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The future of transfusion and transplant microbiology safety: can new molecular technologies improve the safety of blood and transplant?

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Abstract

Infectious diseases pose a major threat to safety of blood transfusion, organ and tissue and cell-based immunotherapies. Blood services worldwide perform very large-scale screening of blood donors for the major transfusion-transmissible infections (TTIs), HIV-1, hepatitis B and C viruses. However, ongoing and rapidly evolving threats to blood and transplant safety include the currently expanding number or arthropod-borne viruses, such as the current rapid northward expansion of West Nile, Chikungunya and Dengue viruses in Europe, and outbreaks of Oropouche and Zika viruses in Central and South America. The impact on blood and transplant safety of human virome components, including the large number of recently described and often highly prevalent human polyomaviruses, parvoviruses, papillomaviruses and anelloviruses, and human herpesviruses (HHVs) such as HHV-6 and −7, remains poorly understood. Advances in genomics technologies, such as next-generation sequencing (NGS) provide the future opportunity to greatly expand the range of pathogens screened in donors, and to better monitor blood and transplant recipients for potential TTIs. A broader screening capability would enable blood banks to rapidly and effectively respond to new pandemic pathogens. However, the value of their future application for donor screening will require a much better understanding of the natural histories and potential disease associations of human virome components and other viruses incidentally detected on NGS screening. Furthermore, while genomic-based detection and ELISAs for pathogen-specific antibody can be readily applied for screening and excluding conventional pathogens, these are incapable of detecting and preventing transmission of proteinopathies, such as Creutzfeldt-Jakob disease (CJD) where the infectious agents possess no nucleic acid genome. The recent evidence for transmission of variant CJD in the UK through blood and plasma transfusion, and potential more extensive transfusion transmission of the amyloid disease, cerebral amyloid angiopathy, present potential existential threats to the ideal of complete blood safety if these findings are confirmed. A better understanding of the nature of "protein-only" transmissible agents in the aetiology of several forms of neurodegenerative disease is urgently required.

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Background

Transfusion is a necessity in modern medicine, essential for treatment of trauma, elective surgery, immunotherapy and supporting patients with malignant disease. However, as therapeutic agents, blood and its derivatives such as platelets, plasma and immunoglobulins are biologically extraordinarily complex and irreplaceable products. With current technologies, it is simply impossible to manufacture synthetic alternatives on the scale needed to act as a plausible alternative to donor-derived blood and plasma components. Prepared blood components are also remarkably complex to handle, store and use safely, with stringent requirements for blood group matching, short shelf lives and maintenance of sterility. Uniquely in modern medicine, vast numbers of volunteer donors and a massive organisational commitment by blood services are required to provide the necessary red cells, platelets, plasma, tissues and organs to support an effective transfusion and transplant service.

At the same time, blood also has to be microbiologically safe and not transmit blood borne pathogens infecting donors, such as human immunodeficiency viruses (HIV-1 and HIV-2), hepatitis B, C and E viruses (HBV, HCV and HEV) amongst many others. This requires highly effective and very large-scale serological screening for pathogen antibodies and antigens, and for viral genome sequences by PCR and related nucleic acid testing (NAT) protocols (Fig. 1).

Most blood banks in Western countries have largely eliminated transfusion and transplant transmitted infections (TTTIs) through microbiological screening (e.g. Figure 1). The effectiveness of this is monitored in real-time though reporting structures within the dedicated haemovigilance organisations such as the Serious Hazards of Transfusion (SHoT) in the UK [1] and the evaluation of substances of human origin (SoHO) by European Centres for Disease Control (ECDC). In practice, delays in transfusion and pulmonary complications such as transfusion-associated circulatory overload are far more common causes of transfusion-associated morbidity and mortality than TTTIs. However, while extremely rare, outcomes such as transmission of HIV-1 to blood recipients through assay insufficiency or testing error have highly visible and often catastrophic consequences; historical failures to introduce timely and adequate testing for HIV-1 and HCV by the UK blood services have led to damning conclusions in the recent Infected Blood Inquiry report with estimates of over 30,000 people becoming infected with HIV-1 and HCV as a result of delayed introduction of screening [2].

There is broadly a relatively mature and effective infrastructure for microbiology screening in most Western and developing countries worldwide, with the application of NAT in particular largely eliminating residual transmission risk from donors in the pre-seroconversion window period before the appearance of antibodies. This review therefore concentrates on what challenges to the microbiological safety of blood lie in the conceivable future, including strategies to deal with threats to blood safety from emerging and pandemic pathogens, protein-only pathogens in the aetiology of acquired dementias such as variant Creutzfeldt-Jacob disease (vCJD), the potential role of pathogen inactivation and how genomics technologies may ultimately provide far broader capability that the current screening repertoire of HIV, HBV, and HCV of most transfusion services.

Main text

Emerging infections and pandemics

There is a sense of inevitability that there will be future eruptions of new or emerging human pathogens that may create similar or greater morbidity and mortality to that experienced worldwide in the 2020–2023 COVID-19 pandemic. There have indeed been repeated pandemics in the 20th Century, specifically by HIV-1 from 1981, and four separate pandemics of influenza A virus (IAV), the most recent being the swine-origin (SO) H1N1 IAV strain in 2009, and, most deadly, the emergence of H1N1 IAV in 1918 (estimated 18–100 million deaths) [3, 4]. Increased travel, habitat destruction, farming practices and global warming have all been attributed as precipitating the emergence of new human pathogens, but the equivalents of pandemics have been fairly consistently recorded throughout recorded human history. The roll call of previous disasters includes the recurrent severe outbreaks of smallpox virus (e.g. Antonine plague, 165 to 180), a suspected filovirus (Ebola)-related haemorrhagic fever (in the plague of Cyprian, AD 251–262), typhus and plague (*Yersinia pestis*) periodically and devastatingly afflicting the Middle East and Europe in multiple outbreaks in recorded classical (Justinian plague, 541–549), mediaeval (e.g. the Black Death in Europe in 1346 – 353), and post-mediaeval periods such as Great Plague of London in 1665). These were often associated with 30% or greater population fatalities, much higher than the case or estimated infection fatality rates of

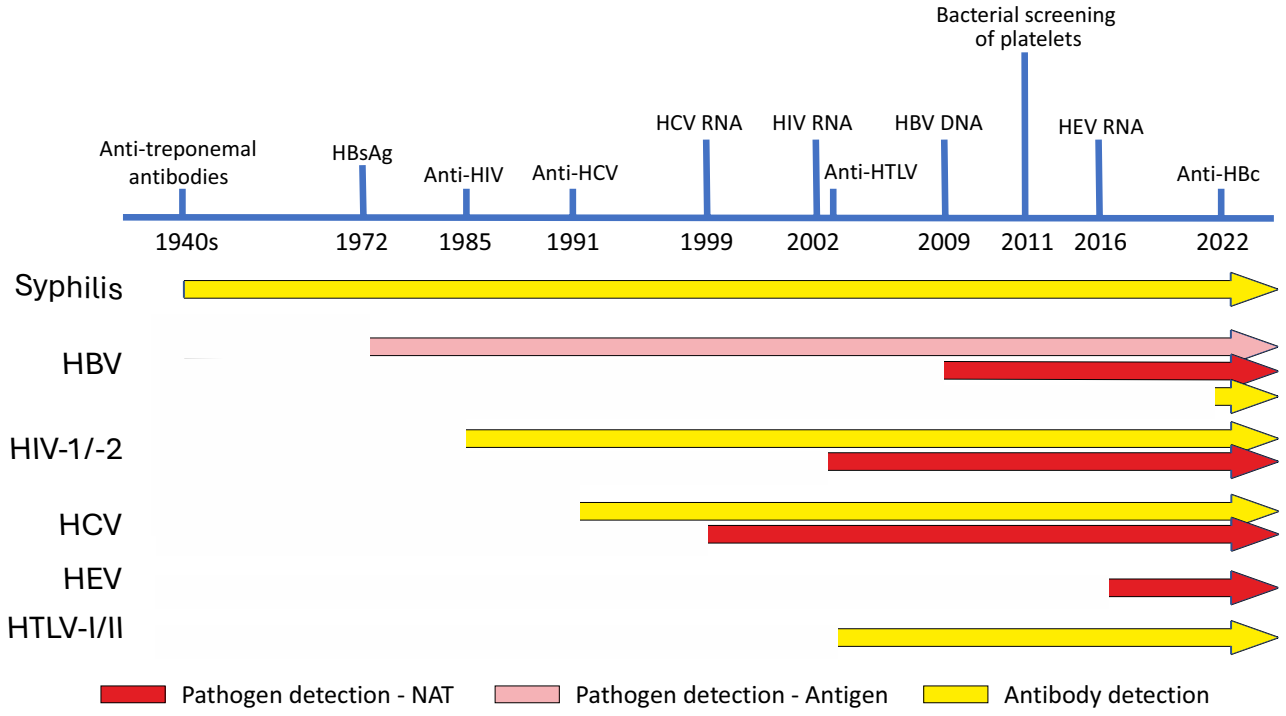

Fig. 1 Blood donor screening in the UK. Time course for the introduction of viral and bacterial screening of blood (and platelet) donors by direct detection of pathogen nucleic acids or antigens and indirect (antibody)-based assay. There is additional screening for West Nile virus and malaria in donors returning from endemic areas of infection. Human T-lymphotropic virus types I and II (HTLV-I/II) screening is for new donors only. Some blood is screened for human cytomegalovirus (HCMV) antibodies to enable seronegative blood to be reserved for previously HCMV-unexposed immunosuppressed recipients

COVID-19 (0.1%-5%). Even with modern public health awareness, global surveillance mechanisms, antibiotics, rapid implementation of large-scale diagnostic screening and accelerated vaccine development, recent experience with SO-IAV and SARS-CoV-2 have both demonstrated how powerless human society currently is to contain outbreaks and prevent their rapid worldwide spread.

Future measures to more effectively respond to and contain future emerging pathogens include expedited vaccine and antiviral development capability, active sentinel population screening and associated global public health monitoring, all elements within current pandemic planning initiatives. Relevantly to the current review, a number of response pathways may be activated by blood services to protect the safety of the blood supply. As a historical example, West Nile virus (WNV) RNA screening had to be urgently introduced in the US from 2002 once the continent-wide spread of WNV circulation in birds became established from 1999 and the *de novo* occurrence of autochthonous human cases (and deaths) over that period was recognised [5, 6]. There have been similar reactive changes to screening in many European countries following the spread northwards of WNV [7] into Germany and the Netherlands. In the UK, the extended range of its most common mosquito vector for WNV, *Culex modestus* [8], and outbreaks of (fatal) Usutu virus (USUV) infection in blackbirds around London [9], has spurred recent increased surveillance efforts. Changes in the range of *Aedes aegypti* and *A. albopictus* in Europe has similarly contributed to the recent alarming spread of Chikungunya virus (CHIKV) and dengue virus types (DENV) in France and Italy [10], necessitating the introduction of donor deferral or screening in several Southern European countries [11]. Very large episodic outbreaks of DENV, CHIKV and Zika virus in Central and South America and South East Asia have been similarly associated with measurable incidences of viraemia and potential infectivity of blood components [12, 13].

These recent examples of emerging arbovirus infections reflect both their often rapidly changing epidemiology and vector distributions, but also their adaptations towards blood-borne routes of transmission through their arthropod vectors. A systematic review from 2022 identifies ten diverse arbovirus species from multiple virus families with documented evidence for transmission through blood or platelet transfusions, and a further 18 with the potential for transmission based on infection incidence in donors or case reports of infections after transfusion or transplant [14]. The dynamics and multiplicity of arbovirus infections in many areas of the world therefore necessitates not only one health surveillance but also ongoing monitoring of donor populations for infections, the establishment of testing infrastructures that enable timely induction of donor screening in

areas of autochthonous infection, and flexible and reactive policies for donor deferral in travellers returning from endemic areas or often very rapidly evolving areas of infection outbreaks.

While most focus on emerging infection threats to blood safety has been or arboviruses, with their known ability to transmit through transfusion, in principle any infection may similarly present a transfusion risk if there is a viraemia during a pre- or asymptomatic phase of infection. Adverse outcomes are also similarly dependent on whether transmissions through a parenteral route leads to same disease presentations as those acquired through more physiological routes of respiratory, enteric and dermatological viruses. As examples, SARS coronavirus type 2 (SARS-CoV-2) infections have not been associated with transfusion risk, because viraemia (or antigenemia) was typically only observed in individuals during severe symptomatic infections [15]. Furthermore, viral RNA or protein detected in blood may not equate to infectivity, as demonstrated by the lack of transmission after transfusion of SARS-CoV-2 RNA-positive blood [16].

There is considerable current concern about the potential emergence of avian-derived H5N1, H9N2 or derived flu strains derived from reassortment from these following adaptive changes that enable more efficient replication and transmission to mammalian hosts [17–23]. Whether the emergence of H5N1, H9N2 or other avian-derived reassortants represent a major risk for blood safety is however uncertain. In the previous pandemic of swine origin (SO) H1N1 IAV in 2009, viraemia was only detected in those with severe respiratory disease or complications [15, 24, 25], i.e. not blood donors; indeed, large scale NAT screening of blood donations over the pandemic period found no evidence of viraemia [26, 27] and there are few if any verified cases of transfusion-transmitted infections of IAV during the pandemic in 2009 or any other period. Of course, whether a newly human-adapted and emergent avian outbreak strain shares the same dynamics of disease induction and propensity for systemic infection as a markedly less pathogenic SO H1N1 pandemic strain remains to be determined.

Assessment of risk

Establishing the key determinants of blood transmission risk for other emerging or pandemic viruses is complex, requiring specific information on multiple parameters. These include epidemiological factors:

a) Infection incidence in the donor population.
b) Frequencies of past infection and immunity from reinfection in blood recipients.
c) Risk profiles of donors, including the existence of shared risk factors for screened viruses such as HIV or HCV.
d) For arboviruses, histories of vector bites and travel from endemic areas of infection.

and properties of the infectious agent:

e) Duration of viraemia.
f) Location of the pathogen in plasma or cellular blood components.
g) Disease outcomes of infection through what may be a non-physiological route of acquisition.
h) Occurrence of viraemia in asymptomatic infections.
i) Timing of viraemia in relationship to disease symptoms.
j) Whether identified as a post-transfusion adverse outcome by haemovigilance.

As a recent example, mpox virus (MPXV) recently emerged from an endemic focus on infection in Central and West sub-Saharan Africa. This primarily infected men who have sex with men (MSMs) in many Western European countries in early 2022, with a further ongoing outbreak of potentially more pathogenic clade 1 strains from 2024 [28]. As summarised in a recent review [29], information on parameters contributing to its transmission risk (listed in simplified form in Fig. 2) comprised (a) Incidence: low even in the outbreak period, (b) Recipient immunity: low/none, (c) considerable overlap of risk factor for infection with HIV, (d) no vector association, (e) prolonged viraemia, (f) uncertain distribution in blood components, detected in plasma, (g) moderately pathogenic, (h) viraemia during asymptomatic infection (i) viraemia precedes development of rash and (j) transmissions not reported in haemovigilance studies. The reported absence of viraemia on actual donor screening in 2022 [30, 31] likely reflects the relatively low sample size relative to incidence and donor representation (a), and its strong association with risk behaviour for HIV infection. Multiple sexual partners, practicing anal sexual intercourse and use of pre-exposure prophylaxis (PrEP) against HIV infection would have excluded the most at-risk donors (c).

Using these metrics, the transfusion risk of human pegivirus type 1 (HPgV-1) has been judged minimal or absent to the extent that is not screened in blood donors. This is despite a mean 3.1% frequency of active infection in all donor populations worldwide [32], an ability to establish persistent infections in immunocompetent individuals, a specific association of infection risk from multiple sexual partners and injecting drug, and demonstrated high infectivity on transfusion of blood components and

Risk factor	HIV-1	WNV	MPXV	EVs	HPgV-1	SARS-CoV-2
Epidemiological factors						
a) Infection incidence	Low	Low	Low	Moderate	Moderate	High
b) Recipient immunity	None	Low	None	Moderate	Low	Moderate
c) Risk Profile[1]	Partly[3]	None	Shared HIV	None	Low	None
d) Vector exposure risk		Unreliable				
Pathogen properties						
e) Infectious viraemia	Long	Short	Long	Short	Long	None
f) Blood compartment	All	Plasma	All	Plasma	Plasma	All
g) Disease severity	Severe	Severe	Moderate	Low	None	Moderate
h) Asymptomatic viraemia	Yes	Yes	Yes	Yes	Yes	Yes
i) Pre-disease viraemia	Yes	Yes	Yes	Yes	Yes	Yes
j) Haemovigilance[2]	Yes	Yes	No	No	No	No

Colour key: Favourable | Some risk | Unfavourable | Non-contributory

Fig. 2 Simplified risk assessment template for examples of blood-borne human viruses. Virus name abbreviations: HIV-1: human immunodeficiency virus type 1; WNV: West Nile virus; EVs: human enteroviruses; HPgV-1: Human pegivirus type 1; SARS-CoV-2: SARS coronavirus type 2. [1] Extent to which a donor risk factors for infection match those of other blood-borne viruses such as HIV-1 and HCV (multiple sexual partners, anal sex, injecting drug use), and which would be excluded from donation. [2] Reports of post-transfusion disease from infection reported by haemovigilance frameworks, such as SHoT (UK). [3] Risk factors for infection are not always reported in HIV-infected donors

plasma-derived blood products [33, 34]. The basis for a decision not to screen and exclude HPgV-1 infected donors revolves entirely around (g) and lack of reported post-transfusion disease in those infected (j). One might however consider its immunomodulatory effects on host responses to other virus infections such as HIV-1 [35] and the evidence from a systematic review associating long term HPgV-1 viraemia with greater likelihood of lymphoma development [36]. SARS-CoV-2 has not been considered a transfusion risk for the different reason that while viral RNA can be frequently detected in plasma from those with active infections, it does not represent genomic RNA from infectious viral particles, instead though to originate from cellular debris from the infection process in the lung [15].

Risk assessment templates and further evaluation of prevention measures are widely used in the blood services to horizon-scan for microbiological transfusion risk, including the UK Standing Advisory Committee on Transfusion Transmitted Infections (SACTII), and the ECDC framework for substances of human origin (SoHO). For the blood services, minimum requirements for advocating additional screening generally require that all the following criteria are met:

a) Defined agent pathogenicity.
b) Demonstrated presence in the donor population.
c) Absence of identifiable risk factors that would otherwise exclude infected donors.
d) Demonstrated transmissibility and recipient susceptibility.
e) Evidence for post-transfusion disease associated with agent transmission from haemovigilance programmes.
f) Economic assessment of the costs of introducing screening set. This is compared to the harm, often expressed in quality adjusted life years (QALYs), of infections occurring in the absence of screening.

While transfusion safety is of paramount importance for blood services worldwide, criteria for the introduction of additional testing beyond standard HIV, HBV, HCV and syphilis antibody testing are clearly complex and multifactorial. As described, they entail requirements for effective haemovigilance to identify whether there is a problem, ongoing review of potential changes in agent epidemiology or of emergence and better understanding of virus pathogenicity and recipient susceptibility, and a robust health economic framework with agreed cost-effectiveness thresholds (see below).

Higher-risk donors

While most risk assessments and surveillance focus on defined pathogens, donor selection additionally excludes particular behaviours associated with infection risk. As examples, donors returning to the UK from areas of high incidence for vector-borne or parasitic infections are typically deferred for three or more months or may be subjected to specific testing for malaria and West Nile virus. Another risk category are individuals who have been previously transfused by blood components or plasma products. In the UK and more variably in other blood

services, such individuals are permanently deferred from donation, primarily motivated in the UK by caution over iatrogenic acquisition of vCJD disease from blood collected in the early 1990s during the "mad cow disease" outbreak (see below).

Injecting drug use and sex with multiple partners predispose individuals for infection with the blood-borne viruses that are currently screened in donors (HCV, HBV and HIV-1). However, these behaviours also increase risk of infection by a range of other transmissible but unscreened potential pathogens, such as MPXV described above, hepatitis A virus [37], human herpesvirus 8, PARV4 [38, 39], and HPgV type 2 [40, 41]. Screen-negativity for HCV, HBV and HIV-1 therefore does not rule increased risk for recipients for other transfusion-transmissible infections and evaluating and excluding donors on the basis of reported risk behaviours remain an essential part of donor selection. The frequent finding of PrEP residues in donation samples in the UK and the Netherlands [42, 43] suggests, however, that its implementation is not always fully effective.

The human virome

The development of next generation sequencing technologies has heralded a quantum leap in knowledge of viral diversity in the environment and in the abundance and range of viruses infecting humans, other animals and plants. Descriptions of a complex flora of "commensal" viruses in human tissues and blood [44, 45] challenges the previous widely held assumption or paradigm that the human body was internally virologically sterile, interrupted only by specific infection episodes with pathogenic viruses. In addition to the literally hundreds of papillomavirus types infecting the skin, many of the 14 distinct polyomaviruses and 9 parvoviruses show evidence for high frequencies of systemic infection, in addition to varying incidences of reactivated herpesvirus infections, adenoviruses, and most remarkably, almost universal sustained replication and high maintained levels of viraemia with at least 5 genera of anelloviruses, and their component species and multiple types. Most mammals appear to possess equally diverse repertoires of viruses specifically adapted to their host niche.

Given the ubiquity of small DNA viruses in particular in the human virome, and the likelihood that blood or transplant recipients likely harbour parallel repertoires of viruses, there is no specific indication to exclude donations based on their presence. Indeed, ubiquity is not the primary problem; it is virome components that do not infect universally that create susceptible recipients. There may indeed be very harmful outcomes if acquired through transfusion or other non-physiological routes, or into susceptible age ranges and those with severe co-morbidities or immunosuppression.

Even if almost ubiquitous, persistent DNA viruses such as the originally described BK polyomavirus (BKPyV) cannot always be assumed to be non-pathogenic. Decades of intensive aetiological investigations have established specific and severe disease associations from BKPyV-associated nephropathy [46]. The problem is that there simply isn't the clinical, virological or epidemiological knowledge required to assess the pathogenic significance of transmission of many of the newly described polyomaviruses, parvoviruses and papillomaviruses that infect systemically, or even their ubiquity or otherwise in different human populations. As described below, enhanced haemovigilance using NGS technologies may provide one means to link post-transfusion or transplant morbidities with infection or reactivation of human virome components.

Proteinopathies

The most enigmatic, poorly understood and uncertain threats to blood and transplant safety are the prion and amyloid diseases. In humans, inherited, sporadic and transmissible forms of CJD are extensively characterised, with instances of transmission through the use of inadequately sterilised surgical equipment, human cannibalism, and administration of human pituitary-derived growth hormone [47]. The aetiological agents of human CJDs and of related diseases in other mammals, such as scrapie in sheep, bovine spongiform encephalopathy (BSE) in cows and chronic wasting disease of elk and deer, are abnormally folded prion proteins (PrP) [48]. Remarkably, a PrP^{sc} "seed" appears to be able to induce misfolding in normal PrP and thus propagate and amplify its infectivity, creating aggregates of fibrils that lead to severe and progressive neuropathology, dementia and death. While CJD most commonly arises sporadically in human populations worldwide, specific mutations in the human PrP gene (reviewed in [49]) predispose towards rare familial forms of CJD and other neurodegenerative diseases.

CJD, and potentially other prion diseases, are recognised as posing a low although measurable threat to blood safety. There is no evidence for the transmission of sporadic CJD through blood component transfusions, transplant or plasma-derived products. However, approximately 177 diagnosed infection-acquired cases of "variant" CJD (vCJD) occurred in humans in the UK, 27 in France and 28 in 10 other countries following outbreaks of BSE in cattle 1985–1995 and their consumption of inadequately cooked meat and offal from affected animals [50, 51]. From these, four cases of secondary transmission of vCJD through blood transfusion and a fifth (pre-clinical) case in a person with haemophilia treated plasma-derived factor VIII concentrate have been since recorded [52–54]. This motivated intensive efforts

to develop sensitive and specific screening tests for the vCJD-associated prion protein [55–57], given the evidence for its presence in peripheral blood preceding the onset of neurological disease in animal models [58, 59]. Methods based on prion "amplification", such as the protein misfolding cyclic amplification assay and real-time quaking-induced conversion assay achieved high analytical sensitivity for abnormal PrP [60–63]; ultimately however, they were never introduced for screening of donors in the UK or elsewhere as the vCJD outbreak greatly subsided from 2013 to 2014 onwards (last case in 2017) and hence they have never been evaluated or scaled up for use in blood donation screening.

Alzheimer's disease (AD) is another, far more common and globally spread neuropathogenic disease associated with abnormal accumulation of aggregates of amyloid-β protein (Aβ) plaques and neurofibrillary tangles. As with prion diseases, Aβ aggregation results from the propagation of misfolded protein [64, 65]. The occurrence of AD and related cerebral amyloid angiopathy (CAA) has always been regarded as sporadic with onsets in later life (reviewed in [66]) but more likely in those with pre-existing mutations in the apolipoprotein E gene, the Aβ encoding amyloid precursor protein gene [67, 68] and pre-senilin gene [69]. Remarkably however, the amyloid-associated CAA has recently been shown to develop in those treated with human growth hormone [70–72] and in those receiving dura mater grafts [73], analogous to iatrogenic transmission routes of CJD. The nightmare scenario for the blood services of a relatively common disease being potentially transmissible through transplant and transfusion came a step nearer with the recent discovery that recipients of blood from donors who subsequently developed CAA, were themselves more likely to develop likely CAA-associated multiple intracerebral haemorrhages [74], with comparable 2.3-2.7-fold odds ratios in independently replicated cohorts in Sweden and Denmark. This remarkable epidemiological observation has spurred current intensive efforts to replicate the findings in other countries and to understand their underlying biology in more detail.

Should the findings be independently verified [75], it would be however highly uncertain how to develop effective screening assays for what may be another "protein-only" infectious agent, and indeed for other aggregating proteins associated with neuropathology, such as tau, α-synuclein and TDP-43. Rather than diagnostic testing for the agent, screening of informative biomarkers in blood, such as neurofilament light chain, Aβ peptides, phospho-tau and glial fibrillary acidic protein AD [76–78] or the 14-3-3 protein in CJD [79], or the detection of signatures of altered host gene expression [80–82] may represent future approaches towards detection and exclusion of donors in prodromal stages of CAA or other proteinopathies.

Future blood and transplant safety

Technologies are rapidly developing for genomics-based microbiological screening of donors and recipients, pathogen inactivation of blood components and towards a manufacturing process that creates entirely synthetic red cells or "oxygen therapeutic agents" such as perfluorocarbons or cell-free haemoglobins (reviewed in [83]) or stem cell-derived erythrocytes [84][1]. These may all have substantial future impacts on blood safety in coming decades and may potentially individually or collectively eliminate pathogen transmission risk.

Genome detection technologies

Target amplification-based methods for pathogen genome detection, such as PCR, reliably achieve assay sensitivities for single copies of specific target pathogens. Virus detection sensitivity of PCR and related NAT technologies is thus limited only by test volume. For blood donor screening, this has driven a trend towards a reduction in pool sizes or the use of individual sample (ID) NAT to increase sample representation and maximise analytical sensitivity as costs for genome testing reduce and increasingly automated testing systems become available [85]. NAT is typically performed on the cell-free plasma donation component, without any obvious current motivation for extending this towards screening blood donors for cellular nucleic acids. While screening targets such as HTLV-I/II and HHV-8 are indeed largely cell-associated, infections may be more effectively detected in these cases through serological assays for virus-specific antibodies. The testing range of NAT screening platform can, however, be greatly expanded to incorporate screening for HEV (UK and many other European countries), discretionary testing for WNV and potentially for other arboviruses should they emerge and pose a transmission risk [14].

As described, the extent to which additional screening may be introduced is dependent on ongoing structured risk assessments by blood services and health departments. These allow estimates of the likely effectiveness of additional assays on reducing TTI risk and associated morbidity in recipients, as well as its downstream impacts on donor exclusion and costs. These considerations are a greater limiting factor towards wider test implementation than whatever technological improvements there might be in NAT screening methodologies, or on the availability of specific serological tests.

[1] The future development of synthetic blood and platelets and their potential introduction however, lies beyond the scope of this review of transfusion microbiology.

A future introduction of NGS-based methods for donor screening would enable much broader virus and other pathogen screening beyond the targets selected from risk assessments described above. The main NGS technologies are based upon highly parallel sequencing of DNA and optionally RNA sequences extracted from a sample; in the two most commonly used sequencing methods, DNA sequences are read from either isolated pre-amplified DNA templates in a flow cell (Illumina) or read from single DNA template sequences as it traverses a protein nanopore (Oxford Nanopore Technologies; ONT). Both methods, particularly Illumina, generate vast quantities of read data; the Illumina NovaSeq produces up to 3000 billion (3×10^{12}) base pair (bp) reads per run, more than enough to read an entire human genome of 3.1×10^{9} bps. The volume, complexity, requirement for assembly and elimination of sequencing errors places high demands on bioinformatic software required to analyse NGS sequence data.

Effective use of NGS data currently requires sophisticated and often highly computer-intensive software and expert bioinformatics supervision to effectively use the sequence data obtained. Even when multiplexed to sequence multiple samples simultaneously (but at lower read depth), NGS methods such as Illumina are still considerably more expensive than standard NAT; they are also encumbered with long (1–2 days) and methodologically exacting library preparation and pre-amplification protocols for running samples. The applicability and usefulness of current NGS methods for large-scale blood donor screening is currently therefore very limited. NGS cannot surpass standard NAT in terms of target sensitivity as there are practical limits in sample representation within a multiplexed sample NGS run; it additionally remains technically and bioinformatically uncertain whether a single pathogen sequence could be reliably detected with 100% specificity by any of the current technologies. In contrast to NAT, current NGS methods are multiple logs away for single target sensitivity (unless the target is pre-amplified by PCR), as demonstrated by our recent comparative valuation of several different NGS-based methods [86]. Current methods also lack assay specificity and possess a propensity for stray reads arising from assay or bioinformatic contamination.

However, ongoing and rapid technological developments in this area, including new sequencing chemistries and formats combined with effective, unsupervised analysis of read data may solve many of these restrictions. It is conceivable that there will ultimately be a "black box" technology capable of rapid detection and appropriate reporting of pre-specified diagnostic targets in a format appropriate for large-scale and potentially cost-efficient pathogen screening. NGS may indeed potentially have the future capability to analyse and report pathogen diagnostic information with similar time-frames and costs to standard NAT assays.

Assuming that NGS and bioinformatic technologies advance to this stage, their potential breadth of detection of virus, bacterial, fungal and amoebic pathogens and parasites in blood and organ donors would be of major value in improving the microbiological safety of transfusion and transplant. It would provide the means to detect and exclude a wider range of potentially pathogenic viruses, and find even extremely rare and previously unreported pathogens. The entirely unexpected presence of rodent lymphocytic choriomeningitis virus (LCMV) in two donors that subsequently led to fatal disease in seven of the eight transplant recipients [87] is a striking historical example. NGS would possess an intrinsic capability to detect novel and emerging pathogens in donors and their exclusion from transfusion without need for introduction of new tests.

However, the greater breadth of detection of NGS methods would bring a new set of operational, ethical and potentially blood supply problems. As a hypothetical example, an unsupervised NGS "black box" would eventually and inevitably report donations with high levels of Merkel cell carcinoma polyomavirus or enterovirus A71, where it is not immediately clear how this information might be used. While both viruses have been previously assessed as not presenting a transfusion safety risk (for example by SACTTI in the UK), both viruses have a large literature on their pathogenicity and occasional severe disease associations, such as an aggressive form of skin cancer or severe potentially fatal neurological disease. Should the transfusion and transplant recipients of these donations be monitored for transmission and possible morbidity? Or should positive donations be intercepted and excluded from transfusion until there is greater certainly on the outcomes of transfusion, particularly in vulnerable immunocompromised or very young recipients? How could such information on potential pathogenicity be obtained if positive units are excluded from transfusion? Is haemovigilance sufficient to exclude adverse events in the absence of targeted screening for these viruses in blood recipients?

More generally, it is unclear to what purpose information on the presence of a wider range of viruses would be put. In addition to HCMV, are any other normal human virome components of relevance for blood and transplant safety? Should the information of the presence of virome-associated viruses be recorded in the recipient medical records? Detailed, stringent and regularly reviewed guidelines on the use of NGS-derived data and data on clinical outcomes from long-term follow-up of infected recipients would clearly be required before its implementation could be considered. Any potential improvement in blood safety from extended screening would also

have to carefully weighed against its damaging impact on the blood supply and indeed, a potential negative psychological effect on the donor if permanently excluded. Rejection of donations on the basis of additional virus detection would have to clinically justified and accompanied by a clear communication strategy to inform the donor of the implications of infection.

Despite these drawbacks, universal screening by NGS or related genome technologies on donation samples would have the incomparable advantage of "catch-all" testing. This would be ideal as a means to ensure blood safety during periods of emergence of new pathogens without need for additional investment and validation of new NAT assays. It might for example, provide the required testing preparedness for the anticipated arrival of USUV and WNV in the South of England in the new few years - and for future pandemics. The breath of NGS-based screening would also be ideal for monitoring recipients of blood and particularly transplant, where their immunosuppression may contribute towards high levels of transmitted or reactivated virus replication. Uncontrolled and potentially harmful levels of replication of one or more DNA virus components of the human virome in addition to anelloviruses may associate with post-transplant morbidity but would likely be missed by targeted diagnostic assays.

The breadth of pathogen detection by NGS methods is therefore both a strength and a weakness of the approach. Implementing NGS for universal donation screening will require substantial virological and operational oversight, and ultimately a much better clinical understanding of the significance or otherwise of adventitious virus detection arising from donation screening. Of course, a compromise solution would be to strictly isolate (or "sandbox") bioinformatic analysis and internally encrypt read data so that it only reported detection of pathogens included in a pre-specified list, and discarded all other reads (including all human DNA sequence data). The target list could be regularly reviewed with oversight from national regulatory committees. Such approaches could readily interface with and share platforms with NGS-based clinical virology and microbiology diagnostics that would possess their own pathogen repertoires.

Pathogen reduction

An alternative or additional pathway towards greater blood safety may be provided by the wider introduction of pathogen reduction (PR) methods. Intercept™ (Cerus) is licensed for inactivation of platelet concentrates, based on a photochemical method in which exposure of amotosalen hydrochloride to ultraviolet (UV)-A light leads to crosslinking of DNA or RNA pyrimidine bases and consequent pathogen inactivation. Similarly acting methods that have been trialled include riboflavin (+ UV (Mirasol™) and a UV-C only method from Theraflex™ (reviewed in [88]). In the same way that heat and solvent-detergent virus inactivation methods transformed the safety of plasma-derived products such as factor VIII clotting factors in the late 1980s, PR has been promoted as a means to achieve blanket reduction or elimination of infectivity of a wide range of RNA and DNA viruses in platelets, and would substantially improve blood safety generally if it could be also used for cellular products derived from whole blood donations.

PR methods irreversibly crosslink genomic DNA or RNA preventing pathogen replication, and are broadly effective for the inactivation of arboviruses and other enveloped viruses [89, 90], most bacteria and parasites [90]. Despite its targeting of nucleic acids, Intercept and Mirasol surprisingly possess much more limited efficacy against non-enveloped viruses [90, 91] (Fig. 3), and with several reports on transmission of HEV and parvovirus B19V from Intercept-treated platelets [92–94]. However, UV-C treatment in the Theraflex protocol may be more effective [95]. No PR methods inactivate sporulated forms of bacteria or prions. Off-target effects beyond damaging nucleic acids may result from induction of oxidative stress and production of free radicals that may interact with proteins or other pathogen or cellular components.

The use of PR also avoids the need to perform bacterial screening of platelets and enables earlier release of platelets by 1–2 days and prolongs shelf-life. Factors limiting the use of PR include its reported aggregating and other damaging effects on platelet function that may require greater usage, and its limited cost-effectiveness compared to existing virus and bacterial screening. Several analyses of its cost-effectiveness model potential beneficial effects on platelet use, avoidance of the need to perform bacterial screening and assessment of its value in preventing transmission of emerging infections. However, by these criteria, most analyses have shown PR technologies to not be cost-effective, with incremental cost-effectiveness ratio (ICER) of over $1 million for each quality-adjusted life-year (QALY) gained previously calculated for Mirasol [96], $8.1 million / QALY for Cerus Intercept [97], €350,000-€650,000 / QALY for Mirasol in Poland [98], and typically over $1 million in the USA using Intercept [99]. Substantially lower ICER scores and a greater cost-effectiveness of PR were modelled for donors in Ghana, which possesses limited screening testing capability and high infectious disease burden [100]. However, studies reporting reported lower ICER values for PR [99, 101] in some scenarios made unrealistic assumptions on the frequency and health impact of undetected pathogens infecting blood donors that significantly skewed their cost-effectiveness calculations [102].

Virion	Virus	Species	Genome	Log reduction
Enveloped				
	Retrovirus	HIV-1 cell associated	ssRNA	>6.64
		HIV-1 cell free		>6.74
		HIV-1 clinical Z84		>3.94
		HIV-2 clinical CBL20		>5.20
		HTLV-I		4.84
		HTLV-II		5.04
	Hepadnavirus	HBV	dsDNA	>5.54
		Duck HBV		>6.74
	Flavivirus	HCV	ssRNA	>4.54
		BVDV		>4.71
		West Nile virus		>6.85
		Zika virus		>6.66
		DENV-1		>5.06
		DENV-2		>5.66
		DENV-3		>4.56
		DENV-4		>5.26
		Yellow fever virus		>5.57
	Alphavirus	Chikungunya virus	ssRNA	>7.67
		Mayaro virus		>6.97
		Ross River virus		>5.17
	Coronavirus	SARS-CoV	ssRNA	>6.27
		MERS-CoV		>4.77
	Influenza virus	IAV H5N1	ssRNA	>5.97
	Arenavirus	LCMV	ssRNA	>5.67
	Herpesvirus	Cytomegalovirus	dsDNA	>6.44
	Poxvirus	Vaccinia virus	dsDNA	>5.24
Non-enveloped				
	Reovirus	Bluetongue virus type 11	dsRNA	5.25
	Adenovirus	Human adenovirus 5	dsDNA	5.68
		Simian adenovirus 15		1.52
	Calicivirus	Feline calicivirus	ssRNA	1.79
	Picornavirus	Hepatitis A virus	ssRNA	0.75
		Hepatitis A virus		0.76
	Parvovirus	Human parvovirus B19	ssDNA	2.14
		Porcine parvovirus		0.38

Fig. 3 Log reductions in infectivity for enveloped and non-enveloped viruses using Intercept (data from [90, 91]). Virus name abbreviations: HIV-1: human immunodeficiency virus type 1; HTLV: Human T lymphotropic virus; BVDV: bovine viral diarrhoea virus; DENV: Dengue virus; SARS-CoV: SARS coronavirus; MERS-CoV: Middle-East respiratory syndrome coronavirus; LCMV: lymphocytic choriomeningitis virus. [1] Mean value between cited studies; highest value used for minimum log reduction measurements. Values have been coloured in proportion to degrees of reported inactivation; Red: no inactivation; Blue: 7 logs or greater

What is an acceptable cost of blood transfusion microbiology safety?

There is no clear economic framework for the "value" of transfusion microbiology screening that might guide the introduction of new tests, as there are huge ambiguities and variation in costs for donation screening in different blood services internationally. There is also no widely accepted standard NAT testing strategy for basic pathogens such HIV, HBV and HCV - blood services may use different pool sizes or screen samples individually or may eschew NAT entirely. Some blood services may supplement HBV screening with surrogate testing for previous

Table 1 HEV RNA detection frequencies in countries where blood services (A) screen or (B) do not screen for HEV RNA by NAT (data based on [105])

Country[1]	Years	Screened	Pool size	Positives	Rate	Frequency[2]	Reference
A) *Currently screening*							
UK	2016–2017	3,515,304	16–24	787	1/4466	0.0224%	[106, 107]
Ireland	2016–2017	279,938	1	59	1/4744	0.0211%	[105]
France	2012–2015	190,668	1–96	118	1/1615	**0.0619%**	[105]
Netherlands	2013–2018	794,580	24–192	400	1/1986	**0.0503%**	[105]
Germany	2015–2017	508,522	24–96	410	1/1240	**0.0806%**	[105]
Spain	2017–2018	111,534	16	29	1/3846	0.0260%	[105]
Austria	2016–2017	155,691	16	29	1/5368	0.0186%	[105]
Japan	2014–2019	1,379,750	1	597	1/2311	0.0433%	[108]
B) *Not screening*							
Denmark	2015–2017	44,374	1/24	34	1/1305	**0.0766%**	[109]
Sweden		95,835	24–96	12	1/7986	0.0125%	[110]
Poland	2014–2015	12,664	1	10	1/1266	**0.0790%**	[111]
USA	2015–2016	69,553	1	5	1/13,910	0.0072%	[112, 113]

[1]Available data from multiple sources where available (such as the multiple studies listed in ref. [105]) were combined for calculation of detection frequencies

[2]Incidences of greater than 0.05% (1: 2000) highlighted in bold

exposure through anti-HBc antibody detection and some may not [103]. While some of this variability reflects differences in epidemiology and prevalence in different blood donor populations, choices are governed by the costs of commercial testing contracts and what blood services are prepared to pay. However configured, it is clear that current serology and NAT screening costs add substantially to the supply costs of blood components and represent a significant spend in health budgets.

The broader issue of the how to reconcile the costs of introducing pathogen screening or other measures to prevent transfusion transmission against a quantifiable health benefit is complex and largely unresolved. Health economic assessments are frequently performed by blood services to evaluate, as one from many recent examples, the cost of introducing NAT screening for HEV viraemia against an estimate of the morbidity and potential mortality of transfusion-acquired infections [104]. That the cost-effectiveness of such screening is marginal or arguable is amply demonstrated by the variability of testing by blood banks that seems little corelated with measured incidences of viraemia in the donor population (Table 1).

In the UK, screening of all donations by HEV RNA NAT in minipools of 24 has been performed since 2016, based on a calculated cost-effectiveness of £1662 / QALY [104]. QALYs are widely used in health economic calculations as a combined metric of morbidity and mortality. In principle, these enable an objective assessment of the relative values of a variety of health interventions, such as new drug treatment, vaccines and operation to be compared. In practice, somewhat informal thresholds of, for example £15,000 - £30,000 / QALY in the UK National Health Service, are adopted to guide which should be used as standard of care in the UK. Similar calculations and thresholds guide health interventions in publicly health systems worldwide.

While seemingly rational, in the specific instance of blood donor microbiology screening, much of the testing is not conventionally cost effective. For example, the currently mandatory NAT testing of blood, platelet and plasmapheresis donations for HCV RNA by NAT, in addition to serology testing, possesses a cost-effectiveness of more than $1 billion / QALY given that HCV infections are now entirely treatable and display minimal morbidity pre-treatment. However, the idea that other screening might be discontinued on costs grounds is immediately problematic. HIV NAT has been universally used for donor screening in the UK since November, 2003, but to date, testing has only intercepted four positive donations from approximately 40 million donations screened that were negative on standard ELISA Ab/Ag (NAT-only) and would otherwise might have been transfused. However, any prospective discontinuation of HIV NAT (and future effectively deliberate infection of patients with HIV-1) on the basis of health economic considerations would seem unconscionable despite its extraordinary cost.

This dichotomy might be perhaps resolved in part by assigning different criteria for the *introduction* of a health intervention for health benefit (such as new drug treatment) and with measures that *avoid harm*, perhaps at a greater threshold of £90,000 / QALY (reviewed in [104]) that would encompass preventing transfusion or transplant acquired infections. For the blood services, this difference highlights the somewhat separate issue of reputational risk. While there may be some public understanding of the UK decision not to introduce new treatments in the NHS on the basis of cost, the use of oseltamivir and zanamivir for treatment of IAV infections [114] being one of many examples, the public will

not tolerate a cost-driven policy to allow blood recipients to be regularly infected with HIV and HCV on the basis that it wasn't economically worth it to screen their donations by NAT. Discontinuation would be a particularly problematic decision where the infrastructure and assays for screening was readily available and straightforward to implement.

The future introduction of NGS and other sophisticated genomics-based screening methodologies, and safe means to inactivate pathogens by PR will however have to be set against their costs and realistic estimates of their actual health benefit compared to existing screening for a minimal set of blood-borne pathogens. While the reagent costs of NGS are tumbling, and increasingly streamlined workflows are developed for library preparation and pre-amplification, the necessary validation steps, quality assurance requirements of CE marking required for the manufacture, quality control, standard use protocols and marketing suggest that the implementation of NGS-based screening will be expensive indeed.

Conclusions

Looking very far ahead, the pace and direction of genomics-based testing suggests that a simple fully automated assay might be developed that could detect, quantify and report the presence of all known and even as yet uncharacterised viruses, bacteria and protozoa accurately and immediately. With his tricorder, Jim "Bones" McCoy in earlier series of Star Trek certainly had access to a medical device that embraced such capability [115], including an as yet unrealised and remarkable ability to detect non-DNA based forms of life that would defeat current NAT and NGS methodologies – famously, "It's life, Jim, but not as we know it.". On that basis, it might conceivably have possessed a capability to detect proteinopathies such as vCJD and AD.

Exploiting the value of universal screening would however require considerably better understanding of the role of infectious agents in human disease. While detection of any bacterial, amoebic or other cellular organisms in blood would be significant, interpretation of the potential harmful effects of infection with or transmission of viruses resident in the human virome remains a matter of future investigation. Among the many polyoma-, parvo-, papilloma-, anello- and herpesviruses that contribute to the "normal" flora of humans, it is clear that some of these, particularly human herpesviruses, may be pathogenic in some circumstances, such as after transfusion to previously unexposed blood recipients, particularly if immunocompromised. Future advances in understanding of host genetic background on susceptibility and clinical outcomes of infections will also be pivotal in this context.

Apart from separate blood issue of units from HCMV-seronegative donors, the general principle of blood services is that donated blood and platelets units are randomly allocated to blood group-matched recipients. This practice therefore fails to consider recipient-specific susceptibilities to infection and largely negates any potential value from detecting human virome components in donors. It is conceivable that transfusion in the future could be tailored through the application of NGS screening to recipients before transfusion to minimise the likelihood of transmission of viruses to which the recipient has not previously exposed. Of course, haemovigilance has not specifically identified specific problems arising from transmission of any of the vast range of DNA viruses infecting humans apart from some human herpesviruses and B19V, but in the absence of targeted diagnostics, post-transfusion morbidity and potential mortality associated with such undetected transmissions may be currently unrecognised. The application of NGS methods to monitor blood and transplant recipients may provide one means to more effectively monitor the impact of virus transmission on post-transplant disease. The value, therefore, of applying of NGS or other broader screening technologies to detect a wider range of viruses that just HIV, HBV and HCV (and HEV) is therefore somewhat of a moot question until more recipient monitoring data can be obtained.

In conclusion, the advance of genome technologies and their application for large-scale screening will have a likely profound effect on medical microbiology and the application to diagnostics in many areas, including blood and transplant donor testing. The great breadth of pathogen detection using current and future NGS and other genomics-based methods or through PR (inactivation) technologies may find major application in preparedness for emerging and pandemic pathogens, as would a future potential tailoring of donations and recipients to minimise transmission of human virome residents. However, neither NGS or PR will really address the problems posed by transmission of proteinopathies, not just CJD and AD but also potentially Parkinson's disease and maybe others to be discovered in the future. A revolution in understanding the nature of these agents, how they are transmitted and how they can be detected or eliminated from transfusion and transplant is urgently required.

Abbreviations

AD	Alzheimer's disease Aβ:amyloid-β protein
BKPyV	BK polyomavirus BVDV: bovine viral diarrhoea virus
BSE	Bovine spongiform encephalopathy CAA: cerebral amyloid angiopathy
CHIKV	Chikungunya virus CJD: Creutzfeldt-Jakob disease
DENV	Dengue virus ECDC: European Centres for Disease Control
HBV	Hepatitis B virus HCMV: human cytomegalovirus
HCV	Hepatitis C virus HEV: hepatitis E virus
HHV	Human herpesvirus HIV: human immunodeficiency virus
HPgV-1	Human pegivirus type 1 HTLV-I/II: Human T-lymphotropic virus types I and II
IAV	Influenza A virus ICER: incremental cost-effectiveness ratio

LCMV	Lymphocytic choriomeningitis virus MERS-CoV: Middle-East respiratory syndrome coronavirus
MPXV	Mpox virus MSM: men who have sex with men
NAT	Nucleic acid testing NGS: next-generation sequencing
ONT	Oxford Nanopore Technologies PrEP: pre-exposure prophylaxis
PrP	Prion protein PR: pathogen reduction
QALY	Quality adjusted life year SACTTI: Standing Advisory Committee on Transfusion Transmitted Infections
SARS-CoV-2	SARS coronavirus type 2 SHoT: Serious Hazards of Transfusion
SoHO	Substances of human origin TTI: transfusion-transmissible infection
TTTI	Transfusion and transplant transmitted infection
USUV	Usutu virus vCJD: variant Creutzfeldt-Jacob disease
WNV	West Nile virus

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