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Epidemiological peculiarities and analysis of the incidence time series of viral airborne infections in Ukraine in 2010–2020

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Abstract: Illnesses with aerosol mode of transmission dominate in the structure of infectious diseases. Influenced by natural, social and biological factors, epidemiological characteristics of the infectious diseases change, that's why the objective of this research was to determine modern peculiar features of the epidemiological situation regarding viral infections with aerosol transmission in Ukraine. Influenza incidence ranged from 31.14–184.45 per 100 thousand people, other acute respiratory viral infections from 13685.24–18382.5. Epidemic process of measles was characterized by increasing incidence in 2018 and 2019. In Ukraine, there is a tendency to reduce the incidence of rubella and mumps ($p < 0.05$). The positive effect of immunization on the incidence of mumps and rubella has been established. Vaccination against measles cannot be considered as evidence of immunity against measles. The demographic situation in Ukraine may indirectly influence the intensity of the epidemic situation of viral infections with aerosol transmission.

Keywords: influenza, acute respiratory viral infections, SARS-CoV-2, measles, vaccination.

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Introduction

Illnesses with aerosol mode of transmission dominate in the structure of infectious diseases. The main pathogens of other acute respiratory viral infections (ARVI) are respiratory syncytial virus, Human metapneumovirus, coronavirus, enterovirus, rhinovirus, influenza and parainfluenza viruses, adenovirus and bocavirus [1]. Influenza affects millions of people worldwide every year, causing significant incidence and mortality. New influenza viruses cause pandemics, and seasonal viruses predetermine increased incidence in autumn and winter [2]. Respiratory syncytial virus is the main reason of acute lower respiratory tract infections in children [3]. Human metapneumovirus is the causative agent of acute respiratory infection, most often in children, immunocompromised patients, elderly people [4]. Adenoviruses usually cause mild infections of the upper and lower respiratory tracts, gastro-intestinal tract and conjunctiva. Adenovirus infections are most often met in young children with dysimmunity. Epidemics can occur in children and adults in closed collectives [5]. The emergence of SARS-CoV-2 after coronavirus of severe acute respiratory syndrome (SARS-CoV) in 2002, coronavirus of Middle Eastern respiratory syndrome (MERS-CoV) in 2012 caused the third highly pathogenic and large-scale epidemics of coronaviral infection in XXI century. Elderly people and persons with severe chronic pathology are primarily susceptible to this infection and prone to serious consequences, which can be connected with the development of acute respiratory distress syndrome and cytokine storm [6, 7].

Measles, rubella and mumps also belong to the infections with aerosol transmission. However, they are characterized by the fact that the intensity of their epidemic process is greatly controlled by immunoprophylaxis [8–11].

Influenced by natural, social and biological factors, epidemiological characteristics of the infectious diseases change, that's why the objective of this research was to determine modern peculiar features of the epidemiological situation regarding viral infections with aerosol transmission in Ukraine.

Materials and Methods

Data of branch-specific statistical reporting of the Ministry of Health of Ukraine, State Institution Public Health Center of the Ministry of Health of Ukraine, State Statistics Committee of Ukraine in 2010–2020 are used in the paper.

Epidemiological and statistical research methods are applied. Statistical processing was conducted using standard methods of variation and correlation statistics. Arithmetic mean value (M), median (Me) and significance point (p) were used. The results of correlation analysis are given as Spearman's rank correlation coefficients (r_s). If the correlation coefficient was 0, the connection between phenomena was considered to

be absent; 0.1 to 0.29 — the connection was estimated as weak; 0.30 to 0.69 — medium; 0.70 to 0.99 — strong; 1 — complete.

Microsoft Office Excel 2010, STATISTICA 6.0 (Statsoft, USA) were used.

Results

Viral infections with airborne transmission continue to be of relevance for health institutions in Ukraine. In 2010–2020 influenza incidence ranged from 31.14 per 100 thousand people to 184.45. Time series are characterized by a greater tendency towards decline in incidence ($p < 0.05$). According to trend equation $y = -8.757x + 1132.9$, we have established the expected incidence of influenza in 2021–2023, namely in 2021 — 27.84 per 100 thousand people; in 2022 — 19.08; in 2023 — 10.33 (Fig. 1).

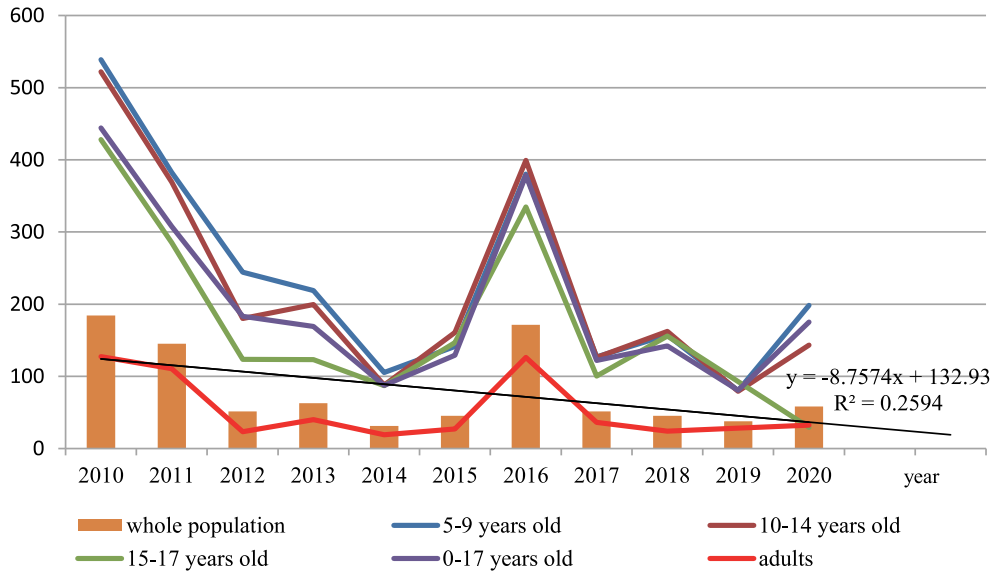

Fig. 1. Influenza incidence rates.

It should be noted that the expected intensity of the epidemic process may change in the case of forming a new pandemic influenza strain and changes in the main demographic indicators. As can be seen from the data of Fig. 1 children's incidence (ranged from 80.72 per 100 thousand child population to 444.16) exceeded of adults(ranged from 19.09 per 100 thousand adult population to 127.35) ($p < 0.05$). Median (Me) incidence of children was 5.3 times higher than Meincidence of adults (Me — 32.31 per 100 thousand adult population) and amounted to 169.22 per 100 thousand child population. The highest rates were in the group of children aged 5 to 17 years old

(p <0.05). In the structure of patients with influenza, the proportion of adults was 55.3%, children — 46.7%. The morbidity trends of children were closely related to the incidence of adults. Direct correlations were established between their incidence rates (r_s = 0.645, p <0.05).

The incidence of other ARVI of the upper respiratory tract in 2010–2020 ranged from 13685.24 per 100 thousand people to 18382.5. According to the trend equation y = -330.8x + 17899, we have established the expected incidence of other ARVI in 2021–2023, namely in 2021 — 13929.4 per 100 thousand people; in 2022 — 13598.6; in 2023 — 13627.8 (Fig. 2).

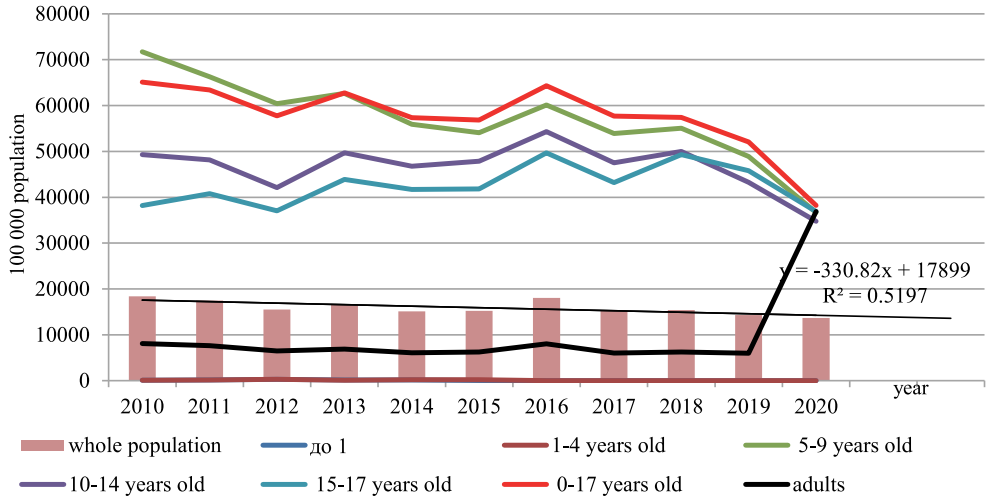

Fig. 2. Other acute respiratory viral infections incidence rates.

As can be seen from the data of Fig. 2 the incidence of child population (ranged from 38221.25 per 100 thousand child people to 65114.45) was higher than the rates of adults (ranged from 5980.26 per 100 thousand adult people to 36885.06). Me incidence of other children's ARVI was 8.9 times higher than Me incidence of adults (Me — 6501.47 per 100 thousand adult people) and amounted to 57720.77 per 100 thousand child people. Children older than 5 years old suffered the most (p <0.05). Their incidence rates were the highest. No statistically significant direct correlations were found between the incidence of children and adults (r_s = 0.145, p <0.05).

During the period under study, the proportion of adults in the structure of patients with other ARVI of the upper respiratory tract was 35.6%, children — 64.4%. By 2020, the incidence of children exceeded the one of adults (p <0.05). In 2020, the situation changed dramatically, the ARVI incidence in the adult population compared

to 2019 increased by 27.7% or 1.4 times. This was due to the circulation of new coronavirus SARS-CoV-2 in Ukraine. In the etiological structure of other ARVI in 2020, the proportion of coronaviruses SARS-CoV-2 was 18.4%.

Another urgent problem for the health institution in Ukraine was measles. In 2010–2020, the incidence of measles ranged from 0.08 per 100 thousand people to 133.69. According to the trend equation y = 7.465x - 16.18, we have established the expected levels of measles in 2021-2023: in 2021 — 73.4 per 100 thousand people; in 2022 — 80.87; in 2023 — 88.33 (Fig. 3).

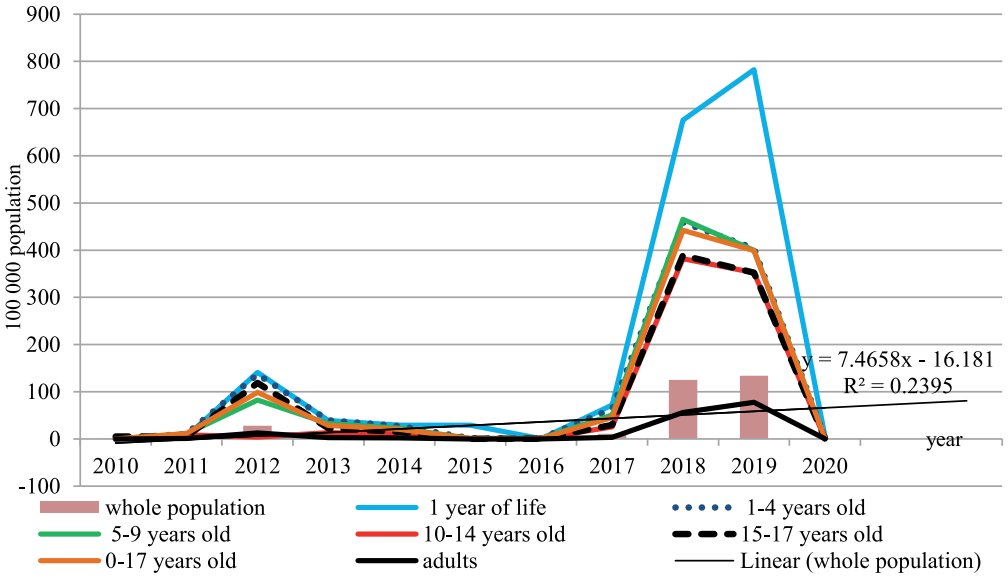

Fig. 3. Measles incidence rates.

As can be seen from the data of Fig. 3 the incidence of child population (ranged from 0.14 per 100 thousand child population to 442.16) exceeded the one of adults (ranged from 0.05 per 100 thousand adult population to 77.71). Me incidence of children was 10.4 times higher than Me incidence of adults (Me — 1.93 per 100 thousand adult population) and amounted to 20.11 per 100 thousand child population. In 2018 and 2019, the incidence rates of children under 1 year of age significantly exceeded the incidence of children of other age groups ($p < 0.05$). Correlations were established between the incidence of children and adults ($r_s = 0.964$, $p < 0.05$). In the age structure of patients with measles, the proportion of adults was quite high and amounted to 40.5%.

The incidence of rubella in Ukraine in 2010–2020 ranged from 0.09 per 100 thousand people to 5.05. According to the trend equation y = -0.674x + 6.352, we have calculated the expected incidence of rubella in 2021-2023, namely in 2021 — (-1.74) per 100 thousand people; in 2022 — (-2.41); in 2023 — (-3.08) (Fig. 4).

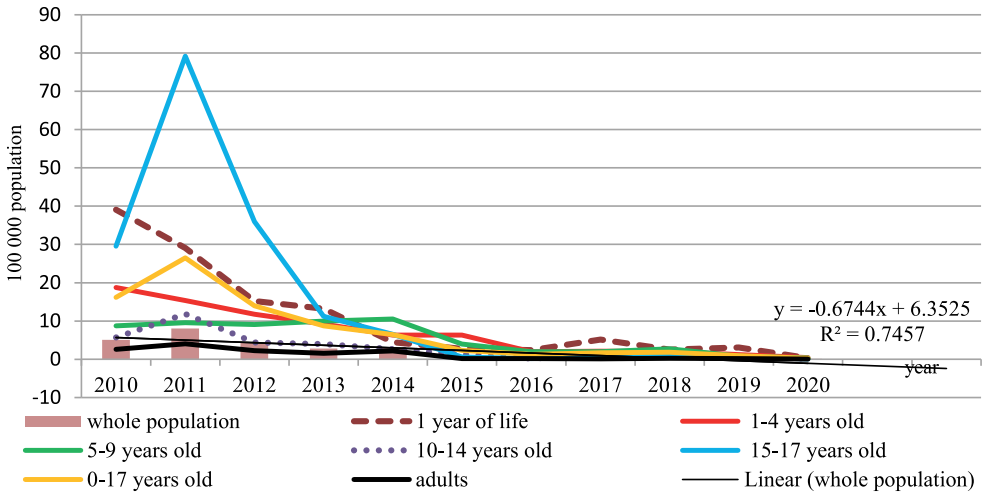

Fig. 4. Rubella incidence rates.

As can be seen from the data of Fig. 4 the incidence of child population (ranged from 0.26 per 100 thousand child population to 26.49) exceeded the one of adults (ranged from 0.05 per 100 thousand adult population to 4.04). Me incidence of child population was 8.2 times higher than Me incidence of adults (Me — 0.28 per 100 thousand adult population) and amounted to 2.3 per 100 thousand child population. Strong direct correlations were established between the incidence of child and adult population (r_s = 0.945, p <0.05). In the age structure of patients with rubella, the proportion of children was 1.3 times higher than of adults and amounted to 55.9%.

Another disease, the incidence of which was rapidly declining, was mumps. In 2010–2020, the incidence of mumps ranged from 0.39 to 2.05 per 100 thousand people. According to the trend equation y = -0.151x + 2.120, we have established the expected incidence of rubella in 2021-2023: in 2021 — 0.31 per 100 thousand people; in 2022 — 0.16; in 2023 — 0.006 (Fig. 5).

As can be seen from the data of Fig. 4 the incidence of child population (ranged from 0.69 per 100 thousand child population to 8.27) exceeded the one of adults (ranged from 0.14 per 100 thousand adult population to 0.75). Me incidence of child population was 16.6 times higher than Me incidence of adults (Me — 0.29 per 100 thousand adult population) and amounted to 4.8 per 100 thousand child population. Strong direct correlations were established between the incidence of children and adults (r_s = 0.961, p <0.05). In the structure of patients with mumps, the proportion of children was 2.9 times higher than of adults and amounted to 74.3%.

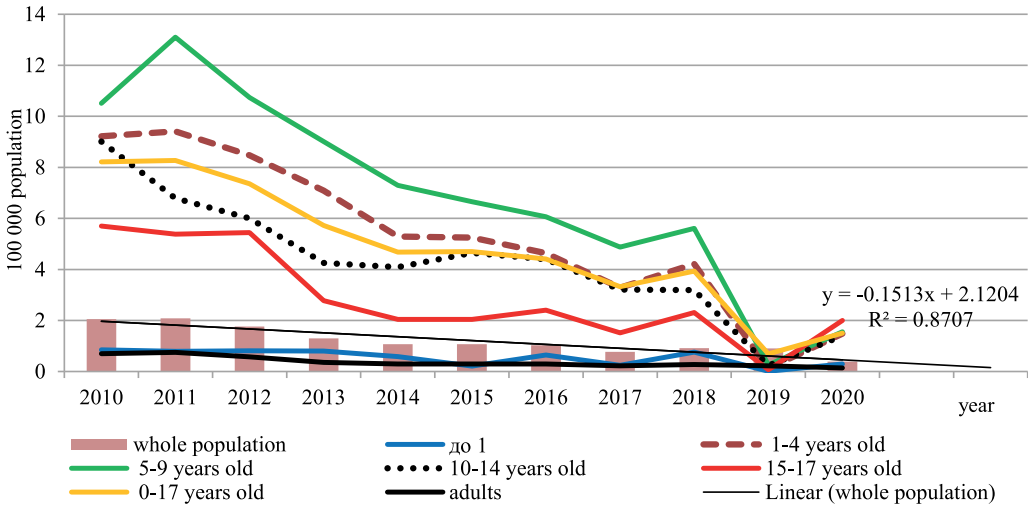

Fig. 5. Mumps incidence rates.

It is common knowledge that the incidence of measles, rubella and mumps is affected by vaccination. We have analyzed the reports of the Ministry of Health of Ukraine on the implementation of preventive vaccination plans. Priorix combined vaccine (manufactured by Glaxosmithkline Biologicals S.A., Belgium), which contains live attenuated strains of measles, mumps and rubella viruses, is used for vaccination against measles, mumps and rubella (MMR) in Ukraine. Vaccinations are done at the age of 12 months (MMR — 1) and 18 months (MMR — 2) of life.

During the period under study, the indicators of vaccination plan performance using MMR — 1 and MMR — 2 vaccines were respectively: in 2010 — 40.7 and 56.1%, in 2011 — 55.6 and 67.0%, in 2012 — 83.7 and 77.8%; in 2013 — 48.6 and 55.1%, in 2014 — 38.7 and 57.0%, in 2015 — 63.2 and 62.1%, in 2016 — 30.2 and 45.5%, in 2017 — 90.7 and 93.3%, in 2018 — 89.5 and 91.0%; in 2019 — 91.7 and 93.2%, in 2020 — 83.3 and 83.4%.

On the results of the conducted correlation analysis, we have failed to establish a positive effect of the vaccination on the incidence of measles and rubella. The results of statistical study have proven to be contradictory and require careful consideration. Significant moderate direct correlations have been found between the measles incidence and the indicators of measles vaccination coverage, which contradicts the existing canons of epidemiology and indirectly shows the ineffectiveness of the vaccine currently used (Table 1).

At the same time, reverse correlations have been established between the incidence of rubella, mumps and the level of vaccination coverage ($p < 0.05$).

Table 1. Correlation coefficients between the incidence of measles, mumps and rubella and the indicators of preventive vaccination coverage (r_s).

Nosological entity		Vaccination (r_s)	
		MMR-1	MMR-2
Measles	total	**0.798***	**0.666***
	children	**0.764***	**0.636***
Rubella	total	**−0.600***	−0.391
	children	**−591***	−0.373
Mumps	total	**−0.689***	−0.557
	children	**−0.727***	−0.564

*p <0.05

Another factor that can really influence the intensity of epidemic process of this group of infections is demographic situation. Number of population in Ukraine is drastically decreasing. In 2010, the population was 45782.6 thousand people. In 2014 it already amounted to 45245.9 thousand people (1.2 % less). During the period 2015–2020, the population decreased by 2.7 % and amounted to 41588.3 thousand people on January 1, 2021. The sharp decline in population was due to the fact that Ukraine currently does not control 7% of its territory, or 46.2 thousand km^2. The proportion of children in the age structure of population was within the range of 17.54 — 18.05%.

An important demographic indicator is population density or the degree of population of the territory of Ukraine. In 2010, the population density was 75.84 people per 1 km^2, in 2011 — 75.53; in 2012 — 75.29; in 2013 — 75.49; in 2014 — 74.95; in 2015 — 76.69; in 2016 — 76.39; in 2017 — 76.08; in 2018 — 75.72; in 2019 — 75.31; in 2020 — 74.59. This was primarily the result of internal migration of the population from certain territories of Ukraine, namely the Crimea and parts of Donbass to other regions of Ukraine.

Natural and migratory movements of the population are important factors forming demographic situation. Natural population migration coefficient of Ukraine ranged from (-3.1) per 10 thousand population in 2012 to (-7.8) per 10 thousand population in 2020. Migratory movement coefficient varied from 0.2 to 1.4 per 10 thousand population.

In order to determine the influence of demographic factor on the intensity of the epidemic process of viral infections with aerosol transmission, the correlations between demographic indicators and incidence were studied. Based on the analysis carried out, significant correlations were established between the population as a whole

and child population, in particular, and the incidence of ARVI; between population, natural population movement and the incidence of rubella and mumps ($p < 0.05$) (Table 2).

Table 2. Correlation coefficients between the incidence of measles, rubella and mumps and demographic indicators (r_s).

Nosological entity	Demographic indicators (r_s)				
	Population	Population density	Child population	Natural population migration coefficient	Migratory movement coefficient
Influenza	−0.155	−0.009	0.291	0.114	−0.298
ARVI	**0.727***	0.482	**0.636***	0.486	0.084
Measles	−0.366	−0.375	−0.309	−0.086	0.564
Rubella	**0.945***	0.036	**0.873***	**0.800***	0.516
Measles	**0.973***	0.098	**0.836***	**0.830***	0.495

*$p < 0.05$

Discussion

Infections with aerosol transmission are widespread in the world. Seasonal flu affects millions of people every year, causing significant incidence and mortality. It has been found that one in five unvaccinated children and one in ten unvaccinated adults are infected with seasonal influenza viruses each year [2]. We have identified that influenza frequency in Ukraine was much lower. Influenza incidence ranged from 31.14–184.45 per 100 thousand people. Me incidence was 51.55 per 100 thousand people. Annually, influenza affected from 0.04 to 0.19% of the population. At the same time, there was a tendency to reduce the incidence ($p < 0.05$).

The global burden of illnesses caused by seasonal influenza virus among children is unknown. The situation is complicated by the fact that the symptoms of influenza and other ARVI are similar. According to the data of meta-analysis, the proportion of influenza in the structure of ARVI in children ranges from 11 to 56 % [12]. It has been proven that this disease is especially dangerous for children under 5 years [13]. Researchers explain high incidence of severe forms of the diseases with immaturity of their immune system [14]. In Ukraine, the incidence of influenza in children is also several times higher than in adults ($p < 0.05$). Influenza virus most often caused the disease progression in a group of children 5 years and older. The expansion of chil-

dren's contacts with their peers at this age was most likely to contribute to the viral spreading. At the same time, it should be noted that growth of incidence among adults in Ukraine will inevitably lead to increase in the incidence of children, as we have established a significant statistical relationship between these indicators ($p < 0.05$).

The group of other ARVI includes parainfluenza, adenoviral, respiratory syncytial, rhinovirus and coronavirus infections. These infectious diseases are extremely common, occur in people of various ages, differ in severity and clinical manifestations depending on the degree of intoxication and the level of respiratory lesion [1, 15, 16]. We found that in Ukraine the incidence of other ARVI was very high, ranging from 13685.24 to 18382.5 per 100 thousand people. Me incidence was 15426.44 per 100 thousand people. The risk group were children, whereof Me incidence was almost 9 times higher than in adults. The proportion of children in the structure of patients was 1.8 times higher than of adults. At the same time, in 2020, the circulation of SARS-CoV-2 changed some epidemiological characteristics of other ARVI. There was a sharp increase in the incidence of other ARVI in adults (compared to 2019 by 6.2 times) and a decrease in children (1.4 times). The proportion of adults in 2020 in the structure of patients with other ARVI increased to 49.5%.

Measles virus is one of the most contagious among known pathogenic viruses. Before the implementation of vaccination, it caused more than 2 million deaths [17]. Under modern conditions, lethal index ranges from <0.01% in industrialized countries to >5% in developing countries. The WHO has set itself the goal of overcoming the endemic transmission of measles virus in six regions of the world by achieving high levels of vaccination coverage [8]. They failed to achieve the goal. In many regions, there is an increasing incidence of measles, and children under 1 year (from 8 to 25%) who have not been vaccinated constitute a significant proportion in the structure of patients [18, 19].

We found that in Ukraine the epidemic process of measles was characterized by increasing incidence in 2012 (27.95 per 100 thousand people) and in 2018 and 2019, when the incidence increased tenfold and amounted to 125.47 and 133.69 per 100 thousand people. Me incidence of measles was 5.13 per 100 thousand people. The risk group was children (their incidence exceeded adults more than 10 times), especially under 1 year of age ($p < 0.05$).

The incidence of children under 1 year of age was the highest, which indirectly showed a low level of immunity in these individuals. Mass immunization against measles has been introduced in Ukraine since the 1970s. Incidence rates have been steadily declining. Fewer and fewer mothers of newborns have post-infectious immunity. Presumably, the mother's post-vaccination immunity does not protect the baby from infected with measles virus in the first 12 months of life [20]. The established statistical relationship ($p < 0.05$) between the incidence of children and adults shows the importance of adults as sources of infection for children.

Before the vaccination rubella was an endemic disease in the whole world. Epidemics occurred at intervals of 6–9 years, pandemics — every 10–30 years [21]. In modern conditions, rubella is still a widespread infectious disease in many regions of the world. Up to 100 thousand cases of congenital rubella syndrome are registered annually [9]. At the same time, it should be noted that as a result of vaccination, the incidence has decreased. In the USA, rubella was eliminated [22].

In Ukraine, there is also a tendency to reduce the incidence of rubella ($p < 0.05$). In 2010–2020 Me incidence was 0.58 per 100 thousand people. The incidence of children ranged 0.26–26.49 per 100 thousand people, of adults — even lower and varied from 0.05 to 4.04 per 100 thousand people.

In recent years there has been an increase in the incidence of mumps in the world [9]. Outbreaks are registered among vaccinated persons in the countries with high vaccination coverage [23]. In Ukraine in 2010–2020 the incidence of mumps decreased ($p < 0.05$). Me incidence amounted to 1.07 per 100 thousand people. Herewith, the incidence of children was 15 times higher than of adults. The proportion of adults was 25.7% in the structure of patients with mumps.

Until recently, it was believed that if a person adheres to the MMR vaccine schedule, the immunity will be lifelong. Schedules of vaccination against measles, mumps and rubella have been developed according to the paradigm that the vaccine protects in the same way as natural infection, and herewith the virus serotype does not change for many decades [16]. Therefore, usually increase in the incidence of measles in the world is explained by researchers as gaps in immunization. The WHO estimates that the coverage of two MMR vaccines in the world is 67%. This level is insufficient to stop the circulation of measles virus.

In Ukraine in 2010–2020, Me coverage of MMR-1 vaccine was 64.9%, of MMR-2 vaccine — 71.2%. We conducted a correlation analysis of dependence of incidence on vaccination coverage of the population subject to scheduled vaccination and the Spearman correlation coefficient was determined. The positive effect of immunization on the incidence of mumps and rubella has been established. An inverse strong ($p < 0.05$) and medium correlation was established between these indicators. At the same time, the paradox of a simultaneous improvement in immunization rates and increase in the incidence of measles casts doubt on whether high vaccination coverage is sufficient to prevent the disease. Mutations in the genomes of the measles virus probably allow it to avoid neutralization by antibodies induced by vaccine. Therefore, vaccination against measles cannot be considered as evidence of immunity against measles, and a positive serological test cannot guarantee protection against the disease.

The clinical picture of mumps is more benign than of measles. The researchers found that almost 70% of patients with mumps were vaccinated. According to them, sometime after vaccination, the concentration of specific antibodies to mumps virus

decreases, the effectiveness of the vaccine decreases and the risk of infection with the virus increases. In the USA, the Advisory Committee on Immunization Practices has even recommended a third dose of MMR vaccine for people from the groups at increased risk of infection to prevent emergencies [23, 24]. The reason for lower-than-expected efficacy of vaccine against mums has been the subject of numerous disputes, ranging from the lowered immunity to emergence of new virus strains that avoid the immunity generated by the vaccine [25].

Researches confirm efficacy of the vaccination against rubella. After the introduction of live attenuated rubella vaccine, the incidence in the world has fallen sharply. The development of effective vaccines is facilitated by genetic stability of the rubella virus [26].

It is well known about indirect effect on the intensity of the epidemic process of viral infections with aerosol transmission of the social factor.

We found that in Ukraine both the population as a whole (9.1%) and of children, in particular (6.7 %) decreased in the period under study. The migratory movement of the population changed number and composition of the population due to its territorial distribution (maximum migratory movement coefficient was in 2012 — 1.4 per 10 thousand people). Natural population movement changed number and composition of the population due to births and deaths (minimum natural movement coefficient was recorded in 2020 (-7.8 per 10 thousand people). Me population density in 2010-2020 was 75.6 per 1 km^2.

According to the results of the correlation analysis conducted, it was found that increase in population will indirectly influence complication of the epidemic situation with other ARVI, rubella, mumps; increase in the natural population movement coefficient — rubella and mumps, as a statistically significant direct correlation was detected between them ($p < 0.05$).

We have discovered no impact of demographic indicators on the incidence of measles in Ukraine. However, according to the results of a comprehensive review of the literature, scientists have established that accumulation of a contingent of people not vaccinated against measles, on the background of external and internal population migration is the main cause of increasing measles incidence [27].

Conclusion

Wide prevalence of diseases with aerosol transmission in Ukraine, variety of their clinical forms causes difficulties in combating them. Children are more susceptible to viral infections with aerosol transmission than adults. There are no effective measures to influence the measles epidemic process in Ukraine. The administration of two doses of measles vaccine does not provide protection against this disease. The demographic situation in Ukraine may indirectly influence the intensity of the epidemic situation of

viral infections with aerosol transmission. Growth in the number and coefficient of natural population movement will contribute to increasing the incidence of other ARVI, rubella and mumps ($p < 0.05$).

Statement of contribution

The manuscript has been read and approved by all authors, and all the authors agreed to the submission of the manuscript to The Editor.

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Conflict of interest

None declared.

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