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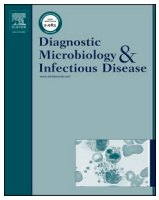

Comparative evaluation of swabbing sites for Omicron variant detection in PCR testing

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ABSTRACT

Purpose: The Omicron variant of SARS-CoV-2 raised concerns about the best sampling sites for PCR testing, with early indications suggesting throat swab samples were better than nasal swab samples. Our study evaluated the sensitivity of detecting SARS-CoV-2 across different swabbing sites.
Methods: Participants undergoing testing at NHS Test and Trace sites in England provided self-collected samples using nose only, throat only, and combined nose and throat swabs, which were analysed by realtime PCR.
Results: Among 815 participants, combined swabs had higher viral concentrations than nose only or throat only swabs. Sensitivity for detecting SARS-CoV-2 by PCR was 91 % for nose only and 97 % for throat only, relative to the combined approach. VC remained stable in nose swabs but declined in throat swabs with time.
Conclusions: Combined nose and throat swabbing remains the most effective method for SARS-CoV-2 detection. If a single swab is used, a throat swab has a higher sensitivity than nose swabs, although VC in the throat decreases faster in later infection stages. The variations in VC over time and intra-person variation between sampling sites underscore the complexity of viral dynamics, highlighting the importance of considering both nose and throat samples for comprehensive testing.

1. Background

The Omicron variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was classified as a variant of concern (VOC) by the World Health Organization in November 2021 [1,2]. Omicron was at that time the most mutated variant, with a high transmission rate and immune invasion, raising global concerns about change in SARS-CoV-2 virus tropism. In the UK, the national standard for polymerase chain reaction (PCR) testing involved swabbing both the nose and throat (N&T). However, nose only swabbing was an alternative option for people for whom N&T swabbing would present accessibility issues, such as those who indicated discomfort while swabbing their throat. At the same time, reports emerged suggesting that the Omicron variant was detectable earlier in the throat than in the nose [3,4,5], compromising the use of nose only methods (a common sampling method for LFD testing) by missing opportunities for early detection.

Previous research, not specific to the Omicron variant, suggested that while combined mid-turbinate nose and throat samples have a high

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sensitivity compared to nasopharyngeal samples, sensitivity in nose only samples was lower, and throat only samples lower still (97 %, 86 % and 68 %, respectively) [6]. Other studies have confirmed low sensitivity of throat only samples with results of 43 % and 44 % [7,8]. However, one study reported no significant differences in sensitivity between nose only and N&T samples [9].

Here we sought to determine whether there was any difference in sensitivity for detecting SARS-CoV-2 in nose only and throat only samples, as in combined N&T samples for PCR testing, by estimating and comparing the viral concentration (VC) obtained from each sample type. In addition, we assessed the relationship between the swabbing approaches and the accuracy related to time from onset of symptoms. We took a pragmatic approach by recruiting participants who were self-sampling at NHS Test and Trace Regional Testing Services to best reflect real-world performance of those accessing testing via the NHS Test and Trace Service as a whole. Our findings are in line with more recent research published since our evaluation was completed suggesting that combined N&T swabbing is better than single site swabbing approaches for detection of SARS-CoV-2 [10,11,12].

2. Methods

2.1. Design

This was a prospective evaluation constrained by the requirement for all participants to receive the standard of care of a N&T PCR test. Participants were eligible if they consented (verbally) to sample and data collection, met one of the criteria for testing (i.e., had symptoms suggestive of COVID-19; or had obtained a positive result on a self-administered lateral flow device (LFD) test; or had been in contact with a PCR-confirmed case), were $\geq$16 years old and were able to self-collect throat and nasal samples. Participants self-reported symptoms and time since symptom onset, alongside basic demographic data, at the time of requesting a test.

The study was conducted in March 2022 under a framework protocol that had approval from Public Health England's Research Ethics and Governance of Public Health Practice Group (PHE REGG, REGG Number: R&D 438).

2.2. Test methods

Participants received three test kits to be used sequentially for same-day self-collection of samples: the first two kits required nose only and throat only swabs (the ordering alternated within each Regional Testing site at pre-defined time-points), the third required a N&T swab. Standard nose and throat swab in use within the NHS T&T supply chain were used for the evaluation. A positive result from any swab was returned to the individual within 72 h to enable public health action.

Two laboratories analysed the samples using real-time reverse transcription PCR (qRT-PCR) according to standard NHS Test and Trace workflows. All three samples collected from each participant were sent to the same laboratory for analysis to enhance consistency; laboratory personnel were unaware of a participant's symptoms or results on other samples.

Due to the different methods used by each laboratory (details in Supplementary Materials), different cycle threshold (Ct) values were produced for samples with the same amount of virus. As the assays used in Laboratory 2 were variant specific and the available reference material lacked the mutations that are detected by these variant specific assays, comparison and normalisation of VC values between the two laboratories was not possible. The two sets of data from individual laboratories were therefore regarded as independent data sets for this analysis.

In Laboratory 1, VC was defined as the number of SARS-CoV-2 viral ribonucleic acid (RNA) copies per mL of viral transport medium, calculated by converting the Ct value from qRT-PCR into a VC using a standard curve derived by dilution of a SARS-CoV-2 inactivated virus preparation (strain Wuhan, quantified by droplet digital PCR). In laboratory 2 VC was defined by titration of synthetic SARS-CoV-2 standard specific to the variant assay and conversion of the Ct value in copies of variant RNA per mL The VCs generated by the two laboratories are not interchangeable but are proxies for the amount of virus present in a person's nasal or oral cavity rather than a direct measure.

2.3. Statistical considerations

The primary interest was in comparing the VC from nose only and throat only samples to a reference standard of combined N&T samples. A target sample size of 200 participants with a positive N&T PCR result provided 90 % power to establish non-inferiority with a 10 % margin of the separate nose only and throat only samples (further details in Supplementary Materials).

The primary analysis consisted of all participants who had a result for each PCR test, with at least two of the results being positive to enable comparison of VC values. VC was $\log_{10}$ transformed and ratios of nose only to N&T and throat only to N&T and their 97.5 % confidence intervals (CIs) were estimated.

Positive results close to the limit of detection (LOD) of the assay were considered positive, were reported as positive and not separately categorised as positive at the LOD. Such results would be expected to have a high CT value/low VC and stochastic effects at the LOD of the assay can change a positive to a negative result, which may also explain discordance between matched samples. The clinical significance of these positive results at the LOD of the assay is difficult to interpret in the absence of a clinical history and context, however results were not, and should not, be considered false positives.

To avoid bias due to positive samples at or below the LOD being excluded which may have been due to low detection rather than true results, sensitivity analyses were performed: nose only and/or throat only samples that returned a negative PCR result due to low VC (60 copies/mL, 10 % below the specified LOD) were imputed when a positive PCR result on another matched sample was observed.

Concordance between samples was analysed: the terms true/false positive/negative refer to PCR testing as the standard testing method and are not meant to indicate that the PCR results are fully accurate, as PCR results can also return false positives and negatives. A result was considered void when a valid result could not be returned, which may be due to problems with the sample or laboratory processes. The difference in sensitivity between samples was assessed using a generalised estimating equations model using an exchangeable correlation structure adjusted for laboratory.

A linear regression model was fitted to assess impact of time from symptom onset on VC, controlling for laboratory and an interaction between laboratory and time from symptom onset.

Statistical analyses were performed using R Statistical Software (v4.3.3; R Core Team 2024).

3. Results

A total of 817 participants were recruited in March 2022. Two were excluded due to having incomplete data for each of the three PCR tests, leaving 815 contributing data for analysis (Supplementary Fig. 1). The mean (standard deviation [SD]) age was 40 (13) years, 56 % were female and 82 % self-reported as white (Supplementary Table 1). The mean (SD) time since symptom onset was 2.04 (1.96) days.

3.1. Concordance

Combining results from the laboratories, there were 786 evaluable (i.e., positive or negative results) nose only samples, 0.5 % of which were false positives and 4.3 % were false negatives when compared to the reference standard of combined N&T samples (Table 1). Estimated

Table 1
Concordance table of the nose and throat PCR results against the nose PCR results and the throat PCR results from both laboratories.

		Nose and throat		
		Positive	Negative	Void
Nose	**Positive**	349 (44.4 %)	4 (0.5 %)	1
	Negative	34 (4.3 %)	399 (50.8 %)	5
	Void	12	9	Void Rate: 3.6 %
	Sensitivity (95 % CI)	91.1 % (87.8 %, 93.8 %)		
		Positive	Negative	Void
Throat	**Positive**	370 (47.3 %)	6 (0.8 %)	2
	Negative	12 (1.5 %)	395 (50.4 %)	3
	Void	13	11	Void Rate: 3.9 %
	Sensitivity (95 % CI)	96.9 % (94.6 %, 98.4 %)		

sensitivity (95 % CI) was 91.1 % (87.8 %, 93.8 %) and the estimated positive predictive value (PPV) (95 % CI) was 98.9 % (97.1 %, 99.7 %).

There were 783 evaluable throat only samples, 0.8 % of which were false positives and 1.5 % were false negatives (Table 1). Estimated sensitivity (95 % CI) was 96.9 % (94.6 %, 98.4 %) and the PPV (95 % CI) was 98.4 % (96.6 %, 99.4 %). There was strong evidence that throat samples were more sensitive than nose samples: after adjusting for laboratory, the estimated difference in sensitivity was 6.06 % (95 % CI 5.32 %, 6.80 %), $p < 0.001$.

3.2. Viral concentration

The positivity rates of the swabs were 48 % (N&T), 43 % (nose only) and 46 % (throat only). Of the 395 positive N&T swabs, 182 were sequenced to assess the VOC: 181 were identified as Omicron, one as Delta. Large differences in VC estimates (overall mean difference of 2.01 $\log_{10}$ copies/mL) were observed between the two laboratories, likely due to differences in SARS-Cov-2 assays used (Table 2). To avoid any confounding with study results, further analyses of VC were stratified by laboratory and only results from Laboratory 1 are included here (Laboratory 2 results are provided in the Supplementary Material). Importantly, the concordance between samples was largely similar between laboratories (Supplementary Table 2). In total, 4 samples were missing VC data from Laboratory 1.

Comparison of the mean of the ratio of single site sample VC to N&T sample VC indicates that VC was lower in the nose only and throat only samples (Table 3). There was evidence of lower VC in the nose only or throat only samples than in the combined N&T sample, with a larger difference observed between the combined and throat only samples than the combined and nose only samples.

The lower CI bound in each instance was lower than 0.9, i.e. −10 % of the mean ratio, therefore a conclusion of non-inferiority is not supported for either nose only or throat only samples compared to combined N&T samples.

Sensitivity analyses with imputed low VC values did not substantially change the mean ratios between samples.

Table 3
Mean ratio of $\log_{10}$ VC for each swabbing location.

	Nose only compared to nose and throat	Throat only compared to nose and throat
Number of paired positive samples	220	243
Mean ratio of $\log_{10}$ VC (97.5 % CI)	0.43 (0.29, 0.63)	0.24 (0.15, 0.39)

3.3. Time from symptom onset analysis

Time from symptom onset was significantly associated with smaller values of $\log_{10}$ VC from the samples that included a throat swab but not for the nose only sample (Table 4). The near zero estimate of the coefficient for time from symptom onset in the nose only model suggests that the VC in the nose remains consistent over the time from symptom onset observed in this study (0–17 days); however, due to the low number of samples collected after 4 days from symptom onset, this may not be the case for the later time period and VC decreases over time after an initial peak. By definition, lower levels of VC in a sampling site will lead to lower levels in the sample taken, which is in turn means testing positive is less likely.

There was evidence that the combined N&T sample had a higher VC than the N- only sample 0-1 days after onset, but from day 2 there was no evidence of a difference in VC (Fig. 1a). Compared to the throat only sample, there was evidence of a higher VC in the N&T sample from 1 day after onset, with a more than double $\log_{10}$ VC in the combined sample from day 2 (Fig. 1b).

Imputation for the sensitivity analysis had no material effect on these conclusions.

3.4. Nose only and throat only comparison

When comparing the VC between nose only and throat only paired samples, there was a high amount of variability (Figs. 2a and 2b).

The scatterplots suggest a lack of association between the VC of the paired samples. In the Bland-Altman plots, the 95 % limits of agreement are high at (−4.4, 4.6), indicating a considerable lack of agreement between the paired samples.

4. Discussion

This evaluation sought to determine whether the Omicron variant of SARS-CoV-2 was as detectable in nose only samples as in combined N&T samples, by comparing sensitivity and VC for each sample type. We also assessed the relationship between the swabbing approaches and the

Table 4
Linear model of $\log_{10}$ VC for each swabbing location.

	Estimate	Standard error	*P*-value
Nose and throat			
Time from onset (Days)	−0.122	0.046	0.010
Nose only			
Time from onset (Days)	−0.021	0.061	0.726
Throat only			
Time from onset (Days)	−0.210	0.049	<0.001

Table 2
Mean (SD) VC ($\log_{10}$ copies/ml) for each positive swab.

PCR test								
Nose only PCR			Throat only PCR			Nose and throat PCR		
N	Missing VC data	Mean (SD)	N	Missing VC data	Mean (SD)	N	Missing VC data	Mean (SD)
226	3	4.47 (1.64)	246	0	4.06 (1.49)	254	1	4.67 (1.39)

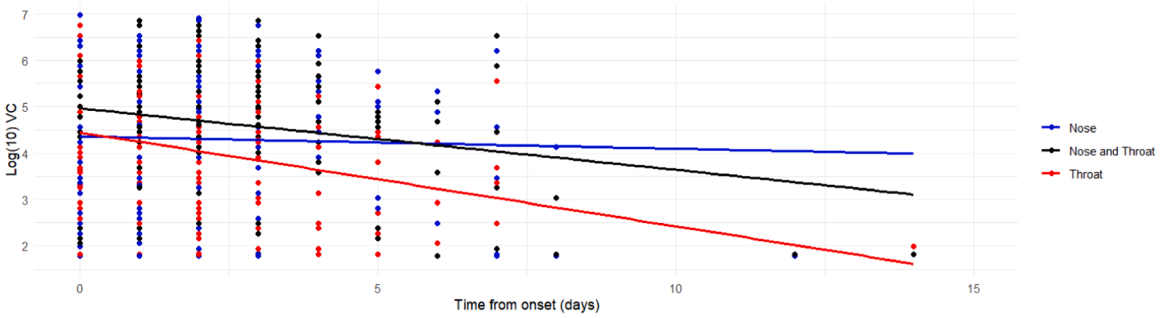

Fig. 1a. Absolute and mean $\log_{10}$ VC values over time from symptom onset.
Note: The lines represent the mean change in $\log_{10}$ VC time as estimated using linear regression.

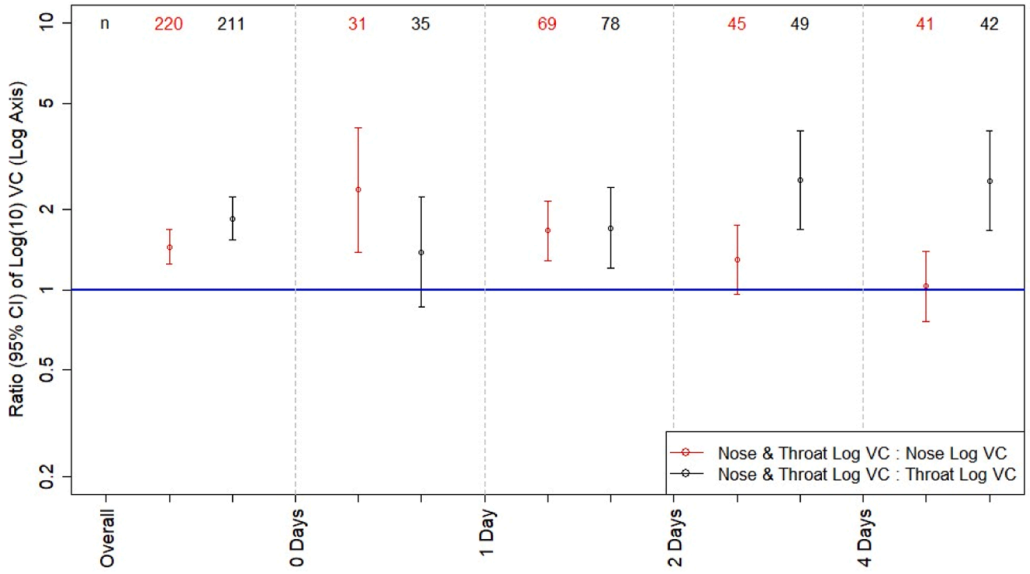

Fig. 1b. Change of mean $\log_{10}$ VC ratio over time from symptom onset.
Note: The overall ratio includes results from participants who tested later than four days after symptom onset. The mean $\log_{10}$ VC ratio is the VC of the nose and throat swab divided by the nose swab for each paired sample. A larger ratio indicates a higher VC in the combined swab.

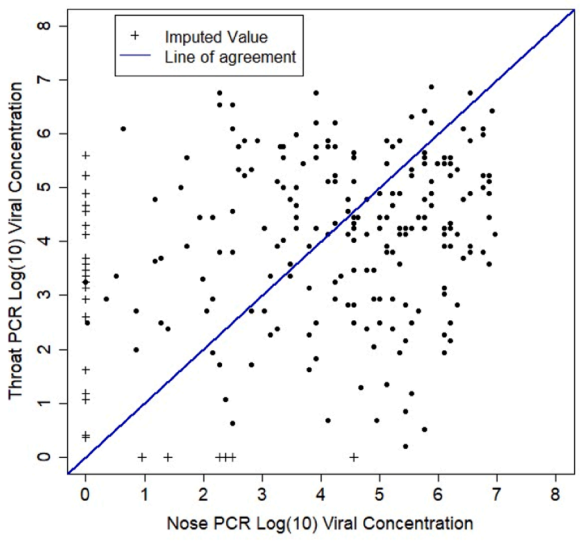

Fig. 2a. Comparison of $\log_{10}$ VC for nose only and throat only paired samples.

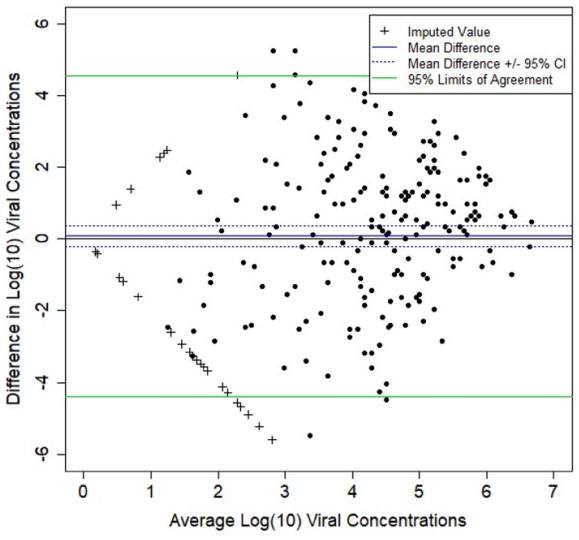

Fig. 2b. Agreement of $\log_{10}$ VC in nose only and throat only paired samples.

accuracy related to time from onset of symptoms.

The estimated sensitivity of nose only and throat only PCRs was 91 % and 97 %, respectively, compared to a reference of a combined N&T sample. The number of false positive results was small for both nose only and throat only samples.

The VC was significantly higher in the N&T samples compared to the nose only sample and to the throat only sample. The difference between the combined and throat only samples was larger than between the combined and nose only samples. In all cases the single site samples were not non-inferior to the combined site sample with a 10 % margin. For both N&T VC and throat only VC, as time from symptom onset increased, viral concentration decreased. However, VC in observed throat only samples decreased at a faster rate than N&T samples. There was no evidence for a change in VC in the nose only samples, however data was sparse beyond 4 days from symptom onset and if more participants had tested later the same effect may have been observed. When comparing the difference in VC between sample locations over time, the difference between the nose only and the N&T samples reduced, while the difference between the throat only and the N&T samples increased.

Overall, these findings support the PCR testing of combined N&T samples as opposed to nose only or throat only samples where possible. While some studies have identified lower sensitivity in throat only swabs and others in nose swabs, a consistent finding in these studies similar to our study is that combined N&T swabbing is a better than nose only or throat only swabbing [6,10,11,12]. Although sensitivity was high for the single site samples and only a small proportion of infections would not be detected, this could lead to a large number of infections being missed due to the large number of PCR tests that are performed. Still, the estimated sensitivity was quite high and may be acceptable considering the practical benefits of using nose or throat only samples, instead of N&T samples. If a single sample site is preferred, given their higher sensitivity, throat swabbing might be the better option. However, the time from symptom onset should also be considered with nose samples potentially being more appropriate for later time-points.

The analysis of the change in VC from symptom onset also confirms the findings of previous studies, where virus is detected earlier and VC peaks earlier in the throat than the nose, but at a lower VC [13,14]. These differences in VC trajectories may explain why a combined N&T sample is significantly better: the virus will be detected regardless of time since onset and current virus site expression. However, an additional study did not find within study participants differences tropism of the virus between sites over time since symptom onset but did identify differences between participants; some participants had higher VC in nose samples and others in throat samples, suggesting two phenotypes of the Omicron variant were detected although detailed genetic analysis was not performed to confirm any underlying genetic differences [15].

The large amount of variability observed between nose only and throat only samples in this study supports previous work that detected variation in VC between the sample sites, irrespective of mechanism. There is a large degree of individual difference in virus site expression, which in turn adds variability to swabbing accuracy in detecting infection. Although all but one of our samples was of the Omicron variant, this may also be true for other COVID-19 variants. This should be taken into account when evaluating swabbing approaches and when defining gold standard measures in accuracy studies.

The sensitivity of diagnostic tests in the detection of SARS-CoV-2 is of particular concern for LFDs. At the time the current evaluation was initiated, there were media concerns that nose only LFDs might not be as sensitive as N&T LFDs due to a suspected lower VC in the nose, particularly early in the course of infection [3,4,10], however there was less concern about PCR testing as this required individuals to swab both nose and throat as part of the testing process. While the current evaluation assessed PCR performance, the findings may also have implications for LFDs. Recent studies [16] suggest that the sensitivity of LFDs is positively associated with the VC in the sample; if VC was lower in nose only samples at early stages of infection, then nose only LFD performance with Omicron may be impacted, while combined N&T LFDs could be more resilient. The current findings do not support the idea that performance of LFD tests, where nose only sampling is used, would be impacted by Omicron and therefore regulatory approval of LFDs is unlikely to be affected. However, based on the current findings alone it is difficult to make firm conclusions about LFDs, due to the different mechanisms of LFD and PCR tests.

The limitations of the current service evaluation relate to the natural design, for example no formal randomisation of participants, but this design provides findings that are highly applicable to real-world testing conditions. Additionally, the use of two laboratories with dissimilar methodology prevented inter-laboratory calibration of VC determination; the two laboratories were used due to time constraints and planned changes in the UK National COVID 19 laboratory infrastructure. Nonetheless, the stratified analysis showed otherwise similar patterns of results. Another limitation is associated with the repeat testing: a lower VC may have been picked up on subsequent swabs, making it difficult to determine whether the VC and sensitivities observed in this evaluation were solely due to the location of the sample or not. However, there was an attempt to counteract this by regularly switching the order of nose only and throat only swabs at testing sites.

Further, due to lack of a better alternative, PCRs using N&T samples were considered the reference standard. If the N&T PCRs were not 100 % accurate at detecting SARS-CoV-2 themselves, then this may have resulted in over- or under-estimations of the numbers of false positives and false negatives of the nose only and throat only PCRs. However, alternatives such as repeated PCR tests or combining PCR tests with other tests, would be impractical and would not be used in this population group in a real-world setting.

Despite limitations, this research contributes greatly to our current understanding of SARS-CoV-2 testing and provides essential evidence on viral dynamics and how the SARS-CoV-2 develops/presents across anatomical sites over time. The findings regarding VC align with findings from other studies [10], but with a larger sample size. Stronger evidence is provided for the lower VC in nose only and throat only samples compared to combined N&T samples, thus providing higher confidence when recommending the use of combined N&T samples for PCR testing and LFD testing.

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CRediT authorship contribution statement

Tom Fowler: Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Edward Blandford:** Writing – review & editing, Supervision. **David Chapman:** Writing – review & editing, Supervision. **Matthias E. Futschik:** Writing – review & editing, Formal analysis. **Raghavendran Kulasegaran-Shylini:** Writing – review & editing, Formal analysis. **Sarah Tunkel:** Writing – review & editing. **Carolyn Lewis:** Writing – review & editing, Supervision. **Alasdair Fellows:** Writing – review & editing, Formal analysis. **Ellie Sheppard:** Writing – review & editing, Formal analysis. **Leanne McCabe:** Writing – review & editing, Formal analysis. **Peter Marks:** Writing – review & editing. **Paul E. Klapper:** Writing – review & editing, Supervision. **Andrew Dodgson:** Writing – review & editing, Supervision. **Malur Sudhanva:** Writing – review & editing, Supervision. **Mike Kidd:** Writing – review & editing, Supervision. **Andy Vail:** Writing – review & editing, Formal analysis. **Susan Hopkins:** Writing – review & editing, Funding acquisition. **Tim Peto:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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TF conceptualised the study. AF, MF, RK-S, ES, LMcC, AV analysed the data. EB, DC, CL, PEK, AD, MS, MK, TP and TF supervised the study and data analysis. TF and SH acquired funding. All authors contributed to writing and reviewing of the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diagmicrobio.2024.116577.

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