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Review Article

Effectiveness of 80% *vs* 30–35% fraction of inspired oxygen in patients undergoing surgery: an updated systematic review and meta-analysis

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Abstract

Background: In 2016, the World Health Organization (WHO) strongly recommended the use of a high fraction of inspired oxygen (FiO_2) in adult patients undergoing general anaesthesia to reduce the risk of surgical site infection (SSI). Since then, further trials have been published, trials included previously have come under scrutiny, and one article was retracted. We updated the systematic review on which the recommendation was based.

Methods: We performed a systematic literature search from January 1990 to April 2018 for RCTs comparing the effect of high (80%) *vs* standard (30–35%) FiO_2 on the incidence of SSI. Studies retracted or under investigation were excluded. A random effects model was used for meta-analyses; the sources of heterogeneity were explored using meta-regression.

Results: Of 21 RCTs included, six were newly identified since the publication of the WHO guideline review; 17 could be included in the final analyses. Overall, no evidence for a reduction of SSI after the use of high FiO_2 was found [relative risk (RR): 0.89; 95% confidence interval (CI): 0.73–1.07]. There was evidence that high FiO_2 was beneficial in intubated patients [RR: 0.80 (95% CI: 0.64–0.99)], but not in non-intubated patients [RR: 1.20 (95% CI: 0.91–1.58); test of interaction; $P=0.048$].

Conclusions: The WHO updated analyses did not show definite beneficial effect of the use of high perioperative FiO_2, overall, but there was evidence of effect of reducing the SSI risk in surgical patients under general anaesthesia with tracheal intubation. However, the evidence for this beneficial effect has become weaker and the strength of the recommendation needs to be reconsidered.

Editorial decision: 05 November 2018; **Accepted:** 5 November 2018

Keywords: general anaesthesia; hyperoxia; postoperative outcome; surgical site infection; surgical wound infection

Editor's key points

- In 2017, the WHO strongly recommended the use of a high FiO_2 in adult patients undergoing general anaesthesia to reduce the risk of surgical site infection (SSI).
- Since then, further studies and debate have raised concerns about this recommendation, so the underlying systematic review has now been updated.
- The updated analysis showed no significant effect of the use of high perioperative FiO_2 overall, but did show evidence of reducing SSI risk in surgical patients under general anaesthesia with tracheal intubation.
- The evidence for a beneficial effect of high perioperative FiO_2 has become weaker.
- The strength of the recommendation needs to be reconsidered, and additional data from high-quality trials are urgently needed.

Surgical site infections (SSIs) are amongst the most common healthcare-associated infections.[1,2] They are a cause of increased morbidity, mortality, and prolonged hospital stay, including significant healthcare costs that are estimated to be as high as US$ 16 billion per year in the USA alone.[1–3] Together with the increasing co-morbidity and complexity of surgical patients and the associated procedures,[4] the emergence of antimicrobial resistance[5,6] and continuous increase in the number of surgical procedures performed,[7] the prevention of SSI remains of major importance to the safety, quality, and affordability of healthcare.

There is evidence from both animal and human experiments that oxygen levels at the surgical incision significantly influence the risk of SSI.[8–12] Low tissue oxygenation is associated with an increased incidence of SSI, and it has been hypothesised that increasing the tissue oxygen tension at the surgical site by administering a higher fraction of inspired oxygen (FiO_2) could reduce SSI.[8,11,12] In 2000, a landmark RCT allocated patients undergoing colorectal surgery to either standard FiO_2 of 30% or an increased FiO_2 of 80%. The risk of SSI was reduced by more than 50% in the intervention group.[13] Since then, further trials were done, but with heterogeneous results.[14–16] Furthermore, concerns related to potential adverse effects, such as atelectasis, respiratory failure, cardiovascular complications, and mortality, have been raised.[17–21]

In 2013, a systematic review concluded that high FiO_2 during mechanical ventilation reduced the risk of SSI without increasing the risk of atelectasis,[22] but this conclusion was later disputed by a Cochrane review that included both intubated patients undergoing general anaesthesia and those undergoing neuraxial anaesthesia.[23] For the development of the WHO guidelines for SSI prevention, published in November 2016, a systematic review and meta-analyses were conducted in 2014 to investigate the effects of the use of high (80%) FiO_2 compared with standard (30–35%) FiO_2 on the incidence of SSI in patients undergoing surgery. The WHO reviewers found that 80% FiO_2 was associated with a significant benefit in reducing SSI without evidence of harm when compared with a standard FiO_2 of 30% or 35% in intubated patients.[24,25] Notably, they found no benefit in studies using neuraxial anaesthesia, where FiO_2 was administered through a face mask or nasal cannula whilst patients were awake.

Based on these findings and extensive discussions by the guideline development group, WHO recommended that, 'Adult patients undergoing general anaesthesia with tracheal intubation for surgical procedures should receive an 80% fraction of inspired oxygen intraoperatively and, if feasible, in the immediate postoperative period for 2–6 h to reduce the risk of SSI'. In line with rigorous WHO standards, details on the guideline development process, summaries of the evidence, rationale for the recommendation, considerations on resource use, values, and preferences, and research gaps were made available.[24] Since then, guidelines by the US Centers for Disease Control and Prevention (CDC) and other organisations have made similar recommendations.[26,27]

However, these recommendations have sparked debate on the benefits and harms of hyperoxia. Stakeholders raised their concerns in editorials and journal correspondence.[28–34] Some concerns were based on evidence from animal studies or clinical settings different from perioperative care, and were countered by the available direct evidence. Other concerns could be resolved through clarification of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[35] and explanations detailing the WHO guideline development process.[36,37] There were also issues that required further investigation and reanalysis of the available evidence, including concerns regarding the exclusion of recently published data,[28–33] about studies using nitrous oxide (N_2O) in the control group,[28,33] and safety issues.[28–33] WHO responded to the commentaries,[36] and agreed that the emerging new evidence on effectiveness and safety should be assessed. Finally, one of the trials included in the WHO initial review[24,25] has since been retracted because of non-reproducible statistics.[38] More retracted trials from the same author were identified,[39,40] and other (not retracted) trials contained discrepancies that require further investigation.[41–43]

We updated the systematic review and meta-analysis on which the WHO recommendation was based. A systematic review of adverse events after the use of high FiO_2 has also been conducted in response to concerns raised.[44]

Methods

This systematic review was conducted to update the one initially conducted for the WHO guidelines for SSI prevention,[24,25] following the *WHO Handbook for Guideline Development*[45] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[46]

Search strategy

A librarian was consulted for the development of the search strategy. Medline (PubMed), Excerpta Medica Database (EMBASE), Index Medicus, Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index to Nursing and Allied Health Literature, and WHO regional medical databases were systematically searched for studies published between January 1, 1990 and April 20, 2018. The updated search was conducted on April 20, 2018. Only studies published from 1990 onwards were considered, as infection prevention practices before 1990 differ from current practice, including important related areas, such as preoperative antibiotic prophylaxis. No language restriction was applied. Search terms included surgical wound infection, surgical infection, postoperative wound infection, wound infection, pre-, peri-, intraoperative, infection, oxygen, oxygen inhalation therapy, oxygenation, inspired oxygen fraction, FiO_2, and related medical subject headings. The complete search strategy is available in Supplementary Table S1.

Study selection

The RCTs investigating the effect of perioperative administration of increased (80%) compared with standard (30–35%) FiO_2 on the incidence of SSI in patients undergoing surgical procedures were eligible. In an effort to capture all relevant publications, no restriction was applied to outcome definitions or length of follow-up. Two authors (J.S. and S.J.) independently screened the titles and abstracts retrieved from the search for potential eligibility. When the title and abstract indicated potential eligibility, or if insufficient information was supplied for assessment, the full-text article was obtained. Any disagreements were resolved through discussion or after consultation with a third author (B.A.).

Data extraction

Two authors (J.S. and S.J.) independently reviewed each eligible article and extracted relevant data using a predefined data extraction form. Data collection included author, publication date, design, scope, participants, type of surgery, procedure duration, outcome definition, intervention, control, postoperative oxygenation, tracheal intubation, base gas, preoperative antibiotics, temperature, fluids, and resource use.

Risk of bias

Two authors (J.S. and S.J.) independently assessed the risk of bias of each of the included studies using the Cochrane Collaboration tool for RCTs.[47] Specifically, risk of attrition bias was considered low if the analysis was according to the intention-to-treat principle, or if attrition was balanced and unlikely to have affected results. If attrition was unbalanced and high relative to the incidence of SSI, risk of bias was considered high. When attrition was insufficiently described, risk of bias was considered unclear. Outcome reporting bias was assessed by reviewing the study registration or protocol. If no outcomes were omitted or altered, risk of bias was considered low. If no trial registration or protocol was available, risk of outcome reporting bias was considered unclear. Conflicts were resolved through discussion or after consultation with a third author (B.A.). The possibility of publication bias was assessed using a contour-enhanced funnel plot.[48] A risk-of-bias graph and summary table were constructed using Review Manager (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Statistical analysis

The primary outcome, SSI, was expressed using the pooled relative risk (RR) with the corresponding 95% confidence interval (CI). A random effects model (DerSimonian and Laird) was used to account for potential clinical and statistical heterogeneity.[49] The χ^2 test for heterogeneity was computed and the amount of heterogeneity was quantified by the I^2 statistic. The extent of heterogeneity was evaluated using the between-study variance (τ^2). Potential sources of heterogeneity were discussed by the guideline development group, and their importance was examined in random effects meta-regression analyses.[50,51] Using sensitivity analyses, we examined the effect of including the studies retracted or under investigation for concerns related to their validity at the time of the conduct of this review. Statistical analyses were performed using Stata version 15.0 (Stata Statistical Software, release 15; StataCorp, College Station, TX, USA).

GRADE assessment

The quality of the retrieved evidence was judged using GRADE methodology (GRADEpro software; http://gradepro.org/).[35]

Results

Study selection

The updated search retrieved 3005 potentially relevant records; one additional study was identified through other sources. After removal of duplicates, 2446 records were screened, and 69 full-text publications were assessed for eligibility. Twenty-one RCTs were critically appraised, including six studies published after the previous systematic review. We excluded four studies by Schietroma and colleagues[38,41–43] because of the retraction of one paper, and discrepancies and concerns pending clarification on the validity of three others. A total of 17 RCTs were included.[13–16,52] The selection procedure is summarised in Figure 1.

Study characteristics

The study characteristics are shown in Table 1. A total of 7817 participants were included in 17 RCTs from Asia, Europe, and North America that compared the effect of high (80%) to standard (30–35%) perioperative FiO_2 on the incidence of SSI. Ten studies used the CDC definition of SSI. The remaining studies used extensive clinical descriptions that overlapped with the CDC definition. Follow-up ranged from 2 to 12 weeks. All studies administered 80% FiO_2 in the intervention group; 16 studies administered 30% FiO_2 in the control group and one study used 35% oxygen. Four studies used N_2O in the gas mixture. The other studies used nitrogen (N_2) or room air. In 12 studies, patients were under general anaesthesia with tracheal intubation and mechanical ventilation. In the remaining five trials, patients were anaesthetised but awake and breathing spontaneously, with the allocated gas mixture delivered via a face mask or nasal cannula. Eleven studies reported the administration of antibiotic prophylaxis in the preoperative period. Amongst the remaining six, three studies reported antibiotic prophylaxis administered after cord

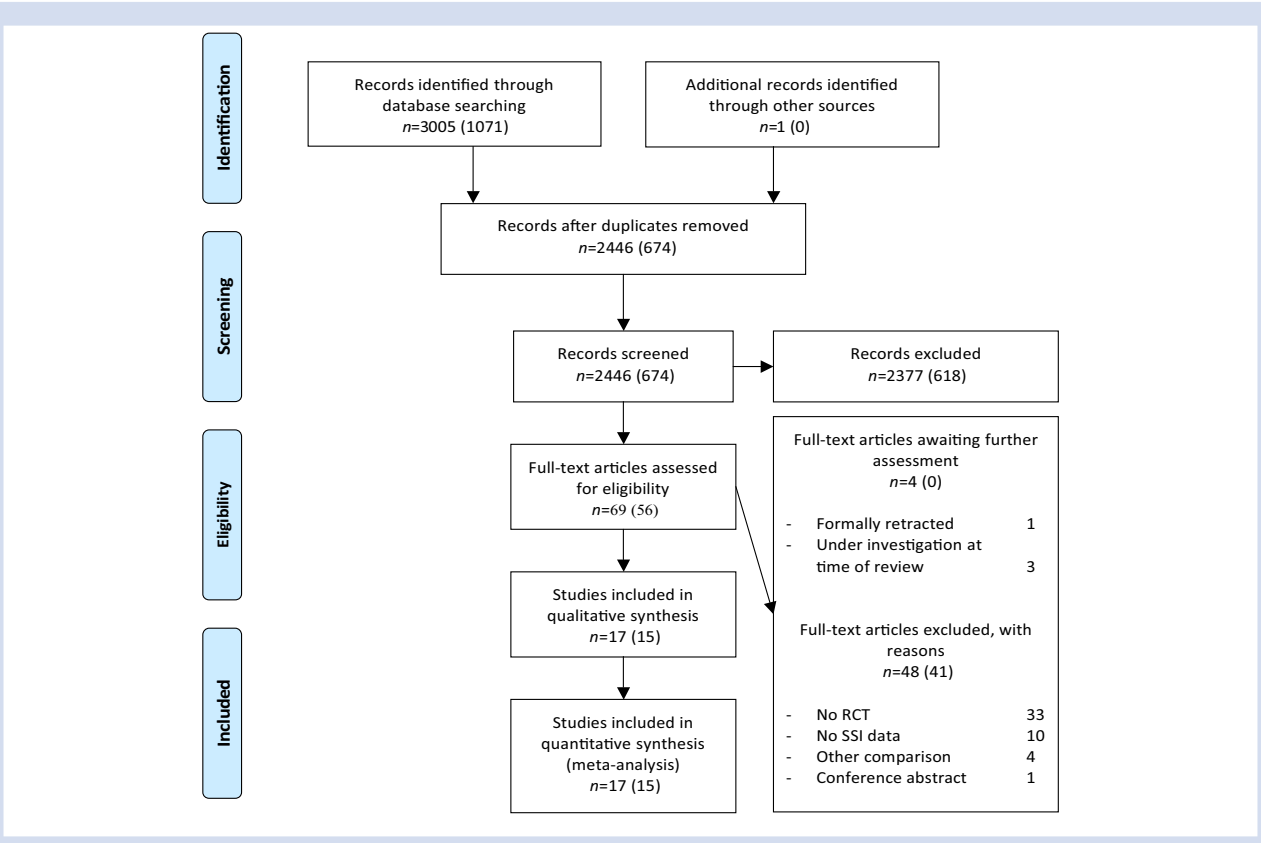

Fig 1. Flow chart of study selection.[46] Numbers between brackets represent the original search dating from 2014. SSI, surgical site infection.

clamping after Caesarean section; no specific information on the timing of antibiotic prophylaxis was provided for the other three. Seven studies described active warming to maintain normal core temperature, whereas the remaining 10 did not describe any method. Fluid regimens ranged from the administration of 15 ml kg^{-1} h^{-1}, and replacement of losses to administration of fluids was limited to measured or calculated deficits. Operative procedures ranged from surgery of the gastrointestinal tract, including five studies specifically on colorectal procedures, to Caesarean sections and trauma surgery. The mean procedure duration ranged from 30 min up to 4 h. Sixteen studies were limited to adult participants, and one included participants of 13 yrs and older.[63]

Risk of bias

The results of the risk-of-bias evaluation are given in Figure 2 and Supplementary Figure S1. Overall, the risk of bias was moderate. It was generally low in all domains, but sometimes unclear and incidentally high. Selective reporting of outcomes led to a high risk of bias in one study.[62] In another study, risk of bias was high because of lack of blinding.[56] Several studies provided too little information to determine the risk of bias. A funnel plot is presented in Supplementary Figure S2; no asymmetry was detected.

Meta-analyses, meta-regression, and sensitivity analyses

Meta-analyses of all included trials showed little evidence of a benefit of perioperative administration of high (80%) FiO_2 on the prevention of SSI compared with standard (30–35%) FiO_2: RR: 0.89; 95% CI: 0.73–1.07 (Table 2). There was evidence of heterogeneity (τ^2=0.055; χ^2 test for heterogeneity P=0.025; I^2=45.4%). The forest plot is presented in Figure 3. The guideline development group noted that the method of delivery of the intervention (i.e. under general anaesthesia with tracheal intubation and mechanical ventilation *vs* oxygen administration via a face mask or nasal cannula without intubation) and the type of procedure could be potential effect modifiers. Meta-regression indicated that the method of oxygen administration modified the effect of administration of high FiO_2 on the incidence of SSI (test of interaction, P=0.048; proportion variance explained, 27%). In patients under general anaesthesia with tracheal intubation and mechanical ventilation, 80% FiO_2 reduced the incidence of SSI [RR: 0.80 (95% CI: 0.64–0.99); τ^2=0.051; χ^2 P=0.043; I^2=46.7%]. In contrast, if patients were awake and breathed spontaneously via a face mask or nasal cannula, there was no evidence of a benefit of the intervention [RR: 1.20 (95% CI: 0.91–1.58); τ^2=0.000; χ^2 test for heterogeneity, P=0.482; I^2=0.0 %]. The type of procedure did not affect the effect estimate (test of interaction, P=0.078). Similarly, there was no evidence that the use of N_2O_2 in the gas mixture influenced the effect (test of interaction, P=0.945).

Sensitivity analysis (Supplementary Table S2) showed that the effects were larger when the four studies either retracted or under investigation were included[41–43]; the overall RR was 0.80 (95% CI: 0.67–0.97) and 0.72 (95% CI: 0.59–0.88) amongst

Table 1 Characteristics of the studies included in the systematic review. Procedure duration: mean, or if not specified, based on exclusion criterion. CDC: Centers for Disease Control and Prevention; NA, not available; N_2, nitrogen; N_2O, nitrous oxide

Study	Design, scope, participants	Type of surgery, procedure duration	Outcome definition (CDC), follow-up	Intervention *vs* control	Postoperative oxygenation	Tracheal intubation	Base gas	Preoperative antibiotics	Temperature regimen	Fluids
Greif and colleagues (2000)[13]	RCT, multicentre, 500	Colorectal surgery, 3.1 h	No, 15 days	80% *vs* 30%	2 h	Yes	N_2	Yes	≥36°C	15 ml kg^{-1} h^{-1}
Pryor and colleagues (2004)[14]	RCT, single centre, 160	Major abdominal surgery, 3.7 h	No, 14 days	80% *vs* 30%	2 h	Yes	NA, N_2O included	Yes	NA	NA
Belda and colleagues (2005)[15]	RCT, multicentre, 291	Colorectal surgery, >1 h	Yes, 14 days	80% *vs* 30%	6 h	Yes	Air	Yes	Active	15 ml kg^{-1} h^{-1}
Mayzler and colleagues (2005)[52]	RCT, single centre, 38	Colorectal surgery, 2.3 h	Yes, 30 days	80% *vs* 30%	2 h	Yes	N_2, N_2O	Yes	≥35.5°C	15 ml kg^{-1} h^{-1}
Myles and colleagues (2007)[53]	RCT, multicentre, 2012	Surgery >2 h, 3.3 h	Yes, 30 days	80% *vs* 30%	No	Yes	N_2, N_2O	Institutional practice	>35.5	Anaesthesiologist's discretion
Gardella and colleagues (2008)[54]	RCT, single centre, 143	Caesarean section, 0.8 h	No, 14 days	80% *vs* 30%	2 h	No	Air	No	NA	NA
Meyhoff and colleagues (2009)[16]	RCT, multicentre, 1386	Laparotomies, 2.2 h	Yes, 14 days	80% *vs* 30%	2 h	Yes	NA, N_2O free	Yes	NA	Only to replace deficits
Bickel and colleagues (2011)[55]	RCT, single centre, 210	Open appendectomy, 0.5 h	No, 14 days	80% *vs* 30%	2 h	Yes	Air and N_2	Yes	Active	NA
Scifres and colleagues (2011)[56]	RCT, single centre, 585	Caesarean section, 1 h	Yes, 4 weeks	80% *vs* 30%	2 h	No	Air	Yes	NA	NA
Thibon and colleagues (2012)[57]	RCT, multicentre, 434	Abdominal, gynaecological, and breast surgery, 1.5 h	Yes, 30 days	80% *vs* 30%	No	Yes	NA	NA	NA	NA
Duggal and colleagues (2013)[59]	RCT, single centre, 831	Caesarean section, NA	Yes plus endometritis, 2 weeks	80% *vs* 30% (after cord clamping)	1 h	No	Air	No	NA	NA
Williams and colleagues (2013)[61]	RCT, single centre, 160	Caesarean section, 0.9 h	Yes plus endometritis, 30 days	80% *vs* 30%	2 h	No	Air	No	NA	NA
Stall and colleagues (2013)[60]	RCT, single centre, 235	Open reduction and internal fixation, 3.8 h	Yes, 12 weeks	80% *vs* 30%	2 h	Yes	NA	Yes	NA	NA

Continued

Table 1 Continued

Study	Design, scope, participants	Type of surgery, procedure duration	Outcome definition (CDC), follow-up	Intervention vs control	Postoperative oxygenation	Tracheal intubation	Base gas	Preoperative antibiotics	Temperature regimen	Fluids
Chen and colleagues (2013)[58]	RCT, single centre, 91	Colorectal surgery, 3.1 h	Yes, 30 days	80% vs 30%	24 h	Yes	N_2, N_2O	Yes	>35.5	Anaesthesiologist's discretion
Kurz and colleagues (2015)[62]	RCT, multicentre, 586	Colorectal surgery, 3.5 h	Yes, 30 days	80% vs 30%	1 h	Yes	N_2	Yes	36°C	10–11 ml kg^{-1} h^{-1}
Fariba and colleagues (2016)[64]	RCT, single centre, 122	Caesarean section, 1 h	No, 14 days	80% vs 30%	6 h	No	Air	NA	NA	NA
Wasnik and colleagues (2015)[63]	RCT, single centre, 64	Appendectomy	No, NA	80% vs 30%	2 h	Yes	NA	Yes	NA	NA

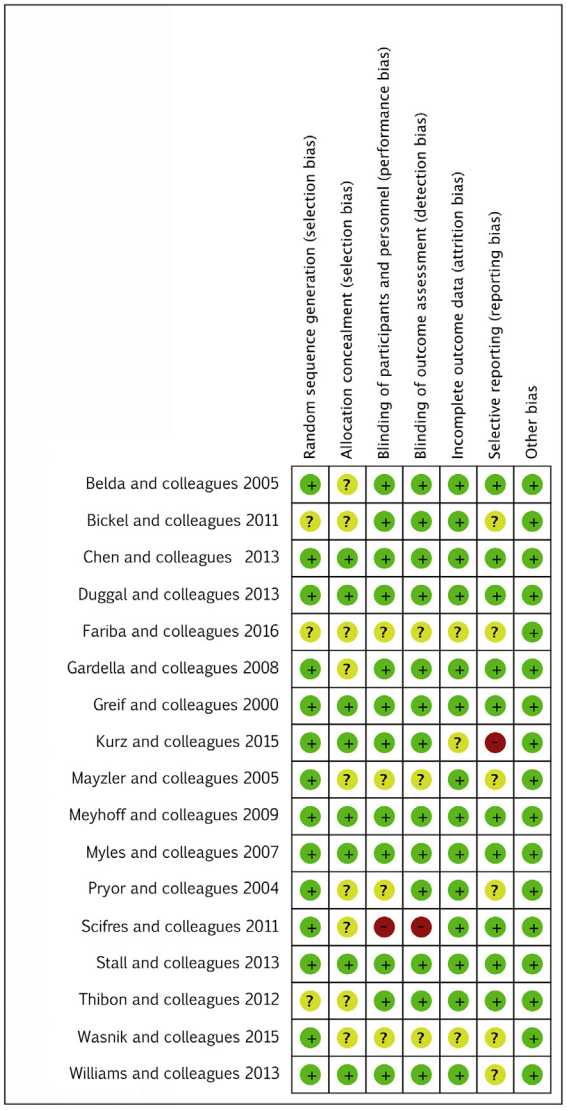

Fig 2. Risk-of-bias summary. Green bubbles represent low risk of bias, yellow bubbles represent unclear risk of bias, and red bubbles represent high risk of bias.

intubated patients only. The results from the meta-regression analyses were similar to the main analysis. The meta-regression analysis comparing the four excluded studies with the 17 included studies indicated that the excluded papers would have significantly influenced the effect (test of interaction, P=0.01).

Quality of the evidence on the relative effect of the use of high FiO_2

The GRADE assessment was restricted to studies describing patients undergoing general anaesthesia with tracheal intubation and mechanical ventilation. All included studies were RCTs, thus resulting in high starting quality. Overall, the quality of evidence was assessed as moderate (Supplementary Table S3).

Table 2 Results of meta-analyses and meta-regression analyses. SSI, surgical site infection

	Studies, *N*	SSI in the intervention groups, *n/N*	SSI in the control groups, *n/N*	Relative risk (95% confidence interval)	Test of interaction from meta-regression (*P*-value)	Between-study variance (τ^2)	Variance explained (%)
Overall							
All	17	446/3889	514/3928	0.89 (0.73–1.07)	NA	0.055	NA
By delivery of oxygen: intubation (yes/no)							
Yes	12	350/2978	431/2998	0.80 (0.64–0.99)	0.048	0.04	27
No	5	96/911	83/930	1.20 (0.91–1.58)			
By type of procedure: colorectal (yes/no)							
Yes	5	87/732	127/743	0.68 (0.49–0.96)	0.078	0.05	9
No	12	359/3157	387/3185	0.98 (0.79–1.23)			
By gas mixture: N_2O (yes/no)							
Yes	4	104/1126	137/1175	0.92 (0.48–1.73)	0.945	0.069	0
No	13	342/2763	377/2753	0.89 (0.73–1.09)			

Discussion

In this update of the previous systematic review performed in January 2014[25] and used for developing the WHO guideline,[24] we applied the same rigorous approach. Subgroup analyses were conducted to investigate possible effect modifications. Furthermore, we adopted a conservative approach in excluding four trials by Schietroma and colleagues,[38,41–43] as one has been recently retracted and others are under

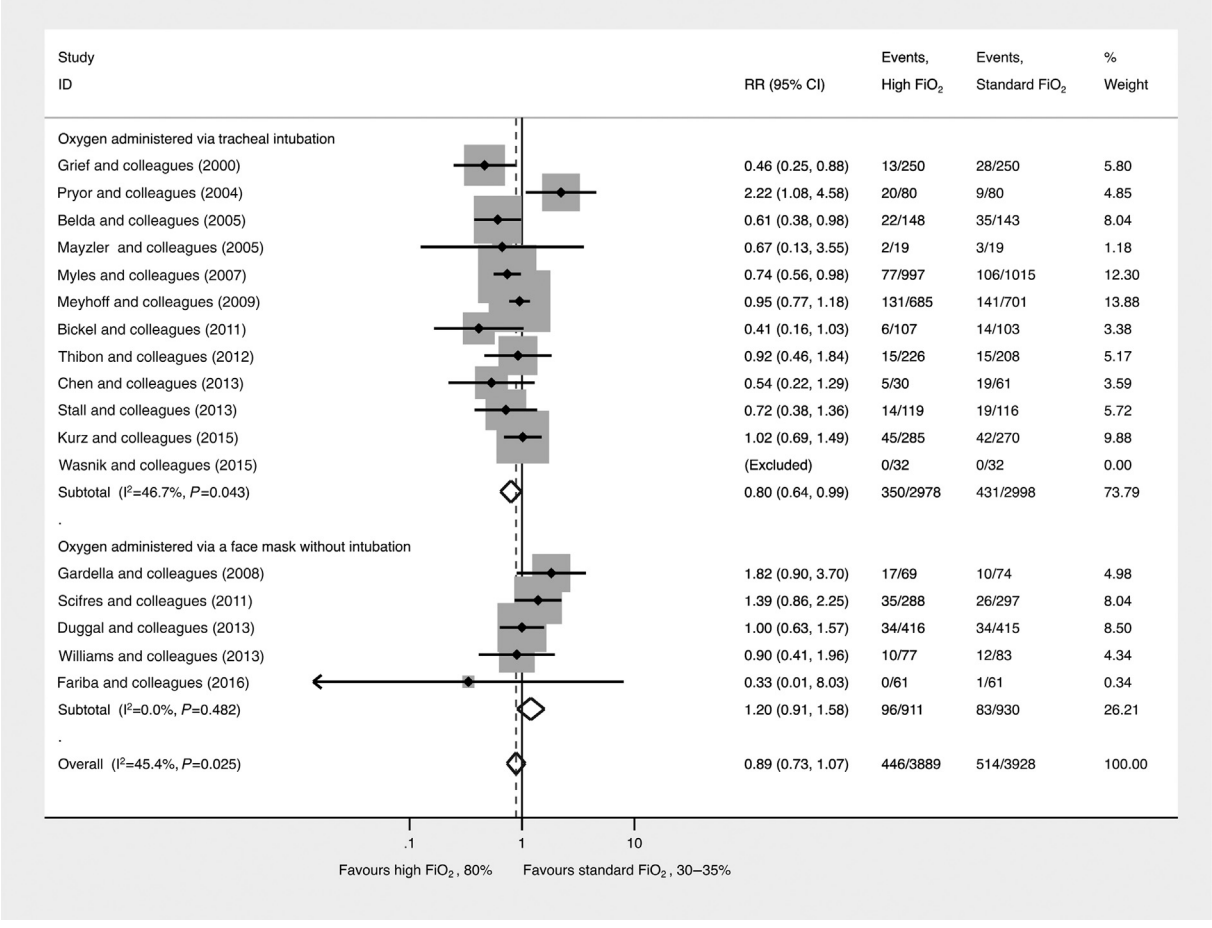

Fig 3. Forest plot analysis by delivery of the intervention. The X-axis represents relative risk (RR); each row on the Y-axis represents an individual study. The solid diamonds and horizontal lines represent point estimates and corresponding 95% confidence intervals (CIs) of the individual studies, respectively. The transparent diamonds represent the pooled estimate and 95% confidence interval of each subgroup, and the overall analysis.

investigation. The meta-analysis of all 17 RCTs, including 6552 patients, showed no evidence for a benefit of the use of high (80%) FiO_2 in reducing the incidence of SSI when compared with standard FiO_2 (30–35%). However, similar to the previous analysis, subgroup analyses and meta-regression showed an association between the delivery of the intervention and the effect estimate. In studies where the intervention was administered under general anaesthesia with tracheal intubation and mechanical ventilation, there was evidence of a benefit of the use of high FiO_2. In contrast, there was no evidence of a benefit or heterogeneity detected when patients were anaesthetised, but breathing their allocated gas mixture administered via a face mask or nasal cannula. Further subgroup analyses showed no evidence for effect modification by surgical procedure type or by gas mixture, as suggested by some commentaries published in response to the initial WHO recommendation.[28–33]

This update of the analysis is in line with our original review and earlier findings by other authors.[22,23,25,65] However, effect modification by means of oxygen administration was not analysed in two recent reviews, despite recognition of the potential relevance of the type of anaesthesia[23,65] and an indication of effect in patients under general anaesthesia with tracheal intubation, as shown in an earlier review.[22] Nonetheless, the evidence from our updated analysis has become weaker after the exclusion of four studies with disputed credibility[38,41–43] and the net addition of four new trials.[58,62–64] The additional information did not strengthen the evidence for effect modification found in the original review and the evidence for a benefit in patients undergoing general anaesthesia with tracheal intubation that led to the strong recommendation in the WHO guidelines.[24,25] The meta-regression analysis indicated that the excluded studies by Schietroma and colleagues[38,41–43] would have significantly influenced the effect if they had been retained in the analysis. The sensitivity analysis, including these trials, showed larger effect estimates and, notably, a significant effect in the overall analysis and strong effect modification according to the method of oxygen administration. However, given the concerns about these trials, inclusion was no longer justified. At present, three large new RCTs on the effect of high perioperative FiO_2 are registered at www.clincaltrials.gov. Once completed, these trials may clarify the issue.

Limitations

This review has some limitations. Although the methodology was developed in a rigorous process consistently applied by WHO when gathering evidence for the development of the guidelines, the subgroup analyses described here and identified as critical by the experts were not prespecified. This is a limitation carrying the risk of Type 1 error. However, the substantial difference in the intervention effect and the clear biological difference in the intervention, and statistical support for effect measure modification, led the guideline development group to believe that reporting of this effect was warranted and should inform the patient population concerned by the recommendation. Other limitations of our analysis are related to pooling studies that span nearly 20 yrs and cover an intervention in a complex and rapidly evolving field, inevitably introducing heterogeneity in the analysis.

The WHO has taken the concerns expressed by external experts on the validity of the evidence base of its recommendation on the use of high FiO_2 very seriously, and has updated the systematic review and conducted further analyses, excluding trials of uncertain validity. Furthermore, in order to respond to concerns about the potential harm of administering high FiO_2, the WHO commissioned a separate independent systematic review on adverse events associated with this intervention in patients undergoing surgical procedures.[44]

In conclusion, whilst no effect of the use of high FiO_2 in the perioperative phase was found in the overall analysis, this intervention delivered through intubation and mechanical ventilation may reduce the risk of SSI. However, the evidence for a beneficial effect has become weaker and the strength of the recommendation needs to be reconsidered. The WHO guideline development group will reconvene to discuss the implications of these findings. Additional data from high-quality trials are urgently needed, as well as a timely revision of the guidelines to account for future relevant newly emerging evidence.

Authors' contributions

Methodology planning: all authors.
Devising search strategies: JS, SJ.
Conducting searches: JS, SJ.
Determining eligibility of search results: JS, SJ.
Data analyses: SJ, JS.
Extracting and assessing data validity: JS, SJ.
Data interpretation: all authors.
Statistical analysis: SJ.
Providing critical advice: JS, ME, YKL.
Writing manuscript: SJ, ME, JS, BA.
Reviewing of final version: all authors.

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Declaration of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the views expressed in this article, and these do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2018.11.024.

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