

PUBLISHED BY

INTECH

open science | open minds

World's largest Science,
Technology & Medicine
Open Access book publisher



3,350+
OPEN ACCESS BOOKS



108,000+
INTERNATIONAL
AUTHORS AND EDITORS



114+ MILLION
DOWNLOADS



BOOKS
DELIVERED TO
151 COUNTRIES

AUTHORS AMONG
TOP 1%
MOST CITED SCIENTIST



12.2%
AUTHORS AND EDITORS
FROM TOP 500 UNIVERSITIES



Selection of our books indexed in the
Book Citation Index in Web of Science™
Core Collection (BKCI)

WEB OF SCIENCE™

Chapter from the book *Insight and Control of Infectious Disease in Global Scenario*
Downloaded from: <http://www.intechopen.com/books/insight-and-control-of-infectious-disease-in-global-scenario>

Interested in publishing with IntechOpen?
Contact us at book.department@intechopen.com

Studies on the Association of Meningitis and Mumps Virus Vaccination

Alejandra Lara-Sampablo^{1,2}, Nora Rosas-Murrieta²,
Irma Herrera-Camacho², Verónica Vallejo-Ruiz¹,
Gerardo Santos-López¹ and Julio Reyes-Leyva^{1*}

¹Laboratorio de Biología Molecular y Virología, Centro de Investigación Biomédica de Oriente, Instituto Mexicano del Seguro Social, Metepec, Puebla;

²Centro de Química, Instituto de Ciencias, Benemérita Universidad Autónoma de Puebla, Puebla, México

1. Introduction

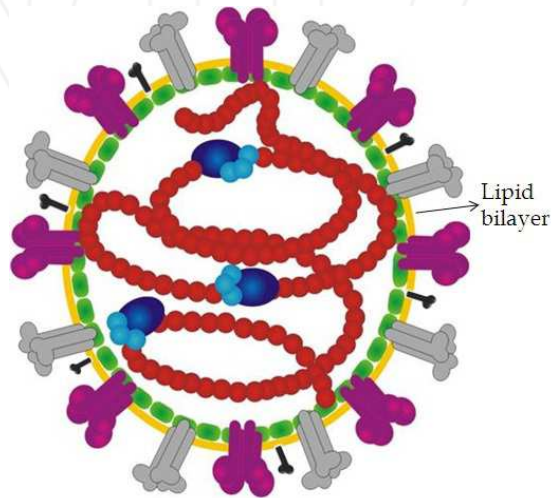
Mumps is an acute viral infection caused by a member of the *Rubulavirus* genus in the *Paramyxoviridae* family. Although it is mostly a childhood disease, with peak incidence occurring among those aged 5–9 years, mumps virus (MuV) may also affect teenagers. MuV is known to affect the salivary glands causing parotid swelling; however, it can also produce an acute systemic infection involving glandular, lymphoid and nervous tissues, leading to some important complications such as pancreatitis, oophoritis orchitis, mastitis, nephritis and thyroiditis. The main central nervous system (CNS) complication of mumps virus infection is aseptic meningitis (in up to 15% of cases); it is also associated rarely with encephalitis, hydrocephalus and sensorineural deafness (affecting approximately 5/100 000 mumps patients) (Carbone & Rubin, 2007; Hviid et al., 2008; Plotkin & Rubin, 2007; World Health Organization [WHO], 2007).

Massive vaccination programs have decreased the incidence of MuV infection worldwide, before the introduction of live attenuated mumps virus vaccines, mumps was the main cause of virus-induced disease in the CNS of children; indeed, the annual incidence of mumps in the absence of immunization was in the range of 100–1000 cases/100 000 people. Although vaccination programs have decreased the incidence of mumps virus infection, outbreaks have not been completely eliminated (WHO, 2007). The main problems associated with MuV vaccination are lack of protection due to vaccine failure and presentation of secondary adverse complications due to the use of relatively virulent vaccine strains; indeed, L-Zagreb, Leningrad-3 and Urabe AM9 strains have been associated with post-vaccinal aseptic meningitis (Brown et al., 1991; Dourado et al., 2000; Galazka et al., 1999; Goh, 1999). The unacceptably high rate of vaccine associated meningitis and parotitis cases has resulted in vaccine withdrawal and public resistance to mumps vaccination (Schmitt et al., 1993). In consequence, mumps epidemics have re-emerged, and the incidence is rising in several countries (Choi, 2010; Dayan et al., 2008).

2. Wild-type mumps virus natural infection and CNS involvement

2.1 Mumps virus

Mumps virus (MuV) is a member of the *Rubulavirus* genus of the *Paramyxoviridae* family. Mumps virions are pleomorphic particles ranging from 100 to 600 nm in size, consisting of a helical ribonucleocapsid surrounded by a host cell-derived lipid envelope. Full-length genome is a non-segmented, single-stranded RNA of negative polarity that consists of 15,384 nucleotides containing 7 genes that code for the nucleoprotein (NP), phosphoprotein (P), matrix (M), fusion (F), small hydrophobic (SH), hemagglutinin-neuraminidase (HN), and large (L) proteins. The genomic organization of the virus from 3' to 5' ends is NP-P-M-F-SH-HN-L (Lamb & Parks, 2007; Pringle, 1997).










Viral protein	Biological activity	Viral protein	Biological activity
 Nucleoprotein (NP)	Protects genomic RNA from cellular proteases; determines helical structure of capsid	 Small hydrophobic (SH)	Unknown function. This protein has been involved in evasion of the host anti-viral response
 Phosphoprotein (P)	Forms part of the transcriptase complex.	 Fusion (F)	Virus-to-cell and cell-to-cell fusion
 Large (L)	Forms part of the transcriptase complex	 Hemagglutinin-Neuraminidase (HN)	Viral attachment and entry. Prevention of self-agglutination
 Matrix (M)	Virion assembly		

Fig. 1. Schematic diagram of mumps virus (not drawn to scale). On the surface of the viral membrane 3 glycoproteins are anchored: HN, F and SH. The M protein is located inside of the viral envelope. In the center of the virion is the ribonucleoprotein complex formed by the nucleocapsid (NP:RNA) and viral RNA polymerase (P:L). Information based on the references: Carbone & Rubin, 2007; Santos-López et al., 2004.

A schematic diagram of the virion and functions of viral proteins are shown in figure 1. On the surface of viral particles and infected cells are projected two glycoproteins, F and HN, which are transmembrane glycoproteins of types I and II, respectively. HN glycoprotein is responsible for mumps virus attachment; it binds to sialic acid-containing cell receptors. Its neuraminidase (sialidase) activity releases the sialic acid residues from viral progeny to prevent self-aggregation during budding; HN glycoprotein also activates the F glycoprotein, which promotes the fusion between viral and cell membranes (Carbone & Rubin, 2007; Lamb & Parks, 2007).

SH is an integral membrane protein without well-known properties; despite this, SH protein has been reported to block the TNF α mediated apoptotic signaling pathway; therefore it has been involved in evasion of the host anti-viral response (Wilson et al., 2006), so it has been proposed as a virulence factor, however, this issue is still controversial (T. Malik et al., 2011; Woznik et al., 2010). Likewise, the sequence of the mumps virus SH gene varies greatly from strain to strain and has therefore been used in molecular epidemiological studies to group mumps virus strains (Orvell et al., 1997).

Inside the envelope lies a helical nucleocapsid core containing the RNA genome and the NP, P, and L proteins, which are involved in virus replication. NP protein is an RNA-binding protein that coats and protects full-length viral (-) sense genomic and (+) sense antigenomic RNAs to form the helical nucleocapsid template (Carbone & Rubin, 2007; Lamb & Parks, 2007). Each NP protein interact with 6 nucleotides of the viral genome, therefore a full-length genome polyhexameric may be required for efficient viral replication (process known as, Rule of Six) (Kolakofsky et al., 1998, 2005; Vulliamoz & Roux, 2001). P and L proteins form an enzymatic complex with RNA-dependent RNA polymerase activity; where L protein has the catalytic domain for RNA polymerization, whereas P protein functions as a cofactor for L protein and is able to bind the ribonucleoprotein complex (RNA-NP) (Kingston et al., 2004; Lamb & Parks, 2007).

M protein resides between the envelope and the nucleocapsid core; this is the most abundant protein in the virion, and it serves to physically link the ribonucleocapsid with the host cell membrane to promote the viral assembly process (Carbone & Rubin, 2007; Lamb & Parks, 2007).

Two nonstructural proteins, V and I, are encoded by the P gene and are synthesized as a result of co-transcriptional editing of messenger RNA (mRNA) (Carbone & Rubin, 2007; Paterson & Lamb, 1990). In this process the viral polymerase moves repeatedly (process known as, stuttering) in a region known as "editing site" of the P gene, which is rich in citidine nucleotides (3'CCCCC 5') inserting some non-template guanidine (G) nucleotides in the nascent transcript (Hausmann et al., 1999; Paterson & Lamb, 1990; Vidal et al., 1990). This editing mechanism involves the production of mRNAs whose ORFs are altered by insertion of G residues (Figure 2); so, the translation of full-transcript (unedited) encodes a V protein, which plays a role in circumventing the interferon (IFN) mediated antiviral responses by blocking IFN signaling and limiting IFN production (Didcock et al., 1999a, 1999b; Fujii et al., 1999; Rodriguez et al., 2003; N. H. Rosas-Murrieta et al., 2010); while, mRNAs generated by inserting 2 and 4 G residues encode a P and I proteins respectively. The generated proteins have the same N-terminus, but differ in their C-terminus (Lamb & Parks, 2007).

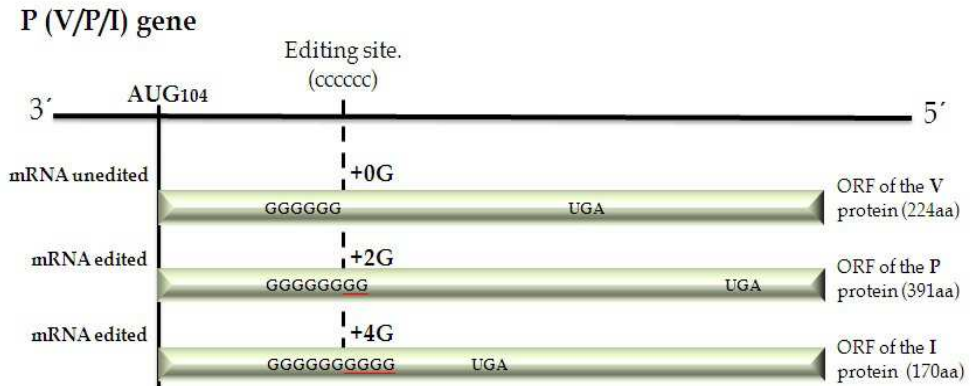


Fig. 2. Schematic representation of mumps virus P gene and mRNA editing mechanism (not drawn to scale). By a stuttering mechanism in the editing site of P gene, the viral polymerase introduces non-templated G residues in the nascent transcript, which generates mRNAs with different ORFs, so, the translation of full-transcript (unedited) encodes a V protein, while mRNAs generated by inserting 2 and 4 G residues encode P and I proteins respectively. AUG and UGA sequence indicate the start and stop codons, respectively. Information based on the references: Hausmann et al., 1999; Lamb & Parks, 2007; Paterson & Lamb, 1990; Vidal et al., 1990.

2.2 Viral pathogenesis and invasion central nervous system

Natural infection with mumps virus is restricted to humans and is transmitted via the respiratory mucosa by direct contact, droplet spread or contaminated fomites. The incubation period is about 15 to 24 days (average 19 days). Infected patients become most contagious 1 to 2 days before onset of clinical symptoms and continue for several days afterwards (Hviid et al., 2008). Mumps virus initially infects the upper-respiratory-tract mucosa where it undergoes a first replication cycle and then the progeny viruses spread to local lymph nodes where they undergo a second replication followed by a systemic spread with involvement of glandular, nervous and other target organs (figure 3) (Carbone & Rubin, 2007; Enders, 1996; Plotkin & Rubin, 2007).

The main clinical manifestation of mumps is parotid swelling. However, parotitis is not a primary or necessary step of mumps virus infection. Mumps virus can also infect urinary tract, genital organs, pancreas, kidney and central nervous system (CNS). It is not yet well-known how mumps virus spreads to the CNS, however, studies in newborn hamster model suggest that virus spreads by passage of infected mononuclear cells across the epithelium to epithelial cells of the choroid plexus (Fleischer & Kreth, 1982; Wolinsky et al., 1976). Alternatively, direct spread of virus is possible. At this site virus is replicated and released persistently from ependymal and choroidal cells, followed by deeper spread into the brain parenchyma causing encephalitis and several neurological complications. There are few data on the histopathology of the brain in mumps encephalitis (since death is rare). The data show the characteristic picture of a parainfectious process, characterized by perivenous demyelination and perivascular infiltration with mononuclear cells (Hviid et al., 2008).

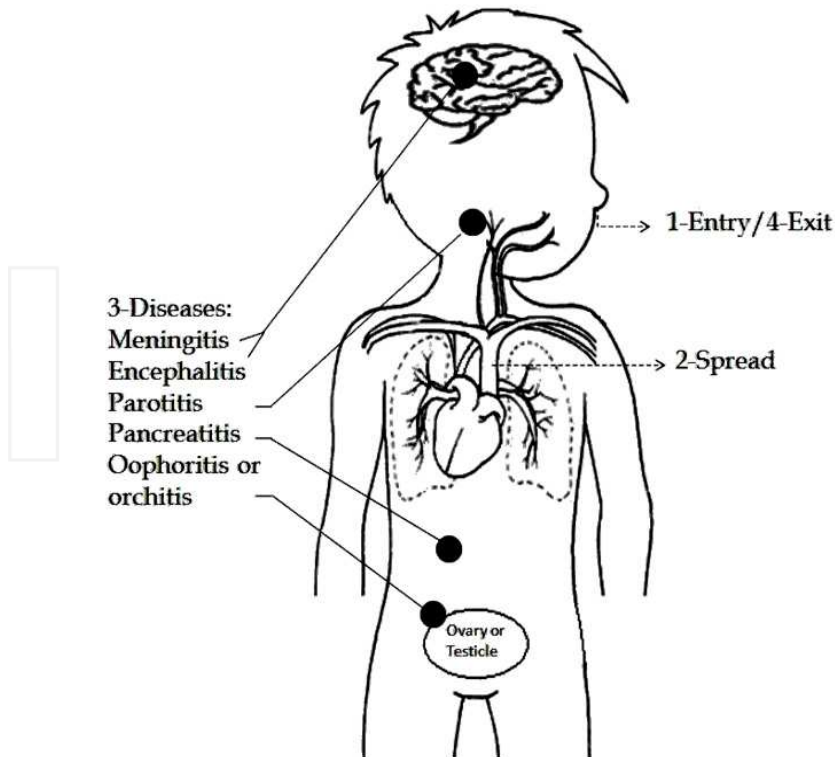


Fig. 3. Pathogenesis of mumps virus infection. Mumps virus is acquired through the upper-respiratory-tract mucosa (1); where it undergoes a first replication, after that new viruses spread (2) to local lymph nodes followed by a systemic spread with involvement of glandular and nervous tissues causing various diseases (3); finally virus is transmitted to another person through droplets or fomites (4). Based on the reference, Enders, 1996.

2.3 Aseptic meningitis and other neurological complications of mumps

Infection of the CNS is the most common extra-salivary gland manifestation of mumps virus infection, being aseptic meningitis the most frequent complication. Although the disease is usually mild should not be underestimated, mumps meningitis affects to 10%-15% of individuals infected by MuV, which is characterized by the sudden onset of fever with signs and symptoms of meningeal involvement as evidenced by changes in cerebrospinal fluid properties, including pleocytosis in absence of bacteria (Bonnet et al., 2006; Plotkin & Rubin, 2007).

Another less frequent but more serious complication of mumps virus infection is encephalitis (0.02-0.3% cases), which can lead to permanent neurologic damage including paralysis, seizures, hydrocephalus and even cause death. Likewise mumps virus infection is a major cause of sensorineural deafness in childhood and affects five per 100,000 patients (Bonnet et al., 2006; Hviid et al., 2008; Plotkin & Rubin, 2007; WHO, 2007).

3. Mumps vaccination

Safe and efficacious vaccines against mumps - based on live, attenuated viral strains - have been available since the 1960s. In most regions of the world the annual incidence of mumps in absence of vaccination ranges from 100 to 1000 per 100 000 of the general population (WHO, 2007). In 2010, the World Health Organization indicated that 61% of countries (figure 4) have incorporated mumps vaccination into their national immunization programs, in most cases using combined measles-mumps-rubella (MMR) vaccine (WHO, 2010).

Countries Using Mumps Vaccine in National Immunization Schedule, 2009

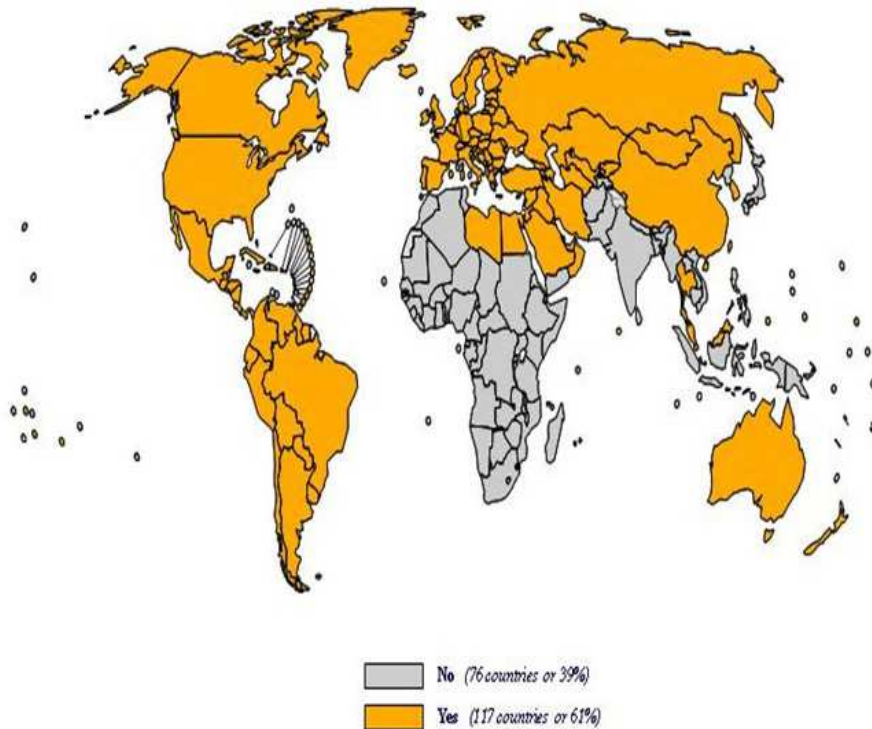


Fig. 4. Countries that have incorporated mumps vaccination in their national immunization programs. Yellow and gray indicate the countries immunized (61%) and unimmunized (39%) respectively. Source: WHO/IVB database, 193 WHO Member States, Data as of July 2010. Date of slide: 19 August 2010.

3.1 Effects of vaccination on epidemic mumps

Use of mumps vaccine (usually administered in measles-mumps-rubella or measles-mumps-rubella-varicella vaccines) is the best way to prevent mumps. Mumps immunization

has been effective at controlling epidemic mumps infection and complications associated with it has been drastically reduced. This is the reason why the WHO defined viral mumps as a disease preventable by vaccination (vaccine-preventable) (WHO, 2007). In countries where there is no vaccination against mumps, its incidence remains high, with epidemic peaks every 2–5 years and those aged 5–9 years consistently being the most affected. In the pre-vaccine era, mumps was a common infectious disease with a high annual incidence, usually >100 per 100 000 population (Dayan et al., 2008; Galazka et al., 1999). It was a very common disease in U.S. children, with as many as 300,000 cases reported every year. After the introduction of mumps virus vaccine in United States in 1967, cases dropped by 98%, from 152,209 cases in 1968 to 2982 cases in 1985. Since 1989, the incidence of mumps has declined, with 266 reported cases in 2001. This decrease is probably due to the fact that children have received a second dose of mumps vaccine (part of the two-dose schedule for measles, mumps, rubella or MMR). Studies have shown that the effectiveness of mumps vaccine ranges from 73% to 91% after 1 dose vaccines and from 79% to 95% after 2 doses. However, we can not let our guard down against viral mumps (Centers for Disease Control and Prevention [CDC], 2010a).

Despite mumps epidemics have decreased from the incorporation of mumps vaccine, in the late 1980s, mumps outbreaks have occurred in both unvaccinated and vaccinated adolescents and young adults. From October 1988 to April 1989 a mumps epidemic was reported in Douglas County, Kansas; of the 269 cases, 208 (77.3%) occurred among primary and secondary school students, of whom 203 (97.6%) had documentation of mumps vaccination. These data suggested that both mumps vaccine failure and the lack of vaccination have contributed to the relative resurgence of mumps. Therefore a change in immunization policy was recommended to two-dose schedule of measles-mumps-rubella vaccine, which should help reduce the occurrence of mumps outbreaks in highly vaccinated populations (Hersh et al., 1991). The widespread use of a second dose of mumps vaccine among U.S. schoolchildren beginning in 1990 was followed by low reports of mumps cases; which was established at 2010 elimination goal, however, various mumps outbreaks have been reported in several countries at different years (Brockhoff et al., 2010; CDC, 2010b; Cheek et al., 1995; Dayan et al., 2008; Dayan & Rubin, 2008; Park et al., 2007; Vandermeulen et al., 2009; Vandermeulen et al., 2004). These reports have suggested that secondary vaccine failure played an important role in mumps outbreaks, thus a more effective mumps vaccine or changes in vaccine policies may be considered to prevent future outbreaks.

3.2 Vaccine strains: preparation, attenuation, induced immune

Mumps vaccines are available in the form of live attenuated virus and may be given alone or in combination with measles and rubella vaccines, according to recommendations from the World Health Organization (WHO, 2007). Mumps viruses are attenuated by adaption in embryonated chicken eggs, chicken or quail embryo fibroblasts or human diploid cells. Through these processes virus mutants are selected because of their increased ability to replicate under new culture conditions but with a reduced capacity to produce disease but stimulating immunity in the natural host (Brown & Wright, 1998; Plotkin & Rubin, 2007).

There are more than 10 strains of mumps virus used as vaccines (Table 1), which induce different levels of seroconversion (80–99%) and protective efficacy (70–95%). Nowadays, the most often used vaccine strains are Jeryl Lynn, RIT 4385, Urabe-AM9, L-Zagreb and Leningrad-3 (Bonnet et al., 2006). The first live attenuated mumps virus vaccine, Jeryl Lynn

B (introduced in the U.S.A in 1967), represents an ideal vaccine because it induces neutralizing antibodies in 95%-98% of vaccinees and few side effects have been associated with its application (Carbone & Rubin, 2007). The Jeryl Lynn strain was attenuated by passage in embryonated hen's eggs and chicken embryo cell culture (Plotkin & Rubin, 2007). The RIT 4385 mumps vaccine was derived from a Jeryl Lynn clone (JL-1) by passage through chicken embryo fibroblast cultures. Comparative studies of the RIT 4385 and Jeryl-Lynn vaccines showed similar seroconversion rates (96-98% for RIT 4385 and 97% for Jeryl Lynn) although the geometric mean titre was significantly higher among recipients of the Jeryl-Lynn vaccine (Crovani et al., 2000; Kanra et al., 2000; Lim et al., 2007). The Urabe Am9 strain was developed by the Biken Institute in Japan from an isolate obtained from the saliva of a mumps patient. Urabe Am9 strain preparations are produced either in the amnion of embryonated hen's eggs or in chicken embryo cell cultures. Seroconversion rates in children aged 12-20 months range from 92-100%. The Rubini mumps vaccine virus was derived from a mumps isolate obtained from the urine of a child in Switzerland in 1974. Comparative efficacy of Rubini, Jeryl-Lynn and Urabe strain mumps vaccine were 80.7, 54.4 and -55.3%, respectively. Thus, Rubini vaccine was discontinued due to poor efficacy (Goh, 1999; Ong et al., 2005). The Leningrad-3 strain was developed in the 1950s in guinea pig kidney cell cultures, with further passages in Japanese quail embryo cultures. The Leningrad-3 vaccine strain has achieved seroconversion rates of 89-98% in children aged 1-7 years and protective efficacy ranged from 92% to 99%. The Leningrad-3 mumps virus was further attenuated in Croatia by adaptation and passages on chicken embryo fibroblast cell cultures. The new mumps strain, designated L-Zagreb, is used in Croatia and India (Bonnet et al., 2006; Plotkin & Rubin, 2007; WHO, 2007).

Vaccine strain	Cell substrate	Sero-conversión	Protective efficacy	Manufacturer	Main area of distribution
Jeryl-Lynn	CWE	80-100%	72.8- 91%	Merck	Worldwide
RIT 4385	CWE	96-98.1%		GlaxoSmithKline	Worldwide
Leningrad- 3	QEF	89-90%	92-99%	Bacterial Medicine Institute, Moscow	Russia
Leningrad- Zagreb	CEF	89-98%	92-99%	Institute of Immunology of Zagreb	Yugoslavia
Urabe AM9	EHE CEF	92-100%	54.4%- 93%	Sanofi Pasteur Biken	Worldwide Japan
Rubini	HDCS	NI	0-33%	Swiss Serum Institute	Discontinued
Hoshino	CEF	NI	NI	Kitasato Institute	Japan
Torii	CEF	NI	NI	Takeda Chemicals	Japan
Miyahara	CEF	NI	NI	Chem-Sero Therapeutic Research Institute	Japan
NL M-46	CEF	NI	NI	Chiba	Japan
S-12	HDCS	NI	NI	Razi State Serum and Vaccine Institute	Iran

NI, No Information; CEF, chicken embryo fibroblasts; HEF, human embryo fibroblasts; QEF, quail embryo fibroblasts; EHE, embryonated hen's eggs; HDCS, human diploid cells.

Information based on the following references: Bonnet et al., 2006; Dayan & Rubin, 2008; Dourado et al., 2000; Galazka et al., 1999; Lim et al., 2007; Peltola et al., 2007; Plotkin & Rubin, 2007; WHO, 2007.

Table 1. Live attenuated mumps vaccine stains.

4. Adverse reactions

In general, adverse reactions to mumps vaccination are rare and mild. Apart from slight soreness and swelling at the injection site, local reactions, low-grade fever, parotitis, and rashes are the most common adverse events. Occasionally, orchitis and sensorineural deafness have been observed after mumps virus vaccination (WHO, 2007).

In a comparative study of the Jeryl Lynn, Urabe, and Leningrad-Zagreb strains in MMR combination vaccines, the frequency of parotitis in vaccinated children was 0-5%, 1-3%, and 3-1%, respectively, compared with 0-2% in unvaccinated controls (Hviid et al., 2008).

A recent study reported adverse reactions following immunization with MMR vaccine that contain the live attenuated mumps virus Hoshino strain; Parotitis was the most frequent event occurring in 1.8% of recipients, followed by fever and convulsions (0.03%), convulsions (0.16%), encephalopathy (0.004%), and anaphylactic reactions (0.004%) in children vaccinated at 12 months and at 4 to 6 years of age (Esteghamati et al., 2011).

4.1 Post vaccine meningitis

One of the most frequent side effects associated with mumps virus vaccine is aseptic meningitis which is also the most frequent complication of naturally acquired mumps infection (Table 2). In November 2006, the Global Advisory Committee on Vaccine Safety (GACVS) reviewed adverse events following mumps vaccination with special reference to the risk of vaccine associated aseptic meningitis (WHO, 2007). Cases of aseptic meningitis and estimates of incidence rates have been reported following the use of the Urabe Am9, Leningrad-Zagreb, Hoshino, Torii and Miyahara strains from various surveillance systems and epidemiological studies. The reported rate of aseptic meningitis that occurs after vaccination ranges widely, from approximately 1 in 1.8 million doses for the Jeryl Lynn strain to as high as 1 in 1000 for the Leningrad-3 strain (Bonnet et al., 2006). However, due to the variability of the methods used in the different studies, no clear conclusion can be drawn on the differences in risk for this complication among these strains.

Urabe AM9 strain was introduced in Canada and UK in 1986 as part of the MMR vaccine. In September 1992, the Urabe AM9-strain was withdrawn from the market worldwide following data indicating a higher rate of vaccination-related cases of meningitis (Schmitt et al., 1993). Despite this, Urabe AM9 strain continued in use several years later in some developing countries including but not limited to Mexico and Brasil (Dourado et al., 2000; Santos-López et al., 2006).

The first reports suggesting a relationship between MMR vaccine (which contained mumps virus strain Urabe AM9, measles virus strain Schwarz and rubella virus strain RA 27/3) and aseptic meningitis showed an estimated incidence of 1/62,000 administered doses (Furesz & Contreras, 1990). Reports of meningitis in patients immunized with Urabe AM9 strain range from 1/233,000 to 16.6/10,000 administered doses (Kimura et al., 1996; Schmitt et al., 1993). An outbreak of aseptic meningitis following the mass immunization campaign with an Urabe-containing vaccine was reported, with an estimated risk of aseptic meningitis 1 per 14,000 doses. This study confirms a link between measles-mumps-rubella vaccination and aseptic meningitis (Dourado et al., 2000). Likewise, no serious adverse effects have been

Vaccine strain	Genetic heterogeneity	Cases of aseptic meningitis/dose administered	Estimated cases of meningitis/100,000 dose	Reference
Jeryl-Lynn	Composed of two distinct viral strains: JL1 and JL2 (Amexis et al., 2002)	0.1/100,000 to 2/500,000	0,1 to 0,4	Bonnet et al., 2006; Makela et al., 2002
Urabe AM9	Composed of quasispecies mix, (Sauder et al., 2006)	1/233,000 to 16.6/10,000	0,4 to 166	Dourado et al., 2000; Furesz & Contreras, 1990; Kimura et al., 1996; Miller et al., 2007; Rebiere & Galy-Eyraud, 1995; Schmitt et al., 1993; Sugiura & Yamada, 1991
Leningrad-3	Composed more than one viral variant (Boriskin et al., 1992)	2/10,000 to 1/1000	20 to 100	Cizman et al., 1989; Plotkin & Rubin, 2007; WHO, 2007
Leningrad-Zagreb	Composed of two major variants: A and B. (Kosutic-Gulija et al., 2008)	1/19,247 to 1/ 3,390	5,1 to 29,5	Arruda & Kondageski, 2001; da Cunha et al., 2002; da Silveira et al., 2002; Phadke et al., 2004
RIT 4385	One strain, clone JL1 (Tillieux et al., 2009)	1/525,312	0,19	Bonnet et al., 2006; Schlipkoter et al., 2002

Table 2. Genetic heterogeneity and Incidence of postvaccine aseptic meningitis.

related to vaccination with RIT 4385 mumps virus strain (Lim et al., 2007). Little epidemiological information is available for other vaccines. Leningrad-Zagreb strain-containing vaccines have been associated with a high rate of aseptic meningitis (da Cunha et al., 2002; da Silveira et al., 2002); however, other reports indicate no evidence to link Leningrad-Zagreb strain with aseptic meningitis (Kulkarni et al., 2005; Sharma et al., 2010). Although high rates of aseptic meningitis ((1/1000 vaccine recipients) have been reported for vaccines containing Leningrad-3 mumps virus strain the evidence confirming causal association is limited (Cizman et al., 1989).

5. Virulence and attenuation of mumps virus strains

Problems with attenuated virus vaccines generally reflect under- or over-attenuation or lack of efficacy respectively. Different studies have attempted to establish molecular markers allow discrimination between an attenuated strain and a virulent strain, nevertheless, the genetic basis for attenuation are still not completed known for any of the mumps vaccines. Likewise the lack the laboratory studies that assure the absence of residual neurotoxicity in mumps vaccine has been a serious problem, as demonstrated by the occurrence of aseptic meningitis in recipients of certain vaccine strains. Thus, some vaccines found to be

neuroattenuated in monkeys were later found to be neurovirulent in humans when administered in large numbers (Rubin & Afzal, 2011).

5.1 Genetic characterization of post vaccination virus isolates (*Helvetica*, 9pt, bold)

The first reports suggesting a relationship between Urabe AM9 strain with the occurrence of aseptic meningitis, suffer however of a lack of molecular markers to discriminate between vaccine- (attenuated) and wild-type strains of the virus, making it difficult to differentiate whether the patient had an infection caused by vaccine or wild type virus. Several laboratories were able to differentiate Urabe AM9 strain from wild-type isolates of mumps virus by RT-PCR and partial sequence analysis of the P, SH, F and HN genes, confirming that mumps virus isolates from post-vaccination meningitis correspond to Urabe AM9 strain, establishing a causal association of virus strain with post-vaccination meningitis (Brown et al., 1991; Forsey et al., 1990; Yamada et al., 1990).

Analysis of cDNA sequences of several isolates from vaccine-associated meningitis and parotitis cases demonstrated that Urabe AM9 strain consisted of a mixture of virus variants that could be distinguished based on the sequence of the hemagglutinin-neuraminidase gene (HN) at nt 1,081 (nt 7,616 of the genome). Viruses containing an A residue at nt 1081 and encoding a lysine at amino acid position 335 were isolated from cases of post-vaccination parotitis or meningitis whereas viruses containing a G residue at nt 1081 that codes for a glutamic acid (aa 335) were not associated with post-vaccination disease, suggesting A₁₀₈₁ (K³³⁵) was a marker of neurovirulence and G₁₀₈₁ (E³³⁵) was a marker of attenuation (Brown et al., 1996). The identification of an A residue at position 1081 in the HN gene sequenced from samples of either patients with post-vaccination meningitis (Afzal et al., 1998; Wright et al., 2000) and patients infected with the wild-type strain (Cusi et al., 1998), supported the previous hypothesis.

However, this hypothesis was questioned by other researchers, reporting that some UrabeAM9 vaccine lots encoding K³³⁵ did not lead to adverse events in vaccinees (Amexis et al., 2001; Mori et al., 1997). Moreover, K³³⁵ was also found in the HN glycoprotein of the Jeryl Lynn vaccine strain, a widely used vaccine not associated with aseptic meningitis (Mori et al., 1997). Nonetheless, Jeryl Lynn strain differs from Urabe AM9 at more than 900 nucleotides, so its safety is likely determined by a number of other genetic changes.

By comparison of the HN gene sequences of several Urabe AM9 vaccine derived isolates, Afzal et al., showed that those sequences differed at several other sites (M89V; N464K; N498D), complicating the interpretation of the initial findings (Afzal et al., 1998). Moreover, heterogeneity at position 464 in the HN glycoprotein (Asn464/Lys) was also reported from sequence analysis of Urabe AM9 vaccine virus and post-vaccination meningitis isolates (Afzal et al., 1998; Amexis et al., 2001; Wright et al., 2000). Further, it was shown that Urabe-AM9 strain is constituted by several virus quasispecies that differ in distinct sites all along their genome, with several amino acids changes in the NP, P, L (involved in replication/transcription), F and HN proteins (involved in the recognition, fusion and release of virus in infected cells), as well as in the intergenic region NP-P (Shah et al., 2009). Sauder et al., showed that genetic heterogeneity at the specific genome sites have a profound effect on the neurovirulent phenotype of Urabe-AM9 strain (Sauder et al., 2006), suggesting there is not a unique genetic marker responsible for virus attenuation, rather the

combination of mutations may be necessary for an adequate viral attenuation (Amexis et al., 2001; Sauder et al., 2006; Shah et al., 2009).

Different vaccine strains exhibit high degree of nucleotide heterogeneity (table 2) across their entire genome making it impossible to determine which genetic change is associated with neurovirulence or neuroattenuation. At respect, the Jeryl Lynn strain contains a mixture of two substrains (JL1 and JL2) that presented 414 nucleotide differences (2.69%), leading to 87 amino acid substitutions (1.67%). Subsequent passage of Jeryl Lynn strain in Vero or CEF cell cultures resulted in rapid selection of the major component JL1, while growth in embryonated chicken eggs (ECE) favored accumulation of the minor component JL2 (Afzal et al., 1993; Amexis et al., 2002; Chambers et al., 2009). Meanwhile, Leningrad-3 strain was characterized as heterogenic on the basis of plaque morphology and with several ambiguities in P and F genes (Boriskin et al., 1992). L-Zagreb vaccine strain was developed by further subcultivation of Leningrad-3 mumps vaccine strain in primary culture of chicken embryo fibroblast (CEF) and its heterogeneity was identified throughout the entire genome (Kosutic-Gulija et al., 2008).

5.2 Structural, functional and antigenic analysis of mumps virus proteins

Mumps vaccine strains, including L-Zagreb, Leningrad-3 and Urabe AM9, have been associated with a high incidence of post-vaccination aseptic meningitis. Although several researchers have focused to study the genetic basis of mumps virus strains virulence/attenuation, there is not genetic marker that help to discriminate between a virulent strain and an attenuated strain. Previous analyses confirmed that Jeryl Lynn, Urabe-AM9, Leningrad-3 and L-Zagreb mumps virus strains are genetically heterogeneous, where each nucleotide changes may contribute to neurovirulence-neuroattenuation of the vaccine. Therefore, caution should be exercised when evaluating genetic markers because more than one nucleotide can influence the attenuation or virulence of a vaccine (Sauder et al., 2006). By other side, functional analysis of point mutations gives relevant information about the properties of a virus variant. A point mutation from guanine (G) to adenine (A) at nucleotide position 1081 in the hemagglutinin-neuraminidase (HN) gene has been associated with neurovirulence of Urabe AM9 mumps virus vaccine. This mutation corresponds to a glutamic acid (E) to lysine (K) change at position 335 in the HN glycoprotein. We have experimentally demonstrated that two variants of Urabe AM9 strain (HN-A₁₀₈₁ and HN-G₁₀₈₁) differ in their replication efficiency in cell culture, where HN-A₁₀₈₁ variant was efficiently replicated in both human neuroblastoma cells (SHSY5Y) and newborn rat brain (10⁵ and 10⁴ PFU respectively), whereas HN-G₁₀₈₁ variant was replicated at low titers (10² PFU in both cases) (Santos-Lopez et al., 2006). These findings can be explained in part by differences in cell receptor binding affinity of each variant, where HN-A₁₀₈₁ variant showed highest affinity towards α 2-6 linked sialic acids that are highly expressed in human nerve cells, whereas HN-G₁₀₈₁ viral variant showed higher affinity towards α 2-3 linked sialic acids that are less expressed in nerve cells, however this latter variant also recognized α 2-6 linked sialic acid but with lesser affinity than HNA₁₀₈₁ virus (Reyes-Leyva et al., 2007). Controversially, two mumps virus that differ at position 335 (K/E) of HN protein exhibited similar growth kinetics in neuronal (SHSY5Y) and non neuronal cell lines (Vero cells) and similar neurotoxicity when tested in rats models. This suggests that amino acid 335 is not a crucial determinant of Urabe neurovirulence,

nevertheless this point mutation can not be excluded as contributing to vaccine virulence (Sauder et al., 2009).

Likewise, we have performed a structure-function analysis of that amino acid substitution, suggesting that the E/K interchange does not affect the structure of the sialic acid binding motif; however, the electrostatic surface differs drastically due to an exposed short alpha helix. Consequently, this mutation may affect the accessibility of HN to substrates and membrane receptors of the host cells (Santos-Lopez et al., 2009). These results suggest that the change K335E affects the biological activity of HN glycoprotein, conferring neurotropism for HN-A₁₀₈₁ viral variant as previously proposed (Brown et al., 1996; Wright et al., 2000). Amino acid 335 is located at an important domain of HN glycoprotein that involves the recognition of an antigenic site, thus all virus variants that possess a Glu at position 335 were completely neutralized, while those containing Lys escaped neutralization (Afzal et al., 1998).

Using a rat based model of mumps neurovirulence, Shah et al. demonstrated that viral variants with a Glu at position 335 of HN glycoprotein is significantly attenuated (hydrocephalus $1.37\% \pm 0.50$) compared to a virus isolated from a patient with post-vaccination meningitis (hydrocephalus $4.70\% \pm 0.77$) and compared with wild type (hydrocephalus $11.47\% \pm 1.16$) which have Lys at this position (Shah et al., 2009).

The importance of amino acid 464 in the HN glycoprotein was demonstrated by mumps virus reverse genetic, which showed that N464S substitution is involved in virus replication in nerve cells (SH-SY5Y) (Ninomiya et al., 2009). Crystal structure studies of the HN glycoprotein of a closely related paramyxovirus Newcastle disease virus, indicates that amino acid position 466 may be at or near the active site of the HN protein (Crennell et al., 2000), thus the substitution around this site (464) might affect enzymatic activity of HN protein and might change the cell specificity of mumps virus. Amino acids 464-466 form a potential N-linked glycosylation site given that substitutions at this site were predicted to result in loss of N-linked glycosylation, and affect virus tropism and virulence (Rubin et al., 2003). Similarly, Malik et al., demonstrated that Ser-466Asp substitution in the HN protein resulted in decreased receptor binding and neuraminidase activity, Ala91Thr change in the fusion protein resulted in decreased fusion activity, and that Ile736Val substitution in the polymerase resulted in increased replication and transcriptional activity (Malik et al., 2007; Malik et al., 2009).

A study based on the extent of hydrocephalus induced in the rat brain after intracerebral vaccine inoculation showed that expression of the F gene of the neurovirulent Kilman strain alone was sufficient to induce significant levels of hydrocephalus, this experiment confirms the importance of surface glycoproteins in neuropathogenesis (Lemon et al., 2007). Moreover, recent studies done in the rat model demonstrated the ability of nucleoprotein/matrix protein of the Jeryl Lynn vaccine strain to significantly neuroattenuate wild-type 88-1961 strain, which is highly neurovirulent (Sauder et al., 2011)

6. Innate immune response against mumps virus infection

Innate immune response acts as a first line of defense during viral infections, through immunoregulatory mechanisms that increase own innate immune response and stimulate

an adaptive immune response. After viral infection, intracellular signaling events are activated and innate cytokine expression are induced as interleukins (IL), tumor necrosis factor (TNF) and interferon (IFN) (Biron & Sen, 2007; Pestka, 2007).

Type-I IFNs (IFN- α/β) are a superfamily of cytokines that were discovered as a result of their induction by and action against virus infections. The interaction between Toll-like receptors (TLR) and pathogen-associated molecular patterns (as genomic RNA and viral proteins), triggers the activation cell signaling pathways that promote activation of some transcription factors such as IRF3 and NF κ B, which are necessary to induce expression of IFN- β . Analogously, RNA helicase molecules (RIG-I and mda-5) trigger TLR-independent pathways that respond to viral nucleic acids (such as dsRNA) generated in the cytoplasm by viral replication, causing activation of IRF3 and NF κ B, which also promote the synthesis of IFN- β (Conzelmann, 2005; Honda et al., 2005; Randall & Goodbourn, 2008; Xagorari & Chlichlia, 2008).

The biological activities of IFNs are initiated by the recognition of IFN- α/β receptor (composed of the products of the IFNAR1 and IFNAR2 genes) on the cell surface, which results in the activation of a signaling pathway known as Jak/STAT pathways. This starts by activation of tyrosine kinases Tyk2 and Jak1 located in the cytoplasmic tail of IFNAR1 and IFNAR2 subunits respectively (de Weerd et al., 2007; Randall & Goodbourn, 2008). Activation of the signal transduction occurs when Tyk2 phosphorylates Tyr⁴⁶⁶ residue on IFNAR1, creating a docking site for STAT2, which is then phosphorylated on Tyr⁶⁹⁰. Phosphorylated STAT2 protein associates with STAT1, inducing its phosphorylation on Tyr⁷⁰¹ by JAK1. Phosphorylated Stat2 and Stat1 proteins form a stable heterodimer that creates a nuclear localization signal (NLS) that permits the transport of these dimers into the nucleus until their dephosphorylation (Randall & Goodbourn, 2008; Schindler et al., 2007). In addition, IFNAR2 subunit is acetylated at Lys³⁹⁹ and promotes the acetylation of IRF9, which is essential to DNA binding (Tang et al., 2007). Association of STAT1-STAT2 heterodimer with IRF9 constitutes ISGF3 (IFN-stimulated gene factor 3) a heterotrimeric transcription factor that binds to the IFN-stimulated response element (ISRE), present in the promoters of several IFN-stimulated genes (ISG). The final step of this signaling pathway is the induction of gene transcription whose expression establishes the antiviral state (Biron & Sen, 2007; Randall & Goodbourn, 2008; Schindler et al., 2007; Sen, 2001).

Numerous ISG products have been described such as Caspases, which are involved in cell death; Protein kinase R (PKR) that inhibits both cellular and viral translation, through phosphorylation of NF- κ B and eIF2 α factor; 2'5'-oligoadenylate synthetase (OAS) that binds to and activates the RNase L, which promotes the degradation cellular and viral RNAs; Mx protein that binds nucleocapsid-like structures, thereby restricting virus replication and assembly (Honda et al., 2005; Randall & Goodbourn, 2008).

6.1 Mumps virus and evasion of innate immune response

Several viruses have evolved strategies to circumvent the antiviral state stimulated by IFN through the expression of proteins that antagonize components of the Jak-Stat signaling pathway, such as the V protein of paramyxoviruses (Gotoh et al., 2002; Randall & Goodbourn, 2008). As mentioned, mumps virus P gene codes for three polypeptides: V, I and P. Their mRNAs are translated by use of overlapping reading frames (ORFs) via

cotranscriptional insertion of nontemplated guanidine nucleotides (mRNA edition) (Lamb & Parks, 2007; Paterson & Lamb, 1990). Mumps virus V protein is a nonstructural protein that counteracts the IFN-induced antiviral response by different mechanisms. In some paramyxoviruses V protein interacts with and inhibits the activity of mda-5 (Andrejeva et al., 2004), but not RIG-I (Komatsu et al., 2007); in other viruses V inhibits interferon-mediated antiviral response through degradation of STAT proteins and thus promotes viral replication (Gotoh et al., 2002; Horvath, 2004; Randall & Goodbourn, 2008).

We have shown that two variants of Urabe AM9 vaccine strain (HN-A₁₀₈₁ and HN-G₁₀₈₁) that were initially characterized by their difference in the HN gene nt 1081, also differ in their replication efficiency in nerve cells, where HN-A₁₀₈₁ variant preferentially infects nerve cells, whereas HN-G₁₀₈₁ variant has limited replication in this cells (Santos-Lopez et al., 2006); These results were associated with differences in the virus binding affinity towards cell receptors and enzymatic activity (Reyes-Leyva et al., 2007). Further experiments showed that differences in sensitivity to IFN determined the replication rate of Urabe AM9 mumps virus variants in nerve cells, where HN-G₁₀₈₁ variant was more sensitive to interferon (from 102.5 to 101.3 TCID₅₀) than HN-A₁₀₈₁ variant (from 103.5 to 102.6 TCID₅₀). Moreover HN-A₁₀₈₁ virus reduced the transcription of cellular IFN responsive genes such as STAT1, STA2, p48 and MxA in both unprimed and IFN-primed cells, whereas HN-G₁₀₈₁ virus just reduced MxA transcription. Sensitivity to IFN was associated with insertion of a non-coded glycine at position 156 in the V protein (V_{Gly}) of HN-G₁₀₈₁ virus variant, whereas resistance to IFN was associated with preservation of wild-type phenotype in the V protein (V_{WT}) of HN-A₁₀₈₁ virus variant (Rosas-Murrieta et al., 2007). Functional analysis of Gly 156 insertion suggested that V_{WT} protein may be more efficient than V_{Gly} protein to inactivate both the IFN signaling pathway and antiviral response due to differences in their finest molecular interaction with STAT proteins (Rosas-Murrieta et al., 2010).

On the other hand the activation of the JAK-STAT pathway by IFN simultaneously activates other processes regulated by IFN such as apoptosis. We studied the relationship between V protein variants of Urabe AM9 vaccine strain and IFN- α induced apoptosis. Our results indicated that V proteins decrease the levels of caspases and DNA fragmentation, suggesting that V_{WT} protein is a better modulator of apoptosis than V_{Gly} in the vaccine strain (Rosas-Murrieta et al., 2011).

7. Conclusions

Several strains of mumps virus used as attenuated vaccines have been associated with post-vaccination meningitis. Experimental data indicates that neurovirulence is a complex issue that involves multiple components either viral or cellular. Further studies are in progress to recognize the role of these in viral attenuation and virulence.

8. References

- Afzal, M.A.; Pickford, A.R.; Forsey, T.; Heath, A.B. & Minor, P.D. (1993). The Jeryl Lynn vaccine strain of mumps virus is a mixture of two distinct isolates. *J Gen Virol*, Vol.74 (Pt 5), pp.917-920, ISSN 0022-1317
- Afzal, M.A.; Yates, P.J. & Minor, P.D. (1998). Nucleotide sequence at position 1081 of the hemagglutinin-neuraminidase gene in the mumps Urabe vaccine strain. *J Infect Dis*, Vol.177, No.1, pp.265-266, ISSN 0022-1899

- Amexis, G.; Fineschi, N. & Chumakov, K. (2001). Correlation of genetic variability with safety of mumps vaccine Urabe AM9 strain. *Virology*, Vol.287, No.1, pp.234-241, ISSN 0042-6822
- Amexis, G.; Rubin, S.; Chizhikov, V.; Pelloquin, F.; Carbone, K. & Chumakov, K. (2002). Sequence diversity of Jeryl Lynn strain of mumps virus: quantitative mutant analysis for vaccine quality control. *Virology*, Vol.300, No.2, pp.171-179, ISSN 0042-6822
- Andrejeva, J.; Childs, K.S.; Young, D.F.; Carlos, T.S.; Stock, N.; Goodbourn, S. & Randall, R.E. (2004). The V proteins of paramyxoviruses bind the IFN-inducible RNA helicase, mda-5, and inhibit its activation of the IFN-beta promoter. *Proc Natl Acad Sci U S A*, Vol.101, No.49, pp.17264-17269, ISSN 0027-8424
- Arruda, W.O. & Kondageski, C. (2001). Aseptic meningitis in a large MMR vaccine campaign (590,609 people) in Curitiba, Parana, Brazil, 1998. *Rev Inst Med Trop Sao Paulo*, Vol.43, No.5, pp.301-302, ISSN 0036-4665
- Biron, C.A. & Sen, G. (2007). Innate responses to viral infections, In: *Fields Virology*, D.M. Knipe & P.M. Howley (Eds.), pp. 250-277, Lippincott Williams & Wilkins, ISBN 0781760607.
- Bonnet, M.C.; Dutta, A.; Weinberger, C. & Plotkin, S.A. (2006). Mumps vaccine virus strains and aseptic meningitis. *Vaccine*, Vol.24, No.49-50, pp.7037-7045, ISSN 0264-410X
- Boriskin, Y.S.; Yamada, A.; Kaptsova, T.I.; Skvortsova, O.I.; Sinityna, O.A.; Takeuchi, K.; Tanabayashi, K. & Sugiyura, A. (1992). Genetic evidence for variant selection in the course of dilute passaging of mumps vaccine virus. *Res Virol*, Vol.143, No.4, pp.279-283, ISSN 0923-2516
- Brockhoff, H.J.; Mollema, L.; Sonder, G.J.; Postema, C.A.; van Binnendijk, R.S.; Kohl, R.H.; de Melker, H.E. & Hahne, S.J. (2010). Mumps outbreak in a highly vaccinated student population, The Netherlands, 2004. *Vaccine*, Vol.28, No.17, pp.2932-2936, ISSN 0264-410X
- Brown, E.G.; Dimock, K. & Wright, K.E. (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. *J Infect Dis*, Vol.174, No.3, pp.619-622, ISSN 0022-1899
- Brown, E.G.; Furesz, J.; Dimock, K.; Yarosh, W. & Contreras, G. (1991). Nucleotide sequence analysis of Urabe mumps vaccine strain that caused meningitis in vaccine recipients. *Vaccine*, Vol.9, No.11, pp.840-842, ISSN 0264-410X
- Brown, E.G. & Wright, K.E. (1998). Genetic studies on a mumps vaccine strain associated with meningitis. *Rev Med Virol*, Vol.8, No.3, pp.129-142, ISSN 1099-1654
- Carbone, K.M. & Rubin, S. (2007). Mumps virus, In: *Fields Virology*, D.M. Knipe & P.M. Howley (Eds.), pp. 1528-1551, Lippincott Williams & Wilkins, ISBN 0781760607.
- CDC. Basics and Common Questions: What Would Happen If We Stopped Vaccinations?, Available from: <http://www.cdc.gov/vaccines/vac-gen/whatifstop.htm#mumps>
- CDC (October 2010). Mumps outbreaks, In: *Mumps*, Available from: <http://www.cdc.gov/mumps/outbreaks.html>
- Cizman, M.; Mozetic, M.; Radescek-Rakar, R.; Pleterski-Rigler, D. & Susec-Michieli, M. (1989). Aseptic meningitis after vaccination against measles and mumps. *Pediatr Infect Dis J*, Vol.8, No.5, pp.302-308, ISSN 0891-3668
- Conzelmann, K.K. (2005). Transcriptional activation of alpha/beta interferon genes: interference by nonsegmented negative-strand RNA viruses. *J Virol*, Vol.79, No.9, pp.5241-5248, ISSN 0022-538X

- Crennell, S.; Takimoto, T.; Portner, A. & Taylor, G. (2000). Crystal structure of the multifunctional paramyxovirus hemagglutinin-neuraminidase. *Nat Struct Biol*, Vol.7, No.11, pp.1068-1074, ISSN 1072-8368
- Crovati, P.; Gabutti, G.; Giammanco, G.; Dentico, P.; Moiraghi, A.R.; Ponzio, F. & Soncini, R. (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*, Vol.18, No.25, pp.2796-2803, ISSN 0264-410X
- Cusi, M.G.; Santini, L.; Bianchi, S.; Valassina, M. & Valensin, P.E. (1998). Nucleotide sequence at position 1081 of the hemagglutinin-neuraminidase gene in wild-type strains of mumps virus is the most relevant marker of virulence. *J Clin Microbiol*, Vol.36, No.12, pp.3743-3744, ISSN 0095-1137
- Chambers, P.; Rima, B.K. & Duprex, W.P. (2009). Molecular differences between two Jeryl Lynn mumps virus vaccine component strains, JL5 and JL2. *J Gen Virol*, Vol.90, No.Pt 12, pp.2973-2981, ISSN 1465-2099
- Cheek, J.E.; Baron, R.; Atlas, H.; Wilson, D.L. & Crider, R.D., Jr. (1995). Mumps outbreak in a highly vaccinated school population. Evidence for large-scale vaccination failure. *Arch Pediatr Adolesc Med*, Vol.149, No.7, pp.774-778, ISSN 1072-4710
- Choi, K.M. (2010). Reemergence of mumps. *Korean J Pediatr*, Vol.53, No.5, pp.623-628, ISSN 2092-7258.
- da Cunha, S.S.; Rodrigues, L.C.; Barreto, M.L. & Dourado, I. (2002). Outbreak of aseptic meningitis and mumps after mass vaccination with MMR vaccine using the Leningrad-Zagreb mumps strain. *Vaccine*, Vol.20, No.7-8, pp.1106-1112, ISSN 0264-410X.
- da Silveira, C.M.; Kmetzsch, C.I.; Mohrdieck, R.; Sperb, A.F. & Prevots, D.R. (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. *Int J Epidemiol*, Vol.31, No.5, pp.978-982, ISSN 0300-5771.
- Dayan, G.H.; Quinlisk, M.P.; Parker, A.A.; Barskey, A.E.; Harris, M.L.; Schwartz, J.M.; Hunt, K.; Finley, C.G.; Leschinsky, D.P.; O'Keefe, A.L.; Clayton, J.; Kightlinger, L.K.; Dietle, E.G.; Berg, J.; Kenyon, C.L.; Goldstein, S.T.; Stokley, S.K.; Redd, S.B.; Rota, P.A.; Rota, J.; Bi, D.; Roush, S.W.; Bridges, C.B.; Santibanez, T.A.; Parashar, U.; Bellini, W.J. & Seward, J.F. (2008). Recent resurgence of mumps in the United States. *N Engl J Med*, Vol.358, No.15, pp.1580-1589, ISSN 1533-4406.
- Dayan, G.H. & Rubin, S. (2008). Mumps outbreaks in vaccinated populations: are available mumps vaccines effective enough to prevent outbreaks? *Clin Infect Dis*, Vol.47, No.11, pp.1458-1467, ISSN 1537-6591
- de Weerd, N.A.; Samarajiwa, S.A. & Hertzog, P.J. (2007). Type I interferon receptors: biochemistry and biological functions. *J Biol Chem*, Vol.282, No.28, pp.20053-20057, ISSN 0021-9258
- Didcock, L.; Young, D.F.; Goodbourn, S. & Randall, R.E. (1999a). Sendai virus and simian virus 5 block activation of interferon-responsive genes: importance for virus pathogenesis. *J Virol*, Vol.73, No.4, pp.3125-3133, ISSN 0022-538X
- Didcock, L.; Young, D.F.; Goodbourn, S. & Randall, R.E. (1999b). The V protein of simian virus 5 inhibits interferon signalling by targeting STAT1 for proteasome-mediated degradation. *J Virol*, Vol.73, No.12, pp.9928-9933, ISSN 0022-538X.
- Dourado, I.; Cunha, S.; Teixeira, M.G.; Farrington, C.P.; Melo, A.; Lucena, R. & Barreto, M.L. (2000). Outbreak of aseptic meningitis associated with mass vaccination with a urabe-containing measles-mumps-rubella vaccine: implications for immunization programs. *Am J Epidemiol*, Vol.151, No.5, pp.524-530, ISSN 0002-9262

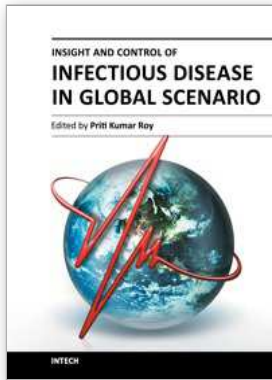
- Enders, G. (1996). Paramyxoviruses, In: *Medical Microbiolog*, S. Baron (Ed), The University of Texas Medical Branch at Galveston, ISBN-10: 0-9631172-1-1, Galveston, Texas.
- Esteghamati, A.; Keshtkar, A.; Heshmat, R.; Gouya, M.M.; Salar Amoli, M.; Armin, S. & Mahoney, F. (2011). Adverse reactions following immunization with MMR vaccine in children at selected provinces of Iran. *Arch Iran Med*, Vol.14, No.2, pp.91-95, ISSN 1029-2977.
- Fleischer, B. & Kreth, H.W. (1982). Mumps virus replication in human lymphoid cell lines and in peripheral blood lymphocytes: preference for T cells. *Infect Immun*, Vol.35, No.1, pp.25-31, ISSN 0019-9567
- Forsey, T.; Mawn, J.A.; Yates, P.J.; Bentley, M.L. & Minor, P.D. (1990). Differentiation of vaccine and wild mumps viruses using the polymerase chain reaction and dideoxynucleotide sequencing. *J Gen Virol*, Vol.71 (Pt 4), pp.987-990, ISSN 0022-1317.
- Fujii, N.; Yokosawa, N. & Shirakawa, S. (1999). Suppression of interferon response gene expression in cells persistently infected with mumps virus, and restoration from its suppression by treatment with ribavirin. *Virus Res*, Vol.65, No.2, pp.175-185, ISSN 0168-1702
- Furesz, J. & Contreras, G. (1990). Vaccine-related mumps meningitis--Canada. *Can Dis Wkly Rep*, Vol.16, No.50, pp.253-254, ISSN 0382-232X
- Galazka, A.M.; Robertson, S.E. & Kraigher, A. (1999). Mumps and mumps vaccine: a global review. *Bull World Health Organ*, Vol.77, No.1, pp.3-14, ISSN 0042-9686.
- Goh, K.T. (1999). Resurgence of mumps in Singapore caused by the Rubini mumps virus vaccine strain. *Lancet*, Vol.354, No.9187, pp.1355-1356, ISSN 0140-6736
- Gotoh, B.; Komatsu, T.; Takeuchi, K. & Yokoo, J. (2002). Paramyxovirus strategies for evading the interferon response. *Rev Med Virol*, Vol.12, No.6, pp.337-357, ISSN 1052-9276
- Hausmann, S.; Garcin, D.; Delenda, C. & Kolakofsky, D. (1999). The versatility of paramyxovirus RNA polymerase stuttering. *J Virol*, Vol.73, No.7, pp.5568-5576, ISSN 0022-538X
- Hersh, B.S.; Fine, P.E.; Kent, W.K.; Cochi, S.L.; Kahn, L.H.; Zell, E.R.; Hays, P.L. & Wood, C.L. (1991). Mumps outbreak in a highly vaccinated population. *J Pediatr*, Vol.119, No.2, pp.187-193, ISSN 0022-3476
- Honda, K.; Yanai, H.; Takaoka, A. & Taniguchi, T. (2005). Regulation of the type I IFN induction: a current view. *Int Immunol*, Vol.17, No.11, pp.1367-1378, ISSN 0953-8178
- Horvath, C.M. (2004). Weapons of STAT destruction. Interferon evasion by paramyxovirus V protein. *Eur J Biochem*, Vol.271, No.23-24, pp.4621-4628, ISSN 0014-2956
- Hviid, A.; Rubin, S. & Muhlemann, K. (2008). Mumps. *Lancet*, Vol.371, No.9616, pp.932-944, ISSN 1474-547X
- Kanra, G.; Ceyhan, M. & Ozmert, E. (2000). Reactogenicity and immunogenicity of a new measles-mumps-rubella vaccine containing RIT 4385 mumps virus strain in healthy Turkish children. *Turk J Pediatr*, Vol.42, No.4, pp.275-277, ISSN 0041-4301.
- Kimura, M.; Kuno-Sakai, H.; Yamazaki, S.; Yamada, A.; Hishiyama, M.; Kamiya, H.; Ueda, K.; Murase, T.; Hirayama, M.; Oya, A.; Nozaki, S. & Murata, R. (1996). Adverse events associated with MMR vaccines in Japan. *Acta Paediatr Jpn*, Vol.38, No.3, pp.205-211, ISSN 0374-5600.
- Kingston, R.L.; Hamel, D.J.; Gay, L.S.; Dahlquist, F.W. & Matthews, B.W. (2004). Structural basis for the attachment of a paramyxoviral polymerase to its template. *Proc Natl Acad Sci U S A*, Vol.101, No.22, pp.8301-8306, ISSN 0027-8424.

- Kolakofsky, D.; Pelet, T.; Garcin, D.; Hausmann, S.; Curran, J. & Roux, L. (1998). Paramyxovirus RNA synthesis and the requirement for hexamer genome length: the rule of six revisited. *J Virol*, Vol.72, No.2, pp.891-899, ISSN 0022-538X
- Kolakofsky, D.; Roux, L.; Garcin, D. & Ruigrok, R.W. (2005). Paramyxovirus mRNA editing, the "rule of six" and error catastrophe: a hypothesis. *J Gen Virol*, Vol.86, No.Pt 7, pp.1869-1877, ISSN 0022-1317
- Komatsu, T.; Takeuchi, K. & Gotoh, B. (2007). Bovine parainfluenza virus type 3 accessory proteins that suppress beta interferon production. *Microbes Infect*, Vol.9, No.8, pp.954-962, ISSN 1286-4579
- Kosutic-Gulija, T.; Forcic, D.; Santak, M.; Ramljak, A.; Mateljak-Lukacevic, S. & Mazuran, R. (2008). Genetic heterogeneity of L-Zagreb mumps virus vaccine strain. *Virol J*, Vol.5, pp.79, ISSN 1743-422X
- Kulkarni, P.S.; Phadke, M.A.; Jadhav, S.S. & Kapre, S.V. (2005). No definitive evidence for L-Zagreb mumps strain associated aseptic meningitis: a review with special reference to the da Cunha study. *Vaccine*, Vol.23, No.46-47, pp.5286-5288, ISSN 0264-410X
- Lamb, R.A. & Parks, G.D. (2007). Paramyxoviridae: The viruses and their replication, In: *Fields Virology*, D.M. Knipe & P.M. Howley (Eds.), pp. 1450- 1497, Lippincott Williams & Wilkins, ISBN 0781760607.
- Lemon, K.; Rima, B.K.; McQuaid, S.; Allen, I.V. & Duprex, W.P. (2007). The F gene of rodent brain-adapted mumps virus is a major determinant of neurovirulence. *J Virol*, Vol.81, No.15, pp.8293-8302, ISSN 0022-538X
- Lim, F.S.; Han, H.H. & Bock, H.L. (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. *Ann Acad Med Singapore*, Vol.36, No.12, pp.969-973, ISSN 0304-4602
- Makela, A.; Nuorti, J.P. & Peltola, H. (2002). Neurologic disorders after measles-mumps-rubella vaccination. *Pediatrics*, Vol.110, No.5, pp.957-963, ISSN 1098-4275
- Malik, T.; Shegogue, C.W.; Werner, K.; Ngo, L.; Sauder, C.; Zhang, C.; Duprex, W.P. & Rubin, S. (2011). Discrimination of mumps virus small hydrophobic gene deletion effects from gene translation effects on virus virulence. *J Virol*, Vol.85, No.12, pp.6082-6085, ISSN 1098-5514.
- Malik, T.; Wolbert, C.; Mauldin, J.; Sauder, C.; Carbone, K.M. & Rubin, S.A. (2007). Functional consequences of attenuating mutations in the haemagglutinin neuraminidase, fusion and polymerase proteins of a wild-type mumps virus strain. *J Gen Virol*, Vol.88, No.Pt 9, pp.2533-2541, ISSN 0022-1317
- Malik, T.H.; Wolbert, C.; Nerret, L.; Sauder, C. & Rubin, S. (2009). Single amino acid changes in the mumps virus haemagglutinin-neuraminidase and polymerase proteins are associated with neuroattenuation. *J Gen Virol*, Vol.90, No.Pt 7, pp.1741-1747, ISSN 0022-1317
- Miller, E.; Andrews, N.; Stowe, J.; Grant, A.; Waight, P. & Taylor, B. (2007). Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom. *Am J Epidemiol*, Vol.165, No.6, pp.704-709, ISSN 0002-9262.
- Mori, C.; Tooriyama, T.; Imagawa, T. & Yamanishi, K. (1997). Nucleotide sequence at position 1081 of the hemagglutinin-neuraminidase gene in the mumps virus Urabe vaccine strain. *J Infect Dis*, Vol.175, No.6, pp.1548-1549, ISSN 0022-1899.
- Ninomiya, K.; Kanayama, T.; Fujieda, N.; Nakayama, T.; Komase, K.; Nagata, K. & Takeuchi, K. (2009). Amino acid substitution at position 464 in the haemagglutinin-neuraminidase protein of a mumps virus Urabe strain enhanced the virus growth

- in neuroblastoma SH-SY5Y cells. *Vaccine*, Vol.27, No.44, pp.6160-6165, ISSN 1873-2518
- Ong, G.; Goh, K.T.; Ma, S. & Chew, S.K. (2005). Comparative efficacy of Rubini, Jeryl-Lynn and Urabe mumps vaccine in an Asian population. *J Infect*, Vol.51, No.4, pp.294-298, ISSN 1532-2742
- Orvell, C.; Kalantari, M. & Johansson, B. (1997). Characterization of five conserved genotypes of the mumps virus small hydrophobic (SH) protein gene. *J Gen Virol*, Vol.78 (Pt 1), pp.91-95, ISSN 0022-1317
- Park, D.W.; Nam, M.H.; Kim, J.Y.; Kim, H.J.; Sohn, J.W.; Cho, Y.; Song, K.J. & Kim, M.J. (2007). Mumps outbreak in a highly vaccinated school population: assessment of secondary vaccine failure using IgG avidity measurements. *Vaccine*, Vol.25, No.24, pp.4665-4670, ISSN 0264-410X
- Paterson, R.G. & Lamb, R.A. (1990). RNA editing by G-nucleotide insertion in mumps virus P-gene mRNA transcripts. *J Virol*, Vol.64, No.9, pp.4137-4145, ISSN 0022-538X
- Peltola, H.; Kulkarni, P.S.; Kapre, S.V.; Paunio, M.; Jadhav, S.S. & Dhare, R.M. (2007). Mumps outbreaks in Canada and the United States: time for new thinking on mumps vaccines. *Clin Infect Dis*, Vol.45, No.4, pp.459-466, ISSN 1537-6591
- Pestka, S. (2007). The interferons: 50 years after their discovery, there is much more to learn. *J Biol Chem*, Vol.282, No.28, pp.20047-20051, ISSN 0021-9258
- Phadke, M.A.; Patki, P.S.; Kulkarni, P.S.; Jadhav, S.S. & Kapre, S.V. (2004). Pharmacovigilance on MMR vaccine containing L-Zagreb mumps strain. *Vaccine*, Vol.22, No.31-32, pp.4135-4136, ISSN 0264-410X.
- Plotkin, S.A. & Rubin, S.A. (December 2007). Mumps vaccine In: *Vaccines*, Available from <http://www.thelancetglobalhealthnetwork.com/wp-content/uploads/2008/03/plotkins_ch020-x3611.PDF>
- Pringle, C.R. (1997). The order Mononegavirales--current status. *Arch Virol*, Vol.142, No.11, pp.2321-2326, ISSN 0304-8608
- Randall, R.E. & Goodbourn, S. (2008). Interferons and viruses: an interplay between induction, signalling, antiviral responses and virus countermeasures. *J Gen Virol*, Vol.89, No.Pt 1, pp.1-47, ISSN 0022-1317
- Rebiere, I. & Galy-Eyraud, C. (1995). Estimation of the risk of aseptic meningitis associated with mumps vaccination, France, 1991-1993. *Int J Epidemiol*, Vol.24, No.6, pp.1223-1227, ISSN 0300-5771.
- Reyes-Leyva, J.; Banos, R.; Borraz-Arguello, M.; Santos-Lopez, G.; Rosas, N.; Alvarado, G.; Herrera, I.; Vallejo, V. & Tapia-Ramirez, J. (2007). Amino acid change 335 E to K affects the sialic-acid-binding and neuraminidase activities of Urabe AM9 mumps virus hemagglutinin-neuraminidase glycoprotein. *Microbes Infect*, Vol.9, No.2, pp.234-240, ISSN 1286-4579
- Rodriguez, J.J.; Wang, L.F. & Horvath, C.M. (2003). Hendra virus V protein inhibits interferon signaling by preventing STAT1 and STAT2 nuclear accumulation. *J Virol*, Vol.77, No.21, pp.11842-11845, ISSN 0022-538X
- Rosas-Murrieta, N.; Herrera-Camacho, I.; Vallejo-Ruiz, V.; Millan-Perez-Pena, L.; Cruz, C.; Tapia-Ramirez, J.; Santos-Lopez, G. & Reyes-Leyva, J. (2007). Differential sensitivity to interferon influences the replication and transcription of Urabe AM9 mumps virus variants in nerve cells. *Microbes Infect*, Vol.9, No.7, pp.864-872, ISSN 1286-4579.
- Rosas-Murrieta, N.H.; Herrera-Camacho, I.; Palma-Ocampo, H.; Santos-Lopez, G. & Reyes-Leyva, J. (2010). Interaction of mumps virus V protein variants with STAT1-STAT2

- heterodimer: experimental and theoretical studies. *Virology*, Vol.7, pp.263, ISSN 1743-422X.
- Rosas-Murrieta, N.H.; Santos-Lopez, G.; Reyes-Leyva, J.; Jurado, F.S. & Herrera-Camacho, I. (2011). Modulation of apoptosis by V protein mumps virus. *Virology*, Vol.8, pp.224, ISSN 1743-422X
- Rubin, S.A. & Afzal, M.A. (2011). Neurovirulence safety testing of mumps vaccines--historical perspective and current status. *Vaccine*, Vol.29, No.16, pp.2850-2855, ISSN 1873-2518
- Rubin, S.A.; Amexis, G.; Pletnikov, M.; Li, Z.; Vanderzanden, J.; Mauldin, J.; Sauder, C.; Malik, T.; Chumakov, K. & Carbone, K.M. (2003). Changes in mumps virus gene sequence associated with variability in neurovirulent phenotype. *J Virol*, Vol.77, No.21, pp.11616-11624, ISSN 0022-538X
- Santos-Lopez, G.; Cruz, C.; Pazos, N.; Vallejo, V.; Reyes-Leyva, J. & Tapia-Ramirez, J. (2006). Two clones obtained from Urabe AM9 mumps virus vaccine differ in their replicative efficiency in neuroblastoma cells. *Microbes Infect*, Vol.8, No.2, pp.332-339, ISSN 1286-4579
- Santos-López, G.; Hernández, J.; Borraz-Argüello, M.T.; Ramírez -Mendoza, H.; Vallejo, V. & Reyes-Leyva, J. (2004). Estructura, función e implicaciones patológicas de las proteínas del Rubulavirus porcino. *Arch. med. vet. [online]*, Vol.36, No.2, pp.119-136, ISSN 0301-732X.
- Santos-Lopez, G.; Scior, T.; Borraz-Arguello Mdel, T.; Vallejo-Ruiz, V.; Herrera-Camacho, I.; Tapia-Ramirez, J. & Reyes-Leyva, J. (2009). Structure-function analysis of two variants of mumps virus hemagglutinin-neuraminidase protein. *Braz J Infect Dis*, Vol.13, No.1, pp.24-34, ISSN 1678-4391
- Sauder, C.J.; Vandenburg, K.M.; Iskow, R.C.; Malik, T.; Carbone, K.M. & Rubin, S.A. (2006). Changes in mumps virus neurovirulence phenotype associated with quasispecies heterogeneity. *Virology*, Vol.350, No.1, pp.48-57, ISSN 0042-6822
- Sauder, C.J.; Zhang, C.X.; Link, M.A.; Duprex, W.P.; Carbone, K.M. & Rubin, S.A. (2009). Presence of lysine at aa 335 of the hemagglutinin-neuraminidase protein of mumps virus vaccine strain Urabe AM9 is not a requirement for neurovirulence. *Vaccine*, Vol.27, No.42, pp.5822-5829, ISSN 1873-2518.
- Sauder, C.J.; Zhang, C.X.; Ngo, L.; Werner, K.; Lemon, K.; Duprex, W.P.; Malik, T.; Carbone, K. & Rubin, S.A. (2011). Gene-specific contributions to mumps virus neurovirulence and neuroattenuation. *J Virol*, Vol.85, No.14, pp.7059-7069, ISSN 1098-5514.
- Schindler, C.; Levy, D.E. & Decker, T. (2007). JAK-STAT signaling: from interferons to cytokines. *J Biol Chem*, Vol.282, No.28, pp.20059-20063, ISSN 0021-9258
- Schlipkoter, U.; Muhlberger, N.; von Kries, R. & Weil, J. (2002). Surveillance of measles-mumps-rubella vaccine-associated aseptic meningitis in Germany. *Infection*, Vol.30, No.6, pp.351-355, ISSN 0300-8126.
- Schmitt, H.J.; Just, M. & Neiss, A. (1993). Withdrawal of a mumps vaccine: reasons and impacts. *Eur J Pediatr*, Vol.152, No.5, pp.387-388, ISSN 0340-6199
- Sen, G.C. (2001). Viruses and interferons. *Annu Rev Microbiol*, Vol.55, pp.255-281, ISSN 0066-4227
- Shah, D.; Vidal, S.; Link, M.A.; Rubin, S.A. & Wright, K.E. (2009). Identification of genetic mutations associated with attenuation and changes in tropism of Urabe mumps virus. *J Med Virol*, Vol.81, No.1, pp.130-138, ISSN 1096-9071.
- Sharma, H.J.; Oun, S.A.; Bakr, S.S.; Kapre, S.V.; Jadhav, S.S.; Dhere, R.M. & Bhardwaj, S. (2010). No demonstrable association between the Leningrad-Zagreb mumps

- vaccine strain and aseptic meningitis in a large clinical trial in Egypt. *Clin Microbiol Infect*, Vol.16, No.4, pp.347-352, ISSN 1469-0691.
- Sugiura, A. & Yamada, A. (1991). Aseptic meningitis as a complication of mumps vaccination. *Pediatr Infect Dis J*, Vol.10, No.3, pp.209-213, ISSN 0891-3668
- Tang, X.; Gao, J.S.; Guan, Y.J.; McLane, K.E.; Yuan, Z.L.; Ramratnam, B. & Chin, Y.E. (2007). Acetylation-dependent signal transduction for type I interferon receptor. *Cell*, Vol.131, No.1, pp.93-105, ISSN 0092-8674
- Tillieux, S.L.; Halsey, W.S.; Sathe, G.M. & Vassilev, V. (2009). Comparative analysis of the complete nucleotide sequences of measles, mumps, and rubella strain genomes contained in Priorix-Tetra and ProQuad live attenuated combined vaccines. *Vaccine*, Vol.27, No.16, pp.2265-2273, ISSN 0264-410X
- Vandermeulen, C.; Leroux-Roels, G. & Hoppenbrouwers, K. (2009). Mumps outbreaks in highly vaccinated populations: What makes good even better? *Hum Vaccin*, Vol.5, No.7, pp.494-496, ISSN 1554-8619
- Vandermeulen, C.; Roelants, M.; Vermoere, M.; Roseeuw, K.; Goubau, P. & Hoppenbrouwers, K. (2004). Outbreak of mumps in a vaccinated child population: a question of vaccine failure? *Vaccine*, Vol.22, No.21-22, pp.2713-2716, ISSN 0264-410X
- Vidal, S.; Curran, J. & Kolakofsky, D. (1990). A stuttering model for paramyxovirus P mRNA editing. *EMBO J*, Vol.9, No.6, pp.2017-2022, ISSN 0261-4189
- Vulliamoz, D. & Roux, L. (2001). "Rule of six": how does the Sendai virus RNA polymerase keep count? *J Virol*, Vol.75, No.10, pp.4506-4518, ISSN 0022-538X
- WHO (February 2007). Mumps virus vaccines, In: *Weekly Epidemiological Record (WER)* Available from: <http://www.who.int/wer/2007/wer8207/en/index.html>
- WHO (December 2010). Mumps, In: *Immunization surveillance, assessment and monitoring*, Available from: http://www.who.int/immunization_monitoring/diseases/mumps/en/index.html
- Wilson, R.L.; Fuentes, S.M.; Wang, P.; Taddeo, E.C.; Klatt, A.; Henderson, A.J. & He, B. (2006). Function of small hydrophobic proteins of paramyxovirus. *J Virol*, Vol.80, No.4, pp.1700-1709, ISSN 0022-538X.
- Wolinsky, J.S.; Klassen, T. & Baringer, J.R. (1976). Persistence of neuroadapted mumps virus in brains of newborn hamsters after intraperitoneal inoculation. *J Infect Dis*, Vol.133, No.3, pp.260-267, ISSN 0022-1899.
- Woznik, M.; Rodner, C.; Lemon, K.; Rima, B.; Mankertz, A. & Finsterbusch, T. (2010). Mumps virus small hydrophobic protein targets ataxin-1 ubiquitin-like interacting protein (ubiquilin 4). *J Gen Virol*, Vol.91, No.Pt 11, pp.2773-2781, ISSN 1465-2099.
- Wright, K.E.; Dimock, K. & Brown, E.G. (2000). Biological characteristics of genetic variants of Urabe AM9 mumps vaccine virus. *Virus Res*, Vol.67, No.1, pp.49-57, ISSN 0168-1702
- Xagorari, A. & Chlichlia, K. (2008). Toll-like receptors and viruses: induction of innate antiviral immune responses. *Open Microbiol J*, Vol.2, pp.49-59, ISSN 1874-2858.
- Yamada, A.; Takeuchi, K.; Tanabayashi, K.; Hishiyama, M.; Takahashi, Y. & Sugiura, A. (1990). Differentiation of the mumps vaccine strains from the wild viruses by the nucleotide sequences of the P gene. *Vaccine*, Vol.8, No.6, pp.553-557, ISSN 0264-410X.



Insight and Control of Infectious Disease in Global Scenario

Edited by Dr. Roy Priti

ISBN 978-953-51-0319-6

Hard cover, 442 pages

Publisher InTech

Published online 21, March, 2012

Published in print edition March, 2012

This book is projected as a preliminary manuscript in Infectious Disease. It is undertaken to cover the foremost basic features of the articles. Infectious Disease and analogous phenomenon have been one of the main imperative postwar accomplishments in the world. The book expects to provide its reader, who does not make believe to be a proficient mathematician, an extensive preamble to the field of infectious disease. It may immeasurably assist the Scientists and Research Scholars for continuing their investigate workings on this discipline. Numerous productive and precise illustrated descriptions with a number of analyses have been included. The book offers a smooth and continuing evolution from the principally disease oriented lessons to a logical advance, providing the researchers with a compact groundwork for upcoming studies in this subject.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Alejandra Lara-Sampablo, Nora Rosas-Murrieta, Irma Herrera-Camacho, Verónica Vallejo-Ruiz, Gerardo Santos-López and Julio Reyes-Leyva (2012). Studies on the Association of Meningitis and Mumps Virus Vaccination, Insight and Control of Infectious Disease in Global Scenario, Dr. Roy Priti (Ed.), ISBN: 978-953-51-0319-6, InTech, Available from: <http://www.intechopen.com/books/insight-and-control-of-infectious-disease-in-global-scenario/studies-on-the-association-of-meningitis-and-mumps-virus-vaccination->

INTECH

open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821