**The geography of measles vaccination in East Africa: are there “coldspots”, and do they spatially cluster?**

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**\*\* Figures and movies (complete) \*\*** <https://www.dropbox.com/sh/uaeznxztvei9p0n/AACJNWmcrP_prKtxIF72Ld6sa?dl=0>

**Abstract**

Background: Expanding access to measles vaccination was one of the most successful public health interventions of recent decades. All WHO regions currently target measles elimination by 2020, yet continued measles circulation makes that goal seem elusive. Contiguous areas of low vaccination coverage may allow the virus to persist, even if overall coverage is high. Here, we quantify spatial patterns of measles vaccination in countries in East Africa between 2009-2014 and identify geographic areas where coverage must be strengthened.

Methods and Findings: Using data from the Demographic and Health Surveys and generalized additive models, we map measles vaccine coverage in ten contiguous countries in the African Great Lakes region. Despite an average reported measles vaccination coverage of 87% across the times considered, seven out of the ten countries have “coldspots” with coverage lower than 80%, with some coldspots covering substantial areas. Spatial heterogeneity in vaccination does not map directly onto sub-national administrative units and transnational vaccination coldspots exist. We estimate that over 15 million children under 5 years of age live in vaccination coldspots across the region, and a total of between 8-12 million children are unvaccinated against measles.

Conclusions: Our results show that there is spatial variation in measles vaccination coverage both between and within countries, and we identify geographic areas and age groups that are failing to meet the WHO measles vaccination goal of 80% coverage in every district. Notably, spatial clustering of low vaccination may lead to pockets of susceptibility that will sustain circulation in an otherwise successful measles elimination program with high overall vaccination coverage. Targeting of at-risk areas and regional coordination to eliminate transnational clusters of susceptibility are likely needed to successfully eliminate measles in the region.

**Introduction**

A potentially high case-fatality rate, combined with the existence of an inexpensive and safe vaccine that provides lifelong immunity, makes measles control one of the most cost-effective public health interventions in existence [[1,2]](https://paperpile.com/c/27GMeh/31Ob+k5Bc). Due to substantial gains in measles vaccination coverage over recent decades, incidence has fallen worldwide from an estimated 146 cases per million and 562,400 deaths in 2000, to 40 cases per million population cases and 114,900 deaths in 2014 [[3]](https://paperpile.com/c/27GMeh/KQ1i). However, measles continues to circulate in many countries and remains one of the leading killers of children globally [[4]](https://paperpile.com/c/27GMeh/ew13).

The target vaccination coverage that must be reached to achieve measles elimination is a function of how efficiently the virus is spread, which is in turn a result of the biology of measles and the contact patterns of infected individuals. The efficiency of viral spread is captured by the basic reproductive number *R0*, defined as the number of secondary cases an infected individual would cause in a fully susceptible population (estimated to be between 10-20 for measles [[5,6]](https://paperpile.com/c/27GMeh/DL78+1p18)). In the simplest analysis, measles requires at least 1/*R0* of a population to be susceptible to measles in order for the virus to persist. Hence for measles, between 90-95% of the population must be immune to interrupt measles transmission. However, this analysis is based on the assumption that unvaccinated individuals are evenly distributed throughout the population, which is unlikely to be true in the real world.

Measles is a directly transmitted infection, and infected individuals must enter into contact with susceptible individuals during the approximately two weeks that they are infectious in order for a chain of transmission to persist [[7]](https://paperpile.com/c/27GMeh/RGk3). Patches of unvaccinated individuals living in close proximity are therefore more likely to sustain a measles epidemic, compared to the same number of unvaccinated people evenly distributed throughout a country. Even when the size of these clusters is below the critical community size required to maintain measles transmission (estimated to be around 300,000 individuals for measles in pre-vaccination England and Wales [[8]](https://paperpile.com/c/27GMeh/ac7k)), they remain a concern: even transient outbreaks can cause significant morbidity and mortality, and seeding of new outbreaks by movement between clusters can potentially maintain regional transmission.

The impact of spatially heterogeneous vaccination has been increasingly recognized in making policy decisions, resulting in a shift in focus from simply setting country-level targets for coverage, to ensuring uniformly high vaccination levels across countries (e.g., the strategy of RED, or Reaching Every District [[9]](https://paperpile.com/c/27GMeh/fkp0)). Although a considerable improvement over a country-level focus, a district-level focus may still miss important aspects of geographical heterogeneity. By taking averages across administratively-defined areas (i.e., districts or provinces), we may miss zones of vulnerability that are small or do not respect national or sub-national administrative boundaries.

Throughout sub-Saharan Africa, home to the majority of the world’s remaining measles burden [[10]](https://paperpile.com/c/27GMeh/ytcw), measles vaccination is predominantly delivered through two activities: routine immunization (i.e., at local health centers) that target children around 9 months of age for their first dose of measles containing vaccine (MCV-1) [[11]](https://paperpile.com/c/27GMeh/zuEW), and supplemental immunization activities (SIAs), which are large campaigns periodically conducted that target a broader age range in an attempt to provide a second vaccine dose to those vaccinated in routine programs and to provide a first dose to those not. This two-pronged vaccination was successful in the Americas, which achieved endemic measles elimination in 2002 [[12]](https://paperpile.com/c/27GMeh/QwGe) (although cases have continued to be imported in the region; e.g., after elimination was declared in Brazil in 2000, there was an average of 50 reported cases per year between 2001-2014 [[13]](https://paperpile.com/c/27GMeh/LqgU)).

The combination of increased routine vaccination coverage and periodic SIAs reduced yearly measles incidence in Africa by 93% between 2001-2008 from 492,000 to 37,000 reported cases [[14,15]](https://paperpile.com/c/27GMeh/TCHk+3gRQ). However, since mid-2009 there has been a resurgence, with approximately 200,000 measles cases reported in 28 countries in sub-Saharan Africa between 2009-2010 [[16,17]](https://paperpile.com/c/27GMeh/TaYA+XVpG). Such outbreaks have been attributed to weak routine vaccination systems and delayed or low-quality SIA campaigns [[18]](https://paperpile.com/c/27GMeh/bGk7). A lack of transnational coordination in the timing of SIAs may also contribute (e.g., Mozambique conducted SIAs in 2008, 2011, and 2013, while neighboring Zimbabwe did so in 2009, 2010, and 2012), potentially allowing the virus to persist in spatial clusters of unvaccinated children that cross international boundaries.

Demographic and Health Surveys (DHS) provide cross-sectional data on the spatial distribution of vaccination in children under 5 years of age across multiple countries, collected using a standardized framework [[19]](https://paperpile.com/c/27GMeh/MrhD). Combining this data with information on the age and geographic distribution of the local population, we here map vaccine-derived immunity against measles in ten East African countries in the Lake Victoria region that use SIA campaigns to boost population-level immunity: the Democratic Republic of Congo (DRC), Uganda, Kenya, Rwanda, Burundi, Tanzania, Zambia, Malawi, Mozambique, and Zimbabwe. Using these maps we identify coldspots of measles vaccination that cross administrative boundaries, foci for elimination efforts, and locations where elimination efforts may be failing. In doing so, we aim to inform the spatial scale at which vaccination policy is most effectively implemented in the region (nationally, sub-nationally, or along which administrative borders), and highlight the complexities and challenges associated with current approaches.

**Methods**

*Data*

Country-level data on measles vaccination status was extracted from the most recent geo-located DHS survey made publicly available by ICF International [[20]](https://paperpile.com/c/27GMeh/kheH). Survey periods ranged from December 2009 to October 2014 (Table 1). A national DHS survey has one record for each interviewed woman’s child 5 years of age and younger at the time of the survey, and is linked to a database of GPS coordinates (longitude and latitude) of respondents’ home locations. GPS coordinates are aggregated into clusters containing approximately twenty households (Figure S1), and randomly displaced up to 2 kilometers in urban areas and up to 5 kilometers in rural areas to protect respondent confidentiality [[21]](https://paperpile.com/c/27GMeh/4hFD). For the purposes of this analysis we assume cluster locations are exact. For each child, we obtained the age at the time of survey, whether the child had ever received a measles vaccine (based on vaccination card or report of parent/guardian), and their GPS location. Ages were rounded up into 1-month classes due to uncertainty in the data, and children under 6 months of age at the time of survey were considered not to be “at risk” for successful vaccination and excluded from the analysis: while routine vaccination with MCV-1 is recommended at 9 months of age, SIA campaigns often set their lower age target at 6 months.

Issues linked to parental recall make this source of information potentially less reliable than card-based validation of vaccination status. Parental recall does not provide the exact date at which a child was vaccinated, and cannot be used to distinguish between vaccination obtained via the routine program or SIA campaigns. However, because vaccination cards are rarely available in the database (as people may frequently lose them), using parental recall allows greater spatial and temporal scope. Parental recall has been shown to provide a relatively robust indicator of vaccination status in other analyses [[22]](https://paperpile.com/c/27GMeh/DgGc) and was appropriate to our needs, as vaccine-derived immunity (whether from the routine program or SIAs) and its spatial heterogeneity was our main focus in this analysis.

Information on the timing and logistics of SIAs were obtained from the WHO [[23]](https://paperpile.com/c/27GMeh/RXAy). SIA campaigns can either be conducted on a national scale or target one or more sub-national regions. In this analysis, we included all SIAs that were completed within the 5 years prior to a country’s DHS survey (Table 1). Spatially structured, population demographic data from 2010 by 5-year age groupings was obtained from the WorldPop project [[24]](https://paperpile.com/c/27GMeh/l9bN) and national and sub-national administrative political boundary shapefiles were obtained from DIVA-GIS [[25]](https://paperpile.com/c/27GMeh/WJJj).

*Definition of coldspots*

One of the milestones for 2015 established in 2010 by the World Health Assembly was to increase routine coverage with MCV-1 for children aged 1 year to at least 90% nationally and at least 80% in every district by every member state [[26]](https://paperpile.com/c/27GMeh/9g41). Hence, in this analysis, we define a coldspot of vaccination to be a spatial unit that has below 80% mean estimated measles vaccination coverage at a given age; therefore coldspots by our definition are age-specific.

*Estimating vaccination coverage*

We performed logistic regression using generalized additive models (GAMs) [[27]](https://paperpile.com/c/27GMeh/smHy) to estimate measles vaccination coverage for each country where the outcome was whether a child *i* was reported as vaccinated (*vi*=1) or not (*vi*=0) in the DHS survey. To account for spatial autocorrelation, we included longitude and latitude as a smoothed (*s*) interaction term. Survey age was also included as a smoothed predictor, and showed a broadly increasing relationship with vaccination coverage (Figure S4). We did not explicitly model national SIAs as a child’s eligibility for being vaccinated during a national campaign is collinear with survey age. However, if a country had any sub-national SIAs during the time period of interest (i.e., Burundi, DRC, and Tanzania), we included individual eligibility for each sub-national campaign *j* as a covariate (where eligibility is based on both survey age and geographic location). The GAM used is shown in Equation 1:

(1)

Model selection was done based on Akaike information criterion (AIC) (Table S1, Table S2). Expected vaccination coverage levels were then determined for each location by laying a 10 km x 10 km grid across the country and interpolating the expected value for each grid cell, combined with spatially explicit data on the population size of children under 5 years of age.

*Sub-national clustering of susceptibility*

At the grid cell scale, we looked along sub-national political boundary levels to determine how measles susceptibility clusters within countries. To account for the nesting of these administrative levels, we used a multi-level modeling framework with random effects for each administrative level [[28]](https://paperpile.com/c/27GMeh/BUdi). We decomposed overall variance by estimating the level-specific intraclass correlation coefficients (ICC), which represent the proportion of overall variance in each country that is explained by that sub-national political boundary level.

All analysis was conducted using the R statistical software, version 3.2.3 (<http://cran.r-project.org>).

**Results**

We estimated measles vaccination coverage at 24 months of age across the region, the result of both routine immunization programs and national SIA campaigns for which children below this age are eligible (Figure 1A). Results indicate large contiguous areas of low vaccination coverage across the region. In particular, in DRC, low vaccination areas are found in the northwest (former Equateur province), central (former Kasaï-Occidental and Kasaï-Oriental provinces) and southeast (former Katanga province). Other countries show greater overall variability: within-country heterogeneity in coverage is particularly pronounced in Tanzania and Mozambique, while Rwanda, Burundi, and Malawi have relatively homogeneous -- and high -- vaccine coverage. In Kenya, vaccination coverage decreases with greater distance from the capital, Nairobi; the opposite qualitative pattern is found in Zimbabwe and in Uganda, with decreased coverage with proximity to the capital cities.

To define key areas of low coverage, we then mapped the coldspots of measles vaccination at 24 months of age indicating areas from Figure 1A where coverage is estimated to be below 80% (i.e., a coldspot) in grey (Figure 1B). Across the region, coldspots span multiple sub-national administrative units (the first sub-national political boundaries (Adm1) shown in light grey). There were no or very few coldspots in Rwanda, Burundi, Malawi, and Zambia. Tanzania and Kenya have large areas covered by coldspots; however, only low percentages (approximately 10%) of children reside within them, as coldspots exist in low population density locations (Table 2). Conversely, DRC and to a lesser extent, Uganda, have large areas covered by coldspots and over 60% of children at 24 months of age live in a coldspot. Summing across children between 6-24 months of age in these countries translates to 2,958,281 (95% confidence interval [CI]: 2,600,271-3,203,347) children in DRC and 1,621,123 (95% CI: 1,184,109-1,904,156) children in Uganda who reside within a coldspot for this age class. In DRC, this high percentage can be attributed to the vast surface area of coldspots, and in Uganda, is due to the observed negative relationship between population density and vaccination coverage.

Estimates of vaccination coverage were combined with data on population size to map the numbers of children between 6-24 months of age who were not vaccinated against measles in routine activities or national SIAs (Figure 2). Numbers of unvaccinated children in these countries range from 156,068 (95% CI: 136,340-179,327) in Burundi to 1,750,619 (95% CI: 1,556,337-1,950,863) in DRC, with an estimated total of 10,095,438 (95% CI: 8,393,147-12,168,760) across the entire region (Table 2). Although Rwanda, Burundi, and Malawi attain high levels of vaccination coverage, these countries are relatively densely populated and thus still have high numbers of unvaccinated children (Table 2). This map of unvaccinated children also shows that despite central DRC having the lowest vaccination coverage and largest coldspots by area, large numbers of unvaccinated individuals cluster elsewhere in the region (Figure 2). Notably, a substantial transnational cluster of unvaccinated children exists in the densely populated region surrounding Lake Victoria (including areas of relatively high vaccination coverage).

Because vaccination coverage varies by age (Movie S1), the locations of areas considered as coldspots vary by age as well (Movie S2). We identified ‘long-term’ coldspots, or areas where vaccination coverage is below 80% over a large proportion of monthly age cohorts between 12-60 months (Figure 3A), shown as dark red cells. The spatial patterns are similar to those in Figure 1A: there are large areas of DRC that are long-term coldspots. To obtain a complete picture of what this indicates in the context of population size, we further partitioned the long-term coldspots into ‘low-density’ and ‘high-density’ areas: coldspots with at least 500 children under 60 months of age per grid cell are shown in Figure 3B. The dark red cells now represent long-term, high-density coldspots (sensitivity analysis to this cutoff value of 500 is provided in Figure S11). This indicates that many of the long-term coldspots are likely of limited epidemiological importance because few people live there: the long-term, high-density coldspots should be a priority due to both low vaccination coverage and significant numbers of unvaccinated children.

In these results, we did not attempt to explicitly model the impact of sub-national SIA campaigns because variability in their age-eligibility (Figure S3) complicates the interpretation of within-country spatial patterns. However, including sub-national campaigns does not change qualitative conclusions (Figure S7, Table S4, Table S8). Most countries only had one or two national SIAs in the time frame of interest, with the exceptions of Burundi with three national SIAs and one sub-national SIA, DRC with one national SIA and 14 sub-national SIAs, and Tanzania with no national SIAs and one sub-national SIA (targeting all parts of the country except for Zanzibar in a national immunization day) [[29]](https://paperpile.com/c/27GMeh/aRJT). Model residual maps do not suggest existence of unmodeled spatial autocorrelation (Figure S5).

Up to this point, our analysis has focused on areas highlighted by vaccination coverage itself. However, as control strategies are usually designed in the context of political boundaries, we also quantified the relative contributions of individual sub-national political boundary levels (i.e., programmatically relevant spatial scales) to the overall variance in measles vaccination coverage within each country (Table 3). In seven out of the ten countries, the largest sub-national administrative level (e.g., provinces) explained the largest proportion of the overall variance; the largest two sub-national administrative levels together (e.g., provinces and districts) accounted for a majority of the variance within each country.

Lastly, we quantified the spatial variation between countries by aggregating data from the ten countries and analyzing the data as a single region. We employed the same GAM framework for this aggregated data, now incorporating a country-level predictor (Table S5) in addition to longitude and latitude, survey age, and sub-national SIA eligibility. In a multi-level modeling framework, we estimated that 54% of the variation in the probability of being vaccinated by any given age is explained by the country in which the individual lives.

**Discussion**

Our results indicate significant heterogeneity in measles vaccine coverage within the ten countries examined. Large coldspots, where large numbers of children remain unvaccinated against measles through their fifth year of life, are found across the region and particularly in countries with low coverage (e.g, DRC). A focus on coverage and coldspots alone does not give a full picture of the measles vaccination landscape, as numbers of susceptible individuals must also be evaluated. We show that the high population density and birth rates around Lake Victoria and throughout the African Great Lakes region mean that even areas with relatively high vaccination coverage are home to large numbers of unvaccinated children. Areas where low coverage and high population density combine should be top priorities for stepped-up immunization efforts for measles control, and become particularly important in the context of elimination.

The approach taken here uses standard techniques with the goal that it could be easily applied across different settings. Country-level estimates of vaccination often average across important sources of heterogeneity, and the methods presented here can be used to identify and visualize coldspots of vaccination (i.e., likely to correspond to geographic clusters of susceptibility) that cross sub-national administrative boundaries, which may not be evident in analyses solely based on these divisions. Characterizing such heterogeneities is especially important as we strive for measles elimination. Translating these vaccination cold-spots into specific interventions will require a formal evaluation of the operational and logistical challenges of spatially targeted efforts.

Our analysis suggests that targeting of efforts at the largest sub-national administrative unit would account for the majority of subnational variation in vaccination coverage. This indicates that in terms of strengthening measles vaccination programs, targeting broad spatial groupings may be effective for the countries here. However, while these large units were the most predictive, the dynamics of measles incidence will be shaped by local heterogeneities that do not necessarily respect these boundaries [[30]](https://paperpile.com/c/27GMeh/e6QJ) and thus cross-province coordination or more focused targeting may be needed depending on the situation.

Spatial clustering of unvaccinated individuals may lead to pockets of measles susceptibility that will sustain circulation, even in an otherwise successful measles elimination program with high overall vaccination coverage [[31]](https://paperpile.com/c/27GMeh/aoH7). Age cohorts missed by routine vaccination in each year will allow continued circulation of the virus, unless they are removed from the pool of susceptibles by natural infection or a broader age range campaign like an SIA. From a programmatic perspective it will be important to consider the specific effects of varying the lower and upper age targets of potential campaigns, and our analysis reveals that these may be spatially context-specific. Our estimates of spatial heterogeneity might thus allow us to leverage sub-national targeting of campaigns.

The heterogeneities in proportions unvaccinated by age revealed by our analysis illustrate that coverage patterns are not static, and may vary across age cohorts (Figure S4; Movie S1; Movie S2). Though the worst-performing areas appear to consistently have problems throughout all birth cohorts, transient coldspots that are only present for a few years may still create important pockets of susceptibility that can later cause problems for measles control, or be a sign of an emergent problem. Ideally, these age profiles of susceptibility could be used to guide control measures. For instance, coldspots of vaccination among older children might suggest the importance of continued SIAs as a key component of efforts to mitigate problems with geographic clustering of measles susceptibility, while coldspots among younger children might suggest the need to strengthen routine health care systems since clusters of measles risk will quickly re-form among young children as a function of the birth rate.

There is some empirical evidence that the patterns uncovered here are relevant to mapping measles risk and informing control. Recent measles outbreaks in DRC followed spatial patterns consistent with our identified coldspots and identified high-density, low vaccination coverage areas [[32]](https://paperpile.com/c/27GMeh/rfRg). However, translating maps of unvaccinated children into maps of susceptible children is complicated by the acquisition of immunity via natural infection [[33]](https://paperpile.com/c/27GMeh/BXSs). For example, Zambia had a major measles outbreak within the 5 years prior to its DHS survey [[34]](https://paperpile.com/c/27GMeh/wZUe) while other countries did not, with important implications for susceptibility that would be complemented by study of age-stratified measles incidence and/or serological data from the region. Furthermore, DHS surveys are not all conducted in the same year, which makes interpretation of between-country comparisons difficult. We currently do not distinguish between immunity acquired through routine vaccination and through SIAs. Disentangling the effects of routine programs, national SIAs, and sub-national SIAs on overall vaccination coverage may provide important programmatic information, and is a key goal of ongoing work.

Spatial heterogeneity in measles vaccination coverage raises a further key public health policy issue: many of the countries investigated here will soon become eligible for Global Alliance for Vaccines and Immunization (GAVI) funding to support the introduction of rubella-containing vaccine [[35]](https://paperpile.com/c/27GMeh/PS6o). Rubella is a mild infection, unless contracted by pregnant women during their first trimester which can lead to the birth of a child with congenital rubella syndrome (CRS). The spatial heterogeneity in measles vaccination coverage documented here could affect the dynamics of rubella in ways that might increase the absolute burden or degree of inequity in the burden of CRS in this region [[36,37]](https://paperpile.com/c/27GMeh/5SXk+EEV5).

The considerable spatial heterogeneities and geographic clustering of low vaccine coverage areas found in our analysis suggest that countries with high levels of national coverage may still be at considerable risk for measles outbreaks. Areas where there is a confluence of high population density and low vaccination coverage (as illustrated in Figure 3B) pose the greatest risk, and if linked, may have the potential to sustain measles transmission regionally despite robust vaccination campaigns nearly everywhere else. If countries can identify and eliminate these high risk vaccination coldspots, they will reduce their risk of measles outbreaks and accelerate progress towards the goal of measles elimination.

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**Figure Legends**

Figure 1: (A) Estimated mean proportion of children 24 months of age who have either received routine measles vaccination or were vaccinated during a national measles SIA campaign. (B) Estimated coldspots of routine and national SIA measles vaccination for children 24 months of age.

Figure 2: Estimated number of children 6-24 months of age per 10x10 grid square who have neither received routine measles vaccination nor were vaccinated during a national measles SIA campaign.

Figure 3: Estimated proportion of months that each grid cell exists as a coldspot of routine and national SIA measles vaccination for children between 12-60 months of age, showing (A) all grid cells (i.e., long-term coldspots) and (B) only grid cells with at least 500 children under 60 months of age (i.e., long-term, high-density coldspots). Capital cities are shown as pink circles.

**Tables**

Table 1: Description of DHS and SIA data included in the analysis by country.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Country | Survey start date | Survey end date | Number of children in survey | Number of GPS clusters in survey | Number of national SIA campaigns, with eligibles in DHS | Number of sub-national SIA campaigns, with eligibles in DHS |
| Burundi | 08/2010 | 01/2011 | 7219 | 376 | 3 | 1 |
| DRC | 08/2013 | 02/2014 | 15807 | 492 | 1 | 14 |
| Kenya | 05/2014 | 10/2014 | 19819 | 1583 | 1 | 0 |
| Malawi | 06/2010 | 09/2010 | 17765 | 827 | 2 | 0 |
| Mozambique | 05/2011 | 12/2011 | 10242 | 609 | 2 | 0 |
| Rwanda | 09/2010 | 04/2011 | 8472 | 492 | 2 | 0 |
| Tanzania | 12/2009 | 05/2010 | 7238 | 458 | 0 | 1† |
| Uganda | 06/2011 | 12/2011 | 7220 | 400 | 1 | 0 |
| Zambia | 08/2013 | 04/2014 | 12617 | 719 | 2 | 0 |
| Zimbabwe | 09/2010 | 03/2011 | 5011 | 393 | 2 | 0 |

†Tanzania had an SIA campaign in 08/2008-09/2008 that targeted all of the country except for Zanzibar, so this campaign is considered to be sub-national.

Table 2: Estimated total number of children 6-24 months of age and 6-60 months of age who have neither received routine measles vaccination nor were vaccinated during a national measles SIA campaign, estimated total number of children 6-24 months of age and 6-60 months of age who reside in measles vaccination coldspots (for routine and national SIAs) for that age by country and total region, and percentage of children 24 months of age and 60 months of age who reside in measles vaccination coldspots for that age by country and total region, with 95% confidence intervals (CI) from the standard errors of GAM predictions.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Country | Total number of unvaccinated children, 6-24 months of age (95% CI) | Total number of unvaccinated children, 6-60 months of age  (95% CI) | Total number of children 6-24 months of age residing in coldspots  (95% CI) | Total number of of children 6-60 months of age residing in coldspots  (95% CI) | Percentage of children 24 months of age residing in coldspots (95% CI) | Percentage of children 60 months of age residing in coldspots (95% CI) |
| Burundi | 156,068  (136,340-  179,327) | 191,896  (156,025-  244,096) | 180,177  (166,093-  199,635) | 180,177  (166,093-  199,905) | 0.00  (0.00-  0.48) | 0.00  (0.00-  0.00) |
| DRC | 1,750,619 (1,556,337-  1,950,863) | 3,487,958 (2,925,631-  4,114,744) | 2,958,281 (2,600,271-  3,203,347) | 6,961,102  (5,511,014-  8,203,324) | 72.73  (55.82-  84.41) | 69.17  (49.21-  83.27) |
| Kenya | 750,212  (690,769-  813,555) | 1,192,916 (1,046,889-  1,360,161) | 983,497  (901,572-  1,075,585) | 1,397,181  (1,156,790-  1,645,873) | 11.01  (7.22-  15.59) | 8.52  (3.71-  12.93) |
| Malawi | 251,975  (225,536-  280,559) | 339,428  (288,553-  401,332) | 325,361  (299,290-  347,980) | 325,361  (299,290-  347,980) | 0.00  (0.00-  0.00) | 0.00  (0.00-  1.66) |
| Mozambique | 517,286  (455,567-  584,442) | 848,657  (703,355-  1,023,875) | 768,479  (668,358-  894,227) | 1,234,139  (969,734-  1,631,374) | 29.54  (19.80-  42.60) | 4.25  (0.00-  13.78) |
| Rwanda | 166,420  (148,047-  188,346) | 199,706  (166,601-  247,749) | 187,509  (174,847-  203,244) | 187,509  (174,847-  205,142) | 0.00  (0.00-  0.00) | 0.00  (0.00-  4.50) |
| Tanzania | 972,005  (852,872-  1,115,518) | 1,479,407 (1,170,994-  1,910,373) | 1,216,867 (1,010,185-  1,561,574) | 1,651,902  (1,217,369-  2,725,044) | 9.99  (5.64-  25.35) | 10.07  (4.06-  32.12) |
| Uganda | 903,020  (793,474-  1,021,542) | 1,491,919 (1,227,133-  1,810,583) | 1,621,123 (1,184,109-  1,904,156) | 2,193,610  (1,223,047-  3,900,628) | 62.88  (28.71-  87.88) | 1.82  (0.00-  49.28) |
| Zambia | 288,108  (259,317-  319,800) | 407,405  (346,086-  482,529) | 348,476  (310,742-  440,571) | 352,954  (310,822-  475,476) | 2.07  (0.19-  14.95) | 0.37  (0.00-  5.02) |
| Zimbabwe | 256,147  (221,298-  294,937) | 456,146  (361,880-  573,318) | 423,753  (288,136-  523,935) | 832,551  (333,995-  1,283,974) | 47.37  (7.90-  72.48) | 23.25  (0.00-  65.80) |
| Total | 6,011,860  (5,339,557-  6,748,889) | 10,095,438  (8,393,147-  12,168,760) | 9,013,523  (7,603,603-  10,354,254) | 15,316,486  (11,363,001-  20,618,720) | 33.87 (21.26-  46.24) | 20.87  (12.84  -38.17) |

Table 3: Intraclass correlation coefficient (ICC) of each sub-national political boundary level (Adm) by country, ranging from 1 (coarse) to 5 (fine). Adm level with largest contribution to overall variance shown in bold.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Country | Adm 1 ICC | Adm 2 ICC | Adm 3 ICC | Adm 4 ICC | Adm 5 ICC | Residual ICC |
| Burundi | **0.5646** | 0.1581 | <0.0001 | <0.0001 | - | 0.2772 |
| DRC | 0.2699 | **0.3473** | 0.2711 | - | - | 0.1117 |
| Kenya | **0.8265** | 0.1038 | 0.0357 | - | - | 0.0341 |
| Malawi | **0.4933** | 0.2983 | 0.0087 | - | - | 0.1997 |
| Mozambique | **0.5416** | 0.3819 | 0.0442 | - | - | 0.0323 |
| Rwanda | 0.3399 | **0.4076** | 0.0860 | <0.0001 | 0.0622 | 0.1043 |
| Tanzania | **0.7469** | 0.1368 | 0.0561 | - | - | 0.0601 |
| Uganda | **0.7776** | 0.1007 | 0.0402 | 0.0006 | - | 0.0809 |
| Zambia | 0.3441 | **0.4091** | - | - | - | 0.2468 |
| Zimbabwe | **0.5980** | 0.2363 | - | - | - | 0.1657 |

Note: some countries have fewer than 5 sub-national political boundary levels.

**Supplementary Information**

Figure S1: Map of the ten countries included in the analysis showing the first sub-national administrative boundaries, and DHS survey locations representing clusters of 1-19 children (red), 20-39 children (blue), and 40-59 children (green). Inset: DHS survey locations in Rwanda and Burundi.

Figure S2: (A) Frequency and (B) cumulative distribution of children’s age (x-axis, in months between 1-60) at DHS survey by country.

Figure S3: Proportion of children who received any measles vaccination at survey age (x-axis, in months between 1-60) by country, with DHS survey weights. Colored bars indicate the range of age-eligibility for national (green) or sub-national (pink) measles SIA campaigns.

Figure S4: Estimated effect of DHS survey age (x-axis, in months between 1-60) by country on the probability of either receiving routine measles vaccination or being vaccinated during a national measles SIA campaign (y-axis) based on the full GAM model, with error bands showing +1 and -1 standard errors.

Figure S5: Averaged residuals from the full GAM model at each DHS cluster by country, where x-axis and y-axis distances are in kilometers.

Figure S6: Estimated mean proportion of children (A) 12 months of age, (B) 18 months of age, and (C) 60 months of age who have either received routine measles vaccination or were vaccinated during a national measles SIA campaign.

Figure S7: Estimated mean proportion of children 24 months of age in (A) Burundi, (B) DRC, and (C) Tanzania and 60 months of age in (D) Burundi, (E) DRC, and (F) Tanzania who have received routine measles vaccination or were vaccinated during a national or sub-national measles SIA campaign, with sub-national SIA eligibility determined by age and location (see Table S4).

Figure S8: Estimated standard error of the mean proportion of children (A) 12 months of age, (B) 18 months of age, (C) 24 months of age, and (D) 60 months of age who have either received routine measles vaccination or were vaccinated during a national measles SIA campaign.

Figure S9: Difference in estimated standard error of the mean proportion of children (A) 18 months of age, (B) 24 months of age, and (C) 60 months of age who have either received routine measles vaccination or were vaccinated during a national SIA measles vaccination, from the estimated standard error of the mean proportion of children 12 months of age who have either received routine measles vaccination or were vaccinated during a national SIA measles vaccination.

Figure S10: Estimated coldspots of routine and national SIA measles vaccination for children (A) 12 months of age, (B) 18 months of age, and (C) 60 months of age.

Figure S11: Estimated proportion of months that each grid cell exists as a coldspot of routine and national SIA measles vaccination for children between 12-60 months of age, showing only grid cells with (A) at least than 100 children under 60 months of age and (B) at least 1,000 children under 60 months of age.

Figure S12: Estimated number of children (A) 6-12 months of age, (B) 6-18 months of age, and (C) 6-60 months of age who have neither received routine measles vaccination nor were vaccinated during a national measles SIA campaign.

Movie S1: Estimated mean proportion of children at monthly intervals between 6-60 months of age who have either received routine measles vaccination or were vaccinated during a national measles SIA campaign.

Movie S2: Estimated coldspots of routine and national SIA measles vaccination for children at monthly intervals between 6-60 months of age.

Table S1: Full and comparison GAM models.

|  |  |  |  |
| --- | --- | --- | --- |
| Model name | Include covariate: longitude, latitude | Include covariate: binned survey age | Include covariate(s): eligibility for sub-national SIAs, if available |
| Full model | yes | yes | yes |
| Comparison 1 (C1) | yes | yes | no |
| Comparison 2 (C2) | yes | no | yes |
| Comparison 3 (C3) | yes | no | no |
| Comparison 4 (C4) | no | yes | yes |
| Comparison 5 (C5) | no | yes | no |
| Comparison 6 (C6) | no | no | yes |

Note: only Burundi, DRC, and Tanzania had sub-national SIA campaigns.

Table S2: Akaike information criterion (AIC) of the full and comparison GAM models described in Table S1. Model with lowest AIC value by country shown in bold.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Country | Full model AIC | C1 model AIC | C2 model AIC | C3 model AIC | C4 model AIC | C5 model AIC | C6 model AIC |
| Burundi | 2498.62 | **2497.28** | 6897.03 | 7102.51 | 2524.98 | 2526.48 | 6985.05 |
| DRC | **14620.19** | 14685.76 | 17797.59 | 20091.18 | 15617.24 | 16079.56 | 19380.24 |
| Kenya | **13478.47** | **-** | 22595.97 | - | 14295.92 | - | - |
| Malawi | **8964.95** | - | 18077.79 | - | 9056.76 | - | - |
| Mozambique | **7043.57** | - | 11772.55 | - | 7558.24 | - | - |
| Rwanda | **2601.51** | - | 7961.55 | - | 2668.13 | - | - |
| Tanzania | 4320.69 | **4318.72** | 7234.04 | 8404.88 | 4600.91 | 4599.18 | 7658.20 |
| Uganda | **5693.19** | - | 8959.76 | - | 5804.07 | - | - |
| Zambia | **7524.84** | - | 14200.43 | - | 7613.26 | - | - |
| Zimbabwe | **3972.84** | - | 6385.17 | - | 4097.60 | - | - |

Table S3: Output of the full GAM model by country.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Country | Estimated df:  s(longitude, latitude) | Estimated df:  s(binned survey age) | Deviance explained | Adjusted R-squared |
| Burundi | 17.6448 | 8.8182 | 0.6560 | 0.7340 |
| DRC | 28.0621 | 8.8866 | 0.3132 | 0.3702 |
| Kenya | 27.3908 | 8.7176 | 0.4193 | 0.4898 |
| Malawi | 25.5333 | 8.8599 | 0.5092 | 0.5903 |
| Mozambique | 25.0780 | 8.7725 | 0.4216 | 0.4904 |
| Rwanda | 19.1305 | 8.7283 | 0.6810 | 0.7538 |
| Tanzania | 25.9167 | 8.8746 | 0.5034 | 0.5692 |
| Uganda | 21.4352 | 8.6249 | 0.3754 | 0.4418 |
| Zambia | 25.2993 | 8.3204 | 0.4766 | 0.5532 |
| Zimbabwe | 19.5219 | 8.8181 | 0.3937 | 0.4625 |

df: degrees of freedom

Table S4: Description and estimated marginal benefit of sub-national SIA campaigns, based on the full GAM model by country.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Country | SIA campaign date | Age target | Location target | Proportion of children in DHS survey eligible for this SIA | Estimate of mean marginal benefit (logit) | Standard error |
| Burundi | 10/2010 | 6-179 m | Bujumbura | 0.0787 | 0.3827 | 0.3312 |
| DRC | 01/2010 | 6-59 m | Bandundu | 0.0142 | 0.4162 | 0.2251 |
| DRC | 02/2011 | 6-59 m | Katanga | 0.0391 | 0.2022 | 0.2546 |
| DRC | 03/2011 | 6-59 m | Sud Kivu | 0.0207 | 0.4291 | 0.2405 |
| DRC | 04/2011 | 6-59 m | Kasai Occidental | 0.0289 | 0.0756 | 0.1477 |
| DRC | 05/2011 | 6-59 m | Katanga | 0.0451 | -0.2326 | 0.2495 |
| DRC | 06/2011 | 6-59 m | Kasai Oriental | 0.0413 | 0.0064 | 0.1202 |
| DRC | 01/2012 | 6-59 m | Bas-Congo | 0.0248 | 0.9172 | 0.2424 |
| DRC | 01/2012 | 6-59 m | Nord Kivu | 0.0315 | 0.4145 | 0.344 |
| DRC | 01/2012 | 6-59 m | Bandundu | 0.0678 | -0.1389 | 0.1312 |
| DRC | 08/2012 | 6-59 m | Nord Kivu | 0.0379 | -0.0921 | 0.3419 |
| DRC | 09/2013 | 6-119 m | Equateur | 0.1237 | -0.0026 | 0.1628 |
| DRC | 09/2013 | 6-119 m | Orientale | 0.0863 | -0.2344 | 0.1904 |
| DRC | 12/2013 | 6-119 m | Nord Kivu | 0.0543 | 0.6075 | 0.2739 |
| DRC | 12/2013 | 6-119 m | Sud Kivu | 0.0571 | 1.8337 | 0.2684 |
| Tanzania | 08/2008-09/2008 | 6-131 m  (6-59 m in Dar es Salaam) | All areas except Zanzibar | 0.4369 | 0.0352 | 0.1645 |

m: months

Table S5: Estimates of country-specific predictors from the full GAM model of the ten countries together.

|  |  |  |
| --- | --- | --- |
| Country | Estimate of mean predictor (logit) | Standard error |
| Burundi | 2.4678 | 0.1039 |
| DRC | 0.2634 | 0.0884 |
| Kenya | 0.6989 | 0.0860 |
| Malawi | 2.0667 | 0.0779 |
| Mozambique | 0.9094 | 0.0869 |
| Rwanda | 2.1207 | 0.0942 |
| Tanzania | 1.0200 | 0.0850 |
| Uganda | 0.5627 | 0.0858 |
| Zambia | 1.2054 | 0.0725 |
| Zimbabwe | 0.2861 | 0.1260 |

Table S6: Estimated numbers of children who have neither received routine measles vaccination nor were vaccinated during a national measles SIA campaign, by country and age group.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Country | Number unvaccinated,  6-12 m  (95% CI) | Number unvaccinated,  13-24 m  (95% CI) | Number unvaccinated,  25-36 m  (95% CI) | Number unvaccinated,  37-48 m  (95% CI) | Number unvaccinated,  49-60 m  (95% CI) | Total number of children, 6-60 m\* |
| Burundi | 139,316  (126,540-151,092) | 16,752  (9,801-28,235) | 12,124  (6,798-21,400) | 12,489  (6,978-22,099) | 11,215  (5,909-21,270) | 1,542,120 |
| DRC | 1,028,247 (967,587-1,080,651) | 722,373 (588,750-870,212) | 592,531 (472,500-730,580) | 563,222 (442,378-703,990) | 581,586 (454,415-729,311) | 10,248,244 |
| Kenya | 574,476  (547,400-599,721) | 175,735 (143,369-213,834) | 152,171 (122,939-187,055) | 149,339 (120,643-183,612) | 141,194 (112,537-175,939) | 6,187,521 |
| Malawi | 212,151  (195,872-227,436) | 39,824  (29,664-53,123) | 28,063  (20,319-38,581) | 29,211  (21,137-40,173) | 30,178  (21,561-42,019) | 2,501,513 |
| Mozambique | 359,860  (333,127-384,097) | 157,425 (122,441-200,345) | 114,810  (86,568-150,878) | 108,305  (81,279-143,059) | 108,256  (79,940-145,495) | 3,883,799 |
| Rwanda | 151,449  (139,398-162,641) | 14,971  (8,650-25,706) | 11,665  (6,616-20,450) | 9,731  (5,403-17,455) | 11,890  (6,535-21,497) | 1,638,796 |
| Tanzania | 744,761  (697,046-788,076) | 227,244 (155,826-327,442) | 178,003 (112,783-275,974) | 161,771 (101,603-253,311) | 167,629 (103,737-265,570) | 7,369,265 |
| Uganda | 602,493  (562,572-637,147) | 300,527 (230,902-384,395) | 224,531 (167,947-295,847) | 198,441 (146,740-264,768) | 165,926 (118,973-228,426) | 6,027,976 |
| Zambia | 218,805  (206,677-229,672) | 69,303  (52,641-90,128) | 46,189  (34,044-62,113) | 36,995  (26,853-50,591) | 36,114  (25,872-50,025) | 2,216,061 |
| Zimbabwe | 177,210  (164,073-188,491) | 78,937  (57,225-106,446) | 62,151  (43,767-86,498) | 72,023  (51,370-98,754) | 65,824  (45,446-93,130) | 1,787,280 |
| Total | 4,208,768 (3,940,292-  4,449,024) | 1,803,091 (1,399,269-  2,299,866) | 1,422,238 (1,074,281-  1,869,376) | 1,341,527 (1,004,384-  1,777,812) | 1,319,812  (974,925-  1,772,682) | 43,402,575 |

\*Data from the WorldPop project. m: months

Table S7: Estimated proportion of children who have either received routine measles vaccination or were vaccinated during a national measles SIA campaign, by country and age group.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Country | Proportion vaccinated,  6-12 m  (95% CI) | Proportion vaccinated,  13-24 m  (95% CI) | Proportion vaccinated,  25-36 m  (95% CI) | Proportion vaccinated,  37-48 m  (95% CI) | Proportion vaccinated,  49-60 m  (95% CI) |
| Burundi | 0.2902 (0.2302-0.3553) | 0.9502 (0.9161-0.9709) | 0.9640 (0.9364-0.9798) | 0.9629 (0.9343-0.9793) | 0.9667 (0.9368-0.9824) |
| DRC | 0.2117 (0.1715-0.2582) | 0.6769 (0.6108-0.7367) | 0.7350 (0.6733-0.7887) | 0.7481 (0.6852-0.8022) | 0.7399 (0.6738-0.7968) |
| Kenya | 0.2705 (0.2385-0.3049) | 0.8698 (0.8416-0.8938) | 0.8873 (0.8614-0.9089) | 0.8894 (0.8640-0.9106) | 0.8954 (0.8697-0.9166) |
| Malawi | 0.3336 (0.2856-0.3848) | 0.9270 (0.9027-0.9456) | 0.9486 (0.9293-0.9628) | 0.9465 (0.9264-0.9613) | 0.9447 (0.9230-0.9605) |
| Mozambique | 0.2720 (0.2230-0.3261) | 0.8142 (0.7636-0.8555) | 0.8645 (0.8219-0.8978) | 0.8722 (0.8312-0.9041) | 0.8722 (0.8283-0.9057) |
| Rwanda | 0.2739 (0.2202-0.3317) | 0.9581 (0.9281-0.9758) | 0.9674 (0.9428-0.9815) | 0.9728 (0.9512-0.9849) | 0.9667 (0.9399-0.9817) |
| Tanzania | 0.2059 (0.1598-0.2568) | 0.8587 (0.7963-0.9031) | 0.8893 (0.8284-0.9299) | 0.8994 (0.8425-0.9368) | 0.8957 (0.8348-0.9355) |
| Uganda | 0.2147 (0.1695-0.2667) | 0.7715 (0.7077-0.8244) | 0.8293 (0.7751-0.8723) | 0.8491 (0.7987-0.8884) | 0.8738 (0.8263-0.9095) |
| Zambia | 0.2242 (0.1857-0.2672) | 0.8567 (0.8136-0.8911) | 0.9045 (0.8715-0.9296) | 0.9235 (0.8954-0.9445) | 0.9253 (0.8965-0.9465) |
| Zimbabwe | 0.2210 (0.1714-0.2787) | 0.7976 (0.7270-0.8533) | 0.8406 (0.7782-0.8878) | 0.8153 (0.7468-0.8683) | 0.8312 (0.7612-0.8835) |

m: months

Table S8: Percentage of children 24 months of age and 60 months of age who reside in measles vaccination coldspots for that age (including the effect of sub-national SIAs) in countries that have sub-national SIAs, and estimated total number of children 6-24 months of age and 6-60 months of age who have neither received routine measles vaccination nor were vaccinated during a national or sub-national measles SIA campaign, with 95% confidence intervals (CI) from the standard errors of GAM predictions.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Country | Percentage of children 24 months of age residing in coldspots (95% CI) | Percentage of children 60 months of age residing in coldspots (95% CI) | Total number of unvaccinated children, 6-24 months of age (95% CI) | Total number of unvaccinated children, 6-60 months of age  (95% CI) |
| Burundi | 0.00  (0.00-0.48) | 0.00  (0.00-0.00) | 154,315  (134,518-177,561) | 188,765  (153,342-240,237) |
| DRC | 68.97  (55.37-79.84) | 58.17  (46.58-72.19) | 1,685,414 (1,526,271-1,850,499) | 3,259,305 (2,813,225-3,753,059) |
| Tanzania | 9.53  (5.38-24.91) | 9.67  (4.34-29.54) | 970,696  (851,112-1,115,349) | 1,464,010 (1,178,123-1,853,354) |

Table S9: WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) of MCV-1 by country and by DHS survey year(s).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Country | 2014 | 2013 | 2012 | 2011 | 2010 | 2009 |
| Burundi |  |  |  | 93 | 92 |  |
| DRC | 77 | 76 |  |  |  |  |
| Kenya | 79 |  |  |  |  |  |
| Malawi |  |  |  |  | 93 |  |
| Mozambique |  |  |  | 82 |  |  |
| Rwanda |  |  |  | 95 | 95 |  |
| Tanzania |  |  |  |  | 92 | 91 |
| Uganda |  |  |  | 75 |  |  |
| Zambia | 85 | 80 |  |  |  |  |
| Zimbabwe |  |  |  | 92 | 90 |  |

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