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Demographics, epidemiology and the impact of vaccination campaigns in a measles-free world – Can elimination be maintained?

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ABSTRACT

Introduction: All six WHO regions currently have goals for measles elimination by 2020. Measles vaccination is delivered via routine immunization programmes, which in most sub-Saharan African countries reach children around 9 months of age, and supplementary immunization activities (SIAs), which target a wider age range at multi-annual intervals. In the absence of endemic measles circulation, the proportion of individuals susceptible to measles will gradually increase through accumulation of new unvaccinated individuals in each birth cohort, increasing the risk of an epidemic. The impact of SIAs and the financial investment they require, depend on coverage and target age range.

Materials and methods: We evaluated the impact of target population age range for periodic SIAs, evaluating outcomes for two different levels of coverage, using a demographic and epidemiological model adapted to reflect populations in 4 sub-Saharan African countries.

Results: We found that a single SIA can maintain elimination over short time-scales, even with low routine coverage. However, maintaining elimination for more than a few years is difficult, even with large (high coverage/wide age range) recurrent SIAs, due to the build-up of susceptible individuals. Across the demographic and vaccination contexts investigated, expanding SIAs to target individuals over 10 years did not significantly reduce outbreak risk.

Conclusions: Elimination was not maintained in the contexts we evaluated without a second opportunity for vaccination. In the absence of an expanded routine program, SIAs provide a powerful option for providing this second dose. We show that a single high coverage SIA can deliver most key benefits in terms of maintaining elimination, with follow-up campaigns potentially requiring smaller investments. This makes post-campaign evaluation of coverage increasingly relevant to correctly assess future outbreak risk.

1. Introduction

The high case fatality rates associated with measles in children, and the existence of an inexpensive, safe vaccine, have led measles control to be called a 'best buy' in public health [1]. Measles vaccine coverage has increased globally over the last decade, and vaccination is estimated to have averted 13.8 million deaths between 2000 and 2012 [2]. This success has led to proposals for a global effort to achieve measles eradication [3–5]. Reduction of global prevalence to zero requires that measles endemic areas achieve elimination, and that elimination be maintained in areas where measles is absent. Formally, this requires reducing the local effective reproduction number, R_E, or number of new infections per infectious individual, below one and maintaining it at that level. Where R_E is below one and measles has been eliminated, by definition, re-introduction of measles will not result in re-establishment of endemic transmission; however, small to mid-sized outbreaks may occur if measles is introduced.

The herd immunity threshold for the elimination of an immunizing pathogen is a central concept in infectious disease epidemiology and public health. The simplest result, ignoring maternal

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immunity, states that R_E can be maintained below one and a pathogen can be eliminated if a fraction greater than, $p_c = 1-1/R_0$, where R_0 is the basic reproduction number, is immunized by vaccination at birth. For pathogens with large R_0, such as measles, this threshold can be difficult to achieve with only a single dose of childhood vaccine; even where routine first dose coverage is high, primary vaccine failure, ~14% at 9 months, due to interactions with maternal immunity can limit immunization below the p_c threshold [6]. Areas that have successfully eliminated measles, such as the countries in the Americas, have maintained their success through the introduction of a routine second vaccine dose. In many countries where measles remains endemic, population immunity is maintained through a combination of a single routine childhood dose and periodic, age-targeted supplemental immunization activities (SIAs). This approach necessarily means that population immunity will fluctuate over time. The proportion immune in the population will decrease in the interval between SIAs [7] as non-immunized susceptibles accumulate [8]. Thus epidemic risk, which scales as a non-linear function of the size and age distribution of the non-immune population [9], will increase. If infection is re-introduced when R_E is transiently greater than one, both the likelihood that the initial infection will lead to an epidemic and the size of the resulting epidemic, increase as a non-linear function of R_E.

Here we consider the ability of combined one-dose routine plus SIA vaccination strategies to maintain elimination once achieved. In the absence of circulating transmission, routine vaccination controls the rate at which susceptible individuals are recruited into the population and SIAs cause a periodic, pulsed reduction of susceptibles within certain age cohorts. Thus, optimization of maintenance strategies that involve SIAs should consider both the average population immunity attained, and the increased outbreak risk during transient periods of low population immunity, since the penalty of even a brief interval with $R_E > 1$ may be a large outbreak. We evaluate vaccination strategies relative to an operational utility function, which we call integrated epidemic risk (IER - see methods below), that accounts for this non-linear change in outbreak risk as a function of the magnitude of R_E.

Though many countries are far from local elimination of measles, some have made dramatic improvements in measles reduction and may be candidates for elimination in the near term [2]. To achieve the larger goal of regional elimination or global eradication, successful countries will need to maintain elimination while the other countries catch up. Thus, evaluating the potential for the current one-dose routine plus SIA vaccination strategies to maintain elimination is critical to planning for future measles vaccine investments. We explore the ability of a range of SIA designs to maintain elimination with scenarios designed to broadly reflect four sub-Saharan African countries, chosen to encompass a range of demographic and vaccination coverage scenarios. We illustrate that while broader age target SIAs necessarily reduce R_E and the risk of outbreaks, the marginal benefits of these campaigns depend on the country context.

2. Materials and methods

We created an age structured epidemiological MSIRV (Maternally immune – Susceptible – Infected – Recovered – Vaccinated) compartmental model, following methods developed by Metcalf et al. [10]. We simulated the progression of the effective reproduction number, R_E, and IER of measles in four different populations under the assumption of no circulating transmission. This requires five steps, detailed below: initializing the starting susceptible population size and distribution, forward simulation of the susceptible population through time, evaluation of R_E at each time point, estimation of the integrated epidemic risk, and marginal benefit comparison.

We initialized populations to broadly reflect the demography of four countries in sub-Saharan Africa chosen to capture a diversity of demographic and vaccination contexts: (i) Ethiopia, with a large urban population and a relatively low historical routine vaccination rate; (ii) Nigeria, the most populated country in Africa and with a moderate historical vaccination rate; (iii) Equatorial Guinea, with a small population and a low vaccination level; and (iv) Swaziland, with a small population but a high vaccination level.

2.1. Initial populations

Initial population age distributions were based on estimates for each country from the WorldPop project [Ref. http://www.worldpop.org.uk/, Tatem et al. 2013] stratified into 225 age groups (monthly strata up to 15 years of age; yearly thereafter). In each age bin, the population is further divided into relevant epidemiological compartments (i.e., susceptible, recovered, vaccinated, etc). We estimated the initial population in each age group that was immunized by vaccination using UNICEF/WHO administrative coverage estimates since 1980 for routine and SIAs, combined with the efficacy of the vaccine (Supplementary Material 1). All individuals are assumed to be born with maternal immunity and its decay with age was modeled as a monthly exponential decline with a rate = 0.45, which translates into less than 5% maternally immune by 7 months [7]. The initial number of individuals with immunity from natural infection ("recovered" individuals) was estimated by assuming a constant hazard of infection with age; thus the probability of remaining susceptible declines as an exponential function of age. We assumed an exponential rate of 0.02, which is equivalent to assuming a mean age of infection of 4 years, but explored a range of values for this parameter (Supplementary Material 1). After allocating the corresponding proportion of the population to the 3 compartments above (V, M and R), the remainder were added to the susceptible compartment.

2.2. Forward simulation

We simulated the trajectory of the population forward for 15 years, from 2015 to 2030. Individuals age into the next age-class in each time step at a rate equal to one over the size of the age group, measured in bi-weekly time-steps (i.e. 1/2 for the monthly age bins, 1/24 for the yearly age bins). Birth rates were taken as the 2015 estimate from World Bank ("http://data.worldbank.org/") and assumed constant throughout the simulation (alternative parametrisation in Supplementary Material 1). All infants are assumed to be born with maternal immunity, described above. Age-specific mortality was estimated by spline interpolating the data from the UN Department of Economic and Social Affairs model life tables (http://esa.un.org/unpd/wpp/Download/Standard/Mortality/), which is given in 5-year age bins, to our age groups.

Immunity through vaccination comes from two sources, routine coverage and SIAs. Routine vaccination coverage levels reflected those achieved in 2014 (the most recently available year in the WHO/Unicef database) and were assumed to remain constant over the simulation time-frame. For SIAs, we explored scenarios reflecting campaigns targeting 3 different age classes (9m to 5y, 9m to 10y, 9m to 15y) occurring every 4 years over a time period of 15 years. The frequency of campaigns reflected WHO recommendations from the global measles and rubella strategic plan [17]. Though the intent of campaigns is to vaccinate a large proportion of susceptibles in the target age class, the proportion of susceptibles immunized in these campaigns may differ from the vaccination coverage because of logistical constraints in implementation,

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