Thus, we feel that the main conclusion in the publication by Youngs *et al.*, claiming a low sensitivity for influenza by the Liat Influenza A/B and RSV assay compared to Fast Track Diagnostics Respiratory Pathogens 21 multiplex assay, is unsubstantiated [1].

Conflict of interest statement
Jan Gorm Lisby has been on the speaker's bureau for Roche Diagnostics.

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Reply to: Concerns regarding the validity of the conclusion in a recently published paper on Roche Liat implementation

Sir,

Lisby and Schneider comment on our finding that the Cobas Liat influenza A/B and respiratory syncytial virus assay (Liat; Roche, Basel, Switzerland) had sensitivity for influenza A or B of 85.4% [1]. They point out that this value is lower than the sensitivity of 97.9—100.0% found in previous verification studies. We agree with this point, and referenced this higher sensitivity estimate in our paper whilst offering an explanation for why our estimate differed [2].

It is important to distinguish between the analytical performance of a test when used under ideal conditions in a verification study as opposed to that following real-world implementation. Many studies have already demonstrated a very high analytical sensitivity of Liat, and we did not seek to repeat this work. In contrast, the purpose of our study was to evaluate and report the performance of Liat in clinical practice after implementation into an emergency department (ED). The lower sensitivity we observed is likely due to combination of errors in sample collection, and transcription errors as the instrument was not initially interfaced into the laboratory information management system (LIMS). The testing of samples and recording of results was a new experience for the regular nursing staff alongside their normal, and highly intense, clinical activities, and outside a formal research setting.

An important corollary of our findings is that the analytical sensitivity of an instrument such as Liat is not the only factor to consider when deploying such point-of-care tests. We have reported our experience in the first year of use [3]. Subsequently, we have improved training, audit and monitoring of the use of Liat, including Liat interfacing directly into our hospital computer systems, and continue to improve the reliablility of the diagnostic process as a whole.

Lisby and Schneider also refer to the fact that negative Liat patients were retested more frequently than positive Liat patients, creating selection bias. The repeat testing of our negative results was to identify other pathogens in a wider screen while further identifying any missed influenza cases. We discussed some implications of this in our paper, but are grateful to Lisby and Schneider for pointing out the effect that this would have upon the estimate of Liat sensitivity.

If we assume that there are no systematic differences between the positive Liat patients that were and were not included (and the same for negative Liat patients), we can estimate the magnitude of this effect. We know that 308/1027 Liat tests were positive for influenza A or B. In the modified analysis, 87 Liat-positive patients were included: 76 true

positive and 11 false negative. If we weight these values by 308/87 (3.54), this predicts that 269/308 positive Liat results would have been true positive results. Applying the same method to the negative Liats, we predict that 703/719 Liats would have been true negative results. This provides the following estimates of performance: sensitivity 269/285 [94.4%, 95% confidence interval (CI) 91.0—96.8]; specificity 703/742 (94.7, 95% CI 92.9—96.2); positive predictive value 269/308 (87.3, 95% CI 83.5—90.4); and negative predictive value 703/719 (97.8, 95% CI 96.5—98.6).

From this analysis, including a higher proportion of Liat-negative patients may have underestimated sensitivity but overestimated specificity. As such, the effect on positive and negative predictive values would have been minimal (i.e. the negative and positive predictive values here are necessarily identical to those in our initial analysis). In our paper, we adjusted these values in an attempt to compensate for the known prevalence in the tested population as determined by Liat [2].

Lisby and Schneider comment on the fact that the 15 false-negative Liat results were all detected at high cycle threshold (Ct) values by real-time polymerase chain reaction (rPCR), and so may actually represent false-positive rPCR results. As there was no evidence of assay and systems contamination during this study by examination of random internal controls, and the Ct valves for these rPCR positives were <39, it its likely that they represented true low levels of target rather than false-positive results. Our own interpretation of the significance of the high Ct values is discussed in our paper [2].

Overall, our conclusion was that Liat performed well in a real ED, and the impact on infection prevention and control outcomes in our accompanying paper was impressive [3]. We continue to use Liat during the current 2018/19 influenza season, and improve the performance of this point-of-care pathway as a whole in our EDs.

Conflict of interest statement
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