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Current concepts in the prevention of pathogen transmission via blood/plasma-derived products for bleeding disorders

Giovanni Di Minno, Carlo Federico Perno, Andreas Tiede, David Navarro, Mariana Canaro, Lutz Güertler, James W. Ironside

1. Introduction

Acute bleeding episodes can arise either because of inherited bleeding disorders (e.g. haemophilia, von Willebrand disease), acquired deficiency of haemostatic components (e.g. due to infection, malignancy or autoimmune disease), trauma, surgery or as a result of infection with an organism that causes haemorrhagic disease (e.g. Ebola or Marburg virus) [1]. Various treatment options exist for preventing or treating acute bleeding episodes, including fresh-frozen plasma/cryoprecipitate, platelets and plasma-derived/recombinant clotting factor concentrates [2,3]. The use of blood-derived and recombinant haemostatic products has increased markedly over recent years, as exemplified by the global increase of use of factor VIII products (Fig. 1) [4]. This increased use has been driven by improved availability of clotting factors, increased life expectancy of people with bleeding disorders [5,6], increased use of prophylaxis for severe bleeding disorders [7,8] and decreased risk of transmission of infectious agents.

Historically, the risk of transmission of infectious agents via blood/plasma-derived products has been of great concern to the medical community. This risk has reduced dramatically since the implementation of stricter donation screening/donor selection procedures and improved purification procedures, but cannot be fully eradicated. Furthermore, the implementation of pathogen inactivation technology for blood/plasma-derived products has further reduced the risk of transmission of both known and emerging pathogens, although results can be variable according to the methods used [9,10]. However, it is important to note that patient risk is highly dependent on the circumstances under which blood products are collected, handled and used. In general, clinicians assess the level of risk associated with the use of blood/plasma-derived products by evaluating factors such as patient characteristics (e.g. age, immune status, geographical location, lifestyle) and the nature of the pathogen (e.g. physical characteristics, level of virulence, chronicity of infection, prevalence). The presence of a particular pathogen within blood/plasma-derived products may pose a significant threat to specific patient groups (e.g. the elderly or immunocompromised), while being of low risk to the general population (e.g. HEV).

While the clinical assessment of risk is based on a variety of factors, the virological assessment of risk is based solely on the presence or absence of pathogens. The presence of pathogens implies the possibility of infection, so only pathogen-free products can be described as entirely risk-free. Adopting the virological approach (i.e. discarding all products
which may contain infectious agents) is effective in reducing the rate of pathogen transmission, but may result in the unnecessary wastage of blood/plasma-derived products.

Since recombinant clotting factors are not derived from blood or plasma, they present a minimal risk of pathogen transmission (particularly third generation factors, which have no contact with blood/plasma-derived components whatsoever) and can therefore be considered safer than using plasma-derived clotting factor concentrates \[11\]. However, there has been concern that the use of recombinant clotting factors may be associated with an increased rate of inhibitor formation in patients who regularly receive these products \[12\]; this is another factor that may influence the overall clinical assessment of patient risk.

Recombinant clotting factors are available for the treatment of haemophilia A (FVIII) and B (FIX) and factor VII/XIII deficiency, while plasma-derived concentrates are available for most other clotting factors (including von Willebrand factor, fibrinogen and the vitamin K dependent clotting factors). In some cases only fresh frozen plasma and cryoprecipitate are available for replacement therapy (e.g. factor V deficiency). Ideally, plasma and plasma-derived products would be completely replaced by recombinant products in order to minimise the risk of pathogen transmission; however, this is not always possible.

A recent article comprehensively reviewed the pathogen safety of plasma-derived and recombinant clotting factors \[13\].

This review examines the potential for transmission of infectious agents that might be present in blood/plasma-derived products used to treat haemostatic disorders. We focus on the identities of these agents and the screening procedures used for their detection, as well as the limitations of screening. Current unmet needs in the field of pathogen safety of blood/plasma-derived products are also discussed.

2. Methodology

The PubMed database was interrogated from 1 January 2000 to the present using the search strings 'bleeding disorders OR haemophilia' and 'pathogens AND blood safety'. The search terms 'virus', 'bacteria', 'haemorrhagic disorders', 'von Willebrand disease', 'FVII deficiency' and 'FXIII deficiency' were added to this search but did not yield any additional pertinent result. The bibliographies of reviews were also used to identify relevant references and individual searches were conducted for information on specific pathogens. Information and opinions were also provided by the authors.

3. Infectious agents present in blood/plasma-derived products: lessons from the past and current concerns

A large number of pathogenic agents (including viruses, protozoan parasites and prions) can be transmitted via blood/plasma-derived products and are capable of causing disease in humans (Table 1). The presence of viruses in plasma-derived products became a concern in the 1980s, when 60–70% of patients with severe haemophilia became infected with human immunodeficiency virus (HIV-1) \[6\]. This concern continued with the discovery that 80% of patients treated with plasma-derived products prior to 1992 had become infected with hepatitis C virus (HCV) \[5\]. Current donor selection and screening practices have improved our ability to detect or reduce the presence of pathogens in blood/plasma-derived products; for example, the residual risk of transfusion-transmitted infection (TTI) with HIV/HBV/HCV has fallen to near or less than 1 per million transfused units \[14,15\]. Despite this success, however, a residual risk still remains.

3.1. Potential risk

The pathogenic agents shown in Table 1 (and the Supplementary Appendix) do not form an exhaustive list. Many microorganisms that are normally non-pathogenic have the potential to cause disease when responding to changes in the biological environment, or when transfused to an immunosuppressed patient. In addition, there is still a risk that new and emerging pathogens may enter the blood supply (Table 2).

4. Screening for pathogens

The standard assays commonly used for blood screening are nucleic acid amplification technology (NAT) and immunoassays for detection of antibody and/or antigen. Immunoassays are frequently used for screening purposes as multiple samples can be processed together and they may yield semi-quantitative results. NAT assays allow earlier pathogen detection than with immunoassays, but they are also more costly and complex. Assay selection is generally determined by the level of accuracy/speed required, but factors such as the resources available (e.g. staff, infrastructure), assay complexity and cost considerations (e.g. consumables) must also be considered. Most assays for blood donation screening are mandatory (particularly in Europe and North America) and the World Health Organization (WHO) recommends that all whole blood (and blood which has been processed by apheresis) should undergo pathogen screening before it is used for clinical or manufacturing purposes. Screening for HIV-1, HIV-2, HBV, HCV and Treponema pallidum subspecies pallidum (T. pallidum; the causative agent of syphilis) is strongly advised. The WHO and World Federation of Hemophilia (WFH) suggest that countries should carry out individual routine screening for further pathogens based on epidemiological information for their region e.g. HTLV-1 and Trypanosoma cruzi \[16\]. The WFH also acknowledges the positive impact of HIV, HBV and HCV screening on global blood safety and recommends that these screening tests be implemented whenever possible \[2\]. Details of the serological tests carried out on individual donor plasma and NAT testing of plasma mini-pools are shown in Tables 3 and 4 \[17\].

It is recommended that the minimum evaluated sensitivity/specificity level of any assay used for blood donation screening should be 99.5% or higher \[16\]. However, not all assays fulfil these criteria as sensitivity/
specificity levels vary according to assay type and type of microorganism being tested for (see Table 1 for details). Therefore, the general advice is to screen donated blood to as high a standard as possible [16].

4.1. Blood donation screening: assays for key pathogens

4.1.1. HIV, HBV and HCV testing

In the early stages of infection with HIV, HBV or HCV, viraemia occurs in the host's bloodstream at variable levels. Viral antigens may appear at the same time as DNA/RNA, but more often become detectable several weeks later. Specific antibodies are measurable 2 to 6 weeks after infection; the time between initial infection and the appearance of detectable parameters of infection (e.g. viral nucleic acid/antigens/antibodies) is known as the ‘window period’ [18–20].

4.1.1.1. HIV. When screening blood for the presence of HIV-1/HIV-2, the use of a combined antigen/antibody assay is advised (combined HIV p24 Ag and anti-HIV-1 + anti-HIV-2 antibodies) as it allows earlier detection of infection. The performance of NAT testing is mandatory in many countries and further reduces the window period (from around 20 to 11 days) [20–22].

4.1.1.2. HBV. The majority of diagnostic laboratories focus on the detection of HBsAg, which is the first detectable serological marker of infection. However, there is a risk that the HBsAg concentration may decline to undetectable levels during the course of infection, yielding a false negative result [23]. Screening for antibodies to HBc is the most conservative approach for identifying potentially exposed donors, as this identifies all individuals who have ever immunologically experienced any type of HBV infection (either current, chronic or resolved) and who may experience viral reactivation during their lifetime (particularly under conditions of immunosuppression). However, assays to measure HBc antibodies are relatively non-specific and do not always correlate with the presence of HBV virus in plasma [18]. Also, we cannot exclude the possibility that donors who test positive for anti-HBc do not have pulsed recurrences of virus replication, resulting in the presence of low levels of HBV-DNA in plasma. For these reasons, national transfusion services do not always routinely screen donations for anti-HBc. NAT assays can be carried out, but their use is restricted by potentially low levels of viral DNA [16,18]. The combined use of HBsAg screening tests and NAT assays has reduced the window period for detection of HBV infection from approximately 60 to 35.5 days [20,24]. Mutant HBV strains (escape variants) should also be considered, as they may occasionally escape serological detection (although most can be detected by NAT assays) [24,25]. These HBV-variants are rare, but therefore more likely to enter and contaminate the blood supply as they are more difficult to detect [25]. In summary, the screening of blood supplies for the presence of HBV is effective, but an optimal screening system has not yet been defined.

4.1.1.3. HCV. HCV (both recent and chronic infection) can be detected by screening blood for the presence of both HCV antigen and HCV antibody (‘anti-HCV’). Seroconversion occurs at approximately 6–8 weeks post-infection; however, steady improvements in screening technology (including the adoption of NAT assays) have reduced the window period to approximately 1–3 weeks [20,26]. As with HIV, NAT assays are more useful for detecting early infection, although the issue of low viral RNA concentration persists [27,28].

4.1.2. HTLV-1 testing

HTLV-1 and HTLV-2 are endemic in some regions, but very rare in others, and therefore screenings are conducted on a geographical or at-risk basis. The presence of virus is mostly inferred by the detection of virus-specific antibodies, using sensitive immunoassays [16].

4.1.3. Syphilis testing

In this instance, screening involves detection of non-specific, non- treponemal or specific treponemal antibodies. NAT assays are generally not used [29]. Specific antibody tests identify all individuals who have ever been exposed to this bacterium (and may continue to yield positive results for more than ten years following initial infection), while the non-specific tests (e.g. VDRL or cardiolipin tests) are primarily of use in identifying donors who may have an active infection. Since T. pallidum is heat-sensitive and cannot readily withstand extended storage at low temperatures, storage at 4 °C for more than three days is sufficient to render the pathogen non-infectious. However, blood components (e.g. platelets) that are stored at temperatures of around 20 °C do present a risk of T. pallidum persistence. Therefore screening for antibodies of this organism is recommended [16].

4.2. Testing for emerging viral pathogens

4.2.1. West Nile virus

Blood can be screened for further pathogens as appropriate, according to geographical location, seasonal activity of the vector and also patient risk factors. A current viral pathogen of interest is the mosquito-borne flavivirus West Nile virus (WNV), which was confirmed to have been transmitted via transfusion in 2002 [30]. An immediate screening policy was put in place in the USA in order to reduce the risk of further transmission. This policy included deferral of any individual displaying symptoms of infection, quarantine of plasma collected during periods of high mosquito activity (when WNV is most prevalent) and the rapid development/use of WNV-specific NAT and serological assays. These measures were highly effective and caused a significant reduction in the number of confirmed cases of WNV transfusion-related transmission. However, WNV outbreaks still occur within the Americas, indicating a potential need for seasonal blood screening for WNV [31]. WNV outbreaks have also occurred in Europe (including Italy and Greece), prompting the implementation of seasonal blood screening procedures in the affected regions of those countries [32].

4.2.2. Chikungunya virus

This is another mosquito-borne pathogen that could potentially pose a risk to transfusion safety, although to date reports of transfusion-related transmission of this virus are rare [33]. A mutated form of the Chikungunya virus has been responsible for several epidemics in the past decade, spreading to the Reunion Islands in the Indian Ocean (2005), Italy (2007) and the Caribbean area (2012/2013) [34–36]. The virus may be detected in blood donors by NAT, which will help to reduce the level of transmission risk [35].

4.2.3. Parvovirus B19

There is also concern about the possibility of parvovirus B19 in the blood supply. B19 is prevalent worldwide, with seroprevalence in blood donors varying from between 0.2–1.3% in the USA, Europe and Africa and 25–40% in Asia [37]. The risk of parvovirus transmission is higher when units of blood are pooled (e.g. to create batches of clotting factor concentrates, albumin etc.) and so individuals with bleeding disorders are at a higher risk of infection. B19 DNA was detected in 26% of clotting factor concentrates in a recent German study [38], and another study found that populations receiving blood-derived products were 1.7 times more likely to display antibodies to B19 than populations who had not received blood products [39]. B19 lacks a lipid envelope, which renders it highly resistant to some methods of pathogen inactivation [40]. Screening of blood donations for B19 DNA is not currently routine, but many manufacturers only process plasma that has been screened for the presence of B19 DNA in order to reduce the risk of transmission [41]. Given the prevalence of B19 in different populations, it is difficult to define the residual TT1 risk of this virus. However, it is clear that a transmission risk does exist.
Table 1  Blood-transmissible pathogens.

<table>
<thead>
<tr>
<th>Transmissible agent</th>
<th>Geographic distribution (% of global population infected)</th>
<th>Testing procedure</th>
<th>Detection level in general clinical use</th>
<th>Minimum detection level possible (in development)</th>
<th>Testing sensitivity</th>
<th>Testing specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prions</strong> vCJD</td>
<td>Rare [94]</td>
<td>Solid state binding matrix/immuno-assay [55,95]</td>
<td>N/A</td>
<td>N/A</td>
<td>≥71% [55,95]</td>
<td>≥98% [55,95]</td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dengue virus</td>
<td>Widespread (prevalent in Africa, Asia and Latin America) [96]</td>
<td>Antibody/NAT [96]</td>
<td>NAT: 40–350 copies/ml [97]</td>
<td>NAT: 10–100 copies/ml [98]</td>
<td>Antibody: varies according to disease stage and test type. Immuno-chromatographic test: 1.9–3.8% (acute infection) ELISA: 3.0% (acute), 84.1% (convalescent) NAT: RT-PCR = 88.3% (acute) [99]</td>
<td></td>
</tr>
<tr>
<td>Chikungunya virus</td>
<td>Widespread; 50% of global population at risk [102]</td>
<td>Antibody/NAT</td>
<td>NAT: 446 copies/ml (whole blood) [100]</td>
<td>NAT: 160–600 copies/ml (DENV-1, 3 and 4) 2000–6000 copies/ml (DENV-2) [103] based on 1 PFU = 1000–3000 RNA copies [104]</td>
<td>Antibody: 96–98% (IgM) [105] NAT: High for DENV-1, 3 and 4; lower for DENV-2 [103]</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>Widespread [69]</td>
<td>Antigen/NAT</td>
<td>NAT: Reliable (≥99% detection) from 84 copies/ml [107] based on 1 IU/ml = 5.6 copies/ml [108]</td>
<td>139 copies/ml (NAT; qPCR) [101] N/A: current main research focus is on developing serotype-specific tests</td>
<td>Antibody: 90% (anti-HBC assay), 98% (anti-HBcAg assay) [109] NAT: 99.3% (Procleix Ulitro) [107]</td>
<td>Antibody: 78–91% (IgM) [105] NAT: 100% [103]</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV)</td>
<td>Widespread; 29% infected, 5% chronically infected [106]</td>
<td>Antibody/NAT</td>
<td>NAT: Reliable (≥99% detection) from 84 copies/ml [107] based on 1 IU/ml = 5.6 copies/ml [108]</td>
<td>139 copies/ml (NAT; qPCR) [101] N/A: current main research focus is on developing serotype-specific tests</td>
<td>Antibody: 90% (anti-HBC assay), 98% (anti-HBcAg assay) [109] NAT: 99.3% (Procleix Ulitro) [107]</td>
<td>Antibody: 78–91% (IgM) [105] NAT: 100% [103]</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td>Widespread; 3% [110]</td>
<td>Antibody/NAT</td>
<td>NAT: Reliable (≥99% detection) from 84 copies/ml [107] based on 1 IU/ml = 5.6 copies/ml [108]</td>
<td>139 copies/ml (NAT; qPCR) [101] N/A: current main research focus is on developing serotype-specific tests</td>
<td>Antibody: 90% (anti-HBC assay), 98% (anti-HBcAg assay) [109] NAT: 99.3% (Procleix Ulitro) [107]</td>
<td>Antibody: 78–91% (IgM) [105] NAT: 100% [103]</td>
</tr>
<tr>
<td>Hepatitis E virus (HEV)</td>
<td>Widespread [115]</td>
<td>Antibody/NAT</td>
<td>NAT: 5.9–114 copies/ml (MP-NAT), 47.3–226 copies/ml (ID-NAT) [116] based on 1 IU/ml = 1.25 copies/ml [117]</td>
<td>NAT: ≥5.8 copies/ml (ID-NAT) [118] based on 1 IU/ml = 1.25 copies/ml [117]</td>
<td>Antibody: 72–98% [119] NAT: High. Varies from 5.9 copies/ml (Real-Star HEV RT-PCR) to 114 copies/ml (Ceeram) for MP-NAT and from 47.3 copies/ml (Real-Star HEV RT-PCR) to 226 copies/ml (ampliCibe HEV RT-PCR) for ID-NAT [116] Antibody: 72–98% [119] NAT: High. Varies from 5.9 copies/ml (Real-Star HEV RT-PCR) to 114 copies/ml (Ceeram) for MP-NAT and from 47.3 copies/ml (Real-Star HEV RT-PCR) to 226 copies/ml (ampliCibe HEV RT-PCR) for ID-NAT [116]</td>
<td>Antibody: 78–96% [119] NAT: High [116]</td>
</tr>
<tr>
<td>Human Herpesvirus-8 (KSHV)</td>
<td>Widespread, with variable prevalence (≤5–50%); endemic in sub-Saharan Africa; parts of Asia and Oceania [120]</td>
<td>Antibody/NAT</td>
<td>NAT: 63 copies/ml (Viracor IFT) [121]</td>
<td>N/A</td>
<td>Antibody: 65–100% [122] NAT: High [63 copies/ml] [121]</td>
<td>Antibody: 96–99% [122] NAT: High — no cross reactivity detected against adenoviruses, BKV, CMV, EBV, HSV-1, HSV-2, HHV-6 variant A, HHV-6 variant B, HHV-7, JCV, parvovirus B19, SV-40 or VZV. [121]</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV-1 and HIV-2)</td>
<td>Worldwide (0.5%); endemic in sub-Saharan Africa (5%) [123]</td>
<td>Antibody/NAT</td>
<td>NAT: 20–50 copies/ml [124]</td>
<td>N/A</td>
<td>Antibody: ≥99.9% [125] NAT: 99.9% (Procleix Ulitro) [107]</td>
<td>Antibody: 99.5–99.9% [125] NAT: 99.8% (Procleix Ulitro) [107]</td>
</tr>
<tr>
<td>Human T-lymphotrophic virus 1 and 2 (HTLV-1/2)</td>
<td>HTLV-1: Endemic in Japan, Africa, South America and Caribbean</td>
<td>Antibody/NAT</td>
<td>Not specified: antibody detection kits routinely used [127,128]</td>
<td>NAT: HTLV-1–1.2 copies/reaction (i.e. 12–48 copies/ml based on a reaction volume of 10–50 μl); HTLV-2–19</td>
<td>Antibody: 100% [130] NAT: 99.4% (HTLV-1 and 2) [131]</td>
<td>Antibody: ≥99.4% [130] NAT: 98.5% (HTLV-1 and 2) [131]</td>
</tr>
<tr>
<td>Transmissible agent</td>
<td>Geographic distribution (% of global population infected)</td>
<td>Testing procedure</td>
<td>Detection level in general clinical use</td>
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<td>Testing sensitivity</td>
<td>Testing specificity</td>
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<tr>
<td>HTLV-2: Prevalent in Central/West Africa, the Americas and Europe [126]</td>
<td></td>
<td>Antibody/NAT</td>
<td>NAT: 668 copies/ml (based on 1 IU/ml = 3.34 copies/ml) [132,133]</td>
<td>NAT: 10 copies/reaction (i.e. 100–500 copies/ml, based on a reaction volume of 10–50 μl) [134]</td>
<td>Antibody: 89.1% [135]</td>
<td>Antibody: 99.4% [135]</td>
</tr>
<tr>
<td>Parvovirus B-19</td>
<td>Widespread, variable prevalence (0.2–40%) in European and Asian blood donors [37]</td>
<td>Antibody/NAT</td>
<td>NAT: 200–500 copies/ml [139,140]</td>
<td>NAT: 10 copies/reaction (i.e. 100–500 copies/ml, based on a reaction volume of 10–50 μl) [134]</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>Parvovirus H</td>
<td>Widespread, variable prevalence (2–35%) [136–138]</td>
<td>NAT</td>
<td>NAT: no general test – PCR used to confirm presence.</td>
<td>NAT: ≥ 100 copies/reaction (i.e. 1000–5000 copies/ml, based on a reaction volume of 10–50 μl) [142]</td>
<td>NAT: Up to 100% [142]</td>
<td>NAT: ≥ 96% [142]</td>
</tr>
<tr>
<td>West Nile virus (WNV)</td>
<td>Widespread (Africa, West Asia, Middle East, Europe and North and South America) [90]</td>
<td>Antibody/NAT</td>
<td>NAT: 100 copies/ml [143]</td>
<td>NAT: ≥ 9.8 copies/ml</td>
<td>Antibody: 50% (IgM), 86% (IgG) [145]</td>
<td>Antibody: 95% (IgM), 69% (IgG) [145]</td>
</tr>
<tr>
<td>Bacteria</td>
<td></td>
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</tr>
<tr>
<td>Treponema pallidum subspecies pallidum</td>
<td>Widespread; (0.5% of global population infected) [146]</td>
<td>Antibody/NAT/dark ground microscopy DGM</td>
<td>NAT: 32,000 copies/ml [147]</td>
<td>NAT: 82% [148]</td>
<td>Antibody: 78–88% (primary syphilis), 100% (secondary), 95–100% (latent), 71–96 (late)</td>
<td>Antibody: 95% [148]</td>
</tr>
<tr>
<td>Yersinia enterocolitica, Salmonella enterica, Listeria monocytogenes, Coxiella burnetii (only during outbreaks)</td>
<td>Rare, donor selection dependent</td>
<td>Not done</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Protozoa</td>
<td></td>
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<tr>
<td>Leishmania spp</td>
<td>Widespread; 1.3 million new cases per year [153]</td>
<td>Antibody/NAT</td>
<td>NAT: ≥ 10 parasites/ml (PCR; sensitivity varies according to method) [154]</td>
<td>NAT: ≥ 10 parasites/ml [154]</td>
<td>Antibody: 75–95% [155]</td>
<td>Antibody: 70–98% [155]</td>
</tr>
</tbody>
</table>

(continued on next page)
positive results in buffy coat/white blood cell samples from a small number of patients with vCJD [56].

4.4. Interpretation of test results and practicalities of screening

4.4.1. Assay specificity and sensitivity

Extensive use of blood donor selection and testing does not always guarantee a safe product. If the test is insufficiently sensitive, then false negatives may occur. Alternatively, tests which are not sufficiently specific (e.g. anti-HBc assay for HBV) may cause false positive results, leading to an unnecessary decrease in the number of clotting products available [16]. Torque Tenovirus (TTV) is an example where testing specificity has been an issue, as this virus exists in various divergent forms [23 distinct genotypes have been identified thus far] [57]. Since TTV is often detected in healthy individuals and is not associated with particular disease, routine screening for this virus is not considered to be necessary; even a test with excellent sensitivity/specificity would not contribute to increase the level of safety of blood/plasma-derived products with regard to TTV.

Insufficient assay sensitivity remains a rare but potential problem when blood donations are screened during the window period of initial HBV, HCV or HIV infection. An increase in testing sensitivity threshold is needed to prevent HBV transmission via blood/plasma-derived products and by blood transfusion, as extremely low concentrations of HBV (e.g. 1.6 copies/ml) is capable of viral transmission (see above section on anti-HBc positive patients) [58]. In the case of HIV and HCV, even NAT testing may not always be sufficient to ensure sufficiently high levels of safety as virus transmission has previously occurred after transfusion of blood with undetectable levels of viraemia [59].

Recent reports have highlighted concerns about the inability of NAT assays to detect different variants of HIV. There have been at least four cases in which the presence of HIV-1 RNA was undetected by NAT assay screening, potentially putting transfusion recipients at risk [21]. Two of these false-negative results occurred due to genetic mutation in the viral RNA regions targeted by NAT assay primers (although in

<table>
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<th>Testing sensitivity</th>
<th>Testing specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trypanosoma cruzi</td>
<td>0.1–0.2% (mostly Latin and South America) [164]</td>
<td>Antibody/NAT</td>
<td>NAT: ≥ 0.5 parasites/ml [165]</td>
<td>Antibody: 75–100% (majority &gt; 90%) [166] NAT: 83.3–94.4% [165]</td>
<td>Antibody: ≥ 97% [166]</td>
<td>Antibody: 85–95% [165]</td>
</tr>
</tbody>
</table>

In cases where no overall figures are available, specificity/sensitivity has been described as low, medium or high (as appropriate).

CATT; card agglutination test for Trypanosomiasis; ID-NAT, individual donation NAT; MP-NAT, mini-pool NAT; NAT, nucleic acid testing; PCR, polymerase chain reaction; PFU, plaque-forming unit.

4.3. Prions

Despite recent advances in methods for the detection of prions, no single method has been developed as a screening test for blood, although several methods in animal models show great promise [51–53]. In humans, a protocol for the evaluation of a blood-based test for its suitability in the diagnosis of variant Creutzfeldt–Jakob disease (vCJD) has been established, but no test yet appears to satisfy the requirements of sensitivity and specificity [54]. The only report so far of a blood-based diagnostic test for vCJD claimed an assay sensitivity of 71.4% and a specificity of 100% in symptomatic patients and its potential applicability as a screening test to detect asymptomatic vCJD infection has recently been investigated [55]. There is currently no strategy for confirming a positive screening result, although the protein misfolding cyclical amplification technique has recently been shown to yield

Table 2

Emerging blood-transmissible pathogens.

<table>
<thead>
<tr>
<th>Recently emerging pathogen</th>
<th>Pathogen structure/classification</th>
<th>Year of emergence</th>
<th>Mode of transmission</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bas Congo virus</td>
<td>Enveloped; rhabdovirus</td>
<td>2009</td>
<td>Direct contact (human–human and zoonotic), nosocomial</td>
<td>[167]</td>
</tr>
<tr>
<td>Huaiyangshan</td>
<td>Enveloped; bunyavirus</td>
<td>2010</td>
<td>Direct contact (human–human), vector-borne, blood-borne, airborne (potentially)</td>
<td>[168,169]</td>
</tr>
<tr>
<td>Bunyavirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza H5N1</td>
<td>Enveloped; orthomyxovirus</td>
<td>2005</td>
<td>Airborne, direct contact (human–human and zoonotic)</td>
<td>[170–172]</td>
</tr>
<tr>
<td>Influenza H7N9</td>
<td>Enveloped; orthomyxovirus</td>
<td>2012</td>
<td>Direct contact (zoonotic and potentially human–human), airborne</td>
<td>[172,173]</td>
</tr>
<tr>
<td>Lujo virus</td>
<td>Enveloped; arenavirus</td>
<td>2008</td>
<td>Airborne, direct contact (human–human and zoonotic), nosocomial, blood-borne (potentially)</td>
<td>[174,175]</td>
</tr>
<tr>
<td>Marseillevirus*</td>
<td>Marseillevirus</td>
<td>2010</td>
<td>Blood-borne, faecal–oral (?)</td>
<td>[175,176]</td>
</tr>
<tr>
<td>MERS coronavirus</td>
<td>Enveloped; coronavirus</td>
<td>2013</td>
<td>Airborne, direct contact (human–human and zoonotic), nosocomial</td>
<td>[177,178]</td>
</tr>
<tr>
<td>SARS coronavirus</td>
<td>Enveloped; coronavirus</td>
<td>2003</td>
<td>Faecal/oral, airborne, direct contact (human–human and zoonotic), nosocomial</td>
<td>[180–182]</td>
</tr>
<tr>
<td>NJ polyomavirus</td>
<td>Non-enveloped polyomavirus</td>
<td>2014</td>
<td>Direct contact, saliva, blood?</td>
<td>[183]</td>
</tr>
</tbody>
</table>

* Unconfirmed — may have been the result of laboratory contamination [184].
**Table 3**

<table>
<thead>
<tr>
<th>Plasma source</th>
<th>Serologic tests performed on individual donor plasma refers to <strong>[17]</strong>.</th>
</tr>
</thead>
<tbody>
<tr>
<td>US paid apheresis (Talecris, Grifols, others)</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVAb, ALT</td>
</tr>
<tr>
<td>United States, recovered, unpaid</td>
<td>Syphilis, HIV-1/2, HTLV-1/2, HBsAg, HBcAb, HCVAb</td>
</tr>
<tr>
<td>Baxter BioScience: United States, Austria, Germany, Sweden, Czech Republic, Switzerland, Norway</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVAb</td>
</tr>
<tr>
<td>CSL Behring: Austria, Denmark, Germany, United States</td>
<td>Syphilis (US), HIV-1/2, HBsAg, HCVAb</td>
</tr>
<tr>
<td>Biotest: Austria, Belgium, Germany, United States</td>
<td>HIV-1/2, HBsAg, HCVAb</td>
</tr>
<tr>
<td>Intersero: Austria, Belgium, Germany</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVAb, ALT</td>
</tr>
<tr>
<td>Germany</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVAb</td>
</tr>
<tr>
<td>Octapharma: Sweden, Austria, Germany</td>
<td>Syphilis, HIV-1/2, HbcAb, HBsAg, HBcAb, HCVAb</td>
</tr>
<tr>
<td>American Community Blood Centers, unpaid (Octapharma)</td>
<td>Syphilis, HIV-1/2, HTLV-1/2, HbcAb = anti-Hbc, HBsAg, HCVab</td>
</tr>
<tr>
<td>Finnish Red Cross BS: Finland, unpaid</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVAb, HTLV-1/2 1st donation</td>
</tr>
<tr>
<td>Sanquin: The Netherlands</td>
<td>Syphilis, HIV-1/2, HTLV-1/2, HBsAg, HCVAb</td>
</tr>
<tr>
<td>LFBB: France</td>
<td>Syphilis, HIV-1/2, HTLV-1/2, HbcAb, HBsAg, HCVAb</td>
</tr>
<tr>
<td>Grifols: Spain, Czech Republic, Slovakia</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVAb</td>
</tr>
<tr>
<td>Kedrion: Italy</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVAb</td>
</tr>
<tr>
<td>National Bioproducts Institute: South Africa</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVAb</td>
</tr>
<tr>
<td>Australian Red Cross Blood Service</td>
<td>Syphilis, HIV-1/2, HTLV-1/2, HBsAg, HCVAb</td>
</tr>
<tr>
<td>New Zealand Blood Service</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVAb, HCVAb</td>
</tr>
<tr>
<td>Centre for Transfusion Medicine, Singapore</td>
<td>Syphilis, HIV-1/2, HbcAb, HCVab</td>
</tr>
<tr>
<td>National Blood Center, Malaysia</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVab</td>
</tr>
<tr>
<td>Hong Kong Red Cross BTS</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVab</td>
</tr>
<tr>
<td>Taiwan Blood Services Foundation</td>
<td>Syphilis, HIV-1/2, HTLV-1/2, HBsAg, HCVAb</td>
</tr>
<tr>
<td>Japan</td>
<td>Syphilis, HIV-1/2, HTLV-1, HbcAb, HBsAg, HCVAb, ALT, B-19 parovirus</td>
</tr>
<tr>
<td>Korean Red Cross: South Korea</td>
<td>Syphilis, HIV-1/2, p-24 antigen, HBsAg, HCVab, ALT</td>
</tr>
<tr>
<td>Shanghai RAAS Blood Products Co: China</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVab, ALT</td>
</tr>
<tr>
<td>Bio Products Laboratory, UK: US paid apheresis</td>
<td>Syphilis, HIV-1/2, HBsAg, HCVab, ALT</td>
</tr>
</tbody>
</table>

| a | Serological targets for HIV detection include p24 antigen and anti-HIV-1/2 antibodies [185,186]. |

| b | Nontreponemal tests are routinely used to screen blood for the presence of *Treponema pallidum* subspecies pallidum (*T. pallidum*, the causative agent of syphilis). These tests measure both proteins from the *Treponema* cell surface and IgG/IgM antiphospholipid antibodies which are produced by the host in response to cell damage in the early stages of infection [150]. |

**4.4.2. The need for multiple methods of screening**

A recent report suggests that it is not necessary to carry out serological screening for multiple HBV markers, and that NAT based screening is preferred [58]. However, there is a risk that the practice of relying upon a single method of screening may lead to a higher incidence of false-negative results. In one case of transfusion-associated parovirus B19 transmission, donated blood was screened for the presence of B19 antigen and deemed to be safe since no antigen was detected. Since the recipient subsequently developed B19 infection, the donation was re-analysed and found to contain B19 DNA [63]. Reports such as this support the argument for multiple parameter testing.

The localisation of pathogens within blood may also influence ease of detection. For example, WNV is present at 10-fold higher levels in whole blood than in plasma in vireamic seropositive donors. The situation is reversed in vireamic seronegative donors, who display higher WNV levels (4-fold) in plasma than in whole blood [64]. Also, cell-associated viruses such as CMV and HTLV-1 are less frequently transmitted with the use of leukoreduced products [65,66], indicating that these viruses are less likely to be found in blood/plasma-derived products. The minimum infective dose (MID: the lowest number of pathogenic particles required to successfully infect a host) of a particular pathogen is more likely to be reached in whole blood or blood-derived components; making the use of plasma-derived or recombinant clotting factors the safest option.

**4.4.3. Infective dose**

To date, studies attempting to measure human MID values have generally determined the viral concentration needed to infect a particular percentage of the exposed population (e.g. 50%). This value (the human infective dose for 50% of the population) is referred to as HID50 and is often described as the human MID [67]. The HID50 value varies greatly between pathogens (even if they are physically similar) [68] and also varies depending upon the immune status of the recipient, as immunocompromised individuals, neonates and the elderly are at greater risk of infection than healthy individuals [67]. When this finding and the prevalence of immunocompromised patients receiving blood products are both taken into account, it implies a need for screening tests to have the highest sensitivity possible.

**4.4.4. Patient characteristics**

The impact of transmission on morbidity and mortality is dependent on patient characteristics. For example, although the vast majority of cases of CMV infection are not clinically important, influencing factors such as genetic predisposition, malnutrition and pre-existing infection can lead to the development of severe disease [69]. National screening programmes do not currently screen for CMV as standard, but NAT assays exist and may be carried out if required, e.g. if blood is specifically intended for vulnerable recipients, such as pregnant women or transplant patients [70]. It is the opinion of the authors that both serological assays and NAT tests should be used in order to reach the highest level of safety possible, particularly when in the case of immunosuppressed patients.

**5. Other means of reducing and managing pathogen risk**

As well as blood donation testing, a range of other measures are used to increase the pathogen safety of blood- and plasma-derived products. These include donor selection and screening, recipient vaccination and the use of blood product purification/inactivation methods. The choice of inactivation method also impacts upon the level of risk.

**5.1. Selection and screening of donors**

Questionnaires are often used to attempt to assess donors’ health status and their potential exposure to various risks. Donors can be accepted or rejected on the basis of these answered questionnaires, or alternatively their blood may be put through additional screening tests as appropriate [16,31].
5.2. Vaccination

Patients with bleeding disorders should be vaccinated against HAV and HBV. European studies have reported that universal HBV vaccination of blood donors could be cost-effective as this measure would reduce the risk of HBV transmission in general and might reduce the risk of HBV escape variants (as described earlier) [71,72].

5.3. Purification and inactivation techniques

Blood/plasma-derived products typically undergo various procedures designed to reduce the pathogen level, although these procedures are not effective against all pathogens. Plasma donations undergo quarantine (approximately 4–6 months) prior to fractionation and when the donor is again screened negative FFP can then be subjected to chromatographic fractionation, solvent-detergent treatment, nanofiltration and/or heat inactivation [73,74]. Prolongation of product storage time can be effective in reducing the infectivity of temperature-sensitive pathogens (such as T. pallidum). Production of recombinant products also follows strict protocols to remove and inactivate any viruses that might be present, even though the risk of viral presence is minimal.

Although current purification/inactivation techniques (such as solvent-detergent treatment, nanofiltration and heat activation) do reduce the risk of pathogen transmission, they are not always sufficient to render blood/plasma-derived products safe [75]. Small non-enveloped viruses (e.g. HAV, B19 and picornavirus) are often highly resistant to inactivation procedures and may still be infectious in some plasma-derived concentrates [75,76].

The presence of prions is also a concern. Attempts to remove prions from plasma-derived products have involved several techniques, including ion-exchange chromatography and nanofiltration [77,78].
Several problems exist with these approaches, in particular the use of exogenous “spikes” derived from prion-infected brain homogenates to measure prion clearance, which may result in an overestimation of the amount of prion removal, and the methods used for the estimation of the reduction in prion load, which ideally should involve bioassay to measure infectivity [79]. Further developments in this field are required to address these issues.

A recently proposed approach for the inactivation of infectious agents in blood is whole-blood treatment with ultraviolet (UV) light in combination with a photosensitiser such as riboflavin or amotosalen [80,81]. The main disadvantage of this approach is that UV treatment has been linked to the formation of neoantigens, which may be generated via modification of the surface antigens of platelets. The presence of neoantigens may provoke a recipient immune response during transfusion of UV-treated platelets, causing them to be rapidly cleared from the circulation [81]. While this approach to pathogen inactivation is currently used for platelets and is effective, it needs further refinement for the inactivation of whole blood [81,82].

5.4. Product choice

The WFH strongly recommends the use of plasma-derived or recombinant products in preference to cryoprecipitate or fresh frozen plasma, as the infectious load of any infectious human pathogen is lower in plasma-derived products than in cryoprecipitate, and even lower in recombinant products [2]. In some European countries, recombinant products have almost completely replaced plasma-derived products [12]. The use of recombinant products, which have been manufactured and formulated with minimal addition of human/animal-derived materials, greatly reduces the risk of recipient exposure to plasma-derived infectious agents and after they have undergone virus removal/inactivation processes, recombinant products can be considered to be as safe as currently possible [83]. Despite these benefits, the use of recombinant products may be limited by higher costs and perceived problems of inhibitor formation [83]. For indications where no recombinant factor concentrates are available, the use of inactivated plasma-derived concentrates is safer than fresh frozen plasma and will reduce the risk of other adverse effects such as hypervolemia, transfusion-related lung injury (TRALI) and hypersensitivity [84].

### 6. Barriers to a minimal risk approach

A minimal risk approach would ensure that patients receive effective treatment with the lowest possible risk, but this is difficult to achieve in practical terms. Regulatory needs in different European countries are usually based on recommendations from the medical community, so in order to achieve minimal risk, it would be ideal for these regulations to be standardised and mandatory in all countries. Directives issued by the European Union Commission describe the regulatory requirements for the safety of whole blood and plasma, stating that “all precautionary measures during their collection, processing, distribution and use need to be taken making appropriate use of scientific progress in the detection and inactivation and elimination of transfusion transmissible pathogenic agents” [85]. However, the relative safety of different screening tests, products and processing methods is not discussed and so individual countries may adopt different approaches towards minimising risk. Although recombinant products are associated with the highest level of pathogen safety, higher costs for development and production may make them too expensive for some healthcare systems [86]. Inhibitor formation also remains an important element of concern with both plasma-derived and recombinant products, particularly with regard to FVIII in haemophilia A [87]. The risk of inhibitor formation was shown to be greater with recombinant versus plasma-derived factor VIII concentrates in some cohort studies [88], but similar in others [89].

In light of these considerations (availability, adverse reactions and cost), it appears that the issue of pathogen safety of blood/plasma-derived products is highly important but may not be the limiting factor with respect to overall patient safety. The benefits of treatment with a hypothetically ‘unsafe’ plasma-derived product may outweigh the risk of a negative outcome (e.g. bleeding, inhibitor formation), although we suggest that it may be clinically simpler to deal with inhibitor formation than to combat an infection from an unknown or untreatable pathogen.

### 7. Current knowledge gaps and areas of unmet need

There are still significant knowledge gaps and areas of unmet need with respect to the pathogen safety of blood/plasma-derived and recombinant products. The incidence of HBV, HCV and HIV TTI has fallen to near or below 1 per million transfused units in the industrialised world, indicating that current donor selection and blood screening strategies have had a positive impact on blood safety [14]. However, it is clear that screening both donors and donated blood cannot exclude all known pathogens or eliminate all risks from emerging pathogens [63,90]. Historical precedent indicates that the blood supply is always vulnerable to contamination by hitherto non-prevalent/unknown pathogens, and that this risk cannot be accurately gauged [91]. As we identify new infectious agents of concern and develop new tests for their detection, it will also be necessary to clearly define the infectious dose range for each agent and use appropriately sensitive tests for their identification. For example, in suspected cases of vCJD infection, considerable challenges remain in the development of screening and confirmatory tests that have sufficient sensitivity and specificity to be of use in both a clinical setting and within blood banks [92].

Surveillance of people with haemophilia is required to monitor pathogen safety issues related to blood and plasma products. The European Haemophilia Safety Surveillance system (EUHASS), which began in 2008, is a pharmacovigilance programme which spans 25 European countries and is designed to detect, monitor and investigate adverse drug reactions. Reports of adverse events (such as acute/allergic events, TTIs and inhibitors) are submitted to EUHASS by participating centres and cumulative patient and clotting factor data are recorded annually [93].

### Table 5

Approximate residual risk of HBV, HCV, HIV and HEV TTI in selected countries.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Country</th>
<th>Residual risk, or prevalence in blood donations (dependent on testing) per 100,000</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>Congo-Kinshasa</td>
<td>390</td>
<td>[188]</td>
</tr>
<tr>
<td></td>
<td>Brazil</td>
<td>289</td>
<td>[189]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>5.9–7.5</td>
<td>[58]</td>
</tr>
<tr>
<td></td>
<td>England/North Wales</td>
<td>&lt;3.7</td>
<td>[190]</td>
</tr>
<tr>
<td></td>
<td>Australia</td>
<td>2</td>
<td>[191]</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>0.4</td>
<td>[192]</td>
</tr>
<tr>
<td></td>
<td>Portugal</td>
<td>0.2</td>
<td>[193]</td>
</tr>
<tr>
<td>HCV</td>
<td>Brazil</td>
<td>191</td>
<td>[189]</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>0.9</td>
<td>[192]</td>
</tr>
<tr>
<td></td>
<td>Portugal</td>
<td>0.03</td>
<td>[193]</td>
</tr>
<tr>
<td>HIV</td>
<td>Congo-Kinshasa</td>
<td>22</td>
<td>[188]</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>0.9–2.4</td>
<td>[21,192]</td>
</tr>
<tr>
<td>HEV</td>
<td>Germany</td>
<td>81</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td>Netherlands</td>
<td>57</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td>England</td>
<td>35</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td>Scotland</td>
<td>6.9</td>
<td>[194]</td>
</tr>
<tr>
<td></td>
<td>Portugal</td>
<td>0.6</td>
<td>[193]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>&lt;2</td>
<td>[195]</td>
</tr>
</tbody>
</table>

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus-1; TTI, transfusion-transmitted infection.
A formal coordinated risk-assessment and management action plan, in addition to a task force, should be developed to respond quickly to any emerging infections. Such a plan should include long-term storage of samples from produced batches (for retesting in the case of outbreaks with known or recently emerged infectious agents) and guidance on responsibility for developing/performing tests for emerging pathogens (industry vs. regulatory agencies). Guidance on approaching patients who have potentially been infected and surveillance strategies for patients at high risk would also be beneficial.

8. Conclusions

The majority of evidence indicates that the concept of clinical safety of blood/plasma derivatives does not necessarily correspond to the concept of pathogen safety; blood can only be classed as microbiobly safe in reference to the infectious agents that are known and have been screened for. Establishing whether the presence of undetected microbes in the blood is clinically relevant will require further long-term, detailed studies. It should also be noted that even though the risk of transmission of key detectable viruses (such as HIV, HBV and HCV) via transfusion has fallen significantly, transmission does still occur.

In general, balancing safety, efficacy and practicalities is a difficult goal to achieve — patient safety is typically the key driver, but striving for near-complete safety at the expense of the patient’s health or quality of life may not be the best course of action for patients or clinicians. The lack of a cohesive international strategy for blood donation and screening is a pressing concern that needs to be addressed. Furthermore, a formal coordinated continuous risk-assessment and management action plan needs to be developed to deal with the constant potential risk of emerging infections. Establishing an international registry (or harmonising data collection in National Registries) and dedicated task force may help to identify newly emerging pathogens more rapidly than in the past and to further improve pathogen safety of blood/plasma-derived products and the blood supply in general.

Practice points

- The use of blood/plasma-derived products for the treatment of bleeding disorders carries a risk of pathogen transmission.
- Blood donations are screened for key pathogens such as HBV, HCV, HIV and the causative agent of syphilis, but other screening tests should be conducted as required according to geographical location and patient risk factors.
- Screening tests for pathogens may lack sensitivity/specificity and so false negatives may occur, resulting in a residual pathogen risk to patients.
- In terms of pathogen safety, recombinant products (products which have had minimal exposure to blood/plasma-derived proteins) are considered to pose the lowest level of risk to patients.

Research agenda

- Regional and international rates of transfusion-transmitted infection for key pathogens and emerging pathogens
- Safety and efficacy of blood/plasma-derived products and recombinant products for treatment of bleeding disorders.

Conflict of interest statement

A.T. has received grants and personal fees from Bayer, grants and personal fees from Baxter, grants and personal fees from CSL Behring, grants and personal fees from Novo Nordisk, grants and personal fees from Pfizer, and grants and personal fees from Octapharma, during the conduct of the study.

C.F.P. has received grants as bureau speaker, consultant, or advisor, from Gilead, Merck Sharp and Dohme, Roche, Pfizer, Abbott, Bristol-Myers Squibb, VIIIV, and Boehringer-Ingelheim. None of these personal activities is in conflict with the opinions he expressed in this manuscript.

D.N. has received honoraria for conferences from Pfizer, Roche Pharma, Roche Diagnostics, Abbott, MSD, and Astellas.

G.D.M. has disclosed the following financial relationships — speaker or a member of a speaker bureau for: Boehringer-Ingelheim, Sanofi-Aventis, Bayer, Novo Nordisk, Pfizer, Biotest, and Grifols. Consultant or ad hoc speaker/consultant for: Boehringer-Ingelheim, Eli-Lilly, Sanofi-Aventis, Bayer, CSL Behring, Novo Nordisk, Pfizer, Biotest, and Grifols.

J.W.I. has received personal fees from Piramal and grants from the Department of Health, UK, outside the submitted work.

L.G. reports no potential conflicts of interest.

M.C. has received research grants, lecture fees, and honoraria for consultancy from Baxter, Bayer, and Pfizer.

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Appendix A. Supplementary data

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