#### Item 25: LIMITATIONS.

Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).

**Examples.** Outcome level:

“The meta-analysis reported here combines data across studies in order to estimate treatment effects with more precision than is possible in a single study. The main limitation of this meta-analysis, as with any overview, is that the patient population, the antibiotic regimen and the outcome definitions are not the same across studies.”

Study and review level:

“Our study has several limitations. The quality of the studies varied. Randomization was adequate in all trials; however, 7 of the articles did not explicitly state that analysis of data adhered to the intention-to-treat principle, which could lead to overestimation of treatment effect in these trials, and we could not assess the quality of 4 of the 5 trials reported as abstracts. Analyses did not identify an association between components of quality and re-bleeding risk, and the effect size in favour of combination therapy remained statistically significant when we excluded trials that were reported as abstracts.

Publication bias might account for some of the effect we observed. Smaller trials are, in general, analyzed with less methodological rigor than larger studies, and an asymmetrical funnel plot suggests that selective reporting may have led to an overestimation of effect sizes in small trials.”

#### Explanation.

A discussion of limitations should address the validity (i.e., risk of bias) and reporting (informativeness) of the included studies, limitations of the review process, and generalizability (applicability) of the review. Readers may find it helpful if authors discuss whether studies were threatened by serious risks of bias, whether the estimates of the effect of the intervention are too imprecise, or if there were missing data for many participants or important outcomes.

Limitations of the review process might include limitations of the search (e.g., restricting to English-language publications), and any difficulties in the study selection, appraisal, and meta-analysis processes. For example, poor or incomplete reporting of study designs, patient populations, and interventions may hamper interpretation and synthesis of the included studies . Applicability of the review may be affected if there are limited data for certain populations or subgroups where the intervention might perform differently or few studies assessing the most important outcomes of interest; or if there is a substantial amount of data relating to an outdated intervention or comparator or heavy reliance on imputation of missing values for summary estimates (Item 14).