# **Understanding the impact of interventions to prevent antimicrobial resistant infections**

**in the long-term care facility; a review and practical guide to mathematical modelling**

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#### **Abstract**

#### *Objectives*

To i) systematically search for all dynamic mathematical models of infectious disease transmission in long-term care facilities (LTCFs); ii) critically evaluate models of interventions against antimicrobial resistance (AMR) in this setting; and iii) develop a checklist for hospital epidemiologists and policy makers to distinguish good quality models of AMR in LTCFs.

### *Methods*

The CINAHL, EMBASE, Global Health, MEDLINE and Scopus databases were systematically searched for studies of dynamic mathematical models of LTCFs. Models of interventions targeting methicillin-resistant *Staphylococcus aureus* in LTCFs were critically assessed. From this we developed a checklist for good quality mathematical models of AMR in LTCFs.

# *Results and discussion*

Eighteen papers described mathematical models that characterised the spread of infectious diseases in LTCFs, with no models of AMR in Gram-negative bacteria in this setting. Future models of AMR in LTCFs require a more robust methodology (ie. formal model fitting to data and validation); greater transparency regarding model assumptions; setting-specific data; more realistic and current setting-specific parameters; and inclusion of movement dynamics between LTCFs and hospitals.

#### *Conclusions*

There is a need to develop mathematical models of AMR in Gram-negative bacteria in the LTCF setting, where these bacteria are increasingly becoming prevalent, to help guide infection prevention and control. Improvements in model parameterisation, fitting and validation are required to develop outputs of sufficient quality to help guide interventions and policy in the future. We suggest a checklist of criteria to be used as a practical guide to determine whether a model is robust enough to test policy.

#### **Introduction**

Dynamic mathematical models have proved to be important tools in epidemiology and public health. They are used to understand the epidemiology of infectious diseases (ID), target interventions appropriately and evaluate their health and economic impact. $1-4$  ID transmission has been modelled extensively in the hospital setting for these purposes.<sup>5</sup>

Likewise, mathematical modelling has the potential to provide insight into the transmission of infections in long-term care facilities (LTCF), otherwise known as care homes or nursing homes.<sup>6,7</sup> In particular, LTCFs have been shown to be an important reservoir of antimicrobial-resistant bacteria.<sup>7-13</sup> Like hospitals, LTCFs form enclosed environments and LTCF residents are more likely than the general population to be older, frailer individuals with chronic conditions which might warrant invasive devices such as catheters and frequent visits to hospitals, which increases their risk of contracting infections.<sup>14</sup> However, LTCFs offer further opportunities for ID transmission than hospitals through many more shared objects and spaces, higher contact between residents and longer lengths of stay, which favour prolonged exposure to the organisms residents might be carrying.<sup>15-17</sup> Hence, existing insights from mathematical models of ID transmission in the hospital may not apply in LTCFs.

Dynamic mathematical models describe changes in processes over time.<sup>1</sup> One of these processes is infection in a population. Infectious disease population dynamic models generally represent changes in infection states (e.g. being susceptible to infection, being infected or being infectious). Changes between these states depend on parameters that vary

over time. These models can be either deterministic or stochastic and either individual-based or compartmental. In a deterministic model, the output of the model is simply determined by its parameters and, as such, the model output remains the same every time the model is run. Stochastic models, however, take into account randomness or variations which might occur by chance, producing different model outputs every time they are run.<sup>1,3</sup> Compartmental models group individuals into categories (e.g. infectious individuals). All individuals in one category are assigned the same set of parameter values. They then transition through infectious states as groups. Individual-based models (IBMs), however, model individuals as separate entities and infection states are recorded for each individual.<sup>1,2</sup> Ideally, models should be fit against empirical data to make them more realistic. This is achieved through the statistical calibration of model parameters.<sup>5</sup> Sensitivity analyses explore the impact of varying parameter values on model outputs. This could also encompass the sensitivity of the model outputs to assumptions surrounding the biology of the infection and transmission which might impact on the model structure. They are important to check for errors in models, test their robustness, increase our understanding of the underlying dynamics and determine uncertainty in model parameters, structure and, therefore, in the outputs. <sup>5</sup> Validation involves comparing the model output to a second dataset.<sup>5</sup>

Dynamic mathematical models allow better interpretation of the long-term impact of any intervention that aims to prevent infection by resistant bacteria in LTCFs than static models, as patient movement dynamics are complex and their impact on control measures are not intuitive. Elderly residents in LTCFs are frequently admitted directly from their LTCF into a hospital and then discharged from the hospital back to the  $LTCF<sup>18</sup>$ . This process may occur repeatedly and is known as the "revolving door syndrome". <sup>14</sup> Patients might acquire infections or be colonised by resistant strains of bacteria present in hospitals which they may then transmit to other residents upon their return to the LTCF. In this scenario, infection

control measures in LTCFs may fail to decrease the prevalence of infection due to the constant re-admission of infected or colonised residents to hospital coupled with high rates of transmission within LTCFs. Infection control measures in hospitals could also be hampered by this amplification of transmission through LTCFs. The "revolving door syndrome" can be simulated using a dynamic mathematical model which incorporates transmission and patient movement.

A previous systematic review of the area focused solely on transmission of healthcare associated infections (HCAI) and antimicrobial resistance (AMR) within the hospital setting<sup>5</sup>. To our knowledge, no systematic review of mathematical models of infectious disease transmission in LTCFs has been conducted. When using mathematical models to inform policy at a local or national level there is a growing consensus as to what is desirable in model design, parameterisation and reporting.<sup>19,20</sup> Despite this, there is no practical guide summarising best practice for clinicians, infection control specialists or policy makers working in LTCFs who need to interpret the validity of findings from mathematical modelling in this setting to aid decision-making.

In this paper we systematically search the published peer reviewed literature that described any dynamic mathematical models relating to infectious disease transmission in long-term care facilities (LTCFs); critically evaluate the methods employed to model interventions against MRSA in this setting; identify ideal practice and, from that, propose a checklist to help infection control specialists and policy makers discern good quality models of AMR in the LTCF setting on which decision-making can be based.

#### **Methods**

The CINAHL, EMBASE, Global Health, MEDLINE and Scopus databases were systematically searched for studies of dynamic mathematical models of LTCFs on the 27<sup>th</sup> of December 2013. This search was then updated on the  $19<sup>th</sup>$  of February 2016 using the same search criteria. The full description of the search strategy is provided in Appendix A. Abstract and titles that included terms relating to "model" AND "long-term care facility" AND "mathematical" were read. All peer reviewed dynamic mathematical models describing infectious disease transmission in LTCFs written in English were included. Those describing animal work, statistical models and within-host models were excluded. We summarised the methods and research themes of the selected 18 papers.

We critically compared all models that explicitly evaluated interventions to reduce resistant bacterial infections in LTCFs. Models that explored altering transfer rates between hospitals and LTCFs were not included as this was not considered a realistic intervention. Three models targeted their interventions against MRSA in LTCFs. Using the criteria obtained from this critical evaluation; a checklist was developed that will enable clinicians and other decision-makers to appraise mathematical models of AMR in LTCFs.

#### **Results and discussion**

### *Evidence base of mathematical modelling in LTCFs*

A full description of results of the systematic search is provided in Appendix A. One thousand and sixty seven abstracts were screened and 23 papers were read in full text. Eighteen papers examined 15 different dynamic models of infectious disease transmission in LTCFs (see Figure 1 and Figure  $2)^{21-38}$ . Six papers simulated the transmission of AMR in LTCFs<sup>21-24,26,34</sup>. Of these, five described MRSA transmission<sup>21-24,34</sup>, one described a generic non-species-specific resistant bacteria<sup>26</sup> and none quantified the transmission of resistant Gram-negative bacteria. A more detailed description of the structure and purpose of each of the models is provided in the Appendix A.

#### *Gaps identified in the literature*

Very few mathematical models have characterised the spread of infectious diseases in LTCFs. The scope of the organisms studied is also limited. Although one study has modelled resistant Gram-negative bacteria in long-term acute care hospitals<sup>39</sup>, none has modelled resistant Gram-negative bacteria in the LTCF setting. These organisms are increasingly becoming problematic in hospitals and LTCFs and interventions to prevent their spread are being trialled<sup>40–43</sup>. In addition, more solid methodology that is fully described is required. Ideally, models should be made available as open source code online. This would provide greater transparency of the assumptions underlying the model and allow models to be reproduced or adapted. Models should be formally fit to data to estimate transmission parameters with greater certainty, and the full uncertainty surrounding the parameters should

be presented. If possible, models should be validated through other available data to allow the generalisability of their findings to be ascertained.

#### *How have interventions been modelled?*

#### *1) Comparison of results of interventions: results from MRSA models*

Three papers have assessed interventions against  $MRSA^{34,21,23}$  in LTCF settings. They found four interventions to be effective in reducing MRSA prevalence: screening and decolonisation, hand hygiene, contact precautions and increasing the staff to patient ratio. Figure 3 describes the interventions assessed, how their action was simulated in the model and the results observed. A detailed description of each intervention studied is provided in Appendix B.

The model pathways that are targeted by an intervention, the parameters associated with it and the assumptions behind it are important because they determine the likely outcome of the intervention. Screening and decolonisation reduces the prevalence of colonisation by moving patients from a colonised state (for Barnes et al.<sup>34</sup>, both persistently colonised and transiently colonised) to a susceptible state (uncolonised). Transmission is also reduced as the pool of infectious individuals is decreased. The other three interventions only prevent or decrease the probability of transmission. In this case, interventions will take longer to reduce the prevalence of colonisation if there are frequently patients admitted to the LTCF who are colonised on admission. The impact of MRSA interventions on a generic susceptibleinfected-susceptible (SIS) model structure is depicted in Figure 4.

#### *2) Realism of models and parameters used*

*a) Dates, setting and methodology*

The models that assessed interventions against  $MRSA^{34,21,23}$  in LTCFs were recent (2011-2013), however, some parameters used by Barnes et al.<sup>34</sup> and Chamchod and Ruan<sup>21</sup> were based on older estimates which might be outdated. Chamchod and Ruan's<sup>21</sup> model only involved one LTCF and neglected the "revolving door syndrome" of patient transfer between hospital and LTCF which might be important in driving transmission. Lee et al.'s IBM model<sup>23</sup> was the most complex, incorporating LTCF, hospital and community settings and accounting for stochasticity. Barnes et al.'s model<sup>34</sup> was the simplest, a deterministic compartmental model.

#### *b) Model structure*

Patients were assumed to mix homogeneously within LTCFs across all models. A particular strength of the model developed by Lee et al., was that it used data to parameterise patient flow between healthcare facilities, where the other models did not. Barnes et al. differentiated between persistently and transiently colonised individuals. Evidence for these different types of colonisation by *S. aureus* is mixed<sup>44</sup>. Chamchod and Ruan<sup>21</sup> and Lee et al.<sup>23</sup> distinguished, respectively, between healthcare workers and residents and between residents taking contact precautions and residents that did not, adapting the disease states in their model to fit the questions addressed.

### *c) Parameter validity, estimation and uncertainty*

Table 1 summarises the key parameters used by Barnes et al.<sup>34</sup>, Chamchod and Ruan<sup>21</sup> and Lee et al.<sup>23</sup>. The parameters used by the models, including the LTCF size, the transmission rates, the prevalence of colonisation and the duration of colonisation were very different in different models and often involved different units of measurement that did not allow for comparison across models. In addition, many parameter estimates were based on expert opinion instead of data, which compromised the quality of the models.

Some factors, such as antibiotic prescription, were not simulated by any of these models. Antibiotic prescribing is a main driver of resistance. It increases the risk of colonisation and subsequent infection by resistant bacteria. Antibiotic stewardship is, therefore, a very important strategy to reduce antibiotic resistance and should be one of the main interventions modelled<sup>45</sup>. However, antibiotic prescribing data for LTCFs is scarce and therefore unavailable to incorporate into models.

The three research groups chose different sizes of LTCFs, ranging from 100 beds<sup>34</sup> to  $2000^{21}$ . However, the average number of beds in care homes registered in England by the Care Quality commission (the regulator of health and social care in England) on the 01/04/2014 was 37 beds<sup>46</sup>. Only 1.3% (116) of care homes are able to cater for over 100 residents and the largest registered LTCF had 215 residents. In the USA, the average nursing home size was 106 beds (ranging from 2 to 1,389) and the average capacity was 38 beds (ranging from 4 to  $582$ <sup>47</sup>. A LTCF with 2000 residents<sup>21</sup> is, therefore, highly implausible in the English and American settings.

No models estimated MRSA transmission parameters directly from appropriately collected LTCF datasets. This meant that each of the parameters were taken from the literature and contained untested assumptions. For example, Chamchod and  $Run<sup>21</sup>$  assumed residentresident transmission was eight times lower than that between healthcare workers and residents and Barnes et al. $^{34}$  and Lee et al. $^{23}$  assumed that transmission rates for hospitals were much higher than those for LTCFs.

Other assumptions, such as that the prevalence of MRSA on admission being broadly equal to the population prevalence of MRSA in the USA $^{34,21}$ , 10% $^{48}$ , may be incorrect as age is a risk factor for MRSA infection<sup>49–52</sup> or may not be generalisable across settings. For example, Lee et al. estimated LTCF MRSA prevalence at 26.1%, which is in line with most of the

published literature (21% in Leeds, 23% in Northern Ireland,17% in Spain and 22% in Hong Kong 53–55). Studies carried out in USA LTCFs, however, have shown double this prevalence  $(59\%$  and 40% respectively)<sup>56,57</sup>.

#### *d) Interventions*

Barnes et al. $34$  and Chamchod and Ruan<sup>21</sup> did not clearly report their intervention outcomes and their relevance for clinical practice was not easy to interpret. Barnes et al.<sup>34</sup> reported prevalence at equilibrium (a theoretical state of model stability) in numerical and graphical form whilst Chamchod and Ruan<sup>21</sup> reported prevalence at equilibrium only in graphical form. For this reason, it was only possible to derive the threshold at which an intervention would eliminate MRSA at equilibrium prevalence or eliminate the probability of invasion. More usefully, Lee et al.<sup>23</sup> reported the median percentage decrease in MRSA prevalence at equilibrium and, in addition, calculated the acquisitions of MRSA adverted under certain adherence conditions, which facilitated interpretation.

Overall, Barnes et al.<sup>34</sup> and Chamchod and Ruan<sup>21</sup> described the assumptions related to the interventions they modelled in very little detail. Barnes et al. $34$  assumed that, on average, two cycles of five-day "decolonisation" treatments were necessary for patients to be successfully decolonised (10 days). After these 10 days, therefore, the intervention was assumed to be 100% effective. Neither the adherence to this protocol, nor the impact of this assumption on the results were reported. Chamchod and  $Run<sup>21</sup>$  merely reported the thresholds of decolonisation rate, duration of colonisation and resident to staff ratio reduction that were necessary to eliminate the equilibrium of prevalence and the probability of invasion. They did not report the effectiveness, adherence or time necessary for the interventions to be successful in achieving these thresholds and did not propose a realistic intervention to reduce the

resident to staff ratio. Therefore, the results from these analyses could not be used to inform policy as their validity cannot be judged.

In contrast, Lee et al.<sup>23</sup> assessed the effect of contact precautions in LTCFs under three different levels of adherence (25%, 50% and 75%). This allowed comparison across a spectrum of scenarios which were realistically parameterised when compared to the literature<sup>58,59</sup>. Their findings were also comparable to that modelled within hospitals, suggesting that focusing interventions on the small minority of clinically apparent MRSA cases will be ineffective<sup>60</sup>. Therefore, the findings from this study are more robust compared to the two other papers. However, this model was not formally fit to data and assumed that transmission was much higher in hospitals than in LTCFs, without appropriate sensitivity analysis to examine the impact of this assumption, therefore, we do not consider this model appropriate to inform policy.

#### *e) Summary and critical evaluation*

The results from the critical appraisal are summarised below in Table 2. The choice of design was justified in all three papers and the importance of the question was made clear in the introductions. Barnes et al.<sup>34</sup> and Lee et al.<sup>23</sup> set clearly focused questions and aims for their paper. In contrast, Chamchod and Ruan<sup>21</sup> set broad objectives and the evaluation of the interventions was purely theoretical and derived from the model behaviour a-posteriori<sup>21</sup>.

Chamchod and Ruan<sup>21</sup> only presented their outcomes in graphical form which made comparison with other studies challenging. Model assumptions governing structure and transmission were made explicit but the assumptions behind interventions were often not explained. None of the models were formally fit to data or validated, which reduced their credibility. Most of the parameters employed in these three studies were chosen from the

literature. Those chosen from older literature might be out-dated. Some of these were based on data but some were based on expert opinion.

#### *What makes a good mathematical model for the evaluation of interventions?*

Dynamic mathematical models of infectious disease transmission are important tools that can help understand the impact of interventions in facilities such as hospitals and LTCFs. We have developed a practical guide in the form of checklist that can be used by infection control specialists and policy makers for the appraisal of mathematical models of AMR in LTCFs (Table 3). Appropriate models for policymaking should define their setting and methods and neither neglect the influence of hospital visits by LTCF residents (the "revolving door syndrome") on driving transmission in LTCFs nor neglect the influence of LTCFs on hospital transmission, as LTCF residents are very frequently admitted to hospitals<sup>18</sup>. Models should also employ formal fitting techniques and carry out sensitivity analyses and validation (if an auxiliary dataset is available) to ensure the model accurately represents the data and is sufficiently robust to produce sound conclusions. They should also address stochasticity in some form as resistant infections in LTCFs, which are small contained environments, are heavily influenced by chance events. Haverkate et al.<sup>61</sup> and Obadia et al.<sup>62</sup> have applied these methods to the analysis of transmission of *Klebsiella pneumoniae* carbapenamase-producing bacteria in long-term acute care hospitals and the transmission of *Staphylococcus aureus* in long-term care hospitals, respectively. Model parameters should be, as far as possible, based on recent data from the particular setting and organism investigated. In addition, results should be made available in numeric form to facilitate comparison across studies. Multiple examples of these good quality models that have evaluated interventions in the hospital setting can be found in the literature<sup>63</sup>.

It is challenging to parameterise mathematical models of AMR transmission in the LTCF setting. Firstly, these facilities vary considerably in their patient populations, sizes and in the type of care they provide. In addition, many epidemiological parameters in this setting are still unknown and there is little data available for fitting and validation purposes. However, it is increasingly becoming apparent that the threat of AMR is an important concern in LTCFs; therefore, robust models that will guide policymaking in this area are necessary. There is room for improvement in the description of MRSA transmission and control in LTCFs through mathematical modelling as the models assessed above are not considered robust enough to test policy. In addition, as infections by Gram-Negative bacteria become more frequent in both hospitals and LTCFs, there is an urgent need for models that simulate their transmission in these settings. Further research is needed to validate the checklist proposed. Future work should also focus on understanding the effectiveness of decolonisation in the LTCF setting and the impact of antibiotic prescribing on the carriage of resistant bacteria.

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#### **Figure legends**

**Figure 1. Flow chart of the review process.** One thousand five hundred and sixty two records were identified through the CINAHL, EMBASE, Global Health, MEDLINE and Scopus databases. After all duplicates were removed, 1,046 records were excluded through abstract screening, seven full-text articles were excluded through full-text assessment, two additional papers were identified through reference searching and two more through in an updated search on the 19/02/16. Eighteen papers were selected for review.

**Figure 2. Infectious disease modelling in LTCFs: publications per year.** Nine papers modelled influenza (five seasonal, three pandemic and one both); five papers methicillinresistant *Staphylococcus aureus* (MRSA); two papers norovirus; one paper antimicrobial resistant (AMR) bacterial transmission and one paper non-species-specific bacterial transmission (bacteria in healthcare (HC)). Two papers on the same model were published in 1993. There were no further publications until 2003. From 2003 there have been a low but regular number of publications on this subject.

**Figure 3. Assessing the effects of interventions against MRSA in LTCFs through modelling.** Three papers have published models of interventions against *methicillin-resistant Staphyloccocus aureus* (MRSA) in long-term care facilities (LTCFs). The models have assessed five types of interventions in this setting. Two reduced the probability of transmission, one reduced the prevalence of colonisation and one reduced the contact rate. The results from the interventions modelled are shown on the right.

# **Figure 4. Impact of MRSA interventions on a generic susceptible (S) –colonised (C) susceptible (S) model structure in the long-term care facility (LTCF).** Whilst hand hygiene, increase of staff to patient ratio and contact precaution decrease the rate of colonisation, screening and decolonisation interventions reduce the prevalence of colonisation, therefore increasing the rate of decolonisation.

**Table 1. Comparison of key parameters used by Barnes et al. (2011)**<sup>64</sup>**, Chamchod and Ruan (2012)**<sup>21</sup> **and Lee et al. (2013)**<sup>23</sup> **.** 

	Barnes et al.	Chamchod and	Lee et al.
	(2011)	Ruan	(2013)
		(2012)	
Size of institution	300 for hospitals,	2000	$228.6$ (mean) for
(beds)	100 for LTCFs and		hospital and 108.6
	20 for hospital		(mean) for LTCFs
	units		
Transmission rate	$0.15$ (low), $0.25$	$0.015$ (resident-	$0.0099a$ (mean) for
parameter $(\beta)$	$(medium)$ , 0.35	resident), 0.12	hospital and
	(high) for hospitals	(healthcare worker	$0.000082*$ (mean) for
	and hospital units.	to resident) and	<b>LTCFs</b>
	$0.05$ (low), $0.075$	0.12 (resident to	
	(medium) and 0.1	healthcare worker)	
	(high) for LTCFs.		
Proportion/probability	10% for both	10%	$6.1\%$ (mean) for
of patients admitted	facilities		hospital and 26.1%
colonised/MRSA			(mean) for LTCF
prevalence			
Duration of	5 for transiently	60/80	
colonisation (days)	colonised and 50		
	for persistently		



<sup>a</sup>rate of transmission per person per day (vs. effective contact (resulting in transmission) rate

averaged per day)

LTCF: long-term care facility.

# **Table 2. Critical appraisal of Barnes et al. (2011)**<sup>34</sup>**, Chamchod and Ruan (2012)**<sup>21</sup> **and Lee et al. (2013)**<sup>23</sup> **.**









LTCF: long-term care facility

MRSA: methicillin-resistant *Staphylococcus aureus*

# **Table 3. Checklist for the critical appraisal of mathematical models of AMR bacteria in**

**LTCFs.** Ideally all high importance criteria should be addressed in a high quality model to permit the evaluation of interventions, generate and test hypotheses, and explore long term scenarios of AMR transmission and control in LTCFs. For the evaluation of interventions where a high level of certainty is required from clinicians or policy makers, all high importance criteria should be present in models. In both cases, medium and low importance criteria increase the quality of the model.









LTCF: long-term care facility

ID: infectious disease

AMR: antimicrobial resistance