TECHNICAL REPORT

Laboratory testing of non-partner sperm donors

An assessment of potential risks involved in changing the current testing protocols for HIV, hepatitis B and hepatitis C

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An assessment of potential risks involved in changing the current testing protocols for HIV, hepatitis B and hepatitis C

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Assisted reproductive technology
CD	Communicable disease
DG	EU Directorates-General
DWP	Diagnostic window period
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ESHRE	European Society of Human Reproduction and Embryology
EIA	Enzyme immunoassay
FFP	Fresh frozen plasma
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
LN	Liquid nitrogen
NAT	Nucleic acid test
SoHO	Substances of human origin
WHO	World Health Organization

Executive summary

The European Centre for Disease Prevention and Control was asked by the European Commission to assess the risk involved in changing the testing requirements for HIV (human immunodeficiency virus), hepatitis B virus (HBV), and hepatitis C virus (HCV) with regard to the quality and safety of non-partner semen donations. Suggested changes in testing requirements will be compared to the requirements defined in Commission Directive 2006/17/EC [1]: current EU legislation requires the serological screening of blood samples from non-partner donors for the presence of HBV, HCV and HIV each time semen is donated. (Throughout this document, this protocol will be referred to as the 'recommended protocol'.)

An alternative Danish protocol requires blood tests for non-partner semen donors at the first semen donation, and every three months after that, as long as donations are ongoing. (The Danish protocol will be called 'alternative protocol' throughout this document). Both serological testing protocols require that semen donations can only be released for human application when the donor blood sample has re-tested negative after the six months of quarantine.

The recommended protocol also stipulates that semen can be released for use without repeat testing after six months if the blood sample of the semen donor is additionally tested using nucleic acid testing (NAT) for HIV, HBV and HCV at the time of donation. According to the alternative protocol, NAT in addition to serological (NAT&ST) screening is applied at first donation, with subsequent NAT&ST retesting every 90 days. Semen donated at the time of screening may be released for use if negative results are obtained. Semen donated within the period of 90 days between NAT&ST screenings may be released for use if test results at the end of this period were negative. Quarantine of semen donation for 180 days is not necessary.

ECDC addressed this issue by setting up an internal expert group. In their assessment, the ECDC experts considered the estimated residual risk of HBV, HCV and HIV transmission through semen donation based on a risk model utilising the incidence, prevalence, and laboratory diagnostic window period (DWP) for these infections [2].

A literature search was performed sifting through literature from 2007 onwards. The search could not identify studies that: a) compare the risk of communicable disease transmission employing recommended or alternative screening protocols; b) estimate the prevalence of previously undiagnosed hepatitis or HIV infection in healthy donors or couples undergoing assisted reproduction procedures; and c) describe any incidents connected to the release for use of non-partner sperm donated in the DWP of HBV, HCV and HIV in recent years.

The evaluation of the Danish protocol shows that this alternative protocol very likely covers the mean and upper limits of serological DWPs for anti-HIV, HBsAg and anti-HCV testing, to an even higher extent than the protocol recommended by legislation. Thus, the alternative protocol removes the element of the residual risk related to possible HIV-, HBV- and HCV-positive semen donations made within the DWP. It is therefore unlikely that Danish changes in the serological screening protocol pose a higher risk to the quality and safety of non-partner semen donations than the recommended protocol. In the recommended protocol, when a donor blood sample is screened using NAT&ST, donations made at the time of testing may be in the molecular DWP. In the alternative NAT&ST screening protocol, semen donated close to, or at the time of screening, may also be in the molecular DWP. To mitigate this risk, it is suggested that the donations at the time of screening (including first-time donations) and donations in the period between the two periodically repeated screenings should be released only after a negative result of the latest NAT test that was performed at a date beyond the DWP (upper limit) of that test. Tissue and cell establishments should apply the longest DWP recommended by the manufacturer of the used laboratory test.

In addition, it is suggested that the alternative screening protocol should have a clearly defined maximum period for serial semen donations and a clearly defined minimal time between subsequent donations that is still appropriate for donations to be considered as serial donation. If the period between semen donations is longer than 90 days, any subsequent donation should be treated as a first-time donation, and blood samples should be screened at the time of semen donation.

Background and methods

In July 2017, the ECDC Director received a communication from the European Commission, Directorate-General Health and Food Safety, Directorate B, which included the following request:

> The EU legislation on the quality and safety of tissues and cells sets out European minimum requirements for the donation, testing, processing, storage and distribution of tissues and cells, including reproductive cells such as sperm and oocytes. During the latest meeting of the Expert group on Substance of Human Origin, the National authorities competent for tissues and cells have asked the Commission to organize for a scientific review of the differences in safety and quality between different testing protocols for testing of sperm donors for infectious markers.
>
> Several Member States have raised concerns about the requirements of testing for HIV and hepatitis B and C for the non-partner donation of reproductive cells, particularly sperm. It concerns a protocol in which sperm donors are tested for HIV, hepatitis B, hepatitis C and syphilis at the time of each sperm collection, which can take place multiple times per week, during a period of several months. Some Member States argue that this testing requirement does not necessarily add to the safety of the process compared to a protocol which foresees a test before the first collection, and every three months after that, as long as donations are ongoing, and again 6 months after the last collection, with release of the gametes for human application only when the 6 month sample has tested negative.
>
> We would like ECDC to develop a solid evidence base, analysing the impact of the differences between these testing protocols on the quality and safety of reproductive cells from non-partner donors.
>
> We believe such an assessment could build effectively on the 2010 assessment developed by ECDC for testing protocols for partner donation of sperm. We would be grateful if ECDC could complete this work by 1 October 2017, so that we can present the findings to the next meeting of the Expert Group which is foreseen on 1–2 December. My services remain at your disposal for further information. Your services can contact Ms Deirdre Fehily (Deirdre.fehily@ec.europa.eu) or Mr Stefaan Van der Spiegel (Stefaan.van-der-spiegel@ec.europa.eu) for further follow-up.

According to the founding regulation of ECDC, Regulation (EC) No 851/2004 Art 9(2) [3], 'the Centre may be requested by the Commission, the Member States, third countries and international organisations (in particular the WHO) to provide scientific or technical assistance in any field within its mission. Scientific and technical assistance provided by the Centre shall be based on evidence-based science and technology'.

Evidence-based public health

Evidence-based decision-making in a public health setting is to carefully incorporate the best available scientific evidence from research and other reliable sources with considerations of values, perceived needs and recourses in the given context. Evidence-based medicine is often defined as a systematic approach to clinical problem solving which allows the integration of the best available research evidence with clinical expertise and patient values [4].

A public health decision might be rather complex and needs to take several determinants of health into account, like genetic factors, lifestyle, physical environment, socioeconomic conditions, biological environment and health services at different levels [5]. Only some of these factors are relevant to the prevention and control of HIV and hepatitis B and C in the donation of reproductive cells.

Evidence-based methodologies

ECDC carried out this analysis in accordance with the following steps of evidence-based methodologies:

- Formulate questions
- Search for evidence
- Assess the evidence
- Formulate an answer
- Disseminate and implement
- Evaluate

Question and definitions

The European Commission has requested that ECDC should assess whether an alternative testing protocol poses a risk to the quality and safety of reproductive cells (particularly semen) from non-partner donors. Since the alternative screening protocol is applied only to semen donation, this assessment only deals with the infectious safety of non-partner semen donations with regard to HIV, HBV and HCV transmission.

The screening of non-partner semen donors for syphilis has not been considered in the assessment because the screening policy of all tissues and cells for the presence of *Treponema pallidum* is under evaluation by the Commission.

For the purpose of this assessment, the expression 'the quality and safety' is used to describe the infectious safety of non-partner semen donation in terms of HIV, HBV and HCV transmission.

Assisted reproductive technologies and blood-borne infections

According to the European Directorate for the Quality of Medicines, the term 'assisted reproductive technology (ART)' refers to medical procedures used to achieve pregnancy and live birth involving the identification, collection, processing and/or storage of at least one of the following reproductive tissues and cells: oocytes, ovarian tissue, sperm, testicular tissue, and embryos [6]. Reproductive cells used in ART procedures may originate from the couple being treated ('partner donation') or from gamete donors ('non-partner donation'). ART services are offered by both public and private providers in virtually all EU Member States [7].

Across the EU, national legislation governing ART and assisted reproduction techniques varies significantly, but there is an EU legal framework setting out minimum requirements for quality and safety standards for tissues and cells. In addition, EU responsibilities cover the area of health threats with cross-border implications, which includes the threat of transmission of sexually transmitted infections and blood-borne infections during ART procedures.

According to the current EU legislation, providers of assisted reproduction services are required to test the donors of reproductive cells for certain sexually transmitted and blood-borne infections at each donation. The main reason for this practice is the possibility of inadvertent transmission of these infections to third parties during collection, processing, storage, and use of these cells. If infections are found, the regulation stipulates that a separate storage system must be devised. This segregation of materials according to potential infection risk is a precautionary risk management measure intended to minimise the risk of transmission to uninfected clients.

Several viruses capable of causing viraemia have been found in semen [8]. The most relevant diseases in terms of their health impact and the current epidemiological situation concerning transmission risks during ART are HIV, hepatitis B, and hepatitis C infections, all of which have been transmitted during ART procedures in the past [9-12]. In particular, procedures for minimising the risk of exposure of third parties have been deemed a priority for control measures. Such third parties include other clients of the service providers (both third party recipients of donated reproductive cells and other clients whose cells are processed on the same premises) and personnel of the ART service providers. The latter, however, should be less of a concern, as appropriate application of universal blood precautions provides protection against the transmission of blood-borne infections.

In any screening procedure, there is a balance to be drawn between the potential benefits/protection from harm that is the result of the particular screening algorithm, and the cost and potentially negative effects of such algorithms.

This analysis is mainly intended to address changes in screening protocols for non-partner donation. These changes refer to the blood sample testing for serial semen donors: instead of conducting blood tests at each semen donation, blood test would be conducted at least every three-month during a 180-day quarantine period.

Laboratory testing of sperm donors

Current legislation on selection criteria and laboratory tests required for donors of reproductive cells

Directive 2004/23/EC [13] and its implementing measures (Directives 2006/17/EC [5] and 2006/86/EC Reproductive cells are notably dealt with in Annex III of Directive 2006/17/EC, which lays down the selection criteria and laboratory tests required for donors) [1,14] set out minimum requirements for quality and safety standards for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, including reproductive cells (intended for human application). As these are minimum requirements, Members States may implement more stringent quality and safety requirements, provided that they comply with the provisions of the Directive. Moreover, the Directive does not affect the decision of Member States prohibiting the donation, procurement, testing, processing, preservation, storage or distribution of a specific type of tissues or cells. However, when the use of a certain type of tissues and cells is legally allowed in a Member State, the EU legislation should apply. Below is an excerpt from the legislation:

> ANNEX II
>
> 1. Biological tests required for donors
>
> 1.1. The following biological tests must be performed for all donors as a minimum requirement:
>
> - HIV 1 and 2 — Anti-HIV-1,2
> - Hepatitis B — HBsAg; Anti HBc
> - Hepatitis C — Anti-HCV-Ab
> - Syphilis — (see 1.4 below)
>
> …
>
> ANNEX III
>
> 3. Donations other than by partners
>
> The use of reproductive cells other than for partner donation must meet the following criteria:
>
> …
>
> 3.2. the donors must be negative for HIV 1 and 2, HCV, HBV and syphilis on a serum or plasma sample, tested in accordance with Annex II, point 1.1, and sperm donors must additionally be negative for chlamydia on a urine sample tested by the nucleic acid amplification testing (NAT);
>
> …
>
> 4. General requirements to be met for determining biological markers
>
> 4.1. The tests must be carried out in accordance with Annex II, points 2.1 and 2.2.
>
> 4.2. Blood samples must be obtained at the time of donation.
>
> 4.3. Sperm donations other than by partners will be quarantined for a minimum of 180 days, after which repeat testing is required. If the blood donation sample is additionally tested by the nucleic acid amplification testing (NAT) for HIV, HBV and HCV, testing of a repeat blood sample is not required. Retesting is also not required if the processing includes an inactivation step that has been validated for the viruses concerned.

Alternative protocol in question

An alternative protocol for sperm donor screening in non-partner donation is in use in Denmark as described by the Danish competent authority for cells and tissues (communicated by the representative of the Danish National Competent Authority, Anne-Cathrine Bollerup). This protocol is described below.

EU Directive 2006/17/EC of 08/02/2006, Annex III, 4.2 (amended in Directive 2012/39/EU of 26/11/2012) and 4.3 regarding the timely connection between non-partner sperm donation and donor blood sampling has been implemented in the Danish law (i.e. BEK no. 764 of 26/05/2015). A guidance document issued by the Danish health authorities (VEJ no. 9356 of 26/05/2015) states [57]:

> 'Sperm donation may take place regularly every week or several times a week over a longer coherent period of time. In such cases, the Danish Patient Safety Authority accepts that blood sampling is performed at the time of the first donation, and subsequently at least every three months. The concurrent donor should be asked every three months about possible changes in relation to risk behaviour. It is a prerequisite that a quarantine period of 180 days is applied, with subsequent retesting of the donor. If the blood donations sample is subject to additional tests for HIV, HBV and HCV by NAT, retesting after 180 days can be omitted.'

The Danish Patient Safety Authority's reason for adopting this approach (blood samples taken and tested at least every three months and not at each time a donor produces a sample of sperm) significantly reduces the amount of diagnostic work: taking blood samples each time a donor produces a sample of sperm may not be practicable and acceptable. In practice, non-partner sperm donors are requested to provide two to three sperm samples per week over the course of several weeks.

The Danish Patient Safety Authority concludes that their procedure for non-partner sperm donation and donor blood sampling will prevent the transmission of the infectious diseases tested for.

Infections covered by Directive 2006/17/EC

Infectious diseases with longer incubation periods that require closer attention are hepatitis B, hepatitis C, and HIV.

Hepatitis B

Hepatitis B is a viral liver infection and can cause both acute and chronic disease. The main symptoms are jaundice, fatigue, nausea, vomiting and abdominal pain. Chronic infection can lead to potentially life-threatening complications like cirrhosis (in 25% of chronically infected persons) or liver cancer (in 5% of chronically infected persons). The incubation period is 90 days on average but can vary from about 30 to 180 days. Hepatitis B virus may be detected 30 to 60 days after infection and persist for widely variable periods of time. Tests can detect a variety of antibody and antigen markers, of which the hepatitis B surface antigen (HBsAg) is the main marker of chronic infection. Nucleic acid testing (NAT) is also available. The likelihood that an infection will become chronic depends on the age at which a person becomes infected, from 90% in children under one year of age to 5% among adults. About 90% of healthy adults who are infected will recover and be completely free of the virus within six months. Transmission is possible from both acutely and chronically infected individuals. Persons who have recovered are immune to reinfection and not infectious. Immunity is long lasting. Person vaccinated with a full vaccination schedule are also immune but vaccination is not 100% effective. The virus is transmitted through contact with the blood, semen, or other bodily fluids of an infected person. The most common modes of transmission are the vertical transmission from an infected mother to her offspring, sexual contact with an infected person, sharing of needles, syringes, or other drug-injecting equipment, or occupational injuries with needles or other sharp instruments. Blood transfusion remains a risk in places where no effective screening is in place. Modes of transmission are the same as for the human immunodeficiency virus, but the hepatitis B virus is 50 to 100 times more infectious. Unlike HIV, it can survive outside the body for at least seven days. During that time, the virus can still cause infection if it enters the body.

About two billion people worldwide are estimated to have been infected with hepatitis B virus, and about 257 million live with chronic infection [15]. Hepatitis B is highly endemic in Africa, the Western Pacific region, China and other parts of Asia. Most people in these regions become infected during childhood, with 8–10% of the adult population being chronically infected. High rates of chronic infection determined by HBsAg seroprevalence varies markedly by geographical region, with the highest prevalence (>5%) in sub-Saharan Africa, East Asia, some parts of the Balkan region, the Pacific Islands and Amazon Basin of South America. Prevalence below 2% is seen in regions such as Central America, North America and western Europe [16]. Recent reviews suggest that the prevalence of chronic hepatitis B infection in the EU is highly variable, ranging from <0.1% in Ireland to 4.4% in Romania [17]. An estimated 600 000 people die each year due to the acute or chronic consequences of hepatitis B, with liver cancer caused by hepatitis B among the first three causes of death from cancer in men, and a major cause of cancer in women [18].

There is no specific treatment for acute hepatitis B. Chronic hepatitis B can be treated with antiviral medication and interferon with varying success. Liver cirrhosis patients might benefit from liver transplants. Liver cancer is almost always fatal. The hepatitis B vaccine is safe and 95% effective in preventing hepatitis B infection and its chronic consequences. Vaccination against hepatitis B has been incorporated into national childhood immunisation programmes in many countries in Europe (all except the UK, Iceland, Norway, Denmark, Sweden and Finland). The Netherlands decided to introduce childhood vaccination in the near future.

HBV has been found in the ejaculate of infected persons, either as a free virus in seminal plasma or as an integrated genome in leukocytes or in sperm [19].

Hepatitis C

Hepatitis C is a viral infection of the liver and a major cause worldwide of acute and chronic liver disease. Main symptoms are the same as for all types of hepatitis including jaundice, fatigue, nausea, vomiting and abdominal pain. Chronic infection develops in approximately 75–85% of cases, and can lead to potentially life-threatening complications like cirrhosis or liver cancer. The incubation period is 45 days on average, but can vary from about 14 to 180 days. HCV infection can be detected by anti-HCV antibody screening tests (enzyme immunoassay) 4–10

weeks after infection. Anti-HCV antibodies can be detected in >97% of people six months after exposure. HCV ribonucleic acid (RNA) can be detected as early as 2–3 weeks after infection. HCV-positive people are those who either show anti-HCV antibodies in their blood, and/or have HCV RNA or HCV core antigen detected in their blood. All HCV-positive people are considered potentially infectious. The anti-HCV antibody test is the most commonly used diagnostic test.

HCV is spread primarily by direct contact with human blood and mainly transmitted through the use of unscreened blood transfusions and re-use of needles and syringes that have not been adequately sterilised, or through vertical transmission from an infected mother to her child. Sharing needles, syringes and paraphernalia by injecting drug users (IDU) is another significant mode of transmission globally. Sexual transmission of hepatitis C has also been reported [20].

HCV infections are common worldwide. WHO estimates that the prevalence of HCV infection globally is at about 1%, and an estimated 71 million people are chronically infected with HCV, with 1.75 million newly infected cases per year [15]. Most European countries with available estimates of prevalence report a prevalence of anti-HCV in the general population of between 0.1 and 2%, but some countries reach prevalence rates of up to 4–6%. Prevalence among IDUs is an order of magnitude higher [17]. ECDC estimates a hepatitis C incidence rate for newly diagnosed cases of 8.6 per 100 000 population across the EU Member States [21].

Until recently, chronic hepatitis C has been treated with combination therapy including interferon plus ribavirin. Novel antiviral treatments allow for interferon-free treatment schemes and have been show to achieve a high rate of cure. Patients with liver cirrhosis might benefit from liver transplants. Hepatocellular carcinoma is almost always fatal. At present, no vaccine against HCV is available. Several approaches are currently being tested. Effective prevention includes general measures such as screening, the testing of blood and organ donors, virus-inactivating processing of plasma-derived products, good infection control and safe injection practices in healthcare settings, and harm-reduction measures for people who inject drugs.

HCV has been found in body secretions, including semen and cervico-vaginal secretions [22].

Human immunodeficiency virus

HIV infection is a viral infection of the lymphocytes, especially T4 helper cells and cells of the monocyte/macrophage lineage. Infection leads to slow deterioration of immune defences, resulting in immunodeficiency. All infections with untreated HIV lead to chronic disease which, if untreated, develops into late-stage disease, AIDS, and eventually death (typically within 10–15 years of infection). HIV testing for diagnostic and screening purposes is performed by conventional ELISA tests that can detect HIV antibodies within 2–8 weeks (average 25 days) of infection. Due to the low specificity of the screening, every positive ELISA result needs to be confirmed by a second 'confirmatory' test, usually western blot. PCR tests can give positive results approximately 15 days after infection.

HIV is spread primarily by direct contact with blood or bodily fluids from an infected person. A high risk of transmission is related to unprotected sexual intercourse (vaginal or anal); treatment with contaminated blood transfusions, blood products or organs/tissue transplants; and the sharing of contaminated needles, syringes or other sharp instruments. It can also be transmitted between a mother and her baby during pregnancy, childbirth and breastfeeding. Transmission is less likely, but also possible, through injuries with contaminated needles or other sharp instruments in an occupational setting, especially if large amounts of contaminated blood is involved in the injury.

In Europe, HIV infection is highly concentrated in vulnerable groups at increased risk. The most important groups at risk are men that have sex with men (gay and bisexual men), injecting drug users and migrants from high-endemic areas. According to UNAIDS, an estimated 36.7 million (30.8 million–42.9 million) people were living with HIV/AIDS worldwide in 2016. Some 1.8 million people were newly infected that year, and a total of 1 million people died of AIDS-related illness [23]. WHO estimates that approximately 2.4 million children and adults were living with HIV in 2016 in the WHO European Region [24]. In 2015, 153 407 people were diagnosed with HIV infection in the region, a rate of 17.6 per 100 000 population [25]. Given the concentration of HIV in at-risk populations, prevalence data for the non-risk group general population in Europe are not widely available.

HIV is usually sexually transmitted and the virus is excreted in the ejaculate. The risk of male-to-female intravaginal HIV-1 transmission is estimated at about one event per 100–2 000 acts of unprotected intercourse [19,26]. Antiretroviral drugs using combination treatment are very effective and will usually stop disease progression [27-31]. At present, no vaccine against HIV is available.

Residual risk and diagnostic window period

Donation of substances of human origin (SoHO) for human use (including semen) is associated with the risk of infectious disease transmission to recipients, with potentially serious consequences to their health. The sources of infectious threats are existing blood-borne infections and emerging/re-emerging pathogens. Prevention of existing blood-borne infections is based on donor information, thorough medical history and laboratory screening for the presence of infection with HIV, HBV and HCV in the donor blood. As none of the currently required control measures is 100% effective in detecting infections, there is always a level of risk inherent in the use of donated materials, usually called 'residual risk'. The concept of residual risk has been extensively investigated in the context of blood donations [32-34].

The residual risk of HIV, HBV or HCV infections in semen donation can be defined as the probability of collecting a donation from an asymptomatic viraemic donor infected with a blood-borne viruses that is not detected by the routine screening assays. The residual risk of viral infection by any screening assay is mainly due to the viraemic phase of its diagnostic window period (DWP), whose length varies and depends on employed assay category and type. Another component of the residual risk is the epidemiology of the infection in the donor population, where the rate of new infections (incidence) in donors determines the probability for donations in the DWP.

The DWP of HIV, HBV and HCV infections begins with the eclipse phase during which the virus is not yet detectable in blood, even by highly sensitive NAT. This non-viraemic phase is followed by the viraemic ramp-up phase during which the virus concentration increases in an exponential fashion in the plasma. For each of the three blood-borne viruses (HIV, HBV and HCV), a specific constant replication rate is apparent until a peak or a plateau phase of maximal viral concentration is reached. The length (in days) of the viraemic phase of the DWPs suggested in the WHO guidelines for determining the residual risk of blood donations is presented in Table 1.

Residual risks of HBV, HCV and HIV reactive reproductive cells donation were estimated in an ECDC risk assessment [2]. For the calculation, the authors used prevalence data supplied by European Society of Human Reproduction and Embryology (ESHRE) and ratios of incidence and prevalence among blood donors to impute incidence data that are not available for donors of reproductive cells in Europe.

The quarantine of frozen cells and tissues takes into account that with the given sensitivity of serological tests, most donors will seroconvert from negative to positive within six months after infection. This strategy has also been recommended for non-partner semen donation. In order two compare two screening protocols, we evaluated whether the alternative screening protocol eliminates the risk related to possible semen donation in the diagnostic window to the same extent as the recommended protocol.

Table 1. Mean length (in days) of the viraemic phase of the diagnostic window period for assay categories

	ID NAT	MP(16) NAT	Antigen EIA/CLIA	Combo EIA/CLIA	Antibody EIA/CLIA	Antigen RDT	Combo RDT	Antibody RDT
HIV	8 *(4)*	11 *(7)*	14	16	21	---	20	28
HBV	27 *(17)*	37 *(27)*	42	---	---	55	---	---
HCV	5 *(3)*	7 *(5)*	9	38	60	---	---	80

Source: Adapted from WHO guidelines, 2016 [35]
Legend:
HIV – human immunodeficiency virus; HBV – hepatitis B virus; HCV – hepatitis C virus; ID – individual donation; MP – mini-pool; NAT – nucleic acid testing; EIA/CLIA – enzyme immunoassay/chemiluminescence immunoassay; RDT – rapid detection test.
The duration of the diagnostic window period (in days) is indicated as in a standard font. The probability of 50% detection in the early ramp-up phase of viraemia may be taken as basis for respective diagnostic window periods (numbers in italics and parentheses).

DWPs are estimates which depend on the sensitivity of applied assays and there may be considerable variation, with some individuals having shorter or longer than average DWPs. Data from the literature show that serological DWPs range from 12 to 99 days for anti-HIV [36], 28–84 days for HBsAg and 20–150 days for anti-HCV [37,38]. Extremely delayed seroconversions are also possible, e.g. a time to seroconversion in a 30-year-old woman which spanned 21 month (HIV) [39].

Methods

ECDC performed a systematic literature search to collect/update the evidence for the risk of HIV, HCV and HBV transmission through semen and analysed the retrieved evidence. The expert group also evaluated and compared the residual risk for HIV-, HCV- and HBV-positive semen donation associated with DWPs at the time of donation for both protocols, the recommended and the alternative protocol.

Systematic literature review

A systematic literature review was carried out for the period from 2007 until 23 August 2017 to seek further evidence for assessing the impact of the two testing protocols on the quality and safety of sperm from non-partner donors. The results of the review served to add to the evidence previously collected for a risk assessment published in 2012 [2] and to provide the most recent data for analysing the impact of a change of testing requirements on the quality and safety of non-partner semen donation.

Search methodology

Original research articles were retrieved from PubMed, Embase, Scopus, and the Cochrane Library (Wiley platform) bibliographic databases on 23 August 2017. Additional searches were performed in Google and UpToDate. The PICO questions for the search were:

- Population: non-partner donors of reproductive cells (sperm/semen) in EU countries or in countries with similar epidemiological profiles
- Intervention: testing for HIV, hepatitis B or hepatitis C, and syphilis infection
- Comparison: between effects of different testing interval protocols.
- Outcome: effect on residual risk for transmission or on safety and quality of the donated reproductive cells (sperm/semen)

The search strategies combined the concepts of the diseases, the tests, and the non-partner sperm donors. The population of non-partner donors in this search combination was enlarged to sperm donors in order to diminish the risk of excluding studies relevant to the question, e.g. guidelines, protocols, recommendations.

Controlled vocabulary was used whenever available (i.e. MeSH and Emtree terms); in addition, natural vocabulary (i.e. keywords) in multiple field combinations was used to represent the concepts in the search strategies.

The search results were in all languages and published from 2007 until 23 August 2017. Search strategies are available in Annex 2; the search summary can be found in Annex 1.

Comparison of recommended and alternative testing protocol

The expert group compared the residual risk reduction in HIV, HBV and HCV transmission through semen donations by the laboratory screening of donor blood samples which utilise recommended and alternative screening protocols. According to the descriptions of the recommended screening protocol in the Directive and the alternative protocol provided by the Danish Patient Safety Authority, we constructed diagram models of these screening protocols employing a) only serological screening and b) NAT in addition to the serological screening. For both screening protocols, we analysed if retesting of the donor blood sample after the quarantine of 180 days would cover the serological DWP of the testing performed at the time of donation (recommended protocol) or testing delayed up to three months after semen donation (alternative protocol). We also analysed differences between protocols in the risk with regard to donation in the DWP when NAT and serological screening were used.

Fully representative prevalence and incidence estimates for the population using ART procedures are not available. In the absence of epidemiological data for the EU, we considered the residual risk estimates from an earlier ECDC risk assessment on partner donation [2]. The length of the diagnostic window periods defined by WHO were used in the analysis [35] (Table2).

Results

Systematic literature review

The literature search (23/08/2017) yielded 106 abstracts for the articles, extracted from six data sources (see Table 2). Three duplicates were eliminated in the first step of the review. The remaining 103 abstracts were reviewed independently by two experts. Using the broad inclusion criteria (i.e. any reference to testing or screening of sperm donors or sperm/semen for any STI, including viral hepatitis B and C and HIV), 68 articles were rejected on the basis of the abstracts evaluation. In total, 35 articles underwent full-text review.

Table 2. Results of the literature search by data source

Data source	Results
PubMed	26
Embase	59
Scopus	57
Cochrane Library (Wiley platform)	18
Google	3
UpToDate	1
Results after de-duplication	106

The search identified no studies that compared the risk of any communicable disease transmission between protocols in which sperm donors are tested at the time of each sperm collection and protocols involving a test before the first collection, every three months after that, as long as donations are ongoing, and again six months after the last collection, with release of the gametes for human application only when the final sample six month after the last collection was negative.

The literature search found no studies that estimated the prevalence of previously undiagnosed hepatitis B and C or HIV infection in healthy donors or couples undergoing assisted reproduction. There was one UK report of two cases where the post-quarantine serology produced a test which was positive for HIV and confirmed by subsequent testing. Neither donor was identified as high risk by the sperm bank [41]. A large study (524 487 laboratory analyses) in Spain among infertile patients and oocyte donors reported the following seroconversion per million patients and months of follow up (spmm): 5 for HIV (8.08 spmm, CI95% 0–22.2), 20 for HBV (30.40 spmm CI95% 4–57.0), and 6 for HCV (9.26 spmm, CI95% 0–24.0) [40].

No studies were found that described any release incidents for use of non-partner sperm donated in the diagnostic window of HBV, HCV and HIV from 2007 onwards, probably due to the screening protocols currently adopted.

Another systematic review found in the literature could not provide any documentation on the prevalence of previously undiagnosed hepatitis B and C or HIV infection in healthy couples undergoing ART treatment or the incidence of seroconversion while having ART treatment with a seronegative partner [42].

Evaluation and comparison of screening protocols

Figures 1 and 2 present two protocols: the protocol recommended in the legislation and the alternative protocol for serological screening (also in combination with molecular screening of the blood samples of non-partner semen donors).

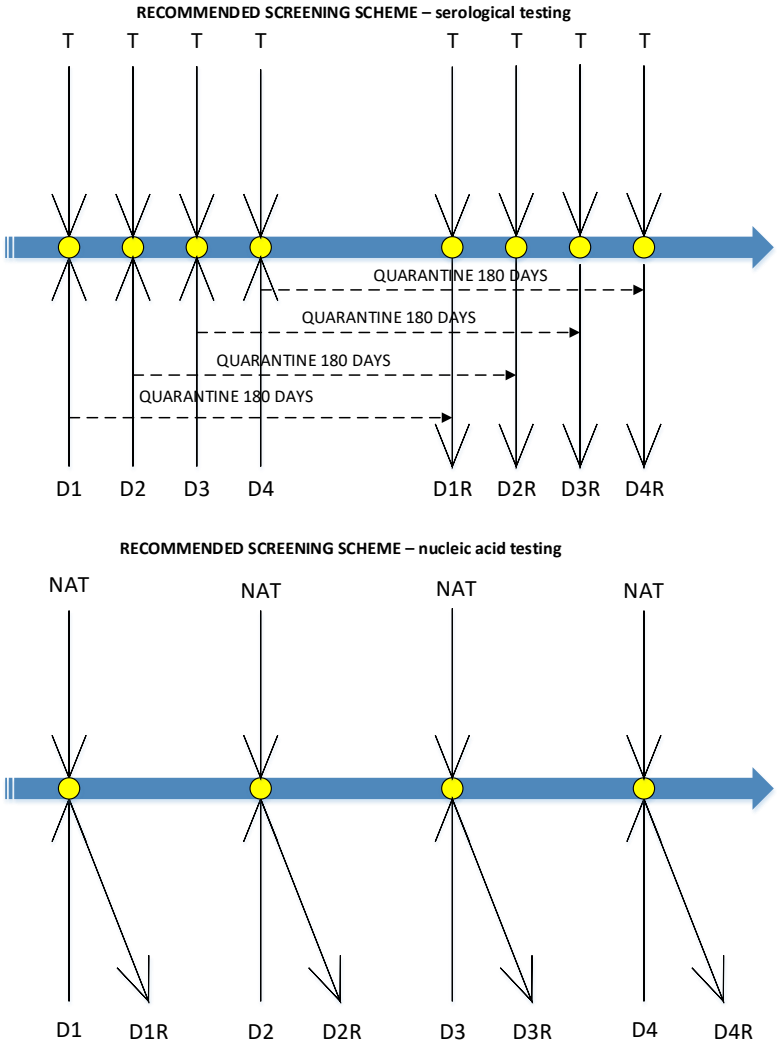
Recommended protocol

The six-month quarantine for non-partner semen donations is recommended in the current legislation as a safety measure when semen donations are only screened serologically. In the recommended screening protocol, donor blood is sampled and tested at two time points: at the time of semen donation and after 180 days of quarantine. If at both times testing is non-reactive, semen can be released for use. This approach takes into account that an infected donor can be viraemic without testing reactive in serological antibody/antigen screening assays (diagnostic window). Considering the given sensitivity of serological tests, the mean DWPs for serological testing are 21 days for anti-HIV, 42 days for HBsAg, and 60 days for anti-HCV [35]. Repeated testing after 180 days will detect a possible reactive donor who was in the DWP at the time of semen donation and subsequently seroconverted. The time between semen donation and laboratory repeat testing covers 8.3 mean DWPs for anti-HIV, 4.3 for HBsAg, and 3.0 for anti-HCV. This time period also covers 1.8 times the upper limit of DWP range for anti-HIV, 2.1 for HBsAg and 1.2 for anti-HCV (Table 3). The HBsAg disappears from blood in one to three months and may not be detectable at repeat screening. Nevertheless, possible HBV viraemic donation will be detected by the presence anti-HBc at repeat screening. Anti–HBc antibodies appear in blood approximately one month after HBsAg and remain

lifelong. A donor with the reactive blood sample at the time of semen donation, or after 180 days of quarantine, will be rejected from donation and the donated semen will be discarded.

When NAT testing is applied, the 180-day quarantine for semen donations and the retesting of donor blood is not recommended. When a donor blood sample is screened using NAT and serological testing, the semen donation at the time of testing may be in the molecular DWP. However, due to short DWPs and a low incidence of these infections in EU populations, the residual risk of NAT HBV-, HCV- and HIV-reactive donation is considered very low.

Figure 1. Recommended screening protocol



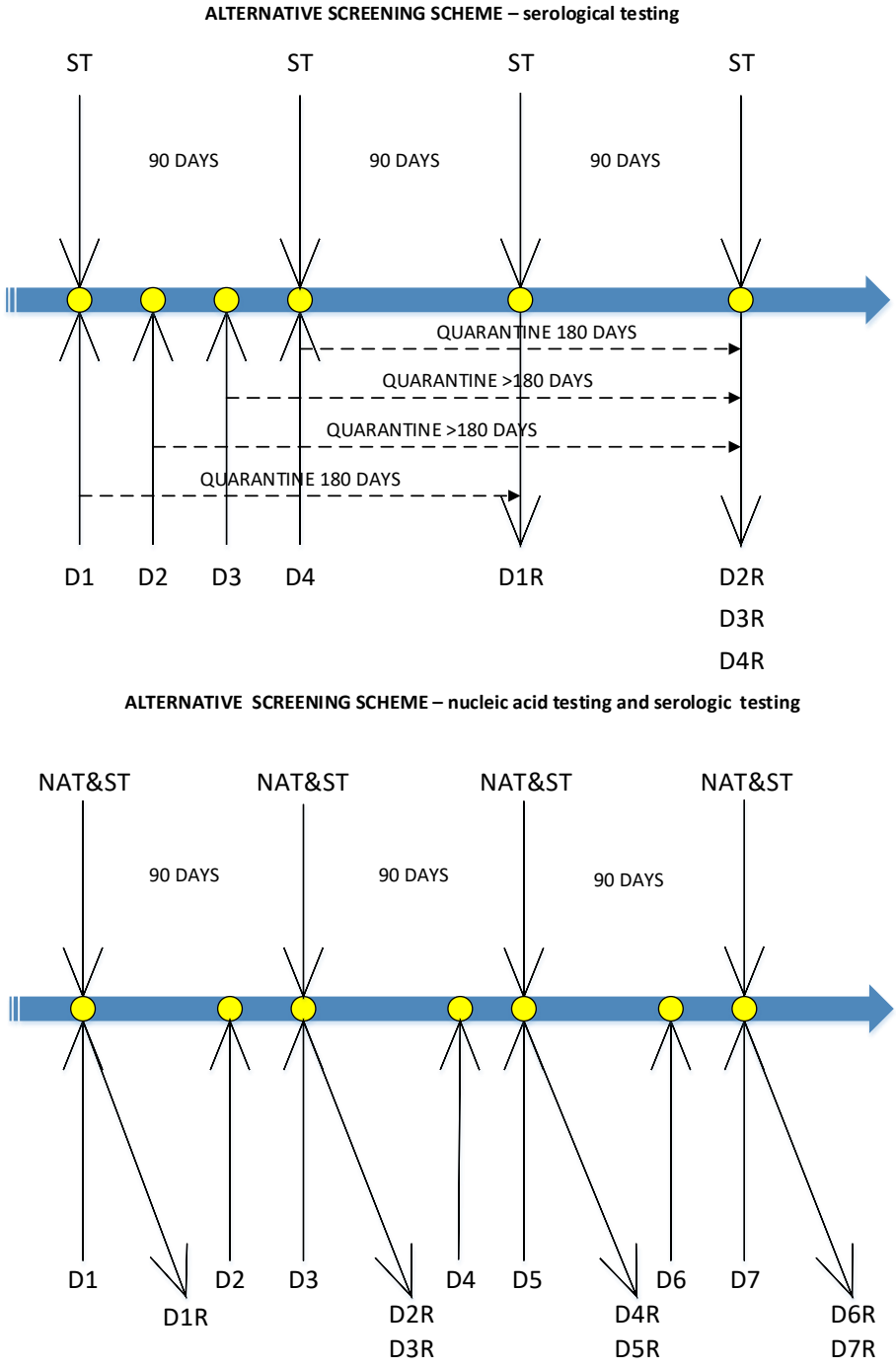
Legend:
D – semen donation; D1...R – semen donation released for use; ST – serological testing for HBsAg, anti HCV and anti-HIV; NAT – nucleic acid testing for HIV RNA, HBV DNA and HCV RNA in addition to serological testing for HBsAg, anti-HCV and anti-HIV.

Alternative protocol

In the proposed alternative screening protocol, the donor blood sample is serologically tested at the time of the first semen donation. For subsequent donations, the donor blood sample is tested only every three months. Donated semen can be released for use if repeated testing after 180 days of quarantine is negative. For the first semen donation, a blood sample is tested at the time of donation, after three months (90 days), and after six months (180 days), and then released for use if non-reactive. For each subsequent semen donation, donor blood samples are checked at three- month intervals after the first donation; donated sperm may be released if quarantined at least 180 days and if the donor blood sample tested negative for infection at the time of release. In this protocol, the time between semen donation and retesting increases from 180 to 269 days, with proportional increases in the time of seroconversion coverage. Thus, repeat screening would cover 8.6–12.8 mean DWPs for anti-HIV, 4.3–6.4 for HBsAg, and 3.0–4.4 for anti-HCV. This time period will also cover 1.8–2.7 of the upper range limit of DWP for anti-HIV, 2.1–3.2 for HBsAg, and 1.2–1.8 for anti-HCV (Table 3).

It seems that the capacity of the alternative serological testing protocol to detect infectious sperm donated within DWPs (means and upper limits) for anti-HIV, HBsAg and anti-HCV testing is the same or higher than that of the recommended protocol.

Figure 2. Alternative screening protocol



Legend:
D – semen donation; D1...R – semen donation released for use; ST – serological testing for HBsAg, anti HCV and anti-HIV; NAT&ST – nucleic acid testing for HIV RNA, HBV DNA and HCV RNA in addition to serological testing for HBsAg, anti-HCV and anti-HIV.

Table 3. Comparison of seroconversion coverage: time between semen donation and screening in the recommended and alternative protocol

Screening protocol	Type of laboratory test	Time between donation and screening (TDS) in days	Seroconversion coverage (HIV/HBV/HCV) by TDS	
			No. of mean DWPs	No. of upper limit DWPs
Recommended	Serologic	180	8.6/4.3/3.0	1.8/2.1/1.2
Alternative	Serologic	180–269	8.6–12.8/ 4.3–6.4/3.0–4.4	1.8–2.7/2.1–3.2/1.2–1.8

Legend:
DWP – diagnostic window period; NAT – nucleic acid testing; TDS – time between donation and screening

According to the alternative protocol, NAT in addition to serological (NAT&ST) screening is applied at first donation, with subsequent NAT&ST retesting every 90 days. Semen donated at the time of screening may be released for use if negative results are obtained. Semen donated within the period of 90 days between NAT&ST screenings may be released for use if test results at the end of this period were negative. Quarantine of semen donation for 180 days is not necessary. In this protocol, semen donated at the time of, or closer to, the screening may also be in the molecular DWP.

Discussion

The reduction of the residual risk related to the viraemia during DWP by quarantine and retesting of the donor after a certain time has been proven effective in increasing the infectious safety of fresh frozen plasma (FFP) [43,44]. According to the European Directorate for the Quality of Medicines guide, the quarantined FFP can be released once the donor has been retested for at least HBsAg, anti-HIV and anti-HCV, with negative results after a defined period of time that was specified to exclude the risk associated with the DWP. A period of six months is generally applied. This time period may be reduced if NAT testing is performed [45]. This principle has also been used as an infectious safety measure in non-partner sperm donation, for which the EU Directive recommends repeat serological screening after the six- month quarantine. Due to demanding logistics and possible significant losses of quarantined FFP units that could not be released from quarantine, pathogen inactivation of FFP is increasingly used [44].

The period between semen donation and repeat screening covers the mean and the upper limits of DWPs for anti-HIV, HBs Ag and anti-HCV screening. In the alternative protocol, serological testing of donor blood sample is performed only at the first semen donation; for subsequent donations, donor blood samples are periodically tested every 90 days, and semen donations remain in quarantine for at least 180 days. This approach also covers the mean and upper serological DWPs for anti-HIV, HBsAg and anti-HCV testing. The alternative protocol thus removes the part of the residual risk of HIV-, HBV- and HCV-positive semen donation related to the DWP. It is therefore unlikely that the Danish changes in the serological screening protocol pose a higher risk to the quality and safety of non-partner semen donation than the protocol recommended by legislation. As the alternative protocol for NAT&ST screening allows the release of semen donated at the time of screening and during the period of between the two periodically repeated screenings, semen donated closer to, or at the time of, screening may also be in the molecular DWP.

The main limitation of this risk assessment is the absence of residual risk estimates that result from the lack of data on the incidence or prevalence of HIV, HBV and HCV infections among non-partner semen donors, and the dependence of DWP on the sensitivity of the employed screening test. There are also differences in the risk of HCV, HBV and HIV transmission through semen. The risk of HIV transmission is significantly lower than that of HBV. The sexual transmission of HCV is currently under investigation but it seems that this route is not very efficient [46,47]. Semen cells to be used for insemination are usually separated from seminal plasma. Such processing might significantly reduce the seminal viral load, making transmission of HCV and HIV extremely unlikely, but transmission of HBV is still possible [48].

Some people, mainly those who are immunocompromised, may have very late seroconversions. Such donors will be rejected for donation after the medical donor interview [49]. It is therefore unlikely that extremely late HCV seroconversions have an impact to the quality and safety of non-partner semen donations. Some recent studies showed a more narrow range of DWPs, especially for anti-HCV [50].

Irrespective to the screening protocol, a minimal residual risk remains from possible rare atypical genetic variants of the pathogen [51], compartmentalisation of the virus replication in the semen [52], and laboratory errors [53]. Compartmentalisation of HIV replication in semen has been demonstrated in some men and, therefore, the HIV blood viral load might not always reflect HIV replication levels in semen [52,54]. Studies have shown that between 3% [28] and 5 % [30] of patients with undetectable HIV levels in their blood had detectable levels of HIV in semen. Such patients are not likely to become donors. A systematic review and meta-analysis of the studies of heterosexual discordant couples did not observe transmission in patients treated with ART and with HIV viral load below 400 copies/ml, but data were compatible with one transmission per 79 person-years. Further studies are also needed to better define the risk of HIV transmission from patients on ART [55]. Thus, sperm donations at the end of the quarantine period should not be released based only on NAT testing alone.

According to both the recommended and the alternative procedure, contaminated semen donations in the DWP or non-screened donations can be stored in the liquid nitrogen (LN), which may pose a risk of cross contamination of other quarantined donations. However, studies demonstrated that the risk of cross contamination through LN for all methods used to collect, cryopreserve, and store human sperm is low; it can, however, not be completely excluded [56].

The evaluation of Danish protocol shows that this alternative protocol very likely covers the mean and upper limits of serological DWPs for anti-HIV, HBsAg and anti-HCV testing, to an even higher extent than the protocol recommended by legislation. Thus, the alternative protocol removes the element of the residual risk related to possible HIV-, HBV- and HCV-positive non-partner semen donations made within the DWP. It is therefore unlikely that Danish changes in the serological screening protocol pose a higher risk to the quality and safety of non-partner semen donations than the recommended protocol. In the recommended protocol, when a donor blood sample is screened using NAT&ST testing, donations made at the time of testing may be in the molecular DWP. In the alternative NAT&ST screening protocol, semen donated closer to, or at the time of screening, may also be in the molecular DWP. To mitigate this risk, it is suggested that the donations at the time of screening (including first-

time donations) and donations in the period between the two periodically repeated screenings should be released only after a negative result of the latest NAT test that was performed at a date beyond the DWP (upper limit) of that test. Tissue and cell establishments should apply the longest DWP recommended by the manufacturer of the used laboratory test.

In addition, it is suggested that the alternative screening protocol should have a clearly defined maximum period for serial semen donations and a clearly defined minimal time between subsequent donations that is still appropriate for donations to be considered as serial donation. If the period between semen donations is longer than 90 days, any subsequent donation should be treated as a first-time donation, and blood samples should be screened at the time of semen donation.

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Annex 1. Literature search summary

Concept 1:	Boolean operator	Concept 2:	Boolean operator	Concept 3:	Boolean operator	Limits:
OR		OR		OR		
DISEASES	AND	**TEST SCREENING SEROLOGY SERODIAGNOSIS**	AND	**NON-PARTNER SPERM DONORS SPERM DONORS**	AND	**TIME LIMIT**
DISEASES + TEST SCREENING SEROLOGY SERODIAGNOSIS	AND	**NON-PARTNER SPERM DONORS SPERM DONORS**				

Annex 2. Search strategies

PubMed

Search	Query	Results
#21	Search (#14 NOT #20)	23
#20	Search (#14 AND #19)	3
#19	Search (#17 OR #18)	1133116
#18	Search (guide[TI] OR guides[TI] OR guideline*[TI] OR guidance[TI] OR guiding[TI] OR recommendation*[TI] OR protocol*[TI] OR pathway*[TI] OR standard*[TI] OR principle*[TI] OR requirement*[TI] OR rule*[TI] OR regulation*[TI] OR directive*[TI] OR advice*[TI] OR strateg*[TI] OR evidence[TI] OR best practice*[TI] OR consensus[TI])	1033042
#17	Search (#15 AND #16)	180149
#16	Search (guide[TW] OR guides[TW] OR guideline*[TW] OR guidance[TW] OR guiding[TW] OR recommendation*[TW] OR protocol*[TW] OR pathway*[TW] OR standard*[TW] OR principle*[TW] OR requirement*[TW] OR rule*[TW] OR regulation*[TW] OR directive*[TW] OR advice*[TW] OR strateg*[TW] OR evidence[TW] OR best practice*[TW] OR consensus[TW])	6380308
#15	Search ('Practice Guideline' [Publication Type] OR 'Practice Guidelines as Topic'[Mesh] OR 'Guideline' [Publication Type] OR 'Guidelines as Topic'[Mesh] OR 'Health Planning Guidelines'[Mesh] OR 'Consensus'[Mesh] OR 'Consensus Development Conference' [Publication Type])	181711
#14	Search (#11 OR #12) Filters: Publication date from 2007/01/01	26
#13	Search (#11 OR #12)	149
#12	Search (#2 AND #10)	26
#11	Search (#1 AND #3 AND #10)	145
#10	Search (#4 OR #5 OR #6 OR #7 OR #8 OR #9)	9813
#9	Search ((internet[TI] OR online[TI] OR web*[TI] OR 'pride angel'[TW]) AND (sperm[TW] OR sperms[TW] OR sperma[TW] OR spermatoz*[TW] OR spermatic*[TW] OR semen[TW] OR gamete*[TW]) AND (donor*[TW] OR donat*[TW] OR extraction*[TW]))	11
#8	Search (Donor Artificial Insemination*[TW] OR 'artificial insemination by donor'[TW] OR 'heterologous sperm donation'[TW] OR 'heterologous sperm donations'[TW] OR 'heterologous sperm donor'[TW] OR 'heterologous sperm donors'[TW])	237
#7	Search (Heterologous[TI] AND (Insemination*[TIAB] OR Sperm[TIAB] OR sperms[TIAB] OR sperma[TIAB] OR spermatoz*[TIAB] OR spermatic*[TIAB] OR semen[TIAB] OR gamete*[TIAB]))	169
#6	Search ('sperm donor'[Mesh] OR 'Sperm Banks'[Mesh] OR 'Insemination, Artificial, Heterologous'[Mesh] OR 'Unrelated Donors'[Mesh])	2585
#5	Search ((sperm[TW] OR sperms[TW] OR sperma[TW] OR spermatoz*[TW] OR spermatic*[TW] OR semen[TW] OR gamete*[TW]) AND (donor*[TW] OR donat*[TW] OR extraction*[TW]))	7978
#4	Search (('Spermatozoa'[Mesh] OR 'Germ Cells'[Mesh:NoExp]) AND (donor*[TI] OR donat*[TI] OR extraction*[TI]))	832
#3	Search ('Clinical Laboratory Techniques'[Mesh] OR 'Complement Fixation Tests'[Mesh] OR 'Diagnostic Tests, Routine'[Mesh] OR 'Enzyme-Linked Immunosorbent Assay'[Mesh] OR 'Immunologic Tests'[Mesh] OR 'Microbiological Techniques'[Mesh] OR 'Nucleic Acid Amplification Techniques'[Mesh] OR 'Physical Examination'[Mesh] OR 'Polymerase Chain Reaction'[Mesh] OR 'Serologic Tests'[Mesh] OR 'Viral Load'[Mesh] OR 'Mandatory Testing'[Mesh] OR Complement fixation test*[TW] OR Conglutinating Complement Absorption Test*[TW] OR Conglutination Reaction*[TW] OR diagnostic test*[TW] OR immunologic screen*[TW] OR immunologic test*[TW] OR mandatory screen*[TW] OR mandatory test*[TW] OR nucleic acid amplification technique*[TW] OR Nucleid acid technique*[TW] OR Nucleid acid test*[TW] OR serologic test*[TW] OR viral load*[TW] OR screen*[TI] OR test*[TI] OR serodiagnos*[TI] OR serolog*[TI])	4283809
#2	Search ('AIDS Serodiagnosis'[Mesh] OR 'Syphilis Serodiagnosis'[Mesh] OR 'VDRL antigen' [Supplementary Concept] OR HBV test*[TW] OR HBV screen*[TW] OR HBV serolog*[TW] OR hepatitis b test*[TW] OR hepatitis b screen*[TW] OR hepatitis b serolog*[TW] OR 'HCV-PCR'[TW] OR hepatitis c pcr[TW] OR hcv test*[TW] OR hcv screen*[TW] OR hcv serolog*[TW] OR hepatitis c test*[TW] OR hepatitis c screen*[TW] OR hepatitis c serolog*[TW] OR AIDS screen*[TW] OR AIDS serodiagnos*[TW] OR AIDS serolog*[TW] OR AIDS test*[TW] OR HIV screen*[TW] OR HIV serodiagnos*[TW] OR HIV serolog*[TW] OR HIV test*[TW] OR syphilis serodiagnos*[TW] OR syphilis serolog*[TW] OR syphilis test*[TW] OR syphilis screen*[TW] OR Wassermann reaction*[TW] OR Kahn test*[TW] OR Wassermann test*[TW] OR Venereal disease research laborator*[TW] OR Vdrl[TW] OR ((hepatitis b[TI] OR hbv[TI] OR hepb[TI] OR hep b[TI] OR hepatitis c[TI] OR hcv[TI] OR hep c[TI] OR hepc[TI]) AND rna[TI] AND (test*[TI] OR screen*[TI] OR serodiag*[TI] OR serolog*[TI])))	27195

Search	Query	Results
#1	Search ('Hepatitis B'[Mesh] OR 'Hepatitis B virus'[Mesh] OR 'Hepatitis B Core Antigens'[Mesh] OR 'Hepatitis B Antigens'[Mesh] OR 'Hepatitis B Antibodies'[Mesh] OR 'Hepatitis C'[Mesh] OR 'Hepacivirus'[MeSH] OR 'Hepatitis C Antibodies'[Mesh] OR 'Hepatitis C Antigens'[Mesh] OR 'HIV Infections'[Mesh] OR 'HIV Antibodies'[Mesh] OR 'Acquired Immunodeficiency Syndrome'[Mesh] OR 'Treponemal Infections'[Mesh] OR 'Treponema pallidum'[Mesh] OR 'Sexually Transmitted Diseases'[Mesh] OR Anti Australia Antigen[TW] OR Anti HBAg[TW] OR Anti HBc[TW] OR Anti HBe[TW] OR Anti HBs[TW] OR HBeAg[TW] OR hbs ag[TW] OR hbsag[TW] OR hbv[TW] OR hep B[TW] OR hepatitides b[TW] OR hepatitis b[TW] OR hepatitis type B[TW] OR hepB[TW] OR type b hepatitis[TW] OR Anti-HCV[TW] OR HCV[TW] OR HCV-RNA[TW] OR hep c[TW] OR hepaciviru*[TW] OR hepatitides c[TW] OR hepatitis c[TW] OR hepatitis type c[TW] OR type c hepatitis[TW] OR human immunodeficiency virus*[TW] OR hiv infect*[TW] OR acquired immunodeficiency syndrome*[TW] OR acquired immuno deficiency syndrome*[TW] OR p24 Antigen[TW] OR (HIV-1[TI] AND HIV-2[TI]) OR HIV-1 infect*[TW] OR HIV-2 infect*[TW] OR Syphilis[TW] OR Treponemal infection*[TW] OR Treponema pallidum[TW] OR Sexual transmission*[TW] OR Sexual transmitted disease*[TW] OR Sexual transmitted infection*[TW] OR Sexually Transmitted Disease*[TW] OR Sexually Transmitted Infection*[TW] OR STD[TW] OR STDs[TW] OR STI[TW] OR STIs[TW] OR 'Transmitted by sexual contact'[TW] OR Venereal Disease*[TW] OR Venereal Infection*[TW] OR Venereal transmission*[TW])	549841

Embase.com

Search	Query	Results
#18	#15 NOT #17	20
#17	#15 AND #16	39
#16	'protocol compliance'/exp OR 'guideline'/exp OR 'practice guideline'/exp OR 'consensus development'/exp OR guide:ab,ti OR guideline*:ab,ti OR guidance:ab,ti OR guiding:ab,ti OR recommendation*:ab,ti OR protocol*:ab,ti OR pathway*:ab,ti OR standar*:ab,ti OR principle*:ab,ti OR requirement*:ab,ti OR rule*:ab,ti OR regulation*:ab,ti OR directive*:ab,ti OR advice*:ab,ti OR strategy:ab,ti OR strategies:ab,ti OR evidence:ab,ti OR 'best practice*':ab,ti	6844963
#15	#12 OR #13 AND [2007-2017]/py	59
#14	#12 OR #13	135
#13	#2 AND #11	57
#12	#1 AND #3 AND #11	109
#11	#4 OR #5 OR #6 OR #7 OR 10	11581
#10	#8 AND #9	289
#9	sperm:ab,ti OR sperms:ab,ti OR sperma:ab,ti OR spermatoz*:ab,ti OR spermatic*:ab,ti OR semen:ab,ti OR gamete*:ab,ti	120296
#8	((heterologous OR secret OR unidentified OR unacknowledged OR nameless OR pseudonymous OR unnamed OR unsigned OR unknown OR anonymous OR internet OR online OR web* OR 'pride angel') NEAR/5 (donor* OR donat* OR extraction*)):ab,ti	2649
#7	(heterologous NEAR/5 insemination*):ab,ti	116
#6	'sperm donor'/exp OR 'sperm bank'/exp OR 'heterologous artificial insemination'/exp OR 'unrelated donors'/exp	6474
#5	((sperm OR sperms OR sperma OR spermatoz* OR spermatic* OR semen OR gamete*) NEAR/5 (donor OR donors OR donat* OR extraction*)):ab,ti	5977
#4	('spermatozoon'/exp OR 'gamete'/exp) AND (donor:ti OR donors:ti OR donat*:ti OR extraction*:ti)	880
#3	'venereal disease reaction test'/exp OR 'complement fixation test'/exp OR 'diagnostic test'/exp OR 'enzyme linked immunosorbent assay'/exp OR 'immunological procedures'/exp OR 'microbiological examination'/exp OR 'nucleic acid amplification'/exp OR 'physical examination'/exp OR 'polymerase chain reaction'/exp OR 'serology'/exp OR 'virus load'/exp OR 'mandatory testing'/exp OR (((test* OR screen*) NEAR/3 ('complement fixation' OR 'conglutinating complement absorption' OR diagnostic OR immunologic OR mandatory OR 'nucleid acid' OR serolog* OR serodiagnos*)):ab,ti) OR 'nucleic acid amplification technique*':ab,ti OR 'nucleid acid technique*':ab,ti OR screen*:ti OR test*:ti OR serodiagnos*:ti OR serolog*:ti	3716628
#2	'syphilis serology'/exp OR 'venereal disease reaction test'/exp OR (((wassermann OR kahn) NEAR/5 (reaction* OR test*)):ab,ti) OR 'venereal disease research laborator*':ab,ti OR vdrl:ab,ti OR (((test* OR screen* OR serolog* OR pcr OR serodiagnos*) NEAR/5 (hbv OR 'hepatitis b' OR 'hep b' OR hepb OR hcv OR 'hepatitis c' OR 'hep c' OR hepc OR aids OR hiv OR syphilis)):ab,ti)	76628
#1	'hepatitis b'/exp OR 'hepatitis b virus'/exp OR 'hepatitis b core antigen'/exp OR 'hepatitis b antigen'/exp OR 'hepatitis b antibody'/exp OR 'hepatitis c'/exp OR 'hepacivirus'/exp OR 'hepatitis c antibody'/exp OR 'hepatitis c antigen'/exp OR 'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus antibody'/exp OR 'acquired immune deficiency syndrome'/exp OR 'treponematosis'/exp OR 'treponema pallidum'/exp OR 'sexually transmitted disease'/exp OR 'anti australia antigen':ab,ti OR 'anti hbag':ab,ti OR 'anti hbc':ab,ti OR 'anti hbe':ab,ti OR 'anti hbs':ab,ti OR 'hbeag':ab,ti OR 'hbs ag':ab,ti OR hbsag:ab,ti OR hbv:ab,ti OR 'hep b':ab,ti OR 'hepatitides b':ab,ti OR 'hepatitis b':ab,ti OR 'hepatitis type b':ab,ti OR hepb:ab,ti OR 'type b hepatitis':ab,ti OR 'anti-hcv':ab,ti OR hcv:ab,ti OR 'hcv-rna':ab,ti OR 'hep c':ab,ti OR hepaciviru*:ab,ti OR 'hepatitides c':ab,ti OR 'hepatitis c':ab,ti OR 'hepatitis type c':ab,ti OR 'type c hepatitis':ab,ti OR 'human immunodeficiency virus*':ab,ti OR 'hiv infect*':ab,ti OR 'acquired immunodeficiency syndrome*':ab,ti OR 'acquired immuno deficiency syndrome*':ab,ti OR 'p24 antigen':ab,ti OR ('hiv-1':ti AND 'hiv-2':ti) OR 'hiv-1 infect*':ab,ti OR 'hiv-2 infect*':ab,ti OR syphilis:ab,ti OR 'treponema pallidum':ab,ti OR std:ab,ti OR stds:ab,ti OR sti:ab,ti OR stis:ab,ti OR (((disease* OR infection* OR transmission* OR transmitted) NEAR/3 (sexual OR sexually OR treponema* OR venereal)):ab,ti)	708101

Scopus

Search	Query	Results
#16	((#4 AND 9 AND #15) OR (#5 AND #15)) AND (LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007))	57
#15	#12 OR #13 OR #14	5,947
#14	TITLE-ABS ((sperm OR sperms OR sperma OR spermatoz* OR spermatic* OR semen OR gamete*) W/5 (donor OR donors OR donat* OR extraction*))	5,801
#13	TITLE-ABS ((heterologous W/5 insemination*))	127
#12	#10 AND #11	282
#11	TITLE-ABS (sperm OR sperms OR sperma OR spermatoz* OR spermatic* OR semen OR gamete*)	144,765
#10	TITLE-ABS ((heterologous OR secret OR unidentified OR unacknowledged OR nameless OR pseudonymous OR unnamed OR unsigned OR unknown OR anonymous OR internet OR online OR web* OR 'pride angel') W/5 (donor* OR donat* OR extraction*))	6,507
#9	#6 OR #7 OR #8	1,137,064
#8	TITLE (screen* OR test* OR serodiagnos* OR serolog*)	1,135,134
#7	TITLE-ABS ({Venereal disease research laboratory}~ OR vdrl)	1,706
#6	TITLE-ABS ((wassermann OR kahn) W/5 (reaction* OR test*))	1,186
#5	TITLE-ABS ((test* OR screen* OR serolog* OR pcr OR serodiagnos* OR {complement fixation} OR {Conglutinating Complement Absorption} OR {Nucleid acid} OR {nucleic acid amplification technique} OR {Nucleid acid technique}) W/5 (hbv OR {hepatitis b} OR {hep b} OR hepb OR hcv OR {hepatitis c} OR {hep c} OR hepc OR aids OR hiv OR syphilis))	450,113
#4	#1 OR #2 OR #3	257,397
#3	TITLE ({HIV-1} AND {HIV-2})	694
#2	TITLE-ABS ((disease* OR infection* OR transmission* OR transmitted) W/3 (sexual OR sexually OR treponema* OR venereal))	48,382
#1	TITLE-ABS ({Anti HBAg} OR {Anti HBc} OR {Anti HBe} OR {Anti HBs} OR {HBeAg} OR {hbs ag} OR hbsag OR hbv OR {hep B} OR {hepatitides b} OR {hepatitis b} OR {hepatitis type B} OR hepb OR {type b hepatitis} OR {Anti-HCV} OR hcv OR {HCV-RNA} OR {hep c} OR hepaciviru* OR {hepatitides c} OR {hepatitis c} OR {hepatitis type c} OR {type c hepatitis} OR {human immunodeficiency virus*} OR {hiv infect*} OR {acquired immunodeficiency syndrome*} OR {acquired immuno deficiency syndrome*} OR {p24 Antigen} OR {HIV-1 infect*} OR {HIV-2 infect*} OR syphilis OR {Treponema pallidum} OR std OR stds OR sti OR stis)	225,502

Cochrane Library (Wiley platform)

Search	Query	Results
#64	#51 not #63	17
#63	#51 and #62	1
#62	#58 or #60 or #61	54771
#61	#59 and #60	2538
#60	#52 or #53 or #54 or #55 or #56 or #57	2539
#59	guide or guides or guideline* or guidance or guiding or recommendation* or protocol* or pathway* or standard* or principle* or requirement* or rule* or regulation* or directive* or advice* or strateg* or evidence or 'best practice' or 'best practices' or consensus:ti,ab,kw (Word variations have been searched)	306553
#58	guide or guides or guideline* or guidance or guiding or recommendation* or protocol* or pathway* or standard* or principle* or requirement* or rule* or regulation* or directive* or advice* or strateg* or evidence or 'best practice' or 'best practices' or consensus:ti (Word variations have been searched)	53476
#57	MeSH descriptor: [Consensus] explode all trees	60
#56	MeSH descriptor: [Health Planning Guidelines] explode all trees	33
#55	MeSH descriptor: [Guideline] explode all trees	26
#54	MeSH descriptor: [Practice Guidelines as Topic] explode all trees	2094
#53	MeSH descriptor: [Guidelines as Topic] explode all trees	2429
#52	MeSH descriptor: [Practice Guideline] explode all trees	16
#51	#49 or #50 Publication Year from 2007 to 2017	18
#50	#39 and #48	0
#49	#20 and #33 and #48	55
#48	#43 or #44 or #45 or #46 or #47	199
#47	MeSH descriptor: [Unrelated Donors] explode all trees	17
#46	MeSH descriptor: [Insemination, Artificial, Heterologous] explode all trees	44
#45	MeSH descriptor: [Sperm Banks] explode all trees	4

Search	Query	Results
#44	(Sperm or sperms or sperma or spermatoz* or spermatic* or semen or gamete*) near (Donor or donors or donat* or extraction*):ti,ab,kw (Word variations have been searched)	157
#43	(#40 or #41) and #42	30
#42	Donor or donors or donat* or extraction*:ti (Word variations have been searched)	4505
#41	MeSH descriptor: [Germ Cells] explode all trees	978
#40	MeSH descriptor: [Spermatozoa] explode all trees	436
#39	#34 or #35 or #36 or #37 or #38	3557
#38	(test* or screen* or serolog* or pcr or serodiagnos*) near (hbv or 'hepatitis b' or 'hep b' or hepb or hcv or 'hepatitis c' or 'hep c' or hepc or aids or hiv or syphilis):ti,ab,kw (Word variations have been searched)	3551
#37	VDRL or 'Venereal disease research laboratory' or 'Venereal disease research laboratories':ti,ab,kw (Word variations have been searched)	13
#36	(wassermann or kahn) near (test* or reaction*):ti,ab,kw (Word variations have been searched)	5
#35	MeSH descriptor: [Syphilis Serodiagnosis] explode all trees	32
#34	MeSH descriptor: [AIDS Serodiagnosis] explode all trees	148
#33	#20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32	156651
#32	nucleic acid amplification technique or 'nucleic acid amplification techniques' or 'Nucleid acid technique' or 'Nucleid acid techniques':ti,ab,kw or screen* or test* or serodiagnos* or serolog*:ti (Word variations have been searched)	26541
#31	(Test* or screen*) near ('complement fixation' or 'Conglutinating Complement Absorption' or diagnostic or immunologic or mandatory or 'Nucleid acid' or serolog* or serodiagnos*):ti,ab,kw (Word variations have been searched)	9967
#30	MeSH descriptor: [Mandatory Testing] explode all trees	4
#29	MeSH descriptor: [Viral Load] explode all trees	2137
#28	MeSH descriptor: [Serologic Tests] explode all trees	1590
#27	MeSH descriptor: [Polymerase Chain Reaction] explode all trees	2308
#26	MeSH descriptor: [Physical Examination] explode all trees	86591
#25	MeSH descriptor: [Nucleic Acid Amplification Techniques] explode all trees	2372
#24	MeSH descriptor: [Immunologic Tests] explode all trees	5310
#23	MeSH descriptor: [Enzyme-Linked Immunosorbent Assay] explode all trees	2454
#22	MeSH descriptor: [Diagnostic Tests, Routine] explode all trees	356
#21	MeSH descriptor: [Complement Fixation Tests] explode all trees	86
#20	MeSH descriptor: [Clinical Laboratory Techniques] explode all trees	43045
#19	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #17 or #18	17218
#18	HIV-1 and 'HIV-2':ti (Word variations have been searched)	4
#17	(disease* or Infection* or transmission* or transmitted) near (sexual or sexually or treponema* or venereal):ti,ab,kw (Word variations have been searched)	2332
#16	Anti Australia Antigen or 'Anti HBAg' or 'Anti HBc' or 'Anti HBe' or 'Anti HBs' or 'HBeAg' or 'hbs ag' or hbsag or hbv or 'hep B' or hepatitides b or 'hepatitis b' or 'hepatitis type B' or hepB or 'type b hepatitis' or 'Anti-HCV' or HCV or 'HCV-RNA' or 'hep c' or hepaciviru* or 'hepatitides c' or 'hepatitis c' or 'hepatitis type c' or 'type c hepatitis' or 'human immunodeficiency virus' or 'human immunodeficiency viruses' or 'hiv infection' or 'hiv infections' or 'hiv infected' or 'acquired immunodeficiency syndrome*' or 'acquired immunodeficiency syndrome' or 'acquired immuno deficiency syndromes' or 'p24 Antigen' or 'HIV-1 infection' or 'HIV-1 infections' or 'HIV-1 infected' or 'HIV-2 infection' or 'HIV-2 infections' or 'HIV-2 infected' or Syphilis or 'Treponema pallidum' or STD or STDs or STI or STIs:ti,ab,kw (Word variations have been searched)	27837
#15	MeSH descriptor: [Sexually Transmitted Diseases] explode all trees	10903
#14	MeSH descriptor: [Treponema pallidum] explode all trees	24
#13	MeSH descriptor: [Treponemal Infections] explode all trees	134
#12	MeSH descriptor: [Acquired Immunodeficiency Syndrome] explode all trees	1271
#11	MeSH descriptor: [HIV Antibodies] explode all trees	245
#10	MeSH descriptor: [HIV Infections] explode all trees	9520
#9	MeSH descriptor: [Hepatitis C Antigens] explode all trees	17
#8	MeSH descriptor: [Hepatitis C Antibodies] explode all trees	121
#7	MeSH descriptor: [Hepacivirus] explode all trees	1262
#6	MeSH descriptor: [Hepatitis C] explode all trees	2676
#5	MeSH descriptor: [Hepatitis B Antibodies] explode all trees	601
#4	MeSH descriptor: [Hepatitis B Antigens] explode all trees	1052
#3	MeSH descriptor: [Hepatitis B Core Antigens] explode all trees	78
#2	MeSH descriptor: [Hepatitis B virus] explode all trees	882
#1	MeSH descriptor: [Hepatitis B] explode all trees	2177

Annex 3. Table of retrieved articles

Author	Title	Source	Year	Vol	Pages	Document type	Database
Human Tissue Authority	EU tissue and cells directives					Web page	Handpicked
U.S. Food & Drug Administration	What You Should Know - Reproductive Tissue Donation					Web page	Handpicked
U.S. Food & Drug Administration	Tissue and tissue products					Web page	Handpicked
E. S. Ginsburg and S. S. Srouji	Donor insemination (2016)	UpToDate				Electronic book section	Uptodate
T. Bourlet, J. Lornage, A. Maertens, A. S. Garret, H. Saoudin, J. C. Tardy, C. Jimenez, J. F. Guerin, B. Pozzetto and R. Levy	Prospective evaluation of the threat related to the use of seminal fractions from hepatitis C virus-infected men in assisted reproductive techniques	Hum Reprod	2009	530-5	3	Journal article	NLM
M. Wingfield and E. Cottell	Viral screening of couples undergoing partner donation in assisted reproduction with regard to EU Directives 2004/23/EC, 2006/17/EC and 2006/86/EC: what is the evidence for repeated screening?	Hum Reprod	2010	3058-65	12	Journal article	NLM
C. Deleage, M. Moreau, N. Rioux-Leclercq, A. Ruffault, B. Jegou and N. Dejucq-Rainsford	Human immunodeficiency virus infects human seminal vesicles in vitro and in vivo	Am J Pathol	2011	2397-408	5	Journal article	NLM
A. J. Loftis, S. Quellie, K. Chason, E. Sumo, M. Toukolon, Y. Otieno, H. Ellerbrok, M. M. Hobbs, D. Hoover, K. Dube, D. A. Wohl and W. A. Fischer, 2nd	Validation of the Cepheid GeneXpert for Detecting Ebola Virus in Semen	J Infect Dis	2017	344-350	3	Journal article	NLM
	2008 Guidelines for gamete and embryo donation: a Practice Committee report	Fertil Steril	2008	S30-44	5 Suppl	Journal article	NLM
A. P. Walsh, A. B. Omar, K. D. Marron, D. J. Walsh, U. Salma and E. S. Sills	Recipient screening in IVF: first data from women undergoing anonymous oocyte donation in Dublin	Reprod Health	2011	8		Journal article	NLM

Author	Title	Source	Year	Vol	Pages	Document type	Database
P. Ping, W. B. Zhu, X. Z. Zhang, Y. S. Li, Q. X. Wang, X. R. Cao, Y. Liu, H. L. Dai, Y. R. Huang and Z. Li	Sperm donation and its application in China: a 7-year multicenter retrospective study	Asian J Androl	2011	644-8	4	Journal article	NLM
D. J. Chan and L. McNally	Assays for the determination of HIV-1 load in semen: a review of indications, methods and performance in vitro	Curr HIV Res	2008	182-8	3	Journal article	NLM
M. D. Kaspersen, P. B. Larsen, E. Kofod-Olsen, J. Fedder, J. Bonde and P. Höllsberg	Human Herpesvirus-6A/B Binds to Spermatozoa Acrosome and Is the Most Prevalent Herpesvirus in Semen from Sperm Donors	PLoS ONE	2012		11	Journal article	Scopus
Z. Kuczyński and A. Wiercińska-Drapało	Validity of VIDAS-HIV DUO tests in the screening of sperm donors and women undergoing facilitated reproduction	HIV and AIDS Review	2007	15-19	4	Journal article	Scopus
S. Alain	Screening for CMV: Fertility, prenatally, postnatally	Human Reproduction	2013	i58		Journal article	Embase
M. L. Giles, S. Barak, G. Baker, S. Tabrizi, V. Greengrass, H. Bourne, G. N. Clarke, S. A. Peak, J. F. Hoy, P. Foster and R. L. Knight	Outcomes from the first assisted reproduction program for HIV serodiscordant couples in Australia	Medical Journal of Australia	2011	599-601	10	Journal article	Embase
H. T. Guan, Z. Wan, L. Zhang, T. Q. Meng, C. L. Xiong and C. L. Li	Analysis of the screening results for 3,564 student sperm donors in Hubei province, China	Journal of Reproductive Medicine	2015	409-414	5	Journal article	Embase
A. A. Kiessling	Infectious disease screening of semen for surrogacy cases	Fertility and Sterility	2016	e320		Journal article	Embase
S. Feinstein and D. S. Seidman	Infertility treatment in HIV serodiscordant couples	Harefuah	2008	38-42	1	Journal article	Scopus
R. Luttmer, M. G. Dijkstra, P. J. F. Snijders, P. G. A. Hompes, D. T. M. Pronk, I. Hubeek, J. Berkhof, D. A. M. Heideman and C. J. L. M. Meijer	Presence of human papillomavirus in semen in relation to semen quality	Human Reproduction	2016	280-286	2	Journal article	Scopus

Author	Title	Source	Year	Vol	Pages	Document type	Database
	Recommendations for gamete and embryo donation: A committee opinion	Fertility and Sterility	2013	47-62.e1	1	Journal article	Embase
C. Anarte, J. De Pablo, J. Agirregoikoa, I. Ausin, M. Barreiro and G. Barrenetxea	Improvements in the screening of semen donors	International Journal of Gynecology and Obstetrics	2009	S611-S612		Journal article	Embase
L. Privitera, J. Remohí, M. Morgan, A. Pellicer and N. Garrido	Hepatitis B (HBV), C (HCV) and human immunodeficiency (HIV) viruses prevalence and seroconversions among infertile patients and oocyte donors in 524487 analysis	Human Reproduction	2011	i122		Journal article	Embase
L. Pepas	Viral screening before each licensed treatment cycle is expensive and unnecessary: A survey of results from an inner city UK clinic	Human Fertility	2011	16	2	Journal article	Embase
V. Smith	Two cases of HIV sero-conversion of sperm donors during the donation period: Critical value of screening quarantined sperm	Human Fertility	2011	17	2	Journal article	Embase
A. Hershlag, A. Trinkoff and M. Barone	Posthumous reproduction: Do parents OFA deceased son have the right to use his sperm?	Fertility and Sterility	2013	S218	3	Journal article	Embase
Z. Raisi Dehkordi and A. Najafi	Ethical issues about sperm donation	Iranian Journal of Reproductive Medicine	2012	122-123		Journal article	Embase
S. Turner, M. Yip, W. Van Seggelen, D. M. Smith, S. Gianella and D. S. Fierer	HCV in semen of HIV-infected men during acute and chronic infection	Hepatology	2015	1113A		Journal article	Embase
M. D. Kaspersen, P. B. Larsen, H. J. Ingerslev, J. Fedder, G. B. Petersen, J. Bonde and P. Höllsberg	Identification of multiple HPV types on Spermatozoa from human sperm donors	PLoS ONE	2011		3	Journal article	Embase
S. Nosarka	Management guidelines for assisted reproduction in the HIV infected couple	Obstetrics and Gynaecology Forum	2013	25-27	1	Journal article	Embase

Author	Title	Source	Year	Vol	Pages	Document type	Database
C. Laprise, H. Trottier, P. Monnier, F. Coutlée and M. H. Mayrand	Prevalence of human papillomaviruses in semen: A systematic review and meta-analysis	Human Reproduction	2014	640-651	4	Journal article	Embase
J. Pettitt, E. S. Higgs, R. D. Adams, P. B. Jahrling and L. E. Hensley	Use of Existing Diagnostic Reverse-Transcription Polymerase Chain Reaction Assays for Detection of Ebola Virus RNA in Semen	Journal of Infectious Diseases	2016	1237-1239	8	Journal article	Embase
S. R. Greenwald, D. Cohan, S. Weber and K. E. Salmeen	The exclusion of sperm donation on the basis of sexual practices	Obstetrics and Gynecology	2016	1097-1099	6	Journal article	Embase
J. Moreira, C. C. Lamas and A. Siqueira	Sexual transmission of zika virus: Implications for clinical care and public health policy	Clinical Infectious Diseases	2016	141-142	1	Journal article	Embase
I. Molina Botella, J. V. Martinez Sanchis, E. Novella-Maestre, J. L. Lopez-Hontangas, J. Frasquet, J. M. Rubio and J. Peman	Liquid nitrogen sterility in sperm, oocyte and embryo banking	Human Reproduction	2017	i91-i92		Journal article	Embase

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