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Epidemiological profile and progress toward rubella elimination in China. 10 years after nationwide introduction of rubella vaccine ☆

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ABSTRACT

Background: Rubella-containing vaccine (RCV) became available in China in 1993 and was introduced nationwide into the Expanded Immunization Program (EPI) in 2008. We evaluated implementation and impact of RCV from 2 years prior to nationwide introduction through the 10 years after nationwide introduction.

Methods: We analyzed RCV lot-release (doses distributed) data, 1- and 2-dose RCV coverage, and rubella data from China's nationwide disease surveillance system to describe the current status and changes in rubella epidemiology between 2005 and 2017.

Results: While the vaccine was included into the routine immunization program in 2008, its full implementation required 4 years due to sporadic vaccine supply constraints. RCV1 and RCV2 coverage increased from 51.5% and 39.0% in 2008 to >95% during 2012 through 2016. From 2005 to 2017, the annual incidences (per million) of rubella ranged from 91.09 in 2008 down to 1.16 in 2017; reductions occurred in all age groups. The proportion of cases among individuals ≥20 years old increased from 0.97% in 2005 to 31.2% in 2017. In the better-developed eastern China, most cases were among adults; in central and western China, most cases were among children or adolescents.

Conclusions: The marked decrease rubella was a result of inclusion of RCVs into EPI targeting children less than 2 years of age and achieving high level of 2-dose coverage. Rubella was reduced in absolute terms, and its epidemiology was changed to older cases with substantial inter-province variation. Ensuring full vaccination of school children and identifying strategies to reach adults with measles and rubella combined vaccines will be important to hasten elimination of rubella and prevent CRS outbreaks.

1. Introduction

Though acquired rubella is usually a benign disease of children and young adults, rubella virus is a highly teratogenic pathogen, particularly when infection occurs during the first 16 weeks of pregnancy. In early-pregnancy infections, the developing organs of the fetus are often damaged, resulting in miscarriage, stillbirth, or an infant born with birth defects - congenital rubella syndrome (CRS). The goal of rubella vaccination programs is prevention of the intrauterine infection that causes CRS [1], and the only way to ensure that CRS does not occur is to eliminate the possibility of exposure to rubella virus. To this end, at the World Health Assembly (WHA) in May 2012, all 194 Member States endorsed the target of eliminating rubella in five of the six WHO Regions by 2020 as part of the Global Vaccine Action Plan (GVAP) of the Decade of Vaccines [2]. Feasibility has been shown by the elimination of endemic transmission of rubella virus in the WHO Region of the Americas, declared in 2009 [3]. In October 2017, the WHO Western Pacific Regional Committee passed unanimously a resolution that "urged that all Member States in the Region aim to eliminate rubella as soon as possible [4]."

China, with a mainland population of more than 1.38 billion and an area of 9.6 million km^2, is the largest country in WHO's Western Pacific Region. Rubella-containing vaccine (RCV) was licensed and made available in China in 1993 and was introduced nationwide into the Expanded Immunization Program (EPI) 10 years ago, in 2008. Given the interest in rubella elimination by WHO and ministries of health, we report a study in China about rubella vaccine use and coverage, the epidemiological profile of rubella, and

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progress and challenges of elimination of rubella from 2005 through 2017. We discuss implications of our findings and make recommendations to help hasten elimination of rubella and prevention of CRS outbreaks in China.

2. Methods

2.1. Study setting

The study is set in mainland of the People's Republic of China, not including Hong Kong Special Administrative Region, Macao Special Administrative Region, and Taiwan.

2.2. Rubella vaccines in China

There are 3 types of rubella containing vaccine (RCV) available in China - standalone rubella vaccine (RV), measles-rubella combined vaccine (MR), and measles-mumps-rubella combined vaccine (MMR). China has used two rubella vaccine virus strains - an imported RA27 strain from international manufacturers and a domestic BRD-II strain. RA27 strain vaccines, once available in the private sector, have not been used in China since 2010. The BRD-II vaccine virus strain was developed by Chinese manufacturers in the 1980s, and has been available in China's private market since 1993. In contrast to EPI vaccines, which are provided at no cost to families, private sector RCV must be paid for by parents and is not monitored strictly for coverage.

Prior to nationwide introduction of RCVs, several provinces had policies to use rubella vaccine in the private sector, under the management of local health departments. In these situations, the provincial government usually purchased the vaccine, but technical recommendations for use of RCV varied by province. For example, starting in 1995, Shandong province used RCV for 1–12 year-old children and women 13–30 years of age. In later years, RCV was used at 8 months and 7 and 12 years of age [5]. Starting in 1997, Heilongjiang province recommended and provided RCV to children <15 years of age and women of reproductive age [6].

Some provinces provided RCV to children through rubella-specific vaccination campaigns, or during measles vaccination campaigns, but using separate vaccines, and usually resulting in a lower RCV coverage. For example, one prefecture in Henan province, during a standalone measles vaccine MV/RV campaign targeting 1–7 year old children in 2000 [7], reported MV coverage of 91% and RV coverage of 31%. Guangdong province also conducted an RV campaign in 2000 [8], reporting RV coverage among the targeted 1–14-year-old children of 40%, compared with MV coverage of 97%.

RCV was included into China's nationwide EPI system in 2008, with a schedule of 1 dose of MR at 8 months and 1 dose of MMR at 18 months. Introduction into EPI meant that the vaccines were provided at no charge to families, but at that time, introduction of rubella came with the understanding that the supply might not keep up with demand. The Ministry of Health recommended that in case of insufficient supply of MMR or MR, the short-supplied vaccine can be replaced by MV or measles-mumps vaccine, essentially dropping RCV. As a result, during the first 4 years of RCV introduction, the schedule was not fully implemented in many parts of China, and provinces varied in their need for vaccine substitution. For example, in 2008 in Heilongjiang province, the RCV schedule was only implemented in two prefectures, with the other prefectures using MV. The schedule was expanded to 7 prefectures in 2010, and finally covered all prefectures in 2011 [6].

Based on RCV doses distribution information published by the China Food and Drug Administration's Lot Release Program from 2008 to 2016, the annual number of doses of each type of RCVs, including RV, MR and MMR, distributed from national level were and obtained to determine the annual volume of RCV used in China.

2.3. Routine immunization and coverage assessment

All vaccines are delivered through government-operated clinics and are offered at no charge to locally-born children and children new to the area who have registered for clinic services. Clinic immunization providers record each dose of vaccine in clinic medical records, in parent-held vaccination booklets, and in a computerized immunization information system, if available. Clinics are required to calculate and report EPI vaccination coverage to county CDCs by dividing the number of children vaccinated in the clinic with a specifically-required dose or dose sequence of vaccine by the number of children registered in the clinic. Data are aggregated from vaccination clinics through the 4-level CDC system, ultimately to China CDC.

We calculated national routine immunization coverage levels for the first dose of RCV (RCV1) and the second dose of RCV (RCV2) from 2008 to 2016 using as denominators the number of age-eligible children registered in clinics. Numerators were the number of children who received rubella-containing vaccine - either MR or MMR. These data were obtained from the national level of the routine immunization information system in China.

2.4. Rubella surveillance in China

In 1990, acquired rubella was made notifiable in China by being declared a "Category C infectious disease" and was included in China's "Law of Prevention and Treatment of Infectious Diseases." Prior to 2004, China monitored rubella through sentinel surveillance sites including the 145 counties of China's 3000 counties that served as disease surveillance points – together covering a population of 11 million (approximately 1% of the total population of China at that time) [9]. In 2004, rubella was made nationally notifiable with a central government mandate to report cases. The National Notifiable Diseases Reporting System (NNDRS), which is a web-based real-time reporting system, was established in 2004 for rubella and other mandatorily-reported infectious diseases. NNDRS permits surveillance data to flow from hospitals and county-level CDCs to the national Center for Disease Control and Prevention, passively collecting and transmitting individual-level rubella case data countrywide.

In 2014, rubella was integrated into the measles surveillance system in China, in accordance with recommendations in the "Measles Elimination Field Guide" issued by the WHO Western Pacific Region [10]. All provinces subsequently conduct case-based, laboratory-supported measles-rubella surveillance, using the following suspected case definition: "fever, maculopapular rash and any one of the following symptoms: cough, coryza, conjunctivitis, cervical and/or suboccipital and/or postauricular adenopathy, or arthralgia/arthritis, or any case for which a health worker suspects measles or rubella infection." Each suspected case is required to be investigated using a uniform questionnaire to gather disease and epidemiological information; and serum samples are collected to test for both measles and rubella IgM. If rubella IgM is positive, the case is classified as laboratory-confirmed rubella; if the suspected case has an epidemiological linkage with a laboratory-confirmed rubella case, the suspected case is classified as confirmed by epi-link; and if clinical specimens are unable to be obtained from a suspected case, but the case is clinically compatible with rubella and cannot be definitely diagnosed as another disease, the case is classified as clinically confirmed rubella.

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