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Primary closure versus delayed or no closure for traumatic wounds due to mammalian bite (Review)

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[Intervention Review]

Primary closure versus delayed or no closure for traumatic wounds due to mammalian bite

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ABSTRACT

Background

Mammalian bites are a common presentation in emergency and primary healthcare facilities across the world. The World Health Organization recommends postponing the suturing of a bite wound but this has not been evaluated through a systematic review.

Objectives

To assess the effects of primary closure compared with delayed closure or no closure for mammalian bite wounds.

Search methods

In July 2019 we searched the Cochrane Wounds Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE (including In-Process & Other Non-Indexed Citations); Ovid Embase and EBSCO CINAHL Plus. We also searched clinical trials registries for ongoing and unpublished studies, and scanned reference lists of relevant included studies as well as reviews, meta-analyses and health technology reports to identify additional studies. There were no restrictions with respect to language, date of publication or study setting.

Selection criteria

We included randomised controlled trials which compared primary closure with delayed or no closure for traumatic wounds due to mammalian bite.

Data collection and analysis

Two review authors independently screened titles, abstracts and full-text publications, applied the inclusion criteria, and extracted data. We pooled data using a random-effects model, as appropriate. We used the Cochrane 'Risk of bias' tool and assessed the certainty of the evidence using the GRADE approach.

Main results

We found three trials (878 participants) that compared primary closure with no closure for dog bites and one trial (120 participants) that compared primary closure with delayed closure. No other mammalian bite studies were identified. The trials were from the UK (one trial), Greece (one trial) and China (two trials). Overall, participants from both sexes and all age groups were represented.

We are uncertain whether primary closure improves the proportion of wounds which are infection-free compared with no closure, as the certainty of evidence for this outcome was judged to be very low (risk ratio (RR) 1.01, 95% confidence interval (CI) 0.97 to 1.05; 2 studies, 782 participants; I^2 = 0%). We downgraded the evidence by one level for high risk of bias and two levels for imprecision. There is no clinically important difference in cosmesis (acceptable physical/cosmetic appearance) of dog bite wounds when primary closure is compared with no closure (mean difference (MD) -1.31, 95% CI -2.03 to -0.59; 1 study, 182 participants). The certainty of evidence for this outcome was judged to be moderate (we downgraded our assessment by one level for imprecision).

We are uncertain whether primary closure improves the proportion of dog bite wounds that are infection-free compared with delayed closure, as the evidence for this outcome was judged to be very low (RR 0.98, 95% CI 0.90 to 1.07; 1 study, 120 participants; I^2 = 0%). We downgraded the evidence by one level for high risk of bias and two levels for imprecision.

None of the four trials reported any adverse outcomes such as death or rabies but they were, in any case, unlikely to have been large enough to have satisfactory power to provide precise estimates for these. Important outcomes like time to complete wound healing, proportion of wounds healed, and length of hospital stay were not evaluated.

Authors' conclusions

All the studies we identified concerned dog bites. There is no high-certainty evidence to support or refute existing recommendations concerning primary closure for dog bites. The potential benefits and harms of primary closure compared with delayed or no closure for mammalian bites remain uncertain and more robust trials are needed.

PLAIN LANGUAGE SUMMARY

Primary closure (immediate stitches) versus delayed closure (delayed stitches) or no closure (no stitches) for traumatic wounds due to mammalian bite

What is the aim of this review?

The aim of this review was to find out whether animal bite wounds heal better when they are closed with stitches straight away (primary closure), or if the wounds are left open to heal for a short time before closure (delayed closure) or not stitched at all (no closure). We wanted to find out which wounds healed fastest, and if the method of closure affected the likelihood of wound infection, the appearance of the scar, the length of time patients were in hospital, and more serious side effects such as death. To answer this question, we collected and analysed all relevant studies (randomised controlled trials). Randomised controlled trials are medical studies where people are chosen at random to receive different treatments. This type of trial provides the most reliable health evidence. We found four relevant studies.

Key messages

All the studies we found concerned dog bites. In terms of wound infection, we cannot be certain whether it is better to close dog bite wounds straight away, or wait a while before stitching, or leave them with no stitches. There was little difference in the appearance of the bite scar. Most of the evidence we found was of low certainty due to the size of the studies and the methods used.

What was studied in the review?

Mammalian bite wounds from animals such as dogs, cats and monkeys are a common problem throughout the world. In developed countries, many bite wounds are caused by domestic pets. In lower-income countries bites can also be caused by wild animals. Dogs are generally responsible for the majority of bites. Bite wounds are at high risk of infection as microbes are transmitted into the wound from the animal's mouth. In lower-income countries these wound infections can lead to serious complications and in some cases death.

The first priorities when treating an animal bite are to stop the flow of blood from the wound, provide pain relief, and prevent infection. This can include appropriate vaccination against tetanus and rabies. It is often recommended that bite wounds are not stitched straight away if infection is suspected, as closing an infected wound could delay healing and be potentially fatal.

What are the main results of the review?

In July 2019 we searched for randomised controlled trials comparing primary closure versus delayed or no closure for mammalian bite wounds. We found four relevant studies on dog bites. They were carried out in the UK, Greece and China. No other mammalian bite studies were identified. Three of the studies we included compared primary closure with sutures (immediate stitches) with no closure for dog bite wounds. One study compared primary closure with delayed closure for dog bites. The people in the studies were followed, where stated, from 14 days to three months. Overall, participants from both sexes and all age groups were represented.

We are uncertain whether primary closure of dog bite wounds increases the proportion of wounds which are infection-free compared with no closure (very low-certainty evidence from two studies including a total of 782 people) and compared with delayed closure (very low-certainty evidence from one study with a total of 120 people). There is little difference in the appearance of dog bite wounds when primary closure is compared with no closure (moderate-certainty evidence from one study with a total of 182 participants). None of the included studies reported proportion of wounds healed, the time to complete wound healing, length of hospital stay or adverse events. The number

of people in the included studies was small, and the people who assessed the outcomes were aware of which treatment had been given. Both of these are reasons why the results are uncertain.

How up to date is this review?

We searched for studies that had been published up to July 2019.

Summary of findings for the main comparison. Primary closure versus no closure for traumatic wounds due to mammalian bite

Primary closure versus no closure for traumatic wounds due to mammalian bite

Patient or population: patients with traumatic wounds due to dog bite
Settings: Emergency Department
Intervention: primary closure
Comparison: no closure

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No closure	Primary closure				
Time to complete wound healing	The trials did not report usable data for this outcome.					
Proportion of wounds which were infection-free Follow-up: 7 to 14 days	**Study population**		**RR 1.01** (0.97 to 1.05)	782 (2 studies)	⊕⊖⊖⊖ **Very low**[1]	We are uncertain whether primary suturing improves the proportion of wounds which are infection-free compared with no closure. Two studies provided patient-level data. In addition one study, which reported wound level data, found that 85/92 (92.3%) wounds in the primary-closure group versus 71/77 (92.2%) wounds in the no-closure group were infection-free.
	921 per 1000	**930 per 1000** (893 to 967)				
Proportion of wounds which were infection-free	The trials did not report data for this outcome.					
Cosmesis using validated cosmetic outcome score at 4 weeks Scale: Vancouver Scar Scale; lower score = better cosmesis	The mean validated cosmetic outcome score in the control group was 3.05	The mean validated cosmetic outcome score in the intervention groups was **1.31 lower** (2.03 to 0.59 lower)	**MD -1.31**, (-2.03 to -0.59)	182 (1 study)	⊕⊕⊕⊖ **Moderate** [2]	Although the effect estimate showed a benefit of primary closure in the cosmesis of dog bite wounds, this difference was too small to be clinically meaningful.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** mean difference

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] We downgraded by one level for high risk of detection bias, and by two levels for imprecision because the number of events was less than the optimal information size of 800 and the confidence intervals included both appreciable benefit and harm.
[2] We downgraded by one level for imprecision because of small sample size. No downgrading was done for risk of bias as outcome assessment for this outcome was blinded.

Summary of findings 2. Primary closure versus delayed closure for traumatic wounds due to mammalian bite

Primary closure versus delayed closure for traumatic wounds due to mammalian bite

Patient or population: patients with traumatic wounds due to dog bite
Settings: Emergency Departments
Intervention: primary closure

Comparison: delayed closure

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Delayed closure	Primary closure				
Time to complete wound healing	Trials did not report data for this outcome					
Proportion of wounds which were infection free on day 7	**Study population**		**RR 0.98** (0.90 to 1.07)	120 (1 study)	⊕⊖⊖⊖ **Very low**[1]	We are uncertain whether primary suturing improves the proportion of wounds which are infection-free after seven days compared with delayed closure.
	950 per 1000	**931 per 1000** (855 to 1000)				

Proportion of wounds which were infection-free	The trials did not report data for this outcome.
Cosmesis using validated cosmetic outcome score at 4 weeks	The trials did not report usable data for this outcome.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] We downgraded by one level for high risk of detection bias in the included trial, and by two additional levels for imprecision because there was a single study with a total sample size of less than the optimal information size and confidence intervals that included both appreciable benefit and harm.

BACKGROUND

Description of the condition

Mammalian bites are a common presentation in emergency and primary healthcare facilities throughout the world. They contribute significantly to mortality as well as morbidity, and are hence considered a public health problem in many regions of the world (WHO 2013). Dogs, cats, and monkeys are most commonly responsible for mammalian bites. Bites due to other mammals like foxes, bears, pigs, sheep, and ferrets vary from less common to rare, depending on the region (Ichhpujani 2008; Rempe 2009). Studies in low- and middle-income nations indicate that dogs are responsible for 76% to 94% of mammalian bites (WHO 2013).

The incidence of mammalian bites is increasing consistently in developed regions like the USA, Canada, Australia, and Europe, owing to the increased domestication of animals; it is also increasing in low- and middle-income nations, owing to increased urbanisation (Smith 2000). Due to increased displacement of wild animals from their natural habitats, wild animal attacks are also becoming more frequent. Estimates indicate that in their lifetime, half of all Americans will be bitten at least once by an animal or another human being (Benson 2006; Griego 1995). Data from low- and middle-income countries are scant owing to lack of surveillance systems and improperly developed health systems, but the burden of mammalian bites is very high (Eng 1993; Fèvre 2005; Ichhpujani 2008; Sambo 2013). Estimated direct costs of pet owners' liability claims due to mammalian bites in the USA is about USD 1 billion annually (Benson 2006).

Dog bite wounds are usually tears and avulsions (an injury in which a bodily structure is torn off), with puncture wounds being less common. Cat bites, on the other hand, are usually of the puncture variety; lacerations, crushed tissues and avulsions are also quite common. In dog and cat bites, the infection is usually a mixture of aerobic and anaerobic organisms, the most common of which being aerobes like *Staphylococus* species,*Streptococcus* species,*Pasteurella* species*, and Neisseria* species and anaerobes like *Fusobacterium* species*, Porphyromonus* species (Abrahamian 2011; Talan 1999). Human bites are usually clenched-fist injuries (injury acquired by a person when one punches another and knuckles are cut against the teeth of the person being punched), causing mixed infection type (Rempe 2009; Talan 1999) with *Streptococcus anginosus (S anginosus), Staphylococcus aureus (S aureus), Eikenella corrodens (E corrodens),* and *Fusobacterium nucleatum (F nucleatum)* being the most common (Talan 2003).

Description of the intervention

Management of a mammalian bite wound involves ensuring haemostasis (stopping the flow of blood from the wound), local wound management, analgesia (pain relief), infection prevention (including prevention of tetanus and rabies where appropriate), recognition and management of complications, and finally ensuring cosmesis of the wound. The management of mammalian bite wounds has been overwhelmingly guided by the necessity to prevent infections, particularly rabies. Once symptoms develop, rabies is almost always fatal. More than 60,000 deaths annually occur due to rabies, most of them in Asia and Africa (WHO 2017).

Wound healing is a dynamic process which is a combination of inflammation, formation of granulation tissue, tissue remodeling and scarring. This is classically divided into three phases: the inflammatory phase, proliferation phase, and maturation or remodelling phase. Wound healing can be achieved by first intention (primary closure), where closure is done soon after cleaning and debridement (intention implies the process of wound healing in itself); by secondary intention (no closure), where the wound is left open and no approximation done; or third intention (delayed closure), where the wound is initially kept open, at least for a period of 48 hours, and closure is achieved after observing that there is no clinical evidence of infection, inflammation, or contamination (Williams 2018).

How the intervention might work

Wound healing is affected by various local and systemic factors. One of the most important factors affecting healing is the presence of infection. In a clean wound with no infection, epithelisation of the wound (the process of the wound being covered by an outermost layer of skin), is expected to occur within one to two days after the wound approximation (bringing together the edges of the wound) (Lorenz 2008). Thus primary closure, theoretically, provides a potential for faster and better wound healing, as well as better cosmesis on account of lesser scar tissue formation. Delayed suturing postpones the wound healing process by up to 48 hours when compared with primary closure. However, if suturing is done when infection persists, it might contribute to non-healing, as well as infections with serious or even fatal consequences (e.g. rabies). The World Health Organization (WHO) recommends postponing the suturing of a wound (in cases of bite), as a measure to prevent rabies and other infections (WHO 2014). The Indian National Guidelines on Rabies Prophylaxis 2013 (NCDC 2013) recommends avoiding suturing, and if suturing cannot be avoided, delaying it for a few hours after infiltration of rabies immunoglobulin to allow diffusion of the antibodies into the tissues. For those wounds which appear clinically infected, or are of a puncture type, many physicians prefer delayed closure. For those wounds which are less than eight hours old, or are located on the face (which has the property of enhanced vascularity and lack of dependent oedema), primary closure is preferred (Anderson 1992; Goldstein 1992). The need for longer duration of hospitalisation, or more hospital visits, or both, in delayed closure of wounds compared with early discharge and quicker recovery in primary closure of wounds, provides significant potential for benefits in terms of economic costs and burden on the health system, from the point of view of consumers as well as policy makers.

Why it is important to do this review

Mammalian bite wounds are a very common clinical problem across the world. Systematic reviews have been conducted to address the role of education in preventing dog bite injuries in adolescents and children (Duperrex 2009), and antibiotic prophylaxis for mammalian bites (Medeiros 2001). A previous systematic review studied primary closure versus delayed closure for non-bite traumatic wounds, but it did not include mammalian bites (Eliya-Masamba 2013). The issue of primary closure of animal bites remains controversial (Garbutt 2004), and this Cochrane Review will help to make an objective assessment of this important question, and enable evidence-based clinical decision-making and guideline development. There is only one other meta-analysis that has been conducted on a similar topic before (Cheng 2014). The existence of this meta-analysis was identified during the conduct of our review and it has a narrower scope than this Cochrane Review.

Please see Agreements and disagreements with other studies or reviews.

OBJECTIVES

To assess the effects of primary closure compared with delayed closure or no closure for mammalian bite wounds.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) for our systematic review. Cluster-randomised trials and cross-over trials are study designs that are not appropriate for answering the systematic review question on account of the nature of the intervention and were therefore not included.

Types of participants

We included any individual presenting with a traumatic bite wound caused by a mammal. We did not include wounds with infection at presentation. We also excluded wounds which had involvement other than the soft tissues (i.e. those with involvement of nerve tendon joints, bones, etc.). We revised the cut-off point from 24 hours to 48 hours from the bite event (see Differences between protocol and review). We included trials where the time was not reported, and conducted a sensitivity analysis to assess this (see Sensitivity analysis and Differences between protocol and review).

Presence of wound infection at presentation was defined as purulent discharge, or erythema associated with pus, or cellulitis, or infection as evidenced by tissue/swab microbial culture (or as defined by the trial authors).

Types of interventions

We compared the primary closure of wounds caused by mammalian bite with the following interventions:

- no closure (i.e. no approximation) of wounds caused by mammalian bite;
- delayed closure (approximation more than 48 hours following wound debridement or cleaning, whichever was appropriate) of wounds caused by mammalian bite.

Types of outcome measures

Primary outcomes

- Time to complete wound healing
- Proportion of wounds healed within 7 days, 10 days and 14 days (from occurrence of bite)
- Proportion of wounds which were infection-free in 7 days, 10 days and 14 days; where wound infection was defined as purulent discharge, or erythema associated with pus, or cellulitis, or infection as evidenced by tissue/swab microbial culture (or as defined by the trial authors)

Secondary outcomes

- Cosmesis measured using any validated cosmetic outcome score (for example Cosmetic Visual Analogue Score (CVAS) or the Wound Evaluation Score (WES)) at 7 days, 10 days and 14 days and up to 4 weeks (from occurrence of bite or at final follow-up) (Quinn 1998). We extended this cut-off point to allow us to include a trial (see Differences between protocol and review for more information).
- Death due to wound/bite-related condition or complication (including rabies and tetanus): short term (30-day mortality or in-hospital mortality), long term (at maximal follow-up)
- Length of hospital stay (if admitted and treated as inpatient) at maximal follow-up

Search methods for identification of studies

Electronic searches

We searched the following electronic databases to identify reports of relevant clinical trials:

- the Cochrane Wounds Specialised Register (searched 10 July 2019);
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 6) in the Cochrane Library (searched 10 July 2019);
- Ovid MEDLINE including In-Process & Other Non-Indexed Citations (1946 to 10 July 2019);
- Ovid Embase (1974 to 10 July 2019);
- EBSCO CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature;1937 to 10 July 2019).

The search strategies for the Cochrane Wounds Specialised Register, CENTRAL, Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus can be found in Appendix 1. We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (Lefebvre 2019). We combined the Embase search with the Ovid Embase filter developed by the UK Cochrane Centre (Lefebvre 2019). We combined the CINAHL search with the RCT filter of CINAHL for EBSCO developed by the Scottish Intercollegiate Guidelines Network (SIGN 2018). We did not restrict the search with respect to language, date of publication or study setting.

Searching other resources

Clinical trial registers

We searched the following trial registers to identify ongoing or recently completed studies:

- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 11 July 2019);
- the WHO International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/trialsearch) (searched 11 July 2019).

Search strategies for clinical trial registries can be found in Appendix 1.

Researchers and organisations

We contacted individual researchers working in the field and related organisations (academic based, research based or advocacy based) to find unpublished trials.

Reference lists

We searched the reference lists of retrieved included trials (identified by the above mentioned methods), as well as relevant

systematic reviews and meta-analyses, to identify other potentially eligible trials or ancillary publications.

We did not perform a separate search for adverse effects of interventions used; we considered adverse effects described in included studies only.

Data collection and analysis

Data collection and analysis were carried out according to methods stated in the published protocol (Bhaumik 2015), which were based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Selection of studies

Two review authors (SB, SC) independently screened studies for consideration of inclusion based on title and abstracts. If decisions about inclusion were unclear at this stage, full texts of the citation were acquired and assessed for eligibility in the next phase of screening. We had planned to scrutinise reports to identify multiple publications from the same data set and obtain all publications related to them, but this was unnecessary as no such trials were detected. Full texts were assessed independently (SB, RK or SC) and any disagreement about final eligibility was resolved by consensus, with the third review author acting as an arbiter. We state reasons for exclusion in the Characteristics of excluded studies table.

Data extraction and management

At least two of the three review authors (SB, SC, RK) independently performed data extraction, using a data extraction form listing the following information:

- study details: location, year, duration, contextual Information;
- methods: study design, total duration of study, study location, study setting, risk of bias information, withdrawals, and period of conduct of study;
- participants: number (N), mean age or age range, inclusion criteria, and exclusion criteria, gender distribution and other demographic variables and wound characteristics (including animal species, location of wounds and time of presentation);
- intervention: description of intervention (timing, nature of suture material, suture technique), comparison, content of both intervention and control condition, and co-interventions;
- outcomes: description of outcomes specified and collected, and at which time points reported;
- other information: funding for trial, and notable conflicts of interest of authors;
- methodological quality of studies (risk of bias assessment).

We also extracted numerical data for all outcomes reported (number of events, number of participants randomised, number of withdrawals or loss to follow-up, risk ratio (RR), mean, standard deviation, standard error of mean, hazard ratio (HR), 95% confidence interval (CI), P values).

Any discrepancies or disagreements were resolved by consensus, with the third review author acting as an arbiter. We planned to contact a member of Cochrane Wounds editorial base if no consensus could be reached at the review author level. One review author (RK) entered data into Review Manager 5 software (Review Manager 2014) and this was cross-checked by at least one of the other review authors (SB or SC).

Assessment of risk of bias in included studies

At least two of the three review authors (SB, SC, RK) independently assessed the risk of bias of each of the included trials, according to the guidelines given in the *Cochrane Handbook* (Higgins 2011b). We assessed risk of bias based on the following domains (Appendix 2):

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective reporting;
- other sources of bias (we considered baseline imbalances in this domain).

Measures of treatment effect

For dichotomous data we used RR with 95% CIs. For continuous data, we used mean difference (MD) between groups with 95% CIs. If the outcomes were measured using different scales, we used standardised mean differences (SMDs) with 95% CIs. For time-to-event outcomes (time to complete wound healing), we planned to use HRs, as they are appropriate where it is possible to obtain data. We had also planned to estimate HRs using the reported values by following the formula given in (Parmar 1998), implemented in an excel template (Tierney 2007), but this was not possible as we could not obtain data from trial authors.

Unit of analysis issues

We planned to use wounds as the unit of analysis. For example, if there were two traumatic wounds in the same person, we planned to consider them as two separate units. If no adjustment was done in the analysis for clustering, we attempted to request data from the trial authors about intra-class correlation values, or raw data, and adjust the estimate for clustering by following methods stated in the *Cochrane Handbook* (Higgins 2011c). Since one of the included trials (Maimaris 1988) reported both wound and patient-level data, and we were unable to obtain information on clustering, we have provided a narrative summary of the wound-level data for this trial and performed a separate analysis with the patient-level data for the other trials.

Dealing with missing data

We made an attempt to contact the trial authors for any missing data. If there was no response, we assumed that the data were missing 'at random' and carried out the analysis based on the intention-to-treat principle, assuming that the missing data on wounds did not heal (i.e. we considered only the denominator, not the numerator). When there was unequal dropout between groups in a trial of more than 10%, we performed an analysis using per protocol population to assess the robustness of the results.

Assessment of heterogeneity

We tested heterogeneity of the intervention effects amongst the included trials by visually inspecting the analysis graphs, the standard Chi^2 test (P value), or the I^2 statistic (Higgins 2003). We considered a P value of less than 0.10 as statistically significant

in terms of heterogeneity. We interpreted the I^2 statistic for heterogeneity according to the following criteria:

- 0% to 40%: no heterogeneity;
- 30% to 60% represents moderate heterogeneity;
- 50% to 90% represents substantial heterogeneity;
- 75% to 100% represents considerable heterogeneity.

We explored the possible cause(s) of heterogeneity when I^2 was greater than 80% by subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

We had planned to use a funnel plot to explore bias if we found 10 RCTs or more but this was unnecessary as the requisite number of trials were not found. We had planned to use the funnel plot effect (Egger 1997) to detect reporting bias. However, this was unnecessary due to the paucity of studies (see Differences between protocol and review).

Data synthesis

We combined details of included studies in a narrative review according to type of comparator and then by outcomes, ordered by time period. We considered clinical and methodological heterogeneity and undertook pooling when studies appeared appropriately similar in terms of wound type, intervention type, duration of follow-up, and outcome type.

We were unable to pre-specify the amount of clinical, methodological, and statistical heterogeneity in the included studies. Thus, we used a random-effects approach for meta-analysis. Conducting meta-analysis with a fixed-effect model in the presence of even minor heterogeneity may provide overly narrow CIs. We would only have used a fixed-effect approach when clinical and methodological heterogeneity was assessed to be minimal, and the assumption that a single underlying treatment effect was being estimated held. We used Chi^2 and I^2 to quantify heterogeneity, but these values were not used to guide the choice of model for meta-analysis.

We presented data using forest plots where possible. For dichotomous outcomes we presented the summary estimate as a RR with 95% CI. Where continuous outcomes were measured, we presented a MD with 95% CI; we planned to pool SMD estimates where studies measured the same outcome using different methods. For time-to-event data, we planned to plot (and, if appropriate, pool) estimates of HRs and 95% CIs as presented in the study reports using the generic inverse-variance method in Review Manager 5 (RevMan 2014). In future updates, where time-to-healing is analysed as a continuous measure but it is not clear if all wounds healed, we will document use of the outcome in the study but will not summarise data or use them in any meta-analysis.

We obtained pooled estimates of treatment effect from the available data using Review Manager 5 software (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We had planned to perform subgroup analyses for the following factors, if sufficient numbers of studies had been available:

- animal species (dogs, cats, humans, monkeys and others);
- location of the wound (hands, arms, head/neck, trunk);
- presentation time of the wounds (less than 8 hours, and 8 to 24 hours).

However, this could not be done due to paucity of studies.

Sensitivity analysis

We planned to conduct sensitivity analyses by excluding studies based on the methodological quality of trials according to the following criteria, but this was not done due to paucity of studies:

- concealment of allocation (allocation adequately concealed versus not reported or inadequate);
- type of randomisation (adequate methods of generating the randomisation sequence versus not adequate or not reported);
- timing of randomisation (randomisation done within 24 hours of bite versus not reported);
- blinding of participants (high risk and/or unclear risk versus low risk);
- blinding of outcome assessment (high risk and/or unclear risk versus low risk);
- incomplete outcome bias (high risk and/or unclear risk versus low risk).

We conducted a sensitivity analysis to evaluate the effect of changing the eligibility criteria for time cut-off on a post-hoc basis (see Differences between protocol and review and Potential biases in the review process).

'Summary of findings' tables

We used the GRADE approach to interpret findings and guide our conclusions and recommendations (Schünemann 2011). We imported data from Review Manager 5 to the GRADEpro GDT software (GRADEpro GDT 2015) and created a 'Summary of findings' table for the comparisons included in the review. We had planned to only include primary outcomes in the 'Summary of findings' table but also included the outcome of cosmesis as a post-hoc decision (see Differences between protocol and review).

The 'Summary of findings' table provides information for each comparison on the overall certainty of the evidence from the trials, the magnitude of the effects of the interventions, and a sum of all data on all the primary outcomes.

Calculation of optimal information size is required for making judgements on imprecision using GRADE methodology (Schünemann 2013). For calculating the optimal information size (OIS), we used the control group risk from the meta-analyses and assumed a relative risk reduction of 20%. This gave an OIS of 800. The OIS should not be treated as optimal sample sizes for any future research; within a GRADE assessment the OIS is used to assess the stability of CIs rather than to assess the appropriateness of a sample size to detect a difference per se. For the continuous outcome of cosmesis measured using mean validated outcome score, we used an OIS of usual standards of $\alpha = 0.05$ and 80% power with an effect size of 0.2 standard deviation to represent a small effect, and calculated the total sample size to be approximately 400. We note however, that such a calculation for a continuous outcome might give false reassurance when achieved (which it was not in our case) but nevertheless this approach has been recommended for

guideline developers as well as systematic reviewers Schünemann 2013.

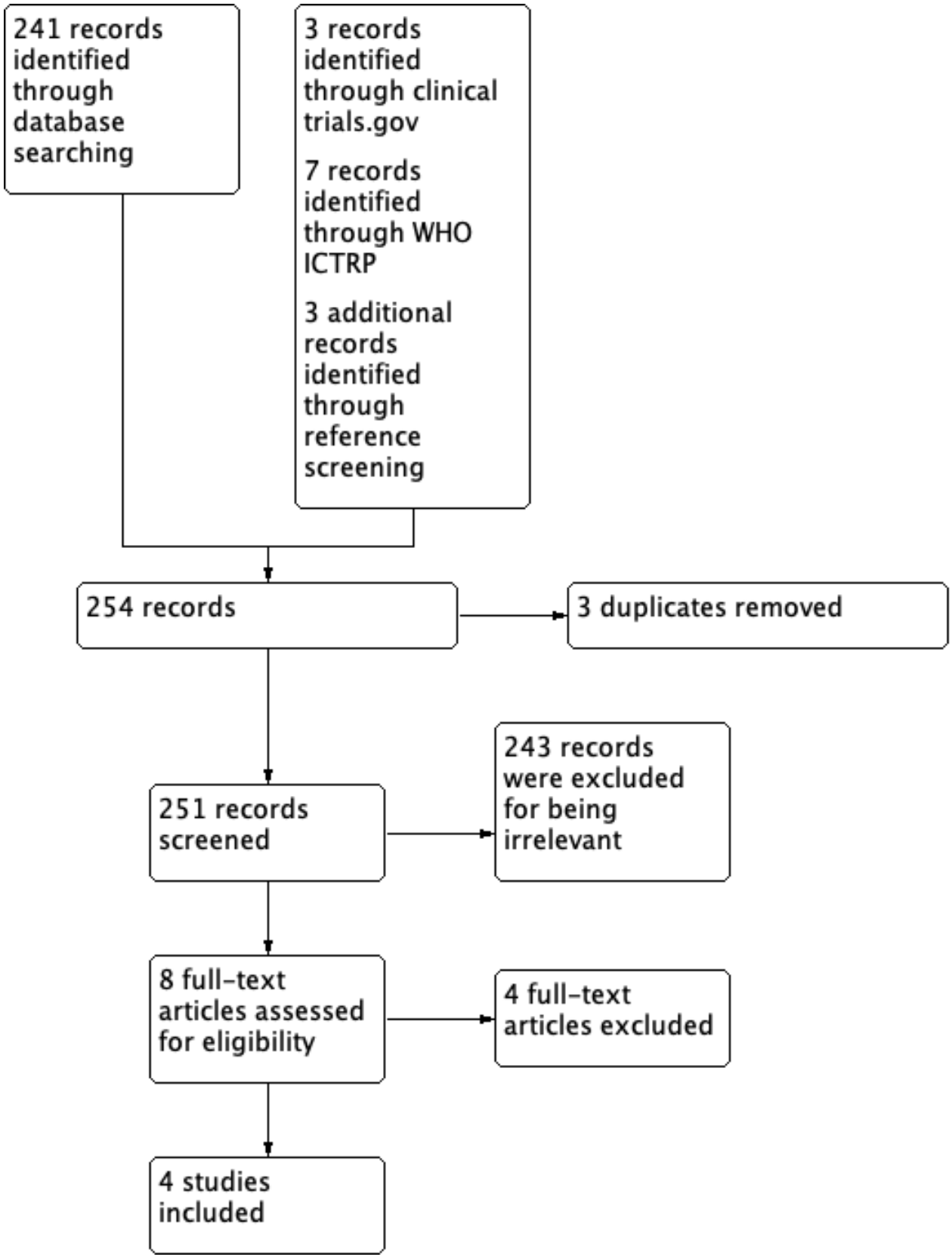
RESULTS

Description of studies

Results of the search

We retrieved 241 records by searching in electronic databases; three records were identified through www.clinical trials.gov, seven through the WHO ICTRP (apps.who.int/trialsearch/), and three through reference screening of included studies. No studies were identified through contacting experts. We removed three duplicate records and screened the remaining records. We retrieved a total of eight full texts (Cheng 2014; Dellinger 1988; Maimaris 1988; Morgan 1995; Paschos 2014; Rui-Feng 2013; Xiaowei 2013; Zubowicz 1991) and finally included four studies (Maimaris 1988; Paschos 2014; Rui-Feng 2013; Xiaowei 2013). Details about the flow of studies are shown in the form of a PRISMA flowchart in Figure 1.

Figure 1. PRISMA Study flow diagram.



Included studies

We identified four RCTs that met our eligibility criteria (Maimaris 1988; Paschos 2014; Rui-Feng 2013; Xiaowei 2013); their characteristics are summarised in Characteristics of included studies. We attempted to contact the author of one study (Maimaris 1988) to acquire more information but this was not successful.

Setting

Two out of the four included RCTs were from China (Rui-Feng 2013; Xiaowei 2013), while one trial was from Greece (Paschos 2014) and one was from England (Maimaris 1988). One study was conducted in a specialised rabies prophylaxis and immunity clinic (Rui-Feng 2013), and the remaining three RCTs were conducted in the emergency department.

Population

Age and sex

All age groups were eligible for participation in three of the included RCTs (Maimaris 1988; Rui-Feng 2013; Xiaowei 2013), while one RCT included only participants who were 16 years and older (Paschos 2014). Two trials did not report the average age but in one trial 60% of participants were less than 30 years old (Maimaris 1988), and in the remaining trial 53% of participants were less than ten years old (Rui-Feng 2013). The average age was 30.8 years ± 8.8 years in Xiaowei 2013, and in Paschos 2014 it was 44.3 years ± 19.4 years in the primary closure group and 43.9 years ± 19.1 years in the no-closure group.

None of the trials had any sex-based inclusion or exclusion criteria. All studies had male and female participants; one study had more female participants than male (Rui-Feng 2013), and the remaining three trials had more male participants than female. Overall, it can be said that all age groups and both sexes were adequately represented.

Animal species

The four studies included dog bite wounds only.

Bite location

One trial (Rui-Feng 2013) included only facial dog bite injuries, while others did not have any such criteria. A detailed distribution of location of bites in individual trials is presented in Table 1. The numbers in each category were too small to enable any meaningful subgroup analyses.

Time from bite to presentation

All four trials had different criteria for eligibility in terms of the time from bite to presentation. One RCT included participants who had presented within 48 hours from the bite (Paschos 2014), while another used an 8-hour cut-off (Rui-Feng 2013) and another a 24-hour cut-off (Xiaowei 2013). One trial included all participants irrespective of presentation time, but made a note of the time delays (Maimaris 1988) (see Differences between protocol and review).

Type of wounds

Details of the types of wound included in the different RCTs included is presented in Characteristics of included studies. Broadly, none of the studies included participants with complicated wounds (involvement of bones, tendons, nerves, viscera or joints), wounds which were infected at presentation, or wounds requiring plastic surgery. Three RCTs did not include participants with known immunocompromised status (Rui-Feng 2013; Paschos 2014; Xiaowei 2013).

Interventions and comparisons

Only one RCT compared primary wound closure (on presentation) with delayed would closure (three days after presentation) (Xiaowei 2013). Three RCTs compared primary wound closure with no closure (Maimaris 1988; Paschos 2014; Rui-Feng 2013).

Excluded studies

We excluded four studies after full-text evaluation. We excluded two studies for having a non-relevant intervention (Dellinger 1988; Zubowicz 1991) and another two studies for improper study design (Cheng 2014; Morgan 1995). Reasons for exclusion are further presented in Characteristics of excluded studies.

Risk of bias in included studies

The risk of bias is graphically represented in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

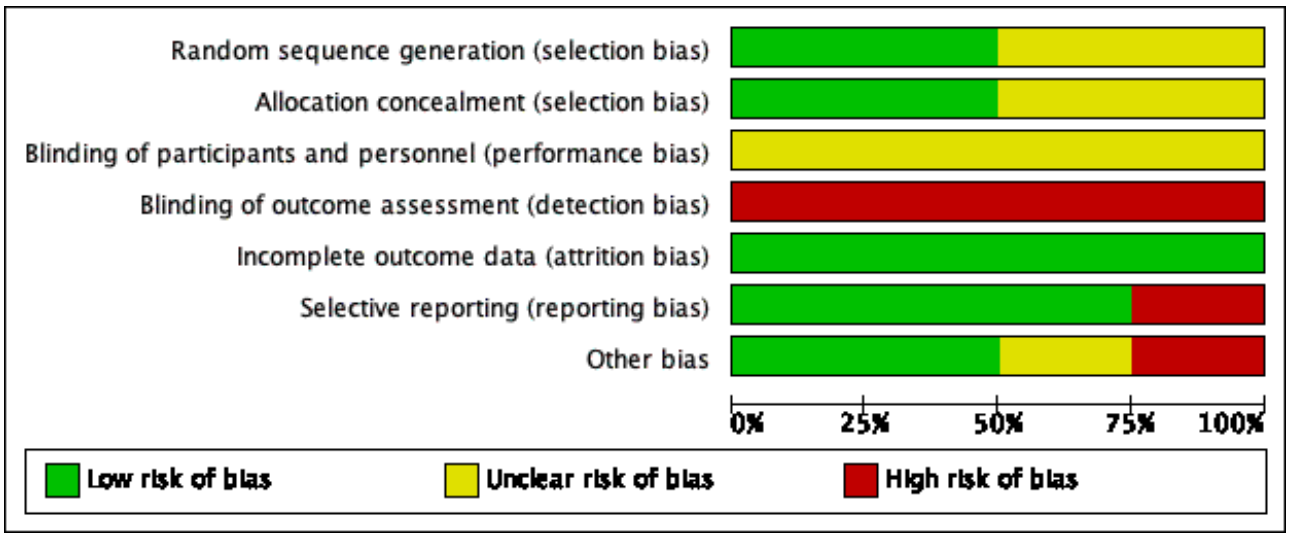
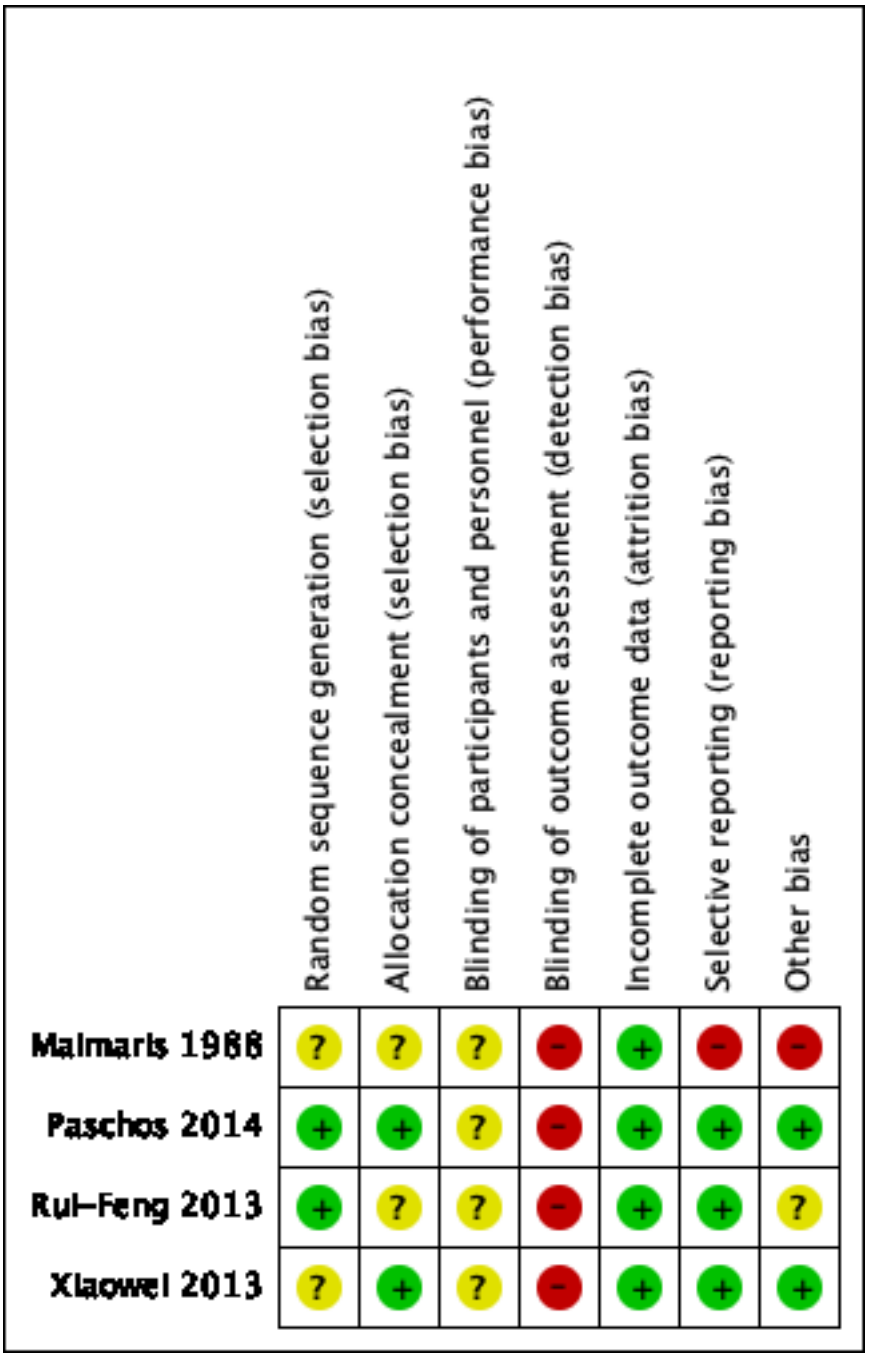


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Two trials did not provide enough information for us to judge the risk of bias for random sequence generation (Maimaris 1988; Xiaowei 2013), and two trials did not provide enough information for us to judge the risk of bias for allocation concealment (Maimaris 1988; Rui-Feng 2013).

We deemed Rui-Feng 2013 and Paschos 2014 to be at low risk of bias for random sequence generation. We judged Xiaowei 2013 and Paschos 2014 to be at low risk of bias for allocation concealment.

Blinding

Due to the nature of the intervention, it is very difficult to blind participants and personnel, and none of the trials reported attempting to do so. We therefore judged the trials to have an unclear risk of performance bias, since there is insufficient information to permit judgement.

Assessment of outcomes like infection-free wounds is subjective in nature, and we therefore judged the trials to be at high risk of detection bias. Where cosmesis was evaluated, the outcome assessors were blinded to allocation and hence we judged the trials to have a low risk of bias although the criteria used for measuring

cosmesis (the Vancouver Scar Scale) has subjective elements like pigmentation, pliability and vascularity (not shown in Figure 2 and Figure 3 as it is a secondary outcome).

Incomplete outcome data

We found no evidence of attrition bias. All participants reported in the studies were accounted for at the end of the studies.

Selective reporting

We found no evidence of selective reporting in three trials (Paschos 2014; Rui-Feng 2013; Xiaowei 2013) and considered all of them as being at low risk of reporting bias. None of the trials had published protocols or trial registrations, but all stated outcomes were reported. We judged one trial (Maimaris 1988) to be of high risk of bias as there was discordance in the manner one outcome was reported in the methods and results section of the report.

Other potential sources of bias

We judged Rui-Feng 2013 to be at unclear risk of other bias as information on important potential confounders in the two groups of the trial was not reported. We judged Maimaris 1988 to be at high risk of other bias because in this study randomisation was done at patient level but results were reported at wound level without accounting for clustering and no differences in baseline were reported either. The other two trials were judged to be at low risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Primary closure versus no closure for traumatic wounds due to mammalian bite; **Summary of findings 2** Primary closure versus delayed closure for traumatic wounds due to mammalian bite

See Summary of findings for the main comparison and Summary of findings 2. We have presented the findings by intervention type.

Comparison 1: primary closure versus no closure (3 studies; 878 participants)

Time to complete wound healing

None of the studies reported this outcome using HRs so we were unable to use these data in analyses. One trial reported mean time-to-healing data which did not meet our prespecified criteria for this outcome.

Proportion of wounds which healed within 7 days, 10 days and 14 days

None of the studies reported this outcome.

Proportion of wounds which were infection-free in 7 days, 10 days and 14 days

All three trials which evaluated this comparison reported this outcome (Maimaris 1988; Paschos 2014; Rui-Feng 2013). However, in Maimaris 1988 data were provided at wound level and failed to take clustering into account; we therefore decided to present the results narratively and separately from Paschos 2014 and Rui-Feng 2013, both of which reported data at the individual level. We are uncertain whether primary suturing improves the proportion of wounds which are infection-free compared with no closure (RR 1.01, 95% CI 0.97 to 1.05; 2 studies, 782 participants; Analysis 1.1). We judged the certainty of evidence for this outcome to be very low. The evidence was downgraded by one level for high risk of detection bias and another two levels for imprecision (Summary of findings for the main comparison). Results from Maimaris 1988 show that 85/92 (92.3%) wounds in the primary-closure group versus 71/77 (92.2%) wounds in the no-closure group were infection-free.

Cosmesis measured by validated cosmetic outcome score

Only a single trial (Paschos 2014) reported this outcome using the Vancouver Scar Scale at four weeks' follow-up (see Differences between protocol and review). The Vancouver Scar Scale assesses cosmesis on four parameters: vascularity, pigmentation, pliability and height (a lower score equals better cosmesis). Although the effect estimate for the comparison of primary closure with no closure showed a benefit of primary closure in the cosmesis of dog bite wounds (MD -1.31, 95% CI -2.03 to -0.59; 1 study, 182 participants) this difference was too small to be clinically meaningful. We judged the certainty of evidence for this outcome to be moderate. The evidence was downgraded due to imprecision (Summary of findings for the main comparison).

One trial also reported on wound cosmesis, in which the wounds were classified into good, fair and poor results (Maimaris 1988). However this was not a relevant outcome for this review as a validated scoring mechanism for measuring wound cosmesis outcomes was not used.

Death due to wound/bite-related condition or complication (including rabies and tetanus)

None of the studies reported these outcomes.

Length of hospital stay

None of the studies reported this outcome.

Comparison 2: primary closure versus delayed closure (1 study; 120 participants)

Only Xiaowei 2013 compared primary closure (on the day of presentation) with delayed closure (three days after presentation).

Time to complete wound healing

The study did not report this outcome.

Proportion of wounds which healed within 7 days, 10 days and 14 days

The study did not report this outcome.

Proportion of wounds which were infection-free in 7 days, 10 days and 14 days

We are uncertain whether primary suturing improves the proportion of wounds which are infection-free after seven days compared with delayed closure (RR 0.98, 95% CI 0.90 to 1.07; 1 study, 120 participants; Analysis 2.1). The outcome was not reported for 10 or 14 days. We judged the certainty of evidence for this outcome to be very low (Summary of findings 2). We downgraded the evidence by one level for high risk of bias and another two levels for imprecision.

Cosmesis measured by validated cosmetic outcome score

The study calculated wound cosmetic scores but reported proportion of wounds which had optimal cosmetic scores and not the scores as a continuous outcome, in accordance with the eligibility criteria for our systematic review. We therefore did not include it in the analyses.

Death due to wound/bite-related condition or complication (including rabies and tetanus)

The study did not report this outcome.

Length of hospital stay

The study did not report this outcome.

DISCUSSION

Summary of main results

The review includes four RCTs that compared primary closure with delayed or no closure for traumatic wounds due to dog bites. We are uncertain whether primary closure reduces the proportion of wounds which are infection-free when compared with no closure as the certainty of evidence has been assessed as very low. There was moderate-certainty evidence of a benefit in cosmesis of dog bite wounds when primary closure was compared with no closure but this was too small to be clinically important. We are uncertain whether primary closure reduces the proportion of dog bite wounds which are infection-free in comparison to delayed closure, as the certainty of evidence has been assessed as very low.

Overall completeness and applicability of evidence

We searched multiple electronic databases and also searched using other methods and we believe no trials which could have influenced the results have been missed. Assessment of publication bias through funnel plots was not undertaken due to the small number of studies found. We did not find any evidence for bites caused by mammals other than dogs.

The evidence we found was from England, Greece and China. There were no trials from low-income countries where health-system related factors like delay in presentation and quality of care might influence outcomes (such as the proportion of infection in wounds due to poor infection prevention and control practices). We did not find information on several important outcomes like proportion of wounds healed, time to complete wound healing and length of hospital stay. Although none of the trials reported any deaths or complications (such as rabies), they were, in any case, unlikely to have been large enough to have satisfactory power to provide precise estimates for these. Cosmesis using a validated score was reported in only one small trial which only included facial dog bites.

Quality of the evidence

We assessed the certainty of the evidence using the GRADE methodology, and presented results for important outcomes in Summary of findings for the main comparison and Summary of findings 2. The overall certainty of evidence is very low for the outcome of proportion of wounds which were infection-free. Due to the nature of the intervention, it is almost impossible to blind the participants and the personnel involved in the wound management. Due to the detection bias associated with the process of assessing whether wounds are infection-free or not (this is difficult to blind also) we judged all trials to be at high risk of this bias. We downgraded for very serious imprecision for the outcome 'proportion of wounds which were infection-free' because the number of events was less than the optimal information size and the confidence intervals included both appreciable benefit and harm.

Only one trial reported cosmesis as an outcome, for the comparison of primary closure with no closure, and the evidence for this was judged to be of moderate certainty. We downgraded the evidence for imprecision because there were too few participants to meet the optimal information size. We did not downgrade for risk of bias, as the risk of detection bias for this outcome was considered to be low (the surgeon who conducted the outcome assessment was blind to allocation). We did not downgrade the evidence for any of the outcomes for indirectness, inconsistency or publication bias.

Potential biases in the review process

In this systematic review we used explicit, prespecified methods which were outlined in a published protocol (Bhaumik 2015). Any deviation from the protocol has been transparently reported in Differences between protocol and review. A key deviation from the initial protocol involves the inclusion of Paschos 2014 which included participants up to 48 hours from the bite event (contrary to our eligibility criteria which excluded studies with participants more than 24 hours post-bite). We decided to include the study as it is the most recent trial on the issue and there is a paucity of trials in this area. We also conducted a sensitivity analyses (not shown) to examine the effects of including this trial and found no differences in the results. We have included the data for the outcome of cosmesis using a validated cosmetic outcome score from Paschos 2014, even though the evaluation was done at four weeks which is not in keeping with our original eligibility criteria that required such data at 14 days. We have done this because this was the only trial which has information for this outcome and the information would be clinically meaningful for decision making.

We reduced the potential of bias due to random errors or mistakes from individual errors by ensuring that all review authors read the papers and extracted data independently, and then came to mutual agreements. We contacted authors to clarify some issues regarding data and methodology but we received no responses. For example, we were unable to obtain the raw data or ICC estimates for adjusting the available data (Maimaris 1988). In the protocol we indicated that we would use wounds as the unit of analysis rather than participants but, due to the reporting of trials, we decided against pooling participant-level and wound-level data to avoid bias.

Agreements and disagreements with other studies or reviews

There is only one meta-analysis that has been conducted on this topic before (Cheng 2014). We became aware of the existence of this meta-analysis during the conduct of our systematic review. In Cheng 2014, primary closure for dog bite wounds was compared with delayed or non-closure together and no statistically significant difference in the incidence of the wound infection was found. The meta-analyses did not evaluate any other outcomes. Our systematic review had a broader eligibility criteria, where we included all mammalian bites; we also included more outcomes and we searched more electronic databases compared with Cheng 2014. In our systematic review we found the same studies as Cheng

and colleagues and, although our overall conclusion is on similar lines, our estimates from the meta-analyses estimate are different. In Cheng 2014, different types of intervention comparisons were pooled together into a single comparison (primary closure versus delayed and no closure), however we felt it was more appropriate to consider the data in two comparisons. Moreover, we used the GRADE approach to make judgements about the certainty of the evidence, which was not done in the earlier meta-analysis. This is important for decision making.

AUTHORS' CONCLUSIONS

Implications for practice

We found very low-certainty evidence that there is no difference in infection rates between primary closure and no closure of traumatic wounds caused by dog bites. We found moderate-certainty evidence that primary closure may have a small effect on cosmesis for dog bites, but this was too small to be clinically important. There is evidence in the literature suggesting many patients opt for scar revision surgery later and even file lawsuit actions against treating physicians in relation to cosmesis (Eppley 2013). Even a mild to modest improvement in scar outcome might be of considerable importance depending on patient values and contexts. As systematic review authors, we have not made judgements on value and preferences, or compared outcomes relative to each other to warrant change in treatment decision (Schünemann 2013). Clinicians might take into consideration the location of the wound along with individual patient preferences when making decisions. Guideline developers and treating clinicians need to consider patient values and contextual issues to formulate recommendations or to make healthcare decisions in addition to the evidence presented in our systematic review.

We found only one trial comparing primary closure versus delayed closure and found very low-certainty evidence on the difference in infection risk between the two methods of closure for dog bite wounds.

Overall, we did not find high-certainty evidence to support or refute existing recommendations concerning primary closure for dog bite wounds. The potential benefits and harms of primary closure compared with delayed or no closure for mammalian bite remain uncertain.

Implications for research

There is an urgent need to conduct robust, randomised clinical trials which compare primary closure (performed within 24 hours of injury) with delayed closure (performed more than 48 hours after injury) and no closure for mammalian bites. Trials should have adequate sample sizes so that they have enough power for adverse outcomes like death due to bite/wound-related condition or complications like rabies to be better understood, and in order to facilitate subgroup analyses (like location of wounds and presentation time of wounds). In order to acquire sufficient sample sizes, large, well-funded multicentric trials might be desirable. Multi-centric trials can also increase external validity. Children as well as adult participants need to be included. There is also a need for these trials to be based in low- and middle-income countries, where quality of care, infection rates and patient awareness are a major cause of concern.

We recommend that trials should not only measure the proportion of wounds which are infection-free but also the time to complete healing (using hazard ratios), cosmesis (using validated cosmetic outcome scores), death due to wound/bite-related conditions or complications, and duration of hospitalisation. We also recommend that future trials have an economic evaluation component so that cost-effectiveness of the intervention can be evaluated.

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Bhaumik S, Kirubakaran R, Chaudhuri S. Primary closure versus delayed or no closure for traumatic wounds due to mammalian bite. *Cochrane Database of Systematic Reviews* 2015, Issue 8. [DOI: 10.1002/14651858.CD011822]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Maimaris 1988

Methods	**Method:** prospective randomised controlled trial **Setting:** Accident and Emergency Department, Leicester Royal Infirmary, England **Study duration:** September 1987 to January 1988
Participants	**Total individuals randomised:** 96 patients were entered and were randomised. 169 wounds were analysed. **Age:** participants were between 2 and 83 years old and 60% of participants who entered the trial were less than 30 years of age. **Sex:** 57 males; 39 females **Inclusion criteria:** wounds requiring surgical treatment (more than 3 mm) **Exclusion criteria:** puncture wounds (less than 3 mm diameter), infected wounds at presentation, wounds with skin loss requiring plastic surgery or wounds where other structures were involved (e.g. nerve, tendon, joint or bone) **Follow-up of participants:** 14 days from the injury
Interventions	**All groups:** all the participants were updated for tetanus immunisation. The lacerations were cleaned with a solution of cetrimide 0.5% and chlorhexidine 0.05%. Debridement of wound and skin edges was undertaken where necessary under local anaesthetic. Irrigation of the wound was then performed with 50 mL of normal saline using a 20-mL syringe and 19-guage needle. The bleeding was stopped and the wound was dried with a swab. All wounds received a Jellonet dressing with gauze and crepe bandage. A high sling was used in the upper limb and elevation was advised for the leg. No antibiotics were used. **Intervention group :** wounds were sutured with 4/0 Ethilon for most lacerations and 6/0 Ethilon to the face. The management of simple lacerations was undertaken by experienced nursing staff in the A&E department. In complicated wounds, especially in the hand, the participants were treated in the operating theatre by an experienced member of the medical staff; 92 wounds were sutured. **Control group:** wounds were left open; 77 wounds were left open.

Maimaris 1988 *(Continued)*

Outcomes	**Infection rate:** serous exudate, inflammation without pus, infection with systemic effects **Wound healing:** classified at each review as completely or partly healed, or gaping **Wound cosmesis:** classified into good, fair and poor results. The maximum width of the wound scar was measured in millimetres.
Notes	Authors were contacted for more information but there was no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was mentioned as being done but the process is unclear.
Allocation concealment (selection bias)	Unclear risk	Not clear from the "patients and methods" section
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Nothing mentioned. Due to the nature of the intervention blinding of participants and personnel is very difficult.
Blinding of outcome assessment (detection bias) All outcomes	High risk	It is mentioned that outcome assessment was done by one of the authors but it is not immediately clear whether they were blinded. However we judged the study to be of high risk of bias as it is not possible to be blinded of the intervention status for assessment of infection status.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome group: none of the participants were lost to follow-up. Incomplete outcome: none mentioned
Selective reporting (reporting bias)	High risk	Wound healing was reported as "satisfactory" in all participants, but in the "patients and methods" section the pre-classified outcomes were "completely healed", "partly healed", and "gaping". This was not mentioned in the results section. The authors randomised patients and analysed the results at wound level without accounting for clustering effect.
Other bias	High risk	Randomisation was done at participant level but results reported at wound level without accounting for clustering; and no differences in baseline are reported either.

Paschos 2014

Methods	**Method:** prospective randomised controlled trial **Setting:** emergency department in Greece **Study duration:** 2009 to 2012
Participants	**Total individuals randomised:** 182 **Age (reported for number analysed, not number randomised - age of participants lost to follow-up unknown):** 44.3 ± 19.4 years (primary-closure group); 43.9 ± 19.1 years (no-closure group) **Sex (reported for number analysed, not number randomised - sex of participants lost to follow-up unknown):** 54 males; 28 females (primary-closure group); 56 males; 30 females (no-closure group)

Paschos 2014 *(Continued)*

	Inclusion criteria: a) the presence of a dog bite wound that penetrated the epidermis and/or dermis (full thickness wounds); b) presentation to the emergency department within the first 48 hours post-injury; and c) participants aged 16 years and older **Exclusion criteria:** presence of a complex or a complicated wound (i.e. presence of a fracture, muscle injury, etc). Patients with any kind of compromised immune system or allergic reaction to the antibiotics were also excluded. **Follow-up of participants:** four weeks from the injury
Interventions	**All groups:** all wounds initially received irrigation under high pressure with a needle and 50-mL syringe with normal saline solution up to a total volume of 500 mL. Subsequently, local scrubbing with the use of povidone-iodine (Betadine 10% solution) was used for wound cleansing. Surgical debridement was performed in all cases as needed, with meticulous care to remove all tissues with compromised viability but with extreme care, so that dermal wounds would not be converted into full thickness injuries if possible. **Control group:** (no closure) wound left open **Intervention group:** (primary closure) wound sutured with Ethilon 3-0 or 4-0 nylon sutures (depending on the location of the wound). Before suturing, anaesthesia was provided by lidocaine 2% (20 mg/mL). Simple interrupted sutures were used in all cases; suturing resulted in approximation of the skin traumatic edges.
Outcomes	**Infection rate:** presence of infection was assessed using definitive and relative criteria. Definitive criteria for infection considered the presence of systematic fever, local abscess, or lymphangitis. Relative criteria included erythema at the edges of the wound, local swelling, increased temperature or tenderness, as well as drainage from the wound (Table 1). **Wound cosmesis:** recording of the cosmetic appearance of the wound conducted at the end of the fourth week following initial injury with the use of the Vancouver Scar Scale (VSS)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	All participants were allocated randomly into two different treatment approaches (primary suturing versus non-suturing) via a computer-based system.
Allocation concealment (selection bias)	Low risk	"The orthopaedic surgeon who evaluated the patient initially, determined whether he/she would be eligible for the study." Subsequently, after the patient gave the informed consent to participate in the study the allocation was "determined based on the computer program operated by another clinician. Therefore, the surgeon entering the patient in the study did not know the randomised allocation."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Nothing mentioned. Information was sought from trial authors but we could not get any response. Due to the nature of the intervention blinding of participants and personnel is very difficult.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Nothing is mentioned about who did the wound infection outcome assessment. However it is not possible to be blinded of the intervention status for assessment of infection status. The figure reflects this as it is primary outcome of interest.

Paschos 2014 *(Continued)*

		A surgeon blinded to the treatment performed the evaluation for Vancouver Scar Scale after four weeks.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data as mentioned in the study were reported. Lost to follow-up in the primary suturing group was 8 and in the non-suturing group was 6, i.e. the attrition was balanced across groups.
Selective reporting (reporting bias)	Low risk	No trial registration or protocol for this study was found but all outcome data mentioned in the study were reported.
Other bias	Low risk	We did not detect any other sources of bias.

Rui-Feng 2013

Methods	**Method:** prospective randomised controlled trial **Setting:** Rabies Prophylaxis and Immunity Clinic, Beijing, China **Study duration:** January 2006 to December 2011
Participants	**Total individuals randomised:** 600 patients entered in this study. All of them were randomised. **Age:** range 1 to 64 years. Average age was not reported but 53% of the participants were less than ten years old. **Sex:** 272 males; 328 females **Inclusion criteria:** patients of any age and gender attending Rabies Prophylaxis and Immunity Clinic, Beijing with facial dog bite were enrolled in the prospective, randomised trial. The facial lacerated wounds requiring surgical treatment (more than 2 cm) were entered into the trial **Exclusion criteria:** puncture wounds (less than 2 mm), small laceration (less than 2cm), infected wounds at presentation or visited doctor's office more than 8 hours after injury, wounds with skin loss requiring plastic surgery, or patients with immune deficiency, using immunosuppressive agent, autoimmune disorder and diabetes **Follow up of participants:** not stated
Interventions	**All groups:** "All the facial lacerations underwent thorough debridement followed by wound closure. All the important impaired or missing facial organ or tissues (such as eyelid, eyeball, nasolacrimal canal, parotid, nose, ear etc) were repaired with a suitable operation after the lacerations reached clinical healing. Wound cleaning was done under local anaesthesia with aseptic carbasus, 20% liquid soap and water. Subsequently, the wounds were alternating douched with 20% liquid soap and physiological saline, and then 3% hydrogen peroxide and physiological saline. The total cleaning time was not less than 15 minutes each wound. A great quantity of 0.05% isoosmia iodophors (1 portion 0.5% iodophors stock solution + 9 portion physiological saline) was used to disinfect the wounds, not less than 5 minutes. Debridement was done keeping the integrity as far as possible with douching the inside part of laceration with 0.05% Iodophors. Passive immunity (Rabies Immunoglobulin or Rabies Antiserm), if necessary, was given at this time. After thorough cleaning and debridement, the laceration was left open in group A; while those in group B was closed immediately with 5/0 or 6/0 stylolite. Tetanus antitoxin (TAT) was given, if necessary. Drain of the wound was replaced or pulled out according to the drainage quantity, usually 24h-48h after operation. All the wounds were covered with sterilized dressing and changed dressings 24h-48h after operation. The stitches in group B was removed 5d-7d after operation according to the wound healing condition." Antibiotics were used only when there was infection and their effect was not mentioned.

Rui-Feng 2013 *(Continued)*

	Intervention group: laceration left open **Control group:** laceration closed immediately
Outcomes	**Infection rate:** a wound was defined to be infected if it met one of three major criteria: fever (body temperature ≥ 38°C), abscess, and lymphangitis; or four of five minor criteria: wound-associated erythema extending more than 3 cm from the edge of the wound, tenderness at the wound site, swelling at the site, purulent drainage, and white-cell count in the peripheral blood 12,000/mL. **Infection time:** interval from being bitten to emerging infection indication **Recovery time:** interval from being bitten to the wounds achieving clinical healing
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "all the patients were randomised by block randomisation and distributed to control group A and trail group B by block random digits table"
Allocation concealment (selection bias)	Unclear risk	None mentioned but hardly possible to do as trial group got sutured and control group did not - obvious difference
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Nothing mentioned. Due to the nature of the intervention blinding of participants and personnel is very difficult.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Nothing is mentioned. However it is not possible to be blinded to the intervention status for assessment of infection status.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up mentioned
Selective reporting (reporting bias)	Low risk	No trial registration or protocol for this study was found but all outcome data as mentioned in the study were reported.
Other bias	Unclear risk	Baseline for important confounders in two groups was not reported, except for gender.

Xiaowei 2013

Methods	**Method:** prospective randomised controlled trial **Setting:** Emergency Department, Peking University, People's Hospital, Beijing, China **Study duration:** April 2010 to April 2011
Participants	**Total individuals randomised:** 120 **Age:** average age was 28.1 ± 9.1 years (range 5 years to 67 years) in primary-closure group; 30.8 ± 8.8 years (range 6 to 68 years) in the delayed-closure group **Sex:** 36 males; 24 females (primary-closure group); 32 males; 28 females (delayed-closure group)

Xiaowei 2013 *(Continued)*

	Inclusion criteria: bite victims who sought medical attention at the emergency department with one or more lacerations were included in the wounds registry **Exclusion criteria:** patients requiring plastic surgery or with fractured bones muscle and tendon damage, visceral injury, bites by confirmed rabid dogs, congenital or acquired immunodeficency an artificial blood vessel, joint implantation, or a delay in presentation of more than 24 hours after the bite **Follow up of participants:** not stated
Interventions	**All groups:** at first presentation lacerations were copiously irrigated at high pressure with normal saline using a pulsatile wound lavage system to minimise infection. The irrigation pressure was approximately 69 kilopascal (kPa). Necrotic and devitalised tissues were debrided completely. Amoxicilin with clavulanic acid was administered orally for three days. Rabies immunoglobulin was infiltrated around the wound if needed. If wounds were found to be infected they were treated with intravenous antibiotics. **Intervention group:** (primary suture) wounds sutured in the emergency treatment room on the initial visit (suture method was simple interrupted suture) **Control group: (**delayed wound closure) wounds left open and the participants returned to hospital to have their dressing changed every day for three consecutive days
Outcomes	**Infection rate:** wound infection defined as the presence of a stitch abscess distance from cellulitis margin to wound margin ≧ 1 cm, or purulent drainage **Wound cosmesis:** scale evaluation at 3 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "we randomised participants using sequentially numbered opaque sealed envelopes in to two groups of primary suture or delay wound closure" Comment: no information on random sequence generation method
Allocation concealment (selection bias)	Low risk	Quote: "we randomised participants using sequentially numbered opaque sealed envelopes in to two groups of primary suture or delay wound closure"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Due to the nature of the intervention blinding of participants and personnel is very difficult.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The wound infection outcome assessment was done by physicians and it is not clear whether they were blinded or not. However it is not possible to be blinded to the intervention status for assessment of infection status. The figure reflects this as it is primary outcome of interest. Wound cosmetic scale evaluation was done by a professional plastic surgeon who was blinded to the intervention status and after three months
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up at the time of suture removal. All participants returned to hospital for a second wound evaluation in the first six months after their suture removal.
Selective reporting (reporting bias)	Low risk	No trial registration or protocol for this study was found but all outcome data as mentioned in the study were reported.

Xiaowei 2013 *(Continued)*

Other bias	Low risk	We did not detect any other bias.

Characteristics of excluded studies *[ordered by study ID]*

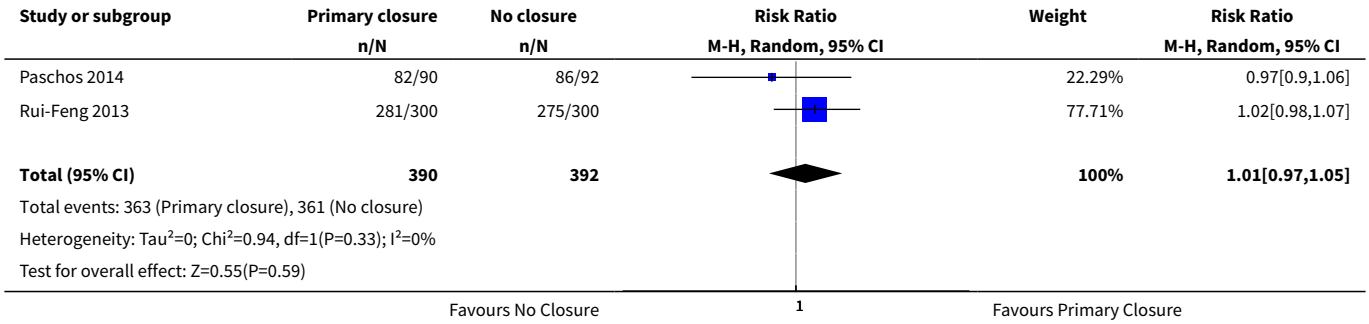
Study	Reason for exclusion
Cheng 2014	Improper study design: meta-analysis
Dellinger 1988	Non-relevant intervention: antibiotics
Morgan 1995	Improper study design: narrative review
Zubowicz 1991	Non-relevant intervention: antibiotics

DATA AND ANALYSES

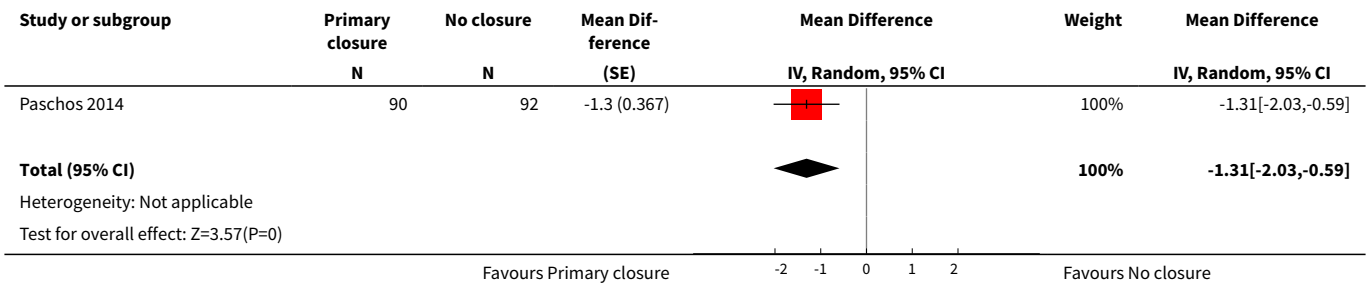
Comparison 1. Primary closure versus no closure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of wounds infection-free	2	782	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.97, 1.05]
2 Validated cosmetic outcome score	1	182	Mean Difference (Random, 95% CI)	-1.31 [-2.03, -0.59]

Analysis 1.1. Comparison 1 Primary closure versus no closure, Outcome 1 Proportion of wounds infection-free.



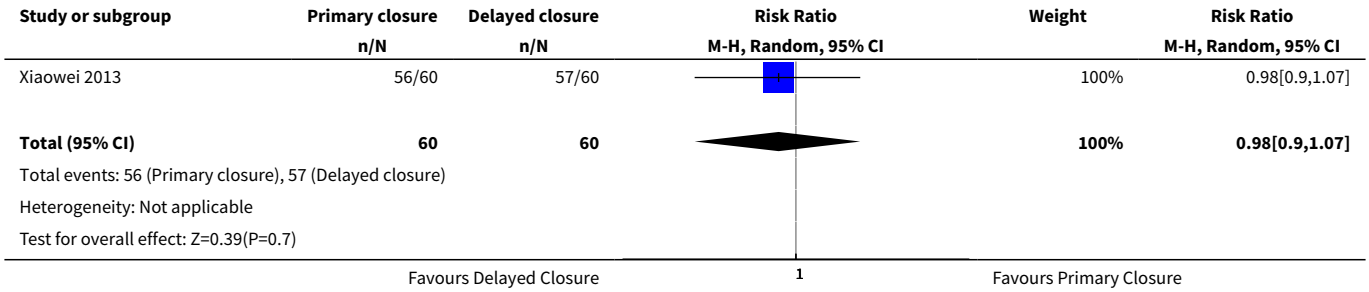
Analysis 1.2. Comparison 1 Primary closure versus no closure, Outcome 2 Validated cosmetic outcome score.



Comparison 2. Primary closure versus delayed closure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of wounds infection-free at 7 days	1	120	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.90, 1.07]

Analysis 2.1. Comparison 2 Primary closure versus delayed closure, Outcome 1 Proportion of wounds infection-free at 7 days.



ADDITIONAL TABLES

Table 1. Distribution of dog bites according to location in various trials

	Primary suture	No suture
Maimaris 1988		
Head and neck	27	14
Upper limb (including hand)	43	53
Lower limb	10	10
Torso/trunk	2	0

Table 1. Distribution of dog bites according to location in various trials *(Continued)*

Paschos 2014		
Head and neck	20	21
Upper limb (including hand)	40	43
Lower limb	16	17
Torso/trunk	6	5
Rui-Feng 2013		
Face	300	300
	Primary suture	**Delayed suture**
Xiaowei 2013		
Head and neck	0	0
Upper limb (including hand)	27	24
Lower limb	24	26
Torso/trunk	9	10

APPENDICES

Appendix 1. Search strategies

Cochrane Wounds Specialised Register

1 MESH DESCRIPTOR Mammals EXPLODE ALL AND INREGISTER
2 (animal* or mammal* or cat* or feline or dog* or canine or monkey* or primate* or donkey* or equine or human* or person* or rat* or bat* or bear* or squirrel* or gerbil* or rabbit* or "guinea pig" or "guinea pigs") AND INREGISTER
3 #1 OR #2
4 MESH DESCRIPTOR Bites and Stings EXPLODE ALL AND INREGISTER
5 bite* or bitten AND INREGISTER
6 #4 OR #5
7 #3 AND #6
8 MESH DESCRIPTOR Wound Closure Techniques EXPLODE ALL AND INREGISTER
9 MESH DESCRIPTOR Suture Techniques EXPLODE ALL AND INREGISTER
10 (primary near5 (closur* or sutur* or heal*)) AND INREGISTER
11 (immediate near5 (closur* or sutur* or heal*)) AND INREGISTER
12 MESH DESCRIPTOR Debridement EXPLODE ALL AND INREGISTER
13 MESH DESCRIPTOR Therapeutic Irrigation EXPLODE ALL AND INREGISTER
14 (delay* near5 (closur* or sutur* or heal*)) AND INREGISTER
15 (debridement* or irrigation*) AND INREGISTER
16 (wound* near5 (open* or "non closure" or "no closure" or unsutur* or "no suture" or "non suture")) AND INREGISTER
17 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
18 #17 AND #7

The Cochrane Central Register of Controlled Clinical Trials (CENTRAL)

#1 MeSH descriptor: [Mammals] explode all trees

#2 (animal* or mammal* or cat* or feline or dog* or canine or monkey* or primate* or donkey* or equine or human* or person* or rat* or bat* or bear* or squirrel* or gerbil* or rabbit* or "guinea pig" or "guinea pigs"):ti,ab,kw
#3 {or #1-#2}
#4 MeSH descriptor: [Bites and Stings] explode all trees
#5 (bite* or bitten):ti,ab,kw
#6 #4 or #5 in Trials
#7 {and #3, #6}
#8 MeSH descriptor: [Wound Closure Techniques] explode all trees
#9 MeSH descriptor: [Suture Techniques] explode all trees
#10 (primary near/5 (closur* or sutur* or heal*)):ti,ab,kw
#11 (immediate near/5 (closur* or sutur* or heal*)):ti,ab,kw
#12 MeSH descriptor: [Debridement] explode all trees
#13 MeSH descriptor: [Therapeutic Irrigation] explode all trees
#14 (delay* near/5 (closur* or sutur* or heal*)):ti,ab,kw
#15 (debridement* or irrigation*):ti,ab,kw
#16 (wound* near/5 (open* or "non closure" or "no closure" or unsutur* or "no suture" or "non suture")):ti,ab,kw
#17 {or #8-#16}
#18 {and #7, #17} in Trials

Ovid Medline

1 exp Mammals/
2 (animal* or mammal* or cat* or feline or dog* or canine or monkey* or primate* or donkey* or equine or human* or person* or rat* or bat* or bear* or squirrel* or gerbil* or rabbit* or "guinea pig" or "guinea pigs").ti,ab.
3 or/1-2
4 exp "Bites and Stings"/
5 (bite* or bitten).ti,ab.
6 or/4-5
7 and/3,6
8 exp Wound Closure Techniques/
9 exp Suture Techniques/
10 (primary adj5 (closur* or sutur* or heal*)).ti,ab.
11 (immediate adj5 (closur* or sutur* or heal*)).ti,ab.
12 exp Debridement/
13 exp Therapeutic Irrigation/
14 (delay* adj5 (closur* or sutur* or heal*)).ti,ab.
15 (debridement* or irrigation*).ti,ab.
16 (wound* adj5 (open* or "non closure" or "no closure" or unsutur* or "no suture" or "non suture")).ti,ab.
17 or/8-16
18 and/7,17
19 randomised controlled trial.pt.
20 controlled clinical trial.pt.
21 randomi?ed.ab.
22 placebo.ab.
23 clinical trials as topic.sh.
24 randomly.ab.
25 trial.ti.
26 or/19-25
27 exp animals/ not humans.sh.
28 26 not 27 (877769)
29 and/18,28

Ovid Embase

1 exp *mammal/
2 (animal* or mammal* or cat* or feline or dog* or canine or monkey* or primate* or donkey* or equine or human* or person* or rat* or bat* or bear* or squirrel* or gerbil* or rabbit* or "guinea pig" or "guinea pigs").ti,ab.
3 or/1-2
4 bite/ or bite wound/ or dog bite/
5 (bite* or bitten).ti,ab.
6 or/4-5
7 and/3,6
8 wound closure/ or exp suturing method/

9 (primary adj5 (closur* or sutur* or heal*)).ti,ab.
10 (immediate adj5 (closur* or sutur* or heal*)).ti,ab.
11 exp debridement/
12 exp lavage/
13 (delay* adj5 (closur* or sutur* or heal*)).ti,ab.
14 (debridement* or irrigation*).ti,ab.
15 (wound* adj5 (open* or "non closure" or "no closure" or unsutur* or "no suture" or "non suture")).ti,ab.
16 or/8-15
17 and/7,16
18 Randomized controlled trials/
19 Single-Blind Method/
20 Double-Blind Method/
21 Crossover Procedure/
22 (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or assign* or allocat* or volunteer*).ti,ab.
23 (doubl* adj blind*).ti,ab.
24 (singl* adj blind*).ti,ab.
25 or/18-24
26 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
27 human/ or human cell/
28 and/26-27
29 26 not 28
30 25 not 29
31 17 and 30

EBSCO CINAHL Plus

S31 S17 AND S30
S30 S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29
S29 TI allocat* random* or AB allocat* random*
S28 MH "Quantitative Studies"
S27 TI placebo* or AB placebo*
S26 MH "Placebos"
S25 TI random* allocat* or AB random* allocat*
S24 MH "Random Assignment"
S23 TI randomi?ed control* trial* or AB randomi?ed control* trial*
S22 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S21 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S20 TI clinic* N1 trial* or AB clinic* N1 trial*
S19 PT Clinical trial
S18 MH "Clinical Trials+"
S17 S7 AND S16
S16 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
S15 TI ((wound* N5 (open* or "non closure" or "no closure" or unsutur* or "no suture" or "non suture"))) OR AB ((wound* N5 (open* or "non closure no closure" or unsutur* or "no suture" or "non suture")))
S14 TI ((debridement* or irrigation*)) OR AB ((debridement* or irrigation*))
S13 TI ((delay* N5 (closur* or sutur* or heal*))) OR AB ((delay* N5 (closur* or sutur* or heal*)))
S12 (MH "Therapeutic Irrigation+")
S11 (MH "Debridement+")
S10 TI ((immediate N5 (closur* or sutur* or heal*))) OR AB ((immediate N5 (closur* or sutur* or heal*)))
S9 TI ((primary N5 (closur* or sutur* or heal*))) OR AB ((primary N5 (closur* or sutur* or heal*)))
S8 (MH "Suture Techniques+")
S7 S3 AND S6
S6 S4 OR S5
S5TI ((bite* or bitten)) OR AB ((bite* or bitten))
S4(MH "Bites and Stings+")
S3S1 OR S2
S2TI ((animal* or mammal* or cat* or feline or dog* or canine or monkey* or primate* or donkey* or equine or human* or person* or rat* or bat* or bear* or squirrel* or gerbil* or rabbit* or "guinea pig" or "guinea pigs")) OR AB ((animal* or mammal* or cat* or feline or dog* or canine or monkey* or primate* or donkey* or equine or human* or person* or rat* or bat* or bear* or squirrel* or gerbil* or rabbit* or "guinea pig" or "guinea pigs"))
S1(MH "Mammals+")

US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov)

closure OR suture OR sutures OR irrigate OR irrigation OR debride OR debridement | Bites

closure OR suture OR sutures OR irrigate OR irrigation OR debride OR debridement | Bites Dog

closure OR suture OR sutures OR irrigate OR irrigation OR debride OR debridement | Bites, Human

"animal bite" OR "mammalian bite" OR "dog bite" OR "cat bite" OR "canine bite" OR "feline bite" OR "monkey bite" OR "human bite" OR "donkey bite" OR "horse bite" OR "equine bite" OR "squirrel bite" OR "bear bite" OR "rat bite" OR "rabbit bite"

World Health Organization International Clinical Trials Registry Platform

bites OR bites OR bitten [Conditon] AND closure OR suture OR sutures OR irrigate OR irrigation OR debride OR debridement [Intervention]

(animal bite) OR (mammalian bite) OR (dog bite) OR (cat bite) OR (canine bite) OR (feline bite) OR (monkey bite) OR (human bite) OR (donkey bite) OR (horse bite) OR (equine bite) OR (squirrel bite) OR (bear bite) OR (rat bite) OR (rabbit bite)

Appendix 2. Cochrane tool for assessing risk of bias

1. Was the allocation sequence randomly generated?

Low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

High risk of bias

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

Unclear

Insufficient information about the sequence generation process provided to permit a judgement of low or high risk of bias.

2. Was the treatment allocation adequately concealed?

Low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.

High risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: use of an open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. envelopes were unsealed, non-opaque, or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information provided to permit a judgement of low or high risk of bias. This is usually the case if the method of concealment is not described, or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias

Any one of the following.

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

High risk of bias

Any one of the following.

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Unclear

Either of the following.

- Insufficient information to permit judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data are unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is not enough to have a clinically relevant impact on the observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following.

- Reason for missing outcome data are likely to be related to the true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is enough to induce clinically relevant bias in the intervention effect estimate.
- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is enough to induce a clinically relevant bias in the observed effect size.
- 'As-treated' analysis done with a substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Either of the following.

- Insufficient reporting of attrition/exclusions to permit a judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

5. Are reports of the study free of suggestion of selective outcome reporting?

Low risk of bias

Either of the following.

- The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).

High risk of bias

Any one of the following.

- Not all of the study's prespecified primary outcomes have been reported.
- One or more primary outcomes is/are reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified.
- One or more reported primary outcomes was/were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review is/are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

Insufficient information provided to permit a judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias

Low risk of bias

The study appears to be free of other sources of bias.

High risk of bias

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

Soumyadeep Bhaumik: conceived, designed and co-ordinated the review; extracted data; checked the quality of data extraction; analysed or interpreted data; undertook and checked quality assessment; produced the first draft of the review; approved the final review prior to submission; and is a guarantor of the review.

Richard Kirubakaran: designed the review; extracted data; checked the quality of data extraction; analysed or interpreted data; undertook and checked quality assessment; performed statistical analysis; checked the quality of the statistical analysis; contributed to writing or editing the review; wrote to study authors/experts/companies; approved the final review prior to submission; and is a guarantor of the review.

Sirshendu Chaudhuri: designed the review; extracted data; checked the quality of data extraction; analysed or interpreted data; undertook and checked quality assessment; checked the quality of the statistical analysis; contributed to writing or editing the review; approved the final review prior to submission; and is a guarantor of the review.

Contributions of the editorial base

Kurinchi Gurusamy (Editor): edited the protocol; advised on methodology, interpretation and protocol content; approved the final protocol prior to submission.

Gill Norman (Editor): edited the review; advised on methodology, interpretation and review content; approved the final review prior to submission.

Gill Rizzello (Managing Editor): co-ordinated the editorial process; advised on interpretation and content; edited the protocol and the review.

Rocio Rodriguez Lopez, Naomi Shaw and Sophie Bishop (Information Specialists): designed and edited the search strategy and search methods section of the protocol and the review and ran the searches.

Ursula Gonthier and Tom Patterson (Editorial Assistants): edited the references and Plain language summary.

DECLARATIONS OF INTEREST

Soumyadeep Bhaumik: none known.
Richard Kirubakaran: none known.
Sirshendu Chaudhuri: none known.

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Internal sources

- Liverpool School of Tropical Medicine, UK.

  SB was as student in LSTM for the major part of the review and received logistical support.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not conduct handsearching of abstracts of related conferences, as mentioned in the protocol, due to pragmatic reasons. We could not carry out any subgroup analyses, or funnel plots for publication bias, due to the small number of studies.

In Paschos 2014, participants were included up to 48 hours from the bite event. We decided to include this trial as it is the most recent trial on the issue and we conducted a sensitivity analyses to examine the effect of this decision.

We have included the data for the outcome of validated cosmetic outcome score from Paschos 2014 even though the evaluation was done at four weeks, which is not in keeping with our original eligibility criteria which required such data at 14 days. We have done this because this was the only trial which has information for this outcome and the information is still clinically meaningful for decision making.

The calculation for optimal information size (using the 20% relative risk reduction criteria for assessment of precision using the GRADE criteria) was done on a post-hoc basis during the review phase.

We have included information on cosmesis, which is a secondary outcome in the 'Summary of findings' table, however this was not planned in the protocol. All primary outcomes apart from one were either not reported or not reported in a format suitable for our purpose.

INDEX TERMS

Medical Subject Headings (MeSH)

*Bites and Stings; *Wound Healing; Randomized Controlled Trials as Topic; Soft Tissue Injuries [*therapy]; Wound Infection [*epidemiology] [prevention & control]

MeSH check words

Humans