# International Biological Reference Preparations for Emerging Infectious Diseases: Vital Tools in Epidemic Preparedness

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## Introduction

- International Reference Preparations (IRPs) are biological reference materials, such as antigens (Ags), antibodies (Abs) and nucleic acids (NA), with carefully standardised biological activity.
- **2016:** WHO launched the Research and Development (R&D) Blueprint for Action to Prevent Epidemics
- Central to the blueprint is a list of priority diseases (see table) each with a roadmap encompassing diagnostics, vaccines and therapeutics.
- During the 2014 EVD outbreak the lack of Zaire Ebola (EBOV) Ab, Ag and NA IRPs hampered the development of accurate diagnostics and vaccines.
  - Interim Ab IRPs for EBOV approved in October 2015.
- This is echoed in the ongoing MERS-CoV[$] and Zika virus epidemics.
- Otherwise availability of serology IRPs for other diseases on the R&D Blueprint is extremely limited (see table).
- Primary bulk material for IRP development is convalescent patient plasma.
- Several institutions provide IRPs to WHO: NIBSC is the leading provider

| Revised list of priority diseases, and diseases considered for conclusion (under annual review) February 2018 | Current status of IRP development |
|---|---|
| **Arenaviral VHFs (not LASV)** | Nil available. Bulk material required. |
| **Lassa Fever (LASV)** | Nil available. Bulk material required. |
| **CCHF*** | Nil available. Bulk material required. |
| **Chikungunya** | Nil available. Bulk material required. |
| **Emergent non-polio enteroviruses (including EV71, D68)** | EV71 Ab IRP available. No other non-polio enterovirus IRPs available. Source material required. |
| **Filoviruses (including Ebola and Marburg)** | EBOV Ab, VP40 Ag & NA BRMs available. No other filovirus BRMs available. Source material required. |
| **MERS-CoV[$] & SARS[£]** | Ab & NA IRPs in development for MERS-CoV. Additional source material required. |
| **Other highly pathogenic coronaviruses (not MERS/SARS)** | Nil available. Bulk material required. |
| **Nipah and related henipaviruses** | Nil available. Bulk material required. |
| **Rift Valley Fever** | Nil available. Bulk material required. |
| **STFS[^]** | Nil available. Bulk material required. |
| **Zika** | NA IRP available. Ab IRP in development. |
| **Disease X (Any disease identified prior to the next review using the Blueprint's decision instrument will be included in the list.** | |

## Why are IRPs important?

### Vaccines & therapeutics

- No current licensed vaccine for any blueprint priority disease
- BRMs would allow for harmonisation, & therefore comparison of Phase 1 & 2 vaccine response data
- Optimise selection of Phase 3 evaluation candidates
- Enable characterisation of the potency, purity and identity of potential immunotherapies

### Diagnostics

- IRPs ensure reliability of in vitro bioassay diagnostics
- IRPs encompassing NAs, Ags & Abs would facilitate development, validation and harmonization of diagnostic assays eg. PCRs, ELISAs & Ag based POCTs

## Problems to address

### Identifying suitable donor patients

- Blueprint diseases are largely rare and outbreaks can be difficult to predict in time and place
- Often occur in remote, resource constrained settings

### Informed consent and ethical oversight processes

- No systematic consent/ethical process currently in place for IRP sample acquisition
- Limited pre-existing guidance for plasma derived products (eg. serum/plasma not covered by UK Human Tissue Act 2004)

### Issues of equitable benefit sharing

- Ensure compliance with existing international legal frameworks aimed at facilitating benefit sharing (eg. Nagoya Protocol)
- Maintain free distribution of IRPs to countries as required

### Sample Provenance, Safe Handling, Export of Samples and Importing Samples to the UK

- Several blueprint diseases are Category A pathogens
- BSL3/4 facilities required for infectious materials
- Safe importation/exportation procedures must be established
- Evidence of sample provenance required, including method of diagnosis, period of convalescence, patient demographics etc.

## Proposed Solution

A collaborative framework to outline processes for the acquisition of samples for the generation of reference materials

- Establish a collaborative endeavour between relevant partners
- Identify IRP needs for each WHO R&D Blueprint priority disease
  - Facilitate generation of an inventory of IRP needs to be fulfilled using the framework
- Identify partners for sample collection and pre-emptive identification of study sites
- Preparation of study documents to include template protocols, participant information sheets, informed consent forms and clinical agreements detailing methods for:
  - Identifying and recruiting potential donors
  - Sample collection, documentation and processing
  - Roles and responsibilities
- Pre-emptive ethical and regulatory approval where possible
- Negotiations between relevant parties, and pre-emptive interaction between researchers and donor country authorities
  - Leading to clearly defined, mutually agreed processes for the equitable acquisition and export of samples
  - Enshrined in legally binding agreements
- Determination of importation regulations and requirements
- To develop and agree a work-plan for WHO R&D Blueprint priority diseases using the agreed framework

## Conclusions

- IRPs are essential tools in the evaluation of vaccines and drugs of priority high threat pathogens with epidemic potential.
- At present, numerous barriers exist that obstruct the prompt, safe, and ethical acquisition of IRP source bulk material for priority diseases.
- Through designing and implementing a structured, systematic, collaborative framework we seek to address these issues, ultimately providing institutions such as NIBSC with material for IRP development.
- Availability of IRPs for these diseases prior to occurrence of outbreaks will facilitate drug and vaccine development, and other research activities.

**Abbreviations:** [$]Middle East Respiratory Syndrome Coronavirus; *Crimean-Congo Haemorrhagic Fever; [£]Severe Acute Respiratory Syndrome; [^]Severe Fever with Thrombocytopenia Syndrome; [@]International Severe Acute Respiratory and Emerging Infections Consortium