**Appendices**

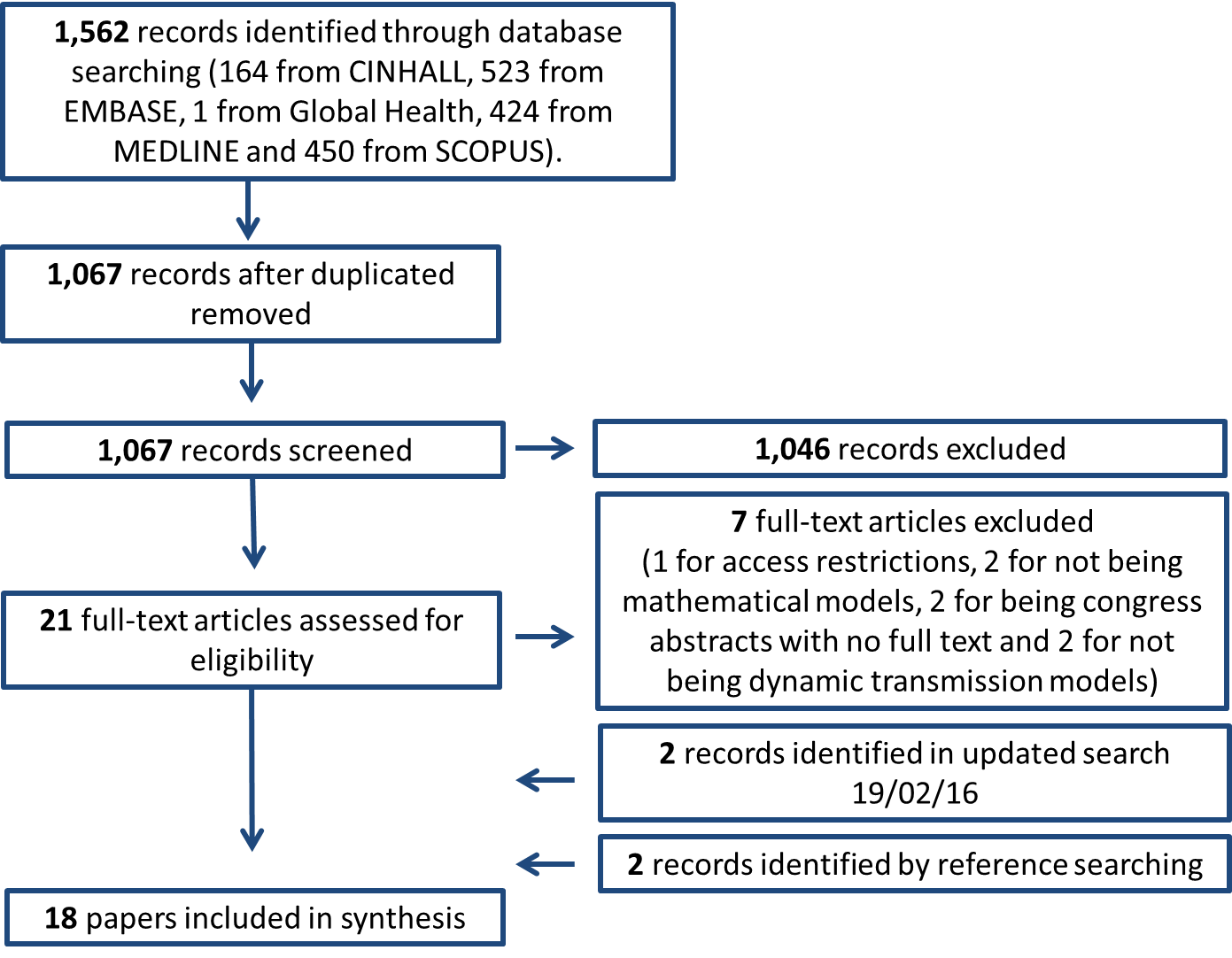
*Appendix A: Review methodology and detailed results*

1. *Database search and abstract screening*

The CINAHL, EMBASE, Global Health, MEDLINE and Scopus databases were systematically searched on the 27/12/13 for abstracts and titles that included terms relating to “model” AND “long-term care facility” AND “mathematical” (see Attachment 1). An outline of the review process can be found in Figure 1. The Scopus search alone bore 5,971 results and, therefore, had to be limited thematically to immunology and microbiology, computer science and mathematics, which yielded 450 results. Under these criteria, the search generated 1,562 results (164 CINAHL, 523 EMBASE, 1 Global Health, 424 MEDLINE, 450 Scopus). Upon de-duplication, these were reduced to 1,067 records (88 CINAHL, 481 EMBASE, 1 Global Health, 76 MEDLINE, 421 Scopus). The abstracts of these 1,067 papers 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 discarded. This left 21 papers. This search was updated on the 19/02/16. Using the same search strategy, the EMBASE search yielded 729 new results, MEDLINE 630, Scopus 133, CINAHL 13 and Global Health zero. Of these, two further studies were included for review.

1. *Full-text assessment*

These 23 papers were read in full text and were assessed under the criteria above. Only one paper was excluded due to access restrictions1. Two papers were excluded because they didn’t include mathematical models2,3, two because they were congress abstracts and there was no full text available4,5 and two because they didn’t include dynamic transmission models but statistical models analysing cost-effectiveness6,7. This left 16 papers8–23. From the references of the selected 16 papers, two additional papers were identified that fulfilled our criteria24,25 giving a total of 18 papers to review. These were scored according to organism, date, setting, theme and methodology.



**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.

1. *Results*

Eighteen papers describing 15 different models were selected for review.8–21,24,25

* 1. *Organism*

The most commonly studied organisms were influenza (nine papers: five seasonal14,17,19,22,25, three pandemic12,18,24 and one both15) and methicillin-resistant *Staphylococcus aureus* (MRSA) (five papers8–11,21). The remaining studies focused on norovirus20,23, generic non-species-specific AMR bacteria13 and generic non-species-specific bacteria in healthcare16 (see Figure 2).

* 1. *Chronology*

The first models studying infectious disease transmission in LTCFs were published in 199319,25. For the ten subsequent years there were no publications in this field. Since 2003 there has been a resurgence of publication in this area. However, the number of papers published remains small, averaging at 1.5 publications per year for the last eight years.

* 1. *Setting*

Six papers modelled transmission within LTCFs8,12,14,15,19,20, six in both LTCFs and hospitals9–11,16,21,23, one in a small population (a small urban US community)18, two in larger populations (a country-size population and a USA state-sized population)17,22 and three did not define their population size13,24,25. Most papers were either explicitly or implicitly set in the USA (six9,10,13,18,21,22) or did not indicate a national setting (five8,12,16,19,25). Two other studies were set in the Netherlands14,15, one in Belgium20, one in France24, one in England23 and one in an unspecified developed country17. One was an international study that utilised data from both Canada and the USA11.

* 1. *Theme*

Thirteen papers assessed one or several interventions8,10–12,14–18,20–22,24. The most common intervention (evaluated in six papers8,12,16,18,20,24) was the isolation of residents. Other commonly studied interventions included decolonisation8,16,21, screening8,12,21, contact precautions10,16 and prophylactic treatment14,17,22,24. Two papers researched the impact of altering patterns and rates of patient transfer and lengths of stay8,11 and another two investigated vaccination15,22,24. Altering staff to patient ratios and increasing staff shifts were each researched in one paper8,12. Other themes researched included the role of LTCFs in infectious disease prevalence and transmission (in five papers8–10,13,21), the impact of patient transfers among institutions (in two papers11,21), the spread of AMR overall (in one paper13), theoretical concepts about a particular model (in two papers19,25)and modelling methodology for small outbreaks23.

* 1. *Methodology*

The majority of these papers (129–12,14–16,18,19,22–25) described stochastic models whilst four papers described deterministic models13,17,20,21, one described a deterministic model with a stochastic component for transmission22 and one described both types8. Nine papers described compartmental models8,12,13,16,17,20–23 and nine IBMs9–11,14,15,18,19,24,25. The three models that were repeated in two different papers each were stochastic IBMs.

Various model structures were described in the papers. One was a modification of a susceptible-infectious-recovered (SIR) model21; five were based on a susceptible-infectious-susceptible (SIS) model8–11,13; one on a susceptible-exposed-infectious (SEI) model18; ten on variants of a susceptible-exposed-infectious-recovered (SEIR) model12,14,15,17,19,20,22–25 and one on two different structures: susceptible-colonised (SC) and susceptible-colonised-infected-isolated (SCII)16.

None of the models were fit to data using formal statistical inference or emulation methods except for the last two published. One used a chi-squared goodness of fit test22 and one used a gradient-based optimisation code to find the maximum-likelihood estimate23. Only two studies validated their findings22,23. Two papers described simple fitting processes for some parameters used in the models11,20 and 11 of the 18 papers did carry out sensitivity analyses of the parameter sets8,10,14,15,17–19,22–25. Of these, three were carried out through Latin hypercube sampling14,15,19.

*Appendix B: Detailed results from the critical review*

1. *Dates, settings and methodologies*

The dates, settings and methodologies for the three papers are summarized in Table S1.

These three models were built within the last five years (2011, 2012 and 2013). Lee et al.10 based their estimates on current sources, using data published from 2007-2011. Length of stay was the only parameter based on data published before 2010. Barnes et al.21, however, based their parameter estimates on literature from 2004 to 2010 and Chamchod and Ruan8 from 1999 to 2010.

Chamchod and Ruan’s model 8 was set within a LTCF. They did not mention the nationality of their setting. Barnes et al.21 modelled patient movement between hospitals and LTCFs in the USA. Lee et al 10 additionally included the non-LTFC community into their model. They made a distinction between those discharged for a short period of time (less than 30 days) and those discharged into the community for longer (these were not readmitted). Their model represented Orange County, California (USA).

Barnes et al.21 built a compartmental deterministic model, Lee et al.10 an individual-based stochastic model and Camchod and Ruan8 built two compartmental models: one stochastic and one deterministic. None of these models were formally fit to data or validated. Barnes et al.21 did not carry out a sensitivity analysis. Chamchod and Ruan8 and Lee et al.10 carried out univariate sensitivity analyses, varying key parameters one at a time and noting the effect of these changes on model outcomes.

**Table S1. Characterisation of the papers that modelled MRSA transmission in LTCFs and assessed the impact of one or more interventions.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Barnes et al. | Chamchod and Ruan | Lee et al. |
| Year | 2011 | 2012 | 2013 |
| Type of model |  |  |  |
| Deterministic/ Stochastic | Deterministic | Both | Stochastic |
| Compartmental/IBM | Compartmental | Compartmental | IBM |
| Formally fit to data? | No | No | No |
| Sensitivity analysis? | No | Yes | Yes |
| Type |  | Univariate | Univariate |
| Formally validated? | No | No | No |
| Population setting | LTCFs and hospitals | LTCF | LTCFs, hospital and community |
| Country setting | USA | Not stated | Orange County, CA, USA |

LTCF: long-term care facilities

IBM: individual-based model

1. *Model structure*
   1. *Patient flow*

The three models varied in the complexity of their institutional structures: Chamchod and Ruan8 modelled transmission of MRSA within a LTCF only with patients mixing homogenously within it. Barnes et al.21 and Lee et al.10 modelled patient flow between two types of facility: LTCFs and hospitals (see Figure S1).

Barnes et al.21 modelled each LFCF and hospital as agents in a network of facilities (Figure S1a). Links between each pair of facilities in the network were assigned a specific weight, which, together with the facility size, determined the probability of transfer between the facilities. Various network configurations with different weights associated to the links were compared. In their model, patients at each facility type were admitted and discharged at the same rate (μ). Barnes et al.21 did not define any finer grain compartments within each LTCF and hospital, therefore, patients were assumed to mix homogeneously within facilities.

Lee et al. 10 also included movement between the facilities and the community (Figure S1b). The authors modelled bidirectional patient flow between the 100 inpatient facilities present in Orange County (71 LTCFs and 29 hospitals) as well as discharge into the community (permanent or temporary, where patients were readmitted within a year of discharge). Their IBM used a 2007 California mandatory hospital dataset where patients were tracked between facilities to inform hospitalisation and rehospitalisation and data from 2006-2008 surveys to inform transfers between hospitals and LTCFs. Patient flow was also determined by the number of licensed beds, the average daily census and the length of stay in LTCFs obtained from a national long-term care dataset. Length of stay distributions for ICU and non-ICU patients in each hospital were used to inform transfers from hospitals. MRSA carriers had longer lengths of stay. LTCF residents with a length of stay of two or more weeks were assigned a daily probability of being transferred to a hospital for a short stay during which their LTCF bed was kept free. The authors assumed each hospital comprised 20-bed general hospital wards, 12-bed intensive care units and 10-bed long-term acute care facilities. Each LTCF contained one ‘ward’ within which patients mixed homogenously.

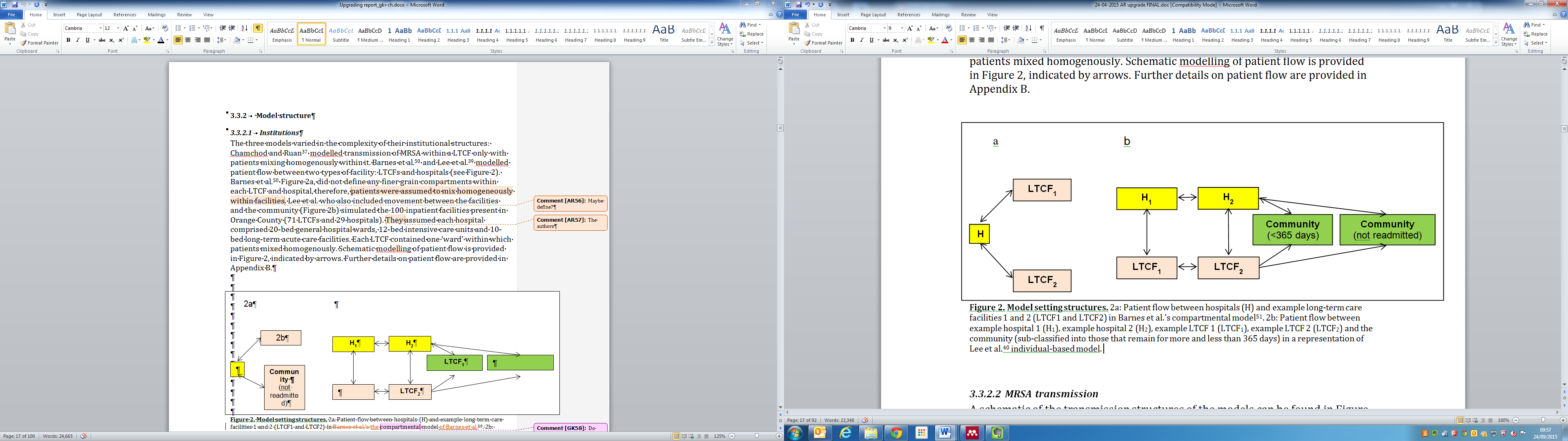


Figure S1. Model setting structures. S1a: Patient flow between hospitals (H) and example long-term care facilities 1 and 2 (LTCF1 and LTCF2) in the compartmental model of Barnes et al.21. S1b: Patient flow between example hospital 1 (H1), example hospital 2 (H2), example LTCF 1 (LTCF1), example LTCF 2 (LTCF2) and the community (sub-classified into those that remain for more and less than 365 days) in a representation of Lee et al.10 individual-based model.

* 1. *MRSA transmission*

A schematic of the transmission structures of the models can be found in Figure S2. Each model considered two basic individual states; colonised with MRSA or uncolonised with MRSA. Infection was not considered in any model.

In Barnes et al.’s model21 (se Figure S2a), individuals could transition between three states: U (uncolonised), P (persistently colonised) and T (transiently colonised). U individuals could become P or T and vice-versa through transmission and recovery, but they could not transition between P and T states of colonisation. Transition from P to U was slower than from T to U. The proportion of transferred patient’s in each disease states were established according to the proportions of U, P and T in the facility they were transferred from.

Chamchod and Ruan8 modelled MRSA transmission between residents, between healthcare workers and between healthcare workers and residents as distinct processes (see Figure S2b). The disease states in residents were only U (uncolonised) and C (colonised). The disease states in healthcare workers were H (uncontaminated) and Hc (contaminated). Patients and residents could transition between the uncolonised (U) and colonised (C) states through transmission and recovery. No distinction was made between the P and T colonisation states. Colonised and uncolonised residents had different probabilities of admission (λ and 1-λ, respectively) and discharge (γc and γu, respectively). Transmission rates were different between residents (βr), from healthcare workers to residents (βh) and from residents to healthcare workers (αh). Colonisation of an uncolonised resident depended on both βr and βh whilst contamination of an uncontaminated healthcare worker depended on αh. Decolonisation rates in residents (ω) differed from decontamination rates in healthcare workers (μ).

Lee et al.’s IBM10 distinguished two patient states: S (susceptible) and I (infectious) (see Figure S2c) which were analogous to uncolonised and colonised. Because the authors were analysing the impact of contact precautions on transmission, they differentiated between residents in a scenario where contact precautions were in use (Sp andIp) and residents in a scenario where they were not (Sφ andIφ). The number of new cases of MRSA per unit per day were calculated following the equation described below:

βSφIφ+β(1-θ)SpIφ+β(1-θ)SφIp+β(1-θ)2SpIp

where p= precautions, φ= no precautions, θ=efficacy of contact precautions.

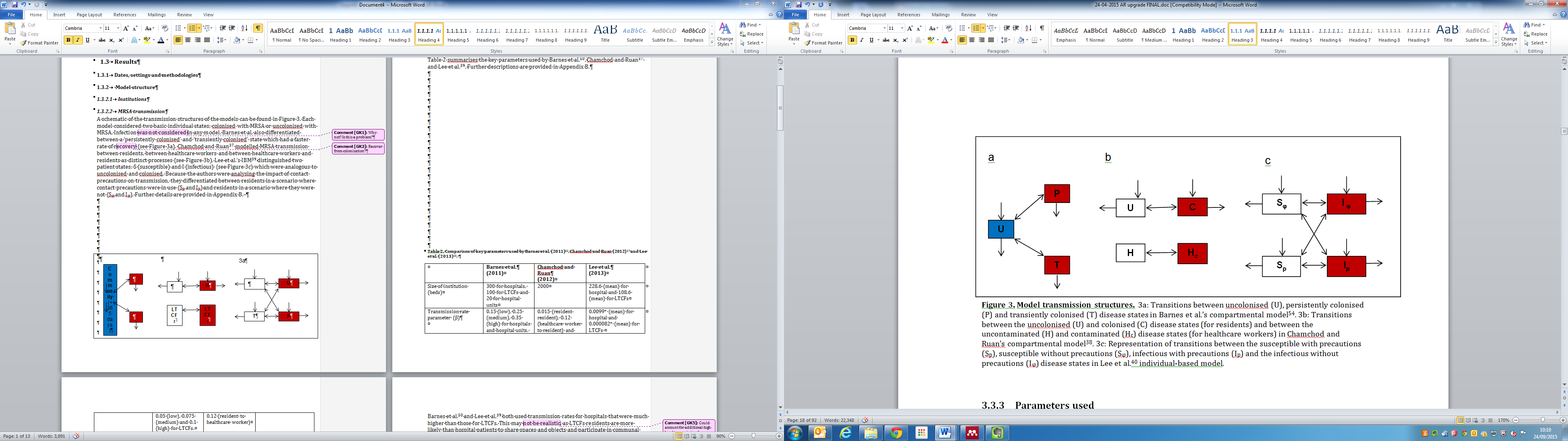


Figure S2. Model transmission structures. S2a: Transitions between uncolonised (U), persistently colonised (P) and transiently colonised (T) disease states in Barnes et al.’s compartmental model21. S2b: Transitions between the uncolonised (U) and colonised (C) disease states (for residents) and between the uncontaminated (H) and contaminated (Hc) disease states (for healthcare workers) in Chamchod and Ruan’s compartmental model8. S2c: Representation of transitions between the susceptible with precautions (Sp), susceptible without precautions (Sφ), infectious with precautions (Ip) and the infectious without precautions (Iφ) disease states in Lee et al.10 individual-based model.

1. *Parameters used*

The LTCF sizes chosen varied greatly between the three models, ranging from 100 beds21 to 20008. The research groups also chose different ways of quantifying transmission. Barnes et al.21 and Chamchod and Ruan8 reported transmission rates as the effective contact (resulting in transmission) rate averaged per day whilst Lee et al.10 quantified the rate of transmission per person per day, explaining why their figures are not of the same magnitude. In addition, Chamchod and Ruan8 broke down their overall transmission rate into resident-resident, healthcare worker-resident and resident-healthcare worker transmission rates. Resident-resident transmission was assumed to be eight times lower than the other transmission types. Their overall transmission rate was a combination of these three rates. Barnes et al.21 used three different rates that were in a similar range than those provided by Chamchod and Ruan8. Barnes et al.21 and Lee et al.10 both used transmission rates for hospitals that were much higher than those for LTCFs. Barnes et al.21 and Chamchod and Ruan8 assumed the same proportion of patients admitted colonised by MRSA (10%). Lee et al.10, however, reported the prevalence of colonisation within the hospitals (6.1%) and LTCFs (26.1%) which was much higher than the overall prevalence of all patients that enter the facility from the general population. Lee et al.10 did not report their assumed duration of colonisation. Camchod and Ruan8 supposed a duration of colonisation similar to that of persistently colonised individuals in Barnes et al.’s model21. Barnes et al.21 reported recovery rates for persistently and transiently colonised individuals of 0.02 and 0.2 respectively that equate to 5 and 50 days of colonisation. These estimates were decided by the authors. Chamchod and Ruan8 chose a middle estimate from the average decolonisation time range published by Kajita et al. (2007)26, which were themselves based on expert opinion. Neither of the duration of colonisation estimates were taken from literature based on data.

1. *Interventions*

Barnes et al. 21 assessed the impact of three screening and decolonisation interventions: decolonisation on admission (no screening); screening by conventional culture on admission and subsequent decolonisation of positive residents and screening by PCR on admission and subsequent decolonisation of positive residents. These interventions reduced the prevalence of MRSA by moving patients from a colonised state (for Barnes et al.21, both P and T) to a susceptible state (uncolonised) where they cannot transmit disease after a duration of 10-13 days (depending on the type of screening carried out). Barnes et al.21 found that all three interventions yielded the same approximate results because facility transfers were frequent, which meant screening at admission was also frequent. Decolonisation decreased equilibrium prevalence in LTCFs by 0.0287-0.1203 and in hospitals by 0.0029-0.0232 (depending on initial institution equilibrium MRSA prevalence). It was assumed that, on average, it would take two cycles of five-day treatments for patients to be successfully decolonised (10 days).

Chamchod and Ruan8 considered the theoretical impact of reducing different importation and transmission parameters on MRSA prevalence. Chamchod and Ruan8 reported that, increasing the recovery rate by more than 0.05 resulted in the elimination of MRSA under equilibrium.

Chamchod and Ruan8 considered the impact of hand hygiene on MRSA prevalence. Hand hygiene measures that target residents aim to decrease the transmission of MRSA from C to U and H (βr and αh). Implementing improved hand hygiene decreases the probability of colonisation per contact of for residents (pr) and the probability of contamination per contact for healthcare workers (qh). The average number of contacts between residents (a) and the average number of required contacts from healthcare workers by residents (b) remains the same. Hand hygiene measures that target healthcare workers aim to alter the transmission of MRSA from Hc to U (βh) by decreasing the probability of colonisation via contacts of healthcare workers (qr) without altering the average number of required contacts from healthcare workers by residents (b). The authors found that when the average duration of colonisation was reduced below 250 days for residents or below 0.15 hours for healthcare workers, the probability of invasion resulting from the introduction of a contaminated healthcare worker/ a contaminated resident was eliminated8.

Chamchod and Ruan modelled the impact of increasing the staff to patient ratio to reduce the contact rate. Assuming that the average number of contacts a resident requires by a healthcare worker (b) is a constant and is distributed amongst the number of healthcare workers, reducing the resident to staff ratio (Nr/Nh) diminishes the frequency at which a particular healthcare worker contacts a resident (b/Nh). Lower Nr/Nh reduces the frequency of contacts between U and Hc and between C and H. When resident to staff ratio was reduced below 6.5, the probability of invasion resulting from the introduction of a contaminated healthcare worker/ a contaminated resident was eliminated8.

Lee et al.10 compared the effect of contact precautions in LTCFs for residents with clinically apparent MRSA infections and for all MRSA carriers. Both interventions reduced the probability of transmission. The first intervention replaced Iφ individuals in the population with Ip. The second intervention replaced individuals in Sφ with Sp in a similar fashion. In their model, contact precautions in residents with clinically apparent MRSA did not significantly decrease MRSA prevalence and the number of MRSA acquisitions averted in Orange County was minimal, even after five years and assuming 75% adherence. However, when contact precautions were taken in all MRSA carriers, a substantial number of MRSA acquisitions were adverted. Assuming 50% adherence, 171 acquisitions of MRSA were projected to be adverted within six months and 4,876 within five years. Even in situations where adherence was lower (25%), 81 acquisitions were to be adverted after six months and 2,442 after 5 years. With high adherence (75%), 7,291 acquisitions were to be adverted after five years10.

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