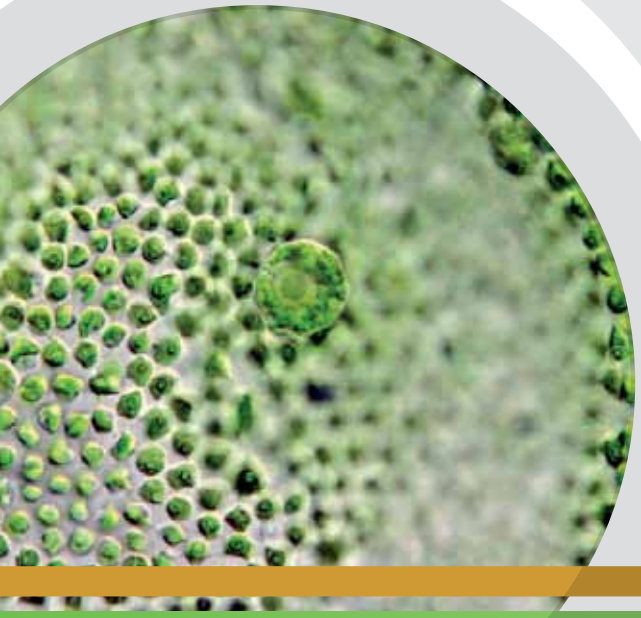

TECHNICAL REPORT

Risk assessment on change of testing requirements for partner donation of reproductive cells

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ECDC TECHNICAL REPORT

Risk assessment on change of testing requirements for partner donation of reproductive cells

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Contents

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ECDC	European Centre for Disease Prevention and Control
EDQM	European Directorate for the Quality of Medicines & HealthCare (Council of Europe)
EEA	European Economic Area
ESHRE	European Society of Human Reproduction and Embryology
HIV	Human immunodeficiency virus
HIV-Ab	Antibodies specific for HIV
HCV	Hepatitis C virus
HCV-Ab	Antibodies specific for HCV
HBV	Hepatitis B virus
HBsAg	Hepatitis B S-antigen
IDU	Injecting drug users
IVF	In vitro fertilisation
MAR	Medically assisted reproduction
NAT	Nucleic acid amplification testing
RNA	Ribonucleic acid
RR	Residual risk
WHO	World Health Organization

Executive summary

Introduction and question for ECDC

An important part of the ECDC's function is to provide its stakeholders with scientific advice upon their request (Regulation EC/851/2004[1]). ECDC received such a request from the European Commission on 11 May 2010.

ECDC was asked to estimate the change of total risk of exposure to hepatitis B (HBV), hepatitis C (HCV) and HIV (human immunodeficiency virus) during reproductive cell handling and storage for secondary parties, if testing donors of reproductive cells, in partner donation (not direct use (as defined in Commission Directive 2006/17/EC[2]), would occur once a year or twice a year compared with the current scheme of testing at each donation. Partner donations are donations where a couple with difficulties to conceive receives (medical) assisted reproductive services to help with conception and in which only the couples' own reproductive cells are used. The question was also limited to situations where the reproductive cells are stored for some time before their use.

Methodology

In accordance with its internal procedures for providing scientific advice, ECDC has addressed the question by setting up an ad hoc expert group consisting of internal and external experts in the field. The expert group has reviewed the available scientific evidence, performing a comprehensive literature review and assessment of the evidence for its validity and generalisability for the question asked.

Based on initial findings and following discussions with the Commission services at the Directorate-General for Health and Consumers, Directorate C 'Public Health and Risk Assessment', ECDC developed a model for the estimation of residual risk using a methodology previously widely applied to blood donations, but applying estimates of prevalence and incidence of the infections concerned derived from assisted reproduction services as far as was possible. For this purpose, data supplied by the European Society of Human Reproduction and Embryology were used and compared with data from numerous other populations. Residual risks under the different testing procedures were compared to estimate the change in risk.

ECDC also used varied key parameters of the residual risk model over reasonable ranges in a sensitivity analysis to be able to see under which epidemiological circumstances risks would increase the most should testing be less frequent.

Results

The estimated residual risks of a case of HIV infection, hepatitis B infection or hepatitis C infection transmitted by undetected infection of reproductive cells, donated for medically assisted reproduction (MAR) services was relatively small, but not insignificant. As expected, the estimated residual risks are clearly higher than in blood donor populations. Residual risks were approximately 18 (HIV), 32 (hepatitis B) and 267 (hepatitis C) cases per million person years under the current testing scheme. If donors would be tested at entry and then only every 24 months, approximately an additional 0.5 (HIV), 2 (hepatitis B) and 9 (hepatitis C) cases would be missed for each one million person years. This does not correspond to a large increase of residual risk, and the increases if testing every 12 months are even smaller.

Sensitivity analysis shows that residual risks in partner donations (not direct use) do not increase substantially over a relatively wide ranges of incidence and prevalence even if testing were to be less frequent than is currently required. Only for hepatitis C might the increase of risk be expected to be significant in some epidemiological circumstances. However, to accurately estimate this, country-specific information on disease prevalence and incidence from assisted reproductive services would be needed but is not currently available.

It should be noted that ECDC was unable to objectively assess the population representativeness of the prevalence data collected and provided by the European Society of Human Reproduction and Embryology, because neither the reporting protocol nor the countries from which the data was collected were disclosed.

Considerations

ECDC would suggest the following issues for consideration by the European Commission.

- Consider requiring collection and centralised reporting of testing result data on blood-borne viral infections for all tissue donations using standardised protocols in the EU region as part of quality assurance for tissue and cell donation establishments.
- Consider the possibility of changing the testing requirements to allow testing once per year, if:
  - the tissue donation establishment can demonstrate that the risk of cross-contamination, staff exposure and potential mix-up of gametes has been addressed and minimised through the use of validated quality and safety processes;

[1] Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European centre for disease prevention and control. OJ L 142, 30.4.2004, p. 1.

[2] Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

  - the establishment has a procedure in place to record and report the number of cases found at different stages during the screening of clients for HIV, hepatitis B and C;
  - the establishment can reliably demonstrate, through a residual risk estimation using own data, that it would be unlikely that the change in testing would lead to a significant increase in undetected cases of HIV, hepatitis B and hepatitis C using the services.
- Consider commissioning a review of the probability of infection of embryos (with HIV, hepatitis B and hepatitis C) and the question of transmission of blood-borne viruses in cryo-storage as well as potential mix-up of gametes.

1 Background and methods

Request from the European Commission

On 11 May 2010, the ECDC Director received the following request from the European Commission, Directorate-General for Health and Consumers, Directorate C 'Public Health and Risk Assessment' (transcript):

> With this letter, I would like to request the assistance of the ECDC to investigate the health risks of a potential change of EU legislation on tissues and cells.
>
> 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.
>
> Several Member States have raised concerns about the requirements of testing on HIV and Hepatitis B and C for each partner donation of reproductive cells. They argue that this testing requirement does not necessarily add to the safety of the process compared to a periodic testing (e.g. once per year) of partners donating reproductive cells.
>
> We (DG SANCO; ECDC clarification) have explained to the Member States that we would need a solid evidence base, demonstrating that such change in the testing protocol would not jeopardise the quality and safety of reproductive cells, in order to further investigate the possibility of amending Directive 2006/17/EC (Annex III).
>
> We would therefore like the ECDC's advice to fully assess the health risks of changing the current requirements to a yearly test.
>
> I suggest that our services get in contact directly for further details.
>
> Signed Andrzej Rys
>
> (Director, Directorate-General for Health and Consumers, Directorate C 'Public Health and Risk Assessment')

Legal authority

According to the founding regulation of ECDC, Regulation (EC) No 851/2004 Art 9(2), 'the Centre may be requested by the Commission, the Member States, third countries and international organisations (in particular the World Health Organization) 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.'

ECDC shall:

- search for, collect, collate, evaluate and disseminate scientific data (Art 3(2)(a));
- provide scientific opinions and timely information (Art 3(2)(b), (c));
- exchange information, expertise and best practices (Art 3(2)(e)); and
- facilitate the development and implementation of joint actions (Art 3(2)(e)).

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 the integration of expertise, values and the best available evidence into the decision-making process [I].

A public health decision might be rather complex, and needs to take several determinants of health into account, like genetic factors, lifestyle, physical environment, socio-economic conditions, biological environment and health services at different levels [II].

Only some of these factors are relevant to the prevention and control of HIV and hepatitis B and C in relation to the donation of reproductive cells.

Evidence-based methodologies

ECDC has carried out this risk assessment 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.

The European Commission asked ECDC to work in cooperation with its own working group on reproductive cells, which was set up following discussions on testing requirements for partner donation not involving direct use (i.e. any procedure where cells are donated and used without being banked) under Directive 2006/17/EC (Annex III) at the meeting of the Competent Authorities on tissues and cells 19–20 October 2009 [1]. The Working Group consists of representatives from the national Competent Authorities for tissues and cells and The European Society of Human Reproduction and Embryology (ESHRE). The cooperation between ECDC and the working group was achieved by sharing documents in progress and by arranging teleconferences between the parties and meetings of the ECDC internal team, external experts and the Commission working group.

Questions from the Commission

After a request for clarifications, the questions posed by the Commission were rephrased as follows.

Main question

What is the estimated change of total risk of exposure to hepatitis B/C and HIV during reproductive cell handling and storage for secondary parties, if testing of donors of reproductive cells, in partner donation (as specified in the EC Regulation), would occur:

1: annually
2: every second year

compared with the current scheme of:

3: testing donors at each donation of reproductive cells?

Secondary question

For comparative reasons, the same question may be addressed for non-partner donations, although this question is not directly incorporated within the original Commission request.

However, in teleconferences held between the Commission representatives and ECDC, it was deemed appropriate to address the question in the risk assessment, to provide a perspective for the work.

Search strategies

To make the questions posed by the Commission searchable in electronic databases, the different questions were split into the following subcategories:

Population: donors of reproductive cells in EU countries.

Intervention: testing for HIV, hepatitis B or hepatitis C infection.

Comparison: comparing the effects of different interventions, i.e. testing intervals.

Outcome: the effect on the residual risk for transmission.

Reviews and original research articles were retrieved from the PubMed, Embase, and Cochrane Library bibliographic databases on 27 October 2010.

Primary search strategies were applied, combining the concepts of cell donors and the different assisted reproduction techniques with hepatitis B, hepatitis C, and HIV. The results were focussed on the prevalence, incidence, risk, models, screening, cross-sectional studies, and controlled clinical trials. Records related to sperm washing and serodiscordant couples were excluded from the searches.

To widen results, secondary surrogate blood donor search strategies were designed in order to enlarge and complement the number of records retrieved in the cell donors search strategies because for the estimation of residual risk, blood studies can be applied to the cell donors.

The surrogate search strategies combined the concepts blood donors, the three observed diseases, and the clinical tests for their detection. Again the results were focussed on the prevalence, incidence, risk, models, screening, cross-sectional studies and controlled clinical trials. Finally, the secondary search result was restricted to studies containing the phrases 'residual risk' or 'retrovirus epidemiology donor'.

Records about organ donor and organ transplantation were excluded from the searches.

The concepts used in all search strategies (cell and blood donors) were using the controlled vocabulary available in the bibliographic databases (i.e. MeSH and Emtree terms). The concepts used were completed with multiple field search combinations by using natural vocabulary (i.e. keywords). The results were limited to English, French, German, Finnish, Swedish, and Spanish with no restriction in time.

For the primary search strategies, a total of 400 abstracts were retrieved and read, 103 publications were selected for full text reading. For the secondary search strategy, a total of 157 abstracts were retrieved and read, 43 publications were selected for full text reading. Some 32 full text articles were selected for inclusion in the evidence base (see Annex 1 for the full search strategy).

Finally, other relevant studies were selected from reading reference lists and by inclusion of a limited number of relevant institutional reports which can be classified as grey literature.

Selections of studies for the evidence base were made according to relevance for the different questions. Selection criteria were decided by a group of reviewers. The articles were read by one reviewer, however in the event of any doubts, questions or uncertainties, these were discussed by a group of reviewers. Due to time constraints it was not possible to retrieve all possible relevant articles from reference lists, and some relevant articles without abstracts in English as well as reports in the grey literature might also have been missed.

Studies were categorised according to the following study designs: grey literature reports, reviews, trials and observational studies.

The following sections were included in the evidence tables (Annex 2):

Bibliographic citation
Type of study
Area covered (geographical)
Number of patients or size of population
Study outcome
Strengths of study
Limitations of study

Assessment of the evidence

Validity. To assess the validity of a study is to evaluate whether the results of the study are trustworthy. The problems faced in this study were connected to the fact that incidence and prevalence data for HIV, hepatitis B and hepatitis C infections for the population under study (donors of reproductive cells) are currently not available in Europe. Therefore, proxy data from blood donors and the general population had to be used. These are likely to differ significantly from the study population, lowering the validity of the modelling study.

Generalisability (external validity). To assess external validity or generalisability is to evaluate whether the studies are transferrable to other settings or circumstances. In this assessment the challenges were connected to uneven comparability of different studies on HIV, hepatitis B and hepatitis C epidemiology and lack of epidemiological studies on the exact study population.

Grading of evidence according to strength of documentation. Working in an evidence-based way implies trying to draw explicit conclusions, and building on the best available evidence, thus giving more weight to the studies which are of the highest quality and that employed the most robust methods. The problems faced in preparing this risk assessment were connected to a lack of studies and systematic reviews for the EU region. The reviewers had to start by assessing studies on different populations than the study population. Nevertheless, such studies can be judged according to their quality; a study can be of high quality even if its design indicates that little weight can be given to the evidence.

References: Background and methods

I. Straus SE, et al. Evidence-Based Medicine. How to Practice and Teach EBM. Churchill Livingstone.

II. Gray M. Evidence-based Health Care and Public Health: How to Make Decisions About Health Services and Public Health. 3rd ed. Churchill Livingstone; 2009.

2 Medically assisted reproductive services and blood-borne infections

Human medically assisted reproduction (MAR) services are offered by different providers in virtually all EU Member States. As has been recently reviewed in a European Commission survey report [2], services are offered by both public and private providers, and are for this risk assessment defined as all those medical services that require any *ex vivo* handling of human reproductive cells (gametes i.e. male spermatozoa or female egg cells (oocytes)) or any embryos (fertilised eggs in various stages of differentiation) resulting from *in vitro* fertilisation (IVF) of such cells for the purpose of use of human assisted reproduction.

Different medical assisted reproduction techniques and procedures have been developed to help people experiencing difficulties having children in a natural way. These address physical inabilities of either partner and range from artificial insemination to more complicated procedures such as *in vitro* fertilisation and intra-cytoplasmic sperm injection.

Across the EU, national legislation governing MAR and assisted reproduction techniques varies significantly, with the rules based on diverse principles ranging from differences in ethical and societal values to quality assurance goals. This largely stems from the agreed division of responsibilities and subsidiary principles between Member States and the Commission in the area of healthcare, of which MAR services are part.

However, there is an EU legal framework setting out minimum requirements for quality and safety standards for tissues and cells (see Section 3). In addition, EU responsibilities cover the area of health threats with cross-border implications. This covers the threat of transmission of sexually transmitted infections and blood-borne infections during MAR service delivery, as some services are provided as cross-border activities.

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 (see Section 3). 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 the 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 risks of transmission to uninfected clients.

The most relevant diseases in terms of their health impact and current epidemiological situation concerning transmission risks during MAR are HIV, hepatitis B and C infections, all of which have been transmitted during MAR procedures in the past [3-8]. In particular, procedures for minimising the risk of exposure of third parties have been deemed a priority for control measures. Such third parties would include other clients of the service providers (both third party recipients of donated reproductive cells and other clients whose cells are manipulated on the same premises) and personnel of the MAR service providers. The latter, however, should be less of a concern, as rigorous application of universal blood precautions provides adequate protection against transmission. Consequently there is no need for routine HIV/hepatitis testing of patients in other medical service settings with the aim of minimising risk to personnel.

In addition to donors of cells to be used for third parties, the current EC legislation stipulates that testing for infectious diseases at each donation must equally be performed for partner donations[3] in which the cells are stored and not used immediately (Directive 2006/17/EC, Annex III para 2. See Section 3 for details).

As the intended recipient of partner donations is only the other partner, and no third parties are recipients of the donated materials, the purpose of the testing requirement is mainly to apply a precautionary principle, i.e. to protect other clients using the service from inadvertent exposure during manipulation or storage of the reproductive cells, including a mix-up of cells. While a proportion of MAR services in Europe supply special services to chronically infected HIV and hepatitis virus carriers, including infection discordant couples, not all establishments have this capacity, so cases found to be infected would need to be referred elsewhere.

In addition to the concerns raised by a number of Member States, some actors within the MAR service field have recently questioned the need for infectious disease testing at each donation in the case of partner donations (not direct use), specifically its cost effectiveness and whether there is any evidence to show that such frequent testing significantly diminishes the risk to third persons [9].

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.

This risk assessment is mainly intended to address the change of residual risk in this category of donations (partner donation (not direct use)) if testing were to be performed with a lower frequency, such as once a year or once every second year instead of at each donation.

[3] E.g. situations where a stable partnership exists and either partner's reproductive cells are collected and manipulated solely for the purpose of assisted reproduction of the partner couple

3 Current EU requirements for testing donors

Directive 2004/23/EC[4] and its implementing measures (Directives 2006/17/EC[5] and 2006/86/EC[6]) 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 applications). 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.

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.

ANNEX III: SELECTION CRITERIA AND LABORATORY TESTS REQUIRED FOR DONORS OF REPRODUCTIVE CELLS AS REFERRED TO IN ARTICLE 3(b) AND ARTICLE 4(2)

1. Partner donation for direct use

Donor selection criteria and laboratory testing do not need to be applied in the case of partner donation of reproductive cells for direct use.

2. Partner donation (not direct use)

Reproductive cells that are processed and/or stored and reproductive cells that will result in the cryopreservation of embryos must meet the following criteria:

…

2.2. the following biological tests must be carried out to assess the risk of cross-contamination:

HIV 1 and 2	Anti-HIV-1,2
Hepatitis B	HBsAg Anti-HBc
Hepatitis C	Anti-HCV-Ab

In case of sperm processed for intrauterine insemination and not to be stored, if the tissue establishment can demonstrate that the risk of cross contamination and staff exposure has been addressed through the use of validated processes, biological testing may not be required;

2.3. where HIV 1 and 2, hepatitis B or hepatitis C test results are positive or unavailable, or where the donor is known to be a source of infection risk, a system of separate storage must be devised;

…

2.6. positive results will not necessarily prevent partner donation in accordance with national rules.

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.

[4] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. OJ L 102, 7.4.2004, p. 48.

[5] Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. OJ L 038, 09.02.2006, p. 40.

[6] Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. OJ L 294, 25.10.2006, p. 32

4 Infections covered by Directive 2006/17/EC, Annex III para 2

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 S-antigen (HBsAg) is the main marker of chronic infection. Nucleic acid amplification testing (NAT) is also available.

The likelihood that an infection will become chronic depends upon 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 or have been vaccinated with a full vaccination schedule are immune to re-infection and not infectious. Immunity is long lasting.

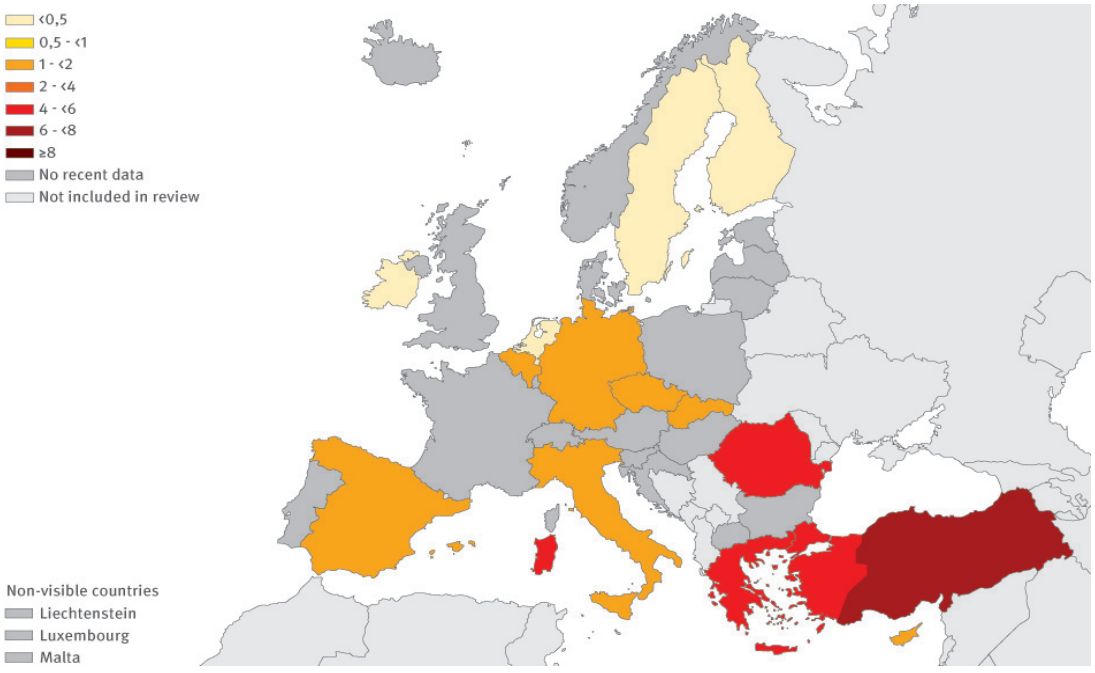
The virus is transmitted through contact with the blood, semen, or other bodily fluids of an infected person. The most common modes of transmission are vertical transmission from an infected mother to her offspring, sexual contact with an infected person, sharing of needles, syringes, or other drug-injecting 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 350 million live with chronic infection. An estimated 600 000 people die each year due to the acute or chronic consequences of hepatitis B.

Hepatitis B is endemic in China and other parts of Asia. Most people in that region become infected during childhood. In these regions, 8 – 10% of the adult population are chronically infected. Liver cancer caused by hepatitis B is among the first three causes of death from cancer in men, and a major cause of cancer in women. High rates of chronic infection are also found in the Amazon region and the southern parts of eastern and central Europe. In the Middle East and on the Indian sub-continent, an estimated 2 – 5% of the general population is chronically infected Compared with less than 1% in North America. Recent reviews suggest that the prevalence of chronic hepatitis B infection in the EU and neighbouring areas is highly variable, ranging from <0.5% in northern Europe to –2% in central and southern Europe and up to 6–8% in eastern Europe and Turkey [10, 11].

Figure 1. The prevalence of HBsAg in the general population (ECDC 2010)



Source: ECDC [10,11]

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 has made a decision to introduce childhood vaccination in the near future.

Additional sources:

http://www.who.int/mediacentre/factsheets/fs204/en/print.html
http://www.euro.who.int/en/what-we-do/health-topics/diseases-and-conditions/hepatitis/facts-and-figures/hepatitis-b
http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview
http://www.cdc.gov/hepatitis/Resources/Professionals/PDFs/ABCTable_BW.pdf
http://www.ecdc.europa.eu/en/healthtopics/Pages/Hepatitis_B.aspx

Hepatitis C

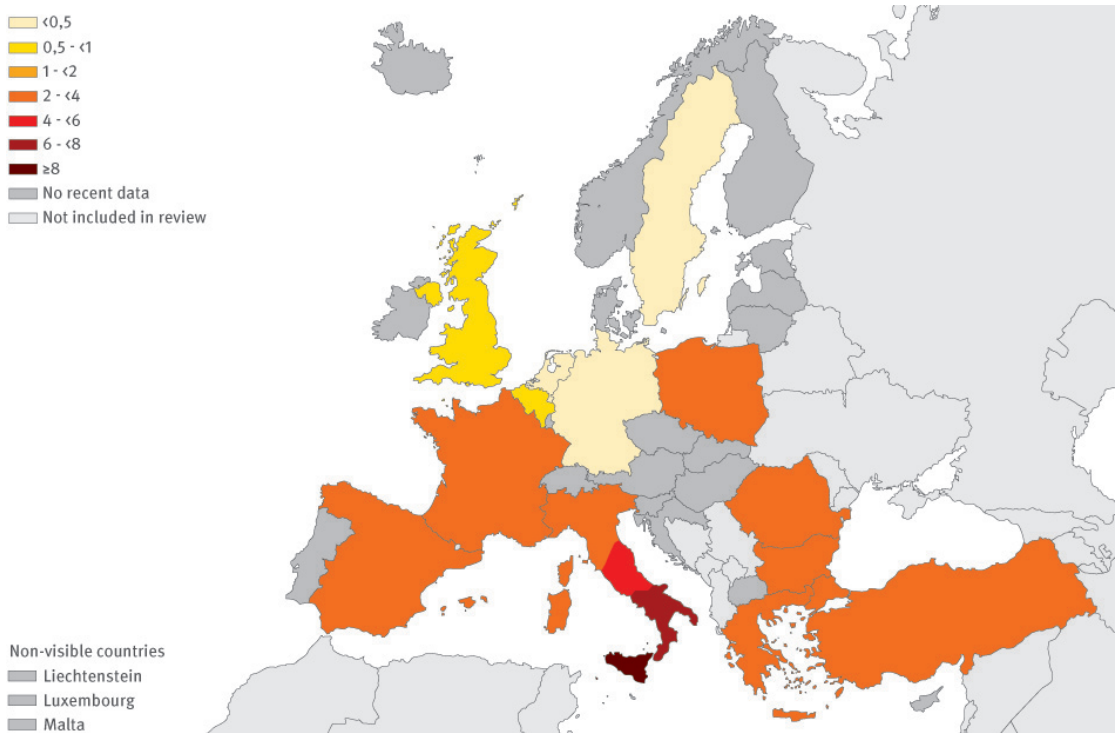
Hepatitis C is a viral infection of the liver, and is a major cause worldwide of acute and chronic liver disease. Main symptoms are the same as for all types of hepatitis including jaundice, fatigue, nausea, vomiting and abdominal pain. Chronic infection develops in approximately 75 – 85% of cases, and 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 antibody can be detected in >97% of persons by six months after exposure. HCV ribonucleic acid (RNA) can be detected as early as 2–3 weeks after infection. HCV-positive persons 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 persons 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.

HCV infections are common worldwide. WHO estimates that about 3% of the world's population has been infected with HCV. Globally, an estimated 130–170 million people are chronically infected with HCV and 3–4 million are newly infected each year. Most European countries report a prevalence of HCV in the general population of between 0.5 and 2%, but some countries reach prevalence rates of up to 4–8%. Prevalence among IDUs is an order of magnitude higher. ECDC estimates a hepatitis C incidence rate of 8.7 per 100 000 population in the EU Member States [10, 11].

Figure 2. The prevalence of anti-HCV antibodies in the general population (ECDC 2010)



Source: ECDC [10,11]

Chronic hepatitis C can be successfully treated with combination therapy including interferon plus ribavirin. Antiviral agents are under development. Patients with liver cirrhosis might benefit from liver transplants. Liver cancer is almost always fatal.

At present, no vaccine against HCV is available. Several approaches are currently in development. Effective prevention includes general measures such as screening, testing blood and organ donors, virus-inactivating processing of plasma-derived products, good infection control and safe injection practices in healthcare settings.

Additional sources:

http://www.euro.who.int/en/what-we-do/health-topics/diseases-and-conditions/hepatitis/facts-and-figures/hepatitis-c
http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm#section1
http://www.cdc.gov/hepatitis/Resources/Professionals/PDFs/ABCTable_BW.pdf
http://www.ecdc.europa.eu/en/healthtopics/hepatitis_C/Pages/index.aspx
http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index1.html

HIV/AIDS

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 HIV lead to chronic disease which 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.

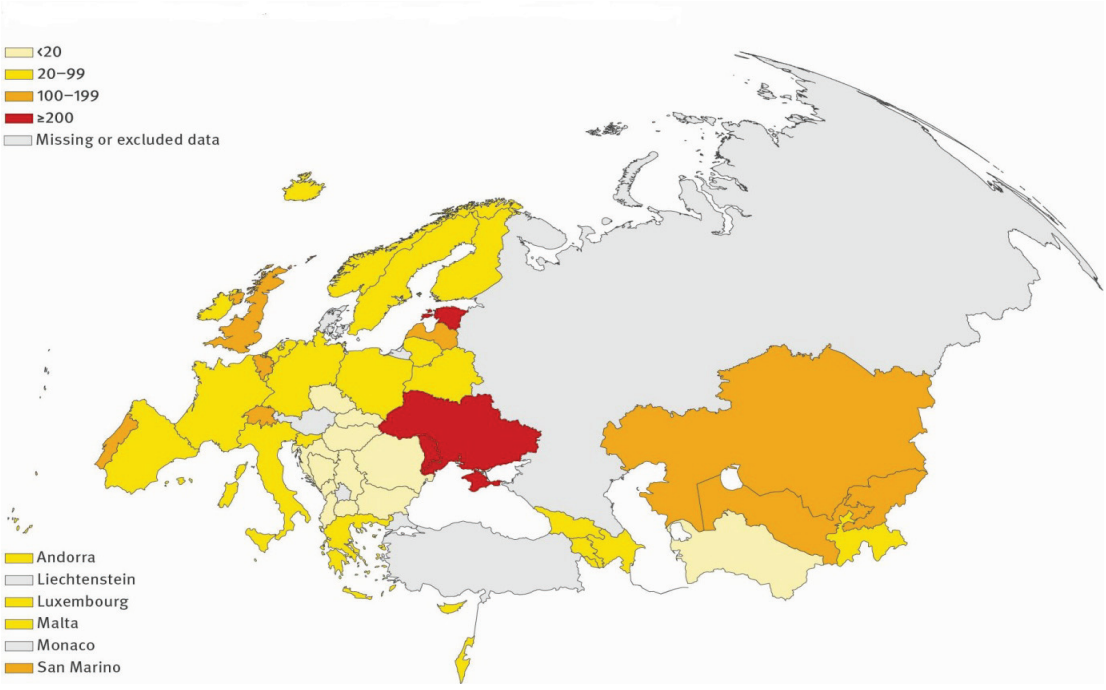
HIV is spread primarily by direct contact with blood or bodily fluids from an infected person. A high risk of transmission is related to unprotected sexual intercourse (vaginal or anal); treatment with contaminated blood transfusions, blood products or organs/tissue transplants; and the sharing of contaminated 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), current or former injecting drug users and migrants from high-endemic areas.

According to UNAIDS, an estimated 33.4 million (31.1 million–35.8 million) people were living with HIV/AIDS worldwide in 2008. Some 2.7 million people were newly infected that year, and a total of 2 million people died of AIDS-related illness [12].

WHO estimates that approximately 1.6 million children and adults were living with HIV in 2001 in the WHO European Region, and that this number increased to 2.4 million people in 2008 and is still rising. In 2008, 51 600 newly reported cases of HIV infection were reported to the joint ECDC/WHO surveillance database, giving a rate of 86.7 per million population. Prevalence data from Europe in the general population are poorly available.

Figure 3. HIV infections per million population, reported for 2008



Source. ECDC/WHO HIV/AIDS surveillance report, 2009 [13].

Antiretroviral drug treatment using combination drugs is very effective and can stop disease progression and even partially reverse immune function for very long time periods. However, treatment is not curative and does not completely remove infectiousness. At present, no vaccine against HIV is available.

Additional sources:

http://ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=470
http://www.ecdc.europa.eu/en/healthtopics/Pages/HIV_AIDS.aspx
http://www.who.int/topics/hiv_aids/en/
http://www.euro.who.int/en/what-we-do/health-topics/diseases-and-conditions/hivaids
http://www.who.int/features/factfiles/hiv/facts/en/index8.html

5 Model(s) for risk estimation

The concept of 'risk' differs depending on context and can have very different meanings for different purposes. Risks may or may not be quantifiable, but for the purpose of comparing changes in risk, a quantifiable measure must be used. In this document, methods used to quantify risk will be based on the models developed in blood transfusion medicine where the residual risk of not detecting blood-borne infections among donations have been widely estimated using highly developed methodology for modelling. These methods are directly applicable to any setting where screening for blood-borne infections is performed. The methods allow for comparisons to be made between different scenarios of screening frequency and also allow examination of the effect of different incidence and prevalence on the residual risk.

Residual risk

In the context of this document, estimating risks of blood-borne infections in the context of donations of human material for human use (blood, cells, tissues and organs) is based on the estimation of the risk of having an un-identified infected donation unit in the process, after the application of control measures which are required for the process. As none of the currently required control measures is 100% effective in detecting and eliminating infections, there is always a level of risk inherent in the use of donated materials. This remaining risk is frequently called the residual risk (RR), which is a concept of risk that has been extensively used in estimating risks in blood donation services [14–23]. The risk is usually expressed as the probability of an infected donation being used or as the number of donations that need to be screened before one is missed. In most cases, only the residual risk associated with the testing for infectious disease is possible to estimate in a quantitative way, such as the sensitivity of a particular test and its window period characteristics can be relatively easily measured. Other control measures, such as deferral of donation based on behavioural risk factors, are outside the scope of this risk assessment.

To be able to estimate residual risk of transmission of blood-borne infections in the context of donations of human material for human use, a set of parameters must either be measured or estimated. The current very low risk of donation-transmitted infectious disease makes observational studies of transmission impractical, because an exceedingly large number of recipients would be required for the risk to be measured accurately. As this is very time and resource consuming and does not provide results before a long observation time during which avoidable infections have occurred, modelling-based estimation of residual risk is the practically and ethically preferred method. Indirect methods of estimating the residual risk have been successfully used for donations of blood and results obtained have been subsequently verified by follow-up through prospective observational studies.

Commonly used methods for the estimation of the residual risk in donations of blood are based on methods first developed by Shwartz et al. [24] and further refined by Schreiber et al. for the Retrovirus Epidemiology Donor Study [25]. The method (and variants thereof) uses incidence and prevalence data among donors to estimate the frequency of donation of materials during the infectious, but seronegative window period when the donors are undergoing seroconversion. This is the time between the start of viral replication after exposure to the infection and appearance of detectable levels of antibodies or other viral markers in blood. Typically, the window period is longer for tests detecting antibodies targeted towards the virus(Ab tests) compared with tests detecting viral antigen (Ag tests) and especially compared with tests detecting viral nucleic acids (so-called 'NAT tests'). As NAT tests are not required by current testing requirements for partner donation (not direct use) in EU, comparisons were restricted to residual risks associated with the use of Ab tests for HIV and hepatitis C (HCV) and the Ag test for hepatitis B (HBV).

Estimating true rates of seroconversion, or incidence, requires the ability to track large numbers of donors for extended periods of time. This is possible in blood donation facilities, but may be more difficult to achieve in some settings for donors of reproductive cells. When rates of seroconversion are combined with estimates of the probability that blood was donated during the donor's window period (which depends on both the viral infection and the technical performance characteristics of the tests used for screening), the residual risks of transmitting infectious disease can be calculated [14–23]. For hepatitis B, it is also necessary to consider that the HBsAg test will only detect a proportion of incident cases, due to the short duration of antigenemia. A correction factor for adjusting the raw incidence based on HBsAg detection was estimated by Korelitz et al. (1997) for a blood donation setting [26]. On the basis of prior reports of the duration of HBsAg-positivity and the observed distribution of inter-donation intervals among the study group, there was an estimated 53% chance that an HBV-infected donor with transient antigenemia would have a positive HBsAg test result. If 70% of newly HBV-infected adults have transient antigenemia, 25% have a primary antibody response without primary antigenemia, and 5% become chronic carriers, the overall chance of being detected by the HBsAg test was 42%, for an adjustment factor of 2.38 [26]. This correction factor has been widely used in later work on residual risk estimation in blood and tissue donation settings.

A second component affecting the residual risk is related to the technical performance of the diagnostic tests used for the screening. While the screening tests and algorithms approved for HIV and hepatitis B and C screening in the EU have very high requirements for sensitivity, they are in reality not 100% sensitive (typically between 99.5 and 99.9% of all positive cases are detected depending on test and viral agent), which still leaves a small proportion of true positive cases undetected by the test. Frequently this component of the test is not considered in calculations of residual risk, as it is not possible to eliminate in most regular screening programmes. However, as the effect of it is cumulative, it should be included in calculations of residual risk when different screening frequencies are compared. Estimates of sensitivity have been incorporated into residual risk estimates for the UK and some studies from Germany and Austria [16, 22–24].

A third component relevant for estimations of residual risk is the proportion of individuals who are already infected at the first donation, i.e. the prevalence of infections in the population. This proportion is important to take into account for calculation of the total residual risk that is dependent on the sensitivity of the test being used.

To be able to estimate the increase in risk which would be a consequence of the proposed change of testing requirements, residual risk must be estimated in model format for both testing schemes, and compared. To evaluate threshold values for which risks increase significantly, key parameters of the model must be varied within reasonable values in a sensitivity analysis scheme.

Data requirements for estimation of residual risk and their availability

To be able to accurately and objectively estimate the residual risk of having unidentified HIV, hepatitis C or hepatitis B donations in the MAR procedure, several parameters must be known. The key parameters needed to describe the epidemiology of the disease in the study population are:.

- The *prevalence* of the infections in the treated population (i.e. the proportion of individuals that are already infected on starting the process and);
- The *incidence* of the infections (i.e. the proportion of individuals that become infected per unit of time spent using the services).

The only way to obtain such estimates is to systematically collect and use the actual data that are generated from the mandatory testing conducted by the tissue establishments themselves. If representative information is not available (as is currently the case for partner donations), proxy data or ranges of reasonable 'guesstimates' have to be used to serve as a basis for the modelling. Using proxy data means using data from another data source to substitute for the population under study. This will, however, almost certainly lead to biases in the results, which may lead to misleading conclusions. To minimise the bias, the populations from which the proxy data are obtained, should be matched as closely as possible to the study population.

For partner donations, the study population consists of the individuals in the process itself, i.e. the male or female counterparts who donate the reproductive cells (the semen/sperm or the oocytes) within the couples.

General population

Persons in MAR services are derived from the general population. In principle there should only be a few differences between them and the average population, which should all be related to the medical eligibility criteria employed for the acceptance of the partners into the assisted reproduction service. These criteria are mainly designed to optimise the likelihood of successful treatment, not at excluding risks of blood-borne or sexually transmitted infections. The major differences from the general population relate to the age bracket and the fact that at least one of the partners has fertility problems. There are few documented *a priori* reasons to assume that incidence or prevalence of HIV, hepatitis B or hepatitis C infection among persons using MAR services would be lower than in the general population. The same is true for partner donation compared with non-partner donation. If anything, as infertility is partly associated with a history of sexually transmitted infections, there is a possibility that the prevalence and incidence of these viral infections may be higher in populations of reduced fertility. Some studies have found reduced rates of fertility among individuals with HIV, hepatitis B or hepatitis C infections [27, 28]. Nevertheless, data for the similar age-bracket of the general population concerning HIV, hepatitis C and hepatitis B incidence and prevalence could be used as a proxy for the estimation of residual risk in populations using MAR services. However, truly representative population-based data for HIV, hepatitis C and hepatitis B incidence and prevalence in Europe are scarce.

Notification-based surveillance data

Incidence data based on recent case reporting are available for HIV infection in Europe [13], but represent an underestimate due to under-ascertainment, underreporting and reporting delay. Case-based reporting is derived from combined physician reporting and diagnostic testing and therefore does not represent a random sample of the general population, as indications for testing vary. Also, denominator data are based on entire national populations, as the numbers of tests performed are generally not collected. Notification data submitted by Member States through the ECDC European Surveillance System (TESSy) is available for 2008 from all EU/EEA countries except Austria, Denmark and Liechtenstein and, outside of the EU/EEA it is not available from Monaco.

For hepatitis B and hepatitis C, similar recent case reporting data are available, but should be used with a high degree of caution, as data comparability is very poor due to very different reporting requirements in the EU Member States [10, 29]. While a single case definition is used for EU-wide notification of HIV infection, various case definitions are used in the European region[7] and even the reportable disease stages differ. Some countries only report acute cases, while other report chronic and acute [10]. As with HIV, results are reported by total populations, not by tested individuals.

Population-representative prevalence data

Some population-representative studies of hepatitis B and hepatitis C prevalence in the European region do exist, but only from a limited number of countries. Further, the prevalence data are not contemporaneous [10, 11].

No truly general population-representative studies of HIV prevalence in the European region exist.

Screening blood donors

Data from blood donors are another potential source of proxy data for prevalence and incidence of blood-borne viruses, as screening of all blood donations for evidence of HIV, hepatitis B and hepatitis C infections is mandatory and systematically performed across the entire European region. As positive cases are excluded from future donation, incident cases can easily be distinguished from prevalent ones.

Results of screening of blood donations in the European region are systematically collected and reported to the Council of Europe European Directorate for the Quality of Medicines & HealthCare (EDQM) [30]. Information is categorised for first-time

[7] The term 'European region' comprises EU/EEA countries and, depending on the context, countries of WHO European Region or country members of the Council of Europe

and repeat donations, and the numbers of annually performed tests and positive results are collected and reported for HIV-Ab (antibodies specific for HIV), HCV-Ab (antibodies specific for HCV) and HBsAg (hepatitis B S-antigen). Relatively recent data are available from most EU and other European region countries [30, 31]. In the 2004 report from the EDQM (30), data are available from all EU Member States except Cyprus, Estonia, France and Portugal. Malta did not report on testing among repeat donors.

Prevalence of blood-borne infections is directly obtained from the positive results of first-time blood donors. This represents a direct estimate of the prevalence among potential blood donors. Similarly, any new positive results among repeat donors represent incident cases, as a previous negative test result has been verifiably obtained at the time of the previous donation.

However, blood donors are a highly selected population, and the selection criteria are specifically designed to exclude individuals with an elevated risk of having blood-borne infections even before the screening tests are performed. Several studies have verified that both first-time blood donors and especially repeat blood donors have a lower incidence of blood-borne virus infection than the general population [21]. The prevalence among first-time donors may be seen as a lower limit of the general population prevalence.

Therefore, using data for prevalence and incidence derived from blood donors as a proxy for residual risk estimation will inevitably result in underestimated RR values for reproductive services.

Screening pregnant women

Data from antenatal screening for HIV, hepatitis B and hepatitis C are currently not systematically collected on a European level. In the past, HIV data from pregnancy screening were collected by the EuroHIV Network. The last such report was published in 2005 [32].

Data on Hepatitis B and C collected from pregnancy screening have been recently reviewed [10, 11]. For hepatitis B, the antenatal prevalence ranged from 0.1% to 4.4% by country. Where both estimates were available, the prevalence in pregnant women tended to be higher than in the general population. This difference in prevalence might be connected to the fact that migrant women, who have a relatively high hepatitis B prevalence, are better represented in studies among pregnant women than in general population studies.

For HCV, the prevalence in pregnant women ranged from 0% to 1.7% by country.

Data from medically assisted reproductive services

Limited information is available on the frequency of HIV, hepatitis B and hepatitis C infection among individuals using medically assisted reproductive services. A system for EU-wide collection and analysis of results from testing for viral infections performed by European MAR services does not exist. For the purpose of performing this risk assessment, ESHRE provided ECDC with data collected through a survey among Member States on the implementation of the Directive 2004/23/EC, specifically on the implementation of viral screening[8]. Six countries provided estimates of the number of positive cases of HIV, hepatitis B and hepatitis C. The information was provided to the ECDC in pooled format. Among the six reporting countries, and among 31 446 treatment cycles per year, HIV, hepatitis B and hepatitis C were tested for. In the background document, the ESHRE estimates that on average, each individual patient undergoes two treatment cycles, therefore the above cycles should correspond to 15 723 individuals. The table below shows the results and the prevalence of each infection in the sampled population calculated from the results.

Table 1. Viral infections among patients of medically assisted reproduction services

	HIV	Hepatitis B	Hepatitis C
Cycles tested	31 446	31 446	31 446
Estimated number of individuals tested	15 723	15 723	15 723
New cases	25	143	130
Prevalence (cases per 100 000)	159	909	827

Source: European Society of Human Reproduction and Embryology

The literature search identified two studies in which data on viral infections were reported among MAR service patients. Wingfield and Cottell described results from seven Irish fertility units with reported prevalence and incidence among MAR service patients [9]. An earlier study by Hart et al. was able to compare prevalence between patients receiving IVF treatment and an antenatal population from the same area in an inner London hospital [33]. These results are shown below for comparison.

[8] EUTC [EU Tissues and Cells Directive] Task Force of ESHRE presentation and background document with extract of EIM data provided to the ECDC on 16 September 2010.

Table 2. Prevalence and incidence of HIV, HBV and HCV among patients of seven fertility units in Ireland

	HIV	Hepatitis B	Hepatitis C
Tests performed	33 087	34 084	33 089
Individuals tested	13 717	13 714	13 716
Prevalent cases	0	18	16
Incident cases	0	0	0
Prevalence (cases per 100 000)	0	131	117

Source: Wingfield and Cottell [9]

Table 3. A comparison of the prevalence of HIV, HBV and HCV among patients receiving IVF treatment and an antenatal population from an inner London area, UK

	HIV	Hepatitis B	Hepatitis C
Patients receiving IVF treatment			
Individuals tested	815	815	815
Prevalent cases	1	11	4
Prevalence (cases per 10^5)	123	1 350	
Patients receiving antenatal services			
Individuals tested	4 291	6 854	not done
Prevalent cases	33	95	not applicable
Prevalence (cases per 100 000)	769	1 386	—

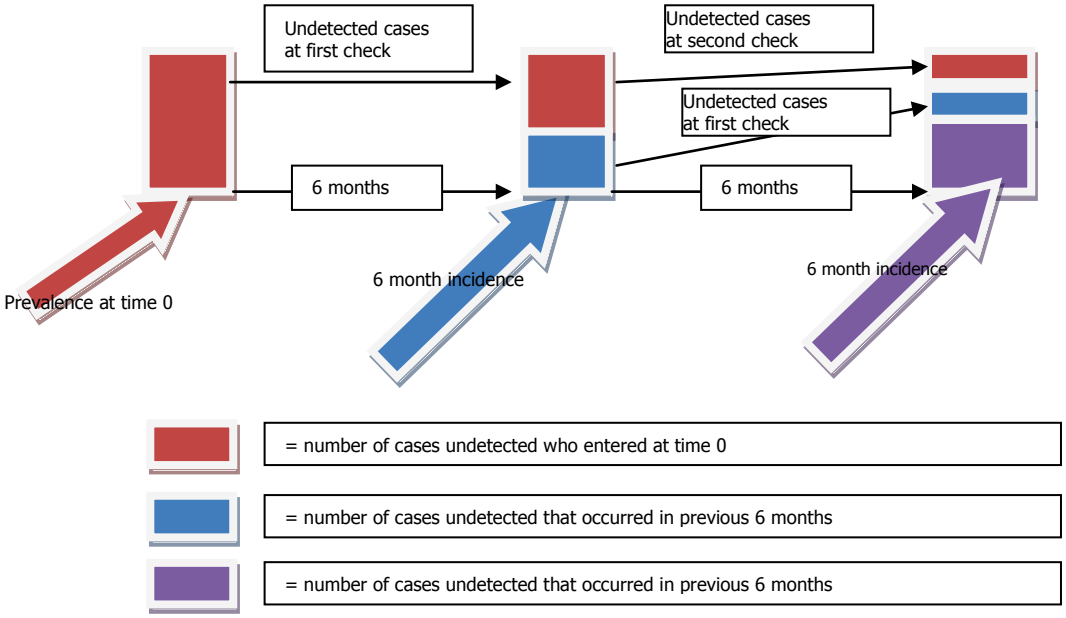
Source: Hart et al. [33]

Schematic of the compared alternative testing schemes

For the modelling of residual risk and the comparison risks under different frequencies of testing, a base case of the current requirements of testing was described, which was then compared with different options of testing. For purposes of simplicity, it was assumed that with current screening requirements, testing takes place at each donation, and there are on average three instances of donation annually (i.e. testing every four months). For the alternative scenarios, the assumption was that testing occurs every six months (two tests per year), once every year (one test per year) and finally once every second year (one test every two years), irrespective of the number of donations that occur.

In the model used for the estimation of the residual risk, i.e. the likelihood of having an unidentified infection in the system, prevalent cases (due to the less than 100% sensitivity of the screening test) and incident cases (infections that have occurred since the last testing occasion or cases which were in the window phase when the test was administered) will affect the residual risk. This is illustrated in Figure 4 below. The scenario shown is for testing every six months.

Figure 4. Comparison of alternative testing schemes



In the figure, the first arrow illustrates the prevalence component (the red arrow) of the risk as individuals enter the service and are tested for the first time: while most positive cases will be detected by the screening test, a small proportion of prevalent cases may be missed and will account for the residual risk (the red box) due to less than 100% sensitivity of the screening test and the proportion of cases that may be in the window phase where antibodies or antigen has not yet developed. The residual risk is directly calculated from the proportion of undetected positive cases out of all cases that were screened.

At the next screening occasion, the residual risk will consist of any cases which are again missed among those few carried over from the previous testing, and any cases missed among incident cases (new infections that have occurred after the last test) due to less than 100 % sensitivity of the test and the proportion of cases who may be in the window phase (blue box). The majority of cases missed at the first screening due to being in the window phase will be probably be detected, as the screening interval in this example is longer that the window period for all of the diseases examined, but a few may be missed (red box). The length of the screening interval can be accurately taken into account in the modelling. Therefore, the major component leading to a residual risk after the second screening (blue box) will come from any incident cases that may occur between the testing occasions (blue arrow).

Upon each next round of screening, the same process is repeated again.

The result of each screening test in terms of affecting the residual risk is that it will remove the majority of the risk due to incident cases, i.e. new cases that occur between the screening occasions. Therefore, more frequent screening will lead to lower residual risk.

However, if incidence and prevalence are very low, more frequent screening may not significantly alter the absolute residual risk, even if the proportional change is significant.

Model for partner donations

This model has been developed based on the previously used approaches described in the literature, and which have been widely used to estimate residual risks of infected donations entering the blood supply [16, 22, 24-26]. Most of the models only take into account residual risk due to the window period. This can be used to estimate the proportion of the annual incidence which is missed. Some models, however, also include residual risk due to less than 100% test sensitivity, which affects both incidence and prevalence when estimates are made. The model presented here tries to capture both components.

In the model, the residual risk is calculated as the biannual probability of an undetected positive case in MAR treatment.

For all models, it is assumed that the donors are in the process at least for one year, and in the case of testing scheme D at least two years.

Assumptions for the base case: **A** All individuals are screened on first donation, the positive cases are excluded or processed using other procedures which prevent them from contributing to the risk; average of three annual donations at regularly spaced intervals; test performed at each donation.

The comparison is performed between alternative testing schemes where testing is not dependent on donations but performed: **B** twice per year, C once per year and **D** once every second year. As testing removes risk only at the time of testing (except for the residual), while donations may be performed between the times of testing, the residual risk in these testing schemes includes the contribution of incidence up until immediately before the first test of the next annual cycle.

Models: Models **A**, **B** and **C** show the annualised residual risk calculation. For comparison with model **D**, they are extended to include the effect of year number 2 on the residual risk.

A Base case: Annualised residual risk at current scheme of testing at each donation (three donations per year)

1 Probability of an undetected positive individual performing initial donation:
(donor disease prevalence x proportion of false negative test)
2 Probability of an undetected positive individual performing first subsequent donation:
(donor disease annual incidence x fraction of year since last test) x (window period as fraction of a length of year since last test) + (donor disease annual incidence x fraction of year since last test) x (1 - window period as fraction of a length of year since last test) x proportion of false negative test + (residual from point 1 x proportion of false negative test)
3 Probability of an undetected positive individual performing second subsequent donation:
(donor disease annual incidence x fraction of year since last test) x (window period as fraction of a length of year since last test) + (donor disease annual incidence x fraction of year since last test) x (1 - window period as fraction of a length of year since last test) x proportion of false negative test + (residual from point 2 x proportion of false negative test)

-> The probability at point 3 is the annualised residual risk for the base case.

B Proposed first alternative scheme (testing twice per year):

1 Probability of an undetected positive individual performing initial donation:
(donor disease prevalence x proportion of false negative test)
2 Probability of an undetected positive individual immediately after second test:
(donor disease annual incidence x fraction of year since last test) x (window period as fraction of a length of year since last test) + (donor disease annual incidence x fraction of year since last test) x (1 - window period as fraction of a length of year since last test) x proportion of false negative test + (residual from point 1 x proportion of false negative test)
3 Probability of an undetected positive until the first test in the next yearly cycle:
(donor disease annual incidence x fraction of year since last test) x (window period as fraction of a length of year since last test) + (donor disease annual incidence x fraction of year since last test) x (1 - window period as fraction of a length of year since last test) x proportion of false negative test + (residual from point 2 x proportion of false negative test)

-> The probability at point 3 is the annualised residual risk for the first alternative testing scheme.

C Proposed second alternative scheme (testing once per year):

1 Probability of an undetected positive individual performing initial donation:
(donor disease prevalence x proportion of false negative test)
2 Probability of an undetected positive until the first test in the next yearly cycle:
(donor disease annual incidence x fraction of year since last test) x (window period as fraction of a length of year since last test) + (donor disease annual incidence x fraction of year since last test) x (1 - window period as fraction of a length of year since last test) x proportion of false negative test + (residual from point 1 x proportion of false negative test)

-> The probability at point 2 is the annualised residual risk for the second alternative testing scheme

D Proposed third alternative scheme (testing once every second year):

1 Probability of an undetected positive individual performing initial donation:
(donor disease prevalence x proportion of false negative test)
2 Probability of an undetected positive until the first test in the next yearly cycle:
(donor disease annual incidence x proportion of false negative test) + (donor disease annual incidence) x (window period as fraction of a year) + (donor disease annual incidence x (1 - window period as fraction of a year) x proportion of false negative test) + (residual from point 1 x proportion of false negative test)

-> The probability at point 2 is the biennial residual risk for the third alternative testing scheme.

Data and definitions used in the modelling

Tests used for the infections:

HIV	HIV-antibody test (HIV-Ab)
Hepatitis B virus	HBs-antigen test (HBsAg)
Hepatitis C virus	HCV-antibody test (HCV-Ab)

Parameters for the model

In all the prevalence and incidence estimates, only data from EU Member States were included, and incidence and prevalence were calculated based on only those countries for which data were available. Hepatitis B and C incidence data based on notifications should be interpreted with great caution, as case definition and reporting criteria are not standardised across Europe (values shown in parenthesis). Denominator data also vary, being total country populations for notifications, and individuals tested for blood donors, pregnant women and prevalence study data. For the ESHRE-supplied data on prevalence among persons in reproductive cell services, the denominator is the number of treatment cycles observed, divided by a factor of two, as ESHRE estimates that on average, each individual undergoes two cycles of treatment.

Table 4: Summary of available data for prevalence (P) and incidence (I) of HIV, Hepatitis B and C

	HIV		Hepatitis B		Hepatitis C	
Cases per 100 000 population (per year for *I*)	*P*	*I*	*P*	*I*	*P*	*I*
Notifications & studies§	—	5.3	921.8	*(1.5)*	2306.9	*(7.1)*
Notifications: 25–44 years old	—	11.9	—	—	—	—
Blood donors†	13.7	2.5	451.0	11.1	235.6	13.9
Pregnant women‡	81.7	—	508.3	—	1024.3	—
Reproductive services	159.0	(29.02)	909.5	(53.66)	828.8	(20.35)

Sources:
§ I: ECDC TESSy surveillance reporting; P: ECDC technical reports [10, 11, 13, 29]
† EQDM: first time and repeat donors, EU region [32]
‡ EuroHIV report 72[34]; ECDC technical reports [13-15, 31]; EU region

Comparing the different data sources, some observations can be made: firstly, both prevalence and incidence data are only available for all infections from the blood donor populations in Europe. Secondly, both prevalence and incidence are the lower among this population than the others.

Data used for point estimates:

Population-specific prevalence of HIV, hepatitis C and hepatitis B infection among donors of reproductive cells was calculated from data provided by ESHRE. For this population, incidence data are not available, but it was estimated by imputation, as previously done for tissue donations [21], using the ratio of incidence and prevalence in data from blood donors in the EU in 2004 [30].

For sensitivity analysis:

The following ranges for the modelling were chosen as reasonable ranges of incidence and prevalence in the European region. The lower limits were based on blood donor data, whereas the upper limits were based on data from groups at higher risk.

	HIV		Hepatitis B		Hepatitis C	
	P	I	P	I	P	I
Min	2	0.5	20	0.5	20	0.5
Max	10 000	50	10 000	300	10 000	300

P: prevalence (per 100 000 population)
I: incidence (per 100 000 person-years)

Fixed parameters:

Sensitivity of testing (from Soldan et. al, 2005 [16]):

HIV: 99.9 % (anti-HIVAb)
HCV: 99.5 % (anti-HCV-Ab)
HBV: 99.5 % (HBsAg)
Window periods (from Screiber et. al, 1996 [25]):

HIV-Ab: 22 days
HCV-Ab: 82 days
HBsAg: 59 days, incidence adjustment factor 2.38 (due to intermittent antigenemia)

Additional assumptions and execution of the model

Testing takes place equally distributed during a year (twice a year = every six months, three times a year = every four months, etc.).

The effect of window periods: Taking into account that the different diseases have a certain window period we have assumed this has a linear correspondence with the reduction in the number of cases newly infected during the length of the period until next test. The reduction is in proportion with the proportion between the window period and the length of the time period between tests. The individuals who are in the window period at the time of the first test are at the second test assumed to be tested as normal.

The input parameters into the model are prevalence (expressed as percentage of the population being infected) and incidence (number of cases per 100 000 person years). The model assumes that individuals will come to all tests during the two year period.

In order to calculate the number of persons infected, the model assumes a population of size 10 million. This number is, however, irrelevant as the final output of the model is the number of infected persons in the population which is independent of the population size.

The model takes into account that a person can be misdiagnosed at the first test during the year but can be detected at a later test that year.

For the sensitivity analysis, 100 x 100 (total 10 000) iterations of incidence and prevalence values within the chosen ranges were calculated for each infection.

The programming was implemented in R version 1.10.

6 Results

All results obtained from the modelling should be interpreted with caution. As fully representative prevalence and incidence estimates for populations using MAR services are not readily available, a number of assumptions have had to be made for the estimation of change in residual risk due to a change in testing frequency. No data on success rates after each subsequent donation were available, and could therefore not be taken into account.

Point estimates

For a first estimate of the effect of a change in testing requirements, point estimates of the residual risk were obtained, using prevalence data supplied by ESHRE and using ratios of incidence and prevalence among blood donors to impute the incidence data which are not available for the donors of reproductive cells in Europe. The data for blood donors were obtained from the EDQM 2004 report [30].

The model, as described above, was used to first generate point estimates of residual risk under the two different screening alternatives. The point estimates were then compared to illustrate the proportional change of the residual risk due to less frequent testing.

HIV

Assuming a test which is 99.9% sensitive.

Prevalence is 159 per 100 000

Incidence is 29 per 100 000 person-years (imputed)

The window period is 22 days

Table 5. Results of modelling residual risk for HIV by testing frequency

	4 months	6 months	12 months	24 months	Difference 4 / 24 months
Residual risk per 1 000 000	17.83	17.87	18.02	18.29	0.467
Risk ratio	1.0000	1.0027	1.0109	1.0262	
Tests to miss one case	56 101	55 949	55 498	54 668	2 140 090

The residual risk of missing a case with today's schedule (assuming testing every four months) is 17.83 per million, i.e. one case is missed for every 56 101 tests.

With the once a year schedule the residual risk is 18.02 per million tests.

With the once every second year schedule the residual risk is 18.29 per million tests.

The residual risk is 1.03 times higher for testing once every second year compared with testing every fourth month.

Comparing the current schedule with testing once every second year, 2.14 million tests would be needed to miss one additional case.

Hepatitis B

Assuming a test which is 99.5% sensitive.

Prevalence is 909.5 per 100 000

Raw incidence is 53.66 per 100 000 person-years (imputed)

The window period is 59 days

Incidence adjustment factor is 2.38

Table 6. Results of modelling residual risk for HBV by testing frequency

	4 months	6 months	12 months	24 months	Difference 4 / 24 months
Residual risk per 1 000 000	32.08	32.27	32.83	34.01	1.932
Risk ratio	1.00	1.01	1.02	1.06	
Tests to miss one case	31 172	30 991	30 460	29 402	517 604

The residual risk of missing a case with today's schedule (assuming testing every four months) is 32 per million, i.e. one case is missed for every 31 172 tests.

With the once a year schedule the residual risk is 33 per million tests.

With the once every second year schedule the residual risk is 34 per million tests.

The residual risk is 1.06 times higher for testing once every second year compared with testing every fourth month.

Comparing the current schedule with testing once every second year, 517 604 tests would be needed to miss one additional case.

Hepatitis C

Assuming a test which is 99.5% sensitive.

Prevalence is 828.8 per 100 000

Incidence is 20.35 per 100 000 person-years (imputed)

The window period is 82 days

Table 7. Results of modelling residual risk for HCV by testing frequency

	4 months	6 months	12 months	24 months	Difference 4 / 24 months
Residual risk per 1 000 000	267.04	268.02	270.93	275.61	8.6
Risk ratio	1.00	1.00	1.01	1.03	
Tests to miss one case	3 745	3 731	3 691	3 628	116 679

The residual risk of missing a case with today's schedule (assuming testing every four months) is 267 per million, i.e. one case is missed for every 3 745 tests.

With the once a year schedule the residual risk is 271 per million tests.

With the once every second year schedule the residual risk is 275 per million tests.

The residual risk is 1.03 times higher for testing once every second year compared with testing every fourth month.

Comparing the current schedule with testing once every second year, 116 679 tests would be needed to miss one additional case.

Sensitivity analysis

To explore the ranges of key variables affecting residual risk, sensitivity analysis was performed by varying values of incidence and prevalence with various testing frequencies. The same values for test sensitivity and window period for the different diseases were used as in the point estimate analysis.

Performing a sensitivity analysis better illustrates how the residual risk varies over a range of plausible values for incidence and prevalence.

Using the ranges of prevalence and incidence defined in the section on model parameters, the following results were obtained for HIV, hepatitis B and hepatitis C. Test sensitivity and window periods were the same as for the point estimates.

For the sensitivity analysis, 100 x 100 iterations of incidence and prevalence values within the chosen ranges were calculated for the residual risk for each infection. From the sensitivity iterations, the median, maximum and minimum of the residual risk ratios were extracted and reported separately.

HIV

Prevalence is 2– 1 000 per 100 000.

Incidence varies between 0.5 and 100 per 100 000 person-years

Table 8. Results of modelling residual risk for HIV by sensitivity analysis

	High/Low	4 months	6 months	12 months	24 months	Difference 4/24 months
Residual risk per million	L	0.31	0.31	0.31	0.32	0.008
	H	61.44	61.61	62.11	63.06	1.6
Residual risk ratio	L	1.0000	1.0027	1.0109	1.0262	
	H	1.0000	1.0027	1.0109	1.0263	
Tests to miss one case	L	3 254 955	3 246 141	3 219 987	3 171 884	124 283 815
	H	16 275	16 231	16 100	15 858	619 111

The median ratio between probabilities to miss a case is 1.03 (1.02 (minimum) – 1.06 (maximum)) higher for testing once every second year compared with testing every fourth month.

For one million donations, the average number of cases not detected would be 0.81 (0.008 – 1.65), that is on average 1.24 (0.62 – 125) million tests would be needed to miss one case if testing once every second year instead of testing every four months.

Hepatitis B

Prevalence is 20–5 000 per 100 000

Incidence varies between 0.5 and 300 per 100 000 person-years

Table 9. Results of modelling residual risk for HBV by sensitivity analysis

	High/Low	4 months	6 months	12 months	24 months	Difference 4/24 months
Residual risk per million	L	0.72	0.72	0.73	0.76	0.043
	H	430.03	432.54	440.07	454.13	24
Residual risk Ratio	L	1.00	1.01	1.02	1.06	
	H	1.00	1.01	1.02	1.06	
Tests to miss one case	L	1 395 267	1 387 162	1 363 390	1 316 150	23 210 904
	H	2 325	2 312	2 272	2 202	41 494

The median ratio between probabilities to miss a case is 1.06 (1.05 (minimum) – 2.80 (maximum)) higher for testing once every second year compared with testing every fourth month.

For one million donations, the average number of cases not detected would be 12 (0.043 – 24.1), that is on average 0.083 (0.042 – 23.2) million (i.e. 83 000) tests would be needed to miss one case if testing once every second year instead of testing every four months.

Hepatitis C

Prevalence is 20 – 5 000 per 100 000

Incidence varies between 0.5 and 300 per 100 000 person-years

Table 10. Results of modelling residual risk for HCV by sensitivity analysis

	High/Low	4 months	6 months	12 months	24 months	Difference 4 / 24 months
Residual risk per million	L	2.81	2.86	3.02	3.36	0.551
	H	1687.36	1717.87	1809.06	1973.93	286
Residual risk ratio	L	1.00	1.02	1.07	1.20	
	H	1.00	1.02	1.07	1.17	
Tests to miss one case	L	355 585	349 269	331 463	297 372	1 816 441
	H	593	582	553	507	3 490

The median ratio between probabilities to miss a case is 1.17 (1.03 (minimum) – 12.3 (maximum)) higher for testing once every second year compared with testing every fourth month.

For one million donations, the average number of cases not detected would be 143 (0.55 – 286), that is on average 0.0070 (0.0035 – 1.81) million (i.e. 7 000) tests would be needed to miss one case if testing once every second year instead of testing every four months.

7 Discussion and conclusions

The residual risks of a case of HIV, HBV or HCV infection transmitted by undetected infection of reproductive cells donated for MAR services estimated using the model developed and the data supplied by ESHRE was relatively small, but not insignificant. For HIV, the estimated risk was 17.83 cases per million person years using the current testing scheme, which is clearly higher than for blood services, where residual risks are 1–2 orders of magnitude lower. The same can be concluded for hepatitis B, where the residual risk was 32.08 cases per million person years, and hepatitis C where the residual risk was 267 cases per million person years. For hepatitis C in particular, even under current testing schemes the residual risk can be considered relatively high. This is likely to be a consequence of a) higher prevalence and incidence among the reproductive cell donors compared with blood donors and b) the use of NAT testing in blood services, while the model assumes only the use of antibody and antigen testing in MAR services.

Comparison of calculated residual risks for testing performed every six, 12 or 24 months, with testing at each donation (assumed to take place at four-month intervals), showed only a modest increase in the residual risk between the different testing frequencies, as seen in Tables 5–10. Comparing testing at each donation and every 24 months, the residual risk for HIV infection increased by a factor of 1.026 (2.6%), and the corresponding increases for HBV and HCV were 1.06 (6%) and 1.03 (3%). In absolute numbers, the additional cases missed due to the 24-month schedule would be 0.46 cases of HIV infection per million, 1.93 cases of HBV infection per million and 8.6 cases of HCV infection per million.

Using the model and the data on prevalence for MAR services, it is evident that changing requirements from testing at each donation to once per year would result in small increases in residual risk. The increase in residual risk is modest: under the once-in-24-months testing scenario, approximately 2.14 million more tests have to be performed before one extra case of HIV infection is found, compared with the current testing scheme every fourth month. For hepatitis B and C the numbers are smaller, but still high. Only for hepatitis C might the increased residual risk result in additional cases that could go undetected during treatment within a reasonable time. The reason for the small increase is that the major contribution of risk comes from the prevalence, and this is practically removed in all scenarios by the first testing.

Sensitivity analysis using low and high threshold values for both prevalence and incidence for all the different testing scenarios showed that the maximum relative increase of residual risk is 1.06 for HIV, 2.8 for hepatitis B and 12.3 for hepatitis C. These maximum relative increases in residual risk did not occur for the highest prevalence/incidence combination, even though this is where the absolute residual risk is the highest. Therefore, there may be combinations of prevalence and incidence where the changes in testing scheme could lead to a relatively high proportional increase in the residual risk. Due to the properties of the risk model, this would be likely in situations of very low prevalence, but very high incidence. Such a situation could occur only if there is a rapidly evolving outbreak in the population.

Assuming that the population using the MAR services is very similar to another population for which the incidence and prevalence data are available, these could be used as proxies. Prevalence and incidence from blood donors were used in a previous draft of this risk assessment, and clearly resulted in much lower residual risk values than those obtained for the point estimate in the final assessment, using data from MAR services supplied by ESHRE.

A conclusion is that using unrepresentative proxy data in the first draft of the risk assessment (dated 17 September 2010) introduced serious bias and uncertainty into the data that had a significant effect on the conclusions drawn. Therefore the use of proxy data should be avoided in future updates of residual risks for MAR and other tissue/cell services and real data should be gathered to enable objective and scientifically sound results to be obtained and used to support decisions on safety measures.

While the modelling based on the ESHRE-submitted values gives a first approximation of the changes in risk that would be a consequence of the proposed changes to testing frequency and the absolute residual risk, there are significant uncertainties in the analysis. The main source of uncertainty is the lack of availability of representative data on HIV, hepatitis B and hepatitis C incidence and prevalence from the reproductive cell donor population. The data available to ECDC only came from six countries whose identity was not known to ECDC. Even if surveillance data from other sources are not useful for direct estimation of residual risk in MAR services, it shows that there are significant differences in the risk of contracting blood-borne viral infections in Europe. Therefore the estimated risk and the change of risk presented in this risk assessment are not necessarily representative of every MAR service in every Member State. It is likely that significant variation in disease prevalence and incidence in different countries will result in different residual risks under different testing scenarios.

This risk assessment only addresses the changes in the residual risk of undetected cases of HIV, HBV or HCV-infected donors undergoing MAR treatment. It does not address the physical risks that the presence of infected individuals using the service would pose through cross-contamination to the other partner, the embryo, other persons receiving treatment in the same facility, staff of the facility or to tissues and cells in cryo-storage. Addressing many of these issues would require different expertise and intimate understanding of the working arrangements within the services. Nevertheless, it might be possible to address the evidence for cross-contamination in cryo-storage and risk of infection for the embryo. The evidence within the review was not evaluated for validity, reliability or generalisability using formal tools for the classification of scientific evidence and the epidemiological data reported are not representative of the entire MAR service field in Europe.

This work has shown that prevalence (and possibly incidence as this was only imputed) of blood-borne viral infections is not negligibly low among donors of reproductive cells. It is clearly higher than among blood donors, and may even be higher than among pregnant women. A possible reason is that there may be an association between sub fertility/infertility and history of sexually transmitted disease. As the latter is a known risk factor for at least HIV and hepatitis B, this might explain a higher-than-average-prevalence among those seeking MAR services.

We did not address the impact of using NAT testing in MAR services, as this is not required at the present time. However, as this reduces the window period for HIV and HCV significantly, this could provide one option for reduction of the residual risk, if desirable.

As the data presented within this risk assessment come from a relatively small population sample, the point estimates of residual risk derived from it should be interpreted cautiously. More and representative data from a larger number of EU Member States would be needed to make truly reliable point estimates of residual risks.

8 Considerations

ECDC would suggest the following issues for the Commission's consideration.

- Consider requiring collection and centralised reporting of testing result data on blood-borne viral infections for all cell and tissue donations using standardised protocols in the EU as part of quality assurance for tissue and cell donation establishments.

Motivation: To reliably and objectively estimate the residual risk of having individuals/donations with undetected HIV, hepatitis B and hepatitis C infection, data on these infections would need to be available for the population using the reproductive cell services. The only way to make such estimates is to collect and use the actual data that are generated from the mandatory testing conducted by the services themselves. An example of successful collection of actual testing data in Europe is the systematic collection of data from blood establishments, as performed by the EDQM of the Council of Europe [30]. This allows for the objective estimation of residual risk and also enables an accurate estimate of the consequences of changing testing requirements regarding the remaining risk [18, 20, 31].

- Consider the possibility of changing the requirements for testing to allow testing once per year, if 1) the tissue establishment can demonstrate that the risk of cross-contamination, staff exposure and potential mix-up of gametes has been addressed and minimised through the use of validated quality and safety processes; 2) the establishment has a process in place to record and report the number of cases found at different stages during the screening of HIV, HBV and HCV among clients; 3) the establishment can reliably demonstrate, through a residual risk estimation using own data, that it would be unlikely that the change in testing would lead to a significant increase in undetected cases of HIV, HBV and HCV using the services.

Motivation: The risk assessment showed that the residual risk changes are minor due to the change in testing frequency. Therefore a once-yearly testing would be a reasonable compromise for a safe but less burdensome risk-management model. It would be important, however, that the establishment commits to safe working procedures and that the unlikely situation of very high rates of infection can be excluded.

- Consider commissioning a review of the probability of infection of embryos and the question of transmission of blood-borne viruses in cryo-storage as well as potential mix-up of gametes.

Motivation: The hypothesis of transmission of blood-borne viruses to embryos and transmission in cryo-storage, particularly in liquid nitrogen storage has not been properly addressed by a comprehensive review of the evidence. Such a review would add value to the assessment of risks for third parties using MAR services.

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Annex 1. Search strategy

PUBMED: Cell donors

Concept 1:	Boolean operator	Concept 2:	Boolean operator	Concept 3:	Boolean operator	Concept 4:
OR		OR		OR		OR
"Reproductive Techniques, Assisted"[Mesh] "Insemination, Artificial"[Mesh] "Reproductive Techniques"[Mesh:NoExp] "assisted reproduction"[Title/Abstract] OR "in vitro fertilisation"[Title/Abstract] "intracyoplasmic"[Title/Abstract] "artificial insemination"[Title/Abstract] "frozen embryo transfer"[Title/Abstract] "intrauterine insemination"[Title/Abstract] "microsurgical epididymal sperm aspiration"[Title/Abstract] "oocyte donation"[Title/Abstract] "single embryo transfer"[Title/Abstract] "sperm donation"[Title/Abstract] "testicular sperm extraction"[Title/Abstract] OR ((donor* OR donat*) AND ("Germ Cells"[Mesh] OR sperm OR spermatoz* OR semen OR ovum* OR "spermatic fluid" OR ovule* OR oocyte* OR cyte* OR egg* OR "reproductive cell" OR "reproductive cells"))	AND	"Hepatitis B"[Mesh] "Hepatitis B virus"[Mesh] "Hepatitis B Core Antigens"[Mesh] "Hepatitis C"[Mesh] "Hepatitis C Antibodies"[Mesh] "HIV Infections"[Mesh] "HIV Antibodies"[Mesh] "HTLV-I Infections"[Mesh] "HTLV-II Infections"[Mesh] "Acquired Immunodeficiency Syndrome"[Mesh] "Human T-lymphotropic virus 1"[Mesh] "Human T-lymphotropic virus 2"[Mesh] "hepatitis b"[Title/Abstract] "hepatitis c"[Title/Abstract] "htlv i"[Title/Abstract] "htlv ii"[Title/Abstract] "htlv 1"[Title/Abstract] "htlv 2"[Title/Abstract] "human immunodeficiency virus"[Title/Abstract] "hiv infections"[Title/Abstract] "acquired immunodeficiency syndrome"[Title/Abstract] "human t lymphotropic virus 1"[Title/Abstract] "human t lymphotropic virus htlv i"[Title/Abstract] "human t lymphotropic virus 2"[Title/Abstract] "human t lymphotropic virus type 1"[Title/Abstract] "human t lymphotropic virus type 2"[Title/Abstract]	NOT	serodiscordant[Title] "sero discordant"[Title] ("sperm"[Title] AND "washing"[Title])	AND	"Cross-Sectional Studies"[Mesh] "Prevalence"[Mesh] "Incidence"[Mesh] "Mass Screening"[Mesh] "Controlled Clinical Trial "[Publication Type] "Controlled Clinical Trials as Topic"[Mesh:NoExp] "Models, Statistical"[Mesh] "Meta-Analysis "[Publication Type] "Meta-Analysis as Topic"[Mesh] "Guideline "[Publication Type] "Evidence-Based Practice"[Mesh] "Consensus Development Conference "[Publication Type] "Consensus Development Conferences as Topic"[Mesh] "systematic review"[Title/Abstract] "cross sectional"[Title/Abstract] "controlled clinical trial"[Title/Abstract] "meta analysis"[Title/Abstract] "screening"[Title] "screen"[Title] "model"[Title] "modelling"[Title] "modeling"[Title] "risk"[MeSH Terms] "risk"[Title]

Limits: English, French, German, Spanish, Finnish, Swedish

EMBASE: Cell donors

Concept 1:	Boolean operator	Concept 2:	Boolean operator	Concept 3:	Boolean operator	Concept 4:
OR		OR		OR		OR
'infertility therapy'/exp 'reproductive techniques':ab 'reproductive techniques':ti 'artificial insemination':ab 'artificial insemination':ti 'assisted reproduction':ab 'assisted reproduction':ti 'in vitro fertilisation':ab 'in vitro fertilisation':ti intracyoplasmatic:ab intracyoplasmatic:ti 'frozen embryo transfer':ab 'frozen embryo transfer':ti 'intrauterine insemination':ab 'intrauterine insemination':ti 'microsurgical epididymal sperm aspiration':ab 'microsurgical epididymal sperm aspiration':ti 'oocyte donation':ab 'oocyte donation':ti 'single embryo transfer':ab 'single embryo transfer':ti 'sperm donation':ab 'sperm donation':ti 'testicular sperm extraction':ab 'testicular sperm extraction':ti OR (('sperm'/exp OR spermatoz* OR 'semen'/exp OR ovum* OR 'spermatic fluid' OR ovule* OR oocyte* OR cyte* OR egg* OR 'reproductive cell' OR 'reproductive cells' OR 'germ cell'/exp) AND (donor* OR donat*))	AND	'hepatitis b'/exp 'hepatitis b antigen'/exp 'hepatitis b virus'/exp 'hepatitis c'/exp 'hepatitis c antibody'/exp 'human immunodeficiency virus infection'/exp 'human immunodeficiency virus antibody'/exp 'human t cell leukemia virus infection'/exp 'acquired immune deficiency syndrome'/exp 'human t cell leukemia virus 1'/exp 'human t cell leukemia virus 2'/exp 'hepatitis b':ab 'hepatitis b':ti 'hepatitis c':ab 'hepatitis c':ti 'htlv i':ab 'htlv i':ti 'htlv ii':ab 'htlv ii':ti 'htlv 1':ab 'htlv 1':ti 'htlv 2':ab 'htlv 2':ti 'human immunodeficiency virus':ab 'human immunodeficiency virus':ti 'hiv infections':ab 'hiv infections':ti 'acquired immunodeficiency syndrome':ab 'acquired immunodeficiency syndrome':ti 'human t lymphotropic virus 1':ab 'human t lymphotropic virus 1':ti 'human t lymphotropic virus htlv i':ab 'human t lymphotropic virus htlv i':ti 'human t lymphotropic virus 2':ab 'human t lymphotropic virus 2':ti 'human t lymphotropic virus type 1':ab 'human t lymphotropic virus type 1':ti 'human t lymphotropic virus type 2':ab 'human t lymphotropic virus type 2':ti	NOT	'sperm washing':ti serodiscordant:ti 'sero discordant':ti	AND	'cross-sectional study'/exp 'prevalence'/exp 'incidence'/de 'screening'/exp 'model'/exp 'controlled clinical trial'/de 'risk'/exp 'evidence based practice'/exp 'systematic review'/exp 'meta analysis'/exp 'practice guideline'/exp 'systematic review':ab 'systematic review':ti 'cross sectional':ab 'cross sectional':ti 'controlled clinical trial':ab 'controlled clinical trial':ti 'meta analysis':ab 'meta analysis':ti 'screening':ti 'screen':ti 'model':ti 'modelling':ti 'modeling':ti 'risk':ti guideline:ti guidelines:ti

Limits: [english]/lim OR [finnish]/lim OR [french]/lim OR [german]/lim OR [spanish]/lim OR [swedish]/lim) AND [embase]/lim

COCHRANE LIBRARY: Cell donors

Search Strategies	Concept 1:	Boolean operator	Concept 2:	Boolean operator	Concept 3:
	OR		OR		OR
	MeSH descriptor **Reproductive Techniques, Assisted** explode all trees MeSH descriptor **Insemination, Artificial** explode all trees MeSH descriptor **Reproductive Techniques** no explode OR ((sperm OR spermatoz* OR semen OR ovum* OR "spermatic fluid" OR ovule* OR oocyte* OR cyte* OR egg* OR "reproductive cell" OR "reproductive cells" OR MeSH descriptor **Germ Cells** explode all trees) AND (donor* OR donat*))	AND	MeSH descriptor **Germ Cells** explode all trees MeSH **descriptor Hepatitis B** explode all trees MeSH descriptor **Hepatitis B virus** explode all trees MeSH descriptor **Hepatitis B Core Antigens** explode all trees MeSH descriptor **Hepatitis B Antigens** explode all trees MeSH descriptor **Hepatitis C** explode all trees MeSH descriptor **Hepatitis C Antibodies** explode all trees MeSH descriptor **HIV Infections** explode all trees MeSH descriptor **HIV Antibodies** explode all trees MeSH descriptor **HTLV-I Infections** explode all trees MeSH descriptor **HTLV-II Infections** explode all trees MeSH descriptor **Acquired Immunodeficiency Syndrome** explode all trees MeSH descriptor **Human T-lymphotropic virus 1** explode all trees MeSH descriptor **Human T-lymphotropic virus 2** explode all trees	NOT	"sperm washing"[Title] serodiscordant[Title] "sero discordant"[Title]

PUBMED: Blood donors

Concept 1:	Boolean operator	Concept 2:	Boolean operator	Concept 3:	Boolean operator	Concept 4:	Boolean operator	Concept 5:
OR		OR		OR		OR		OR
"Tissue Donors"[Mesh:NoExp] "Blood Donors"[Mesh] "Blood Transfusion"[Mesh] "blood donor"[Title/Abstract] "blood donors"[Title/Abstract] "blood transfusion"[Title/Abstract] "plasma donor"[Title/Abstract] "plasma donors"[Title/Abstract]	AND	"Hepatitis B"[Mesh] "Hepatitis B virus"[Mesh] "Hepatitis B Core Antigens"[Mesh] "Hepatitis C"[Mesh] "Hepatitis C Antibodies"[Mesh] "HIV Infections"[Mesh] "HIV Antibodies"[Mesh] "HTLV-I Infections"[Mesh] "HTLV-II Infections"[Mesh] "Acquired Immunodeficiency Syndrome"[Mesh] "Human T-lymphotropic virus 1"[Mesh] "Human T-lymphotropic virus 2"[Mesh] "hepatitis b"[Title/Abstract] "hepatitis c"[Title/Abstract] "htlv i"[Title/Abstract] "htlv ii"[Title/Abstract] "htlv 1"[Title/Abstract] "htlv 2"[Title/Abstract] "human immunodeficiency virus"[Title/Abstract] "hiv infections"[Title/Abstract] "acquired immunodeficiency syndrome"[Title/Abstract] "human t lymphotropic virus 1"[Title/Abstract] "human t lymphotropic virus htlv i"[Title/Abstract] "human t lymphotropic virus 2"[Title/Abstract] "human t lymphotropic virus type 1"[Title/Abstract] "human t lymphotropic virus type 2"[Title/Abstract]	NOT	((transplant* OR donor* OR donat*) AND organ) Field: Title	AND	"Clinical Laboratory Techniques"[Mesh] "Immunologic Tests"[Mesh] "Microbiological Techniques"[Mesh] "Viral Load"[Mesh] "Physical Examination"[Mesh] "Serologic Tests"[Mesh] "Nucleic Acid Amplification Techniques"[Mesh] "Mandatory Testing"[Mesh] "Diagnostic Tests, Routine"[Mesh] "Tissue and Organ Harvesting"[Mesh] "Tissue and Organ Procurement"[Mesh] "mandatory screening"[Title/Abstract]) "mandatory screenings"[Title/Abstract] "diagnostic test"[Title/Abstract] "diagnostic tests"[Title/Abstract] "mandatory test"[Title/Abstract] "mandatory testing"[Title/Abstract]""mandatory tests"[Title/Abstract] "nucleic acid amplification techniques"[Title/Abstract] "nucleic amplification techniques"[Title/Abstract] "serologic test"[Title/Abstract] "serologic tests"[Title/Abstract] "viral load"[Title/Abstract] "immunologic tests"[Title/Abstract] "immunologic test"[Title/Abstract]	AND	"Cross-Sectional Studies"[Mesh] "Prevalence"[Mesh] "Incidence"[Mesh] "Mass Screening"[Mesh] "Controlled Clinical Trial "[Publication Type] "Controlled Clinical Trials as Topic"[Mesh:NoExp] "Models, Statistical"[Mesh] "Meta-Analysis "[Publication Type] "Meta-Analysis as Topic"[Mesh] "Guideline "[Publication Type] "Evidence-Based Practice"[Mesh] "Consensus Development Conference "[Publication Type] "Consensus Development Conferences as Topic"[Mesh] "systematic review"[Title/Abstract] "cross sectional"[Title/Abstract] "controlled clinical trial"[Title/Abstract] "residual risk"[Title/Abstract] "retrovirus epidemiology donor"[Title/Abstract] "meta analysis"[Title/Abstract] "screening"[Title] "screen"[Title] "model"[Title] "modelling"[Title] "modeling"[Title] "risk"[MeSH Terms] "risk"[Title]

Limits: English, French, German, Spanish, Finnish, Swedish

EMBASE: Blood donors

Concept 1:	Boolean operator	Concept 2:	Boolean operator	Concept 3:	Boolean operator	Concept 4:	Boolean operator	Concept 5:
OR		OR		OR		OR		OR
'blood donor'/exp/mj 'blood transfusion'/exp/mj	AND	'hepatitis b'/exp 'hepatitis b antigen'/exp 'hepatitis b virus'/exp 'hepatitis c'/exp 'hepatitis c antibody'/exp 'human immunodeficiency virus infection'/exp 'human immunodeficiency virus antibody'/exp 'human t cell leukemia virus infection'/exp 'acquired immune deficiency syndrome'/exp 'human t cell leukemia virus 1'/exp 'human t cell leukemia virus 2'/exp 'hepatitis b':ab 'hepatitis b':ti 'hepatitis c':ab 'hepatitis c':ti 'htlv i':ab 'htlv i':ti 'htlv ii':ab 'htlv ii':ti 'htlv 1':ab 'htlv 1':ti 'htlv 2':ab 'htlv 2':ti 'human immunodeficiency virus':ab 'human immunodeficiency virus':ti 'hiv infections':ab 'hiv infections':ti 'acquired immunodeficiency syndrome':ab 'acquired immunodeficiency syndrome':ti 'human t lymphotropic virus 1':ab 'human t lymphotropic virus 1':ti 'human t lymphotropic virus htlv i':ab 'human t lymphotropic virus htlv i':ti 'human t lymphotropic virus 2':ab 'human t lymphotropic virus 2':ti 'human t lymphotropic virus type 1':ab 'human t lymphotropic virus type 1':ti 'human t lymphotropic virus type 2':ab 'human t lymphotropic virus type 2':ti	NOT	(transplant*:ti OR donor:ti OR donat:ti) AND organ:ti	AND	'diagnostic test'/exp 'mandatory testing'/exp 'virus load'/exp 'microbiological examination'/exp 'immunological procedures'/exp 'tissue and organ harvesting'/exp 'tissue and organ procurement'/exp 'serologic tests'/exp 'nucleid acid amplification techniques' 'nucleid amplification techniques' 'immunologic test' 'immunologic tests'/exp' mandatory screening' 'mandatory screenings' 'mandatory test'/exp 'mandatory tests' 'diagnostic test'/exp 'diagnostic tests'	AND	'cross-sectional study'/exp 'prevalence'/exp 'incidence'/exp 'screening'/exp 'model'/exp 'controlled clinical trial'/exp 'risk'/exp 'evidence based practice'/exp 'systematic review'/exp 'meta analysis'/exp 'practice guideline'/exp 'systematic review':ab 'systematic review':ti 'cross sectional':ab 'cross sectional':ti 'controlled clinical trial':ab 'controlled clinical trial':ti "residual risk":ab "residual risk":ti "retrovirus epidemiology donor" "retrovirus epidemiology donor" 'meta analysis':ab 'meta analysis':ti 'screening':ti 'screen':ti 'model':ti 'modelling':ti 'modeling':ti 'risk':ti guideline:ti guidelines:ti

Limits: [english]/lim OR [finnish]/lim OR [french]/lim OR [german]/lim OR [spanish]/lim OR [swedish]/lim) AND [embase]/lim

COCHRANE LIBRARY: Blood donors

Concept 1:	Boolean operator	Concept 2:	Boolean operator	Concept 3:
OR		OR		OR
MeSH descriptor **Tissue Donors**, this term only MeSH descriptor **Blood Donors** explode all trees MeSH descriptor **Blood Transfusion** explode all trees	AND	MeSH descriptor **Germ Cells** explode all trees MeSH descriptor **Hepatitis B** explode all trees MeSH descriptor **Hepatitis B virus** explode all trees MeSH descriptor **Hepatitis B Core Antigens** explode all trees MeSH descriptor **Hepatitis B Antigens** explode all trees MeSH descriptor **Hepatitis C** explode all trees MeSH descriptor **Hepatitis C Antibodies** explode all trees MeSH descriptor **HIV Infections** explode all trees MeSH descriptor **HIV Antibodies** explode all trees MeSH descriptor **HTLV-I Infections** explode all trees MeSH descriptor **HTLV-II Infections** explode all trees MeSH descriptor **Acquired Immunodeficiency Syndrome** explode all trees MeSH descriptor **Human T-lymphotropic virus 1** explode all trees MeSH descriptor **Human T-lymphotropic virus 2** explode all trees	AND	MeSH descriptor **Clinical Laboratory Techniques** explode all trees MeSH descriptor **Immunologic Tests** explode all trees MeSH descriptor **Microbiological Techniques** explode all trees MeSH descriptor **Viral Load** explode all trees MeSH descriptor **Physical Examination** explode all trees MeSH descriptor **Serologic Tests** explode all trees MeSH descriptor **Nucleic Acid Amplification Techniques** explode all trees MeSH descriptor **Mandatory Testing** explode all trees MeSH descriptor **Diagnostic Tests, Routine** explode all trees

Annex 2. Evidence tables

Residual risk

Citation	Title	Type of study	Area covered	Population/Sample size	Outcome	Strengths	Limitations
Velati, C., et al., 2005. Euro Surveill. 10; 2: 12-4	Impact of nucleic acid amplification technology (NAT) in Italy in the three years following implementation (2001-2003)	Epidemiological study, 3 y	Italian blood donors	219 blood transfusion centres, 3.894.894 HCV tested, 2.186.468 HIV tested	RR before/after NAT implementation	Large sample size, standard incidence/window period model	Pre-selected population, risk factor sensoring, pooled analysis of samples for NAT (minipools)
Soldan, K., et al., 2005. Euro Surveill. 10; 2: 17-9	Estimates of the frequency of HBV, HCV, and HIV infectious donations entering the blood supply in the United Kingdom, 1996 to 2003	Epidemiologicalstudy, 8 y	U.K. Blood donors	All U.K. donations 1996-2003	RR (with NAT) due to i) the window period, ii) assay failures and iii) human and technical errors in testing and processing	Large sample size, improved standard incidence/window period model	Pre-selected population, risk factor sensoring, pooled analysis of samples for NAT (minipools), raw data not shown
Pillonel, J. and Laperche, S., 2005. Euro Surveill. 10; 2: 5-8	Trends in risk of transfusion-transmitted viral infections (HIV, HCV, HBV) in France between 1992 and 2003 and impact of nucleic acid testing (NAT)	Epidemiologicalstudy, 11 y	French Blood donors	15 blood donation centers; 50 % of donations in France	RR (with NAT)	Large sample size, standard incidence/window period model	Pre-selected population, risk factor sensoring, pooled analysis of samples for NAT (minipools)
Offergeld, R., et al., 2005. Euro Surveillance. 10; 2: 8-11	Human immunodeficiency virus, hepatitis C and hepatitis B infections among blood donors in Germany 2000-2002: risk of virus transmission and the impact of nucleic acid amplification testing	Epidemiologicalstudy, 3 y	German Blood donors	Practically all donations 2000-2002; 17.925.610	RR (with NAT)	Large sample size, standard incidence/window period model, NAT for HBV also	Pre-selected population, risk factor sensoring, pooled analysis of samples for NAT (minipools)
Niederhauser, C., et al., 2005. Euro Surveill. 10; 2: 14-6	Incidence of viral markers and evaluation of the estimated risk in the Swiss blood donor population from 1996 to 2003	Epidemiologicalstudy, 8 y	Swiss Blood donors	Practically all donations 1006-2003; 3.759.671	RR (with NAT)	Large sample size, standard incidence/window period model	Pre-selected population, risk factor sensoring, pooled analysis of samples for NAT (minipools)
Alvarez do Barrio, M., et al., 2005. Euro Surveill. 10; 2:	Residual risk of transfusion-transmitted viral infections in Spain, 1997-2002, and impact of nucleic acid testing	Epidemiological study, 6 y	Spanish Blood donors	22 blood donation centers	RR (with NAT)	Large sample size, standard incidence/window period model	Pre-selected population, risk factor sensoring, pooled analysis of samples for NAT (minipools)
Zou, S., et al., 2004. N Engl J Med. 351; 8: 751-9	Probability of viremia with HBV, HCV, HIV, and HTLV among tissue donors in the United States	Epidemiological and modelling study	U.S. Tissue donor	11.391 tissue donors	RR (no NAT)	Age- and sex specific estimates available, standard incidence/window period model	Partly selected population, incidence imputed from ratio of incidence/prevalence among blood donors
Korelitz, J. J., et al., 1997. Transfusion. 37; 6: 634-40	A method for estimating hepatitis B virus incidence rates in volunteer blood donors. National Heart, Lung, and Blood Institute Retrovirus Epidemiology Donor Study	Epidemiological and modelling study	US	586,507 multiple-time donors giving 2,318,356 donations and observed for 822,426 person-years	Adjustment factor for crude HBV incidence rate	Very large number of events and observation time	May not generalise to all settings
Schreiber, G. B., et al., 1996. N Engl J Med. 334; 26: 1685-90	The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study	Epidemiological and modelling study	U.S. blood donor	586,507 donators; 2,318,356 blood donations	RR (no NAT)	Large sample size, Developed standard incidence/window period model for RR, Estimated effect of NAT	Pre-selected population, risk factor sensoring
Schwartz, D. W., et al., 1995. Ann Hematol. 70; 4: 209-13	Risk of human immunodeficiency virus (HIV) transmission by anti-HIV-negative blood components in Germany and Austria	Epidemiological and modelling study	Germany (Göttingen), Austria (Vienna)	1,931,151 + 160,453 blood donations	RR (no NAT)	Original publication of residual risk model using window period, test sensitivity, error factor	Pre-selected population, risk factor sensoring

Reviews and grey literature reports

Citation	Title	Type of study	Area covered	Population/Sample size	Outcome	Strengths	Limitations
Wingfield, M. and Cottell, E., 2010. Hum Reprod.	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?	Policy assessment/ review	EU	Irish donors of reproductive cells	Recommendation to replace testing at each donation for annual testing	Comprehensive review of objectives for screening	Lack of representative data on prevelence and incidence; no residual risk estimation
van de Laar, M. J. ECDC 2010	Hepatitis B and C Surveillance and Prevention in Europe	Technical report (survey)	EU	EU Member States	Review of surveillance of HBV and HCV in the EU	Close to 100 % participation rate	n/a
SANCO/2008/C6/051 2010. Report of the European Commission. Final revised version 19.2.2010; 91	Comparative Analysis of Medically Assisted Reproduction in the EU: Regulation and Technologies	Report (survey)	EU	The majority of MAR clinics in the MS	Data on treatments	Good coverage	Infectious disease screening results not collected/reported

Epidemiology

Citation	Title	Type of study	Area covered	Population/Sample size	Outcome	Strengths	Limitations
Wingfield, M. and Cottell, E., 2010. Hum Reprod.	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?	Retrospective epidemiological review	Ireland	Irish partner donors of reproductive cells 13 717 donors tested	Prevalence and incidence for HIV, HCV and HBV No incidence detected	Only study reporting on incidence among partner donations	Lack of representative data on prevalence and incidence; observation time for incident cases not reported
Hart, R., et al., 2001. BJOG. 108; 6: 654-6	Screening for HIV, hepatitis B and C infection in a population seeking assisted reproduction in an inner London hospital	Retrospective epidemiological review	UK, Inner London	Inner London fertility clinic clients and antenatal service clients	Prevalence and incidence for HIV, HCV and HBV	Comparison of MAR and Antenatal clients	Lack of representative data
ECDC 2009	HIV/AIDS surveillance in Europe 2008	Surveillance Report	WHO European Region	Case reports on entire European population	Notification rates as proxies for incidence, trends, risk groups	Comprehensive surveillance with agreed case-definitions and variable set	Lack of denominator; reporting delays; underreporting
ECDC 2009	Annual Epidemiological Report on Communicable Diseases in Europe 2009	Surveillance report	EU	Case reports on entire EU population (Hepatitis B &C)	Notification rates as proxies for incidence, trends	Good coverage	Lack of denominator; reporting delays; underreporting; differing case definitions
van de Laar, M. J. Salminen, M. ECDC 2010	Hepatitis B and C in the EU neighbourhood: Prevalence, burden of disease and screening policies	Technical report (literature review)	EU and neighbourhood	Variable	Estimate of available prevalence data in the region	Systematic review	Limited to english scientific literature

Citation	Title	Type of study	Area covered	Population/Sample size	Outcome	Strengths	Limitations
EuroHIV 2005	HIV prevalence among pregnant women. HIV / AIDS Surveillance in Europe	Mid-year report 72	WHO European Region	Case reports on entire European population	Notification rates as proxies for incidence, trends, risk groups	Comprehensive surveillance with agreed case-definitions and variable set	Underreporting; not all countries reported
Poel C et al. 2004. COUNCIL OF EUROPE European Committee (Partial Agreement) on blood transfusion	Report on the collection, testing and use of blood and blood components in Europe in 2004.	Report (survey)	Europe	All blood donations and donors in Europe	Prevealence among first time donors, incidence among repeat donors	Almost complete coverage, uniform definitions, trend analysis	Sensoring of risk factors, no general population representativeness
Velati, C., et al., 2005. Euro Surveill. 10; 2: 12-4	Impact of nucleic acid amplification technology (NAT) in Italy in the three years following implementation (2001-2003)	Epidemiological study, 3 y	Italian blood donors	219 blood transfusion centres, 3.894.894 HCV tested, 2.186.468 HIV tested	Prevalence and incidence	Large sample size,	Pre-selected population, risk factor sensoring, pooled analysis of samples for NAT (minipools)
Soldan, K., et al., 2005. Euro Surveill. 10; 2: 17-9	Estimates of the frequency of HBV, HCV, and HIV infectious donations entering the blood supply in the United Kingdom, 1996 to 2003	Epidemiological study, 8 y	U.K. Blood donors	All U.K. donations 1996-2003	Prevalence and incidence	Large sample size	Pre-selected population, risk factor sensoring, pooled analysis of samples for NAT (minipools), raw data not shown
Pillonel, J. and Laperche, S., 2005. Euro Surveill. 10; 2: 5-8	Trends in risk of transfusion-transmitted viral infections (HIV, HCV, HBV) in France between 1992 and 2003 and impact of nucleic acid testing (NAT)	Epidemiological study, 11 y	French Blood donors	15 blood donation centers; 50 % of donations in France	Prevalence and incidence	Large sample size	Pre-selected population, risk factor sensoring, pooled analysis of samples for NAT (minipools)

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Niederhauser, C., et al., 2005. Euro Surveill. 10; 2: 14-6	Incidence of viral markers and evaluation of the estimated risk in the Swiss blood donor population from 1996 to 2003	Epidemiological study, 8 y	Swiss Blood donors	Practically all donations 1006-2003; 3.759.671	Prevalence and incidence	Large sample size	Pre-selected population, risk factor sensoring, pooled analysis of samples for NAT (minipools)
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Schreiber, G. B., et al., 1996. N Engl J Med. 334; 26: 1685-90	The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study	Epidemiological and modelling study	U.S. blood donor	586,507 donators; 2,318,356 blood donations	Prevalence and incidence	Large sample size,	Pre-selected population, risk factor sensoring

Blood-borne viruses, STIs and risk during medically assisted reproduction

Citation	Title	Type of study	Area covered	Population/Sample size	Outcome	Strengths	Limitations
Kalu, E., et al., 2010. HIV Medicine. 11; 1: 90-93	Fertility needs and funding in couples with blood-borne viral infection	Retrospective chart review	UK	205 couples with at least 1 partner HIV positive	33.3% male infertility factor among HIV positive men; 40.8% tubal disease among women	Confirms previous results	Small study size
Waters, L., et al., 2007. International Journal of STD and AIDS. 18; 1: 1-6	HIV infection and sub-fertility	Editorial review	Global	n/a	n/a	Provides overview on literature	No primary data
Araneta, M. R., et al., 1995. JAMA. 273; 11: 854-8	HIV transmission through donor artificial insemination	Look-back studies	US	199 women, 5 HIV infected donors	3.52% of recipients became infected	Direct exposure known	Small study size