Rubella

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THE MICROORGANISM AND ITS CLINICAL PRESENTATION

Rubella is a contagious respiratory viral infection caused by the rubellavirus. Rubellavirus is an enveloped single stranded positive sense RNA virus belonging to the Matonaviridae family [ICTV 2020]. It was the sole member of the Rubivirus genus, but recently two closely related viruses were discovered in mammals [Bennett 2020].

Up to 50% of infections are asymptomatic or subclinical, especially in children [Leung 2019]. The incubation time ranges between 12 and 23 days (average 1416 days) [Leung 2019, WHO 2021, Lanzieri 2020]. In symptomatic disease, also called "German measles", the initial symptoms following the incubation period typically include lowgrade fever, malaise, lymphadenopathy and an upper respiratory infection for 15 days followed by a brief appearance of a rash [Leung 2019, White 2012]. Forchheimer spots (petechiae on the soft palate) may precede or accompany the rash. The rash is mild and maculopapular, beginning on the face and extending downwards. It occurs approximately 14 to 17 days after exposure and typically lasts three days. Occasionally the rash is accompanied by pruritus [White 2012, Lanzieri 2020]. Rubella is generally a mild, selflimiting infectious disease [Leung 2019]. Enlarged postauricular and suboccipital lymph nodes, which precede the rash, are characteristic of rubella and last for 5–8 days. (https://www.ecdc.europa.eu/en/rubella/factsheet). Definite diagnosis on clinical features is unreliable and needs confirmation.
The vaccine used is a live attenuated vaccine that also can cause a rubellalike disease but is not contagious! Neonatal protection by maternal antibodies is 45 months.

COMPLICATIONS

The real threat arises when acute rubella infection occurs in pregnancy, particularly in the first trimester when it can infect the fetus, which may lead to miscarriage (20%), intrauterine fetal death, premature labour, intrauterine growth retardation, or congenital rubella syndrome (CRS) [Leung 2019, Voordouw 2019, Lambert 2015] producing anomalies in the

developing fetus. Cataract, congenital heart defect, and sensorineural deafness are the classic triad of congenital rubella syndrome [Leung 2019].

In postnatal infections rubella frequently leads to joint symptoms including arthralgia or arthritis in women (up to 70%) along with conjunctivitis, but these are rare in males and children [White 2012, Lanzieri 2020]. Haemorrhagic manifestations (mainly thrombocytopenic purpura) occur in approximately 1 per 3000 cases. Effects may last from days to months, and most patients recover. Encephalitis with an estimated incidence of 1 in 6000 cases is reported and may be fatal. Additional rare complications include granulomas in persons with primary immune deficiencies, orchitis, neuritis, and a late syndrome of progressive panencephalitis [Lanzieri 2020].

EPIDEMIOLOGY

Rubella is a moderately contagious infection, with an estimated basic reproductive rate of 7-8 [LCI 2015]. Postnatal transmission of the virus is primarily by inhalation of droplets or direct contact with naso-pharyngeal secretions from infected persons [White 2012]. The infectious period starts one week before onset of clinical symptoms and continues for one week after development of the characteristic rubella rash [Leung 2019]. Infants with congenital rubella syndrome (CRS) shed large quantities of the rubella virus from their bodily secretions for more than a year postpartum and are highly contagious [White 2012]. Transmission may also occur from persons with asymptomatic or subclinical infection [White 2012], highlighting the challenges of preventing virus transmission.

Rubella affects people globally. In the absence of vaccination, the mean age of rubella infection is 5–9 years with annual seasonal outbreaks usually occurring in the spring. Large epidemics occur every 3–8 years [Lambert 2015]. The last small rubella outbreak in The Netherlands occurred in 2013 with 54 reported cases. Vaccination programs have led to a shift in demography to individuals of childbearing age, which increases the risk of CRS [White 2012]. Antibodies against rubella virus after natural infection persist longer than antibodies mounted after vaccination [Waaijenborg 2013]. Epidemic outbreaks continue to occur, particularly in settings with partial vaccination strategies [Lambert 2015, Abrams 2016], for example the ‘Bible Belt’ in The Netherlands. Especially with inadequate vaccination coverage rubella remains endemic world wide [White 2012].

DIAGNOSTIC TESTING

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

Techniques

- Molecular: Rubella PCR to detect RubellaRNA in throat swab, saliva or urine. Rubella causes a lowlevel, shortlived viraemia which is difficult to detect [Abernathy 2009].*
- Serology: EIA IgM capture has the highest specificity to prove recent infection [Wandinger 2011, Hubschen 2017]. Test >4 days after onset of rash [Abernathy 2009, Kurata 2019]. All commercial immunoassays are calibrated against a WHO international standard, but no other criteria are tested nor standardized [ValoupFellous 2018]. Results can therefore not be compared.
- An IgG EIA with standard reference for intensity of response will confirm specificity or in paired serum samples (one acute and one 2 weeks later) showing a fourfold or substantial increase in antibodies to prove infection. IgG will be positive >4 days after onset rash, increasing rapidly and being high for 23 months then declining slowly but remaining positive for life.**
- IgG-avidity: a commercially available test that proves or exclude a recent infection in pregnancy or in doubtful cases and in absence of a second serum [Böttiger 1997]. This can be requested at the RIVM.

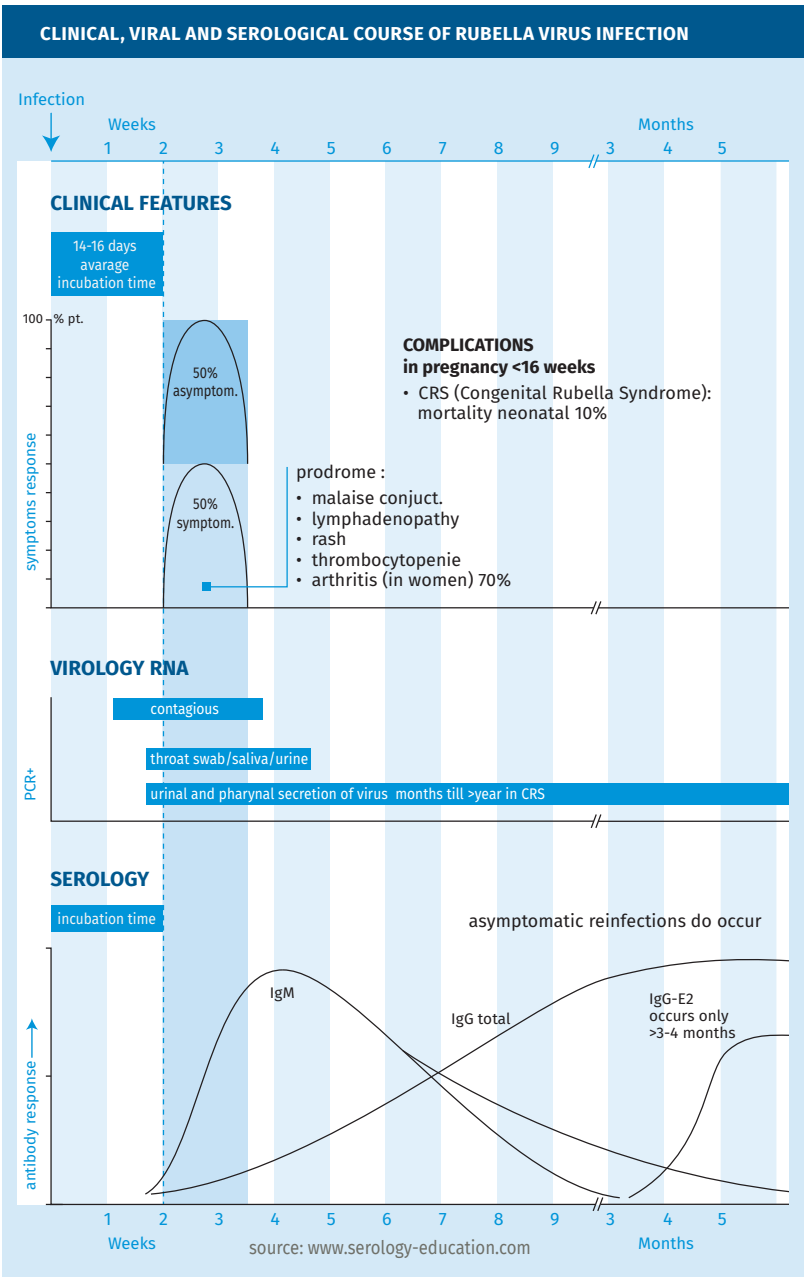
PRACTICAL USE OF SEROLOGY

Screening

Immunity after vaccination or past infection is do with a specific IgG test, validated with a reference. Level of antibody titers are not indicative of protective immunity. Results should always be confirmed in case of Screening complications like CRS. IgM can be positive after vaccination and can stay positive for >1 year [Thomas 1992, Banatvala 1985]. In these cases of possible recent infection confirmation is deemed necessary and infection can be proven by PCRRV or IgGavidity testing on a single serum sample or with a validated IgG EIA on a paired serum sample.

- *Virus culture: as the occasion arises virus can be cultured at the RIVM.
- **IgG-E2: E2 envelope protein in rubella virus (RV) occurs 3-4 months after onset of infection. Can be used in pregnancy to exclude recent infection (used in several European countries). A Commercial EIA is available.

FIGURE 1.



[Hubschen 2017, Dimech 2018, O'Shea 1983, Davidkin 2008, Wilson 2006, Valoup Fellous 2007]

Suspected infection in immunocompetent patients including pregnant women

This is proven by a rubella specific IgM which starts to be positive >4 days and remaining high for 13 months after the onset of the rash. Serum should be collected 530 days after development of rash. If collected within 5 days after the onset of rash or start of symptoms rubella PCR or a paired serum with at least 2 weeks in between is recommended for laboratory diagnosis of a recent infection [WHO 2018, Kurata 2019, Abernathy 2009, Cordoba 1991, Uchino 2020]. Avidity testing in pregnancy can be done to determine the start and duration of infection.

A suspected infection in immunocompromised patients

This needs a RubellaPCRRNA to prove infection. If immunoglobulins are present tests similar to immunocompetent patients can be performed.

Congenital Rubella Syndrome cases

PCR on saliva at birth, postnatal IgM and PCR on urine with followup serology is necessary.

INTERPRETATION OF SEROLOGY

TABLE 1. SEROLOGY IN AN IMMUNOCOMPETENT PERSON WITH CLINICAL SIGNS OF RV INFECTION

IgM	IgG	Most probably interpretation	Action / tests to be done
Negative	Negative	Samples collected too early or no infection	If suspect repeat >2 weeks or collect samples for PCR-RV
Negative	Positive	Past infection or breakthrough-infection	Exclude breakthrough infection after vaccination with paired IgG for titer raise or by collection of samples for PCR-RV
Positive	Negative	Recent infection orfalse positive	Collect samples for PCR-RV or Confirm results with another IgM-EIA (at another laboratory) or collection of an additional second serum sample >2 weeks to evaluate an increase of the IgG titer.
Positive	Positive	Recent infection or false positives or persistent IgM	IgG-avidity testing or PCR-RV to exclude vaccination or Collection of additional serum sample >2 weeks to evaluate increase IgG titer

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 after the onset of symptoms (see table 1) or use paired serum samples whatever the result of the first sample to prove a fourfold/significant titer rise.

TABLE 2. SEROLOGY IN A NEWBORN CHILD (<6 MONTHS) SUSPECTED OF CRS

IgM	IgG	Interpretation	Action
Negative		Child below <1 months of age: negative or sample might be too early, repeat testing after 1-2 months	PCR RV on throat swab and urine
Positive		CRS probable	Confirm by PCR RV on throat swab and urine

[Voordouw 2019].

SENSITIVITY AND SPECIFICITY

Specificity of the commercially available rubella IgM kits in general is high, but sensitivities depend very much on people, time after onset, cutoffs used and format of antigens [WHO 2018, Echevarria 1985]. WHO has collected sera from all over the world and assessed the performance of EIA's against PCR confirmed cases. The results of these comparison studies will be presented soon [PubMed (nih.gov) 2021].

TABLE 3.

	Sensitivity*	Specificity	PPV	NPV
IgM	75-80%	90%	80%	100%
IgG	60-80%	>95%	100%	60%
PCR-buccal	60%	100%		

PITFALLS

- See for pitfalls [Best 2002] and cross reactions [Lefrere 1987] the general chapter "Pitfalls in serology".
- Rubella has no specific clinical or pathognomonic presence.

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KEYWORDS

Rubella virus, German measles, three-day measles, Congenital rubella syndrome