Dental care as a risk factor for transfusion transmissible infections in blood donors: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND AND OBJECTIVES. The deferral policy for blood donation after dental care is based on the precautionary principle. The aim of this systematic review is to give an overview of the scientific evidence concerning the risk of transfusion transmissible infections (TTI's) after dental care.

MATERIALS & METHODS. Four databases were searched: Medline, the Cochrane Library, Embase and Web of Science. Screening was independently performed by two reviewers. The quality of evidence was evaluated using the GRADE principle. A meta-analysis was performed to assess the association between dental treatment and TTI markers.

RESULTS. 22 studies were included. Meta-analysis of 16 studies showed an increased association of TTI's with dental treatment, however with large heterogeneity. Subgroup analysis revealed a significant increased association of HBV with dental treatment (OR 1.79, 95%CI [1.48;2.18]). There was conflicting evidence concerning the risk of HCV. One study could not demonstrate a statistically significant increased association of HTLV-1 with dental treatment.

Three studies showed a significant increased association of HCV with tooth extraction (OR 1.48, 95%CI 1.11;1.97)). Finally, there is conflicting evidence concerning the risk of HBV or HCV after dental cleaning. One study could not demonstrate an association between HIV and dental cleaning. All evidence is of very low certainty and results cannot be considered precise.

CONCLUSION. Studies of high quality concerning the risk of TTI after dental care in blood donors are scarce. An association of HBV after dental treatment and HCV after tooth extraction was demonstrated but evidence is of very low certainty. The currently identified studies are of too low certainty to make any suggestions regarding the value of deferral or deferral times.

KEYWORDS: blood donation, dental care, systematic review, transfusion transmissible infection,

What is known about the topic?

- Dental care is a common reason for blood donor exclusion.
- The deferral policy for blood donation after dental care is based on the precautionary principle.
- Current deferral policy for dental care is based on the assumption that only transient bacteraemia might pose a problem.

What does this paper add?

- Viral infections after dental care might also pose a problem for the safety of donor blood.
- Studies of very low quality show an association between hepatitis B virus infection and dental treatment in blood donors. Limited evidence shows an increased risk of hepatitis C after tooth extraction.
- The currently identified studies are of too low quality to make any suggestions regarding deferral policy. More high-quality studies are necessary to investigate the relationship between dental treatment and TTI's.

INTRODUCTION

Blood donation and transfusion are a hallmark of modern healthcare. An adequate supply of safe blood products is therefore invaluable. Because of this, blood donor selection is needed to minimize the risk of infection for the recipient of the blood product. Blood donor deferral measures are essential to modern blood-banking since they are effective and can be implemented rapidly in case of emerging threats (e.g. HIV in the 1980's) ¹⁻³.

In general, the available evidence for current deferral reasons is of low quality, and for 60% of the top 30 reasons for excluding donors in Belgium, no evidence was found. Therefore, to maximize safety, exclusion criteria are always defined with a broad safety margin. This is called the precautionary principle, which implies that in the interest of public health, risk management actions should be taken even in the absence of certainty about risk, thus aiming for maximum safety ¹.

Blood donor deferral is based on a questionnaire filled out by the donor. This questionnaire aims to disclose risks for adverse reactions to the donor or infection of the recipient. Questions directed at donor safety include age, interval between donations, pregnancy and use of medication. To protect the recipient from possible TTI's, donors are screened for foreign travel, surgery, procedures involving needles, exposure to human blood, drug use, sexual risk behaviour, acute or chronic illness, vaccination history and dental care ³. In Flanders, Belgium, 4% of the deferrals for blood donation is because of recent dental care ¹.

The oral cavity is a natural habitat for a large number of microorganisms. Routine dental care procedures are generally open and invasive with possible skin and probable mucosal lesions and thus can pose a significant risk of cross-contamination and even systemic infection. This is of particular importance to transfusion medicine since systemic infection after dental care may include TTI's and thus does not only put the donor but also the receiver of blood products at risk of viral and bacterial infections ^{4, 5}.

Contamination in the dental office may occur through different pathways. A first possible pathway is through the instruments and surfaces used in dental care: patient-to-patient transmission of pathogens may occur by not properly sterilizing equipment used before, during or after dental care. A second possible pathway is the dental care staff (dentists, assistants) who can cause contamination by not adopting hygiene protection measurements such as dental/surgical masks covering nose and mouth and single-use gloves. Finally, aerosols created by dental equipment or tap water used to rinse after the procedure

when skin or mucosal lesions are present, may cause contamination with pathogens present in the dental unit waterlines ^{6, 7}. Other factors influencing patient contamination during dental care are the patients' immune status, dose of pathogen transmitted, virulence of the pathogen as well as frequency of exposure ⁴.

Throughout the last decades several infection control measures have been widely applied in dentistry. Recommended measures such as wearing masks, single-use gloves and autoclaving of instruments have become standard precautions. Also, the concept of universal infection control, whereby all patients are treated as potential carriers of pathogenic micro-organisms, has become accepted as best practice ^{8, 9}.

According to guidelines of the World Health Organization (WHO) on blood safety, blood donors should be deferred for 24 hours after simple procedures and up to 7 days after endodontic procedures (root canal therapy) or tooth extraction ³. The current guidelines for deferral are based on common sense and expert opinions and are regulated by European and Belgian legislation. This deferral policy is based on the assumption that only transient bacteraemia might pose a problem, while also viral infections could be transmitted. Therefore, this review aims to identify the best available scientific evidence on the association between all possible TTI's (bacterial and viral) and dental care in otherwise healthy blood donors. For this, the following PICO question was formulated: In blood donors (P), is dental treatment (I), compared to no dental treatment (C) a risk factor for TTI's (O)?

METHODS OF THE REVIEW

This systematic review was carried out in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (Appendix I). No protocol was registered for this review.

Search strategy

The search was divided in two phases. For both phases, following databases were searched: Medline (using the PubMed interface), Embase (using the Embase.com interface), the Cochrane Library and ISI Web of Science.

In a first phase, we searched for existing systematic reviews investigating risk factors for TTI's in blood donors. Subsequently, the in- and excluded studies of selected systematic reviews were checked and

studies including dental care as a risk factor were withheld. For this phase, databases were searched from date of inception until January 10, 2017.

In a second phase, an update of the evidence from the identified systematic reviews was carried out by searching for studies that included dental care as a risk factor for TTI's in blood donors. Databases were searched from March 1, 2014 until July 12, 2018.

Search strategies for both phases can be found in Appendix II.

Study selection

Titles and abstracts were screened by two reviewers independently after which full texts were evaluated.

A third reviewer was consulted to resolve any discrepancies between the reviewers. The following inclusion and exclusion criteria were used:

For the population, healthy blood donors, without age or gender restriction, were included. Populations not exclusively consisting of blood donors were excluded. The following interventions or risk factors were included: dental treatment, dental procedure, dental therapy, tooth extraction/filling/scaling, dental/teeth cleaning, dentistry or dental treatment accompanied by haemorrhage. Dental surgery and dental treatment performed by a person other than a dentist were excluded. The comparison was no dental treatment. The outcomes included were markers of TTI's, such as HBsAg, HCV, HIV, HTLV-1, bacterial infections.

The following study design was included in phase 1: systematic reviews, only if the search strategy and selection criteria are clearly described. Included for phase 2 were experimental studies: randomized controlled trials, controlled clinical trials, before-after studies; or observational studies: cohort studies or case-control studies. The following study types were excluded for both phases: case series, cross-sectional studies, animal studies, ex vivo or in vitro studies, studies reporting no quantitative data, studies reporting only means, but no standard deviations (SDs), effect sizes or p-values.

Language: studies in all languages were included, if an English abstract was available.

Data extraction

Data concerning study design, study population, intervention, outcome measures and study quality were extracted by two reviewers independently. Data are presented as odds ratios (OR) with 95% confidence

intervals (CI). A p-value <0.05 was considered significant. If studies reported both unadjusted and adjusted effect measures, only adjusted effect measures were extracted. Odds ratios were calculated with Review Manager software ¹⁰ if only raw data were available. Authors were contacted if any information was missing.

Quality assessment.

The methodological quality of included studies was assessed by using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach ¹¹. For each individual study, limitations in study design are assessed. These limitations include inappropriate eligibility criteria, inappropriate methods for exposure and outcome variables, no control for confounding factors, inappropriate or inadequate follow-up and possible other limitations. Subsequently, the level of evidence of the body of evidence was determined and was downgraded based on following items: limitations in study design as described above, inconsistency between different studies (caused by differences in population, interventions or outcomes), imprecision (due to low number of events or limited sample size, large variability of results or lack of data), indirectness (indirect population, intervention, comparator) or publication bias. Publication bias was assessed by visual inspection of funnel plots and by formal testing with linear regression analysis of funnel plot symmetry (R statistical software package) if sufficient studies were available. Based on these criteria, the level of evidence can range from a high level (A) of evidence to a moderate (B), low (C) or very low (D) level of evidence.

Meta-analysis

In order to evaluate the overall effect of association between dental care and TTI markers, a meta-analysis for the different TTI's was conducted. Only outcomes for which data from several studies was available were combined in a meta-analysis. Where possible, raw data were used to calculate the overall effect size and p-value. Heterogeneity was assessed by visual inspection of the forest plot and by using the I² statistic and the Chi²-test. We defined heterogeneity to be significant if I² was higher than 60% and if p<0.10. For studies where no raw data was available, we constructed a random-effects model using the generic inverse variance method by calculating the log[OR] and its corresponding standard error (= [upper limit of the 95% CI – lower limit of the 95%CI]). All effect measures were pooled per outcome. If heterogeneity was found, a subgroup analysis according to the type of dental treatment was done in

order to try to explain the heterogeneity. Review Manager Software was used to calculate OR and 95%CI¹⁰. The inverse variance heterogeneity model was used for meta-analysis, and calculated with MetaXL in Microsoft Excel¹².

RESULTS

Study identification and selection

The study identification took place in two phases. In a first phase, where we searched for systematic reviews, a total of 1014 references were identified. After duplicate removal, 872 references were initially screened on title and abstract, followed by full text screening. Finally 18 systematic reviews were withheld from which 14 individual studies were included (Figure 1). In the second phase, where we searched for studies published since the most recent relevant systematic review, a total of 5744 studies were identified. After removal of duplicates, 4270 references were initially screened for title and abstract, followed by full text screening of the remaining references. Finally 8 studies were included. Figure 2 gives an overview of the study selection of phase 2.

In total, 22 studies were included in this systematic review.

Study characteristics

An overview of the study characteristics can be found in table 1. Four studies investigated risk factors for HBV in blood donors. 14 studies looked at risk factors for HCV, one study investigated both HBV and HCV cases separately and one study combined donors with HBV and HCV as cases. Furthermore, one study investigated risk factors for HTLV-1 and one study looked at risk factors for HIV in blood donors. Five studies came from high-income countries (Israel, Kuwait, Poland and 2 from USA). The majority of the studies came from upper middle-income countries (n=14: Iran, n=4; Mexico, n=2; China, n=5; Serbia, n=1 and Thailand, n=2) and 3 studies were performed in lower middle-income countries (Egypt, Morocco and India), as defined by the World Bank list of economies¹³.

All 5 studies investigating hepatitis B were case-control studies including a total of 5081 participants¹⁴⁻¹⁸. The risk factor analysed was specified as dental cleaning in one study¹⁵, 2 studies did not further specify 'dental treatment'^{16, 18} and 2 studies narrowed 'dental treatment' down to treatment executed by a dentist¹⁴ or in dental clinics¹⁷. The timeframe used to study exposure was in 2 studies defined as a

lifetime exposure^{15, 16}. In the remaining 3 studies the questioned time period for exposure was unclear^{14, 17, 18}.

15 included studies investigated hepatitis C. All were case-control studies, including a total of 50303 participants¹⁹⁻³². The studied risk factor was in a few studies well defined as dental cleaning¹⁵, invasive dental treatment (with haemorrhage)²⁷, tooth extraction^{26, 28, 30} or teeth cleaning^{26, 28}. Three studies defined the risk factor as dental treatment executed by a dentist^{19, 20, 25}. The other studies did not specify and just mentioned dental treatment^{21-24, 29, 31, 32}. The timeframe used to study exposure was in 2 studies defined as 'ever', thus a lifetime exposure^{15, 28}, and one study implemented a time period of 6 months before diagnosis of infection²². In the remaining 12 studies the questioned time period for exposure was unclear^{19-21, 23-27, 29-32}.

In one study the cases had either hepatitis B and/or hepatitis C infection³³. This study included a total of 560 participants. The studied risk factor was dental treatment by a dentist in the 5 years prior to completing the questionnaire.

One study looked at the association between invasive dental treatment (with bleeding) and HTLV-1 infection³⁴ and included 1092 participants. There was no information on which time period the risk factors were questioned.

Finally, one study looked at the association between dental cleaning and HIV infection³⁵ and included 726 participants. They questioned whether the participant ever had dental cleaning, thus a lifetime exposure.

Study results

Association between dental treatment and TTI's

16 studies looked at dental treatment as a risk factor for TTI. Of these, 4 studied HBV, 11 studied HCV and 1 studied HTLV-1.

We combined all studies in a meta-analysis, showing an increased association of TTI's with dental treatment (OR 2.01, 95%CI [1.19;3.41], $p < 0.05$), however, there was large heterogeneity ($I^2 = 94\%$, $p < 0.00001$). Therefore, a subgroup analysis was performed, analysing data for different TTI's in different subgroups. The subgroup analysis showed a significant increased association of HBV with dental treatment (OR 1.79, 95%CI [1.48;2.18], $p < 0.00001$, $I^2 = 0\%$, $p = 0.76$).

There is conflicting evidence concerning the risk of HCV after dental treatment. Abdelaziz et al (OR 1.71, 95%CI [1.15;2.54], $p=0.008$), Baha et al (OR 3.86, 95%CI [3.28;4.52], $p<0.00001$), Guerrero-Romero et al (OR 5.82, 95%CI [1.66;20.38], $p=0.006$), He et al (aOR 4.76, 95%CI [2.00-8.41], $p<0.0001$), Rezaei et al (OR 2.26, 95%CI [1.84;2.77], $p<0.001$) and Wong et al (OR 2.67, 95%CI [1.20;5.98], $p<0.02$) showed a statistically significant increased association of hepatitis C with dental treatment^{19, 21, 23, 24, 29, 32}. However, two studies showed a statistically significant decreased association of hepatitis C with dental treatment with OR 0.36, 95%CI [0.21;0.64], $p=0.0005$ and OR 0.492, 95%CI [0.379;0.637], $p<0.0001$ respectively^{20, 25}. Furthermore, in 3 studies, a statistically significant increased association of hepatitis C with dental treatment, compared to no dental treatment, could not be demonstrated^{22, 27, 31}. In addition, one study analysed the risk of infection with HBV and/or HCV after dental treatment by a dentist³³. In this study an increased association of infection with dental treatment could not be demonstrated (OR 1.04, 95%CI [0.70;1.54], $p=0.86$).

One study looked at invasive dental treatment as a risk factor for HTLV-1 infection, however, a statistically significant increased association could not be demonstrated (OR 1.33, 95%CI [0.96;1.86], $p=0.09$)³⁴. A summary of the association between TTI and dental treatment, including a risk of bias graph, can be found in figure 3.

Association between tooth extraction and TTI's

Three studies investigating the risk of TTI's after tooth extraction were combined in a meta-analysis^{26, 28, 30}. Results show a statistically significantly increased association of HCV with tooth extraction (OR 1.48, 95%CI [1.11;1.97], $p=0.007$; $I^2=28\%$). A summary of the association between TTI and tooth extraction, including a risk of bias graph, can be found in figure 4.

Association between dental cleaning and TTI's

There is conflicting evidence concerning teeth cleaning. Kerzman et al studied two different blood donor sub-populations finding a statistically significant decreased association of HCV in both subpopulations with teeth cleaning (OR 0.40, 95%CI [0.20;0.81], $p<0.05$ and OR 0.32, 95%CI [0.19;0.53], $p<0.05$, respectively)²⁶. Murphy et al found a statistically significant increased association of HCV with having teeth cleaned (OR 1.42, 95%CI [1.05;1.93], $p=0.02$)²⁸. Furthermore, Huang et al could not demonstrate a statistically significant increased association of HBV or HCV (OR 0.81, 95%CI [0.62;1.07], $p=0.14$)¹⁵.

One study examined a lifetime exposure to dental cleaning as a risk factor for HIV infection. A statistically significant increased association of HIV could not be demonstrated (OR 1.05, 95%CI [0.61;1.79], $p=0.87$)³⁵. A summary of the association between TTI and dental cleaning, including a risk of bias graph, can be found in figure 5.

Level of evidence

Since all studies were observational case-control studies, they had an initial low level of evidence, according to the GRADE approach¹¹. Below we describe the final level of evidence for each of the treatment types.

Dental treatment

In 3 out of 16 studies we found inappropriate eligibility criteria: there was insufficient matching between cases and controls^{16, 17, 19}. All studies showed to have used appropriate methods for outcome variables (same laboratory testing was carried out for both cases and controls) but 5 studies showed unclear or inadequate methods for exposure, meaning insufficient or no blinding of interviewing personnel or participants which could result in reporting bias^{16, 18, 29, 32, 34}. 13 studies did not (sufficiently) control for confounding factors^{16, 17, 19-23, 25, 27, 29, 31, 32, 34}. There were no limitations concerning follow-up. Six studies were found to have other limitations, such as unclear reasons for exclusion of participants, possible recall bias or lacking information on blinding of researchers^{16, 17, 20, 22, 27, 32}. Ten studies had imprecision of results due to a low number of events^{14, 16, 18, 22-25, 27, 31, 32} and 6 studies had imprecision due to a large variability of results^{14, 16, 22, 27, 31, 34}. Visual inspection of the funnel plot for HCV might demonstrate publication bias (i.e. funnel plot asymmetry). However, no evidence of publication bias was found based on the linear regression test of funnel plot asymmetry ($p=0.4388$). Overall, because of limitations in study design and imprecision, the quality of the body of evidence for dental treatment was downgraded from low to very low.

Tooth extraction

One study had inappropriate eligibility criteria, showing differences in demographic data between cases and controls²⁶, however, all studies used appropriate methods for outcome variables (same laboratory testing was carried out for both cases and controls). The same study had inappropriate methods for

exposure variables ^{26, 32}. One study did not control for confounding factors ³⁰. There were no limitations concerning follow-up. We found two studies to also have other limitations concerning e.g. population and response rates ^{26, 28}. After evaluating the studies for imprecision, we found all studies to show imprecision due to low number of events and/or large variability of results ^{26, 28, 30}.

Overall, because of limitations in study design and imprecision, the quality of the body of evidence for tooth extraction was downgraded from low to very low.

Dental cleaning

The majority of the studies showed inappropriate eligibility criteria showing significant differences between cases and controls ^{15, 26, 35}. All studies used appropriate methods for outcome variables (same laboratory testing was carried out for both cases and controls), however, one study had inappropriate methods for exposure variables ²⁶. Two studies did not control for confounding factors ^{15, 35}. There were no limitations concerning follow-up, but all studies also had other limitations concerning e.g. population and response rates ^{15, 26, 28, 35}. We found all studies to show imprecision due to low number of events and/or large variability of results. Overall, because of limitations in study design and imprecision, the quality of the body of evidence for dental cleaning was downgraded from low to very low.

DISCUSSION

The aim of this systematic review was to investigate the association between dental treatment and TTI's in blood donors. Currently, deferral of blood donors after dental care is based on the precautionary principle, which implies that in the interest of public health, risk management actions should be taken even in the absence of certainty about risk, thus aiming for maximum safety ¹. The current guidelines for deferral are based on the assumption that only transient bacteraemia might occur after dental treatment. In this review, we investigated the association between both bacterial and viral TTI's and dental treatment.

We identified 22 studies investigating the association between HBV, HCV, HIV or HTLV-1 and different forms of dental care (dental treatment, tooth extraction or dental cleaning). No studies were identified concerning other viral or bacterial infections such as herpes simplex, herpes zoster, mycobacterium, pseudomonas, legionella, staphylococcus or streptococcus.

For dental treatment, there was limited evidence from 16 studies. Meta-analysis showed an increased association of TTI's after dental treatment, however with large heterogeneity. Subgroup analysis revealed a significant increased association of HBV after dental treatment. There was conflicting evidence concerning the risk of HCV. One study looked at the association of HTLV-1 with dental treatment, but a statistically significant increased association could not be demonstrated.

Three studies investigated the association between TTI's and tooth extraction, showing a statistically significant increased association of HCV.

Finally, there is conflicting evidence from 4 studies concerning the association of HBV or HCV with dental cleaning. One study examined the association of HIV with dental cleaning, but a statistically significant increased association could not be identified. All evidence is however of very low certainty and results cannot be considered precise.

The meta-analysis for dental treatment showed a large heterogeneity in results which could not be clarified by subgroup analysis based on country income or high or low prevalence of the infectious parameter. A possible explanation could be the timeframe used to study exposure (lifetime exposure versus recent exposure) and the frequency of possible exposure to infectious agents.

Some studies show a protective effect of teeth cleaning, although other studies contradict this. It could however be hypothesized that when dental cleaning or dental care is performed on a regular basis and oral health is maintained, a decrease in invasive dental treatment could be expected, therefore leading to a decrease in TTI. Though, if dental treatment is postponed, more complex and invasive treatment may be needed with a possible increased risk of TTI. A study by Lockhart et al corroborates this hypothesis and demonstrates that indeed, more invasive treatments do increase the risk of bacteraemia, but only if the treatment causes mucosal lesions in the oral cavity ³⁶.

There was large heterogeneity present between the studies, which is why meta-analysis was performed by using the inverse variance heterogeneity model, rather than using the random effects model. The random effects model suffers from poor error estimation if large heterogeneity is present, possibly posing a threat to decision-making in evidence-based health practice ³⁷. The inverse variance heterogeneity model produces more robust findings by calculating pooled estimates favouring larger trials, having more conservative confidence intervals and exhibiting a lesser observed variance irrespective of the degree of heterogeneity ¹².

This systematic review has some important limitations. An important limitation is that only observational data from case-control and cross-sectional studies were included. It is therefore difficult to establish causal associations. Furthermore, the type of dental treatment was often poorly reported. Most studies investigated 'dental treatment' without any specification of the type of treatment. Some studies specified tooth extraction or dental cleaning. It was therefore difficult to assess the invasiveness of the dental treatment. A third important limitation is that most studies did not report if they questioned for risk factors within a specific time period. After contacting the authors, it seems that mostly it was questioned whether participants ever had dental treatment. This precludes us from making any conclusions regarding deferral time.

No studies concerning transient bacteraemia could be identified in healthy blood donors. It might therefore be interesting to search for studies in the healthy general population.

To improve the quality of evidence regarding this topic more research needs to be done. Experimental studies could clarify the causal relationship between dental treatment and TTI's, but because of ethical implications on studies performed in humans we rather suggest more observational studies including a focus on the timeframe, frequency of exposure to dental care and the invasiveness of dental treatment performed. In order to replace the current precautionary, principle-driven deferral policies for blood donors by evidence-based deferral policies, we need more high-quality primary research studies to investigate the relationship between dental treatment and TTI's. This needs to be discussed with the Blood Services. The association indicated in this review is certainly something to look further into. Guideline producers such as the WHO and legislators should look into the possible transmission of viral TTI's after dental care, taking into account the prevalence of these viral infections in their country. The currently identified studies are of too low quality to make any suggestions regarding deferral times.

CONCLUSION

In conclusion, the evidence presented in this systematic review is of very low certainty but does show an association between hepatitis B virus infection and dental treatment. Furthermore, limited evidence shows an increased association of hepatitis C with tooth extraction, but conflicting evidence concerning the association of dental treatment or teeth cleaning and hepatitis C. Additionally, an increased risk of HIV or HTLV-1 after dental treatment could not be demonstrated. These results are of very low certainty

and therefore not sufficient to give an indication of the optimal deferral time after dental treatment. Further high quality research is needed to determine the risk of viral and bacterial TTI's after dental treatment.

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APPENDICES

Appendix I: PRISMA checklist

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

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 + figs 1-2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7 + table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9 + figs 3-5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8 + figs 3-5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8+ figs 3-5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Appendix II: Complete search strategies

Phase 1: search strategies used to identify published systematic reviews regarding blood donor population and risk factors for transfusion transmittable infections (search date 10/01/2017):

The Cochrane Library (systematic reviews) using the following search strategy:

1. [mh "Blood Donors"] OR "blood don*":ti,ab,kw OR [mh "Blood Banks"] OR "blood bank":ti,ab,kw OR "blood banks":ti,ab,kw OR "blood service*":ti,ab,kw OR "blood center*":ti,ab,kw OR "blood centre*":ti,ab,kw OR "transfusion service*":ti,ab,kw OR "transfusion cent*":ti,ab,kw OR "blood withdraw*":ti,ab,kw
2. [mh "Bacterial Infections"] OR bacterial:ti,ab,kw OR bacteriaemia:ti,ab,kw OR bacteremia:ti,ab,kw OR bacteriemia:ti,ab,kw OR [mh "Virus Diseases"] OR viral:ti,ab,kw OR virus:ti,ab,kw OR viremia:ti,ab,kw OR viraemia:ti,ab,kw OR [mh "Sepsis"] OR [mh "Toxemia"] OR sepsis:ti,ab,kw OR toxemia:ti,ab,kw OR toxaemia:ti,ab,kw OR septicaemia:ti,ab,kw OR septicemia:ti,ab,kw OR "blood poisoning":ti,ab,kw OR [mh "Herpes Simplex"] OR "herpes simplex":ti,ab,kw OR HSV:ti,ab,kw OR [mh "Herpesvirus 3, Human"] OR [mh "herpes zoster"] OR "varicella zoster":ti,ab,kw OR VZV:ti,ab,kw OR [mh "HIV"] OR "human immunodeficiency virus":ti,ab,kw OR HIV:ti,ab,kw OR [mh "Hepatitis"] OR hepatitis:ti,ab,kw OR HBV:ti,ab,kw OR HCV:ti,ab,kw OR [mh "Mycobacterium"] OR mycobacterium:ti,ab,kw OR [mh "Tuberculosis"] OR tuberculosis:ti,ab,kw OR TBC:ti,ab,kw OR TB:ti,ab,kw OR [mh "Pseudomonas"] OR pseudomonas:ti,ab,kw OR [mh "Legionella"] OR legionella:ti,ab,kw OR [mh "Staphylococcus"] OR [mh "Streptococcus"] OR staphylococc*:ti,ab,kw OR streptococc*:ti,ab,kw OR [mh "Methicillin-Resistant Staphylococcus aureus"] OR MRSA:ti,ab,kw OR [mh "Enterobacteriaceae"] OR enterobacteria*:ti,ab,kw OR ESBL:ti,ab,kw OR CPE:ti,ab,kw
3. #1 AND #2

MEDLINE (via PubMed interface) for systematic reviews using the following search strategy:

1. "Blood Donors"[Mesh] OR blood don*[TIAB] OR "Blood Banks"[Mesh] OR blood bank*[TIAB] OR blood service*[TIAB] OR blood center*[TIAB] OR blood centre*[TIAB] OR transfusion service*[TIAB] OR transfusion cent*[TIAB] OR "blood withdraw*"[TIAB]

2. "Bacterial Infections"[Mesh] OR "Virus Diseases"[Mesh] OR "Sepsis"[Mesh] OR "Toxemia"[Mesh] OR "bacterial infection"[TIAB] OR sepsis[TIAB] OR bacterial[TIAB] OR bacteriaemia[TIAB] OR bacteriemia[TIAB] OR bacteremia[TIAB] OR viral[TIAB] OR virus[TIAB] OR viremia[TIAB] OR viraemia[TIAB] OR septicaemia[TIAB] OR septicemia[TIAB] OR toxemia[TIAB] OR toxaemia[TIAB] OR "blood poisoning"[TIAB] OR "herpes simplex"[TIAB] OR "Herpes Simplex"[Mesh] OR HSV[TIAB] OR "varicella zoster"[TIAB] OR "Herpesvirus 3, Human"[Mesh] OR "herpes zoster"[Mesh] OR VZV[TIAB] OR "human immunodeficiency virus"[TIAB] OR HIV[TIAB] OR "HIV"[Mesh] OR hepatitis[TIAB] OR "Hepatitis"[Mesh] OR HBV[TIAB] OR HCV[TIAB] OR tuberculosis[TIAB] OR "Tuberculosis"[Mesh] OR TBC[TIAB] OR TB[TIAB] OR mycobacterium[TIAB] OR "Mycobacterium"[Mesh] OR pseudomonas[TIAB] OR "Pseudomonas"[Mesh] OR legionella[TIAB] OR "Legionella"[Mesh] OR "methicillin-resistant staphylococcus aureus"[Mesh] OR staphylococc*[TIAB] OR "Staphylococcus"[Mesh] OR "Streptococcus"[Mesh] OR streptococc*[TIAB] OR MRSA[TIAB] OR enterobacteria*[TIAB] OR "Enterobacteriaceae"[Mesh] OR ESBL[TIAB] OR "carbapenemase-producing gram-negative bacteria"[TIAB] OR CPE[TIAB]
3. Systematic review filter: (((((((((((Meta-Analysis as Topic[Mesh])) OR ((meta analy*[TIAB])) OR ((metaanaly*[TIAB])) OR ((Meta-Analysis[Publication Type])) OR ((systematic review*[TIAB] OR systematic overview*[TIAB])) OR ((Review Literature as Topic[Mesh])) OR ((cochrane[TIAB] OR embase[TIAB] OR psychlit[TIAB] OR psyclit[TIAB] OR psychinfo[TIAB] OR psycinfo[TIAB] OR cinahl[TIAB] OR cinhal[TIAB] OR science citation index[TIAB] OR bids[TIAB] OR cancerlit[TIAB])) OR ((reference list*[TIAB] OR bibliograph*[TIAB] OR handsearch*[TIAB] OR relevant journals[TIAB] OR manual search*[TIAB])) OR (((selection criteria[TIAB] OR data extraction[TIAB])) AND ((Review[PT])))) NOT ((Comment[PT] OR Letter[PT] OR Editorial[PT] OR animal[Mesh] NOT (animal[Mesh] AND human[Mesh]))))
4. 1-3 AND

Embase (via Embase.com interface) for systematic reviews using the following search strategy:

1. 'blood donor'/exp OR (blood NEXT/1 don*):ab,ti OR 'blood bank'/exp OR 'blood bank':ab,ti OR
 'blood banks':ab,ti OR (blood NEXT/1 service*):ab,ti OR (blood NEXT/1 (center* OR cen-
 tre*)):ab,ti OR (transfusion NEXT/1 service*):ab,ti OR (transfusion NEXT/1 cent*):ab,ti OR
 'blood withdraw*':ab,ti
2. 'Bacterial Infection'/exp OR bacterial:ab,ti OR bacteriaemia:ab,ti OR bacteriemia:ab,ti OR bacte-
 remia:ab,ti OR 'Virus Infection'/exp OR viral:ab,ti OR virus:ab,ti OR viremia:ab,ti OR
 viraemia:ab,ti OR 'Sepsis'/exp OR 'Toxemia'/exp OR sepsis:ab,ti OR toxemia:ab,ti OR toxae-
 mia:ab,ti OR septicaemia:ab,ti OR septicemia:ab,ti OR 'blood poisoning':ab,ti OR 'Herpes
 Simplex'/exp OR 'herpes simplex':ab,ti OR HSV:ab,ti OR 'Varicella Zoster virus'/exp OR 'herpes
 zoster'/exp OR 'varicella zoster':ab,ti OR VZV:ab,ti OR 'Human immunodeficiency virus'/exp OR
 'Human Immunodeficiency Virus':ab,ti OR HIV:ab,ti OR 'Hepatitis'/exp OR hepatitis:ab,ti OR
 HBV:ab,ti OR HCV:ab,ti OR 'Mycobacterium'/exp OR mycobacterium:ab,ti OR 'Tuberculo-
 sis'/exp OR tuberculosis:ab,ti OR TBC:ab,ti OR TB:ab,ti OR 'Pseudomonas'/exp OR
 pseudomonas:ab,ti OR 'Legionella'/exp OR legionella:ab,ti OR 'Staphylococcus'/exp OR 'Strep-
 tococcus'/exp OR staphylococc*:ab,ti OR streptococc*:ab,ti OR 'Methicillin Resistant
 Staphylococcus aureus'/exp OR MRSA:ab,ti OR 'carbapenemase producing Enterobacteri-
 aceae'/exp OR 'Enterobacteriaceae'/exp OR enterobacteria*:ab,ti OR ESBL:ab,ti OR CPE:ab,ti
3. Systematic review filter: 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'meta analy-
 sis':ab,ti OR 'meta-analysis':ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp
 OR 'cochrane':ab,ti OR 'embase':ab,ti OR 'pubmed':ab,ti OR 'medline':ab,ti OR 'reference
 list':ab,ti OR 'reference lists':ab,ti OR 'bibliography':ab,ti OR 'bibliographies':ab,ti OR 'hand-
 search':ab,ti OR 'manual search':ab,ti OR 'relevant journals':ab,ti OR 'selection criteria':ab,ti OR
 'data extraction':ab,ti
4. 1-3 AND

Web of Science (via WebOfScience.com interface) for systematic reviews using the following
 search strategy:

1. TS=("blood don*") OR TI=("blood don*") OR TS=("blood bank*") OR TI=("blood bank*") OR
 TS=("blood service*") OR TI=("blood service*") OR TS=("blood center*") OR TI=("blood center*")

OR TS=("blood centre*") OR TI=("blood centre*") OR TS=("transfusion service*") OR TI=("transfusion service*") OR TS=("transfusion cent*") OR TI=("transfusion cent*") OR TS=("blood withdraw*") OR TI=("blood withdraw*")

2. TS=(bacterial) OR TI=(bacterial) OR TS=(bacteraemia) OR TI=(bacteraemia) OR TS=(bacteriemia) OR TI=(bacteriemia) OR TS=(bacteremia) OR TI=(bacteremia) OR TS=(viral) OR TI=(viral) OR TS=(virus) OR TI=(virus) OR TS=(viremia) OR TI=(viremia) OR TS=(viraemia) OR TI=(viraemia) OR TS=(sepsis) OR TI=(sepsis) OR TS=(toxemia) OR TI=(toxemia) OR TS=(toxaemia) OR TI=(toxaemia) OR TS=(septicaemia) OR TI=(septicaemia) OR TS=(septicemia) OR TI=(septicemia) OR TS=("blood poisoning") OR TI=("blood poisoning") OR TS=("herpes simplex") OR TI=("herpes simplex") OR TS=(HSV) OR TI=(HSV) OR TS=("varicella zoster") OR TI=("varicella zoster") OR TS=("herpes zoster") OR TI=("herpes zoster") OR TS=(VZV) OR TI=(VZV) OR TS=("human immunodeficiency virus") OR TI=("human immunodeficiency virus") OR TS=(HIV) OR TI=(HIV) OR TS=(hepatitis) OR TI=(hepatitis) OR TS=("HBV") OR TI=("HBV") OR TS=("HCV") OR TI=("HCV") OR TS=("mycobacterium") OR TI=("mycobacterium") OR TS=("tuberculosis") OR TI=("tuberculosis") OR TS=("TBC") OR TI=("TBC") OR TS=("TB") OR TI=("TB") OR TS=("pseudomonas") OR TI=("pseudomonas") OR TS=("legionella") OR TI=("legionella") OR TS=("staphylococc*") OR TI=("staphylococc*") OR TS=("streptococc*") OR TI=("streptococc*") OR TS=("MRSA") OR TI=("MRSA") OR TS=("enterobacteria*") OR TI=("enterobacteria*") OR TS=("ESBL") OR TI=("ESBL") OR TS=("CPE") OR TI=("CPE")

3. 1 AND 2

Phase 2: search strategies used to update selected systematic reviews from phase 1 (search date 29/08/2017):

The Cochrane Library searched using the following search strategy:

1. [mh "Blood Donors"] OR "blood don*":ti,ab,kw OR [mh "Blood Banks"] OR "blood bank":ti,ab,kw OR "blood banks":ti,ab,kw OR "blood service*":ti,ab,kw OR "blood center*":ti,ab,kw OR "blood centre*":ti,ab,kw OR "transfusion service*":ti,ab,kw OR "transfusion cent*":ti,ab,kw OR "blood withdraw*":ti,ab,kw
2. [mh "Bacterial Infections"] or bacterial:ti,ab,kw or bacteriaemia:ti,ab,kw or bacteriemia:ti,ab,kw or bacteremia:ti,ab,kw or [mh "Virus Diseases"] or viral:ti,ab,kw or virus:ti,ab,kw or viremia:ti,ab,kw or viraemia:ti,ab,kw or [mh Sepsis] or [mh Toxemia] or sepsis:ti,ab,kw or toxemia:ti,ab,kw or toxaemia:ti,ab,kw or septicaemia:ti,ab,kw or septicemia:ti,ab,kw or "blood poisoning":ti,ab,kw or [mh "Herpes Simplex"] or "herpes simplex":ti,ab,kw or HSV:ti,ab,kw or [mh "Herpesvirus 3, Human"] or [mh "herpes zoster"] or "varicella zoster":ti,ab,kw or VZV:ti,ab,kw or [mh HIV] or "human immunodeficiency virus":ti,ab,kw or HIV:ti,ab,kw or [mh Hepatitis] or hepatitis:ti,ab,kw or HBV:ti,ab,kw or HCV:ti,ab,kw or [mh Mycobacterium] or mycobacterium:ti,ab,kw or [mh Tuberculosis] or tuberculosis:ti,ab,kw or TBC:ti,ab,kw or TB:ti,ab,kw or [mh Pseudomonas] or pseudomonas:ti,ab,kw or [mh Legionella] or legionella:ti,ab,kw or [mh Staphylococcus] or [mh Streptococcus] or staphylococc*:ti,ab,kw or streptococc*:ti,ab,kw or [mh "Methicillin-Resistant Staphylococcus aureus"] or MRSA:ti,ab,kw or [mh Enterobacteriaceae] or enterobacteria*:ti,ab,kw or ESBL:ti,ab,kw or CPE:ti,ab,kw
3. Publication date filter: 2014 – 2017
4. 1-3 AND

MEDLINE (via PubMed interface) searched using the following search strategy:

1. "Blood Donors"[Mesh] OR blood don*[TIAB] OR "Blood Banks"[Mesh] OR blood bank*[TIAB] OR blood service*[TIAB] OR blood center*[TIAB] OR blood centre*[TIAB] OR transfusion service*[TIAB] OR transfusion cent*[TIAB] OR "blood withdraw*"[TIAB]
2. "Bacterial Infections"[Mesh] OR "Virus Diseases"[Mesh] OR "Sepsis"[Mesh] OR "Toxemia"[Mesh] OR "bacterial infection*"[TIAB] OR sepsis[TIAB] OR bacterial[TIAB] OR

bacteraemia[TIAB] OR bacteriemia[TIAB] OR bacteremia[TIAB] OR viral[TIAB] OR virus[TIAB]
 OR viremia[TIAB] OR viraemia[TIAB] OR septicaemia[TIAB] OR septicemia[TIAB] OR toxemia[TIAB] OR toxaemia[TIAB] OR "blood poisoning"[TIAB] OR "herpes simplex"[TIAB] OR
 "Herpes Simplex"[Mesh] OR HSV[TIAB] OR "varicella zoster"[TIAB] OR "Herpesvirus 3, Human"[Mesh] OR "herpes zoster"[Mesh] OR VZV[TIAB] OR "human immunodeficiency virus"[TIAB] OR HIV[TIAB] OR "HIV"[Mesh] OR hepatitis[TIAB] OR "Hepatitis"[Mesh] OR
 HBV[TIAB] OR HCV[TIAB] OR tuberculosis[TIAB] OR "Tuberculosis"[Mesh] OR TBC[TIAB] OR TB[TIAB] OR mycobacterium[TIAB] OR "Mycobacterium"[Mesh] OR pseudomonas[TIAB] OR
 "Pseudomonas"[Mesh] OR legionella[TIAB] OR "Legionella"[Mesh] OR "methicillin-resistant staphylococcus aureus"[Mesh] OR staphylococc*[TIAB] OR "Staphylococcus"[Mesh] OR "Streptococcus"[Mesh] OR streptococc*[TIAB] OR MRSA[TIAB] OR enterobacteria*[TIAB] OR
 "Enterobacteriaceae"[Mesh] OR ESBL[TIAB] OR "carbapenemase-producing gram-negative bacteria"[TIAB] OR CPE[TIAB]

3. "Epidemiologic Studies"[Mesh] OR "case control"[TIAB] OR "case-control"[TIAB] OR
 ((case[TIAB] OR cases[TIAB]) AND (control[TIAB] OR controls[TIAB])) OR "cohort study"[TIAB]
 OR "cohort analysis"[TIAB] OR "follow up study"[TIAB] OR "follow-up study"[TIAB] OR "observational study"[TIAB] OR longitudinal[TIAB] OR retrospective[TIAB] OR "cross sectional"[TIAB]
 OR "cross-sectional"[TIAB] OR questionnaire[TIAB] OR questionnaires[TIAB] OR survey[TIAB]
4. Publication date filter: 01/03/2014 – 29/08/2017
5. 1-4 AND

Embase (via Embase.com interface) searched using the following search strategy:

1. 'blood donor'/exp OR (blood NEXT/1 don*):ab,ti OR 'blood bank'/exp OR 'blood bank':ab,ti OR
 'blood banks':ab,ti OR (blood NEXT/1 service*):ab,ti OR (blood NEXT/1 (center* OR centre*)):ab,ti OR (transfusion NEXT/1 service*):ab,ti OR (transfusion NEXT/1 cent*):ab,ti OR
 'blood withdraw*':ab,ti
2. 'bacterial infection'/exp OR bacterial:ab,ti OR bacteraemia:ab,ti OR bacteriemia:ab,ti OR bacteremia:ab,ti OR 'virus infection'/exp OR viral:ab,ti OR virus:ab,ti OR viremia:ab,ti OR
 viraemia:ab,ti OR 'sepsis'/exp OR 'toxemia'/exp OR sepsis:ab,ti OR toxemia:ab,ti OR toxaemia:ab,ti OR septicaemia:ab,ti OR septicemia:ab,ti OR 'blood poisoning':ab,ti OR 'herpes

simplex'/exp OR 'herpes simplex':ab,ti OR hsv:ab,ti OR 'varicella zoster virus'/exp OR 'herpes
 zoster'/exp OR 'varicella zoster':ab,ti OR vzv:ab,ti OR 'human immunodeficiency virus'/exp OR
 'human immunodeficiency virus':ab,ti OR hiv:ab,ti OR 'hepatitis'/exp OR hepatitis:ab,ti OR
 hbv:ab,ti OR hcv:ab,ti OR 'mycobacterium'/exp OR mycobacterium:ab,ti OR 'tuberculosis'/exp
 OR tuberculosis:ab,ti OR tbc:ab,ti OR tb:ab,ti OR 'pseudomonas'/exp OR pseudomonas:ab,ti
 OR 'legionella'/exp OR legionella:ab,ti OR 'staphylococcus'/exp OR 'streptococcus'/exp OR
 staphylococc*:ab,ti OR streptococc*:ab,ti OR 'methicillin- resistant staphylococcus aureus'/exp
 OR mrsa:ab,ti OR 'carbapenemase producing enterobacteriaceae'/exp OR 'enterobacteri-
 aceae'/exp OR enterobacteria*:ab,ti OR esbl:ab,ti OR cpe:ab,ti

3. 'clinical study'/exp OR 'cohort analysis'/exp OR 'case control':ab,ti OR 'case-control':ab,ti OR
 ((case:ab,ti OR cases:ab,ti) AND (control:ab,ti OR controls:ab,ti)) OR 'cohort study':ab,ti OR 'co-
 hort analysis':ab,ti OR 'follow up study':ab,ti OR 'follow-up study':ab,ti OR 'observational
 study':ab,ti OR longitudinal:ab,ti OR retrospective:ab,ti OR 'cross sectional':ab,ti OR 'cross-sec-
 tional':ab,ti OR questionnaire:ab,ti OR questionnaires:ab,ti OR survey:ab,ti OR 'epidemiological
 study':ab,ti
4. Publication date filter: 2014 – 2017
5. 1-4 AND

Web of Science (via WebOfScience.com interface) searched using the following search strategy:

1. TS=("blood don*" OR "blood bank*" OR "blood service*" OR "blood center*" OR "blood centre*" OR "transfusion service*" OR "transfusion cent*" OR "blood withdraw*")
2. TS=("bacterial" OR "bacteriaemia" OR "bacteriemia" OR "bacteremia" OR "viral" OR "virus" OR "viremia" OR "viraemia" OR "sepsis" OR "toxemia" OR "toxaemia" OR "septicaemia" OR "septicemia" OR "blood poisoning" OR "herpes simplex" OR "HSV" OR "varicella zoster" OR "herpes zoster" OR "VZV" OR "human immunodeficiency virus" OR "HIV" OR "hepatitis" OR "HBV" OR "HCV" OR "mycobacterium" OR "tuberculosis" OR "TBC" OR "TB" OR "pseudomonas" OR "legionella" OR "staphylococc*" OR "streptococc*" OR "MRSA" OR "enterobacteria*" OR "ESBL" OR "CPE")
3. Publication date filter: 2014 – 2017

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TABLES

Table 1: Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Outcome measure
Abdelaziz, 2017, Egypt	Observational: case-control study	Study period: April 2011 – March 2012. 631 voluntary blood donors, 57 excluded (because HBs Ag positive) resulting in 574 blood donors included: 138 HCV-positive cases (aged between 20-40 years, 90 male, 48 female) and 436 HCV negative controls (aged 20-40 years old, 379 male, 57 female).	Treatment by a dentist	HCV infection
Akhtar, 2005, Kuwait	Observational: case-control study	Study period: October 15, 2001 to March 15, 2002. 324 in total: 64 cases (HBsAg positive blood donors) + 260 controls (HBsAg negative blood donors), age 18-64 years, Pakistani nationality (47% of cases and 61% of controls belong to Mohajir ethnicity), all male population.	History of dental treatment by dentist	HBV infection
Alavian, 2002, Iran	Observational: case-control study	Study period: April 1996 to June 1998. 389 in total: 193 cases (HCV-positive blood donors, 177 male + 16 female, mean age 35.7 ± 9.9 years) + 196 controls (HCV-negative blood donors, 176 male + 20 female, mean age 37.9 ± 9.2 years)	Treatment by dentist	HCV infection
Baha, 2013, Morocco	Observational: case-control study	Study period: January 1 st , 2008 to December 31, 2010. 41269 in total: 651 cases (anti-HCV positive volunteer blood donors, age: 144 <40 years, 507 >40 years; 185 female + 466 male) + 40 618 controls (anti-HCV negative volunteer blood donors, age: 16686 <40 years, 23932 >40 years; 12312 female + 28306 male)	Dental therapy	HCV infection
Czerwinski, 2017, Poland	Observational: case-control study	Study period: July 2002 – June 2014. 188 blood donors in total: 47 HCV cases (mean age 28.5 years, 43 male + 4 female) + 141 controls (mean age 28.6 years, 129 male + 12 female). Controls were negative for all screened infection markers.	Dental procedures	HCV infection
Guerrero-Romero, 1996, Mexico	Observational: case-control study	Study period: June 1993 to December 1994.	Dental work	HCV infection

		357 in total: 87 cases (anti-HCV positive blood donors, mean age $38,7 \pm 12$ years, 78 male + 9 female) + 270 controls (anti-HCV negative blood donors, mean age not specified, 240 male + 30 female)		
He, 2011, China	Observational: case-control study	Study period: July 2006 to June 2007. 915 volunteer blood donors in total: 305 cases (anti-HCV positive blood donors, 166 male + 139 female, age range 18-55 years) + 610 controls (anti-HCV antibody negative, 332 male + 278 female, age range 18-55 years)	Dental treatment	HCV infection
Hedayati-Moghaddam, 2015, Iran	Observational: case-control study	Study period: September 2011-August 2013. 1092 in total: 316 HTLV-1 cases of which 246 (181 males + 65 females, mean age 39.1 ± 10.6 years) were referred for consulting and were subsequently interviewed. Four controls were individually matched to each case ($n=1241$) on the basis of age (± 2 years), gender, and date and centre of donation. 776 controls (613 males + 163 females, mean age 38.3 ± 10.6 years) agreed to be interviewed.	Invasive dental treatment (with bleeding)	HTLV-1 infection
Huang, 2015, China	Observational: case-control study	Study period: 2009-2011. Part of the NHLBI Retrovirus Epidemiology Donor Study-II (REDS-II) program. HBV and HCV cases and controls from 5 blood centres in China. 1227 in total: 364 HBV cases (148 aged ≤ 25 years, 88 aged 26-35 years, 121 aged > 35 years; 251 male + 108 female; 313 first time donors + 31 repeat donors), 174 HCV cases (51 aged ≤ 25 years, 43 aged 26-35 years, 78 aged > 35 years; 96 male + 77 female; 143 first time donors + 31 repeat donors) + 689 controls (219 aged ≤ 25 years, 180 aged 26-35 years, 274 aged > 35 years; 430 male + 245 female; 193 first time donors + 424 repeat donors)	Dental cleaning	HBV infection or HCV infection
Kasraian, 2016, Iran	Observational: case-control study	Study period: March 21, 2012 to March 21, 2013. 118 in total: 59 cases (blood donors with positive results in HCV screening test followed by positive confirmatory test) + 59 controls	Going to a dentist	HCV infection

		(blood donors who had negative screening test results) No information on age or gender.		
Kerzman, 2007, Israel	Observational: case-control study	Study period: Data gathered between May 2002 and June 2003. 434 in total: 2 study groups: - <i>Native Israeli's (NI)</i> : 50 cases (all HCV seropositive NI blood donors who were detected in 2000 to 2001 and from 2002 + 6 additional FSUI donors who had immigrated to Israel between 1950 and 1965, 74% male, 16% <30 years of age) + 128 controls (HCV-seronegative NI BDs, randomly selected from the MDA computerized databank, 77,3% male, 48,4% <30 years of age) - <i>Immigrants from the former Soviet Union (FSUI)</i> : 128 cases (blood donors who immigrated from the FSU to Israel in 1989 (5) or since 1990 (123) and were diagnosed as HCV-positive when donating blood in 2000-2001, 82% male, 53,9% <30 years of age) + 128 controls (HCV-seronegative blood donors who had immigrated from the FSU since 1990 and were randomly selected from the MDA computerized databank, 73,4% male, 68% <30 years of age)	Tooth extraction and teeth cleaned	HCV infection
Jagannathan, 2010, India	Observational: case-control study	Study period: April 2003 to March 2006. 283 in total: 71 cases (blood donors seropositive for HBsAg; age range 18-45 years) + 212 controls (blood donors with unknown HBsAg status sampled at mobile blood donation camps; age range 18-45 years)	Dental, ever	HBV infection
Mitrovic, 2015, Serbia	Observational: case-control study	Study period: January 1 st – December 31 st 2013 in 10 transfusion centres in Serbia. 27160 voluntary blood donors who gave blood for the first time were enrolled in the study. 96 in total: 32 cases (HCV-positive blood donors, 25 males + 7 females, mean age 32.1±8.4 years) + 64 controls (HCV-negative blood donors, 50 males + 14 females) Two sex-matched and age-matched controls were selected from the same population of inclusion as the case patients,	Invasive dental treatment (accompanied by haemorrhage)	HCV infection

		without HCV infection or other parenterally acquired diseases.		
Murphy, 2000, USA	Observational: case-control study	Study period: 1994-1995. 1797 in total: 758 cases (HCV-seropositive blood donors; 400 male + 351 female; 64 aged <29y, 607 aged 30y-49y, 72 aged >50y) + 1039 controls (HCV-seronegative blood donors; 568 male + 463 female; 81 aged <29y, 815 aged 30y-49y, 131 aged >50y)	Tooth extraction and teeth cleaned	HCV infection
Nuchprayoon, 1992, Thailand	Observational: case-control study	Study period: January 1989 to July 1990. 2626 in total: 876 cases (HBsAg positive blood donors, age 28.2 ± 9.7 years, 622 male + 254 female, 100% Thai nationality) + 1750 controls (HBsAg negative blood donors, age 32.7 ± 9.2 years, 1342 male + 408 female, 99.7% Thai nationality, 1596 controls donated more than once)	Treatment in dental clinics	HBV infection
Rezaei, 2016, Iran	Observational: case-control study	Study period: 2009-2013. 2512 in total: 970 cases (HCV-positive blood donors, 913 males (mean age 36.46 ± 9.18 years) + 38 females (mean age 42.21 ± 10.28 years)) + 1542 controls (HCV-negative blood donors, 1471 males (mean age 36.51 ± 9.26 years) + 54 females (mean age 36.37 ± 8.89 years))	Dentistry	HCV infection
Thaikruea, 2004, Thailand	Observational: case-control study	Study period: January 2001 - June 2002. 495 in total: 166 cases (HCV-positive blood donors, age >18 years) + 329 controls (HCV-negative blood donors, age >18 years)	History of having a tooth extracted	HCV infection
Vences-Avilés, 2005, Mexico	Observational: case-control study	Study period: 1995 – 2003. 112 in total (18 females with average age of 39 years + 94 males with average age of 33 years): 45 cases (blood donors who were	Dental treatment	HCV infection

		HCV-positive after RIBA testing) + 67 controls (blood donors who were HCV-negative after RIBA testing)		
Wang, 2013, China	Observational: case-control study	Study period: March 2010 - March 2011 726 in total: 77 cases (HIV-positive blood donors, 63 male + 14 female; 21 aged ≤25 years, 31 aged 26-35 years, 22 aged >35 years) + 649 controls (HIV-negative blood donors, 412 male + 223 female; 201 aged ≤25 years, 170 aged 26-35 years, 262 aged >35 years)	Dental cleaning	HIV infection
Wong, 2018, China	Observational: case-control study	Study period: January 1, 2014 – December 31, 2016 46 HCV-positive blood donors (median age 33 (range 16-60); 19 male, 27 female), 138 HCV-negative blood donors (median age 31 (range 16-60); 57 male, 81 female), matched by age and sex.	Dental procedure	HCV infection
Younus, 2009, USA	Observational: case-control study	Study period: October 2001 – March 2002 560 in total: 166 cases (blood donors positive for HCV antibody and/or HBsAg, 57 aged 18-25 years, 93 aged 26-40 years, 16 aged >40 years; all males; Pakistani nationality) + 394 controls (HCV and HBV seronegative blood donors, 212 aged 18-25 years, 159 aged 26-40 years, 23 aged >40y; all males; Pakistani nationality)	Dental treatment by dentist	HCV and/or HBV infection
Zhong, 2016, China	Observational: case-control study	Study period: January 2011 – October 2012 795 in total (mean age 32.69±10.23 years; 501 males): 265 cases (HBsAg-positive blood donors, age range 18-55 years; 167 male + 98 female) + 530 controls (HBsAg-negative blood donors, age range 18-55 years; 334 male + 284 female)	Dental treatment	HBV infection

FIGURE LEGENDS

Figure 1: Flowchart of study selection for the search for systematic reviews (phase 1).

Figure 2: Flowchart for study selection for the search for individual studies (phase 2).

Figure 3: Forest plot for risk of TTI after dental treatment, including risk of bias graph.

Figure 4: Forest plot for risk of TTI's after tooth extraction, including risk of bias graph.

Figure 5: Forest plot for risk factors of TTI's after dental cleaning, including risk of bias graph.

Risk of bias legend

- (A) Inappropriate eligibility criteria
- (B) Inappropriate methods for exposure and outcome variables
- (C) Not controlled for confounding
- (D) Incomplete or inadequate follow-up
- (E) Other limitations

Risk of bias legend

- (A) Inappropriate eligibility criteria
- (B) Inappropriate methods for exposure and outcome variables
- (C) Not controlled for confounding
- (D) Incomplete or inadequate follow-up
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Figure 5

Risk of bias legend
(A) Inappropriate eligibility criteria
(B) Inappropriate methods for exposure and outcome variables
(C) Not controlled for confounding
(D) Incomplete or inadequate follow-up
(E) Other limitations

Figure S1

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