Supplementary appendix

The global landscape of smallpox vaccination history: Implications for current and future orthopoxvirus susceptibility

Contents

S1 Vaccination coverage heterogeneity

To capture age-specific vaccination coverages, we leverage scar survey data from each nation, where available. If age-specific coverage rates were available, the 5-14 age group coverage was used for all individuals of that age range at the time of the scar survey, younger than 5, or born between the scar survey and the cessation date, while the ≥15 age group coverage, if available, or the overall coverage, was used for all individuals born 15 years or more prior to the scar survey. Country-specific vaccination policies varied in the age of primary smallpox vaccination, with some children vaccinated at 3-4 years of age and others when they entered primary school at 5-6 years of age. By using the 5-14 age group, we ensure that the entire age group is eligible for the primary smallpox vaccination and have more complete coverage data since all members of the age group can be vaccinated.

Not all scar surveys were carried out near vaccination cessation, so we assume constant vaccination coverage from the year of a scar survey to cessation of routine vaccination in each country. It is thus possible that decreased coverage near elimination could lead to slightly lower vaccination rates in cohorts born in the 1970s. On the other hand, some countries continued some vaccination beyond cessation and eradication (e.g., the DRC had a vaccination rate of 41% in 1981 declining to 4% by 1985[30]) and thus our vaccination estimates may be conservative for cohorts born near cessation. We could not find data describing smallpox vaccination coverage at the admin-1 level for most countries, so we assumed that scar surveys are nationally representative and uniform. Where available, we incorporate admin-1 variability in vaccination coverage and cessation into our uncertainty analysis, and find that these assumptions do not significantly reduce confidence in our susceptibility estimates. For a significant number of countries, we were unable to find information on vaccination coverage. We filled this gap with estimates from nearby, similar countries and call on the global health community to assist in filling remaining data gaps.

S2 Estimating uncertainty in vaccination coverage estimates

In order to address uncertainty inherent in aggregating historical or incomplete data, we used a parametric bootstrapping approach. We placed bounds on plausible values for the cessation date and vaccination coverage for each country, and varied the age distribution of each admin-1 region to represent the uncertainty in these values. We estimated probable distributions of values within these cessation and coverage bounds and drew 5000 samples for vaccination coverage and cessation date for each country, and for uncertainty for each age group for each admin-1 region to generate the range of plausible outcomes under this level of uncertainty. With each pair of independently sampled cessation dates and scar survey coverages, and renormalized admin-1-level age distributions, we re-estimated population vaccination, generating 5000 estimates, from which we took the mean and standard deviation for each admin-1 region or for each age group at the country-level.

We estimated bounds on cessation date values depending on whether the cessation date was known for a given country. If the cessation date was known, the lower bound of uncertainty was that date and the higher bound was one year after the known cessation date with a right-skewed distribution to reflect higher likelihood on the known cessation date and the possibility of a brief delay in enacting the policy change during which vaccination continued. If no cessation date was known, the standard deviation of all known cessation dates was used as a default interval, ± 3 years, with a symmetric distribution with a mode at the 1980 WHO-recommended cessation date. For some countries, WHO documents reported a higher bound at which point vaccination no longer occurred, but the lower bound was unknown. In these cases, the lower bound is assumed to be 1970 as this was among the earliest known cessation

dates globally, and a uniform distribution was used to reflect the lack of a known or estimated cessation date during this period.[31] For more information on the type of data available, the estimates and ranges used, and sources by country, see Table S1.

Depending on where our highest certainty fell in the cessation date range, we sampled possible cessation dates from a beta-binomial distribution (for the symmetric, left-skewed, and right-skewed cases) or a discrete uniform (for cases where we lacked confidence in a most likely value). For the symmetric case, we used d_L + Beta-Binomial(n, $\alpha = 2$, $\beta = 2$); for the right-skewed case, we used d_L + Beta-Binomial(n, $\alpha = 0{\cdot}4$, $\beta = 1{\cdot}5$); and for the left-skewed case, we used d_L + Beta-Binomial(n, $\alpha = 1{\cdot}5$, $\beta = 0{\cdot}4$). In all cases, n was parameterized by the difference between the upper bound date and lower bound date, and d_L was the lower bound date.

We estimated uncertainty on vaccination coverage values, where possible, using known spatial heterogeneity in coverage levels from admin-1 regions within a country or from spatially proximate, similar sociopolitical countries. Coverage rates were determined as the average of two to four spatially proximate, similar countries in the same region with shared socioeconomic or political structures. For example, known information from Sweden and Denmark were used to impute information for other Scandinavian countries, while information from France and Italy were used for other democratic Western European countries. In these cases, the bounds and the shape of the distribution of plausible values were represented by the empirical distribution of within-country or among spatially proximate, similar countries' coverage values, whether it be symmetric, left-skewed or right-skewed, with a mean defined by the average of the available values. In cases where a country's known scar survey did not include admin-1 coverages, a default interval of ± 13%, equivalent to the standard deviation of all known coverage rates, from the overall coverage was used with a symmetric distribution with the mean at the overall value. In cases where the default coverage of 80% was used, a uniform distribution was used with a default interval equivalent to the standard deviation of all known coverage rates, ± 13%. For more information on the type of data available, the estimates and ranges used, and sources by country, see Table S1.

Depending on where our highest certainty fell in the coverage range, we sampled possible coverage values from a transformed beta distribution (for the symmetric, left-skewed or right-skewed cases) or a uniform distribution. We parameterized and transformed the beta distribution as such: c_{low} + ($c_{high} - c_{low}$) Beta(a, b), with $b = 2$ and $a = 2 \cdot (c_{mean} - c_{low})/(c_{high} - c_{mean})$, and c_{low} and c_{high} as the lower and higher bounds of the plausible coverages for a country, and c_{mean} as the mean of the available coverages.

We estimated age distribution uncertainty by comparing 2010 admin-1-level age distributions from the GPW dataset aggregated to the country-level with 2020 country-level age distributions provided by the UN.[32] The mean absolute difference was 0·9%, and these differences tended to be greater in younger age groups (< 35 years old), with the GPW 2010 dataset typically overestimating the proportion of individuals in these age groups. We note that these younger age groups are not highly relevant to our core analyses, since they were all born after cessation of smallpox vaccination. Nevertheless, to account for these discrepancies, we recorded the maximum difference across all age groups for each country, δ_i. For each age group in each admin-1 we added the original proportion in that age group to a sample from Normal(0, $\delta_i/3$) and renormalized the age distribution. Thus, we used a slightly different age distribution for each admin-1 for each of the 5000 bootstrapping iterations informed by differences with more recent country-level age distributions.

S3 Role of natural immunity

We considered potential natural immunity arising from natural smallpox infections prior to eradication and monkeypox outbreaks in endemic countries. Even in endemic areas, monkeypox outbreaks are typically small and self-limiting.[1] While, monkeypox incidence has recently increased in many endemic areas[33,34] larger outbreaks have cumulatively affected very small percentages of the population (e.g., 0·013% of the DRC population) and are therefore likely to be negligible in susceptibility calculations, especially in regions with high vaccination coverage.[8,35-37] However, monkeypox cases in endemic areas may be underestimated due to lack of diagnostics and testing, clinical similarity to other illnesses, and underdeveloped or underutilized disease surveillance systems.[38]

Likewise, we expect the contribution of natural smallpox immunity to the smallpox immunity landscape to be insignificant. In countries with endemic smallpox after 1967 (the start of the intensified WHO eradication campaign), cumulative incidence was extremely low (rarely exceeding 1% of a country's population by 1980, relative to the 1970 population size) and evidence of prior infection was concentrated in adults, who are now 65 or older and often compose a small proportion of the age distribution of the affected countries, which tend to have young populations (Figures S22-24). Overall, the proportion of people naturally infected with either smallpox or monkeypox is markedly outweighed by the relatively high levels of coverage resulting from mass vaccination campaigns that confer much greater levels of population immunity.

As such, we assumed that natural immunity for smallpox and monkeypox was negligible.

Vaccine effectiveness: Waning and cross protection

In Figure S31, we present a review of data on *Vaccinia*-based smallpox vaccine effectiveness against a range of orthopoxviruses. The data from monkeypox outbreaks estimate effectiveness as ≈ 85% for outbreaks in the 1980s,[5–7] and 80·7% − 80·9% during outbreaks in the 2000s.[8,10] The data from *Variola major* outbreaks have a weighted average effectiveness of 91·1%,[39–41] while for *Variola minor* outbreaks the weighted average effectiveness is 74·9%.[42,43]

Second, we consider the scenario of waning vaccine effectiveness. We note that multiple studies have found elevated antibody and memory B cell responses persist over 50 years after vaccination and, although T cells wane after 15 to 20 years, T cell levels remain over ten times that of unvaccinated individuals for decades.[14,25,44,45] Epidemiological estimates of waning vaccine effectiveness post-eradication are not available, however. To illustrate the impact of potential waning in vaccine effectiveness, we consider hypothetical scenarios with lower vaccine effectiveness values assuming overall waning and age-specific waning based on time since vaccination, assuming individuals were vaccinated around 5 years of age and vaccine effectiveness declines at 1·4% per year since vaccination.[24] Due to the limitations of available age data, we assumed each 5-year age cohort was vaccinated, on average, 7 years after the first individuals in the cohort were born, or in 1980, whichever was earlier. For this analysis we used the mean estimated vaccination percentage for each age group at the country-level, an output of our parametric bootstrapping uncertainty analysis.

S4 Checking consistency to field data

To validate our population immunity estimates, we make comparisons to smallpox vaccination take data.

We compare our age-specific estimates of the likelihood of being smallpox vaccinated against recent (i.e., 2003 onward) age-specific data on protection against smallpox from five countries. In particular, we

use scar survey data from a census in Guinea-Bissau in 2005 with a sample size of 1,751;[20] from a census in the Democratic Republic of the Congo in 2006 with a sample size of 4,676;[8] from scar survey data of a cross-section of a rural population in the Brazilian state of Minas Gerais in 2012 with a sample size of 240;[21] from a scar survey of a population of farm workers and their household members in Colombia in 2016 with a sample size of 134;[22] and from an antibody study from routine laboratory samples from Italy in 2003 with a sample size of 523.[23] For each of these cases, we compare the vaccination coverage of each age group as estimated by our model to empirical estimates. For comparison to the scar survey data, we estimate the expected smallpox vaccination coverage of each age group at the time of the scar survey relative to vaccination cessation in the given country (e.g., for a 2003 scar survey and a 1971 cessation with 70% vaccination coverage in 0-15 year olds (yo) and 90% coverage in 15+ yo at cessation, the 2003 age-specific vaccination coverage estimates would be: 1-31 yo = 0%, 32-47 yo = 70%, 48+ yo = 90%). For comparison to the antibody study data, we generate expected age-specific smallpox vaccination coverage at the time of the study (as described above) and scale this estimate by the contemporaneous vaccine effectiveness estimate of 80·7% as a proxy for serological protection. We show 95% confidence intervals on the model estimates based on standard deviations measured from our model uncertainty analysis, and 95% confdence intervals on the empirical estimates based on Wald intervals.

In Figure S27, we show that most age-specific model estimates are consistent with age-specific empirical estimates. The estimates for Brazil and Colombia are the least consistent, though both studies have small sample sizes and are in clustered, rural populations.

S5 Military vaccination after 1980

In estimating orthopoxvirus susceptibility in the U.S., we do not include military vaccination policies due to the small proportion of individuals vaccinated relative to the U.S. population as a whole. Although the U.S. ended routine smallpox vaccination in 1972, military personnel were routinely vaccinated until 1990. In response to the potential threat of smallpox as a biological weapon, the U.S. military restarted its smallpox vaccination program and has continued vaccinating military personnel since the early 2000s. Between December 2002 and November 2017, approximately 2.08 million military personnel and 39,500 civilian healthcare workers received smallpox vaccinations.[46,47] The majority of military personnel vaccinated during this period (71%) were too young to have been vaccinated previously, so are likely not included in our estimates of U.S. population susceptibility. However, the total number of military vaccinees is less than 1·5% of the U.S. population between the ages of 18 and 64, and less than 0·7% of the general U.S. population,[48] so incorporating these vaccinations would likely result in minimal changes to our population susceptibility estimates. Other countries may have conducted military-specific vaccination campaigns as well, although these efforts also are unlikely to contribute significantly to population susceptibility estimates.

S6 Age distribution data and mapping

Age distributions procured from Gridded Population of the World (GPW) data[19] date back to 2010, when some countries had different admin-1-level jurisdictions than today. As a result, to map these old admin-1 divisions to more recent ones documented in the Database of Global Administrative Areas (GADM), we had to merge some GPW admin-1 regions into one GADM admin-1 region, or split other GPW admin-1 regions amongst multiple GADM admin-1 regions.

Maps are created using the Database of Global Administrative Areas (GADM) dataset, version 4.0.[49]

S7 Spatial analysis

To further quantify the spatial heterogeneity in our estimates, we calculated Moran's I across all admin1 regions with neighbors (no islands, and excluded Maldonado, Uruguay due to an error in the spatial connectivity) to be 0·94 (p-value < 0·0001), indicating high clustering of vaccinated populations. We found little to no correlation between population size or density and percentage of the population vaccinated at the admin-1 (Pearson correlations of 0·04 and -0·004, respectively), -2 (-0·01 and -0·04, respectively), and -3 (0·03 and -0·05, respectively) level.

S8 Finer-scale US analysis

To investigate how finer spatial data on age, location of birth, and heterogeneity in vaccination coverage affect our estimates, we conducted a case study on the United States. Using the Public Use Microdata Sample (PUMS) dataset from the U.S. Census, which provides a sample of individuals representative at the scale of PUMAs, geographic areas containing at least 100,000 individuals,[50] we estimated population vaccination coverage at the PUMAs-level. For each individual, the age, location of birth (U.S. state if U.S.-born or country if foreign-born), and current PUMA of residence is known, and an appropriate survey weight is provided. While individuals in this dataset are considered representative on the characteristics of age, sex, race/ethnicity, and marital status, they are not necessarily representative by birthplace, so this may be introducing a small bias into our results. Similar to our global approach, we used age and vaccination coverage to estimate the proportion of individuals vaccinated in each age group. However, the likelihood of vaccination differed depending on location of birth: for U.S.-born individuals, the coverage in their state of birth and the U.S. cessation date was used. For non-U.S.-born individuals, we used the coverage and cessation date in their country of birth. Thus, we incorporate sub-national heterogeneity in vaccination coverage in the U.S. using spatial heterogeneity in polio vaccination for U.S.-born individuals and (average) coverage in country of birth for foreign-born individuals. All estimates are aggregated by current PUMA of residence (accounting for intranational migration away from location of birth). In this process, we assume that immigrants to the U.S. had equivalent healthcare access in their location of birth to individuals who did not emigrate and that individuals left their country of birth when old enough to be vaccinated.

Because smallpox vaccination coverage data is not available at the state-level, we estimated spatial heterogeneity in smallpox vaccination coverage based on state-level 1995 vaccination rates for 24 month old children with ≥3 doses of polio vaccine. We chose 1995 polio vaccination coverage as it was a comparable routine childhood vaccination against a pathogen nearing elimination in the U.S. at the earliest date the data were provided by the CDC.[51] Other routine childhood vaccination data for complete series in 24 month old children in 1995 demonstrate a high degree of correlation to polio vaccination patterns, including DTaP (Pearson's ρ = 0·79) and MMR (Pearson's ρ = 0·73), indicating that polio vaccination data represents common trends in spatial heterogeneity of U.S. vaccination patterns and is a suitable proxy for spatial heterogeneity in smallpox vaccination coverage (Figure S32).[52,53]

There is high heterogeneity in smallpox vaccination coverage across the U.S. with PUMA-level vaccination levels ranging from 12% to 67%. Regions in Florida and Arizona are the most vaccinated, while a number of regions in Utah are the least vaccinated. We additionally consider how the vaccination landscape would differ in the U.S. if there had been no immigration in the last century or if we do not incorporate sub-national heterogeneity in vaccination (Figure S30). We find notable decreases in vaccination along the U.S./Mexico border and in large urban areas (e.g., Chicago, D.C., NYC, Miami, Houston) when foreign-born individuals are excluded, which highlights that foreign-born individuals

residing in the U.S. have higher vaccination rates on average (43% population vaccination among foreign-born residents versus 33% among U.S.-born residents). This result reinforces the demographic effect we highlight above as foreign-born individuals in the U.S. tend to be older than U.S.-born individuals (45 versus 38, on average), and the residents of high immigration locations in the U.S. tend to have a lower average age.[54]

SR Supplementary References

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S9 Supplementary figures

https://github.com/bansallab/mpx_landscape/blob/main/TableS1.csv

Table S1. This table contains raw data on cessation dates, vaccination coverage, estimates of uncertainty intervals, and sources for our estimates.

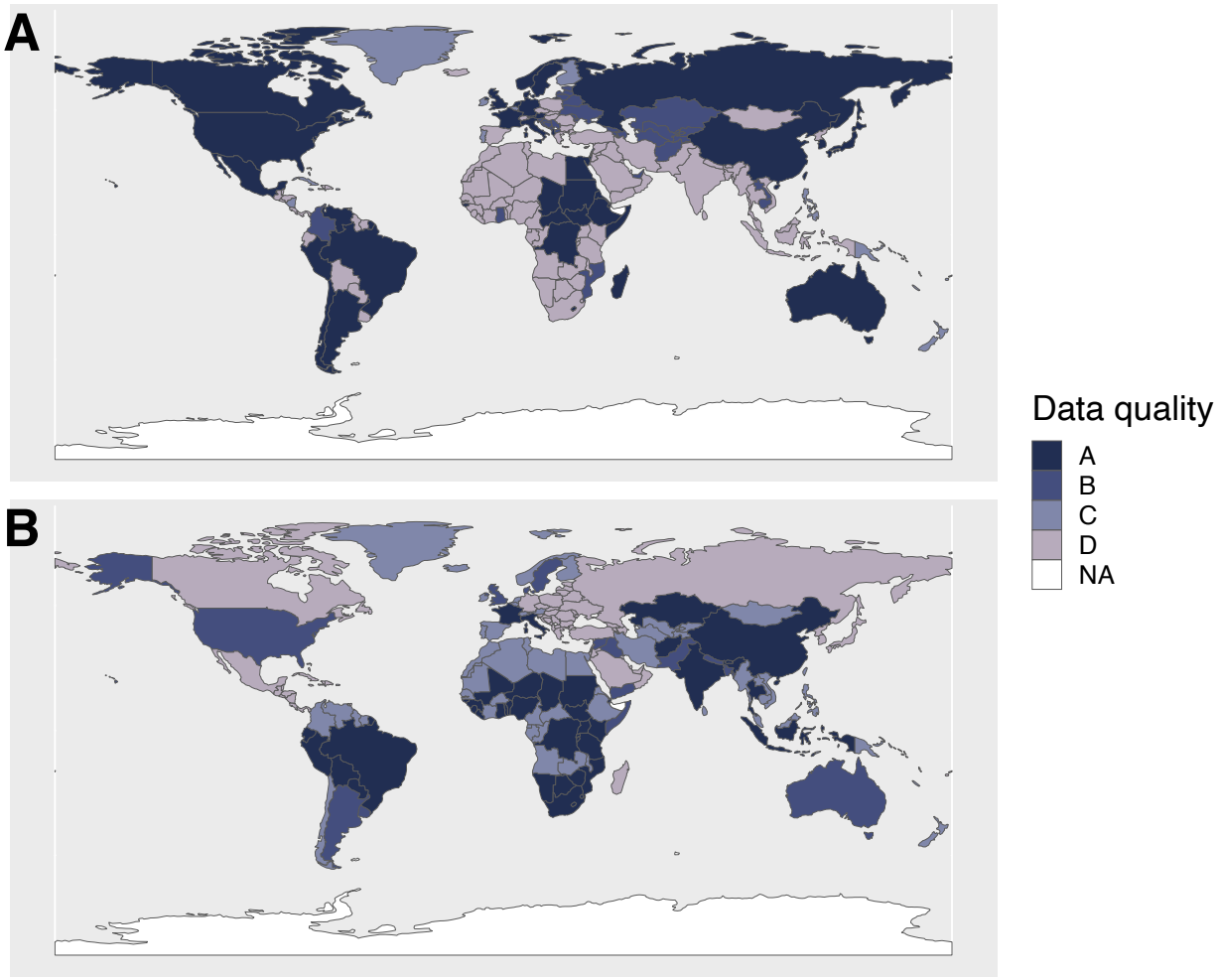


Figure S1. **Maps depicting data quality for (A) cessation date and (B) vaccination campaign coverage globally.** Grade A signifies good evidence (e.g., known scar/serum survey; known cessation date from literature). Grade B indicates some evidence (e.g., vaccination coverage estimate mentioned in text or model without known scar/serum survey data; cessation date range). Grade C denotes no direct evidence, and the use of country-specific assumptions (e.g., average of coverage estimates from spatially proximate, similar countries or governing countries of overseas territories; only one known bound (high or low) for cessation date). Grade D indicates default values were used. See Supplement section XX for these values.

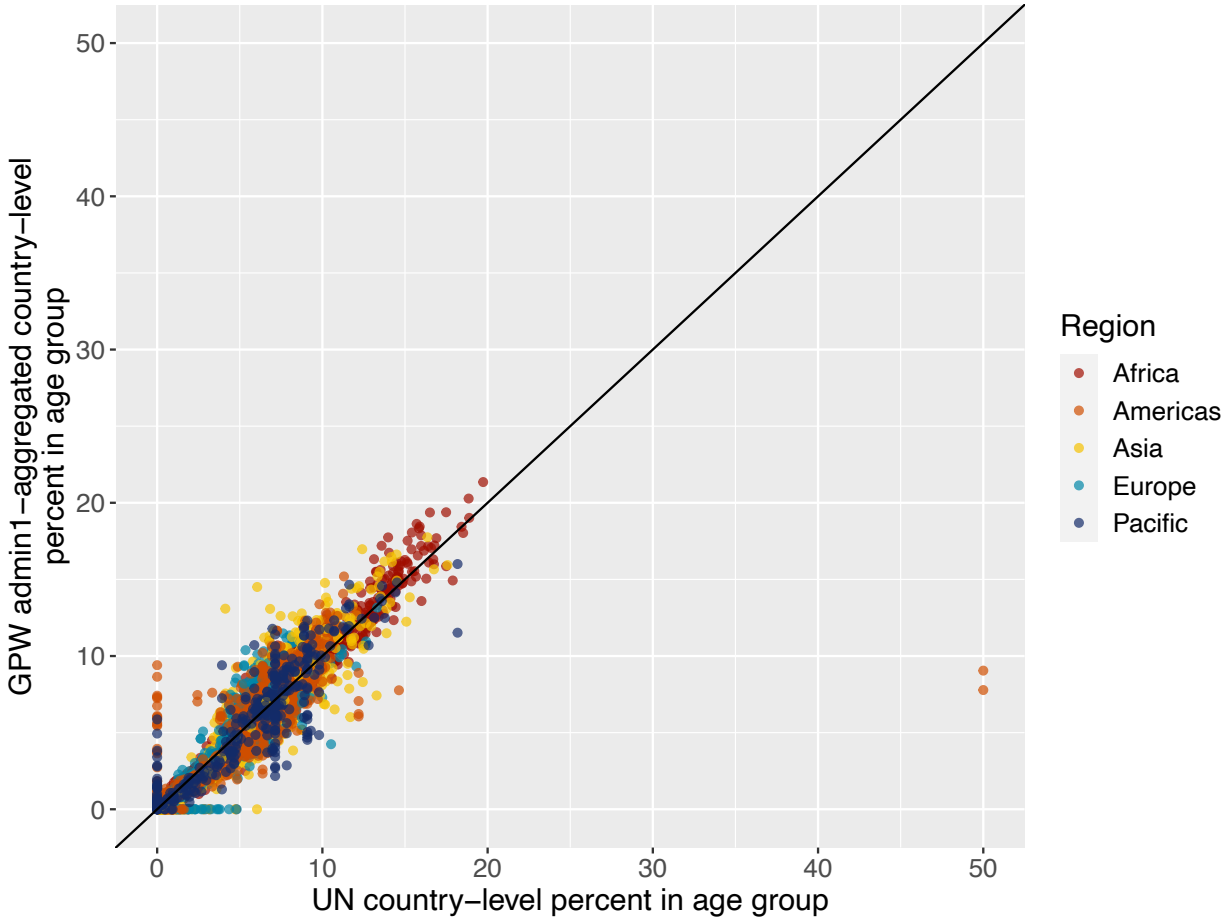


Figure S2. **Admin-1 2010 age distributions[19] aggregated to the country-level exhibit slight differences from 2020 country-level age distributions provided by the UN.[32]** The mean absolute difference across age groups is 0.9%, with slightly larger differences in younger age groups where the admin-1 level GPW dataset overestimates the proportion of individuals. These differences are incorporated into the uncertainty analysis.

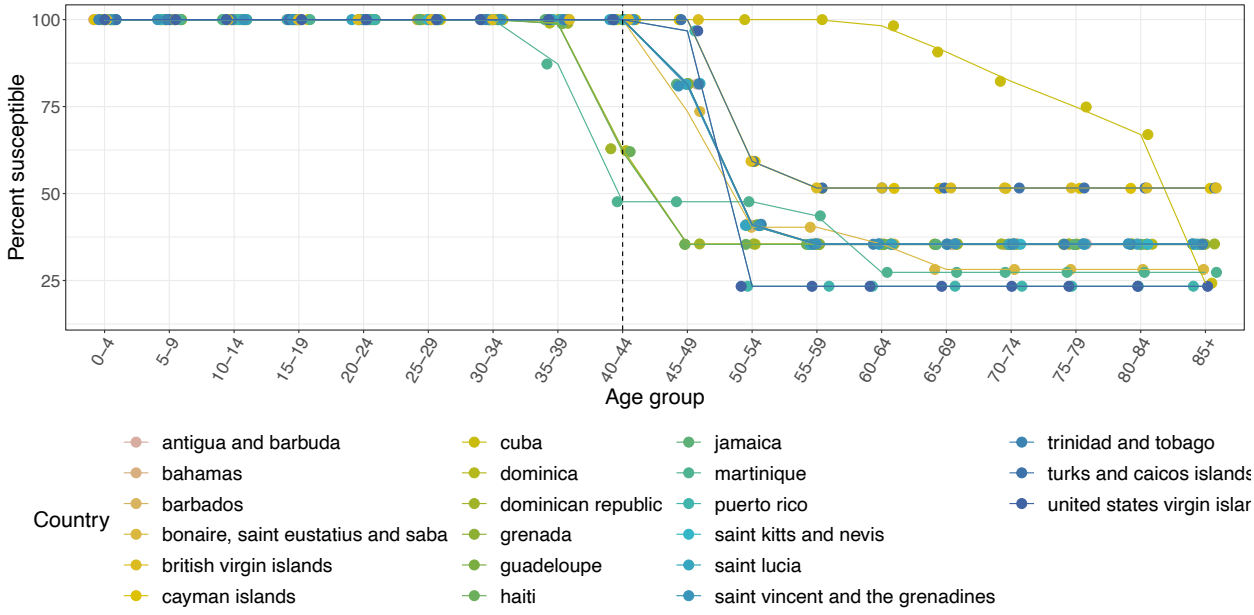


Figure S3. **Country-specific monkeypox susceptibility profiles for countries in the Caribbean.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

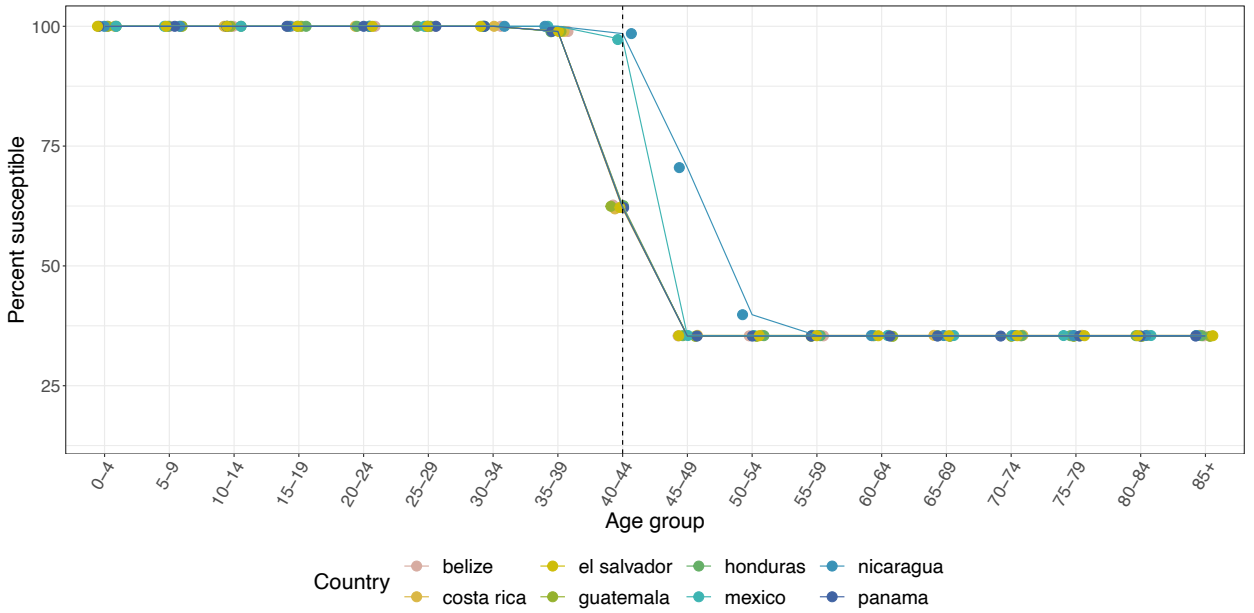


Figure S4. **Country-specific monkeypox susceptibility profiles for countries in Central America.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

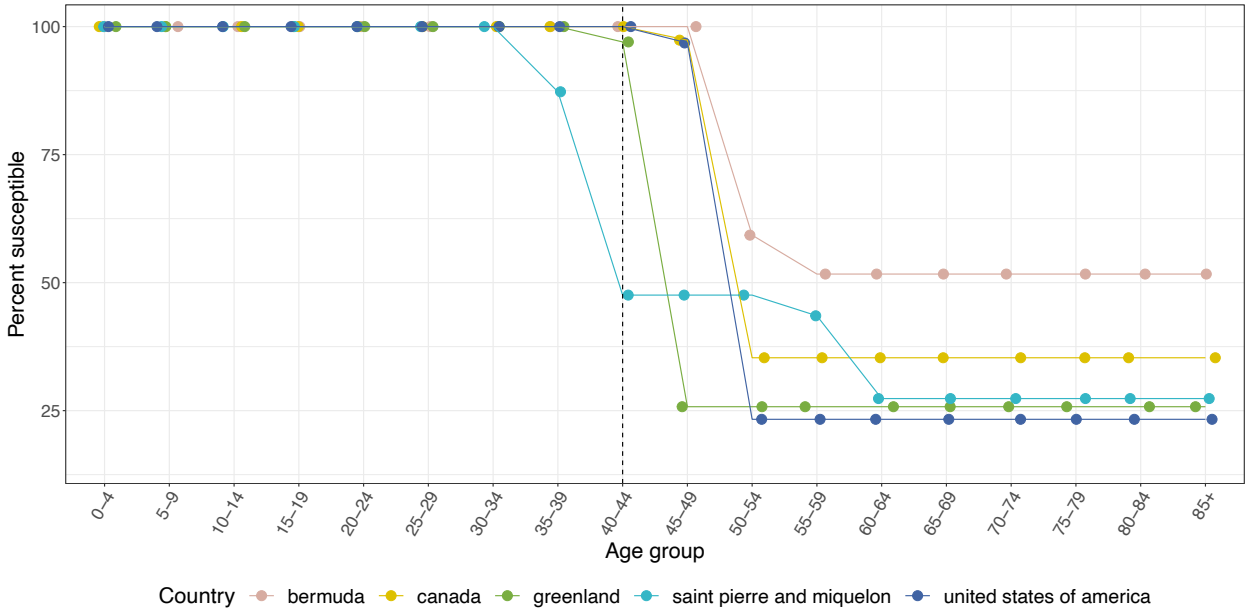


Figure S5. **Country-specific monkeypox susceptibility profiles for countries in Northern America.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

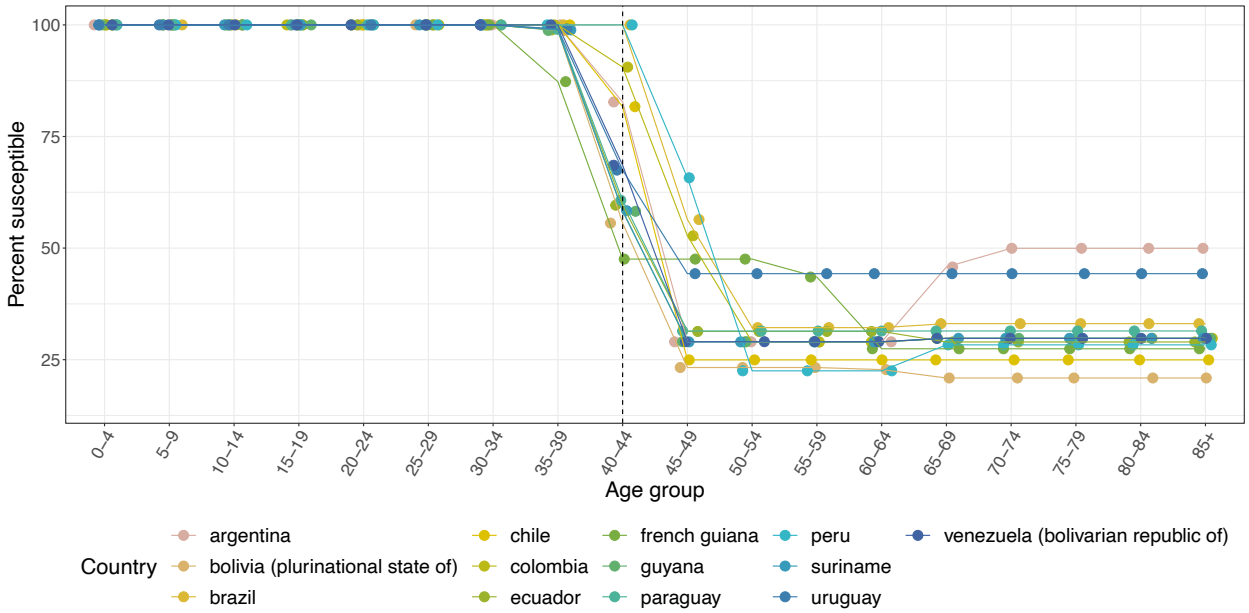


Figure S6. **Country-specific monkeypox susceptibility profiles for countries in South America.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

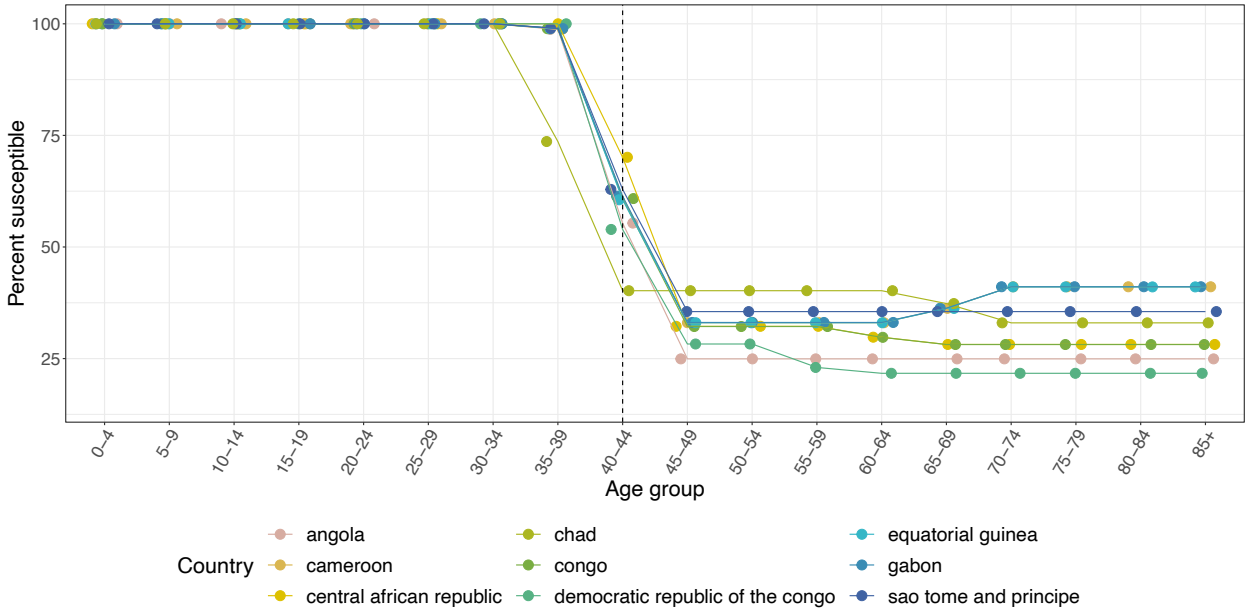


Figure S7. **Country-specific monkeypox susceptibility profiles for countries in Middle Africa.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

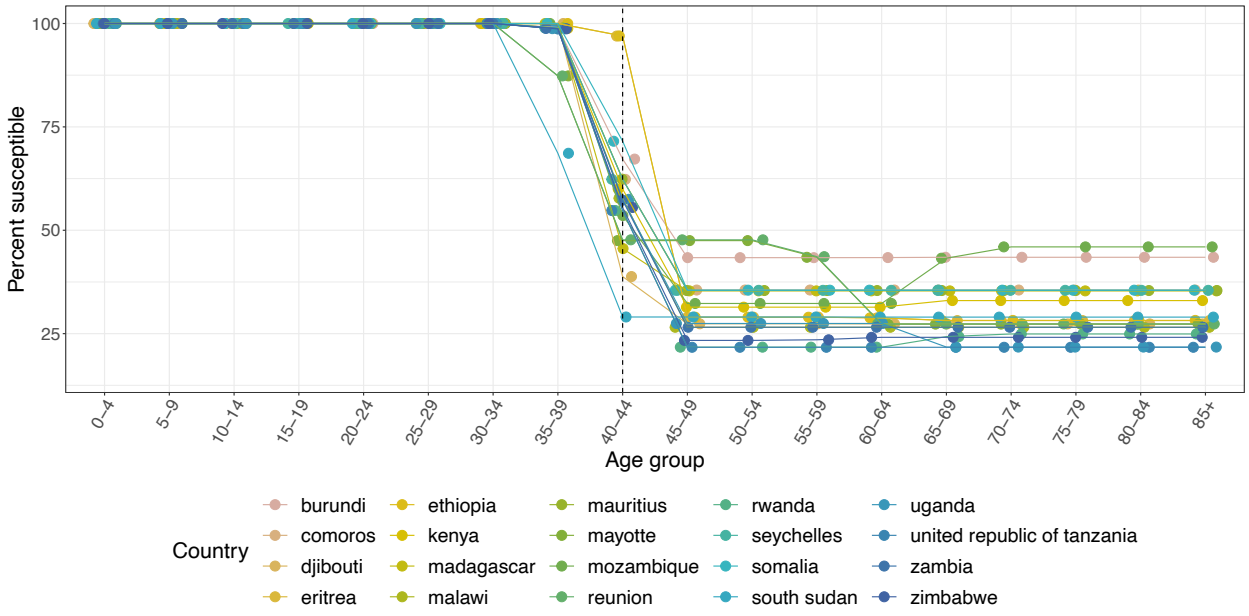


Figure S8. **Country-specific monkeypox susceptibility profiles for countries in Eastern Africa.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

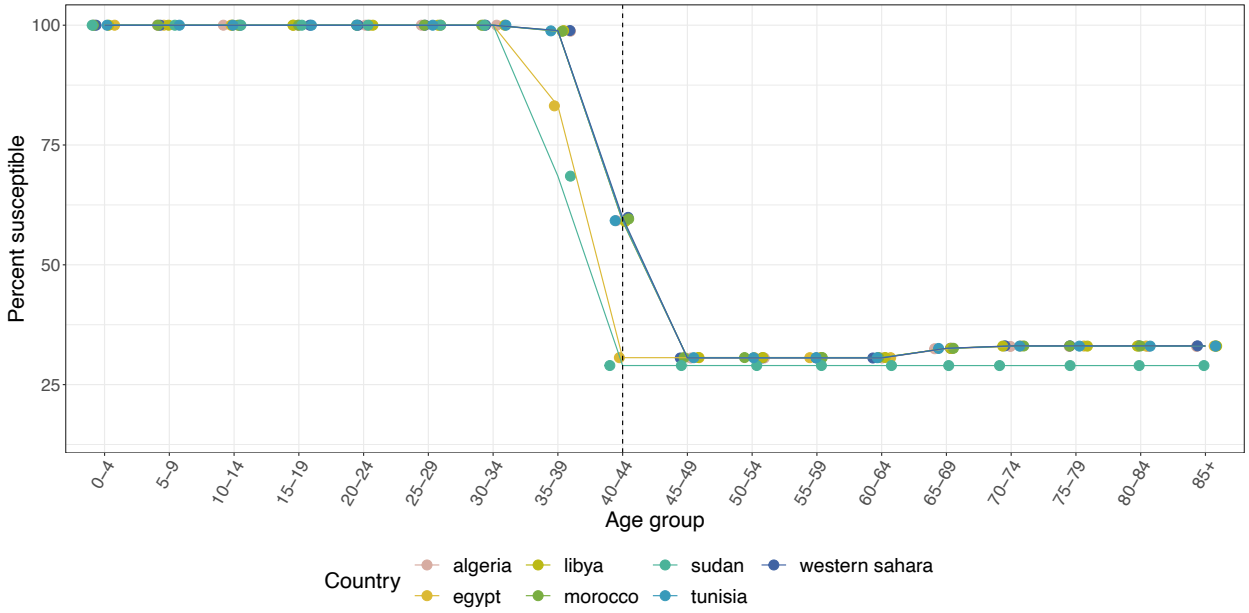


Figure S9. **Country-specific monkeypox susceptibility profiles for countries in Northern Africa.** Susceptibility is calculated as 1−(*ϵ*·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

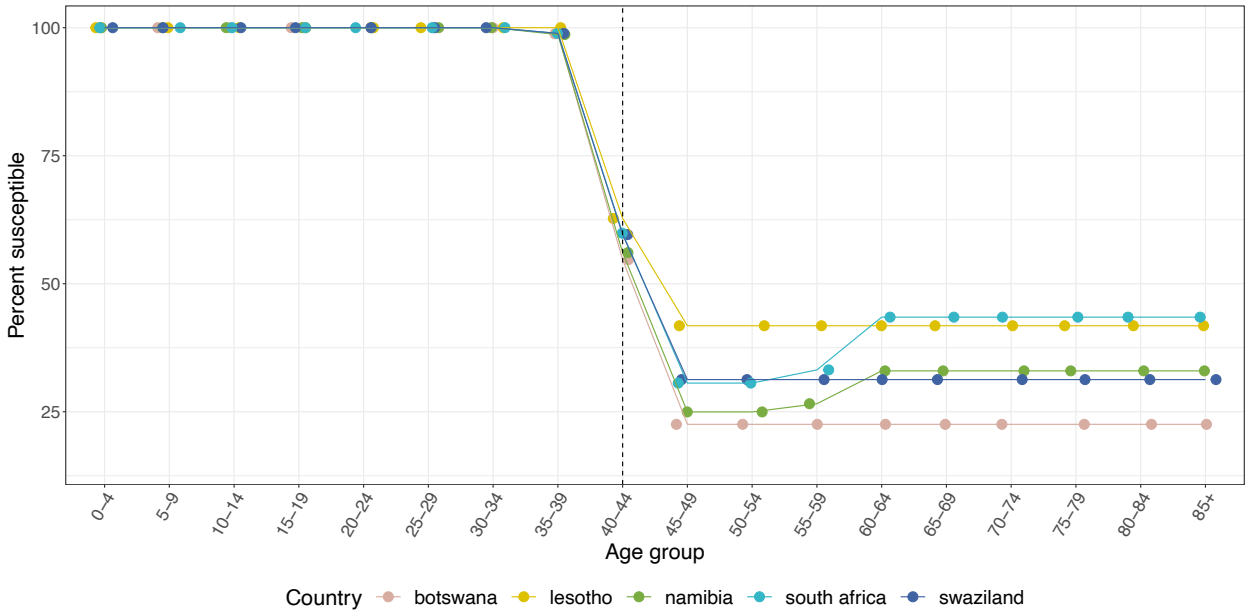


Figure S10. **Country-specific monkeypox susceptibility profiles for countries in Southern Africa.** Susceptibility is calculated as 1−(*ϵ*·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

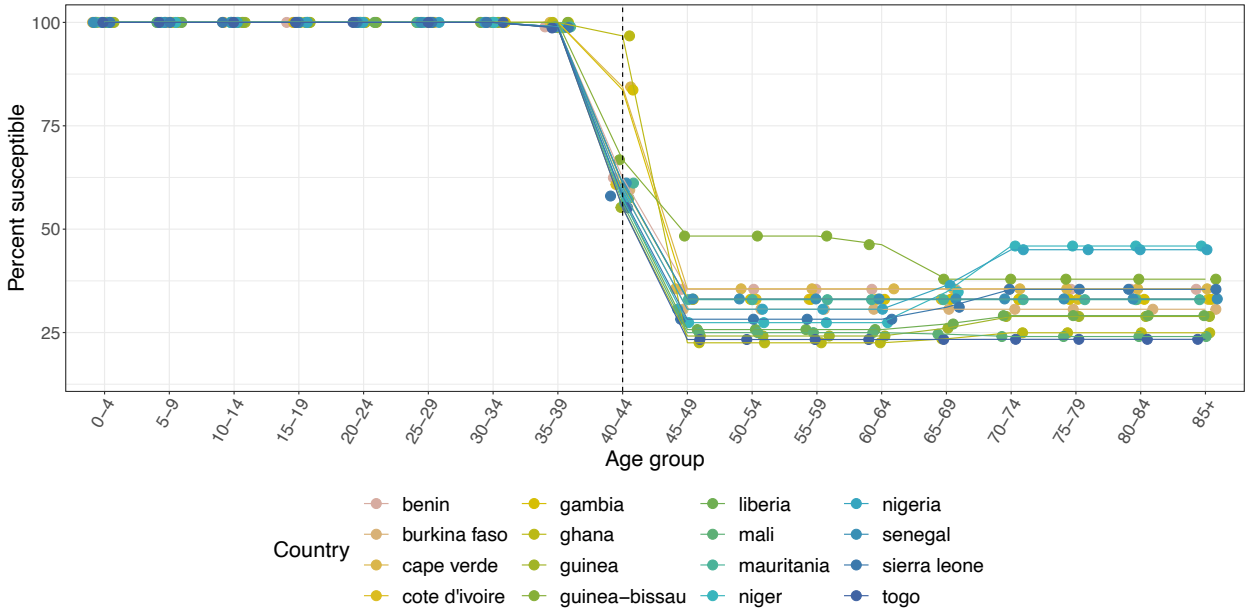


Figure S11. **Country-specific monkeypox susceptibility profiles for countries in Western Africa.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

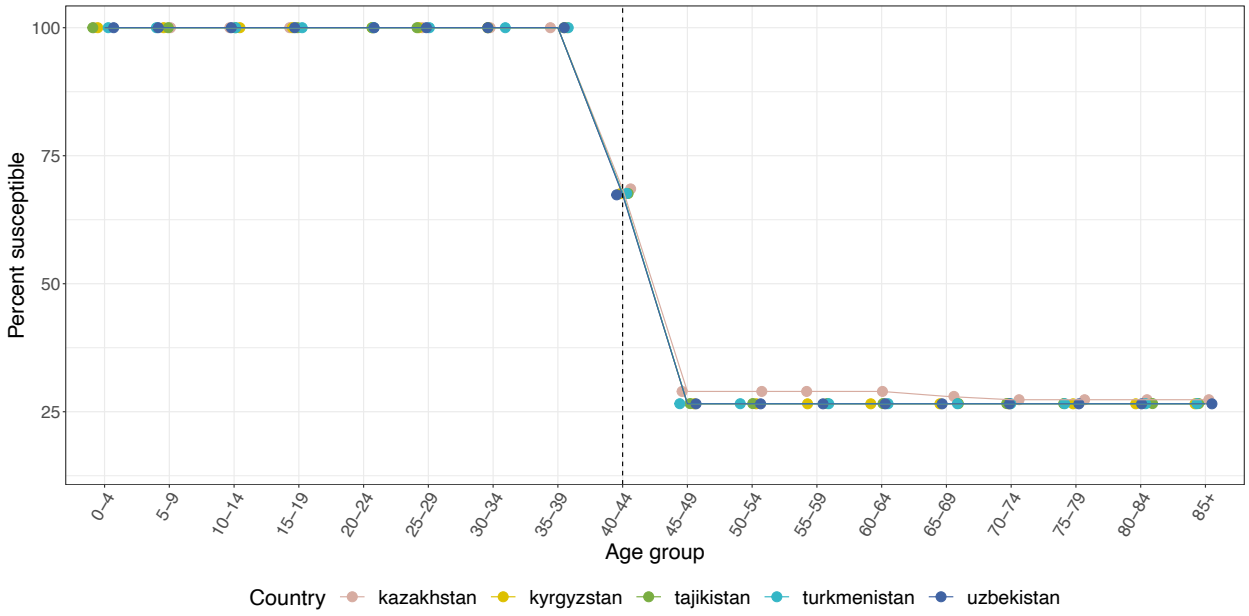


Figure S12. **Country-specific monkeypox susceptibility profiles for countries in Central Asia.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

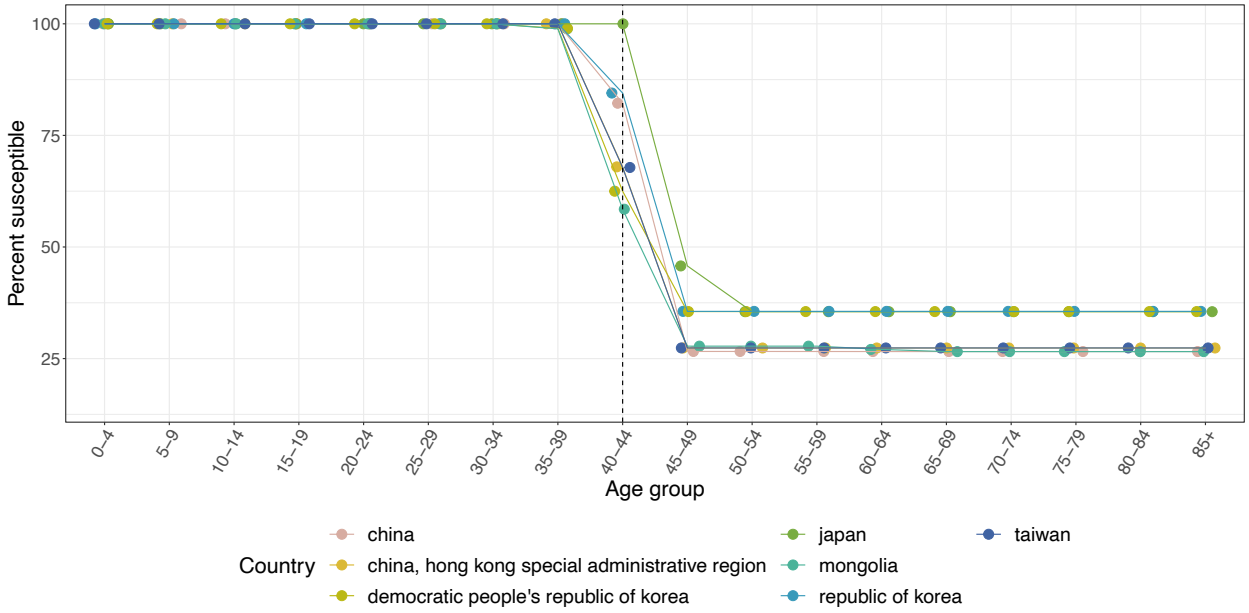


Figure S13. **Country-specific monkeypox susceptibility profiles for countries in Eastern Asia.** Susceptibility is calculated as $1 - (\epsilon \cdot \text{proportion vaccinated})$ for each 5-year age group, where $\epsilon = 80 \cdot 7\%$ is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

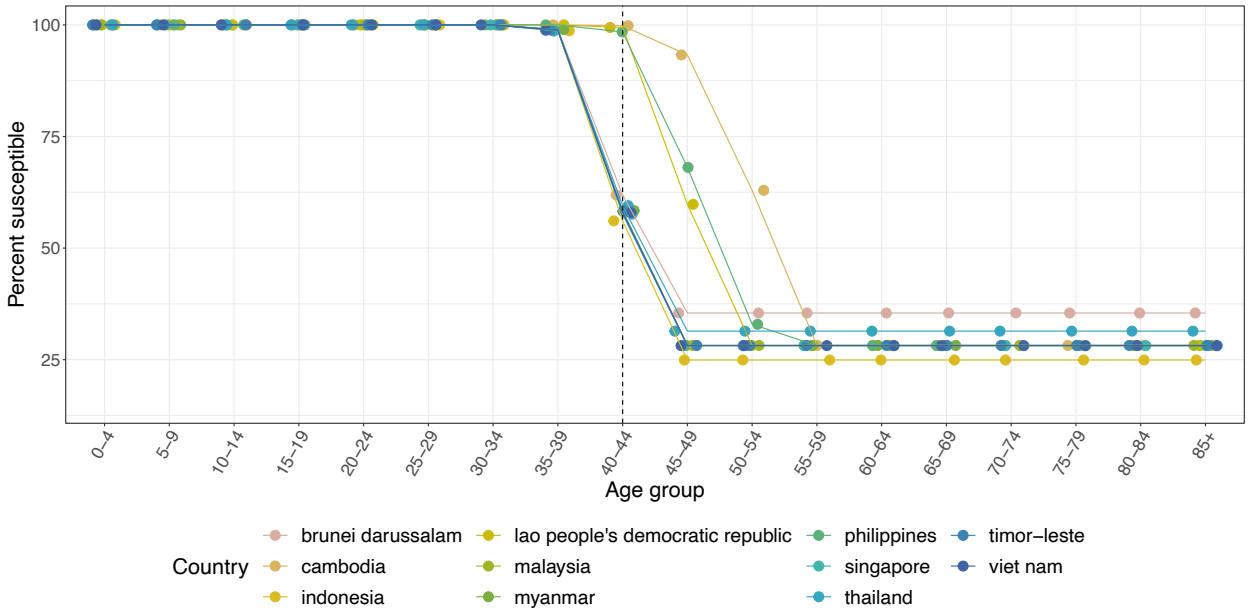


Figure S14. **Country-specific monkeypox susceptibility profiles for countries in Southeastern Asia.** Susceptibility is calculated as $1-(\epsilon \cdot \text{proportion vaccinated})$ for each 5-year age group, where $\epsilon = 80 \cdot 7\%$ is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

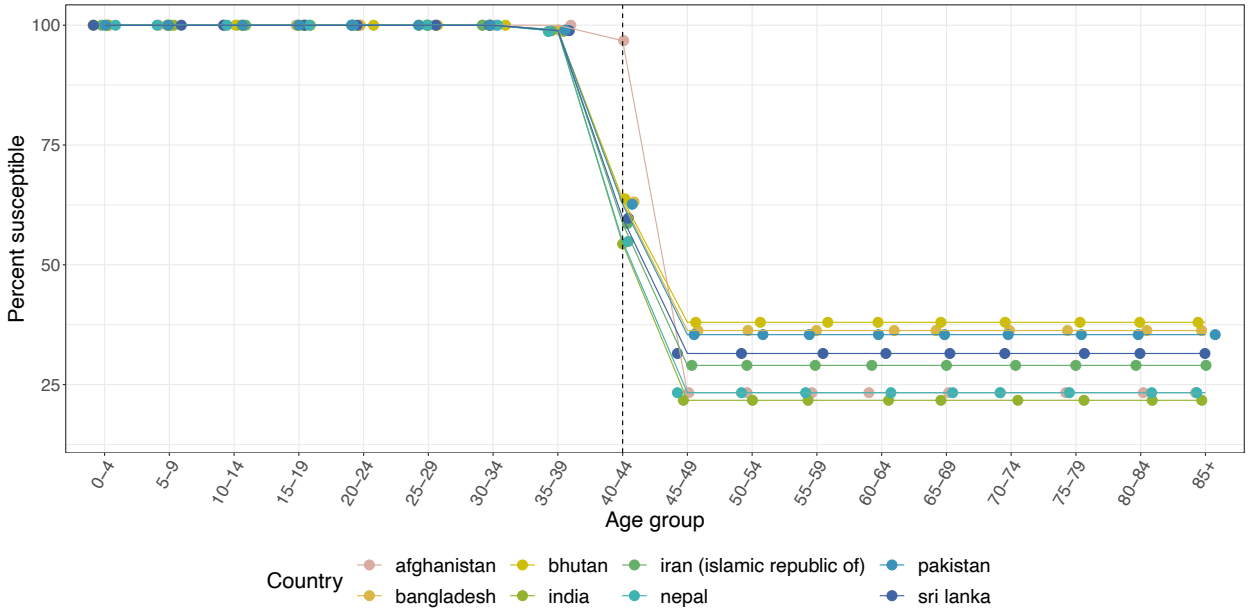


Figure S15. **Country-specific monkeypox susceptibility profiles for countries in Southern Asia.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

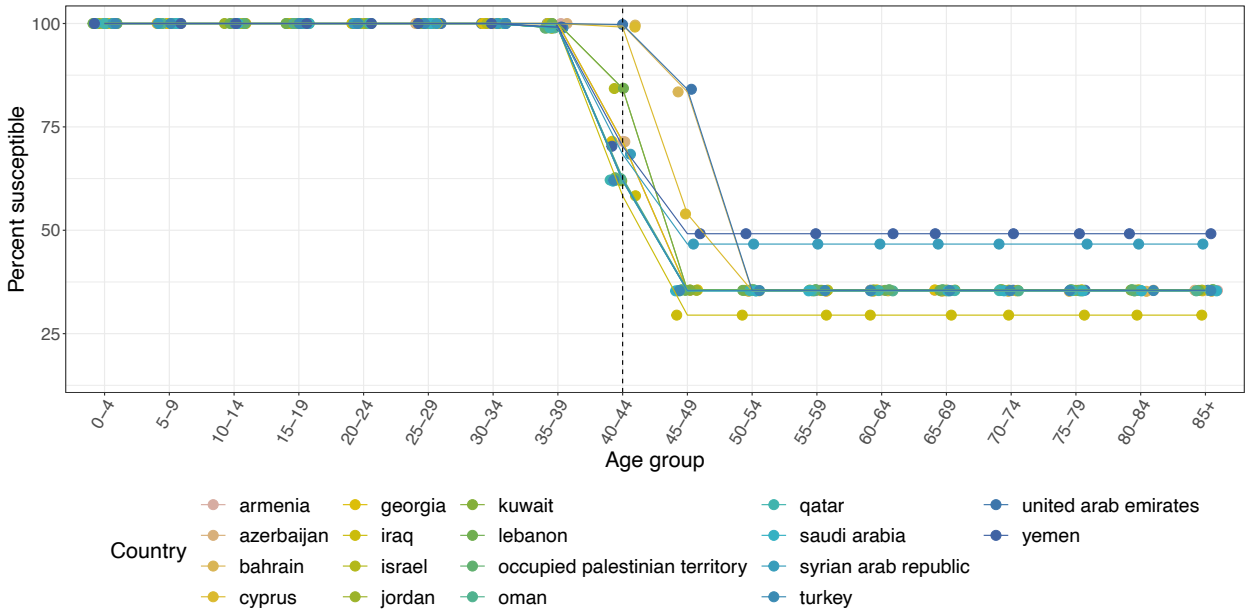


Figure S16. **Country-specific monkeypox susceptibility profiles for countries in Western Asia.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

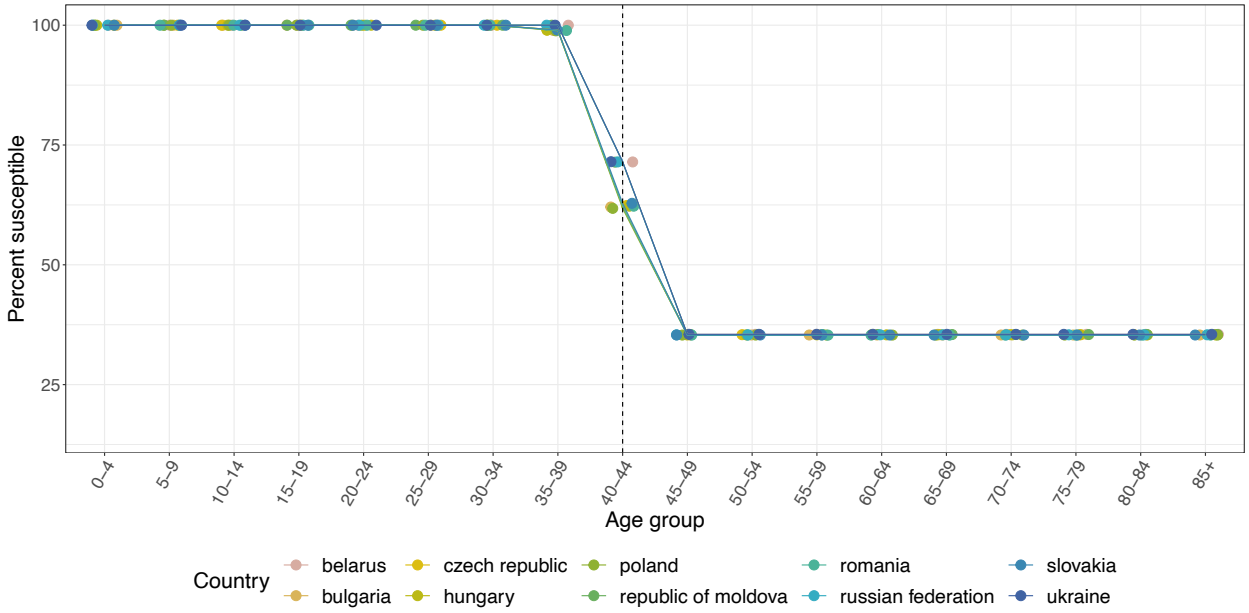


Figure S17. **Country-specific monkeypox susceptibility profiles for countries in Eastern Europe.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

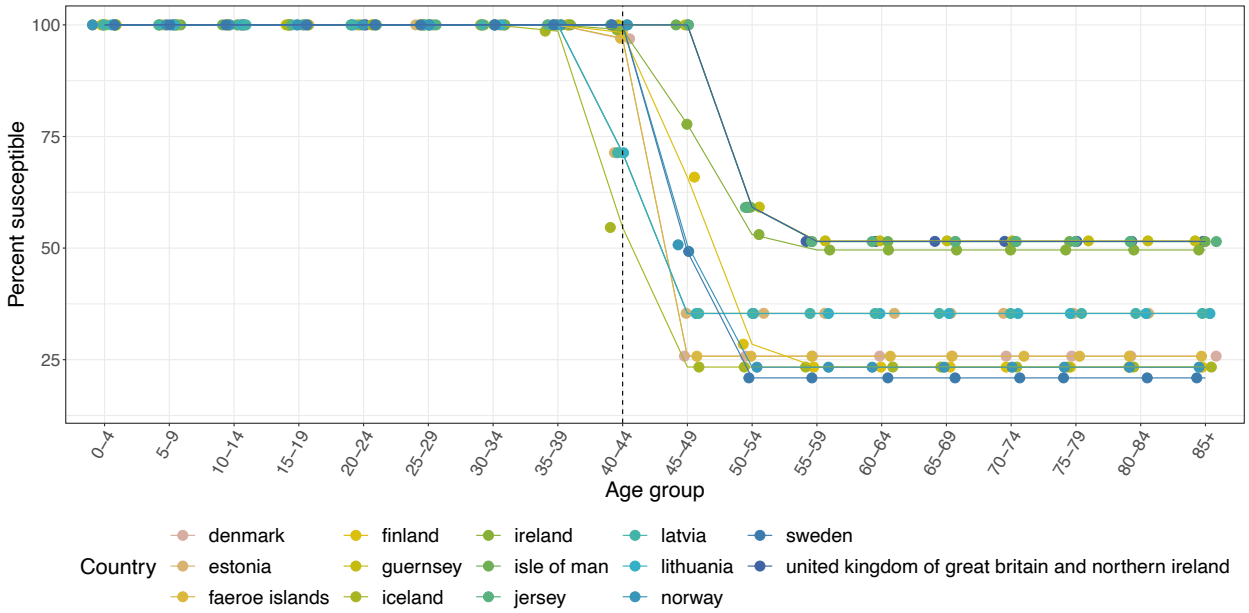


Figure S18. **Country-specific monkeypox susceptibility profiles for countries in Northern Europe.** Susceptibility is calculated as 1 − (ϵ · proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

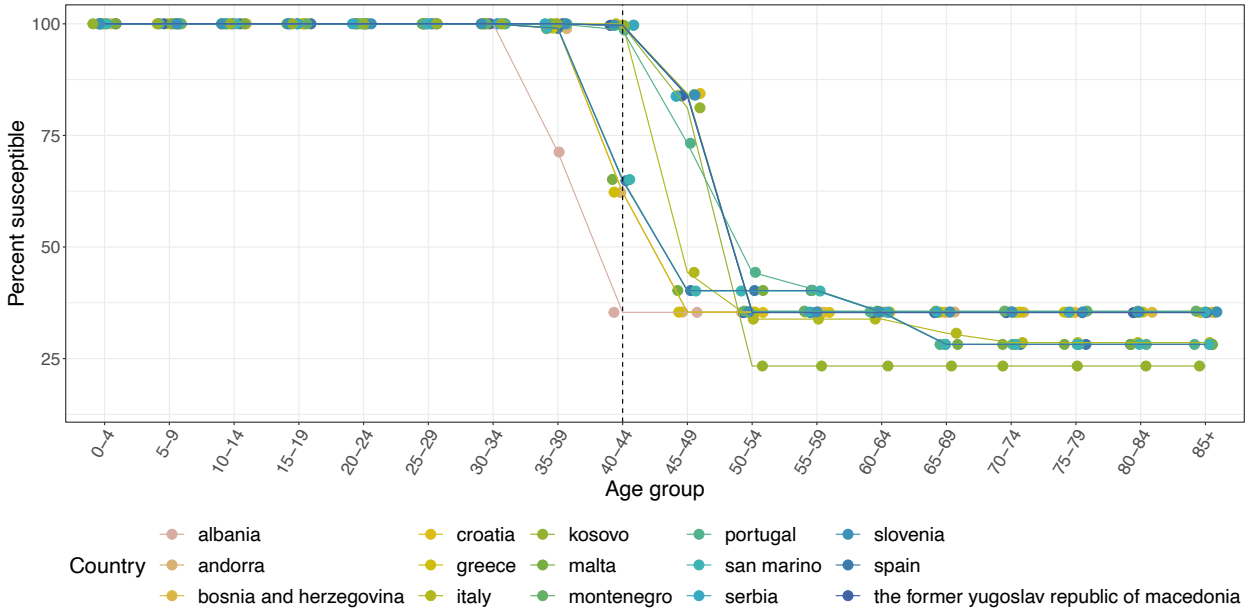


Figure S19: **Country-specific monkeypox susceptibility profiles for countries in Southern Europe.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

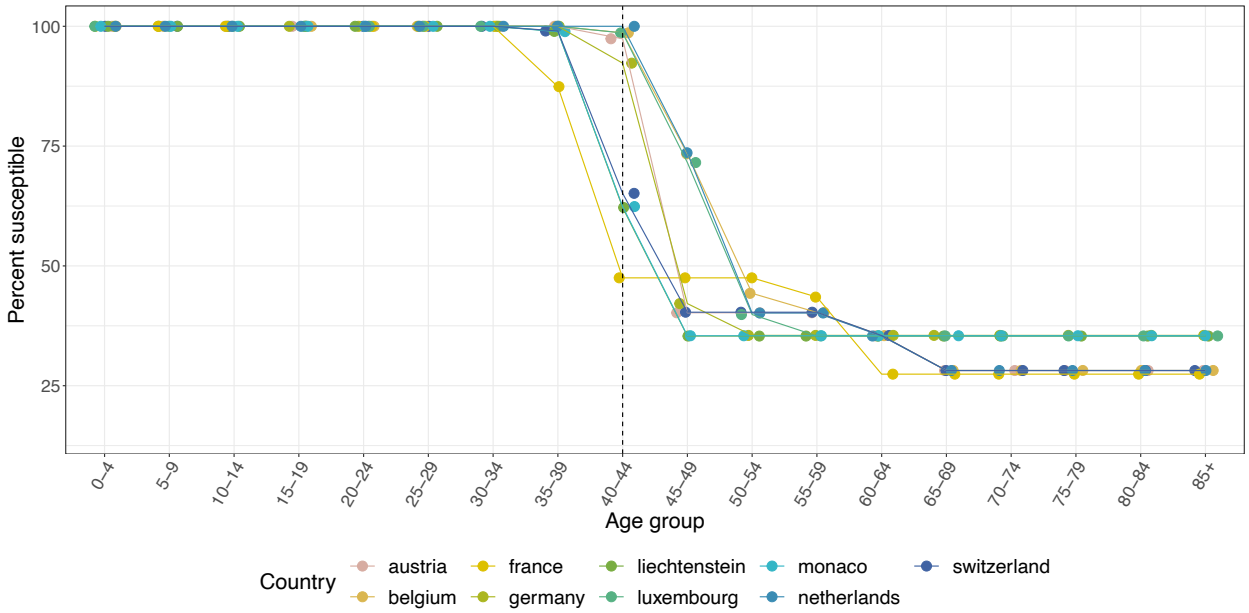


Figure S20. **Country-specific monkeypox susceptibility profiles for countries in Western Europe.** Susceptibility is calculated as 1−(ϵ·proportion vaccinated) for each 5-year age group, where ϵ = 80·7% is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

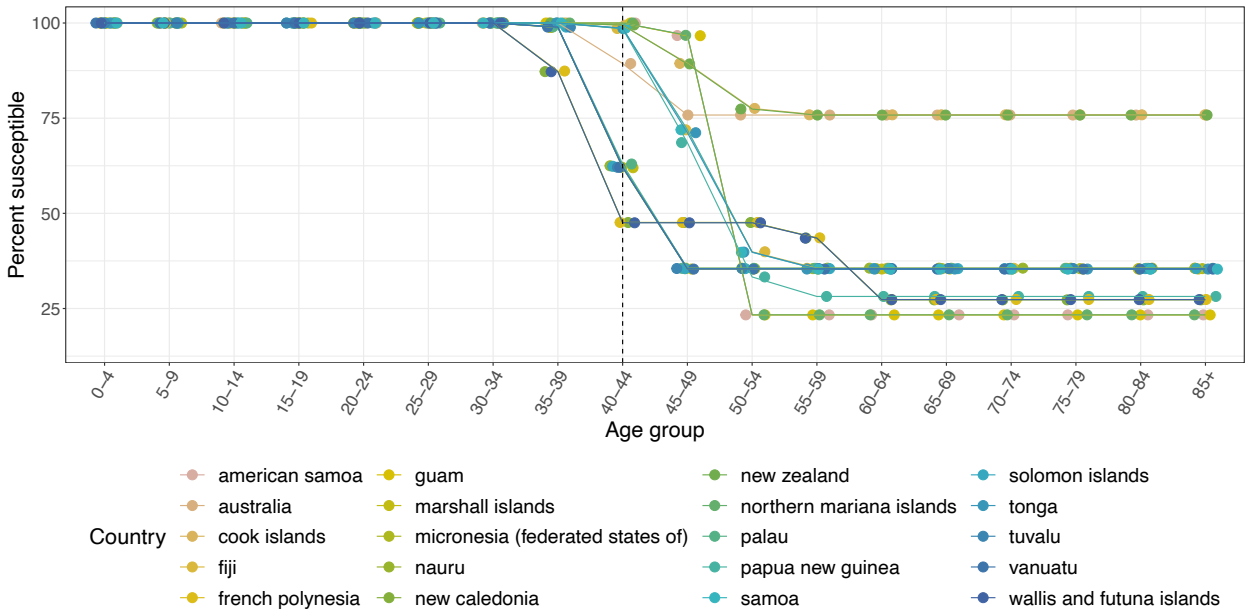


Figure S21. **Country-specific monkeypox susceptibility profiles for countries in Oceania.** Susceptibility is calculated as $1 - (\epsilon \cdot \text{proportion vaccinated})$ for each 5-year age group, where $\epsilon = 80 \cdot 7\%$ is the smallpox vaccine effectiveness against monkeypox. Dashed line indicates last age group in which some individuals were born before global smallpox eradication (1980). Points are jittered horizontally for visual aid.

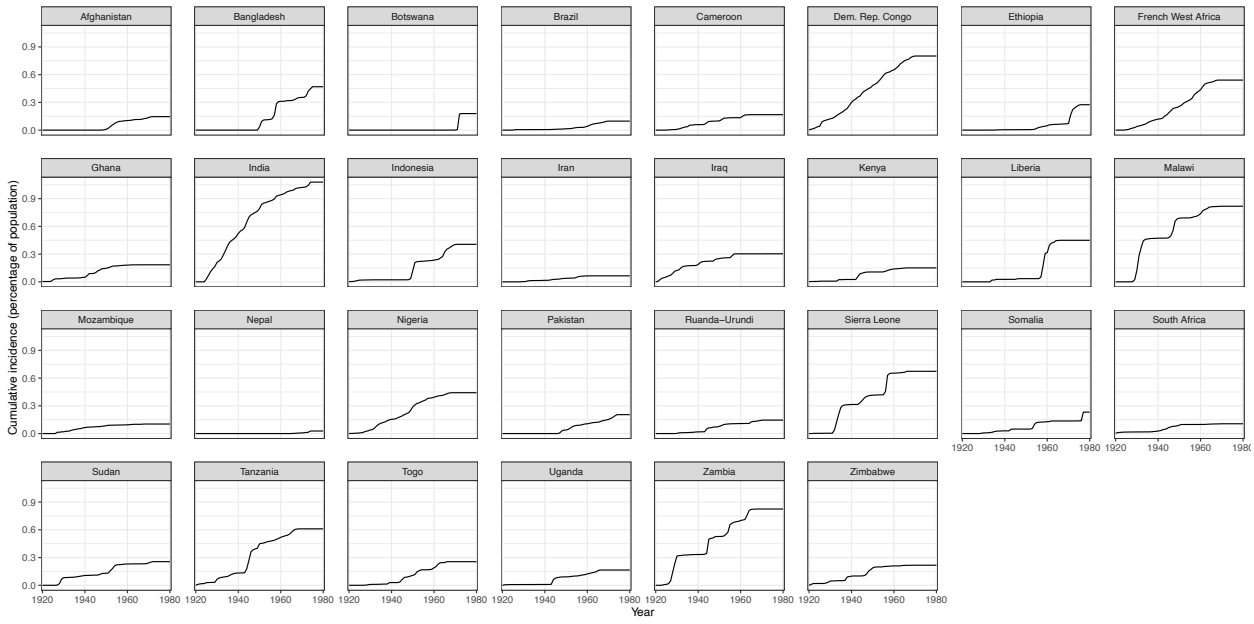


Figure S22. **Cumulative incidence in countries with endemic smallpox spread in 1967 or later rarely exceeds 1% of the 1970 population.** Ruanda-Urundi includes present-day countries Rwanda and Burundi; French West Africa includes present-day countries Benin, Burkina Faso, Côte d'Ivoire, Guinea, Mali, Mauritania, Niger, and Senegal.

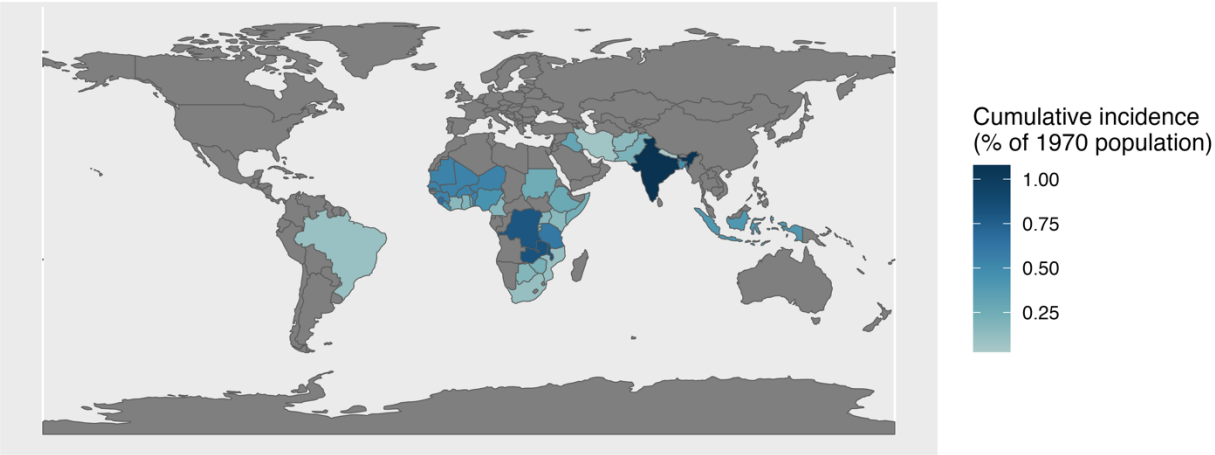


Figure S23. **Map of cumulative incidence in countries with endemic smallpox spread in 1967 or later.** Countries with natural immunity are concentrated in Africa and Southern and Western Asia and only a small proportion of the population was infected.

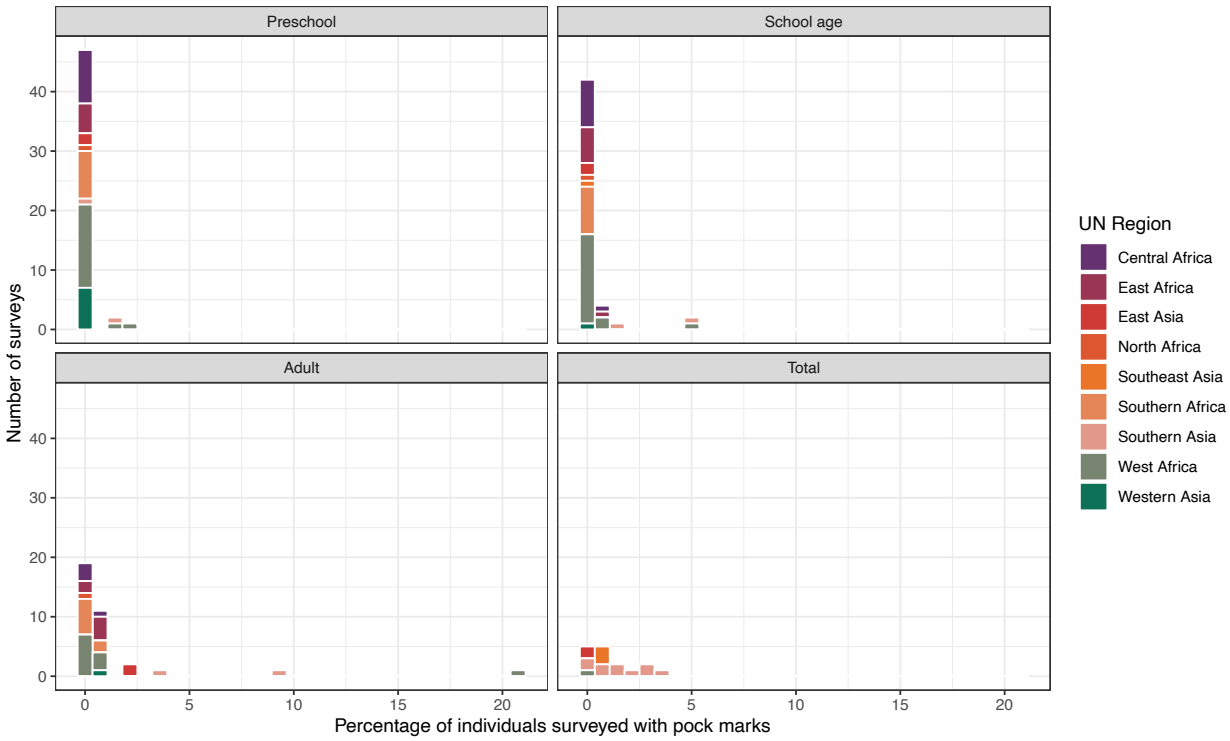


Figure S24. **Pockmark survey data indicate few children were naturally infected with smallpox in the 1960s and 70s.** Facial pockmark surveys were used to assess the progress of smallpox eradication campaigns, as individuals who had natural smallpox infection generally presented with facial scarring. Here, we use these survey results to demonstrate the low percentages of preschool and school-aged children with signs of natural smallpox infection in the years preceding smallpox eradication. In only 11%

of surveys did the percentage of individuals with pockmarks exceed 1% and only in adults did the percentage of pockmarked individuals ever exceed 5%. Adults, who were ≥ 15 years old at the time of these surveys, would be over 65 years old in 2022. Total percentages are provided when an age-specific breakdown of individuals with pockmarks was not available.

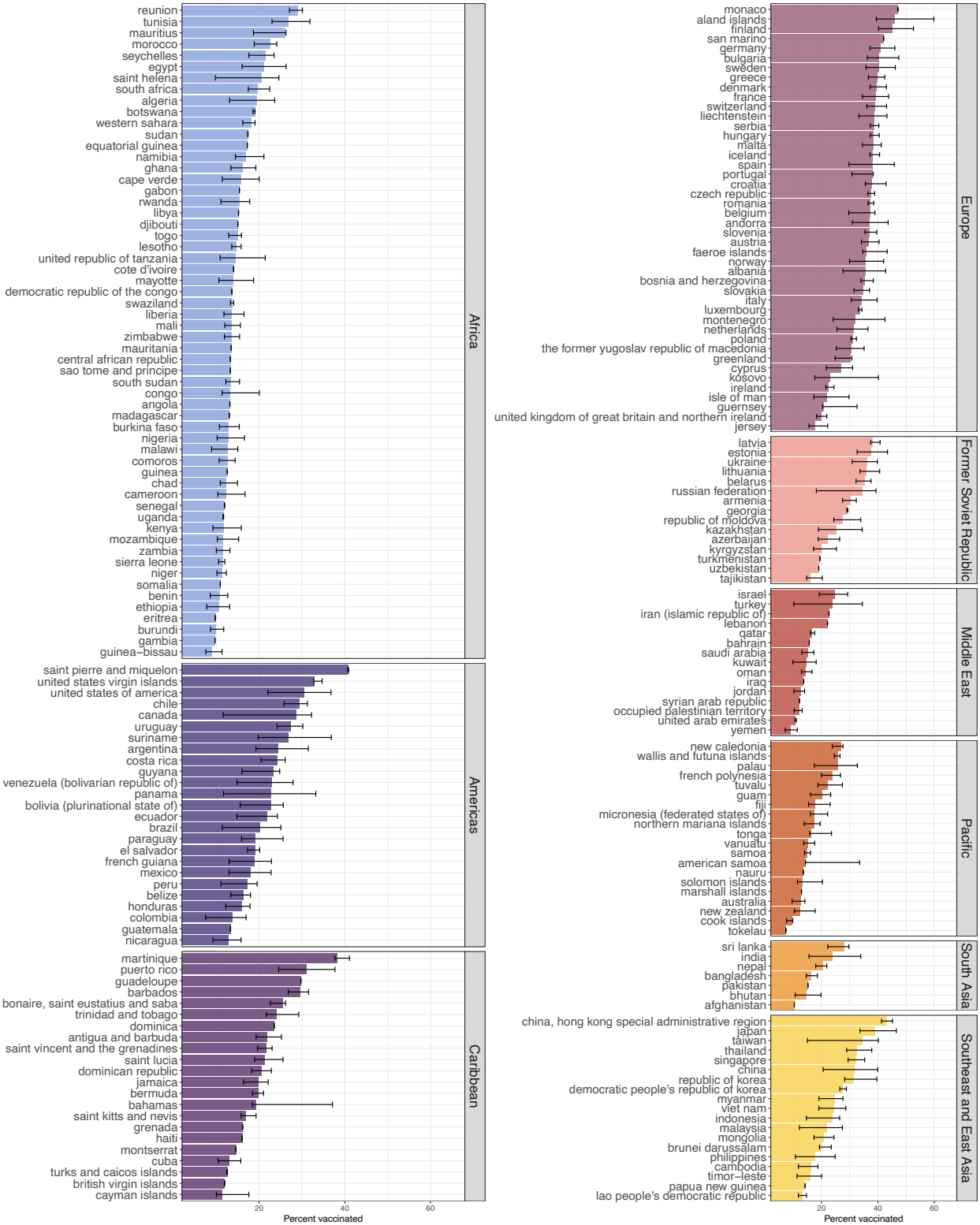


Figure S25. **Estimates of population vaccination level by country and region.** Error bars show range of estimated vaccination levels across admin-1 regions in each country shown in Figure 1A.

A

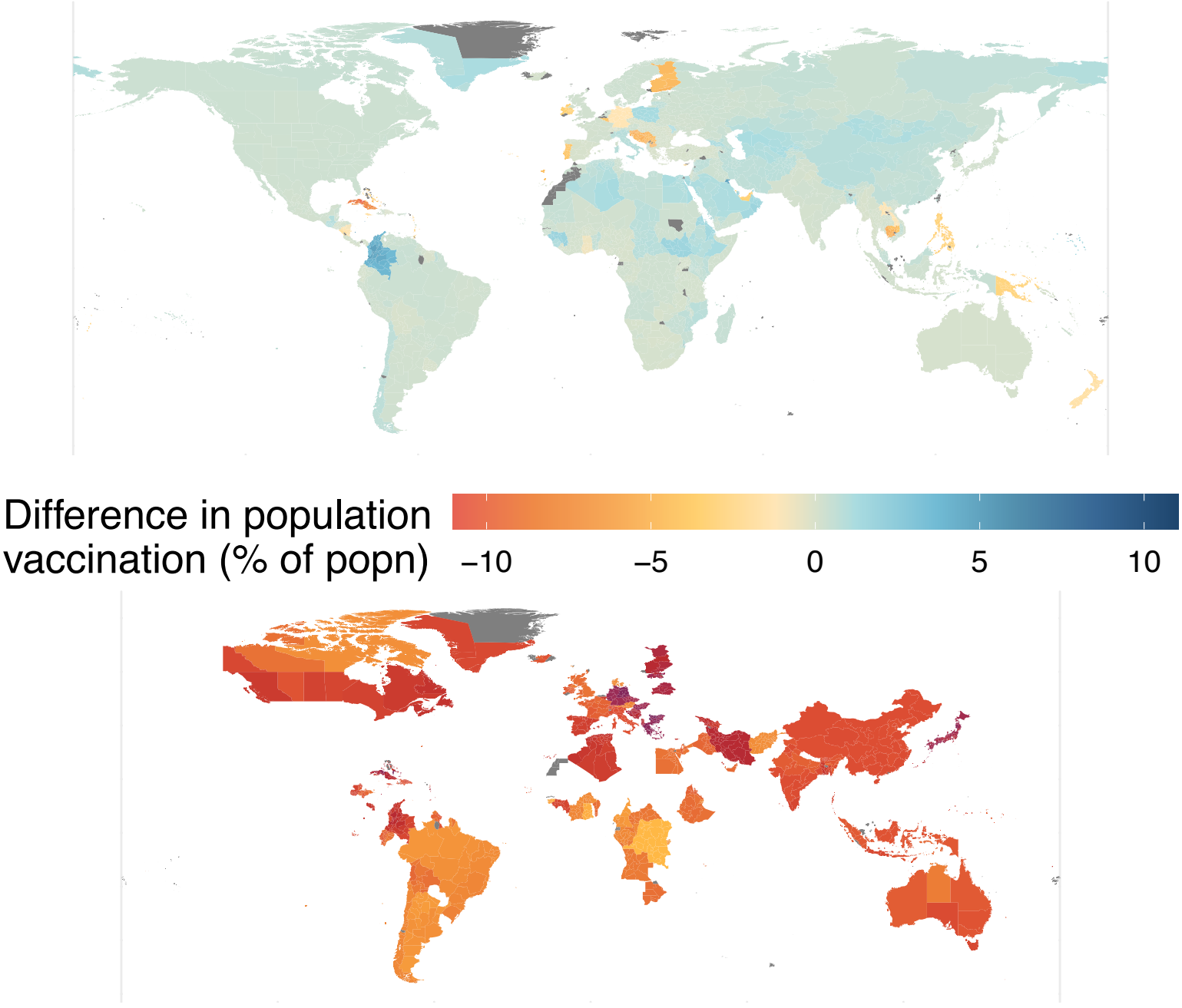


Figure S26. **Uncertainty analysis shows results are qualitatively (and quantitatively) robust.** (A) Mean difference between original and simulated estimates is greatest in regions in Cuba, Kosovo, and Montenegro. 76% of admin-1 regions have an absolute difference less than 1%, and 96% have a difference less than 5%. (B) The standard deviation for 99.6% of regions is within 5%, and are greatest in regions of St. Pierre and Miquelon, Monaco, Kuwait, and Bulgaria. Two regions in St. Pierre and Miquelon with standard deviations exceeding 11% are not shown on the map. Results are from 5000 samples each of vaccination coverage, vaccination cessation date, and admin-1-level age distributions with additional details in Appendix S2.

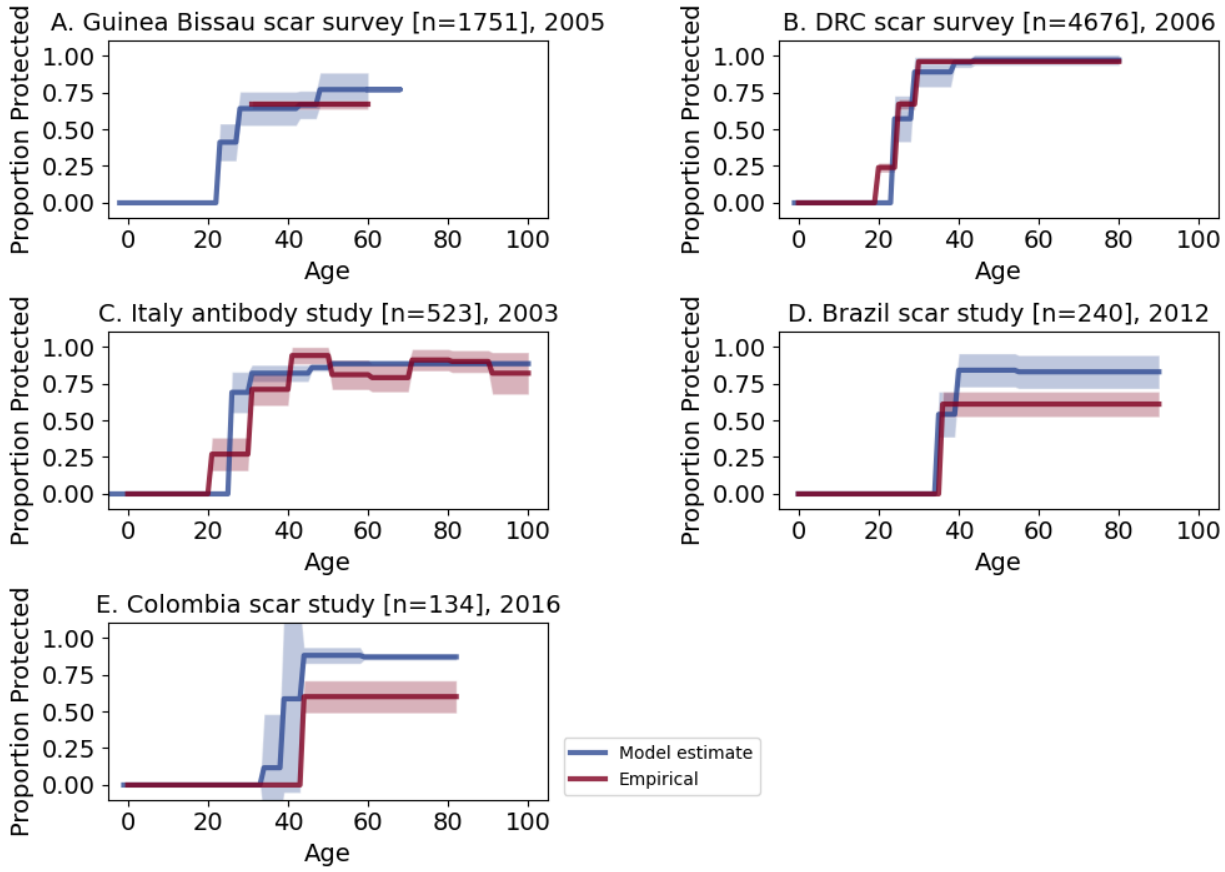


Figure S27. **Comparison of our population susceptibility estimates to field data.** In panels (A)-(E), we compare the smallpox population immunity (vaccination or vaccination*serological protection) of each age group as estimated by our model (blue) to empirical estimates (red). The varying age ranges for the empirical data reflect the age groups defined by each study. Our model estimates are at 5-year age groups. Uncertainty estimates are 95% confidence intervals; however, age-specific sample sizes are unavailable for the DRC study, so the interval cannot be calculated.

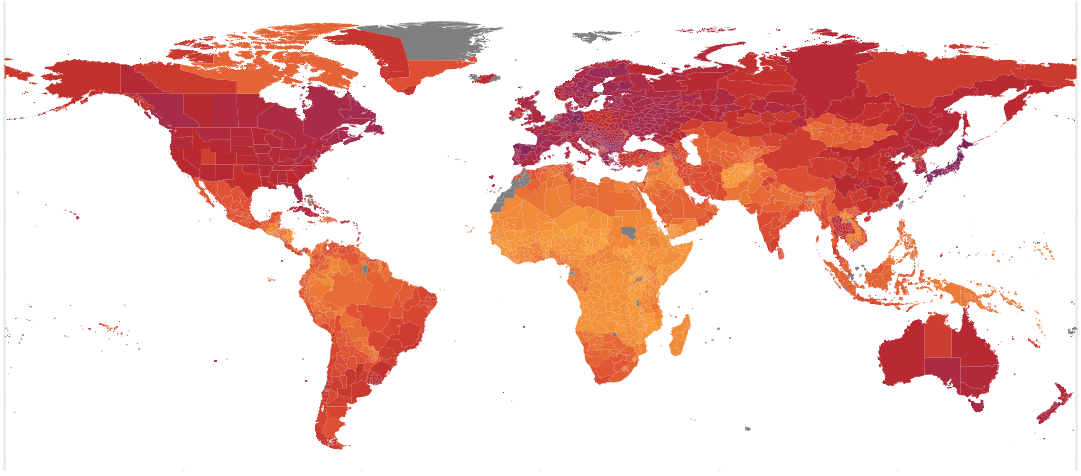
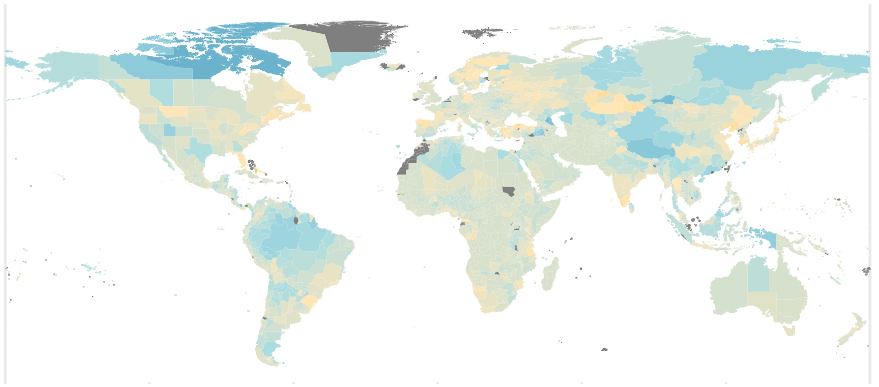

Average age
50
40
30
20
10

Figure S28. **Average age in each admin-1 unit.** Average global age is 30·5.



Difference in population vaccination (% of popn)

25

0

−25

Figure S29. **Scenario analysis to identify how using national age distributions affects vaccination estimates.** In this scenario, we consider homogeneous national demography (i.e., all administrative regions within a country share the the same age distribution as the national average) with age distribution data from 2010.

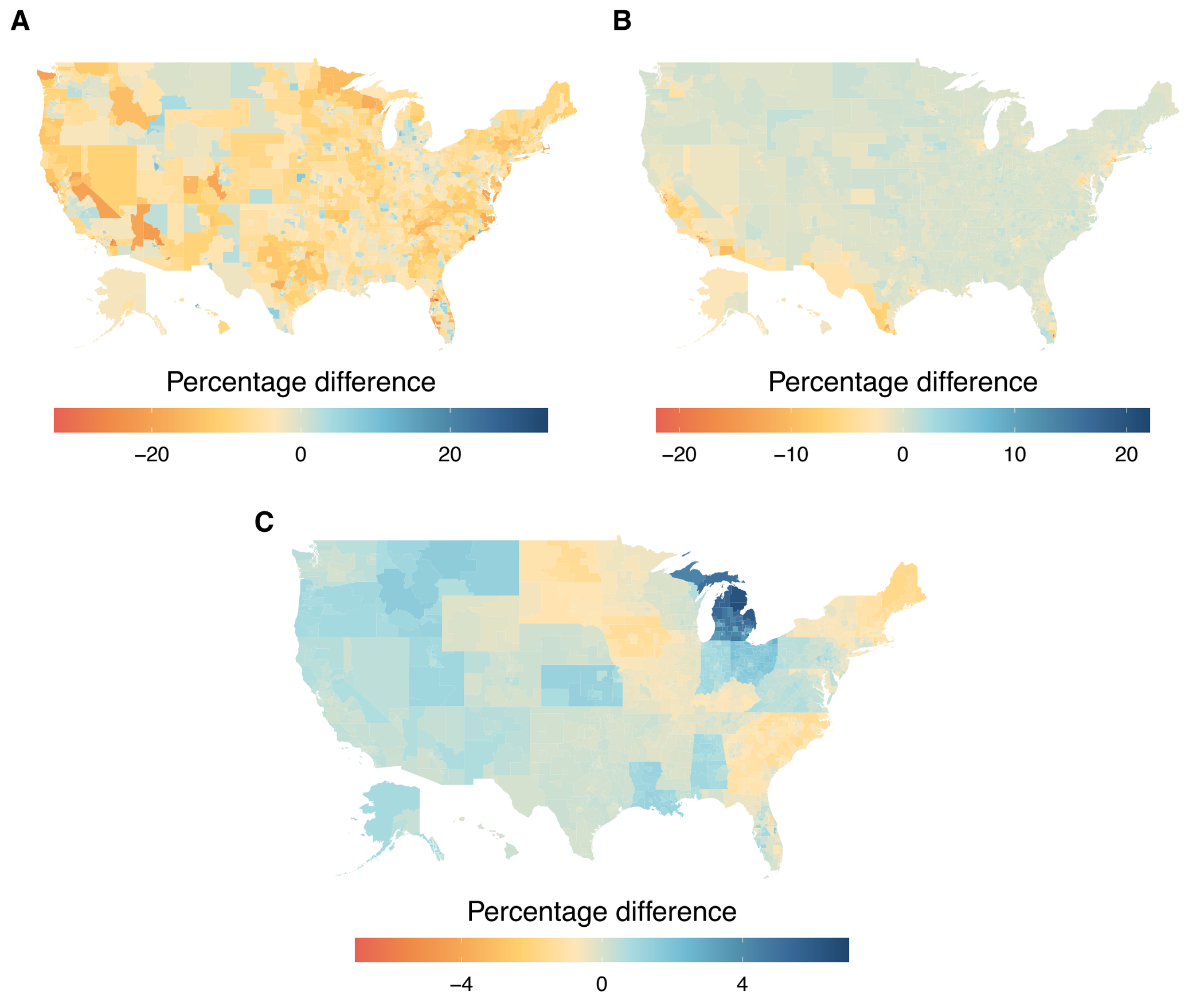

A
Percentage difference
−20
0
20
B
Percentage difference
−20
−10
0
10
20
C
Percentage difference
−4
0
4

Figure S30. **Using higher-resolution spatial data affects vaccination estimates.** US data aggregated to the state (admin-1) level is available from the Gridded Population of the World dataset; finer-scale PUMAs level data is available from the U.S. Census Bureau. PUMAs level data also allows consideration of foreign-born individuals in the U.S. (A) Difference between state-level GPW estimates of vaccination to PUMAs-level estimates assuming homogeneous U.S. vaccination coverage. (B) Difference between PUMAs-level estimates excluding versus including foreign-born individuals. (C) Difference between PUMAs-level estimates assuming homogeneous vaccination across the U.S. versus incorporating state-level heterogeneity using polio vaccination records from 1995.

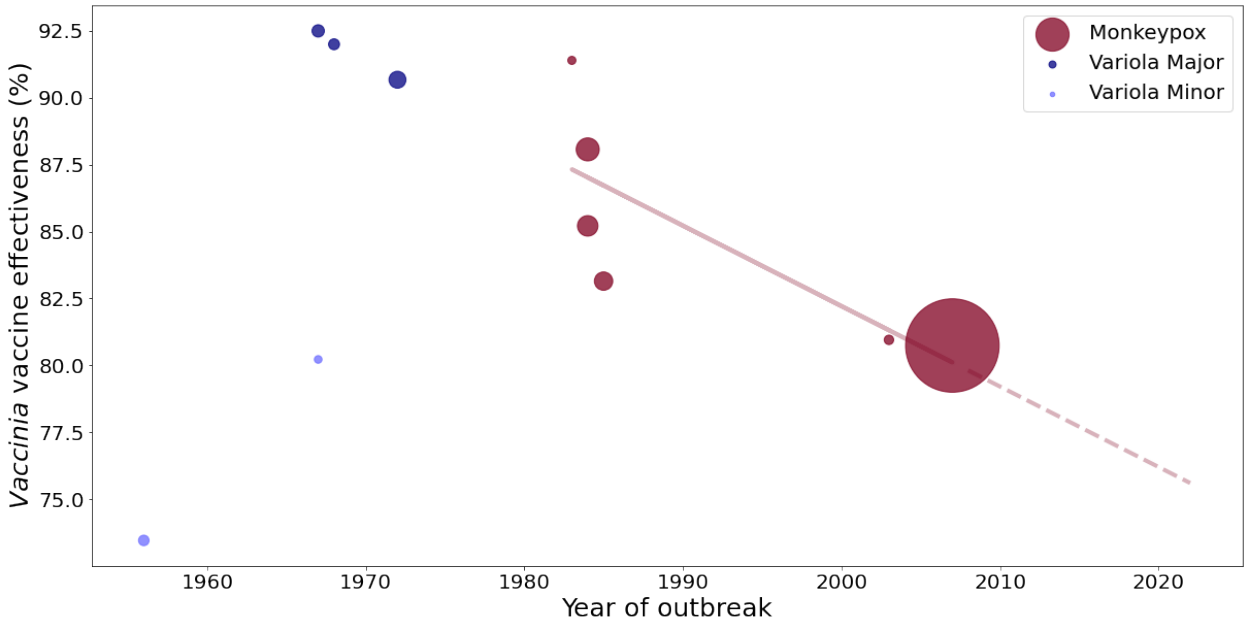


Figure S31. **Smallpox (*Vaccinia*) vaccine effectiveness against orthopoxviruses.** Data are from a literature search, and include studies that provided data on cases and non-cases by vaccination status. Additionally, studies after 1990 were only included if they differentiated smallpox-vaccine eligible (e.g., born before 1980) individuals. The marker size denotes study sample size. The line is based on a linear regression of all available monkeypox data, and the dashed portion is an extrapolation of this relationship to 2022.

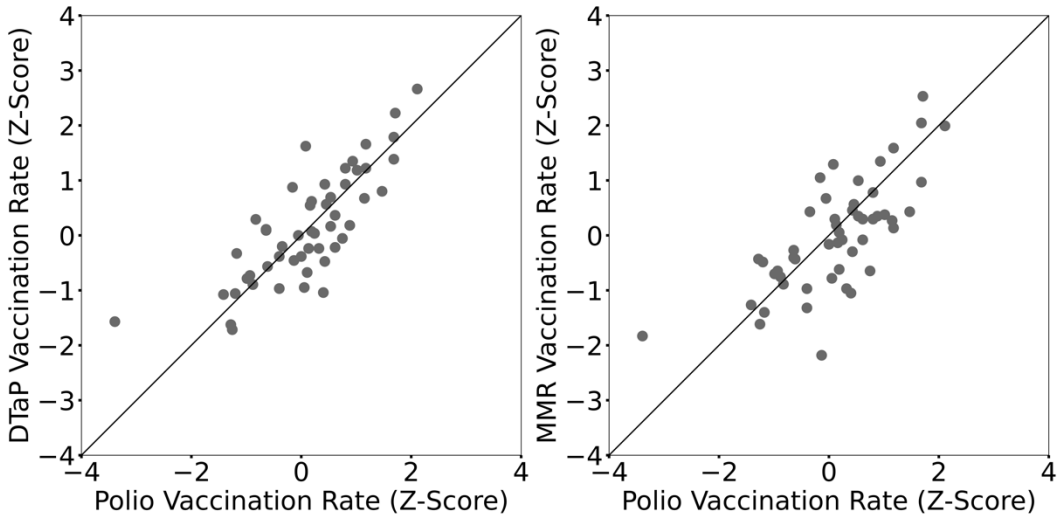


Figure S32. **Spatial heterogeneity in vaccination coverage by US state is consistent between polio and other routine childhood vaccinations.** (Left) Spatial heterogeneity between 1995 vaccination data for polio (≥3 doses in 24-month-old children) and DTaP (≥4 doses in 24-month-old children) displays high correlation at the US state level *(Pearson's r = 0.79)*. (Right) Spatial heterogeneity is also highly correlated (*Pearson's r = 0.73)* at the US state level between 1995 vaccination data for polio and MMR (≥2 doses in 24-month-old children).