

# Mumps

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Mumps is a common childhood infection caused by the mumps virus. The hallmark of infection is swelling of the parotid gland. Aseptic meningitis and encephalitis are common complications of mumps together with orchitis and oophoritis, which can arise in adult men and women, respectively; other complications include deafness and pancreatitis. Clinical diagnosis can be based on the classic parotid swelling; however, this feature is not present in all cases of mumps and can also occur in various other disorders. Laboratory diagnosis is based on isolation of virus, detection of viral nucleic acid, or serological confirmation (generally presence of IgM mumps antibodies). Mumps is vaccine-preventable, and one dose of mumps vaccine is about 80% effective against the disease. Routine vaccination has proven highly effective in reducing the incidence of mumps, and is presently used by most developed countries; however, there have been outbreaks of disease in vaccinated populations. In 2005, a large epidemic peaked in the UK, and in 2006 the American midwest had several outbreaks. In both countries, the largest proportion of cases was in young adults. In the UK, susceptible cohorts too old to have been vaccinated and too young to have been exposed to natural infections were the primary cause of the mumps epidemic. In the USA, effectiveness and uptake in combination appear not to have been sufficient to obtain herd immunity for mumps in populations such as college students.

## Introduction

Mumps is best known as a common childhood viral disease, and is characterised by swelling of the parotid gland (figure 1). The disease is preventable by vaccine, and mumps vaccination is almost universally used in developed countries nowadays. Compared with other common vaccine-preventable diseases, such as measles and pertussis, mumps is more benign. Consequently, topics relating to mumps have been somewhat neglected; however, large outbreaks in the UK and USA have sparked a new interest in mumps.

## Pathobiology

### Mumps virus

Mumps virus, the causative agent of mumps infection, is an enveloped RNA virus that belongs to the genus *Rubulavirus* in the family *Paramyxoviridae*.<sup>1,2</sup> In electron microscopy, the virion presents as a particle with a shape that varies between spherical and pleiomorphic with a diameter of about 200 nm (figure 2). The viral genome is contained in a linear molecule of single-stranded, negative-strand RNA, 15 384 nucleotides in length, which encodes six structural proteins and at least two



Figure 1: Hallmark swelling of parotid gland in a child with mumps  
Photo courtesy of CDC/NIP/Barbara Rice.

non-structural proteins. The capsid consists of the major structural nucleocapsid protein, the phosphoprotein, and the large protein; the last two are thought to constitute the RNA polymerase. The envelope is a lipid bilayer membrane composed of the matrix protein, and two surface glycoproteins. The surface glycoproteins—haemagglutinin-neuraminidase and fusion protein—bring about viral adsorption and fusion of the virion membrane with the host cell membrane, respectively; both are needed for cell-to-cell fusion. Virion membrane fusion seems to be associated with neurovirulence.<sup>3,4</sup> The lipid membrane renders the virus susceptible to ether and alcoholic disinfectants. The virus is stable at 4°C for days.

Population genetics of mumps have been based on genotyping of the small hydrophobic gene, the most variable part of the viral genome. The function of the protein it encodes is not known. Genotypes show nucleotide variation of 2–4% within genotypes and at least 6% between genotypes.<sup>5</sup> 12 mumps virus genotypes, designated A to L, have been described,<sup>6,7</sup> and their geographic distribution varies: in the western hemisphere,

### Search strategy and selection criteria

Material for this Seminar was primarily based on journal publications identified through a comprehensive search of the PubMed database. Search terms included “mumps”, “pathogenesis”, “diagnosis”, “epidemiology”, and “vaccination”. The searches were inclusive of all languages and article types (eg, reviews, case reports, and editorials). The publication dates covered were 1957 to January, 2007. Seminal work and, where appropriate, recently published articles were preferentially selected. Key textbook chapters were also included. Furthermore, references identified through the above material were also considered, where appropriate.

genotypes C, D, E, G, and H prevail, and in Asian countries, genotypes B, F, and I predominate. Several genotypes might circulate simultaneously in a region, and there can be temporal shifts in genotype distribution;<sup>6</sup> the factors that drive genotype distribution are not known. Mumps virus is not classified into serotypes; however, findings *in vivo* and *in vitro* suggest that cross-neutralisation between genotypes might be reduced.<sup>8,9</sup> The significance and effect of reduced cross-neutralisation between genotypes with respect to mumps epidemiology and vaccination remain to be established.

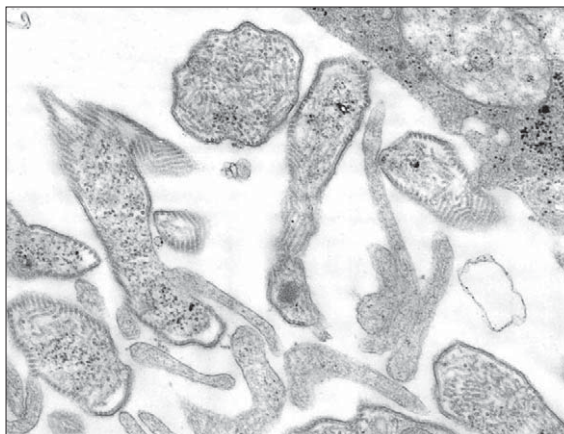
### Transmission and pathogenesis

Mumps is a moderately to highly contagious infection that is restricted to human beings. Transmission of the virus is by direct contact, droplet spread, or contaminated fomites. The incubation period is about 15 to 24 days (median, 19 days).<sup>10</sup> Infected patients become most contagious 1 to 2 days before onset of clinical symptoms and continue so for several days afterwards. Mumps virus can, however, be isolated from saliva as early as 7 days before and until 9 days after onset of clinical symptoms.<sup>11</sup>

Mumps is acquired through inoculation and replication of the virus in the nasal or upper-respiratory-tract mucosa.<sup>12–14</sup> Infection can remain localised to the respiratory tract.<sup>12</sup> Transient plasma viraemia is probably frequent, occurs late in the incubation period, and leads to viral spread into organs.<sup>15,16</sup> Infected mononuclear cells can also contribute to systemic viral spread.<sup>17</sup> The parotids are the most commonly affected organs, but parotitis is not a primary or necessary step for mumps infection. The central nervous system (CNS), urinary tract, and genital organs can also be affected. Infection of the kidneys leads to viruria, which is present in most patients and lasts for 10–14 days.<sup>18,19</sup> Plasma viraemia seems to be restricted by the humoral immune response,<sup>16</sup> and salivary secretion of the virus correlates inversely with the local production of virus-specific secretory IgA.<sup>20</sup>

### Pathology

Mumps virus has an affinity for the glandular epithelium. Viral replication in the parotid gland includes the ductal epithelium, and leads to periductal interstitial oedema and local inflammation with infiltrates of lymphocytes and macrophages.<sup>21</sup> A similar microscopic picture can be seen in mumps pancreatitis and orchitis, and interstitial haemorrhage can occur.<sup>22</sup> Increased pressure caused by oedema and an inelastic tunica albuginea can lead to necrosis, atrophy of the germinal epithelium, hyalinisation of the seminiferous tubules, and subsequent atrophy of the testes.<sup>23,24</sup> The pathological changes and complications seen in mumps orchitis are most probably a direct or indirect consequence of viral propagation. Mumps virus has been isolated from semen and testicular biopsy samples during mumps orchitis.<sup>25,26</sup> Antisperm antibodies do not seem to have a pathogenetic role.<sup>27</sup> The primary sites of viral replication in the kidney are the epithelial



**Figure 2: Transmission electron micrograph showing the ultrastructural details of mumps virions grown in Vero cells**

Image courtesy of CDC/A Harrison and F A Murphy.

layers of the distal tubules, calyces, and ureter.<sup>21</sup> Use of animal models suggest that the virus enters the cerebrospinal fluid (CSF) via the choroid plexus or infected mononuclear cells during plasma viraemia.<sup>17,28</sup> Productive infection of choroidal and ependymal epithelial cells serves as a source for viral spread throughout the CNS.<sup>28</sup> 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, characterised by perivenous demyelination, perivascular infiltrations with mononuclear cells, and a relative sparing of neurons.<sup>29,30</sup> Direct extension of the virus into neurons within the brain parenchyma seems to occur, however, as shown by virus isolation from brain tissue in a rare case of presumed primary mumps encephalitis.<sup>31,32</sup> A proliferative necrotising villitis and the presence of intracytoplasmic inclusion bodies in decidual cells have been described in spontaneous and induced abortions.<sup>33</sup> Mumps virus has also been isolated from fetal tissue after first-trimester abortion on the fourth day of maternal mumps and from an 8-day-old infant whose mother developed mumps 4 days before delivery.<sup>34</sup>

### Clinical presentations

About a third of mumps infections arise without recognised symptoms.<sup>35</sup> Clinically manifest infections might start with a short prodromal phase of low-grade fever, anorexia, malaise, and headache (table).

### Parotitis

The hallmark of mumps is painful parotitis, which occurs in 60–70% of infections and 95% of patients with symptoms.<sup>35</sup> Swelling of the parotid gland—lifting the ear lobe outward and obscuring the angle of the mandible—progresses over 2–3 days, and persists for about a week. The degree of pain and tenderness is related to the progression and resolution of parotitis. In many cases, the orifice of the Stensen's duct is

	Cases (%)
Clinical symptoms	60–70% of infections
Parotitis	95% of patients with clinical symptoms
Epididymo-orchitis	15–30% of adult men with infection
Bilateral orchitis	15–30% of epididymo-orchitis cases
Oophoritis	5% of adult women with infection
Meningitis	1–10% of infections
Encephalitis	0.1% of infections
Death	1.5% of encephalitis cases
Permanent unilateral deafness	0.005% of infections
Spontaneous abortion	27% of first-trimester pregnancies after mumps infection
Pancreatitis	4% of infections

**Table: Clinical presentations of mumps infection**

oedematous and erythematous. Swelling of the contralateral parotid gland is common (90% of parotitis cases), and is generally delayed for several days. Body temperature might be raised and returns to normal with the resolution of symptoms. Complications of parotitis are very rare, but sialectasia with recurrent sialadenitis has been described.<sup>36</sup> The submandibular and sublingual glands are less commonly affected (about 10% of infections), and present in most cases as bilateral swelling in conjunction with parotitis. Obstruction of the lymphatic drainage by bilateral glandular swelling is thought to lead to presternal oedema in 6% of patients and to rare cases of suprasternal oedema.<sup>37,38</sup>

#### Epididymo-orchitis and oophoritis

Epididymo-orchitis arises in 15–30% of adult men with mumps infection, but it is rare before puberty.<sup>35,39–45</sup> In 15–30% of cases with orchitis, both testes are affected.<sup>39,40</sup> Orchitis manifests generally 4–8 days after parotitis; however, intervals of up to 6 weeks have been reported.<sup>43</sup> The clinical course starts with abrupt swelling, warmth, and tenderness of the affected testicle, and inflammation of the scrotum. Epididymitis is present in most cases;<sup>44</sup> constitutional symptoms include (high) fever, vomiting, headache, and malaise. Similar to parotitis, symptoms progress for 2–3 days and resolve within a week or two, although residual testicular tenderness can persist for weeks. There has been much anxiety about the potential consequences of mumps orchitis on fertility in men. Some degree of reduced testicular size can be seen in up to half of affected patients, and abnormalities of spermatograms (in terms of sperm count, morphology, or motility) arise in up to 25% of patients.<sup>39</sup> The influence of mumps orchitis on the endocrine function of the testes is controversial: results from one study showed decreased testosterone and increased follicle-stimulating-hormone concentrations, whereas results from other studies showed only transient or no changes in hormone concentrations associated with mumps orchitis.<sup>45,46</sup> Studies to assess the effect of mumps orchitis on

endocrine function are difficult to perform owing to small sample sizes, bias attributable to case selection, and the absence of baseline data for comparison. In any case, patients should be advised that sterility from mumps orchitis (other than psychogenic sterility) is rare even after bilateral orchitis.<sup>47,48</sup> There is no evidence for an association between mumps orchitis and an increased risk of testicular cancer.<sup>40,49</sup> Oophoritis develops in 5% of postpubertal women with mumps, and presents with lower-abdominal pain, fever, and vomiting. Although infertility and premature menopause have been reported after mumps oophoritis, they are rare complications.<sup>50</sup> Mumps can also present with mastitis in postpubertal women.<sup>35</sup>

#### CNS infection

Infection of the CNS is the most common extrasalivary-gland manifestation of mumps infection. CSF pleiocytosis occurs in at least half of all mumps infections, mostly without other signs or symptoms of meningitis.<sup>51</sup> Clinically manifest meningitis arises in 1–10% of mumps infections, and encephalitis in 0.1%. Greater proportions of male than of female patients are affected.<sup>52</sup> CNS infection manifests about 5 days after the onset of parotitis, but it can precede parotitis by a week or it can manifest up to 2 weeks after the appearance of parotitis.<sup>51,53–55</sup> In up to 50% of cases, mumps meningitis occurs in the absence of salivary-gland involvement.<sup>14,56</sup> The severity of parotitis does not predict CNS involvement.<sup>51</sup> Mumps meningitis is a benign entity with no essential risk of mortality or long-term sequelae. The typical clinical symptoms are high fever, headache, vomiting, neck stiffness, and lethargy;<sup>56–59</sup> symptoms peak for about 48 h to resolve thereafter—for a total duration of illness of 7–10 days. Patients who develop persistent sequelae after mumps CNS infection are presumed to have had encephalitis. The presence of seizures, pronounced changes in the level of consciousness, or focal neurological symptoms are indicative of mumps encephalitis.<sup>54</sup> Ataxia, behavioural changes, and abnormalities at electroencephalography can be seen in children during convalescence, but they resolve after a few weeks.<sup>57</sup> Mortality associated with mumps encephalitis is low (about 1.5%), and long-term morbidity is rare.<sup>54,57,59,60</sup> Unfavourable outcomes are more common in adults than in children. Sensorineural hearing loss is a well known complication of mumps. Transient high-frequency-range deafness was occurred in 4.1% of patients with mumps in an adult male (military) population.<sup>61</sup> Permanent unilateral deafness caused by mumps arises at an estimated frequency of one in 20 000 cases;<sup>62</sup> bilateral, severe hearing loss is very rare. For other mumps complications, hearing loss can be the sole clinical manifestation,<sup>63</sup> but it can also occur frequently in patients with meningoencephalitis.<sup>64</sup> Onset of impaired hearing can be acute or gradual, and vertigo is frequent; however, vestibular function in later screening is normal.

Rare CNS manifestations of mumps are facial palsy,<sup>65</sup> cerebellar ataxia,<sup>66</sup> transverse myelitis,<sup>67</sup> ascending polyradiculitis (Guillain-Barré syndrome),<sup>68</sup> and flaccid paralysis.<sup>69</sup> There is clinical and experimental evidence for aqueductal stenosis and hydrocephalus caused by mumps CNS infection.<sup>70-72</sup>

### Mumps during pregnancy

Spontaneous abortion can be a complication of mumps infection in early pregnancy.<sup>73</sup> In a study by Siegel and colleagues,<sup>73</sup> fetal death after first trimester mumps infection was recorded in 27% of pregnancies compared with 13% in the control group; however, Enders and co-workers' more recent study<sup>74</sup> showed that the rate of abortion was not increased in women with mumps. There is, however, no firm evidence for an association between mumps and low birthweight or congenital malformations.<sup>75,76</sup> There might be a relationship between intrauterine mumps and endocardial fibroelastosis.<sup>77-79</sup> Perinatal mumps infection has been reported and generally seems to take a benign course.<sup>80-83</sup>

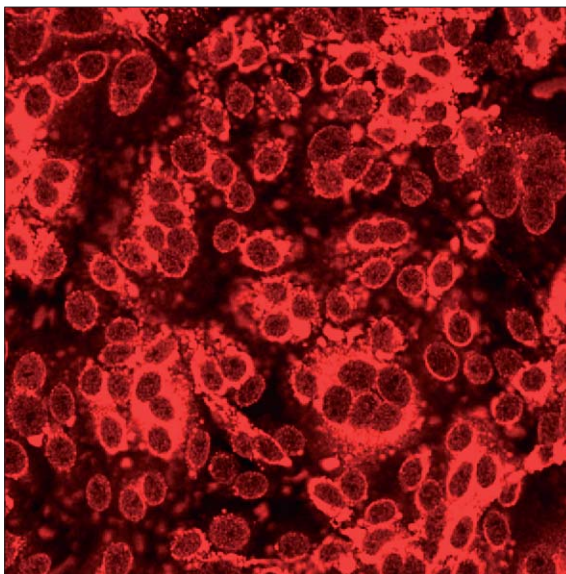
### Miscellaneous manifestations

Pancreatitis arises in about 4% of mumps infections, mostly subclinically or with a mild course.<sup>84</sup> Severe haemorrhagic pancreatitis has been rarely reported.<sup>22</sup> Electrocardiographic abnormalities—such as depressed ST segments, flattened or inverted T waves, and prolonged PR intervals—are seen in up to 15% of mumps infections.<sup>85,86</sup> Clinically manifest myocarditis is rare; however, fatal cases have been reported. Mumps can affect large and small joints, especially in adults.<sup>87,88</sup> The clinical picture can be single-joint arthritis or migratory polyarthritis. Residual damage to joints has not been reported. Abnormal renal function is frequent during mumps;<sup>89</sup> severe, fatal nephritis is, however, rare.<sup>90</sup> Hepatitis, acalculous cholecystitis,<sup>91</sup> kerato-uveitis,<sup>92</sup> haemophagocytic syndrome,<sup>93</sup> and thrombocytopenia<sup>94</sup> are also rare manifestations of mumps. A causal link between mumps and juvenile diabetes mellitus has been suggested, but not substantiated, by case reports and a correlation of incidence time trends.<sup>95-97</sup>

## Diagnosis

### Clinical diagnosis

The standard clinical case definition of mumps is acute onset of unilateral or bilateral swelling of the parotid or other salivary glands lasting 2 or more days without any other apparent cause.<sup>98</sup> Although parotitis is indeed the hallmark of mumps, in many cases, salivary-gland swelling is not apparent, especially in individuals with mumps meningitis, many of whom present without detectable salivary-gland enlargement.<sup>33,35</sup> Salivary-gland swelling is also caused by other infectious agents, drugs, and disorders (see differential diagnosis section below); the effect of such alternative aetiologies greatly reduces the positive predictive value of a clinical diagnosis when



**Figure 3:** HeLa cell culture immunohistochemically stained with a monoclonal antibody to mumps virus (MAB846, Chemicon International) showing fluorescent signal indicating virus antigen expression on day 3 after incubation with a mumps-virus clinical isolate

the disease incidence is low.<sup>99,100</sup> In addition to consideration of the other widely varying constitutional mumps symptoms in the clinical diagnosis, laboratory testing is essential for case confirmation.

In most cases of mumps, white blood cell and differential counts are normal, although leucocytosis has been reported in people presenting with meningitis, orchitis, or pancreatitis. Serum amylase concentrations are raised in most cases of parotitis or pancreatitis. In cases of meningitis or encephalitis, lymphocytes are the predominant cell type reported in the CSF, with white blood cell counts of  $10 \times 10^6$  to  $2000 \times 10^6$  per L. CSF pressure, and glucose and protein concentrations are generally within the normal range, however, hypoglycorrhachia and raised protein concentrations have been reported.<sup>60,101</sup> Meningitis, which can be diagnosed by positive Brudzinski's and Kernig's signs, can be differentiated from encephalitis by a normal electroencephalogram and absence of clinical findings suggestive of supratentorial involvement (eg, decreased mental alertness). In many cases, a raised CSF or serum antibody ratio lends support to the diagnosis of mumps CNS infection.<sup>102</sup>

### Laboratory diagnosis

A laboratory diagnosis is based on isolation of the mumps virus, detection of viral nucleic acid, or serological confirmation—generally by measurement of IgM antibody concentrations. There is a limited window of opportunity for successful virus isolation or detection because mumps-virus replication is transient. Virus can be readily isolated from saliva, CSF, urine, or seminal fluid within the first week of manifestation of

symptoms.<sup>26,103</sup> Rates of successful virus isolation greatly decrease beyond the first week. Despite the apparent frequency of viraemia, the mumps virus has only rarely been isolated from blood and only during the first 2 days of illness.<sup>104</sup> The difficulty in isolating the mumps virus might be related to the coincident presence of antibodies to the virus.

The presence of virus is typically detected by immunofluorescence staining of clinical specimens (figure 3). The specimens can be tested directly by means of cytospin preparations<sup>105</sup> or after incubation with cell lines.<sup>106</sup> Either Vero (African green monkey kidney) cells or Caco-2 (human colorectal adenocarcinoma epithelium) cells are recommended for virus isolation because they are among the most permissive to mumps virus infection.<sup>107</sup> Although time taken is longer, the use of an intervening cell-culture step has the advantage of amplifying a virus that might exist in undetectable numbers in the original clinical specimen. Reliance solely on the characteristic cytopathic effects of mumps virus in cell culture—ie, syncytial formation followed by lysis—is not recommended since some strains of mumps virus are not cytopathic and many of the viruses in the differential diagnosis of mumps cause cellular pathological changes that are indistinguishable from those induced by the mumps virus. Detection of virus based on immunohistochemical techniques has been supplanted by the more rapid, sensitive, and specific technique of RT-PCR.

RT-PCR is done directly on the clinical specimen; an intervening in-vitro tissue-culture step is not necessary. The mumps virus small hydrophobic gene is the most common target for RT-PCR assays: detection of this gene confirms infection; sequence analysis from the gene region can be used to identify the specific viral strain, and for molecular epidemiological studies. In examinations of CSF and oral fluid specimens, RT-PCR was universally found to be more sensitive than cell culture-based methods—eg, mumps virus RNA was detected by RT-PCR in the CSF of 44 (96%) of 46 patients with a clinical diagnosis of viral CNS disease; by contrast, CSF specimens from only 18 (39%) of these 46 patients were positive by culture followed by immunohistochemical staining.<sup>108</sup> In another study of cases of aseptic meningitis,<sup>109</sup> 19 (70%) of 27 CSF specimens were positive for mumps virus by RT-PCR, but only six (22%) of these 27 specimens tested positive by cell culture and immunohistochemical staining. Similar results of better detection sensitivity of RT-PCR compared with cell culture-based methods were obtained with oral fluids.<sup>109</sup> By contrast, the sensitivity of virus detection in urine specimens by standard cell-culture techniques was greater than that by RT-PCR, perhaps because PCR inhibitors were present in urine.<sup>110</sup>

In addition to standard nested RT-PCR, quantitative real-time RT-PCR is increasingly being used in investigations of mumps infection. This method has the

advantage over standard RT-PCR of the ability to quantify viral burden, but seems to be only marginally more sensitive than standard nested RT-PCR.<sup>109,110</sup>

In the absence of successful virus culture or RT-PCR detection, serological markers can provide a definitive diagnosis. Serological confirmation is typically based on detection of virus-specific IgM antibody, measured by direct or indirect ELISA. In a study of oropharyngeal swabs from 27 children with parotitis, 22 (81%) were positive by RT-PCR; but mumps-specific IgM was detected by ELISA in serum from only 18 (67%) of the 27 children.<sup>111</sup> The apparent false-negative results of IgM ELISA testing might have been related to the timing of serum collection or possible previous exposure to the mumps virus. Although some reports suggest that IgM can be reliably detected by the onset of clinical disease,<sup>112</sup> other studies have reported false-negative IgM results for serum collected before day 4 of clinical presentation.<sup>113,114</sup> The optimum time for serum collection for IgM testing seems to be 7–10 days after symptom onset.<sup>114,115</sup> Importantly, IgM might not be detectable in previously infected or immunised individuals because it is not a major constituent in the secondary immune response. Thus, in cases where IgM testing of appropriately timed serum samples is negative, suggesting possible earlier exposure or vaccination, IgG testing is recommended.<sup>116</sup> In such cases, a convalescent serum sample should also be obtained to verify IgG seroconversion, which is shown by a significant rise in titre relative to that of the acute-phase serum sample. In individuals who are initially seronegative, a four-fold rise in IgG titre between serum samples from the acute and convalescent phases has conventionally been used as a means of confirming a seroconversion event; however, this rise in titre might not occur in vaccinated individuals and its absence should not be used to rule out mumps. Virus-specific IgM and IgG can also be detected in CSF in patients with mumps meningitis or encephalitis.<sup>117</sup>

ELISA (owing to the ease with which IgG and IgM can be measured and quantified) has for the most part supplanted the use of more labour-intensive tests—complement fixation, haemagglutination inhibition, or virus neutralisation—of which, virus neutralisation is the most specific and informative. ELISA has been reported to be more sensitive than the virus neutralisation assay; however, in cases of low concentrations of antibodies, the virus neutralisation assay can be more sensitive, presumably because higher initial dilutions of serum are used in the ELISA.<sup>118,119</sup> Both virus-neutralising and non-neutralising antibodies yield positive results in the ELISA; therefore, the ELISA can be prone to give false-positive results in the context of assessing immunity—eg, seroconversion has been shown by ELISA even in the absence of demonstrable neutralising antibody.<sup>120</sup> Results of the virus neutralisation assay are difficult to interpret because there is no established neutralising antibody titre that can be used as a surrogate marker of protection. Studies done in the USA in

the 1960s when mumps was endemic, have shown that any detectable concentration of mumps virus neutralising antibody would provide protection against natural infection;<sup>121</sup> however, over the past two decades, there have been many outbreaks in highly vaccinated populations. Since evidence exists for possible antigenic differences among certain strains of mumps virus,<sup>9,122,123</sup> immunity induced by one strain of mumps might be inadequate against other strains; however, this has not been proven.<sup>8,9,124</sup> Thus, although serological investigations by either method are informative for mumps diagnosis, their predictive value in assessing immunity is limited.

### Differential diagnosis

When parotitis is present during a mumps outbreak or epidemic, the clinical diagnosis of mumps is generally straightforward; however, when the rate of mumps is low, other causes of parotitis should be considered—eg, other viral infections (Epstein-Barr virus, parainfluenza virus types 1 and 3, influenza A virus, coxsackievirus, adenovirus, parvovirus B19, lymphocytic choriomeningitis virus, and HIV) and suppurative infections (*Staphylococcus aureus* and atypical mycobacteria).<sup>103</sup> These agents do not produce parotitis on an epidemic scale and all can be easily differentiated from mumps virus by serology or culture. The effect of these alternative causes of parotitis on a clinical diagnosis of mumps was suggested by a study in Victoria, Australia, where the rate of mumps was low. Only seven (9%) of 74 cases clinically diagnosed as mumps parotitis could be confirmed by serology; seven (16%) of 43 laboratory-rejected cases were positive for Epstein-Barr virus by serology.<sup>99</sup> In a study of 601 acutely ill, mumps-seronegative children presenting with mumps-like symptoms in Finland, the most common viral causes, by ELISA, were Epstein-Barr virus (7%), parainfluenza virus (4%), and adenovirus (3%). In a smaller subset of serum samples tested (n=114), human herpesvirus 6 was the causative agent in 4% of patients.<sup>125</sup> The Australian and Finnish studies highlight the importance of laboratory confirmation in diagnosing mumps, especially under non-outbreak conditions. Other possible causes of parotid swelling include starch ingestion, drugs (eg, phenylbutazone, thiouracil, iodides, and phenothiazines), malnutrition, tumours, cysts, salivary stones, certain metabolic disorders (eg, diabetes mellitus, cirrhosis, and uraemia), and other rare disorders (eg, Mikulicz's, Parinaud's, and Sjögren's syndromes).<sup>103</sup> In the absence of parotitis or other salivary-gland enlargement, symptoms of other visceral organs or CNS involvement can predominate, and thus laboratory confirmation of the diagnosis is needed, even during an epidemic.

### Treatment

There is no specific antiviral therapy for mumps. Since the illness is generally benign and self-resolving, treatment is mostly symptomatic and supportive—eg, use of analgesic medications to relieve pain associated

with parotitis or orchitis; or lumbar puncture to relieve headache associated with meningitis. Use of steroids should be avoided in the treatment of mumps orchitis because steroids can decrease testosterone concentrations, and can increase concentrations of follicle-stimulating and luteinising hormones, which could facilitate, rather than alleviate, testicular atrophy.<sup>126</sup>

There is evidence that intramuscular administration of mumps immune globulin could be helpful early in the course of the illness in selected cases;<sup>127</sup> however, mumps immune globulin has not been shown to be effective during an epidemic,<sup>128</sup> and is no longer available in most countries. Intravenous immunoglobulin (IVIG, to distinguish it from intramuscular mumps immune globulin), is not used as a mumps-specific treatment, and its efficacy has not been established; however, IVIG has been used successfully to treat certain mumps symptoms that can be autoimmune-based, such as postinfectious encephalitis, Guillain-Barré syndrome, or idiopathic thrombocytopenic purpura.<sup>129–131</sup> Nonetheless, IVIG administration might be of potential therapeutic value in treating mumps-specific symptoms because there are substantial amounts of antimumps virus antibodies in most commercial IVIG preparations.<sup>132</sup>

Other potentially viable specific treatments include subcutaneous administration of interferon alfa-2b for treating mumps orchitis. In a study of four patients with bilateral mumps orchitis, acute symptoms resolved within 2–4 days of treatment with interferon alfa-2b, with no evidence of testicular atrophy during a follow-up of 6–15 months. Three of these patients presented with oligoasthenospermia (subfertility), and progressed to normospermia 2–4 months after interferon treatment.<sup>45</sup> In another study of 21 patients with mumps orchitis, of 13 treated with interferon alfa-2b, symptoms resolved within 2–3 days of treatment and no testicular atrophy was noted during follow-up, although oligoasthenospermia continued to be detected in four of these patients. By contrast, of the eight control patients (who received standard symptomatic treatment only), symptoms resolved within 4–5 days, and testicular atrophy was reported in three patients and oligoasthenospermia in four.<sup>46</sup>

### Vaccination

All available mumps vaccines consist of live attenuated mumps virus.<sup>133</sup> At least 11 strains are presently in use throughout the world: the Jeryl Lynn and Urabe Am9 strains have been the most commonly used followed by the Leningrad-Zagreb, Leningrad-3, and Rubini strains; the newer RIT 4385 strain has been derived from the Jeryl Lynn strain. The use of other available mumps strains has been limited, in most cases to one country only. Mumps vaccines (panel) are available as monovalent vaccines or in combination with other vaccines (which is almost universal), such as the measles-mumps-rubella (MMR) combination.

### Immune response to vaccination

Studies have shown that initial seroconversion rates for mumps virus neutralising antibodies after vaccination are satisfactorily high for all strains in general, with some variation.<sup>134</sup> Titres of neutralising antibody are related to clinical protection, but there is no surrogate immunological marker for protection. In comparative studies of the Urabe and Jeryl Lynn strains in trivalent combinations, Urabe seemed to be the most immunogenic strain.<sup>135–138</sup> The RIT 4385 strain has similar immunogenic properties to the Jeryl Lynn strain from which it was derived.<sup>139</sup> Age influences the immune response to mumps vaccination. Intrinsic deficiencies in the humoral response and the possible presence of maternally acquired passive antibodies during infancy reduce the seroconversion rates of mumps vaccine in infants younger than 6 months.<sup>140,141</sup>

Although, the long-term persistence of neutralising antibodies after mumps vaccination is not well documented, neutralising-antibody titres persisted for 12 years after administration of the vaccine containing the Jeryl Lynn strain in one rare study;<sup>142</sup> however, there was some evidence that the vaccine effect was boosted by asymptomatic reinfection. In a comparative study, seronegativity rates of 15% for Urabe and 19% for Jeryl Lynn were detected 4 years after vaccination.<sup>143</sup> In children vaccinated at age 18 months, a second dose of mumps vaccine at age 12 years, increased seropositivity rates from 73% to 93%.<sup>144</sup> In a similar study, a second dose of vaccine 4–5 years after the first dose at age 14–18 months, increased seropositivity rates from 86% to 95%.<sup>145</sup> 9 years after the first vaccination, the seropositivity rate had returned to 86%.

### Efficacy and effectiveness of vaccination

True vaccine efficacy is assessed before licensing in randomised clinical trials. The rate of mumps is compared in vaccinated children and in unvaccinated children, or those assigned placebo. Few such studies have been undertaken because withholding of a vaccine from a control group of children once its efficacy has been established is regarded as unethical.<sup>146</sup> The original randomised clinical trials were undertaken in the USA and yielded efficacy estimates of more than 95% for the monovalent vaccine containing the Jeryl Lynn strain.<sup>121,147</sup>

Vaccine effectiveness is assessed after a vaccine has been introduced into general use, and, as such, occasional outbreaks tend to be used as the setting for estimation of vaccine effectiveness. Many outbreak studies exist with consistently lower effectiveness estimates for mumps vaccine than would be predicted by the original clinical efficacy estimates and immunogenicity results.<sup>148,149</sup> Most notable is the almost complete absence of protection offered by the Rubini strain in some studies.<sup>150,151</sup> WHO recommends that mumps vaccines containing the Rubini strains should not be used in routine vaccination programmes.<sup>152</sup> The average effectiveness of the Jeryl Lynn and Urabe strain vaccines was 77% (range, 61–91%)

### Panel: Characteristics of mumps vaccines

#### Type of vaccine

- Live attenuated mumps virus
- Primarily administered in the measles–mumps–rubella combination

#### Common strains

- Jeryl Lynn, RIT 4385, Urabe Am9, Rubini, Leningrad-Zagreb, and Leningrad-3

#### Efficacy (prelicensure)

- ~95% (Jeryl Lynn strain in original randomised clinical trials in the USA)

#### Effectiveness (postlicensure)

- ~80% (the Rubini strain is associated with low effectiveness)

#### Safety

- Local reactions, fever, rashes, and parotitis. Aseptic meningitis for the Urabe and the Leningrad strains

#### Schedule

- First dose at age 12–15 months. Possibly a second dose from age 13 months to 13 years

in outbreak studies.<sup>148</sup> In most comparative studies the Urabe strain seems to offer greater protection than the Jeryl Lynn strain.<sup>150,153</sup>

Possible causes of the moderate effectiveness of the mumps vaccine in outbreak situations are:<sup>154</sup> first, the less than optimum herd immunity in the high-risk settings for exposure—such as schools and college campuses—where outbreaks tend to happen; second, improper storage of the vaccine—eg, disruption of the cold chain, exposure to light, or delayed use—that results in reduced vaccine potency;<sup>155</sup> third, primary vaccine failure (no seroconversion after vaccination) as a result of immaturity (either age-related or genetic) of the immune system;<sup>140,141</sup> fourth, secondary vaccine failure (waning of immunity);<sup>156–158</sup> fifth, heterologous reinfection facilitated by a genotype-specific neutralising antibody response; and sixth and final, confounding and selection bias resulting in the underestimation of effectiveness, a common drawback in outbreak studies.<sup>154,159</sup> The relative contributions are unclear and somewhat controversial, especially for heterologous reinfection.

### Safety of vaccination

Adverse reactions to mumps vaccination are, in general, rare and inconsequential. Local reactions, low-grade fever, parotitis, and rashes are the most common adverse events. In a randomised clinical trial, the safety of monovalent Jeryl Lynn strain-containing vaccine and MMR combination vaccines was compared among children with seroconversion.<sup>160</sup> Monovalent mumps vaccine resulted in more local reactions than the MMR vaccines (14% vs 5–8%). By contrast, fever and rashes

were more common after MMR vaccination than after monovalent mumps vaccination (fever: 30–36% vs 22%; rashes: 17–20% vs 2%). 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.<sup>29</sup>

Aseptic meningitis, a frequent complication of natural mumps infection, is also a possible adverse reaction to mumps vaccines. Initial reports from Canada, the UK, and Japan showed a link between aseptic meningitis and the Urabe strain-containing vaccine. The reported rates were one case per 62 000 distributed vaccine doses (based on eight virologically confirmed cases) in Canada,<sup>161,162</sup> one case per 11 000 doses (based on seven cases of aseptic meningitis arising 15–35 days after vaccination) in the UK,<sup>163</sup> and one case per 6500 doses (based on 96 virologically confirmed cases) in Japan, where in one prefecture, the rate was one case per 900 doses (based on 13 virologically confirmed cases).<sup>164,165</sup> Such reports based on postlicensure surveillance have shortcomings that should be taken into account when in assessment and comparison of results. Reports relying on coincidental cases without virological confirmation cannot take into account the background incidence of viral meningitis, and reports relying on laboratory diagnosis might include cases that are not clinically relevant. Although high rates of aseptic meningitis have been reported with Leningrad-Zagreb or Leningrad-3 strain-containing vaccines, the evidence is limited for the Leningrad-3 strain and controversial for the Leningrad-Zagreb strain.<sup>166–168</sup> The Jeryl Lynn and RIT 4385 strains have not been associated with aseptic meningitis.<sup>169,170</sup> Urabe-strain-containing vaccines were withdrawn from some countries in the beginning of the 1990s; however, the use of Urabe-strain-containing vaccines (and Leningrad-Zagreb and Leningrad-3 strains) in national vaccination programmes is thought to be acceptable by the WHO<sup>152</sup> and is justified by several factors. First, aseptic meningitis after mumps vaccination is generally benign and short term with no sequelae. Second, postvaccinal aseptic meningitis is rare compared with natural mumps meningitis. In Japan, where routine mumps vaccination was discontinued in 1993, Nagai and colleagues<sup>171</sup> compared the rate of aseptic meningitis after natural mumps infection and after vaccination with three different Japanese mumps vaccine strains and reported a rate of one per 2700 virologically confirmed cases of aseptic meningitis after vaccination; however, aseptic meningitis was 17 times more likely with natural mumps infection in the same setting. Third, Urabe seems to be more immunogenic than, for example, Jeryl Lynn. Fourth and final, Urabe is cheaper—the cost of MMR vaccine containing that strain is about 50–60% of the cost of MMR vaccine containing the Jeryl Lynn strain.<sup>153</sup>

### Mumps vaccines in routine use

As of December, 2006, 109 (57%) of the 192 WHO member states use mumps vaccines in their national vaccination schedules.<sup>172</sup> The Americas and Europe have the highest usage with 97% and 94%, respectively, followed by the western Pacific and eastern Mediterranean regions with 62% and 37%, respectively. Only a few countries in southeast Asia (9%) and Africa (4%) use mumps vaccines in their national schedules. MMR vaccine is almost exclusively used, with a first dose at 12–15 months of age. Most of the mumps-vaccinating countries use a two-dose schedule (86%), with a second dose given at any age from 13 months to 13 years of age.

Since mumps vaccine was first licensed in 1968, rates of mumps have fallen substantially in countries carrying out mumps vaccination. In the USA, a reduction of 99% between 1968 and 1993 was seen.<sup>173</sup> Finland introduced national mumps vaccination in 1982 with an MMR vaccine in a two-dose schedule. 16 years later, Finland was free of indigenous mumps with only occasional imported cases.<sup>174</sup> Other European countries have experienced similarly substantial reductions.<sup>134</sup> Among the countries using a two-dose schedule, the reductions ranged from 97% to more than 99%. Among countries using a one-dose schedule, the reductions ranged from 88% to 98%. Despite the striking effect of mumps vaccination, occasional outbreaks continue to occur.

Although mumps in itself is generally a mild, self-limiting disease and severe sequelae are uncommon, almost all individuals in an unvaccinated population will eventually become infected. The sheer burden of disease justifies vaccination, and cost-effectiveness of mumps vaccination is high, especially when done through MMR combinations. The present two-dose schedule of MMR in the USA was estimated to have a cost-benefit ratio of 14.2 for direct costs (eg, medical expenses) and 26.0 when indirect costs, such as productivity losses for patients and carers, were included.<sup>175</sup> The cost-benefit ratios for mumps alone were 13.2 for direct costs and 24.9 for societal costs.

## Epidemiology

### Prevaccine era

Historically, mumps gained recognition as a disease arising in military and other similar crowded settings.<sup>176</sup> With increased urbanisation, mumps became known as a common childhood disease. Seroprevalence and notification data from European countries have been used to derive characteristics of mumps epidemiology in the prevaccination era.<sup>177</sup> During this period, mumps was characterised by interepidemic periods of 4–5 years, a peak in the force of infection among children aged 5–7 years, and a basic reproductive number of 4.4 (varying according to assumptions about mixing patterns from 3.3 to 10.3). In a summary of serosurveys from around the world, 50% of children aged 4–6 years and 90% of children aged 14–15 years were seropositive, which shows that almost all individuals in an unvaccinated population



will eventually become infected.<sup>134</sup> Average incidences of about 290 cases per year per 100 000 population were reported in Europe from 1977 to 1985.<sup>134</sup> Substantial under-reporting is likely: as much as 90% was shown by a survey from the USA.<sup>178</sup> In temperate climates, mumps shows strong seasonality with a peak in winter and spring.<sup>179</sup> Although there is no difference between the sexes in mumps infections, boys are more likely to have complications.<sup>52</sup> In the prevaccine era, mumps was one of the major causes of aseptic meningitis, and an important cause of sensorineural hearing loss.<sup>180,181</sup>

### Vaccine era

As previously described, the rate of mumps has been greatly reduced by vaccination. The resulting epidemiology of mumps is determined by the characteristics of the vaccination programme, such as number of doses, age at vaccination, and, most importantly, vaccine uptake. As uptake increases, the average age at infection increases until the degree of population immunity needed to block transmission of mumps (herd immunity threshold) has been achieved.<sup>182</sup> Insufficient vaccine uptake can lead to an increase in serious complications as the burden of disease shifts to higher age groups in which mumps sequelae are more common. Serosurveys in western Europe have been used to characterise the epidemiology of mumps in the vaccine era.<sup>183</sup> In countries with less than optimum uptake, there were large proportions of susceptible older children and adolescents. For mumps, the herd immunity threshold has been estimated to be within the range of 70–90%.<sup>177</sup> Consequently, with an effectiveness of about 80% for mumps vaccines, achievement of herd immunity with one dose might not even be possible; two doses of vaccine are probably needed.

Other features of mumps epidemiology change after the introduction of vaccination. With less exposure to mumps virus, boosting of immunity by asymptomatic reinfection becomes less common. Natural infection seems to confer lifelong immunity, but immunity can wane after vaccination.<sup>156,157</sup> Maternal antibodies are transferred across the placenta and protect against mumps during infancy.<sup>184</sup> The transition from naturally acquired immunity to vaccine-derived immunity in mothers will probably affect the degree and duration of passively acquired protection during infancy, putting infants at increased risk.

### Recent mumps outbreaks

Mumps outbreaks have not been uncommon in populations with routine mumps vaccination. Notably, the UK and the USA have had large outbreaks. In the UK, a large epidemic began in 2004 and peaked in 2005 with about 56 000 reported cases.<sup>112,185</sup> Most of these cases were in young adults attending colleges or universities—a group of susceptible individuals too old to have been vaccinated and too young to have been exposed to natural infection.<sup>186</sup>

In the USA in 2006, more than 5800 cases were reported during the mumps outbreaks. Most of these cases were seen in the American midwest, with the largest number in the state of Iowa.<sup>98</sup> Similarly to the UK, most of the cases were in young adults aged 18–24 years (median 22 years) attending college. By contrast to the UK, most of the cases had been MMR-vaccinated, in itself not surprising when a vaccine that is less than 100% effective has a high degree of uptake in a population. In Iowa, of the 1798 mumps cases with complete follow-up, 123 (7%) were unvaccinated, 245 (14%) had received one dose of MMR, 884 (49%) had received at least two doses of MMR, and 546 (30%) were of unknown vaccination status.<sup>98</sup> By the screening method, vaccine effectiveness can be estimated given the proportion of cases vaccinated and the proportion of the population vaccinated;<sup>187</sup> 90% uptake of two doses of MMR (no data are available on MMR uptake—in college students, for example) is assumed to yield an effectiveness of 87%. This estimate corresponds to 78% population immunity, which is just below the generally accepted herd-immunity levels for mumps—Anderson and May<sup>188</sup> quoted a basic reproductive number of 7·1 for mumps corresponding to 86% herd immunity. In the USA, vaccine effectiveness and uptake in combination have probably not yielded population immunity high enough to block transmission in populations such as college students, and spread of infection during these outbreaks has probably been facilitated even further by crowded environments such as college dormitories. Further information on vaccine uptake in the affected populations and more detailed analysis are needed before recommendations for future prevention can be made.

### Future research

Unresolved issues—related to mumps vaccines and vaccination—should be given high priority. First, the causes of the moderate effectiveness of mumps vaccines, and their relative contributions must be established. Second, immunological markers of immunity against mumps should be identified. Third, ideal schedules for mumps vaccination in different settings should be established to optimise the control of mumps with vaccines. Nowadays, most countries that use routine mumps vaccination have a two-dose schedule, but with very large variation in the age at the second dose—the optimum age at the second dose remains to be established. Fourth, the epidemiology of mumps in developing countries is poorly described, and should be studied in further detail. Most countries without routine mumps vaccination are developing countries, and the burden of disease must be established to assess the cost-benefit of routine mumps vaccination in those countries.

### Conflict of interest statement

We declare that we have no conflict of interest.

## Disclaimer

The findings and conclusions in this article have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any agency determination or policy.

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