founder [5]. We controlled for the significant differences between groups by adjusting for the correspondents’ variables in the multivariable analysis and treating the confounding through purposeful selection method [3].

If we consider hospitalization for pneumonia, the adjusted hazard ratio (HR) decreased when the 2 covariates history of hospitalization for pneumonia and number of outpatient visits were added into the model. The adjusted HR was 0.81 (95% CI, 0.66–1.00; \( P = .060 \)) without these variables and 0.74 (95% CI, 0.59–0.92; \( P = .007 \)) when both variables were included in the final model. These 2 variables were statistically significant. The maximum change in the coefficients for any other variable remaining in the model was <11%. In this model, influenza vaccination was not a confounder. When the influenza vaccine status was added, the associations were essentially unchanged (pneumococcal vaccine HR, 0.76; 95% CI, 0.60–0.97; \( P = .026 \)). The maximum change in all coefficients was <12%.

As can be seen in table 4 of our article [4], the effectiveness of pneumococcal polysaccharide vaccine for reducing hospitalization for pneumonia during influenza seasons was significant (HR, 0.69; 95% CI, 0.49–0.97; \( P = .031 \)). This table only indicates the adjusting covariates in the initial models, but does not indicate the covariates in the final models. With regard to hospitalization for pneumonia during the influenza period, influenza vaccination status was neither statistically significant nor an important confounder.

In summary, we have estimated the effect of pneumococcal polysaccharide vaccine in parsimonious and robust models that adjusted for all covariates considered in previous studies. However, as commented on in the discussion, “as with all observational studies, the possible influence of residual confounding can not be completely excluded” [5, p.863].

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References


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Pharmacokinetics of Rifampicin

To the Editor—Nijland et al. [1] present interesting data regarding the pharmacokinetics of rifampicin in patients with tuberculosis and diabetes mellitus. However, their conclusions are weakened by 2 important flaws in the study design. First, they used the area under the curve between 0 and 6 h (AUC\(_{0<6} \)) as a surrogate for total rifampicin exposure. Time points beyond 6 h are routinely used to examine rifampicin pharmacokinetics, because the maximum concentration may occur as late as 8 h after administration of the dose [2]. The data presented in table 2 and figure 1 of the article strongly suggest delayed rifampicin absorption in the diabetic subjects, compared with the nondiabetic subjects. The median time to the maximum concentration was 4 h (the upper limit of the range was 6 h) in the diabetic subjects, compared with 2 h (upper limit of range, 4 h) in nondiabetic subjects; even though this difference was not statistically significant, it appears to have been a significant confounder. Furthermore, the relative decrease in rifampicin plasma concentrations between 4 and 6 h was ~47% in the nondiabetic subjects versus ~30% in the diabetic subjects, suggesting ongoing absorption in at least some subjects during this time. Examination of the plasma rifampicin concentrations at a later point would have greatly enhanced confidence that the difference in rifampicin pharmacokinetics between diabetic and nondiabetic patients with tuberculosis was an effect of malabsorption, as opposed to delayed absorption.

Second, the authors did not match the diabetic and nondiabetic subjects by weight and sex, which have both been associated with significant differences in rifampicin exposure [2]. Linear regression is inadequate to adjust for the difference in weights among the diabetic and nondiabetic subjects, particularly given the small sample size. As can be seen in figure 2 of Nijland et al. [1], 11 of the 17 nondiabetic subjects weighed <50 kg (compared with 4 of 17 diabetic subjects), and there is a cluster of 8 nondiabetic subjects who weighed <50 kg and who had very high rifampicin AUC\(_{0<6} \) values, suggesting a nonlinear relationship between subject weight and rifampicin exposure at higher doses (in mg/kg). The area under the curve for nondiabetic subjects who weighed ≥50 kg falls well within the range for diabetic subjects in this study.

In short, the data presented by Nijland et al. [1] are tantalizing, but because of serious limitations, do not clearly demonstrate that type 2 diabetes is associated with decreased exposure to rifampicin.

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Reply to Gadkowski and Stout

To the Editor—Gadkowski and Stout [1] comment that the area under the curve between 0 and 6 h (AUC_{0–6 h}) cannot serve as a surrogate for total exposure (AUC_{0–24 h}) to rifampicin and that the results of our study [2] could be explained by delayed absorption of rifampicin in patients with tuberculosis (TB) who have type 2 diabetes (DM). We recently recorded full pharmacokinetic curves of rifampicin in 48 Indonesian patients with TB (unpublished data). Only 2 of 48 patients had a time to maximum concentration (T_{max}) of >4 h. The AUC_{0–6 h} based on sampling at 0, 2, 4, and 6 h appeared to be an excellent surrogate for AUC_{0–24 h} (Pearson correlation coefficient, 0.923; P < .001). Of course, this only applies in the absence of delayed absorption. In our study patients who had TB, with or without DM [2], the median T_{max} for rifampicin was 4 h in patients with TB and DM, compared with 2 h among those with TB alone. Individual T_{max} values show why this difference was not significant (P = .52) and certainly do not point to delayed absorption (table 1).

Gadkowski and Stout [1] also suggest that slightly different relative decreases in average rifampicin plasma concentrations between 4 and 6 h after administration of the dose indicate ongoing absorption in patients with TB and DM. As a rough approximation, we calculated rate constants on the basis of rifampicin concentrations at 4 and 6 h in all participants and used these to estimate AUC_{0–24 h} values (linear/log trapezoidal rule). The geometric mean ratio for AUC_{0–24 h} (patients with TB and DM versus those with TB alone) is 0.57, similar to the results we obtained based on the AUC_{0–6 h}.

Gadkowski and Stout [1] also state that we did not match for sex and weight. However, we did match for sex, as mentioned in our publication. Matching for weight was not feasible, because patients with (type 2) DM generally have higher body weights. Therefore, in the multivariate analysis, we chose to assess the contributions of DM and body weight to the pharmacokinetics of rifampicin. As a rule of thumb, 15 subjects are required for every predictor in multiple linear regression [3]. Because our linear regression equation contained 2 predictors, the study group comprised 34 subjects, and all assumptions were met, linear regression was applicable. We agree that other linear models may also be valid to extrapolate the association between weight and area under the curve to those weight ranges in which few data were available (i.e., low weights in patients with TB and DM and high weights in patients with TB alone). Considering the amount of data, no model can be preferred above the other. Of note, AUC_{0–6 h} in subjects who weighed >50 kg was much lower in patients with both TB and DM than in those with TB alone (geometric mean ratio, 0.63), contrary to the statement made by Gadkowski and Stout [1]. Finally, the strong inverse association between fasting blood glucose level and rifampicin AUC_{0–6 h} clearly confirms the importance of DM as an independent predictor besides body weight.

We conclude that our results are valid and remain tantalizing. Indonesian patients with TB and DM have lower plasma concentrations of rifampicin, which can be ascribed to differences in weight and diabetes or hyperglycemia. Follow-up studies to confirm these findings are underway.

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References

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