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Assessment of humoral immunity to the measles virus in healthcare workers

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ABSTRACT

BACKGROUND: Measles is a highly contagious, anthroponotic viral disease. In Russia, measles outbreaks were recorded in 2003, 2014, and 2019, with a rise in incidence noted since 2022. Catch-up vaccination of at-risk groups and revaccination of individuals previously vaccinated with a single dose continue. Determining antibody levels in the serum of vaccinated individuals and those with unknown vaccination and post-infection history remains relevant.

AIM: To present the results of a study on humoral immunity to the measles virus among healthcare workers, including those vaccinated against measles and individuals with unknown vaccination and post-infection history.

MATERIALS AND METHODS: An observational, single-center, cross-sectional, uncontrolled study was conducted. Inclusion criteria: employment in a healthcare organization; age over 18 years; documented history of vaccination and revaccination with a live measles vaccine completed at least three weeks before blood sampling, or unknown vaccination and post-infection status; absence of infectious disease symptoms at the time of blood sampling. The study was conducted over one month in 2024. Venous blood samples were collected, and measles virus-specific IgG antibodies (IU/ml) were determined in the serum using an enzyme-linked immunosorbent assay kit Vector-Best (Novosibirsk, Russia). The quantitative level of class G (IgG) antibodies to the measles virus was assessed. Statistical analysis was performed using StatTech v.4.1.9 software (developed by Stattech LLC, Russia).

RESULTS: The median age of vaccinated participants ($n = 133$) was 48 years (Q1–Q3: 41–54, max 76). In 66% of cases (88/133), antibody titers were at a protective level, with a mean antibody titer of 0.62 IU/ml (Q1–Q3: 0.07–2.52, max 5.0 IU/ml). During the evaluation of the relationship between antibody titers and the time since revaccination at the time of titer measurement, an inverse, weak correlation was observed. The mean age of individuals with unknown vaccination and post-infection history ($n = 40$) was 63.3 ± 6.25 years (95% CI: 61.3–65.3), with a mean antibody level of 2.17 IU/ml (95% CI: 1.47–2.81).

CONCLUSIONS: The ongoing occurrence of measles outbreaks, the presence of individuals with unknown vaccination and post-infection history, the low levels of protective post-vaccination antibodies among healthcare workers (34%; 45/133 in this study), along with the detection of protective antibody levels in all tested individuals with unknown history (100%; 40 participants), underscore the need for continued epidemiological monitoring. Timely vaccination and/or revaccination strategies are essential for maintaining population immunity.

Keywords: measles; antibodies; vaccination.

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Оценка гуморального иммунитета к вирусу кори у работников медицинских организаций

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АННОТАЦИЯ

Обоснование. Корь — антропонозное вирусное заболевание, характеризующееся высокой контагиозностью. В Российской Федерации вспышки кори регистрировались в 2003, 2014, 2019 годах, и отмечается подъём заболеваемости с 2022 года. Продолжается подчищающая вакцинация групп риска, ревакцинация лиц, привитых однократно. Актуально определение антител в сыворотке крови у привитого населения и у лиц с неизвестным прививочным и постинфекционным анамнезом.

Цель исследования — представить результаты изучения гуморального иммунитета к вирусу кори у работников медицинских организаций, привитых от кори и с неизвестным прививочным и постинфекционным анамнезом.

Материалы и методы. Исследование обсервационное одноцентровое одномоментное выборочное неконтролируемое. Критерии отбора: сотрудник медицинской организации; возраст старше 18 лет; наличие вакцинации и ревакцинации живой коревой вакциной, после завершения которой прошло не менее 3 недель, либо отсутствие информации о прививочном и постинфекционном статусе; отсутствие на момент отбора крови признаков инфекционных заболеваний. Исследование проводилось в течение 1 месяца в 2024 году. У исследуемых отбиралась венозная кровь, в сыворотках определялись специфические IgG (в МЕ/мл) к вирусу кори иммуноферментным методом с помощью набора «Вектор-Бест» (Новосибирск, Россия). Оценивался количественный уровень антител класса G (IgG) к вирусу кори. Статистический анализ проводился с использованием программы StatTech v.4.1.9 (разработчик — ООО «Статтех», Россия).

Результаты. Медиана возраста привитых обследуемых ($n=133$) составила 48 лет (Q1–Q3: 41–54, max 76). В 66% случаев (88/133) значения титра антител к вирусу кори у исследуемых были на уровне протективного, среднее значение уровня титра антител составило 0,62 МЕ/мл (Q1–Q3: 0,07–2,52, max 5,0 МЕ/мл). При оценке зависимости уровней титра антител от давности вакцинации после ревакцинации на момент проверки титров установлена обратная связь слабой тесноты. Средний возраст лиц с неизвестным прививочным и постинфекционным анамнезом ($n=40$) составил $63,3 \pm 6,25$ года (95% ДИ: 61,3–65,3), среднее значение количественного уровня антител — 2,17 МЕ/мл (95% ДИ: 1,47–2,81).

Заключение. Продолжающаяся регистрация вспышек кори, наличие лиц с неизвестным прививочным и постинфекционным анамнезом, низкий уровень защитных поствакцинальных антител в группе работников медицинских организаций (в данном исследовании 34%, у 45 из 133 обследованных), а также обследование лиц с неизвестным анамнезом для уточнения наличия защиты (по результатам исследования у 100%/40 человек имелся защитный уровень антител) подтверждают необходимость мониторингирования эпидемической ситуации для своевременного принятия мер по поддержанию иммунитета путём проведения вакцинации и/или ревакцинации.

Ключевые слова: корь; антитела; вакцинация.

Как цитировать:

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BACKGROUND

Vaccination is the most effective measure for preventing infectious diseases. In the USSR, measles vaccination was introduced in 1968 [1]. As a result, the incidence rate in 1969 decreased 3.6-fold compared with 1967 (254 and 909 cases per 100,000 population, respectively). Since 1970, the vaccination target population included children up to 14 years of age¹ Starting in May 1986, measles vaccination was administered at 12 months of age². Revaccination of children prior to school enrollment was introduced between 1987 and 1989, and was later officially incorporated into the National Immunization Schedule for children at the age of 6 years³. The current National Immunization Schedule provides for measles immunization of children and adults up to 35 years of age, and for individuals in risk groups—including healthcare personnel—up to 55 years of age⁴. As measles vaccination began in 1968, the majority of healthcare personnel are expected to have been vaccinated. However, healthcare facilities employ individuals who are not subject to vaccination based on age, including those with unknown vaccination and post-infection histories, which may contribute to their involvement in the epidemic process and necessitate screening for protective antibodies. Healthcare personnel are considered a risk group due to contact with patients with measles, and they themselves may become sources of nosocomial transmission to patients and colleagues.

The epidemiological situation of measles remains tense in various regions of Russia: during the elimination phase, new outbreaks have been reported, primarily due to migration and the presence of unvaccinated populations. For example, in the Krasnoyarsk Territory, 88% of 126 measles cases were unvaccinated; among the cases, healthcare personnel accounted for 2%, and rotational shift workers arriving from other regions, including foreign nationals, accounted for 51% [2]. According to measles surveillance data in Astrakhan Region from 2013 to 2018, 49% of cases ($n = 776$) were adults, including 6 healthcare personnel. During the same period, the proportion of seronegative individuals, reflecting the level of herd immunity to measles, reached up to 23.8% [3]. In another study, the proportion of seronegative healthcare personnel for measles virus antibodies was 19% among 515 individuals tested. Additionally, the authors noted an

inverse correlation between antibody levels and time elapsed since vaccination ($p < 0.05$), with high levels of protective antibodies observed only in the age groups of 40–49 and 50 years and older: 4.8% (95% CI, 0.98–8.62) and 7% (95% CI, 3.26–10.74), respectively [4]. In Samara, serological screening of 1503 individuals showed that 34.16% of vaccinated participants had non-protective measles antibody levels, predominantly among those under 40 years of age [5]. These findings highlight the waning immunity in vaccinated healthcare workers and the need for regular antibody monitoring with consideration for catch-up revaccination as necessary.

AIM

The work aimed to present the results of a study on humoral immunity to the measles virus among healthcare workers, including those vaccinated against measles and individuals with unknown vaccination and post-infection history.

METHODS

Study Design

It was an observational, single-center, cross-sectional, sample-based, uncontrolled study.

Eligibility Criteria

Inclusion criteria:

- Healthcare personnel
- Age over 18 years
- Prior vaccination and revaccination against measles, with at least 3 weeks having passed since the last dose, or absence of documented vaccination and history of measles infection
- No signs of infectious disease at the time of the study
- Signed informed consent

The results of the study were obtained in quantitative units. According to the manufacturer's instructions, an IgG antibody titer to measles virus below 0.18 IU/mL was considered negative, indicating no immune response, whereas values above this threshold indicated the presence of immunity, either post-vaccination or post-infection.

Study Setting

The study was conducted in Kazan (Republic of Tatarstan). The participants included healthcare workers from the Republican Dermatovenerologic Dispensary, Pediatric Polyclinic No. 11, and the Republican Blood Center.

Study Duration

The study was conducted in 2024. The planned enrollment period was 2 weeks; blood sample collection and laboratory analysis were carried out over the following 2 weeks. The total study duration was 1 month. No deviations from the planned schedule occurred during the study.

¹ Order No. 476 of the USSR Ministry of Health dated June 12, 1972, On Strengthening Measles Prevention Measures. Available at: <https://e-ecolog.ru/docs/QgJMBI08XXGyGkviZhp/>

² Order No. 426 of the USSR Ministry of Health dated March 28, 1986, On Measures to Improve Measles Prevention. Available at: <https://base.garant.ru/4101055/>

³ Order No. 375 of the Ministry of Health of the Russian Federation dated December 18, 1997, On the Immunization Schedule. Available at: <https://base.garant.ru/5365060/>

⁴ Order No. 1122n of the Ministry of Health of the Russian Federation dated December 6, 2021, On Approval of the National Immunization Schedule, the Immunization Schedule for Epidemiological Indications, and the Procedure for Preventive Vaccinations. Available at: <https://www.garant.ru/products/ipo/prime/doc/403158640/>

Intervention

To select study subjects, data from vaccination records—Form No. 063/u “Preventive Vaccination Record”—were reviewed. The aim and procedures of the study were explained to the selected individuals. A schedule for blood sampling was then prepared, and healthcare workers who had given prior verbal consent were invited to participate. Before blood collection, participants completed and signed a written informed consent form. On the day of the study, 5–8 mL venous blood samples were collected in the morning after an overnight fast, using vacutainers, in accordance with standard procedures for biological specimen collection and infection control protocols. The collected serum samples were delivered to the laboratory for testing of measles virus-specific IgG by enzyme-linked immunosorbent assay using the “Vector-Best” diagnostic kit (Novosibirsk, Russia), in accordance with the manufacturer’s instructions. Serum samples were allowed to be stored at +4 to +8°C for up to 48 hours.

Main Study Outcome

The level of measles virus-specific IgG antibodies was measured in IU/mL.

Subgroup Analysis

Among the participants, 133 healthcare workers had completed a full course of vaccination (i.e., both primary and revaccination) more than 3 weeks prior to study inclusion ($n = 133$). In 40 healthcare workers, no records of vaccination or history of measles infection were available.

Outcomes Registration

The analysis included data from Form 063/u “Preventive Vaccination Record” and statistical evaluation of serum samples for measles virus-specific antibody levels.

Ethics Approval

The study protocol was reviewed and approved by the local ethics committee of the Federal State Budgetary Educational Institution of Higher Education Kazan State Medical University, Ministry of Health of the Russian Federation (excerpt from meeting minutes No. 6 dated June 18, 2024). All study participants signed the informed consent form prior to enrollment; the consent form was approved by the ethics committee as part of the study protocol.

Statistical Analysis

The sample size was calculated based on the proportion of seropositive individuals following a complete measles vaccination course in the relevant age group, using data from previous studies [6–8] and the following formula:

$$n = (z^2 P(1-P))/d^2,$$

where n is the required sample size, z corresponds to the chosen significance level, P is the proportion of seropositive individuals, and d is the allowable margin of error.

According to previous studies, the seropositivity rate following a completed measles vaccination course ranges from 91% to 94%.

Accordingly, the z -score corresponding to a significance level of $p = 0.05$ is 1.96, and the formula is as follows:

$$\begin{aligned} n &= 1,96^2 \times 0,91 \times (1-0,91) / 0,05^2, \\ n &= 0,3146 / 0,0025 = 125.851, \\ n &\approx 126. \end{aligned}$$

The calculated sample size was 126 participants. Taking into account refusals to participate and employee absences during the study, the sample size was increased by 5%, resulting in 133 participants.

Statistical analysis was performed using StatTech software version 4.1.1 (developed by StatTech LLC, Russia).

Quantitative variables were assessed for normality using the Shapiro–Wilk test (for sample sizes less than 50).

Quantitative variables with a normal distribution were described using means (M), standard deviations (SD), and 95% confidence intervals (95% CI).

If the data were not normally distributed, quantitative variables were described using the median (Me) and interquartile range (Q_1 – Q_3).

Categorical variables were presented as absolute counts and percentages.

The direction and strength of the correlation between two quantitative variables were assessed using Spearman’s rank correlation coefficient (for non-normally distributed data).

A predictive model characterizing the dependence of a quantitative variable on factors was developed using linear regression analysis. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Participants

Healthcare personnel aged over 18 years with documented measles vaccination and revaccination completed at least 21 days prior, or individuals without documented measles vaccination and no history of measles infection, who were informed about the study objectives and provided signed voluntary informed consent, and who had no signs of infectious disease at the time of blood sampling.

Primary Results

The study included healthcare workers who had received measles vaccination and revaccination with a live measles vaccine or measles-mumps vaccine, with an average time elapsed since completion of 12 years ($Q1$ – $Q3$: 6–25, maximum 54 years).

To study post-vaccination immunity, vaccination certificate data from healthcare workers were analyzed to select individuals for whom more than 3 weeks had passed since completion of vaccination ($n = 133$), as well as individuals with unknown vaccination and infection history ($n = 40$).

Among vaccinated individuals, 66% (88/133) had protective antibody titers above 0.18 IU/mL, with a mean titer of 0.62 IU/mL (Q1–Q3: 0.07–2.52, maximum 5.0).

A correlation analysis was performed to assess the relationship between antibody titers and the time elapsed since completion of vaccination (see Fig. 1).

An inverse correlation of weak strength according to the Chedoke scale was found between the quantitative antibody titer level (IU/mL) and the time elapsed since revaccination (years): $r = -0.274$; $p = 0.001$.

The observed relationship between time elapsed since revaccination and quantitative antibody level (IU/mL) is described by the simple linear regression equation:

$$Y_{\text{time elapsed since revaccination}} = -2,101 \times X_{\text{quantitative antibody level}} + 19,87.$$

An increase of 2.1 years in time elapsed since revaccination corresponds to an expected decrease of 1 IU/mL in the quantitative antibody level. The obtained model

explains 7.7% of the observed variance in time elapsed since revaccination (see Fig. 1).

In the group with unknown vaccination and post-infection immunity status, protective measles virus antibody titers were present in all individuals (100%), with a mean antibody titer level of 2.17 IU/mL (95% CI: 1.47–2.81). No correlation was found between antibody titer and the age of the participants. In this group, a 1-year increase in age is not expected to result in changes in the quantitative antibody titer level.

DISCUSSION

Summary of Primary Results

In 66% of cases (88/133), the measles virus antibody titers among the study participants were at a protective level, with a noted tendency for antibody titers to decline as time elapsed after vaccination. In the group with unknown vaccination and post-infection immunity status, antibodies to the measles virus were detected in 100% of cases, with no established correlation between antibody titer and the age of the participants. The mean IgG antibody titer to measles virus was 0.62 IU/mL (Q1–Q3: 0.07–2.52, max 5.0) in the vaccinated group and 2.17 IU/mL (95% CI: 1.47–2.81) in the group with unknown vaccination and post-infection status.

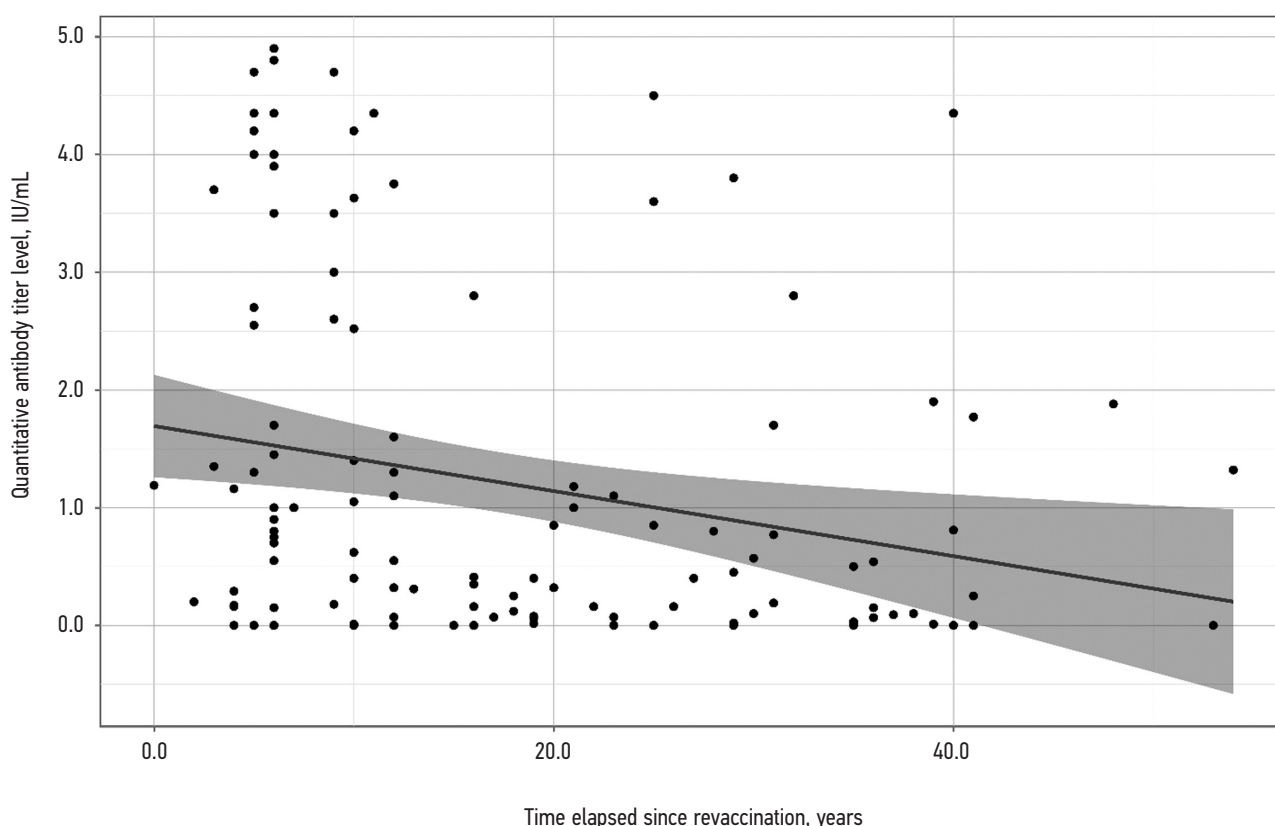


Fig. 1. Dependence of the quantitative level of measles virus antibody titers (IU/mL) on the time elapsed since revaccination (time since vaccination).

Interpretation

Detection of measles virus antibodies enables assessment of the humoral immunity formed either post-vaccination or after natural infection. Maintaining antibody levels at a high threshold requires revaccination.

Following revaccination, IgG antibody levels reach high values and remain elevated for a prolonged period [9–11].

The conducted study demonstrates the presence of sustained post-vaccination immunity for several years, though a tendency toward declining IgG levels with increasing time since vaccination was observed. The need for additional revaccination, i.e., a third vaccine dose, has been described by other authors as well [6, 7, 12–14].

In a study of individuals without documented vaccination history, 80% (274 of 351) demonstrated protective antibody levels according to serological analysis [6]. It is most likely that individuals in this group had experienced measles, as antibodies following natural infection are known for their durability and persistence [15, 16].

Study Limitations

A limitation of this study is its relatively small sample size. The limited number of participants did not allow stratification of the vaccinated group by time elapsed since completion of the vaccination course. Additionally, the study included only adults.

CONCLUSION

The ongoing occurrence of measles outbreaks, individuals with unknown vaccination and post-infection history, the low levels of protective post-vaccination antibodies among healthcare workers (34%; 45/133 in this study), along with the detection of protective antibody levels in all tested individuals with unknown history (100%; 40 participants), underscore the need for continued epidemiological monitoring in order to timely perform vaccination and/or revaccination strategies, which are essential for maintaining population immunity.

ADDITIONAL INFORMATION

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Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. Zh.G. Ereemeeva, E.S. Ardabatskaya, S.A. Ardabatsky, N.V. Ilyina, K.G. Levchenko, E.O. Ivanova, E.V. Bogdanova, R.I. Valiev: concept and design of the study, collection and analysis of literary data, Zh.G. Ereemeeva, I.R. Iskandarov writing and editing the article.

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