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Short communication

Rethinking results from the Japanese 23-valent pneumococcal polysaccharide vaccine randomized clinical trial

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ABSTRACT

We review a previously published randomized clinical trial of 23-valent pneumococcal polysaccharide vaccine (PPSV23) that has been used extensively globally to support PPSV23 use among adults. We argue that serious issues with internal and external validity exist that affect the usefulness of these data when evaluating pneumococcal vaccines for the general adult population. As one example of internal data inconsistency, the values reported for the percent of all pneumonia cases due to pneumococcus and the vaccine efficacy (VE) for all cause pneumonia are mutually inconsistent, even based on unrealistically high values for PPSV23 VE against vaccine serotypes and the proportion of pneumococcal pneumonias due to vaccine serotypes.

1. Introduction

A randomized, controlled trial (RCT) of 23-valent pneumococcal polysaccharide vaccine (PPSV23) among 1006 elderly Japanese adults (average age, 85 years) living in one of 23 nursing homes was conducted during 2006–8 and published during 2010 [1]. This study reported a vaccine efficacy (VE) against pneumococcal pneumonia of 64% and against all cause pneumonia of 45%; a reduction in pneumococcal pneumonia mortality as a fraction of all mortality; and no impact on all-cause mortality (Table 1). Since that time, this study has been incorporated into meta-analyses and position statements globally as an RCT [2–8] and its results have often been considered as the primary source to evaluate PPSV23 efficacy against pneumococcal and all-cause pneumonia. For example, the National Immunization Technical Advisory Group (NITAG) in Germany, STIKO, includes this study in a meta-analysis of PPSV23 vaccine efficacy/effectiveness (VE) and allocates a significant weight to it because it is an RCT [9–11].

An editorial published along with the original article by Maruyama et al. identified several concerns. The incidence of pneumonia was higher than previous reports, however this could have been due to the specific nursing home population under study and in any event should not affect internal validity. The editorial also notes that the authors did not use a standard definition for radiological confirmation of pneumonia, but this should not affect the VE estimate against pneumonia as defined in the trial. Lastly, the editorial pointed out that most pneumococcal cases were identified by urinary antigen detection, which has limited sensitivity and specificity; but this should result in non-differential misclassification and a bias of VE towards the null, rather than the extreme high value reported in the manuscript.

As might be expected, these relatively minor issues have not prevented the study's subsequent incorporation into different meta-analyses and economic assessments, often overweighted because of the RCT design. Given the importance of this study in influencing pneumococcal vaccination policy among adults, we evaluated the plausibility of study results, particularly the high reported VE values against relatively non-specific outcomes.

2. Overview of study methods

Maruyama et al. assessed PPSV23 VE in 23 nursing homes, each affiliated with one of nine hospitals. Non-immunocompromised subjects were randomized by blinded nursing home staff to receive either PPSV23 or placebo, both in identical single dose syringes that were identifiable only by a sequential study number. Subjects and study staff were blinded to vaccine allocation until the end of follow-up.

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Table 1
Efficacy of 23-valent pneumococcal polysaccharide vaccine against pneumonia and mortality outcomes (1).

	Vaccine Group (n = 502)	Placebo Group (n = 504)	% Reduction in Incidence (95% CI)	p value
Pneumonia				
All-cause pneumonia*	63 (12.5%)	104 (20.6%)	–	
Incidence†	55	91	44.8% (22.4–60.8)	0.0006
Pneumococcal pneumonia‡	14 (2.8%)	37 (7.3%)	–	
Incidence†	12	32	63.8% (32.1–80.7)	0.0015
Mortality				
Pneumococcal pneumonia	0/13 (0%)	13/37 (35.1%)		0.0105
Non-pneumococcal pneumonia	13/49 (26.5%)	13/67 (19.4%)		0.3632
All-cause pneumonia	13/63 (20.6%)	26/104 (25.0%)		0.5181

* Sputum, blood cultures, and urinary antigen tests were done for 97 of the 167 cases.
† Incidence per 1000 person-years.
‡ Of the 51 cases, 49 were diagnosed by urinary antigen test, 41 were additionally diagnosed by sputum culture, and 3 by blood culture.

Medical staff at the nursing homes reported any symptoms among subjects to study team members and also conducted medical examinations of each subject on a weekly basis. Suspected pneumonia cases were referred to the affiliated hospital. Pneumonia was diagnosed based on clinical symptoms (not otherwise defined) and a new infiltrate on chest radiography. The latter was assessed by an independent reader and in 70% of cases confirmed by chest computed tomography.

Pneumococcal pneumonia was diagnosed based on the BinaxNOW pneumococcal urine antigen detection test, high quality sputum, or blood culture. The co-primary outcomes were pneumonia and pneumococcal pneumonia.

3. Risk of bias assessment

For this assessment, we referred to the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [12]. Several gaps in reporting were identified that could reflect deficiencies that in turn could have led to study bias. Randomization was done using a random number table, with participants assigned to their group by nursing home staff. However, no statement was made as to whether subjects were randomized individually or using some other method. If non-individual randomization was done, and pneumonias clustered within the unit of randomization, then randomization may have failed.

If block randomization was not done within participating centers, it is possible that some centers had an unequal distribution of patients assigned to intervention or control. If nursing homes differed with respect to factors contributing to pneumonia diagnosis – such as focal outbreaks, or access to x-ray facilities – it may also have undermined randomization. The authors reported that pneumonia incidence did not differ among the 23 participating nursing homes, but data to support this statement were not provided.

The authors indicated that allocation concealment was maintained until "the end of follow-up" but no statement is made as to whether blinding was maintained until the study database was locked and duplicate copies provided to different investigators. This allows for the possibility that knowledge of allocation could have influenced the final database.

None of the issues described above indicate that bias occurred, only that it cannot be ruled out by the manuscript text.

4. Internal validity

4.1. Definition

Internal validity in an RCT is defined as the extent to which the study is free from bias [12] and as such reflects the degree to which a study provides results that can be interpreted within the context of the study.

4.2. Proportion of pneumonia due to pneumococcus and all cause pneumonia PPSV23 VE

Maruyama et al. reported that 31% (51 of 167) of pneumonia cases were due to pneumococcus with a VE against pneumococcal pneumonia of 64% (Table 1). To achieve this VE against pneumococcal pneumonia, one would need to assume that 64% of pneumococcal pneumonia was due to PPSV23 serotypes with a PPSV23 VE of 100% against these vaccine serotypes; that 100% of pneumococcal pneumonia was due to PPSV23 serotypes with a PPSV23 VE of 64% against these vaccine serotypes; or some combination of values between these extremes.

If we assume that 64% of pneumococcal pneumonia was due to PPSV23 serotypes, by multiplying 31% * 64% = 19.5%, we calculate an upper bound of the proportion of all pneumonias due to PPSV23 serotypes (see Fig. 1). With 100% PPSV23 VE against vaccine serotypes (over double the VE found for PCV13 against vaccine type CAP in a randomized controlled trial in The Netherlands [13]), we should arrive at a PPSV23 VE against all cause pneumonia of 19.5% * 100% = 19.5%, substantially lower than the reported 45%. The calculation is the same if we assume the other extreme, namely 100% of pneumococcal pneumonia due to PPSV23 vaccine serotypes * 64% VE against these serotypes * 31% of pneumonia due to pneumococcus. In short, the values for the percent of all pneumonia cases due to pneumococcus and the VE for all cause pneumonia are mutually inconsistent, even using unrealistically high values of between 64% and 100% for PPSV23 VE against vaccine serotypes and the proportion of pneumococcal pneumonias due to vaccine serotypes.

One potential solution to this conundrum exists, namely that the proportion of pneumonia cases due to pneumococcus is underestimated, for example due to imperfect sensitivity of the diagnostic tests. The diagnostic tests used in the study were sputum culture, blood culture, and BinaxNOW urine antigen detection kit, and causative pathogens were found in 167 pneumonia patients despite only 97 of 167 having a full set of tests. Pneumococcal pneumonia was diagnosed in 51 participants: 49 by urinary antigen test, 41 by sputum culture, and three by blood culture. If, rather than 31% of pneumonia due to pneumococcus, 70% were due to pneumococcus, values would be internally consistent but only if PPSV23 VE against VT pneumonia and the proportion of pneumococcal pneumonias due to vaccine serotypes remained no lower than 64–100%. Moreover, as described in more detail below, we have found no study where the proportion of all cause pneumonia due to pneumococcus is 70%.

4.3. Mortality

Maruyama et al., reported case fatality ratios (CFRs) among vaccinated and unvaccinated persons for different pneumonia outcomes (Table 1). While not reported by the authors, one can also

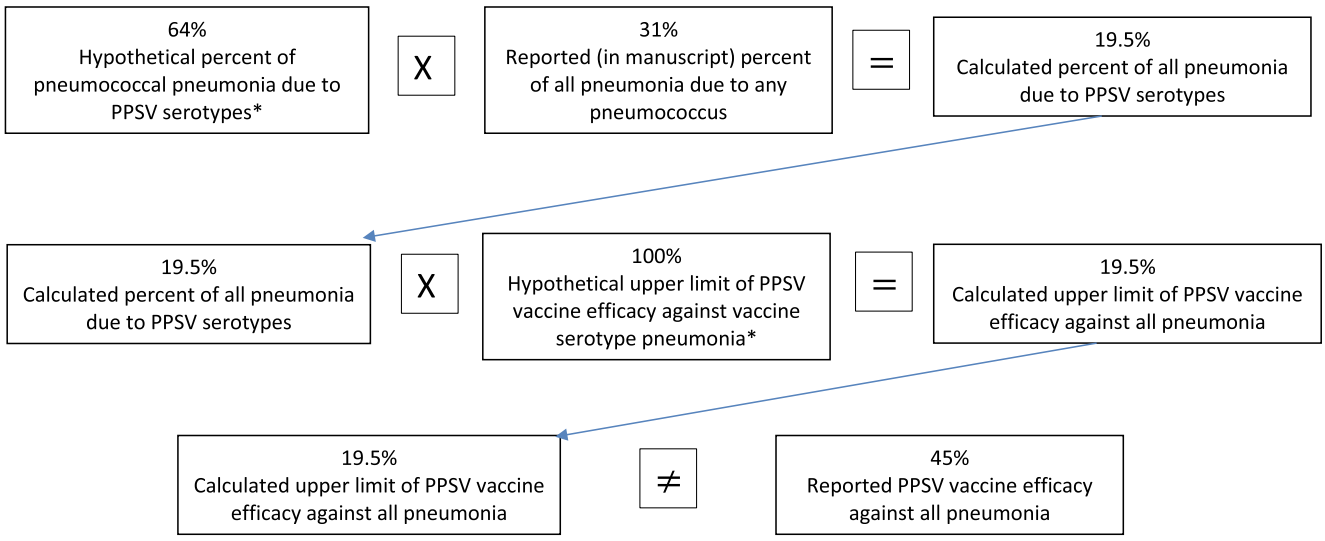

Fig. 1. Calculated and reported 23-valent pneumococcal polysaccharide vaccine (PPSV) efficacy against all pneumonia. * The authors reported 64% vaccine efficacy against all pneumococcal pneumonias; to achieve this, one would need to assume that 64% of pneumococcal pneumonia was due to PPSV23 serotypes with a PPSV23 VE of 100% against these vaccine serotypes; that 100% of pneumococcal pneumonia was due to PPSV23 serotypes with a PPSV23 VE of 64% against these vaccine serotypes; or some combination of values between these extremes. The Figure models the first assumption but conclusions are the same regardless.

look at cause specific mortality rates using as the denominators the total enrolled persons in the vaccinated (n = 502) and placebo (n = 504) groups. Using this approach, we calculated the mortality rate ratio (vaccinated/placebo) as 0 (95% CI, undefined) for pneumococcal pneumonia; 1.0 (95% CI, 0.47–2.1) for non-pneumococcal pneumonia; and 0.50 (95% CI, 0.26–0.97) for all cause pneumonia (OpenEpi, available at website: http://www.openepi.com/Menu/OE_Menu.htm, last accessed February 14, 2019). The 50% reduction in all cause pneumonia mortality has the same issues as discussed above for the 45% reduction in all cause pneumonia regardless of outcome.

Another issue with mortality exists. The authors reported 89 total deaths among 502 vaccinated persons and 80 total deaths among 504 persons in the placebo group. Among the vaccinated and placebo groups, 0 and 13 persons died of pneumococcal pneumonia, respectively. Simple arithmetic then implies that 89 of 502 persons in the vaccine group and 67 of 504 in the placebo group died of a cause other than pneumococcal pneumonia, leading to a mortality rate ratio of 1.41 (95% CI, 1.02–1.96). Yet we are unaware of a plausible hypothesis by which PPSV23 simultaneously would prevent pneumococcal pneumonia deaths and increase all other causes of death, and by approximately the same magnitude.

5. External validity

5.1. Definition

External validity in an RCT is defined as the degree to which a trial is generalisable or applicable in settings outside of the study itself [12]. For topics such as PPSV23 VE, where a substantial amount of data exist outside of the study in question, one measure of external validity is the degree to which study data are consistent with data from other studies.

5.2. VE against all cause pneumonia

The 45% PPSV23 VE against all cause pneumonia is inconsistent with a recent observational study in Japan showing VE of 5% [14]. Consistent with this, a meta-analysis of RCTs for PPSV23 VE against all-cause CAP reported a pooled VE of 13% (95% CI, 2%–24%); however, this result included data from Maruyama et al., which was the only one of seven studies that reported a statistically significant result, with VEs for the remaining six varying from −15% to 14% [15]. This same meta-analysis reported that during analysis stratified by geography, only the pooled results for the three Japanese trials (including the study by Maruyama et al.) identified a robust VE of 28% (95% CI, 12%–41%) while the single US study (which included 152,723 of 156,010 [98%] subjects in the combined seven studies) and the pooled three Western European studies (which included 1336 of 3287 [41%] non-US subjects) had VE point estimates of 4% (95% CI, −18% to 22%) and 2% (95% CI, −27% to 24%), respectively.

The most robust method of comparing PPSV23 and PCV13 VE against all cause pneumonia is within the same study among a population using both vaccines. To date, only a single example exists from the literature, namely in Germany, where during two observational analyses, VE for PPSV23 was 3.3% [16] and for PCV13 was 11.9% (p0.028) [17]. However, referring again to issues of internal validity, the data reported by Maruyama et al., do not afford any room for PCV13 to have a substantially higher VE against all cause CAP than PPSV23.

5.3. VE against mortality outcomes

As noted above, Maruyama et al., reported a VE against pneumococcal pneumonia mortality of 100% and data in the manuscript allowed us to calculate a VE (as measured by 1 – rate ratio) against all cause pneumonia mortality of 50%. By comparison, in their observational study from Japan, Suzuki et al. reported a small and non-significant impact on pneumococcal pneumonia mortality (VE, 9.6%; 95% CI, −218% to 74%) [14]. The meta-analysis of RCTs reported a modest and non-significant effect on all-cause pneumonia mortality (VE, 33%; 95% CI, −4% to 57%) among four available studies, again including the study by Maruyama et al. [15]; when excluding the latter, VEs ranged from 0 to 31% with lower CIs ranging from −85% to −312%.

5.4. Proportion of all cause pneumonia due to pneumococcus

As noted above, the reported proportion of pneumonia due to pneumococcus by Maruyama et al. was 31%, and to prevent mutually exclusive data being reported the true value for this outcome would need to be 70% or higher. However, the study by Suzuki

et al., in Japan – using sputum PCR (presumably highly sensitive, if not specific), sputum culture, urinary antigen test, and blood culture – found 21% of patients positive for pneumococcal infection [14]. A randomized controlled trial of PCV13 in elderly Dutch persons found that in the placebo arm, 174 of 787 (22%) first episode CAP cases were due to pneumococcus, in a setting that added a sensitive serotype specific urinary antigen detection test [13]. A systematic review and meta-analysis that included 35 studies reported an estimated proportion of community acquired pneumonia cases due to pneumococcus of 27.3% (95% CI, 23.9%–31.1%) [18]. One might expect pneumonias amenable to lung tap to have a higher proportion of pneumococcus identified. However, a Japanese study of adults age 15 years and older with community acquired pneumonia found that of 60 patients with a lung tap, 12 (20%) had pneumococcus identified [19]. An additional lung tap study of 109 subjects with CAP presenting to a Spanish emergency room found that 27 (30%) had pneumococcus identified [20].

6. Discussion

As well as risk of bias, data from the Maruyama et al. study raise concerns for both internal and external consistency. We do not know why this is so, and the authors themselves offer no explanation for such surprising results. Several possible biologically plausible reasons seem unlikely. For example, in theory the study population could have experienced a clonal outbreak from a single serotype which was exquisitely sensitive to PPSV23 induced immunity. However, the study was conducted in 23 distinct nursing homes, making this an unrealistic explanation. The study population was older than in other studies, with an average age of 85 years, and in theory this population could have had a dramatically increased likelihood of pneumococcal etiology among all pneumonia cases. However, in Japan PPSV23 VE has been reported to be lower among persons age 75 years compared to persons age 65–74 years [14]. Lastly, if PPSV23 provided non-specific protection against non-VT pneumococcal etiologies, it could explain the high all cause pneumonia VE. In support of this, Maruyama reported a non-significant 29% VE against non-pneumococcal pneumonia; however, it is not possible to distinguish whether this was a true non-specific effect, the result of misclassification bias due to the lack of highly sensitive diagnostic tests, or a random finding. The trial by Suzuki et al., found no impact of PPSV23 against non-VT pneumococcal pneumonia [14].

While this was an RCT, the manuscript does not provide enough information to assure that randomization did not fail and that allocation concealment was not broken before database locking. Some analyses that were not presented could have provided some assurance that these events did not occur, such as case accumulation by nursing home, or assessment of VE by diagnostic test. Assuming that randomization did not fail and allocation concealment was maintained until the point of analysis, it is possible that in the Maruyama study setting – namely patients with an average age of 85 years living in the close confines of a Japanese nursing home, with a particular pneumococcal epidemiology unique to that time and place – for unknown reasons a large proportion of pneumonias were due to PPSV23 serotypes and PPSV23 was particularly effective against the prevalent serotypes. Regardless of whether or not this occurred, we think the issues we raise here are serious enough that when national decision-makers globally are weighing the benefits of different pneumococcal vaccines in the general adult population, the Maruyama study should be considered an outlier whose relevance – if any – should be limited to the unique population in which the study was conducted.

Author contributions

Contributors: Study concept and design: BDG, CT, LJ; acquisition of data: BDG, CT; data analysis: BDG, CT; interpretation of data: BDG, CT, LJ; first draft of manuscript: BDG. All authors reviewed and approved the final manuscript for submission.

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Declaration of Competing Interest

BDG, CT, and LJ are employees of Pfizer Inc.

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