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Scheduling of measles vaccination in low-income countries: Projections of a dynamic model

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ABSTRACT

Large-scale vaccination campaigns (SIAs) and improved routine immunization (RI) have greatly reduced measles incidence in low-income countries. However, the interval between SIAs required to maintain these gains over the long term is not clear. We developed a dynamic model of measles transmission to assess measles vaccination strategies in Cambodia, Ghana, India, Morocco, Nigeria, and Uganda. We projected measles cases from 2008 to 2050 under (a) holding SIAs every 2, 4, 6, or 8 years, (b) improvements in first dose routine measles vaccine (MCV1) coverage of 0%, 1%, 3% annually, and (c) introducing MCV2 once MCV1 coverage reaches 70%, 80%, 90%. If MCV1 continues improving, then India and Nigeria could hold SIAs every 4 years without significant probability of large outbreaks, and the other countries every 6–8 years. If RI remains stagnant, India and Nigeria should hold SIAs every 2 years, and the other countries every 4–6 years.

1. Introduction

In the 1990s, endemic measles was dramatically reduced and – according to many – completely eliminated in the Americas through large-scale supplemental immunization activities (SIAs) and efforts to strengthen routine immunization (RI) programs by improving coverage of the first scheduled dose of measles-containing vaccine (MCV1) and by introducing a second scheduled dose (MCV2) [1]. Subsequently, these "second opportunity" strategies were extended to 45 priority countries, mostly in Africa and Asia [1]. As a result, the estimated number of worldwide measles-related deaths declined from 873,000 in 1999 to 345,000 in 2005 [1]. However, measles disease burden remains high in absolute terms, and many of these countries only recently held their first SIA and are far from introducing MCV2 [1,2]. Therefore, decision-makers continue to face challenges in determining the optimal interval between SIAs and the optimal criteria for introducing MCV2 in the priority countries. At the same time, new measles vaccine technologies are in development. These include DNA primers that make conventional measles vaccine more effective in infants [3]. Other technologies simplify administration and waste disposal by administering vaccine via aerosolized droplets [4], dry powder formulations [5], and needle-free syringes [6]. Decision-makers therefore also face challenges in determining how to invest in these new technologies, particularly given the rapidly changing landscape of global measles disease burden.

To meet these challenges, credible projections of future measles cases under various possible vaccination strategies are needed. Such projections can be obtained using dynamic disease transmission models [7]. Dynamic models incorporate transmission mechanisms and can thereby capture herd immunity effects, whereby vaccination also protects unvaccinated individuals by reducing disease transmission in the population and thus reducing the force of infection (the rate at which a susceptible person is infected) [8]. As a result, an infectious disease can be eliminated in a population with an imperfectly efficacious vaccine, and without vaccinating everyone. Herd immunity effects become particularly pronounced at higher coverage levels, near the elimination threshold in vaccine coverage [8]. Hence, dynamic models are excellent choices for projecting the impact of vaccination programs when coverage levels are high, as might occur under successful measles SIA and RI efforts. Dynamic models are referred to as dynamic because they can capture how the force of infection evolves over time due to factors such as the introduction of vaccination. By comparison, widely used static models (e.g. cohort models) assume a fixed, unchanging force of infection and do not capture herd immunity [9]. Therefore, they incorrectly predict that disease elimination can only occur when a perfectly efficacious vaccine is given to everyone in a population, which contradicts the local elimination

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of measles that has been observed in many countries immediately following SIA efforts.

A dynamic model of particular relevance for measles is the age-structured SEIR compartmental model. This model and variations thereof have long been applied for assessing vaccination programs for pediatric infectious diseases, and has been validated against pre- and post-vaccination age-stratified case reports and seroprevalence surveys for measles [8,10–12]. Previous analyses have tailored measles models to settings where birth rates and transmission rates are high [13,14] as well as campaign settings [15,16]. The SEIR model has also been applied in very policy-specific settings, such as in New Zealand where an age-structured measles model was used by the Ministry of Health to predict an epidemic of measles and to design optimal vaccination schedules for that country [17]. The SEIR model has since been developed into metapopulation models of measles transmission, such as have been used recently to understand the spatio-temporal dynamics of measles outbreaks in western Africa [18].

The objective of this study was to develop a simplified compartmental model of measles transmission and vaccination in low-income settings. The model was developed for use in a pilot project that will assess the cost-effectiveness of potential innovations in measles vaccination technologies in low-income countries. Here, we demonstrate the stand-alone utility of the model for assessing the effectiveness of second opportunity strategies with the current vaccine. A model with relatively simple structure was developed because there are often not sufficient data for many low-income countries to populate the parameters of more complex models. As a result, we did not include stochastic, spatial, seasonal or other effects that are relevant in certain contexts [8,12,18,19]. However, because of its limited data requirements, the model can be easily adapted to any given country. The present model requires country-specific vaccine coverage, vital statistics, and (optionally) measles case fatality rate. Most other parameters are specific to low-income countries generally.

Accordingly we developed country-specific versions of the model for six countries, chosen on the basis of their relatively high annual number of cases (India, Nigeria), the availability of vaccine cost data that will be used in the pilot project on cost-effectiveness that will use this model (Cambodia, Ghana, Morocco), or because they provide illustrative examples of cases where data availability is quite limited (India, Uganda). These countries also represent a wide range of measles disease burden and vaccine coverage. To illustrate the utility and specific policy implications of the model, we explored projected cases in these countries under various possible scenarios for (1) interval between SIAs, (2) criteria for introducing MCV2, and (3) rate of improvement of MCV1 coverage. We also compared the projections of the compartmental model to those of the corresponding static model.

2. Methods

2.1. Model structure

We developed an age-structured MSEIRV compartmental model, whereby individuals are allocated into one of a number of mutually exclusive categories based on their epidemiological status and age. Epidemiological categories were: maternally immune (naturally derived), maternally immune (vaccine-derived), susceptible, exposed, infectious, recovered, and vaccinated. We distinguished between vaccine- and naturally derived maternal immunity because they wane at different rates [20,21]. We define naturally derived maternal immunity as maternal immunity conferred to a child by a mother who was exposed to measles infection in the past (and may or may not have been vaccinated), and we define vaccine-derived maternal immunity as maternal immunity conferred to a child by a mother who was vaccinated against measles but never infected. Age classes were: <1 month old, 1 month old, 2 months old, . . ., 59 months old, 5 years old, 6 years old, . . ., 9 years old, 10–14 years old, 15–19 years old, . . ., 75–79 years old. Fine age stratification in the younger age classes can allow us to study the impact of measles innovations such as the DNA vaccine under the associated pilot project (DNA priming may make conventional vaccine more effective below 9 months of age [3]). Although the model structure allows for a large upper limit on ages, we note that the actual sizes of older age compartments are small since the model is parameterized with country-specific historical and projected demographic data [22]. We do not include seasonal forcing in the baseline model since there are little data that can be use to estimate country-specific estimates of seasonal forcing amplitudes. However, the impact of seasonal forcing on model outcomes is explored in Section 3. We also assume that vaccine-derived immunity wanes at some specified rate [23,24]. Fig. 1 presents a schematic diagram of the model. Model equations appear in Supplementary Appendix 1.

The total number of susceptible (resp. exposed, infectious, etc.) individuals in age class i at a given time is denoted S_i (resp. E_i, I_i, etc.). Individuals are born at rate $b(t)$ per year, where the birth rate can depend on the year t according to historical demographic data and future projections. Individuals are born with naturally derived maternal immunity, vaccine-derived maternal immunity, or are susceptible. The relative proportion of individuals born into each of these three categories at a given time depends upon the number of women of childbearing years in the R_i, V_i, or S_i compartments at that time, respectively. Individuals in age class i with naturally (resp. vaccine-) derived maternal immunity lose it at rate ρ_i^N (resp. ρ_i^V), becoming fully susceptible. Susceptible individuals in age class i become infected at rate $\lambda_i = \sum_{j=1}^{80} \beta_{ij} I_j / N_j$, where N_j is the total number of individuals of age class j and β_{ij} is the rate at which an infectious person of age class j transmits to a susceptible person of age class i. Newly infected individuals remain "exposed" for $1/\sigma$ days on average and then enter the "infectious" class, where they remain for $1/\gamma$ days on average. After this, a proportion d_i^M of individuals die from measles-related complications, while the remainder acquired lifelong immunity and enter the R_i class. A proportion ε_i of vaccinees enter the V_i class (ε_i is the vaccine effectiveness) while $1-\varepsilon_i$ remain susceptible. Individuals in the vaccinated class lose their immunity at rate w, thereby becoming fully susceptible again. Each month, individuals of age class i move to age class $i+1$ (i.e., they age by 1 month), except for a proportion $d_i(t)$ who die due to causes other than measles.

2.2. Review of epidemiologic data for low-income countries

Measles incidence patterns can vary significantly across populations according to population density [7,8], or behavioural factors [13,25]. However, measles epidemiology tends to exhibit certain broad features in low-income countries, as compared to high-income countries [13]. For instance, the mean age at infection in unvaccinated populations in low-income countries is 1–3 years, which is much lower than the 4–6 years observed before mass vaccination in high-income countries in the 20th century [8,13,25,26]. Supplementary Appendix 2 summarizes eight studies reporting age-stratified attack rates in Indian and African populations from the 1970s and 1980s, before vaccination was widespread. The summary shows that the measles attack rate peaks in <1, 1, or 2-year olds. Supplementary Appendix 2 also summarizes the percent of children exhibiting measles antibodies by age 5 according to eight seroprevalence surveys from Indian and African populations in the 1970s and 1980s. The average percent infected by age 5 was 78%, with most studies falling between 70% and 90%. The force of infec-