landscape, we compared estimates under three counterfactual scenarios: simultaneous cessation (ie, all countries shared a routine smallpox vaccination cessation date of 1984); universal vaccination efforts (ie, all countries achieved 100% vaccination coverage before cessation); and homogeneous demography (ie, all countries and regions shared the global average age distribution). In figure 2, we summarise the effect of each scenario relative to the empirical estimates (summarised in figure 1A). All three counterfactuals highlight substantial differences in population vaccination coverage under different conditions. These results demonstrate that demography is the largest contributing factor to the smallpox vaccination landscape and allowed us to geographically localise these effects nationally and subnationally. The simultaneous cessation scenario (figure 2A) highlights that later smallpox vaccination

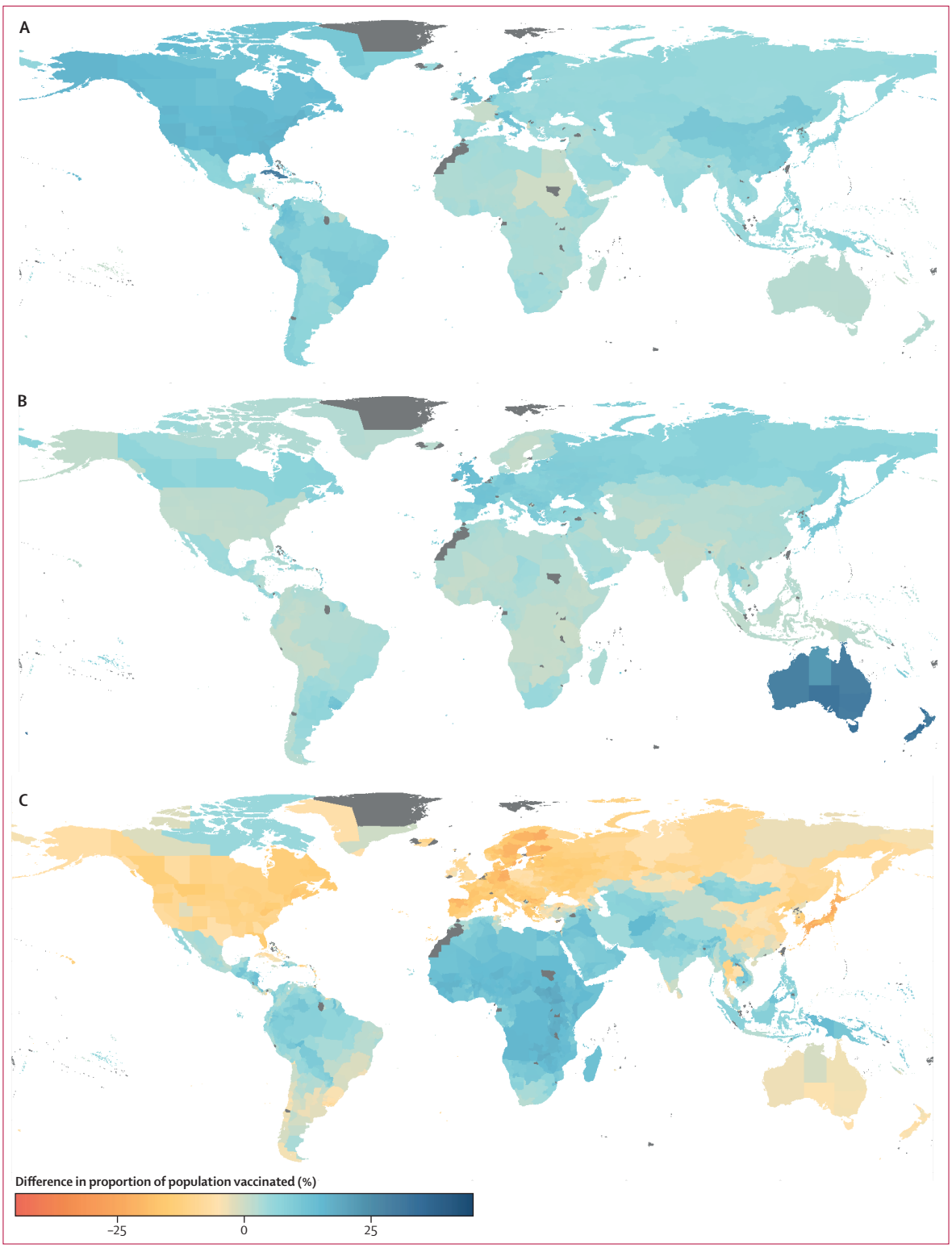

Figure 2: **The role of demography and vaccination coverage in shaping the current smallpox vaccination landscape**
Differences from the main model in current vaccination coverage due to three counterfactual scenarios. Grey colours show no available data. (A) All countries ceased routine smallpox vaccination in 1984. (B) All countries reached 100% vaccination coverage before cessation. (C) All administrative regions have the same global average age distribution.

cessation would lead to a systematic global increase in population vaccination coverage. The effect of later cessation was small in most countries, with some of the largest average increases in vaccination coverage of 29% in Cuba and 16% in the USA, countries that stopped routine smallpox vaccination before 1975. The universal vaccination counterfactual (figure 2B) also led to small increases in most national vaccination coverages worldwide, except for New Zealand and Australia (which had particularly low historical coverage). In contrast, the homogeneous demography scenario (figure 2C) revealed substantial changes in the landscape of contemporary vaccination coverage. These changes were greatest in countries with age structures that deviated substantially from the global average: African, southern Asian, and northern South American nations had an increase in average age with this counterfactual, leading to higher current vaccination coverage. Countries in North America, Europe, northern Asia, and Australia had decreases in average age in the counterfactual, relative to the populations' actual average age, reducing current vaccination coverage substantially. At a finer geographical scale, we found that the north–south gradients observed in India and Brazil (in figure 1A) were driven by differences in age distributions (appendix pp 26–27). Results assuming homogeneous demography within countries are shown in the appendix (pp 28–29) to highlight the role of subnational demographic data. In the appendix (pp 30–31), we highlight that the absence of demographic data at finer scales might be obscuring additional subnational spatial heterogeneity.

We translated these vaccination coverage data into susceptibility estimates under different scenarios of vaccine effectiveness in four countries (figure 3). Susceptibility profiles for other countries, assuming 85% vaccine effectiveness, are shown in the appendix (pp 11–20). Although we emphasise that current-day effectiveness is unknown against any orthopoxvirus, for context, *Vaccinia*-based smallpox vaccine effectiveness against a range of orthopoxviruses was: 91·1% effectiveness against *Variola major* outbreaks, 74·9% effectiveness against *Variola minor*, 85% vaccine effectiveness against monkeypox outbreaks in 1981–86, and 80·7% effectiveness during outbreaks in 2006–07 (appendix p 31). An alternative scenario (age-specific waning assuming that everyone was vaccinated once as a young child, with an initial vaccine effectiveness of 85%) amounted to effectiveness of less than 30% in the oldest cohorts (this was not consistent with effectiveness estimates from recent outbreaks[3]). All scenarios showed that orthopoxvirus susceptibility was highly age specific, with complete susceptibility for younger individuals and partial susceptibility for older cohorts born before cessation in that country. Relative levels of susceptibility between middle-aged versus older individuals depended on the history and age profile of vaccination campaigns in that country and become further differentiated among the older cohort in the age-specific waning scenarios. Crucially, the overall age profile of susceptibility was conserved across different scenarios of vaccine effectiveness.

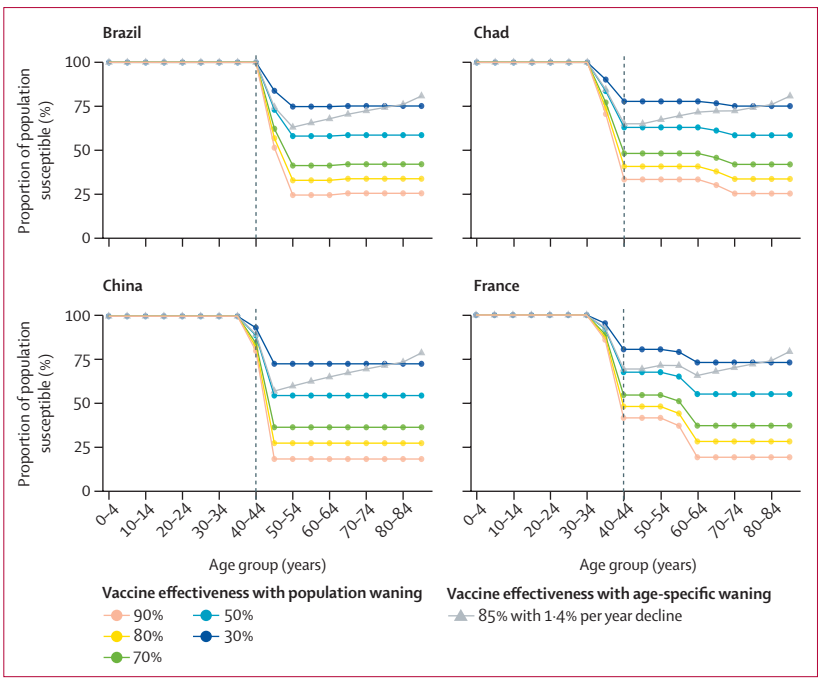

Figure 3: **Susceptibility profiles for countries, as determined by differences in demography, vaccine effectiveness, and waning of vaccine immunity**

Susceptibility profiles in four countries (Brazil, Chad, China, and France) with varying vaccination cessation dates and reported coverages with a population-level waning scenario and age-specific waning scenario. The individual-level waning scenario includes 1·4% per year loss of vaccine effectiveness since the time of vaccination, assuming all eligible individuals were vaccinated by age 5 years or in 1980, whichever was earlier. Vaccine effectiveness values were selected to overlap with reported literature estimates for orthopoxviruses (appendix p 31).

Discussion

Despite the massive success and organisational prowess of the global smallpox eradication campaign, fine-scale vaccination coverage estimates are scarce and only focus on the period near eradication in the 1980s. Contemporary estimates are needed for public health officials to make informed decisions in the context of increasing orthopoxvirus emergence. We addressed this gap by creating a comprehensive, high-resolution global map of current population smallpox vaccination coverage, accounting for demographic changes since smallpox was eradicated. We identified substantial global vaccination coverage against smallpox that might translate to other orthopoxvirus diseases. We characterised notable, previously undocumented, spatial heterogeneity in protection, at national and subnational scales, and demonstrated that this heterogeneity was driven by changes in demography since eradication, and was less influenced by differences in historical smallpox vaccination efforts.

The 2022 global monkeypox outbreak has highlighted the immediate relevance of mapping this susceptibility

landscape, but our work has broader implications for future risks from all orthopoxviruses. As time passes since smallpox eradication, the proportion of human populations with any acquired immunity to orthopoxviruses (from vaccination or infection) decreases, and other orthopoxviruses stand to benefit from the increasing pool of susceptible individuals (known as competitive release in ecological terms).[15] Indeed, the incidence of human cases of a number of orthopoxviruses appears to be rising.[11–13] Our work quantified the geographical distribution of vulnerability to this ensemble of zoonotic viruses via the construction of national susceptibility profiles. The effectiveness and durability of *Vaccinia*-based vaccines against other zoonotic orthopoxviruses are unknown (although for some viruses, such as buffalopox, their close genetic relationship to *Vaccinia* makes substantial cross-protection probable). Therefore, absolute estimates of susceptibility are not possible. Nevertheless, by characterising the spatial patterns of smallpox vaccine distribution, our mapping reveals the landscape of relative risk from any human-infecting orthopoxvirus. Determining the strength and waning rates of cross-protection against all orthopoxviruses is an important research frontier and will enable absolute estimates of susceptibility against these emerging threats.

Another dimension of our findings is the age structure of protection, which is robust to unknown vaccine effectiveness. We translated our estimates of vaccination history to age-specific susceptibility profiles by considering a range of hypothetical vaccine effectiveness values. The limited current understanding of smallpox vaccine effectiveness against orthopoxviruses arises mostly from monkeypox and variola outbreaks from the 1970s to the 2000s and from public health settings and transmission routes quite distinct from the 2022 monkeypox infections. These estimates (which range from 80% to 85% for monkeypox) primarily quantify susceptibility to symptomatic disease, and thus the full implications for infection or onward transmission are not known. Smallpox vaccination also entails a diversity of vaccine types, injector types, and booster schedules, each of which can influence effectiveness and durability.[14,25] Our scenario analyses produced estimates of age-specific population susceptibility, which can inform epidemiological risk analyses and public health decision making but are vulnerable to these unknown programmatic factors. Susceptibility is closer to dichotomous at the individual level, with individuals who are unvaccinated being generally vulnerable to infection and disease and individuals who are vaccinated having some degree of protection. Our core findings on the age structure of vaccination history are centred on this robust distinction. The age-assortative nature of human contact patterns, which can amplify age-specific infection risks, increases the potential effect of this heterogeneity in individual susceptibility.

For more on the **living database** see https://github.com/bansallab/mpx_landscape

The process of finding and aggregating country-specific data from frequently incomplete historical records brings inevitable uncertainty to the data and our estimates. We adopted a strategy of finding the best data available for each location, grading its quality explicitly in our public database, and conducting an uncertainty analysis to assess the effect of data gaps on our study outputs. Despite some dismaying gaps in the retrievable evidence base (eg, no estimate of smallpox vaccination coverage could be found for 37% of countries and 14% of the world population), our analysis showed that current-day vaccination history could be estimated within 5% in 99·6% of countries. This precision arises from the fact that current-day coverage is driven chiefly by demographic factors, and details of historical vaccination programmes have relatively weak influence compared with demographic factors. Nevertheless, we call on the global health community to assist in filling these gaps and to provide the infrastructure for continuing contributions to our living database. Some additional uncertainty arose from an absence of data within the last 10 years on demographic age structure at the admin-1 level, and we urge that such data be made available. Modern approaches to data collection could make invaluable contributions to validating and extending our vaccination estimates. In particular, calls for large-scale, routine, and representative serological surveys to characterise population immune histories could provide essential data to validate our model.[26]

In this study, we compiled the first high-resolution global map of smallpox vaccine history using demographic and smallpox vaccination data. Our work revealed the vast spatial heterogeneity of current vaccination coverage, highlighting the need to consider spatial clustering of susceptible individuals, whether due to age or other factors, and underscoring the importance of fine-scale spatial analysis in assessing risks of orthopoxvirus emergence and establishment. In response to the 2022 global monkeypox outbreak, we contribute an open database of all our subnational estimates and uncertainties as an immediate resource for the global health community. We also invite the community to contribute both historical information and data in the future (eg, on the distribution of the ACAM2000 and JYNNEOS vaccines) to this database. Until data emerges on vaccine effectiveness from the current outbreak, our scenario-based age-specific susceptibility profiles can guide the targeting of high-risk groups for vaccination and treatment. Additionally, these profiles highlight that older age groups (born before the cessation of smallpox vaccination) are at substantial risk of infection due to the combined effects of imperfect initial coverage, imperfect vaccine effectiveness against monkeypox, and possible waning over the decades since vaccines were administered. This prediction, alongside behavioural research that indicates that contact rates relevant to current transmission patterns, including

sexual and close skin contact, are non-negligible in older adult age groups,[27] aligns with evidence of substantial numbers of cases among older adults in the current outbreak.[28] In addition, there are continuing concerns about the potential for transmission in other social contexts, including congregate living facilities such as retirement homes or prisons. The hope remains that the current outbreak will be contained; however, if transmission becomes widespread, our current characterisation of the smallpox vaccination landscape can inform public health efforts on assessing risks of geographical introductions, allocation of scarce vaccine supplies, and predicting transmission dynamics in concert with data on contact patterns, mobility, and real-time prevalence.

Contributors

JCT did the analyses, interpreted the findings, and drafted and edited the manuscript. ECR collected the data, interpreted the findings, drafted, and edited the manuscript. JOL-S interpreted the findings and edited the manuscript. SB conceived and supervised the study, did analyses, interpreted the findings, and edited the manuscript. JCT, ECR, and SB accessed and verified the data. All authors were responsible for the decision to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All code to reproduce figures and data to produce our estimates (as of Sept 20, 2022), as well as the vaccination coverage estimates generated by our study, are available at https://github.com/bansallab/mpx_landscape. Information on how to contribute to this database is also available at that link.

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