Comment

No definitive evidence for L-Zagreb mumps strain associated aseptic meningitis: a review with special reference to the da Cunha study

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Abstract

The study by da Cunha et al. published in 2002 reported that MMR vaccine containing L-Zagreb mumps strain manufactured by Serum Institute of India Ltd. caused a high incidence of aseptic meningitis (AM) from routine surveillance during two mass immunization campaigns (MIC) conducted in 1998 in two states in Brazil. Since the results were contrary to those in India, Egypt and Bahamas, a critical analysis of the study was done. Several inconsistencies were found in the study, which undermined the conclusions drawn. Two similar studies from Brazil reported similar results. Review of these studies and those done on the vaccine from Zagreb, Croatia showed that in no study the L-Zagreb mumps virus has been isolated from cerebrospinal fluid (CSF) of an AM case. Isolation of the vaccine virus is necessary for definite causal association of AM with the vaccine. There is no such evidence to causally link MMR vaccine containing L-Zagreb mumps strain with AM.

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We recently collected retrospective data on the Indian experience on using MMR vaccine with Leningrad-Zagreb mumps strain manufactured by Serum Institute of India Ltd. for a period of 5 years, which has been published in Vaccine, October 2004 [1]. The study found the incidence of aseptic meningitis (AM) to be one in 95,361.5 doses administered (95% CI 0.5033–1.5519 per 100,000). Another retrospective study in India showed no case of AM in more than 57,000 doses of this vaccine [2]. Reported incidence of AM with the same vaccine in Bahamas mass immunization campaign was 0.96 per 100,000 doses used [3]. A prospective study done on the mass campaign in Egypt found similar results with respect to AM [4]. On the other hand, the study by da Cunha et al. [5], which was published in 15 January 2002 issue of Vaccine showed exactly opposite results on the incidence of AM with this vaccine, compared to these four studies from three countries. In the study by da Cunha et al., data from routine surveillance during two mass immunization campaigns (MIC) conducted in 1998 in two states in Brazil with MMR vaccine using Leningrad-Zagreb mumps strain, were analyzed to estimate the risk of vaccine-related meningitis and mumps. The two states were Mato Grosso (MT) and Mato Grosso do Sul (MS). Increase in the incidence of the two diseases i.e. AM and Parotitis was reported in both states, 3 weeks after the vaccination campaigns. The estimated number of doses applied per one case of vaccine-related meningitis ranged from 6199 (95% CI: 4,854-8,058) to 19,247 (95% CI: 12,648–29,513) depending on the diagnostic criteria used and state of the patients. It was 300 doses (95% CI: 286–317) for each case of mumps.

After our studies showed the situation to be different in India and Egypt, we became acutely aware of the unnecessary adverse impact the da Cunha study could have caused on the worldwide use of MMR vaccine containing L-Zagreb mumps strain, and the immunization programmes in general in some countries. The report of high incidence of AM with the MMR vaccine containing L-Zagreb mumps has resulted in some countries not using the vaccine for mass vaccination campaigns. Instead these countries used, the bivalent...
measles-rubella vaccine or the monovalent measles vaccine rather than the more expensive Jeryl Lynn MMR vaccine [6]. An opportunity to control mumps disease was thus lost. Considering the gross differences in the results between the studies from three countries and the present study and its adverse impact on immunization programmes in some countries, one needed to critically analyze the Brazil study. On analysis, to our surprise, many questions arose, especially on the methods used and the conclusions drawn from the results. We have following issues to ponder over this article.

1. The diagnosis of aseptic meningitis was based on two criteria: clinical and laboratory. Doctors conducting immunization and nurses made the clinical diagnosis of AM in this study. It is stated that the doctors/nurses who made clinical diagnosis of AM, had access to laboratory results. However, in the absence of documented laboratory results on the notification form, only clinical criterion becomes unreliable. The differences in the incidence of AM with two criteria are also high, which makes the clinical criteria redundant.

2. The target populations in MS and MT were 473,718 children and 580,587 children respectively. The vaccinated populations were 442,962 children (93.5% coverage) and 402,927 children (69.4% coverage) in MS and MT respectively. But the article gives data of AM in targeted populations. It does not give a comparison of incidence of AM in vaccinated and unvaccinated target populations. In absence of knowing the incidence of AM in 30,756 (MS) and 177,660 (MT) unvaccinated children associating the AM only to the vaccine is erroneous.

3. The incidence of AM was 1 in 13,415 doses (MS) and 1 in 6199 doses (MT) with the clinical criteria. The same with laboratory criteria was 1 in 19,247 (MS) and 1 in 7900 (MT) unvaccinated children associating the AM with laboratory criteria was 1 in 19,247 (MS) and 1 in 7900 (MT). It is estimated to 39 cases in 208,416 unvaccinated children i.e. 1 case per 5344 children. Since the vaccine-unrelated incidence is more than vaccine-related, this suggests an epidemic of wild mumps or other viral meningitis at the time of campaign. When we know that there was an epidemic going on, the cases due to infection could get attached to vaccine, which indicates that even the 1 in 16,918 doses incidence may not be realistic.

4. The study also found a mumps outbreak (?) following the campaign with incidence of parotitis 1 per 300 doses i.e. 0.33%. This is far below the rates reported in the worldwide literature with different mumps vaccines [7].

All these points seriously undermine the conclusions drawn by the authors on the incidence of AM with L-Zagreb containing MMR vaccine. Aseptic (viral) meningitis is known to be endemic in Brazil [8–10]. In a study in aseptic meningitis patients in Bahia during non-epidemic periods, it was found that enteroviruses, and leptospira were the commonest causes of aseptic meningitis [8]. Though lymphocytic meningitis with concomitant mumps decreased in Salvador after introduction of mumps vaccine, lymphocytic meningitis continues to be there [9]. In another study in Brazil in meningitis cases, 21% of the total meningitis cases were due to viral infection [10]. Moreover, person-to-person spread of these viruses causing aseptic meningitis at places of overcrowding is known [11]. During the campaigns, there is congregation of huge number of subjects for vaccination. Since mumps vaccine virus does not spread from vaccinees to contacts [12], spread of some circulating virus seems to be responsible for high number of aseptic meningitis cases. This fact is additionally proved by the fact that the incidence of post-vaccination AM in two states (1 in 19,247 in MS and 1 in 7900 in MT) was dependent on the pre-vaccination incidence of AM in these states (0.71 cases per week in MS and 1.9 cases per week in MT). Since children are more prone to viral meningitis than other age groups, the epidemic of AM was limited to the target group.

Coincidental meningitis after vaccination may occur as a result of other viruses and even wild-type mumps virus [13]. Moreover, the clinical symptoms and signs, including lymphocytic pleocytosis in the CSF, of the natural disease and the vaccine-associated AM are similar [14].
Two similar studies have been reported from Brazil on similar campaigns with the same vaccine [15.16]. These studies also reported a high incidence of AM after MMR campaign in Brazil. Of all three studies in Brazil [5.15.16], the study by Arruda et al. tested CSF of eight cases of AM for mumps virus and all of them were found to be negative [16], indicating that these cases were neither due to wild mumps virus nor MMR vaccine.

For the MMR vaccine containing L-Zagreb mumps strain from Zagreb, Croatia, Kraigher, in a personal communication [17], reported a risk of two cases per 100,000 doses. Beck et al. [18] reported distribution of 10 million doses of L-Z in Yugoslavia and elsewhere with rare reports of aseptic meningitis. Tesovic et al. [19] found 50 cases of AM following vaccination with an estimate of nine cases of aseptic meningitis. [18] reported distribution of 10 million doses of L-Z in Yugoslavia and elsewhere with rare reports of aseptic meningitis. Tesovic et al. [19] found 50 cases of AM following vaccination with an estimate of nine cases of aseptic meningitis per 10,000 doses. However, routine CSF virudal cultures were negative in all but one case, where Coxsackie virus B4 was isolated.

In fact, there is no published report, which has shown isolation of L-Zagreb mumps virus in CSF of an AM case. This is in stark contrast with Urabe vaccine, which was proved to cause meningitis in vaccine recipients by nucleotide sequence analysis of post-vaccination isolates of mumps virus [20]. Even isolation of a Jeryl-Lynn-like strain was reported in one patient who developed AM after vaccination in Germany [21]. Although, the causal association of aseptic meningitis with MMR vaccine can only be confirmed when mumps virus isolate is definitely identified as the vaccine strain [7], even with MMR vaccine can only be confirmed when mumps virus isolate is definitely identified as the vaccine strain [7], even with MMR vaccine can only be confirmed when mumps virus isolate is definitely identified as the vaccine strain [7], even with MMR vaccine can only be confirmed when mumps virus isolate is definitely identified as the vaccine strain [7], even with MMR vaccine can only be confirmed when mumps virus isolate is definitely identified as the vaccine strain [7], even with MMR vaccine can only be confirmed when mumps virus isolate is definitely identified as the vaccine strain. [22]. The term AEFI, when used appropriately, denotes that the occurrence of such an event after an exposure (immunization) does not imply by itself that the event was caused by the exposure. A temporal relation of an outcome to a given exposure is an insufficient condition for the inference of a causal relation [23]. We sincerely feel that the authors of this study have not been able to prove an unequivocal causal association of the epidemic of AM with the MMR vaccine used in the MIC, and moreover, there is no definitive evidence to causally link L-Zagreb mumps strain with AM.

References