Introduction

Blood product transfusions have become the most frequently performed “procedure” in the inpatient population in some national healthcare systems (1). With a growing number of transfusions, the concerns surrounding blood safety have also grown in proportion. These concerns include whole blood versus component therapy, appropriate transfusion triggers, product ratios in massive transfusions, and transfusion transmitted infections. In this review, we will focus on how to respond to new microbial threats in blood safety and lessons learned from previous emerging infections. In order to respond appropriately to these threats, we must examine our present form of response and create a new approach based on the tools currently available. Many factors have changed since the emergence of hepatitis and the HIV epidemic, some of which may place us at a higher risk and others that enhance our ability to combat new threats. Rapid urbanization and increased global travel have increased our risk, while improved detection of outbreaks and intervention methods have protected us. The appropriate response to new microbial threats cannot simply consist of added testing; it must include improving safe blood supply, early recognition of zoonoses, assessment of public threat, economic analysis, and evidence based intervention.

Historical perspective

Our current culture of hypervigilance and immediate response to microbial threats in blood products is appropriately based on our historical experiences. The first publication to demonstrate that HIV was a transfusion transmissible infection was published in 1982, and the 3 years that followed were filled with denial, disagreement between transfusion societies, and slow test development due to lack of funding (2). It wasn’t until 1985 that the FDA granted licenses to blood collection centers to perform screening of products by ELISA (3). And this was considered a relatively rapid response on an international scale. Many countries would follow in the footsteps of the United States, if it was financially feasible. An estimated 12,000–25,000 cases of transfusion transmitted HIV occurred in the United States during that time before testing was implemented, and as a result, public confidence...
was lost (4).

The experience with West Nile virus (WNV) in the United States was much different, not only because of our heightened sensitivity, but also because of an improved understanding of virology, epidemiology, and test development. 23 cases of transfusion transmitted WNV were recorded in 2002, and a ribonucleic acid (RNA) test was in place by 2003 (5). The approach to Zika virus in the Americas was similar and mostly based on the observed effects on fetal development. Evidence of its ability to be transmitted via transfusion was based on 4 case reports from Brazil and its risk to the blood supply remains low (6-8).

Rapid development of testing kits and implementation of mandatory donor screening was widely deemed a success and kept public fears under control. In the aftermath, what is rarely discussed outside of the blood donor center community is the delay in infectious disease screening due to the send out Zika virus test, added cost, and increasing data suggesting a waning pandemic and very low risk. An American Red Cross study that followed implementation of mandatory Zika testing found nine positive results from donors over a 15-month period. This resulted in a cost of $42 million, or approximately $5.3 million per positive result. Many have suggested revisiting our testing policies in light of the emerging data and perhaps limiting screening to a small volume to serve high risk recipients (9,10). But are we capable of reversing screening decisions after an FDA guidance or do we need to have a more proactive and measured approach to assessing microbial threats before reacting?

Safe blood supply & early recognition

Developing countries face a much larger problem regarding blood safety and the debate about test development and implementation is secondary to creating a stable voluntary donor base. Establishing a safer donor population as a primary measure would combat emerging threats but also reduce risks from existing ones. The major consequence of not having a voluntary donor base is the increased risk that is associated with paid donors. This risk is exacerbated by increased prevalence of transfusion transmissible infections in low income countries and barriers to high quality and complete infectious disease screening. The proportion of blood donations testing positive for HIV in high income countries is 0.003% (range <0.001–0.04%) while the rate in low income countries is 1.08% (range 0.56–2.69%) (11). That is a 360 times higher rate for the entire donor population and does not even account for the differences between paid and voluntary donors. This would not be such a pressing issue if donor screening was 100% implemented and effective, but that is largely not the case in some low income settings. Many countries deal with shortages of test kits and do not have quality assurance standards in place. Thirty-five out of the 180 countries surveyed in 2013 reported an inability to complete infectious disease testing for HIV, HBV, HCV, or syphilis because of test kit shortages. Lower income countries have higher rates of discarded blood, with the largest contributing factor being the high rates of infectious disease test positive donations. Low-income countries reported a discard rate of 9.0% whereas the discard rate in high-income countries was only 5.7%. This can have a significant impact on the economics of collecting blood and additionally emphasizes the need for appropriate utilization.

The first step in our approach requires a recognition of potential microbial threats and an assessment of their risk to the blood supply. Fortunately, we have an extensive array of resources available to us today that did not exist in the 80’s and 90’s. This was first limited to major national and international organizations that would report outbreak information as it was passively gathered, but has now evolved into event-based active surveillance systems which analyze multiple sources for trends (12,13). The Global Public Health Intelligence Network (GPHIN) is one of these systems and it extracts information from news reports, web searches, forums, and even social media (14,15). GPHIN was able to identify a growing respiratory illness during the Severe Acute Respiratory Syndrome (SARS) outbreak in China and report it to the World Health Organization before traditional methods triggered a response (15).

After identifying a potential threat, the next step may involve computational simulation of an epidemic. One of the well-established models for this purpose is the Global Epidemic and Mobility (GLEAM) model (www.gleamviz.org). These models incorporate human mobility and various other transmission factors into divided subpopulations to predict epidemic spread and peak. Our ability to simulate regional spread of a microbial threat can play an important role in deciding where and when to implement an intervention. This strategy is currently being used in the Northeast United States where Babesia microti infections are more prevalent than in the rest of the country (16). The American Red Cross has prospectively screened donations in endemic areas since 2012 and found 1,299 reactive donations (17). Not only does this method ensure a safer blood supply, it is a cost effective process in risk mitigation. Of course this approach also needs to consider the morbidity...
associated with the pathogen in question and its potential to be transmitted via transfusion of blood products.

### Transfusion transmission risk

In order to consider a microbe a threat to the blood supply, it must have demonstrated the ability to be transmitted in blood products from case reports or theoretically pose a significant risk based on endemic spread, asymptomatic viremia period, and high viral load during infection. One issue that arises with using inferred (theoretical) risk models is that they do not account for differences in infectivity between donors and the general population, transmission efficiency of a pathogen, or the effect of processing and storage on a pathogen. Hemovigilance data suggests that true transfusion transmission rates are lower than population or donor infectivity rates. This overestimation may result in increased incentive to implement intervention and skew the economic analysis (18-20).

One well established risk model for emerging infectious diseases is the European Up-Front Risk Assessment Tool (EUFRAT). This model not only estimates the rate of asymptomatic individuals attempting to donate blood, it is capable of calculating the actual risk of transmitting an infection to the recipient. The model creates this estimate by breaking down the transmission process into the following four sequential calculations:

I. Risk of an individual being infectious at the time of donation;

II. Number of donations collected from an infected donor based on prevalence from step 1 and donation frequencies;

III. Number of infected units released from inventory based on step 2 and after accounting for inactivation of pathogens due to processing, storage, and pathogen reduction technology (PRT) (if available);

IV. Risk of a recipient being infected based on above 3 calculations, transfusion transmission efficiency of the pathogen, and immune status of the population.

The EUFRAT model has been used to estimate the risk of two potentially emerging pathogens, chikungunya and dengue, and even estimated the residual risk that travelers to endemic regions pose to the blood supply upon return (21,22). The decision to use a risk model to determine intervention would vary and depend on characteristics of the pathogen in question. This would be reasonable for a well characterized infectious agent that is becoming endemic/pandemic but is not associated with high morbidity. It would likely be bypassed for a newly emerging threat that is uncharacterized or one that has known devastating sequelae, such as HIV. A point of interest here is that the FDA did not perform transmission modelling before implementing blood donor screening for Zika virus. **Table 1** summarizes information on several examples of known infectious agents that have been on the transfusion community’s radar and may pose a transmission risk.

### Economic and impact analysis

The economics of transfusion medicine is unique and controversial. In an ideal setting, there would be an abundant supply of regular volunteer donors and a limitless budget for screening tests and pathogen reduction. In reality, blood products are a limited resource and healthcare economics apply to them as well. This has been a controversial subject since the HIV epidemic. Government agencies have responded to new threats out of perceived public fear and pressure as opposed to calculated public health risks. Two terms that are reluctantly discussed in

<table>
<thead>
<tr>
<th>Infectious disease</th>
<th>Asymptomatic infection time frame</th>
<th>Total infectious period</th>
<th>Transfusion transmission</th>
<th>Other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chikungunya</td>
<td>0–3 days (23)</td>
<td>7–17 days (24)</td>
<td>Likely (25)</td>
<td>Transfusion transmitted cases not reported but high likelihood of suspicion</td>
</tr>
<tr>
<td>Dengue</td>
<td>1–2 days (26)</td>
<td>4–14 days (27)</td>
<td>Yes (28)</td>
<td>Rapid worldwide increase of population incidence (29)</td>
</tr>
<tr>
<td>Babesia</td>
<td>Widely variable</td>
<td>&gt;1 year (30)</td>
<td>Yes (31)</td>
<td>Higher prevalence and rate of transfusion transmission in NE USA (16,32)</td>
</tr>
<tr>
<td>Plasmodium</td>
<td>&gt;1 year</td>
<td>&gt;1 year (33)</td>
<td>Yes (34)</td>
<td>1.1% of blood donors in the US are deferred due to malaria risk after travel (35)</td>
</tr>
</tbody>
</table>
blood banking are cost-utility analysis (CUA) and quality adjusted life years gained (QALYs). CUA is used to estimate the ratio between the cost of a healthcare intervention and the benefit it produces in QALYs. QALYs are given a numerical value from 0 to 1, with 0 being the poorest state of health, and 1 being the best state. Many countries have established specific values per QALY that would make an intervention cost-effective compared to no intervention. For example, in many countries, the threshold for a valuable healthcare intervention is in the range of $50,000–$100,000/QALY in US dollars (36).

The controversy becomes very apparent because healthy life is given a monetary value, but this is an unfortunate reality in many low- and middle-income countries where there isn’t the option of adding an endless array of screening tests and PRT. This type of cost analysis has been outlawed in the United States with the passing of the Affordable Care Act due to thresholds resulting in age and disability discrimination for medical insurance coverage and reimbursements (37). Table 2 demonstrates various interventions in blood banking and their associated cost-effectiveness.

The above table demonstrates that interventions can be cost-effective when implemented in the appropriate scenario. On the other hand, they can be extremely wasteful when the donor population doesn’t warrant it or if there are intervention redundancies. Performing minipool nucleic acid testing (NAT) for HIV, HBV, and HCV alone is arguably within the cost-effectiveness threshold, but adding this testing to serology causes that cost to rise drastically. NAT for these viruses is known to detect infections with a shorter window period and our aim for the development of improved screening tools should be to replace previous methods instead of adding them on. This measure should not be viewed with a hard threshold and is only one factor in the economics. For instance, although the cost-effectiveness of HTLV screening in the Netherlands is poor due to low population prevalence and removal of the pathogen via leukoreduction, it is a relatively small added cost in screening because it is one additional analyte on the enzyme immunoassay platform (41). This caveat makes it difficult to reverse trends in infectious disease screening and can make it easy to add on additional tests without a legitimate risk when we are operating in a culture of immediate and excessive response to perceived threats.

The recently available PRT has the ability to effectively inactive viral, bacterial and parasitic infectious agents in blood products. It can be especially helpful in dealing with emerging infectious agents even before the blood bank community gets a chance to fully learn about a new infectious risk and develop testing strategies. A cost-effectiveness analysis of adding PRT to the existing extensive (and expanding) infectious disease marker testing system will likely demonstrate poor cost-effectiveness. To tackle the cost-effectiveness problem and to enhance blood safety without making safe blood less affordable, a reconsideration of our past approach of incrementally adding more and more testing and interventions into the blood screening process may be called for. One multi-institution study examined the effects of implementing pathogen reduced platelets and removing current testing and found that this would result in a significant offsetting of the added cost. If irradiation is also removed, future add-on tests are avoided, and there is decreased wastage by extending the shelf-life to 7 days, the process could offset approximately $140/unit (42). This could potentially result in a cost-equivalence or cost savings depending on the degree of redundant safety measures that are removed and the variable added cost of PRT platelets (approximately $100/unit) (43).

### Conclusions

The effective approach to deal with new microbial threats needs to be multifaceted and should follow a sequence

<table>
<thead>
<tr>
<th>Country</th>
<th>Intervention compared to no screening</th>
<th>Cost-effectiveness (US$/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>Individual NAT for HIV/HBV/HCV</td>
<td>17 (38)</td>
</tr>
<tr>
<td>USA</td>
<td>Minipool NAT for HIV/HBV/HCV</td>
<td>110,000 (38)</td>
</tr>
<tr>
<td>USA</td>
<td>Minipool NAT &amp; Serology for HIV/HBV/HCV</td>
<td>7,600,000 (39)</td>
</tr>
<tr>
<td>USA</td>
<td>Minipool NAT &amp; Serology for HIV/HBV/HCV with removal of p24 testing</td>
<td>6,100,000 (39)</td>
</tr>
<tr>
<td>USA</td>
<td>Recipient-targeted antibody and PCR screening for babesia in high endemic region</td>
<td>148,000 (40)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>HTLV screening of new donors</td>
<td>2,500,000 (41)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>HTLV screening of each donation</td>
<td>51,000,000 (41)</td>
</tr>
</tbody>
</table>
of evaluations and interventions that are proactive and preventative. The methodology should cast a broad net on infectious diseases and avoid targeted reactionary interventions. We have historically implemented various strategies that have a wide impact on existing and emerging transfusion transmitted infections and should continue to identify processes that have a similar effect. These include cold storage of blood products, leukoreduction, and pathogen reduction technology. This method starts with advanced outbreak monitoring and continued development of a safer blood donor supply. If an emerging pathogen is calculated to be a rising risk, and sufficient data exists, we must model the particular risk to the blood supply and not allow public perceptions to force decisions. This evidence based approach should then continue in any decisions regarding interventions and determine the added safety in the context of increased donor deferral, delays in distribution due to screening, and added cost that is forwarded to hospitals and patients. With this type of strategy in place, we will have a more effective and sustainable approach to new microbial threats and make informed decisions about the safety of our blood supply.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References
