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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.

histopathology [3,14,18,19]. Frequently, non-inflammatory damage to cardiovascular endothelial tissue can be found microscopically. This persistent infection of fetal endothelial tissue is proposed to result in interrupted vascular function, leading to enhanced vertical transmission of the virus via the placenta, as well as some of the most common manifestations of clinical CRS (including cardiac defects, neurodegenerative changes, and organ damage) [19]. Placental insufficiency caused by interrupted vascular function may also contribute to fetal loss and retardation of fetal growth [11,14,19].

Pathophysiology of rubella virus and the developing fetus

While other mosquito-borne alphaviruses demonstrate high cell culture virulence with relatively short in vivo incubation periods, rubella virus actually demonstrates high persistence and low viral replication. In vitro cellular damage and death due to apoptosis is a latent event, and recent work indicates that the rubella capsid protein is highly efficient at blocking apoptosis mediated through multiple levels of cellular events [20]. These include, but are not completely dependent on, direct interaction with pro-apoptotic proteins such as Bax [21]. Conversely, the capsid is pro-apoptotic in direct interaction with mitochondria resulting leakage of Cyt-C and mitochondrial inactivation [21–24]. This activity is highly related to phosphorylation state of the capsid and may, in fact, afford the virus protection from the innate immune pathways that destroy foreign RNA [21,24]. This inhibition of these pathways is hypothesized to lead to unimpeded establishment of infection. Exact mechanisms of end-stage malformation may be related to these cellular pathways or include many others depending on cell type.

Measles

Measles molecular epidemiology

Circulating strains of measles virus are represented by 23 recognized genotypes contained within eight clades, designated A through H [25,26]. Three patterns of measles genotype distribution have been identified through study of data obtained though the World Health Organization database "LabNet" [25]. The first pattern occurs in regions with endemic transmission of measles where one or more endemic genotype, with multiple circulating lineages within the endemic genotype(s), cause the majority of infections. In regions where endemic transmission has been eliminated, an imported virus of becomes the main circulating strain. Finally, in countries where endemic control is limited by vaccination, but occasional outbreaks are seen in susceptible populations, single genotypes may be reintroduced with sustained transmission. In Africa, genotype B2 has been most widely detected [27–31]. In the Americas, genotypes B3 and D4 have been seen most frequently, however other genotypes have been introduced [32•,33]. Genotypes D4 and D5 have recently been responsible for large numbers of clinical cases in Europe, with evidence of sustained activity [25]. Middle Eastern countries have sustained transmission of the D4 genotype [34–37]. Genotypes D4 and D8 have been isolated in endemic outbreaks on the Indian subcontinent, while genotypes D5 and G2 have been predominated in Southeast Asia [25]. Endemic transmission of genotype H1 has also occurred across Asia [25].

Measles clinical disease

Measles typically begins with infection of the epithelium of the nasopharynx following contact with infected droplets [38–40]. The virus then replicates and spreads to local lymph nodes via dendritic cells. An initial fever generally accompanies the first wave of viremia within three days post-infection, followed by a second wave of viremia (Table 1). In most adult patients, clinical signs (particularly respiratory signs) follow the secondary viremia and mark the beginning of the prodrome period [40]. As the disease progresses, generalized lymphadenopathy and pathognomonic Koplik spots on the mucous membranes become apparent, followed by the eruption of a maculopapular rash which begins in the cranial/cervical region and spreads distally along the body and limbs [40]. Complications can be non-specific and occur most frequently in adults over 20 years of age. In cases where the patient suffers from impaired immune responses, viral RNA may persist in both blood and organ tissue for months following resolution of clinical infection [39,41,42]. In children, this persistent viral RNA can lead to devastating neurological complications and increased chances of infection due to prolonged immunosuppression [42].

One of the most serious complications is the development of one of four types of measles associated encephalitis, which the U.S. Centers for Disease Control and Prevention (CDC) estimates is the cause of neurological sequelae in 25% of clinical cases [39,43]. Primary measles encephalitis affects 0.1–0.3% of all measles patients, when the virus invades neurological tissue during the rash phase of infection [43]. Acute post-measles encephalitis is the most common neurological sequelae associated with measles, and occurs in approximately 0.1% of pediatric cases due to immune mediated inflammation in neurological tissues [43–49]. Measles inclusion body encephalitis occurs within one year of infection and most frequently affects immunodeficient children. This form of measles encephalitis occurs when viral RNA persists within brain cells following ineffective clearance by the immune system, and generally carries a serious prognosis (mortality ~75%) [43]. Finally, subacute sclerosing pancencephalitis (SSPE) affects children more frequently than adults (~0.02% of pediatric cases under one year of age) and occurs when the virus is not adequately cleared from the body [43,47]. The virus mutates, resulting in persistent infection of the grey matter followed by

the white matter (and continue on to affect the brainstem), and often manifesting as severe neurological effects including cognitive and behavioral changes, as well as death [43].

Mumps

Mumps molecular epidemiology

There are 12 recognized genotypes of the mumps virus, denoted A-N [50]. The SH gene, is considered to be the most variable in the mumps genome, and is usually recommended for genotyping (but not recognized as a virulence factor) [50]. Virulence of the mumps virus is generally attributed to the hemagglutinin-neuraminidase (HN) and the fusion (F) surface proteins. Mutations in the sequences coding for the HN protein often lead to increased neuroinvasiveness, while mutations in the sequences coding for the F protein typically lead to changes in the pathogenicity of the virus but not increased neurological disease associated with mumps infection [50,51]. Like measles, specific mumps virus genotypes appear to circulate in their endemic regions, making it possible to trace imported cases. Since 2010, approximately half of the globally reported mumps cases have been attributed to circulation of genotype G; genotypes H, C, F, K, and D have also been detected [50].

Mumps clinical disease

Mumps infection generally begins in the nasopharynx, when direct contact is made with respiratory droplets [52]. Viremia occurs two to three weeks following initial infection, during which the virus spreads throughout the body [52]. Infection causes nonspecific signs in the prodrome period, often progressing to parotitis that can affect multiple salivary glands simultaneously [7,52–55]. Unlike measles, mumps is known to asymptomatically affect as many as 20% of infected cases [7]; those who are asymptomatic may still be contagious [52]. Unfortunately, it is currently unknown how vaccination changes the clinical manifestation of disease, and many cases likely go unreported [55]. The most common complications for adults include pancreatitis, transient deafness and orchitis in males, and oophoritis in females with limited apparent effect on fertility [7,52,55,56•]. Prior to license of the first mumps vaccine, transient deafness was known to affect males disproportionately when compared to females, and up to 10% of all symptomatic adults were likely to experience aseptic meningitis [52].

Like measles, mumps infection during the first trimester of pregnancy is associated with higher incidence of spontaneous abortions and fetal death [7,55]. However, infection during pregnancy is not believed to be associated with specific congenital abnormalities [55]. Symptomatic infection tends to be more common in adolescent children and young adults, and outbreaks usually occur in primary school or college environments [7,52,54]. Mumps differs from measles in that children tend to show classical signs of disease progression and adults are more likely to experience adverse complications [7,55].

Vaccination strategies for the MMR viruses

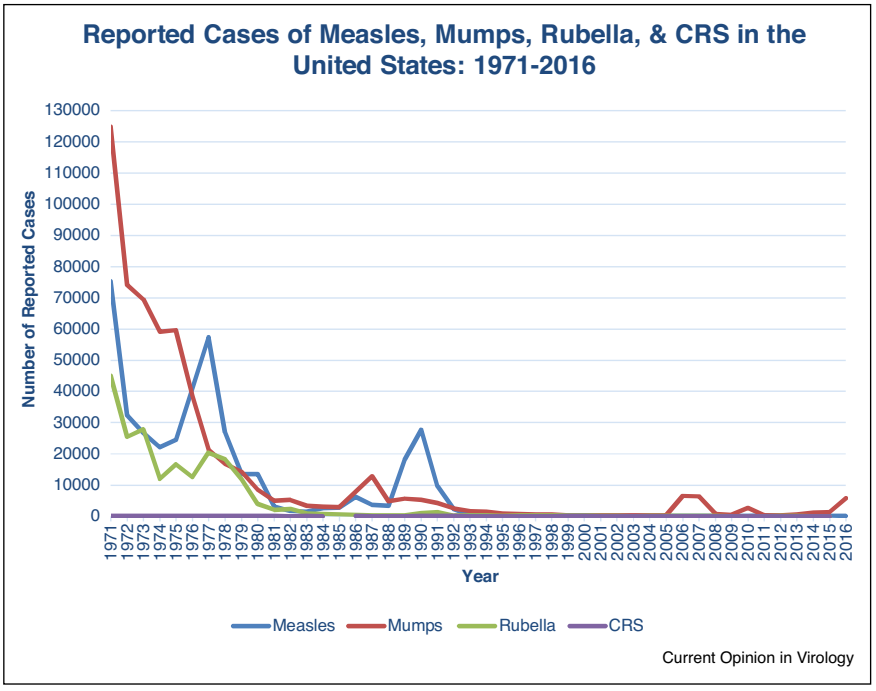
Prior to the late 1960s, rubella outbreaks were commonplace. In 1964, an epidemic in the U.S. caused devastating disease in children with over 20,000 affected newborns, resulting in an estimated $840 million invested in treating the sick and preventing new cases [8]. In 1966, rubella became a nationally notifiable disease in the U.S. [8]. Vaccination proved to be an effective method for controlling endemic rubella cases, and incidence of both rubella and CRS steadily declined from the 1970s until 2004 when the U.S. was declared free of the virus [8,16]. Between 2004–2012, only 85 cases of rubella were reported and only six of those resulted in CRS; all of these cases were imported from other regions of the world [57]. In April 2015, the WHO declared the entire Region of the Americas to be free of endemic transmission [15]. The MMR vaccine for rubella affords long-term, effective immunity against the virus, resulting in few localized outbreaks or imported cases in the Americas since the 1990s.

Prior to the licensure of the MMR vaccine in the late 1960s, reportable cases of mumps exceeded 200,000 per year [52]. There is evidence to suggest that immunity to mumps may wane after the second dose of the MMR vaccine, explaining why vaccinated college-aged individuals have seen the highest incidence in recent history [54,58•,59]. However, in past outbreaks, communities where two-dose MMR vaccination status was high seemed to be well protected against the spread of infection [60].

Prior to the first licensed vaccine entering the market in 1963, it was estimated that 90% of all children under the age of 15 years would succumb to measles infection [40]. Often fatal in developing countries lacking access to proper supportive care services, complications frequently affect children under five years of age [40]. Malnourishment and vitamin A deficiency may predispose neonates to particularly high rates of infection and the CDC estimates that as many as 25% of infections in children may end in fatality [40]. Although vaccination has reduced prevalence of the disease by approximately 95%, relative resurgence of the virus was seen in the late 1980s and again in the late 2000s, with cases generally attributed to vaccine failure in school-aged children [40].

Measles continues to cause outbreaks throughout the world, with the most severe and expensive complications affecting children [61]. Most infections occur in cases with unknown or incomplete vaccination histories [62••]. Likewise, mumps continues to be a global disease of concern. Recent evidence has pointed to a shift in the

Figure 1



Reported cases of measles, mumps, rubella, and CRS in the United States from 1971 to 2016. All MMR diseases show a decreasing trend in reported clinical cases following introduction of the multivalent MMR vaccine in 1971. Spikes in the number of cases of measles and mumps can be seen in the late 1980s and early 1990s, as well as the 2000s. Modern reported cases are dramatically decreased from pre-vaccination times.
*Data for mumps, rubella, and CRS from 2007 to 2016 obtained from the WHO Vaccine Preventable Diseases Monitoring System [59].
** All other data obtained from the CDC Summary of Notifiable Infectious Diseases [73].

genotype responsible for outbreaks in the U.S. and across Europe [53]. Although considered eradicated from the Western Hemisphere, Rubella and CRS also carry global economic consequences – the true extent of which is unknown [63••].

Although vaccination campaigns have been responsible for decreasing the transmission of perinatal communicable diseases, the battle has not yet been won. Figure 1 illustrates the number of reported MMR cases in the U.S. from 1971 until 2016. The WHO has set a goal for eradication of MMR and CRS by 2020 [2,62••], but challenges to attaining this goal remain. Vaccination hesitancy is proving to be most problematic in the U.S. and Europe, while civil unrest and weak healthcare infrastructure remain significant hurdles in the developing world [2]. Elimination of rubella from the Western Hemisphere implies that future outbreaks in the U.S. will likely be due to imported cases [16]. There remains concern that recent trends towards lower vaccination coverage – especially in school-aged children and women of childbearing age – may leave people in the U.S. vulnerable to infection.

Conclusions

Measles, mumps, and rubella are important viruses that represent a massive threat to public health. The recent Zika virus outbreaks have shown the world just how heartbreaking the effects of teratogenic viruses can be. With lasting neonatal and pediatric consequences, the potential for the MMR viruses to cause devastating health outcomes should not be underestimated. While effective vaccines do exist, the relative resurgence of these diseases exemplify how important it is to continue to address the multifaceted and complex reasons expressed by parents hesitant to immunize their children with the MMR (and MMRV) vaccine. History has proven that widespread vaccination campaigns are effective intervention strategies responsible for halting the spread and effects of these diseases. As a global community, we cannot afford to remain passive. With 2020 rapidly approaching, current trends in MMR outbreaks make the WHO target goal of worldwide eradication unlikely. As long as vaccination failure continues to occur through the spread of misinformation and misconceptions, these preventable diseases will persist and we will continue to see devastating perinatal consequences.

Conflicts of interest

None.

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- •• of outstanding interest

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