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A HERD IMMUNITY TO RUBELLA VIRUS IN SELECTED GEOGRAPHICAL REGIONS

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Abstract. Since 2017, the incidence rate of rubella in the Russian Federation has been below 1 case per million total population. In addition, no circulation of endemic strains of the rubella virus is recorded evidencing about achieving infection elimination phase. In modern conditions, it is important to constantly monitor the level of herd immunity to the rubella virus to identify epidemically significant population groups, especially in countries lacking rubella vaccination or featured with insufficient disease control. Purpose: to study herd immunity to the rubella virus in selected countries in Eurasia and Africa. *Materials and methods.* Between 2018 and 2021, 15,594 samples of blood sera were tested for IgG and IgM antibodies to the rubella virus from subjects of different ages obtained from regional measles and rubella surveillance centers in the Northwestern Federal District (NWFD) of the Russian Federation, the Republic of Serbia, South Vietnam, and the Republic of Guinea. The "Anti-Rubella Virus ELISA (IgM)" and "Anti-Rubella Virus ELISA (IgG)" (Euroimmun, Germany) test kits were used. Statistical data processing was carried out using the MS Excel, Prizm 5.0 (GraphPad Software Inc.), and Statistica 8.0 (StatSoft Inc.) software package. *Results.* During the observation period (2018–2020) the population seroprevalence of the to the rubella virus in the NWFD of the Russian Federation was 96.6–97.7% and fluctuated slightly both in separate years and among individual age groups evidencing about high coverage of rubella vaccination. In the Republic of Serbia conducting two-fold immunization against rubella the overall seroprevalence rate was lower than in the Russian Federation and comprising 86.8%. The minimum number of IgG-positive sera was recorded in the 2–4-year-old age group pointing to the shortcomings of routine vaccination. In South Vietnam, children aged 1–3 years (41.9%) predominated among those recovering from rubella, i.e. the age cohort that should be protected by vaccination at the age of 18 months. No rubella vaccination is carried out in Guinea. The total proportion of seropositive individuals was 75%; herd immunity to the rubella virus was established mainly among children and adolescents, reaching 90% only in the older age group. 30% of unprotected subjects of the most active reproductive age were identified among the females surveyed in Guinea. *Conclusion.* Insufficient herd immunity to the rubella virus, identified in a number of countries, may contribute to the maintenance of the infectious process and the spread of infection. Globalization contributes to the virus importation into regions being at the stage of measles and rubella elimination. The results obtained suggest about a need to continue efforts aimed at maintaining epidemiological wellbeing regarding rubella in diverse countries of the world.

Key words: *rubella, herd immunity, vaccination, Russian Federation, Republic of Serbia, South Vietnam, Republic of Guinea.*

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КОЛЛЕКТИВНЫЙ ИММУНИТЕТ К ВИРУСУ КРАСНУХИ В НЕКОТОРЫХ ГЕОГРАФИЧЕСКИХ РЕГИОНАХ

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Резюме. Начиная с 2017 г. в Российской Федерации показатель заболеваемости краснухой находится на уровне ниже 1 случая на 1 млн населения. Также отсутствует циркуляция эндемичных штаммов вируса краснухи. Это свидетельствует о достижении фазы элиминации инфекции. В современных условиях важным является постоянный мониторинг уровня коллективного иммунитета к вирусу краснухи для выявления эпидемически значимых групп населения, особенно в странах, где вакцинация против краснухи не проводится или контроль недостаточен. Цель исследования: изучение коллективного иммунитета к вирусу краснухи в ряде стран Евразии и Африки. *Материалы и методы.* В период с 2017 по 2021 г. на IgG- и IgM-антитела к вирусу краснухи исследовано 15 594 образца сывороток крови лиц разного возраста, полученные из региональных центров по надзору за корью и краснухой в СЗФО РФ, Республике Сербия, в Южном Вьетнаме, в Гвинейской Республике. Использовали ИФА тест-наборы «Anti-Rubella Virus ELISA IgM» и «Anti-Rubella Virus ELISA (IgG)» (Euroimmun, Германия). Статистическая обработка результатов проводилась с помощью пакета программ MS Excel, Prizm 5.0 (GraphPadSoftware Inc.), Statistica 8.0 (StatSoft Inc.). *Результаты.* В СЗФО РФ за период наблюдения серопревалентность населения к вирусу краснухи составляла 96,6–97,7% и колебалась незначительно как по отельным годам, так и среди отдельных возрастных групп, что свидетельствуют о высоком охвате вакцинацией против краснухи. В Республике Сербия общий показатель серопревалентности оказался ниже, чем в РФ, и составил 86,8%. Наименьшее количество IgG-положительных сывороток регистрировали в возрастной группе 2–4 года, что говорит о недостатках плановой вакцинации. В Южном Вьетнаме среди переболевших краснухой преобладали дети в возрасте 1–3 года (41,9%), то есть та группа, которая должна быть максимально защищена плановой прививкой против краснухи в 18 месяцев. В Гвинее специфическая профилактика краснухи не проводится. Общая доля серопозитивных лиц составила 75%, коллективный иммунитет к вирусу краснухи формировался, в основном, среди детей и подростков, достигая 90% лишь в старшей возрастной группе. Среди обследованных женщин Гвинеи выявлено 30% незащищенных лиц наиболее активного репродуктивного возраста. *Заключение.* Недостаточный уровень коллективного иммунитета к вирусу краснухи, выявленный в ряде стран, может способствовать распространению инфекции, а условия глобализации — импортированию вируса в регионы, находящиеся на этапе элиминации кори и краснухи. Полученные результаты свидетельствуют о необходимости продолжения усилий, направленных на поддержание эпидемиологического благополучия в отношении краснухи в разных странах мира.

Ключевые слова: *краснуха, коллективный иммунитет, вакцинопрофилактика, Российская Федерация, Республика Сербия, Южный Вьетнам, Гвинейская Республика.*

Introduction

The Strategic Program for Measles and Congenital Rubella Prevention was developed by the WHO in 2002, and in 2004 it also included the rubella elimination target [17, 18]. Postnatal rubella is a mild infectious disease, predominantly of childhood, characterized by a maculopapular rash and an unexpressed syndrome of general intoxication. Congenital rubella infection is a severe systemic lesion of organs and tissues with intrauterine fetal damage in a pregnant woman sick with rubella.

In 1999, about 800 000 cases of rubella were reported in Europe. By 2008, their number dropped to 18 000. Such a significant decrease in the spread of infection in the region was primarily due to rubella vaccination campaigns in the Russian Federation and CIS countries [14]. However, against the background of a general reduction in incidence in 2009, there was a large outbreak in the Republic of Bosnia and Herzegovina (523 cases). A large number of rubella cases in 2015–2020 were reported in several countries in East, South-East and South Asia, as well as in the WHO African Region [1, 3, 5, 13, 16, 19, 21].

Rubella cases continued to decline in countries in the WHO European Region in 2020–2021. In 2020, 184 cases were detected in only 15 out of 53 states. The largest number of cases was registered in Poland, Ukraine, Germany, Turkey and Italy [15]. In 2021, 102 cases of rubella were registered in Europe, with 7136 cases of rubella in the world. It is likely that COVID-19 prevention and control measures taken in 2020–2021, and above all the complete or partial lockdown that took place in many countries, contributed to a further decrease in the number of reported rubella cases.

In the Russian Federation, an increase in the number of people vaccinated against rubella, both through routine immunization and the supplementary immunization campaign conducted in 2006–2007 as part of the "National Health" project, contributed to a sharp decrease in the incidence of this infection. As a result of the measures taken, the number of peo-

Table 1. 2018 to 2020 detection of rubella virus-specific IgG antibodies in the NWFD population

Years	Total sera tested	Including anti-rubella IgG+	
		abs.	share (%) M±m
2018	4989	4827	96.9±0.28
2019	4780	4639	97.05±0.24
2020	3772	3644	96.61±0.29
Total	13 541	1310	96.9±0.15

ple vaccinated against rubella increased by more than 15 million. This not only significantly reduced the incidence of rubella, but also prevented the occurrence of new cases of congenital rubella syndrome (CRS) [8, 14]. Since 2017, the rubella incidence rate in Russia has been below 1 case per million population. There was also no circulation of endemic strains of the rubella virus. All this testifies to the achievement of the rubella elimination phase in Russia [14].

At the same time, during the COVID-19 pandemic, routine vaccination against a number of infections, including measles and rubella, may have been disrupted due to the increased number of medical exemptions. In addition, there was an interruption or temporary suspension of epidemiological surveillance due to the diversion of medical staff and other resources to counter the COVID-19 pandemic. Achieving optimal coverage (≥ 95%) with two doses of measles and rubella-containing vaccine at all subnational levels (provinces, regions, districts), along with addressing gaps in population immunity, is considered critical by experts from different countries and WHO experts [9, 15, 16, 18].

In modern conditions of globalization, it is important to constantly monitor the level of herd immunity to pathogens of certain infections, including the rubella virus, in order to identify epidemically significant population groups [6, 7, 11, 20]. It is especially important to organize such monitoring in countries where rubella vaccination is not conducted, or control by methods of specific prophylaxis is not sufficient. Such studies help limit the spread of rubella into WHO regions at the measles and rubella elimination stage. The purpose of this study was to study herd immunity to the rubella virus in selected countries in Eurasia and Africa.

Materials and methods

A total of 15 594 blood serum samples from individuals aged 3 months to 82 years, obtained in the period from 2017 to 2021, were studied. Samples were provided by virological laboratories of the regional measles and rubella surveillance centers in the Northwestern Federal District (NWFD) of the Russian Federation, in the Republic of Serbia, in South Vietnam, and in the Republic of Guinea. Samples obtained from apparently healthy individuals (N = 15 272) of different ages were tested for IgG antibodies to the rubella virus. Samples obtained from patients (N = 322) of different ages with general infectious syndrome and maculopapular rash were tested for IgM antibodies to the rubella virus.

To determine IgM antibodies to the rubella virus, the "Anti-Rubella Virus ELISA (IgM)" diagnostic kit (Euroimmun, Germany) was used. For determination of IgG antibodies, the "Anti-Rubella Virus ELISA (IgG)" diagnostic kit (Euroimmun, Germany) was used according to manufacturer instructions. Statistical processing of results was carried out using the MS Excel, Prizm 5.0 (GraphPad Software Inc.), and Statistica 8.0 (StatSoft Inc.) software packages. Parametric and nonparametric methods were used. The probability value $p < 0.05$ was designated as the threshold for the significance of differences [12].

Results

Study of herd immunity to rubella virus within the framework of vaccine-based infection prevention

Among the regions included in the study, rubella vaccination is conducted in the Russian Federation, the Republic of Serbia, and the Socialist Republic of Vietnam [2, 4, 14]. In Russia and Serbia, routine vaccination includes two vaccinations: for children aged 12 months and six years old in Russia; and for children 15 months and 7 years old in Serbia. Vaccination in both countries is carried out by combined vaccines, including measles and rubella components. In Vietnam, the National Immunization Schedule includes one rubella vaccination for children aged 18 months.

In Russia's NWFD in 2018–2020, the proportion of seropositive individuals, out of 13 511 examined patients, was 96.9% and fluctuated slightly over three years (Table 1).

The intensity of immunity to the rubella virus in a population cohort in the NWFD aged 3 to 49 years (divided into six age groups) was determined in total over three years of observation (Table 2). Among those surveyed aged 4 to 29, including four age groups, significant fluctuations in the proportion of persons immune to the rubella virus were not detected.

The differences between the number of seropositive individuals under the age of 29 and those of older age (30–49 years) were statistically significant ($p < 0.05$). The proportion of those protected from rubella in the older age group was considerably lower (95.27%) than among children and young adults (97.0–98.0%), as well as compared with the average seroprevalence (96.9%).

In the Republic of Serbia, 1400 blood sera of apparently healthy individuals (aged 2 to 76 years, divided into four age groups) were examined for the presence of IgG antibodies to the rubella virus in the period 2018–2019 (Table 3).

In the first group (2–4 years), the smallest number of IgG-positive sera (72.0%) was recorded in relation to the other three age groups (89.0–90.0%). The differences were statistically significant ($p < 0.05$). Among 8–14 year-old children, adolescents and 15–49 year-old adults, seroprevalence increased to 87.2–89.0%, reaching a maximum (90.8%) in people aged 50 years and older.

When studying the intensity of immunity to the rubella virus (Table 4), it was found that a low level of anti-rubella IgG antibodies (11.0–50.0 IU/ml) was generally determined in 41.8% of the examined, main-

ly in the age groups of 8–14 (49%) and 15–25 (57.3%) year-old. Presumably, these are post-vaccination antibodies. High antibody titers (> 150 IU/ml), indicating a recent illness, were detected in 18.9% of the examined, mainly among people over 50 years old.

In the Socialist Republic of Vietnam, rubella vaccination is also included in the National Calendar. As mentioned earlier, children at the age of 18 months should be vaccinated once.

In this study, 322 blood sera from the serum bank of the Virology Laboratory of the Measles and Rubella Surveillance Center in South Vietnam were used. Sera were received in 2020–2021 from patients with exanthemic manifestations of the infectious process, aged from 3 months to 63 years (divided into 5 age groups). In accordance with the protocol adopted in the laboratory, sera were tested only for IgM antibodies to rubella virus. The obtained results are presented in Table 5. In 9.7% of the studied sera, virus-specific IgM antibodies were detected. Cases of the disease were unevenly distributed between the groups, with a significant predominance of children aged 1–3 years (41.9%) and 7–14 years (22.6%) in the overall structure of cases.

Children of preschool and primary school age (7–14 years old) form the second most important group. Among adolescents from 15 years old and adults, single cases of the disease were recorded.

Study of herd immunity to rubella virus in the absence of vaccination

Among the countries included in the study, the Republic of Guinea is a region where routine rubella vaccination is not conducted; herd immunity is formed in the conditions of natural infectious spread. Herd immunity to the rubella virus was determined by the presence of IgG antibodies in the blood sera of apparently healthy residents of the capital of Guinea, Conakry, in 2017–2018. The results are presented in Table 6.

The fewest blood serum samples (n = 42) were obtained from persons under 20 years of age due to the difficulty of obtaining clinical samples from apparently healthy children and adolescents in Guinea.

In the first four age groups (up to 50 years of age), the proportion of seropositive patients did not differ significantly and ranged from 71.4 to 75.0%, rising to 95% only in the age group of 50 years and older.

When determining seroprevalence among women (n = 109), it turned out that in general the proportion of those seropositive to the rubella virus was 80.7%. This is somewhat higher than in the population as a whole, apparently due to closer contact with female children. The proportion of seropositive patients ranged from 70% (20–29 years old) to 86% (40–49 years old). It is important to emphasize that among the surveyed young women (20–29 years old), about a third were seronegative to the rubella virus.

Table 2. Detection of rubella virus-specific IgG antibodies in different age groups of the NWFD population (2018–2020)

Age group (years)	Total sera tested	Including anti-rubella IgG+	
		abs.	share (%) M±m
3–4	2632	2579	98.0±0.27
9–10	3133	3069	97.0±0.30
16–17	2859	2754	96.33±0.35
25–29	1957	1896	97.2±0.37
30–35	1745	1669	95.6±0.49
40–49	1191	1128	94.7±0.65
Total	13 511	13 094	96.9±0.15

Table 3. Detection of rubella virus-specific IgG in different age groups of the population of the Republic of Serbia

Age (years)	Number of persons surveyed	Including anti-rubella IgG+	
		abs.	share (%) M±m
2–4	200	144	72.0±3.2
8–14	200	178	89.0±1.6
15–49	400	349	87.2±1.6
≥ 50	600	545	90.8±1.2
Total	1400	1216	86.8±0.9

Discussion

Rubella is an infection controlled by means of specific prophylaxis.

The WHO proposal to include rubella in the measles elimination program is based on the fact that rubella is less contagious than measles. In most countries, combination vaccines are in use that include a rubella-containing component [16, 17, 18, 19]. Thus, the elimination of rubella can be achieved during the implementation of the measles elimination program. It should be taken into account that the rubella elimination strategy is based primarily on achieving and maintaining a high level (> 95%) of routine vaccination coverage as a means of creating strong herd immunity.

Table 4. Intensity of rubella virus-specific humoral immunity in the population of Serbia by age group

Age (years)	Number of persons surveyed	Including anti-rubella IgG level (IU/ml)				
		< 11.0	11.0–50.0	> 50.0–100.0	> 100.0–150.0	> 150.0
		abs./%	abs./%	abs./%	abs./%	abs./%
2–4	200	56/28.0	66/32.5	27/13.5	17/8.5	35/17.5
8–14	200	22/11.0	98/49.0	40/20.0	18/9.0	22/11.0
15–25	200	30/4.9	115/57.3	12/5.0	15/7.5	29/14.4
≥ 50	400	81/20.2	140/35.0	44/11.0	32/8.0	103/25.7
Total	1000	189/18.9	418/41.8	123/12.3	82/8.2	189/18.9

Table 5. Age-related distribution of rubella cases in South Vietnam

Age, years	Total subjects examined	Including IgM+		Proportion of cases in the age group out of total number
		Abs.	Proportion, %	
< 1	165	4	2.4	12.9
1–3	74	13	17.6	41.9
4–6	15	2	13.3	6.5
7–14	38	8	18.4	22.6
15–29	10	3	30.0	9.7
30–39	7	1	14.3	3.2
40 and >	12	3	8.1	3.2
Total	322	31	9.7	100

In Russia, during the observation period (2018–2020), rubella virus seroprevalence among the NWFD population was 96.6–97.7%; it fluctuated slightly both in specific years and among specific age groups. However, the proportion of those protected from rubella in the older age group was significantly lower (95.27%) than among children and young adults (97.0–98.0%), as well as compared with the average seropositivity (96.9%).

Perhaps these differences are due to the fact that within the framework of the National Project "Health" (2007), girls and women aged 15–17 and 18–25 were subject to revaccination against rubella. Males were not immunized, which could affect the overall level of IgG-positive sera among older age groups. In general, the consistently high seroprevalence rates identified in this study in Russia's Northwestern Federal District indicate a high vaccination coverage against rubella and the effectiveness of specific infection prevention, both being part of routine and additional immunization of the population.

In the Republic of Serbia, overall seroprevalence was significantly lower than in Russia and amounted to 86.8%. At the same time, the smallest number of IgG-positive sera (72.0%) was recorded in the first age group (2–4 years). Further, the proportion of seropositive persons consistently increased with age, reaching a maximum (90.8%) in persons aged 50 years and older. Such an age distribution of persons protected from infection is more typical for the formation of herd immunity in the conditions of the natural spread of rubella. The smallest proportion of young children (2–4 years) protected from infection indicates the disadvantages of rubella vaccination. This is confirmed by a low intensity of immunity, mainly in the age groups of 8–14 (49%) and 15–25 (57.3%) years. Such low intensity is among people who should have received not only the first, but also the booster vaccination against rubella. The insufficient level of immunization coverage with the MMR vaccine, which includes the rubella component, was revealed by us earlier when studying humoral immunity to the measles virus among the population of Serbia [2, 10].

Table 6. Detection of rubella virus-specific IgG antibodies in different age groups of the population of the Republic of Guinea

Age, years	Examined individuals	Anti-rubella IgG+, abs.	Anti-rubella IgG+, %M±m
< 20	42	30	71.4±6.97
20–29	143	102	71.3±3.78
30–39	64	48	75.0±5.41
40–49	42	31	73.8±6.78
≥ 50	40	38	95.0±3.45
Total	331	249	75.2±2.37

A similar trend was found in South Vietnam when analyzing rubella cases that occurred in 2019–2020. Among those who recovered, children aged from 1 to 3 (41.9%) predominated, which represent the age cohort that should be protected by vaccination as much as possible. The second age group, where a large number of cases were observed, is represented by children of primary and secondary school age (22.6%). Thus, it can be assumed that herd immunity to rubella in Vietnam is most actively formed due to the involvement of children and adolescents in the infectious process. Consequently, routine rubella vaccination that children 18 months of age are subject to in Vietnam does not provide adequate control of the infection.

In the Republic of Guinea, unlike the other regions included in this study, there is no specific prophylaxis for rubella. It was of undoubted interest to estimate the herd immunity formation in the population as a whole, as well as in a socially significant group (women of reproductive age), under the conditions of natural spread of rubella.

The proportion of seropositive individuals, both under 20 years and in the range from 20 to 49 years old, was 73% and increased to 95% only in the age group of 50 and older. That is, herd immunity to the rubella virus in Guinea is formed mainly among children and adolescents and remains at the same level in the population. The exception is the elderly, where a higher proportion of seropositive individuals is apparently due to their closer contact with children in families. At the same time, 30% of unprotected people of the most active reproductive age were identified among the examined women; this indicates the potential for their becoming infected during pregnancy and the birth of children with congenital rubella infection. In general, under conditions of natural distribution, 75.2% of the examined persons had IgG antibodies to the rubella virus, which corresponds to the characteristics of the infection as a widespread disease with low contagiousness.

Conclusion

This study shows that vaccination has a significant impact on the formation of immunity to the rubella virus. In Russia, where for a long period of time there has been a high coverage of the population with prophylactic rubella vaccinations, seroprevalence rates

remain high, significantly exceeding 95% of persons protected from the infection in all surveyed age groups. This is illustrated by the example of such a large region as the Northwestern Federal District.

Indirectly, through identified cases of rubella infection, one can judge the insufficient coverage of routine rubella vaccination in South Vietnam. The infectious process in this region is developed mainly among children who should have received a routine rubella vaccination according to their age.

In Serbia, where double rubella immunization is carried out, there seem to be shortcomings and failures of routine vaccination as well. This is evidenced by low seroprevalence in various age groups, especially in children between 2 and 4 years (who should be protected by rubella vaccination).

The smallest proportion of seropositive individuals was registered in Guinea, which is associated with the lack of specific rubella prophylaxis and its low contagiousness. Under these conditions, women of reproductive age represent the most vulnerable group of the population, among whom up to 30% of persons susceptible to infection with the rubella virus have been identified.

The insufficient level of herd immunity to rubella, identified in a number of regions included in this study, may contribute to maintenance of the infectious process and spread of infection. Conditions of globalization contribute to virus importation into regions at the stage of measles and rubella elimination. This indicates the need for continued efforts for maintaining the epidemiological freedom from rubella in different countries of the world.

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