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Disease transmission model for community-associated *Clostridium difficile* infection

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SUMMARY

Participating researchers and public health personnel at a Canadian workshop in 2007, noted considerable gaps in current understanding of community-associated *Clostridium difficile* infection (CA-CDI), specifically infection sources and risk factors. A disease transmission model for CA-CDI was requested as an initial step towards a risk assessment, to analyse infection sources and risk factors, addressing priority research areas. The developed model contains eight infection states (susceptible, gastrointestinal exposure, colonized, diseased, deceased, clinically resolved colonized, relapse diseased, and cleared) and notes directional transfers between the states. Most published research used focused on hospital-associated *C. difficile* infection (HA-CDI) and further studies are needed to substantiate the use of HA-CDI knowledge in the transmission of CA-CDI. The aim was to provide a consistent framework for researchers, and provide a theoretical basis for future quantitative risk assessment of CA-CDI.

Key words: *Clostridium difficile*, infectious disease epidemiology, transmission.

INTRODUCTION

Clostridium difficile is a Gram-positive anaerobic bacterium that may be found in the intestinal flora of humans and animals. As a spore former, it can persist for prolonged periods outside the host. It can be carried asymptomatically by hosts or cause a wide range of disease, from minor diarrhoea and cramping to pseudomembranous colitis and, on occasion, death [1–7]. First described in 1935 as a component of infant faecal flora [1] it was not regarded as a relevant pathogen until the 1970s, following identification of an association with antimicrobial-associated diarrhoea and pseudomembranous colitis in humans [8]. Subsequent studies identified antimicrobial administration as an important risk factor for *C. difficile* infection (CDI); and CDI is now the most commonly diagnosed cause of antimicrobial- and hospital-associated diarrhoea [3, 5, 7, 9–11].

Until recently, CDI was considered to be a hospital-based infection, due to its substantial association with antimicrobials, and frequent occurrence in the immunocompromised population [12, 13]. Healthcare workers and close proximity of patients also provide short vectors of transmission for *C. difficile* to expose susceptible patients [13, 14]. However, the prevalence and severity of CDI are increasing; and CDI is appearing in the community, in patients lacking known risk factors such as hospitalization, antimicrobial treatment and proton pump inhibitors [5, 9, 15, 16].

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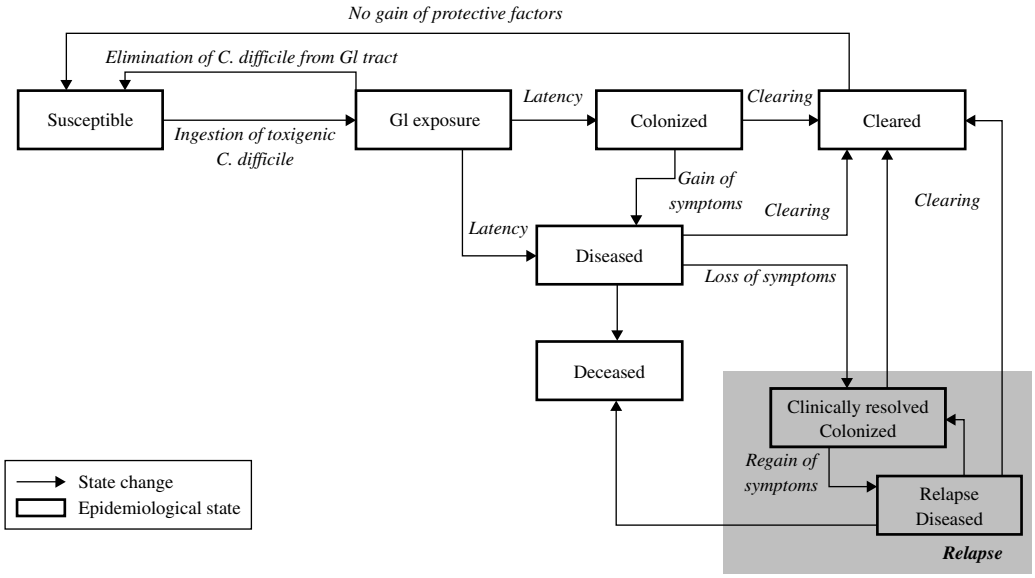

Fig. 1. Transmission model of community-associated *C. difficile*, infection states and state transfers.

Routes of exposure and the manner with which *C. difficile* is transmitted in the community are not well understood.

Public Health Agency of Canada convened a workshop of community-associated *C. difficile* infection (CA-CDI) and food safety experts in February 2007. There was general agreement on the lack of understanding regarding CA-CDI and its increasing relevance as a public health matter. Prevalence of *C. difficile* colonization, risk factors and transmission routes for CA-CDI were all included in this lack of general knowledge.

A disease transmission model of CA-CDI was requested to provide a consistent understanding of community transmission of CDI, and to highlight gaps in current knowledge. The disease transmission model is a template that the mathematical relationships of a risk assessment model may be developed around. Encompassed in the model are sources of exposure and transfers between the susceptible, gastrointestinal exposure, colonized, diseased, deceased, clinically resolved colonized, relapse diseased and cleared states. Only toxigenic *C. difficile* is considered within the model, as toxin production is required for infection. The terms CDI or infection are used to collectively refer to states in which *C. difficile* is present in the intestinal tract with symptoms, i.e. the diseased and relapse diseased states of the model; and the term colonized is used to collectively refer to states in which *C. difficile* is present in the intestinal tract without symptoms, i.e. the colonized and clinically resolved colonized states of the model.

TRANSMISSION MODEL

Epidemiological states and state movements

The disease transmission path proposed for CA-CDI contains eight epidemiological states, labelling populations as susceptible, gastrointestinal exposed, colonized, diseased, deceased, clinically resolved colonized, relapse diseased or cleared. Figure 1 shows the directional movements through the model. The states are defined in Table 1, excluding the deceased state which includes those with *C. difficile* listed as the cause of death. Several of the states are clinically indistinguishable, as only three clinical states exist (healthy, infected, deceased); but eight states exist in the proposed pathway because the course a person takes to arrive in a clinical state is of relevance to the study of CA-CDI.

C. difficile is transferred through the faecal–oral route [17]; once exposed, an incubation period is accounted for by time spent in the gastrointestinal exposed state before a tertiary state. A CDI study review lead to the concept that *C. difficile* exposure may result in one of three outcomes: development of CDI, or colonization following an incubation of a few days, or no infection [3, 4]. To account for this, the tertiary states from the exposed state are diseased, colonized and susceptible. Individuals in the colonized state may still transfer from the colonized to the diseased state, as observed for both adult and infant patients [4, 12].

Individuals experiencing intermittent symptoms may be experiencing relapse or re-infection. These

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Table 1. *Clinical definitions of seven states within the community-associated* C. difficile *infection model of Figure 1*

State	Toxigenic *C. difficile* cells or spores present	*C. difficile* toxin present	*C. difficile* symptoms present
Susceptible	−	−	−
Gastrointestinal exposure	+	−	−
Colonized	+	+/−	−
Diseased	+	+	+
Cleared	−	+/−	−
Clinically resolved colonized	+	+/−	−
Relapse diseased	+	+	+

+, Must be present; −, must not be present; +/−, may or may not be present.

two events may be distinguished by typing isolates to compare CDI strains, with a new strain indicating re-infection; however, re-infection with an indistinguishable strain can also occur. With this technique, two separate studies found 5/10 and 12/27 patients may have experienced relapse, as they were excreting the same strain during their previous CDI episode [18, 19]. Relapse of CDI occurs from the diseased state of infection and is proposed as a pathway first taking the individual to a state of clinically resolved colonization. In this state no symptoms are apparent, but *C. difficile* is still present in the individual's intestinal tract. The individual may then move to the relapse diseased state to account for subsequent periods of infection. Relapse may occur indefinitely by moving between the clinically resolved colonized and relapse diseased states, or an individual may leave the relapse pathway by clearing *C. difficile*, or dying as a result of their symptoms.

Rather than relapse, persons may leave the colonized and diseased states to enter the cleared state, when symptoms resolve and *C. difficile* vegetative cells and spores are expelled. The transition of patients to the cleared state, a loss of symptoms without later relapse, has been observed by both spontaneous resolving of symptoms and through antimicrobial treatment [10, 20].

Persons may remain in the cleared state due to protective factors or return to a susceptible state with the possibility of re-infection. Of recurrences recently observed, 10% of hospital-associated *C. difficile* infection (HA-CDI) cases followed were due to re-infection [5]. Even greater, at least 56% of recurrent cases were attributed to re-infection in an earlier HA-CDI study [19].

Death may occur due to CDI, movement from diseased or relapse diseased to deceased. Deaths of *C. difficile*-infected patients have been reported at rates of 4%, 13% and 15·2% in Canadian, American and Swedish studies, respectively [5–7]; but those with *C. difficile* listed as the cause of death had lower rates of 0·6%, 0·7% and 1·5%, respectively.

Exposure routes

To fully account for CA-CDI exposure risks, community *C. difficile* sources are separated into four broad categories: consumption, person-to-person contact, animal-to-person contact, and environment-to-person (Fig. 2). Sources of *C. difficile* in the community may be placed in one of these four categories and must have the potential to result in ingestion of toxigenic *C. difficile* spores or vegetative cells.

The dashed lines in Figure 2 link general reservoirs of *C. difficile* to infection sources; for example, infected individuals may be a source of infection within the community, and therefore, the number of persons in the colonized and diseased states affect the influence of the human infection reservoir on the person-to-person and environmental exposure risks. The change in risk depends on both the number of infected people shedding *C. difficile* and the amount each individual sheds. Non-human infection reservoirs may exist as well, affecting the risk of *C. difficile* exposure through consumption, or direct contact with animals and the environment. The relative risks of each exposure in the community are unknown at this time, but both documented and presumed routes are included in the transmission pathway.

Food and water consumption

Individuals in the community may be exposed to *C. difficile* through consumption of contaminated food and water, creating the potential for developing CDI. One of the largest studies of community *C. difficile* contamination was performed in South Wales in the 1990s, with 5·5% of tap water and 2·3% of raw vegetables tested carrying *C. difficile*. Animal products were not directly tested, but the faecal samples of cattle, sheep, pigs, poultry and horses tested positive at a level of <1% [2]. In 2005, 20% of ground meat

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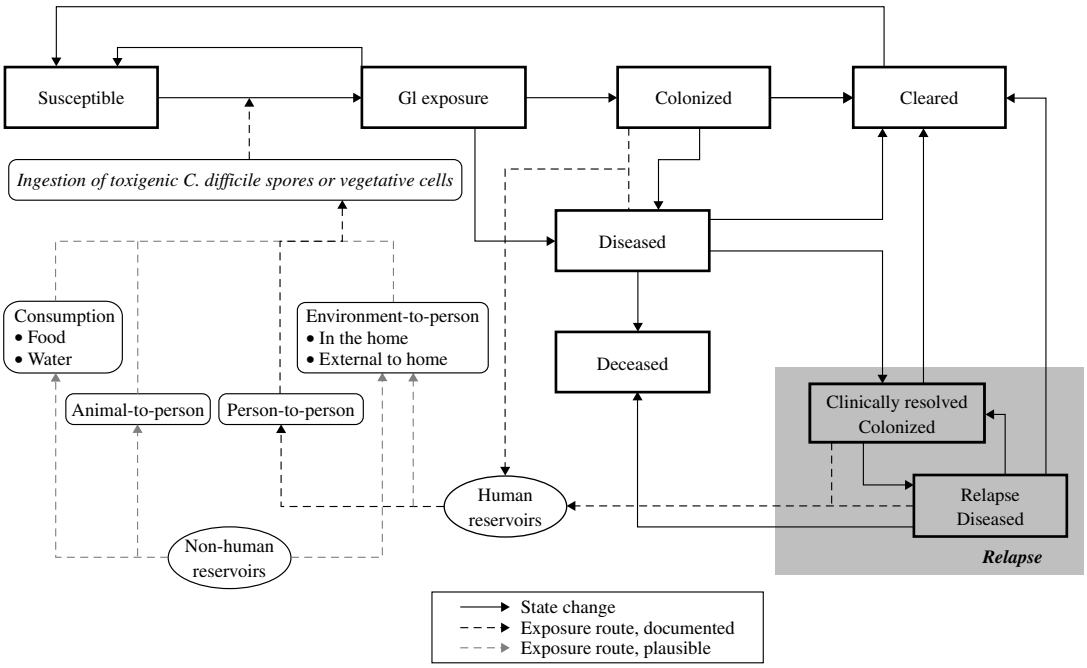

Fig. 2. Transmission model of community-associated *C. difficile*, with infection source categories.

samples collected from Ontario and Quebec stores were *C. difficile* positive [21]; and a subsequent 2006 study, with more nationally comprehensive sampling, found 6·1% prevalence of *C. difficile* in beef and veal [22]. *C. difficile* prevalence in raw and ready-to-eat retail meat in Arizona, purchased over 3 months in 2007, was 42% [23]. These differences may be due to geographical or seasonal differences or method of testing; and while produce, animal products and water may be potential reservoirs of *C. difficile*, none have been proven to transmit disease.

As well as contamination during processing, the possibility of food contamination during final preparation could be included to account for food preparation by an infected family member or food handler. Although this route has not been investigated, it is believed to be a potentially important route which requires study. Of relevance is the finding that spores of *C. difficile* may survive at the recommended cooking temperature of 71 °C for ground beef, even if held for 120 minutes (A. Rodriguez-Palacios, unpublished data).

Person-to-person transmission

Direct contact with family members may be significant in *C. difficile* exposure as both diseased and colonized persons are considered potential sources of infection, with diseased individuals shedding more *C. difficile* due to diarrhoeal symptoms [13, 24]. Close proximity with a diseased or colonized individual increases the exposure risk in the hospital; it is therefore assumed that this is also true in the home and community setting. Hospital studies have linked *C. difficile* cases to the admittance of an infected patient with the identical strain, or ended an outbreak by isolating *C. difficile*-positive patients, implicating these carriers as the disease reservoir for others [3, 14, 25]. Additional hospital investigations implicated person-to-person transmission as indistinguishable strains isolated from infected patients were not isolated from the environment [11, 26]; however, infection strains have been found in the hospital environment during other studies, creating uncertainty as to whether infection is resulting from person-to-person or environmental contacts, or both [13, 24, 27]. Proximity to patients with *C. difficile* in the hospital has been shown to influence infection rates of susceptible patients; 21·7% of those roomed near an infected patient acquired *C. difficile* in a HA-CDI study [13]. Of 10 peripartum and 23 CA-CDI cases recorded within the USA, from early 2003 to mid-2005, five resulted after close contacts with other diagnosed CA-CDI cases, implying person-to-person transmission [15].

A study of community person-to-person transmission considered a class of university students and

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university employees over a 1-year period, with positives typed for comparison. While similar types were not seen in the students, employees were infected with the same strain [28]; however, environmental testing was not conducted so an environmental source cannot be ruled out. Community transmission was also documented when an infant treated for CDI returned home and developed a recurrent case outside the hospital setting. Testing of the home resulted in 12·2% positive swabs, as well as the discovery of a colonized sibling [12]. While infection of the siblings from a common environmental source cannot be discounted, person-to-person transmission is plausible.

Another important component of person-to-person spread is the potential for a family member employed in a high *C. difficile*-risk environment to bring *C. difficile* home on clothing or hands. Transfer of *C. difficile* to the uniforms of healthcare workers has been documented, with 19% of uniforms testing positive after a shift. Uniforms at the study hospital were cleaned through home laundering [29]. The common practice of taking uniforms out into the community may make healthcare workers a reservoir for community infection [30]. American researchers found 25/27 patients hospitalized with CDI had at least one of five skin sites positive for *C. difficile* when swabbed; and a ten-patient subset of the study showed a 30–70% transmission rate for *C. difficile* from the patients to a gloved hand, depending on the skin site tested, only 1 hour after showering [31]. While gloves were used to control variables in the study, this supports the concept of transfer from patient to healthcare worker, even during contact possibly considered as low risk, e.g. touching the forearm or chest.

Those working at veterinary clinics and daycare centres may also be at risk of carrying home the organism to family members from infected animals or children. An Ontario veterinary teaching hospital found 19% of 360 dogs to be positive for toxigenic *C. difficile* over an 8-month period in 2001; including both CA and HA colonizations [32]. While the possibility of transfer to staff was not included in the study, animal-to-person transfer is plausible. Daycare workers may also become contaminated with *C. difficile* due to the high incidence of infant colonization; a 48% colonization rate of children in three Japanese day-care centres as well as environmental contamination in the facilities was found by researchers [33]. Agricultural workers exposed to contaminated soil or farm animals may pose a risk, as soil samples positive for *C. difficile* have been reported from South Wales at a prevalence of 21% [2].

Person-to-person transmission through contact with non-family members may also transfer *C. difficile* from an infected individual, or from the hands or clothing of someone who works in a high-risk environment to susceptible persons in the community.

Animal-to-person transmission

Direct contact with colonized or diseased animals is a likely source of infection for humans, as animals may transfer the organisms in a close contact situation. The presence of CDI in animals is documented by several studies, but without proof of transmission to humans. CDI rates of 0–26% have been reported for domestic dogs [2, 34, 35], with higher rates, 9–40%, reported for dogs in veterinary hospitals [34–37]. Similarly, CDI prevalence in domestic cats has been recorded from 2% to 32% [2, 34]; and 25–38% for those admitted to veterinary hospitals [34, 36, 37]. A Canadian veterinary teaching hospital recently reported that upon admission, 11% of 366 dogs and cats presented with *C. difficile* colonization that could be linked to community onset [32].

The possible connection of such infections to human infections was investigated by molecular typing of *C. difficile* from humans, dogs, horses, a cat, and a calf. Twenty-five percent of isolates from those species were indistinguishable from human isolates, supporting the theory of inter-species transmission [38]. A case of probable inter-species transmission, from humans to a dog, was recorded when a hospital visitation dog was confirmed to be infected with ribotype 027, while a hospital frequented by the dog was experiencing untyped CDI cases [39].

Persons in contact with agricultural animals may also be at risk of CDI as it has been found at different prevalence levels; 11·2% of Canadian calves tested were infected with *C. difficile* [40]; and cattle, sheep, pigs, poultry and horses showed infection rates of 0%, 1%, 0%, 1·7% and 1%, respectively, in South Wales [2]. The possibility of increased exposure risks to *C. difficile* due to animal contact must be more conclusively investigated.

Environment-to-person contamination

Infected persons and domestic animals may contaminate the home or community environment, leaving *C. difficile* spores on common contact surfaces.

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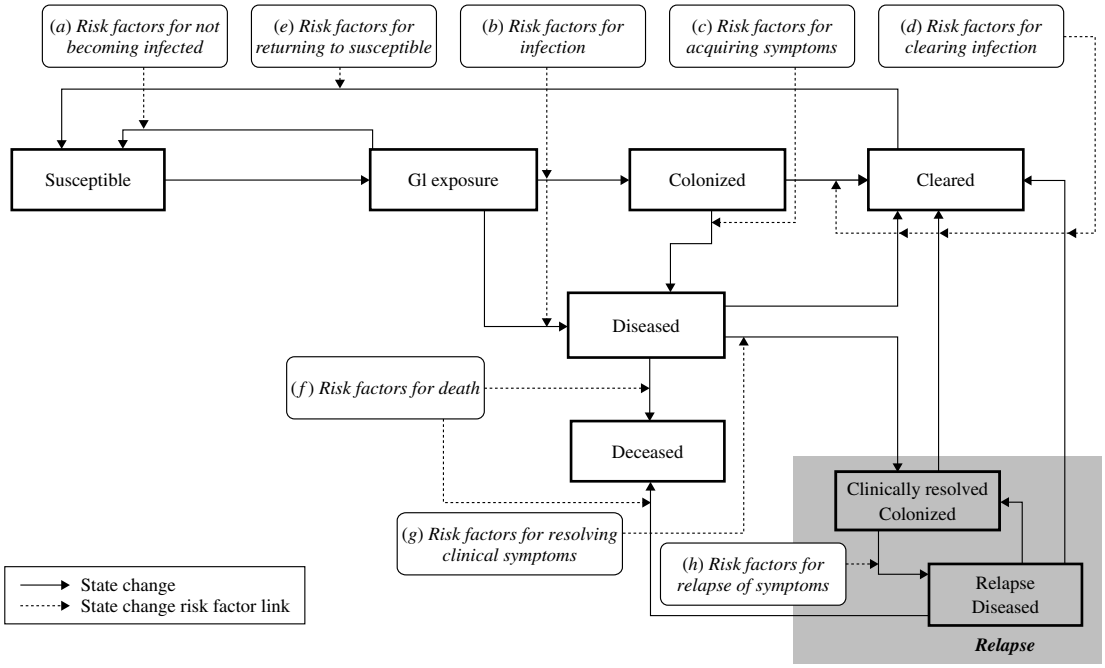

Fig. 3. Transmission model of community-associated *C. difficile*, with risk factors required for complete risk assessment model.

Environmental contamination has been shown to increase in proximity of colonized and diseased persons and animals. Hospital rooms of diseased, colonized and *C. difficile*-negative patients were positive at rates of 19·6%, 6·8% and 2·6%, respectively [24]. Similarly, positive samples from diseased, colonized and *C. difficile*-negative patients' rooms at another facility were obtained at rates of 49%, 29%, and 8%, respectively [13]. Both sets of results show the increased contamination due to a diseased individual; but that colonized persons still create contamination in their surroundings, to a greater extent than those that are *C. difficile* negative. Testing of hospital environments found samples from diseased and colonized patients' rooms ranged from 0% to 53·3% positive with an average of 32·5%, while control rooms ranged from 0% to 7% with an average of 1·3% [27]. Again, shedding by *C. difficile* patients created more contaminated environments. It was also observed that once patients were either removed from a room or treated for CDI, the number of positive samples as well as the concentration in positive samples decreased; evidence that the contamination was caused by the patient.

A community study of day-care centres found that the floors of two separate facilities were contaminated with strains indistinguishable from those infecting the children at each respective location [33]. The timeline of infections *vs.* environmental contamination was not available, so it cannot be stated which came first, but it is likely that the children themselves were contaminating their environment. With regards to contamination by animals, 11·4% of environmental samples at a veterinary hospital where infected animals were treated were positive for *C. difficile*. Subsequent sampling from an infected dog's home setting, however, failed to show *C. difficile* contamination in any of six sites tested [36]. Recently, two environmental household studies have been conducted to examine *C. difficile* contamination at 10 sites within households in Ontario, Canada. The first study, considering households with dogs, found 31% of households had at least one site positive for *C. difficile*; however, the dog and environmental ribotypes did not match in any of the four households where concurrent positives were collected (J. S. Weese, unpublished data). The second study, consisting of randomly selected households, found 34% of households to have at least one site positive for *C. difficile* (R. Finley, personal communication).

Environmental contamination in soil and water may be encountered during activities such as gardening and swimming. Water samples taken from rivers, sea, lakes and drainage water in South Wales resulted in 87·5%, 43·7%, 46·7% and 27% positive samples, respectively. Four of eight swimming pools in the area

were also positive for *C. difficile*. Soil taken from public places in the region showed *C. difficile* in 21% of sites [2]. Both samples taken from the yard of a house where one child was colonized and another was diseased were positive for *C. difficile* [12]. Clearly, environmental contamination can be found in areas both with and without colonized and diseased human and animals, and may be a source of community infection in humans.

DISCUSSION

In proposing the transmission model of Figure 1, and the terminology and state definitions of Table 1, we have provided a common tool for the study of *C. difficile* in the community by researchers. This is intended to limit confusion between researchers of *C. difficile* in different fields, which was listed as an issue from the February 2007 workshop. The disease transmission model proposed has been developed as far as possible with the information currently available. We have outlined known and potential reservoirs and highlighted areas with larger knowledge gaps. For instance, many potential exposure sources were based on studies of HA-CDI, with little or no verification of the same factors playing a role in CA-CDI; these risks must be studied in the realm of CA-CDI to determine relevance.

The states and transitions defined in Figure 1 also facilitate the future creation of a risk assessment model, a tool deemed useful in further CA-CDI research. Infection sources in the community as presented could be utilized; but it is important to note that the four general reservoirs of infection in the community will carry different levels of exposure risk for each individual based on lifestyle and quantitative levels of risk for each factor have not been determined. Those in larger families or with more varied community exposure will potentially come in contact with more persons and therefore may be more likely to contact an infected person; those dealing with animals or children at work may be more likely to come in contact with *C. difficile* from these sources; and so on. Further investigation is required to determine quantitative levels for each reservoir and infection source. Also required for an assessment would be investigation of the eight categories of risk factors not explored in this paper, as shown in Figure 3. The inclusion of additional state transfer risk factors would allow the community to be more accurately modelled and in turn provide more useful results when analysing scenarios such as food contamination and the resultant effect on community illness rates.

The lack of CA-CDI data for mathematical modelling limits the results possible for risk assessment of CA-CDI at this time, as the majority of information published is HA-CDI related. Further epidemiological studies of CA-CDI are warranted to create thorough and correct models of the disease within the community setting, rather than substituting HA-CDI data for community transmission. The model of Figure 1 offers a starting point for consistency in CA-CDI communication; and a quantitative risk assessment model may be constructed and used as a research tool to gain a better understanding of potential risks, using a scenario-based approach. The model may be improved and become more accurate as the following data become available for CA-CDI: current values for infected and colonized individuals in the community; prevalence and concentration rates of *C. difficile* present in infection sources; and risk factors applicable to all CA-CDI state transfers and their quantitative effects.

DECLARATION OF INTEREST

None.

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