Dear Dr. Turner,

Manuscript ID BMJ.2015.029119 entitled "Safety of Live Attenuated Influenza Vaccine in Children with Egg Allergy: a multi-centre, non-randomised intervention study"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to make a final decision on it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Elisabeth Loder
eloder@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Decision: Put points

Present: Elizabeth Loder (chair); Rafael Perera (statistical consultant); Wim Weber; Jose Merino: Jessamy Bagenal; Alison Tonks; Helen Macdonald; Rubin Minhas

* We are very interested in this work and feel that it will add important information for doctors and parents. That said, the conclusion of safety appears to us to be an overstatement. You can say that based on these findings the SAEs are likely to be less than X but it seems unwise to claim safety.

* Our statistician noted that some of the subgroup analyses (particularly in the youngest group) are underpowered but point towards some increased risk. Paradoxically this is not apparent in the ASthma score but this should also be discussed.

* Our statistician also thought that exploration of dose-effect on adverse event should also be done.

* Given that severely allergic children were excluded, we did not think we would be completely reassured by this paper if we had a severely allergic child, especially when the vaccine is for a disease that isn't uniformly fatal. A serious adverse event with a probability of even 1:1000 would be quite significant, so some toning down is required, especially of 'what this study adds'.

* We would like you to do a sensitivity analysis with the denominator being the roughly 1/3 of children who had a previous anaphylactic reaction to egg. We think the resulting confidence interval would be informative.

* We agree with the reviewer who would like to see clarification of what "physician diagnosed allergy" means. About half the children had received flu vaccine in prior years. Does this mean we know they are not allergic to egg products? Do you know which vaccines they had received?

* Can you also clarify what is meant by "evidence of wheeze" and where it comes from? From trials? From reporting systems? Can you also clarify what is meant by severe unstable asthma?

* The risks of vaccine should be weighed against benefits; we do not have that information presented anywhere in the paper.

* We were also slightly surprised by the uncontrolled design, which means we can't gauge the incidence of reactions relative to children who are not egg allergic.

* We were also surprised that parents were willing to subject their children to a treatment that might induce a life threatening reaction. How many parents did you approach to get to their final sample?

* We also thought that outcomes were not clearly defined, for example: "The primary outcome was the incidence of allergic reaction as an adverse event following immunisation (AEFI) occurring within 2 hours of LAIV administration in eggallergic children"-- determined how?

* We thought you should focus on explanations and discuss the "maximum impact" for serious and mild reactions – both are important. Please also make clear -- in the paper and also the abstract-- that seriously allergic children were excluded so results don't apply to them.

* We need more detail in the methods about the harms and adverse events: how were they measured or reported, how were they defined? We also need more detail on exactly what happened clinically. These details of each AE could be included in an appendix document.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
Figure 1 indicates that 13 children were excluded as not eligible. Why were these children excluded? How many had very severe anaphylaxis to egg requiring intensive care? How many had had asthma symptoms in the preceding 72 hours?

In the final paragraph, the authors state that the current study supports published guidance that indicates that children with "very severe anaphylaxis to egg requiring intensive care" and those with "evidence of the active wheezing in the 72 hours prior two LAIV" should not receive LAIV. It would seem more appropriate to state that although such children were excluded, it is not known whether or not they are at greater risk for vaccine reactions and may not be at increased risk.

The actual guidance cited in reference number 18 states that even "children with a history of severe anaphylaxis to egg which has previously required intensive care, should be referred to specialists for immunisation in hospital" and that although LAIV "should be deferred in children with a history of active wheezing in the past 72 hours or those who have increased their use of bronchodilators in the previous 72 hours. If their condition has not improved after a further 72 hours then, to avoid delaying protection in this high risk group, these children should be offered an inactivated influenza vaccine." It seems important to state that even children in these groups should be vaccinated with these precautions and that the precautions themselves may be unnecessary.

Additional Questions:
Please enter your name: John Kelso

Job Title: MD

Institution: Scripps Clinic

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Do you hold any stocks or shares in an organisation that may in any way
gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
The study and manuscript by Turner et al represents a well-designed observational study of the safety of LAIV in children with egg allergy, some of whom also had well-controlled asthma or recurrent wheeze. The discussion of the results and the conclusions are supported by the data presented. I have a few minor comments for author consideration:

Page 10, lines 38-44: The grammar of the sentence "Secondary outcomes were: incidence..." appears to be suboptimal as generally a colon should not follow a verb and the list of secondary outcomes is difficult to understand with clarity (I believe there were 2 in total and that the ACT outcome was the change between prior to vaccination and 1 month following?).

Page 11, line 13: I believe there is a missing close parentheses after "12 months"

Page 11, line 19: "prior influenza administration..." would be better stated as "prior receipt of any influenza vaccination (IIV or LAIV) and prior receipt of LAIV" or something similar

Results:

The non-significantly higher rate of wheeze in younger children is not unexpected given the pathophysiology of childhood wheeze. It is not clear how this analysis addresses the question of whether LAIV induces a higher rate of wheeze in children less than 5 years of age. The authors may wish to clarify the utility of their finding, perhaps by contrasting it with the ACT score in the various age groups, which provides a pre- and post-vaccination assessment within the same children, controlling for age effects.

Table 2: Rates of parent-reported wheeze and medically-attended wheeze in children following LAIV are available as "wheeze" and "medically-attended wheeze" in Ambrose et al EJCMID 2012, Ashkenazi et al PIDJ 2006, and Fleming et al PIDJ 2006. The time intervals for collection appear to differ from the Turner et al study however.

Discussion:
Limitations of the current study should be discussed, in particular that the study was not a randomized placebo-controlled study and thus event rates can only be compared to historical data and/or a clinical assessment of relevance.

The authors may wish to clarify that the selection of LAIV with a high ovalbumin content represent something of a worse-case scenario given that much of the vaccine used has much lower ovalbumin content.

It is notable that ACT score improved following LAIV in children 2-11 years. A reduction in wheeze following LAIV has been observed in randomized studies (Fleming et al, PIDJ 2006). This may be due to short-term non-specific antiviral immunity induced by innate immunity mechanisms (see Zhu et al, Vaccine 2010).

Additional Questions:
Please enter your name: Chris Ambrose

Job Title: Vice President, Infectious Disease, US Medical Affairs

Institution: AstraZeneca

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may
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Do you hold any stocks or shares in an organisation that may in any way
gain or lose financially from the publication of this paper?: Yes

If you have any competing interests (please see BMJ policy) please declare them here: I am an employee of AstraZeneca, the manufacturer of LAIV

Reviewer: 3

Recommendation:

Comments:
This article describes the occurrence of AEFI in egg-allergic patients administered the quadrivalent live attenuated influenza vaccine. While there is now large evidence that injectable influenza vaccines are safe in egg-allergic patient, the submitted paper expands the evidence that LAIV is also safe for these patients. This is a very good study, with a large number of patients, well selected and a good follow-up to detect the occurrence of adverse events. I only have minor comments to help clarify the results.

P13 line 15-22 "For this study, we sourced vaccine with detectable ovalbumin. In 667 (86%) children, the LAIV batch used contained >0.3 ng/ml ovalbumin, of whom 511 (66%) received a dose containing >1ng/mL ovalbumine"

The amount of ovalbumine is greater than 0.3 ng/ml or 0.1 ng/ml. Please describe the upper value of the amount of ovalbumine or the range of values.

P14 Line 37 "Therefore, no child experienced a systemic reaction following LAIV"
This should be reworded to say "Therefore, no child experienced a systemic reaction "caused" by LAIV

P15 line 19 "Sixty-two children (8.1%, 95% CI for population 6.3-10.3%) experienced lower respiratory symptoms …P15 line 27 To assess this, in an additional exploratory analysis, we compared the rate of lower respiratory symptoms in children with asthma or recurrent wheeze: children under 5 years were slightly more likely to develop lower respiratory symptoms compared to those over 5 years, although this did not reach statistical significance (22/149 (15%) vs 26/296 (8.7%),P=0.07)". I understand that only 14 [62 – (22+26)=14] children with lower respiratory symptoms did not have asthma or recurrent wheeze. Please also provide the percentage stratified by age (under 5 and ≥5). The group "over 5 years" should probably be labeled "5 years and older"

P15 line 52 "There was no significant change in ACT score for children 12 years and over (p=0.12). In those aged 2-11 years, there was a small but significant improvement in ACT following LAIV (p<0.001). A similar improvement was also noted when the analysis was restricted to children under 5 years (p<0.001)."
Please provide the actual change in ACT scores for the different groups.

Additional Questions:
Please enter your name: Gaston De Serres

Job Title: Professor of Epidemiology

Institution: Laval University, Quebec, Canada

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may
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Do you hold any stocks or shares in an organisation that may in any way
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If you have any competing interests (please see BMJ policy) please declare them here: Research grants from GSK for studies on Hepatitis B and measles.

Reimbursment by GSK of travel expenses to attend an ad hoc advisory board meeting. No honorarium

Honorarium from the Ontario Nurse Association for expert testimony on the "Vaccinate or mask policy"

Reviewer: 4

Recommendation:

Comments:
Overall:
This is a well-conducted, rigorous study that in my opinion is long overdue, which should finally dispel the myth that the trace egg in any influenza vaccine—IIV or LAIV--is a risk for the egg allergic individual. Their analysis of wheeze risk is brilliant and answers another lingering question about the initially reported risk of LAIV to kids who have wheezed previously (and who ironically are most in need of the mucosal immunity from LAIV but have been contraindicated from receiving it). Having conducted TIV research myself, I have appreciation for how hard recruitment is to adequately power a study to essentially find an event akin to finding a needle in a haystack. I think they've done an excellent job, and this should be a high impact publication that has major policy implications. And it will decrease morbidity. Again, liberation of this vaccine to this population is long overdue and will be of major long-term health and economic benefit.

Introduction:
No comments regarding any changes. This is clearly written and elucidates the clinical problem. Given the scope of the trial

and the reach this report may have to other westernized nations, I would ask the authors to consider expansion of possible case numbers (lines 38-42) in two ways. The first would be to be to elucidate number of egg allergic individuals in the UK, in Europe, Australia, Canada, and the US (these numbers are easily available in the Allergy literature, and will serve to emphasize that this affects hundreds of thousands of kids, so as not to minimize the issue of why a change in policy based on these data may be urgently indicated. The second would be to stratify the number of estimated egg allergic children with asthma or history of transient wheeze (or reactive airways), which is the highest risk group for influenza related complications. Again approximate estimations should be easy to compile, and again I think this strengthens the message of this manuscript. The policy implications for these findings are very large, and thus strengthening the scope of problem that these data could solve will serve to maximize the potential impact of the manuscript.

Methods:
Line 11 (page 9): please elaborate on what you mean by "physician diagnosed egg allergy". This makes all the difference in terms of how any policy may be interpreted. What were the criteria—history of reaction, documented failed egg oral challenge, positive skin test or sIgE >95%PPV, or other? This must be explicitly stated to provide diagnostic validity and provide a basis for who will ultimately be included in a policy shift. Also, what type of physician makes this diagnosis--I assume you imply Allergy specialist here but if a GP or pediatrician made some of these diagnoses, but again the validity of who makes the diagnosis can vary, and this would potentially affect your pre-test probability of the child being at risk for possible egg related adverse reactions attributable to this as a vaccine excipient (e.g., I trust an allergist's diagnosis far more than a non-allergist's). A table for the criteria would suffice for emphasis in translating the findings to policy, and if these differ from prior TIV/IIV or LAIV studies, please justify/explain the variation.

Line 17, page 11: please provide evidence to substantiate what I would say is a ridiculous claim of airborne reaction to egg. I have no doubt this is a route of exposure to which reactivity is attributed, but short of directly snorting/inhaling dehydrated egg powder or water in which egg protein was boiled and protein leached, I am not aware of any case reports or rigorously conducted studies showing that any egg protein can be inhaled in vapor and be realistically attributed to causing a reaction. This route has been reported for shellfish, and debunked for peanut. This group itself would be reportable.

Line 22 (same page): why were recipients previously tolerant of LAIV included? Was a pre-specified sensitivity analysis planned to exclude these cases?

Line 30-40: What was the estimated power for this sample size? I understand the difficulty of finding a confidence interval around a highly improbable event, but I think precursory power should be reported. For comparison, can you list what the rate of reaction to LAIV in the general population is, and show power based on difference in those populations, which would be the better comparison, rather than trying to show power to demonstrate the effective rate you expected to find in this population would be "nil"? Though this is a bit of post hoc dabbling, it could be considered a secondary analysis, and you'd be showing there was adequate power for this. For affecting policy, I would argue that it's less important (but not unimportant) to show that this vaccine causes virtually no reactions in the egg allergic, and more important to show it causes no higher rate of reaction than would be expected in the general population.

Results:
Line 32, page 13: I'd argue to exclude the sensitized children who have never eaten egg before, or at least analyze them as a separate subgroup. These kids are an artifact of past (and erroneous, in my opinion) thinking that we can paternalistically prevent kids from "reacting", and few if any of these PPV's are derived from population based samples and at best represent a poor understanding of posterior probability limited to a clustered sample and not otherwise able to generalize to other settings. Health Nuts in Australia is the only such study actually. The clinical definition of allergy is sensitization in the setting of clear symptoms typical of IgE mediated reactivity. Inclusion of this group may represent a realistic group managed as "egg allergic", but a harsh critic could argue these kids are standard risk until it's definitively proven they react to egg (as opposed to a view that they are highly probable to react to egg). Thus, I'd rather see these kids analyzed as a subgroup, or a sensitivity analysis showing the rate with and without these kids included to make sure the population is enriched with true reactors.

Line 29 page 14: what were these kids tested to? I presume LAIV but this is not stated, and it should be. Were they tested to other excipients in the vaccine as well?

Discussion: I am not sure I'd make such a big deal over a rate of ~1% of localized IgE mediated reactions, and would like to see what the rate is in the non-egg allergic population (and that you show this is not significantly different, thus reassuring the reader this is mere background noise that happens to a few in the course of receiving vaccination). I also think the point of there being lower ovalbumin in successive lots each year is moot. This happened with IIV too, yet the contraindication remained until the US/Canadian effort debunked this was unsafe in 2009-2012. I'd challenge you to find any actual proof that ovalbumin in any type of influenza vaccine was ever actually attributable to a bona-fide IgE mediated reaction, as opposed to historical paranoia that this "could" be a risk factor without any actual proof of danger. The issue here is that this is not a "clean" vaccine, and it has lots of excipients equally or more likely to cause a reaction than the minute quantity of egg. I think you can be much more forward here in saying this is definitively safe, and de-emphasize the ovalbumin levels.

Please do more to emphasize the safety of LAIV in the child with reported wheeze. The use of the ACT as an objective outcome measure was quite brilliant. You should be able to comment if there was enough power to find an effect greater than the index MCID. I agree wholeheartedly with the ridiculous US contraindication, but the CDC and ACIP take a very conservative approach to this concept. Please trust me in that you will be doing the US a huge favor by really hammering home these data that you have. While this may not be enough in and of itself to convince the CDC to change the policy, it may be enough to encourage a US group to explore this subgroup more deeply, which would help make that policy change.

I'd also encourage you to revise your assessment that this vaccine would not be safe for those with severe anaphylaxis. Yes,

you didn't discretely study this, but that doesn't mean that it is not equally as safe. I'd argue that any child who is at risk for anaphylaxis is potentially at risk for ventilation given the right circumstances and these are not two separate populations of kids with anaphylaxis. They are one, and thus the findings would have exceptionally high probability of extrapolating. You have no data to say it's not safe, though equally you have no data to prove it is. You could argue practically that the number of kids meeting that criteria are low, and maybe then you should consider showing the number of expected cases that would be excluded from the policy to show how minimal that would be. These kids are essentially collateral damage from study exclusion, and the probability they'd be fine and benefit from LAIV has to be considered.

But overall this was a fantastic study, and will make a huge, positive impact.

Additional Questions:
Please enter your name: Matthew Greenhawt

Job Title: Assistant Professor

Institution: Children's Hospital Colorado/University of Colorado Denver School of Medicine (starting Nov. 1)

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: Yes

Fees for consulting?: Yes

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If you have any competing interests (please see BMJ policy) please declare them here: -Member of specialty advisory board and have received honorarium from Nutricia for conference lectures
-Member of the medical advisory team for Kids With Food Allergies Foundation and the International Association for Food Protein Enterocolitis (non-financial)
-Consultant to Deerfield Industries, bioIndustries, Gerber, Canadian Transport Agency, Aimmune, and Huron Consulting
-Received research support from a private foundation through the University of Michigan Food Allergy Center
-Received support from NIH grant #2KL2TR000434 and NIH grant #UL1RR024986
-Member of AAAAI EGID, Anaphylaxis, Adverse Reaction to Food, Health Technologies and Joint Task Force on Quality Improvement Measures Committees
-Member ACAAI Conferences On-Line Allergy, Abstract, Practice Improvement, and Adverse Reaction to Food committees
-AAAAI/ACAAI advisor to CDC-ACIP on Egg Allergy/Influenza Vaccine Safety
-ACAAI representative to consensus statement on early feeding guidelines
-Member, NIAID Expert Panel on early introduction of peanut to prevent peanut allergy
-Associate Editor, Annals of Allergy, Asthma, and Immunology
-Editorial board: Allergy and Rhinology; Medscape Pediatrics; Infectious Diseases in Children
-Officer, Michigan Allergy and Asthma Society (2010-July 2013); served as legislative advocacy liaison
-Have testified to Michigan State Legislature on behalf of Michigan State Medical Society and Michigan Allergy and Asthma Society
-Member, Scientific Advisory Council, National Peanut Board
-Medical Advisory Chair, Food Allergy and Anaphylaxis Connection Team
-Member of Joint Task Force on Allergy Practice Parameters

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