## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Vaccination of children with egg allergy, with vaccine containing egg residue. |
| **AUTHORS** | Bård Anders Forsdahl |

## VERSION 1 - REVIEW

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| **REVIEWER** | Mich Erlewyn-Lajeunesse<br>Consultant in Paediatric Allergy<br>Southampton University Hospitals NHS Trust<br>Southampton UK |
| **REVIEW RETURNED** | 22/06/2011 |

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| **THE STUDY** | The aim of the study has not been clearly stated ie safety of immunisation in a high risk group for reaction. The author alos talks about concomitant atopic disease in the conclusion but the imprtance of this has not been addressed elsewhere. Outcome meaures are not explicitly stated. No stats are addressed. Abstract does not describe how many had severe egg allergy (or indeed what ths might mean). English is not of a publication standard and needs to be rewritten throughout. |
| **RESULTS & CONCLUSIONS** | The results section is confused. Table 1 is OK but it would be better to tabulate the demographics by exposure to egg and immunisation. Table 2 is redundant. Talk of slight differences between groups - no reference to any statistical work.<br><br>No attempt to discuss results in the light of recent evidence of vaccine safety Refs 17 and 18.<br><br>Data suggest that sensitised individuals are safe to be immunised and have mild reactions only - yet conclusion is that they are at risk of severe reaction to the vaccine.<br><br>Data also suggests (liek ref 18) that fractionated (split) dose vaccination is as safe as single dose. In that none reacted to the 1/10th initial dosing. Not stated in text. |
| **REPORTING & ETHICS** | The statement around ethical approval is too vague. Was there prospective approval for the conduct of this study. or was it a retrospective audit? It does not appear that subjects signed written consent. |
| **GENERAL COMMENTS** | Thank you for asking me to review your article. We have very limited data on the safety of influenza immunisation in egg allergic children and your cohort adds to the safety data.<br>However, there are some major issues with your manuscript which should be addressed. I hope that you find my comments of help.<br>1. It is normal practice to refer to a vaccine by its type rather than its trade name. Pandemrix and its manufacturer should only be stated in the methods and abstract. Otherwise it sounds like an advert.<br>2. The emerging pH1N1 pandemic occurred in July 2009 not in the fall |

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| | 3. State the aims of your study at end of the introduction<br>4. Was their prospective ethical approval and written consent of participants? If not then your data could be described as an audit – although you may wish to get written consent for publication of the case histories of those who reacted to the vaccine.<br>5. Please spell my name correctly! But better to write a sentence that does not use names – just the facts with a reference for the statement at the end of the sentence.<br>6. Were there age inclusion criteria as well? Exclude the adult who was immunised.<br>7. Time from ssIgE to immunisation is a key variable as many children will outgrow their egg allergy and may no longer be allergic at the time of immunisation. Data should be described in the text.<br>8. Table 1 is OK but I think that it would be better to divide your cohort into groups like so:<br>a. Single dose vaccine<br>b. Fractionated (split) dose – sensitised but never exposed<br>c. Fractionated (split) dose – severe previous reaction to egg or severe asthma<br>9. State number of children with previous anaphylaxis to egg in text.<br>10. Table 2 is redundant and should be removed or incorporated into your new table 1<br>11. Please use statistical analysis to describe differences between groups "slight difference" in number of asthmatics is not acceptable.<br>12. Conclusions do not discuss your data in light of recent articles on the subject your refs 17 and 18 – how does your data add to their findings - I think that the higher OVA content of Norwegian Pandemrix is the key element here.<br>13. I don't agree with your conclusions – first three paragraphs don't address the main issues of your paper. Data suggest that sensitised individuals are safe to be immunised and have mild reactions only - yet conclusion is that they are at risk of severe reaction to the vaccine.<br>14. Data also suggests (like ref 18) that fractionated (split) dose vaccination is as safe as single dose. In that none reacted to the 1/10th initial dosing. Not stated in text.<br>15. The safety of the guidelines that you used is also not addressed – these were published without data of their safety – just an assumption based on previous published work. |

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| **REVIEWER** | Gaston De Serres<br>Medical epidemiologist<br>Institut national de santé publique du Québec<br>Quebec, Canada<br><br>Conflicting interest: I am conducting a study on the vaccination of egg-allergic patients |
| **REVIEW RETURNED** | 24/06/2011 |

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| **THE STUDY** | This paper reports the results of the vaccination of 81 egg-allergic patients with Pandemrix, the GSK adjuvanted monovalent H1N1 pandemic influenza vaccine. The protocol used to vaccinate patients was than proposed by Erlewyn-Lajeunesse et al in the BMJ where patients received one dose if they were at low risk and 2 doses (10% and 90%) at 30 minute interval if patients were at high risk. However the author considered patients who tested positive to eggs but had never eaten eggs at high risk who were vaccinated accordingly. |

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| | The inclusion criteria required IgE levels to be > 0.35kU/L but this was assessed with two methods (Immulite and Immunocaps). These assays are not directly comparable (ref: Wang et al JACI 2008;121:1219) and IgE level measured by one method does not correspond to the same value with the other and pooling seems inappropriate. The proportion (and number) of patients tested with each method should be presented separately.<br><br>To confirm allergy, the > 0.35kU/L IgE threshold was used both for patients who had eaten eggs and presented an allergic reaction and for those who never ate eggs. The positive predictive value of allergy with this threshold is higher in patients who had eaten eggs than in those who did not. For patients who never ate eggs, higher thresholds that vary with age (<2 years vs 2 years+) are preferable. The results should present the number of patients who never ate eggs who were above these higher thresholds.<br><br>The amount of ovalbumin injected is critical. Arepanrix which is the same monovalent adjuvanted vaccine manufactured by GSK in its Canadian plant had an ovalbumin content <0.03 microgram/mL (Ref Gagnon R JACI 2010). This is 20 times less than the <0.66 microgram/mL reported for Pandemrix by the author and is quite surprising given that both products are from the same manufacturer and generally presented as equivalent. Confirmation of the actual ovalbumin content in the lots administered to his patients is needed. |
| **RESULTS & CONCLUSIONS** | P 11 line 32 The author says that the reaction in the first patient was a definitive reaction to the vaccine. The description may be compatible with an allergic reaction but is largely non specific and cannot be called a definitive allergic reaction.<br><br>P11 line 42 For the third patient (8 year old) it should be repeated beside the SSIgE level (14.6 kU/L) that this was assessed three years before. When was the last SPT done and what was the result?<br><br>P15 line 31 "The one patient with a definite reaction to the vaccine, and the two with possible reactions to vaccine had never been exposed to egg. This warrant for a cautious approach when vaccinating anyone tested positive for egg allergy, but never have been exposed to egg. These patients should be treated as if they had had severe reactions to egg exposure when vaccinating with a vaccine containing egg residue."<br><br>To recommend to treat patients who had never eaten eggs as if they had had severe reactions is inappropriate. The evidence to support this is flimsy. None of the clinical problems in these patients appears to be a definitive allergic reaction. No controls were included in this study, preventing the author to be in position to be very assertive about his inferences.<br><br>While the paper cites four recent studies on vaccination of egg allergic patients, there is no discussion comparing the results of the current study with those from these other studies. The discussion lacks depth and perspective on the issue of vaccination of egg allergic patients. |
| **REPORTING & ETHICS** | P5 line 15 "The Regional Committee for research ethics had no objections to this study."<br><br>This is an unusual wording. Was the study approved? If so, please rephrase in a more positive way. |
| **GENERAL COMMENTS** | This paper is not bad but its interest is limited given its relatively |

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| | small number of patients and its focus on a monovalent pandemic vaccine. Several other articles on the same issue have been published in the past two years and included more patients and/or assessed the safety of the trivalent seasonal vaccine which is more relevant outside the pandemic. (Chung 2010, Gagnon 2010, Greenhawlt 2010, Owens 2011) |

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| **REVIEWER** | John M. Kelso, MD<br>Division of Allergy, Asthma and Immunology<br>Scripps Clinic<br>San Diego CA USA<br><br>No competing interests. |
| **REVIEW RETURNED** | 21/06/2011 |

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| **GENERAL COMMENTS** | The comma would best be deleted from the title.<br><br>On page two, the article focus would better read, "We wanted to vaccinate children severely affected by egg allergy with the same vaccine as the rest of the Norwegian population and that contained egg residue."<br><br>The first bullet under key message would better read, "It is safe to vaccinate egg allergic children who are severely..."<br><br>The second bullet under key message would better read, "The level of serum specific IgE to egg does not..."<br><br>The third bullet under key message would better read, "... should be treated as if they are egg allergic." as opposed to "…had had a serious reaction toward egg." since this notion is based only on the fact that the single patient with a definite reaction to the vaccine had never knowingly eaten eggs.<br><br>The strength and limitations of the study would better be listed in only two bullets. The first would read, "A strength of the study is that the same doctor thoroughly evaluated all of the patients before vaccination." The second bullet would remain as "A weaknesses is that the numbers are rather small." eliminating what is now the second bullet.<br><br>In the abstract on page 3, after the sentence which concludes on line 26, another sentence should be included to read, "The remainder received one-tenth of the dose followed 30 minutes later by nine-tenths."<br><br>On page 3, line 28 and throughout the manuscript, the word ovalbumin should not be capitalized.<br><br>The abstract would best end after the sentence on line 39 as "... even with severe egg allergy." deleting the words on line 42 since as I will comment on later, the split vaccine approach is likely unnecessary.<br><br>On page 4, line 6, it would better read, "... severe egg allergy with influenza vaccine."<br><br>The next sentence which begins on line 9 then would better read, "The available vaccine (Pandemrix from GlaxoSmithKline) contained egg... |

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| | Line 14 would better read, "...vaccine available, however the first doses..."<br><br>Line 25 would better read, "...allergies and that patients with ..."<br><br>Beginning on line 31, we are told that patients with severe reactions included those with the listed symptoms including urticaria. This makes it sound as though patients with only urticaria were regarded as having had severe reactions, but this is apparently not the case as described later in the paper. This should be clarified.<br><br>Beginning on line 56, we are told that the patients who could eat "even only the slightest amount of egg" received their vaccine at the community center. Does this include egg-containing baked goods? The vast majority of patients who will react to the ingestion of eggs directly can eat egg-containing baked goods without reaction. This does not necessarily indicate the severity of their reaction to the ingestion of egg directly.<br><br>Page 5, line 32 would better read, "... was a diagnosis sensitization to egg..." as what is being described here is evidence of IgE antibody not clinical reactivity.<br><br>On line 49, we are told that a criterion to be in the study was being unable to eat any amount of egg without an allergic reaction. Again does this included egg-containing baked goods? Further this would indicate that the patients needed to have a history of reacting to egg to be in the study when this is not the case as there are quite a number who had never knowingly ingested egg. This should be clarified.<br><br>On line 52, we are told that patients were "registered" if they had other atopic disease only if they were on medication for these. This does mean that patients without other atopic diseases were excluded? This does not appear to be the case. This needs to be clarified.<br><br>On page 7, line 3, we are told that no new blood samples were taken to demonstrate IgE to egg. This is acceptable but we should be told from how far in the past evidence of egg-specific IgE was acceptable for inclusion since egg allergy is commonly outgrown and some patients may no longer have been egg allergic.<br><br>Similarly on page 10, line 11, we should be told the mean and range of the time since the specific IgE levels had been done.<br><br>On line 37 and 53 and 60, we are given various numbers and percentages of patients who had other atopic disease, but these numbers are confusing and do not match. We are told, for example, that 64 patients had other atopic diseases, but later are told that 44 patients had other allergies besides egg allergy. Does this mean other food allergies? This apparently also is not the case since after that we are told that 32 patients had other food allergies. These descriptions of other atopic diseases need to be clarified.<br><br>Beginning on line 40, we are told that there is a slight difference in the groups of those receiving the fractionated or a single dose in terms of percentages having other atopic diseases. The difference between 82% and 71% is not likely to be statistically significant and is certainly not a large absolute difference. Consideration |

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| | should be given to deleting this statement.<br><br>The paragraph that begins on line 17 of page 14, I believe can be deleted since the discussion of the potential sex disparity for food allergy in general seems superfluous to the current paper.<br><br>On page 15, line 34, I think we would more appropriately read "This may warrant a cautious approach..."<br><br>I believe the word "severe" can be deleted from line 42 for the reasons outlined above.<br><br>On page 16, the authors conclude that patients with prior serious reactions to egg can be vaccinated, which seems like an appropriate conclusion. However they state that these patients can be vaccinated with a fractionated vaccine approach. Since of all the patients tolerated the 10% dose and ultimately went on to receive the 90% dose either with no reaction at all or the one patient with a very mild reaction, it would seem that the authors could conclude that fractioning the dose was likely unnecessary. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: John M. Kelso, MD
Division of Allergy, Asthma and Immunology
Scripps Clinic
San Diego CA USA

No competing interests.

1.The comma would best be deleted from the title.

OUR RESPONS. We agree with the comment, the title is reworked and it now reads:
Reactions of Norwegian children with severe egg allergy to an egg-containing influenza A(H1N1) vaccine – a retrospective audit.

2.On page two, the article focus would better read, "We wanted to vaccinate children severely affected by egg allergy with the same vaccine as the rest of the Norwegian population and that contained egg residue."

OUR RESPONS. We agree with the comment, it now reads:
«We wanted to vaccinate the children severely affected by egg allergy with the same vaccine that the rest of the Norwegian population, was receiving at the time, and that vaccine contained egg residue.»

3.The first bullet under key message would better read, "It is safe to vaccinate egg allergic children who are severely..." ."

OUR RESPONS. We agree with the comment, it now reads:
«It is safe to vaccinated children with severe egg allergy with a vaccine containing a low level of egg residue – even if these children suffer from concurrent atopic diseases.»

3.The second bullet under key message would better read, "The level of serum specific IgE to egg does not..." ."

OUR RESPONS. We agree with the comment, it now reads:
«The level of serum specific IgE to egg does not predict a reaction to the vaccine.»

4.The third bullet under key message would better read, "... should be treated as if they are egg allergic." as opposed to "…had had a serious reaction toward egg." since this notion is based only on the fact that the single patient with a definite reaction to the vaccine had never knowingly eaten eggs.

OUR RESPONS. We agree with the comment, it now reads:
«Children with a positive serum-specific IgE test to egg allergy who had never been exposed to egg, should be treated as if they are allergic to egg.»

5.The strength and limitations of the study would better be listed in only two bullets. The first would read, "A strength of the study is that the same doctor thoroughly evaluated all of the patients before vaccination." The second bullet would remain as "A weaknesses is that the numbers are rather small." eliminating what is now the second bullet. ."

OUR RESPONS. We agree with the comment, it now reads:
«The strength of this study is that it is the same doctor who thoroughly evaluated all the patients before vaccination also evaluated the patients with suspected reactions to the vaccine.
A weakness is that the number of participants in the study is quite small.»

6. In the abstract on page 3, after the sentence which concludes on line 26, another sentence should be included to read, "The remainder received one-tenth of the dose followed 30 minutes later by nine-tenths."

OUR RESPONS. We agree with the comment, it now reads:
« The remainder received one-tenth of the dose followed 30 minutes later by nine-tenths.»

7. On page 3, line 28 and throughout the manuscript, the word ovalbumin should not be capitalized.

OUR RESPONS. We agree with the comment and have corrected it throughout the manuscript.

8.The abstract would best end after the sentence on line 39 as "... even with severe egg allergy." deleting the words on line 42 since as I will comment on later, the split vaccine approach is likely unnecessary.

OUR RESPONS. We agree with the comment, and it now reads:
«Conclusion This study indicates that it is safe to vaccinate children even if the suffer from severe egg allergy.»

9. On page 4, line 6, it would better read, "... severe egg allergy with influenza vaccine."

OUR RESPONS. We agree with the comment and it now reads:
«However, the WHO, American Center for Disease Control (CDC) and American Academy of

Pediatrics (AAP) all warned that individuals with severe egg allergy with should not be given the influenza vaccine.3,4,5»

10. The next sentence which begins on line 9 then would better read,
"The available vaccine (Pandemrix from GlaxoSmithKline) contained egg...

OUR RESPONS. We agree with the comment, and it now reads:
«The available monovalent Influenza A H1N1 vaccine at the time contained egg-protein (ovalbumin) residue.»

11. Line 14 would better read, "...vaccine available, however the first doses..."
OUR RESPONS. We agree with the comment and it now reads:
«An egg-free vaccine was expected, but would not be available in Norway before the first week of December 2009 and then only in a very limited number of doses. 6»

12. Line 25 would better read, "...allergies and that patients with

OUR RESPONS. We agree with the comment and it now reads:
«An NHA appointed advisory group recommended that patients with egg allergy should be examined by a physician with a special competence in allergies and that patients with anaphylactic shock reactions to egg should not be vaccinated at all.7 In addition, it was recommended that patients who exhibit a severe reaction to egg should be subjected to a skin prick test to determine whether or not the individual could be safely vaccinated.»

13. Beginning on line 31, we are told that patients with severe reactions included those with the listed symptoms including urticaria. This makes it sound as though patients with only urticaria were regarded as having had severe reactions, but this is apparently not the case as described later in the paper. This should be clarified.

OUR RESPONS. This listing of allergic reactions is the same listing the NHA appointed advisory group used when they gave their recommendations. When we listed the reactions with urticaria first, it was the same way they listed the allergic reactions. We understand the confusion that it can create, and it is therefore changed. It now reads:
«The advisory group regarded one or more of the following reactions to egg as severe: , angioedema, airway oedema, asthma, urticaria , rhinitis or vomiting.»

14. Beginning on line 56, we are told that the patients who could eat "even only the slightest amount of egg" received their vaccine at the community center. Does this include egg-containing baked goods? The vast majority of patients who will react to the ingestion of eggs directly can eat egg-containing baked goods without reaction. This does not necessarily indicate the severity of their reaction to the ingestion of egg directly.

OUR RESPONS. The patients included in this study were unable to eat egg containing baked goods without a reaction. This is now included in the text and it reads:
«The only patients to be vaccinated at the outpatient clinic were those unable to digest the slightest amount of egg, including egg-containing baked goods.»

15. Page 5, line 32 would better read, "... was a diagnosis sensitization to egg..." as what is being described here is evidence of IgE antibody not clinical reactivity.

OUR RESPONS. We agree with the comment and it now reads:
«The first criterion was a diagnosed sensitisation to egg demonstrated by a positive skin prick test (SPT) or positive serum analysis for specific IgE- (SSIgE-) mediated egg allergy.»

16. On line 49, we are told that a criterion to be in the study was being unable to eat any amount of egg without an allergic reaction. Again does this included egg-containing baked goods?

OUR RESPONS. This is corrected, and it now reads:
«The second criterion was that the patient had to be on an egg-free diet and be unable to eat any food containing any amount of egg, including egg-containing baked goods, without an allergic reaction to egg protein.»

17. Further this would indicate that the patients needed to have a history of reacting to egg to be in the study when this is not the case as there are quite a number who had never knowingly ingested egg. This should be clarified.

OUR RESPONS. We agree with the comment, the text now reads:
«We also included patients who were sensitised to egg but had never been exposed to egg or egg-containing baked goods and were on an egg-free diet.»

18. On line 52, we are told that patients were "registered" if they had other atopic disease only if they were on medication for these. This does mean that patients without other atopic diseases were excluded? This does not appear to be the case. This needs to be clarified.

OUR RESPONS. We agree with the comment and it now reads:
«Concurrent atopic diseases We recorded other atopic diseases in the included patients only if they were on current medication for asthma, allergy or eczema or if they were on a diet that avoided food other than egg. The other atopic diseases had been diagnosed by a physician prior to vaccination. No other diseases than atopic diseases were recorded.»

19. On page 7, line 3, we are told that no new blood samples were taken to demonstrate IgE to egg. This is acceptable but we should be told from how far in the past evidence of egg-specific IgE was acceptable for inclusion since egg allergy is commonly outgrown and some patients may no longer have been egg allergic.

OUR RESPONS. We agree that most children outgrow their egg allergy. But all our patients, with the exception of the patients never exposed to egg, had prior reactions to egg. The last time they ingested egg or egg containing baked goods they had an allergic reaction and were staying on an egg free diet. The rest of the patients were sensitized and were staying on an egg free diet. This was as close we could get to exclude the patients that had outgrown their egg allergy. The only way to be 100% sure of their status regarding egg allergy would have been to perform an oral provocation test, and we did not have time or resources to do that. Therefore we did not have any exclusion criteria based on how old the egg-spesific IgE was.

20. Similarly on page 10, line 11, we should be told the mean and range of the time since the specific IgE levels had been done.

OUR RESPONS. We agree with the comment, and the values of SSIgE can now be found in table 1 and in the text, it now reads:

«A total of 73 patients (91%) had a positive SSIgE test, although we did not know the exact value of the SSIgE test of two of them. The remaining seven (9%) had shown a reaction to egg in only the skin prick. Median SSIgE level to egg-protein, for the whole group, was 17.0 kU/L. Eleven (15%) patients had an SSIgE >99 kU/L, while 25 (35%)patients had an SSIgE between 0.8≤8.3 kU/L.».....« The groups were indistinguishable with regard to SSIgE level and time since the SSIgE level had been done. There was also no difference in the median and the range of SSIgE between the two groups. SSIgE had been measured between one month and 10 years before, with a mean time 28.6 months. Half of the patients who had their SSIgE measured were older than one year, and the SSIgE had a median value of 25.4 kU/L.»

21. On line 37 and 53 and 60, we are given various numbers and percentages of patients who had other atopic disease, but these numbers are confusing and do not match. We are told, for example, that 64 patients had other atopic diseases, but later are told that 44 patients had other allergies besides egg allergy. Does this mean other food allergies? This apparently also is not the case since after that we are told that 32 patients had other food allergies. These descriptions of other atopic diseases need to be clarified.

OUR RESPONS. We agree that the information is unclear, the paragraph is rewritten and the text now reads:
«A high number of patients - 63 (79%) - had atopic diseases other than those caused by egg allergy and 39 (49%) patients were on treatment for asthma. A total of 38 (48%) patients suffered from ongoing eczema.
There were 43 (54%) patients with other allergies apart from egg allergy, including food and inhalation allergies. All in all, these 43 patients suffered from a total of 134 recorded allergies. Food allergies were the most common (32 (40%) patients), while 24 (30%) of the patients presented with an inhalation allergy.»

22. Beginning on line 40, we are told that there is a slight difference in the groups of those receiving the fractionated or a single dose in terms of percentages having other atopic diseases. The difference between 82% and 71% is not likely to be statistically significant and is certainly not a large absolute difference. Consideration should be given to deleting this statement.
The statement is taken out, as there is no significant differences.

23. The paragraph that begins on line 17 of page 14, I believe can be deleted since the discussion of the potential sex disparity for food allergy in general seems superfluous to the current paper.

OUR RESPONS. We agree with the comment and have taken the paragraph out.

24. On page 15, line 34, I think we would more appropriately read "This may warrant a cautious approach..."

OUR RESPONS. We agree with the comment and it now reads:
«This could indicate that a cautious approach is needed in the vaccination of individuals who had tested positive for egg allergy but had never been exposed to egg.»

25. I believe the word “severe” can be deleted from line 42 for the reasons outlined above.
OUR RESPONS. We agree with the comment and it now reads:
«When immunised with and egg-containing vaccine, these patients should be treated as if they had in fact exhibited a reaction to egg exposure.»

26. On page 16, the authors conclude that patients with prior serious reactions to egg can be vaccinated, which seems like an appropriate conclusion. However they state that these patients can be vaccinated with a fractionated vaccine approach. Since of all the patients tolerated the 10% dose and ultimately went on to receive the 90% dose either with no reaction at all or the one patient with a very mild reaction, it would seem that the authors could conclude that fractioning the dose was likely unnecessary.

OUR RESPONS. We agree with the comment and has changed the conclusion regarding fractioning. The new conclusion reads:
«Dose fractionation In this study we chose to vaccinate either with a fractionated or a single dose. All patients tolerated the 10% dose, and ultimately received the 90% dose,. and only one patient showed a mild reaction. This indicates that in the case of a vaccine with an ovalbumin level of <0.333 µg/ml, all patients could in fact have received the vaccine as a single dose without serious complications.»

Reviewer: Mich Erlewyn-Lajeunesse
Consultant in Paediatric Allergy
Southampton University Hospitals NHS Trust
Southampton UK

The aim of the study has not been clearly stated ie safety of immunisation in a high risk group for reaction. The author alos talks about concomitant atopic disease in the conclusion but the imprtance of this has not been addressed elsewhere. Outcome meaures are not explicitly stated. No stats are addressed. Abstract does not describe how many had severe egg allergy (or indeed what ths might mean). English is not of a publication standard and needs to be rewritten throughout.

The results section is confused. Table 1 is OK but it would be better to tabulate the demographics by exposure to egg and immunisation. Table 2 is redundant. Talk of slight differences between groups - no reference to any statistical work.

No attempt to discuss results in the light of recent evidence of vaccine safety Refs 17 and 18.

Data suggest that sensitised individuals are safe to be immunised and have mild reactions only - yet conclusion is that they are at risk of severe reaction to the vaccine.

Data also suggests (liek ref 18) that fractionated (split) dose vaccination is as safe as single dose. In that none reacted to the 1/10th initial dosing. Not stated in text.

The statement around ethical approval is too vague. Was there prospective approval for the conduct of this study. or was it a retrospective audit? It does not appear that subjects signed written consent.

Thank you for asking me to review your article. We have very limited data on the safety of influenza immunisation in egg allergic children and your cohort adds to the safety data. However, there are some major issues with your manuscript which should be addressed. I hope that you find my comments of help.

1. It is normal practice to refer to a vaccine by its type rather than its trade name. Pandemrix and its manufacturer should only be stated in the methods and abstract. Otherwise it sounds like an advert.
OUR RESPONS. We agree with the comment, and have changed it according to comment. The

trade name is now only mentioned in the abstract and in material and methods.

2. The emerging pH1N1 pandemic occurred in July 2009 not in the fall

OUR RESPONS. We agree with the comment, and it now reads:
"In July 2009, the World Health Organisation (WHO) recommended vaccination against the emerging pandemic Influenza A (H1N1) virus.1"

3. State the aims of your study at end of the introduction.

OUR RESPONS. We have inserted a sentence, and it now reads:
«The objective of this study was to determine the safety of administring a monovalent Influenza A H1N1 vaccine to egg allergic patients following the guidelines in the article.8»

4. Was their prospective ethical approval and written consent of participants? If not then your data could be described as an audit – although you may wish to get written consent for publication of the case histories of those who reacted to the vaccine.

OUR RESPONS. We have written consent from the case histories presented in this article.
We did not have the approval from the the Regional Committee for Research Ethics in Northern Norway before we vaccinated the children and adolescents, but we applied in November 2010. The answer came 17 december 2010, their answer is translated from Norwegian, the Norwegian text follows below.

"The committee consider the vaccination to be part of ordinary treatment, even though it can have been experimental. The project is therefore outside the mandate of the committee. It must be added that the committee consider that the applicant both should and has the right to publish the treatment. "

"Komiteen vurderer det slik at den vaksineringen som har skjedd i prosjektet er å anse som ledd i ordinær behandling, selv om den kan ha vært eksperimentell eller utprøvende. Prosjektet faller således utenfor komiteens mandat. Det må likevel tilføyes at komiteen vurderer det slik at søker både bør, og har rett til, å publisere behandlingen."

We have changed the the paragraph in the article and it now reads:
«Ethical aspects
We obtained the written consent of the parents of the case histories presented in this article.
We did not obtain approval for the study from the Regional Committee for Research Ethics in Northern Norway before commencing the vaccination drive, but we applied for approval in November 2010. The Committee responded that it considered the vaccination drive as 'part of ordinary treatment', even though it could have been experimental, and that the project therefore fell outside its mandate. However, it added that we as the applicants had the right to 'publish the treatment'.»

5. Please spell my name correctly! But better to write a sentence that does not use names – just the facts with a reference for the statement at the end of the sentence.

OUR RESPONS. We are terribly sorry for wrong spelling your name. The sentence now reads:
«In October 2009 Erlewyn-Lajeunesse et al. recommended that patients allergic to egg should receive only vaccines containing <1.2 µg/ml ovalbumin, and that a two-dose split protocol should be used in individuals with severe egg allergy.8»

6. Were there age inclusion criteria as well? Exclude the adult who was immunised.

OUR RESPONS. There were no age inclusion criteria, apart from that of not to vaccinate children under 6 months of age.
We vaccinated the children and adolescents that normally would get their treatment at the department of pediatrics. The adult in our material is taken out.

7. Time from ssIgE to immunisation is a key variable as many children will outgrow their egg allergy and may no longer be allergic at the time of immunisation. Data should be described in the text.

OUR RESPONS. We agree that many children outgrow their allergy to egg. We tried to exclude all the patients no longer allergic to egg by having two criterion. The first a sensitation to egg, and the second being on an egg free diet. In addition the parents and patients were also asked twice, once by the nurse before they got the outpatient appointment and once by the doctor examining the patient before vaccination, if they could digest the slightest amount of egg, including egg-containing baked goods without a reaction. All parents and patients cofirmed the inability to digest without a reaction. The patients never exposed to egg could not answer this question, but confirmed the egg free diet. In this way we tried to exclude all the patients no longer allergic to egg, without having to do an oral provocation test. An oral provocation test would have been impossible to do at that time.
Data regarding time from SSIgE to immunization is now incorporated in Table 1, and in two paragraphs in the article:

«A total of 73 patients (91%) had a positive SSIgE test, although we did not know the exact value of the SSIgE test of two of them. The remaining seven (9%) had shown a reaction to egg in only the skin prick. Median SSIgE level to egg-protein, for the whole group, was 17.0 kU/L. Eleven (15%) patients had an SSIgE >99 kU/L, while 25 (35%)patients had an SSIgE between 0.8≤8.3 kU/L.»
«The groups were indistinguishable with regard to SSIgE level and time since the SSIgE level had been done. There was also no difference in the median and the range of SSIgE between the two groups. SSIgE had been measured between one month and 10 years before, with a mean time 28.6 months. Half of the patients who had their SSIgE measured were older than one year, and the SSIgE had a median value of 25.4 kU/L.»

8. Table 1 is OK but I think that it would be better to divide your cohort into groups like so:
a. Single dose vaccine
b. Fractionated (split) dose – sensitised but never exposed
c. Fractionated (split) dose – severe previous reaction to egg or severe asthma

OUR RESPONS. Table 1 is now rewritten with the three groups, single dose, fractioned dose-sensitised but never exposed, and fractioned dose because of severe previous allergic reaction to egg. We do not have the data for which of the patients that has a severe asthma. We only registered that the patients used asthma medications regularly, We did not ask about dosage. The use of inhaled corticosteroids is widespread in Norway, and we now find that almost all children with asthma use inhaled corticosteroids with their Beta-2 agonist.

9.State number of children with previous anaphylaxis to egg in text.

OUR RESPONS. When we registered the children and adolescents we registered them as either severe reaction to egg or mild reaction to egg as described in your article. The severe reactions to egg were: prior anaphylaxis, cardiovascular complication or collaps. This includes respiratory symptoms, hypotension and circulatory shock and severe abdominal pain.
The mild reactions to egg were: mild gastrointestinal and dermatological reactions, including urticaria, angioedema and vomiting.
We registered the patients to either one of these groups, but we did not register if the reaction was respiratory symptoms or circulatory collaps, or urticaria or vomiting to name a few.
Therefore we can only say that 19 patients had a severe previous reaction to egg the last time they were exposed to egg.

10.Table 2 is redundant and should be removed or incorporated into your new table 1
OUR RESPONS. Table 2 is taken out, and the relevant information is incorporated either in table 1 or in the text. It now reads:
"The groups of patients receiving the vaccine fractioned or as one dose were indistinguishable regarding age, SSIgE level, and time since the SSIgE level was done. Both the median and the range of SSIgE shows no differences between the groups receiving the vaccine fractioned or not. The range for when the SSIgE was done was one month to ten years, the mean time for when the SSIgE was taken was 28,6 months. Half of the SSIgE was older than 1 year, and the median value of those were 25,4 kU/l."

11. Please use statistical analysis to describe differences between groups "slight difference" in number of asthmatics is not acceptable.

OUR RESPONS. We have redone the table 1, and done a complete reanalysis of the data regarding significans, and can not find any significant differences between the three groups, except when it comes to the age between the patients with a prior severe reaction to egg, and the patients never exposed to egg

12. Conclusions do not discuss your data in light of recent articles on the subject your refs 17 and 18 – how does your data add to their findings - I think that the higher OVA content of Norwegian Pandemrix is the key element here.
OUR RESPONS. Before we decided to vaccinate the children and adolescents in this study, we contacted GlaxoSmithKline, we were the informed that the ovalbumin level in the Pandemrix vaccine was <0.66 µg/ml.
When we saw the comments in the review regarding ovalbumin level, we contacted GlaxoSmithKline again. We were then informed that According to GlaxoSmithKline Biologicals Certificate of analysis/Summary Protocol – final bulk vaccine have no more than <0.333 µg/ml.
We apologize for the confusion this has created.

13.I don't agree with your conclusions – first three paragraphs don't address the main issues of your paper. Data suggest that sensitised individuals are safe to be immunised and have mild reactions only - yet conclusion is that they are at risk of severe reaction to the vaccine.

OUR RESPONS. We agree with the comment and the section regarding Discussion and conclusions are rewritten.

14. Data also suggests (like ref 18) that fractionated (split) dose vaccination is as safe as single dose. In that none reacted to the 1/10th initial dosing. Not stated in text.

OUR RESPONS. We agree with the comments and has changed the conclusion, it now reads: «Dose fractionation In this study we chose to vaccinate either with a fractionated or a single dose. All patients tolerated the 10% dose, and ultimately received the 90% dose,. and only one patient showed a mild reaction. This indicates that in the case of a vaccine with an ovalbumin level of <0.333 µg/ml, all patients could in fact have received the vaccine as a single dose without serious complications.»

15.The safety of the guidelines that you used is also not addressed – these were published without data of their safety – just an assumption based on previous published work.

OUR RESPONS. We agree on the comment, and this is now adressed in the article.
«Safety of vaccination in patients allergic to egg The study confirmed that patients allergic to egg can be safely vaccinated with a regular influenza vaccine containing < 0.333 µg/ml ovalbumin, even if these patients had displayed previous anaphylactic reactions to egg and had been diagnosed with concurrent atopic diseases. By following the guidelines in the article, we were able to vaccinate the patients allergic to egg.8 If future influenza vaccines were to contain considerably larger amount of ovalbumin, we would consider to use the same guidelines as in this study.»
Reviewer: Gaston De Serres
Medical epidemiologist
Institut national de santé publique du Québec
Quebec, Canada

I am conducting a study on the vaccination of egg-allergic patients.

This paper reports the results of the vaccination of 81 egg-allergic patients with Pandemrix, the GSK adjuvanted monovalent H1N1 pandemic influenza vaccine. The protocol used to vaccinate patients was than proposed by Erlewyn-Lajeunesse et al in the BMJ where patients received one dose if they were at low risk and 2 doses (10% and 90%) at 30 minute interval if patients were at high risk. However the author considered patients who tested positive to eggs but had never eaten eggs at high risk who were vaccinated accordingly.

1.The inclusion criteria required IgE levels to be > 0.35kU/L but this was assessed with two methods (Immulite and Immunocaps). These assays are not directly comparable (ref: Wang et al JACI 2008;121:1219) and IgE level measured by one method does not correspond to the same value with the other and pooling seems inappropriate. The proportion (and number) of patients tested with each method should be presented separately.

OUR RESPONS. We agree that the IgE values from Immulite and Immunocap are not directly comparable, and the differences between them are greatest when it comes to diagnosing food allergy. This difference is of particular interest in the group of patients that has never been exposed to egg, and less interesting when the patients have a clinical reaction to egg. The group that never has been exposed to egg have three IgE values that are <13,2 kU/L, all are analysed with Immunocap, the values are 1,7 kU/L, 2,2 kU/L and 8,1 kU/L. The patients were 32 months, 52 months, and 14 months old when the IgE levels were measured. The IgE levels were measured 0 months, 1 month and 2 months prior to the vaccination.
We do not have the data for alle the patients whether the method was Immulite or Immunocap, the reason for this is that we have conflicting information for the exact date when the transfer from Immulite to Immunocap happened. The three patients referred in the previous paragraph all had their IgE levels taken so recently that we could establish the method.

2. To confirm allergy, the > 0.35kU/L IgE threshold was used both for patients who had eaten

eggs and presented an allergic reaction and for those who never ate eggs. The positive predictive value of allergy with this threshold is higher in patients who had eaten eggs than in those who did not. For patients who never ate eggs, higher thresholds that vary with age (<2 years vs 2 years+) are preferable. The results should present the number of patients who never ate eggs who were above these higher thresholds.

OUR RESPONS. We agree that the positive predective value of allergy in a test differ if the patient has been exposed to egg or not, and regarding to age (<2 years vs 2 years+). As the previous answer describes, the patient less than 2 years had a Immunocap IgE level 8,1kU/L, the two other patients were more than 2 years old.

3. The amount of ovalbumin injected is critical. Arepanrix which is the same monovalent adjuvanted vaccine manufactured by GSK in its Canadian plant had an ovalbumin content <0.03 microgram/mL (Ref Gagnon R JACI 2010). This is 20 times less than the <0.66 microgram/mL reported for Pandemrix by the author and is quite surprising given that both products are from the same manufacturer and generally presented as equivalent. Confirmation of the actual ovalbumin content in the lots administered to his patients is needed.

OUR RESPONS. Before we decided to vaccinate the children and adolescents in this study, we contacted GlaxoSmithKline, we were the informed that the ovalbumin level in the Pandemrix vaccine was <0.66 µg/ml.
When we saw the comments in the review regarding ovalbumin level, we contacted GlaxoSmithKline again. We were then informed that According to GlaxoSmithKline Biologicals Certificate of analysis/Summary Protocol – final bulk vaccine have no more than <0.333 µg/ml.
We apologize for the confusion this has created.

4. P 11 line 32 The author says that the reaction in the first patient was a definitive reaction to the vaccine. The description may be compatible with an allergic reaction but is largely non specific and cannot be called a definitive allergic reaction.

OUR RESPONS. We agree that the patient in question had a mild allergic reaction. The combination of a respons from both the gut and the skin makes this an allergic reaction. We have modified the text and it now reads:
«This patient had a mild allergic reaction to the vaccine.»
«Of the patients who participated in this study, one showed a clear adverse reaction to the egg-containing vaccine and two had a possible adverse reaction. All reactions were mild and needed no immediate intervention.»
«The patient with an allergic reaction to the vaccine and the two patients with possible reactions had never before been exposed to egg. «
«All patients tolerated the 10% dose, and ultimately received the 90% dose,. and only one patient showed a mild reaction.»

5. P11 line 42 For the third patient (8 year old) it should be repeated beside the SSIgE level (14.6 kU/L) that this was assessed three years before. When was the last SPT done and what was the result?
The last SPT was done January 2009, the result was a ++++ reaction in the skin. We classify the skin reaction regarding to the size of the positive histamine control, when the positive control is >3mm. This SPT is considered a positive reaction to egg.

6. P15 line 31 "The one patient with a definite reaction to the vaccine, and the two with possible reactions to vaccine had never been exposed to egg. This warrant for a cautious approach when

vaccinating anyone tested positive for egg allergy, but never have been exposed to egg. These patients should be treated as if they had had severe reactions to egg exposure when vaccinating with a vaccine containing egg residue."
To recommend to treat patients who had never eaten eggs as if they had had severe reactions is inappropriate. The evidence to support this is flimsy. None of the clinical problems in these patients appears to be a definitive allergic reaction. No controls were included in this study, preventing the author to be in position to be very assertive about his inferences.

Our respons. We agree with the objection the reviewer has to this paragraph and it has been taken out.

While the paper cites four recent studies on vaccination of egg allergic patients, there is no discussion comparing the results of the current study with those from these other studies. The discussion lacks depth and perspective on the issue of vaccination of egg allergic patients.

7. P5 line 15 "The Regional Committee for research ethics had no objections to this study."
This is an unusual wording. Was the study approved? If so, please rephrase in a more positive way.

We have written consent from the case histories presented in this article. We did not have the approval from the the Regional Committee for Research Ethics in Northern Norway before we vaccinated the children and adolescents, but we applied in November 2010. The answer came 17 december 2010, their answer is translated from norwegian, the Norwegian text follows below.

"The committee consider the vaccination to be part of ordinary treatment, even though it can have been experimental. The project is therefore outside the mandate of the committee. It must be added that the committee consider that the applicant both should and has the right to publish the treatment. "

"Komiteen vurderer det slik at den vaksineringen som har skjedd i prosjektet er å anse som ledd i ordinær behandling, selv om den kan ha vært eksperimentell eller utprøvende. Prosjektet faller således utenfor komiteens mandat. Det må likevel tilføyes at komiteen vurderer det slik at søker både bør, og har rett til, å publisere behandlingen."

We have changed the the paragraph in the article and it now reads:
«Ethical aspects
We obtained the written consent of the parents of the case histories presented in this article. We did not obtain approval for the study from the Regional Committee for Research Ethics in Northern Norway before commencing the vaccination drive, but we applied for approval in November 2010. The Committee responded that it considered the vaccination drive as 'part of ordinary treatment', even though it could have been experimental, and that the project therefore fell outside its mandate. However, it added that we as the applicants had the right to 'publish the treatment'.»

This paper is not bad but its interest is limited given its relatively small number of patients and its focus on a monovalent pandemic vaccine. Several other articles on the same issue have been published in the past two years and included more patients and/or assessed the safety of the trivalent seasonal vaccine which is more relevant outside the pandemic. (Chung 2010, Gagnon 2010, Greenhawlt 2010, Owens 2011)

**VERSION 2 - REVIEW**

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| **REVIEWER** | John M. Kelso, MD<br>Scripps Clinic<br>San Diego CA USA<br><br>No competing interests. |
| **REVIEW RETURNED** | 29/07/2011 |

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| **GENERAL COMMENTS** | The authors have adequately addressed my concerns. |