

Title: Dressing and securement for central venous access devices (CVADs): a Cochrane Systematic Review

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Contribution of the Paper

What is already known about the topic

- Central venous access devices (CVADs) play an important role in the management of patients, however they are associated with complications including bloodstream infection.
- An important strategy in the prevention of CVAD complications are the use of dressing and securement products. However there is a large range of products available from which clinicians may select, with varying levels of evidence to support clinical decision making.

What this paper adds

- Medication-impregnated dressing products reduce the incidence of CVAD-related bloodstream infections, relative to all other dressing types.
- Chlorhexidine gluconate-impregnated dressings, relative to plain polyurethane dressings, reduce the frequency of CVAD-related bloodstream infections per 1000 patient days and the risk of catheter tip colonisation. However most studies were conducted in intensive care settings.
- More high quality research is needed regarding the effectiveness of other dressing and securement products to prevent other causes of CVAD complication and failure.

Abstract:

Objectives: To compare the available dressing and securement devices for central venous access devices (CVADs).

Design: Systematic review of randomised controlled trials.

Data sources: Cochrane Wounds Group Specialised Register, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews and of Effects, NHS Economic Evaluation Database, Ovid MEDLINE, CINAHL, EMBASE, clinical trial registries and reference lists of identified trials.

Review methods: Studies evaluated the effects of dressing and securement devices for CVADs. All types of CVADs were included.

Outcome measures were CVAD-related bloodstream infection, CVAD tip colonisation, entry and exit site infection, skin colonisation, skin irritation, failed CVAD securement, dressing condition and mortality. We used standard methodological approaches as expected by The Cochrane Collaboration.

Results: We included 22 studies involving 7,436 participants comparing nine different types of securement device or dressing. All included studies were at unclear or high risk of performance bias due to the different appearances of the dressings and securement devices.

It is unclear whether there is a difference in the rate of CVAD-related bloodstream infection between securement with gauze and tape and standard polyurethane (RR 0.64, 95% CI 0.26 to 1.63, low quality evidence), or between chlorhexidine gluconate-impregnated dressings and standard polyurethane (RR 0.65, 95% CI 0.40 to 1.05, moderate quality evidence). There is high quality evidence that medication-impregnated dressings reduce the incidence of CVAD-related bloodstream infection relative to all other dressing types (RR 0.60, 95% CI 0.39 to 0.93).

There is moderate quality evidence that chlorhexidine gluconate-impregnated dressings reduce the frequency of CVAD-related bloodstream infection per 1000 patient days compared with standard polyurethane dressings (RR 0.51, 95% CI 0.33 to 0.78). There is moderate quality evidence that catheter tip colonisation is reduced with chlorhexidine gluconate-impregnated dressings compared with standard polyurethane dressings (RR 0.58, 95% CI 0.47 to 0.73), but the relative effects of gauze and tape and standard polyurethane are unclear (RR 0.95, 95% CI 0.51 to 1.77, very low quality evidence).

Conclusions: Medication-impregnated dressing products reduce the incidence of CVAD-related bloodstream infection relative to all other dressing types. There is some evidence that chlorhexidine gluconate-impregnated dressings, relative to standard polyurethane dressings, reduce CVAD-related bloodstream infection for the outcomes of frequency of infection per 1000 patient days, risk of catheter tip colonisation and possibly risk of CVAD-related bloodstream infection. Most studies were conducted in intensive care unit settings. More, high quality research is needed regarding the relative effects of dressing and securement products for CVADs.

This article is based on a Cochrane Review published in the Cochrane Database of Systematic Reviews (CDSR) 2015, Issue 9, DOI: 10.1002/14651858.CD010367 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the CDSR should be consulted for the most recent version of the review

Keywords:

Central venous catheters; catheter-related infections; occlusive dressings; vascular access devices; evidence-based practice

Introduction

Central venous access devices (CVADs)

CVADs play an important role in the management of patients, serving as reliable vascular access and the site of venous pressure monitoring. They are inserted when a patient requires venous access over an extended period of time, and allow the intravenous administration of complex drug treatments, blood products and nutritional support without the trauma associated with repeated needle insertions [1]. Although mostly used in intensive-care units and oncology settings, CVADs are increasingly being used in other wards and outpatient settings.

There are multiple types of CVADs in use throughout clinical practice. A CVAD can be designated by: its intended life span (e.g. temporary or short-term versus permanent or long-term); its site of insertion (e.g. subclavian, femoral, internal jugular or peripherally inserted central catheter) its pathway from skin to vessel (e.g. tunnelled versus non-tunnelled); its physical length (e.g. long versus short) or some other special characteristic(s) (e.g. impregnation with heparin or number of lumens) [2].

Owing to the invasive procedure necessary for inserting a CVAD and the resulting break in the skin (integument), complications such as exit-site infections and bloodstream infections can develop [3]. A serious complication of CVADs is CVAD-related blood stream infections, also known as 'catheter sepsis'. CVAD-related bloodstream infection rates are influenced by patient-related factors, such as severity and type of illness (e.g. full-thickness burns versus post-cardiac surgery), by CVAD-related factors (such as the condition under which the catheter was placed and catheter type), and by institutional factors (e.g. bed numbers, academic affiliation) [2]. Many studies have estimated the incidence of CVAD-related bloodstream infection, generally reporting a range between 1 and 3.1 per 1000 patient days [4, 5], but rates have been shown to decrease to zero after interventions [3]. The attributable cost of catheter related bloodstream infection varies between USD 3,124 and USD 60,536 per event [4, 6], and is associated with an attributable mortality of 0% to 11.5% [7].

CVADs are foreign objects, and, as such, require their external component to be both protected adequately from microbial contamination from the surrounding environment and secured to the skin. Dressings and securements must ensure CVADs do not dislodge or fall out (or both), or move within or out of the great veins. This can occur via movement or pressure on the external component of the device, through forced removal, or 'drag' from infusion tubing or 'catching' on environmental structures [8]. Movement of the CVAD to a location outside the target placement can result in line failure or cardiovascular instability. In critical situations line failure (e.g. the interruption of inotropic support during cardiogenic shock) can have catastrophic consequences for the patient's morbidity and mortality.

Dressing and securement for CVADs

There is a plethora of CVAD dressings and securements from which clinicians may select. The earliest securement approach was simple tape or gauze-tape, with plastic film dressings becoming prominent in the 1980s. First-generation occlusive standard polyurethane dressings were later developed to become semi-permeable to oxygen, carbon dioxide and water vapour (e.g. OpSite IV 3000[®], Smith and Nephew; Tegaderm Plus[®], 3M), as occlusive dressings trap moisture on the skin

and provide an ideal environment for quick growth of local microflora [9]. Each dressing is transparent, permitting continuous visual inspection of the catheter site. A recent approach to CVAD securement is the bordered polyurethane dressing that retains the clear central polyurethane component of standard polyurethane dressings with an added external adhesive border of foam or cloth fabric to maximise catheter security (e.g. Tegaderm Advanced®, 3M).

The majority of CVAD-related bloodstream infection are caused by micro-organisms found in the patient's own commensal skin flora, such as *Staphylococcus epidermidis* and *Staphylococcus aureus* [7]; consequently, we have seen the arrival of medication-impregnated dressings in recent years. The most common of these are the chlorhexidine gluconate-impregnated dressings. These chlorhexidine gluconate-impregnated dressings release chlorhexidine gluconate on the cutaneous underlying surface when placed over the catheter insertion site. Chlorhexidine gluconate is a cationic biguanide that provides rapid antiseptics because of its broad spectrum of germicidal activity against most bloodstream infection-causing pathogens [10]. The chlorhexidine gluconate impregnates the whole dressing, or is applied using an impregnated sponge (e.g. Biopatch®) and covered by a transparent polyurethane dressing. Other medication-impregnated dressings include silver-impregnated and iodine-impregnated dressings [11]. The iodine-impregnated dressings release free iodine when exposed to wound exudate, while the silver-impregnated dressings expose the entrance site to silver ions, both of which have antimicrobial properties. Some researchers recommend the use of hydrocolloidal dressings for the dressing of CVADs. This type of dressing is traditionally used on open wound sites to promote moist healing as the hydrocolloid matrix absorbs excess moisture away from the skin surface. This reduces the likelihood of microbial growth [12].

Securement of the CVAD is also facilitated by mechanisms other than dressings. Traditionally, CVADs were routinely sutured in place, prior to a dressing being applied [2]. In addition to this option, clinicians frequently reinforced the device security using non-commercial options including sterile strips or non-sterile tape. Recently, sutureless securement devices have become available commercially. These are used in addition to transparent dressings, and use a large adhesive footplate and an underlying pad with a device-locking clasp (e.g. StatLock®, Bard). These theoretically reduce movement, kinking and flow impedance, maximising catheter stabilisation [13].

Each of these CVAD dressing and securement types has different therapeutic goals and is readily available for clinicians and patients to purchase from numerous suppliers. The diversity of dressings and securements available to clinicians (including variation within each of the types discussed above) makes evidence-based decision-making difficult in this area. With the availability of increasingly sophisticated and expensive CVAD dressings and securements, practitioners need to know how effective these dressings are compared with more traditional dressings.

Role of dressing and securement to prevent CVAD failure

The ideal CVAD dressing should:

1. provide a barrier protection from colonisation and infection, preventing CVAD-related bloodstream infection;
2. provide adequate securement to prevent accidental removal, partial dislodgement and micro-motion, preventing CVAD failure;
3. be comfortable and non-irritating for the patient;
4. be easy to use; and

5. be cost-effective.

Several studies have reported the effectiveness of interventions to reduce CVAD-related bloodstream infection rates, including maximal sterile precautions during insertion, skin antisepsis, securement devices and antimicrobial catheter coatings [3, 7, 14]. The role of the CVAD dressing in preventing CVAD-related bloodstream infection is to provide a barrier protection, thereby preventing migration of skin organisms at the insertion site into the cutaneous catheter tract - and subsequent colonisation of the CVAD tip - and preventing direct contamination of the CVAD by contact with hands and other materials [2].

Significance

Decreasing the incidence of CVAD-related bloodstream infection and preventing CVAD failure are important objectives with a significant impact on patient morbidity and mortality, yet there is no consensus on the optimal dressing type to use with CVADs, despite more than two decades of research and debate. The previous Cochrane review "Gauze and tape and polyurethane dressings for central venous catheter" focused on only two product types [1], and, therefore, does not adequately address the variety of products now available in the clinical environment. A large variety of dressings and types of securement are currently available for use with CVADs, as well as reports from many research studies that used different outcomes and comparisons.

To compare the available dressings and securement devices for CVADs, in terms of catheter-related bloodstream infection, catheter colonisation, entry- and exit-site infection, skin colonisation, skin irritation, failed catheter securement, dressing condition and mortality.

Methods

The Cochrane systematic review protocol was registered and published prior to review commencement[15].

Eligibility criteria

We included all randomised controlled trials (RCTs) that evaluated the effects of CVAD dressings and securement devices for their impact on catheter-related bloodstream infection, catheter colonisation, entry- and exit-site infection, skin colonisation, skin irritation, catheter security, dressing condition or mortality, irrespective of publication status or language. We would have included controlled clinical trials only in the absence of RCTs. Controlled clinical trials are studies in which the trial involves testing an intervention and a control, with concurrent enrolment and follow-up of test and control-treated groups, but the method of allocation is not considered to be strictly random [16]. We also excluded cross-over and cluster randomised trials in order to minimise potential bias in accordance with [17]

We included any person of any age requiring a CVAD in any healthcare or community setting. All CVADs were included, i.e. short- and long-term CVADs, tunnelled and non-tunnelled, port-a-caths, haemodialysis catheters, and peripherally-inserted central catheters. For studies that included other types of vascular catheter, only data pertaining to CVADs were included. We included trials comparing any CVAD dressings or securements.

Primary and secondary outcome measures are described in Table 1.

Table 1: Primary and secondary outcomes

Primary outcome

- 1) Incidence of CVAD-related blood stream infection: as defined by one of the following three criteria:
 - a) Primary bacteraemia/fungaemia with at least one positive blood culture from a peripheral vein with no other identifiable source for the bloodstream infection other than the CVAD, plus, one of: a positive semiquantitative (> 15 colony-forming units) or quantitative ($> 10^3$ colony forming units) device culture, with the same organism (species and antibiogram) isolated from the device and blood [18, 19].
 - b) Two blood cultures (one from an CVAD hub and one from a peripheral vein), that both meet the CVAD- related bloodstream infection criteria for quantitative blood cultures (three-fold greater colony count of growth for the same organism as from the peripheral blood), or differential time to positivity (growth of the same microbe from hub drawn blood at least two hours before growth from the peripheral blood) [20].
 - c) Two quantitative blood cultures of samples obtained through two CVAD lumens in which the colony count for the blood sample drawn through one lumen is at least three-fold greater than the colony count for the blood sample from the second lumen [20].

Secondary outcomes

- 2) Frequency of CVAD-related bloodstream infection per 1000 patient days: CVAD-related bloodstream infection as previously defined.
- 3) Incidence of CVAD tip colonisation: positive semi-quantitative (> 15 colony forming units/catheter segment) or quantitative ($> 10^3$ colony forming units/catheter segment) culture from a proximal or distal catheter segment [18].
- 4) Incidence of entry and exit site infection: as described by the trial investigator.
- 5) Incidence of skin/site colonisation: positive semi-quantitative (>15 colony forming units) or quantitative ($>10^3$ colony forming units) culture from the skin around the CVAD site [18].
- 6) Incidence of skin irritation or damage: as described by the study investigator using a formal assessment tool.
- 7) Incidence of failed CVAD securement: frequency of accidental or forced removal or dislocation resulting in CVAD failure.
- 8) Dressing condition/durability: incidence or mean score using a formal assessment tool.
- 9) Mortality from any cause.

CVAD= Central venous access device

Studies must have reported at least one pre-specified outcome, in accordance with these definitions, in order to be included in this systematic review.

Identification of studies

We searched the Cochrane Wounds Group Specialised Register (5 June 2015); the Cochrane Central Register of Controlled Trials (The Cochrane Library 2015, Issue 6); the Database of Abstracts of Reviews of Effects (The Cochrane Library 2015, Issue 6); NHS Economic Evaluation Database (*The Cochrane Library* 2015, Issue 6); Ovid MEDLINE (1946 to June 04, 2015); Ovid MEDLINE (In-Process & Other Non-Indexed Citations, June 04, 2015); Ovid EMBASE (1974 to June 04, 2015); EBSCO CINAHL

(1982 to June 04, 2015). The search strategy used in Cochrane Central Register of Controlled Trials can be found on Supplementary Table 1

We adapted this strategy to search Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL. We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) [16]. We combined the EMBASE search with the Ovid EMBASE filter developed by the UK Cochrane Centre [16]. We combined the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network [21]. There were no restrictions on the basis of date, study setting, language or publication status. We also searched clinical trial registers. We hand-searched bibliographies of all retrieved and relevant publications identified by these strategies for further relevant studies. We contacted experts in the field to ask for information relevant to this review. We also contacted dressing and securement device manufacturers for unpublished data in order to counteract publication bias.

Study screening

Independently, two review authors (AU and MM) assessed titles and abstracts of retrieved studies for relevance. After this initial assessment, we retrieved full versions of all potentially eligible studies. Independently, the same two review authors checked the full papers for eligibility. We resolved discrepancies between review authors through discussion and, where required, consulted a third independent review author (CR). For transparency we have published a summary of the selection of studies, including excluded studies and reasons for exclusion, using the PRISMA flowchart [22]

Data extraction

We extracted details from eligible studies and summarised them using a data extraction sheet. Due to the large number of studies included in this review, teams of two review authors reviewed specific interventions including: chlorhexidine gluconate-impregnated dressing studies, gauze studies, sutureless securement devices studies, paediatric and neonatal studies, and the remaining studies. These teams extracted data independently, which were cross-checked for accuracy and agreed upon. We resolved any discrepancies through discussion and arbitration by a third review author, when necessary. For studies that were published in duplicate, we extracted maximal data from all relevant publications, but we did not duplicate data in analyses. When there were any data missing from the papers, we attempted to contact the trial authors to retrieve them.

We used a data extraction sheet to extract summary data from each trial. The data extraction sheet contained baseline characteristics of the study participants: their number; age; gender; disease; treatment; type of CVAD; dressing or securement, or both; number of dressing changes during the dwell time of the CVAD; and healthcare setting in which the intervention occurred. We listed each trial's criteria for participant inclusion and exclusion, a description of the intervention(s), the number of people randomised to each intervention, and primary and secondary outcome measures.

Assessment of risk of bias in included studies

Each eligible study was independently assessed for methodological quality and bias using the Cochrane Collaboration 'Risk of bias' assessment tool. This tool addresses six specific domains, namely, sequence generation, allocation and concealment, blinding of participants/care providers, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, as well as other issues that potentially may bias the study [23]. In accordance with Higgins, Altman [23], assessment for 'other' bias concerned baseline balance between treatment groups, early cessation of the trials and commercial sponsorship. We have completed a 'Risk of bias' table for each eligible study and outcome using the categories of 'low', 'high' or 'unclear' risk of bias. The criteria for judging risk of bias assessments (i.e. categories of low, high or unclear) were made in accordance with recommendations in Higgins, Altman [23]. Assessment of risk of bias is discussed within the text and the judgements are presented as a 'Risk of bias' summary figure, which cross-tabulates judgements by study. Together these tools have been used to assess overall risk of bias, in combination with the "Grading of Recommendations Assessment, Development and Evaluation" approach [24]. The "Grading of Recommendations Assessment, Development and Evaluation" approach assesses the quality of evidence per comparison and outcome throughout five factors: risk of bias, indirectness of the population, interventions and outcomes, inconsistency amongst studies, imprecision (including information size and confidence intervals) and publication bias.

We undertook data extraction for risk of bias from the included studies using the same approach explained above in Data extraction and management. We extracted and summarised data using a data extraction sheet. Teams of two review authors reviewed specific interventions, extracted data independently and cross-checked the data for accuracy and agreement. We resolved any discrepancies through discussion and arbitration by a third review author, when necessary. We contacted trial authors if data pertaining to risk of bias was missing, including protocol-based assessments of selective outcome reporting. The review authors searched trial registries, as previously described, to identify research protocols to enable assessment for selective outcome reporting.

Data analysis

Our primary analysis involves pair-wise comparisons of treatment effect between dressing and securement types, using all the described outcomes. For dichotomous outcomes, we have calculated risk ratio (RR) plus 95% confidence intervals (CI). For the outcome best presented as a rate-per-time-period (i.e. CVAD related bloodstream infection per 1000 patient days), we have used rate ratios (RaR) and standard errors (SE) to inform inverse-variance analysis. This analysis required the provision of patient days per intervention group. As CVADs are inserted for variable durations, the rate of CVAD-related bloodstream infection per 1000 patient days was used to describe the variable frequency of CVAD-related bloodstream infection across the catheter duration between the CVAD securement and dressing options. A meta-analysis was undertaken if more than one study used the same intervention and reported the same outcome.

In addition to the main pair-wise analysis described above, in order to inform clinical decision-making we planned to undertake pair-wise comparisons using the 'clustering' of interventions on the basis of patient treatment goals and outcomes. These clustering comparisons were done because of the heterogeneity of populations that use CVADs, and the way their goals for treatment differ. In

order to minimise bias, these clustering comparisons were identified prior to undertaking the analyses.

The majority of the included RCTs randomized participants and not their CVADs. Two studies [25, 26] recruited participants multiple times for multiple CVADs. Cross-over and cluster-randomized trials were not included. Carrer, Bocchi [25] recruited 82 participants with 107 CVADs; Chambers, Sanders [26] recruited 95 participants with 114 CVADs. These studies falsely assumed independence of the CVADs, which provides a potential risk of bias. For the current review, attempts were made to contact the study authors in order to obtain the results for one CVAD per participant, but these data were not available. For these studies, data involving CVADs as the unit of analysis were included. Future updates of this review will incorporate studies that used CVADs as the unit of analysis, rather than participants, in a sensitivity analysis to examine for potential risk of bias.

In accordance with Higgins, Altman [23], for included studies that involved the comparison of multiple interventions using a single control, we split the 'shared' control group to avoid additional unit of analysis issues. We did this to distribute the appropriate study weight and maintain independent comparisons fairly.

When there was evidence of missing data, attempts were made to contact the study authors to request the missing information. When after several attempts to contact the author the missing data were not provided we analysed the available data only. We emailed the authors of ten included studies to ask for further information and clarification of key aspects of their study methods and results. Study authors from seven of the ten trials responded [12, 14, 27-31], with four authors able to provide all information required [14, 27, 30, 31]. We have also addressed the potential impact of the missing data on the findings of the review in the Discussion.

Loss to follow-up and attrition data were adequate and well described by ten studies [10, 26, 29-36]. Five studies had high levels of attrition and loss to follow-up [12, 14, 25, 37, 38]. The remaining seven studies provided inadequate information regarding loss to follow-up and attrition for us to assess for bias [11, 13, 27, 28, 39-41].

A random-effects model was used for data synthesis because of predicted clinical heterogeneity. We have considered clinical, methodological and statistical heterogeneity and undertook an assessment of comparability of the studies prior to meta-analysis. We investigated the degree of statistical heterogeneity, that is, variation between the true intervention effects underlying the different studies, by a combination of methods. This involved visual inspection of the meta-analytic model and interpretation of the Chi^2 and I^2 statistics that examine the total variance across studies due to heterogeneity rather than chance [42].

We have reported each outcome separately. We have used funnel plots to assess reporting biases for the main analysis [43]. Any asymmetry of the funnel plot may indicate possible publication bias.

Initially we conducted a structured narrative summary of the studies included in the review. We entered quantitative data into Review Manager 5.3 and analysed them using Review Manager analysis software. We pooled data for meta-analysis using Review Manager 5.3, and used a random-effects model because of the clinical heterogeneity.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses for the primary outcomes, but were unable to complete them due to insufficient data within each pair-wise comparison.

- Adult participants versus paediatric participants versus neonatal participants.
- Participants diagnosed with haematology/oncology conditions versus other participants.
- CVAD type (tunnelled versus non-tunnelled, short-term versus long-term, dialysis versus non-dialysis, peripherally inserted central catheter versus centrally-inserted CVAD).
- Participants receiving the intervention in an acute versus a community setting.
- Participants receiving lipid and parenteral nutrition versus patients not receiving lipid and parenteral nutrition.

Sensitivity analysis

We planned to perform a sensitivity analysis by excluding studies as indicated by the results of the final meta-analysis. This would have involved the exclusion of the studies of the lowest quality. We planned to only include studies that were assessed as having a low risk of bias in all key domains, namely adequate generation of the randomisation sequence, adequate allocation concealment, and blinding of outcome assessor, for the estimates of treatment effect. We were unable to perform the analyses on CVAD-related bloodstream infection, as we were not able to delineate the risk of bias within the included studies due to incomplete information. There were insufficient studies in the other comparisons to permit a meaningful analysis on the remaining intervention comparisons.

Results

Search results

The results of the search and selection of studies are summarised in the PRISMA study flow diagram (Figure 1). The search of electronic bibliographic databases identified 415 records, 69 of which were duplicates. Searches of clinical trial registries did not identify additional studies, but the hand-searching of bibliographies identified three studies for potential inclusion. Of the 349 titles screened, 305 were excluded. We screened 44 full-text articles for potential inclusion, and excluded 21 (see supplementary table 2). We identified four studies which we have not yet retrieved in full text or are awaiting information from the trial authors [44-47].

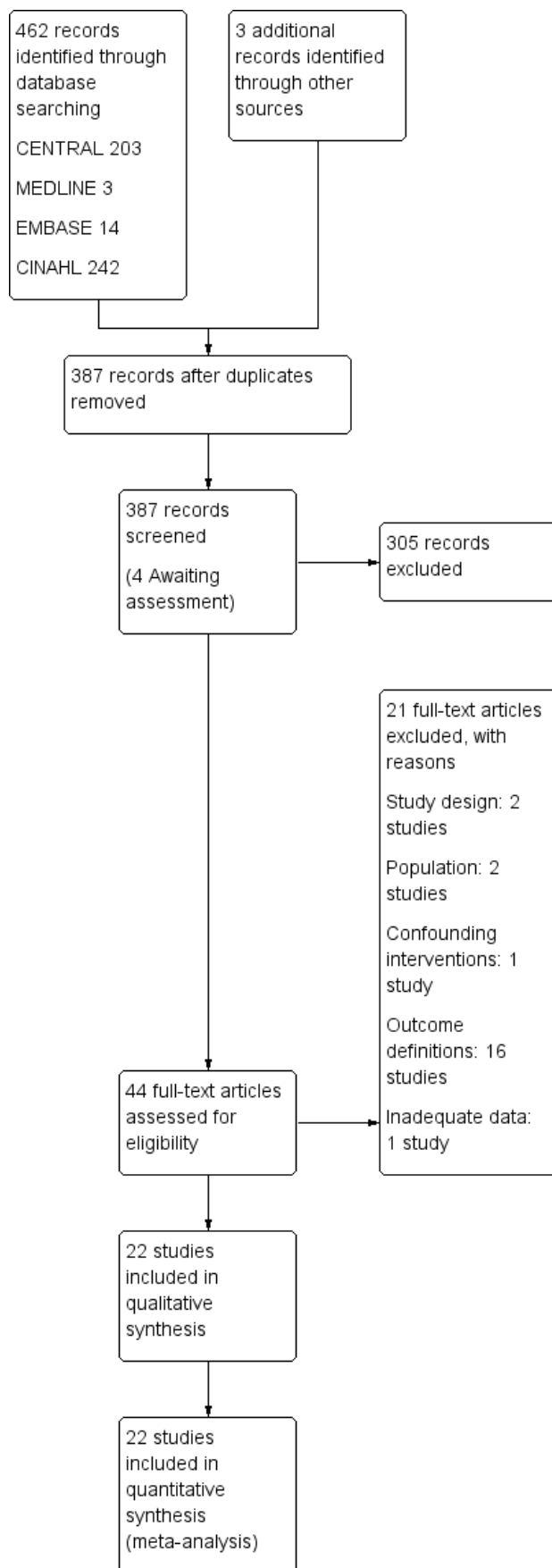


Figure 1 PRISMA flow chart of study selection process

Included studies

The 22 included studies, with a total of 7,436 participants, are described in Table 2. The studies were RCTs conducted in 25 countries, including the USA (five studies), Canada (three studies), France and Australia (two studies each), Greece, Italy, New Zealand, Spain, Turkey, Sweden, Israel, Brazil, Germany and the Netherlands (one study each).

Table 2: Key characteristics of included studies

Author	Methods	Participants	Interventions	Outcomes	Notes
Arvanati, Lathyris [32]	RCT in 5 Intensive Care Units in Greece	306 participants admitted to Intensive Care Units requiring a multilumen CVAD <i>Inclusion criteria:</i> CVAD predicted to stay in Intensive Care Unit patient for ≥ 3 days; first CVAD in Intensive Care Unit <i>Exclusion criteria:</i> < 18 years; neutropenic patients; pregnant women; patients with an expected Intensive Care Unit stay of < 3 days; known allergy to silver or chlorhexidine	Group I: standard polyurethane changed every 3 days or sooner if spoiled or contaminated Group II: standard polyurethane and a chlorhexidine-impregnated sponge (Biopatch™) changed every 7 days Both groups had sterile gauze over the entry site for the first 24 hours	CVAD-related bloodstream infection; Catheter-tip colonisation; Failed catheter security; Mortality	Group III: Additional 159 participants not included in the review: silver-impregnated CVAD (Oligon™) due to co-intervention
Brandt, DePalma [33]	RCT in the USA	101 participants undergoing autologous bone marrow transplant with newly inserted long-term triple-lumen, tunnelled Hickman™ CVADs <i>Inclusion criteria:</i> > 18 years old; alert, orientated, able to give informed consent; admitted to the bone marrow transplant unit for autologous bone marrow transplant; surgical insertion of a long-term CVAD in the operating room <i>Exclusion criteria:</i> pre-existing bacteraemia or fungaemia within 14 days of study entry; CVAD placement was intended to be short-term	Group I: standard polyurethane (Opsite 3000™; Smith and Nephew) moisture vapour permeable dressing changed every 7 days Group II: sterile gauze with tape changed daily	CVAD-related bloodstream infection; Entry- and exit-site infection; Failed catheter security	Dressing condition/durability reported: did not use a tool with established validity and reliability
Carrer,	Randomised,	82 participants admitted to a	Group I: gauze and tape with low sterile	Skin/site	

Bocchi [25]	factorial controlled trial in a single Italian Intensive Care Unit	medical-surgical Intensive Care Unit <i>Inclusion criteria:</i> non-tunnelled CVAD; predicted dwell time of > 72 hours <i>Exclusion criteria:</i> not reported	barrier Group II: transparent standard polyurethane with low sterile barrier Group III: gauze and tape with maximum sterile barrier Group IV: standard polyurethane with maximum sterile barrier For the purposes of the review: Groups I and III (gauze) were combined and Groups II and IV (standard polyurethane) were combined	colonisation	
Chambers, Sanders [26]	RCT in a single site in New Zealand	95 participants admitted to a haematology unit <i>Inclusion criteria:</i> admitted to a haematology unit and undergoing chemotherapy tunnelled, cuffed CVAD; adult <i>Exclusion criteria:</i> unable to give informed consent; known allergy to chlorhexidine	Group I: no dressing Group II: chlorhexidine gluconate-impregnated dressings consisting of a 2.5 cm hydrophilic polyurethane foam disk containing chlorhexidine gluconate in a sustained-release formulation, with a standard polyurethane (Opsite IV3000™), changed weekly or as needed until catheter removal Both groups had sterile gauze and standard polyurethane applied until the exit site was dry and free from exudate	CVAD-related bloodstream infection; Entry- and exit-site infection; Mortality	Patients recruited more than once: CVAD unit of analysis
Conly, Grieves [37]	RCT in a single site in Canada	79 participants admitted to medical, surgical, paediatric or Intensive Care Unit <i>Inclusion criteria:</i> admitted to any medical, surgical or paediatric ward or Intensive Care Unit CVAD inserted for a duration ≥ 3 days <i>Exclusion criteria:</i> CVADs for short term haemodynamic monitoring	Group I: dry gauze and tape Group II: standard polyurethane (Opsite™) A pressure dressing was allowed for the first 24-48 hours for both groups	CVAD-related bloodstream infection; Catheter tip colonisation	

de Barros, Arenas [27]	RCT in Spain	66 participants with long-term CVADs for haemodialysis <i>Inclusion criteria:</i> internal jugular CVAD for haemodialysis treatment inserted by nephrologists; end-stage renal disease <i>Exclusion criteria:</i> acute renal failure undergoing dialysis via a femoral CVAD	Group I: standard polyurethane (Tegaderm™) changed every 7 days or as needed Group II: sterile gauze with tape changed at each dialysis session	CVAD-related bloodstream infection; Catheter tip colonisation; Failed catheter security
Garland, Alex [10]	RCT in 6 neonatal Intensive Care Units in the USA	705 participants admitted to a neonatal Intensive Care Unit would likely require a CVAD for at least 48 hours percutaneous and surgically inserted <i>Exclusion criteria:</i> not clearly reported. Changed after 15 months of study recruitment related to adverse reactions; infants < 26 weeks who required a CVAD before 1 week of age were excluded	Group I: standard polyurethane cleansed with 10% povidone iodine. Percutaneous CVAD dressings were changed every 7 days, surgically inserted CVAD dressings were changed twice weekly Group II: chlorhexidine gluconate-impregnated dressing (Biopatch™) with 250 µg/mg of chlorhexidine gluconate and standard polyurethane. Cleansed with 70% isopropyl. Both percutaneous and surgically inserted CVAD dressings were changed weekly	CVAD-related bloodstream infection; Catheter-tip colonisation; Skin irritation or damage
Giles, Aksoy [34]	RCT in a general surgery department in Turkey	72 participants with single-lumen polyurethane CVADs inserted pre-operatively <i>Inclusion criteria:</i> not clearly outlined. "patients undergoing surgical procedures for various benign or malignant gastrointestinal disorders" (p 256) and "the aims of CVC	Group I: transparent occlusive dressing changed every 7 days unless signs of local inflammation Group II: sterile gauze changed daily and insertion site cleaned by 10% povidone-iodine solution	CVAD-related bloodstream infection; catheter tip colonisation; skin/site colonisation

		insertion were either for monitoring or TPN administration" (p 256) <i>Exclusion criteria:</i> not reported			
Hagerstrom, Matthiesen [39]	RCT in Sweden in 2 dialysis units	14 participants with long-term CVADs for haemodialysis <i>Inclusion criteria:</i> requiring haemodialysis treatment for renal insufficiency <i>Exclusion criteria:</i> not reported	Group I: standard polyurethane (OpSite IV3000™) changed after haemodialysis procedure (approximately twice/week) Group II: sterile gauze with tape changed after haemodialysis procedure (approximately twice/week)	CVAD-related bloodstream infection	
Hill, Baldwin [40]	RCT in a neonatal Intensive Care Unit in the USA	100 participants admitted to a neonatal Intensive Care Unit <i>Inclusion criteria:</i> admitted to neonatal Intensive Care Unit for at least 72 hours; requiring a peripherally inserted central catheter to be placed <i>Exclusion criteria:</i> CVAD <i>in situ</i> , pre-existing skin condition or discolouration	Group I: standard polyurethane (Tegaderm™). Dressings changed every 3 weeks, unless otherwise indicated Group II: silver-impregnated dressing (Algidex Ag IV PATCH™) secured with a sterile strip. The patch, extraluminal catheter and exit site were then covered with a standard polyurethane dressing (Tegaderm™). Dressings changed every 2 weeks, unless otherwise indicated	Skin irritation or damage: signs of redness, swelling or discolouration Mortality	CVAD-related bloodstream infection was a secondary outcome of study, but was not defined
Le Corre, Delorme [38]	RCT in Canada	58 participants with long-term CVADs for haemodialysis <i>Inclusion criteria:</i> > 18 years old; requiring haemodialysis treatment for chronic terminal renal insufficiency; tunnelled jugular CVAD inserted by vascular radiologist; competent to provide informed consent <i>Exclusion criteria:</i> receiving systemic antibiotic therapy; history of bacteraemia within previous 3 months without	Group I: standard polyurethane (Tegaderm™) changed every 7 days Group II: sterile gauze with tape changed every 2-3 days	CVAD-related bloodstream infection	

change of CVAD					
Levy, Katz [14]	RCT in a single paediatric cardiac Intensive Care Unit in Israel	145 participants admitted to the paediatric cardiac Intensive Care Unit <i>Inclusion criteria:</i> 0-18 years age; require a CVAD for > 48 hours; inserted in an operating theatre by an anaesthetic specialist <i>Exclusion criteria:</i> not reported	Group I: standard polyurethane (Tegaderm™) only changed when required Group II: chlorhexidine gluconate-impregnated (Biopatch™) and standard polyurethane only changed when required	Catheter tip colonisation; Skin irritation or damage:	CVAD-related bloodstream infection: data collected as a secondary outcome, but study definition did not match review definition
Nikoletti, Leslie [12]	RCT in an adult Intensive Care Unit in Australia	150 participants with CVADs inserted in Intensive Care Unit <i>Inclusion criteria:</i> ≥ 18 years old; insertion of a multilumen CVAD in Intensive Care Unit <i>Exclusion criteria:</i> CVAD inserted for < 24 hours; inserted outside IC; inserted via guidewire exchange; tunnelled or implanted CVADs	Group I: standard polyurethane (Tegaderm™) changed every 5 days or earlier if soiled or non-adherent Group II: hydrocolloid dressing (Comfeel™) changed every 5 days or earlier if soiled or non-adherent	Catheter-tip colonisation	CVAD-related bloodstream infection and skin colonisation outcomes were described, but did not meet the review's outcome definition
Olson, Rennie [28]	RCT in an inpatient and outpatient oncology setting in Canada	78 participants undergoing treatment for cancer <i>Inclusion criteria:</i> 18-75 years old; life expectancies of 6 months or more; receiving their first CVAD; double or triple lumen CVAD; available for follow-up; visually and cognitively competent; able to read and write English <i>Exclusion criteria:</i> not stated	Group I: sterile gauze dressing, changed daily if neutropenic or every second day if not neutropenic; cleansed with 4% chlorhexidine in 70% alcohol Group II: no dressing Both groups were treated as if in Group I until day 21 post CVAD insertion, when they were randomised	CVAD-related bloodstream infection	
Pedrolo, Danski [35]	RCT in Brazil	21 participants admitted to Intensive Care Unit <i>Inclusion criteria:</i> > 18 years; non-	Group I: standard polyurethane (Tegaderm™) changed every 7 days or when exudate or displacement made it	CVAD-related bloodstream infection;	

		tunnelled CVADs; recruited within 24 hours of Intensive Care Unit admission or 8 hours of CVAD insertion <i>Exclusion criteria:</i> not reported	necessary Group II: sterile gauze with tape changed daily	Catheter tip colonisation; Dressing condition durability; Skin irritation or damage	
Roberts and Cheung [41]	RCT in a single Intensive Care Unit in Australia	33 participants admitted to Intensive Care Unit <i>Inclusion criteria:</i> CVADs inserted in Intensive Care Unit <i>Exclusion criteria:</i> not reported	Group I: standard polyurethane (Opsite IV3000™), changed and cleansed with 0.5% chlorhexidine in 70% alcohol every 5 days and as necessary Group II: chlorhexidine gluconate-impregnated dressing (Biopatch™) with standard polyurethane (Opsite IV3000™), changed and cleansed with 0.5% chlorhexidine in 70% alcohol every 5 days and as necessary	Catheter tip colonisation; Exit-site infection	Participants could be recruited more than once. Unit of analysis was the CVAD not the participant
Ruschulte, Franke [36]	RCT in Germany	601 participants with haematological and oncological conditions <i>Inclusion criteria:</i> triple lumen, jugular or subclavian CVADs, inserted by anaesthetic consultants; undergoing chemotherapy for treatment of haematological and oncological conditions <i>Exclusion criteria:</i> expected admission for ≤ 5 days; previous reaction to chlorhexidine	Group I: standard polyurethane changed regularly after 7 days or if they had been lifted Group II: chlorhexidine gluconate-impregnated dressing (Biopatch™) with standard polyurethane. Changed regularly after 7 days or if they had been lifted	CVAD-related bloodstream infection	
Shivnan, McGuire [29]	RCT in the USA	98 participants undergoing autologous or allogenic bone marrow transplant with pre-existing or newly inserted right	Group I: standard polyurethane (Tegaderm™) changed every 4 days Group II: sterile gauze with tape changed daily	CVAD-related bloodstream infection; Entry- and exit-site	

		atrial CVADs <i>Inclusion criteria:</i> 2-60 years old; haematologic malignancy or immune-deficiency disease; pre-existing or newly inserted right atrial CVAD; admitted to the bone marrow transplant unit for autologous or allogenic bone marrow transplant <i>Exclusion criteria:</i> not described	Both groups received gauze for the first 24 hours	infection; Skin/site colonisation	
Timsit, Schwebel [30]	RCT in France	2051 participants in Intensive Care Unit s <i>Inclusion criteria:</i> CVADs or arterial catheters for > 48 hours; > 18 years <i>Exclusion criteria:</i> peripherally inserted central catheter; pulmonary arterial catheters; haemodialysis catheters; allergy to study products	Group I: standard polyurethane dressing (Tegaderm™) changed every 3 or 7 days Group II: chlorhexidine gluconate-impregnated sponge dressing (BioPatch™) with standard polyurethane changed every 3 or 7 days	CVAD-related bloodstream infection; Catheter tip colonisation	Published manuscript includes arterial lines; additional information provided to report CVAD-only results
Timsit, Mimoz [31]	RCT in France	1879 participants in Intensive Care Unit s <i>Inclusion criteria:</i> CVADs or arterial catheters for > 48 hours; > 18 years <i>Exclusion criteria:</i> peripherally inserted central catheter; pulmonary arterial catheters; haemodialysis catheters; allergy to study products; catheters inserted before Intensive Care Unit admission	Group I: standard polyurethane dressing (Tegaderm™) Group II: chlorhexidine gluconate-impregnated dressing (Tegaderm CHG IV Securement Dressing™) Group III: highly adhesive transparent dressing (Tegaderm HP Transparent™)	CVAD-related bloodstream infection; Catheter tip colonisation	Published manuscript includes arterial lines; additional information provided to report CVAD-only results
Wille, Blusse	RCT in the	101 adult participants requiring a	Group I: standard polyurethane (OpSite™)	CVAD-related	

van Oud Alblas [11]	Netherlands	subclavian or jugular CVAD <i>Inclusion criteria:</i> age > 16 years; hospitalised for major elective surgery <i>Exclusion criteria:</i> not stated	with moisture vapour permeability of 800 g m ⁻² . Changed regularly every 3 days. Group II: new generation standard polyurethane (OpSite IV3000™) with increased moisture vapour permeability (2000 g m ⁻²). Dressing changed every 3 days	bloodstream infection
Yamamoto, Solomon [13]	RCT in the USA	170 adult participants requiring a peripherally inserted central catheter <i>Inclusion criteria:</i> not stated <i>Exclusion criteria:</i> not stated	Group I: securement via 2.0 prolene sutures and standard polyurethane dressing. Changed regularly every 3 days or more frequently if necessary Group II: securement via a sutureless securement devices (StatLock™) and standard polyurethane. Dressing changed every 3 days, sutureless securement device every 6 days When participant discharged home, dressings changed weekly	CVAD-related bloodstream infection; Skin irritation or damage; Failed catheter securement

CVAD = Central venous access device; RCT= Randomised controlled trial

Studies were undertaken in Intensive Care Units [10, 12, 14, 25, 30-32, 35, 40, 41], oncology and haematology units [26, 28, 29, 36], including bone marrow transplantation units [33], haemodialysis centres [27, 38, 39], general surgical units [11, 13, 34] and throughout the hospital [37]. One study [38] continued to study participants after discharge from acute care. Eleven studies restricted participation to adults [11-13, 26, 28, 30-33, 35, 38]; one study to paediatric participants [14]; two studies to neonates [10, 40]; while two studies had a combination adults and children [29, 37]. The age of participants was not described in six studies [25, 27, 34, 36, 39, 41]. The types of CVADs studied were restricted to tunnelled CVAD in four studies [26, 33, 38, 39], non-tunnelled, percutaneous CVAD in six studies [12, 14, 25, 35, 36, 41], peripherally inserted central catheters in two studies [13, 40], and a combination of CVAD types in four studies [10, 30, 31, 37]. The type of CVAD was not described in six studies [11, 27-29, 32, 34].

As expected, the studies included many different interventions and comparisons. Researchers compared:

- sterile gauze with standard polyurethane in nine studies [25, 27, 29, 33-35, 37-39];
- standard polyurethane and chlorhexidine gluconate-impregnated dressings in six studies [10, 14, 30, 32, 36, 41];
- standard polyurethane and silver-impregnated dressings in one study [40];
- standard polyurethane and hydrocolloidal dressing in one study [12];
- second generation gaseous permeability standard polyurethane with first generation standard polyurethane (old generation standard polyurethane) in one study [11];
- standard polyurethane, highly adhesive transparent dressings with chlorhexidine gluconate-impregnated dressings in one study [31]
- standard polyurethane and sutureless securement devices in one study [13];
- sterile gauze with no dressing in one study [28]; and
- Chlorhexidine gluconate-impregnated with no dressing in one study [26].

There was variability in the reporting of outcomes. Our primary outcome of CVAD-related bloodstream infection was reported by 17 studies [10, 11, 13, 26-39]. Each of these studies defined the outcome of CVAD-related bloodstream infection in accordance with the definition of our review. Several other studies reported CVAD infection or sepsis, but did not meet the definition as described in our protocol; these studies are described in Appendix 4: Characteristics of excluded studies.

Eight studies reported the patient day information required for our secondary outcome of 'frequency of CVAD-related bloodstream infection per 1,000 patient days' [11, 13, 26, 30-32, 36, 38]. We attempted to contact the remaining eight study authors, one provided patient day information [27], two were unable to locate the data [28, 29], two did not respond [10, 35] and contact information could not be found for the remaining three [33, 34, 39].

The remaining secondary outcomes were reported inconsistently. Twelve studies [10, 12, 14, 25, 27, 30-32, 34, 35, 37, 41] reported the incidence of CVAD tip colonisation as per our protocol definitions. Two studies reported the incidence of skin or site colonisation as per our protocol definitions [29, 34]. The incidence of entry and exit site infection was reported by four studies [26, 29, 33, 41], skin irritation or damage was reported by five studies [10, 13, 14, 35, 40]; incidence of failed CVAD security by four studies [13, 27, 32, 33] and mortality from any cause by four studies [26, 32, 35, 40].

The incidence of dressing durability or condition was assessed using an a priori definition by one study [35] however no studies reported a mean score for dressing condition or durability using a formal assessment tool.

Due to the small number of studies that reported each outcome, clustering comparisons were only undertaken for catheter-related bloodstream infection, and medication-impregnated dressings (chlorhexidine gluconate, povidone-iodine and silver-impregnated) versus non-impregnated dressings (standard polyurethane, bordered polyurethane, gauze and tape, hydrocolloid).

Methodological quality of studies

There was no evidence of funnel plot asymmetry to indicate potential reporting bias in the included studies (see Supplementary Figure 1). We judged that the majority of the studies had an unclear risk of bias for most criteria; Supplementary Figure 2 presents the overall risk of bias. We did not downgrade the quality of the evidence for unclear risk of bias

Nine of the 22 included studies described an adequate method of sequence generation [10, 12-14, 28, 30-32, 38]. An adequate method of allocation concealment was reported in only two of the studies [10, 13]. No study blinded personnel or participants, as this is not achievable due to the visibility of the intervention. Only six studies blinded the outcome assessor [12, 27, 30-32, 36]. Five studies provided incomplete outcome data with high percentages of undescribed attrition and loss-to-follow up [14, 25, 37, 38, 41]. Seven studies reported complete outcome data [30-32, 34-36, 40]. Protocols were available for two studies that had been registered in clinical trial registries [30, 31]. Five studies did not provide some of their outcomes per interventional group [25, 26, 28, 37, 41]. Five of the studies were sponsored by product manufacturers [10, 11, 13, 29, 31]. Three studies described systematic differences between the intervention and control groups at baseline [32, 37, 40], while three studies provided no participant baseline data, only CVAD information [11, 35, 39]. The majority of the included RCTs randomised participants and not their CVADs. Two studies recruited participants multiple times for multiple CVADs [25, 26]. One study stopped early for unknown reasons [28].

Effectiveness of interventions

The main results are displayed in Table 3, describing the pairwise meta-analytic comparisons of the CVAD dressing and securement devices.

Table 3: Meta-analyses for CVAD dressing and securement devices across primary and secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1. CVAD-related bloodstream infection				
Gauze and tape versus standard polyurethane	8	506	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.26, 1.63]
Chlorhexidine gluconate-impregnated versus standard polyurethane	5	4876	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.40, 1.05]
Medication-impregnated dressings versus all others	6	5687	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.39, 0.93]
2. Frequency of CVAD-related bloodstream infection per 1,000 patient days				
Gauze and tape versus standard polyurethane	2		Rate Ratio (Random, 95% CI)	0.71 [0.20, 2.52]
Chlorhexidine gluconate-impregnated versus standard polyurethane	4		Rate Ratio (Random, 95% CI)	0.51 [0.33, 0.78]
3. Catheter tip colonisation				
Gauze and tape versus standard polyurethane	5	342	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.51, 1.77]
Chlorhexidine gluconate-impregnated versus standard polyurethane	6	4431	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.47, 0.73]
4. Entry- and exit-site infection				
Gauze and tape versus standard polyurethane	2	199	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.34, 2.07]
5. Skin / site colonisation				
Gauze and tape versus standard polyurethane	2	170	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.30, 2.51]
6. Skin irritation or damage				
Chlorhexidine gluconate-impregnated versus standard polyurethane	2	850	Risk Ratio (M-H, Random, 95% CI)	11.17 [0.84, 149.48]
7. Failed catheter securement				
Gauze and tape versus standard polyurethane	2	167	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.33, 2.49]

CI= Confidence interval; CVAD=Central venous access device

Incidence of CVAD-related bloodstream infection

Figure 2 displays the results of the meta-analysis for CVAD-related bloodstream infection for the pair-wise comparisons.

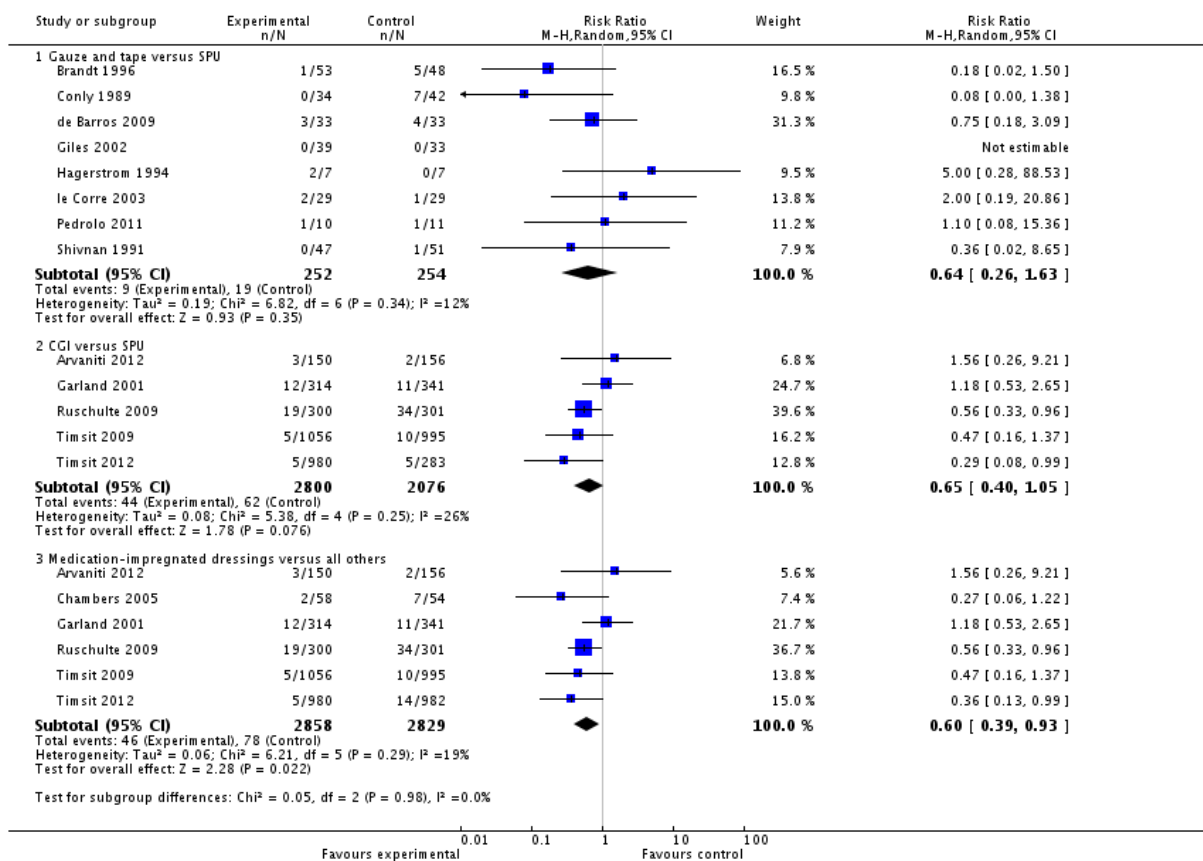


Figure 2: Primary analysis: CVAD-related bloodstream infection

Gauze and tape compared with standard polyurethane dressings was examined by eight studies across various settings. There was no clear difference between gauze and tape and standard polyurethane dressings on the incidence of CVAD-related bloodstream infection (RR 0.64, 95% CI 0.26 to 1.63). One small study in an adult oncology setting [28] reported on the effect of gauze and tape compared with no dressings and also found no clear difference in the incidence of CVAD-related bloodstream infection (RR 1.47, 95% CI 0.72 to 3.00) however this study was too small to detect a difference should it exist.

One small study in an adult surgical setting [11] found clear difference in the incidence of CVAD-related bloodstream infection between standard polyurethane dressings and "old generation" standard polyurethane dressings (RR 0.33, 95% CI 0.04 to 3.04) however because this study was so small we cannot be confident that a difference does not exist. One study in an adult Intensive Care Unit setting [31] found no clear difference in CVAD-related bloodstream infection between a highly adhesive transparent dressing and standard polyurethane dressings (RR 0.60, 95% CI 0.20 to 1.77).

We pooled five trials [10, 30-32, 36] comparing chlorhexidine gluconate-impregnated with standard polyurethane dressings. It is unclear whether chlorhexidine gluconate-impregnated dressings reduce the risk of CVAD-related bloodstream infection compared with standard polyurethane dressings as although there was a reduction in risk of catheter-related bloodstream infection this did not reach traditional levels of statistical significance (P=0.08) (RR 0.65, 95%, CI 0.40 to 1.05). Five studies in adult Intensive Care Unit (3620), neonatal Intensive Care Unit (705) and adult haematology/oncology

(601) units/wards reported this intervention and outcome, with 106 participants out of 4876 developing a CVAD-related bloodstream infection. One study (adult Intensive Care Unit) found no clear difference in the incidence of CVAD-related bloodstream infection [31] between chlorhexidine gluconate-impregnated dressings and a highly adhesive transparent dressing (RR 0.48, 95% CI 0.14 to 1.66). There was also no clear difference in the incidence of CVAD-related bloodstream infection between chlorhexidine gluconate-impregnated dressings and no dressing in one small study (RR 0.27, 95% CI 0.06 to 1.22). This study was based in an adult haematology setting [26]. However when all medication-impregnated dressings were compared with all other dressing types (six trials, 5687 participants) there was *high quality evidence* that medication-impregnated dressings reduce the risk of CVAD-related bloodstream infection compared with all other dressings (RR 0.60, 95% CI 0.39 to 0.93; P value 0.02).

There were fewer cases of CVAD-related bloodstream infection with standard polyurethane dressings than hydrocolloid dressings in a single study in adult Intensive Care Unit [12] (RR 0.53, 95% CI 0.29 to 0.97) and with standard polyurethane than sutureless securement devices in a single study in adult general acute and home care settings [13] (RR 8.00, 95% CI 1.02 to 62.58, P value 0.05).

Frequency of CVAD-related bloodstream infection per 1,000 patient days

Table 2 and supplementary Figure 2 presents the results of the meta-analysis for CVAD-related bloodstream infection per 1,000 patient days for the pair-wise comparisons.

There was no clear evidence of a difference in the frequency of CVAD-related bloodstream infection per 1,000 patient days when gauze and tape was compared with standard polyurethane dressing (RR 0.71, 95% CI 0.20 to 2.52), or when standard polyurethane was compared with old generation standard polyurethane (RR 0.35, 95% CI 0.01 to 18.61). One study in general adult acute and home settings [13] found no difference between standard polyurethane and sutureless securement devices in the frequency of CVAD-related bloodstream infection per 1000 patient days (RR 0.13, 95% CI 0.00 to 5.82).

The pooled results of four studies (in adult Intensive Care Unit; 32,958 patient days) and haematology/oncology; 9731 patient days) [30-32, 36] show that chlorhexidine gluconate-impregnated dressings reduce the frequency of CVAD-related bloodstream infection per 1000 patient days compared with standard polyurethane (RR 0.51, 95% CI 0.33 to 0.78, P value 0.002).

One study in adult Intensive Care Unit [30] found no difference in the frequency of CVAD-related bloodstream infection per 1000 patient days between highly adhesive transparent dressings and standard polyurethane (RR 0.67, 95% CI 0.14 to 3.11) and one study in adult haematology [26] found no difference in the frequency of CVAD-related bloodstream infection per 1,000 patient days between chlorhexidine gluconate-impregnated dressings and no dressing (RR 3.98, 95% CI 0.76 to 20.91).

Incidence of catheter tip colonisation

Table 2 and Supplementary Figure 3 display the results of the meta-analysis for catheter tip colonisation for the pair-wise comparisons.

Pooling the results of six trials (Chi² 6.41; P value 0.27; I² 22%) showed that the risk of catheter tip colonisation is reduced with chlorhexidine gluconate-impregnated compared with standard polyurethane dressings (RR 0.58, 95% CI 0.47 to 0.73). This analysis is based upon participants from adult Intensive Care Unit (3581), neonatal Intensive Care Unit (705) and paediatric Intensive Care Unit (145) settings.

There was no clear difference in the risk of catheter tip colonisation between gauze and tape and standard polyurethane dressings (RR 0.95, 95% CI 0.51 to 1.77). There was no difference in single adult Intensive Care Unit setting study [31] on the incidence of catheter tip colonisation between highly adhesive transparent dressings and standard polyurethane (RR 1.32, 95% CI 0.88 to 1.98). A small study in adult Intensive Care Unit [12] also found no difference in the incidence of catheter tip colonisation between standard polyurethane and hydrocolloid dressings (RR 1.88, 95% CI 1.03 to 3.42).

Incidence of entry- and exit-site infections

The pooled results of two studies [29, 33] comparing the use of gauze and tape with standard polyurethane dressings found no clear difference in the incidence of entry- and exit-site infections (RR 0.84, 95% CI 0.34 to 2.07; Chi² 0.15; P value 0.69; I² 0%). These studies took place in adult bone marrow transplant unit and paediatric and adult oncology settings.

A single study in adult Intensive Care Unit [41] also found no clear difference in the incidence of entry- and exit-site infections between standard polyurethane and chlorhexidine gluconate-impregnated dressings (RR 0.80, 95% CI 0.21 to 3.02). A single small study in an adult haematology setting [26] found fewer entry- and exit-site infections with chlorhexidine gluconate-impregnated than with no dressing (RR 0.20, 95% CI 0.06 to 0.66).

Incidence of skin or site colonisation

Within the two studies [29, 34] comparing gauze and tape with standard polyurethane in gastroenterology and paediatric and adult oncology settings there was no difference in the incidence of skin or site colonisation (RR 0.86, 95% CI 0.30 to 2.51).

Incidence of skin irritation or damage

Table 2 and supplementary Figure 4 presents the results of the meta-analysis for CVAD-related bloodstream infection per 1000 patient days for the pair-wise comparisons.

There was no clear evidence of difference in skin irritation or damage between gauze and tape and standard polyurethane in a single study (adult Intensive Care Unit) [35] (RR 6.60, 95% CI 0.95 to 45.75). There was also no clear evidence of a difference in the incidence of skin irritation or damage between chlorhexidine gluconate-impregnated dressings and standard polyurethane when two studies were pooled (Chi² 2.17; P value 0.14; I² 54%) [10, 14] (RR 11.17, 95% CI 0.84 to 149.48). These studies took place in neonatal Intensive Care Unit (705) and paediatric Intensive Care Unit (145) settings. Higher rates of skin irritation or damage were evidence in the neonatal than the paediatric population.

A single small study [40] compared the effects of standard polyurethane and other medication-impregnated dressings, in this case silver, on the rate of skin irritation or damage in neonatal Intensive Care Unit and found no difference (there was no irritation or skin damage in either group). A single small study [13] found no difference in the incidence of skin irritation or damage between standard polyurethane and sutureless securement devices in general adult acute and home-care settings. (RR 0.61, 95% CI 0.06 to 5.78).

Incidence of failed catheter securement

The pooled results of two studies [27, 33] found no difference between gauze and tape and standard polyurethane dressings in the incidence of failed catheter securement (RR 0.90, 95% CI 0.33 to 2.49). One study in adult Intensive Care Unit [32] compared standard polyurethane with chlorhexidine gluconate-impregnated dressings and found no difference in the incidence of failed catheter securement (RR 2.40, 95% CI 0.47 to 12.20). One study in adult acute and home care settings compared [13] standard polyurethane with sutureless securement devices and found no difference in the incidence of failed catheter securement (RR 1.20, 95% CI 0.55 to 2.63).

Dressing condition or durability

One very small study in adult Intensive Care Unit [35] compared gauze and tape with standard polyurethane and found no difference in dressing condition or durability (RR 0.57, 95% CI 0.10 to 3.27).

Mortality

One very small study in adult Intensive Care Unit [35] compared mortality in people receiving either gauze and tape or standard polyurethane and found no clear difference (RR 1.10, 95% CI 0.19 to 6.41). One study in adult Intensive Care Unit [32] reported an increase in mortality with standard polyurethane compared with chlorhexidine gluconate-impregnated dressing (RR 3.71, 95% CI 2.48 to 5.55). This study had a high mortality rate, with a total of 80 out of 606 participants dying. One study in neonatal Intensive Care Unit [40] found no clear difference in mortality between standard polyurethane and other medication-impregnated dressings (impregnated with silver) (RR 1.53, 95% CI 0.14 to 16.31). One study in adult haematology [26] found no clear difference in mortality between chlorhexidine gluconate-impregnated and no dressing (RR 1.33, 95% CI 0.55 to 3.25). *Low quality evidence* (downgraded for risk of bias and imprecision)

Sensitivity analyses

We planned sensitivity analyses for two major outcomes, CVAD-related bloodstream infection and catheter tip colonisation, to evaluate the impact of excluding studies based on the risks of selection and attrition bias. We were unable to perform the analyses on CVAD-related bloodstream infection, as poor reporting meant we were not able to identify those studies at high risk bias. We performed sensitivity analyses on catheter tip colonisation, for the comparison of chlorhexidine gluconate-impregnated dressings versus standard polyurethane. There were insufficient studies for the other comparisons to permit a meaningful analysis to be performed.

The exclusion of two studies [14, 41] with a high risk of attrition bias did not alter the pooled estimates substantially when we compared chlorhexidine gluconate-impregnated dressings with

standard polyurethane on the incidence of catheter tip colonisation ('without' attrition bias: RR 0.59, 95% CI 0.46 to 0.77, compared to 'with' attrition bias: RR 0.58 95% CI 0.47 to 0.73).

Discussion

Chlorhexidine gluconate-impregnated dressings may reduce CVAD-related blood stream infection relative to standard polyurethane and other dressings (moderate quality of evidence). This direction of effect is consistent for the outcomes of relative risk of CVAD-related blood stream infection, rates of blood stream infection per 1,000 patient days and catheter tip colonisation however there is uncertainty around the result for the primary outcome of relative risk and no difference cannot be excluded. There is high quality evidence that the use of medication-impregnated dressing products reduce the incidence of CVAD-related bloodstream infection in comparison with all other dressing types. The class of interventions termed 'medication-impregnated dressings' included only chlorhexidine gluconate-impregnated dressings in various forms (e.g. patch or whole dressing), whilst the 'all other dressing types' group involved standard polyurethane, highly adhesive transparent dressings and no dressing. There was moderate quality evidence for a reduction in the frequency of CVAD-related bloodstream infection per 1000 patient days with the use of chlorhexidine gluconate-impregnated dressings, compared to standard polyurethane. There was also moderate quality evidence in the reduction in the risk of colonisation of the CVAD tip with chlorhexidine gluconate-impregnated dressings compared to standard polyurethane. Colonisation of the CVAD tip is considered an indirect measure of CVAD-related bloodstream infection. Most studies were conducted in Intensive Care Unit settings. The evidence for the effectiveness of chlorhexidine gluconate-impregnated dressings is probably not generalisable beyond these settings.

One large RCT comparing chlorhexidine gluconate-impregnated and standard polyurethane dressings was excluded from this review ([60] 1401 participants); this RCT compared the effectiveness of chlorhexidine gluconate-impregnated dressings with standard polyurethane for the securement and dressing of arterial catheters, pulmonary artery catheters and CVAD. The trial found a significant reduction in the incidence of CVAD-related bloodstream infection for participants receiving chlorhexidine gluconate-impregnated dressings (P value < 0.05). This study was excluded because the outcome data were not provided separately for catheter type. We contacted the study authors, but they were not able to provide us with the CVAD outcomes. Exclusion of these results may have had a significant impact on the results of the meta-analyses included in this review. If we had been able to include these data, it is highly likely that our estimates of effect for the incidence of CVAD-related bloodstream infection would have become significant and favoured chlorhexidine gluconate-impregnated dressings compared to standard polyurethane.

There is some concern in the current literature regarding the increased risk of skin irritation or damage for chlorhexidine gluconate-impregnated dressings. Our current analysis results were heavily influenced by a single study that examined 705 neonatal Intensive Care Unit participants (59.2% of participants in the meta-analysis; [10]). The majority of reactions occurred in neonates up to 28 weeks gestational age and up to 1,000g in weight. Local contact dermatitis from the chlorhexidine gluconate-impregnated dressing may limit its use in acutely ill low-birthweight neonates or others with impaired skin integrity [10].

We identified a large number of studies in which the population, intervention, comparison and outcomes matched our pre-specified selection criteria. The studies were conducted in 25 different

countries, in a range of settings and age-related populations, with different CVAD types. Despite this, the majority of dressing and securement products have not been adequately compared, due to the large variety that are currently available. This means that there is ongoing uncertainty regarding the effectiveness of several of the commercially and clinically available products. Additionally, several of our outcomes, that reported on skin or site colonisation and dressing durability, were poorly reported. CVAD security was not adequately addressed by the included studies. Considering the serious consequences associated with accidental CVAD removal due to poor security, this is an outcome that needs to be investigated.

Risk of bias was difficult to assess in most studies because of poor reporting. Since it was not possible to blind personnel or participants to the CVAD dressing and securement product, there was a potential source of performance bias and staff or patients may have behaved differently given knowledge of the intervention; this seems unlikely however. Blinding of outcome assessors was feasible for the primary outcome, but was achieved and reported adequately by only six of the studies [12, 27, 30-32, 36]. Only two studies achieved and reported the minimisation of selection bias adequately via both random sequence generation and allocation concealment [10, 13]. Several of the trials reported receiving partial or full manufacturer sponsorship [10, 11, 13, 29, 31], however it is unclear whether this had an impact on the reported results. It is common within the field of intravascular device research for investigators to receive partial or full sponsorship for the completion of research. The funnel plot did not reveal any underlying positive or negative publication bias.

We followed clearly described procedures to prevent potential bias in the review process. The comprehensive search of multiple sources and the methods we used are transparent and reproducible. The previous version of this review 'Gauze and tape and polyurethane dressings for central venous catheter' identified a four-fold increase in the rate of CVAD-related bloodstream infection when a polyurethane dressing was used, compared with gauze and tape [1]. However, with the widening of the inclusion criteria to include recently published research and participants in community settings, this difference has ceased to be significant.

The Centers for Disease Control and Prevention recommend the use of either a sterile gauze or standard polyurethane dressing to cover the CVAD site [2]. By comparison, 'epic3', the English national evidence-based guidelines [68], recommend the use of standard polyurethane, unless the insertion site is perspiring profusely or the insertion site is bleeding or leaking. Both the CDC and epic3 guidelines advocate the use of a chlorhexidine gluconate-impregnated dressing as a strategy to reduce CVAD-related bloodstream infection, but Centers for Disease Control and Prevention recommend chlorhexidine gluconate-impregnated dressings only for temporary short-term catheters in patients over two months of age and then only if the CVAD-associated bloodstream infection rate is not decreasing despite adherence to basic prevention methods.

Our review suggests that CVAD-related bloodstream infection may be reduced with chlorhexidine gluconate-impregnated compared with standard polyurethane, and that the risk of CVAD-related bloodstream infection is reduced with medication-impregnated dressings compared with all others. Additionally, we identified a reduction in the incidence of catheter tip colonisation when using a chlorhexidine gluconate-impregnated dressing compared to standard polyurethane. A previous meta-analysis [69] that compared the effectiveness of chlorhexidine gluconate-impregnated

dressings to standard polyurethane for intravascular and epidural catheters had similar results. That meta-analysis identified a significant reduction in intravascular catheter or exit-site bacterial colonisation for chlorhexidine gluconate-impregnated dressings compared to standard polyurethane (14.8% versus 26.9%; odds ratio (OR) 0.47, 95% CI 0.34 to 0.65; P value < 0.00001) and a trend towards a reduction in intravascular catheter-related bloodstream infection or central nervous system infection (2.2% versus 3.8%; OR 0.58, 95% CI 0.29 to 1.14; P value 0.11). Participants who had their intravascular and epidural catheters dressed with a chlorhexidine gluconate-impregnated dressing had a significantly increased rate of local cutaneous reactions in comparison to those dressed with standard polyurethane (OR 8.17, 95% CI 1.19 to 56.14, P value 0.04), and the majority of these reactions occurred in neonatal patients.

A recent meta-analysis, [70] evaluated the efficacy of chlorhexidine gluconate-impregnated dressing compared to 'conventional' dressings for CVAD, pulmonary artery or peripheral arterial catheters. This analysis identified that the use of a chlorhexidine gluconate-impregnated dressing compared to a 'conventional' dressing reduced the risk of catheter-related bloodstream infection (RR 0.60, 95% CI 0.41 to 0.88; P value 0.009) and catheter colonisation (RR 0.52, 95% CI 0.43 to 0.64; P value < 0.001). These results agree with this review, even with the inclusion of pulmonary artery and arterial catheters, in addition to CVAD.

Conclusions

There is some evidence that chlorhexidine gluconate-impregnated dressings used for securing CVADs may reduce the risk of CVAD-related bloodstream infection, compared with standard polyurethane dressings and other (non-impregnated) dressing types. This evidence mainly comes from Intensive Care Unit settings. The evidence for the relative effects of different dressing and securement comparisons, including gauze and tape versus standard polyurethane, on catheter tip colonisation and CVAD-related bloodstream infection is unclear. There was inadequate research to permit us to make recommendations about CVAD security using the different dressing and securement products.

More, high quality research is needed regarding the relative effects of dressing and securement products for CVADs. New products are continually becoming commercially available, and researchers need to provide the evidence to inform clinical decision making in this area. Clinically important outcomes including CVAD security have not been adequately addressed by current research. Future research may adjust the estimates of effect for the products included in this review. Researchers should plan their protocols so that the risk of bias in each domain is minimised and should report trials clearly in accordance with the CONSORT guidelines [71].

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Conflicts of interest:

Griffith University has received unrestricted educational grants from 3M (a manufacturer of CVAD dressings and securement devices) to assist with the costs of Claire Rickard's (CR) research nurses' travel to present independent research at conferences in 2015 and 2016. Griffith University received a consultancy payment from 3M in 2013 for CR, and in 2015 for Amanda Ullman (AU), to present an educational lecture based on their independent research. Griffith University received unrestricted investigator initiated research grants from 3M in 2014, 2015 and 2016 to support research studies on which CR is an investigator. One study had no relevance to CVAD dressings; two studies describe skin microbiology and skin integrity associated with CVAD dressings, but neither are clinical trials comparing efficacy, nor are included in this review. Studies involving 3M's CVAD dressings (Tegaderm range) are included in this review but the conclusions do not recommend these over competitor products. Griffith University received an unrestricted investigator-initiated research grant from Centurion Medical (manufacturer of CVAD dressings) as part-funding for research led by CR and AU. No trials investigating Centurion Medical's dressings were included in this review. Griffith University received an unrestricted research grant in 2015 to part-support an investigator initiated project on which CR is an investigator, from Entrotech Life Sciences, a manufacturer of CVAD dressings not included in this review.

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Frances Lin: nothing to declare

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Debbie A Long: nothing to declare

Gabor Mihala: nothing to declare

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