UDC 613.95: 614.47
DOI: 10.21668/health.risk/2024.4.09.eng

Read online

Research article

RISK OF DECLINING VACCINE-INDUCED IMMUNITY STRESS TO MEASLES, DIPHTHERIA AND PERTUSSIS IN CHILDREN UNDER EXPOSURE TO AIRBORNE METALS AND AROMATIC HYDROCARBONS

N.V. Zaitseva[1,2], O.Yu. Ustinova[1,2], V.G. Makarova[1], S.L. Valina[1], I.E. Shtina[1]

[1]Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, 82 Monastyrskaya St., Perm, 614045, Russian Federation
[2]Perm State University, 15 Bukireva St., Perm, 614068, Russian Federation

Vaccine-induced immunity stress is largely determined by safety of the environment. The aim of this study was to estimate vaccine-induced immunity stress to measles, diphtheria and pertussis in children under airborne exposures and its relationship with levels of metals and aromatic hydrocarbons in patients' blood.

The observation group was made of 417 children aged 6–17 years who lived in an area with ambient Mn, Cr, Ni and benzene levels equal to 1.0–13.8 average annual MPLs. The reference group included 196 children who lived in a tentatively safe area. The children were selected using the following criteria: completed vaccination / re-vaccination against preventable infections; living for more than 3 years in a selected area; absence of any disease in its decompensation state or ARVI; provided informed consent to participation. Chemical-analytical tests to identify levels of chemicals in blood were conducted in conformity with the valid methodical guidelines. Levels of vaccine-induced antibodies were identified by ELISA tests with their results interpreted in accordance with the requirements provided with employed test-systems.

The study established health risks in the area where the observation group lived; if expressed through hazard indexes, they amounted to 4.3 (alerting risk) for the immune system and 6.8 (high risk) for blood. A direct correlation was established between impaired vaccine-induced immunity to measles and elevated Mn and benzene levels (R^2 = 0.19–0.26; b_0 = (-1.19) – (-3.10); b_1 = 32.50–39.59; $p < 0.001$); diphtheria and elevated Mn, Cr and Ni levels (R^2 = 0.13–0.78; b_0 = (-2.95) – (-4.19) b_1 = 85.22–302.60; $p < 0.001$)); pertussis and elevated Mn level (R^2 = 0.19; b_0 = -1.19; b_1 = 39.59; $p < 0.001$). Mn (0.0210 ± 0.0012 μg/cm^3) and benzene (0.00072 ± 0.00020 μg/cm^3) levels resulted in 1.7 times lower levels of JgG to measles and thrice as high likelihood of low seroprotection (OR = 3.0; CI = 1.68–5.31). Elevated levels of Mn, Ni (0.0057 ± 0.0007 μg/cm^3) and Cr (0.0061 ± 0.0008 μg/cm^3)were associated with 1.8 times lower levels of antibodies to diphtheria and 4 times higher likelihood of low seroprotection in primary schoolchildren (OR = 3.92; CI = 1.10–13.97). Mn occurrence in blood reduced levels of antibodies to pertussis by 1.4 times and increased likelihood of impaired specific immunity by 1.8 times (OR = 1.77; CI = 1.25–2.51). Creation of high-level vaccine-induced immunity to preventable infections in children with metals and aromatic hydrocarbons in blood requires serologic monitoring, additions made in the National calendar for preventive vaccination and implementation of specialized medical and preventive technologies.

Keywords: *vaccine-induced immunity, stress dynamics, children, measles, pertussis, diphtheria, metals, aromatic hydrocarbons.*

Nina V. Zaitseva – Academician of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor, Scientific Director; Professor of Microbiology and Immunology Department (e-mail: znv@fcrisk.ru; tel.: +7 (342) 237-25-34; ORCID: http://orcid.org/0000-0003-2356-1145).

Olga Yu. Ustinova – Doctor of Medical Sciences, Deputy Director responsible for Clinical Work; Professor of Microbiology and Immunology Department (e-mail: ustinova@fcrisk.ru; tel.: +7 (342) 236-32-64; ORCID: https://orcid.org/0000-0002-9916-5491).

Venera G. Makarova – Head of the Clinical Group of Medical and Preventive Technologies (e-mail: venermakarova1969@mail.ru; tel.: +7 (342) 237-30-70; ORCID: https://orcid.org/0000-0001-9683-156X).

Svetlana L. Valina – Candidate of Medical Sciences, Head of the Department for Children and Teenagers Hygiene (e-mail: valina@fcrisk.ru; tel.: +7 (342) 237-27-92; ORCID: https://orcid.org/0000-0003-1719-1598).

Irina E. Shtina – Candidate of Medical Sciences, Leading Researcher, Head of the Laboratory for Complex Issues of Children's Health with a Clinical Group (e-mail: shtina_irina@mail.ru; tel.: +7 (342) 237-27-92; ORCID: http://orcid.org/0000-0002-5017-8232).

At present, vaccination is considered the most effective and economically expedient approach to maintaining control over preventable infections (diphtheria, measles, and pertussis) provided that 95–98 % of population is covered with mass immunization and, as a result, stressed herd immunity is created [1–4].

In Russia, vaccination against diphtheria and pertussis has been included in the National calendar for preventive vaccination since 1953. Primary vaccination involves three doses of the DPT vaccine (adsorbed pertussis diphtheria tetanus vaccine or AKDS in Russian) given to a child at the age of 3, 4.5 and 6 months. The first revaccination is accomplished at the age of 18 months (AKDS); the second, 6–7 years (ADS-M, diphtheria, tetanus); the third, 14 years (ADS-M); later on, revaccination should take place every 10 years (ADS-M) [5]. A conventional Russian-made three-component AKDS vaccine, which is used in immune prophylaxis, contains a corpuscular pertussis component as well as diphtheria and tetanus toxoids sorbed on aluminum hydroxide. In its turn, ADS-M consists of a mixture of purified diphtheria and tetanus toxoids that are also sorbed on aluminum hydroxide [3]. At present, immune prophylaxis against measles (the primary vaccination was included in the National calendar for preventive vaccination in 1967 and revaccination in 1987) relies on using a Russian-made parotiditis-measles di-vaccine or mono-vaccine against measles. Both vaccines are based on live attenuated strains of the measles virus. The immunization schedule includes two stages regardless of which vaccine is used: primary vaccination is accomplished among children aged 12 months and revaccination takes place at the age of 6 years [6].

Introduction of mass immune prophylaxis against preventable infections has a considerable effect on diphtheria, measles and pertussis prevalence. Prior to mass immunization in Russia, annual measles incidence amounted to 700–1400 thousand people (698–1192 cases per 100 thousand people) and lethality reached 0.15 % (1.4 deaths per 100 thousand people). By the end of 20th century, incidence rates went down by 6.1–9.2 times and deaths caused by measles became rare exception [6, 7]. However, the measles-related epidemiological situation has deteriorated considerably since 2021, both in Russia and abroad [8]. In 2022, measles outbreaks were detected in 37 countries across the globe (predominantly in Africa) against 22 countries in 2021 [9]. In 2023, the WHO established 60,860 measles cases in 41 countries all over the world; 95 % of them were detected in Azerbaijan, Kazakhstan, Kyrgyzstan, Russian Federation, Rumania and Turkey[1]. In 2019, 4491 measles cases were detected in Russia but the number reached 12,812 in 2023 [1]. By the end of February 2024, more than 1160 new measles cases were detected in half of the RF regions; the highest rates were established in the Rostov Oblast (more than 200 cases) and the Khanty-Mansi Autonomous Area (106 cases) [10].

Pertussis used to be one of the most common childhood infections up to 50ties last century. Introduction of mass immune prophylaxis in Russia made it possible to reduce pertussis incidence from 400–450 cases per 100 thousand people (50ties of the 20th century) to 5.8–10.8 cases per 100 thousand people (60–70ties of the 20th century). But then there was a decline in the proportion of population covered by immune prophylaxis in 80–90ties last century and this resulted in growing pertussis incidence in the country. However, annual incidence rates remained relatively stable up to 2018: 4795 cases in 2010 and 5411 cases in 2017. In 2019, there was an abrupt rise in pertussis incidence, when the total number of patients with the disease amounted to 14,407 in Russia [11, 12]. At present, pertussis incidence is wavelike in Russia and if it was 9.8 cases per 100 thousand people in 2019 (14.4 thousand cases), then it went down to 0.76 cases (1.1 cases overall) in 2021 to grow again in 2022 up to 2.18 cases per 100 thousand people (3.1 thousand cases overall). In 2023, a drastic rise in pertussis incidence was detected in Russia (36.1 cases per 100 thousand people) and the overall number of pertus-

[1] WHO EpiBrief: a report on the epidemiology of selected vaccine-preventable diseases in the European Region: No. 1/2024: technical document. *WHO*, 2024. Available at: https://www.who.int/europe/publications/i/item/WHO-EURO-2024-10248-50020-75273 (September 12, 2024).

sis cases equaled 52.8 thousand, which is the highest over the last 30 years [13]. This ascending trend in pertussis incidence persists in 2024; the number of hospital admissions due to pertussis grew by 300 % among children against the 2023 level over the first four months of the year [14]. A similar trend can be traced abroad: approximately 157 pertussis cases per 100 thousand people used to be detected in the USA prior to introduction of anti-pertussis vaccination but after mass immune prophylaxis was introduced, the number declined to 1 case per 100 thousand people. In late 90ties last century, the corpuscular pertussis component in the DPT vaccine was replaced with a less reactogenic cell-free one in most foreign countries. This resulted in a growth in pertussis incidence and epidemic outbreaks of the disease. In 2018, the WHO reported more than 151,000 pertussis cases across the globe and this ascending trend in incidence persisted over the following years in most European countries and in America[2]. In the USA, 14,569 pertussis cases were detected over 9 months of 2024 (four times as high as in 2023). Over the whole 2023 and till April 2024, more than 60 thousand pertussis cases were diagnosed in the European Union countries as well as in Norway, Iceland and Liechtenstein, which is 10 times as high as in 2022[3] [15].

Diphtheria incidence varied between 40 and 144 cases per 100 thousand people in Russia prior to introduction of mass immune prophylaxis. In 60ties last century, this rate declined considerably due to scheduled specific prevention activities and did not exceed 1.11–5.02 cases per 100 thousand people. In fell further in 70–80ties last century and was below 0.5 cases [16–28]. In 1989–1995, a considerable growth in diphtheria incidence was detected in the RF but already in 1996–1998 the number of detected diphtheria cases went down by 9.6 times; diphtheria-caused deaths, by 11.5 times; the total contamination decreased by 9 times [19]. Diphtheria incidence has been sporadic in Russia since 2009. Over the last 10 years, the maximum number of infected patients was detected in 2019 (5 people); 1 case was detected in 2020, 4 cases in 2021, and no diphtheria cases were detected in 2022–2023 [5, 20]. However, the epidemiological situation per diphtheria remains rather unfavorable at the global level. Annually between 5000 and 9000 diphtheria cases are detected across the globe and 10 % result in a fatal outcome. In 2021, 8328 diphtheria cases were detected worldwide and 94 % of infected patients resided in Ethiopia, India, Yemen, Indonesia and Afghanistan. In 2022, Austria, Belgium, France, Germany, Norway, and Switzerland reported 92 diphtheria cases among immigrants from Afghanistan, Syria, Morocco, Tunis, Bangladesh, India, Liberia and Turkey [2]. In 2023, diphtheria outbreaks were registered in Nigeria (5898 cases) and Guinea (538 cases)[4].

Therefore, analysis of the epidemiological situation as regards these preventable infections gives evidence of certain unfavorable trends in measles and pertussis incidence among Russians. Another serious threat is that diphtheria might be brought into the country due to enhancing economic and political relations between the RF and African, South-Eastern Asian and Middle East countries as well as more active migration from these regions. These infections have serious epidemiological and clinical outcomes; bearing this in mind, creation of herd (95–98 % of the population) stressed immunity is a reliable barrier able to prevent their spread [3, 4, 10].

When considering reasons that impede creation of proper herd immunity against measles, pertussis and diphtheria in Russia, most experts primarily mention the following: parents' refusal from vaccination / revaccination;

[2] Gusarova M. V Rossii zabolevaemost' koklyushem pobila 30-letnii rekord [Pertussis incidence has broken its 30-year record in Russia]. *RBK*. Available at: https://www.rbc.ru/society/28/05/2024/6655b2da9a794756999fe113 (October 04, 2024) (in Russian).

[3] OrgzdravEkspert: the web-portal for decision-makers in healthcare. Available at: https://www.orgzdrav.com/news/world/18457/ (October 04, 2024) (in Russian).

[4] Disease Outbreak News: Diphtheria – Guinea. *WHO*, October 18, 2023. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON492 (October 08, 2024); Disease Outbreak News: Diphtheria – Nigeria. *WHO*, September 13, 2023. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON485 (October 08, 2024).

adults refusing from revaccination; improper time and volumes of vaccinations / revaccinations; ungrounded refusals from immune prophylaxis due to contraindications [4, 10, 17, 18, 21]. Strict limitations introduced in 2020–2022 due to the COVID-19 pandemic had a considerable effect on prevalence of manifested preventable infections resulting in its reduction; however, the situation became worse already starting from early 2023 due to a drastic decrease in the proportion of the population covered by immune prophylaxis in previous years [1]. According to official statistical data, in 2020, 23 million children in the RF did not have all due vaccinations in accordance with the National calendar for preventive vaccination. This is not only the highest number over the last 10 years but also is by 3.7 million children higher than in 2019 [22]. The WHO reported that the proportion of children who got their first anti-measles vaccination went down to 69–92 % worldwide in 2020–2022; the proportion of those who got their second dose decreased down to 45–85 %; in some countries, not more than 48–66 % of children completed three-dose anti-diphtheria vaccination [4, 5, 17]. A growing number of children born due to assisted reproductive technologies is a large risk group as regards likelihood of preventable infections, both in Russia and abroad. Refusals from immune prophylaxis due to medical contraindications are rather typical for such children. In Russia, such patients are timely vaccinated against diphtheria and pertussis only in 71 % cases if a child is born full-term. If a child is born premature, frequency of properly completed vaccination / revaccination against diphtheria and pertussis does not exceed 6.4 % during the first three years of child's life; the same frequency reaches 51 % for anti-measles vaccination / revaccination [23].

Apart from smaller proportions of children covered by immune prophylaxis, another serious problem is insufficient vaccine-induced immunity stress. Most experts believe violations of immunization procedures to be the most frequent reason for absence of antibodies or their low levels [2, 5, 10, 17, 20]. At the same time, there is a well-known fact that sometimes, despite proper and timely immunization, a protective antibody titer is either not formed at all or lost rather rapidly. It is impossible to avoid recurrent epidemic disease outbreaks despite high proportion of population being covered by immune prophylaxis [20, 24]. According to serologic monitoring data, the proportion of such children can reach 10 % or even higher of the total number of vaccinated children [25]. Results obtained by clinical and epidemiological studies show that children who are often sick for long periods of time account for a big part of this group; the same goes for children with allergic and autoimmune diseases as low levels of vaccine-induced antibodies to measles are detected in 42 % of them and diphtheria, 16 % [25, 26]. It is established that when vaccination is accompanied with immunomodulatory therapy in such children, production of specific antibodies is reinforced for a short time; however, it does not help preserve them for a longer period [26]. Another reason for insufficient vaccine-induced immunity stress is replacement of the Russian-made AKDS vaccine with less reactogenic cell-free foreign vaccines, which are now commonly used in Russia: PENTAXIM (France), INFANRIX, INFANRIX-HEXA (Belgium), or ADACEL (Canada) [14]. Child's individual peculiarities (low gamma-interferon production, disordered bilirubin, alanine, asparagine, glutamine metabolism, etc.) also impede development of full-fledged stressed vaccine-induced immunity since these substances take active part in antibody synthesis as immunomodulators or immune protectors [24–27]. Some studies emphasize a relation between vaccine-induced immunity stress and a patient's age. In particular, the highest frequency of sufficient vaccine-induced immunity stress to diphtheria was established in adults aged 20 years or older (100 %); the lowest, in children aged 1–4 years (30.6 %) [2, 3]. A different picture is revealed concerning dynamics of vaccine-induced immunity stress when it comes down to pertussis: a number of people unprotected from the disease grows already 3 years after revaccination and a proper protective level of anti-pertussis IgG is detected only in 28 % of vaccinated adolescents and adults [21].

At present, great attention is paid to quality and safety of the environment among various reasons that determine vaccine-induced immu-

nity stress and duration of its preservation. In particular, the focus is on pollution created by man-made chemicals in environmental objects [28–30]. Few researchers who investigate the issue report that frequency of improper vaccine-induced immunity formation grows by 2.7–5.7 times among children and adolescents and by 4.0–4.4 times among adults with completed vaccination / revaccination in case they are exposed to chemical pollution in ambient air, drinking water and soils [28]. Serologic monitoring results indicate that the number of people with absent protective levels of vaccine-induced antibodies reaches 6.4–8.7 % in these population groups [30]. Some authors believe low absolute levels and weaker functional activity of immunocompetent cells caused by exposure to man-made chemical pollutants in environmental objects to be the basic reason for persisting negative trends associated with poor vaccine-induced immunity stress in residents of large industrial centers [29, 31]. At the same time, literature analysis indicates that known research results are based on comparative assessment of vaccine-induced immunity in people living in different sanitary-hygienic environmental conditions. They do not contain any data on assessment of its impairments in children and adolescents with different levels of man-made chemicals in blood and do not provide objective description of relations between revealed impairments and chemical levels in biological media. All foregoing gave grounds for accomplishing the present study.

The aim of this study was to estimate stress and impairments of vaccine-induced immunity to measles, diphtheria and pertussis in children with elevated levels of metals (manganese, chromium, and nickel) and aromatic hydrocarbons (benzene) in blood under airborne exposures.

Materials and methods. The observation group was made of 417 schoolchildren aged 6–17 years: 6–9 years, 151 children; 10–13 years, 148 children; 14–17 years, 118 children. The children from the observation group lived in a large industrial center where air quality monitoring established levels of airborne manganese (0.00014 ± 0.00003 mg/m^3), chromium (0.00011 ± 0.00001 mg/m^3), nickel (0.000051 ± 0.000008 mg/m^3) and benzene (0.0159 ± 0.0044 mg/m^3) to be equal to 1.0–13.8 average annual MPLs.

The reference group was made of 196 children of similar ages (6–9 years, 68 children; 10–13 years, 72 children; 14–17 years, 56 children), who lived in a tentatively safe area. Levels of airborne manganese did not exceed 0.000039 ± 0.000008 mg/m^3 ($p < 0.0001$ against the observation group; 0.8 average annual MPL) in this area; chromium, 0.000017 ± 0.000003 mg/m^3 ($p < 0.0001$ against the observation group; 2.1 average annual MPL); nickel, 0.000014 ± 0.000003 mg/m^3 ($p < 0.0001$ against the observation group; 0.3 average annual MPL); benzene, 0.0025 ± 0.0004 mg/m^3 ($p < 0.0001$ against the observation group; 0.5 average annual MPL).

The children were selected for participation using the following criteria: completed vaccination / re-vaccination against measles, pertussis and diphtheria with vaccines allowed for use by the valid regulatory documents[5] (any deviations from the recommended vaccination schedule did not exceed 3 months); age of 6–17 years; living for more than 3 years in a selected area; absence of any chronic somatic disease in its decompensation state or ARVI; written informed voluntary consent to medical interventions was provided.

The following criteria were used to exclude children from the study: documentarily confirmed measles, pertussis or diphtheria case in medical history; violated dates or improper number of vaccinations; use of cell-free vaccines; age younger than 6 or older than 17 years; living for less than 3 years in a selected area; presence of any chronic somatic disease in its decompensation state or ARVI; written informed voluntary consent to medical interventions was not provided.

Chemical-analytical tests were conducted to identify metals (manganese, chromium and

[5] Ob utverzhdenii natsional'nogo kalendarya profilakticheskikh privivok, kalendarya profilakticheskikh privivok po epidemiologicheskim pokazaniyam i poryadka provedeniya profilakticheskikh privivok: Prikaz Minzdrava RF ot 06.12.2021 g. № 1122n (s izmeneniyami na 12 dekabrya 2023 goda) [On Approval of the National calendar for preventive vaccination, calendar for preventive vaccinations per epidemiological indications and the procedure for preventive vaccination: the Order of the RF Ministry of Health dated December 06, 2021 No. 1122n (last edited as of December 12, 2023)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/727605537 (September 13, 2024) (in Russian).

nickel) and aromatic hydrocarbons (benzene) in biological media (blood) of all participating children. The tests were performed in conformity with the valid methodical guidelines at certified laboratories using proven equipment[6].

Levels of specific IgG antibodies to measles and pertussis virus as well as diphtheria toxoid were examined by ELISA tests to assess vaccine-induced immunity stress[7]. Research results were estimated per threshold protection values specified in appendixes to the employed test-systems: measles, < 0.12 IU/ml negative, 0.12–0.18 IU/ml uncertain, > 0.18 IU/ml positive; pertussis, < 9 a.u. negative, 9–11 a.u. uncertain, > 11 a.u. positive; diphtheria, < 0.1 IU/ml negative, 0.1–1.0 IU/ml positive. Research results were statistically analyzed using Statistica 10 software package with MS-Office applications. Parametric and non-parametric statistic procedures were applied considering distribution of analyzed variables. Results obtained by statistical analysis of laboratory tests were given as simple mean and its error ($M \pm m$) or proportions of laboratory samples with differences from the same indicator in the reference group. Statistical validity (p) of differences was estimated using Student's t-test ($t > 2.0$) and Fisher's f-test ($F \geq 3.96$) (significance taken at $p < 0.05$)[8]. Risks and likelihood of negative outcomes were assessed according to the conventional procedure[9]. Cause-effect relations were built according to the principle: 'Chemical Level in Blood – Likelihood of Declining Vaccine-Induced Immunity Stress'.

Results and discussion. The hazard quotient for the immune system per exposure to chromium reached its alerting level (HQ = 1.1) and high level per exposure to benzene (HQ = 3.2) in the area where the observation group lived. Simultaneously, its value calculated for the hematopoietic system corresponded to its high level (nickel, HQ = 3.6; benzene, HQ = 3.2). Overall, the hazard index (HI) calculated for the observation group reached 4.3 (alerting level) for the immune system and 6.8 (high level) for the hematopoietic system[9].

The hazard quotients calculated for the reference group as regards likely negative health outcomes in the immune system (HQ_1) and blood (HQ_2) did not exceed permissible levels per exposure to chromium and nickel ($HQ_1 = 0.17–0.5$; $HQ_2 = 0.5–1.0$). The hazard index did not exceed its minimal level for the immune system (HI = 0.67) and permissible level for the hematopoietic system (HI = 1.5).

Chemical analytical tests reveal 1.6–2.5 times authentically higher levels of chemicals in blood in the observation group against reference values ($p \leq 0.0001$) (Table 1). In addition, manganese levels in blood were 1.6 times higher than in the reference group ($p < 0.0001$); chromium, 2.4 times higher ($p < 0.0001$); nickel, 1.7 times higher ($p = 0.001$); benzene, 1.3 times higher ($p = 0.04$). Toluene levels did not differ between two groups ($p = 0.34$). Levels of manganese, chromium and nickel identified in the reference group did not differ from respective reference values ($p = 0.23–0.99$). Proportions of blood samples with chemical contents above

[6] MUK 4.1.3230-14. Izmerenie massovykh kontsentratsii khimicheskikh elementov v biosredakh (krov', mocha) metodom mass-spektrometrii s induktivno-svyazannoi plazmoi: metodicheskie ukazaniya, utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii A.Yu. Popovoi 19 dekabrya 2014 g. [Methodical guidelines MUK 4.1.3230-14. Measurement of mass concentrations of chemical elements in biological media (blood, urine) with mass spectrometry with inductively coupled plasma; approved by A.Yu. Popova, the Head of the federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector on December 19, 2014]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/495856222 (September 14, 2024) (in Russian); MUK 4.1.765-99. Gazokhromatograficheskii metod kolichestvennogo opredeleniya aromaticheskikh (benzol, toluol, etilbenzol, o-, m-, p-ksilol) uglevodorodov v biosredakh (krov'): metodicheskie ukazaniya, utv. Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 6 iyulya 1999 g. [Gas chromatography for quantification of aromatic (benzene, toluene, ethyl benzene, o-, m-, p-xylene) hydrocarbons in biological media (blood): methodical guidelines, approved by G.G. Onishchenko, RF Chief Sanitary Inspector on July 6, 1999]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200039012 (September 14, 2024) (in Russian); T.V. Nurislamova, Doctor of Chemical Sciences, the head of the Chemical Analysis Laboratory of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies.

[7] O.V. Dolgikh, Doctor of Medical Sciences, Associate Professor, the head of the Department of Immunobiological Diagnostics of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies.

[8] Glants S. Mediko-biologicheskaya statistika [Biomedical statistics]. Moscow, Praktika Publ., 1998, 459 p. (in Russian).

[9] Guide 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals. Moscow, The Federal Center for State Sanitary and Epidemiological Surveillance of the RF Ministry of Health, 2023, 221 p. (in Russian).

Table 1

Chemical levels in blood of the children from the study groups, μg/cm^3

Chemical	Reference level (N. Tietz, 2003)	Observation group (n = 417)	Reference group (n = 196)	Validity of intergroup differences, ($p < 0.05$)	
				Against reference group	Against reference level
Manganese	0.0130	0.0210 ± 0.0012	0.0129 ± 0.0011	< 0.0001	< 0.0001
Chromium	0.0027	0.0061 ± 0.0008	0.0026 ± 0.0003	< 0.0001	< 0.0001
Nickel	0.0023	0.0057 ± 0.0007	0.0033 ± 0.0005	0.001	< 0.0001
Benzene	0	0.00072 ± 0.0002	0.00057 ± 0.0002	0.04	< 0.0001
Toluene	0	0.00014 ± 0.00003	0.00007 ± 0.00002	0.34	0.0001

reference values were higher in the observation group than in the reference one. They equaled 49.6 % per manganese (against 25.2 % in the reference group, $p < 0.0001$), 78.1 % per chromium (against 16.8 %, $p < 0.0001$), 74.3 % per nickel (against 38.8 %, $p < 0.0001$), 52.4 % per benzene (against 31.1 %, $p < 0.0001$), and 66.3 % per toluene (against 46.8 %, $p < 0.0001$).

Average group levels of anti-measles antibodies reached 0.71 ± 0.04 IU/ml in the observation group made of children aged 6–17 years, which was higher than the respective protective level (0.18 ± 0.00 IU/ml, $p < 0.001$). At the same time, comparative analysis of the indicator in age dynamics showed a considerable decline in its value over age: average group levels of anti-measles antibodies amounted to 1.12 ± 0.13 IU/ml among schoolchildren aged 6–9 years but they went down to 0.59 ± 0.10 IU/ml among schoolchildren aged 10–13 years (1.9 times lower than in the previous age group, $p = 0.0001$), and then dropped further down to 0.42 ± 0.12 IU/ml among schoolchildren aged 14–17 years (2.7 times lower than in junior schoolchildren from the first age group, $p < 0.0001$). Our study of individual indicators established that only 71.7 % of the examined children aged 6–17 years in the observation group had a proper protective level of vaccine-induced anti-measles IgG, which is hardly sufficient for creating solid herd immunity (not lower than 95–98 %) [1, 6]. Our findings clearly indicate that 19.9 % of the examined schoolchildren with elevated contents of metals and aromatic hydrocarbons in blood are not protected from measles in spite of complete and timely vaccination; 8.4 % of them have an uncertain antibody titer and should be revaccinated (Table 2).

Frequency of impaired specific immunity to measles was significantly different in different age groups of the schoolchildren from the observation group. The share of schoolchildren

Table 2

The number of children with different stress of vaccine-induced immunity to measles in the study groups, %

Age (years)	6–17	6–9	10–13	14–17	Validity of differences, $p < 0.05$		
Observation group	***n* = 417**	***n* = 151**	***n* = 148**	***n* = 118**	p^1	p^2	p^3
Protective level is absent (< 0.12 IU/ml)	19.9	6.6	19.6	29.7	0.001	0.05	0.000
Uncertain level (0.12–0.18 IU/ml)	8.4	3.3	11.5	9.3	0.007	0.56	0.04
Protective level (> 0.18 IU/ml)	71.7	90.1	68.9	61.0	0.000	0.05	0.000
Of them, high protective level (> 1.0 IU/ml)	19.1	38.2	21.6	13.9	0.002	0.11	0.000
Reference group	***n* = 196**	***n* = 68**	***n* = 72**	***n* = 56**	p^1	p^2	p^3
Protective level is absent (< 0.12 IU/ml)	7.7	2.9	6.9	12.5	0.27	0.28	0.04
Uncertain level (0.12–0.18 IU/ml)	5.5	2.9	8.3	8.9	0.17	0.90	0.15
Protective level (> 0.18 IU/ml)	86.8	94.2	84.8	78.6	0.07	0.36	0.01
Of them, high protective level (> 1.0 IU/ml)	27.9	51.6	39.3	27.8	0.14	0.17	0.007

Note: p^1 means the number of children with different vaccine-induced immunity strain among those aged 6–9 and 10–13 years; p^2 means the number of children with different vaccine-induced immunity strain among those aged 10–13 and 14–17 years; p^3 means the number of children with different vaccine-induced immunity strain among those aged 6–9 and 14–17 years.

with the protective level of antibodies reached 90.1 % among those aged 6–9 years. It declined down to 68.9 % among schoolchildren aged 10–13 years (p = 0.0001) and even further to 61.0 % among adolescents (p = 0.0001). Likelihood of a declining number of children with a proper protective level of vaccine-induced anti-measles IgG grew by more than 4 times in the age group of 10–13 years (OR = 4.1; CI = 2.16–7.73) and by 5.8 times in the age group of 14–17 years (OR = 5.8; CI = 3.03–11.09). It is noteworthy that children with high seroprotection levels able to ensure long-term vaccine-induced protection were more frequently revealed among juniors (38.2 %), which was authentically higher than among schoolchildren aged 10–13 years (21.6 %, p = 0.002) and adolescents (13.9 %, p = 0.0001). Likelihood of a declining number of children with high seroprotection level grew by 2.3 times by the age of 10–13 years (OR = 2.3; CI = 1.36–3.77) and by 4 times by the age of 14–17 years (OR = 3.98; CI = 2.14–7.40) against the youngest age group. Overall, likelihood of an increase in a number of children with contents of vaccine-induced anti-measles antibodies below the protective level grows by 5.8 times by the age of 14–17 years among schoolchildren with elevated chemical levels in blood. A number of children protected from measles declines by one third against the junior schoolchildren (90.1 % among those aged 6–9 years against 61.0 % among those aged 14–17 years, $p < 0.0001$). A number of unprotected children who need booster vaccination grows by 3.9 times (9.9 % among those aged 6–9 years against 39.0 % among those aged 14–17 years, $p < 0.0001$) (Table 2).

The average group level of anti-measles IgG amounted to 0.98 ± 0.01 IU/ml in the children from the reference group (aged 6–17 years), which was authentically higher than in the observation group (0.71 ± 0.04 IU/ml0, $p < 0.0001$). Comparative analysis of the indicator in its age dynamics also established its decline over age. Thus, it amounted to 1.38 ± 0.04 IU/ml among juniors aged 6–9 years (1.12 ± 0.13 IU/ml in the observation group, p = 0.0001), and then went down to 0.87 ± 0.11 IU/ml among schoolchildren aged 10–13 years (0.59 ± 0.10 IU/ml in the observation group, p = 0.0002) and even lower down to 0.71 ± 0.03 IU/ml among adolescents aged 14–17 years (0.42 ± 0.12 IU/ml in the observation group, $p < 0.0001$). However, its values were still higher in all age groups in the reference group against the observation one: 1.2–1.5 times higher among those aged 6–9 years and 10–13 years respectively and 1.7 times higher in the age group of 14–17 years. Our analysis of individual levels of vaccine-induced anti-measles IgG established that only 86.8 % of the schoolchildren form the reference group aged 6–17 years had the proper protective level of specific anti-bodies (71.7 % in the observation group, $p < 0.0001$); 7.7 % of the schoolchildren in the reference group were not protected from measles (19.9 % in the observation group, $p < 0.0001$); 5.5 % had an uncertain antibody titer (8.4 % in the observation group, p = 0.20) (Table 2).

Further analysis established that likelihood of insufficient vaccine-induced protection against measles was 3.0 times higher among children aged 6–17 years with elevated chemical levels in blood than among their peers in the reference group (OR = 3.0; CI = 1.68–5.31). Moreover, it should be noted that an authentic decline in the number of children with sufficient vaccine-induced immunity occured only by the age of 14–17 years in the reference group (p = 0.01) whereas it happened at younger age of 10–13 years in the observation group (p = 0.0001) (Table 2). Mathematic modeling made it possible to establish a cause-effect relation between a decline in levels of vaccine-induced IgG to the measles virus and elevated levels of benzene (R^2 = 0.26; b_0 = -3.10; b_1 = 32.50; $p < 0.001$) and manganese (R^2 = 0.19; b_0 = -1.19; b_1 = 39.59; $p < 0.001$) in blood.

Therefore, elevated manganese and benzene levels in blood caused 3.0 times higher likelihood of insufficient vaccine-induced protection in schoolchildren aged 6–17 years who received completed and timely vaccination / revaccination against measles, reduced the number of protected people by 1.3 times already by the age of 10–13 years and caused 5.8 times higher likelihood of a growing number of children with antibody levels being below the protective one among adolescents aged 14–17 years against junior schoolchildren. Absolute levels of anti-measles JgG were 1.2–1.7 times lower in various age groups of the examined

children with elevated manganese and benzene levels in blood against the reference group.

In this study, we investigated stress of antitoxic immunity to diphtheria among schoolchildren. As a result, the protective antibody level was revealed in 94 % of the examined schoolchildren aged 6–17 years in the observation group, which is very close to the epidemiological safety level (95 %, $p = 0.89$). In addition, it is noteworthy that levels of antitoxic IgG to diphtheria were higher than 1.0 IU/ml in each third case (27.8 %) in the observation group (the protective level is 0.1–1.0 IU/ml). This indicates quite sufficient protection from the disease (Table 3).

Absolute average group levels of vaccine-induced antitoxic IgG corresponded to the required protective level in all analyzed age groups and amounted to 0.54 ± 0.03 IU/ml among schoolchildren aged 6–9 years; 0.33 ± 0.01 IU/ml, 10–13 years; 0.76 ± 0.02 IU/ml, 14–17 years. However, comparison of these levels in different age groups established some variations in their absolute values: levels of vaccine-induced antitoxic IgG to diphtheria were 1.6 times higher ($p < 0.0001$) in the age group of 6–9 years against the age group of 10–13 years. In addition, this level was 2.3 times lower in the latter group ($p < 0.0001$) against the age group of 14–17 years. Test results obtained for the age group of 6–9 years indicated that 9.3 % of the children in this group did not have any reliable protection from diphtheria and it was the maximum proportion among all analyzed age groups (6.1 % among those aged 10–13 years, $p = 0.30$; 2.5 % among those aged 14–17 years, $p = 0.07$). Likelihood of absent protection from diphtheria was established to be four times as high in junior schoolchildren in the observation group against adolescents ($OR = 3.92$, CI = 1.10–13.97). Trends typical for the middle age group (10–13 years) included not only declining levels of antitoxic IgG but also a two-time decrease in the number of children with their high levels (18.9 % against 37.1 % in the age group of 6–9 years, $p < 0.0001$). The most favorable situation as regards anti-diphtheria protection was established among adolescents where absent protection was considered a rare exception (2.5 %) and each second adolescent (54.2 %) had high levels of antitoxic IgG (Table 3).

In the reference group made of schoolchildren aged 6–17 years, a proper protective IgG level was established in 96.9 % of the cases and this was not different from the observation group (94.0 %, $p = 0.12$). However, the number of children with high levels of antitoxic antibodies was 1.6 times higher than in the observation group (44.8 % against 27.8 %, $p < 0.0001$), ($OR = 2.1$; CI = 1.44–3.01) (Table 3). Absolute average group levels of vaccine-induced antitoxic IgG to diphtheria also corresponded to the proper protective level in all analyzed age groups within the reference group and amounted to 0.69 ± 0.01 IU/ml in the age

Table 3

The number of children with different stress of vaccine-induced immunity to diphtheria in the analyzed groups, %

Age (years)	6–17	6–9	10–13	14–17	Validity of intergroup differences, $p < 0.05$		
Observation group	***n* = 417**	***n* = 151**	***n* = 148**	***n* = 118**	p^1	p^2	p^3
Protective level is absent (< 0.1 IU/ml)	6.0	9.3	6.1	2.5	0.30	0.07	0.01
Protective level (0.1–1.0 IU/ml)	66.2	53.6	75.0	43.3	0.000	0.000	0.12
High protective level (≥ 1.0 IU/ml)	27.8	37.1	18.9	54.2	0.000	0.000	0.005
Reference group	***n* = 196**	***n* = 68**	***n* = 72**	***n* = 56**	p^1	p^2	p^3
Protective level is absent (< 0.1 IU/ml)	3.1	5.9	5.6	1.7	0.94	0.26	0.24
Protective level (0.1–1.0 IU/ml)	52.1	50.0	70.6	32.1	0.000	0.000	0.04
High protective level (≥ 1.0 IU/ml)	44.8	44.1	23.8	66.2	0.000	0.000	0.01

Note: p^1 is the number of children with different stress of vaccine-induced immunity to diphtheria in age groups of 6–9 and 10–13 years; p^2 is the number of children with different stress of vaccine-induced immunity to diphtheria in age groups of 10–13 and 14–17 years; p^3 is the number of children with different stress of vaccine-induced immunity to diphtheria in age groups of 6–9 and 14–17 years.

group of 6–9 years (against 0.54 ± 0.03 IU/ml in the observation group, $p < 0.001$); 0.58 ± 0.02 IU/ml in the age group of 10–13 years (against 0.33 ± 0.01 IU/ml, $p < 0.001$); 0.91 ± 0.02 IU/ml in the age group of 14–17 years (against 0.76 ± 0.02 IU/ml, $p < 0.001$). Overall, these levels were 1.2–1.8 times higher against the observation group. Similar to the observation group, absolute average group levels of antitoxic IgG were also different in different age groups within the reference group. Thus, the antibody level was 1.2 times higher among those aged 6–9 years against the level identified in the age group of 10–13 years ($p < 0.001$); the latter was 1.6 times lower ($p < 0.0001$) than among adolescents aged 14–17 years. However, these variations were less marked than in the observation group (by 1.6 and 2.3 times respectively). Absent protection from diphtheria was identified in 5.9 % of the children aged 6–9 years in the reference group (9.3 % in the observation group, $p = 0.39$), which was not significantly different from other age periods (5.6 % among those aged 10–13 years, $p = 0.94$; 1.7 % among those aged 14–17 years, $p = 0.24$) (Table 3). In addition, proportions of schoolchildren with different seroprotection levels did not differ among the age groups of 10–13 and 14–17 years in the reference group against the same indicators in the observation group ($p = 0.13$–0.40).

Mathematic modeling made it possible to establish a cause-effect relation between declining levels of antitoxic IgG to diphtheria and elevated levels of blood manganese ($R^2 = 0.40$; $b_0 = -4.45$; $b_1 = 125.50$; $p < 0{,}001$), nickel ($R^2 = 0.78$; $b_0 = -4.19$; $b_1 = 302.60$; $p < 0.001$) and chromium ($R^2 = 0.13$; $b_0 = -2.95$; $b_1 = 85.22$; $p < 0.001$).

Therefore, elevated chemical levels in blood have less marked effects on stress of vaccine-induced immunity to diphtheria than to measles. At the same time, elevated manganese, nickel and chromium levels in blood create four times as high likelihood of absent protection from diphtheria in junior schoolchildren against adolescents and lead to 1.6–2.3 times decline in levels of antibodies in various age groups.

Our study of specific immunity to pertussis in schoolchildren aged 6–17 years established that the average group level of specific IgG reached 16.86 ± 1.13 a.u. in the observation group, which was higher than the respective protective level (> 11 a.u., $p < 0.0001$). However, analysis of age-specific dynamics of the indicator (13.38 ± 1.04 a.u. in the age group of 6–9 years; 17.43 ± 1.12 a.u., 10–13 years; 19.87 ± 1.28 a.u., 14–17 years) established certain differences in levels of specific antibodies to pertussis against measles and diphtheria. An average group level of antipertussis IgG grew constantly with age; it was 1.3 times higher among schoolchildren aged 10–13 years against juniors ($p < 0.0001$) and even 1.5 times higher among adolescents ($p < 0.0001$). Our study of individual levels of specific IgG established that only 50.1 % of the schoolchildren aged 6–17 years had a proper protective level in the observation group, which meant absence of reliable protection at the population level. Moreover, 35.3 % of schoolchildren aged 6–17 years with elevated levels of metals and aromatic hydrocarbons in blood were not protected from pertussis regardless of getting all necessary vaccinations in accordance with the National calendar for preventive vaccination; 14.6 % of them had an uncertain titer of specific JgG (Table 4).

The proportion of schoolchildren with the proper protective level of antibodies amounted to only 43.1 % in the age group of 6–9 years in the observation group. It grew by 1.3 times in the age group of 10–13 years (54.8 %, $p = 0.043$) and by 1.4 times among adolescents (61.8 %, $p = 0.002$) against the junior age group (Table 4). Overall, likelihood of a growing number of schoolchildren with high levels of IgG to pertussis increased more than twofold by 14–17 years ($OR = 2.15$; CI = 1.31–3.51). It is noteworthy that the maximum number of schoolchildren with elevated chemical levels in blood who were not protected from pertussis was established in the age group of 6–9 years, which was 1.5 times higher than among adolescents (56.9 against 38.2 %, $p = 0.002$). However, approximately 38.2 % of the schoolchildren in the observation group aged 14–17 years did not have reliable protection from pertussis.

Average group levels of specific IgG to pertussis amounted to 21.88 ± 1.11 a.u. among the schoolchildren from the reference group (aged 6–17 years), which was higher than the respective protective level and 1.3 times higher

Table 4

The number of children with different stress of vaccine-induced immunity to pertussis in the analyzed groups, %

Age (years)	6–17	6–9	10–13	14–17	Validity of intergroup differences, $p < 0.05$		
Observation group	***n* = 417**	***n* = 151**	***n* = 148**	***n* = 118**	p^1	p^2	p^3
Protective level is absent (< 9 a.u.)	35.3	39.7	32.4	28.0	0.19	0.44	0.05
Uncertain level (9–11 a.u.)	14.6	17.2	12.8	10.2	0.29	0.51	0.10
Protective level (> 11 a.u.)	50.1	43.1	54.8	61.8	0.04	0.25	0.002
Reference group	***n* = 196**	***n* = 68**	***n* = 72**	***n* = 56**	p^1	p^2	p^3
Protective level is absent (< 9 a.u.)	26.7	33.9	26.5	19.6	0.34	0.36	0.08
Uncertain level (9–11 a.u.)	9.7	13.2	8.8	7.1	0.40	0.73	0.27
Protective level (> 11 a.u.)	63.6	52.9	64.7	73.3	0.16	0.30	0.02

Note: p^1 is the number of children with different stress of vaccine-induced immunity to diphtheria in age groups of 6–9 and 10–13 years; p^2 is the number of children with different stress of vaccine-induced immunity to diphtheria in age groups of 10–13 and 14–17 years; p^3 is the number of children with different stress of vaccine-induced immunity to diphtheria in age groups of 6–9 and 14–17 years.

against the observation group (16.86 ± 1.13 a.u., $p < 0.0001$). Analysis of age-specific dynamics in the indicator also established that the level of specific IgG to pertussis grew with age. Average group levels of IgG to pertussis amounted to 18.08 ± 1.19 a.u. in the age group of 6–9 years in the reference group (13.38 ± 1.04 a.u. in the observation group, $p = 0.0001$); they grew to 21.87 ± 0.67 a.u. in the age group of 10–13 years (17.43 ± 1.12 a.u. in the observation group, $p = 0.0001$) and then to 25.74 ± 1.43 a.u. in the age group of 14–17 years (19.87 ± 1.28 a.u. in the observation group, $p < 0.0001$). They were 1.3–1.4 times higher in all age groups within the reference group against the observation one. Our study of individual levels of specific IgG to pertussis revealed that only 63.6 % of the schoolchildren aged 6–17 years in the reference group had the proper protective level of specific IgG (50.1 % in the observation group, $p = 0.002$), which was also insufficient for ensuring epidemiological safety as regards pertussis. At the same time, likelihood of impaired anti-pertussis immunity was 1.8 times higher in the observation group against the reference one (*OR* = 1.77; CI = 1.25–2.51) (Table 4).

The proportion of children with the protective level of antibodies to pertussis amounted to 52.9 % in the age group of 6.9 years within the reference group (against 43.1 % in the observation group, $p = 0.18$). It reached 64.7 % in the age group of 10–13 years (against 54.8 % in the observation group, $p = 0.16$) and 73.3 % among adolescents (against 61.8 % in the observation group, $p = 0.14$). Likelihood of a growing number of children with the protective level of antibodies to pertussis grew by 2.4 times by the age of 14–17 years in the reference group (*OR* = 2.43; CI = 1.14–5.19). Similar to the observation group, the maximum number of schoolchildren not protected from pertussis was established in the age group of 6–9 years (47.1 against 56.9 % in the observation group, $p = 0.18$); still, each fourth adolescent did not have reliable protection from pertussis (26.7 against 38.2 % in the observation group, $p = 0.14$). We established a cause-effect relation between declining levels of specific IgG to pertussis and elevated levels of manganese in blood ($R^2 = 0.19$; $b_0 = -1.19$; $b_1 = 39.59$; $p < 0.001$).

Therefore, 49.9 % of schoolchildren aged 6–17 years with elevated manganese levels in blood did not have reliable protection from pertussis; likelihood of impaired specific immunity was 1.8 times higher among such children against the reference group. The maximum number of unprotected schoolchildren (56.9 %) was established among junior schoolchildren (aged 6–9 years); however, up to 38.2 % of the examined adolescents did not have reliable protection form pertussis. Elevated manganese levels in blood led to a 1.3–1.4 times decline in the absolute levels of antibodies in various age groups.

Creation of proper protection with 95–98 % of children with protective levels of vaccine-induced specific antibodies from infections preventable by vaccination (measles, diphtheria, and pertussis) is the most reliable and economically justified approach to ensuring epidemiological safety. Search for and elimination of reasons that cause 'vaccination failures' [24] including absence / insufficient vaccine-induced immunity or its rapid loss is a promising trend in finding solutions to the outlined problem. At present, quality and safety of the environment is given great significance among various reasons underlying disruptions of vaccine-induced immunity formation. First of all, attention should be paid to chemical pollution in environmental objects since it creates immunological tolerance to vaccine antigens [28–32].

Our findings revealed that an adequate stress of vaccine-induced immunity to measles persisted only in junior schoolchildren (94.2 % among those aged 6–9 years) during 1–3 years after scheduled revaccination at the age of 6 years even in a relatively safe environment with favorable sanitary-hygienic conditions when the hazard index of adverse outcomes in the immune system and blood due to exogenous exposure to metals and aromatic hydrocarbons corresponded to minimal or permissible levels (HI = 0.67–1.5). In case subsequent revaccinations were absent, the number of schoolchildren with the protective level of specific immunity declined with age (among middle and high school children) by 6–10 %; as a result, each fifth adolescent aged 14–17 years did not have adequate protection from the measles virus. Our findings are consistent with results obtained by other authors [26] and give solid grounds for a suggestion to make alterations in the National calendar for preventive vaccination, which is to estimate levels of seroprotection against measles among schoolchildren aged 14–17 years and provide unprotected ones with additional revaccination.

According to our findings, the hazard index that describes likelihood of negative outcomes in the immune system and blood reaches alerting or even high levels (HI = 4.3–6.8) for children who live in an environment with unfavorable sanitary-hygienic conditions due to exogenous exposure to metals and aromatic hydrocarbons. For them, insufficient protection against measles becomes an especially significant issue. Elevated levels of metals (manganese) and aromatic hydrocarbons (benzene) in children's blood decrease the absolute levels of vaccine-induced IgG to measles virus by 1.2–1.7 times in various age groups and create thrice as high likelihood of low seroprotection. Even among junior schoolchildren, only 90.1 % have an adequate protective level and the number of protected children falls by 30 % in the age group of 10–13 years. By 14–17 years, this cohort is 5.8 times more likely to grow against junior schoolchildren and likelihood of a decline in the number of children with high seroprotection level is four times as high. Lower seroprotection levels among children with elevated benzene and manganese levels in blood are caused by immunotropic effects produced by these chemicals. These effects are manifested through disorganization and inhibition of basic stages in synthesis of specific IgG: a decline in absolute levels and weaker functional activity of phagocytes as a launching component in identification of vaccine antigens; suppression of T-lymphocytes that transfer relevant information in a population of immunocompetent cells and also stimulate proliferation and differentiation of B-lymphocytes; inhibition of functional activity typical for B-lymphocytes as immunoglobulin producers against the background oxidative stress and disrupted energy metabolism in cells [33–35]. All obtained data make it possible to suggest introduction of additional immune prevention activities on territories that are deemed unsafe per contents of metals and aromatic hydrocarbons in environmental objects. These additional activities should include assessment of seroprotection to measles in schoolchildren starting from the age of 10 years (middle school) and subsequent revaccination provided for them as a relevant medical and preventive technology aimed at correcting negative health outcomes associated with chemical exposures.

Results obtained by investigating stress of antitoxic immunity to diphtheria revealed a satisfactory level of vaccine-induced immunity (0.58 ± 0.02–0.91 ± 0.02 IU/ml) in 96.9 % of the examined schoolchildren aged 6–17 years who lived in a tentatively safe area with favor-

able sanitary-hygienic conditions. Wave-like changes in the absolute levels of vaccine-induced antitoxic IgG in children from different age groups coincided with the revaccination schedule. The first revaccination at the age of 6 years and the second one at the age of 14 years were accompanied with higher levels of antitoxic IgG in junior schoolchildren (0.69 ± 0.01 IU/ml) and high school children (0.91 ± 0.02 IU/ml) against those aged 10–13 years (0.58 ± 0.02 IU/ml in the reference group). At the same time, the absolute level of vaccine-induced antitoxic IgG corresponded to its value labeled as 'protective' even in schoolchildren aged 10–13 years. This is consistent with findings reported by other authors [3, 16, 17] and allows considering the existing program for vaccine prevention of diphtheria to be adequate for this children group.

Assessment of vaccine-induced immunity to the diphtheria agent in children with elevated manganese, nickel and chromium levels in blood revealed sufficient absolute levels of specific IgG in 94.0 % of children aged 6–17 years (0.33 ± 0.01 – 0.76 ± 0.02 IU/ml); age-related variations in these levels also coincided with the revaccination schedule; however, their absolute values were 1.2–1.8 times lower than those identified in the reference group ($p < 0.001$). Chemical levels in blood 1.6–2.5 times higher than RfC resulted in thrice as low likelihood of strong vaccine-induced immunity. Junior children were the most susceptible to the diphtheria agent with 9.3 % of them not having adequate protection from it. These identified peculiarities of vaccine-induced immunity in children with elevated manganese, nickel and chromium levels in blood are caused by immunotoxic effects produced by these metals involving lower production of T-regulatory cells $CD4^+CD127^-$, $CD3^+CD25^+$, $CD3^+CD95^+$, lower production of p53 as a transcription factor that regulates the cellular cycle and developing sensitization reactions with humoral immunity switching partially to synthesis of specific IgE [35, 36].

Less marked disorders of vaccine-induced immunity to diphtheria against measles are most likely associated with regular revaccinations, which allows maintaining an adequate level of specific IgG in most children and adolescents. It is advisable to perform serologic monitoring per diphtheria one year after the second revaccination in areas with unfavorable sanitary-hygienic conditions per metal contamination in environmental objects. The major goal is to identify junior school children with insufficient / absent seroprotection to diphtheria and, subsequently, to provide additional vaccination against the disease for unprotected children.

According to the National calendar for preventive vaccination, revaccination against pertussis is accomplished at the age of 1.5–2 years; no further revaccination is scheduled in the calendar. ADACEL, a combined cell-free vaccine (manufactured by Sanofi Pasteurs Limited, Canada) and Russian multi-component cell-free vaccines, which could be used for revaccination at the age of 4–6 years and 11–17 years, have not been widely used in Russia so far [37].

All examined children were covered with the last scheduled revaccination against pertussis in due time and the absolute levels of specific antibodies identified in children aged 6–17 years, who lived in relatively favorable sanitary-hygienic conditions, were two times higher than the relevant protective level. However, the total number of protected children amounted to only 63.6 %. Analysis of age-specific dynamics in specific immunity revealed that the absolute number of specific IgG grew by 1.4 times over the period from junior school to adolescence and the number of children with proper protective levels of these antibodies grew by 20.4 %.

Similar dynamics in levels of specific antibodies and proportions of protected children was identified in the observation group made of schoolchildren who lived in unfavorable sanitary-hygienic conditions and had elevated manganese levels in blood. However, these levels and proportions were 1.2–1.4 times lower in all age groups against the reference group and likelihood of impaired specific immunity was 1.8 times higher.

Our study findings indicate that a protective level of antibodies to the pertussis agent is absent in practically each second junior schoolchild in the analyzed groups and that the pertussis agent circulates in child population resulting in undiagnosed disease cases. This confirms the necessity to perform repeated revaccinations against pertussis at the age of 4–6 years and 14–17 years. Lower seroprotec-

tion levels in children with elevated manganese contents in blood give grounds for revaccination as a specialized preventive technology aimed at correcting negative outcomes in the immune system caused by chemical exposures.

Conclusions:

1. Ambient metals (manganese, chromium, and nickel) and aromatic hydrocarbons (benzene) in levels equal to 1.0–13.8 average annual MPL are the reason for alerting levels of the hazard quotient for the immune system ($HQ_{chromium}$ = 1.1; $HQ_{benzene}$ = 3.2) and high levels for the hematopoietic system (HQ_{nickel} = 3.6; $HQ_{benzene}$ = 3.2). The hazard index reaches its alerting level (HI = 4.3) for the immune system and high level (HI = 6.8) for the hematopoietic system.

2. We established a direct correlation between impaired vaccine-induced immunity to measles and elevated manganese and benzene levels in blood (R^2 = 0.19–0.26; b_0 = (-1.19) – (-3.10); b_1 = 32.50–39.59; $p < 0.001$); between impaired vaccine-induced immunity to diphtheria and elevated manganese, chromium and nickel levels in blood (R^2 = 0.13–0.78; b_0 = (-2.95) – (-4.19); b_1 = 85.22–302.60; $p < 0.001$; between impaired vaccine-induced immunity to pertussis and elevated manganese levels in blood (R^2 = 0.19; b_0 = -1.19; b_1 = 39.59; $p < 0.001$).

3. Levels of metals (manganese, chromium, and nickel) and aromatic hydrocarbons (benzene), which are 1.6–2.5 times higher than RfC, create thrice as high likelihood of impaired vaccine-induced immunity to the measles virus (*OR* = 3.0; CI = 1.68–5.31), 1.8 times as high likelihood of impaired vaccine-induced immunity to the pertussis agent (*OR* = 1.77; CI = 1.25–2.51), four times as high likelihood of low seroprotection to the diphtheria agent among junior schoolchildren (*OR* = 3.92, CI = 1.10–13.97).

4. To make immune prophylaxis against measles more effective in children living in unsafe areas with environmental objects contaminated with metals (manganese) and aromatic hydrocarbon (benzene), it is necessary to estimate seroprotection levels in schoolchildren starting from the age of 10 years in order to identify sero-negative ones and provide subsequent revaccination for them as a medical and preventive technology aimed at correcting negative effects of chemical exposures.

5. It is advisable to perform serologic monitoring per diphtheria one year after the second revaccination in areas with unfavorable sanitary-hygienic conditions per metal contamination (manganese, chromium and nickel) in environmental objects. The major goal is to identify schoolchildren with insufficient / absent seroprotection to the diphtheria agent and, subsequently, to provide additional vaccination against the disease for unprotected children.

6. To raise effectiveness of immunization as regards pertussis, repeated revaccination is necessary for all children at the age of 4–6 and 14–17 years. It should be supported by additional technologies aimed at correcting negative effects produced by manganese on the immune system in areas where environmental objects are contaminated with this metal.

Funding. The research was not granted any financial support.

Competing interests. The authors declare no competing interests.

References

1. Mamaeva T.A., Rubalskaya T.S., Zherdeva P.E., Metelskaya V.A., Toptygina A.P. Determination of the immune response type in measles patients of different ages from a high-incidence area. *Rossiiskii immunologicheskii zhurnal*, 2024, vol. 27, no. 1, pp. 49–58. DOI: 10.46235/1028-7221-16572-DOT (in Russian).

2. Ershevskaya A.B., Ivanova A.A., Antropova G.A., Toyirov Y.A. Pertussis: aspects of pathogenesis and post-vaccination Immunity in children. *Vestnik NovSU*, 2024, no. 2 (136), pp. 247–255. DOI: 10.34680/2076-8052.2024.2(136).247-255 (in Russian).

3. Niiazalieva M.S., Toygombaeva V.S., Djumalieva G.A., Aldjambaeva I.Sh. The condition of post-vaccination immunity to diphtheria and tetanus in population of the Republic of Kyrgyzstan. *Problemy sotsial'noi gigieny, zdravookhraneniya i istorii meditsini*, 2021, vol. 29, no. 4, pp. 988–991. DOI: 10.32687/0869-866X-2021-29-4-988-991 (in Russian).

4. Dimitrieva M.A., Mikhailova A.S., Stepenova A.A., Anisimova T.A. The incidence of measles in Russia and abroad: causes and trends. *Naukosfera*, 2024, no. 5–1, pp. 94–97. DOI: 10.5281/zenodo.11188933 (in Russian).

5. Shershneva N.N., Kolesnikov P.S., Samosadova P.V. Mishutkina Ya.V., Mardanly S.G. The relevance of serological monitoring of antitoxic immune to diphtheria. *Poliklinika*, 2022, no. 4, pp. 47–50 (in Russian).

6. Grinchik P.R., Namazova-Baranova L.S., Fedoseenko M.V., Girina A.A., Kovalev S.V., Mazokha A.V., Makushina E.D., Malinina E.I. [et al.]. Comparative Analysis of Immunization and Immunization Coverage in Children of Russian Federation Federal Districts. *Pediatricheskaya farmakologiya*, 2022, vol. 19, no. 1, pp. 6–19. DOI: 10.15690/pf.v18i6.2351 (in Russian).

7. Avramenko A.A., Isaeva M.A., Kushnir S.A., Sadovski K.A., Bocharova K.A. Aktual'nye problemy uvelicheniya zabolevaemost'yu kor'yu na territorii Rossiiskoi Federatsii i Belgorodskoi oblasti. Problemy i prognozy po razvitiyu ochagov vspyshki zabolevaniya [Current problems of increasing measles incidence in the Russian Federation and the Belgorod region. Problems and forecasts for the development of disease outbreaks]. *Flagman nauki*, 2023, vol. 11, no. 11, pp. 98–104. DOI: 10.37539/2949-1991.2023.11.11.019 (in Russian).

8. Molochkova O.V., Kovalev O.B., Kosyreva M.A., Ilyina N.O., Shamsheva O.V., Getmanova E.N., Korsunsky A.A., Galeeva E.V., Guzhavina A.A. Characteristics of measles in children during the rise in incidence in 2019. *Detskie infektsii*, 2022, vol. 21, no. 4, pp. 27–31. DOI: 10.22627/2072-8107-2022-21-4-27-31 (in Russian).

9. Dik D.A. Istoriya izucheniya kori, krasnukhi i epidemicheskogo parotita [History of studying measles, rubella and mumps]. *Flagman nauki*, 2023, no. 9 (9), pp. 140–142 (in Russian).

10. Kurmaeva D.Yu., Afonin A.V., Rybalkin S.B., Melnikov V.L., Nikolskaya M.V. Epidemiological and clinical features of measles on the example of an outbreak in the Penza region. *Sibirskii nauchnyi meditsinskii zhurnal*, 2024, vol. 44, no. 4, pp. 168–173. DOI: 10.18699/SSMJ20240419 (in Russian).

11. Tyukavkina S.Yu., Voronina N.A., Balakhnova V.V. Osnovnye faktory postvaktsinal'nogo immuniteta u privitykh AKDS-vaktsinoi [The main factors of post-vaccination immunity in those vaccinated with DPT vaccine]. *Mikrobiologicheskie aspekty diagnostiki infektsionnykh zabolevanii: sbornik nauchno-prakticheskikh rabot IX Vserossiiskoi nauchno-prakticheskoi onlain-konferentsii.* Rostov-on-Don, 2021, pp. 56–58 (in Russian).

12. Nilova L.Yu., Orishak E.A., Fomenko V.O. Measles: global diagnostics programm and heard immunity. *Problemy meditsinskoi mikologii*, 2022, vol. 24, no. 2, pp. 108 (in Russian).

13. Svetlichnaya S.V., Elagina L.A., Popovich L.D. Evaluation of the economic efficacy of vaccination against pertussis based on real-world data. *Real'naya klinicheskaya praktika: dannye i dokazatel'stva*, 2023, vol. 3, no. 1, pp. 9–19. DOI: 10.37489/2782-3784-myrwd-27 (in Russian).

14. Alyabeva I.A., Kazakova V.S., Kosyakova K.G. Features of the spread of pertussis infection. *Zdorov'e – osnova chelovecheskogo potentsiala: problemy i puti ikh resheniya*, 2023, vol. 18, no. 2, pp. 395–401 (in Russian).

15. Basov A.A., Tsvirkun O.V., Gerasimova A.G., Zakoreeva A.K. The problem of pertussis in some geographic regions of the world. *Infektsiya i immunitet*, 2019, vol. 69, no. 2, pp. 354–362. DOI: 10.15789/2220-7619-2019-2-354-362 (in Russian).

16. Fedorova I., Serhiyenka E., Rybak N., Matush L., Romanova O., Rybak V. Forgotten but Undecomputed Infection of the XXI Century – Diphtheria (Part 1). *Klinicheskaya infektologiya i parazitologiya*, 2023, vol. 12, no. 3, pp. 252–256. DOI: 10.34883/PI.2023.12.3.032 (in Russian).

17. Serhiyenka E., Rybak N., Fedorova I., Matush L., Romanova O., Rybak V. Forgotten but Undecomputed Infection of the XXI Century – Diphtheria (Part 2). *Klinicheskaya infektologiya i parazitologiya*, 2023, vol. 12, no. 3, pp. 257–265. DOI: 10.34883/PI.2023.12.3.033 (in Russian).

18. Kolesnikov P.S. ELISA and RPGA as methods of serological monitoring of diphtheria. *Bakteriologiya*, 2021, vol. 6, no. 1, pp. 48–53. DOI: 10.20953/2500-1027-2021-1-48-53 (in Russian).

19. Markina S.S., Maksimova N.M., Petina V.S., Koshkina N.A., Fisenko V.A. Epidemicheskaya situatsiya po difterii v Rossii [Epidemic situation per diphtheria in Russia]. *Moscow Research Institute of Epidemiology and Microbiology named after G.N. Gabrichevsky*. Available at: http://www.gabrich.com/science/rdift.htm.html (October 09, 2024) (in Russian).

20. Niyazalieva M.S., Toigombaeva V.S., Adambekov D.A., Aldzhambaeva I.Sh., Abdykerimova N.A., Kaipova U.T. Features of the epidemic process of measles, mumps and rubella at the present stage. *Alatoo Academic Studies*, 2023, no. 3, pp. 490–496. DOI: 10.17015/aas.2023.233.49 (in Russian).

21. Bezrodnova S.M., Demurcheva I.V., Kravchenko O.O. Study of postvaccinal immunity to whooping cough in children with connective tissue dyslasia syndrome. *Detskie infektsii*, 2021, vol. 20, no. 1 (74), pp. 28–33. DOI: 10.22627/2072-8107-2021-20-1-28-33 (in Russian).

22. Dmitrieva T.G., Nestereva M.E. An analysis of infectious morbidity in children in the Sakha Republic (Yakutia) from 2012 to 2021. *Vestnik Severo-Vostochnogo federal'nogo universiteta im.*

M.K. Ammosova. Seriya «Meditsinskie nauki», 2023, no. 1 (30), pp. 37–46. DOI: 10.25587/SVFU. 2023.30.1.001 (in Russian).

23. Mikheeva E.M., Penkina N.I. Vaccine prophylaxis in children conceived with the help of assisted reproductive technologies. *Lechenie i profilaktika*, 2023, vol. 13, no. 2, pp. 51–58 (in Russian).

24. Ereshchenko A.A., Gusyakova O.A., Baldina O.A. Predicting the formation of post-vaccine measles humoral immunity in health care workers. *Laboratornaya meditsina*, 2023, vol. 14, no. 3–4, pp. 19–26. DOI: 10.58953/15621790_2023_14_3-4_19 (in Russian).

25. Fridman I.V., Lybimova N.A., Goleva O.V., Konstantinova Yu.E., Kostik M.M. Safety of antibodies to measles, mumps, rubella and diphtheria in patients with juvenile idiopathic arthritis. *Zhurnal infektologii*, 2021, vol. 13, no. 2, pp. 44–52. DOI: 10.22625/2072-6732-2021-13-2-44-52 (in Russian).

26. Shafalinov A.V., Rediako A.A., Ivanov D.V. Measles. Problem issues. *Vestnik Vostochno-Sibirskoi otkrytoi akademii*, 2024, no. 52 (52) (in Russian).

27. Krieger E.A., Samodova O.V. Measles humoral immunity in health-care workers. *Infektsiya i immunitet*, 2021, vol. 11, no. 3, pp. 523–529. DOI: 10.15789/2220-7619-HIT-1452 (in Russian).

28. Kryazhev D.A., Boev V.M., Kryazheva E.A. Vzaimosvyazi i prognosticheskie modeli faktorov sredy obitaniya, vliyayushchie na sostoyanie postvaktsinal'nogo immuniteta u naseleniya [Relationships and prognostic models of environmental factors influencing the state of post-vaccination immunity in the population]. *Al'manakh molodoi nauki*, 2017, no. 3, pp. 3–10 (in Russian).

29. Shvetsova A.A., Kryazheva E.A. Vzaimosvyaz' antropogennogo zagryazneniya so snizheniem postvaktsinal'nogo immuniteta u naseleniya Orenburgskoi oblasti [The relationship of anthropogenic pollution with a decrease in post-vaccination immunity among the population of the Orenburg region]. *Materialy XII s"ezda Vserossiiskogo nauchno-prakticheskogo obshchestva epidemiologov, mikrobiologov i parazitologov*. In: A.Yu. Popova, V.G. Akimkin eds. Moscow, 2022, pp. 533–534 (in Russian).

30. Kryazhev D.A., Boev M.V., Tulina L.M., Neplokhov A.A., Boev V.M. Comprehensive assessment of environmental factors and postvaccinal immune state. *Gigiena i sanitariya*, 2016, vol. 95, no. 3, pp. 229–232. DOI: 10.18821/0016-9900-2016-95-3-229-232 (in Russian).

31. Ilina S.V., Savilov E.D. Technogenic Environmental Pollution and the Effectiveness of Vaccination in Children's Population. *Epidemiologiya i vaktsinoprofilaktika*, 2009, vol. 47, no. 4, pp. 57–62 (in Russian).

32. Akhmadiev G.M. The dependence of the extinction of immunoglobulins in the blood of mammalian offspring by state habitat. *Aktual'nye issledovaniya gumanitarnykh, estestvennykh, obshchestvennykh nauk: materialy VIII Vserossiiskoi s mezhdunarodnym uchastiem nauchno-prakticheskoi konferentsii*. Novosibirsk, OOO "TsSRNI" Publ., 2016, pp. 8–15 (in Russian).

33. Pospelova S.V., Horovits E.S., Krivtsov A.V., Dolgikh O.V. Study of protective anti-bacterial mechanisms in children living in the conditions of exposure to emissions of the enterprise of black metallurgy. *Laboratornaya sluzhba*, 2021, vol. 10, no. 2, pp. 22–27. DOI: 10.17116/labs20211002122 (in Russian).

34. Dolgikh O.V., Krivtsov A.V., Bubnova O.A., Otavina E.A., Bezruchenko N.V., Kolegova A.A., Mazunina A.A., Guselnikov M.A. Features of fixing the genetic polymorphism in dyads "mother – child" in the conditions of aerogenous exposure to metals. *Gigiena i sanitariya*, 2017, vol. 96, no. 1, pp. 26–29. DOI: 10.47470/0016-9900-2017-96-1-26-29 (in Russian).

35. Starkova K.G., Dolgikh O.V., Kazakova O.A. Features of the immune status of middle and high school students in conditions of high blood content of a number of exogenous chemical impurities. *Gigiena i sanitariya*, 2021, vol. 100, no. 5, pp. 501–506. DOI: 10.47470/0016-9900-2021-100-5-501-506 (in Russian).

36. Alikina I.N. Assessment of cell-mediated immunity in workers employed in underground chrome ore mining. *Rossiiskii immunologicheskii zhurnal*, 2019, vol. 22, no. 3, pp. 1089–1092. DOI: 10.31857/S102872210007231-9 (in Russian).

37. Kostinov M.P., Prutskova E.V., Cherdantsev A.P., Feiskhanova G.R., Kostinov A.M., Vlasenko A.E., Polishchuk V.B. Safety of pertussis vaccines for adolescents. *Zhurnal infektologii*, 2020, vol. 12, no. 4, pp. 29–36. DOI: 10.22625/2072-6732-2020-12-4-29-36 (in Russian).

Zaitseva N.V., Ustinova O.Yu., Makarova V.G., Valina S.L., Shtina I.E. Risk of declining vaccine-induced immunity stress to measles, diphtheria and pertussis in children under exposure to airborne metals and aromatic hydrocarbons. Health Risk Analysis, 2024, no. 4, pp. 97–112. DOI: 10.21668/health.risk/2024.4.09.eng

Received: 12.11.2024
Approved: 02.12.2024
Accepted for publication: 19.12.2024