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**WHO Guidance on Xenogeneic Infection/Disease  
Surveillance and Response: A Strategy for International  
Cooperation and Coordination**

**World Health Organization**

Department of Communicable Disease Surveillance and  
Response

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## 1. Introduction<sup>1</sup>

The objective of this document is to facilitate consideration for the development and implementation of an international xenogeneic infection/disease event surveillance network for efficiently and effectively detecting, reporting and responding to xenogeneic infection and disease events using internationally harmonized, cooperative and coordinated surveillance activities.

This objective is derived from the realization that:

- interest in performing clinical xenotransplantation continues;
- there are inherent infectious disease risks associated with xenotransplantation;
- attempts to perform xenotransplantation are not always accompanied by efforts to prevent, detect or manage possible xenogeneic infection and disease.

Therefore, a strategy is needed for detecting and responding to xenogeneic infection and disease events should they occur. That strategy should include a mechanism for international cooperation and coordination which will:

- harmonize surveillance activities for maximizing global public health usefulness;
- be flexible enough to accommodate a diversity of quality controlled and valid surveillance approaches as found in different countries;
- foster the ability to detect and respond effectively to xenogeneic infection and disease events.

Current international systems for disease surveillance and response do not completely meet the unique challenges posed by potential xenogeneic infection and disease events. Therefore, to meet its objective, this document focuses on presenting information and guidance to ministries of health and other parties interested in xenotransplantation on how one might approach the development of an international mechanism for xenogeneic infection/disease event surveillance and response. Non-infectious xenogeneic diseases such as those resulting from congenital defects in the

### 1.1 Xenotransplantation, infectious disease risks, and surveillance

#### 1.1.1 Xenotransplantation

Xenotransplantation is any procedure that involves the transplantation, implantation, or infusion into a human recipient of either:

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<sup>1</sup> See Annex 1 for definitions of terms used in this document.

- live cells, tissues, or organs from a nonhuman animal source, or
  - human body fluids, cells, tissues or organs that have had *ex vivo* contact
- with live nonhuman cells, tissues, or organs.

It is a diverse area of current research which may become part of medical practice as an alternative or additional approach for alleviating the global shortage of human tissues and organs available for allotransplantation (the transplantation of living cells, tissues or organs of human origin), for providing treatment for diseases with no other effective therapeutic intervention, or for diseases where xenotransplantation may offer additional therapeutic benefits. If xenotransplantation is proven safe and efficacious, interest in its practice will increase worldwide.

### **1.1.2 Risks associated with xenotransplantation**

The risks associated with xenotransplantation encompass a wide spectrum of different types of infectious agents, different levels of transmission potential, and different levels of agent - host interface. They involve both probable and theoretically possible hazards, and they exist irrespective of the species of source-animal involved and the type of xenotransplantation procedure being performed.

Xenotransplantation is a potential vehicle for directly introducing both known and as yet unknown infectious agents into xenotransplantation product recipients. The severity and effects of these xenogeneic infections might be predictable for some known agents, but for unknown agents or for agents which change in pathogenicity as a result of xenotransplantation, the threat they present to human health is not currently quantifiable.

Also, meaningful predictions of transmission behaviour in the xenotransplantation environment are not currently possible. Infections may remain limited to individual xenotransplantation product recipients. Some infectious agents may have transmission potential only under certain specific activities such as blood donations. Other xenogeneic infectious agents may have broader transmission potential and pose a danger to the wider public health. (For example, a worst case scenario would be the emergence of a new life-threatening influenza virus, transmissible by aerosol and having pandemic capability.)

Furthermore, it is speculated that the different forms of xenotransplantation could be associated with different levels of infectious disease risk, with the proximity of the recipient's vascular supply to the xenotransplantation product or the duration of exposure to the xenotransplantation product possibly being the principal determinants of risk. (For example, a permanent whole liver xenotransplantation might present a greater risk for xenogeneic infection than an encapsulated islet cell xenotransplantation; an *ex vivo* perfusion technique might be associated with less risk than a permanent organ xenotransplantation.)

Finally, not all infectious agents pose a unique infectious disease risk in

xenotransplantation, and not all are pathogenic or of public health significance. For example, the practice of allotransplantation is not without infectious disease risk. Allotransplantation associated infections, too, can cause significant morbidity and mortality if transplanted materials are contaminated with infectious agents. Also an infectious agent may not be considered a risk factor if it is found in a xenotransplantation source-animal but not in that animal's xenotransplant tissue (i.e., a gastrointestinal parasite like *Trichuris suis* (whipworm of swine) when a heart transplant is performed). The significance of any infection should be viewed with respect to it representing a true additional risk to the xenotransplantation product recipient or other persons.

### **1.1.3 The need for international xenogeneic infection/disease event surveillance**

Because of the nature of the known risks involved and the gaps in knowledge about the emergence, hazard and significance of different types of infections or diseases potentially associated with xenotransplantation, public health interests should be protected through the exercise of prevention strategies (methods of xenogeneic infection/disease prevention are discussed in the WHO document *Xenotransplantation: Guidance on Infectious Disease Prevention and Management* [WHO/EMC/ZOO/98.1]), and the development and implementation of surveillance and response strategies to detect and manage xenogeneic infectious disease events should they occur. At present, however, international xenogeneic infection/disease event surveillance does not exist.

Furthermore, since all people in all countries, both those practising and those not practising xenotransplantation, are potentially the 'population at risk' for xenogeneic infection and/or disease, surveillance should possess characteristics which address not just national interests, but international ones as well. Data derived from different independent national surveillance activities should be comparable and compatible so that it can be used internationally for meaningful analysis. This will require the development and application of internationally agreed surveillance norms on essential data sets and reporting. The use of such norms will promote complementary and supportive national and multi-national actions for addressing xenogeneic infection and disease events and help avoid unproductive and inappropriate unilateral responses with international consequences.

## **2. Surveillance Concepts Relevant to Xenotransplantation and Xenogeneic Infection/Disease**

### **2.1 Case definition of xenogeneic infection/disease event**

The criteria used to determine the presence of a xenogeneic infection or disease in a person can be defined as:

- a. Probable xenogeneic infection - Demonstration of the presence of an

infectious agent of source-animal origin (xenogeneic) in the biologic specimen(s) of a xenotransplantation product recipient or xenotransplantation contact.

The biologic specimens should have a plausible temporal link with a significant exposure to the:

- xenotransplantation product or source-animal,
- performance of the xenotransplantation, and/or
- xenotransplantation product recipient.

The infectious agent may originate from the xenotransplantation product source-animal, or from a contamination of the xenotransplantation product source-animal or xenotransplantation product with a xenogeneic infectious agent.

b. Possible xenogeneic infection - The detection in the biologic specimens of a xenotransplantation product recipient of agents or biologic materials of source-animal origin, which are possibly but not proven to be infectious. The biologic specimens may contain cells of human host origin and/or cells of source-animal origin.<sup>2</sup>

c. Probable xenogeneic disease syndrome - The occurrence of signs, symptoms or pathologic processes in a xenotransplantation product recipient or xenotransplantation contact which have a plausible temporal link with a significant exposure to the:

- xenotransplantation product or source-animal,
- performance of the xenotransplantation, and/or
- xenotransplantation product recipient;

and which can be etiologically attributed to a xenogeneic infectious agent (in the absence of alternative human-origin infectious agents which could account for the signs/symptoms/pathologic processes seen) d. Suspected xenogeneic disease syndrome - The occurrence of signs, symptoms or pathologic processes in a xenotransplantation product recipient or xenotransplantation contact which have a plausible temporal link with a significant exposure to the:

- xenotransplantation product or source-animal,
- performance of the xenotransplantation, and/or
- xenotransplantation product recipient;

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<sup>2</sup> For the moment these are included in the case definition as a precautionary surveillance decision indicating the need for further research into their significance for xenogeneic infection and disease. In the future, with greater understanding of xenogeneic infection/disease risk, it may be reasonable to refine this criterion or drop it from the case definition.

and for which an etiologic link with a xenogeneic infectious agent is suspected but not conclusively proven (either because of a suspicion that an infectious agent of source-animal origin is present but not demonstrated, or because of the presence of a concurrent infectious agent not of source-animal origin which could be responsible for the signs/symptoms or pathologic processes seen).

e. Risk of xenogeneic infection - Evidence of a xenogeneic infectious agent in abiologic specimen of the source animal used for a xenotransplant procedure. This finding puts the recipient of xenotransplant products at risk for infection and efforts should be made to evaluate the recipient for infection. A plausible temporal link should exist between the presence of an infectious agent in the source-animal and the xenotransplantation product recipient's exposure.

As more understanding of xenotransplantation associated infection and disease is gained, a more refined and exact case definition can be developed.

## **2.2 Definition of xenogeneic infection/disease event surveillance**

Surveillance is the structured collection, reporting, analysis and interpretation of a xenogeneic infection/disease event. It is dependent on the ability of detectors (health care providers, diagnostic laboratory workers and others) to identify and properly respond to xenogeneic infection/disease event occurrence. Surveillance serves as the basis for developing timely information about the event, which is, in turn, disseminated to those responsible for the event's management.

**The value of surveillance lies in its ability to trigger appropriate responses; it is more than just the compilation of statistics.**

Surveillance includes:

- The detection and reporting of events which fit the xenogeneic infection/disease event case definition. (Both active and passive surveillance can be used to detect xenogeneic infection and disease events fitting the case definition. The identification of an event should result in its immediate reporting to appropriate health care providers and to authorities responsible for xenogeneic infection/disease event surveillance and response.)
- The routine collection and analysis of data on the population(s) and activities at risk.

Activities required in support of surveillance include the establishment of case definitions and data and reporting norms, the training and supervision of surveillance system participants, the development of appropriate diagnostic laboratory capability, the establishment of clear, rapid and easy-to-use

communications, and effective management of resources to conduct surveillance. The absence of, or weaknesses in these activities can lead to delayed

infection/disease event detection, poor reporting, ineffective and resource-wasteful responses, public misunderstanding or mistrust, and very importantly, unnecessary case morbidity or mortality.

### 2.3 Uses of surveillance

The power of surveillance lies in its simplicity and its ability to interact with and empower or direct other public health and epidemiologic tools. Data on both events and the population and activities at risk are used in event investigation and in the performance of epidemiologic studies. Epidemiologic studies use aggregations of data to detect and analyse trends and causal associations. They can assist in the recognition of infection or disease event occurrences not necessarily identified or reported as individual events.

In general, surveillance uses are:

- **risk detection** - the recognition of the occurrence of xenogeneic infection and disease events,
- **risk characterization** - event analysis and interpretation (i.e. is the reported infection/disease serious; is it transmissible; is it associated with a particular procedure, a particular source-animal, etc.), and ultimately
- **risk reduction** - the execution of appropriate short and long term responses which lead to improved public health and protection (i.e. policy making, regulatory actions, and detection and response system feedback and evaluation).

With time, surveillance together with clinical, laboratory and epidemiologic investigations can be used to expand and refine the understanding of xenogeneic infection and disease events, facilitate xenogeneic infection/disease risk analysis, and engender such surveillance system improvements as:

- better case definitions,
- use of suitable event detection methodology (i.e., active, passive or a combination of surveillance methods),
- selection of optimal time frames for reporting event detections and initiating responses (i.e. emergency vs routine).

### 2.4 Outputs of xenogeneic infection/disease event surveillance

The outputs of xenogeneic infection/disease event surveillance should be clearly identifiable, concise, relevant and beneficial to the maintenance of public health. They should be produced in a timely manner, and lead to accurate

assessments and appropriate management of the infection/disease events. They should contribute to public confidence in and cooperation with health authorities. In general terms, surveillance outputs are the systematic and regular generation of timely and valid data, which are analysed and transformed into meaningful information, and which, in turn, is communicated to decision makers who develop and execute appropriate responses to the acquired information.

**data → information → response**

### 2.4.1 Data

Data for xenogeneic infection/disease event surveillance must be timely, accurate, valid, and as complete as possible. It should be limited to only that which is necessary for improving patient care and protecting public health. Very importantly, data must be communicated and translatable into useful information. Therefore, it must be comparable with data from different reporters so that aggregated data is meaningful. Also, all data relating to a procedure or an individual xenotransplantation product recipient should be linked to other sources of relevant data for proper event analysis and interpretation.

Oversight for data quality is necessary and usually will take the form of nationally regulated and monitored adherence to standards of performance for source-animal production, laboratory procedures, clinical care, xenotransplantation procedures, and registry and archive operation and administration. Public health authorities will need to decide what data are necessary for xenogeneic infection/disease event detection, and any resulting investigation or response.

The sources of data can be clinical examinations and laboratory tests undertaken during active searches for xenogeneic infection or disease events in xenotransplantation product recipients, xenotransplantation contacts and source-animals. Investigations of passive reports from xenotransplantation product recipients and xenotransplantation contacts of unusual or unexplained health events are also sources of data. The use of both surveillance formats will aid in the detection of early events and events with unusual or unexpected presentations. (See Annex 2 for examples of potential sources of data.)

In general, data should be generated and quality controlled closest to where it is most immediately obtained and used, the patient (or for source-animal data, the source-animal herd). The masking of patient identifying data should be undertaken whenever it is reported beyond its generation site. This will help standardize data input into the surveillance system, protect patient privacy, and prevent misuse of data. For international purposes, it is unnecessary to report data with personal identifiers. Such data can be masked through aggregation. (See Annex 3 for examples of reporting forms that mask personal identifiers.) At all times, individual country rules and regulations on data reporting and use must be respected.

Finally, the compilation, storage and analysis of data can be facilitated by the use of databases, registries and specimen archives. These tools for xenogeneic infection/disease event identification and study can be operated near the source of the data, or at more centralized locations depending on the preferences and practices of the national authorities concerned.

### **2.4.2 Databases**

A database is collected and organized data. It is used for detecting and determining rates of infection and/or disease event occurrence. A database should be able to link patient, source animal, and xenotransplantation procedure data. It should facilitate the accurate linkage and tracing of events to xenotransplantation product exposures and xenotransplantation product source-animals, and speed the notification of individuals, clinical centres and communities about any arising xenogeneic infection/disease event risks or trends. Public health authorities should have immediate access to the database in case of need. This can be facilitated by the use of registries and archives, the form and character of which are a national authority decision. (See Annex 4 for an example of a xenotransplantation database.)

A xenotransplantation database should be able to provide information on:

- who is conducting xenotransplantation,
- xenotransplantation source-animals.
- xenotransplantation product recipients,
- the type and outcomes of the xenotransplantation performed, and very importantly,
- xenogeneic infection and disease events.

### **2.4.3 Registries**

A registry is a system for data collection and recording. Those responsible for the registry should have the authority, funding and capacity to maintain an accurate, up-to-date and usable xenotransplantation database. A terms of reference for the registry should include a description of its reporting relationship with government xenotransplantation regulatory and policy authorities, and how it generates information on xenotransplantation safety and efficacy, and on procedure performance.

The exact form of the registry (i.e. centralized with all data maintained in one location nationally or decentralized with data kept at multiple centres; based on paper files or electronic; publicly or privately administered, etc.) should be decided upon by the public health authorities overseeing xenotransplantation-associated activities in the country.

The registration and maintenance of accurate, valid and up-to-date records

will facilitate the:

- detection and investigation of a xenogeneic infection or disease event occurrence (including any secondary cases),
- tracking and detection of additional events resulting from the use of xenotransplantation product(s) associated with the original event (i.e. different xenotransplantation products from the same contaminated source-animal may be used in more than one recipient), and
- prevention and management of xenogeneic infection/disease risk.

#### **2.4.4 Biologic specimen and record archives**

Archives of biologic specimens and records from source-animals, their sentinels or cohorts, and human xenotransplantation product recipients and other persons having significant contact with xenotransplantation products or recipients are desirable for epidemiologic investigations of possible xenogeneic infection/disease events. As appropriate, biologic specimens include samples of sera, peripheral blood lymphocytes, and other materials, and are taken both pre- and post-xenotransplantation. (See Annex 5 for examples of possible biological specimens for archiving.) Records include:

- a xenotransplantation product recipient's health care records,
- source-animal husbandry, veterinary care and microbiological testing records,
- xenotransplantation performance records, etc.

Archives should be established and maintained according to approved and quality controlled standard operating procedures for proper storage and prompt retrieval of biologic specimens and records. Archived materials should be linked and traceable to xenotransplantation procedures and xenotransplantation product records and to the xenotransplantation database. By whom and where archives are maintained and who should have access to the materials they contain should be decided upon by the public health authorities overseeing xenotransplantation-associated activities.

#### **2.4.5 Information**

Information is the surveillance output derived from the analysis of collected data. It should be timely, verifiable and should represent a meaningful analysis and summary of the xenogeneic infection/disease event(s) under surveillance. It should be as complete as possible (but compatible with the need for timeliness) and should include only that which is essential for the understanding of the event(s) under surveillance.

Surveillance-derived information should include:

- descriptions of facilities where xenotransplantation is performed and where source-animals are raised and held,

- what personnel are at risk at both types of facilities (i.e. have potentially significant exposure to xenotransplantation source-animals or xenotransplantation products),
- the types of xenotransplantation performed, including information on xenotransplantation products, procedures and complications,
- patient demographics, and
- other relevant medical information on patients.

Very importantly, the information must also include:

- a description of any xenogeneic infection/disease event, including date and location,
- the clinical/medical care and follow-up of the patient(s), and
- the identity of the pathogen(s) involved.

An analysis of the information obtained through surveillance should be reviewed for trends, and the results of those analyses should be transformed into reports which are usable by both patient care and public health decision makers. Information reports should facilitate the understanding of the event(s) and serve as an aid in any needed clinical or public health investigation. Information reports can also be used to provide public notification about an event, and be used as a tool for evaluating the xenogeneic infection/disease event surveillance system. More importantly, reports should prompt decision makers to undertake effective evidence-based responses and review and evaluate any clinical, regulatory and ethical guidance in use and applicable to xenotransplantation.

#### **2.4.6 Response**

The response undertaken by decision makers as a result of the receipt and consideration of surveillance-derived information should be timely, proportionate, and lead to the effective management of the event(s). It should be targeted towards determining if further investigation of the event is warranted, limiting unnecessary xenogeneic disease morbidity and mortality, and preventing or decreasing xenogeneic infection transmission. The selected response must be scientifically appropriate, but it must also be legally, ethically and politically acceptable within its national and social contexts.

Responses can be thought of as including:

- communication,
- investigation,
- reduction (event management, review of how an event developed, initiation or refinement of preventive or management activities),
- feed-back for improved future surveillance and response (evaluating and if necessary improving surveillance capability).

All responses will be influenced by the nature of the xenogeneic infection/disease events, the capacity to detect them, the expertise used to assess and handle them, and resources available for their conduct. Under some circumstances, the conscious, well reasoned and documented decision not to undertake a response may also be appropriate.

In some cases, international responses may represent the most effective and plausible avenue for managing a xenogeneic infection/disease event. They would be most beneficial for the defining, reporting and management of cross-border events.

## 2.5 Ethical issues raised by xenogeneic infection/disease event surveillance

Xenotransplantation poses a number of particular ethical issues for consideration. First, in so far as xenotransplantation product recipients are currently considered human subjects of medical research, they benefit from what has become the standard worldwide practice of placing their well-being and freedom of choice above all other considerations. But, because xenotransplantation raises the possibility of introducing new and unknown infectious agents into the human population, its practice simultaneously invokes the ethical need to protect public health. This latter attempts to balance the well-being of the individual with that of the community. It will not invariably lead to priority being given to an individual's welfare and freedom of choice.

With respect to xenotransplantation these two ethical perspectives can be expressed as:

**Patient Protection:** The rules applied to xenotransplantation should not vary from those stated in the Helsinki Declaration, the CIOMS guidelines, and other commonly-accepted international formulations for human experimentation. Individual recipients of xenotransplantation products must be informed of all possible benefits and risks, and must be guaranteed protection of privacy and confidentiality. They must be at liberty to withdraw from the 'experiment' at any stage, including xenogeneic infection/disease event surveillance.

**Public Health Protection:** Xenotransplantation product recipients and xenotransplantation contacts may be subjected to restrictions on personal liberty and confidentiality to enable public health officials to minimize potential risks to the community. Given the possible chance that xenotransplantation could introduce a catastrophic infectious agent into the human population, xenotransplantation product recipients and xenotransplantation contacts may be required to submit to ongoing surveillance, possibly life-long, and possibly in the absence of true informed consent. (The exact meaning of informed consent with respect to xenotransplantation requires much further discussion. Furthermore, in some countries it may be interpreted as an exclusionary precondition to the performance of a xenotransplantation procedure.)

The conflicts in these ethical standards remain to be resolved. This is not surprising given the high stakes involved, both to the individual recipient and to the public, and to the fact that an accurate estimation of the risks will take further study. A global consensus will need to be reached to permit the issuance of specific international ethical guidance, even though differences in ethical viewpoints both within and between societies may make the development of this consensus a difficult and time-consuming task. (For a more complete discussion see Annex 6.)

### **3. An International Surveillance Network for Xenogeneic Infection/Disease Event Surveillance and Response**

It should be recognized that with the potential for worldwide transmission of xenogeneic infection or disease, both countries engaged in xenotransplantation and those not wishing to do so, will be at risk from xenogeneic infection and disease exposure. The development of and participation in international xenogeneic infection/disease event surveillance and response, therefore, will assist all countries manage their xenogeneic infection/disease risks whether those risks originate from within their borders or from outside.

To be effective, the system chosen to meet the needs of international xenogeneic infection/disease event surveillance and response must possess three basic attributes. First, it must harmonize surveillance outputs in order to be internationally useful. Harmonization can be attained through:

- an internationally agreed to xenogeneic infection/disease case definition,
- internationally agreed to norms for standardizing data, information and reporting (Data derived from different independent national surveillance activities must be comparable and compatible for meaningful international interpretation of event occurrence and importance. The use of such norms will complement and support national and multi-national actions to manage xenogeneic infection/disease events and help avoid unproductive or inappropriate unilateral responses.),
- agreement on what surveillance activities are essential internationally (For example:
  - the detection and reporting of xenogeneic infection/disease events,
  - the routine collection and analysis of data about the population(s) at risk.).

Second, the system must have flexibility to accommodate a diversity of quality-controlled and valid surveillance approaches as found in different countries. The framework for international surveillance should provide a suitable and accessible avenue for:

- encouraging international cooperation and coordination,

- benefiting from the different perspectives, approaches and possible contributions of its participants, and
- permitting adjustments and refinements to:
  - the xenogeneic infection/disease event case definition, and
  - surveillance norms and activities

as the understanding of xenogeneic infection/disease risk evolves and the capability to diagnose and detect xenogeneic infection/disease events improves.

Thirdly, the system must be able to detect and report events of international magnitude. This is accomplished through the:

- generation of timely, validated data on xenogeneic infection/disease events and xenotransplantation performance,
- analysis and transformation of data into meaningful information, and
- communication of information to decision makers who develop and execute appropriate responses to the events under surveillance.

A network for international xenogeneic infection/disease event surveillance can encompass the above surveillance attributes. The advantages of an international xenogeneic infection/disease event surveillance and response network are that:

- its foundation can be its standardized and comparable outputs; and it
- takes advantage of this standardization to maximize investigative and epidemiological study of reported events worldwide (enhanced sensitivity for detecting very rare events);
- facilitates the widest possible access to expert interpretation of surveillance data and information, and provides guidance to those interested in international event management;
- provides a mechanism for coordinating international responses for maximum effectiveness, without duplication of effort; and
- strengthens both national and international capacity to flexibly meet the challenges faced in xenogeneic infection/disease event occurrences.

Furthermore, a network composed of national ministry of health and other relevant members, connected by channels of communication, can:

- be tailored to reflect the various biologic behaviours and characteristics of the spectrum of potential xenogeneic infectious agents;
- be made to complement and synergize with other existing successful surveillance systems in order to gain cost savings and efficiency;
- derive strength from the diversity of its contributing members;
- promote international surveillance credibility by providing a neutral, central platform for information dissemination both to national authorities and to the interested public;

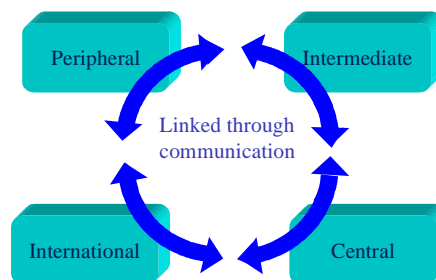
- enlist both national and international assistance for any necessary responses to occurring events.

### 3.1 Framework of network

In most instances, surveillance and response is a national function. Furthermore, most countries have a public health framework based on the performance of functions at the peripheral (community), intermediate (region or state), and central or country-wide administrative levels. These levels can be used as an administrative template for the design of a national xenogeneic infection/disease event surveillance and response network. An international coordinating level could then be added to complement and connect country run networks. An example of one possible framework, a network, is described below. It incorporates the effective attributes already mentioned and also allows for flexibility for adjusting and refining xenogeneic infection/disease event surveillance and response as our understanding of the risks evolve and our capability to diagnose and detect xenogeneic infection/disease events improve.

### 3.2 Surveillance and response network levels

Four administrative levels could be considered for the network, peripheral, intermediate, central or country-wide, and international.



### 3.2

#### .1 The peripheral network level

This is the network's nearest point to the xenotransplantation product production and use and therefore

xenogeneic infection/disease risk. Peripheral level members may be the:

- recipients' (or xenotransplantation contacts if these persons are the sentinel events) primary care providers,
- local or community health services,
- xenotransplantation centres or programmes,
- laboratories performing diagnostic testing, or
- other public or private partners interested in xenotransplantation such as the biomedical industry or source-animal producers.

Peripheral level network members detect and report xenogeneic infection/disease events. They also generate the data defining those events and the data defining the populations potentially at risk. Peripheral network members are responsible for the quality of their data. Detection and characterization of a xenogeneic infection/disease event should include confirmatory procedures (usually laboratory diagnostic procedures); however, these procedures should not delay the reporting of a suspected xenogeneic infection or disease event, nor should they delay the implementation of measures to treat the patient or prevent potential transmission. Surveillance records should be compatible with and be incorporated in standard clinical record keeping practices, and should be conducive to protecting patient confidentiality.

The peripheral level communicates with intermediate or central network levels by either regularly submitting data for analysis or by submitting reports of analysed data (depending on the customs and preference of the national oversight authorities). Collection and reporting of data must be simple and easy to perform, and should be done in a timely manner. Emergency reports of potentially severe and transmissible xenogeneic infectious or disease events should be communicated to the intermediate or central level as soon as possible. This usually means within a few days, but should be specifically defined by national authorities. When necessary, these emergency reports should also be communicated to the international coordinator. (See Annex 3 for examples of reporting forms.)

Finally, the peripheral network level should receive feedback from the intermediate and central levels on the quality of its data, data use, information derived from the data, and on how the peripheral level network members might improve or refine their activities.

### **3.2.2 The intermediate network level**

Depending on the public health, social and administrative organization of a country, this level may play a large role in the network (for example in administratively decentralized countries where public health functions are done by district, provincial or state public health services), or it may play a lesser role in countries where most public health functions are carried out by the national public health authority only. This level may also include large xenotransplantation programmes conducting activities in multiple centres at different locations; diagnostic laboratories serving more than one xenotransplantation centre; voluntary

associations among xenotransplantation centres or programmes; or other public or private interested partners.

The purpose of the intermediate level is to facilitate surveillance and response activities. This includes:

- aggregate and analyse data generated by the peripheral level,
- perform peripheral-level quality assurance oversight,
- provide laboratory services not available at the peripheral level,
- provide xenogeneic infection/disease event information feedback to the peripheral level,
- speed information sharing on suspected/confirmed occurrences of xenogeneic infection/disease events with other levels.

The intermediate level can also provide expertise and advice on surveillance matters to peripheral and central level network members, and provide a focal point for a multi-site investigation of xenogeneic infection/disease events. It can serve to identify trends in xenogeneic infection or disease not otherwise identifiable at the peripheral level, and may provide a mechanism for identifying them faster than at the central level.

Administratively, the intermediate level should only facilitate, never hinder the speed of data generation and event reporting, investigation and response.

### **3.2.3 Central or country-wide network level**

The central or country-wide network level is composed of a country's authorities or other bodies appointed or accredited by the country for national xenogeneic infection/disease event surveillance and response. These other bodies may include both public and private collaborating centres or programmes. When the central level functions are not performed directly by government authorities, they should be overseen and regulated by those authorities. The central level is best suited for providing input into national policies on xenogeneic infection/disease event surveillance and response, and on resource allocation for their support.

Different countries will have different regulatory and administrative preferences and practices for determining the specific manner in which the central level carries out its functions, but in general, the central level is responsible for:

- determining what xenotransplantation performance and xenogeneic infection/disease event data should be collected or otherwise be available for surveillance purposes (See Annex 4 for an example of potentially included data.),

and assure that:

- xenogeneic infection/disease event data and records are maintained and accessible,
- xenogeneic infection/disease event data are properly analysed and interpreted into useful information,
- resulting information is communicated to the most appropriate decision makers for determining and initiating any necessary responses (such as investigation, institution of management measures, etc.),
- xenogeneic infection/disease events are reported to the international network coordinator (See Annex 3 for an example of a possible international reporting form D.),
- feedback and xenogeneic infection/disease event surveillance news, both international and domestic, are provided to peripheral and intermediate level members.

Central level activities should also encompass:

- event investigation and response through:
  - verification of xenogeneic infection/disease event occurrence(s),
  - analysis of events for public health significance and impact;
- the formulation and communication of recommendations to appropriate persons or authorities for event responses;
- assurance that appropriate responses are undertaken to xenogeneic infection/disease event occurrences by the various network levels;
- support other levels by providing access to services not otherwise available at those levels,
- liaising with the international coordinator for detecting and responding to events of international magnitude,
- support for surveillance network capacity building, and
- the conduct or facilitation of epidemiologic study for:
  - performing infection/disease statistical analyses for trends and detection of rare events,
  - mobilizing resources for xenogeneic infection/disease event management activities,
  - quality assurance and evaluation activities.

The central level of the network does not perform the same function as a country's xenotransplantation regulatory authority which has oversight and authorization responsibility for the performance of xenotransplantation in the country. The two are very complementary however, and in some cases both functions may be performed by the same or overlapping groups of people or offices. Independent of administrative structure, these two functions should be performed in close synchrony with one another to address xenotransplantation-associated infectious disease risks.

### **3.2.4 The international network level**

The international level is the coordinator of the worldwide surveillance and response network, and can take the form of either a single organization or a consortium or cooperative body with a central secretariat and representing different partners interested in xenogeneic infection/disease event surveillance and response. No matter what its composition or form, the international coordinator must be given a clear mandate and sufficient resources to coordinate international event reporting, investigation, and response activities.

The international coordinator's principal activities are to:

- promote the use of internationally accepted norms for surveillance data, information, and reporting,
- facilitate clear and open channels of communication for reporting,
- register reports of xenotransplantation performance and xenogeneic infection/disease event occurrences,
- verify received information about xenogeneic infection/disease events,
- facilitate international event investigation and notification to countries and network members;
- encourage national and international capacity building,
- provide feedback to members on xenotransplantation performance, xenogeneic infection/disease events and network activities, and if necessary,
- guide and coordinate activities in response to events of international magnitude.

### **3.3 Other partners in the network**

Network membership by other partners interested in xenogeneic infection/disease event surveillance and response is desirable for strengthening and facilitating network functions and capabilities. These partners (multi-national companies conducting research-and-development clinical trials in xenotransplantation, relevant public and private professional societies, and organizations conducting infection/disease event surveillance and response activities, etc.) can be integrated into all levels of the network, participating according to their level of expertise and commitment. Different national and international regulatory and administrative norms will determine the specific principles and processes under which this can be accomplished.

### **3.4 Communication: the cement for the international network**

The key to the success of any international network is communication. In both emergency and non-emergency situations, communication channels must be reliable, easy to access, and be sufficiently resourced. Communication channels should:

- be conducive to both routine and emergency xenogeneic infection/disease event reporting, analysis and response,
- enhance cooperation among network members, and
- encourage improvements in:
  - data generation and analysis,
  - information production, reporting and feedback, and
  - information input into decision making and response activities.

Data and information reporting should move smoothly and quickly through the network and should be frequent enough to trigger timely responses. Xenogeneic infection/disease event reports should be made to receptive and expert persons or authorities capable of receiving, processing and responding to the reports. This can be enhanced by having pre-designated network contact points within participating countries. Also, routine surveillance reports should include zero or no event reporting to distinguish the state of 'no event occurring' from that of 'no report being generated'.

### **3.5 Network evaluation**

Performance indicators are useful tools for evaluating the functioning of all network levels. These indicators should reflect the ability of the network to produce all its expected outputs - data, information and response - in a timely, efficient and effective manner which in turn demonstrates the capability of the network to meet its xenogeneic infection/disease risk detection, characterization and resolution end results. (Examples of possible indicators are provided in Annex 7.)

### **3.6 Operational requirements of the network**

The surveillance network presented in this paper is only one model that could serve the need for international xenogeneic infection/disease event surveillance and response. For it or any other system to work, however, international cooperation and collaboration will be essential.

#### **3.6.1 Terms of reference**

If it is concluded that an international network is desired, then a small group of experts in the fields of xenotransplantation and xenogeneic infection/disease event surveillance can be invited to draft a terms of reference on network:

- international norms for:
  - a case definition,
  - surveillance data content and quality assurance,
  - surveillance information content and quality assurance, and
  - xenotransplantation performance and xenogeneic infection/disease event detection (including early alert systems) reporting; and
- a description of how :
  - all valid interests are considered in network decisions,

- resource allocation and priority setting is undertaken,
- activities are organized and executed,
- surveillance outputs (data, information and reporting) are quality assured, and
- how members will financially support the network at the international level.

This draft terms of reference could then be submitted to potential network members for review, refinement and agreement. If countries and other partners interested in international xenogeneic infection/disease event surveillance then wish to voluntarily join and support the network they could do so as individual members.

### **3.6.2 Day-to-day operation**

The day-to-day operation of an international network should reflect a combination of good leadership, and engender trust and confidence in the network's ability to fulfill its international role. This could be achieved by a small core of workers dedicated to performing notification and appropriate communication and response activities. This would have to be agreed to by the members at the initiation of the network.

### **3.6.3 Network resources**

Finally, a xenogeneic infection/disease event surveillance and response network will require support, both administrative and financial. Without such support, sustained xenogeneic infection/disease event surveillance and response activities, either national or international, cannot be accomplished. Resources will be needed to establish the network; provide adequate manpower and expertise; generate continuing commitment, both public and private; and invest in capacity building for ensured sustainability. It will be important for the network to be owned by all its members, sharing the benefits, as well as the costs and responsibilities.

### Glossary of xenotransplantation and infection/disease terms used in this document

**Centre:** Any institution, facility, hospital, clinic or other locality where xenotransplantation procedures involving human recipients (research, pre-clinical or clinical) are conducted. Centres need to have the capacity and capability to perform xenotransplantation to the same clinical and surgical standards as for comparable allotransplantation, have access to virology and microbiology services from nationally (or relevant) accredited laboratories, and have ability to generate, maintain and access xenotransplantation records and samples for xenotransplantation procedure follow-up, analysis and xenogeneic infection/disease event determination or evaluation.

**Contact:** A person who is in close association with a xenotransplantation product recipient, a xenotransplantation product or its source-animal, or an environment contaminated with a xenogeneic infectious agent, and because of the close nature of that association (i.e. intimate relations with the recipient, contamination of breaks in skin or mucus membrane barriers, etc.), has the potential of acquiring a xenogeneic infection. Recipient contacts may change over time and are not necessarily associated with the recipient at the time of the xenotransplantation. During an investigation of a xenogeneic infection/disease event in a xenotransplantation product recipient, contacts with xenotransplantation source-animals or xenotransplantation products prior to their use, may serve as useful indicators of the presence and transmission potential of a previously unrecognized or emerging infectious agent of xenotransplantation source-animal origin.

**Product(s):** Live cells, tissues or organs used in xenotransplantation. Xenotransplantation products include transplantable xenografts or xenotransplants as well as xenotransplantation products used in extra-corporeal procedures. They can be composed of live source-animal cells, tissue or organs alone or in combination with drugs or devices. Xenotransplantation products include human body fluids, cells, tissues or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues, or organs.

**Product recipient:** A person who receives or who undergoes *ex vivo* exposure to a xenotransplantation product.

**Programme:** May be an individual xenotransplantation centre or a multi-centre organization, but has only one administrative head responsible for all xenotransplantation-associated work conducted under it. In the context of this paper, a xenotransplantation programme may be a peripheral or intermediate level network member.

**Source-animal:** An animal from which xenotransplantation products are obtained. These animals may or may not be transgenically or otherwise genetically engineered to make their xenotransplantation products more suitable for xenotransplantation use.

All source-animals however, should be specified-pathogen-free for infectious agents known or thought to be relevant to the practice of xenotransplantation. This specified-pathogen-free status is usually achieved through the establishment of closed colonies of source-animals which are maintained under barrier-facility standards for animal health monitoring and biosecure husbandry. (See *Xenotransplantation: Guidance on Infectious Disease Prevention and Management* WHO/EMC/ZOO/98.1, *Report of WHO Consultation on Xenotransplantation* WHO/EMC/ZOO/98.1; UKXIRA draft 'Guidance Notes on Biosecurity Considerations in Relation to Xenotransplantation'; Onions D & Witt C *Xenotransplantation: an overview of microbiological risks and potentials for risk management*. Rev Sci Tech Off Int Epiz, 2000, 19(1) 289-301; and Onions D, Cooper DK & Alexander TJ et.al. *An Approach to the Control of Disease Transmission In Pig-To-Human Xenotransplantation*. Xenotransplantation 2000; 7(2)143-155; for further details.)

**Xenogeneic infection:** The development, spread or transfer of a xenogeneic agent in a human as a result of the process of xenotransplantation. It can involve either the xenotransplantation recipient, the xenotransplantation contacts, or a wider human population. It is the subject of xenogeneic infection/disease event surveillance. Presence or transmission of xenogeneic infection may occur with or without accompanying clinical signs, symptoms or disease.

**Xenogeneic infectious agent:** A microbial organism of source-animal origin. These agents (sometimes referred to as xenozoonosis) can be viruses, bacteria, fungi, agents responsible for Transmissible Spongiform Encephalopathies, or other known or as yet un-known agents, capable of invading and multiplying within the xenotransplantation recipient's or contact's body (infection). Xenogeneic infectious agents include those which develop through the occurrence of recombination or re-assortment within the new host. They also include agents which acquire the capability of being transmitted between humans because of the unique facilitating circumstances of xenotransplantation.

**Xenogeneic disease:** A clinical or subclinical pathologic process or state resulting from infection by and expression of a xenogeneic agent.

**Xenotransplantation:** Any procedure that involves the transplantation, implantation, or infusion into a human recipient of either:

- live cells, tissues, or organs from a nonhuman animal source, or
- human body fluids, cells, tissues or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues, or organs.

### Potential sources of xenogeneic infection/disease event surveillance data

The time points and methods of data collection for xenogeneic infection/disease event surveillance may include:

#### A. Recipients:

##### 1. Laboratory

- a. prior to xenotransplantation procedure: baseline blood and other body fluid and tissue samples (both for examination and archiving);
- b. at the time of the xenotransplantation: tissue and blood samples (both for examination and archiving);
- c. post-xenotransplantation:
  - i. immediately post-procedure (within the first week for examinations and archives), and
  - ii. at frequent intervals during the convalescence period and at periodic intervals long-term (for examinations, probably not less than every 6 months after the first year post-procedure, and probably life-long for the foreseeable future). See Annex 5 for examples of archive specimens.
  - iii. Non-routine sampling and archiving should be conducted as clinically indicated.

##### 2. Clinical

- a. pre-xenotransplantation: clinical assessment;
- b. at the time of xenotransplantation: continuous active clinical assessment;
- c. post-xenotransplantation: clinical review at all periodic check-ups and complete assessments of infection/disease events possibly associated with xenotransplantation. (This is accomplished with both active and passive surveillance activities.)

#### B. Xenotransplantation product recipient contacts:

##### 1. Laboratory

- a. prior to xenotransplantation or initial contact which could represent a significant exposure to a xenogeneic infectious agent: if possible, baseline blood samples archived;
- b. at the time of transplantation: probably not necessary unless a percutaneous or other significant exposure occurs;
- c. post-xenotransplantation: Testing and archiving of blood specimens if any adverse or unexplained events of possible xenotransplantation origin occur (including cord blood samples from neonates born to recipients); and probably at periodic and predetermined intervals until future reassessment of need.

2. Clinical

- a. prior to xenotransplantation or initial contact which could represent a significant exposure to a xenogeneic infectious agent: if possible, clinical history, physical examinations until future reassessment of need for establishing pre-existing conditions.
- b. at the time of transplantation: probably not necessary;
- c. post-xenotransplantation or after a contact that could represent a significant exposure to a xenogeneic infectious agent: if possible, active clinical surveillance, at scheduled recipient visits; passive reporting of any adverse or unexplained events of possible xenotransplantation origin<sup>3</sup> unless a percutaneous or other significant exposure exists.

**C. Xenotransplantation product contacts (laboratory workers or xenotransplantation product procurement workers):**

1. Laboratory

- a. prior to xenotransplantation product exposure: baseline blood specimens archived;
- b. at the time of exposure: archiving and testing of specimens only if significant exposure to xenotransplantation product or body fluids of recipient occurs;
- c. post-xenotransplantation or xenotransplantation product procurement:
  - i. archiving and testing of specimens only if significant exposure to xenotransplantation product or body fluids of recipient occurs, or
  - ii. if unexplained signs/symptoms occur which could be attributed to transmission of a xenogeneic infectious agent.

Such occurrences should be followed up with further investigation as appropriate if recipient is found to harbour a xenogeneic infection/disease with transmission potential.

2. Clinical

- a. prior to xenotransplantation: maintenance of up-to-date and comprehensive occupational health records consistent with a country's norms and regulations and complemented with xenotransplantation-specific data such as frequency and extent of source-animal or xenotransplantation product exposure, etc.;
- b. at the time of xenotransplantation or xenotransplantation product procurement: active surveillance through occupational health programme of any untoward events possibly associated with exposure to xenotransplantation product or recipient body fluids;

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<sup>3</sup> Consideration should be given to the theoretical possibility that a sentinel event will occur in a xenotransplantation contact before evidence of a xenogeneic infection or disease is detected in the xenotransplantation product recipient.

- c. post-xenotransplantation or xenotransplantation product procurement: active surveillance through an occupational health programme of any untoward events possibly associated with exposure to xenotransplantation products or recipient body fluids.<sup>3</sup>

#### **D. Xenotransplantation product contacts (animal care workers):**

##### 1. Laboratory

- a. prior to significant exposure to xenotransplantation product source-animals and source-animal herds: baseline blood samples archived;
- b. during active performance of animal care activities: probably not necessary unless a percutaneous or other significant exposure occurs, then archive blood specimens (plasma and leucocytes);
- c. at the cessation of all activities requiring exposure to source-animals or source-animal herds: testing and archiving of blood specimens (plasma and leucocytes);
- d. after cessation of work with source-animals: if unexplained symptoms occur which could be attributed to transmission of a xenogeneic infectious agent. Such occurrences should be followed up with further investigation as appropriate if source-animals are found to harbour a xenogeneic infection or disease with transmission potential.

##### 2. Clinical

- a. prior to significant exposure to xenotransplantation product source-animals and source-animal herds: baseline occupational health record consistent with national regulations and norms and complemented with xenotransplantation specific data such as frequency and extent of source-animal exposure;
- b. during active performance of animal care activities: active and passive surveillance through occupational health programme for any untoward events possibly associated with infectious disease of xenotransplantation significance;
- c. at the cessation of all activities requiring exposure to source-animals or source-animal herds: passive surveillance of any untoward events possibly associated with infectious disease of xenotransplantation significance.<sup>3</sup>

## **E. Xenotransplantation product source-animals:**

1. Laboratory<sup>4</sup>
  - a. prior to xenotransplantation product procurement:
    - i. test and archive blood specimens (plasma [or serum], and leucocytes for archives) and
    - ii. body fluids or tissues (as deemed necessary for either testing or archiving);
  - b. at the time of xenotransplantation product procurement:
    - i. test and archive blood specimens (plasma and leucocytes) and
    - ii. body fluids or tissues (as deemed necessary for either testing or archiving);
  - c. post-xenotransplantation product procurement: continued surveillance of source-animal herd and sentinels for untoward events possibly associated with infectious agents relevant to xenotransplantation; archiving of specimens for retrospective analysis.
2. Clinical
  - a. prior to xenotransplantation product procurement: animal health surveillance examinations, including laboratory and microbiological testing;
  - b. at the time of xenotransplantation product procurement: review of animal and herd health surveillance results including review of microbiological test records of source animal and the source-animal herd; physical examination of whole animal; examination of xenotransplantation product(s) at procurement;
  - c. post-xenotransplantation: continued surveillance of source-animal herd and its sentinels for untoward events.

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<sup>4</sup> Clinical laboratory examinations should be conducted by an accredited laboratory competent to undertake veterinary and zoonotic disease analyses including microbiological testing for agents of the source-animal species. Clinical examinations should be conducted by a veterinarian with expertise in the source-animal species and in requirements for the production of biologics quality animal-origin products.

**ANNEX 3****Examples of network reporting forms**

The level of detail required on a country's xenotransplantation performance and xenogeneic infection/disease event reporting forms will vary according to that country's administrative and regulatory framework for xenotransplantation oversight and surveillance activities, its health care system, and the phase of xenotransplantation practice (i.e. clinical trial, post-marketing practice, etc.). As such, these examples should only serve as starting points for developing such reporting forms. It should be recognized that any eventual forms will need to be periodically reevaluated, revised and up-dated.

The use of short forms (see following pages) for reporting aggregated data may be possible where complete databases are maintained at the peripheral or intermediate level, and the information they contain can be linked and accessed through the use of registration, authorization or licensing codes. More extensively detailed reporting forms may be necessary if a country's authorities prefer to maintain all relevant data in a centralized location. In such cases, reporting forms may reflect the level of detail presented in Annex 4 on database contents.

Reporting standardization and timeliness can be enhanced through the use of electronic forms and other aspects of computer and internet technology.

**A. Peripheral or intermediate level to central level reporting form**

<b>XENOTRANSPLANTATION PERFORMANCE REPORT<sup>1</sup></b> (for peripheral or intermediate level to central level reporting)		
<b>1. Period covered in this report:</b> (i.e. 1 January 2000 to 1 April 2000)		
<b>2. Reporting Official</b> Name and Title:		<b>Date of report:</b>
Position or affiliation:		Telephone:
Address:		E-mail: FAX:
<b>3. Xenotransplantation Centre</b> (for programmes list each centre on a separate sheet)		
Name:	Code number:	
Centre's Responsible Official:(name and title)		
Address:	Telephone:	E-mail: FAX:
<b>4. Xenotransplantations performed during the reporting period:</b> (use separate sheet for each type of procedure performed and for each centre where they are conducted)		
Type of xenotransplantation(s) performed:		
Total number of type performed during reporting period:		
<b>Registration codes:</b>		
a. Recipient undergoing the above procedure: (list each recipient separately using an assigned code or other unique identifier; use additional sheets as necessary)	b. Code for xenotransplantation product used in the recipient:	c. Protocol code
<b>5. Name and address of facility where records of the xenotransplantation procedure(s) are maintained:</b> (if other than the Centre listed above)		
<b>6. Number, type and date of identified xenogeneic infection/disease event(s) known to have resulted from these reported procedures:</b> (Each xenogeneic infection/disease event should have been reported immediately at the time of detection using an independent event reporting form as exemplified in form C. Copies of these initial reports of xenogeneic infection/disease events should also be submitted immediately to the international network coordinator.)		
<b>7. <input type="checkbox"/> Check if NO xenotransplantation(s) have been performed during this reporting period for the centre (name) _____ covered on this form.</b>		
<b>8. <input type="checkbox"/> Check if NO xenogeneic infection/disease events have been reported during this reporting period.</b>		

<sup>1</sup> A copy of this form should be shared with the international network coordinator within 15 days of the end of the reporting period.

**B. Central level to international level reporting form**

<b>XENOTRANSPLANTATION PERFORMANCE REPORT<sup>1</sup></b> (for reporting to international level)		
<b>1. Period covered in this report:</b> (i.e. 1 January 2000 to 1 March 2000)		
<b>2. Reporting Official</b> Name and affiliation:		<b>Date of report:</b>
Address:		Telephone: E-mail: FAX:
<b>3. Source of information:</b> (e.g. ministry of health, national registry, xenotransplantation centre, xenotransplantation programme, physician, other health care provider, etc.)		
<b>4. Information on xenotransplantation performed during this period:</b> (use separate listing for each type of procedure performed and for each centre where they are conducted.)		
<b>Type of xenotransplantation(s) performed:</b>	<b>Number of transplantations performed:</b>	<b>Authorization code or other national identifying information on xenotransplantation performer (i.e. centre):</b>
Responsible national authority to contact for further information:		
Name:		
Position:		
Address:		
Telephone:		
E-mail:		
FAX:		
<b>5. Number, type and date of xenogeneic infection/disease events known to have resulted from these reported procedures :</b> (Initial reports of xenogeneic infection/disease events should be submitted to the international network coordinator immediately using form D)		
<b>6. <input type="checkbox"/> Check if NO xenotransplantation(s) have been performed during this reporting period for _____ (country, state, province, district etc. covered in this report.</b>		
<b>7. <input type="checkbox"/> Check if NO xenogeneic infection/disease events have been reported during this reporting period.</b>		

<sup>1</sup> This report should be completed and submitted to the international network coordinator within 15 days of the end of the reporting period.

### C. Peripheral or intermediate level to central level xenogeneic infection/disease event reporting form

Page 1		
<b>XENOGENEIC INFECTION/DISEASE EVENT REPORT<sup>1</sup></b> (for peripheral or intermediate level to central level reporting)		
<b>1. Report date</b>	<b>2. Report type</b> _____initial _____follow-up	
<b>3. Report Author:</b> _____ Position: _____ Affiliation:(xenotransplantation centre, health care facility, etc.) Address: _____ Telephone: _____ E-mail: _____ FAX: _____		
<b>4. Xenotransplantation procedure performed:</b>		
Date of procedure: _____		Protocol code: _____
<b>5. Patient identification code:</b>	<b>6. Xenotransplantation centre code:</b>	<b>7. Source-animal code:</b>
<b>8. Xenogeneic infection/disease event</b> a. Description of event (in medical terms - include related signs/symptoms, diagnosis, treatment, course and outcome. Use additional sheets as needed)		
b. Date of onset of first sign/symptom of event:		
c. Is event thought to be due to or associated with the xenotransplantation product? _____ YES                      _____ NO                      _____ UNKNOWN		
d. If yes, is the suspected/confirmed cause of the event an infectious pathogen? _____ YES                      _____ NO		
e. If yes, please state:		
1. Identity of pathogen:		
2. Method of identification:		
3. Laboratory specimen(s) tested:		
4. Date of specimen collection:		
5. Identification number of specimen:		
6. Name, location and contact information of laboratory conducting diagnostic testing:		

<sup>1</sup> This report must be submitted to the central network level as soon after the detection of a xenogeneic infection/disease event as possible. This usually means within a few days. The submission of this report should be accompanied by a xenotransplantation performance report (or an interim report) as exemplified in form A for the reporting period in which this event(s) has occurred. A copy of these reports should be simultaneously shared with the network international coordinator.

**XENOGENEIC INFECTION/DISEASE EVENT REPORT<sup>1</sup>**  
(for peripheral or intermediate level to central level reporting)

**9. Patient's current health status.** (Check all that apply)

- patient died (date: \_\_\_\_\_ )                       hospitalized
- critical or life threatening                                       outpatient care
- stable, but persistence of significant disability or incapacity
- other serious condition or medical events (state)

**10. Status of xenotransplantation product at the time of this report** (Check all which apply)

- present in patient       functional       removed (date of removal: \_\_\_\_\_ )

**11. Patient's current health care provider** (If other than the author of this report)

Name:

Position (or affiliation)

Address:

Telephone:

E-mail:

FAX:

**12. Xenotransplantation associated treatments, clinical-care and follow-up examination records.**

a. Name, address, and telephone number of centre or facility where patient's treatment, clinical-care and follow-up examination records are maintained.

b. Name, address and telephone number of responsible official of centre or facility.

**13. Laboratory diagnostic records.**

Name, address, and telephone number of laboratory where diagnostic or other laboratory test records are maintained.

**14. Biologic specimens archive facility maintaining patient's biologic specimens and records.**

Name, address, and telephone number of archive facility.



**XENOGENEIC INFECTION/DISEASE EVENT REPORT<sup>1</sup>**  
(for reporting to international level)

**7. Laboratory specimens taken?**

YES  NO

List the type, date and results of relevant laboratory testing done on case. Please also provide name and contact information for laboratory performing diagnostic testing.

**8. Are there secondary cases?**

YES  NO

a. If yes, how many?:

b. Date(s) of presentation: (List all)

c. Case definition criteria used to identify secondary cases:

d. Number of secondary cases that have resulted in death:

**9. Associated laboratory tests:**

List the type, date and results of relevant laboratory testing done on all secondary cases. Please also provide name and contact information for laboratory(ies) performing diagnostic testing.

**10. Action taken or planned by health care provider and/or national authority:**

**11. Is assistance from international coordinator requested?:**  YES  NO

### **Example of potential contents of a xenotransplantation database**

The below is a comprehensive list of possible data fields that could be included in a xenotransplantation database. The decision on which data fields are essential and therefore must be included in a particular database is the responsibility of national authorities. International databases should contain only information essential for the international coordination of surveillance activities, and therefore should complement but not duplicate or replace databases maintained at other levels.

#### **A. Data on xenotransplantation centre**

1. Name and address of centre (institution/hospital/clinic, etc.) conducting the xenotransplantation.
2. Name and contact information of responsible official of the centre.
3. If centre is part of a multi-centre xenotransplantation programme, name and contact information of that programme's responsible official.
4. Name and contact information of person responsible for actually performing the xenotransplantation procedure.
5. Licence/registration number or other authorizing designation for the centre.
6. Name and contact information for the body issuing the licence/registration number or other authorizing designation.

#### **B. Data on xenotransplantation recipient**

1. Recipient's unique identifier (name, number, code, etc.).
2. Recipient's:
  - a. Contact information (address, telephone, e-mail, fax, etc.),
  - b. Gender,
  - c. Birth date,
  - d. Place of birth,
  - e. Race or ethnic background.
3. Recipient's clinical data, including:
  - a. Name and contact information of physician or attending health care provider,
  - b. Patient blood type,
  - c. Indication for xenotransplantation procedure,
  - d. Other presenting conditions.

#### **C. Xenotransplantation procedure data**

1. Procedure type (implant, bridge, duration of bridge, etc.).
2. Procedure protocol number or code.
3. Anatomic site of procedure.
4. Date of procedure.

5. Location where xenotransplantation was performed (name and address of xenotransplantation centre if different from data provided in part A.) and performing physician or health care provider (if different from that in B.3.a.).
6. Location of (or information needed to access) clinical records of xenotransplantation procedures and clinical care including laboratory reports.
7. Type of xenotransplantation product used and trace-back identifiers including:
  - a. Xenotransplantation product name and unique identification number (lot number, source-animal number etc.),
  - b. Name and address of producer of xenotransplantation product,
  - c. Name and contact information of producer's responsible official.

#### **D. Xenotransplantation source data**

1. Animal producer:
  - a. Name, address and registration/authorization/licence number of source-animal producer,
  - b. Name and contact information of responsible official,
  - c. Name and address of source-animal facility,
  - d. Name and contact information of responsible facility veterinarian.
2. Source-animal:
  - a. Type of source-animal (species/strain/genetic background, etc.),
  - b. Source-animal's unique identification number or code,
  - c. Date of animal's birth,
  - d. Location of source-animal health and husbandry records (name and contact information for accessing records),
  - e. Name, identification number or code, location of source-animal herd.
  - f. Location of source-animal herd health and husbandry records if other than in d. above.
3. Xenotransplantation product procurement:
  - a. Name, address and registration/authorization/license number of xenotransplantation procurement facility,
  - b. Name and contact information of procurement facility's responsible official,
  - c. Date of xenotransplantation procurement,
  - d. Name and contact information of person responsible for the procurement.

#### **E. Xenotransplantation follow-up data**

1. Xenotransplantation product recipient name/unique identifier number or code and contact information.
2. Date of follow-up procedure.
3. Name and address of follow-up centre.
4. Name, contact information and registration/authorization/licence number of follow-up physician or health care provider.

5. Status of xenotransplantation product (i.e. present/functional/removed [date]).
6. Recipient's health status (reported, confirmed).
7. Follow-up examination and laboratory report results.
8. Location and access information for clinical examination and laboratory records.

## **F. Xenogeneic infection/disease event report data**

1. Recipient infection/disease event data:
  - a. Recipient name/unique identifier number or code and contact information,
  - b. Date of infection/disease event report,
  - c. Name and address of event reporting centre or programme,
  - d. Name, contact information and registration/authorization/licence number of the reporting physician, health care provider or official,
  - e. Recipient's health status (reported, confirmed),
  - f. Status of xenotransplantation product (i.e. present/functional/removed [date]),
  - g. Description of suspected/confirmed event,
  - h. Event follow-up examination and laboratory report results,
  - i. Suspected/confirmed cause of event (xenogeneic infectious agent or disease process),
  - j. Location of and contact information for accessing examination and laboratory records,
  - k. Location and contact information for accessing archived biologic specimens.
2. Xenotransplantation product recipient or xenotransplantation contact data (event and follow-up):
  - a. Name/unique identifier number or code and contact information,
  - b. Date of follow-up procedure,
  - c. Name and address of follow-up centre,
  - d. Name, contact information and registration/authorization/licence number of follow-up physician or health care provider,
  - e. Duration and nature of contact with xenotransplantation product recipient or xenotransplantation products,
  - f. Recipient's health status (reported, confirmed),
  - g. Follow-up examination and laboratory reports.,
  - h. Location and contact information for accessing examination and laboratory records.
3. Source-animal data:
  - a. Name and contact information of animal facility and facility's responsible official,
  - b. Name and contact information of responsible facility veterinarian,
  - c. Unique identification number or code of animal experiencing xenotransplantation-relevant infection or disease,
  - d. Source-animal species/strain/genetic background,
  - e. Source-animal date of birth,

- f. Source-animal's herd identification number and herd location,
- g. Date of infection/disease event in source-animal/ source-animal herd,
- h. Description of suspected/confirmed infection/disease event,
- i. Infection/disease event follow-up examination and laboratory reports,
- j. Suspected/confirmed cause of infection/disease (xenogeneic infectious agent),
- k. Outcome of source-animal/source-animal herd infection/disease event,
- l. Location and contact information for accessing examination and laboratory records,
- m. Archive location and contact information for accessing source-animal/source-animal herd biologic specimens.

### **G. Xenotransplantation product recipient death report**

1. Recipient name/unique identifier number or code and last contact information.
2. Date and location of death.
3. Name and address of centre reporting death.
4. Name, contact information and registration/authorization/licence number of physician, health care provider or official reporting death.
5. Suspected/confirmed cause of death.
6. Status of xenotransplantation product at time of death (present/functioning/non-functioning/removed [date, by who], infection or contamination).
7. Autopsy findings.
8. Name and contact information of person performing autopsy.
9. Autopsy microbiology and pathology laboratory results.

## Examples of possible biologic specimens for storage in xenotransplantation archives

### A. Xenotransplantation product recipient:

1. Biologic specimens designated for retrospective public health investigations of possible xenogeneic infection or disease event occurrences. They should be archived for at least 50 years beyond the date of the xenotransplantation procedure. Specimens should be easily accessible to public health authorities and be identified in such a way as to permit their linkage with source-animal health records and archived specimens, the centre or programme conducting the xenotransplantation procedure and the health records of the recipient. The type and quantity of specimens may and should vary with the clinical procedure and the age of the recipient, but the below examples should be considered as typical.

#### 2. Specimen type and volume:

- a. at least 3 to 5 0.5 ml aliquots of citrated or EDTA-anticoagulated plasma,
- b. two aliquots of viable ( $1 \times 10^7$ ) leukocytes,
- c. other body fluid or tissue specimens as deemed appropriate for the recipient's care and the xenotransplantation procedure to be undertaken,
- d. specimens from any xenotransplantation product that is removed (i.e. post-rejection or at the time of recipient death).

#### 3. Timing of specimen collection:

- a. prior to xenotransplantation procedure, ideally 2 sets of samples taken one month apart (if possible), with one set of specimens taken at the beginning of the procedure,
- b. set of specimens taken in the immediate (within the first week) post-xenotransplantation period, then at one month and 6 months post procedure,
- c. set of specimens taken at intervals no greater than annually for the first two years post procedure,
- d. set of specimens taken at intervals no greater than every five years (for the foreseeable future) probably for the remainder of the recipient's life.

A more frequent sampling schedule may be undertaken if indicated by the recipient's clinical course or by the specific xenotransplantation protocol.

4. At the time of the recipient's death, paraffin embedded tissue, snap-frozen ( $-70^{\circ}$  C) tissues and tissues suitable for electron microscopy should be collected and suitably archived (duration of 50 years).

### B. Persons other than the xenotransplantation product recipient:

1. Biologic specimens designated for retrospective public health investigations of possible xenogeneic infection or disease event occurrences. They should be archived for at least 50 years beyond the date of the xenotransplantation procedure, contact or exposure. Specimens should be easily accessible to public health authorities and be identified in such a way as to permit their linkage with source-animal health records and archived specimens, the centre or programme conducting the xenotransplantation procedure and the health records of the recipient and relevant contacts. The timing, type and quantity of specimens may and should vary with the reason why the specimens are taken (i.e. clinical illness), the type of contact experienced with the xenotransplantation recipient or product, and the age of the concerned person. The below examples should be considered as typical.

2. Xenotransplantation product recipient contacts:

a. Specimen type and volume:

- i. at least 3 to 5 0.5 ml aliquots of citrated or EDTA-anticoagulated plasma,
- ii. two aliquots of viable ( $1 \times 10^7$ ) leukocytes,
- iii. specimens as appropriate to the clinical condition under investigation (if necessary).

b. Timing of specimen collection:

- i. baseline sample (if possible) before recipient's xenotransplantation procedure or before any contact with recipient that represents a serious exposure to a xenogeneic infectious agent,
- ii. after mucosa or skin barriers are broken or other form of significant exposure occurs (including parturition; if repeated events, consideration should be given to developing a practical sampling schedule),
- iii. if unexplained symptoms occur in the contact which could be attributable to the transmission of a xenogeneic infectious agent from the recipient,
- iv. if possible, during a post-infection convalescent period of such an occurrence (if appropriate and suspected to be associated with a xenogeneic infection transmission),
- v. possibly at one year intervals until future reassessment of need, but probably not less than every five years.

The frequency of sampling should be adjusted to reflect the recipient's and/or the contacts clinical course.

3. Xenotransplantation product contacts (laboratory workers and animal care workers having direct contact with xenotransplantation products or source-animals, and who could serve as useful indicators for the presence and transmission potential of previously unrecognized or emerging xenogeneic infectious agents.

- a. Specimen type and volume:
  - i. at least 3 to 5 0.5 ml aliquots of citrated or EDTA-anticoagulated plasma,
  - ii. two aliquots of viable ( $1 \times 10^7$ ) leukocytes,
  - iii. specimens as appropriate to the clinical condition under investigation (if necessary).
- b. Timing of specimen collection:
  - i. baseline specimens before first contact with any xenotransplantation product or source-animal,
  - ii. after mucosa or skin barriers are broken or other form of significant exposure occurs during contact with xenotransplantation products or source-animals. (if repeated events, consideration should be given to developing a practical sampling schedule),
  - iii. if unexplained symptoms occur which could be attributable to the transmission of a xenogeneic infectious agent from the xenotransplantation product or source-animal,
  - iv. if possible, during a post-infection convalescent period of such an occurrence (if appropriate and suspected to be associated with a xenogeneic infectious agent transmission).

The frequency of sampling should be adjusted to reflect the recipient's or the contacts clinical course.

### **C. Source-animals:**

1. Biologic specimens designated for public health investigations. They should be taken at the time of xenotransplantation product procurement or harvesting and be archived to permit any necessary retrospective analysis by public health authorities. Such specimens should be readily accessible and identifiable for linkage with both source-animal and xenotransplantation product recipient health records. Animal specimens and animal health records including records of microbiological testing should be kept for at least 50 years beyond the date of the animal's death.
2. Prior to xenotransplantation product procurement (i.e. one month prior to procurement), specimens considered for collection should include:
  - a. plasma, (preferred)
    - i. ideally at least 10 0.5 ml aliquots of citrated or EDTA-anticoagulated, and
    - ii. stored to permit subsequent serology and viral testing;
  - or alternatively
  - b. serum,
    - i. ideally at least 10 0.5 ml aliquots, and
    - ii. stored to permit subsequent serology and viral testing; and
  - c. leukocytes,
    - i. at least 5 aliquots of viable ( $1 \times 10^7$ ) cells, and

- ii. cryopreserved for subsequent isolation of nucleic acid and proteins, viral co-culture assays, or other tissue culture assays;
- d. other specimens as deemed necessary for future analysis of detected health conditions relevant to xenotransplantation.

3. At the time of procurement, specimens considered for collection should include:

- a. plasma, (preferred)
  - i. ideally at least 10 0.5 ml aliquots of citrated or EDTA-anticoagulated, and
  - ii. stored to permit subsequent serology and viral testing;or alternatively
- b. serum,
  - i. ideally at least 10 0.5 ml aliquots, and
  - ii. stored to permit subsequent serology and viral testing; and
- c. leukocytes,
  - i. at least 5 aliquots of viable ( $1 \times 10^7$ ) cells, and
  - ii. cryopreserved for subsequent isolation of nucleic acid and proteins, viral co-culture assays, or other tissue culture assays;
- d. paraffin-embedded, formalin fixed, and cryopreserved tissue samples from source-animal organs
  - i. relevant to the specific xenotransplantation being performed, and from
  - ii. major organ systems (e.g. spleen, liver, bone marrow, central nervous system, lung) if the animal dies during xenotransplantation product procurement (harvesting).
- e. other specimens as deemed necessary for future analysis of detected health conditions relevant to xenotransplantation.

4. If necropsy on the animal is performed at a time subsequent to the xenotransplantation product procurement or harvesting, tissues of major organ systems (ie. spleen, liver, bone marrow, central nervous system, lung) should be cryoperserved and archived.

## Ethical principles applicable to xenogeneic infection/disease surveillance and response

As xenogeneic infection/disease event surveillance and response is based on the collection, storage and use of detailed data on individuals, and groups of xenotransplantation product recipients and xenotransplantation contacts, consideration must be given to the ethical issues resulting from the need to protect the rights of individuals and the need to provide for the safety and health of communities. Health care personnel, epidemiologic investigators and users of surveillance information will be required to address these issues thoughtfully and with an understanding of the established principles for the ethical conduct of clinical practice and epidemiologic study. The applicable internationally-accepted ethical principles (as presented in the *International Guidelines for Ethical Review of Epidemiological Studies* [CIOMS 1991] and the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* [CIOMS 1993]) include:

1. Respect for individual autonomy. This includes protection for those with diminished capacity for self-determination against harm or abuse, and provides for:

- informed consent whenever data is linked to private or personal identifiers;
- ethical body oversight of data use and distribution when informed consent cannot be sought, as in the case of:
  - the use of publicly available information, (the definition of 'public' may vary between countries and the definition used in the country of the individuals(s) concerned should be respected),
  - government legislation or legal contracts with the individual which waive the requirement for informed consent for the sake of minimizing risk of harm to the individual or for overwhelming public benefit;
- notification of individuals or their public representatives that their data might be used for future epidemiological studies that are undetermined at the time of the notification;
- protection of confidentiality by:
  - omitting from analyses or distribution that data which might lead to the identification of individuals,
  - limiting access to identifying data in registries and archives,
  - incorporating confidentiality safeguards in the administration of individual records, registries and sample archives,
  - overseeing registries and archives for the safe and effective storage of data, samples and specimens;
- respect for an individual's wishes about the use of that person's data (overseen exceptions can be made if there is clear and overwhelming danger to public health).

2. The obligation to maximize possible benefit and minimize possible harm to the individual through the use of his data. Activities which promote this include:

- informing individuals either directly or indirectly of study findings which pertain to their health,
- applying findings to public health measures to improve the individual's and public health.

3. The use of safeguards against avoidable harm to the individual (stigmatization, prejudice, loss of prestige or self-esteem, or economic loss as a result of being a subject of an xenogeneic infection/disease event surveillance activity). Data analyses should always be presented in a manner which anticipates and avoids misinterpretation that might cause harm to individuals. This can be accomplished by unlinking data from personal identifiers or masking personal identifiers necessary for data analysis in order to protect individual confidentiality.

4. Cases which are considered scientifically alike should be treated alike during epidemiologic investigation and xenogeneic infection/disease event management responses. This means that studies should be designed to obtain knowledge that benefits the class of individuals which the studied person(s) represents.

5. Epidemiologic investigators should respect the ethical standards of both their own countries and that of the xenotransplantation product recipient or others under study.

Finally, there will also be xenotransplantation-specific ethical issues which must be given consideration both internationally and within the context of different countries' social, cultural, and religious beliefs and legal norms. These include among others, the question of subjecting xenotransplantation product recipients or xenotransplantation contacts to lifelong surveillance, or expecting recipients (and contacts) to continue participating in surveillance activities in the event of an unsuccessful xenotransplantation procedure outcome.

### Examples of possible indicators for xenogeneic infection/disease event surveillance and response network evaluation

network level	activity under evaluation	indicators
peripheral	data generation	<p>No. of data sets generated during the reporting period on:</p> <ol style="list-style-type: none"> <li>Xenotransplantation(s) performed,</li> <li>Follow-up procedures conducted,</li> <li>Xenogeneic infection/disease events detected,</li> <li>Xenotransplantation product sources and production procedures, and/or</li> <li>Other data sources needed for database.</li> </ol> <p>- % of data sets in each category which have been quality assured and assessed for validity and completeness.</p> <p>- % of data sets with operational links to all other relevant data sources of database.</p>
	data analysis, interpretation and use	<p>No. of xenogeneic infection/disease event reports (from either raw or locally analysed data) made to xenotransplantation product recipient's or xenotransplantation contact's health care provider during the reporting period.</p> <ul style="list-style-type: none"> <li>- % of these reports made within 24 hours of data generation.</li> <li>- % of these reports resulting in the undertaking of patient care or transmission-prevention measures.</li> <li>- % of infection/disease reports which resulted in treatment measures not beneficial to the patient or not preventing transmission.</li> </ul> <p>No of xenogeneic infection/disease event reports (from either raw or analysed data) on source-animals, source-animal herds, xenotransplantation product procurement procedures etc., made to appropriate responsible authorities during the reporting period.</p> <ul style="list-style-type: none"> <li>- % of these reports made within 24 hours of data generation.</li> <li>- % of these reports documenting cause of event.</li> <li>- % of these reports resulting in the implementation of effective measures to exclude infectious animals/xenotransplantation products from xenotransplantation product use.</li> </ul> <p>No. of communications made within the reporting period to local data users (health care providers, infection control officers, centre administrators etc. ) summarizing local and network surveillance findings.</p> <p>No. of feedback communications received from data users on the quality and usefulness of generated data and information.</p>

**Examples of possible indicators for xenogeneic infection/disease event surveillance and response network evaluation**

	<b>activity under evaluation</b>	<b>indicators</b>
<b>peripheral</b>	data reporting to network	<p>No. of xenotransplantation(s) and post-xenotransplantation follow-up procedures performed during the reporting period.</p> <ul style="list-style-type: none"> <li>- % reported to next level in network.</li> <li>- % of reports with complete data sets.</li> <li>- % of reports made within designated deadline for submission.</li> </ul> <p>No. of reports submitted to next level in network during reporting period of:</p> <ol style="list-style-type: none"> <li>a. recipient xenogeneic infection/disease events,</li> <li>b. source-animal(herd) infection/disease events relevant to xenotransplantation, and</li> <li>c. infection/disease events in xenotransplantation contacts which possibly originated from xenotransplantation recipient (or product) exposure.</li> </ol> <ul style="list-style-type: none"> <li>- % with complete data sets.</li> <li>- % reported within designated deadline for submission.</li> </ul> <p>No. of peripheral level reports resulting in assistance from other network levels for:</p> <ol style="list-style-type: none"> <li>a. analysing generated data.</li> <li>b. responding to suspected/confirmed occurrences of xenogeneic infection/disease events.</li> </ol> <p>No. of multi-level network responses resulting in successful resolution of reported event.</p> <p>No. of feedback communications received from other network levels on quality and use of generated data and on effectiveness and possible improvements in peripheral level responses.</p>

**Examples of possible indicators for xenogeneic infection/disease event surveillance and response network evaluation**

network level	activity under evaluation	indicators
<b>intermediate</b> (Where intermediate level serves a peripheral function, those indicators also apply)	data generation/ aggregation	No. of data sets generated and/or aggregated during the reporting period on: <ol style="list-style-type: none"> <li>a. Xenotransplantation(s) performed,</li> <li>b. Follow-up procedures conducted,</li> <li>c. Xenotransplantation product sources and production procedures,</li> <li>d. Other data as needed for databank, including</li> <li>e. Any xenogeneic infection/disease events detected.</li> </ol> - % of data sets in each category which have been quality assured and assessed for validity and completeness - % of data sets with operational links to all other relevant data sources of database.
	data/information analysis	No. of epidemiologic studies and trend analyses performed by the intermediate level on generated and aggregated data and information (on a. through e. above) during the reporting period. <ul style="list-style-type: none"> <li>- % of these analyses meeting established quality assurance standards.</li> <li>- % of these analyses hindered by difficulty in accessing data or information maintained at the peripheral level.</li> </ul> No. of xenogeneic infection/disease events investigated/confirmed by intermediate level during reporting period. <ul style="list-style-type: none"> <li>- % of event investigations hindered by difficulty in accessing or interpreting data or information maintained at the peripheral level.</li> </ul>
	data/information reporting	No. of intermediate level reports (generated from (raw or analysed data or information) submitted during reporting period to: <ol style="list-style-type: none"> <li>a. central level,</li> <li>b. international coordinator.</li> </ol> - % of intermediate level reports on a. through e. above sent to central level within the designated time-frame for receipt. - % of intermediate level reports on xenogeneic infection/disease events sent to central level and shared with international coordinator within the designated time-frame for receipt.

**Examples of possible indicators for xenogeneic infection/disease event surveillance and response network evaluation**

Network level	activity under evaluation	indicators
<b>intermediate</b>	data and information use	<p>No. of intermediate level epidemiologic analyses of aggregated data/information conducted during the reporting period which lead to the identification of trends or events not recognized at the peripheral level.</p> <p>No. of reports on xenogeneic infection/disease events leading to specific intermediate level actions taken to address them. - % of events not addressed by intermediate level because of problems accessing data maintained at the peripheral level.</p> <p>No. of intermediate level reports resulting in assistance from the central or other levels for:</p> <ol style="list-style-type: none"> <li>a. analysing generated and aggregated data.</li> <li>b. responding to suspected/confirmed xenogeneic infection/disease events.</li> </ol> <p>No. of feedback communications received from other network levels on quality and use of data generated or aggregated at level and on the effectiveness and possible improvements in intermediate level operations.</p> <p>No. of feedback communications made to peripheral level during reporting period (covering generation, quality and use of data at the peripheral level).</p> <p>No. of public communications made during the reporting period by the intermediate level on xenogeneic infection/disease event occurrences.</p>

**Examples of possible indicators for xenogeneic infection/disease event surveillance and response network evaluation**

network level	activity under evaluation	indicators
<b>central</b>	data and information registration	<p>No. of registrations made during reporting period on:</p> <ul style="list-style-type: none"> <li>a. xenotransplantation procedures performed,</li> <li>b. post-xenotransplantation follow-up procedures conducted,</li> <li>c. xenogeneic infection/disease events detected.</li> </ul> <p>- % of registrations made within the designated time-frame for registration of:</p> <ul style="list-style-type: none"> <li>a. xenotransplantation procedures,</li> <li>b. follow-up reports,</li> <li>c. xenogeneic infection/disease event reports made within the designated deadline for reporting an event detection.</li> </ul> <p>- % of a., b., and c. above containing complete and quality assured data and information.</p>
	data and information analysis	<p>No. of epidemiologic studies and trend analyses (using a predetermined and quality-controlled standard operating procedure for epidemiologic analysis) performed by level on received data and information and reported during reporting period to:</p> <ul style="list-style-type: none"> <li>a. national authority,</li> <li>b. international coordinator.</li> </ul> <p>- % of these reports which can be linked to specific actions taken by the national authority to improve xenogeneic infection/disease event surveillance and response, or prevent or manage xenogeneic infection/disease events.</p> <p>- % of these epidemiologic studies and trend analyses hindered by difficulty in accessing data or information maintained at the peripheral or intermediate levels.</p> <p>No. of xenogeneic infection/disease events investigated/confirmed by central level during reporting period.</p> <p>- % of these reports on xenogeneic infection/disease events sent within the designated deadline to:</p> <ul style="list-style-type: none"> <li>a. national authority,</li> <li>b. international coordinator.</li> </ul> <p>- % of event investigations by the central level hindered by difficulty in accessing or interpreting data maintained at the peripheral or intermediate levels.</p>

(cont'd)

**Examples of possible indicators for xenogeneic infection/disease event surveillance and response network evaluation**

network level	activity under evaluation	indicators
<b>central</b>	notification and response	<p>No. of reports on xenogeneic infection/disease events which can be linked to specific actions taken by the national authority or the international coordinator to address the event.</p> <p>No. of public communications made by central level on xenogeneic infection/disease event occurrences during the reporting period.</p> <p>No. of feedback communications made to intermediate and peripheral levels during reporting period (covering generation, quality and use of data at those levels).</p>

**Examples of possible indicators for xenogeneic infection/disease event surveillance and response network evaluation**

Network level	activity under evaluation	indicators
<b>international coordinator</b>	international registration and monitoring	<p>No. of reports on the performance of xenotransplantation procedures registered by the international coordinator.</p> <ul style="list-style-type: none"> <li>- % of those reports registered by the coordinator within the designated time-frame.</li> <li>- % of reports containing complete and quality assured information on procedures performed.</li> </ul> <p>No. of reports produced within the reporting period on the epidemiologic trends identified thru the analysis of internationally compiled information.</p>
	international notification and response	<p>No. of xenogeneic infection/disease events registered by international coordinator during the reporting period.</p> <ul style="list-style-type: none"> <li>- % of events registered within the designated time-frame for event reporting.</li> <li>- % of reports containing sufficient information for adequate event identification and verification.</li> <li>- average duration of time taken to complete an international verification of reported events.</li> </ul> <p>No. of internationally coordinated activities undertaken as a result of event reports.</p> <ul style="list-style-type: none"> <li>- average duration of time required to mount an internationally coordinated activity.</li> <li>- % of internationally coordinated activities contributing to an effective resolution of the reported event.</li> </ul> <p>No. of internationally coordinated activities evaluated by international coordinator and used to improve network functioning and enhance xenogeneic infection/disease event surveillance and response.</p>

### Useful references on xenotransplantation

The following documents provide further information on xenotransplantation and surveillance.

Committee on Xenotransplantation, Health Council of the Netherlands (1998): Xenotransplantation. No. 1998/01E, Rijswijk

Département Médical et Scientifique, Etablissement Français Des Greffes (1998): Xénogreffes, Evolution possible des pratiques médicales: Problématiques des risques microbiologiques Propositions pour un encadrement de ces pratiques. 5 rue lacuée, 75012 Paris

International Society for Heart and Lung Transplantation (2000): Report of the Xenotransplantation Advisory Committee of the International Society for Heart and Lung Transplantation: The Present Status of Xenotransplantation and Its Potential Role in the Treatment of End-Stage Cardiac and Pulmonary Diseases. *Journal of Heart and Lung Transplantation* 19(12), 1125-1165.

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National Transplant Commission of Spain (1999): Report of the Xenotransplantation Commission: Recommendations for the Regulation of Xenotransplantation Activities. Spain, [www.msc.es/ont/ing/f\\_comision.htm](http://www.msc.es/ont/ing/f_comision.htm)

Nuffield Council on Bioethics (1996): Animal-to-Human Transplants. The Ethics of Xenotransplantation. Nuffield Council in Bioethics, 28 Bedford Square, London, WC1B 3EG

Organization for Economic Cooperation and Development (1999): Xenotransplantation: International Policy Issues. Paris, [www.oecd.org/dsti/sti/s\\_t/biotech](http://www.oecd.org/dsti/sti/s_t/biotech)

Swedish Committee on Xenotransplantation (1999): From One Species To Another - Transplantation from Animals to Humans. Swedish Government Official Report No. 1999:120. Stockholm

Therapeutic Products Programme (TPP) of Health Canada: Proposed Canadian Standard for Xenotransplantation. Ottawa, [www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/btox.html](http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/btox.html)

United Kingdom Department of Health (1996): Animal Tissue into Humans. A report by the Advisory Group on the Ethics of Xenotransplantation. UK Department of Health, P.O. Box 777, London SE1 6XH, [doh@prologistics.co.uk](mailto:doh@prologistics.co.uk)

United Kingdom Xenotransplantation Interim Regulatory Authority Secretariat:  
Draft Report of the Infection Surveillance Steering Group of the UKXIRA.  
Department of Health, Room 311, Wellington House, 133-155 Waterloo Road,  
London, SE1 8UG

United Kingdom Xenotransplantation Interim Regulatory Authority Secretariat  
(2000): Guidance note on Biosecurity considerations in relation to  
xenotransplantation. Department of Health, Room 311, Wellington House, 133-155  
Waterloo Road, London, SE1 8UG  
[www.doh.gov.uk/ukxira.htm](http://www.doh.gov.uk/ukxira.htm)

United States Public Health Service: Draft Guidance for Industry: Precautionary  
Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and  
Blood Products from Xenotransplantation Product Recipients and Their Contacts.  
Washington DC,  
[www.fda.gov/cber/gdlns/zooxeno.txt](http://www.fda.gov/cber/gdlns/zooxeno.txt)

United States Public Health Service: Draft Public Health Service Guideline in  
Infectious Disease Issues in Xenotransplantation. Washington DC,  
[www.fda.gov/cber/gdlns/xeno.txt](http://www.fda.gov/cber/gdlns/xeno.txt)

United States Public Health Service (1999): Guidance for Industry: Public Health  
Issues Posed by the Use of Nonhuman Primate Xenografts in Humans. Washington  
DC,  
[www.fda.gov/cber/gdlns/xenoprim.txt](http://www.fda.gov/cber/gdlns/xenoprim.txt)

World Health Organization (1998): Consultation on Xenotransplantation: Infectious  
Diseases Prevention and Ethical Considerations. World Health Organization, Geneva  
Switzerland, (WHO/EMC/ZOO/98.2), [www.who.int/emc-documents/zoonoses](http://www.who.int/emc-documents/zoonoses)

World Health Organization (1998): Xenotransplantation: Guidance on Infectious  
Disease Prevention and Management. World Health Organization, Geneva  
Switzerland, (WHO/EMC/ZOO/98.1), [www.who.int/emc-documents/zoonoses](http://www.who.int/emc-documents/zoonoses)

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