The role of preformed silos in the management of infants with gastroschisis: a systematic review and meta-analysis

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Structured Abstract

Background: The pre-formed silo (PFS) is increasingly used in the management of gastroschisis but its benefits remain unclear. We performed a systematic review and meta-analysis of the literature comparing use of a PFS with alternate treatment strategies.

Methods: Studies comparing the use of a PFS with alternate strategies were identified and data extracted. The primary outcome measure was length of time on a ventilator. Mean difference (MD) between continuous variables and 95% confidence intervals were calculated. Risk difference (RD) and 95%CI were determined for dichotomous data.

Results: Eighteen studies, including one randomised controlled trial, were included. Treatment strategy and outcome measures reported varied widely. Meta-analysis demonstrated no difference in days of ventilation but a longer duration of parenteral nutrition (PN) requirement (MD 6.4 days [1.3, 11.5]; p=0.01) in infants who received a PFS. Subgroup analysis of studies reporting routine use of a PFS for all infants demonstrated a significantly shorter duration of ventilation with a PFS (MD 2.2 days [0.5, 3.9]; p=0.01) but no difference in duration of PN requirement. Other outcomes were similar between groups.

Conclusion: The quality of evidence comparing PFS with alternate treatment strategies for gastroschisis is poor. Only routine use of PFS is associated with fewer days on a ventilator compared with other strategies. No strong evidence to support a preference for any strategy was demonstrated. Prospective studies are required to investigate the optimum management of gastroschisis. Standardised outcome measures for this population should be established to allow comparison of studies.

Introduction

The optimum surgical treatment of infants born with gastroschisis remains unclear. Following Watkins's first report of primary closure of the abdominal wall in 1943,[1] the principle of surgical treatment has remained returning the eviscerated abdominal organs to the abdomen as soon as possible whilst avoiding the potential complications of viscero-abdominal disproportion (i.e. abdominal compartment syndrome and/or need for prolonged ventilation). Traditionally, surgeons have aimed to achieve primary abdominal wall closure whenever safe and, if not, to fashion a surgical 'silo' to allow gradual visceral reduction prior to definitive abdominal wall closure.

Over the past 20 years a pre-formed silo (PFS) comprising a transparent silastic bag fitted with a spring loaded ring has been introduced and its use adopted widely. This has led to a change of practice such that many units now use placement of a PFS on the neonatal intensive care unit without general anaesthesia (GA) as an alternate to attempted emergency abdominal wall closure under GA. This is followed by gradual reduction of the abdominal contents and delayed abdominal wall closure in a semi-elective setting. Recent national and international surveys confirm the uptake of this technique [2, 3]. Outcomes of infants treated with a PFS have been reported by a number of institutions and in some instances compared with those of infants treated with primary closure. Several reports describe the benefits of using a PFS for both patient and surgeon and propose their routine use [4, 5]. However, other authors have highlighted potential pitfalls with the use of the PFS [6, 7]. As a result, the precise role for the PFS in the treatment of infants with gastroschisis remains unclear.

The aim of this study was to evaluate current evidence comparing the use of a PFS with alternate treatment strategies in infants with gastroschisis. We performed a systematic review of the existing literature. We also aimed to perform a meta-analysis of available data by applying strict eligibility criteria to ensure comparability.

Methods

We searched Medline, Embase and the Cochrane controlled trials register from inception to July 2014 using the terms 'gastroschisis', 'gastroschisis AND silo', 'preformed silo' and 'silastic silo'. Abstracts of the unfiltered literature were reviewed and full text versions of selected publications were assessed for inclusion. Reference lists of these publications were also checked to identify additional relevant reports. The literature search, assessment for inclusion and data extraction were performed independently by 3 reviewers and disagreements resolved by consensus.

Studies were selected for inclusion in the review if they reported comparative outcomes between infants treated with a PFS and infants treated with an alternate treatment strategy. Studies were excluded if they reported a cohort of infants treated only with a PFS with no comparative group, reported a cohort of infants treated with a PFS grouped with infants treated with another treatment strategy such as a hand-sewn silo, originated from a non-developed country or were not in English. For infants treated with a PFS no selection was made on the basis of final technique of abdominal wall closure (i.e. all were included).

All outcomes were selected *a priori*. The primary outcome measure was time on a ventilator. Secondary outcomes were number of infants never ventilated, time on parenteral nutrition (PN), time to achieve full enteral feeds, length of hospital stay, incidence of necrotising enterocolitis, number of unplanned re-operations, infectious complications, mortality and occurrence of ventral hernia following repair.

Where studies reported outcomes of more than 2 treatment types (e.g. PFS, primary closure and staged closure using a hand-sewn silo) we selected the group undergoing primary closure as the comparator group and excluded the other group(s) from the analysis.

Data were extracted and entered into Review Manager (v5.1, The Cochrane Collaboration) and meta-analysis was performed using a random effects model due to variation in study design and reporting. Summary statistics for continuous variables are reported as mean difference (MD) with 95% confidence interval (95%CI) and dichotomous variables as risk difference (RD) with 95%CI in order to allow inclusion of studies with zero events.[8] An I^2 statistic for heterogeneity was calculated for each pooled dataset. For the purposes of meta-analysis continuous data are required to be in the format of mean and standard deviation (SD). For studies that only reported median and range, mean and SD were estimated using validated formulae specifically developed for this purpose [9].

We anticipated a large proportion of the data available would arise from retrospective cohort studies. Our *a priori* intention was therefore to perform subgroup analysis that included only studies reporting pre-planned management strategies for gastroschisis. Only studies that used an intended policy to treat all infants routinely with a PFS unless clinically contra-indicated were included in this subgroup analysis. If it was unclear whether such a policy existed then it was assumed that none did and the study was excluded from this subgroup analysis. The subgroup analysis therefore allows a

comparison of outcomes based on an 'intention to treat' all infants in the PFS group with a PFS unless clinically contra-indicated.

Results

Search results

One-thousand, five-hundred and sixty-seven articles were identified using the specified search criteria and their abstracts reviewed. Following application against our inclusion criteria, 1440 were excluded on the basis of their abstract alone and the full text of 127 publications was scrutinised. One hundred and seven of these were subsequently excluded as they did not report a comparative group, did not use a PFS, or did not report outcomes from a group all treated with a PFS. Two further reports were excluded to avoid duplication of patients; the study by Bonnard et al [10] was excluded as it reported patients included in another report during an overlapping time period from the same centre [11] and the study by Allotey et al [4] was excluded as all patients included were subsequently included in a larger report from the same centre 7 years later by Charlesworth et al [12]. The remaining 18 publications were included in this systematic review. Characteristics of included studies are shown in Table 1. Of these 18, four met the criteria for inclusion in the subgroup analysis (Figure 1).

There was one prospective randomised controlled trial (RCT) comparing use of a PFS with primary fascial closure [11]. This was a multi-centre study which recruited 54 infants over a 5½ year period and was terminated prior to full recruitment due to low accrual rate. Seventeen of the 18 included studies were cohort studies including 3 reporting data collected from multiple centres during national cohort studies on gastroschisis [13-15]. Two of these report separate outcomes from the same dataset obtained from a national cohort study in the United Kingdom [13, 14]. To avoid duplication we extracted data exclusively from one or other of these reports for each outcome measure. The single RCT and 3 other studies met the criteria for inclusion in the intention to treat analysis; all infants in these reports who received a PFS did so as part of a pre-planned management strategy (either as part of an institutional policy [5, 12, 16] or as part of a RCT [11]) to treat all infants reported as receiving a PFS with a PFS unless clinically contra-indicated.

Outcome measures reported by individual studies varied. The outcomes most frequently reported were number of days of ventilation, time to achieve full enteral feeds and length of stay. It was possible to retrieve data on the primary outcome measure (number of days of ventilation) from 8 of

the 18 included papers. Other clinically important outcomes including incidence of necrotising enterocolitis, need for further surgery and mortality were variably reported.

Patients and treatment received

In total 1516 patients are included in this review of whom 666 were treated with a PFS. The intention to treat subgroup analysis includes data from 318 patients of whom 133 were treated with a PFS. There were no significant differences between infants treated with a PFS and those treated with an alternate treatment strategy in gestational age (MD 0.05 weeks [-0.3, 0.41]; p=0.77), birth weight (MD 0.01 kg [-0.09, 0.1]; p=0.94) or gender distribution (difference in proportion of males 2% [-9%, 13%]; p=0.67).

All infants included in the PFS group were treated with a PFS. The comparator group consists of infants treated with an alternate strategy including predominantly primary closure with GA, but also primary closure at the cotside without GA, and attempted primary closure with a 'handsewn silo' or PFS if primary closure could not be achieved (Table 1). In the intention to treat subgroup analysis, the comparator group was attempted primary closure under general anaesthesia with formation of either a handsewn silo [5, 12, 16] or insertion of a PFS [11] if primary closure was not possible.

Infants with complex gastroschisis as defined by the criteria of Molik [17] were excluded in 6 studies whilst others included both simple and complex cases (Table 1). In the intention to treat subgroup analysis 3 studies included all infants with simple and complex gastroschisis [5, 11, 16] and 1 study specifically excluded infants with atresia, gut infarction or short bowel syndrome [12]. It was not possible to perform an additional subgroup analysis for simple and complex gastroschisis as outcome data were not reported by severity of disease in the majority of studies.

Quantitative analysis of outcomes

The primary outcome of number of days of ventilation was reported in 8 studies (641 patients). In the overall analysis there was no statistically significant difference in number of days of ventilation between infants treated with a PFS and alternate techniques (Figure 2A). However in the intention-to-treat analysis, use of PFS was associated with a significant reduction in days of ventilation of 2.2 days (0.47, 3.93); p=0.01 (Figure 2B). There was significant heterogeneity between studies in the overall analysis (I^2=70%, p=0.002) but not in the subgroup analysis (I^2=35%, p=0.2). Five studies reported the proportion of infants in each group who were never mechanically ventilated. None of these were in the intention-to-treat subgroup analysis. There was no difference in the proportion of

infants never ventilated in each group and significant heterogeneity between studies likely as a result of differing indications for use of the PFS in different settings (Figure 2C).

Overall duration of PN was significantly longer in infants treated with a PFS (MD 6.38 days [1.3, 11.46]; p=0.01) whereas time to reach full enteral feeds and length of stay were similar between groups (Figure 3). In the intention to treat subgroup analysis, duration of PN, time to reach full enteral feeds and length of stay were all similar between infants treated with a PFS and those with an alternate strategy (Figure 4). There was again significant heterogeneity between results of individual studies in both the overall and intention-to-treat subgroup analyses.

All other outcomes were similar between infants treated with a PFS and those with an alternate strategy in the main analysis and subgroup analysis (Table 2) with the exception of need for unplanned re-operation and occurrence of ventral hernia. In the intention-to-treat analysis fewer infants treated with a PFS required an unplanned operation and in the overall analysis fewer infants treated with a PFS developed a ventral hernia following repair. No study in the subgroup analysis reported incidence of ventral hernia.

Discussion

This systematic review aimed to determine comparative outcomes for infants with gastroschisis treated with either a PFS or alternate treatment strategy. Overall the quality of evidence currently available in this field is poor; to date only one randomised controlled trial has been reported [11]. Whilst meta-analysis is typically aimed as synthesising evidence obtained in RCTs, where such studies are lacking, data obtained from studies using alternate methodology may be valuable. The majority of studies included were retrospective cohort studies which compared outcomes between PFS and alternate strategies either contemporaneously or in some cases between separate defined time periods. In several studies the indication for treatment with a PFS or alternate strategy was poorly defined, if at all. As a result there is significant potential for both treatment and selection biases to influence the findings of this analysis.

The influence of bias is one of the difficulties encountered when combining data from multiple retrospective series. The key source of bias in this review is indication for treatment received resulting in significant selection bias. For instance it is possible that infants with least abdomino-visceral discrepancy were treated with primary closure and those with greater discrepancy received a PFS. Alternatively in some studies infants who received a PFS were allocated to that treatment on the basis that they had failed treatment by an alternate (preferred) method. This bias likely has an

effect on the findings of this meta-analysis. We considered from the outset the value of including all comparative series in this meta-analysis compared to focussing only on those reports using a pre-planned management strategy. In the interest of greater data transparency we included all reports and additionally performed a pre-planned subgroup analysis. Studies were selected for inclusion in the subgroup analysis if they reported data from series where there was a pre-planned strategy, either at an institutional level or as part of a RCT, to use a PFS for all infants reported in the PFS group unless clinically contra-indicated.

Whilst this approach has the advantage of reducing the impact of selection bias from the group treated with a PFS, it should be noted that it also introduces selection bias in some cases to the comparator group as some of those infants were by definition not suitable for treatment with a PFS. The sole RCT [11] reports two groups without selection bias although it could be claimed that selection bias may exist at the level of trial recruitment as only a small proportion of eligible patients were recruited. It may be that surgeons recruiting to the trial maintained a degree of bias and that this influenced their decision of whether to offer the trial to their patients or not.

The quantitative findings of this review suggest that clinically important outcomes are similar between infants who received a PFS and those treated with an alternate treatment strategy. We selected days of ventilation as the primary outcome measure as a surrogate marker of increased abdominal pressure, a phenomenon that may be avoided when using a PFS. Whilst factors other than abdominal pressure may influence need for ventilation, the absence of a sudden increase in intra-abdominal pressure that can be achieved with a PFS when compared to primary closure in particular has been cited as a potential advantage of the PFS[16]. Further we believe that days of ventilation is an important outcome measure in a critical care setting. Overall there was no statistically significant difference in days of ventilation between groups. The proportion of infants never ventilated, time to achieve full enteral feeds and total length of stay were also similar between groups, although duration of parenteral nutrition (PN) was significantly shorter in infants treated with an alternate treatment strategy than with a PFS. Longer duration of PN in infants treated with a PFS has been reported by a number of the individual studies contributing to this review [18-20]. This may be explained by the inherent added time taken to achieve abdominal wall closure in infants treated with a PFS which contributes to a delay in starting enteral feeds and overall a longer requirement for PN.

In contrast to the overall findings, in the intention to treat subgroup analysis use of a PFS was associated with a shorter duration of ventilation. This demonstrates that when a PFS is used as a

preferred treatment strategy or in a randomised trial, duration of ventilation can be reduced. Indeed many infants included in the included studies never required ventilatory support. Unfortunately, none of the studies eligible for inclusion in the subgroup analysis formally reported this figure thereby precluding quantitative meta-analysis of this outcome. Additionally, the association between PFS use and increased duration of PN seen in the overall analysis is not seen in the subgroup analysis. We believe that selection bias is the most likely cause of these two differences and justifies our use of a pre-planned subgroup analysis.

A number of authors have commented on the proposed benefits or disadvantages of the PFS compared to other strategies [5, 12, 16, 18]. Despite collating the largest body of comparative data to date, all remaining outcomes were similar between the groups in both the overall analysis and subgroup analysis with the exception of the number of unplanned re-operations and development of ventral hernia (Table 2). Fewer unplanned operations were reported in infants treated with a PFS and this difference was statistically significant in the intention-to-treat analysis. Within the intention to treat analysis these operations were for necrotising enterocolitis, intestinal perforation, stricture or obstruction.[5, 12, 16]. Particular concern has been raised that use of a PFS may be associated with bowel necrosis within the PFS [7]. Bowel necrosis may also be due to high abdominal pressure after primary closure. Both the overall and the intention to treat analysis did not reveal any significant difference in bowel necrosis with PFS or alternate strategy. Regarding the development of ventral hernia following repair, infants treated with a PFS had a lower incidence of ventral hernia in the overall analysis. It should be noted there was significant heterogeneity in individual study outcomes in this analysis which likely reflects different abdominal wall closure (as opposed to reduction) techniques between studies. We believe the final technique of abdominal wall closure is likely a better predictor of later herniation than the technique of visceral reduction.

The results of this review and meta-analysis require careful interpretation in terms of implications for clinical practice. The association between PFS use and increased duration of PN in the overall analysis suggests that infants treated with a PFS may be being subjected to an unnecessarily long duration of PN dependency. We speculate that a delay in commencing enteral feeds whilst waiting for abdominal wall closure may be responsible for this difference. Whether such a delay is strictly necessary has never been formally tested to our knowledge. Conversely, a treatment strategy of primary fascial closure may achieve a shorter duration of PN at the expense of longer duration of ventilation with its associated risks and cost implications. Which of these detriments is preferable is not known.

Whilst we selected days of ventilation as the primary outcome for this review it is unclear which of the outcome measures reported is of greatest importance to clinicians and/or parents. For instance, whilst some may view a reduction in days of ventilation of greatest importance others may place greater emphasis on duration of PN or total length of stay. No doubt the range of outcomes reviewed here encompasses the majority of those felt to be important to clinicians. Whether parents and indeed other stakeholder groups consider these to be important is unknown. The importance of this is in selecting the right outcomes by which to measure success or otherwise of any treatment intervention known as a core outcome set. To our knowledge no such core outcome set exists for infants with gastroschisis.

This study highlights the lack of high quality evidence regarding the optimum treatment strategy for infants with gastroschisis. Whilst it would be easy to propose a RCT as the optimal solution to this controversy, the difficulties in designing a RCT that is acceptable to both surgeons and parents should not be underestimated as Pastor and colleagues' experience demonstrates [11]. In particular, surgeons would have to overcome the prejudice formed during their previous accumulated clinical experience of treating infants with gastroschisis. The widespread adoption of the PFS with its clear logistical advantages over emergent primary fascial closure is another obstacle. The PFS may be placed by a suitably trained trainee at any time of day thereby avoiding out-of-hours emergency operating by a consultant/attending surgeon. It is likely therefore that the PFS is here to stay. However by casting aside such prejudices we do believe it possible to perform a robust investigation of the available treatment strategies for these infants. We therefore favour further study in the form of prospective, multicentre, protocol driven collaboration.

Recently Kunz and colleagues have presented the findings of a similar piece of work comparing outcomes between primary closure and staged closure using any type of silo (including both PFS and handsewn silo). There are several important differences between Kunz's review and ours which are relevant. Firstly Kunz and colleagues only included reviews that compared staged closure with primary fascial closure. Any other closure technique such as immediate bedside reduction followed by 'sutureless' or 'plastic' closure was not included in their review. Secondly they grouped infants treated with a PFS together with infants treated with a traditional handsewn silo. It is our observation from the literature and our communication with paediatric surgeons worldwide that the PFS is now used in preference to a handsewn silo almost universally (where available and affordable) and that many surgeons perform immediate reduction and plastic closure if the clinical situation

permits. Our review focuses entirely on the controversy surrounding the use of the PFS versus all of the alternate strategies which we believe accurately reflects the treatment options employed by the modern paediatric surgeon.

In summary this review demonstrates that use of a PFS results in largely equivalent outcomes compared to alternate treatment approaches for infants with gastroschisis. Although planned use of a PFS is associated with fewer days on a ventilator such a strategy may expose some infants to unnecessary prolonged durations of PN. Further investigation is required to identify not only the optimal treatment pathway for infants with gastroschisis which will likely include a case by case decision algorithm, but also the tools by which to measure success.

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Table 1: Description of included studies

Study	Year	Study design	Multi-Centre	Comparative groups and number	Exclusions	Key findings
Alali[21]	2011	retrospective review	N	PFS (34) Primary Repair (52)	None reported	PFS associated with more ventilator days and longer duration of PN
Bradnock[14]	2011	prospective national cohort study	Y	PFS (99) Primary Closure (120)	Complex GS excluded	PFS associated with longer TTFF, longer duration of PN and longer LoS
Charlesworth[12]*	2014	retrospective review	N	PFS (67) Attempted primary closure (89)	Excluded infants with SBS, atresia and gut infarction	PFS associated with shorter ventilation but longer duration of PN
Chiu[22]	2006	retrospective review	N	PFS (20) Primary Closure (28)	None reported	PFS associated with fewer complications and lower incidence of NEC
Choi[20]	2012	retrospective review	N	PFS (23) Primary closure without GA (44)	Complex GS excluded	No difference in any outcome related to method of closure
Fischer[23]	1995	retrospective review	N	PFS (10) Primary Closure without GA (25)	None reported	No difference in any outcome related to method of closure
Kidd[24] $	2003	retrospective review	N	PFS (53) Primary closure (27)	Co-existing lethal abnormalities or complications not related to surgical treatment of gastroschisis	Staged closure associated with fewer infectious complications and compartment syndrome but longer length of stay
Kimble[25]	2001	prospective cohort study	Y	PFS (4) Primary Closure without GA (25)	Excluded complex GS and those with severe respiratory distress	Descriptive results only
Lobo[7]	2010	retrospective review	N	PFS (27) Primary Closure (10)	None reported	PFS associated with more ventilator days
McNamara[26]	2011	retrospective review	N	PFS (9) Primary Closure (8)	None reported	PFS associated with shorter LoS (non-significant trend)
Minkes[16]*	2000	retrospective review	N	PFS (13)	None reported	PFS associated with fewer

				Attempted Primary Closure (30)		ventilator days, shorter LoS , fewer complications and is cheaper
Owen[18]	2006	retrospective review	N	PFS (21)	Complex GS excluded	PFS associated with fewer ventilator days
				Primary closure (27)		
Owen[13]	2010	prospective national cohort study	Y	PFS (120)	Complex GS excluded from outcome analysis	No difference in any outcome related to method of closure
				Attempted Primary Closure (170)		
Pastor[11]*	2008	prospective RCT	Y	PFS (28)	<1500g or <34 weeks excluded	PFS associated with fewer ventilator days (non-significant trend)
				Attempted Primary Closure (27)		
Schlatter[5]*	2003	retrospective review	N	PFS (26)	None reported	PFS associated with fewer ventilator days, shorter TTFF and fewer complications.
				Attempted Primary Closure (39)		
Singh[19]	2003	retrospective review	Y	PFS (30)	None reported	No difference in any outcome related to method of closure
				Primary Closure (151)		
Skarsgard[15]	2008	contemporaneous data collection	Y	PFS (35)	None reported	PFS associated with longer LoS
				Attempted Primary Closure (55)		
Weil[6]	2012	retrospective review	N	PFS (147)	None reported	PFS associated with longer TTFF and LoS but fewer ventral hernias and wound infections
				Primary Closure (43)		

*= included in 'intention to treat' subgroup analysis; $^\text{\$}$only data from 1998 onwards included

GS=gastroschisis; PFS=preformed silo; RCT=randomised controlled trial; TTFF=time to full feeds; PN=parenteral nutrition; LoS=length of stay

Primary closure' indicates infants who actually had successful primary closure; i.e. infants with failed primary closure with subsequent silo placement are not included

Attempted primary closure includes cases in which primary closure was attempted but was converted to an alternate (e.g. hand-sewn silo, patch repair, PFS); *non-significant trend* indicates a p value of <0.1 but >0.05

Table 2 – Results of other outcomes included in this meta-analysis

Outcome	Overall analysis					'Intention to treat' subgroup analysis				
	Studies	PFS	Alternate	Risk Difference	p	Studies	PFS	Alternate	Risk Difference	p
Bowel ischaemia (not NEC)	3	6/77	3/81	0.03 (-0.04, 0.1)	0.38	1	1/27	1/27	0.00 (-0.1, 0.1)	1.0
Infectious complications	10	69/434	90/541	0.00 (-0.09, 0.09)	1.05	3	13/66	38/96	0.18 (-0.07, 0.44)	0.16
NEC	11	37/554	47/534	0.00 (-0.04, 0.04)	0.78	4	13/133	19/185	0.02 (-0.08, 0.11)	0.71
Unplanned re-operation	7	29/276	54/365	0.06 (-0.05, 0.16)	0.27	2	4/39	16/69	0.14 (0.02, 0.27)	0.03
Mortality	12	20/534	19/567	0.00 (-0.02, 0.02)	0.82	3	1/120	4/155	0.01 (-0.02, 0.05)	0.45
Ventral hernia	5	33/224	79/291	0.24 (0.02, 0.53)	0.03	-				

PFS – pre-formed silo

Figure 1 – Flowchart of article selection

Figure 2 –- Forest plots of duration of ventilation (days) for the overall analysis (A) and intention to treat subgroup analysis (B). Panel C – Forest plot for need for ventilation at any stage.

Figure 3 – Forest plots of duration of parenteral nutrition (top panel, A), time taken to achieve full enteral feeds (middle panel, B) and length of hospital stay (bottom panel, C) for the overall analysis.

Figure 4 – Forest plots for the intention-to-treat subgroup analyses showing duration of parenteral nutrition (top panel, A), time taken to achieve full enteral feeds (middle panel, B) and length of hospital stay (bottom panel, C).

Appendix – PRISMA Checklist:

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
22Title	1	Identify the report as a systematic review, meta-analysis, or both.	*Title*
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-8