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Mumps: Achievements, Problems and Solutions

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Abstract

Introduction: *To highlight the current state of the problem of mumps in the world and the Russian Federation.* ***Materials and methods:*** *Electronic resources PubMed, eLIBRARY, CyberLeninka were used as research materials. Research methods-analysis and generalization of scientific literature. The study of population immunity to mumps in the study area was carried out using serological research methods.* ***Results:*** *Despite the success of vaccination, there is a widespread but uneven spread of mumps infection in various regions of the world, both in the form of sporadic cases and large epidemic outbreaks. Evaluation of population immunity to mumps in the study area (2018) revealed a fairly high number of seronegative individuals (the largest number was found among adults 20-39 years of age). In addition to vaccination failures among vaccinated children, the main cause of the outbreak is a decrease in the intensity of post-vaccination immunity among the adult population. The immune defense created by the vaccine strain does not have the same intensity and duration as in a natural infection, and some genotypes of "wild" variants of the mumps virus can break through the immune barrier, causing the disease. Antigenic differences between vaccine and circulating strains, and a low inoculation dose may contribute to weakening the immune system and reducing the effectiveness of mass vaccination.* ***Conclusion:*** *The ways of solution for anticipating the unfavorable epidemic situation for mumps are proposed.*

Keywords: *circulating genotypes; diagnostics; morbidity; mumps; vaccination*

Introduction

In the second decade of the XXI century, mumps continues to attract the attention of scientists and practitioners around the world for its epidemiological, social and economic significance. A widespread but uneven spread of mumps infection has been found in various regions of the world: in Europe, the Eastern Mediterranean, South-East Asia, Africa, America, and the Western Pacific [1,2].

In mumps there is not only a lesion of glandular organs (mumps, submandibulitis, sublinguitis, pancreatitis, orchitis, prostatitis, oophoritis – 5% of cases in girls, mastitis – 31% of cases in girls older than 14 years, thyroiditis, dacryoadenitis), but also due to long - term circulation of the pathogen in the blood, it is possible to develop sufficiently clinically significant severe conditions-serous meningitis and meningoencephalitis, myelitis, encephalomyelitis, cranial nerve damage. In the outcome, mumps often leads to residual effects of Central nervous system damage, forms infertility in men (50% of cases older than 25 years) and secondary diabetes mellitus among the population living in large cities with a population of more than 1 million and in small industrial centers of the Russian Federation [3].

The WHO classifies mumps as infections that can be eliminated by means of specific vaccination. The WHO goal of reducing the incidence rate to 1 or less per 100,000 population in Russia by 2010 or earlier was achieved (2009 – the registered incidence rate was 0.65 per 100,000). However, currently the incidence is registered in many countries of the world, both in the form of sporadic cases and in the form of large epidemic outbreaks.

Materials and method

Electronic resources PubMed, eLIBRARY, and CyberLeninka were used as research materials. Research methods-analysis and generalization of scientific literature. The study of population immunity (n=593) to mumps in the study area (2018) was carried out by serological method using the test system of Vector Best "Vectorparotit–IgM", "Vectorparotit-IgG".

Results and discussion

The viral nature of mumps was first established in 1934 by researchers E. Goodpascher and K. Johnson. The mumps virus is assigned to the family Paramyxoviridae, the genus Rubulavirus. The mumps virus has the following biological properties: a spherical virion with a diameter of 100-300 nm; the genome is represented by a single-stranded, non-segmented infectious RNA that includes seven genes organized by 3' - NP-P-M-F-SH-HN-L-5'. An important role in the acquisition of surface proteins play hemagglutinin neuraminidase (HN) and the fusion protein (F), responsible for adhesion and aggregation of viral envelope with

the cell membrane, and that they formed neutralizing antibodies [2].

Currently, there are 12 virus genotypes circulating in the world (A, B, C, D, E, F, G, H, I, K, L), identified based on differences in the nucleotide sequence of the SH and HN transmembrane protein genes. Heterogeneity in the nucleotide sequence of wild virus genes is from 6 to 20% [2,4,5]. Along with the endogenous circulation of a specific genotype of the virus in a separate territory, exogenous (imported) strains of the mumps virus can also appear. For example, in Australia in 2007-2008. with a wide endogenous circulation of genotype j virus in recent years (2015), the predominance of the circulating mumps virus of genotype G was established [6].

In the world practice over the last ten years circulating virus mumps - a genotype G as the most widely distributed, found most frequently in epidemiological investigation of major outbreaks (20 cases) in the US, the UK, the Netherlands, Australia, South of China, Canada, Norway, India, Scotland, Israel, Japan, Korea and France [5-15]. Genotype F of the virus is circulating in Central China, and genotype K of the virus is circulating in Vietnam [16-18].

In our country, since the introduction of mass routine immunization of children against mumps (since 1981), within the framework of the National calendar of preventive vaccinations, as well as throughout the world, there has been a decrease in the incidence of mumps (from 483,0 to 1,38 per 100 thousand population in 2018) (Figure 1) [19,20].

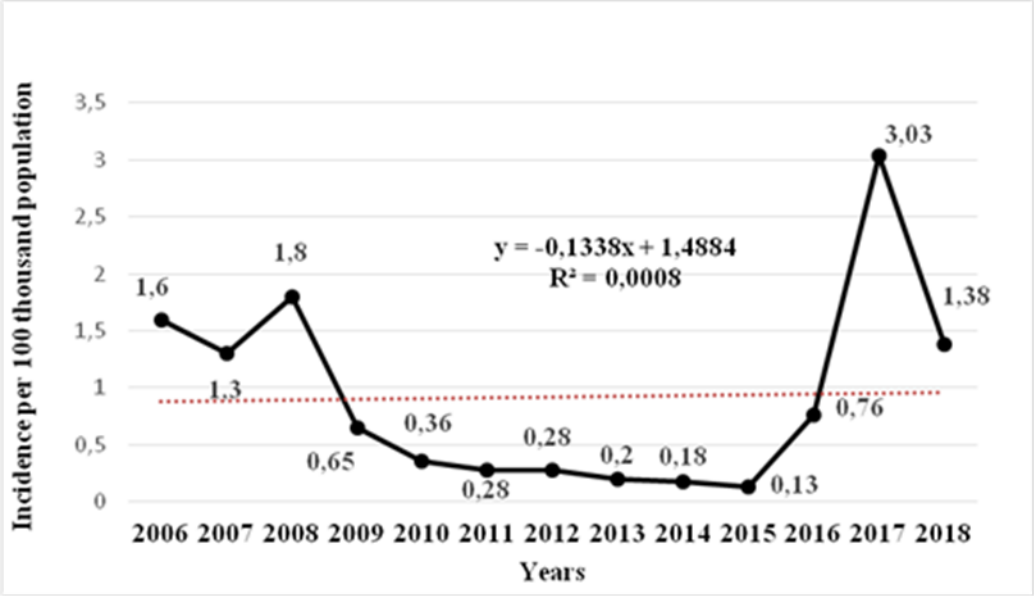

Figure 1. Dynamics of mumps incidence in the Russian Federation (in terms of 100 thousand people).

When analyzing the incidence of mumps according to Federal statistical observation data in the period 2016-2018, the risk territory - the North Caucasus Federal district-was revealed in comparison with the level of mumps incidence in the Russian Federation [21].

A comparative assessment of the age-sex structure of patients with mumps has established a shift in the incidence of adolescents who attend secondary schools, and adults. Currently, the proportion of school children and adults aged 17-19 and 20-25 years is more than 60% [6,7,12]. Thus, in the study area (Perm region), 34 cases (94,5%) out of 36 cases in 2018 occurred in adults of working age – from 18 to 49 years [22]. On the territory of the Russian Federation, 2 genotypes of the mumps - C and H virus have been etiologically decoded on the territory of the Siberian Federal district [23]. At the moment, the circulating strain of the virus in other territories of the Russian Federation and, most importantly, in the territories of risk remains, unfortunately, etiologically unknown.

In the Russian Federation, the standard for providing specialized medical care for children does not provide for etiological laboratory diagnostics for mumps. In the existing clinical recommendations for providing medical care to children, the use of the enzyme immunoassay method is recommended as a confirmatory laboratory test, and in the case of verification of atypical forms of infection, the molecular biological method is recommended [24-26].

Specific IgM antibodies to mumps are detected on day 1-4 after the first clinical symptoms appear, their concentration rapidly increases and becomes maximum by day 40-50 of the disease. It is believed that their diagnostic value increases with the fifth day of the disease. At the same time, specific IgM antibodies to mumps may be absent or circulate for a short time in vaccinated individuals [27,28]. The presence of specific IgG antibodies to mumps in the blood serum of patients does not allow establishing the period of limitation for the development of the disease. In this case, the dynamic increase in the titer of specific IgG antibodies to the mumps virus 4 or more times in the second blood sample, 2-3 weeks after the onset of the disease, is considered to be diagnostically significant [15,20].

In the Russian Federation, to confirm the clinical diagnosis of mumps by the serological method, domestic test systems are used for conducting enzyme immunoassay of the following manufacturers: «Vector-best», «Ecolab», and «Bioservice», which are focused only on qualitative and semi-quantitative

determination of the level of specific antibodies to mumps. National certified test systems for PCR diagnostics in our country remain undeveloped [29,30].

During the outbreak in the study area of the mumps from November 2017 to February 2018 with the number of victims 12 aged 21 to 27 years in 100% of individuals, the mumps was confirmed by serological method using the test system of vector best CJSC "Vectorparotit–IgM", "Vectorparotit-IgG". Of the 12 cases, specific IgM antibodies to the EP virus were detected in 4 people (33,3%), and a dynamic 4-fold increase in specific IgG antibodies was detected in 8 people (66,7%). The conducted screening serological dynamic examination of communicating individuals with the source of the infectious agent revealed initially 26 (84%) seropositive individuals and 2 (6%) - with doubtful results (the coefficient of positivity of antibodies-IgG was 0.8-1.0), in the future there was an increase in the number of cases with doubtful results to 3 (10%).

The use of molecular genetic methods (PCR) among patients previously vaccinated against mumps in the study of non - invasive biological material-the contents of a buccal smear and nasopharyngeal washes is the most informative for verification of EP [2,15,31]. The mumps virus is detected within 9 days of the onset of clinical symptoms [2,32,33]. However, among vaccinated individuals, virus isolation is short-lived and occurs up to 2-3 days [15,28]. The information content of the diagnostic methods used, molecular genetic and serological, in everyday clinical and epidemiological practice depends directly on the duration of the disease. The greatest diagnostic significance in confirming the diagnosis in the first days of the disease is the method of back-transcriptase PCR (OT-PCR) with real-time detection, which allows detecting the genetic material of the mumps virus in the contents of nasopharengial and buccal smears from patients with mumps [15,20,31]. The use of the PCR method in clinical practice as a confirmatory test allows for the etiological interpretation of patients with mumps infection, and timely prescribing adequate and systemic therapy for patients, on the one hand. On the other hand, the use of this method in epidemiological practice makes it possible to determine the circulating genotypes of the virus in a specific territory-endogenous strains, differentiate endogenous circulating strains of mumps from imported (exogenous) ones, isolate "wild" mumps viruses and compare them with the vaccine strain, confirm or exclude post-vaccination complications, and identify changes in the mumps virus itself of an adaptive and phylogenetic nature [4,5,34].

In the world of clinical and epidemiological practice, along with enzyme immunoassay, the OTP-PCR method is widely used. It is used to determine the causes and conditions of the spread of large epidemic outbreaks during epidemiological investigation. Thus, the OT-PCR method was used for typing biological material in epidemic outbreaks in Germany (2008-2011), the USA (2016), Canada (2007-2017), Australia (2007-2015), France (2013), Norway (2016), Israel (2017) [6,7,15,23,31,35,36]. In the Udmurt Republic (2008), in the course of a detailed epidemiological investigation of an epidemic outbreak of mumps with a number of 176 cases, along with serological methods, the molecular genetic method of OT-PCR was used in the diagnosis of mumps-nucleic acids were isolated using the "QIAmp Viral RNA Mini Kit", "Qiagen", Germany. Among patients with common clinical manifestations of mumps, an identical pathogen of the mumps virus with common biological properties was found [20].

In the Russian Federation the procedure for the identification, treatment, isolation of patients, official records and statistical monitoring of cases of mumps in accordance with the applicable sanitary and epidemiological regulations "Prevention of measles, rubella and mumps", which is approved by the Chief state sanitary doctor of the Russian Federation from 28 July 2011 Before the start of mass vaccine prevention in 1970-1980, up to 300-600 thousand people per year were ill, for comparison, in 2018, 2027 cases of mumps were registered in the Russian Federation [21].

Implemented mumps vaccination in the Russian Federation, conducted since 1981, has reduced the level of morbidity and mortality, the severity coefficient with a significant reduction in complications-more than 2500 lives were saved, about 2,5 million cases of serous meningitis were prevented, as well as tens of thousands of cases of orchitis, oophoritis, pancreatitis, and later diabetes, mastitis, and premature abortions. At the moment, more than 200 million people have been vaccinated. In order to achieve sufficient population immunity to mumps, the coverage of preventive vaccinations among decreed individuals must be at least 95%. In Russia, since 2002, the coverage of timely vaccination has exceeded 97,5% annually. At the same time, the immune layer in mumps did not reach the standard level. For example, in 2007-2011, among the total population of Moscow and the Moscow region, the proportion of seronegative individuals with mumps in different age groups ranged from 4,0% at the age of 40-49 to 21,4% at the age of 20-29 and 16,7% in 30-39-year-olds [20,44]. At the same time in 2017-2018 there was an increase in the incidence of mumps to 3,03 per 100000 population and 1,38 respectively [20,37].

In the world practice of mumps vaccination, the following vaccine strains are used: Jeryl Linn and its derivative Rit 43/85 (USA), Leningrad-3 (Russia), Urabe, Hoshino, Torit, Miyahara (Japan), Leningrad-Zagreb (Croatia), Rubine (Switzerland), Sofia-6 (Bulgaria) [29].

In the Russian Federation specific prophylaxis is carried out a live mumps vaccine in the National vaccination calendar and calendar epidemic indications (administered within 7 days after identification of the first patient in the epidemic focus). In our country for the implementation of vaccine prevention, mumps is licensed and registered in accordance with the established procedure-mumps monovaccine, mumps-measles vaccine, and associated vaccine (measles-mumps-rubella). Mono - and divacin is a cultural live dry vaccine, produced by NPO "Microgen". They produce vaccines from the Leningrad-3 strain, which is cultivated in the primary culture of Japanese quail fibroblasts. Mumps monovaccine and divaccine contain more than 20000 TCD50 viruses of the Leningrad-3 strain in one inoculation dose [37].

Associated vaccins measles-mumps-rubella have been registered for the prevention of MMR-II - a vaccine manufactured by «Merck Sharp and Dome» (USA), containing the Geryl-Linn vaccine strain as a mumps component (at least 20000 TCD50 in 1 dose). MMR-II is the world's first registered combined vaccine for measles, mumps, and rubella. The MMR-II vaccine is characterized by high safety, low reactogenicity and high immunogenic activity [38-41]. The Priorix vaccine-a vaccine manufactured by GlaxoSmithKline (Belgium) as a mumps

component contains 103,7 TCD50 of the RIT43/85 strain (derived from Jeryl-Linn) in 1 dose, as in the case of MMR-II, and is cultured separately on a chicken embryo cell culture. Vaccina measles-mumps-rubella produced by Serum Institute (India), where Leningrad - Zagreb is used as a vaccine strain (at least 5000 TCD50 in 1 dose), cell substrates for mumps it is fibroblasts of chicken embryos [20,37,42]. Currently, the national combined vaccine (measles-mumps-rubella) "Vaktrivir" is being registered by the state [43].

The assessment of population immunity (n=593) to mumps in the study area (2018) revealed a fairly high number of seronegative individuals. Among children aged 3-4 years, their share was 9,5%, in 16-17 year olds – 6%, among 20-29 year olds – 13,3%, 30-39 year olds -19,4%, and in 40-49 year olds – 8,4%. The largest number of seronegative individuals was found among adults 20-39 years of age. At the same Time, the national calendar of preventive vaccinations does not specify a decreed age group for revaccination among adults.

In the second half of the XX century in many countries mass vaccination of mumps was introduced into national immunization programs and the incidence decreased significantly. At the same time, the unfavorable epidemic situation in the mumps continues to grow – the outbreak incidence is registered in groups with ideal vaccination coverage (up to 98%). According to M. Maillet (2013), P. A. Maple (2015) and V. S. Fields (2019), two doses of the vaccine were previously given to 62-92% of individuals [2,7,15]. The main reasons and conditions for the occurrence of epidemic outbreaks were the lack of regulatory coverage of vaccination and revaccination in the past among the decreed groups, vaccination failures among vaccinated people, a decrease in post-vaccination immunity, untimely and ineffective implementation of primary anti-epidemic (preventive) measures in the emerging foci of infection [2,10,45]. According to G. E. Nelson (2013), C. V. Cardemil (2017), A. M. May (2017), M. Marin (2018) found that after applying the third dose of the vaccine to contact persons in outbreaks, against the background of high coverage previously with two doses of the vaccine in secondary schools and universities as a preventive measure, the incidence stopped [44-47].

In the context of measles elimination at logical "cleans" immunization measles to 55 years to use vaccine measles-mumps vaccine or measles-mumps-rubella, because it is not vaccinated against measles face, most likely earlier, did not vaccinate and from mumps. Meanwhile, in the Russian Federation, the national calendar of preventive vaccinations does not define a decreed age group for revaccination among adults. For example, measles vaccination is given to adults under 55 who are not ill, have not been vaccinated, or have been vaccinated once; rubella vaccination is given to women between 18 and 25 years of age who have not been ill, have not been vaccinated, have been vaccinated once, or do not have information about rubella vaccinations.

The lack of production control of produced vaccines for the prevention of mumps-full compliance of the applied vaccine strain with circulating "wild" strains causes insufficient protection of the population from circulating "wild" strains [12,16,48]. The immune defense created by the vaccine strain does not have the same intensity and duration as in a natural infection, and some genotypes of "wild" variants of the mumps virus can break through the immune barrier, causing the disease [31,49]. Antigenic differences between vaccine and circulating strains, and a low inoculation dose may contribute to weakening immunity and reducing the effectiveness of mass vaccination [44,47,50]. Due to the possibility of adaptive and phylogenetic variability of the circulating mumps strain, it is necessary to introduce a regulated production control of compliance of the used vaccine strain with the circulating "wild" virus strains [12,16,31].

Conclusion

The ongoing epidemic problem of mumps in the Russian Federation, the shift in the incidence of diseases in the age structure of patients in the direction of adolescence and adults dictates the need to develop and implement a standard definition of a clinical case of mumps in order to correctly verify the diagnosis, followed by laboratory confirmation of the clinical diagnosis, taking into account the available epidemiological data.

In addition to vaccination failures among vaccinated children, the main cause of the outbreak is a decrease in the intensity of post-vaccination immunity among the adult population. In the context of the implementation of "clean-up" immunization against measles, the introduction of a planned revaccination vaccination for adults in the framework of the National calendar of preventive vaccinations currently requires scientific justification.

To prevent an unfavorable epidemic situation in the case of mumps, it is necessary to implement a regulated production control over the use of vaccine strains with the determination of the correspondence between the vaccine and circulating strains of the mumps virus with the justification of an adequate vaccination dose..

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