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Seasonality and community interventions in a mathematical model of *Clostridium difficile* transmission

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SUMMARY

Background: *Clostridium difficile* infection (CDI) is the leading cause of antibiotic-associated diarrhoea with peak incidence in late winter or early autumn. Although CDI is commonly associated with hospitals, community transmission is important.

Aim: To explore potential drivers of CDI seasonality and the effect of community-based interventions to reduce transmission.

Methods: A mechanistic compartmental model of *C. difficile* transmission in a hospital and surrounding community was used to determine the effect of reducing transmission or antibiotic prescriptions in these settings. The model was extended to allow for seasonal antibiotic prescriptions and seasonal transmission.

Findings: Modelling antibiotic seasonality reproduced the seasonality of CDI, including approximate magnitude (13.9–15.1% above annual mean) and timing of peaks (0.7–1.0 months after peak antibiotics). Halving seasonal excess prescriptions reduced the incidence of CDI by 6–18%. Seasonal transmission produced larger seasonal peaks in the prevalence of community colonization (14.8–22.1% above mean) than seasonal antibiotic prescriptions (0.2–1.7% above mean). Reducing transmission from symptomatic or hospitalized patients had little effect on community-acquired CDI, but reducing transmission in the community by $\geq$7% or transmission from infants by $\geq$30% eliminated the pathogen. Reducing antibiotic prescription rates led to approximately proportional reductions in infections, but limited reductions in the prevalence of colonization.

Conclusion: Seasonal variation in antibiotic prescription rates can account for the observed magnitude and timing of *C. difficile* seasonality. Even complete prevention of transmission from hospitalized patients or symptomatic patients cannot eliminate the pathogen, but interventions to reduce transmission from community residents or infants could have a large impact on both hospital- and community-acquired infections.

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Introduction

Clostridium difficile infection (CDI) is among the most common hospital-associated infections and antibiotic-associated infections in the world [1–7]. Infection is characterized by mild-to-severe diarrhoea, frequent recurrences and considerable mortality [8]. However, asymptomatic colonization is also common, especially in infants [9]. *C. difficile* transmission occurs both within and outside hospitals [10]. Recent whole-genome sequencing studies suggest that up to 25% of hospital-onset infections and up to 19% of all infections can be attributed to contact with another symptomatic patient in hospital [11,12].

Approximately 5% of hospitalized patients are already asymptomatically colonized at the time of admission [9,13]. Modelling studies have highlighted the importance of these colonized admissions, with some demonstrating that within-hospital transmission alone is insufficient to sustain the presence of the pathogen [14–16]. However, much less is known about transmission outside hospitals. Nearly all interventions to reduce transmission have been hospital-based, and the effect of these interventions on community-acquired and community-onset cases has only rarely been studied or modelled [17,18]. Seasonal variation in antibiotic prescriptions [19] and the reduction of fluoroquinolone prescription in the UK [20] have been shown to correlate with CDI; however, the contributions of prescriptions in the community and hospital have not been disentangled. Only one other modelling study has considered the effect of small reductions in prescriptions to transmission outside hospitals [17], but the potential impact of large reductions is unknown.

CDI is moderately seasonal, with incidence peaking in late winter or early autumn [21]. The seasonality of CDI correlates with seasonal antibiotic prescription rates [20], seasonal rainfall and temperature [22], seasonal incidence of influenza [20,23] and seasonal incidence of respiratory syncytial virus (RSV) [20]. However, like other seasonal infections such as RSV and influenza, the mechanisms driving *C. difficile* seasonality are not well understood [24]. Many mechanisms have been proposed for seasonal respiratory infections, including seasonal transmissibility (through seasonal contact rates or pathogen survival) and seasonal host susceptibility (through seasonal changes in immunity) [25]. Similar biological or behavioural factors may contribute to the seasonality of *C. difficile*, but this has not been demonstrated. Prior use of antibiotics is a key risk factor for developing CDI [13,26]. As antibiotic prescriptions rates are seasonal, they are likely to contribute to the observed seasonality of CDI [27].

This study used an existing mathematical model of *C. difficile* transmission in a population that includes a hospital and the surrounding community [28] to explore two inter-related gaps in the *C. difficile* literature. The seasonal patterns in *C. difficile* colonization and infections produced by seasonal antibiotic prescription rates and seasonal transmissibility or susceptibility of the pathogen were explored. In addition, the potential impact on the incidence of CDI and the prevalence of colonization of reducing the transmission of *C. difficile* from various subpopulations or reducing antibiotic prescriptions to various subpopulations within and outside of hospitals were evaluated.

Methods

Description of the model

The existing mathematical model is described in detail elsewhere [28] and summarized diagrammatically in Figures A.1 and A.2 (see Appendix A, online supplementary material). Briefly, the model has a compartmental structure with compartments differentiating patient setting (hospital or community), *C. difficile* status (negative, colonized or infected), gut flora status (disrupted or intact) and immune response to toxins (naïve, immune or immune suppressed/elderly). The model also includes separate compartments to represent infants in the community. All *C. difficile*-positive people in each model setting (hospital or community) can infect those in the same setting. Disruption of gut flora allows the overgrowth of *C. difficile*, and therefore increases infectiousness and leads to the development of symptoms in non-immune patients in the model. Hospitalized patients with symptoms are assumed to be treated with additional contact precautions that reduce their infectiousness. Colonized infants do not develop symptoms but are infectious.

Parameters and sensitivity analyses

The parameters for the base scenario for the intervention analyses and the seasonal average parameters in the seasonality analyses were estimated in a previous paper [28], and are summarized in Table A.1 (see Appendix A, online supplementary material). As the parameters were estimated using Western European infant colonization prevalence data [29,30], nationwide estimates for the incidence of CDI in the USA [31] and CDI hospital admissions data from the USA [32], they reflect the current epidemiology in high-income countries as closely as possible. In the sensitivity analysis (SA), estimated model parameters were refit for different assumptions of the prevalence of colonization and infant infectiousness. Estimates of the prevalence of colonization in the general community are highly variable [9]. The base assumption was that general prevalence of colonization in adults was 5%, but a range of 2–10% was considered in the SA. The relative infectiousness of infants and adults has not been well quantified, although asymptomatically colonized infants may be as infectious as adults with CDI [30]. For the base scenario in this article, it was assumed that infants were 0.5 times as infectious as symptomatic adults (SA 0.1–1 times as infectious), which is equivalent to infants being 3.3 times as infectious as asymptomatically colonized adults with intact gut flora (SA 0.5–9.8 times as infectious). Higher infant infectiousness, especially when the prevalence of colonization in adults was low, led to poor model fit and an implausibly high proportion of infections attributable to infants, and so was excluded.

Modelling the seasonality of C. difficile

Two mechanisms that may account for seasonal CDI rates were modelled: seasonal antibiotic prescription rates and seasonal transmissibility. The transmission rate parameter

combined human and pathogen factors that influence transmissibility and susceptibility, and may be affected by seasonal changes in the environment and human behaviour: spore shedding rate, contact rates, pathogen survival, and human susceptibility to colonization. Therefore, increasing the transmissibility of the pathogen from all carriers and increasing the susceptibility of the whole population were mathematically equivalent in the model. The amplitude of antibiotic prescription seasonality was extracted from seasonal prescription data for different classes of antimicrobials in the USA [27]. In the absence of data on seasonal transmissibility/susceptibility, and to make fair comparisons between the mechanisms, the same amplitude was applied to both seasonal antibiotic prescription and transmission rate parameters. Each mechanism was simulated independently. Under the assumption that current seasonal CDI is entirely due to the estimated amplitude of seasonal antibiotic prescriptions, estimates were made of the reduction in the annual incidence of CDI, peak incidence of CDI and mean prevalence of colonization that would be achieved if antibiotic prescription rates were reduced to their seasonal low levels all year round.

Modelling the reduction of transmission or antibiotic prescriptions

The remainder of the intervention analyses considered the effect of reducing the transmission and antibiotic prescription rate parameters in a non-seasonal version of the model. Five overlapping target groups/populations were considered for reducing transmission: hospitalized patients, community residents (including infants), symptomatic carriers, recipients of antibiotics, and infants. Four overlapping target groups were considered for reducing events that disrupt gut flora: hospitalized patients, community residents, the elderly or immunosuppressed population who are at high risk of developing CDI, and adults who are not in the high-risk group. For each scenario, reductions of 0–100% in the relevant rate parameter(s) were considered, and the reduction in the incidence of CDI or the prevalence of colonization was calculated as a percentage of the base incidence or prevalence of colonization.

The prevalence of colonization in the hospital and community subpopulations was calculated, and the incidence of CDI was separated into hospital-acquired and community-acquired cases in two ways: (1) the actual location of colonization simulated in the model; and (2) the apparent source of acquisition as classified by surveillance definitions similar to those recommended by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America [34]. It has been shown previously that the recommended definitions misclassify many community-acquired cases as hospital-acquired [35], so this enabled comparison of the apparent effect on interventions with the actual effect. The model used a minor variant of recommended definitions employed by Lessa *et al.* [31], and accounted for underreporting of community-onset cases, as implemented in the authors' previous paper [28].

Results

Seasonal variation in antibiotic prescription rates and seasonal transmissibility/susceptibility produced different patterns of *C. difficile* seasonality (Figure 1). The estimated amplitude of the variation in antibiotic prescriptions was 16.2%

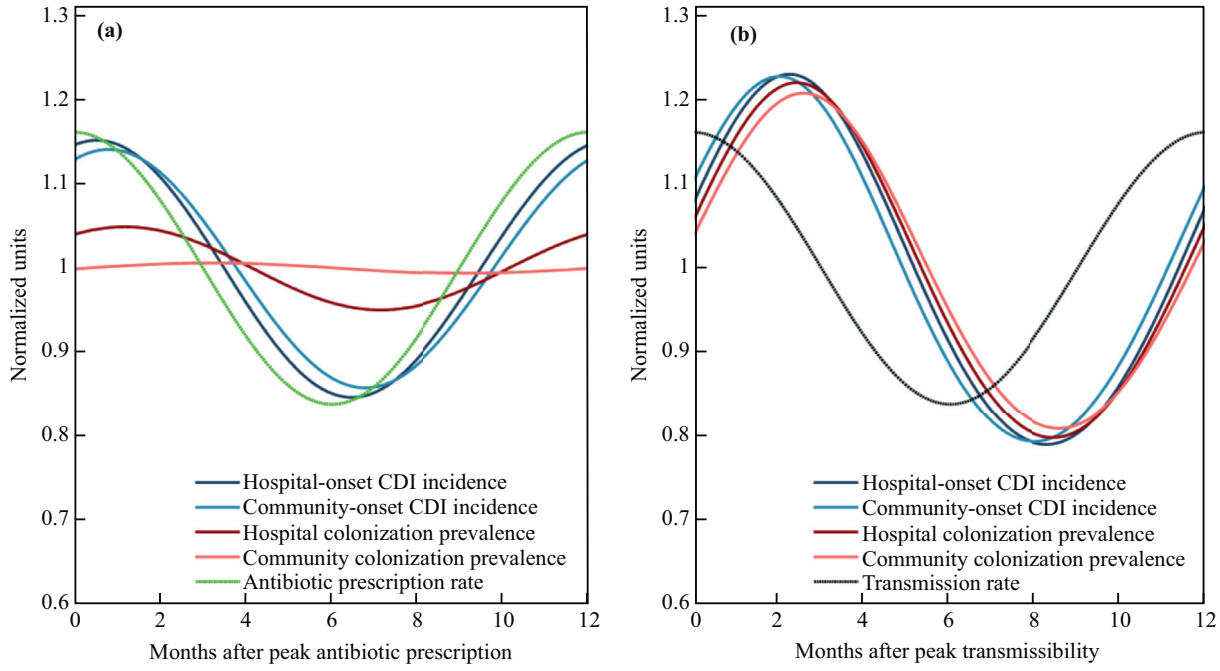

Figure 1. Comparison of seasonal patterns in the incidence of *Clostridium difficile* infection (CDI) and the prevalence of colonization produced by (a) seasonal antibiotic prescription rates and (b) seasonal transmissibility or susceptibility. Incidence, prevalence of colonization and seasonal rate parameters have been rescaled so that the annual mean is 1. The base assumptions for infant infectiousness (half as infectious as adults with CDI or 3.3 times as infectious as asymptomatically colonized adults with intact gut flora) and general prevalence of colonization in adults (5% in the community) were used for this figure.

(i.e. the seasonal high and seasonal low were 116.2% and 83.8% of the annual mean). Both seasonal antibiotics and seasonal transmissibility/susceptibility led to large, annually repeating variation in the total incidence of infection, with peak incidence 14% (SA 13.9–15.1%) and 23% (SA 18.2–25.3%) above annual mean incidence, respectively. The timing and magnitude of infection seasonality were similar for hospital-onset and community-onset infections. The annual peak in total (i.e. hospital and community combined) incidence of infection was 2.0 months (SA 1.4–2.3 months) after peak transmissibility in the seasonal transmissibility model, and 0.8 months (SA 0.7–1.0 months) after peak prescriptions in the seasonal antibiotics model.

Seasonal transmissibility/susceptibility led to large seasonal variations in the prevalence of colonization in both the hospital (peak 22.0% above mean; SA 20.3–25.1%) and the community (peak 20.8% above mean; SA 14.8–22.1%), with timing similar to the seasonality of the incidence of infection (Figure 1B). In contrast, seasonal antibiotic prescriptions led to seasonal variation in the prevalence of colonization in hospitals with similar timing (peak prevalence 1.2 months after peak prescriptions; SA 1.1–1.4 months), but less than half the amplitude (peak prevalence 4.8% above mean; SA 2.2–10.1%) of hospital-onset CDI seasonality. Seasonal antibiotic prescriptions led to very little seasonal variation in the prevalence of colonization in the community (0.6% above mean; SA 0.2–1.7%), which peaked 3.2 months (SA 2.4–3.6 months) after peak prescriptions (Figure 1A). In a sensitivity analysis for the amplitude of antibiotic prescription seasonality, the timing of peaks was independent of amplitude (results not shown).

Reducing antibiotic prescription rates to the seasonal low reduced peak incidence of CDI by 30% (SA 27–41%), annual incidence by 20% (SA 16–32%), and mean prevalence of colonization by 6% (SA 1–21%). These reductions were approximately linear, so halving seasonal excess prescriptions led to approximately half the above reductions in incidence and prevalence.

The effect of reducing transmission in the non-seasonal model is summarized in Figure 2, and further explored in Figures B.1 and B.2 (see Appendix B, online supplementary material). Modest reductions in transmission from community residents (10%, SA 7–27%) eliminated all CDI in the hospital and the community. For the base assumption, a 47.5% reduction in transmission from infants eliminated all CDI in the population. However, this finding was very sensitive to the parameter assumptions. At one extreme — with infants one tenth as symptomatic as adults and the prevalence of colonization in adults at 10% — preventing all transmission from infants only reduced the incidence of CDI by 5%. At the other extreme — with infants as infectious as symptomatic adults and the prevalence of colonization in adults at 2% — a 30% reduction in transmission from infants eliminated *C. difficile* from the population. Reducing hospital-based transmission led to approximately proportional reductions in hospital-acquired

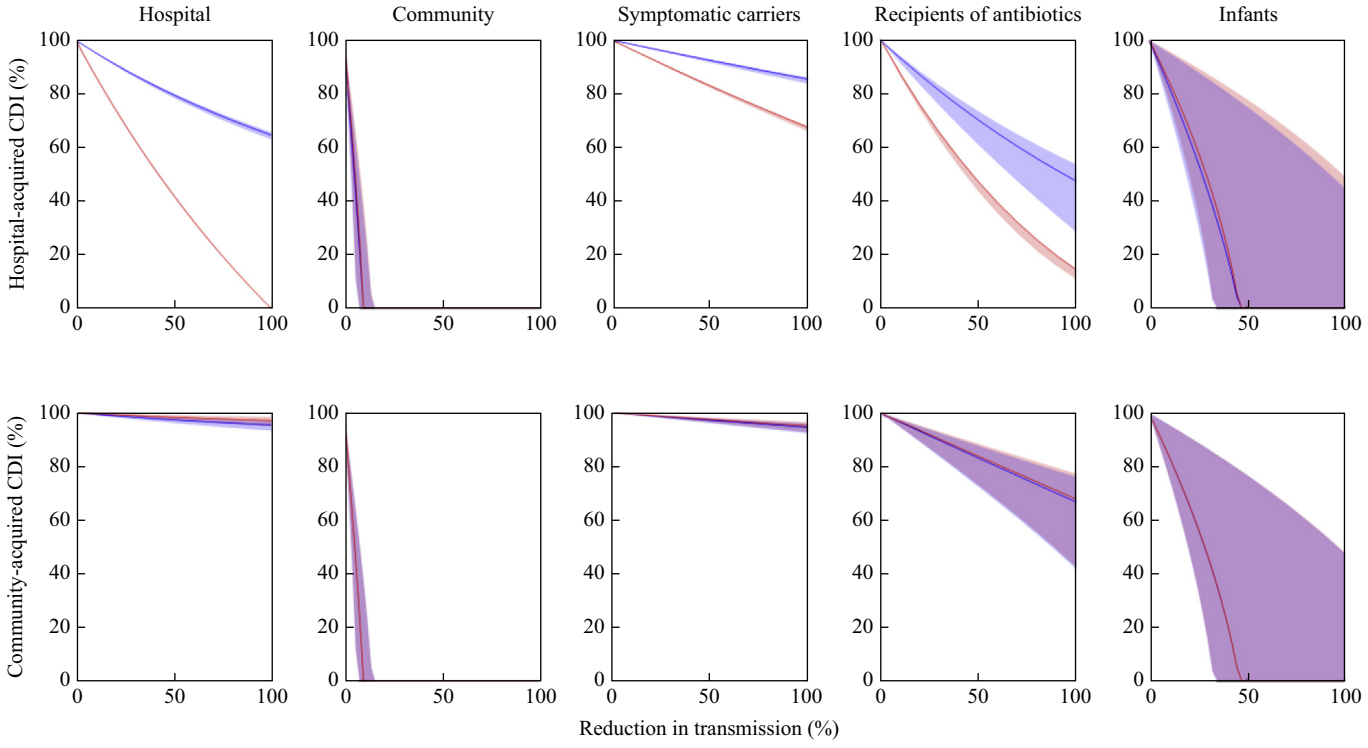

Figure 2. Comparison of the effect in the hospital (top row) and community (bottom row) of reducing *Clostridium difficile* transmission from various overlapping target populations (columns). Each figure compares the actual reductions (red) and the apparent reductions (blue), which differ due to misclassification of cases as hospital- or community-acquired. The shaded region around each line indicates the range in the sensitivity analysis for infant infectiousness. A purple shaded region indicates overlapping sensitivity analysis ranges for apparent and actual reductions. The general prevalence of colonization in adults is 5%. See Figure B.1 (Appendix B, online supplementary material) for further sensitivity analyses.

CDI, but only modest reductions in community-acquired cases. Reducing transmission from symptomatic carriers alone was much less effective than reducing transmission from all those who had taken antibiotics recently; however, neither could eliminate hospital- or community-acquired infections.

In the non-seasonal model, reducing the disruption of gut flora reduced the prevalence of colonization (due to reduced transmission from those colonized without disruption of gut flora), but this reduction was not sufficient to interrupt transmission in the population (Figure 3). Reducing the disruption of gut flora led to reductions in incidence through the combination of reduced transmission (and hence prevalence of colonization) and reduced risk of developing symptoms (Figure 3). Reducing the disruption of gut flora in either setting (hospital or community) led to reduced infections and colonization in both the hospital and the community. Comparing the reduction of prescriptions for the high-risk elderly population and the remaining low-risk population, the former led to approximately twice the reduction in incidence and a comparable reduction in the prevalence of colonization.

When reducing transmission or antibiotic prescriptions, the apparent and actual reductions in incidence were similar for community-acquired cases (Figures 2 and 3). However, when transmission was reduced in hospital residents alone, symptomatic carriers alone or recent recipients of antibiotics alone, the apparent intervention effect was much smaller than the true effect. For instance, even the complete prevention of all hospital-based transmission appeared to prevent <40% of hospital-acquired cases due to the misclassification of community-acquired cases.

Discussion

Modelling the observed seasonal variation in antibiotic prescription rates reproduced the observed seasonal pattern of CDI, including a delay of approximately one month between peak antibiotic prescription rates and peak incidence of CDI (in agreement with correlative time-series analysis studies [20,23]) and the size of the peak in the incidence of CDI [21]. According to the model, if biological and behavioural mechanisms influencing transmissibility or susceptibility are the major factors driving seasonal incidence of CDI, one should also expect to see large seasonal variation in the prevalence of colonization in both the hospital and the community. On the other hand, if seasonal antibiotic prescription rates are the primary or only mechanism, one should expect to see little to no seasonal variation in the prevalence of colonization in the community and only moderate seasonality in hospitals. Consistent with either mechanism, a study in two Australian hospitals found that the prevalence of colonization was seasonal [36]. However, the present authors are not aware of any published studies investigating seasonality of the prevalence of

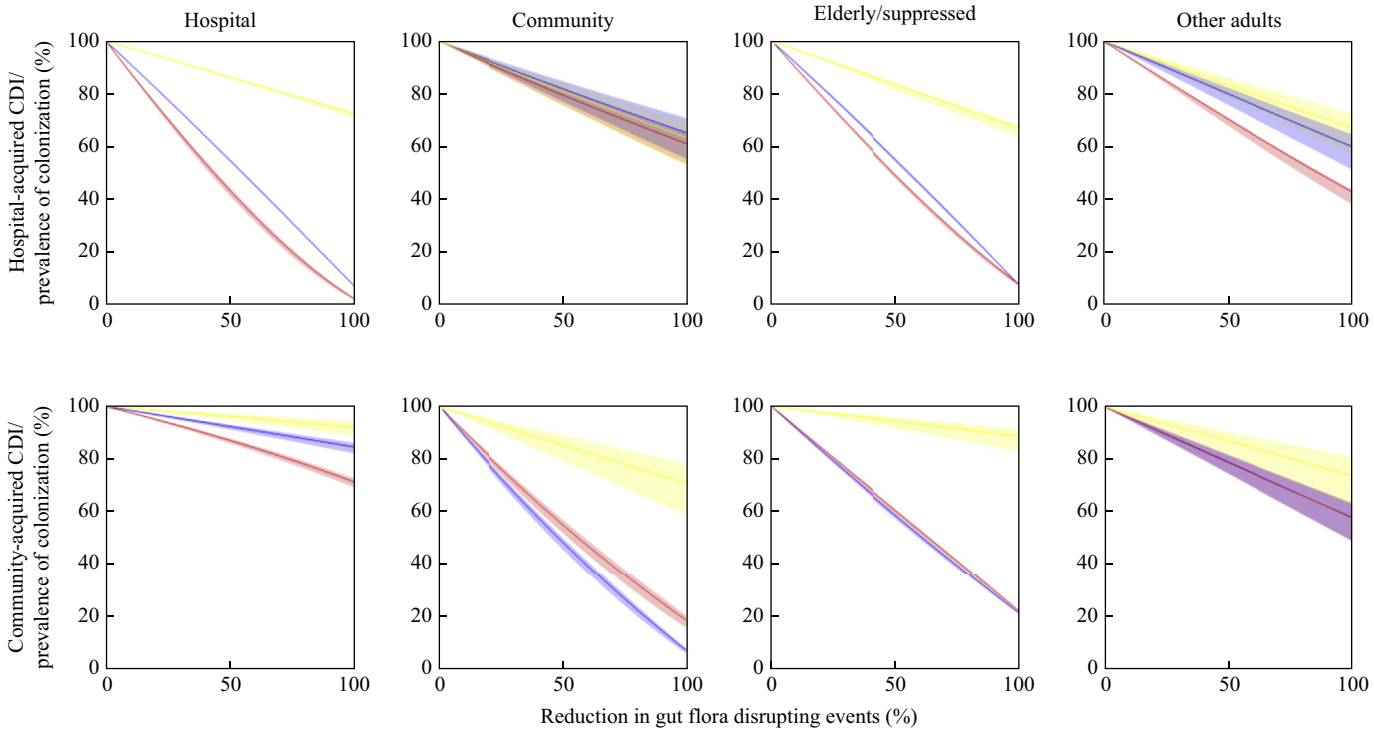

Figure 3. Comparison of the effect in the hospital (top row) and community (bottom row) of a reduction in antibiotic prescriptions to various overlapping target populations (columns). Each row displays reductions in infections acquired in that setting, and the prevalence of all colonization (yellow) in that setting (including colonizations acquired in the other setting). The actual reductions (red) and the apparent reductions (blue) in the incidence of infection differ due to misclassification of cases as hospital- or community-acquired. The shaded region around each line indicates the range in the sensitivity analysis for infant infectiousness. Purple and brown shaded regions indicate overlapping sensitivity analysis ranges. The general prevalence of colonization in adults is 5%. See Figure B.2 (Appendix B, online supplementary material) for further sensitivity analyses.

colonization in the community. Longtin *et al*. screened hospital admissions for *C. difficile* colonization as part of an intervention to reduce transmission from asymptomatically colonized patients [37]. Their unpublished results suggest that the prevalence of colonization on admission is not significantly seasonal (personal communication). Although hospital admissions may not be entirely representative of the community, this observation suggests that seasonal variation in transmissibility and susceptibility is minor, and that *C. difficile* seasonality is largely driven by antibiotics. However, seasonal mechanisms affecting transmissibility or susceptibility cannot be ruled out without further study into seasonality of the prevalence of colonization in the community.

Many antibiotic prescriptions for seasonal respiratory tract infections are clinically inappropriate [38], so some of the excess prescriptions in winter months could be avoided with improved prescribing practices. The model suggests that halving excess seasonal prescriptions would decrease the annual incidence of CDI by 8–16%, which is equivalent to approximately 36,000–72,000 infections per year in the USA alone [31].

In the model, reducing hospital-based transmission alone had a small effect on the incidence of community-acquired cases. Moreover, the systematic misclassification of community-acquired cases as hospital-acquired cases meant that only a fraction of those cases classified as hospital-acquired could be prevented by reducing hospital-based transmission. Consequently, the true proportion of hospital-acquired cases prevented by reducing a given amount of hospital-based transmission was approximately twice the apparent reduction. Importantly, even if the complete prevention of transmission within hospitals could be achieved, misclassification would maintain the appearance of continuing within-hospital transmission.

On the other hand, modest reductions in transmission in the community were found to reduce incidence dramatically, and could even interrupt transmission. This is in agreement with the only other modelling article to address this topic, which found that the incidence of CDI was more responsive to changes in community-based transmission than hospital-based transmission [17]. In practice, targeted interventions may be more achievable than community-wide improvements in hygiene. This study found that reducing transmission from symptomatic patients in hospitals and communities would only lead to small reductions in incidence. On the other hand, it was estimated that halving transmission from recent recipients of antibiotics would reduce the incidence of hospital- and community-acquired CDI by half (SA 24–86%) and one-sixth (SA 4–66%), respectively. Encouraging patients taking antibiotics (who are mostly unaware of the association between antibiotics and CDI [46]) to adopt improved hygiene has the potential to reduce the transmission of *C. difficile* and other pathogens to and from these patients, so this may underestimate the true effect. Remarkably, this study found that reducing transmission from asymptomatically colonized infants by as little as 30% could be sufficient to eliminate infections and colonization from the entire population. However, the required reduction was highly sensitive to the uncertain relative infectiousness of infants and adults. Although a high prevalence of colonization in infants is well established [29,30,40], there has been little research investigating transmission from infants [41–45], and the proportion of transmission attributable to infants is unknown. A greater understanding of the contribution of infants should be a research priority.

The study model suggested that year-round reductions in antibiotic prescriptions in the hospital or in the community would lead to approximately proportional reductions in infections in the same setting. In agreement with a recent meta-analysis, most of the improvement was attributable to the reduction of prescriptions to elderly or immunosuppressed individuals [47]. However, no plausible reduction in antibiotic consumption was enough to interrupt transmission in the hospital or community. Therefore, antimicrobial stewardship should be combined with interventions to reduce transmission in the community.

There is evidence of *C. difficile* transmission between human and livestock populations [48], and that contamination of meat products with *C. difficile* may be seasonal [49]. It has been shown previously that if the proportion of infections attributable to animals is sufficiently high (>3.5–26.0%), preventing transmission from animals could eliminate all CDI in humans [28,50]. However, the proportion of human infections that are attributable to direct or indirect transmission from livestock is unknown. Therefore, the model does not account for this source of transmission or capture its seasonality. This omission may mean that the model overestimated the impact of reducing person-to-person transmission.

Another limitation of this study is that the model does not distinguish between strains of *C. difficile* [51] or differentiate between antibiotics with different risk profiles for CDI [26]. This may influence the analysis of *C. difficile* seasonality and the effect of reducing prescription rates. A 40% reduction in fluoroquinolone prescriptions in the UK coincided with near elimination of CDI caused by fluoroquinolone-resistant strains [19]. This non-linear effect contrasts with the authors' prediction of proportional reduction, but could be due to concurrent improvements in transmission control [52], other strain-specific factors, or strain competition factors that were not captured in the model.

This analysis supports the hypothesis that seasonal prescription of antibiotics is the main driver of seasonal CDI. Further research into seasonality of the prevalence of colonization in the community and the extent of transmission from animals could clarify the role of seasonal transmissibility, susceptibility or exposure to livestock reservoirs. The authors have provided an estimate of the potential gains for *C. difficile* control that could be achieved by reducing inappropriate seasonal antibiotic prescriptions. The model supports the use of antimicrobial stewardship to reduce infections, but highlights the need to explore interventions to reduce transmission from the large population of asymptomatically colonized individuals in the community.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.03.001.

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