

**Protecting
the Blood Supply
During Infectious
Disease Outbreaks**

**Guidance for
National Blood Services**

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Protecting the blood supply during infectious disease outbreaks: guidance for national blood services
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Preface

This guidance document has been produced by WHO to assist blood services in the development of national plans to respond to any emerging infectious threats to the sufficiency or safety of the blood supply, whether from an existing infectious agent that is changing in incidence and spread, or from a newly identified infectious agent. It is intended that this document be followed to guide the national blood service through the process of planning how to respond in a timely, controlled and appropriate way to any specific infectious threat that may subsequently emerge. It is acknowledged that it is not only the blood supply that may be affected by such emerging infectious threats; in those countries undertaking transplantation, the supply of cell, tissues and organs may also be threatened. Increasingly, blood services are taking overall national responsibility for transplantation in their capacity as the organization responsible for the collection, processing, storage and supply of cells, tissues and organs. This approach is both sensible and appropriate, as the overall donor selection and screening processes are the same or very similar. This guidance document can therefore also be used to assist those bodies responsible for the provision of cells, tissues and organs to prepare for an emerging infectious threat.

In the preparation of the document, WHO has tried to ensure that it has included all of the elements that would need to be considered by blood services, providing some background rationale for their inclusion and guidance on different response options that may be available. Importantly, blood services must consider both the threat from transmission of an infectious agent via transfusion and the threat from infectious agents that may have no or a very low risk of transfusion transmission but may have public health consequences. Such consequences could include interruption to the blood supply because of a lack of donors, with a resultant reduction in component availability; whilst the demand for some blood components may reduce, demand for platelet components is more likely to remain at a constant level. The consequences of illness in the population could also include disruption of a wide range of support services and supply chains. Although the two main threats are different and have different outcomes, they are both critical to the functioning of the blood service.

The elements included are those for which a blood service would need to obtain the relevant data, local or otherwise relevant to the country, to be used to inform their own risk assessments of that particular infectious threat. However, it is not possible to predict the nature of every infectious threat to the blood supply, and it is therefore expected that blood services will review the elements in the document and assess their own situation, needs, capabilities and resources, together with any additional relevant country-specific factors, in the development of their own response plans.

It may be useful if, ahead of any emerging threat, blood services review these guidelines and consider using them to develop a template for a national plan. Such a template would include all of the key elements that a blood service would need to consider when planning a specific response, and would lead directly to a risk assessment and subsequently to a decision-making process. Specific data about any emerging infectious threat can be entered into the template as they become available, enabling decisions to be made as much as possible on the basis of available evidence.

The annexes contain additional information and other factors that may assist blood services in the development of their own plans. They include an assessment tool that can be used to determine the level of threat of an individual emerging infectious agent, and basic risk assessment frameworks that may help in identifying and assessing risks to the blood service in relation to both loss of donors and donations and risk of transmission of infection via transfusion. Understanding the level of risk then allows the appropriate response to be determined and, as and when necessary, implemented.

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Glossary

Term	Definition
Affected area	Areas where locally transmitted cases have been identified
Blood service	The (national) organization with responsibility for the collection, screening, processing, storage and supply of blood and components for clinical use. The blood service may be a governmental body or run by a nongovernmental organization on behalf of the government.
Case definition	A set of diagnostic criteria that must be fulfilled in order to identify a case of a particular disease. Case definitions can be based on clinical, laboratory, epidemiological, or combined clinical and laboratory criteria. A set of criteria that is standardized for the purpose of identifying a particular disease is referred to as a “standard case definition”. A “surveillance case definition” is one that is standardized and used to obtain an accurate detection of all cases of the targeted disease or condition in a given population, while excluding the detection of other similar conditions.
Deferral	The temporary or permanent exclusion of a donor because of an identified risk. The risk may be to the donor’s health or to the safety of the donated products, and consequently to a recipient’s health.
Donor selection	The process by which potential donors of blood and other donated products are assessed for suitability prior to donation.
Emerging infectious disease	Infections that have recently appeared within a population or whose incidence or geographical range is rapidly increasing or threatens to increase in the near future. Emerging infections can result either from previously known infectious agents or from previously undetected or unknown infectious agents.
Hazard	A possible source of exposure to injury, harm or loss.
Incidence	The rate of new or newly diagnosed cases of a disease, generally reported as the number of new cases occurring within a specified period of time.
Infectious threat	The existence of an infectious agent in donors, with consequent potential threats to the supply of blood and other donated products through donor illness, or to patient safety if donations are collected from infected donors.
International Health Regulations	An agreed code of conduct adopted by the World Health Assembly in May 2005 to protect against the spread of serious risks to public health and the unnecessary or excessive use of restrictions in traffic or trade. The International Health Regulations (2005) came into force on 15 June 2007.
Molecular screening	Screening of donations for the presence of nucleic acids of an infectious agent.
National focal point	The national centre, designated by each State Party, to liaise with and be accessible to WHO and States Parties at all times for the purpose of giving effect to the International Health Regulations.

Nongovernmental organization	<p>A State-independent organization with which the United Nations has a relationship; an organization founded on private initiative in order to fulfil aims of public interest. A nongovernmental organization will usually:</p> <ul style="list-style-type: none"> ■ have the structure of an organization, with statutes and legal form; ■ be founded by individuals or organizations independent of the State; ■ make decisions independently of government authorities; ■ have non-lucrative aims of public interest and go beyond the interests of its own members.
Outbreak	<p>The occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season. An outbreak may last for a few days or weeks, or for several years. Any disease outbreak may impact blood safety or sufficiency.</p>
Preparedness	<p>Activities and measures taken in advance to ensure an effective response to the impact of a threat.</p>
Prevalence	<p>The actual number of cases of a disease alive either during a period of time (period prevalence) or at a particular date in time (point prevalence). Period prevalence provides the better measure of the disease load, since it includes all new cases and all deaths between two dates, whereas point prevalence only counts those alive on a particular date.</p>
Public health emergency of international concern	<p>An occurrence or imminent threat of an illness or health condition, caused by bioterrorism, epidemic or pandemic disease, or a novel and highly fatal infectious agent or biological toxin, that poses a substantial risk of a significant number of human fatalities or incidents or permanent or long-term disability.</p>
Risk	<p>An evaluation of the probability of occurrence and the magnitude of the consequences of any given hazard.</p>
Safety	<p>The minimization of any health risks to donors through the donation process and any health risks to recipients from donated products.</p>
Serology screening	<p>Screening of donations for serological evidence of the presence of an infectious agent.</p>
Sufficiency	<p>A secured supply of blood and components sufficient to meet the needs of the country's health care system.</p>

1. Background

Ensure that a safe and sufficient supply of blood and components is maintained during an infectious disease outbreak

The provision of a continuous supply of safe blood and blood components is an essential element of an effective national blood service and must be safeguarded against events that may negatively impact this requirement. However, there are situations in which either the supply of blood and components may be affected, or the safety of the blood supply may be compromised. Either or both of these situations may occur in the event of an infectious disease outbreak at local, national or global level, potentially resulting in (a) loss of donors, and consequently donations, due to exposure risk; and (b) risk of transmission to recipients through donations containing the infectious agent. The core principles in this guidance may also be applied to cells, tissues and organs (see section 10).

All national blood services must be able and prepared to respond rapidly in appropriate and proportionate ways to any infectious threat to safeguard the sufficiency and safety of the blood supply in their countries. To be able to do this, blood services must understand the implications and consequences of such infectious threats and how they may affect the activities of a blood service. The following questions are pertinent.

- Is the infectious agent present in or likely to enter the donor population?
- Is the infectious agent likely to be present in donated blood?
- Is the infectious agent likely to be transmitted to recipients via transfusion?
- Would the infectious agent cause any significant harm in recipients?
- Is the infectious agent one that, although unlikely to be transmitted via transfusion, would be a public health issue that may reduce donations and adversely impact infrastructure?

Blood services must have strategies in place that enable them to identify, assess and respond to such types of threats, and – importantly – to plan and act rapidly once a specific threat has been identified. Whilst blood services cannot control how a particular infectious threat may develop, they can influence the impact of such a threat on the blood service and the blood supply. Very often quick action not only minimizes any impact but also promotes a positive image of a proactive blood service.

Key elements in responding to an infectious threat are:

- early awareness of the existence of a potential threat;
- clear understanding of the implications of the threat;
- accurate and reliable information on the threat;
- identification of possible actions to respond to the threat;
- effective and accurate risk assessment of the threat to determine the most appropriate and proportionate action;
- clear communication about the threat, its impact on the population and its impact on the blood service and the supply of blood and components;
- clear communication of action to be taken;
- timely implementation of the agreed action;
- planned regular reassessment of risk to determine if, when and how risk has changed.

How a blood service responds to an infectious threat depends to some extent on the structure and organization of the blood service. Those blood services that are part of the governmental structure of a country are often more closely linked to the national public health system, and

this may facilitate a more rapid response with full government support. However, whatever the organizational structure and accountability, when significant infectious threats arise the blood service must actively work with the health care system and with other relevant government departments to ensure that the appropriate actions are identified and taken.

The blood service must be identified as a key service that may be negatively affected by such a threat. Consequently, it must be directly linked into any national emergency planning team and be fully supported in the actions to be taken to minimize risk to blood safety and sufficiency. Involvement of the government, and of the blood service by the government, is essential to ensure a timely, effective, appropriate and fully coordinated response to the threat. Communication must be constant and transparent so that relevant information is passed to the Blood Service as quickly as possible and in the same way the Blood Service must also pass relevant information back to the national co-ordination.

An important, and often poorly considered, issue when dealing with any threat is the proportionality of the response:

The actions taken by the blood service must be proportionate to the threat.

Does the level of the threat really justify the planned response? There is always a danger that, in the rush to counteract an emerging infectious threat, the response of the blood service far outweighs the actual level and extent of the threat. This is understandable, given the potential adverse publicity surrounding blood safety issues, but at the same time it can be problematic, as there is a danger of the blood service locking itself into a strategy that it cannot sustain. A proportionate response to the threat can be hard to judge and depends on having accurate and reliable information available, together with the ability to properly analyse and assess the information. The existence of a potential threat in a particular location does not require all blood services globally to immediately implement protective measures; it simply means that blood services should have plans in place on how they will respond if their own jurisdiction is threatened. Similarly, the importation of a single case of an emerging infectious agent should not automatically trigger implementation of protective measures; rather, the situation should be monitored and appropriate and proportionate measures implemented, only increasing the level and extent of protective measures if the threat develops within the country.

However, no matter how good the advance planning, the key to the response to any infectious threat is the availability of accurate and reliable information about the infectious agent, including biology, pathology, epidemiology, normal mode of transmission, case numbers, laboratory identification and confirmation. To be able to determine the appropriate and proportionate response, this information must be available as soon as possible, and must be as accurate as possible. Obtaining and collating such information requires not only a national approach, but also a regional and global approach that ensures broad capture of all of the required information and its subsequent dissemination. The wide range of expertise needed to achieve this aim may be only partially present in many countries and may not exist at all in affected countries. Recent major international infectious disease outbreaks, some of which have had broad global effects, have demonstrated the importance of integrated global responses, utilizing expertise and resources from a number of different countries to focus on the outbreak and determine appropriate courses of action. Any country affected by a significant infectious outbreak must act as quickly as possible to contain and minimize the effects of the outbreak, if necessary seeking external help and support.

2. Global collaboration in monitoring for infectious threats to the blood supply

Monitor for approaching infectious threats that may impact the blood service

Although individual blood services need to assess their own risks and determine their own responses to any emerging infectious threat, many countries depend on the international responses to such infectious threats to provide the information and data needed to inform any national responses. Only a limited number of institutions and organizations globally have the considerable resources needed – knowledge and expertise, laboratory facilities, organizational ability and financial means – to thoroughly investigate infectious disease outbreaks, identify the infectious agent, perform the required epidemiological studies and disseminate the information. Effective responses to any emerging infectious threat therefore require coordination on a global basis to ensure that outbreaks are investigated effectively, and that the information gained is then made available globally. Not only is such information necessary to safeguard the blood supply, it may also assist in protecting the health of the population as a whole.

2.1 MONITORING FOR EMERGING INFECTIOUS THREATS

All blood services should be actively monitoring for emerging infectious threats to blood safety, either themselves or through an appropriate existing national or international programme that they can access. It is only through monitoring for such threats that blood services can prepare themselves in advance, allowing a more measured and effective response.

All countries should have in place basic public health protection measures, including continuous monitoring for emerging infectious threats. Not all of these will be threats to blood services and the blood supply. Nevertheless, any national monitoring programme should be aware of the need to consider such threats and to include the blood service as a key stakeholder.

2.1.1 WHO surveillance of emerging infectious diseases

As stipulated by the International Health Regulations (2005), the World Health Organization (WHO) is mandated to protect international public health security by ensuring effective global surveillance of all hazards, including infectious disease threats. This entails that emerging public health threats are detected early; that the response is appropriate and based on well-founded risk assessments and best practices; that the international community is provided with timely and accurate information about the event; and that international assistance, when requested, is rapidly provided to control threats at their source.

WHO continuously monitors public health threats through the Epidemic Intelligence from Open Sources or EIOS, an electronic platform that detects and monitors threats of known or unknown etiology by combining and monitoring a wide range of information sources (for example, news, media, social media, blogs and specialized news aggregators) in any language. These are filtered, collated (initially electronically) and then assessed by WHO for reliability and accuracy, including through collaboration with the affected country to have the event verified through the designated national focal point for International Health Regulations

(2005).¹ The national focal point plays a crucial role in communications involving WHO and national bodies engaged in the implementation of the International Health Regulations (2005), including through reporting and notification to WHO of health events that may constitute a public health emergency of international concern. The national focal point is normally in the department of communicable diseases (or equivalent) within the ministry of health or within the central public health institute and is expected to disseminate any relevant outbreak information to the appropriate national authorities and bodies so that they are fully informed and the appropriate action can be taken.

Following the identification of a potential public health threat, WHO offers assistance and carries out a joint risk assessment with the affected Member State through the national focal point to evaluate the likelihood and impact of adverse public health consequences. This process is crucial as it determines the course of action to be undertaken in response to a health threat.

All the available information is then collated by WHO and is disseminated globally through the International Health Regulations Event Information Site, a secure website accessed by national focal points, selected organizations and technical networks.

2.1.2 Open surveillance of emerging infectious diseases

There are many surveillance tools available. In some countries, depending on resources and capabilities, the national focal point may be monitoring continuously or undertaking event-based surveillance and disseminating the information obtained.

The use of open online tools such as HealthMap, ProMED (a programme of the International Society for Infectious Diseases)² and others provide an additional very quick and easy way for any blood service to set up a basic monitoring system, which can subsequently be added to from other sources. Individuals as well as institutions provide data to ProMED so that emerging events can be reported very quickly from local sources, even if the causative agent has not yet been identified or confirmed. The European Centre for Disease Prevention and Control³ and the United States Centers for Disease Control and Prevention⁴ are both bodies that actively monitor emerging outbreaks and may provide advice and guidance in relation to the safety of a range of donated substances. This information is made freely available online.

2.2 ASSESSMENT OF MONITORING REPORTS

Monitoring can identify a wide range of potential infectious threats. Most health monitoring programmes, however, look at a wide range of factors extending beyond threats to blood safety or sufficiency. Blood services therefore need access to relevant information so that they can filter and identify those potential or actual threats that may specifically impact the blood supply, assess each threat, and respond appropriately and proportionately. Regular continuing analysis and assessment of monitoring reports are needed to identify the relevant threats and, ideally, to grade the level of threat from “no action required” through to “immediate action required”. This will enable threats that only require continued monitoring to be differentiated

¹ World Health Organization. Strengthening health security by implementing the International Health Regulations (2005) (<http://www.who.int/ihr/nfp/en/>).

² International Society for Infectious Diseases: <http://isid.org>.

³ European Centre for Disease Prevention and Control: <https://ecdc.europa.eu/en/home>.

⁴ United States Centers for Disease Control and Prevention: <https://www.cdc.gov/>.

from those where specific action is now needed. Such analysis and assessment can be performed by the blood service, if necessary utilizing appropriate expertise from other national agencies or organizations.

This process can be simplified if a system is put in place that collects and collates all infectious disease reports, including those related to known and emerging infectious agents appearing over a defined and appropriate period, into a single document that would then be analysed and assessed by the blood service, along with actions undertaken. Annex 1 contains an extract from a monthly monitoring and surveillance report used by a national blood service to provide information on potential emerging infectious threats. The report is reviewed monthly and each entry is assessed, and the identified action level recorded. Although resources are needed to develop such a programme, the investment is minimal given the information available online. At the simplest level all that is required is a system of regular monitoring of global infectious disease reports, filtering of those of most relevance to a blood service and generating a regular report.

3. Accurate and reliable information about a threat

Obtain accurate and reliable epidemiological and surveillance data and analyse the data appropriately

3.1 INVESTIGATION OF OUTBREAKS

The initial investigation of any suspected infectious disease outbreak provides the initial data and impetus from which the subsequent and expanding investigations stem. Globalization of scientific and health care resources has significant benefits, as expertise can be utilized on a global basis, not only to investigate outbreaks but also to teach and train at local levels. The investigation of any emerging infectious disease outbreak requires considerable resources. Whilst financial resources are an important element, having the knowledge, expertise and scientific resources to investigate and identify outbreaks is also crucial (though such resources are often limited).

The global population is highly mobile, as modern global transport systems enable people, and any infectious agents that they may be carrying, to move over extensive areas and long distances very quickly. This potentially exposes large numbers of people to infectious agents, as demonstrated by a series of recent virus disease outbreaks – chikungunya (2014), Ebola (2015) and Zika (2015–2016). Outbreak investigation, although it may initially centre on a single country or region, should involve international collaboration using the international expertise available. This will enable outcomes and findings to be generated and disseminated more quickly, allowing individual blood services to review and assess the information and implement any actions required in a timely manner.

In most cases the initial investigations identify the infectious agent, if it is not already known, and enable a link to be made between the presence of the agent and any adverse clinical effects, although the full extent of these may not be fully understood in the early stages of an outbreak. Unfortunately, the potential for transmission of the infectious agent through blood and other donated products is not one of the first things considered during a disease outbreak. Blood services therefore need to alert public health services and governmental departments to this issue so that relevant information can be sought as soon as possible.

3.2 EPIDEMIOLOGY

Accurate and reliable epidemiological and surveillance data on a disease outbreak are essential, as are clear case definition and reliable and accurate incidence and prevalence figures. However, to produce accurate figures, reliable laboratory identification and confirmation of cases are needed. A disease outbreak may involve an existing infectious agent that is increasing in incidence and spreading, or a “new” infectious agent to which the population has not been previously exposed.

The resources available to a country and the extent of its surveillance system will influence its ability to provide accurate and reliable data on national case numbers. To obtain those and other data, blood services should work closely with national surveillance and epidemiology teams. If there are no national data currently available, the accuracy and reliability of any external data need to be assessed in collaboration with national surveillance and epidemiology teams prior to making decisions based upon those data alone.

WHO defines a disease outbreak as follows: “The occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season. An

outbreak may occur in a restricted geographical area, or may extend over several countries. It may last for a few days or weeks, or for several years.” Any disease outbreak may affect blood safety or sufficiency.

3.3 ENDEMIC OR IMPORTED

When a disease outbreak occurs, whether the infectious agent is already present and established in the country is an important factor influencing how the blood service responds and the time frame for any response.

3.3.1 Infectious agent already present or endemic

An outbreak of an infectious agent already endemic (at a low level) within a country may result in a more rapid spread and therefore more immediate pressure on the blood service, but there may also be mitigating factors such as immunity within the population as a whole, or existing control measures that may be in place.

Any infectious agent already present in a population or country may spread more rapidly if there is a change in the exposure rate, which may be due to a change in vector, an increase in population susceptibility or a decrease in existing control measures. If the infectious agent was already present in the population but is now spreading, reasons for the change must be determined. Changes to the donor deferral criteria may also be required if there is a new or additional risk present in donors that needs to be identified and included.

The presence of natural or vaccine-induced immunity in the population as a result of previous exposure or vaccination programmes may also help prevent any rapid spread within a population. Pre-existing immunity may favour the collection of donations from regular and previously exposed donors, reducing the risk of the agent entering the blood supply. Similarly, recipients may have pre-existing immunity and may therefore be less likely to acquire infection via blood and blood components.

3.3.2 Infectious agent not already present

For many blood services, the situation most likely to occur is the appearance or emergence of an infectious agent elsewhere in the world that may present a threat to blood services but is restricted at a local level, at least at the beginning of the outbreak, to imported cases. At this stage deferral of donors who have been in an affected area and thus potentially exposed to the infectious agent is often the most appropriate and proportionate initial response to the situation.

Whether such an infectious agent could be successfully imported into a currently unaffected area depends on a number of factors. The presence of a means of spreading the agent is a key requirement. This is often an arthropod vector but there may also be other direct human-to-human routes (outside the realm of health care). The individual imported cases must be sufficiently infectious and the infected individuals must be able to pass on a viable infectious agent, directly or indirectly, to other susceptible individuals. From the blood service perspective, the primary target is those donors who may have been directly exposed to the infectious agent because of travel or residency in an affected area. The secondary target may then be close contacts of such travellers, but this depends very much on the determined routes of transmission of the infectious agent. Whether the infectious agent could then spread more widely is very dependent upon whether a specific vector is involved and whether that vector is present. In the recent outbreaks of West Nile, chikungunya and Zika viruses the spread of the vector was the primary trigger for the spread of the infectious agent into previously unaffected areas.

3.4 DEFINING AN AREA AS AFFECTED

Identifying those donors who should be deferred entails knowing where the risks lie, and this requires accurate information on the development of a disease outbreak. Key questions include: When does a country or region become affected? How many cases need to be identified before a country is defined as affected, and can then be included in a list of affected countries from which returning travellers should be deferred from donation?

Affected areas can be defined as those reporting at least one confirmed locally acquired case within a defined period, normally one to three months. However, to properly understand the situation and to ensure case reports are only of confirmed cases, information is also needed on the rate of increase of incident infections.

The accuracy and reliability of reporting is critical, especially when an unaffected country is formulating an effective deferral process for donors recently returned from affected countries. In many poorly resourced affected countries with limited ability to identify and confirm cases, and with limited monitoring of the situation across the country, it is likely that there will be significant underreporting of the situation. For each case reported there could be many more unidentified cases, especially early in an outbreak. This must be taken into account by countries using such external data to determine travel deferral guidelines.

3.5 REMOVING AFFECTED STATUS

Any response to an infectious disease outbreak should include consideration of how to respond as the incidence of infections decreases. Infections commonly decrease to the point at which the outbreak is either over or is no longer affecting the blood supply in a country that had previously been affected; at this point, the implemented measures could be relaxed or removed altogether.

Lack of new cases over a defined period, say 3–12 months, is a generally accepted measure of the end of an outbreak. However, a background level of infection may remain in a country if the vector is still present or a route of human-to-human transmission remains. The infectious agent is then considered to be endemic. In those countries where the blood service or its regulator (if there is one) has implemented protective measures because of the outbreak, formal removal of those measures by the blood service could also be used by other national blood services as a signal that the country is no longer considered to be affected.

4. Understanding the implications of the threat

Obtain information on the biology and pathology of the infectious agent

Infectious disease outbreaks are not unusual, but most are localized, involve common infectious agents, and are quickly and easily contained. In most cases such outbreaks have little, if any, impact on blood safety and sufficiency. However, larger and more significant outbreaks of infectious agents, when they do occur, can impact blood safety and sufficiency, locally, nationally, regionally and globally. In general, such infectious agents were once relatively uncommon or geographically restricted, but changing conditions – climatic, environmental or social – have resulted in either the introduction of a infectious agent not previously present in the population, or more favourable conditions for an already present but naturally controlled infectious agent that have facilitated its spread and persistence. The emergence of a newly identified infectious agent is not a common event.

Once an infectious agent is present and established, the implications of its presence to the blood service need to be determined. It is possible that, depending on the particular infectious agent, there are no or only limited implications associated with its presence – there are infectious agents which may be transmitted via blood and components but which have no identified pathology associated with infection and transmission. However, in all cases, the potential implications need to be identified and assessed in a systematic way. In general, those infectious agents that may impact blood services do so either through transmission to recipients with consequent adverse effects or through loss of donors due to illness.

4.1 TRANSMISSIBLE BY TRANSFUSION

An early factor to determine is whether the infectious agent is transmissible by transfusion. Will the potential outcome of the outbreak be transmission to recipients, or lack of donations due to donor illness?

4.1.1 Transfusion transmission likely

The potential for transmission via transfusion is not necessarily problematic in all cases. The following questions apply if the infectious agent is transmissible.

- Is there sufficient infectious agent present to result in infection of a recipient?
- Is there associated pathology that would then result in significant disease in infected recipients?
- Is the infectious agent associated with all blood components or only specific components?

Depending on whether the blood service uses whole blood or prepares blood components, the association of the infectious agent with specific components may minimize risk of transmission through those components that naturally would have no or lower levels of infectious agent present.

The focus is to minimize the risk of infected donations being collected and the consequent potential for transmission via transfusion.

4.1.2 Transfusion transmission unlikely or very low risk

There are infectious agents that have no or very low risk of transmission via transfusion but may have other public health consequences, with the potential for loss of donors and donations if donors become infected or symptomatic, and hence are unable to donate until they have recovered.

It is likely that blood services themselves could suffer from reduced staffing and therefore activity levels. Depending on the severity and extent of any outbreak, the likely continuing need for blood and components must be assessed. If the outbreak spreads widely across the population it may have a significant impact on many aspects of daily life, with a resultant reduction in demand for blood as health care facilities refocus on maintaining urgent and emergency activities only. However, the opposite may also occur, namely an increase in demand if the associated pathology of the infectious agent is such that blood or components are required to support infected individuals.

4.2 BIOLOGY AND PATHOLOGY

Understanding the biology of the infectious agent and any associated pathology is necessary to understand the overall consequences of the infectious agent. The presence of an infectious agent in donated products does not necessarily lead to transmission, and transmission itself does not necessarily result in disease in the recipient. There are transmissible agents that currently have no identified significant pathology, have a high prevalence in many populations and consequently are present in blood donations, and appear to be transmitted regularly with no adverse effects currently having been identified. Arguably, such infectious agents do not present a threat to recipients and therefore are not generally of direct concern to blood services. However, currently only a few such infectious agents have been identified – most infectious agents do have associated pathology with clinical consequences, although the severity of any resultant disease is a factor that may need to be considered by blood services when considering what action needs to be taken to deal with the particular infectious agent.

Some infectious agents usually give rise to highly symptomatic infections, and in that situation infected donors are highly unlikely to attend to donate. Any donor presenting with acute symptoms should be identified and deferred through the donor selection process. If the infectious agent is highly symptomatic the donor selection process does become more straightforward, as it is easier for donors to self-defer and for potentially infected donors to be identified at the collection site prior to donation. Identifying donors who are infected but not yet symptomatic can be problematic, but educating donors to immediately contact the blood service if they have any symptoms occurring in the weeks immediately following donation can identify such cases. Depending on the supply levels and timescale, there may be sufficient time to remove their donations from the inventory. Donor reporting of post-donation illness is an important element in helping to minimize risk of transmission of infection at all times, not just during disease outbreaks, and should be part of the blood service's general donor education programme.

Where an infectious agent does indeed have associated pathology, whether there is a difference between the clinical consequences of transmission via the “natural” route of infection and transmission via transfusion needs to be considered. Transmission through the natural route of infection, most commonly through insect bite, may have less clinically significant consequences as the infectious dose is generally smaller, and the infected individual is less likely to have any underlying condition or be immunocompromised in any way. On the other hand, transmission via transfusion generally results in a much higher infectious dose being received – the recipient has an underlying condition requiring transfusion, which may include being immunocompromised for any number of reasons, and transfusion may therefore result in more serious consequences. A further potential complication is that the disease process

associated with infection may itself require transfusion support as part of any treatment given, further increasing the potential risk to infected individuals, and the pressures on the blood service.

Whilst transfusion of components containing an infectious agent does present a risk, there is a minimum infectious dose for each infectious agent, so the presence of an infectious agent in a transfused product may not always lead to the development of a productive infection. Although the transfusion of a unit of blood is potentially a large inoculum, if an infectious agent is present at a low level, or if the infectious agent is not highly infectious, or if the recipient has previously been exposed to the infectious agent and has a degree of immunity, transmission of the infectious agent with the consequent development of a productive infection in the recipient may be less likely.

4.3 SCREENING TARGETS

Understanding the biology of infection and interaction between the host and the infectious agent identifies the potential screening targets if the laboratory screening of blood donations for evidence of infection is considered.

If laboratory screening is to be considered, the most appropriate screening target must be identified. Screening for evidence of infection by infectious agents that give rise to acute infections that then resolve, with or without subsequent immunity, is most likely to rely upon detection of nucleic acid rather than a serological target. However, if a blood service does not have access to reliable and sensitive molecular screening technology, this may restrict the ability to provide effective laboratory screening. In such situations the detection of a serological target antigen may offer an alternative approach. Detection of antibody is generally of limited value, as in such cases antibodies generally appear after the acute infection has resolved and the individual is (usually) no longer considered to be infectious.

4.4 IMMUNITY

There is a possibility that the infectious agent causing the disease outbreak is one from which recovery leads to immunity. In addition, the population, or at least a section of it, may have previously been exposed to the infectious agent, either naturally or through a vaccination programme, leading to some pre-existing population immunity. This may have a number of possible consequences.

- If a proportion of donors have been infected and are immune, it is less likely that a donation containing the infectious agent would enter the blood supply.
- If a proportion of donors have been infected and are immune, there is the potential for passive transfer of immunity to a recipient through transfused components, which may prevent or at least ameliorate any infection resulting from transmission via transfusion.
- If a proportion of recipients have been infected and are immune, it is less likely that the transfusion of an infectious agent present in blood or a blood product would result in infection in the recipient.

The development of immunity on recovery from infection is also an important factor in the management of exposed and previously infected donors. Those infectious agents that give rise to prolonged chronic carriage or are sequestered and persist in the individual for life may result in permanent donor deferral; however, recovery from infectious agents that only give rise to acute infections allows donors to be safely reinstated once the infection has resolved. In situations where sufficiency of the blood supply is likely to be affected, effective donor management is essential to be able to maintain the blood supply over the longer term (see section 4.6 on donor management).

Immunity from a vaccination programme, whilst protecting individuals, may affect a donor's suitability. Recently vaccinated donors may need to be deferred for a period of time depending on the vaccination type; donors vaccinated with a live vaccine need to be deferred, while donors vaccinated with a non-live vaccine would not normally need to be deferred if they meet all of the other donor assessment requirements.

4.5 AVAILABILITY OF TREATMENT

The availability of effective treatment for the specific infectious agent should not be used as a reason for lack of intervention by the blood service. However, the availability of treatment may factor in the risk assessment performed, potentially providing some flexibility in response, which may be important in resource-limited situations. Availability of treatment is also a factor in the management of infected donors. If they can be treated effectively, previously infected donors may be reinstated, and potentially more quickly if the treatment can be shown to clear the infection within a defined time.

4.6 DONOR MANAGEMENT

Blood services have responsibilities. They have a clear duty of care, and in the management of any donors identified as infected or who could possibly be infected. If clinical intervention is required, donors must be provided with this care, or referred to those who can provide it.

However, many of the acute viral infections that have more recently emerged and caused global health problems have no specific treatment. Treatment is symptomatic only, and in such cases donors should be given the appropriate information on how to care for their own health, including the likely outcome, which for healthy individuals is generally the resolution of infection with full recovery.

Once recovered, the majority of individuals can be accepted again as donors after a suitable deferral period. It is important to ensure that such donors are actively managed, with a clearly defined deferral period that is sufficient to ensure that any infection would have resolved before reinstatement. Blood services should manage their existing donors as effectively as they can; continually having to recruit new donors is expensive, and in some countries the motivation of the population to donate is declining and the recruitment of regular donors is becoming more difficult.

4.7 PATHOGEN INACTIVATION, REDUCTION AND REMOVAL

In addition to the other aspects, it is important to obtain some information about the physical characteristics of the infectious agent so that the likely effectiveness of pathogen inactivation (PI) and other reduction and removal methodologies can be included as part of the risk assessment and as potential mitigation of the threat (see section 5.5).

5. Possible actions to respond to a threat

Identify all possible response options available

Prior to performing a risk assessment and taking any action, all of the possible options available to respond to the threat must be identified, even if some of the possible actions are not appropriate in the particular circumstances or for that blood service or country, and even if some of the options are disproportionate to the threat. However, the emergence or presence of an infectious agent does not automatically define a threat and the option of not taking any action must be included. Additionally, the initial course of action decided upon and implemented may need to be changed if the circumstances surrounding the threat change. Any action taken must be appropriate and – importantly – always proportional to the threat.

For most blood services in most circumstances there are only so many response options available. Blood services need to work actively with both donor groups and organizations and with clinical users to ensure that blood supplies are maintained as much as possible and that blood and blood components are used only when absolutely necessary. However, in reality the blood service cannot control the underlying situation surrounding the emerging threat and has to respond to donor issues and clinical needs as they arise.

Possible options are:

- no action;
- identification and deferral of at-risk donors;
- cease collections in affected areas – if the country is affected, but the outbreak is geographically restricted within the country, localized cessation of collections may be appropriate and effective;
- implement specific screening of donations from at-risk donors for the infectious agent;
- implement universal screening of all donations for the infectious agent;
- utilize specific inactivation procedures or other processing approaches that would remove or reduce any infectious agent in the blood or blood components;
- seek to (temporarily) import blood and components from non-affected countries or from countries that undertake specific screening for the infectious agent.

5.1 NO ACTION

In some situations it is possible that there is no action that the blood service could or should take, either initially or at all. An effective surveillance system with good analysis of the information should alert blood services to any potential threats in good time, and in many cases in advance of any action being needed apart from continual, and possibly more frequent, monitoring of the situation. Any threat is minimal for as long as the infectious agent is not present in the donor population.

There are also situations when a blood service may decide that, although an infectious agent is present, no action is required, for example:

- the rate of any transmission via transfusion is minimal compared with the community-acquired infection rate, and transmission via transfusion would not lead to more significant disease than that seen in community-acquired infection;

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- there is sufficient immunity within the population, which means that (a) there is a reduced likelihood of an infectious donation being collected; and (b) there is a reduced likelihood of any transmission via transfusion resulting in infection in the recipient.

The hepatitis E situation in Europe is an example of a situation where the risk of acquiring hepatitis E virus is much higher from food than via transfusion, and a number of countries have either not implemented screening for hepatitis E virus or delayed implementation. Screening has been implemented in some countries primarily because of the potential for problems from persistent hepatitis E virus infection in immunocompromised recipients, with the consequent clinically significant impact.

Parvovirus B19 is an example of an infectious agent that is present at high levels in many populations globally, is generally quite benign in its clinical impact, and is transmitted via transfusion, but for which donated blood is rarely screened. Most populations have sufficient background immunity that donations with high levels of virus are uncommon, and it is likely that most recipients have sufficient immunity to protect against B19 infection. It is also possible that some transmissions do occur, but the recipient is most likely to be asymptomatic with no clinical consequences that would raise any concerns.

5.2 IDENTIFICATION OF AT-RISK DONORS

The identification of at-risk donors and their deferral is an effective first action step in the response of any blood service to an infectious disease threat. To support deferral, the length of the deferral period needs to be determined. Understanding the biology and epidemiology of the infectious agent enables:

- the appropriate deferral period to be determined;
- identification of all of the potential routes by which donors may be infected;
- identification of the specific risks that need to be included in the donor selection process.

5.2.1 Deferral of at-risk donors

Defining the deferral period for any infectious agent is important, and in the absence of any specific national or international guidance a minimum deferral for twice the defined incubation period could be considered a suitable guideline.

A key issue is whether at-risk donors can be effectively and reliably identified by the donor selection process. A donor may be at risk for a number of obvious and easily identifiable reasons, but may also unwittingly be at risk from sources that the donor is not aware of. In the context of an infectious disease outbreak, donor risk is through exposure to the infectious agent with the consequent risk of development of active infection. Exposure is most likely through contact with the vector, but exposure may have occurred through other more direct human-to-human routes, including health care interventions and close contact.

In countries currently unaffected by the infectious agent, the risk is solely that of importation by individuals returning or travelling from affected countries. These donors can be easily identified by asking about recent travel history. This approach requires that a list of currently affected countries is available, and that such a list is kept up to date in the event of the outbreak spreading from country to country.

In countries currently affected by the infectious agent the risk is more general, and it is harder to identify individual at-risk donors when there is a general background risk and no specific high-risk activities or other factors. A country may be affected only in certain areas;

in such situations, donors living in or recently returned from such areas may be identified and deferred for an appropriate period.

The decision whether deferral is the most appropriate course of action depends largely on the numbers of donors likely to be categorized as at risk. If there are only low numbers, which can be easily managed and will not affect sufficiency, deferral is the most appropriate course of action. Not all outbreaks will result in locally acquired cases. In a number of countries where the vectors are not present most (if not all) cases are likely to be imported, and the total number of cases may be too few to require further intervention. However, if the numbers are higher, including locally acquired cases, and there is a possibility of sufficiency becoming an issue, laboratory screening may have to be considered.

5.2.2 Deferral of contacts of at-risk donors

A further complication, highlighted by the Ebola and Zika outbreaks in 2014–2015 and 2015–2016 respectively, is the potential for onward transmission of infection via sexual contact, and possibly via other close household or family contact. Since the initial reports of finding Zika virus RNA persisting in immune-privileged sites, with the consequent persistence for long periods in semen (far beyond the period for viraemia), a number of other viruses have been found to demonstrate similar properties. Although detected using molecular techniques, in a number of individuals with high levels of virus detected in semen the virus has been grown in culture, indicating the potential for the virus present in such sites, and shed through other routes, to generate a productive infection. Consideration should therefore also be given to the deferral of donors who have not travelled but who have had sexual contact with individuals recently returned from an affected country. As part of the response to the 2015–2016 Zika outbreak across Central and South America, many blood services introduced additional deferral for donors who had not travelled to affected areas but had had sexual contact with individuals who had been confirmed to be Zika infected. Commonly, donors having had sexual contact within the last month with anyone diagnosed with Zika within the previous six months would be deferred for at least a month after their last sexual contact. This principle can be applied to any similar acute viral infection, and may be considered to be proportionate, given the current findings of virus in immune-privileged sites and evidence of sexual transmission.

5.3 CESSATION OF COLLECTIONS IN SPECIFIC AREAS

In some circumstances an outbreak may be geographically restricted within a country or region, in which case it may be possible to cease collections in the affected area. Additionally, donors who may present to donate in a non-affected area but who live in or had recently returned from travel in an affected area can be identified. There are obvious potential sufficiency issues with this approach, but it can be an effective and relatively quick way to minimize the impact of a more localized outbreak.

Depending on the circumstances, needs and capacity in the system, the loss of donations from a specific area may need to be addressed by increasing recruitment and collections in non-affected areas. Publicity drives may be needed to increase awareness and encourage donation.

5.4 SPECIFIC SCREENING OF DONATIONS

The laboratory screening of donations, if performed using an appropriate strategy, should generally be considered to be definitive in terms of identifying donations from infected donors, and also helps balance sufficiency against safety. Although screening is effective,

its effectiveness and reliability are very dependent on the availability of a suitable screening assay, the specific screening targets used, the screening strategy adopted, and the availability of the appropriate confirmation of screen reactivity.

Although most blood services will already have a screening programme in place covering the usual mandatory bloodborne infectious agents, it is likely that the focus is serological rather than molecular screening. The current infectious threats to blood services are usually from infectious agents that give rise to acute infections; molecular screening would thus be required to directly detect the presence of the infectious agent itself. Although detection of antigen is theoretically an alternative approach, it is increasingly rare for antigen assays for such infectious agents to be manufactured. Molecular techniques, although focused on a different target, are generally a more sensitive approach to the detection of the presence of the infectious agent, and molecular technology is becoming more accessible and applicable to large-scale screening needs. Although still limited in the number of fully automated screening platforms available, molecular screening is being implemented by increasing numbers of blood services as technology improves in reliability, systems become simpler and smaller, and costs decrease.

5.4.1 Possibility of laboratory screening

A factor that impacts the ability to perform laboratory screening, but which is outside the control of blood services, is the availability of a suitable screening assay with which to identify infected donors. If the decision to implement laboratory screening is made, there must be at least one suitable screening assay that is available and, ideally, able to be run on the existing laboratory system within that blood service.

Unfortunately, suitable assays are not always available to a blood service, as in the following scenarios.

The speed of development of the outbreak has been faster than the assay manufacturers can develop a suitable assay. Whilst some countries are able to develop in-house assays if there is no other option, these are generally for local use only.

The national or international regulatory requirements for such assays are so strict and varied that the assay manufacturers cannot meet all of the requirements within the time frame needed.

Assay manufacturers are unable to access the broad range and large number of samples from infected individuals required to demonstrate assay effectiveness.

The quality of the screening assays used to screen donors and donations is critical, and blood services are encouraged to use high-quality assays from international manufacturers to help ensure overall sensitivity, specificity and result reliability. However, the majority of assays from the major international manufacturers are designed to be run on the dedicated automated closed system (black box) from that particular manufacturer. There are fewer open system assays – those that can be run on a range of non-dedicated, semi-automated systems – resulting in reliance on just a small number of manufacturers to develop and make available assays for any newly emerging infectious threat.

The occurrence of a number of disease outbreaks in the last few years has challenged assay manufacturers, but the appropriate screening assays have been made available within as short a time frame as is reasonable, given the development and testing needed to meet the regulatory requirements of different countries for assays used for infectious disease screening of blood and other donated products.

5.4.2 Assay selection

If screening is to be implemented a suitable assay needs to be identified. Assuming an assay is available, this requires evaluation of assay performance against sufficient suitable

samples to generate enough reliable data to have confidence that the assay will detect the presence of the infectious agent.

The ability of a blood service to undertake the appropriate evaluation is an important factor to determine, but it is expected that blood services already have some mechanism in place for evaluating screening assays prior to their selection and implementation. If the blood service does not have the capability or capacity to undertake such an evaluation, the national central public health laboratories should have the necessary capability and capacity, and would be expected either to perform the evaluation themselves or to assist the blood service to perform it.

Whatever the circumstances, blood services should also contact WHO and other relevant international organizations for help in obtaining the evaluation and other assay performance data that they require. At a time when an infectious agent is newly identified, the well provenanced samples required for local evaluations are not likely to be readily available. At this stage there has to be reliance on both the assay manufacturers and acknowledged competent and expert international laboratories to undertake the initial work and provide suitable data to enable assay selection. Additionally, if the ability to appropriately evaluate assays is not available within either the blood service or the national public health laboratories, the use of such external data is the only way in which the blood service can evaluate performance and select the most appropriate assay.

In the face of such an emerging infectious threat, and the need to develop suitable screening assays and provide performance data, WHO should ensure that international expert laboratories and organizations, the assay manufacturers and WHO itself all work together to provide, as quickly as possible, the samples required to develop and evaluate assays, so that the consequent assay performance data can be made freely available to those considering and assessing the implementation of screening.

It is likely that for a newly emerging infectious agent there will only be one or two assays initially available, with very limited data to support their use. In this situation continuing close monitoring of assay performance is required until there are sufficient data available to have confidence that the assay is indeed identifying those donations with evidence of infection.

In the case of infectious agents that have been known about for some time but that are now increasing in incidence, assays are more likely to already be available and suitable, and appropriate performance data are also likely to be available from expert laboratories. These data, together with any manufacturer's data and any pertinent local data, need to be obtained to undertake an initial paper evaluation of available assays. The paper evaluation should identify those assays that would appear to be most suitable for donation screening and allow the blood service either to select the assay directly or to obtain samples and undertake additional assay evaluation.

A final issue that needs to be taken into account, but that should not prevent the implementation of laboratory screening, is the compatibility of the selected assay with the existing screening platforms in use. However, if the assay cannot be run on the existing platforms and implementation of screening is necessary, then either it has to be made clear to the assay supplier that it must also supply a suitable platform or an alternative assay must be found that can be run on an existing platform.

5.4.3 Selective screening

Selective screening, assuming an appropriate screening assay is available, is a relatively easy way of dealing with the problem of disease outbreaks when at-risk donors can be easily and reliably identified, and where the numbers are such that sufficiency may become a factor if deferral alone is adopted. Assuming that screening systems are already in place, screening of donations only from at-risk donations is relatively easy and not too costly. However, if the numbers of at-risk donations increase, both the logistics of picking out the sample tubes

for these donations and the inventory management of the screened donations need to be considered. There is a point at which it may be easier to adopt universal screening.

Alternatively, if identifying at-risk donors is not reliable, depending on the infectious agent and the clinical consequences of transfusion transmission, there may be specific recipient groups who would be susceptible to infection with adverse consequences, and for whom selective screening of random donations could be implemented to provide sufficient screened blood and components for their needs.

5.4.4 Universal screening

If the number of donors likely to be at risk starts to rise to a significant level, the point at which that level becomes critical needs to be defined by each blood service based upon their own circumstances and the resources available. At that level, the implementation of universal screening may become the most appropriate response. However, this does have significant cost and logistical implications, balancing risk of transmission and sufficiency against cost. As with selective screening, effective confirmation of screen reactivity and consequent donor management are essential.

5.4.5 Confirmation of screening reactivity

The implementation of any screening programme should be accompanied by the availability of effective confirmation of the status of any screen-reactive donations identified. Although all screen-reactive donations could be considered to be true infections and discarded on that basis, this is not best practice. Best practice requires full confirmation of screen reactivity with consequent proper informing and management of the confirmed infected donors. However, in many countries where appropriate confirmatory testing is not available for those infectious agents for which screening is routinely undertaken (for example hepatitis B virus, HIV), confirmatory testing for a newly emerged infectious agent is even less likely to be available, at least in the initial stages of the outbreak.

If a blood service does implement screening it is important that confirmation of the screen reactivity is sought, that the true number of cases in the population is known, and that the performance of the assays in use is understood and measured.

5.5 SPECIFIC INACTIVATION OR REMOVAL OF THE INFECTIOUS AGENT

The use of pathogen inactivation (PI) technology or physical methods to remove certain components of blood may in certain circumstances be an appropriate approach to the reduction or removal of any infectious agent that may be present. Although such approaches may not remove or inactivate all of any infectious agent that may be present, they may reduce the level to below that likely to result in transmission or development of a productive infection in the recipient.

Current PI systems can be effective against certain infectious agents present in donated blood. Although work is continuing on PI systems that can apply an effective PI system to whole blood, at present PI is most effective against plasma and platelet preparations. However, depending on the strategy in place within a blood service, it is possible that PI could be applied to plasma to reduce risk of transmission of infection, and if the red cells are suspended in additive solution the amount of residual plasma in the red cell components could be too low to contain sufficient infectious agent to transmit infection.

In addition to the more modern PI systems there are older, well established inactivation or removal systems, such as heat inactivation and filtration, which have been applied primarily to plasma and plasma products for many years. Although such approaches may have limited

application and usefulness, there may be situations when inactivation of an infectious agent in plasma or other blood components would be an effective factor in breaking the transmission chain.

Alternatively, if an infectious agent is known to partition within a particular fraction of whole blood it is possible that the particular fraction could be physically separated and removed, thereby reducing the risk of transmission. Leucodepletion to minimize risk of cytomegalovirus and human T-lymphotropic virus infections is one such approach.

5.6 IMPORTATION OF SCREENED OR OTHERWISE LOW-RISK BLOOD AND COMPONENTS

A potential solution in some situations is the cessation of all blood collection activities in all or a part of a country and importation of “safe” blood or components from unaffected regions of the country, an unaffected country or a country that is screening its blood supply for the particular infectious agent. The supplying region or service must have sufficient stocks to be able to provide the blood or components required without compromising its own supply. There are also logistical issues surrounding the safe transport of labile medicinal products to be dealt with, but this approach has been shown to be effective during past outbreaks. The significant chikungunya outbreak on the island of Réunion, a French territory, during 2005–2006 led to the cessation of all blood collection activities on the island, and the provision of blood and components directly from France.

This approach is also a potential solution when the effect of the disease outbreak is insufficiency of supply as donors become ill and blood collection activities have to be reduced, but demand for blood and components continues at a higher level than can be supplied at the current collection level.

6. Risk assessment of the threat and options

Where possible link into any national risk assessment process that is dealing with the outbreak from the national perspective

6.1 PERFORMING A RISK ASSESSMENT

A comprehensive and accurate risk assessment is critical in the response to any threat, and needs to be undertaken as soon as possible. An early response will facilitate management of the situation and reduce the likelihood of sufficiency or safety issues. However, before such a risk assessment can be carried out the required data and information need to be collected together; risk assessments, if they are to be effective and useful, must be based on accurate data and information.

There may be situations when a more rapid initial response would be beneficial, followed by the continuing collection of data to inform a more involved and longer-term response. As long as there are sufficient relevant data to allow an initial assessment to be undertaken and appropriate initial actions to be put in place, this approach may be necessary and beneficial in both slowing down any impact on the blood service and generating public confidence that the situation is under review and action is being taken. The previous sections in this document have discussed key elements that need to be considered by blood services when generating preparedness plans – identifying the information and data needed to be able to respond to a threat, and organizing those data in a logical way so that they can feed directly into any risk assessment. However, on a country-by-country basis there may be other more specific factors that need to be considered and included in any risk assessment. The risk assessment should include review and analysis of all of the information and data currently available, and also identify all of the possible options available to the blood service, assessing each one in terms of implementation, impact and outcome.

Additionally, it has to be accepted that very often the data available are such that any risk assessment cannot be totally objective, at least not in the early stages, and that there may be a significant level of subjectivity in the assessment.

Annex 2 is an example of a template that enables an initial assessment of the infectious agent itself, and whether it is likely to present a threat to the blood service.

Annex 3 provides a pair of simple risk assessment frameworks, one for sufficiency and one for safety, with the accompanying breakdown of the information required to support the risk assessments.

6.2 ACCEPTABLE LEVEL OF RISK

There are risk assessment tools available that blood services may use to determine levels of risk and the actions required; there may also be national risk assessment frameworks available. Whatever tool is used it is important to include every possible facet of the threat, all of the risks, and the potential outcomes or effects. However, a major element that needs to be determined prior to undertaking the risk assessment is the level of risk that is deemed to be acceptable or tolerable. The purpose of a risk assessment is to identify risk and the possible approaches that can be taken to mitigate the risk. At the end of the process the identified risks are quantified in some way to enable the most appropriate course of action to be identified, with the action to be taken determined by the overall level of risk deemed acceptable.

In the context of the safety and sufficiency of the blood supply, however, there is no position of zero risk. Whatever approach is taken will result in a level, no matter how low, of residual risk, and it is the acceptable level of this residual risk that needs to be determined. Whilst in most cases such a decision belongs at government level, it is critical that (a) there is input from the blood services in such decision-making; and (b) a decision is actually made and an acceptable and realistic level of risk identified.

6.3 NATIONAL APPROACH

It is crucial to adopt a national approach to dealing with infectious disease threats, as there may be a potentially significant impact across many areas of health and social care. National strategic plans should be in place, including a national risk assessment drawing from many sources, including the health care system in general, and specifically including the blood service and other national bodies such as the public health authorities. Ideally the risk assessment performed by the blood service then becomes an integral part of the government's national risk assessment, which encapsulates all threats to the country as a whole. In addition, any proposed actions under the blood service's risk assessment are accommodated within the range of national actions identified by the national risk assessment. Good communication should be maintained between the major actors and plans should be integrated, as there may be a high-level government plan to interrupt transmission such that the blood service may not need to act in the way that its own risk assessment had indicated.

6.4 REVIEWING THE RISK ASSESSMENT

Importantly, whilst a one-off risk assessment may be able to provide a way forward in the first instance, infectious disease outbreaks are changing pictures and no country should rely on a risk assessment that has been performed at a specific point in time and then not reviewed. Integral to any risk assessment is the need for review on a regular basis, and immediately if the situation changes significantly. There must be a programme in place that, at the very least, monitors the data that were used to perform the initial risk assessment and that, if these data change, triggers a review and if necessary a further risk assessment. At the beginning of an outbreak, a country that is currently unaffected (no locally acquired cases) and is responding to a potential threat may decide that imply defer donors recently returned from affected areas. However, if the outbreak then spreads into that country and locally acquired cases appear, a different approach will be needed, and the risk assessment should be reviewed and further actions identified and taken.

7. Communication

Clear communication at all times is crucial

When faced with an infectious threat, blood services must communicate clearly to ensure that both donors and recipients, and the population as a whole, are properly informed of the situation, and that donors, recipients and government are aware of and understand the planned actions of the blood service. Whether communication is provided centrally by government or directly by the blood service, the message must be the same. Communication from government is preferable as part of the overall national response to the situation.

In addition, there must be effective cross-governmental and cross-organizational communication to ensure that all available information is collated centrally and then made available in a timely manner to those parts of government and other organizations that need it to support their own plans. The blood service, whether a governmental or a nongovernmental organization, must be included in this dissemination of information.

7.1 PUBLIC CONFIDENCE

The issue of public confidence in a national blood service and people's understanding of the sufficiency and safety of the blood supply varies significantly from country to country, depending on specific circumstances, but is nonetheless important. The public must have confidence in the systems in place to ensure a sufficient supply at all times, and to minimize any risk of transmission of infection via transfusion.

In a number of countries, however, the provision of blood when needed is not taken for granted, and family replacement and paid (professional) donors are still used, for example the provision of blood for transfusion dependent thalassaemia patients. The concept of a national blood service is not something that exists across most of the population of these countries despite the efforts of WHO and patient-orientated NGOs. In such circumstances the microbiological safety of the blood supply cannot be assumed.

In countries without fully developed health care systems, the transmission of infection via transfusion, even if only at a local level, can lead to a loss of confidence in the safety of the blood supply and may result in patients refusing what could be lifesaving transfusions. In countries with more developed health care and communication systems, transmission of infection via transfusion would be widely communicated very quickly, with the potential for nationwide loss of confidence. This could have serious larger-scale consequences if patients nationally then start to refuse transfusions, and some donors react by ceasing their donations.

A further problem that has been encountered by some blood services is the belief of donors that they may become infected by donating. Informing and educating donors not only about the importance of blood donation but also about the safety of donating is important and should be continual, irrespective of the emergence of any infectious threat.

Loss of public confidence can happen over a short period, while recovering that confidence is usually a very long process requiring significant resources, which can drain available blood service resources. It is therefore critical that any blood service considers the potential consequences in terms of public confidence in their response to any emerging outbreak. Although criticism may result from a perceived overreaction to a potential threat, such criticism is highly unlikely to result in any loss of public confidence.

7.2 EDUCATION OF STAFF

All blood services should have appropriate continuing education programmes in place for the general training and updating of all staff, as well as any specific training of staff required. Blood service staff (especially those who have direct contact with donors), other health care professionals, and senior government and business leaders are the first who need education and training on infectious threats and the changes that are being put in place to deal with any threat. Clear and comprehensive communication to staff is the first step in ensuring that clear messages are sent out to donors, patients, other health care professionals, families of patients, and ultimately the population as a whole.

7.3 EDUCATION OF DONORS

During any outbreak situation, donor education is required to alert donors to any changes in either the donor selection process or in the screening of donations. Donors are more likely to understand the situation and therefore be able to either self-defer or answer the donor selection questions more easily, accurately and honestly if they fully understand the situation, the actions being taken by the blood service and why those actions are being taken.

It is crucial that donors understand if and when they can return to donate. Once recovered from any infection, depending on the infectious agent and the timescale for full recovery, and whether laboratory screening has been implemented, donors can return to donate and should be encouraged to do so, once the safety of that process has been established.

Information leaflets are an effective way of educating donors. They can be sent out to donors in advance of donating or made available at donation sessions. They are a simple and effective way of providing up-to-date information quickly and in a simple format, and they can be updated at short notice when necessary.

It is also important to remind donors that they should always contact the blood service if they develop any symptoms within at least two weeks following donation; this may be extended, depending on the nature of the emerging threat and the timescale for appearance of symptoms. Although the donation may already have been transfused, if components have been produced some may still be unused and can be withdrawn. Where components have already been transfused the clinicians caring for the recipient can be informed so that the appropriate monitoring and intervention can be implemented.

7.4 EDUCATION OF HEALTH CARE PROFESSIONALS AND RECIPIENTS

Both health care professionals in the clinical environment and blood or component recipients need to be educated about the blood service's response to an infectious disease outbreak.

In many cases the health care professionals in direct contact with patients are the only people who are providing information directly to patients. In that situation, any blood-related information given by health care professionals is not controlled by the blood service, and may simply be based on the personal understanding of the health care professional. Therefore, if health care professionals are properly educated and informed about any situation that has arisen, in most cases the patients will then also be properly informed.

Informing recipients directly can be achieved if the blood service produces patient information leaflets that very simply and clearly set out the threat, the action being taken and the potential risks. However, the sudden appearance of such a leaflet at such a time may cause concern amongst some recipients. Consequently, it would be better practice for the blood services to produce patient information leaflets as a matter of normal practice, so that recipients are well informed of the baseline background risks of transfusion in advance of

any additional infectious threat. It is generally easier to explain additional risk to an already informed population.

7.5 APPROPRIATE CLINICAL USE OF BLOOD

A further important issue, which becomes an even more critical factor in situations where the blood supply is threatened, is that of the appropriate clinical use of blood. Although as a matter of routine appropriate clinical use of blood should be built into all clinical training and practice, in situations where the normal sufficiency or safety of the blood supply may be compromised, only giving blood and components when absolutely necessary will help to both safeguard supplies and protect recipients from unnecessary exposure to a potentially infectious clinical product. There needs to be clear communication and discussion with senior health care professionals responsible for transfusion activities to ensure that they and their staff are aware of the situation and all work to ensure that blood and components are only used where clinically appropriate.

8. Haemovigilance

Understand fully the risks associated with transfusion

All blood services and national authorities should put in place a national haemovigilance system to capture and analyse any adverse events associated with transfusion. When an infectious threat emerges, any possible cases of transmission via transfusion should be identified and properly investigated to determine if transmission via transfusion has actually occurred or if the recipient was infected via another route.

A haemovigilance system ensures a consistent approach to the investigation of potential transmission events, enables all such reports to be collated and consequently a true understanding of any transmission events to be obtained. In the case of a newly emerging infectious agent with limited information available on transmission via transfusion, haemovigilance data are invaluable in helping to understand the risk from blood and components and the overall effectiveness of the measures taken by the blood service in responding to the disease outbreak.

WHO has guidance available on the development of a national haemovigilance system: <http://www.who.int/bloodsafety/haemovigilance/haemovigilance-guide/en/>

9. Resolution of an outbreak

Plan what to do as the outbreak and threat resolves

Eventually the outbreak, and consequently the threat, will subside and preparedness planning should include, depending on any lasting outcome, planned downscaling of the response with the possible removal of some or all of the changes implemented and controlled return to normal activities. However, depending on the situation remaining after the outbreak has subsided, some of the changes may need to remain if the infectious agent is transmitted via transfusion, the vector or other route of transmission remains present, and the infectious agent is now considered to be endemic in the country, whether or not significant numbers of case are occurring.

The end of the outbreak is primarily determined by a decrease in the number of confirmed cases in the country, either locally acquired or imported (if locally acquired cases have not occurred). In general, transmission can be considered to have been successfully interrupted if no new cases are reported within 3–12 months. If no new cases have been identified over a 12-month period then the outbreak is over and it is unlikely that the infectious agent has become endemic in the country. If screening had been implemented and no cases identified, the value of continuing can be questioned. If, however, only donor deferral had been implemented, it may be appropriate to leave the donor deferral requirements in place to mitigate the continuing risk of imported cases from countries in which the outbreak is not over, or in which the infectious agent either was already present or has now become endemic. Continuing to monitor the situation both nationally and globally is important so that the list of affected countries can be kept up to date and any donors recently returned from these countries can still be identified and deferred.

As the outbreak subsides a cautious response is needed, which includes careful review of the implemented measures and, depending on any residual risk, gradual removal considered. Communication of the actions being taken by the Blood Service to all parties must continue. In situations in which a country does not have locally acquired cases, cases are only in travellers returning from affected countries, the actions of blood services and/or regulators in those affected countries, reversing any actions or removing restrictions put in place, should be used as indicators of when donors returning from such countries no longer require deferral.

It is important that the blood service learns from any outbreak situation and thoroughly reviews and, as necessary, updates its existing overall strategies and guidelines for dealing with such events, the plans drawn up and actions taken at the time, and the resultant outcomes of these actions throughout the outbreak so that:

- any shortcomings or other failings are identified, analysed in more detail and measures put in place to ensure that these do not reoccur;
- any actions taken that were particularly successful are identified and noted, and where appropriate either introduced into routine practice or specifically identified as actions to be considered as part of the planning in the event of any similar future threat.

10. Non-blood donors and donations

Some blood services are also the national organizations responsible for managing non-blood donors and donations; the same guiding principles apply to these products

As health care systems develop and the use of cells, tissues and organs increases in many countries, it has been recognized that the existing blood service may be the most appropriate organization to take responsibility for these other donated products; indeed, in a number of countries the national blood service does now have responsibility for the management, collection, screening, storage and supply of all such non-blood donations.

Where the blood service is the organization responsible for non-blood donations it must include this element of its activities in the risk assessments performed. Where the blood service is not the organization responsible for non-blood donations it should ensure that government is aware of the potential threat to these other donated products so that the responsible organizations are included in the national planning to deal with the emerging threat and have performed their own risk assessments.

Although the donated products themselves are very different and have different requirements in terms of collection, storage and use, the donor selection and donation screening requirements are usually based upon the same guiding principles and in practice are usually the same or very similar. In the face of an emerging infectious threat, the same issues surrounding blood sufficiency and safety apply to non-blood donations, although whilst the analysis of potential risks and threats is broadly the same, the interpretation and use of the outcomes may be quite different.

- The number of non-blood donations is usually very small compared to the numbers of blood donations.
- Whilst all donations are valuable, it is easier to replace blood donations than tissue, cell or organ donations.
- The clinical value of non-blood products is usually assessed in a different way to blood products, and is often considered to be higher.

Consequently, although the information on blood and non-blood donations included in the risk assessments may be similar, the outcomes may be different. For a number of these the level of accepted risk would generally be higher as the clinical needs of and clinical benefits to tissue, cell and organ transplant recipients are usually greater.

11. Responsibilities of WHO and national blood services

Whilst the responsibility for the development and implementation of national strategies and guidelines for dealing with any emerging infectious threats sits firmly with each blood service, responding to any specific threat requires support and assistance from WHO in respect of overall guidance and provision of specific information and data that are fed into the national plans.

WHO has a responsibility to Member States to look at health from the global perspective, and to ensure that information about any emerging infectious outbreak is collated, analysed, verified and disseminated to Member States. WHO must also ensure that Member States understand the value of this information and should encourage Member States to ensure that the information provided is disseminated nationally to those organizations and bodies that need to be aware of emerging infectious threats.

WHO also has a responsibility for the top-level identification, implementation and management of global responses to infectious outbreaks, and for providing global advice, guidance and information to Member States on all aspects of the outbreak. Such information includes how to identify cases, mode of spread, containment, provision of appropriate clinical care for infected individuals, any potential long-term issues, and monitoring programmes. The output of WHO should also include information about the implications of the outbreak for the sufficiency and safety of blood and other donated products.

However, during outbreaks there are many conflicting demands on resources, and it is important that blood services are proactive in seeking relevant information, advice and guidance from WHO through the WHO country representatives or regional advisers, as well as from other sources. WHO is viewed as a reliable and authoritative source of such information, and in most situations governments are more likely to accept recommendations from blood services that are underpinned by information and guidance provided by WHO, and are therefore more likely to provide the resources required to enable the blood service to respond appropriately to the threat.

During disease outbreaks, WHO provides a broad range of information on its website, often creating a specific set of pages dealing with all aspects of the infectious agent and the outbreak. Blood services should regularly access these pages to ensure that new and updated information is noted and, where relevant, use that information to update risk assessments and action plans.

However, blood services must be proactive in accessing and engaging with their national focal point, together with other national sources of information, to ensure that they are included in the general dissemination of any information about an infectious threat that could impact their activities and the blood supply in any way, and to ensure that blood safety is one of the key issues to be included in national responses to any emerging infectious threats.

Blood services should also ensure that they maintain close contact with WHO at local, regional and global levels through their country representatives, their regional advisers, the WHO Blood Safety Unit and the WHO website.

12. Checklist for dealing with a disease outbreak

The following are suggested components of a checklist for dealing with every stage of a disease outbreak, including actions to be taken before, during and after the outbreak.

- 1. Be prepared (in advance of any outbreak)**
 - Develop a national strategy for dealing with emerging infectious threats
 - Use WHO guidance to develop a basic template to facilitate planning in the face of any emerging infectious threat
 - Regularly review and, as necessary, revise these documents
 - Ensure that there is effective monitoring for emerging infectious threats
 - Ensure that government disaster planning includes the blood service as a stakeholder in the process.
- 2. Identify the specific risk**
 - Identify the infectious agent
 - Obtain information on the biology and pathology of the infectious agent
 - Determine if the agent is likely to be transmissible via transfusion
 - Determine if the infectious agent is already present in the country
 - Determine if the vectors are present in the country
 - Determine if other transmission routes are present
 - Actively monitor cases occurring both nationally and internationally.
- 3. Determine the potential consequences**
 - Whether the key risk is transmission or sufficiency
 - Whether at-risk donors can easily be identified
 - Whether the infectious agent is likely to spread across the country
 - Whether the infectious agent is likely to become endemic
 - If infected individuals are likely to need additional transfusion support.
- 4. Determine the possible actions that could be taken**
 - No action
 - Donor deferral
 - Selective screening
 - Universal screening
 - Cessation of collections in a defined region
 - Cessation of all collections
 - Importation of safe blood and components.
- 5. Perform risk assessment to determine action to be taken**
 - Link into any national response to the outbreak, including any national risk assessment
 - Identify all of the risks and potential outcomes to be included
 - Identify current action
 - Continue to monitor threat
 - Determine when reassessment is needed.

6. Plan and implement

- Draw up an action plan based upon the risk assessment
- Implement the plan
- Monitor the outcomes and review and update plan as necessary.

7. Communicate

- Develop communication plan as soon as possible
- Link in with any national communication plan
- Communicate with donors, providing information to help self-referral
- Communicate with patients and relatives
- Communicate with other health care professionals.

8. Stand down as outbreak ceases

- Plan for the outbreak to subside
- Determine if the infectious agent is likely to now be considered endemic in the country
- Determine if any of the introduced measures can be removed
- Determine how to reduce the measures implemented
- Ensure that effective infectious disease monitoring is in place
- Review plan, actions taken and outcomes
- Identify any lessons to be learned, good and bad.

Annexes

Annex 1

Obtaining the information required to enable a response

To be able to respond to any emerging infectious threat, a country must have information about the threat. This is possibly one of the most important elements in determining the response to a threat. The information must be accurate, up to date, and relevant.

Example of a monthly monitoring programme used by a national blood service to alert it to any emerging infectious threats

Month	Year	Source	Infectious agent/disease	Country/region	Status (for consideration)	Type of incident	Comment
9	2017	European Centre for Disease Prevention and Control	Chikungunya	Europe	Update: may require review	Surveillance	The two outbreaks in France and Italy are unrelated and result from separate introductions of the virus, probably from Africa and Asia respectively, but highlight that the environmental conditions in 2017 are favourable for local transmission. In France, response measures, including vector control, have been implemented. In Italy, this is the first known transmission of chikungunya in central and southern Italy. The likelihood of further spread within Italy is still moderate, with suitable but less favourable conditions for vector activity in the coming weeks. In the affected areas more cases can be expected in the near future. There is a low likelihood of the virus being introduced and subsequent local transmission in other European Union countries where <i>Aedes albopictus</i> is present and active.
9	2017	Public Health England	Chikungunya	France	Update: may require review	Surveillance	As of 27 September, a total of 11 locally acquired cases (9 confirmed) had been reported: 9 from Le Cannet-des Maures and 2 from Taradeau (newly reporting), all in the Var department. An epidemiological link between the two clusters has been established. Dates of onset ranged from 28 July to 30 August, but an additional six cases are under investigation. Vector control activities are continuing.
9	2017	Public Health England	Chikungunya	Italy	Update: may require review	Surveillance	As of 26 September, 183 cases had been reported from Anzio, Latina and Rome, of which 109 were confirmed. Mosquitoes collected near the house of the first three cases were PCR positive for chikungunya. Italy first reported an outbreak of chikungunya in 2007 in the north-east of the country, with over 200 cases.
9	2017	Public Health England	Malaria	Cyprus	Update: may require review	Surveillance	On 8 September, the United Kingdom reported three cases of <i>Plasmodium vivax</i> in travellers with recent travel to Kyrenia district, in northern Cyprus. This is the first time locally acquired malaria has been reported from the northern part of Cyprus. The presence of suitable vectors and climatic conditions make local transmission possible. Further cases may be identified.
9	2017	Public Health England	Malaria	Europe	Update: may require review	Surveillance	Malaria cases reported acquired in four European Union countries: France, Italy, Greece, and for the first time the northern part of Cyprus. Further cases may be identified. The presence of suitable vectors and climatic conditions make local transmission possible. European Union Member States may decide whether to implement preventive blood safety measures for persons returning from the affected areas in non-endemic countries.

Month	Year	Source	Infectious agent/disease	Country/region	Status (for consideration)	Type of incident	Comment
9	2017	Public Health England	Malaria	France	Update: may require review	Surveillance	On 7 September, France reported two locally acquired cases of <i>Plasmodium falciparum</i> malaria in Auvergne-Rhône-Alpes region. Both cases attended the same wedding in Moulins, Auvergne-Rhône-Alpes region, before onset of symptoms. There was a case of malaria imported from Burkina Faso in an individual who stayed in Moulins during the two weeks prior to the wedding. No further cases have been reported. Entomological investigations failed to identify mosquito vectors capable of transmission. Investigations are continuing into possible routes of transmission. The risk of further malaria spread in the area is very low.
9	2017	Public Health England	Malaria	Greece	Update: may require review	Surveillance	Local transmission of both <i>P. vivax</i> (five cases) and <i>P. falciparum</i> (one case) occurred during July and August. Vivax malaria has been detected in Greece most years since 2009.
9	2017	Public Health England	Malaria	Italy	Update: may require review	Surveillance	On 5 September, Italy reported a fatal case of <i>P. falciparum</i> malaria in a girl with no overseas travel history in Trento, northern Italy. The child was hospitalized in Trento from 16 to 21 August for diabetes. Two patients with <i>P. falciparum</i> were hospitalized in the same ward during her stay in Trento but no breach in medical procedures were identified that could have led to nosocomial transmission. The risk of further malaria spread in the area is very low.
9	2017	Public Health England	Plague	Madagascar	Update: may require review	Surveillance	The plague outbreak has spread to the cities for the first time. Madagascar commonly reports plague between September and April; however, this outbreak is now occurring in non-endemic areas and in densely populated cities. As of 30 September, 10 cities have reported pneumonic plague cases. The three most affected districts are the capital city and suburbs of Antananarivo (27 cases, 7 deaths), Toamasina (18 cases, 5 deaths), and Faratshio (13 cases, 1 death). A basketball player from the Seychelles attending a tournament was among the fatal cases.

Month	Year	Source	Infectious agent/disease	Country/region	Status (for consideration)	Type of incident	Comment
9	2017	European Centre for Disease Prevention and Control	Plague	Madagascar	Update: may require review	Surveillance	There is a low but definite possibility that a traveller infected with plague in Madagascar may be asymptomatic on boarding a return flight to the European Union but may become unwell, either during the flight or after disembarkation, although exit screening has been introduced in Madagascar. The risk of further transmission in Madagascar is considered very high until public health prevention and control measures are fully implemented. The risk of regional spread in the Indian Ocean region is considered moderate. The risk for travellers from the European Union or for importation to the European Union is considered low. WHO considers the risk for international spread of plague to be very low.
		Transfusion	Various	United States	Update: may require review	Letter	Letter to editor suggests prudent duration of deferral for potential donors who have been exposed to a live viral or bacterial therapeutic – may be indefinite until further data become available.
9	2017	Epi and infect	Arboviruses	Canada	Update: only information	Research	Emerging arboviruses in Quebec, Canada: assessing public health risk by serology in humans, horses and pet dogs. The regional seroprevalences for California serogroup viruses (CSGV) were high and generally higher than for West Nile virus, suggesting that physicians should include CSGV as well as West Nile virus in their differential diagnosis of acute human encephalitis, even though the risk of developing clinical signs when infected by CSGV seems to be low.
9	2017	CID	Bacterial	Australia	Update: only information	Case report	Donor-derived <i>Mycoplasma hominis</i> and an apparent cluster of <i>M. hominis</i> cases in solid organ transplant recipients. The donor for patient 1 was a previously well young adult female who developed a hypoxic brain injury following cardiac arrest. Culture prior to donation resulted in growth of methicillin-sensitive <i>Staphylococcus aureus</i> , but following the diagnosis of patient 1, this specimen was retrieved and <i>M. hominis</i> was identified by specific culture and molecular techniques. Initially presumed to represent nosocomial transmission, patients 2 and 3 were found to have distinct isolates from patient 1 and from each other.

Annex 2

Assessment of the probability of exposure of the donor population to an infectious agent that may impact sufficiency or safety

The following example shows a simple framework that enables a blood service to perform an initial assessment of the likely impact of an infectious agent on its activities. The effectiveness of this framework depends on the data available and the reliability of these data. However, the assessment can, and should, be reviewed as more data become available.

Infectious agent: _____

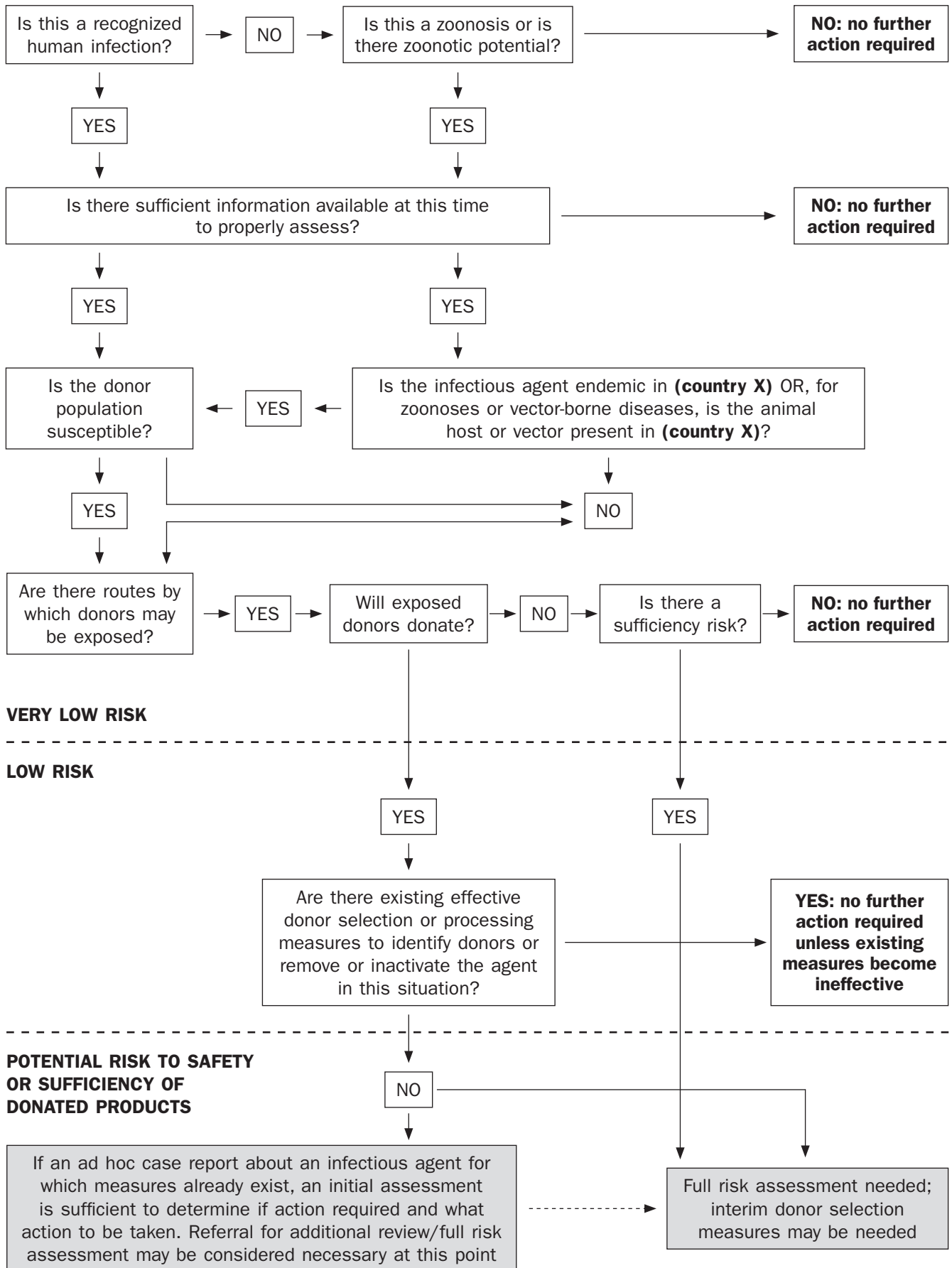
Date assessment performed: _____

Assessors: _____

Question	Outcome (yes/no/not known)	Quality of evidence (excellent/good/poor) ^a
Is this a recognized human infection?		
Is this a zoonosis or is there zoonotic potential?		
Is the donor population susceptible?		
Is the infectious agent endemic in (country X) OR, for zoonoses or vector-borne diseases, is the animal host or vector present in (country X)?		
Are there routes by which donors may be exposed?		
Will exposed donors donate?		
Is there a risk to sufficiency rather than a risk of transmission?		
Are there existing effective donor selection or processing measures in place to identify such donors or remove or inactivate the infectious agent?		

^a If current quality of evidence is poor, additional evidence must be sought before completing the assessment.

Flow chart to determine action required



Annex 3

Risk assessment of the threat to blood sufficiency or safety from an emerging infectious agent

Risk assessments consider **hazards** – situations with the potential to cause harm, and **risks** – the probability that a specific adverse event will occur in a specific time period or as a result of a specific situation. Risk is therefore the combination of the likelihood and the consequences of a hazard being realized.

To be able to perform an appropriate and effective risk assessment, a basic set of information is needed. In the context of an emerging infectious agent and its potential impact on a blood service, specific information about the infectious agent, its spread or potential spread, and its potential for causing harm needs to be obtained and analysed. Obtaining the information identified in the categories below will enable the risk of an emerging infectious agent affecting either or both the sufficiency and the safety of the blood supply to be assessed. The categories cover a wide range of factors, some of which may have limited relevance for some blood services. However, as long as the individual blood service can provide the data in each of those categories relevant to the specific situation and relevant to the blood service, effective risk assessments using the grids in section A3.6 of the present annex can be undertaken.

The grids have been constructed to look at the two separate potential impacts of an emerging infectious agent on blood services, sufficiency and safety, and identify the possible actions that can or should be taken as the overall risk to sufficiency or safety increases. Although the risk categorization is primarily subjective, it is anticipated that once the risk level has been determined, the actions for each risk level listed below each grid will help blood services identify and implement the appropriate responses. Although there is overlap between the two grids, with a number of similar actions and with some of the action outcomes of one grid impacting the other, the two key issues of sufficiency and safety must be risk assessed separately, as an outbreak may threaten sufficiency without having a significant safety risk and vice versa.

A3.1 Information on agent epidemiology, pathogenicity and transmissibility by transfusion

The infectious agent

Newly discovered or emerging (already present in the population or donors but changing in incidence and prevalence).

- Nature of the infectious agent
- Biology of the infectious agent
- Potential screening targets
- Transmission and natural history
- Vectors and hosts
- Likelihood of transfusion transmission.

Pathogenicity of infectious agent

- Known pathology
- Likely proportion of asymptomatic versus symptomatic infections
- Disease progression
- Immune response to the agent
- Available treatment
- Relevant cases in non-human hosts
- Influence of transfusion route of infection on disease outcome.

Infection in blood donors

- Numbers of human cases
- Incidence and prevalence in overall population and donor population
- Any relevant local, national or regional studies
- Existence of identifiable risk factors in donors
- Presence of any identifiable signs or symptoms that may lead to donor deferral
- Prevalence of asymptomatic infectious donations
- Frequency of infection with any possible seasonal variation
- Duration of infectious stage
- Frequency of persistence or reoccurrence of infection in donors.

Identifiable risk groups

- Any known susceptibility factors in recipients
- Any specific recipient groups that may be more susceptible to infection
- Identification of recipients specifically at risk for development of disease
- Frequency of susceptible recipient groups
- Availability of methods to identify recipients specifically susceptible to or resistant to infection (tests for detection of past exposure or immunity).

Transfusion transmissibility

- Partitioning of infectious agent in specific blood components
- Propensity for transmission via transfusion
- Likely level of infectious agent in the bloodstream
- Information on relationship between level of agent and transmissibility
- Effects of blood component processing and storage conditions on infectivity
- Possibility of presence of specific antibody reducing likelihood of transmission
- Reported cases of transmission via transfusion
- Occurrence of reinfection in already infected individuals; impact on existing disease occurrence
- Possibility of secondary spread of transfused agent to contacts of infected recipient.

A3.2 Existence of preventative, inactivation or removal steps for the infectious agent

Donor exclusion

- Existence of identifiable travel that could be used to identify and defer at-risk donors
- Existence of identifiable behaviours or other factors that could be used to identify

-
- and defer at-risk donors
- Existence of identifiable symptoms that could be used to identify and defer infected donors.

Donation exclusion

- Existence of serological or molecular screening assays that could be used to identify donations from infected donors
- Compatibility of any additional screening assays with existing operational practices
- Likely effectiveness of any donation screening; sensitivity and specificity of assays
- Availability of methods to confirm infection in screen-reactive donations
- Overall likely effectiveness of screening in the reduction or elimination of transmission via transfusion and occurrence of disease.

Infectious agent inactivation during blood component or product processing

- Any information on stability of the infectious agent in donated blood
- Availability of information on cell tropism
- Availability of information on physical removal methods (e.g. leucoreduction)
- Availability of information on susceptibility of the infectious agent to inactivation procedures
- Existence of evidence for the effectiveness of conventional blood product inactivation or removal procedures to remove infectivity in fractionated blood products
- Impact of the introduction of any modified inactivation procedures on the manufacturing process
- Impact of the introduction of any modified inactivation procedures on the quality and efficacy of the products.

A3.3 Impact on the blood supply and methods to prevent transmission

Blood collection and donors

- Possible impact of additional donor selection requirements on the blood collection process
- Willingness of donors to donate during any outbreak
- Quality of information on prognosis and treatment options for infected donors
- Staff resource issues if or as the outbreak spreads and staff become ill.

Impact on public perception of blood safety

- Adverse publicity associated with identification of a “new” and potentially transmissible infectious agent
- Potential positive and negative changes in the perception of the safety of blood transfusion associated with the introduction of new screening measures
- Potential significant consequences of infection in any particular recipient groups.

Blood and blood component supply

- Frequency of donations reactive in assays for the infectious agent
- Proportion of donations lost through additional screening.

A3.4 Efficacy of donor and donation screening

Frequency of transmission

- Any evidence for transmission of the infectious agent by transfusion
- Any information on frequency of development of post-transfusion disease
- Any evidence of the failure of donor selection process to identify at-risk donors
- Any evidence of the failure of donation screening to identify donations from infected donors.

A3.5 Impact on recipients

Recipient assessment

- Scope for introduction of additional donation screening for susceptible recipients (e.g. anti-cytomegalovirus screening)
- Introduction of methods to assess recipient susceptibility (e.g. antibody tests for measurement of past infection or immunity)
- Effectiveness and availability of immunization in multi-transfused individuals.

Recipient treatment

- Scope for prophylaxis or treatment of identified transfusion-associated infections.

Recipient monitoring

- Enhanced surveillance of blood recipients to enable early detection of any infections likely to have been transmitted via transfusion.

A3.6 Evaluation and scoring of risk

Grid 1. Donor risk

Consequence	Risk of infectious agent entering the general or donor population				
	Rare	Unlikely	Possible	Likely	Almost certain
Loss of donors and loss of donations highly unlikely	Low	Low	Low	Moderate	Moderate
Some donor loss possible but minimal effect on overall number of donations collected	Low	Low	Moderate	Moderate	High
Loss of some donors with some loss of donations requiring increased collection activities	Low	Moderate	Moderate	High	High
Loss of increasing numbers of donors and donations requiring restriction of supply of blood and components for critical and urgent cases only	Moderate	Moderate	High	High	Extreme
Loss of significant numbers of donors and donations resulting in inability to provide sufficient blood and components to cover clinical needs	Moderate	High	High	Extreme	Extreme

Actions

Low risk: monitor situation; as appropriate implement additional donor selection measures; review existing contingency plans (draw up action plans if none exist) to safeguard sufficiency if the situation escalates. Plans should include as many options as possible and include the implementation of specific donation screening (if available) and early communication with clinical users and the ministry of health and government.

Moderate risk: increase collection activities; put initial measures in place to increase public awareness of the need for blood and increase recruitment activities; consider specific donation screening – if specific screening assays are not available, assess other possible screening targets as indirect evidence of presence of the infectious agent in donors or donations; consider and assess other possible laboratory options to reduce risk; alert ministry of health and hospitals of potential issue and need for the appropriate clinical use of blood and to prepare to prioritize usage if the situation escalates further.

High risk: maximize collection activities; implement specific donation screening or screening for other targets if specific screening assays are not available; implement any other laboratory options identified to reduce risk; put measures in place to assess and limit blood usage to urgent or critical cases; continue with increased recruitment activities; implement specific donation screening; investigate the option of pathogen inactivation; investigate the possibility of obtaining blood or components from external sources.

Extreme risk: limit usage to only most critical and urgent cases; continue recruitment activities; continue laboratory screening or pursuing other laboratory interventions to reduce risk; implement any pathogen inactivation measures available; if available, obtain blood or components from external sources.

Grid 2. Recipient risk

Consequence	Risk of infectious agent entering the blood supply				
	Rare	Unlikely	Possible	Likely	Almost certain
Transmission highly unlikely	Low	Low	Low	Moderate	Moderate
Transmission could occur, but no associated clinical consequences in most cases	Low	Low	Moderate	Moderate	High
Transmission with minimal clinical consequences and no long-term sequelae in most cases	Low	Moderate	High	High	High
Transmission with morbidity and possibility of death or disability	Moderate	High	Extreme	Extreme	Extreme
Transmission with significant morbidity and high risk of death or disability	High	High	Extreme	Extreme	Extreme

Actions

Low risk: monitor situation; ensure clinical users are aware of the need to identify any potential cases of post-transfusion infection; review existing contingency plans (draw up action plans if none exist) to implement specific donor selection or selective or universal donation screening activities (if screening available). Plans should include as many options as possible and include early communication with clinical users and the ministry of health and government.

Moderate risk: implement specific donor deferral; assess the implementation of specific selective screening, if available; consider use of pathogen inactivation.

High risk: implement specific donation screening – if specific screening assays are not available, assess other possible markers or screening targets as indirect evidence of presence of the infectious agent in donors or donations; consider and assess other possible laboratory options to reduce risk; assess use of pathogen inactivation or other component processing and treatment methodologies.

Extreme risk: implement pathogen inactivation or other methodologies available to remove or inactivate any infectious agent present in blood or components.

A3.7 Review

All risk assessments generated must be reviewed on a regular basis throughout any outbreak. A time frame for review of the risk assessment must be set, which should be frequent during an outbreak, as both the information available about the infectious agent and the underlying situation of the outbreak can change rapidly, with the possibility that the additional information may indicate a significant impact risk entailing a review of the actions required.

As an outbreak subsides and the threat diminishes, the risk assessment reviews should reflect this to allow, as appropriate, implemented measures to be reduced in a controlled way.

Annex 4

Blood safety-focused risk assessment tools

Whilst there are tools available to assess risk, the level of assessment needed depends very much on the nature of the infectious agent and the situation or likely situation in any specific country. If a country is likely to only be affected through donors travelling and visiting an affected area, then a more simplified response can be put in place without the need for an in-depth risk assessment. However, no matter how good the tool or other approach used, in all cases the quality of the input data is critical to achieving an accurate and reliable outcome. In general, the more complex the risk assessment the more data required and the greater the reliance on the accuracy of those data.

European Up-Front Risk Assessment Tool (EUFRAF)

<http://eufrattool.ecdc.europa.eu/>

EUFRAF was developed for researchers and policy-makers to allow quantification of the risk of transmission of an emerging infectious disease by blood transfusion. The tool estimates the number of transfusion recipients who become infected through transfused blood, either during a local outbreak of an infectious disease or because donors visited an outbreak area.

Alliance of Blood Operators

<https://allianceofbloodoperators.org/abo-resources/risk-based-decision-making/rbdf-framework.aspx>

This risk-based decision-making framework provides a structured and systematic process for considering all relevant factors in decisions on blood safety, and for ensuring that finite resources are allocated to the most significant blood safety risks. The framework has been developed to help blood service operators achieve two main objectives. The first is to optimize the safety of the blood supply by enabling the proportional allocation of finite resources to mitigate the most serious risks, recognizing that the elimination of all risk is not possible. The second purpose of the framework is to analyse and account for a series of qualitative factors that affect decision-making in the management of blood risks. The framework takes a societal perspective, enabling consideration of social, economic and ethical perspectives that go beyond quantitative calculations of risk, and that can alter risk tolerability.

Annex 5

Example of emerging infectious threat and subsequent actions

The following presents an example of an emerging infectious threat and actions available and taken based on the Zika outbreak developing across Central and South America and the Caribbean in 2015.

In the early part of 2015 reports started to emerge from Brazil of cases of an apparent viral infection that at that time had not been identified. In mid-2015 Zika virus was identified, and through the rest of the year and well into 2016 increasing numbers of cases across Central and South America were reported. The rapidly increasing numbers of cases and countries affected, and the appearance of Zika-associated microcephaly and other neurological disorders, led WHO to identify the situation as a public health emergency of international concern.

Zika virus is an arthropod-borne flavivirus that can also be transmitted via transfusion from an infected donor, although there are few reported and well provenanced cases in the literature. However, the increasing number of cases of Zika across many countries in the region and the emerging possible links with the appearance of abnormalities in infants born to infected mothers did constitute a blood safety risk. Because of the potential catastrophic effect of transmission of Zika virus via transfusion to a pregnant recipient, blood services in many non-affected countries began implementing measures to minimize risk of the virus entering their blood supply.

When faced with an emerging disease outbreak blood services have limited options:

- no action
- deferral of at-risk donors
- screening of donations from at-risk donors
- screening of all donations
- pathogen inactivation.

POTENTIAL RESPONSES TO THE ZIKA OUTBREAK

a. Affected or endemic countries

No action. Given the increasing numbers of cases, “no action” was theoretically not an option, although for a time the options available to blood services were very limited.

Deferral of at-risk donors. Given the spread of the virus across the general population and the asymptomatic nature of the infection in many infected individuals, how could an “at-risk donor” be identified? Only donors with symptoms or diagnosed as infected – or subsequent to the identification of sexual contact as a route of transmission, donors whose partners are infected – could be identified and deferred. In addition to the deferral of symptomatic donors, donors accepted for donation need to be advised that they should contact the blood service if they develop symptoms within two weeks of donation (some blood services may opt to increase this to four weeks).

Screening of donations from at-risk donors or all donations. The absence of an appropriate and effective screening assay for Zika virus ruled out this option until late in the outbreak.

However, if resources are available, this could be a viable option in those countries where Zika virus disease is now established and where the incidence of infection remains high.

Pathogen inactivation. This option is potentially effective for plasma and platelet components, but the technology is not sufficiently proven as effective for red cell and whole blood components. The process would therefore not ensure inactivation or removal of Zika virus from red cell and whole blood components and would be high risk, given the potential numbers of donations that could be Zika infected.

b. Non-affected and non-endemic countries

No action. Taking no action would be appropriate if donors had not been exposed to Zika virus, but in some countries donor travel is significant, and if that travel includes affected countries then action would be required.

Deferral of at-risk donors. Only donors having recently returned from affected areas would be at risk. These donors can easily be identified from their travel history. The list of affected countries would need to be kept up to date. The identification of sexual transmission as an additional route of infection can be dealt with by deferring sexual partners of Zika-infected individuals. Appropriate deferral periods would need to be determined, one for travellers who have returned from an affected area and have had no symptoms, and a second one for travellers who have returned and either have had compatible symptoms (but no diagnosis) or have been diagnosed with Zika virus.

Screening of donations from at-risk donors or all donations. The absence of an appropriate and effective screening assay for Zika virus ruled out this option until late in the outbreak. For most non-affected countries this may not prove to be a necessary or viable option if the numbers of at-risk donors remain relatively low.

Pathogen inactivation. This option is potentially effective for plasma and platelet components but would not be a proportionate response, as at-risk donors could be identified and deferred.

Annex 6

Actions needed from WHO

Initial informal consultation with individuals in several blood services has identified a number of common themes in respect of the expectations that blood services have of WHO in supporting their ability to respond to an emerging infectious threat. The expectations primarily relate to the provision of information about the infectious agent, its spread and associated pathology.

Specific areas in which WHO should be proactive and provide support and information are:

- ensuring that the protection of sufficiency and safety of blood and other donated products is one of the key issues that WHO identifies and includes in its information sheets when an infectious threat arises;
- ensuring that the importance of maintaining the sufficiency and safety of blood and other donated products is promulgated throughout WHO, through the regional offices to the country representatives;
- supporting blood services and, where separate, those organizations responsible for the supply of cells, tissues and organs, in collaboration with the ministry of health, to access the resources needed to respond to the threat;
- ensuring that the current WHO global system of outbreak surveillance and reporting identifies to the national focal points the importance of including national blood services and, where applicable, those organizations responsible for the supply of cells, tissues and organs in their information dissemination pathways;
- providing specific recommendations and advice to blood services on dealing with the threat;
- collating and making available information on how blood services in different countries are responding to the threat.

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