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MMR and MMRV vaccines

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ABSTRACT

Measles, mumps, rubella and varicella are viral infections which can implicate seriously long-term sequelae of infected individuals or even the unborn child. Vaccines against the individual diseases have long been available. Global measles vaccination is estimated to have prevented more than 20 million deaths during 2000–2015. During the same time period, measles incidence decreased from 146 to 36 cases per million populations. Today vaccinations against measles, mumps, rubella and varicella are now carried out mainly with combination vaccines. These are today known as immunogenic and safe. MMRV had similar immunogenicity and overall safety profiles to MMR administered with or without varicella vaccine. This issue provides a review of the different vaccines, mode of administration, catch up immunization and postexposure prophylaxis as well as contraindications and adverse effects of the immunization against measles, mumps, rubella, and varicella. The article presents an overview of important information of preventing these diseases with a focus on the existing combination vaccines.

1. Introduction

Childhood and adolescent immunizations are effective means of preventing serious illnesses. Vaccination protects both the individual immunized and, in certain circumstances, non-vaccinated people who benefit from herd immunity and the failure of disease to spread throughout a highly-immunized population. Measles, mumps, rubella (German measles) and varicella (chicken pox) are viral infections capable of causing serious long-term sequelae in infected individuals and unborn children. Vaccines against each disease alone have been available for a long time. The current availability of combination vaccines has resulted in increased vaccination rates. It is estimated, for example, that global measles vaccination prevented more than 20 million deaths during the period 2000–2015 [1]. During the same period, the incidence of measles decreased from 146 to 36 cases per one million people (Fig. 1).

A routine measles-mumps-rubella (MMR) vaccine schedule, which includes a second dose administered between 4- and 6-years-of-age, resulted in a 96%–99% reduction in the incidence of each of the 3 targeted diseases in Finland, Sweden and the United States [2–4]. All 3 diseases were eliminated in Finland in 1996–1997 after 14–15 years of a routine 2-dose MMR vaccine program [3]. Despite a drastic reduction in the incidence of disease, a significant number of measles cases still occur each year in the United States, often imported from other countries and spread among nonimmunized individuals who fail to comply with vaccine recommendations [5].

Although varicella-zoster virus (VZV) vaccines are licensed in many countries, they are not always included in national immunization programs. Consequently, the rate of VZV vaccination is low [6]. A combined measles-mumps-rubella-varicella (MMRV) vaccine was originally designed as an alternative to separate MMR and VZV vaccines, based upon similar vaccination schedules and acceptable concomitant safety profiles [7]. The rationale for the development of MMRV vaccines was to reduce the number of injections required for each vaccine administered alone, and to increase overall acceptance and coverage of the VZV vaccine [8]. This article intends to provide an overview of the current state of MMR and VZ vaccination.

2. MMR and MMRV vaccine formulations

Most live attenuated measles vaccines contain derivatives of the Edmonston virus strain, only four vaccines derive from other strains (i.e., CAM-70, Shanghai-191, Leningrad-16, TD97) [9]. In most cases, the virus is propagated in chick embryos; in some cases, human diploid cells are used as well. Additionally, the vaccines include antibiotics, and sorbitol and gelatin for stabilization. More than 10 different virus strains are used worldwide to produce the mumps vaccine: Jeryl Lynn, Urabe, Leningrad-3, l-Zagreb,

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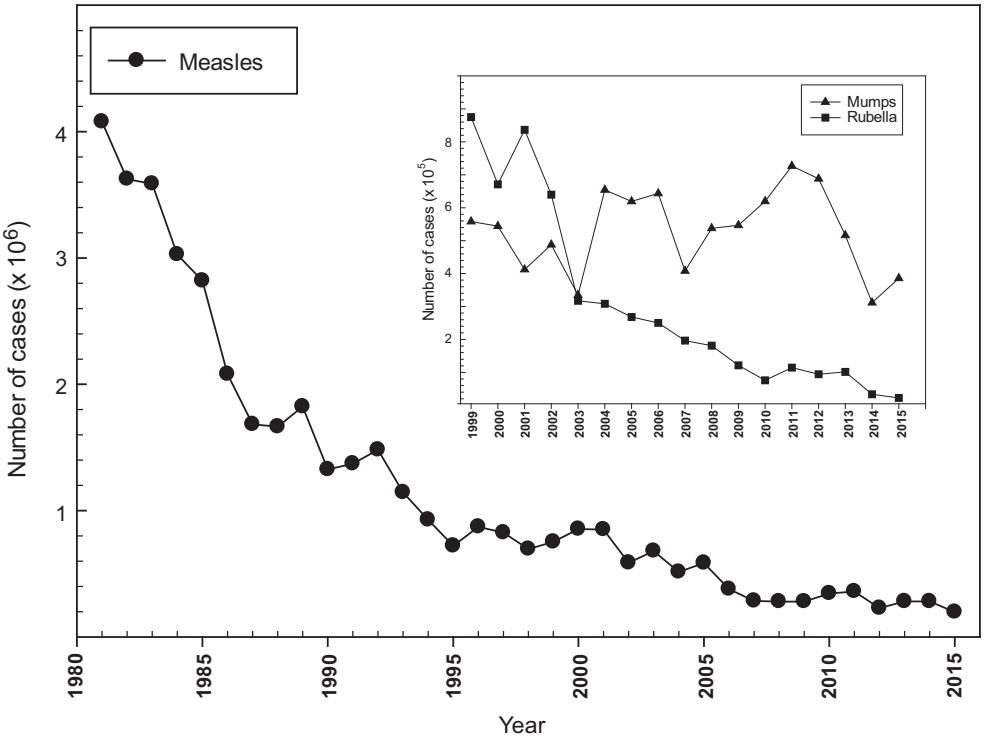

Fig. 1. Confirmed, global annual reported cases of measles (1981–2015). Confirmed cases of mumps and rubella (1999–2015) are shown in the inset. Data are derived from The World Health Organization incidence report: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencemeasles.html.

Miyahara, Hoshino, Rubini, Torii, NK M-46, S-12 and RIT 4385, but the Jeryl Lynn strain is used most often. The virus is frequently propagated in chick embryo fibroblasts, but human and quail embryo fibroblasts are also used. Rubella vaccines are almost exclusively based upon the RA 27/3 virus strain due to its strong immunogenic properties and comparably low side effects [10]. Other virus strains, i.e., Matsuura (grown in quail embryo fibroblasts) and Matsuba, DCRB 19, Takashashi and TO-336 (grown in rabbit kidney cells), are only used in Japan to produce rubella vaccines. There are at least five known combination MMR vaccines; the first was licensed in the USA in the 1960s. The five vaccines and their compositions are listed in Table 1.

Monovalent VZV vaccine consists of the Oka virus strain isolated from a normal child in Japan infected with naturally-occurring varicella, which was subsequently attenuated by sequential passage in cultures of: human embryonic lung cells, embryonic guinea-pig cells and the human diploid cell line WI-38 (Varivax vaccine) or MCR-5 (Varilrix vaccine). The titer of VZV is ~14 times higher in the MMRV vaccines described immediately below than the monovalent VZV vaccine [11].

Two MMRV vaccines have been available since mid-2000: ProQuad (Merck & Co., Inc, West Point, PA) and Priorix-Tetra (GlaxoSmithKline Biologicals, Rixensart, Belgium). Both vaccines are used worldwide. Development of combination MMRV vaccines was based upon preexisting MMR and VZV vaccines [7]. Different schedules and formulations were tested during development. The resultant compositions of the ProQuad and Priorix-Tetra vaccines are not entirely different. While the measles strains differ, the mumps strain comprising Priorix-Tetra derives from the ProQuad strain. The rubella and varicella strains are the same, albeit the vaccine formulations differ slightly in terms of attenuated virus titers (Table 2).

3. MMR and MMRV vaccines – a global perspective

Currently, no national health policy recommends immunization against measles, mumps, and rubella using three separate vaccines. Instead, the MMR vaccine is used in 90 countries worldwide including more than 50 European countries, the USA, Canada, Australia and New Zealand [9]. Indeed, the MMR vaccine is included in the World Health Organization's "Expanded Program on Immunization." As such, the worldwide incidence of measles, for example, has declined significantly over the past 35 years (Fig. 1). The incidence of rubella, but not mumps, exhibited a similar decline.

Table 1
Combination MMR vaccines.

Vaccine[a]	Company	Composition					
		Measles		Mumps		Rubella	
Triviraten	Berna	Edmonston-Zagreb	≥1000 $TCID_{50}$	Rubini	≥5000 $TCID_{50}$	Wistar RA 27/3	≥1000 $TCID_{50}$
MMR	Merck	Enders attenuated Edmonston	≥1000 $TCID_{50}$	Jeryl Lynn	≥20000 $TCID_{50}$	Wistar RA 27/3	≥1000 $TCID_{50}$
Morupar	Chiron	Schwarz	≥1000 $TCID_{50}$	Urabe AM 9	≥5000 $TCID_{50}$	Wistar RA 27/3	≥1000 $TCID_{50}$
Priorix	GlaxoSmithKline	Schwarz	≥1000 $CCID_{50}$	RIT 4385	≥5000 $CCID_{50}$	Wistar RA 27/3	≥1000 $CCID_{50}$
Trimovax	Pasteur-Merieux	Schwarz	≥1000 $TCID_{50}$	Urabe AM 9	≥5000 $TCID_{50}$	Wistar RA 27/3	≥1000 $TCID_{50}$

[a] The manufacturer, three attenuated virus strains and titers (where $TCID_{50}$ = 50% tissue culture infectious dose and $CCID_{50}$ = 50% tissue culture infectious dose) are provided for each vaccine listed.

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