



**Predictive Risk Factors for Methicillin-Resistant *Staphylococcus aureus*  
(MRSA) Colonisation among Adults in Acute Care Settings: A  
Systematic Review**

Submitted by

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A thesis submitted in total fulfilment of the requirements for the degree of  
Master of Clinical Science  
The Joanna Briggs Institute, Faculty of Health Sciences  
The University of Adelaide  
December 2011

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**THESIS DECLARATION**

This work contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief contains no material previously published or written by another person, except where due reference has been acknowledged in the text.

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I hereby certify that the statement of contribution is accurate

Yifan Xue.....Date.....

## **ACKNOWLEDGEMENTS**

I would like to thank all people who have helped and inspired me during my Master degree study. First and foremost, my utmost gratitude to my supervisor, Craig Lockwood, who has supported me throughout my thesis with his patience and knowledge whilst allowing me the room to work in my own way; without his supervision the thesis would not have been completed or written. I thank my supervisors Professor Judy Lumby and Professor Jos Kleijnen, they encouraged me to pursue professional growth. Last but not least, I would like to thank Dr. Aye Aye Gyi for her friendship and help in the past two years.



## Abstract

**Background:** Limited by the structure of individual health care settings and patient recruitment, primary studies do not provide a comprehensive definition of independent risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) colonisation among adults on admission to acute care settings. A systematic review was performed to identify and evaluate the association between risk factors and MRSA colonisation.

**Methods:** MEDLINE, EMABSE, and CINAHL databases were searched for prognostic studies published between 1990 and 2010 that examined the association between risk factors and MRSA colonisation. The summary statistic extracted or calculated for each factor was the odds ratio (OR), comparing patients with MRSA colonisation to non-MRSA carriers.

**Results:** Fifteen prospective studies, including a total 16,467 patients, were eligible for inclusion in the meta-analyses. More than 30 independent risk factors were identified and aggregated. The risk factors associated with MRSA colonisation in the meta-analyses include hospitalisation within the last 24 months (OR 3.4309, 95% CI 2.9732 – 3.9590,  $p < 0.0001$ ), previous admission to a long-term care facility (LTCF) or a rehabilitation facility within the last 18 months (OR 6.7004, 95% CI 4.2609 – 10.5364,  $p = 0.0001$ ), antibiotic use within the past 12 months (OR 3.7694, 95% CI 3.2453 - 4.3781,  $p < 0.0001$ ), the presence of skin lesion (OR 3.525, 95% CI 2.6194 - 4.7437,  $p < 0.0001$ ), surgical intervention within the last 60 months (OR 2.9807, 95% CI 2.5261 - 3.5172,  $p < 0.0001$ ), indwelling urinary catheter (OR 4.3898, 95% CI 3.4317 - 5.6156,  $p < 0.0001$ ), intensive care unit (ICU) admission in the last 5 years (OR 3.8845, 95% CI 1.6605 – 9.0871,  $p = 0.0018$ ), previous MRSA colonisation (OR 6.7329, 95% CI 2.4504 – 18.4995,  $p = 0.0019$ ), intra-hospital transfer (OR 2.0955, 95% CI 1.6966 - 2.5881,  $p < 0.0001$ ), male sex (OR 1.8167, 95% CI 1.5180 - 2.1742,  $p < 0.0001$ ), comorbidity of chronic health evaluation class C or D (OR 3.025, 95% CI 2.1844 - 4.1891,  $p < 0.0001$ ), and the presence of fatal illness (OR 1.7591, 95% CI 1.4259 - 2.1702,  $p < 0.0001$ ).

**Conclusion:** The identification of risk factors for MRSA colonisation on admission may contribute to improved effectiveness and efficiency of current MRSA prevention strategies and control MRSA spread and acquisition in acute care settings. The outcomes of this review may facilitate prediction model

development to quickly identify potential MRSA carriers before admission. More and larger scale prospective studies on risk factors for MRSA carriage in community settings are needed to explore the spread of MRSA among health care setting, community and carrier families.

**Key Words:** methicillin-resistant *Staphylococcus aureus*, MRSA, colonisation, risk factor, screening, acute care

## Chapter 1: Background

### 1.1 Origins of methicillin-resistant *S. aureus*

*Staphylococcus aureus* (*S. aureus*) is a ubiquitous microorganism that is able to colonise the anterior nares and skin of healthy individuals. It has been estimated up to 50% of adults are either persistent or intermittent *S. aureus* carriers.<sup>1</sup> This microorganism is a versatile pathogen causing a broad spectrum of infections (*S. aureus* infections range from common skin infections, such as furunculosis and impetigo, to severe infections). *S. aureus* ranks first among bacterial pathogens causing bloodstream infections<sup>2</sup> and, is the leading cause of nosocomial pneumonia as well as being associated with endocarditis.<sup>3</sup>

The introduction of penicillin in the 1940s to treat *S. aureus* infections was also the beginning of the phenomena of antibiotic resistance. The introduction of methicillin in 1959 (which was stable to the enzyme penicillinase, the cause of earlier resistance) initially appeared to have solved the problem. However, in 1961 methicillin-resistant *S. aureus* (MRSA) was identified and subsequent strains developed and reached epidemic proportions. MRSA strains caused major infection outbreaks in various countries during the 1980s and were considered endemic in healthcare facilities from the 1990s.<sup>4</sup>

Several phenotypic and genotypic characteristics differentiate methicillin-susceptible *S. aureus* (MSSA) from MRSA. Firstly, MRSA tends to be multi-drug resistant, not only to  $\beta$ -lactam antibiotics but also to a range of different antibiotic classes, such as fluoroquinolones, tetracyclines, macrolides, lincosamides and aminoglycosides.<sup>5,6</sup> Over time strains have emerged with an intermediate susceptibility or full resistance to vancomycin (VISA and VRSA, respectively); the antibiotic that has represented the cornerstone of therapy for MRSA for two decades.<sup>7</sup>

## 1.2 Epidemiology of MRSA

In 2007, the European Antimicrobial Surveillance System, a free network that connects more than 600 laboratories in 31 European countries, reported an incidence of MRSA bacteraemia per 100,000 patient-days ranging from 0.2 in Sweden to 24.4 in Portugal.<sup>8</sup> In 2005, data from the USA Surveillance Network, an electronic network that collects microbiology data from 300 clinical microbiology laboratories across the USA, reported that *S. aureus* isolates represented 59% of methicillin-resistant strains among non-intensive care unit (non-ICU) inpatients, 55% among ICU inpatients, and 48% among outpatients, respectively.<sup>9</sup>

Methicillin-resistant *S. aureus* was first reported in Australia in 1968.<sup>10</sup> It has since been estimated that approximately 6,900 episodes of *S. aureus* bacteraemia occur in Australia annually, which equates to 35 episodes per 100,000 populations.<sup>10</sup> A survey, conducted by the Australian Group for Antimicrobial Resistance, reported that methicillin-resistant strains ranged from 22.5% of *S. aureus* isolates in Western Australia to 43.4% in New South Wales/Australian Capital Territory.<sup>10</sup> In 2005, 32% of *S. aureus* isolates causing infection >48 hours after hospitalisation were methicillin-resistant.<sup>11</sup>

## 1.3 Hazards of MRSA infection and colonisation

Two meta-analyses with similar methodology and outcomes showed that bloodstream infections due to MRSA were associated with two folds higher mortality (OR 1.93; 95% CI, 1.54 - 2.42 and relative risk (RR) 2.03 95% CI, 1.55 – 2.65) than those due to methicillin-susceptible *S. aureus* (MSSA).<sup>12,13</sup> Costs per patient-day of hospitalisation were also substantially higher for bloodstream infections due to MRSA than those due to MSSA.<sup>14</sup> In Australia, the additional hospital costs associated with nosocomial *S. aureus* bacteraemia alone are estimated at approximately 150 million Australian dollars.<sup>10</sup> Effective infection control measures of MRSA have been shown to reduce nosocomial infection significantly and to result in substantial savings.<sup>15</sup>

MRSA colonised or infected patients are significant reservoirs of and modes for MRSA transmission in acute care facilities.<sup>16</sup> A substantial proportion of MRSA-colonised patients subsequently develop

MRSA infections.<sup>17</sup> A study of subjects in whom MRSA colonisation had been identified during a previous hospital stay reported that the risk of developing an MRSA infection, such as bacteraemia, pneumonia, or soft tissue infection, within 18 months after detection of MRSA colonisation was 29%.<sup>18</sup> A systematic review with meta-analysis estimating the risk of infection following colonisation with MRSA compared with colonisation by MSSA, found colonisation by MRSA was associated with a 4-fold increase in the risk of infection (OR 4.08, 95% CI, 2.10 - 7.44) than those colonised with MSSA.<sup>19</sup>

## **1.4 Control strategies**

In healthcare facilities antibiotic use provides a selective advantage for MRSA to survive. There are clinical practice guidelines published by government, public health and professional organisations. These outline control measures that include active surveillance (health service level), screening to identify patients with colonisation or infection (patient level), isolation of patients with MRSA positive (patient level), decolonisation therapy and antimicrobial stewardship (patient level), contact precautions and hand hygiene (health service level), and environmental decontamination and equipment cleaning (health service level).<sup>4,16,17</sup>

In early 2007 a survey of infection control professionals in Australia and New Zealand was conducted to evaluate current local practice in the acute care setting and compare the outcomes with published guidelines.<sup>20</sup> There was wide variation in active surveillance protocols for MRSA although 80% of respondents reported routine screening of particular patient groups. The most common patient groups targeted by active surveillance programs were those previously known to be MRSA positive (65%), transfers from other healthcare or long term care facilities (50%), ICU patients (42%) and prior to high-risk surgery (37%).<sup>20</sup>

Asymptomatically colonised MRSA carriers serve as a substantial reservoir for person-to-person transmission of MRSA in the acute care setting. Studies have shown that routine use of clinical cultures alone does not identify the full reservoir of asymptomatically colonised patients and, it has been suggested that this results in an underestimating the overall hospital-wide prevalence of MRSA by as

much as 85%.<sup>21</sup> Furthermore, it has been argued that early identification of asymptotically colonised MRSA carriers (on admission) can reduce misclassification of MRSA isolates, so that subsequent MRSA isolates do not contribute to intra-facility transmission.<sup>22</sup>

Screening programs are a major aspect of controlling the spread of MRSA through the identification of colonised or infected patients and, then, managing them to reduce the risk of MRSA transmission to other individuals. Several screening models have been implemented and evaluated in healthcare settings across the world. These include models such as general screening for all inpatients, admission screening, discharge screening, peri operative screening, and high-risk population/patients pre-admission screening. Girou and his colleagues<sup>23</sup> comparing systematic screening of all admitted patients and selective screening of patients at risk, found that overall rates of imported and acquired cases were similar between the two periods (6.8% vs 7.5%, and 2.9% vs 2.4%, respectively). A 19-month prospective study assessing the effectiveness of a selective screening program with other MRSA control policy, found that 48% of the predicted number of hospital acquired MRSA infections were prevented by the screening program.<sup>24</sup> Due to similar sensitivity and being cost-effective, selective screening strategies continue to be recommended as an effective measure to reduce hospital-acquired MRSA (HA-MRSA) infections.<sup>23,24</sup>

## **1.5 Risk Factors for MRSA colonisation**

The criteria for a selective screening strategy are generally based on risk factors associated with MRSA colonisation. Known risk factors for MRSA colonisation include severe underlying illness or comorbid conditions;<sup>16,17</sup> prolonged hospital stay;<sup>4,16,17</sup> exposure to broad-spectrum antimicrobials (quinolones, glycopeptides, cephalosporins and other  $\beta$ -lactams);<sup>4,16,17,25</sup> the presence of foreign bodies and invasive therapies, such as central venous catheters<sup>4,17</sup> indwelling urinary catheters<sup>16,17</sup>; and frequent contact with the healthcare system or healthcare personnel.<sup>4,16,17</sup> These risk factors are summarised by experts' experience and knowledge or individual studies.

Characterisation of risk factors for colonisation allows prediction of the probability of developing infection among specific populations; this aids in understanding pathophysiologic mechanisms and is useful for defining screening criteria and subsequent prevention strategies. A large number of studies explore risk factors for MRSA colonisation and acquisition in different populations on admission or following admission to varying healthcare settings. The ability to detect meaningful statistical associations between infection and risk factors is also dependent on the accuracy and reliability of terminology used to define and describe risk factors. Some factors may be caused by more than one etiologic agent and, conversely, some may lead to a broad spectrum of infections. Statistical association may represent a true causal relationship or a confounding association with another risk factor.

## **1.6 Appropriate Research Methods on Predictive Risk Factors**

There is an extensive body of evidence from bench science to clinical studies that investigate MRSA colonisation and transmission. The types of interventions studied have varied in scope and complexity and span from the needs of individual patients and practitioners to whole of system methods for screening, right through to greenfields (new) hospital design. The most common forms of research to inform the effectiveness of clinical practice may arise from bench research that is translated into clinical trials. Clinical trials that utilize controls, blinding and randomization are the most ideal methods to test the effectiveness of healthcare interventions. These methods minimize the risk of systematic bias and, facilitate objective assessment of whether an intervention was the probable true cause of an outcome. Hierarchies of evidence tend to place the randomized controlled trial (RCT) as one of the highest levels of evidence because of these characteristics. The Joanna Briggs Institute (JBI) levels of evidence for effectiveness are typical in that a systematic review of trials is the highest level evidence, followed by a well designed RCT, then other forms of experimental research designs are further preferenced over observational or descriptive research.<sup>26</sup> The Centre for Evidence Based Medicine in Oxford has a very similar structure for its hierarchy of evidence, as do most international agencies, including the Canadian Task Force on the Periodic Health Examination and, the United States Preventive Services Task Force (USPSTF).<sup>27</sup> The reliability of experimental research is related both to the robust methods of controlling

for confounding factors or risk of bias and, is also a feature of the requirement for detailed, a-priori protocols that guide each step and stage of the research project. The a-priori protocol reduces the risk of spurious changes in order to generate a result and, facilitates the auditability and transparency of the research process. The Consolidated Standards of Reporting Trials (CONSORT) statement was developed by international consensus of academics, researchers and journal editors in order to promote more reliable reporting of RCT methods and findings. The purpose of the CONSORT statement is to ensure that the reporting of published RCTs actually capitalizes on the internal validity of trials, by ensuring that the reporting in peer reviewed journals includes the elements of RCT methods associated with rigor, indeed there is now a database of exemplars of well reported RCTs.<sup>28</sup>

While the quality of RCT reporting has improved with the introduction of the CONSORT statement, there are naturalistic limitations associated with the design that limit its utility; particularly in relation to complex or multi faceted interventions, including population based interventions. However, while the RCT may provide the ideal form of primary evidence, with its emphasis on prediction and, control of factors that may cause systematic bias, effective MRSA control and prevention requires questions of significance that do not fit the RCT model. For example, it would be unethical to randomize groups where one group would be exposed to MRSA in order to test the effectiveness of a new intervention or treatment program. Not only would there be an ethical conflict, complex interventions such as treatment programs contain multifaceted interventions making it difficult to establish whether a particular component of the intervention was effective. Sanson-Fisher et al <sup>27</sup> highlight that the limitations are associated with issues such as population availability, contamination, duration of follow-up, generalisability versus internal validity, costs, ethics and informed consent, and the inhibition of innovative research questions.

The authors go on to suggest that the notion of best practice is based on the systematic identification of the best available evidence in the context of how the phenomena of interest can be most appropriately studied, meaning that the RCT may not be the optimal design for responding to complex questions. This, other authors have argued does not imply an increased risk of false positive results. Benson and



Hartz <sup>29</sup> in a meta analysis of 136 papers compared outcomes from RCTs and observational cohort studies. Their analysis shows that there were no differences in the resulting estimates of treatment effects. This suggests that primary designs other than RCT can be appropriately applied to health care in order to establish the most appropriate form of evidence to inform clinical practice. The view that evidence is broader than the RCT is not a new phenomenon and, is widely accepted, indeed, the Joanna Briggs Institute conceptual model of evidence-based healthcare (established in 2005) is inclusive of all empirical evidence and, in the absence of empirical evidence, suggests that text and opinion (when suitably appraised and synthesized) is more appropriate than anecdote.<sup>30</sup> The conceptual model utilized by the Institute is based on a hierarchy of evidence that both preferences rigorous systematic reviews and, allows for inclusive understandings of what constitutes evidence. The Institute's levels of evidence address the nature of knowledge, and include the following definitions of evidence in the JBI scale known as FAME:<sup>26</sup>

- Feasibility: the extent to which an activity is practical and practicable. Clinical feasibility is about whether or not an activity or intervention is physically, culturally or financially practical or possible within a given context.
- Appropriateness: the extent to which an intervention or activity fits with or is apt in a situation. Clinical appropriateness is about how an activity or intervention relates to the context in which care is given.
- Meaningfulness: the extent to which an intervention or activity is experienced by the patient. Meaningfulness relates to the personal experience, opinions, values, thoughts, beliefs and interpretations of patients or clients.
- Effectiveness: the extent to which an intervention, when used appropriately, achieves the intended effect. Clinical effectiveness is about the relationship between an intervention and clinical or health outcomes.

The Institute's definitions facilitate the reliable reporting of evidence (other than or in addition to evidence of effectiveness) related to the broader knowledge needs associated with complex interventions. These definitions inform the types of questions that healthcare practitioners may face,

and are linked with the JBI Conceptual Model for Evidence-based Healthcare (EBHC). The model illustrates the cycle of systems that promote best practice, but also includes a focus on the types of evidence that inform best practice (Figure 1).

NOTE:  
This figure is included on page 17 of the print copy of  
the thesis held in the University of Adelaide Library.

*Figure 1: JBI Conceptual Model of Evidence-based Healthcare.*

The types of evidence associated with the JBI FAME scale cross all empirical research methods and incorporate text and opinion. However, within each domain of evidence, the highest level of evidence is a systematic review. The systematic review is also a major aspect of the JBI model for EBHC. In challenging the role of RCTs in relation to complex interventions Sanson-Fisher et al <sup>27</sup> undertook a systematic review with meta analysis. Systematic reviews provide high level evidence in relation to the effects of interventions, and as the study by Sanson-Fisher et al <sup>27</sup> concludes, they can also be used to test the reliability and magnitude of an effect size across study designs. A further benefit of systematic reviews is the ability to overview a body of literature rather than rely upon the findings of single studies. Systematic reviews therefore provide a useful overview of a body of literature and, also include

strategies to minimize the influence of poor quality studies on the overall findings; therefore they have a higher utility than individual studies. This is particularly the case where studies on the same interventions, measuring the same outcomes report differing treatment effects. The role of systematic reviews, with or without meta analysis has been described in the Cochrane Handbook for Systematic Reviews of Interventions.<sup>31</sup> A review is described as the process of collating all empirical evidence that meets a-priori inclusion criteria on a particular topic, intervention and population. A review uses particular strategies to minimize the risk of bias, and on the basis of its methods and comprehensiveness, is able to provide more reliable findings to inform policy or practice. The handbook goes on to indicate that a systematic review includes:

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies.

Meta analysis is described in the Cochrane handbook as a statistical approach to combine the estimates of effect from similar, individual studies into one result. The benefits of meta analysis are described as increasing the power and precision of estimates of the effects of healthcare interventions, particularly when compared with the power and precision of individual studies. Meta analysis does not disrupt the methodological rigour in individual studies, rather it preserves the statistical benefits of randomisation, thus having no negative effect on the risk of bias.<sup>31</sup> For these reasons, a systematic review is considered the highest level of evidence. However, a systematic review is a complex undertaking. The nature of the evidence being sought (feasibility, appropriateness, meaningfulness or effectiveness) as well as the challenges of systematic identification of a diverse body of evidence have been noted previously, particularly in relation to complex interventions.<sup>32</sup> Sweet and Moynihan indicate that when one moves away from the review of studies single interventions and, toward the review of

complex topics in public health [such as risk factors] population diversity, terminology variations, indexing and aspects of analysis become more challenging. In spite of these challenges, a systematic review is still considered to provide the optimal evidence associated with healthcare policy or practice .<sup>27,32</sup>

The topic of this dissertation, although relevant to public health, is specific to the identification of risk factors of significance associated with the transmission of MRSA. Systematic reviews and meta analysis of the effects of healthcare interventions are based upon an established methodology and methods (meta analysis was first published in the 1970's by Gene Glass). However, systematic reviews on risk factors and the association between risk and harm are a far more recent innovation. Previous reviews of risk factors have addressed other complex topics such as risk factors for posttraumatic stress disorder <sup>33</sup> and whether antibiotic exposure increases the risk of MRSA isolation.<sup>25</sup> In both of these publications, the authors identified challenges associated with heterogeneity, lack of external generalisability of study samples to the wider population, duration of follow up in longitudinal studies, the challenges with indexing in databases, risks of bias and confounding in the primary research literature (including the potential dose/effect relationship).<sup>25,33</sup> In light of these challenges, the call for a clear and detailed a-priori protocol, as recommended in the JBI Handbook for Systematic Reviews ( <sup>26</sup> further reinforces the benefits of systematic identification, assessment of internal validity, and synthesis of studies selected according to quality and inclusion criteria as providing a higher level of evidence than single studies.

Although several guidelines recommended active surveillance testing in prevention of MRSA transmission, the target populations involved in the strategy are not well defined. A systematic review and meta-analysis on risk factors for MRSA colonisation has yet to be undertaken. Therefore, the purpose of this systematic review is to provide evidence on risk factors for MRSA colonisation in adult subjects on admission to acute care settings and, to develop a better understanding of their epidemiology. Identifying the factors associated with colonisation has the potential to facilitate

development of a predictive model for selective screening program that has specificity and sensitivity to MRSA.

## **Chapter 2: Methods**

### **2.1 Review questions/objectives**

The overall objective of this review was to identify and summarise independent risk factors for MRSA colonisation among adults. The secondary objectives were:

- to evaluate the strength of association between risk factors and MRSA colonisation on admission to acute care facilities, and
- to detect heterogeneity among current eligible studies.

### **2.2 Inclusion criteria**

#### **2.2.1 Types of studies**

This review considered quantitative studies identifying the independent risk factors for MRSA colonisation in adults at the time of admission in an acute care setting. The time of assessment needed to be on admission in order to ensure quantitative correlation between risk factors and colonisation. This review considered research papers utilising the following study types:

- Randomised controlled designs;
- Pseudo-randomised controlled designs;
- Cohort studies;
- Case-control trials;
- Cross-sectional studies.

In general, cohort and case-control studies are main designs associated with the study of risk factors associated with diseases. These designs compare a variety of patients and environment characteristics between cohort and case-control studies, and can be evaluated using multivariable logistic regression analysis to identify independent factors.

## 2.2.2 Types of participants

Studies that included all adult (more than 18 years old) patients on admission in acute care settings were considered for inclusion in this review. Studies that were conducted in outbreak settings were not included in this review; because infection control policy variations and, higher relative prevalence is associated with such environments and may induce higher colonisation pressure.

Definitions of types of MRSA carriers in this review:

- Colonisation: when a patient has MRSA in or on a body site but has no clinical signs or symptoms of disease. A person colonised with MRSA may be a temporary or a longer term carrier of MRSA.<sup>4</sup>
- Infection: when MRSA enters a body site and multiplies in tissue causing clinical manifestations of disease. This is usually evident by fever, a rise in the white blood cell count, or purulent drainage from a wound or body cavity. The distinction between colonisation and infection is a clinical one. Such a distinction should be determined by the clinician, not by culture results alone.<sup>4</sup>

The carrier status must be clearly defined in included studies. In this review, MRSA colonisation at admission is defined as an admission nasal surveillance culture positive for MRSA or any clinical culture positive for MRSA within 48 hours after hospital admission. MRSA acquisition was defined as an admission nasal surveillance culture negative for MRSA and subsequent isolation of MRSA from a surveillance or clinical culture performed more than 48 hours after admission.

## 2.2.3 Types of Exposures and interest interventions

A risk factor (condition determinant, predisposing factors) in this review is defined as an individual factor that is positively or negatively associated with the occurrence of MRSA colonisation. There are three categories of factors: attribute (intrinsic), exposure (externally environmental) and association with setting. Attribute factors are an intrinsic characteristic of the individual (e.g., genetic susceptibility, age, sex, and previous disease or therapy history). Exposure factors are determinants that are in the environment external to the individual (e.g., invasive therapy, burns,

wounds, or antibiotics). Setting factors are associated with the characteristic of individual units or settings.

To identify independent risk factors, appropriate biological screening techniques or laboratory diagnostic tests must be reported in all included studies. In this review it was required that all included studies also report that surveillance specimens were obtained from the anterior nares and at least one other active surveillance site, such as axillae, throats, groin, perineum, active skin breakdown or draining wounds. Traditional culture based and molecular testing techniques are widely used and can provide precise and direct identification of MRSA using surveillance cultures. Both were accepted in this review as an essential prerequisite for each included studies.

#### **2.2.4 Types of outcomes**

The primary outcome of interest was presence and absence of MRSA on admission in selected studies, and then the carriage status of MRSA (colonisation and infection) were identified by active screening program on admission. Colonisation was intended to include asymptotically colonised MRSA carriers, differentiated from MRSA infection, MSSA colonisation and *S. aureus* negative populations. The secondary outcome of interest was risk factors associated with MRSA colonisation on admission, and the risk factors were part of exposures of patients and clearly recorded in selected studies.

#### **2.2.5 Types of effect measures**

The presence of MRSA colonisation was expressed by prevalence or incidence rate in selected studies and summarised in this review. All statistical correlation indicators between risk factors and colonisation, such as risk ratio (RR) or likelihood ratio (LR) and odds ratio (OR) comparing MSSA carriage and *S. aureus* negative populations were checked and included in this review. All statistical measurements (for dichotomous data) and weighted mean differences (for continuous data) and their 95% confidence intervals (CIs) were calculated in the analysis where the prevalence data on included studies was available from included studies or could be obtained by contacting the



authors.

## 2.3 Search strategy

The search included both published and unpublished studies written in the English language. A three-step search strategy was used. An initial search of Medline and CINAHL databases was undertaken to identify optimal search terms, followed by a second, database specific, detailed search using all identified key words and index terms. Thirdly, the reference list of all identified reports and articles were searched for additional studies. The search strategy per database incorporated the period 1990 to June 2010; as MRSA strains were considered endemic in healthcare facilities from the 1990s.<sup>4</sup> (see Appendix I).

*Initial search terms included:*

- *Methicillin-resistant Staphylococcus aureus*
- *Meticillin-resistant Staphylococcus aureus*
- *MRSA*
- *Nosocomial infection/ hospital acquired infection*
- *Risk, risk assessment, risk management, risk factor*
- *Infection control practices*
- *Colonisation, carriage, carriers and acquisition*

*The following databases were searched:*

- CINAHL (1990 - 2010)
- Medline (1990 - 2010)
- The Cochrane Central register of controlled trials (CENTRAL) (1990 - 2010))
- Embase (1990 - 2010)
- ACP online (1990 – 2010)

- BioMed Central (1990 - 2010)
- Health Technology Assessment database (1990 – 2010)
- Current controlled trials (1990 - 2010)
- AGAR (1990-2010)
- CENTURY (1990-2010)

*The search for unpublished studies or grey literature included the following databases:*

- Grey Literature Report: The New York Academy of Medicine Library (1990 - 2010)
- The Networked Digital Library of Theses and Dissertations (NDLTD) (1990 - 2010)
- DIVA Academic Archive Online (1990 - 2010)

## **2.4 Critical Appraisal**

Independent critical appraisal was performed by both investigators (Y.X and A.A.G). Each investigator was blinded to the other investigator's critical appraisal. It was planned that in the case of disagreement between the two reviewers, a third reviewer (C.L) would be consulted, however, there were no significant disagreements over the quality assessment, or subsequent decision to include or exclude particular studies.

Selected studies were assessed using a standardised critical appraisal instrument that was developed focusing on the characteristics of prognostic studies in infection control field. This critical appraisal instrument was based on Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information package (SUMARI), and modified to facilitate inclusion of prognostic factors specific to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria.<sup>34</sup> Three criteria were highlighted as priorities for weighting in the modified appraisal checklist, principally to assist with managing the risks of bias associated with observational or descriptive studies (Appendix II). Patient information collected across all included studies was categorised as:

1. demographic data including age, gender and race;

2. administrative data referring to hospitalisation within certain period, LTCF residence, routine, rehabilitation and clinic visits, transfers;
3. clinical data including previous MRSA carriage, comorbid conditions, chronic conditions, degree of disability, presence of urinary catheter, tracheotomy, skin lesions, comorbidity index, severity scores of underlying and fatal disease, anaesthesiology score; and
4. and therapeutic data, referring to antibiotic treatment within certain period, intravenous therapy, dialysis and chemotherapy.

The classifications of collected information covered all potentially independent risk factors which were identified in primary studies. The risk of bias was associated with the potential problems in recall or documentation accuracy.

## **2.5 Confounding factors**

### **2.5.1 Hospital infection control policy**

Current guidelines advocated by experts and organisations include the requirement to perform frequent surveillance cultures in order to attempt to identify and the isolate all individuals who asymptotically carry MRSA (because MRSA colonisation places patients at high risk for nosocomial infection). Control strategies combine screening, cohort allocation, early implementation of contact isolation, or standard control precaution, and topical decolonisation to reduce MRSA incidence in hospital. Early MRSA identification after admission is vital to the whole control strategy and, identification requires appropriate sampling methods, the accurate recording of time of sampling, and laboratory diagnostic tests undertaken. The sensitivity of surveillance specimens obtained from a variety of sites has been evaluated in multiple settings and patient populations. Although testing of no single site will detect all MRSA colonised persons, the anterior nares appear to be the most frequently positive site. Because of this and the accessibility of the site, the anterior nares are generally considered to be the primary site for sampling in MRSA screening programs. Aizen et al <sup>35</sup> observed that samples from multiple sites could ensure

detection of most MRSA carriers. Cultures of the nares were positive in 58.3% of admissions with MRSA carriage, and combining nasal and throat cultures was found to lead to detection of 87.4% of admissions with MRSA carriage. Nasal, throat and clinical samples were found to further increase the detection rate, up to 91.7%.<sup>35</sup>

Therefore, in this systematic review, all included studies were required to document that surveillance specimens were obtained from anterior nares and at least one other surveillance area, such as axillae, throat, groin, perineum, active skin breakdown or draining wounds. Traditional culture based and molecular testing techniques are widely used, and can provide precise and direct identification of MRSA using surveillance cultures. Both methods were accepted in this review as an essential prerequisite for each included study.

## **2.5.2 Numbers of dropouts and missing data**

There are a number of important issues to consider in evaluating an observational cohort study in infection control. One issue is loss to follow up, particularly differential loss to follow up. Loss to follow up occurs when, during the study period, individuals drop out of the study. Differential loss to follow up is when the dropout rate differs in the exposed and not exposed groups. The concern is that differential loss to follow up introduces bias into the study. The number of patients that drop out of a study should give concern if the number is very high. Conventionally, a twenty percent dropout rate is regarded as acceptable, but in observational studies conducted over a lengthy period of time a higher dropout rate is to be expected.<sup>34</sup> A decision on whether to downgrade or reject a study because of a high dropout rate is a matter of judgement based on the reasons why people dropped out, and whether drop-out rates were comparable in the exposed and unexposed groups. Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well conducted study.

## **2.6 Data collection/ extraction**

The data of interest include all features of individual studies:

- Study design,
- Duration of follow-up,
- Settings of patient admission,
- Population and allocation,
- Sample sizes of case and control groups,
- Prevalence of MRSA identification,
- Screening protocol (timing and sampling sites),
- Study interests of risk factors,
- Information collection (demographic, administrative, clinical and therapeutic data),
- Hospital infection control policy (hospital surveillance, infection standard precautions, isolation and cohorting, and decolonisation measures),
- And numbers or percentage of dropouts and missing data.

Data were collected from included papers in the review using the standardised data extraction tool from the JBI SUMARI Program; however the data extraction form was modified based on the characteristics of prognostic studies for infection control (Appendix III).

Additional data was extracted and summarized by tables to longitudinally compare relevant aspects of quality of included studies, which included information recall, individual hospital MRSA control policy, and case and control numbers for each risk factor reported by selected studies.

## **2.7 Data synthesis**

As some studies did not present the data for factors that were not statistically significant by multivariate logistic regression, a complete dataset was not always obtainable for each factor evaluated in every single study. All risk factors (identified by univariate logistic regression) in included studies were aggregated depending on their clinical characteristics. Data of any aggregated factors was pooled into

meta analyses based on univariate estimates and multivariate estimates separately when more than two groups of data in selected studies were available.

The odds ratio (OR) with 95% CI was used to estimate the strength of association for dichotomous variables. Assessment of heterogeneity between trials was tested using both Cochrane Q test and I-squared test. The Q statistic was compared with chi-square distribution with K-1 DF. Significant heterogeneity was set at  $P < 0.05$ , and  $I^2 > 50\%$ . Because of adequate consideration of the source of variability in the data of selected studies, a random effects model (DerSimonian-Laird test) was used.<sup>36</sup>

For each factor, a Forest plot was produced to compare effect size of each selected study. In sensitivity analysis, funnel plots were produced for each identified significant risk factor to assess possible publication bias.<sup>37,38</sup> All calculations and graphical representations were performed using commercially available meta-analysis software.<sup>39</sup>

## Chapter 3: Results

### 3.1 Characteristics of the studies

The search process identified 1021 titles and abstracts through electronic bibliographic sources, hand searches of various sources, reference lists and citation indices. After reviewing titles and abstracts, 980 articles were filtered out by screening against the review inclusion criteria. Studies that were removed, consisted of 225 duplicates, 191 diagnostic studies, 153 literature reviews, 139 MRSA breakout reports, 129 studies on paediatric patients, 75 case reports, 31 studies on health care workers and 7 studies on prisoners, 27 clinical guidelines and 3 predictive rules based on previous prognostic studies. Following screening forty-one studies were assessed for eligibility and subject to critical appraisal following retrieval of the full-text of each study. Of which thirteen studies were excluded since these studies were conducted in non-acute care settings, eleven studies were not selected due to unidentified MRSA carriage status of patients, and two studies reported data were partly repeated with other included studies. No studies were excluded in critical appraisal phase because of poor quality. Finally, fifteen studies reporting seventeen trials were included in this review.<sup>40-54</sup> The characteristics of excluded studies are described in Appendix IV. Figure 2 shows the process involved in the selection of studies for this review.

The fifteen studies were published between 1998 and 2009 and conducted in Australia, France, Japan, Spain, Switzerland, the United Kingdom, and the United States of America. In general, study quality was good, and no studies were excluded on the basis on poor methodological quality. Strict epidemiological study design and statistical methods were well implemented, and all included studies were prospective designed.

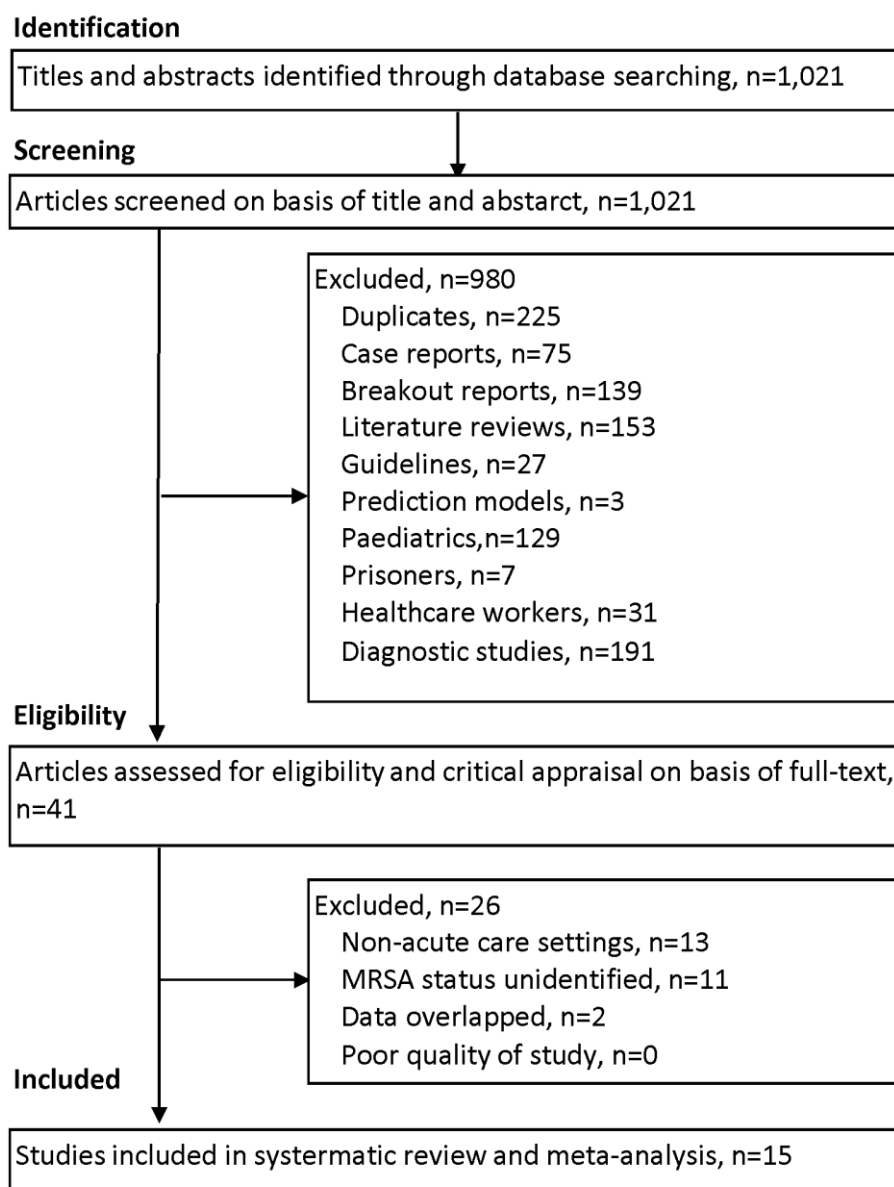


Figure 2: Flow diagram of the included and excluded studies

Sample sizes varied from 138 to 6,035, with a median of 1,097. A total of 16,467 patients were included in the selected studies. The incidence of admission MRSA colonisation ranged from 1.4% to 14.6% in selected studies. The settings of the studies were altered: six studies were set in whole tertiary hospital, three were carried out in the surgical departments, three were conducted in the ICUs, two were set in the acute geriatric wards and one was conducted in the emergency department. Four studies samples were specifically of older adult patients and, known MRSA carriers were excluded in five studies (Table 1).



Table 1 Details of studies included in the meta analyses

Study ID	Study Design	Duration of follow up	Setting	Population	Samples Size		Prevalence	Risk Factors (Identified by multivariate regression)
					Case	Control		
Casas 2007 Spain	Cohort	18 months	Tertiary	Adults Previous Unknown	17	1111	1.40%	Advanced age Hospitalisation within 12mo Admission to LTCF within 12mo
Eveillard 2002 France	Cohort	5 weeks	Two geriatric ward of tertiary	Elderly	35	204	14.60%	Hospitalisation within 6mo Wounds/bedsores Urinary tract catheter ASA score $\geq$ 3
Gopal Rao 2007 UK	Cohort	12 months	ED of Tertiary	Adults	433	5602	6.70%	Hospitalisation within 12mo Previous Known MRSA within 24mo Current admission to LTCF
Harbarth 2008 Switzerland	case-control	9 months	Surg Depart, Tertiary	Adults Previous Unknown	57	348	3.20%	Aged>75yo Hospitalisation within 12mo Antibiotic within 6mo
Harbarth 2006 Switzerland	case-control	7 months	Tertiary	Adults Previous Unknown	204	802	3.30%	Male Aged>75yo Intra-hospital transfer Hospitalisation within 12mo IV therapy within 12mo

								Urinary tract catheter Carbapenems within 6mo Cephalosporins within 6mo Fluoroquinolones within 6mo
Hidron 2005 U.S.	Cohort	1 month	Tertiary	Adults	53	673	7.30%	Hospitalisation within 12mo Skin or soft tissue infection HIV infection Antimicrobial within 3mo Alternative housing Previous Known MRSA within 12mo
Jernigan 2003 U.S.	case-control	2 months	Tertiary	Adults	26	78	2.70%	Hospitalisation within 12mo Admission to LTCF within 12mo Previous known MRSA colonisation Current antibiotic
Lucet 2005 France	Cohort	3 months	Tertiary	Elderly>75yo Previous Unknown	63	797	7.90%	Chronic skin lesion LTCF, Rehab unit within 18mo Poor chronic health status APACHE C,D
Lucet 2003 France	Cohorts	6 months	14ICUs in 6Tertiary	Adults Previous Unknown	162	2189	6.90%	FOR TRANSFERRED PTS (53:693) Aged>60yo Hospitalised >21d before ICU Stoma FOR DIRECTLY ADMITTED PTS (43:1400)

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								Aged>60yo Hospitalised ICU within 5yr Surgery within 5yr Open skin lesions Hospitalisation within 5yr Antimicrobial within 6mo Rehab or LTCF within 5yr Poor chronic health status APACHE C,D Fatal disease McCabe Simplified Acute Physiology Score II>40 Central venous catheter
Marshall 2002 Australia	Cohort	10 months	ICU in Tertiary	Adults	80	1105	6.80%	Previous ICU stay Trauma/Orthopedics wards Neuro/Endo/Rheum/Renal wards LOS of ICU >3d
Nishikawa 2009 Japan	Cohort	6 weeks	Geriatric Tertiary	Elderly>65yo	11	127	8.00%	Hypoalbuminemia Bedridden status Referred from LTCF Pressure sores Respiratory failure
Sax 2005 Switzerland	Cohorts	10 months	Geriatric Tertiary	Elderly>75yo	27	671	7.30%	Hospitalisation within 2yr Recent antibiotic <1mo Intra-hospital transfer

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Warren 2006 U.S.	Cohort	15 months	SICU in Tertiary	Adults	82	693	8.00%	1-2 admission within 12mo >2 admission within 12mo LOS >5d Pre-ICU COPD Diabetes mellitus MRSA isolation <6mo
Troillet 1998 Switzerland	case-control	3 months	Tertiary	Adults	10	377	2.60%	Previous Known MRSA within 24mo Open skin lesions Diabetes mellitus Injection therapy Admission to LTCF within 12mo Antibiotic within 6mo HCW home visit within 6mo
Samad 2002 UK	Cohort	3 months	Surg Depart, Tertiary	Adults	23	407	5.30%	Hospitalisation within 12 mo LTCF referred Male Aged >70yo

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### **3.2 Quality of included studies**

The general quality of include studies is good, although there are limitations on study design (prospective observational design) and research area (multidrug resistant bacteria). The sample size of the studies ranged from 104 to 6,035 with a median of 1,097. All studies used similar statistical analyses: variables associated with MRSA carriage were compared using chi-square or Fisher's exact test, as appropriate. Continuous variables were compared using the student's *t* test or non parametric Wilcoxon rank sum test, as appropriate. Categories were defined, and odds ratio (OR) with their 95% confidence intervals (CIs) were calculated by comparing to reference categories. All variables yielding *p* values no greater than 0.1 on the univariate and multivariate analyses were entered into a forward stepwise logistic regression model. All tests were two-tailed, *p* values less than 0.05 were considered significant. No studies reported missing data, 10 of 15 studies did not state dropouts. Four studies reported dropouts ranging from 0.1% to 2.2%. However, a multicentre study which covered 14 French ICUs and enrolled 2,399 patients reported 5.2% dropouts.

### **3.3 MRSA identification**

In order to differentiate MRSA colonisation on admission from hospital MRSA acquisition, 13 included studies utilized admission screening in first 48 hours of new hospitalisation. One study even introduced pre-admission screening in the emergency department.<sup>42</sup>

Two groups of samples were taken in all included studies. One was surveillance culture samples, taken from the nose, throat, groin, and axilla of the patients.<sup>42,45,46,49,50,54</sup> The other was active surveillance culture, which includes all surveillance culture sites as well as from catheter insertion sites, skin lesions and other sites when clinically indicated.<sup>40,41,43,44,47,48,51-53,</sup>

### **3.4 Hospital MRSA control policy**

Current guidelines advocated by experts and organisations are to perform frequent surveillance cultures to attempt to identify and isolate all individuals who asymptotically carry MRSA, because

MRSA colonisation places patients at high risk for nosocomial infection. The control strategies combine screening, cohorting, early implementation of contact isolation, or standard control precaution, and topical decolonisation to reduce MRSA incidence in hospital. In all included studies, surveillance was well designed and conducted. In 11 of 15 studies, standard infection control precautions were strictly performed. Limitations with regard to availability of isolation rooms and human resources were evident problems for some hospitals developing or implementing their isolation measurements. Eight of 15 studies described an isolation policy (Table 2).

### **3.5 Collection of patient's information**

Patient's information were collected in all selected studies, including: demographic data including age, gender and race; administrative data referring to hospitalisation within certain period, LTCF residence, routine, rehabilitation and clinic visits, transfers; clinical data including previous MRSA carriage, comorbid conditions, chronic conditions, degree of disability, presence of urinary catheter, tracheotomy, skin lesions, comorbidity index, severity scores of underlying and fatal disease, Anaesthesiology score; and therapeutic data, referring to antibiotic treatment within certain period, intravenous therapy, dialysis and chemotherapy. In relation to antibiotic treatment, two studies provided the data of current prescriptions, three studies provided the data within 3 months, and four studies recalled antibiotics history of patients within 6 months. Only one study recorded the patient's antibiotic administration history up to 12 months. Five studies did not record a set timeframe for antibiotic administration data. No studies reported missing data, 10 of 15 studies did not state dropouts, and 4 reported dropouts were less than 2.2%, the other was 5.2%.

Table 2 Hospital control policies and recorders of patient's information

Study ID	Infection Control Policy				Patient's Information			
	Surveillance	Standard control Precautions	Isolation	Decolonisation	Demographi c	Administrative	Clinical	Antimicrobial
<i>Casas 2007</i>	YES	NA	NA	NA	YES	Location <12mo	YES	Antibiotic <6mo
<i>Eveillard 2002</i>	YES	NA	NO	NA	YES	Location <6mo	YES	Antimicrobial<15d
<i>Gopal Rao 2007</i>	YES	YES	YES	YES	YES	Location <12mo	YES	No
<i>Harbarth 2008</i>	YES	YES	YES	YES	YES	Location <12mo	YES	Antibiotic <6mo
<i>Harbarth 2006</i>	YES	YES	YES	YES	YES	Location <12mo	YES	Antibiotic <6mo
<i>Hidron 2005</i>	YES	NA	NA	NA	YES	Location <12mo	YES	Antibiotic <12mo
<i>Jernigan 2003</i>	YES	YES	YES	NA	YES	Location <12mo	YES	Current antibiotic
<i>Lucet 2005</i>	YES	YES	YES	YES	YES	Location <18mo	YES	No info of antibiotic
<i>Lucet 2003</i>	YES	YES	NA	NA	YES	Location <5yr	YES	Current antibiotic
<i>Marshall 2002</i>	YES	YES	PARTLY	NA	YES	Limited	YES	No info of antibiotic
<i>Nishikawa 2009</i>	YES	YES	NA	NA	YES	YES	YES	No info of antibiotic
<i>Sax 2005</i>	YES	YES	YES	YES	YES	Location <2yr	YES	Recent antibiotic <1mo
<i>Warren 2006</i>	YES	YES	YES	NA	YES	Location <12mo	YES	Antibiotic <6mo
<i>Troillet 1999</i>	YES	NA	NA	NA	YES	Location <5yr	YES	Antibiotic <3mo
<i>Samad 2002</i>	YES	YES	NA	NA	YES	Location <12mo	YES	NA

### 3.6 Aggregation of risk factors

These thirteen categories covered all four types of patient information: demographic characteristics (age and gender), administrative data (hospitalisation, admission to long-term care facilities (LTCF) and rehabilitation facilities), clinical data (previous known MRSA carriage, skin lesions, chronic disease and status) and therapeutic data (Antibiotic uses, invasive and intravenous therapy) (refer to Table 3).

*Table 3 Summary of risk factors predicting MRSA colonisation reported in the included literature*

<b>Aggregated Factors</b>	<b>Individual Factors</b>
Age	Aged over 60 years old, over 75 years old
Gender	male sex
Hospitalisation	Hospitalisation within 6 months, 12 months, 2 years and 5 years; and emergency department admission
Previous surgery	Surgery within 3 months, 12 months and 2 years
Previous ICU admission	ICU admission within 12 months and 5 years
Intra hospital transfer	Intra-hospital transfer
History of admission to LTCF and rehabilitation facilities	Admission within 12 months, 18 months and 5 years
Previous known MRSA carriage	Within 6 months, 12 months, and 24 months
Antibiotic use	Current use; within 1 month, 3 months, 6 months and 12 months
Skin lesion	Bedsore, pressure ulcer, skin and soft tissue infection, open skin lesion, and chronic skin lesion
Chronic disease and status	Diabetes mellitus; COPD and Respiratory failure; Chronic renal disease; hypoalbuminemia; bedridden status and complete dependence; HIV infection; fatal diseases; APACHE score C or D, SAPS II score over 40, ASA score more than 3 and Barthel index less than 65
Transferred to ICU	Length of stay more than 3 days before admission to ICU and more than 21 days; transferred from trauma wards, from neurological wards
Invasive and IV therapy	Urethral catheter; central venous catheter; stoma; IV therapy within 12



### 3.7 Meta analyses of risk factors

There were twelve risk factors identified by more than three studies. Meta-analyses were performed for each factor by random effects model, calculating odds ratios with 95% confidential intervals and the associated  $p$  value. The sample size for each factor ranged from 2,344 to 12,434. The combined odds ratios varied from 1.7591 to 6.7329 and the  $p$  value of all factors was less than 0.002. Heterogeneity tests were also undertaken with each meta-analysis. The outcome of the  $I^2$  for heterogeneity was greater than 50%, which indicated heterogeneity among the original studies has been reported in Table 4.

All twelve meta analyses revealed significant association between risk factors with MRSA colonisation on admission. No significant heterogeneity was found among studies which identified recent antibiotic uses, male sex, previous hospitalisation, indwelling urinary catheter, intra hospital transfer, previous surgical experience, skin lesion, chronic comorbidity (categorised in APACHE C or D) and ultimately and rapidly fatal diseases based on univariate estimates. A moderate heterogeneity was found among nine studies which identified previous admission to LTCF and rehabilitation facilities as a risk factor for MRSA colonisation ( $I^2 = 42.44\%$ ). However, significant heterogeneity was detected among studies that investigated previous MRSA colonisation and previous ICU admission. Although significant odds ratios were found by pooled data, the results should be considered with caution due to inconsistent reporting across the studies on previous MRSA colonisation and previous ICU admission. Funnel plots that aid assessment of publication bias are reported in Appendix 5 (Figures 23 - 34).

Age greater than 60 years was strongly associated with MRSA carriage on admission and, is independent of other risk factors, such as skin lesion and antibiotic uses. Five studies in the review identified increased age as independent risk factor for MRSA colonisation.<sup>40,43,44,48,51</sup> Two studies required the patient's age to be more than 65 years as enrolment criterion,<sup>41,50</sup> and two studies only enrolled patients older than 75 years.<sup>47,52</sup> A study found that the high risk age was  $73.88 \pm 14.66$  years

old (OR 1.04,  $p = 0.04$ ),<sup>40</sup> the other studies found the different age category as independent risk factors, such as older than 60 years,<sup>48</sup> older than 70 years,<sup>51</sup> and 75 years.<sup>47,48</sup> Due to different data types used in selected studies, meta-analysis was not able to be conducted.

*Table 4 Results of meta-analyses of independent risk factors*

<b>Risk Factor</b>	<b>No. of studies</b>	<b>Sample Size</b>	<b>Odds Ratios</b>	<b>95% CI</b>	<b>P value</b>	<b>Heterogeneity <math>I^2</math></b>
Antibiotic Uses	8	7,038	3.7694	3.2453 - 4.3781	0.0001	0.00%
Chronic Health (APACHE C,D)	3	2,344	3.025	2.1844 - 4.1891	0.0001	0.00%
Male sex	3	2,507	1.8167	1.5180 - 2.1742	0.0001	0.00%
Hospitalisation	11	12,748	3.4309	2.9732 - 3.9590	0.0001	1.05%
Indwelling Urinary Catheter	5	3,126	4.3898	3.4317 - 5.6156	0.0001	0.00%
Intra Hospital Transfer	3	2,749	2.0955	1.6966 - 2.5881	0.0001	0.00%
LTCF & Rehab Residency	9	11,788	6.7004	4.2609 - 10.5364	0.0001	42.44%
McCabe Scores (fatal disease )	4	4,647	1.7591	1.4259 - 2.1702	0.0001	0.36%
Previous MRSA Colonisation	3	7,990	6.7329	2.4504 – 18.4995	0.0019	96.71%
Previous ICU admission	4	5,101	3.8845	1.6605 - 9.0871	0.0018	63.07%
Previous Surgery	5	4,967	2.9807	2.5261 - 3.5172	0.0001	0.00%
Skin Lesion	8	6,056	3.5250	2.6194 - 4.7437	0.0001	11.32%

### 3.7.1 Antibiotic uses

Antibiotic use was regarded a direct reason including multidrug resistant bacteria, especially MRSA.<sup>41</sup> Nine papers reported on ten studies (one paper included two studies) explored the relationship between previous antibiotic therapy and MRSA colonisation.<sup>40,43-46,48,52-54</sup> In one study, only current antibiotic treatment was recorded and previous treatment was not reported.<sup>46</sup> Harbarth and colleagues<sup>43</sup> only reported the odds ratio of antibiotic uses in case and control arms, and did not report the patient numbers in the two arms. A meta-analysis including eight studies with total 7,038 new admissions was conducted. The results showed that antibiotic treatment within the past 1 to 12 months was an independent risk factor for MRSA colonisation (OR 3.7694, 95% CI 3.2453 – 4.3781,  $p < 0.0001$ ) (Figure 3). There was no heterogeneity among the included studies ( $I^2 = 0\%$ ).

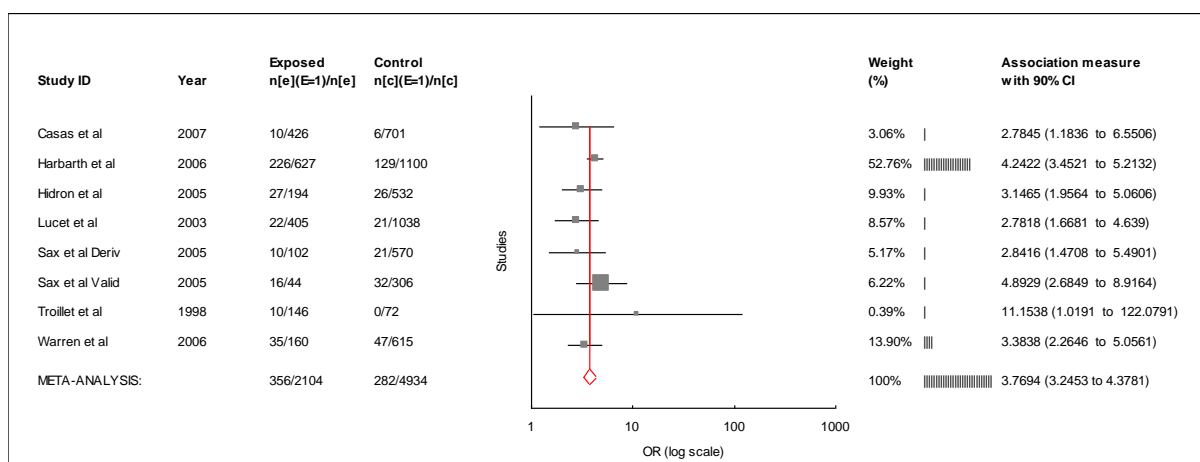


Figure 3: Meta-analysis of recent antibiotic use as a risk factor

### 3.7.2 Chronic health evaluation (APACHE) score C or D

The Acute Physiology and Chronic Health Status Evaluation (APACHE) is a method of indexing the severity of disease and predicting mortality that has been widely used by ICUs for measuring illness severity in groups of critically ill patients within first 24 hours on admission.<sup>55</sup> In the frame of APACHE classification C or D, the chronic health evaluation includes seven comorbid conditions: acquired immunodeficiency syndrome (AIDS), hepatic failure, lymphoma, solid tumour with metastasis, leukaemia/multiple myeloma, immunosuppression, and cirrhosis.<sup>55</sup> Three studies explored the cause relationship between existing conditions in category C,D of APACHE score and MRSA colonisation on

admission.<sup>46-48</sup> A meta-analysis was conducted including a total 2,344 admissions. The results showed that the conditions scored APACHE C and D was an independent risk factor for MRSA colonisation on patient admission (OR 3.025, 95% CI 2.1844 – 4.1891,  $p < 0.0001$ ) (Figure 4). There was no significant heterogeneity among pooled studies ( $I^2 = 0\%$ ).

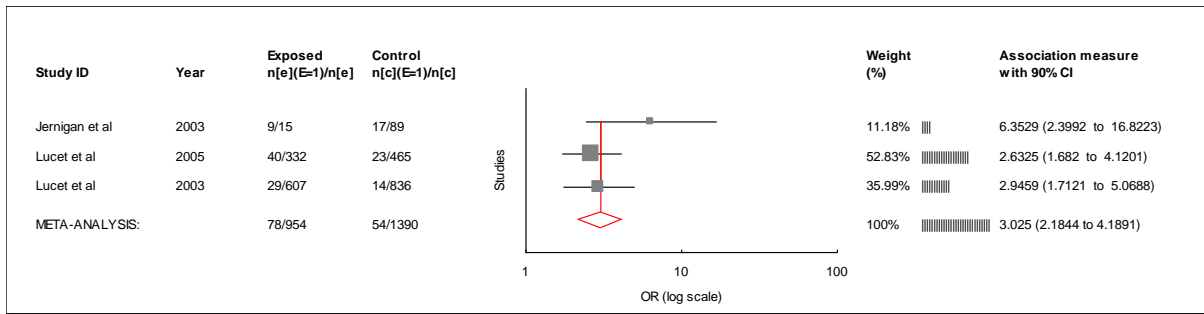


Figure 4: Meta-analysis of APACHE C or D conditions as a risk factor

### 3.7.3 Male sex

Three studies found that male sex was a risk factor for MRSA colonisation on patient admission to a hospital.<sup>41,51,52</sup> A meta-analysis was conducted including a total 2,507 new admissions. The result showed that the odds ratio was 1.8167 (95% CI 1.5180 - 2.1742,  $p < 0.0001$ ) (Figure 5). No significant heterogeneity was found among pooled studies ( $I^2 = 0\%$ ).

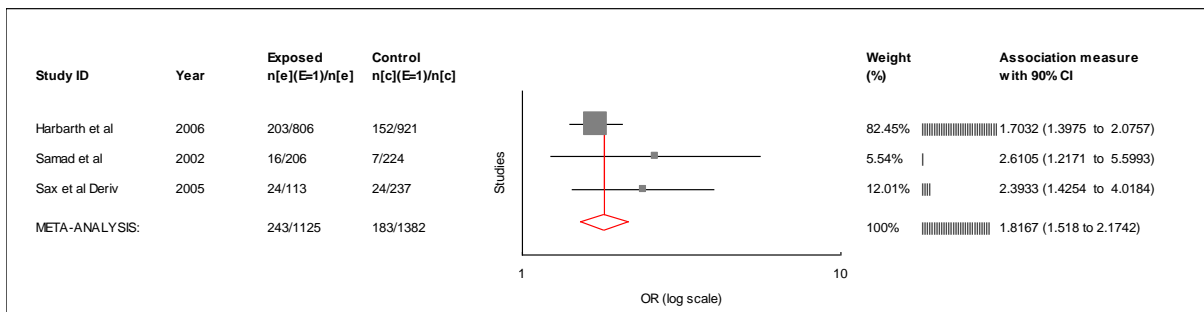


Figure 5: Meta-analysis of male sex as a risk factor

### 3.7.4 Previous hospitalisations

Previous hospitalisation (in some guidelines) had been regarded as an independent risk factor for patients known to be positive for MRSA colonisation.<sup>4,16,17</sup> Twelve studies in this reviews explored the relationship between previous hospitalisation and MRSA colonisation on admission to a hospital unit.<sup>40-46,48,50-52,54</sup> The period of hospitalisation prior to the admission in these studies ranged from 6 months to 5 years. Warren et al<sup>54</sup> calculated the odds ratio for between 1-2 hospital admissions and more than two hospital admissions separately. However, two studies did not provide the patient numbers for case and control groups, but provided the odds ratios of previous hospitalisation between the two arms. Thus, the meta-analysis illustrated below includes ten papers reporting eleven trials with a total 12,748 new admissions. The results showed that previous hospitalisation in last 6 months to 2 years was an independent risk factor for MRSA colonisation on admission (OR 3.4309, 95% CI 2.9732 – 3.9590,  $p < 0.0001$ ) (Figure 6). The heterogeneity test revealed no significant heterogeneity among the eleven trials ( $I^2 = 1.05\%$ ).

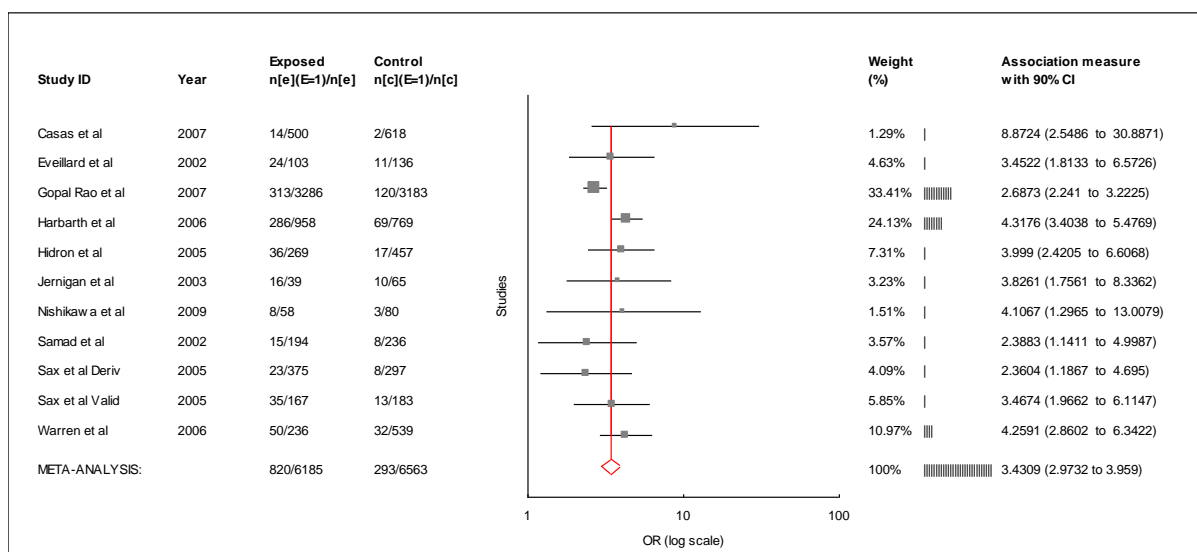


Figure 6: Meta-analysis of hospitalisation as a risk factor

### 3.7.5 Indwelling urinary catheter

Long term indwelling urinary catheters may increase patient susceptibility to urinary tract infections. Four studies with five groups of data reported patients with urinary catheter on admission to a

hospital.<sup>41,44,50,52</sup> A total of 3,126 new admissions was included in the meta-analysis. The result showed a strong relationship between indwelling urinary catheter and MRSA carriage on admission (OR 4.3898, 95% CI 3.4317 - 5.6156,  $p < 0.0001$ ) (Figure 7). No significant heterogeneity was found among pooled studies ( $I^2 = 0\%$ ).

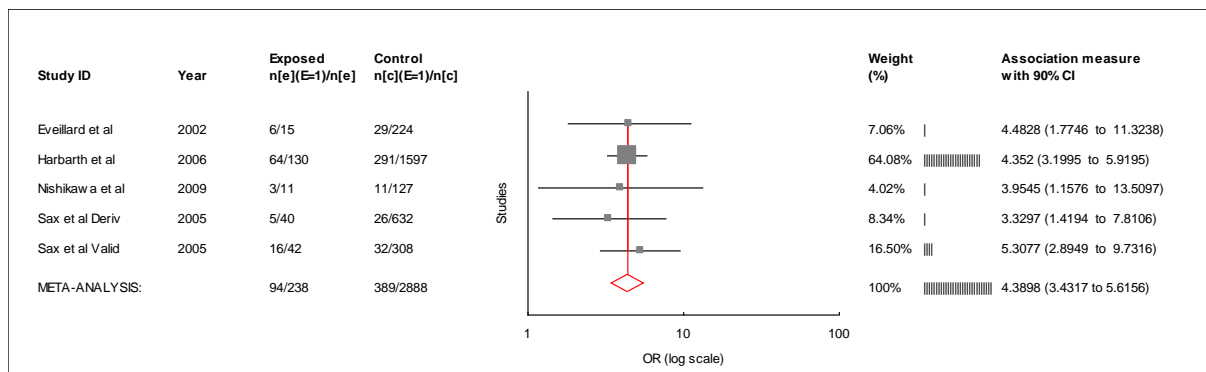


Figure 7: Meta-analysis of indwelling urinary catheter as a risk factor

### 3.7.6 Intra-hospital transfer

Two papers with three studies reported patient intra hospital transfer and MRSA colonisation on admission to a new unit in the same hospital.<sup>44,52</sup> A total 2,749 new admissions was included in the random effects meta-analysis. The results showed that intra-hospital transfer in an independent risk factor for MRSA colonisation (OR 2.0955, 95% CI 1.6966 - 2.5881,  $p < 0.0001$ ) (Figure 8). There was no significant heterogeneity among pooled studies ( $I^2 = 0\%$ ).

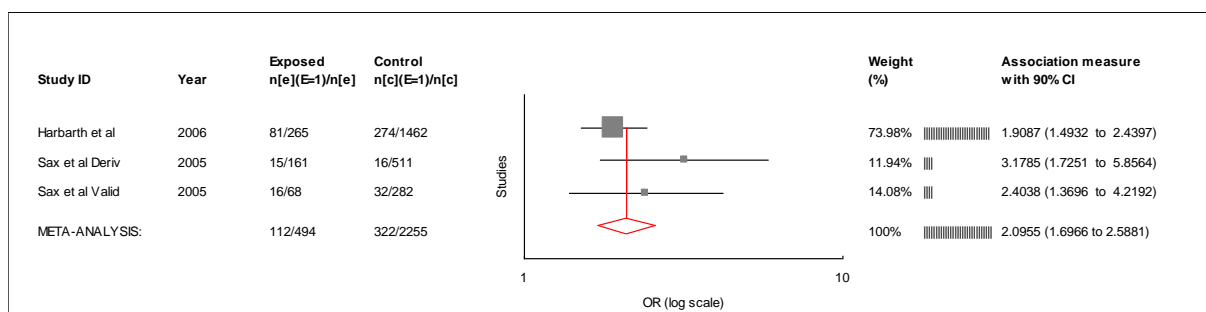


Figure 8: Meta-analysis of intra hospital transfer as a risk factor

### 3.7.7 Previous admission to LTCF and Rehabilitation facilities

The experience of admission to a LTCF or rehabilitation facility had been regarded as a risk factor for MRSA colonisation in many studies within the last 15 years.<sup>16</sup> Ten studies reported the patient history of admission to a LTCF or rehabilitation setting.<sup>40,41,44,46-48,50,51,53,54</sup> The duration of admission to LTCF or rehabilitation setting prior to hospital admission ranged from past 12 months to 5 years, and a majority of studies recorded the history within previous 18 months to the admission, except one study with 5-year admission records.<sup>48</sup> The following meta-analysis included nine studies with a total of 11,788 new admissions and was conducted. The heterogeneity test indicated significant heterogeneity among pooled studies ( $I^2 = 42.44\%$ ). The results showed that the odds ratio of previous admission to LTCF in the last 18 months is 6.7004 (95% CI 4.2609 – 10.5364,  $p = 0.0001$ ) (Figure 9).

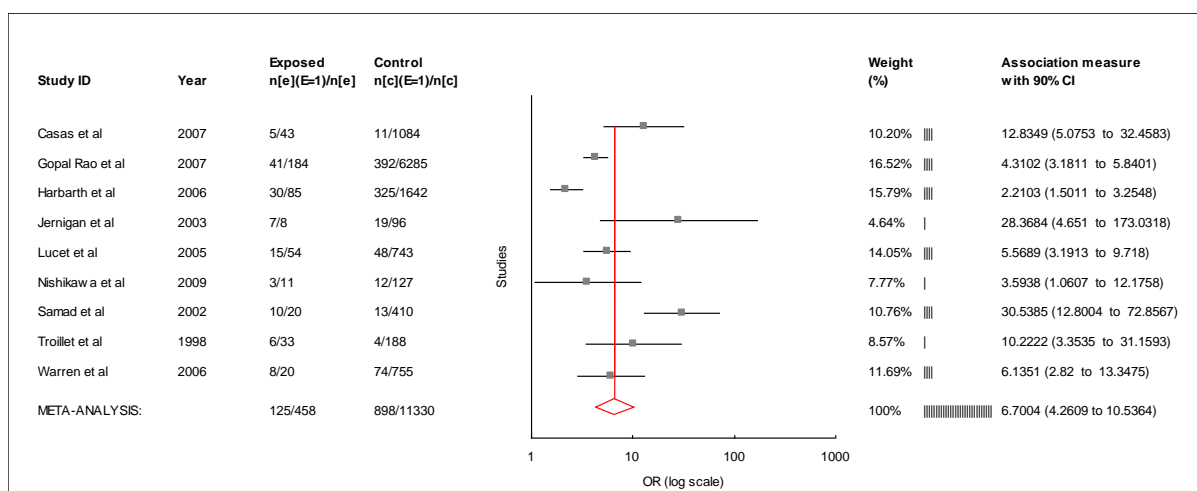


Figure 9: Meta-analysis of previous stay in LTCF and rehabilitation facilities as a risk factor

### 3.7.8 Ultimately and rapidly fatal disease (McCabe Classification)

McCabe classification is commonly used in emergency departments and intensive care units to define ultimately and/or rapidly fatal illness.<sup>56</sup> Four studies reported patients with McCabe classifications of 2 or 3 on admission to an acute care setting.<sup>40,44,48,52</sup> A total 4,647 new admissions were included in a random effects meta-analysis. The result showed a close relationship between ultimately rapidly fatal disease and MRSA colonisation (OR = 1.7591, 95% CI 1.4259 - 2.1702,  $p < 0.0001$ ) (Figure 10). No statistical heterogeneity was found among pooled studies ( $I^2 = 0.36\%$ ).

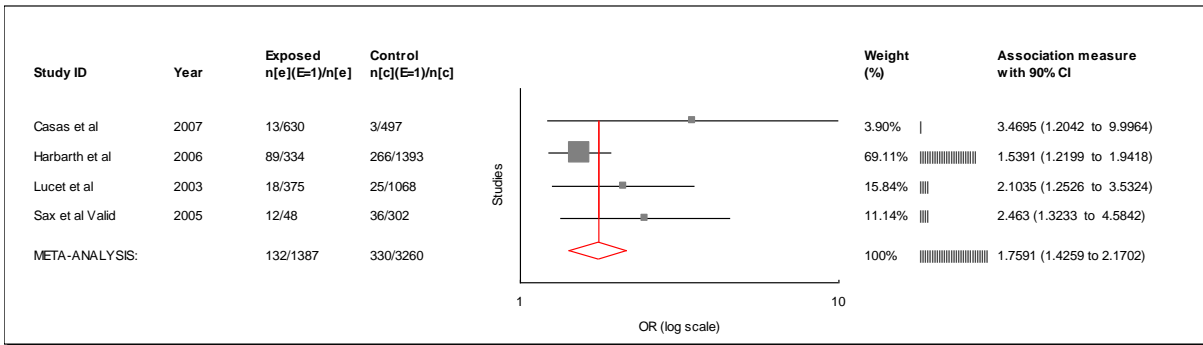


Figure 10: Meta-analysis of ultimately and rapidly fatal diseases as an independent risk factor

### 3.7.9 Previous MRSA colonisation

Previous MRSA colonisation is regarded to a high risk factor for recurrent MRSA colonisation and infection in some guidelines.<sup>4,16,17</sup> Five studies included in this review did not include patient with known MRSA carriage prior to admission.<sup>40,43,44,47,48</sup> Five studies explored the quantitative relationship between previous MRSA carriage and current MRSA colonisation on admission to a hospital.<sup>42,45,46,53,54</sup> However, two studies did not identify patients with known MRSA colonisation before allocation.<sup>46,53</sup> Consequently, only three studies were included in the following meta-analysis. There was significant heterogeneity among the three studies ( $I^2 = 96.71\%$ ). A random effects model meta-analysis including 7,990 new admissions was conducted. The result showed that previous MRSA colonisation was an independent risk factor for recurrent MRSA colonisation (OR 6.7329, 95% CI 2.4504 – 18.4995,  $p = 0.0019$ ) (Figure 11).

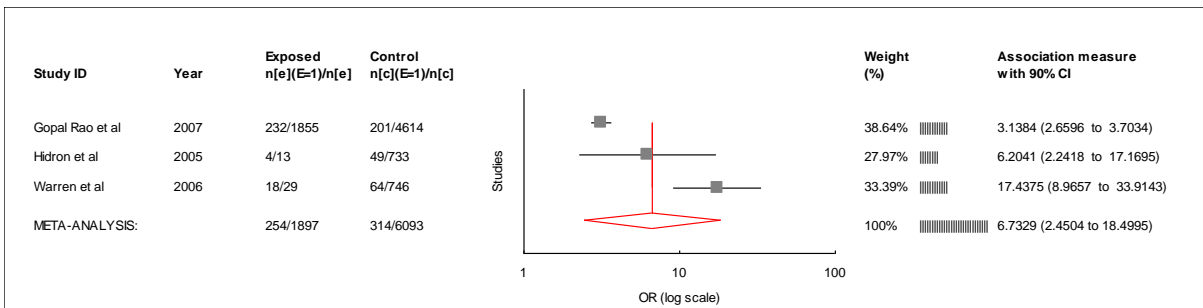


Figure 11: Meta-analysis of previous MRSA colonisation as a risk factor



### 3.7.10 Previous ICU admission

Three studies with four groups of data reported the cause relationship between previous ICU stay and MRSA carriage on new admissions to a hospital.<sup>44,48,49</sup> The period of ICU admission prior to current admission ranged from 12 months to 5 years. A meta-analysis of 5,101 new admissions was conducted. The result showed significant heterogeneity among pooled studies ( $I^2 = 63.07\%$ ). Therefore a meta analysis using random effects model was reported in the following figure, showing a close relationship between ICU admission in last 1 to 5 years and MRSA colonisation (OR = 3.8845, 95% CI 1.9036 - 7.9266,  $p = 0.0018$ ) (Figure 12).

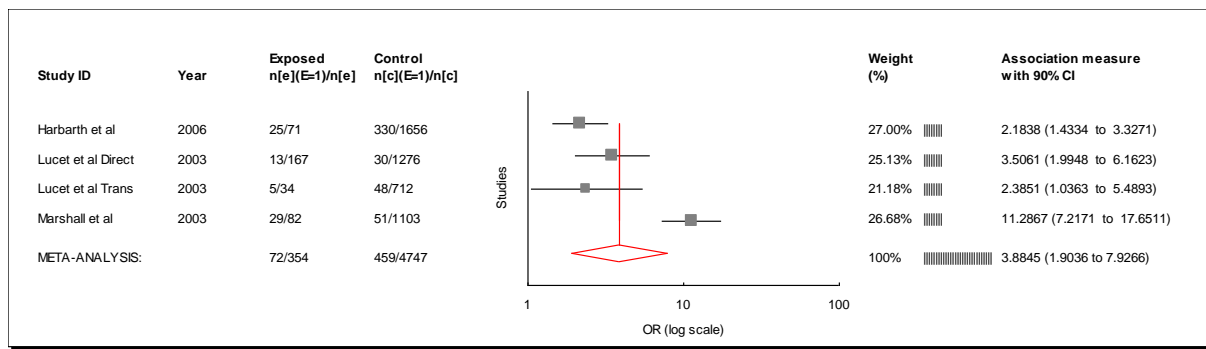


Figure 12: Meta-analysis of previous ICU admission as a risk factor

### 3.7.11 Previous Surgery

Four papers reporting the results of five studies identified previous surgery as a risk factor for admission MRSA colonisation.<sup>44,48,52,54</sup> The surgical history recorded in these four papers ranged from 3 months to 5 years. The following meta-analysis included a total of 4,967 new admissions. The result showed that surgical intervention within the last 3 months to 5 years was an independent risk factor for admission MRSA carriage (OR 2.9807, 95% CI 2.5261 - 3.5172,  $p < 0.0001$ ) (Figure 13). There was no heterogeneity among pooled studies ( $I^2 = 0\%$ ).

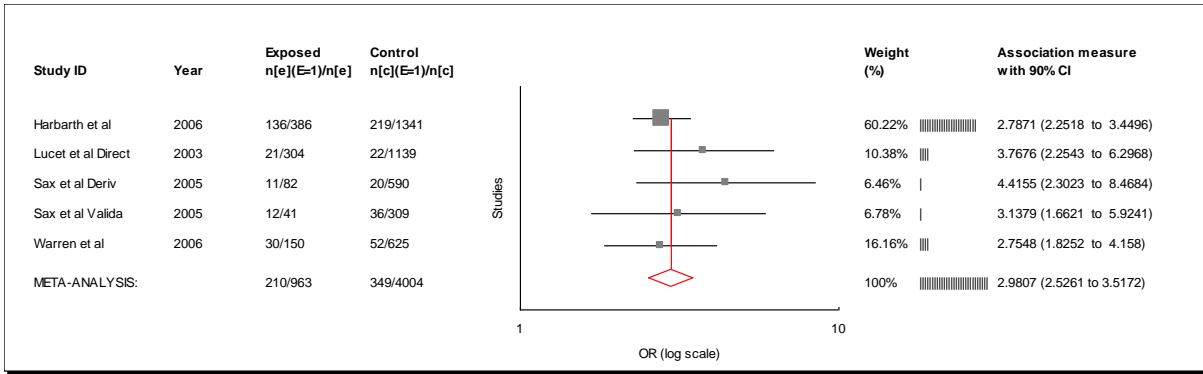


Figure 13: Meta-analysis of previous surgery as a risk factor

### 3.7.12 Skin lesion

The presence of skin lesions provides a potential reservoir for bacteria. Seven studies with eight sets of data reported the risk outcomes associated with skin lesion when patients were admitted to a hospital.<sup>41,44,45,47,48,50</sup> The types of skin lesion reported in these studies included pressure ulcer, skin and soft tissue infection, chronic skin lesion, open lesion and bedsores. A meta-analysis including 6,056 new admissions showed a strong relationship between skin lesion on admission and MRSA colonisation (OR 3.525, 95% CI 2.6194 - 4.7437,  $p < 0.0001$ ) (Figure 14). There was no evidence of significant heterogeneity among the seven studies ( $I^2 = 11.32\%$ ).

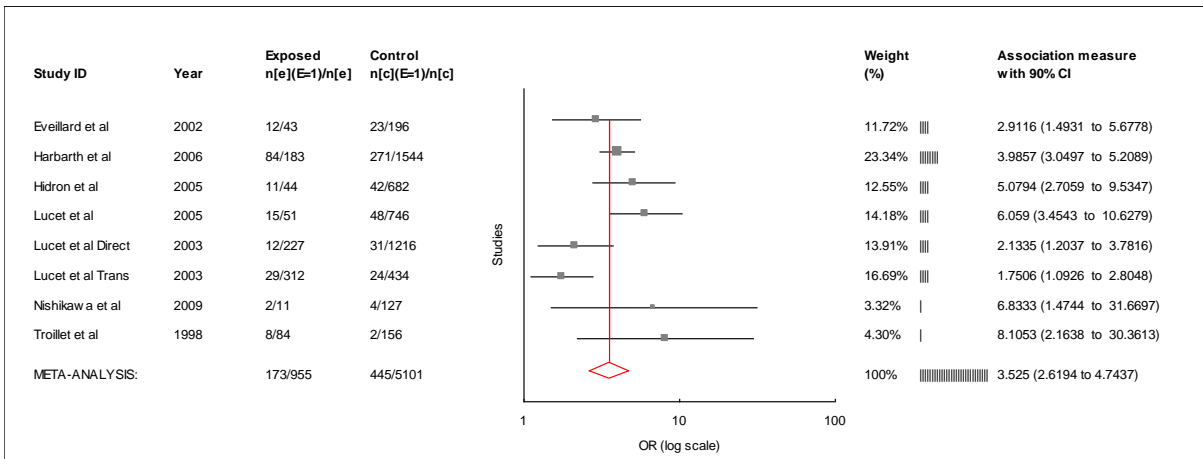


Figure 14: Meta-analysis of skin lesion as a risk factor

### 3.8 Meta analyses of risk factors by multivariate estimates only

There were eight risk factors identified by more than three studies with multivariate regressions. Meta analyses were performed for each factor by random effects model to calculate odds ratios, 95% confidential intervals and the  $p$  value. The sample size of each factor ranged from 2,020 to 6,141. The combined odds ratios varied from 2.0955 to 13.3416 and the  $p$  values of eight analyses were all less than 0.005. Heterogeneity tests were conducted and in case  $I^2$  of heterogeneity was greater than 50%, a significant heterogeneity among the original studies was indicated (Table 5).

All eight meta analyses reveal significant association between risk factors with MRSA colonisation on admission. There are no significant heterogeneity among studies which identified recent antibiotic uses, previous hospitalisation, indwelling urinary catheter, intra hospital transfer, and previous surgical experience. Admission to LTCF and rehabilitation facilities showed the stronger correlation with MRSA colonisation on admission (OR 13.3416) than other factors, although a moderate heterogeneity ( $I^2 = 24.8\%$ ) was found among selected studies.

There was significant heterogeneity in the studies which identified previous ICU admission and skin lesion as independent risk factors. A low to moderate heterogeneity ( $I^2 = 18.79\%$ ) was found in the assessment for skin lesion, but a high heterogeneity ( $I^2 = 74.09\%$ ) among selected studies which identified previous ICU admission as an independent risk factor (Table 5 and Figure 15 - 22). Funnel plots that aid assessment of publication bias are presented in Appendix 6 (Figure 35 - 42).

Table 5 Results of meta-analyses of independent risk factors by multivariate estimates

Risk Factor	No. of studies	Sample Size	Odds Ratios	95% CI	P value	Heterogeneity I <sup>2</sup>
Antibiotic Uses	6	5,136	3.8812	3.2932 – 4.5742	0.0001	0.00%
Chronic health (APACHE C,D)	2	2,240		Insufficient data for meta analysis		
Male Sex	2	2,157		Insufficient data for meta analysis		
Hospitalisation	9	6,141	3.9325	3.3555 - 4.6088	0.0001	0.00%
Indwelling Urinary Catheter	4	2,988	4.4091	3.4291 - 5.6690	0.0001	0.00%
Intra Hospital Transfer	3	2,749	2.0955	1.6966 - 2.5881	0.0001	0.00%
LTCF & Rehab Residency	5	2,020	13.3416	7.1697 - 24.8265	0.0001	24.8%
McCabe Scores (fatal disease)	1	1,443		Insufficient data for meta analysis		
Previous MRSA Colonisation	2	1,926		Insufficient data for meta analysis		
Previous ICU admission	3	4,355	4.4278	1.8679 - 10.4959	0.0046	74.09%
Previous Surgery	3	2,465	3.7334	2.656 - 5.2478	0.0001	0.00%
Skin Lesion	7	4,329	3.4745	2.3628 - 5.1093	0.0001	18.79%

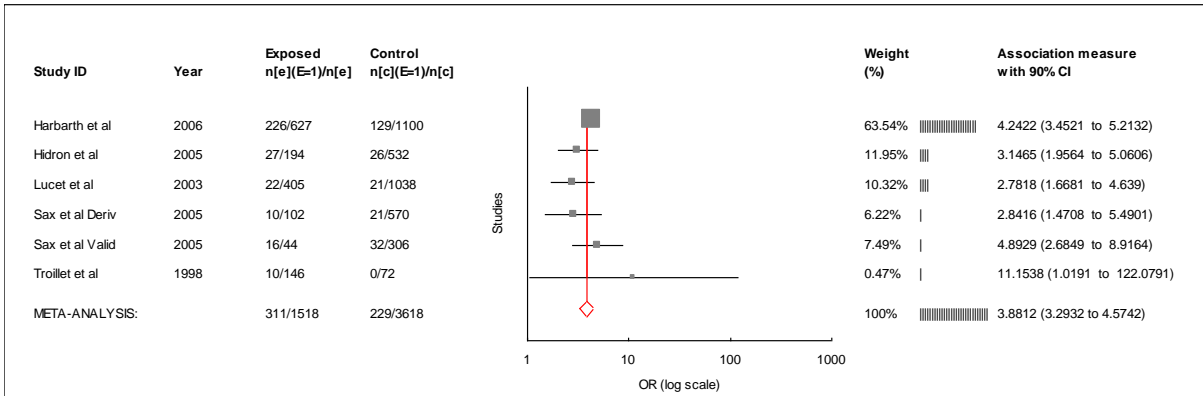


Figure 15: Meta-analysis of recent antibiotic use as a risk factor based on multivariate estimates

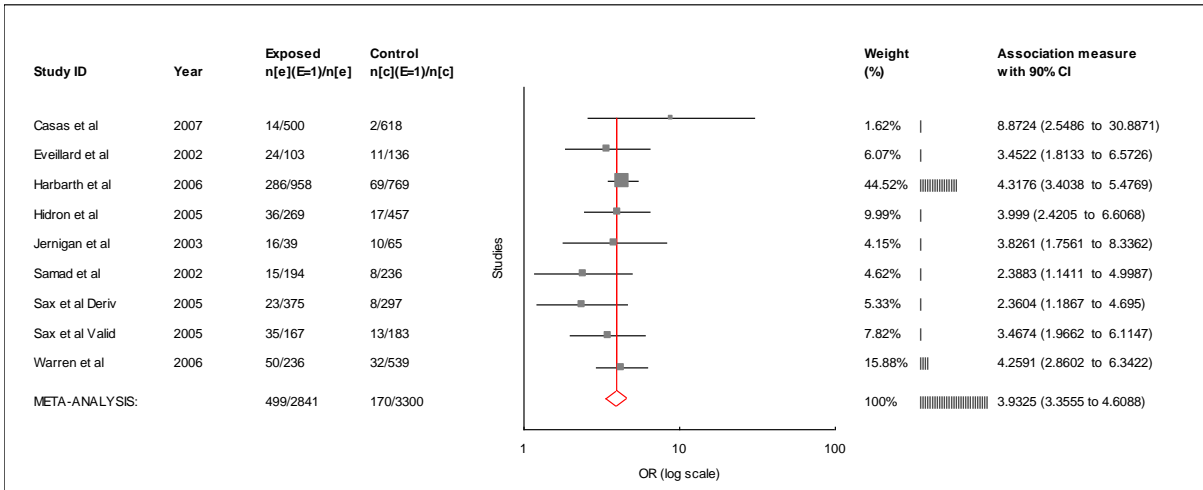


Figure 16: Meta-analysis of hospitalisation as a risk factor based on multivariate estimates

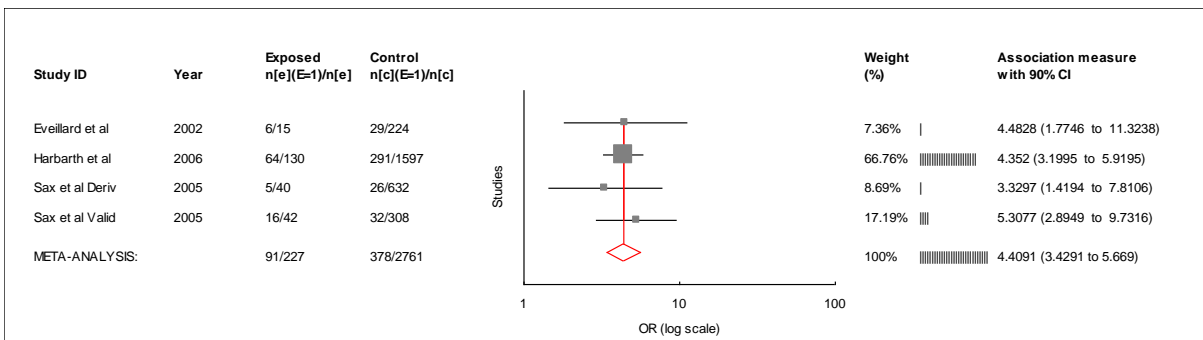


Figure 17: Meta-analysis of indwelling urinary catheter as a risk factor based on multivariate estimates

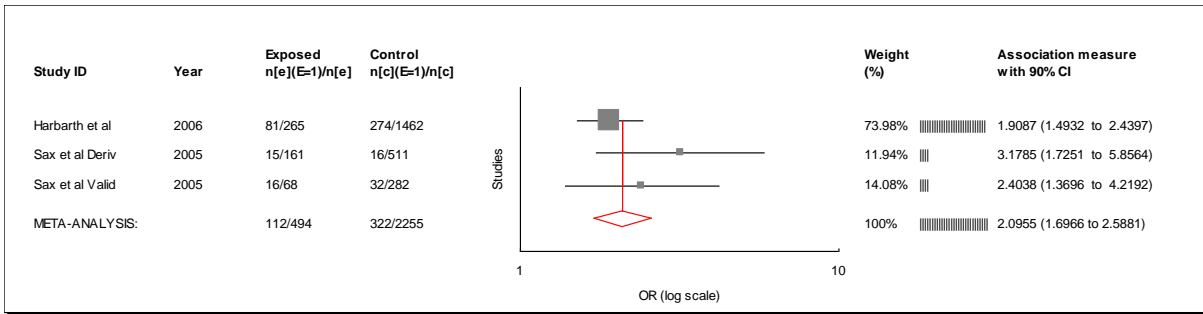


Figure 18: Meta-analysis of intra hospital transfer as a risk factor based on multivariate estimates

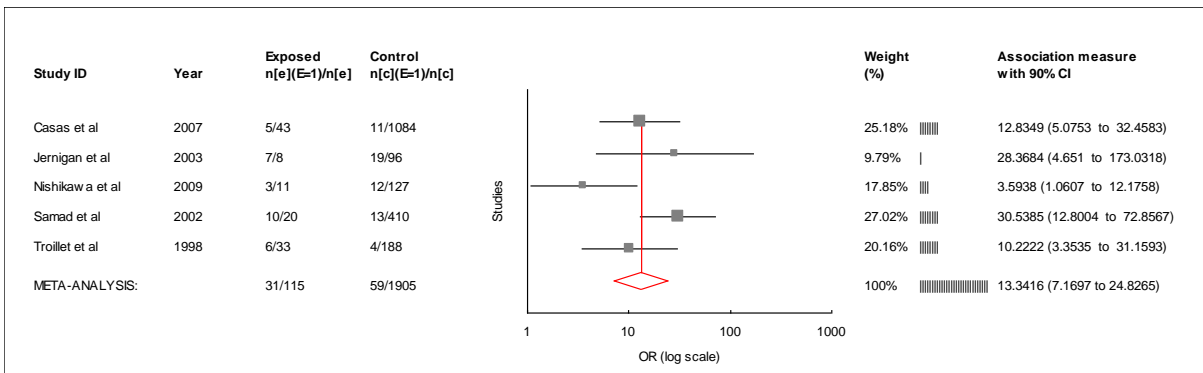


Figure 19: Meta-analysis of admission to LTCF and rehabilitation facilities as a risk factor based on multivariate estimates

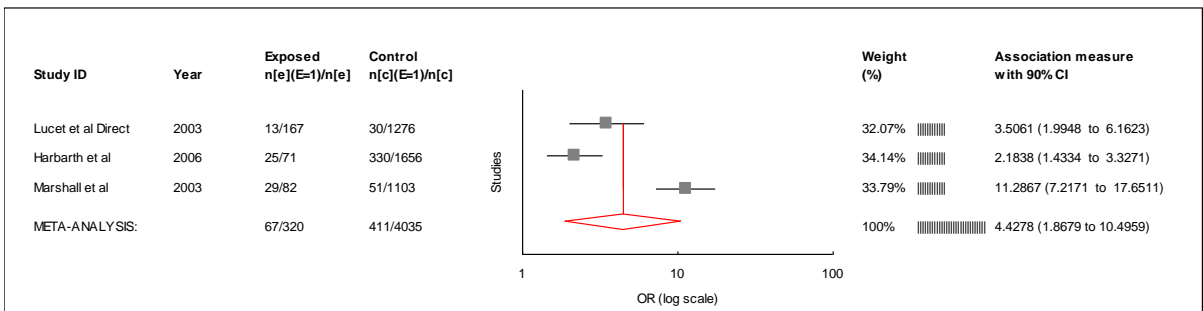


Figure 20: Meta-analysis of previous ICU admission as a risk factor based on multivariate estimates

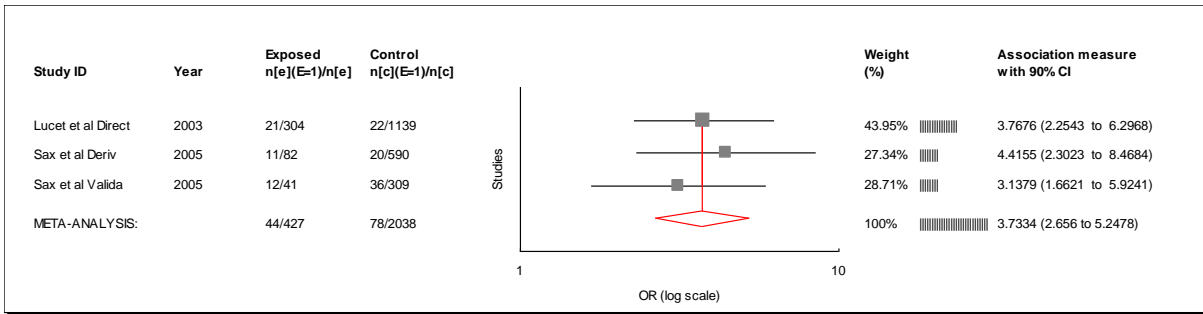


Figure 21: Meta-analysis of previous surgery as a risk factor based on multivariate estimates

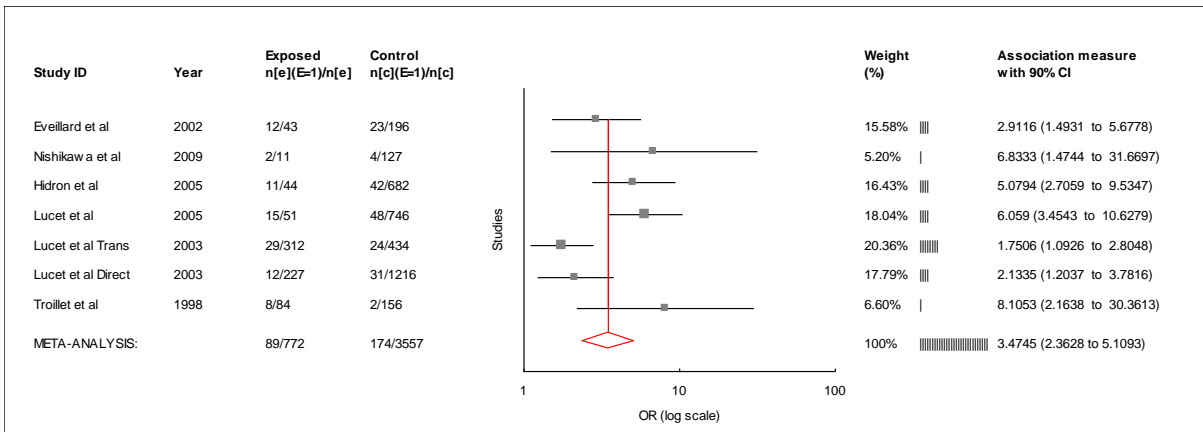


Figure 22: Meta-analysis of skin lesion/s as a risk factor based on multivariate estimates

## Chapter 4: Discussion

Although many studies have evaluated prognostic risk factors for MRSA colonisation on patient admission to an acute care setting (including development and validation of a predictive risk model based on their local cohort of patients) a comprehensive review of all the prognostic risk factors was not identified in a preliminary search of the literature. In this review with meta analyses, twelve aggregated risk factors were identified by univariate estimates in at least three studies each, and all risk factors were significantly associated with MRSA colonisation. Further to these findings, among eight risk factors multivariate estimates were possible and, all eight risk factors subsequently showed significant correlation with MRSA colonisation. The findings were reported in the previous chapter. This chapter explores and discusses the implication of those findings.

In overview, this study has found that of risk factors reviewed, the following were significant for increased colonisation of MRSA. Hospitalisation within the last 24 months (OR 3.4309, 95% CI 2.9732 - 3.9590,  $p < 0.0001$ ), previous admission to a LTCF or a rehabilitation facility within the last 18 months (OR 6.7004, 95% CI 4.2609 - 10.5364,  $p = 0.0001$ ), antibiotic use within the past 12 months (OR 3.7694, 95% CI 3.2453 - 4.3781,  $p < 0.0001$ ), the presence of skin lesion (OR 3.525, 95% CI 2.6194 - 4.7437,  $p < 0.0001$ ), surgical intervention within the last 5 years (OR 2.9807, 95% CI 2.5261 - 3.5172,  $p < 0.0001$ ), indwelling urinary catheter (OR 4.3898, 95% CI 3.4317 - 5.6156,  $p < 0.0001$ ), ICU admission in the last 5 years (OR 3.8845, 95% CI 1.6605 - 9.0871,  $p = 0.0018$ ), previous MRSA colonisation (OR 6.7329, 95% CI 2.4504 - 18.04995,  $p = 0.0019$ ), intra hospital transfer (OR 2.0955, 95% CI 1.6966 - 2.5881,  $p < 0.0001$ ), male sex (OR 1.8167, 95% CI 1.5180 - 2.1742,  $p < 0.0001$ ), comorbidity of chronic health evaluation class C or D (OR 3.025, 95% CI 2.1844 - 4.1891,  $p < 0.0001$ ), and the presence of ultimately and rapidly fatal illness (OR 1.7591, 95% CI 1.4259 - 2.1702,  $p < 0.0001$ ) were identified as prognostic factors for MRSA colonisation on patient admission to an acute care setting. These findings are in agreement with previous observational studies and highlight the most important variables to consider when assessing risk of MRSA colonisation.



The pooled multivariate estimates also showed the significant association between risk factors and MRSA colonised. There are hospitalisation within the last 24 months (OR 3.9325, 95% CI 3.3555 – 4.6088,  $p < 0.0001$ ), previous admission to a LTCF or a rehabilitation facility within the last 18 months (OR 13.3416, 95% CI 7.1697 – 24.8265,  $p < 0.0001$ ), antibiotic use within the past 12 months (OR 3.8812, 95% CI 3.2932 – 4.5742,  $p < 0.0001$ ), the presence of skin lesion (OR 3.4745, 95% CI 2.3628 – 5.1093,  $p < 0.0001$ ), surgical intervention within the last 5 years (OR 3.7334, 95% CI 2.6560 – 5.2478,  $p < 0.0001$ ), indwelling urinary catheter (OR 4.4091, 95% CI 3.4291 – 5.6690,  $p < 0.0001$ ), ICU admission in the last 5 years (OR 4.4278, 95% CI 1.8679 – 10.4959,  $p = 0.0046$ ), and intra hospital transfer (OR 2.0955, 95% CI 1.6966 - 2.5881,  $p < 0.0001$ ).

Comparing the pooled odds ratios of each risk factor by univariate estimates, less selected studies and smaller sample size contributed to meta analysis of each factor by multivariate estimates. Less than three studies identified previous MRSA colonisation, male sex, comorbidity of chronic health evaluation class C or D and the presence of fatal illness as independent risk factors for MRSA colonisation by multivariate regressions, therefore the meta analyses for the four risk factors were not able to be conducted by multivariate estimates. The pooled odds ratios for previous hospitalisation, recent antibiotic use, skin lesion, previous surgery, indwelling urinary catheter, ICU admission and intra hospital transfer were not significantly changed comparing with the pooled odds ratios by univariate estimates. However, for the factor of admission to a LTCF or rehabilitation setting, a substantially increased pooled odds ratio was found from 6.7 to 13.3 and the heterogeneity among selected studies was decreased from 42.44% to 24.8% (Table 6). In the heterogeneity tests, previous ICU admission was the only one risk factor with  $I^2$  greater than 50% during the meta analyses using univariate and multivariate estimates. Therefore, the pooled odds ratios by multivariate data further confirmed that previous hospitalisation, recent antibiotic use, skin lesion, previous surgery, indwelling urinary catheter, intra hospital transfer and admission to a LTCF or rehabilitation setting were predictive risk factors for MRSA colonisation when patient on admission. Although the pooled odds ratios illustrated the significant association with MRSA colonisation, the following factors (previous ICU admission, existing

chronic conditions and fatal disease, male sex) should be interpreted cautiously due to the limited number of qualifying studies and limitations inherent in observational studies.

Table 6 Results of meta-analyses of risk factors by univariate and multivariate estimates

Risk factors	No. of studies		Sample size		OR and 95% CI	
	Univariate estimates	Multivariate estimates	Univariate estimates	Multivariate estimates	Univariate estimates	Multivariate estimates
Antibiotic Uses	8	6	7,038	5,136	3.7694	3.8812
Hospitalisation	11	9	12,748	6,141	3.4309	3.9325
Indwelling Urinary Catheter	5	4	3,126	2,988	4.3898	4.4091
Intra Hospital Transfer	3	3	2,749	2,749	2.0955	2.0955
LTCF & Rehab Residency	9	5	11,788	2,020	6.7004	13.3416
Previous ICU admission	4	3	5,101	4,355	3.8845*	4.4278*
Previous Surgery	5	3	4,967	2,465	2.9807	3.7334
Skin Lesion	8	7	6,056	4,329	3.525	3.4745

\*  $I^2$  was more than 50% in heterogeneity test.

#### 4.1 Antibiotic use

Previous antibiotic use is frequently reported as a risk factor for MRSA isolation over the last 20 years. A systematic review with meta-analysis identified the role of antibiotics as a risk factor for MRSA isolation in adult patients. Seventy-six studies were included in the meta-analysis, and results showed that the risk of MRSA acquisition was increased 1.8-fold in patients who had taken antibiotics. The highest risk was associated with the use of quinolones (relative risk, RR = 3.0), followed by the use of glycopeptides (RR = 2.9), cephalosporins (RR = 2.2) and other  $\beta$ -lactams (RR = 1.9).<sup>25</sup> The meta-analysis determined the antibiotic exposure in  $126 \pm 184$  days preceding MRSA isolation, and the length

of time associated with antibiotic exposure was the most probable source of significant heterogeneity that was detected among analysed studies (7 - 1080 days). There are several differences between this, earlier review and the study this dissertation is based upon. Firstly, this systematic review identifies previous antibiotic uses as an independent risk factor to MRSA colonisation on admission rather than MRSA acquisition within hospitals. Secondly, the finding of the meta analysis undertaken in this study shows that antibiotic use within 12 months prior to a current admission is an independent risk factor for MRSA colonisation on admission. The analysis appears robust, although it needs to be acknowledged that exact records of the duration of antibiotic exposure are not possible to determine from the primary studies since retrospective data regarding antibiotic usage was obtained from patients or their caregivers in most of current studies. Additionally, we cannot analyse odds ratios of single classes of antibiotics due to limited data of single class antibiotics reported in the selected studies. Unfortunately, some characteristics of antibiotics therapy, such as duration of therapy and dosage of antibiotics, were not reported in analysed studies.

## **4.2 Comorbidity of chronic conditions and fatal illness (APACHE C, D and McCabe Scores)**

In the category C and D of APACHE classification, a bench of chronic organic failures and immunosuppression status are combined and assessed as an independent variable.<sup>55</sup> McCabe classification is simpler and based on the subjective assessment of life expectancy due to underlying diseases.<sup>56</sup> Both assessment tools are usually used in the emergency department and ICU to identify comorbid conditions on patient admission. Although there are clear and significant outcomes of both meta-analyses, some limitations should be considered in interpreting our results. The selected studies in both meta-analyses were conducted in ICU and emergency department, and the patients were not routinely admitted. Thus, the outcomes are not represented in routine general medical and surgical admissions.

### **4.3 Male sex**

There was evidence to suggest that gender, male gender in particular was a factor of significance in relation to MRSA colonisation or transmission. The meta analysis indicated that being male increased the odds of MRSA transmission by a factor of 1.8 times. The confidence interval for this result was narrow, and heterogeneity was not significant. Therefore, it seems appropriate that male gender be considered a risk factor for MRSA transmission.

### **4.4 Previous hospitalisation**

Frequent contact with the health care system is widely accepted as a risk factor for MRSA acquisition and, has been considered as such in the infection control field for the last 20 years.<sup>4,16,17</sup> Frequent contact with the health care system includes prior hospitalisation, history of admission to LTCF or rehabilitation settings, previous surgery, previous ICU admission, and intra-hospital transfer in this review. The odds ratio of each risk factor ranged from 2.0955 (intra-hospital transfer) to 6.7004 (previous admission to LTCF or rehabilitation facilities). Based on heterogeneity tests, there was low statistical probability of heterogeneity among studies for the risk factors of previous hospitalisation, previous surgical experience and intra hospital transfer. Although, these factors concern to long term of contact with health care system, these hospitalisation characteristics, such as numbers of admission, lengths of stay, wards concerned and types of surgical procedures were not recorded in selected studies and it is impossible to obtain accurately such information retrospectively.

### **4.5 Indwelling urinary catheter**

Indwelling urinary catheters have been regarded as a high risk factor for catheter associated urinary tract infection (CAUTI) and nosocomial infections by many guidelines.<sup>57,58</sup> This review confirmed that the patients with an indwelling urinary catheter were a high risk population and had 4-fold chance of being colonised MRSA comparing to those without a urinary catheter. This finding is consistent with most current guidelines for MRSA control.<sup>4,16,17</sup>

## **4.6 Intra hospital transfer**

Intra hospital transfer may be regarded as a risk factor for more frequent exposure to hospital-acquired organisms, due to more healthcare system contacts and more complex comorbid conditions.<sup>49</sup> Marshall and colleagues<sup>49</sup> explored the prevalence of MRSA colonisation of ICU patient and the previous wards/units before ICU admission.<sup>49</sup> After adjustment was made for length of stay (LOS) it was identified that patients transferred from trauma/ orthopaedics wards had a higher risk for MRSA colonisation (OR 2.9, P < 0.5, 95% CI 1.2 - 7.2 ).<sup>49</sup>

## **4.7 Admission to LTCF and rehabilitation facilities**

A moderate degree of heterogeneity existed among included studies identifying the factor of previous admission to LTCF or rehabilitation facilities. Two possible reasons may explain the heterogeneity; one is a variety of patients from several age groups and, where patients came from before admission among selected studies. In some studies, most patients were elderly and came from community settings. These studies were conducted in geriatric wards of acute care setting. Some studies were conducted in emergency and surgical department and, patients were young adults and came directly from their home. The other factor is recall bias that may occur when collecting information of LTCF or rehabilitation facilities among very older patients and / or their families and care givers.

## **4.8 Previous MRSA colonisation**

Patients with a history of MRSA colonisation in previous 12 months were 6 times likely to be colonised with MRSA on admission than patients without MRSA harbouring. Estimates of long-term-persistence of MRSA colonisation varied widely, from several months to more than 3 years.<sup>59</sup> Decolonisation therapy, including nasal mupirocin and chlorhexidine baths, had been used with varying degrees of success to decrease the prevalence of long-term colonisation.<sup>60</sup> The efficacy of these treatments depended on the antibiotic agents, the body sites and MRSA epidemiology in a certain setting.<sup>60</sup> These are two shortages in this review. One is the duration of MRSA colonisation prior to admission was recalled in last 12 months in analysed studies. A study made a survey and recalled medical records for 5 year history of MRSA colonisation, however, no patients of control group with previous known MRSA

carriage.<sup>53</sup> The other is all relevant data obtained from patient medical records retrospectively on admission. Due to the varying policy of patient screening and contents of medical records, among hospitals patient previously admitted, the numbers of patient with history of MRSA colonisation would be under estimated. Both of the two shortages may underestimate the odds ratio of previous MRSA colonisation.

#### **4.9 Previous ICU admission**

A significant heterogeneity was found among studies in which previous ICU admission was identified as an independent risk factor for patient admission with MRSA colonisation. Lengths of stay in ICU and the wards in which patients stayed prior to ICU admission were possible reasons that results in the heterogeneity among the selected studies. A study tried to quantitatively identify the risk of wards where patients stays prior to transfer to ICU.<sup>33</sup> Since the factor of previous ICU admission is partly associated with other independent risk factors, such as hospitalisation, previous surgery, intra-hospital transfer, severity of illness, indwelling urinary catheter and mechanical ventilation, it should be regarded to a sensitive and independent risk factor for MRSA colonisation on admission to an acute care unit.

#### **4.10 Previous surgery**

Previous surgery is associated with a history of hospitalisation, and no included studies differentiated between hospital surgery and day surgery. Thus it's very hard to discuss the role of previous surgery as the concept was not well defined among included studies, and reporting was therefore confounded by the varied models and definitions.

#### **4.11 Skin lesions**

Skin lesion, including pressure ulcers, skin and soft tissue infection, bedsores, chronic and open lesion was proved to be a reservoir of MRSA in this review. Although the meta analyses were conducted by fixed effect and random effects models based on univariate and multivariate estimates, the pooled odds ratios were an approximation to each other (3.525 and 3.4745). This indicates skin lesion is an independent risk factor from MRSA colonisation on admission to an acute care setting.

## **4.12 Colonisation pressure**

Acquisition of antibiotic-resistant organisms was primarily affected by prevalence and colonisation pressure, comorbid illnesses, recent antibiotics therapy, and compliance of infection control practice and contact precautions in acute care settings. Once MRSA is introduced into a healthcare setting, transmission and persistence of the resistant strain is determined by the availability of vulnerable patients, selective pressure exerted by antimicrobial use, increased potential for transmission from larger numbers of colonised or infected patients. This is relevant to colonisation pressure (CP).<sup>61</sup> Merrer et al evaluating colonisation pressure, work load and patient severity in patient acquisition of MRSA found that colonisation pressure was the only independent predictive factor for MRSA acquisition. It was established that more than 30% of colonisation pressure weekly being associated with the risk of acquisition of MRSA was approximately five times higher.<sup>61</sup> In this review, colonisation pressure was regarded as a key ward and index term on searching process, however, no study was found to reveal the correlation between colonisation pressure and MRSA colonisation on admission to an acute care setting.

## **4.13 Limitations**

This review with meta-analyses has several limitations. Meta-analyses of the effects of interventions are based on the results of randomised controlled trials (RCTs).<sup>37</sup> In prognostic studies that assess risk factors RCTs are not the dominant study design due to ethical and logistic reasons. However, the predominant study designs associated with risk (cohort and case-control studies) are more prone to population bias that may affect the analysis. Likewise, the small number of studies that assessed each specific prognostic factor meant that subgroup analysis was not possible due to the low numbers of studies that evaluated individual factors. Finally, other prognostic factors such as older age, patient admission from alternative housing, single classes of antibiotics, comorbidity of diabetes mellitus, COPD, Chronic renal disease, HIV infection, patient with mechanical ventilation, and other variables could not be assessed due to a lack of published studies that evaluated these risk factors.

In this review, MRSA prevalence on admission ranged from 1.4% to 14.6%. The low prevalence of MRSA colonisation on admission may not have allowed the accurate detection of differences between case and control groups as a result of low statistical power. Recall bias may have occurred in studies reporting past exposures, particularly with respect to previous antibiotic treatment, previous MRSA colonisation, or admissions to LTCFs and rehabilitation facilities.

The lack of long term prospective studies is also a limitation of this review. One study in which 5-year administrative and therapeutic data was collected <sup>48</sup> is the exception in this review, with the other 14 studies reporting on study durations between 1 – 24 months. This contrasts with the known mean duration of asymptomatic colonisation that has been reported to be three years of MRSA.<sup>59</sup>

All included studies applied consecutive or randomised sampling methods when recruiting patients and a majority of studies reported that less than 2% patients did not have screening samples collected within 72 hours of admission. However, in the presence of gaps in screening, detection bias remains a risk in the implementation of the selected cohort and case series studies. Three studies stated that more than 5% of patients were not available for screening samples and cultures in the first three days of their admission.<sup>45,48,49</sup> Four included studies recruited older patients alone,<sup>41,47,50,52</sup> and patients with unknown MRSA carriage prior to admission alone were recruited in five studies.<sup>40,43,44,47,48</sup>



## **Chapter 5: Conclusions**

Since MRSA infections are associated with considerable mortality and excess hospital costs, preventing MRSA transmission is priority in hospital infection control. Despite much debate about the evidence and the cost-effectiveness of various infection control policies, the majority of prevention strategies in hospitals have targeted cross-transmission among hospitalised patients. Knowledge of the variables that identify patients at higher risk of being carriers with MRSA may assist clinicians in targeting preventive measures and optimising antibiotic use. Targeted screening could be used to limit the potential for MRSA transmission from unrecognised patient reservoirs from early in their hospital admission. Although the influx of MRSA into the hospital may not change, the benefit of early detection would be to reduce the period during which these patients are at risk of contributing to the transmission of MRSA.

### **5.1 Implications for practice**

The identification of risk factors for MRSA colonisation on admission will improve effectiveness and efficiency of current MRSA prevention strategies and control MRSA spread and acquisition in acute care settings by following approaches:

- drawing a profile of patients with MRSA colonisation on admission,
- early identifying asymptomatic carriers,
- establishing local selective screening strategies with high sensitivity and low cost,
- improving effectiveness and of screening program by reduced unnecessary screening tests, and
- detecting reservoir and source of spread.

### **5.2 Implications for research**

The methods of this review may promote primary studies and systematic reviews on risk factors for MRSA acquisition in special settings, such as community settings or alternative housing, and promote primary studies and systematic reviews on risk factors for MRSA acquisition in special population, such as geriatric patients or paediatric patients.

The outcomes of this review may be utilised to derivate predictive rules and prediction models and further validate the predictive studies. The findings of this review may promote to develop economic evaluations of various screening programs in different levels of settings.

In this review, some factors cannot be qualitatively analysed since the lack of sufficient clinical data. More and larger scale prospective studies on risk factors for MRSA colonisation on admission and discharge are needed to detect and summarize relevant uncommon factors.

More prognostic studies on risk factors for MRSA carriage in community settings and among patients and health care workers are needed to explore the MRSA spread among health care setting, community and carrier families.

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## Appendix I: Search Strategy: MEDLINE (OVID)

1. MRSA.mp. or exp \*Methicillin-Resistant Staphylococcus aureus/
2. Methicillin-Resistant Staphylococcus aureus/
3. exp staphylococcal infections/
4. Staphylococcus aureus/
5. Staphylococcus/
6. (staphylococc\$ adj2 (infect\$ or aureus)).tw.
7. ("s.aureus o r s aureus" or "staph aureus").tw.
8. or/3-7
9. beta-Lactam Resistance/
10. exp penicillin resistance/
11. ((met?icillin or penicillin or "beta-lactam" or "beta lactam oxacillin") adj2 resist\$).tw.
12. ((multidrug\$ or "multi-drug\$" or (multi adj drug\$) or "multiple-drug\$" or (multiple adj drug\$)) adj2 resist\$).tw.
13. or/9-12
14. 8 and 13
15. (mrsa or emrsa).tw.
16. 14 or 15
17. exp risk/
18. Risk Assessment/
19. risk\$.tw.
20. Risk Management/
21. Risk Factors/
22. or/17-21
23. Mass Screening/
24. (screen? or screened or screening).tw.
25. ("active surveillance" or "targeted surveillance").tw.

26. or/23-25
27. 16 and 22 and 26
28. colonization.mp.
29. colonisation.mp.
30. colonized.mp.
31. colonised.mp.
32. Carrier State/ or carriage.mp.
33. 28 or 29 or 30 or 31 or 32
34. 27 and 33
35. limit 34 to (abstracts and english language and humans)

## **Appendix II: JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control**

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NOTE:

This appendix is included on pages 75-76 of the print copy of the thesis held in the University of Adelaide Library.

## Appendix III: Data Extraction Form for Comparable Cohort/ Case Control

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Author \_\_\_\_\_ Year \_\_\_\_\_ Record Number \_\_\_\_\_  
 Study Design \_\_\_\_\_ Duration of follow- up \_\_\_\_\_  
 Setting \_\_\_\_\_ Country \_\_\_\_\_  
 Sampling Sites \_\_\_\_\_ Size \_\_\_\_\_ Incidence \_\_\_\_\_  
 Size case \_\_\_\_\_ Control \_\_\_\_\_

---

### INFORMATION COLLECTION \_\_\_\_\_

Demographic \_\_\_\_\_ Administrative \_\_\_\_\_ Clinical \_\_\_\_\_ Antimicrobial Therapy \_\_\_\_\_

### MRSA INFECTION CONTROL STRATEGIES \_\_\_\_\_

Active Surveillance \_\_\_\_\_ Standard IC Precautions \_\_\_\_\_

Isolation \_\_\_\_\_ Decolonisation \_\_\_\_\_

### CARRIAGE STATUS

Colonisation \_\_\_\_\_ Previous Known \_\_\_\_\_ Previous Unknown \_\_\_\_\_

Infection \_\_\_\_\_ Previous Known \_\_\_\_\_ Previous Unknown \_\_\_\_\_

### RESULTS

Risk Factors	Univariate Analysis				Multivariate Analysis	
	MRSA +	MRSA -	OR/95% CI	P value	OR/95% CI	P value



## Appendix IV: Excluded studies and reasons for exclusion

Study ID	Reasons of exclusion
Aizen 07	The study was conducted in a non-acute care setting.
Alp 09	MRSA carriage status was no identified.
Chen 10	MRSA carriage status was no identified.
Eveillard 06	MRSA carriage status was no identified, and only part of patients attended the study.
Furuno 06	Data of the study was duplicated with the other included study.
Furuno 04	MRSA carriage status was no identified.
Girou 98	MRSA carriage status was no identified.
Goetz 99	The study was conducted in a non-acute care setting.
Graffunder 02	MRSA carriage status was no identified.
Haley 07	The study was conducted in a non-acute care setting.
Harris 10	MRSA carriage status was no identified, and only part of patients attended the study.
Higgins 11	The study was conducted in a general hospital including non-acute care units.
Hsu 08	MRSA carriage status was no identified.
Lodise 03	The study was conducted in a non-acute care setting.
Manian 02	MRSA carriage status was no identified.
Melo 09	MRSA carriage status was no identified.
Nseir 10	MRSA carriage status was no identified.
Panhotra 05	MRSA carriage status was no identified.
Papia 99	MRSA carriage status was no identified.
Patel 08	MRSA carriage status was no identified.
Reilly 10	The study was conducted in a non-acute care setting.
Rezende 02	MRSA carriage status was no identified.
Scanvic 01	MRSA carriage status was no identified.
Thomas 07	The study was conducted in a non-acute care setting.
Wang 10	MRSA carriage status was no identified.
Wang 10	The study was conducted in a non-acute care setting.

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## Appendix V: The assessment of publication bias for meta analyses based on univariate estimates

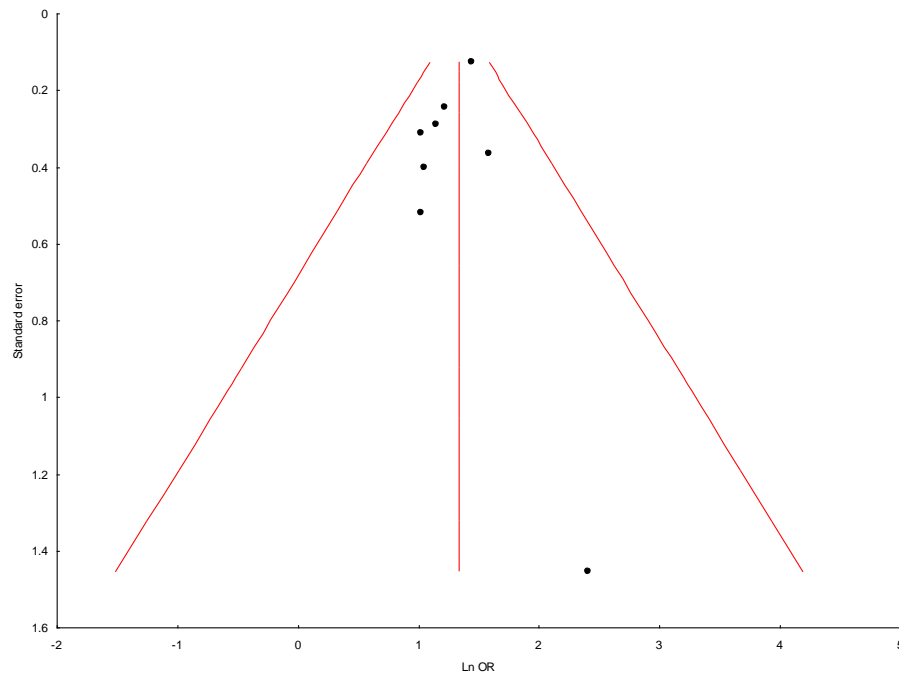


Figure 23: Funnel plot of pooled univariate odds ratios of antibiotic uses

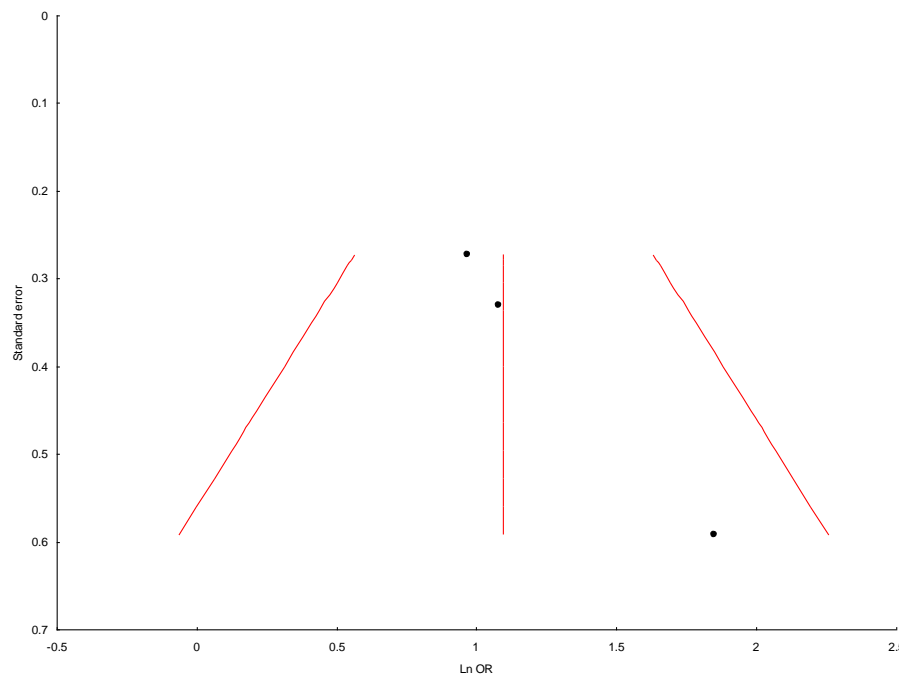


Figure 24: Funnel plot of pooled univariate odds ratios of comorbidity of chronic health evaluation class C or D (APACHE C,D)

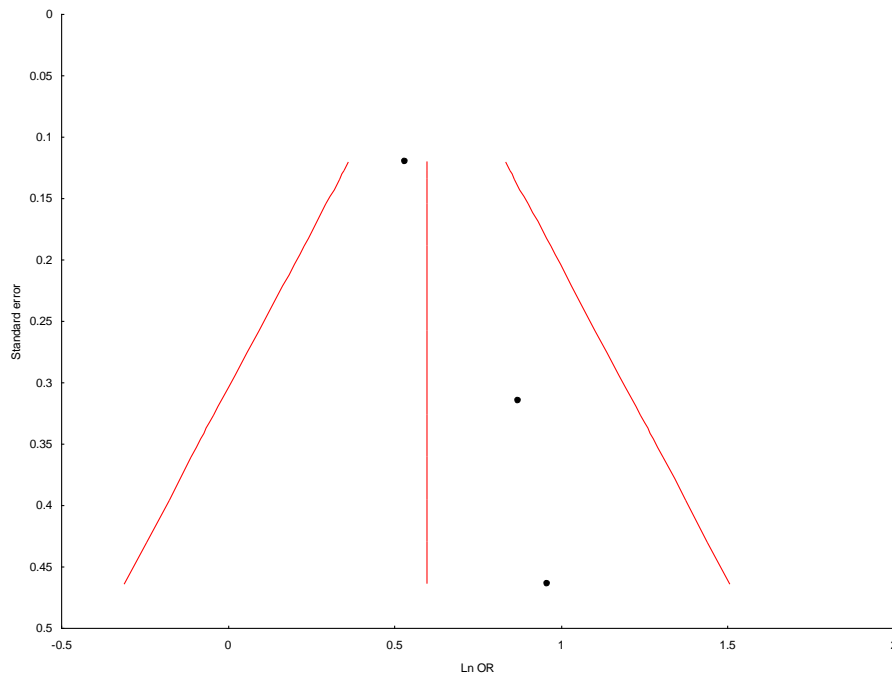


Figure 25: Funnel plot of pooled univariate odds ratios of male sex

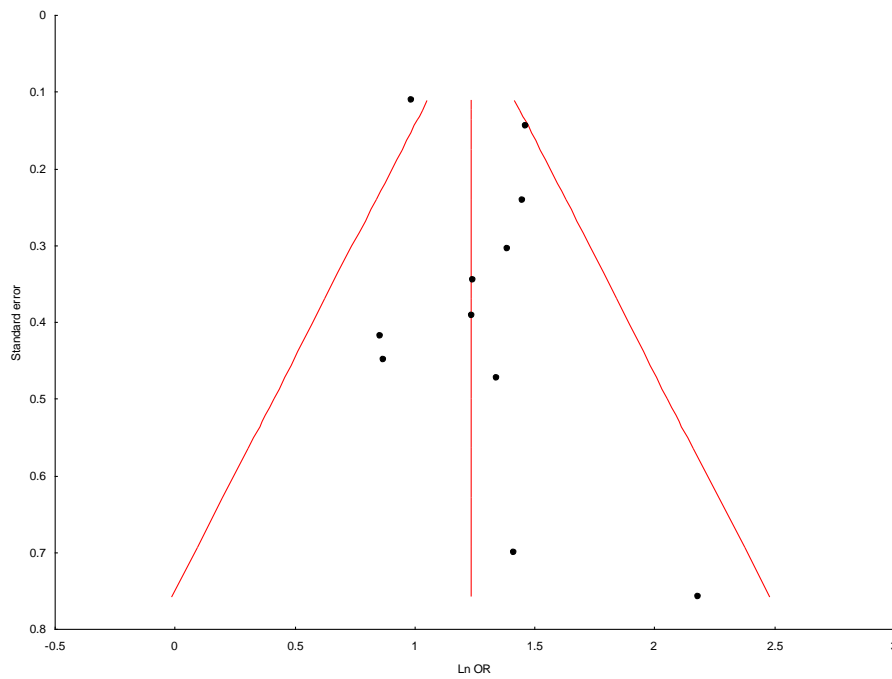


Figure 26: Funnel plot of pooled univariate odds ratios of recent hospitalisation

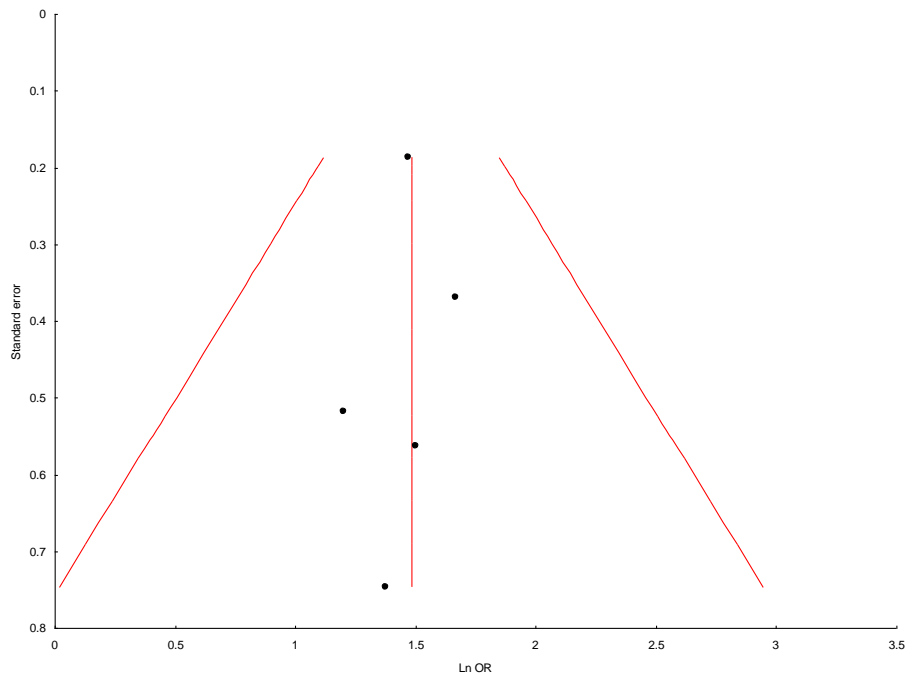


Figure 27: Funnel plot of pooled univariate odds ratios of indwelling urinary catheter

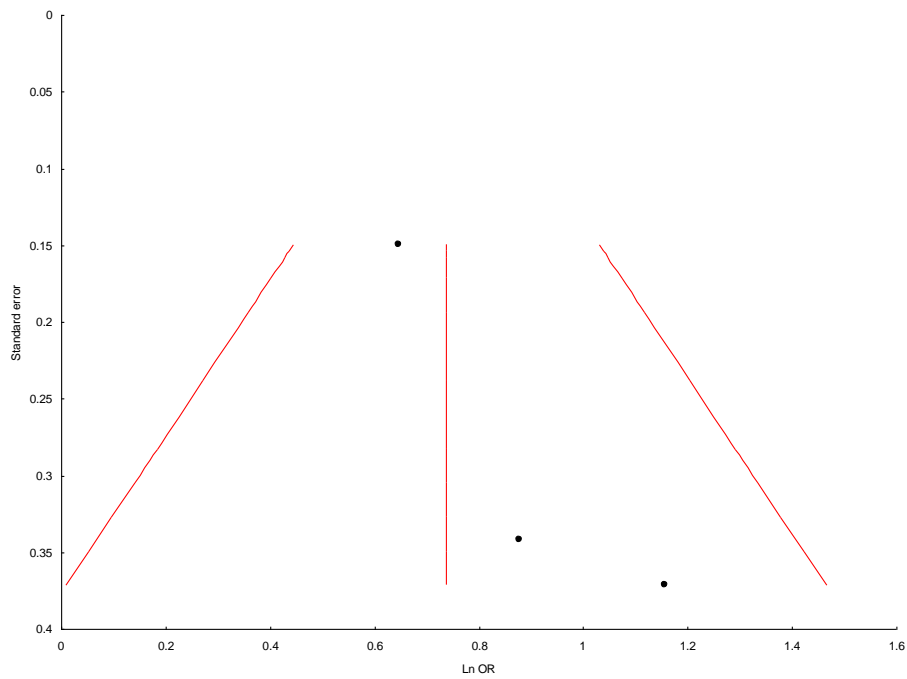


Figure 28: Funnel plot of pooled univariate odds ratios of intra hospital transfer

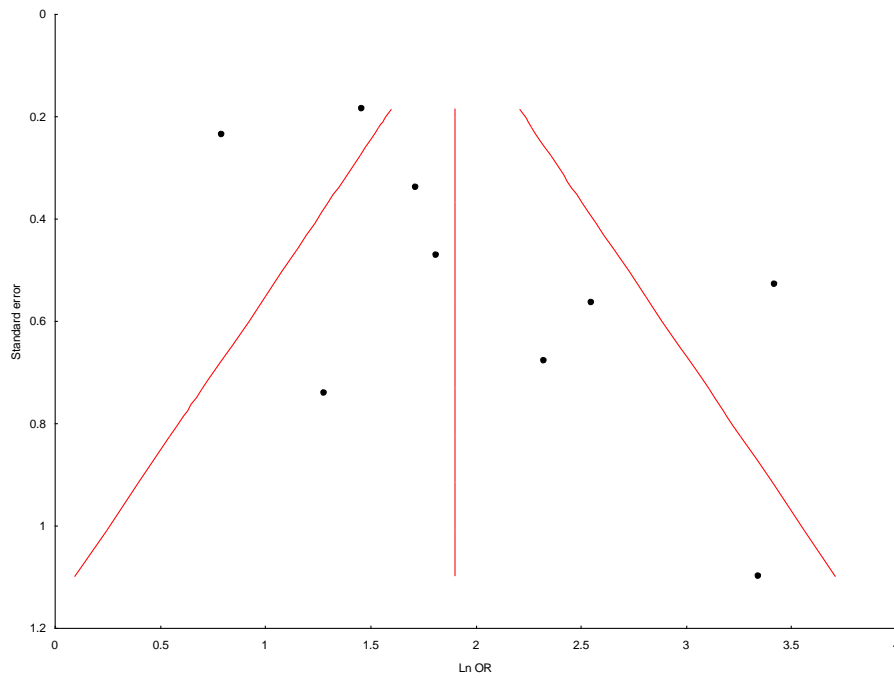


Figure 29: Funnel plot of pooled univariate odds ratios of admission to LTCF and rehabilitation facilities

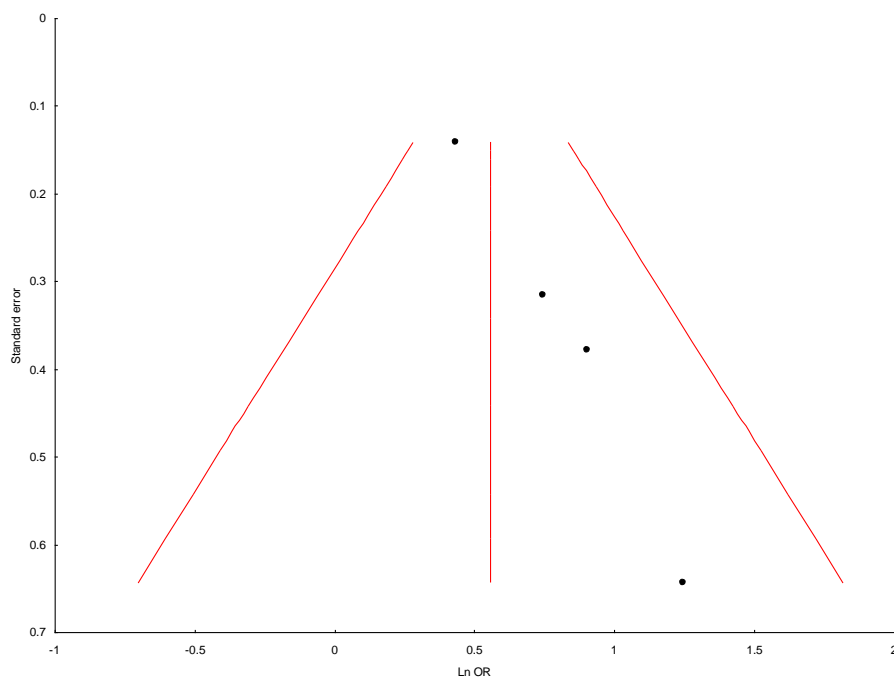


Figure 30: Funnel plot of pooled univariate odds ratios of existing ultimately and rapidly fatal disease (McCabe classification)

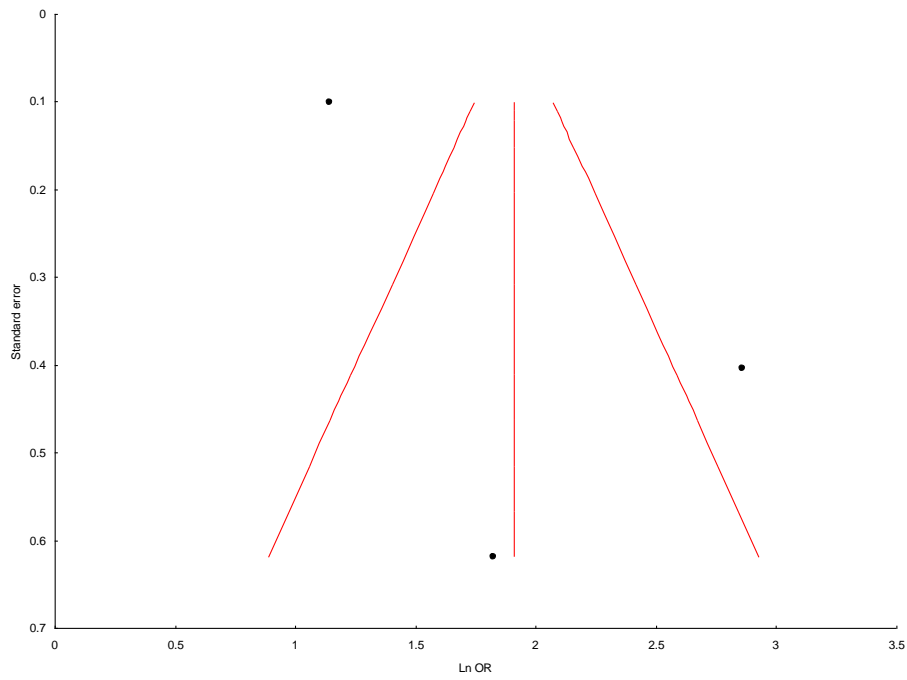


Figure 31: Funnel plot of pooled univariate odds ratios of previous MRSA colonisation

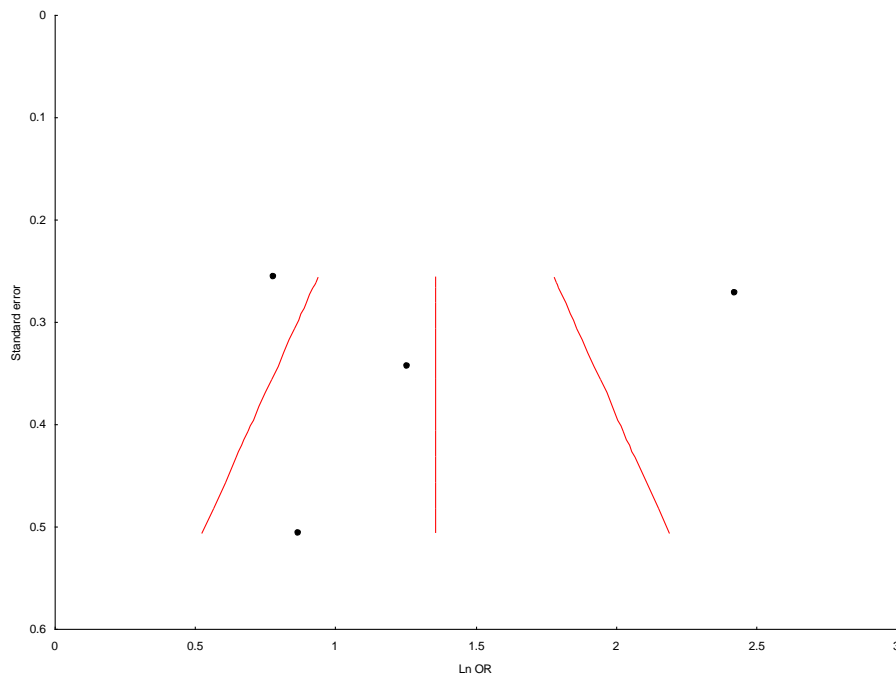


Figure 32: Funnel plot of pooled univariate odds ratios of previous ICU admission

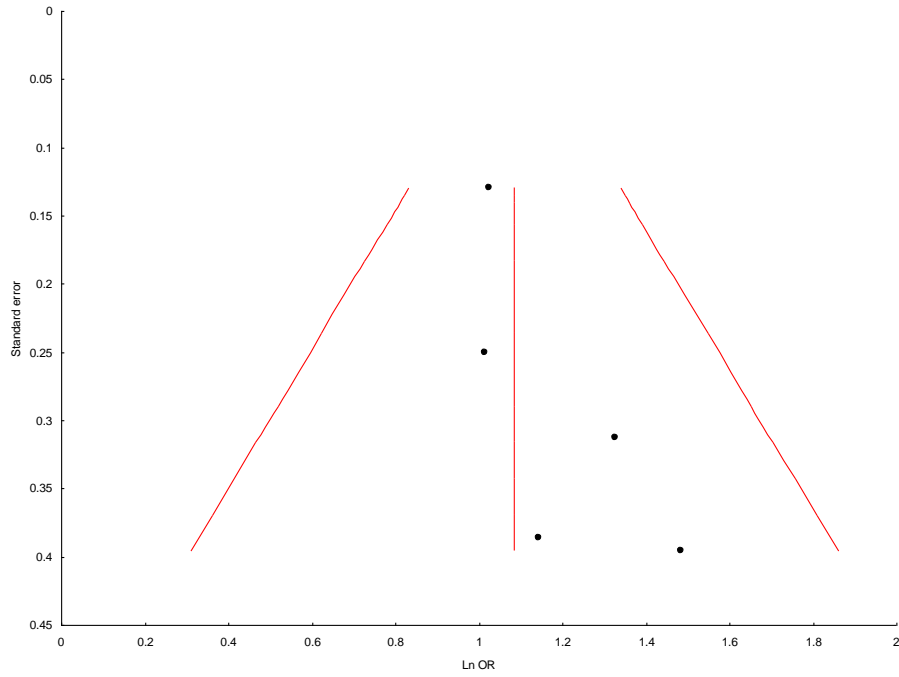


Figure 33: Funnel plot of pooled univariate odds ratios of previous Surgery

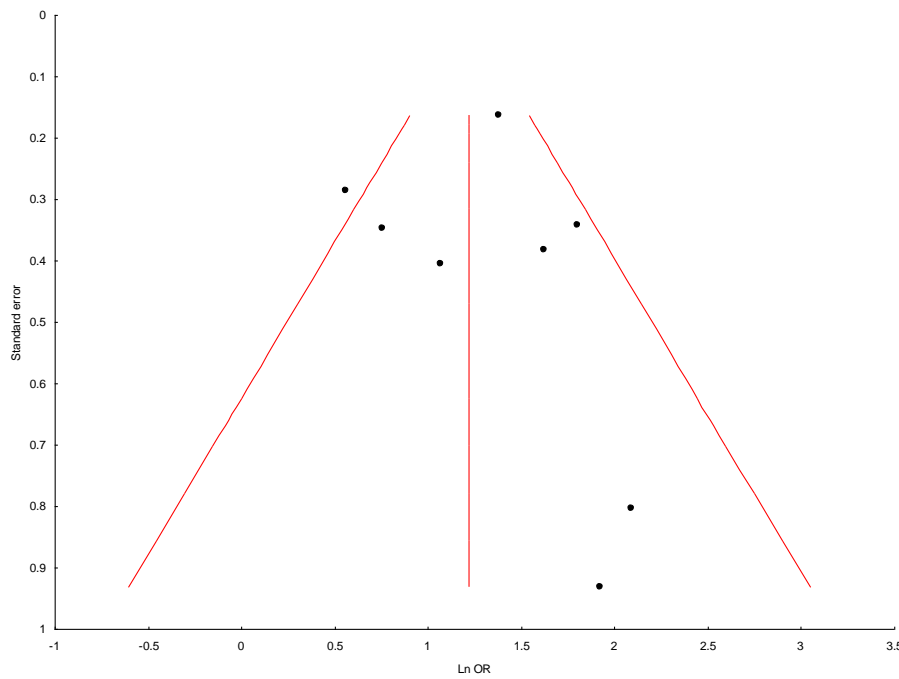


Figure 34: Funnel plot of pooled univariate odds ratios of skin lesion/s



## Appendix VI: The assessment of publication bias for meta analyses based on multivariate estimates

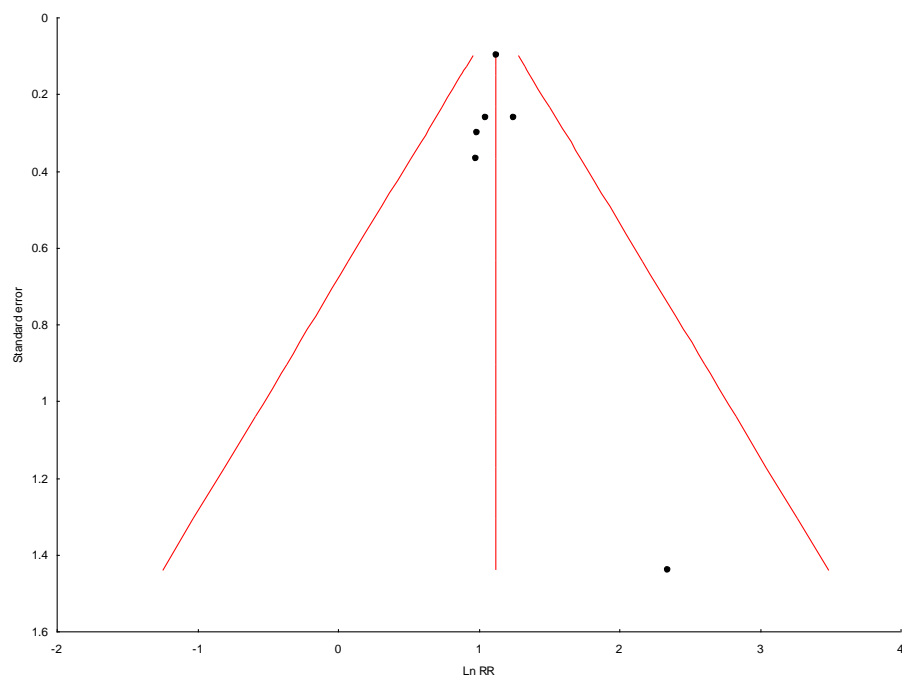


Figure 35: Funnel plot of pooled multivariate odds ratios of antibiotic uses

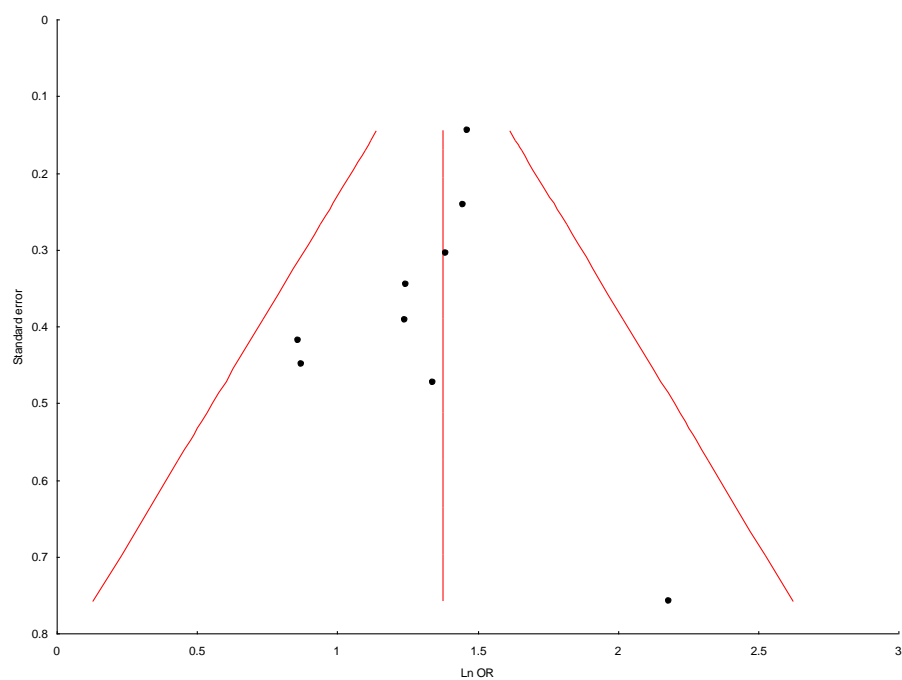


Figure 36: Funnel plot of pooled multivariate odds ratios of recent hospitalisation

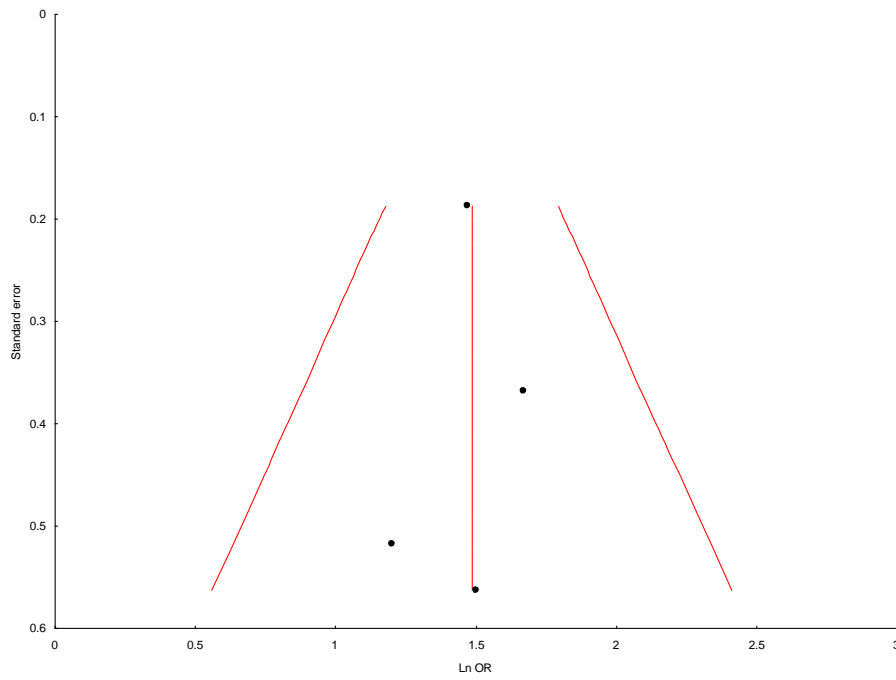


Figure 37: Funnel plot of pooled multivariate odds ratios of indwelling urinary catheter

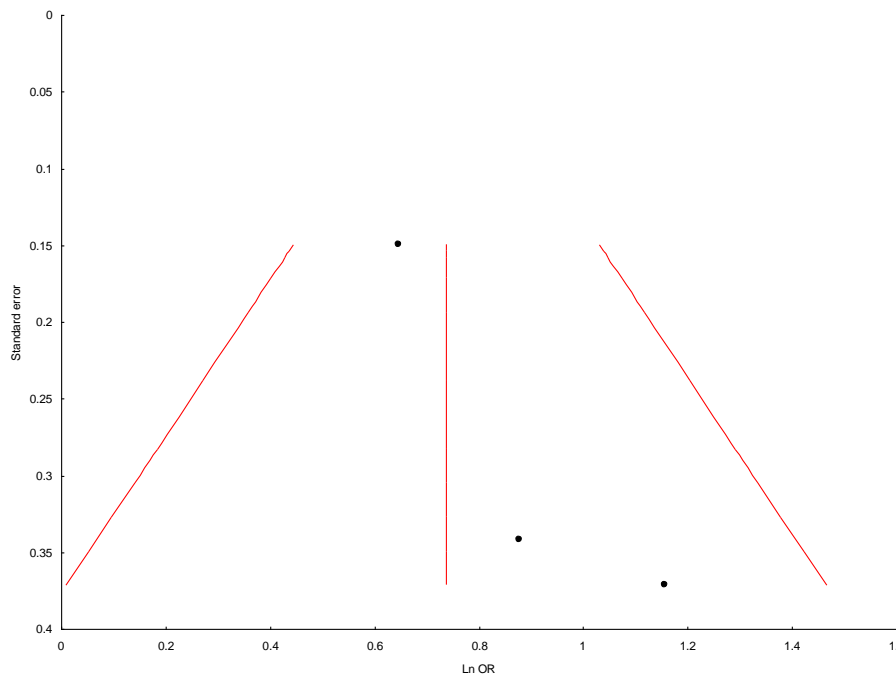


Figure 38: Funnel plot of pooled multivariate odds ratios of intra hospital transfer

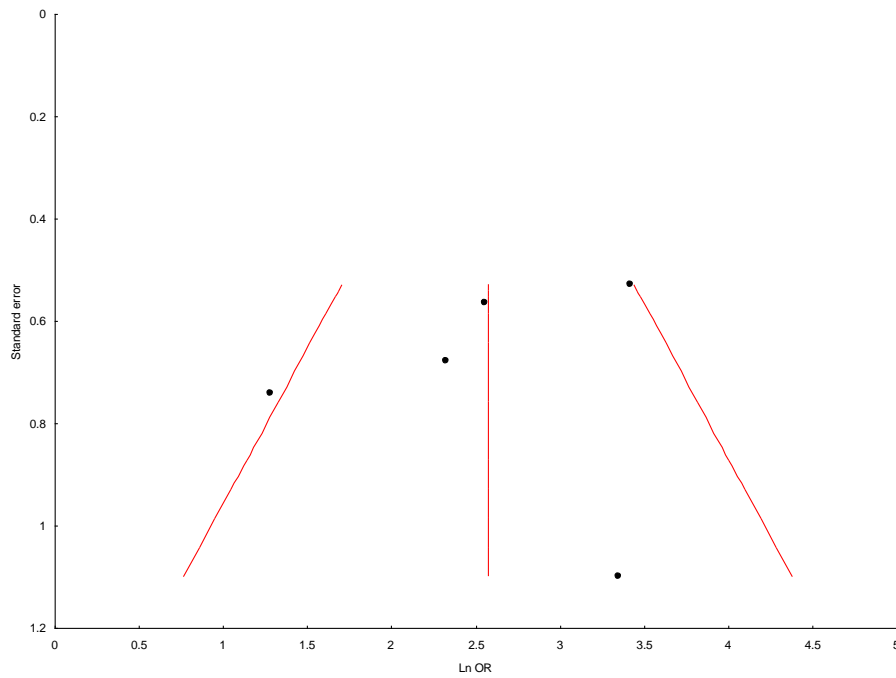


Figure 39: Funnel plot of pooled multivariate odds ratios of admission to LTCF and rehabilitation facilities

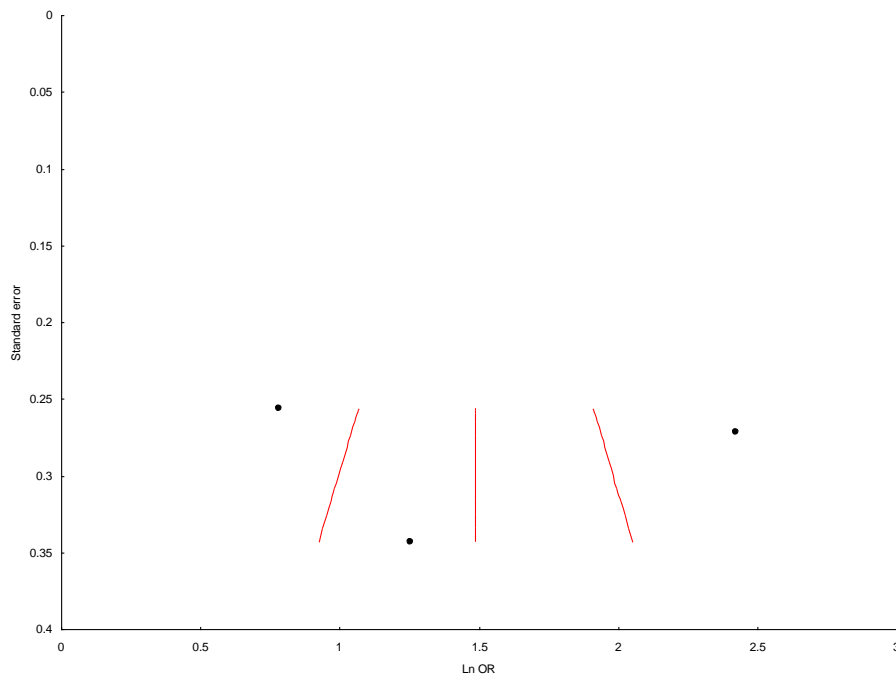


Figure 40: Funnel plot of pooled multivariate odds ratios of previous ICU admission

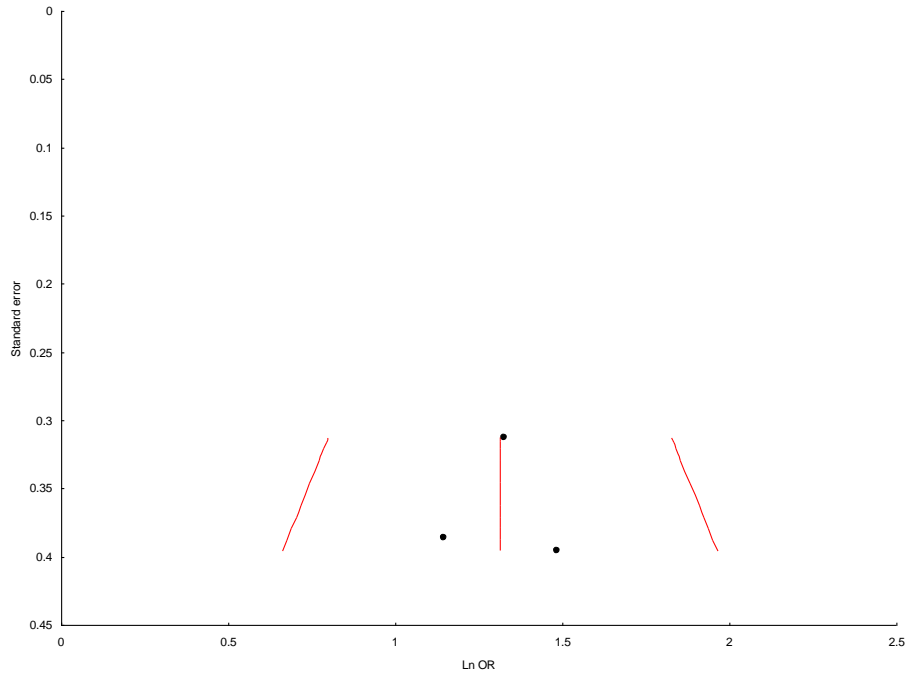


Figure 41: Funnel plot of pooled multivariate odds ratios of previous Surgery

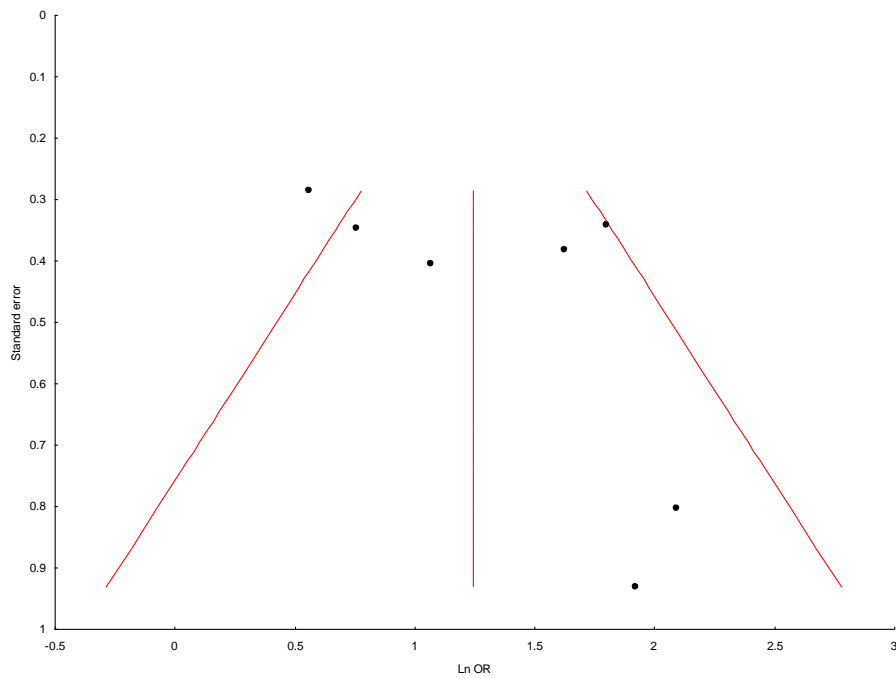


Figure 42: Funnel plot of pooled multivariate odds ratios of skin lesion/s