Appendix 2: Parameter Estimation

All parameters used in the transmission model, their estimated values and sources are provided in Table A2.1. A further description of the parameter estimation process is provided below. Parameters and their estimation procedure are taken from a comprehensive study for the Department of Health, England.[1]

Population parameters

Ward Size

For the baseline scenarios evaluations were performed using an intensive care unit of 10 beds. Sensitivity analyses used intensive care units of 5 and 20 beds. These values are representative of intensive care unit sizes in England, Wales and Northern Ireland where, according to current Intensive Care National Audit and Research Centre (ICNARC) figures, the mean intensive care unit size (median) is 9.8 (8) beds, the interquartile range is 6–12 beds and the overall range is 2–27 beds.

Patient movements

Parameters describing patient discharge and death were estimated using a time-dependent model described in Bartnett *et al.*[32] which was amended to give unadjusted daily probabilities of discharge and death which varied by day of intensive care unit stay and MRSA infection status (Table A2.2).

Prevalence on admission

In the base case scenarios a patient admitted to the intensive care unit had a probability of 0.05 of being colonised with MRSA when admitted. This is broadly consistent with data from a number of UK intensive care units.[2-7] Scenarios where intensive care units had a higher and lower MRSA prevalence were also considered, with probabilities that a patient was colonised on admission of 0.1 and 0.02 respectively (broadly representing the extremes found from the literature).[3 7]

A number of studies detail known risk factors for MRSA colonisation or infection, as well as the use of such risk factors for infection control purposes.[33-34] We used the definition of 'high-risk' similar to that in the study by Harbarth et al.[8] which used multivariable analysis to identify nine independent risk factors which were used to determine the probability of carriage for each patient. However, we simplified this model such that there were two (rather than three) risk groups. The probability of being colonised on admission in the high risk population was assumed to be 2.4 times greater than that in the low risk population. It was assumed that the accuracy with which the hospital could identify high-risk admissions was 100% and that 18% of patients were in this group. The relative prevalence in the high risk (compared to low risk) group, and the proportion of patients considered high risk were based on the studies by Eveillard *et al.*[9] and Harbarth *et al.*[8]. Given these baseline estimates, if detection is limited to the high risk admission population, at least 47% of positive admissions will be missed. This is taken into account in the transmission model.

Intervention parameters

A computerised search to identify existing systematic reviews in each subject area was performed. Relevant sources were found through PubMed, the Cochrane Database of Systematic Reviews, The Health Technology Assessment (HTA) database, the Database of

Abstracts of Reviews of Effects (DARE) and the National Health Service Economic Evaluation database (NHS EED). The search was restricted to systematic reviews published between January 1997 and December 2007 and was carried out in December 2007. Further literature searches to identify primary literature were undertaken using PubMed. These were limited to the period since the cut-off date of the most recent systematic review (for topics for which a systematic review existed). Abstracts of articles selected by the search strategy were filtered according to the following exclusion criteria: the pathogen under investigation was not MRSA; the MRSA was community and not hospital associated; the setting was neonatal or not in a hospital; the study was not a randomised controlled trial or interrupted time series study; the study was entirely retrospective; the study was an interrupted time series with fewer than three data points before and after the intervention; the study was methodologically unclear;[41] the article was written in a language other than English. Full articles were reviewed by JR and filtered by study type.

Screening

A recent review by Malhotra-Kumar *et al.*[42] was used as the primary evidence source for test characteristics (sensitivities, specificities and turn-around times) of chromogenic agars and polymerase chain reaction methods. Only those studies from the review that evaluated chromogenic agars using pooled swabs from at least three screening sites (including nose and throat) and only studies which used direct inoculation (i.e. without broth enrichment) were used for parameter estimation. For polymerase chain reaction evaluations only studies included in the review that used a nasal sample site alone were used. In addition to the studies identified through this review, any recent studies identified through a literature search on screening coupled with interventions that reported sensitivity and specificity and turn-around time of any of the above technologies were included.

Reported test times were used to estimate turn-around times. However, as these only accounted for the time from the swab being taken to the test result, adjustments were made to allow for additional time delays using adjustments from Harbarth *et al.*[16]

Due to the differences in setting, infection control methods used and case mix, these studies evaluating screening were not used to determine effectiveness of accompanying intervention methods, only to determine screening test characteristics. Estimates for the effectiveness of isolation and decolonisation are described below.

Isolation

There was little available evidence on the effectiveness of individual isolation measures as found by the systematic review by Cooper *et al.*[43] and, through our literature review of studies since, few additional studies were found.

Kypraios *et al.*[29] assessed the effectiveness of contact precautions, in the form of gloves and gowns, in reducing MRSA transmission in eight adult intensive care units (all comprised of single occupant rooms). This was the only study able to provide direct estimates of the effectiveness of contact precautions in reducing MRSA transmission. This study used data collected in a United States hospital and the generalisability to a UK setting is therefore debatable. However, these estimates were considered the best available evidence on contact precaution effectiveness, and were therefore used in our model.

Decolonisation

Effectiveness of mupirocin was taken from the recent Cochrane review of mupirocin use,[31] taking the relative risk from high quality studies only. Estimates derived using elicitation of expert opinion (methodology described below) were used to perform sensitivity analysis to the effectiveness of mupirocin. Effectiveness was measured in terms of: i) the reduction in daily probability of acquiring MRSA for an MRSA-free patient undergoing mupirocin treatment; ii) the reduction in the daily probability of transmission of MRSA to a MRSA-free patient from an MRSA colonised or infected patient undergoing mupirocin treatment; iii) the reduction in the daily probability of progression (self-infection) for an MRSA- colonised patient undergoing mupirocin treatment. Chlorhexidine effectiveness was derived using Markov models on individual-level data, as described below.

Transmission parameters

Transmission parameters were estimated using individual level data. Daily probabilities of a susceptible patient becoming colonised or infected given exposure to a single MRSA positive patient were estimated by fitting a continuous time multistate Markov model to MRSA surveillance and infection data. This was performed using R version 1.91 and the multi-state modelling package (multi-state modelling with R: the msm package, Version 0.7.4, 2007, Jackson, C, Medical Research Council Biostatistics Research Unit, Cambridge, UK). These data were derived from 4,570 patients admitted to two 15-bed general intensive care units at a London hospital between 2002 and 2006. These data were also used to estimate the daily probability of an MRSA colonised patient progressing to an infected state in the absence of any other MRSA sources, and to assess the impact on these parameters of a daily chlorhexidine based antiseptic protocol. Full details of these data and the intervention are given in Batra *et al.*[10]

The Markov model had five states: i) susceptible (uncolonised and uninfected); ii) colonised with MRSA; iii) infected with MRSA; iv) discharged alive from the intensive care unit; v) died. Parameter estimates were obtained by fitting the Markov models to the data using a maximum likelihood procedure. Daily transition probabilities were derived from the fitted continuous time Markov models and confidence intervals were obtained by bootstrapping using 1000 bootstrap replicates for each model.

Elicitation of Expert Opinion

Five UK-based experts were recruited to undertake the elicitation process. Each had extensive subject area expertise, was actively involved with research in the area, had a thorough knowledge of the relevant literature and general understanding of the topic and was, to our knowledge, impartial. The experts were provided with background information on the question topics and aims of the study via email at least a week before the formal elicitation was conducted. Following this, the formal elicitation followed an interview structure. Training on elicitation techniques was given to the experts, including example questions and distribution elicitation methods. To reduce the risk that the example answers inadvertently "anchored" the experts' subsequent answers, distorting the elicitation process, all examples were of extreme and highly unrealistic scenarios. A thorough description of why each question was being asked and any additional background information was provided. Any units were specified and definitions made clear. Probability distributions were elicited using the direct technique of response scales, where a visual representation of the full range of responses is provided and respondents simply mark their estimates of the possible values

along this scale.[44] Uncertainty was captured by limiting the respondent to 20 estimates each representing 5% certainty, with which to distribute over the provided scale.

Cost Parameters

Costs

Cost parameters and their sources are provided in Table A2.3. Estimated infection related treatment costs of £530 were for vancomycin therapy and therapeutic monitoring for 14 days (the standard of care in the UK for uncomplicated MRSA bacteraemia). The average cost of an intensive care unit bed day was £1,353. This was based on National Health Service reference costs.[48]

Health Benefits

QALYs accrued post-discharge were estimated using a recent cohort study by Cuthbertson *et al.* for the first five years after intensive care unit discharge.[49]After five years, the mortality rates were similar to those of the general population and age and sex matched life expectancies and quality adjustments were used (from the Office of National Statistics cohort expectations of life years and UK population norms, respectively). After discounting at 3.5% per year (as recommended by the national Institute for Health and Clinical Excellence[50]) this gave a discounted QALY expectancy (95% confidence intervals) on intensive care unit discharge of 11.61 (10.74, 12.48). We approximated this with a normal distribution with a mean (standard deviation) of 11.61 (0.45).

Dealing with uncertainty

Probabilistic sensitivity analyses were performed as described in Spiegelhalter *et al*, section 9.8.3 [51], by drawing 1000 samples from the parameter probability distributions and averaging over 10,000 simulations of the stochastic model for each sampled set of parameter values.

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