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Does the use of topical honey result in a faster rate of second intention wound healing in dogs?

A Knowledge Summary by

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Editorial notice: Upon conducting the literature search for this Knowledge Summary the author discovered that the same paper had been published in two separate journals and that a third paper by the same author appeared to have used data from the same experimental subjects as the duplicate publication, despite reporting different methodology. The duplicate publications have been appraised by the author as one paper. The editorial office alerted the journals in question which resulted in the article that appeared in the Iranian Journal of Veterinary Surgery (Jalali, F.S. S., Tajik, H., Saifzaideh, S and Fartash, B. (2007b) Topical Application of Natural Urmia Honey on Experimental Burn Wounds in the Dog: Clinical and Microbiological Studies. *Iranian Journal of Veterinary Surgery.* 2(2), 13–21) being retracted: http://www.ivsajournals.com/article_114759.html. See our own policy on duplicate publication for more information.

KNOWLEDGE SUMMARY

PICO question

In healthy dogs undergoing open wound management, does the topical application of honey, when compared to wounds treated with daily saline washes only, reduce the time to complete wound healing?

Clinical bottom line

Category of research question

Treatment

The number and type of study designs reviewed

Two studies satisfied the inclusion criteria for answering the PICO; both were prospective randomised controlled trials

Strength of evidence

Weak

Outcomes reported

The studies demonstrated a possible effect size of clinical importance of the use of honey in the treatment of canine wounds in terms of time to complete wound healing and antibacterial effect. However, the strength of the evidence provided by both studies is severely weakened by flaws in trial design, implementation and reporting, and the possible risk of pseudo replication between the two trials reported

Conclusion

The use of topical honey in canine open wound management may reduce time to complete wound healing. However, the evidence for this is weak. At present, the evidence that use of topical honey in canine wounds reduces time to healing is insufficient to warrant a change in clinical practice

How to apply this evidence in practice

The application of evidence into practice should take into account multiple factors, not limited to: individual clinical expertise, patient's circumstances and owners' values, country, location or clinic where you work, the individual case in front of you, the availability of therapies and resources.

Knowledge Summaries are a resource to help reinforce or inform decision making. They do not override the responsibility or judgement of the practitioner to do what is best for the animal in their care.

Clinical Scenario

A 7-year-old, male neutered Standard Poodle acquired an open wound to the left lateral thorax after having been accidentally scalded with boiling water. The initial dimensions of the wound were approximately 4 cm x 2 cm. The wound was irrigated daily with sterile saline solution and dressed with a non-adhesive dressing. The wound was considered fully healed, defined as fully epithelialised with no eschar or scabbing, 28 days after the accident. Would the topical application of honey have resulted in a shorter time to wound healing in this patient?

The evidence

A systematic literature search found three papers relevant to the PICO (Jalali et al., 2007a; Jalali et al., 2007b; and Jalali et al., 2007c). However, two papers (Jalali et al., 2007a; and Jalali et al., 2007b) were confirmed to be the same paper published in two separate journals and have been designated a duplicated publication. Consequently, two papers in total have been critically reviewed for this knowledge summary. It was also noted that Jalali et al. (2007a/b) and Jalali et al. (2007c) appear to have used data from the same experimental subjects, despite reporting different methodology.

Both the studies by Jalali et al. (2007a/b; and 2007c) were prospective randomised controlled trials using experimentally induced burn wounds in dogs. They both reported that honey decreased the time to wound healing in dogs when compared to the saline-treated control. Objective outcomes measured by Jalili et al. (2007a/b) and Jalali et al. (2007c) included observation of macroscopic wound changes during healing and qualitative and quantitative microbial assessment of the wounds at days 0 and/or 1, 3, 7, 14 and 21 and compared with a saline control. In addition, Jalali et al. (2007a/b) measured the reduction of the wound area over time and Jalali et al. (2007c) compared the microscopic appearance of honey-treated and control wounds at day 21.

Neither study provided a definition for complete wound healing nor had a clearly stated endpoint and both appear to have concluded before wound healing was complete (Jalali et al., 2007a/b; and Jalali et al. 2007c). As a result, 'time to wound healing', considered a fundamental outcome measure for the PICO was not reported, despite the authors claiming it was a primary objective. Furthermore, the results relied heavily on subjective descriptive narrative, were profoundly exposed to the influence of bias and often overstated. Consequently, the confidence that the effect reported resembles the actual effect of honey on wounds is low, the evidence cannot be used to answer the PICO reliably and, by extension, inform a change in clinical practice.

Summary of the evidence

Jalali et al. (2007a and 2007b)	
Population:	Healthy, adult (4.5 ± 0.5 years old), medium sized (20 ± 4.25 kg) 'mongrel' dogs of both sexes
Sample size:	10 wounds (10 dogs)
Intervention details:	• Healthy dogs were selected on the basis of a physical examination and blood test ('CBC' and serum biochemistry). • Animals were kept in individual cages and had access to food and water *ad libitum*. • Honey samples, from Targarvar Bee Keeping Corporations, Urmia, were filtered with a sterile mesh and stored at 2–8 ^{o}C until used. • Five dogs were randomly assigned to either a control (CG) or honey treatment (HTG) group and then anaesthetised (anaesthetic protocol provided) and a single experimental burn wound on the dorsum (Hoekstra model - Brans et al., 1994), resulting in a wound area of 2 cm x 3 cm. • In the experimental group, 10 ml of undiluted Urmia honey was applied once daily. • In the CG, the burns were treated with normal saline. • After daily treatment, all wounds were covered with a non-adhesive dressing.

	• All wounds were observed for evidence of infection, exudation or leakage until healing. • On days 0, 7, 14 and 21, quantitative and qualitative microbiological assessments were carried out for each wound. • Digital photographs of each wound were taken on days 0, 7, 14 and 21. Photographs were scanned and wound areas measured using digital scanning software (SigmaScan Pro 5.0 software).
Study design:	Non-blinded, prospective randomised controlled study
Outcome studied:	**Primary outcomes:** • Description of macroscopic changes during wound healing including degree of exudation, oedema, formation of granulation tissue and presence of epithelialisation (subjective). • Wound area in mm^2 and % decrease in wound area on days 0, 7, 14, 21 (objective). **Secondary outcomes:** • Qualitative description of microbial population on days 0 (methods) and/or 1 (abstract), 7, 14, 21 (objective). • Quantitative estimation of bacterial numbers (x 10^5 cm^{-1}) day 0 (methods) and/or 1 (abstract), 7, 14, 21 (objective). **Statistical analysis:** • An unpaired student's t-test was used to compare the two groups for bacterial count and wound area size. A $p < 0.05$ was used to indicate significance.
Main findings: (relevant to PICO question):	• **Description of macroscopic changes (subjective, generalised commentary comparing all wounds across both groups):** **Day 1 and 2**: No gross difference in wound appearance between the treatment groups (HTG and CG); inflammation and exudation observed. **Day 7**: Crusting of HTG wounds with evidence of epithelialisation. CG wounds still inflamed and exudative. **Day 14**: HTG wounds reduced considerably in size and recognised as healed, the wounds of the CG were still crusting. **Day 21**: The wounds of the HTG were approximately closed; the wounds of the CG were still crusting. These results indicate a possible treatment effect of honey, although it is impossible to determine its magnitude. • **Comparison mean wound area reduction (mm^2):** **Day 0:** HTG (n = 5) 688.60 mm^2, standard deviation (SD) = 42.22 mm^2.

	CG (n= 5) 644.18 mm^2, SD = 64.86 mm^2. No significant difference between the groups at day 0. **Day 7:** HTG (n = 5) 364.40 mm^2, SD = 16.26 mm^2. CG (n = 5) 486.60 mm^2, SD = 44.82 mm^2. The mean wound size of the HTG at day 7 is significantly smaller ($p < 0.05$. **Day 14:** HTG (n = 5) 62.24 mm^2, SD = 24.44 mm^2. CG (n = 5) 206.86 mm^2, SD = 48.26 mm^2. The mean wound size of the HTG is significantly smaller than the CG at day 14 ($p < 0.05$. **Day 21:** HTG (n=5) 10.64 mm^2, SD = 8.64 mm^2. CG (n = 5) 89.58 mm^2, SD = 12.84 mm^2. The mean wound size of the HTG at day 21 is significantly smaller than the CG ($p < 0.05$. • **Qualitative description of microbial population:** **'Before commencement of the study [*sic*]'**; *Escherichia coli, Staphylococcus aureus, Streptococcus pyogenes* and *Candida albicans* were isolated from the skin of dogs in both groups. **Day 1, 3 and 7**; *S. aureus* and *E. coli* were isolated from wounds of the HTG. *E. coli, S. aureus, S. pyogenes* and *Candida albicans* were isolated from the wounds of the CG dogs. **Day 14;** *S. aureus* and *E. coli* were isolated from the wounds of the HTG. *S. aureus* and *E. coli* from the CG. **Day 21;** *S. aureus* was isolated from the HTG and the CG. The spectrum of microbial colonisation is comparable to those of burn wounds in studies elsewhere. • **Quantitative estimation of mean (assumed) microbial count (cm^{-2}):** **'Before commencement of the study':** HTG = 9.00 x 10^5 cm^{-2}, SD = 0.50 x 10^5 cm^{-2}. CG = 2.00 x 10^4 cm^{-2}, SD = 0.60 x 10^4 cm^{-2}. The bacterial count of the HTG is significantly higher than the CG at day 0 of the study ($p < 0.05$, calculated by L Marcombes). **Day 1:** HTG = 5.00 x 10^5 cm^{-2}, SD = 0.60 x 10^5 cm^{-2}. CG = 3.00 x 10^4 cm^{-2}, SD = 0.60 x 10^4 cm^{-2}. The bacterial count is significantly higher in the HTG on day 1 ($p < 0.05$, calculated by L Marcombes). **Day 7:** HTG = 1.00 x 10^6 cm^{-2}, SD = 0.6 x 10^6 cm^{-2}. CG = 7.00 x 10^5 cm^{-2} SD = 0.6 x 10^5 cm^{-2}. On day 7 there is not significant difference in mean microbial count between the HTG and CG.

	Day 21: HTG = 3.00 x 10^4 cm^{-2}, SD = 0.30 x 10^4 cm^{-2}. CG = 3.00 x 10^5 cm^{-2}, SD = 0.50 x 10^5 cm^{-2}. At day 21 the mean bacterial count of the CG is significantly higher than the HTG ($p < 0.05$.
Limitations:	• The randomisation process was not adequately described. • There was a lack of blinding for the evaluation of outcomes. • The start and end point of the study was poorly defined. • The duration of the study was stated to be 28 days; however, data was only collected up to day 21. This loss of data is unexplained. • The end point (21 days) was not justified. • The sample size was very small and not justified by a power calculation. • No null hypothesis was provided for statistical testing. • Time taken to wound healing for each wound was stated as a measured outcome, however this was not reported. • A definition of complete wound healing was not given. • It was not stated whether or not there were any losses from the study. • The methodology for quantitative and qualitative microbiological data collection was not adequately described. • The described methods were not consistent with reported results; it was stated microbiological assessment was done on days 0, 7, 14 and 21. However, microbiology data of both groups was reported for day 1 and 3 instead of day 0. No reason was given for this discrepancy. • The collection of microbial data on day 3 was not mentioned in the methods section. • There is an inconsistency in naming timepoints (e.g. “day 0” and “before commencement of the study”), they are used interchangeably and without justification. • For the gross macroscopic changes, quantitative and qualitative microbial data, it is not clear if the results given are of individual wounds or an overall trend in the study group. • The treatment group had a significantly higher microbiological count prior to the study, an indication the two groups were not from the equivalent populations prior to the study. • The authors fail to discuss why microbial count increased in the HTC during the first 7 days when they claimed their results showed an antimicrobial effect. • There was no discussion of study limitations and an overall tendency to overstate findings; the phrase “potent topical agent” is used to describe honey in the abstract. • The standard used for the method of burn injury was based on a porcine model, the suitability of this standardisation for canine skin is an assumption. • The results of a stated outcome measure (time to wound healing) were inadequately reported.

	• The identical paper appears to have been published in two separate journals, which constitutes a potential violation of the ethics of academic publication, a possible infringement of copyright law, and pads the evidence-base with redundant material. • The paper reports almost identical results to another publication (Jalali et al., 2007c), despite discrepancies and omissions between the methods of the two studies, which calls into question the authenticity of the results. • Data missing for quantitative microbial count on day 3 and day 14. • A significantly higher bacterial count in the HTG at day 0 suggests this study was not adequately controlled. • Conflicts of interest (or absence of) not declared.

Jalali et al. (2007c)	
Population:	Adult (4–5 years old), medium sized (21 ± 4.24 kg), 'mongrel' dogs of both sexes
Sample size:	15 wounds (15 dogs), five wounds per study group

Intervention details:	• The animals were kept in individual cages.
	• The dogs were randomly divided into three study groups: control (CG = 5); honey treatment (HTG = 5); and silver sulphasalazine treatment (SSD = 5).
	• All animals were anaesthetised (anaesthetic protocol given) and an experimental 2 cm x 3 cm burn was created using a standardised technique (Hoekstra model) over the dorsal thoracolumbar area.
	• Honey was sourced from beehives in Urmia, filtered with a sterile mesh and stored at 2–8 ^{o}C. The samples were collected and prepared by one investigator while experiments were performed blindly by the others.
	• The groups had received the following treatment:
	  ○ Control: daily washing with saline.
	  ○ Honey-treated: wounds were washed daily with normal saline then 5 ml of honey was administered topically.
	  ○ SSD-treated wounds: 5 ml of 1% SSD ointment applied.
	• All wounds were covered with non-adhesive dressing after daily treatment.

Study design:	Prospective blinded randomised controlled trial
Outcome studied:	**Primary outcomes:** • Time taken to complete wound healing • Description of macroscopic changes during wound healing including degree of exudation, oedema, formation of granulation tissue and presence of epithelialisation (subjective). • Description of microscopic features of wound healing at day 21 (subjective).

	Secondary outcomes: • Qualitative description of microbial population on days 1, 7, 14, 21 (objective). • Quantitative estimation of bacterial numbers (x 10^5 cm^{-1}) day 1, 7, 14, 21 (objective). **Statistical analysis:** • The time taken to healing and total bacterial count of the three groups were compared for significant difference using a one-way analysis of variances (ANOVA). A $p < 0.05$ was considered significant.
Main findings: (relevant to PICO question):	**(Data set for SSD treatment group has been omitted as not relevant to the PICO question)** • **Time taken to complete wound healing:** HTG: all wounds considered fully healed on day 21**.** CG**:** Not reported; however, not fully healed by day 21. • **Observation of gross wound healing:** **Day 1, 2:** No difference in appearance (necrosis and inflammation) between HTC and CG. **Day 7:** HTG wounds showed signs of epithelialisation, whereas the CG wounds retained an inflammatory appearance. **Day 14:** The HTG wounds were at a more advanced stage of healing than the CG. **Day 21:** HCG were almost completely healed, whereas wounds of the CG were still significantly ulcerated. • **Observation of microscopic wound healing:** **Day 21:** HTG had microscopic features of more mature granulation tissue and reduced inflammatory cells population when compared to the control group. • **Qualitative microbial assessment:** **Day 1, 3, 7:** *Candida albicans, S. pyogenes, S. aureus* and *E. coli* were isolated from CG, and *S. aureus* and *E. coli* isolated from the HTG. **Day 14:** *S. aureus* and *E. coli* were isolated from CG and the HTG. **Day 21:** *S. aureus* was the only isolate found in the control and treatment groups. • **Quantitative estimation of mean (assumed by the author of this Knowledge Summary) microbial count (cm^{-2}):** **'Before the use of preparations':** HTG = 9.00 x 10^5 cm^{-2}, CG = 2.00 x 10^4 cm^{-2}. Mean values only provided, so unable to calculate the significance of the difference between the two groups. **Day 21:** HTG = 3.00 x 10^4 cm^{-2} CG = 3.00 x 10^5 cm^{-2}. Microbial count in HTG group is significantly lower at day 21 ($p < 0.05$).

Limitations:	• The process of randomisation was not adequately described. • The process of blinding was not adequately described, particularly as it is a challenge to use honey in blinded trials due to its appearance and odour. • The start and end point of the study was poorly defined. • A definition of wound healing was not given. • Experimental subjects were not adequately screened for co-morbid disease and generally very limited information was provided about their environment during the study. • The end point (21 days) was not justified. • A small study population was used and there was no power calculation to justify this. • No null hypothesis given for statistical testing • The methodology for quantitative and qualitative microbiological data collection was not adequately described. • Qualitative and quantitative microbial data provided for "day 3", despite this not being mention in abstract or methods. • The authors fail to discuss why microbial count increased in the HTG during the first 7 days when they claimed their results showed an antimicrobial effect. • The standard used for the method of burn injury was based on a porcine model, the suitability of this standardisation for canine skin is an assumption. • It is not stated if any animals/wounds were lost to the study. • Time to healing for the CG is not given. • Most of the results were given over to a generalised narrative of macroscopic and microscopic features of healing in the three groups, which is highly subjective and impossible for the reader to draw any meaningful conclusion. • Microbial outcomes are identical to data published elsewhere (Jalali et al., 2007a/2007b) which suggests the same experimental data set has been used, despite having been subjected to different methodology. • Incomplete reporting of statistical analysis. • For the gross macroscopic and microscopic changes, and quantitative and qualitative microbial data, it is not clear if the results given are of individual wounds or an overall trend in the study group. • There is an inconsistency in naming timepoints (e.g. 'day 0' and 'before commencement of the study'), they are used interchangeably and without justification. • Quantitative microbial data not adequately reported. • Conflicts of interest (or absence of) not declared.

Appraisal, application and reflection

Numerous clinical properties have been attributed to honey, including antimicrobial activity, a debriding action, anti-inflammatory effect, antioxidant activity, stimulation of wound granulation and epithelialisation (Van Hengel et al., 2013). This has prompted a degree of research activity in the veterinary and human medicine fields to determine if these properties have a clinical application in wound healing.

This Knowledge Summary seeks to appraise the evidence for the effect of topically applied honey on the healing rate in canine wounds when compared to a saline control. A literature search initially found three papers that met the search criteria (Jalali et al., 2007a; 2007b; and 2007c). Two papers (Jalali et al., 2007a; and 2007b) were found to be an identical manuscript in two different journals and therefore have been treated as a single publication in this summary. Furthermore, the third study by this group, (Jalali et al., 2007c), is strongly suspected of having derived data from the same experimental procedure, despite there being a disparity in the methods used and outcomes measured, which degrades the evidence.

The measurement of wound healing of the skin is a visual process and therefore, one would intuit, relatively easy to implement in the experimental setting. However, care must be taken to ensure that appropriate end points are used and to minimise the risk of bias in measurements (Gottrup et al., 2010). A further challenge to experiments involving topical wound treatments is the difficulty of implementing an effective blinding protocol. This is particularly tricky in the case of honey, with its distinct colour and odour. Both papers (Jalali et al., 2007a/b; and Jalali et al., 2007c) used an unjustified end point of 21 days, and Jalali et al. (2007c) claimed that their trial was blinded, although the method of blinding was not reported. It was not stated by Jalali et al. (2007 a/b) whether or not blinding was used.

The experimental variable most relevant to the PICO is time to complete wound healing. Both studies (Jalali et al., 2007a/b; and Jalali et al., 2007c) claimed to have measured this, despite having failed to define complete wound healing. In addition, both used an end point which appeared to be set before wound healing was complete in the control groups. Overall, the results provided were ambiguous, with opaque, sweeping statements such as 'on day 21, the wounds gaps of treatment group [*sic*] were approximately closed' (Jalali et al., 2007 a/b). As it is apparent that the trials were concluded before the wounds were fully healed, they cannot provide the evidence most pertinent to the PICO.

Jalali et al. (2007a/b) instead recorded the wound healing rate by measuring the reduction of wound area over time. This has been shown to be a useful comparator between treatment groups in human studies (Gotrupp et al., 2010). The method for measuring wound area, however, needs to be carefully standardised as measurements can be subject to over-estimation of up to 44% due to irregular wound shape (Schutz et al., 2005) and therefore risk of under-estimation of the rate of healing. Jalili et al. (2007 a/b) measured this outcome using computer-assisted analysis of digital photographs. The software used, SigmaScan Pro 5.0 (SPSS Science, Chicago, IL), has been shown to have an accuracy within 4.7% (95% CI 3.4% – 5.9%) (Molnar et al., 2009) and so there is confidence that measurements taken using this method should yield reliable results, which here have demonstrated that the mean honey treated wound area was significantly smaller than the control at days 7, 14 and 21 ($p < 0.05$).

Both papers (Jalili et al., 2007a/b; and Jalali et al., 2007c) used qualitative and quantitative microbiological data as evidence that honey possesses antibacterial properties. The qualitative data consisted simply of a list of the micro-organisms isolated from each group at days 0 (Jalali et al., 2007 a/b), 1 (Jalali et al, 2007c), 3, 7, 14 and 21 days. The spectrum of isolates over time was similar for both groups, and the authors did not comment further on this, except to state the range organisms isolated were similar to those of a historical human study (Lawrence, 1994) Therefore the relevance of this variable to the PICO remains poorly elaborated and its evidential value doubtful.

The quantitative bacterial results (Jalili et al., 2007a/b; and Jalali et al., 2007c) showed bacterial counts from the honey-treated wounds were significantly lower at day 21 ($p < 0.05$) and the authors claimed that this demonstrated an antimicrobial effect. However, the data also showed a higher bacterial count in the honey-treated group up to day 14, which appears to contradict this claim, and this anomaly was not discussed. The discrepancy was, however, mitigated by the fact that wounds in the treatment group appeared to have had a significantly higher bacterial count at day 0. But then this would suggest the control and treatment groups were not equivalent and that the trial was not adequately controlled.

A systematic review has shown of human burns studies has shown that high wound bacterial counts may predict worse clinical outcomes (Halstead et al., 2018). They also found that wound swabs are relatively insensitive in discriminating clinically significant wound infection from incidental wound contamination, and that serial tissue culture, via biopsy, is a superior technique for quantifying bacterial load of wounds. Consequently, the quantitative microbial data derived from wound swabs by Jalali et al. (2007a/b; and 2007c) is unlikely to be reliable, and so this variable cannot be used to answer the PICO. It was also noted that the microbiological data reported by both papers were identical, suggesting it was derived from the same experimental procedure, despite differing methodology.

A recent Cochrane review of the use of honey in human wound healing (Jull et al., 2015) reported there was some good quality evidence that honey heals partial thickness burns more quickly than conventional dressings, and that honey is more effective than antiseptic for healing infected post-surgical wounds. However, the authors were ultimately obliged to downgrade most of the evidence derived from the 26 studies found, due to high risk of bias and problems of study design. Which are issues similar to those identified in the papers that have been appraised for this Knowledge Summary.

An early draft of the PICO had specified Manuka Honey as the treatment intervention. Honey from different flower sources vary in their biological properties, and monofloral Manuka honey is considered to possess antibiotic and antioxidant properties superior to those of honey derived from other sources (Alvarez-Suarez et al., 2014). It is the medical-grade form of Manuka honey that is used most widely and it was considered that studies using Manuka honey would be most relevant to clinical practice. Somewhat surprisingly, no studies using Manuka honey on canine wounds were found, and the PICO had to be expanded to encompass all forms of honey. Jalili et al. (2007a/b) and Jalali et al. (2007c) used Urmia honey, which was not medically graded and therefore likely to limit relevance to clinical veterinary practice.

A couple of studies were found that tested Manuka honey in experimental wounds in other species. A randomised, controlled study in equine patients (Bischofberger et al., 2013), of moderate evidential quality, supported the hypothesis that honey reduces time to complete wound healing, here defined as 'when granulation tissue was no longer visible'. In addition, Haryanto et al. (2012) have shown that Manuka honey accelerates the formulation of granulation tissue during wound healing in mice.

Honey is purported to possess properties that provide favourable healing conditions for every stage of the healing pathway (inflammatory, debridement, granulation, contraction/epithelialisation). However, this is in contrast to the general convention in veterinary clinical practice of limiting the use of honey to the inflammatory and debridement stages only (Van Hengel et al., 2013). Nakajima et al. (2013) observed that Japanese honey appeared to retard the granulation and contraction phases of wound healing in a murine model. Furthermore, Haryanto et al. (2012) demonstrated, also in a murine model, that Manuka honey might delay the wound-contraction phase. This highlights the need for future studies that adopt a study design which discriminates between the healing phases, as this may allow a more substantial treatment effect of honey to be demonstrated.

This Knowledge Summary has found that there is weak evidence (Jalali et al., 2007a/b; and Jalali et al., 2007c) that topical honey may have reduced the healing time from 28 days in the clinical scenario case. However, this evidence is of such low quality due to the high risk of bias, problems with the study design, and ambiguous

results of the two papers appraised, that it cannot be used to justify a change in clinical practice. Although, supported by the better-quality evidence found elsewhere, it does justify further research effort into the effect of topical honey on wound healing rate. Adequately powered, randomised and blinded trials, using medical grade Manuka honey, and scrutinising each healing stage may be powerful enough to reveal a treatment effect that has been diluted in studies to date. The confirmed antibiotic effect of honey in the clinical setting would be of particular interest as a means of reducing the use of systemic antibiotics in canine wound care.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts on OVID interface (1973–2020 week 05) PubMed on the NCBI interface (1960–2020 week 05)
Search terms:	CAB Abstracts: 1. (dog or dogs or canine* or canis or bitch* or puppy or puppies or pup or pups).mp. or exp dogs/ or exp bitches/ or exp puppies/ or exp canidae/ or exp canis/ 2. (wound* or lesion* or burn* or abrasion* or ulcer* or 'infected wound' or 'open wound' or 'wound breakdown').mp. or exp wounds/ 3. (honey* or Manuka or inhibines or apipharmacothera*).mp. or exp honey/ 4. (heal* or improv* or regenerat* or epitheli* or harm* or advers* or toxic* or efficac* or safe* or effect* or hyperaem* or angiogen* or granulat* or contract* or antimicrob* or anti-microb* or 'anti microb' or antibacter* or anti-bacter* or 'anti bacter*' or 'secondary intention').mp. or exp antibacterial agents/ 5. 1 and 2 and 3 and 4 PubMed: 1. dog OR dogs OR canine OR canis OR bitch OR bitches OR puppy OR puppies OR pup OR pups 2. wound OR lesion OR burn OR abrasion OR ulcer OR infected wound OR open wound OR wound breakdown 3. honey* or Manuka or inhibines or apipharmacothera* 4. 1 and 2 and 3
Dates searches performed:	13 Feb 2020

Exclusion / Inclusion Criteria	
Exclusion:	Conference proceedings, single case reports, case series, non-systematic reviews, articles not relevant to the PICO, articles that were not accessible and chapters from textbooks. Any language not in the English or French language. Studies that used honey mixed with another substance.
Inclusion:	Studies that used dogs as subjects, studies that involved more than one animal, or controlled trials. The studies were required to examine the effect of topical honey on canine wounds.

Search Outcome							
Database	**Number of results**	**Excluded – Proceedings, single case reports, etc.**	**Excluded – Not relevant to the PICO**	**Excluded – In a language other than English or French**	**Excluded - Duplicated publication**	**Excluded – Not accessible**	**Total relevant papers**
CAB Abstracts	79	17	57	2	1	0	2
PubMed	23	1	22	0	0	0	0
Total relevant papers when duplicates removed							**2**

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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