A detection dog to identify patients with *Clostridium difficile* infection during a hospital outbreak.

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ABSTRACT

Objectives
Early and rapid identification of Clostridium difficile infections (CDI) is important to prevent transmission. In this study we assessed the diagnostic accuracy of a trained detection dog for detecting CDI cases on hospital wards in an outbreak setting.

Methods
During a CDI outbreak in a large Dutch university hospital, we screened affected hospital wards repeatedly with a trained detection dog. The dog’s response was compared to the clinical diagnosis, supported by laboratory results.

Results
During a total of 9 hospital visits, the dog performed 651 screenings involving 371 participants. The dog correctly identified 12 out of 14 CDI cases [sensitivity 86% (95% confidence interval (CI): 56-97%)] and 346 out of 357 CDI negative participants [specificity of 97% (95% CI: 94-98%)]. Interestingly, of the 11 CDI negative participants that were ‘falsely’ indicated by the dog as positive, 2 (18%) did actually develop CDI during the 3 months of follow-up after the detection period; compared to only 12 of the 346 participants (3.5%) that the dog identified as C. difficile negative (p= 0.06).

Conclusion
A trained detection dog can accurately detect CDI in hospitalized patients during an outbreak. A (repeated) positive dog response is a strong indication of a CDI episode coming, be it the next day or possibly up to a month.
INTRODUCTION

Clostridium difficile infection (CDI) is a common health care-associated infection that mainly occurs after patients receive antimicrobial therapy. It causes toxin-mediated intestinal disease with a spectrum ranging from mild diarrhoea to severe pseudomembranous colitis. C. difficile can be transmitted via personal contact or environmentally.\(^{(1)}\) Over the past decades more frequent and severe infections have emerged, and large hospital outbreaks have occurred that required extensive infection control measures, sometimes leading to ward closures.\(^{(2-4)}\)

Early and rapid identification of CDI cases is important to prevent transmission by adequate isolation measures and treatment.\(^{(5)}\) This prompted us to investigate whether a detection dog can be trained to recognize C. difficile in stool samples and in CDI patients. The advantage of a detection dog is the possibility to rapidly screen multiple hospital wards for infected patients. Such screening could overcome common delays in diagnosis and thus help prevent and control CDI outbreaks.

In 2010 we conducted a proof of principle study which showed that a trained dog can detect C. difficile with high sensitivity and specificity both in stool samples (sensitivity and specificity both 100%), as well as in infected patients (sensitivity 83%, specificity 98%).\(^{(6)}\) This promising result raised further questions: e.g. will the dog perform equally well in an outbreak setting rather than in a case-control design, when several patients in one room or adjacent rooms could be affected?

Three years after the pilot study, an outbreak of CDI occurred in the VU University medical centre (VUmc). Hence, we took the opportunity to assess the diagnostic accuracy of a trained dog in detecting CDI patients in an outbreak setting.

PATIENTS AND METHODS

The dog

The detection dog used in this study was a five-year-old male beagle called Cliff (figure 1). The dog was trained to identify C. difficile in CDI patients for the proof of principle study in 2010 by a professional detection dog instructor (HL). A reward-based training method was used in which the correct behaviour is reinforced by a reward (e.g. a snack). He was taught to indicate the presence of the specific C. difficile scent by sitting or lying down. The dog had not been trained for detection purposes before. For detailed information on the methods of training used, see Bomers et al.\(^{(6)}\)

In the two years before this outbreak study the dog was not used for CDI detection or any other purpose, nor did he receive any additional training. He had not visited the hospital in 18 months; his skills were maintained on a basic level by regular training, at least five times a week.
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Study design
The VU University medical centre (VUmc) in Amsterdam is a tertiary clinical care centre. During May-July 2013 we noticed an increase in \textit{C. difficile} (ribotype 027) infections in the VUmc, which prompted us to start this study. We scanned the affected wards with the dog twice weekly during the following month (July 9\textsuperscript{th} – August 9\textsuperscript{th}). On this detection round the dog, his trainer (HL), and a member of the research team (MKB) simply walked past the beds of all patients present on the ward, i.e. those with CDI and those not affected. The trainer classified the dog’s response as either positive (dog sitting down), intermediate (dog showing excitement, taking extra time etc., without actually sitting down) or negative (showing no particular interest). In case of doubt, the round was repeated once. Both the trainer and the research team member were blind to which participants were, or recently had been, CDI positive.

After the detection period we checked which of the screened participants were tested for CDI (either a week before or during the detection period, or during a follow-up period of three months after the detection period) and which were found positive. Subsequently, we compared the dog’s classification (positive; intermediate or negative) with the clinical diagnoses based on the laboratory results. Both an intermediate and a positive dog response were considered positive in this study, since our proof of principle research showed that this approach obtains the highest sensitivity without significant loss of specificity.

Case definition
In the VUmc two different tests are performed on stool samples of suspected patients to check for \textit{C. difficile} infection: a toxin enzyme immunoassay (EIA)
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(VIDAS® Clostridium difficile A& B) to test for presence of C. difficile toxins (in a stool sample or a cultured C. difficile strain), and an anaerobic culture of the stool sample on a standard medium. Both tests are performed daily. Stool samples were tested on clinical indication (i.e. in patients with diarrhoea) or occasionally on the basis of a positive dog response only. This means we obtained cultures of all Cliff positive participants (independent of symptoms) to verify their C. difficile status if they had not already been tested. In this study CDI cases were defined as having diarrhoea and a positive stool culture with a toxigenic strain of C. difficile in a faecal sample and those classed as CDI negative did not. The dog’s response was interpreted as ‘correct’ if he gave at least one positive response to a case (within seven days before or after the positive stool test) or exclusively negative responses to CDI negative participants.

Safety precautions
We consulted the hospital’s infection control committee to discuss the potential hazards of allowing a dog to enter the hospital and come near patients. In accordance with recent guidelines, special attention was given to hand hygiene, making sure staff and patients washed their hands both before and after any animal contact. During detection rounds, the dog had no physical contact with patients, and contact with their environment (bed, chair etc.) was avoided as much as possible. He did not visit food preparation areas and neonatal-, haematology or intensive care wards.

The dog receives a health evaluation by a licensed veterinarian four times a year. He is not fed raw meat. When at work, he neither barks nor shows aggressive behaviour, he is easily recognized by his outfit (figure 1) and is continuously on a leash. Participants were notified in writing prior to the detection round and were given the opportunity to refuse participation. The research protocol was approved by the institutional review board.

Results
During a total of 9 hospital visits to 8 different wards, the dog performed 651 screenings involving 371 participants. A video to illustrate how the rounds were conducted can be found on the journal’s website (example of a negative dog response [video 1] and a positive dog response[video 2]): http://www.journalofinfection.com/article/S0163-4453(14)00169-8/fulltext.

Patient characteristics
The mean age of patients was 60.0 years (range 18-94 years, standard deviation (SD) 19.6 years). 205 participants (55.3%) were male. 136 participants (36.7 %) stayed on a medical ward, 124 participants (33.4%) stayed on a surgical ward and 111 participants stayed (29.9%) on an acute care ward with both medical and surgical patients.

Fourteen of 371 patients met the CDI case definition (diarrhoea plus positive stool culture with a toxigenic strain of C. difficile), the remaining 357 patients
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were classed as CDI negative. Thirteen of these cases had both a positive direct toxin EIA test on the stool sample and a positive culture. One case (case number 11) had direct toxin EIA positive/ culture positive stool tests on June 27th and later recurrent symptoms but direct toxin EIA negative/ culture positive stool tests on August 7\textsuperscript{th} (see also figure 2 on timing of samples and detection rounds).

**Identification of positive and negative patients**
The dog correctly identified 12 out of 14 CDI cases, i.e. there was at least one intermediate or positive dog response within 7 days before or after the day a positive stool sample was collected. For a detailed graphic overview of the identification of the CDI cases, see figure 2. Cases 5 and 10 generated a false negative response. Case 10 did actually provoke an intermediate dog response eight days before the stool samples tested positive, but this was followed by 2 negative responses within 7 days of the sampling date. 346 out of 357 CDI-negative patients were correctly identified, i.e. the dog gave exclusively negative responses. These results correspond to a sensitivity of 86\% (95\% confidence interval (CI): 56-97\%) and specificity of 97\% (95\% CI: 94-98\%).

**Testing of CDI negative participants**
Out of 357 CDI negative participants, 46 participants underwent testing during the screening period (+/- 7 days, i.e. between July 2nd and August 16th). Five of 46 had a positive test at any point during the screening period, but not within a week of a sniffing round and were therefore classified as CDI negative. They all had negative dog responses. These 5 participants had either been discharged (n=4) or moved to another ward that did not participate in the screening rounds (n=1) when they developed CDI 10, 14, 15, 18 and 32 days later, respectively.

**Cliff positive/ CDI negative participants**
There were 11 out of 357 (CDI negative) participants that the dog incorrectly scored positive; all tested negatively for *C. difficile*. Of these, 9/11 had had diarrhoea and were therefore tested in the week leading up to (or on the day of) the sniffing round; two were only tested in the week after the detection round. One had been asymptomatic and was tested on the basis of a positive dog response only. Interestingly, of the 11 CDI negative participants that were ‘falsely’ indicated by the dog as CDI positive, 2 (18\%) did actually developed CDI during the 3 months of follow-up after the detection period (i.e. between August 16\textsuperscript{th} and October 9\textsuperscript{th}); compared to only 12 of the 346 participants (3.5 \%) that the dog identified as *C. difficile* negative (p= 0.06). These patients with initial negative microbiological tests stand out: the dog gave a positive response on multiple occasions as illustrated in figure 3. Both patients developed CDI between 14 and 46 days later, respectively, similar to case 11 in figure 2.

**Figure 2:** Overview of cases with *C. difficile* infection (CDI). The results of stool tests are above the timeline, the detection dog visits below the timeline and *C. difficile* treatment periods are indicated by the blue bars. ‘Pos’. refers to a positive result, ‘neg’. refers to a negative result and ‘intermed’. refers to an intermediate result. ‘Absent’ means a patient was not available on a detection round, for instance because he/she was away for a diagnostic test or physiotherapy etc.
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Consistency of dog responses
The dog did not consistently indicate all CDI cases as positive on every consecutive visit, as is illustrated in figure 2. This could, for instance, be related to the severity of symptoms. However, case 14 provoked a negative response on the day the C. difficile positive stool sample was taken. This patient therefore must have been symptomatic when the dog visited; yet the dog incorrectly did not give a positive response. Furthermore, case 4 and 7 suffered two CDI episodes, of which only one was indicated correctly by the dog.

Discussion
This study shows that a trained detection dog can accurately identify CDI positive patients in a C. difficile hospital outbreak setting. Using the dog to screen affected wards twice weekly had both high sensitivity and specificity for finding CDI cases. Moreover, the dog does not need a stool sample or physical contact with patients and he is quick and efficient: all 20-30 patients on a hospital ward can be screened for the presence of C. difficile infection in less than 10 minutes. Sensitivity is high but not perfect, so vigilance for clinical symptoms of CDI remains essential.

The dog’s response to CDI-positive cases occasionally was inconsistent, stressing the desirability of repeated screening rounds for adequate sensitivity. This variation in response could for instance be due to the waxing and waning of symptoms, possibly related to bacterial or toxin load. Results show that a (intermediate or) positive dog response indicates disease, whether or not followed by negative responses in the consecutive rounds. In this respect, case

Figure 3: Results for 2 patients that were initially classed as CDI negative (although identified by the dog as positive) but that did develop symptomatic disease during the 3 months of follow-up after the detection period.
Results of stool tests are found above the timeline, the detection dog visits below the timeline and C. difficile treatment periods are indicated by the blue bars. ‘Pos’. refers to a positive result, ‘neg’. refers to a negative result and ‘intermed’. refers to an intermediate result. ‘Absent’ means a patient was not available on a detection round, for instance because he/she was away for a diagnostic test, physiotherapy etc. The shaded area depicts the detection period.

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11 (figure 2), patient 15 and patient 16 (figure 3) are particularly interesting, illustrating that repetitively positive responses are a strong indication of symptomatic disease to come, be it even over a month later. In daily practice, positive dog responses should therefore prompt high clinical suspicion for CDI both in present and future, and perhaps justify at least immediate diagnostic testing, and possibly also hygienic measures.

Except for the few abovementioned cases in which the dog signalled an infection before it was confirmed by the laboratory, this study did not lead to quicker diagnoses and treatment. However, on the day our study started, 6 of the 14 cases had already been diagnosed with CDI, making it impossible for the dog to ‘beat the lab’. Also, perhaps on a more frequent surveillance schedule, e.g. with four times weekly or even daily screening, the dog might actually signal new cases before the laboratory can confirm them. And even though the dog was trained especially for this purpose in 2010, lately his skills had only been maintained on a basic level. With a ‘refresher course’ before recommencing his screening tasks, the dog could possibly perform even better.

There are several limitations and drawbacks to the study. Some pertain to the concept of using a dog for hospital health care purposes (hygienic concerns, generalizability to other dogs and trainers etc.) and have been extensively discussed in the previous paper.(6) With regards to this study, we want to point out that even though the research team was not aware who was a CDI case during the detection round, it is difficult to blind one from isolation measures like use of single rooms etc. Secondly, the follow-up took place by revising hospital charts. Although we feel this approach will probably have identified the bulk of CDI episodes in the follow up period, CDI episodes could have occurred after discharge and been diagnosed and treated without showing up in our files.

In conclusion, this study provides proof-of-concept that a trained detection dog can accurately detect CDI in hospitalized patients during an outbreak. We think these findings indicate that a trained detection dog might aid to control a CDI outbreak, and we suggest this possibility warrants further investigation.
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REFERENCE LIST


