Vaccine 33 (2015) 3223–3227

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Effectiveness of Rubella vaccine in a rubella outbreak in Guangzhou city, China, 2014

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ARTICLE INFO

Article history:
Received 13 January 2015
Received in revised form 5 April 2015
Accepted 23 April 2015
Available online 16 May 2015

Keywords:
Rubella
Vaccine effectiveness
Outbreak
Secondary attack rate

ABSTRACT

Background: WHO recommends the use of rubella-containing vaccine (RCVs) to prevent rubella and congenital rubella syndrome (CRS). Most licensed rubella vaccines in use globally are based on RA27/3 strains and have estimated vaccine effectiveness (VE) rates of 95–100%. In contrast, China uses a BRD-II strain-based rubella vaccine. Few field studies have been conducted that estimate VE of China's RCV. On March 17, 2014, a rubella outbreak was reported in a middle school in Guangzhou city, China. We conducted an investigation to understand reasons for the outbreak, and we used that investigation to estimate vaccine effectiveness of China's rubella vaccine.

Methods: To identify cases, investigators reviewed records kept by the school doctor and absentee records kept by teachers. Self-administered questionnaires were sent to parents of all students to collect information about the students' symptoms, the results of any physician consultation, and disease history. We obtained demographic information and illness information for all students in the school; vaccination status was determined by inspection of official, parent-held vaccination records. A retrospective cohort study was conducted in 13 classes that had secondary cases of rubella. Using the secondary attack rates, we evaluated VE by the number of RCV doses received and age at vaccination.

Results: During the period February 17–May 23, 2014, 162 students (50 suspected cases, 88 probable cases, 24 confirmed cases) were diagnosed with rubella, yielding an overall attack rate of 10% (162/1621). Cases occurred in 27 classes (73%) of 37 classrooms. Secondary cases occurred in 13 classes (35%) of 37 classrooms. A total of 1130 students (69.7%) have vaccination certificates; 419 (37%) students were record-confirmed to have received RCV. For those vaccinated using BRD-II strain vaccine, vaccine effectiveness (VE) was 94% (95%CI: 75–98). VE for measles, mumps, and rubella (MMR) vaccine which is based on either BRD-II or RA27/3 strain was 89% (95%CI: 56–97). VE of a single dose of domestic monovalent rubella vaccine that used BRD-II strain vaccine was 93% (95%CI: 73–98). VE for those who received the vaccine between 1 and 2 years of age was 95% (95% CI: 67–99) while the VE was 100% for those vaccinated after 2 years of age. VE among those who received RCV <12 years ago was 100% while VE among those who received RCV ≥12 years ago was 92% (95%CI: 70–98).

Conclusions: The rubella vaccines used in China that are based on the BRD-II rubella vaccine strain have VE of 94%, which is similar to the more commonly used RA27/3-based RCVs. Low vaccination coverage contributed to this outbreak; early reporting of an outbreak is necessary for effective outbreak response immunization.

1. Introduction

Rubella is a viral illness characterized by a mild, maculopapular rash [1]. The virus is transmitted through direct or droplet contact from nasopharyngeal secretions [2]. Rubella infection in pregnant

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http://dx.doi.org/10.1016/j.vaccine.2015.04.083
0264-410X/

women, especially during the first trimester, can result in miscarriages, stillbirths, and congenital rubella syndrome (CRS) [3,4]. Rubella and CRS are preventable through vaccination. In 2000, the World Health Organization (WHO) recommended that all countries use rubella-containing vaccine (RCVs) to prevent rubella and CRS. Vaccines based on the RA27/3 strain of rubella vaccine virus are the most widely used RCVs globally.

A BRD-II rubella strain vaccine was developed in the 1980s in China [5], and has been available in the Chinese private market since 1993 [6]. All monovalent rubella and measles and rubella combined (MR) vaccines in use in China are based on the BRD-II rubella strain. A domestic measles, mumps and rubella combined vaccine (MMR) based on BRD-II strain has been available in China's private market since 2003. There is also an imported RA27/3 strain-based vaccine available in China. The reactogenicity and immunogenicity of the BRD-II strain is similar to RA27/3 rubella vaccine strain [7]. However, there are few field vaccine effectiveness (VE) studies of BRD-II strain RCVs.

On March 17, the Chinese Center for Disease Control and Prevention (China CDC) was notified of a rubella outbreak in a middle school in a suburb of Guangzhou city, located in the south of China. Despite implementation of control measures, the epidemic spread rapidly. An outbreak investigation was initiated to identify factors contributing to the high rate of transmission and to assess the effectiveness of BRD-II strain RCVs. We report results from that investigation.

2. Materials and methods

2.1. Case definitions

For this school-based outbreak, a suspected rubella case was defined as a teacher or student with a generalized rash lasting 1–3 days that had onset between February 17 and May 23, 2014. A probable rubella case was defined as a suspected rubella case with fever >37.5 °C and at least one of the following symptoms: arthralgia, arthritis, lymphadenopathy, or conjunctivitis [1]. A laboratory-confirmed case required a positive serologic test for rubella IgM antibody. An epidemiologically linked, confirmed case was defined as a suspected case or a probable case that was not laboratory-confirmed, but that was geographically and temporally related to a laboratory-confirmed case.

We classified cases into primary and secondary cases. A primary case was the first student with rubella in a classroom. Secondary cases were classmates in the same class with rubella onset 14–21 days after rubella onset of a primary case. A coprimary case was defined as a classmate with rubella onset earlier than 14 days following a primary case onset.

2.2. Case finding efforts

To identify cases, investigators reviewed medical records kept by the school's doctor and absentee records kept by teachers. Self-administered standard questionnaires were sent to parents of all students to collect information on symptoms, results of physician consultation, and disease history. Parents were interviewed by telephone to obtain information that was missing or unclear in the records.

2.3. Vaccination status

Students were asked to provide their vaccination certificate. All vaccination histories were verified against these official immunization records, and included vaccine type, date of vaccination, and dose number. We considered the vaccination history as unknown if no vaccination card was available. A person was categorized as vaccinated if an RCV had been administered at least 30 days prior to onset of the outbreak.

2.4. Emergency vaccination

We used MR vaccine and MMR vaccine to conduct emergency vaccination. Students with a history of rubella, fever or acute illness, and whose parents refused vaccine for their child were excluded from emergency vaccination.

2.5. Laboratory testing

In accordance with WHO recommendations [7], we tested rubella IgM and IgG using enzyme-linked immunosorbent assay (Institute Virion/Serion, Germany).

2.6. Statistical analyses

Excel software and Epi Info™ 7.1.4 statistical software were used for data analysis. Differences between proportions were calculated by using χ^2 tests; P values were 2-sided and considered significant at the 0.05 level. Secondary attack rates (SARs) were calculated by dividing the number of secondary cases by the number of students with no history of current rubella minus those with primary and coprimary cases [8]. Secondary attack rates were used to calculate risk ratio (RR), and 95% confidence intervals (CIs) were calculated using the log rate of the SE of the ratio [9]. We estimated vaccine effectiveness using the secondary attack rate. Vaccine effectiveness (%) = [(secondary attack rate in unvaccinated contacts − secondary attack rate in vaccinated contacts)/secondary attack rate in unvaccinated contacts] × 100 [10]. We only used laboratory- or epidemiologically confirmed cases to calculate VE.

3. Results

3.1. Outbreak setting

School A is a middle school with a total of 1621 students enrolled in the seventh, eighth, and ninth grades, with a total of 37 classes. All students are day students, and they eat their meals at home. The school canteen only provides meals for some teachers. No school bus is available to students. This school has no full-time school doctor, only a part-time health teacher. Students were born between 1998 and 2001.

3.2. Outbreak epidemiology

All cases were students; no teachers had rubella during the outbreak. Between February 17 and May 23, 162 rubella cases among 1621 students were detected, including 50 suspected cases, 88 probable cases, and 24 confirmed cases. No cases were severe. The overall attack rate was 9.99%. In addition to characteristic rash (100%), 69 (42.59%) students had a temperature >37.5 °C; 34 (20.99%) had lymphadenopathy; 7 (4.32%) had conjunctivitis, and 2 (1.23%) had arthralgia.

By the end of the outbreak, cases had occurred in 27 classes (72.97%) across 37 classrooms. The highest class attack rate was 58.14%, and the second highest was 53.85%. A total of 68 (5.06%) secondary cases were found to have signs and symptoms of the rubella. Secondary cases occurred in 13 classes (35.14%) of 37 classrooms.

Although cases began to appear in February, official notification of an outbreak did not occur until March 17. The outbreak lasted for 95 days and ended on May 23. Distinct peaks of cases occurred at 7-day intervals during March and May (Fig. 1).

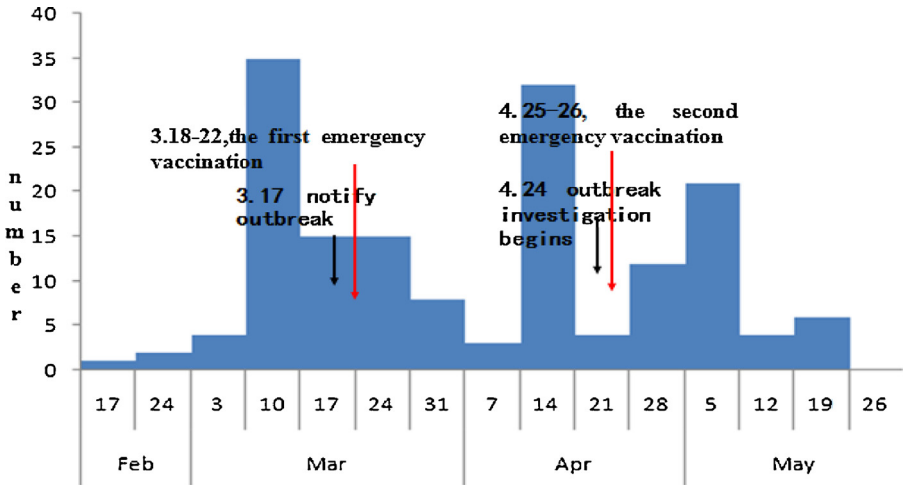

Fig. 1. Weekly distribution of rubella cases in a middle school Guangzhou from February 17 to May 23, 2014.

3.3. Vaccination status

All registered students completed questionnaires. A total of 1130 students (69.7%) provided vaccination certificates; 419 (37.08%) students were confirmed to have received RCV. The highest class rubella vaccination coverage rate was 65.22%; the lowest coverage rate was 18.18% (Fig. 2). Among the 419 vaccinated students, 239 students received monovalent rubella vaccine as their first rubella vaccine dose, 4 students received MR vaccine. All monovalent rubella and MR vaccines were based on the BRD-II rubella strain. However, 176 students received MMR vaccine which was based on either the RA27/3 strain or the BRD-II strain as their first rubella vaccination.

3.4. Vaccine effectiveness

To diminish the influence of subclinical rubella and bias of differential exposure in the classroom, we used secondary attack rate to estimate vaccine effectiveness; 13 classes with secondary cases were selected for this analysis. We selected students with known immunization status in the 13 classes, and categorized them into a vaccinated group and a not vaccinated group (Fig. 3).

The secondary attack rates among students' contacts that were vaccinated with monovalent rubella and aggregated BRD-II strain vaccine were 2.35% and 2.33%, respectively (Table 1). For those vaccinated using BRD-II strain vaccine, VE was 94% (95%CI: 75–98). The VE for MMR vaccine which based on BRD-II or RA27/3 strain was 89% (95%CI: 56–97). We considered the vaccination status as unknown if no card or no record was available to verify vaccination status. With the assumption that vaccine efficacy is the same for vaccinated students in this group compared with record-proved vaccinated students, estimated VE for this unknown vaccination status group was 58%, which implies that approximately 63.2% students in the unknown status group had been vaccinated prior to the outbreak.

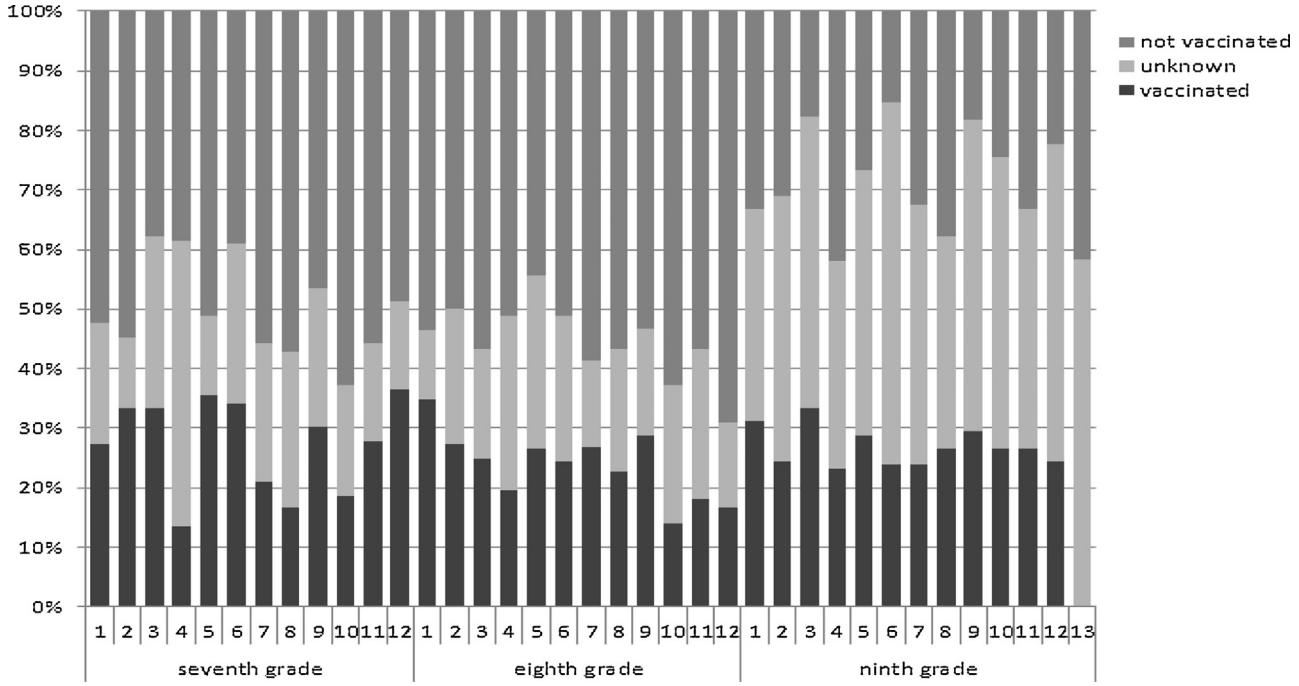

Fig. 2. Distribution of rubella vaccination statuses for students, by class, in a middle school in Guangzhou from February 17 to May 23, 2014.

Table 1
Rubella vaccine effectiveness for different types of vaccine in a middle school, Guangzhou city, 2014.

Vaccination status	Secondary cases	Exposed persons	SARs(%)	RR (95%CI)	VE (%,95%CI)	*P* value
Not vaccinated	65	171	38.01	Ref	Ref	Ref
Monovalent	2	85	2.35	0.06 (0.02–0.25)	94(75–98)	0.000
MR	0	1	0			0.441
Aggregate(BRD-II)	2	86	2.33	0.06 (0.02–0.24)	94 (75–98)	0.000
MMR(BRD-IIor RA27/3)	2	47	4.26	0.11 (0.03–0.44)	89 (56–97)	0.000
Unknown	20	125	16	0.42 (0.27–0.66)	58 (34–73)	0.000

Table 2
Rubella containing vaccines effectiveness for different vaccine dose numbers in a middle school, Guangzhou city, 2014.

Vaccination status	Secondary cases	Exposed persons	SARs (%)	RR (95%CI)	VE (%, 95%CI)	*P* value
0 dose	65	171	38.01	Ref	Ref	Ref
1 dose	2	78	2.56	0.07 (0.02–0.27)	93 (73–98)	0.000
2 doses or more	0	7	0	–	–	0.041

Table 3
Rubella-containing vaccine effectiveness for different vaccination ages in a middle school, Guangzhou city,2014.

Age at vaccination	Secondary cases	Exposed persons	SARs(%)	RR (95%CI)	VE (%, 95%CI)	*P* value
Not vaccinated	65	171	38.01	Ref	Ref	Ref
<1years old	1	10	10	0.26 (0.04–1.71)	74 (0–96)	0.074
1–2 years old	1	56	1.79	0.05 (0.01–0.33)	95 (67–99)	0.000
>2 years old	0	19	0	–	–	0.001

Table 4
Rubella vaccine effectiveness relating to the number of years since vaccination in a middle school, Guangzhou city, 2014.

Years since vaccination	Secondary cases	Exposed person	SARs (%)	RR (95%CI)	VE (%,95%CI)	*P* value
Not vaccinated	65	171	38.01	Ref	Ref	Ref
<12 years	0	15	0	–	–	0.004
≥12 years	2	70	2.86	0.08 (0.02–0.30)	92 (70–98)	0.000

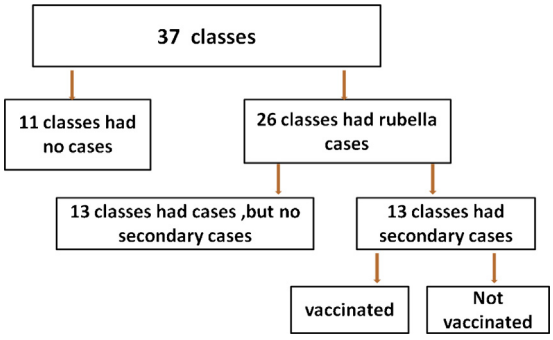

Fig. 3. Profile of study cases.

Our study focused on VE for a domestic monovalent vaccine that used the BRD-II strain. We evaluated VE of different vaccine doses numbers, age at vaccination, and persistence of antibody using the secondary attack rate.

Among the 256 exposed students, 0.33% (2/256) had received at least 1 dose of rubella-containing vaccine before the outbreak. The secondary attack rate among students who received zero, one, or two doses was 38.01%, 2.56%, and 0%, respectively (Table 2). Single-dose domestic monovalent vaccine effectiveness was 93% (95%CI, 73–98).

The secondary attack rate among students' contacts who were vaccinated at <1 year of age, 1–2 years old, and >2 years old was 10.00%, 1.79% and 0%, respectively (Table 3). Vaccination effectiveness for those who received the vaccine between 1 and 2 years of age was 95% (95% CI: 67–99) while the vaccine effectiveness was 100% for those vaccinated after 2 years of age.

The secondary attack rates of rubella among students' contacts who had been vaccinated <12 years ago and ≥12 years were 0% and 2.86%, respectively (Table 4). VE among those who received RCV <12 years ago was 100% while VE among those who received RCV ≥12 years ago was 92% (95% CI: 70–98).

3.5. Emergency vaccination activities

During the outbreak, rubella emergency vaccination activities were launched twice. On March 18–22, 33 students received MMR vaccine in a community service center. After investigating the outbreak, we suggested that the school should conduct an emergency vaccination program targeting all students whose parents agreed to have them vaccinated. On March 26, 957 students received an MR vaccine at temporary vaccination points set up by the community service center at the school. After the second emergency vaccination, 44 students were reported to have rubella before the epidemic ended. The last case happened on May 22.

4. Discussion

We have shown that the rubella vaccines used in China that are based on the BRD-II rubella vaccine strain have a vaccine effectiveness of 94%, which is similar to the more commonly used RA27/3-based RCVs. Our study also showed that VE for those who received the vaccine between 1 and 2 years of age was 95%, while it was 100% for those vaccinated after 2 years of age. The duration protection is apparently at least 12 years, as VE among those who received RCV <12 years ago was 100%, while VE among those vaccinated over 12 years prior to the outbreak was 92%. A single dose of RCV reduced the risk of rubella by 93%, and among students who received two doses, the rubella risk was reduced by 100%. Our

estimate of VE for the group of students with unknown vaccination status was 58%, which implied that approximately 63.2% of the students in that group had been vaccinated prior to the outbreak.

Low vaccination coverage levels contributed to this outbreak, which reflects the relatively recent inclusion of RCV into the immunization program in China. Initial outbreak response vaccination efforts were not effective, and it is not clear the degree to which the second vaccination response effort curtailed the outbreak.

4.1. Strengths and weaknesses

Our study took advantage of the rubella outbreak to evaluate VE of BRD-II strain RCVs in China. We used secondary attack rate to calculate the VE to diminish the influence of subclinical rubella and bias of differential exposure in the classroom. Although we had a group of students with unknown vaccination status, all vaccination histories were verified with vaccination cards. Our study has potential for recall bias in which students may not remember important characteristics of their illnesses, making clinical inference subject to this bias. Not all the cases had laboratory confirmation of rubella, however, all suspected and probable cases were geographically and temporally related to at least one laboratory-confirmed case. We estimated the apparent RCV coverage of the students with unknown vaccination status, but to do so, we had to assume VE was the same as with other students.

4.2. Strengths and weaknesses in the context of other literature

In our study, no student who received 2 RCV doses had rubella in this school-based outbreak. Although only one routine RCV dose is felt to be essential for rubella elimination, a second dose appeared to have some additional benefit over one dose in our study. This may be reflected in other industrialized countries' use of a second dose of MMR vaccine, which can boost low rubella antibody levels [11]. In general, however, the high seroconversion rate and long-term protection of a single dose of rubella vaccine does not support the need for a routine second dose of rubella vaccine [12]. One study has reported that a rubella seroconversion rate of $\geq$90% when children are vaccinated at 9–12 months of age. Rubella vaccine is usually administered routinely at 12 months of age or older, and maternal antibodies have usually disappeared by then [12]. Our study was consistent with vaccination at or after 12 months of age, since students vaccinated at <1 year of age had a slightly higher rate of rubella compared with children vaccinated at or after one year of age. We found that significant protection did extend to at least 12 years following vaccination, which is similar to other studies, [13,14] which have shown that 95% of vaccine recipients remain seropositive 10 years after immunization.

4.3. Program implications

Our study provided supportive evidence that the BRD-II-based RCV is comparable in effectiveness with the RA27/3 vaccine, supporting the vaccine's use in the Chinese immunization program. Without considering vaccine failure, the rubella vaccine coverage rate must be at least 85% to interrupt rubella virus transmission and lead to elimination of rubella. However, only 37% of students were able to be confirmed by official records to have received RCV. Prior to 2008, the cost of rubella vaccination had to be paid by the child's family; in 2008, China induced rubella vaccine in the national immunization program, which not only made the vaccine free for all families, but it put rubella prevention into the program's strategic planning [15]. Of interest, all of the students involved in the outbreak were born between 1998 and 2001 when the rubella vaccine coverage rate was lower and when the program was not implementing a rubella prevention strategy.

We did not find rubella cases among family members. All of the students ate meals at home and did not take the bus to school, implying that rubella virus spread during class time. The school involved in the outbreak had no full-time doctor, and the part-time health educator had not received training on infectious disease surveillance and outbreak control. Perhaps as a consequence, although cases began to appear in February, official notification of an outbreak did not occur until March 17. We therefore missed the best chance to control the epidemic.

4.4. Recommendations and next steps

Our findings support several recommendations. First, BRD-II-based rubella vaccine should remain in the national immunization program. It appears to be sufficiently effective to achieve the protective levels necessary to eliminate rubella. Second, achieving high vaccination coverage level through routine immunization will be necessary for effective control and elimination of rubella. Third, use of additional training or guidelines on identification and reporting of an infectious disease outbreak should be considered for the school systems in China. Earlier detection and reporting may have allowed a more effective outbreak response vaccination effort. Fourth, because long-term protection afforded by RCV is not known with certainty, VE should be assessed periodically when opportunities arise.

Acknowledgments

We gratefully acknowledge the health workers from Panyu CDC and their affiliate community health service center who participated in the field investigation. We thank teacher Peiqin Wei, Dr Huiming Luo, Chenggang Wu, Shuqing Zhao, Xiaoping Shao, Qi Zhu, Yu Liu, Qiru Su and Yan Li for your critical support for this study. We thank Dr Shannon Rutherford for critically reading the manuscript. We thank Dr Lawrence Rodewald for critical support and review of the manuscript and response to the editor's and reviewer's comments.

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