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"Methods for microbial needleless connector decontamination: A systematic review and meta-analysis" – Interpret results with caution

To the Editor:

We recently read with interest the systematic review and meta-analysis by Flynn et al,[1] which aimed to "compare the effectiveness of connector decontamination with 70% alcohol wipes, alcoholic chlorhexidine gluconate wipes, or alcohol impregnated caps to prevent catheter-associated bloodstream infection (CABSI)." The article concludes that "alcohol impregnated caps and alcoholic chlorhexidine gluconate wipes were associated with significantly less CABSI than 70% alcohol wipes," and that these results require confirmation in randomly assigned controlled trials.

Among the 5 studies included in this meta-analysis, 2 compared chlorhexidine gluconate in isopropyl alcohol (IPA) wipes with IPA wipes for catheter-associated bloodstream infection (CABSI) (Fig 2), and 3 compared IPA caps versus IPA wipes for CABSI (Fig 3). We commend the authors for performing this interesting study. However, we have several statistical suggestions and queries that we would like to share with them.

The authors state that they used a random effect model, but present the results of a fixed effect model, which can be used if there is no heterogeneity. Higgin's I^2 was used to assess heterogeneity. Although this approach is widely mentioned, the point estimate I^2 should be interpreted cautiously when a meta-analysis has few studies,[2] and the confidence interval should be provided.

Conventional meta-analysis relies on several within- and between-study distributional assumptions that are sometimes hidden.[3]

Performing meta-analysis with low event rates or with few studies is challenging, as some of the standard methods are not well suited. For example, estimating between-study heterogeneity is difficult in this situation, and inaccurate estimation of heterogeneity may lead to too narrow confidence intervals.

Different methods may give different results, and using a suboptimal approach may lead to erroneous conclusions.[4]

To avoid selective reporting and to assess the robustness of the results, we performed a sensitivity analysis using a range of statistical methods by using the data provided by Flynn et al.[1]

Frequentist and Bayesian meta-analysis were performed. For frequentist meta-analysis, several methods are available for the random effect model (eg, the Hartung-Knapp-Sidik-Jonkman approach), instead of the classical DerSimonian and the Laird's approach.[5,6] We also used the Mandel-Paule method[7] and Profile Likelihood,[8] with Bartlett's correction.

For Bayesian meta-analysis, we used a binomial-normal model (ie, modeling probabilities of success in each group), instead of modeling estimates of log odds-ratios directly (normal-normal model),[9] with weakly informative priors for the between–trial heterogeneity. We also used a beta-binomial model, which has shown good statistical properties for meta-analysis of sparse data.[7]

Statistical analyses were performed with Stata software (Version 15; StataCorp, LLC, College Station, TX) for the frequentist meta-analysis and R software (R Foundation for Statistical Computing, Vienna, Austria) for Bayesian meta-analysis.

All estimates are shown in Table 1. All confidence intervals (credible interval) contain 1 (except with the DerSimonian-Laird method, which should not be used in the case of meta-analysis with a few studies). That means that alcohol impregnated caps were not associated with significantly less CABSI than 70% alcohol wipes.

In conclusion, the results of this study are interesting. However, readers should interpret them with caution according to the statistical methods used for meta-analysis.

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Conflicts of interest: None to report.

Table 1
Sensitivity analysis performed using different statistical methods to compare IPA cap versus IPA wipe for CABSI

Model/method	Relative risk (95% confidence interval)	II2 (95% confidence interval)	Odds ratio (95% credible interval)
Fixed effect*	0.42 (0.28-0.65)	—	—
Random effect (DerSimonian-Laird)	0.45 (0.22-0.93)	—	—
Random effect (Hartung-Knapp-Sidik-Jonkman)	0.46 (0.14-1.55)	0.0% (0.0%-97.6%)	—
Random effect (Mandel-Paule)	0.43 (0.18-1.07)	59.7% (0.0%-99.4%)	—
Profile likelihood with Bartlett's correction	0.46 (0.055-2.31)	0.0% (0.0%-86.5%)	—
Bayesian (binomial-normal)	—	—	0.38 (0.07-1.45)
Bayesian (beta-binomial)	—	—	0.58 (0.15-2.64)

CABSI, catheter-associated bloodstream infection; *IPA*, isopropyl alcohol.
*As performed by Flynn et al.[1]

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Response to the Letter to the Editor regarding "Methods for microbial needleless connector decontamination: A systematic review and meta-analysis"

To the Editor:

We wish to thank Glélé et al for their interest in our article, "Methods for microbial needleless connector decontamination: A systematic review and meta-analysis" by Flynn et al.[1] We hope that this is a demonstration of a growing interest in needleless connector decontamination and will help increase the quality and quantity of research on the topic.

Glélé et al are correct, we stated that a random effects model was used, but included the fixed effect model instead. We performed both random and fixed effects approaches, for which the findings hardly differed (Fig 1), however we were remiss in not clarifying this in the published manuscript.

We used the Cochrane methodology (Higgins and Green[2] and Review Manager [RevMan version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014]) software to conduct the meta-analyses. As Glélé et al suggested, there are multiple acceptable approaches to analyze these data, nevertheless, the Cochrane Collaboration uses robust, open-source, replicable methodology.[2] Figure 1A shows the original meta-analysis of the alcohol impregnated cap versus the isopropyl alcohol wipe using the fixed methods approach, and Figure 1B shows the same comparison, using the random effects model. This demonstrates similar risk ratio and confidence intervals, and so in this case the decision to use a fixed or random effects model had no impact on results.

We used the Mantel-Haenszel model for meta-analysis of dichotomous variables in RevMan, as the Mantel-Haenszel model has been shown to perform well for fixed effects analysis and in the case of sparse data.[3] Glélé et al suggest that this is not appropriate because of the (possible) statistical heterogeneity due to low number of studies in the review (our analyses demonstrated moderate I^2 values.) The decision for which meta-analysis model to use in a review is much more nuanced[3] than a consideration of statistical heterogeneity alone, and should incorporate elements of clinical setting or patient characteristics. The alternative models suggested by Glélé et al including the Bayesian binomial model certainly offer an alternative statistical approach to be considered for future reviews, in which randomized controlled trials are to be included.[4]

We concluded in our original publication, in-line with Glélé et al, the results should be interpreted cautiously. We believe this is primarily because of the lack of randomized studies, overall low sample sizes, and data quality. Decontamination products are used across the world every day to prevent severe complications such as bloodstream infection. However, our study has demonstrated that this practice is based on low quality evidence. We believe this is a clinical practice that can be causing significant harm, and innovations need to be evaluated using high quality studies, including randomized controlled trials as soon as possible.

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