PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Safety and immunogenicity of a new 13-valent pneumococcal conjugate vaccine versus a licensed 7-valent pneumococcal conjugate vaccine: study protocol of a randomized non-inferiority trial in China
AUTHORS	Chen, Jing Jing; Yuan, Lin; Huang, Zhen; Shi, Nian Min; Zhao, Yu Liang; Xia, Sheng Li; Li, Guo Hua; Li, Rong Cheng; Li, Yan Ping; Yang, Shu Yuan; Xia, Jie-Lai

VERSION 1 - REVIEW

REVIEWER	Claudia Gaviria-Agudelo Valley head Clinic United States
REVIEW RETURNED	26-May-2016

GENERAL COMMENTS	-What is the rationale behind the locally developed and manufactured 13-valent pneumococcal conjugate vaccine (Page 2 Line 41) having a tetanus toxoid carrier protein instead of the CRM197 (Diphtheria toxin) carrier protein of PCV7? -If there is already an approved PCV13 developed by Pfizer what is the rationale not to use that PCV13 vaccine as control for the trial instead of PCV7? Is this because PCV13 has not been licensed in mainland China? Is there any possibility that PCV13 could be used in this trial for research purposes? Sylvia H. Yeh et al (Reference 6 PMID: 20732948) used PCV7 as comparison but before 2010 we did not have a licensed PCV13 vaccine available. It is possible that comparing the locally developed and manufactured 13-valent pneumococcal conjugate vaccine with the PCV13 developed by Pfizer would yield more robust information regarding vaccine elicited antipneumococcal opsonophagocytic activity (OPA) geometric mean titers (GMTs) and IgG geometric mean concentrations (GMCs) for ALL 13 vaccine serotypes. It is important to note that in the mentioned study (Reference 6 PMID: 20732948) 6B and 9V serotypes CI values did not meet non inferiority criteria. - Regarding"not involving the assessment of concomitantly immunization with other vaccines specified in pediatric vaccination might be seen as potential limitation of this trial (Page 2 line 51). How much variation does China have regarding its National Vaccine Schedule (and expanded program on immunization EPI Page 13 line 4) compared with other countries, for example the United States? Are the researches at least going to suggest the medical personnel in charge of vaccine administration that other concomitant vaccines should be injected into the opposite site? This could be also

	important for the appropriate report of adverse events of the local reaction type (Page 6 line 8). -When it comes to power size calculation authors report an anticipated drop out rate of 20% (Page 8 line 25). In the equivalent study in the US study (Reference 6 PMID: 20732948) they had a drop out rate around 30%, taking into account the population available for analysis after completion of booster dose. Most of the excluded subjects were removed from the analysis because they had no pre toddler of post toddler assay results. Wouldn't be a more conservative to do the sample size calculation around this number? - Is the Equivalence Margin of the power size calculation 5? (Page 8 line 18). Can the authors provide more details about the software used to calculate the sample size needed to achieve the desired power?

REVIEWER	Pei Liu School of public health, Southeast University, P.R.China
REVIEW RETURNED	31-May-2016

GENERAL COMMENTS	The strict statistical design in this article impressed me a lot. In the sequential procedure, UIT was used to analyze the non-inferiority of shared strains between PCV13 and PCV7, then IUT... But I still have some advice: 1. I think there is a small mistake("98.25%") in page 4 line 16(and line20). 2. In the section "sample size", you did not assume the percentage of vaccine recipients reaching the serotype-specific IgG concentration threshold of 0.35μg/ml in PVC13. 3. You adjusted beta from 0.2 to 0.2/7.what is the theory basis of this correction and how to apply this correction to the statistical analysis? If the power of every serotypes should not less than 0.97?

VERSION 1 – AUTHOR RESPONSE

For reviewers' comments, we respond as follows:
1. What is the rationale behind the locally developed and manufactured 13-valent pneumococcal conjugate vaccine (Page 2 Line 41) having a tetanus toxoid carrier protein instead of the CRM197 (Diphtheria toxin) carrier protein of PCV7?
R: The advantage of a Tetanus Toxoid (TT) carrier protein has been confirmed by many licensed vaccines, and the research and development team of Walvax has rich experience with protein TT in conjugate vaccines, so TT has been chosen as the carrier of the investigational PCV13.

2. If there is already an approved PCV13 developed by Pfizer what is the rationale not to use that PCV13 vaccine as control for the trial instead of PCV7? Is this because PCV13 has not been licensed in mainland China? Is there any possibility that PCV13 could be used in this trial for research purposes?
Sylvia H. Yeh et al (Reference 6 PMID: 20732948) used PCV7 as comparison but before 2010 we did not have a licensed PCV13 vaccine available.
It is possible that comparing the locally developed and manufactured 13-valent pneumococcal conjugate vaccine with the PCV13 developed by Pfizer would yield more robust information regarding vaccine elicited antipneumococcal opsonophagocytic activity (OPA) geometric mean titers (GMTs) and IgG geometric mean concentrations (GMCs) for ALL 13 vaccine serotypes.
It is important to note that in the mentioned study (Reference 6 PMID: 20732948) 6B and 9V

serotypes CI values did not meet non inferiority criteria.
R: Complying with the Chinese regulation, since PCV13 developed by Pfizer has not been licensed by the CFDA, it is still not available in mainland China, even for research purposes.

We designed this study with reference to a WHO guidance, which stated “non-inferiority to antibody response for each of the serotypes in the registered vaccine is desirable but not an absolute requirements”. If the serotype 6B or 9V failed to be declared non-inferiority with this trial, the non-inferiority of the investigational PCV13 will be assessed combining with other comprehensive consideration.

3. Regarding"not involving the assessment of concomitantly immunization with other vaccines specified in pediatric vaccination might be seen as potential limitation of this trial (Page 2 line 51).
How much variation does China have regarding its National Vaccine Schedule (and expanded program on immunization EPI Page 13 line 4) compared with other countries, for example the United States?
Are the researches at least going to suggest the medical personnel in charge of vaccine administration that other concomitant vaccines should be injected into the opposite site? This could be also important for the appropriate report of adverse events of the local reaction type (Page 6 line 8).
R: Compared the National Vaccine Schedule of China (http://www.chinanip.org.cn/zstd/mycx/201209/t20120927_69741.htm, accessed 11 Jun 2016) to the Immunization Schedules for Infants and Children recommended by US CDC (http://www.cdc.gov/vaccines/schedules/easy-to-read/child.html, Accessed 11 Jun 2016), we did see some differences between them. Take DTaP for example, in the US, infants will receive a 3-dose series at 2, 4, and 6 months of age respectively, and a dose between age of 4 and 6 years. While in China, infants will receive a 3-dose series at 3, 4, and 5 months of age respectively, and a dose between 18 and 24 months of age. We have already consulted to medical personnel and requested at least a fortnight interval between two kinds of vaccination during this trial. Other instructions for concomitant administration have been specified in site operation manuals.

4. When it comes to power size calculation authors report an anticipated drop out rate of 20% (Page 8 line 25). In the equivalent study in the US study (Reference 6 PMID: 20732948) they had a drop out rate around 30%, taking into account the population available for analysis after completion of booster dose. Most of the excluded subjects were removed from the analysis because they had no pre toddler of post toddler assay results.
Wouldn't be a more conservative to do the sample size calculation around this number?
R: We designed this trial as a non-inferior study, and discussed the dropout rate with all the primary investigators and senior consultants. Given the CFDA may regard a vaccine study with a dropout more than 20% as a failure, we have had to set the parameter at this level and drawn up plans to promote participants retentions.

5. Is the Equivalence Margin of the power size calculation 5?(Page 8 line 18). Can the authors provide more details about the software used to calculate the sample size needed to achieve the desired power?
R: We did not mentioned Equivalence Margin in this manuscript and cannot find this information in line 18 page 8. For each of the 6 additional serotypes in PCV13 only, we set the target rate as 70%, and divided the beta by 6 to achieve the desired power. All the calculations have been conducted by PASS 11.0.

6. I think there is a small mistake("98.25%") in page 4 line 16(and line20).
R: Thanks for reminding, they were typos. The correct figure is 98.75%, and we will fix it.

7. In the section "sample size", you did not assume the percentage of vaccine recipients reaching the serotype-specific IgG concentration threshold of 0.35μg/ml in PVC13.
R: In the sample size section, we have specified that: For each of the 7 common serotypes in PCV13, we assumed the percentage of vaccine recipients reaching the serotype-specific IgG concentration threshold of 0.35μg/ml would be 85%. And for each of the 6 additional serotypes in PCV13 only, we hypothesized that the proportion of vaccine recipients reaching the serotype-specific IgG concentration threshold of 0.35μg/ml in the test group would be about 80%.

8. You adjusted beta from 0.2 to 0.2/7.what is the theory basis of this correction and how to apply this correction to the statistical analysis? If the power of every serotypes should not less than 0.97?
R: In order to maintain the overall power of the test of the 7 common serotypes at the level of 80%, we employed the Bonferroni method and adjusted beta with the way correcting alpha to modify multiple test. The power of each serotype could be regarded as 0.97 when we did the sample size calculation.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but highlight the changes in paper by using the track changes mode.
We appreciate Editor and Reviewers' warm work earnestly, and hope the revision will meet with approval.