This article has been accepted for publication and will appear in a revised form, subsequent to peer review and/or editorial input by SHEA in Infection Control & Hospital Epidemiology published by Cambridge University Press.

Understanding the impact of interventions to prevent antimicrobial resistant infections in the long-term care facility; a review and practical guide to mathematical modelling

Alicia Rosello, MPH;*[1,2] Carolyne Horner, PhD;[3] Susan Hopkins, FRCP;[4,5] Andrew C. Hayward, Prof;[1] Sarah R. Deeny, PhD.[2,6]

[1]Institute of Health Informatics, Farr Institute of Health Informatics Research, UCL, London, UK

[2]Modelling and Economics Unit, National Infection Service, Public Health England, London, UK

[3]Regional Laboratory Leeds, Public Health England, Leeds, UK

[4]Healthcare Associated Infections Surveillance, National Infection Service, Public Health England, London, UK

[5]Department of Infectious Diseases and Microbiology, Royal Free London NHS Foundation Trust, London, UK

[6]Data analytics, The Health Foundation, London, UK

Corresponding author:

Alicia Rosello

Modelling and Economics Unit, National Infection Service, Public Health England

61 Colindale Ave, London. NW9 5EQ

T: 02083277148

Email: alicia.rosello@phe.gov.uk

Abbreviated title: Mathematical modelling in LTCFs

Word count: 3,131

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.[5]

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.[6,7] In particular, LTCFs have been shown to be an important reservoir of antimicrobial-resistant bacteria.[7–13] 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.[14] 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.[15–17] 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.[1] 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.[1,3] 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.[1,2] Ideally, models should be fit against empirical data to make them more realistic. This is achieved through the statistical calibration of model parameters.[5] 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.[5] Validation involves comparing the model output to a second dataset.[5]

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[18]. This process may occur repeatedly and is known as the "revolving door syndrome". [14] 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[5]. 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.[19,20] 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 27th of December 2013. This search was then updated on the 19th 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 [21–24,26,34]. Of these, five described MRSA transmission[21–24,34], one described a generic non-species-specific resistant bacteria[26] 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[39], 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[40–43]. 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.[34], 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 susceptible-infected-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.[34] and Chamchod and Ruan[21] were based on older estimates which might be outdated. Chamchod and Ruan's[21] 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[23] was the most complex, incorporating LTCF, hospital and community settings and accounting for stochasticity. Barnes et al.'s model[34] 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[44]. Chamchod and Ruan[21] and Lee et al.[23] 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.[34], Chamchod and Ruan[21] and Lee et al.[23]. 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[45]. 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[34] 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[46]. 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)[47]. A LTCF with 2000 residents[21] 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 Ruan[21] assumed resident-resident 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[49–52] 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)[56,57].

d) Interventions

Barnes et al.[34] and Chamchod and Ruan[21] did not clearly report their intervention outcomes and their relevance for clinical practice was not easy to interpret. Barnes et al.[34] reported prevalence at equilibrium (a theoretical state of model stability) in numerical and graphical form whilst Chamchod and Ruan[21] 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.[23] 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.[34] and Chamchod and Ruan[21] 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 Ruan[21] 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.[23] 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[58,59]. 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[60]. 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.[34] and Lee et al.[23] set clearly focused questions and aims for their paper. In contrast, Chamchod and Ruan[21] set broad objectives and the evaluation of the interventions was purely theoretical and derived from the model behaviour a-posteriori[21].

Chamchod and Ruan[21] 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[18]. 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.[61] and Obadia et al.[62] 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[63].

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.

Acknowledgments

This work was funded by Public Health England. All authors report no conflict of interest relevant to this article.

References

1 Vynnycky E, White R. An introduction to Infectious Disease Modelling. New York: Oxford University Press, 2010.

2 Opatowski L, Guillemot D, Boëlle P-Y, Temime L. Contribution of mathematical modeling to the fight against bacterial antibiotic resistance. *Curr Opin Infect Dis* 2011; **24**: 279–87.

3 Doan TN, Kong DCM, Kirkpatrick CMJ, McBryde ES. Optimizing Hospital Infection Control: The Role of Mathematical Modeling. *Infect Control Hosp Epidemiol* 2014; **35**: 1521–30.

4 Bonten MJM, Austin DJ, Lipsitch M. Understanding the Spread of Antibiotic Resistant Pathogens in Hospitals: Mathematical Models as Tools for Control. *Clin Infect Dis* 2001; **33**: 1739–46.

5 van Kleef E, Robotham J V, Jit M, Deeny SR, Edmunds WJ. Modelling the transmission of healthcare associated infections: a systematic review. *BMC Infect Dis* 2013; **13**: 294.

6 Nicolle LE. Infection control in long-term care facilities. *Clin Infect Dis* 2000; **31**: 752–6.

7 European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European long-term care facilities. Stockholm, 2014 http://ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-point-prevalence-survey-long-term-care-facilities-2013.pdf.

8 Ludden C, Cormican M, Vellinga A, Johnson JR, Austin B, Morris D. Colonisation with ESBL-producing and carbapenemase-producing Enterobacteriaceae, vancomycin-resistant enterococci, and meticillin-resistant Staphylococcus aureus in a long-term care facility over one year. *BMC Infect Dis* 2015; **15**: 168.

9 Lim CJ, Cheng AC, Kennon J, *et al.* Prevalence of multidrug-resistant organisms and risk factors for carriage in long-term care facilities: a nested case-control study. *J Antimicrob Chemother* 2014; **69**: 1972–80.

10 Mavroidi A, Miriagou V, Malli E, *et al.* Emergence of Escherichia coli sequence type 410 (ST410) with KPC-2 β-lactamase. *Int J Antimicrob Agents* 2012; **39**: 247–50.

11 Centres for Disease Control and Prevention. Carbapenem-Resistant Klebsiella pneumoniae Associated With a Long-Term-Care Facility—West Virginia, 2009-2011. *Ann Emerg Med* 2012; **59**: 434–6.

12 van Buul LW, van der Steen JT, Veenhuizen RB, *et al.* Antibiotic use and resistance in long term care facilities. *J Am Med Dir Assoc* 2012; **13**: 568.e1–13.

13 U.S. Department of Health & Human Services. National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination. 2013. http://www.health.gov/hai/pdfs/hai-action-plan-cover-toc.pdf (accessed Sept 16, 2014).

14 Care Quality Commission. Working together to prevent and control infections. A study of the arrangements for infection prevention and control between hospitals and care homes. 2009 http://www.suffolkextranet.nhs.uk/LinkClick.aspx?fileticket=C17XcO4fBO8%3D&tabid=1994&mid=5126.

15 Smith PW, Bennett G, Bradley S, *et al.* SHEA/APIC Guideline: Infection prevention and control in the long-term care facility. *Am J Infect Control* 2008; **36**: 504–35.

16 Forder J, Fernandez J-L. Length of stay in care homes, Report commissioned by Bupa Care Services, PSSRU Discussion Paper 2769. Canterbury: PSSRU, 2011.

17 Hospital Episode Statistics Analysis (Health and Social Care Information Centre). Hospital Episode Statistics. Admitted Patient Care, England - 2013-14. 2015 http://www.hscic.gov.uk/catalogue/PUB16719/hosp-epis-stat-admi-summ-rep-2013-14-rep.pdf.

18 Smith P, Sherlaw-Johnson C, Ariti C, Bardsley M. Focus on: Hospital admissions from care homes. 2015 http://www.health.org.uk/sites/default/files/QualityWatch_FocusOnHospitalAdmissionsFromCareHomes.pdf.

19 Bilcke J, Beutels P, Brisson M, Jit M. Accounting for methodological, structural, and parameter uncertainty in decision-analytic models: a practical guide. *Med Decis Making* 2011; **31**: 675–92.

20 Jit M, Levin C, Brisson M, *et al.* Economic analyses to support decisions about HPV vaccination in low- and middle-income countries: a consensus report and guide for analysts. *BMC Med* 2013; **11**: 23.

21 Chamchod F, Ruan S. Modeling the spread of methicillin-resistant Staphylococcus aureus in nursing homes for elderly. *PLoS One* 2012; **7**: e29757.

22 Lee BY, Bartsch SM, Wong KF, *et al.* The importance of nursing homes in the spread of methicillin-resistant Staphylococcus aureus (MRSA) among hospitals. *Med Care* 2013; **51**: 205–15.

23 Lee BY, Singh A, Bartsch SM, *et al.* The potential regional impact of contact precaution use in nursing homes to control methicillin-resistant staphylococcus aureus. *Infect Control Hosp Epidemiol* 2013; **34**: 151–60.

24 Lesosky M, McGeer A, Simor A, Green K, Low DE, Raboud J. Effect of patterns of transferring patients among healthcare institutions on rates of nosocomial methicillin-resistant Staphylococcus aureus transmission: A Monte Carlo simulation. *Infect Control Hosp Epidemiol* 2011; **32**: 136–47.

25 Nuno M, Reichert TA, Chowell G, Gumel AB. Protecting residential care facilities from pandemic influenza. *Proc Natl Acad Sci U S A* 2008; **105**: 10625–30.

26 Smith DL, Dushoff J, Perencevich EN, Harris AD, Levin SA. Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: Resistance is a regional problem. *Proc Natl Acad Sci U S A* 2004; **101**: 3709–14.

27 Van Den Dool C, Hak E, Bonten MJM, Wallinga J. A model-based assessment of oseltamivir prophylaxis strategies to prevent influenza in nursing homes. *Emerg Infect Dis* 2009; **15**: 1547–55.

28 van den Dool C, Bonten MJ, Hak E, Heijne JC, Wallinga J. The effects of influenza vaccination of health care workers in nursing homes: insights from a mathematical model. *PLoS Med* 2008; **5**. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed11&AN=18959470.

29 Simon CP, Percha B, Riolo R, Foxman B. Modeling bacterial colonization and infection routes in health care settings: Analytic and numerical approaches. *J Theor Biol* 2013; **334**: 187–99.

30 Ferguson NM, Mallett S, Jackson H, Roberts N, Ward P. A population-dynamic model for evaluating the potential spread of drug-resistant influenza virus infections during community-based use of antivirals. *J Antimicrob Chemother* 2003; **51**: 977–90.

31 Haber MJ, Shay DK, Davis XM, *et al.* Effectiveness of interventions to reduce contact rates during a simulated influenza pandemic. *Emerg Infect Dis* 2007; **13**: 581–9.

32 Ma JZ, Peterson DR, Ackerman E. Parameter sensitivity of a model of viral epidemics simulated with Monte Carlo techniques. IV. Parametric ranges and optimization. *Int J Biomed Comput* 1993; **33**: 297–311.

33 Vanderpas J, Louis J, Reynders M, Mascart G, Vandenberg O. Mathematical model for the control of nosocomial norovirus. *J Hosp Infect* 2009; **71**: 214–22.

34 Barnes SL, Harris AD, Golden BL, Wasil EA, Furuno JP. Contribution of interfacility patient movement to overall methicillin-resistant Staphylococcus aureus prevalence levels. *Infect Control Hosp Epidemiol* 2011; **32**: 1073–8.

35 Peterson D, Gatewood L, Zhuo Z, Yang JJ, Seaholm S, Ackerman E. Simulation of stochastic micropopulation models--II. VESPERS: epidemiological model implementations for spread of viral infections. *Comput Biol Med* 1993; **23**: 199–213.

36 Carrat F, Luong J, Lao H, Sallé A-V, Lajaunie C, Wackernagel H. A 'small-world-like' model for comparing interventions aimed at preventing and controlling influenza pandemics. *BMC Med* 2006; **4**: 26.

37 O'Dea EB, Pepin KM, Lopman BA, Wilke CO. Fitting outbreak models to data from many small norovirus outbreaks. *Epidemics* 2014; **6**: 18–29.

38 Wendelboe AM, Grafe C, McCumber M, Anderson MP. Inducing Herd Immunity

against Seasonal Influenza in Long-Term Care Facilities through Employee Vaccination Coverage: A Transmission Dynamics Model. *Comput Math Methods Med* 2015; **2015**: 178247.

39 Davies SC. Annual Report of the Chief Medical Officer, Volume Two, 2011. Infections and the rise of antimicrobial resistance. London, 2013.

40 Knudsen JD, Andersen SE. A multidisciplinary intervention to reduce infections of ESBL- and AmpC-producing, gram-negative bacteria at a University Hospital. *PLoS One* 2014; **9**: e86457.

41 Perez KK, Olsen RJ, Musick WL, *et al.* Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. *J Infect* 2014; **69**: 216–25.

42 Pogue JM, Mynatt RP, Marchaim D, *et al.* Automated alerts coupled with antimicrobial stewardship intervention lead to decreases in length of stay in patients with gram-negative bacteremia. *Infect Control Hosp Epidemiol* 2014; **35**: 132–8.

43 Tacconelli E, Cataldo MA, Dancer SJ, *et al.* ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. *Clin Microbiol Infect* 2014; **20 Suppl 1**: 1–55.

44 Shenoy ES, Paras ML, Noubary F, Walensky RP, Hooper DC. Natural history of colonization with methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE): a systematic review. *BMC Infect Dis* 2014; **14**: 177.

45 van Buul LW, van der Steen JT, Veenhuizen RB, *et al.* Antibiotic use and resistance in

long term care facilities. *J Am Med Dir Assoc* 2012; **13**: 568.e1–13.

46 Care Quality Commission. Active locations for providers registered under the Health and Social Care Act. CQC database at 1st April 2014. http://www.cqc.org.uk/.

47 Harris-Kojetin L, Sengupta M, Park-Lee E VR. Long-Term Care Services in the United States: 2013 Overview. 2013. http://www.cdc.gov/nchs/data/nsltcp/long_term_care_services_2013.pdf (accessed Sept 16, 2014).

48 Gorwitz RJ, Kruszon-Moran D, McAllister SK, *et al.* Changes in the prevalence of nasal colonization with Staphylococcus aureus in the United States, 2001-2004. *J Infect Dis* 2008; **197**: 1226–34.

49 Viallon A, Marjollet O, Berthelot P, *et al.* Risk factors associated with methicillin-resistant Staphylococcus aureus infection in patients admitted to the ED. *Am J Emerg Med* 2007; **25**: 880–6.

50 Bradley SF. Methicillin-resistant Staphylococcus aureus in nursing homes. Epidemiology, prevention and management. *Drugs Aging* 1997; **10**: 185–98.

51 Denkinger CM, Grant AD, Denkinger M, Gautam S, D'Agata EMC. Increased multi-drug resistance among the elderly on admission to the hospital--a 12-year surveillance study. *Arch Gerontol Geriatr* 2013; **56**: 227–30.

52 Laupland KB, Church DL, Mucenski M, Sutherland LR, Davies HD. Population-based study of the epidemiology of and the risk factors for invasive Staphylococcus aureus infections. *J Infect Dis* 2003; **187**: 1452–9.

53 Horner C, Parnell P, Hall D, Kearns A, Heritage J, Wilcox M. Meticillin-resistant

Staphylococcus aureus in elderly residents of care homes: colonization rates and molecular epidemiology. *J Hosp Infect* 2013; **83**: 212–8.

54 Baldwin NS, Gilpin DF, Hughes CM, *et al.* Prevalence of methicillin-resistant Staphylococcus aureus colonization in residents and staff in nursing homes in Northern Ireland. *J Am Geriatr Soc* 2009; **57**: 620–6.

55 Cheng VCC, Tai JWM, Wong ZSY, *et al.* Transmission of methicillin-resistant Staphylococcus aureus in the long term care facilities in Hong Kong. *BMC Infect Dis* 2013; **13**: 205.

56 Stone ND, Lewis DR, Lowery HK, *et al.* Importance of bacterial burden among methicillin-resistant Staphylococcus aureus carriers in a long-term care facility. *Infect Control Hosp Epidemiol* 2008; **29**: 143–8.

57 Mody L, Kauffman CA, Donabedian S, Zervos M, Bradley SF. Epidemiology of Staphylococcus aureus colonization in nursing home residents. *Clin Infect Dis* 2008; **46**: 1368–73.

58 Clock SA, Cohen B, Behta M, Ross B, Larson EL. Contact precautions for multidrug-resistant organisms: Current recommendations and actual practice. *Am J Infect Control* 2010; **38**: 105–11.

59 Manian FA, Ponzillo JJ. Compliance with routine use of gowns by healthcare workers (HCWs) and non-HCW visitors on entry into the rooms of patients under contact precautions. *Infect Control Hosp Epidemiol* 2007; **28**: 337–40.

60 Cooper BS, Medley GF, Stone SP, *et al.* Methicillin-resistant Staphylococcus aureus in hospitals and the community: stealth dynamics and control catastrophes. *Proc Natl Acad Sci U S A* 2004; **101**: 10223–8.

61 Haverkate MR, Bootsma MCJ, Weiner S, *et al.* Modeling Spread of KPC-Producing Bacteria in Long-Term Acute Care Hospitals in the Chicago Region, USA. *Infect Control Hosp Epidemiol* 2015; : 1–7.

62 Obadia T, Silhol R, Opatowski L, *et al.* Detailed contact data and the dissemination of Staphylococcus aureus in hospitals. *PLoS Comput Biol* 2015; **11**: e1004170.

63 Opatowski L, Guillemot D, Boëlle P-Y, Temime L. Contribution of mathematical modeling to the fight against bacterial antibiotic resistance. *Curr Opin Infect Dis* 2011; **24**: 279–87.

64 Barnes SL, Harris AD, Golden BL, Wasil E a, Furuno JP. Contribution of interfacility patient movement to overall methicillin-resistant Staphylococcus aureus prevalence levels. *Infect Control Hosp Epidemiol* 2011; **32**: 1073–8.

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 methicillin-resistant *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.

Tables

Table 1. Comparison of key parameters used by Barnes et al. (2011)[64], Chamchod and Ruan (2012)[21] and Lee et al. (2013)[23].

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

	colonised across all institution types		

[a]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)[34], Chamchod and Ruan (2012)[21] and Lee et al. (2013)[23].

	Barnes et al. (2011)	Chamchod and Ruan (2012)	Lee et al. (2013)
Was the choice of design justified?	Authors chose deterministic compartmental model as an "introductory model" on the subject	Authors chose both stochastic and deterministic models model variations due to chance	Authors chose individual based model to simulate patient movement in complex Orange County facility network
Were the question and aims appropriately and clearly focused?	Specific goal: Determine the effect of patient movement between hospitals and LTCFs on steady-state prevalence Secondary question: Study screening and decolonisation effectiveness.	Broad goals: What is the persistence and prevalence of MRSA and possible means of control in LTCFs?	Specific goal: Can contact precautions in LTCFs reduce MRSA prevalence in LTCFs and hospitals?
Was the importance of	Yes, in introduction	Yes, in	Yes, in

the question made clear?	of paper.	introduction of paper.	introduction of paper.
Was the methodology appropriately described?	Some confusion about terms “hybrid” and “agency-based model”	Clearly described	Clearly described
Were the outcome measures used to answer the study question relevant and measured and valued appropriately?	Yes, steady-state prevalence reported. Resulting graphs included numbers which helped interpretation	Yes, prevalence and equilibrium prevalence are commonly used measures. Graphical outcomes only with no numerical reporting.	Yes, median percentage decrease in MRSA prevalence and MRSA acquisitions adverted (shown in tables) reported. Graphical example of change in prevalence over time provided a good additional explanation. Numerical values also reported.
Were any assumptions made explicit?	The adherence to the intervention was not	The effectiveness of the	Clearly outlined

	addressed. Other assumptions were made explicit.	interventions and the adherence to these were not addressed. Other assumptions were made explicit.	
Were data used for formal model fitting and/or validation?	No	No	Data from a national long-term care dataset, 2006-2008 hospital and LTCF surveys, 2007 California mandatory hospital dataset and patient screenings were used to parameterise the model but the model was not formally fit to data
Were the parameters appropriate?	Some parameters were chosen from the literature 2004 to 2010 and some by	Parameters were chosen from literature 1999-2010 (some could	Parameters based on data published 2007-2011 (above). Antibiotic

	the authors. Antibiotic prescription was not considered	be outdated). Some of this literature based their parameters on data and some on expert opinions. Antibiotic prescription was not considered	prescription was not considered

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.

Themes of appraisal	Importance	Checklist questions
Setting and methodology		
	High	Is the LTCF setting clearly defined?
	High	Is the flow of patients between hospitals and LTCFs modelled?
	High	Have sensitivity analyses been performed?
	High	Is the methodology employed fully described in publication including the assumptions underlying the interventions?
	High	Has stochasticity been addressed in the model?
	Medium	Has the model been fit to data?
	Medium	Have formal fitting techniques (e.g. least square criterion,

		maximum likelihood estimation, Markov Chain Monte Carlo) been used to fit the model to data?
	Low	Is hospital transmission included?
	Low	Have models been validated using an auxiliary dataset (if this is available)?
Parameters		
	High	Is the source of the model parameters described?
	High	Is the prevalence of colonisation on admission to the LTCF from the community based on data specific to LTCFs or, in its absence, to the elderly population?
	High	Is the prevalence of colonisation on admission to the LTCF from hospitals different to that from the community?
	Medium	Are any parameters based on data rather than the literature?

	Medium	If any parameters are based on data, are the data relevant to the setting?
	Medium	Have transmission parameters appropriate to each setting (e. g. healthcare facility, bacteria) been employed? OR has model fitting been used to estimate transmission parameters from available data, following Haverkate et al.[61]? OR if none are available, has a full sensitivity analysis been conducted?
	Medium	If any parameters are based on data, are these recent data?
	Medium	Is antibiotic prescription included in the model?
	Medium	Has country-specific data been used to describe institution size, facility structure and patient movement?
Interventions		
	Medium	Have numeric results of the

		outcome of interventions been made available to permit comparison across studies?
	Low	Is the model exploring organism-intervention combinations that are novel (i.e. have not previously been evaluated in the LTCF context)?

LTCF: long-term care facility

ID: infectious disease

AMR: antimicrobial resistance