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# *Clostridium difficile* PCR ribotype 027: assessing the risks of further worldwide spread

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Highly virulent strains of *Clostridium difficile* have emerged since 2003, causing large outbreaks of severe, often fatal, colitis in North America and Europe. In 2008–10, virulent strains spread between continents, with the first reported cases of fluoroquinolone-resistant *C difficile* PCR ribotype 027 in three Asia-Pacific countries and Central America. We present a risk assessment framework for assessing risks of further worldwide spread of this pathogen. This framework first requires identification of potential vehicles of introduction, including international transfers of hospital patients, international tourism and migration, and trade in livestock, associated commodities, and foodstuffs. It then calls for assessment of the risks of pathogen release, of exposure of individuals if release happens, and of resulting outbreaks. Health departments in countries unaffected by outbreaks should assess the risk of introduction or reintroduction of *C difficile* PCR ribotype 027 using a structured risk-assessment approach.

## Introduction

*Clostridium difficile* is a major cause of diarrhoea in patients in hospital and long-term care facilities.<sup>1,2</sup> *C difficile* infection is through exposure to the organism or its spores via the faecal-oral route; the spores can persist in the environment for many months. Once infected, the person might remain asymptomatic or progress to *C difficile* disease. Infection and progression to disease are facilitated by use of antibiotics, which disrupt the normal flora and permit proliferation of the toxin-producing *C difficile*. A wide range of antibiotics have been implicated historically, including cephalosporins, penicillins, and clindamycin.<sup>3–5</sup> Infection ranges in severity; in its most severe form it can cause toxic megacolon with subsequent colonic perforation, peritonitis, shock, and death. Colectomy might be needed to avert perforation but is associated with high risk given the age and medical comorbidities of typical patients infected with *C difficile*. Infection is associated with hospitals and long-term care facilities because of frequent antibiotic use, widespread contamination of the patient's environment with spores, and the density of people at high risk (ie, elderly people with several comorbidities).

In the past two decades, the incidence of *C difficile* infection has increased in many industrialised countries,<sup>6–13</sup> particularly among elderly people.<sup>12</sup> Groups previously thought to be low risk, including otherwise healthy people in the community without prior exposure to antibiotics,<sup>14,15</sup> children,<sup>16</sup> and peripartum women, have also been affected.<sup>17–19</sup> Concurrent with an increase in incidence, an alarming increase in severity of infection has been reported, starting with reports of hospital outbreaks in Quebec, Canada, from 2003. These outbreaks were associated with high case-fatality rates<sup>20,21</sup> and were estimated to have caused about 2000 deaths.<sup>22</sup> This happened at the same time as an increase in severity of infection in the USA, characterised by increases in reported *C difficile* infection-related admission to hospital, colectomies, and deaths, dated retrospectively from the mid-1990s.<sup>13,23–26</sup> Muto and colleagues<sup>8</sup> noted a four-times increase in severe cases (resulting in colectomy or death)

from 1999 to 2001 in a hospital outbreak in Pittsburgh, PA. A similar pattern of emergence has developed in Europe since 2005, with increasing incidence of infection<sup>10,27</sup> and some hospital outbreaks with more severe cases and higher case-fatality rates than previously experienced.<sup>28,29</sup> Outbreaks have been particularly severe in the UK, with a six-times increase in *C difficile* infection-related mortality from 1999 to 2006,<sup>30,31</sup> which preceded a stabilisation and substantial decline in incidence and mortality from 2007 to 2009.<sup>32,33</sup>

These North American and European outbreaks (figure 1) coincided with the emergence of a hypervirulent strain of *C difficile*, PCR ribotype 027/North American pulse-field type 1,<sup>34,35</sup> that caused more severe colitis and higher mortality than other strains.<sup>37,63–65</sup> Increased virulence might be due to genetic mutations in a toxin regulator gene (*tcdC*) that cause hyperproduction of toxins A and B.<sup>66,67</sup> The strain also produces a binary toxin associated with severe diarrhoea.<sup>68,69</sup> Unlike isolates of *C difficile* PCR ribotype 027 obtained before 2001, isolates obtained during the North American and European epidemics were resistant to fluoroquinolones and genetically closely related.<sup>34–36,64,70</sup>

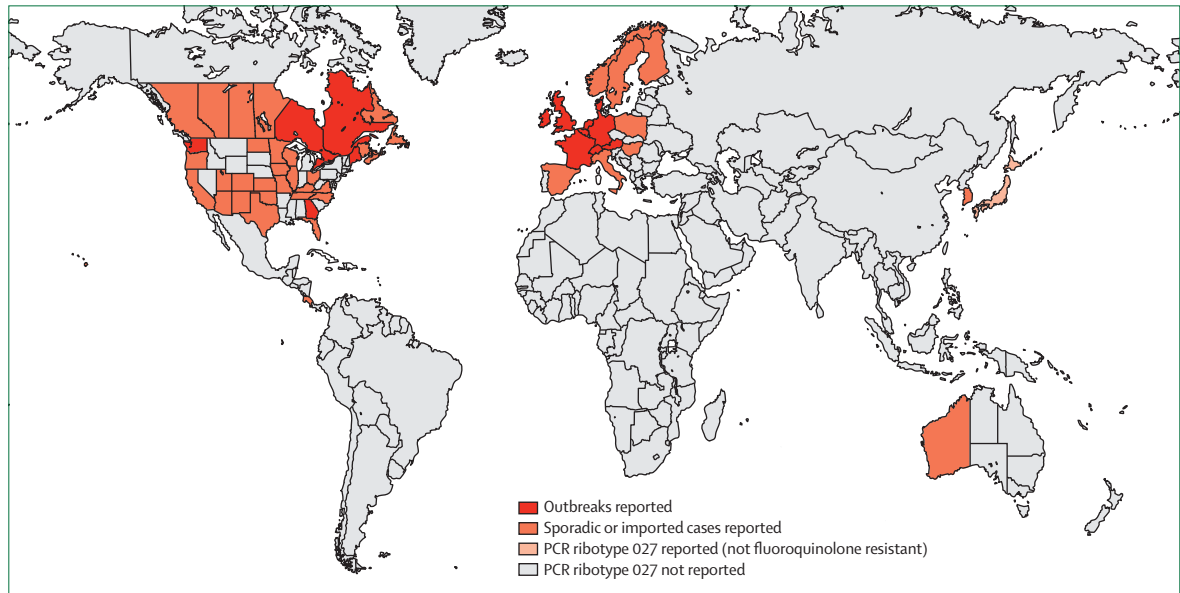
So far, continents other than North America and Europe have been spared outbreaks of *C difficile* PCR ribotype 027 infection, and evidence suggests a decline in the incidence of infection associated with this ribotype in the UK<sup>32</sup> and the Netherlands.<sup>71</sup> However, alarmingly in 2008–10, the first cases of *C difficile* PCR ribotype 027 infections were reported in Western Australia,<sup>57</sup> South Korea,<sup>58</sup> Hong Kong,<sup>59</sup> and Costa Rica,<sup>50</sup> showing the potential of this organism to spread between continents beyond its current north Atlantic domain.

The emergence of *C difficile* PCR ribotype 027 is of worldwide concern, both for affected and unaffected countries. It is uncertain if the failure to detect the strain in many countries means it is truly absent, because molecular genotyping is rarely used. Many industrialised countries now rely on enzyme-linked immunoassays for diagnosis, which do not identify specific strains,<sup>72</sup> whereas most developing countries have no *C difficile* surveillance

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**Figure 1: Countries\* where *Clostridium difficile* PCR ribotype 027 has been reported**

Sources of information include reports from the USA<sup>8,34</sup> and Canada,<sup>35</sup> reporting hospital outbreaks since 2001; the UK,<sup>29,36</sup> the Netherlands,<sup>37-39</sup> Belgium,<sup>40</sup> and Ireland,<sup>41</sup> reporting hospital outbreaks since 2005; France,<sup>28,42</sup> Switzerland,<sup>43</sup> and Luxembourg,<sup>44</sup> reporting hospital outbreaks since 2006; Germany,<sup>45-47</sup> reporting hospital outbreaks since 2007; and Austria<sup>27,48</sup> and Denmark,<sup>44,45,49</sup> reporting hospital outbreaks since 2008. Sporadic or imported cases of infection caused by *C difficile* PCR ribotype 027 have also been reported from Costa Rica,<sup>50</sup> Finland,<sup>51,52</sup> Hungary,<sup>45,53</sup> Italy,<sup>54</sup> Norway,<sup>55</sup> Poland,<sup>44,45</sup> Spain,<sup>45</sup> Sweden,<sup>56</sup> Western Australia,<sup>37</sup> South Korea,<sup>58</sup> and Hong Kong.<sup>59</sup> The earliest known isolate from the Netherlands was collected in 2002,<sup>37</sup> but—like earlier strains of PCR ribotype 027 in North America, isolates from Japan,<sup>60,61</sup> and the majority of recent isolates from Sweden<sup>56,62</sup>—it was susceptible to fluoroquinolones and is thought a historic strain not associated with the recent international epidemic. \*And states or provinces of the USA, Canada, and Australia.

or do routine diagnostic investigation. However, these countries must identify this strain if, where, and when it emerges to avoid the large epidemics of North America and parts of Europe. We review the types and sources of evidence that need to be assembled to understand the risks of further worldwide emergence of this and other international epidemic strains of *C difficile*.

### Risk assessment frameworks

Risk analysis, comprising risk management, assessment, and communication, is an emerging branch of epidemiology that provides a structured, evidence-based, approach to addressing health risks. Approaches are framed by international standards such as those of the Food and Agriculture Organization/World Health Organization Codex Alimentarius for microbiological risk assessment<sup>73</sup> or the Office International des Epizooties (OIE) system,<sup>74</sup> primarily aimed at international movement of veterinary and zoonotic pathogens. Risk assessment (the technical component of risk analysis) is fundamentally based on the clear definition of a risk question. Using the OIE framework as an example, risk assessment comprises four consecutive analytic components: release assessment, exposure assessment, consequence assessment, and risk estimation.<sup>74</sup> During each of the first three, all available evidence from published work and expert opinion is reviewed and organised on the basis of a diagrammatic construction of risk pathways. The final risk estimation involves the

combination of the results of the preceding three stages to produce an overall estimate of risk.

Quantitative risk assessment uses a probabilistic risk model to derive numerical expressions of risk and associated uncertainties, whereas qualitative risk assessment permits ranking or categorisation of risk. There are many reported applications of quantitative risk assessment to veterinary, zoonotic, and food-borne diseases, including Alban and colleagues<sup>75</sup> who investigated risk of human salmonellosis and campylobacteriosis associated with consumption of pork products in Denmark, Bemrah and colleagues<sup>76</sup> who investigated risk of listeriosis from consumption of unpasteurised cheese, and Bronsvort and colleagues<sup>77</sup> who investigated risk of importation of classic swine fever into Denmark. However, there are few examples for infectious diseases primarily involving transmission between people, and none reported for *C difficile* infection.

For *C difficile* infection, risk is likely to depend on the infection history of the country of interest. If *C difficile* PCR ribotype 027 is not known to be present (as in most countries in the Asia-Pacific region, Africa, and Latin America), the risk question could focus on the likelihood of introduction through specified, hazardous, movements across boundaries. Alternatively, the risk question could consider endogenous emergence through a set of hazardous biological mechanisms, such as patterns of use of specific antibiotics. If *C difficile* PCR ribotype 027 has been detected but has not caused outbreaks (as in

Australia, Korea, Hong Kong, and parts of Europe), the risk question could focus on the likelihood of reintroduction or an outbreak due to endogenous transmission. If *C difficile* PCR ribotype 027 is present and outbreaks have happened (as in North America and parts of western Europe), the assessment of risk could focus on the likelihood of recurrence, the effect of a particular intervention (or no intervention) on the size or frequency of outbreaks, or of previously unaffected groups in the population becoming affected. We focus on the risk of introduction, or reintroduction, of *C difficile* PCR ribotype 027 to countries that have not experienced epidemics associated with this strain.

### Vehicles of introduction

The movements of people, animals, vectors, and inanimate objects across international boundaries has spread many infectious diseases, including influenza,<sup>78</sup> severe acute respiratory syndrome,<sup>79</sup> dengue,<sup>80</sup> chikungunya,<sup>81,82</sup> and malaria.<sup>83</sup> However, identification of imported *C difficile* PCR ribotype 027 is probably much more difficult than for these infections because screening of travellers is not done and outbreaks associated with importation of this strain are likely to happen months or years after importation, leading to delayed identification of the incursion.

For importation of the *C difficile* epidemic strain, a major hazard of interest is international transfer of hospital patients. There is evidence that asymptomatic carriage is common among patients admitted to hospital, and these carriers can act as a source of transmission in settings where *C difficile* PCR ribotype 027 is present.<sup>84,85</sup> Theoretically, either a diarrhoeic or asymptotically infected patient transferred between health-care institutions (including those in different countries) could act as a source of this strain. The first documented case of infection due to PCR ribotype 027 in Ireland was in a patient transferred from a hospital in the UK,<sup>41</sup> and the only reported case in Western Australia was in a patient transferred from the USA.<sup>37</sup> Other anecdotal reports also suggest this as a possible (although unproven) means of international spread. For example, transfer of patients from Belgium was investigated as a potential source of introduction of *C difficile* PCR ribotype 027 to France in 2006<sup>42</sup> and the index case of infection with this strain in Switzerland had previously been admitted to hospital in Spain.<sup>43</sup>

Another potential hazard is movement of people from the community across boundaries (eg, tourists, business travellers, international migrants, and military personnel). A tourist from the UK was reported to have had pseudomembranous colitis caused by *C difficile* PCR ribotype 027 while on holiday in Austria; endogenous cases were subsequently reported in that country.<sup>45</sup> A person with community-acquired, fluoroquinolone-susceptible, *C difficile* PCR ribotype 027 infection in Sweden had previously travelled to Italy,<sup>36</sup> suggesting (but not confirming) recreational travel as a

potential source. However, asymptomatic carriage is less studied in the community than in hospital patients and the role of asymptomatic carriers in the movement of *C difficile* strains between jurisdictions is unknown. The often quoted prevalence of asymptomatic *C difficile* carriage in healthy adults, 2–3%, comes from a 1981 report;<sup>86</sup> however, recent evidence of an increase in incidence of community-acquired cases in some countries warrants studies to update estimates of prevalence of asymptomatic carriage in the community. The role of antibiotic use in the community as a factor promoting carriage of *C difficile* is also poorly understood. In a French study of people prescribed antibiotics in the community,<sup>87</sup> one of 262 had detectable pretreatment colonisation and seven had detectable post-treatment infection with toxigenic strains of *C difficile*.

Although animals have not previously been implicated in any known events of *C difficile* crossing boundaries, they can be symptomatically or asymptotically infected. *C difficile* is recognised as an important cause of enteric disease in piglets<sup>88–91</sup> and horses.<sup>92,93</sup> Identical strains of *C difficile* have been isolated in people and dogs, horses, and pigs.<sup>94–98</sup> These findings also pertain to *C difficile* PCR ribotype 027: studies in North America isolated this strain from calves,<sup>99</sup> a dog,<sup>98,100</sup> and a horse with colitis.<sup>101</sup>

Toxigenic strains of *C difficile*, including PCR ribotype 027, have been isolated from commercially available meat.<sup>102,103</sup> Recent studies in Arizona, USA, and four provinces of Canada, found a high proportion of retail meat samples containing *C difficile* PCR ribotype 027.<sup>104,105</sup> An unspecified toxigenic *C difficile* strain has been isolated from meat for consumption by pets.<sup>106</sup> Isolation of toxigenic strains of *C difficile* from salad in the UK<sup>107</sup> suggests that the bacterium could be widely distributed in a range of human foodstuffs.<sup>108</sup> These studies combined show a potential for transmission between animals and people (either directly or via the food chain), and international spread of toxigenic strains of *C difficile* via movement or trade in livestock, companion animals, meat, and other foodstuffs is therefore possible.

### Risk of pathogen release in new areas

Assuming individuals with known infection are treated in the country of origin or prevented from entering the destination country, the probability of release of the pathogen is dependent on the disease status of the country of origin, the proportion of individuals screened as part of disease surveillance in the country of origin, the performance (ie, sensitivity and specificity) of diagnostic tests used in screening, the frequency of movement between countries, and the proportion of individuals that are screened (and performance of screening tests) on arrival in the destination country.

Several countries have reported infections with *C difficile* PCR ribotype 027 (figure 1), but the disease status of all other countries is unknown because of a lack of routine surveillance and, in many countries, a lack of

	Number of visas, 2006–07	Number of visas, 2007–08
UK	674 771	631 900
USA	385 384	400 906
Germany	138 230	144 852
Canada	101 276	114 457
France	101 505	112 143

Visas granted to citizens of selected countries from which fluoroquinolone-resistant *Clostridium difficile* PCR ribotype 027 has been reported, 2006–07 and 2007–08, from the Department of Immigration and Citizenship annual reports.<sup>122</sup>

**Table 1: Number of offshore visitor visas granted for travel to Australia**

capacity or resources for diagnostic testing, including genotyping. Clearly, risk of release depends on surveillance practices in both the country of origin and the importing country because the effectiveness of surveillance establishes the probability of infected individuals moving between the originating and importing countries without being detected, and the bacterium being contained.

Information on *C difficile* surveillance can be obtained for most countries affected by outbreaks of *C difficile* PCR ribotype 027 from published questionnaire studies of hospital laboratory practices. A study in eight European countries found that the reasons for *C difficile* testing (eg, physician request vs routine screening for samples fulfilling preset criteria such as age of patient and stool consistency) and the tests used, varied widely between laboratories and countries.<sup>109</sup> Findings were similar in studies in Australia,<sup>110</sup> the UK,<sup>11,111</sup> Ireland,<sup>112</sup> Canada,<sup>113</sup> and the USA.<sup>7,114</sup> In some European countries, national laboratory surveillance has been instigated in response to emergence of *C difficile* PCR ribotype 027. A national laboratory network was set up in France to characterise strains of *C difficile*.<sup>28</sup> In Belgium, laboratory-based surveillance of clusters of cases of *C difficile* infection and prospective hospital-based surveillance have been set up, finding PCR ribotype 027 strains in 150 (52.1%) of 288 isolates.<sup>115</sup> A national laboratory surveillance system was also set up in the Netherlands, finding that 218 (25.3%) of 863 cases were caused by PCR ribotype 027 in 2005–06.<sup>37</sup>

Additionally, laws and mandates relating to diagnosis and reporting of *C difficile* can be reviewed to understand surveillance practices. In the UK, laboratory surveillance was made mandatory by the Health Protection Agency (HPA) in January, 2004.<sup>111,116</sup> All stool specimens from diarrhoeic patients older than 65 years were tested for *C difficile* toxins A and B, with the number of *C difficile* infections in each hospital required to be reported to the HPA;<sup>117</sup> in 2007, mandatory reporting was extended to include individuals older than 2 years.<sup>118</sup> Isolates from hospital outbreaks and a sample of other isolates are sent to a national reference laboratory for genetic typing.<sup>119</sup> Some provinces in Canada have mandatory reporting of *C difficile* infections,<sup>120,121</sup> as do a few US states, and some

countries of the European Union.<sup>45</sup> Continent-wide surveillance studies in Europe are under development,<sup>45</sup> but surveillance in the USA and Canada is hampered by the lack of a nationwide approach.

Risk of release is proportional to the frequency of movement of individuals between countries. This can be estimated from various sources that are illustrated here by examples from Australia. All people visiting Australia, apart from citizens of Australia and New Zealand, require an entry visa from the Department of Immigration and Citizenship and, for an assessment of risk focusing on international spread via tourists or business visitors, annual numbers of visitors from specific countries of origin can be estimated by the number of offshore visas granted (table 1). Alternatively, the frequency of movement of individuals can be estimated by the carrying capacity of international airlines on specific international routes (figure 2). For the assessment of risk focusing on international transfers of patients, numbers of patients entering from affected countries can be obtained from medical retrieval companies. Australia has strict regulations regarding the species of domestic animals entering and countries from which animals can be imported, and a risk assessment focusing on animal sources could make use of quarantine records to estimate the number of domestic animals entering by country of origin (table 2). Importation of livestock is highly regulated in Australia and this is an unlikely source of *C difficile* PCR ribotype 027, but for other countries livestock trade data can be used to establish the number of animals entering. Similarly, for Australia and other countries, data on trade in meat products could also be obtained (eg, from the UN Commodity Trade Statistics Database).

### Risk of exposure in new areas

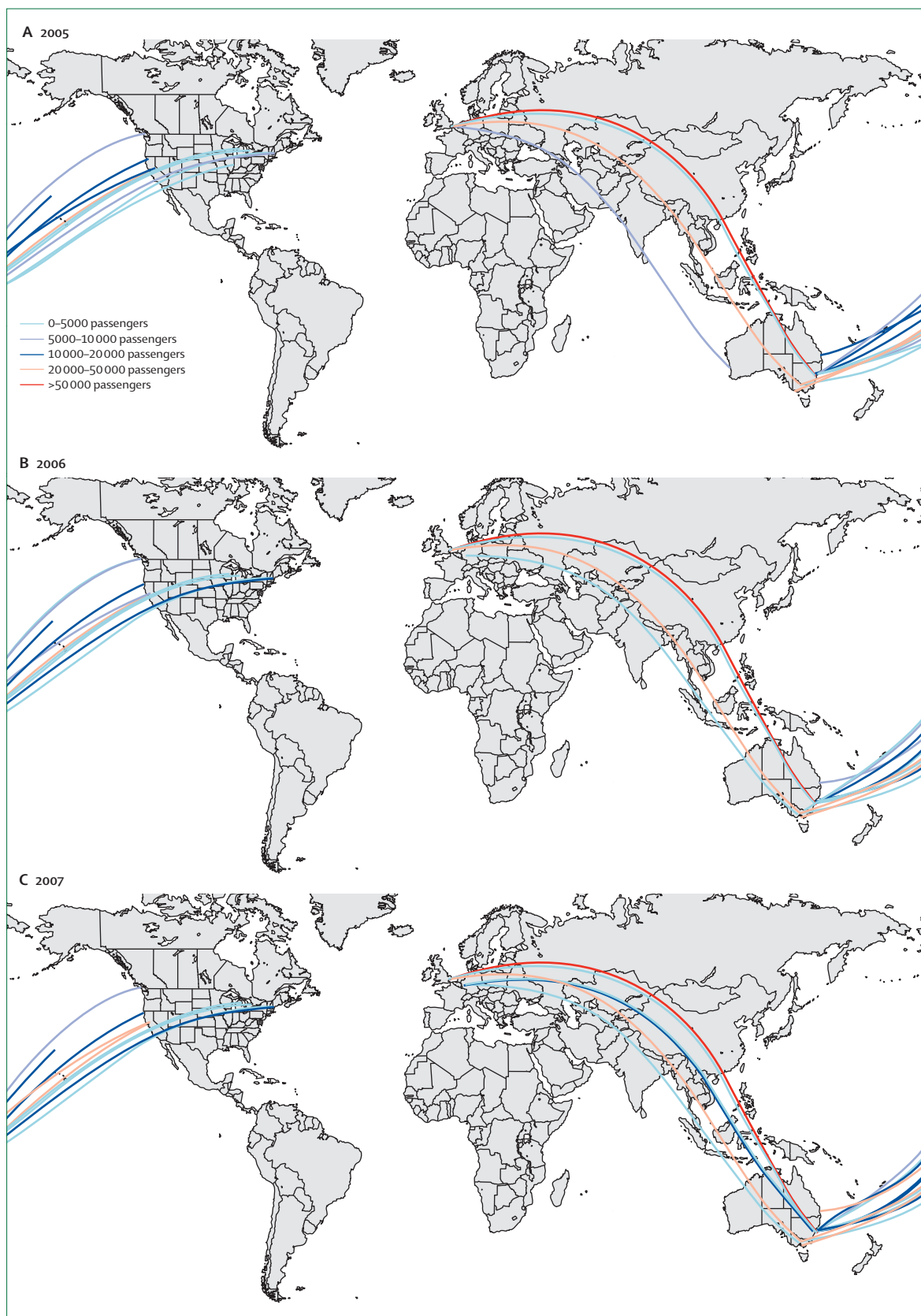
Exposure to *C difficile*, leading to transmission, can be via several pathways. In hospitals, workers' hands and the environment are major modes of transmission,<sup>85,124–126</sup> aerial dissemination is also possible.<sup>127</sup> Transmission is also increasing in the community and recent studies have raised the possibility of additional means of transmission, such as via the food chain<sup>102</sup> or contact with companion animals or livestock.

Establishing the risk of exposure to *C difficile* requires information on contact rates between infected carriers and individuals free of infection; the contact pattern, either via direct contact or indirect contact with a health-care worker or contaminated environment; the duration of shedding by asymptomatic individuals with the infection; the amount of environmental contamination

**Figure 2: Annual passenger-carrying capacity of international air-transport links between countries affected by fluoroquinolone-resistant *Clostridium difficile* PCR ribotype 027 and Australia**

Frequency of indirect travel between affected countries and Australia via international hubs can also be estimated. Data from the International Air Transport Association.<sup>123</sup>

For the UN Commodity Trade Statistics Database see <http://comtrade.un.org/>



	Number of animals, 2005	Number of animals, 2006	Number of animals, 2007	Number of animals, 2008
UK	2594	3028	3113	2610
USA	1022	1160	1153	1213
Canada	231	270	332	320
Netherlands	129	118	121	115
Germany	89	116	111	134
France	75	87	93	62

Number entering from selected countries from which fluoroquinolone-resistant *Clostridium difficile* PCR ribotype 027 has been reported, 2005–08. Estimated on the basis of travel permits granted by the Australian Quarantine and Inspection Service (Lam G, Australian Quarantine and Inspection Service, Canberra, ACT, Australia, personal communication).

**Table 2: Number of dogs, cats, and horses entering Australia each year**

(numbers of spores shed) by asymptomatic individuals with the infection; duration of survival of the pathogen in the environment; and the effect of infection-control interventions.

Observational studies to establish values for variables such as contact rates between infected and susceptible individuals, duration of shedding and survival of pathogens, and effect of intervention strategies are difficult and expensive to do, and suffer from issues such as poor generalisability, inadequate statistical power, and many types of inherent bias. Therefore, many investigations of infectious-disease transmission use mathematical models, which are built using multiple sources of available evidence to estimate plausible values for many of these parameters. Uncertainties surrounding these estimates are often captured by use of a stochastic Monte Carlo simulation approach. Only two publications,<sup>128,129</sup> both by the same group, present mathematical models for *C difficile* transmission and focus exclusively on the health-care setting, using a single ward-based model. Exposure assessment is likely to be the most challenging aspect of *C difficile* risk assessment and substantial future research is needed to understand the transmission dynamics of this organism.

### Risk of infections and outbreaks

The consequences of transmission, including infections and outbreaks, depend on the risk profile of the population into which the pathogen has been introduced. Antibiotic use is the main factor determining susceptibility to infection in an individual exposed to *C difficile* and data on levels of use of different types of antibiotic will probably provide the most important source of information for assessing the risk of infections and outbreaks. Availability of antimicrobial drugs varies widely between countries, with those countries that do not have good systems for regulating the use of antimicrobial drugs (particularly developing countries) also being the countries with the poorest systems for monitoring use and associated disease risks.

Studies have shown variation in levels of antibiotic prescribing between countries<sup>130</sup> and over time.<sup>131</sup> Goossens and colleagues<sup>132</sup> investigated levels of antibiotic prescribing in the community in 26 European countries, with estimates ranging from 10·0 defined daily doses per 1000 people in the Netherlands to 32·2 defined daily doses per 1000 people in France (although different assessment methods were used in each country), and varying by season, with a marked winter peak. Patrick and colleagues<sup>130</sup> also showed seasonal variation (characterised by a winter peak) in antibiotic prescribing in Denmark and British Columbia, Canada. Interestingly, seasonal variation in rates of *C difficile* infection, with a winter peak, have also been reported in the USA.<sup>6</sup>

Fluoroquinolone use has been identified as a major risk factor for infection in settings where *C difficile* PCR ribotype 027 is present,<sup>8,21,35,65,133,134</sup> and increasing fluoroquinolone use in hospitals has been shown to precede outbreaks of infection associated with this strain,<sup>8</sup> possibly because fluoroquinolone resistance gives the strain a selective advantage.<sup>34</sup> Linder and colleagues<sup>131</sup> reported on fluoroquinolone prescribing patterns in the USA, using data from national surveys of emergency department and outpatient clinic visits. They found a rapid (three times) increase in fluoroquinolone prescriptions from 1995 to 2002, and that fluoroquinolones had become the most common class of antibiotics prescribed to adults in 2002. Patrick and colleagues<sup>130</sup> also showed an increase in fluoroquinolone prescribing in British Columbia from 1997 to 2000. Clindamycin was the predominant risk factor for infection in a study by McFarland and colleagues<sup>135</sup> and some recent isolates of *C difficile* PCR ribotype 027 are resistant to this antibiotic.<sup>43,136</sup>

Monitoring of veterinary antibiotic use, potentially including manufacturing, sales, distribution, prescribing, and administration data, has been highlighted as an area of importance for risk assessment of emerging antibiotic resistance in human pathogens.<sup>137,138</sup> In livestock, prolonged oral administration of broad-spectrum antibiotics and inadvertent under dosing increase the risk of emergence of antibiotic resistance that can then be passed to human pathogens.<sup>139</sup> Comprehensive veterinary prescription surveillance systems exist in the Netherlands and Nordic countries (Denmark, Finland, Norway, and Sweden). However, there is a lack of comprehensive, systematically collected, or readily available veterinary prescribing data in the USA<sup>137</sup> and other countries<sup>138</sup> and a lack of consensus on the optimum approach to surveillance of antibiotic use in animals.<sup>140</sup>

Other established risk factors for *C difficile* infection are advanced age and presence of comorbidities,<sup>4,8,21,135,141–145</sup> current or previous admission to hospital,<sup>4,21,133,135,141,146,147</sup> and sharing an environment with other people infected with *C difficile*.<sup>4,141,144</sup> Risk-based surveillance, whereby specific high-risk groups (eg, patients who are elderly, are receiving antibiotics, have a previous history of hospital admission, or are in international transfer) are

### Search strategy and selection criteria

Data for this Review were obtained from publications identified by a systematic search of PubMed, focusing on those published from January, 2001, to March, 2010. Search terms included "Clostridium difficile", "ribotype 027", "NAP 1", "international epidemic strain", "risk", and "surveillance". Abstracts of English, French, and Spanish language papers were read and considered for inclusion, although only English language papers were selected for the final review. Secondary, manual, searches of the cited references of these articles were done and relevant articles were included, some of which were published before 2001. The last search of published work was done on March 17, 2010.

systematically targeted by hospital preadmission screening programmes, should be investigated in future risk assessment studies as a potential means of reducing the risk of incursion of epidemic strains.

### Conclusions

Pépin and colleagues<sup>21,148</sup> give a compelling theory of the evolution of the international *C difficile* PCR ribotype 027: a new, fluoroquinolone-resistant, hyper-virulent strain<sup>149</sup> causing more severe diarrhoea and, therefore, more intense environmental contamination, was circulating at low levels across a wide geographical region<sup>150</sup> until widespread, increasing, use of fluoroquinolones<sup>151</sup> in highly susceptible populations (characterised by increasing age and frequency of comorbidities, located in under-resourced, overcrowded, health-care facilities) precipitated a rapidly emerging epidemic that spread internationally. Many of the factors that precipitated the epidemics in North America and Europe are present in countries without known circulation of *C difficile* PCR ribotype 027, such as hospital overcrowding and understaffing, high levels of antibiotic (particularly fluoroquinolone) use, and an ageing population of hospital patients with increasing numbers and severity of comorbidities. Additionally, international travel is increasing and there is a high volume of international travel between affected and unaffected countries. It is highly probable that *C difficile* PCR ribotype 027 already has been or will be introduced undetected into countries not affected at present, via hospital transfers, asymptomatic carriers, or other vehicles, due to a lack of screening and the frequent movement of people and commodities across boundaries.

If *C difficile* PCR ribotype 027 is introduced into an unaffected country or if a highly pathogenic strain emerges, it is improbable with current surveillance that they would be identified until a large outbreak of severe *C difficile* infection happens, leading to otherwise preventable illness, colectomies, deaths, and huge costs to health services. Now is the time to act to assemble an evidence base for reducing the risk and consequences of future outbreaks in unaffected countries.

### Contributors

ACAC had the original idea for the Review, searched the published work, created figures and tables, and drafted the paper. RJSM oversaw the risk assessment component and contributed to the drafts. AJT provided figures and contributed to the drafts. DLP oversaw the epidemiological description of *Clostridium difficile* infection and contributed to the drafts. TVR oversaw the microbiological description of *C difficile* and contributed to the drafts. All authors approved the final version.

### Conflict of interests

We declare that we have no conflicts of interest.

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