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COMMENTARY

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# Prevention of measles, mumps and rubella: 40 years of global experience with M-M-$R_{II}$

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**ABSTRACT**

Measles, mumps, and rubella are highly contagious diseases that caused significant global mortality and morbidity in the pre-vaccine era. Since its first approval in the United States over 40 years ago, M-M-$R_{II}$ has been used in >75 countries for prevention of these diseases. The vaccine has been part of immunization programs that have achieved dramatic global reductions in case numbers and mortality rates, as well as the elimination of measles and rubella in several countries and regions. This report summarizes over four decades of global safety, immunogenicity, efficacy, and effectiveness data for the vaccine. We include studies on the use of M-M-$R_{II}$ in different age groups, concomitant use with other routine childhood vaccines, administration via different routes, persistence of immunity, and vaccine effectiveness during outbreaks of measles and mumps. We conclude that M-M-$R_{II}$ is well tolerated and has shown consistently high performance during routine use in multiple countries, in randomized controlled trials with diverse designs, and in outbreak settings, including use as measles postexposure prophylaxis. Physicians, parents, and the public can continue to have a high degree of confidence in the use of M-M-$R_{II}$ as a vital part of global public health programs.

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## Introduction

Measles, mumps, and rubella are common viral infections of childhood that caused severe illness, long-term complications and death, as well as a significant burden on global health care systems in the pre-vaccine era.[1–3] Prior to the development of vaccines for these diseases, there were an estimated 30 million cases annually and 2.6 million deaths from measles worldwide; the incidence of mumps was 100–1,000 cases per 100,000 persons; and congenital rubella syndrome affected an estimated 0.1–0.2 per 1,000 live births with the number of cases increasing to 0.8–4 per 1,000 live births during epidemics, which historically occurred every 5–9 years.[4–7] Vaccination programs have since dramatically reduced the burden of measles, mumps, and rubella. The number of global deaths from measles decreased by 73% between 2000 and 2018, the incidence of mumps fell to <1 case per 100,000 people within ten years of implementing national immunization programs, and rubella was eliminated in 81 countries by 2019.[4,5,6,7]

The history and impact of M-M-$R_{II}$ (Measles, Mumps, and Rubella Vaccine Live, manufactured by Merck & Co., Inc., Kenilworth, NJ, USA), have been summarized elsewhere.[8,9] Briefly, monovalent measles, mumps, and rubella vaccines were first developed by Maurice Hilleman and other researchers in the late 1960s and early 1970s. Although these vaccines were a major public health achievement, Hilleman had a vision of a trivalent measles, mumps, and rubella vaccine that he described as a long-term dream "that it might be possible, one day, to develop a vaccine that would protect against these three diseases in a single shot."[10] The first-generation MMR vaccine developed by Hilleman and his team was licensed in the United States in 1971. M-M-$R_{II}$, which incorporated an improved rubella vaccine strain, was licensed in the United States in 1978 and is the only trivalent vaccine that has been used in the United States since 1978. M-M-$R_{II}$ has also been used extensively in >75 other countries, with >803 million doses distributed globally as of May 2021 (internal data). The vaccine is prequalified by the World Health Organization.[11,12, 13]

In the United States, the annual burden of measles, mumps, and rubella before 1970 was approximately 530,000, 162,000, and 47,000 cases, respectively. Measles alone caused approximately 48,000 hospitalizations, 500 deaths, and 1,000 cases of permanent brain damage each year.[12–14] By 2017, the number of cases decreased by >99% for measles, 96% for mumps, and 99% for rubella, and the combined mortality for the three diseases had declined by >99%.[15,16] Measles was declared eliminated in the United States in 2000, and rubella and congenital rubella followed in 2004.[15-20]

Decades of successful immunization programs have alleviated the public's longstanding fear of measles, mumps, and rubella. However, in recent decades the fear of these diseases has been replaced by the fear of vaccines themselves; in fact, vaccine hesitancy has been cited as one of the top ten threats to global health.[21] Other factors – medical contraindications, religious and philosophical objections, socioeconomic circumstances, and systemic barriers – further threaten vaccine uptake.[22-32] In the years preceding the COVID-19 pandemic, the uptake of routine childhood vaccinations in many countries had decreased to the point

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that once-eliminated diseases, including measles, were beginning to resurge.[26–32] The COVID-19 pandemic caused further declines in immunization rates, thus compounding the problem.[33] While the current focus of immunization programs worldwide is justifiably on vaccination against COVID-19, it is important to point out that measles is more contagious than SARS-CoV-2 (basic reproductive number of 12–18 versus 2–3) and has a higher fatality rate than COVID-19 (~15% versus 0.5–5%), underscoring the seriousness of declining MMR vaccine uptake.[1,29,33-42]

Prevention of measles, mumps, and rubella continues to be an important public health initiative and M-M-$R_{II}$ plays an important role in the prevention of these diseases. This report summarizes the efficacy, effectiveness, immunogenicity, and safety of M-M-$R_{II}$, over more than 40 years since its first approval in the United States. This report highlights information from randomized controlled trials (RCTs) and observational studies and expands on previous papers by including data from broader age groups, alternative administration methods, and outbreak settings. This represents the most comprehensive summary to date of the long-term performance of M-M-$R_{II}$.

## Results

Three literature reviews were performed to assess the performance of M-M-$R_{II}$ in different settings and populations.[43-45] The reviews collectively identified 122 reports on 88 studies (75 RCTs and 13 observational studies). One study was subsequently excluded as participants had received a monovalent measles injection at 6 months of age prior to immunization with M-M-$R_{II}$ or Triviraten Berna® Vaccine (Swiss Serum and Vaccine Institute) 6 months later.[46] Forty-one RCTs studied the concomitant administration of M-M-$R_{II}$ with other routine vaccines.[47-87] M-M-$R_{II}$ has also been used as a comparator in trials of investigational MMR vaccines, as well as quadrivalent vaccines that protect against measles, mumps, rubella, and varicella.[8,43,45,62,66-69,88-92] The effectiveness and safety of M-M-$R_{II}$ during outbreaks of measles and mumps has also been studied.[93-103] The results of these studies are presented here.

### *Safety*

Safety was assessed in 25 RCTs in which M-M-$R_{II}$ was administered alone and 42 RCTs in which one or more other routine vaccines was administered concomitantly. No safety data were reported for participants <1 year of age. Most of the safety data for M-M-$R_{II}$ were from 62 studies conducted in children 12 months to 6 years of age. The studies used different methods to assess adverse events (AEs), but all studies showed that first and second doses of the vaccine were generally well tolerated in all age groups, when administered alone or in combination with other vaccines. The most commonly reported AEs were injection site reactions, fever, and measles- or rubella-like rash (Table 1).

Table 2 presents safety data from three studies in which individuals received two doses of M-M-$R_{II}$.[67,78,104] Among participants who received a second dose of M-M-$R_{II}$ 6 weeks to 3 months after the first, the rates of injection site reactions were generally lower after the second dose; however, the reverse was true in one study in which a second dose was administered 2–3 years after the first. Fever and measles- or rubella-like rash occurred at a decreased rate after the second dose in all 2-dose trials.

Vaccine-related serious adverse events after immunization with M-M-$R_{II}$ alone or in combination with other vaccines were rare. The 18 vaccine-related or possibly vaccine-related serious adverse events identified in >20,000 subjects in the 88 studies reviewed included six cases of febrile convulsions, two cases each of fever, fever with rash, otitis media, and immune thrombocytopenic purpura, and one case each of vomiting, diarrhea, toxic skin eruptions, and seizure disorder.[47,58,60,66,68,69,78,91,92,121] Five deaths occurred, four of which were ruled not vaccine related; the outcome of the other fatality was not known.[45,67,68,76,78]

A retracted report published in 1998 that has since been deemed fraudulent suggested a connection between measles, mumps, and rubella vaccination and autism,[135] resulting in a decrease in vaccination uptake in the United Kingdom and elsewhere.[136,137] Multiple subsequent studies, including a Cochrane Review that analyzed data from studies that collectively enrolled 14,700,000 children, have reported that no association was found between MMR vaccines and autism spectrum disorders.[138-143]

Routine post-marketing surveillance is an important source of real-world data on vaccine safety, although the data are by nature incomplete, can contain reporting biases, and rarely allow causality to be determined. In 2012, data from 32 years of routine global post-marketing surveillance for M-M-$R_{II}$ were summarized.[8] The review analyzed 17,536 AEs reported to Merck's Worldwide Adverse Experience System between 1978 and 2010. The most common AEs reported were fever, rash, injection site reactions, and febrile convulsions. Of the 136 deaths reported, the majority involved bacterial and viral infections that were not related to the vaccine. Fourteen fatalities occurred in people with immunocompromising conditions, which are listed in vaccine package inserts as contraindications for immunization with M-M-$R_{II}$. Four of these fatalities were reported in detail as case studies.[144-147] No unusual patterns or clustering were identified among the deaths reported.[8]

A more recent review summarized data on AEs reported after M-M-$R_{II}$ administration from 1989 to 2019, as reported in the US Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiological Research system. Among the >158,000 total AE reports from the United States, the only disproportionately reported AE for M-M-$R_{II}$ compared to AEs for all other vaccines was orchitis; no safety signal was detected for severe orchitis or other AEs.[148]

### *Immunogenicity*

The immunogenicity of M-M-$R_{II}$ has been studied in all age groups, with and without concomitant administration of other vaccines. The overall range of seroconversion rates after vaccination was 87.4–100% for measles, 79.5–100% for mumps,[a] and 90.0–100% for rubella (Table 3). The vaccine was shown to perform consistently over 21 years of evaluation in clinical trials.[40]

**Table 1.** Adverse events after administration of M-M-$R_{II}$, by participant age[a].

| | Fever | | Measles- or rubella-like Rash | | Injection Site Reactions | |
|---|---|---|---|---|---|---|
| Age and vaccine(s) administered | Number of- studies | (%) | Number of studies | (%) | Number of studies | (%) |
| 12 months–6 years | | | | | | |
| First dose, M-M-$R_{II}$ alone | 14[b] | 0–61 | 1[c] | 2–3 | 11[d] | 6–36[e] |
| Second dose, M-M-$R_{II}$ alone | 3[f] | 5–34 | 1[c] | 0–1 | 3[f] | 15–52[e] |
| First dose, M-M-$R_{II}$ + other vaccine(s) | 28[g] | 1–66 | 19[h] | 0–13 | 34[i] | 8–59[e] |
| Second dose, M-M-$R_{II}$ + other vaccine(s) | 4[j] | 3–30 | 2[k] | 0–2 | 5[l] | 22–91[e] |
| ≥7 years | | | | | | |
| M-M-$R_{II}$ alone | 5[m] | 0–12 | 1[n] | 0 | 4[o] | 12–33 |
| M-M-$R_{II}$ + other vaccine(s) | 1[p] | 2 | - | NR | - | NR |

NR, Not Reported.

In studies that specified a reporting timeframe for systemic AEs, the follow-up period ranged from 11 to 42 days. The collection of adverse events and the definition of fever varied from study to study. Some studies are reported in more than one of the references cited.

[a]Table 1 excludes studies shown in Table 2.

[b]References: [104-117]

[c]Results are from Wiedmann et al., 2015 which included two study arms.[104] After the first dose, rash was reported by 3.2% of participants who received M-M-$R_{II}$ with rHA and 1.6% of participants who received M-M-$R_{II}$ with HSA. After the second dose, rash was reported among 0% in the M-M-$R_{II}$ with HSA group and 0.5% rash in the M-M-$R_{II}$ with rHA group.)

[d]References: [104,107-115,118]

[e]The majority of studies in participants 12 months to 6 years of age reported a range of injection site reactions from 6–48%, with outliers at 52%, 59%, 68%, 72%, 84%, and 91%. The duration of follow-up for reactions varied from study to study.

[f]References: [67,104,119,120]

[g]References: [50,51,54,55,57,60-62,64,65,68-71,73,74,76,77,79-84,86,87,91,92,121-128]

[h]References: [14,58,62,68,70,73,74,78-80,82,83,86,91,92,124-128]

[i]References: [50,54-58,60-62,64,65,68-70,74,76-83,86,87,91,92,119,122,124-128]

[j]References: [49,66,72,123,129,130]

[k]References: [66,129,130]

[l]References: [48,49,63,66,72,119,130]

[m]References: [88,121,131-134]

[n]References: [88,121]

[o]References: [88,121,132-134]

[p]Reference: [53]

In the single study that vaccinated children <12 months of age (specifically at 9 months), the seroconversion rates for measles, mumps, and rubella were 87.4%, 92.3%, and 91.2%, respectively.[149] This is an important finding considering the potential need to use M-M-$R_{II}$ in children <12 months of age in outbreak settings or for protection during international travel.[103]

Among children 12 months to 6 years of age, seroconversion rates after a first dose of M-M-$R_{II}$ in 46 studies (31 with and 15 without concomitant administration of other vaccines) were 87.5–100% for measles, 90.0–100% for mumps, and 92.0–100% for rubella.[14,47,51,52,54,55,57-62,64,65,67-70,72,74-77,79-83,85,87,91,92,104-114,118,122,149,150,155] Five studies in this age range reported on the immunogenicity of a second dose of M-M-$R_{II}$ (three with and two without concomitant administration of other vaccines); the response rates for measles, mumps, and rubella after the second dose were 98.4–100%, 98.6–100%, and 99.6–100%, respectively.[49,66,67,72,151] In two studies in which immunogenicity was assessed after both a first and a second dose, the seroresponse rates or antibody titers for all antigens increased after the second dose compared to the first.[67,151]

Seroconversion rates in participants ≥7 years of age enrolled in seven studies (six without and one with concomitant administration of other vaccines) were 96.0–100% for measles, 94.5–100% for mumps, and 91.3–100% for rubella.[53,88-90,131-134,153,154]

## Concomitant use with other routine vaccines

Forty-four studies have shown that M-M-$R_{II}$ can be safely administered with other routinely recommended vaccines, and that immunogenicity is not affected. Some studies administered two or more other pediatric vaccines concomitantly with M-M-$R_{II}$, and not every study reported seropositivity rates for measles, mumps, and rubella; we included all studies that reported immunogenicity and/or safety data for M-M-$R_{II}$. In participants 12 months to 6 years of age, varicella vaccine was the most commonly co-administered vaccine with a first dose of M-M-$R_{II}$ (20 studies). M-M-$R_{II}$ was also concomitantly administered in this age group with vaccines against hepatitis A and *Haemophilus influenzae* type b (seven studies each), diphtheria-tetanus-pertussis-poliovirus (DTaP) and quadrivalent meningococcal conjugate vaccines (two studies each), and pneumococcal conjugate vaccine, Japanese encephalitis chimeric virus vaccine, and live attenuated influenza vaccine (one study each).[47-52,54-86,150] A second dose of M-M-$R_{II}$ was administered concomitantly in this age range in four studies with DTaP and one study with varicella vaccine.[48,49,63,66,72] In 25 concomitant use studies that reported on the immunogenicity of M-M-$R_{II}$, the seropositivity rates for measles, mumps, and rubella administered with other vaccines were 87.5–100%, 79.5–100%, and 92.0–100%, respectively, compared to 90.4–100%, 90.0–100%, and 90.0–100%, respectively, when M-M-$R_{II}$ was administered alone (Table 3). A single study in 11–12-year-olds reported on the use of M-M-$R_{II}$ administered concomitantly with tetanus-diphtheria (Td) vaccine or hepatitis B and Td vaccines, with 100% seropositivity for measles, mumps, and rubella in both study arms.[53] In all studies of concomitant use, antibody response rates to both M-M-$R_{II}$ and the other vaccines administered were generally comparable when vaccines were administered alone or concomitantly.

**Table 2.** Adverse events after administration of a first and second dose of M-M-$R_{II}$ in two-dose studies.

| Study | Age at first dose | Interval between doses | Adverse event reporting period | Dose | *n*[a] | Concomitantly administered vaccine(s) | Fever (%) [b] | Measles- or rubella-like rash (%) | Injection site reactions (%) |
|---|---|---|---|---|---|---|---|---|---|
| MMR-161 study group[67] | 12–15 months | 42 days | 42 days (4 days for injection site reactions) | 1 | 1,526 | Hepatitis A, Varicella (all participants) plus PCV13 (764 participants) | 40–42 | NR | 20 |
| | | | | 2 | 1,456 | None | 32–34 | NR | 15 |
| Senders[78] | 12–23 months | ~3 months | 42 days (5 days for injection site reactions) | 1 | 611 | Varicella | 10–11 | 0–2 | 41 |
| | | | | 2 | 533 | Varicella | 8–9 | 0 | 31–35 |
| Wiedmann[104] | 12–18 months | 2–3 years | 42 days (5 days for injection site reactions) | 1 | 1,279 | None | 9–10 | 2–3 | 22–27 |
| | | | | 2 | 373 | None | 5–7 | 0–1 | 42–45 |

NR, Not reported.
[a]*n* indicates number of participants receiving M-M-$R_{II}$ in each study.
[b]Data collection methods and the definition of fever differed across the studies.

### Route of administration

The licensed formulation of M-M-$R_{II}$ may be delivered by subcutaneous or intramuscular injection. In a head-to-head comparison, safety and immunogenicity results were comparable for both subcutaneous or intramuscular administration of M-M-$R_{II}$ with a varicella vaccine.[58]

### Persistence of immune response

Antibody persistence has been demonstrated for 11–13 years, the longest period studied. Six additional studies (four assessing a first dose and two a booster dose) with short-term follow up (1–2 years) reported high rates of antibody persistence in >6,000 participants after administration of M-M-$R_{II}$ alone (three studies) or concomitantly with vaccines against varicella (two studies) or Japanese encephalitis (one study).[47,61,64,111,131,153]

### Effectiveness of M-M-$R_{II}$ in outbreak settings

Real-world observational studies have confirmed that M-M-$R_{II}$ is highly effective in outbreak settings in different countries and age groups. Four studies of measles outbreaks and six studies of mumps outbreaks are summarized in Table 4.[93,94,96-103] No published data were found on the use of M-M-$R_{II}$ during outbreaks of rubella, which are infrequent in countries with high rates of vaccine coverage.[7]

During a 1998 US outbreak of measles, vaccine effectiveness (VE) was 94.1% among participants who had previously received two doses of M-M-$R_{II}$.[99] A study conducted during a 2011 Canadian measles outbreak reported an overall VE of 95.5% among participants who had previously received two doses of M-M-$R_{II}$; the VE was higher in subjects who had received their first dose at ≥15 months of age than in those who had received their first dose at 12 months (97.5% versus 93.0%).[96] A small study of the VE of an early first dose of M-M-$R_{II}$ (offered at 6–14 months of age rather than the scheduled 14 months) during a Dutch outbreak of measles in 2013–2014 reported an unadjusted VE of 94%; adjusting for confounding factors resulted in a VE of 71%.[103] In a postexposure study conducted during a 2013 US outbreak, a single dose of M-M-$R_{II}$ was used prophylactically within 72 hours of exposure to measles in 318 children from 6 months to 19 years of age. The VE was 83.4%.[93]

In three studies conducted during mumps outbreaks, the VE of one- or two-dose regimens of M-M-$R_{II}$ compared to no vaccination ranged from 80 to 86%.[97,98,100] Another study concluded that participants who had received a second dose of M-M-$R_{II}$ >13 years before the outbreak had a nine-fold higher risk of contracting mumps (VE 32%) than those who had received a second dose within the preceding 13 years (VE 89%).[94] An additional study of 584 undergraduate students did not assess VE, but reported a mumps attack rate of 2–8% for persons who had received two doses of M-M-$R_{II}$, compared with 31–48% for unvaccinated controls.[95]

The administration of a third dose of M-M-$R_{II}$ during US mumps outbreaks has also been assessed. In a study of 4,738 university students, VE increased from 60% at the time of third

**Table 3.** Seroconversion rates after vaccination with M-M-$R_{II}$, alone or with other routine vaccinations.

| | Seroconversion rates (%) | | |
|---|---|---|---|
| Category | Measles | Mumps | Rubella |
| By age group[a] | | | |
| <12 months[b] | 87.4 | 92.3 | 91.2 |
| 12 months–3 years[c] | 92.8–100 | 91.1–100 | 92.8–100 |
| 4–6 years[d] | 99.3–100 | 100 | 99.4–100 |
| ≥7 years[e] | 96.0–100 | 94.5–100[f] | 91.3–100 |
| By dose number, 12 months–6 years | | | |
| First dose[g] | 87.5–100 | 90.0–100 | 92.0–100 |
| Second dose[h] | 98.4–100 | 98.6–100 | 99.6–100 |
| Concomitant use with other vaccine(s), first dose | | | |
| M-M-$R_{II}$ alone[i,j,k] | 90.4–100 | 90.0–100 | 90.0–100 |
| Diphtheria-tetanus-pertussis and (oral or inactivated) poliovirus (DTaP)[i,j,l] | 95.0–100 | 97.0–100 | 92.0–100 |
| *Haemophilus influenzae* type b (Hib)[i,m] | 95.7–99.4 | 98.4–100 | 97.0–100 |
| Hepatitis A[i,n] | 96.3–100 | 97.6–100 | 98.3–100 |
| Hepatitis B[j,o] | 100 | 100 | 100 |
| Influenza[i,p] | 97.0 | >96.0 | >97.0 |
| Japanese encephalitis[i,q] | 97.6–100 | 98.8–99.5 | 100 |
| Varicella[i,r] | 87.5–100 | 79.5–100 | 92.8–100 |
| Concomitant use with other vaccine(s), second dose | | | |
| M-M-$R_{II}$ alone[i,s] | 99.3 | 100 | 100 |
| DTaP[i,j,t] | 98.9–100 | 98.9–100 | 99.4–100 |
| Hepatitis B[j,o] | 100 | 100 | 100 |
| Varicella[i,u] | 100 | 100 | 100 |
| Alternative administration methods[v] | | | |
| Intramuscular[w] | 94.3 | 97.7 | 98.1 |

Assays used and time for collection of sera may have differed across the studies. Some studies are reported in more than one of the references cited.
[a]Subjects ≤3 years of age received a first or first and second dose of M-M-$R_{II}$; subjects ≥4 years of age received a second or possible third dose of M-M-$R_{II}$.
[b]Reference: [149]
[c]References: [47,51,52,54,58-62,64,65,67-70,73,74,76,77,79-83,85-87,91,92,122,123,125-128,150]
[d]References: [49,66,72,104,129,130,151,152]
[e]References: [53,88-90,121,131-134,153,154]
[f]Most studies in this age group reported a range of 94.5–100% for mumps seropositivity. The authors of the paper that reported the single low outlier of 65% stated that 'the mumps antibody levels obtained with the present tests may not accurately reflect actual immunity.'[153]
[g]References: [47,51,52,54,58-62,64,65,67-70,73,74,76,77,79-83,85-87,91,92,104,122,123,125-128,150]
[h]References: [49,66,67,72,119,129,130,151,152]
[i]Ranges include data from participants 12 months to 6 years of age.
[j]Ranges include data from participants ≥7 years of age.
[k]References: [46,88-90,104-115,118,121,131-134,149,153-156]
[l]References: [53,54,77,86]
[m]References: [51,60,74,82]
[n]References: [47,52,59,62,67-69,76,119,127-129,150]
[o]Reference: [53]
[p]Reference: [70]
[q]Reference: [61]
[r]References: [55,57,58,60,64,65,70,73,76,79-81,83,85,86,91,92,122,125,126]
[s]References: [67,119,151]
[t]References: [49,53,66,129,130]
[u]References: [72,152]
[v]Two studies assessed the safety and immunogenicity of M-M-$R_{II}$ delivered by alternative, non-licensed methods – aerosol or needle-free jet injector.[90,134] Immunogenicity by aerosol administration was 100%, 98.3%, and 100% for measles, mumps, and rubella, respectively. Immunogenicity in the needle-free jet injector study was reported as geometric mean ratios (GMR) for each antibody compared to a positive control. The values for the GMR at week 12 by needle-jet injector versus subcutaneous administration for measles, mumps, and rubella were 0.74 versus 0.89, 0.94 versus 0.90, and 2.07 versus 1.87, respectively.
[w]Reference: [58]

dose administration to 78% four weeks later.[94] During an outbreak in a highly vaccinated population 9–14 years of age, administration of a third dose of M-M-$R_{II}$ reduced the mumps attack rate from 0.24% to 0.09%, although the difference was not statistically significant.[101] Finally, in a 2009–2010 study in which 1,755 participants 11–17 years of age were given a third dose of M-M-$R_{II}$ during a mumps outbreak in a religious community, the attack rate declined by 96.0% in the target age group and by 75.6% in the community as a whole.[102]

These studies confirm that routine use of M-M-$R_{II}$ provides effective protection during outbreaks, and that the vaccine is also an effective public health tool in preventing measles post-exposure. Administration of a third dose of M-M-$R_{II}$ may be useful in certain situations, as recommended by the US Advisory Committee on Immunization Practices.[157]

Additional research is needed to assess the long-term protection afforded by M-M-$R_{II}$, particularly considering the lack of exposure to wildtype infection in many countries. Modelling studies may be a useful tool in addressing this question. In addition, it will be important to continue to assess the effectiveness of the vaccine in situations where non-vaccine genotypes become dominant. These data will be useful in determining whether additional doses of vaccine are needed in certain circumstances or populations.

**Table 4.** Vaccine effectiveness (VE) of M-M-$R_{II}$ during measles and mumps outbreaks.

| Outbreak | Study | Study period | *n* | Age range | Case definition (if specified) | Dose number comparison | VE (%) |
|---|---|---|---|---|---|---|---|
| Measles | Lynn[99] | 1998 | 3,679 | 13–21 years | | 2 vs. 1 | 94 |
| | De Serres[96a] | 2011 | 1,306 | High school students, median 15 years (range not specified) | | 1 vs. 0 | 96 |
| | | | | | Classical | ≥2 vs. 0 | 96 |
| | | | | | Classical + attenuated | ≥2 vs. 0 | 94 |
| | Arciuolo[93] | 2013 | 318 | 6 months to 19 years | Postexposure prophylaxis | 1 vs. 0 | 83 |
| | Woudenberg[103b] | 2013–2014 | 1,230 | 6–14 months | Clinical | 1 vs. 0 | 71 |
| | | | | | Self-reported | 1 vs. 0 | 43 |
| Mumps | Hersh[97c] | 1988–1989 | 1,713 | Junior high school students (age not specified) | | ≥1 vs. 0 | 83 |
| | Marin[100] | 2006 | 2,363 | ≥7 years, college students(range not specified) | | 1 vs. 0 | 84 |
| | | | | | | 2 vs. 0 | 80 |
| | Ogbuanu[102] | 2009–2010 | 2,265 | 11–17 years | | 3 vs. ≤2 | 88 |
| | Nelson[101d] | 2009–2010 | 3,239 | 9–14 years | | 3 vs. ≤2 | 60 |
| | Livingston[98] | 2010 | 2,176 | ≥5 years (range not specified) | | 1 vs. 0 | 83 |
| | | | | | | 2 vs. 0 | 86 |
| | | | | | | ≥1 vs. 0 | 86 |
| | Cardemil[94] | 2015–2016 | 20,496 | 18–24 years | | 3 vs. 2 | 60–78 |
| | | | | | | 2 vs. 0 (vaccinated <13 years before outbreak) | 89 |
| | | | | | | 2 vs. 0 (vaccinated ≥13 years before outbreak) | 32 |

All studies were conducted in the United States except De Serres (Canada) and Woudenberg (Netherlands).
No use of M-M-$R_{II}$ during rubella outbreaks was reported.
[a]M-M-$R_{II}$ was generally used, but vaccines also included Connaught Canada monovalent measles vaccine.
[b]Study was designed to assess the effectiveness of an early first dose of M-M-$R_{II}$ during an outbreak.
[c]Only eight participants were unvaccinated. Vaccines included monovalent mumps vaccine as well as M-M-$R_{II}$.
[d]Vaccine effectiveness was not provided in the original publication and was therefore estimated by calculating 1 – the reported relative risk.

## Conclusions

M-M-$R_{II}$ has been used globally for over 40 years, has helped substantially reduce morbidity and mortality from measles, mumps, rubella, and congenital rubella syndrome, and has contributed to the elimination of these diseases in several countries. The abundance of data that have been generated for M-M-$R_{II}$, summarized herein, attest to the vaccine's safety, immunogenicity, efficacy, and effectiveness. The data are reassuring in that M-M-$R_{II}$ has been evaluated in multiple locations, administered over decades in different settings by different researchers, and still yielded highly consistent performance. The public health impact of this vaccine has been enormous, and countries with established universal vaccination programs with M-M-$R_{II}$ serve as an example for other countries that reduction and/or elimination of measles, mumps, and rubella is possible with a strong vaccination program and high vaccination rates.

## Notes

[a] See footnote B in Table 3 for additional information on an outlier of 65%.

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## Disclosure statement

MP is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and stockholder of Merck & Co., Inc., Kenilworth, NJ, USA.

ES is an employee of Certara, Loerrach, Germany, and was a consultant for Merck & Co., Inc., Kenilworth, NJ, USA and paid for their services.

BK was an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA at the time of the study.

GSM reports involvement as an investigator and consultant for GlaxoSmithKline, Merck, Seqirus, Pfizer, and Sanofi Pasteur and also as a speaker for Sanofi Pasteur.

JF is a consultant for Merck & Co., Inc., Kenilworth, NJ, USA, Sanofi Pasteur and GSK. Investigator for Pfizer, and AstraZeneca. Speaker for Merck, Pfizer, and AstraZeneca.

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