Review of: "[Short Communication] Measles: 1963-2023, Immunology of a Morbillivirus"

Paolo Bellavite

Potential competing interests: No potential competing interests to declare.

Qeios ID: U2OBT7

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Paolo Bellavite (Verona, Italy)
MD, independent researcher, retired professor of General Pathology at Verona University

Email: paolo.bellavite@gmail.com

The paper is a short review of the immunology of measles virus (MeV). The presentation is valuable, but there are some aspects that should be better covered and discussed, particularly concerning the disease epidemiology and the vaccine effectiveness.

The entire discussion of the immunological basis of the response to MeV, the cells involved and the role of the various cytokines is interesting, correct and well detailed. It would be interesting to know more comparative details with what happens in the immune system following "artificial" infection with an attenuated strain as a vaccine. In particular, it would be very important to know whether the described phenomena of partial immunosuppression also occur with the MeV of the vaccine.

In various points, including the abstract, the article mentions a very high mortality rate of measles, but it should be better specified (also in the introduction) that this essentially concerns resource-limited countries. Several environmental factors undoubtedly contributed to the decrease of severity of the disease, besides immunization [1].

The work seems to give all the importance of the decrease of measles to vaccinations, but careful studies have shown that mortality from this disease in Western countries had practically dropped to zero at the beginning of the 1980s, even before the introduction of vaccination. In Italy, vaccination against measles began to be recommended in 1976, but it became a mass immunization practice only after 1999, when trivalent vaccination (MMR) was introduced. At that time, mortality from measles was 5-10 cases per year, in a population of 50 million inhabitants (of which less than 10% vaccinated), i.e., 1-2 cases per 10 million inhabitants [2]. Already in 1975 measles mortality in England was defined as "unimportant" and the rare deaths recorded only concerned children with congenital defects or immunosuppression [3]. Regarding morbidity, figure 3C of the cited work [2] demonstrates that it was constantly decreasing throughout the 20th century, so that it is very difficult to observe a change in the trend following the introduction of mass vaccination. For these

reasons, the sentence in the Abstract “The introduction of MMR immunisation previously and after reduced mortality to around 110,000 annually” it is not acceptable without careful clarification of the limits within which it applies.

The Author suggests that MeV remains “the third pathogen to potentially be eradicated”. However, there are several indicators that the strategy of wanting to eradicate measles by increasing vaccination coverage does not and cannot work. Dutch researchers [4], observing that measles is present even in highly vaccinated populations, asked themselves the question of how high coverage should be to ensure that no major outbreak can break out. This largely depends on the contagiousness of the virus, which is basically expressed by the basic reproduction number R0 (i.e., how many people a sick person infects in a non-vaccinated population). The R0 value indicated in the Introduction is in the range 12-18. For a vaccine that provides complete protection, epidemiological theory holds that the coverage needed to stop the spread of the microbe (Population coverage, %Pc) is:

%Pc = 100-100/R0

For example, if R0 is 15, the coverage % needed will be 100-100/15, i.e., 100-6.666 = 93.33%. The problem at this point, however, is that this calculation assumes 100% effectiveness. It should be remembered that the vaccine is very effective in causing "seroconversion" (as reported in the technical data sheets) but is less effective "in the field". The data provided by the Italian Istituto Superiore di Sanità demonstrate that in the Italian outbreak of 2017 the field effectiveness (VE) of the vaccine was around 80%. Recent European epidemiological data shows that among measles cases that occurred in 2022, 20% of children were vaccinated and 28% of adults were vaccinated (https://www.who.int/data/gho/data/indicators/indicator-details/GHO/measles---number-of-reported-cases). Also very interesting are the data from Kennedy and Poland [5] who, 17 years after regular vaccination with two doses, found a drop in neutralizing antibodies (normal neutralizing Ab titer of 120 mIU/mL) in 42% of the subjects. The authors also tested a third dose, which led to a transient increase in antibody titer, but immunity from a third dose returns to pre-vaccination levels in approximately 1 year. This suggests that an individual has a predetermined immunological set-point, and any protection provided by a third dose of MMR will be temporary [5].

When a vaccine shows waning or incomplete immunization power, the correct formula to use, which takes into account its effectiveness “on the field” (VE), is:

%Pc = (100-100/R0)/VE

Therefore, with the above example, we have %Pc = 93.33/0.8 = 116.7 % of the entire population. This is obviously impossible.

Moreover, reports of pauci-symptomatic measles cases in vaccinated individuals [6] indicate that waning measles immunity among vaccinated individuals may result in attenuated disease. Compared to measles cases in nonimmune or indeterminate individuals, cases in vaccinated individuals were less likely to report fever, rhinitis, and cough. This also means that many cases can go unnoticed and still spread the virus.

All these facts suggest that vaccination is not fully effective and that the “eradication” mentioned in the paper is probably a

myth. Recent outbreaks in highly vaccinated countries have totalled 1092 cases in UK in 2019 and 1275 cases in USA in 2020, the highest rate since 2009 in that country (https://www.who.int/data/gho/data/indicators/indicator-details/GHO/measles---number-of-reported-cases). In reality, eradication in a couple years had been predicted as early as 1965 in the USA - “The taming of a virus”, as claimed by The New York Times at that time [7] - but it was never successful.

These considerations are not intended to argue that individual measles vaccination is useless, but only to reduce its importance in controlling the disease, through the achievement of herd immunity, compared to the other factors considered. The claim of wanting to eradicate the disease through extreme coverages achievable only with compulsory vaccination, as happened in various countries even recently, seems more a political than a scientific goal.

Measles is a serious disease and must be fought, starting from understanding the mechanisms of infection and clinical damage. We all agree that disease should be "understood better" in order to find the remedies, which are not only compulsory vaccination for everyone, but also the improvement of conditions of life (household size, education, surrounding conflicts) and nutrition (underweight prevalence, vitamin A deficiency, general malnutrition)[1, 8, 9].

Further important aspects that need to be addressed for possible changes before publication:

1. The abstract focuses on the epidemiology of measles and the invention of the vaccine, but actually it does not summarize the major content of the article, which mainly concerns the mechanisms of penetration of the virus and the changes induced in the immune system.
2. Furthermore, where the development of the measles vaccine is discussed, not only the Edmonston strain should be mentioned, but also the “Schwarz” and “Moraten” strains, which are the most used today [10]
3. The quotes [1][2][3] at the end of the first paragraph of the Introduction do not concern the content of the topic covered by the same paragraph.
4. The second paragraph reports the cloning of a virus in 1995 and cites supplementary materials, but it is difficult to find which supplementary materials, among the many provided, this is about.
5. The introduction mentions the "Efficacy and safety" of the MMR vaccine and also the quadrivalent one, which includes the addition of the varicella component. In reality, the text only talks about effectiveness but not about safety. A recent survey on the paediatric population in an Italian region [11] found, through active pharmacovigilance, very high rates of serious adverse reactions causally associated with the measles, mumps, rubella and varicella (MMRV) vaccine and precisely 38 serious AEFIs/1000 enrolled [12]. If compared to a cohort of 430,000 Italian children, this corresponds to 16,340 serious adverse reactions. The latter aspect is fundamental, above all for the evaluation of the relationship between risks and benefits of a vaccine in epidemiological conditions in which diseases are rare or not very serious.
6. The first paragraph of the section “Development of Measles Research” states that “the MeV particle utilised one predominant receptor discovered in 1993 (CD46) that could be predominantly blocked by either polyclonal or monoclonal antibodies akin to a pharmacological antagonist preventing cellular infection etc.” However, the CD46 receptor is used by the attenuated virus for vaccination purposes, not by the WT virus [10, 13, 14]. This is an important clarification in a review of the molecular mechanisms of infection.

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