BMJ

BMJ 2014;348:g2197 doi: 10.1136/bmj.g2197 (Published 31 March 2014)

RESEARCH

Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis

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Abstract

Objectives To determine the effect on mortality of selective digestive decontamination, selective oropharyngeal decontamination, and topical oropharyngeal chlorhexidine in adult patients in general intensive care units and to compare these interventions with each other in a network meta-analysis.

Design Systematic review, conventional meta-analysis, and network meta-analysis. Medline, Embase, and CENTRAL were searched to December 2012. Previous meta-analyses, conference abstracts, and key journals were also searched. We used pairwise meta-analyses to estimate direct evidence from intervention-control trials and a network meta-analysis within a Bayesian framework to combine direct and indirect evidence.

Inclusion criteria Prospective randomised controlled trials that recruited adult patients in general intensive care units and studied selective digestive decontamination, selective oropharyngeal decontamination, or oropharyngeal chlorhexidine compared with standard care or placebo.

Results Selective digestive decontamination had a favourable effect on mortality, with a direct evidence odds ratio of 0.73 (95% confidence interval 0.64 to 0.84). The direct evidence odds ratio for selective oropharyngeal decontamination was 0.85 (0.74 to 0.97). Chlorhexidine was associated with increased mortality (odds ratio 1.25, 1.05 to 1.50). When each intervention was compared with the other, both selective digestive decontamination and selective oropharyngeal decontamination were superior to chlorhexidine. The difference between selective digestive decontamination and selective oropharyngeal decontamination was uncertain.

Conclusion Selective digestive decontamination has a favourable effect on mortality in adult patients in general intensive care units. In these patients, the effect of selective oropharyngeal decontamination is less certain. Both selective digestive decontamination and selective oropharyngeal decontamination are superior to chlorhexidine, and there is a possibility that chlorhexidine is associated with increased mortality.

Introduction

The bacterial ecology of the oropharynx of patients in intensive care units undergoes substantial alteration.[1 2] This can lead to ventilator associated pneumonia, other infections, and death. In an attempt to reduce the incidence of these complications, approaches to decontamination include various forms of antibiotic prophylaxis or the use of topical oropharyngeal antiseptic agents (mostly chlorhexidine). Antibiotic prophylaxis can include any combination of oropharyngeal, intragastric, and intravenous antibiotics. There are, however, two main approaches: selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD).

Selective digestive decontamination consists of oropharyngeal and gastric application of non-absorbable antibiotics—often polymyxin, tobramycin, and amphotericin—along with a short course of an intravenous antibiotic, often cefotaxime. Oropharyngeal antibiotics are applied as a paste, usually four times a day, during routine mouth care; gastric antibiotics are administered as a suspension through a nasogastric tube. Surveillance bacteriology, often twice a week, can be used to assess efficacy of decontamination. The choice of therapeutic antibiotics aims to minimise interference with the native anaerobic flora by avoiding agents such as broad spectrum penicillins. Selective oropharyngeal decontamination is the application of the topical antibiotic paste to the oropharynx only,

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Appendix: Medline electronic search strategy, approach to studies with three arms, and table A (raw outcome data)

without enteral or empirical intravenous antibiotics.[3] Chlorhexidine is applied as part of routine mouth care in gel or liquid form up to four times a day.

There has been considerable debate about the role of antibiotic prophylaxis,[4-6] and antibiotic prophylaxis is seldom used in the United Kingdom.[7] Topical oropharyngeal antiseptic agents (usually chlorhexidine) have, by contrast, gained more widespread acceptance and appear as a key recommendation in UK,[8] European,[9] and US[10] guidelines. Nevertheless, interest in this topic remains current.[11]

Numerous meta-analyses of antibiotic and antiseptic prophylaxis have been published over the years. A 2009 Cochrane review suggested that mortality was significantly reduced by selective digestive decontamination.[12] Another review and meta-analysis from 2007 concluded that mortality was unaffected by oropharyngeal antibiotic or antiseptic decontamination.[13] More recent meta-analyses of oropharyngeal antiseptics (mostly chlorhexidine) have focused on the incidence of ventilator associated pneumonia,[14-16] although some meta-analyses of oropharyngeal chlorhexidine have reported a trend towards increased mortality.[15 17]

Despite the favourable results seen in meta-analyses of selective digestive decontamination, interpretation should be tempered by the use of standard care as a control group in the contributory trials. Given the likely widespread use of chlorhexidine, any putative mortality advantage of selective digestive decontamination or selective oropharyngeal decontamination needs to be re-defined. As we are not aware of any clinical trials directly comparing selective digestive decontamination or selective oropharyngeal decontamination with topical chlorhexidine, we aimed to use a network meta-analysis to compare the effect of these interventions on mortality. This required us to undertake an updated systematic review looking for randomised controlled trials reporting the effect of selective digestive decontamination, selective oropharyngeal decontamination, and topical chlorhexidine on mortality in adult patients in general intensive care units. We also wanted to update conventional intervention-control meta-analyses of the three interventions in light of any recent studies. We elected not to study the outcome of ventilator associated pneumonia as we consider mortality to be the most robust outcome, and this was the focus of recent large trials of selective digestive decontamination.[18 19]

Method

Sources of data

We searched Medline, Embase, and the Cochrane Register of Clinical Trials from 1984 until December 2012. We constructed a search strategy around patients in intensive care, intervention with antibiotic or antiseptic prophylaxis, and the outcome of death. The Medline search strategy is shown in the appendix and similar strategies were applied to the Embase and CENTRAL databases. There were no language restrictions. We screened results of the database searches by title and abstract. Given the extent of previous systematic reviews, we reviewed recent meta-analyses (published from 2005 to 2012[12-16 20-28]) for included studies that were missed in database searches. Congress abstracts were searched from 2005 to 2012 for the European Society for Intensive Care Medicine, Society for Critical Care Medicine, Symposium of Intensive Care and Emergency Medicine, and Chest. The contents pages of the journals Intensive Care Medicine, Critical Care Medicine, Chest, Critical Care, American Journal of Respiratory and Critical Care Medicine, Journal of Hospital Infection, and Infection Control and Hospital Epidemiology were reviewed from January 2005 to December 2012. The website controlled-trials.com was used to search registers of clinical trials. We did not search for unpublished studies or contact experts in the field. We wrote to authors if indicated.

Inclusion criteria

We sought prospective randomised controlled clinical trials in adult patients in general intensive care units. We did not stipulate placebo control or blinding. We defined "selective digestive decontamination" as the application of a combination of poorly absorbable antibiotics to the oropharynx and the stomach combined with empirical intravenous antibiotics. "Selective oropharyngeal decontamination" was defined as the application of a combination of poorly absorbable antibiotics only to the oropharynx. "Chlorhexidine" was defined as the application of any concentration of chlorhexidine in any formulation to the oropharynx. The control group must have received only standard care or placebo.

Exclusion criteria

We excluded trials that recruited only children, populations not in intensive care, and specialised populations (such as cardiac surgery and liver transplantation). We excluded trials in which both groups received active topical drugs or in which the control group received empirical intravenous antibiotics. Finally we excluded studies combining oropharyngeal and gastric application of antibiotics or gastric or subglottic application alone from the selective oropharyngeal decontamination meta-analysis.

Quality assessment

We summarised potential biases with the Cochrane risk of bias tool. There are six domains: sequence generation; allocation concealment; blinding; if the outcomes reported were prespecified; completeness of outcome data; and other potential sources of bias. We have also presented information on each study to show potential issues of clinical heterogeneity.

Data extraction

Results were extracted from the included studies, from our own communication with authors, or from previous meta-analyses if intention to treat data had been verified with the original study authors.

Consensus

Two authors (RP, JG) independently performed study inclusion, data extraction, and quality assessment. Disagreement at the stage of abstract screening was resolved by inclusion of the full paper for review. Disagreement at later stages was resolved by discussion. Our approaches to studies with a three arm design are presented in the appendix.

Statistical methods

Intervention-control pairwise meta-analyses

We summarised data from each study with log odds ratios and 95% confidence intervals. This approach was used to allow the inclusion of the study by de Smet and colleagues,[19] which used a cluster randomised crossover design analysed by the authors using multilevel logistic regression. We used the log odds ratios and standard errors that de Smet and colleagues[19] reported and calculated the log odds ratios and standard errors for the remaining studies based on the reported events and sample sizes.

Forest plots are included as a visual aid to interpret the direct evidence. Pairwise meta-analyses were done in Review Manager (RevMan), version 5.0 (Cochrane Collaboration, 2008).

Network meta-analysis

We used a generalised linear modelling framework as outlined in Dias and colleagues[29] to do a network meta-analysis. A "trial level" approach was used, in which the data modelled were the summary log odds ratios and standard errors for each trial as outlined above. All model parameters were estimated within a Bayesian framework with WinBUGS software.[30] We present estimates of treatment effects as odds ratios and 95% central credible intervals (CrI). The credible interval shows the degree of uncertainty around estimated treatment effects.

We also calculated individual estimates of the probability of death for each intervention. These estimates were derived from the model by using a baseline distribution for the probability of death in the control group, in combination with the odds ratio between each intervention and control. Vague prior distributions were used on the necessary parameters: the log odds ratios of intervention procedures versus control and the standard deviation between studies. A run-in period of 50 000 iterations was adequate to achieve convergence, and a further 100 000 samples were taken.

Results

Systematic review

We identified 29 studies as suitable for inclusion[18 19 31-57] (figure 1⇓). Tables 1-3⇓⇓⇓ show the components of the Cochrane risk of bias tool for each intervention. Tables 4-6⇓⇓⇓⇓ show areas of potential clinical heterogeneity between the studies and our data source. Raw outcome data are presented in table A in the appendix.

Intervention-control pairwise meta-analyses

The random effects estimate for selective digestive decontamination compared with control on mortality gave an odds ratio of 0.73 (95% confidence interval 0.64 to 0.84), favouring selective digestive decontamination (fig 2⇓). For selective oropharyngeal decontamination and chlorhexidine the odds ratios were 0.85 (0.74 to 0.97) and 1.25 (1.05 to 1.50), respectively (figs 3⇓ and 4⇓). The only direct evidence for selective digestive decontamination compared with selective oropharyngeal decontamination was from a single trial,[19] which gave an odds ratio of 0.97 (0.79 to 1.18). Results are summarised in table 7⇓.

Results of network meta-analyses

The odds ratios (95% credible interval) for mortality for active treatment compared with control were 0.74 (0.63 to 0.86) for selective digestive decontamination, 0.82 (0.62 to 1.02) for selective oropharyngeal decontamination, and 1.23 (0.99 to 1.49) for chlorhexidine (table 7⇓). For the comparison between treatments, the odds ratios were 0.61 (0.47 to 0.78) for selective digestive decontamination compared with chlorhexidine and 0.67 (0.48 to 0.91) for selective oropharyngeal decontamination compared with chlorhexidine. There was uncertainty around the difference between selective digestive decontamination and selective oropharyngeal decontamination. Table 8 shows probabilistic ranking of interventions⇓.

Discussion

Using a network meta-analysis to compare each intervention indirectly, we conclude that both selective digestive decontamination and selective oropharyngeal decontamination are superior to chlorhexidine in preventing death in adults in intensive care. This suggests that the mortality advantage of both these options remains relevant even if chlorhexidine is widely used. Any difference between these treatments is inconclusive, with considerable uncertainty.

Our finding that selective digestive decontamination is associated with a survival benefit in adults in general intensive care units agrees with the conclusions of earlier meta-analyses, but we have now integrated the results of a large cluster randomised crossover trial. Results were similar with both conventional and Bayesian analysis. Selective oropharyngeal decontamination was associated with a reduction in death in the meta-analysis of direct evidence. Contrary to our expectations, use of oropharyngeal chlorhexidine was associated with an increase in mortality in adults in general intensive care units.

Limitations of our study

Despite our inclusion criteria, our results are limited by the inevitable heterogeneity among the included studies (tables 4-6⇓⇓⇓⇓), with some common themes.

Within the chlorhexidine studies, the concentration of chlorhexidine used varied from 0.12% to 2% and the number of daily applications varied from one to four. In addition, the duration of the course of treatment varied and in one study was limited to seven days.[54]

Within the selective digestive decontamination studies, most were not blinded and were not placebo controlled. Of those that were blinded,[36 38 39] only one explicitly reported concealment of microbial culture results.[39] We consider that this lack of blinding would have had the least influence on the robust outcome of mortality. We could not find any suggestion of differential treatment of patients in the active treatment group over control patients, although we cannot entirely exclude it. Infected patients were excluded in three studies.[34 37 38] There was some variability in the exact antimicrobial regimen used; the influence of different regimens has previously been discussed[58] and has been shown to influence at least infective outcomes.[42] Two studies differed slightly in their protocols by locally decontaminating blind bowel loops and tracheal stomas and by treating persistent tracheal colonisation with aerosolised polymyxin or amphotericin.[18 19]

For each included selective digestive decontamination study, the total proportion of patients in the intensive care unit that were included in the trial was generally unclear. The only included study to use a whole unit approach[18] showed a mortality benefit that was greater than that seen in meta-analyses (although problems with this study have been highlighted.)[59 60] Thus the generalisability of these studies to a unit where selective digestive decontamination or selective oropharyngeal decontamination is applied to every patient needs to be considered as selective digestive decontamination can alter the ecology of the unit.[32 61 62]

When we considered all studies, there was variability in the minimum predicted ventilator time or stay in the intensive care unit. The proportion of ventilated patients varied from 36% in one study[55] to 100%.

A network meta-analysis rests on the comparability of a common control group. Given the temporal variation (year of publication ranging from 1989 to 2011) and wide geographic representation

(tables 4-6⇓⇓⇓), there is probably variation among the control groups of the included studies. Control group treatments were generally poorly detailed, although we have identified some variation—for example, the use of topical bicarbonate[48 50] or potassium permanganate.[55] When other control group treatments were described, they were generally limited to the use of gastric ulcer protection or non-pharmacological mouth care strategies.

When we considered the effect of chlorhexidine on mortality, mortality was not the primary outcome of any of the included studies and a significant increase in mortality was seen in only one[54] of the 11 studies. Additionally, we are aware of one further study[63] of the use of oropharyngeal chlorhexidine that could have fulfilled our inclusion criteria, but we were unable to include it as we could not obtain mortality data.

Implications of this study

In adult patients in general intensive care units, and within the limits of a network meta-analysis, we propose that both selective digestive decontamination and selective oropharyngeal decontamination are superior to chlorhexidine. In keeping with results of earlier studies, we have shown that selective digestive decontamination is associated with reduced mortality. We raise the possibility that oropharyngeal chlorhexidine might be associated with an increase in mortality, and we therefore question whether oropharyngeal chlorhexidine is "safe and effective."[11] Certainly our findings are at odds with the apparently favourable effects of chlorhexidine on the incidence of ventilator associated pneumonia,[14-16] although the attributable mortality of this might be small.[64] We consider that the role of oropharyngeal chlorhexidine in these patients needs to be explored further. We agree that it would be appropriate to undertake additional prospective studies comparing selective digestive decontamination, selective oropharyngeal decontamination, and chlorhexidine[11 65] after barriers to implementation or any further trials have been explored.[66]

We thank Amanda Wright for librarian services, Silvia Hernandez for translation services and obtaining additional information from a study author, and Artur Pryn. We also thank Angela Berry, Cindy Munro, and Frank Scannapieco for providing additional data; and Fernando Bellissimo Rodrigues, Michele Darby, Mirelle Koeman, Mercedes Palomar, and Miguel Sanchez Garcia for providing additional information.

Contributors: RP and GM designed the study. RP and JG did the literature search, reviewed studies for inclusion, assessed the included studies, and extracted data. GM analysed the data. All three authors wrote, reviewed, and then approved the manuscript. RP is guarantor.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: No additional data available.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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What is already known on this topic

Numerous studies and meta-analyses have shown a mortality benefit with use of selective digestive decontamination in patients in intensive care

Meta-analyses have shown that oropharyngeal chlorhexidine is associated with a reduced incidence of ventilator associated pneumonia, without a measurable effect on mortality

What this paper adds

This network meta-analysis showed that both selective digestive decontamination and selective oropharyngeal decontamination confer a mortality benefit when compared with chlorhexidine in adult patients in general intensive care units

In these patients, selective digestive decontamination was associated with reduced mortality, as in earlier meta-analyses, but the current analysis integrated a large recent cluster crossover study

It is possible that use of chlorhexidine is associated with an increase in mortality

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Accepted: 03 March 2014

Cite this as: BMJ 2014;348:g2197

Tables

Table 1| Methodological aspects of included trials on effect of selective digestive decontamination (SDD) for prevention of death in adults in intensive care

	Adequate sequence generation	Allocation concealment	Blinding	Outcome prespecified	Incomplete outcome data addressed	Other bias
Aerdts[31]	Yes	Yes*[12]	No	Per protocol mortality reported in published paper	Intention to treat analysis possible from previous communication with authors*[12]	—
Blair[32]	Unclear	Yes*[12]	No	Mortality reported	Intention to treat analysis possible from data provided	—
Boland[33]	Yes*[12]	Unclear	Yes	Mortality not reported	Intention to treat analysis possible from previous communication with authors*[12]	Published only in abstract form
Cockerill[34]	Yes	Yes	No	Mortality reported	Intention to treat analysis performed	—
De Jonge[18]	Yes	Yes	No	Study powered for mortality. Mortality reported	Intention to treat analysis performed	Active and control ICUs, potential for other differences in care
De Smet[19]	Yes	Yes	No	Study powered for mortality. Mortality reported	Adjusted 28 day mortality used: 1979/1990 in standard care; 2018/2045 in SDD	Statistical correction of baseline differences discussed
Jacobs[35]	Unclear	Yes	No	Mortality reported	Intention to treat analysis possible from data provided	Uncorrected relevant baseline imbalance
Kreuger[36]	Yes	Yes	Yes	Mortality reported	Intention to treat analysis performed	—
Palomar[37]	Yes	Yes*[12]	No	Per protocol mortality reported in published paper	Intention to treat analysis possible from previous communication with authors*[12]	Uncorrected relevant baseline imbalance
Rocha[38]	Yes	Yes	Yes	Per protocol mortality reported in published paper	Intention to treat analysis possible from previous communication with authors*[12]	Placebo group had high mortality for the unit norm
Sanchez-Garcia[39]	Yes	Yes	Yes	Mortality defined secondary endpoint. Mortality reported	Intention to treat analysis performed	—
Stoutenbeek[40]	Yes	Yes	No	Mortality primary endpoint. Mortality reported	401/405 analysed	Minor baseline imbalances.
Ulrich[41]	Unclear	Yes*[12]	No	Mortality reported (incomplete)	Intention to treat analysis possible from previous communication with authors*[12]	—
Verwaest[42]	Yes	Yes	No	Mortality a defined endpoint. Mortality reported	Intention to treat analysis possible from previous communication with authors*[12]	—
Winter[43]	Yes	Yes	No	Mortality reported	Intention to treat analysis performed	—

*Information taken from Cochrane[12] or Chan[13] after their correspondence with authors.

Table 2| Methodological aspects of included trials on effect of selective oropharyngeal decontamination (SOD) for prevention of death in adults in intensive care

	Adequate sequence generation	Allocation concealment	Blinding	Outcome prespecified	Incomplete outcome data addressed	Other bias
Bergmans[44]	Unclear	Yes	Yes	Mortality defined secondary endpoint. Mortality reported	226/245 patients analysed	—
De Smet[19]	Yes	Yes	No	Study powered for mortality. Mortality reported	Adjusted 28 day mortality used: 1979/1990 in standard care; 1886/1904 in SOD	Statistical correction of baseline differences discussed
Pugin[45]	Unclear	Yes*[12]	Yes	Per protocol mortality reported in published paper	Intention to treat analysis possible from previous communication with authors*[12]	—
Rios[46]	Unclear	Unclear	Yes	Per protocol mortality reported in published paper	96/116 patients analysed	Published only in abstract form

*Information taken from Cochrane[12] or Chan[13] after their correspondence with authors.

Table 3| Methodological aspects of included trials on effect of topical oropharyngeal chlorhexidine for prevention of death in adults in intensive care

	Adequate sequence generation	Allocation concealment	Blinding	Outcome prespecified	Incomplete outcome data addressed	Other bias
Bellissimo-Rodrigues[47]	Unclear	Yes	Yes	Mortality a defined secondary endpoint. Mortality reported	194/200 patients analysed. Reasons for exclusions discussed	—
Berry[48]	Yes	Yes	No	Mortality not reported	Intention to treat data obtained from author	—
Cabov[49]	Yes	Unclear	Yes	Mortality reported	Intention to treat analysis performed	—
Fourrier 2000[50]	Yes	Unclear	Partial	Mortality reported	Intention to treat analysis performed	—
Fourrier 2005[51]	Unclear	Yes	Yes	Mortality a defined secondary endpoint. Mortality reported	Intention to treat analysis performed	Censored at 28 days
Koeman[52]	Yes	Unclear	Yes	Mortality defined secondary endpoint. Mortality reported as hazard ratio only	Intention to treat analysis possible from previous communication with authors*[13]	—
MacNaughton[53]	Unclear	Unclear	Yes	Mortality not reported	Unclear	Published only in abstract form
Munro[54]	Yes	Unclear	No	Mortality reported (subgroup of total population)	Intention to treat data obtained from author	Stopped intervention at day 7
Panchabhai[55]	Unclear	Unclear	No	Mortality a defined secondary endpoint. Per protocol mortality reported	471/512 patients analysed. Reasons for exclusions discussed	—
Scannapieco[56]	Yes	Yes	Yes	Mortality a defined secondary endpoint Mortality reported	Intention to treat data obtained from author	Censored at 21 days
Tantipong[57]	Unclear	Unclear	No	Mortality reported	Intention to treat analysis performed	—

*Information taken from Cochrane[12] or Chan[13] after their correspondence with authors.

Table 4| Other aspects of included trials on effect of selective digestive decontamination (SDD) for prevention of death in adults in intensive care

	Topical drugs	Intravenous drugs	Control group	Accrual period	Population	Place study undertaken	Projected ventilator or ICU time	Timing of outcome
Aerdts[31]	Polymyxin, Norfloxacin, Amphotericin	Cefotaxime 500 mg TDS/5 days	No antibiotic prophylaxis. 2 control groups: either penicillin or cephalosporin based therapeutic antibiotics	May 1986-Sep 1987	Mixed	Nijmegen, Netherlands	>5 days of mechanical ventilation	ICU discharge
Blair[32]	Polymyxin, Tobramycin, Amphotericin	Cefotaxime 50 mg/kg/day/4 days	Standard antibiotic therapy	Sep1988-Jan1990	Mixed, 93% ventilated	Belfast, UK	>48 hr in ICU	ICU discharge
Boland[33]	Polymyxin, Tobramycin, Nystatin	Cefotaxime/3 days	Placebo	Not specified	Multiple trauma, all ventilated	Charleston, WV, US	>5 days intubated	ICU discharge
Cockerill[34]	Polymyxin, Gentamicin, Nystatin	Cefotaxime 1 g TDS/3 days	No antibiotic prophylaxis	1986-1989	Mixed, uninfected, 85% ventilated	Rochester, MN, US	>3 days in ICU	ICU discharge
De Jonge[18]	Polymyxin, Tobramycin, Amphotericin	Cefotaxime 1 g QDS/4 days	No antibiotic prophylaxis	Sep 1999- Dec 2001	Mixed, 85% ventilated	Amsterdam, Netherlands	>48 hr of mechanical ventilation or 3 days in ICU	ICU discharge
De Smet[19]	Polymyxin, Tobramycin, Amphotericin	Cefotaxime 1 g QDS/4 days, or none.	No antibiotic prophylaxis	May 2004-July 2006	Mixed, 90% ventilated	Multiple sites (13), Netherlands	>48 hr of mechanical ventilation or 3 days in ICU	28 days
Jacobs[35]	Polymyxin, Tobramycin, Amphotericin	Cefotaxime 50 mg/kg/day/4 days	Normal management. Low gastric pH encouraged.	July 1989-Aug 1990	Mixed, 50% neurological, all ventilated	Cardiff, UK	>3 days in ICU	Unclear
Kreuger[36]	Polymyxin, Gentamicin (Vancomycin & Amphotericin)	Ciprofloxacin 400 mg BD/4 days	Placebo	2.5 yr, dates not given (published 2002)	90% surgical and trauma	2 sites, Tübingen, Germany	>48 hr in ICU	ICU discharge
Palomar[37]	Polymyxin, Tobramycin, Amphotericin	Cefotaxime 1 g TDS/4 days	No antibiotic prophylaxis	July 1989- July 1991	Mixed, uninfected	Multiple sites (10), Catalonia, Spain	>4 days of mechanical ventilation	ICU discharge
Rocha[38]	Polymyxin, Tobramycin, Amphotericin	Cefotaxime 2 g TDS/4 days	Placebo	14 months, dates not given (published 1992)	80% trauma, uninfected	La Coruna, Spain	>3 days of mechanical ventilation and > 5 days ICU stay	ICU discharge
Sanchez-Garcia[39]	Polymyxin, Gentamicin, Amphotericin	Ceftriaxone 2 g OD/3 days	Placebo	Not stated (published 1998)	Mixed, 70% medical	Multiple sites (5), Madrid, Spain	>48 hr of intubation	ICU discharge
Stoutenbeek[40]	Polymyxin, Tobramycin, Amphotericin	Cefotaxime 1 g QDS/4 days	Standard antibiotic therapy for each centre	Oct 1991-June 1994	Blunt multi trauma, all ventilated	Multiple sites (17): Europe, Australia, New Zealand	Not a criterion	ICU discharge or up to 2 weeks following ICU discharge
Ulrich[41]	Polymyxin, Norfloxacin, Amphotericin	Trimethoprim 500 mg OD/3 days	Appropriate perioperative prophylaxis	Oct 1986-Sep 1987	Mixed	Hague, Netherlands	>5 days in ICU	ICU discharge
Verwaest[42]	Ofloxacin, Amphotericin	Ofloxacin 200 mg OD/4 days	Conventional antibiotic policy	19 months, dates not given (published 1997)	75% surgical, third cardiac	Leuven, Belgium	>48 hr of mechanical ventilation	ICU discharge
Winter[43]	Polymyxin, Tobramycin, Amphotericin	Ceftazidime 50 mg/kg/day/3 days	Nothing specified	22 months, dates not given (published 1992)	Mixed	Bristol, UK	>48 hr in ICU	Hospital discharge

Table 5| Other aspects of included trials on effect of selective oropharyngeal decontamination (SOD) for prevention of death in adults in intensive care

	Topical drugs	Control group	Accrual period	Population	Place study undertaken	Projected ventilator or ICU time	Timing of outcome
Bergmans[44]	Gentamicin, Polymyxin, Vancomycin / QDS	Placebo	Sep 1994-Dec 1996	Mixed ICU, all ventilated	Multiple sites (3), Netherlands	>48 hr of mechanical ventilation	ICU discharge
Pugin[45]	Polymyxin, Neomycin, Vancomycin / 4 hourly	Placebo	Apr-Nov 1989	Surgical ICU, all ventilated	Geneva, Switzerland	>48 hr of intubation	Hospital discharge
Rios[46]	Polymyxin, Gentamicin / TDS	Placebo	Uncertain	Uncertain	Buenos Aires, Argentina	>4 days of mechanical ventilation	Unclear

Table 6| Other aspects of included trials on effect of oropharyngeal chlorhexidine for prevention of death in adults in intensive care

	Chlorhexidine	Control group	Accrual period	Population	Place study undertaken	Projected ventilator or ICU time	Timing of outcome
Bellissimo-Rodrigues[47]	0.12% solution TDS	Placebo	Mar 2006-Feb 2008	Mixed ICU, 69% ventilated	Sao Paulo, Brazil	>48 hr in ICU	ICU discharge
Berry[48]	0.2% solution BD	Either water or bicarbonate mouth rinses	Uncertain, 15 month recruitment period	Mixed ICU, 100% ventilated	Sydney, Australia	Not specified	ICU discharge
Cabov[49]	0.2% gel TDS	Placebo	Mar 2008- Dec 2008	Surgical ICU, 100% ventilated	Zagreb, Croatia	>3 days in ICU and requiring mechanical ventilation	ICU discharge
Fourrier 2000[50]	0.2% gel TDS	Bicarbonate mouth rinses	June 1997- July 1998	Mixed ICU, 100% ventilated	Lille, France	>5 days in ICU and requiring mechanical ventilation	Unclear
Fourrier 2005[51]	0.2% gel TDS	Placebo	Jan 2001-Sep 2002	Mixed ICU, 100% ventilated	Multiple sites (6), Lille, France	>5 days in ICU and requiring mechanical ventilation	28 days
Koeman[52]	2% gel QDS	Placebo	Feb 2001 - Mar 2003	Mixed ICU, 100% ventilated	Multiple sites (7), Netherlands	>48 hr of mechanical ventilation	ICU discharge
MacNaughton[53]	0.2% BD	Placebo	Uncertain	Mixed ICU, 100% ventilated	Plymouth, UK	>48 hr of mechanical ventilation	ICU discharge
Munro[54]	0.12% solution BD	Either usual care or toothbrushing groups	Uncertain	Mixed ICU, 100% ventilated	Richmond, VA, US	Not specified.	Hospital discharge
Panchabhai[55]	0.12% solution BD	0.01% potassium permanganate	Uncertain, 8 month recruitment period	Mediconeuro ICU, 171/471 ventilated	Mumbai, India	> 48 hr in ICU	ICU discharge
Scannapieco[56]	0.12% solution OD or BD	Placebo	Mar 2004-Nov 2007	Trauma ICU, 100% ventilated	Buffalo, NY, US	Not specified	21 days
Tantipong[57]	2% solution QDS	Normal saline	Jan 2006-Mar 2007	Surgical or medical ICU or general medical ward, 100% ventilated	Bangkok, Thailand	Not specified	Unclear

Table 7| **Results of meta-analyses of effect of selective digestive decontamination (SDD), selective oropharyngeal decontamination (SOD), and topical oropharyngeal chlorhexidine for prevention of death in adults in intensive care**

	OR (95% CI/CrI)	
Comparison	**Direct evidence**	**Mixed (direct and indirect) evidence**
Chlorhexidine *v* control	1.25 (1.05 to 1.50)	1.23 (0.99 to 1.49)
SDD *v* control	0.73 (0.64 to 0.84)	0.74 (0.63 to 0.86)
SOD *v* control	0.85 (0.74 to 0.97)	0.82 (0.62 to 1.02)
SDD *v* chlorhexidine	—	0.61 (0.47 to 0.78)
SOD *v* chlorhexidine	—	0.67 (0.48 to 0.91)
SDD *v* SOD	0.97 (0.79 to 1.18)	0.91 (0.70 to 1.19)

Table 8| **Probabilistic ranking of interventions and estimated probability of death in adults in intensive care treated with selective digestive decontamination (SDD), selective oropharyngeal decontamination (SOD), or topical oropharyngeal chlorhexidine**

Intervention	Rank	Estimated probability of death	Probability of intervention being best
SDD	1	0.213	0.740
SOD	2	0.228	0.260
Control	3	0.266	<0.001
Chlorhexidine	4	0.305	<0.001

Figures

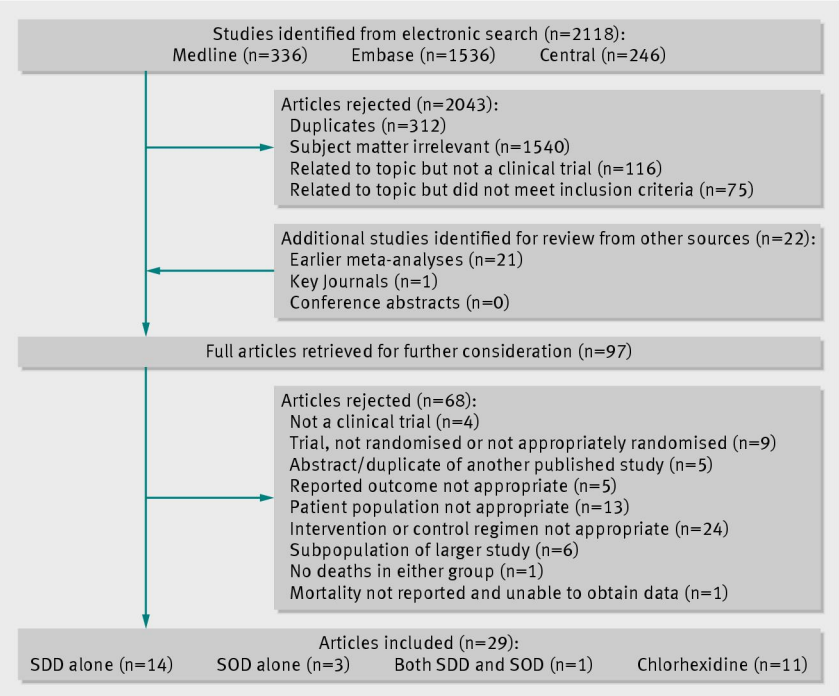

Fig 1 Inclusion of studies in analysis of effect of selective digestive decontamination (SDD), selective oropharyngeal decontamination (SOD), and topical oropharyngeal chlorhexidine for prevention of death in adults in intensive care

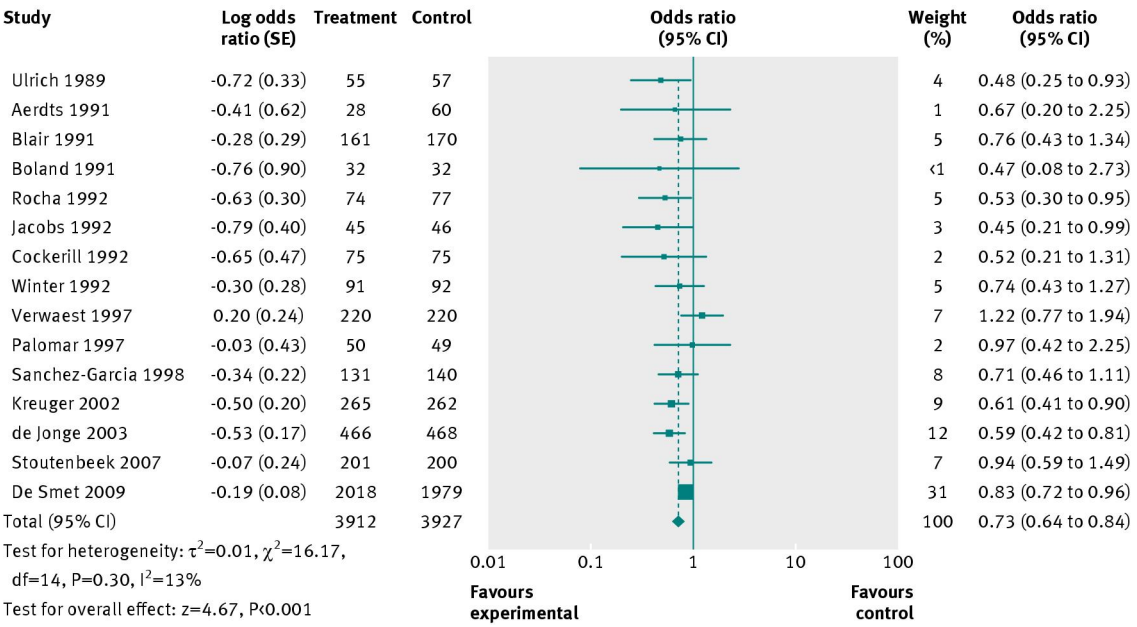

Fig 2 Forest plot of intervention-control pairwise meta-analysis of selective digestive decontamination v control in adult patients in intensive care

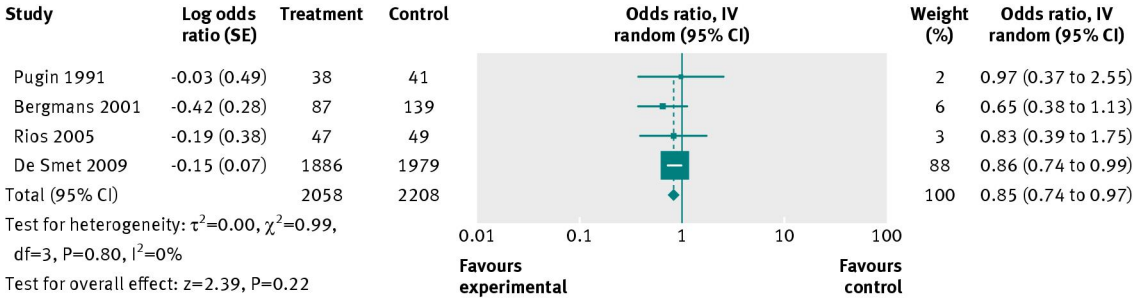

Fig 3 Forest plot of intervention-control pairwise meta-analysis of selective oropharyngeal decontamination v control in adult patients in intensive care

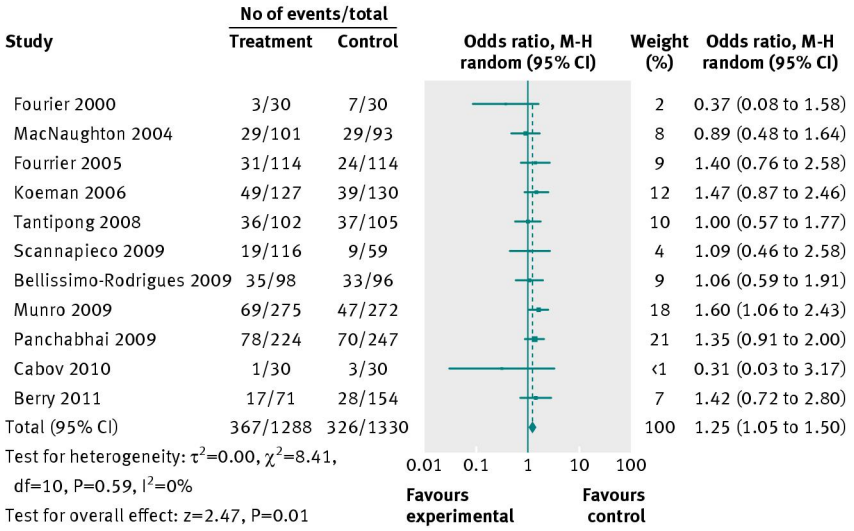

Fig 4 Forest plot of intervention-control pairwise meta-analysis of chlorhexidine v control in adult patients in intensive care