Assessing the burden of congenital rubella syndrome in China and evaluating mitigation strategies: a metapopulation modelling study

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For the Chinese translation of the abstract see Online for appendix 1

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Summary

Background **A rubella vaccine was licensed in China in 1993 and added to the Expanded Programme 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. We aimed to evaluate possible supplemental immunisation activities (SIAs) to accelerate elimination of rubella and congenital rubella syndrome.**

Methods **We analysed residual samples from the national serological survey done in 2014, data from monthly rubella surveillance reports from 2005 and 2016, and additional publications through a systematic review. Using an age-structured population model with provincial strata, we calculated the reproduction numbers and evaluated the gradient of the metapopulation effective reproduction number with respect to potential supplemental immunisation rates. We corroborated these analytical results and estimated times-to-elimination by simulating SIAs among adolescents (ages 10–19 years) and young adults (ages 20–29 years) using a model with regional strata. We estimated the incidence of rubella and burden of congenital rubella syndrome by simulating transmission in a relatively small population lacking only spatial structure.**

Findings **By 2014, childhood immunisation had reduced rubella's reproduction number from 7·6 to 1·2 and SIAs among adolescents were the optimal elimination strategy. We found that less than 10% of rubella infections were reported; that although some women with symptomatic first-trimester infections might have elected to terminate their pregnancies, 700 children could have been born with congenital rubella syndrome during 2014; and that timely SIAs would avert outbreaks that, as susceptible adolescents reached reproductive age, could greatly increase the burden of this syndrome.**

Interpretation **Our findings suggest that SIAs among adolescents would most effectively reduce congenital rubella syndrome as well as eliminate rubella, owing both to fewer infections in the immunised population and absence of infections that those immunised would otherwise have caused. Metapopulation models with realistic mixing are uniquely capable of assessing such indirect effects.**

Funding **WHO and National Science Foundation.**

Introduction

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

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 recognised, even symptomatic maternal infections might not be suspected of causing infant conditions, particularly those not diagnosed until long after birth (eg, hearing impairment, developmental delay). Finally, the spontaneous abortions, fetal deaths, and stillbirths that maternal rubella infections can cause are inestimable.

As rubella is a vaccine-preventable disease, during May of 2012, the World Health Assembly endorsed its elimination by 2020 as a goal for five of the 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 South 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 km².

Research in context

Evidence before this study

We searched for publications on May 8, 2020, using the terms "rubella", "congenital rubella syndrome", and "China" since 2015 because the Chinese Center for Disease Control and Prevention and WHO Country Office in China jointly hosted a consultation on measles and rubella elimination on Nov 21–26, 2016. In preparation, staff compiled the information published by Su and colleagues, results of a cross-sectional serological survey of rubella-specific IgG antibodies during 2014 (unpublished), 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

We estimated parameters of several metapopulation models of rubella virus transmission in the Chinese population from available information. By analysing or simulating our models, we identified the risk of rubella outbreaks, extent of under-reporting, burden of congenital rubella syndrome, and most effective strategy for reducing the average number of secondary infections per infectious person, which must remain below 1 to eliminate pathogens from host populations. By simulating supplemental immunisation activities among adolescents and young adults, the optimal and an alternative strategy, we corroborated our analytical results. We also determined that, although catch-up campaigns among susceptible adolescents during the first months of the next several school years are not optimal for measles, using the combined measles–rubella or measles–mumps–rubella vaccine would accelerate elimination of the pathogens causing both diseases. The extent of acceleration 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 congenital rubella syndrome.

Implications of all the available evidence

Sustained routine immunisation 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 modelling is necessary to estimate the impact of vaccination accurately insofar as it depends on the absence of infections that immunised people would otherwise cause.

A rubella-containing vaccine was first licensed in China in 1993. Until 2008, some provinces offered this vaccine among their routine services, but parents were responsible for the cost.[6,7] In 2008, China extended the Expanded Programme on Immunization (EPI) to include rubella-containing vaccine, which began being offered without charge among routine immunisation services. Measles–rubella vaccine was used for the first dose at 8 months and measles–mumps–rubella vaccine for the second at 18–23 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 rubella-containing vaccines became available, administrative estimates of routine uptake (ie, 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 hospitalised case reports at prefecture-level Centers for Disease Control and Prevention (CDCs) and integration at the national CDC. During the period from 2004 to 2013, reported incidence peaked at 9·11 per 1 million people during 2008.[8] In 2014, rubella was integrated into the measles surveillance system, whereupon case-based, laboratory-supported surveillance began being done routinely. This system has met or exceeded WHO surveillance quality criteria continuously since 2011.[10] Reported incidence declined to 1·22 per 1 million people by 2017, but increased to 2·83 per 1 million 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 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 congenital rubella syndrome, and strengthen the birth defects surveillance system. During the period 2009–13, 1670 children suspected of having congenital rubella syndrome were reported, 661 from Heilongjiang and 1009 from Shandong province. Only five were laboratory confirmed, all from Heilongjiang province.

During 2015, health authorities at the Chinese CDC (China CDC) began collaborating with mathematical modellers in assessing the burden of vaccine-preventable diseases and weighing alternative elimination strategies. In this study, we aimed to quantify the burden of congenital rubella syndrome in China, to determine the optimal strategy for accelerating the elimination of rubella, and to estimate how long it would take. We refer

Panel: Key terms and symbols used in this Article

Basic reproduction number in subpopulation *i* (R_{0i})
Average numbers of secondary infections in wholly susceptible subpopulations i=1,..., n (effective contacts while infectious)

Effective reproduction number in subpopulation *i* (R_{Ei})
Average numbers of secondary infections per primary infection in subpopulations i=1,..., n

Subpopulation
One of 15 age groups and three or 31 spatial locations in our metapopulation models of rubella in China

Metapopulation
A cross-classified or stratified population (a population composed of subpopulations)

See Online for appendix 2

Metapopulation reproduction numbers (R_E, R_0)
Reproduction numbers in a metapopulation composed of n subpopulations

Gradient (∇R_E)
Multivariate partial derivative of R_E with respect to subpopulation immunisation rates

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

Routine immunisation programme
Vaccination against multiple pathogens on recommended schedules, typically consisting of primary series and booster doses

Seasonal forcing
Phenomena that are not modelled (eg, school calendar) that affect modelled ones (eg, contact rates)

Supplementary immunisation activities (SIAs)
Campaigns to supplement the routine (generally childhood) immunisation programme

to the 31 province-level jurisdictions (22 provinces, five municipalities, and four autonomous administrative regions) comprising mainland China. Neither Taiwan nor the special administrative regions (Hong Kong and Macau) are included.

Methods

Immunity to rubella and SIAs

During 2014, health authorities did 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 6 months at locations selected by the Chinese Academy of Preventive Medicine (now China CDC) by virtue of their representative demographic and socioeconomic characteristics. Authorities used multi-stage cluster sampling to enrol 31 024 people aged 1–29 years. We tested 30 321 residual sera samples that were adequate in quality or quantity for rubella-specific IgG antibodies via Serion ELISA (Institut Virion/Serion, Würzburg, Germany; unpublished). We considered an IgG titre of 10 IU per mL or greater to be evidence of protective immunity. We did logistic regressions with single years of age modelled as third-order polynomials.[12] National, three regional, and 31 provincial regressions provided proportions immune for our simulations and effective reproduction number (R_E) calculations.

After corroborating the reported uptake of rubella-containing vaccine via the routine vaccination programme (appendix 2 p 12), we considered 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. However, we considered all possible age groups.

Metapopulation modelling

As no single model would answer the questions posed as simply as possible, we analysed or simulated two models of rubella virus transmission in the Chinese population. The models were stratified by immune status (susceptible to infection, infected but not yet infectious, infectious, and recovered or immunised) and either by age (0, 1–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, ≥65 years) alone or also by spatial location.

We chose the susceptible, exposed, infectious, removed (SEIR) structure for our metapopulation models (panel) 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, ten central, and 12 western provinces).

In our age-stratified modelling, we use a mixing function with parameters from a study of face-to-face conversations, a proxy for contacts by which respiratory pathogens might be transmitted. Because the age structure of observations from a study in southern China[13] is too crude for accurate transmission modelling,[14] we use European ones.[15] In our modelling stratified by age and location, we use a function by which contacts also decline exponentially with distance between locations at age-dependent rates.[16]

Calculations

From a pre-vaccination cross-sectional serological survey,[17] we calculated hazard rates (or forces) of infection among susceptible people and proportions infectious in modelled age groups. Women with asymptomatic infections during their first trimesters might nonetheless bear children with congenital rubella syndrome,[18] 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 European study,[18] we calculated age-specific probabilities of infection on contact with an infectious person. These calculations are detailed in appendix 2 (pp 7–9).

Together with proportions immune from the 2014 serosurvey, periods between infection, onset of infectiousness, and recovery, and longevity, those rates and probabilities enabled us to estimate the metapopulation reproduction numbers, defined as average numbers of secondary infections per newly infectious person in wholly (R_0) or partially (R_E) susceptible populations (panel). The next-generation-matrix approach[19] permits estimation of age-specific contributions to R_0 and equilibrium prevalence. For age-stratified models without demographic dynamics, Glasser and colleagues[20] describe these calculations, the results of which are illustrated in appendix 2 (pp 9–10). For age-stratified models with demographic dynamics, they are described by Feng and colleagues.[21]

From our model stratified by age and province, we calculated the reproduction numbers either via the next-generation matrix, which allows us to use the realistic mixing function described here, or an explicit expression derived by Feng and colleagues[16] that requires proportional mixing (panel). This approach enables us to calculate the gradient of R_E with respect to supplemental vaccination rates, ∇R_E (panel), which provides information about the relative importance of strata in vaccine allocation; the proof can be found in section 3.6 of Feng and colleagues.[22] Thus, this vector-valued quantity indicates the optimal means of reducing R_E or allocating limited amounts of vaccine. Were the goal to descend a mountain (versus reduce R_E) quickly (eg, were a storm approaching), the gradient would be the route of steepest descent.

Using data on national rubella vaccine uptake,[8] measles vaccine uptake by location,[14] and their temporal relationship, we estimated rubella vaccine uptake in all 31 provinces. Then, via the relationship between rates and proportions, we calculated routine vaccination rates (appendix 2 p 12).

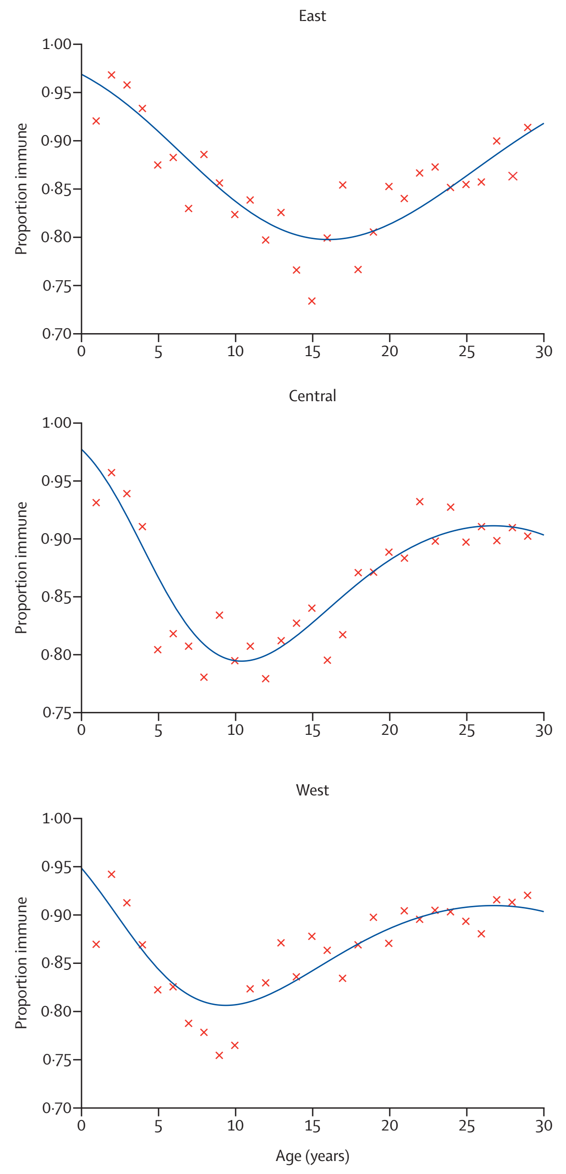

Figure 1: **Immunity to rubella in eastern, central, and western China, 2014**
The curves are weighted logistic regressions with observations by single year of age modelled as cubic polynomials. Provincial results are included in appendix 2 (pp 21–32).

Simulations

Although the policy goal is to accelerate rubella elimination, vaccinating susceptible adolescents would protect reproductive-aged women from infection indirectly, whereas vaccinating susceptible young adults would protect them directly. Insofar as vaccine-induced immunity to rubella endures, immunised adolescent girls would also be protected directly when they reached their childbearing years.

Accordingly, we simulated rubella virus transmission in our SEIR model population stratified by age and region, by evaluating the numerical solution of the system of ordinary differential equations described by Feng and colleagues,[16] with routine vaccination alone or also with SIAs among children aged 10–19 years or adults aged 20–29 years (to whom we refer as adolescents and young adults, respectively) beginning in 2018. Because differential equations exhibit damped oscillations, but rubella reports are seasonal, we forced (panel) 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 of

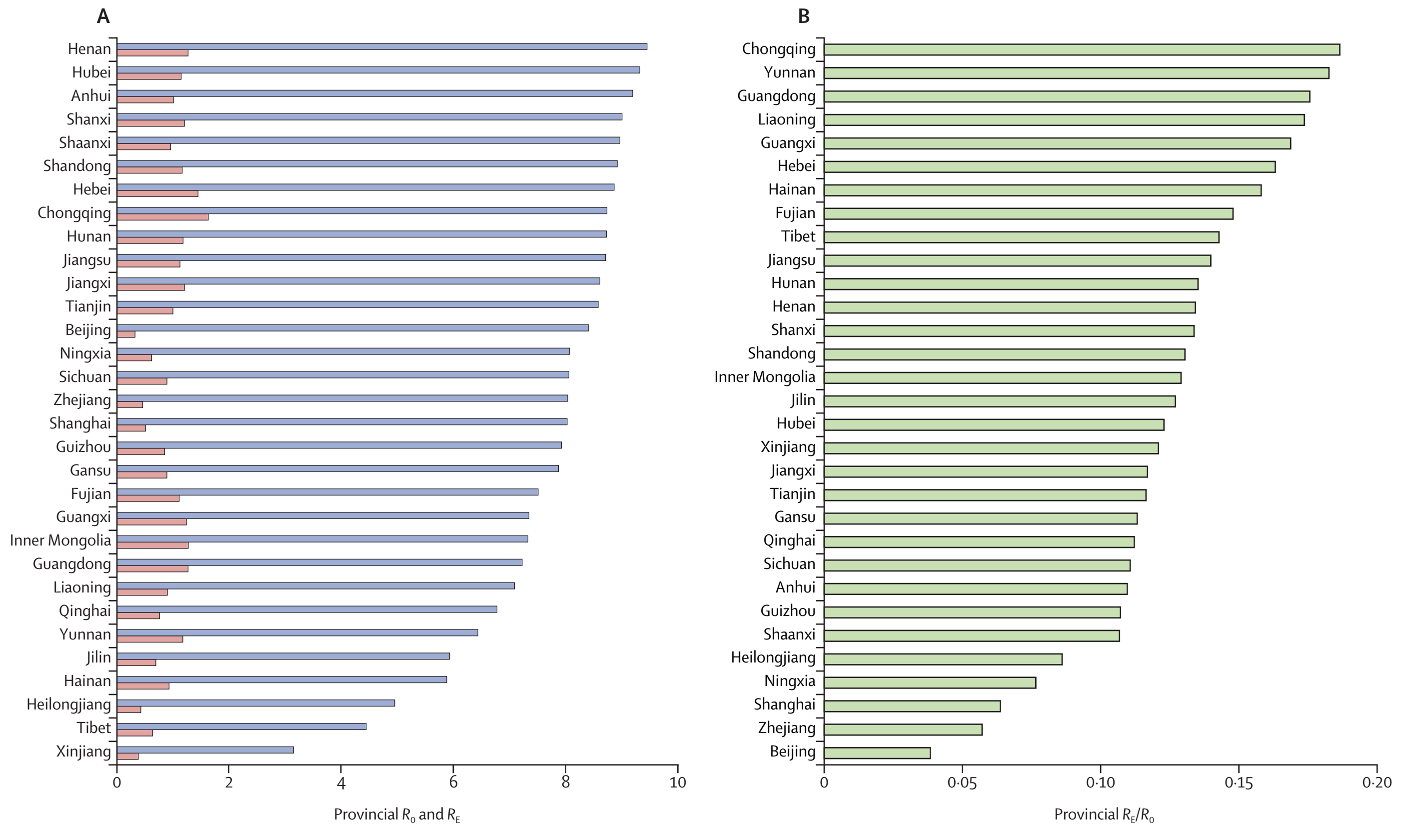

Figure 2: **Reproduction numbers and their ratios by province**
(A) Provincial R_{0i} (blue bars) and 2014 R_{Ei} (red bars) estimates range from 3·15 to 9·45 and from 0·32 to 1·45, respectively. (B) Ratios R_{Ei}/R_{0i} are interpretable as proportions of subpopulations *i* that are susceptible. We tabulate these numbers and ratios in appendix 2 (pp 10–12). R_{0i}=basic reproduction number in subpopulation *i*. R_{Ei}=effective reproduction number in subpopulation *i*.

less than one per 1 million people and infections with mild or no symptoms inevitably are underreported, we also scaled the contact rates to reproduce reported infections before assessing times-to-elimination. These calculations are detailed in appendix 2 (pp 12–14).

We did the deterministic simulations and all calculations using Mathematica 12 (Wolfram Research, Champaign, IL, USA). We simulated the transmission of rubella virus in our age-structured SEIR model population of 100 000 people with the age and sex 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[23] (programmed in C++). In appendix 2 (pp 16–19), we describe our estimation of the risk of outbreaks, R_E (for comparison with that deduced from our model stratified by age and province),[24] incidence of rubella, extent of under-reporting, and burden of congenital rubella syndrome. As the global burden assessment of Vynnycky and colleagues[25] included China, but our results differ, we compare their methods to ours in appendix 2 (pp 20–21).

Role of the funding source

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 for publication.

Results

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. We estimate that rubella's R_0 and 2014 R_E in China are 7·6 and 1·2, respectively, with substantial heterogeneity among provinces (figure 2). For these estimates, we used our SEIR model stratified by age and province[16] with proportions susceptible by age and location from the 2014 serological survey (appendix 2 pp 22–32), age-specific contact rates that vary with inter-province distances, and age-specific probabilities of infection on contact with infectious people (appendix 2 p 9).

The ratios R_{Ei}/R_{0i} are interpretable as proportions of provincial populations that are susceptible (figure 2) because (neglecting current vaccination) provincial effective reproduction numbers (R_{Ei}) are products of provincial basic numbers (R_{0i}) and proportions susceptible (panel). The numbers illustrated in figure 2 are tabulated in appendix 2 (pp 10–12). We are not aware of comparable estimates of the R_E, but our R_0 is within the range reported for rubella.[26]

The 2014 gradient ∇R_E, illustrated by region in figure 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 R_E in China the most. In appendix 2 (p 12), we describe how we estimated the requisite 2014 routine vaccination rates. Also in appendix 2 (pp 21–32), we present the gradient by province.

Depending on newly infectious individual ages, 0·21 to 0·82 of the simulations of our stochastic SEIR model resulted in outbreaks (appendix 2 p 19). Assuming that infants are unlikely to initiate rubella outbreaks (ie, older people are more likely to travel, be infected elsewhere, and, on returning home, introduce the pathogen to their communities), the average of the remaining proportions is 0·34, corresponding to an R_E of 1·5,[24] which resembles our analytical result of 1·2.

The same plausible assumption yields estimates of the incidence of rubella of 9·5 (95% CI 7·38–11·65) and of congenital rubella syndrome of 0·051 (0·039–0·064) per 100 000 people during 2014 (averages of the estimates shown in figure 4). In our model population, 1011 births occur per year on average, so approximately 5·1 children ([0·051 / 1011] × 100 000) could have been born with congenital rubella syndrome per 100 000 livebirths that year.

As the reported incidence was 8·7 per 1 million people during 2014,[8] evidently only 9·1% of rubella infections were reported. These calculations are detailed in appendix 2 (pp 19–20). As the population of China was 1 367 881 995, we estimate that 700 children could have been born with congenital rubella syndrome during 2014. Inasmuch as women with first-trimester symptomatic infections can elect to terminate their pregnancies, fewer such children might in fact have been born.

Simulation of our model stratified by age and region indicates that, conditional on routine vaccination, SIAs among susceptible people could accelerate elimination of rubella and congenital rubella syndrome (adolescent results shown in figure 5), with times-to-elimination being shorter for adolescents than young adults (eg, 5 and 7 years, respectively, for 15% uptake, adult results not shown). Thus, although the gradient is for 2014 and simulated SIAs began in 2018, results from our models of the Chinese population stratified by province and region are consistent.

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

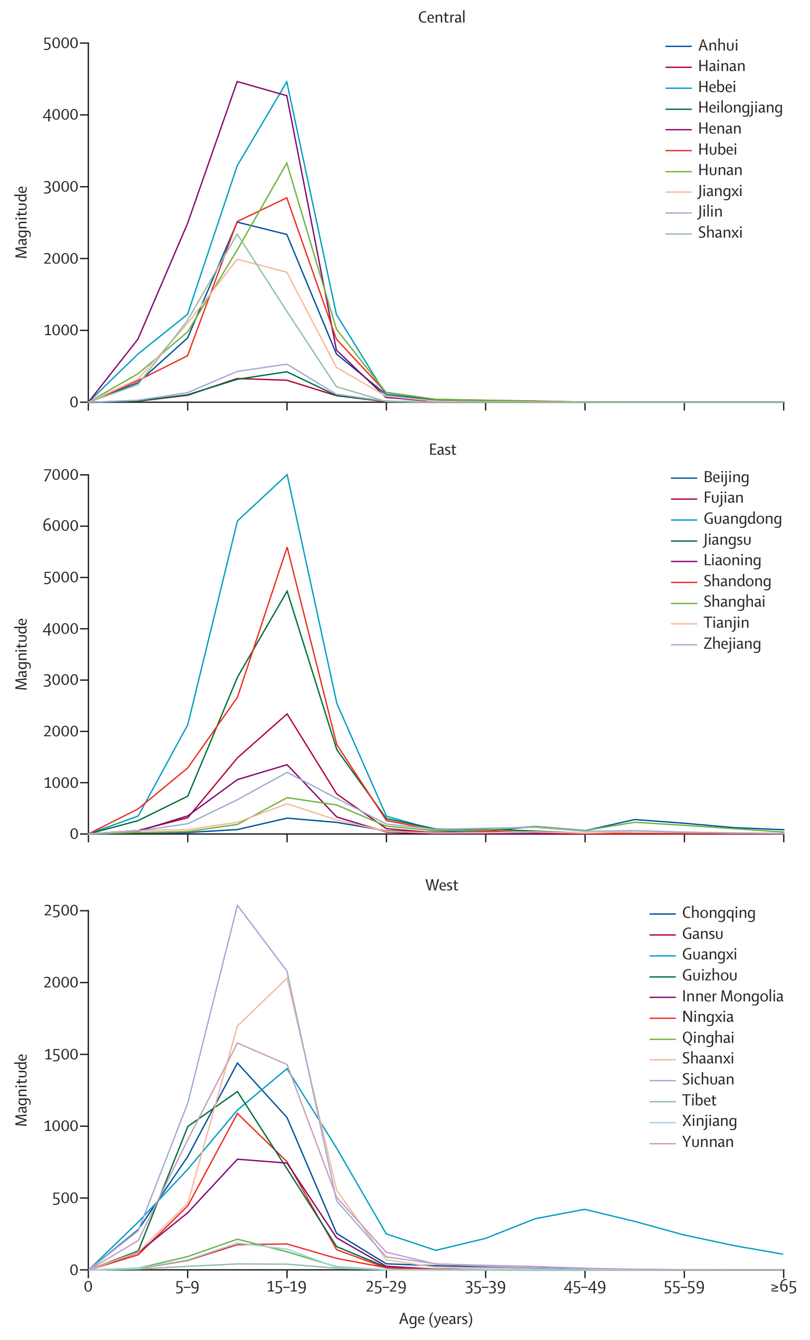

Figure 3: **Gradient of the 2014 effective reproduction number with respect to supplemental immunasation rates in eastern, central, and western China**
Provincial results are included in appendix 2 (pp 21–32).

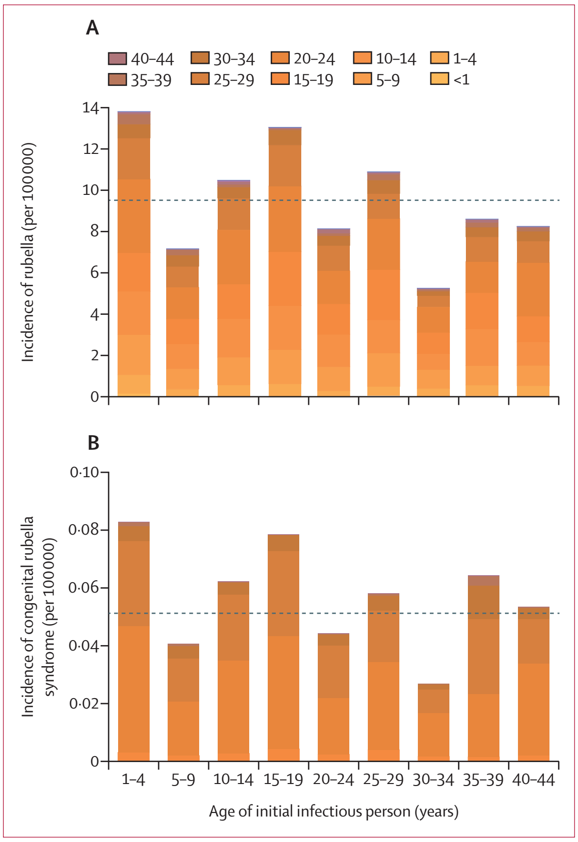

Figure 4: **Estimated annual incidence of (A) rubella and (B) congenital rubella syndrome (per 100 000 people) as functions of the age of the initial newly infectious person**

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 congenital rubella syndrome. Dotted lines represent averages over all ages of initial newly infectious people.

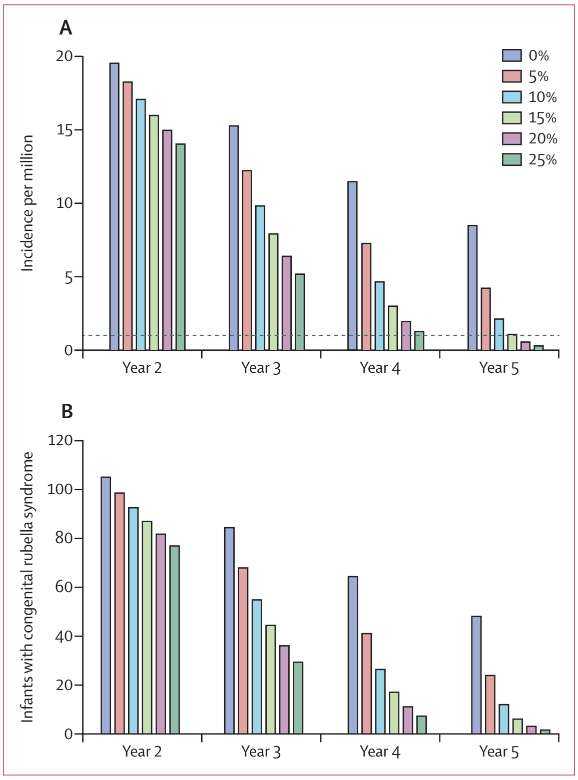

Figure 5: **Impact of supplemental immunisation activities among susceptible adolescents**

(A) Time to rubella elimination (reported annual incidence of one per 10^6 people, the horizontal dotted line) and (B) elimination of congenital rubella syndrome as functions of rubella vaccine uptake.

Discussion

To evaluate SIAs by which health authorities might eliminate rubella and congenital rubella syndrome from China, we modelled 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 characteristics 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 congenital rubella syndrome. By analysing a model stratified by age and province, 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 a model stratified by age and region with person-to-person contact rates scaled and seasonally forced to reproduce surveillance reports.

Causal relations between natural phenomena are most easily recognised 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 might not be available for those purposes, even in developed countries. Consequently, demographically realistic modelling is the most reliable means of assessing the burden of congenital rubella syndrome. Although some women with first-trimester symptomatic infections might have terminated their pregnancies, we estimated the number of Chinese children who could have been born with congenital rubella syndrome in 2014. Depending on whether we use reported or simulated female infections, our estimates are 38 (appendix 2 pp 14–15) or 700, respectively, roughly an 18-fold difference. As both calculations rely on livebirth rates, neither includes the spontaneous abortions, fetal deaths, and stillbirths due to maternal rubella infections.

Our estimate of the incidence of congenital rubella syndrome in 2014, 5·1 per 100 000 livebirths, is roughly five times that of Vynnycky and colleagues.[25] This discrepancy seems largely attributable to different estimates from the same observations of the forces or hazard rates of infection among adults. In appendix 2 (pp 16–19 and 20–21, respectively), we describe our calculations in detail and comment on those authors' methods. With one exception, the preconception care programme,[27] contemporary reports of rubella susceptibility throughout China[28–31] resemble ours (figure 1; appendix 2 pp 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 programmes or upon the addition of new vaccines to established programmes. A rubella-containing vaccine 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 (appendix 2 p 12). Given its limited availability, rubella-containing vaccine was introduced without a wide-age-range catch-up campaign,[8] as recommended by WHO. Thus, the susceptible adolescents illustrated in figure 1 were protected from infection when they were younger by the vaccination of others. In 2014, most younger immune people had been vaccinated, whereas virtually all older ones had been infected.

Experience with measles vaccination, which began in 1965, informed China's rubella vaccination programme. In 1978, when the EPI was established in China, the routine childhood schedule included single-antigen measles vaccine at 8 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 18–23 months. Upon addition to the EPI, uptake of rubella-containing vaccine was both faster and more consistent among provinces than that of measles-containing-vaccines.[14] Consequently, despite multiple outbreaks and numerous SIAs since 1965, some national and others regional, measles susceptibility presently is concentrated among adults,[32] with considerable residual heterogeneity.[14]

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 a third of simulations beginning with single newly infectious people aged 1–44 years resulted in outbreaks with routine vaccination alone. The resulting estimate of R_E is consistent with that from our model of the entire Chinese population stratified by age and province, suggesting that rubella elimination is within reach. But the large outbreak that occurred during 2019 involved primarily adolescents and reproductive-aged adults (appendix 2 p 18),[33] 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

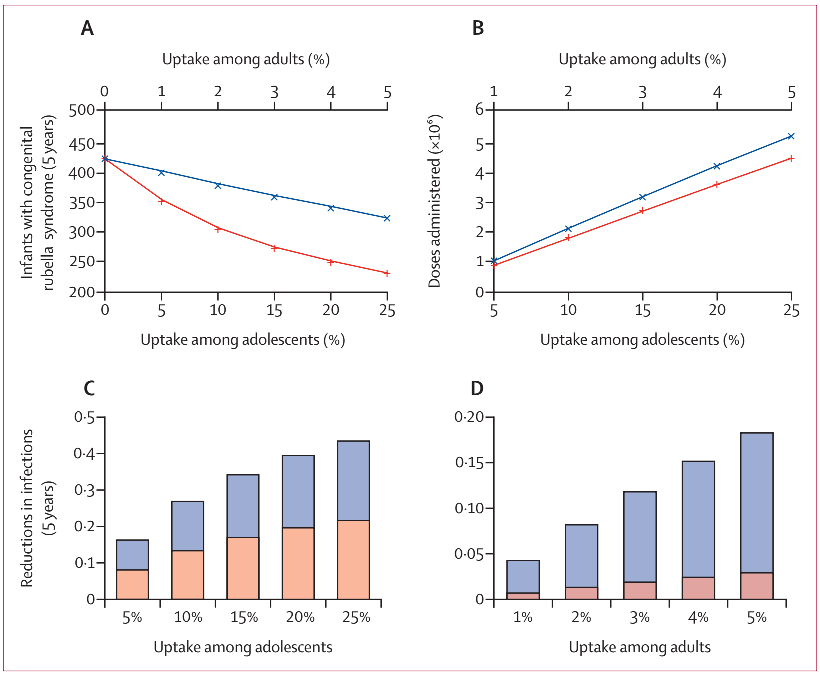

***Figure 6*: Comparisons of adolescent and young adult vaccination**

(A) Cumulative numbers of infants with congenital rubella syndrome during a 5-year period and (B) doses administered (× 100 000) during supplemental immunisation activities among susceptible adolescents and young adults. Uptake is less among young adults (blue) than adolescents (orange) for similar numbers of doses because, while a greater proportion of young adults is immune (figure 1), there are more of them (appendix 2 p 15). Direct (orange) and indirect (blue) effects of (C) adolescent and (D) young adult vaccination and their respective impacts. Reductions in vaccinated age classes are largely direct, while reductions in other age classes are necessarily indirect.

doses of vaccine containing measles and rubella to their community health clinics. However, during 2014, an outbreak occurred in a middle school in Guangzhou where vaccine coverage was only 25·8%.[28] 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 document adequate protection. Such a school-based catch-up effort will accomplish what a catch-up campaign over a wide age range during the introduction of rubella-containing vaccine would have accomplished had vaccine supply sufficed.

Using our model stratified by age and location, 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 or measles–mumps–rubella vaccines used, these campaigns also could accelerate measles elimination despite the disparate age-susceptibilities to measles and rubella infection in China.[14]

Our results are subject to several limitations. In our modelling stratified by age and location, 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 eight European countries.[15] Those data resemble observations from southern China,[13] whose age structure however is too crude for accurate transmission modelling. In appendix 2 (pp 7–9), we explain why we used the European observations themselves rather than a synthetic mixing matrix derived from them.[34] Our estimate of R_0 is within the range of Bayesian estimates using various hypothetical mixing matrices.[26]

We simulated a demographically realistic SEIR model to assess the incidence of rubella, extent of under-reporting, risk of outbreaks, and burden of congenital rubella syndrome. We used the best information available for parameters, initial conditions, and mixing, but extrapolated results from a representative population of only 100 000 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 10 000 times larger than this model population and spatially heterogeneous, and because the interval between infection with rubella virus and the onset of infectiousness is relatively long, travellers infected elsewhere must frequently return home before becoming infectious. Consequently, our estimates of rubella and congenital rubella syndrome 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 Heilongjiang, total fertility apparently is about half the Chinese average); thus, we could not compare simulation results with the National Health Commission's pilot congenital rubella syndrome 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 might be age-biased. Because disease elimination is a national phenomenon defined in terms of reported infections, we calibrated (ie, adjusted the contact rates) our SEIR model of rubella stratified by age and location 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, the coefficients of which we estimated from surveillance (appendix 2 pp 12–14). Neither of these adjustments should have affected the relative impact of simulated SIAs.

We made these metapopulation models for different proximate, but the same ultimate purpose, to inform public health decision making. Because one model is calibrated and others are not, results are comparable qualitatively, but not quantitatively. Although our demographically realistic model's predictions are as accurate as humanly possible, we subscribe to the view that "Truth...is much too complicated to allow anything but approximations."[35]

Contributors
QS contributed to study design, provided information, and reviewed the manuscript. CM, JEH, and GBG provided information and reviewed the manuscript. ZF did analyses and simulations and reviewed the manuscript. LH supervised the work and reviewed the manuscript. NW, CF, and HY provided information and reviewed the manuscript. LER contributed to study design and reviewed the manuscript. HW contributed to study design, supervised the work, provided information, and reviewed the manuscript. JWG did analyses and simulations and wrote the manuscript.

Declaration of interests
We declare no competing interests.

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