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The scrutiny of identifying community-acquired pneumonia episodes quantified bias in absolute effect estimation in a population-based pneumococcal vaccination trial

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Abstract

Objectives: To determine the accurateness of detecting community-acquired pneumonia (CAP) in the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), a community-based, double-blind, randomized placebo-controlled trial in which the needed to treat (NNT) for prevention of vaccine-type pneumococcal CAP was 1,007 [95% confidence interval (CI): 613, 2,646].

Study Design and Setting: Study participants developing pneumonia were identified in 58 participating hospitals by research nurses (RNs) using local-adapted protocols. In addition, general practitioner (GP) records were screened for hospital referrals for suspected pneumonia. Two independent reviewers determined reasons for not identifying pneumonia episodes, and the NNT adjusted for missed episodes was estimated.

Results: Of 2,183 hospital referrals with suspected pneumonia detected in GP records, 232 (11%) were admitted outside established screening routes and 102 (5%) were not suspected of pneumonia on admission. Of the remaining 1,849 episodes, 1,374 (63% of all episodes and 74% of identifiable episodes) were identified by RNs. Several causes of missing episodes were identified. After adjustment for missed episodes, the NNT reduced to 634 (95% CI: 386, 1,675).

Conclusion: With the screening procedure, 63% of suspected pneumonia episodes were identified, and the estimated NNT reduced from 1,007 to 634. Root cause analysis of unidentified episodes provides guidance for improving pneumonia detection in future trials.

Keywords: Community-acquired pneumonia; Community-based; Trial; End point detection; Completeness; Missing outcome data

1. Introduction

Reliable measurement of outcome events in clinical intervention studies is of major importance [1]. Biased observations may lead to overestimation or underestimation of relative effects of interventions, which can be prevented by random treatment assignment, blinding of patients and investigators, and using intention-to-treat analysis. These measures ensure that, on average, measurement errors will be the same for all study groups, provided that interventions do not influence measurement accuracy, ensuring a valid relative risk estimate [2]. However, missing outcome events, even if equally distributed among study groups, will reduce absolute effect estimates, such as risk differences, number needed to treat (NNT), or number needed to harm (NNH). As such, missing event data may severely compromise health outcome analyses leading to unjustified acceptance or rejection of interventions. For instance, harmful interventions may be implemented if serious adverse events are missed and the NNH is overestimated, and beneficial interventions may be rejected if outcome events are missed and hence the NNT is overestimated. Missed outcome events in clinical trials can be taken into account by describing reasons for withdrawal and loss to follow-up [3–6], but this is not possible if outcome events are missed while subjects remain under study.

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What is new?

Key findings

- Thirty-seven percent of pneumonia admissions were missed in a large community-based randomized controlled trial which impacted the number needed to treat observed in the trial.
- Reasons for nonidentification (of which some preventable, e.g., admission via nonscreened routes and misinterpretation of referral indications or of diagnoses by research nurses) are identified and presented.

What this adds to what was known?

- This study shows how well we were able to timely identify pneumonia admissions in a community-based trial and where improvements are possible.

What is the implication and what should change now?

- Analysis of identification failure causes provides guidance for improved design of future trials.
- Absolute effect estimates from trials should be adjusted for the accurateness of end point identification.

Community-acquired pneumonia (CAP) is an infection with a high incidence and high mortality rate, and *Streptococcus pneumoniae* is recognized as the most important pathogen for CAP [7,8]. In the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTAs), the 13-valent pneumococcal conjugate vaccine reduced the incidence of a first episode of vaccine-type (VT) CAP in immunocompetent elderly by 46% [9]. In this randomized, placebo-controlled, double-blind study, 84,496 immunocompetent community-dwelling subjects, aged 65 years and older, were recruited between September 2008 and January 2010 and end point detection was materialized through identifying study subjects with a clinical suspicion of pneumonia in 59 sentinel centers (58 hospitals and 1 outpatient clinic) between September 2008 and August 2013. The median follow-up duration for study participants was 4 years. Based on the detected primary end points, the NNT to prevent one episode of VT-CAP was 1,007.

In the current analysis, we aimed to determine the number of missed primary end points, estimated the effect of missed episodes on the NNT, and categorized the reasons for missing episodes, thus demonstrating the limitations of absolute effect estimation from clinical trials without proper adjustment for the accurateness of end point identification and providing guidance for improved outcome detection in future studies.

2. Methods

2.1. Data collection

Details of the CAPiTA have been described elsewhere [9]. Two data sources were used in the present study: the study database of identified episodes in the 58 participating hospitals and the general practitioner (GP) records of participating subjects. In the original study 59 centers were used for identification of pneumonia episodes, of which one was a diagnostic center; [9] patients referred to this center were not included in the current analysis unless the patient was subsequently referred to one of the hospitals. Study subjects presenting to one of the hospitals with suspected pneumonia were identified by research nurses (RNs), who were trained to perform daily screening of emergency room (ER) registries of internal medicine, pulmonology, and cardiology. For each hospital, screening procedures were implemented according to local circumstances. Among patients with a suspicion of pneumonia, trial participation was cross checked with a study identification database. Primary end point determination required presence of at least two clinical criteria, chest X-ray abnormalities compatible with pneumonia, and detection of vaccine serotype *S. pneumoniae* in a blood culture, other sterile culture, or serotype specific urinary antigen detection (UAD) assay. A positive UAD test was needed in most (i.e., blood culture negative) pneumococcal CAP cases, for which urine had to be collected within 48 hours of admission. For this reason, pneumonia admissions identified by the RN more than 48 hours after admission were considered as missed. Pneumonia admissions that were identified within the time window but where the urine sample was not available for another reason (e.g., in case of anuria) were categorized as identified for the purpose of this analysis.

In the Netherlands, every inhabitant is registered with a single GP, who is routinely informed about important medical affairs and, therefore, should receive all discharge letters from hospital admissions or ER visits. As part of the study, dedicated study monitors checked GP records twice yearly for new information of participants indicating hospital referral for (suspected) pneumonia. This information was linked to the study database of episodes detected in the hospitals, and if the GP-detected episode was not present in the study database, additional information was collected in the related hospital. This information included all medical letters and medical records from the ER, laboratory data at admission, radiology data within 48 hours after admission, discharge letters, and information from RN for reasons of missed identification.

During the study, potentially missed episodes were independently reviewed by two of four investigators [C.H.v.W., S.M.H., F.P.P. (authors) and A.N. (see Acknowledgments)], and reasons for missing were allocated according to a predefined protocol (Appendix Figures 1 and 2 at www.jclinepi.com, see Box 1 for definitions). Discrepant classifications were discussed until consensus was reached. If consensus