# PERSPECTIVES

# RISING MUMPS CASES IN INDIA- NEED FOR INCLUSION OF MMR VACCINE IN NATIONAL IMMUNISATION PROGRAM

Nandhini Selvanesan <sup>(1)</sup>, Kanagabala Balasubramanian <sup>(1)</sup>, Kumaravel Ilangovan <sup>(2)</sup>, Vinay Kumar Krishnamurthy <sup>(1)</sup>

(1) Directorate of Public Health and Preventive Medicine

(2) John Snow India Private Limited, New Delhi

# **INTRODUCTION**

Mumps is an acute disease of children and young adults, caused by a paramyxovirus of which there is only a single serotype.<sup>1</sup> Humans are the only known natural host for the mumps virus and the virus spreads through respiratory droplets or direct contact with an infected person's saliva.<sup>2</sup> Mumps is frequently reported in children aged 5-9 years of age, although both adolescents and adults may be affected.<sup>1</sup>

Incubation period of mumps usually ranges from 16 to 18 days, while it can even extend up to 25 days. Non-specific prodromal symptoms include headache, low-grade fever, myalgia, anorexia, and malaise. The normal presentation of mumps is parotitis, or swelling of the parotid gland, or other salivary gland enlargement that lasts for around five days. Both unilateral and bilateral parotitis are possible.<sup>1</sup> People with mumps are infectious from 2 days before through 5 days after parotitis onset.<sup>3</sup> Although, natural infection with this virus is thought to confer lifelong protection<sup>4</sup>, mumps virus reinfections do seem to occur.<sup>5</sup> Complications of mumps occur with or without parotitis or other salivary gland swelling and generally encompass conditions such as orchitis, oophoritis, mastitis, pancreatitis, hearing impairment, meningitis, and encephalitis. Nephritis, myocarditis and other sequelae like paralysis, seizures, cranial nerve palsies, and hydrocephalus have also been reported occasionally. Complications associated with mumps are usually more common among adults than children.<sup>6</sup> Despite its generally low mortality rate, the potential to cause profound morbidity and complications underscores the importance of preventive measures, with vaccination emerging as the most effective solution.7

# **Global and Indian Disease Burden:**

Globally, there is a substantial mumps case burden, particularly among countries where the vaccine is not routinely administered. With 100–1,000 cases per 1,00,000 people reported in countries without routine mumps immunization programs, the mumps incidence worldwide is still rather high.<sup>8</sup>

A study on the disease burden of seven vaccinepreventable diseases in Shandong province, China, from 2013 to 2017 reported that mumps had a relatively low disease burden both at the population level (0.43 DALYs per year) and at the individual level (0.27 DALYs per 100 infections).

India has a high disease burden, as evidenced by the reports of both cyclic outbreaks and sporadic cases from every part of the nation. Mumps resulted in many outbreaks in India. According to the IDSP and IAP-web-based network, between September 2009 and May 2015, 2892 mumps cases were reported.<sup>9</sup> Between July and September 2017, IDSP documented 15 outbreaks and 260 cases of mumps within the region.<sup>10</sup> Mumps is a significant public health concern in India, yet insufficient data from various regions underestimate its actual burden.<sup>11</sup>

India reported 764 mumps cases between 2021-22 as per Global Health Observatory (GHO) data repository, indicating a substantial burden of mumps, particularly affecting children.<sup>12</sup> The rising number of mumps cases in India among children in Maharashtra, Uttar Pradesh, Odisha, and Rajasthan, is a concerning trend.<sup>13-15</sup> The fact that this surge has been observed after 4-5 years raises questions about the factors contributing to the resurgence of the disease in these regions. In October and November 2023, mumps outbreaks in Idukki and Palakkad in Kerala, Sivagangai in Tamil Nadu, Udupi in Karnataka, and Rajnandgaon in Chhattisgarh, served as poignant reminders of the challenges posed by this infectious disease.<sup>13</sup>

In Tamil Nadu, During the year 2021-22, only 61



Please Scan this QR Code to View this Article Online Article ID: 2024:04:04:10 Corresponding Author: Nandhini Selvanesan e-mail : preethiselvanesan@gmail.com cases of mumps were reported. In the year 2022-23, we saw a slight increase with 129 number of cases of mumps. In 2023-24 there was a dramatic increase compared to the previous two years, a totally 1,091 cases of mumps were reported during this period. This increase in incidence could be attributed to outbreak of mumps in 2023-24.<sup>16</sup>

#### Mumps orchitis and Male infertility:

Orchitis is the most common complication of mumps in post-pubertal men, affecting about 20%-30% of cases: 10%-30% are bilateral. Orchitis usually occurs 1-2 weeks after parotitis.<sup>17</sup> Of the affected, 30%-50 % show a degree of testicular atrophy.Within the first few days of infection the virus attacks the testicular glands, leading to parenchymal inflammation, separation of seminiferous tubules, and perivascular interstitial lymphocyte infiltration. The tunica albugenia forms a barrier against oedema, and the subsequent rise in intratesticular pressure leads to pressure-induced testicular atrophy.<sup>18</sup>

Adamopoulos et al.<sup>19</sup> studied the effects of mumps orchitis on Leydig cell function and found low testosterone levels, elevated luteinizing hormone levels and an exaggerated pituitary response to luteinizing hormone-releasing hormone (LHRH) stimulation in the acute phase. Whilst basal testosterone concentrations returned to normal after several months, mean basal follicle stimulating hormone and luteinizing hormone concentrations remained significantly increased at 10 and 12 months after the acute phase.

The causal link between mumps orchitis and anti-sperm antibodies has been unclear. Although the antibodies were suspected to impair fertility, Kalaydjiev et al.<sup>20</sup> demonstrated that both the incidence and the level of serum anti-sperm antibodies among mumps orchitis patients were low, and did not support the hypothesis of an enhanced humoral immunity against spermatozoa.

Mumps orchitis rarely leads to sterility but it may contribute to subfertility. It can also can lead to oligospermia, azoospermia, and asthenospermia (defects in sperm movement). Unilateral disease can significantly, but only transiently, diminish sperm count, mobility, and morphology. Impairment of fertility is estimated to occur in about 13% of patients, while 30%-87% of patients with bilateral mumps orchitis experience infertility.<sup>21</sup>

### Vaccine efficacy and safety:

Live attenuated mumps vaccines based on live attenuated virus strains including the Jeryl-Lynn, RIT 4385, Leningrad-3, Leningrad-Zagreb, Urabe Am9, S79, Rubini, and others, have been available since the 1960s. However, due to the low level of seroconversion obtained with the Rubini strain, WHO has recommended that this strain should not be used in national immunization programmes. These vaccines are produced by growing the virus in cell cultures or in embryonated chicken eggs. The virus is then purified, formulated with a stabilizer such as gelatine or sorbitol and lyophilized. Mumps vaccines are available as a monovalent vaccine, a bivalent measles-mumps vaccine, or as a trivalent measles-mumps-rubella vaccine (MMR).<sup>22</sup> The mumps vaccine, commonly administered as part of the measles, mumps, and rubella (MMR) combination, has shown high efficacy in preventing mumps and its complications. One dose of MMR vaccine is 93% effective against measles, 78% effective against mumps, and 97% effective against rubella. Two doses of MMR vaccine are 97% effective against measles and 88% effective against mumps. The vaccine is welltolerated, with adverse events being rare and mild.<sup>23</sup>

## **Global Impact of Mumps Vaccination Programs:**

According to WHO, mumps was adopted in the vaccination schedule of 57% of the member countries (110 countries) in 2005.<sup>24</sup> Many countries did not introduce mumps vaccine into their national programs until immunization coverage with BCG, poliovirus, diphtheriapertussis-tetanus, and measles vaccines exceeded 80%, often above 90%. Countries that introduced mumps vaccine into their immunization programs exhibited a rapid decline in mumps morbidity. Countries administering MMR vaccine at high coverage levels reported sharp reductions in mumps incidence.<sup>25</sup> MMR vaccine simultaneously provides protection for measles, mumps and rubella.

The mumps vaccine, as part of the MMR vaccine, has been instrumental in significantly reducing the incidence of the disease since its introduction in 1967 in the United States<sup>26</sup> The success of vaccination programs has been noteworthy, with the incidence of mumps dropping to less than 0.1 case per 100,000 people in many developed countries by 2001<sup>27</sup> This achievement demonstrated the effectiveness of widespread immunization in controlling the disease, marking a substantial triumph in public health.<sup>28</sup>

At the end of 2007, 114 countries were administering mumps vaccine, compared with 104 countries at the end of 2002. However, as of 2012, 120 (62%) countries have adopted routine mumps vaccination in their NIPs<sup>29</sup> The reduction in mumps incidence varies from 88% to 97% in countries adopting single or two doses of vaccine, respectively.<sup>30</sup> A recent meta-analysis in China found the overall vaccine effectiveness for mumps-containing vaccine (either one dose or two doses) to be 85% (95% CI 76%-90%) from cohort studies and 88% (95% CI 82%-92%) from case-control studies.<sup>31</sup>

MMR was introduced in state immunization program of Delhi in 1999 as a single dose administered between 15-18 months of age (MMR-I).<sup>23</sup> There is no effectiveness data available from India since mumps is not part of NIP and only few states and Union Territories are providing mumps vaccine in form of MMR vaccine.<sup>12</sup> Though the MMR vaccine is offered by private sector, the coverage and field-efficacy data are not available. Yadav, et al.<sup>33</sup> reported high mumps seropositivity rates (96-100%) with use of single dose of MMR vaccine in Delhi children. In another Indian study conducted amongst 1-10 year old children in Pune, a single dose of MMR (with Leningrad-Zagreb mumps virus strain) was able to maintain mumpsspecific IgG (seropositivity rate) in 95% after 6 years.<sup>34</sup>

# The National Immunization schedule:

Choice of vaccines in National Immunization Schedule warrants careful decision and periodic reviews. 1978, India adopted the Expanded Programme on Immunization (EPI) promoted by World Health Organization (WHO). In 1985, EPI was renamed as Universal Immunization Program (UIP). Measles vaccine is administered at 9 months of age considering the morbidity and mortality caused by the disease. Poor immune response to measles vaccine is noted in infants less than one year of age, which necessitates administration of second dose for immune protection.<sup>35</sup> Though one dose of mumps vaccine confers 88%-98% protection in the community, accumulated global experience has shown that 2 doses of mumps vaccine are required for a long-lasting protection.<sup>36</sup> Measles-Mumps-Rubella (MMR) vaccine in a two dose schedule has successfully eliminated measles, mumps and rubella from many developed countries.37

However, the Government of India (GoI) has announced its decision to include the rubella vaccine in the form of a bivalent Measles-Rubella (MR) vaccine in its Universal Immunization Program (UIP).<sup>38</sup> The two-dose MR vaccine shall be provided at 9 months in place of the standalone measles vaccine, and at 16–24 months along with the first booster of the Diphtheria-Tetanus-Pertussis (DTP) vaccine.<sup>39</sup> The main reasons why GoI has not considered mumps for inclusion in the National Immunization Program are: a) the disease is not considered a serious public health issue, b) lack of published data on the community burden of mumps, and c) lastly the higher cost of the MMR vaccine in comparison to MR vaccine.<sup>40</sup> However, this is not the fact rather many outbreaks of mumps have been witnessed. The replacement of the MR (Measles, Rubella) vaccine with the MMR vaccine within the national immunization schedule (NIS) is suggested as a prospective remedial action, supported by extensive research on mumps-containing vaccines conducted in India.<sup>41</sup>

# Factors contributing to resurgence of mumps:

Several factors may have contributed to this recent rise in mumps cases across India. In India, children are offered the MR vaccine in a two-dose strategy for children at 9 and 15 months to cover measles and rubella but not mumps.<sup>42</sup> MMR vaccine is only available in the private sector in India and remains out of bounds for over 80% of the children of the country.<sup>43</sup> One of the important reasons for mumps resurgence in India, which has predominantly a naive child population due to the absence of mumps component in UIP, is because prior to introduction of vaccination, mumps was an epidemic disease, with a cycle of 4-5 years.<sup>44</sup> Additionally, overcrowding, inadequate sanitation, and limited and remote access to healthcare facilities in certain regions may facilitate the rapid spread of the virus.<sup>45</sup>

# Challenges and Opportunities in Implementing MMR Vaccination:

Funding is identified as a key challenge for achieving measles and rubella elimination targets. SAGE working group in 2013 found that the vaccine requirement of combined vaccine will increase directly in proportion to decrease in measles only vaccine. Moreover, there is no anticipated shortage in the supply of combined vaccine, and can be completely obviated by the planned phase-out of measles-only vaccines and gradual introduction of combined vaccine.<sup>46</sup>

Ensuring vaccine security (defined as the consistent availability of high-quality vaccines at affordable price) requires robust collaboration with industry and stakeholders. The introduction of the combined MMR vaccine is estimated to increase the cost per dose by approximately INR 37.89 -INR 51.42.<sup>41</sup> However, given the inevitability of cyclical mumps outbreaks in the absence of vaccination and the existing burden of rubella, the inclusion of the MMR vaccine in the immunization schedule should be prioritized.

Measles with higher secondary attack rate and mortality is given priority amongst the vaccine preventable diseases. States have been advised to boost immunity against measles by providing two doses of measles vaccine. One given at 9 months of age as a part of national immunization schedule and the second measles vaccine dose administered through catch up campaign or as MMR vaccine. States with immunization coverage more than 80% administer second dose in routine immunization by MMR or measles vaccine.<sup>47</sup>

Mumps appears to pose a notable public health challenge in India, yet it often goes unnoticed due to the lack of a robust surveillance and documentation system. Also, it is still not a notifiable disease. The Indian Academy of Pediatrics (IAP) has argued very strongly for the inclusion of the MMR vaccine instead of the MR vaccine because the children may get extra protection using the same logistics and operational feasibility.

#### **Cost-effectiveness analysis:**

Data from industrialized countries have proved the cost-effectiveness of mumps when translated to reduced school- and work-absenteeism and reduction in associated long term complications and costs of associated hospitalization. As per an economic analysis of mumps vaccination in US, the average cost per case of mumps prevented was \$3614, which was greater than costs incurred with prevention of single measles case (\$2207). The total annual costs averted by MMR vaccination was \$7,878,378,382 with a benefit-to- cost ratio of 0.49.<sup>48</sup> Similarly, the additional benefit of routine mumps vaccination exceeded additional costs of vaccine in a cost-effectiveness analysis in Japan.<sup>49</sup>

## **CONCLUSION**

Although mumps is generally a benign and selflimiting disease, the potential for missed complications cannot be overlooked. Epidemiological shifts in the affected age group and inadequate treatment practices can lead to significant harm to patients. The occurrence of repetitive mumps outbreaks in the community and the epidemiological transition of disease affecting older age group with a higher risk of complications emphasize the need for an effective vaccination policy of MMR vaccine in India.

Given the potential complications of mumps orchitis, including subfertility, oligospermia, and infertility, vaccination is essential in preventing these outcomes. The MMR vaccine significantly reduces the incidence of mumps and its complications, including orchitis. Therefore, widespread vaccination is crucial to protect reproductive health and minimize long-term fertility issues.

Vaccination, particularly the Measles-Mumps-Rubella (MMR) vaccine, has proven to be an effective and cost-effective solution in preventing mumps and its complications. The success of mumps vaccination in other countries demonstrates its potential to reduce disease incidence, school and work absenteeism, and the associated healthcare costs. The inclusion of the MMR vaccine in India's National Immunization Program could significantly decrease the burden of mumps, especially among children and young adults, while preventing severe complications such as orchitis and infertility.

Although the cost of the MMR vaccine is a concern, economic analyses show that the long-term benefits, including reduced healthcare expenditures and fewer complications, far outweigh the initial investment. The costeffectiveness of mumps vaccination has been demonstrated in other countries, and similar benefits could be expected in India. Given the high burden of disease, the inclusion of the MMR vaccine in India's immunization schedule should be a priority for improving public health outcomes and reducing the financial burden on families during outbreaks.

Just because of the lack of proper documents and studies in India when such evidence is already available elsewhere in the world, we cannot neglect one of the major vaccinepreventable diseases, for which an effective vaccine exists. The use of the MR vaccine in place of the MMR vaccine is considered a 'missed opportunity' to target a significant VPD that also has a significant impact on child health. By ensuring access to and promoting the uptake of the MMR vaccine, we can effectively mitigate the risk of mumps outbreaks, safeguard public health, and foster a healthier future for all individuals across the nation.

#### **CONFLICT OF INTEREST**

None

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