Author's response to reviews

Title: Recurrent 6th nerve palsy in a child following different live attenuated vaccines: Case Report

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Version: 2 Date: 29 March 2012

Author's response to reviews: see over
29th March 2011

Jigisha Patel
Editor in Chief
BMC Infectious Diseases

Dear Dr Patel,

**Re: Manuscript Number 1669205421638499**
Title: Recurrent 6th nerve palsy in a child following different live attenuated vaccines: Case Report

On behalf of the authors of this manuscript, I would like to re-submit an edited manuscript for consideration.

These are the considerations and comments that have been assessed.

<table>
<thead>
<tr>
<th>Editorial Comments</th>
<th>Response</th>
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<tbody>
<tr>
<td>1. Abstract: Please ensure that you include an abstract in the manuscript file, and that the abstract is identical in the manuscript file and on the submission system. Abstracts should not cite references, nor refer to figures or tables. Please check the instructions for authors to ensure that your abstract follows the correct structure for this journal and article type.</td>
<td>Noted and adjusted to fit journal criteria.</td>
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<tr>
<td>2. Abstract: Statement: ?Benign 6th nerve palsy is not due to a sinister underlying cause, with an excellent prognosis and recovery expected?. This may be better as ?The majority of 6th nerve palsies do have a sinister cause and have an excellent prognosis etc..?</td>
<td>Corrected.</td>
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<td>3. P4 (brackets): ?Initial blood investigations included normal full blood examination (Hb 128 g/L (105-135); Platelets 284 x109/L (150-450); leukocytes 11.1 x 109/L (4.0-11.0))?</td>
<td>Normal ranges are the numbers in brackets – removed for ease of reading.</td>
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4. P5. ?On this occasion it commenced following a different live virus vaccination?  Corrected

5. P6. ?There have been no documented cases in the literature after varicella immunization?. The authors have missed another review in which one child is reported to have a recurrent 6th nerve palsy with recurrence after a VZV vaccine. Arch Dis Child. 2009 May;94(5):394-6. Epub 2009 Jan 8. Benign recurrent sixth (abducens) nerve palsies in children. Mahoney NR, Liu GT. Corrected and included in table/case report. Manuscript text adjusted to include reference.


7. Table 1. Sturm et al (3). The time post vaccination was 5 days not 6 months. Corrected.

Reviewer 1

Abstract Page 1
Benign 6th nerve palsy is not due to a sinister underlying cause, with an excellent prognosis and recovery expected. The exact pathophysiology is unknown, although hypotheses including autoimmune mechanisms and direct viral invasion could explain the pathophysiology behind immunization related nerve palsies. It is important rule out other aetiologies with thorough history, physical examination and investigations.

Comment [DB1]: ? should have to before rule Corrected.

Background section, Page 2
Comment – 6th nerve palsy has only rarely been associated with wild measles and I was unable to find any reference to it after varicella disease.

Comment [DB2]: did the authors check with the VAERS passive adverse event system for any reported similar incidents after measles/varicella immunisation? VZV and sixth nerve palsy has been noted in literature previously.


This has been added to the case report. Nil events on the VAERS system were found.

Case Report section
Comment – the child is a boy with a right sided lesion – in the literature most of the reported cases are female and the lesion is usually left sided - ? is this worth a short note in the discussion

A short note has been added to the discussion section of the manuscript.

A previously healthy 12 month old boy presented to Corrected.
| hospital with a right 6th nerve palsy seven days after his routine 12 month immunizations: measles, mumps, rubella  
Comment [DB3]: ?rubella |
|---|
| Comment [DB4]: this I feel is the really critical part of the paper – ie the authors are suggesting a case of recurrent 6th nerve palsy after 2 live vaccines but apart from a temporal relationship and an absence of clinical preceding infection, the evidence for such an occurrence is based on 23 prior cases of reported 6th n palsy following immunization – I think a stronger causal case has to be made  
The time course puts both vaccines as possible triggers to the events described. In the absence of an alternative hypothesis this a strong association with appropriate expert review as included.  
A tissue diagnosis (e.g. biopsy) is unfortunately unethical as a result is unlikely to help management and the previous case reports included strengthen the discussion. |
| Minor issues not for publication”  
Page 7  
Therefore, a thorough history and physical examination is recommended, in combination with a MRI brain scan. Comment [DB6]: ?? an before MRI Corrected. |
Comment re: Hypotheses include damage from autoimmune mediation or direct viral invasion causing demyelination, localized arteritis or genetic predisposition, which could increase susceptibility to such nerve palsies. (5, 9) - I wonder how likely the first two hypotheses are when the first onset was only 5 days after the MMR – if that was indeed the cause – I am aware that 6th nerve palsy has been reported after HepB vaccine. I think this is the one section of the paper that could usefully be expanded to explore the suggested aetiological mechanisms in more detail.

We acknowledge that a Hep B-Hib vaccine was also administered; this is highlighted in the text.

Delayed onset (5 days) makes Hep B-Hib causation very unlikely and less biologically plausible. As it is an inactivated vaccine, one would expect to see most reactions occur within 24 hours post immunisation. There is no evidence that Hep B is associated with other auto-immune phenomenon such as multiple sclerosis as listed in these references:


Delayed neurological AEFI have been well described post -attenuated live vaccines such as MMR and varicella.

**DISCUSSION, Page 8**

Comment re The typical incubation period for wild type measles infection is approximately 10 days (range 7-18 days); attenuation has been shown to increase the incubation period for some vaccines including measles. (14) This is also reflected in varicella infections, where antibody reactions to vaccine strain virus appear later compared to those in wild type infection (range 10-21 days for wild type). (15)

Yes, it is in reference to antibody development post vaccination. The wording has been changed to clarify this point.

The authors state that the right sided 6th nerve palsy came on after two live attenuated vaccines – namely MMR (as Priorix) and Varicella: however, the first presentation was after MMR and Hib-HepB and the authors don’t elucidate why they rejected the possible aetiological role of Hib-HepB – I assume that the authors didn’t think the Hib-HepB of relevance since the child had received previous doses of both these vaccines without any problems but I would expect this to be discussed, and the reasons for excluding HibHepB to be clarified.

As noted above re: Hib-HepB
I think it really important that the authors make both a clearer and stronger case for the suggestion that the recurrent 6th nerve palsy came on after first MMR and then varicella vaccine.

As noted above

### Reviewer 2

<table>
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<th>Page 7. Near the top, the authors quote that a third of palsies have a neonatal origin - this sentence should be appropriately referenced</th>
<th>Neoplastic origin.</th>
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<td>This has been appropriately referenced as suggested.</td>
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| Page 7. In the sentence beginning "Therefore, a thorough history..." the recommendation also includes performing MRI scan and a reference a publication from 1970 - did that paper really reference MRI? is there not a more recent publication that the authors can quote? | An updated reference has been included in the manuscript. |

All co-authors have read, reviewed and agreed to the content of the revised manuscript.

I look forward to a favourable reply from you at your earliest convenience.

Yours Sincerely,

Nigel Crawford

(on behalf of the co-authors)