Published in final edited form as:

Lancet Infect Dis. 2021 July ; 21(7): 1004–1013. doi:10.1016/S1473-3099(20)30475-8.

Assessing the burden of Congenital Rubella Syndrome in China and evaluating mitigation strategies: a meta-population modeling study

Qiru Su, PhD[1,2], **Zhilan Feng, PhD**[3] **[Professor]**, **Lixin Hao, PhD**[1], **Chao Ma, PhD**[1], **José E Hagan, MD**[4,5], **Gavin B Grant, MD**[4], **Ning Wen, MD**[1], **Chunxiang Fan, MD**[1], **Hong Yang, MD**[1], **Lance E Rodewald, MD**[1,4,6], **Huaqing Wang, PhD**[1,†], **John W Glasser, PhD**[4]

[1]Chinese Center for Disease Control and Prevention, 27 Nanwei Road, Xicheng District, Beijing 100050 PRC

[2]Institute of Pediatrics, Shenzhen Children's Hospital, 7019 Yitian Road, Shenzhen, Guangdong 518038 PRC

[3]Purdue University, 150 North University Street, West Lafayette, Indiana 47907 USA

[4]Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, GA 30333 USA

[5]Expanded Programme on Immunization, World Health Organization Regional Office for the Western Pacific, United Nations Avenue, Ermita, Manila 1000 Philippines

[6]Office of the World Health Organization Representative in China, 23 Dongzhimenwai Dajie, Chaoyang District, Beijing 100600 PRC

Abstract

Background: A rubella vaccine was licensed in China in 1993 and added to the Expanded Program on Immunization in 2008, but a national cross-sectional serological survey during 2014 indicates that many adolescents remain susceptible. Maternal infections during the first trimester often cause miscarriages, stillbirths and, among livebirths, congenital rubella syndrome (CRS). We aimed to evaluate possible supplemental immunization activities (SIAs) to accelerate rubella and CRS elimination.

---

†Corresponding author: Huaqing Wang PhD, National Immunization Program, Chinese Center for Disease Control and Prevention, 27 Nanwei Road, Xicheng District, Beijing 100050 PRC, Voice: +86 10 63171724; facsimile: +86 10 83159534, hqwang@vip.sina.com.

Author Contributions

QS contributed to study design, provided information, and reviewed the manuscript; CM, JH, and GG provided information and reviewed the manuscript; ZF performed analyses and simulations and reviewed the manuscript; LH supervised the work and reviewed the manuscript; NW, CF, HY provided information and reviewed the manuscript; LR contributed to study design and reviewed the manuscript; HW contributed to study design, supervised the work, provided information, and reviewed the manuscript; and JG performed analyses and simulations and wrote the manuscript.

Appendix

In the Appendix, we describe our meta-population models, parameter values or their sources, and our calculations, analyses and simulations in greater detail than possible here.

Declaration of Interests

The authors have no conflicts of interest to disclose.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or other institutions with which they are affiliated.

Methods: We analyzed the serosurvey, rubella surveillance from 2005–16, and relevant publications. Using an age-structured population model with provincial strata, we calculated the reproduction numbers and evaluated the gradient of the effective number with respect to supplemental immunization rates. We corroborated these analytical results and estimated times-to-elimination by simulating SIAs among adolescents and young adults (ages 10–19 and 20–29 years, respectively) using a model with regional strata. And we estimated the incidence of rubella and burden of CRS by simulating transmission in a relatively small population lacking only spatial structure.

Findings: By 2014, childhood immunization had reduced rubella's reproduction number from 7·6 to 1·2 and SIAs among adolescents were the optimal elimination strategy. We estimate that a) less than 10% of rubella infections were reported; b) while some women with symptomatic first trimester infections may have elected to terminate their pregnancies, 700 children could have been born with CRS during 2014; and c) timely SIAs would avert outbreaks that, as susceptible adolescents reach reproductive age, could greatly increase the burden of CRS.

Interpretation: The finding that SIAs among adolescents would most effectively reduce CRS as well as eliminate rubella is due to fewer infections than immunized people would otherwise have caused, which meta-population models with realistic mixing are uniquely capable of assessing.

Funding: This work was supported by the World Health Organization (Cooperative Projects 090171 and 090187 to China CDC) and National Science Foundation (DMS-1022758 and DMS-1814545 to Zhilan Feng).

Keywords

rubella in China; vaccination strategies; accelerating elimination; meta-population modeling

Introduction

Rubella is a mild respiratory disease typically of children absent vaccination.[1] Infections during pregnancy, especially the first trimester,[2] however, often cause miscarriages, fetal deaths or stillbirths, and a constellation of severe birth defects collectively known as congenital rubella syndrome (CRS): cataracts, congenital heart disease, hearing impairment, and developmental delay.

Because rubella is a mild disease, even in adults, with 20–50% of infections asymptomatic, maternal infections are under-ascertained even by active surveillance. Moreover, because causal relations between discrete phenomena that follow one another in close succession are most likely to be recognized, even symptomatic maternal infections may not be suspected of causing infant conditions, particularly those not diagnosed until long after birth (e.g., hearing impairment, developmental delay). Finally, the spontaneous abortions, fetal deaths and stillbirths that maternal rubella infections may cause are inestimable.

As rubella is a vaccine-preventable disease, the World Health Assembly, during May of 2012, endorsed elimination by 2020 as a goal for five of the World Health Organization (WHO)'s regions.[3] Rubella has since been eliminated from the Region of the Americas.[4] More recently, the Western Pacific Regional Committee urged member states to establish target dates for rubella elimination.[5] So far, cessation of endemic rubella transmission has been verified in Australia, Brunei, Macao, New Zealand, and the Republic of Korea. Rubella remains endemic in China, the largest country in the Western Pacific Region with a mainland population of more than 1·38 billion and area of approximately 9·6 million km^2.

A rubella-containing vaccine (RCV) was first licensed in China during 1993. Prior to 2008, some provinces offered RCV among their routine services, but parents were responsible for the cost.[6,7] In 2008, China extended the Expanded Program on Immunization (EPI) to include RCV, which began being offered without charge among routine immunization services. Measles and rubella vaccine (MR) was used for the first dose at 8 months and measles-mumps-rubella vaccine (MMR) for the second at 15–18 months. Due to shortages of these vaccines when first included in the EPI, however, the schedule was not fully implemented throughout China until 2011. Nor was a campaign to catch-up older children conducted. Nonetheless, as RCVs became available, administrative estimates of routine uptake (i.e., quotients of doses administered and target population size) increased rapidly.[8]

Rubella has been a notifiable disease in China since 1990, but incidence was monitored initially through sentinel surveillance in 145 prefectures,[9] a population of 11 million people (approximately 1% of the population at that time). In 2004, the National Notifiable Diseases Reporting System was implemented. This web-based real-time reporting system permitted passive collection of hospitalized case reports at prefecture-level CDCs and integration at the national CDC. During the period from 2004–13, reported incidence peaked at 9·11 per 10^6 people during 2008.[8] In 2014, rubella was integrated into the measles surveillance system, whereupon case-based, laboratory-supported surveillance began being conducted routinely. This system has met or exceeded WHO surveillance quality criteria continuously since 2011.[10] Reported incidence had declined to 1·22 per 10^6 people by 2017, but increased to 2·83 per 10^6 the next year. And the number of infections reported during 2018 was exceeded by March of 2019.

Congenital Rubella Syndrome is not a notifiable condition in China, but the National Health and Family Planning Commission (now National Health Commission) has collaborated with the WHO since 2009 on pilot surveillance in Ji Nan and Yan Tai Prefectures of Shandong Province and Harbin and Qiqihar Prefectures of Heilongjiang Province. Their goals are to enhance surveillance for rubella, follow-up pregnant women suspected of having been infected, investigate children suspected of having CRS, and strengthen the birth defects surveillance system. During the period 2009–13, 1 670 children suspected of having CRS were reported, 661 from Heilongjiang and 1 009 from Shandong Province. Only five were laboratory confirmed, all from Heilongjiang Province.

During 2015, health authorities at the Chinese Center for Disease Control and Prevention (China CDC) began collaborating with mathematical modelers in assessing the burden of vaccine-preventable diseases and weighing alternative elimination strategies. In this study, we aimed to quantify the burden of CRS in China, to determine the optimal strategy for accelerating the elimination of rubella, and to estimate how long it would take. We refer to the 31 province-level jurisdictions (22 provinces, five municipalities and four autonomous administrative regions) comprising the People's Republic of China as provinces. Neither Taiwan nor the special administrative regions (Hong Kong and Macau) are included.

Methods

Immunity to Rubella

During 2014, health authorities conducted a national serological survey to assess the impact of efforts to mitigate the burden of hepatitis B virus infection.[11] The study population had resided for at least six months at locations selected by the Chinese Academy of Preventive Medicine (now Chinese Center for Disease Control and Prevention) by virtue of its representative demographic and socioeconomic characteristics. Authorities used multi-stage cluster sampling to enroll 31 024 people aged 1–29 years.

We tested 30 321 residual sera samples that were adequate in quality or quantity for rubella-specific immunoglobulin G antibodies (IgG) via Serion ELISA.[12] We considered an IgG titer of 10 IU per ml or greater to be evidence of protective immunity. We performed logistic regressions with single years of age modeled as third-order polynomials.[13] National, three regional and 31 provincial regressions provided proportions immune for our simulations and effective reproduction number calculations.

Supplemental Immunization Activities

After corroborating the reported uptake of RCV via the routine vaccination program, we considered Supplemental Immunization Activities (SIAs). One possible target is children who might have been vaccinated when younger had vaccine been available. Another is adults, especially reproductive-aged women, born before vaccination began. But we considered all possibilities.

Meta-population Modeling

As no single model would answer the questions posed as simply as possible, but not more so, we analyzed or simulated two models of rubella virus transmission in the Chinese population. They are stratified by immune status (susceptible to infection; infected, but not yet infectious; infectious; and recovered or immunized) and either by age (0, 1–4, 5–9, …, 65+ years) alone or also by spatial location.

We chose the susceptible, exposed, infectious, removed (SEIR) structure for our cross-classified or meta-population models (definitions) because the period between being infected and becoming infectious with rubella virus (called 'exposed' to avoid confusion with 'latent') is long relative to the infectious period. In our spatially stratified models, locations are either the 31 province-level jurisdictions of mainland China or three regional composites (nine eastern, 10 central and 12 western provinces).

In our age-stratified modeling, we use a mixing function with parameters from a study of face-to-face conversations, a proxy for contacts by which respiratory diseases might be transmitted. Because the age structure of observations from a study in Southern China[14] is too crude for accurate transmission modeling,[15] we use European ones.[16] In our age- and location-stratified modeling, we use a function by which contacts also decline exponentially with distance between locations at age-dependent rates.[17]

Calculations

From a pre-vaccination cross-sectional serological survey,[18] we calculated hazard rates (or forces) of infection among susceptible people (figure S1b) and proportions infectious in modeled age groups (figure S2b). Women with asymptomatic infections during their first trimesters may nonetheless bear children with CRS,[19] but we assumed only that 10% of those with serological evidence of infection were neither symptomatic nor consequently infectious. Using daily contact rates and proportions by age from the above-mentioned European study, we calculated age-specific probabilities of infection on contact with an infectious person (figure S3). These calculations are detailed in the Appendix, on pages 7–9.

Together with proportions immune from the serosurvey, periods between infection, onset of infectiousness, and recovery, and longevity from the literature, those rates and probabilities enabled us to estimate basic and effective reproduction numbers, denoted $\Re_0$ and $\Re_E$ and defined as average numbers of secondary infections per newly-infectious person in wholly- or partially-susceptible populations (definitions). The next-generation-matrix approach[20] also permits estimation of age-specific contributions to $\Re_0$ and equilibrium prevalence (figures S4). For age-stratified models without demographic dynamics, Glasser et al.[21] describe these calculations, whose results are illustrated in the Appendix, on pages 9–10. For age-stratified models with demographic dynamics, they are described by Feng et al.[22]

From our age- and province-stratified model, we calculated the reproduction numbers either via the next-generation matrix, which allows us to use the realistic mixing function described above, or an explicit expression derived by Feng et al.[17] that requires proportional mixing (definitions). This enables us to calculate the gradient of $\Re_E$ with respect to supplemental vaccination rates, $\nabla\Re_E$ (definitions), which provides information about the relative importance of strata in vaccine allocation; the proof can be found in section 3.6 of Feng et al.[23] Thus, this vector-valued quantity indicates the optimal means of reducing $\Re_E$ or allocating limited amounts of vaccine. Were the goal to descend a mountain (versus reduce $\Re_E$) quickly (e.g., were a storm approaching), the gradient would be the route of steepest descent.

Using national rubella uptake,[8] measles uptake by location,[15] and their temporal relationship (figure S5a), we estimated rubella uptake in all 31 provinces. Then, via the relationship between rates and proportions, we calculated routine vaccination rates (Appendix, page 12).

Simulations

While the policy goal is to accelerate rubella elimination, vaccinating susceptible adolescents (which the analyses described above identify as the optimal strategy) would protect reproductive-aged women from infection indirectly, whereas vaccinating susceptible young adults – a reasonable alternative – would protect them directly. Insofar as vaccine-induced immunity to rubella endures, moreover, immunized adolescent girls also would be protected directly when they reached their childbearing years.

Accordingly, we simulated rubella virus transmission in our age- and region-stratified SEIR model population, by evaluating the numerical solution of the system of ordinary differential equations described by Feng et al.,[17] with routine vaccination alone or also with SIAs among children aged 10–19 or adults 20–29 years (to which we refer as adolescents and young adults, respectively) beginning in 2018. Because differential equations exhibit damped oscillations, but rubella reports are seasonal, we force (definitions) the regional contact rates via a harmonic function whose coefficients we estimated from monthly disease surveillance during the period 2005–16. Because elimination is defined as reported annual incidence < 1 per 10^6 people and infections with mild if any symptoms inevitably are under-reported, we also scaled the contact rates to reproduce reported infections before assessing times-to-elimination. These calculations are detailed in the Appendix, on pages 12–14.

We performed those deterministic simulations and all calculations using Mathematica 12 (Wolfram Research, Inc.). In contrast, we simulated the transmission of rubella virus in our age-structured SEIR model population of 10^5 people having the age- and gender-distributions, immunity profile, vaccination rates and vital statistics of China in 2014 after making single individuals of various ages newly infectious via the discrete event/time method[24] (programmed by Denis Taneri in C++). In the Appendix, on pages 16–19, we describe our estimation of the risk of outbreaks, effective reproduction number (for comparison with that deduced from our age- and province-stratified model),[25] incidence of rubella, extent of under-reporting, and burden of CRS. As the global CRS assessment of Vynnycky et al.[26] included China, but our results differ, we compare their methods to ours in the Appendix, on pages 20–21.

Role of the funding sources

The sponsors had no role in the study design; in the collection, analysis, or interpretation of data; in the writing of this report; or in the decision to submit the paper for publication. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Results

Immunity to Rubella

In 2014, immunity was 95% among infants, declined to a nadir of about 80% among adolescents, and then increased to about 90% among young adults (figure 1). The nadir is oldest in the eastern provinces and progressively younger in the central and western ones.

Calculations

We estimate that rubella's basic and 2014 effective reproduction numbers in China are 7·6 and 1·2, respectively, with substantial heterogeneity among provinces (figure 2a). For these estimates, we used our age- and province-stratified SEIR model[17] with proportions susceptible by age and location from the 2014 serological survey (figures S13a), age-specific contact rates that vary with inter-province distances, and age-specific probabilities of infection on contact with infectious people (figure S3).

The ratios $\Re_{Ei}/\Re_{0i}$ are interpretable as proportions of provincial populations that are susceptible (figure 2b) because (without current vaccination) provincial effective reproduction numbers $\Re_{Ei}$ are products of provincial basic numbers $\Re_{0i}$ and proportions susceptible (definitions). The numbers illustrated in figures 2 are tabulated in the Appendix, on pages 10–12. We are not aware of comparable estimates of the effective reproduction number, but our basic number is within the range reported for rubella.[27]

The 2014 gradient $\nabla\Re_E$, illustrated by region in figures 3, identifies provinces – those whose magnitude is greatest – where vaccination would be most beneficial. But its direction consistently indicates that vaccinating adolescents would reduce rubella's $\Re_E$ in China the most. In the Appendix, on page 12, we describe how we estimated the requisite 2014 routine vaccination rates. Also in the Appendix, on pages 21–32, we present the gradient by province (figures S13b).

Simulations

Depending on newly infectious individual ages, 0·21 to 0·82 of the simulations of our stochastic SEIR model resulted in outbreaks (table S7). Assuming that infants are unlikely to initiate rubella outbreaks (i.e., older people are more likely to travel, be infected elsewhere and, on returning home, introduce the pathogen to their community), the average of the remaining proportions is 0·34, corresponding to an $\Re_E$ of 1·5,[25] which resembles our analytical result reported above.

The same plausible assumption yields estimates of the incidence of rubella and of pregnant women infected during their first trimesters, respectively, of 9·5 (95% CI 7·38, 11·65) and 0·051 (95% CI 0·039, 0·064) per 10^5 people during 2014 (averages of the estimates shown in figure 4). In our model population, 1 011 births occur per year on average, so approximately 5·1 children ([0·051/1 011]×100 000) could have been born with CRS per 10^5 live births that year.

As reported incidence was 8·7 per 10^6 people during 2014,[8] evidently only 9·1% of rubella infections were reported. These calculations are detailed in the Appendix, on pages 19–20. As the population of China was 1 367 881 995, we estimate that 700 children could have been born with CRS during 2014. Inasmuch as women with first trimester symptomatic infections may elect to terminate their pregnancies, fewer such children may in fact have been born.

Simulation of our age- and region-stratified model indicates that, conditional on routine vaccination, SIAs among susceptible people could accelerate elimination of rubella and CRS (adolescent results shown in figures 5), with times-to-elimination being shorter for adolescents than young adults (e.g., 5 and 7 years, respectively, for 15% uptake). Thus, while the gradient is for 2014 and simulated SIAs began in 2018, results from our province- and region-stratified models of the Chinese population are consistent.

Moreover, we found that vaccinating susceptible adolescents would be twice as effective as young adults in reducing CRS (figures 6a and b) and almost three times as effective in reducing the incidence of rubella (figures 6c and d). Adolescent vaccination would reduce infections in vaccinated and unvaccinated age classes similarly, whereas unvaccinated age classes would benefit the most from young adult vaccination.

Discussion

To evaluate SIAs by which health authorities might best eliminate rubella and CRS from China, we modeled transmission of rubella virus among members of the population stratified by immune status and either age alone or together with location. We estimated initial conditions and most parameters from cross-sectional serological surveys, disease surveillance and demographic observations of the Chinese population during 2014. By simulating an age-stratified model, we estimated the incidence of rubella, extent of under-reporting, and burden of CRS. By analyzing an age- and province-stratified model, we determined the optimal strategy for eliminating these diseases. As elimination is defined in terms of reported infections, we corroborated and extended those analytical results by simulating SIAs representing the optimal strategy and a reasonable alternative using an age- and region-stratified model with person-to-person contact rates scaled and seasonally forced to reproduce surveillance reports.

Causal relations between natural phenomena are most easily recognized if they are distinct and follow one another in close succession. However, congenital defects become apparent long after typically mild if any symptoms of maternal rubella infection. Active surveillance or investigation of birth defects are resource-intensive activities, and resources may not be available for those purposes, even in developed countries. Consequently, demographically realistic modeling is the most reliable means of assessing the burden of CRS. While some women with first-trimester symptomatic infections may have terminated their pregnancies, we estimated the number of Chinese children who could have been born with CRS in 2014. Depending on whether we use reported or simulated female infections, our estimates are 38 or 700, roughly an 18-fold difference. As both calculations rely on live birth rates, neither includes the spontaneous abortions, fetal deaths and stillbirths due to maternal rubella infections.

Our estimate of the incidence of CRS in 2014, 5·1 per 10^5 live births, is roughly 5 times that of Vynnycky et al.[26] This discrepancy seems largely attributable to different estimates from the same observations of the forces or hazard rates of infection among adults. In the Appendix, on pages 16–19 and 20–21, we describe our calculations in detail and comment on those authors' methods, respectively. With one exception, the preconception care program,[28] contemporary reports of rubella susceptibility throughout China[29–32] resemble ours (figure 1; Appendix, pages 21–32).

The indirect effect of vaccination – a reduction in the force of infection that unvaccinated people experience by virtue of the vaccination of others – is evident whenever uptake increases slowly, as it typically does at the beginning of vaccination programs or upon the addition of new vaccines to established programs. A RCV was licensed in China in 1993 and added to the EPI in 2008, but was in short supply until 2011, and even then, uptake was only 80% of measles-containing vaccines (figure S5). Given the limited availability of vaccine, RCV was introduced without a wide-age-range catch-up campaign,[8] as recommended by the WHO. Thus, the susceptible adolescents illustrated in figures 1 were protected from infection when they were younger by the vaccination of others. In 2014, most younger people had been vaccinated while virtually all older ones had been infected.

Experience with measles vaccination, which began in 1965, informed China's rubella vaccination program. In 1978, when the EPI was established in China, the routine childhood schedule included single-antigen measles vaccine at eight months of age. Authorities recommended that children aged 7 years receive a second dose in 1986, but – motivated by the age-distribution of reported infections – in 2005 changed the recommended age to 18 to 23 months. Upon addition to the EPI, uptake of RCV was both faster and more consistent among provinces than that of measles-containing-vaccines.[15] Consequently, despite multiple outbreaks and numerous SIAs since 1965, some national and others regional, measles susceptibility presently is concentrated among adults,[33] with considerable residual heterogeneity.[15]

Our demographically realistic model of rubella transmission in a small, spatially homogeneous, but otherwise representative population incorporates the chance nature of encounters between infectious and susceptible people and other events. Roughly 1/3 of simulations beginning with single newly infectious people aged 1–44 years resulted in outbreaks with routine vaccination alone. The resulting estimate of the effective reproduction number is consistent with that from our age- and province-specific model of the entire Chinese population, suggesting that rubella elimination is within reach. But the large outbreak that occurred during 2019 involved primarily adolescents and reproductive-aged adults (cf. figure S10b),[34] underscoring the urgency of mitigation efforts.

Currently, kindergarten and elementary school staff in China are supposed to review the vaccination records of entering children and refer those lacking evidence of two doses of measles- and rubella-containing vaccine to their community health clinics. However, during 2014 an outbreak occurred in a middle school in Guangzhou where vaccine coverage was only 25·8%.[29] To reinforce the importance of school-entry vaccination record reviews, identify schools whose students are inadequately protected, and mitigate concern about vaccinating the same children repeatedly, health authorities envision middle and high school staff checking the records of three successive entering classes and nurses from the local community health clinic vaccinating on site any child who cannot demonstrate adequate protection. Such a school-based catch-up effort will accomplish what a wide-age-range catch-up campaign during RCV introduction would have accomplished had vaccine supply sufficed.

Using our age- and location-stratified model, we estimate that rubella virus could be eliminated from China within 5 years if at least 15% of susceptible or incompletely protected adolescents entering middle and high school were vaccinated during the first months of three successive fall terms. Were the measles-rubella (MR) or measles-mumps-rubella (MMR) vaccines used, these campaigns also could accelerate measles elimination despite the disparate age-susceptibilities to measles and rubella in China.[15]

Limitations

In our age- and location-stratified modeling, we use a two-dimensional mixing function whose age-specific contacts and rates of decline with distance we derived from a composite of face-to-face conversations observed in 8 European countries.[16] Those data resemble observations from southern China,[14] whose age-structure however is too crude for accurate transmission modeling. In the Appendix, on pages 7–9, we explain why we used the European observations themselves rather than a synthetic mixing matrix derived from them.[35] Our estimate of the basic reproduction number, derived using our function, is within the range of Bayesian estimates using various hypothetical mixing matrices.[27]

We simulated a demographically realistic SEIR model to assess the incidence of rubella, extent of under-reporting, risk of outbreaks, and burden of CRS. We used the best information available for parameters, initial conditions and mixing, but extrapolated results from a representative population of only 10^5 people. Simulations began with single newly infectious people aged 1–44 years and continued until infections no longer occurred, typically for 2–3 years. Because the Chinese population is more than 10^4 times larger than our model population and spatially heterogeneous, and because the interval between infection with rubella virus and the onset of infectiousness is relatively long, travelers infected elsewhere must frequently return home before becoming infectious. Consequently, our estimates of rubella and CRS incidence are based on simulations resulting in outbreaks.

We were unable to find recent birth rates by age of mother in Shandong and Heilongjiang Provinces, in the latter of which total fertility apparently is about half the Chinese average, so could not compare simulation results with the National Health Commission’s pilot CRS surveillance in Ji Nan and Yan Tai Prefectures of Shandong Province and Harbin and Qiqihar Prefectures of Heilongjiang Province.

Rubella is a mild disease, with as many as 50% of infections asymptomatic, so infections are under-reported and reporting may be age biased. Because disease elimination is a national phenomenon defined in terms of reported infections, we calibrated (i.e., adjusted the contact rates) our age- and region-stratified SEIR model of rubella to reproduce disease surveillance in China. Reports vary seasonally, but systems of ordinary differential equations exhibit damped oscillations, so we also forced them via a harmonic function whose coefficients we estimated from surveillance (Appendix, pages 12–14). Neither of these adjustments should have affected the relative impact of simulated SIAs.

We made these meta-population models for different proximate, but the same ultimate purpose, to inform public health decision-making. Because one is calibrated and others are not, results are comparable qualitatively, but not quantitatively. While our demographically realistic model’s predictions are as accurate as humanly possible, moreover, we subscribe to the view that “Truth … is much too complicated to allow anything but approximations.”[36]

Research in Context

Evidence before this Study

We searched for publications using the words “rubella”, “congenital rubella syndrome”, and “China” since 2015 because the Chinese CDC and WHO office in China jointly hosted a consultation on measles and rubella elimination during November of 2016. In preparation, staff compiled the information since published by Su et al.,[8] results of cross-sectional serological surveys of rubella-specific IgG antibodies during 2014,[12] and other information about the epidemiology of rubella and mitigation efforts in the provinces, municipalities and autonomous regions of mainland China. Subsequently, they compiled recommendations for the National Health and Family Planning Commission.

Added Value of this Study

The authors estimated parameters of several meta-population models of rubella virus transmission in the Chinese population from available information. By analyzing or simulating their models, they identified the risk of rubella outbreaks, extent of under-reporting, burden of CRS, and most effective strategy for reducing the average number of secondary infections per infectious person, which must remain below one to eliminate pathogens from host populations. By simulating SIAs among adolescents and young adults, the optimal strategy and an alternative, they corroborated their analytical results. They also determined that, while catch-up campaigns among susceptible adolescents during the first months of the next several school years are not optimal for measles,[15] using the combined measles-rubella or measles-mumps-rubella vaccine would accelerate elimination of the pathogens causing both diseases. How much would of course depend on uptake. Such campaigns also would avert impending outbreaks of rubella that, by virtue of the population-immunity profile, would substantially increase the burden of CRS.

Implications of all the Available Evidence

Sustained routine immunization likely would eliminate rubella virus from China eventually, but catch-up campaigns among susceptible adolescents or young adults could accelerate elimination, preventing rubella outbreaks among those adolescents who currently are susceptible before they age into their reproductive years. Transmission modeling is necessary to estimate the impact of vaccination accurately insofar as it depends on the absence of infections that immunized people would otherwise cause.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

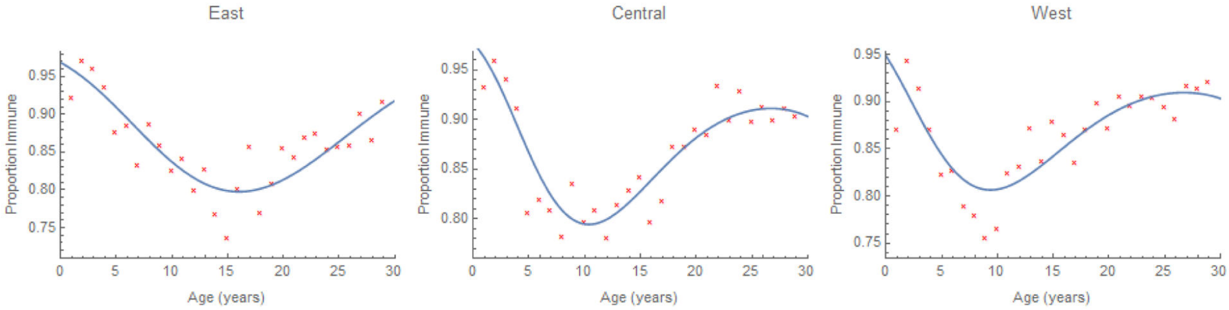
Acknowledgements

We are grateful to Andrew Hill and Glen Satten for advice about estimating incidence from stochastic simulations, to Andrew for the topographic analogy of the gradient, to Aaron Curns for drawing choropleth maps of the provincial reproduction numbers, and to Aaron and several anonymous reviewers for constructive critiques of earlier drafts of the manuscript.

References

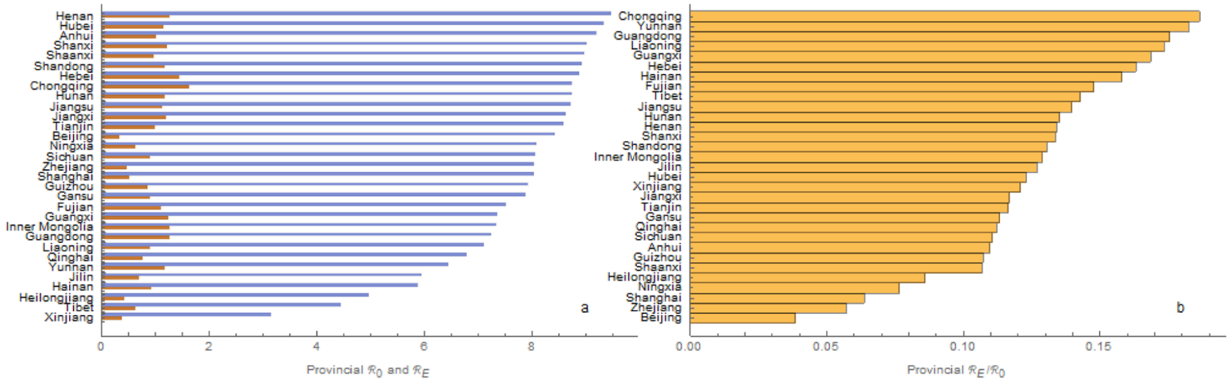
1. Reef SE, Plotkin SA. Rubella vaccines. Pp 970–1000 in Plotkin's Vaccines. 7th Ed. Plotkin SA, Orenstein WA, Offit PA, Edwards KM, eds. Philadelphia, PA: Elsevier, 2018
2. Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. Lancet 1982; 320:781–84
3. WHO, SAGE Working Group. Status report on progress towards measles and rubella elimination (http://www.who.int/immunization/sage/meetings/2012/november/1_Status_Report_Measles_Rubella_22_Oct.pdf)
4. WHO, Pan American Health Organization. Americas region is declared the world's first to eliminate rubella (http://www.paho.org/us/index.php?option=com_content&view=article&id=135:americas-region-free-of-rubella&Itemid=223&lang=en)
5. WHO, Western Pacific Regional Office. Measles and rubella elimination. WPR/RC68.R1 (http://www.wpro.who.int/about/regional_committee/68/resolutions/wpr_rc68_r1_measles_and_rubella_elimination.pdf?ua=1)
6. Zhao W, Wang Y, Jiang W, et al. Analysis on measles SIA and rubella massive vaccination in Zhou Kou city. Chin J Health Lab Technol (Chinese) 2002; 12:586
7. Wu C, Shu J, Han K, et al. Impact of different rubella immunization strategies on rubella in Guangdong province. Dis Surveill (Chinese) 2012; 27:110–13
8. Su Q, Ma C, Wen N, et al. Epidemiological profile and progress toward rubella elimination in China 10 years after nationwide introduction of rubella vaccine. Vaccine 2018; 36:2079–85 [PubMed: 29550193]
9. Zhu Z, Abernathy E, Cui A, et al. Rubella virus genotypes in the People's Republic of China between 1979 and 2007: a shift in endemic viruses during the 2001 Rubella Epidemic. J Clin Microbiol 2010; 48:1775–81 [PubMed: 20351211]
10. Ma C, Rodewald LE, Hao L, et al. Progress toward measles elimination – China, January 2013-June 2019. MMWR Morb Mortal Wkly Rep 2019; 68:1112–16 [PubMed: 31805034]
11. Cui F, Shen L, Li L, et al. Prevention of chronic hepatitis B after 3 decades of escalating vaccination policy, China. Emerg Infect Dis 2017; 23:765–72 [PubMed: 28418296]
12. Su Q, Zhu Z, Hao L, et al. The first population-based rubella serologic survey of 1–29 years old in China: are we close to rubella elimination? Manuscript (in preparation)
13. McCullagh P, Nelder JA. Generalized Linear Models. 2nd Ed. London, UK: Chapman and Hall, 1983
14. Read JM, Lessler J, Riley S, et al. Social mixing patterns in rural and urban areas of southern China. Proc R Soc B 2014; 281:20140268
15. Hao L, Glasser JW, Su Q, et al. Evaluating vaccination policies to accelerate measles elimination in China: a meta-population modeling study. Int J Epidemiol 2019; 48:1240–51 [PubMed: 30977801]
16. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med 2008; 5:381–91
17. Feng Z, Hill AN, Curns AT, Glasser JW. Evaluating targeted interventions via meta-population models with multi-level mixing. Math Biosci 2017; 287:93–104 [PubMed: 27671169]
18. Su W Rubella in the People's Republic of China. Rev Infect Dis 1985; 7:S72
19. Cooper LZ. Rubella, a preventable cause of birth defects. Birth Defects Orig Artic Ser 1968; 4:23–35
20. van den Driessche P, Watmough J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math Biosci 2002; 180:29–48 [PubMed: 12387915]
21. Glasser JW, Taneri D, Feng Z, et al. Evaluation of targeted influenza vaccination strategies via population modeling. PLoS ONE 2010; 5(9):e12777 (https://doi:10.1371/journal.pone.0012777) [PubMed: 20862297]
22. Feng Z, Feng Y, Glasser JW. Influence of demographically realistic mortality schedules on vaccination strategies in age-structured models. Theor Popul Biol 2020; 132:24–32 [PubMed: 32027879]

23. Feng Z, Hill AN, Smith PJ, Glasser JW. An elaboration of theory about preventing outbreaks in homogeneous populations to include heterogeneity or non-random mixing. J Theor Biol 2015; 386:177–87 [PubMed: 26375548]
24. Renshaw E Modeling Biological Populations in Space and Time. Cambridge, England: Cambridge Univ Press, 1991
25. Allen LJS, Lahodny GE. Extinction thresholds in deterministic and stochastic epidemic models. J Biol Dyn 2012; 6:590–611 [PubMed: 22873607]
26. Vynnycky E, Adams EJ, Cutts FT, et al. Using seroprevalence and immunisation coverage data to estimate the global burden of congenital rubella syndrome, 1996–2010: A systematic review. PLoS ONE 2016; 11(3): e0149160 (doi:10.1371/journal.pone.0149160) [PubMed: 26962867]
27. Kanaan MN, Farrington CP. Matrix models for childhood infections: a Bayesian approach with applications to rubella and mumps. Epidemiol Infect 2005; 133:1009–21 [PubMed: 16274497]
28. Zhou Q, Wang Q, Shen H, Zhang Y, Zhang S, Li X, Acharya G. Rubella virus immunization status in preconception period among Chinese women of reproductive age: A nation-wide, cross-sectional study. Vaccine 2017; 35:3076–81 [PubMed: 28456531]
29. Chang C, Ma H, Liang W, Hu P, Mo X, An Z, Zheng H. Rubella outbreak and outbreak management in a school setting, China, 2014. Hum Vaccines Immunother 2017; 13:772–75
30. Meng Q, Luo J, Li L, et al. Rubella seroprevalence among pregnant women in Beijing, China. BMC Infect Dis 2018; 18:130 [PubMed: 29544450]
31. He H, Yan R, Tang X, Zhou Y, Deng X, Xie S. Vaccination in secondary school students expedites rubella control and prevents congenital rubella syndrome. BMC Infect Dis 2016; 16:723 [PubMed: 27899091]
32. Lin W, Wang D, Xiong Y, Tang H, Liao Z, Ni J. Rubella Seroprevalence among the general population in Dongguan, China. Jpn J Infect Dis 2015; 68:192–95 [PubMed: 25672349]
33. Chong K, Zhang C, Jia KM, et al. Targeting adults for supplementary immunization activities of measles control in central China: A mathematical modelling study. Sci Rep 2018; 8:16124 (10.1038/s41598-018-34461-0) [PubMed: 30382120]
34. WHO. Western Pacific Regional Office. Measles-Rubella Bulletin 2019 (https://iris.wpro.who.int/handle/10665.1/14338)
35. Prem K, Cook AR, Jit M. Projecting social contact matrices in 152 countries using contact surveys and demographic data. PLoS Comput Biol 2017; 13:e1005697 (10.1371/journal.pcbi.1005697) [PubMed: 28898249]
36. von Neumann J The Mathematician. Pp 180–96 in Works of the Mind. RB Haywood, ed. Chicago, IL: Univ of Chicago Press, 1947



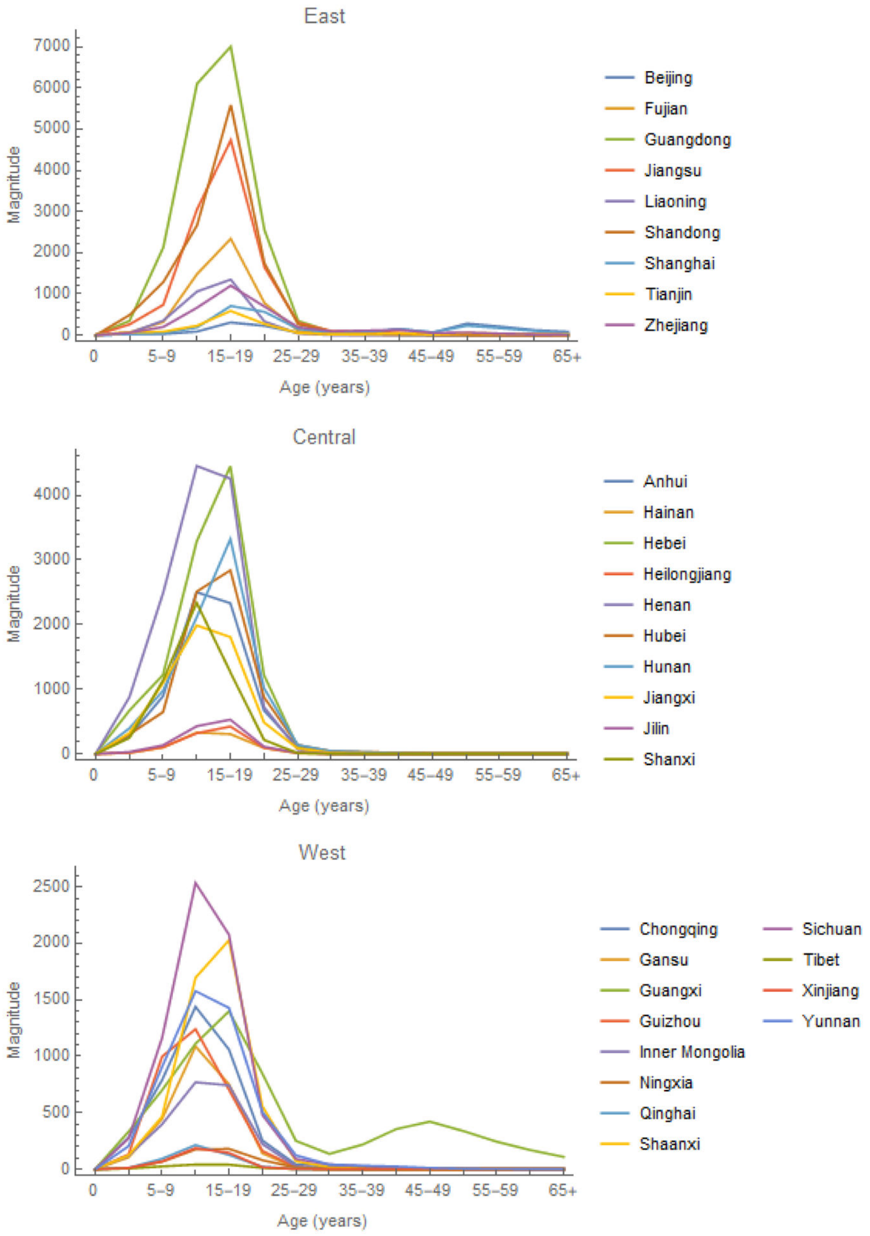
Figures 1.

Immunity to rubella in Eastern, Central and Western China, 2014. The curves are weighted logistic regressions with observations by single year of age modeled as cubic polynomials. Appendix pages 21–32 include provincial results.



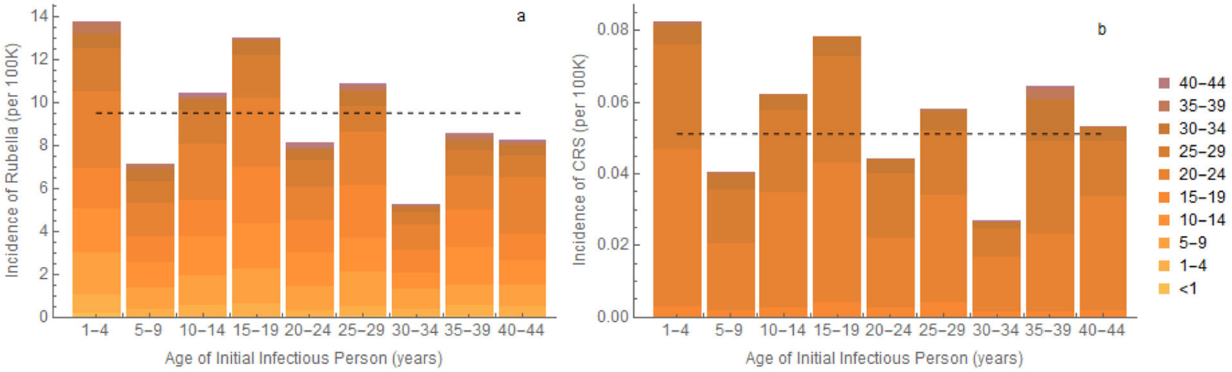
Figures 2.

Reproduction numbers and their ratios by province. a) Provincial basic $\Re_{0i}$ (blue bars) and 2014 effective $\Re_{\mathrm{E}i}$ (red bars) reproduction numbers range from 3·15 to 9·45 and from 0·32 to 1·45, respectively. b) Ratios $\Re_{\mathrm{E}i}/\Re_{0i}$ are interpretable as proportions of sub-populations i that are susceptible. We tabulate these numbers and ratios in the Appendix, on pages 10–12.



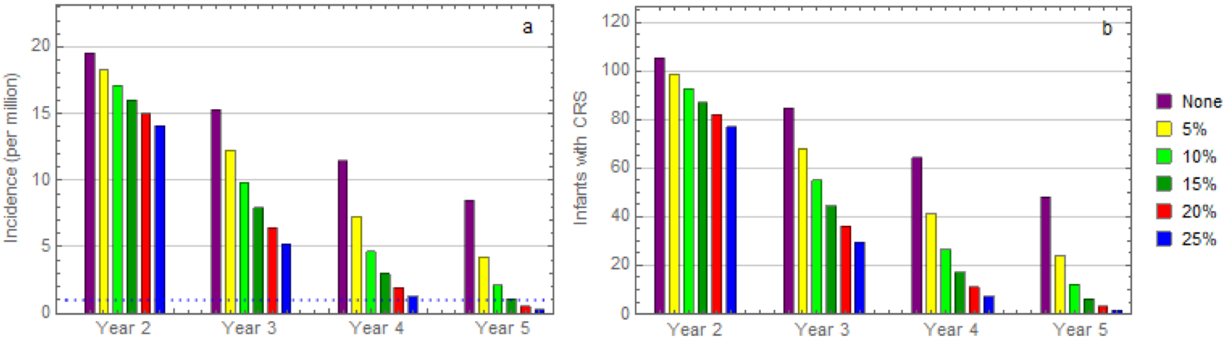
Figures 3.

Gradient of the 2014 effective reproduction number with respect to supplemental vaccination rates in Eastern, Central and Western China. Appendix pages 21–32 include provincial results.



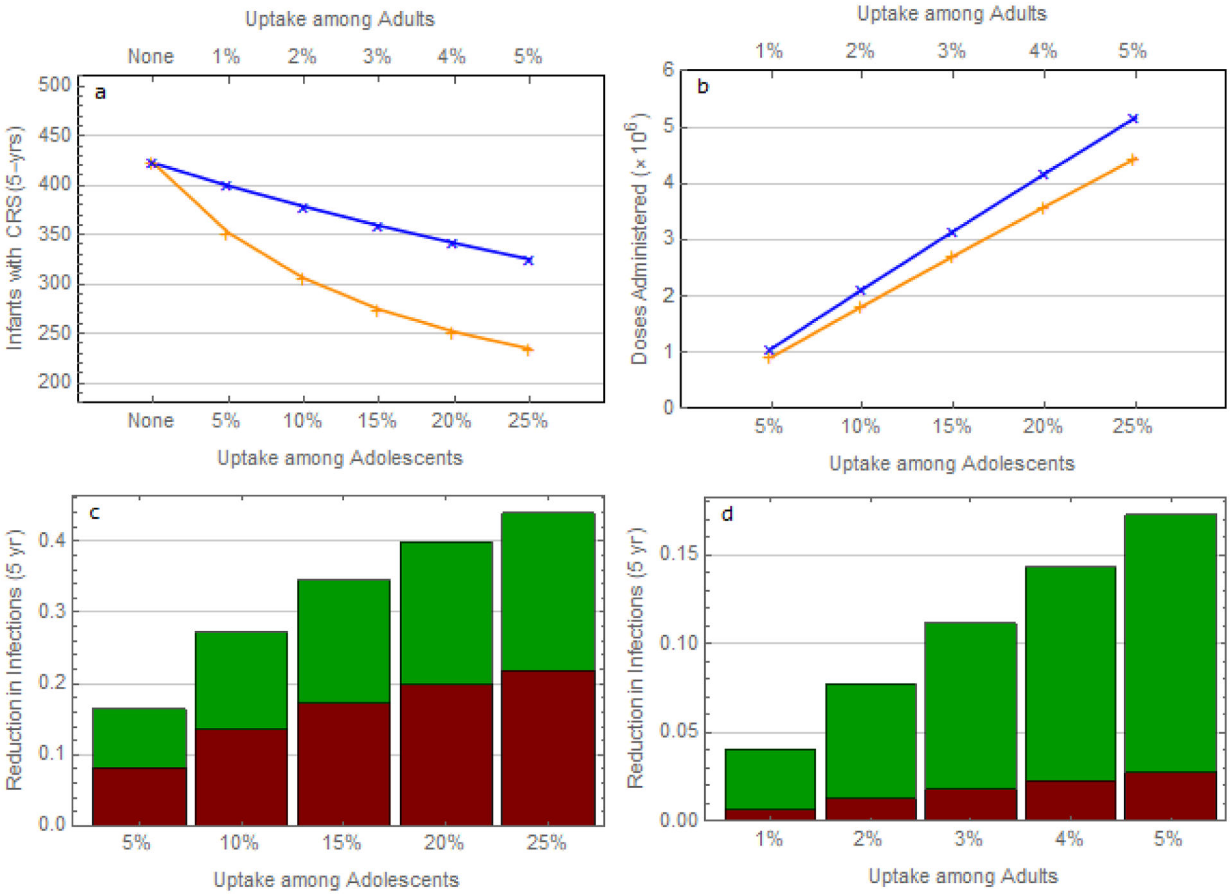
Figures 4.

Estimated annual incidence of a) rubella and b) CRS (both per 10^5 people) as functions of the age of the initial newly infectious person. Each bar represents 200 stochastic simulations, with shades indicating contributions by age in the case of rubella or age of mother in the case of CRS, and dotted lines averages over all ages of initial newly infectious people.



Figures 5.

Impact of SIAs among susceptible adolescents: a) time to rubella elimination (reported annual incidence of 1 per 10^6 people, the horizontal dotted line) and b) infants with CRS as functions of uptake.



Figures 6.

Comparisons of a) cumulative numbers of infants with CRS during a 5-year period with b) doses administered (× 10^6) during SIAs among susceptible adolescents (orange) and young adults (blue) and direct (dark red) with indirect (green) effects of c) adolescent and d) young adult vaccination. A greater proportion of young adults is immune (figure 1), but there are more of them than adolescents (table S5), so uptake is less among young adults than adolescents for similar numbers of doses.

Definitions

Quantity	Symbol	Meaning
Meta-population		A cross-classified or stratified population (a population composed of sub-populations)
Sub-population		One of 15 age groups and 3 or 31 spatial locations in our meta-population model of rubella in China
Effective reproduction number in sub-population i	$\Re_{\mathrm{E}i}$	Average numbers of secondary infections per primary in sub-populations $i = 1, \ldots, n$
Basic reproduction number in sub-population i	$\Re_{0i}$	Average numbers in wholly susceptible sub-populations $i = 1, \ldots, n$ (effective contacts while infectious)
Meta-population reproduction numbers	$\Re_{\mathrm{E}}$, $\Re_0$	Reproduction numbers in a meta-population composed of n sub-populations
Proportional mixing	$\frac{a_j N_j}{\sum_{k=1}^{n} a_k N_k}$	The probability of contacting a member of group j is proportional to the product of the number of people in that group, N_j and their *per capita* contact rate, a_j relative to the sum of this product over all n groups
Gradient	$\nabla \Re_{\mathrm{E}}$	Multi-variate partial derivative of meta-population $\Re_{\mathrm{E}}$ with respect to sub-population immunization rates
Routine immunization program		Vaccination against multiple pathogens on recommended schedules, typically consisting of primary series and booster doses
Supplemental immunization activities	SIAs	Campaigns to supplement the routine (generally childhood) immunization program
Seasonal forcing		External phenomena (e.g., school calendar) that affect internal ones (e.g., contact rates)