World Health Organization Responds to Concerns about Surgical Site Infection Prevention Recommendations

To the Editor:

We read with great interest the editorial by Hedenstierna *et al.*[1] on the recent World Health Organization (WHO) guidelines for the prevention of surgical site infections (SSIs). Some of the issues raised have been already addressed in *Lancet Infectious Diseases* in response to previous comments.[2,3]

It is important to note that guidelines developed by WHO are not based simply on meta-analyses, as suggested by Hedenstierna *et al*. Rather, WHO uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the quality of a body of evidence and to produce information that is used by guideline panels to formulate recommendations. This includes carefully considering the balance of benefits and harms and aspects related to patient values and preferences, resource implications, feasibility, and acceptability.[4] The guideline panels are composed of international experts from several countries and with different professional and cultural backgrounds.[5] Through this process, the issues raised by Hedenstierna *et al.* were examined, and the panel consensus deemed it appropriate to formulate a recommendation for this intervention.

Hedenstierna *et al.* argue that the administration of an 80% fraction of inspired oxygen (F_{IO_2}) in surgical patients does not lead to a reduced risk of SSIs. Our meta-analysis of all available randomized controlled studies at that time (n = 15) indicated that 80% F_{IO_2} may reduce SSI incidence.[6] However, there was substantial clinical and statistical heterogeneity in the studies, and the 95% CI included no effect (odds ratio [OR] 0.84; 95% CI, 0.66 to 1.06). Upon detailed review, the guideline panel reasoned that an important portion of the heterogeneity was related to differences in the patient population characteristics and delivery of the intervention. Subsequently, subgroup and metaregression analyses were done to investigate the sources of the heterogeneity. These analyses showed robust evidence for a reduction of SSIs in patients under general anesthesia with endotracheal intubation receiving 80% F_{IO_2}, and the panel decided that this intervention should be recommended for this group (OR: 0.72; 95% CI, 0.55 to 0.94). We emphasize that the recommendation is not only based on this subgroup, it is strictly limited to it. There is no generalization of this recommendation to other patients, unlike the recently published recommendations by the American College of Surgeons and Surgical Infection Society, who recommend it for all patients undergoing general anesthesia.[7] Of note, the WHO recommendation for this group of patients was recently echoed in the Centers for Disease Control and Prevention guideline for the prevention of SSIs.[8]

Hedenstierna *et al.* are concerned about the lack of "solid and large trials." We agree that such trials would have made the panel's task easier, but in their absence, the panel had to make recommendations based on the best available evidence from smaller trials. The combined sample size from these trials exceeded the optimal information size by a large margin, and there was thus no serious imprecision.[9] Of note, the largest trial included more than 2,000 patients and showed a statistically significant reduction in SSIs.[10] Hedenstierna *et al.* suggest that if we had excluded this study, which used 70% nitrous oxide (N_2O) in place of oxygen in the control group, the effect would no longer be statistically significant. Excluding this trial *post hoc* would be inappropriate because it met all the inclusion criteria of the systematic review. To address the concerns raised, we conducted a subgroup analysis of trials without the use of N_2O. The estimate from these trials was in line with the overall effect (OR 0.74; 95% CI, 0.58 to 0.95), and there was no evidence for modification of the effect of 80% F_{IO_2} dependent on whether or not patients received N_2O. The results from all other trials were compatible with a reduction in SSIs, except for one small outlying trial.[11] There was little evidence that results differed between trials at higher and lower risk of bias, and risk of bias was generally low.

The study by Kurz *et al.*[12] was not included because it was published outside the predetermined time period of our review. We included this study in a *post facto* analysis, and we found little effect on the estimates: OR 0.75 (95% CI, 0.59 to 0.96) including the Kurz *et al.* study *versus* OR 0.72 (95% CI, 0.55 to 0.94) when excluding it.

The editorialists also expressed concern about potential harms of hyperoxia. However, the literature cited in support of these concerns is based on evidence from settings that differ from the routine clinical settings our recommendations relate to, for example, intensive care units or an animal model.[1] In the review of studies used for our analysis, which included more than 5,000 patients, no evidence of excess pulmonary dysfunction (atelectasis, pneumonia) was found in the groups of patients treated with 80% F_{IO_2}. Furthermore, the WHO guidelines state that patients with chronic lung disease were excluded from most trials, and therefore our recommendation does not apply to these patients.

Finally, Hedenstierna *et al.* used unfortunate language suggesting that we advocated for in-hospital production of oxygen, which would be a gross misrepresentation of the WHO guidelines. The guidelines highlight that the production or procurement of oxygen is an additional cost for the healthcare facility or patient in resource-limited settings. We did not suggest, nor intend to suggest, that oxygen local production should be given priority in low-income countries. Several panel members from low- and middle-income countries contributed to formulating

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the text and were confident that the guidelines adequately informed decision-makers in resource-limited settings.

Competing Interests

The authors declare no competing interests.

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In Reply:

We thank Dr. Solomkin *et al*. for their Letter to the Editor regarding our critical editorial on perioperative hyperoxia and surgical site infection (SSI).[1] A Letter was expected and desirable to settle issues where we are at variance. We will therefore make fully clear that we are not arguing against the statistical tools that have been used to calculate the meta-analyses that serve as the basis for the World Health Organization (WHO) recommendations for perioperative hyperoxia. We are also pleased to read that the WHO panel considers their primary analysis of perioperative hyperoxia to prevent SSI statistically insignificant and with high heterogeneity.

What we were concerned with, and still are, is how this can form the basis for a strong recommendation with moderate quality of evidence.[2] Our concerns are based on two major points:

1. Quality of evidence from randomized clinical trials starts according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach as "high-quality evidence" on the scale: high-, moderate-, low-, very low-quality evidence.[3,4] However, it may be downgraded for several reasons within the domains of (1) study limitations, (2) indirectness of evidence, (3) inconsistency of results, (4) imprecision of results, and (5) publication bias. The WHO recommendation for SSIs is "moderate-quality evidence" (that is, downgraded one level due to inconsistency),[2] but this is in contrast to the current Cochrane review, [5] which interprets evidence from almost the same trials as "low quality of evidence" (that is, downgraded two levels due to risk of bias and imprecision).[5]

Available evidence from trials investigating perioperative hyperoxia for SSI comes from trials of which approximately two thirds are at high or unclear risk of bias,[2,5] and quality of evidence should therefore be downgraded one level for overall risk of bias.[5] Imprecision of results is also an issue, because the CI is wide (*e.g.*, from a 44% relative risk reduction to a 6% relative risk increase for SSI in the primary WHO analysis).[2] Another limitation is the inconsistency of results, because the high overall heterogeneity is not eliminated in the subgroup of patients undergoing general anesthesia with endotracheal intubation (I^2 = 44%, P = 0.05), although the reasons for undertaking the *post hoc* subgroup analyses is stated to be identification of reasons for heterogeneity. In addition, we cannot see the scientific basis as to why the WHO panel "reasoned that an important portion of the heterogeneity was related to differences in the patient population characteristics and delivery of the intervention."

Higgins and Green[4] strongly advise against performing numerous *post hoc* subgroup analyses, because "it is usually possible to find an apparent, but false, explanation for heterogeneity by considering lots of different characteristics." We are still not able to understand the biologic difference between administering oxygen through a face mask or through an endotracheal tube. Although we acknowledge