Jacob Puliyel

Comments 1 to 20 of 22

- Combined hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type B vaccine; Infanrix™ hexa: twelve years of experience in Italy.

  Baldo V.Hum Vaccin Immunother. 2014.20 comments

  Jacob Puliyel2015 Feb 06 1:11 p.m. (6 days ago) 0 of 2 people found this helpful

  Dear Dr Ferenci

  The EMA I understand is obliged by European Union law to engage the precautionary principle. Until the full scientific evidence is available, where there is evidence of risk, it must take precautionary measures. The comments here indicate the evidence is of more than a risk, but of the harm itself.

  You say Dr. Franco cited studies that Infanrix Hexa is safe. Which ones and where? I can see Dr Franco has cited WHO and CDC statements. The TOKEN study I cited is the largest study done prospectively, as far as I am aware.

  You claim I dishonestly "only cited half of the results" of the TOKEN study. Not so. You cite a different analysis using a different model (Model 2). It is scientifically untenable to claim one cancels out the other.

  The second model does not show statistically significant decrease in risk in the relevant period [4 to 7 days] as you claim. The absence of significance in one model where the

comparator and risk periods are completely different does not cancel out the statistically significant difference shown in the first analysis covering the relevant period.

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- Jacob Puliyel2015 Feb 04 1:12 p.m. 0 of 2 people found this helpful

  I thank Ferenci and Miller for their responses. I will address the three points made by Dr Ferenci

  1) The data I have quoted (from Table 36) was made available by the manufacturers GSK, to defend the safety record of Infanrix Hexa to the regulatory authority (- the EMA). The data suggests a cluster on and following the day of vaccination. If the reporting is so bad the clusters aren't real, then the data can't/shouldn't be used to defend its safety. If the reporting is good, then the clusters are real too, and the vaccine looks unsafe.

  2) Dr Ferenci writes " ..it is immediately obvious from 3A appendices (pp. 301-522, pp. 857-1064) that no matter which disease-group we look at, the vast majority of spontaneous reports with known time are definitely coming from the first few days!"

  The sources for the the reports in the 3A appendices are different. 3A data is self-reported. It is no crime if a parent does not report to the doctor that their child developed leg pain a few days after being administered Infanrix.

  But SIDS deaths are different and have to be reported mandatorily to those like coroners who must determine the cause of death. They are investigated by professional forensic experts. SIDS are 'deaths under suspicious circumstances' - unexplained death that could be infanticide unless proved otherwise. Forensic experts are unlikely to 'forget' to mention immunization, simply because it was not given on the day of death but on the previous day. Reporting bias is less likely to be an issue with such forensic reports. Under-reporting on all days will of course still occur for all the reasons it occurs for other serious adverse events. But it is difficult to argue convincingly that higher under-reporting is likely on the day just after a vaccine is administered, compared to the day of vaccination.

  3) Finally, Dr Ferenci says that active vaccine safety studies are better than passively acquired data. For well designed, managed and executed studies I wholeheartedly agree with him.

  The TOKEN study aimed to assess comprehensively a possible causal relationship between vaccination and unexplained sudden unexpected death of children between their 2nd and 24th month of life. The study was supported and sponsored by the Paul-Ehrlich-Institute (PEI) and the Federal Ministry of Health (Bundesministerium für Gesundheit). Unfortunately this large study with a wealth of data has not been published in an indexed peer reviewed journal as yet. It is available here:

http://www.rki.de/DE/Content/Gesundheitsmonitoring/Studien/Weitere_Studien/TOKEN_Studie/Studyreport.pdf?__blob=publicationFile

Parents of children who had died of SIDS were requested to participate in the study. 37.6% (254 cases) could be included in the study, where parental consent was obtained. Tables 31 and 36 show significantly increased risk of unexplained sudden unexpected death in the first 3 days after hexa- or pentavalent vaccination (1st and 2nd year of life).

So it appears that active studies have confirmed that there are two vaccines which cause 'sudden deaths'. I am grateful that the Italian Court has allowed public scrutiny of GSK's PSUR reports held as confidential by the EMA.

Jacob Puliyel

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- Jacob Puliyel2015 Jan 22 08:55 a.m.edited 0 of 2 people found this helpful

  I thank the authors for their response to my comment.

  I was presuming that in the countries from where this data was gathered, sudden infant death or SIDS is considered 'unnatural death'. If that is so, these deaths will have been investigated by a competent forensic team and the immunization records will have been examined to check if the infant was up to date with its vaccinations or whether there was an element of neglect. Reporting bias (based on parents perception that vaccine was the trigger for events that lead to the death of their child) would have little or no role under these circumstances.

  The authors quote from the 'Guidelines for good pharmacovigilance practices'; that *events that are expected, common and mild, or occur late after vaccination,* are less likely to be reported. That is not applicable here, as *SIDS is completely unexpected and a catastrophic event.*

  Further, the analysis in Table 2 of the linked article http://jacob.puliyel.com/paper.php?id=345 (Please download pdf version) shows that there were 42 deaths in the first 3 days and only 16 in the next 3 days. It is difficult to imagine that reporting bias is responsible for this big a change, in so short a time.

  We will need to find a more plausible explanation. Otherwise we have to accept that the deaths were caused by the vaccine and the diagnosis of SIDS was wrong.

  Jacob Puliyel

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- Jacob Puliyel2015 Jan 19 08:02 a.m.edited 0 of 2 people found this helpful

Apropos the earlier posting there are a couple of other facts that we must consider when looking at the incidence of sudden unexplained deaths immediately following vaccination with Infanrix.

a) The safety assessment document has used the number of doses of vaccine distributed as the denominator. The report acknowledges that all the doses of the vaccine distributed, need not have been utilized.

There can be another argument against using this denominator. As each child is given up to 5 doses (https://www.gsksource.com/gskprm/htdocs/documents/INFANRIX.PDF) and they could die after any one of the doses (and you can die only once), perhaps it would be more appropriate to look at the number of deaths against the number of babies vaccinated (rather than the number of units of vaccine distributed). The appropriate denominator would be about one fifth the denominator used in the report.

b) Appendix 5A in the document sent to the regulator gives the International Event Report in 13 fatal cases. It can be seen in this sample that there were more deaths after the first dose than after the second and more after the second than after the third dose. This is a pattern seen with adverse events following immunization (AEFI) that are causatively related.

c) In May 2005, Zinka and colleagues have reported six cases of sudden infant deaths caused by another hexavalent vaccine (similar to Infanrix), called Hexavac Zinka B, 2006. Marketing authorization in the European Union was withdrawn in August 2005 (Doc.Ref.EMEA/207369/2005).

d) The CIOMS /WHO have revised the widely used Brighton Protocol for assessment of AEFI. The new scheme facilitates misclassification of vaccine related deaths as [Not an AEFI] and this has been discussed on PubMed Commons earlier.
(http://www.ncbi.nlm.nih.gov/pubmed/19061929)
(http://www.ncbi.nlm.nih.gov/pubmed/23452584)
(http://www.ncbi.nlm.nih.gov/pubmed/24021304).

e) In some ways the deaths with Infanrix is similar to deaths seen with the use in Asia of Pentavalent vaccine against 5 disease (DPT, hepatitis B, Hib) Puliyel J, 2013. Some of these deaths have been investigated by the WHO using this revised method and the vaccine had been declared safe.
http://www.who.int/vaccine_safety/committee/topics/hpv/GACVSstatement_pentavalent_June2013.pdf

f) The deaths are completely unnecessary as the vaccines could have been given separately, and separately they have a long track record of safety. One hopes that the findings will result in an honest assessment of the harms being done by these new combined vaccines.

Conclusion

As mentioned earlier there is nothing sacrosanct about the original Brighton Classification (http://www.who.int/vaccine_safety/publications/AEFI_aide_memoire.pdf) but one has to evaluate the two schemes (Brighton vs CIOMS) from the point of view of patient safety to see which scheme would react to rare vaccine related adverse reaction signals early. "The causality scheme that insists on calling all reactions as 'indeterminate' or 'inconsistent/coincidental' just because they were not noticed in the original small clinical trials, undermines the very raison d'être of post marketing surveillance. Patient safety (meaning protecting patients) rather than vaccine safety (protecting vaccines) should be more important."

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- Jacob Puliyel2015 Jan 13 06:40 a.m.edited 0 of 2 people found this helpful

  Baldo and colleagues quote 2 references to suggest that in Germany, a population-based evaluation demonstrated a possible safety signal for DTPa-HBV-IPV-Hib-SP but failed to show an imbalance between observed and expected SUD cases for DTPa-HBV-IPV/Hib von Kries R, 2005 von Kries R, 2006. However this seems to be contradicted by the data that was submitted by the manufacturer to the regulatory authority and the analysis below.

  The GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance's confidential report to the Regulatory Authority on Infanrix hexa (combined Diptheria Tetanus and Acelluar Pertusis, Hepatitis B, inactivated Poliomyelitis and Haemophilus influenza type B vaccine for the period 23 October 2009 to 22 October 2011 (the 15th and 16th Periodic Safety Update Report (PSUR)) has been made available to the public by the Italian Court of Justice Nicola Di Leo and is now available on the internet (http://autismoevaccini.files.wordpress.com/2012/12/vaccin-dc3a9cc3a8s.pdf)

  Section 9.3.1.1 on pages 246-249 documents an evaluation of whether the number of 'sudden deaths' reported, exceeded the number one could expect to occur by coincidence - that is from the natural background incidence of sudden death. The background incidence of 0.454/1000 live births in the first year and 0.062/1000 live births is used, with a healthy vaccine correlation factor of 0.8 applied. Table 36 on page 249 tabulates the number of sudden death that would be expected to occur by chance within a range of days post vaccination.

  Table 1 Cumulative number of observed and expected cases of Sudden Death following Infanrix hexa in children in their first or second year of life

  This is available here: http://jacob.puliyel.com/paper.php?id=345 (Please download pdf version)

  (Source: Table 36 The GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance report to Regulatory Authority)

According to this analysis, the number of sudden death cases reported after vaccination with Infantrix hexa is below the number of cases expected in children in the first year of life. It is equal or below the number of cases expected in children in the 2nd year of life.

> However if one analyses the data looking at deaths in first 10 days after administration of vaccine and compares it to the deaths in the next 10 days, it is clear that 97% of deaths (65 deaths) in the infants below 1 year, occur in the first 10 days and 3% (2 deaths) occur in the next 10 days. Had the deaths been coincidental SIDS deaths unrelated to vaccination, the numbers of deaths in the two 10 day periods should have been the same.

Similarly in children older than 1 year, 87.5% deaths (7 deaths) occurred in the first 10 days and 12.5% (1 death) occurred in the next 10 days.

If we consider the number of deaths in the second 10-day-window-period as the baseline SIDS rate in these healthy children coming for immunization, we can see that there was an excess of 63 (65 – 2 = 63) deaths in the first year and excess of 6 deaths (7 – 1 = 6) among those vaccinated between 1 and 2 years.

In the reporting period, one must conclude that Infanrix hexa vaccine could have been responsible for at least 69 deaths. These are all deaths within a small window period (of 3 weeks) after a catastrophic event which has been investigated thoroughly (forensic investigation of sudden unexpected deaths - SIDS/SUDS), therefor ascertainment bias is unlikely to have played a major role.

Table 2 The daily increment in Sudden Death following Infanrix hexa in children ' is tabulated and made available here: http://jacob.puliyel.com/paper.php?id=345 (Please download pdf version)

The decelerating incremental-deaths further supports the contention that there is a clear relationship of ‘sudden death’ to the vaccination episode. **42 deaths** had taken place in the **first three days** after vaccination, **16 deaths** in the **next 3 days** between day 3 and day 5, **3 deaths** between **day 6 and day 8**, **2 deaths** between day **9 and day 11**, and there were only **2 deaths** in all of the **remaining 10 days**. The fact that rate of deaths decreases rapidly and continuously as time elapses after immunization, makes it clear that the deaths are related to the vaccination episode.

This is being posted on PubMed Commons to put it up for open review by the scientific community, on account of its urgency, as this is a matter that involves the lives of children and there is a continuing risk to children.

As the authors of this article are best qualified to peer review this submission, I am inviting each of the authors castrom@wustl.edu paolo.bonanni@unifi.it mclaudia@fei.edu.br giovanni.gabutti@unife.it franco@med.uniroma2.it fem75838@gsk.com r.prato@unifg.it fvitale@igiene.unipa.it to review it and to post their review on PubMed Commons.

Jacob Puliyel MD MRCP M Phil

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- Team science and the creation of a novel rotavirus vaccine in India: a new framework for vaccine development.

Bhan MK.Lancet. 2014.1 comment

Jacob Puliyel2014 Aug 23 6:43 p.m. 0 of 2 people found this helpful

Comment removed by moderators.

116E Rotavirus Vaccine Efficacy Against Death is 10% of Projected Figures

A member of the National Technical Advisory Group on Immunization (NTAGI India) responded to my posting and I quote him below.

> "With respect to your recent comments on 116 E Rota virus vaccine, inferring that it will save only one fifth of the projected deaths, I think an error has occured in presuming that rotavirus diarrhea of any severity, if managed in the community, shall result in 1% deaths. **The articles cited Lal S, 1994 Kosek M, 2003 for this presumption mention diarrhea cases and deaths and not specifically rotavirus diarrhea deaths.** We all know that case fatality rate due to rotavirus diarrhea is more than all cause diarrhea because of its severity and in most children occurrence of severe vomiting, thus not permitting oral rehydration therapy. I hope, after correcting this error, number of children required to be vaccinated to avert on death due to rotavirus diarrhea will come down and will be in line with the article published on 116 E vaccine."

As this was written in an email to me (and not as a response on PubMed) I will maintain his anonymity. However as it was a response to my PubMed posting I feel the objection and my response to him must be published on the forum. I have redacted his name.

I accept that objection that the mortality (1%) I used for calculations is from figures for diarrhea due to all causes and not specifically for rotavirus diarrhea. I will recalculate with data for rotavirus, specifically.

"Kang in her article Tate JE, 2014 suggests that there are 11.37 million diarrhea episodes due to rotavirus each year, in children under 5 years and there are 78500 deaths. She states that 70 to 89% of hospital admissions (more severe rotavirus infections) occur under 2 years. Professor Bhan writes Bhan MK, 2014 that 70% admissions occur under 1 year. Extrapolating the 70% figure of Dr Bhan, we can calculate that 7.9 million episodes or rotavirus diarrhea occur in the first year.

If 78500 deaths occur in 11.37 million episodes of diarrhea the mortality is 0.69%. The rotavirus deaths prevented by vaccination will be only 8213 rather than 11904, that I had calculated.

If we assume more mortality in infants, that there is zero mortality in the 30% rotavirus infection that occur after age 1 year and all the 78500 deaths occur among the 7.9 million rotavirus diarrhea in the first year (and there are no deaths in the 3.5 million rotavirus diarrhea after 1 years), the mortality rate works out to be 1% which matches the figure I used for my calculations. (It must be noted that I have used the NNT over 2 years not the first year.) If 8000 deaths are prevented (of the projected 78500 deaths said to be caused by rotavirus) efficacy against rotavirus death is a mere 10% not 50%!

If the efficacy against death is 50% and only 8000 deaths are prevented, one must conclude that the total deaths caused by rotavirus are about 16,000 (and the 78500 deaths from rotavirus projected, is an exaggeration – the real figure has been enhanced 500%). The recommendation to use the vaccine was based on projections that are not supported by properly acquired empirical evidence. I hope you agree with these estimates and calculations or else I will be happy to revise my estimates.

The time lines described by Professor Bhan Bhan MK, 2014 suggest that the private manufacturer to set up the plant for manufacture of this vaccine was funded by PATH, B&MG and the Government of India (DBT) in 2000, where as the Phase 3 trial only started in 2008. It is clear that regardless of efficacy in the phase 3 trial (or any objections by NTAGI members,) the vaccine had to be rolled out, if there was to be any returns on the investment.

I am less concerned about this waste of scarce resources. I am more concerned about safety http://www.ncbi.nlm.nih.gov/pubmed/25091662#cm25091662_5770. Dr Bhan has promised complete transparency with the data. I have written to him asking for the safety data in each of the three centers (which has not been published except in an aggregated form). This will help us understand the situation with regard safety issues better. I await his reply which he could share with this group in the interest of transparency."

- Jacob Puliyel2014 Aug 15 06:14 a.m.edited 2 of 5 people found this helpful

Team science must not be allowed to influence objectivity

Projections of deaths exaggerated 5 times

The authors must be congratulated for describing the team effort involved in the development of the new 116E rotavirus vaccine. In this process the Government of India through its funding of the Department of Science and Technology, the Bill and Melinda Gates foundation and PATH; all became partners who had a stake in getting this vaccine licensed and commercialized. Objectivity can become a casualty in the process.

The authors for example argue that the need for this vaccine is evident from the fact that rotavirus causes 75000-122000 deaths each year. The magnitude of the problem is not in disputed but the efficacy of the remedy needs to be evaluated. The vaccine is said to have efficacy of 50%. However it reduces only 10% of the projected mortality.

Empirical data from the trial with the 116E vaccine however suggests that at best, (assuming 100% coverage with the vaccine,) deaths prevented will only be one tenth of the 100,000 deaths said to be caused by rotavirus.

Data from the trial of the 116E vaccine showed that during the first two years after vaccination, the number of infants that needed to be immunized to prevent one episode of rotavirus diarrhea of any severity was 21 (NNT = 21) Bhandari N, 2014. Assuming case fatality from rotavirus diarrhea (all cases regardless of severity) is 1% with community management Lal S, 1994 Kosek M, 2003, 2100 babies will have to be vaccinated to prevent one death from diarrhea in the first 2 years of life. If the birth cohort of 25 million are vaccinated only 11,904 lives may be saved. Either the efficacy figures are wrong or we must assume the projections of death from rotavirus infection are exaggerated - multiplied 5 times.

Empirical evidence on intussusception from the same trial, have been described elsewhere in PubMed Commons http://www.ncbi.nlm.nih.gov/pubmed/25091662#cm25091662_5770.

Thus we salute the effort that went in to make the vaccine, but that enthusiasm must not stand in the way of dispassionate evaluation of risks and benefits of the drug.

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- Active surveillance for intussusception in a phase III efficacy trial of an oral monovalent rotavirus vaccine in India.

  John J.Vaccine. 2014.1 comment

  Jacob Puliyel2014 Aug 14 9:58 p.m. 0 of 2 people found this helpful

  Licensing the vaccine for general use (in remote areas of India), seems impossible to justify

  I commend Dr John and colleagues for this report on the trial with the 116E Indian rotavirus vaccine. However the authors limit their discussion to comparisons with the trials of Rotarix and Rotateq which recruited some 60,000 patients each. It will be more useful to compare the 116E trial safety results with the RotaSheild vaccine trials http://www.path.org/vaccineresources/files/RotaShield_Fact_Sheet_CDC.pdf.

  RotaSheild trial

The RotaSheild trial recruited double the numbers recruited in the present 116E study. RotaSheild was licensed after the trial involving 14,687 patients (10,054 received the rotavirus vaccine and 4,633 received placebo). In the study there was one case of intussusceptions among the 4633 receiving placebo. This suggests that the 'normal rate of intussusception' was approximately 2/10,000, in that population. Five cases of intussusceptions occurred among 10,054 RotaSheild vaccine recipients. Thus there were an excess of 3 cases of intussusceptions for each 10,000 children vaccinated. **All the intussusceptions were among infants who received a second or a third dose of vaccine**. The difference between the vaccinated and placebo recipients was not statistically significant
http://www.path.org/vaccineresources/files/RotaShield_Fact_Sheet_CDC.pdf.

116E Trial

With the 116E vaccine trial there were 6 cases of intussusceptions in 2267 controls which works out to be 2.6 cases per 1000 placebo recipients. The 'normal rate of intussusception' in this study was at least 10 times higher than the RotaSheild trial (where it was 0.2 cases per 1000 placebo recipients). There were 17 cases of ultrasound confirmed intussusceptions among the 4532 given the 116E vaccine which is 3.75 cases per 1000 babies vaccinated. The comparative figure for the RotaShield study was 0.5 cases/1000. In the 116E trial there was an excess of 1 case of intussusceptions for every 1000 children vaccinated with the rotavirus vaccine (compared to the RotaSheild trial where there were 3 excess intussusceptions per 10,000 vaccinated). RotaSheild vaccine was withdrawn after licensing, on account of unacceptable risk of intussusception. The risk of intussusception in the 116E trial was three times higher than with the RotaSheild trial. We are told that in the 116E trial, 50% intussusceptions diagnosed by ultrasound, resolved spontaneously John J, 2014. In the remaining 50% there is need for urgent treatment by a radiologist or pediatric surgeon. In remote parts of India, without motorable roads, let alone radiologists and pediatric surgeons, mortality will be near 100% http://emedicine.medscape.com/article/930708-overview. Such specialized care (radiological or surgical reduction of intussusception) is not available in vast swathes of India and we can assume vaccinated babies would die at home passing blood and mucus in the stools and it will be presumed they had died of dysentery and sepsis rather than intussusception caused by the vaccine.

Intussusception risks compared to diarrhea deaths avoided

Assuming only 50% ultrasound diagnosed intussusceptions need urgent treatment John J, 2014 we can assume that one child in 2000 vaccinated babies will develop this life threatening condition. The possible harm in remote areas (deaths from intussusceptions 1/2000) is not offset by benefits (diarrhea deaths avoided using the 116E vaccine).

In the first two years after vaccination, there number of infants that needed to be immunized to prevent one episode of rotavirus diarrhea of any severity was 21 Bhandari N, 2014. Assuming mortality from rotavirus diarrhea to be 1% in the first 2 years of life

with community management Lal S, 1994 Kosek M, 2003 2100 babies will have to be vaccinated to prevent one death from diarrhea in the first 2 years of life.

When 2100 babies are vaccinated to prevent that 1 death from rotavirus diarrhea - 1 child will have intussusceptions and die in remote areas of the country. This is why, given the limited evidence of this 116E trial, licensing the vaccine for general use (in remote areas of India), seems impossible to justify.

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- Intussusception in southern India: comparison of retrospective analysis and active surveillance.

  Jehangir S.Vaccine. 2014.1 comment

  Jacob Puliyel2014 Aug 12 08:51 a.m.edited 0 of 2 people found this helpful

  I congratulate the authors of this analysis. However their analysis begs more questions than it answers.

  They found that there were 581 cases of ultrasound diagnosed intussusception per 100,000 child years, during the Rotavirus trial, which works out to be 1 intussusception in every 172 children, each year, or 1 intussusception for every 86 children who were followed up for 2 years in the study (approximately - not counting 6 weeks before vaccination).

  Bhandari et al Bhandari N, 2014 have reported that 40 babies have to be vaccinated to prevent one severe rotavirus gastroenteritis episode (NNT = 40) in the 2 year of study.

  The analysis by Jehangir et al Jehangir S, 2014 of data from the Rotavirus vaccine trial showed that 1 in every 86 babies in the trial: 1) developed symptoms and signs of intussusception confirmed by a study pediatrician (namely pass blood in stools, or have continuous vomiting, abdominal distension or abdominal lump) and 2) had the diagnosis of intussusception confirmed on ultra sound.

  About half the cases resolved spontaneously. In field conditions, the other half will need urgent radiographic reduction or surgery and if these are not available (in remote villages where the vaccine will be administered), mortality is near 100%

  Jehangir and colleagues report intussusception in the study sample, without differentiating the babies who received the study drug (rotavirus vaccine) from those who received placebo. This differentiation is crucial because the rate of intussusception in the controls can be assumed to be the natural rate of intussusception using the surveillance methods described in the study.

As the study has now been analysed after unmasking the vaccine recipients, this data on how many among the trial drug recipients and how many among the placebo recipients developed (ultrasound proven)intussusception, should be provided on the PubMed Commons. From this we can determine the NNT for intussusception (numbers of babies that need to be vaccinated to cause intussusception in 1 child) The authors need to publish data on the number of ultrasound diagnosed intussusception per 100,000 child years among those who received rotavirus vaccine and the corresponding figure for placebo recipients.

Instead of this comparison, the authors do a retrospective analysis of data on intussusception treated at their tertiary referral hospital, between 1 January 2010 and 31 August 2013.

Only babies who had intussusception that needed surgical or radiological treatment and which was confirmed on ultrasound examination, were included.

Thus only cases qualifying as intussusception at Level 1 diagnostic certainty, were included and all those whose intussusception resolved spontaneously (without medical intervention) were excluded from the retrospective study.

Under these circumstances it is meaningless to assert that all the babies selected for analysis in the retrospective study needed some intervention but only about 44% of those that were identified in the rotavirus vaccine-trial-active-surveillance, needed intervention.

The authors then go on to conclude that, as 56% of babies with ultrasound diagnosed intussusception in the vaccine trial recovered spontaneously, active surveillance is not a good method to detect adverse events following immunization, and that sentinel hospital based surveillance (for post marketing surveillance after rotavirus vaccine introduction) was better.

The rationale for this conclusion is difficult to fathom. Children who come to tertiary centers (and sentinel surveillance hospitals) with intussusception usually survive. It is the babies in remote areas, far away from roads and transport who die untreated and undiagnosed after intussusception.

The sentinel surveillance will have no record of these cases of intussusception or deaths. Their deaths will not even be counted using the WHO recommended strategy of sentinel hospital based surveillance. That is the big tragedy.

PermalinkShare

- Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian children in the second year of life.

  Bhandari N.Vaccine. 2014.1 comment

Jacob Puliyel2014 Aug 12 01:11 a.m.edited 0 of 2 people found this helpful

I read with interest this paper that describes efficacy and safety of the 116E rotavirus vaccine in the 2nd year of the trial. The results for the first year were published earlier in June 2014 Bhandari N, 2014. The authors need to be congratulated for this study.

However some of the data appears incongruous. According to the clinical trial registry http://clinicaltrials.gov/show/NCT01305109 one of the secondary outcome measures was to be "safety of ORV 116E for intussusception events [Time Frame: Up to 2 years of age] Safety of ORV 116E for intussusception events in comparison to a placebo will be assessed in all subjects, from day of 1st dose till the age of 2 years (24 months) + up to 14 days". The term used here is 'intussusception events' not specifically only cases with Level 1 certainty.

The multicenter trial was conducted in 3 centers at Delhi, Pune and Vellore. The study was done in 6799 infants of whom 4532 received the 116E rotavirus vaccine and 2267 received placebo. In the Vellore limb of the study 1000 received the vaccine and 500 were given placebo.

Bhandari N, 2014 reports that 8 babies developed intussusception (intussusception by Brighton Level 1 criteria) during the 2 year follow up . However Jehangir et al, in the same issue of the journal Vaccine Jehangir S, 2014 report that there were 16 cases of intussusception (diagnosed on ultrasound) in the 1500 infants followed up at Vellore. 7 of these required radiological reduction meeting Brighton criteria level 1.

It seems unlikely that there were 16 children with intussusception in Vellore center (7 meeting level 1 criteria) and there were only 11 cases in the entire trial. This would mean that there were 7 cases (meeting level 1 criteria) in Vellore among 1500 children studied and only 4 case among the 5041 children at Delhi and Pune. In view of this, I will request the authors to report in the PubMed Commons how many babies in the two group (vaccinated and placebo group) had intussusception (any level of diagnostic certainty by Brighton criteria) and how many had Level 1, Level 2 and Level 3 certainty.

PermalinkShare

- Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program.

  Carlin JB.Clin Infect Dis. 2013.1 comment

  Jacob Puliyel2014 May 22 11:21 a.m.edited 2 of 3 people found this helpful

  Post-marketing surveillance cannot properly estimate risks

  The authors must be congratulated for conducting a study whose scope was so vast. However it must be recognized that RCTs are the best method to look for risks and

benefits. Post-marketing surveillance is relied on to detect rare adverse events. It has severe limitations in quantifying the magnitude of risks. The present study highlights the problem well.

1 The authors estimate the risk of intussusceptions (IS) in two window periods after immunization. Previously surveillance had found that the incidence of IS was significantly increased in the first 3 weeks and more after the first dose than after the second dose. But that does not imply the risk of IS is limited to this window period alone. Only long term RCTs can really identify the full risk of IS after immunization and can categorically confirm that there is no risk in other periods.

2 For estimating reduction of diarrhea the authors use the hospital discharge diagnosis coded rota virus (A08.0) or acute gastroenteritis excluding rota virus (A01-A09, K32 excluding A08.0) multiplied by proportion of the cases estimated to be rota virus.

I am not sure how coding is done in the National Morbidity Database of the Australian Institute of Health and Welfare, but in many countries, diarrhea where rota virus is identified is coded as rota virus diarrhea, even where other pathogenic organisms are identified alongside and rota virus may not be the cause of the episode of diarrhea. The new rota virus vaccine strain from India, the monovalent human-bovine (116E) rotavirus, was cultured from an asymptomatic neonate in India. http://www.ncbi.nlm.nih.gov/pubmed/24629994. Some strains of rota virus could be a harmless commensals. The harmless rota virus may be protecting the individual imparting natural immunity without need for vaccines. Just because an organism is identified in a child with diarrhea, it does not necessarily imply that the organism is the cause of the diarrhea.

Furthermore, there are obvious problems in assuming that a fixed proportion of all diarrhea which are 'not coded as rota virus,' are due to rota virus.

Given these drawbacks, the estimate of 6500 rota virus hospitalizations avoided in Australia may not be accurate.

The judgment on acceptability of the risk-benefit equation pivots on the trade off between the putative 6500 rota virus admissions avoided on the one hand and the 14 cases of IS caused by the vaccine on the other, and these figures may not be reliable in the first place.

3 In their conclusions in the Abstract the authors say the "balance of risks and benefits at population level was highly favorable – a finding likely to extend to other settings despite varying incidence of IS and potentially higher morbidity and mortality from gastroenteritis and IS." This conclusion is clearly debatable.

The morbidity and mortality from gastroenteritis may be high in developing countries, but the morbidity and mortality for IS is disproportionately higher. Most developing countries can manage dehydration but facilities for surgical and radiological management

of IS may not be available in large areas, making the risk unacceptable in accordance with the principle of primum non nocere.

4 Another factor the authors do not consider in their conclusion (that the findings are likely to extend to other countries,) is the varying vaccine efficacy seen in different countries. While the efficacy is nearly 90% in Western countries it is barely 50% in the tropics. Although the authors do not refer to the study by Madhi et al http://www.ncbi.nlm.nih.gov/pubmed/20107214 it is often quoted in this context. Severe rota virus gastroenteritis (SRVGE) was more common in Malawi than South Africa (13.1 vs. 5.4) and even though efficacy was lower in Malawi (49.4% vs. 76.9%) more cases of SRVGE were prevented by vaccination (6.7 vs. 4.2) in Malawi. This is often given as the justification for using the vaccine (with such low efficacy) in poor tropical countries.

This does not apply to all nations in the tropics. Although the incidence of gastroenteritis is high in India, the incidence of rota virus diarrhea was even less than South Africa. The incidence SRVGE in the unvaccinated in India was 3.4% compared to 13.1 in Malawi and 5.4 in South Africa. The absolute risk reduction (ARR) by vaccination was tiny in India (1.7). This is much lower than the benefit in Malawi (6.7) and even South Africa (4.2). It raises questions about the need for the vaccine in countries like India using the 'disease burden' argument. http://www.ncbi.nlm.nih.gov/pubmed/24629994#cm24629994_3808. Clearly each country needs to evaluate local risks and benefits and a blanket recommendation for all countries for the vaccine is perhaps not appropriate.

5 **In conclusion:** This study clearly shows the problems of relying on post marketing surveillance to evaluate harms. After unusual adverse events have been identified during post marketing surveillance, (if they are serious in nature) the vaccine must be withdrawn and reassessed in RCTs of sufficient size.

6 The data from the small 2-year follow-up RCT of the Indian vaccine 116E (4500 children received the new rota virus vaccine) will help understand if the '3 week window' is adequate to identify all adverse events. This follow-up paper is awaited. The preliminary report is available http://www.ncbi.nlm.nih.gov/pubmed/24629994#cm24629994. From the initial data it appears that the incidence of IS may be higher with this vaccine and so it may be a good vaccine to study the 'window period' of increased risk of IS.

PermalinkShare

- Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial.

  Bhandari N.Lancet. 2014.5 comments

  Jacob Puliyel2014 Apr 18 06:03 a.m. 1 of 3 people found this helpful

Comment removed by moderators.

The authors have not responded to my invitation to participate in this discussion on the PubMed Commons as yet.

One of the authors Professor Gagandeep Kang has however sent a response to another discussion group discussing the comment. I will quote her concluding statement below.

"While I agree with Dr. Puliyel that AEFI surveillance is essential (and more critically, providing increased access to care in any medical emergency), I would question the ethics of waiting for a rate of a rare event before licensing a vaccine, that while imperfectly effective at 56% efficacy, clearly did not produce intussusception in 4500 immunised children. Based on available evidence, I do not think that this live oral vaccine is perfectly safe and I anticipate that in post-marketing surveillance we will find that there is a risk of intussusception, but I do believe that all testing so far has shown that the vaccine has the potential to prevent more morbidity and mortality in India than it could possibly cause, particularly among those most vulnerable."

I will respond to that on this forum, as I feel it is more appropriate.

1) In the study there were 50% more intussusceptions among the vaccinated. There seems to be 1 excess case of intussusceptions (?vaccine induced intussusception) for every 2000 babies vaccinated. Obviously the sample size was not adequate to look for statistical significance. For the present we have to assume that this difference will hold when the sample size is enlarged.

This is 6 times worse that Rotasheild which was withdrawn for causing 1 case of intussusceptions for every 12,000 vaccinated.

2) NNT for preventing 1 case of diarrhea (SRVGE) was 55. When 2000 children are vaccinated 36 cases of diarrhea would be avoided and 1 child may develop intussusception.

Intussusceptions are difficult to diagnose and treat in rural India where the vaccine will be used. Meier and colleagues suggest that children with intussusceptions treated at a hospital in a developing country have a significantly longer duration of symptoms, an increased incidence of nonviable bowel, and a mortality of 18% < PMID: 8798362> Many in India will not even reach a surgical center before they die.

I submit that it will be dangerous to launch this vaccine without further proof that it is safe.

- Jacob Puliyel2014 Apr 15 2:02 p.m.edited 1 of 3 people found this helpful

50% More Intussusception Among Vaccinated: Full Trial Data Is Awaited

According to the Clinical Trials Registry this study, started in March 2011 was estimated to be complete in April 2014.

The data published in Lancet on March 12, 2014 refers only to the first half of the study (efficacy and safety of ORV 116E assessed in the first year of life). Data on efficacy and safety up to 2 years (from 14 days following the 3rd dose till the age of 2 years (24 months) + up to 14 days.) is still awaited.

Even in this small sample studied for 1 year, the incidence of intussusception among the vaccinated was 50% more than controls. The rush to recommend licensing this drug before presenting the full trial data is surprising.

Furthermore, contrary to expectations, it is now known that transplacental rotavirus IgG interferes with immune response to the live oral rotavirus vaccine (ORV-116E) in Indian infants Appaiahgari MB, 2014. The very low incidence of severe rotavirus gastroenteritis (SRVGE)seen in the study of Bhandari N, 2014 may be due to the protective effect of the transplacental antibodies. The vaccine is probably not needed in these circumstances.

However Appaiahgari MB, 2014 found that higher doses of the vaccine was able to overcome the inhibitory effect of this RV IgG. The safety of the high-dose-vaccine has not been studied and so cannot be recommended as yet.

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- Jacob Puliyel2014 Apr 04 3:26 p.m.edited 0 of 2 people found this helpful

MINISCULE RISK REDUCTION MAKES $1 ROTAVIRUS VACCINE (116E) UNECONOMICAL IN INDIA

The authors must be congratulated for this study and the candid reporting of the absolute risk reduction (ARR) and numbers needed to treat (NNT).

LOW DISEASE BURDEN

Although rotavirus vaccine efficacy is lower in developing countries, it is advocated for poor countries because of the higher disease burden. Severe rotavirus gastroenteritis (SRVGE) was more common in Malawi than South Africa (13.1 vs. 5.4) and even though efficacy was lower in Malawi (49.4% vs. 76.9%) more cases of SRVGE were prevented by vaccination (6.7 vs. 4.2) Madhi SA, 2010. This is often given as the justification for using the vaccine with such low efficacy in poor countries.

The incidence SRVGE was low very low in the unvaccinated in India (3.4%) compared to 13.1 in Malawi and 5.4 in South Africa. This raises questions about the need for the vaccine in India using the ‘disease burden’ argument.

The absolute risk reduction (ARR) by vaccination was small (1.7). This is much lower than the benefit in Malawi (6.7) and even South Africa (4.2) Madhi SA, 2010.

The NNT was 55. At $3/child, vaccination will cost $ 165 per SRVGE avoided. This is four times the societal cost of hospitalized diarrhea in India ($40.60) Mendelsohn AS, 2008

RISK OF INTUSSUSCEPTIONS

Intussusceptions are more dangerous in developing countries where facilities for its diagnosis and treatment are not easily available in remote areas. The earlier rotavirus vaccine RotaShield had been approved after clinical trials involving 10,054 children. It was then withdrawn from the market for causing intussusceptions (1 in 12,000 children).

After the RotaSheild fiasco, FDA approval of RotaTeq based on results of three phase III trials of the drug which treated a combined 72,324 infants in 11 countries.

The 116E has been studied in only 4532 with 2187 controls (total 6719). This is grossly inadequate for studying safety of this drug. The authors seem to suggest that this small study is sufficient for licensing the drug and safety can be examined during post marketing surveillance! It will indeed be a very brave licensing authority who, based on this study of 6719 children, will license the drug in countries like India where active post marketing surveillance is non-existent and where there is no proper 'VAERS-like' system available. In this context Paul King has proposed an effective system for AEFI surveillance with meaningful penalties for any healthcare provider's failure to report any possible AEFI to those maintaining this AEFI database.

Perhaps those keen on the roll out of the vaccine may put such a system in place and some good may come from this vaccine.

Saurabh Kumar, Jacob Puliyel

PermalinkShare

- Comprehensive assessment of serious adverse events following immunization by health care providers.

  Williams SE.J Pediatr. 2013.1 comment

  Jacob Puliyel2014 Mar 21 03:07 a.m.edited 0 of 2 people found this helpful

  Williams and colleagues have described assessment of AEFI employing the algorithm described by Halsey < PMID: 22507656>.

I have posted two very detailed comments to an article by Tozzi Tozzi AE, 2013 which discusses the same subject of the revised WHO Classification of AEFI. I will not repeat the points I have made there but it may be viewed here.

As this is a matter of patient safety I think it is important that the experts who understand the new scheme must explain why the revision was needed and that it will not miss opportunities of picking up new signals. The question is whether the new scheme would have picked up and flagged the signal of adverse-effects like the RotaShield-reactions, had the scheme been in use in 1999. The purpose of this posting is to invite the learned authors of this article on causality assessment to respond to the issues raised in the postings to the Tozzi article and I propose to flesh out those concerns a little further in the context of the article in Pediatrics by Williams and colleagues.

1) Williams and colleagues Williams SE, 2013 suggest that the first step in the general approach to evaluating serious AEFI is to establish a clear diagnosis using Brighton Collaboration case definitions.

The second step is to consider known biological mechanisms.

Neither of these would have been evident when the intussusceptions signal was picked up by the old scheme (and the vaccine was withdrawn expeditiously preventing unnecessary distress to thousands of babies). Even today although a case definition has been developed for 'intussusceptions', the biological mechanism is not clearly defined and so the second step described by Williams et al cannot be completed.

It was reported recently that Pentavalent vaccine (DPT co-administered with measles vaccine (MV) and yellow fever (YF) vaccine) is associated with increased mortality compared to MV + YF alone Fisker AB, 2014. It is pertinent to mention that the biological mechanisms involved are not understood.

Neither is the biological mechanism for increased female mortality in recipients of the high-titer Edmonston-Zagreb vaccine known, although this was first noticed 2 decades ago. < PMID: 8237989>, Aaby P, 1993.

2) It will be instructive to look at how the new algorithm has failed to flag up the deaths following Pentavalent vaccine used in Asia (DPT + Hib + Hepatitis B) and as a result, numerous children continue to be exposed to the risks of this vaccine.

The glossary of the User Manual for the [Revised WHO classification](who.int/vaccine*safety/publications/aevi*manual.pdf) suggests ways and means to rule out a causal association. It defines causal association as a cause-and-effect relationship between the causative factor and a disease with no other factor intervening in the process.

There have been many deaths following use of this Pentavalent vaccine in Sri Lanka. The committee WHO vaccine safety examined 19 deaths in Sri Lanka, 14 of them between 2010 and 2012. In six of the 19, a congenital heart disease was reported.

Does preexisting congenital heart disease rule out a causal association between the vaccine and the deaths? Under this definition the 6 deaths in children with heart disease were not causally related to the vaccination.

The older Advisory Committee on Causality Assessment Collet JP, 2000 looked at the problem more logically and holistically. For example it noted that elderly persons with concomitant or preceding chronic cardiac failure can develop cardiac decompensation after influenza vaccination due to a vaccine-caused elevation in temperature or from stress from a local reaction at the site of vaccinating. The vaccine is considered to have contributed to cardiac failure in this specific situation. It is obvious that with the older method of assessment of AEFI, caution would have been exercised when administering influenza vaccine to persons with preceding chronic cardiac failure, to avoid decompensation.

The deaths in children with heart disease following administration of Pentavalent vaccine could well be due to decompensation. The Pentavalent vaccine must be used with caution in the presence of an underlying heart condition albeit asymptomatic. However detection of asymptomatic heart disease prior to vaccination in developing countries is impractical where the vaccine is administered by health workers who are barely literate. Is it prudent to use the vaccine under these circumstances given the findings of the Sri Lanka investigation? The new system disregards this real danger.

3) Step 2 Checklist 4 of the revised [WHO classification for causality assessment](who.int/vaccine*safety/publications/aevi*manual.pdf) asks to check if the event can occur independently of vaccination (background rate). Thus it seems that until the deaths from vaccine AEFI are frequent enough as to increase the age specific mortality-rate in a statistically significant manner, they are to be ignored.

The question of what background rate to use is not addressed specifically and this can further confound objective assessment of the AEFI. The Pentavalent vaccine in Asia is administered after 6 weeks of age. Would the local post-neonatal infant mortality rate (PN IMR) in the community before introduction of the vaccine be the comparator?

Most of this post-neonatal IMR is made of babies who are very sick with pneumonia, diarrhea, sepsis, meningitis etc. The fact that the AEFI babies were brought by the mother for routine immunization suggests that the child was not sick and the mother did not consider the child was likely to die in the next day or two. The comparator must really be the SIDS rate in the locality for babies of a comparable age.

Deaths in Bhutan were investigated and local newspapers reported on the various official explanations. It was argued that the deaths could have been due to encephalitis although there was little evidence for it. Officials explained that the encephalitis death rate in the years after the vaccine was introduced (even after adding AEFI deaths) had not increase significantly. This was sufficient grounds to accept the ‘coincidental encephalitis’ theory. One cheeky health official however pointed out that there were no cases of meningo-

encephalitis reported among children below one year, in the eight months when Pentavalent vaccine was suspended in Bhutan.

4) Another factor related to the deaths following Pentavalent vaccine is that the vast majority have occurred after the first dose and fewer after the second dose. A random event or coincidental SIDS cannot explain these deaths. However the new algorithm does not take this important factor into consideration.

For all these reasons it would appear that the new algorithm is not a comprehensive means to assess serious adverse events. Its use will delay withdrawal of vaccines that result in serious AEFI and in the end it will erode confidence in the entire immunization programme and those who administer it.

Can I suggest that we need to go back use older scheme namely Brighton Classification of AEFI till we find a better method to assess AEFI.

PermalinkShare

- Assessment of causality of individual adverse events following immunization (AEFI): a WHO tool for global use.

  Tozzi AE.Vaccine. 2013.14 comments

  Jacob Puliyel2014 Feb 20 4:02 p.m.edited

  Comment deleted by user.

- In reply to a comment by Jacob Puliyel2014 Feb 04 1:10 p.m.

  Jacob Puliyel2014 Feb 20 4:36 p.m. 0 of 1 people found this helpful

  Tozzi and colleagues state that their article describes the new tool for causality assessment of AEFI as set out in the User Manual for the Revised WHO Classification

  1) However this manual it seems has been developed without adequate care and without thinking through the consequences of the changes.

  a) One pointer to this is how the manual cites an example of vaccines being wrongly blamed for events unrelated to its administration (Page 13). It says that vaccines were wrongly blamed for deaths resulting from consumption of the Cassia occidentalis beans causing a syndrome of acute hepato-myoencephalopathy. However the article they quote describes Japanese B encephalitis being blamed for the deaths – not the vaccine Panwar RS, 2008

  b) Dr Madhavi put the new classification to a simple test. She tested how the system would have responded if the revised AEFI classification been in place in 1999. She

suggests that the intusussceptions following use of RotaShield would have been classified as ‘inconsistent with causal association’ because:

i) other qualifying factors like previous similar reaction (re-challenge equivalent) were not available

ii) nor was biological plausibility demonstrated at that time

iii) and background rate, other exposures etc were not ruled out.

Under this category ‘inconsistent with causal association’ it would never activate the analysis reserved for ‘indeterminate’ reactions – “Information on AEFIs that are classified as indeterminate should be pooled and analyzed by time and place, in order to understand if the AEFI represents a new signal of an unrecognized event. Should this be the case, a more comprehensive epidemiological investigation should be performed.” Tozzi AE, 2013

These intusussceptions would have continued for years before the vaccine was pulled off the shelves.

2) In my previous comment I had pointed out that the experts investigating the Sri Lanka deaths from Pentavalent vaccine deleted the categories ‘Probable’ and ‘Possible’ from the Brighton classification and reported that although they found no alternate explanation for the deaths, the deaths were unlikely to be related to the vaccine. An apologist for the distorted Brighton Classification told me at that time that it was ‘experts’ who developed the Brighton Classification and it is alright for other experts to alter the classification. That was prescient. The new system makes a virtue of this ability to disregard the algorithm when it suits any expert. It says “Finally, instead of assigning a final category through an automatic classification process, the final outcome of the case investigation depends on the personal judgment of the assessor.” Tozzi AE, 2013

3) Post marketing surveillance is used to monitor the safety of a drug. Since drugs are approved on the basis of clinical trials which involve a relatively small numbers of people who have been selected for this purpose - meaning that they normally do not have other medical conditions which may exist in the general population - post marketing surveillance can further refine, or confirm or deny, the safety of a drug after it is used in the general population by large numbers of people who have a wide variety of medical conditions. (Abridged from Wikipedia)

The effort of the revised WHO Causality assessment of an AEFI is to deny adverse events noticed on post marketing surveillance, are caused by the vaccine (unless they had been observed in the original small clinical trials).

Events that occur 1 in 10,000, for example the intussusceptions with RotaShield will be noticed only in post marketing surveillance.

The AEFI in individuals was responsible for the 'signal'. Evidence of causality in the individual provided evidence of causality in the population. The new system stands this logic on its head when it says on Page 5 that causality in the population must be known before causality in the individual can be ascribed.

"Causality assessment of AEFI should be performed at several different levels. The first is the population level, where it is necessary to test if there is a causal association between the use of a vaccine and a particular AEFI in the population. Secondly, at the level of the individual AEFI case report, one should review previous evidence and make a logical deduction to determine if an AEFI in a specific individual is causally related to the use of the vaccine. The third level of assessment is in the context of the investigation of signals."

I am not stating that there is something sacrosanct about the original Brighton Classification but one has to evaluate the two schemes (Brighton vs CIOMS) from the point of view of patient safety to see which scheme would react to rare RotaShield-like-reactions first. The causality scheme that insists on calling all reactions as 'indeterminate' or 'inconsistent/coincidental' just because they were not noticed in the original small clinical trials, undermines the very raison d'être of post marketing surveillance. Patient safety (meaning protecting patients) rather than vaccine safety (protecting vaccines) is what is important.

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- Jacob Puliyel2014 Mar 12 10:47 p.m. 0 of 1 people found this helpful

  6500 PENTAVALENT-VACCINE AEFI-DEATHS IN INDIA EACH YEAR CANNOT BE ACCEPTABLE

  I thank Dr Malik for endorsing the opinion that the AEFI guidelines need to be revised. Unfortunately neither Tozzi and colleagues, nor Bonhoeffer et al (Bonhoeffer J, 2009) have responded and we do not know if the authors agree with us.

  Dr Malik's comment points out that India lacks a strong system of AEFI surveillance and investigation. This is undisputable. The fact of this poor surveillance in some States is clearly illustrated by the data obtained under the Right to Information from the Government of India, published by the Center for Science and Environment in their magazine – Down to Earth. Goa - a State with good surveillance and a low infant mortality rate (IMR 10/1000 live births) reported 26 AEFI deaths per 100,000 infants vaccinated with the Pentavalent vaccine whereas Gujarat, with poorer health infrastructure and high IMR, reported only 0.4 deaths per 100,000 infants vaccinated (Gujarat IMR is 50/1000 live births). The correlation between reported AEFI rate and IMR is illustrated here (R2 = 0.458).

  Clearly AEFI deaths (following Pentavalent vaccination) in States like Goa and Kerala is much higher than previously (with the older DPT vaccine). If the Goa 'AEFI-death-rate'

(reliable data from the state with the lowest IMR and presumably the best health infrastructure and surveillance systems) is projected nationwide and 26 babies are to die among every 100,000 babies vaccinated, 6500 AEFI deaths can be anticipated when the year's birth cohort of 25 million babies in India are vaccinated. This cannot be acceptable.

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- Jacob Puliyel2014 Mar 18 12:28 p.m. 2 of 4 people found this helpful

  Dr Malik, as part of the India Government Ministry of Health, has information on the AEFIs with Pentavalent vaccine and their investigation. I mention individual instances because Dr Malik is familiar with them and it best illustrates the harm done by the new system of AEFI classification.

  Of the 54 deaths reported to the Government of India some have been investigated and the AEFI reports are available here

  The deaths as described below could well have been caused by 'multisystem generalized reaction to one or more vaccine components' (page 50 of the CIOMS/WHO report). But a case definition for this entity has not been developed as yet by the Brighton group. When such multisystem reactions occur they appear like the multiple organ dysfunction syndrome (MODS) that follow sepsis but it must not be confused with it. The AEFI committee assumes that all MODS are due to due to sepsis or, if it is associated with unconsciousness, it must be meningitis/encephalitis. The new AEFI algorithm seems to promote and propagate this confusion.

  1) The manner in which the deaths are declared as unrelated to the vaccine is instructive. The first of these deaths was in a child who was vaccinated at 11 AM. That evening at 5 PM the child had fever for which she was given paracetamol. The baby woke up several times that night crying. She was found dead in her bed next morning. There was blood around the nostrils.

  On postmortem examination a large swelling around the injection site 9.8 x 7.9 x 4.7 cm with edema and infiltration involving muscle and subcutaneous tissue was noted. The internal organs including brain, kidneys and lungs were congested. There were petechiae on the surface of the lungs and bilateral adrenal bleeds. The report said the autopsy findings were consistent with death due to hypersensitivity reaction.

  The AEFI report however says the death is unlikely to be a programme error or 'due to vaccine associated to the vaccination' (sic)

  2) The central team looked at the 15 deaths in Kerala . One death in Pathanamthitta is reported in detail. The healthy 6 week baby was vaccinated on 26 December 2012 at 12 noon. The mother noted swelling of legs and the baby was 'grunting' and reluctant to feed. She was given 4 drops of paracetamol syrup for 'fever and crying' at 5 PM and 2

times on the next day. The baby was found dead with blood stained discharge from the nose at 4-30 AM on the morning of the 28th. No postmortem examination was performed.

The AEFI report classified this death as "Unknown unclassifiable category" in spite of the fact that the parents are available and gave a detailed history as part of the verbal autopsy.

3) The AEFI report has more interesting details that I quote verbatim: "Temporality of vaccination with death cannot be established as a causal relationship since it may also be possible that in the child had a subclinical infection (therefore no obvious signs and symptoms) and it aggravated in cold conditions, led to Bronchiolitis and death. This may be the reason for death due to pulmonary edema (manifesting as blood from the nose and in some postmortem findings of blood in respiratory tract)."

The cold conditions reported as leading to pulmonary edema and death is intriguing. Kerala has a climate that borders between a tropical savanna climate and a tropical monsoon climate. As a result it does not experience distinct seasons. The mean maximum temperature is 34 °C mean minimum temperature is 21 °C and the lowest temp recorded in December in Thiruvanthapuram was 20 °C..

The death in babies in Kerala who were apparently completely well in the morning when they went for immunization but who became unwell soon after vaccination and deteriorated rapidly to death cannot rationally be attributed to 'subclinical bronchiolitis infection aggravated by cold conditions' leading rapidly to pulmonary edema and death.

Any explanation no matter how outlandish seems adequate but the likelihood of there being a causative association with the vaccination, which is obvious, is not considered.

This is akin to a person found dead under the rubble after a house collapse. The house-insurance-company may refuse to pay the next of kin, saying the house collapse could have been coincidental and cannot be blamed for the death till it is proved that the deceased had not suffered a heart attack just before the house collapsed.

4) 8 deaths in Kashmir were investigated by the AEFI team.

There had been 1 death each in June September and December 2013, but in October there were 11 deaths according to a RTI response (AD/FW/K/RTI/822-24).

Many local newspapers reported the deaths in October were associated with use of a brand of Pentavalent vaccine called Easyfive which vaccine had previously been disqualified because of quality concerns but had just been reintroduced. Easyfive is not being used in the Kashmir Government immunization programme currently.

Like in Kerala, the deaths in Kashmir were attributed blithely to sepsis with metabolic disorder (in Aisha who had convulsions and normal CSF and no blood culture evidence

of sepsis), meningitis (in Mozim based on persistent vomiting, metabolic acidosis, convulsions and crying excessively), pneumonia with aspiration (in Nida with fast breathing and gasping respiration with a family history of sibling death following pneumonia), liver disorder with metabolic acidosis (in Karneez with fever followed by repeated seizures but no CSF examination), sepsis with metabolic acidosis (in Shaistha crying excessively and irritable for 3 days after vaccination, convulsions on the third day, put on ventilator till death on 9th day). It is paradoxical, these diagnoses were reached on the clinical symptoms and laboratory findings of MODS without specific blood culture evidence of sepsis or CSF evidence of meningitis, suggesting the criteria for making these diagnoses are not strict like the algorithm needed to arrive at a diagnosis of death caused by vaccine. No death was attributed to MODS due to 'multisystem generalized reaction to one or more vaccine components'. The most obvious possibility is not even mentioned in the differential diagnosis.

5) The doctors in the Kashmir hospital who noted the sudden increase in cases of deaths in October (11 cases in one month against the previous rate of 1 case in 2 months) sent telephonic text messages to senior government officials in the central government and state government to appraise them of these events but the AEFI team comes down heavily on them for sending these messages "as if to report 'breaking news'". Apparently they were expected not to take notice of these deaths and continue with business as usual and perhaps not to alert anyone.

It seems that after the October spike in incidence of AEFI deaths, the brand of vaccine was changed and the numbers of death have come down but the Government AEFI report does not mention it. It appears that although all brands of the vaccine have been associated with AEFI deaths in different countries, some brands may be particularly lethal.

A good AEFI reporting system must have picked up all these linkages which the new algorithm makes studious efforts to avoid.

PermalinkShare

- Guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems.

  Bonhoeffer J.Vaccine. 2009.1 comment

  Jacob Puliyel2014 Mar 05 04:45 a.m. 1 of 3 people found this helpful

  IT IS EXPEDIENT BUT IS IT PRUDENT TO LABEL ADVERSE EVENTS FOLLOWING IMMUNIZATION AS 'NOT AN EVENT OF [AEFI]'?

  The old scheme of monitoring signals for vaccine safety (adverse events following immunization – AEFI monitoring), of the Advisory Committee on Causality Assessment Collet JP, 2000 has been overtaken by the Revised WHO Classification of AEFI. The

changes have been described in 4 PubMed articles Tozzi AE, 2013, Bonhoeffer J, 2009, Halsey NA, 2012, Williams SE, 2013.

I wrote two very detailed comments to the article by Tozzi et al Tozzi AE, 2013 on the PubMed Commons which is envisaged as a forum for open constructive criticism and discussion of scientific issues. To facilitate meaningful discussion it has a link to 'Invite an author to comment'. Tozzi and colleagues have not responded so far. PubMed suggests that the main reason for not getting a response is a changed email contact address.

As this is a matter of patient safety I think it is important that the experts who understand the new scheme must explain why the revision was needed and that it is an improvement over the old scheme - that it will not miss opportunities of picking up new signals by classifying AEFI as 'Not a case of [AEFI]'. I will not repeat the posting but it may be viewed here

The purpose of this posting is to invite the learned authors of this article on causality assessment Bonhoeffer J, 2009 to respond. The article by Bonhoeffer and colleagues mostly describes a guideline for collection of data which is unexceptional, but the subsequent 'analysis and presentation of vaccine safety data in the surveillance system' may cause signals to be ignored because they are classified as ‘Not a case of [AEFI]’. Would the new scheme have picked up and flagged signals of adverse-effects like the RotaShield-reactions, had the scheme been in use in 1998?

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Jacob Puliyel

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Comments 21 to 22 of 22

- Assessment of causality of individual adverse events following immunization (AEFI): a WHO tool for global use.

  Tozzi AE.Vaccine. 2013.14 commentsPaul King, Brandon Horn and 9 others also commented

  Jacob Puliyel2014 Feb 04 1:10 p.m. 3 of 5 people found this helpful

  DEATHS IN DEVELOPING COUNTRIES WILL COUNT FOR LESS

  Tozzi et al describe causality assessment for AEFI using criteria from the CIOMS/WHO working group on pharmacovigilence . AEFI is any untoward medical occurrence following immunization. A causal relationship is not implied. The Brighton collaboration classified reactions as very likely/certain; probable; possible; unlikely; unrelated; unclassifiable, based on temporal criteria and evidence of alternate etiological explanation. Deaths soon after immunization without an alternate explanation were classified as 'probably related to vaccine'.

  THE NEED FOR A NEW CLASSIFICATION

  With use of Pentavalent vaccine (Diphtheria, Tetanus, Pertussis, Hib and Hepatitis B) in developing countries, there have been many AEFI deaths. WHO experts investigated these deaths in Sri Lanka. They could find no alternate explanation for 3 deaths. The experts write in the report that they deleted the categories 'probable' and 'possible' from the Brighton classification and after that, although they could not attribute deaths to another cause, they were declared unlikely to be related to the vaccine. The association to vaccine should have been classified as 'probable'. The BMJ published a letter about this Saxena KB, 2010

  1. The CIOMS/WHO report came after the BMJ letter. The committee, composed of 40 members (19 were vaccine-industry representatives), proposed changes to how AEFI are investigated and reported. The 194-page document has serious implications for developing countries.
  2. Case definitions for different adverse events were developed. Illogically, the inclusion criteria for the proposed case definitions are too strict to be of scientific value in most countries. For example, to diagnose 'encephalitis' one needs the child with fever and encephalopathy to live at least 24 hours after AEFI onset, and have a CSF examination, an EEG or neuro-imaging and one of these investigations must be positive, to reach a level 2 diagnosis (page 73).
  3. Presume that a healthy child is vaccinated. Suppose she develops high fever within 2 hours, has convulsions, then lapsed into a coma and dies within 10 hours. (Variations of this scenario have been enacted repeatedly with Pentavalent vaccine). Using CIOMS/WHO definitions, as the encephalopathy lasted less than 24 hours, it cannot be classified as encephalitis. In many countries, the facilities for a lumbar puncture may be unavailable, much less those for an EEG and CT/MRI. Under the report's scheme, this would be labeled, "Insufficient

information to distinguish both acute encephalitis and ADEM; Case unable to be definitely classified".

4. Further, on page 170 (i) (in very small print), the report says, "Such a case must be classified as 'Not an AEFI'". This last step, which classifies an "AEFI" as "Not an AEFI", is patently unscientific, illogical and Orwellian.
5. The scenario described could well have been caused by 'multisystem generalized reaction to one or more vaccine components' (page 50). The encephalopathy, fever and convulsions could follow systemic inflammatory response but CIOSM does not have case definition for this, and inability to exclude causes of encephalopathy, is sufficient to classify the reaction as 'not an AEFI'.
6. The risk is not merely theoretical. In March 2013 WHO investigated 12 deaths in Viet Nam from the same Pentavalent vaccine. The Viet Nam report stated, "no fatal AEFI has ever been associated with this vaccine". The 2008 WHO experts had earlier classified the Sri Lanka deaths as AEFI unlikely to be related to vaccine. The Viet Nam report stating 'no fatal AEFI has ever been associated with this vaccine' suggests the Sri Lanka AEFI is now reclassified as "Not an AEFI".
7. Tossi et al suggest that 'events with a consistent temporal relationship but with insufficient evidence for vaccine as a cause, according to well designated epidemiological studies – in such cases, further studies are encouraged if other similar events are identified'. There have been 54 deaths temporally related to the vaccine in India. Instead of taking them as a group the new system looks at 'individual adverse events' and then labels them as 'not an AEFI' making way for many more deaths.
8. Tossi and colleagues report different clinical scenarios (Supplementary material). The scenario in Asia is also worth considering. Pentavalent vaccine is selectively promoted in developing countries with poor surveillance systems. Eighty three deaths following Pentavalent inoculation have been reported from Asian countries Puliyel J, 2013. There is no plausible alternate explanation. Most deaths occurred after the first vaccine dose, fewer after the second, and hardly any after the third. This pattern argues against the deaths being random events. Yet, the WHO to maintains that a cause and effect relationship has not been established.
9. This contrasts with what happened in 1998 when RotaShield was approved in the US. When intussusceptions were reported to the Vaccine Adverse Event Reporting System (VAERS) and only 12 children were affected the vaccine was withdrawn. No one needed to be 'certain'.
10. A public health expert in India, Dr Y Jain has filed a public interest petition in the Supreme Court asking for these deaths to be investigated. The petition states that in the first six months, when the 40,000 doses were administered to children in the southern state of Kerala, at least five children died. Extrapolated to the 25 million babies born in India each year, 3,125 deaths can be expected from the vaccine each year. Using the best evidence from the Minz study Minz S, 2008 the incidence of Haemophilus influenzae type b meningitis in India is 7/100,000 children under 5. Using the Unicef rapid method to estimate Hib Pneumonia 350 deaths from Hib disease will be prevented over 5 years by vaccinating one birth cohort of 25 million. 3125 deaths from AEFI cannot be acceptable to prevent 350 Hib deaths.

11. The Infant Mortality Rate (IMR) in Kerala is 14. Seven of these deaths occur in the first month. The other seven deaths occur in the remaining 11 months of the infant's first year. Pentavalent vaccine is administered six weeks after birth to babies who have survived neonatal life. Of the first five deaths from the vaccine, four occurred within 24 to 48 hours of the first dose of this vaccine. The death rate of babies in the first days after vaccination works out to be two to four times higher than Kerala's post neonatal IMR.
12. The first 14 deaths in Kerala were investigated by AEFI experts. They reported 6 children had co-morbid conditions and the other 8 died of sudden infant death syndrome (SIDS). This SIDS rate on day after vaccination is higher than the all-cause IMR.
13. Under the new scheme, fatal AEFI in developing countries will be falsely recorded as 'Not an AEFI', simply because some time or test criterion was not met. Death is the worst AEFI possible. Continued use of the CIOMS/WHO scheme will result in missing an important opportunity to pick up signals that could save lives. This is dangerous. Perhaps we need to get back to the Brighton Classification.

PermalinkShare

- Impact and cost-effectiveness of Haemophilus influenzae type b conjugate vaccination in India.

  Clark AD.J Pediatr. 2013.1 comment

  Jacob Puliyel2014 Feb 04 05:43 a.m.edited 1 of 3 people found this helpful

  This comment has been written after correspondence through the journal with the authors.

  The WHO considers programmes cost-effective, if they cost less than 3 X GDP per capita per DALY averted. Such thresholds are less meaningful in developing countries where funds are limited and there are numerous worthwhile projects (costing even less than 1 X GDP per capita per DALY), vying for scarce health care resources. Efficient allocation of resources involves selecting programmes that provide the best value for money till the budget is exhausted. The base-case cost-effectiveness is used for this selection of programmes. It is therefore important that this base-case-estimate must be as accurate as possible.

  Clark and colleagues note that the addition of the Hib vaccine will increase the cost of immunization per child four fold in India. They found that incidence of Hib pneumonia deaths and efficacy of the vaccine against Hib pneumonia, were factors that crucially influenced cost effectiveness.

  We find that the authors have used data that overestimates benefits of the vaccine.

Pneumonia

Evidence based medicine requires the use of the best evidence available for decision making and when properly conducted RCTs and case control data are available, other less empirical estimates of Hib disease burden should not be used.

a) The authors write that their estimate that 7% of all pneumonias are caused by Hib is broadly consistent with the pooled 5% reduction in radiological pneumonia found in combining results of 2 Hib vaccine studies in Asia. Gessner BD, 2005, Baqui AH, 2007 They use inverse variance meta analysis with 64% weight assigned to the Indonesian study. However they write, mistakenly, that the Indonesian study found vaccine efficacy of -10% (95% CI -33% to 9), where the study actually reported efficacy of -12% (95% CI -33 to 9). In the Bangladesh study vaccine efficacy was 16% (CI -11 to 37) for pneumonia identified by WHO experts (n=675) and not 32% as stated in the cost-effectiveness report.
Meta analysis combining the vaccine efficiency from this case control study in Bangladesh with the vaccine efficacy in the cohort study from Indonesia was not possible with the data published in the two papers. However the arithmetic mean using the weights provided by Clark et al (Indonesia (weight 64%): vaccine efficacy -12% and Bangladesh (weight 36%): vaccine efficacy 16%; it gives a pooled efficacy is -1.9% (and not 5% as reported in the paper).

b) The author did sensitivity testing assuming vaccine efficacy against pneumonia to be 50% of the base case figure used by the authors, which was 7%. In their worst case scenario, vaccine efficacy was 3.5% which is more optimistic than even the calculated base-case rate of vaccine efficacy of -1.9%.

c) They estimate that 7% of pneumonia deaths in children aged 1-59 months are caused by Hib, just because according to them, Hib is responsible for 7% of all pneumonias. This can be true only is all pneumonia-causing-bacteria are equally lethal. There is no evidence in literature to support this assumption.

Meningitis

In the same way the authors used data from the Minz study on Hib meningitis. Minz S, 2008 However they trebled the incidence to 22/100,000, ostensibly to account for children without access to hospitals and cases not detected in the laboratory. Inflating the meningitis numbers was not reasonable for the following reasons:

a. The Minz study was a community based with households visited fortnightly. Tests were done free of cost at the nearest hospital. Adjusting for poor access here was superfluous.

b. Minz used a Latex Agglutination Test (LAT) which is particularly sensitive for detecting Hib (Sensitivity 93 per cent for Hib infections but 39 per cent for Neisseria

meningitides). LAT would miss only 7% cases of Hib. Most of cases of purulent meningitis where no organism was identified were probably not Hib disease.

c. The authors assume that parents, who don't bring children to hospital when they have respiratory infections (a relatively trivial disorder), will not bring them when suffering from meningitis either. In doing so they overestimate the numbers not presenting to hospital with meningitis and in them they assume mortality would be 100%. The burden of Hib meningitis has been exaggerated in this way. The authors have written that even when they tested a scenario with the unadjusted Hib meningitis incidence (7 per 100,000 per year, <5yrs) as a minimal estimate, the cost per DALY averted remained below 3 GDP per capita. As discussed in the introduction such thresholds are not very useful for developing countries.

Non pneumonia Non meningitis

As the incidence of non pneumonia non meningitis (NPNM) is taken directly as a fraction of the incidence of meningitis; exaggerating the incidence of meningitis three fold (compared to empirical data from Minz) has the effect of trebling the calculated incidence of NPNM disease. The authors have responded that Hib NPNM accounts for only 1% of the estimated deaths prevented. Reducing the contribution of Hib NPNM would not alter the findings of the paper.

Conclusion

We hope the authors will be able to provide a more accurate base-case estimate of costs and benefits in the light of the above discussion. Such a base case estimate must include cost of treating the 1.9% increase in pneumonia in the vaccinated and also include the increased deaths from pneumonia.

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