

Is the use of chlorhexidine contributing to increased resistance to chlorhexidine and/or antibiotics?

Literature Review

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Is the use of chlorhexidine contributing to increased resistance to chlorhexidine and/or antibiotics?

Review Team:

Associate Professor Kay Price¹ (Lead and author for this review)

Dr David Evans¹

Dr Rasika Jayasekara¹ (Project Leader)

Expert Advisor:

Dr Rietie Venter – Head Microbiology, School of Pharmacy and Medical Science, Division of Health Sciences, University of South Australia

Academic Librarian:

Ms Carole Gibbs²

Research Assistants:

Ms Dianne Gall¹

Ms Kate Kennedy¹

¹School of Nursing & Midwifery, Division of Health Sciences, University of South Australia

²University of South Australia

Introduction and Background

The National Health and Medical Research Council (NHMRC) commissioned this independent literature review to provide assurance that the revision of the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* is grounded in the most up-to-date and relevant scientific evidence.

This literature review has been undertaken to specifically address the clinical question: Is the use of chlorhexidine contributing to increased resistance to chlorhexidine and/or antibiotics?

Resistance is a common theme in infection control and there is a dynamic relationship between resistance and use of medicines like chlorhexidine. Maintaining susceptibility of disease-causing bacteria to chlorhexidine and/or antibiotics is an imperative.

Chlorhexidine belongs to a group of medicines called antiseptic antibacterial agents and are widely used in healthcare, general practice and aged care settings. This product is available in numerous different forms: Dressing; Gel/Jelly; Lotion; Solution; Liquid; Pad; Sponge; Cream (NHMRC 2010). Appendix 1 provides a list of thirty three (n=33) chlorhexidine products listed in MIMS.

The focus on biocides like chlorhexidine has been of global interest for many years. The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) (2009) for example published an 'Assessment of the Antibiotic Resistance Effects of Biocides (2009)' given the 'large and increasing use of biocides and the continuous increase of bacterial resistance to antibiotics'. In conclusion the SCENIHR (2009) stated:

Biocides are invaluable compounds that provide society with numerous benefits. They play an important role in the control of bacteria in a variety of applications. They are a precious resource that must be managed to avoid any loss in activity for as long as possible. Therefore, in order to preserve the role of biocides in infection control and hygiene, it is paramount to prevent the emergence of bacterial resistance and cross resistance through their appropriate and prudent use (SCENIHR, 2009 p. 61).

In the 2014 Annual Report from the Australian Group on Antimicrobial Resistance (Coombs et al., 2016) it was concluded that

...antimicrobial resistance in SAB [Staphylococcus Aureus bacteraemia] in Australia is a significant problem and continues to be associated with high mortality. This may be due, in part, to the high prevalence of methicillin-resistance SAB in Australia, which is significantly higher than most EU/EEA countries.

Skin cleansing with Chlorhexidine plays an important role in reducing the incidence of hospital-acquired infections (Hijazi et al. 2016; Karki & Cheng 2012). If the use of, and duration of use of, Chlorhexidine in a specific setting or population is changing bacteria in such a way that may protect bacteria or a specific bacterium from an antibiotic, then this may contribute to antibiotic resistance. Concern has arisen regarding the potential of co-resistance to antibiotics and disinfectants like chlorhexidine. Therefore if bacteria are non-susceptible to chlorhexidine the question is whether this also by the same mechanism confers resistance to other antibiotics or disinfectants.

Definitions

The following definitions were agreed upon before commencing the literature review.

Chlorhexidine 'resistance'

There is no standardised method and no consensus on the definition of chlorhexidine 'resistance'. There are no clinical breakpoints for chlorhexidine 'resistance'. Although chlorhexidine 'resistance' is used extensively in the literature, minimum inhibitory concentrations (MIC) values indicate tolerance / susceptibility to chlorhexidine rather than resistance. The determination of MIC in vitro is not an accurate replication of the situation in a hospital setting where e.g. a much higher concentration of chlorhexidine ($\geq 20,000$ mg/L) is applied for a very short time. This review therefore considered reduced susceptibility / non-susceptibility also as resistance i.e. where no kill-kinetics or minimal bactericidal concentrations (MBC) were reported. MIC values of ≥ 4 mg/l for Gram-positive organisms and ≥ 50 mg/l for Gram-negative organisms will be considered as "increased tolerance".

Antimicrobial resistance

According to the World Health Organisation (WHO) (updated 2016) antimicrobial resistance happens when microorganisms (such as bacteria, fungi, viruses, and parasites) change when they are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals and antimalarial). As a result, the medicines become ineffective and infections persist in the body, increasing the risk of spread to others. Chlorhexidine is an antiseptic antibacterial agent that has the potential to change bacteria because of exposure to chlorhexidine. Exposure to chlorhexidine can be by different dosage forms and duration of use of a specific dosage form, and the duration of use regardless of dosage form including stratification of exposure (prolonged exposure versus one off).

Antibiotic resistance

Antibiotic resistance occurs when bacteria change in response to the use of antibiotics (WHO updated 2015). Bacteria, not humans, become antibiotic resistant. These bacteria may then infect humans and are harder to treat than non-resistant bacteria. Resistance against antibiotics will be defined by using the clinical breakpoints for resistance as specified by the European Committee on Antimicrobial Susceptibility testing (EUCAST) or the Clinical and Laboratory Standards Institute (CLSI). Depending on the testing method used for example if testing was performed according to EUCAST guidelines, the breakpoints published by EUCAST will be used and vice versa.

Outcome Measures

In broad terms, the outcomes are chlorhexidine resistance however defined or measured in relation to chlorhexidine use and chlorhexidine use leading to antibiotic-resistant strains of bacteria. To address the question 'Does exposure (different dosages, duration of use, and stratification of exposure) to any form of chlorhexidine results in 'chlorhexidine resistance' within different healthcare settings?' the outcomes include:

- 'Chlorhexidine Resistance' (with definition / measures used) to chlorhexidine established.
- A specific intervention identified as contributing to resistance to chlorhexidine in a specific population and / or setting.
- A specific exposure of a specific intervention identified as contributing to resistance to chlorhexidine in a specific population and / or setting.

To address the question 'Does exposure (different dosages, duration of use, and stratification of exposure) to any form of chlorhexidine increases the incidence and/or prevalence of antibiotic-resistant strains of bacteria in any person within different healthcare settings?' the outcomes include:

- 'Resistance against antibiotics' defined by using the clinical breakpoints for resistance as specified by the European Committee on Antimicrobial Susceptibility testing (EUCAST) or the Clinical and Laboratory Standards Institute (CLSI).
- Increase in the incidence (rate) of antibiotic-resistant strains of bacteria established through the use of chlorhexidine identifying dosage form, exposure and specific population and / or setting. Antibiotic-resistant strain of bacteria through the use of chlorhexidine to be recorded.
- Increases in the prevalence (frequency) of antibiotic-resistant strains of bacteria established through the use of chlorhexidine identifying specific dosage form, exposure and specific population and / or setting. Antibiotic-resistant strain of bacteria through the use of chlorhexidine to be recorded.

Methodology

The aim of the literature review was to collate relevant literature to address the review questions. A brief overview of the methodology is presented in this section with the full details provided in the Technical Report.

The review questions were:

1. Does exposure (different dosages, duration of use, and stratification of exposure) to any form of chlorhexidine result in 'chlorhexidine resistance' within different healthcare settings?
2. Does exposure (different dosages, duration of use, and stratification of exposure) to any form of chlorhexidine increase the incidence and/or prevalence of antibiotic-resistant strains of bacteria in any person within different healthcare settings?

Research literature was sourced that addressed:

- All patients (isolates) / participants (isolates) including children and adults
- Different health care settings including acute care, residential aged care, paediatric, neonatal and primary care and rehabilitation as well as the laboratory setting,
- All forms of use of chlorhexidine in humans and all different exposures (dosage form, duration, stratification of exposure) across different settings.

Search Strategy

Electronic searches

The following information sources were searched:

- CENTRAL (Cochrane Central Register of Controlled Trials, The Cochrane Library)
- CINAHL (Cumulative Index to Nursing & Allied Health Literature)
- Cochrane Database of Systematic Reviews
- DARE (Database of Abstracts of Reviews of Effects)
- Joanna Briggs Institute EBP Database
- EMBASE-OvidSP
- MEDLINE-OvidSP
- Science Citation Index Expanded (Web of Science)

The two core biomedical databases MEDLINE/EMBASE were searched; The Cochrane Library and also relevant allied health databases e.g. CINAHL and Joanna Briggs. In addition, two multidisciplinary databases that index high quality journals and have good health coverage e.g. Scopus and Web of Science were also included. NCCHTA and WHO Library Information System databases were not searched.

The databases searched form the base set used for most health sciences literature searches at this university and are generally supplemented with other databases depending on the subject area, including multidisciplinary databases. The point of searching additional databases and in particular, multidisciplinary databases, is to capture papers that are not indexed by the two core biomedical

databases. This is especially relevant when the types of studies may not be higher level evidence e.g. RCTs.

Grey literature

A grey literature search was conducted by the Lead Reviewer to identify studies not indexed in the databases listed above.

- AHRQ (Agency for Healthcare Research and Quality)- www.ahrq.gov
- Grey Literature Report (New York Academy of Medicine) <http://greylit.org/>
- NICE (National Institute for Health and Clinical Excellence) www.nice.org.uk/
- Open Grey <http://www.opengrey.eu/>

Key international infection control and health care organisations were searched for relevant reports related to one of the review objectives but none were identified. These international organisations included:

- USA - Department of Health & Human Services (<http://www.hhs.gov/>)
- USA - Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>)
- USA - Infectious Disease Society of America (www.idsociety.org).
- Australia - Department of Health (<http://www.health.gov.au/>)
- Australia - National Health and Medical Research Council (<http://www.nhmrc.gov.au/>)
- Australian Institute for Health and Welfare (<https://www.aihw.gov.au/>)
- Australian Commission on Safety and Quality in Health Care (<http://www.safetyandquality.gov.au/>)
- NZ – Department of Health (<http://www.health.govt.nz/>)
- World Health Organization (<http://www.who.int/en/>)
- Centres for Disease Control and Prevention (<http://www.cdc.gov/>)
- European Centre for Disease Prevention and Control (<http://ecdc.europa.eu/en/Pages/home.aspx>)
- European Society for Clinical Microbiology and Infectious Diseases (www.escmid.org)
- British Society for Antimicrobial Chemotherapy (www.bsac.org.uk)
- Infectious Diseases Research Network (www.idrn.org).
- Canada - IPAC (<http://www.ipac-canada.org/>)
- UK Healthcare Infection Society (<https://www.his.org.uk/>)
- Therapeutic Goods Administration (<https://www.tga.gov.au/>)

Trial Registries

The following registries were searched for ongoing and completed trials but none were identified:

- Australian New Zealand Clinical Trials registry <http://www.anzctr.org.au/BasicSearch.aspx>
- ClinicalTrials.gov, US National Institutes of Health (NIH) <http://clinicaltrials.gov/>
- ICTRP (International Clinical Trials Registry Platform, World Health Organization (WHO) <http://www.who.int/ictcp/en/>
- metaRegister of Controlled trials- www.controlled-trials.com

Keywords

A combination of the search terms from concepts 1-4 (see Table 1) were used to identify potentially relevant peer reviewed publications. Synonymous terms, related MeSH headings, truncation symbols and wildcards were used to expand the search as appropriate. This formative phase of the search strategy was an integral part of a three-phase search process. The second phase of the search process involved the analysis of text words contained in the title and abstract of retrieved citations and of the index terms used to describe identified publications. The third step involved an integrated validation search using all identified key words and index terms, through the same databases.

Table 1. Key words and MeSH terms used in the search strategy.

Concept	Key words	MeSH
1.	Chlorhexidine, CHG, mk412a or mk-412a, Novalsan, Sebidin, Tubulicid, Gluconate, Biocide*, Eludril, Corsodyl, Chlorhexamed forte, Chlorohex, Cholorohexadine, Consepsis, Dentosan, Denzin, Ebuross, Fimeil, Hexadol, Periogard, Promax, Soretol	Chlorhexidine/
2.	Bacteriocid*, Microbicid*, Skin decolonization, Root canal implant*, Dressing, Gel, Jelly, Lotion, Solution, Liquid, Pad, Sponge, Cream, Vaginal, Bactericid*, Bacteriostatic, Antiseptic, Disinfectant, Anti-infective agents, Anti-microbial* agents, Anti-micro bacterial agents	Anti-infective agents/, Anti-bacterial agents/, Anti-infective agents, local/, Hand disinfection/, Hand sanitizers Disinfectants/, Dental disinfectants/, "root canal irrigants"/, Anti-infective agents, urinary/
3.	Efflux system*, Efflux pump*, Time Kill, Time to Kill, Kill time, MIC, MBC, Kirby Bauer, Minimum inhibitory concentration, Minimum bacterial concentration	
4.	Susceptibility, Resistance, Tolerance	

Timing of search

The search results were limited to 2006 -2016. The initial Medline search in September 2016 retrieved (5,677 results). The chlorhexidine set was combined with the others using OR. After reviewing a sample of the initial results, the researchers decided that many of the results were not relevant and the Medline search was revised on 14/10/16 to make it more specific. Some of the terms were removed as they were also considered irrelevant and the combinations were also changed at this point.

The results of the MEDLINE search is provided in Table 2 as an example and the other searches are provided in the Technical Report.

Table 2. Search strategy run in MEDLINE.

Search #	Search terms	Results
1.	Chlorhexidine/	6993
2.	Chlorhexidine OR CHG OR mk412a OR mk-412a OR Novalsan OR Sebidin OR Tubulicid OR Gluconate OR Biocide* OR Eludril OR Corsodyl (.mp)	19074
3.	Chlorhexamed forte OR Chlorohex OR Cholorohexadine OR Consepsis OR Dentosan OR Denzin OR Ebuos OR Fimeil OR Hexadol OR Periogard OR Promax OR Soretol (.mp)	443
4.	OR/ 1-3	19421
5.	Anti-infective agents/	45063
6.	Anti-bacterial agents/	280043
7.	Anti-infective agents, local/	15403
8.	Hand disinfection/	4948
9.	Hand sanitizers/	68
10.	Disinfectants/	11107
11.	Dental disinfectants/	600
12.	"root canal irrigants"/	2804
13.	Anti-infective agents, urinary/	2568
14.	Bacteriocid* OR Microbicid* OR Skin decolonization OR Root canal implant* OR Dressing OR Gel OR Jelly OR Lotion OR Solution OR Liquid OR Pad OR Sponge OR Cream OR Vaginal OR Bactericid* OR Bacteriostatic OR Antiseptic OR Disinfectant (.mp)	1366279
15.	(agents AND (Anti-infective OR Anti-microbial* OR Anti-mycobacterial)) (.mp)	120250
16.	OR/ 5-15	1672113
17.	Efflux system* OR Efflux pump* (.mp)	6944
18.	Time Kill OR time-kill OR Time to Kill OR Kill time OR Kill-time OR MIC OR MBC OR Kirby bauer (.mp)	35632
19.	MIC OR MBC OR Minimum inhibitory concentration OR Minimum bacterial concentration (.mp)	36730
20.	OR/ 17-19	45047
21.	Susceptibility OR Resistance OR Tolerance (ti,ab.)	897046
22.	AND/ 4, 16, 20-21	271
23.	Limit 22 to English language	255
24.	Limit 23 to humans	96
25.	Limit 24 to yr="2006-Current"	74

Inclusion criteria

Studies were only included if they:

- Made clear the population of study
- Had isolates from humans
- Made clear the intervention – dosage form and exposure
- Made clear the health care setting or laboratory setting
- Defined or measured 'chlorhexidine resistance' / reduced susceptibility to chlorhexidine / non – susceptibility to chlorhexidine
- Defined 'antibiotic-resistant strain of bacteria.'

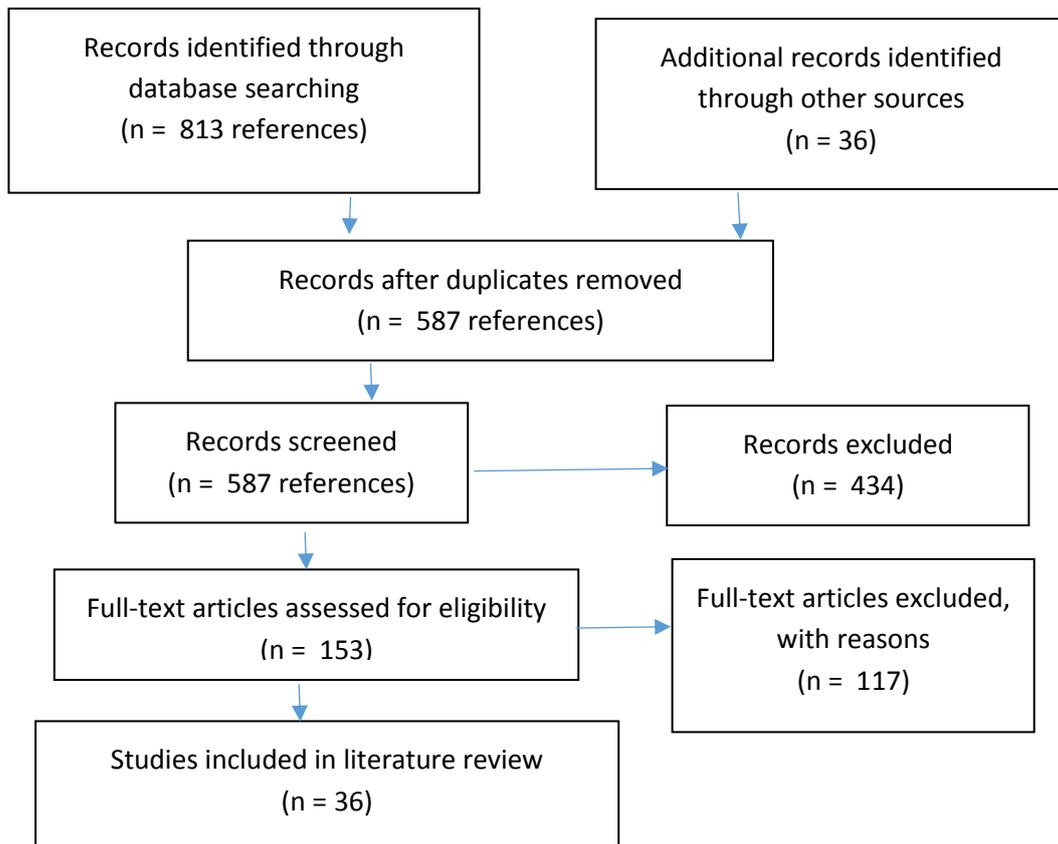
No use of chlorhexidine was excluded from the literature review.

Studies were excluded when:

- The focus was only on the use and effectiveness of chlorhexidine and not resistance
- Chlorhexidine resistance however stated was not systematically assessed
- Isolates were not from humans
- Focus was antibiotic resistance not related to chlorhexidine use
- Setting was schools or domestic home.

The Lead Reviewer with the Expert reviewed potential studies to ensure relevance. No systematic reviews published during the search period met the inclusion criteria. To identify potentially missed papers, the Lead Reviewer checked bibliographies of the relevant papers for articles missed by the initial search. To complement primary research literature, case reports and evidence based / expert reviews provided supportive and background information. Qualitative studies were excluded. Figure 1 details the screening process in a PRISMA (Moher et al. 2009) Flow Diagram.

Figure 1. PRISMA Flow Diagram



Results

The majority of the N=36 publications included in the review were controlled laboratory / susceptibility studies. N=24 (66%) were susceptibility testing/controlled laboratory studies, n=5 (14%) were case control/ cross sectional/ retrospective cohort studies and n=2 (6%) were case reports. The remaining publications n=5 (14%) were literature/ expert reviews.

Critical appraisal of the case control/cross sectional/ retrospective cohort studies and the case reports was undertaken using the McMaster University Critical Review Form – Quantitative Studies (Law et al. 1998) by two reviewers. No biases were noted by any researchers in these studies and findings from these low level evidence studies need to be interpreted with caution. None of the five literature/expert reviews included search strategies to check the publications included. The quality of the laboratory/susceptibility studies were difficult to determine. Given the specialised expertise and potential for controlled laboratory / susceptibility testing to be prone to numerous biases, an Expert in Microbiology worked with the Lead Reviewer in screening publications to be included in this review and to ensure publications included were suitable.

When comparing the publication dates of research publications included, the focus on the use of chlorhexidine contributing to increased resistance to Chlorhexidine and/or antibiotics is increasingly being discussed in the scientific literature. Only n=6 primary research publications were retrieved from 2006 – 2010 and the other n=25 research publications were published from 2011 – 2016. Countries where the primary research (n=31) was conducted included:

- United Kingdom (n= 6)
- United States of America (n=4)
- China (n=3)
- Taiwan (n=3)
- Japan (n=2)
- Hong Kong (n=1)
- Sweden (n=1)
- Israel (n=1)
- Iraq (n=1)
- Turkey (n=1)
- Geneva (n=1)
- Canada (n=1)
- Mexico (n=1)
- Kuwait (n=1)
- Malaysia (n=1)
- Denmark (n=1)
- Global (n=2)

Clinical isolates of primary research studies included were only from humans and obtained from catheter related bloodstream infection, urine, pus, nares, groin, perineum, axilla, throat, rectal, ear infections, prosthesis and perioperative biopsies. Clinical isolates were in the main from adult hospitalised patients (one study in a paediatric hospital setting), residents of residential care facilities, and theatre and intensive care unit staff.

A range of microorganisms were studied. These included

- MRSA and MSSA
- *Staphylococcus epidermidis*
- *Staphylococcus aureus*
- *Acinetobacter species* – *A. baumannii*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*

In summary the number of primary research studies focused on review Question 1 totalled 24/36. Studies showing a correlation between chlorhexidine use and increase in tolerance/reduced susceptibility totalled n=20/24. Studies showing no correlation between chlorhexidine use and an increase in tolerance/reduced susceptibility totalled n= 4/24 and 1 of those 4 studies was on *Staphylococcus epidermidis*. The number of primary research studies that focused on review Question 2 totalled 9/36. Studies showing a link to chlorhexidine use and antibiotic resistance totalled n=8/9. Expert / Literature reviews and case reports were not included in these numbers.

Review question 1:

To address the question 'Does exposure (different dosages, duration of use, and stratification of exposure) to any form of chlorhexidine results in 'chlorhexidine resistance' within different healthcare settings?' the outcomes included:

- 'Chlorhexidine Resistance' (with definition / measures used) to chlorhexidine established.
- A specific intervention identified as contributing to resistance to chlorhexidine in a specific population and / or setting.
- A specific exposure of a specific intervention identified as contributing to resistance to chlorhexidine in a specific population and / or setting.

A total of n=24 primary research publications were collated to address Question 1 and these are presented in Tables 3 and 4. Studies showing a correlation between chlorhexidine use and an increase in tolerance/reduced susceptibility totalled n=20/24. Studies showing no correlation between chlorhexidine use and an increase in tolerance/reduced susceptibility totalled n= 4/24 and of those four studies, one was on *Staphylococcus epidermidis*.

Most of the focus of collated research literature is on the implications of chlorhexidine based decolonisation / universal chlorhexidine use on MRSA *qacA/B* genes among hospitalized patients especially ICU patients and/or whether the carriage of *qacA/B* can account for some of the decolonization failures including the role of *qacA/B* and decreased susceptibility to chlorhexidine.

To assist with identifying what primary research studies addressed, Table 3 summarises primary research studies related to resistant genes (n=16) and identifies the name of the authors, year published and country where research was conducted, the type of study conducted, the purpose of the study and findings relevant to the review question and outcomes. Table 4 summarises primary research studies focussing on clinical outcomes of resistance (n=8).

Table 3. Primary research publications focussing on resistant genes to address Review Question 1

Authors, year and country	Type of study conducted and purpose	Findings relevant to Review Question 1
Batra, R., Cooper, B.S., Whiteley, C., Patel, A.K., Wyncoll, D. and Edgeworth, J.D., 2010. St. Thomas Hospital, United Kingdom.	A retrospective interrupted time series study based on the argument that hospital MRSA strains can differ in virulence and response to infection control interventions identified whether a chlorhexidine-based decolonization strategy could interrupt transmission of different MRSA strains in an intensive care unit.	Found strains of MRSA that carry <i>qacA/B</i> genes may be unaffected or potentially spread more rapidly by the chlorhexidine-based decolonization strategy.
Ho, C.M., Li, C.Y., Ho, M.W., Lin, C.Y., Liu, S.H. and Lu, J.J., 2012. Taiwan	A case control study was conducted to determine whether more clinical <i>S. aureus</i> isolates from chlorhexidine impregnated catheter related bloodstream infections have the biocide-resistant genes (<i>qacA/B</i>) than those from other infections.	Similar to previously reported results, fewer MSSA isolates were found to harbor <i>qacA/B</i> than MRSA isolates potentially due to the wide application of chlorhexidine use in clinical procedures. The researchers propose the possibility of increased catheter related bloodstream infections episodes as a result of more MRSA isolates containing <i>qacA/B</i> .
Lee, A.S., Macedo-Vinas, M., François, P., Renzi, G., Schrenzel, J., Vernaz, N., Pittet, D. and Harbarth, S., 2011. University of Geneva Hospital	A nested case-control study of methicillin resistant <i>S. aureus</i> (MRSA) carriers who received decolonisation therapies that included chlorhexidine bathing daily for seven days. Focus was genotypic chlorhexidine resistance.	The N=75 case patients and 75 control patients were similar except that those persistently colonised were older with longer lengths of hospital stay. The researchers recognised selection bias influenced their results such that the association between resistance and decolonization failure may be underestimated in the current study. In this study of MRSA-colonized inpatients, carriage of strains with combined low-level mupirocin and genotypic chlorhexidine resistance significantly increased the risk of persistent MRSA carriage after decolonization therapy rendering this MRSA control measure ineffective.
Liu, Q., Zhao, H., Han, L., Shu, W., Wu, Q. and Ni, Y., 2015. China	A susceptibility study to determine distribution of biocide resistant genes in clinical isolates of high level mupirocin resistant MRSA gathered from 6 university hospitals and to evaluate susceptibility of these isolates to different concentrations of chlorhexidine.	Results showed that the plasmid-borne biocide resistance genes existed extensively in high level mupirocin resistant MRSA isolates and the authors suggest the high rate of high-level chlorhexidine tolerance isolates should cause concern. Call to establish a biocide surveillance system for continued monitoring of such isolates in China and to ensure biocides used appropriately in practice at the correct concentrations.

Table 3 continued ...

Authors, year and country	Type of study conducted and purpose	Findings relevant to Review Question 1
Longtin J, Seah C, Siebert K et al. 2011 Canada	Susceptibility surveillance study of two intensive care units in Canada to determine frequency of <i>qacA</i> , <i>qacB</i> , and <i>smr</i> genes in MRSA isolates and to determine the effect of the presence of these genes on <i>in vitro</i> susceptibility. Methods to determine chlorhexidine gluconate susceptibility have not been standardised.	<i>qacA</i> , <i>qacB</i> , and <i>smr</i> genes infrequently found in MRSA. However, the researchers argue an increase in chlorhexidine gluconate usage in routine patient care warrants periodic monitoring of susceptibility in order to detect any raise in either gene associated with resistance, as well as phenotypic testing to identify any other mechanisms of resistance.
Lu, Z., Chen, Y., Chen, W., Liu, H., Song, Q., Hu, X., Zou, Z., Liu, Z., Duo, L., Yang, J. and Gong, Y., 2014. China	A susceptibility study of 178 MSSA and 145 MRSA isolates from clinical specimens collected in intensive care environments from distinct geographical areas and different sources. Study based on ongoing reports of <i>qacA/B</i> gene conferring resistance to chlorhexidine in <i>S. aureus</i> isolates.	Higher prevalence of <i>qacA/B</i> in MRSA from superficial sites of intensive care patients than from clinical specimens. A reduced susceptibility of <i>S. aureus</i> isolates to chlorhexidine was observed possibly due to carriage of <i>qacA/B</i> . The researchers argue a need to study how to reduce the spread of <i>qacA/B</i> -positive <i>S. aureus</i> , especially in ICU patients.
McNeil, J.C., Kok, E.Y., Vallejo, J.G., Campbell, J.R., Hulten, K.G., Mason, E.O. and Kaplan, S.L., 2016. United States of America	Susceptibility testing of nosocomial <i>S. aureus</i> isolates of 247 hospitalised children (median age 2.4 months) in a paediatric hospital for the presence of genes associated with tolerance to chlorhexidine.	44.9% of isolates had either or both <i>smr</i> and <i>qacA/B</i> genes. 10.9% of isolates had both. At the hospital, chlorhexidine, the researchers' state, is used for cleansing and maintenance of central venous lines which they argue may account for the <i>smr</i> and <i>qacA/B</i> genes in isolates in bloodstream infections.
Otter, J.A., Patel, A., Cliff, P.R., Halligan, E.P., Tosas, O. and Edgeworth, J.D., 2013. United Kingdom	Susceptibility testing of selected MRSA blood stream infection isolates including MRSA clones for <i>qacA</i> in response to institutional MRSA control program that included chlorhexidine based decolonisation.	Authors argue the study provides the first evidence that <i>qacA</i> might confer a selective advantage in response to chlorhexidine based decolonization in some, but not other, MRSA clones. Authors argue these data, combined with previously published evidence, support a hypothesis that infection control practice may drive changing MRSA epidemiology raising concerns about the sustainability of decolonization practice and the urgent need for a better understanding of antiseptic resistance mechanisms and more sensitive and specific phenotypic detection methodologies.

Table 3 continued ...

Authors, year and country	Type of study conducted and purpose	Findings relevant to Review Question 1
Shamsudin, M.N., Alreshidi, M.A., Hamat, R.A., Alshrari, A.S., Atshan, S.S. and Neela, V., 2012. Malaysia	Susceptibility and screening study into the prevalence of <i>qacA/B</i> resistant genes in clinical isolates of MRSA collected from the largest public hospital in Kuala Lumpur.	The carriage rate of <i>qacA/B</i> and <i>smr</i> gene was reported for Malaysian MRSA isolates. The researchers argue their findings emphasize that the carriage of <i>qacA/B</i> is associated with reduced susceptibility, albeit they state in the susceptible range.
Sheng, W.H., Wang, J.T., Lauderdale, T.L., Weng, C.M., Chen, D. and Chang, S.C., 2009. Taiwan	Susceptibility testing of 206 randomly selected MRSA isolates from 26 hospitals across Taiwan to chlorhexidine and determination of the prevalence of <i>qacA/B</i> in the isolates.	More than one third of isolates were highly resistant to chlorhexidine with these carrying <i>qacA/B</i> genes. Authors argue the presence of <i>qacA/B</i> genes in certain MRSA clones, such as ST239-III in Taiwan, might limit the choice of drugs for treating MRSA infections, and presents a difficult problem in MRSA infection control.
Skovgaard, S., Larsen, M.H., Nielsen, L.N., Skov, R.L., Wong, C., Westh, H. and Ingmer, H., 2013. Denmark	Susceptibility testing of chlorhexidine and carriage of <i>qacA/B</i> was determined for <i>S. epidermidis</i> isolates from scrub nurses heavily exposed to chlorhexidine hand rubs compared to non-users. <i>S. epidermidis</i> blood isolates collected before the wider use of chlorhexidine were also included.	The researchers report that they were unable to correlate the use of chlorhexidine in scrub nurses with colonisation of <i>S. epidermidis</i> isolates tolerant to chlorhexidine in the presence of <i>qacA/B</i> genes. They found the susceptibility of hospital isolates to chlorhexidine was similar to that of community isolates as well as to that of blood isolates obtained in the 1960s before the introduction of chlorhexidine. However, the researchers state, that in contrast to current blood isolates, the <i>qacA/B</i> gene were absent in the isolates collected in the 1960s, suggesting that selection has occurred.
Smith, K., Gemmell, C.G. and Hunter, I.S., 2008. United Kingdom – Glasgow	Susceptibility testing and screening for the presence of <i>qacA/B</i> genes for 94 clinical isolates of <i>S. aureus</i> – including hospital and community acquired MRSA and isolates of MSSA.	Based on their results, the researchers' state if biocides are used at concentrations recommended for use by the manufacturer in the hospital environment, then <i>S. aureus</i> isolates should be killed, as even the increased tolerance displayed in isolates failed to develop into complete resistance. However they state that the presence of <i>qacA/B</i> genes in the clinical <i>S. aureus</i> population and their ability to develop increased tolerance highlights the importance of effective and rigorous infection cleaning and infection control strategies and the use of biocides at concentrations recommended by the manufacturer.

Table 3 continued ...

Authors, year and country	Type of study conducted and purpose	Findings relevant to Review Question 1
Wand ME, Bock LJ, Bonney LC, Sutton JM 2016 United Kingdom	In this controlled laboratory study, the focus was on whether adaptation of clinical <i>K. pneumoniae</i> isolates to chlorhexidine caused cross resistance to other biocides and antibiotics. Chlorhexidine ranged from 0.2% in catheter maintenance solutions, 0.2% mouthwash, 0.5% chlorhexidine impregnated wound dressing and 2 and 4% solutions usually in alcohol. The underlying mechanisms of increased resistance to chlorhexidine in <i>K. pneumoniae</i> were also investigated particularly in connection with the observed cross resistance to colistin.	To understand what mechanisms are responsible for increased tolerance to chlorhexidine all chlorhexidine adapted strains and their respective parental counterparts were whole genome sequenced. The researchers consider that overall this study has identified a novel resistance mechanism to chlorhexidine that may potentially operate in a number of different species. They argue that clearly increased smvA expression is important for chlorhexidine adaptation in <i>K. pneumoniae</i> but it is not the only mechanism and may operate in conjunction with other regulatory processes. Chlorhexidine-adaptation is also associated with the generation of mutations in PhoPQ, which affect a number of known regulatory targets (notably pmrD and pmrK). Upregulation of these genes also correlates with the presence of colistin resistance. That increased colistin and chlorhexidine resistance may occur in clinical isolates without significant loss of fitness/virulence highlights the potential challenges associated with critical infection control procedures and the use of chlorhexidine as an antiseptic to control healthcare-associated infections.
Wang, J.T., Sheng, W.H., Wang, J.L., Chen, D., Chen, M.L., Chen, Y.C. and Chang, S.C., 2008. Taiwan	A longitudinal analysis of chlorhexidine susceptibilities to understand the changes in susceptibility to chlorhexidine in <i>S. aureus</i> isolates from a hospital as well as to the prevalence of MRSA isolates carrying <i>qacA/B</i> genes.	Researchers found that the proportion of MRSA isolates with high chlorhexidine minimum inhibitory concentrations at the National Taiwan University Hospital increased from 1990 to 1995 and remained steady thereafter. More than half (55.4%) of the isolates with high chlorhexidine minimum inhibitory concentrations harboured the <i>qacA/B</i> gene, leading the researchers to state that the presence of these genes may contribute to the spread of specific MRSA clones.
Warren DK., Prager M., Munigala S., Wallace MA., Kennedy CR., Bommarito KM., Mazuski JE. and Burnham CD 2016 United States of America	A retrospective cohort study of patients admitted to 24 bed surgical intensive care unit to determine changes in the frequency of <i>qacA/B</i> gene carriage among a random sample of banked nasal MRSA isolates in an 8 year period during and following implementation of a universal chlorhexidine intervention.	A long-term, daily CHG bathing protocol was associated with a change in the frequency of <i>qacA/B</i> genes in MRSA isolates recovered from the anterior nares over an 8-year period. The researchers argue that the change in the frequency of <i>qacA/B</i> genes is most likely due to patients in those years being exposed in prior admissions. They consider future studies need to further evaluate the implications of universal CHG daily bathing on MRSA <i>qacA/B</i> genes among hospitalized patients.

Table 4. Primary research publications focussing on clinical outcomes of resistance to address Review Question 1

Authors, year and country	Type of study conducted and purpose	Findings relevant to Review Question 1
Bock, L.J., Wand, M.E. and Sutton, J.M., 2016. United Kingdom	A susceptibility study that tested different commercially available chlorhexidine formulations (variety of applications, different concentrations ranging from 0.02% - 4% and different contact times) against variety of <i>K. pneumoniae</i> clinical strains isolated before and after the routine use of chlorhexidine was introduced into practice.	Found a significant difference between pre-chlorhexidine and modern <i>K. pneumoniae</i> strains for all time points with the modern strain showing higher tolerance of chlorhexidine. While the study found <i>K. pneumoniae</i> can be killed by chlorhexidine when used at sufficient concentration and exposure time also found that not all chlorhexidine formulations kill <i>K. pneumoniae</i> after the recommended exposure time. Not all commercially available formulations reach the minimum required concentration to achieve a satisfactory level of bacterial kill. Activity, especially against chlorhexidine-adapted strains, depends on additional ingredients.
EKİZOĞLU, M., SAĞIROĞLU, M., Kilic, E. and HASÇELİK, A.G., 2016. Turkey	A susceptibility study testing 120 hospital isolated strains of 7 bacterial genera against chlorhexidine diglunocate of varying concentrations (0.02 – 4%).	As the concentrations of chlorhexidine digluconate decreases below 4% the susceptibility of isolates of <i>S.aureus</i> and <i>P. aeruginosa</i> increases rapidly. 4% chlorhexidine at 5 minute contact time effective against range of bacteria.
Kawamura-Sato, K., Wachino, J.I., Kondo, T., Ito, H. and Arakawa, Y., 2010. Japan	Susceptibility time dependent survey using 283 strains of <i>Acinetobacter spp.</i> clinically isolated from hospitals in Japan in 2002.	No acquisition of resistance to disinfectants (varying concentrations) found. About 10% of the isolates (28 strains) were found to demonstrate reduced susceptibility to chlorhexidine gluconate.
Kawamura-Sato, K., Wachino, J.I., Kondo, T., Ito, H. and Arakawa, Y., 2008. Japan	Susceptibility testing of 283 strains of <i>Acinetobacter spp.</i> from 97 Japanese hospitals in 2002. Chlorhexidine considered one of several disinfectants indispensable to perform appropriate infection control.	No resistance to chlorhexidine was detected among clinically isolated <i>Acinetobacter</i> species by MIC measurements. To prevent hospital-acquired infections caused by this kind of microbe, the profile of susceptibility to disinfectants used appropriately in practice at the correct concentrations and for adequate contact times, as well as to antimicrobial agents, must be carefully monitored and checked among <i>Acinetobacter</i> species isolated from both clinical specimens and environments.

Table 4 continued ...

Authors, year and country	Type of study conducted and purpose	Findings relevant to Review Question 1
<p>McDanel, J.S., Murphy, C.R., Diekema, D.J., Quan, V., Kim, D.S., Peterson, E.M., Evans, K.D., Tan, G.L., Hayden, M.K. and Huang, S.S., 2013. United States of America</p>	<p>A susceptibility testing study that determined chlorhexidine resistance in isolates from nasal samples taken from 3,806 residents in 26 residential aged care homes and examined characteristics associated with resistance.</p>	<p>Chlorhexidine resistance was not commonly found in MRSA isolates but mupirocin resistance rates were higher than previously found in the community and from acute care facilities and varied substantially across facilities.</p>
<p>Mendoza-Olazarán, S., Camacho-Ortiz, A., Martínez-Reséndez, M.F., Llaca-Díaz, J.M., Pérez-Rodríguez, E. and Garza-González, E., 2014. Mexico</p>	<p>Susceptibility testing of isolates collected during an intervention study in an adult medical and an adult surgical intensive care unit (total 20 beds) within a hospital where <i>A baumannii</i> is endemic.</p>	<p><i>A baumannii</i> isolates recovered from patients who received body washing with 2% chlorhexidine presented with a significant decrease in chlorhexidine minimum inhibitory concentrations. The researchers state this was associated with a change in clonality associated with increased biofilm production.</p>
<p>Morrissey, I., Oggioni, M.R., Knight, D., Curiao, T., Coque, T., Kalkanci, A., Martinez, J.L. and BIOHYPO Consortium, 2014.</p>	<p>Susceptibility testing to determine chlorhexidine minimum inhibitory concentrations or minimal bactericidal concentrations of 3327 clinical isolates belonging to relevant microbial pathogen species to measure chlorhexidine resistance.</p>	<p>While their results may reflect the lack of resistance the researchers state they may also suggest a full replacement of susceptible microorganisms by more resistant ones. This situation they say has been named as minimum inhibitory concentration MIC-creep, defined as “the constant rise over time in the basal intrinsic resistance of an average isolate of a given bacterial species”. Secondly, the researchers say their analysis reflects the current steady state of the overall susceptibility to biocides of the studied microbial populations.</p>
<p>Naparstek, L., Carmeli, Y., Chmelnitsky, I., Banin, E. and Navon-Venezia, S., 2012. Israel</p>	<p>A susceptibility study to test susceptibility of chlorhexidine digluconate used as a disinfectant among clinical isolates of extremely drug resistant <i>K. pneumoniae</i> from unique patients and different sources.</p>	<p>The clinical relevance of higher minimum inhibitory concentrations of chlorhexidine for <i>K. pneumoniae</i> specifically ST258 clone should be considered in the context of the global threat of these extremely drug-tolerant strains. It is possible that the resistance of this strain to chlorhexidine contributes to its ability to persist in the hospital environment.</p>

To provide supportive literature to the primary research studies listed in Tables 3 and 4, Table 5 summarises two case reports related to Review Question 1.

Table 5. Case reports related to Review Question 1

Authors, year and country	Type of study conducted and purpose	Findings relevant to Review Question 1
Johnson, R.C., Schlett, C.D., Crawford, K., Lanier, J.B., Merrell, D.S. and Ellis, M.W., 2015. United States of America	This is a case report of an 18 year old male soldier who utilised 4% chlorhexidine gluconate for showering as part of a prospective cluster randomized controlled trail to prevent skin and soft tissue infections.	The researchers state that despite its widespread use, the prevalence of chlorhexidine resistance in the United States is low (approximately 1%). They go onto state though that when used in 'large trials in both community and hospital settings, chlorhexidine resistance has been only rarely reported. Nevertheless, with the widespread and increasing use of this agent, experience has shown that concern about the potential emergence of chlorhexidine resistance is appropriate.'
Vali, L., Dashti, A.A., El-Shazly, S. and Jadaon, M.M., 2015. Kuwait	A survey of plasmid mediated quinolone resistant (<i>qnr-positive</i>) <i>Klebsiella spp</i> with reduced sensitivity to chlorhexidine in diabetic patients from three major hospitals in Kuwait identified a case report of <i>K. oxytoca</i> with reduced sensitivity to chlorhexidine that contains <i>qacE</i> gene in a diabetic foot ulcer infection (48 year old female).	The researchers claim this is the first report of <i>K. oxytoca</i> with reduced sensitivity to chlorhexidine that contains <i>qacE</i> gene in a diabetic ulcer. To avoid continuous low level exposure of <i>K. oxytoca</i> to biocides which may result in emerging strains with reduced sensitivity to these agents, the researchers argue that dilution standards in hospitals specifically in developing countries and the hospital's adherence to infection control policies should be strictly monitored.

Review question 2:

To address the question 'Does exposure (different dosages, duration of use, and stratification of exposure) to any form of chlorhexidine increase the incidence and/or prevalence of antibiotic-resistant strains of bacteria in any person within different healthcare settings?' the outcomes included:

- 'Resistance against antibiotics' defined by using the clinical breakpoints for resistance as specified by the European Committee on Antimicrobial Susceptibility testing (EUCAST) or the Clinical and Laboratory Standards Institute (CLSI).
- Increase in the incidence (rate) of antibiotic-resistant strains of bacteria established through the use of Chlorhexidine identifying dosage form, exposure and specific population and / or setting. Antibiotic-resistant strain of bacteria through the use of chlorhexidine to be recorded.
- Increases in the prevalence (frequency) of antibiotic-resistant strains of bacteria established through the use of chlorhexidine identifying specific dosage form, exposure and specific population and / or setting. Antibiotic-resistant strain of bacteria through the use of chlorhexidine to be recorded.

A total of n=9 primary research publications were collated to address Question 2 and these are presented in Table 6. Table 6 identifies the name of the authors, year published and country where research was conducted, the type of study conducted, the purpose of the study and findings relevant to the review question and outcomes. Studies showing a link to chlorhexidine use and antibiotic resistance totalled n= 8/9.

Table 6. Primary research publications to address Review Question 2

Authors, year and country	Type of study conducted and purpose	Findings relevant to Review Question 2
Abuzaid, A., Hamouda, A. and Amyes, S.G.B., 2012. United Kingdom	Susceptibility study of 64 <i>K. pneumoniae</i> clinical isolates to determine minimum inhibitory concentrations of antibiotics namely cefotaxin, colistin, chloramphenicol, gentamicin, polymyxin B, rifampicin, trimethoprim, ceftazidime, imipenem and meropenem and 1% chlorhexidine gluconate.	The researchers conclude there was a close link between carriage of efflux pump genes, <i>cepA</i> , <i>qacDE</i> and <i>qacE</i> genes and reduced biocide susceptibility, but not antibiotic resistance, in <i>K. pneumoniae</i> clinical isolates.
Aka, S.T. and Haji, S.H., 2015. Iraq	Susceptibility testing of 22 isolates of <i>Pseudomonas aeruginosa</i> collected from specimens of ear infections of hospital patients to measure if sub-minimum inhibitory concentrations of antibiotics can induce biofilm of <i>Pseudomonas aeruginosa</i> in the presence and absence of chlorhexidine.	Phenotypic change of chlorhexidine and induction of gene expression due to antibiotics action might enhance bacterial resistance and further stronger biofilm formation. Incubating the isolates of <i>P. aeruginosa</i> to sub-MIC of antibiotics exhibited induction of biofilm in the presence of chlorhexidine. The study concluded that incubating the isolates of <i>P. aeruginosa</i> in sub-MIC of antibiotics exhibited induction of biofilm in the presence of chlorhexidine. Therefore, this study will help establish the medical application to guide antibiotic therapy and hospital disinfection that would suppress the biofilm induction.
McNeil, J.C., Kok, E.Y., Vallejo, J.G., Campbell, J.R., Hulten, K.G., Mason, E.O. and Kaplan, S.L., 2016. United States of America	Susceptibility testing of nosocomial <i>S. aureus</i> isolates of 247 children (median age 2.4 months) in a paediatric hospital for the presence of genes associated with tolerance to chlorhexidine	Despite the fact that the in vitro chlorhexidine minimum inhibitory concentrations for these organisms are well below the concentrations in commercially available preparations, the associated co-resistance to systemic antimicrobials is of clinical importance. <i>smr-positive S. aureus</i> strains were more often associated with methicillin resistance, fluoroquinolone resistance, and a trend toward higher rates of clindamycin resistance. <i>qacA/B-positive S. aureus</i> isolates were more often associated with a vancomycin minimum inhibitory concentration of 2 g/ml than <i>qacA/B-negative</i> strains were.

Table 6 continued ...

Authors, year and country	Type of study conducted and purpose	Findings relevant to Review Question 2
Morrissey, I., Oggioni, M.R., Knight, D., Curiao, T., Coque, T., Kalkanci, A., Martinez, J.L. and BIOHYPO Consortium, 2014.	Susceptibility testing to determine chlorhexidine minimum inhibitory concentrations or minimal bactericidal concentrations of 3327 clinical isolates belonging to relevant microbial pathogen species to measure chlorhexidine resistance.	The researchers state that their finding that in most cases, they did not find bimodal distributions indicates the lack of a relevant percentage of biocide resistant isolates at natural populations. If biocide resistant mutants are rare they say this would imply that co-selection or cross-selection of antibiotic resistance should also be a rare event in natural populations. The researchers state that the fact that we did not find bimodal minimum inhibitory concentrations or minimal bactericidal concentration distributions in current populations may reflect the lack of resistance but also a full replacement of susceptible microorganisms by more resistant ones. This situation that has been named as MIC-creep, which can be defined as “the constant rise over time in the basal intrinsic resistance of an average isolate of a given bacterial species” has been described for different antibiotics.’ They also state their ‘analysis reflects the current steady state of the overall susceptibility to biocides of the studied microbial populations. These observed distributions are the consequence of the emergence of resistance, but also of its spread and stability, the latter being mainly dependent on the fitness costs associated to the acquisition of resistance.’
Naparstek, L., Carmeli, Y., Chmelnitsky, I., Banin, E. and Navon-Venezia, S., 2012. Israel	A susceptibility study to test susceptibility of chlorhexidine among clinical isolates of extremely drug resistant <i>K. pneumoniae</i>	The findings demonstrate the existence of tolerant subpopulations. Hetero-resistance towards antibiotics has been described previously for other opportunistic pathogens such as <i>Acinetobacter baumannii</i> ; however, to the researchers’ knowledge, this is the first study to demonstrate population heterogeneity towards chlorhexidine. The researchers state that the presumably transient nature of these subpopulations raises questions about the underlying mechanism.
Oggioni, R., Rosado Coelho, M., Furi, J., Knight, LR., Viti, D., Orefici, C., Martinez, G., Teresa Freitas, JL., Coque, AM., and Morrissey, I., 2015. BIOHYPO consortium	An investigation of the relationship between susceptibility profiles of chlorhexidine and antibiotics by determining susceptibility profiles of commonly used antibiotics in 1632 clinical <i>S. aureus</i> isolates with known susceptibility profiles of chlorhexidine.	Findings show a moderate correlation between susceptibility profiles of bis-biguanide chlorhexidine and some classes of antibiotics.

Table 6 continued ...

Authors, year and country	Type of study conducted and purpose	Findings relevant to Review Question 2
<p>Wand ME, Bock LJ, Bonney LC, Sutton JM 2016 United Kingdom</p>	<p>In this controlled laboratory study, the focus was on whether adaptation of clinical <i>K. pneumoniae</i> isolates to chlorhexidine caused cross resistance to other biocides and antibiotics. The underlying mechanisms of increased resistance to chlorhexidine in <i>K. pneumoniae</i> were also investigated particularly in connection with the observed cross resistance to colistin.</p>	<p>To understand what mechanisms are responsible for increased tolerance to chlorhexidine all chlorhexidine adapted strains and their respective parental counterparts were whole genome sequenced. The researchers consider that overall this study has identified a novel resistance mechanism to chlorhexidine that may potentially operate in a number of different species. They argue that clearly increased smvA expression is important for chlorhexidine adaptation in <i>K. pneumoniae</i> but it is not the only mechanism and may operate in conjunction with other regulatory processes. Chlorhexidine-adaptation is also associated with the generation of mutations in PhoPQ, which affect a number of known regulatory targets (notably pmrD and pmrK). Upregulation of these genes also correlates with the presence of colistin resistance. That increased colistin and chlorhexidine resistance may occur in clinical isolates without significant loss of fitness/virulence highlights the potential challenges associated with critical infection control procedures and the use of chlorhexidine as an antiseptic to control healthcare-associated infections.</p>
<p>Wu, D., Lu, R., Chen, Y., Qiu, J., Deng, C. and Tan, Q., 2016. China</p>	<p>A susceptibility study where the <i>S. aureus</i> reference strain ATCC 25923 as well as 14 clinical isolates were exposed to antibiotics (ciprofloxacin, gentamicin, and tetracycline), chlorhexidine and antimicrobial Chinese herbs at sublethal doses for up to 14 days.</p>	<p>The researchers state ‘all isolates were cross-resistant to more than one other antibiotic following tetracycline exposure, and increased resistance (≥ 4-fold MIC increase) to chlorhexidine and antimicrobial Chinese herbs was observed in six and three isolates, respectively. Following selection by chlorhexidine, most of the treated strains showed no significant change in sensitivity to CHX. However, all strains developed cross-resistance to at least one antibiotic.’ The researchers conclude that their results ‘imply that antibiotics, biocides and antimicrobial Chinese herbs might employ some of the same mechanisms of action against bacteria, triggering mutual cross-resistance to further foster the development of bacterial resistance.’</p>

Table 6 continued ...

Authors, year and country	Type of study conducted and purpose	Findings relevant to Review Question 2
<p>Zhang, M., O'Donoghue, M.M., Ito, T., Hiramatsu, K. and Boost, M.V., 2011. China</p>	<p>A comparative cross-sectional study. Nurses were recruited from 15 local hospitals and designated as 'fresh' (<2 years of nursing experience in the hospital) or 'experienced' (2 years of work experience). <i>qacA/B</i> gene positivity levels were compared with 186 <i>S. aureus</i> and a random selection of 200 coagulase-negative staphylococci isolated from 775 healthy adults with no healthcare association participating in a study of carriage of MRSA in the general population. They consisted of families of university students and their friends.</p>	<p>The researchers state: 'Samples were obtained from 249 nurses, of whom 157 (63.1%) were experienced and 92 (36.9%) fresh. There was no significant difference between <i>S. aureus</i> carriage rates of nurses (51/249; 20.5%) and the general population (186/775; 24%). Eight nurses (3.2%), seven experienced, were colonised with MRSA compared with only 4/775 (0.5%) of the general population (OR: 6.4; 95% CI: 1.9e21.4; P% 0.002). Resistance to several antibiotics was significantly more frequent in <i>qac</i> gene-positive than -negative isolates. Whereas there were no differences in MICs for CHG in <i>qac</i>-positive isolates from nurses and the general public, the MBCs were significantly higher for nurses' isolates (MBC50 nurses 8 mg/L, general public 2mg/ L; MBC90 nurses 16 mg/L, general public 8 mg/L; P< 0.001).' The researchers argue the use of antiseptics may be selecting for antibiotic-resistant strains and assisting their survival in the healthcare environment. The association between <i>mecA</i> and <i>qacA/B/smr</i> may contribute to survival of MRSA in the hospital environment. They may pose an infection control risk by persisting in areas with low level antiseptic residues.</p>

Discussion

Prior to commencing this review, it was agreed that there is no standardised method and no consensus on the definition of chlorhexidine 'resistance'. Unlike for antibiotics, there are no clinical breakpoints available for chlorhexidine 'resistance'. Although chlorhexidine 'resistance' is used extensively in the literature, minimum inhibitory concentration values indicate tolerance / susceptibility to chlorhexidine rather than resistance.

Within established clinical breakpoints for microorganisms against antibiotics, organisms that have a minimum inhibitory concentration below the breakpoint for that specific organism and antibiotic are classified as sensitive, while a minimum inhibitory concentration above the breakpoint is classified as resistant. This understanding for antibiotics may create confusion of what should be considered chlorhexidine 'resistance'. When a substantial increase in minimum inhibitory concentration of chlorhexidine for strains after exposure to chlorhexidine were observed in studies, the terms 'resistance', 'increased tolerance' or 'reduced susceptibility' were used in these studies. In this literature review, the term 'increased tolerance' was used for this phenomenon. However, it should be noted that in the absence of any breakpoints and epidemiological data the term 'resistance' should be acceptable even though the minimum inhibitory concentration might still be lower than the concentration of chlorhexidine in standard applications. This is especially the case as some factors might hugely limit the effectiveness of chlorhexidine for example (i) the different exposure times between clinical application and MIC measurement, (ii) failure to reach the stated concentration in the application for the required length of time and (iii) the role of organics in reducing the effectiveness of chlorhexidine.

To be included in the review, research studies published during the search timeframe had to make clear the population of study, the isolates had to be from humans, the dosage form and exposure of chlorhexidine was required to be stated, the research had to be undertaken in a health care setting or laboratory and a definition for or measurement of 'chlorhexidine resistance' / reduced susceptibility to chlorhexidine / non – susceptibility to chlorhexidine and/or antibiotic-resistant strain of bacteria had to be included. No use of chlorhexidine was excluded from the literature review.

The majority of primary research studies included (n=24/29) were conducted in the laboratory setting on human isolates collected in the main from adult hospital settings. The quality of the laboratory/susceptibility studies included in this literature review was difficult to determine. Susceptibility testing performed in clinical microbiology laboratories can confirm susceptibility to chosen agents and/or detect resistance in individual bacterial isolates (Jorgensen and Ferraro, 2009). The correct use of appropriate testing processes for specific organisms and, knowing that the interpretation of results of a susceptibility test must be in the clinical laboratory by persons with the necessary expertise, are biases that can impact on the quality of results disseminated. Given the specialised expertise and potential for controlled laboratory / susceptibility testing to be prone to numerous biases, an Expert in Microbiology worked with the Lead Reviewer in screening publications to be included and ensuring those included in this review were of suitable quality.

In this literature review of primary research studies, a recurring conclusion amongst researchers was one of raising concerns about the non-critical or inappropriate use of chlorhexidine regardless of form, dosage or exposure. This view is expressed given acknowledgement of Chlorhexidine's valuable use where there is definite patient benefit. At the same time, primary research included in this review acknowledged that in vitro susceptibility testing is not an accurate replication of the situation in a hospital setting where a much higher concentration of chlorhexidine is usually applied.

The main focus of research literature included in this review related to Review Question 1 and generally focussed on the implications of chlorhexidine based decolonisation / universal chlorhexidine use on MRSA *qacA/B* genes among hospitalized patients especially intensive care patients / whether the carriage of *qacA/B* can account for some of the decolonization failures / role of *qacA/B* and decreased susceptibility to chlorhexidine. Studies that found an increase in chlorhexidine tolerance and/or antibiotic resistance were studies where phenotypic tolerance/resistance was measured and many of those did find the *qacA/B* or other similar genes. Studies were not included if they only identified the genes but did not also measure resistance.

As resistance to chlorhexidine was not measured before decolonisation procedures with chlorhexidine were implemented in practice, there are no starting minimum inhibitory concentration values to compare (only 2 studies identified strains isolated before chlorhexidine was introduced). Therefore, with no start minimum inhibitory concentration value, there could have been a significant increase of minimum inhibitory concentration range in the 60 or so years since chlorhexidine was introduced (called MIC creep). Therefore, any minimum inhibitory concentration measure is only measuring whatever happens now after many years of chlorhexidine use.

Most studies in this review only report minimum inhibitory concentration values and even though minimum inhibitory concentration values could still be lower than the actual amount of chlorhexidine in the products, minimum inhibitory concentration values are measured completely differently from how chlorhexidine is used. Therefore, strains that have minimum inhibitory concentration values that would put them in the tolerant rather than resistant grouping could still survive treatment with chlorhexidine and we know that decolonisation failure does occur.

A limited number of primary research studies were identified in relation to Review Question 2 (n=9/36). A recent publication by Wand, Bock, Bonney and Sutton (2016) focussing on the potential risk of colistin resistance (colistin is referred to as a last resort antibiotic) emerging in the gram negative pathogen *K. pneumoniae* as a consequence of exposure to chlorhexidine is important to highlight given reports of increasing prevalence in hospitals of multidrug resistant (particularly carbapenem-resistant) *K. pneumoniae* infections and outbreaks. This study showed adaptation of clinical *K. pneumoniae* isolates to chlorhexidine exposure can not only lead to stable resistance to chlorhexidine but also cross-resistance to colistin. As Wand, Bock, Bonney and Sutton (2016) state 'that increased colistin and chlorhexidine resistance may occur in clinical isolates without significant loss of fitness/virulence highlights the potential challenges associated with critical infection control procedures and the use of chlorhexidine as an antiseptic to control healthcare-associated infections.'

To provide supportive and background information to the findings from primary research literature collated, evidence based literature / expert reviews identified through the search strategy are now discussed.

Horner, Mawer, and Wilcox (2012) in their expert review assessed available methods to detect reduced susceptibility to chlorhexidine and the prevalence of co-resistance and reviewed the clinical significance of efflux-mediated resistance genes in staphylococcus to what they refer to as an 'emergent threat'. Based on their findings, they argue a need for a standardized method for the detection of reduced susceptibility to in-use concentrations of chlorhexidine and consensus on a definition of chlorhexidine 'resistance' particularly given the impact of environmental factors on the development of reduced susceptibility. Given their view that the clinical use of chlorhexidine will continue to increase, they raise the possibility of this leading to the emergence of new clones with reduced susceptibility pointing to discouraging the 'indiscriminate chlorhexidine use in the absence of efficacy data'.

Harbarth, Tuan Soh, Horner, & Wilcox (2014) argue that 'international standards to determine reduced susceptibility to biocidal agents in vitro need to be established to enable investigations 'prospectively in a controlled and systematic manner'. Their view was that biocides like chlorhexidine 'should be used in a targeted manner, and should be restricted to indications with proven clinical benefit (e.g. central venous catheter care) rather than in an indiscriminate manner.'

In a literature review undertaken by Edgeworth (2011), the focus was on an increased use of chlorhexidine in intensive care units. Noting the 'recent observation that MRSA strains carrying the antiseptic resistance genes *qacA/B* can be clinically resistant to chlorhexidine', Edgeworth (2011) cautions 'its unfettered use' saying the 'dissemination of chlorhexidine-resistant MRSA would have implications for the decolonization of individual patients and for preventing transmission'. Noto and Wheeler (2015) in their expert review on understanding chlorhexidine decolonization of the mouth and skin of critically ill patients state 'although chlorhexidine-based decolonization may be of benefit in select situations and should remain in the armamentarium of strategies to prevent HAIs, universal implementation of these practices warrants caution and further consideration in light of the available evidence and potential for harm.'

Kampf (2016) in his review of published data from clinical isolates with chlorhexidine minimum inhibitory concentrations (MICs) compared to epidemiological cut-off values to determine resistance concluded:

'Based on the fairly high resistance rates in *Enterobacter spp.*, *Pseudomonas spp.*, *Proteus spp.*, *Providencia spp.* and *Enterococcus spp.*, the ability of *Acinetobacter spp.*, *K. pneumoniae* and *Pseudomonas spp.* to adapt to chlorhexidine and the potential for cross-resistance to some antibiotics, it seems prudent to restrict the use of chlorhexidine to those applications with a clear patient benefit and to eliminate it from applications without any benefit or with a doubtful benefit.'

Based on the findings of primary research included in this review, suggested areas for further research are summarised as:

1. The implications of chlorhexidine based decolonisation / universal Chlorhexidine use on MRSA qacA/B genes among hospitalized patients especially intensive care unit patients / whether the carriage of qacA/B can account for some of the decolonization failures / role of qacA/B and decreased susceptibility to Chlorhexidine (Batra et al., 2010; Edgeworth, 2011; Ho et al., 2012; Longtin, Seah, Siebert et al. 2011; Lee at al., 2011; Lu et al., 2014; Mendoza-Olazarán et al., 2014; Otter et al., 2013; Prag et al., 2014; Shamsudin, et al., 2012; Sheng at al., 2009; Skovgaard et al., 2013; Warren et al., 2016; Zhang et al., 2011).
2. How to ensure correct use and application of chlorhexidine in clinical practice as an antiseptic and as a disinfectant to control and/or prevent healthcare-associated infections, no off label use, challenges associated with critical infection control procedures (Bock, Wand & Sutton, 2016; EKİZOĞLU, SAĞIROĞLU, Kilic, and HASÇELİK, 2016; Johnson et al., 2015; Kawamura-Sato, 2008, 2010; Liu et al., 2015; Smith, Gemmell and Hunter, 2008; Vali et al., 2015; Wand et al., 2016).
3. Risks to antibiotic therapies and whether resistance of certain strains of bacteria to chlorhexidine contributes to these strains persisting in the hospital environment (Morrisey et al., 2014; Naparstek et al., 2012; Oggioni et al., 2015).
4. The role of chlorhexidine in biofilm formation and how best to suppress the biofilm induction (Aka & Haji 2015).

In addition, as discussed with the Expert, there is currently no practice for monitoring Chlorhexidine resistance / increased tolerance in Australia. The Antimicrobial Use and Resistance in Australia (AURA please see <https://www.safetyandquality.gov.au/antimicrobial-use-and-resistance-in-australia/>) currently only monitor antibiotic resistance and chlorhexidine could be included under the umbrella of AURA.

Conclusion

Is the use of chlorhexidine contributing to increased resistance to chlorhexidine and/or antibiotics?

The question as to whether chlorhexidine is contributing to increased resistance to chlorhexidine and to antibiotics cannot be answered conclusively based on this literature review. Primary research identified in this review is mostly conducted in the laboratory setting and caution is needed when interpreting the results to relate to chlorhexidine exposure (different dosages, duration of use, and stratification of exposure) in the clinical setting.

Of primary research studies in this literature review and supported by other published expert/literature reviews, it is reported that the use of chlorhexidine is contributing to an increase in tolerance/reduced susceptibility to a variety of chlorhexidine applications and that there is a link with chlorhexidine use and antibiotic resistance. It is also noted that there remains no standardised method and no consensus on the definition of chlorhexidine 'resistance'.

The need for a greater understanding of how resistance mechanisms are changing the susceptibility of disease-causing bacteria to chlorhexidine and/or antibiotics is evident within published literature. While this understanding is gathered, the use of chlorhexidine for only those applications that have demonstrated a clear patient benefit with surveillance processes to ensure the specific chlorhexidine

application is used correctly is suggested as an urgent requirement. Applications without any benefit or with a doubtful benefit should be eliminated or at a minimum restricted in use.

Understanding that the quality use of chlorhexidine must be judicious, appropriate, safe and efficacious is a view argued by researchers and experts of publications included in this review.

Implications:

The quality use of chlorhexidine may require its application to only those that have demonstrated a clear patient benefit and ensure it is used correctly and to eliminate it from applications without any benefit or with a doubtful benefit. In the majority of publications included in this review, chlorhexidine is not referred to as a medicine rather as a biocide, antiseptic or disinfectant. As a medicine, the quality use of Chlorohexidine, like the quality use of antibiotics, is guided by the National Medicines Policy (2000) which aims to improve positive health outcomes for all Australians through their access to and wise use of medicines. A biocidal stewardship focussing specifically on chlorhexidine given its widespread use, similar to antibiotic stewardship, could be considered in Australia.

As there is no practice for monitoring chlorhexidine resistance in Australia and there is a need for standardised methods to measure chlorhexidine resistance and the resistance/increased tolerance, could chlorhexidine be monitored and reported to a central body such as AURA (Antimicrobial Use and Resistance in Australia)? AURA currently only monitor antibiotic resistance and chlorhexidine could be included under the umbrella of AURA.

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Appendix 1. Chlorhexidine products listed in MIMS as of December 2016

[Bactigras Dressing \[Smith & Nephew\]](#)

[Dressing, gauze - Chlorhexidine acetate - Paraffin, white soft](#)

Use: Infected skin lesions; prophylactic dressing

Dose: Change dressing daily or as required

MIMS Class: [Surgical antiseptics and applications](#)

[Drug Interactions](#)

[Baxter Chlorhexidine Acetate 0.015% with Cetrimide 0.15% Antiseptic Solution \[Baxter\]](#)

[Chlorhexidine acetate - Cetrimide](#)

Use: General antiseptic. Wound cleaning, disinfecting; treatment of burns

Dose: Please open [Abbreviated PI](#) for Dosage

MIMS Class: [Topical antiseptics, anti-infectives](#)

[Drug Interactions](#)

[Baxter Chlorhexidine Acetate 0.05% and Cetrimide 0.5% Antiseptic Solution. \[Baxter\]](#)

[Chlorhexidine acetate - Cetrimide](#)

Use: General antiseptic. Wound cleaning, disinfecting; treatment of burns

Dose: Please open [Abbreviated PI](#) for Dosage

MIMS Class: [Topical antiseptics, anti-infectives](#)

[Drug Interactions](#)

[Baxter Chlorhexidine Acetate 0.1% and Cetrimide 1.0% Antiseptic Solution . \[Baxter\]](#)

[Chlorhexidine acetate - Cetrimide](#)

Use: General antiseptic. Wound cleaning, disinfecting; treatment of burns

Dose: Please open [Abbreviated PI](#) for Dosage

MIMS Class: [Topical antiseptics, anti-infectives](#)

[Drug Interactions](#)

[Baxter Chlorhexidine Acetate Aqueous Antiseptic Solution Topical solution \[Baxter\]](#)

[Chlorhexidine acetate](#)

Use: General antiseptic. Wound cleaning, disinfecting; treatment of burns

Dose: Individualise dose and duration of use; rinse affected area with water, apply minimum undiluted amount to cover wound, wash gently, allow to air dry for 3 min

MIMS Class: [Surgical antiseptics and applications](#)

[Drug Interactions](#)

[Bepanthen First Aid Antiseptic Cream \[Bayer\]](#)

[Chlorhexidine hydrochloride](#)

Use: Topical antiseptic. Treatment, prevention of infection in minor cuts, wounds, abrasions, insect bites, minor burns

Dose: General use: clean wound and surrounding skin and apply liberally to affected area, ensuring wound completely covered; may repeat application. Minor burns: immediately apply cold water for greater tha...

MIMS Class: [Topical antiseptics, anti-infectives](#)

[Drug Interactions](#)

[Chlorhexidine 0.015% and Cetrimide Aqueous Irrigation Solution \[Pfizer\]](#)

[Chlorhexidine gluconate - Cetrimide](#)

Use: Antiseptic, disinfectant with surfactant properties. Cleansing, irrigation of skin, dirty wounds; infection control

Dose: Please open [Abbreviated PI](#) for Dosage

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

Chlorhexidine 0.05% and Cetrimide Aqueous Irrigation Solution [\[Pfizer\]](#)

Chlorhexidine gluconate - Cetrimide

Use: Antiseptic, disinfectant with surfactant properties. Cleansing, irrigation of skin, dirty wounds; infection control

Dose: Please open [Abbreviated PI](#) for Dosage

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

Chlorhexidine 1% Hand Lotion [\[Perrigo Australia\]](#)

Ethanol - Chlorhexidine gluconate

Use: Antiseptic, disinfectant. Cleansing of hands, skin where hand washing not practical

Dose: Apply 1-2 pumps (2-4 mL) to hands, rub over all surfaces of hands, allow to dry. Visibly soiled hands: wash and dry before applic

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

Chlorhexidine Aqueous Cream [\[Extemporaneous\]](#)

Chlorhexidine gluconate - Paraffin, liquid - Cetostearyl alcohol - Cetomacrogol 1000

MIMS Class: [Emollients, antipruritics and protective preparations](#)

Drug Interactions

Chlorhexidine Irrigation Solution [\[Pfizer\]](#)

Chlorhexidine gluconate

Use: Antiseptic, disinfectant. 0.1%: skin, wound irrigation to prevent, control infection; 0.2%: cleanse external genitalia prior to urinary catheterisation

Dose: Use undiluted. 0.1%. Rinse affected area with water; apply min amount to cover wound area, wash gently, rinse again thoroughly. Apply as nec. 0.2%. Irrigate external genitalia before catheterisation

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

Chlorhexidine Obstetric Lotion

[\[Perrigo Australia\]](#)

Chlorhexidine gluconate

Use: Disinfectant, lubricant. Obstetric, gynaecology procedures

Dose: Apply liberally, undiluted

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

Chlorhexidine Pre-Op Wash 4% Solution [\[Perrigo Australia\]](#)

A

Chlorhexidine gluconate

Use: Antiseptic, disinfectant. Preop cleanser, surgical disinfection of intact skin

Dose: 50 mL tube covers single applic. Wash day before and day of operation. Apply undiluted to entire body incl hair, hairy areas, skin folds, crevices, navel, nose and operation site; lather progressively;...

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

[Chlorhexidine Surgical Scrub 4% Solution](#) [Perrigo Australia]

PI

[Chlorhexidine gluconate](#)

Use: Antiseptic, disinfectant. Skin cleanser

Dose: Wet hands, arms with warm water; dispense two pumps (approx. 4 mL) to hands, rub hands to form a lather for greater than or equal to 2 mins; scrub nails with nailbrush; rinse, repeat process;

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

[DeBug Hand Hygiene Solution Topical solution](#) [Perrigo Australia]

[Chlorhexidine gluconate - Isopropyl alcohol](#)

Use: Antiseptic, disinfectant. Antibacterial hand solution

Dose: Use undiluted. Squirt 3 mL (sufficient to completely cover both hands) into a cupped hand. Rub all over both hands for 30 sec. Apply further 3 mL, repeat rubbing and allow to dry

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

[Diffiam-C Anti-inflammatory Antiseptic Solution](#) [iNova]

[Benzydamine hydrochloride - Chlorhexidine gluconate](#)

Use: Painful mouth and throat conditions

Dose: Adults: 15 mL (approx. 1 tablespoon) gargled (for throat conditions) or swirled in mouth (for oral lesions) for 30 secs every 1.5-3 hours as needed; expectorate after use, do not swallow; use undilute...

MIMS Class: [Topical oropharyngeal medication](#)

Drug Interactions

[Hemocane Ointment](#) [Key]

[Hamamelis extract - Allantoin - Lidocaine \(lignocaine\) - Zinc oxide - Chlorhexidine acetate](#)

Use: Haemorrhoids, anal fistula, anal pruritus

Dose: Apply morning and night and after each bowel movement

MIMS Class: [Topical anorectal medication](#)

Drug Interactions

[Herron Lip-Eze Oralife Peppermint Lip Ointment](#) [Perrigo Australia]

Abbreviated PI

[Paraffin, white soft - Propylene glycol - Wool fat - Chlorhexidine gluconate](#)

Use: Emollient lip balm. Prevention, relief of dry lips due to moisture loss

Dose: Apply thin film to lips as necessary

MIMS Class: [Emollients, antipruritics and protective preparations](#)

Drug Interactions

[Lignocaine with Chlorhexidine Gel](#) [Pfizer]

[Lidocaine \(lignocaine\) - Chlorhexidine gluconate](#)

Use: Local anaesthetic, antiseptic. Anaesthesia, lubricant during catheterisation, endourethral operation, exam; cystoscopy; symptomatic painful cystitis, urethritis treatment

Dose: Individualise dose. Urethral. Males: 20 mL in 2 portions; females: 5-10 mL in small portions; cystoscopy: less than or equal to 40 mL in 3-4 portions; see full PI. Children < 12 yrs: ...

MIMS Class: [Anaesthetics - local and general](#)

Drug Interactions

[Microshield 2 Solution](#) [J&J Medical]

[Chlorhexidine gluconate](#)

Use: Body wash (preop, postop), hand hygiene, showering

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

[Microshield 4 Solution](#) [\[J&J Medical\]](#)

[Chlorhexidine gluconate](#)

Use: Preop antiseptics, hand hygiene, showering

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

[Microshield 5 Solution](#) [\[J&J Medical\]](#)

[Chlorhexidine gluconate](#)

Use: Skin prep (preop, postop); umbilical cord disinfection; emergency instrument disinfection

Dose: Dilute before use

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

[Microshield Handrub Solution](#) [\[J&J Medical\]](#)

[Chlorhexidine gluconate - Ethanol](#)

Use: Hand, skin disinfection

Dose: Apply 1 mL to hands, proportionate amount for other skin areas, rub in until dry

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

[Microshield Tincture](#) [\[J&J Medical\]](#)

[Chlorhexidine gluconate - Ethanol](#)

Use: Preop skin antiseptics; emergency clean instrument disinfection

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

[Mycil Healthy Feet Tinea Dusting Powder](#) [\[Reckitt Benckiser\]](#)

Tolnaftate - [Chlorhexidine hydrochloride](#)

Use: Itching, burning and soreness assoc with tinea and other skin infections (incl ringworm)

Dose: Apply 2-3 times daily; continue for 2 weeks to prevent recurrence

MIMS Class: [Topical antifungals](#)

Drug Interactions

[Nasalate Nose Cream](#) [\[Care Pharmaceuticals\]](#)

[Chlorhexidine gluconate - Phenylephrine hydrochloride](#)

Use: Nasal vestibulitis; acute epistaxis, postop bleeding; post nasal surgery anti-infective

Dose: Apply direct or on nasal packing 3-4 times daily; max 7 days

MIMS Class: [Topical nasopharyngeal medication](#)

Drug Interactions

[Pharmacy Action Antiseptic Cream](#) [\[Generic Health\]](#)

[Chlorhexidine gluconate - Lidocaine \(lignocaine\) - Bufexamac](#)

Use: Antiseptic, anaesthetic, anti-inflammatory. First aid treatment of minor cuts, abrasions, insect bites, stings, itches, minor burns, sunburn

Dose: Apply to affected area 3-4 times daily. For initial treatment of

minor burns apply cold water and apply cream later

MIMS Class: [Topical antiseptics, anti-infectives](#)

Drug Interactions

[Riotane Chlorhexidine 0.5% in Alcohol 70% Tinted Pink Topical solution](#) [\[Perrigo Australia\]](#)

[Chlorhexidine gluconate - Ethanol](#)

Use: Hospital grade disinfectant effective against Gram -ve and Gram +ve bacteria

Dose: Use undiluted. Pre-clean all surfaces first. Do not return unused soln to bottle

MIMS Class: [Surgical antiseptics and applications](#)

Drug Interactions

[Rivacol Chlorhexidine Mouthwash 0.2%](#) [\[Perrigo Australia\]](#)

[Chlorhexidine gluconate - Ethanol](#)

Use: Antiseptic, disinfectant. Throat, mouth infections

Dose: Adults: dilute 10-15 mL of mouthwash with 10-15 mL of warm water; rinse, gargle for 1-2 mins then expel; may use up to 3 times daily after meals or as directed by a doctor or dentist

MIMS Class: [Topical oropharyngeal medication](#)

Drug Interactions

[Savacol Freshmint Antiseptic Mouth & Throat Rinse](#) [\[Colgate-Palmolive\]](#)

[Chlorhexidine gluconate - Ethanol](#)

Use: Antiseptic. Gum disease, dental plaque, mouth ulcers; use after dental treatment (on dental advice)

Dose: Rinse or gargle (adults: 15 mL, children < 10 yrs: 7.5 mL) for one minute 2-3 times daily; then spit out. Can be used as a denture rinse

MIMS Class: [Topical oropharyngeal medication](#)

Drug Interactions

[Savacol Mouth & Throat Rinse](#) [\[Colgate-Palmolive\]](#)

[Chlorhexidine gluconate](#)

Use: Mouth ulcers and minor throat infections; reduce dental plaque and incidence of gingivitis; denture hygiene

Dose: Adults, children > 10 years: rinse mouth or gargle with 10 mL for 1 min after meals. Children < 10 years: rinse mouth or gargle with 5 mL diluted with 5 mL warm water for 1 min after meals. Ulcers: .

MIMS Class: [Topical oropharyngeal medication](#)

Drug Interactions

[Savlon Antiseptic Cream](#) [\[Reckitt Benckiser\]](#)

[Cetrimide - Chlorhexidine hydrochloride](#)

Use: Topical antiseptic. Cut, scratch, blister, graze, windburn, sunburn, nappy rash, insect bite, cracked/ itchy skin

Dose: Clean surrounding skin. Apply directly or on lint/ cotton wool

MIMS Class: [Topical antiseptics, anti-infectives](#)

Drug Interactions

[SOOV Cream](#) [\[Ego\]](#)

[Lidocaine \(lignocaine\) - Chlorhexidine gluconate - Phenoxyisopropanol - Cetrimide](#)

Use: Cuts, grazes, minor burns, scalds, sunburn; itching due to haemorrhoids

Dose: Apply to affected area 2-4 times/day

MIMS Class: [Anaesthetics - local and general](#)

[Drug Interactions](#)