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Consequences of perinatal infections with rubella, measles, and mumps

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Measles, mumps, and rubella have recently taken the stage as re-emerging diseases of public health importance — particularly in regards to the consequences seen with perinatal infections. Effective vaccination strategies have successfully reduced the spread of measles, mumps, and rubella in the United States, but a current trend of increased vaccination hesitancy, fear of vaccine safety, and spread of misconceptions surrounding the science of vaccines have led to a relative resurgence of these diseases in the developed world. This article aims to explore why measles, mumps, and rubella should continue to be on the radar of medical professionals, and why the study of these diseases is important for understanding other teratogenic viruses of public health importance.

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Introduction

Once believed to be largely eradicated from the Western Hemisphere, measles, mumps, and rubella (MMR) are taking the spotlight in the national conversation about re-emerging vaccine-preventable diseases. Generally, the MMR viruses are thought of in context together, since a commercially licensed multivalent vaccine became available in the 1971 [1]. Although these three viruses share clinical similarities, they have unique characteristics that contribute to their public health importance. All three cause upper respiratory symptoms, lymphadenopathy, maculopapular rashes, and adverse complications when infection occurs in pregnant women. Although Rubella infection results in the most severe disease for the developing fetus, perinatal disease is also very serious with late-term infection with mumps and measles viruses.

The contemporary world has witnessed a decline in MMR cases since the development of effective multivalent vaccines in conjunction with massive inoculation campaigns [2]. However, the recent emergence of Zika virus in the Americas demonstrates the need for global dialogue that includes exploration of the threat of other viruses that have devastating gestational and perinatal consequences. There are five classifications of vertically transmitted human infections that account for 2–3% of congenital anomalies known by the acronym "TORCH" (diseases caused by **T**oxoplasmosis, **O**ther [syphilis, varicella-zoster, parvovirus B19], **R**ubella, **C**ytomegalovirus [CMV], and **H**erpes infections). Of the TORCH diseases, rubella provides a unique opportunity to study the historical, biological, and societal consequences of a devastating perinatal disease. Vaccination remains the most efficacious means of reducing transmission of the MMR viruses, including rubella. However, factors such as an increasing public fear of vaccine adjuvants, the concern of deleterious effects of superfluous childhood vaccine administration, and the constant spread of electronic (mis)information has increased the probability of increasing clinical cases of vaccine-preventable diseases, including MMR.

Rubella

Rubella molecular epidemiology

Of the MMR viruses, rubella is a unique member of group A *Togaviridae* family, and is the sole occupant of the genus *Rubivirus*. There is one circulating serotype, with two recognized clades composed of 10 and 3 genotypes in clade 1 and 2, respectively [3,4••]. Sequence diversity of the E1 protein encoding region is used to determine the phylogenetic relationship of viruses [4••,5,6•]. Of circulating rubella strains, only four of the recognized genotypes are commonly detected and include 1E, 1G, 1J, and 2B. Of these four genotypes, 2B is most common globally; 2B and 1E have the widest distribution [4••,5]. Recent work has shown that genotype 2B is responsible for causing symptoms characteristic of congenital rubella syndrome (CRS) in children; however, since genotypes 2B and 1E have such a wide geographic distribution, it is difficult to trace the origin of imported cases belonging to these genotypes [6•]. Eradication efforts rely heavily on being able to trace the source of an outbreak or imported case of rubella, thus it has been suggested that characterizing circulating rubella strains by sublineage would be beneficial to tracking global prevalence and tracing back outbreaks [6•,7].

Rubella clinical disease

Direct transmission of the rubella virus (RV) occurs through nasopharyngeal contact with infected respiratory droplets; the virus then replicates in the nasopharynx and associated lymph nodes [8–10]. Rubella virus infection in adult patients causes nonspecific signs during the prodrome period and may be asymptomatic in up to 50% of cases [10]. The first sign of RV infection is usually fever, and the prodrome period may be preceded by mucosal petechiae on the soft palate [11,12]. A maculopapular rash begins in the cranial/cervical regions and progresses distally (Table 1). Unlike both measles and mumps, arthralgia and arthritis are frequently seen in adult cases. Complications from rubella infection are rare but occur most commonly in adults, causing chronic arthritis, encephalitis, and hemorrhagic syndromes [7].

Compared to the other MMR viruses, perinatal rubella infection carries the greatest risk to pregnant women and neonates [9]. Although young children may experience only mild symptoms of disease, infection of the developing fetus often results in interference of fetal growth and development through mitotic interruption, directly damaging a variety of organ systems [2,8,9,13,14]. The severity of CRS lesions depends on the point of gestation during which the mother was infected [7,9,14]. If infected prior to 11 weeks of gestation, a pregnant woman carries an extremely high chance (85–90%) of transplacentally infecting her child [3,7,15]. During first trimester infection, any fetal organ may be affected, often resulting in death of the fetus and/or spontaneous abortion [3,8,10–12]. Children who are infected early in gestation and survive until parturition are often born with severe transient defects and permanent congenital malformations, such as microcephaly, cardiac defects, deafness, ocular manifestations, and systemic organ damage [2,8,10,16]. After 20 weeks of gestation, infection most often results in deafness, while other systemic malformations and complications are rarely seen; *in utero* recovery of the fetus may also be possible at this time [7,17••]. The risk of vertical transmission gradually decreases as a pregnancy progresses, until week 31 when the risk begins to increase again [3]. By week 36, there is almost a 100% chance of vertical transmission if the mother is infected [3]. Children who are born without clinical signs of CRS, irrespective of when they were infected *in utero*, may develop delayed manifestations of the disease (i.e. diabetes mellitus, encephalopathies, autism) and may shed virus in bodily fluids for over a year [3,8].

Infection at any point throughout gestation can lead to persistent fetal infection, albeit with limited

Table 1

Comparison of viral characteristics, disease progression, clinical signs, and complications of measles, mumps, and rubella [7,8,16,40,52]

	Measles ("rubeola")	Mumps	Rubella ("German measles")
Virus type	− sense ssRNA	− sense ssRNA	+ sense ssRNA
Family	*Paramyxoviridae*	*Paramyxoviridae*	*Togaviridae*
Genus	*Morbilivirus*	*Rubulovirus*	*Rubivirus*
Reservoir	Human	Human	Human
Transmission	Respiratory droplet	Respiratory droplet	Respiratory droplet
Incubation	10–12 days	12–25 days	14 days
Replication site	Nasopharynx, local lymph nodes	Nasopharynx, local lymph nodes	Nasopharynx, local lymph nodes
Prodrome length	2–4 days	3–5 days	1–5 days (adults)
Clinical signs	• Fever • Cough, runny nose, conjunctivitis • Lympadenopathy • [a]Koplik spots • Maculopapular rash (coalescing)	• Fever • Non-specific • [a]Parotitis • Respiratory signs • Asymptomatic (up to 20% of cases) • Maculopapular rash	• Fever • Subclinical/asymptomatic (up to 50% of cases) • Respiratory signs • Lymphadenopathy • Forchhiemer spots • Maculopapular rash (often pruritic) • Arthralgia/arthritis
Complications (adults)	• Non-specific • Diarrhea • Pneumonia • Encephalitis • Subacute sclerosing panencephalitis (SSPE) – rare	• Orchitis (males) • Oophoritis (females) • Pancreatitis • Transient deafness • Aseptic meningitis	• Encephalitis, panencephalitis • Hemorrhagic syndromes • Orchitis (males)
Complications (children)	• Diarrhea • Pneumonia • Otitis media • Encephalitis	• Rare	CRS (organ damage, birth defects, developmental defects, etc.) Encephalitis Deafness
Complications (pregnancy)	• Abortion/premature delivery • Fetal death • Low birth weight	• Abortion/premature delivery • Fetal death	• Abortion/premature delivery • Fetal death • Congenital defects

[a] Denotes pathognomonic signs.

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