Author's response to reviews

Title: Deficiency in immunity to poliovirus type 3: A lurking danger?

Authors:

Claudia Reinheimer (claudia.reinheimer@kgu.de)
Imke Friedrichs (imke.friedrichs@kgu.de)
Holger F Rabenau (rabenau@em.uni-frankfurt.de)
Hans W Doerr (h.w.doerr@em.uni-frankfurt.de)

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Author's response to reviews: see over
Dear Editor,

Dear Reviewer #1 and #2

thank you very much for the opportunity to revise our manuscript entitled “Deficiency in immunity to poliovirus type 3: A lurking danger?”

We want to thank Reviewer #1 and #2 for the helpful suggestions for improvement. We took account of all the notes (see below) and hope we implemented the suggested corrections satisfactorily and as requested. We furthermore paid attention to the correction of language and syntax.

Our modifications are red-marked in the manuscript.

1) Interestingly, an age-related drop in immunity could be found. The lowest neutralizing antibody titres were detected in the age group of 15 to 29 years. The authors should include a possible explanation of this phenomenon. Is it due to the IPV vaccination? How could the immunity against PV3 be improved. What about the age group of <10 years?

Thank you for this suggestion – this, for sure, is an aspect we have to discuss.

We inserted the following paragraph:

“An interesting aspect is that lowest seroprevalences of antibodies to PV1 - 3 were observed in the group aged 1-14 years (Fig. 2). This phenomenon may be coherent with the implementation of IPV in Germany in 1998 [1, 2]. When OPV was used, no such gap was observed [21]. Remarkably, immunity to PV3 is not only the lowest among the types but also in all of our defined age-groups (Fig. 2). This phenomenon has previously been described [18, 19, 20, 21, 22, 23, 24, 25]. Furthermore, our study confirms an aspect that also has previously been observed: the immunity-level to PV3 is the lowest among all types of poliovirus [16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26]. This phenomenon of deficiency can be explained by a reduced antigenicity of PV3 when compared to PV1 and PV2 [26]. This should be an aspect of interest in future vaccine development.”

2) The writing style is quite clunky, I would recommend having a colleague read through it who has a better command of formal English and grammar, as is required with publishing peer-reviewed research in English language journals. The style is too informal for me; referring to the polio eradication programme as a ‘happy-go-lucky situation’ and referring to an “inwards” view will be too much for most readers.

We revised our style and diction and hope the modifications are satisfying.
3) What I find interesting about the sero-prevalence is that the PV3 prevalence reduces much more than PV1 or PV2. What are the hypothesised reasons for this? My understanding is that children are currently vaccinated with IPV, that contains all three polioviruses? Has the formulation or even the brand changed during the study? However, judging by the age-distribution of your 2010 cohort, you have a mixture of people that as children would have been vaccinated with OPV or IPV. For example people over 30 in 2010 would have been <2 years of age in 1980. This is before the switch from OPV to IPV. Perhaps analysing your data with this in mind may explain your observations. Age-specific analysis of this kind of data is very important.

Thank you for this suggestion and see 1)

4) Do you have records of the routine coverage going back to when these cohorts were born? It would be interesting to compare the coverage achieved and the current sero-prevalence.

Regrettably, we do not have any data regarding this aspect.

5) Please observe the criteria for writing research articles for the journal you have submitted to. Please observe how you refer to abbreviations. I understand that each should be in full when you first use them. Objective should not have a separate heading, and results and conclusion should be separate.

Thank you very much. We once more read the instructions carefully and amended the manuscript accordingly.

6) Referring to a range of sero-prevalences with 95%CI is inappropriate

Thank you for this note.

We are not quite sure if we understand your comment correctly. As it is common we have used the 95%CI, to describe the upper and lower limit and the reliability of the value.

7) Use epidemiological terminology when referring to a study population. ‘Collective’ is not the correct term. Paralyzing ‘courses’ is not the correct term.

Thank you for this note. We changed “collective” into “study population” or “cohort” and “course” into “paralytic polio” or “fatal case”.
8) Statistical tests should be specified concisely and without confusion. This is not done here.

We inserted the following sentence in the methods-part of our manuscript: “Statistical analysis was done by using the 95% confidence interval (95%CI) with a significance level of p=0.05, Chisquare test or the Fisher’s exact test in the case of low sample numbers by using the program BIAS for Windows 8.3 (Epsilon Verlag, Hochheim Darmstadt 2007)”

9) Sero-prevalence is not a rate.

Instead of the terminus “rate” we now modified into “levels of seropositivity” or “seroprevalence”. For example: “Highest levels of seropositivity were detectable for PV2: seropositivity was 90.8% (87.5-90.6), 91.3% (89.3-93.1) and 89.8% (88.7-90.9) in 2001, 2005 and 2010, respectively. Lowest seroprevalences were observed for PV3: values ranged between 76.6% (72.2-80.6), 69.8% (66.6-72.8) and 72.9% (67.8-77.5) in 2001 and 2005 and 2010, respectively. For 2005 and 2010, a significant lower immunity to PV3 was detected.”

10) The figures are not good. At least use a box-plot to represent your data.

Thank you for this hint. We modified our figures.

11) A non-significant test is not represented by a figure. It is represented by a statistical test.

Please apologize our imprecise use of language – we changed the terminus “95%CI are illustrated by verticals” into “95%CI are represented by verticals” in our figures.

12) There are more sero-prevalence studies than you have cited. Whilst there aren’t many, I disagree with your comment that they are ‘barely available’.

Thank you for this suggestion. We inserted the studies by Grotto et al and Trivello et al and furthermore one investigation by a Chinese group (Liu GY et al., Surveillance on poliomyelitis neutralization antibody level in the border areas in Jilin province. Zhongguo Yi Miao He Mian Yi. 2009 Jun;15(3):249-50). The abstract is available in English, see PubMed-ID 20084894]

The modified paragraph is:

“Immigrants from less developed countries in North-East Italy were seropositive to PV 1,2,3 in 98.3%, 99.6% and 95.9%, respectively [23]. Furthermore in Israel, 18-year-old soldiers recruited to the Israel Defence Forces were tested for antibodies to PV1,2,3 were and found to be protected in 98.7%, 99.6% and 96.4%, respectively [24]. In Jilin Region, China, 95%, 94.6% and 92.3%, had positive test results of NA against Polio type 1,2,3, respectively [25]. In comparison to our PV-seroprevalences (and also to former studies from Germany [16, 18, 19, 20, 21]) the
results mentioned above are markedly higher. The reason for this phenomenon is unclear. In which way it is influenced by the way and counting of dilution (absolut dilution vs. serum dilution) remains unclear.”

Our number of references amounts 29, now, and “barely available” is changed into “available on a limited degree”

13) Your conclusion is not about your study – what have we learnt from the study?

We modified the conclusion in this way: “Despite intensive efforts in the fight against polio, it remains endemic in India, Pakistan, Afghanistan and Nigeria. Therefore, vaccination campaigns are as important as maintaining surveillance to monitor enteroviral events - including those countries, which are deemed to be polio-free by WHO. Even if the European countries are known to be polio-free the danger has not been completely averted: we observed a distinctive gap in immunity to PV3 in all age-groups and furthermore a decreasing immunity to PV, overall. Thus, we learnt that vaccination against polio is absolutely necessary further on to preserve our present polio-free situation”

14) You need to describe your cohort population better. Are they only tested for PV? Do you know anything about their nationality, for example?

We inserted the following paragraph: “As we conducted an unlinked anonymous retrospective study, patients’ data regarding age and sex were available. However, data concerning nationality, residence or concomitant diseases were not available.”

Kind regards, on behalf of the other authors.

Claudia Reinheimer