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Lauren Beryl Guterman Date

Modeling the Impact of Maternal Immunization Programs in a Low Income Setting

By

Lauren Beryl Guterman
Master of Science in Public Health

Epidemiology

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Faculty Advisor

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B.S.
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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

Modeling the Impact of Maternal Immunization Programs in Low Income Settings
By Lauren Beryl Guterman

The WHO recommends that countries implementing seasonal influenza vaccination give the highest priority to pregnant women because they are at a higher risk for adverse outcomes attributable to influenza infection. Additionally, maternal immunization has shown to have an impact on the protection of their new born infants. We developed a preliminary deterministic ordinary differential equation model to simulate seasonal influenza transmission. Our model utilizes previously published demographic, seasonality and social mixing data for Kenya to assess the impact of a maternal immunization program in a low-income setting. Approximately six months following the introduction of vaccination, a smaller secondary peak in incidence and prevalence took place in both the maternal and infant populations. In addition, these secondary peaks appear to increase in amplitude as vaccination coverage increases. The model shows a linear increase in cases averted in both the pregnant and infant populations as maternal immunization coverage increases and vaccination modeled continuously throughout the year. Several elements of this model need further development, specifically in its parameterization. Due to limited available data, elements of the model structure and several parameters do not accurately simulate the interplay of population dynamics and influenza transmission in low income settings. Therefore, further development and data collection is needed for this model.

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Introduction

In 2012, the WHO recommended countries implementing seasonal influenza vaccination give the highest priority to pregnant women(1). Pregnant women are at a higher risk, in comparison to non-pregnant women, for adverse outcomes attributable to influenza infection, such as cardiopulmonary events, hospitalization and death due to respiratory disease complications (2, 3). Maternal immunization also showed to have an impact on the protection to their new born infants in several studies conducted in low income settings, such as South Africa, Nepal and Mali(4-6).

Several interacting factors must be considered when deciding to invest in a global maternal immunization program for seasonal influenza, such as seasonality, social behavior and population dynamics and their effect on transmission, vaccine efficacy in low income settings and the nature of immunization program. Dynamic transmission models can aid in the decision making by integrating both disease and population dynamics into the simulation of seasonal influenza transmission to assess the potential impact of such interventions.

A dynamic model that assesses the impact of maternal seasonal influenza immunization programs in low income settings has yet to be characterized. Many of the current dynamic influenza transmission models have been developed to assess the effect of interventions on pandemic influenza transmission (7-10). Current models that simulate seasonal influenza transmission focus on the effect of age-targeted vaccination programs (11-13) or transmission within specific social settings of developed countries, such as college campuses, day care centers or nursing homes (14, 15). Recent attempts to assess the impact of maternal immunization programs in developing countries use statistical models that do not consider the dynamic nature of influenza transmission, such as seasonality and social mixing patterns (16).

As a result, current models do not provide sufficient evidence to support whether an investment in maternal immunization programs would have a substantial impact on the incidence of influenza among maternal and infant populations in low income countries. This will be the first dynamic transmission model that considers country specific demographic, seasonality and social mixing data to investigate the impact of maternal immunization programs on seasonal influenza transmission in a low income setting.

Materials and Methods

Parameters

Demographic parameters

Demographic data including age and sex specific population sizes and mortality rates were collected from the US census bureau International database for 2015 (17). Initial conditions for the three populations of interest were obtained using the US census bureau International database for 2015 and the Demographic and Health Surveys Stat Compiler accessed at http://www.statcompiler.com/en/. Sedgh et al estimated region-specific induced abortion ratios using national reporting systems data and UN estimates, where abortion is defined as the sum of safe and unsafe induced abortions (18). Using these published data, we calculated the pregnancy rate per day, θ (Equation 1). Where number of births per year in Kenya (*birth*, Equation 2a) was obtained from the US census bureau International database, fetal loss per day for East Africa, *FL*, were calculated from Sedgh et al. data and their assumptions for estimating the number of spontaneous abortions (Equation 2b).

$$\boldsymbol{\theta = (birth * N_m) + (FL * N_m)} \qquad \text{Equation 1}$$

Such that

$$\boldsymbol{birth = \frac{number\ of\ births}{1000\ population\ for\ 2015} * \frac{total\ population\ size}{365\ days}} \qquad \text{Equation 2a}$$

$$\boldsymbol{FL} = \frac{\boldsymbol{induced\ abortions}}{\boldsymbol{day}} + \frac{\boldsymbol{spontaneous\ abortions}}{\boldsymbol{day}} \qquad \text{Equation 2b}$$

$$= \left(\frac{\boldsymbol{induced\ abortions}}{\boldsymbol{100\ live\ births}} * \boldsymbol{birth}\right) + (\boldsymbol{0.2 * birth + 0.1 * induced\ abortions})$$

Disease transmission parameters

The force of infection (λ(t)) is dependent on age-specific contact rates taken from published social contact survey data, the probability of infection given a contact and the seasonal forcing equation for influenza transmission (Equation 3).

$$\boldsymbol{\lambda(t)_i = a_i * \tau * \sum \left(seas * c_{ij} * \frac{I_j}{total_j} \right)} \qquad \text{Equation 3}$$

Where i is the participant age group, j is the contact age group, a is the total average daily contacts, c is the proportion of daily contacts of participant group i with contact group j, τ is the probability of transmission given contact with an infected individual and *seas* is the seasonal forcing equation (19). Age specific contact rates were calculated from published literature on social mixing. An exhaustive literature search was performed to obtain country specific social mixing data using search terms: social contact patterns, social mixing patterns respiratory and ("social contact survey" OR "social mixing") AND "infectious" on the search engine GoogleScholar. Studies conducted in developed countries such as Western Europe and North America, were excluded since their social mixing patterns do not reflect low income settings. For example, institutions such as daycare centers and nursing homes are not present in low income countries. Current knowledge regarding social mixing patterns in low income settings are limited (Table 3). Good quality data were obtained for 5 countries/locations: Vietnam, Zimbabwe, South Africa, Southern China and Kenya (Table 4) (20-23).

For studies with raw data available (20, 22, 23), we employed methods reported by Kiti et al. to calculate the total daily contacts per age participant group i with contact age group j, T_{ij} (Equation 4) (23).

$$\boldsymbol{T_{ij}} = \sum \boldsymbol{y_{ij,k}} \qquad \text{Equation 4}$$

Where $y_{ij,k}$ is the number of contacts that participant k in age group i has with respondents in age group j. Then we calculated the average daily contacts for age group i with age group j, μ_{ij}, by dividing the total daily contacts per age participant group i with contact age group j by the total population size of age group i, N_i (Equation 5).

$$\boldsymbol{\mu_{ij}} = \frac{\mathbf{1}}{\boldsymbol{N_i}} * \boldsymbol{T_{ij}} \qquad \text{Equation 5}$$

For studies without raw data available, contact matrices were collapsed across age groups and weighted by size of participant age groups to create the age strata of interest: young infants, childbearing age, and general population. Since contacts made between age groups i and j in social contact surveys are unlikely to be symmetric due to the use of open cohorts (only participants record their contacts, not those who they come into contact with), the contact matrices were corrected for differential reporting of participants and contact groups via methods employed by Steele et al (19). The corrected contact rates, B_{ij}, were calculated using Equation 6.

$$\boldsymbol{B_{ij}} = \frac{\boldsymbol{N_i * R_{ij} + N_j * R_{ji}}}{\boldsymbol{2N_i}} \qquad \text{Equation 6}$$

Where *N* is the total number of individuals in each age group and *R* is the average daily contact rate between the specified groups. By dividing the weighted sum by $2N_j$ we assume that contacts of individuals within the sample (N_i) made contacts with individuals outside of

the sampled population. To create the final contact matrix, the proportion of daily contacts, c_{ij}, were then calculated across participant age groups i using the following equation (Equation 7, Figure 3).

$$\boldsymbol{c_{ij} = B_{ij}/a_i} \qquad \text{Equation 7}$$

Where a_i represents the total average daily contacts across contact age groups j (19).

To incorporate seasonality we used the seasonal forcing equation reported by Steele et al (19) where the seasonal amplitude, β_1, increases or decreases the force of infection and the seasonal offset parameter, ω, shifts the curve towards peak influenza seasons (Equation 8).

$$\boldsymbol{seas = 1 + \beta_1 * \cos(2\pi * t + \omega)} \qquad \text{Equation 8}$$

Due to the lack of good quality surveillance data (in terms of magnitude of reporting) β_1 was assumed to be between 0.1 and 0.2, indicating that peak influenza transmission months resulted in 10-20% increase influenza incidence in comparison to non-peak influenza transmission months (24). The value of the offset parameter, ω, was fit to published monthly incidence of respiratory disease and data extracted from the FluNet database, which is contributed by 143 National Influenza Centers in 113 countries and accessed at http://www.who.int/influenza/gisrs_laboratory/flunet/en/ (25-28). Fitting was performed using maximum likelihood estimation methods and nonlinear optimization, using the nloptr package in R using the Subplex Algorithm which is freely available at (http://ab-initio.mit.edu/wiki/index.php/NLopt). The model was fit two at least two sources of

average monthly incidence and the reported month of peak influenza transmission by Hirve et al. (24-26). Data reported for 2009 were excluded from the fitting process to avoid the effects of pandemic H1N1 influenza surveillance on our estimates.

Loss of immunity was estimated conservatively to be 365 days to simulate susceptibility to new incoming influenza strains each year. The aging rate was incorporated to simulate infants losing their maternal antibody protection from their vaccinated mothers after six months of age (5). For infected infants, the aging rate was not applied because duration of infection is a short duration of time and its effects would be negligible. Recovery rate is calculated as the inverse of duration of infection(14, 29).

The model

Seasonal influenza transmission was modeled via a deterministic Susceptible-Infected-Recovered (SIR) ordinary differential equation (ODE) compartment model (Fig 1, Fig 2). Through the deterministic ODE model, we can simulate the dynamic transmission of seasonal influenza throughout the year in high risk populations, such as pregnant mothers and young infants, using country-specific demographic and seasonality data. We chose to model the impact of maternal immunization programs in a Gavi eligible country because these countries represent low income settings with the greatest capability of implementing vaccine programs due to Gavi's current or past contributions there (30). Of the 70 Gavi eligible countries, we chose to model Kenya because it has good quality published literature on social mixing and disease incidence(23, 25, 26).

The model simulates influenza transmission dynamics throughout the year via country specific demographic and seasonality data (Table 1-2). For each country's model, we ran a "burn in" period of 5 years with an introduction of one infectious individual at time zero to obtain stable conditions before the introduction of the intervention. A longer burn in

period was not required because the model is not strain specific and we assume the loss of immunity is one year. All analyses were performed in R Studio 1.0.136 using the EpiModel package (31).

Vaccination

Vaccination was modeled by incorporating a "Protected" class for both the pregnant and the young infant populations and a "Vaccinated" class for the pregnant population (Figure 1, Figure 2). The rate at which the pregnant population becomes protected was modeled using two parameters: proportion of the target population that receives the vaccine, ν, which was modeled from zero to 100% at 5% intervals and vaccine efficacy, $\nu_{e,}$ where mothers were vaccinated at time of becoming pregnant (4). Pregnant mothers that do not become protected enter the vaccinated class for the duration of the influenza cycle. The rate at which young infants become protected is dependent on two parameters: birth rate among the protected and vaccinated mother populations, *birth*, and vaccine efficacy among infants of conferred maternal antibody protection, ν_{Ab}, which is measured as vaccine efficacy among infants whose mothers received the influenza vaccine during gestation (5).

Uncertainty analysis

To quantify the sensitivity of our model to the uncertainty of our parameters we performed Latin hypercube sampling for six parameters of interest: probability of transmission given a contact with an infectious individual, τ, seasonal amplitude, $\beta 1$, recovery rate, ρ, vaccine efficacy in pregnant mothers, $\nu_{e,}$ and vaccine efficacy among infants whose mothers were vaccinated during pregnancy, ν_{Ab}. Ranges for each parameter were

taken from published. All parameters were assumed to be uniformly distributed across the specified ranges. The model was run using the 100 different combinations of parameters.

Results

Model fitting

The best fit for the seasonal offset parameter, ω, was 2.638 for both surveillance data from Lwak and Kiberia and National Sentinel Surveillance for influenza (Figure 4). Using the fit seasonal offset parameter, the epidemic curve for the general population was forced to peak in the months of June to July and January.

Vaccination Impact

By implementing maternal immunization in Kenya there was an overall decrease in daily influenza incidence in both pregnant and infant populations (Figures 5-6). Approximately six months following the introduction of vaccination, a smaller secondary peak in incidence and prevalence took place in both the maternal and infant populations. In addition, these secondary peaks appear to increase in amplitude as vaccination coverage increases. The model shows a linear increase in cases averted in both the pregnant and infant populations as maternal immunization coverage increases and vaccination modeled continuously throughout the year (Figure 7-9). The model shows that there is a high impact of maternal immunizations in a low income setting for both pregnant mothers and their infants. However, the reported number of cases averted are too high should be interpreted as preliminary output. Therefore, the model requires further calibration to better quality data (Figure 7-9). When incorporating the uncertainty analysis, the mean number of cases averted among the pregnant population is higher than that of the median cases averted. This indicates the mean number of cases averted among the pregnant population are being skewed by certain combinations parameters for the model.

Discussion

Discussion of results

The epidemic curve for the general population was forced to peak in the months of June to July and January. These results are consistent with CDC and NIVEL influenza surveillance, which consists of several data sources such as FluNet, PAHO and national surveillance data (24-26). However, these results are not consistent the conclusions of Hirve et al who report Kenya to have year round influenza activity(24). Considering the published data on the seasonality of influenza and Kenya's proximity to the equator, the seasonal trends of influenza transmission is most likely year-round with minor peaks (less than 10% increase in cases) in July and January (24-26). A major limitation to our fitting process was that we were unable to fit the seasonal amplitude parameter to surveillance data due to limited information on underreporting of influenza in Kenya and other low-income settings. Due to its mild symptoms within low risk populations and the lack of access to health care in low income settings, specifically in rural areas, seasonal influenza infection is underreported (32). In addition, by not fitting the seasonal amplitude parameter our model assumes that underreporting takes place at the same rate throughout the year which is not consistent with the findings of Bigogo et al (32). Therefore, further collaboration and data collection on seasonal influenza surveillance and its underreporting is needed to better parameterize our model.

Following the introduction of maternal immunization, a secondary peak in incidence and prevalence took place and is more pronounced as vaccination coverage increased. These peaks could be due to the buildup in susceptible populations following changes in to the system's population distribution. For example, recovered and susceptible infants age out and enter the susceptible general population to represent the loss of potential maternal

antibody protection and recovered individuals reenter the susceptible class after one year of immunity to represent susceptibility of individuals to new dominant circulating strains of influenza.

The model shows a linear increase in cases averted in both the pregnant and infant populations as maternal immunization coverage increases and vaccination is modeled continuously throughout the year. Year round vaccination may be less feasible in most low-income settings due to factors such as vaccine production and distribution rates and access to healthcare among high risk populations (32). This linear relationship represents the average impact of vaccination on pregnant and infant populations because the model does not consider stochasticity of the system over time. The estimated number of cases averted are preliminary results and are most likely an overestimation. This reiterates that further collaboration and data collection on seasonal influenza surveillance and its underreporting is needed to better parameterize our model.

Limitations

This is a preliminary model characterized to estimate the impact of maternal immunization programs in low income settings. Several elements of this model need further development, specifically in its parameterization. Due to limited available data, several parameters do not accurately simulate the interplay of population dynamics and influenza transmission in low income settings. For this model, induced abortions were assumed to be homogenous across United Nations defined regions and spontaneous abortions were assumed to be a function of the number of births and induced abortions per time step. These assumptions are not accurate representations of country specific population dynamics

and more sophisticated methods will need to be developed to better estimate pregnancy rates.

The social mixing data also limits the model's prediction potential. The age structured contact matrices used in this model assume average daily contacts rates are constant throughout the country. However, frequency of contacts is different between urban and rural areas. Furthermore, the definition of a contact for which a transmission can occur is not well established. As a result, there is uncertainty associated with the estimate of effective contact rate. Social contact surveys are also subject to recall bias because they require subjects to recount all contacts they encounter the 24 hours preceding their interview. There was only one good quality social contact study available for Kenya and as a result we are limited in methods to validate these data. These data also did not collect information on the sex of the contact. Therefore, contact rates representing the pregnant mother population do not reflect differences in social behavior by sex. The social contact survey reported age as integers, therefore contact rates for young infants (less than six months of age) were represented by the social mixing behavior of infant less than or equal to one year of age. Finally, the duration of contacts was not considered in this model which does not accurately simulate the probability of infection given social contacts because the model assumes that each contact has the same probability of disease transmission.

Future directions

The data presented are preliminary and the model developed for Kenya is a first step to creating a global dynamic transmission model to assess the impact of investing in maternal immunization programs in all Gavi eligible countries. This model has the potential to assess

the impact of not only seasonal influenza maternal immunization programs but also other vaccines and potential vaccine targets, such as RSV. We also wish to incorporate a "mother of young infants" class to the model to account for the higher contact rates between mothers and their young infants which we believe to be a major source of disease transmission among young infants. Additionally, we intend to introduce stochasticity into our model to account for random events that may occur in the system and explore the range of possible outcomes. We will also explore different vaccination strategies such as vaccination at different points in gestation and different points throughout the year. We are also interested in incorporating other disease transmission parameters such as waning immunity among young infants and the effect of HIV infection among pregnant mothers and their young infants.

Figures

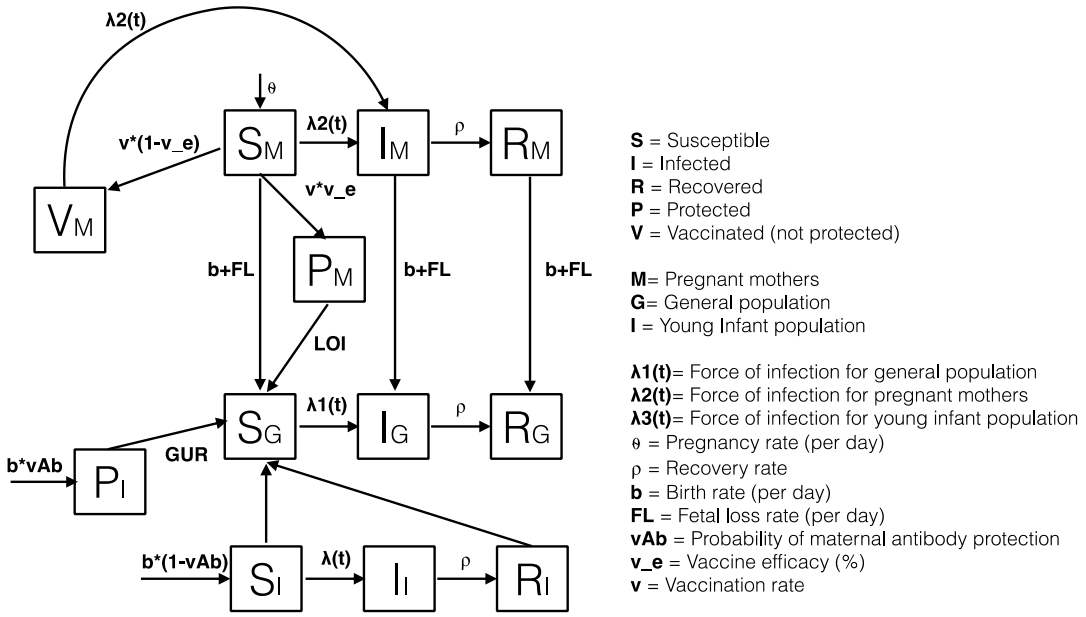

Figure 1 Compartment model diagram

General population

$$\frac{dS_g}{dt} = birth * S_m + FL * S_m + GUR * P_i + GUR * S_i + GUR * R_i + LOI * R_g + LOI * P_m - FOI_1 * S_g - \theta - \mu_g * S_g$$

$$\frac{dI_g}{dt} = FOI_1 * S_g + birth * I_m + FL * I_m - \rho * I_g - \mu_g * S_g$$

$$\frac{dR_g}{dt} = \rho * I_g + birth * (I_m + P_m) + FL * (I_m + P_m) - LOI * R_g - \mu_g * R_g$$

Pregnant Mother Population

$$\frac{dS_M}{dt} = \theta(1 - vaccinated) - FOI_2 * S_M - birth * S_m - FL * S_m - \mu_M * S_M$$

$$\frac{dI_M}{dt} = FOI_2 * S_M + FOI_2 * V_M - birth * I_m - FL * I_m - \rho * I_M - \mu_M * I_M$$

$$\frac{dR_M}{dt} = \rho * I_M - birth * R_m - FL * R_m - \mu_M * R_M$$

$$\frac{dP_M}{dt} = \theta * (v * v_e * vacc_{era}) - LOI * P_M - birth * P_m - FL * P_m - \mu_M * P_M$$

$$\frac{dV_M}{dt} = \theta * (v * (1 - v_e) * vacc_{era}) - birth * V_M - FL * V_M - FOI_2 * V_M - LOI * V_M - \mu_M * V_M$$

Infant Population

$$\frac{dS_I}{dt} = birth * (1 - v_{Ab}) * (P_M + \mathrm{V_M}) + birth * (S_M + I_M + R_M) - FOI_3 * S_I - GUR * S_i - \mu_I * S_I$$

$$\frac{dI_I}{dt} = FOI_3 * S_I - \rho * I_I - \mu_I * I_I$$

$$\frac{dR_I}{dt} = \rho * I_I - GUR * R_i - \mu_I * R_I$$

$$\frac{dP_I}{dt} = birth * v_{Ab} * (\mathrm{P_M} + \mathrm{V_M}) - GUR * P_i - \mu_I * P_I$$

Figure 2 Ordinary differential equations associated with the compartment model diagram

Kenya				
	Contact age group (j)			
Participant age group (i)	Infants <1 year	Childbearing age (15-49)	General Population	Total contacts per day per age group
Infants <1 year	0.024324324	0.406756757	0.568918919	8.604651163
Childbearing age (15-49)	0.068596171	0.539881495	0.391522334	19.07826087
General Population	0.085673586	0.34961335	0.564713065	19.5

Figure 3 Age structured social contact matrix for Kenya where the internal cells represent the proportion of average daily contacts the participant makes with each contact age group. The external cells show the average total contacts per day made by each participant age group in the study.

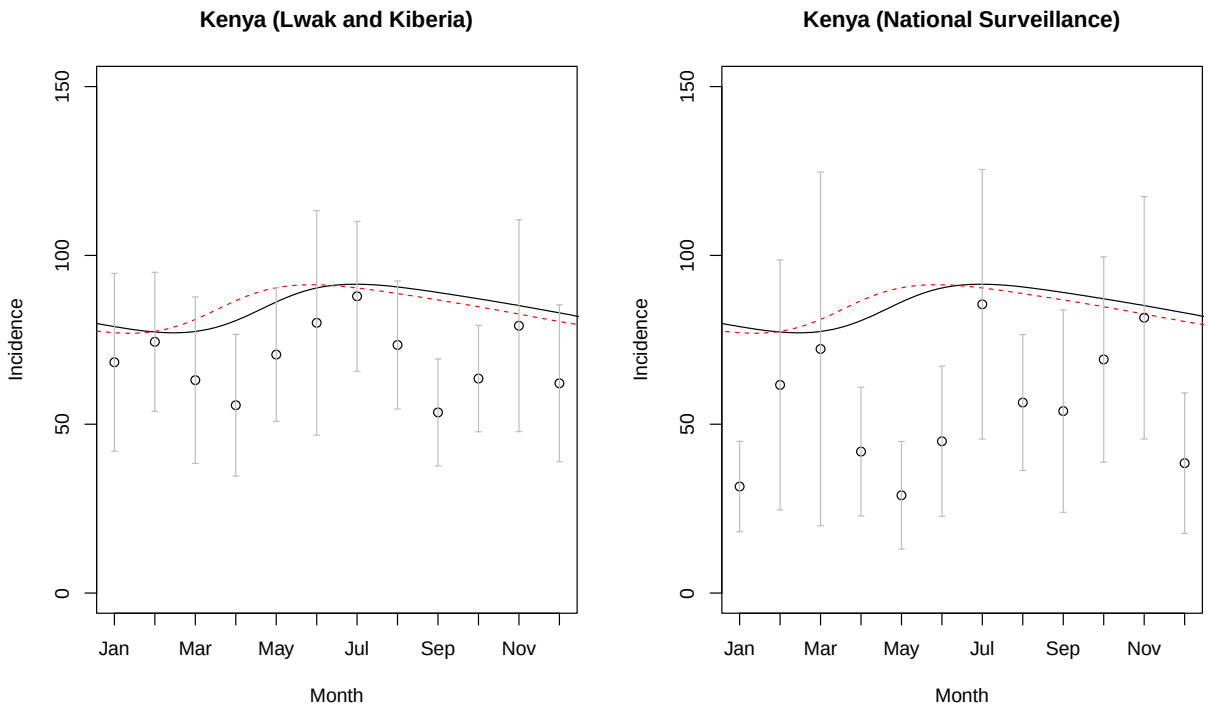

Figure 4 Modeling fitting results. The points represent the average monthly cases of influenza in Lwak and Kiberia with 95% CI The black solid line represents the modeled monthly incidence of influenza among the general population before model fitting. The dashed red line is the modeled monthly incidence after model fitting with nonlinear optimization (Left panel). The points represent the average monthly cases of influenza in Kenya with 95% CI from National Sentinel Surveillance data (Right panel).

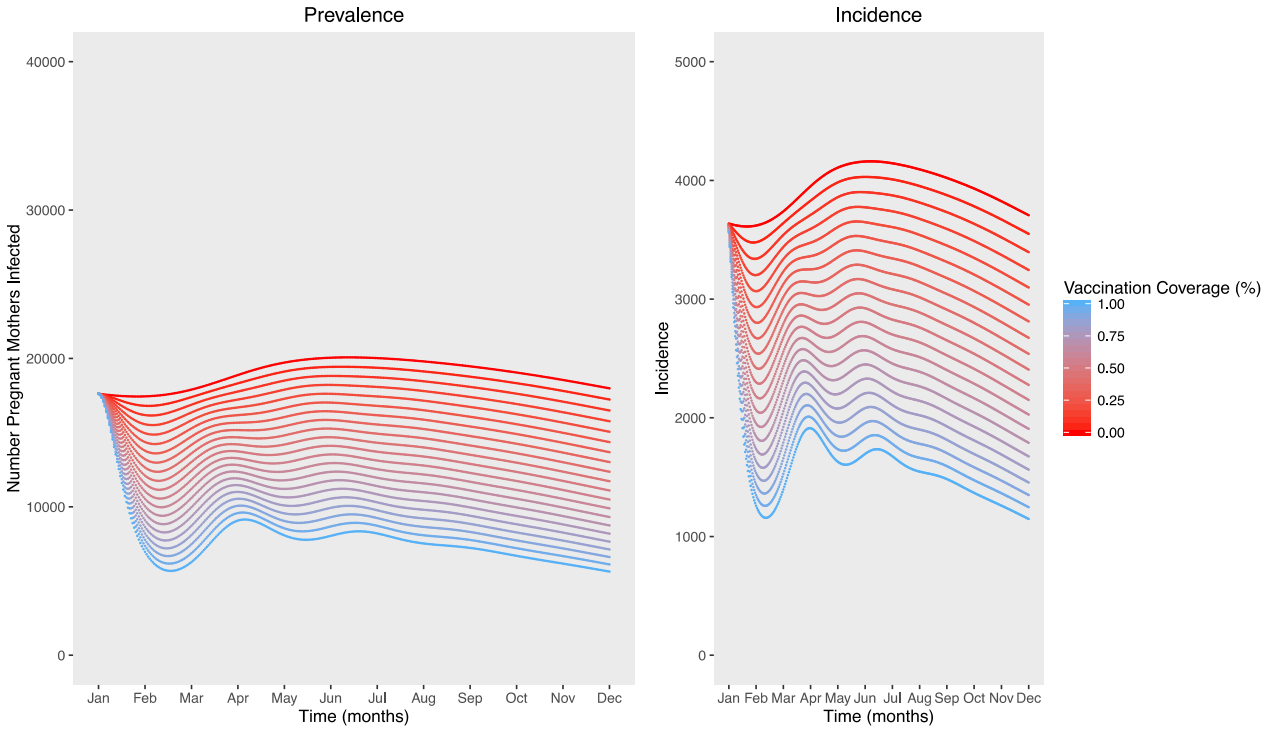

Figure 5 Daily prevalence and incidence of seasonal influenza among pregnant populations of Kenya given different vaccination coverage.

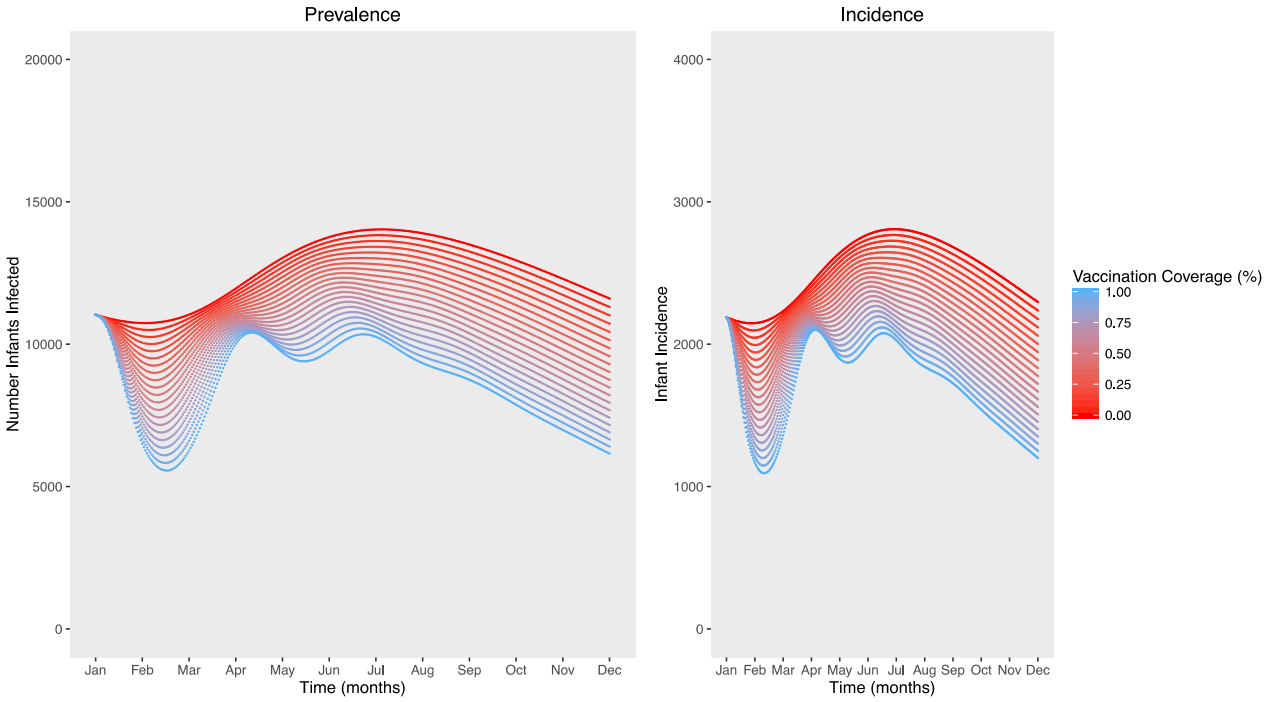

Figure 6 Daily prevalence and incidence of seasonal influenza among young infant populations of Kenya given different vaccination coverage

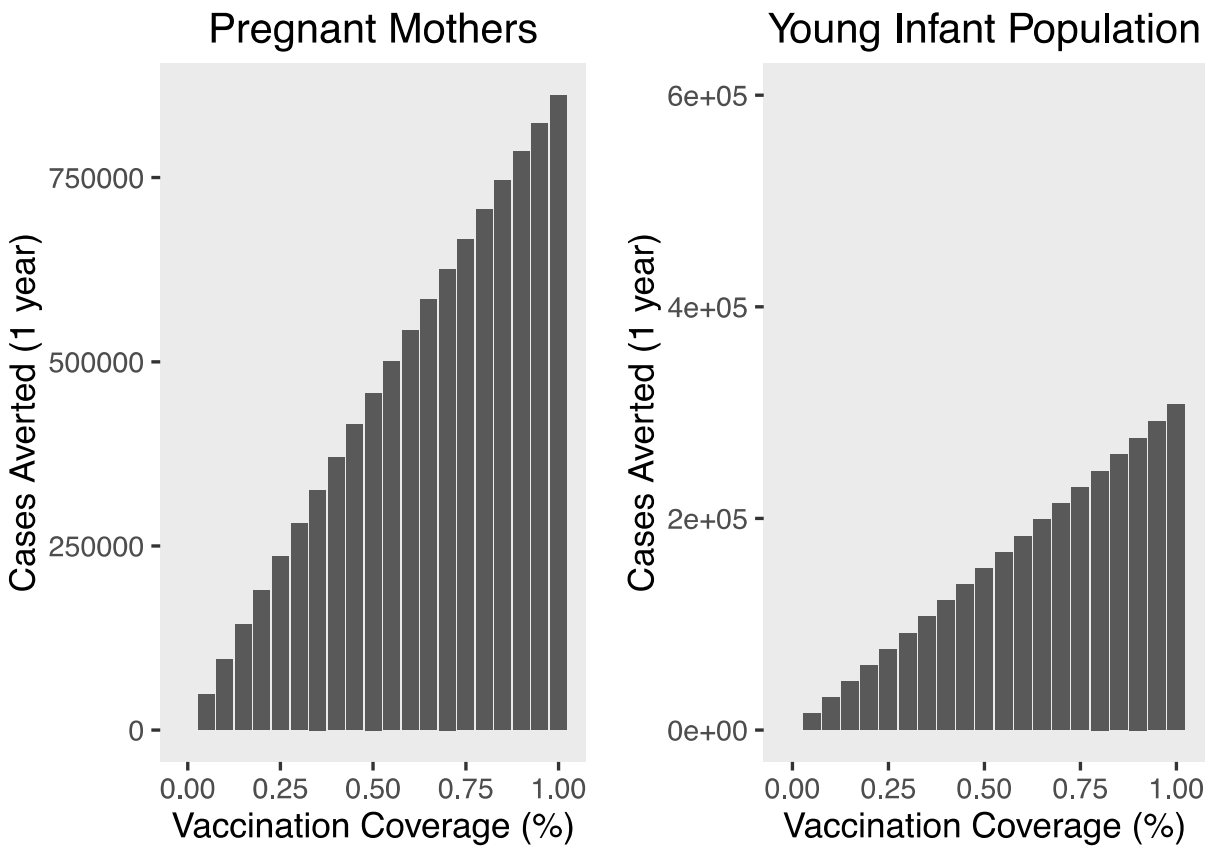

Figure 7 Cases averted among pregnant mothers (left panel) and young infants (right panel) given different vaccine coverage for a single combination of parameters reported in Table 1.

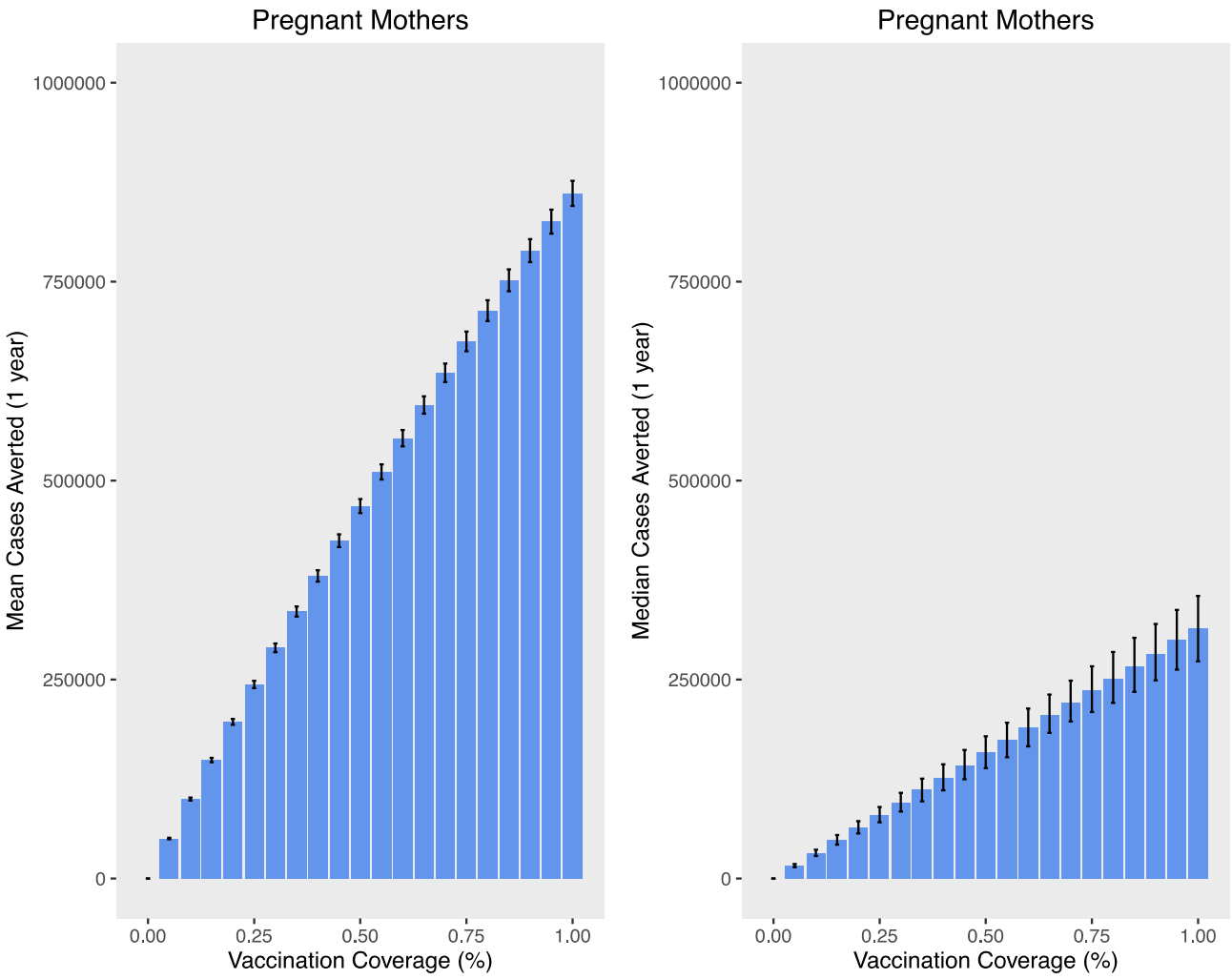

Figure 8 Mean and (95%CI, left panel) and median (IQR, right panel) cases averted among pregnant mothers given different samples of parameters using Latin hypercube sampling

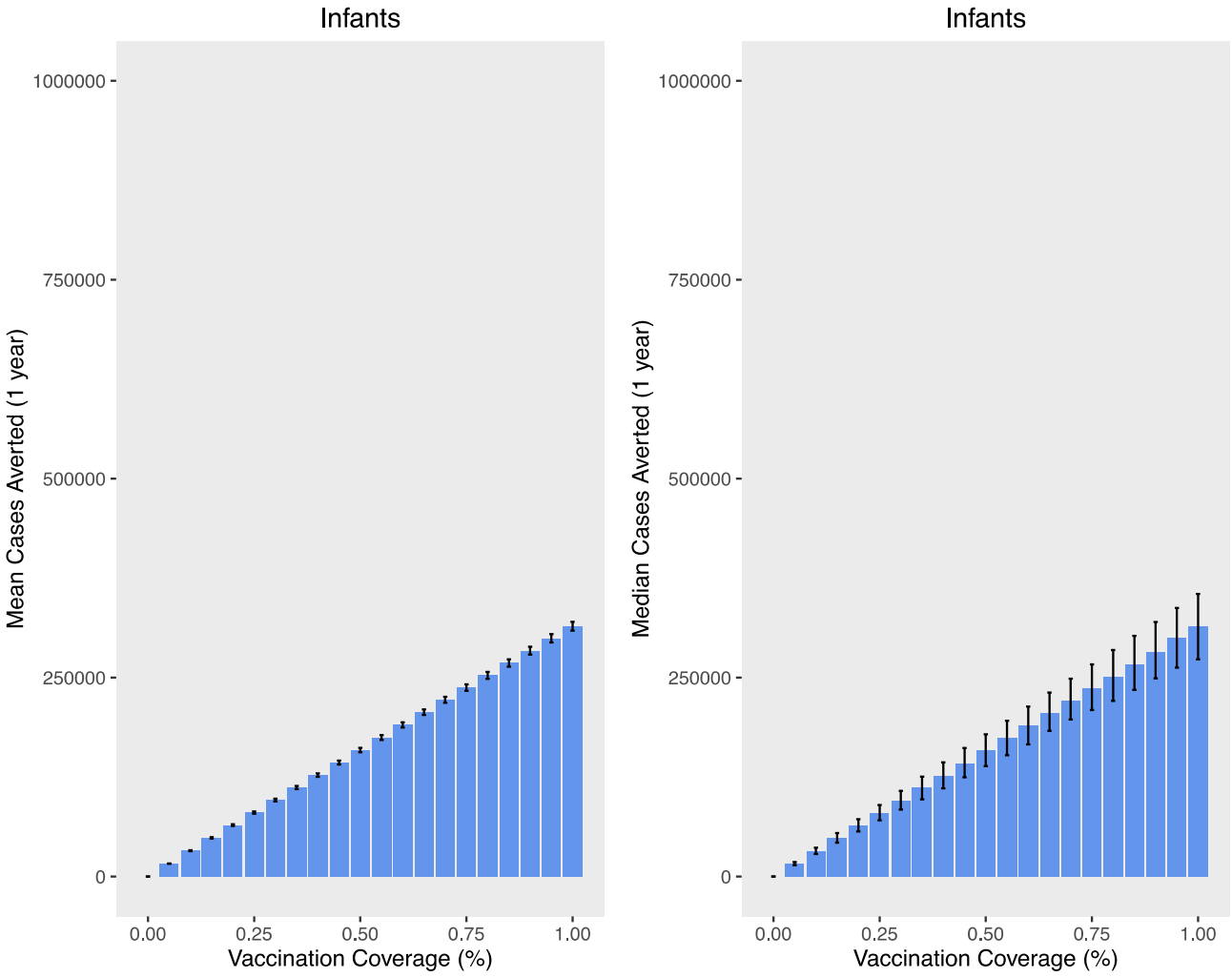

Figure 9 Mean and (95%CI, left panel) and median (IQR, right panel) cases averted among young infants given samples of parameters using Latin hypercube sampling.

Tables

Table 1: Parameter list for ODE compartment model

Parameter	Definition	Function/Constant	Citation
$\lambda(t)$	Force of infection	Calculated	See methods
θ	Pregnancy rate	Calculated	(17, 18)
ρ	Recovery rate	1/5 days	(29)
birth	Birth rate	0.004991057 (birth per pregnant woman per day)	(17)
FL	Fetal loss rate	Calculated	(17, 18)
v_{Ab}	Vaccine efficacy for young infants of vaccinated mothers	0.488	(33)
v_e	Vaccine efficacy among pregnant mothers	0.5	(33)
v	Vaccination rate	0-100%	Experimental
$\beta 1$	Seasonal amplitude parameter	0.2	Estimated
ω	Seasonal offset parameter	2.3678	Fit

Table 2: List of compartments for ODE compartment model

Population Compartment	Definition	Citation
S_g	Susceptible general population	(17)
I_g	Infected general population	Calculated
R_g	Recovered general population	Calculated
S_m	Susceptible pregnant mother population	(17, 18) http://www.statcompiler.com/en/
I_m	Infected pregnant mother population	Calculated

R_m	Recovered pregnant population	(29)
P_m	Protected pregnant population	(4)
V_m	Vaccinated pregnant population that is no protected	(4)
S_i	Susceptible young infant population (<6 months of age)	(17)
I_i	Infected young infant population (<6 months of age)	Calculated
R_i	Recovered young infant population (<6 months of age)	(29)
P_i	Protected young infant population (<6 months of age)	(5)

Table 3: Characteristics of publications from literature search on social mixing

Author	**Search term**	**Search engine**	**Year of analysis**	**Location of analysis**	**Infant age groups**	**Have the raw data**	**Citation**
Horby et al	Social contact patterns	Googlescholar	2011	North Vietnam	Participants <1 Contacts 0-4	Yes	(20)
Read et al	Social contact patterns	Googlescholar	2009-2010	Northeast of Guangzhou, China	Participants: 5 yr age bands Contacts 0-5	Yes	(22)
Stein et al	Social contact patterns	Googlescholar	2012-2013	Students from two Bangkok universities	NA	No	(34)
Johnstone-Roberston et al	Social contact patterns	Googlescholar	2010	South African township in 2010	0-5	No**	(35)
Kiti et al	social mixing patterns respiratory	Googlescholar	2014	Northern part of the Kilifi Health and Demographic Surveillane	< 1	Yes	(23)

				System (KHDSS)			
Fu et al	social mixing patterns respiratory	Googlescholar	2010	Taiwan	0-18	No	(36)
Grijalva et al	social mixing patterns respiratory	Googlescholar	2009-2011	Peru	0-2	No*	(37)
Ibuka et al	social mixing patterns respiratory	Googlescholar	2011	Japan	0-2	No	(38)
Eisenberg et al	social mixing patterns respiratory	Googlescholar	2003-2005	Northernmost province on the Ecuadorian coast	Unknown	No**	(39)
Kumar et al	social mixing patterns respiratory	Googlescholar	Unknown	Ballabgarh, Haryana	Unknown	No**	(40)
Ajelli et al	social mixing patterns respiratory	Googlescholar	2016	Tomsk, Russia	0-4	No**	(41)

*Not permitted to provide individual level data

**Data requested but not provided before analysis was performed

Table 4: Characteristics of publications with good quality social mixing data

Authors (citation)	Year	Country of analysis	Study population size	Weighted urban vs rural	Age range for childbearing aged women	Age range for young infants	Definition of a contact
Horby et al	2011	Vietnam	860	No	15-49	Participants <1 Contacts 0-4	A physical contact: kin to skin contact Nonphysical contact: two-way conversation with three or more works in the physical presence of another person but not skin to skin contact
Kiti et al	2014	Kenya	568	Yes*	15-49	< 1	Someone with whom the participant had a direct physical encounter (a "contact"), and involved direct skin-to-skin touch such as embracing, kissing, or shaking hands.
Melegaro et al**	2013	Zimbabwe	11,569	No	15-44	<1	Interaction between two individuals, either physical (when involving skin-to-skin contact), or non-physical (when involving a two-way conversation with three or more words in the physical presence of another person, but no skin-to-skin contact)
Read et al	2009-2010	Southern China	568	No	20-64	<5	An event where contacts are reported, either as an encounter with an individual or a group, and count each individual contacted in such an event as a 'contact'; hence, a participant's total number of contacts is the number of individuals reported across all contact events.

Johnstone-Roberston et al**	2010	South African township in 2010	571	No	15-44	<5	Close contacts were defined as those involving physical touch (type I) or those involving a 2-way conversation with 3 or more words in the physical presence of another person without physical touch (type II). Casual contacts (type III) were defined as those occurring in an indoor location but not satisfying the criteria for a close contact.

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