



Measles is Back – Considerations for laboratory diagnosis

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ABSTRACT

Measles is a highly contagious viral illness that continues to cause significant mortality among young children worldwide despite the availability of a safe and effective vaccine. During the first half of 2019, over 182 countries reported more than 300,000 measles cases; greater than double the number from the same period in 2018. Timely recognition and laboratory confirmation of infected individuals as well as appropriate infection prevention measures are crucial to avert further transmission. This review highlights the importance of early recognition of the signs and symptoms of measles and provides details on the laboratory methods commonly employed to confirm cases, investigate outbreaks and characterize the virus. It's critical that clinicians, laboratorians and public health administrations work together to rapidly identify, confirm and contain the spread of measles globally.

1. Description of the virus

Measles (rubeola) virus (MV) is a member of the *Morbillivirus* genus in the family *Paramyxoviridae*. It is a single stranded, non-segmented, negative sense RNA virus with a genome of approximately 15,900 nucleotides containing six genes encoding for eight proteins. The virion is enveloped and pleomorphic with diameter ranging from 100 to 250 nm. The virus has only one serotype but antigenic and genotypic variability among wild-type and vaccine viruses can occur [1].

2. Transmission and epidemiology

Measles is a highly contagious viral illness characterized by fever, malaise, cough, coryza, and conjunctivitis, followed by exanthem [2,3]. MV transmission occurs via person-to-person contact through respiratory droplets. Droplets may remain airborne for several hours and virus may be recovered from contaminated surfaces, enhancing transmission potential [2,4], enhancing their infectious potential. A patient infected with measles may transmit the virus from approximately 4

days before the appearance of rash to 4 days after rash onset. The chance of contracting the disease in a susceptible individual exposed to measles is 90 percent [2].

Measles remains one of the leading causes of death among young children worldwide, despite the availability of a safe and effective vaccine. Before widespread vaccination, MV caused 2–3 million deaths globally per year [5]. The World Health Organization (WHO) estimated that between 2000–2017, measles vaccination prevented 21.1 million deaths resulting in an 80 % decrease in measles deaths worldwide [6,7]. Unfortunately, in 2017 there were still approximately 110,000 deaths from measles infection globally, mostly in children ≤5 years of age. Between January and July 2019, 182 countries reported approximately 364,808 measles cases, exceeding the 129,239 cases reported during the same time in 2018 [8,9]. WHO regions with the largest increases in measles cases between January and July 2019 were the Africa Region (900 %, 186,675 cases), European region (120 %, 97,503 cases), Eastern Mediterranean Region (50 %, 17,717 cases) and the Western Pacific Region (230 %, 56,055 cases).

Following the introduction of the first licensed measles vaccine into

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Table 1
Suitability of specimen types for laboratory diagnosis of measles infection.

Specimen Type	Utility of laboratory method				
	RT-PCR	Culture	IgM serology	IgG avidity	Genotyping
serum (from 4 up to 30 days after rash onset)	+	–	+++	++	+/-
respiratory (throat/NP within 7–10 days after rash onset)	+++	++	–	–	++
urine (10–50 mL, concentrated)	++	+	–	–	++

the U.S. in 1963, the incidence of measles declined rapidly [10] the disease was officially eliminated by 2000 [11]. Unfortunately, this achievement was temporary as localized measles outbreaks occurred sporadically throughout the U.S. due to travelers who brought the virus back from other countries, and spread the virus to unvaccinated and under-vaccinated subpopulations [12]. Between January and October 2019, 1248 measles cases and 22 measles outbreaks were reported in the U.S. [13]. This marks the most cases recorded in the U.S. since 1992. Similarly, although up to 70 % (37/53) of European countries have been verified as having achieved measles elimination, the recent resurgence has continued and over 300,000 measles cases have been reported between January and October 2019 (note reported not yet complete; <https://www.who.int/immunization/newsroom/measles-data-2019/en/>).

3. Clinical significance

Almost all MV contacts result in symptomatic infections. After an incubation time of 7–14 days, the disease characteristically starts with high fever, coughing, coryza and conjunctivitis. Koplik spots, punctate blue-white spots on the buccal mucosa, can occur 1–2 days before the rash to 1–2 days after the rash. They are specific for measles infection but not always detectable. The typical measles exanthem occurs about 3–5 days after the first clinical symptoms. It is a non-itching, maculopapular rash, and blanches under pressure. The rash begins on the forehead and at the face, then spreads gradually downward to the neck, trunk, and lower limbs. With progression of the exanthem, the prodromal symptoms diminish. In uncomplicated cases the fever usually decreases when the rash reaches the feet, and then the rash fades out gradually downwards. This phase is followed by skin desquamation over a period of up to two weeks [3,10].

About 20 % of measles infections show respiratory complications such as pneumonia, otitis media and laryngotracheobronchitis. Diarrhea, occasionally leading to severe dehydration, may also occur. Furthermore, ocular complications such as purulent conjunctivitis, keratitis and xerophthalmia have been observed and can lead to blindness. Neurological complications including acute measles encephalomyelitis, subacute measles encephalitis (also known as measles inclusion body encephalitis) and subacute sclerosing panencephalitis (SSPE) occur in approximately 1 in 1000 infections. Mortality due to measles occurs in less than 1% of cases, predominantly due to pneumonia, encephalitis or dehydration. In malnourished children, the mortality rate may be up to 10 %. Measles may also be severe in pregnant women and lead to an increased risk of prematurity or fetal loss [3,10].

In children who acquire measles early in life, SSPE may occur as a late complication. SSPE is a chronic progressive disease caused by defective MV strains and is associated with irreversible destruction of brain tissue. The first clinical symptoms of SSPE are observed a few years after measles infection, and include progressive changes in behavior, development of muscle spasms, seizures, and dementia. In most cases, the course of SSPE takes about 1–3 years and is consistently fatal. Overall SSPE is rare, but measles infections in very young infants may lead to SSPE in 1:600 cases [14].

Following measles infection, the host immune system is impaired for several years. Measles viruses infect and destroy preexisting B- and

T-memory cells, which are directed against other infectious agents and thus cause “immune amnesia”. Thus measles infection may limit the antimicrobial response of the host for some time and increase susceptibility to other infections [15].

4. Laboratory testing

4.1. Specimens

Samples including serum, respiratory tract specimens and/or urine should be collected from all individuals with suspected measles for laboratory confirmation (Table 1). Throat and nasopharyngeal (NP) swabs for molecular detection and viral isolation should be collected using a flocked synthetic swab and placed in 1–3 mL of viral transport medium (VTM) [16]. NP aspirates and bronchoalveolar lavage (BAL) specimens are also acceptable. Ideally, due to the cell-associated nature of the virus, urine (10–50 mL) should be centrifuged at 500xg for 10 min at 4 °C and the sediment re-suspended in VTM. All samples can be maintained at 4 °C if testing will occur soon after collection, otherwise respiratory and urine specimens can be frozen and transported at –20 °C or –70 °C for molecular detection [1].

4.2. Antibody detection

The detection of measles virus-specific IgM antibodies in serum is the standard laboratory method for the rapid confirmation of measles [17]. This is usually accomplished using enzyme immunoassays (EIA) or, more recently, chemiluminescent immunoassays [18,19]. A variety of commercial EIA tests are available which are easy to perform and permit high-throughput testing.

In the majority of patients, measles virus-specific IgM antibodies will be detectable ≥ 3 days after the onset of rash. As a caveat, IgM antibodies can be low or undetectable within the first three to four days [17]. In addition, breakthrough infections can present with low or even undetectable levels of IgM antibodies warranting RT-PCR analysis from throat swabs and/or testing of follow-up sera. The interpretation of serological assays is further hampered by false-positive IgM results. This is especially true for laboratories in regions close to measles elimination where the positive predictive value of a positive IgM result is low [19]. Alternative laboratory methods and/or testing of follow-up sera are therefore recommended in these cases [19].

After acute infection measles virus IgM antibodies decline to undetectable levels over a time period of up to 6–8 weeks. In rare cases, they can persist for longer. Measles virus-specific IgG antibodies will develop shortly after the appearance of IgM and usually remain detectable for life.

Recent infection can also be diagnosed using acute and convalescent sera (taken 10–14 days apart) by demonstrating a $\geq$ four-fold increase of measles virus-specific IgG antibodies or seroconversion from a negative to a positive IgG result. Measles virus-specific IgG avidity testing can complement the diagnosis and has been proven useful in situations such as suspected vaccine failure [20]. Briefly, low avidity IgG indicates weaker binding to antigen which is suggestive of acute or recent infection. High avidity IgG binding is indicative of remote infection or vaccination.

Quantification of measles IgG in serum and CSF can be used to

estimate the level of intrathecal antibody production [21]. Intrathecal IgG is diagnostic of SSPE but can also help with diagnosing measles encephalitis.

Although commercial antibody detection assays are most often used, the plaque reduction neutralization test (PRNT) is still considered the gold standard and allows detection of neutralizing antibodies in serum [22]. However, PRNT is laborious, requires virus culture facilities and is time consuming.

4.3. Molecular detection

Molecular detection of MV RNA using nucleic acid amplification tests (NAAT) is another mainstay to confirm acute infection. Viral RNA can be detected in respiratory specimens (e.g. NP swabs) and urine up to 14 days after rash onset but early sampling is recommended to ensure highest sensitivity [19]. In serum, MV RNA may be detected by RT-PCR within the first few days after symptom onset; however, viremia may be short-lived and a negative result later in the course of disease does not preclude infection [17].

A number of different laboratory-developed (real-time) RT-PCR assays have been described. RT-PCR formats are preferred as they are less contamination-prone, provide rapid results, and allow evaluation of (semi)-quantitative data [23]. The wide availability of published NAATs is complemented by a growing number of commercially available molecular assays. Recently, RT-PCR assays differentiating between wild-type and vaccine MV have been described [24]. Differentiation of MV strains is especially important in highly vaccinated populations in order to initiate appropriate public health interventions.

Whereas the detection of viral RNA is confirmatory for acute measles infection a negative result does not exclude contagion. Low concentrations of MV have been observed in breakthrough infections and can be challenging to detect [25]. In addition, although the MV genome possesses a low genetic variability, mutations can detrimentally affect the performance of molecular assays. Constant monitoring and updating of primer/probe sequences is therefore required [26].

4.4. Virus isolation

Although cell culture is less often used for routine measles virus diagnosis, it is important for maintaining the measles virus strain bank collection curated by the U.S. CDC. Cultured strains provide valuable material for research and also support outbreak investigations as more genetic material is often required for whole genome sequencing. Details on specimen collection, preparation for cell culture and methods for virus isolation can be found in the WHO guidelines [17]. Specimens for viral culture should be collected within 3 days of rash onset to maximize the potential for recovery; however, virus may still be recovered up to 7–10 days after rash appearance. Culture of MV is performed under standard BSL-2 precautions including the use of a class II biologic safety cabinet and is best accomplished using Vero/hSLAM cells [27] in which Vero cells have been transfected with a plasmid encoding the gene for human SLAM, a known cellular receptor for measles virus [28]. The typical cytopathic effect (CPE) produced by measles virus replication in cell culture consists of the formation of syncytia, which appear as large multinucleated cells caused by fusion of infected cells. Cell culture confirmation of MV isolation is done using either RT-PCR, immunofluorescence or immunohistochemistry [17].

4.5. Genotyping

Genetic characterization of circulating MV strains is an important part of outbreak investigation and global surveillance, contributing to the goal of measles elimination. These activities are supported by the WHO Global Measles and Rubella Laboratory Network (GMRLN) who also host and maintain the global Measles Nucleotide Sequence database (MeANS; http://www.who-measles.org/Public/Web_Front/main.php). Importantly, all cases of measles are diagnosed, viruses genotyped and data systematically collected at the national and international level.

Genotyping is usually performed on MV RNA from clinical samples. Sequencing of the 450 nucleotides (nts) coding the carboxy-terminal of the nucleoprotein (N450) is recommended as the primary target for genotyping, and the entire coding region of the hemagglutinin (H) gene (1854 nt) as the secondary target [29,30]. The N450 region shows up to 12 % nucleotide variation between genotypes [29]. However, the diversity of circulating MV has decreased considerably in countries where the virus has already been eliminated or is nearing elimination [31,32]. In these countries, outbreaks are often caused by strains with identical N450 sequences and the usual genotyping data is insufficient to differentiate whether the outbreak is a result of ongoing endemic transmission or repeated importation events. The use of extended sequencing including the hypervariable, noncoding region between the matrix (M) and fusion (F) genes (MF-NCR) has recently been recommended by WHO [29,31–33]. Although methods for whole genome sequencing and sequencing of the MF-NCR region have been developed, these have not yet been standardized for routine use. Furthermore, only limited sequence data is available for MF-NCR and full genomes, with sequences determined for only 14 of 24 measles virus genotypes.

Most importantly, genotyping results should always be reviewed together with epidemiological information, such as travel, exposure and vaccination histories. Genotyping data can help to confirm, disprove, or detect new connections among measles cases. It can also be used to inform whether a person has wild-type or vaccine-associated measles virus infection.

5. Clinical and public health management

Information on the management of measles is available from the WHO [34]. There is no specific antiviral treatment for measles. Primary treatment is supportive including hydration, antipyretics and rest. Treatment for secondary bacterial infections requires antibiotics. Additionally, the WHO recommends administration of once daily Vitamin A for 2 days at 200,000 IU to all children ages 12 months and older, and 100,000 IU daily to all children under 12 months of age. Vitamin A administration has been shown to reduce the risk of mortality by 64 % [35,36] possibly in the context of vitamin A deficiency, but the exact mechanisms remain unknown.

Public health authorities should be notified of all suspected cases of measles within 24 h, while laboratory results should be available within 48 h from notification. Additional requirements are collection of: i) demographic, clinical and vaccination status data, ii) data on potential exposure and spread among contacts and iii) data on travel to areas with active measles outbreaks. The source of infection is likely contact with a measles infected individual 7–23 days before the patient's rash onset. When the infection is travel related the identification of the source might be particularly difficult and this is a situation where MV genotyping may be useful. Timely identification of epidemiologic links and patterns are essential to interrupt the chain(s) of transmission, which is of particular importance when fragile patient groups such as transplant recipients or neonates are involved. All cases are classified by WHO according to their confirmation status (laboratory-confirmed, epidemiologically linked, clinically compatible, non-measles) and by source of infection (imported, importation-related, endemic, unknown).

Susceptible individuals having had contact with a measles case within four days before or after their rash onset, may have been infected and should be monitored by public health authorities for 23 days from last contact. At risk contact refers to: i) sharing the same enclosed air space, such as being in the same room, school, health facility waiting room, office or transport for any length of time with a case during the case's infectious period, ii) having been in the case's air space up to two hours after the case, iii) having been in contact with surfaces potentially contaminated by case's respiratory secretions up to two hours after the

case left the room. In some investigations, contacts are considered those sharing an enclosed airspace with a case within two hours of when the case was there. Contact tracing is particularly important in schools due to the close contacts and the potential high proportion of non-immune subjects. Health care settings are also notable for measles transmission due to the presence of vulnerable, susceptible populations such as the very young and immunocompromised individuals.

Unvaccinated contacts ≥ 6 months of age who are eligible for vaccination should be immunized within 72 h of exposure to prevent or reduce the risk of complications following measles infection [2,36]. For contacts that have contraindications to measles vaccine (e.g. pregnant women, infants < 6 months of age and immunocompromised patients), human immune globulin may be administered intramuscularly within six days of exposure to prevent illness or reduce its severity.

6. Prevention and infection control

The measles virus vaccine is a live attenuated vaccine, either combined with mumps and rubella vaccines as MMR or with mumps, rubella, and varicella vaccines as MMRV. The U.S. CDC recommends two doses of measles containing vaccine, separated by at least 4 weeks, for all children 12 months of age and older [2,37]. Administration prior to 12 months of age has the potential for maternal antibodies to inactivate the vaccine. The second dose is routinely given between the ages of 4–6 years. If the MMR vaccine is given before the age of 12 months, it should not be counted as part of the two-dose vaccine schedule. The MMR vaccine is recommended for adults as the MMRV is FDA-approved for ages 12 months through 12 years only.

Due to the highly infectious nature of MV, standard and airborne transmission based precautions should be implemented in anyone with suspected measles [36,38]. Infected patients should be placed in a negative air pressure single room. If a negative pressure room is not available, the patient room door must be kept closed at all times and special ventilation should be used with room air exhausted directly to the outside or recirculated through high-efficiency particulate air (HEPA) filters. Susceptible healthcare personnel should not enter the patient's room or should a respirator (i.e. N95). Airborne transmission precautions are indicated for 4 days after the onset of rash in otherwise healthy children and for the duration of illness in immunocompromised patients. Exposed susceptible patients and healthcare providers without evidence of measles immunity should be offered the first dose of MMR and placed on airborne precautions from day 5 after first exposure until 21 days following their last exposure [36,38].

7. Conclusions

In spite of the availability of an efficacious vaccine and despite the implementation of universal vaccination programs, recent years have seen resurgence in the incidence of MV worldwide due in part to a rise in hesitancy toward vaccination. Significant efforts in surveillance programs are being implemented by European countries and the U.S. in an attempt to control what appears to be an upsurge of a vaccine preventable disease. It is somewhat surprising that recent large measles outbreaks have been sustained and made possible by a progressive decrease in vaccine coverage. It is particularly worrisome to see the numbers of unvaccinated individuals increase not for the lack of economic resources, but for a mounting distrust in vaccination itself. However, studies that confirm the safety and efficacy of measles vaccine have been promoted, informational campaigns have been implemented and, in some instances, compulsory vaccination has been adopted. As scientists and health care providers we remain optimistic that eradication of MV is possible despite these challenges. As these efforts continue, clinicians, laboratorians and public health administrations must work together to rapidly identify, confirm and contain the spread of measles in our communities.

Considerations for laboratory testing

- 1 Collect clinical samples for RT-PCR (and/or viral culture) as soon as possible after rash onset to maximize recovery or detection of MV (ideally within 3 days after appearance of the rash but at least within 7–10 days).
- 2 If a serum sample collected within 3 days of rash onset for IgM testing is negative, a second sample can be collected within 10 days and retested; IgM antibodies may not be detectable very early in the course of disease.
- 3 Viral culture and genotyping are usually performed in public health and reference laboratories. Virus genotyping supports outbreak investigations and global surveillance.

Disclosures/Disclaimers

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