Does povidone-iodine application in surgical procedures help in the prevention of surgical site infections? An updated meta-analysis

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> Videosurgery Miniinv 2022; 17 (2): 261–278 DOI: https://doi.org/10.5114/wiitm.2021.112479

Abstract

Introduction: Surgical site infections (SSIs) occur after an operative procedure and can range from superficial to deep wound infections. The World Health Organization (WHO) and the Centers for Disease Control (CDC) have proposed guidelines recommending measures to prevent SSIs. Intraoperative measures are largely focused on decontamination of the skin and intraoperative wound irrigation using soap and antiseptics and are simple, efficient, and cost-effective measures to reduce SSIs. Povidone-iodine (PVI) is a topical antiseptic widely used for the reduction of SSIs. *Aim:* A meta-analysis was conducted to determine the efficacy of preoperative or intraoperative use of PVI from randomized controlled trials (RCTs).

Material and methods: A systematic literature review was conducted using MEDLINE and Central databases for RCTs that involved PVI application versus saline or no treatment control groups across various surgical categories. The primary outcome was SSI or post-operative wound infections. A random-effects model was used to calculate the pooled risk ratio and subgroup analyses were performed.

Results: A total of 59 RCTs were included in the meta-analysis with information from 20,497 patients. A reduction in overall SSI incidence was found ($RR = 0.70, 0.60-0.80, p = 0.0002, l^2 = 44\%$). Subgroup analyses showed that the comparator treatment and type of procedure did not modify the effect of PVI on SSI incidence. However, inconsistent results on SSI incidence were obtained when the data were stratified by PVI application method and surgery category.

Conclusions: The results of the meta-analysis provide support for the preoperative or intraoperative use of PVI in decreasing the incidence of SSI.

Key words: povidone iodine, surgical site infections, skin preparation, wound irrigation, normal saline.

Introduction

Surgical site infections (SSIs) occur after an operative procedure and can range from superficial to deep wound infections. Global estimates of SSIs have ranged from 0.5% to 15%, whereas studies in India have consistently shown higher rates from 23% to 38% [1]. SSIs are a substantial cause of morbidity, prolonged hospitalization, hospital readmissions, and death and pose a considerable financial burden on healthcare systems [2, 3]. Thus, prevention and minimization of SSIs improve patient outcomes and reduce resource consumption [4, 5].

Strategies to reduce the risk of SSIs include interventions that can be delivered preoperative-

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ly, intraoperatively, or postoperatively. The World Health Organization (WHO) and the Centers for Disease Control (CDC) have proposed guidelines recommending measures to prevent SSIs [6-8]. Sterile procedures, maintaining patient homeostasis, wound closure interventions, and prophylactic antibiotics are commonly used to reduce SSI risk [9]. Intraoperative measures primarily focus on decontamination of the skin and intraoperative wound irrigation using soap and antiseptics and are a simple, efficient, and cost-effective measure to reduce SSIs [10]. The most frequently used antiseptic is povidone-iodine (PVI), commonly applied as irrigation or a spray. PVI is an iodophor in which iodine is complexed with the polymer povidone. The microbicidal activity of iodine involves inhibition of vital bacterial cellular mechanisms and structures [11].

In contrast to antibiotics, antiseptics have a broader spectrum of activity and a reduced likelihood of resistance. However, despite the potential usefulness of topical antiseptics, current clinical practice is variable and largely dependent on surgeon preference. Furthermore, the routine use of topical antibiotics and antiseptics has been associated with adverse effects such as tissue toxicity and interference with wound healing [12, 13].

Although systematic reviews and meta-analyses on the benefits of PVI in reducing the incidence of SSIs have been published, there has been no definite conclusion on the effectiveness of PVI in different surgical categories [10, 14–16].

Aim

The objective of this paper is to synthesize current evidence from available randomized controlled trials evaluating the efficacy of PVI vs. saline/no treatment controls in decreasing the incidence of SSI.

Material and methods

The meta-analysis was carried out using the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) normative recommendations in this study with the registration number LPH#/ IRB/2021/1025.

Informed consent was not taken because of meta-analysis nature of this study.

Search strategy

A systematic literature search was conducted of MEDLINE (PubMed) and Cochrane Register of Controlled Trials (CENTRAL) in June 2021. No time limit was applied as several studies were published earlier than 1990. The following search terms were used in various combinations: surgical site infection, wound infection, SSI, post-operative, povidone-iodine, betadine, irrigation, and spray, and lavage, intraoperative and anti-infective agents. Additionally, a comprehensive list of search terms, including Medical Subject Headings (MeSH) terms, was applied. The titles and abstracts of potentially relevant studies were scanned, and the full-text versions of the relevant articles were read. Additional studies were identified by cross-checking the reference lists of the relevant studies.

Study selection or inclusion/exclusion criteria

Randomized controlled studies (RCTs) and prospective randomized studies that compared povidone-iodine application in any form (irrigation, spray, lavage, scrub) either preoperatively or intraoperatively were included across various surgical categories. The comparator treatment in the studies was primarily saline or no treatment. All studies reporting SSIs or wound infections as outcomes were included irrespective of the definition of SSI used. Exclusion criteria were non-randomized studies, animal studies, and studies with bacteriological counts as endpoints.

Data extraction and quality assessment

Following identification of articles that met the inclusion criteria, data were extracted using a predefined data extraction form that included the following items: study author, publication year, surgery category, inclusion criteria, intervention, control, SSI data in each group, PVI administration method, follow-up time, type of procedure, any systemic or prophylactic antibiotic use and other comments (if necessary).

The Cochrane Collaboration's risk of bias tool was used to assess the methodological quality of the included studies [17]. This tool includes the following criteria: randomization, allocation concealment, blinding, and completeness of follow-up. In addition, the risk of bias for each item was graded as high, low, or unclear risk.

Statement of ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable standards. Informed consent was not required due to the meta-analysis nature of this study. This study was approved by the Research Ethics Committee of Liyang People's Hospital with the registration number of LPH#/IRB/2021/1025.

Quantitative data synthesis

Meta-analysis was performed using Review Manager (RevMan, Version 5. Copenhagen: The Nordic Cochrane Center, the Cochrane Collaboration. 2020). Absolute numbers of participants in each study developing a wound infection or SSI and the total number of participants in each group (intervention and control group) were used to calculate the risk ratio and the 95% confidence interval (CI). Meta-analyses were done using a random-effects model (Mantel-Haenszel method), and heterogeneity in the included studies was evaluated using the I^2 statistic, with small heterogeneity for I^2 values of 25%, moderate heterogeneity for I^2 values of 25% to 50%, and high heterogeneity for l^2 values > 50% [18]. Forest plots were constructed, and p < 0.05 was statistically significant. Subgroup analyses were also performed according to the type of comparator, PVI administration method, surgery category, and type of procedure.

Publication bias was assessed by a funnel plot in which the log risk ratio for each study was plotted against its standard error. Egger's and Begg's tests were performed using Comprehensive Meta-Analysis (Version 3.3.070) [19].

Results

Identification of studies

A total of 1976 records were identified by database searching, of which 1856 were screened by title and abstract. Duplicates and irrelevant records were removed (n = 1758), and 98 RCTs were assessed for eligibility. However, 39 RCTs were excluded due to reasons such as inappropriate comparator (other antiseptic or PVI of different concentrations), duplicate data, use of antiseptics other than PVI, or absence of information on SSI or wound infection as an outcome. The process of selection is shown in Figure 1.

Study characteristics

Fifty-nine RCTs totaling 20,497 participants met the inclusion criteria (PVI intervention group: 10148 participants and control group: 10349 participants). These RCTs involved the comparison of PVI intervention to saline or no treatment control groups across various surgical categories. All studies were randomized controlled trials or prospective randomized studies with sample sizes ranging from 29 to 3027. The studies included male and female participants undergoing various elective and urgent surgical procedures.

In 34 of the selected studies, PVI was administered as an irrigation solution, and it was given as a dry powder spray in 13 studies. The comparators in the studies were no treatment or propellant only and saline. The concentration of PVI ranged from 0.35% to 10%. Table I shows the characteristics of the intervention and control groups of the studies included for meta-analysis [20–78].

Characteristics of surgical interventions

Most studies were conducted in participants undergoing abdominal surgery (n = 26), gynecological procedures, specifically elective or urgent cesarean section (n = 17), and appendectomy (n = 8). Elective operations were performed in 25 studies, urgent operations in 12 studies, and mixed operations in 22 studies. The use of antibiotics was inconsistent between the studies but was administered in both



Figure 1. Flow chart for identification and inclusion of studies in the meta-analysis

Reference	Intervention	Control	Type of PVI administration
Anderson 2020 [20]	PVI	None	Irrigation
Alobaidy 2020 [21]	PVI	None	Irrigation
Aref 2018 [22]	10% PVI solution	None	Irrigation
Asad 2017 [23]	PVI solution	None	Irrigation
Asghania 2011 [24]	10% PVI solution	None	Scrub
Barat 2016 [25]	10% PVI solution	None	Irrigation
Barr 1978 [26]	PVI	None	Lavage
Calkins 2019 [27]	Dilute Betadine and 10% Betadine	Saline	Lavage
Chang 2006 [28]	0.35% PVI + 2000 ml normal saline	2000 ml normal saline	Irrigation
Charoenviboonphan 2011 [29]	1% PVI paint	None	Paint
Cheng 2005 [30]	0.35% PVI + 2000 ml normal saline	Saline	Irrigation
Cohen 2020 [31]	0.35% PVI	Saline	Irrigation
de Jong 1982 [32]	1% and 10% PVI solution	None	Irrigation
Foster 1981 [33]	PVI dry powder	None	Spray
Galland 1977 [34]	PVI dry powder	None	Spray
Galland 1983 [35]	PVI aerosol	None	Spray
Galle 1980 [36]	PVI solution	Saline	Irrigation
Ghafouri 2016 [37]	1% PVI solution	Saline	Irrigation
Gilmore 1974 [38]	PVI dry powder	None	Spray
Gilmore 1975 [39]	PVI dry powder	Propellant alone	Spray
Gilmore 1977 [40]	PVI dry powder	Propellant alone	Spray
Gray 1981 [41]	PVI dry powder	None	Spray
Guzman 2002 [42]	PVI solution	Saline	Irrigation
Haas 2010 [43]	1% PVI solution	None	Scrub
Haider 2018 [44]	1% PVI solution	None	Irrigation
Harihara 2006 [45]	PVI solution	Saline	Irrigation
Hassan 2016 [46]	10% PVI solution	Saline	Irrigation
lqbal 2015 [47]	1% PVI solution	None	Irrigation
Johnson 1985 [48]	50 ml of 1% PVI	Saline	Irrigation
Karuserci 2019 [49]	10% PVI + saline	Saline	Irrigation
Ko 1992 [50]	0.5% PVI solution in saline	Saline	Irrigation
Kokavec 2008 [51]	0.35% PVI solution	Saline	Irrigation
Kothi 1981 [52]	PVI solution	None	Irrigation
Lau 1986 [53]	10 ml 1% PVI solution	None	Irrigation
Mahomed 2016 [54]	50 ml 10% PVI solution	None	Irrigation
Memon 2011 [55]	10% PVI	None	Scrub
McCluskey 1976 [56]	10% PVI solution	None	Irrigation

Table I. Characteristics of intervention and control groups of the included studies

Table I. Cont.

Reference	Intervention	Control	Type of PVI administration
Morgan 1978 [57]	PVI spray	None	Spray
Naunton Morgan 1980 [58]	PVI dry powder	None	Spray
Muller 2018 [59]	1000 ml PVI solution	1000 ml Ringer's lactate solution	Irrigation
Mwangi 2013 [60]	PVI solution	None	Irrigation
Nandi 2015 [61]	PVI	None	Scrub
Oestreicher 1989 [62]	10% PVI solution	Saline	Irrigation
Olmez 2013 [63]	PVI solution	None	Irrigation
Parker 1985 [64]	10% PVI solution	Water	Lavage
Pollock 1978 [65]	PVI spray	Sterile saline	Spray
Reid 2001 [66]	10% PVI solution	None	Scrub
Rogers 1983 [67]	10% PVI solution	Normal saline	Irrigation
Sherlock 1984 [68]	PVI spray	None	Spray
Sindelar 1979a [69]	0.1% PVI solution	Saline	Irrigation
Sindelar 1979b [70]	10% PVI solution	Saline	Irrigation
Sindelar 1985 [71]	1% PVI solution	Saline	Irrigation
Starr 2005 [72]	5% PVI solution	None	Scrub
Stokes 1977 [73]	PVI spray	None	Spray
Vallance 1985 [74]	100 ml PVI + saline	Normal saline	Lavage
Vinay 2019 [75]	5% PVI solution	Normal saline	Irrigation
Walker 2013 [76]	10% PVI solution	Saline	Gauze soaked
Walsh 1981 [77]	0.5% Betadine spray	None	Spray
Yildirim 2012 [78]	PVI solution	None	Irrigation

intervention and control groups of the studies with prophylactic antibiotics (n = 21). Table II summarizes the characteristics of the surgical procedures and types of procedures included for quantitative synthesis.

Bias assessment

The results of the risk of bias evaluation are shown in Figure 2. Overall, there was a high risk of bias due to unclear or high risk related to selection and performance bias and unclear risks associated with detection and reporting bias.

The funnel plot was asymmetrical (Figure 3), and Egger's and Begg's tests were statistically significant, indicating the possibility of publication bias.

Surgical site or wound infection rates

The incidence of SSI or wound infection in the included studies is shown in Table III. The SSI incidences ranged from 0% to 84.6% in the PVI group and from 0.6% to 75% in the control group (no treatment or saline). The overall incidence of SSI was 6.6% in the PVI intervention group and 9.4% in the control group.

Meta-analysis results

The results of the meta-analysis for all the studies included (n = 59) showed a reduction in the incidence of SSI and wound infections with the application of PVI in any form across all surgical categories compared to saline treatment or no treatment controls, which was statistically significant (RR = 0.70, 0.60 to 0.80, p = 0.0002, $l^2 = 44\%$) (Figure 4).

Stratification of the results by the type of comparator showed that the decrease in SSI incidence remained statistically significant for PVI vs. saline or no treatment control groups (Figure 5). The test for subgroup differences indicated no statistically sig-

Reference	Surgery type	Type of procedure (Urgent/elective)	Sample size	Follow-up
Anderson 2020 [20]	Abdominal	Urgent	100	1 year
Alobaidy 2020 [21]	Gynecological	Elective	400	NS
Aref 2018 [22]	Gynecological	Elective	207	NS
Asad 2017 [23]	Gynecological	Urgent	434	3 weeks
Asghania 2011 [24]	Gynecological	Elective	568	NS
Barat 2016 [25]	Gynecological	Elective	400	6 weeks
Barr 1978 [26]	Abdominal	Mixed	88	NS
Calkins 2019 [27]	Orthopedic	Elective	457	90 days
Chang 2006 [28]	Spinal	Elective	244	19 months
Charoenviboonphan 2011 [29]	Gynecological	Mixed	599	NS
Cheng 2005 [30]	Spinal	Elective	414	15.5 months
Cohen 2020 [31]	Spinal	Elective	153	30 days
de Jong 1982 [32]	Abdominal+mixed	Mixed	582	4 weeks
Foster 1981 [33]	Abdominal	Urgent	236	4 weeks
Galland 1977 [34]	Abdominal	Mixed	78	NS
Galland 1983 [35]	Abdominal	Urgent	200	4 weeks
Galle 1980 [36]	Abdominal		67	NS
Ghafouri 2016 [37]	Trauma	Urgent	389	NS
Gilmore 1974 [38]	Abdominal	Mixed	300	4 weeks
Gilmore 1975 [39]	Abdominal	Mixed	144	6 weeks
Gilmore 1977 [40]	Non-abdominal	Mixed	101	6 weeks
Gray 1981 [41]	Abdominal	Elective	153	2 weeks
Guzman 2002 [42]	Gynecological	Elective	160	NS
Haas 2010 [43]	Gynecological	Elective	300	1 month
Haider 2018 [44]	General	Elective	600	4 weeks
Harihara 2006 [45]	Gastric and colorectal	Elective	107	NS
Hassan 2016 [46]	Gynecological	Elective	100	NS
lqbal 2015 [47]	Abdominal	Urgent	166	30 days
Johnson 1985 [48]	Proctectomy for carcinoma	Elective	56	3 months
Karuserci 2019 [49]	Abdominal	Mixed	200	30 days
Ko 1992 [50]	Cardiopulmonary bypass	Mixed	1980	30 days
Kokavec 2008 [51]	Orthopedic	Elective	162	1.5 month
Kothi 1981 [52]	Abdominal	Elective	220	2 weeks
Lau 1986 [53]	Abdominal	Urgent	315	6 weeks
Mahomed 2016 [54]	Gynecological	Elective and Urgent	3027	4 weeks
McCluskey 1976 [55]	Abdominal	Mixed	110	4 weeks
Memon 2011 [56]	Gynecological	Mixed	200	NS

Table II. Characteristics of included studies

Table II. Cont.

Reference	Surgery type	Type of procedure (Urgent/elective)	Sample size	Follow-up
Morgan 1978 [57]	Accident trauma	Urgent	320	6 days
Naunton Morgan 1980 [58]	Accident trauma	Urgent	572	NS
Muller 2018 [59]	Abdominal	Elective	44	30 days
Mwangi 2013 [60]	Gynecological	Mixed	397	2 weeks
Nandi 2015 [61]	Gynecological	Mixed	294	NS
Oestreicher 1989 [62]	Mixed	Mixed	540	NS
Olmez 2013 [63]	Gynecological	Mixed	667	NS
Parker 1985 [64]	Resection of bowel carcinoma	Elective	45	NS
Pollock 1978 [65]	Abdominal	Mixed	139	4 weeks
Reid 2001 [66]	Gynecological	Elective	430	NS
Rogers 1983 [67]	Abdominal+mixed	Mixed	187	4 weeks
Sherlock 1984 [68]	Abdominal	Urgent	75	4 weeks
Sindelar 1979a [69]	Abdominal	Elective	168	NS
Sindelar 1979b [70]	General	Mixed	500	12 weeks
Sindelar 1985 [71]	Abdominal	Mixed	75	NS
Starr 2005 [72]	Gynecological	Elective	308	NS
Stokes 1977 [73]	Abdominal	Urgent	117	NS
Vallance 1985 [74]	Abdominal	Mixed	29	1 month
Vinay 2019 [75]	Abdominal	Elective	180	30 days
Walker 2013 [76]	Vascular	Elective	67	6 weeks
Walsh 1981 [77]	Abdominal	Mixed	627	4 weeks
Yildirim 2012 [78]	Gynecological	Mixed	669	6 weeks

NS – not specified.

nificant subgroup effect (p = 0.63), suggesting that comparator type does not modify the effect of PVI. However, the heterogeneity was high ($l^2 = 60\%$) in the saline comparator subgroup, suggesting inconsistency in the studies included.

Subgroup analysis by PVI application method showed that the decrease in SSI incidence was statistically significant when PVI was administered as irrigation or spray compared to saline or no treatment. However, PVI application as a lavage or scrub did not cause any significant decrease in SSI vs. control (Figure 6). Further, the test for subgroup analysis revealed no statistically significant subgroup effect (p = 0.38), suggesting that the PVI application method does not modify the effect of PVI. However, a smaller number of studies contributed to data in the lavage and scrub subgroups. Subgroup analysis by surgery category showed inconsistent effects of PVI on SSI incidence. Statistically significant results were seen in abdominal, gynecological, spinal, and orthopedic procedures, whereas no statistically significant effects were seen in accident surgery (Figure 7). The test for subgroup differences was not statistically significant (p = 0.05). The heterogeneity statistic (l^2 value) and the number of studies in each subgroup were inconsistent.

Stratification by the type of procedure (elective, urgent, or mixed) showed a reduction in SSI incidence, which was statistically significant and which was consistent across all subgroups (Figure 8). The test for subgroup differences indicated no statistically significant subgroup effect (p = 0.94), suggesting that type of procedure does not modify the effect of PVI. Heterogeneity was low to moderate in the subgroups.



Figure 2. Risk of bias summary for studies included in the meta-analysis

Discussion

The present study provides current and valuable information on the usefulness and efficacy of PVI in decreasing SSI incidence across various surgical categories and procedures. This meta-analysis showed that topical application of PVI in the preoperative or intraoperative phase for the 59 RCTs resulted in a decreased incidence of SSI by 30%. This favorable effect was mainly observed for patients undergoing abdominal and gynecological (cesarean section) surgery with a 22% and 19% reduction in SSI incidence. The heterogeneity values were low to moderate for these surgical categories, providing confidence in the values of the pooled risk ratios. Although beneficial effects were also seen for orthopedic and spinal surgery, the number of studies was insufficient and the I^2 heterogeneity statistic high. The high heterogeneity values can be attributed to diverse patient characteristics as some studies were carried out in pediatric populations.

Significant and consistent benefits of PVI were also observed in elective, urgent, and mixed procedures, although the studies showed moderate heterogeneity. This heterogeneity can be attributed to the type of surgery performed and variable patient characteristics. The effects of PVI were not consistent depending upon the application method, although the subgroup effect was not significant. PVI administration as irrigation or spray resulted in a significant decrease in SSI incidence, whereas administration as a lavage or scrub did not provide significant benefit. However, the number of studies for the lavage and scrub groups was too small (n = 10 studies) to allow a definite conclusion to be made.

The type of comparator (saline or no treatment) does not modify the effect of PVI. However, studies carried out using either comparator showed a significant decrease in SSI when PVI was administered in any form compared to the control.

In only one study, Muller *et al.* [59], laparoscopic surgery was done in 78.3% of procedures in the PVI group and 81% of procedures in the control group. However, individual SSI incidences for the laparoscopic vs. conventional methods were not reported.

Although the current meta-analysis suggests that preoperative or intraoperative use of PVI is associated with an overall decrease in SSI compared to saline or no treatment, it is essential to understand



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

the limitations of the studies included. Risk of bias analysis showed uncertain quality for most domains for the RCTs, indicating the possibility of selection, performance, and detection bias, raising concerns over the reliability of the studies. Adequate methods of allocation concealment and blinding were unclear in the studies, making it challenging to assess the trial quality. Additionally, prophylactic antibiotic administration and post-operative antibiotic use were not consistent between the RCTs. Preoperative antibiotics were administered to PVI and control groups in 28 studies without a relationship between SSI incidence and antibiotic use. Antibiotic use can significantly affect SSI rates and produce an inflated estimate of SSI reduction which may not be related to PVI treatment. Follow-up times for observation of SSI development differed between the studies. The current CDC definition for an SSI recommends a follow-up time of 30 days [8], whereas a few studies reported shorter time frames for post-surgery observation, which is an additional cause of variability for the outcome. Included studies were heterogeneous with regards to populations, prophylactic antibiotic use, and time of PVI application. Since several studies included in the meta-analysis were published before 1990 (n = 27), it is essential to consider possible changes in surgical practices that can modify the benefits of PVI.

Conclusions

Regardless of possible limitations, the present meta-analysis indicates that preoperative and intraoperative use of PVI is beneficial in decreasing SSI incidence. However, for surgeons to justify the use of PVI,

Reference	SSI incid	ence (%)
	Intervention: PVI	Control: saline or no treatment
Anderson 2020 [20]	12	16
Alobaidy 2020 [21]	0.5	1
Aref 2018 [22]	3.8	5.9
Asad 2017 [23]	1.4	3.7
Asghania 2011 [24]	3.5	3.2
Barat 2016 [25]	6	6.5
Barr 1978 [26]	3.6	38.3
Calkins 2019 [27]	0.4	3.4
Chang 2006 [28]	0	4.8
Charoenviboonphan 2011 [29]	0.3	1.3
Cheng 2005 [30]	0	3.4
Cohen 2020 [31]	1.3	2.6
de Jong 1982 [32]	12.9	16.1
Foster 1981 [33]	24.4	23.1
Galland 1977 [34]	35.9	46.2
Galland 1983 [35]	13.7	13.3
Galle 1980 [36]	29	25
Ghafouri 2016 [37]	7.7	7.3
Gilmore 1974 [38]	8.1	15.9
Gilmore 1975 [39]	8.6	24.3
Gilmore 1977 [40]	0	3.8
Gray 1981 [41]	9.9	24.4
Guzman 2002 [42]	8.8	5
Haas 2010 [43]	4.5	6.9
Haider 2018 [44]	6.3	8
Harihara 2006 [45]	14.8	15.1
Hassan 2016 [46]	2	14
lqbal 2015 [47]	10.8	19.3
Johnson 1985 [48]	35.7	75
Karuserci 2019 [49]	6	12

Table III. Surgical site infection (SSI) or wound infection incidences in the included studi	ies
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Reference	SSI incidence (%)				
	Intervention: PVI	Control: saline or no treatment			
Ko 1992 [50]	1.1	0.6			
Kokavec 2008 [51]	0	2.7			
Kothi 1981 [52]	15.7	12.7			
Lau 1986 [53]	5.7	1.9			
Mahomed 2016 [54]	9.5	9.8			
McCluskey 1976 [55]	37.5	25.9			
Memon 2011 [56]	1	3			
Morgan 1978 [57]	6	14.3			
Naunton Morgan 1980 [58]	5.3	14.6			
Muller 2018 [59]	17.4	9.5			
Mwangi 2013 [60]	6.5	10.2			
Nandi 2015 [61]	2.9	5.1			
Oestreicher 1989 [62]	6	5.5			
Olmez 2013 [63]	10.5	17			
Parker 1985 [64]	4.5	39.1			
Pollock 1978 [65]	26.2	35.1			
Reid 2001 [66]	5.5	8.5			
Rogers 1983 [67]	4.7	10.9			
Sherlock 1984 [68]	15.4	36.1			
Sindelar 1979a [69]	1.3	10.2			
Sindelar 1979b [70]	2.9	15.1			
Sindelar 1985 [71]	2.7	7.9			
Starr 2005 [72]	0.7	1.2			
Stokes 1977 [73]	20	33.9			
Vallance 1985 [74]	84.6	62.5			
Vinay 2019 [75]	10	7.8			
Walker 2013 [76]	3.2	8.3			
Walsh 1981 [77]	9.1	12.5			
Yildirim 2012 [78]	1.8	2.7			

its application must be carried out taking into consideration current surgical practices and procedures.

What is the 'take-home' message for the clinician?

Antisepsis of the surgery region and antibiotic prophylaxis are critical preoperative preventative treatments. In visceral surgery, intraoperative wound irrigation with povidone-iodine solution decreases SSI.The use of intra-operative PVI may help to lower SSI rates. Because there are few recent studies and surgical techniques may have changed, modern, properly powered, and well-designed clinical trials, stratified by antibiotic treatment and wound contamination, and using an up-

Events Total Fordal Col 1 Col Tandom, 95% CI Anderson 2020 6 50 8 50 1.5 0.75 0.28 2.00 Arderson 2020 6 50 8 50 1.5 0.75 0.28 2.00 Asad 2017 3 217 8 217 1.0 0.38 0.10 1.10 0.46 (0.13) Asad 2016 12 200 1.3 2.00 2.1 0.92 (0.43, 1.97) Barat 2016 12 2.00 1.3 2.00 2.00 0.00 0.01 0.66 Cheng 2005 1 7.20 7.66 0.2 0.07 0.00 1.15	Study or subgroup	Р	VI	Co	ntrol	Weight	Risk ratio M-H,	Risk ratio M-H,
Alobaidy 2020 1 200 2 200 0.3 0.50 0.55 4.00 Arder Son 2020 6 50 8.50 1.5 0.75 0.28 2.00 Aref 2018 4 106 6 101 1.1 0.64 0.18 2.19 Asphania 2011 10 244 9 284 1.7 1.11 0.44 2.29 Bart 1270 11 2.20 13 2.00 2.1 0.02 0.04 0.09 0.01 0.66 Charg 2006 0 0.20 0.47 0.02 0.061 0.04 0.05 3.33 Charg 2006 0 0.206 7 2.06 0.20 0.000 0.05 3.33 Goldeo Ng 1982 39 303 45 7.79 3.6 0.80 0.54 1.19 Galland 1977 14 39 1.89 2.90 0.78 0.45 0.03 0.49 0.05 1.03 0.14 0.03 0.21 0.03 0.22 0.03 0.49 0.05 0.22 <th></th> <th>Events</th> <th>Total</th> <th>Events</th> <th>Total</th> <th>(%)</th> <th>random, 95% CI</th> <th>random, 95% Cl</th>		Events	Total	Events	Total	(%)	random, 95% CI	random, 95% Cl
Anderson 2020 6 50 8 50 1.5 0.75 (28, 2.00) Acad 2017 3 217 8 217 1.0 0.38 (0.10, 1.39) Acad 2017 1 10 244 9 244 1.7 1.11 (0.45, 2.69) Barat 2016 1.2 200 1.3 200 2.1 0.92 (0.43, 1.97) Barat 2016 1.2 200 1.3 200 2.1 0.92 (0.43, 1.97) Calking 2016 1.2 200 1.3 200 2.1 0.92 (0.43, 1.97) Calking 2016 1.2 299 4 0.5 0.109 (0.01, 0.66) Chargeroloonpin 2011 1 299 4 0.5 0.2 0.07 (0.00, 1.15) Chargeroloonpin 2011 1 299 4 0.5 0.2 0.07 (0.00, 1.15) Chargeroloonpin 2011 1 0.7 2 7 6 0.3 0.49 (0.05, 5.13) de long 1982 39 303 45 279 3.6 0.80 (0.54, 1.19) de long 1982 39 303 45 279 3.6 0.80 (0.54, 1.19) de long 1982 39 303 45 279 3.6 0.80 (0.54, 1.19) de long 1982 39 303 45 279 3.6 0.80 (0.54, 1.19) de long 1982 39 303 45 279 3.6 0.80 (0.54, 1.19) de long 1982 13 9 5 14 105 2.3 1.03 (0.51, 2.20) de long 1982 13 9 5 14 105 2.3 1.03 (0.51, 2.20) de long 1982 13 9 5 14 105 2.3 1.03 (0.51, 2.20) de long 1982 13 9 5 14 105 2.3 1.03 (0.51, 2.07) de long 1982 13 9 5 14 105 2.3 1.03 (0.51, 2.07) de long 1977 14 39 18 39 2.9 0.78 (0.45, 1.33) de long 1977 6 7 0 18 42 2 53 0.2 0.22 (0.01, 4.48) Gallen 1983 13 9 514 100 2.5 0.51 (0.26, 0.98) Gilmore 1974 0 48 2 53 0.2 0.22 (0.01, 4.48) di monto 1974 0 48 2 53 0.2 0.22 (0.01, 4.48) Gilmore 1975 6 70 18 47 1.8 0.35 0.73 duarman 0.02 7 8 55 10 845 1.1 1.75 (0.53, 5.73) duarman 0.02 8 21 1.00 1.45 0.59 (0.26, 1.20) duarman 0.02 8 21 1.00 0.14 (0.02, 0.02) duarman 0.02 8 21 1.00 0.14 (0.02, 0.28) duarman 0.02 8 21 1.00 0.16 0.50 (0.20, 0.28) duarman 0.02 8 21 1.00 0.16 0.50 (0.20, 0.28) duarman 0.02 8 11 1.00 0.5 0.12 (0.00, 0.28) dua	Alobaidy 2020	1	200	2	200	0.3	0.50 (0.05–5.47)	
Aref 2018 4 106 6 101 1.1 0.64 (0.18, 2.19) Asghani 2011 10 284 217 10.0 38 (0.10, 1.8)	Anderson 2020	6	50	8	50	1.5	0.75 (0.28, 2.00)	
Asad 2017 3 2 217 8 217 1.0 0.38 (0.10, 1.39) Barat 2016 1.2 200 13 200 2.1 0.92 (0.43, 1.97) Barat 2016 1.2 200 13 200 2.1 0.92 (0.43, 1.97) Barat 2016 1.2 200 13 200 2.1 0.92 (0.43, 1.97) Calkins 2019 1 2.23 8 2.44 0.4 0.13 (0.02, 1.04) Chang 2006 1.01 1 2.29 4 300 0.4 0.25 (0.03, 2.23) Chang 2006 1.01 1 2.29 4 300 0.4 0.25 (0.03, 2.23) Chang 2006 1.01 1 2.29 7 7 6 0.3 0.49 (0.05, 5.33) Cohen 2020 1 77 2 76 0.3 0.49 (0.05, 5.33) Cohen 2020 1 77 2 76 0.3 0.49 (0.05, 5.33) Cohen 2020 1 77 2 76 0.3 0.49 (0.05, 5.33) Cohen 2020 1 77 2 76 0.3 0.49 (0.05, 5.33) Cohen 2020 1 77 2 76 0.3 0.49 (0.05, 5.33) Cohen 2020 1 77 2 76 0.3 0.49 (0.05, 5.33) Cohen 2020 1 77 2 76 0.1 10 405 3.250 Cohen 2020 1 77 2 0.48 2.2 0.51 (0.26, 0.98) Cohen 2020 1 7 1 20 42 151 2.5 0.51 (0.26, 0.98) Cohen 2020 7 180 4 80 1.1 1.175 (0.53, 5.75) Haas 2010 7 155 10 144 100 0.5 0.14 (0.02, 1.06) Corear 9197 0 48 2 53 0.2 0.22 (0.01, 4.48) Corear 9197 0 48 2 1.38 0.1 1.175 (0.53, 5.75) Haade 2018 1 9 300 2.4 300 2.8 0.79 (0.44, 1.41) Haade 2018 1 9 300 2.4 300 2.8 0.79 (0.44, 1.41) Haade 2018 1 9 300 2.4 300 2.8 0.79 (0.44, 1.41) Haade 2018 1 9 300 2.4 300 2.8 0.79 (0.44, 1.41) Haade 2016 1 50 14 100 0.5 0.14 (0.02, 1.06) Corear 91981 1 6 102 15 118 2.5 0.16 (0.02, 1.06) Korthi 1981 1 6 102 15 118 2.5 1.23 (0.46, 2.37) Korthi 1981 1 6 102 15 118 2.5 0.24 (0.21, 0.65) Korthi 1981 1 6 102 15 118 2.5 1.23 (0.44, 2.37) Manome 2016 1 44 1520 147 1507 4.5 0.97 (0.78, 1.21) Machanel 2016 1 44 1520 17 2.93 3.3 0.63 (0.43, 3.13) Machine 2018 4 2.3 2 2.1 0.7 1.63 (0.37, 8.56) Managan 1976 10 166 2.2 1.54 2.2 0.47 (0.21, 0.65) Managan 1976 10 166 2.2 1.54 2.2 0.47 (0.21, 0.65) Managan 1976 10 166 2.2 1.54 2.2 0.47 (0.21, 0.65) Managan 1976 11 1 100 3 100 0.4 0.33 (0.44, 3.13) Machine 2016 4 1.43 5.07 1.7 2.13 3.3 0.43 (0.43, 1.14) Machanel 2016 1 4.4 1520 1.7 2.9 3.3 5.0 4.6 (0.43, 2.13) Managan 1985 11 3.7 3 3.8 0.4 0.34 (0.43, 1.16) Managan 1985 11 3.7 3 3.8 0.4 0.34 (0.04, 3.14) Machanel 2016 1 4.4 1520 1.7 2.9	Aref 2018	4	106	6	101	1.1	0.64 (0.18, 2.19)	
Asghania 2011 10 284 9 284 1.7 1.11 (0.46, 2.69) Barr 1978 1 28 23 60 0.5 0.09 (0.01, 0.66) Chang 2006 0 1.20 2.1 8.23 6.0 0.5 0.09 (0.01, 0.66) Chang 2006 0 1.20 6 1.24 0.2 0.03 (0.02, 1.16) Chang 2006 0 2.09 4 300 0.4 0.25 (0.03, 2.23) Chang 2005 0 2.07 2.06 0.20 (0.01, 0.15) 0.00 0.10 (0.01, 0.15) Chang 2005 0 2.07 2.06 0.27 (0.05, 1.67) 0.07 (0.05, 1.67) Galland 1977 14 39 2.9 2.3 1.06 (0.51, 2.07) Galland 1983 13 95 14 105 2.3 1.02 (0.51, 2.07) Galland 1977 6 70 18 74 18 0.35 (0.26, 1.67) Galle 1980 9 31 9 6.20 0.22 (0.01, 4.48) 0.11 1.75 (0.53, 5.75) Galle 1980 9 31 9 2.40	Asad 2017	3	217	8	217	1.0	0.38 (0.10, 1.39)	
Baral 2016 12 200 13 200 2.1 0.92 (0.43, 1.97) Galkin 3019 1 223 8 234 0.4 0.13 (0.02, 1.04) Charg 2006 12 0 120 6 124 0.2 0.08 (0.00, 1.04) Charg 2006 12 0 208 7 206 0.2 0.08 (0.00, 1.04) Charg 2006 12 1 2 23 7 266 0.2 0.08 (0.00, 1.04) Charg 2006 12 1 2 23 7 2 6 0.2 0.07 (0.00, 1.15) Cohen 2020 1 9 77 2 7 6 0.3 0.49 (0.05, 3.33) Cohen 2020 1 9 77 2 7 6 0.3 0.49 (0.05, 3.33) Cohen 2020 1 9 77 2 7 6 0.3 0.49 (0.05, 1.35) Cohen 2020 1 9 77 2 7 6 0.3 0.49 (0.05, 1.35) Cohen 2020 1 9 77 2 7 6 0.3 0.49 (0.05, 1.35) Cohen 2020 1 9 77 1 2 7 6 0.3 0.49 (0.05, 1.35) Cohen 2020 1 9 77 1 2 7 7 0 0.3 0.49 (0.05, 1.35) Cohen 2020 1 9 71 11 7 33 10.69 (0.52, 2.13) Cohen 2020 1 9 71 12 149 12 149 12 149 12 1.10 (0.53, 2.56) Galland 1983 13 9 51 4 105 2.3 0.10 (0.51, 2.37) Gallen 1980 9 3 31 9 36 2.0 1.16 (0.53, 2.56) Gallen 1987 0 4 8 2 53 0.2 0.22 (0.01, 4.48) Gilmore 1977 0 48 2 53 0.2 0.22 (0.01, 4.48) Gilmore 1977 0 48 2 53 0.2 0.22 (0.01, 4.48) Gilmore 1977 0 48 2 1 300 2.8 0.79 (0.44, 1.41) Harkas 2010 7 155 10 145 1.6 0.65 (0.26, 1.67) Haider 2018 19 300 24 300 2.8 0.79 (0.44, 1.41) Harkas 2010 7 155 10 145 1.6 0.65 (0.26, 1.67) Haider 2018 19 300 24 300 2.8 0.79 (0.44, 2.4) Hassan 2016 1 50 14 100 0.5 0.14 (0.02, 1.06) Kothi 1981 16 102 215 118 2.5 1.23 (0.64, 2.37) Kothi 1981 16 102 215 118 2.5 1.23 (0.64, 2.37) Kothi 1981 16 102 215 118 2.5 1.23 (0.64, 2.37) Kothi 1981 16 102 215 118 2.5 1.23 (0.64, 2.37) Kothi 1981 16 102 215 118 2.5 1.23 (0.64, 2.37) Kothi 1981 16 102 215 128 2.24 0.24 (0.63 (0.2, 1.28) Mangan 1976 11 100 3 100 0.4 0.33 (0.04, 3.13) Machand 2015 4 13 2.01 47 1507 4.5 0.97 (0.78, 1.21) Machand 2015 4 13 2.01 2.02 156 1.24 0.25 (0.18) Mangan 1978 10 146 2.23 45 309 2.8 0.37 (0.24, 0.86) Mangan 1978 11 10 103 300 0.4 0.38 (0.04, 3.13) Machand 2015 4 13 0.27 125 0.27 0.24 (0.25, 1.28) Mangan 1978 11 10 106 3.4 0.38 (0.37, 2.96) Mangan 1978 10 146 2.25 0.59 (0.31, 1.11) Machand 2015 4 13 0.7 2.9 0.9 0.7 0.2 0.29 (0.31, 1.21) Mangan 1985 11 2.5 0.5 0.44 (0.33, 0	Asghania 2011	10	284	9	284	1.7	1.11 (0.46, 2.69)	
bar 1978 1 28 23 60 0.5 0.09 (0.0), 0.60 Chang 2006 0 120 6 124 0.2 0.08 (0.00, 1.40) Chang 2005 0 208 7 206 0.2 0.07 (0.00, 1.15) Cheng 2005 0 208 7 206 0.07 (0.00, 1.15) Gohen 2020 1 77 2 76 0.3 0.04 (0.05, 5.33) de jong 1982 39 303 45 279 3.6 0.80 (0.9.4, 6.167) Galand 193 13 39 14 105 2.13 108 (0.52, 1.167) Galand 193 13 9 3.6 2.0 1.16 (0.53, 2.56) 1.66 Gilmore 1975 6 7 12 49 2.4 1.11 1.75 (0.52, 7.15) Gilmore 1975 6 7 12 2.9 2.0 0.2 0.21 (0.01, 6.46) 0.46 Gilmore 1975 6 7.1 0.8 2.0 0.2 (0.21, 0.66) 1.11 1.75 (0.52, 7.75) Gilmore 1975 6 7.1 0.8	Barat 2016	12	200	13	200	2.1	0.92 (0.43, 1.97)	
Calking 2019 1 223 8 224 0.4 0.1 8 (0.2, 1.04) Charg 2006 1 1 206 6 124 0.2 0.08 (0.00, 1.24) Charg 2005 0 208 7 206 0.2 0.07 (0.00, 1.15) Cohen 2020 1 777 2 76 0.3 0.44 (0.05, 5.33) Galland 1972 14 39 18 9 2.79 3.6 0.88 (0.54, 1.19) Foster 1981 2 9 119 27 117 3.3 106 (0.67, 1.67) Galland 1973 14 39 18 9 2.9 0.78 (0.45, 1.33) Galland 1983 13 95 14 105 2.3 1.03 (0.51, 2.07) Galland 1983 13 95 14 105 2.3 1.03 (0.51, 2.07) Galland 1983 13 95 14 105 2.3 1.03 (0.51, 2.07) Galland 1983 7 71 20 82 2.0 0.24 (0.16, 0.98) Gilmore 1975 6 70 18 74 1.8 0.33 (0.15, 0.48) Gilmore 1977 0 48 2 53 0.22 (2.01, 4.48) Galland 1977 1 1 20 82 2.0 0.24 (0.16, 0.98) Galland 1977 0 48 2 53 0.22 (2.01, 4.48) Galland 1977 0 48 2 1.0 0.51 (2.06, 0.98) Galland 1975 10 145 1.6 0.65 (2.6, 1.67) Gilmore 1975 6 70 18 74 1.8 0.33 (0.15, 0.48) Galland 1977 0 48 2 2.0 0.44 (0.18, 0.99) Galland 1975 10 145 1.6 0.65 (0.26, 1.20) Galland 1975 10 128 21 28 2.90 4.84 (0.28, 0.27) Hassan 2016 1 50 14 100 0.5 1.48 (0.26, 1.20) Galland 1 100 3 100 0.4 0.48 (0.82, 2.54) Galland 1 100 13 100 0.4 0.48 (0.82, 2.54) Galland 1 100 3 100 0.4 0.38 (0.04, 3.15) Galland 1 50 14 0.2 15 1.88 (0.68, 0.27, 1.21) Machaned 2016 144 150 147 1507 4.5 0.97 (0.78, 1.21) Machaned 2016 144 23 4 2 1 0.7 1.88 (0.36, 1.94) Galland 1985 10 224 7 13 2.3 0.66 (0.32, 1.24) Machaned 2016 144 23 4 2 1 0.7 1.88 (0.37, 8.96) Galland 1985 10 224 7 33 3.4 0.66 (0.32, 1.24) Machaned 2016 144 2.3 17 2.3 0.56 (0.24, 2.09) Galland 1985 11 100 3 100 0.4 0.38 (0.04, 3.15) Galland 1979 7 11 55 21 6.2 2.5 0.59 (0.31, 1.11) Machaned 2016 144 2.6 110 1.3 0.48 (0.4, 3.10) Galland 1979 7	Barr 1978	1	28	23	60	0.5	0.09 (0.01, 0.66)	
Chargenyloophan 2011 299 4 300 0.4 0.25 (0.03, 2.23) Chargenyloophan 2011 77 2 76 0.3 0.49 (0.05, 2.23) de long 192 39 303 45 279 3.6 0.80 (0.34, 1.19) de long 192 39 303 45 279 3.6 0.80 (0.34, 1.19) Calland 197 14 39 18 39 2.9 0.78 (0.45, 1.33) Galand 193 13 91 14 105 2.3 1.08 (0.57, 1.67) Galand 193 13 91 94 105 2.3 1.08 (0.57, 1.67) Galand 193 13 91 94 105 2.3 1.08 (0.52, 2.13) Galand 193 13 91 94 36 2.0 1.16 (0.53, 2.56) Galand 193 13 91 94 36 2.0 1.16 (0.53, 2.57) Galand 197 6 70 18 73 1.26 0.26 (0.64, 1.67) Galand 197 6 70 18 73 1.28 0.29 (0.78, 6.67) Galand 197 7 15 6 10 12 140 224 151 2.5 0.51 (0.26, 0.98) Galand 197 7 0 448 2.0 0.22 (0.018, 6.69) Galand 197 7 0 78 4 00 1.0 77 0.18 (0.30, 1.68, 6.69) Galand 197 7 15 0 14 00 0.5 0.94 (0.42, 2.71) Harno2006 8 544 8 53 1.2 0.79 (0.44, 1.41) Hardhao 2006 8 544 8 53 1.2 0.79 (0.44, 1.41) Hardhao 2006 8 544 8 53 1.2 0.56 (0.26, 1.20) Harno2010 7 155 0 14 00 0.5 0.94 (0.02, 2.16) Harno2010 1 9 88 16 83 2.1 0.56 (0.26, 1.20) Harno2010 1 6 100 12 100 1.6 0.59 (0.20, 1.28) Kausec 2019 6 100 12 100 1.6 0.59 (0.20, 1.28) Kausec 2019 6 100 12 100 1.6 0.59 (0.20, 1.28) Kausec 2019 1 199 6 990 1.5 1.83 (0.68, 4.94) Marnomed 2015 14 4 2.3 1.27 0.74 (0.81, 1.06.77) Kausec 2019 6 100 12 100 1.6 0.59 (0.20, 1.28) Marnomed 2015 14 2.2 145 2.9 0.48 (0.13, 3.7) Kausec 2018 1 35 332 5.7 33 3.6 0.62 (0.42, 0.2) Marnomed 2015 14 2.2 147 118 2.5 1.38 (0.68, 4.94) Marnomed 2015 14 2.2 147 107 4.5 0.97 (0.78, 1.21) Marnomed 2015 14 2.2 15 2.2 0.42 (0.21, 0.86) Marnomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) Marnomed 2015 14 2.2 147 118 2.5 1.23 (0.44, 0.31, 0.45, 1.29) Marnomed 2015 14 2.2 147 18 2.2 1.23 (0.44, 0.31, 0.45, 1.29) Marnomed 2014 14 2.3 4 5.2 11 0.7 1.83 (0.37, 8.96) Muller 2018 4 2.3 4 2.2 10.66 0.33 (0.04, 3.16) Marnomed 2015 14 2.2 0.47 (0.45, 1.24) Marnomed 2015 14 136 0.87 (0.33, 0.77 (0.46, 1.24) Ma	Calkins 2019	1	223	8	234	0.4	0.13 (0.02, 1.04)	
Charler Monounphan 201 1 1 299 4 300 04 02 02 005 (2.0) (1.5) Cohen 2020 1 77 2 76 0.3 0.44 (0.05, 5.3) Golen 2020 1 77 2 76 0.3 0.44 (0.05, 5.3) Foster 1981 29 119 27 117 3.3 106 (0.67, 1.67) Foster 1981 29 119 27 117 3.3 106 (0.67, 1.67) Galand 1977 14 39 18 9 2.9 0.78 (0.45, 1.33) Galand 1983 13 95 14 105 2.3 103 (0.51, 2.07) Galand 1983 13 95 14 105 2.3 103 (0.51, 2.07) Galand 1983 9 9 31 9 36 2.0 1.16 (0.53, 2.76) Ginore 1974 12 149 24 151 2.5 0.51 (0.26, 0.98) Ginore 1975 6 70 18 74 1.8 0.35 (0.15, 0.84) Ginore 1977 0 48 2 53 0.2 21 (0.01, 4.48) Ginore 1975 6 70 18 74 1.8 0.35 (0.15, 0.84) Ginore 1975 6 70 18 74 1.8 0.35 (0.25, 1.75) Hass 2010 7 155 10 145 1.6 0.65 (0.26, 1.67) Ginore 1975 6 70 18 74 1.8 0.35 (0.26, 1.69) Ginore 1975 6 70 18 74 1.8 0.35 (0.26, 1.69) Ginore 1975 10 145 1.6 0.65 (0.26, 1.69) Ginore 1975 10 145 1.6 0.65 (0.26, 1.20) Ginore 1975 10 145 1.6 0.65 (0.26, 1.20) Ginore 1975 10 12 200 1.4 (0.18, 0.99) Hass 2010 1 50 14 100 0.5 0.14 (0.02, 1.06) Ginore 1975 10 128 21 28 2.9 0.48 (0.26, 0.26) Hass 2010 1 50 14 100 0.5 0.14 (0.02, 1.20) Kauser 2019 6 100 12 100 1.6 0.50 (0.20, 1.20) Kolavec 2008 0 89 2 73 0.2 0.14 (0.01, 3.37) Kolavec 2008 0 89 2 73 0.2 0.14 (0.02, 1.20) Mahomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) McCluskey 1976 21 56 14 54 2.8 1.44 (0.82, 2.54) Mahomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) McCluskey 1976 21 56 14 54 2.8 0.43 (0.42, 3.15) Mahomed 2016 144 1320 147 1507 4.5 0.97 (0.78, 1.21) McCluskey 1976 21 56 14 54 2.9 0.43 (0.24, 3.15) Mahomed 2016 144 1320 147 11 1.3 0.43 (0.43, 3.16) Mahomed 2016 144 23 5 2.1 0.7 1.83 (0.38, 9.16) Mahomed 2016 144 23 5 2.2 1.4 0.7 (0.58, 0.17, 1.94) Mahomed 2016 144 130 17 13 13 0.10 6 0.4 0.38 (0.04, 3.10) Mahomed 2016 144 2.8 140 (0.43, 1.24) Mahomed 2016 12 157 122 9 2.5 0.50 (0.12, 0.06) Maler 2013 13 3 0.7 2 (0.46, 1.14) Mahomed 2016 142 2.6 7 13 2.4 1.09 (0.55, 2.16) Maler 2013 1 3 3 6 0.4 0.39 (0.04, 3.13) Mahomed 2016 142 2.7 7 18 0.9 8 8.5 0.12 (0.00, 0.84) Ma	Chang 2006	0	120	6	124	0.2	0.08 (0.00, 1.40)	
Line 2003 0 2008 7 2008 0 2 000 0 0 0 0 0 0 0 0 0 0 0 0 0	Change 2005		299	4	300	0.4	0.25(0.03, 2.23)	
Content 2020 1 1 1 1 2 0 15 0.49 (0.05, 0.53) Froster 1981 29 119 27 11.7 3.3 1.06 (0.67, 1.67) Galland 1977 14 39 18 39 2.9 0.78 (0.45, 1.33) Galland 1983 13 95 14 105 2.3 1.03 (0.51, 2.07) Galland 1983 13 95 14 105 2.3 1.05 (0.52, 2.13) Gilmore 1975 6 70 18 7.4 1.8 0.35 (0.15, 0.84) Gilmore 1977 0 48 2.5 0.2 2.00 (0.40 (0.18, 0.90) Gray 1981 7 7.1 2.0 8.2 0.0 0.01 (0.44, 84) Gray 1981 7 7.1 2.0 8.2 0.0 0.01 (0.44, 14) Haider 2016 1 50 1.4 100 0.5 0.14 (0.02, 1.66) Iphason 1985 10 2.8 0.37 (0.20, 1.28) 0.48 (0.28, 0.22) 0.48 (0.28, 0.22) Koth 1992 11 990 6 990 1.83 (0.	Cheng 2005	1	208	2	206	0.2	0.07 (0.00, 1.15)	· · ·
Display 33 33 33 43 34 35 14 133 106 (6.67, 1.67) Galland 1981 13 95 14 105 23 116 (5.67, 1.67) Galland 1983 13 95 14 105 23 106 (6.7, 1.67) Galle 1980 9 31 9 62 0.0 116 (0.53, 2.56) Galle 1980 9 31 9 62 0.0 116 0.53, 2.56 Gilmore 1974 12 149 24 151 2.5 0.51 0.26, 0.88 Gilmore 1977 0 48 2 30 0.2 0.20 0.4 0.35 0.16 0.6 Garana 2002 7 80 4 80 1.1 1.75 0.53 5.75 1.4 Haider 2018 19 300 2.4 300 2.8 0.48 0.21 0.21 0.21 0.21 0.21 0.21	do long 1082	20	202	Z 15	270	2.6	0.49(0.05, 5.55)	_ _
Content 1983 22 10 2.2 0.78 100	Easter 1981	29	110	4J 27	117	2.2	1.06(0.54, 1.19)	
Galand 197, 14 15 15 15 15 15 15 15 15 15 15 15 15 15 15 16 15 12 106 15 12 106 15 12 106 15 12 106 15 12 106 15 12 106 15 12 106 15 12 106 15 106 15 106 15 106 15 106 10	Calland 1977	29	30	27 18	30	2.2	1.00(0.07, 1.07) 0.78(0.45, 1.33)	_ + _
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Galland 1983	17	95	10	105	2.9	1.03(0.43, 1.33)	
$ \begin{array}{c ccccc} \label{eq:constraint} \\ \hline Constraint} \\ \hline Constraint \\ \hline Constraint} \\ \hline Constra$	Galle 1980	9	31	9	36	2.5	1.05 (0.51, 2.07)	
Cilimore 1974 12 149 14 157 25 15 15 15 15 15 15 15 15 15 15 15 15 15	Ghafouri 2016	15	196	14	193	2.0	1.10 (0.53, 2.30)	
Cillmore 1975 6 70 18 74 1.8 0.35 (0.15, 0.84) Gilmore 1977 0 48 2 53 0.2 0.22 (0.01, 4.48) Gray 1981 7 71 20 82 20 0.40 (0.18, 0.90) Guzman 2002 7 80 4 80 1.1 1.75 (0.53, 5.75) Haider 2018 19 300 24 300 2.8 0.79 (0.44, 1.41) Harhara 2006 8 54 8 53 1.7 0.98 (0.40, 2.42) Harhara 2006 1 50 14 100 0.5 0.14 (0.02, 1.06) Iqual 2015 9 83 16 83 2.1 0.56 (0.26, 1.67) Haider 2018 10 28 21 28 2.9 0.48 (0.28, 0.82) Karuseci 2019 6 100 12 100 1.6 0.50 (0.26, 1.20) Kor 1992 11 990 6 990 1.5 1.83 (0.88, 4.94) Kokave 2008 0 89 2 73 0.2 0.16 (0.01, 3.37) Kothi 1981 16 102 15 118 25 1.23 (0.64, 2.37) Mahomed 2016 14 1520 147 1507 45 0.97 (0.78, 1.21) MacCuskey 1976 21 56 14 54 2.8 1.46 (0.82, 2.54) Memon 2011 1 100 3 100 0.4 0.33 (0.04, 3.15) Mergan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Manard 2016 4 4 23 2 21 0.7 1.83 (0.37, 8.96) Mahomed 2016 14 263 45 309 2.8 0.37 (0.21, 0.65) Mwangi 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) McCuskey 1976 21 56 14 54 2.8 0.43 (0.37, 1.24) Mergan 1978 10 166 22 157 33 5.6 0.62 (0.42, 0.92) Mahomed 2016 4 4 23 2 21 0.7 1.83 (0.37, 8.96) Mahomed 2016 14 263 45 309 2.8 0.37 (0.21, 0.65) Muanton Morgan 1980 14 263 45 309 2.8 0.37 (0.21, 0.65) Muanton Morgan 1986 1 22 9 23 0.5 0.12 (0.02, 0.84) Mandi 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Destreicher 1989 16 267 15 2.73 2.4 1.09 (0.55, 2.16) Mandi 2015 4 136 7 138 2.0 120 196 2.4 0.63 (0.32, 1.23) Mater 2013 35 332 57 335 6 0.62 (0.42, 0.29) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Polock 1978 7 65 26 74 3.1 0.74 (0.45, 1.24) Maler 2013 35 332 57 335 6 0.60 (0.32, 1.23) Mater 2013 1 3 2.01 20 196 2.4 0.63 (0.32, 1.23) Mater 2013 1 3 2.01 20 196 2.4 0.63 (0.32, 1.23) Mater 2013 1 3 1 3 38 0.4 0.34 (0.04, 3.16) Mater 2013 1 31 3 38 0.4 0.34 (0.04, 3.16) Start 2005 1 1 142 2 166 0.3 0.58 (0.95, 6.38) Total (95% C) 10148 1034 9 1000 0.70 (0.66, 0.80) Malker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Mater 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Mater 2015 1 13 0 16 3.4 0.39 (0.04, 3.53) Mater 1985 1 28 308 40 319	Gilmore 1974	12	149	24	151	2.5	0.51 (0.26, 0.98)	-
Gilmore 1977 0 48 2 53 0.2 0.22 (0.01, 4.48) Gray 1981 7 71 20 82 2.0 0.40 (0.18, 0.90) Gray 1981 7 715 10 145 1.6 0.65 (0.26, 1.67) Haas 2010 7 155 10 145 1.6 0.65 (0.26, 1.67) Haas 2010 7 155 10 2.4 300 2.8 0.79 (0.44, 1.41) Harihara 2006 8 54 8 53 1.7 0.98 (0.40, 2.42) Hassan 2016 1 50 14 100 0.5 0.14 (0.02, 1.06) Iqbal 2015 9 83 16 83 2.1 0.56 (0.26, 1.20) Johnson 1985 10 2.8 21 2.8 2.9 0.48 (0.28, 0.82) Karuserci 2019 6 100 12 100 1.6 0.50 (0.20, 1.28) Kothi 1981 16 102 15 118 2.5 1.23 (0.64, 2.37) Kothi 1981 16 102 15 118 2.5 1.23 (0.64, 2.37) Mahomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) McClusky 1976 21 56 14 54 2.8 1.46 (0.82, 2.54) Mwangi 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Mwangi 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Mwangi 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Mandmid 2016 14 263 530 2.8 0.37 (0.21, 0.65) Muller 2018 4 23 2 21 27 1.83 (0.37, 0.24) Mandmi 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Mwangi 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Mandmid 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Mandmid 2015 4 136 7 138 0.11 0.58 (0.17, 1.94) Mandmid 2013 13 301 20 196 2.4 0.63 (0.32, 1.24) Mandmid 2015 4 136 7 138 0.11 0.58 (0.17, 1.94) Mandmid 2015 4 136 7 138 0.14 (0.43, 2.14) Mandmid 2015 4 136 7 138 0.14 (0.43, 2.14) Mandmid 2015 4 136 7 138 0.14 (0.43, 1.24) Mandmid 2015 4 136 7 138 0.14 (0.43, 1.24) Mandmid 2015 4 136 7 138 0.14 (0.28, 0.09) Mandmid 2013 13 301 20 196 2.4 0.63 (0.32, 1.13) Mandmid 2015 4 136 7 138 0.14 (0.29, 0.08) Muller 2018 4 237 2.9 2.3 0.5 0.12 (0.02, 0.84) Muller 1985 1 2.2 9 2.3 0.5 0.12 (0.02, 0.94) Sindelar 1979b 7 242 2 9 2.58 0.50 (0.44, 0.32) Malkr 1981 2.8 308 40 319 3.3 0.72 (0.46, 1.14) Muller 1985 1 37 3 3.8 0.4 0.34 (0.04, 3.14) Malkr 1981 2.8 308 40 319 3.3 0.72 (0.46, 1.14) Muller 1985 1 37 3 3.8 0.4 0.39 (0.44, 3.58) Muller 2015 1 13 1 0 16 3.4 1.35 (0.87, 2.11) Muller 1985 1 1 31 0 16 3.4 1.35 (0.87, 2.11) Muller 1985 1 1 31 0 16 3.4 1.35 (0.87, 2.11) Muller 1985 1 1 13 0 16 3.4 1.35 (0.87, 2.11) Muller	Gilmore 1975	6	70	18	74	1.8	0.35 (0.15, 0.84)	-
Gray 1981 7 7 71 20 82 2.0 0.40 (0.18, 0.90) Guzman 2002 7 80 4 80 1.1 1.75 (0.53, 5.73) Haider 2018 19 300 24 300 2.8 0.79 (0.44, 1.41) Harhara 2006 8 54 8 53 1.7 0.98 (0.40, 2.42) Harhara 2006 1 50 14 100 0.5 0.14 (0.02, 1.06) Igbal 2015 9 83 16 83 2.1 0.56 (0.26, 1.20) Johnson 1985 10 2.8 2.1 28 2.9 0.48 (0.28, 0.82) Karuseri 2019 6 100 12 100 1.6 0.50 (0.20, 1.28) Karuseri 2019 6 100 12 100 1.6 0.50 (0.24, 2.37) Lau 1986 9 159 3 156 1.0 2.94 (0.81, 10.67) Mahomed 2016 144 1520 147 1507 4.5 0.07 (0.78, 1.21) McCluskey 1976 21 55 114 2.2 1.23 (0.64, 2.37) Margan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Margan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Margan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Margan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Margan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Mandie 2015 4 135 7 138 1.1 0.58 (0.17, 1.94) Mcluskey 1976 21 56 14 753 39 2.8 0.37 (0.21, 0.65) Margan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Mandie 2015 4 136 7 138 1.1 0.95 (0.17, 1.94) Morgan 1978 10 166 22 155 2.73 2.4 1.09 (0.55, 2.16) Margan 1978 10 20 9 196 2.4 0.63 (0.32, 1.24) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Mandie 2015 4 136 7 138 1.1 0.95 (0.17, 1.94) Morgan 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Mardi 2015 4 136 7 138 1.1 0.95 (0.17, 1.94) Destreicher 1989 16 267 15 2.73 2.4 1.09 (0.55, 2.16) Margan 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Margan 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Margan 1979 7 242 99 2.58 0.5 0.12 (0.02, 0.84) Follock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Margan 1979 7 242 99 2.58 2.0 0.19 (0.09, 0.42) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Margan 1985 1 37 3 38 0.4 0.34 (0.04, 3.14) Margan 1985 1 37 3 38 0.4 0.34 (0.04, 3.14) Margan 1985 1 37 3 38 0.4 0.34 (0.04, 3.14) Margan 1985 1 3 30 7 3.3 0.72 (0.46, 1.14) Walkin 1981 2.8 308 40 319 3.3 0.72 (0.46, 1.14) Walkin 1981 2.8 308 40 319 3.3 0.72 (0.46, 1.14) Walkin 1981 2.8 308 40 319 3.3 0.72 (0.46, 1.14) Walkin 1981 2.8 308 40 319 3.3 0.72 (0.46, 1.14) Walkin 1981 2.8 308 4	Gilmore 1977	õ	48	2	53	0.2	0.22 (0.01. 4.48)	
Curran 2002 7 80 4 80 1.1 1.75 0.53 5.75 Haas 2010 7 155 10 145 1.6 0.65 (0.25, 1.67) Haas 2016 1 9 300 2.8 0.79 0.44 1.41 Harbar 2006 8 54 8 53 1.7 0.98 (0.40, 2.42) Hassan 2016 1 50 14 100 0.5 0.14 (0.20, 1.28) Johnson 1985 10 2.2 1.2 1.00 1.6 0.56 (0.26, 1.20) Karuserci 2019 6 100 1.2 100 1.6 0.50 (0.20, 1.28) Kokavec 2008 0 89 2 7.3 0.2 0.16 (0.03, 3.37) Kothi 1981 16 102 15 1.8 2.5 1.23 (0.64, 2.37) Mclaukey 1976 2.1 56 1.4 54 2.8 1.46 (0.82, 2.54) Muler 2018 4 2.3 2.1 1.00 0.43 (0.21, 0.85) 1.	Grav 1981	7	71	20	82	2.0	0.40 (0.18, 0.90)	_ _
Haa 2010 7 155 10 145 1.6 0.65 (0.26, 1.67) Haider 2018 19 300 24 300 2.8 0.79 (0.44, 1.41) Harihara 2006 8 54 8 53 1.7 0.98 (0.40, 2.42) Hassan 2016 1 50 14 100 0.5 0.14 (0.02, 1.06) Johnson 1985 10 2.8 21 28 2.9 0.48 (0.28, 0.82) Karuserci 2019 6 100 12 100 1.6 0.50 (0.26, 1.20) Johnson 1985 10 2.8 21 28 2.9 0.48 (0.28, 0.82) Karuserci 2019 6 100 12 100 1.6 0.50 (0.20, 1.28) Karuserci 2019 6 100 12 100 1.6 0.50 (0.20, 1.28) Karuserci 2019 6 100 12 100 1.6 0.50 (0.20, 1.28) Karuserci 2019 6 100 12 15 118 2.5 1.23 (0.64, 2.37) Lau 1986 9 159 3 156 1.0 2.94 (0.81, 10.67) Machined 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) McCluskey 1976 21 56 14 54 2.8 1.46 (0.82, 2.54) Memon 2011 1 100 3 100 0.4 0.33 (0.04, 3.15) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Mwangi 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Manding 2013 41 326 7 138 1.1 0.58 (0.17, 1.94) Marding 2013 41 326 7 138 1.1 0.58 (0.17, 1.94) Marding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Manding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Manding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Manding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Marding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Marding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Marding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Marding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Marding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Marding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Marding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Marding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Marding 2013 43 201 20 196 2.4 0.63 (0.32, 1.24) Marding 2013 4 2.2 17 18 2.13 2.3 0.65 (0.32, 0.34) Marding 1978 10 16 2.4 1.4 0.63 (0.44, 1.29) Sindelar 1979 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979 1 14 55 21 66 0.3 0.58 (0.05, 6.38) Marding 1978 1 13 10 16 3.4 1.35 (0.87, 2.11) Marding 2015 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.51) Marding 1978 1 13 10 16 3.4 1.35 (0.87, 2.11) Marding 1985 1 13 10 16 3.4 1	Guzman 2002	7	80	4	80	1.1	1.75 (0.53, 5.75)	
Haider 2018 19 300 24 300 2.8 0.79 (0.44, 1.41) Harihara 2006 8 54 8 53 1.7 0.98 (0.40, 2.42) Harihara 2016 1 50 14 100 0.5 0.14 (0.02, 1.06) Iqbal 2015 9 83 16 83 2.1 0.56 (0.26, 1.20) Johnson 1985 10 2.8 2.1 2.8 2.9 0.48 (0.28, 0.82) Karuseri 2019 6 100 12 100 1.6 0.50 (0.20, 1.28) Ko 1992 11 990 6 990 1.5 118 2.06 4, 2.37) Kothi 1981 16 102 15 118 2.5 1.23 (0.64, 2.37) Kautos 106 144 1520 147 1507 4.5 0.97 (0.78, 1.21) Mahomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) MacCluskey 1976 21 56 14 54 2.8 1.46 (0.82, 2.54) Meron 2011 1 1 100 3 100 0.4 0.33 (0.04, 3.15) Morgan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Muller 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Nandi 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Oestreicher 1989 16 267 15 2.73 2.4 1.09 (0.55, 2.16) Olimez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Reid 2001 12 2.17 18 213 2.3 0.65 (0.32, 1.33) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 1 142 2 166 0.3 0.32 (0.02, 0.94) Sindelar 1979b 1 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 1 142 2 166 0.3 0.38 (0.63, 3.14) Wailance 1985 1 37 3 38 0.4 0.34 (0.14, 1.29) Sindelar 1979b 1 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 1 142 2 166 0.3 0.39 (0.04, 3.53) Wailer 2013 1 33 61 1.8 0.43 (0.14, 1.29) Sindelar 1979b 1 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 1 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 1 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 1 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 1 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 1 240 39 300 0.70 (0.60, 0.80) Malker 2013 1 31 3 36 0 4.0 33 (0.04, 3.53) Waiker 2013 1 31 3 36 0 4.0 33 (0.04, 3.53) Waiker 2013 1 31 3 36 0 4.0 33 (0.04, 3.53) Waiker 2013 1 31 3 36 0 4.0 3.90 (0.04, 3.53) Waiker 2013 1 31 3 36 0 4.0 3.90 (0.04, 3.53) Waiker 2013 1 31 3 36 0 4.0 3.90 (0.04, 3.53) Waiker	Haas 2010	7	155	10	145	1.6	0.65 (0.26, 1.67)	
Harihara 2006 8 54 8 53 1.7 0.98 (0.40, 2.42) Hassan 2016 1 50 14 100 0.5 0.14 (0.02, 1.06) Johnson 1985 10 28 21 28 2.9 0.48 (0.28, 0.82) Karuseriz 2019 6 100 12 100 1.6 0.50 (0.22, 0.82) Karuseriz 2019 6 100 12 100 1.6 0.50 (0.22, 0.82) Ko 1992 11 990 6 990 1.5 1.83 (0.68, 4.94) Kokavec 2008 0 89 2 73 0.2 0.16 (0.01, 3.37) Ko 1992 11 990 6 990 1.5 1.83 (0.68, 4.94) Kokavec 2008 0 89 2 73 0.2 0.16 (0.01, 3.37) Kothi 1981 16 102 15 118 2.5 1.23 (0.64, 2.37) Lau 1986 9 159 3 156 1.0 2.94 (0.81, 10.67) Mahomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) McCluskey 1976 21 56 144 54 2.8 1.46 (0.82, 2.54) Memon 2011 1 100 3 100 0.4 0.33 (0.04, 3.15) Mergan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Naunton Morgan 1980 14 2263 45 309 2.8 0.37 (0.21, 0.65) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Muller 2018 4 23 2 2 1 0.7 1.83 (0.37, 8.96) Muller 2018 4 136 7 138 1.1 0.58 (0.17, 1.94) Oestreicher 1989 16 267 15 273 2.4 1.09 (0.55, 2.16) Olmez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Polock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Polock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Polock 1978 17 86 21 66 0.3 0.58 (0.18, 1.00) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.84) Polock 1978 17 3 3 38 0.4 0.34 (0.14, 1.29) Sheriock 1984 6 39 113 36 1.8 0.43 (0.14, 1.29) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979 7 1 85 21 62 2.5 0.59 (0.31, 1.11) Viany 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.51) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 0.0 1.6 3.4 0.93 (0.04, 3.53) Walker 2013 1 31 0.0 1.6 3.4 0.39 (0.04, 3.53) Walker 2013 1 31 0.0 1.6 3.4 0.39 (0.04, 3.53) Walker 2013 1 31 0.0 1.6 3.4 0.39 (0.04, 3.53) Walk	Haider 2018	19	300	24	300	2.8	0.79 (0.44, 1.41)	
Hassan 2016 1 50 14 100 0.5 0.14 (002, 1.06) Iqbal 2015 9 83 16 83 2.1 0.56 (0.26, 1.20) Johnson 1985 10 28 21 28 2.9 0.48 (0.28, 0.82) Karuseri 2019 6 100 12 100 1.6 0.50 (0.20, 1.28) Ko 1992 11 990 6 990 1.5 118 2.5 1.23 (0.64, 2.37) Lau 1986 9 159 3 156 1.0 2.94 (0.81, 10.67) Mahomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) McCluskey 1976 21 56 14 54 2.8 1.46 (0.82, 2.54) Memon 2011 1 100 3 100 0.4 0.33 (0.04, 3.15) Margan 1978 10 166 22 154 2.2 0.42 (0.21, 0.65) Muller 2018 4 23 2 210 0.7 1.83 (0.37, 8.96) Mwangi 2013 13 201 20 196 2.4 0.63 (0.32, 124) Mandi 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Octime 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Reid 2001 12 217 18 213 2.3 0.65 (0.32, 1.33) Reid 2001 12 217 18 213 2.3 0.65 (0.32, 1.33) Sherlock 1984 6 39 13 3 6 0.4 0.34 (0.04, 3.14) Sherlock 1985 1 37 3 3 8 0.4 0.34 (0.04, 3.14) Sherlock 1984 6 39 13 3 6 0.4 0.34 (0.04, 3.14) Sherlock 1984 13 0.1 101 1.3 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 3 6 0.4 0.34 (0.04, 3.14) Sherlock 1984 6 39 13 3 6 0.4 0.34 (0.04, 3.14) Sherlock 1984 6 39 13 3 6 0.4 0.34 (0.04, 3.14) Sherlock 1985 1 37 3 38 0.4 0.39 (0.05, 0.38) Sherlock 1984 6 39 13 3 6 0.4 0.34 (0.04, 3.14) Sherlock 1985 1 37 3 3 36 0.4 0.34 (0.04, 3.14) Sherlock 1985 1 37 3 33 6 0.4 0.39 (0.04, 3.53) Muller 2013 1 31 3 0.6 0.4 3.12 (0.02, 0.94) Sherlock 1984 6 39 13 3 6 0.4 0.34 (0.04, 3.14) Sherlock 1985 1 37 3 3 36 0.4 0.39 (0.04, 3.53) Muller 2013 1 31 3 0.6 0.4 0.39 (0.04, 3.53) Muller 2013 1 31 3 3 6 0.4 0.39 (0.04, 3.53) Muller 2013 1 31 3 3 6 0.4 0.39 (0.04, 3.53) Muller 2013 1 31 3 3 6 0.4 0.39 (0.04, 3.53) Muller 2013 1 31 3 3 6 0.4 0.39 (0.06, 0.80) Muller 2013 1 31 3 3 6 0.4 0.39 (0.06, 0.80) Muller 2013 1 31 3 3 6 0.4 0.39 (0.06, 0.80) Muller 2013 1 31 3 3 6 0.4 0.39 (0.06, 0.80) Muller 2013 1 31 0 0 16 3.4 0.39 (0.06, 0.80) Muller 2013 1 31 0 0 16 3.4 0.39 (0.06, 0.80) Muller 2013 1 31 0 0 16 3.4 0.39 (0.06, 0.8	Harihara 2006	8	54	8	53	1.7	0.98 (0.40, 2.42)	
	Hassan 2016	1	50	14	100	0.5	0.14 (0.02, 1.06)	
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	lqbal 2015	9	83	16	83	2.1	0.56 (0.26, 1.20)	
Karuseri 2019 6 100 12 100 1.6 0.50 (0.20, 1.28) Ko 1992 11 990 6 990 1.5 1.83 (0.68, 4.94) Kokavec 2008 0 89 2 73 0.2 0.16 (0.01, 3.37) Kothi 1981 16 102 15 118 2.5 1.23 (0.64, 2.37) Mahomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) McCluskey 1976 21 56 14 54 2.8 1.46 (0.82, 2.54) Memon 2011 1 100 3 100 0.4 0.33 (0.04, 3.15) Morgan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Maunton Morgan 1980 14 263 45 309 2.8 0.37 (0.21, 0.65) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Mwangi 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Nandi 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Oestreicher 1989 16 267 15 273 2.4 1.09 (0.55, 2.16) Olmez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Parker 1985 1 32 257 335 3.6 0.65 (0.32, 1.33) Generation 12 2.17 18 213 2.3 0.65 (0.32, 1.24) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.84) Parker 1985 1 37 3 38 0.4 0.34 (0.14, 1.29) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.84) Pollock 1984 6 39 13 36 1.8 0.43 (0.18, 1.00) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 36 1.8 0.43 (0.18, 1.00) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 30 16 3.4 1.35 (0.87, 2.11) Viany 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 10 16 3.4 1.39 (0.06, 0.80) Total (events 665 97	Johnson 1985	10	28	21	28	2.9	0.48 (0.28, 0.82)	
Ko 1992 11 990 6 990 1.5 1.83 (0.68, 4.94) Kokavec 2008 0 89 2 73 0.2 0.16 (0.01, 3.37) Kokbi 1981 16 102 15 118 2.5 1.23 (0.64, 2.37) Lau 1986 9 159 3 156 1.0 2.94 (0.81, 10.67) Mahomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) McCluskey 1976 21 56 14 54 2.8 1.46 (0.82, 2.54) Memon 2011 1 1 000 3 100 0.4 0.33 (0.04, 3.15) Morgan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Muller 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Nandi 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Oestreicher 1989 16 267 15 2.73 2.4 1.09 (0.55, 2.16) Olimez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Reid 2001 12 217 18 213 2.3 0.65 (0.32, 1.33) Rogers 1983 4 86 11 101 1.3 0.43 (0.14, 1.29) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 13 0 16 3.4 1.35 (0.87, 2.11) Valiance 1985 1 37 3 38 0.4 0.34 (0.04, 3.14) Star 2005 1 1 142 2 166 0.3 0.58 (0.05, 6.38) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 0 16 3.4 1.35 (0.87, 2.11) Vianzee 2013 1 31 3 10 16 3.4 1.35 (0.87, 2.11) Vianzee 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 201	Karuserci 2019	6	100	12	100	1.6	0.50 (0.20, 1.28)	
Kokavec 2008 0 89 2 73 0.2 0.16 (0.01, 3.37) Kothi 1981 16 102 15 118 2.5 1.23 (0.64, 2.37) Lau 1986 9 159 3 156 1.0 2.94 (0.81, 10.67) Mahomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) McCluskey 1976 21 56 14 54 2.8 1.46 (0.82, 2.54) Mermon 2011 1 100 3 100 0.4 0.33 (0.04, 3.15) Morgan 1978 10 166 2.2 154 2.2 0.42 (0.21, 0.65) Muller 2018 4 2.3 2 21 0.7 1.83 (0.37, 8.96) Musangi 2013 13 201 20 196 2.4 0.05 (0.22, 124) Oestreicher 1989 16 267 15 273 2.4 1.09 (0.55, 2.16) Olmez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92)	Ko 1992	11	990	6	990	1.5	1.83 (0.68, 4.94)	· · · · · · · · · · · · · · · · · · ·
Kothi 1981 16 102 15 118 2.5 1.23 (0.64, 2.37) Lau 1986 9 159 3 156 10 2.94 (0.81, 10.67) Mahomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) McCluskey 1976 21 56 14 54 2.8 1.46 (0.82, 2.54) Memon 2011 1 100 3 100 0.4 0.33 (0.04, 3.15) Morgan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Maunton Morgan 1980 14 263 45 309 2.8 0.37 (0.21, 0.65) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Muller 2018 4 126 7 15 273 2.4 1.09 (0.55, 2.16) Omez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Reid 2001 12 217 18 213 2.3 0.65 (0.32, 1.33) Rogers 1983 4 86 11 101 1.3 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.00) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979a 1 80 9 48 0.5 0.19 (0.09, 0.42) Sindelar 1979a 1 80 9 48 0.5 0.19 (0.09, 0.42) Sindelar 1979 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979 1 1 55 21 62 2.5 0.59 (0.31, 1.11) Valiance 1985 11 37 3 38 0.4 0.34 (0.04, 3.14) Starr 2005 1 1 42 2 166 0.3 0.58 (0.05, 6.38) Stokes 1977 11 55 21 62 2.5 0.59 (0.31, 1.11) Valiance 1985 11 31 3 0.16 3.4 1.35 (0.87, 2.11) Valiance 1985 11 11 3 10 16 3.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 0.16 1.24 (0.50, 3.30) Walker 2013 1 31 3 0.16 1.4 0.59 (0.24, 1.86) Total (95% CI) 10148 10349 1000 0.70 (0.60, 0.80) Walker 2013 1 31 3 0.16 1.4 0.59 (0.24, 1.86) Total (95% CI) 10148 10349 1000 0.70 (0.60, 0.80) Walker 2013 1 31 0.16 3.4 0.34 (0.24, 1.86) Total (95% CI) 10148 10349 1000 0.70 (0.60, 0.80) Walker 2013 1 31 0.16 3.4 0.39 (0.04, 3.53) Walker 2013 1 0.16 4.5 0.59 (0.24, 1.86) Total (95% CI) 10148 10349 1000 0.70 (0.60, 0.80) Walker 2013 1 0.16 104 1034 10349 1000 0.70 (0.60, 0.80) Walker 2013 1 0.16 104 1034 10349 1000 0.70 (0.60, 0.80) Walker 2013 1 0.16 104 1004 1004 1004 1004 1004 1004	Kokavec 2008	0	89	2	73	0.2	0.16 (0.01, 3.37)	· · · · · · · · · · · · · · · · · · ·
Lau 1986 9 159 3 156 1.0 2.94 (0.81, 10.67) Mahomed 2016 144 1520 147 1507 4.5 0.97 (0.78, 1.21) McCluskey 1976 21 56 14 54 2.8 1.46 (0.82, 2.54) Morgan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Naunton Morgan 1980 14 263 45 309 2.8 0.37 (0.21, 0.65) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Muller 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Nandi 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Oestreicher 1989 16 267 15 273 2.4 1.09 (0.55, 2.16) Olmez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Reid 2001 12 217 18 213 2.3 0.65 (0.32, 1.24) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 7 1 37 3 38 0.4 0.34 (0.04, 3.14) Start 2005 1 1 142 2 166 0.3 0.58 (0.56, 6.38) Stokes 1977 11 55 21 62 2.5 0.59 (0.31, 1.11) Valiance 1985 11 1 3 10 16 3.4 1.35 (0.87, 2.11) Value 2019 9 9 0 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 0.1148 10349 1000 0.70 (0.60, 0.80) Total (95% CI) 10148 10349 1000 0.70 (0.60, 0.80) Total (95% CI) 10148 10349 1000 0.70 (0.60, 0.80) Future 2014 effect: $Z = 4.91$ ($p < 0.00001$): $P = 44\%$	Kothi 1981	16	102	15	118	2.5	1.23 (0.64, 2.37)	
Mahomed 2016 144 1507 4.5 0.97 0.78 1.21 McCluskey 1976 21 56 14 54 2.8 1.46 (0.82, 2.54) Memon 2011 1 100 3 100 0.4 0.33 (0.04, 3.15) Morgan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Naunton Morgan 1980 14 263 45 309 2.8 0.37 (0.21, 0.65) Mwangi 2013 13 201 20 196 2.4 0.63 (0.32, 124) Nandi 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Oestreicher 1989 16 2.67 15 2.73 2.4 1.09 (0.55, 2.16) Olmez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 2.2 9 2.3 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 2.6 74 3.1 0.74 (0.45, 1.124) Reid 2001 12 2.17 18	Lau 1986	9	159	3	156	1.0	2.94 (0.81, 10.67)) _
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Mahomed 2016	144	1520	147	1507	4.5	0.97 (0.78, 1.21)	
Memon 2011 1 1 100 3 100 0.4 0.3 (0.04, 3.15) Morgan 1978 10 166 22 154 2.2 0.42 (0.21, 0.86) Naunton Morgan 1980 14 263 45 309 2.8 0.37 (0.21, 0.65) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Mwangi 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Nandi 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Oestreicher 1989 16 267 15 273 2.4 1.09 (0.55, 2.16) Olmez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Reid 2001 12 217 18 213 2.3 0.65 (0.32, 1.33) Rogers 1983 4 86 11 101 1.3 0.43 (0.14, 1.29) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1985 1 37 3 38 0.4 0.34 (0.04, 3.14) Starr 2005 1 142 2 166 0.3 0.58 (0.05, 6.38) Stokes 1977 11 55 21 62 2.5 0.59 (0.31, 1.11) Vilay 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 01 6 3.4 1.35 (0.87, 2.11) Vinay 2019 9 90 7 90 1.6 1.29 (0.04, 3.53) Walsh 1981 28 308 40 319 3.3 0.72 (0.46, 1.14) Vilayince 1985 11 13 10 16 3.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 0.148 10349 100.0 0.70 (0.60, 0.80) Total (95% CI) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $r^2 = 0.11; \chi^2 = 103.58, df = 58 (p = 0.0002): l^2 = 44\%$	McCluskey 1976	21	56	14	54	2.8	1.46 (0.82, 2.54)	
$ \begin{array}{l c c c c c c c c c c c c c c c c c c c$	Memon 2011	1	100	3	100	0.4	0.33 (0.04, 3.15)	<u> </u>
Naunton Morgan 1980 14 263 45 309 2.8 0.37 (0.21, 0.65) Muller 2018 4 23 2 21 0.7 1.83 (0.37, 8.96) Maragi 2013 13 201 20 196 2.4 0.63 (0.32, 1.24) Nandi 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Oestreicher 1989 16 267 15 273 2.4 1.09 (0.55, 2.16) Olmez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Reid 2001 12 217 18 213 2.3 0.65 (0.32, 1.33) Rogers 1983 4 86 11 101 1.3 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1985 1 377 3 38 0.4 0.34 (0.04, 3.14) Starr 2005 1 142 2 166 0.3 0.58 (0.05, 6.38) Stokes 1977 11 55 21 62 2.5 0.59 (0.31, 1.11) Valiance 1985 11 31 3 0 16 3.4 1.35 (0.87, 2.11) Vinay 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 0 16 3.4 0.39 (0.04, 3.53) Walker 2013 1 0 16 3.4 0.39 (0.04, 3.54) Walker 2013 1 0 16 3.4 0.39 (0.04, 3.53) Walker 2013 1 0 10 16 3.4 0.39 (0.04, 3.53) Walker 2013 1 0 10 16 3.4 0.39 (0.04, 3.53) Walker 2013 1 0 10 16 0.4 0.39 (0.04, 3.53) Walker 2013 1 0 10 10 0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 103.58$, $df = 58$ ($p = 0.0002$): $l^2 = 44\%$ Test for overall effect: $Z = 4.91$ ($p < 0.00001$)	Morgan 1978	10	166	22	154	2.2	0.42 (0.21, 0.86)	_
Muller 2018 4 23 2 21 0.7 1.8 (0.37, 8.96) Mwangi 2013 13 201 20 196 2.4 0.63 (0.32, 1 24) Nandi 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Oestreicher 1989 16 267 15 273 2.4 1.09 (0.55, 2.16) Olmez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Reid 2001 12 217 18 213 2.3 0.65 (0.32, 1.33) Rogers 1983 4 86 11 101 1.3 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.18, 1.00) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1985 1 37 3 38 0.4 0.34 (0.04, 3.14) Starr 2005 1 142 2 166 0.3 0.58 (0.55, 6.38) Stokes 1977 11 55 21 62 2.5 0.59 (0.31, 1.11) Valiance 1985 11 13 10 16 3.4 1.35 (0.87, 2.11) Valiance 1985 11 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 2013 1 31 3 36 0.4 0.67 (0.24, 1.86) Total events 665 974 Heterogeneity: $r^2 = 0.11; \chi^2 = 103.58, df = 58 (p = 0.0002)$: $\rho = 44\%$ Test for overall effect: $Z = 4.91 (p < 0.00001)$	Naunton Morgan 1980	14	263	45	309	2.8	0.37 (0.21, 0.65)	
Numargi 2013 13 201 20 196 2.4 0.63 (0.32, 124) Nandi 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Oestreicher 1989 16 267 15 273 2.4 1.09 (0.55, 2.16) Olmez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Reid 2001 12 217 18 213 2.3 0.65 (0.32, 1.33) Rogers 1983 4 86 11 101 1.3 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.18, 1.00) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.94, 3.14) Starr 2005 1 142 2 166 0.3 0.58 (0.57, 3.30) </td <td>Muller 2018</td> <td>4</td> <td>23</td> <td>2</td> <td>21</td> <td>0.7</td> <td>1.83 (0.37, 8.96)</td> <td></td>	Muller 2018	4	23	2	21	0.7	1.83 (0.37, 8.96)	
Name 2015 4 136 7 138 1.1 0.58 (0.17, 1.94) Oestreicher 1989 16 267 15 273 2.4 1.09 (0.55, 2.16) Olmez 2013 35 332 57 335 3.6 0.62 (0.42, 0.92) Parker 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Reid 2001 12 217 18 213 2.3 0.65 (0.32, 1.33) Sherlock 1984 6 39 13 36 1.8 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.18, 1.00) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1985 1 37 3 38 0.4 0.34 (0.04, 3.14) Starr 2005 1 142 2 166 0.3 0.58 (0.05, 6.38) Stokes 1977 11 55 21 62 2.5 0.59 (0.31, 1.11) Valiance 1985 11 13 10 16 3.4 1.35 (0.87, 2.11) Vinay 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walker 1981 28 308 40 319 3.3 0.72 (0.46, 1.14) Yildirim 2012 6 334 9 335 1.4 0.67 (0.24, 1.86) Total events 665 974 Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 103.58$, $df = 58$ ($p = 0.0002$): $l^2 = 44\%$ Test for overall effect: $Z = 4.91$ ($p < 0.00001$)	Mwangi 2013	13	201	20	196	2.4	0.63 (0.32, 1.24)	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Nandi 2015	4	136	1	138	1.1	0.58 (0.17, 1.94)	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Olesciencier 1989	10	207	15	2/3	2.4	1.09 (0.55, 2.16)	
Pollock 1985 1 22 9 23 0.5 0.12 (0.02, 0.84) Pollock 1978 17 65 26 74 3.1 0.74 (0.45, 1.24) Reid 2001 12 217 18 213 2.3 0.65 (0.32, 1.33) Rogers 1983 4 86 11 101 1.3 0.43 (0.14, 1.29) Sherlock 1984 6 39 13 36 1.8 0.43 (0.18, 1.00) Sindelar 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1985 1 37 3 38 0.4 0.34 (0.04, 3.14) Starr 2005 1 142 2 166 0.3 0.58 (0.05, 6.38) Stokes 1977 11 55 21 62 2.5 0.59 (0.31, 1.11) Valiance 1985 11 13 10 16 3.4 1.35 (0.87, 2.11) Valiance 1985 11 13 10 16 3.4 1.35 (0.87, 2.11) Vinay 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walkh 1981 28 308 40 319 3.3 0.72 (0.46, 1.14) Yildirim 2012 6 334 9 335 1.4 0.67 (0.24, 1.86) Total (95% CI) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11; \chi^2 = 103.58, df = 58 (p = 0.0002): l^2 = 44\%$ Test for overall effect: $Z = 4.91 (p < 0.00001)$	Darker 1085	35	33Z	57	335	3.0	0.62 (0.42, 0.92)	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Parker 1965 Pollock 1078	17	2Z 65	9	25 74	0.5	0.12 (0.02, 0.64) 0.74 (0.45, 1.24)	
Red 200112217132132.30.03 (0.32, 1.35)Rogers 1983486111011.30.43 (0.14, 1.29)Sherlock 198463913361.80.43 (0.18, 1.00)Sindelar 1979a1809880.50.12 (0.02, 0.94)Sindelar 1979b7242392582.00.19 (0.09, 0.42)Sindelar 19851373380.40.34 (0.04, 3.14)Starr 2005114221660.30.58 (0.05, 6.38)Stokes 1977115521622.50.59 (0.31, 1.11)Valance 1985111310163.41.35 (0.87, 2.11)Vinay 20199907901.61.29 (0.50, 3.30)Walker 20131313360.40.39 (0.04, 3.53)Walker 20131313351.40.67 (0.24, 1.86)Total (95% CI)1014810349100.00.70 (0.60, 0.80)Total events665974974Heterogeneity: $\tau^2 = 0.11; \chi^2 = 103.58, df = 58 (p = 0.0002): l^2 = 44\%$ 0.010.11Total (95% CI)1014810349100.00.70 (0.60, 0.80)Total events6659741000.11100Total events665974110100Test for overall effect: $Z = 4.91 (p < 0.00001)$ 11100	Poid 2001	17	217	20 18	7 4 212	2.1	0.74(0.43, 1.24) 0.65(0.32, 1.33)	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Pogers 1983	12	86	10	101	2.5	0.03(0.32, 1.33) 0.43(0.14, 1.29)	
Sinclear 1979a 1 80 9 88 0.5 0.12 (0.02, 0.94) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1985 1 37 3 38 0.4 0.34 (0.04, 3.14) Starr 2005 1 142 2 166 0.3 0.58 (0.05, 6.38) Stokes 1977 11 55 21 62 2.5 0.59 (0.31, 1.11) Valiance 1985 11 13 10 16 3.4 1.35 (0.87, 2.11) Vinay 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walsh 1981 28 308 40 319 3.3 0.72 (0.46, 1.14) Yildirim 2012 6 334 9 335 1.4 0.67 (0.24, 1.86) Total (95% CI) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11; \chi^2 = 103.58, df = 58 (p = 0.0002): l^2 = 44\%$ Test for overall effect: $Z = 4.91 (p < 0.00001)$	Sherlock 1984	+ 6	30	11	36	1.5	0.43(0.14, 1.29) 0.43(0.18, 1.00)	
Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1979b 7 242 39 258 2.0 0.19 (0.09, 0.42) Sindelar 1985 1 37 3 38 0.4 0.34 (0.04, 3.14) Starr 2005 1 142 2 166 0.3 0.58 (0.05, 6.38) Stokes 1977 11 55 21 62 2.5 0.59 (0.31, 1.11) Valiance 1985 11 13 10 16 3.4 1.35 (0.87, 2.11) Vinay 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walsh 1981 28 308 40 319 3.3 0.72 (0.46, 1.14) Yildirim 2012 6 334 9 335 1.4 0.67 (0.24, 1.86) Total (95% CI) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11; \chi^2 = 103.58, df = 58 (p = 0.0002): l^2 = 44\%$ Test for overall effect: $Z = 4.91 (p < 0.00001)$	Sindelar 1979a	1	80	9	88	0.5	0.43 (0.10, 1.00) 0.12 (0.02, 0.94)	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Sindelar 1979b	7	242	39	258	2.0	0.19 (0.09 0.42)	
Start 2005 1 142 2 166 0.3 0.58 (0.05, 6.38) Stokes 1977 11 55 21 62 2.5 0.59 (0.31, 1.11) Valiance 1985 11 13 10 16 3.4 1.35 (0.87, 2.11) Vinay 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walsh 1981 28 308 40 319 3.3 0.72 (0.46, 1.14) Yildirim 2012 6 334 9 335 1.4 0.67 (0.24, 1.86) Total (95% Cl) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11; \chi^2 = 103.58, df = 58 (p = 0.0002): l^2 = 44\%$ Test for overall effect: $Z = 4.91 (p < 0.00001)$	Sindelar 1985	, 1	37	3	38	0.4	0.34 (0.04, 3.14)	
Stokes 1977 11 55 21 62 2.5 0.59 (0.3, 0.36) Valiance 1985 11 13 10 16 3.4 1.35 (0.87, 2.11) Vinay 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walsh 1981 28 308 40 319 3.3 0.72 (0.46, 1.14) Yildirim 2012 6 334 9 335 1.4 0.67 (0.24, 1.86) Total (95% CI) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11; \chi^2 = 103.58, df = 58 (p = 0.0002): l^2 = 44\%$ Test for overall effect: $Z = 4.91 (p < 0.00001)$	Starr 2005	1	142	2	166	0.3	0.58 (0.05, 6.38)	
Valiance 1985 11 13 10 16 3.4 1.35 (0.87, 2.11) Vinay 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walsh 1981 28 308 40 319 3.3 0.72 (0.46, 1.14) Yildirim 2012 6 334 9 335 1.4 0.67 (0.24, 1.86) Total (95% CI) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11; \chi^2 = 103.58, df = 58 (p = 0.0002): l^2 = 44\%$ Test for overall effect: $Z = 4.91 (p < 0.00001)$	Stokes 1977	11	55	21	62	2.5	0.59 (0.31, 1.11)	_ ↓
Vinay 2019 9 90 7 90 1.6 1.29 (0.50, 3.30) Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walsh 1981 28 308 40 319 3.3 0.72 (0.46, 1.14) Yildirim 2012 6 334 9 335 1.4 0.67 (0.24, 1.86) Total (95% CI) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 103.58$, $df = 58$ ($p = 0.0002$): $l^2 = 44\%$ Test for overall effect: $Z = 4.91$ ($p < 0.00001$)	Valiance 1985	11	13	10	16	3.4	1.35 (0.87. 2.11)	_
Walker 2013 1 31 3 36 0.4 0.39 (0.04, 3.53) Walsh 1981 28 308 40 319 3.3 0.72 (0.46, 1.14) Yildirim 2012 6 334 9 335 1.4 0.67 (0.24, 1.86) Total (95% Cl) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11; \chi^2 = 103.58, df = 58 (p = 0.0002): l^2 = 44\%$ 0.01 0.1 1 10 100 Test for overall effect: $Z = 4.91 (p < 0.00001)$ 0.00001 0.1 1 10 100	Vinay 2019	9	90	7	90	1.6	1.29 (0.50. 3.30)	
Walsh 1981 28 308 40 319 3.3 0.72 (0.46, 1.14) Yildirim 2012 6 334 9 335 1.4 0.67 (0.24, 1.86) Total (95% CI) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 103.58$, $df = 58$ ($p = 0.0002$): $l^2 = 44\%$ Test for overall effect: $Z = 4.91$ ($p < 0.00001$)	Walker 2013	1	31	3	36	0.4	0.39 (0.04. 3.53)	_ _ +
Yildirim 2012 6 334 9 335 1.4 0.67 (0.24, 1.86) Total (95% CI) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 103.58$, $df = 58$ ($p = 0.0002$): $l^2 = 44\%$ Test for overall effect: $Z = 4.91$ ($p < 0.00001$)	Walsh 1981	28	308	40	319	3.3	0.72 (0.46. 1.14)	-
Total (95% Cl) 10148 10349 100.0 0.70 (0.60, 0.80) Total events 665 974 Heterogeneity: $\tau^2 = 0.11; \chi^2 = 103.58, df = 58 (p = 0.0002): l^2 = 44\%$ 0.01 0.1 Test for overall effect: $Z = 4.91 (p < 0.00001)$ 0.00001 0.01 1	Yildirim 2012	6	334	9	335	1.4	0.67 (0.24, 1.86)	
Total events $665 974$ Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 103.58$, $df = 58$ ($p = 0.0002$): $l^2 = 44\%$ Test for overall effect: $Z = 4.91$ ($p < 0.00001$) $0.1 1 10 100$	Total (95% CI)	-	10148	-	10349	100.0	0.70 (0.60, 0.80)	♦
Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 103.58$, $df = 58$ ($p = 0.0002$): $l^2 = 44\%$ Test for overall effect: $Z = 4.91$ ($p < 0.00001$)	Total events	665		974			. , , ,	
Test for overall effect: $Z = 4.91$ ($p < 0.00001$) 0.01 0.1 1 10 100 Environmentation	Heterogeneity: $\tau^2 = 0.11$;	$\chi^2 = 103$	3.58, d <i>f</i> =	= 58 (p =	0.0002)	$I^2 = 44\%$, D	
	Test for overall effect: Z =	4.91 (p	< 0.000	01)				

Figure 4. Forest plot of studies included in the meta-analysis (n = 59) using a random effects model. Risk ratios and 95% confidence intervals are shown

Study or subgroup	Р	VI .	Со	ntrol	Weight	Risk ratio M-H,		Risk ratio M-H,	
	Events	Total	Events	Total	(%)	random, 95% CI		random, 95% Cl	_
2.1.1. Saline		222	0	224	0.4	0.12 (0.02, 1.04)			
Calkins 2019	1	223	8	234	0.4	0.13 (0.02, 1.04)	-		
Chang 2006	0	120	6	124	0.2	0.08 (0.00, 1.40)	-		
Cheng 2005	0	208	/	206	0.2	0.07 (0.00, 1.15)	•		
Conen 2020	1	//	2	76	0.3	0.49 (0.05, 5.33)			
Galle 1980	9 15	31	9	30	2.0	1.16 (0.53, 2.56)			
Ghafouri 2016	15	196	14	193	2.3	1.06 (0.52, 2.13)			
Haribara 2006	/	6U E 4	4	6U E 2	1.1	1.75(0.55, 5.75)			
Harriara 2000	0	54	0 14	25 100	1.7	0.96(0.40, 2.42) 0.14(0.02, 1.06)			
Johnson 1985	10	20	21	28	3.0	0.14(0.02, 1.00) 0.48(0.28, 0.82)			
Karuserci 2019	6	100	12	100	1.6	0.40(0.20, 0.02) 0.50(0.20, 1.28)			
Ko 1992	11	990	6	990	1.0	1 83 (0 68 4 94)		-	
Kokavec 2008	0	89	2	73	0.2	0.16 (0.01, 3.37)	-		
Oestreicher 1989	16	267	15	273	2.4	1.09 (0.55, 2.16)			
Pollock 1978	17	65	26	74	3.1	0.74 (0.45, 1.24)			
Rogers 1983	4	86	11	101	1.3	0.43 (0.1 4, 1.29)			
Sindelar 1979a	1	80	9	88	0.4	0.12 (0.02, 0.94)	_		
Sindelar 1979b	7	242	39	258	2.0	0.19 (0.09, 0.42)			
Sindelar 1985	1	37	3	38	0.4	0.34 (0.04, 3.14)			
Valiance 1985	11	13	10	16	3.5	1.35 (0.87, 2.11)			
Vinay 2019	9	90	7	90	1.6	1.29 (0.50, 3.30)			
Walker 2013	1	31	3	36	0.4	0.39 (0.04, 3.53)			
Subtotal (95% CI)		3157		3267	30.3	0.65 (0.46, 0.92)		\bullet	
Total events	136		236						
Heterogeneity: $\tau^2 = 0.33$; Test for overall effect: Z =	χ ² = 52. = 2.43 (p	52, d <i>f</i> = = 0.02)	21 (p = 0).0002);	l ² = 60%				
2.1.2 No treatment									
Alobaidy 2020	1	200	2	200	0.3	0.50 (0.05, 5.47)			
Anderson 2020	6	50	8	50	1.5	0.75 (0.28, 2.00)		- _	
Aref 2018	4	106	6	101	1.1	0.64 (0.1 8, 2.19)			
Asad 2017	3	217	8	217	1.0	0.38 (0.1 0, 1.39)			
Asghania 2011	10	284	9	284	1.7	1.11 (0.46, 2.69)			
Barat 2016	12	200	13	200	2.1	0.92 (0.43, 1.97)		- _	
Barr 1978	1	28	23	60	0.5	0.09 (0.01, 0.66)			
Charoenviboonphan 201	1 1	299	4	300	0.4	0.25 (0.03, 2.23)			
de Jong 1982	39	303	45	279	3.7	0.80 (0.54, 1.19)		-•†	
Foster 1981	29	119	27	117	3.4	1.06 (0.67, 1.67)			
Galland 1977	14	39	18	39	3.0	0.78 (0.45, 1.33)		-++	
Galland 1983	13	95	14	105	2.3	1.03 (0.51, 2.07)		_	
Gilmore 1974	12	149	24	151	2.5	0.51 (0.26, 0.98)			
Gilmore 1975	0	/0	18	/4 50	1.8	0.35(0.15, 0.84)			
	0	48	2	23	0.2	0.22 (0.01, 4.48)		•	
Gray 1981	7	/ I 1 E E	20	8Z 1 / E	2.0	0.40(0.18, 0.90)			
Hads 2010 Haidar 2018	10	200	24	200	1.0	0.03(0.20, 1.07) 0.70(0.44, 1.41)			
labal 2015	0	200	16	200	2.0	0.79(0.44, 1.41) 0.56(0.26, 1.20)			
Kothius 1981	16	102	15	118	2.1	1.23 (0.64, 2.37)			
Lau 1986	9	159	3	156	1.0	2 94 (0 81 10 67)			
Mahomed 2016	144	1520	147	1507	4.6	0.97 (0.78, 1.21)		4	
McCluskey 1976	21	56	14	54	2.9	1.45 (0.82, 2.54)			
Memon 2011	1	100	3	100	0.4	0.33 (0.04, 3.15)			
Morgan 1978	10	166	22	154	2.3	0.42 (0.21, 0.86)			
Morgan 1980	14	263	45	309	2.8	0.37 (0.21, 0.65)		_ _	
Mwangi 2013	13	201	20	196	2.4	0.63 (0.32, 1.24)			
Nandi 2015	4	136	7	138	1.1	0.58 (0.1 7, 1.94)			
Olmez 2013	35	332	57	335	3.7	0.62 (0.42, 0.92)			
Reid 2001	12	217	18	213	2.3	0.65 (0.32, 1.33)			
Sherlock 1984	6	39	13	36	1.8	0.43 (0.1 8, 1.00)			
Starr 2005	1	142	2	166	0.3	0.58 (0.05, 6.38)			
Stokes 1977	11	55	21	62	2.6	0.59 (0.31, 1.11)			
Walsh 1981	28	308	40	319	3.4	0.72 (0.46, 1.14)			
Yildirim 2012	6	334	9	335	1.4	0.67 (0.24, 1.86)			
Subtotal (95% CI)	F A A	6946	707	/038	69.7	0./1 (0.61, 0.82)		•	
Total events Heterogeneity: $\tau^2 = 0.05$; Test for overall effect: <i>Z</i> =	524 χ ² = 48. = 4.60 (p	78, df = < 0.000	727 34 (p = 0 01)).05); /² =	= 30%				
	4							.	
Total (95% CI)		10103		10305	100.0	0.70 (0.61, 0.81)		♦	
Total events	660		963					.	
Heterogeneity: $\tau^2 = 0.10$;	$\chi^2 = 98.$	75, df =	56 ($p = 0$).0004);	I² = 43%				1
Test for subgroup different for subgroup dif	= 4.90 (p nces: χ ² :	< 0.000 = 0.23, c	01) df = 1 (p =	= 0.63); /	¹² = 0%		0.01	0.1 1 10 1 Favours PVI Favours control	00

Figure 5. Forest plot for subgroup analysis of comparator type in studies using a random effects model. Risk ratios and 95% confidence intervals are shown



Figure 6. Forest plot for subgroup analysis of PVI application method in studies using a random effects model. Risk ratios and 95 confidence intervals are shown

Study or subgroup	P١	/I	Cor	itrol	Weight	Risk ratio M-H,		Risk ratio M-H,	
4.1.2. Ab dam: a al	Events	Total	Events	Total	(%)	random, 95% Cl		random, 95% Cl	
4.1.2 Abdominal	6	50	0	50	16				
Rarr 1978	0	28	0 23	50 60	0.5	0.75 (0.28, 2.00)			
de Jong 1982	39	303	45	279	4.5	0.90 (0.54, 1.19)		_ _	
Foster 1981	29	119	27	117	4.0	1.06 (0.67, 1.67)		_ _	
Galland 1977	14	39	18	39	3.5	0.78 (0.45, 1.33)		-++	
Galland 1983	13	95	14	105	2.6	1.03 (0.51, 2.07)		-+	
Gabe 1980 Gilmore 1974	9 12	31 1/0	9 24	30 151	2.2	1.16(0.53, 2.56) 0.51(0.26, 0.98)			
Gilmore 1975	6	70	18	74	2.8	0.31 (0.20, 0.98)			
Gray 1981	7	71	20	82	2.2	0.40 (0.18, 0.90)		_	
Harihara 2006	8	54	8	53	1.8	0.98 (0.40, 2.42)		_	
Iqbal 2015	9	83	16	83	2.4	0.56 (0.26, 1.20)		— - +	
Karuserci 2019	6	100	12	100	1.7	0.50(0.20, 1.28)			
1 201 1086	10 Q	102	3	110	2.0 1 1	1.25 (0.04, 2.57) 2.94 (0.81, 10.67)			
McCluskev 1976	21	56	14	54	3.3	1.45 (0.82, 2.54)			
Muller 2018	4	23	2	21	0.7	1.83 (0.37, 8.96)		— <u> </u>	
Pollock 1978	17	65	26	74	3.6	0.74 (0.45, 1.24)		-++	
Rogers1983	4	86	11	101	1.4	0.43 (0.14, 1.29)			
Sindelar 1984	0	39 80	13	30 88	2.0	0.43 (0.18, 1.00) 0.12 (0.02, 0.94)			
Sindelar 1985	1	37	3	38	0.4	0.12(0.02, 0.94) 0.34(0.04, 3.14)			
Stokes 1977	11	55	21	62	2.9	0.59 (0.31, 1.11)		_ _	
Valiance 1985	11	13	10	16	4.1	1.35 (0.87, 2.11)			
Vinay 2019	9	90	7	90	1.7	1.29 (0.50, 3.30)		_	
Walsh 1981	28	308	40	319	4.0	0.72 (0.46, 1.14)			
Total events	297	2305	416	2402	60.4	0.78 (0.64, 0.95)		•	
Heterogeneity: $\tau^2 = 0.10$;	$\chi^2 = 44.4$	10, d <i>f</i> =	25(p=0)	.010); / ²	= 44%				
Test for overall effect $Z =$	2.49 (p =	= 0.01)	4	,,					
4.1.2 Currencelogical									
Alobaidy 2020	1	200	2	200	03	0 50 (0 05 5 47)			
Aref 2018	4	106	6	101	1.1	0.64 (0.18, 2.19)			
Asad 2017	3	217	8	217	1.0	0.38 (0.10, 1.39)		— <u> </u>	
Asghania 2011	10	284	9	284	1.9	1.11 (0.46, 2.69)		_ --	
Barat 2016	12	200	13	200	2.3	0.92 (0.43, 1.97)		_ _	
Charoenviboonphan 2011	17	299	4	300	0.4	0.25 (0.03, 2.23) 1 75 (0 53 5 75)			
Haas 2010	7	155	10	145	1.2	0.65 (0.26, 1.67)			
Hassan 2016	1	50	14	100	0.5	0.14 (0.02, 1.06)	-	e	
Mahomed 2016	144	1520	147	1507	5.8	0.97 (0.78, 1.21)		+	
Memon 2011	1	100	3	100	0.4	0.33 (0.04, 3.15)			
Mwangi 2013	13	201	20	196	2./	0.63 (0.32, 1.24)			
Olmez 2013	4 35	332	7 57	335	1.Z 4.5	0.58(0.17, 1.94) 0.62(0.42, 0.92)			
Reid 2001	12	217	18	213	2.6	0.65 (0.32, 1.33)			
Starr 2005	1	142	2	166	0.3	0.58 (0.05, 6.38)		-	
Yildirim 2012	6	334	9	335	1.5	0.67 (0.24, 1.86)			
Subtotal (95 CI)	262	4573	222	4617	29.7	0.81 (0.69, 0.95)		◆	
Heterogeneity: $\tau^2 = 0.00$.	262 $\gamma^2 - 14$	51 df-	333 16 (n - 0	$56) \cdot l^2$	- 0%				
Test for overall effect $Z =$	$\chi = 14.2$ 2.62 (p =	= 0.009)	10 (p = 0)	.50); 1 -	= 0 %				
	4	,							
4.1.4 Orthopaedic	1	222	0	224	0.5	0 1 2 (0 0 2 1 0 4)			
Kakavec 2008	1	223	8 2	234 73	0.5	0.13(0.02, 1.04) 0.16(0.01, 3.37)	_		
Subtotal (95 CI)	0	312	2	307	0.2	0.14 (0.03, 0.78)	•		
Total events	1		10						
Heterogeneity: $\tau^2 = 0.00$;	$\chi^2 = 0.01$, $df = 1$	(<i>p</i> = 0.90	$); I^2 = 0$	%				
Test for overall effect: $Z =$	2.25 (p	= 0.02)							
4.1.5 Accident									
Ghafouri 2016	15	196	14	193	2.6	1.06 (0.52, 2.13)		_ _	
Morgan 1978	10	166	22	154	2.5	0.42 (0.21, 0.86)		_ _	
Morgan 1980	14	263	45	309	3.2	0.37 (0.21, 0.65)			
Subtotal (95 CI)	30	625	Q1	656	8.4	0.54 (0.28, 1.02)			
Heterogeneity: $\tau^2 = 0.21$:	$\gamma^2 = 5.69$	df = 2	(p = 0.06)	b): $l^2 = 6$	5%				
Test for overall effect $Z =$	1.89 (p =	= 0.06)	ų	,,					
116 Spinal									
Chang 2006	0	120	6	174	0.2	0.08 (0.00 1.40)	-		
Cheng 2005	õ	208	7	206	0.2	0.07 (0.00, 1.15)	-		
Cohen 2020	1	77	2	76	0.3	0.49 (0.05, 5.33)		_	
Subtotal (95 CI)		405		406	0.8	0.16 (0.03, 0.76)			
Total events	1	- مار -	15	-) in -	0/				
The terogeneity: $\tau^2 = 0.00$;	$\chi^2 = 1.56$	o, df = 2 - 0 0 0	(p = 0.46)	$(); I^2 = 0$	70				
Total (95 CI)	2.51 (p =	- 0.02) 8220		8388	100.0	0.72 (0.63 0.83)			
Total events	600		855	2200		(0.05, 0.05)		•	
Heterogeneity: $\tau^2 = 0.08$;	$\chi^2 = 79.6$	8, d <i>f</i> =	50 (p = 0	.005); <i>I</i> ²	= 37%			•	
Test for overall effect $Z =$	4.43 (p <	0.0000)1)	0.05) 		⊢		I.
lest for subgroup differer	nces: $\chi^2 =$	9.34, d	ı <i>f</i> = 4 (<i>p</i> =	0.05), I	- = 57.2%		0.01	0.1 1 10 1	00
								Favours PVI Favours control	

Figure 7. Forest plot for subgroup analysis of surgery category in studies using a random effects model. Risk ratios and 95 confidence intervals are shown



Test for overall effect: Z = 4.95 (p < 0.00001)Test for subgroup differences: $\chi^2 = 0.12$, df = 2 (p = 0.94), $l^2 = 0\%$

Figure 8. Forest plot for subgroup analysis of type of procedure in studies using a random effects model. Risk ratios and 95 confidence intervals are shown

Favours PVI

Favours control

dated and uniform definition of SSI, are needed to validate these findings.

Review criteria: how did you gather, select and analyze the information you considered in your review?

A systematic literature search was conducted of MEDLINE (PubMed) and Cochrane Register of Controlled Trials (CENTRAL) in June 2021. No time limit was applied as several studies were published earlier than 1990. The following search terms were used in various combinations: surgical site infection, wound infection, SSI, post-operative, povidone-iodine, betadine, irrigation, and spray, and lavage, intraoperative and anti-infective agents.

Conflict of interest

The authors declare no conflict of interest.

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Received: 2.08.2021, accepted: 19.09.2021.