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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Povidone-Iodine for Breast Implant Surgery: A Review of Clinical Effectiveness and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	May 16, 2019
Report Length:	14 Pages

CADTH

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Cite As: Povidone-Iodine for breast Implant Surgery: A Review of Clinical Effectiveness and Guidelines. Ottawa: CADTH; 2019 May. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Abbreviations

FDA	Food and Drug Administration
RCT	randomized controlled trial
PVI	povidone-iodine

Context and Policy Issues

It is estimated that, globally, more than four million women undergo breast implant surgery for either aesthetic or reconstructive purpose.[1] Breast implant surgery involves the creation of a breast pocket followed by insertion of a breast implant. There may be complications associated with the procedure. There is potential for development of capsular contracture, which may be due to chronic subclinical infection around the implant.[2,3] Capsular contracture is progressive and disfiguring and frequently results in reoperation.[2] Also, implanting a foreign material is associated with risk of infection.[2,3] The potential for bacterial infection, and the correlation between capsular contracture and biofilm formation, prompted the perioperative use of antimicrobial agents for soaking implants and for breast pocket irrigation.[3,4] These agents include several antibiotics (e.g., cefuroxine, cefazolin, gentamicin) and antiseptics (e.g., povidone-iodine [PVI]).[5]

In 2000, the US Food and Drug Administration (FDA) recommended against the direct contact of PVI with implants, due to concerns about PVI causing implant deflation.[4,6] Subsequently, Jewell and Adams,[7] reported that in 2017, the US FDA approved a request by one of the manufacturers of breast implants for removal of the warning regarding the use of Betadine (povidone-iodine 10% solution). There appears to be some uncertainty regarding the use of PVI for pocket irrigation and implant soaking, in breast implant surgery.

The purpose of this report is to review the clinical effectiveness of PVI for pocket irrigation and implant soaking in breast implant surgery. Additionally, this report aims to review the evidence-based guidelines regarding the use of povidone-iodine for biofilm mitigation and prevention of infection during and after breast implant surgery.

Research Questions

1. What is the comparative clinical effectiveness of povidone-iodine solutions versus other antiseptic solutions for pocket irrigation in breast implant surgery?
2. What is the comparative clinical effectiveness of povidone-iodine solutions versus other antiseptic solutions for implant soaking in breast implant surgery?
3. What are the evidence-based guidelines regarding the use of povidone-iodine solutions for biofilm mitigation and to prevent infection during and after breast implant surgery?

Key Findings

Low quality evidence, suggests that povidone-iodine breast pocket irrigation is effective in reducing capsular contracture in patients undergoing breast augmentation surgery with implants.

No relevant studies on clinical effectiveness of soaking implants with povidone-iodine were identified. No relevant evidence-based guidelines were identified regarding the use of povidone-iodine for breast implant surgery.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and April 20, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients undergoing breast implant surgery
Intervention	Povidone-iodine formulations (e.g., Betadine)
Comparator	Q1-2: Other anti-septic solutions (e.g., other povidone-iodine formulations, sterile water, sterile water infused with antibiotics)
Outcomes	Q1-2: Clinical effectiveness and safety (e.g., infection prevention, prevention of silicone breakdown or breakdown of implant, prevention of capsular contractures) Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews/meta-analyses, randomized controlled trials, non-randomized studies, and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2009. Systematic reviews with all relevant primary studies included in an included systematic review were excluded. Primary studies were excluded if they had been included in an identified systematic review. Guidelines with unclear methodology were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2 checklist.[8] Summary scores were not calculated for the included systematic reviews, rather, the strengths and limitations of each individual systematic review was described narratively.

Summary of Evidence

Quantity of Research Available

A total of 71 citations were identified in the literature search. Following screening of titles and abstracts, 55 citations were excluded and 16 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search for full text review. Of these potentially relevant articles, 14 publications were excluded for various reasons, and two publications met the inclusion criteria and were included in this report. These comprised two systematic reviews.[1,4] No relevant randomized controlled trial, non-randomized study, or evidence-based guideline was identified. Appendix 1 shows the PRISMA[9] flowchart of the study selection.

Summary of Study Characteristics

Study characteristics are summarized, and additional details are provided in Appendix 2, Table 2.

Study Design

Two relevant systematic reviews[1,4] were identified. One systematic review[4] included three RCTs, two comparative retrospective studies and 4 case-series studies published between 1986 and 2013. The second systematic review[1] had a broad focus and included several studies, of which two comparative retrospective studies, published in 2007 and 2013, were relevant for this current report. In both systematic reviews, multiple databases were searched. For one systematic review[4] the search period was from 1966 to 2015 and the other systematic review[1] search period was 2000 to 2016.

Country of Origin

One systematic review[4] was from the UK and was published in 2015. The included studies in this systematic review[4] were from the US (7 studies), UK (1 study), and Finland (1 study). The second systematic review[1] was from the US and was published in 2017. The included studies in this systematic review[1] were from the US.

Population

Both systematic reviews[1,4] involved patients who underwent breast augmentation surgery with implants. The numbers of patients in the systematic reviews were 3,794 in one systematic review[1] and 1,786 in the other systematic review.[4] The age of the patients were not presented.

Interventions and Comparators

In one systematic review,[4] in the included comparative studies, PVI was compared with saline for breast pocket irrigation and in the included case-series studies PVI was used for breast pocket irrigation. In the other systematic review[1] breast pocket irrigation with and without PVI were examined. The concentrations of PVI used in the studies varied (5%, 7.5%, or 10%) or was not mentioned.

Outcomes

Outcomes reported included capsular contracture rates[1,4] and deflation or rupture rates.[4]

Summary of Critical Appraisal

Critical appraisal of the included studies is summarized below and details are presented in Appendix 3,Table 3.

In both the included systematic reviews,[1,4] the objective was clearly stated, multiple databases were searched, article selection was described, characteristics of the included studies were described but details were sparse, and the authors mentioned that there were no conflicts of interest. In one systematic review,[4] article selection was done in duplicate, but it was unclear if data extraction and quality assessment were done in duplicate; the quality of the studies was variable. In one systematic review,[1] it was unclear if article selection and data extraction were done in duplicate; and if quality assessment was undertaken, however, the authors mentioned that the evidence was of low quality. In both systematic reviews, a list of excluded studies was not presented, and publication bias does not appear to have been explored. Many of the included studies were non-randomized studies and retrospective in nature, hence there is potential for selection and reporting biases.

Summary of Findings

Two systematic review,[1,4] were identified regarding the clinical effectiveness of PVI for breast implant surgery. Relevant findings are summarized and a table of the main findings, and authors' conclusions are presented in Appendix 4, Table 4.

Clinical Effectiveness of povidone-iodine

Clinical effectiveness of povidone-iodine solutions for pocket irrigation in breast implant surgery

Capsular contracture:

In both systematic reviews,[1,4] capsular contracture rates in breast implant surgery were reported in all the included primary studies. One systematic review,[1] found contracture rates to be variable with and without PVI irrigation; lower rates with PVI were reported in some instances but the differences were not always statistically significant. One systematic review[4] found capsular contracture rates to be statistically significantly lower with PVI compared to saline. In both systematic reviews, it was mentioned that findings need to be interpreted with caution as they were based on low quality evidence.

Implant rupture rate:

Of the two included systematic reviews,[1,4] one[4] reported on implant rupture rates. In this systematic review, four of the nine included primary studies reported on implant rupture rates. Implant rupture rates with PVI irrigation were variable, from 0.0% to 0.65%. Implant rupture rates with saline were unclear. The authors mentioned that findings need to be interpreted with caution as they were based on low quality evidence.

Clinical effectiveness of povidone-iodine solutions for implant soaking in breast implant surgery

No relevant studies on clinical effectiveness of PVI for implant soaking were identified; therefore, no summary can be provided.

Guideline

No relevant evidence-based guideline on the use of PVI for breast implant surgery was identified; therefore no summary can be provided.

Limitations

The primary studies in the included systematic reviews varied with respect to study design, implant type, surgical approach, prophylactic antibiotic use, concentrations of PVI used, perioperative management, and follow up times hence, comparison across studies was difficult. Furthermore, majority of the studies were non-randomized studies and retrospective in nature; hence there is potential for biases in the findings. There was overlap in one study, included in the systematic reviews (Appendix 5, Table 5).

The included studies investigated pocket irrigation, however, no studies on implant soaking were identified. No studies on infection prevention were identified.

No studies on use of PVI for patients undergoing breast reconstruction as part of cancer treatment were identified.

No relevant evidence-based guidelines were identified.

Conclusions and Implications for Decision or Policy Making

Two relevant systematic reviews[1,4] on clinical effectiveness of use of PVI for pocket irrigation for breast implant surgery, were identified. No relevant studies on clinical effectiveness of soaking implants with PVI were identified. No relevant evidence-based guidelines were identified regarding the use of PVI for breast implant surgery.

Low quality evidence, suggests that povidone-iodine breast pocket irrigation is effective in reducing capsular contracture in patients undergoing breast augmentation surgery with implants. The findings need to be interpreted in the light of limitations that were described above.

Two publications that did not meet our inclusion criteria due to various reasons (such as unclear or irrelevant interventions, or irrelevant design) were not included. However, they provided some useful insights and are discussed here. Calobrace et al.[10] conducted a 10-year risk factor analysis for occurrence of capsular contracture in patients undergoing breast implant surgery, and reported that use of PVI (Betadine) did not appear to be a risk factor for capsular contracture. Calobrace et al.[10] also indicated that the device features, surgical factors, the development of hematoma or seroma, and the use of a surgical bra appeared to be risk factors for capsular contracture. The study by Carvajal et al.[11] investigated the use of PVI for preoperative skin preparation but not for breast pocket irrigation or for soaking the implant, so was not included. It mentioned that for preoperative skin preparation for breast augmentation surgery, chlorohexidine gluconate was more effective than PVI in preventing capsular contracture.

High quality studies are needed to determine definitively the clinical effectiveness of PVI for pocket irrigation in breast implant surgery. Furthermore studies investigating the clinical effectiveness of PVI for implant soaking in breast implant surgery are warranted.

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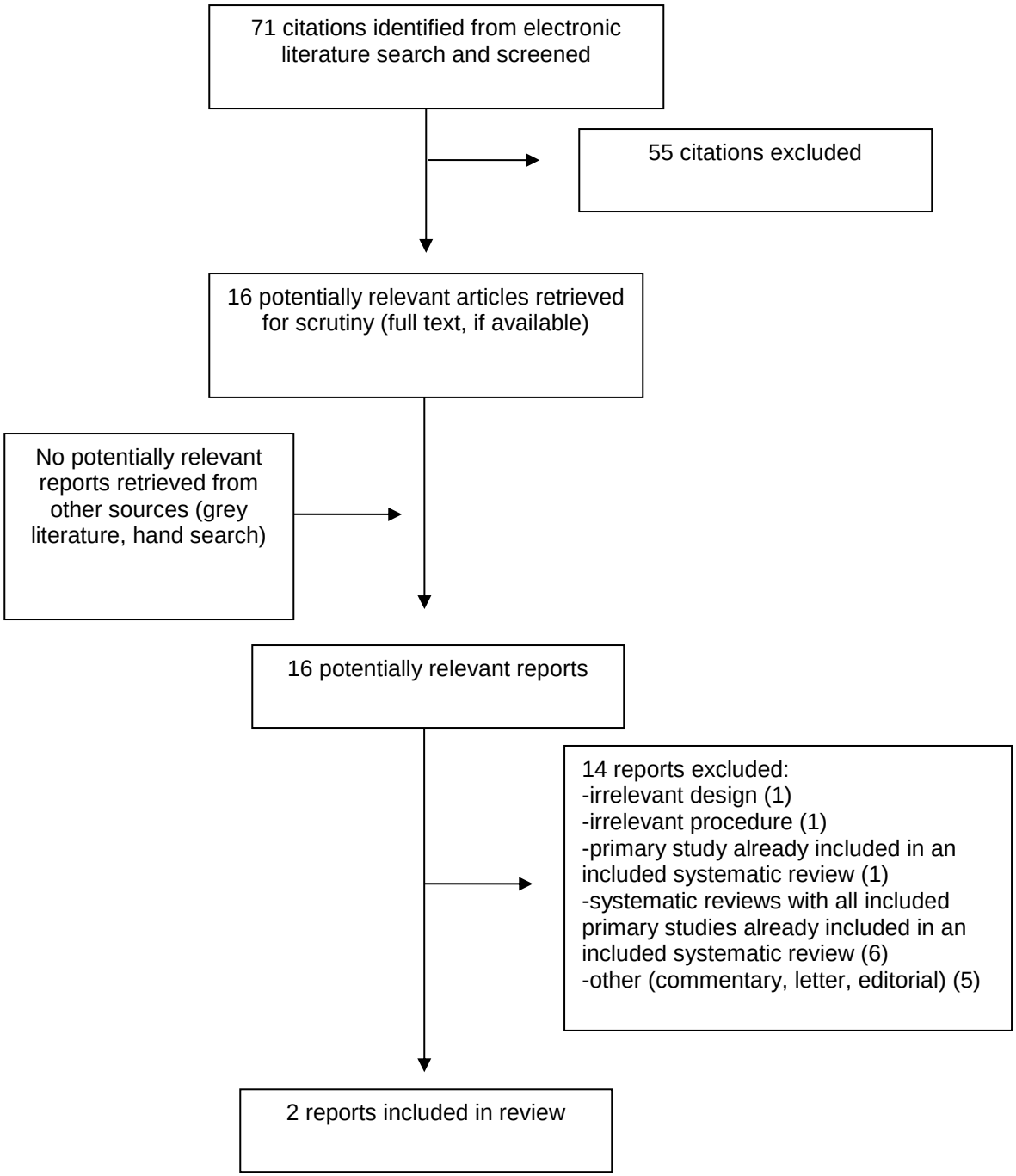
11. Carvajal J, Carvajal M, Chavez D, Hernandez G. Back to basics: could the preoperative skin antiseptic agent help prevent biofilm-related capsular contracture? *Aesthet Surg J.* 2018.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Horsnell, 2017, UK	Systematic review including 2 retrospective studies that were relevant for the current report. Both studies in US. (This systematic review had a broad focus and included several studies of which only the two studies that were relevant for this current report are included here)	Individuals undergoing aesthetic breast augmentation N = 3,794 Age: NR	With or without PVI (1 study) PVI with or without saline rinse or with use of nipple shield (1 study) PVI concentrations used were not mentioned.	Capsular contracture Mean FU (months): 60 (1 study) and 45, 24, 11, and 5 (in one study with 4 groups [i.e., 4 phases] with different PVI procedures)
Yalanis, 2015, US	Systematic review including 9 studies (3 RCTs, 2 retrospective comparative studies, and 4 case series) published between 1986 and 2013. Seven studies in US, one in UK and one in Finland.	Individuals undergoing primary breast augmentation with implants. N= 1,786 (1191 in PVI group, 595 in saline group) considering RCTs and retrospective comparative studies N = 3,291, considering the 4 case-series studies. Age: NR	PVI versus saline for irrigation of surgical pockets, in the comparative studies. PVI concentrations used were 5%, 7.5%, or 10% PVI for irrigation of surgical pockets, in the case-series studies. PVI concentrations used were not mentioned.	Capsular contracture rate, and deflation rate. Mean FU (months) range: 21 to 45 for the 3 RCTs and 2 comparative retrospective studies; 14 to 73 for the case-series

FU = follow up; PVI = povidone-iodine; RCT = randomized controlled trial;

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[8]

Strengths	Limitations
Horsnell, 2017, UK[1]	
• The objective was clearly stated • Multiple databases (MEDLINE, Embase, and Scopus) were searched from 2000 to 2016. • Study selection was described and a flow chart was presented • A list of included studies was provided • Though it was not explicitly mentioned that article selection was done in duplicate, it was however mentioned that article selection was conducted by the team and any disagreement regarding inclusion was resolved by a senior team member. • Characteristics of the included studies were presented, however details were lacking • The authors mentioned that there were no conflicts of interest	• A list of excluded studies was not provided • Unclear if article selection was done in duplicate, however it was mentioned that article selection was conducted by the team and any disagreement regarding inclusion was resolved by a senior team member. • Unclear if data extraction was conducted in duplicate • Unclear if quality assessment of the included studies was conducted • Meta-analysis was not conducted • Publication bias does not appear to have been examined
Yalanis, 2015, US[4]	
• The objective was clearly stated • Multiple databases (PubMed/MEDLINE, Embase, and Scopus) were searched from 1966 to December 2014. • Study selection was described and a flow chart was presented • A list of included studies was provided • Article selection was done independently by two reviewers • Data extraction was conducted using a structured form • Quality assessment was conducted using the Jadad scale for RCTs (good quality if score ≥3 and poor quality if score <3), and the Methodological Index for Non-Randomized Studies for non-randomized studies (high quality if score ≥16 and low quality if score<16). Quality was variable: high for 3 studies and low for 6 studies. • Characteristics of the included studies were presented • Meta-analysis was conducted when appropriate • The authors mentioned that there were no conflicts of interest	• A list of excluded studies was not provided • Unclear if data extraction was conducted in duplicate • Unclear if quality assessment was conducted in duplicate • Publication bias does not appear to have been examined

RCT = randomized controlled trial

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings Included Systematic Reviews and Meta-Analyses

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Horsnell, 2017, UK[1]</td></tr>
<tr><td>Findings from two retrospective studies.

Capsular contracture

In one retrospective study there were 4 groups (i.e., 4 phases). In Phase-1, PVI irrigation alone was used; then in Phase-2 due to regulation change, PVI irrigation was followed by saline rinse, in Phase-3, use of saline rinse was stopped; and in Phase-4, the use of nipple shield was added to the PVI irrigation and the rates of capsular contracture was 1.3%, 4%, 3% and 0.5% respectively. The difference in capsular contracture rates between Phase-1 and Phase-2, and between Phase-3 and Phase-4 were statistically significant (P <0.001 for each comparison), and there was no statistically significant difference between Phase-2 and Phase-3.

One retrospective study showed that the there was no statistically significant difference in rates of capsular contracture, with or without PVI irrigation (OR, 0.9; 95% CI, 0.49 to 1.54)</td><td>"There was limited evidence to support intra-operative techniques to reduce capsular contracture rate. Where available the literature tends to support the use of antibiotic and povidone-iodine irrigation, the use of insertion funnels and nipple shields and the avoidance of drains. However due to the poor quality of the evidence these findings should be treated cautiously." (p. 282)</td></tr>
<tr><td colspan="2">Yalanis, 2015, US[4]</td></tr>
<tr><td>Outcomes were reported for PVI compared with saline when used for irrigation for breast implant surgery (patients were categorized as PVI group if they received PVI with or without antibiotics and as saline group or control group if they received saline irrigation. Also, outcomes were reported for PVI from case-series studies.

Capsular contracture rate:

<table>
<tr><th>No. of studies</th><th>No. of patients</th><th>Capsular contracture, OR (95% CI)</th><th>Heterogeneity (%), I^2</th></tr>
<tr><td>4 (2 RCTs & 2 comparative retrospective studies)</td><td>1,786</td><td>0.30 (0.18 to 0.50) Favors PVI</td><td>0</td></tr>
</table>
PVI had a lower rate of capsular contracture compared with saline irrigation (2.7% versus 8.9%); using data from the 4 studies mentioned above.

The capsular contracture rate varied between 0.5% and 2.0% with PVI (from 4 case series studies including 3,291 patients).

Deflation or implant rupture:
One RCT reported no spontaneous implant deflation. The second RCT reported that two patients (3.3%) experienced spontaneous unilateral deflation of smooth, inflatable saline implants but it was unclear in which group this occurred.

A retrospective comparative study with four groups (in four phases), reported deflation rates: 0.37% in Group1 (irrigation with 7.5% PVI, mean FU = 45m), 0% in Group 2 (irrigation with 7.5% PVI followed by saline, mean FU = 24m),</td><td>"Based on current evidence provided by this systematic review and meta-analysis, we conclude that povidone-iodine breast pocket irrigation is effective in reducing capsular contracture in aesthetic breast augmentation patients with implants. Furthermore, we found no association between povidone-iodine pocket irrigation and spontaneous implant rupture. However, the low methodologic quality of several included studies limits recommendation of povidone-iodine irrigation as the standard of practice in aesthetic breast augmentation. Additional high-quality trials are warranted to corroborate the findings of this meta-analysis." (p.697)</td></tr>
</table>

Table 4: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
0.65% in Group 3 (irrigation with 7.5% PVI no saline rinse later, mean FU, 11m)), and 0% in Group 4 (added coverage of nipple-areola complex and incision with 7.5% PVI, mean FU=5m). One case series study (on fourth generation textured, cohesive, silicone gel implants [1012 implants in 511 patients]) reported an implant rupture rate of 0.4%. The other three case-series studies did not mention rupture rate.	

CI = confidence interval; FU = follow up; OR = odds ratio; PVI = povidone-iodine;

Appendix 5: Overlap between Included Systematic Reviews

Table 5: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Yalanis, 2015[4]	Horsnell, 2017[1]
Adams, 2006	y	
Aarco, 2007	y	
Burkhardt, 1986	y	
Burkhardt, 1994	y	
Burkhardt, 1995	y	
Giordano 2013	y	
Stevens, 2008	y	
Stevens, 2010	y	
Stevens, 2013		y
Weiner, 2007	y	y

y indicates that the primary study is included in the systematic review