The Immunological Basis for Immunization Series

Module 16: Mumps

Immunization, Vaccines and Biologicals

World Health Organization

The Immunological Basis for Immunization Series

Module 16: Mumps

Immunization, Vaccines and Biologicals

World Health Organization

WHO Library Cataloguing-in-Publication Data

The immunological basis for immunization series: module 16: mumps / by Huong Q Mclean, Carole J Hickman and Jane F Seward.

(Immunological basis for immunization series ; module 16)

1.Mumps - immunology. 2.Mumps virus - immunology. 3.Mumps vaccine - therapeutic use. 4.Immunization. I.Mclean, Huong Q. II.Hickman, C. J. III.Seward, Jane F. IV.World Health Organization. V.Centers for Disease Control and Prevention (U.S.). VI.Series.

ISBN 978 92 4 150066 1 (NLM classification: WC 520)

The Department of Immunization, Vaccines and Biologicals thanks the donors whose unspecified financial support has made the production of this document possible.

This module was produced for Immunization, Vaccines and Biologicals, WHO, by:

Huong Q McLean; Carole J Hickman and Jane F Seward
Centers for Disease Control and Prevention (CDC), Atlanta, USA

Printed in November 2010

Copies of this publication as well as additional materials on immunization, vaccines and biological may be requested from:

World Health Organization
Department of Immunization, Vaccines and Biologicals
CH-1211 Geneva 27, Switzerland
• *Fax:* + 41 22 791 4227 • *Email:* vaccines@who.int •

Printed by the WHO Document Production Services, Geneva, Switzerland

Contents

Abbreviations and acronyms

CI	confidence interval
CMI	cell-mediated immunity
CTL	cytotoxic T-cell
DNA	deoxyribonucleic acid
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
F	fusion protein
HLA	histocompatibility leukocyte antigen
HN	haemagglutinin-neuraminidase protein
Ig	immunoglobulin
L	large protein
M	matrix protein
MMR	measles, mumps, and rubella
NP	nucleoprotein
P	phosphoprotein
PAHO	Pan American Health Organization
RNA	ribonucleic acid
RT-PCR	reverse transcriptase-polymerase chain reaction
SH	short hydrophobic protein
USA	United States of America
WHO	World Health Organization

Preface

This module is part of the series *The Immunological Basis for Immunization*, which was initially developed in 1993 as a set of eight modules focusing on the vaccines included in the Expanded Programme on Immunization (EPI)[1]. In addition to a general immunology module, each of the seven other modules covered one of the vaccines recommended as part of the EPI programme, i.e. diphtheria, measles, pertussis, polio, tetanus, tuberculosis and yellow fever. These modules have become some of the most widely used documents in the field of immunization.

With the development of the Global Immunization Vision and Strategy (2005–2015) (http://www.who.int/vaccines-documents/DocsPDF05/GIVS_Final_EN.pdf) and the expansion of immunization programmes in general, as well as the large accumulation of new knowledge since the original papers were published, the decision has been taken to update and extend this series.

The main purpose of publishing vaccine-specific modules is to give immunization managers and vaccination professionals a brief and easily understood overview of the scientific basis for vaccination, and background information upon which the WHO policies on immunization published in the *WHO Vaccine Position Papers* are based. (http://www.who.int/immunization/documents/positionpapers_intro/en/index.html).

WHO would like to thank all the people who were involved in the development of the initial *Immunological Basis for Immunization* series, as well as those involved in its updating, and the development of new modules.

[1] This programme was established in 1974 with the aim of providing immunization for children in developing countries.

1. Mumps disease and virus

1.1 Mumps disease

Mumps is an acute viral illness characterized by unilateral or bilateral tenderness or swelling of the parotid or other salivary glands. Mumps is transmitted through person-to-person contact or by direct contact with respiratory droplets or saliva from an infected person. By comparison to measles and varicella, which can be transmitted by aerosol spread, mumps is less infectious (Hope-Simpson, 1952). The mumps virus replicates in the nasopharynx and regional lymph nodes, with a secondary viremia occurring late in the incubation period. During those three to five days of viremia, the virus spreads into the major target organs. Although the salivary glands are most commonly affected, the central nervous system, pancreas, liver, spleen, kidneys and genital organs can also be involved. The average incubation period is 16 to 18 days, with a range of 12 to 25 days (Hope-Simpson, 1952). Mumps is believed to be most infectious around the time of onset of parotid swelling. However, mumps virus has been isolated from saliva as early as seven days prior to, and as late as eight days after, onset of parotitis (Utz et al., 1957; Ennis & Jackson, 1968).

The clinical presentation ranges from asymptomatic infection or nonspecific, mainly respiratory symptoms, to complications with or without parotitis. Parotitis is the most common manifestation, occurring in approximately 60% to 70% of mumps infections, but can range between 50% and 95% depending on age and immunity of the population (Philip et al., 1959; Reed et al., 1967). Parotitis typically lasts seven to ten days, and may be initially unilateral, but becomes bilateral in about 65% of cases (Sullivan et al., 1985a). Prodromal symptoms are nonspecific, consisting of myalgia, anorexia, malaise, headache, low-grade fever and vomiting. Inapparent infections may be more common in young children and older adults than in school-aged children (Philip et al., 1959).

Complications of mumps vary with age and sex, and can occur without parotitis. Severe complications, including deaths, are rare (Azimi et al., 1969). The rate of complications increases markedly in those above 15 years of age and, predominately due to orchitis, is generally higher in males than in females (Falk et al., 1989). Complications involving the central nervous system, in the form of aseptic meningitis, are common. The meningitis is generally benign and resolves without sequelae. Asymptomatic meningitis occurs in up to 55% of patients in studies where lumbar punctures were performed routinely (Bang & Bang, 1943; Brown et al., 1948), whereas clinical symptoms suggestive of meningitis occur in 0.02% to 10% of mumps cases (Laurence & McGavin., 1948; Russell & Donald, 1958; Reed et al., 1967; Witte & Karchmer, 1968; Falk et al., 1989). Encephalitis occurs in 2–4 per 1000 mumps cases, and can be fatal (Witte & Karchmer, 1968; Hayden et al., 1978).

In males, orchitis is the most common complication, occurring in approximately 30% of postpubertal men (range: 19% to 44%) (Laurence & McGavin., 1948; Philip et al., 1959; Association for the Study of Infectious Diseases, 1974; Beard et al., 1977; Arday et al., 1989). There may be some degree of testicular atrophy, but sterility is rare. In postpubertal women, mastitis occurs in up to 30% and oophoritis in approximately 5% of cases (Philip et al., 1959; Reed et al., 1967; Sullivan et al., 1985a).

Less common complications include pancreatitis, deafness, myocarditis, arthralgias, arthritis, thyroiditis, nephritis, endocardial fibroelastosis, thrombocytopenia, cerebellar ataxia, transverse myelitis, and ascending polyradiculitis. Transient, high frequency deafness occurs in 4% of cases, with permanent deafness in approximately one per 20 000 cases (Vuori et al., 1962; Westmore et al., 1979; Bitnun et al., 1986; Hall & Richards, 1987; Okamoto et al., 1994; McKenna, 1997; Doshi et al., 2009).

1.2 Mumps virus

Mumps virus is a single-stranded, negative sense, enveloped ribonucleic acid (RNA) virus in the Paramyxoviridae family, Paramyxovirinae sub-family, genus Rubulavirus. Mumps virions are pleomorphic but generally spherical structures, and range in size from 85 nm to 300 nm in diameter (Cantell, 1961). The viral genome is 15 384 nucleotides in length and encodes nine proteins from seven genes. The mumps genome is encapsidated by nucleoprotein (NP) and the phosphoprotein (P) and large (L) protein are associated with the encapsidated RNA to comprise the ribonucleoprotein complex. The envelope is a lipid bilayer membrane and contains the two surface glycoproteins — a haemagglutinin-neuraminidase (HN) and fusion (F) hemolysin protein as well as a matrix (M) and a short hydrophobic (SH) membrane-associated protein (Wilson et al., 2006). The function of the SH protein is unclear. However, the gene encoding the SH protein is highly variable and has been used as the basis of genotyping mumps viruses for molecular epidemiological purposes (Jin et al., 1999; Muhlemann, 2004). Genotypes show nucleotide variation of 2% to 4% within genotypes, and 6% to 19% between genotypes (Johansson et al., 2002). There is one mumps virus serotype; 12 genotypes A to L have been described. A thirteenth genotype, M, has been proposed, but not officially adopted (Jin et al., 2005). The last two proteins, V and I, are nonstructural proteins. The V protein plays a role in interferon signaling and production, while the role of I protein is not known.

1.3 Mumps vaccines

The first mumps vaccine was developed in 1946 (Habel, 1946). It was based on formalin-inactivated virus, but was discontinued because immunity was short-lived (Habel, 1951). Since then numerous mumps vaccine strains have been developed and used in vaccines throughout the world. These vaccines have varied efficacy and safety profiles.

1.3.1 Jeryl Lynn

The first live attenuated mumps vaccine using the Jeryl Lynn strain was developed in the United States of America (USA) using an isolate from a child with mumps, and passaged in embryonated hens' eggs and chick embryo cell cultures (Buynak & Hilleman, 1966). Vaccines containing the Jeryl Lynn strain contain two distinct, but genetically related viruses (Afzal et al., 1993). The Jeryl Lynn vaccine is distributed worldwide and has been used exclusively in the USA since it was licensed in 1967.

1.3.2 RIT 4385

A mumps vaccine using the strain RIT 4385 was developed from the dominant virus component in the Jeryl Lynn vaccine strain. Vaccines containing this strain appear to have safety and efficacy profiles similar to vaccines containing the Jeryl Lynn strain.

1.3.3 Urabe Am 9

Another widely distributed mumps vaccine uses the Urabe Am 9 strain. The vaccine was developed in Japan from an isolate obtained from the saliva of a child with mumps, and passaged in chick embryo amniotic cavity and quail embryo fibroblasts. The strain contains at least two variants, one potentially more neurovirulent than the other (Yamanishi et al., 1973; Brown et al., 1996). Vaccines containing the Urabe Am 9 strain were primarily used in Canada, European countries and Japan; however, it has been withdrawn from Canada, Japan, the United Kingdom, and several other countries due to the increased incidence of aseptic meningitis following vaccination. There has been one report of transmission of the vaccine virus from a vaccinated child who developed parotitis 19 days after vaccination of a sibling. The deoxyribonucleic acid (DNA) sequence isolated from the child was specific to the Urabe Am 9 strain (Sawada et al., 1993).

1.3.4 Rubini

The isolate for the mumps vaccine containing the Rubini strain was attenuated in WI-38 (human diploid cell line) hens' eggs, and MRC-5 cells (Gluck et al., 1986). The vaccine containing the Rubini strain was introduced in some countries that had discontinued the use of vaccines containing the Urabe Am 9 strain. However, increased mumps incidence, including outbreaks in highly vaccinated populations (Toscani et al., 1996; Chamot et al., 1998; Goncalves et al., 1998; Goh, 1999; Schlegel et al., 1999; Pons et al., 2000), and reports of high attack rates among children vaccinated with the Rubini vaccine strain (Goh, 1999; Ciofi Degli Atti et al., 2002; Montes et al., 2002) in countries using vaccines containing the Rubini vaccine strain (Italy, Portugal, Singapore, Spain and Switzerland), indicated low efficacy of the vaccine. Subsequent investigations confirmed the vaccine to have little or no efficacy, and the World Health Organization recommended that the Rubini strain vaccine should not be used in national immunization programmes (WHO, 2001). The vaccine was consequently withdrawn.

1.3.5 Leningrad–3 and Leningrad–Zagreb

The mumps vaccine containing the Leningrad-3 strain was developed in 1967 in the former Soviet Union. It was obtained from a combination of five isolates of mumps viruses, and attenuated through passages in chick embryos and Japanese quail embryo cultures (Smorodintsev et al., 1965). A further attenuation of the Leningrad-3 mumps vaccine strain, Leningrad-Zagreb (L-Zagreb) vaccine strain, was developed in the 1970s in Croatia (formerly Yugoslavia). It was passaged on specific pathogen-free chick embryo fibroblast cell cultures (Beck et al., 1989). Several cases of transmission of L-Zagreb and Leningrad-3 vaccine strains have been reported, including a mumps case complicated by aseptic meningitis after transmission (Atrasheuskaya et al., 2006; Kaic et al., 2008; Vukic et al., 2008).

1.3.6 Other mumps vaccines

Many more mumps vaccines have been developed using additional vaccine strains, but have more limited distribution. They include: Sofia 6, developed in Bulgaria; S-12; BBM-18, a strain derived from the S-12 strain; S_{79}, derived from the Jeryl Lynn vaccine strain and licensed in China; PAVIVAC, used in the Czech Republic; and the Japanese strains, Hoshino, Torii Miyahara, and NK-M46 (Makino et al., 1976; Saskai et al., 1976; Fedova et al., 1987; Odisseev & Gacheva, 1994; Feiterna-Sperling et al., 2005; Fu et al., 2008; Plotkin & Rubin, 2008).

1.3.7 Mumps vaccine formulations

The trivalent measles, mumps, and rubella (MMR) vaccine formulation is the most commonly- used formulation for the mumps vaccine. However, the mumps vaccine is also available in monovalent, bivalent (measles and mumps), and tetravalent (measles, mumps, rubella and varicella) formulations.

1.3.8 Significant adverse reactions to mumps vaccination

Adverse reactions to mumps vaccination are rare, occurring 2–4 weeks after vaccination, and resolving without sequelae. The most common adverse reactions are parotitis and low-grade fever. However, post-vaccine aseptic meningitis does occur, but is generally mild to moderate and resolves within a week. Rates of reported post-vaccination aseptic meningitis are challenging to compare as they vary depending on vaccine strain, case definitions, ascertainment methods, clinical suspicion, age of the vaccine recipient, and whether the vaccine recipient received the first or subsequent dose (Bonnet et al., 2006). The rates of reported aseptic meningitis following mumps vaccination range from lowest with the Jeryl Lynn strain (<1 per 100 000 doses) to rates over 25 per 100 000 doses for vaccines containing the Urabe Am 9, Leningrad-3, Leningrad-Zagreb, Torii, Miyahara, or Hoshino strains (Table 1). The Urabe Am 9 vaccine virus has been isolated from several patients with meningitis within weeks of vaccination (Brown et al., 1991; Fujinaga et al., 1991), and an outbreak of aseptic meningitis occurred in Brazil following mass vaccination campaigns with MMR vaccine containing the Urabe Am 9 strain (Dourado et al., 2000). Although studies have reported incidence of aseptic meningitis following vaccination with L-Zagreb strain below one per 100 000 doses (Pan American Health Organization, 1999; Phadke et al., 2004; Kulkarni et al., 2005), several studies with baseline incidence data on aseptic meningitis found elevated incidence 2–4 weeks following mass vaccination campaigns with MMR vaccine containing L-Zagreb strain (da Cunha et al., 2002; da Silveira et al., 2002).

Furthermore, a prospective study in Croatia using virally confirmed cases of aseptic meningitis, found the incidence of aseptic meningitis 15 to 31 days following vaccination with L-Zagreb strain vaccine was 49 per 100 000 (Tesovic & Lesnikar, 2006).

Table 1: Incidence of aseptic meningitis following mumps vaccination

Reference	Country	Number of doses	Population vaccinated	Ascertainment of cases	Incidence per 100 000 doses
Jeryl Lynn/RIT 4385					
(Fescharek et al., 1990)	Germany	~5 500 000		Drug side-effect surveillance	0.1
(Schlipkoter et al., 2002)	Germany	1 575 936	≤15 years	National hospital surveillance system	<0.2
(Miller et al., 2007)	United Kingdom	>99 000	12–23 months	Hospital discharge diagnoses	<1
(Black et al., 1997)	United States	~300 000	12–23 months	Hospital discharge diagnoses	<1
Urabe Am 9					
(Al-Mazrou et al., 2002)	Saudi Arabia	2 412 078	6–13 years*	National, hospital, and school surveillance	0.3
(Jonville-Bera et al., 1996)	France		11 months – 10 years	Reports to regional pharmacovigilance centres or manufacturer	0.82 (95% CI: 0.77– 0.92)
(Furesz & Contreras, 1990)	Canada	250 000-300 000		Laboratory reports	1.6
(Rebiere & Galy-Eyraud, 1995)	France	3 290 470	Children (mostly <24 months)	Vaccine manufacturer's surveillance system and laboratory surveillance	3.5 (95% CI: 1.5–5.6)
(Farrington et al., 1995)	England	77 200	12–24 months	Hospital discharge diagnoses	6.7
(Dourado et al., 2000)	Brazil	452 344	1–11 years	State surveillance and prospective hospital admission following mass-vaccination campaign	7.1
(Miller et al., 2007)	United Kingdom	49 585	12–23 months	Hospital discharge diagnoses	8.0 (95% CI: 2.2–21)
(Sugiura & Yamada, 1991)	Japan	630 157	1–6 years	Passive surveillance to Ministry of Health	12–15
(Miller et al., 1993)	United Kingdom	78 300	12–24 months	Public Health Laboratories and hospital discharge diagnosis	17
(Colville & Pugh, 1992)	United Kingdom	22 817	12–24 months	Laboratory records	26 (95% CI: 5.3–47)
(Fujinaga et al., 1991)	Japan	11 750	1–6 years	Hospital surveillance	110
(Ueda et al., 1995)	Japan	6542		Prospective surveillance following vaccination	110
Leningrad 3					
(Cizman et al., 1989)	Yugoslavia	115 253	≤15 years	Hospital records	100

Reference	Country	Number of doses	Population vaccinated	Ascertainment of cases	Incidence per 100 000 doses
L-Zagreb					
(Pan American Health Organization, 1999)	Bahamas	>100 000	4–40 years	Surveillance activities not mentioned (note: small proportion of doses were Jeryl Lynn mumps strain)	0.96
(Phadke et al., 2004)	India	190 723	Children	Post-marketing surveillance surveys to paediatricians (note: response rate 68%)	1.0
(da Cunha et al., 2002)	Brazil	845 889	Children†	Routine surveillance system and hospital records	5.2–16
(Arruda & Kondageski, 2001)	Brazil	590 609	2–39 years	National surveillance	17
(da Silveira et al., 2002)	Brazil	110 629	1–11 years	Passive surveillance	29
(Dos Santos et al., 2002)	Brazil	2 226	6–12 years	Active follow-up	45
(Tesovic & Lesnikar, 2006)	Croatia	96 994	12–46 months	Prospective hospital study	49 (95% CI: 36–66)
(Tesovic et al., 1993)	Croatia		10 months–6 years	Hospital records	90 (95% CI: 64–116)
Torii					
(Ueda et al., 1995)	Japan	961		Prospective surveillance following vaccination	107
(Kimura et al., 1996)	Japan	8600	1–6 years	Active surveillance	140
Hoshino					
(Kimura et al., 1996)	Japan	21 717	1–6 years	Active surveillance	126
(Ueda et al., 1995)	Japan	3603		Prospective surveillance following vaccination	187

* Probable second dose.
† Campaign dose, irrespective of prior vaccination history.

2. Immunological response to natural infection

The immune response to mumps virus infection is likely to be the result of a complex interplay between both the humoral and cellular arms of the immune response, and no definitive correlates of protection have yet been identified. Studies on the immune response to mumps infection are quite limited in comparison to those described for measles and rubella infections.

2.1 Antibody response to mumps infection in unvaccinated individuals

In naive individuals immunoglobulin M (IgM) antibodies are measurable within a few days of symptom onset. IgM peaks about one week after the onset of parotitis or symptoms, and is detectable for weeks to months after parotitis onset (Ukkonen et al., 1981; Benito et al., 1987). Low avidity IgG may also be present at the time of symptom onset, although generally at a low level (Narita et al., 1998). IgG antibody increases rapidly and reaches maximum levels about three weeks after onset of symptoms. IgG antibodies remain at that level for about two to three months before they decrease again (Gotlieb et al., 1953; Ukkonen et al., 1981), and have been assumed to persist for life, though some more recent data question this assumption (see section 2.4). Mumps-specific salivary IgA antibodies can be detected up to five weeks after onset of illness before gradually decreasing, becoming undetectable around 10 weeks after onset (Chiba et al., 1973; Friedman, 1982).

2.2 Cell-mediated immunity following natural mumps disease

Lymphocytes are known to play an important role in host response to viral infections, and are believed to have a significant function in the immune response to mumps and recovery from mumps infection. While the presence of a plaque reduction neutralization titre to mumps appears to be associated with the development of mumps immunity, less is known about the development, significance, and function of mumps-specific cell-mediated immunity (CMI). Specific lymphocyte mediated cytotoxicity has been shown to correlate well with the presence, or absence, of detectable humoral responses to mumps, but failed to correlate with the magnitude of the antibody response (Rola-Pleszczynski et al., 1976). Mumps-specific cytotoxic T-cell (CTL) activity has been observed in individuals with natural mumps disease, with a peak response at 2–4 weeks after disease onset, and was associated with an antecedent lymphocyte proliferative response (Tsutsumi et al., 1980).

2.3 Maternal antibody

Maternal antibody (IgG) to mumps following natural infection is transferred across the placenta and is believed to provide protection to infants against clinical mumps. Clinical mumps occurs less frequently in infants aged less than one year (12% to 17%) compared to children aged one to four years (68%) (Philip et al., 1959; Meyer, 1962; Reed et al., 1967). Also, during an outbreak, two out of three infants under 12 months of age born to mothers with no history of clinical mumps developed mumps after exposure, while no infants under 12 months of age born to 10 mothers with prior history of clinical mumps developed disease (Meyer, 1962). In a separate study among 18 infants, most infants had detectable neutralizing antibodies at age two months (94%) and five months (66%), but by age 12 months none of the infants had detectable antibodies (Hodes & Brunell, 1970). Similarly, two other studies found 4% of 74 infants (Leineweber et al., 2004) and 25% of 32 infants (Sato et al., 1979) with detectable neutralizing antibodies at age 12 months.

2.4 Duration of immunity to natural mumps infection

Natural mumps virus infection is generally believed to provide long-lasting immunity. Twenty or more years after their mumps illness, most (82%) individuals still had detectable haemagglutination-inhibiting antibodies (Levitt et al., 1970). However, cases of clinically apparent mumps reinfection that have been confirmed with epidemiological links or laboratory tests have been reported (Meyer, 1962; Gut et al., 1995; Crowley & Afzal, 2002; Yoshida et al., 2008), and may be more common than previously thought.

3. Immunological response to vaccination

3.1 Antibody response following vaccination

In general, over 90% of infants and children develop detectable antibodies against mumps following vaccination with mumps vaccines (Table 2). Seroconversion rates are comparable for vaccine combinations with Jeryl Lynn, RIT 4385 and Urabe Am 9 strains (Isomura et al., 1973; Vesikari et al., 1983b; Usonis et al., 1998; Usonis et al., 1999; Usonis et al., 2001; Lee et al., 2002) except for one study that suggested higher serconversion for children receiving vaccines containing Urabe Am 9 than those receiving Jeryl Lynn-containing vaccines (Vesikari et al., 1983a). However, serological tests available for mumps antibodies are not consistent and rates vary depending on the method used. As a result, seroconversion rates vary widely from 74% to 100% for vaccines containing the Jeryl Lynn strain, 88% to 98% for vaccines containing the RIT 4385 strain, 79% to 100% for vaccines containing the Urabe Am 9 strains, 35% to 95% for vaccines containing the Rubini strain and 89% to 98% for vaccines containing the Leningrad-3 strain (Table 2). There is no difference in seroconversion between monovalent, bivalent, trivalent, or tetravalent formulations of the mumps vaccine (Weibel et al., 1973; Lerman et al., 1981; Shinefield et al., 2005; Bernstein et al., 2007).

Vaccination with the mumps vaccine induces relatively low levels of antibodies compared with natural infection. The mean neutralizing antibody titres detectable after vaccination were over five times lower than those produced after natural infection (Weibel et al., 1967; Hilleman et al., 1968). Similarly, haemagglutination-inhibiting titres after natural disease were 1:9 compared to 1:5 after vaccination (Weibel et al., 1967).

Six month old infants who were vaccinated in the presence of maternal antibody had lower neutralizing antibody titres and seroconversion rates compared to infants vaccinated at 9 and 12 months of age. Lower seroconversion was not only seen when vaccinated in the presence of passive antibody but also in the absence of maternal antibody, suggesting an intrinsic deficiency in young infants in antiviral antibody production (Gans et al., 2003). Seroconversion rates did not differ between infants vaccinated at nine months, 12 months, or 15 months of age (Schoub et al., 1990; Forleo-Neto et al., 1997; Klinge et al., 2000; Redd et al., 2004).

Table 2: Seroconversion following mumps vaccination

Strain	Number of studies	Seroconversion (%)		References
		Median	Range	
Jeryl Lynn, monovalent	6	95.9	74.2, 99.6	(Weibel et al., 1967; Hilleman et al., 1968; Sugg et al., 1968; Brunell et al., 1969; Vesikari et al., 1983b; Fedova et al., 1987)
Jeryl Lynn, bivalent	3	90.0	83.5, 90.6	(Weibel et al., 1973; Vesikari et al., 1983a; Popow-Kraupp et al., 1986)
Jeryl Lynn, trivalent	11	94	89, 97	(Borgono et al., 1973; Ehrenkranz et al., 1975; Schwarz et al., 1975; Lerman et al., 1981; Popow-Kraupp et al., 1986; Schwarzer et al., 1998; Usonis et al., 1998; Usonis et al., 1999; Klinge et al., 2000; Redd et al., 2004; Feiterna-Sperling et al., 2005)
Jeryl Lynn, tetravalent	4	99.5	98, 100	(Watson et al., 1996; Shinefield et al., 2005; Kuter et al., 2006; Bernstein et al., 2007)
RIT 4385, trivalent	8	96.4	88, 98.6	(Usonis et al., 1998; Gatchalian et al., 1999; Usonis et al., 1999; Crovari et al., 2000; Lee et al., 2002; Nolan et al., 2002; Stuck et al., 2002; Lim et al., 2007)
Urabe Am 9, monovalent	3	94.8	82.6, 97	(Isomura et al., 1973; Ehrengut et al., 1983; Vesikari et al., 1983b)
Urabe Am 9, bivalent	2	84.2	78.7, 96.9	(Vesikari et al., 1983a; Popow-Kraupp et al., 1986)
Urabe Am 9, trivalent	5	99	96.9, 100	(Berger et al., 1988; Robertson et al., 1988; Dunlop et al., 1989; Schoub et al., 1990; Forleo-Neto et al., 1997)
Rubini	5	93.3	23.3, 95	(Gluck et al., 1986; Just et al., 1986; Berger et al., 1988; Schwarzer et al., 1998; Khalil et al., 1999; Crovari et al., 2000)
Leningrad-3	4	93.5	89, 98	(Smorodintsev et al., 1970)
Leningrad-Zagreb	2	89.4	88.1, 90.7	(Beck et al., 1989)
BBM-18	1	84.8		(Feiterna-Sperling et al., 2005)
Sofia 6	2	93.4	92.6, 94.1	(Odisseev & Gacheva, 1994)
Hoshino	2	98.4	96.8, 100	(Makino et al., 1990)
S-12	1	93		(Sassani et al., 1991)

3.2 Immune responses to revaccination

Studies have examined presence of antibodies prior to and following the second dose of mumps vaccine. In a prospective study, <1% of subjects were seronegative before a second dose of mumps vaccine and, following the second dose, IgM was detectable in only 2% of individuals, suggesting that most vaccine recipients had mounted a secondary immune response to revaccination (LeBaron et al., 2009). Although up to 30% of individuals were reported to be seronegative prior to revaccination in other studies, 75% to 97% seroconverted following the second dose of mumps vaccine. There was no assessment to determine if seronegativity was due to primary vaccine failure, or having antibody below the level of test detection (Broliden et al., 1998; Gothefors et al., 2001).

Among individuals with neutralizing antibodies prior to receipt of a second dose, an increase in antibody levels generally occurred following revaccination. More than 50% of those revaccinated had a four-fold increase in antibody titres (LeBaron et al., 2009). In addition, the proportion of individuals with low titres was significantly reduced.

3.3 Cell-mediated immunity following mumps vaccination

Following vaccination with live attenuated mumps vaccine, most, but not all children with anti-mumps antibody in their sera, demonstrated a lymphocyte proliferative response to mumps antigen (Ilonen, 1979; Ilonen et al., 1984). Unlike the humoral immune response to mumps, cellular responses were equivalent in all age groups and were independent of the presence of maternal antibody (Gans et al., 2001). In addition, associations of specific histocompatibility leukocyte antigen (HLA) haplotypes with higher or lower frequencies of mumps antigen reactive T lymphocytes, have been observed (Bruserud & Thorsby, 1985; Hyoty et al., 1986; Bruserud et al., 1987; Tan et al., 2001; Ovsyannikova et al., 2008), suggesting that host genetic factors may influence the immune response to mumps.

3.4 Duration of immunity to mumps vaccination

Data regarding long-term immunity against mumps after vaccination are limited. Studies indicate that one dose of MMR vaccine can provide persistent antibodies to mumps. Between 70% and 99% of individuals had detectable anti-mumps antibodies using enzyme-linked immunosorbent assay (ELISA) or neutralization tests approximately ten years after initial vaccination (Broliden et al., 1998; Gothefors et al., 2001; LeBaron et al., 2009) (Table 3). Differences in laboratory method may account for the wide variation in detection rates. In addition, among adults who were vaccinated in childhood, T-cell immunity to mumps was high (70%) and comparable to adults who acquired natural infection in childhood (80%) (Hanna-Wakim et al., 2008).

Table 3: Long-term persistence of mumps antibodies following vaccination with mumps Jeryl Lynn vaccine

Reference	Country	Years after vaccination	Number seropositive/ Number tested (%)	Serological method used
1 dose				
(LeBaron et al., 2009)	United States	10	304/308 (99)	Plaque-reduction neutralization
(Gothefors et al., 2001)	Sweden	~10	230/299 (70)	ELISA
(Broliden et al., 1998)	Sweden	~11	167/229 (73)	Neutralizing antibodies
2 doses				
(LeBaron et al., 2009)	United States	7	17/189 (91)	Plaque-reduction neutralization
(Date et al., 2008)	United States	≥11	134/146 (92)	Commercial EIA
(LeBaron et al., 2009)	United States	12	146/154 (95)*	Plaque-reduction neutralization
(Davidkin et al., 2008)	Finland	15	67/90 (74)	Commercial EIA

* All subjects were seropositive prior to receipt of second mumps vaccine.

In two-dose recipients, mumps antibodies were detectable in 95% and 74% of children 12 and 15 years after receipt of a second dose of MMR, respectively, but antibody levels declined with time (Table 3) (Davidkin et al., 2008; LeBaron et al., 2009). The geometric mean neutralizing antibody titre among persons vaccinated within five years was higher than those vaccinated 15 or more years ago, but increased time since receipt of second dose was not associated with having undetectable antibodies (Date et al., 2008). No clear advantage in terms of level of neutralizing antibody was seen in deferring the second dose MMR from kindergarten to middle-school students since, by age 17, both groups had similar levels of neutralizing anti-mumps antibody (LeBaron et al., 2009). However, loss of antibodies does not necessarily imply the loss of clinical protection. Mumps antigen-specific lymphoproliferative responses have been detected among vaccine recipients who have undetectable antibody levels (Jokinen et al., 2007; Vandermeulen et al., 2009). In a study among individuals with either seronegative (28%) or low antibody titres, 98% had a proliferative response to mumps antigen approximately 15 years after a second dose of mumps vaccine (Jokinen et al., 2007). Furthermore, a study in Belgium demonstrated that CMI responses were more persistent than antibody responses (Vandermeulen et al., 2009). The significance and function of mumps-specific CMI in protection against mumps disease has yet to be determined. Finally, the role of external boosting from exposure to wild mumps virus in maintaining immunity has not been studied.

3.5 Correlates of immunity

Humoral immunity is important in protection against mumps, and antibody measurements are often used as a surrogate measure of immunity to viral infections. However, there is poor correlation between assays that measure neutralization and less labour-intensive methods that measure the presence of mumps antibody (Pipkin et al., 1999). While no serological test available for mumps consistently and reliably predicts immunity, neutralizing antibodies appear to be a reasonable marker for immunity. Antibodies directed against haemagglutinin-neuraminidase protein (HN) have been shown to neutralize the infectivity of mumps virus, and animal models suggest that antibodies against F, the other mumps surface glycoprotein, may also be involved in neutralization (Orvell, 1978; Love et al., 1986; Houard et al., 1995). In several outbreaks among unvaccinated individuals, there have been correlations between neutralizing antibodies and susceptibility to mumps, where those with neutralizing antibody titres above 1:2 (Brunell et al., 1968) and 1:4 (Meyer et al., 1966; Ennis, 1969) were protected from mumps infection. In addition, the vaccinated children who developed mumps during pre-licensure studies had low (<1:2) or undetectable neutralizing antibodies after vaccination (Hilleman et al., 1968).

A seropositive response by ELISA may not necessarily represent protection, and decreased levels of anti-mumps IgG antibody, or lack of anti-mumps IgG antibody, does not necessarily translate to susceptibility. ELISAs can provide overestimates if all positive results are considered an indication of protection against disease, since both neutralizing and non-neutralizing antibodies give positive results (Christenson & Bottiger, 1990). In addition, false-negative results may be obtained because antibody levels to mumps following vaccination are frequently low, and may be missed. The level and specificity of antibody or neutralizing antibody necessary for protection is unclear, as is the role of cell-mediated immunity in facilitating or enhancing protection. It is worth noting that 41 out of 43 military personnel who developed mumps disease within three months to five years after joining the military

were positive for mumps IgG antibodies measured by ELISA at entry (Eick et al., 2008). Potential explanations for this include the possibility that total mumps IgG does not necessarily correlate with protection from mumps infection, or that immunity waned below protective levels during the time from blood screening to time of mumps infection. More studies are needed on correlates of immunity, including CMI markers, and whether presence of CMI enables a rapid enough initiation of immune response following exposure to prevent mumps.

4. Laboratory diagnosis of mumps

A clinical diagnosis of mumps is frequently made when parotitis is evident at the time of patient examination. However, since parotitis may be caused by other viral or non-viral diseases or conditions, laboratory confirmation using virological or serological techniques may be needed, especially as mumps disease becomes rare due to increased vaccination.

4.1 Virological methods

Mumps virus is stable for several days at 4°C. Stability increases with decreasing temperature and the virus can be stored indefinitely at -70°C. Specimen quality appears to greatly impact the ability to culture mumps virus and detect mumps RNA using reverse transcriptase-polymerase chain reaction (RT-PCR) (Utz et al., 1958). Mumps virus and RNA can be detected from blood, saliva, cerebrospinal fluid and urine. However, the sensitivity of mumps RNA detection in urine is poor (Krause et al., 2006). Since mumps virus replication is transient, there is a limited timeframe for virus isolation which appears to be most successful immediately prior to, and within the first few days after, onset of parotitis (Centers for Disease Control and Prevention, 2008). Mumps viral load and mumps RNA detection decreases over the first three days after onset of symptoms, and is lower in individuals who have been vaccinated or had prior history of disease (Okafuji et al., 2005; Bitsko et al., 2008; Rota et al., 2009). One study demonstrated highest isolation rates (64%) among unvaccinated cases, followed by vaccinated cases (41%) and cases with previous history of mumps (17%) (Yoshida et al., 2008). Detection of mumps RNA is generally more sensitive than culture-based methods (Poggio et al., 2000; Uchida et al., 2005).

4.2 Serological methods

Detection of mumps-specific IgM antibody in serum or saliva is a good diagnostic measure in unvaccinated patients. Timing of specimen collection is important to consider in interpreting laboratory results. Negative IgM ELISA results may occur when serum is collected prior to day four of clinical presentation (Cunningham et al., 2006; Krause et al., 2007). By contrast, patients who mount a secondary immune response, as occurs in the majority of vaccinated mumps cases, may not have an IgM response, or it may be transient and not detected depending on timing of specimen collection. Therefore, a high number of false-negative results may occur in previously-vaccinated individuals, and the absence of an anti-mumps IgM response in a vaccinated or previously infected individual presenting with clinically compatible mumps does not rule out mumps as a diagnosis. Failure to detect mumps IgM in previously-vaccinated individuals has been well documented (Ukkonen & Penttinen, 1981; Gut et al., 1985; Narita et al., 1998; Pebody et al., 2002; Krause et al., 2006; Rota et al., 2009).

The ability to detect IgM varies by vaccination status and is highest in unvaccinated cases (80% to 100%) (Sakata et al., 1985), intermediate in one-dose recipients (60% to 80%) (Briss et al., 1994; Narita et al., 1998) and lowest in two-dose recipients (13% to 14%) (Bitsko et al., 2008; Rota et al., 2009). IgM test methods and kits vary considerably in their sensitivity and specificity. The capture IgM ELISA is the most sensitive method, but has limited commercial availability.

When IgM is negative, a convalescent serum demonstrating seroconversion or a significant rise (four-fold) in IgG titre between the acute and convalescent serum sample can be used to confirm diagnosis of mumps. However, this rise in titre may not occur in vaccinated individuals. IgG avidity testing is an important tool that can be used to differentiate between primary and secondary vaccine failure (Narita et al., 1998; Sanz-Moreno et al., 2005; Park et al., 2007) and can assist in determining the role of waning immunity in current outbreaks. In the case of reinfection or mumps infection in previously vaccinated individuals, an elevated titre of high avidity mumps-specific IgG is observed (Gut et al., 1995) (Table 4).

Table 4: Immune response to mumps wild-type infection based on exposure history

Previous infection history	IgM	IgG	Avidity	Comments	References
Unvaccinated No history of mumps	+	+ or -	Low	IgM may be detected for weeks to months Low levels of low avidity IgG may be present at disease onset	(Meurman et al.. 1982; Sakata et al., 1985)
Previously vaccinated 1 dose	+ or -	Likely +	Low: primary vaccine failure High: secondary vaccine failure	Serum collected: 1–10 days: 50% IgM+ >10 days: 50%–80% IgM +	(Narita et al., 1998; Jin et al., 2004; Krause et al., 2007)
Previously vaccinated 2 doses	+ or -	Likely +	Low: primary vaccine failure High: secondary vaccine failure	Serum Collected: 1–3 days: 12%–14% IgM+	(Bitsko et al., 2008; Rota et al., 2009)
Wild-type mumps	+ or -	+	High	IgM infrequently detected	

4.3 Diagnostic challenges

Laboratory diagnosis of mumps in highly-vaccinated populations is challenging, and new laboratory tools and diagnostic approaches are needed to accurately identify cases and better understand the epidemiology of mumps in highly-vaccinated populations. During the 2006 mumps outbreak in the USA, the majority of patients who had received two doses of MMR and presented with symptoms that were clinically compatible with mumps could not be laboratory confirmed using the serological, virological, or molecular methods that have been so successful in confirming mumps in unvaccinated populations (Dayan et al., 2008). RT-PCR and cell culture are the best diagnostic tests currently available to detect mumps infection in previously vaccinated individuals (Bitsko et al., 2008; Rota et al., 2009).

5. Vaccine performance

5.1 Vaccine efficacy

Prelicensure studies conducted in over 7000 children enrolled in nursery or elementary schools found a single dose of mumps vaccines containing the Jeryl Lynn strain to be approximately 95% effective in preventing mumps disease (Hilleman et al., 1967; Weibel et al., 1967; Sugg et al., 1968). However, duration of follow-up was short (up to 20 months). In a smaller study, with 193 children exposed to persons with clinical mumps, the efficacy of the mumps vaccine containing the Leningrad-3 strain was 94% (95% CI: 76% to 98%) (Smorodintsev et al., 1965). Additional studies using vaccines containing Leningrad-3 strain found efficacy between 97% and 99% (Smorodintsev et al., 1970).

5.2 Vaccine effectiveness

5.2.1 Vaccine effectiveness of one dose

In postlicensure studies, vaccine effectiveness estimates for prevention of mumps disease have been lower (Table 5). In 18 studies from outbreaks (primarily school children) in North America and Europe, the median estimate for vaccine effectiveness of one dose of the Jeryl Lynn mumps vaccine was 79% (range: 62% to 91%) (Lewis et al., 1979; Kim-Farley et al., 1985; Sullivan et al., 1985; Chaiken et al., 1987; Wharton et al., 1988; Hersh et al., 1991; Cheek et al., 1995; Toscani et al., 1996; Chamot et al., 1998; Schlegel et al., 1999; Richard et al., 2003; Harling et al., 2005; Ong et al., 2005; Sartorius et al., 2005; Cohen et al., 2007; Schaffzin et al., 2007; Marin et al., 2008; Castilla et al., 2009). Similarly, the median vaccine effectiveness estimates for vaccines containing the Urabe Am 9 strain in five studies was 73% (range: 54% to 87%) (Toscani et al., 1996; Chamot et al., 1998; Goncalves et al., 1998; Schlegel et al., 1999; Ong et al., 2005). Although there are several studies that include populations that may have received mumps vaccines containing the RIT 4385 strain (Harling et al., 2005; Cohen et al., 2007), no studies have examined vaccine effectiveness exclusively for mumps vaccines containing the RIT 4385 strain. The vaccine effectiveness of vaccines containing the RIT 4385 strain is expected to be similar to the Jeryl Lynn strain because it was derived from that strain.

Table 5: Mumps vaccine effectiveness

Reference	Country	Population	Number in study	Vaccine effectiveness (%)
Jeryl Lynn — one dose				
(Chamot et al., 1998)	Switzerland	Close contacts		62 (95% CI: 0, 85)
(Harling et al., 2005)	England	Population	353	64 (95% CI: 40, 78)
(Toscani et al., 1996)	Switzerland	School		65 (95% CI: 11, 86)
(Sartorius et al., 2005)	Sweden	Population	Screening method	65
(Castilla et al., 2009)	Spain	Population (children)	1057	66 (95% CI: 25, 85)
(Richard et al., 2003)	Switzerland	Population (young children)	324	70 (95% CI: 50, 80)
(Lewis et al., 1979)	Canada	School	495	75
(Wharton et al., 1988)	United States	School	385	78 (95% CI: 65, 86)
(Schlegel et al., 1999)	Switzerland	Population (children)	44	78 (95% CI: 64, 82)
(Schaffzin et al., 2007)	United States	Camp attendees and staff	67	80 (95% CI: 42, 93)
(Sullivan et al., 1985)	United States	School	434	81 (95% CI: 71, 88)
(Ong et al., 2005)	Singapore	Child care centre and school	1325	81 (95% CI: 58, 91)
(Cheek et al., 1995)	United States	School	307	82 (95% CI: 77, 86)
(Marin et al., 2008)	United States	College population	235	82 (95% CI: 0, 98)
(Hersh et al., 1991)	United States	School	1721	83 (95% CI: 57, 94)
(Kim-Farley et al., 1985)	United States	School	66	85 (95% CI: 39, 94)
(Cohen et al., 2007)*	England	Population	Screening method	88 (95% CI: 83, 91)
(Chaiken et al., 1987)	United States	School	165	91 (95% CI: 77, 93)
Jeryl Lynn — two doses				
(Marin et al., 2008)	United States	College population	2141	79 (95% CI: 0, 97)
(Castilla et al., 2009)	Spain	Population (children)	425	83 (95% CI: 54, 94)
(Harling et al., 2005)*	England	Population	153	88 (95% CI: 62, 96)
(Marin et al., 2008)	United States	Close contacts	74	88 (95% CI: 63, 96)
(Sartorius et al., 2005)	Sweden	Population	Screening method	91
(Schaffzin et al., 2007)	United States	Camp population	461	92 (95% CI: 83, 96)
(Cohen et al., 2007)*	England	Population	Screening method	95 (95% CI: 93, 96)
Urabe Am 9				
(Ong et al., 2005)	Singapore	Childcare centre and school	804	54 (95% CI: -16, 82)
(Goncalves et al., 1998)	Portugal	Population	242	70 (95% CI: 25, 88)
(Chamot et al., 1998)	Switzerland	Close contacts		73 (95% CI: 42, 88)
(Toscani et al., 1996)	Switzerland	School		76 (95% CI: 36, 91)
(Schlegel et al., 1999)	Switzerland	Population	48	87 (95% CI: 76, 94)
Rubini				
(Pons et al., 2000)	Spain	School	422	-340
(Ong et al., 2005)	Singapore	Childcare centre and school	2308	-55 (95% CI: -122, -9)
(Schlegel et al., 1999)	Switzerland	Population	87	-4 (95% CI: -218, 15)
(Goncalves et al., 1998)	Portugal	Population	369	1 (95% CI: -108, 53)
(Chamot et al., 1998)	Switzerland	Close contacts		6 (95% CI: -46, 40)
(Toscani et al., 1996)	Switzerland	School		12 (95% CI: -102, 62)
(Pons et al., 2000)	Spain	School	124	40 (95% CI: -66, 78)

Reference	Country	Population	Number in study	Vaccine effectiveness (%)
(Richard et al., 2003)	Switzerland	Population (young children)	213	30 (95% CI: -30, 60)
(Paccaud et al., 1995)	Switzerland	School	156	50 (95% CI: -19, 81)
Leningrad-Zagreb				
(Beck et al., 1989)	Yugoslavia	Pre-school		97-100
Leningrad-3				
(Smorodintsev et al., 1965)		School	193	94 (95% CI: 76, 98)
S_{79}				
(Fu et al., 2008)	China	Population (8 month–12 years)	937	86 (95% CI: 77, 92)
(Fu et al., 2009)	China	Population (8 month–12 years)	366	83 (95% CI: 68, 91)
Sofia 6				
(Odisseev & Gacheva, 1994)	Bulgaria	Contacts		98

* Some of the study population may have received mumps vaccine containing RIT 4385 strain.

With regard to the Rubini strain mumps vaccine, several studies in outbreak settings indicated that the vaccine had little or no effectiveness against disease (Table 5). The vaccine effectiveness estimates from Portugal, Singapore, Spain and Switzerland ranged from -55% to 50% (Paccaud et al., 1995; Toscani et al., 1996; Chamot et al., 1998; Goncalves et al., 1998; The Benevento and Compobasso Paediatricians Network for the Control of Vaccine-Preventable Diseases, 1998; Goh, 1999; Schlegel et al., 1999; Pons et al., 2000; Richard et al., 2003; Ong et al., 2005). Mumps vaccine containing the Rubini strain is no longer licensed or available. Limited studies with the Leningrad-Zagreb (Beck et al., 1989), Leningrad-3 (Smorodintsev et al., 1965), S_{79} (Fu et al., 2008; Fu et al., 2009) and Sofia 6 (Odisseev & Gacheva, 1994) strains, estimate the vaccine to be between 77% and 100% effective (Table 5). Data on vaccine effectiveness of other strains are not available in English peer-review publications.

5.2.2 Vaccine effectiveness of two doses

Studies on vaccine effectiveness of two doses have only been conducted for vaccines containing the Jeryl Lynn strain. Seven estimates of vaccine effectiveness of two doses of Jeryl Lynn mumps vaccine are available from six studies with a median estimate of 88% (range: 79% to 95%) (Table 5) (Harling et al., 2005; Sartorius et al., 2005; Cohen et al., 2007; Schaffzin et al., 2007; Marin et al., 2008; Castilla et al., 2009). Although five of the six studies had higher vaccine effectiveness for two doses compared to one dose, only one study reached statistical significance, and this was probably due to the large sample size (Cohen et al., 2007). Despite relatively high two-dose vaccine effectiveness, high two-dose vaccine coverage may not be sufficient to prevent all outbreaks (Cortese et al., 2008; Dayan & Rubin, 2008).

A number of studies documented increased risk of developing mumps with increasing time after vaccination (Vandermeulen et al., 2004; Cortese et al., 2008; Castilla et al., 2009), and data from the United Kingdom indicates vaccine effectiveness may decrease with age, which probably also reflects increasing time from vaccination (Cohen et al., 2007).

Antigenic variation among mumps viruses has been cited as a possible explanation for vaccine failure or reinfection, and reduced cross-neutralization between strains of different genotypes has been observed (Nojd et al., 2001; Crowley & Afzal, 2002; Orvell et al., 2002; Rubin et al., 2006; Rubin et al., 2008). The significance of these differences is unclear. While antigenic differences could lead to decreases in vaccine effectiveness, mumps vaccine (genotype A virus) has been highly effective in preventing mumps during outbreaks due to genotype G in Europe and the USA (Cohen et al., 2007; Schaffzin et al., 2007). Mumps vaccines manufactured from different strains/genotypes have also been highly effective in controlling mumps throughout the world. Differences in neutralization capability between mumps virus strains may become significant when levels of neutralizing antibody are already low and force of infection is high. Additional studies are needed to establish a link between protection and a particular level of neutralizing anti-mumps antibodies, and to investigate the role of heterologous mumps strains in decreased vaccine efficacy.

References

Afzal MA et al. (1993). The Jeryl Lynn vaccine strain of mumps virus is a mixture of two distinct isolates. *The Journal of General Virology*, 74 (Pt. 5):917–920.

Al-Mazrou Y et al. (2002). Safety evaluation of MMR vaccine during a primary school campaign in Saudi Arabia. *Journal of Tropical Pediatrics*, 48(6):354–358.

Arday DR et al. (1989). Mumps in the US Army 1980–86: should recruits be immunized? *American Journal of Public Health*, 79(4):471–474.

Arruda WO, Kondageski C (2001). Aseptic meningitis in a large MMR vaccine campaign (590,609 people) in Curitiba, Parana, Brazil, 1998. *Revista do Instituto de Medicina Tropical de São Paulo*, 43(5):301–302.

Association for the Study of Infectious Diseases (1974). A retrospective survey of the complications of mumps. *The Journal of the Royal College of General Practitioners*, 24(145):552–556.

Atrasheuskaya AV et al. (2006). Horizontal transmission of the Leningrad-3 live attenuated mumps vaccine virus. *Vaccine*, 24(10):1530–1536.

Azimi PH et al. (1969). Mumps meningoencephalitis in children. *JAMA : The Journal of the American Medical Association*, 207(3):509–512.

Bang HO, Bang J (1943). Involvement of the central nervous system in mumps. *Acta medica scandinavica*, 113:487–505.

Beard CM et al. (1977). The incidence and outcome of mumps orchitis in Rochester, Minnesota, 1935 to 1974. *Mayo Clinic Proceedings. Mayo Clinic*, 52(1):3–7.

Beck M et al. (1989). Mumps vaccine L-Zagreb, prepared in chick fibroblasts. I. Production and field trials. *Journal of Biological Standardization*, 17(1):85–90.

Benito RJ et al. (1987). Persistence of specific IgM antibodies after natural mumps infection. *The Journal of Infectious Diseases*, 155(1):156–157.

Berger R et al. (1988). Interference between strains in live virus vaccines. I: Combined vaccination with measles, mumps and rubella vaccine. *Journal of Biological Standardization*, 16(4):269–273.

Bernstein HH et al. (2007). Comparison of the safety and immunogenicity of a refrigerator-stable versus a frozen formulation of ProQuad (measles, mumps, rubella, and varicella virus vaccine live). *Pediatrics*, 119(6):e1299–e1305.

Bitnun S et al. (1986). Acute bilateral total deafness complicating mumps. *The Journal of Laryngology and Otology*, 100(8):943–945.

Bitsko RH et al. (2008). Detection of RNA of mumps virus during an outbreak in a population with a high level of measles, mumps, and rubella vaccine coverage. *Journal of Clinical Microbiology*, 46(3):1101–1103.

Black S et al. (1997). Risk of hospitalization because of aseptic meningitis after measles-mumps-rubella vaccination in one- to two-year-old children: an analysis of the Vaccine Safety Datalink (VSD) Project. *The Pediatric Infectious Disease Journal*, 16(5):500–503.

Bonnet MC et al. (2006). Mumps vaccine virus strains and aseptic meningitis. *Vaccine*, 24(49–50):7037–7045.

Borgono JM et al. (1973). A field trial of combined measles-mumps-rubella vaccine. Satisfactory immunization with 188 children in Chile. *Clinical Pediatrics*, 12(3):170–172.

Briss PA et al. (1994). Sustained transmission of mumps in a highly vaccinated population: assessment of primary vaccine failure and waning vaccine-induced immunity. *The Journal of Infectious Diseases*, 169(1):77–82.

Broliden K et al. (1998). Immunity to mumps before and after MMR vaccination at 12 years of age in the first generation offered the two-dose immunization programme. *Vaccine*, 16(2–3):323–327.

Brown EG et al. (1991). Nucleotide sequence analysis of Urabe mumps vaccine strain that caused meningitis in vaccine recipients. *Vaccine*, 9(11):840–842.

Brown EG et al. (1996). The Urabe AM9 mumps vaccine is a mixture of viruses differing at amino acid 335 of the hemagglutinin-neuraminidase gene with one form associated with disease. *The Journal of Infectious Diseases* 174(3):619–622.

Brown JW et al. (1948). Central nervous system involvement during mumps. *The American Journal of the Medical Sciences*, 215(4):434–441.

Brunell PA et al. (1968). Ineffectiveness of isolation of patients as a method of preventing the spread of mumps. Failure of the mumps skin-test antigen to predict immune status. *The New England Journal of Medicine*, 279(25):1357–1361.

Brunell PA et al. (1969). Evaluation of a live attenuated mumps vaccine (Jeryl Lynn). With observations on the optimal time for testing serologic response. *American Journal of Diseases of Children (1960)*, 118(3):435–40.

Bruserud O, Thorsby E (1985). HLA control of the proliferative T lymphocyte response to antigenic determinants on mumps virus. Studies of healthy individuals and patients with type 1 diabetes. *Scandinavian Journal of Immunology*, 22(5):509–518.

Bruserud O et al. (1987). The mumps-specific T cell response in healthy individuals and insulin-dependent diabetics: preferential restriction by DR4-associated elements. *Acta Pathologica, Microbiologica, et Immunologica Scandinavica. Section C, Immunology*, 95(4):173–175.

Buynak EB, Hilleman MR (1966). Live attenuated mumps virus vaccine. 1. Vaccine development. *Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.)*, 123(3):768–775.

Cantell K (1961). Mumps virus. *Advances in Virus Research*, 8:123–164.

Castilla J et al. (2009). Effectiveness of Jeryl Lynn-containing vaccine in Spanish children. *Vaccine*, 27(15):2089–2093.

Centers for Disease Control and Prevention (2008). Updated recommendations for isolation of persons with mumps. *MMWR. Morbidity and Mortality Weekly Report*, 57(40):1103–1105.

Chaiken BP et al. (1987). The effect of a school entry law on mumps activity in a school district. *JAMA : The Journal of the American Medical Association*, 257(18): 2455–2458.

Chamot E et al. (1998). [Estimation of the efficacy of three strains of mumps vaccines during an epidemic of mumps in the Geneva canton (Switzerland)]. *Revue d'Épidémiologie et de Santé Publique*, 46(2):100–107.

Cheek JE et al. (1995). Mumps outbreak in a highly vaccinated school population. Evidence for large-scale vaccination failure. *Archives of Pediatrics & Adolescent Medicine*, 149(7):774–778.

Chiba Y et al. (1973). Virus excretion and antibody response in saliva in natural mumps. *The Tohoku Journal of Experimental Medicine*, 111(3):229–238.

Christenson B, Bottiger M (1990). Methods for screening the naturally acquired and vaccine-induced immunity to the mumps virus. *Biologicals : Journal of the International Association of Biological Standardization*, 18(3):213–219.

Ciofi Degli Atti ML et al. (2002). Pediatric sentinel surveillance of vaccine-preventable diseases in Italy. *The Pediatric Infectious Disease Journal*, 21(8):763–768.

Cizman M et al. (1989). Aseptic meningitis after vaccination against measles and mumps. *The Pediatric Infectious Disease Journal*, 8(5):302–308.

Cohen C et al. (2007). Vaccine effectiveness estimates, 2004–2005 mumps outbreak, England. *Emerging Infectious Diseases*, 13(1):12–17.

Colville A, Pugh S (1992). Mumps meningitis and measles, mumps, and rubella vaccine. *Lancet*, 340(8822):786.

Cooney MK et al. (1975). The Seattle Virus Watch. VI. Observations of infections with and illness due to parainfluenza, mumps and respiratory syncytial viruses and Mycoplasma pneumoniae. *American Journal of Epidemiology*, 101(6):532–551.

Cortese MM et al. (2008). Mumps vaccine performance among university students during a mumps outbreak. *Clinical Infectious Diseases : an official publication of the Infectious Diseases Society of America*, 46(8):1172–1180.

Crovari P et al. (2000). Reactogenicity and immunogenicity of a new combined measles-mumps-rubella vaccine: results of a multicentre trial. The Cooperative Group for the Study of MMR vaccines. *Vaccine*, 18(25):2796–2803.

Crowley B, Afzal MA (2002). Mumps virus reinfection—clinical findings and serological vagaries. *Communicable Disease and Public Health /PHLS*, 5(4):311–313.

Cunningham C et al. (2006). Importance of clinical features in diagnosis of mumps during a community outbreak. *Irish Medical Journal*, 99(6):171–173.

da Cunha SS et al. (2002). Outbreak of aseptic meningitis and mumps after mass vaccination with MMR vaccine using the Leningrad-Zagreb mumps strain. *Vaccine*, 20(7–8):1106–1112.

da Silveira CM et al. (2002). The risk of aseptic meningitis associated with the Leningrad-Zagreb mumps vaccine strain following mass vaccination with measles-mumps-rubella vaccine, Rio Grande do Sul, Brazil, 1997. *International Journal of Epidemiology*, 31(5):978–982.

Date AA et al. (2008). Long-term persistence of mumps antibody after receipt of 2 measles-mumps-rubella (MMR) vaccinations and antibody response after a third MMR vaccination among a university population. *The Journal of Infectious Diseases*, 197(12):1662–1668.

Davidkin I et al. (2008). Persistence of measles, mumps, and rubella antibodies in an MMR-vaccinated cohort: a 20-year follow-up. *The Journal of Infectious Diseases*, 197(7):950–956.

Dayan GH, Rubin S (2008). Mumps outbreaks in vaccinated populations: are available mumps vaccines effective enough to prevent outbreaks? *Clinical Infectious Diseases : an official publication of the Infectious Diseases Society of America*, 47(11): 1458–1467.

Dayan GH et al. (2008). Recent resurgence of mumps in the United States. *The New England Journal of Medicine*, 358(15):1580–1589.

Dos Santos BA et al. (2002). An evaluation of the adverse reaction potential of three measles-mumps-rubella combination vaccines. *Revista Panamericana de Salud Pública = Pan American Journal of Public Health*, 12(4):240–246.

Doshi S et al. (2009). Ongoing measles and rubella transmission in Georgia, 2004–05: implications for the national and regional elimination efforts. *International Journal of Epidemiology*, 38:182–191.

Dourado I et al. (2000). Outbreak of aseptic meningitis associated with mass vaccination with a urabe-containing measles-mumps-rubella vaccine: implications for immunization programmes. *American Journal of Epidemiology*, 151(5):524–530.

Dunlop JM et al. (1989). An evaluation of measles, mumps and rubella vaccine in a population of Yorkshire infants. *Public Health*, 103(5):331–335.

Ehrengut W et al. (1983). The reactogenicity and immunogenicity of the Urabe Am 9 live mumps vaccine and persistence of vaccine-induced antibodies in healthy young children. *Journal of Biological Standardization*, 11(2):105–113.

Ehrenkranz NJ et al. (1975). Clinical evaluation of a new measles-mumps-rubella combined live virus vaccine in the Dominican Republic. *Bulletin of the World Health Organization*, 52(1):81–85.

Eick AA et al. (2008). Incidence of mumps and immunity to measles, mumps and rubella among US military recruits, 2000–2004. *Vaccine*, 26(4):494–501.

Ennis FA (1969). Immunity to mumps in an institutional epidemic. Correlation of insusceptibility to mumps with serum plaque neutralizing and hemagglutination-inhibiting antibodies. *The Journal of Infectious Diseases*, 119(6):654–657.

Ennis FA, Jackson D (1968). Isolation of virus during the incubation period of mumps infection. *The Journal of Pediatrics*, 72(4):536–537.

Falk WA et al. (1989). The epidemiology of mumps in southern Alberta 1980–1982. *American Journal of Epidemiology*, 130(4):736–749.

Farrington P et al. (1995). A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet*, 345(8949):567–569.

Fedova D et al. (1987). Detection of postvaccination mumps virus antibody by neutralization test, enzyme-linked immunosorbent assay and sensitive haemagglutination inhibition test. *Journal of Hygiene, Epidemiology, Microbiology, and Immunology*, 31(4):409–422.

Feiterna-Sperling C et al. (2005). Open randomized trial comparing the immunogenicity and safety of a new measles-mumps-rubella vaccine and a licensed vaccine in 12- to 24-month-old children. *The Pediatric Infectious Disease Journal*, 24(12):1083–1088.

Fescharek R et al. (1990). Measles-mumps vaccination in the FRG: an empirical analysis after 14 years of use. II. Tolerability and analysis of spontaneously reported side-effects. *Vaccine*, 8(5):446–456.

Forleo-Neto E et al. (1997). Seroconversion of a trivalent measles, mumps, and rubella vaccine in children aged 9 and 15 months. *Vaccine*, 15(17–18):1898–1901.

Friedman MG (1982). Radioimmunoassay for the detection of virus-specific IgA antibodies in saliva. *Journal of Immunological Methods*, 54(2):203–211.

Fu C et al. (2008). Matched case-control study of effectiveness of live, attenuated S79 mumps virus vaccine against clinical mumps. *Clinical and Vaccine Immunology : CVI*, 15(9):1425–1428.

Fu CX et al. (2009). Evaluation of live attenuated S79 mumps vaccine effectiveness in mumps outbreaks: a matched case-control study. *Chinese Medical Journal*, 122(3):307–310.

Fujinaga T et al. (1991). A prefecture-wide survey of mumps meningitis associated with measles, mumps and rubella vaccine. *The Pediatric Infectious Disease Journal*, 10(3):204–209.

Furesz J, Contreras G (1990). Vaccine-related mumps meningitis—Canada. *Canada Diseases Weekly Report = Rapport Hebdomadaire des Maladies au Canada*, 16(50):253–254.

Gans H et al. (2001). Immune responses to measles and mumps vaccination of infants at 6, 9, and 12 months. *The Journal of Infectious Diseases*, 184(7):817–826.

Gans H et al. (2003). Measles and mumps vaccination as a model to investigate the developing immune system: passive and active immunity during the first year of life. *Vaccine*, 21(24):3398–3405.

Gatchalian S et al. (1999). A randomized comparative trial in order to assess the reactogenicity and immunogenicity of a new measles mumps rubella (MMR) vaccine when given as a first dose at 12–24 months of age. *The Southeast Asian Journal of Tropical Medicine and Public Health*, 30(3):511–517.

Gluck R et al. (1986). Rubini, a new live attenuated mumps vaccine virus strain for human diploid cells. *Developments in Biological Standardization*, 65:29–35.

Goh KT (1999). Resurgence of mumps in Singapore caused by the Rubini mumps virus vaccine strain. *Lancet*, 354(9187):1355–1356.

Goncalves G et al. (1998). Outbreak of mumps associated with poor vaccine efficacy — Oporto Portugal 1996. *Euro Surveillance : Bulletin Européen sur les Maladies Transmissibles = European Communicable Disease Bulletin*, 3(12):119–121.

Gothefors L et al. (2001). Immunogenicity and reactogenicity of a new measles, mumps and rubella vaccine when administered as a second dose at 12 y of age. *Scandinavian Journal of Infectious Diseases*, 33(7):545–549.

Gotlieb T et al. (1953). Studies on the prevention of mumps. V. The development of a neutralization test and its application to convalescent sera. *Journal of Immunology (Baltimore, Md. : 1950)*, 71(2):66–75.

Gut JP et al. (1985). Rapid diagnosis of acute mumps infection by a direct immunoglobulin M antibody capture enzyme immunoassay with labeled antigen. *Journal of Clinical Microbiology*, 21(3):346–352.

Gut JP et al. (1995). Symptomatic mumps virus reinfections. *Journal of Medical Virology*, 45(1):17–23.

Habel K (1946). Preparation of mumps vaccine and immunization of monkeys against experimental mumps infection. *Public Health Reports*, 61:1655–1664.

Habel K (1951). Vaccination of human beings against mumps; vaccine administered at the start of an epidemic. II. Effect of vaccination upon the epidemic. *American Journal of Hygiene*, 54(3):312–318.

Hall R, Richards H (1987). Hearing loss due to mumps. *Archives of Disease in Childhood*, 62(2):189–191.

Hanna-Wakim R et al. (2008). Immune responses to mumps vaccine in adults who were vaccinated in childhood. *The Journal of Infectious Diseases*, 197(12):1669–1675.

Harling R et al. (2005). The effectiveness of the mumps component of the MMR vaccine: a case- control study. *Vaccine*, 23(31):4070–4074.

Hayden GF et al. (1978). Current status of mumps and mumps vaccine in the United States. *Pediatrics*, 62(6):965–969.

Hersh BS et al. (1991). Mumps outbreak in a highly vaccinated population. *The Journal of Pediatrics*, 119(2):187–193.

Hilleman MR et al. (1967). Live attenuated mumps-virus vaccine. IV. Protective efficacy as measured in a field evaluation. *The New England Journal of Medicine*, 276(5):252–258.

Hilleman MR et al. (1968). Live, attenuated mumps-virus vaccine. *The New England Journal of Medicine*, 278(5):227–232.

Hodes D, Brunell PA (1970). Mumps antibody: placental transfer and disappearance during the first year of life. *Pediatrics*, 45(1):99–101.

Hope-Simpson RE (1952). Infectiousness of communicable diseases in the household (measles, chickenpox, and mumps). *Lancet*, 2(6734):549–554.

Houard S et al. (1995). Protection of hamsters against experimental mumps virus (MuV) infection by antibodies raised against the MuV surface glycoproteins expressed from recombinant vaccinia virus vectors. *The Journal of General Virology*, 76 (Pt. 2):421–423.

Hyoty H et al. (1986). Cell-mediated and humoral immunity to mumps virus antigen. *Acta Pathologica, Microbiologica, et Immunologica Scandinavica. Section C, Immunology*, 94(5):201–206.

Ilonen J (1979). Lymphocyte blast transformation response of seropositive and seronegative subjects to herpes simplex, rubella, mumps and measles virus antigens. *Acta Pathologica, Microbiologica, et Immunologica Scandinavica. Section C, Immunology*, 87C(2):151–157.

Ilonen J et al. (1984). Immune responses to live attenuated and inactivated mumps virus vaccines in seronegative and seropositive young adult males. *Journal of Medical Virology*, 13(4):331–338.

Isomura S et al. (1973). Studies on live attenuated mumps vaccine. I. Comparative field trials with two different live vaccines. *Biken Journal*, 16(2):39–42.

Jin L et al. (1999). Genetic heterogeneity of mumps virus in the United Kingdom: identification of two new genotypes. *The Journal of Infectious Diseases*, 180(3): 829–833.

Jin L et al. (2004). Genetic diversity of mumps virus in oral fluid specimens: application to mumps epidemiological study. *The Journal of Infectious Diseases*, 189(6):1001–1008.

Jin L et al. (2005). Proposal for genetic characterization of wild-type mumps strains: preliminary standardization of the nomenclature. *Archives of Virology*, 150(9): 1903–1909.

Johansson B et al. (2002). Proposed criteria for classification of new genotypes of mumps virus. *Scandinavian Journal of Infectious Diseases*, 34(5):355–357.

Jokinen S et al. (2007). Cellular immunity to mumps virus in young adults 21 years after measles-mumps-rubella vaccination. *The Journal of Infectious Diseases*, 196(6): 861–867.

Jonville-Bera AP et al. (1996). Aseptic meningitis following mumps vaccine. A retrospective survey by the French Regional Pharmacovigilance centres and by Pasteur-Merieux Serums & Vaccins. *Pharmacoepidemiology and Drug Safety*, 5(1): 33–37.

Just M et al. (1986). Evaluation of a combined vaccine against measles-mumps-rubella produced on human diploid cells. *Developments in Biological Standardization*, 65:25–27.

Kaic B et al. (2008). Transmission of the L-Zagreb mumps vaccine virus, Croatia, 2005–2008. *Euro Surveillance : Bulletin Européen sur les Maladies Transmissibles = European Communicable Disease Bulletin*, 13(16).

Khalil M et al. (1999). Response to measles revaccination among toddlers in Saudi Arabia by the use of two different trivalent measles-mumps-rubella vaccines. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 93(2):214–219.

Kim-Farley R et al. (1985). Clinical mumps vaccine efficacy. *American Journal of Epidemiology*, 121(4):593–597.

Kimura M et al. (1996). Adverse events associated with MMR vaccines in Japan. *Acta Paediatrica Japonica; Overseas edition*, 38(3):205–211.

Klinge J et al. (2000). Comparison of immunogenicity and reactogenicity of a measles, mumps and rubella (MMR) vaccine in German children vaccinated at 9–11, 12–14 or 15–17 months of age. *Vaccine*, 18(27):3134–3140.

Krause CH et al. (2006). Real-time PCR for mumps diagnosis on clinical specimens—comparison with results of conventional methods of virus detection and nested PCR. *Journal of Clinical Virology : the official publication of the Pan American Society for Clinical Virology*, 37(3):184–189.

Krause CH et al. (2007). Comparison of mumps-IgM ELISAs in acute infection. *Journal of Clinical Virology : the official publication of the Pan American Society for Clinical Virology*, 38(2):153–156.

Kulkarni PS et al. (2005). No definitive evidence for L-Zagreb mumps strain associated aseptic meningitis: a review with special reference to the da Cunha study. *Vaccine*, 23(46–47):5286–5288.

Kuter BJ et al. (2006). Safety and immunogenicity of a combination measles, mumps, rubella and varicella vaccine (ProQuad). *Human Vaccines*, 2(5):205–214.

Laurence D, McGavin MD (1948). The complications of mumps. *British Medical Journal*, 1(4541):94–97.

LeBaron CW et al. (2009). Persistence of mumps antibodies after 2 doses of measles-mumps-rubella vaccine. *The Journal of Infectious Diseases*, 199(4):552–560.

Lee CY et al. (2002). A new measles mumps rubella (MMR) vaccine: a randomized comparative trial for assessing the reactogenicity and immunogenicity of three consecutive production lots and comparison with a widely used MMR vaccine in measles primed children. *International Journal of Infectious Diseases : IJID : official publication of the International Society for Infectious Diseases*, 6(3):202–209.

Leineweber B et al. (2004). Transplacentally acquired immunoglobulin G antibodies against measles, mumps, rubella and varicella-zoster virus in preterm and full term newborns. *The Pediatric Infectious Disease Journal*, 23(4):361–363.

Lerman SJ et al. (1981). Clinical and serologic evaluation of measles, mumps, and rubella (HPV-77:DE-5 and RA 27/3) virus vaccines, singly and in combination. *Pediatrics*, 68(1):18–22.

Levitt LP et al. (1970). Mumps in a general population. A sero-epidemiologic study. *American Journal of Diseases of Children (1960)*, 120(2):134–138.

Lewis JE et al. (1979). Epidemic of mumps in a partially immune population. *Canadian Medical Association Journal*, 121(6):751–754.

Lim FS et al. (2007). Safety, reactogenicity and immunogenicity of the live attenuated combined measles, mumps and rubella vaccine containing the RIT 4385 mumps strain in healthy Singaporean children. *Annals of the Academy of Medicine, Singapore*, 36(12):969–973.

Love A et al. (1986). Monoclonal antibodies against the fusion protein are protective in necrotizing mumps meningoencephalitis. *Journal of Virology*, 58(1):220–222.

Makino S et al. (1976). Studies on the development of a live attenuated mumps virus vaccine. II. Development and evaluation of the live "Hoshino" mumps vaccine. *The Kitasato Archives of Experimental Medicine*, 49(1–2):53–62.

Makino S et al. (1990). A new combined trivalent live measles (AIK-C strain), mumps (Hoshino strain), and rubella (Takahashi strain) vaccine. Findings in clinical and laboratory studies. *American Journal of Diseases of Children (1960)*, 144(8):905–910.

Marin M et al. (2008). Mumps vaccination coverage and vaccine effectiveness in a large outbreak among college students—Iowa, 2006. *Vaccine*, 26(29–30):3601–3607.

McKenna MJ (1997). Measles, mumps, and sensorineural hearing loss. *Annals of the New York Academy of Sciences*, 830:291–298.

Meurman O et al. (1982). Determination of IgG- and IgM-class antibodies to mumps virus by solid-phase enzyme immunoassay. *Journal of Virological Methods*, 4(4–5):249–256.

Meyer MB (1962). An epidemiologic study of mumps; its spread in schools and families. *American Journal of Hygiene*, 75:259–281.

Meyer MB et al. (1966). Evaluation of mumps vaccine given after exposure to mumps, with special reference to the exposed adult. *Pediatrics*, 37(2):304–315.

Miller E et al. (1993). Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. *Lancet*, 341(8851):979–982.

Miller E et al. (2007). Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom. *American Journal of Epidemiology*, 165(6):704–709.

Montes M et al. (2002). Mumps outbreak in vaccinated children in Gipuzkoa (Basque Country), Spain. *Epidemiology and Infection*, 129(3):551–556.

Muhlemann K (2004). The molecular epidemiology of mumps virus. *Infection, Genetics and Evolution : Journal of Molecular Epidemiology and Evolutionary Genetics in Infectious Diseases*, 4(3):215–219.

Narita M et al. (1998). Analysis of mumps vaccine failure by means of avidity testing for mumps virus-specific immunoglobulin G. *Clinical and Diagnostic Laboratory Immunology*, 5(6):799–803.

Nojd J et al. (2001). Mumps virus neutralizing antibodies do not protect against reinfection with a heterologous mumps virus genotype. *Vaccine*, 19(13–14): 1727–1731.

Nolan T et al. (2002). Reactogenicity and immunogenicity of a live attenuated tetravalent measles-mumps-rubella-varicella (MMRV) vaccine. *Vaccine*, 21(3–4):281–289.

Odisseev H, Gacheva N (1994). Vaccinoprophylaxis of mumps using mumps vaccine, strain Sofia 6, in Bulgaria. *Vaccine*, 12(14):1251–1254.

Okafuji T et al. (2005). Rapid diagnostic method for detection of mumps virus genome by loop-mediated isothermal amplification. *Journal of Clinical Microbiology*, 43(4):1625–1631.

Okamoto M et al. (1994). Sudden deafness accompanied by asymptomatic mumps. *Acta Oto-laryngologica. Supplementum*, 514:45–48.

Ong G et al. (2005). Comparative efficacy of Rubini, Jeryl Lynn and Urabe mumps vaccine in an Asian population. *The Journal of Infection*, 51(4):294–298.

Orvell C (1978). Immunological properties of purified mumps virus glycoproteins. *The Journal of General Virology*, 41(3):517–526.

Orvell C et al. (2002). Antigenic relationships between six genotypes of the small hydrophobic protein gene of mumps virus. *The Journal of General Virology*, 83(Pt. 10):2489–2496.

Ovsyannikova IG et al. (2008). Human leukocyte antigen and cytokine receptor gene polymorphisms associated with heterogeneous immune responses to mumps viral vaccine. *Pediatrics*, 121(5):e1091–e1099.

Paccaud MF et al. (1995). [A look back at 2 mumps outbreaks]. *Sozial- und Präventivmedizin*, 40(2):72–79.

Pan American Health Organization (1999). Evaluation of the Bahamas' MMR campaign. *EPI newsletter / c Expanded Program on Immunization in the Americas*, 21(1):4–5.

Park DW et al. (2007). Mumps outbreak in a highly vaccinated school population: assessment of secondary vaccine failure using IgG avidity measurements. *Vaccine*, 25(24):4665–4670.

Pebody RG et al. (2002). Immunogenicity of second dose measles-mumps-rubella (MMR) vaccine and implications for serosurveillance. *Vaccine*, 20(7–8):1134–1140.

Phadke MA et al. (2004). Pharmacovigilance on MMR vaccine containing L-Zagreb mumps strain. *Vaccine*, 22(31–32):4135–4136.

Philip RN et al. (1959). Observations on a mumps epidemic in a virgin population. *American Journal of Hygiene*, 69(2):91–111.

Pipkin PA et al. (1999). Assay of humoral immunity to mumps virus. *Journal of Virological Methods*, 79(2):219–225.

Plotkin SA, Rubin SA (2008). Mumps vaccine. In: Plotkin S, Orenstein W, Offit P, eds. *Vaccines*, 5th ed. Philadelphia, Saunders, 435–465.

Poggio GP et al. (2000). Nested PCR for rapid detection of mumps virus in cerebrospinal fluid from patients with neurological diseases. *Journal of Clinical Microbiology*, 38(1):274–278.

Pons C et al. (2000). Two outbreaks of mumps in children vaccinated with the Rubini strain in Spain indicate low vaccine efficacy. *Euro Surveillance : Bulletin Européen sur les Maladies Transmissibles = European Communicable Disease Bulletin*, 5(7):80–84.

Popow-Kraupp T et al. (1986). A controlled trial for evaluating two live attenuated mumps-measles vaccines (Urabe Am 9-Schwarz and Jeryl Lynn-Moraten) in young children. *Journal of Medical Virology*, 18(1):69–79.

Rebiere I, Galy-Eyraud C (1995). Estimation of the risk of aseptic meningitis associated with mumps vaccination, France, 1991–1993. *International Journal of Epidemiology*, 24(6):1223–1227.

Redd SC et al. (2004). Comparison of vaccination with measles-mumps-rubella vaccine at 9, 12, and 15 months of age. *The Journal of Infectious Diseases*, 189 (Suppl. 1):S116–S122.

Reed D et al. (1967). A mumps epidemic on St. George Island, Alaska. *JAMA : The Journal of the American Medical Association*, 199(13):113–117.

Richard JL et al. (2003). Comparison of the effectiveness of two mumps vaccines during an outbreak in Switzerland in 1999 and 2000: a case-cohort study. *European Journal of Epidemiology*, 18(6):569–577.

Robertson CM et al. (1988). Serological evaluation of a measles, mumps, and rubella vaccine. *Archives of Disease in Childhood*, 63(6):612–616.

Rola-Pleszczynski M et al. (1976). 51 Chromium-release microassay technique for cell-mediated immunity to mumps virus: correlation with humoral and delayed-type skin hypersensitivity responses. *The Journal of Infectious Diseases*, 134(6):546–551.

Rota JS et al. (2009). Investigation of a mumps outbreak among university students with two measles-mumps-rubella (MMR) vaccinations, Virginia, September–December 2006. *Journal of Medical Virology*, 81(10):1819–1825.

Rubin SA et al. (2006). Serological and phylogenetic evidence of monotypic immune responses to different mumps virus strains. *Vaccine*, 24(14):2662–2668.

Rubin SA et al. (2008). Antibody induced by immunization with the Jeryl Lynn mumps vaccine strain effectively neutralizes a heterologous wild-type mumps virus associated with a large outbreak. *The Journal of Infectious Diseases*, 198(4):508–515.

Russell RR & Donald JC (1958). The neurological complications of mumps. *British Medical Journal*, 2(5087):27–30.

Sakata H et al. (1985). Enzyme-linked immunosorbent assay for mumps IgM antibody: comparison of IgM capture and indirect IgM assay. *Journal of Virological*, 12(3–4):303–311.

Sanz-Moreno JC et al. (2005). Detection of secondary mumps vaccine failure by means of avidity testing for specific immunoglobulin G. *Vaccine*, 23(41):4921–4925.

Sartorius B et al. (2005). An outbreak of mumps in Sweden, February–April 2004. *Euro Surveillance : Bulletin Européen sur les Maladies Transmissibles = European Communicable Disease Bulletin*, 10(9):191–193.

Saskai K et al. (1976). Studies on the development of a live attenuated mumps virus vaccine. I Attenuation of the Hoshino 'wild' strain of mumps virus. *The Kitasata Archives of Experimental Medicine*, 49:43–52.

Sassani A et al. (1991). Development of a new live attenuated mumps virus vaccine in human diploid cells. *Biologicals : Journal of the International Association of Biological Standardization*, 19(3):203–211.

Sato H et al. (1979). Transfer of measles, mumps, and rubella antibodies from mother to infant. Its effect on measles, mumps, and rubella immunization. *American Journal of Diseases of Children (1960)*, 133(12):1240–1243.

Sawada H et al. (1993). Transmission of Urabe mumps vaccine between siblings. *Lancet*, 342(8867):371.

Schaffzin JK et al. (2007). Effectiveness of previous mumps vaccination during a summer camp outbreak. *Pediatrics*, 120(4):e862–e868.

Schlegel M et al. (1999). Comparative efficacy of three mumps vaccines during disease outbreak in Eastern Switzerland: cohort study. *BMJ (Clinical research ed.)*, 319(7206):352.

Schlipkoter U et al. (2002). Surveillance of measles-mumps-rubella vaccine-associated aseptic meningitis in Germany. *Infection*, 30(6):351–355.

Schoub BD et al. (1990). Measles, mumps and rubella immunization at nine months in a developing country. *The Pediatric Infectious Disease Journal*, 9(4):263–267.

Schwarz AJ et al. (1975). Clinical evaluation of a new measles-mumps-rubella trivalent vaccine. *American Journal of Diseases of Children (1960)*, 129(12):1408–1412.

Schwarzer S et al. (1998). Safety and characterization of the immune response engendered by two combined measles, mumps and rubella vaccines. *Vaccine*, 16(2–3):298–304.

Shinefield H et al. (2005). Evaluation of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. *The Pediatric Infectious Disease Journal*, 2005, 24(8):665–669.

Smorodintsev AA et al. (1965). Data on the Efficiency of Live Mumps Vaccine from Chick Embryo Cell Cultures. *Acta Virologica*, 9:240–247.

Smorodintsev AA et al. (1970). Experience with live rubella virus vaccine combined with live vaccines against measles and mumps. *Bulletin of the World Health Organization*, 42(2):283–289.

Stuck B et al. (2002). Concomitant administration of varicella vaccine with combined measles, mumps, and rubella vaccine in healthy children aged 12 to 24 months of age. *Asian Pacific Journal of Allergy and Immunology / launched by the Allergy and Immunology Society of Thailand*, 20(2):113–120.

Sugg WC et al. (1968). Field evaluation of live virus mumps vaccine. *The Journal of Pediatrics*, 72(4):461–466.

Sugiura A, Yamada A (1991). Aseptic meningitis as a complication of mumps vaccination. *The Pediatric Infectious Disease Journal*, 10(3):209–213.

Sullivan KM et al. (1985a). Mumps disease and its health impact: an outbreak-based report. *Pediatrics*, 76(4):533–536.

Sullivan KM et al. (1985b). Effectiveness of mumps vaccine in a school outbreak. *American Journal of Diseases of Children (1960)*, 139(9):909–912.

Tan PL et al. (2001). Twin studies of immunogenicity—determining the genetic contribution to vaccine failure. *Vaccine*, 19(17–19):2434–2439.

Tesovic G et al. (1993). Aseptic meningitis after measles, mumps, and rubella vaccine. *Lancet*, 341(8859):1541.

Tesovic G, Lesnikar V (2006). Aseptic meningitis after vaccination with L-Zagreb mumps strain—virologically confirmed cases. *Vaccine*, 24(40–41):6371–6373.

The Benevento and Compobasso Paediatricians Network for the Control of Vaccine-Preventable Diseases (1998). The Benevento and Compobasso Paediatricians Network for the Control of Vaccine-Preventable Diseases field evaluation of the clinical effectiveness of vaccines against pertussis, measles, rubella and mumps. *Vaccine*, 16(8):818–822.

Toscani L et al. (1996). [Comparison of the efficacy of various strains of mumps vaccine: a school survey]. *Sozial- und Präventivmedizin*, 41(6):341–347.

Tsutsumi H et al. (1980). T-cell-mediated cytotoxic response to mumps virus in humans. *Infection and Immunity*, 30(1):129–134.

Uchida K et al. (2005). Rapid and sensitive detection of mumps virus RNA directly from clinical samples by real-time PCR. *Journal of Medical Virology*, 75(3):470–474.

Ueda K et al. (1995). Aseptic meningitis caused by measles-mumps-rubella vaccine in Japan. *Lancet*, 346(8976):701–702.

Ukkonen P et al. (1981). Mumps-specific immunoglobulin M and G antibodies in natural mumps infection as measured by enzyme-linked immunosorbent assay. *Journal of Medical Virology*, 8(2):131–142.

Ukkonen P, Penttinen K (1981). Immunity induced by formalin-inactivated mumps virus vaccine: suppression of IgM antibody response. *The Journal of Infectious Diseases*, 144(5):496–497.

Usonis V et al. (1998). Comparative study of reactogenicity and immunogenicity of new and established measles, mumps and rubella vaccines in healthy children. *Infection*, 26(4):222–226.

Usonis V et al. (1999). Reactogenicity and immunogenicity of a new live attenuated combined measles, mumps and rubella vaccine in healthy children. *The Pediatric Infectious Disease Journal*, 18(1):42–48.

Usonis V et al. (2001). Neutralization activity and persistence of antibodies induced in response to vaccination with a novel mumps strain, RIT 4385. *Infection*, 29(3): 159–162.

Utz JP et al. (1957). Clinical and laboratory studies of mumps. I. Laboratory diagnosis by tissue-culture technics. *The New England Journal of Medicine*, 257(11):497–502.

Utz JP et al. (1958). Clinical and laboratory studies of mumps. II. Detection and duration of excretion of virus in urine. *Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.)*, 99(1):259–261.

Vandermeulen C et al. (2004). Outbreak of mumps in a vaccinated child population: a question of vaccine failure? *Vaccine*, 22(21–22):2713–2716.

Vandermeulen C et al. (2009). Evaluation of cellular immunity to mumps in vaccinated individuals with or without circulating antibodies up to 16 years after their last vaccination. *The Journal of Infectious Diseases*, 199(10):1457–1460.

Vesikari T et al. (1983a). Comparison of the Urabe Am 9-Schwarz and Jeryl Lynn-Moraten combinations of mumps-measles vaccines in young children. *Acta Paediatrica Scandinavica*, 72(1):41–46.

Vesikari T et al. (1983b). Evaluation in young children of the Urabe Am 9 strain of live attenuated mumps vaccine in comparison with the Jeryl Lynn strain. *Acta Paediatrica Scandinavica*, 72(1):37–40.

Vukic BT et al. (2008). Aseptic meningitis after transmission of the Leningrad-Zagreb mumps vaccine from vaccinee to susceptible contact. *Vaccine*, 26(38):4879.

Vuori M et al. (1962). Perceptive deafness in connection with mumps. A study of 298 servicemen suffering from mumps. Acta Oto-Laryngologica, 55:231–236.

Watson BM et al. (1996). Safety and immunogenicity of a combined live attenuated measles, mumps, rubella, and varicella vaccine (MMR(II)V) in healthy children. *The Journal of Infectious Diseases*, 173(3):731–734.

Weibel RE et al. (1967). Live attenuated mumps-virus vaccine. 3. Clinical and serologic aspects in a field evaluation. *The New England Journal of Medicine*, 276(5):245–251.

Weibel RE et al. (1973). Combined live measles-mumps virus vaccine. *Archives of Disease in Childhood*, 48(7):532–536.

Westmore GA et al. (1979). Isolation of mumps virus from the inner ear after sudden deafness. *British Medical Journal*, 1(6155):14–15.

Wharton M et al. (1988). A large outbreak of mumps in the postvaccine era. *The Journal of Infectious Diseases*, 158(6):1253–1260.

Wilson RL et al. (2006). Function of small hydrophobic proteins of paramyxovirus. *Journal of Virology*, 80(4):1700–1709.

Witte JJ, Karchmer AW (1968). Surveillance of mumps in the United States as background for use of vaccine. *Public Health Reports*, 83(2):5–100.

WHO (2001). Mumps virus vaccines. *Weekly Epidemiological Record*, 76:345–356.

Yamanishi K et al. (1973). Studies on live mumps virus vaccine. V. Development of a new mumps vaccine "AM 9" by plaque cloning. *Biken Journal*, 16(4):161–166.

Yoshida N et al. (2008). Mumps virus reinfection is not a rare event confirmed by reverse transcription loop-mediated isothermal amplification. *Journal of Medical Virology*, 80(3):517–523.

The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

Department of Immunization, Vaccines and Biologicals

Family and Community Health

World Health Organization
20, Avenue Appia
CH-1211 Geneva 27
Switzerland
E-mail: vaccines@who.int
Web site: http://www.who.int/immunization/en/

ISBN 978 92 4 150066 1