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Accuracy of composite diagnostic standards for pneumococcal pneumonia in vaccine trials

M. Suzuki[1], S. Katoh[1,2], R. Miyahara[1,3], K. Ariyoshi[1,2] and K. Morimoto[1]

[1]Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan; [2]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan and [3]Department of Human Genetics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Short Paper

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Author for correspondence:
M. Suzuki, E-mail: mosuzuki@nagasaki-u.ac.jp

Abstract

Because of a lack of gold standard diagnostics, a combination of multiple diagnostic tests, or composite diagnostic standard, has been used to measure pneumococcal pneumonia (PP) in pneumococcal vaccine trials. We estimated the accuracy of composite diagnostic standards for PP used in previous randomised controlled trials by simple formulas. A systematic literature review identified five eligible trials and all trials had used different combinations of diagnostic tests for PP. The estimated values of sensitivity and minimum specificity of composite diagnostic standards varied substantially between trials: 48.4% to 98.1% and 71.0% to 97.3%, respectively. Without standardizing the outcome measurements, pneumococcal vaccine efficacy estimates against PP are not comparable between trials and their pooled estimates are biased.

Key Findings

- Different combinations of diagnostic tests have been used in pneumococcal vaccine trials.
- The estimated accuracy of composite diagnostic standards varied substantially between trials.
- Pneumococcal vaccine efficacy estimates are uncomparable and their pooled estimates are biased.

Pneumococcal pneumonia (PP) is a major cause of morbidity and mortality among adults. A 23-valent pneumococcal polysaccharide vaccine (PPV23) has been recommended for adults aged ⩾65 years to prevent invasive pneumococcal diseases in many countries, while its protective efficacy against PP remains to be questioned [1–5]. Recently, a vaccine trial demonstrated the protective efficacy of 13-valent pneumococcal conjugate vaccine (PCV13) against vaccine-type PP among older adults [6]. However, there is no study that formally compared the efficacy of PPV23 and PCV13.

One of the major limitations in pneumococcal vaccine trials is a lack of gold standard diagnostics for PP [7]. Almost all tests for identifying pneumococcus from blood, sputum and urine samples are imperfect [8–10]. Blood culture has been a gold standard for pneumococcal bacteremia; however, its sensitivity for diagnosing PP is very low because only up to a quarter of PP cases are bacteremic [8]. Culture and polymerase chain reaction-based methods using sputum samples are believed to be less specific despite an absence of supporting evidence. A commercial urinary immunochromatographic test for pneumococcal antigen (ICT) is sufficiently specific (93–100%) but less sensitive (67–82%) and its test accuracy varies by settings [10].

To overcome this limitation, pneumococcal vaccine studies often use a composite diagnostic standard [11]: pneumonia patients are screened by multiple diagnostic tests and the diagnosis of PP is made if any of the tests show positive result. A use of multiple imperfect tests increases the overall sensitivity but decreases the overall specificity [12] and a use of inaccurate diagnostic test underestimates true vaccine efficacies (VEs [13, 14]. However, because of the absence of reference standards and analytical methods, to the best of our knowledge, no study has evaluated the performance of composite diagnostic standard as an outcome in pneumococcal vaccine trials. In this study, we estimated the accuracy of composite diagnostic standards for PP from previous trial results by using a novel approach.

To establish formulas to calculate the sensitivity and specificity of an outcome measurement, we used a simple randomised controlled trial (RCT) model similar to that used in a previous study [13]. In this model, vaccinated and unvaccinated people are followed up during a specified period. If they develop all-cause pneumonia (ACP), samples are collected and tested for pneumococcus. The VE was calculated as a 1-risk ratio.

The observed VE against ACP (ve_a), observed VE against PP (ve_p) and true VE against PP (ve_π) are described using the following parameters:

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a_c = observed risk of ACP in unvaccinated individuals.
a_v = observed risk of ACP in vaccinated individuals.
p_c = observed risk of PP in unvaccinated individuals.
p_v = observed risk of PP in vaccinated individuals.
π_c = true risk of PP in unvaccinated individuals.
π_v = true risk of PP in vaccinated individuals.
Se = test sensitivity for diagnosing PP.
Sp = test specificity for diagnosing PP.

To simplify the following discussion, we introduce four assumptions:

Assumption 1 (A1): the misclassification in the diagnosis of ACP is non-differential.

Assumption 2 (A2): the pneumococcal vaccine does not change the risk of non-PP.

Assumption 3 (A3): the directions of ve_a and ve_p are identical and the value of ve_p is equal to or greater than that of ve_a (i.e., $0 < ve_a \leqslant ve_p$ or $ve_p \leqslant ve_a < 0$).

Assumption 4 (A4): the pneumococcal vaccine does not affect Se and Sp.

Then, Se and the minimum value of Sp ($Sp_{\min}$) are given as follows (technical details are provided in Supplementary materials):

$$Se = \frac{p_c - p_v}{a_c - a_v},$$

$$Sp_{\min} = \begin{cases} 1 - \dfrac{p_v}{a_v} & \text{if } 0 < ve_a \leq ve_p \leq 1 \\ 1 - \dfrac{p_c}{a_c} & \text{if } ve_p \leq ve_a < 0 \end{cases}.$$

We conducted a systematic literature review to identify RCTs that investigated the efficacy of pneumococcal vaccines against ACP and PP for adult population. We searched PubMed for English language articles published between 1 January 1977 and 30 March 2017, with the terms '*Streptococcus pneumoniae*', 'pneumococcus', 'pneumococcal', 'vaccine', 'efficacy', 'trial', and 'adult'. We also reviewed relevant articles identified in previous systematic reviews [1–3]. Studies were included if they were RCTs (either they used placebo, other vaccines, or no vaccine as controls), measured both ACP and PP as outcomes and fulfilled the assumption A3; otherwise, they were excluded. Data were extracted from published results. The median values and 95% credible intervals (CIs) for ve_a, ve_p, Se and Sp_{min} were estimated based on non-informative priors using WinBUGS 1.4.3 (Medical Research Council and Imperial College London, UK) [15], a statistical software package designed for Bayesian analysis. For the Markov Chain Monte Carlo procedures, we took 50 000 iterations with 20 000 for burn-in.

We identified seven RCTs that investigated the efficacy of pneumococcal vaccines against ACP and PP for the adult population. Two RCTs were excluded because one did not fulfill the assumption A3 ($ve_a < ve_p < 0$ in the study) [16] and one did not include a sufficient number of PP events (two in vaccinated group and one in the placebo group) [17]. Finally, five RCTs including one 14-valent PPV trial, three PPV23 trials and one PCV13 trial were included in our analysis.

Characteristics of included RCTs are shown in Table 1. All but one PPV23 trial conducted by Örtqvist *et al.* [18] showed positive VE results. All RCTs used different combinations of diagnostic tests for PP. Four PPV trials used respiratory specimen culture,

Table 1. Estimated accuracy of composite diagnostic standards for pneumococcal pneumonia in randomised controlled pneumococcal vaccine trials

Trial	Type of vaccine	Diagnosis of PP	No of PP/ACP/total participants in vaccinated group	No of PP/ACP/total participants in unvaccinated group	ve_a, % (95% CI)	ve_p, % (95% CI)	Sensitivity, % (95% CI)[a]	Minimum value of specificity, % (95% CI)
Riley 1977 [31]	PPV14	Lung aspirate culture, blood culture	2/44/5946	14/62/6012	27.9 (−5.2 to 51.1)	81.6 (41.9–96.1)	69.5 (33.3–141.0)	94.0 (83.0–98.7)
Örtqvist 1998 [18]	PPV23	Serological assay, sputum culture, blood culture, urine ICT	19/63/339	16/57/352	−14.7 (−59.0 to 17.0)	−22.6 (−133.9 to 35.2)	48.4 (14.3–141.0)	71.0 (52.4–83.5)
Alfageme 2006 [32]	PPV23	Respiratory specimen culture	0/25/298	5/33/298	23.6 (−23.8 to 53.6)	87.8 (15.7–99.6)	65.4 (21.8–182.8)	97.3 (84.9–99.9)
Maruyama 2010 [33]	PPV23	Urine ICT, sputum culture, blood culture	12/55/502	32/91/504	39.1 (17.4–55.6)	61.1 (28.3–80.1)	56.5 (32.9–94.8)	77.2 (60.0–88.0)
Bonten 2015 [6]	PCV13	Serotype-specific UAD, urine ICT, sterile culture	135/747/42 240	174/787/42 256	5.0 (−4.9 to 14.0)	22.3 (2.8–37.9)	98.1 (63.3–151.9)	81.9 (78.3–84.9)

PP, pneumococcal pneumonia; ACP, all-cause pneumonia; ve_a, observed vaccine efficacy against ACP; ve_p, observed vaccine efficacy against PP; PPV14, 14-valent pneumococcal polysaccharide vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; ICT, immunochromatographic test; CI, credible interval.
[a]As the estimated sensitivity is given as a risk difference ratio in our formula, its value can exceed 100%. When the assumption A3 holds, the median value of estimated sensitivity does not exceed 100%; however, its 95% credible interval may still include 100%.

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while the PCV13 trial [6] used a newly developed serotype-specific urinary antigen detection (UAD) assay [19]. Only one trial by Örtqvist *et al.* used serological assays to detect antibodies against pneumolysin [20, 21]. Estimated *Se* and Sp_{min} values of composite diagnostic standards substantially varied by trials: 48.8% to 98.1% and 69.0% to 97.3%, respectively. The highest *Se* value was observed in the PCV13 trial, while the lowest *Se* and Sp_{min} values were observed in the PPV23 trial by Örtqvist *et al.*

In this study, we demonstrated that: (1) different combinations of diagnostic tests have been used to measure PP in pneumococcal vaccine trials; and (2) the estimated accuracy of composite diagnostic standards substantially varied by trials. The use of inaccurate diagnostic test underestimates true VEs; less specific tests more largely affect VE estimates than less sensitive tests [13, 14]. Our findings indicate that pneumococcal VE estimates against PP are not directly comparable between RCTs.

Recent meta-analyses for PPV23 efficacy against PP in older adults showed inconsistent findings [3–5]. Although two meta-analyses showed a non-significant protective trend [3, 4], a meta-analysis by Falkenhorst *et al.* demonstrated a significant PPV23 efficacy against PP excluding trials which had used serological assays [5]. The serological assays for PP had been developed in the early 1990s [20, 21] and used in epidemiological studies. However, their inaccuracy has been demonstrated in later validation studies [5, 22] and the assays are rarely used recently. In the trial by Örtqvist *et al.*, most PP cases had been diagnosed by the assays. In fact, among five RCTs included in our study, the lowest *Se* and Sp_{min} values were observed in their study. The inclusion of this study in meta-analyses must cause biased pooled-VE estimates.

On the other hand, high *Se* and Sp_{min} values were observed in the PCV13 trial. The majority of PP cases in this trial were diagnosed by the serotype-specific UAD and a validation study demonstrated that its sensitivity and specificity for the diagnosis of invasive pneumococcal disease are 98% and 100%, respectively [23]. These findings suggest that the PCV13 efficacy estimates are uncomparable with the PPV efficacy estimates which had been measured by less accurate diagnostic tests.

The lack of standardized pneumonia outcome is a major limitation in pneumococcal vaccine trials [7]. Although current pneumococcal vaccines do not cover all pneumococcal serotypes, few trials have measured vaccine-type PP [24]; instead, almost all previous trials have measured less specific outcomes such as ACP and PP using different definitions [1–5]. ACP includes a variety of aetiology other than pneumococcus such as *Haemophilus influenzae* and viruses [25] and PP includes a substantial proportion of non-vaccine-type PP. The inclusion of these vaccine-unrelated pneumonia decreases the specificity of outcome and underestimates the VEs. In the current study, as long as the assumption A2 holds, the proportion of non-PP in ACP does not affect our estimated accuracy of outcome for PP. If the risk of non-PP increases in the vaccinated individuals due to a replacement, our method overestimates the true accuracy; if the risk decreases in the vaccinated individuals due to a cross-protection, our method underestimates the true accuracy. However, such effects have not been observed in previous studies including our recent vaccine effectiveness study [24]. On the other hand, to apply our method for estimating the accuracy of outcome for vaccine-type PP, an additional assumption of zero-efficacy against non-vaccine-type PP is required. This assumption may not hold in real settings because of the serotype replacement induced by the PCVs [26]. Another limitation of the use of the composite diagnostic standard in pneumococcal vaccine trials is that not all samples among ACP cases are always tested for pneumococcus. This missing test results may decrease the overall sensitivity and specificity of outcome as reflected in our estimates.

In this study, we proposed and applied a new method to estimate the accuracy of composite diagnostic standards for PP used in pneumococcal vaccine trials. The latent class analysis (LCA) has been used to estimate the sensitivity and specificity of individual tests for diagnosing PP in the absence of gold standard [27–29]. The LCA estimates the accuracy of each test based on the observed frequency of the possible combinations of test results. The advantage of our method is its ability to assess the accuracy of outcomes measured by multiple diagnostic tests without using individual test results. Although several assumptions are required, our method may be also useful for evaluating pneumonia outcomes used in pediatric PCV trials [30].

Our study has limitations. We assumed that the sensitivity and specificity for PP are identical between vaccinated and unvaccinated groups, although there is no evidence to support this assumption. If the proportion of the tested samples among ACP cases is different between the vaccinated and unvaccinated groups, our estimates may be biased; however, we can reasonably assume that the probability of testing is almost identical between the two groups in RCTs. Additionally, systematic and random errors in the trial may affect our estimates. The observed difference in our accuracy estimates by RCTs may be partially explained by the different population characteristics (eg. general population [6, 31] *vs.* high-risk population [18, 32, 33]). Notably, the trials with highest PP incidence (the trials by Örtqvist *et al.* [18] and Maruyama *et al.* [33]) were those with the lowest sensitivity. Other factors than just the outcome definition must affect the estimates. Finally, only the minimum value of specificity can be estimated in this approach.

In conclusion, the accuracy of composite diagnostic standards for PP varies by RCTs because of the use of different combinations of imperfect tests. Without standardizing the outcome measurement, pneumococcal VE estimates are uncomparable and their pooled estimates are biased.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0950268818000651

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