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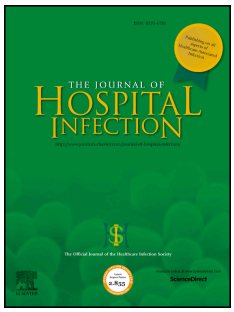

Systematic review and meta-analysis of the risk of microbial contamination of parenteral doses prepared under aseptic techniques in clinical and pharmaceutical environments: an update

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Systematic review and meta-analysis of the risk of microbial contamination of parenteral doses prepared under aseptic techniques in clinical and pharmaceutical environments: an update

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SUMMARY

Background: Administration of parenteral doses with microbial contamination can lead to infective morbidity or death.

Aim: To test whether aseptic preparation of parenteral doses or additives to sterile doses undertaken in dedicated pharmaceutical rather than clinical environments reduces the risk of microbial dose contamination.

Methods: Data identified from a systematic review were examined using random effects meta-analyses, and *t*-tests were used to compare dose contamination frequencies.

Findings: In all, 16,552 doses from 34 studies (33 records) were identified. For all the data combined there was a significantly higher frequency of contamination of doses prepared in clinical than in pharmaceutical environments {3.7% [95% confidence interval (CI): 2.2, 6.2; N = 10,272 doses] vs 0.5% (95% CI: 0.1, 1.6; N = 6280 doses); P = 0.007}. Contamination of doses was significantly higher when prepared as individual lots than as part of a batch in pharmaceutical environments [2.1% (95% CI: 0.7, 5.8; N = 168 doses) vs 0.2% (95% CI: 0.1, 0.9; N = 6112 doses); P = 0.002]. There was a significantly higher frequency of dose contamination if additions were made to sterile parenteral doses in clinical environments [risk ratio: 2.121 (95% CI: 1.093, 4.114); P = 0.026]. The overall quality of the studies was judged to be low.

Conclusion: Reported rates of parenteral dose contamination were orders of magnitude higher than accepted reference standards, which may increase infection risk. The limited evidence on contamination rates supports dose preparation in pharmaceutical rather than clinical environments, and does not support batch preparation in clinical environments.

Keywords:

Aseptic

Batch

Contamination

Environment

Individual lots

Introduction

Administration of a parenteral dose with microbial contamination may result in infective morbidity and death. Recent examples include: postoperative sepsis after inadequate aseptic handling of intravenous anaesthetic; loss of vision or further surgery due to endophthalmitis as a consequence of contaminated intravitreal injections in the USA; an outbreak of bloodstream infections requiring withdrawal of relevant stock due to contaminated intravenous analgesia in Taiwan; and deaths in newborns as a consequence of contaminated parenteral nutrition in France and the UK.[1–4] This means it is important to implement safe procedures in routine practice to prevent inadvertent microbial dose contamination. For example, the risk of contamination is expected to be lower when procedures are undertaken in an environment with a low density of microbes than one with a high density. Therefore, it is often recommended to move aseptic preparation of parenteral doses away from a clinical environment (with a higher density of microbes) into a specially designed pharmaceutical environment [with a lower density of microbes (and particulates)] in line with recognized standards operating in countries such as the USA or the UK.[5–7] For example, in the immediate area used to prepare parenteral medicines there could be more than 90 times the number of colony-forming units falling on to a 90 mm diameter trypticase soy agar plate in a 4 h period in a clinical environment than is allowed by the standards applied to pharmaceutical environments in some countries.[7,8] The use of a pharmaceutical environment is particularly important in the preparation of batch doses, which carry the risk of contaminating multiple lots of individual doses, and where there is likely to be a period of storage before administration to patients. However, since pharmaceutical environments meeting recognized standards for aseptic dose preparation are costly and require operational expertise that may not always be readily available, they are not always used. Therefore, there is a need to balance the advantages and disadvantages of the procedures and the environments

in which they are undertaken in order to obtain the desirable effects in routine clinical practice.

In 2009 we published a systematic review with meta-analysis to summarize published frequencies of contamination of parenteral doses prepared in clinical and pharmaceutical environments under aseptic techniques.[9] This provided some evidence favouring dose preparation in the pharmaceutical environment, but the conclusions were weakened by the small number of studies which were generally of low quality. It is possible that some earlier studies may have been missed because the initial review used only one database search engine (PubMed from 1947 onwards). Since our review, a considerable amount of new information has become available which needs to be incorporated into the analyses. In the meantime, clinical concern about methods to reduce morbidity and cost due to infections has been increasing. For example, an international initiative has sought to rationalize and harmonize standards for aseptic preparation of parenteral doses throughout Europe.[10,11] It is clear that the existing evidence base needs to be reviewed, updated, and clarified by providing a more precise definition of the pharmaceutical environment.[9] Therefore, the aim of this study was to clarify and extend the evidence base to address the following three hypotheses: one, the risk of infective contamination is different for aseptic preparation in a clinical and pharmaceutical environment; two, the risk is also different for aseptic preparation of individual and batch doses within the same type of environment; and three, the risk is different for additives rather than no additives to sterile doses prior to administration. We also sought to consider future research needs in light of the current evidence base.

Methods

The literature search was undertaken on 10 February 2014 with a wider protocol than that undertaken by the previous review.[9] The present literature search used an additional search term, truncated search terms, and combination of three search terms only if more than 5000 results were returned for any two search term combination. Three databases were used for all available years: Medline from 1946 onwards using OvidSP; Embase from 1947 onwards using OvidSP; and the Cochrane Library. Attempts were made to identify further papers by hand searching.

The literature search included studies that involved microbial contamination with bacteria and/or fungi. The studies involved preparation of doses for parenteral administration to patients prepared under aseptic techniques, including simulation studies. Studies were excluded if they were not reported in the English language, if they only involved animals, or if they reported the rate of contamination of infusate stock (an infusate in a single container used to prepare multiple doses) rather than actual or simulated prepared doses (for example,

contamination of multi-dose vials after repeated use). Studies were also excluded if they involved the use of blood or a blood component, if there was freezing/thawing of prepared doses, or if there was reuse of equipment during dose preparation (except when used in the preparation of a single batch). For an environment to qualify as a pharmaceutical environment the recognized standard of the cabinet in which the doses were prepared and the room in which that cabinet was situated had to be specified in the record (journal article). When a single record reported more than one outcome, for example when using different preparation environments, each outcome was included as a separate study. Consistent data within the same record were combined only if whole groups of data could be combined.

The search terms (including variations and truncated terms) and number of results are shown in Table I. In brief, each of four search terms was combined with each of four further search terms, unless a combination returned more than 5000 results, in which case a third search term was added in an attempt to capture the most relevant results. It can be seen from Table I that a third search term was required on five occasions. Additional papers were sought through cross-referencing and discussion with experts in the field.

The literature search identified 42,246 records (17,662 from Medline, 20,824 from Embase and 3760 from the Cochrane Library) and 28,020 after duplicates had been removed. The title and abstract (if necessary and accessible) of each of the 28,020 identified records was evaluated and excluded if it did not meet the above inclusion criteria. This left 137 records, which were individually subjected to a full text review to confirm relevance and compliance with the above criteria to yield a final total of 34 studies from 33 records.[8,12–43] Each of the final 19 studies from 17 records identified in our 2009 search were identified in the present search but five of those studies from four records were excluded due to inadequate and/or inadequately described pharmaceutical environments.[9,12,14–16,18–22,24,33,36,43–47] The methodological stages of the search are shown in Figure 1. As previously, the included studies were divided into groups according to whether doses were prepared in a clinical or pharmaceutical environment (hypothesis 1), whether doses had been prepared as individual lots or as part of a batch (hypothesis 2), and whether doses had been sampled without or before administration or during or after administration to a patient (due to a risk of contamination from manipulations after preparation and potential differences in time between preparation and sampling which may have affected recovery of damaged microbial cells).[9] Doses were considered to be either contaminated or not contaminated without any attempt to identify the density of any micro-organisms present; the types of micro-organisms, where these were reported, are briefly summarized.

Two of the authors (P.D.A. and K.S.H.) independently assessed the quality of the included studies using the GRADE system with subsequent discussion to resolve any disagreement.[48,49] The recommendations of the UK National Health Service Centre for Reviews and Dissemination (CRD) and Cochrane as well as the PRISMA guidelines for reporting systematic reviews were considered at all stages during this review.[50–52]

Statistical analysis

The point estimate, standard error and 95% confidence interval for the contamination rate of each separate group was obtained by logarithmic (logit) transformation. When there was zero contamination in a group, a value of 0.5 contaminated doses was used to overcome the mathematical difficulties associated with logarithmic transformation (the $\log_{10}$ of zero is minus infinity). Data amalgamation and the meta-analyses were undertaken using a random effects model and the software Comprehensive Meta Analysis version 2 (Biostat, Englewood, NJ, USA). One-group meta-analyses were used for hypotheses 1 and 2 and a two-group meta-analysis was used for hypothesis 3 due to the nature of the available studies. The random effects model was chosen because of the clinical heterogeneity of the studies, but the I^2 statistic is also presented. Comparisons between group means were undertaken using unpaired *t*-tests, with a two-tailed $P < 0.05$ considered statistically significant.

Results

Quality of studies

For the purpose of this review, both raters graded all of the included studies as low to very low quality, with three disagreements within these categories. After discussion, the majority of the studies were graded as low quality primarily because they were non-randomized, and four studies were graded as very low quality primarily due to small sample size and limited procedural detail and high contamination rate.[18,34,36,40]

Overview of the rate of contamination of doses prepared in clinical and pharmaceutical environments

A grand total of 16,552 doses eligible for inclusion were identified from 34 studies taken from 33 records, which are summarized in Table II.[8,12–43] The single record identified through other sources in our previous review was identified by the present literature search.[9,12] Excluding control groups, this represents an increase of 133% in the number of doses (16,552 vs 7101), 79% in the number of studies (34 vs 19), and 94% in the number of records (33 vs 17) from the 2009 review.[9] If the five studies not meeting the inclusion criteria of the present review are withdrawn from the first review, there is an increase of 173% in the number of doses (16,552 vs 6074), 143% in the number of studies (34 vs 14), and 154% in the number of records (33 vs 13).

Of the total 33 records, only seven involved head-to-head comparisons. One record compared batch doses and individual lots in a clinical environment and six records compared additives and no additives to sterile doses in a clinical environment.[15,18,21,28,29,35]

Figure 2 shows the forest plot obtained when all the study data were combined in a meta-analysis grouped according to environment (pharmaceutical or clinical) and type of dose preparation (individual or batch). The majority (94%) of the doses that had been prepared as individual lots in clinical environments (N = 4141) had been sampled during or after administration, and all of the other doses had been sampled without or prior to administration. When only the 4141 doses prepared as individual lots in clinical environments were included there was a non-significantly higher frequency of contamination of doses sampled without or prior to administration than during or after administration [5.3% (95% CI: 2.7, 10.0; N = 3889 doses) (I^2 = 93.07%; P < 0.001) vs 2.3% (95% CI: 0.5, 10.1; N = 252 doses) (I^2 = 56.45%; P = 0.101); P = 0.314].

Nineteen of the 22 studies with contamination reported the type of microbe.[8,13,14,16–19,21–24,27–33,35,39,41,42] In pharmaceutical environments this was limited to coagulase-negative staphylococci (including *Staphylococcus epidermidis*), *Bacillus* spp., and *Propionibacterium* spp.[17,39] The same microbes were identified in clinical environments, where more pathogenic microbes were also found, including *Staphylococcus aureus*, *Serratia marcescens*, *Klebsiella* spp., *Enterobacter* spp., and fungi (including *Candida* spp.).[13,14,16,19,21–24,27,29–31,33,35,42]

Hypothesis 1: dose preparation in a clinical compared to a pharmaceutical environment

Individual and batch doses combined

All identified doses. The analysis involved 16,552 doses from 34 studies (33 records[8,12–43]). Of these, 10,272 doses from 27 studies (26 records[8,13–16,18–25,27–33,35–38,42,43]) had been prepared in clinical environments and 6280 doses from seven studies (seven records[12,17,26,34,39–41]) had been prepared in pharmaceutical environments. When all the data were combined there was a significantly higher frequency of contamination of doses prepared in clinical than in pharmaceutical environments [3.7% (95% CI: 2.2, 6.2; N = 10,272 doses) (I^2 = 95.35%; P < 0.001) vs 0.5% (95% CI: 0.1, 1.6; N = 6280 doses) (I^2 = 69.18%; P = 0.003); P = 0.007]. The between-study contamination was more variable in the clinical than in the pharmaceutical environment (range: 0.1–55.7 vs 0.0–2.6 respectively).

Doses sampled without or prior to administration. There were 12,663 doses from 21 studies (21 records[8,12,13,16,17,19–21,23,25–27,30,33,34,37–42]) that had been sampled without administration or prior to administration, of which 6383 doses from 14 studies (14 records[8,13,16,19–21,23,25,27,30,33,37,38,42]) had been prepared in clinical environments and 6280 doses

from seven studies (seven records[12,17,26,34,39–41]) had been prepared in pharmaceutical environments. When all the data were combined, there was a significantly higher frequency of contamination of doses prepared in clinical than in pharmaceutical environments [2.5% (95% CI: 1.2, 5.5; n = 6383 doses) (I^2 = 95.69%; P < 0.001) vs 0.5% (95% CI: 0.1, 1.6; n = 6280 doses) (I^2 = 69.18%; P = 0.003); P = 0.044]. The between-study contamination was more variable in the clinical than in the pharmaceutical environment (range: 0.1–28.4% vs 0.0–2.6% respectively).

Doses sampled during or after administration

It was not possible to compare doses prepared in clinical and pharmaceutical environments that had been sampled during or after administration due to lack of data in the pharmaceutical environment.

Individual doses

All identified doses. The analysis involved 4309 doses from 18 studies (18 records[14,15,17,18,21,22,24,27–32,35–37,40,43]). Of these, 4141 doses from 16 studies (16 records[14,15,18,21,22,24,27–32,35–37,43]) had been prepared in clinical environments and 168 doses from two studies (two records[17,40]) had been prepared in pharmaceutical environments. When all the data were combined, there was a non-significantly higher frequency of contamination of doses prepared in clinical than in pharmaceutical environments [4.7% (95% CI: 2.5, 8.4; N = 4141 doses) (I^2 = 91.64%; P < 0.001) vs 2.1% (95% CI: 0.7, 5.8; N = 168 doses) (I^2 = 00.00%; P = 0.856); P = 0.190]. The between-study contamination was more variable in the clinical than in the pharmaceutical environment (range: 0.2–55.7% vs 2.0–2.6% respectively).

Doses sampled without administration or prior to administration. There were 420 doses from five studies (five records[17,27,30,37,40]) that had been sampled without administration or prior to administration, of which 252 doses from three studies (three records[27,30,37]) had been prepared in clinical environments and 168 doses from two studies (two records[17,40]) had been prepared in pharmaceutical environments. When all the data were combined there was a non-significantly higher frequency of contamination of doses prepared in clinical than in pharmaceutical environments [2.3% (95% CI: 0.5, 10.1; N = 252 doses) (I^2 = 56.45%; P = 0.101) vs 2.1% (95% CI: 0.7, 5.8; N = 168 doses) (I^2 = 00.00%; P = 0.856); P = 0.923]. The between-study contamination was more variable in the clinical than in the pharmaceutical environment (range: 0.6–6.3% vs 2.0–2.6% respectively).

Doses sampled during or after administration. It was not possible to compare doses prepared in clinical and pharmaceutical environments that had been sampled during or after administration due to lack of data in the pharmaceutical environment.

Batch doses

All identified doses. The analysis involved 12,243 doses from 16 studies (16 records[8,12,13,16,19–21,23,25,26,33,34,38,39,41,42]). Of these, 6131 doses from 11 studies (11 records[8,13,16,19–21,23,25,33,38,42]) had been prepared in clinical environments and 6112 doses from five studies (five records[12,26,34,39,41]) had been prepared in pharmaceutical environments. When all the data were combined, there was a significantly higher frequency of contamination of doses prepared in clinical than in pharmaceutical environments [point estimate: 2.7% (95% CI: 1.1, 6.2; N = 6131 doses) (I^2 = 96.48%; P < 0.001) vs 0.2% (95% CI: 0.1, 0.9; N = 6112 doses) (I^2 = 56.49%; P = 0.056); P < 0.001]. The between-study contamination was more variable in the clinical than in the pharmaceutical environment (range: 0.1–28.4% vs 0.0–2.4% respectively).

Doses sampled without or prior to administration. Since all of the identified doses had been sampled without or prior to administration, a comparison of doses prepared in clinical and pharmaceutical environments that had been sampled without or prior to administration yields the same results as all of the combined data (above).

Doses sampled during or after administration. It was not possible to compare doses prepared in clinical and pharmaceutical environments that had been sampled during or after administration due to lack of data in either the clinical or pharmaceutical environment.

Hypothesis 2: dose preparation as individual lots or as part of a batch

Clinical and pharmaceutical environments combined

All identified doses. The analysis involved 16,552 doses from 34 studies (33 records[8,12–43]). Of these, 4309 doses from 18 studies (18 records[14,15,17,18,21,22,24,27–32,35–37,40,43]) had been prepared as individual lots and 12,243 doses from 16 studies (16 records[8,12,13,16,19–21,23,25,26,33,34,38,39,41,42]) had been prepared as part of a batch. When all the data were combined there was a significantly higher frequency of contamination of doses prepared as individual lots than as part of a batch [4.4% (95% CI: 2.5%, 7.6%; N = 4309 doses) (I^2 = 90.77%; P < 0.001) vs 1.3% (95% CI: 0.5%, 3.0%; N = 12,243 doses) (I^2 = 96.68; P < 0.001); P = 0.022]. The between-study contamination was more variable for doses prepared as individual lots than as part of a batch (range: 0.2–55.7% vs 0.0–28.4% respectively).

Doses sampled without administration or prior to administration. There were 12,663 doses from 21 studies (21 records[8,12,13,16,17,19–21,23,25–27,30,33,34,37–42]) that had been sampled without administration or prior to administration, of which 420 doses from five studies (five records[17,27,30,37,40]) had been prepared as individual lots and 12,243 doses from 16 studies (16 records[8,12,13,16,19–21,23,25,26,33,34,38,39,41,42]) had been prepared as part of a batch. When all the data were combined, there was a non-significantly higher frequency of contamination of doses

prepared as individual lots than as part of a batch [point estimate: 2.7% (95% CI: 1.2, 6.0; N = 420 doses) (I^2 = 28.53%; P = 0.231) vs 1.3% (95% CI: 0.5, 3.0; N = 12,243 doses) (I^2 = 96.68%; P < 0.001); P = 0.231]. The between-study contamination was more variable for doses prepared as part of a batch than as individual lots (range: 0.0–28.4% v 0.6–6.3%, respectively).

Doses sampled during or after administration. It was not possible to compare doses prepared as individual lots and as part of a batch that had been sampled during or after administration due to lack of data for doses prepared as part of a batch.

Clinical environments

All identified doses. The analysis involved 10,272 doses from 27 studies (26 records[8,13–16,18–25,27–33,35–38,42,43]). Of these, 4141 doses from 16 studies (16 records[14,15,18,21,22,24,27–32,35–37,43]) had been prepared as individual lots and 6131 doses from 11 studies (11 records[8,13,16,19–21,23,25,33,38,42]) had been prepared as part of a batch. When all the data were combined, there was a non-significantly higher frequency of contamination of doses prepared as individual lots than as part of a batch [4.7% (95% CI: 2.5%, 8.4%; N = 4141 doses) (I^2 = 91.64%; P < 0.001) vs 2.7% (95% CI: 1.1%, 6.2%; N = 6131 doses) (I^2 = 96.48%; P < 0.001); P = 0.299]. The between-study contamination was more variable for doses prepared as individual lots than as part of a batch (range: 0.2–55.7% vs 0.1–28.4% respectively).

Doses sampled without or prior to administration. There were 6383 doses from 14 studies (14 records[8,13,16,19–21,23,25,27,30,33,37,38,42]) that had been sampled without or prior to administration, of which 252 doses from three studies (three records[27,30,37]) had been prepared as individual lots and 6131 doses from 11 studies (11 records[8,13,16,19–21,23,25,33,38,42]) had been prepared as part of a batch. When all the data were combined, there was a non-significantly higher frequency of contamination of doses prepared as part of a batch than as individual lots [point estimate: 2.7% (95% CI: 1.1, 6.2; N = 6131 doses) (I^2 = 96.48%; P < 0.001) vs 2.3% (95% CI: 0.5, 10.1; N = 252 doses) (I^2 = 56.48%; P = 0.101); P = 0.856]. The between-study contamination was more variable for doses prepared as part of a batch than as individual lots (range: 0.1–28.4% vs 0.6% to 6.3% respectively).

Doses sampled during or after administration. It was not possible to compare doses prepared as individual lots and as part of a batch that had been sampled during or after administration due to lack of data for doses prepared as part of a batch.

Pharmaceutical environments

All identified doses. The analysis involved 6280 doses from seven studies (seven records[12,17,26,34,39–41]). Of these, 168 doses from two studies (two records[17,40]) had been

prepared as individual lots and 6112 doses from five studies (five records[12,26,34,39,41]) had been prepared as part of a batch. When all the data were combined there was a significantly higher frequency of contamination of doses prepared as individual lots than as part of a batch [2.1% (95% CI: 0.7, 5.8; N = 168 doses) (I^2 = 00.00%; P = 0.856) vs 0.2% (95% CI: 0.1, 0.9; N = 6112 doses) (I^2 = 56.49%; P = 0.056); P = 0.002]. The between-study contamination was more variable for doses prepared as part of a batch than as individual lots (range: 0.0–2.4% vs 2.0–2.6% respectively).

Doses sampled without or prior to administration. Since all of the identified doses had been sampled without or prior to administration, a comparison of doses prepared as individual lots and as part of a batch that had been sampled without or prior to administration yields the same results as all of the combined data (above).

Doses sampled during or after administration. It was not possible to compare doses prepared as individual lots and as part of a batch that had been sampled during or after administration, since no relevant doses that had been prepared as either individual lots or as part of a batch had been identified.

Hypothesis 3: undertaking additions to terminally sterilized doses

The maximum expected contamination rate of doses terminally sterilized according to appropriate and validated procedures is one per million.[53]

Clinical and pharmaceutical environments combined

It was not possible to combine doses from clinical and pharmaceutical environments, since no studies that reported the contamination rate of sterile doses with and without additives undertaken in pharmaceutical environments had been identified.

Clinical environments

The analysis involved 1723 doses from six studies (six records[15,18,21,28,29,35]). Of these, additions had been made to 1108 doses and no additions had been made to 615 doses. All of the doses had been prepared as individual lots and sampled during or after administration. Figure 3 shows the forest plot when all of the study data were combined in a meta-analysis. There was a significantly higher frequency of contamination of doses with additives than without additives [risk ratio: 2.121 (95% CI: 1.093, 4.114); P = 0.026], with a low statistical heterogeneity (I^2 = 22.50%; P = 0.265).

Pharmaceutical environments

It was not possible to compare sterile doses with and without additives in pharmaceutical environments, since no relevant studies had been identified.

Discussion

This update identified more than double the number of doses than the 2009 review, which we have attempted to summarize to help inform judgements when establishing policy and clinical practice that ultimately aim to reduce patient infection rates.[9] Overall, the contamination frequency was lower when doses had been prepared in pharmaceutical than in clinical environments, but reported rates were often unacceptably high in both settings. For example, the mean reported study frequency of microbial contamination of doses prepared under aseptic techniques in pharmaceutical environments could be >100 times higher than that expected from following the procedures recommended in Europe (>2.0% compared with 0.02%), and >2750 times higher in clinical environments than that expected in a pharmaceutical environment (>55.0% compared to 0.02%).[11] The greater number of studies identified in this update meant that a previously non-significant but intuitive finding of the previous review achieved statistical significance in the present review (Hypothesis 3).[9]

Hypothesis 1: dose preparation in a clinical compared to a pharmaceutical environment

There was a consistently lower frequency of contamination of doses prepared in pharmaceutical environments compared to clinical environments. However, this finding was not found to be statistically significant for doses prepared as individual lots, despite up to more than a two-fold difference in the overall frequency of dose contamination (4.7% vs 2.1% for all individual doses combined, and 2.3% vs 2.1% for only those individual doses sampled without administration or prior to administration). This lack of statistical significance could at least in part be explained by the limited data identified for doses prepared as individual lots in pharmaceutical environments (N = 168) (a potential type 2 error due to inadequate statistical power), which could have been compounded by necessary mathematical corrections during the analyses (see limitations below). A consistently narrower range of between-study frequencies of dose contamination was found for doses prepared in pharmaceutical than in clinical environments.

The lower frequency and variability of contamination of doses prepared in pharmaceutical than in clinical environments is intuitive since pharmaceutical facilities are constructed and operated to restrict the number of environmental microbes, incorporate specialized equipment operated by staff wearing special clothing to minimize shedding of micro-organisms (and particles) and who have more consistent and extensive training in the validation in the use of aseptic techniques.[8] When reported, the types of micro-organisms found after preparation in pharmaceutical environments were generally of low pathogenicity. The same bacteria were reported in doses prepared in clinical environments, but a wider range of micro-organisms was found in this setting, including various Gram-negative bacteria and fungi that have greater pathogenic potential. Not only are limited or no environmental control

procedures followed in clinical environments, but the closer proximity of drug preparation to patients serves as an additional source of micro-organisms that are antibiotic resistant and/or more pathogenic. Indeed, perceived benefits of pharmaceutical rather than clinical environments for aseptic preparation of parenteral doses have been noted in national documents, such as in the UK, and particularly for high-risk products such as parenteral nutrition.[54–56]

In addition to potential clinical benefits it is also necessary to consider the economic consequences of where doses are prepared. None of the reviewed studies undertook a cost-effectiveness analysis but the start-up costs for building a new facility to create an appropriate pharmaceutical environment would be high (e.g. several million national currency units in Europe or the USA). There are also substantial ongoing costs (including operator training, maintenance, monitoring for environmental contaminants, and the need for an appropriately qualified manager). In addition, logistic issues created by a centralized facility, such as the need to reallocate staff resource from wards to the pharmacy department, and the need to safely and efficiently deliver drugs to points of use, would have to be addressed.

Hypothesis 2: dose preparation as individual lots or as part of a batch

For all the doses in both clinical and pharmaceutical environments combined, contamination was found to be higher in doses prepared as individual lots rather than as part of a batch. This difference was found to be significant in pharmaceutical environments but not in clinical environments. It is intuitive that individual doses would be a higher risk than batch doses in pharmaceutical environments since the risks of batch preparation are offset by fewer environmental contaminants, less variable techniques, and the availability of specialized equipment. It is also intuitive that potential benefits of batch preparation would be lost in an uncontrolled environment with greater contaminants where more variable techniques are employed and no specialized equipment for batch production is available. These findings support recommendations to limit the expiry of parenteral doses prepared under aseptic techniques in clinical environments, for example to 24 h in the UK, which effectively preclude batch preparation, and which do not apply to pharmaceutical environments (although different additional requirements do apply).[56]

Hypothesis 3: the effect of undertaking additions to terminally sterilized doses

It is reasonable to suggest that aseptic manipulations to a sterile dose can only increase the risk of microbial contamination, but there is limited evidence for such an effect. Unlike the 2009 review, which reported no significant effect of additions to sterilized doses, this updated review found a significantly higher contamination rate of sterile doses subjected to additions compared to those that were not [a risk ratio of 1.459 (P = 0.682) and 2.121 (P =

0.026) respectively].[9] This difference can be explained by use of a meta-analysis based on only three studies with high statistical heterogeneity (I^2 = 66.45%, P = 0.055) in the 2009 review, and a meta-analysis based on six studies with lower heterogeneity (I^2 = 22.50%, P = 0.265) in the present review.[9,15,18,21,28,29,35] This finding is consistent with the intuitive idea that aseptic manipulations should be minimized in uncontrolled environments such as hospital wards whenever possible. Nevertheless, adequate protocols and training are still required when it is necessary to prepare doses in clinical environments under aseptic technique. The updated conclusion that additions to sterile doses in clinical environments increase the contamination rate is in line with the findings for the previous two hypotheses.

Limitations

The evidence base was limited and generally based on poor quality studies, weakening the conclusions of this paper. One of the main limitations is that the studies did not primarily set out to examine the hypotheses raised in this review and so did not use the most appropriate study designs to address the hypotheses raised in this review. Furthermore, although there are substantially more studies in the current review than in the 2009 review,[9] there is still the possibility that a type 2 error may have arisen when testing specific hypotheses. For example, there were only 168 individual doses prepared in pharmaceutical environments identified. The risk of type 2 error may have also been increased by the need to add 0.5 contaminated doses in a group when it in reality there were no contaminated doses. For example, the effect on the rate of contamination of doses prepared as individual lots in a pharmaceutical environment in one study was reported as 0.0% (zero contaminated doses from a total of 18 doses) but was included in the analyses as 2.4% (0.5 contaminated doses from a total of 18 doses).[40] The relevance of this mathematical complication is reduced as the sample size increases. Another potential limitation is that the studies spanned a period of >40 years (1972 to 2013), most of which were more than 10 years old [79% (27 from 34 studies)], which raises the possibility that the overall results do not exactly reflect current practice with currently used products. Finally, the general lack of head-to-head trials (seven from a total of 33 records) has meant that in some cases less robust analyses had to be used. In standard meta-analyses involving head-to-head trials, the differences between two groups of individual studies are established and amalgamated (two group meta-analysis). By contrast, in the present work for hypotheses 1 and 2 the average results from studies involving each group were amalgamated separately (one group meta-analysis) and then compared with each other. This increases the risk of bias since the products tested and conditions in the two comparator groups are less well matched. For example, 38% (3889 from 10,272) of the doses prepared in clinical environments had been sampled during or after administration compared to none (from 6280) of the doses

prepared in pharmaceutical environments, and 40% (4141 from 10,272) of doses prepared in clinical environments had been prepared as individual lots compared to 3% (168 from 6280) in pharmaceutical environments.

Recommendations

It is logical that the safest environment should be used to prepare parenteral doses under aseptic technique but several high-profile incidents (including deaths) in recent years make the continued lack of high-quality data in this field surprising. The limited and low-quality evidence base supports the use of pharmaceutical rather than clinical environments for aseptic parenteral dose preparation and does not support batch preparation in clinical environments, but further data are required. There is a need for high-quality head-to-head trials with large sample sizes to strengthen the available evidence base. Such studies would better inform decisions and policies in clinical practice. In particular, at the present time there are limited published data for doses prepared as individual lots in pharmaceutical environments (N = 168), and for doses prepared as individual lots in clinical environments without administration to patients (N = 252). In addition, the introduction of a reporting system for contamination rates achieved during routine clinical practice and/or routine simulation studies used to verify competence of operator aseptic technique that takes into account the sampling procedures employed would be of benefit. Future work in this area should also consider the risk of contamination and infection with different types of microbes, the clinical risks associated with contamination of different types of preparation (e.g. intuitively an intraocular preparation sounds higher risk than a preparation intended for bolus intravenous administration), and the economic implications, including cost-effectiveness, of drug preparation in clinical and pharmaceutical environments.

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Conflict of interest statement

None declared.

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Table I

The terms and number of results for the literature search undertaken on February 10th, 2014 to identify parenteral doses prepared under aseptic techniques in clinical and pharmaceutical environments

Database	Search row	Search terms	Results (*N*)
Medline (OvidSP)	1	(syringe or syringes).mp. or syring*.tw.	21,041
	2	(bag or bags).mp. or bag*.tw.	18,909
	3	(infusion or infusions).mp. or infus*.tw.	258,728
	4	(vial or vials).mp. or vial*.tw.	6066
	5	(microbial or microbiological).mp. or micro*.tw.	2,017,452
	6	(bacterium or bacteria).mp. or bact*.tw.	598,873
	7	(fungus or fungi).mp. or fung*.tw.	134,157
	8	(contaminated or contamination).mp. or contam*.tw.	166,465
	9	prepared.mp. or prep*.tw. or manufactured.mp. or manuf*.tw. or compounded.mp. or compound*.tw.	1,110,191
	10	(1 and 5) or (1 and 6) or (1 and 7) or (1 and 8) or (2 and 5) or (2 and 6) or (2 and 7) or (2 and 8) or (3 and 5 and 9[b]) or (3 and 6 and 9[c]) or (3 and 7) or (3 and 8) or (4 and 5) or (4 and 6) or (4 and 7) or (4 and 8)	19,123
	11	limit 10 to English language	17,662
Embase Classic and Embase (OvidSP)	1	(syringe or syringes).mp. or syring*.tw.	32,435
	2	(bag or bags).mp. or bag*.tw.	30,560
	3	(infusion or infusions).mp. or infus*.tw.	352,153
	4	(vial or vials).mp. or vial*.tw.	10,079
	5	(microbial or microbiological).mp. or micro*.tw.	2,221,231
	6	(bacterium or bacteria).mp. or bact*.tw.	952,057

	7	(fungus or fungi).mp. or fung*.tw.	252,530
	8	(contaminated or contamination).mp. or contam*.tw.	253,438
	9	prepared.mp. or prep*.tw. or manufactured.mp. or manuf*.tw. or compounded.mp. or compound*.tw.	1,697,262
	10	(1 and 5) or (1 and 6) or (1 and 7) or (1 and 8) or (2 and 5) or (2 and 6) or (2 and 7) or (2 and 8) or (3 and 5 and 9[b]) or (3 and 6 and 9[c]) or (3 and 7) or (3 and 8) or (4 and 5) or (4 and 6) or (4 and 7) or (4 and 8)	23,099
	11	limit 10 to English language	20,824
The Cochrane Library (Wiley Online Library)[a]	#1	“syringe” or “syringes” or syring*	1364
	#2	“bag” or “bags” or bag*	4467
	#3	“infusion” or “infusions” or infus*	36,233
	#4	“vial” or “vials” or vial*	1325
	#5	“microbial” or “microbiological” or micro*	66,334
	#6	“bacterium” or “bacteria” or bact*	25856
	#7	“fungus” or “fungi” or fung*	2759
	#8	“contaminated” or “contamination” or contam*	3453
	#9	“prepared” or prep* or “manufactured” or manuf* or “compounded” or compound*	64,682
	#10	(#1 and #5) or (#1 and #6) or (#1 and #7) or (#1 and #8) or (#2 and #5) or (#2 and #6) or (#2 and #7) or (#2 and #8) or (#3 and #5 and #9[b]) or (#3 and #6[c]) or (#3 and #7) or (#3 and #8) or (#4 and #5) or (#4 and #6) or (#4 and #7) or (#4 and #8)	3760

[a]All document search.

[b]The combination of search terms 3 and 5 yielded 57,265 results in Medline, 33,340 results in Embase, and 7464 results in the Cochrane Library, and 4848, 671, and 876 results respectively when search term 9 was also included in the combination.

[c]The combination of search terms 3 and 6 returned 6363 results in Medline and 9036 results in Embase, and 689 and 784 results respectively when search term 9 was included in the combination. The third search term was not required for the combination of search terms 3 and 6 in the Cochrane Library since 1565 results were returned.

Table II

Summary of studies that reported the frequency of microbial contamination of parenteral doses prepared under aseptic techniques in clinical and pharmaceutical environments

Study	Country	Dose	Individual or batch preparation (or treated as one or the other)	Preparation environment[a]	Administration to patients[b]	Additives/repackaging group		Control group (no additives)	
						Total doses (*N*)	Contaminated doses (*N*)	Total doses (*N*)	Contaminated doses (*N*)
Austin *et al.*[12]	England	Growth medium	Batch	Pharmaceutical	No	1002	0	–	–
Austin *et al.*[8]	England	Growth medium	Batch	Clinical	No	778[c]	19[c]	–	–
Aydin *et al.*[13]	Turkey	Propofol with and without lidocaine	Batch	Clinical	No	1920[d]	1[d]	–	–
Bach *et al.*[14]	Germany	Anaesthetic agents	Individual	Clinical	Yes	1228*	47	–	–
Breheny *et al.*[15]	Australia	Parenteral nutrition	Individual	Clinical	Yes	150*	0	96	0
Burke *et al.*[16]	USA	5% w/v glucose	Batch	Clinical	No	95	27	–	–

Choy *et al.*[17]	USA	Various, including parenteral nutrition	Individual	Pharmaceutical	No	150[e]	3[e]	–	–
D'Arcy *et al.*[18]	Ireland	Various	Individual	Clinical	Yes	61*	34	40	5
Dominik *et al.*[19]	Germany	Contrast media	Batch	Clinical	No	1000	9	–	–
Driver *et al.*[20]	USA	Various for obstetric theatre use	Batch	Clinical	No	756	0	–	–
Ernerot *et al.*[21,]†	Sweden	Various	Batch	Clinical	No	50	0	–	–
Ernerot *et al.*[21,]†	Sweden	Various	Individual	Clinical	Yes	131*	3	40	2
Farrington *et al.*[22]	England	Midazolam or propofol	Individual	Clinical	Yes	100*	7	–	–
Fleer *et al.*[23]	The Netherlands	Parenteral nutrition	Batch	Clinical	No[f]	428	81	–	–
Hernandez-Ramos *et al.*[24]	Mexico	Various	Individual	Clinical	Yes	1011*	60	–	–

Jackson and Gallo[25]	USA	Insulin	Batch	Clinical	No	159[g]	0		
Jacobson *et al.*[26]	USA	Filgrastim (G-CSF)	Batch	Pharmaceutical	No	60[h]	0[h]	–	–
Khalili *et al.*[27]	Iran	Crystalloid fluids	Individual	Clinical[i]	No	92[j]	1[j]	–	–
Kundsin *et al.*[28]	USA	Not stated	Individual	Clinical	Yes[k]	432*	5	247	1
Letcher *et al.*[29]	USA	'Medications'	Individual	Clinical	Yes	224[m,]*	13[m]	142[m]	5[m]
Lorenz *et al.*[30]	Austria	Propofol	Individual	Clinical	No[f]	80[n]	5[n]	–	–
Macias *et al.*[31]	Mexico	Various[p]	Individual	Clinical	Yes	101*	8	–	–
Madeo *et al.*[32]	England	Epidural analgesia	Individual	Clinical	Yes	46[q,]*	3[q]	–	–
Magee *et al.*[33]	England	Anaesthetics, 0.9% w/v sodium chloride and growth medium	Batch	Clinical	No	195	8	–	–

Micard *et al.*[34]	France	Meglumine gadoterate	Batch	Pharmaceutical	No	20	0	–	–
Poretz *et al.*[35]	USA	0.9% w/v sodium chloride in 5% w/v glucose in Ringer's lactate	Individual	Clinical[i]	Yes[j]	110*	10	50	2
Soong[36]	Australia	Propofol	Individual	Clinical	Yes	5*	0	–	–
Spiliotis *et al.*[37]	Greece	Parenteral nutrition	Individual	Clinical	No	80[r]	0[r]	–	–
Stjernstrom *et al.*[38]	Sweden	'Saline' and growth medium	Batch	Clinical	No	100	0	–	–
Thomas *et al.*[39]	USA	Growth medium	Batch	Pharmaceutical	No	2030[s]	7[s]	–	–
Urbano *et al.*[40]	Japan	Growth medium	Individual	Pharmaceutical	No	18	0	–	–
van Doorne *et al.*[41]	The Netherlands	Growth medium	Batch	Pharmaceutical[t]	No	3000	1	–	–

van Grafhorst *et al.*[42]	The Nethelands	Growth medium	Batch	Clinical[i]	No	650	151	–	–
Yorioka *et al.*[43]	Japan	Electrolytes and dobutamine	Individual	Clinical	Yes	290*	0	–	–

*Asterisks indicate doses that were sampled during or after administration, and the absence of an asterisk indicates doses that were sampled without or prior to administration.

†Different aspects examined within the same record.

[a]A clinical environment includes hospital wards or operating theatres; to be classified as a pharmaceutical environment, the record must state compliance with a recognized standard for both the preparation cabinet and immediate room surrounding that cabinet environment.

[b]'Yes' if the doses were sampled during or after administration and 'no' if the doses were sampled without or prior to administration.

[c]In this study, 19 of 276 doses prepared by nurses were contaminated; zero of 502 doses prepared by a pharmacy operator were contaminated.

[d]The data from part 2 of this study have been excluded since they involved unacceptable methodology (a delay in drawing up the dose).

[e]Of the 150 prepared doses, 52 were parenteral nutrition and all of the three contaminated doses were parenteral nutrition.

[f]These doses were administered to patients after they had been sampled.

[g]This record reports that one additional prepared dose was misplaced and not tested.

[h]Includes only those doses prepared in a standardized pharmaceutical environment.

[i]Only the data from a clinical environment are included since the nature of the pharmaceutical environment used is unacceptable/unclear.

[j]Excludes data from vial residues.

[k]Simulated patient administration.

[m]The data reported from the containers rather than from the associated giving sets.

[n]The data from sample 2 of group I have been excluded since they represented the same doses, and data from group II have been excluded due to unacceptable conditions.

[p]Study design excluded patients receiving electrolytes, antibiotics or cancer chemotherapy.

[q]Data reported from cases without reuse of administration sets.

[r]Data from sampling immediately after dose preparation, not those same doses sampled after infusion (when three contaminated samples were identified).

[s]Data from standardized pharmaceutical conditions since the environment used for the negative control doses is unclear.

[t]Excludes the doses prepared in uncontrolled pharmaceutical environments.

Figure 1. The methodological stages of the literature search used to identify studies that report the rate of contamination of doses prepared under aseptic techniques in clinical and pharmaceutical environments.

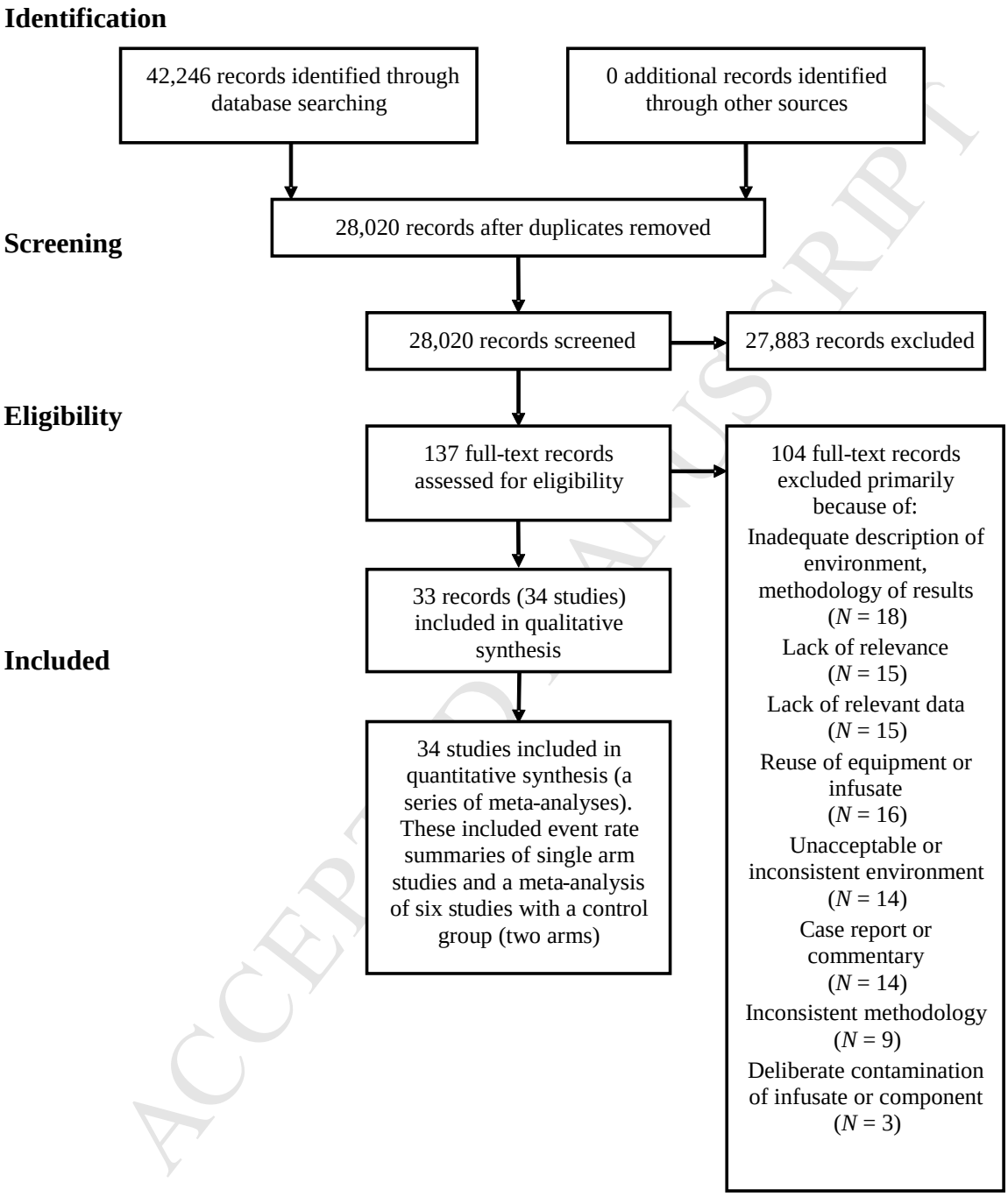

Figure 2.

Forest plot and summary statistics of the frequency of the contamination rates of parenteral doses prepared aseptically in clinical and pharmaceutical environments. Asterisks indicate doses that were sampled during or after administration, and the absence of an asterisk indicates doses that were sampled without or prior to administration. CI, confidence interval.

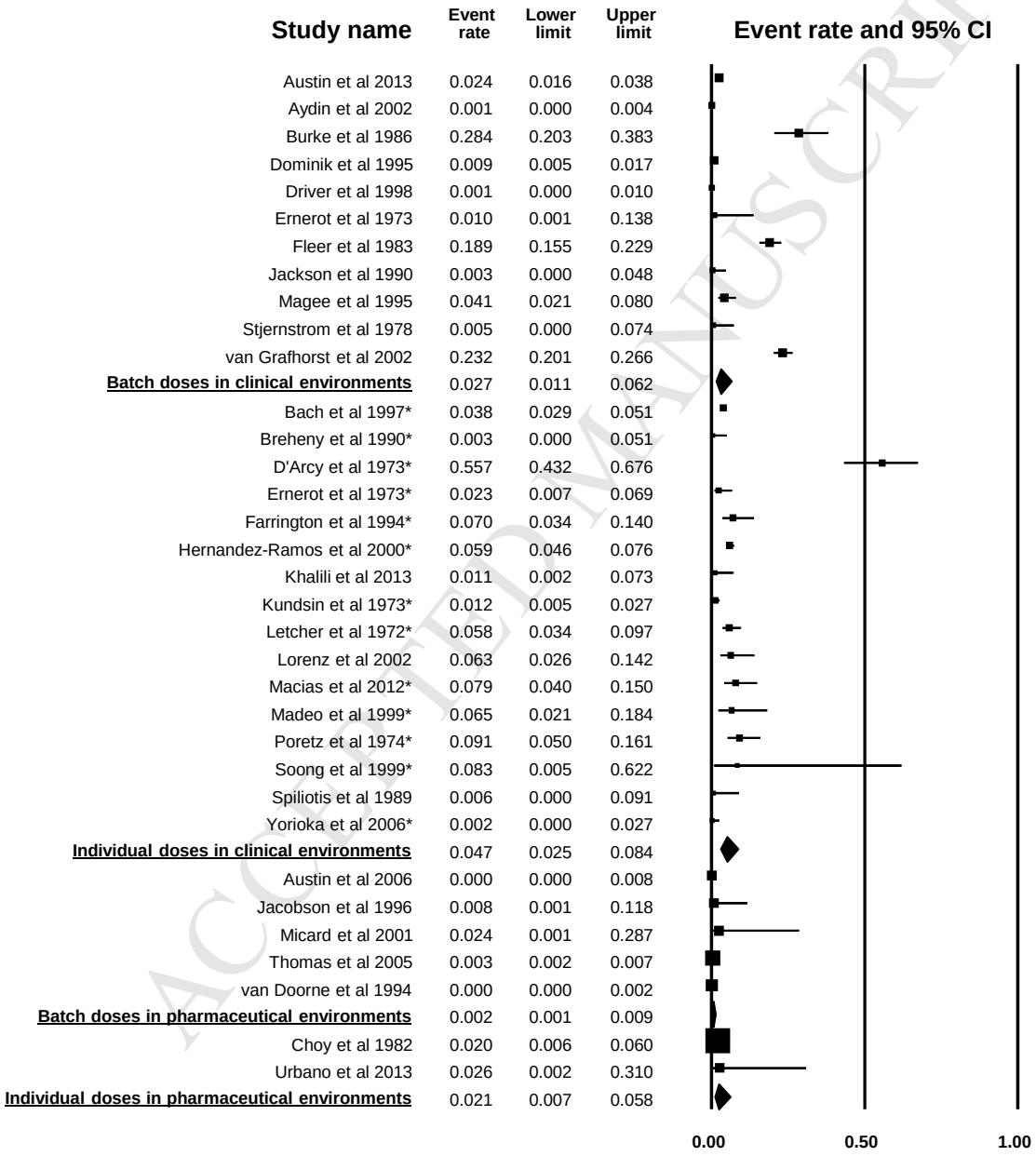

Figure 3. Forest plot of random effects meta-analysis comparing contamination rates of sterile parenteral doses with and without additives in clinical environments. Asterisks indicate doses that were sampled during or after administration. CI, confidence interval.