Meta-analysis

Meta-analysis of intraoperative povidone–iodine application to prevent surgical-site infection

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Background: **The effectiveness of intraoperative povidone–iodine (PVI) application in the reduction of surgical-site infection (SSI) remains controversial. This meta-analysis was performed to assess the effect of intraoperative PVI application compared with no antiseptic solution (saline or nothing) on the SSI rate.**

Methods: **The meta-analysis included randomized controlled trials that compared intraoperative PVI lavage with no PVI in patients undergoing surgery with SSI as the primary outcome. A fixed-effects or random-effects model was used as appropriate, and heterogeneity was assessed by the Cochran Q and the I^2 value.**

Results: **Twenty-four randomized controlled trials totalling 5004 patients (2465 patients with PVI and 2539 patients without) were included: 15 in the main analysis and nine in the sensitivity analysis. The rate of SSI was 8·0 per cent in the PVI group and 13·4 per cent in the control group. Intraoperative PVI application significantly decreased the SSI rate (relative risk 0·58, 95 per cent confidence interval 0·40 to 0·83; $P = 0·003$) and consistent results were observed in subgroup analyses according to the method of PVI administration, its timing and the type of surgery.**

Conclusion: **The meta-analysis results suggested that the use of intraoperative PVI reduced rates of SSI.**

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Introduction

Surgical-site infection (SSI) is the most common hospital-acquired infection after surgery[1]. In France[2] and the UK[3], SSIs are the third most common hospital-acquired infection overall (14 per cent), and the most common in Finland (29 per cent)[4]. They result in increased duration of postoperative hospital stay, increased mortality[5] and higher costs[6]. Reducing the SSI rate is thus a major priority for infection control teams.

Surgeons' practices differ with regard to intraoperative lavage, and particularly the solutions used (antiseptic or saline). In 2005, Whiteside and colleagues[7] found that 97 per cent of general surgeons used intraoperative peritoneal lavage in patients with peritonitis; saline was the most frequently used fluid and povidone–iodine (PVI) the most frequent antiseptic. Another survey of orthopaedic surgeons in 2008 revealed that 87 per cent used saline lavage alone, or with bacitracin, for open fracture management, 6 per cent used an iodine-based antiseptic and 2 per cent chlorhexidine; the majority of surgeons believed that iodine was more effective than saline[8].

Many studies have compared the SSI rate between patients with and without intraoperative antiseptic lavage, but their results are controversial. The most frequently used antiseptic is PVI, applied either by irrigation or by spray. A recent literature review reported the potential efficacy of intraoperative irrigation of PVI in preventing SSI[9], but the authors did not perform a meta-analysis to quantify this effect. Several guidelines for the prevention of SSI have already been published[10,11]. These mainly focused on preoperative preparation (skin disinfection, hair removal, antibiotic prophylaxis). Recently, the National Institute for Health and Clinical Excellence (NICE) has published guidelines on SSI prevention, including the intraoperative phase[12]. Its methodology was not well detailed and some randomized trials comparing the SSI rate between patients with and without intraoperative PVI were not included in its literature review.

The main goal of this meta-analysis was to assess the effectiveness of intraoperative PVI in the reduction of SSI.

The secondary goal was to assess its effectiveness according to the method of administration (spray or irrigation).

Methods

The QUOROM (quality of reporting meta-analyses) statement[13] and Cochrane Collaboration handbook[14] were used as guidance for the completion of this meta-analysis.

Search strategy

An extensive unrestricted computerized literature search was conducted on several sources (MEDLINE, ScienceDirect, LILACS and Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, database of abstracts of reviews of effects, Health Technology Assessment database) to identify studies published from the inception of each database to November 2009. The following keywords were used in various combinations: antiseptics, antisepsis, povidone–iodine AND irrigation, fluid lavage, wound irrigation, spray, spraying AND surgery, surgical wound infections. The titles and abstracts of studies that were potentially relevant were scanned. When the studies seemed to meet eligibility criteria, or when information was insufficient to exclude them, the full articles were read. The reference lists of the retrieved articles, or of articles dealing with literature review, were scanned for additional studies. Data from abstracts, conference proceedings and correspondence were included as long as the data were not subsequently duplicated in published articles.

Inclusion and exclusion criteria

Randomized controlled trials that compared intraoperative PVI application *versus* no PVI during surgery, with postoperative SSI as the primary outcome were included. Intraoperative application was defined as PVI just before or after wound closure.

Exclusion criteria were: non-randomized trials, studies reporting only bacterial endpoints (bacteriological counts) and studies performed on animals. Articles dealing with interventions for a SSI, or patients having emergency sutures, or with lacerations or burn wounds were also excluded. Review articles were excluded, although these papers were identified and searched for additional references.

Data abstraction and quality assessment

Two reviewers independently screened articles eligible for inclusion. Disagreements were settled by discussion with a third reviewer who was unaware of the reason for discrepancies. A standard form was used to assess the eligibility of each study on the basis of the full article. Information was extracted on study characteristics (randomization procedure, blind assessment at baseline and follow-up, follow-up interval, intention-to-treat analyses and losses to follow-up), participants (inclusion criteria, numbers of individuals in randomized groups, age of participants, baseline comparisons, and country and date of recruitment), intervention and outcomes. Methodological quality assessment was performed based on several criteria: randomization, concealment of allocation, blinding and completeness of follow-up. The risk of bias was consequently graded as low, moderate or high[14].

To explore potential sources of heterogeneity, the number of patients who also had antibiotic prophylaxis or treatment was recorded, as well as the type of surgery and publication date.

Quantitative data synthesis

All analyses were performed with Stata® software version 10 (StataCorp, College Station, Texas, USA). The pooled effect estimates for binary variables were expressed as a relative risk (RR) with 95 per cent confidence interval. Meta-analyses were done using a fixed-effects model, unless significant heterogeneity was observed, in which case a random-effects model was used. Cochran Q and I^2 measure of inconsistency[15] were used to assess the heterogeneity of results, which was defined as low, moderate and high according to I^2 values of 25, 50 and 75 per cent respectively.

A sensitivity analysis was done by including studies with a lower methodological quality (studies with a risk of bias graded as moderate). Separate analyses were performed according to the method of administration of PVI (spray *versus* irrigation). Subgroup analyses were also carried out according to publication date, type of surgery, timing of application of PVI (before or after wound closure) and the depth of any subsequent infection (superficial or deep).

Publication bias was assessed by a funnel plot, in which the RR for each study was plotted against its standard error. It was also assessed by the Begg[16] and Egger[17] tests.

Results

Identification of studies

Of 474 unique citations, 447 were excluded either on initial screening or after full review.

Twenty-seven randomized controlled trials met the inclusion criteria and were retrieved for full critical appraisal (*Fig. 1*). Three of these were excluded: a congress

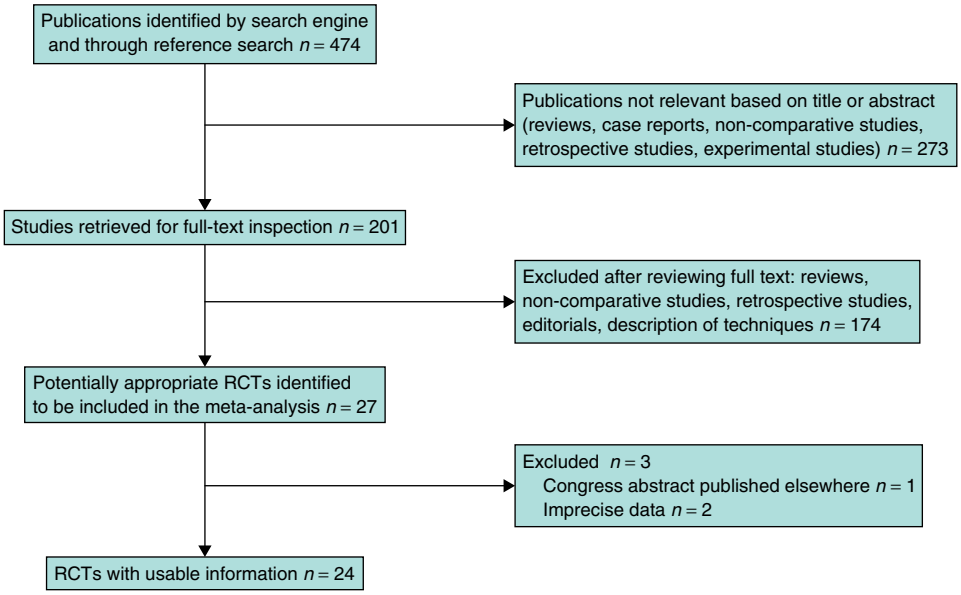

Fig. 1 Flow chart showing the process of identification of randomized controlled trials (RCTs) for inclusion in the systematic review

Table 1 Characteristics of studies included in the main and sensitivity analyses

Reference	Surgery	Country	Study interval	Sample size
Studies included in the main analysis				
Gilmore and Sanderson[22]	Abdominal surgery	UK	1975*	144
Gilmore *et al.*[23]	Non-abdominal surgery	UK	1977*	101
Galland *et al.*[25]	Laparotomy	UK	1977*	76
Foster *et al.*[26]	Appendicectomy	UK	1978	236
Rogers *et al.*[27]	General surgery	USA	1979	187
Sindelar and Mason[28]	General surgery	USA	1979*	500
Sindelar and Mason[29]	Laparotomy	USA	1979*	168
Galle and Homesley[30]	Gynaecological malignancies	USA	1980*	67
Walsh *et al.*[21]	Abdominal surgery	Australia	1981*	627
Galland *et al.*[24]	Appendicectomy	UK	1983*	200
Sherlock *et al.*[31]	Perforated or gangrenous appendicitis	UK	1984*	75
Sindelar *et al.*[32]	Abdominal surgery	USA	1985*	135
Chang *et al.*[33]	Spinal surgery	Taiwan	2002–2003	244
Cheng *et al.*[34]	Spinal surgery	Taiwan	2002–2003	414
Harihara *et al.*[35]	Gastric and colorectal surgery	Japan	2004	107
Studies included in the sensitivity analysis				
Gilmore and Martin[36]	Appendicectomy	UK	1974	300
Stokes *et al.*[37]	Abdominal surgery	UK	1975–1976	117
McCluskey[38]	Abdominal surgery	Australia	1976*	110
Pollock *et al.*[39]	Abdominal surgery	UK	1976	139
De Jong *et al.*[40]	Intra-abdominal surgery and inguinal hernia	The Netherlands	1980–1981	558
Gray and Lee[41]	Abdominal surgery	UK	1981*	153
Haig[42]	General surgery	UK	1985*	126
Vallance and Waldron[43]	Laparotomy	UK	1985*	34
Kokavec and Fristáková[44]	Orthopaedic surgery (children)	Slovakia	2006–2007	162

*Publication date if study interval was not mentioned.

abstract[18] later published in an article included in the meta-analysis, one lacking the required data[19], and one that compared both shaving and irrigation but without detailed data[20]. Fifteen of the remaining studies which were graded as having a low risk of bias were included in the main analysis[21–35], and nine graded as having a moderate risk of bias were included only in the sensitivity analysis[36–44]. Owing to the nature of irrigation, blinding

of surgeons was not possible, but wound assessment was evaluated blind in seven of the 15 articles included in the main analysis. Moreover, ten of 15 articles reported methods to ensure allocation concealment.

Study characteristics

In total, 24 randomized controlled trials totalling 5004 patients met the inclusion criteria. The trials randomly allocated 2465 patients to PVI lavage and 2539 patients to no PVI. All included studies were parallel-design randomized controlled trials. Sample sizes in the trials ranged from 34[43] to 627[21] participants. The trials enrolled men and women having both elective and emergency surgery. One study dealing with orthopaedic surgery included only children[44].

Study characteristics and quality are summarized in *Tables 1* and *2*. The 15 studies[21–35] that better fulfilled methodological requirements were included in the main analysis, totalling 3281 patients: 1605 who had PVI and 1676 in the control group. Half of the studies ($n = 12$) were from the UK[22–26,31,36,37,39,41–43], and five from North America[27–30,32]. Most studies ($n = 20$) were published before 1990[21–32,36–43]; only four[33–35,44] were published after 2000 (*Table 1*).

In 13 studies, PVI was applied by irrigation (*Table 3*); the control group was given saline in 11 of these[27–30,32–35,42–44] and in two studies[38,40] the control group was given nothing. In all studies dealing with irrigation and included in the main analysis, all patients in the control group received saline lavage. In the 11 studies where PVI was applied by spraying, the control group

Table 2 Methodological quality assessment of included trials

Reference	Adequate randomization	Blind evaluation	Explicit inclusion and exclusion criteria	Baseline similarities	Overall risk of bias	Comments
Studies included in the main analysis						
Gilmore and Sanderson[22]	Yes	Single blind	Unclear	Yes	Low	
Gilmore *et al.*[23]	Yes	Single blind	Unclear	Yes	Low	
Galland *et al.*[25]	Yes	Single blind	Yes	Yes	Low	
Foster *et al.*[26]	Unclear	Single blind	Unclear	Yes	Low	
Rogers *et al.*[27]	Yes	Unclear	Yes	Unclear	Low	
Sindelar and Mason[28]	Unclear	Unclear	Yes	Yes	Low	
Sindelar and Mason[29]	Unclear	Unclear	Yes	Unclear	Low	
Galle and Homesley[30]	Unclear	Unclear	Unclear	Unclear	Low	
Walsh *et al.*[21]	Yes	Single blind	Unclear	Yes	Low	
Galland *et al.*[24]	Yes	Single blind	Yes	Yes	Low	
Sherlock *et al.*[31]	Yes	Single blind	Yes	Yes	Low	
Sindelar *et al.*[32]	Yes	Unclear	Yes	Yes	Low	
Chang *et al.*[33]	Yes	Unclear	Yes	Yes	Low	
Cheng *et al.*[34]	Yes	Unclear	Yes	Yes	Low	
Harihara *et al.*[35]	Unclear	Unclear	Unclear	Yes	Low	
Studies included in the sensitivity analysis						
Gilmore and Martin[36]	Yes	Single blind	Unclear	Unclear	Moderate	If peritoneal lavage was required, 0·9% saline or 0·05% chlorhexidine solution was used
Stokes *et al.*[37]	Yes	Single blind	Unclear	Unclear	Moderate	
McCluskey[38]	Yes	Single blind	Yes	Yes	Moderate	Some patients excluded on the basis of personal preference or discretion of the surgeon
Pollock *et al.*[39]	Yes	Single blind	Yes	Unclear	Moderate	
De Jong *et al.*[40]	Unclear	Unclear	Yes	Unclear	Moderate	Results presented as number of site infections and not as number of infected patients (statistical unit)
Gray and Lee[41]	No	Unclear	Yes	Yes	Moderate	Mistakes in randomization
Haig[42]	Unclear	Unclear	Unclear	Unclear	Moderate	
Vallance and Waldron[43]	Unclear	Unclear	Unclear	Unclear	Moderate	
Kokavec and Fristáková[44]	Unclear	Unclear	Unclear	Unclear	Moderate	Not detailed

Table 3 Details of povidone–iodine administration and control group treatment

Reference	Control group	PVI group*	Time of PVI administration	Further information on irrigation
Studies included in the main analysis				
Gilmore and Sanderson[22]	Propellant	Spray (NR)	After peritoneal closure	Not adequate
Gilmore *et al*.[23]	Propellant	Spray (NR)	Before wound closure	Not adequate
Galland *et al*.[25]	Nothing	Spray (NR)	After peritoneal closure and after closing the skin	Not adequate
Foster *et al*.[26]	Nothing	Spray (NR)	After peritoneal closure	Not adequate
Rogers *et al*.[27]	Saline	Irrigation (10%)	After fascia closure	Irrigation for 1 min with saline, followed by PVI irrigation in PVI group
Sindelar and Mason[28]	Saline	Irrigation (10%)	After fascia closure	Irrigation for 60 s
Sindelar and Mason[29]	Saline	Irrigation (1%)	Intraperitoneal irrigation	Irrigation of peritoneal cavity for 60 s with either 1000 ml PVI or saline
Galle and Homesley[30]	Saline	Irrigation (NR)	After fascia closure	Irrigation with saline or PVI for 60 s
Walsh *et al*.[21]	Nothing	Spray (5%)	After peritoneal closure	Not adequate
Galland *et al*.[24]	Nothing	Spray (NR)	After peritoneal closure and after closing the skin	Not adequate
Sherlock *et al*.[31]	Nothing	Spray (NR)	After peritoneal closure	Not adequate
Sindelar *et al*.[32]	Saline	Irrigation (1%)	Intraperitoneal irrigation	1000 ml irrigation
Chang *et al*.[33]	Saline	Irrigation (0·35%)	NR	Irrigation with 2000 ml saline in both groups preceded by PVI irrigation for 3 min in PVI group
Cheng *et al*.[34]	Saline	Irrigation (0·35%)	NR	Irrigation with 2000 ml saline in both groups preceded by PVI irrigation for 3 min in PVI group
Harihara *et al*.[35]	Saline	Irrigation (NR)	Before skin closure	Irrigation with 500 ml saline in both groups, followed by PVI application using swabs in PVI group
Studies included in the sensitivity analysis				
Gilmore and Martin[36]	Nothing	Spray (NR)	After peritoneal closure	Not adequate
Stokes *et al*.[37]	Nothing	Spray (NR)	After peritoneal closure and again after complete closure of the wound	Not adequate
McCluskey[38]	Nothing	Irrigation (10%)	After peritoneal closure	10 ml solution instilled into wound, and a further 10 ml of the same solution instilled when suture of aponeurotic layers complete
Pollock *et al*.[39]	Saline	Spray (NR)	Before skin closure	Not adequate
De Jong *et al*.[40]	Nothing	Irrigation (first 1% and second 10%)	Lavage after fascia closure	Lavage for 1 min
Gray and Lee[41]	Nothing	Spray (NR)	Before wound closure	Not adequate
Haig[42]	Saline	Irrigation (10%)	NR	NR
Vallance and Waldron[43]	Saline	Irrigation (NR)	Before wound closure	Irrigation with 100 ml saline, added with 100 ml PVI in PVI group
Kokavec and Fristáková[44]	Saline	Irrigation (0·35%)	Before final wound closure	PVI irrigation for 2–3 min

Dose of povidone–iodine (PVI) is shown in parentheses. NR, not reported

was given either nothing[21,24–26,31,36,37,41], propellant[22,23] or saline[39]. Where information was available, the concentration of PVI varied from 0·35 per cent[33,34,44] to 10 per cent[27,28,38,42] (*Table 3*).

Characteristics of surgical interventions

Most studies ($n = 16$) dealt with abdominal surgery[21,22,32,37–41], including gastric and colorectal surgery[35], appendicectomy[24,26,31,36] and laparotomy[25,29,43]; the remainder dealt with general surgery[27,28,42], neurosurgery[33,34], gynaecological surgery[30], orthopaedic surgery[44] and non-abdominal surgery[23]. (*Table 1*).

Antibiotic therapy was given inconsistently between the different studies. All patients in each group were given antibiotics in five studies[24,29,33,34,44], but most often some patients in each group received antibiotics and there were no detailed data on SSI rate in relation to antibiotic use.

Table 4 Point estimates of effect of intraoperative povidone–iodine application on surgical-site infection

Reference	SSI rate (%)		Relative risk
	PVI	No PVI	
Studies included in the main analysis			
Gilmore and Sanderson[22]	9	24	0·35 (0·15, 0·84)
Gilmore *et al*.[23]	0	4	0·22 (0·01, 4·48)
Galland *et al*.[25]	40	42	0·94 (0·55, 1·61)
Foster *et al*.[26]	24·4	23·1	1·06 (0·67, 1·67)
Rogers *et al*.[27]	5	10·9	0·43 (0·14, 1·29)
Sindelar and Mason[28]	2·9	15·1	0·19 (0·09, 0·42)
Sindelar and Mason[29]	1	10	0·12 (0·02, 0·94)
Galle and Homesley[30]	29	25	1·16 (0·53, 2·56)
Walsh *et al*.[21]	9·1	12·5	0·73 (0·46, 1·14)
Galland *et al*.[24]	14	13·3	1·03 (0·51, 2·07)
Sherlock *et al*.[31]	15	25	0·62 (0·24, 1·56)
Sindelar *et al*.[32]	3	13	0·23 (0·05, 1·01)
Chang *et al*.[33]	0	4·8	0·08 (0·00, 1·40)
Cheng *et al*.[34]	0	3·4	0·07 (0·00, 1·15)
Harihara *et al*.[35]	15	15	0·98 (0·40, 2·42)
Studies included in the sensitivity analysis			
Gilmore and Martin[36]	8·1	15·9	0·51 (0·26, 0·98)
Stokes *et al*.[37]	20	34	0·59 (0·31, 1·11)
McCluskey[38]	38	26	1·45 (0·82, 2·54)
Pollock *et al*.[39]	26	35	0·74 (0·45, 1·24)
De Jong *et al*.[40]	12·9	13·3	0·97 (0·64, 1·48)
Gray and Lee[41]	10	24	0·40 (0·18, 0·90)
Haig[42]	22	59	0·38 (0·23, 0·64)
Vallance and Waldron[43]	71	70	1·02 (0·66, 1·58)
Kokavec and Fristáková[44]	0	3	0·16 (0·01, 3·37)

Values in parentheses are 95 per cent confidence intervals. SSI, surgical-site infection; PVI, povidone–iodine.

Table 5 Summary estimates of pooled relative risk of intraoperative povidone–iodine application in subgroup analyses

Subgroup analysis	No. of patients*		Effect		Heterogeneity	
	PVI	Control	Pooled RR†	*P*	*P*	I^2
Main analysis[21–35]	1605 (8·0)	1676 (13·4)	0·58 (0·40, 0·83)	0·003	0·002	54
Sensitivity analysis including articles with moderate risk of bias[21–44]	2465 (10·5)	2539 (16·6)	0·64 (0·51, 0·82)	< 0·001	< 0·001	55
According to method of administration						
Spray[21–26,31]	717 (13·5)	742 (17·0)	0·81 (0·62, 1·05)	0·110	0·327	12
Irrigation[27–30,32–35]	888 (3·5)	934 (10·5)	0·35 (0·16, 0·75)	0·007	0·005	61
According to type of surgery						
Abdominal surgery[21,22,24–26,29,31,32,35]	870 (12·4)	898 (16·7)	0·74 (0·54, 1·01)	0·058	0·121	35
General surgery[27,28]	328 (3·3)	359 (13·9)	0·24 (0·13, 0·44)	< 0·001	0·244	26
Neurosurgery[33,34]	328 (0)	330 (3·9)	0·07 (0·01, 0·55)	0·011	0·928	< 25
According to publication date						
Before 1990[21–32]	1223 (9·8)	1293 (15·7)	0·59 (0·41, 0·87)	0·007	0·004	58
After 2000[33–35]	382 (2·1)	383 (5·5)	0·23 (0·02, 2·25)	0·210	0·039	57
According to timing of PVI application						
Before wound closure[23,29,32,35]	249 (4·4)	262 (10·7)	0·36 (0·12, 1·13)	0·080	0·127	43
After wound closure[21,22,24–28,30,31]	1028 (11·4)	1084 (16·9)	0·67 (0·46, 0·97)	0·035	0·006	61
According to antibiotic administration						
Studies in which all patients received antibiotics[24,29,33,34]	503 (2·8)	523 (6·9)	0·21 (0·04, 1·29)	0·093	0·017	63
According to the definition of SSI						
Purulent discharge or micro-organism[21–23,27,28,31]	793 (6·4)	841 (14·1)	0·43 (0·26, 0·71)	0·001	0·084	47
According to the depth of infection						
Superficial infection[32–34]	365 (0·3)	368 (1·1)	0·34 (0·05, 2·09)	0·244	0·985	< 25
Deep infection[29,32–34]	445 (0·7)	456 (6·6)	0·13 (0·05, 0·37)	< 0·001	0·852	< 25

Values in parentheses are *percentage with surgical-site infection (SSI) and †95 per cent confidence intervals. PVI, povidone–iodine; RR relative risk.

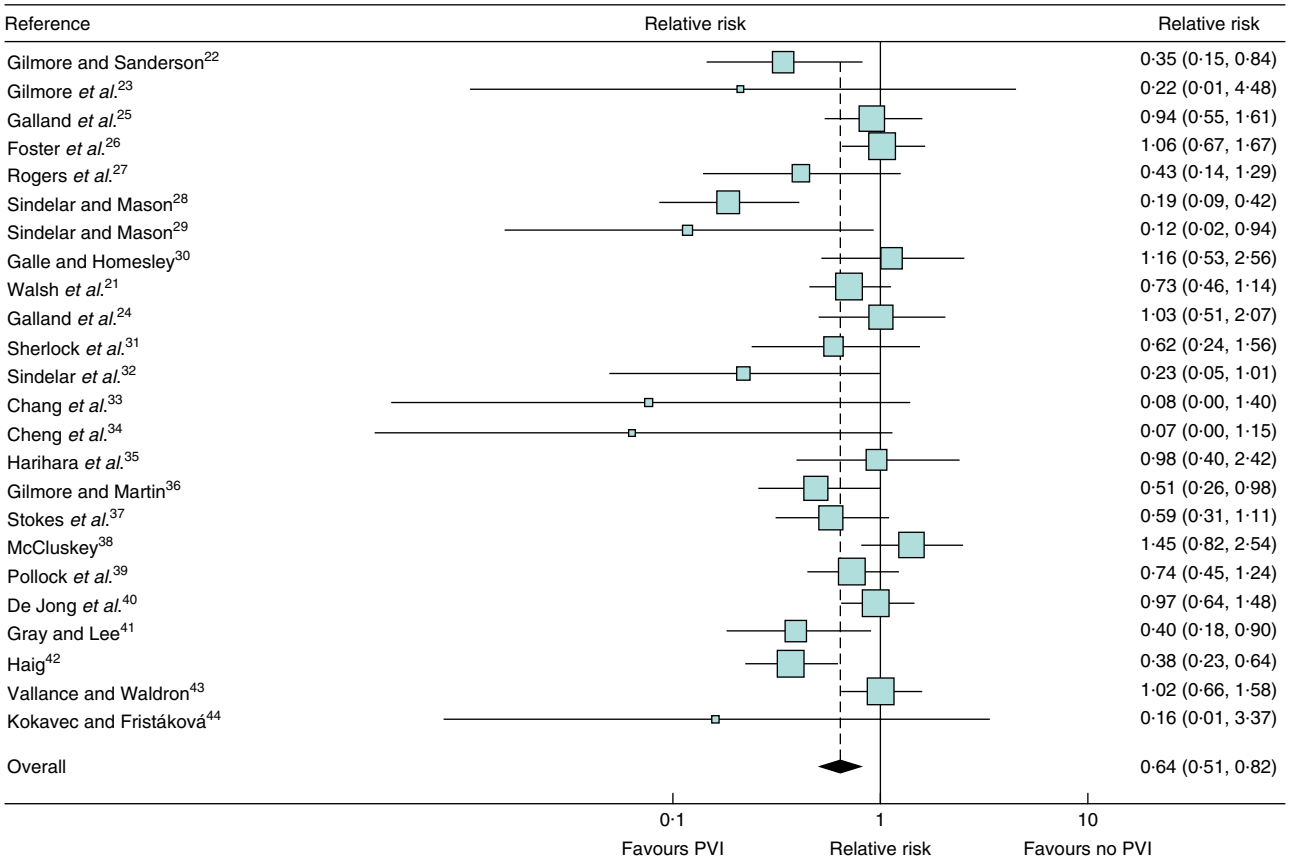

Fig. 2 Forest plot of studies included in the meta-analysis using a random-effects model. Relative risks are shown with 95 per cent confidence intervals. The vertical dashed line represents the summary estimate. PVI, povidone–iodine

Surgical-site infection rates

In studies included in the main analysis, the SSI rate varied from 0 per cent[23,33,34] to 40 per cent[25] in the PVI group, and from 3·4 per cent[34] to 42 per cent[25] in the control group (*Table 4*); the overall SSI rate was 8·0 per cent in the PVI group and 13·4 per cent in the control group. Intraoperative PVI application led to a significant decrease in SSI (RR 0·58, 0·40 to 0·83; $P = 0·003$). A sensitivity analysis including articles with a lower methodological quality led to consistent results, with an underestimation of the treatment effect (*Table 5*, *Fig. 2*).

When the analysis was further stratified by the method of PVI administration, the decrease in SSI rate remained statistically significant for PVI irrigation *versus* saline irrigation (10·5 to 3·5 per cent; $P = 0·007$). A similar trend was observed for PVI spraying: the SSI rate dropped from 17·0 per cent in the control group to 13·5 per cent in the PVI group ($P = 0·110$).

Further subgroup analyses led to consistent results for the type of surgery, publication dates, the timing of application of PVI and for deep infections (*Table 5*). In abdominal surgery, general surgery and neurosurgery, the SSI rate was significantly lower in the PVI group than in the control group. Whether the antiseptic was applied before or after wound closure, PVI was always associated with a significant decrease in SSI rate compared with that

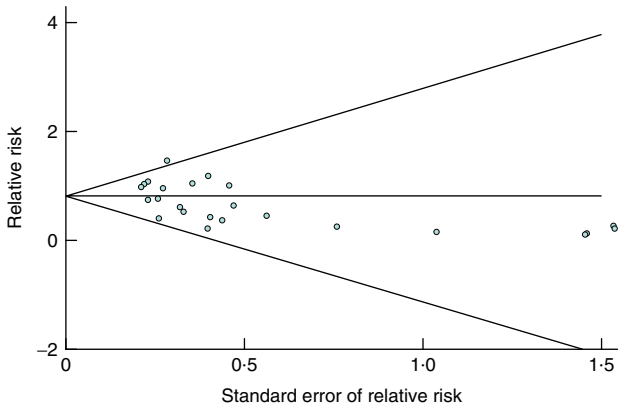

Fig. 3 Funnel plot to assess publication bias in the meta-analysis

in the control group. In studies published before 1990, the SSI rate was significantly lower in the PVI group; the trend was less marked in articles published since 2000 (2·1 *versus* 5·5 per cent; $P = 0·210$).

Analysis of the funnel plot (*Fig. 3*) suggested that small studies in which there was no benefit from PVI administration were less often published. However, Begg's and Egger's tests were not statistically significant.

Discussion

The present meta-analysis provided useful information on the overall protective effect of intraoperative PVI application in the prevention of SSI. The pooled results from all trials that assessed the effect of intraoperative application *versus* no antiseptic showed a statistically significant reduction in SSI rates. These results accord with a previous literature review by Chundamala and colleagues[9], who assessed PVI irrigation only, using both randomized and non-randomized trials, but without quantifying this effect. More recently, the NICE SSI guidelines recommended abandoning wound irrigation or intracavity lavage[12]. Nevertheless, their different subgroup analyses, although they included a smaller number of studies, were in accordance with the present results. The NICE analyses dealt with several antiseptics: PVI, taurolidine and acidic oxidative potential water. Regarding PVI specifically, NICE undertook different analyses. The first dealt only with the study by Sindelar and Mason[28] which compared saline with PVI irrigation, and in which a significant reduction in SSI was observed. The second analysis dealt with antiseptic lavage; NICE pooled data from the studies of Sindelar and colleagues[32] and Baker *et al.*[45], but the former used PVI whereas the latter used taurolidine. The third analysis was performed on three trials[21,31,41] that compared PVI spray *versus* control, and the latest was conducted on one recent trial dealing with PVI application[35]. However, the present analysis included further trials dealing with PVI spray[22–26,36,37,39], and three other recent trials of PVI irrigation[33,34,44]. Overall, inclusion and exclusion criteria were not very detailed in the NICE review, and the most recent studies were not included. Moreover, it was recommended that, although topical PVI spray or wound irrigation may reduce the incidence of SSI, PVI should not be applied during surgery. NICE argued that PVI is licensed only for intact skin, although it is used widely on open wounds.

The present analysis quantified the effect of PVI on the rate of postoperative SSI through a meta-analysis that took into account a large number of randomized controlled trials. Among the 24 studies included, six showed a significant reduction in SSI rate when intraoperative PVI was used[22,28,29,36,41,42]. The 18 other studies did not show any significant differences between the two groups, although for most the observed SSI rate was lower in the PVI group than in the control group. For five studies, however, SSIs were more common in the PVI group, although this was not significant statistically[24,26,30,38,43]. In three[24,26,43] the difference in SSI rates was very small (0·4–1·4 per cent), which might be explained by sampling fluctuations. One study[30] included only women with gynaecological malignancy. There might have been a selection bias in the study with the most important difference between PVI and control groups[38], as some patients were excluded on the basis of personal preference or discretion of the surgeon. This is why McCluskey's study[38] was included in the sensitivity analysis only.

The present study confirmed the effectiveness of PVI irrigation in reducing SSIs. As regards PVI spraying, the statistically non-significant differences observed may be explained by a lack of numbers, as the power to detect a significant decrease in SSI rate between the PVI and control groups was only 42 per cent with the available sample.

Included trials were heterogeneous with respect to population enrolled, antibiotic administration and timing of PVI administration. To take into account this heterogeneity, a random-effects model was used to combine the trial results. The subgroup analyses also allowed better homogeneity between the studies according to different parameters.

The endpoint used in the present meta-analysis was the presence of SSI. Definitions of SSI varied between trials. In most, SSI was diagnosed either when there was a purulent discharge or a serosanguinous discharge with positive bacterial culture[21–23,27,28,31,36,38,40]. In other studies SSI was defined as a purulent discharge[24,25,30,41,43] or as intra-abdominal abscesses[29], whereas some authors either did not define SSI[32,35,39,42] or invented their own definition[33,34,37]. The subgroup analysis on the six trials with the best methodological quality and using a similar and less restrictive definition[21–23,27,28,31] confirmed the effectiveness of PVI irrigation.

In most studies, SSI was assessed on wound inspection by an observer blinded to the treatment allocation[21–26,31,36–39]. Follow-up varied from 1 month[21,24,26,27,36,38,39,42,43] to 3 months[28,33,34], when reported. Sindelar and colleagues[32] also relied on clinical observation. Patients with suspected abscesses underwent surgical exploration. An autopsy was done on patients who died before the end of the 3-month observation. As SSI

covered both deep and superficial infections, a further subgroup analysis was performed according to the depth of infection. PVI application significantly reduced the rate of deep infection, yet no significant difference was observed regarding superficial infections. Infections were rare and the study population was small.

As most of the identified studies were published before 1990, surgical procedures will have changed. Trials were included provided that they were well designed, whatever their publication date. Even if surgical practices have changed, subgroup analysis of recent trials gave consistent results. Although the difference was not statistically significant in this subgroup analysis, this result supported the hypothesis that intraoperative PVI application might also reduce SSI rates in contemporary surgery. The three most recent randomized controlled studies totalled only 765 patients, with SSI rates of 2·1 per cent after PVI *versus* 5·5 per cent for the control group.

The included studies dealt with several types of surgery. Wound contamination (clean, clean-contaminated, contaminated or dirty) is a well known factor for SSI. Unfortunately, it was not possible to conduct subgroup analysis according to wound classification as this information was not always available; even when it was, randomization was seldom stratified. In all subgroups studied, PVI was associated with a lower SSI rate, for general surgery, abdominal surgery or neurosurgery, irrespective of antibiotic administration and timing of antiseptic application.

PVI is a well tolerated antiseptic; the main risks are related to thyroid function[9]. In the systematic review, no serious harm was reported in any included article. Other antiseptics used in surgery are chlorhexidine gluconate and sodium hypochloride. The present literature search did not identify any controlled trials that aimed to compare the SSI rate with sodium hypochloride *versus* no antiseptic. Regarding chlorhexidine, this antiseptic should not be applied to mucosal surfaces, and therefore cannot be used in intraoperative lavage or irrigation.

The limitations of the present study stemmed from the design of the individual trials as well as the methods of meta-analysis. First, several included trials lacked adequate allocation concealment, mainly owing to inaccuracy of allocation method; the use of intention-to-treat analysis remained unclear in many trials. Poor reporting of trial methodology meant that trial quality could not be assessed precisely. However, only the best studies were used in the main and subgroup analyses in order to get the most reliable results. The results were always consistent; exclusion of studies of lower methodological quality led to minor differences and to an overestimation of the RR.

Second, all meta-analyses are inherently vulnerable to publication bias. This was minimized by searching sources of both published and unpublished data. In particular, the literature search was performed without any restriction on language or publication date. Moreover, neither Begg's nor Egger's test was indicative of a publication bias.

The present analysis suggests that the use of intraoperative PVI may reduce rates of SSI. As there are few recent studies and surgical practices may have changed, contemporary, adequately powered and well designed clinical trials, stratified according to antibiotic administration and wound contamination, with an updated and standardized definition of SSI, are needed to confirm these results.

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References

1 Hedrick TL, Anastacio MM, Sawyer RG. Prevention of surgical site infections. *Expert Rev Anti Infect Ther* 2006; **4**: 223–233.
2 Thiolet JM, Lacave L, Metzger MH, Tronel H, Gautier C, L'Heriteau F *et al*. Prévalence des infections nosocomiales, France, 2006. *Hygienes* 2007; **15**: 349–354.
3 Smyth ET, McIlvenny G, Enstone JE, Emmerson AM, Humphreys H, Fitzpatrick F *et al*. Four country healthcare associated infection prevalence survey 2006: overview of the results. *J Hosp Infect* 2008; **69**: 230–248.
4 Lyytikäinen O, Kanerva M, Agthe N, Möttönen T, Ruutu P; Finnish Prevalence Survey Study Group. Healthcare-associated infections in Finnish acute care hospitals: a national prevalence survey, 2005. *J Hosp Infect* 2008; **69**: 288–294.
5 Astagneau P, Rioux C, Golliot F, Brücker G; INCISO Network Study Group. Morbidity and mortality associated with surgical site infections: results from the 1997–1999 INCISO surveillance. *J Hosp Infect* 2001; **48**: 267–274.
6 Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA Jr. Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. *J Am Coll Surg* 2004; **199**: 531–537.
7 Whiteside OJ, Tytherleigh MG, Thrush S, Farouk R, Galland RB. Intra-operative peritoneal lavage – who does it and why? *Ann R Coll Surg Engl* 2005; **87**: 255–258.
8 Petrisor B, Jeray K, Schemitsch E, Hanson B, Sprague S, Sanders D *et al*. Fluid lavage in patients with open fracture wounds (FLOW): an international survey of 984 surgeons. *BMC Musculoskeletal Disorders* 2008; **9**: 7.

9 Chundamala J, Wright JG. The efficacy and risks of using povidone–iodine irrigation to prevent surgical site infection: an evidence-based review. *Can J Surg* 2007; **50**: 473–481.

10 Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1999; **20**: 250–278.

11 Société Française d'Hygiène Hospitalière. Gestion Pré-opératoire du Risque Infectieux. Conférence de Consensus, Paris, 5 Mars 2004. *Hygiènes* 2004; **12**: 185–193.

12 National Institute for Health and Clinical Excellence (NICE). *Surgical Site Infection. Prevention and Treatment of Surgical Site Infection. NICE Clinical Guideline 74*. NICE: London, 2008.

13 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; **354**: 1896–1900.

14 Higgins J, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.0*. John Wiley & Sons: Chichester, 2008.

15 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.

16 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088–1101.

17 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–634.

18 Gilmore OJ, Welbourn RB. Proceedings: controlled trial of wound spraying with poly-antibiotic or povidone iodine aerosols. *Br J Surg* 1973; **60**: 910–911.

19 Tighe B, Anderson M, Dooley C, Egan T, Domhnaill SO, Delaney PV. Betadine irrigation following appendicectomy – a randomized prospective trial. *Ir Med J* 1982; **75**: 96.

20 Ko W, Lazenby WD, Zelano JA, Isom OW, Krieger KH. Effects of shaving methods and intraoperative irrigation on suppurative mediastinitis after bypass operations. *Ann Thorac Surg* 1992; **53**: 301–305.

21 Walsh JA, Watts JM, McDonald PJ, Finlay-Jones JJ. The effect of topical povidone–iodine on the incidence of infection in surgical wounds. *Br J Surg* 1981; **68**: 185–189.

22 Gilmore OJ, Sanderson PJ. Prophylactic interparietal povidone–iodine in abdominal surgery. *Br J Surg* 1975; **62**: 792–799.

23 Gilmore OJ, Reid C, Strokon A. A study of the effect of povidone–iodine on wound healing. *Postgrad Med J* 1977; **53**: 122–125.

24 Galland RB, Karlowski T, Midwood CJ, Madden MV, Carmalt H. Topical antiseptics in addition to peroperative antibiotics in preventing post-appendicectomy wound infections. *Ann R Coll Surg Engl* 1983; **65**: 397–399.

25 Galland RB, Saunders JH, Mosley JG, Darrell JH. Prevention of wound infection in abdominal operations by peroperative antibiotics or povidone–iodine. A controlled trial. *Lancet* 1977; **2**: 1043–1045.

26 Foster GE, Bourke JB, Bolwell J, Doran J, Balfour TW, Holliday A *et al*. Clinical and economic consequences of wound sepsis after appendicectomy and their modification by metronidazole or povidone iodine. *Lancet* 1981; **1**: 769–771.

27 Rogers DM, Blouin GS, O'Leary JP. Povidone–iodine wound irrigation and wound sepsis. *Surg Gynecol Obstet* 1983; **157**: 426–430.

28 Sindelar WF, Mason GR. Irrigation of subcutaneous tissue with povidone–iodine solution for prevention of surgical wound infections. *Surg Gynecol Obstet* 1979; **148**: 227–231.

29 Sindelar WF, Mason GR. Intraperitoneal irrigation with povidone–iodine solution for the prevention of intra-abdominal abscesses in the bacterially contaminated abdomen. *Surg Gynecol Obstet* 1979; **148**: 409–411.

30 Galle PC, Homesley HD. Ineffectiveness of povidone–iodine irrigation of abdominal incisions. *Obstet Gynecol* 1980; **55**: 744–747.

31 Sherlock DJ, Ward A, Holl-Allen RT. Combined preoperative antibiotic therapy and intraoperative topical povidone–iodine. Reduction of wound sepsis following emergency appendectomy. *Arch Surg* 1984; **119**: 909–911.

32 Sindelar WF, Brower ST, Merkel AB, Takesue EI. Randomised trial of intraperitoneal irrigation with low molecular weight povidone–iodine solution to reduce intra-abdominal infectious complications. *J Hosp Infect* 1985; **6**(Suppl A): 103–114.

33 Chang FY, Chang MC, Wang ST, Yu WK, Liu CL, Chen TH. Can povidone–iodine solution be used safely in a spinal surgery? *Eur Spine J* 2006; **15**: 1005–1014.

34 Cheng MT, Chang MC, Wang ST, Yu WK, Liu CL, Chen TH. Efficacy of dilute betadine solution irrigation in the prevention of postoperative infection of spinal surgery. *Spine* 2005; **30**: 1689–1693.

35 Harihara Y, Konishi T, Kobayashi H, Furushima K, Ito K, Noie T *et al*. Effects of applying povidone–iodine just before skin closure. *Dermatology* 2006; **212**(Suppl 1): 53–57.

36 Gilmore OJ, Martin TD. Aetiology and prevention of wound infection in appendicectomy. *Br J Surg* 1974; **61**: 281–287.

37 Stokes EJ, Howard E, Peters JL, Hackworthy CA, Milne SE, Witherow RO. Comparison of antibiotic and antiseptic prophylaxis of wound infection in acute abdominal surgery. *World J Surg* 1977; **1**: 777–782.

38 McCluskey B. A prospective trial of povidone iodine solution in the prevention of wound sepsis. *Aust N Z J Surg* 1976; **46**: 254–256.

39 Pollock AV, Froome K, Evans M. The bacteriology of primary wound sepsis in potentially contaminated abdominal operations: the effect of irrigation, povidone–iodine and

cephaloridine on the sepsis rate assessed in a clinical trial. *Br J Surg* 1978; **65**: 76–80.
40 de Jong TE, Vierhout RJ, van Vroonhoven TJ. Povidone–iodine irrigation of the subcutaneous tissue to prevent surgical wound infections. *Surg Gynecol Obstet* 1982; **155**: 221–224.
41 Gray JG, Lee MJ. The effect of topical povidone iodine on wound infection following abdominal surgery. *Br J Surg* 1981; **68**: 310–313.
42 Haig G. Povidone–iodine 10 per cent isotonic solution ('Betadine' irrigating solution) and infection in general surgical wounds. *J Hosp Infect* 1985; **6**(Suppl 1): 217.
43 Vallance S, Waldron R. Antiseptic *vs.* saline lavage in purulent and faecal peritonitis. *J Hosp Infect* 1985; **6**(Suppl A): 87–91.
44 Kokavec M, Fristáková M. [Efficacy of antiseptics in the prevention of post-operative infections of the proximal femur, hip and pelvis regions in orthopedic pediatric patients. Analysis of the first results.] *Acta Chir Orthop Traumatol Cech* 2008; **75**: 106–109.
45 Baker DM, Jones JA, Nguyen-Van-Tam JS, Lloyd JH, Morris DL, Bourke JB *et al*. Taurolidine peritoneal lavage as prophylaxis against infection after elective colorectal surgery. *Br J Surg* 1994; **81**: 1054–1056.