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Is sexual risk behaviour associated with an increased risk of transfusion-transmissible infections in blood donors from Western and Pacific countries? A systematic review and meta-analysis

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Background and Objectives The donor medical questionnaire is designed to aid blood establishments in supporting a safe blood supply. According to blood donor deferral policies, sexual risk behaviour (SRB) leads to a (temporary) deferral from blood donation. This systematic review aimed to scientifically underpin these policies by identifying the best available evidence on the association between SRB and the risk of transfusion transmissible infections (TTIs).

Materials & Methods Studies from three databases investigating the link between SRB (excluding men who have sex with men (MSM)) and TTIs (HBV, HCV, HIV, *Treponema pallidum*) in donors from Western and Pacific countries were obtained and assessed on eligibility by two reviewers independently. The association between SRB and TTIs was expressed by calculating pooled effect measures via meta-analyses. The GRADE methodology (Grades of Recommendation, Assessment, Development and Evaluation) was used to assess the quality of evidence.

Results We identified 3750 references and finally included 15 observational studies. Meta-analyses showed that there is a significant ($P < 0{\cdot}05$) positive association between the following SRB and HBV and/or HCV infection: having sex with an intravenous drug user (high-certainty evidence), receiving money or goods for sex (moderate-high certainty evidence), having a sex partner with hepatitis/HIV (moderate-certainty evidence) and paid for sex or anal sex (low-certainty evidence).

Conclusion Sexual risk behaviour (including having sex with an intravenous drug user, receiving money or goods for sex or having a sex partner with hepatitis/HIV) is probably associated with an increased risk of HBV/HCV infection in blood donors from Western and Pacific countries.

Key words: donor health, donor recruitment, donors.

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Introduction

The blood supply chain starts with the blood donor and ends with the patient. Various factors can affect the safety

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of blood supply including a range of donor, product and storage/handling factors. Importantly, collection of blood only from donors who are at low risk for transfusion-transmitted infections is a cornerstone of blood safety. A rigorous process to assess donor's eligibility is therefore essential to safeguard the health of both recipients of transfusion and blood donors themselves, while ensuring that eligible donors are not deferred unnecessarily [1].

An important safety tool to assess donor eligibility is the donor health questionnaire which primarily aims to identify risk behaviour for potential transfusion-transmissible infections (TTI) and to defer people from donation (temporarily). Deferral policies (often of 12 months duration), for persons whose sexual behaviour puts them at risk of acquiring TTIs, are commonly applied by blood transfusion services in Western countries [2]. Based on evidence from epidemiological and modelling studies, an international working group concluded that men who have sex with men (MSM) and commercial sex workers are groups at risk [3]. Hence, the two main approaches currently used for sexual behaviour eligibility assessment are time-based deferrals after the last male-to-male sexual contact and after high-risk sexual behaviour, usually defined as new partners or multiple partners of either sex.

As proposed by EU blood directives, an evidence-based approach is recommended for developing donor selection criteria on the best available scientific evidence [4]. In 2015, our group published a systematic review that identified studies describing the risk of TTIs in MSM blood donors [5]. Today, no systematic collection, synthesis and critically appraisal of studies is available that investigates the risk of TTIs in sexual risk behaviour other than MSM, such as a new sexual partner, paying for sex, group sex, multiple sex partners, received money or goods for sex, sex with an intravenous drug user, sex with a person infected with HBV, HCV, HIV, syphilis or other sexually transmitted disease. This information can support blood services and policy-makers to further scientifically underpin sexual risk behaviour items on the donor health questionnaire and with corresponding deferral policies.

The general aim of this systematic review was to identify and synthesize all available scientific evidence on the association between sexual risk behaviour (excluding MSM) and the risk of infection by transfusion-transmissible diseases in a Western blood donor population. This review will primarily inform policy-makers on donor selection by the Belgian Red Cross and other European blood services.

Material & methods

We carried out a systematic literature review according to a predefined protocol [6]. We planned and reported the systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA checklist, Appendix S1) [7].

Data sources and searches

A literature search was performed in MEDLINE (via the PubMed interface), Embase (via Embase.com) and the Cochrane Library for eligible studies from the time of inception of the database until April 2017. We developed search strategies for each database including the use of index terms and free text terms (Appendix S2). Search yields were exported to a citation program (EndNote X7·5), duplicates were discarded, and title and abstract screening was initiated. The reference lists of included studies and also the first 20 similar articles in PubMed were screened for other relevant publications.

Study selection

Studies were eligible for inclusion if they answered the following PICO question: "Is sexual risk behaviour (intervention/risk factor) a risk factor for transfusion-transmissible infections (TTIs) (outcome) compared to no sexual risk behaviour (comparison) in blood donors from Western and Pacific countries (population)?" The review was restricted to original articles published in English, French and Dutch. Relevant other foreign language references were assessed and potentially included if an English, Dutch or French title and/or abstract was available. Full texts of potentially relevant articles were reviewed according to the following inclusion and exclusion criteria:

Population

Inclusion: Blood donors, living in areas most relevant for our Blood Service, that is the following Western and Pacific countries according to the Cold War definition of Samuel P Huntington [8]: Northern, Western, and Southern Europe (Albania, Andorra, Austria, Belgium, Bosnia and Herzegovina, Croatia, Denmark, Estonia, Finland, France, Germany, Gibraltar, Greece, Iceland, Italy, Ireland, Kosovo, Latvia, Liechtenstein, Lithuania, Luxembourg, Macedonia, Malta, Monaco, Montenegro, the Netherlands, Norway, Poland, Portugal, San Marino, Serbia, Slovenia, Spain, Sweden, Switzerland, United Kingdom, Vatican City), the USA, Canada, Australia and New Zealand. *Exclusion:* Populations that were potentially eligible to give blood but not explicitly defined as blood donors, and populations containing blood donors but not exclusively blood donors.

Intervention/Risk factor

Inclusion: sexual risk behaviour such as a new sexual partner, paying for sex, group sex, multiple sex partners,

received money or goods for sex, sex with an intravenous drug user, sex with a person infected with HBV, HCV, HIV, syphilis or other sexually transmitted disease. *Exclusion:* Men who had sex with men (risk factor that was studied in another systematic review [5]). We excluded composite measures that combined different sexual risk behaviour factors (e.g. sexual promiscuity) or composite measures that combined a sexual risk behaviour factor of interest with another risk factor (e.g. sex with an intravenous drug user combined with number of men who had sex with men).

Comparison

Inclusion: no sexual risk behaviour.

Outcome

Inclusion: markers of TTIs from the following pathogenic microorganisms in the blood: HIV, HBV, HCV and *Treponema pallidum* (causing syphilis).

Study design

Inclusion: Experimental studies: randomised controlled trials, controlled clinical trials, before- and after-studies; Observational studies: cohort studies and case–control studies. *Exclusion:* Non-controlled studies, cross-sectional studies without appropriate analysis (i.e. case–control analysis), case reports, case series, letters, comments, opinion pieces and narrative reviews.

Two reviewers independently performed the title and abstract screening followed by the full-text assessment according to these inclusion and exclusion criteria. Disagreements were resolved by discussion or by consulting a third reviewer.

Data extraction

Data concerning study design, population characteristics, risk factor (i.e. sexual risk behaviour), outcome measures (markers of TTIs expressed as risk ratio, odds ratio or incidence ratio) and study quality were extracted independently by two reviewers. In the case that studies reported both unadjusted as well as adjusted effect measures, only the adjusted effect measures were extracted.

Grading of the evidence

The GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) was used to assess the certainty of the evidence [9]. The certainty of the evidence was graded as high, moderate, low or very low. Observational studies (e.g. case–control studies) receive an initial grade of low by default and are downgraded based on the following prespecified criteria: (1) limitations in study design in case the following items were present in the majority of studies: inappropriate eligibility criteria, inappropriate methods for exposure and outcome variables, not controlled for confounding, incomplete or inadequate follow-up, (2) inconsistency (substantial unexplained inter-study heterogeneity, I^2 >50% and $P < 0{\cdot}10$), (3) indirectness (presence of factors that limit the generalizability of the results), (4) imprecision (limited total population size or limited number of events ($n < 300$), and/or large 95% confidence intervals (no effect + relative risk reduction/increase >25%) and (5) publication bias (significant evidence of small-study effects). Three prespecified criteria might upgrade the certainty of the evidence: when a large magnitude of effect, with no plausible confounding, exists (upgrade with one level in case of a large effect (OR = 2–5), upgrade with two levels in case of a very large effect (OR > 5)), when there is a dose–response gradient or when all plausible confounders or other biases increase our confidence in the estimated effect.

Data synthesis

Review Manager 5·3 was used to perform meta-analyses. Heterogeneity was assessed by inspection of the forest plot and by using the Chi^2-test and the I^2 statistic. Significant heterogeneity was present in case $P < 0{\cdot}10$, I^2> 50% and no/limited overlap in the 95% confidence intervals exists (visual inspection). If these criteria were met, the meta-analysis was not carried out. Effect measures of association between sexual risk behaviour and markers of transfusion-transmissible infections were expressed as odds ratios (ORs) with or without adjustment for confounding factors (i.e. adjusted ORs and unadjusted ORs, respectively). By calculating log[OR] and its corresponding standard error (standard error=(upper limit of the 95% confidence interval – lower limit of the 95% confidence interval)/3·92), a random-effects model was constructed using the generic inverse variance method [10]. Firstly, the effect measures for each outcome (HIV, HBC and HCV) were pooled (one effect measure per study) in different models (one model per outcome). Secondly, different subgroup analyses (per outcome) were conducted to explain potential heterogeneity across studies: (1) matched studies with adjustment for confounding factors (via multivariate regression analysis) versus unmatched studies without adjusted effect measures (to explain the potential impact of matched groups and considering confounding factors) and (2) studies performed in European countries versus

non-European countries (to serve as a basis for the current European Directive). A *P*-value <0·05 was considered as statistically significant.

Results

Study selection

The systematic literature search resulted in a total of 2735 citations (after removing duplicates) which were scrutinised by two reviewers independently. Figure 1 represents the study selection process used. We eventually included 15 case–control studies comparing blood donors that were tested positive for HCV antibodies (in 14 studies), HBV antibodies (in two studies) or HIV antibodies (in one study) (cases) with donors that were seronegative for any infectious marker (controls). No studies were identified that reported associations between sexual risk behaviour and *Treponema pallidum*.

Sixty percent (n = 9) of the case–control studies were matched for age (n = 9), gender (n = 9), donor venue (n = 6), donation status (n = 3), donation date (n = 2), donation type (n = 1) and/or race/ethnicity (n = 1) whereas the other 6 case–control studies (40%) were unmatched. Mean age, gender and number of cases/controls were reported in seven studies, 12 studies and 15 studies, respectively: cases (mean age 37·2 years, 64% males, n = 4600) vs. controls (mean age 39.6 years, 62% males, n = 8656). In all studies, a structured questionnaire (via face-to-face/telephone interview or via email) dealing with a list of potential risk factors (including factors related to sexual risk behaviour) for HBV, HCV or HIV transmission was used. These questionnaires included the following sexual risk behaviour: sex with a drug user (12 studies), number of (lifetime) sexual partners (10 studies), sex partner with hepatitis/HIV (five studies), paid or received money for sex (four studies), sex with a blood transfusion recipient (three studies), anal sex (two studies), sex with partner from HBV endemic area (one study), orogenital sex (one study), sex during menstruation (one study). According to the CDC statistics, the mean HBV and HCV prevalence in the countries of included studies was low (0·44% and 0·87%, respectively) (Table S1) [11,12]. Five studies (33%) were published in the past ten years (2008–2018), three (20%) in the period between 2000 and 2007 and seven (47%) before 2000. About half of the included studies (47%) were conducted in the European region (United Kingdom (n = 3), Switzerland (n = 1), Denmark (n = 1), Serbia (n = 1) and Sweden (n = 1)). The other 8 studies were performed in the American regions ((Canada (n = 4) and USA (n = 3)) and in Australia (n = 1). Details on the characteristics of the included studies can be found in Table 1.

Association between sexual risk behaviour and HBV infection

Two unmatched studies conducted in Danish HBsAg-positive donors and American anti-HBc positive donors (without positive for HBV DNA) found that sexual risk behaviour was significantly associated with HBV infection (OR: 4·39, 95%CI[1·78, 10·86], P = 0·001 for paid sex; OR: 6·21, 95%CI [2·50, 15·43], P < 0·0001 for received money or goods for sex; pooled OR: 9·02, 95%CI [2·86, 28·49], P = 0·0002 for sex with an intravenous drug user; pooled OR: 4·22, 95%CI [2·14, 8·32], P < 0·0001 for sex partner with hepatitis; OR: 5·52, 95%CI [1·11, 27·45], P = 0·04 for sex partner with HIV). A statistically significant association for the factors group sex or multiple sex partners, sex partner from HBV endemic area or sex with blood transfusion recipient could not be demonstrated (Fig. 2) [13,14].

The evidence was graded as moderate for sex with an intravenous drug user (upgraded (+2) for a large effect, downgraded (−1) for indirectness); low for received money or goods for sex and sex partner with hepatitis/HIV (upgraded (+1) for a large effect, downgraded (−1) for indirectness); low for paid sex (downgraded (−1) for indirectness, upgraded (+1) for a large effect); very low for group sex or multiple sex partners, sex partner from HBV endemic area (downgraded for indirectness (−1) and imprecision (−1)), and sex with a blood transfusion recipient (downgraded for indirectness (−1) and imprecision (−1) and upgrade for a large effect (+1)) (Table S2).

Association between sexual risk behaviour and HCV infection

Fourteen case–control studies investigated the association between sexual risk behaviour and HCV infection and found a significant association for the following behaviour: received money or goods for sex (pooled OR: 5·78, 95%CI [1·92, 17·37], P = 0·002); sex with an intravenous drug user (pooled OR: 8·19, 95%CI [5·87, 11·43], P < 0·00001); sex partner with hepatitis (pooled OR: 4·84, 95%CI [2·32, 10·07], P < 0·0001); orogenital sex (OR: 1·50, 95%CI [1·10, 2·05], P = 0·01); anal sex (OR: 1·71, 95%CI [1·21, 2·41], P = 0·002); sex during menstruation (OR: 2·42, 95%CI [1·75, 3·35], P < 0·00001); and sex with a blood transfusion recipient (pooled OR: 1·88, 95%CI [1·16, 3·03], P = 0·01). A statistically significant association for the following sexual risk behaviour could not be demonstrated: group sex or multiple sex partners (although a trend towards an increased risk was observed), paid for sex and sex partner with HIV (Fig. 3) [14–27].

Subgroup analyses revealed that the well-designed case–control studies (i.e. matched groups and considering

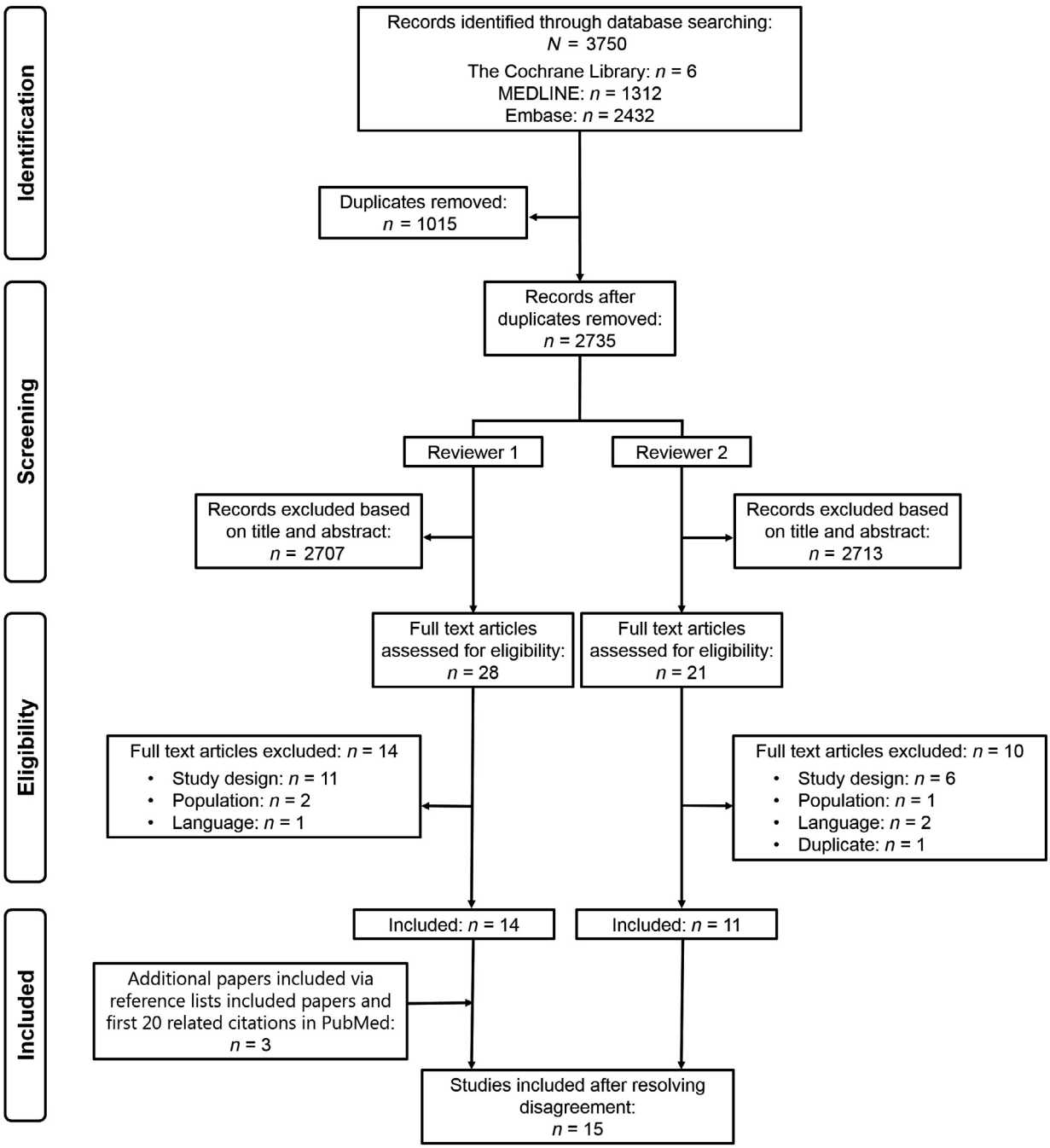

Fig. 1 Study identification and selection process of the systematic review.

other confounding variables via a multivariate logistic regression analysis) found a (statistically) significant relation with sexual risk behaviour (Fig. S1). These findings were also observed in the matched case–control studies without adjustment for confounding factors (Fig. S2). No statistically significant associations were found in the unmatched case–control studies with/without adjustment for confounding factors, except for sex with an intravenous drug user (Figs S3 and S4, respectively). Evidence from the European studies showed a statistically significant link with 1 sexual risk behaviour item (i.e. sex with an intravenous drug user) whereas non-European studies found 8 sexual risk behaviour items to be significantly related to HCV infection (Figs S5 and S6).

The evidence was graded as moderate for received money or goods for sex and sex with an intravenous drug

Table 1 Characteristics of included studies

Author, year, Country	Study design	Population	Risk factor	Risk factor assessment and laboratory testing procedures
Outcome: HBV infection				
Christensen, 2001 [13], Denmark	Observational: case–control study (unmatched)	Danish blood donors (County of Funen, Denmark): 44 repeat-reactive donors confirmed as anti-HBc positive: median age of 48 years, 52.3% males (cases) were compared with 585 consecutive anti-HBc-negative blood donors: median age of 43 years, 64% males (controls)	(1) Lifetime sexual partners (2) Bought or sold sex (3) Sex with partner from HBV endemic area (4) Sex partner with hepatitis (5) Sex partner drug addict	Risk factor assessment: information on risk factors was assessed by an anonymous questionnaire derived from Danish donor selection criteria and the literature of risk factors for hepatitis B.Laboratory testing: Screening for anti-HBc and repeat-reactive samples were confirmed by supplementary testing.
Outcome: HCV infection				
Delage, 1999 [15], Canada	Observational: case–control study (matched for sex, age, site of donation and date)	Blood donors from four Canadian Transfusion centres (Montréal, Toronto, Winnipeg and Vancouver): 267 confirmed anti-HCV-positive blood donors (cases) and 1068 seronegative blood donors (controls). Age cases/controls: <20 years: 0.9%, 20–40 years: 61%, >40 years: 38.1. Gender cases/controls: 67% males	(1) Having had sex with someone who previously received a transfusion (2) Orogenital sex (3) Anal sex (4) Lifetime sexual partners (5) Sex with intravenous drug user (6) Sex during menstruation (7) Sex with a person with hepatitis	Risk factor assessment: The interview was carried out by telephone using a structured questionnaire consisting of 107 questions.Laboratory testing: Cases tested positive for HCV antibody by both ELISA and strip immunoblot assay. Controls were blood donors who tested negative for anti-HCV by ELISA.
Goodrick, 1994 [17], United Kingdom	Observational: case–control (matched for age and sex)	Blood donors (South Western Transfusion Centre in England): 50 HCV antibody-positive blood donors: 35 (range 24–60) years, 64% males (cases) and 50 matched blood donors without HCV infection: 37	(1) Sex with IVDU (2) Paid sex	Risk factor assessment: Socio-demographic details and data on exposure to known risk factors for HCV were systematically collected by use of a structured questionnaire. For geographical reasons a small number of the control interviews, but no case interviews, were done over the

Table 1 (Continued)

Author, year, Country	Study design	Population	Risk factor	Risk factor assessment and laboratory testing procedures
		(range 21–57) years and 64% male (controls).	(3) More than 10 partners in past 5 years	telephone.Laboratory testing: A unit of blood was considered to show evidence of HCV if one or more of the following tests were positive: 1) a minimum of two ELISA assays (Abbatt, UBI, Ortho or Welcome); 2) two or more bands by recombinant immunoblot assay (RIBA-2); 3) HCV RNA by polymerase chain reaction (PCR).All confirmed positives were positive by both ELISA and RIBA-2 assays. AU indeterminate cases with positive ELISA but indeterminate RIBA-2 were included when PCR was found to be positive.
Kaldor, 1992 [18], Australia	Observational: case–control (unmatched)	220 Australian blood donors with positive RIBA for HCV antibodies: 64% males, 10% >45 years (cases) and 210 blood donors without HCV infection: 60% males, 44% >45 years (controls)	More than one lifetime sexual partner	Risk factor assessment: A standard questionnaire sought information about demographic characteristics, history of liver disease or its symptoms, contact with hepatitis or sexually transmissible disease, number of lifetime sexual partners and a number of factors related to potential parenteral exposure to HCV, including history of injecting drug use, blood transfusion and having been tattooed.Laboratory testing: Initial screening was by ELISA based on the C100-3 antigen. All donations which were repeatedly reactive on initial screening were tested using the RIBA.
MacLennan, 1994 [19], United Kingdom	Observational: case–control (unmatched)	117 UK blood donors confirmed to be anti-HCV positive: 58% males, 41% >40 years (cases) and 771 donors: 62% males, 43% >40 years (controls 1)Because sexual risk behaviour was not asked to controls 1, a group of 14 false-positive donors was selected (controls 2)	Sexual contacts of IVDU	Risk factor assessment: During a counselling interview, a questionnaire was administered, enquiring into any history of blood transfusion, drug use of scarification (ear-piercing, tattooing, acupuncture or electrolysis). The control group was asked to complete an anonymous questionnaire about blood transfusion history, scarification and occupations with a potential for exposure to blood or needles.Laboratory testing: Screening by ELISA-2, reactive sera were retested in duplicate using the same assay. Repeatably reactive donations -> RIBA-2. When 2 or more antigens reactive on RIBA-2 -> 'confirmed positive' (included for this analysis), only 1 antigen reactive -> 'indeterminate' (excluded from our analysis), all viral antigens negative -> 'false-positive' (excluded from our analysis).
Mitrovic, 2015 [20], Serbia	Observational: (multi-centre) case–control (matched for sex and age)	32 Serbian blood donors (from 10 transfusion centres) with confirmed anti-HCV positivity: 78.1% males, 9%	(1) Anal sex	Risk factor assessment: An anonymous questionnaire was compiled and completed by the participants in private. The first part is devoted to general demographic data, the second

Table 1 (Continued)

Author, year, Country	Study design	Population	Risk factor	Risk factor assessment and laboratory testing procedures
		>45 years (cases) and 64 seronegative blood donors: 78.1% males, 9% >45 years (controls)	(2) number of sexual partners	part explores all the risk factors confirmed or discussed previously in the literature.Laboratory testing: Every single unit of blood is tested for transmissible diseases: HIV infection, hepatitis B, hepatitis C and syphilis. A third-generation HCV ELISA test, which detects anti-HCV antibodies, is used to test the blood. If the initial test is positive, then one more testis performed – the ELISA confirmation test.
Murphy, 2000 [21], USA	Observational: case–control (matched for age, sex, race/ethnicity, blood centre, and first-time versus repeat-donor status)	2316 HCV-seropositive US blood donors (cases): 53% males, 51% >40 years and 2316 seronegative US donors (controls): 55% males, 51% >40 years	(1) Sex with an IDU (2) Sex with hepatitis case (3) Sex with transfusion recipient (4) Gave money for sex (5) Received money for sex (6) Number of lifetime partners	Risk factor assessment: anonymous questionnaires were mailed by the blood centres to all HCV seropositives and controls.Laboratory testing: HCV cases had positive reactions on both an enzyme immunoassay and recombinant immunoblot.
Neal, 1994 [22], United Kingdom	Observational: case-control (matched for age, sex and donor venue)	74 blood donors from United Kingdom confirmed positive for hepatitis C infection: 62% males, mean age 34.6 years (males) and 37.6 years (females) (cases) and 150 matched controls: 61% males, mean age 34.2 years (males) and 36.6 years (females) (controls)	(1) Sex with drug user (2) Number of lifetime partners	Risk factor assessment:Interview using a structured questionnaire concerned with personal, past medical, family, occupational and travel histories, along with specific questions on potential risk factors (misuse of injected drugs, receipt of blood or blood products, tattoos, ear-piercing, acupuncture, number of sexual partners, and sexual orientation).Laboratory testing: Routine screening ELISA test + confirmatory test using the RIBA-2 test.
O'Brien, 2008 [23], Canada	Observational: case–control (matched for age (±2 years), sex, date of donation (±1 day), and site of donation	184 HCV-positive first-time donors from 4 Canadian blood centres (cases) and 736 matched HCV-negative blood donors that were randomly selected (controls).Age and gender not specified per group in article.	Sex with IVDU	Risk factor assessment: confidential scripted telephone interview about risk factorsLaboratory testing: First, second and third-generation ELISA + confirmatory testing by RIBA, since 1999 NAT was implemented as an additional screen assay for HCV. Donors were considered to be positive if they were confirmed positive for anti-HCV and/or HCV NAT.
O'Brien, 2010 [24], Canada	Observational: case–control (matched for age, sex, donation status and	145 Canadian blood donors: 29 anti-HCV positive IVDU (cases) (90% >40 years, 69% males) and 116 anti-HCV negative	Had sex with an IVDU	Risk factor assessment: Via an anonymous questionnaire, donors were asked whether they had ever injected non-prescription intravenous drugs, as well as questions about

Table 1 (Continued)

Author, year, Country	Study design	Population	Risk factor	Risk factor assessment and laboratory testing procedures
	geographic region of donation)	(controls) (90% >40 years, 69% males)17–29 years: 6,9%, 30-39 years: 3,4%, 40–49 years: 34,5%, 50 + years: 55,2%; 69% was male.		other drug taking and sexual risk factors and demographic questions.Laboratory testing: First, second and third-generation ELISA + confirmatory testing by RIBA, since 1999 NAT was implemented as an additional screen assay for HCV. Donors were considered to be positive if they were confirmed positive for anti-HCV and/or HCV NAT.
Orton, 2004 [25], USA	Observational: case–control (unmatched)	65 confirmed American HCV + blood donors: 54% males, mean age of 34 years (cases) and 225 HCV- (falsely positive) controls: 54% males, mean age of 41 years (controls)	(1) Sex with IVDU (2) Two or more sexual partners (3) Sex partner had hepatitis	Risk factor assessment: A questionnaire adapted from the CDC's Sentinel Counties Study of Acute Viral Hepatitis was used. This survey included questions relating to the donor's demographic characteristics, health, behaviour, and travel information.The questionnaires were administered in the course of a face-to-face interview, conducted by trained donor counsellors ordonor centre physicians.Laboratory testing: NAT-reactive donors were identified + confirmation HCV RNA result. Cases = positive for the presence of HCV RNA, controls = false-positive NAT results (i.e. nonreactive transcription-mediated amplification and/or PCR results in supplemental testing on the donation sample and/or on a follow-up sample and were unequivocally free of HCV infection.
Shev, 1995 [26], Sweden	Observational: case–control (matched for age and sex)	51 2nd generation anti-HCV and HCV-RNA positive Swedish blood donors: 86% males, median age 32 years (range 25–53) (cases) and 51 matched anti-HCV negative blood donors: age and gender not specified (controls)	Sex with IVDU	Risk factor assessment: Interview using a questionnaire dealing with potential risk factors for hepatitis C transmission. Both the interviewer and the interviewed blood donors were aware of the donor's HCV status.Laboratory testing: Routine screening ELISA test (1^{st} or 2^{nd} generation) + confirmatory test using the RIBA test + tested for HCV-RNA (i.e. chronic hepatitis infection)
Tullen, 1993 [27], Switzerland	Observational: case–control (unmatched)	74 anti-HCV ab Swiss donors (cases) and 103 donors with high ALAT levels, but with no antibodies to HCV nor detectable circulating viral DNA (controls).Age/gender not reported	Multiple sexual partners (>5 during 1 year)	Risk factor assessment:Different risk factors were assessed by a questionnaireLaboratory testing:Anti-HCV antibodies were detected by ELISA 2^{nd} generation + determination of ALAT levels and looked for circulating RNA virus by amplification of the non-coding region of the viral genome (RTPCR).
Outcome: HBV infection and HCV infection				
Goldman, 2009 [16], Canada	Observational: case–control (matched for age (±5 years), sex, donation type, donation status (first	Canadian whole blood donors: 88 HCV-positive donors (HCV cases), 69 HBsAg-positive donors (HBV cases) and 349	Sex with IVDU	Risk factor assessment: An anonymous questionnaire was mailed. Donors were asked if they had ever had a tattoo, ears pierced, or any other body piercing and whether or not they had participated in the activity in the past

Table 1 (Continued)

Author, year, Country	Study design	Population	Risk factor	Risk factor assessment and laboratory testing procedures
	time or repeat) and geographic region	matched donors (HCV controls), 275 matched donors (HBV controls)		6 months.Laboratory testing: Antibody to human immunodeficiency virus (HIV)-1/2, hepatitis C virus (HCV), and human T-lymphotropic virus (HTLV)-I/II, and hepatitis B surface antigen (HBsAg) was detected with a chemiluminescent assay (Abbott PRISM HIV O Plus, Abbott Diagnostics Division, Wiesbaden, Germany). Confirmatory testing for HIV was performed using the HIV-1 Western blot (Calypte Biomedical Corp., Rockville, MD), for HCV using a third-generation recombinant immunoblot assay (Chiron Corp., Emeryville, CA), for HBsAg using the Abbott PRISM confirmatory assay, and for HTLV-I/II using the HTLV Western blot assay (Version 2.4, Genelabs Diagnostics Ltd., Singapore Science Park, Singapore). Nucleic acid testing (NAT) was performed for HIV and HCV (Roche Molecular Systems, Branchburg, NJ) using 24-unit minipools.
Outcome: HBV infection, HCV infection and HIV infection				
Custer, 2015 [14], USA	Observational: case–control (unmatched)	American donors with serologic and NAT or NAT-only confirmation testing on: 196 HIV cases: 76% males, 32 ± 11.8 years (cases 1), 292 HBV cases: 65% males, 37.8 ± 14.0 years (cases 2), 316 HCV cases: 59% males, 44.7 ± 12.5 years (cases 3) and 1587 donors with false-positive results: 48% males, 41.7 ± 15.7 years (controls)	(1) Multiple partners, last year (2) Sex for money or drugs, ever (3) Sex with injecting drug user (4) Sex with hepatitis positive partner (5) Sex with HIV positive partner (6) Sex with blood transfusion recipient	Risk factor assessment:A risk factor questionnaire was developed that focused on behaviours associated with human-to-human transmission of HIV, HCV, HBV and HTLV. Interview via telephone, all participants who completed the risk factor interview were provided a fixed participation reimbursement.Laboratory testing: Confirmed positive = viral-specific NAT + serologically confirmed or if seronegative and NAT reactive and confirmed by virus-specific NAT using an independent sample. False-positive = repeat reactive testing on one test but unconfirmed based on further serologic testing and NAT.

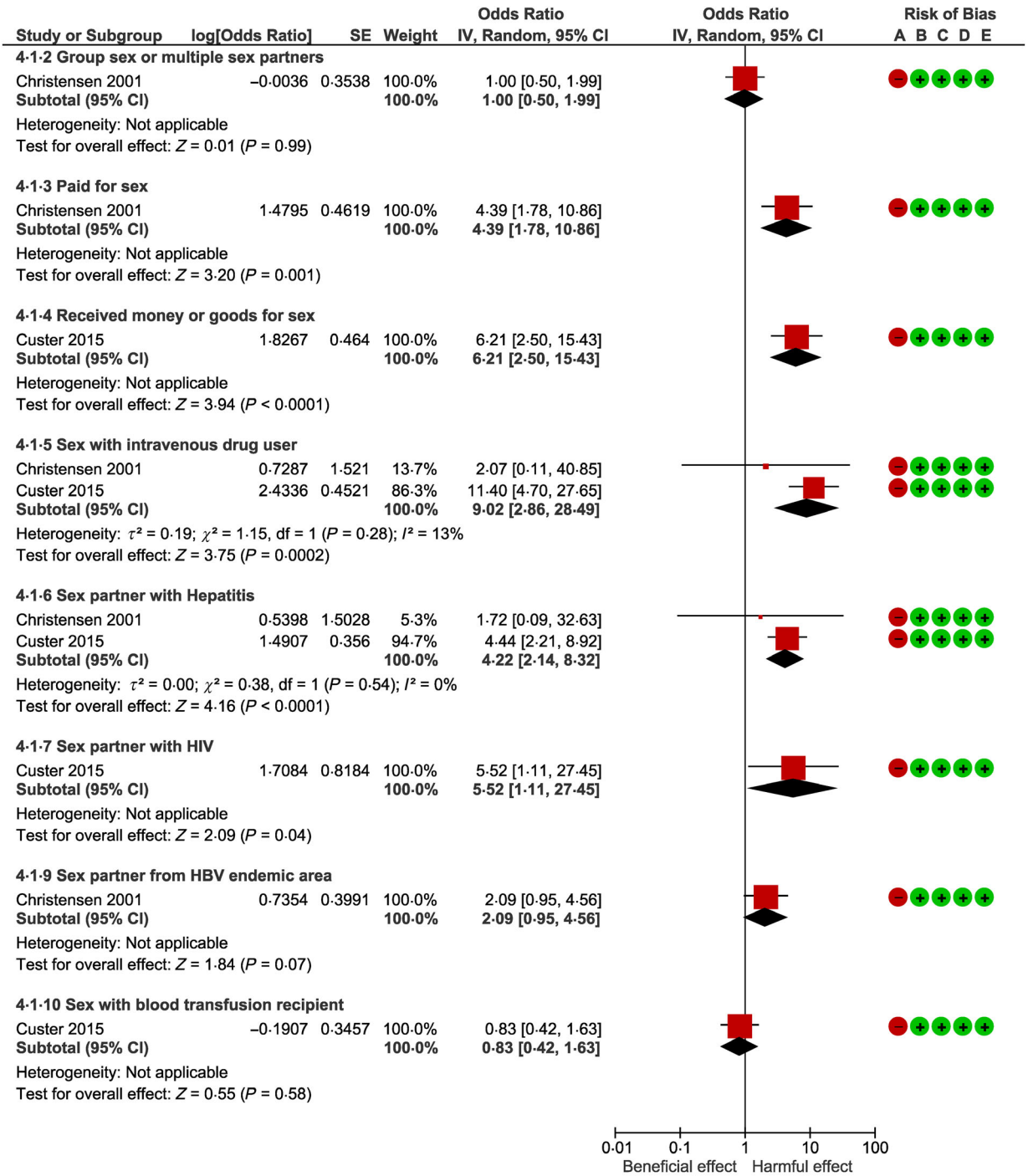

Fig. 2 HBV: study-specific odds ratios (ORs) representing the association between sexual risk behaviour and infection in blood donors. Each dot represents the odds ratio of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. ⊕Low risk of bias, ⊖high risk of bias, ?unclear. [Colour figure can be viewed at wileyonlinelibrary.com]

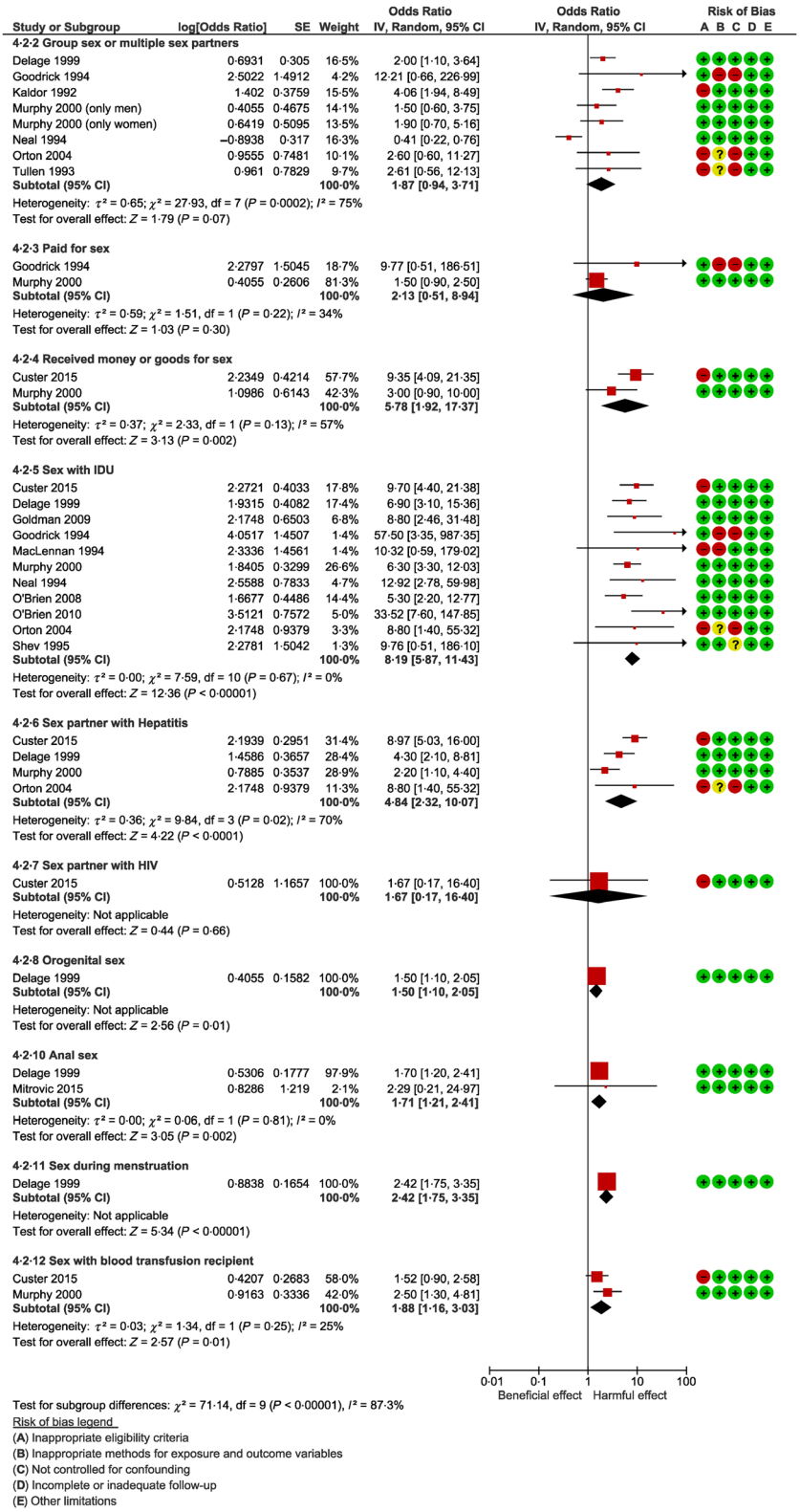

Fig. 3 HCV: study-specific odds ratios (ORs) representing the association between sexual risk behaviour and infection in blood donors. Each dot represents the odds ratio of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. ⊕Low risk of bias, ⊖high risk of bias, ?unclear. [Colour figure can be viewed at wileyonlinelibrary.com]

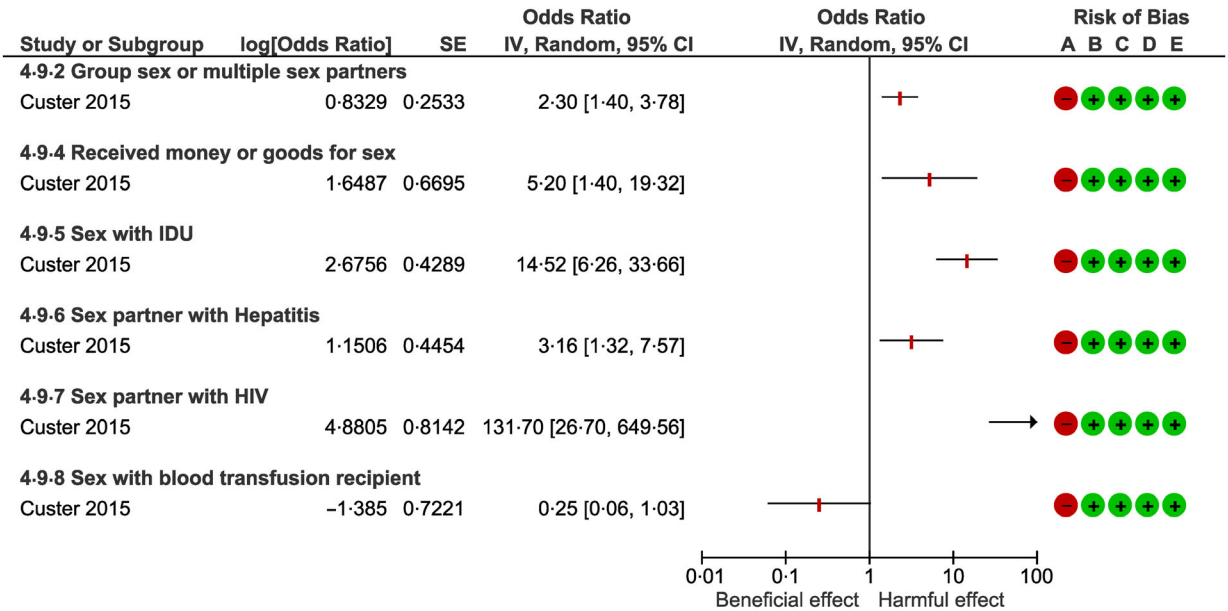

Fig. 4 HIV: study-specific odds ratios (ORs) representing the association between sexual risk behaviour and infection in blood donors. Each dot represents the odds ratio of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. Low risk of bias, high risk of bias, unclear. [Colour figure can be viewed at wileyonlinelibrary.com]

user [upgraded (+2) for a very large effect, downgraded (−1) for indirectness]; low for sex partner with hepatitis [upgraded (+1) for a large effect, downgraded (−1) for indirectness]; low for paid for sex [downgraded (−1) for indirectness, upgraded (+1) for a large effect] and anal sex [downgraded (−1) for indirectness]; very low for sex partner with HIV [downgraded for indirectness (−1) and imprecision (−1)] and group sex or multiple sex partners, origenital sex and sex during menstruation [downgraded for imprecision (−1) and indirectness (−1)] (Table S3).

Association between sexual risk behaviour and HIV infection

One unmatched case–control study conducted in American donors found that the following sexual risk behaviour was significantly associated, after controlling for donor status, age, gender, race/ethnicity, income and other risk factors (tattoo, piercing, injecting drug use, MSM and detention): group sex or multiple sex partners (OR: 2·30, 95%CI [1·40, 3·78]); received money or goods for sex (OR: 5·20, 95%CI [1·40, 19·32]; sex with an intravenous drug user (OR: 14·52, 95%CI [6·26, 33·66]); sex partner with hepatitis (OR: 3·16, 95%CI [1·32, 7·57]) and sex partner with HIV (OR: 131·70, 95%CI [26·70, 649·56]). A statistically significant difference in HIV infection for the risk factor sex with a blood transfusion recipient could not be demonstrated (Fig. 4) [14].

The evidence was graded as very low for all sexual risk behaviour [downgraded for indirectness (−1)] (Table S4).

Discussion

The present systematic review identified 15 case–control studies that investigated the association between sexual risk behaviour (excluding MSM) and TTIs in a Western blood donor population. Meta-analyses showed that the following sexual risk behaviour is probably linked to TTIs (moderate certainty evidence): having sex with an intravenous drug user (HBV/HCV infection), received money or goods for sex (HBV/HCV infection) or sex partner with HIV (HBV infection). There may be an association between a sex partner with hepatitis and HBV/HCV infection or between paid for sex and HBV infection (low

certainty evidence). We are uncertain whether other sexual risk behaviour is associated with an increased HBV/HCV/HIV infection risk (very low certainty evidence). No studies were identified that reported associations between sexual risk behaviour and *Treponema pallidum*.

The major strength of the present systematic review is that it is the first review that used rigorous and transparent Cochrane methodology standards to investigate the link between sexual risk behaviour, other than MSM, and TTIs in a Western blood donor population. Moreover, we were able to quantify the pooled effect estimates via different meta-analyses. Hereby, we improved statistical power and precision (due to larger sample size), we quantified inconsistencies in results between studies and conducted appropriate subgroup analyses.

Three decades after the implementation of donor deferral policies, sexual risk behaviour (especially MSM) has been frequently discussed in the media, in the scientific literature and among policy-makers. For example, European Union legislation (from 2004) distinguishes sexual behaviour "at risk" and "at high risk" to define a temporary and permanent deferral from blood donation, respectively [28]. A resolution of the European Committee of Ministers concluded in 2013 that countries should only introduce deferral policy for a given sexual behaviour when having demonstrated that this sexual behaviour does put the donors at high risk of acquiring blood-borne infectious diseases [29]. Based on the best available evidence [3,5,14,30–34], national regulatory bodies worldwide have changed their recommendation from the permanent deferral for MSM to a temporary deferral since the last MSM contact (usually 12 months) [2].

In 2014, the US Food and Drug Administration (FDA) concluded that for other sexual behaviour deferrals than MSM, insufficient data are available to support a change to their existing deferral recommendations [35]. Therefore, the results of this review can be used as a scientific basis for policy-makers to further scientifically underpin the current international legislation concerning sexual behaviour deferrals.

There are four limitations concerning the design and publication date of the included studies, the selection criteria of this review and the (non-)compliance of filling in the medical questionnaire. Firstly, only observational data from case–control studies were included in this review. Causal associations are generally difficult to establish and interpretation is limited by potential confounding effects of other established risk factors such as the use of intravenous drugs, previous transfusion or percutaneous needle treatments (tattoo, acupuncture or piercing). Our results showed that, after correction for these confounding variables, the association between sexual risk behaviour and HCV infection was still present. Further studies of higher quality are needed (e.g. prospective cohort studies) to gain a comprehensive understanding of the association between sexual risk behaviour and TTIs. Secondly, the data from this review were extracted from predominantly older studies (i.e. 80% of studies were conducted before 2010) and only apply to a certain geographic area, namely Western countries (Northern, Western and Southern Europe, USA, Canada, Australia and New Zealand). Therefore, assuming that hygiene regulations and changes in TTI prevalence improved over time, our data might overestimate the current risk of sexual risk behaviour and TTIs. In addition, because the epidemiology of sexual transmissible diseases, sexual risk behaviour and hygiene regulations are different in developing countries, the results of this systematic review cannot be generalized.

Thirdly, searching in only three databases might serve as a potential limitation, however, with the identification of 15 studies, the potential impact of additional evidence from other databases or grey literature sources on our results/conclusions is expected to be minimal. Finally, we did not account for (non-)compliance in filling out the medical questionnaire, as it is impossible to deduce from the studies what percentage of donors were honest about sexual risk behaviour. Further research about the impact of different deferral strategies on non-compliance is needed.

Besides appropriate donor selection criteria, laboratory testing, safe processing and appropriate use of blood are also important to ensure that recipients receive the safest possible blood products. Today, many blood banks have implemented nucleic acid testing (NAT) in addition to antibody testing for HBV/HCV/HIV, which reduced the window period to less than 10 days and introduced standardization of procedures such that error rates in testing are extremely low [36,37]. Nevertheless, all blood screening programs have limitations and absolute safety, in terms of freedom from infectious risk, cannot be guaranteed. In order to establish effective national programs to ensure quality-assured screening of donated blood for TTIs, blood banks need to additionally invest in the safety of the blood supply by developing evidence-based donor selection criteria.

Conclusion

Evidence from a systematic review of 15 observational studies showed that sexual risk behaviour (including having sex with an intravenous drug user, receiving money or goods for sex or having a sex partner with hepatitis/HIV) is probably associated with an increased risk of HBV/HCV infection in blood donors from Western and Pacific countries. This review serves as a direct scientific basis for blood donor deferral policies on sexual risk behaviour.

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Conflict of interests

The authors declare that they have no conflicts of interest relevant to the manuscript. This work was made possible through funding from the Foundation for Scientific Research of the Belgian Red Cross.

Author contributions

VC, PV and EDB conceived and designed the topic; HVR and WM analysed the data; HVR and WM wrote the paper; HVR, VC, PV and EDB formulated the research question and selection criteria; HVR and WM performed the literature search and study selection.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Study-specific odds ratios (ORs) representing the association between sexual risk behaviour and HCV infection in blood donors. Subgroup analysis: matched groups with adjustment for confounding factors. Each dot represents the odds ratio of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis.
Fig. S2 Study-specific odds ratios (ORs) representing the association between sexual risk behaviour and HCV infection in blood donors. Subgroup analysis: matched groups without adjustment for confounding factors. Each dot represents the odds ratio of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis
Fig. S3 Study-specific odds ratios (ORs) representing the association between sexual risk behaviour and HCV infection in blood donors. Subgroup analysis: unmatched groups with adjustment for confounding factors. Each dot represents the odds ratio of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis.
Fig. S4 Study-specific odds ratios (ORs) representing the association between sexual risk behaviour and HCV infection in blood donors. Subgroup analysis: unmatched groups without adjustment for confounding factors. Each dot represents the odds ratio of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis.
Fig. S5 Study-specific odds ratios (ORs) representing the association between sexual risk behaviour and HCV infection in blood donors. Subgroup analysis: studies conducted in European countries. Each dot represents the odds ratio of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis.
Fig. S6 Study-specific odds ratios (ORs) representing the association between sexual risk behaviour and HCV infection in blood donors. Subgroup analysis: studies conducted in non-European countries. Each dot represents the odds ratio of

the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis.

Table S1 HBV/HCV prevalence of the general population across countries of included studies (according to the CDC statistics). N/A: not available.
Table S2 GRADE assessments for outcome HBV infection. CI:Confidence interval; OR: Odds ratio; a. Limited generalizibility: few and/or old studies; b. Large variability in results.
Table S3 GRADE assessments for outcome HCV infection. CI: Confidence interval; OR: Odds ratio; a. Limited generalizibility: few and/or old studies; b. Large variability in results.
Table S4 GRADE assessments for outcome HIV infection.
Appendix S1 PRISMA checklist.
Appendix S2 Detailed information on the search strategies in the different databases.