



MUMPS: ACHIEVEMENTS, PROBLEMS AND WAYS OF SOLUTION

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The aim. The article highlights the current state of the problem of mumps in the world and the Russian Federation.

Materials and methods. The materials of the study were electronic resources WHO infection control, Cochrane, Elsevier, ScienceDirect, CDC infection diseases database, PubMed, eLibrary, CyberLeninka. The research methods were the analysis and generalization of scientific literature. The assessment is presented by the immunological structure of the population in different age groups to mumps (n = 593) in the study area (2018) according to the data of the Center for Hygiene and Epidemiology in the Perm Territory.

Results. The spread of mumps is found to be widespread and uneven in different regions of the world in the form of sporadic cases and large epidemic outbreaks, despite the world practice of vaccine prevention of mumps. Analysis of the immunological structure to mumps in different age groups revealed a fairly high number of seronegative individuals (the largest number was found among adults aged 20–39 years) in the study area (2018). A decrease in the tension of post-vaccination immunity is the main cause for the emergence of an outbreak among the adult population, in addition to vaccination failures among vaccinated children. The immune defenses created by the vaccine strain do not have the same intensity and duration as with natural infection, and some genotypes of “wild” variants of the mumps virus can break through the immune barrier and cause disease. Antigenic differences between vaccine and circulating strains, low inoculation dose can weaken immunity and reduce the effectiveness of mass vaccine prevention.

Conclusion. Ways of solving the problem were proposed to forestall an unfavorable epidemic situation with mumps.

Keywords: mumps; morbidity; diagnostics; vaccine prevention; circulating genotypes

Abbreviations: WHO – World Health Organization; RT-PCR – reverse transcription polymerase chain reaction; TDC – tissue cytopathogenic dose

ЭПИДЕМИЧЕСКИЙ ПАРОТИТ: ДОСТИЖЕНИЯ, ПРОБЛЕМЫ И ПУТИ РЕШЕНИЯ

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Цель. Анализ современного состояния проблемы эпидемического паротита в мире и Российской Федерации.

Материалы и методы. В качестве материалов исследования использованы электронные ресурсы WHO infection

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control, Cochrane, Elsevier, ScienceDirect, CDC infection diseases database, PubMed, eLIBRARY, CyberLeninka. Методы исследования – анализ и обобщение научной литературы. Дана оценка иммунологической структуры населения в различных возрастных группах к эпидемическому паротиту ($n=593$) на изучаемой территории (2018 г.) по данным ФБУЗ «Центр гигиены и эпидемиологии в Пермском крае».

Результаты. Несмотря на мировую практику вакцинопрофилактики эпидемического паротита установлено повсеместное и неравномерное распространение паротитной инфекции в различных регионах мира, как в виде спорадических случаев, так и крупных эпидемических вспышек. Оценка иммунологической структуры в различных возрастных группах к эпидемическому паротиту на изучаемой территории (2018) выявила достаточно высокое число серонегативных лиц (наибольшее число установлено среди взрослых в возрасте 20–39 лет). Помимо вакцинальных неудач среди привитых детей, главной причиной возникновения вспышечной заболеваемости среди взрослого населения является снижение напряженности поствакцинального иммунитета. Иммунная защита, создаваемая вакцинным штаммом, не имеет такой напряженности и такой длительности, как при естественной инфекции, и некоторые генотипы «диких» вариантов вируса эпидемического паротита могут прорывать иммунный барьер, вызывая заболевание. Антигенные различия между вакцинными и циркулирующими штаммами, низкая прививочная доза могут способствовать ослаблению иммунитета и снижению эффективности массовой вакцинопрофилактики.

Заключение. Предложены пути решения для упреждения неблагоприятной эпидемической ситуации по эпидемическому паротиту.

Ключевые слова. Эпидемический паротит, заболеваемость, диагностика, вакцинопрофилактика, циркулирующие генотипы

Список сокращений: ВОЗ – Всемирная организация здравоохранения; ОТ-ПЦР – обратнo-транскриптазная полимеразная цепная реакция; ТДЦ – тканевая цитопатогенная доза; ЭП – эпидемический паротит.

INTRODUCTION

Mumps continues to attract the attention of scientists and practitioners around the world for its epidemiological, social and economic significance in the second decade of the 21st century. Mumps is widespread, but unevenly in different regions of the world: in Europe, the Eastern Mediterranean, Southeast Asia, Africa, America and the Western Pacific [1, 2]. Large outbreaks took place in the USA (2006, 2014, 2017 years) with 6585, 1521, 5629 victims, Australia (2015–2016) – 893, Belgium (2012–2013) – 4061, Israel (2014–2015) – 262, Jerusalem (2009–2011) – 3130, Poland (2013) – 2436, Czech Republic (2005–2006) – 5998, Austria (2006) – 214, Norway (2015–2016) – 232, Scotland (2014–2015) – 341, Canada (2016) with 1242 cases and others [3–11].

The glandular organs are affected in mumps (mumps, submandibulitis, sublinguitis, pancreatitis, orchitis, prostatitis, oophoritis – in 5% of cases in girls, mastitis – in 31% of cases in girls over 14 years old, thyroiditis, dacryoadenitis), and severe conditions may develop – serous meningitis and meningoencephalitis, myelitis and encephalomyelitis, damage to the cranial nerves due to prolonged circulation of the pathogen in the blood. Mumps can lead to residual consequences of damage to the central nervous system, can form infertility in men (in 50% of cases over 25) and secondary diabetes mellitus, not uncommon [12].

The World Health Organization (WHO) classifies mumps as an infection that can be eradicated by specific vaccinations. It was possible to achieve the WHO goal of reducing the incidence by 2010 or earlier to a level of 1 or less per 100,000 population in Russia (2009 – the registered incidence rate was 0.65 per 100,000 population). However, at present, the incidence is recorded in many

countries of the world in the form of sporadic cases and in the form of large epidemic outbreaks.

THE AIM. The article highlights the current state of the problem of mumps in the world and the Russian Federation.

MATERIALS AND METHODS

Research materials are electronic resources WHO infection control, Cochrane, Elsevier, ScienceDirect, CDC infection diseases database, PubMed, eLIBRARY, CyberLeninka. Research methods are analysis and generalization of scientific literature. The immunological structure of the population was analyzed in different age groups to mumps ($n = 593$) in the study area (2018) according to the data of the Center for Hygiene and Epidemiology in the Perm Territory, the study was carried out by a serological method using the Vector Best test system «Vector Parotitis-IgM», «Vector Parotitis-IgG».

RESULTS AND DISCUSSION

Etiology of mumps

The viral nature of mumps was first established in 1934 by researchers E. Goodpascher and K. Johnson. The mumps virus belongs to the family *Paramyxoviridae*, genus *Rubulavirus* (Fig. 1). The mumps virus has biological properties: a spherical virion with a diameter of 100–300 nm; the genome is represented by a single-stranded, unsegmented infectious RNA comprising seven genes organized by 3'-NP-P-M-F-SH-HN-L-5'. The surface proteins hemagglutinin, neurominidase (HN), and fusion protein (F) are responsible for the adhesion and aggregation of the viral envelope with the cell membrane and have an important role in infection, and it is to them that virus neutralizing antibodies are formed [2].

Currently, 12 genotypes of the virus (A, B, C, D, E, F, G, H, I, K, L) circulate in the world, they are isolated on the basis of differences in the nucleotide sequence of the SH and HN transmembrane protein genes. The heterogeneity of the nucleotide sequence of wild virus genes ranges from 6 to 20% [2, 14, 15]. Exogenous (imported) strains of the mumps virus can appear along with the endogenous circulation of a particular genotype of the virus in a particular area. Thus, the prevalence of circulating mumps virus of genotype G in Australia in 2007–2008 was established with a wide endogenous circulation of the virus of genotype J in recent years (2015) [3].

The mumps virus genotype G has been circulating in the world for the last ten years, it is the most widespread and is most often detected during epidemiological investigations of large epidemic outbreaks (20 or more cases of infection) in the USA, Great Britain, the Netherlands, Australia, southern China, Canada, Norway, India, Scotland, Israel, Japan, Korea and France [3, 15–24]. The genotype of the mumps virus F circulates in the central part of China, the genotype of the virus K circulates in Vietnam [25–27].

Epidemiology of mumps

In Russia, as in the rest of the world, there has been a decrease in the incidence of EP (from 483.0 to 1.38 per 100 thousand population in 2018) since the introduction of mass routine immunization of children against mumps (since 1981) within the framework of the National Calendar preventive vaccinations (Fig. 2) [28, 29].

The analysis of the incidence of mumps identified the territory of risk in the Russian Federation – the North Caucasian District according to the federal statistical observation in the period 2016–2018 (Table 1) [30].

Comparative assessment of the age structure of patients with mumps revealed a shift in morbidity in adolescents and adults. At present, the proportion of school-children and adults aged 17–19 and 20–25 is more than 60% [3, 16, 21]. In the study area (Perm Territory), out of 36 cases in 2018, 34 cases (94,5%) accounted for adults of working age from 18 to 49 years old [31].

Diagnosis of mumps

Etiological laboratory diagnostics in mumps is not provided for in the standard for the provision of specialized medical care for children. In the existing clinical guidelines for the provision of medical care to children, the use of the enzyme immunoassay method is recommended as a confirmatory laboratory test; in the case of verification of atypical forms of infection, the molecular biological method should be used [32–34].

Specific IgM antibodies to mumps are detected 1–4 days after the onset of the first clinical symptoms, their concentration rapidly increases and becomes

maximum by 40–50 days of illness. It is believed that their diagnostic value increases from the fifth day of the disease. Specific IgM antibodies to mumps may be absent altogether or circulate for a short time in vaccinated individuals [35, 36]. The presence of specific IgG antibodies to mumps in the blood serum of patients does not allow establishing the age of the disease. A dynamic increase in the titer of specific IgG antibodies to mumps virus by 4 or more times after 2–3 weeks from the onset of the disease is considered diagnostically significant [24, 29].

During an outbreak of mumps in the study area from November 2017 to February 2018, with 12 cases of mumps aged 21 to 27 years in 100% of individuals, mumps was confirmed by a serological method using the Vector Best test system “Vector Parotitis-IgM”, “Vector Parotitis-IgG”. Of the 12 patients specific IgM antibodies to the mumps virus were detected in 4 people (33,3%), a dynamic four-fold increase in specific IgG antibodies was in 8 people (66.7%). The performed screening serological dynamic examination of contact persons with the source of the infectious agent revealed initially 26 (84%) seropositive persons and 2 (6%) with dubious results (the coefficient of positiveness antibodies-IgG was 0.8-1.0). Subsequently, there was an increase in the number of cases with dubious 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 secretions is the most informative for the verification of mumps [2, 24, 37]. The mumps virus is detected within 9 days of the onset of clinical symptoms [2, 38, 39]. However, among the vaccinated, the isolation of the virus occurs short-term and is observed up to 2–3 days [24, 36]. The informative value of the molecular genetic and serological diagnostic methods used in everyday clinical and epidemiological practice directly depends on the timing of the disease. The greatest diagnostic value in confirming the diagnosis in the first days of the disease has the method of reverse transcriptase PCR (RT-PCR) with real-time detection, this method reveals the genetic material of the mumps virus in the contents of nasopharyngeal secretions and buccal smears from patients [24, 29, 37]. The PCR method in clinical practice, as a confirmatory test, provides an etiological decoding of patients with mumps, and timely prescribes adequate and systemic therapy for the sick. This method determines the circulating genotypes of the virus in a separate territory – endogenous strains, this allows differentiating the endogenous circulating strains of mumps from imported (exogenous) ones, isolating “wild” mumps viruses and comparing them with a “vaccine” strain, confirming or excluding the emerging post-vaccination complications, revealing changes in the mumps virus of adaptive and phylogenetic nature [14, 15, 40].

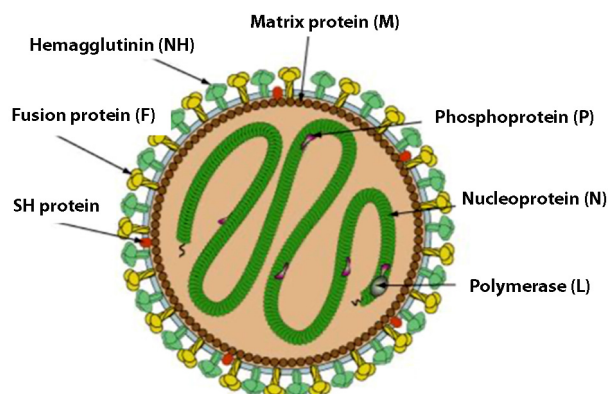


Figure 1 – The structure of the mumps virus according to N. Litsov, 2018 [13]

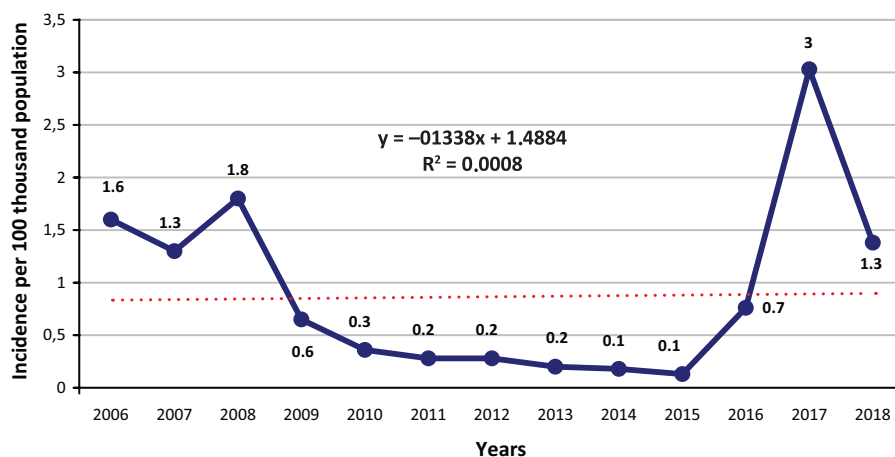


Figure 2 – Dynamics of the incidence of mumps in the Russian Federation (in terms of per 100 thousand population)

Table 1 – Territories of the Russian Federation with a high incidence of mumps in 2018

Territory	Absolute number	Indicator per 100 thousand population
Russian Federation	2027	1.38
Republic of Dagestan	1390	45.53
Chechen Republic	165	11.57

Table 2 – Characteristics of vaccine strains

Vaccine type	Vaccine name	Characteristics of the vaccine strain of mumps
Monovaccine (mumps)	Cultured live dry vaccine	Vaccine strain Leningrad-3 (one inoculation dose contains more than 20000 TCD50)
Divaccine (measles-mumps)	Cultured live dry divaccine	Vaccine strain Leningrad-3 (one inoculation dose contains more than 20000TCD50)
Trivaccine (measles-mumps-rubella)	MMR-II	Jeryl-Lynn vaccine strain (one vaccination dose contains at least 20000 TCD50)
	Priorix	Vaccine strain RIT 43/85 (one vaccination dose contains at least $10^{3.7}$ TCD50)
	Measles-mumps-rubella	Vaccine strain Leningrad-Zagreb (one vaccination dose contains at least 5000 TCD50)
Quadrivaccine (measles-mumps-rubella-varicella)	Priorix-Tetra	Vaccine strain RIT 43/85 (one vaccination dose contains at least 4,4 lg TCD50)

The RT-PCR method is used quite widely; in the world clinical and epidemiological practice, along with enzyme immunoassay, it is used to establish, in the course of an epidemiological investigation, the causes and conditions of the spread of large epidemic outbreaks. The RT-PCR method was used for typing biological material in epidemic outbreaks in Germany (2008–2011), USA (2016), Canada (2007–2017), Australia (2007–2015), France (2013), Norway (2016), Israel (2017) [3, 16, 24, 37, 41, 42]. The molecular genetic method RT-PCR by isolating nucleic acids was used along with serological methods in the diagnosis of mumps in the course of a detailed epidemiological investigation of an epidemic outbreak of mumps with 176 cases in the Udmurt Republic (2008). An identical causative agent of the mumps virus with common biological properties has been established among the diseased along with common clinical manifestations [29].

The procedure for identifying, treating, isolating patients, official registration and statistical observation of mumps cases are determined in the Russian Federation in accordance with the current sanitary and epidemiological rules. About 300–600 thousand people suffered from mumps per year before the introduction of mass routine vaccine prophylaxis in 1970–1980, for comparison, in 2018, 2027 cases of mumps were registered in the Russian Federation [30].

Mumps prevention

Vaccine prophylaxis of mumps has been carried out in the Russian Federation since 1981; it has reduced the incidence and mortality rate, and has reduced the severity rate and the number of complications. Vaccine prophylaxis saved more than 2,500 lives, prevented about 2.5 million cases of serous meningitis, tens of thousands of cases of orchitis, oophoritis, pancreatitis, and subsequently diabetes mellitus, mastitis and premature abortions. To date, over 200 million people have been vaccinated. Coverage of preventive vaccinations should be at least 95% among decreed persons in order to achieve sufficient population immunity to mumps. In the Russian Federation, coverage with timely vaccination has exceeded 97,5% annually since 2002. However, the immune layer in mumps did not reach the normative level when assessing the immunological structure of the population in different age groups. For example, the proportion of seronegative individuals for 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% at the age of 30–39 among the total population of Moscow. and the Moscow region in 2007–2011 [29, 43]. At the same time, in 2017–2018, the increase in the incidence of mumps was noted to 3.03 per 100 thousand population in 2017 and 1,38 per 100 thousand population in 2018 [29, 44].

The vaccine strains used in the world practice of vaccine prevention of mumps: Jeryl Lynn and its derivative Rit 43/85 (USA), Leningrad-3 (Russia), Urabe, Hoshino, Torit, Miyahara (Japan), Leningrad-Zagreb (Croatia), Rubine (Switzerland), Sofia-6 (Bulgaria) [45].

In the Russian Federation, specific prophylaxis is carried out with a live mumps vaccine within the framework of the National Calendar of Preventive Vaccinations and the Calendar for Epidemic Indications (vaccination is carried out within 7 days from the moment the first case is detected in the epidemic focus). Mumps mono vaccine, mumps-measles divaccine, tri-vaccine (measles-mumps-rubella) and quadrivalent vaccine (measles-mumps-rubella-varicella) are licensed and registered in the prescribed manner for the implementation of vaccine prevention of mumps in the Russian Federation (Table 2) [44].

The Leningrad-3 strain is a part of mono- and divaccines and is cultivated in the primary culture of Japanese quail fibroblasts [44]. Jeryl-Lynn vaccine strain and RIT43/85 (derived from Jeryl-Lynn) are included in the MMR-II, Priorix (trivaccine) and Priorix-Tetra vaccines; it is cultured separately in a chicken embryo cell culture [46–48]. The Leningrad-Zagreb vaccine strain is a part of the trivaccine (measles-mumps-rubella), it is cultivated in fibroblasts of chicken embryos [11, 29, 44]. Currently, the domestic combined trivaccine (measles-mumps-rubella) “Vaktrivir” is registered in the Russian Federation [50].

Assessment of the immunological structure of the population revealed a fairly high number of seronegative individuals to mumps in different age groups ($n = 593$) in the study area (2018). Among children aged 3–4 years, their share was 9,5%, at the age of 16–17 years – 6%, at the age of 20–29 years – 13,3%, 30–39 years – 19,4% and 40–49 year olds – 8,4%. The largest number of seronegative individuals is found among adults aged 20–39 years. At the same time, the decreed age group for revaccination among adults is not defined in the National Calendar of Preventive Vaccinations.

In the second half of the 20th century, in many countries of the world, mass vaccine prophylaxis of mumps was introduced into national immunization programs and the incidence of the disease decreased significantly. However, the unfavorable epidemic situation in mumps continues to grow in some countries of the world, outbreak incidences are recorded in them in collectives with ideal vaccination coverage (up to 98%). According to M. Maillet (2013), P.A. Maple (2015), V.S. Fields (2019) among patients with mumps, previously received two doses of the vaccine to 62–92% of individuals [2, 16, 24]. The main reasons and conditions for the emergence of epidemic outbreaks are the lack of normative coverage of vaccination and revaccination in the past among the decreed groups, vaccination failures among vaccinated, decreased post-vaccination immunity, untimely and ineffective primary anti-epidemic (preventive) measures in the emerging epidemic foci of infection [2,

19, 51]. G.E. Nelson (2013), C.V. Cardemil (2017), A.M. May (2017), M. Marin (2018) found that the incidence stopped after the use of the third dose of vaccine among contact persons in outbreaks against the background of high coverage with two doses of vaccine earlier in mainstream schools and universities as a preventive measure [43, 51–53].

The lack of production control of the produced vaccines for the prevention of mumps – the full compliance of the applied vaccine strain with circulating “wild” strains leads to insufficient protection of the population from circulating “wild” strains [21, 25, 54]. The immune defense created by the vaccine strain does not have the same intensity and duration as in natural infection, and some genotypes of “wild” variants of the mumps virus can break through the immune barrier and cause disease [11, 37]. Antigenic differences between vaccine and circulating strains, low inoculation dose can weaken immunity and reduce the effectiveness of the implemented mass vaccine prevention [44, 47, 50]. In connection with the possibility of adaptive and phylogenetic variability of the circulating “wild” strain of mumps, it is necessary to introduce regulated production control of the conformi-

ty of the vaccine strains used with the circulating “wild” strains of the virus [21, 25, 37].

CONCLUSION

The ongoing epidemic trouble with mumps in certain territories of the Russian Federation, the shift in the incidence in the age structure of patients towards adolescence and adults dictates the need to develop and introduce into medical practice a standard clinical definition of a mumps case in order to correctly verify the diagnosis with subsequent laboratory confirmation of the clinical diagnosis, taking into account the existing epidemiological data.

The main reason for the emergence of an outbreak is a decrease in the tension of post-vaccination immunity among the adult population, in addition to vaccination failures among vaccinated children.

Anticipating an unfavorable epidemic situation in mumps requires the introduction of regulated production control over the use of vaccine strains and the determination of the correspondence between the vaccine and circulating strains of the mumps virus with a justification for an adequate vaccination dose.

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AUTHORS' CONTRIBUTION

Semerikov V.V. – concept and design of the study, obtaining data for analysis, writing the text of the manuscript;
Yuminova N.V. – concept and design of the study, partly collection of material;
Postanogova N.O. – review of publications on the topic of the article, writing the text of the manuscript;
Sofronova L.V. – review of publications on the topic of the article, writing the text of the manuscript

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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