MEASLES ELIMINATION: INDICATORS, PROGRESS AND CHALLENGES

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Abstract

Measles is highly infectious viral disease that continued to be a challenge for many countries worldwide and remains a leading vaccine-preventable cause of child mortality. Measles virus is a member of the family Paramyxovridae, genus Morbillivirus and has a negative - sense, single-stranded RNA genome. The wild-type measles virus consists of 24 genotypes, three of them (B3, D8 an H1) have dominated circulation in the world. Laboratory confirmation of measles is provided by serological (ELISA test for detection of IgM and IgG antibodies), molecular (detection of viral nucleic acid) and viral isolation by Vero/hSLAM cells methods. Measles virus genotyping can play an important role in tracking transmission pathways during outbreak investigations. Under the Global Vaccine Action Plan, measles is targeted for elimination by 2020. High vaccination coverage across all of the population is crucial to reach the goals of measles elimination. Another important challenge is timely laboratory diagnosis in WHO accredited laboratory. Latest data, from World Health Organization shows that the number of measles cases has increased in America, European and Pacific region. Many countries remain endemic to the spread of measles virus. The global increase in the disease incidence has been attributed to a fall of vaccination and surveillance. Countries and regions aiming to eliminate measles urgently need to improve the implementation and monitoring of both routine and mass vaccination campaign strategies and epidemiological and laboratory monitoring of infection.

Introduction

Measles is highly infectious viral disease that continued to be a challenge for many countries worldwide and remains a leading vaccine-preventable cause of child mortality. It continues to cause outbreaks in communities with low vaccination coverage in industrialized nations [1]. Before the introduction of measles vaccines, measles virus infected 95%–98% of children by age 18 years [2]. Measles virus (MV) is a member of the family Paramyxoviridae, genus Morbilivirus. It is a pleomorphic virus ranging in diameter from 100 to 300 nm and has a single, non-segmented negative-sense RNA genome. Each gene contains a single open reading frame (except P), transcriptional start and stop signals, and a polyadenylation signal. The encapsulated genomic RNA is termed the nucleocapsid (NC) and serves as a template for transcription and replication. The nucleoprotein (N) mRNA is transcribed first and N is the most abundant of the viral proteins. The World Health Organization (WHO) recognized 8 clades of measles virus (designed A to H) and 24 genotypes [1,3] There are two envelope glycoproteins, which mediated viral entry. These are the F (fusion) protein which is responsible for fusion of virus and host cell membrane, viral penetration, and the H (haemagglutinin) protein, which is responsible for binding of virus to the cells [3]. Three are the host cell receptors which are responsible for the entry of the virus participle-CD 150 (signaling lymphocyte activation marker or SLAM), Nectin-4 and CD46. CD150 is expressed mainly of dendritic cells, lymphocytes and some macrophages. CD46 is a complement regulatory molecule expressed on all nucleated cells in humans. Nectin-4 was identified as the epithelial cell receptor for MV. Wild-type MV binds to cells primarily through the cellular receptor SLAM, whereas most vaccine strains bind to CD46, as well as to SLAM [1, 3-4]. MV is serologically monotype virus.

Pathogenesis

The transmission of the measles is by the infectious aerosols by delivering infectious virus to epithelial cells of respiratory tract of susceptible hosts [1, 4]

The incubation period of the illness continued 8-12 days. During this period measles virus replicates and spreads in the infected host. The initial viral replication begins in the epithelial cells in the upper respiratory tract, and then the virus spreads to the local lymphatic tissue. Replication in local lymph nodes is followed by viremia and the dissemination of the virus to many organs, including lymph nodes, skin, kidney, gastrointestinal tract in which virus replicates in the epithelial and endothelial cells, and in lymphocytes, monocytes, macrophages [1, 2]. Immune responses to measles virus into the host organism are essential for the clinical recovery and the establishment of long - term immunity. Early innate immune responses include activation of natural killer (NK) cells and increase production of interferon (IFN) α and β [1]. The adaptive immune response includes production of specific MV antibodies. Measles begins with a prodrome phase haracterized by increasing fever (to 39 - 40,5^{0}C) and the presence of one or more typical symptoms: cough, coryza or conjunctivitis. During the prodrome phase might be visible Koplik's spot, which are small white lesions on the buccal mucosa inside the mouth. Symptoms intensify over the 2-4days before the onset of rash and peak on the first day of rash. The erythematous maculopapular rash is usually first appeared on the face and then spreads to the trunk and the extremities. The rash lasts for 3-4 days after which it fades, disappearing from the face first [1, 2, 3]. Recovery from measles produces lifelong immunity. However during and after acute infection, patient experiences transient immunosupression, which is substantiated by the suppression of delayed-type hypersensitivity responses [5]. Measles virus induced immunosuppression can cause development of secondary bacterial infections [4, 14]. Complication rates are increased by immune deficiency disorders, malnutrition, vitamin A deficiency. Complications of measles have been described in almost every organ system (Table 1).

Measles immune response

During the course of the disease, specific class immunoglobulins IgM, IgA and IgG antibodies of the humoral immune response are appeared (Figure 1). The first two species disappear for about two months, and the latter persist for life.

Measles laboratory confirmation

Laboratory diagnosis of measles is based on one of the following indicators (specimen required, optimal timing of sample collection) [Commission decision of 28/IV/2008 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council]:

- antibody testing: positive IgM antibody or seroconversion to IgG (serum, oral fluid: > 4 days to 2-3 months);
- molecular testing: detection of measles RNA (oral fluid, urine and serum; up to 5 days);
- virus isolation in cell cultures: isolation of measles virus from clinical specimen (throat swab, nasopharyngeal aspirate, conjunctival swab, urine; up to 5 - 7 days);
- detection of measles virus antigen by Direct Fluorescent Assay in a clinical specimen using measles virus specific monoclonal antibodies.

Epidemiology

In the pre-vaccine era, outbreaks occurred in late winter, early spring in countries with temperate climate, whereas in tropical climate outbreaks mainly occurred in the dry season.

This seasonal nature of measles corresponds to the public school calendar in developed countries or to yearly migration of agriculture workers [6, 7]

In 2000, the Fourth United Nations Millennium Development Goal was adopted, with the main task of reducing child mortality by two-thirds by 2015. The maintenance of high vaccine coverage against measles virus is a major indicator of progress in the elimination process.

In 2010, all 53 countries in the World Health Organization (WHO) European Region (EUR) reconfirmed their commitment to eliminating measles and rubella and congenital rubella syndrome. This goal was included in the European Vaccine Action Plan 2015-2020 as a priority.

The WHO-recommended strategies for control and surveillance of the circulating measles virus include [8]:

1) Achieving and maintaining ≥95% coverage with 2 doses of measles-containing vaccine (MCV) through routine immunization services;
2) Providing measles and rubella vaccination opportunities, including supplementary immunization activities to population susceptible to measles and rubella
3) Reduction of global measles cases to less than 5 cases per million population.
4) Decrease in global mortality caused by measles by 95% and achievement of measles elimination in at least 5 WHO regions by the end of 2020.

The world is divided into six regions in order to implement the WHO's strategic plan to eradicate measles. These are the African region, American, the Eastern Mediterranean region, the SEE region and the Western Pacific Region WPR). Countries in all six WHO regions adopt the target plan for the eradication of measles before 2020. Criteria for achieving this are determined on the basis of the absence of endemic transmission of measles virus in a region or other defined geographical area for more than 12 months in the presence of a national surveillance system. However, the targets set by the WHO in 2015 have not been fully achieved and only in one region - the American declared measles elimination.

To achieve measles elimination in EUR, measures are needed to strengthen immunization programs in every district of each country, offering supplemental measles vaccination to susceptible adults, maintaining high-quality surveillance for rapid case detection and confirmation, and ensuring effective outbreak preparedness and response.

The measles vaccine has been in use since the 1960s [10, 11]. World Health Organization (WHO) recommends immunization for all susceptible children and adults for whom measles vaccination is not contraindicated. Reaching all children with two doses of measles vaccine, either alone, or in a measles-rubella (MR) or measles-mumps-rubella (MMR) combination, should be the standard for all national immunization programs. MMR vaccine (strains: Edmonston-Schwarz for measles, Urabe/Jeryl Lynn for mumps and RA 27/3 for rubella) is in use in the country since 1992, The National Immunization Schedule includes two doses of MMR vaccine as routine immunization of children: on age of 13 months (first dose) and 12 years (second dose).

Since 2002, all 53 countries in EUR have included 2 MCV doses in routine childhood vaccination schedules.

Surveillance data are reported monthly to WHO from all EUR countries either directly or via the European Centre for Disease Prevention and Control.

The WHO European Measles and Rubella Laboratory Network provide laboratory confirmation and genotyping of measles virus isolates from patients with reported cases.
However, the number of cases of measles in European countries in 2018 is more of 13 000, and by the middle of 2019 - 10 958 (in France, Bulgaria, Italy, Poland and Lithuania) [16].

Measles circulation in Bulgaria

In the first decade of the 21st century, against a background of low morbidity, epidemic measles leaks were recorded in a number of Western and Central European countries. It is in Bulgaria that in 2009-2011, after a long inter-epidemic period (7 years), one of the largest epidemics in the European Region develops - more than 24 thousand people (24 365) and 24 (mortality - 0.3 ‰, lethality - 0.1%) [9]. In the period 2011-2013, major epidemics of measles are also registered in France, Ukraine, Georgia and Turkey. Explosions of measles in Bulgaria were reported in 2013 [12] and in the full half of 2017 [13]. In 2018 number of confirmed measles cases were 13, mainly imported from Ukraine, with measles genotypes B3 and D8. In 2019 a measles outbreak was reported and number of measles cases by the middle of the year was more than 1000 from 12 affected regions on the country and detected measles genotype was B3. Infected patients over the years are mainly unvaccinated individuals [15].

Regarding measles in Bulgaria (1969 - 2013), the development of infection prophylaxis and immunization program goes through several stages, characterized by different vaccine schemes and approaches (monovalent vaccines (containing Leningrad strain 16) and combined vaccines (Measles, Mumps, and Rubella, MMR) that affect the spread of the disease differently.

Conclusion

The WHO strategic goal of measles elimination in the European Region imposes increased requirements for epidemiological and laboratory surveillance of this disease. Although measles is a vaccine preventative infection, the virus still poses a public health problem, a proof of which is the case for 2019 cases and outbreaks in Europe and Bulgaria. The highest proportion of those affected is the non-immunized, as is the Roma ethnic group. Elimination of the disease is only possible by maintaining constantly high immunization coverage of the population (≥95%) with two doses of the MMR vaccine, as well as performing enhanced seroepidemic surveillance with a mandatory immunoenzymatic and molecular-biological study of any suspected case - combined laboratory approach. Parallel to this, among the high-risk groups, in order to stop transmission of the virus, it is necessary to conduct sero-epidemiological studies to establish the level of collective immunity and to apply additional immunization activities for its promotion.

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Table 1. Possible post-measles clinical complications

Measles complications	Frequency
Diarrhea	8%
Secondary bacterial infection	7%
Measles pneumonia	mainly in immunocompromised patients
Acute encephalitis	1:1000-5000
Subacute measles encephalitis	only in immunocompromised patients
Subacute sclerosing panencephalitis (SSPE)	1-4: 100,000 in diseased and 0.14: 100,000 among immunized individuals
Myocarditis	<1%
Thrombocytopenic purpura	<1%

Figure 1. Immune response in acute measles infection (according to https://www.who.int/immunization/monitoring_surveillance/burden/laboratory/manual_section1.3/en/)