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Studies on the Association of Meningitis and Mumps Virus Vaccination

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1. Introduction

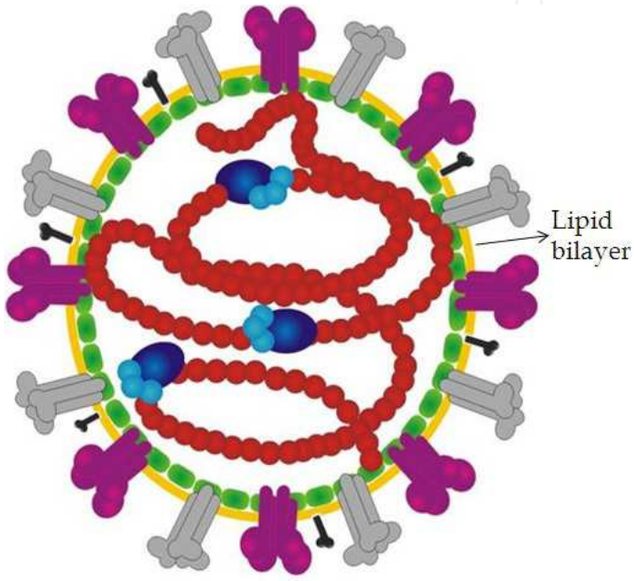
Mumps is an acute viral infection caused by a member of the *Rubulavirus* genus in the *Paramyxoviridae* family. Although it is mostly a childhood disease, with peak incidence occurring among those aged 5–9 years, mumps virus (MuV) may also affect teenagers. MuV is known to affect the salivary glands 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 nucleocapside (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 TNFα 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; Vulliemoz & 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 nucleocapside 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'CCCCCC 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).

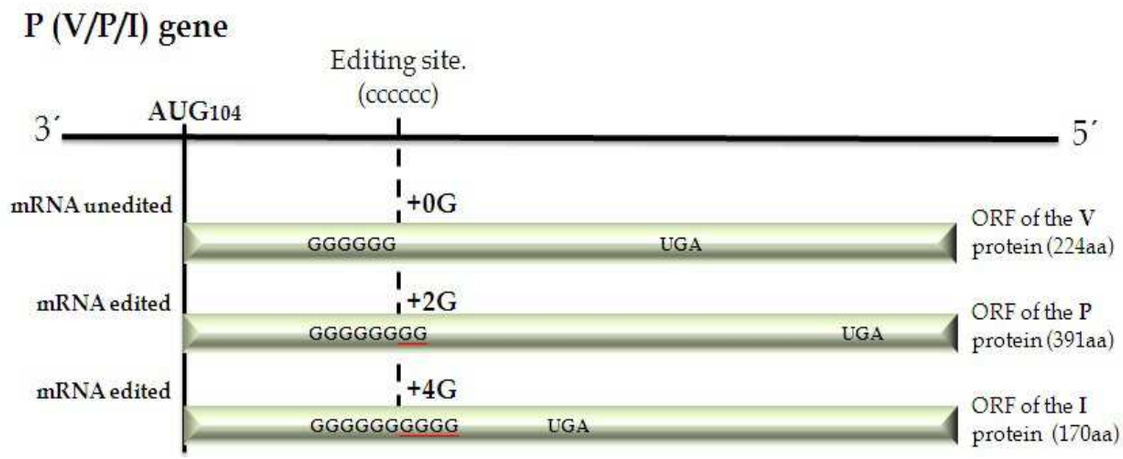


Fig. 2. Schematic representation of mumps virus P gene and mRNA editing mechanism (not drawn to scale). By a stuttering mechanism in the editing site of P gene, the viral polymerase introduces non-template G residues in the nascent transcript, which generates mRNAs with different ORFs, so, the translation 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 undergo 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 demyelinisation and perivascular infiltration with mononuclear cells (Hviid et al., 2008).

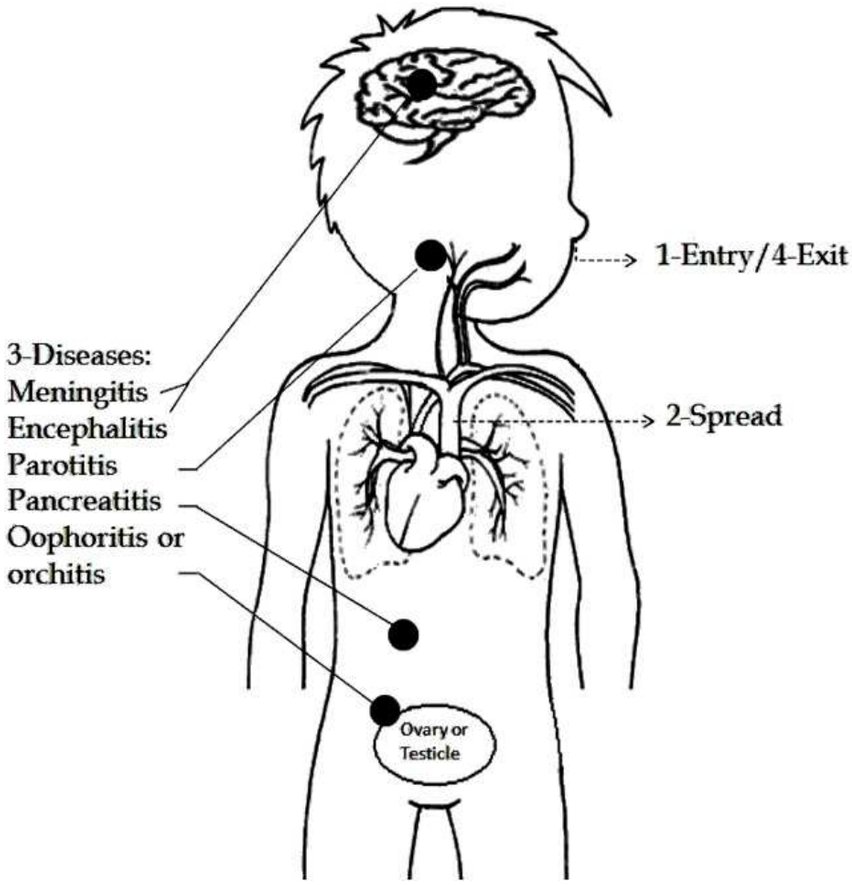


Fig. 3. Pathogenesis of mumps virus infection. Mumps virus is acquired trough the upper-respiratory-tract mucosa (1); where it undergo a first replication, after that new viruses spread (2) to local lymph nodes followed by a systemic spread with involvement of glandular and nervous tissues causing various 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).

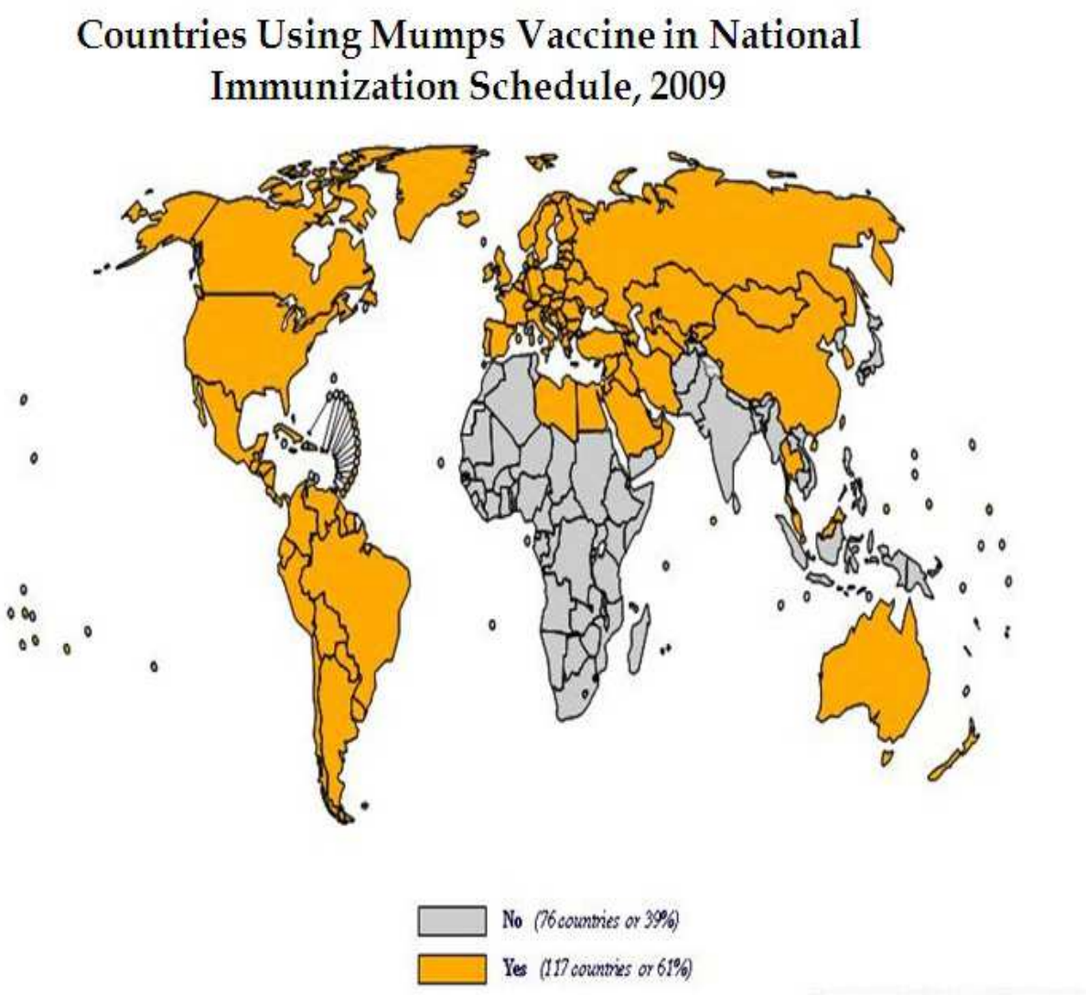


Fig. 4. Countries that have incorporated mumps vaccination in their national immunization programs. Yellow and gray indicate the countries immunized (61%) and unimmunized (39%) respectively. Source: WHO/IVB database, 193 WHO Member States, Data as of July 2010. Date of slide: 19 August 2010.

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 (Crovari 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	92-100%	54.4%- 93%	Sanofi Pasteur	Worldwide
	CEF			Biken	Japan
Rubini	HDCS	N I	0-33%	Swiss Serum Institute	Discontinued
Hoshino	CEF	N I	N I	Kitasato Institute	Japan
Torii	CEF	N I	N I	Takeda Chemicals	Japan
Miyahara	CEF	N I	N I	Chem-Sero Therapeutic Research Institute	Japan
NL M-46	CEF	N I	N I	Chiba	Japan
S-12	HDCS	N I	N I	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 fewer, 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 A_{1081} (K^{335}) was a marker of neurovirulence and G_{1081} (E^{335}) 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 K^{355} did not lead to adverse events in vaccinees (Amexis et al., 2001; Mori et al., 1997). Moreover, K^{335} 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-A_{1081} and HN-G_{1081}) differ in their replication efficiency in cell culture, where HN-A_{1081} variant was efficiently replicated in both human neuroblastoma cells (SHSY5Y) and newborn rat brain (10^5 and 10^4 PFU respectively), whereas HN-G_{1081} variant was replicated at low titers (10^2 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-A_{1081} variant showed highest affinity towards α2-6 linked sialic acids that are highly expressed in human nerve cells, whereas HN-G_{1081} viral variant showed higher affinity towards α2-3 linked sialic acids that are less expressed in nerve cells, however this latter variant also recognized α2-6 linked sialic acid but with lesser affinity than HNA_{1081} 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-A_{1081} 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% ± 0.50) compared to a virus isolated from a patient with post-vaccination meningitis (hydrocephalus 4.70%±0.77) and compared with wild type (hydrocephalus 11.47%±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 Newcatle 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-liked 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 NFκB, 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 NFκB, wich 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 tysosine 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 Tyr^{466} residue on IFNAR1, creating a docking site for STAT2, which is then phosphorylates on Tyr^{690}. Phosphorylated STAT2 protein associates with STAT1, inducing its phosphorylation on Tyr^{701} by JAK1. Phosporylated 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-κB and eIF2α 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-A_{1081} and HN-G_{1081}) that were initially characterized by their difference in the HN gene nt 1081, also differ in their replication efficiency in nerve cells, where HN-A_{1081} variant preferentially infects nerve cells, whereas HN-G_{1081} 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-G_{1081} variant was more sensitive to interferon (from 102.5 to 101.3 TCID50) than HN-A_{1081} variant (from 103.5 to 102.6 TCID50). Moreover HN-A_{1081} 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-G_{1081} 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-G_{1081} virus variant, whereas resistance to IFN was associated with preservation of wild-type phenotype in the V protein (V_{WT}) of HN-A_{1081} 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 Vgly 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.

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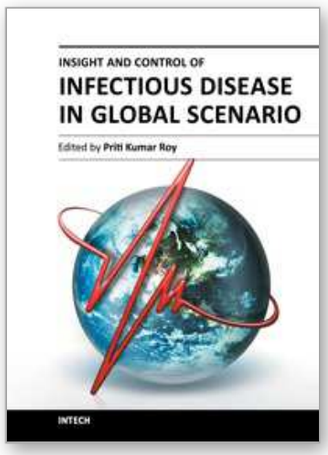

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This book is projected as a preliminary manuscript in Infectious Disease. It is undertaken to cover the foremost basic features of the articles. Infectious Disease and analogous phenomenon have been one of the main imperative postwar accomplishments 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.

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