Measles

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THE MICROORGANISM AND ITS CLINICAL PRESENTATION

Measles is a highly contagious respiratory viral infection caused by the measles virus, an enveloped, single stranded RNA-virus, member of the Morbillivirus genus in the family of *Paramyxoviridae* [Moss 2017, ICTV 2020]. 24 measles virus genotypes have been recognized, genotypes most frequently reported in the EU region in recent years are B3 and D8 [Brown 2019].

Incubation time from infection to onset of initial symptoms is approximately 10 days (7-18) [Moss 2017]. Initial prodromal symptoms usually include a high fever (often >40°C), Koplik spots, malaise, loss of appetite, red eyes, runny nose, and sometimes cough (typical 3 C's: cough, conjunctivitis, coryza). Koplik spots are mouth-clustered white spots in the buccal mucosa of the mouth and are considered pathognomonic for measles. They usually appear 2–3 days prior to the occurrence of the characteristic rash that may last 3–7 days [Rota 2016]. The rash is typically maculopapular and erythematous and covers much of the body [Naim 2015]. Leucopenia is common in this stage. The infectious period starts shortly before the prodromal period, around 4 days before and lasts till 4 days after onset of rash [Rota 2016]. Live attenuated measles vaccine is used and may produce in 5-15% a mild measles-like or inapparent non-communicable disease!

COMPLICATIONS

Complications resulting from viral replication or bacterial superinfection occur especially in malnourished children. Measles infections cause a transient immune suppression, resulting in increased susceptibility to opportunistic infections [Mina 2015, Mina 2019, Gadroen 2018, Laksono 2018].

Particularly at risk are those too young to be immunized or older patients and individuals with vitamin A deficiency. A substantial number of measles infections requires hospitalization, mainly for respiratory superinfections, with 22% reported in France to 30% in South Africa [Kabra 2013]. Case-fatality rate is between 0,5-6% [Rota 2016, Cairns 2010].

In approximately 1 in 1000 patients acute or late encephalitis or post-measles encephalopathy occurs within days-weeks-months following infection. Another rare complication, the subacute sclerosing panencephalitis (SSPE), is a delayed complication occurring 5-10 years after acute illness and reported in 1:10.000 to 1:100.000 patients, mainly in children acquiring measles before the age of 2 years. After progressive deterioration, SSPE results in death [Moss 2017].

EPIDEMIOLOGY

The epidemiology is largely determined by the respiratory mode of transmission through droplets or direct contact with nasal or throat secretions of infected persons; less commonly by airborne spread or through secretions of nose and throat [Moss 2017, WHO 2020]. Estimated basic reproductive rate of 12-18 [LCI 2020]. The estimated burden of infection for measles depends upon the vaccination coverage. In temperate climates annual outbreaks of measles typically occur in winter and early spring. In tropical regions outbreaks have a more variable seasonal pattern, and in regions with high birth rates, highly irregular large measles outbreaks may occur. Measles vaccination coverage also reflects the main age of infection, with lower age in low vaccination coverage settings [Moss 2017, Rota 2016]. Neonates are protected by maternal antibodies only in the first months [Rota 2016, Waaijenborg 2013].

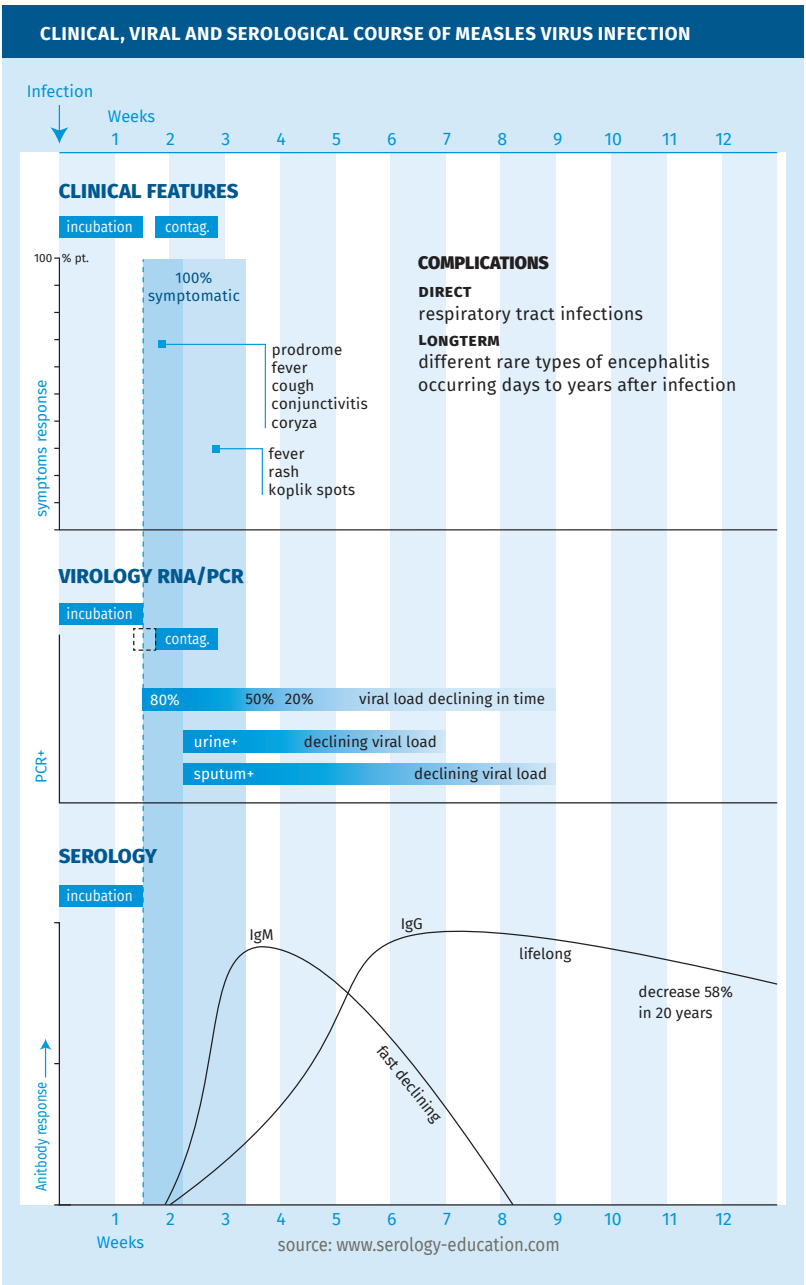
DIAGNOSTIC TESTING

The clinical, viral and serological course are depicted in figure 1.

Techniques

- Measles RNA-PCR can be used on various clinical specimens, such as throat swab, oral fluid or urine sample. Samples for PCR can be collected within 3 days after the onset of clinical signs (exanthema) to 5 weeks for urine or to 7 weeks for sputum [WHO 2018].
- Serology: detection of anti-measles IgM antibodies can be performed using an EIA test to prove a recent/acute infection on a blood sample taken from 4 days after onset of rash. A laboratory diagnosis can also be based on seroconversion or a more than four-fold titer rise in measles virus- specific IgG in paired sera (at least two weeks in between) or collected during the acute and convalescent phase of the disease [WHO 2018, Hubschen 2017, Ma 2019, Helfland 1997]. For prevalence studies IgG EIA's are the first choice.

FIGURE 1.



[**Clinic**: LCI 2020, Chin 2000, Moss 2017, Rota 2016. **Virology:** WHO 2018, Hubschen 2008, Cui 2018, Dietz 2007, Riddell 2007. **Serology:** Davidkin 2008, Riddell 2007, Helfland 1997, Bull WHO 2018, Warrener 2011]

- Avidity testing can be performed using anti-measles IgG antibodies to confirm the duration of time after exposure [Paunio 2000, Mercader 2012]*.

PRACTICAL USE OF SEROLOGY

Screening

Test EIA-IgG measles antibody in case contact of investigations or confirmation of specificity antibodies in a patient with a positive IgM antibody test. However, the current EIA assays have suboptimal sensitivity and therefore have limitations for determine protective antibodies against measles vaccinated individuals [Dorigo-Zetsma 2015].

Suspected infection in immunocompetent child or adult

Suspected infection is tested for the presence of anti-measles IgM antibodies using a measles-specific capture IgM EIA. In breakthrough infections or suspected measles infection in a person with a recent history of travel in a measles endemic region an IgM must be confirmed with a PCR from throat swabs, oral fluid or urine [Bolotin 2017, Cui 2018, Helfland 1998]. However, in infected individuals - previously vaccinated - there is often no IgM response. In this situation the practical first choice to prove infection is PCR on a throat, saliva or urine sample. An IgM test can be performed only if a PCR sample (taken late after onset) is negative.

Suspected infection in immunocompromised child or adult

Patients with measles exposure may not develop clinical signs of measles (fever, skin rash, cough, coryza or conjunctivitis) while measles infection can cause severe and even fatal disease and may not have a detectable IgM response. These patients should therefore be tested with PCR.

- * Avidity testing is used in breakthrough infections (often without IgM response) or if test results are inconclusive and only one serum Is available.

INTERPRETATION OF SEROLOGY

TABLE 1. IN AN IMMUNOCOMPETENT PERSON

IgM	IgG	Interpretation	Action
Negative	Negative	Samples collected too early or no measles virus infection.	Collect samples for PCR if suspect of samples collected too early or request repeat after >2 weeks
Negative	Positive	Past infection or vaccination or recent infection in a vaccinated individual: check history of patient.	If suspect of a recent infection in a previously vaccinated person: collect samples for PCR or collect 1 acute serum and 1 after >2 weeks for evaluation of a rise in IgG titer. Another option could be to test the avidity of the IgG antibodies
Positive	Negative	Recent infection or recent vaccination.	Based on history of patient, collect samples for PCR (see pitfalls) and/or collect paired sera. False positivity: confirm specificity with measles IgG or repeat with another immuno-assay.
Positive	Positive	Recent infection/ vaccination/false positivity.	Confirm with another IgM-EIA, collect samples for PCR or collect paired sera for IgG testing. If no additional samples after the first are available, IgG avidity testing can distinguish between recent infection and false positivity.

* Additional explanation of the interpretation and possible solutions to discriminate between the options can be found in the section "pitfalls".

In symptomatic but vaccinated patients a single serum sample can not provide definite proof of an infection. For diagnostic purpose always collect sample(s) for PCR within 1 week of onset symptoms (see table 1) or use paired serum samples whatever the result of the first sample to prove a fourfold/significant titre rise.

SENSITIVITY AND SPECIFICITY

Sensitivity of serology is best in the convalescence phase 6-14 days after the onset of symptoms (see table 2).

TABLE 2.

	Sensitivity	Specificity	PPV	NPV
IgMcapture	82.8-88.6*	86.6-99.6	88.2-99.6	91.4-95.9
IgG	99	100	100	75.7

*The two figures for IgM are for a low and for a high cut-off point.

According to WHO evaluation, the IgM anti-measles antibody testing had a sensitivity of 75-98.1% and a specificity of 86.6-99.5%, with possible false positives in Parvovirus IgM B19 positive samples. The IgM capture test performed best [Hiebert 2021].

PITFALLS

- In persons previously vaccinated for measles, breakthrough infections can occur, often with relatively mild symptoms. In these cases, measles virus-specific IgM can remain below the detection levels of the available EIA, while measles virus-specific IgG antibodies are detected. In persons suspected of having measles infection, who have been previously vaccinated, either collection of PCR samples or paired serum samples, to detect significant anti-measles IgG titer increase, is recommended [Hahné 2016, Sundell 2019].
- Vaccination with the MMR vaccine can also result in a measles virusspecific IgM response [Helfland 1998] and measles-like symptoms within 2 weeks after vaccination and this does not have to be tested!
- Differentiation between vaccine-derived virus and wild type virus can be achieved through specific measles PCRs and through PCR amplification and subsequent sequencing in order to determine the measles virus genotype [Roy 2017, Tran 2018].

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KEYWORDS

Measles virus, Morbilli