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Successes and challenges for preventing measles, mumps and rubella by vaccination

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The measles, mumps and rubella (MMR) vaccine has an outstanding safety record and is highly efficacious. High coverage with MMR has led to the elimination of endemic measles, rubella, and congenital rubella syndrome in the US. The biggest challenges to global measles and rubella control and elimination are insufficient vaccination coverage globally and increasing hesitancy. Despite high two dose coverage rates, mumps has made a resurgence in the US and other countries. Mumps outbreaks have occurred primarily in close contact, high-density settings and most cases had received a second dose 10 or more years previously. Waning humoral immunity and antigenic variation of circulating wild-type mumps strains may play a role in the mumps resurgence.

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Introduction

Measles, mumps, and rubella (MMR) vaccine was licensed in the United States in 1971; MMR contains three live attenuated viral vaccine strains. MMR vaccine has an outstanding safety record, and high coverage with MMR has led to the elimination of endemic measles and rubella in the US (Figure 1) and to a substantial reduction in the number of mumps cases compared to the pre-vaccine era. MMR vaccine is used in 121 countries [1]; some countries are using MR or M based on the status of their measles and rubella control programs. In this report, we provide an update on the status of prevention of the three diseases and describe the unique challenges associated with controlling these viral infections by vaccination.

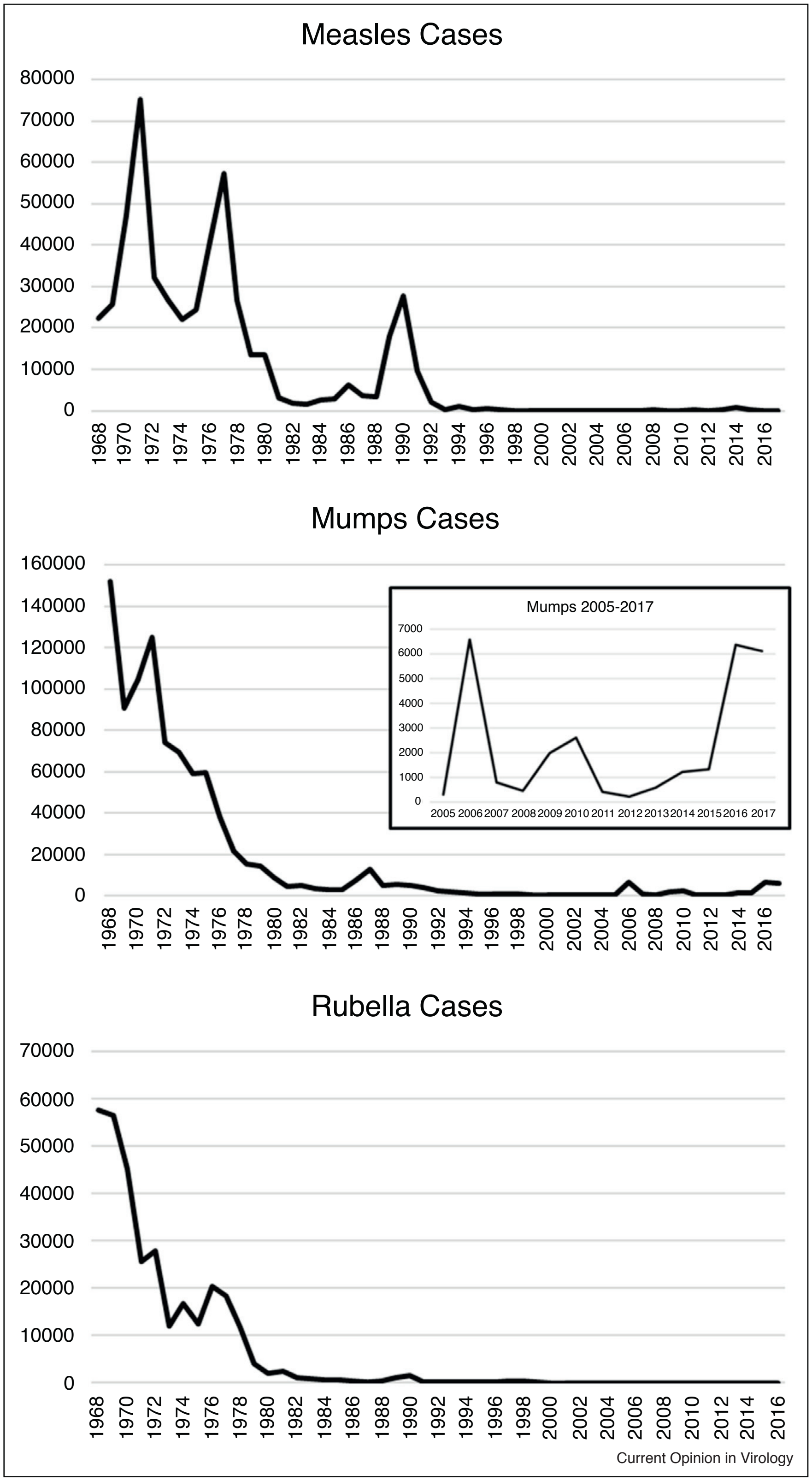
Measles

Measles virus (MeV), a member of the genus *Morbillivirus* in the family *Paramyxoviridae*, causes fever, a maculopapular (non-vesicular) rash and cough, coryza (rhinitis) and/or conjunctivitis. The prodrome, with non-specific symptoms including fever, malaise, sneezing, and coughing, begins approximately 10 days after infection, followed by the onset of rash around day 14. MeV is spread by inhalation of respiratory droplets; patients are considered infectious from four days before to four days after rash onset [2••]. In industrialized countries, the case fatality rate for measles is approximately 0.1% [3]; however, in developing countries, case fatality rates can exceed 5% [3]. In addition to the more frequent complications of the acute illness, such as pneumonia and diarrhea, MeV causes rare but severe neurologic sequelae, including subacute sclerosing panencephalitis (SSPE). SSPE is a persistent infection of the central nervous system that develops 7–10 years after the acute measles infection [4]. A study from the U.S. estimated the incidence of SSPE to be 22/100 000 measles cases [5].

MeV is a single sense, negative stranded RNA virus with a genome size of 15 894 nucleotides [2••]. While MeV is considered monotypic, multiple genetically distinct lineages of wild-type virus have been described [6]. The World Health Organization (WHO) currently recognizes 24 genotypes of MeV based on the sequence variation of the 450 nucleotides that code for the 150 amino acids at the carboxyl terminus of the nucleoprotein (N-450) and the complete coding sequences of the H gene [7]. Sequence analysis has been used to track transmission pathways, characterize endemic genotypes, verify lack of endemic transmission, and to distinguish between wild-type infection and vaccine reactions. In addition, sequencing results show that the measles vaccine does not cause SSPE. Antigenic variations between wild-type and vaccine strains have been described [8]. However, the necessity for conservation of the receptor-binding domains on the H protein limits antigenic drift and explains why the measles vaccines are highly effective against currently circulating wild-type viruses [9•].

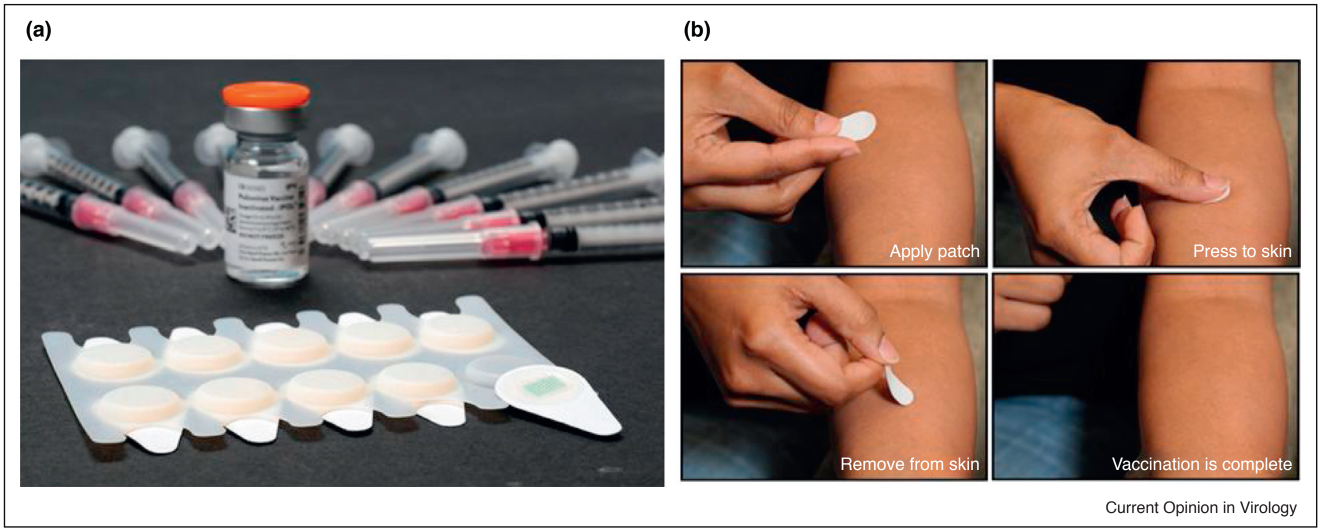
Because of the high R_0 of 12–18, measles elimination requires high levels of population immunity [2••]. This is achieved by coverage with two doses of measles-

Figure 1



Measles, mumps, and rubella cases in the United States, 1968–2017. MMR vaccine was introduced in 1971 with a routine second dose recommendation for 1989. Insert in second panel shows number of mumps cases for 2005–2017. Note that significant drops in incidence of

Figure 2



Development of microneedle patches for delivery of measles containing vaccine. Microneedle patches are shown in the foreground panel A, with a vial of vaccine and examples of traditional hypodermic needles shown in the background. Panel B shows how microneedle patches can be self-administered to a person's forearm (http://drugdelivery.chbe.gatech.edu/gallery_microneedles.html; Photo credit: Gary Meek, Georgia Tech).

containing vaccine (MCV). Endemic measles was eliminated from the United States in 2000 [10], but outbreaks resulting from importations continue to occur. The annual incidence of measles was less than one case per 1 000 000 from 2000 to 2015, with 69.5% of cases in unvaccinated persons, 17.7% of cases in persons with unknown vaccination status, and 12.9% of cases in vaccinated individuals [11]. Only 17% of importations caused outbreaks with three or more cases, indicating that vaccination coverage is high enough to disrupt transmission [12].

Countries in all six WHO regions have adopted goals for measles elimination by or before 2020. Worldwide, the estimated coverage with the first dose of measles-containing vaccine (MCV1) increased from 72% to 85% and the estimated coverage with a second dose (MCV2) increased from 15% to 64% from 2000 to 2016 [13]. In 2016, 63% of countries had $\geq$90% coverage with MCV1. In 2016, 31 countries provided MCV2 during vaccination campaigns, called supplementary immunization activities (SIAs), while 164 countries offer MCV2 as part of their routine health services. The increase in vaccination coverage lead to an 84% reduction in the estimated number of deaths from 550 100 to 89 780 over the same period [13]. A recent expert review concluded that, although significant advancements toward elimination had been made, progress had slowed [14••].

The biggest challenges to measles control are insufficient vaccination coverage globally and increasing hesitancy. Concern about vaccine safety continues to threaten herd immunity in many countries [15–17], despite a large body of research demonstrating the safety of measles vaccines [18–22]. In addition, vaccine hesitancy may cluster geographically [23], creating pockets of susceptible persons at risk for measles outbreaks. Measles remains endemic in many regions of the world, including many European countries [13]. Travelers to and from these regions continue to import measles into countries that have eliminated measles. Increases in global MCV1 coverage have stagnated since 2009 and vaccination systems and surveillance efforts must improve to achieve measles elimination goals [10,13]. Current measles vaccines are safe and effective; however, alternative delivery methods that eliminate the need for cold chain transportation and injection could improve vaccine delivery in resource-limited settings. The development of microneedle patches (Figure 2) for the delivery of measles and rubella vaccine may improve vaccination coverage and support measles elimination efforts [24,25••]. Improving coverage in endemic settings will require significant financial investments and increased country ownership [14••].

Mumps

Mumps virus (MuV), a member of the family *Paramyxoviridae*, genus *Rubulavirus* causes an acute viral disease

(Figure 1 Legend Continued) measles and rubella occurred before MMR introduction in 1971 due to use of monovalent measles and rubella vaccines (Centers for Disease Control and Prevention. National Notifiable Diseases Surveillance System, 2017 Annual Tables of Infectious Disease Data. Atlanta, GA. CDC Division of Health Informatics and Surveillance, 2018. Available at: https://www.cdc.gov/nndss/infectious-tables.html).

characterized by fever, swelling and tenderness of one or more salivary glands, most typically the parotid gland. MuV is spread by respiratory droplets and is less infectious than measles or rubella (R_0 4–7). Nonspecific prodromal symptoms precede parotitis by several days and include myalgia, anorexia, malaise, headache, low grade fever, and vomiting. Approximately 30–40% of mumps infections produce parotitis, 20–30% of infections are asymptomatic, and 50% are associated with nonspecific or respiratory symptoms. Parotitis can be unilateral or bilateral and complications can occur with or without parotitis and include orchitis, encephalitis, meningitis, oophoritis, mastitis, and sensorineural hearing loss. The average incubation period is 16–20 days, but cases may occur from 12 to 25 days after exposure. Mumps is most infectious several days before and after parotitis onset and most transmission likely occurs before and within five days of parotitis onset [26]. Transmission also likely occurs from persons with asymptomatic infections and from persons with prodromal symptoms, contributing to difficulties in identifying and containing disease.

MuV is a negative sense, single stranded RNA virus with a genome size of 15 384 nucleotides. The WHO currently recognizes 12 genotypes of MuV, assigned letters from A to N (excluding E and M), which are based on the nucleotide sequences of the small hydrophobic (SH) and haemagglutinin-neuraminidase (HN) genes [27]. There is only one serotype of MuV so antibody generated in response to infection with one strain of the virus can recognize genetically divergent strains [28,29]. Variation in the neutralizing antibody response to vaccination is observed such that two to six fold higher titers may be needed to neutralize wild-type strains compared to the JL vaccine strain.

Recent studies have indicated that mumps memory B cell frequencies are low compared to measles and rubella and mature mumps IgG avidity indices were in the 40–60% range, lower than measles which had a mean avidity index of 80% [30,31•]. In addition, there is no defined correlate of immunity for mumps disease, making it difficult to reliably predict if vaccinated persons are protected. Neutralization assays are considered a reasonable measure of immunity since they measure functional neutralizing antibodies. Serologic IgG assays typically used for immunity testing may overestimate immunity since they measure antibody to the nucleoprotein, which is the predominant antibody produced in response to vaccine but is non-neutralizing.

Immunization with mumps containing vaccine remains the best way to prevent mumps infection. In the U.S., the mumps vaccine was introduced in 1967 and recommended for routine use in 1977. In 1989 a second dose of MMR was recommended for enhanced measles control and by the early 2000's there was a 99% decline in mumps cases with a record low of 231 cases reported in 2003 [32]. Unexpectedly in 2006, the U.S. experienced the largest mumps outbreak in almost 20 years (6584 cases) [32] (Figure 1). In contrast to measles where cases are typically identified among unvaccinated persons, the majority of mumps outbreak cases have been observed in adults that received two MMR doses [32]. From 2006 to the present time, outbreaks have continued and, from 2016 through 2017, over 12,000 cases of mumps were reported in the US [33].

Immunization coverage estimates of 79–100% are believed to be necessary for herd immunity. Despite US two dose coverage rates >90% and dramatic decreases in mumps cases, mumps has made a resurgence in the US and other countries with high two dose coverage. Mumps outbreaks have occurred primarily in close-contact, high-density settings such as colleges, schools, and sports teams. Most cases in 2006 had received a second dose 10 or more years previously [34]. Waning humoral immunity, and antigenic variation of circulating wild-type mumps strains may play a role in susceptibility and have been proposed as factors contributing to the mumps resurgence.

Mumps outbreaks have occurred in US and internationally among both vaccinated and unvaccinated persons. Low vaccine coverage and lack of vaccination due to vaccine hesitancy are a risk factor for mumps outbreaks and unvaccinated persons with overseas travel have been the source patients for many of the recent US outbreaks [35–37]. Unimmunized persons shed more virus in urine than vaccinated persons [38] and have a higher rate of complications [39•]. Primary vaccine failure is not likely responsible for current outbreaks among two-dose recipients since seroconversion rates are 92–95% after one dose and approximately 95–100% after two doses. Most cases among two dose vaccinated populations appear to be due to secondary vaccine failure and likely the result of long-term waning that may have been masked previously by subclinical boosting through exposure to wild-type virus. Recently, the Advisory Committee on Immunization Practices (ACIP) reviewed the available epidemiological and laboratory data on the effect of a third MMR dose on mumps and determined that a third dose of MMR vaccine was safe and had at least a short-term benefit for persons in outbreak settings [40]. A recommendation was given that persons previously vaccinated with two doses of a mumps-containing vaccine who are identified by public health authorities as being part of a group or population at increased risk for acquiring mumps because of an outbreak should receive a third dose of a mumps virus–containing vaccine to improve protection against mumps disease and related complications. Expanding and improving vaccination coverage and global surveillance for mumps particularly in developed countries with vaccination programs will also be necessary to prevent outbreaks.

Rubella

Rubella virus (RuV) is a member of the *Togaviridae* family, genus *Rubivirus*. RuV virions are about 70 nm in diameter and are composed of a positive-strand RNA genome (~9760 nucleotides), the viral protein C, and a viral envelope containing two viral glycoproteins, E1 and E2 [41].

RuVs currently circulating in the world can be divided into two clades differing by about 10% at the nucleotide level [42,43]. Groups of related viruses within the clades have been classified by nucleotide sequences into 12 recognized genotypes and one provisional genotype [44]. There is sufficient subgenotype clustering of RuV sequences to allow lineages to be defined, although a formal nomenclature for these has not been adopted [45•]. Immunity to one genotype of RuV has so far proved sufficient to protect against clinical disease caused by other genotypes of RuV.

Postnatal rubella is characterized by acute onset of a generalized maculopapular rash with mild fever and may include arthritis or arthralgia, lymphadenopathy, and conjunctivitis. Because disease caused by rubella virus is often mild, about 50% of postnatal rubella cases do not present clinically.

A fundamental property of rubella virus, crucial to its clinical significance, is its ability to replicate as persistent infections. In 1941, N. McAlister Gregg first recognized that cataracts in children followed maternal rubella during gestation [46]. The association between congenital rubella infection and a spectrum of significant birth defects including cardiovascular abnormalities and cataracts (congenital rubella syndrome (CRS) is now accepted. RuV is the most potent infectious teratogenic agent yet identified. When rubella occurs in a pregnant woman in the first 11 weeks of gestation, there is a high likelihood of defect(s) in the infant (about 90%). After 18 weeks, the likelihood of birth defect is much lower, although the infant may still be born with a rubella infection. By definition CRS requires a live birth; thus miscarriages and stillbirths associated with rubella infection are not counted as CRS. Multiple cell types can be affected including, endothelial cells, neurons, cardiac and interstitial fibroblast and epithelial cells of lung, kidneys and ciliary body of the eye [47]. Rubella infection of these cell types is consistent with abnormalities seen in CRS. Persistent rubella infection in CRS may result in additional clinical problems presenting later in life, possibly due to direct damage or because of immunopathological mechanisms.

Good suspect CRS case identification using a standardized CRS case definition is crucial to effective CRS surveillance. Nevertheless, laboratory confirmation of rubella virus infection in the newborn by either serologic or virus detection techniques is also critical, especially when only a single defect presents [48]. Other persistent rubella virus infections of clinical significance include Fuch's Uveitis [49] and granuloma in primary immune deficient individuals [50•].

Humans appear to be the only species in which RuV circulates. Postnatal transmission of rubella virus is often by close contact with an infected individual, such as occurs in institutional settings. Infants with CRS shed significant amounts of virus, so infection control measures, notably restricted contact with non-immune women of child-bearing age, can minimize the risk of transmission.

The last major U.S. rubella epidemic was in 1964 to 1965, when approximately 20 000 CRS cases and 2100 neonatal deaths occurred [51]. Introduction of rubella vaccine in the US (licensed in 1969) immediately broke the 6- to 9-year epidemic cycle of rubella. Rubella is less infectious than measles and a population immunity of 87.5% in the United States is accepted as being sufficient to eliminate significant endemic transmission [52]. Rubella and CRS have been eliminated in the United States; for example, from 2004 to 2012, only 79 cases of rubella and six cases of CRS were reported in the U.S. [53,54]. Most US mothers of CRS children were born in countries without rubella immunization programs or with recently organized programs [55]. Indigenous rubella and CRS have also been eliminated from the Americas [56].

The global Measles and Rubella Strategic Plan (2012–2020) includes goals to eliminate rubella and CRS in at least two WHO regions by 2015, and at least five WHO regions by 2020 [57]. The safety and high vaccine efficacy of the live rubella virus vaccine strains most widely used (RA 27/3) is well documented [58]. Nevertheless, rubella remains endemic in many countries and about 100 000 CRS [59] cases occur annually in the world. It is underappreciated that infant deaths among CRS cases can be as high as 30% [47,60].

Conclusions

Despite the challenges described in this report, widespread use of MMR vaccine remains a safe, low cost, and effective means to prevent infections with measles, mumps, and rubella viruses. This vaccine has saved millions of lives and prevented countless numbers of severe birth defects and complications.

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