Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/20310
DOI URL: http://dx.doi.org/10.21474/IJAR01/20310

RESEARCH ARTICLE

NEW EMERGING VIRUSES AND TRANSFUSION SAFETY

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Manuscript Info

Manuscript History
Received: 25 November 2024
Final Accepted: 28 December 2024
Published: January 2025

Key words:-
SARS-CoV2, HTLV, HHV-8, Mpox, Arbovirus, Transfusion Safety

Abstract

Blood transfusion is one of the most sensitive and delicate activities in a health system, due to the human nature of the products used. Viral safety remains a major concern. SARS-CoV2, Ebola virus, hepatitis E, Human T-lymphotrophic viruses type I and II (HTLV), Monkeypox (Mpox), Human herpesvirus (HHV-8), Erythrovirus and Arboviruses. In addition to being infections transmitted by vectors (mainly mosquitoes), they have the common denominator of being responsible for epidermal explosions when the conditions for entomological expansion are met. These infections have the particularity of being responsible for a viremia that is generally short-lived (less than aweek on average), but which precedes the appearance of clinical signs by 1 to 2 days, a period during which a subject is infectious and can pass the filter of the pre-donation interview. The transfusion safety associated with SARS-CoV2, Ebola virus, Hepatitis E, HTLV, Mpox, HHV-8, Erythrovirus and Arboviruses were only recognized. The dawn of the 21st century for the oldest and much more recently for the others. This paradox is due to the fact that most of these viral infections have been known and described since the 1950s, mainly in tropical countries with a low socio-economic level where the transfusion risk has long been neglected. It was not until these infections became established in territories applying modern haemovigilance rules that transfusion safety was formally identified. In this work, we describe the different experiences of several countries that have experienced major obstacles when performing blood transfusions, due to epidemics of SARS-CoV2, Ebola virus, Hepatitis E, HTLV, Mpox, HHV-8, Erythrovirus and Arboviruses.

Introduction:-

Transfusion has long been recognized as life-saving and its safety has improved considerable over the years. Transfusion support can be described as an adjunctive treatment which, indicated with varying degrees of urgency,

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can treat patients with abnormalities affecting red blood cells and leading to major pathological consequences resulting in tissue hypoxia that can be life-threatening. These abnormalities can occur suddenly, in the event of hemorrhage, or subacutely, following a production defect secondary to treatment or to specific hematological pathologies [1]. Blood transfusion is therapeuticmedical procedure that involves taking safe blood from a donor as whole blood or blood products and given to another individual, a recipient or to the same person in the case of autologous transfusion [2]. However, this therapy is one of the most sensitive and delicate procedure in medical practice worldwide, Whole blood and blood products are of human origin, and for this reason it is regulated, under the control of a national organization and dedicated vigilance [3].

Like every treatment modality, it presents risks of various kinds, which should be weighed against the expected benefits. Some, of such risk like viral infections, are specific tocertain geographic locations blood transfusion centers, while others are linked to the use of blood products in health establishments, such as immuno-hematological risks and the risk of volume overload [4]. As a result, health authorities are subject to ethical of protecting humanity and technical of working on the most appropriate practices to guarantee the quality and safety of products [5].

The issue of safety in the healthcare world, and in particular patient safety, is a fairly recent concept in medical practice [6].

Indeed, in the field of transfusion, transfusion safety has been the primummovens of the development of this discipline from the beginning. It is defined by a series of measures, some specific, others indirect, ranging from stricter selection of blood donors to physicochemical treatment of blood products, which have been introduced over time to reduce or eliminate the immunological and infectious risks associated with the transfusion of blood and blood products [7]. Between all these different stages of the transfusion chain that must be supervised and controlled, transfusion centers implement a whole series of measures to strengthen transfusion safety. The hospital stage is crucial, it includes the decision to transfuse, the ordering of transfusion products, the transfusion itself and the assessment of the benefits and possible adverse effects for the patient. One of the means used to achieve this objective was the creation of a haemovigilance system. This system is based on a strict organization between the different actors at different levels, with precise tasks to be carried out [8].

The ultimate objective of haemovigilance is to contribute to the improvement of transfusion safety and the quality of care, and therefore to the optimal use of LSPs(called a labile blood product or LBP), which are products for therapeutic use with precise indications and a level of efficacy justifying their use [9]. The national transfusion system also experiences difficulties in its operation, particularly in terms offinancing, organization, management of equipment and personnel, blood supply and promotion of blood donation.

Diagnostic and epidemiological tools available in developed countries make it possible to distinguish post-transfusion cases from those transmitted by vectors. Emerging viruses can be imported into Morocco during blood donations by expatriates, migrants in Morocco, military personnel and occasional Moroccan travelers to sub-Saharan Africa.

Transfusion safety has so far remains a challenge due to changes in the nature and epidemiology of blood-borne viral infections, prompting transfusionists to maintain surveillance of active infections and exposure to major established viral infections identified in blood donors and to ensure that screening test performance remains optimalwith high efficacy and sensitivity. Monitoring genotypic variability within viral species may also be useful in establishing an international reference materials for the evaluation and validation of screening tests [10]. Therefore, our aim in this review is to describe our current understanding of the most recent viral outbreaks (SARS-CoV2, ebola virus, hepatitis E, Human T-lymphotrophic viruses type I and II (HTLV), Monkeypox (Mpox), Human herpesvirus (HHV-8), Erythrovirus and Arboviruses) that may challenge established reactive protective measures in place for transfusion safety.

EmergingViruses

1. SARS-CoV-2

The emergence of SARS-CoV-2 has led to the global spread of COVID-19, affecting human health. This virus is one of the three main coronaviruses that have appeared in the last 20 years. Its rapid emergence raised concerns about its impact on blood transfusion medicine. The main transmission route is respiratory, yet the pandemic raised questions about the safety of blood products. So far, there have been no reported cases of transmission through

blood transfusions from SARS-CoV, MERS-CoV, or SARS-CoV-2. Studies showed RNA detection in patients infected with these viruses, including asymptomatic and symptomatic SARS-CoV-2 patients at the time of blood donation. However, a case in Asia reported an asymptomatic donor who did not transmit the virus to blood recipients, indicating a minimal risk of transmission through blood [11]. Due to earlier uncertainties during the pandemic, blood donation centers implemented protocols to prevent infected individuals from donating, leading to significant blood supply shortages. The COVID-19 pandemic highlights the short- and long-term effects that emerging viruses can have on blood transfusion medicine. The qualitative detection of viral RNA is done using the RT-PCR method.

2. Ebola

Ebola virus (EBOV), which comes from bats, has gained attention for its ability to infect humans. It spreads through mucous membranes and non-intact skin and uses certain immune cells to reach lymph nodes where it replicates [12]. Ebola can cause serious outbreaks, especially in Africa, and belongs to the Filoviridae family, leading to severe hemorrhagic fever and potential death. Fruit bats are the main natural hosts of the virus. Human-to-human transmission is most likely through direct contact with infected fluids and can also occur through droplets and aerosols. The incubation period can last up to 21 days, complicating outbreak control. The Zaire strain is particularly deadly. Symptoms include flu-like signs, rash, and bleeding, and patients can transmit the virus through blood. Blood transfusions are essential for treatment, but precautions are necessary to prevent transmission during outbreaks, as the infectious dose is very low. It is unlikely that viremic patients with EBOV infection will be allowed to donate blood during an outbreak, as viremia is associated with symptomatic disease. However, infectious virus and RNA have been detected in various body fluids several months after resolution of clinical illness. Furthermore, the infectious dose would be about 10 viral particles [13], which is very low. Precautions should therefore be taken to avoid possible transfusion transmission.

3. Human T-lymphotrophic viruses types I and II (HTLV)

Human T-lymphotrophicviruses type I and II (HTLV) are RNA retroviruses that can be found in blood and other body fluids, mainly in lymphocytes. They are transmitted parenterally and are not commonly found in plasma or acellular fluids. HTLV is more common in some regions than others. HTLV-I and HTLV-II share many similarities but have different distributions and health effects. Screening for HTLV involves detecting antibodies for both types. While there is some cross-reactivity between them, it does not catch all cases of HTLV-II. Antibody levels are usually high and remain detectable after infection. Effective testing can help identify contaminated blood donations. To prevent HTLV transmission through transfusions, countries where HTLV is common should carefully consider implementing screening, using sensitive tests for anti-HTLV antibodies. Non-endemic countries should also test blood for HTLV before use in medical treatments [14].

4. Monkey pox

Monkeypox (Mpox) is a viral disease that has recently spread around the world, with over 87,000 cases reported by April 2023 [15]. It is caused by a double-stranded DNA virus and can cause symptoms like fever, chills, and body raches [16]. The incubation period lasts from 5 to 21 days [17]. The virus spreads mainly through sexual contact, direct contact with sores, and contaminated objects, though there are concerns about blood transmission [18]. Rapid systemic spread and viremia in infected patients have been reported, raising concerns about blood-borne transmission, and many have questioned the safety of blood transfusionsin relation to this virus, although the primary route of transmission is skin-to-skin contact [19].

5. Human herpes virus

Human herpesvirus (HHV-8) causes Kaposi's sarcoma and is mainly spread through sexual contact. Its prevalence is about 2-4% in blood donors in the United States and 2% in France. While there are suggestions of transmission through blood transfusions and kidney transplants, a study in Kenya found higher rates of seroconversion in transfused individuals but no clinical infections. Due to the low incidence of the virus, no specific preventive measures have been established, except for leukoreduction of lab blood products [20].

6. Erythrovirus

Erythrovirus, also known as parvovirus B19, was found in 1975 while testing blood for HBsAg. It causes a short period of high virus levels in the blood but can persist at low levels in some cases. The virus targets red blood cell precursors, hindering the production and development of red blood cells. It can lead to aplastic crisis in individuals with various haemolytic disorders and can be transmitted from pregnant women to their babies, causing severe

complications. The virus circulates in the bloodstream about seven days after infection, with very high viral load during the acute phase. To prevent spread, plasma donations identified as parvoviremic are excluded from pooling [21, 22].

7. Hepatitis E

Hepatitis E virus (HEV) causes acute hepatitis, which often resolves on its own in most adults, but can become chronic in those with weakened immune systems. Discovered in 1983 during an outbreak among Soviet soldiers [23], is classified into four genotypes: 1, 2, 3, and 4. Genotypes 1 and 2 mainly occur in developing regions like Africa and Asia and are linked to waterborne outbreaks. Genotypes 3 and 4 can infect humans and pigs, with genotype 3 found worldwide and genotype 4 mostly in Asia [24]. There is rising concern about HEV transmission through blood transfusions, as donors are often asymptomatic and not regularly tested, leading to reported cases in transfused patients [25].

8. Arbovirus

Arboviruses like dengue, Japanese encephalitis, West Nile, chikungunya, Zika, and yellow fever viruses cause serious diseases. They are associated with varying degrees of morbidity and mortalityin both rich and poor countries, often due to weak surveillance systems.

a. Dengue

Dengue virus, part of the Flavivirus genus in the Flaviridae family, has four types: DENV 1, 2, 3, and 4. Infection provides long-lasting immunity to one type, but not to the others, meaning previous infections can increase the risk of severe illness. Fifty to ninety percent of cases, are asymptomatic. Symptoms usually appear three to seven days after exposure, starting with a sudden fever, headache, muscle pain, joint pain, and sometimes ~~a~~ rashes. Severe dengue can occur when fever subsides, leading to severe blood vessel leakage, shock, or major bleeding.Viremia, or the presence of the virus in the blood, starts a day before symptoms and lasts for up to seven days. Diagnosis is done through tests that detect the virus's genetic material within seven days of symptoms starting and through serological tests from the fifth day [26].

b. West Nile Virus

West Nile virus emerged in North America between 1999 and 2005 and is known for being spread by insects and tissues. There have been confirmed cases of transmission through blood transfusions in the United States since 2002, leading to the implementation of donor screening by viral genomic diagnosis in July 2003. In Europe, donors returning from areas with human transmission must wait 28 days before donating [27].

c. Yellow fever (YF)

Yellow fever virus is a type of flavivirus. The disease mainly occurs in Africa and South America, especially in Brazil and French Guiana. There is a possible risk of spreading yellow fever from vaccinated travelers and military personnel visiting areas where the virus is common in sub-Saharan Africa and Central/South America. Those vaccinated should wait 2 weeks before donating blood [28].

d. Chikungunya and Zika

Two other arboviruses, chikungunya and the Zika virus, identified in the 1950s in tropical Africa (Uganda in 1949 for ZIKV and Tanzania in 1952 for CHIKV), have recently been the subject of various epidemics in the Indian Ocean, the Pacific Ocean and now in Central (CHIKV) and South (ZIKV) America.

Chikungunya virus belongs to the genus Alphavirus of the Togaviridae family. There are three genotypes: West African, Asian and East African, Central and South African genotype (ECSA). The strains circulating in the Indian Ocean since 2005-2006 and in India belong to the ECSA genotype [29]. They have a mutation, A226V, which gives them better adaptation to the Aedes. albopictus mosquito, vector of the epidemic in La Réunion and the Indian Ocean islands in 2005-2006. The strain responsible for an epidemic in Italy in 2007, from a case imported from India, also had the A226V mutation [30]. Symptoms appear after an incubation period of 1 to 12 days (average 2 to 4) and include sudden onset of fever, often severe arthralgia, myalgia, headache and often a rash. They last one to two weeks but arthralgia can persist for several months or even years [31]. These persistent arthralgias affect 13 to 70% of patients depending on the study. During the outbreak in La Réunion, 57% of patients had persistent arthralgia at 15 months [32]. Viremia begins the day before symptoms and most often lasts up to seven days. Diagnosis is based on detection of the viral genome by RT-PCR up to seven days after the onset of symptoms and on serology from the fifth day. There are only a few commercial reagents and no technique for routinely screening donated blood or blood donors currently [33].

The Zika virus is a flavivirus and is caused by an arbovirus (virus transmitted by insects), belonging to the Flaviviridae family, of the flavivirus genus. The insect vector of the disease is the female mosquito of the genus Aedes which is identifiable by the presence of black and white stripes on its legs. The species currently capable of transmitting the Zika virus is the Aedesaegypti, native to Africa. The Aedesalbopictus (tiger mosquito, native to Asia) could also prove to be a vector of the Zika virus, as it already is for dengue and chikungunya [34]. This virus was first isolated from a rhesus monkey in 1947 in Uganda. Anti-Zika antibodies have been found in primates in Africa and Asia, suggesting the existence of a sylvatic cycle for this virus [35].Vector transmission occurs when the mosquito becomes infected with the virus during a blood meal from a person infected with the Zika virus. The virus multiplies the mosquito without harming the insect. Then, during a subsequent bite, the mosquito releases the virus into the blood of a new person. Symptoms appear 3 to 12 days after the bite, but during this time, the person can infect other mosquitoes if bitten again. Therefore, patients with Zika virus should avoid being bitten in order to interrupt the cycle of virus transmission [36].

The main route of transmission of Zika virus is the Aedes mosquito. However, sexual transmission of the virus may also be possible, with limited evidence in a few cases [37]. Presence of the virus in biological fluids In addition to blood and semen, has been established. Finally, the viral genome has been detected in urine when the virus was no longer detectable in blood and this two to three weeks after the onset of clinical signs [38]. The disease appears to be asymptomatic in 74–81% of cases with an incubation period of 3 to 12 days [38]. Symptoms are often very mild or absent. When symptomatic, the infection may include a rash, fever, arthralgia and conjunctivitis. Zika virus infection during pregnancy is a cause of congenital Zika syndrome and may also be a trigger for Guillain-Barré syndrome [39].

It is based on the detection of the viral genome by RT-PCR.

- in the blood: viremia is transient and the viral load low and brief (0 to 7 days after the onset of clinical signs);
- in saliva: the virus is present and detected for the same duration as in the blood; the value of the viral load is unknown;
- in urine: the virus is present up to 10 days after symptoms and the viral load is higher [40].

Detection of specific IgM +/- IgG anti-Zika antibodies. Zika virus-specific IgM can be detected by ELISA or immunofluorescence in the serum of infected patients, approximately five days after the onset of symptoms and can allow a later diagnosis of the infection than RT-PCR on blood and urine. The major problem with the use of this serological test, with the techniques currently available, is its unreliability due to the existence of cross-reactions between antibodies (anti-Zika) and those from infections by other flaviviruses, in particular the dengue virus which very often co-circulates with the Zika virus. In other words, a positive result for the search for anti-ZikaIgM does not specifically prove an infection by the Zika virus and a titration of neutralizing antibodies (at least those of the Zika and dengue viruses) by seroneutralization must complete the serological test to make a diagnosis. It should be noted, however, that the seroneutralization test itself is sometimes difficult to interpret, particularly in subjects previously infected with another flavivirus or vaccinated against a flavivirus, such as the yellow fever virus. In addition, this technique is quite cumbersome and complex (secure laboratory), which makes it difficult to implement in routine diagnosis [41].

Transfusion safety

In addition to non-specific measures for the clinical selection of donors and the exclusion of those presenting potential risks, particularly following a return from a risk area, the viral safety of PSLs is mainly based on three types of measures:

- Targeted biological tests for the detection of certain viruses,
- PSL leukocytedepletion
- Implementation of large-scalepathogen inactivation techniques.
- These three types of measures are briefly described below.

1. Targetedbiological screening tests

The tests focus on major viruses like HIV, HBV, HCV, and HTLV. They include immunological methods to detect antibodies and serum antigens, as well as molecular methods for viral genomic diagnosis, used in France and Morocco for HIV, HCV, and HBV. Molecular tests help to shorten the detection period and screen for variant viruses not found by immunological tests. Recent findings show that molecular detection of HBV in blood donors can prevent contamination from variant strains [42]. Specific tests can also identify emerging viruses. For instance,

WNV was diagnosed in North America during transfusion cases, and testing was established for CHIK-V during its epidemic in Réunion. While any emerging agent can potentially be screened, adapting these methods for widespread use presents organizational and economic challenges [43].

2. Leukocytedepletion techniques

France has been using a method since 1998 to lower the number of leukocytes in blood below 106 per unit. This method is very effective at removing certain intracellular viruses like HHV-8, and retroviruses such as HIV and HTLV [44]. It also cuts the risk of prion disease by about 50% and helps reduce the chances of HLA immunization and infections by bacteria or protozoa.

3. Non-specific inactivation of pathogens

Various methods like Epstein Barr, Cytomegalovirus and Human herpes 8for non-specifically inactivating infectious agents in PSLs are detailed in many publications. These technologies effectively target a wide range of agents, including new and emerging ones [44].

4. Plasma inactivation techniques

Techniques for plasmainactivation focus on specific methods. These include physicochemical treatments using solvent-detergents that eliminate enveloped viruses by breaking down their lipid envelopes. There are also treatments using phenothiazine dyes like methylene blue, which produce oxidation in viral genomes when activated by light. Additionally, physical nanofiltration techniques are used to filter out organisms larger than the nanofilter's pores.

5. Inactivation techniques suitable for plasma and plateletconcentrates

Three techniques that use ultraviolet light are suitable for treating plasma and platelet concentrates. The first is the Intercept process, which uses amotosalen as the active ingredient. The second is the Mirasol process, which uses riboflavin (vitamin B2). The third is the Theraflex UV process, which combines ultraviolet light with intense shaking to create cyclobutyl rings. These methods are effective against many pathogens, including viruses, bacteria, and protozoa. While platelet yield decreases, especially with amotosalen, their activation, adhesion, and aggregation properties remain. The Intercept system was tested successfully during the CHIK-V epidemic in Réunion.

6. Redbloodcellconcentrate inactivation techniques

Red blood cell inactivation methods are currently being tested in clinical trials. Three main approaches using nucleic acid blocking agents are in advanced evaluation. The first method uses riboflavin (Caridian), the second is based on a binary ethyleneimine called Inactine (PEN110) from Vitex, and the third involves an alkylating agent named S3003 or amustaline (Cerus), which works by exposure to acidic pH rather than irradiation.

Conclusion:-

Surveillance is essential to identify emerging viruses in potential reservoirs, biological vectors and genome sequencing, allowing early detection of new variants. These measures are essential to prevent future epidemics and pandemics.

For decades, global efforts have been made to reduce transfusion-transmitted infections and successfully mitigate the risk of many infectious diseases. However, complete elimination of transfusion-transmitted infections has not yet been achieved. Therefore, efforts to improve transfusion safety must continuefor a better blood transfusion services globally.

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