EVALUATION OF CANINE DETECTION OF COVID-19 INFECTED INDIVIDUALS UNDER CONTROLLED SETTINGS

Short running title: EVALUATION OF COVID 19 DOG DETECTION

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ABSTRACT

RT-PCR is currently the standard diagnostic method to detect symptomatic and asymptomatic individuals infected with SARS-CoV-2. However, RT-PCR results are not immediate and may falsely be negative before an infected individual sheds viral particle in the upper airway where swabs are collected. Infected individuals emit volatile organic compounds (VOCs) in their breath and sweat that are detectable by trained dogs. Here we evaluate the diagnostic accuracy of dog detection against SARS-CoV-2 infection. Fifteen dogs previously trained at two centres in Australia were presented to axillary sweat specimens collected from known SARS-CoV-2 human cases and non-cases. The true infection status of the cases and non-cases were confirmed based on RT-PCR results as well as clinical presentation. Across dogs, the overall diagnostic sensitivity (DSe) was 95.6% (95%CI: 93.6%-97.6%) and diagnostic specificity (DSp) was 98.1% (95%CI: 96.3%-100.0%). The DSp decreased significantly with non-case specimens sourced from UAE (*P*-value < 0.001). The location of evaluation did not impact the detection performances. The accuracy of detection varied across dogs and experienced dogs revealed a marginally better DSp (*P*-value = 0.003). The potential and limitations of this alternative detection tool are discussed.

Keywords: COVID 19; SARS CoV2 canine detection; detection dogs; screening tool; diagnostic accuracy

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first reported in humans in Wuhan, China in December 2019, is the cause of COVID-19 disease (Wiersinga et al., 2020). As of 26th February 2021, WHO (World Health Organisation) reported over 110 million COVID-19 confirmed cases and 2.5 million associated deaths globally (*WHO Coronavirus Disease (COVID-19) Dashboard*, n.d.). Viral replication and shedding in the upper respiratory tract begins 2-3 days prior to the onset of COVID-19 symptoms in the pre-symptomatic phase (He et al., 2020). Disease modelling from Singapore and China suggested that 48%-62% of transmissions come from pre-symptomatic individuals (Ganyani et al., 2020). People exposed to a positive case or who are pre-symptomatic may take time to self-present for testing, leading to disease transmission and a potential outbreak.

To effectively reduce transmission of SARS-CoV-2, a reliable, scalable, accurate and inexpensive testing to detect both symptomatic and asymptomatic individuals is required (Wiersinga et al., 2020). The standard diagnostic test for COVID-19 is SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) performed on respiratory specimens (nasopharyngeal swabs or lower respiratory tract samples) (Wiersinga et al., 2020). The detectability varies with the adequacy of specimen collection, time from onset of symptoms and specimen source (Sethuraman et al., 2020; Wang et al., 2020). Performing SARS-CoV-2 RT-PCR testing is labour intensive, time consuming, expensive and susceptible to reagents' shortage. Cost can be prohibitive for resource poor countries which may also be unable to access reagents, and protracted turn-around time can hamper case and contact identification adversely affecting public health responses. A scalable, cost-effective, non-invasive, rapid screening tool could improve targeted testing and public health responses, helping to control the spread of disease.

Volatile organic compounds (VOCs) are emitted by our body, breath and sweat, and reflect our metabolic condition (Shirasu & Touhara, 2011). Development of infectious or metabolic disease results in changes in VOCs profile with some being disease specific and potentially used as diagnostic olfactory markers (Shirasu & Touhara, 2011). Canines can detect VOCs and, if formally trained, can discriminate between infected and non-infected humans (Guest et al., 2019; McCulloch et al., 2006; Taylor et al., 2018). Recent pilot studies showed that dogs were able to detect patients infected (symptomatic or not) with SARS-CoV-2 using respiratory secretion specimens (Jendrny et al., 2020), heat-treated urine and saliva samples (Essler et al., 2021) and sweat samples (Grandjean et al., 2020) . Respiratory secretions are likely to contain viral particles and sweat specimens were investigated instead to reduce the risk of infection to the operators collected (Fathizadeh et al., 2020).

This study evaluated of the accuracy of detector dogs in identifying SARS-CoV-2 infected individual from axillary sweat specimens at two dog training centres in Australia. This report complies with the STARD 2015 standards to report diagnostic accuracy (Cohen et al., 2016).

MATERIAL AND METHODS

Detection dogs and their trainers

A total of 15 dogs, seven with no experience and six with experience in explosive detection from the Australian Border Force (ABF), and two repurposed dogs from the South-Australian Metropolitan Fire Services (SAMFS) were recruited. ABF dogs were bred, developed and selected for their environmental stability, play and hunt drive. Each dog was consistently handled by the same experienced handler from ABF, SAMFS or the Australian Department of Agriculture.

Specimens sourcing

Specimens were collected from 12 primary and tertiary healthcare facilities (hospitals, clinics, screening stations, etc) across France, the United Arab Emirates (UAE) and Australia. Only volunteers who were at least 18 years old, provided written consent and agreed to comply with the collection instructions were recruited (Human Ethics reference CALHN 13698 and HREC/20/CALHN/71). Individuals who recovered from COVID-19 within 45 days or received a therapy against SARS-CoV-2 infection at least 24h prior were not sampled. Axillary (armpit) sweat specimens were collected following the same standard protocol and media across all locations, except for the duration of impregnation. Participants placed one piece of standard sized (7.5x7.5 cm) sterile gauze under each armpit in direct contact with the skin for 20 minutes in France and Australia or for one minute in UAE. Impregnated gauzes were transferred into a labelled plastic bag/container. The outer bags/containers were then disinfected with an alcohol wipe and placed into a second bag labelled identically using a no-touch technique outside the room where the collection occurred. Study staff assisting the collection of specimens from confirmed SARS-CoV-2 cases used personal protective equipment (face mask shield, gloves) and procedures in line with WHO and their respective countries' regulations.

Specimens were shipped refrigerated (+4°C to +8°C) to the dog training facilities in Australia by mail and in separate packaging for cases and non-case specimens. In Australia, specimens were kept refrigerated between testing or frozen for longer term storage. Specimens were not used for longer than 15 days after first bag/container opening.

Specimens' case definition

A 'case specimen' was an axillary sweat sample collected from a participant who yielded a positive RT-PCR against SARS-CoV-2 within 7 days prior collection. A RT-PCR was considered positive if the cycle threshold value (Ct) was < 34, regardless of COVID-19 symptoms, or if Ct

≤ 40 when the person was (i) symptomatic (anosmia, ageusia, muscle aches, respiratory symptoms, diarrhoea, fever, fatigue, headache) or with an (ii) image scanner and/or clinical picture suggestive of SARS-CoV2 infection or (iii) had a history of recent contact (≤ 48hours) with a known SARS-CoV-2 infected person. No Ct information was available for tests conducted in the UAE, therefore, any positive RT-PCR provided by local health authorities was considered positive.

A 'non-case specimen' was an axillary sweat sample collected from a participant who yielded a negative RT-PCR against SARS-CoV-2 (Ct > 40) on the day of collection (specimens sourced in France and the UAE) or from a participant who resided in an area with negligible risk of infection (i.e. from a state with no case of SARS-CoV-2 community transmission for more than 30 days) and did not experience COVID-19 symptoms. Specimens from persons without COVID-19 symptomatic and without suspicious history of contact but yielding a Ct value of ≥ 34 and < 40 were not included. All samples were collected on similar swab types (Australian negative specimens were sampled using French or Australian gauzes).

Specimen screening

For detection, specimens were transferred into a clean glass jar and connected to a presentation stainless steel cone (hide) of a construction similar to those developed previously (Grandjean et al., 2020). The study dogs were trained to display a 'conditioned response' behaviour (sustained sit with focus on the target) on a hide containing the target odour through reward-based training techniques. A key training requirement was hide screening independent of handler cues to eliminate the potential 'Clever Hans bias'. The full training protocol is available upon request to the corresponding author. Dogs were trained at two separate sites, in Adelaide (Roseworthy

Veterinary School) and Melbourne (ABF Canine Detection Unit), and the same locations were used to assess their detection accuracy.

Within an evaluation run, a total of nine hides were used with one case specimen or none per run. Dog handlers were blinded to both - the hide and the run true status. The presence of a case specimen and the specimens' hide order was formally randomised using a smartphone application (Random Number Generator ©2013 Nicholas Dean). Running of individual dogs was ordered in such a manner that each dog had an equitable number of first passes on a set of specimens. Each case specimen was used once per dog. When possible, case and non-case specimens sourced from the same location were presented in the same run to avoid possible interference of background odours. This was the case for all runs using specimens from UAE. As all but one specimen from France was a case and all specimens from Australia were non-cases (gauzes from France were also used to collect sweat from Australian non-cases), these two locations were used conjointly within runs.

A primary data recorder, who was not blinded to the true status of the hides, was located in a booth with one-way screens so they could have direct sight on the hides but could not be seen by the blinded handler or the blinded secondary/back-up data recorder. Data recording involved recording individual specimen identifiers and hide order, whether or not a hide was searched, a dog's search behaviours, and the presence (or absence) of any conditioned response (i.e. sitting in front of the hide). Each run was recorded on video for data quality control and assurance. The data from both recorders were then compared at the end of each day and video evidence was examined to resolve any conflicts.

Evaluation of detection accuracy

The evaluation of detection accuracy was conducted at the individual hide level. Hides not sampled by the dog (dog did not screen the hide) were excluded from the analysis.
The detection accuracy was measured using the conventional parameters used for diagnostic test accuracy - diagnostic sensitivity (DSe) and specificity (DSp). Here, the DSe refers to the proportion of hides containing a case specimen where the dog displayed a conditioned response behaviour (i.e. true positive rate) while DSp corresponds to the proportion of hides containing a non-case specimen from a non-case where the dog did not display a conditioned response behaviour (i.e. true negative rate). The DSe complements the rate of false-negatives while the DSp reflects the rate of false-positives. The DSe and DSp were estimated for (i) UAE specimen only, (ii) for all the other specimens (France and Australia) and (iii) for all specimens combined.

Two separate logistic regression models were built - one for DSe using the esults from hides containing only a case specimen and one for DSp using the results from hides containing a non-case specimen. To estimate the overall detection accuracy across all dogs, the models included 'dog' and 'specimen' as crossed random effects to account for the fact that a given specimen could be repeatedly screened within and across dogs. The effects of dog experience (yes or no) and evaluation location (Adelaide vs Melbourne) on DSe and DSp were also investigated by including these factors as fixed effect in the models. Comparison of accuracy between dog experience levels and evaluation locations were not investigated for UAE specimens due to the limited number of runs for this source. The population averaged estimates for the models and their 95% CI were reported.

Dog-specific estimates were only estimated with specimens from France and Australia, dog was included as a fixed effect within the model with specimen remaining as a random effect. Due to the model estimation approach, dogs with perfect scores were dropped from the model. For those

'perfect' dogs, we estimated their DSe or DSp and their corresponding Exact Binomial 95% CI directly and ignoring the repeated usage of specimens. Dog-specific estimates for UAE specimens were not obtained because of the paucity of data.

RESULTS

Evaluation runs description

A total of 520 impregnated specimens were used during the evaluation runs - 100 were from infected cases (16 from UAE and 84 from France) and 420 were from non-cases (29 from UAE, 1 from France and 390 from Australia). Detection results were collected on 1,333 fully blinded runs completed by 15 dogs over 33 open days across two locations (Adelaide and Melbourne) between the 4th of January and the 4th of March, 2021. Of the completed runs, 90.2% (n = 1,203) included one hide with a case specimen. Each dog completed 89 runs on average (range: 56-137). After excluding the 5,580 non-sampled hides (41.8%), the final dataset included a total of 7,705 hide screenings - 1,203 with case specimens (1,099 using French and 104 using UAE specimens) and 6,502 with non-case specimens (27 using French, 6,129 using Australian and 346 using UAE specimens).

Overall detection accuracy

Of the 1,203 hides with a case specimen, 1,158 yielded a conditioned response from the detection dog. After accounting for the fact that observations were clustered within dogs and that the same specimens were used multiple times (i.e. observation not fully independent) between dogs, the overall detection dog diagnostic sensitivity (DSe) was 95.6% (95%CI: 93.6%-97.6%). In other words, 4.4% of the case hides are expected to yield a false-negative. Of the 6,502 hides with a non-case specimen, 6,419 did not yield a conditioned response and, after observation dependence

adjustment, the overall diagnostic specificity (DSp) was 98.1% (95%CI: 96.3%-100.0%). That is, 1.9% of the non-case hides are expected to yield a false-positive.

The DSp, and to a lesser extend the DSe, seemed affected by the specimens' country of origin with UAE specimens being detected with less accuracy (Table 1). While the DSp significantly decreased with UAE samples (P-value < 0.001), the decrease in DSe was not significant (P-value = 0.324). The location of the evaluation (Melbourne or Adelaide) did not significantly impact the DSe (P-value = 0.261) or the DSp (P-value = 0.261).

Table 1. Diagnostic sensitivity (DSe) and specificity (DSe) estimates by country of origin of the specimens.

Specimen origins	Run completed	Case hide count	DSe (95%CI)	Non-case hide count	DSp (95%CI)
France (cases) & Australia (non-cases)	1,212	1,099	95.9% (94.0%-97.8%)	6,156	98.6% (98.0%-99.1%)
UAE (cases & non-cases)	121	104	93.0% (86.4%-99.8%)	346	94.2% (89.7%-98.8%)
All origins	1,333	1,203	95.6% (93.6%-97.6%)	6,502	98.1% (96.3%-100.0%)

Dog-specific detection accuracy

Accuracy of detection varied across dogs (Table 2, Figure 1). Across dogs, the DSe ranged from 87.6% to 100.0% and the DSp from 96.6% to 100.0%. One experienced dog (Matilda) achieved perfect DSe and DSp, and one repurposed dog (Cuba) achieved perfect DSe. Experienced dogs did not show a significantly better DSe (*P*-value = 0.102) but showed a significantly better DSp (*P*-value = 0.003) which improved by 1.3%, which is marginally relevant.

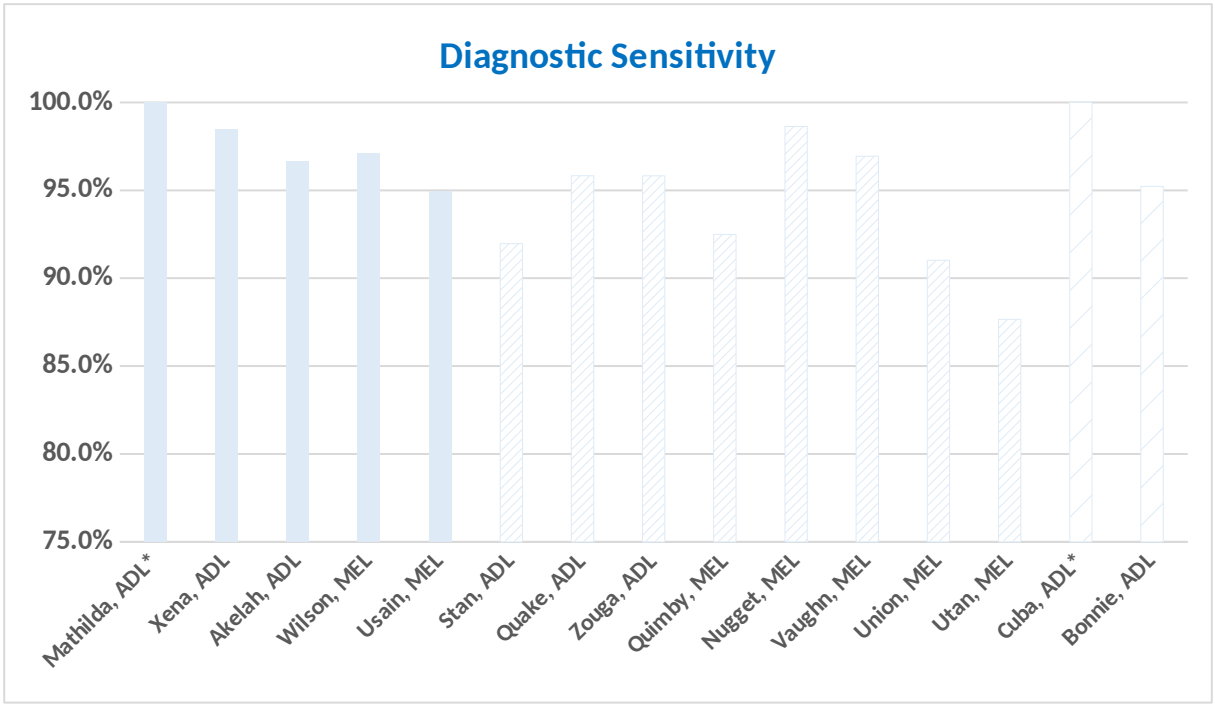
Table 2. Dog-specific and overall estimates of diagnostic sensitivity (DSe) and specificity (DSp) excluding specimens from UAE (i.e. case specimens from France and non-case specimens from Australia).

*Because of perfect scores, these estimates could not be modelled and were estimated separately with their Binomial Exact 95% CI

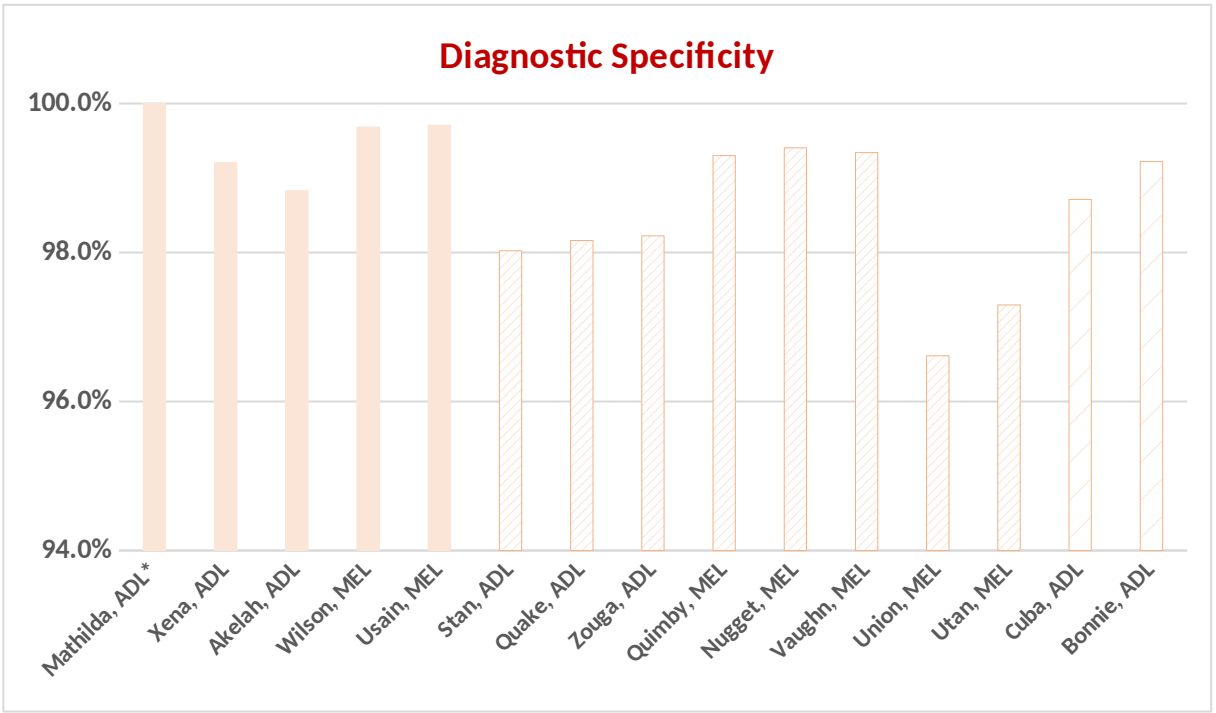
Dog	Evaluation location	Dog detection experience level	Run completed	Case hide screening count	DSe (95%CI)	Non-case hide screening count	DSp (95%CI)
Matilda	Adelaide	Experienced	98	92	100.0%* (96.1%-100%)	424	100.0%* (99.1%-100%)
Xena	Adelaide	Experienced	110	102	98.5% (95.5%-100%)	486	99.2% (98.3%-100%)
Akelah	Adelaide	Experienced	101	91	96.7% (92.2%-100%)	521	98.8% (97.8%-99.9%)
Stan	Adelaide	Unexperienced	110	102	92.0% (85.7%-98.2%)	580	98.0% (96.6%-99.4%)
Quake	Adelaide	Unexperienced	114	101	95.8% (91.2%-100%)	663	98.2% (96.9%-99.4%)
Zouga	Adelaide	Unexperienced	92	82	95.8% (90.3%-100%)	451	98.2% (96.9%-99.6%)
Cuba	Adelaide	Repurposed	82	76	100.0%* (95.3%-100%)	428	98.7% (97.6%-99.9%)
Bonnie	Adelaide	Repurposed	63	56	95.2% (89%-100%)	272	99.2% (98.1%-100%)
Wilson	Melbourne	Experienced	71	64	97.1% (92.8%-100%)	324	99.7% (99.1%-100%)
Usain	Melbourne	Experienced	68	59	95.0% (89.1%-100%)	362	99.7% (99.1%-100%)
Quimby	Melbourne	Unexperienced	56	52	92.5% (85.2%-99.8%)	313	99.3% (98.3%-100%)
Nugget	Melbourne	Unexperienced	65	60	98.6% (95.7%-100%)	368	99.4% (98.6%-100%)
Vaughn	Melbourne	Unexperienced	63	57	96.9% (92.4%-100%)	323	99.3% (98.4%-100%)
Union	Melbourne	Unexperienced	58	51	91.0% (83.2%-98.9%)	306	96.6% (94.5%-98.7%)
Utan	Melbourne	Unexperienced	61	54	87.7% (78.5%-96.8%)	335	97.3% (95.5%-99.1%)

Figure 1. Comparison of diagnostic sensitivity (A.) and specificity (B.) estimates across individual dogs. The error bars represent the 95% CI of the estimates. Full bars are experienced dogs, dashed bars are inexperienced dogs and dotted bars are repurposed dogs. **Be aware of the different y-axis scale used between graphs.**

A.



B.



DISCUSSION

This study provides evidence to support that detector dogs are an accurate and effective tool to determine people infected with SARS-CoV-2 using an easily implemented collection method in placing a gauze swab in the axillary area for a short time. The diagnostic sensitivity (DSe) and specificity (DSp) of the individual dogs involved in the trial varied, with some operating at 100%, and all comparing favourably with the diagnostic accuracy of RT-PCR testing.

All results from the detector dogs are compared to RT-PCR, which are not perfect and whose accuracy depends on viral load being shed. Viral load and thus PCR Cycle threshold (Ct - number of cycles of amplification of the sample genetic material) varies through infection. When the viral load is low (very early stage of infection or during recovery), the Cycle threshold is high, when viral load is high (peak of infection), the Cycle threshold is lower. However, there is no standard on the "Ct" between different laboratories and countries and thus PCR positive or negative results need to be interpreted cautiously. High number of Ct poses a risk of patients being misclassified as being actively infected. To reduce the risk of presenting specimens that are falsely considered positive, high numbers of Ct (> 34) were paired with clinical information or recent history of contact with COVID 19 infected persons. This was not done for UAE samples where Ct values were not available and which can explain the lower DSe and DSp for these specimen origins.

Careful selection of case specimens is both a strength and limitation of this study. Dogs detect Volatile Organic Compounds (VOCs) produced during active infection, but it is unknown for how long the VOCs are emitted by the organism after the infection ceased. It is therefore unknown if dogs can still detect patients that are recovering. While RT-PCR on nasopharyngeal swabs will remain positive days after active infection ceased (residual viral RNA genome fragments but no active viral particles), dogs might not be able to detect convalescing patients. Further research

using longitudinal swabbing of people infected with SARS-CoV-2 is needed to determine the period of infection during which a dog will accurately detect an infection.

The Aravelo-Rodrihuez *et al.* systematic review reveals that up to 54% of COVID 19 patients may have an initial false-negative RT-PCR. These findings reinforce the need to develop tools able to identify infected patients during the incubation phase. In our study, all dogs gave a conditioned response on two non-case specimens from the UAE, one from a symptomatic patient (headache, muscle ache, dry cough) and one from an asymptomatic patient. Retrospective investigations to elucidate if the patients were or not actively infected or in the incubation phase during sweat collection are ongoing.

The UAE specimens were included to trial if dogs could detect VOCs in sweat specimens collected for only one minute. Although the DSp decreased significantly in the UAE compared to the French samples, dogs were exposed to UAE samples with no initial training to one min samples which might have led to detection threshold issues and can explain the lower DSe on those samples. Further research is needed to confirm how the length of swab placement in the axillary area may or not not impact on diagnostic accuracy for the detector dogs.

Dogs were trained using case specimens from both the UAE and France, and non-case specimens from three countries (UAE, France and Australia). This is likely to have helped the dogs to generalise their target scent, as samples originated from different environments, and participants were from different ethnic groups. In training detector dogs for odours such as explosives and drugs, there may be problems in dogs generalising from the odours they are trained with versus the more variable odours in the field (Moser et al., 2019). While the dogs worked in a controlled environment in the current study, the variability of samples makes it more likely they would

maintain diagnostic accuracy if deployed to a new environment. On the other hand, sourcing most non-cases from the same country could help dog's discrimination, to alleviate this issue, we have diversified the source of cases and have used gauzes from the same sources to collect non-case specimens in Australia. Case and non-case specimens were collected in the same locations in the UAE and dogs' results suggest that discrimination remains accurate in these conditions.

SARS-CoV-2 evolves through time and undergoes mutations and recombination which might possibly alter the VOCs profile. The dogs trained in this study were exposed to sweat samples from patients affected by different strains and were able to generalise to new strains with no further training. For ongoing use of this new disease screening tool, we recommend that their olfactory memory library is regularly updated by exposing them to recent cases from a variety of strains.

Dogs were trained using positive reinforcement-based methods, with food and/or a toy used as the reward. Positive reinforcement has been shown to be the most effective method of dog training, and protects dog welfare while building a positive relationship with the dog handler (Ziv, 2017). There has been a lack of scientific study of the specific training protocols used for odour detection by dogs in order to determine which are the most effective in terms of time to train to criterion and accuracy of detection (Hayes et al., 2018). In a study using rats trained to detect odours, an intermixed training method was more effective than sequential single-odour training (Keep et al 2021). In the present study the sweat samples would have presented an intermixed odour, which may have helped in training the dogs to generalise across different samples. With the potential use of detector dogs for not only COVID but also other diseases such as malaria (Guest et al 2019) further research is needed to optimise the selection and training methods used in these dogs.

Although the dogs may generalise the scent of a case for SARS-CoV-2 infection, context is also important in the training of detector dogs (Gazit et al., 2005). If the dogs are deployed, in the early stages of deployment and in a new environment it will be important to validate their sensitivity and specificity again prior to full deployment. An important facet of the training protocol used is that an axillary sweat sample can be easily and quickly provided by people, or there is also the potential for dogs to screen people, for example if they are seated and dogs can scent their axillary area. Other protocols using respiratory, or urine or saliva heat inactivated samples (Jendrny et al., 2020; Essler et al 2021) may not be amenable to deployment in areas such as airports due to either risk of infection, or inability to supply the sample in a timely manner.

CONCLUSION

This study supports the diagnostic accuracy of detector dogs for screen people infected with SARS-CoV-2. Detector dogs may not replace the existing screening with RT-PCR, but could be a complementary method that could be quickly and effectively deployed to provide immediate results. Their additional value may lie in being able to detect infection in pre-symptomatic people before virus is shed and when RT-PCR is still negative. Further research is needed to uncover which VOC is specific to SARS-CoV2 infection and to reveal VOC persistence through the course of infection. Our study shows that trained dogs can accurately detect SARS-CoV-2 infection using axillary sweat samples. Canine screening has the potential as a scalable, inexpensive, efficient and reliable tool.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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