Review

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Mumps virus: a comprehensive review

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Abstract. Once very common in children, mumps virus infection is now much rarer thanks to vaccination, recommended in the majority of countries in the world. This virus of the family Paramyxoviridae has a marked tropism for glandular tissues which explains the great diversity of pathologies related to this virus, including parotitis, orchitis or meningitis. Due to the lower circulation of the virus, the proportion of infected adults increases. A surveillance system for mumps virus infections at the national and international levels is organized, particularly at the molecular level. In France, it is provided by the national reference center for Measles, Mumps and Rubella. Although it has led to a significant reduction in the number of cases, the long-term effectiveness of mumps vaccination is questionable. The nature of the vaccine strains and the lack of regular stimulation of populations by circulating wild viruses may explain, in part, the decrease in immunity over time. Thus, the vaccination recommandations could evolve in the future to reach eradication in a medium or long term.

Key words : mumps virus, paramyxoviridae, parotitis, vaccination

Résumé. Autrefois très fréquente chez les enfants, l'infection par le virus des oreillons est aujourd'hui beaucoup plus rare grâce à la vaccination, recommandée dans la majorité des pays dans le monde. Ce virus de la famille des *Paramyxoviridae* a un tropisme marqué pour les tissus glandulaires ce qui explique la grande diversité des pathologies liées à ce virus, notamment les parotidites, les orchites ou les méningites. Compte tenu de la circulation plus faible du virus, la proportion des cas d'adultes infectés augmente. Un système de surveillance des infections par le virus des oreillons au plan national et international est organisé, notamment au plan moléculaire. En France, il est assuré notamment par le centre national de référence Rougeole-Oreillons-Rubéole. Bien qu'elle ait permis une diminution important du nombre de cas, l'efficacité de la vaccination anti-ourlienne à long terme est remise en cause. La nature des souches vaccinales et l'absence de stimulation régulière des populations par des virus sauvages circulants pourraient expliquer, en partie, la diminution de l'immunité dans le temps. Ainsi, le calendrier vaccinal pourrait évoluer dans l'avenir pour envisager l'éradication à moyen ou long terme.

Mots clés : virus des oreillons, paramyxoviridae, parotidite, vaccination

Ἐπάρματα δὲ παρὰ τὰ ὦτα, πολλοῖσιν ἑτερόρροπα καὶ ἐξ ἀμφοτέρων τοῖσι πλείστοσιν ἀπύροισιν ὀρτοστάδην (...). Ἦν δὲ ὁ τρόπος αὐτέων, χαῦνα, μεγάλα κεχυμένα, οὐ μετὰ φλεγμονῆς, ἀνώδυνα, πᾶσιν ἀσήμως ἠφανίσθη. Ἐγένετο δὲ ταῦτα μειρακίοισιν ἐοῦσιν, ἀκμάζουσι ; καὶ τουτέων τοῖσι περί παλαίστρην, καὶ γυμνάσια πλείστοισιν˙ γυναιξὶ δὲ ὀλίγησι ἐγένετο. (...) Φλεγμοναί μετ' ὀδύνης ἐς ὄρχιν ἑτερόῤῥοπαι, τοῖσι δὲ ἐς ἀμφοτέρους· πυρετοὶ τοῖσι μὲν, τοῖσι δὲ οὔ· ἐπιπόνως ταῦτα τοῖσι πλείστοισιν τὰ δ'ἄλλα, ὁκόσα κατ'ἰητρεῖον, ἀνόσως διῆγον.

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History

The mumps virus (MuV) has long been responsible for one of the most common infections in children. The vernacular name "mumps" appeared at the end of 16th century. It comes from the old English verb "to mump", which means to speak in a low indistinct manner as a typical consequence of the characteristic infection of the parotid glands causing a submaxillary swelling moving back from the jaw to the ear. One first description of an epidemic of mumps would be the work of ιπποκράτηζ (Hippocrates) in the 5th century BC [1]. In 1934, Johnson and Goodpasture demonstrated the viral origin of mumps [2]. Then, in a second study, the following year, they validate the postulate of Koch by causing mumps in young children by inoculation of a parotid filtrate of infected monkeys [3]. Since the introduction of vaccination in the 1980s and the inclusion of the vaccine in the World Health Organization's (WHO) Expanded Program on Immunization (EPI), the number of cases of mumps has dropped significantly, without disappearing completely. As in the case of measles, there has been a resurgence of mumps epidemics in recent years in our high-resource countries, notably because of the population's lack of confidence in vaccination, but also of the insufficient protection conferred by certain vaccine strains.

Origin and nomenclature

The MuV belongs to the order *Mononegavirales*, the family *Paramyxoviridae*, the subfamily *Paramyxovirinae* and the genus Rubulavirus. The closest known virus of MuV is a bat virus, the MuV-like bat virus described in 2009 [4]. The virus is strictly human, and there is only one serotype, but a multitude of wild genotypes circulating on the surface of the globe are described. Under certain conditions, it is possible to infect laboratory animals, notably rhesus macaque and hamster, but also rats, marmosets, mice or ferrets.

WHO proposed a revision of the MuV nomenclature in 2012, and described 12 different genotypes (A to D, F to L and N) based on analysis of the small hydrophobic (SH) and hemagglutinin-neuraminidase (HN) genes [5]. The number of MuV sequences available in GenBank is very limited, since it was only in 2015 that sequences from the 12 genotypes have been available [6]. The nomenclature used for the description of the strains contains the location (city.country by ISO3 code), the date (week.year) and the assigned genotype (*e.g.* MuVs/London.GBR/11.03 [D]). Genotype A, the most divergent of the other genotypes, was the first to be isolated in 1945 and did not circulate since the 1990s. The majority of current strains diverged from a common ancestor between 60 and 100 years ago, except for genotype C that probably appeared 100 to 125 years ago [6]. Since 2010, only six of these genotypes (C, D, F, G, H and K) have been identified in sporadic cases or epidemics. Genotypes C, G, H, J and K were shown to circulate more in western countries, whereas genotypes B, F, I and L would rather circulate in Asia. These observations should be taken with caution because of the limited number of sequences available and laboratories isolating the MuV strains, which probably partially biased this analysis (*figure 1*).

Structure and replication

The MuV is a pleomorphic enveloped virus of 100 to 600 nm in diameter (*figure 2*). Its genome is a non-segmented single-stranded RNA of negative polarity, composed of 15,384 nucleotides. The sequence of genes within MuV genome was determined in 1988 by Elango *et al*. [7]. It is summarized in *figure 3*. It comprises, from the 3' to 5' end of the genome: a leader sequence comprising the genomic promoter elements; seven units of transcription: nucleoprotein N, V/P/I proteins, matrix protein M, fusion protein F, small hydrophobic protein SH, hemagglutinin neuraminidase HN, and large protein L. It ends with a trailer sequence comprising the anti-genomic promoter elements. The V, P and I proteins are encoded by the same gene through a mechanism of RNA editing, which allows the insertion of additional G nucleotides during the synthesis of the mRNAs. Each of the three proteins starts with a common part, then the addition of two or four additional G nucleotides in the mRNA shifts the reading frame, respectively creating the I and P chimeric proteins whose terminal end are different, modifying therefore their properties.

The viral particle consists of an envelope bearing on the surface two envelope glycoproteins: haemagglutinin-neuraminidase (HN) and fusion protein (F). The nucleocapsid (NC) of helical symmetry is composed of the RNA genome surrounded by multiple copies of the N protein that protect the integrity of the genome. The large protein (L) and the phosphoprotein (P) come together to form the transcription complex [8]. The matrix protein (M), located under the envelope, allows anchoring of the nucleocapsid under the phospholipid bilayer and facilitates the budding of the infectious particle.

This RNA molecule forms, with multiple copies of the N protein, a ribonucleoprotein complex of helical symmetry to protect the integrity of the genome. The virus attaches to the sialic acids of the target cell *via* the hemagglutinin-neuraminidase [9]. The fusion of the envelope and the membrane of the host cell is ensured by the fusion protein. The phosphoprotein and the large L protein associate to form the replication complex. The P protein will thus

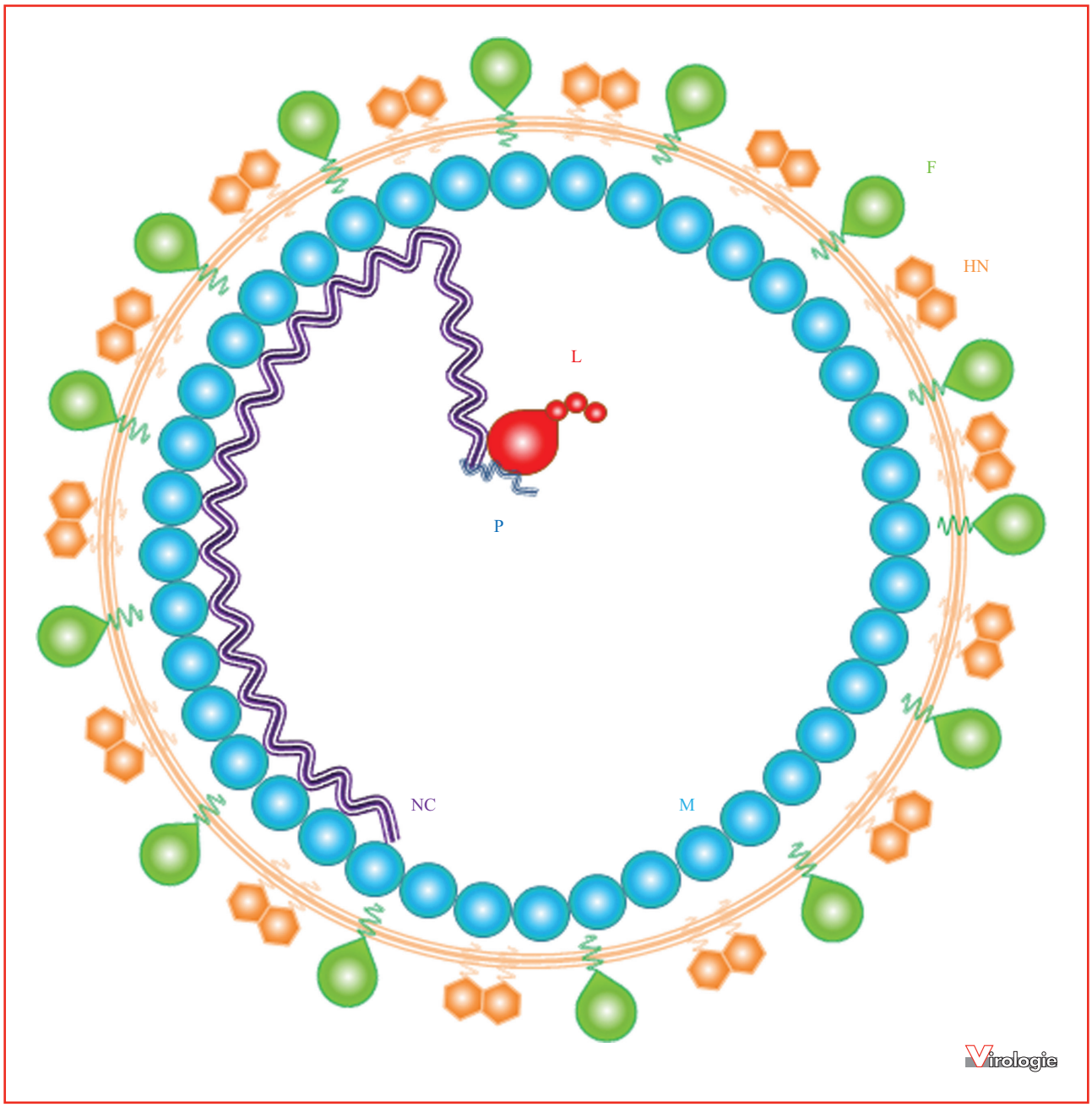

Figure 1. Schematic representation of the mumps virus particle. NC: nucleocapsid. P: phospho. M: membrane. F: fusion. SH: small hydrophobic. HN: hemagglutinin-neuraminidase and L: large protein genes.

enable the stowing and positioning of the RNA dependent RNA polymerase on the nucleocapsid so that it can initiate the synthesis of the viral RNA [8]. This complex will play a dual role: a replicase role in order to copy the RNA of negative polarity into RNA of positive polarity, and a role of transcriptase in order to synthesize the mRNAs from the promoter located at the 3' end of the genome [9]. The matrix protein provides the anchoring of the nucleocapsid beneath the host cell membrane where F and HN glycoproteins are addressed from the endoplasmic reticulum and the Golgi apparatus, leading to the budding of new viral particles. Protein V is involved in the viral escape from the host antiviral defenses in particular by inhibiting the innate immunity receptor MDA5 by binding to its helicase domain

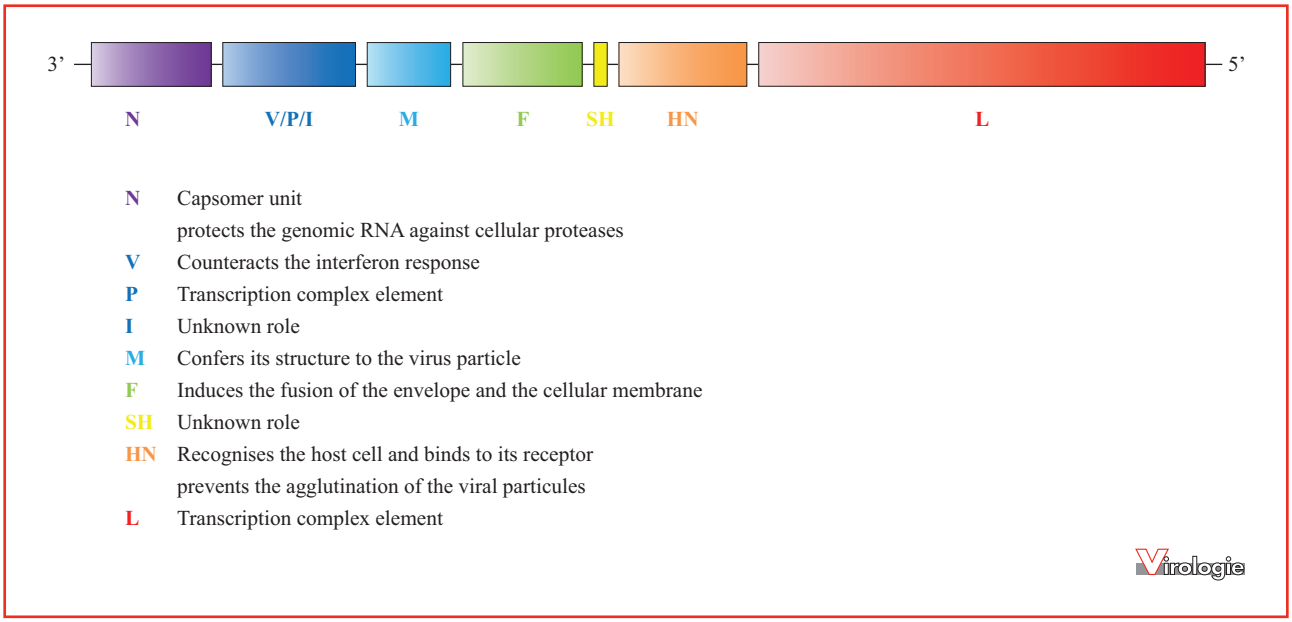

Figure 2. Schematic representation of the RNA genome of the mumps virus. Each rectangle represents an independent transcription unit frame.

[10, 11]. The role of the SH protein, which is not essential to viral multiplication, could be similar, but this has never been demonstrated. The role of protein I is unknown [9].

Natural history of the infection

Mumps evokes, in the first place, the characteristic inflammation due to the infection of the parotid glands. In many cases, the infection is asymptomatic or induces non-specific signs, fever or inflammation of the upper airways [9, 12]. In the 1940s, in the experimental infection of healthy subjects, about half of the patients (8/15) showed no clinical signs [12]. Nevertheless, the MuV is responsible for very diverse pathologies, either directly linked to the replication of the virus in a given organ, or to the origin of an immuno-pathological phenomenon. The MuV is a virus with multiple tropisms, mainly epithelial and glandular but also neurological [9]. Mumps is transmitted by respiratory contamination *via* infected droplets of contaminated saliva, as shown in the past by studies of infection of healthy volunteers [2, 12]. As for all respiratory viruses, a first stage of replication in the upper airway epithelium is observed. The virus then spreads to the target organs, probably *via* the bloodstream, although the virus is very rarely detected in the blood.

Parotitis

Inflammation of the parotid glands appears two to three weeks after infection [12]. In its common form, it is frequently bilateral, and starts from the lobe of the ear to the angle of the mandible. It is often painful, and can last from two to 10 days. This inflammation may be accompanied by fever, spontaneously resolving after a few days. The orifice of the Stensen canal is erythematous and edematous [13]. Submaxillary, submandibular and sublingual glands may also exhibit inflammation as a result of this infection, and rare cases of supraglottic edema have been described [14]. Perivascular and interstitial infiltration by mononuclear cells, as well as edematous pressure induced by infection, leads to congestion of the glandular tubes, to hemorrhages and sometimes to necrosis of these same glandular tubes [15]. A sialectasis, accompanied by chronic sialadenitis, may be observed following infection, although rarely [16]. The virus is detectable in saliva one week before and up to one week after parotitis occurs [12, 17].

Orchitis

Orchitis is the most frequent manifestation when infection is acquired during or after puberty [18]. The incidence is estimated at about 15 to 40% in some older studies. This observation is important because the absence of continuous circulation of the virus in the population increases the risk of becoming infected at a later age in unvaccinated or inadequately protected boys and thus developing such complications. The orchitis associated with MuV infection usually results in unilateral and painful swelling of a testicle during a few days and up to two months after parotitis occurs. It may be accompanied by high fever, vomiting,

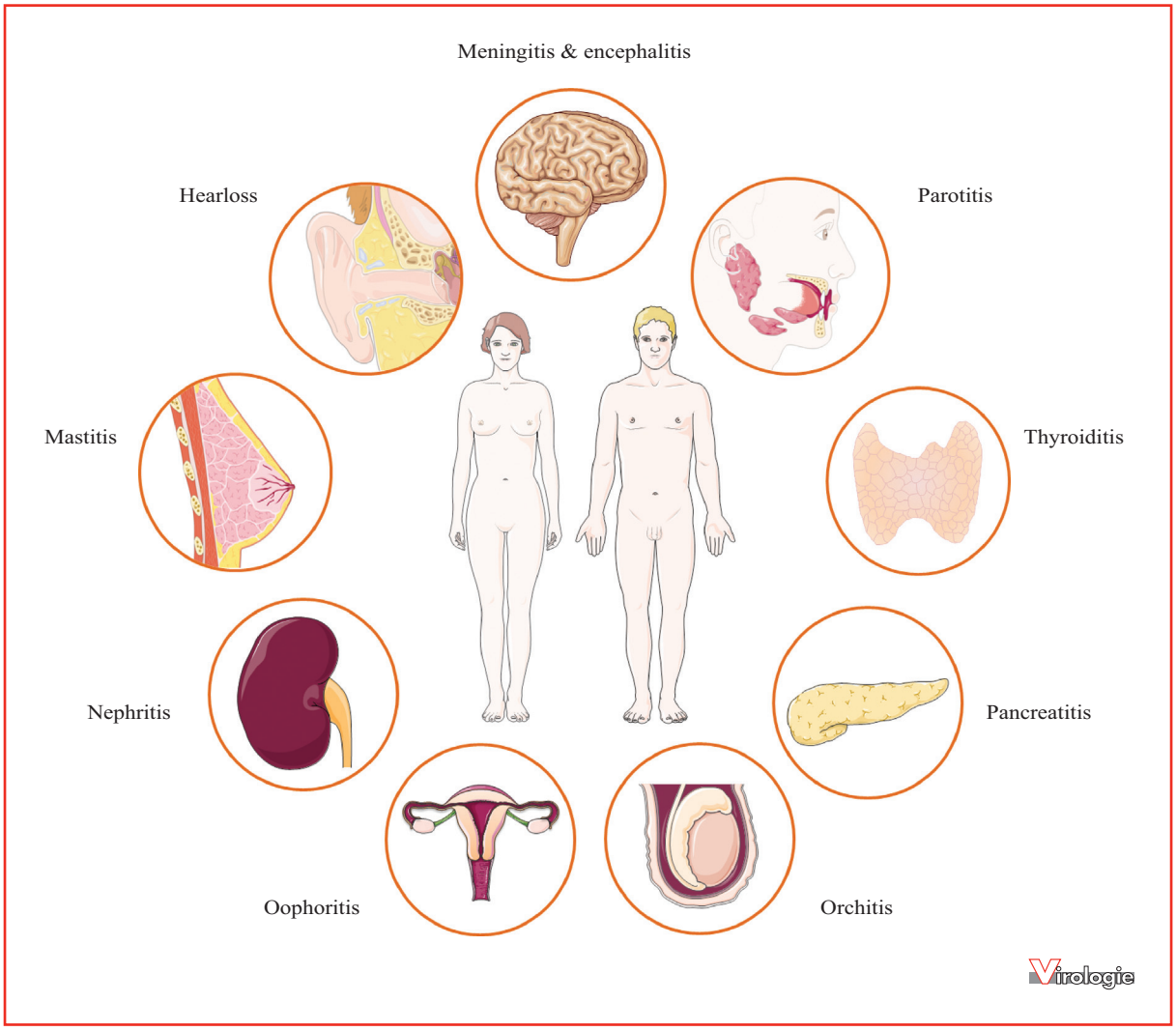

Figure 3. Key clinical manifestations of mumps infection.

headache and discomfort. The examination of the scrotum, often sensitive and inflammatory, shows a hot and swollen testicle, characteristic of orchitis. Epididymitis is associated with orchitis in 85% of cases, and often precedes orchitis. The symptoms regress spontaneously in three to 15 days, but the testicle may remain sensitive for several weeks [19].

The complications of orchitis are severe: total or partial infertility and testicular atrophy. On the other hand, the link between mumps orchitis and increased risk of testicular cancer, a time referred to, has been ruled out by several epidemiological studies [20].

Infertility results primarily from tissue destruction associated with parenchyma edema during infection with the virus. The pressure induced by the congestion of the seminiferous tubules, and the perivascular lymphocytic infiltration, leads to necrosis of these seminiferous tubules. Hyalinization of these tubes can lead to fibrosis or testicular atrophy [21]. Total infertility is rare and occurs in severe and bilateral forms, but partial infertility is estimated at 13% of patients. It can occur in patients without any evidence of testicular atrophy [22]. Testicular atrophy is frequently reported after the onset of orchitis, although it is difficult to assess. It involves 30-50% of testes with inflammation following MuV infection [23]. Spermatogenesis abnormalities were observed in nearly half of the patients, three months after healing, with anomalies in the number of spermatozoa, their mobility and morphology [22]. Three years after the cure, a study of 298 patients showed that 24% of adults and 38% of adolescents had a defect in sperm quality, and that this defect was directly correlated with the severity of the

orchitis. Hormonal changes may also explain both testicular atrophy and dysfunction of spermatogenesis [24].

Oophoritis

Oophoritis is an inflammation of the ovary, which, unlike orchitis, is rarely diagnosed, given the cryptic position of the ovaries and clinical manifestations similar to those seen in acute appendicitis [25]. The virus can be isolated directly from vaginal secretions. A recent study in animals has shown that MuV infection inhibits ovarian steroidogenesis and induces the apoptosis of ovarian granulosa cells, which are the major constituent of the ovary [26]. Infection of the ovary with mumps is associated with infertility and early menopause [27].

Mastitis

Inflammation of the mammary gland is an infrequent complication of mumps infection, but it is described in both sexes [28]. In the lactating woman, a temporary stop of milk production is described [29].

Pancreatitis

Pancreatitis is an infrequent complication of mumps infection but has been described since the early 19th century [30]. It appears a few days before or after other clinical signs of MuV infection (parotitis or orchitis), but cases where pancreatitis is the only manifestation of mumps are described. Pancreatitis is characterized by elevated amylase concentration in serum and peritoneal fluid. It induces abdominal pain, sometimes intense, and sensitivity to palpation that persist three to seven days in common forms. Severe forms associate diffuse pancreatic necrosis and the formation of pseudocysts, which can be fatal in very rare cases [30].

Subacute thyroiditis

The MuV has a privileged tropism for glandular epithelia and may be responsible for subacute thyroiditis [31]. It results in limited and transient inflammation of the thyroid gland, associated with general non-specific signs (fever and myalgia), especially in women [32]. Infection of thyroid follicles results in cellular infiltration, and tissue destruction probably mediated by cytotoxic lymphocytes. The virus is present in thyroid tissue and can be isolated from cultured tissue biopsies [33]. On the other hand, the MuV has never been incriminated as a trigger for a much more frequent autoimmune thyroiditis [31].

Nephritis

The urinary excretion of the MuV is well known, and makes it possible to isolate the virus in culture. The infection of the nephron is therefore commonly accepted. On the other hand, cases of frank nephritis are rarely described, but regular since the second half of the 19th century [34]. The anatomopathological study of a nephron explanted from a transplant recipient with acute nephritis associated with a bilateral parotitis, showed the presence of MuV particles in the cytoplasm of the tubular epithelial cells [35].

CNS infections

In the past, when young children were the most affected by infection, central nervous system (CNS) infections were the main clinical manifestations after parotitis.

The most common, especially among boys, are meningitis, which occurs in 1 to 10% of cases of mumps infection [13, 36]. Frequently, there is pleiocytosis in the cerebrospinal fluid, even without any clinical sign of meningitis, but this is rarely demonstrated in the absence of systematic lumbar puncture [37]. Clinical signs of meningitis appear from one week before to two weeks after the appearance of parotitis; when it is present because the two manifestations are independent [36, 37]. As for Enterovirus meningitis, MuV meningitis is usually benign, spontaneously resolving, and mortality or long-term sequelae are exceptions. Symptoms associated with these meningitis are classic and associate fever, neck stiffness, vomiting, headache, and lethargy [38, 39]. They disappear within 48 hours, but clinical signs lasting up to 10 days are described.

Encephalitis associated or not with meningitis are much more rare, but are more frequent when the infection occurs in adults than in children. Some authors have associated the occurrence of meningoencephalitis with the passage of cerebrospinal fluid from infected mononuclear cells through the choroid plexus [38, 40]. They are characterized by very diverse manifestations, and overall mortality, estimated at 1.5%, or the long-term consequences, are infrequent [41-43]. Acute encephalitis may include altered consciousness, focal neurological deficits, epileptic seizures, electroencephalogram abnormalities, or ataxia. These signs decline in a few days to a few weeks [42].

Other neurological consequences of MuV infection include Guillain-Barré syndrome, transverse myelitis, cerebellar ataxia, facial paralysis or flaccid paralysis [13].

Deafness

Mumps are one of the most common causes of neurosensory hearing loss [44]. The estimated incidence varies significantly between studies because the populations observed are not homogeneous; it varies according to age, sex, immunization coverage of the country, in particular. It can range from 0.5/100,000 to 1/1,000 [45, 46]. Hearing loss occurs four to five days after other clinical signs but is not related

to the intensity of other clinical manifestations (flu-like or parotitis syndrome), except for the occurrence of meningoencephalitis [47, 48]. It is generally unilateral and of varying intensity, often reversible, but cases of severe and definitive deafness are described [45]. Deafness would result from a direct action of the virus and would be intimately linked to infection of the cerebrospinal fluid (CSF) since virus is detected in the endolymph and the perilymph of the cochlea. The perilymph of the tympanic ramp is derived directly from the CSF and is infected by this pathway [9, 49, 50]. The virus induces atrophy of the hair cells of the Corti organ and *stria vascularis*, as well as destruction of the myelin sheath around the vestibulocochlear nerve [48, 49, 51]. An infection of the vestibular ganglia is also evoked, and would explain the vertigo sometimes observed in infected patients [52].

Other manifestations

Spontaneous abortions

Mumps infection in pregnancy is not associated with an increase in congenital abnormalities in babies, even when the mother is infected during the first trimester of pregnancy. On the other hand, there is a significant increase in spontaneous abortions and *in utero* fetal deaths [53].

Lipschütz ulcers

Lipschütz ulcer (or *ulcus vulvae acutum*) is a unique outbreak of genital ulceration, unrelated to sexual transmission, and caused by an infection most often of viral origin. It is mainly described during EBV infection, but other viral infections, as MuV, may be responsible for such ulcer [54]. This ulceration of labia minora or majora may be accompanied by fever, lymphadenopathy, angina or diarrhea, and inflammation of the parotid glands during infection with the MuV. It differs from infections with the herpes simplex virus (HSV), genital aphtoses or Behçet's disease by the strict absence of recurrence. Physiopathology is not known. It is not known whether it results from secondary localized infection of the epithelium, or from an immunopathological reaction [54].

Epidemiology

Mumps is a ubiquitous, strictly human virus transmitted primarily by respiratory contamination *via* contaminated droplets of Pflügge. The virus can be isolated in saliva seven days before and up to eight days after the appearance of parotitis, but it is commonly accepted that transmission occurs within five days before and after the onset of parotitis [55]. The base reproduction rate R0 of the MuV is evaluated between 7 and 10, which makes it a highly contagious virus. Global epidemiology has undergone major changes following the introduction of the vaccine in many countries. Mumps databases are not as comprehensive as those available for measles. In the United States, data collected since 1922 show a peak incidence of up to 250 cases/100,000 inhabitants in 1941 (*figure 4*). Since then, the generalization of vaccination in 1968 has seen a collapse in incidence: from 76 cases/100,000 inhabitants to less than one case/100,000 inhabitants since the early 1990s (with the exception of 2006) [56]. Over the past 15 years, the overall incidence of mumps has changed little as shown in *figure 5*. In 2015, 76 countries reported cases of mumps ($n = 384{,}333$; WHO source: http://www.who.int/immunization/monitoring_surveillance/data/en/), more than two-thirds of which are in the People's Republic of China and Japan. All the recent epidemics occurred with a virus of genotype G.

In the past, the virus circulated in an endemic-epidemic fashion with peak incidence in the winter and spring months with epidemic peaks every two to five years [57]. Today, the virus remains endemic in countries where mumps vaccine has not been implanted in national immunization programs (see *figures 6 and 7*).

In other countries, local epidemic outbreaks are occasionally observed on the same pattern as for measles [59, 64, 71]. Thus, as in the case of measles, these epidemic outbreaks are likely the result of insufficient vaccination coverage and the presence of groups of populations that are not immune for ethnic, religious or access to healthcare settings reasons [63]. On the other hand, for mumps, some observations are different [72]. Indeed, in some of these epidemic episodes, a very high proportion of patients who had received two doses of mumps vaccine [62, 72, 73] are described. Some publications even claim that there are re-infections, but the virological evidence of the two successive episodes is not formally provided [74].

The presence of neutralizing antibodies provides protection against infection, and antibody levels have been shown to decrease with time [75, 76]. The absence of stimulation by circulating viral strains could thus explain the progressive decrease, or the disappearance of protective antibodies. In addition, immunogenicity and vaccine protection of strains used in different vaccines on the market may vary, and certain strains could protect less than others against infection (see the vaccine section).

Among the epidemiological changes of recent years, there is a change in incidence by age group. Mumps was an early childhood illness, and today it affects adolescents and young adults [34, 58, 60, 61]. If the number of cases is much lower, the proportion of cases with complications is greater and more severe in patients after puberty, especially

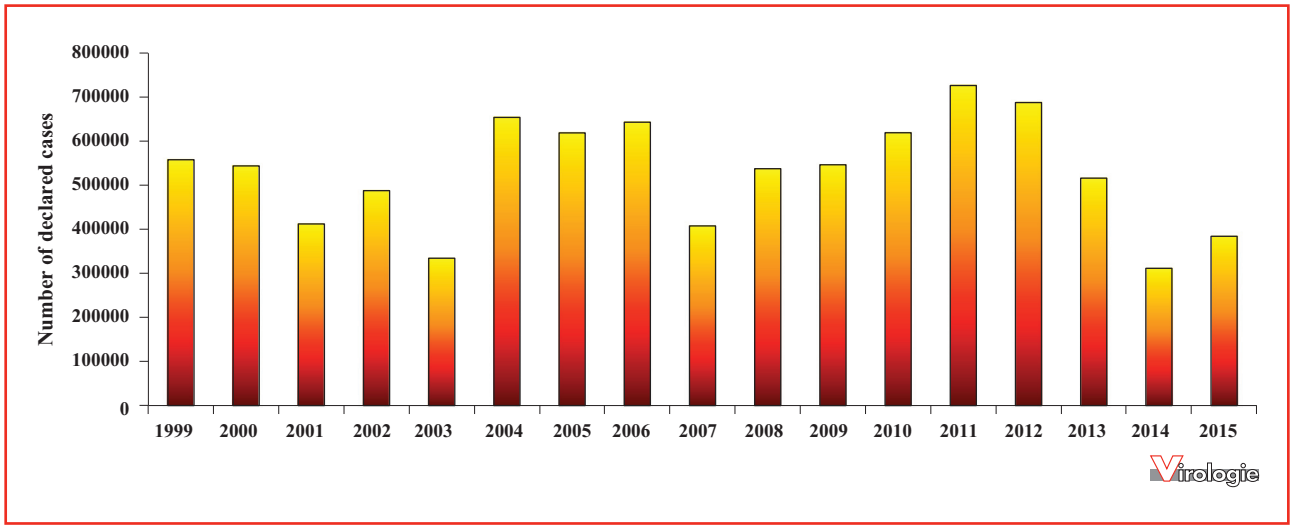

Figure 4. Global incidence of mumps cases reported to WHO from 1999 to 2015.
According to WHO: http://www.who.int/immunization/monitoring_surveillance/data/en/

for orchitis and oophoritis. In vaccinated youngsters, the complications are less frequent, but can be observed in few cases [77].

Virological diagnosis

Given the very low number of cases observed in the general population since the generalization of MMR vaccination, the highly variable clinical presentation of mumps infection, and the lack of experience of the youngest physicians, the sensitivity and specificity of clinical diagnosis of mumps is estimated to be low. The diagnosis of MuV infection, therefore, must involve, apart from an epidemic context, a serological diagnosis and a direct diagnosis (PCR), or only a direct diagnosis because it provides a diagnosis of certainty (see http://www.cdc.gov/vaccines/pubs/surv-manual/chpt09-mumps.html#laboratory).

Serological diagnosis

Since the early 1980s, the diagnosis of MuV infection has been made by demonstrating specific anti-mumps IgM, or by a significant increase in the IgG level between two samples taken during the acute phase and in the convalescent phase [78]. In practice, the interpretation of the presence of IgM is difficult, as Benito *et al*. suggested since 1987 [79], and the positive predictive value is far from 100% [80]. IgM are present during primary infection, but may persist for several months [79]. A positive signal can be observed during non-specific polyclonal activation of the immune system. It may also correspond to a cross-reaction with other IgMs, or to a false positive whose origin is unknown. As for the negative predictive value of these tests, it is even worse, as recently demonstrated by Krause *et al*. [80]. The presence of IgM should therefore be only one element of the diagnosis, among a bundle of biological, clinical and epidemiological arguments. Serology should only be performed at a distance from any MMR vaccination that induces the production of mumps IgM and elevated IgG levels.

Molecular diagnosis

Molecular diagnosis is an important factor in the diagnosis of mumps infections because of its excellent specificity [81]. In most cases reported in recent outbreaks of parotitis, mumps serology shows the presence of IgG only, while direct search of the virus by RT-PCR is positive. It is preferably carried out on a salivary sample. Saliva swab collection is recommended at the exit of the parotid gland channel, swabbing between the space between the cheek and the gum at the upper molars and at the opposite space at the lower molars (http://www.cdc.gov/mumps/lab/specimen-collect.html). Looking for the virus in the urine is also useful, but the RNA extraction techniques used must be validated to limit the presence of PCR inhibitors. During a suspicion of MuV meningitis, the cerebrospinal fluid is also a sample of choice for diagnosis. The identification of the genotype is recommended by the WHO, and is a key element of the epidemiological surveillance. It is performed by RT-PCR and sequencing in the SH gene.

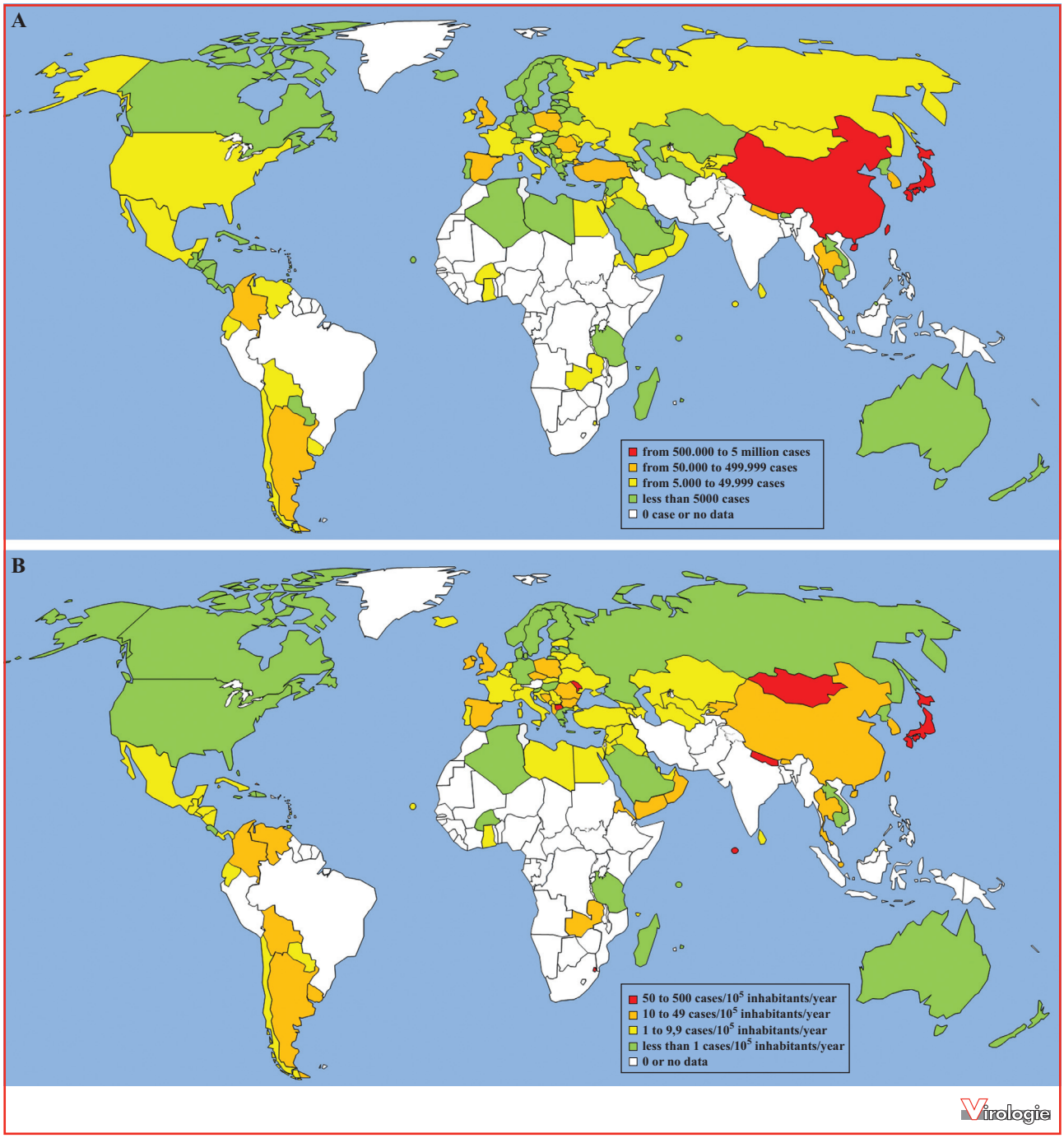

Figure 5. Epidemiology of mumps infections (2005-2014).
(A): number of infections declared to the WHO from 2005 to 2014. (B): Cumulative incidence of mumps infections based on the number of cases declared to the WHO from 2005 to 2014. The estimated population in 2014 was used to calculate this cumulative incidence.

Viral isolation

Viral isolation on cultured cell, on embryonated eggs, or after inoculation on sensitive animals, are techniques of reference but are rarely used outside expert laboratories. They have the advantage of making it possible to reach a diagnosis even on very divergent strains, where the primers

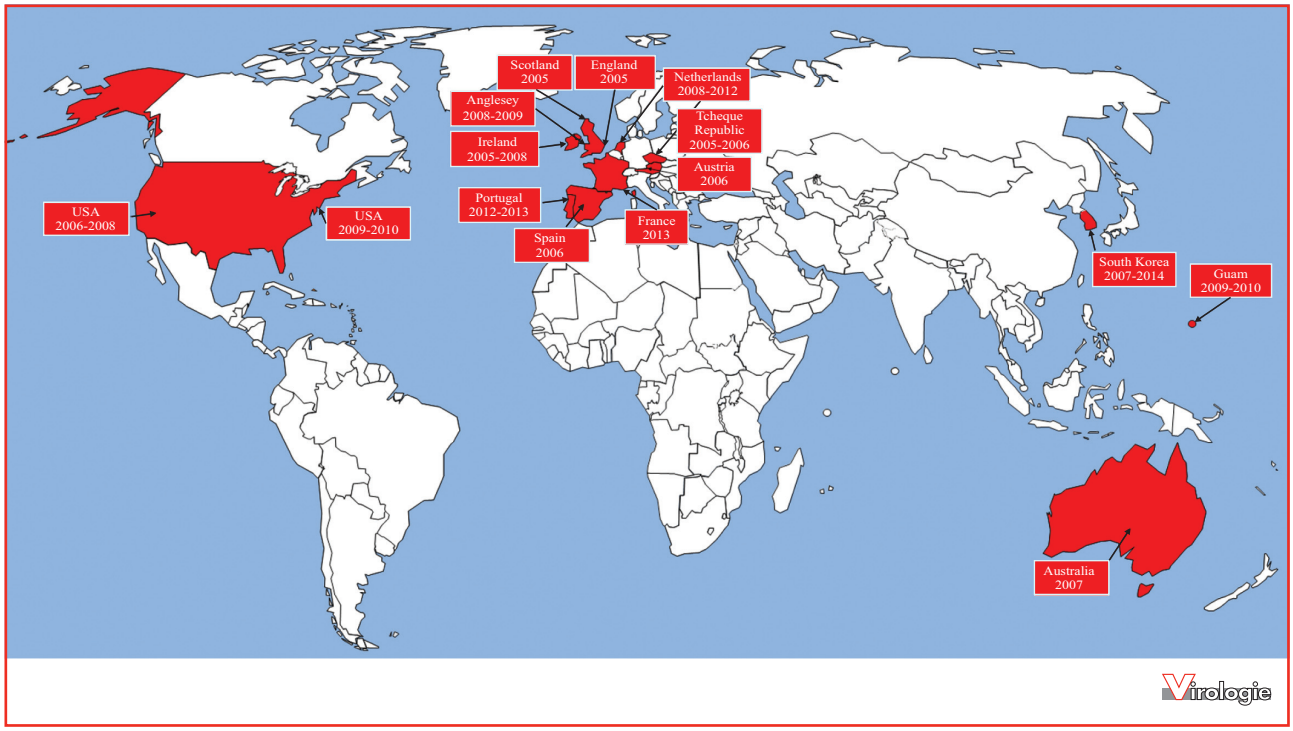

Figure 6. Recent Mumps epidemics described in the literature (2005-2015).
Source: [23, 34, 58-70].

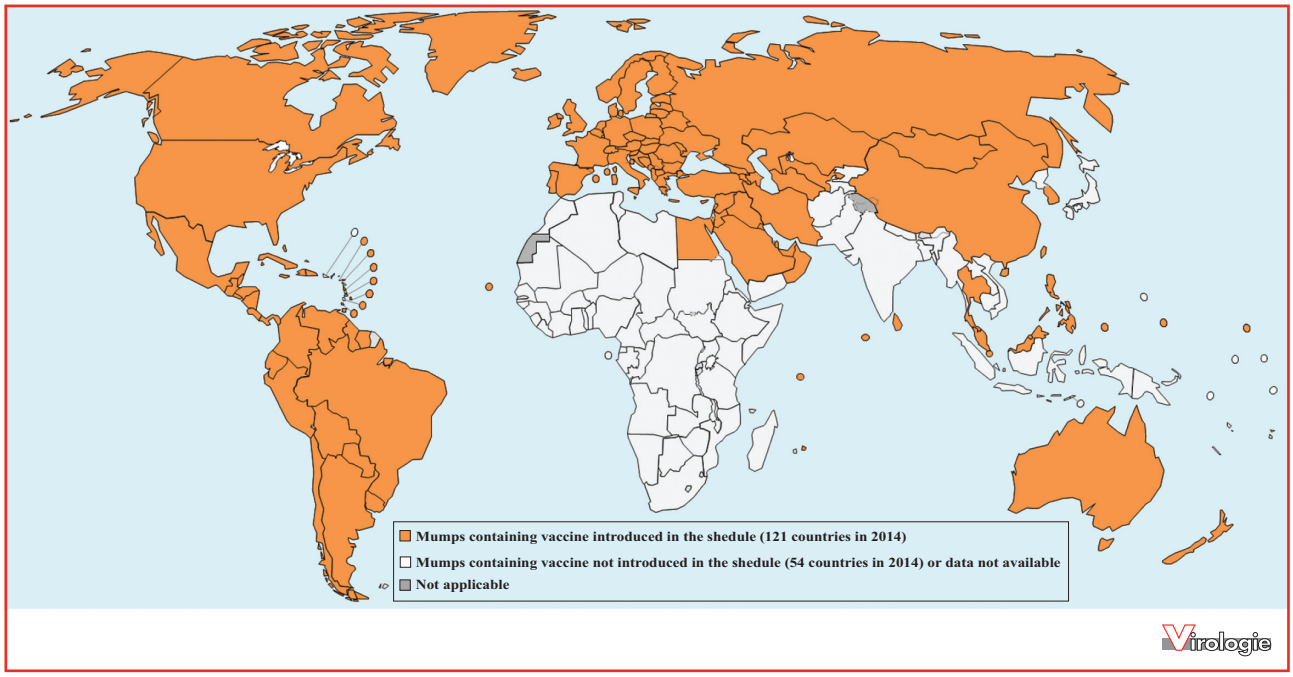

Figure 7. Countries that introduced mumps vaccine into their vaccine schedule in 2014.
Source: WHO/IVB database, July 2015.

and probes of PCR can be unadapted [9, 81]. Nevertheless, viral isolation is less sensitive than molecular biology, especially in samples with a low viral load.

Prevention

Apart from traditional isolation measures, and the use of standard and droplet protective measures around cases [55, 82], the best way to prevent mumps is vaccination [83]. In countries where large-scale mumps vaccination has been implemented, the incidence has dropped dramatically, as in the USA where the incidence dropped from 250 per 100,000 persons in 1968, to less than 1 per 100,000 persons nowadays [57]. It is often associated with the measles and rubella vaccine (MMR) in a single vaccine and implanted in national immunization programs in 121 countries. WHO considers it useful to integrate mumps into a combined two-dose MMR regimen, but that measles and rubella vaccination is a higher priority because of their greater morbidity and mortality than mumps [57]. Some major countries have decided not to integrate it, as Japan (withdrawn from the calendar in 1993), which keeps a high incidence of infection (*figure 7*). Moreover, in countries where the health system does not provide sufficient immunization coverage, vaccination may lead to an epidemiological shift in the incidence of mumps to higher age classes, thereby increasing morbidity and complications when they occur at a later age [57].

The mumps vaccine is based on the use of live attenuated viral strains. It has been used since the 1960s. A first inactivated vaccine, used between the 1950s and 1970s in the United States, was quickly abandoned due to limited efficacy and too fleeting immunity. Are the antibodies induced after immunization with MMR vaccine predictive of protection against infection? S Gouma et al. measured the fraction of neutralizing antibody in a cohort of patients who had mumps and for whom sera were available before and after infection. The authors concluded that, in the case of this outbreak of genotype G mumps virus infections, the titre of G-specific genotype-specific neutralizing antibodies was predictive of protection. The presence of anti-mumps IgG is thus considered to be the correlate of protection [84]. A first inactivated vaccine, used between the 1950s and 1970s in the United States, was quickly abandoned due to limited efficacy and too fleeting immunity.

Each manufacturer uses its own manufacturing protocol in terms of cell substrate for propagation of the strain, or method of manufacture [85]. The different vaccine strains used are listed in *table 1*. They are derived from at least four different A, B, H and N genotypes.

The first strain used was the Jeryl-Lynn strain, approved in 1967 in the United States [86]. It is derived from a virus of genotype A, attenuated by successive passages on embryonated eggs, and on culture of embryonic chicken cells. The vaccine is actually composed of two very similar strains: JL-2 and JL-5. The strain RIT 4385 is derived from the Jeryl-Lynn strain and has similar seroconversion rates [57]. In China, the use of the strain S79, derived from the Jeryl-Lynn strain, is also widespread. In contrast, Rubini strain of genotype A, also used in the 1980s and 1990s, is no longer recommended due to very low or no vaccine efficacy in some studies [87, 88].

Several vaccine strains are derived from attenuated genotype B viruses. The first registered strain, used on a large scale, is the Urabe Am9 strain, isolated in Japan in 1967. This strain induces seroconversion rates and vaccine efficacy comparable to, or slightly higher than, those observed with the Jeryl-Lynn strain [57, 87, 88]. The strains Hoshino, Torii, Miyahara and NKM-46 are also strains of genotype B comparable to the Urabe Am9 strain and whose immunogenicity is close [57, 89]. Their use is limited to Japan and the Korean Peninsula.

Two strains of H genotype, isolated on monkey kidney cells in 1986 and attenuated on MRC-5 cells, are used as vaccine strains: strains S-12 and its derivative BBM-18 [89, 90]. Their use is limited, especially to Iran.

Two strains of genotype N have been widely used as vaccine strains: the Leningrad-3 and Leningrad-Zagreb strains. The Leningrad-3 strain was isolated in 1953 on guinea-pig kidney cells and attenuated on a culture of Japanese quail embryos. Immunogenicity and vaccine efficacy are considered excellent. The Leningrad-Zagreb strain [89] is derived from the Leningrad-3 strain, after further attenuation on chicken embryo fibroblasts. Its effectiveness is considered equivalent.

Finally, the Sofia-6 strain, of undetermined genotype, was used from 1972 to 1982 in Bulgaria, but stopped since then because of a very high number of aseptic meningitis in vaccinated children [91].

Given the effectiveness of the vaccines, sometimes considered as suboptimal, especially after the description of multiple outbreaks in vaccinated patients, new strains continue to be attenuated and tested as vaccine candidate [67-70]. A new genotype F strain shows promising results in terms of immunogenicity in a recent phase I study [92]. Structural explanations for both the HN protein and the F protein have been reported to explain this time-limited efficacy [93, 94].

Immunization schedule

Regarding vaccine recommendations, WHO defines a two-dose regimen, with a first vaccination between 12 and 18 months, followed by a second between the second year of life and entry to school (around 6 years), with a minimum of one month between the two injections [57]. In France, the

Table 1 Vaccine strains used for the manufacture of mumps vaccines.

Genotype	Strain	Manufacturer	Commercial distribution area
A	Jeryl-Lynn	Merck/Aventis Pasteur MSD	USA and Europe
		Netherlands Vaccine Institute	Netherland
		Sevapharma Inc. Company	Tcheque Republic
	RIT 4385	GSK	Whole world
	S79	Dalian Jingjang-Anti Bioproducts	China
	Rubini[a]	Swiss Serum Institute	Europe
B	Urabe AM9	Sanofi Pasteur	In numerous limited settings
		GSK	[c]
		Biken	Japan
	Hoshino	Kitasato Institute	Japan
	Miyahara	Chemo-Sero Ther Research Inst (Japan)	Japan
	Torii	Takeda Chemicals	Japan
	NK M-46	Chiba	Japan
H	S-12	Razi State Serum and Vaccine Inst	Iran
	BBM-18	Berna Biotech	Europe
N	Leningrad-3	Moscow Bacterial Medicine Institute	Russia
	L-Zagreb	Institute Immunology Zagreb	Croatia, Slovenia
		Serum Institute India	India
Unknown	Sofia-6	Centre Inf Parasitic Dis (Bulgaria)	Bulgaria[b]

[a] Not recommended by WHO due to lack of efficacy. [b]Suspended since May 1982. [c]Removed from the market by GSK.

2016 schedule recommends a first injection at 12 months and a second one between 16 and 18 months [95]. The second vaccination is not a booster because the immunity acquired after a first vaccination is considered to be of long duration, but it is likely a catch-up for the non-seroconverted subjects during the first vaccination. Some countries, such as the United States or the Netherlands, recommend punctual administration of a third dose, especially in the event of an epidemic. The vaccine is injected subcutaneously.

Vaccine safety

The mumps vaccine alone, or in combination in the MMR vaccine, has extensive experience with effective adverse effects monitoring systems. Several billion doses of vaccine have been administered since the introduction of vaccine recommendations by WHO. Vaccine safety, and the occurrence of adverse events, is highly dependent on the vaccine composition. A recent comprehensive review of the literature showed that there is no association between MMR vaccination and autism [96], as authors published it in the *Lancet* in the 1990s. These false allegations led to a very significant reduction in vaccination coverage, particularly in the United Kingdom, thus promoting the resurgence of large-scale measles and mumps epidemics. On the other hand, there is a proven over-risk of anaphylactic reactions and febrile convulsions in vaccinated children, but these events are extremely rare [96]. There are moderate arguments for the association of MMR vaccination with transient arthralgia and thrombocytopenic purpura. All these rare adverse effects do not in any way call into question the usefulness of this MMR vaccination given the morbidity and mortality associated with these three infections.

Concerning the only vaccination with attenuated MuV strains, there are great differences between the strains. The main adverse effect of anti-mumps vaccination is the occurrence of aseptic meningitis with clear fluid [97]. While this is a rare event with genotype A vaccines, vaccines of genotype B, in particular the Urabe AM9 strain, or genotype N (Leningrad-3 and L-Zagreb) are more likely to induce aseptic meningitis [97]. These adverse reactions have led, in some cases, to the production stoppage of vaccine strains, such as the Sofia-6 strain in 1982, or the withdrawal of mumps vaccination from the vaccine schedule, as in Japan since 1993 [91, 98].

The occurrence of symptomatic infection by a vaccine strain is a very rare but described event [97, 99].

Conclusion

The MuV is an old human virus, and very contagious. It is responsible for various pathologies in children and adults.

Although the number of infections due to the MuV has declined significantly since the advent of specific attenuated live vaccines, some 50 years ago, it remains a global health concern. Many countries continue to report cases, particularly those where mumps vaccination is not included in the vaccination schedule, and a prospect for mumps eradication cannot be considered in the short- to medium-term. Apart from concerns about poor immunization coverage, the effectiveness of long-term mumps vaccination is undetermined. The nature of vaccine strains and the lack of regular stimulation of populations by circulating wild viruses could partly explain the decrease in immunity over time. Changes in prevention policies may be observed in the coming years in order to limit epidemics and the number of patients affected each year in the world.

Conflicts of interests : none.

References

1. Hippocrate. *Des épidémies. Livre I*. Charpentier, Fortin, Masson, et C^ie^, 1845.

2. Johnson CD, Goodpasture EW. An investigation of the etiology of mumps. *J Exp Med* 1934 ; 59 : 1-19.

3. Johnson CD, Goodpasture EW. The etiology of mumps. *Am J Epidemiol* 1935 ; 21 : 46-57.

4. Drexler JF, Corman VM, Muller MA, *et al*. Bats host major mammalian paramyxoviruses. *Nat Commun* 2012 ; 3 : 796.

5. Mumps virus nomenclature update: 2012. *Wkly Epidemiol Rec* 2012 ; 87 : 217-24.

6. Jin L, Orvell C, Myers R, *et al*. Genomic diversity of mumps virus and global distribution of the 12 genotypes. *Rev Med Virol* 2015 ; 25 : 85-101.

7. Elango N, Varsanyi TM, Kovamees J, Norrby E. Molecular cloning and characterization of six genes, determination of gene order and intergenic sequences and leader sequence of mumps virus. *J Gen Virol* 1988 ; 69(Pt 11) : 2893-900.

8. Cox R, Plemper RK. The paramyxovirus polymerase complex as a target for next-generation anti-paramyxovirus therapeutics. *Front Microbiol* 2015 ; 6 : 459.

9. Rubin S, Eckhaus M, Rennick LJ, Bamford CG, Duprex WP. Molecular biology, pathogenesis and pathology of mumps virus. *J Pathol* 2015 ; 235 : 242-52.

10. Fontana JM, Bankamp B, Rota PA. Inhibition of interferon induction and signaling by paramyxoviruses. *Immunol Rev* 2008 ; 225 : 46-67.

11. Ramachandran A, Horvath CM. Dissociation of paramyxovirus interferon evasion activities: universal and virus-specific requirements for conserved V protein amino acids in MDA5 interference. *J Virol* 2010 ; 84 : 11152-63.

12. Henle G, Henle W, Wendell K, *et al*. Isolation of mumps virus from human beings with induced apparent or inapparent infections. *J Exp Med* 1948 ; 88 : 223-32.

13. Hviid A, Rubin S, Muhlemann K. Mumps. *Lancet* 2008 ; 371 : 932-44.

14. Ishida M, Fushiki H, Morijiri M, *et al*. Mumps virus infection in adults: three cases of supraglottic edema. *Laryngoscope* 2006 ; 116 : 2221-3.

15. Weller TH, Craig JM. The isolation of mumps at autopsy. *Am J Pathol* 1949 ; 25 : 1105-15.

16. Travis LW, Hecht DW. Acute and chronic inflammatory diseases of the salivary glands: diagnosis and management. *Otolaryngol Clin North Am* 1977 ; 10 : 329-38.

17. Ennis FA, Jackson D. Isolation of virus during the incubation period of mumps infection. *J Pediatr* 1968 ; 72 : 536-7.

18. Davis NF, McGuire BB, Mahon JA, Smyth AE, O'Malley KJ, Fitzpatrick JM. The increasing incidence of mumps orchitis: a comprehensive review. *BJU Int* 2010 ; 105 : 1060-5.

19. Ternavasio-de la Vega HG, Boronat M, Ojeda A, *et al*. Mumps orchitis in the post-vaccine era (1967-2009): a single-center series of 67 patients and review of clinical outcome and trends. *Medicine (Baltimore)* 2010 ; 89 : 96-116.

20. Prener A, Hsieh CC, Engholm G, Trichopoulos D, Jensen OM. Birth order and risk of testicular cancer. *Cancer Causes Control* 1992 ; 3 : 265-72.

21. Gall EA. The histopathology of acute mumps orchitis. *Am J Pathol* 1947 ; 23 : 637-51.

22. Bartak V. Sperm count, morphology and motility after unilateral mumps orchitis. *J Reprod Fertil* 1973 ; 32 : 491-4.

23. Senanayake SN. Mumps: a resurgent disease with protean manifestations. *Med J Aust* 2008 ; 189 : 456-9.

24. Dejucq N, Jegou B. Viruses in the mammalian male genital tract and their effects on the reproductive system. *Microbiol Mol Biol Rev* 2001 ; 65 : 208-31.

25. Taparelli F, Squadrini F, De Rienzo B, Lami G, Fornaciari A. Isolation of mumps virus from vaginal secretions in association with oophoritis. *J Infect* 1988 ; 17 : 255-8.

26. Wang Q, Wu H, Cheng L, *et al*. Mumps virus induces innate immune responses in mouse ovarian granulosa cells through the activation of Toll-like receptor 2 and retinoic acid-inducible gene I. *Mol Cell Endocrinol* 2016 ; 436 : 183-94.

27. Morrison JC, Givens JR, Wiser WL, Fish SA. Mumps oophoritis: a cause of premature menopause. *Fertil Steril* 1975 ; 26 : 655-9.

28. Happel JS. Mastitis in the male – a rare complication of mumps. *Br Med J* 1965 ; 2 : 1041.

29. Anderson OW. Mumps mastitis. *J Pediatr* 1977 ; 91 : 687.

30. Parenti DM, Steinberg W, Kang P. Infectious causes of acute pancreatitis. *Pancreas* 1996 ; 13 : 356-71.

31. Desailloud R, Hober D. Viruses and thyroiditis: an update. *Virol J* 2009 ; 6 : 5.

32. Nishihara E, Ohye H, Amino N, *et al*. Clinical characteristics of 852 patients with subacute thyroiditis before treatment. *Intern Med* 2008 ; 47 : 725-9.

33. Eylan E, Zmucky R, Sheba C. Mumps virus and subacute thyroiditis; evidence of a causal association. *Lancet* 1957 ; 272 : 1062-3.

34. Cordeiro E, Ferreira M, Rodrigues F, Palminha P, Vinagre E, Pimentel JP. Mumps outbreak among highly vaccinated teenagers and children in the central region of Portugal, 2012-2013. *Acta Med Port* 2015 ; 28 : 435-41.

35. Aiello FB, Calabrese F, Furian L, *et al*. Mumps-associated nephritis mimicking acute rejection in a patient under chronic dialysis treatment because of graft dysfunction. *Transpl Int* 2002 ; 15 : 523-4.

36. Johnstone JA, Ross CA, Dunn M. Meningitis and encephalitis associated with mumps infection. A 10-year survey. *Arch Dis Child* 1972 ; 47 : 647-51.

37. Bang HO, Bang J. Involvement of the central nervous system in mumps. *Acta Med Scand* 1943 ; 113 : 487-505.

38. Irani DN. Aseptic meningitis and viral myelitis. *Neurol Clin* 2008 ; 26 : 635-55.

39. Murray HG, Field CM, McLeod WJ. Mumps meningoencephalitis. *Br Med J* 1960 ; 1 : 1850-3.

40. Wolinsky JS, Klassen T, Baringer JR. Persistence of neuroadapted mumps virus in brains of newborn hamsters after intraperitoneal inoculation. *J Infect Dis* 1976 ; 133 : 260-7.

41. Koskiniemi M, Donner M, Pettay O. Clinical appearance and outcome in mumps encephalitis in children. *Acta Paediatr Scand* 1983 ; 72 : 603-9.

42. Azimi PH, Cramblett HG, Haynes RE. Mumps meningoencephalitis in children. *JAMA* 1969 ; 207 : 509-12.

43. Bruyn HB, Sexton HM, Brainerd HD. Mumps meningoencephalitis; a clinical review of 119 cases with one death. *Calif Med* 1957 ; 86 : 153-60.

44. Cohen BE, Durstenfeld A, Roehm PC. Viral causes of hearing loss: a review for hearing health professionals. *Trends Hear* 2014 ; 18, pii : 2331216514541361.

45. Hashimoto H, Fujioka M, Kinumaki H. An office-based prospective study of deafness in mumps. *Pediatr Infect Dis J* 2009 ; 28 : 173-5.

46. Everberg G. Deafness following mumps. *Acta Otolaryngol* 1957 ; 48 : 397-403.

47. Hall R, Richards H. Hearing loss due to mumps. *Arch Dis Child* 1987 ; 62 : 189-91.

48. Kanra G, Kara A, Cengiz AB, Isik P, Ceyhan M, Atas A. Mumps meningoencephalitis effect on hearing. *Pediatr Infect Dis J* 2002 ; 21 : 1167-9.

49. Westmore GA, Pickard BH, Stern H. Isolation of mumps virus from the inner ear after sudden deafness. *Br Med J* 1979 ; 1 : 14-5.

50. Pujol R. *Voyage au Centre de l'audition*. Neuroreille; www.cochlea.eu.

51. McKenna MJ. Measles, mumps, and sensorineural hearing loss. *Ann N Y Acad Sci* 1997 ; 830 : 291-8.

52. Tsubota M, Shojaku H, Ishimaru H, Fujisaka M, Watanabe Y. Mumps virus may damage the vestibular nerve as well as the inner ear. *Acta Otolaryngol* 2008 ; 128 : 644-7.

53. Ornoy A, Tenenbaum A. Pregnancy outcome following infections by coxsackie, echo, measles, mumps, hepatitis, polio and encephalitis viruses. *Reprod Toxicol* 2006 ; 21 : 446-57.

54. Chanal J, Carlotti A, Laude H, Wallet-Faber N, Avril MF, Dupin N. Lipschutz genital ulceration associated with mumps. *Dermatology* 2010 ; 221 : 292-5.

55. Kutty PK, Kyaw MH, Dayan GH, *et al*. Guidance for isolation precautions for mumps in the United States: a review of the scientific basis for policy change. *Clin Infect Dis* 2010 ; 50 : 1619-28.

56. Carbone KM, Steven R. Mumps virus. *Fields virology*, 5th ed. (vol. 1). Philadelphia : Lippincott Williams & Wilkins, 2007. pp. 1528-50.

57. Mumps virus vaccines. *Wkly Epidemiol Rec* 2007 ; 82 : 51-60.

58. Whyte D, O'Dea F, McDonnell C, *et al*. Mumps epidemiology in the mid-west of Ireland 2004-2008: increasing disease burden in the university/college setting. *Euro Surveill* 2009 ; 14, pii : 19182.

59. Park SH. Resurgence of mumps in Korea. *Infect Chemother* 2015 ; 47 : 1-11.

60. Dayan GH, Quinlisk MP, Parker AA, *et al*. Recent resurgence of mumps in the United States. *N Engl J Med* 2008 ; 358 : 1580-9.

61. Donaghy M, Cameron JC, Friederichs V. Increasing incidence of mumps in Scotland: options for reducing transmission. *J Clin Virol* 2006 ; 35 : 121-9.

62. Roberts C, Porter-Jones G, Crocker J, Hart J. Mumps outbreak on the island of Anglesey, North Wales, December 2008-January 2009. *Euro Surveill* 2009 ; 14, pii : 19109.

63. Karagiannis I, van Lier A, van Binnendijk R, *et al*. Mumps in a community with low vaccination coverage in the Netherlands. *Euro Surveill* 2008 ; 13, pii : 18901.

64. Gupta RK, Best J, MacMahon E. Mumps and the UK epidemic 2005. *BMJ* 2005 ; 330 : 1132-5.

65. Schmid D, Holzmann H, Alfery C, Wallenko H, Popow-Kraupp TH, Allerberger F. Mumps outbreak in young adults following a festival in Austria, 2006. *Euro Surveill* 2008 ; 13, pii : 8042.

66. Gerstel L, Lenglet A, Garcia Cenoz M. Mumps outbreak in young adults following a village festival in the Navarra region, Spain, August 2006. *Euro Surveill* 2006 ; 11 : E061109 061104.

67. Gobet A, Mayet A, Journaux L, *et al*. Mumps among highly vaccinated people: investigation of an outbreak in a French Military Parachuting Unit, 2013. *J Infect* 2014 ; 68 : 101-2.

68. Kutty PK, McLean HQ, Lawler J, *et al*. Risk factors for transmission of mumps in a highly vaccinated population in Orange County, NY, 2009-2010. *Pediatr Infect Dis J* 2014 ; 33 : 121-5.

69. Nelson GE, Aguon A, Valencia E, *et al*. Epidemiology of a mumps outbreak in a highly vaccinated island population and use of a third dose of measles-mumps-rubella vaccine for outbreak control – Guam 2009 to 2010. *Pediatr Infect Dis J* 2013 ; 32 : 374-80.

70. Sane J, Gouma S, Koopmans M, *et al*. Epidemic of mumps among vaccinated persons, The Netherlands, 2009-2012. *Emerg Infect Dis* 2014 ; 20 : 643-8.

71. Botelho-Nevers E, Gautret P. Outbreaks associated to large open air festivals, including music festivals, 1980 to 2012. *Euro Surveill* 2013 ; 18 : 20426.

72. Barskey AE, Glasser JW, LeBaron CW. Mumps resurgences in the United States: a historical perspective on unexpected elements. *Vaccine* 2009 ; 27 : 6186-95.

73. Boxall N, Kubinyiova M, Prikazsky V, Benes C, Castkova J. An increase in the number of mumps cases in the Czech Republic, 2005-2006. *Euro Surveill* 2008 ; 13, pii : 8042.

74. Yoshida N, Fujino M, Miyata A, *et al*. Mumps virus reinfection is not a rare event confirmed by reverse transcription loop-mediated isothermal amplification. *J Med Virol* 2008 ; 80 : 517-23.

75. LeBaron CW, Forghani B, Matter L, *et al*. Persistence of rubella antibodies after 2 doses of measles-mumps-rubella vaccine. *J Infect Dis* 2009 ; 200 : 888-99.

76. Peltola H, Jokinen S, Paunio M, Hovi T, Davidkin I. Measles, mumps, and rubella in Finland: 25 years of a nationwide elimination programme. *Lancet Infect Dis* 2008 ; 8 : 796-803.

77. Gouma S, Hahne SJ, Gijselaar DB, Koopmans MP, van Binnendijk RS. Severity of mumps disease is related to MMR vaccination status and viral shedding. *Vaccine* 2016 ; 34 : 1868-73.

78. Nicolai-Scholten ME, Ziegelmaier R, Behrens F, Hopken W. The enzyme-linked immunosorbent assay (ELISA) for determination of IgG and IgM antibodies after infection with mumps virus. *Med Microbiol Immunol* 1980 ; 168 : 81-90.

79. Benito RJ, Larrad L, Lasierra MP, Benito JF, Erdociain F. Persistence of specific IgM antibodies after natural mumps infection. *J Infect Dis* 1987 ; 155 : 156-7.

80. Krause CH, Molyneaux PJ, Ho-Yen DO, McIntyre P, Carman WF, Templeton KE. Comparison of mumps-IgM ELISAs in acute infection. *J Clin Virol* 2007 ; 38 : 153-6.

81. Krause CH, Eastick K, Ogilvie MM. Real-time PCR for mumps diagnosis on clinical specimens – comparison with results of conventional methods of virus detection and nested PCR. *J Clin Virol* 2006 ; 37 : 184-9.

82. Bockelman C, Frawley TC, Long B, Koyfman A. Mumps: an emergency medicine-focused update. *J Emerg Med* 2018 ; 54 : 207-14.

83. Kowalzik F, Faber J, Knuf M. MMR and MMRV vaccines. *Vaccine* 2017 ; pii : S0264-410X(17)30959-3. doi: 10.1016/j.vaccine.2017.07.051.

84. Gouma S, Ten Hulscher HI, Schurink-van 't Klooster TM, *et al*. Mumps-specific cross-neutralization by MMR vaccine-induced antibodies predicts protection against mumps virus infection. *Vaccine* 2016 ; 34 : 4166-71.

85. Betakova T, Svetlikova D, Gocnik M. Overview of measles and mumps vaccine: origin, present, and future of vaccine production. *Acta Virol* 2013 ; 57 : 91-6.

86. Young ML, Dickstein B, Weibel RE, Stokes Jr. J, Buynak EB, Hilleman MR. Experiences with Jeryl Lynn strain live attenuated mumps virus vaccine in a pediatric outpatient clinic. *Pediatrics* 1967 ; 40 : 798-803.

87. Schlegel M, Osterwalder JJ, Galeazzi RL, Vernazza PL. Comparative efficacy of three mumps vaccines during disease outbreak in Eastern Switzerland: cohort study. *BMJ* 1999 ; 319 : 352.

88. Ong G, Goh KT, Ma S, Chew SK. Comparative efficacy of Rubini, Jeryl-Lynn and Urabe mumps vaccine in an Asian population. *J Infect* 2005 ; 51 : 294-8.

89. Kaaijk P, van der Zeijst B, Boog M, Hoitink C. Increased mumps incidence in the Netherlands: review on the possible role of vaccine strain and genotype. *Euro Surveill* 2008 ; 13, pii : 18914.

90. Alirezaie B, Aghaiypour K, Shafyi A. Genetic characterization of RS-12 (S-12), an Iranian isolate of mumps virus, by sequence analysis and comparative genomics of F, SH, and HN genes. *J Med Virol* 2008 ; 80 : 702-10.

91. Odisseev H, Gacheva N. Vaccinoprophylaxis of mumps using mumps vaccine, strain Sofia 6, in Bulgaria. *Vaccine* 1994 ; 12 : 1251-4.

92. Liang Y, Ma J, Li C, *et al*. Safety and immunogenicity of a live attenuated mumps vaccine: a phase I clinical trial. *Hum Vaccin Immunother* 2014 ; 10 : 1382-90.

93. Kubota M, Takeuchi K, Watanabe S, *et al*. Trisaccharide containing alpha2,3-linked sialic acid is a receptor for mumps virus. *Proc Natl Acad Sci U S A* 2016 ; 113 : 11579-84.

94. Santak M, Orvell C, Gulija TK. Identification of conformational neutralization sites on the fusion protein of mumps virus. *J Gen Virol* 2015 ; 96 : 982-90.

95. InVS. Calendrier des vaccinations et recommandations vaccinales 2016. *BEH* 2016 : 1-47.

96. Maglione MA, Das L, Raaen L, *et al*. Safety of vaccines used for routine immunization of U.S. children: a systematic review. *Pediatrics* 2014 ; 134 : 325-37.

97. Bonnet MC, Dutta A, Weinberger C, Plotkin SA. Mumps vaccine virus strains and aseptic meningitis. *Vaccine* 2006 ; 24 : 7037-45.

98. Rubin SA, Afzal MA. Neurovirulence safety testing of mumps vaccines – historical perspective and current status. *Vaccine* 2011 ; 29 : 2850-5.

99. Lievano F, Galea SA, Thornton M, *et al*. Measles, mumps and rubella virus vaccine (M-M-RII): a review of 32 years of clinical and postmarketing experience. *Vaccine* 2012 ; 30 : 6918-26.