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Recent trends in seroprevalence of rubella in Korean women of childbearing age

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Complete List of Authors:	Choi, Rihwa; Green Cross Corp, Laboratory Medicine, Green Cross Laboratories; Sung Kyun Kwan University School of Medicine at Samsung Medical Center Cancer Center, Department of Laboratory Medicine and Genetics Oh, Yejin; Green Cross Corp, Department of Laboratory Medicine, Green Cross Laboratories Oh, Youngju; Green Cross Corp, Department of Laboratory Medicine, Green Cross Laboratories Kim, Sung Ho; Green Cross Corp, Department of Laboratory Medicine, Green Cross Laboratories Lee, Sang Gon; Green Cross Corp, Department of Laboratory Medicine, Green Cross Laboratories
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Recent trends in seroprevalence of rubella in Korean women of childbearing age

Running title: Rubella seroprevalence in Korean women

Rihwa Choi [1,2], Yejin Oh [1], Youngju Oh [1], Sung Ho Kim [1], and Sang Gon Lee [1,*]

[1] Department of Laboratory Medicine, Green Cross Laboratories, Yongin, Gyeonggi, Republic of Korea

[2] Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

*Corresponding author: Sang Gon Lee, M.D.

Department of Laboratory Medicine, Green Cross Laboratories, 107, Ihyeonro 30 beon-gil, Giheng-gu, Yongin-Si, Gyeonggi-do, Republic of Korea

Tel; +82-31-260-9209, fax; +82-31-260-0964, e-mail; sglee@gclabs.co.kr

Abstract

Objectives: The aim of this study was to investigate the epidemiology of rubella using the serologic status of rubella-specific IgG antibodies (anti-rubella IgG) in Korean women of childbearing age (15-49 years).

Design: Retrospective cross-sectional study.

Setting: Population-based cross-sectional study in South Korea.

Participants: Between January 2010 and December 2017, test results from Korean women age 15-49 years who had visited an obstetric private clinic (nationwide institutions) and had requested rubella-specific IgG antibody tests from Green Cross Laboratories were obtained from the laboratory information system.

Results: Between 2010 and 2017, 329,707 tests from 327,637 Korean women age 15-49 years who had visited obstetric private clinics (1,438 institutions nationwide) were retrospectively analyzed by year and age group. Results: The overall rate of women that were anti-rubella IgG- and defined as 'unimmunized' was 7.8-9.7%. Over the 8-year study period, the rate of unimmunized women ranged from 7.8-9.7%. Over the study period, the rate of women who were IgG+ (from 81.0% in 2010 to 73.0% in 2017) decreased and the rate of women who had 'equivocal' results from 2010 to 2017 (10.3% in 2010 to 17.6% in 2017) increased. Among the age groups, women in their 40s were the most unprotected from rubella infection (11.8%).

Conclusions: In consideration of the immunization status by age group and the decrease in prevalence of unimmunized women, future public health efforts should be focused on catch-up activities. The results of this study could be used to strengthen disease control and prevent rubella, including a nationwide immunization program.

Strengths and limitations of this study

► The main strength of the study, lies in its sample size, due to the fact that it is a nationwide study with one of the broadest samples to date in South Korea.

► The study provided a recent information of the seroprevalence of anti-rubella IgG that have not been available at this scale before.

► The huge sample size of this study allowed for precise information of the age related seroprevalence of anti-rubella IgG and this study provides valuable information for establishing a catch-up vaccination program in South Korea.

► One limitation of this study was the lack of detailed clinical information, however, seroprevalence studies are an essential tool to monitor the efficacy of vaccination programmes, to understand population immunity and to identify populations at higher risk of infection.

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Competing interests

None declared.

Introduction

Rubella disease, so-called German measles, is caused by rubella virus (belonging to the family Togaviridae and the only member of the genus *Rubivirus*).[1] Although most cases of infection lead to a mild, self-limiting measles-like disease, the real threat arises when rubella virus infects the fetus, particularly during the first trimester when infection can lead to miscarriage or congenital rubella syndrome.[1] Worldwide, over 100,000 babies are born with congenital rubella syndrome every year, and the World Health Organization (WHO) recommends that all countries that have not yet introduced a rubella vaccine should consider doing so using existing, well-established measles immunization programs.[2] The WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommends an increased focus on improving national immunization systems in general to better control rubella.[2] Under the Global Vaccine Action Plan 2011–2020, rubella is targeted for elimination in five WHO Regions by 2020.[3 4] As has been reported in Europe, suboptimal coverage levels in childhood (<95%) can lead to a prolonged inter-epidemic period and to a paradoxical shift of disease incidence towards older age groups, including women of childbearing age, with a consequent increase of congenital rubella syndrome.[5] Serosurveys may represent an effective instrument to measure infection- and vaccine-induced immunity in a specific population, and serosurveys can effectively support strategies aimed at eliminating the disease.[5]

In Korea, a rubella vaccination program used in combination with mumps and measles vaccines (MMR) has been included in the national immunization program since 1985 for disease control and prevention.[6] A second MMR vaccine dose was introduced in 1997, and a catch-up measles-rubella vaccine for school-aged children was introduced in 2001.[6] In 2002, a two-dose MMR keep-up program through the verification of vaccination history was introduced at elementary schools (6-7 years).[6] A new vaccination policy was formed by the 2012 Military Healthcare Service, and since then, MMR vaccines have been routinely administered to all new recruits early in basic training.[7]

Although there have been several studies on rubella in Korea, most of the studies have only been focused on surveillance of newly identified cases, seroprevalences of rubella IgG in children, or had been conducted in the early 1990s.[6-12] Although a recent meta-analysis assessing global seroprevalence of rubella among pregnant and childbearing age women, no data from Korean populations were included in the study.[5] In a recent 16-year review of seroprevalence studies on rubella, only one Korean study on children and adolescents was included.[3] To our knowledge, no recent data have been collected on rubella immunization status with rubella-specific IgG antibodies in Korean women of childbearing age in a large study population, which could provide basic knowledge on nationwide immunization strategies.

Therefore, in this study, we aimed to investigate the epidemiology of rubella and to share baseline data for future immunization policies. The aim of this study was to investigate the epidemiology of rubella immunization status using serologic assays for rubella-specific IgG antibodies in Korean women of childbearing age. In addition, we assessed rubella immunization status according to year and age group.

Materials and Methods

Participants' involvement and data collection

No patients were involved in the development of the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked for advice regarding the interpretation or writing of results. There are no plans to disseminate the study results to the relevant patient community.

Study populations

Between January 2010 and December 2017, test results from Korean women age 15-49 years who had visited an obstetric private clinic (nationwide institutions) and had requested rubella-specific IgG antibody tests from Green Cross Laboratories were obtained from the laboratory information system. Green Cross Laboratories are one of the largest referral clinical laboratories in Korea. Test results from women whose age was unknown were excluded. All data were anonymized before being transferred to analysis for age- and year-specific seroprevalences. Missing age and sex data were excluded. The results of this study were prone to ascertainment bias and the use of a population based study minimised selection bias.[13] This study was conducted according to guidelines in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Institutional Review Board of Green Cross Laboratories (GCL 2017-1010-02).

Analytical procedures

All serum samples were tested for anti-rubella IgG using a chemiluminescent microparticle immunoassay (CMIA, Architect i2000SR, Abbott Diagnostics, Abbott Park, IL, USA) according to the manufacturer's instructions. For the rubella IgG assay, the presence of ≥10 IU/mL was defined as 'positive' and considered 'immunized.' Antibody levels of 0.0-4.9 IU/mL were defined as 'negative,' and antibody levels between 5.0-9.9 IU/mL were defined as 'equivocal.' Positive rubella-specific IgG results are indicative of past exposure to rubella virus.

Definition

Women who had 'negative' results were defined as unimmunized. Birth cohorts were defined based on the vaccination program: pre-catch-up, 1976-1984; catch-up, 1985-1993; and keep-up, ≥ 1994.[6] The pre-catchup (1976-1984) cohort was women who had presumptively limited MMR vaccination coverage with only one dose provided by the public program. The catch-up (1985-1993) cohort was woman who had limited MMR vaccination coverage, but were given the measles-rubella (MR) vaccine during the 2001 catch-up campaign.[6] The keep-up (≥ 1994) cohort was women who were candidates for the keep-up program.[6]

Statistical analysis

Categorical variables are presented as frequencies and percentages. The chi-squared test was used to compare categorical variables. We used nonparametric methods when data were not normally distributed. To assess rubella immunization status according to the year and age group, a Cochran-Armitage trend test was performed. Statistical analysis was executed using MedCalc Statistical Software version 18.5 (MedCalc Software bvba, Ostend, Belgium). *P*-values were considered significant at the 0.05 level.

Results

General characteristics of the study population

Between January 2010 and December 2017, 329,701 tests from 327,637 Korean women age 15-49 years who had visited obstetric private clinics (from 1,438 institutions nationwide) and had requested rubella-specific IgG antibody tests from Green Cross Laboratories were obtained from the laboratory information system and included in the study. The numbers of the study subjects by each year and age group are summarized in Table 1.

Rubella immunization status for Korean women of childbearing age

The overall rate of IgG- women who were defined as 'unimmunized' was 8.7%, and the overall rate of IgG+ women was 76.4%. Rubella-specific IgG antibody test results by year are summarized in Table 2 and Figure 1. There was a decrease in the rate of women who had positive rubella-specific IgG antibody results (from 81.0% in 2010 to 73.0% in 2017), and an increase in the rate of women who had 'equivocal' results from 2010 to 2017 (10.3% in 2010 to 17.6% in 2017, $p < 0.05$, Figure 1). The rate of positive rubella-specific IgG antibody results by age were 76.7%, 77.9%, 75.3%, and 79.0% for women in their 10s, 20s, 30s, and 40s, respectively. The rate of negative results by age were 6.9%, 7.1%, 9.7%, and 11.8% for women in their 10s, 20s, 30s and 40s, respectively. Among the age groups and birth cohorts, women in their 40s and the pre-catch-up cohort (IgG-, 9.9%) were the most unprotected for rubella infection (IgG-, 11.8%, Supplementary Figure S1). Different numbers of anti-rubella IgG tests had been requested between geographic regions during the 8-year study period (Figure 2, Supplementary Tables S1 and S2). In this study, women living in Sejong city were the most protected from rubella infection (IgG+, 81.3%), while women living in South Jeolla Province were the most unprotected from rubella infection (IgG-, 10.6%, Supplementary Table S1). Less than 1,000 women had been tested for anti-rubella IgG in the Gangwon province and Ulsan.

Discussion

In this study, we investigated the seroprevalence of rubella in Korean women of childbearing age within the past 8 years. The strength of this study was the large study population over a long study period (8 years) and the novelty of the study population (Korean women of childbearing age were assessed for the first time in Korea).

Understanding the spread of infectious diseases and designing optimal control strategies is a major goal of public health.[14 15] In the present study, the seronegativity prevalence was 8.7% in Korean women of childbearing age. A recent 16-year review of seroprevalence studies on rubella assessing 97 articles between January 1998 and June 2014 had reported that seroprevalence ranged from 53.0% to 99.3% for rubella studies.[3] A recent meta-analysis of rubella among pregnant and childbearing age women had reported that approximately 88% of the studies conducted on pregnant women had reported a seronegativity rate >5%, and the pooled rubella seronegativity prevalence was 9.3%.[5] The study had reported that global seronegativity prevalence was of concern, considering that WHO set the rubella susceptibility threshold at 5% for women of childbearing age. Previous studies that had been included in the meta-analysis had used more than 1,000 subjects and had been published within the past 10 years are summarized in Table 3.

The seroprevalence of rubella in Korean populations was assessed previously in infants, children, and adolescents.[8-12] One study on 5,393 students from 8 elementary schools in the Gyeonggi province, Korea in 1993, 1996, and 1996 had reported that the age-adjusted rubella susceptibility rate was 22.9%.[10] Another study performed during the same study period had reported that rubella antibody loss rates were 14.3-15.8% in Korean children.[8] In a 2005 population-based survey in Nonsan, Korea, age-appropriate immunization among urban-rural children aged 24-35 months had reported that the age-appropriate MMR immunization rate was 61.1%-97.4%.[12] A recent study conducted between September 2009 and December 2010 assessing seroprevalence of rubella in 295 infants and 80 of their mothers had reported that seropositive rates were 22.4% in infants and 98.8% in mothers (79/80).[9] In that study, because none of the infants had a history of MMR vaccination, natural infection, or contact with an infected person, it was assumed that specific antibodies were passed from their mothers to their infants.[9] Moreover, among the 80 mothers, 55 (68.8%) had experienced either immunization or past rubella infection.[9]

During the study period, the rate of unimmunized women ranged from 7.8-9.7%, and the overall percentage of positive rubella IgG was 76.4% among Korean women of childbearing age. There was an increase in the rate of equivocal results. This result suggests that 23.6% of women were still unprotected from rubella in the elimination era. According to the Infectious Disease Surveillance Yearbook 2017 published by the Korean Ministry of Health and Welfare and the Korean Centers for Disease Control and Prevention, the incidence rate of rubella from 2001-2017 decreased (from 0.17 per 100,000 populations in 2001 to 0.01 per 100,000 populations in 2017). No rubella outbreak had been reported in South Korea over 8 years (2010-2017) according to the Infectious Disease Surveillance Yearbook. Among the different age groups, older women were more likely to have negative IgG results and no protection from rubella infection. Women in their 30s had the lowest rate of IgG+ results in this study. According to recent data from Korean Statistical Information (KOSIS), the average maternal age at delivery for Korean women was 32.4 years in 2016. Because of this, public health efforts should be focused on catch-up activities. The results of this study could be used as basic knowledge to support strengthening disease control and prevention of rubella, including a nationwide immunization program. Susceptible woman of childbearing age is indeed a priority, and public health efforts should be focused on catch-up activities in order to reduce the rate of susceptible young adults, especially for all women of childbearing age.[16] Gynecologists and general practitioners should be encouraged to propose rubella screening for women of childbearing age before they become pregnant to identify those women who lack rubella antibodies, whether acquired as the result of vaccination or a natural infection.[16] Finally, active surveillance from laboratories that perform rubella immunity testing should be planned; laboratories should notify the Public Health Authority about every woman of childbearing age with a negative test, and the Public Health Authority should engage these women to promote immunization against rubella.[16] Serological surveillance is an important tool for the evaluation of vaccination programs and avoids the limitations of passive disease reporting systems; this is one of the entry points for congenital rubella syndrome surveillance, where gaps limit the ability to monitor progress towards its elimination.[16]

In this study, women living in Sejong city were the most protected from rubella infection (IgG+, 81.3%). In early 2007, the South Korean government had created a special administrative district from parts of the South Chungcheong and North Chungcheong provinces, near Daejeon, to relocate nine ministries and four national agencies from Seoul. Various government programs for encouraging more births, such as incentives, in different regions may have affected the results.[4] In this study, less than 1,000 women had been tested for anti-rubella IgG in the Gangwon province and Ulsan. This may affect the percent seropositivity of anti-rubella IgG in the present study. Future studies are needed to define the effect of regional differences of government strategies on rubella seroprevalences.

One limitation of this study was the lack of clinical information, such as vaccination history or contact history with rubella-infected individuals. However, we do not yet understand what surrogate markers, other than antibodies, show longer-term cell-mediated immunity and protection from disease.[1] Seroprevalence studies are an essential tool to monitor the efficacy of vaccination programmes, to understand population immunity and to identify populations at higher risk of infection.[17] This study is a cross-sectional study and merely descriptive analyses were adopted in this study. The results of this study were prone to ascertainment bias. The present study did not include men, women with older ages, or foreigners living in South Korea. Therefore, the findings are not generalisable to these groups. A systems-level approach to understanding the development and maintenance of acute and long-term immunity to rubella and a rubella-containing vaccine is needed.[1]

Conclusions

In conclusion, this study investigated immunization status of rubella among Korean women of childbearing age. Considering the immunization status by age group and the increased prevalence of women with equivocal results, future public health efforts should be focused on catch-up activities. The results of this study could be used as foundational knowledge for strengthening disease control and prevention of rubella, including a nationwide immunization program.

Contributors

All authors contributed to manuscript preparation; R. Choi, Y. Oh, Youngju Oh, and S.G. Lee collected the data or contributed to data analysis; R. Choi and S.G. Lee designed the study; S.G. Lee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Patient consent for publication

Not required.

Ethics approval

This study was approved by the Institutional Review Board of Green Cross Laboratories (GCL 2017-1010-02).

Supplementary materials

Supplementary material associated with this article can be found, in the online version.

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Table 1 Age distribution each year of 327,637 Korean women tested for rubella IgG antibodies.

	2010	2011	2012	2013	2014	2015	2016	2017	Total
15-20 years	429	586	603	538	557	520	518	358	4,109 (1.3%)
	1.1%	1.4%	1.4%	1.3%	1.4%	1.3%	1.3%	0.9%	
21-30 years	17,189	18,130	17,850	15,922	14,856	14,543	13,962	12,874	125,326 (38.3%)
	45.7%	44.0%	40.1%	38.1%	37.0%	35.0%	33.8%	32.7%	
31-40 years	19,187	21,604	24626	24,256	23,617	25282	25521	24,692	188,785 (57.6%)
	51.0%	52.4%	55.3%	58.0%	58.8%	60.8%	61.8%	62.7%	
41-49 years	802	902	1,477	1,114	1,130	1,229	1,281	1,482	9,417 (2.9%)
	2.1%	2.2%	3.3%	2.7%	2.8%	3.0%	3.1%	3.8%	
	37,607	41,222	44,556	41,830	40,160	41,574	41,282	39,406	327,637

Table 2 Trend of immunization status among Korean women of childbearing age over an 8-year period.

	Positive		Equivocal		Negative		Total
	n	%	n	%	n	%	
2010	30,460	81.0%	4,055	10.8%	3,092	8.2%	37,607
2011	31,589	76.6%	5,627	13.7%	4,006	9.7%	41,222
2012	34,102	76.5%	6,472	14.5%	3,982	8.9%	44,556
2013	31,415	75.1%	6,545	15.6%	3,870	9.3%	41,830
2014	31,154	77.6%	5,887	14.7%	3,119	7.8%	40,160
2015	31,692	76.2%	6,584	15.8%	3,298	7.9%	41,574
2016	31,172	75.5%	6,626	16.1%	3,484	8.4%	41,282
2017	28,749	73.0%	6,929	17.6%	3,728	9.5%	39,406

Table 3 Previous studies on rubella seronegativity in women that included more than 1,000 subjects and were published within the past10 years, grouped by World Health Organization region.

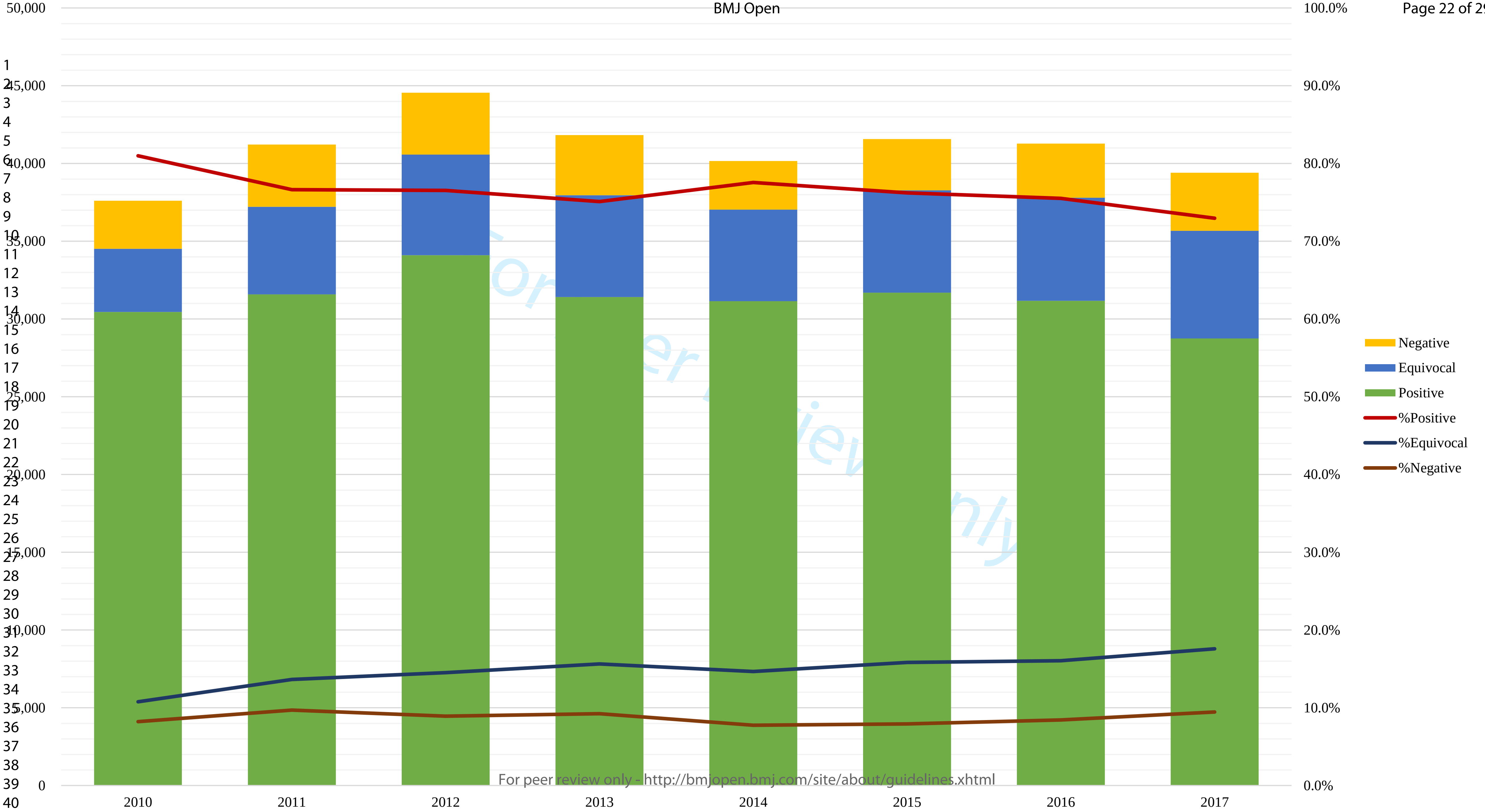
WHO region	Publication year	N	Country	Seronegativity (%)	Population	Reference	Measurement method
AFR	2009	7,430	South Africa	6.2	WCBA	Schoub et al. [18]	Bio-Rad Platelia Rubella IgG ELISA
AMR	2009	8,939	Brazil	28.4	Pregnant	Inagaki et al. [19]	Q-Preven IgG-DBS kit
AMR	2011	9,610	Brazil	11.6	Pregnant	Artimos de Oliveira et al. [20]	Beckman Coulter Access RUBELLA IgG ChLIA or bioMérieux VIDAS RUB IgG II ELFA
AMR	2016	54,717	Brazil	4.5	Pregnant	Avila Moura et al. [21]	Q-Preven IgG-DBS kit
AMR	2009	5,783	Canada	7.0	Pregnant	McElroy et al. [22]	Hemagglutination inhibition test
AMR	2013	459,963	Canada	4.4	WCBA	Lim et al. [23]	Abbott AxSYM Rubella IgG MEIA
AMR	2015	157,763	Canada	15.9	Pregnant	Lai et al. [24]	Abbott ARCHITECT Rubella IgG CMIA
EMR	2014	4,062	Kuwait	6.8	Pregnant	Madi et al. [25]	Abbott ARCHITECT Rubella IgG CMIA
EMR	2013	2,284	Morocco	9.8	Pregnant	Belefquih et al. [26]	Siemens Enzygnost Anti-Rubella-Virus IgG EIA
EMR	2014	10,276	Saudi Arabia	8.7	Pregnant	Sharifa et al. [27]	Dade Behring ELISA BP III
EUR	2012	424,876	England	2.6	Pregnant	Byrne et al. [28]	Microgen Mercia Rubella G EIA
EUR	2013	1,090	Germany	1.6	Pregnant	Enders et al. [29]	Hemagglutination inhibition test
EUR	2013	74,810	Ireland	6.2	Pregnant	O'Dwyer et al. [30]	Method not described
EUR	2012	2,385	Italy	8.0	Pregnant	De Paschale et al. [31]	DiaSorin ETI-RUBEK-G PLUS EIA
EUR	2015	22,681	Spain	5.9	Pregnant	Vilajeliu et al. [32]	Siemens ADVIA Centaur Rubella G ChLIA
EUR	2010	41,637	Sweden	4.2	Pregnant	Kakoulidou et al. [33]	Abbott AxSYM Rubella IgG MEIA
EUR	2009	1,972	Turkey	3.9	Pregnant	Tamer et al. [34]	Abbott AxSYM Rubella IgG MEIA
EUR	2012	5,959	Turkey	1.9	Pregnant	Uysal et al. [35]	bioMérieux VIDAS RUB IgG II ELFA
EUR	2011	11,987	UK	4.4	Pregnant	Matthews et al. [36]	DiaSorin ETI-RUBEK-G EIA
EUR	2016	19,046	UK	6.3	Pregnant	Ogundele et al. [37]	Roche E602 MODULAR analyzer
SEAR	2011	2,224	Nepal	9.2	WCBA	Upreti et al. [38]	Enzygnost Anti-Rubella-Virus IgG EIA
SEAR	2014	1,988	Vietnam	28.9	Pregnant	Miyakawa et al. [39]	bioMérieux Mini VIDAS EIA
WPR	2008	1,020	Australia	2.7	WCBA	Nardone et al. [40]	Siemens Enzygnost Anti-Rubella-Virus IgG EIA
WPR	2008	2,741	Japan	6.7	Pregnant	Okuda et al. [41]	Hemagglutination inhibition test
WPR	2013	13,924	Japan	2.7	Pregnant	Hanaoka et al. [42]	Hemagglutination inhibition test
WPR	2014	20,363	Japan	4.7	Pregnant	Yamada et al. [43]	Hemagglutination inhibition test
WPR	2017	782,293	China	33.8	WCBA	Liu et al. [44]	Method not described
WPR	2011	43,640	Taiwan	10.9	Pregnant	Lin et al. [45]	Abbott AxSYM Rubella IgG MEIA and Beckman Coulter Access RUBELLA IgG ChLIA
WPR	2012	14,090	Taiwan	6.5	Pregnant	Lin et al. [46]	Abbott AxSYM Rubella IgG MEIA
WPR	2019	327,637	Republic of Korea	8.7	WCBA	This study	Abbott ARCHITECT Rubella IgG CMIA

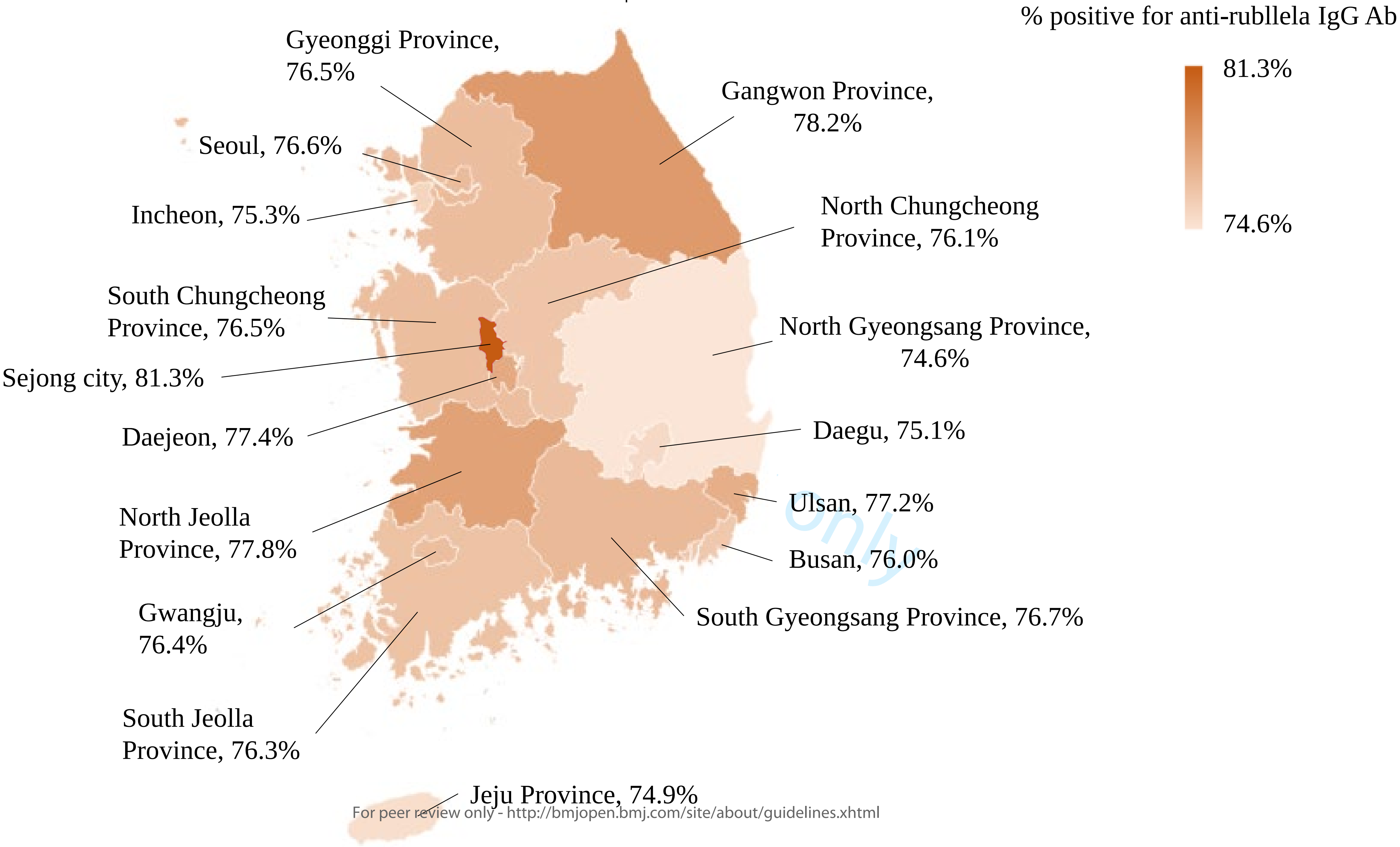
Abbreviations**:** AFR, Africa Region; AMR, American Region; EMR, Middle East Region; EUR, European Region; SEAR, East Asian Region; WCBA, Women of childbearing age; WHO, World Health Organization; WPR, Western Pacific Region.

Figure Legends

Figure 1 Trend of immunization status among Korean women of childbearing age over an 8 year period (2010-2017). Numbers of women (left axis) and the percentage of rubella specific IgG results (right axis) are plotted against years they have tested.

Figure 2 Percent positive rate of rubella-specific IgG antibody in South Korea.


50,000
45,000
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
2010
2011
2012
2013
2014
2015
2016
2017
Negative
Equivocal
Positive
%Positive
%Equivocal
%Negative

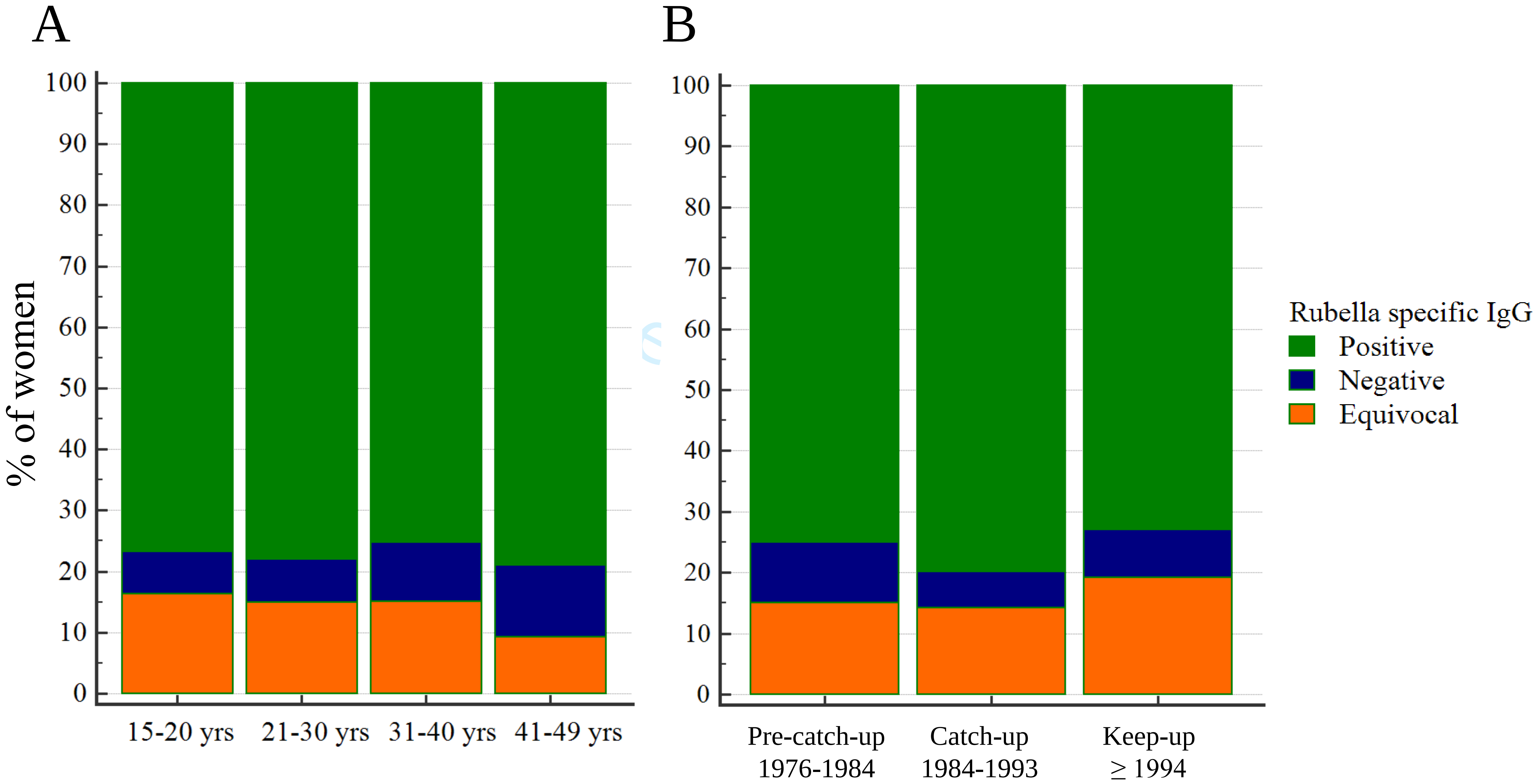

% positive for anti-rubllela IgG Ab
81.3%
74.6%
Gyeonggi Province, 76.5%
Gangwon Province, 78.2%
Seoul, 76.6%
Incheon, 75.3%
North Chungcheong Province, 76.1%
South Chungcheong Province, 76.5%
North Gyeongsang Province, 74.6%
Sejong city, 81.3%
Daejeon, 77.4%
Daegu, 75.1%
Ulsan, 77.2%
North Jeolla Province, 77.8%
Busan, 76.0%
Gwangju, 76.4%
South Gyeongsang Province, 76.7%
South Jeolla Province, 76.3%
Jeju Province, 74.9%

Supplementary Table S1. Rubella-specific IgG antibody in South Korea by geographic region.

Region	Positive	Equivocal	Negative	Total	%Positive	%Equivocal	%Negative
Gyeonggi Province	100240	19766	11048	131054	76.5%	15.1%	8.4%
Seoul	49817	9634	5561	65012	76.6%	14.8%	8.6%
Jeju Province	17527	3515	2358	23400	74.9%	15.0%	10.1%
Daegu	10973	2337	1296	14606	75.1%	16.0%	8.9%
South Jeolla Province	10552	1813	1470	13835	76.3%	13.1%	10.6%
Daejeon	9657	1844	968	12469	77.4%	14.8%	7.8%
Busan	9391	1795	1173	12359	76.0%	14.5%	9.5%
North Jeolla Province	9307	1602	1051	11960	77.8%	13.4%	8.8%
North Chungcheong Province	8363	1718	905	10986	76.1%	15.6%	8.2%
Incheon	7236	1500	868	9604	75.3%	15.6%	9.0%
South Chungcheong Province	6413	1290	684	8387	76.5%	15.4%	8.2%
South Gyeongsang Province	3415	591	447	4453	76.7%	13.3%	10.0%
Sejong City	3218	469	270	3957	81.3%	11.9%	6.8%
North Gyeongsang Province	1577	343	195	2115	74.6%	16.2%	9.2%
Gwangju	1570	291	193	2054	76.4%	14.2%	9.4%
Gangwon Province	552	104	50	706	78.2%	14.7%	7.1%
Ulsan	525	113	42	680	77.2%	16.6%	6.2%

Supplementary Table S2. Positive rate of rubella-specific IgG antibody in South Korea by geographic region and year.

Region	2010	2011	2012	2013	2014	2015	2016	2017	2010-2017
Gyeonggi Province	80.6%	76.4%	76.8%	75.6%	78.1%	76.6%	75.7%	73.2%	76.5%
Seoul	81.9%	76.6%	76.8%	75.4%	77.9%	76.3%	75.6%	73.9%	76.6%
Jeju Province	79.5%	75.9%	76.0%	74.1%	75.9%	73.5%	74.0%	71.2%	74.9%
Daegu	80.0%	76.4%	74.8%	73.4%	73.5%	73.2%	71.6%	75.7%	75.1%
South Jeolla Province	80.7%	76.8%	71.8%	69.6%	76.4%	74.6%	75.4%	72.6%	76.3%
Daejeon	82.0%	77.9%	77.1%	74.8%	79.5%	76.4%	77.3%	74.0%	77.4%
Busan	79.8%	76.4%	75.6%	74.3%	75.1%	74.4%	74.7%	71.2%	76.0%
North Jeolla Province	80.2%	77.2%	78.9%	77.5%	80.5%	77.8%	76.7%	72.4%	77.8%
North Chungcheong Province	82.6%	75.2%	76.7%	73.6%	77.8%	76.2%	74.4%	71.0%	76.1%
Incheon	81.6%	77.0%	79.2%	77.3%	79.1%	77.1%	74.9%	70.7%	75.3%
South Chungcheong Province	85.5%	76.9%	76.2%	74.3%	76.4%	76.9%	76.5%	73.6%	76.5%
South Gyeongsang Province	81.4%	76.9%	72.1%	72.9%	73.6%	74.6%	83.0%	68.2%	76.7%
Sejong City	82.2%	83.8%	80.2%	81.6%	83.5%	80.3%	83.2%	70.2%	81.3%
North Gyeongsang Province	71.8%	68.0%	74.2%	76.9%	78.0%	76.5%	72.4%	68.9%	74.6%
Gwangju	82.2%	77.0%	78.3%	75.8%	77.8%	80.0%	78.2%	71.3%	76.4%
Gangwon Province	81.7%	60.0%	80.0%	94.3%	87.0%	82.9%	78.3%	73.3%	78.2%
Ulsan	93.3%	75.4%	71.3%	84.3%	73.1%	80.7%	75.0%	100.0%	77.2%


A
B
% of women
100
90
80
70
60
50
40
30
20
10
0
15-20 yrs
21-30 yrs
31-40 yrs
41-49 yrs
Pre-catch-up 1976-1984
Catch-up 1984-1993
Keep-up ≥ 1994
Rubella specific IgG
Positive
Negative
Equivocal

Supplementary Figure Legends

Supplementary Figure S1 Test results of rubella-specific IgG antibody (A) by age group and (B) by birth cohort based on nationwide immunization programs.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	*5*
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	6-7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Recent trends in seroprevalence of rubella in Korean women of childbearing age: a cross-sectional study

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Complete List of Authors:	Choi, Rihwa; Green Cross Corp, Laboratory Medicine, Green Cross Laboratories; Sung Kyun Kwan University School of Medicine at Samsung Medical Center Cancer Center, Department of Laboratory Medicine and Genetics Oh, Yejin; Green Cross Corp, Department of Laboratory Medicine, Green Cross Laboratories Oh, Youngju; Green Cross Corp, Department of Laboratory Medicine, Green Cross Laboratories Kim, Sung Ho; Green Cross Corp, Department of Laboratory Medicine, Green Cross Laboratories Lee, Sang Gon; Green Cross Corp, Department of Laboratory Medicine, Green Cross Laboratories Lee, Eun Hee; Green Cross Corp, President, Green Cross Laboratories
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Recent trends in seroprevalence of rubella in Korean women of childbearing age: a cross-sectional study

Running title: Rubella seroprevalence in Korean women

Rihwa Choi [1,2], Yejin Oh [1], Youngju Oh [1], Sung Ho Kim [1], Sang Gon Lee [1,*], and Eun Hee Lee [1,*]

[1] Department of Laboratory Medicine, Green Cross Laboratories, Yongin, Gyeonggi, Republic of Korea

[2] Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

*Co-corresponding authors: Sang Gon Lee, M.D.

Department of Laboratory Medicine, Green Cross Laboratories, 107, Ihyeonro 30 beon-gil, Giheng-gu, Yongin-Si, Gyeonggi-do, Republic of Korea

Tel; +82-31-260-9209, fax; +82-31-260-0964, e-mail; sglee@gclabs.co.kr

*Co-corresponding authors **Eun Hee Lee,** M.D., Ph.D.

Department of Laboratory Medicine, Green Cross Laboratories, 107, Ihyeonro 30 beon-gil, Giheng-gu, Yongin-Si, Gyeonggi-do, Republic of Korea

Tel; +82-1566-0131, fax; +82-31-260-0964, e-mail; ehlee@gclabs.co.kr

Abstract

Objectives: The aim of this study was to investigate the immunity against rubella using the serologic status of rubella-specific IgG antibodies (anti-rubella IgG) in Korean women of childbearing age (15-49 years).

Design: Retrospective cross-sectional study.

Setting: Population-based cross-sectional study in South Korea.

Participants: Between January 2010 and December 2017, test results from Korean women age 15-49 years who had visited an obstetric private clinic (nationwide institutions) and had requested rubella-specific IgG antibody tests from Green Cross Laboratories were obtained from the laboratory information system.

Results: Between 2010 and 2017, anti-rubella IgG test results from 328,426 Korean women aged 15-49 years who had visited private obstetric clinics (1,438 institutions nationwide) were retrospectively analysed by tested year, age, cohort, and geographic regions. Over the 8-year study period, the rate of unimmunized women ranged from 7.8-9.7%. Multivariable-adjusted logistic regression models showed that the odds of being immune to rubella (positive and equivocal results of anti-rubella IgG test) were lower in 2017 compared to 2010, in women in their 40s, in a pre-catch up cohort, and in women living in Incheon, Busan, South Gyeongsang, North and South Jeolla, and Jeju provinces ($p < 0.0001$).

Conclusions: In consideration of the factors associated with prevalence of women unimmunized to rubella, future public health efforts should be focused on catch-up activities. The results of this study could be used to strengthen disease control and prevent rubella, including a nationwide immunization program.

Strengths and limitations of this study

► The main strength of the study, lies in its sample size, due to the fact that it is a nationwide study with one of the broadest samples to date in South Korea.

► The study provided a recent information of the seroprevalence of anti-rubella IgG that have not been available at this scale before.

► The huge sample size of this study allowed for precise information of the age related seroprevalence of anti-rubella IgG and this study provides valuable information for establishing a catch-up vaccination program in South Korea.

► One limitation of this study was the lack of detailed clinical information, however, seroprevalence studies are an essential tool to monitor the efficacy of vaccination programmes, to understand population immunity and to identify populations at higher risk of infection.

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Competing interests

None declared.

Introduction

Rubella disease is caused by rubella virus (belonging to the family Togaviridae and the only member of the genus *Rubivirus*).[1] Although most cases of infection lead to a mild, self-limiting measles-like disease, the real threat arises when rubella virus infects the fetus, particularly during the first trimester when infection can lead to miscarriage or congenital rubella syndrome.[1] Worldwide, over 100,000 babies are born with congenital rubella syndrome every year, and the World Health Organization (WHO) recommends that all countries that have not yet introduced a rubella vaccine should consider doing so using existing, well-established measles immunization programs.[2] The WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommends an increased focus on improving national immunization systems in general to better control rubella.[2] Under the Global Vaccine Action Plan 2011–2020, rubella is targeted for elimination in five WHO Regions by 2020.[3 4] As has been reported in Europe, suboptimal coverage levels in childhood (<95%) can lead to a prolonged inter-epidemic period and to a paradoxical shift of disease incidence towards older age groups, including women of childbearing age, with a consequent increase of congenital rubella syndrome.[5] Serosurveys may represent an effective instrument to measure infection- and vaccine-induced immunity in a specific population, and serosurveys can effectively support strategies aimed at eliminating the disease.[5]

The incidence of rubella infection in South Korea was 107 cases in 2000 that decreased to 7 cases in 2017, corresponding to incidence rates below 0.1 per 100,000 persons according to the Infectious Diseases Surveillance Yearbook, 2017.[6] Although the exact number of cases for congenital rubella syndrome was not available for the surveillance book, 17 cases in 2010 of congenital rubella syndrome were reported, which using the Korean Classification of Disease code P350 for congenital rubella syndrome on the Healthcare Bigdata Hub by the Health Insurance Review and Assessment Service (HIRA).[7] According to the reported measles and rubella cases and incidence rates by WHO member states, 0-3,947 confirmed rubella cases corresponding to incidence rates of 0-11.54 per 1,000,000 total population were reported in 2018 in the western pacific region.[8]

In Korea, a rubella vaccination program using the measles, mumps in rubella (MMR) vaccine has been included in the national immunization program since 1985 for disease control and prevention.[9] A second MMR vaccine dose was introduced in 1997, and a catch-up measles-rubella vaccine for school-aged children was introduced in 2001.[9] In 2002, a two-dose MMR keep-up program through the verification of vaccination history was introduced at elementary schools (6-7 years).[9] A new vaccination policy was formed by the 2012

Military Healthcare Service, and since then, MMR vaccines have been routinely administered to all new recruits early in basic training.[10] The national guidelines in Korea regarding ascertainment of rubella immunity are based on laboratory evidence for rubella antibodies and the Korea Centers for Disease Control and Prevention recommends that women of childbearing age whose anti-rubella specific IgG is negative should receive 1 dose of the MMR vaccine although they did have histories of rubella vaccination (total numbers of vaccination in one individual should be ≤ 3).[11]

Although there have been several studies on rubella in Korea, most of the studies have only been focused on surveillance of newly identified cases, seroprevalences of rubella IgG in children, or had been conducted in the early 1990s.[9 10 12-16] Although a recent meta-analysis assessing global seroprevalence of rubella among pregnant and childbearing age women, no data from Korean populations were included in the study.[5] In a recent 16-year review of seroprevalence studies on rubella, only one Korean study on children and adolescents was included.[3] To our knowledge, no recent data have been collected on rubella immunization status with rubella-specific IgG antibodies in Korean women of childbearing age in a large study population, which could provide basic knowledge on nationwide immunization strategies. Green Cross Laboratories is one of the largest referral clinical laboratories throughout South Korea that has its own bio-logistics and provides clinical specimen analysis services including rubella-specific IgG antibody tests to nationwide clinics and hospitals. According to the provider data on the National Health Insurance Statistical Yearbook 2017 published by HIRA in South Korea, 1,319 private obstetric clinics and 1,433 hospitals with or without obstetric clinics are providing health services.[17] Among a total of 91,545 health care providing institutions (public and private), 4.1% (3,746 institutions) were public or national provider institutions.[17] According to the review records of delivery by provider type in the same book, 89.9% (523/582) of delivery institutions nationwide were private obstetric clinics and hospitals.[17] Among the 358,285 deliveries carried out in 2017, 93.5% (335,119) were delivered in private obstetric clinics and hospitals.[17]

Therefore, in this study, we aimed to investigate the immunity against rubella and to share baseline data for future immunization policies in South Korea. The aim of this study was to investigate the epidemiology of rubella immunization status using serologic assays for rubella-specific IgG antibodies in Korean women of childbearing age. In addition, we assessed rubella immunization status according to year and age group.

Materials and Methods

Participants' involvement and data collection

No patients were involved in the development of the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked for advice regarding the interpretation or writing of results. There are no plans to disseminate the study results to the relevant patient community.

Study populations

Between January 2010 and December 2017, test results from Korean women age 15-49 years who had visited an obstetric private clinics and hospitals (nationwide institutions) and had requested rubella-specific IgG antibody tests from Green Cross Laboratories were obtained from the laboratory information system. Missing data for age, sex, and geographic regions were excluded. Test results from women whose tests were duplicated were excluded. All data were anonymized before being transferred to analysis for age-, year-, birth cohort, and geographical region-specific anti-rubella IgG seroprevalences. This study was conducted according to guidelines in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Institutional Review Board of Green Cross Laboratories (GCL 2017-1010-02).

Data collection

Annual incidence of rubella infection in South Korea was obtained from reported cases in the Infectious Diseases Surveillance Yearbook, 2017 by the Korea Centers for Disease Control and Prevention.[6] Data for the incidence of congenital rubella syndrome was obtained from the Healthcare Bigdata Hub by HIRA using Korean Classification of Disease code P350 in South Korea.[7]

Analytical procedures

All serum samples were tested for anti-rubella IgG using a chemiluminescent microparticle immunoassay (CMIA, Architect i2000SR, Abbott Diagnostics, Abbott Park, IL, USA) according to the manufacturer's instructions. For the rubella IgG assay, the presence of ≥10 IU/mL was defined as 'positive'. Antibody levels of 0.0–4.9 IU/mL were defined as 'negative,' and antibody levels between 5.0–9.9 IU/mL were defined as 'equivocal.' During the eight-year study period, the laboratory protocol was maintained without any changes and all tests requested for anti-rubella specific IgG were analysed automatically and tested once without re-test.

Definition

Positive rubella-specific IgG results are indicative of past exposure to rubella virus or being vaccinated.[18] Women who had 'negative' results were defined as 'unimmunized'. Women were classified as 'immune' if their anti-rubella IgG was positive or showed equivocal results.[18] Birth cohorts were defined based on the vaccination program: pre-catch-up, 1976-1984; catch-up, 1985-1993; and keep-up, ≥ 1994.[9] The pre-catchup (1976-1984) cohort was women who had presumptively limited MMR vaccination coverage with only one dose provided by the public program. The catch-up (1985-1993) cohort was woman who had limited MMR vaccination coverage, but were given the measles-rubella (MR) vaccine during the 2001 catch-up campaign.[9] The keep-up (≥ 1994) cohort was women who were candidates for the keep-up program.[9]

Statistical analysis

Categorical variables are presented as frequencies and percentages. The chi-squared test was used to compare categorical variables. The Cochran-Armitage test for trend was performed to evaluate the seroprevalence of anti-rubella IgG by year and cohort. Multivariable-adjusted logistic regression models were used to estimate the odds ratio (OR) of being immune to rubella based on the results of the anti-rubella IgG seroprevalence test for the tested years, age, birth cohort, and geographic region in South Korea. Variables with univariate *p*-values less than 0.05 were included as adjusted variables for the multivariable analysis. Statistical analysis was executed using MedCalc Statistical Software version 18.5 (MedCalc Software bvba, Ostend, Belgium). *P*-values were considered significant at the 0.05 level.

Results

General characteristics of the study population

Between January 2010 and December 2017, anti-rubella IgG test results from 328,426 Korean women age 15-49 years who had visited obstetric private clinics (from 1,438 institutions nationwide) and had requested rubella-specific IgG antibody tests from Green Cross Laboratories were obtained from the laboratory information system and included in the study. The numbers for anti-rubella IgG results for the study subjects by each year and age group are summarized in Table 1.

Rubella immunity in Korean women of childbearing age

The overall proportion of IgG-negative women who were defined as ‘unimmunized’ was 8.6%, and the overall proportion of IgG-equivocal women was 15.0% and IgG-positive women was 76.4%. Rubella-specific IgG antibody test results with an annual incidence of rubella infection and congenital rubella syndrome from surveillance data by year are summarized in Figure 1. There were significant differences in the rate of unimmunized women during the 8-year study period ($p < 0.05$), although there was no significant trend ($p > 0.05$). There was a decrease in the rate of women who had positive rubella-specific IgG antibody results (from 81.0% in 2010 to 73.0% in 2017, $p < 0.05$), and an increase in the rate of women who had ‘equivocal’ results from 2010 to 2017 (11.0% in 2010 to 17.6% in 2017, $p < 0.05$, Figure 1). There were significant differences in the rate of unimmunized women among different age groups, cohorts, and geographic regions ($p < 0.05$). For example, less than 1,000 women had been tested for anti-rubella IgG in the Gangwon province and Ulsan.

Multivariable–adjusted logistic regression models showed that the odds of being immune to rubella (positive and equivocal results of anti-rubella IgG tests) were decreased in 2017 compared to 2010 (OR 0.63, 95% confidence interval, [CI] 0.60–0.67, $p < 0.0001$) and women in their 40s (OR 0.85, 95% CI ,0.79–0.90, $p < 0.0001$, Table 2). Among different cohorts, catch-up (being born in 1985–1993) and keep-up (born ≥ 1994) cohorts had higher ORs for being immune to rubella compared with pre-catch up cohorts (born in 1976–1984, $p < 0.0001$). Among different geographic regions, women living in Incheon, Busan, South Gyeongsang, North and South Jeolla, and Jeju provinces had lower ORs and women living in Sejong city and Daejeon had higher ORs for being immune to rubella in comparison with women living in Seoul ($p < 0.0001$).

Discussion

In this study, we investigated the seroprevalence of rubella in Korean women of childbearing age within the past 8 years. The strength of this study was the large study population over a long study period (8 years) and the novelty of the study population (Korean women of childbearing age were assessed for the first time in Korea). Because previous studies focused on the different measurement methods and immunization status, this suggested that equivocal results might be due to being immune to rubella infection, [18 19] thus, the authors focused on and analysed factors associated with those whose anti-rubella IgG results were negative.

Understanding the spread of infectious diseases and designing optimal control strategies is a major goal of public health.[20 21] In the present study, the seronegativity prevalence was 8.6% in Korean women of childbearing age. A recent 16-year review of seroprevalence studies on rubella assessing 97 articles between January 1998 and June 2014 had reported that seroprevalence ranged from 53.0% to 99.3% for rubella studies.[3] A recent meta-analysis of rubella among pregnant and childbearing age women had reported that approximately 88% of the studies conducted on pregnant women had reported a seronegativity rate >5%, and the pooled rubella seronegativity prevalence was 9.3%.[5] The study had reported that global seronegativity prevalence was of concern, considering that WHO set the rubella susceptibility threshold at 5% for women of childbearing age. Previous studies that had been included in the meta-analysis had used more than 1,000 subjects and had been published within the past 10 years are summarized in Table 3.

The seroprevalence of rubella in Korean populations was assessed previously in infants, children, and adolescents.[12-16] One study on 5,393 students from 8 elementary schools in the Gyeonggi province, Korea in 1993, 1996, and 1996 had reported that the age-adjusted rubella susceptibility rate was 22.9%.[14] Another study performed during the same study period had reported that rubella antibody loss rates were 14.3-15.8% in Korean children.[12] In a 2005 population-based survey in Nonsan, Korea, age-appropriate immunization among urban-rural children aged 24-35 months had reported that the age-appropriate MMR immunization rate was 61.1%-97.4%.[16] A recent study conducted between September 2009 and December 2010 assessing seroprevalence of rubella in 295 infants and 80 of their mothers had reported that seropositive rates were 22.4% in infants and 98.8% in mothers (79/80).[13] In that study, because none of the infants had a history of MMR vaccination, natural infection, or contact with an infected person, it was assumed that specific antibodies were passed from their mothers to their infants.[13] Moreover, among the 80 mothers, 55 (68.8%) had experienced either immunization or past rubella infection.[13]

The historical immunization coverage in pre-school children right before admission to elementary school, which was evaluated based on a telephone survey, reported 99.5% in 2001 and 97.3% of school-aged children (catch-up cohort) were vaccinated with the MR vaccine.[22] According to the Infectious Disease Surveillance Yearbook 2017, published by the Korean Ministry of Health and Welfare and the Korean Centers for Disease Control and Prevention, the incidence rate of rubella from 2001–2017 decreased (from 0.17 per 100,000 population in 2001 to 0.01 per 100,000 population in 2017).[6] In this study, ORs for being immune to rubella infection were higher in the catch-up (born 1985–1993) and keep-up (born ≥ 1994) cohorts than in pre-catch up cohorts (born 1976–1984) which suggests that catch-up and keep-up immunization was effective.[22] The vaccine coverage rate was maintained at > 95% from 2010 to 2017 in South Korea (ranges 97.0% in 2012 to 99.8% in 2010).[22] No rubella outbreak had been reported in South Korea over 8 years (2010-2017) according to the Infectious Disease Surveillance Yearbook. Among the different age groups, older women were more likely to have negative IgG results and no protection from rubella infection. Women in their 30s had the lowest rate of IgG+ results in this study. According to recent data from Korean Statistical Information (KOSIS), the average maternal age at delivery for Korean women was 32.4 years in 2016. Because of this, public health efforts should be focused on catch-up activities. The results of this study could be used as basic knowledge to support strengthening disease control and prevention of rubella, including a nationwide immunization program.

In South Korea, national guidelines in force to control and prevention measles and rubella include national immunization program and active disease surveillance system.[2 4 22] MMR vaccination has been covered by national health insurance that provides free of charge immunization to all children aged ≤ 12 years and clinical laboratory screening for rubella immunization status using anti-rubella specific IgG tests in pregnant women has been covered by the national health insurance free of charge for women visiting obstetrics clinics.[17] Susceptible woman of childbearing age is indeed a priority, and public health efforts should be focused on catch-up activities in order to reduce the rate of susceptible young adults, especially for all women of childbearing age.[23] Gynecologists and general practitioners should be encouraged to propose rubella screening for women of childbearing age before they become pregnant to identify those women who lack rubella antibodies, whether acquired as the result of vaccination or a natural infection.[23] Finally, active surveillance from laboratories that perform rubella immunity testing should be planned; laboratories should notify the Public Health Authority about every woman of childbearing age with a negative test, and the Public Health Authority should engage these women to promote immunization against rubella.[23] Serological surveillance is an important tool for the evaluation of vaccination programs and avoids the limitations of passive disease reporting systems; this is one of the entry points for congenital rubella syndrome surveillance, where gaps limit the ability to monitor progress towards its elimination.[23]

In this study, women living in Sejong city were the most protected from rubella infection. In early 2007, the South Korean government had created a special administrative district from parts of the South Chungcheong and North Chungcheong provinces, near Daejeon, to relocate nine ministries and four national agencies from Seoul. Various government programs for encouraging more births, such as incentives, in different regions may have affected the results.[4] In this study, less than 1,000 women had been tested for anti-rubella IgG in the Gangwon province and Ulsan. This may affect the percent seropositivity of anti-rubella IgG in the present study. Future studies are needed to define the effect of regional differences of government strategies on rubella seroprevalences.

One limitation of this study was the lack of clinical information, such as vaccination history or contact history with rubella-infected individuals. The results of this study were prone to ascertainment bias because the study population was based on mostly private obstetric clinics, thus results might be different from those obtained from individuals using national or public health care providing institutions, although the use of a population-based study minimized selection bias.[24] Because the exact proportions of pregnant women in Korea who utilized public health facilities to test for anti-rubella IgG, and their socio-demographics as well as rubella vaccine coverage among the population seeking health care from private and public sectors and the proportion of pregnant women as well as the general population seeking care from the private sector across provinces were not available, future studies to evaluate those factors associated with rubella control and prevention are needed. However, we do not yet understand what surrogate markers, other than antibodies, show longer-term cell-mediated immunity and protection from disease.[1] Seroprevalence studies are an essential tool to monitor the efficacy of vaccination programmes, to understand population immunity and to identify populations at higher risk of infection.[25] This study is a cross-sectional study and merely descriptive analyses were adopted in this study. The results of this study were prone to ascertainment bias. The present study did not include men, women with older ages, or foreigners living in South Korea. Therefore, the findings are not generalisable to these groups. A systems-level approach to understanding the development and maintenance of acute and long-term immunity to rubella and a rubella-containing vaccine is needed.[1]

Conclusions

In conclusion, this study investigated immunization status of rubella among Korean women of childbearing age. Considering the immunization status by age group and the increased prevalence of women with equivocal results, future public health efforts should be focused on catch-up activities. The results of this study could be used as foundational knowledge for strengthening disease control and prevention of rubella, including a nationwide immunization program.

Contributors

All authors contributed to manuscript preparation; Rihwa Choi and Sang Gon Lee, conception, design, statistical analyses and interpretation of the data; Rihwa Choi, Youngju Oh, Sung Ho Kim, and Sang Gon Lee, data acquisition; Rihwa Choi, article drafting; Rihwa Choi, Sang Gon Lee, and Eun Hee Lee, critical article revision for important intellectual content; Sang Gon Lee and Eun Hee Lee, obtaining funding; Rihwa Choi, Yejin Oh, Youngju Oh, and Sung Ho Kim, administrative and technical support; Rihwa Choi, Youngju Oh, and Sung Ho Kim, collection and assembly of data. All authors read and approved the final manuscript.

Patient consent for publication

Not required.

Ethics approval

This study was approved by the Institutional Review Board of Green Cross Laboratories (GCL 2017-1010-02).

Data sharing statement

The datasets generated and/or analysed during the current study are not publicly available due to individual privacy regulations, but are available from the corresponding author on reasonable request.

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Table 1 Test results for anti-rubella IgG by each tested-year and age for 328,465 Korean women tested for rubella IgG antibodies.

Test year	15-20 years				21-30 years				31-40 years				41-49 years			
	N	E	P	Total	N	E	P	Total	N	E	P	Total	N	E	P	Total
2010	8	48	312	368	1,332	2,499	13,628	17,459	1,640	1,601	16,691	19,932	87	102	623	812
	2.2%	13.0%	84.8%	9.4%	7.6%	14.3%	78.1%	14.1%	8.2%	8.0%	83.7%	10.4%	10.7%	12.6%	76.7%	8.6%
2011	25	64	451	540	1,717	3,024	13,376	18,117	2,167	2,600	17,668	22,436	120	103	687	910
	4.6%	11.9%	83.5%	13.8%	9.5%	16.7%	73.8%	14.6%	9.7%	11.6%	78.8%	11.8%	13.2%	11.3%	75.5%	9.6%
2012	30	105	439	574	1,381	2,899	13,388	17,668	2,321	3,438	19,407	25,166	225	137	1,125	1,487
	5.2%	18.3%	76.5%	14.7%	7.8%	16.4%	75.8%	14.2%	9.2%	13.7%	77.1%	13.2%	15.1%	9.2%	75.7%	15.8%
2013	23	113	379	515	1,195	2,491	11,989	15,675	2,477	3,867	18,106	24,450	135	106	875	1,116
	4.5%	21.9%	73.6%	13.2%	7.6%	15.9%	76.5%	12.6%	10.1%	15.8%	74.1%	12.8%	12.1%	9.5%	78.4%	11.8%
2014	35	100	405	540	778	2,032	11,793	14,603	2,142	3,662	17,906	23,710	111	108	919	1,138
	6.5%	18.5%	75.0%	13.8%	5.3%	13.9%	80.8%	11.8%	9.0%	15.4%	75.5%	12.4%	9.8%	9.5%	80.8%	12.1%
2015	29	84	398	511	674	2,032	11,596	14,302	2,407	4,361	18,467	25,235	137	91	997	1,225
	5.7%	16.4%	77.9%	13.1%	4.7%	14.2%	81.1%	11.5%	9.5%	17.3%	73.2%	13.2%	11.2%	7.4%	81.4%	13.0%
2016	39	79	389	507	651	1,887	11,152	13,690	2,573	4,532	18,304	25,409	142	105	1,029	1,276
	7.7%	15.6%	76.7%	13.0%	4.8%	13.8%	81.5%	11.0%	10.1%	17.8%	72.0%	13.3%	11.1%	8.2%	80.6%	13.5%
2017	39	78	228	345	779	1,985	9,922	12,686	2,689	4,709	17,151	24,549	162	118	1,196	1,476
	11.3%	22.6%	66.1%	8.8%	6.1%	15.6%	78.2%	10.2%	11.0%	19.2%	69.9%	12.9%	11.0%	8.0%	81.0%	15.6%
Total	228	671	3,001	3,900	8,507	18,849	96,844	124,200	18,416	28,770	143,700	190,886	1,119	870	7,451	9,440
	5.8%	17.2%	76.9%		6.8%	15.2%	78.0%		9.6%	15.1%	75.3%		11.9%	9.2%	78.9%	

Abbreviations: E, equivocal; N, negative; P, positive

Table 2 Association between seroprevalence of anti-rubella IgG (being immune to rubella)* and population characteristics

	Total	Immune		Univariable logistic regression			Multivariable logistic regression		
	n	n	%	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Tested year									
2010	38,571	35,504	92.0						
2011	42,002	37,973	90.4	0.81	0.78-0.86	<0.0001	0.79	0.75-0.83	<0.0001
2012	44,895	40,938	91.2	0.89	0.85-0.94	<0.0001	0.85	0.81-0.89	<0.0001
2013	41,756	37,926	90.8	0.86	0.81-0.90	<0.0001	0.78	0.74-0.82	<0.0001
2014	39,991	36,925	92.3	1.04	0.99-1.10	0.1368	0.91	0.86-0.96	0.0003
2015	41,273	38,026	92.1	1.01	0.96-1.07	0.6586	0.84	0.80-0.89	<0.0001
2016	40,882	37,477	91.7	0.95	0.90-1.00	0.0520	0.75	0.72-0.79	<0.0001
2017	39,056	35,387	90.6	0.83	0.79-0.88	<0.0001	0.63	0.60-0.67	<0.0001
Age of women									
15-20 years	3,900	3,672	94.2						
21-30 years	124,200	115,693	93.2	0.84	0.74-0.97	<0.0001			
31-40 years	190,886	172,470	90.4	0.58	0.51-0.67	<0.0001			
41-49 years	9,440	8,321	88.1	0.46	0.40-0.54	<0.0001	0.85	0.79-0.90	<0.0001
Cohort									
Pre-catch up (1976-1984)	228,176	205,536	90.1						
Catch-up (1985-1993)	94,056	88,887	94.5	1.89	1.84-1.95	<0.0001	1.99	1.92-2.05	<0.0001
Keep-up (≥1994)	6,194	5,733	92.6	1.37	1.24-1.51	<0.0001	1.50	1.36-1.65	<0.0001
Geographic locations									
Seoul	65,380	59,821	91.5						
Gyeonggi Province	131,157	120,183	91.6	1.02	0.98-1.05	0.3078			
Incheon	9,611	8,747	91.0	0.94	0.87-1.01	0.1111	0.93	0.86-1.00	0.0382
Gangwon Province	703	654	93.0	1.24	0.93-1.66	0.1478			

Sejong City	3,859	3,623	93.9	1.43	1.25-1.63	<0.0001	1.20	1.05-1.37	0.0076
Daejeon	12,496	11,553	92.5	1.14	1.06-1.22	0.0004	1.07	1.00-1.15	0.0484
North Chungcheong Province	11,186	10,306	92.1	1.09	1.01-1.17	0.0252			
South Chungcheong Province	8,390	7,710	91.9	1.05	0.97-1.14	0.2178			
Daegu	14,781	13,473	91.2	0.96	0.90-1.02	0.1739			
Ulsan	660	625	94.7	1.66	1.18-2.34	0.0037			
North Gyeongsang Province	2,075	1,891	91.1	0.96	0.82-1.11	0.5577			
South Gyeongsang Province	4,426	3,994	90.2	0.86	0.78-0.95	0.0039	0.85	0.77-0.95	0.0023
Busan	12,574	11,376	90.5	0.88	0.83-0.94	0.0002	0.86	0.81-0.91	<0.0001
Gwangju	2,035	1,845	90.7	0.90	0.78-1.05	0.1848			
North Jeolla Province	11,911	10,890	91.4	0.99	0.92-1.06	0.8031	0.93	0.87-0.99	0.0213
South Jeolla Province	13,621	12,233	89.8	0.82	0.77-0.87	<0.0001	0.79	0.75-0.84	<0.0001
Jeju Province	23,561	21,232	90.1	0.85	0.81-0.89	<0.0001	0.83	0.79-0.87	<0.0001

[*]Positive and equivocal results of anti-rubella specific IgG test results were defined as 'immune' in this study.[18]

Table 3 Previous studies on rubella seronegativity in women that included more than 1,000 subjects and were published within the past10 years, grouped by World Health Organization region.

WHO region	Publication year	N	Country	Seronegativity (%)	Population	Reference	Measurement method
AFR	2009	7,430	South Africa	6.2	WCBA	Schoub et al. [26]	Bio-Rad Platelia Rubella IgG ELISA
AMR	2009	8,939	Brazil	28.4	Pregnant	Inagaki et al. [27]	Q-Preven IgG-DBS kit
AMR	2011	9,610	Brazil	11.6	Pregnant	Artimos de Oliveira et al. [28]	Beckman Coulter Access RUBELLA IgG ChLIA or bioMérieux VIDAS RUB IgG II ELFA
AMR	2016	54,717	Brazil	4.5	Pregnant	Avila Moura et al. [29]	Q-Preven IgG-DBS kit
AMR	2009	5,783	Canada	7.0	Pregnant	McElroy et al. [30]	Hemagglutination inhibition test
AMR	2013	459,963	Canada	4.4	WCBA	Lim et al. [31]	Abbott AxSYM Rubella IgG MEIA
AMR	2015	157,763	Canada	15.9	Pregnant	Lai et al. [32]	Abbott ARCHITECT Rubella IgG CMIA
EMR	2014	4,062	Kuwait	6.8	Pregnant	Madi et al. [33]	Abbott ARCHITECT Rubella IgG CMIA
EMR	2013	2,284	Morocco	9.8	Pregnant	Belefquih et al. [34]	Siemens Enzygnost Anti-Rubella-Virus IgG EIA
EMR	2014	10,276	Saudi Arabia	8.7	Pregnant	Sharifa et al. [35]	Dade Behring ELISA BP III
EUR	2012	424,876	England	2.6	Pregnant	Byrne et al. [36]	Microgen Mercia Rubella G EIA
EUR	2013	1,090	Germany	1.6	Pregnant	Enders et al. [37]	Hemagglutination inhibition test
EUR	2013	74,810	Ireland	6.2	Pregnant	O'Dwyer et al. [38]	Method not described
EUR	2012	2,385	Italy	8.0	Pregnant	De Paschale et al. [39]	DiaSorin ETI-RUBEK-G PLUS EIA
EUR	2015	22,681	Spain	5.9	Pregnant	Vilajeliu et al. [40]	Siemens ADVIA Centaur Rubella G ChLIA
EUR	2010	41,637	Sweden	4.2	Pregnant	Kakoulidou et al. [41]	Abbott AxSYM Rubella IgG MEIA
EUR	2009	1,972	Turkey	3.9	Pregnant	Tamer et al. [42]	Abbott AxSYM Rubella IgG MEIA
EUR	2012	5,959	Turkey	1.9	Pregnant	Uysal et al. [43]	bioMérieux VIDAS RUB IgG II ELFA
EUR	2011	11,987	UK	4.4	Pregnant	Matthews et al. [44]	DiaSorin ETI-RUBEK-G EIA
EUR	2016	19,046	UK	6.3	Pregnant	Ogundele et al. [45]	Roche E602 MODULAR analyzer
SEAR	2011	2,224	Nepal	9.2	WCBA	Upreti et al. [46]	Enzygnost Anti-Rubella-Virus IgG EIA
SEAR	2014	1,988	Vietnam	28.9	Pregnant	Miyakawa et al. [47]	bioMérieux Mini VIDAS EIA
WPR	2008	1,020	Australia	2.7	WCBA	Nardone et al. [48]	Siemens Enzygnost Anti-Rubella-Virus IgG EIA
WPR	2008	2,741	Japan	6.7	Pregnant	Okuda et al. [49]	Hemagglutination inhibition test
WPR	2013	13,924	Japan	2.7	Pregnant	Hanaoka et al. [50]	Hemagglutination inhibition test
WPR	2014	20,363	Japan	4.7	Pregnant	Yamada et al. [51]	Hemagglutination inhibition test
WPR	2017	782,293	China	33.8	WCBA	Liu et al. [52]	Method not described
WPR	2011	43,640	Taiwan	10.9	Pregnant	Lin et al. [53]	Abbott AxSYM Rubella IgG MEIA and Beckman Coulter Access RUBELLA IgG ChLIA
WPR	2012	14,090	Taiwan	6.5	Pregnant	Lin et al. [54]	Abbott AxSYM Rubella IgG MEIA
WPR	2019	327,637	Republic of Korea	8.7	WCBA	This study	Abbott ARCHITECT Rubella IgG CMIA

Abbreviations: AFR, Africa Region; AMR, American Region; EMR, Middle East Region; EUR, European Region; SEAR, East Asian Region; WCBA, Women of childbearing age; WHO, World Health Organization; WPR, Western Pacific Region.

Figure Legends

Figure 1 Rubella-specific IgG antibody test results with annual incidence of rubella infection and congenital rubella syndrome from surveillance data by year (2010 – 2017). Percentage of rubella specific IgG results in this study (left axis) and numbers of cases for incidence of rubella from surveillance data (right axis) are plotted against years tested.

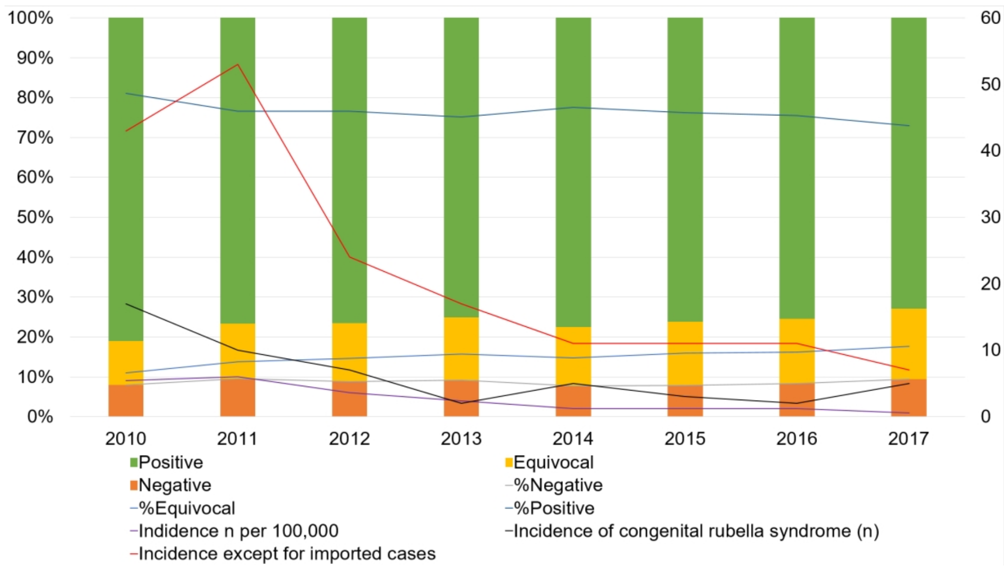

Figure 1 Rubella-specific IgG antibody test results with annual incidence of rubella infection and congenital rubella syndrome from surveillance data by year (2010 – 2017). Percentage of rubella specific IgG results in this study (left axis) and numbers of cases for incidence of rubella from surveillance data (right axis) are plotted against years tested.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6-7
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	6-7
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.