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Research Article

Concerns on Control Measures for Methicillin-Resistant *Staphylococcus Aureus* Colonization Dissemination in Long-Term Care Facilities: A Meta-Analysis and Systematic Review

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Abstract

Methicillin-Resistant *Staphylococcus Aureus* (MRSA) can cause colonisation and infection in anatomical sites such as the nares, axillae, groin. Sepsis, pneumonia, skin and other diseases can result. Three individualised strains exist: Hospital-Associated, Community-Associated and Livestock-Associated (HA-MRSA, CA-MRSA, LA-MRSA).

Healthcare Workers (HCW) are apprehensive about the spread of MRSA. Hospital administrators and Healthcare authorities express concern about Multi-Resistant Organisms (MRO) and dictate control measures.

In Long-term Care Facilities (LTF), Infection Control Professionals (ICP) are required to balance the risk of propagation of MRO with the adverse effects of measures on healthcare and rehabilitation programs. One must consider their potential pitfalls – such as the overuse of antibiotics, selective pressure to the hospital flora and intrusion on care and rehabilitation programs – against desired effects.

Patients in LTF feature an extended stay, while not being actively sick. Some measures against MRSA may be ineffective or even detrimental to those patient's care and rehabilitation.

We present the first comprehensive bibliography review concerning measures against MRSA in LCF. We searched multiple databases, with no language limits, with the objective to evaluate the effectivity of all actions against MRSA. We analysed 7 Randomised Control Trial (RCT) studies (out of 539 records found). We assessed the bias of studies according to the Cochrane methodology. We calculated the Risk Ratio (with a fixed effect) of the Prevalence of MRSA using Revman and made a Meta-analysis of the studies.

None of the RCT showed evidence of the effect of the measures studied against MRSA prevalence.

We conclude there is no evidence of efficacy of any measures on the Prevalence of MRSA in LCF. Studies evidence that some procedures are not cost-effective and obstacle rehabilitation. LCF need to accordingly re-evaluate routines against MRSA to minimise both unnecessary and ineffective procedures. After cost-effectivity evaluation of unfavourable effects, it is advisable to stop using unnecessary measures.

We did not find RCT studying the Quality of Life (QOL) of patients. Further studies are necessary to establish the interference of measures on the QOL of rehabilitation patients.

Keywords: MRSA; Meta-Analysis; Systematic Review; Long-term Care Facilities; Epidemiology; Prevention and Control

Abbreviations

CNSI: Central Nervous Injured; CA-MRSA: Community-Associated MRSA; CI: Confidence Interval; CP: Contact Precautions; HH: Hand Hygiene; HF: Healthcare Facilities; HCW: Healthcare Workers; HIC: Hospital Infection Control; HA-MRSA: Hospital-Associated; HIV: Human Immunodeficiency Virus; LTF: In Long-term Care Facilities; ICP: Infection Control Professionals; ICR: Intraclass Correlation Ratio; IP: Isolation Precautions; LA-MRSA: Livestock-Associated; MRSA: Staphylococcus aureus MRSA; MRO: Multiresistant organisms; QOL: Quality of Life; RCT: Randomised Control Trials; RR: Rate Ratio; SCI: Spinal Cord Injured; SE: Standard Error; SP: Standard Precautions.

Introduction

Methicillin-Resistant *Staphylococcus Aureus* (MRSA) was first discovered in 1961 (Barber 1961; Jevons 1961; Knox 1961). Community-associated MRSA (CA-MRSA, USA300 MRSA) probably emerged in the 1990s [1]. A Livestock-Associated MRSA strain (ST398) has developed and can be associated with a human origin and with the use of antibiotics in animals [2].

MRSA is a bacterium that can cause colonisation and infection in both healthy and immunosuppressed people. The nares, oral cavity, axillae, groin, rectum and perineal area, the large bowl can be affected by colonisation and infections such as skin and soft tissue, pneumonia, sepsis, can result. Its prolonged persistence as non-pathogenic coloniser may result in contamination of the hospital environment and community [3-5]. Healthcare workers may carry organisms from one patient to another [6,7]. A given bacterium can relay resistance to others [8-10].

MRSA can cause both local and systemic infections when associated with disrupted anatomic barriers or in patients presenting immunosuppression. Some examples of risk factors are former hospital or nursing home admission; prior use of antibiotics; previous MRSA infection or colonisation; haemodialysis [11,12]. MRSA can directly cause skin lesion and abscess; surgical wound infection; urinary infection; Central Nervous (CNS) infection; upper respiratory tract infection and (nosocomial) pneumonia; sepsis among other diseases.

As most MRSA strains are also resistant to multiple antibiotics [4,13] they may present a treatment dilemma. The interchange of resistance characteristics and the emergence of Vancomycin-Resistant strains [10] is of great concern. MRSA dissemination can become a problem for other initially not contaminated patients [3,11].

While it is essential to contain the dissemination of such strains, reliable laboratory screening for MRSA with traditional methods can be difficult and costly due to some of its characteristics such as heterogeneous resistance [14], intermittent colonisation, and co-colonisation and competition with *S. aureus* susceptible strains (MSSA) and *S. epidermidis*.

MRSA strains represent a continuing challenge for Hospital Infection Control (HIC) in LTF not only because of their capabilities of environmental persistence in hospital flora but also because eradication from colonised patients can be time-consuming and difficult [4]. Measures such as mobility restriction of patients, used in other hospitals, may be unnecessary in Rehabilitation facilities [15]. Some patients at risk include people with Human Immunodeficiency Virus (HIV); any immunosuppressed patients; aged people; disabled and stationary people; Spinal Cord Injured (SCI); and Central Nervous Injured (CNI) patients (Peters 2013); and any otherwise institutionalised people. Behavioural factors may apply [11].

Those institutions may impose strict measures of isolation such as Isolation Precautions (IP) and CP (CP). MRSA can also induce overuse of antibiotics. That may impose not only additional costs but also prejudice and discomfort on the affected individuals, compromising the nursing care and limiting rehabilitation programs [15]. Isolation precautions may induce less attention to patients by health personnel. Patients such as aged people or patients in rehabilitation facilities often grudge preconceived attitudes towards them [16,17]. Also, in patients such as SCI and CNS rehabilitation units, those measures may deter or shorten their rehabilitation program [18]. On the other hand, overuse of antibiotics targeted at MRSA may impose extra costs to the health system and result in the selection of (MRO) in the hospital flora (Coia 2006).

Patients on LTF feature longer stays when compared to those in acute care hospitals. They often do not present sickness besides their disabilities. MRSA may colonise them not-pathogenically during extended periods. The colonisation of healthy, people and HCW has been documented, and protocols for that eradication proposed [6,7,19]. The establishment of more straightforward measures

such as CP and IP may suffice to determine a low endemicity of hospital MRSA and save the inconveniences associated with the other protocols [18].

While it is vital to contain MRSA strains, it is possible that Standard Precautions (SP), either alone or associated with adequate CP, are sufficient measures for the containment of MRSA in LTF. Those measures of control include Conscientious Hand Hygiene (HH) techniques and practical environmental hygiene methods.

The EUREGIO MRSA-NET (Germany/The Netherlands) has recognised *S. aureus* as responsible for most of the healthcare-associated infections worldwide. It has been established initially with the objective to protect the population in the Dutch-German border region Twente/Münsterland against MRSA infections. It aims to systematically screen and control the prevalence of MRSA and to establish international cooperation for handling its dissemination across the border and the German-Dutch facilities.

Banwan [13] reviewed the use of antibiotics against multi-resistant Gram-positive bacteria in Veterans Affairs SCI rehabilitation facilities. Claus [18] calculated the economic burden of measures against MRSA in rehabilitation facilities in the border. Balbale [20] surveyed the effectivity of guidelines against MRSA in SCI units in the Veterans Affairs Health Care System. Gurusamy [21] made a meta-analysis on the antibiotic prophylaxis against MRSA in surgical patients.

We found no previous Systematic Review comparing different measures to prevent the dissemination of MRSA in LTF.

A better understanding of the epidemiology of MRSA in the context of residents of such facilities might mean a wiser use of the preventive measures, thus avoiding antibiotic overuse, limitations to admission and rehabilitation procedures, the emergence of new resistant organisms and other untoward consequences.

Objectives

- To assess the effects of MRSA control measures for MRSA infection/colonisation in residents of LTF.
- To determine whether some control measures are ineffective for LTF
- To evaluate the economic burden of MRSA prevention measures in LTF and its effects on quality of care.
- To propose the re-evaluation of measures against MRSA in LCF.

Methods

Description of the interventions

Many measures have been proposed for the control of MRSA, among them [3];

- Contact Precautions (CP)
- Standard Precautions (SP)
- MRSA screening
- Mupirocin® or other antimicrobials
- Reinforced Hand hygiene on Healthcare Facilities (HF)
- Periodic environment decontamination

How those interventions might work

CP and SP help to prevent the dissemination of MRSA from people to the environment and back since that agent is transmitted either by direct or by indirect contact, with surfaces, skin or body fluids.

MRSA screening is done in the anatomical sites possibly colonised on the resident, thus allowing targeted decolonisation. That would mean avoiding the dissemination of MRSA from one resident to another, and from residents to the environment.

Environment cleaning and decontamination is a measure targeting the bacteria that might be colonising surfaces of the hospitals, thus breaking the cycle of transmission.

As bacteria may temporarily colonise staff and other people, and the hands are considered the most often places of temporary residence and transmission of MRSA [3], promoting and reinforcing the best Hand Hygiene practices would work effectively against the dissemination of MRSA.

It is possible to achieve MRSA decontamination/decolonisation through a variety of chemical agents, such as Mupirocin®, retapalumin® and Chlorhexidine® of even systemic antimicrobials. Its eradication from colonising sites and the treatment of infected residents is expected to diminish dissemination.

Criteria for considering studies for this review

We included only Randomised Controlled Trials (RCT), that compared at least one measure for prevention of the dissemination of MRSA with another measure or with either placebo or standard care measures, and any measures against the spread of MRSA within each institution. Studies were selected irrespective of blinding, language, publication status, sample size. Study settings were limited to any LTF, such as Spinal Cord Unit/Stroke/Cerebral Palsy rehabilitation units; Veterans hospitals; Nursing Homes; rehabilitation facilities; Presidiums; and Military Units of long permanence. We included no other study designs in the meta-analysis.

The detailed criteria for considering studies for this review were as follows:

- A comprehensive bibliography in various databases, with no language restriction.
- Search including key Grey Literature sources with various keywords.
- Selection of any Randomized Controlled Trials (RCT) in LTF about measures of prevention of the dissemination of MRSA were for the Review.
- Searching also for RCT where economic analysis and quality of life analysis was carried out.
- Statistical analysis to determine the effect of the measures on the Prevalence of MRSA in LCF

Types of participants

Participants included were:

- Any LTF, their staff and residents.
- The main LTF included: Nursing homes, Rehabilitation hospitals (residents with Stroke, Spinal Cord Injury, Cerebral Palsy, HIV, drug user's rehabilitation facilities and others).

Types of interventions

Interventions searched for were:

- Educational measures as to Infection Control, SP, IP, CP, and any hygiene measures.
- Environmental disinfection and cleaning measures.
- Screening high-risk and low-risk patients, susceptible or sick individuals for MRSA, either by standard bacteriological examination (takes up to 72 Hours) or by Polymerase Chain Reactions (PCR, takes hours) or any other proposed.
- Preventive use of topic antibacterial agents such as chlorhexidine®, retapalumin®, mupirocin® and other antibiotics, in dermatological preparations, soaks or baths.

Types of outcome measures outcomes searched for include:

- The incidence of MRSA colonisation or infection, defined as the frequency of new cases over a given period.
- Prevalence of MRSA colonisation or infection, defined as the frequency of cases of MRSA in a given period.
- MRSA infection – any local, organic, or systemic disease; any wound infection, Urinary Tract Inferior or other caused by MRSA
- Any outcome that indicated morbidities of MRSA infection, such as: worsening of conditions not previously associated with the presence of MRSA; delay in wound or surgical wound attributed to the secondary infection with MRSA; or prolonging and worsening of any condition attributable to secondary infection or co-infection with MRSA.
- We considered only the outcomes collected within the institutions investigated, their staff or residents.
- We used standard measuring units for Incidence and Prevalence.
- We calculated the results of the measures by evaluating the RR with a fixed effect.

Search methods

We performed a comprehensive bibliography in various databases, with no language restriction. We searched the following databases:

- Ovid® Medline (12th May 2018);
- Ovid® Embase: Science citation index (12th May 2018);
- Cochrane Clinical Trials Register® (12th May 2018);
- The Cumulative Index of Nursing and Allied Health Literature® (CINAHL) (12th May 2018);
- The WHO trials register ClinicalTrials.gov® (12th May 2018).

- Also, the following Grey Literature databases (19th April 2018):
- The Biblioteca Científica Eletrônica Virtual (SciELO®);
- The MRSA NETZWERK (a specific Dutch-German group of study of MRSA and prevention of its dissemination)
- The British Library® (19th April 2008);
- The Grey Literature database®.
- ДАЛЬНЕВОСТОЧНЫЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ (http://www.fesmu.ru , The Far-Eastern State Medical University)
- ЭПИДЕМИОЛОГИЧЕСКИЙ МОНИТОРИНГ ЦИРКУЛЯЦИИ ЭПИДЕМИЧЕСКИ ЗНАЧИМЫХ ШТАММОВ MRSA НА ТЕРРИТОРИИ КЕМЕРОВСКОЙ ОБЛАСТИ (https://elibrary.ru/, The Electronic Library, Russia)

Data collection and analysis

We identified the trials for inclusion in the review, according to the titles and, whenever available, to the abstracts. We obtained the chosen studies, selected all RCT trials and extracted the data directly from the surveys. For dichotomous variables, we calculated the risk ratio (RR) with 95% confidence interval (CI). We extracted and analysed the Log [Rate Ratio] with a fixed effect, and the Standard Error [SE] directly from the studies. Whenever those data were not available, we calculated those from other data in the reviews. For the Cluster-Randomised studies, we adjusted the SE by using an Intraclass Correlation Ratio (ICR) of 0,01 [12,22]. We performed a meta-analysis using a fixed-effect model and a random-effects model. We planned to evaluate Publication Bias using Funnel Plot and Eggers Test.

Results

Main results

We found seven eligible RCTs with a total of 8992 residents (for the studies Schora 2014 [23] and Peterson 2016, the number of residents not available because the measuring unit was patient-day) and included six of them in a meta-analysis. (flowchart of searching shown on Figure 1, below). All studies were RCT, even though blinding was not possible in all of them. Interventions were different for each study (as described below, on the short description of the studies).

The meta-analisis of the six main studies is shown on Forrest Plot 1, which also shows the assessment of bias in individual studies. As per the evaluation of the log[RR] of MRSA Prevalence at each institution, no individual trial showed evidence of effect of the measures. Forrest Plot 2 shows the evaluation of the study by Peterson, that was excluded from the meta-analysis because they stated a dual measure (two times decolonisation) rather than only one intervention. As per evaluation of MRSA Prevalence, that study also did not show evidence of effect (RR=0.5 [0.17 – 1.49]).

We performed a subgroup analysis to determine whether there were differences among the types of institutions (3 Nursing Homes, 2 Tertiary Long-Term Healthcare facilities and an inpatient drug rehabilitation facility for people with HIV) That analysis showed no evidence of difference (Forrest plot shown on supplement)

We performed an exploratory Sensitivity Analysis by excluding one of the studies. That Subgroup Analysis nor the Sensitivity Analysis demonstrates any evidence of a difference. (Forrest plot shown on supplement).

We analysed all studies individually as for the measures taken and, in the outcomes. (Individual Forrest Plots are shown on Supplement).

Short description of the studies

We briefly describe each study and show the RR with a fixed effect [95% CI] of MRSA prevalence for each study.

Amirov (2017), in a single single-centre study conducted in an academic tertiary care facility, showed a not statistically significant difference of 71% on the incidence of MRSA conversion after the use of 2% mupirocin impregnated washcloths (RR = 0.95 [0.87, 1.04]) difference. Baldwin [22] showed higher average infection control audit scores, but no statistically significant difference in MRSA positivity (RR = 1.09 [0.89, 1.35]) after Infection Control Education and training versus usual practice continued. Bellini (2015) found no statistically significant reduction on MRSA carriage at the units where residents were screened for MRSA and subsequently treated against units that practised only standard precautions (SP). (RR = 0.90 [0.28, 2.94]) Chuang [24] showed a not statistically significant decrease in prevalence and intra-facility MRSA transmission after an intervention bundle – including hand hygiene enhancement, environmental decontamination, and modified CP (RR = 1.08 [0.98, 1.20]) Gordon [25] showed the use of a 2% mupirocin nasal ointment suppressed the colonisation both of residents colonised and not colonised at baseline (but infection rates were not affected) (RR = 0.86 [0.46, 1.61]).

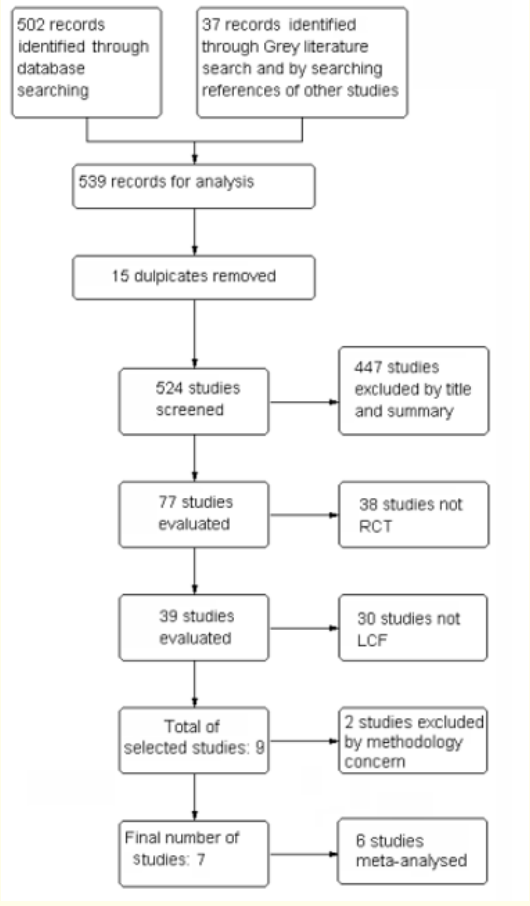

Figure 1: Flow Chart of searching and selecting the studies.

Schora 2017 (IL, USA) investigated 3 LCF for Positive nasal MRSA (surveillance using In-house PCR for MRSA) + decolonisation of carriers (intervention) versus control (usual care). Decolonisation was achieved with nasal mupirocin and chlorhexidine bathing (RR = 0.65 [0.18, 2.35]). Peterson used PCR rapid detection + with a 5 day of Mupirocin® calcium 2 X daily, and intensive decolonisation regimen, performed twice (consisting of minocycline - 100 mg orally twice daily for 5 days, rifampin - 600 mg orally once daily for 5 days ; 2% mupirocin ointment applied to the anterior nares twice per day for 7 days, plus a bath or shower with 4% chlorhexidine once per week for 2 weeks in cases of decolonisation failures). His study showed no statistically significant difference. (RR = 0.50 [0.17, 1.49]). Both studies changed conditions after year 2, and we excluded Peterson from the Metanalysis because it used a dual intervention (figure 2).

We show the individual Forrest Plot of the study by Peterson below. The survey by Peterson was not included in the meta-analysis because it involved a dual set of interventions rather than individually analyse one intervention (Figure 3).

Discussion

Claus [18] studied the Epidemiology of MRSA in German LTF. They constructed a decision tree, considering several factors such as the prevalence of MRSA in Germany, costs of prevention and screening, measures, the possibility of transmission of infection from patient to patient.

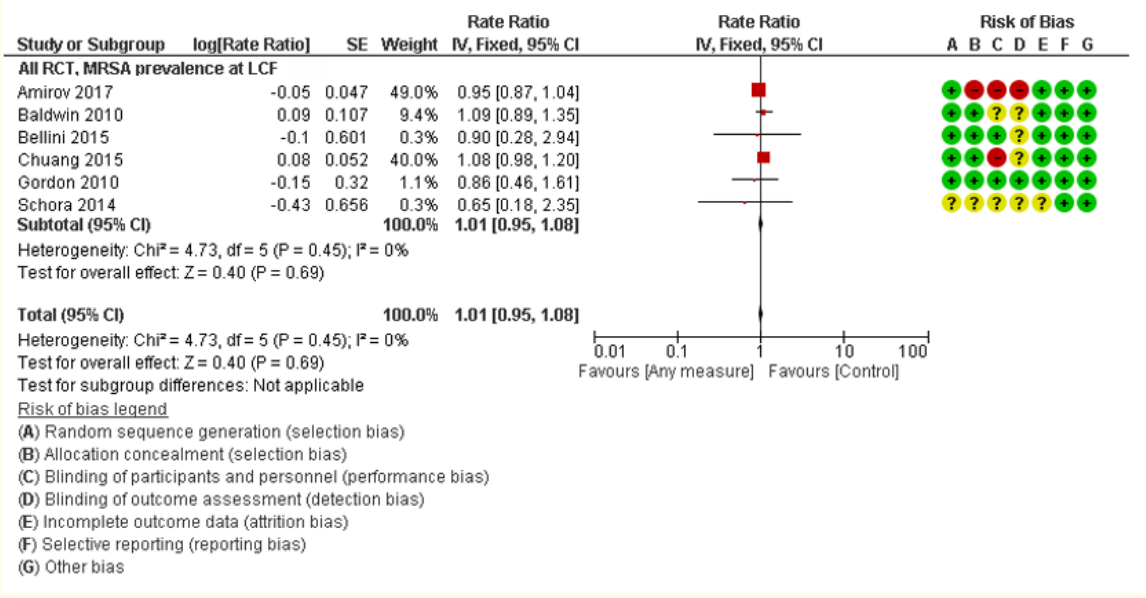

Figure 2: Forrest Plot 1. Any measures against MRSA dissemination X control (usual care), outcome: MRSA Positivity, six studies.

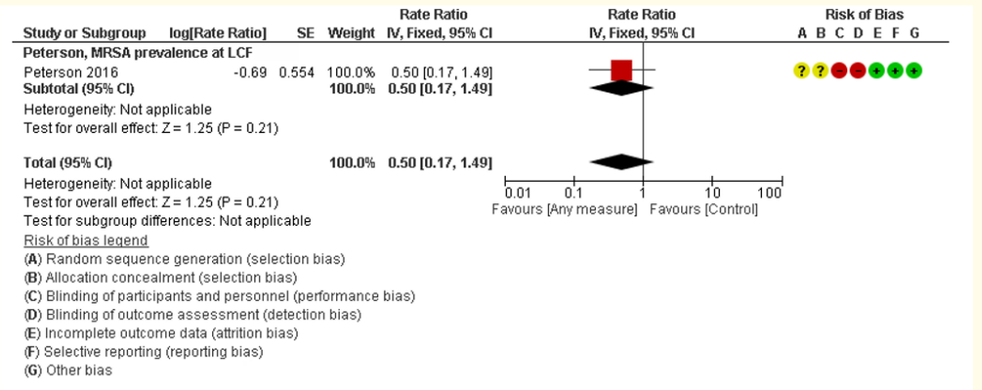

Figure 3: Forrest Plot 2. Nasal MRSA surveillance (using In-house PCR for MRSA) + decolonisation of carriers (intervention) versus control (usual care). Outcome: MRSA Positivity.

They made a risk analysis using two different scenarios. - an optimistic scenario – considering all values set at their lowest, and a pessimistic one – considering all higher settings.

Performing MRSA screening in all patients was the most expensive policy in both scenarios, followed by performing the risk-oriented screening. No-measure at all (meaning neither screening nor decolonising any patients) was the cheapest policy of all. The conclusion was that, while LTF should reinforce appropriate hygienic measures, the German Government should establish adequate economic incentives if all LTF were to implement specific measures against MRSA.

Despite a thorough search, we found few intervention studies of excellent quality intended to determine the effectiveness of preventive measures against MRSA. Subgroup analysis and a Sensitivity analysis on the RCT found (supplement data) showed no evidence of the significative effect of any actions against MRSA among different types of LTF (Nursing Homes, Tertiary Long-term-Hospital Care Facilities, an inpatient drug rehabilitation facility for people with HIV). Each of the studies used individual measures or bundles of policies and observed different outcomes. That precluded a comprehensive meta-analysis of excellent quality [26-46].

Authors Conclusion

We conclude that only seven among 539 studies presented low bias when addressing measures against MRSA in LCF. Those studies showed no evidence of efficacy of any actions against MRSA in LCF.

While some authors evidence such measures are not cost-effective, some procedures are costly and may be harmful to rehabilitation patients. LCF need to accordingly establish new routines against MRSA that minimise unnecessary procedures and overuse of antibiotics. Given costs, low effectivity and possibilities of untoward effects, it is advisable to stop using some of those measures.

More robust studies are needed to address this question in the face of the continuous emergence and dissemination of MRSA strains, antibiotic resistance and usage. It is advisable that each LCF studies its own set of measures, considering inconveniences, costs and antagonistic effects linked to those measures against real benefits in their rehabilitation programs and patients.

Supplement

This supplement contains all the statistical data of the study. The intention of making it available is to be open to evaluation of all readers with interest on the methodologies and statistics while keeping the main published study simpler and easier to read. It contains the full methodological and statistical description of the

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Funding

The study was elaborated during the corresponding author's study at MSc Evidence-Based Healthcare at UCL. All resources were self-funded.

Methods

Criteria for considering studies for this review

We included only Randomised Controlled Trials (RCT), that compared at least one measure for prevention of the dissemination of MRSA with another measure or with either placebo or standard care measures, and any measures against the spread of MRSA within each institution. Studies were selected irrespective of blinding, language, publication status, sample size. Study settings were limited to any Long-care Facilities (LCF), such as Spinal Cord Unit/Stroke/Cerebral Palsy rehabilitation units; Veterans hospitals; Nursing Homes; rehabilitation facilities; Presidiums; and Military Units of long permanence. We included no other study designs in the meta-analysis.

study.

The detailed criteria for considering studies for this review were as follows:

- We made a comprehensive bibliography in various databases, with no language restriction.
- The Search included Grey Literature with various keywords.
- We selected any Randomized Controlled Trials (RCT) in LCF about measures of prevention of the dissemination of MRSA were for the Review
- We also searched for RCT where economic analysis was carried out.

Types of participants

Participants included were:

- Any LCF, their staff and residents.
- LCF included: Nursing homes, Rehabilitation hospitals (residents with Stroke, Spinal Cord Injury, Cerebral Palsy, HIV, drug user's rehabilitation facilities and others).

Types of interventions

Interventions searched for were:

- Educational measures as to Infection Control, Standard Precautions, Isolation Procedures and hygiene measures.
- Environmental disinfection and cleaning measures.
- Screening high-risk and low-risk patients, susceptible or sick individuals for MRSA, either by standard exams (takes up to 72 Hours) or by Polymerase Chain Reactions (PCR, takes hours).
- Use of topic antibacterial agents such as chlorhexidine®, retapalumin®, mupirocin® and other antibiotics, in dermatological preparations, soaks or baths;

Types of outcome measures outcomes searched for include:

- The incidence of MRSA colonisation or infection, defined as the frequency of new cases over a given period.
- Prevalence of MRSA colonisation or infection, defined as the frequency of new cases of MRSA in a given period.
- MRSA infection – any local, organic, or systemic disease; any wound infection, Urinary Tract Inferior or other caused by MRSA.
- Any outcome that indicated morbidities of MRSA infection, such as worsening of conditions not previously associated with the presence of MRSA, delay in wound/surgical wound attributed to the secondary infection with MRSA, or prolonging/worsening of any condition attributable to secondary infection/co-infection with MRSA.
- We considered only the outcomes collected within the institutions investigated, their staff or residents.
- We used standard measuring units for Incidence and Prevalence.

Searching strategies

The databases searched included in the search are shown below:

Database	Date of search	Nº hits
EMBASE	12th May 2018	46
1 exp penicillin resistance/ 11820		
2 exp Staphylococcus infection/		46147
3 exp Staphylococcus aureus/		151734
4 2 or 3		177602
5 1 and 4		4863
6 *long term care/		20059
7 long-term care.ti,ab.		22262
8 (long stay adj2 (care or healthcare or service? or treatment? or patient? or resident?)).ti,ab.		1455
9 (function* adj2 (dependen* or independen* or limit* or decline* or status or impair*)).ti,ab.		184502
10 (candidate? adj3 (institution* or deinstitution* or home or place*)).ti,ab.		506
11 or/6-10		220897
12 5 and 11		46

Table a

Database	Date of search	Nº hits
Science citation index	12th May 2018	35
# 8 - # 7 and #6 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years		35
# 7 - TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo*) - Indexes=SCI-EXPANDED, CPCI-S Timespan=All years		1,971,611
# 6 - #5 AND #1 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years		305
# 5 - #4 OR #3 OR #2 - Indexes=SCI-EXPANDED, CPCI-S Timespan=All years		211,684

# 4 - TS=(candidate? near/3 (institution* or deinstitution* or home or place*)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	281
# 3 - TS=(function* near/2 (dependen* or independen* or limit* or decline* or status or impair*)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	192,680
# 2 - TS=(long stay near/2 (care or healthcare or service? or treatment? or patient? or resident?)) - Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	19,562
# 1 - TS=(methicillin-resistan* or meticillin-resistan* or MRSA) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	32,065

Table b

Database	Date of search	Nº hits
Cochrane Clinical Trials Register	12th May 2018	14
#1 MeSH descriptor: [Methicillin resistance] explode all trees		158
#2 MeSH descriptor: [Staphylococcal infections] explode all trees		1190
#3 #1 MeSH descriptor: [Staphylococcus aureus] explode all trees		905
#4 #2 or #3		1511
#5 #1 and #4		150
#6 #1 MeSH descriptor: [Methicillin-resistant Staphylococcus aureus] explode all trees		278
#7 (methicillin resistan* or meticilin resistan* or MRSA)		1278
#8 #5 or #6 or #7		1278
#9 MeSH descriptor: [Long-term Care] explode all trees		1256
#10 long-term care		23068
#11 (long stay near/2 (care or health or service? Or treatment? Or patient? Or resident?))		478
#12 (function* near/2 (dependen* or independen* or limit* or decline* or status or impair*)). ti, ab		849
#13 (candidate? Near/3 (institution* or deinstitution* or home or place*))		23
#14 #9 or # 10 or #11 or #12 or #13		23500
#15 #8 and #14		117

Table c

Database	Date of search	Nº hits
CINAHL	12th May 2018	249
S15 S8 and S14		249
S14 S9 or S10 r S11 or S12 or S13		66694
S13 TI (candidate? N3 (institution* or deinstitution* or home or place*)) OR AB (Candidate? (N3 Institution* N# (institution* 0r deinstitution* or home or place)		85
S12 TI (function N2 institution (dependen* or independen* or limit* or decline* or status or impair)) or AB function* N2 (dependen*or independen* or limit/* or decline* or status or impair.		37739
S11 TI (long-stay N2 (care or healthcare or service? or treatment? or patient? or resident?))		523
S10 TI long-term care or AB long-term care		16352
S9 MH ("Long Term Care)		22810
S8 S5 or S6 or S7		10104
S7 TI methicillin-resistant* or meticillin resistan*vor MRSA) OR AB (methicillin-r3wiwqn* or meticillin resistan* or MRSA)		7825
S6 MH Methicillin-Resistant Staphylococcus Aureus		4303
S5 S1 and S4		3635
S4 S2 or S3		14301
S3 MH Staphylococcus aureus		9223
S2 MH staphylococcal infections		9704
S1 MH methicillin resistance		4229

Table d

Database	Date of search	Nº hits
WHO trials register:	12th May 2018	21
Title: Long term care		21

Table e

Database	Date of search	Nº hits
ClinicalTrials.gov:	12th May 2018	1
long-term care | Interventional Studies | Methicillin Resistant Staphylococcus Aureus | Phase 2, 3, 4		1

Table f

Grey literature databases searched

The electronic database Biblioteca Científica Eletrônica Virtual (SciELO) was consulted with keywords in Portuguese and English (Date of search: 19th April 2008) - Nº of hits: 21

Keywords in English included: *Staphylococcus aureus*, *Staphylococcus*, MRSA, MSSA, VISA, GISA, CA-MRSA, HA-MRSA, LA-MRSA, Glycopeptide, infection, colonization, Resistance, emergence, Methicillin, Penicillin, infection, control, infectious disease(s), cross-infection, isolation, epidemiology, intervention, colonization, decolonization, eradication, epidemiology, hospital, bacterial, drug, resistance, communicable disease control, infection control, Hospital infection control, cost, cost burden, budget, economic analysis, MRSA (Mupirocin Resistant MRSA), MS MRSA, intranasal, Chlorhexidine,

Keywords used in Portuguese included: *Staphylococcus aureus* resistente à meticilina, farmacorresistência bacteriana, resistência, descolonização, colonização; eradicação, methicillin-resistant *Staphylococcus aureus* or meticillin or MRSA) and (triagem or busca ou diagnóstico)

Keywords in English included: *Staphylococcus aureus*, *Staphylococcus,* MRSA, MSSA, VISA, GISA, CA-MRSA, HA-MRSA, LA-MRSA, Glycopeptide, infection, colonization, Resistance, emergence, Methicillin, Penicillin, infection, control, infectious disease(s), cross-infection, isolation, epidemiology, intervention, colonization, decolonization, eradication, epidemiology, hospital, bacterial, drug, resistance, communicable disease control, infection control, Hospital infection control, cost, cost burden, budget, economic analysis, MRSA (Mupirocin Resistant MRSA), MS MRSA, intranasal, Chlorhexidine,

The MRSA NETZWERK sites were manually searched. That Dutch-German group studies and attempts to prevent MRSA dissemination across the border. The URLs below were consulted (19th April 2008) with keywords in German and Dutch[2].

We found no RCT about MRSA in LCF. We found one Bachelor thesis was Dutch that, being a Review, we screened for other RCT's (14 studies about MRSA, no RTC's in LCF)

- http://www.kreis-unna.de/hauptnavigation/kreis_region/leben_im_kreis/gesundheit/mre_mrsa_netzwerk/mrsa/informationen_zum_mrsa_netzwerk.html
- http://www.gesunde.sachsen.de/MRE.html
- http://www.landkreis-rastatt.de/,Lde/MRE-Netzwerk.html MRSA NETZWERK
- http://www.landkreis-rastatt.de/,Lde/MRE-Netzwerk.html MRSA NETZWERK

The Keywords we used included:

- In German: Methicillin-resistenter *Staphylococcus aureus*, Randomisierte Studie, *Staphylococcus aureus MRSA*, Randomisierte kontrollierte Studie, MRE, Multiresistente erreger, Wirtschaftsstudie.
- In Dutch: Gerandomiseerde studie, *Staphylococcus aureus* MRSA, Gerandomiseerd onderzoek met controlegroep, *Stapylococcus aureus* Stämmen, economische studie.
- The British Library: URL consulted with keywords in English: MRSA, Staphylococcus (19th April 2008)

http://explore.bl.uk/primo_library/libweb/action/search.do?vid=BLVU1

The grey literature database: (URL consulted with keywords in English, French, German, Dutch. Portuguese and French):

The Grey Literature database (19th April 2008) –: 3 hits for MRSA, no new RCT's in LCF) – URL:

Http://www.greylit.org/library/search

The two databases below were also searched with the same keywords in Russian, (19th April 2008) and returned 1 RCT (which was not performed on LCF), 1 review (which produced no new references) and one translation of a Cochrane review (that had been already mentioned on the search on the Cochrane database) – URL:

- https://elibrary.ru/
- http://www.fesmu.ru/

Searching other resources

We searched the references of the included trials and of the reviews found to identify further relevant studies. We also contacted experts in MRSA infection to identify additional surveys. We used the Mendeley "suggest" tool to search for similar studies.

We used Science Direct "similar studies indication" and PubMed's "similar articles" features.

(URL: https://www.ncbi.nlm.nih.gov/pubmed/to try to identify other studies.

Data collection and analysis

We performed a systematic review following the instructions in the Cochrane Handbook for Systematic Reviews of Intervention [26].

Selection of studies

We based the selection of studies on titles and abstracts that evaluated the stated outcomes, had as objective to study any preventive members towards the dissemination of MRSA, were located at any LCF and were RCT. We obtained the studies chosen using the selection criteria. Whenever the study languages were other than Portuguese or English, we evaluated those after translating them with the use of a Computer Assisted Translation (CAT) tool:

Urls of CAT tools:

1. https://www.freetm.com/
2. https://www.memsource.com/
3. https://www.smartcat.ai/

We identified the trials using the inclusion and exclusion criteria. For data extraction, we considered:

1. Year and language of publication of the trial report.
2. Year in which trial was conducted.
3. Country
4. Whether the trial was an RCT
5. Whether the trial was conducted on an LCF
6. Type of LTF.
7. Details of interventions
8. Frequency and duration.
9. Outcomes (as described above).
10. Risk of bias (as described below).
11. Source of funding.

We searched for and excluded repeated essays.

Evaluation of bias

We followed the instructions in the Cochrane Handbook for Systematic Reviews of Intervention to assess the risk of bias [26].

The primary author made the first bias evaluation using the Cochrane Tool in the assessment of Bias in Randomised Control Trials (Cochrane 2016). Those same studies were blindly given for the review of two independent collaborators, ACPFM and ECN (both Infection Control professionals) to evaluate using the same methodology. The disagreements were resolved either by discussion or by a majority of 2 evaluators against 1).

We intended to evaluate the studies according to the proposed interventions, evaluate the measures through efficiency measures such as Risk Ratio, and produce a meta-analysis using Revman5 software [11] as a tool, and try to determine the most effective measures using effect measures by using MRSA positivity as a primary outcome.

Measures of treatment effect

For dichotomous variables, we calculated the risk ratio (RR) with 95% confidence interval (CI).

Subgroup analysis

We made an exploratory subgroup analysis by grouping the studies according to the types of institutions.

Sensitivity analysis

We performed a sensitivity analysis by excluding one study (which presented some methodology issues) from the meta-analysis.

Data synthesis

We found a total of 7 RCT studies in LCF, examining different interventions across studies. There were some methodology and epidemiologic heterogeneity across studies. None of the studies showed a statistically significant difference or evidence of effect. A subgroup analysis was made, in what we divided the institutions into three groups: Nursing homes (3 studies), Tertiary Long-Term Hospital Care Facilities (2 reviews) and an inpatient drug rehabilitation facility for people with HIV (1 review). There was no evidence of a difference between the subgroups. We performed an exploratory sensitivity analysis by excluding one study of Gordon [25] based on methodologic issues and found this had no evidence of difference on the results.

Results

Results of the search

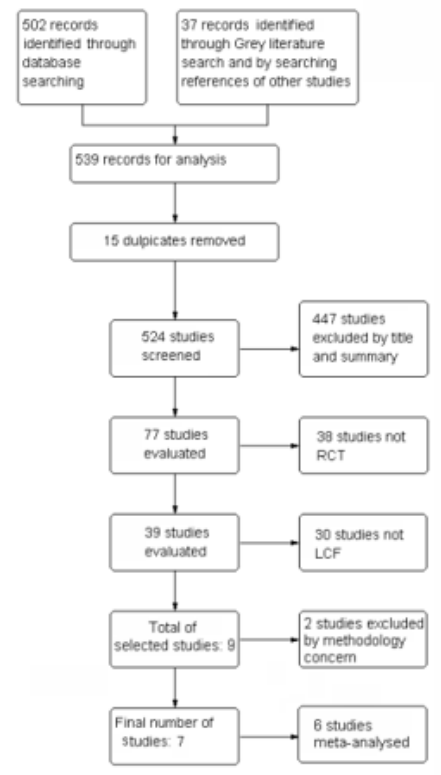


Figure 4: Flowchart of the selection of studies.

We identified a total of 539 unique references through electronic searches, including 15 duplicates. We excluded 447 irrelevant references through reading titles and abstracts. We retrieved 77 references in full for further assessment. We eliminated 38 references because the studies were not RCT, and then 30 studies because the institutions were not LCF**.** A total of 9 studies initially met the inclusion criteria. Among those, two studies [27,28] were not considered in the review because of methodology concerns.

The study by Héquet 2017 was excluded because, though registered as RCT, it was considering as having a high risk of bias on Random Sequence Generation (meaning it was not an RCT). This study used the randomisation of a previous study (with 104 nurseries), then added 33 nursing homes for which they stated no criteria for randomisation.

The study by David 2014 was a cluster RCT, but its outcomes were excluded from this analysis since they present an 'as treated' analysis, where they compared the groups according to the treatment they received. This compromised randomisation, resulting in bias and loss of validity of the statistical tests.

For Schora 2014, we included only the outcomes at one year, since they changed study conditions at one year to 2 years.

The data of Peterson 2016 was excluded from the meta-analysis since it presented two different kinds of interventions. However, we considered it in the description of studies. This author investigated the surveillance of MRSA nasal carriage with targeted decolonisation, coupled with enhanced, against MRSA dissemination.

Risk of bias in the included studies

None of the studies presented a high risk of bias for Random Sequence generation or allocation concealment. The studies by Amirov and Chuang presented a high risk of bias for blinding, where all the others presented either unknown or low risk. The types of LCF consisted of Nursing Homes (three studies, a resident´s drug rehabilitation facility for persons with HIV), and Tertiary Long-Term Care facilities (3 reviews: 1 single centred, two multicentred). We summarise the evaluation of bias on Figure 5 and 6, below.

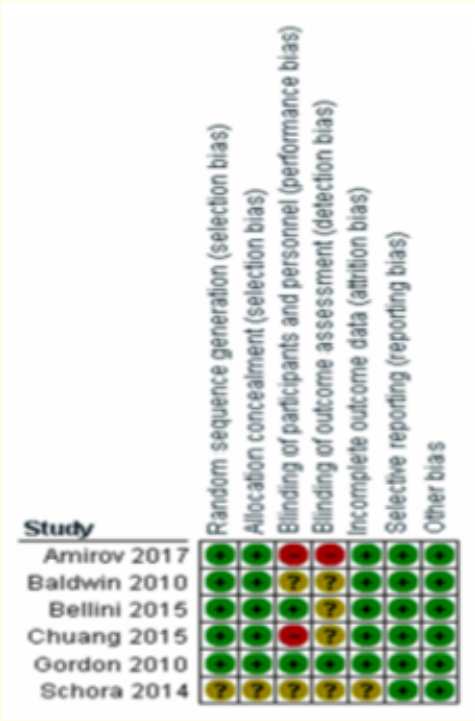


Figure 5: Risk of Bias table.

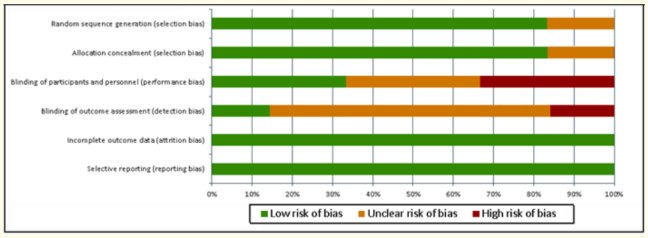


Figure 6: Summary of Risk of Bias.

Data-analysis

We produced a meta-analysis to evaluate the effect of any measures (versus control) against MRSA dissemination. FIG]. We performed a subgroup analysis, which showed no evidence of difference across the evaluated studies (3 Nursing Homes, two tertiary Long-term Rehabilitation facilities, one inpatient drug rehabilitation facility for persons with HIV). We executed an exploratory sensitivity analysis by excluding the study by Chuang [24] (2015) on methodological assumptions (This study had presented some unprogrammed changes, did not check MRSA prevalence among staff and did not culture perineal, groin or throat samples from residents). Those analyses did not demonstrate evidence of a difference of effect at the meta-analysis level.

Due to the clinical and methodological heterogeneity of the measures and the differences of measures across studies, it may be best to evaluate the effects of each study individually.

Reporting and publication bias

We checked for publication bias and excluded any duplicates we found from the meta-analysis. We tried to avoid location and language bias by doing searches in several databases and different Grey Literature sources. By using multiple search strategies, we attempted to minimise citation bias.

It was not possible to evaluate the reporting and publications bias because there were only six selected studies, which is below the minimum amount of studies required for effectively assess the Funnel Plot or calculate the Egger Test.

Interventions found included:

- 2% Chlorhexidine® bath (versus no bath).
- Chlorhexidine® skin cloths for hygiene versus water skin cloths versus no cloth used for personal hygiene.
- Chlorhexidine® ointment versus placebo ointment
- Standard Precautions versus Isolation Precautions (such as described by CDC).
- Screening and disinfection versus screening with no disinfection (continued care only)
- Infection Control Training and education versus usual care
- Universal screening + decolonisation (using different strategies) versus just Isolation Precautions.

Types of outcome measure found included:

- Prevalence of MRSA colonisation.
- Time to MRSA infection.
- MRSA positivity (3, 6, 12 months).
- MRSA prevalence (1,5 years after intervention).
- Positive MRSA tests (after one year, after two years).
- MRSA Carriage (at six months).
- Monthly *S aureus* colonisation analysis.

Characteristics of the studies

Amirov 2017

Type of study	**Cluster RCT (03 clusters)**
Participants	Country: Canada (3 Academic Long Care Facilities)
	Number randomised: 35 [I] + 87 [C] = 122
	Post-randomisation drop-outs: not stated
	Revised sample size: 212
	Average age: 88 [I], 89 [C]
Inclusion criteria:	Consenting MRSA-negative interns
Interventions	Group 1: A daily bath with 2% CHG-impregnated cloth
	Group 2: A daily bath with non-antiseptic cloth
Outcomes	MRSA incidence Time-to MRSA conversion Braden scale score (measures the risk of developing pressure ulcers)
Conflicts of Interest	C.M.A. reports that he received research funding from Sage Product LLC (Cary, IL).
Source of funding	Sage Products LLC (Cary, IL).

Table 1: Risk of bias table made with *Revman* software.

Amirov 2017

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random number generator Microsoft Excel 2010) was described.
Allocation concealment (selection bias)	High risk	A random number generator concealed allocation
Blinding of participants and personnel (performance bias)	High risk	No blinding (Open-label study).
Blinding of outcome assessment (detection bias)	High risk	Blinding was not clearly described and had the potential to outcomes
Incomplete outcome data (attrition bias)	Low risk	The outcome was described for all patients that started the study – no drop-outs
Selective reporting (reporting bias)	Low risk	All outcomes of interest have been reported.
Other bias	Low risk	

Table 2:

Baldwin 2020

Baldwin 2020

Type of study	**Custer RCT (16 clusters)**
Participants	Country: Ireland (32 Nursing homes)
	Number randomised: 392 [I] + 401 [C] = 793
	Post-randomisation drop-outs: 315
	Revised sample size: 234 [I]+ 244 [C] = 478
	Average age: 84 [I], 82 [C]
	Male: female ratio: 110/392 [I], 127/401 [C]
Inclusion criteria:	All residents aged #65 years (excluding the terminally ill or those attending on a day-care basis only) All nursing home staff (all occupations)
Intervention	Group 1: Infection Control Education and training program Group 2: usual care (no special education)
Outcomes	Primary outcome: MRSA prevalence in residents and staff (3, 6, 12 months) Secondary outcome: a change in infection control audit scores.
Conflicts of Interest	None declared
Source of funding	Funded under a Health and Social Services Research and Development Fellowship to N. Baldwin. M. Tunney is funded as a UK National Career Scientist by the Health and Social Care Research and Development, Public Health Agency, Northern Ireland.

Table 3

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random sequence generator was used (NQuery version 6)
Allocation concealment (selection bias)	Low risk	Nurseries were batched in pairs and randomly selected as intervention/control. A random sequence generator was used (NQuery version 6).
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding is impossible due to the nature of the intervention. Influence of blinding on outcomes is difficult to evaluate.
Blinding of outcome assessment (detection bias)	Unclear risk	Outcome assessment was difficult to blind.
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced among both groups.
Selective reporting (reporting bias)	Low risk	All outcomes of interest have been reported.
Other bias	Low risk	

Table 4

Bellini 2015

Bellini 2015

Type of study	**Cluster RCT (104 clusters)**
Participants	Country: Switzerland 157 Nursing Homes.
	Number randomised: 2,112 [I] +2,338 [C] = 4,450
	Post-randomisation drop-outs: 11% in both intervention and control (actual # not stated)
	Revised sample size: 89 % of original (actual# not stated)
	Average age: 83.4 ±5.4 [I], 83.7 ±8.1 [C]
	Female sex proportion: 73%± 10 [I], 72± 12 [C]
Inclusion criteria:	Al residents except for residents for whom the planned length of stay was <3 weeks, those in a terminal condition (i.e., life expectancy <1 week), those who had had hypersensitivity to ≥1 of the substances used for decolonisation. Besides, the residents were temporarily ineligible until resolution of condition) if they were infected with MRSA or if they had an MRSA bacteriuria or a stage 4 chronic ulcer (according to NPUAP staging28).
Intervention	Group 1: Universal MRSA screen + topical decolonisation + environmental disinfection + Standard Precautions. Group 2: Standard Precautions alone (usual care)
Outcomes	Mean MRSA prevalence Mean change in MRSA prevalence
Conflicts of interest	None declared
Source of funding	public

Table 5

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random sequence generator was used.
Allocation concealment (selection bias)	Low risk	A random sequence generator concealed the allocation
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel were blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	It is not stated whether outcome assessment was blinded
Incomplete outcome data (attrition bias)	Low risk	Reasons for missing data unlikely to be related to the exact outcome
Selective reporting (reporting bias)	Low risk	All outcomes of interest were reported in a pre-specified way
Other bias	Low risk	

Table 6

Chuang 2015

Chuang 2015

Type of study	**Cluster RCT (36 clusters)**
Participants	Country: China. 50 residential care homes for the elderly
	Number randomised: 1,865 [I} =1,631 [C] =3,496
	Post-randomisation drop-outs: 2,129
	Revised sample size: 1367 [I] + 1116 [C] = 1483
	Average age: not stated
	Male: female ratio: 564/1505 [I], 456/1271 [C]
Inclusion criteria:	All consenting staff and residents
Interventions	Group 1: Infection control bundles focused on hand hygiene (HH), environmental hygiene, and modified contact precautions Group 2: usual care
Outcomes	MRSA Prevalence MRSA transmission to MRSA free residents Aliquots of the "glove juice" were then extracted for MRSA culture. To assess environmental hygiene, an area of about 10x10cm of each pre-defined high touch spot (i.e. surfaces that hands touch frequently) was swabbed with pre-moistened sterile cotton swabs and these were subsequently sent for MRSA culture.
Conflicts of Interest	None declared
Source of funding	This work was supported by the Research Fund for the Control of Infectious Diseases (RFCID) of the Food and Health Bureau of Hong Kong SAR Government (grant number CHP-NS-04).

Table 7

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random sequence generator (Excel 2003) was used.
Allocation concealment (selection bias)	Low risk	Allocation concealment was used by a random sequence generator
Blinding of participants and personnel (performance bias)	High risk	Attempt to blind participant and staff was made, but its effectivity was probably low due to the characteristics of the study.
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of outcome assessment was not described.
Incomplete outcome data (attrition bias)	Low risk	All original patients were evaluated for outcomes.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes of interest were reported
Other bias	Low risk	

Table 8

Gordon 2010

Gordon 2010

Type of study	**RCT (not Cluster RCT)**
Participants	Country: USA (5o interns from an inpatient drug rehabilitation facility for people with HIV)
	Number randomised: 50 [I} + 50 [C] = 100
	Post-randomisation drop-outs: 8
	Revised sample size: 46 [I} + 46 [C] = 92
	Average age: not stated 43.0 6 6.7 [I], 42.7 6 7.5 [C]
	Male: female ratio: 38/8 [I], 37/9 [C]
Inclusion criteria:	All residents invited. Exclusion criteria included hypersensitivity to mupirocin or glycerol, pregnancy, lactation, expected discharge within a month, and treatment with intranasal mupirocin within two months.
Interventions	Group 1: 2% intranasal mupirocin Group 2: placebo ointment
Outcomes	MRSA prevalence MRSA infection
Conflicts of Interest	None declared
Source of funding	Not stated (GlaxoSmithKline provided 2% mupirocin calcium ointment)

Table 9

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Study identification numbers were pre-randomized
Allocation concealment (selection bias)	Low risk	Study identification numbers were pre-randomized 1:1 in blocks of 4 to receive either mupirocin or placebo by the Columbia University Research Pharmacy (CURP). [Gordon 2010]
Blinding of participants and personnel (performance bias)	Low risk	Participants and staff were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Data collection was made by a blinded professional.
Incomplete outcome data (attrition bias)	Low risk	The reasons for study incompletion were balanced, and the outcomes were probably not statistically different between treatment groups.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported.
Other bias	Low risk	

Table 10

Peterson 2016

Type of study	Cluster RCT (12 clusters)
Participants	Country: USA (3 LCF)
	Number randomised: not stated.
	Post-randomisation drop-outs: not stated
	Revised sample size: not stated
	Average age: not stated
Inclusion criteria:	12 nursing units from the following three categories: nursing, rehabilitation, and dementia care
Interventions	Group 1: MRSA decolonisation two times 91 month apart, using 2% Mupirocin twice daily, applied to the nares and any open wounds) Group 2: MRSA screening only irrespective of isolation or contact precautions
Outcomes	MRSA prevalence from 6 point-prevalence studies
Conflicts of Interest	None declared
Source of funding	Not reported

Table 11

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of Random Sequence generation is not informed
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not informed
Blinding of participants and personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding, which likely influenced evaluation
Incomplete outcome data (attrition bias)	Low risk	No drop-offs were described.
Selective reporting (reporting bias)	Low risk	The study protocol is available, and outcomes were pre-specified
Other bias	Low risk	

Table 12

Schora 2014

Type of study	Cluster RCT (12 clusters)
Participants	Country: USA (3 LCF)
	Number randomised: not stated.
	Post-randomisation drop-outs: not stated
	Revised sample size: not stated
	Average age: not stated
	12 nursing units from the following three categories: 1 of 3 categories: skilled nursing, rehabilitation, or dementia care)
Inclusion criteria:	Group 1: MRSA screening + decolonisation with Mupirocin + CHG Group 2: MRAS Screening only
	MRSA prevalence from point-prevalence studies
Interventions	Group 1: MRSA screening + decolonisation with Mupirocin + CHG Group 2: MRSA Screening, without disclosing results or decolonising procedure
Outcomes	Prevalence of MRSA (point-prevalence every four months) MRSA colonisation at discharge (1 year)
Conflicts of Interest	None declared
Source of funding	Not reported

Table 13

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described
Blinding of participants and personnel (performance bias)	Unclear risk	Method of blinding not described
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of outcome assessment not described.
Incomplete outcome data (attrition bias)	Unclear risk	The study design was changed which may plausibly have altered the outcomes.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	

Table 14

Characteristics of excluded studies

David 2014

Reason for exclusion: The study was classified as an "As-treated analysis".

Héquet 2017

Reason for exclusion: The study was not considered an RCT indeed after evaluation of bias.

Short description of included studies

In Amirov 2017 (Canada), the intervention studied was bathing of patients with 2% chlorhexidine-impregnated antiseptic washcloths, compared to non-antiseptic bathing. A total of 122 patients in 3 hospitals were enrolled for 12 months of the trial. Chlorhexidine baths resulted in a not statistically significant difference of 71% on the incidence of MRSA conversion after the use of 2% mupirocin impregnated washcloths non-significative reduction in MRSA prevalence. (RR = 0.95 [0.87, 1.04]). The study was carried out at Baycrest Health Sciences, a 992-bed, tertiary, academic facility located in Toronto, Canada.

Baldwin 2010 (Ireland) studied 16 nursing care homes as intervention and 16 as control units (no intervention, or usual care), showing MRSA prevalence in residents and staff as the primary outcome, and a change in infection control audit scores as the secondary outcome. The intervention was an infection control education and training programme on MRSA prevalence. Outcome measures were nasal swabs taken at 0, 3, 6 and 12 months and Infection Control Audit scores. They found that the intervention produced higher average infection control audit scores in the intervention units. However, there was no statistically significant difference in MRSA positivity(RR = 1.09 [0.89, 1.35]). It is possible to attribute their lack of findings to some limitations of the study, namely that that not all professionals participated, there was mobility of professionals across nurseries and *swabs* had not been taken by the personnel.

Bellini 2015 (Switzerland) produced enforced standard precautions in 157 Nursing Homes and compared the combined measures of screening and topical decolonisation + environmental disinfection (intervention) versus only standard precautions for MRSA in LCF nurseries. They found their intervention produced no evidence of a difference in the prevalence of MRSA carriage rate at one year when compared with controls. (RR = 0.90 [0.28, 2.94]). The primary outcome was MRSA prevalence in nurseries.

Chuang 2014 (China) evaluated the effectiveness of an infection control bundle (focused on hand hygiene, environmental hygiene, and modified contact precautions) in controlling MRSA at 36 residential care homes for the elderly. The intervention elicited an immediate effect of a 2.4% absolute decrease in the prevalence and a 3.7% reduction in the intra-facility transmission, but there was no statistically significant difference. (RR = 1.08 [0.98, 1.20]) The outcome measure was the MRSA prevalence (measured by the percentage of residents with an MRSA positive result in any of the specimens collected). The intra-facility transmission was

determined by the overall percentage of MRSA-free residents who converted to MRSA carriers in the subsequent phase, excluding those who acquired MRSA during hospitalisation events.

Gordon 2010 (NY, USA) studied HIV-positive patients at an inpatient drug rehabilitation centre to determine whether monthly repeated nasal application of 2% mupirocin® calcium ointment (having a placebo group as control) would decrease the odds of *S. aureus* nasal colonisation in 100 patients over eight months. They performed intent-to-treat analyses using SAS 9.1.3 software. They considered drug/alcohol use relapse and antibiotic use in the preceding month as independently associated with monthly *S. aureus* colonisation. Controlling for these variables, the odds of colonisation were 83% lower in the mupirocin® versus a placebo group. (RR = 0.86 [0.46, 1.61]), The outcomes considered were colonisation at baseline and one month after each treatment.

Peterson 2016 (IL, USA) studied intervention in nurseries at three separate LCF, consisting of universal decolonisation using intranasal mupirocin® and a chlorhexidine® bath performed twice (2 decolonisation-bathing cycles one month apart) at the start of the intervention period versus controls **(**standard care). They studied the intervention for one year. Subsequently, in year 2, after initial decolonisation, all admissions were screened on site using real-time PCR, and those who were MRSA positive were decolonised, but not isolated (RR = 0.50 [0.17, 1.49]) All nursing unit personnel received education on the nature of pathogen transmission, the need for effective cleaning and disinfection of healthcare facility surfaces and equipment, and the importance of hand hygiene. The outcomes were a point prevalence survey for MRSA nasal colonisation that was performed at the beginning of the study (March 2011) and then repeated five additional times. They concluded that rapid, Real-time PCR surveillance for MRSA nasal carriage with targeted decolonisation, coupled with enhanced environmental cleaning,

Schora 2017 (IL, USA) investigated if nasal MRSA surveillance (using In-house PCR for MRSA) + decolonization of carriers (intervention) versus control (usual care) would successfully lower overall MRSA colonization in randomly assigned intervention units that received decolonization with nasal mupirocin and chlorhexidine bathing + enhanced environmental cleaning with bleach every 4 months in 3 LCF. Outcomes were: MRSA colonisation monitored using point prevalence testing every 4-6 months. (RR = 0.65 [0.18, 2.35]).

Both studies by Peterson (2016) and Schora (2014) changed the design of the reviews. We excluded the study of Peterson the meta-analysis because it presented two different sets of measures. For the study of Schora, we considered in the meta-analysis only the first year of the study.

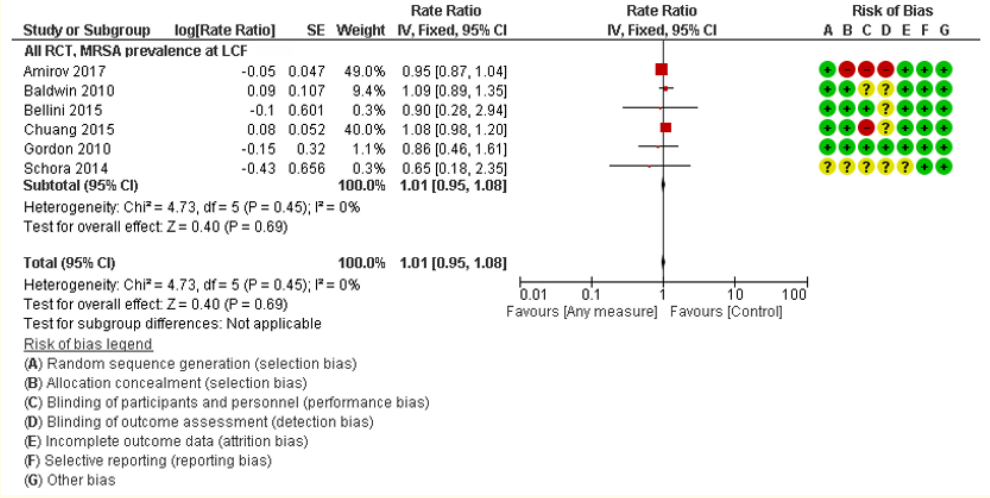
Methods of diagnosing colonisation were different across studies: standard swab and culture (4 reviews), Polymerase Chain Reaction (PCR), two reviews. As to the method of screening, all studies used nasal swabs as a sample; the study by Baldwin 2010 also used urine samples; Bellini 2015 and Chuang 2014reported also using wound samples; Bellini 2015 also reports taking samples from Groin and ulcer, and the study by Baldwin used both nares swab and urine samples. Decolonisation/treatment strategies were also different across studies.

Untoward effects of the measures. Amirov (2017) conducted passive and active monitoring for any adverse events that might be associated with CHG and found no event attributable to the use of CHG. They also monitored the Braden scale score (a measure for the risk of developing pressure ulcers) and MRSA colonisation pressure (measures MRSA reservoir on a unit). CHG resistance was not addressed.

Data analysis

We present a meta-analysis where the different measures studied against MRSA are compared with usual care (i.e., without any policies against MRSA) to try to determine the effectivity of each action in six studies (figure 4). The survey by Peterson 2014 had to be excluded from the meta-analysis because it presented two different sets of policies. It is Forrest Plot is shown individually, below (Forrest Plot 10, below).

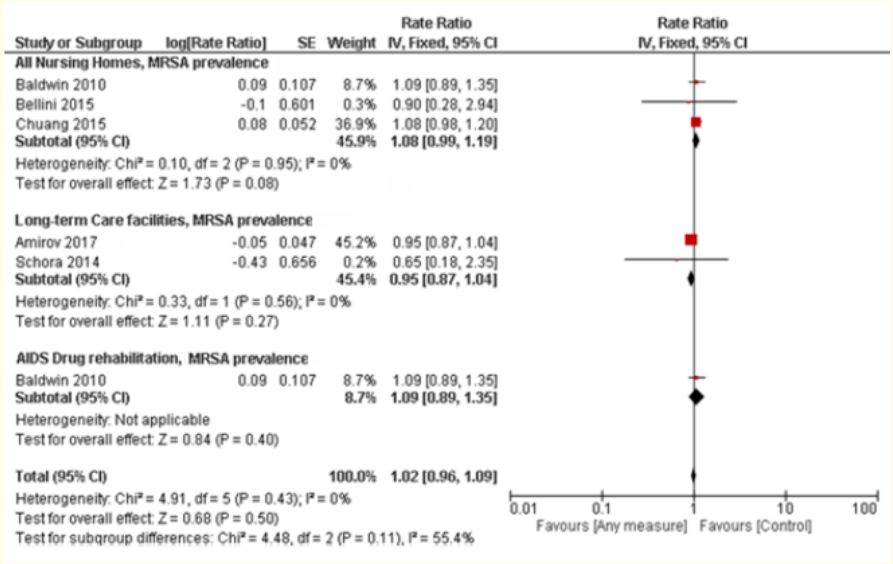
None of the measures, when analysed individually, presented evidence of effect, with an overall effect of 1,.01 at the meta-analysis level. Some of the studies (Amirov 2017; Bellini, 2015) may be insufficiently powered to produce significant results. The data of the meta-analysis is shown in the Forrest Plot 1, below.



Forrest Plot 1: Any measures against MRSA dissemination X control (usual care), outcome: MRSA Positivity, six studies.

Subgroup analysis

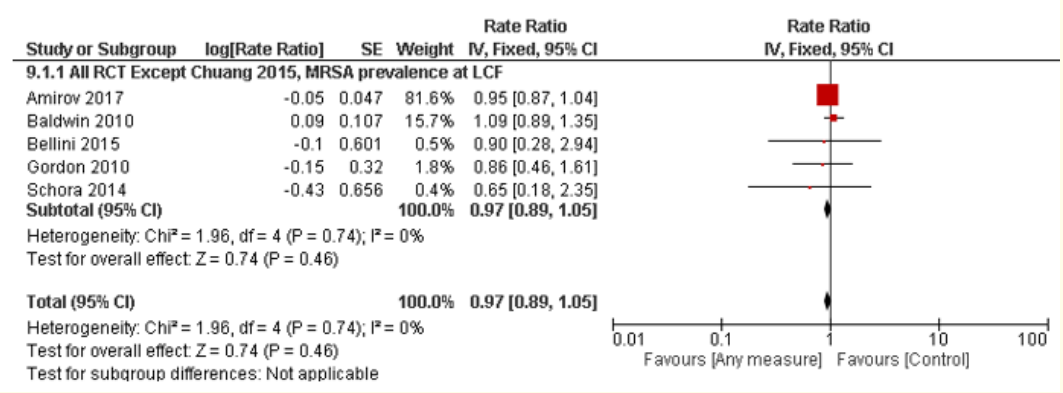
There was evidence of clinical and methodological heterogeneity (there were notable variations in the type of LCR (Long-term Care Facilities versus Nursing Homes versus rehabilitation institution), the definition of positives (by swabs of nasal cavities versus by use of additional sites of colonisation), by type of study (RCT versus Cluster RCT). Therefore, we performed an exploratory subgroup analysis where we divided the studies by type of institution (2: (Long-term Care Facilities, 3 Nursing Homes 1 and an inpatient drug rehabilitation facility for people with HIV. That is shown on the Forrest Plot 2, below.



Forrest Plot 2: Any measures against MRSA dissemination X control (usual care), outcome: MRSA Positivity (Figure 2), six studies, according to the type of facility.

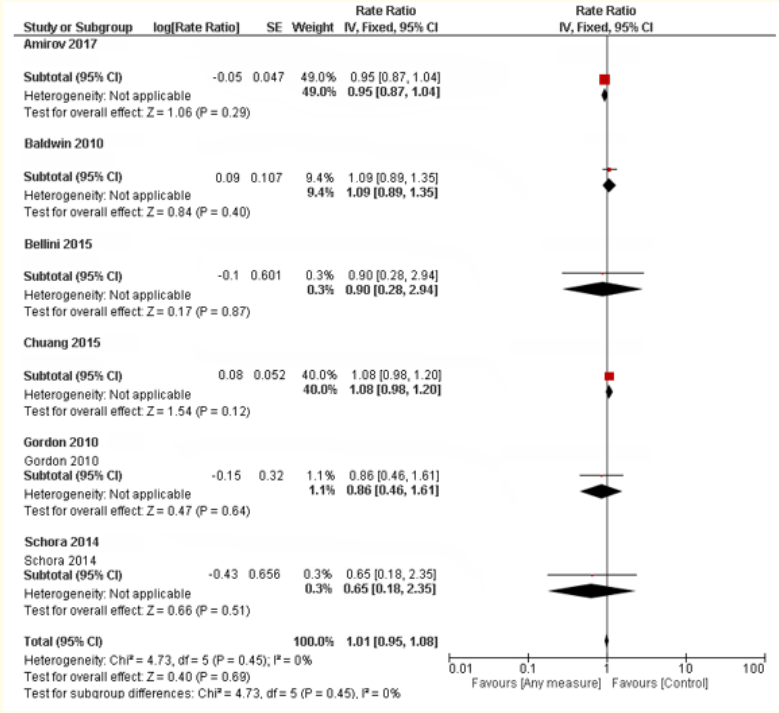
Sensitivity analysis

We also performed an exploratory sensitivity analysis by excluding the study by Chuang 2015, which presented some methodologic issues: some methodologic alterations during the survey, not measuring MRSA carriage among staff, not checking perineal, groin or throat MRSA samples on the interns.



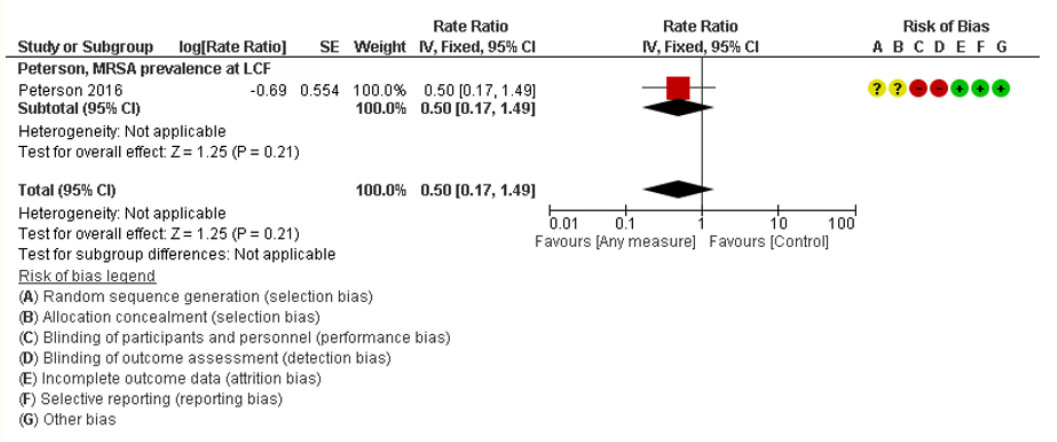
Forrest Plot 3: Any measures against MRSA dissemination X control (usual care), outcome: MRSA Positivity. Sensitivity analysis, all studies except Chuang 2014.

The individual Forrest Plots of the studies are shown below.



Forrest Plots 4 to 10: Studies included in the meta-analysis, any measures against MRSA dissemination X control (usual care), outcome: MRSA positivity.

The individual Forrest Plot of the study by Peterson is shown below.



Forrest Plot 11: Nasal MRSA surveillance (using In-house PCR for MRSA) + decolonisation of carriers (intervention) versus control (usual care). Outcome: MRSA Positivity.

Summary of Findings table

The summary of findings table for all studies is shown below. There was only one study for each measure or bundle of policies.

SOF. Summary of findings for the main comparison. Any measures against MRSA.

Any measures against the dissemination of MRSA in LCF, a total number of studies = 7				
1. A daily bath with 2% CHG-impregnated washcloth versus daily bath with non-antiseptic cloth				
Comparisons	Rate Ratio (95%CI]	# Participants	Studies	Quality of evidence
MRSA incidence	0.35 [0.03 – 4.22]	122	Amirov	U™™ Very low 1, 2, 6, 11
2. Infection Control education and training versus usual care				
MRSA prevalence	1.09 [0.89-1.35]	132	Baldwin	Y Very low 2, 3,11
3. Universal MRSA screening + decolonisation of carriers + environment disinfection + Standard Precautions versus Standard Precautions alone				
MRSA prevalence	0.90 [0.28 – 2.94]	4,450	Bellini	U™™ Very low 2,6,11
4. Hand hygiene enhancement + environmental decontamination + modified Contact Precautions versus usual care				
MRSA prevalence	1.08 [0.98 – 1.20]	3,256	Chuang	U™™ Very low 2,11
5. 2% Mupirocin ointment versus placebo				
MRSA prevalence	0.86 [0.46 – 1.61]	100	Gordon	U™™ Very low 2, 8,11
6. MRSA rapid PCR screening + targeted decolonisation with Mupirocin + CHG versus screening only				
MRSA prevalence	0.65 [0.18 – 2.35	-	Peter	U™™ Very low 2, 10,11
7. MRSA PCR screening + targeted decolonisation with Mupirocin versus Screening only				
MRSA prevalence	0.50 [0.17 – 1.49]	-	Schora	Y Very low 2, 10

Table 15

Reasons for downgrading the evidence:

1. Single centre study
2. Cluster randomisation
3. 3Residents and staff from Intervention and Control environments had contact with each other.
4. There was some drop-off of participants
5. Unprogrammed change of frequency of on-site visits during the program
6. Study was underpowered
7. Some subjects' treatment was missed, or could not be confirmed
8. Lack of some culture data meant researchers were unable to verify all the MRSA infections occurring
9. Discharge testing was limited to 25% of the study period
10. The study was modified before the end.
11. 1No statistically significant evidence

NH – Nursing Homes

CHG - Chlorhexidine

GRADE Working Group grades of evidence:

- **YYYY (High) High quality:** further research is improbable to change our confidence in the estimate of effect
- **YYY□ (Moderate) Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- **YY□□ (Low), Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- **Y□□□ (Very low) Very low quality:** we are very uncertain about the estimate

Other outcomes

We could not find any eligible RTC studies showing evidence regarding other outcomes such as transmission of MRSA to the hospital flora, staff and other patients; antibiotic use; quality of medical and nursing care; quality of life of the interns; cost evaluation/economic burden of the measures and others.

The studies of Peterson 2016 and Schora 2014 both stated that the routine and socialising of the residents were not affected since the interventions did not directly address or alter those. (Peterson 2016, Schora 2014). However, they did not present direct evidence of that.

No evidence of difference concerning adhesion to the measures was present. Some studies evaluated either hand colonisation or surface cleaning, but there was also no evidence of a difference. Although this meta-analysis did not address those as to statistical significance and effect, those procedures could constitute some guidance for future studies

Further studies are determined to explore the effectivity, costs and untoward effects associated with the measures against MRSA dissemination in LCF, as no study presents statistically sign.

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