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Research article

COMMON IMMUNOLOGICAL PATHWAYS OF ANTI-INFECTION IMMUNITY AND ALLERGIC REACTIVITY MODIFICATION IN CHILDREN ASSOCIATED WITH PECULIARITIES OF THE MODERN EDUCATIONAL PROCESS AND ENVIRONMENT QUALITY

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This study is relevant due to humoral and cellular pathways of the immune response having much in common as well as its high sensitivity to factors of the modern educational process in school when building up anti-infection and anti-allergy protection. Our research objects were secondary schools with profound studies of some subjects (Type 1 schools) and ordinary secondary schools (Type 2 schools); overall, we examined 842 schoolchildren from Type 1 schools and 540 schoolchildren from Type 2 schools.

The aim of this study was to establish conditions and common pathogenetic sections of immunological pathways of anti-infection immunity and allergic reactivity modification associated with environmental exposures and exposure to factors of the modern educational process.

We analyzed how educational activities were organized in the analyzed schools; what food products were consumed by the participating schoolchildren daily and their chemical structure; basic aspects of schoolchildren's lifestyles; quality of indoor air in classrooms; quality of ambient air in areas where the analyzed schools were located; prevalence of allergic diseases (ADs) and anti-infection immunity disorders; results of immunological tests and chemical blood tests; intensity of humoral anti-infection and post-vaccination immunity. The study involved odds ratio calculation, linear regression analysis, and neural network modeling.

As a result, we established that high educational loads, improper duration of breaks and periods of work with electronic teaching aids (ETAs), insufficient sleeping time, too low physical activity and too high digital activity among schoolchildren, manganese, nickel, chromium and formaldehyde in air inside classrooms in levels up to 1.8–8.5 higher than RfCchr, and unhealthy diets created 1.3 times higher risks of ADs, 2.3 times higher risks of insufficient production of IgG to herpesviruses, 3.1–5.4 times higher risks of an increasing proportion of people seronegative to measles and diphtheria antigens (OR = 1.33–5.40). Activation of cellular-mediated reaction of adaptive immunity response (an increase in levels of CD3+-, CD3+CD25+-, CD3+CD8+- lymphocytes) and declining activity of the non-specific resistance system (a decline in absolute phagocytosis, phagocytic number, and levels of CD16+56+- lymphocytes) were common pathogenetic sections of immunological pathways of anti-infection immunity and allergic reactivity modification upon exposure to a set of priority factors. Isolated contributions made by various factors to likelihood of risk-associated ADs amounted to 35.7–74.0 % for peculiarities of the modern educational process; chemical factors, 7.6–33.1 %; lifestyle, 7.6–31.2 %. Contributions to humoral post-infection and post-vaccination immunity disorders amounted to 14.6–44.0 % for diet-related factors; educational process, 13.5–30.8 %; lifestyle, 11.4–29.4 %; chemical factors, 6.5–19.9 %.

Keywords: *schoolchildren, post-infection and post-vaccination immunity, allergic diseases, immunological pathways of modification, neural network modeling, factor contribution.*

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The RF President Order dated June 18, 2024 No. 529 names preventive and personalized healthcare as well as provision of healthy long life a priority trend in scientific and technological development[1].

Schoolchildren's health directly depends on conditions and organization of the educational process in schools, qualitative and quantitative structure of their diet, physical activity, optimal study and rest regime, levels and structure of digital activity, education provided by their families and family environment [1, 2].

At present, the leading role in maintaining homeostasis undoubtedly belongs to the immune system. Its functioning can go beyond physiological parameters inducing immunopathological processes, which implement genetically determined programs upon exposure to various environmental factors [3, 4].

Although chronic stress-induced diseases and anthropogenic diseases gradually displace communicable ones, over the last decade a growth has been observed in incidence of 'eradicated' infections. This has again attracted attention to stability of the specific anti-viral and anti-bacterial immunity created by vaccination [5, 6].

Long-term observations in some European countries indicate that prevalence of allergic diseases (ADs) grows twofold every ten years, which allows describing allergy as a pandemic process [7, 8]. Children with ADs are established to have substantial changes in humoral immunity upon vaccination as compared to healthy peers. Antibody production tends to be less intensive, highly protective specific immunoglobulins do not accumulate well, and post-vaccination immunity is lost very rapidly. At the same time, it is a well-known fact that children with allergy do need protection from infections, which do not only strengthen and prolong the allergic process by determining a cascade of immune reactions but also act as ADs triggers [9–11].

Results obtained by epidemiological studies and medical statistics data give evidence that prevalence of chronic infections as well as their persistence is considerably higher among children with ADs against their peers without any signs of allergic pathology [12, 13]. The range of infectious agents is rather diverse but viruses, as a rule, occupy leading places. Herpesvirus infections remain a priority interdisciplinary challenge for practical healthcare due to high infection rates among the population either with one or more often with several human herpes viruses (Herpes simplex virus (HSV) 1 and 2; Varicella zoster virus; Epstein – Barr virus; Cytomegalovirus; Human herpesvirus 6). All these viruses are able to produce immunotropic effects [14].

At present, the conventional concept highlights the leading role that belongs to imbalance between subpopulations of Th1/Th2-helper T-lymphocytes in pathogenesis of chronic infections, post-vaccination immunity, and ADs. Prevalence of Th2-immune response in patients with allergic pathology involves production of IL-4, IL-5, IL-10, and IL-13 cytokines, induces IgE synthesis and a decline in the level of interferon-γ, which weakens anti-viral protection and promotes long-term virus persistence. Common humoral and cellular pathways of the immune response underlie comorbidity of allergic and infectious diseases as well as disrupted formation of specific immunity as a response to vaccination [15]. Apart from internal factors determined by a patient's individual peculiarities, some external factors can also act as causes for insufficient effectiveness of the global fight with its aim to both eliminate vaccine-managed infections and decrease ADs incidence. Industrial and transport emissions, changes in lifestyle and diets, more intensive educational activities and stress play a significant role in changes of immunological reactivity [16–18].

[1] Ob utverzhdenii prioritetnykh napravlenii nauchno-tekhnologicheskogo razvitiya i perechnya vazhneishikh naukoemkikh tekhnologii: Ukaz Prezidenta Rossiiskoi Federatsii ot 18.06.2024 № 529 [On Approval of priority trends in scientific and technological development and the list of the most significant science-intense technologies: the Order by the RF President dated June 18, 2024 No. 529]. *Prezident Rossii*. Available at: http://www.kremlin.ru/acts/bank/50755 (April 10, 2025) (in Russian).

The modern school environment is a multicomponent dynamic system. Given that, it is becoming especially vital to establish factors and biomarkers, which correlate with intensity of vaccine-induced, post-infection and allergic immune responses [19, 20].

Therefore, issues related to conjugate post-vaccination immunity disorders and allergic reactivity in children and adolescents remain in a focus of intensive researchers' attention, first of all, due to the immune system being highly sensitive to external exposures, the necessity to develop methods for predicting intensity of an immune response as well as activities aimed at establishing, eliminating, or mitigating adverse impacts exerted by relevant risk factors.

The aim of this study was to establish conditions and common pathogenetic regularities of immunological pathways of anti-infection immunity and allergic reactivity modification in schoolchildren associated with environmental exposures and exposure to factors of the modern educational process.

Materials and methods. The article relies on using data obtained by studies accomplished over 2019–2024 within scientific research conducted in conformity with Rospotrebnadzor's Brunch Scientific Research Program. All studies were accomplished in compliance with the valid principles of biomedical ethics and approved by the local ethics committee (LEC) of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies (the LEC Meeting Protocols No. 3 dated March 01, 2019; No. 1 dated February 06, 2020; No. 1 dated February 04, 2021; No. 3 dated February 17, 2022; No. 3 dated February 14, 2023). Our research objects were secondary schools with profound studies of some subjects (Type 1 schools) and ordinary secondary schools (Type 2 schools); overall, we performed profound clinical and laboratory examinations of 1382 primary, middle and high school students from the analyzed schools. The observation group was made of 842 schoolchildren from Type 1 schools, their median age being 12 (10; 15) years; the reference group consisted of 540 schoolchildren from Type 2 schools, the median age being 12 (9; 15) years.

Educational processes in two different types of the analyzed schools were comparatively assessed as regards their conformity with the valid sanitary legislation[2]. The assessment involved analyzing school schedules, breaks, and time studies of work with electronic teaching aids (ETAs) during classes.

Consumption of food products by schoolchildren was analyzed by comparing averaged data taken from school menus with recommended average daily sets of food products[3]. We determined how well a diet satisfied average daily needs in basic nutrients and energy by calculating the chemical structure and caloric contents of a schoolchild's daily diet with the

[2] SP 2.4.3648-20. Sanitarno-epidemiologicheskie trebovaniya k organizatsiyam vospitaniya i obucheniya, otdykha i ozdorovleniya detei i molodezhi; utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 28.09.2020 g. № 28; vved. v deistvie s 01.01.2021 g. [Sanitary Rules SP 2.4.3648-20. Sanitary-epidemiological requirements to organizing education, leisure and health improvement of children and youth; approved by the Order of the RF Chief Sanitary Inspector on September 28, 2020 No. 28; came into force on January 01, 2021]. *GARANT: information and legal portal*. Available at: https://base.garant.ru/75093644/ (April 11, 2025) (in Russian); SanPiN 1.2.3685-21. Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya (s izmeneniyami na 30 dekabrya 2022 goda), utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 28 yanvarya 2021 goda № 2; vved. v deistvie s 01.03.2021 g. [SanPiN 1.2.3685-21. Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people (edited as of December 30, 2022), approved by the Order of the RF Chief Sanitary Inspector on January 28, 2021 No. 2; came into force on March 01, 2021]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (April 11, 2025) (in Russian).

[3] SanPiN 2.3/2.4.3590-20. Sanitarno-epidemiologicheskie trebovaniya k organizatsii obshchestvennogo pitaniya naseleniya (s izmeneniyami na 22 avgusta 2024 goda), utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 27 oktyabrya 2020 goda № 32; vved. v deistvie s 01.01.2021 g. [Sanitary Rules and Standards SanPiN 2.3/2.4.3590-20. Sanitary-epidemiological requirements to organizing catering provided for population (edited as of August 22, 2024), approved by the Order of the RF Chief Sanitary Inspector on October 27, 2020 No. 32; came into force on January 01, 2021]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/566276706 (April 11, 2025) (in Russian).

use of relevant data from the reference book[4] (Appendix No. 10 SanPiN 2.3/2.4.3590-20[3]).

Socioeconomic statuses of schoolchildren's families, involvement in additional educational activities, daily routines, physical and digital activity were examined by conducting a survey using the authors' questionnaire.

Air quality inside classrooms and ambient air quality in areas near the analyzed schools as well as manganese, nickel, chromium, formaldehyde, benzene and toluene levels in blood were examined by chemical-analytical tests conducted by experts from the Department of Analytical Chemistry Analysis, Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, in 2019–2024 in accordance with valid methodical guidelines[5].

ADs such as allergic rhinitis (AR), bronchial asthma (BA), and atopic dermatitis (AD) were diagnosed based on data taken from Medical Case Histories for Schools (Official Form No. 026/y-2000) and results of profound clinical and laboratory examinations. Anti-infection immunity disorders were established per clinical-laboratory indicators including levels of IgG to herpesvirus infection caused by Herpes simplex virus 1 (HSV-1 infection)

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[4] Tutelyan V.A. Khimicheskii sostav i kaloriinost' rossiiskikh produktov pitaniya: spravochnik [Chemical structure and caloric contents of Russian food products: reference book]. Moscow, DeLi plus Publ., 2012, 284 p. (in Russian).

[5] MUK 4.1.1045-01. VEZhKh opredelenie formal'degida i predel'nykh al'degidov (S2-S10) v vozdukhe: metodicheskie ukazaniya, utv. Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii – Pervym zamestitelem Ministra zdravookhraneniya Rossiiskoi Federatsii G.G. Onishchenko 5 iyunya 2001 g. [MUK 4.1.1045-01. HPLC determination of formaldehyde and saturated aldehydes (C_2-C_{10}) in ambient air: methodical guidelines, approved by G.G. Onishchenko, the RF Chief Sanitary Inspector and the First Depute to the RF Minister of Health on June 5, 2001]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200029341 (April 11, 2025) (in Russian); MUK 4.1.3167-14. Gazokhromatograficheskoe opredelenie geksana, geptana, benzola, toluola, etilbenzola, m-,o-,p-ksilolov, izopropilbenzola, n-propilbenzola, stirola, metilstirola, benzal'degida v atmosfernom vozdukhe, vozdukhe ispytatel'noi kamery i zamknutykh pomeshchenii: metodicheskie ukazaniya, utv. Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii 16 iyunya 2014 g. [MUK 4.1.3167-14. Gas chromatography identification of hexane, heptane, benzene, toluene, ethylbenzene, м-, o-, p-xylene, isopropyl benzene, n-propyl benzene, styrene, a-methyl styrene, benzaldehyde in ambient air, air inside test chamber and closed premises: methodical guidelines, approved by the Order of the RF Chief Sanitary Inspector on June 16, 2014]. *GARANT: information and legal portal*. Available at: https://base.garant.ru/72079584/ (April 11, 2025) (in Russian); MUK 4.1.3481-17. Izmerenie massovykh kontsentratsii khimicheskikh elementov v atmosfernom vozdukhe 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 RF 15.06.2017 [MUK 4.1.3481-17. Measurement of mass concentrations of chemicals in ambient air by inductively coupled plasma mass-spectrometry: methodical guidelines, approved by the Order of the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector on June 15, 2017]. *MEGANORM: the system for regulatory documents*. Available at: https://meganorm.ru/mega_doc/norm/metodicheskie-ukazaniya/0/muk_4_1_3481-17_4_1_metody_kontrolya_khimicheskie_faktory.html (April 11, 2025) (in Russian); MUK 4.1.2111-06. Izmerenie massovoi kontsentratsii formal'degida, atsetal'degida, propionovogo al'degida, maslyanogo al'degida i atsetona v probakh krovi metodom vysokoeffektivnoi zhidkostnoi khromatografii: metodicheskie ukazaniya, utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 9 avgusta 2006 g. [MUK 4.1.2111-06. Identification of mass concentrations of formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, and acetone in blood samples by using high performance liquid chromatography: methodical guidelines, approved by G.G. Onishchenko, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing and the RF Chief Sanitary Inspector on August 9, 2006]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200065243 (April 11, 2025) (in Russian); MUK 4.1.765-99. Gazokhromatograficheskii metod kolichestvennogo opredeleniya aromaticheskikh uglevodorodov (benzol, toluol, etilbenzol, o-,m-,p-ksilol) v biosredakh (krov'): metodicheskie ukazaniya, utv. Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 6 iyulya 1999 g. [MUK 4.1.765-99. Quantification of aromatic hydrocarbons (benzene, toluene, ethyl benzene, o-,m-,p-xylene) in biological media (blood) by using gas chromatography: methodical guidelines, approved by G.G. Onishchenko, the RF Chief Sanitary Inspector on July 6, 1999]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200039012 (April 11, 2025) (in Russian); 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. [MUK 4.1.3230-14. Identification of mass concentrations of chemicals in biological media (blood and urine) by using inductively coupled plasma mass spectrometry: methodical guidelines, approved by A.Yu. Popova, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing and 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 (April 11, 2025) (in Russian).

and 5 (Cytomegalovirus infection (CMVI)) (post-infection immunity) as well as intensity of a specific humoral immune response to measles, diphtheria, and pertussis vaccine antigens (post-vaccination immunity).

All obtained data were analyzed using conventional statistical methods involving establishment of absolute, relative, and median values. Odds ratio (OR) and its 95 % confidence interval were determined to assess risk levels. Logistic regression was applied for estimating likelihood of ADs, disorders of humoral immunity to infections managed with specific prevention means, as well as changes in immunological indicators upon exposure to relevant risk factors.

We employed building of artificial neural networks to reveal deeper, mutual influence taken into account, cause-effect relations between likelihood of a decline in humoral, post-vaccination, and post-infection immunity and risk factors; between likelihood of changes in immunological indicators and analyzed factors; between likelihood of weakening anti-infection humoral immunity and immunity indicators. The networks were built using *neuralnet* library and R-studio software. We used the determination coefficient calculated as the square of the correlation coefficient between predicted and actual value to perform quantitative assessment of prediction quality. We estimated sensitivity of neural network models and established priority factors using elasticity coefficients, which showed a relative change in response at the output layer upon a relative change in input data at the first neuron layer. Ultimate contributions made by factors affecting levels of post-infection and post-vaccination antibodies were established based on integral elasticity coefficients.

Results and discussion. We analyzed how the educational process was organized in the examined schools; as a result, we revealed that long and short breaks were reduced against the standard duration by 1.3–2 times in some of them. On average, they equaled 16.87 ± 0.47 and 8.8 ± 0.36 minutes respectively in Type 1 schools against 18.0 ± 0.53 and 9.4 ± 0.31 in Type 2 schools (p = 0.060–0.130). Weekly educational loads were 5.5–19.2 % higher than their permissible levels in Type 1 schools. In Type 1 schools, duration of using a personal computer (PC) and interactive whiteboards (IWB) during a lesson was 1.2–2.2 times longer than its permissible length and 1.4–2.6 times longer than in Type 2 schools. Total daily duration of ETAs use was 1.4 times longer than established by safe standards and 2.5 times longer than in Type 2 schools.

Our study of schoolchildren's diets gave evidence of negative trends in daily rations of all examined children. In Type 1 schools, milk, sour milk products, curds, butter, meat and fish were consumed in quantities 1.5–8.4 times lower than the norm; fresh fruits and vegetables, 1.3–4.7 times; eggs, 5.2–10.0 times; cereals and beans, up to 1.6 times; wheat bread, up to 4.9 times (p < 0.001–0.007). We established excessive consumption of macaroni (1.2–1.7 times higher than the norm) and confectionary products (6.1–12.3 times) (p < 0.001–0.022). The chemical structure of average daily diet consumed by schoolchildren from Type 1 schools did not contain many nutrients in quantities meeting physiological needs; thus, contents of proteins, fats, and carbohydrates were 1.2–2 times lower than necessary; calcium, phosphor and magnesium contents, 1.2–1.4 times lower; vitamins B1 and A were introduced with food in quantities up to 1.2 times lower than needed; there was an age-specific decline in vitamin B2 consumption; caloric contents were 1.3 times lower than in the reference group (Type 2 schools) (p < 0.001).

We analyzed socioeconomic statuses of the examined schoolchildren's families; as a result, we established that average monthly incomes did not exceed 15,000 rubles per one family member in each second family in Type 2 schools. The proportion of families with such incomes was only 26.8 % in Type 1 schools; 30.4 % had monthly incomes varying between 15,001 and 30,000 rubles per a family member (p < 0.001). The proportion of schoolchildren involved in additional educational activities was 1.4 times higher in Type 1 schools against Type 2 schools (85.6 against 60.3 %, p < 0.001). Night sleep not shorter than

8 hours was mentioned in the questionnaire by 17.3 % of the schoolchildren from Type 1 schools and 18.4 % of their peers from Type 2 schools ($p = 0.057$). One or less days a week and less than 6 hours a week were spent doing sports or physical exercises by 11 and 66.7 % of the schoolchildren from Type 1 schools respectively and 18.6 and 77.6 % of their peers from Type 2 schools ($p = 0.002–0.04$). Our analysis of digital activity revealed that the proportion of children who operated three or more devices and spent more than 2 hours every day on screen time amounted to 33.1 and 77.6 % respectively in Type 1 schools; 22.1 and 66.5 % respectively in Type 2 schools ($p = 0.011–0.045$).

Hygienic assessment of ambient air quality in areas near the analyzed schools established that average manganese and formaldehyde levels were up to 1.8–8.5 times higher than reference concentrations upon chronic inhalation exposure ($p < 0.005$). Nickel and chromium levels were found to be up to 3.6 times higher than RfC for chronic exposure in sporadic ambient air samples taken in areas near the analyzed schools ($p < 0.005$).

Our analysis of air samples taken inside classroom in the analyzed schools revealed average manganese levels in some schools and average formaldehyde levels in most schools to be up to 1.9–6.4 times higher than RfC for chronic inhalation exposure ($p < 0.005$). Nickel and chromium were detected in levels 1.1–1.5 times higher than RfC for chronic exposure in sporadic air samples taken inside classrooms in Type 1 and Type 2 schools ($p < 0.005$). Benzene and toluene levels did not exceed single maximum and average daily MPC and were below RfC for chronic exposure in ambient air in areas near the schools and in air samples taken inside them.

Chemical blood tests found benzene and toluene in blood of 46.0 % of the examined children; toluene was found 1.2 times more frequently in blood of schoolchildren from Type 1 schools and average group concentrations of aromatic hydrocarbons were significantly higher in them against their peers from Type 2 schools ($p = 0.0001–0.002$). Formaldehyde contents were higher than the background level in blood of 97.9–98.6 % of the examined children and average group levels were 3.4–4.3 times higher than the background level ($p < 0.005$). In the observation group (Type 1 schools), three fourths of the schoolchildren had nickel and chromium levels in blood higher than the background level; the proportion of schoolchildren with elevated manganese contents in blood was 1.2 times higher in this group against the reference one (Type 2 schools) ($p = 0.006–0.013$).

Significant relationships between blood manganese, nickel, chromium, formaldehyde, toluene and benzene levels and a dose of chemicals introduced with ambient air were established by modeling methods ($0.16 \le R^2 \le 0.50$; $31.97 \le F \le 214.88$; $p < 0.005$). This allowed us to consider elevated blood levels of these chemicals as markers of exposure.

We comparatively analyzed ADs prevalence and anti-infection immunity disorders using the results of clinical and laboratory research. The analysis did not establish any significant intergroup differences within three levels of school education (primary, middle and high school; $p = 0.146–0.971$). Still, ADs prevalence tended to grow with age by 1.4 times among schoolchildren from Type 1 schools (from 162 to 228 cases per 1000 examined, $p = 0.042$; OR = 1.33; CI = 1.02–1.74); we did not find any significant positive dynamics in prevalence of anti-infection immunity disorders ($p = 0.084$) whereas there was a decline in the reference group, by 2.4 times (from 124 to 51 cases per 1000 examined, $p = 0.029$).

Our assessment of post-infection immunity against herpesviruses found that the high stress of serological response (IgG titers: 1:800–3200) to CMVI and HSV-1 infection was detected 1.2–1.6 times less frequently in schoolchildren from Type 1 schools against their peers from the reference group (26 against 43 % and 53.5 against 63.2 % respectively, $p = 0.002–0.068$); insufficient production of IgG (titers: 1:100–400) to CMVI was detected 1.9 times more frequently against the reference group (32.6 against 17.5 %, $p = 0.002$; OR = 2.30; CI = 1.76–2.99).

Our analysis of age-specific immune response to vaccine antigens revealed that the proportion of schoolchildren seropositive to the measles virus went down by 1.2 times in high school against primary school in the observation group (Type 1 schools) (from 74.4 to 60.8 %, p = 0,03; in Type 1 schools, from 77.2 to 75.4 %, p = 0.790); the number of schoolchildren with the negative result grew by 2.5 times (from 12.3 to 30.5 %, p < 0.005; OR = 3.11; CI = 1.88–5.36; in Type 2 schools, from 11.9 to 13.8 %, p = 0,720). The proportion of schoolchildren who did not have protective antibodies to diphtheria grew fivefold in middle school against primary school in the observation group (Type 1 schools) (from 2.7 to 13.4 %, p = 0.003; OR = 5.40; CI = 2.79–11.14; in Type 2 schools, from 1.5 to 3.7 %, p = 0.120). The proportion of schoolchildren with proper protective levels declined 1.25 times more intensively in high school against primary school in Type 1 schools (from 79.5 to 40.0 %, p < 0.005; in Type 2 schools, from 64.2 to 40.3 %, p = 0.007). The proportion of schoolchildren seronegative to the pertussis agent declined 1.2 times less intensively in high school against primary school in Type 1 schools than in Type 2 schools (from 34.5 to 23.8 %, p = 0.090 against from 32.9 to 19.3 %, p = 0.040).

Previously published works reported some results obtained by regression analysis with its aim to establish negative impacts of various factors not conforming to safe standards including the educational process, diets, lifestyles, chemical contamination of biological media on likelihood of allergic rhinitis and declining humoral immunity to diphtheria and pertussis [21, 22]. Table 1 provides data about relationships between the analyzed factors and BA and AD incidence established by building one-factor regression logistic models.

Table 1

Parameters of one-factor linear regression models describing relationships between BA and AD and priority risk factors

Factor		Response	*b0*	*b1*	R^2	*F*	*p*
Educational process	Weekly educational loads	AD	-8.98	0.22	0.47	59.4	<0.001
	Duration of IWB use in class	AD	-2.84	0.05	0.73	210	<0.001
		BA	-1.68	0.02	0.58	53.5	<0.001
	Total IWB use in school per day	AD	-2.69	0.04	0.82	108	<0.001
	Duration of PC use in class	AD	-2.63	0.02	0.30	5.81	<0.001
		BA	-2	0.02	0.79	143.7	<0.001
	Total PC use in school per day	AD	-2.77	0.04	0.36	44.7	<0.001
Diet	Wheat bread consumption	AD	-0.16	0	0.27	78.9	<0.001
	Confectionary products consumption	BA	-3.22	0.01	0.55	111	<0.001
	Poultry consumption	BA	-2.40	0.01	0.39	77.3	<0.001
Lifestyle	Periodicity of doing sports or physical exercises	AD	-0.26	-0.13	0.68	369.37	<0.001
		BA	-1.93	-0.09	0.63	303.54	<0.001
	Duration of doing sports or physical exercises	AD	-0.54	-0.06	0.25	56.90	<0.001
	The number of devices in use	AD	-0.69	0.04	0.10	29.3	<0.001
Chemical exposures	Benzene levels in blood	BA	-2.31	99.68	0.17	68.47	<0.001
		AD	-0.80	309.70	0.35	197.06	<0.001
	Toluene levels in blood	BA	-2.47	364.55	0.15	28.6	0.005
		AD	-1.65	118.65	0.15	31.7	0.0002
	Manganese levels in blood	BA	-3.08	43.37	0.10	45.80	<0.001
		AD	-2.34	83.11	0.31	61.17	<0.001
	Nickel levels in blood	AR	-0.70	56.55	0.18	89.89	<0.001
		BA	-2.96	102.70	0.33	203.19	<0.001
		AD	-1.60	45.06	0.19	65.0	<0.001
	Formaldehyde levels in blood	BA	-3.14	18.96	0.67	848.95	<0.001

Weekly educational loads ($R^2_{AR, AD}$ = 0.19–0.47), duration of IWB and PC use in one class and total weekly use of these devices ($R^2_{AR, AD, BA}$ = 0.30–0.82) are priority factors of the educational process, which influence ADs incidence. We also established a dose-dependent impact exerted by duration of small breaks on levels of IgG to the pertussis agent (R^2 = 0.17).

Consumption of milk (R^2_{AR} = 0.64; $R^2_{diphtheria}$ = 0.65), wheat bread ($R^2_{AR, AD}$ = 0.27–0.66), meat ($R^2_{diphtheria, pertussis}$ = 0.21–0.34), fish, eggs, sour milk products ($R^2_{pertussis}$ = 0.60–0.96), confectionary products (R^2_{BA} = 0.55), and poultry ($R^2_{BA, AR}$ = 0.39; $R^2_{diphtheria}$ = 0.86) are significant diet-related factors as regards post-vaccination immunity and allergic reactivity modification in schoolchildren.

Periodicity ($R^2_{AR, BA, AD}$ = 0.19–0.68) and duration of doing physical exercises or sports (R^2_{AD} = 0.25) as well as the number of devices in use (R^2_{AD} = 0.10) were the most significant lifestyle aspects out of all analyzed ones with the greatest influence on changes in incidence of allergic diseases and post-vaccination humoral immunity.

Levels of toluene ($R^2_{BA, AD, AR}$ = 0.15–0.64), benzene ($R^2_{BA, AD, AR}$ = 0.17–0.35), manganese ($R^2_{BA, AR, AD}$ = 0.10–0.31; $R^2_{pertussis, diphtheria}$ = 0.19–0.40), nickel ($R^2_{AR, AD, BA}$ = 0.18–0.33; $R^2_{diphtheria}$ = 0.78), chromium (R^2_{AR} = 0.58; $R^2_{diphtheria}$ = 0.12), and formaldehyde (R^2_{BA} = 0.67) were priority chemical factors, impacts of which on post-vaccination immunity and allergic reactivity modification were confirmed by building the above-mentioned regression models.

In addition, the artificial neural network method was employed to establish deeper relationships and to quantify contributions made by environmental factors, the modern educational process, diets, and lifestyles to formation of anti-infection (post-infection and post-vaccination) immunity. Machine learning of artificial neural networks is being widely used both in Russia and abroad; it seems an effective method for establishing qualitative and quantitative regularities of immunologic reactivity formation considering mutual influence exerted by multiple factors [23, 24]. Our created neural network models have an external input layer proportionate to the number of analyzed factors, internal layers, and an output layer corresponding to likelihood of a decline in levels of IgG to herpesvirus infection HSV-1 and CMVI (post-infection immunity) as well as to the measles virus, diphtheria toxin and pertussis antigen (post-vaccination immunity). Orientation of influence was determined by a numeric experiment, which involved consequent 1 % growth in each risk factor and subsequent prediction of changes in likelihood of post-vaccination and post-infection immunity disorders (herpesvirus infection HSV-1 and cytomegalovirus infection). Table 2 provides ranking of risk factors, which determine additional likelihood of a decline in levels of IgG specific to herpesvirus infection HSV-1 and CMVI.

According to neural network modeling results, likelihood of changes in production of specific antibodies to herpesvirus infection HSV-1 and CMVI is modified upon 1 % changes in factors related to the modern educational process, up to 26.75 and 17.68 % respectively; diets, up to 5.37 and 3.05 %; environmental factors, up to 20.08 and 23.82 %; lifestyle-related factors, up to 60.43 and 6.22 % respectively (Table 2).

The most pronounced modifying effects on likelihood that production of specific antibodies to the measles virus will deviate from the proper protective level are produced by changes in such factors related to the educational process as weekly educational loads (up to 99.38 %); the pertussis agent, duration of short breaks (up to 70.5 %); to the diphtheria toxin, duration of long breaks (up to 82.71 %) (Table 3).

Likelihood of a decline in production of specific antibodies to the measles virus is modified by diets, up to 797.65 % (consumption of confectionaries); to the pertussis agent, up to 45.6 % (consumption of fish); to the diphtheria toxin, up to 58.75 % (consumption of meat). Priority chemical environmental risk factors that modify likelihood of weakening post-vaccination humoral immunity include

Table 2

Results of neural network modeling to describe influence of priority risk factors on formation of humoral post-infection immunity, %

Factor		Changes in likelihood of declining IgG to HSV-1 (layers 9; 5, $R^2 = 0.144$)	Changes in likelihood of declining IgG to CMVI (layers 14; 7, $R^2 = 0.233$)
Educational process	Duration of long breaks	26.75	17.68
	Duration of short breaks	3.99	16.58
	Weekly educational loads	14.95	2.43
	Duration of PC use in class	3.21	3.45
	Duration of IWB use in class	1.44	2.30
Diets	Milk in typical daily diet	4.77	2.12
	Confectionaries in typical daily diets	3.69	0.73
	Cereals and beans in typical daily diet	3.66	0.26
	Macaroni in typical daily diet	3.64	0.26
	Sour milk products in typical daily diet	3.61	0.90
	Fish in typical daily diet	3.08	0.36
	Fresh vegetables in typical; daily diet	3.06	1.32
	Proteins in typical daily diet	5.73	0.40
	Vitamin B1 in typical daily diet	4.18	0.10
	Vitamin B2 in typical daily diet	1.50	1.67
	Caloric contents in typical daily diet	3.29	3.05
Environment	Manganese in ambient air	20.08	15.68
	Nickel in ambient air	3.76	6.97
	Chromium in ambient air	3.62	0.78
	Toluene in ambient air	13.79	0.93
	Benzene in ambient air	2.04	10.15
	Formaldehyde in ambient air	9.75	0.30
	Nickel in air inside classrooms	5.90	0.51
	Toluene in air inside classrooms	19.63	2.16
	Benzene in air inside classrooms	3.15	1.48
	Formaldehyde in air inside classrooms	6.97	2.54
	Manganese in air inside classrooms	2.31	23.82
	Chromium in air inside classrooms	2.36	2.02
Lifestyle	Duration of night sleep	60.43	0.56
	Involvement in additional education	4.55	6.22
	Monthly income per a family member	5.06	3.76
	Total time spent on using devices a day	3.72	0.33
	Duration of doing sports or physical exercises	0.37	2.25

Table 3

Results of neural network modeling to describe influence of priority risk factors on formation of humoral post-vaccination immunity, %

Factor		Changes in likelihood of declining IgG to measles (layers 5; 2, $R^2 = 0.152$)	Changes in likelihood of declining IgG to pertussis (layers 15; 10, $R^2 = 0.175$)	Changes in likelihood of declining IgG to diphtheria (layers 10; 8, $R^2 = 0.180$)
Educational process	Duration of long breaks	97.27	2.4	82.71
	Duration of short breaks	56.52	70.5	55.39
	Weekly educational loads	99.38	55.2	38.66
	Duration of PC use in class	50.38	17.4	5.89
	Duration of IWB use in class	22.15	10.5	9.05
	Total PC use in school per day	58.52	13.5	2.0
	Total IWB use in school per day		12.5	2.33

End of the Table 3

Factor		Changes in likelihood of declining IgG to measles (layers 5; 2, $R^2 = 0.152$)	Changes in likelihood of declining IgG to pertussis (layers 15; 10, $R^2 = 0.175$)	Changes in likelihood of declining IgG to diphtheria (layers 10; 8, $R^2 = 0.180$)
Diets	Milk in typical daily diet	60.55	34.5	1.67
	Confectionaries in typical daily diets	797.65	0.2	14.55
	Cereals and beans in typical daily diet	95.82	11.8	1.62
	Macaroni in typical daily diet	636.25	16.3	12.08
	Sour milk products in typical daily diet	435.74	5.2	15.0
	Fish in typical daily diet	720.21	45.6	15.82
	Fresh vegetables in typical; daily diet	70.36	9.9	14.93
	Fresh fruits in typical; daily diet	80.87	9.8	9.29
	Meat in typical daily diet	309.51	1.2	58.75
	Wheat bread in typical daily diet	71.78	10.6	16.4
	Eggs in typical daily diet	58.93	8.7	5.69
	Proteins in typical daily diet	410.12	12.0	5.84
	Vitamin B1 in typical daily diet	10.63	0.1	6.19
	Vitamin B2 in typical daily diet	11.55	3.2	3.49
	Vitamin A in typical daily diet	92.39	3.6	2.5
	Caloric contents in typical daily diet	30.85	7.4	11.62
	Iron in typical daily diet	115.76	3.0	23.86
	Magnesium in typical daily diet	27.96	6.6	21.78
Environment	Manganese in ambient air	70.71	42.2	34.89
	Nickel in ambient air	85.79	3.9	6.9
	Chromium in ambient air	59.73	7.4	14.96
	Toluene in ambient air	19.22	12.6	2.73
	Benzene in ambient air	68.78	25.5	7.2
	Formaldehyde in ambient air	37.84	20.3	4.69
	Nickel in air inside classrooms	19.22	5.2	8.7
	Toluene in air inside classrooms	110.17	3.40	12.19
	Benzene in air inside classrooms	31.13	13.1	0.21
	Formaldehyde in air inside classrooms	109.31	28.8	14.56
	Manganese in air inside classrooms	378.36	24.4	13.57
	Chromium in air inside classrooms	156.09	8.5	30.01
Lifestyle	Duration of night sleep	89.01	101.5	26.12
	Involvement in additional education	58.36	8.6	26.75
	Monthly income per a family member	72.25	3.6	62.08
	Total time spent on using devices a day	9.92	3.3	6.93
	Duration of doing sports or physical exercises	25.26	27.3	3.7
	Periodicity of doing sports or physical exercises	19.7	12.9	7.1

the following: for measles, manganese in air inside classrooms (378.36 %); for pertussis, benzene in ambient air (25.5 %); for diphtheria, manganese in ambient air (34.89 %). Shorter duration of night sleep modifies likelihood of insufficient production of specific antibodies to the measles and pertussis agents by 89.01 and 101.5 % respectively whereas monthly incomes per a family member have turned out to be the most significant lifestyle-related factor for anti-diphtheria immunity (62.08 %).

Intergroup comparison of the results obtained by immunological studies and subsequent mathematical modeling has made it possible to establish negative effects on the immune system and pathogenetic regularities of anti-infection immunity and allergic reactivity modification in children. It is associated with specific features of the modern

educational process, the environment, diets and lifestyles.

Under combined exposure to the analyzed factors, weakened reactivity of humoral immunity is evidenced by 1.2 times lower relative levels of CD19+-lymphocytes in children from Type 1 schools against their peers form Type 2 schools, (12 (10; 14) against 14 (11; 16) %, $p = 0.046$) and levels of antibodies of the late phase in immune response (IgG) below physiological ranges in 30.5–54.7 % of children in the observation group.

Activation of a cellular adaptive immune response in children from Type 1 schools is evidenced by higher relative levels of CD3+-lymphocytes (68 (64; 73) against 66 (62; 70), $p = 0.040$) and high levels of activated T-cells (CD3+CD25+-lymphocytes) in 20.3 % of them.

Prevalence of a cytotoxic effector pathway of immune response in the children from the observation group is accompanied with higher relative levels of CD3+CD8+-lymphocytes (25 (22; 23) against 23 (21; 26) %, $p = 0.023$).

Elevated quantities of lymphocytes with CD95 receptor are observed in each third schoolchild both in their relative (35.7 %) and absolute values (21.4 %). This indicates that programmed cell death pathways have intensified and immune reactions have become less active.

Weakening activity of the non-specific protection system is accompanied with low absolute phagocytosis values in 15.6 % of the children from the observation group (against 2.0 % in Type 2 schools, $p = 0.03$), phagocytic number (PN) in 40.6 % (against 33.3 %, $p = 0.236$), phagocytic index (PI) in 4.4 % (against 0.9 %, $p = 0.157$), and phagocytosis percentage in 12.5 % (against 2.0 %, $p = 0.080$). Natural killers (CD16+CD56+-lymphocytes), which are conventionally considered a significant component of innate immunity and not only are responsible for a prompt effector response to presence of infected cells but also coordinate interaction between innate and adaptive immunity, are also registered in lower levels in the observation group against the reference one (10 (6; 14) against 12 (9; 17) %, $p = 0.060$).

Our analysis of levels of the immune system cytokines responsible for intercellular cooperation, positive or negative immune regulation, has established 1.2 times higher levels of gamma-interferon in the children from Type 1 schools against their peers from Type 2 schools (2.02 (1.49; 2.55) against 1.75 (1.28; 2.54) pg/ml, $p = 0.595$) and 2.5 times lower levels of its antagonist IL-4 (0.88 (0.55; 1.32) against 2.24 (0.58; 2.7) pg/ml, $p = 0{,}036$), which indicates that an adaptive response primarily develops per Th1 pathways.

IL-6 and IL-10, which, just as IL-4, promote transition of B-lymphocytes to antibodies-producers, are also detected in the children from Type 1 schools in lower levels (1.48 (1.18; 2.19) against 1.58 (0.85; 2.27) pg/ml and 3.18 (1.73; 4.9) against 3.27 (1.97; 4.75) pg/ml respectively).

IL-8 is able to support anti-inflammatory activity of monocytes / macrophages and promote development of immune reactions mediated by Type 1 T-helpers. Its levels have been found to be higher than their physiological range in 21.4 % of the children from Type 1 schools.

Levels of the tumor necrosis factor (TNF) that promotes formation of antibodies proliferation and differentiation of T-helpers and B-lymphocytes and simulates phagocytosis, are 1.2 times lower in the children from Type 1 schools against their peers from Type 2 schools (1.94 (1.28; 2.29) against 2.31 (1.74; 2.73) pg/ml, $p = 0.008$).

Interleukin 1-beta (IL-1ß) is able to stimulate T- and B-cells; IL-17 ensures activation and migration of neutrophils, stimulates production of IL-1ß, tumor necrosis factor and IL-6 by peripheral blood monocytes and is also able to negatively and positively regulate IgE synthesis and influence development and clinical course of allergic diseases. Upon exposure to the analyzed factors, their levels are 1.8 times lower in the observation group against the reference one (1.53 (0.88; 2.63) against 2.75 (1.44; 3.23) pg/ml, $p = 0.049$ and 1.13 (0.72; 4.02) against 1.67 (1.05; 3.18) pg/ml, $p = 0.543$ respectively).

Relationships between negative laboratory indicators of the immune system and rele-

vant factors of the modern educational process and the environment have been established by creating one-factor regression logistic models (Table 4).

We have established the relationship between relative levels of CD16+56+-lymphocytes and all analyzed factor groups: diet (R^2 = 0.53), chemical factors (R^2 = 0.10–0.24), lifestyle (R^2 = 0.16), and the educational process (R^2 = 0.10). Some lifestyle-aspects, chemical exposures, and diet are priority risk factors affecting levels of IgG (R^2 = 0.65, R^2 = 0.10–0.32 and R^2 = 0.10–0.13 respectively) and relative levels of CD3+-lymphocytes (R^2 = 0.10, R^2 = 0.10–0.87 and R^2 = 0.46 respectively). Relative levels of CD3+CD8+- (R^2 = 0.13–0.69), CD3+CD25+-lymphocytes (R^2 = 0.10–0.79) and IL-8 level (R^2 = 0.71–0.87) depend on occurrence of chemicals in blood.

The next stage in neural network modeling has been performed to establish additional relationships between likelihood of negative responses by the immune system and the analyzed factors (Table 5 and 6).

Table 4

Parameters of one-factor regression logistic models for describing relationships between immunological indicators and relevant risk factors

Factor		Immunological indicator	Trend	*b0*	*b1*	R^2	F	*p*
Educational process	Duration of short breaks	CD16+56+-lymph., rel.	Lower	-1.88	-0.064	0.10	14.33	0.002
Diet	Eggs in daily diet	IgG	Lower	-1.03	-0.01	0.13	34.50	<0.001
	Confectionaries in daily diet	IgG	Lower	-1.19	0.002	0.10	15.87	<0.001
	Poultry in daily diet	CD3+-lymph., rel.	Higher	-4.21	0.04	0.46	162.26	<0.001
		CD16+56+-lymph., rel.	Lower	-2.90	0.022	0.53	387.81	<0.001
Lifestyle	The number of devices in use	IgG	Lower	-2.36	-0.12	0.65	811.27	<0.001
		CD3+-lymph., rel.	Higher	-4.15	0.11	0.10	46.96	<0.001
		CD16+56+-lymph., rel.	Lower	-2.71	0.13	0.16	85.37	<0.001
	Periodicity of doing sports or physical exercises	CD3+-lymph., rel.	Higher	-2.95	-0.04	0.10	5.27	0.027
Chemical factors	Benzene in blood	IgG	Lower	-1.36	209.22	0.10	9.12	0.004
		IL-8	Higher	-1.79	144.20	0.87	311.78	<0.001
		CD3+CD8+-lymph., rel.	Higher	-4.01	702.28	0.66	631.46	<0.001
	Toluene in blood	IgG	Lower	-2.85	621.93	0.32	35.66	<0.001
		IL-8	Higher	-4.90	1626.11	0.71	61.30	<0.001
		CD3+-lymph., rel.	Higher	-3.05	77.81	0.79	497.88	<0.001
		CD3+CD8+-lymph., rel.	Higher	-3.52	377.31	0.69	527.79	<0.001
		CD16+56+-lymph., rel.	Lower	-2.57	81.44	0.10	11.83	0.002
	Manganese in blood	CD3+CD25+-lymph., rel.	Higher	-2.92	82.72	0.10	8.74	0.005
		CD3+-lymph., rel.	Higher	-5.20	120.36	0.43	173.60	<0.001
		CD3+CD8+-lymph., rel.	Higher	-4.4	53.47	0.13	47.45	<0.001
		CD16+56+-lymph., rel.	Lower	-3.11	52.43	0.15	62.50	<0.001
	Nickel in blood	CD3+CD25+-lymph., rel.	Higher	-2.88	282.79	0.79	342.37	<0.001
		CD3+-lymph., rel.	Higher	-4.81	247.03	0.14	18.50	<0.001
		CD3+CD8+-lymph., rel.	Higher	-3.67	118.84	0.21	84.35	<0.001
		CD16+56+-lymph., rel.	Lower	-2.98	71.99	0.11	49.18	<0.001
	Chromium in blood	CD3+-lymph., rel.	Higher	-5.01	174.01	0.87	719.84	<0.001
		CD16+56+-lymph., rel.	Lower	-3.15	129.54	0.24	129.01	<0.001
	Formaldehyde in blood	CD3+CD8+-lymph., rel.	Higher	-4.02	20.48	0.62	646.93	<0.001
		CD16+56+-lymph., rel.	Lower	-2.66	4.93	0.10	35.49	<0.001

Table 5

Results of neural network modeling to show influence of priority risk factors on immune indicators (cellular and humoral components of the adaptive immune system), %

	Risk factor	CD3+-lymph., rel. (layers 10; 4, $R^2 = 0.144$)	CD3+CD8+-lymph., rel. (layers 5; 2, $R^2 = 0.195$)	CD19+-lymph., rel. (layers 18; 8, $R^2 = 0.124$)	CD3+CD25+-lymph., rel.. (layers 14; 4, $R^2 = 0.587$)	CD16+56+-lymph., rel. (layers 15; 2, $R^2 = 0.155$)	CD3+CD95+-lymph., abs. (layers 11; 11, $R^2 = 0.342$)	CD3+CD95+-lymph., rel. (layers 10; 5, $R^2 = 0.663$)	IgG (layers 12; 10, $R^2 = 0,146$)
Educational process	Weekly educational loads	0.14		0.33		0.54			
	Duration of short breaks	0.29			0.76	0.07			1.71
	Duration of long breaks		12.16	0.04	2.03				
	Duration of IWB use in class	0.08	0.16	0.05		0.08	0.03		
	Total weekly IWB use	0.08			0.38	0.15			
	Duration of PC use in class	0.02	1.28	0.03	0.06		0.03	0.01	0.81
	Total weekly PC use in school	0.04	0.51		0.06		0.03	0.02	1.9
Lifestyle	Involvement in additional education		0.71			0.23	0.13		2.53
	Duration of night sleep			0.21		0.59	0.72		5.61
	Monthly incomes per a family member		1.7	0.18	0.18	0.08		0.13	1.08
	Total average daily time spent on using devises			0.18	0.05		0.12	0.04	2.43
	Periodicity of doing sports or physical exercises			0.17				0.05	
	Duration of doing sports or physical exercises			0.1					1.72
Diet	Milk in a daily diet	0.15		0.02	0.17			0.05	
	Eggs in a daily diet	0.04					0.05		
	Fresh vegetables in a daily diet	0.02	5.5			0.04	0.05	0.03	
	Fresh fruits in a daily diet			0.1			0.06		
	Meat in a daily diet	0.02	1.1		0.07				0.63
	Sour milk products in a daily diet	0.09	5.53	0.11	0.11	0.07			
	Confectionaries in a daily diet	0.10	0.64		0.11				0.23
	Fish in a daily diet	0.06			0.04		0.03	0.02	
	Wheat bread in a daily diet	0.06				0.08	0.06		
	Cereals and beans in a daily diet	0.03	5.81		0.11			0.01	0.48
	Macaroni in a daily diet		0.86	0.03				0.04	
	Proteins in a daily diet	0.09		0.15	0.04			0.03	
	Caloric contents in a daily diet	0.03	0.15			0.06	0.06		
	Vitamin B1 in a daily diet				0.14	0.01		0.07	0.38
	Vitamin B2 in a daily diet	0.10		0.02	0.01		0.05		0.59
	Vitamin A in a daily diet			0.05		0.08			
	Iron in a daily diet	0.02	4.47	0.02			0.05	0.01	
	Magnesium in a daily diet	0.01		0.1	0.16	0.02			1.47
Chemical factors	Manganese in ambient air	0.24	6.85	0.06	0.13		0.08		1.54
	Chromium in ambient air	0.07			0.1			0.01	
	Nickel in ambient air	0.05		0.01		0.06			
	Formaldehyde in ambient air	0.12			0.56			0.11	4.3
	Benzene in ambient air	0.02			0.25	0.09	0.03	0.11	0.38
	Toluene in ambient air	0.05	0.54		0.28	0.06	0.11	0.05	
	Manganese in air inside classrooms		3.15		0.29			0.24	2.65
	Nickel in air inside classrooms	0.09				0.04	0.01	0.01	0.27
	Chromium in air inside classrooms		1.28	0.03		0.03	0.1		
	Formaldehyde in air inside classrooms	0.21		0.21	0.26			0.02	
	Benzene in air inside classrooms	0.01			0.14	0.15		0.11	
	Toluene in air inside classrooms	0.03					0.06	0.02	

Table 6

Results of neural network modeling to show influence of priority risk factors on immune indicators (the phagocyte system and cytokines), %

	Risk factor	Absolute phagocytosis (layers 10; 4, $R^2 = 0.144$)	Phagocytosis percentage (layers 18; 5, $R^2 = 0.313$)	Phagocytic index (layers 13; 13, $R^2 = 0.108$)	Phagocytic number (layers 5; 3, $R^2 = 0.105$)	IL-4 (layers 6; 5, $R^2 = 0.485$)	IL-6 (layers 12; 12, $R^2 = 0.137$)	IL-10 (layers 12; 9, $R^2 = 0.112$)	IL-17 (layers 16; 11, $R^2 = 0.374$)	IL-1ß (layers 12; 2, $R^2 = 0.306$)	INFγ (layers 8; 8, $R^2 = 0.202$)	TNF (layers 8; 3, $R^2 = 0.185$)
Educational process	Weekly educational loads	0.1		0.08			1.36	0.36	0.67			
	Duration of short breaks			0.28		1.48		0.67		0.33		
	Duration of long breaks	0.56		0.83			0.3		1.42	0.64	0.01	14.96
	Duration of IWB use in class	0.01		0.05	0.01	0.2				0.13		2.46
	Total weekly IWB use			0.08		0.05	0.12	0.17	0.92			

End of the Table 6

	Risk factor	Absolute phagocytosis (layers 10; 4, $R^2 = 0.144$)	Phagocytosis percentage (layers 18; 5, $R^2 = 0.313$)	Phagocytic index (layers 13; 13, $R^2 = 0.108$)	Phagocytic number (layers 5; 3, $R^2 = 0.105$)	IL-4 (layers 6; 5, $R^2 = 0.485$)	IL-6 (layers 12; 12, $R^2 = 0.137$)	IL-10 (layers 12; 9, $R^2 = 0.112$)	IL-17 (layers 16; 11, $R^2 = 0.374$)	IL-1ß (layers 12; 2, $R^2 = 0.306$)	INFγ (layers 8; 8, $R^2 = 0.202$)	TNF (layers 8; 3, $R^2 = 0.185$)
	Duration of PC use in class	0.13	0.03		0.02		0.02			0.11	0.02	0.77
	Total weekly PC use in school	0.03			0.01			0.22		0.1		0.14
Lifestyle	Involvement in additional education		0.07	0.39		0.16		0.62				
	Duration of night sleep	0.28	0.53		0.14	3.63				0.56	0.75	
	Monthly incomes per a family member		0.14				0.75	0.92	0.34			
	Total average daily time spent on using devises		0.01		0.02				0.06			
	Periodicity of doing sports or physical exercises	0.29		1.09	0.01	0.04	0.04		0.55		0.07	1.69
	Duration of doing sports or physical exercises		0.08	0.04	0.02		1.15	0.29				2.57
Diets	Milk in a daily diet	0.08	0.02				0.05	0.01	0.1			
	Eggs in a daily diet	0.15	0.01	0.07	0.02	0.07	0.02			0.05	0.03	1.13
	Fresh vegetables in a daily diet			0.49				0.09			0.09	
	Fresh fruits in a daily diet			0.04		0.05	0.04			0.03		1.78
	Meat in a daily diet							0.01			0.02	
	Sour milk products in a daily diet	0.12		0.49	0.01	0.05			0.04	0.05	0.01	0.89
	Confectionaries in a daily diet			1.9		0.09	0.26	0.19				
	Fish in a daily diet		0.01			0.2					0.02	
	Wheat bread in a daily diet		0.03	0.58					0.17		0.01	
	Cereals and beans in a daily diet	0.04			0.01	0.05	0.01	0.09	0.18		0.01	
	Macaroni in a daily diet	0.19	0.06	0.42			0.11		0.06		0.03	
	Proteins in a daily diet	0.25				0.07				0.12	0.08	
	Caloric contents in a daily diet			0.68		0.43	0.74	0.4	2.66		0.01	
	Vitamin B1 in a daily diet	0.04	0.02						2.01		0.05	0.39
	Vitamin B2 in a daily diet		0.02			0.25	0.09	0.29	2.23		0.03	
	Vitamin A in a daily diet	0.5	0.05	0.03		0.03			0.85	0.01		
	Iron in a daily diet		0.01	0.19					0.15		0.05	
	Magnesium in a daily diet	0.01			0.01	0.03			2.01		0.05	
Chemical factors	Manganese in ambient air	0.13								0.1		1.09
	Chromium in ambient air	0.01				0.42	0.24					0.33
	Nickel in ambient air	0.15				0.21	0.19		0.01			1.88
	Formaldehyde in ambient air						0.16	0.36		0.12		
	Benzene in ambient air		0.01		0.01	0.1		0.18	0.98	0.26		
	Toluene in ambient air	0.25	0.07		0.01	0.43		0.02		0.22		
	Manganese in air inside classrooms		0.05					0.52	2.58		0.07	
	Nickel in air inside classrooms			0.71	0.02					0.07		0.51
	Chromium in air inside classrooms		0.03	0.2		0.14	0.17	0.1				
	Formaldehyde in air inside classrooms	0.2		0.57			1.03				0.07	1.08
	Benzene in air inside classrooms			0.06	0.02	0.31	0.12	0.01				1.32
	Toluene in air inside classrooms		0.02	0.1				0.16	0.01		0.02	

Table 7

Parameters of regression logistic models to describe relationships between immunological indicators and allergic diseases / post-vaccination immunity disorders

Allergic disease / post-vaccination immunity disorders	Immunologic indicator	Trend	*b0*	*b1*	R^2	F	*p*
Allergic rhinitis	CD3+-lymphocytes, rel.	Higher	-0.42	0.25	0.10	20.84	<0.001
	CD3+CD25+- lymphocytes, rel.	Higher	-1.18	0.08	0.30	27.17	<0.001
	IL-8	Higher	-2.72	0.34	0.38	19.77	<0.001
Bronchial asthma	CD16+56+- lymphocytes, rel.	Higher	-1.98	-0.04	0.17	61.40	<0.001
	CD3+CD8+- lymphocytes, rel.	Higher	-4.48	0.07	0.22	73.80	<0.001
	CD3+CD25+- lymphocytes, rel.	Higher	-4.21	0.18	0.25	20.13	<0.001
	IgG	Higher	-1.93	-0.05	0.10	16.82	<0.001
Atopic dermatitis	CD3+- lymphocytes, rel.	Higher	-1.30	0.43	0.18	69.60	<0.001
	CD3+CD25+- lymphocytes, rel.	Higher	-3.33	15.94	0.69	8.78	0.033
	CD16+56+-lymphocytes, rel.	Higher	-0.40	-0.02	0.16	59.26	<0.001
IgG to pertussis	IgG	Lower	4.15	-0.36	0.43	14.10	0.005

Data provided in Tables 5 and 6 give evidence that indicators of cellular adaptive immunity and functional activity of immune-competent cells are more frequently influenced the most by factors related to the educational process and lifestyle. Any changes in these factors raise likelihood that levels of T-lymphocytes and cytokines will deviate from their physiological norms by 12.2–15.0 and 1.7–3.6 % respectively. Quantitative assessment of additional likelihood of changes in humoral adaptive immunity has established that the studied lifestyle aspects and chemical factors most frequently have the greatest influence on the IgG level raising likelihood of its decline by up to 5.61 and 4.3 % respectively. Lifestyle factors and diets are the most significant ones for a growth in likelihood of innate immunity indicators deviating from the physiological norm. Any change in these factors by 1 % increases likelihood of a decline in the phagocytic system indicators by up to 3.63 and 1.9 % respectively.

The list of laboratory immunological indicators of risk-associated ADs and post-vaccination immunity disorders is the ultimate result of consequent regression logistic modeling. For them, a consequent relationship has been proven: factor → change in laboratory (immunologic) indicator → allergic disease / post-vaccination immunity disorder (Table 7).

The results obtained by neural network modeling of relationships between laboratory indicators of disrupted immune homeostasis and a decline in levels of specific G class antibodies to herpesvirus infection HSV-1, CMVI, measles, diphtheria, and pertussis and conformity with biological feasibility principle made it possible to enhance the list of indicators of risk-associated post-vaccination immunity disorders and to determine laboratory immunological indicators of risk-associated post-infection immunity disorders (Table 8).

Having generalized all obtained data, we have created lists containing immunological indicators of risk-associated ADs and anti-infection immunity disorders. Thus, immunological indicators of risk-associated ADs upon combined exposure to risk factors related to the educational process, environment, diets, and lifestyle include elevated relative contents of CD3+-, CD3+CD25+-lymphocytes and a decline in relative contents of CD16+56+-lymphocytes. Likelihood of anti-infection immunity disorders associated with combined exposure to the analyzed factors is estimated per the following immunological indicators: elevated relative levels of CD3+CD8+-, CD3+CD95+-lymphocytes, declining levels of IgG, absolute phagocytosis, phagocytic index, IL-17, IL-1ß, and TNF.

Table 8

Results of neural network modeling to describe the relationship between likelihood of changes in the level of specific class G antibodies to herpesvirus and vaccine-managed infections and immunological indicators, %

Immunological indicator	IgG to HSV (layers 15; 11, $R^2 = 0.323$)	IgG to CMV (layers 11; 5, $R^2 = 0.143$)	IgG to measles (layers 15; 10, $R^2 = 0.323$)	IgG to diphtheria (layers 5; 2, $R^2 = 0.514$)	IgG to pertussis (layers 5; 2, $R^2 = 0.508$)
CD3+CD8+-lymphocytes, rel.	1.79	4.89	37.78	0.24	7.05
CD19+- lymphocytes, rel.			1.41	4.55	25.52
CD3+CD95+- lymphocytes, abs.				1.40	277.78
CD3+CD95+- lymphocytes, rel.	3.58	34.72		2.70	
IgG	15.84		7.15	2.58	
Absolute phagocytosis	3.94			0.98	16.92
Phagocytosis percentage				2.49	
Phagocytic index	20.54			0.03	4.41
Phagocytic number		2.23			28.17
IL-4		17.26	0.81		
IL-6		16.01			
IL-10			45.89		
IL-17	1.56	36.43		0.05	43.13
IL-1β	1.11	8.54	2.10	30.94	
INFγ		0.93			13.55
TNF	2.28		37.33		23.31

Common mechanisms of anti-infection immunity and allergic reactivity modification in children, which is associated with specific features of the modern educational process and quality of the environment, include imbalance of humoral and cellular immunity components together with activation of cellular-mediated reactions of the adaptive immunity response. This process involves a growth in relative levels of CD3+- and CD3+CD25+-lymphocytes (immunological indicators of risk-associated allergic diseases) and CD3+CD8+-lymphocytes (an immunological indicator of anti-infection immunity modification). A decline in absolute phagocytosis and the phagocytic index indicate weaker activity of the non-specific protection system when anti-infection immunity modification occurs upon exposer to environmental factors, factors related to the modern educational process, diets and lifestyle. Allergic reactivity modification is indicated by a decline in levels of natural killers, which are conventionally considered cellular components of innate immunity.

The results of the accomplished multifactorial logistic modeling have established that an isolated contribution made by the modern educational process to likelihood of risk-associated AR amounts to 61.8 %; chemical exposures, 30.6 %; lifestyle factors, 7.6 %; likelihood of BA associated with the analyzed factors is contributed by the modern educational process, 35.7 %; chemical exposures, 33.1 %; lifestyle, 31.2 %. Leading contributions made to likelihood of risk-associated AD belong to the modern educational process (74.0 %), followed by lifestyle factors (18.4 %), and chemical exposures (7.6 %).

We have accomplished quantitative assessment of likelihood of a decline in IgG antibodies to herpesvirus infection HSV-1 based on neural network modeling. As a result, we have established that lifestyle and diets, with their contributions equaling 28.9 and 26.2 % respectively, have the greatest influence on humoral immunity to herpesvirus infection; contributions made by ambient air quality and peculiarities of the modern educational process amount to 13.7 and 13.5 % respectively. Too short night sleep (10.0 %) makes the greatest contribution among lifestyle factors; among diet-related factors, the greatest contributions are made by high contents of confectionaries in a typical daily diet (4.8 %) and low magnesium contents in it (2.9 %); among chemical environmental factors, elevated formaldehyde levels in ambient air (its contribution is 7.5 %). The

greatest contributions to declining levels of IgG-antibodies to CMVI are made by diets (44.0 %), the modern educational process (17.9 %), chemical exposures (12.5 %, air quality inside classrooms), and lifestyle (12.3 %). Low caloric contents in a typical daily diet and insufficient consumption of cereals and beans hold a special place among other violations of a diet structure and quality as they make the greatest contributions (9.1 and 2.9 % respectively) to a disrupted humoral response to CMVI. Among factors related to the modern educational process, the greatest contribution is made by duration of long breaks (9.5 %), followed by quality of air inside classrooms per elevated manganese levels in it (9.2 %), and lifestyle as too short night sleep (5.3 %).

The greatest contributions to declining levels of specific Class G antibodies to measles are made by the modern educational process (30.8 %), including shorter duration of long breaks (26.7 %); diets (30.3 %), including insufficient contents of sour milk products (6.4 %) and iron (4.4 %) in a typical daily diet. The contribution made by ambient air quality equals 12.4 %, including elevated manganese levels (8.1 %); lifestyle, 11.4 %, including too short duration of doing sports or physical exercises (3.2 %). The greatest contribution made to changes in levels of specific antibodies to diphtheria toxin is made by lifestyle (29.4 %), the modern educational process (20.5 %), and environmental exposures (19.9 %). Among lifestyle factors, too short night sleep holds the leading place per its contribution (16.7 %); among factors related to the modern educational process, shorter duration of long breaks (11.2 %); among environmental exposures, elevated formaldehyde levels in ambient air (7.2 %). Diet has the greatest influence on declining levels of IgG-antibodies to pertussis with its contribution reaching 34.0 %. The most significant contributions within an unhealthy diet are made by low contents of sour milk products (2.6 %) and low caloric contents (5.1 %) in a typical daily diet. The second place per a contribution to declining humoral immunity to pertussis belongs to factors related to the modern educational process (21.9 %), including too short long breaks (19.1 %); the third place is occupied by lifestyle factors (18.4 %), including too short night sleep (8.5 %).

Conclusion. Therefore, innovative educational volumes according to educational programs accepted in secondary schools with profound studies of some subjects are frequently completed involving too high educational loads for schoolchildren, which typically mean violations of safe standards for the organization of the educational process. High 'physiological costs' of education caused by elevated educational loads, too much time spent at school, too much time spent on doing homework, and intensive involvement in additional education make a substantial contribution to changes in schoolchildren's lifestyles and diets.

In Type 1 schools, two rest phases are not provided for schoolchildren (duration of breaks is shortened by 1.3–2 times), educational loads do not conform to age-specific capabilities (weekly loads are 5.5–19.2 % higher than their maximum permissible levels), the central nervous system is overloaded and this results in overall exhaustion (duration of work with IWB is 1.2–2.2 times longer than allowed by safe standards). Optimal environmental conditions are not provided either as some chemicals are established in ambient air near these schools and in air inside classrooms in levels higher than RfC for chronic exposure including manganese and formaldehyde, 1.8–8.5 times; in sporadic air samples, nickel and chromium in levels up to 3.6 times higher than chronic RfC; benzene and toluene have been established in levels not higher than RfC for chronic exposure. All the foregoing combined with unhealthy diets, too short night sleep, too low physical activity and too high digital activity lead to a 1.3 times growth in ADs risks over the whole period of school; insufficient production of IgG to herpesviruses indicating a threat that such infections could be activated, 2.3 times; a growth in the proportion of seronegative persons to measles and diphtheria antigens, 3.1–5.4 times (OR = 1.33–5.40; CI = 1.02–11.14).

We have established pathogenetic modification regularities and the list of immunological indicators of risk-associated ADs and anti-infection immunity disorders. Upon exposure to the analyzed factors, children with ADs tend to have more pronounced activation of the cellular adaptive immune response (↑CD3+-, CD3+CD25+-lymphocytes,

relative) and declining natural cytotoxic activity (↓CD16+56+-lymphocytes, relative). The immune status of children with risk-associated anti-infection immunity disorders is characterized with a prevailing cytotoxic effector pathway of the immune response (↑CD3+CD8+-lymphocytes, relative), strengthening pathways of programmed cell death (↑CD3+CD95+-lymphocytes, relative), a decline in reactivity of the humoral immunity component (↓IgG), weakening activity of the non-specific protection system (↓absolute phagocytosis, PN, PI, and the phagocytosis percentage), deregulated intercellular cooperation (↓IL-17, IL-1ß, TNF). Activation of cellular-mediated reactions of the adaptive immunity response (↑CD3+-, CD3+CD25+-lymphocytes, relative, and ↑CD3+CD8+-lymphocytes, relative) and weakening phagocytic activity (↓absolute phagocytosis, PI and ↓CD16+56+-lymphocytes, relative) are common immunological pathways of anti-infection immunity and allergic reactivity modification associated with exposure to environmental factors and factors related to the modern educational process.

Maximum isolated contributions made to likelihood of risk-associated ADs are made by specific features of the modern educational process, 35.7–74.0 %; isolated contributions made by chemical exposures and lifestyles are comparable and amount to 7.6–33.1 and 7.6–31.2 % respectively.

Our ranking of risk factors determining likelihood of declining humoral post-infection and post-vaccination immunity has revealed that the maximum contribution to declining levels of IgG-antibodies to herpesvirus infections is made by diets (26.2–44.0 %) followed by lifestyles (12.3–28.9 %), the modern educational process (13.5–17.9 %), and chemical exposures holding the fourth rank place (9.2–13.7 %). Contributions made by the analyzed factors to declining levels of IgG-antibodies to vaccine-managed infections are ranked as follows: the modern educational process (20.5–30.8 %) and diets (14.6–34.0 %), followed by lifestyles (11.4–29.4 %) and chemical exposures (6.5–19.9 %).

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