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Meta-population modelling to evaluate vaccination policy alternatives vis-à-vis measles and rubella in China

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Background: Measles and rubella are rash illnesses that typically afflicted young children in the pre-vaccination era, but rubella usually is mild while measles may be severe. Because child deaths to which measles contributes often have other proximate causes, measles mortality is under-ascertained. Rubella during the first trimester invariably causes miscarriages, stillbirths and, among livebirths, congenital rubella syndrome (CRS), an array of individually severe afflictions that often co-occur. As childhood vaccines commonly include antigens to the viruses causing both diseases, vaccination programs must be designed to attain disparate goals: prevent measles among young children and rubella among young women. By virtue of increasingly effective routine vaccination, together with targeted supplemental immunization activities (SIAs), health authorities in the People's Republic of China have reduced measles' reproduction number from about 18 to 2.3. Despite substantial residual susceptibility among young adults, more in some province-level jurisdictions than others, sustained childhood immunization likely would eliminate measles eventually. Because routine vaccination against rubella began more recently, residual susceptibility is concentrated among adolescents. Nonetheless, childhood immunization has reduced rubella's reproduction number from 7.6 to 1.2. To support global eradication efforts, as well as expedite morbidity and mortality reductions in China, we evaluated alternative SIAs via mechanistic mathematical modelling.

Methods: Our model Chinese population is stratified by immune status (susceptible to infection; infected, but not yet infectious; infectious; and recovered or immunized), age (0, 1-4, 5-9, ..., 65+ years), and location (31 provinces, municipalities or administrative regions). It includes a function by which contacts between members of different groups are a mixture of preferential and proportionate with respect to age, but decline exponentially with distance at age-dependent rates. We estimated initial conditions and most parameters from recent cross-sectional serological surveys, disease surveillance and demographic observations. Then we evaluated the effective reproduction numbers and their partial derivatives with respect to sub-population immunization rates. Within regions, these gradients identify province-level jurisdictions where vaccination would reduce the effective reproduction number the most. And within jurisdictions, they identify age classes where vaccination would be most effective. We corroborated our analytical results by simulating adolescent and young adult SIAs using a deterministic model with seasonally-forced person-to-person contact rates. And, using a demographically-realistic stochastic model of a relatively small but representative population, we estimated the risk of rubella outbreaks, burden of CRS, and impact of adolescent vaccination.

Findings: Measles' gradients are more heterogeneous than rubella's, but generally indicate that vaccinating young adults is the optimal strategy. Simulations corroborate this, but indicate that a catch-up campaign among adolescent schoolchildren would accelerate elimination nonetheless, with timing dependent on uptake. Moreover, this strategy is optimal for rubella, which is woefully under-reported, especially among adults. Thus, using measles-rubella or measles-mumps-rubella vaccine in SIAs during the first months of several consecutive school years would both accelerate measles elimination and avert impending outbreaks of rubella that, because of the immune profile in China, would greatly increase the incidence of CRS. Interpretation: These results are largely due to indirect effects (i.e., fewer infections than vaccinated people might otherwise cause), which meta-population models with realistic mixing are uniquely capable of reproducing accurately.

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