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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 20 to 24 March 2023

Requests to initiate new WHO reference material projects for biologicals

NOTE:
This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Comments MUST be received by **6 March 2023** and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Technical Standards and Specifications (TSS). Comments may also be submitted electronically to the Responsible Officer: **Dr Ivana Knezevic** at email: knezevici@who.int.

Proposed new projects

1. WHO Reference Reagent for Diphtheria Antitoxin Equine (for Flocculatin test)
2. WHO 1st International Standard for anti-genococcal serum (human)
3. WHO Reference Reagent for mRNA-LNP
4. WHO 1st International Standard for Mpox antibody
5. WHO 3rd International Standard for Hepatitis B immunoglobulin
6. WHO 3rd International Standard for Hepatitis A immunoglobulin
7. WHO 2nd International Standard for Varicella Zoster Virus immunoglobulin
8. WHO 4th International Standard for Inactivated Poliomyelitis vaccine
9. WHO 1st International Standard for anti-SARS-Cov-1 IgG
10. WHO 1st International Standard for Anti-tTG IgA and IgG
11. WHO 1st International Reference Reagent for anti-Ross River Virus (Immunoglobulin G) Neutralizing Antibodies)

Proposal (title)	1st WHO Reference Reagent for Diphtheria Antitoxin Equine for use in Flocculation Test		
Proposer (name of Institution)	MHRA	**Principal contact**	Rob Tierney
Rationale	The flocculation test is an immunological binding assay in which the flocculation value (Lf) of a toxoid (or toxin) is determined using the number of antitoxin units required to produce an optimally flocculating mixture forming visible antibody-antigen complexes. The measurement of Lf content is a critical step in the production process of diphtheria vaccines as the final product is formulated based on the Lf units in the bulk purified toxoid. The measurement of Lf content is also used to determine antigenic purity where the Lf content is expressed per mg of protein nitrogen. Diphtheria toxoid for use in the production of diphtheria vaccines for human use must be shown to meet minimum requirements for purity. The reference reagent for equine diphtheria antitoxin is important for the standardization of the flocculation test which is used to calculate Lf units of diphtheria toxoid. The reference reagent 63/007, diphtheria antitoxin equine for flocculation test, was established in 1963 as the 4th British Reference preparation and was widely used (average 300 ampoules/year). This rate of use is likely to continue. The stocks of 63/007 are now completely depleted.		
Anticipated uses and users	This reference reagent will be used for the standardization of flocculation tests used to determine diphtheria antigen content of bulk toxoid in Lf units, mainly by vaccine manufacturers using the flocculation method.		
Source/type of materials	Equine diphtheria antitoxin, with an approximate potency of 1250 IU/ml, has been purchased from Premium Serums, India. There is sufficient material available to produce up to 2,000 ampoules of the final product.		
Outline of proposed collaborative study	A collaborative study will be used to calibrate the candidate standard in Lf-equivalent units per ampoule against the 3rd IS Diphtheria Toxoid for use in Flocculation Test using the WHO recommended flocculation (Ramon) method. Participants from laboratories representing multiple countries will be included.		
Issues raised by the proposal	The candidate material, because of its equine origin, has been very difficult to source which has led to a delay in initiating a project to replace 63/007.		

Action required	ECBS to endorse proposal.		
Proposer's project reference	SLP0008	**Date proposed:**	March 2023
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	Combination vaccines containing diphtheria toxoid are licensed globally.		
Number of products or methods	There are more than 20 different vaccine products containing diphtheria toxoid.		
Public health importance	The diphtheria antitoxin equine standard facilitates use of the flocculation test for measurement of antigen content of diphtheria toxoids used to formulate final bulk vaccine. This is essential for the quality control of diphtheria vaccines.		
Global importance	Diphtheria vaccines are one of the most widely used and successful human vaccines. They form an essential component of the primary immunization schedule of children, as well as being used for the reinforcement of immunity in adults and adolescents.		
Global need from regulatory & scientific considerations	Diphtheria toxoids for use in the production of vaccines for human use must meet minimum requirements for antigenic purity (Lf units per milligram of protein nitrogen). Standardization of tests used to determine antigen content (in Lf units) is essential to allow manufacturers to reliably measure antigenic purity and to formulate the final bulk vaccine.		
ECBS outcome			

Proposal (title)	1st WHO International Standard for Anti-Gonococcal Serum, Human		
Proposer (name of Institution)	MHRA	**Principal contact**	Paul Stickings
Rationale	Gonorrhoea is a sexually transmitted infection (STI) with >80 million cases reported in 2020. Infection does not confer a protective immune response (reinfection is common) and can lead to inflammatory complications, infertility, adverse pregnancy outcomes and an increased risk for HIV. Although treatable, recent increases in gonococcal antimicrobial resistance (AMR) are a significant threat to prevention and control. The WHO Global Health Sector Strategy on STIs has set 2030 targets to reduce incidence of *N. gonorrhoeae* infection by 90% - with the recognition that effective vaccines will be needed to help meet this target. Measuring responses to vaccination will require serological assays that measure binding antibodies (e.g. ELISA) and functional antibodies (e.g. serum bactericidal assays or opsonophagcytic assays). A human gonococcal antiserum standard will enable laboratories to set up and monitor these assays potentially allowing harmonisation of the measurement of antibody responses across different laboratories and clinical trials.		
Anticipated uses and users	Laboratories involved in measurement of anti-gonococcal antibody responses. The primary intended use is for measurement of responses to immunisation		
Source/type of materials	Pooled human serum from immunised volunteers		
Outline of proposed collaborative study	A collaborative study will be run to demonstrate that the candidate standard is fit for purpose for use in binding and functional assays measuring anti-gonococcal antibodies. Fitness for purpose demonstration will include evidence that the candidate standard improves the between laboratory agreement for these measurements. An arbitrary unit will be assigned to the candidate standard		
Issues raised by the proposal	Sourcing suitable material to develop the candidate will depend on access to pooled human serum from early stage clinical trials		
Action required	ECBS to endorse proposal.		
Proposer's project reference	N/A	**Date proposed:**	March 2023

CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)	
Approval status of medicine or in vitro diagnostic method	Vaccine development has been slow due to high frequency antigenic variation and challenges identifying suitable immunogens. However, outer-membrane vesicle vaccines to *N. meningitidis* serogroup B may confer cross-protection and have been estimated to be 30% effective against gonococcal infection. These observations have demonstrated the potential for the development of gonococcal-specific vaccines and efforts to develop a vaccine are increasing. WHO preferred product characteristics for gonococcal vaccines were published in 2021 and note that the development pathway for gonococcus-specific vaccine is likely to be 10-12 years
Number of products or methods	Currently there is no licensed vaccine for *N. gonorrhoeae* and most vaccine development is at a pre-clinical or early clinical stage Outer membrane vesicle vaccines are one of the main approaches being explored – but other approaches include purified protein subunit vaccines and nucleic acid based vaccines
Public health importance	WHO Global Health Sector Strategy on STIs has set 2030 targets to reduce incidence of N. gonorrhoeae infection by 90%. Gonococcal vaccines could have a wide ranging positive impact in terms of preventing individual infection, disease and related sexual and reproductive health complications and could potentially reduce community transmission – including strains resistant to commonly used antimicrobial treatments
Global importance	Both the WHO Global Roadmap to Advance STI Vaccine Development and the WHO Product Development for Vaccines Advisory Committee (PDVAC) have highlighted the need for gonococcal vaccines for global use. Vaccines targeting this infection are also an important part of the wider global strategy to combat antimicrobial resistance
Global need from regulatory & scientific considerations	Currently there are 5 known vaccines in early development for gonococcal infection with 2 or 3 expected to advance into human clinical studies within the next 2 years. An international reference serum will be required for standardizing the serum titres post-vaccineation and important for the comparison of results between products as well as for comparison of outcomes at different test centers.
ECBS outcome	

Proposal (title)	WHO Reference Reagent for mRNA-LNP		
Proposer (name of Institution)	MHRA	**Principal contact**	Paul Stickings
Rationale	Lipid nanoparticle (LNP) encapsulated messenger RNA (mRNA) has been the platform used for two of the most widely used COVID-19 vaccines and has highlighted the power of this approach for development of safe and effective medicines. Many other mRNA-LNP products are now under clinical development for prevention and treatment of other infectious diseases, cancer and genetic diseases. As such, there is an increasing need for laboratories to develop the analytical capabilities to characterise and routinely test batches of these products. A robust, stable and well characterised reference material will support the development, validation and control of some of these analytical methods		
Anticipated uses and users	The reference reagent is intended to serve as a control material to help with assay set up, troubleshooting and routine performance monitoring. Anticipated users include manufacturing laboratories, contract research organisations, academic labs and national control laboratories The proposed reference reagent is not a calibrant and is not intended to define any regulatory parameters		
Source/type of materials	LNP encapsulated mRNA with a generic mRNA target such that the reference reagent is product agnostic		
Outline of proposed collaborative study	A collaborative study will be run to demonstrate that the candidate reference reagent is fit for purpose across different analytical methdos – including separation techniques and expression assays		
Issues raised by the proposal	Progression of the project is dependent on securing a donation of appropriate source material		
Action required	ECBS to endorse proposal.		
Proposer's project reference	N/A	**Date proposed:**	March 2023
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			

Approval status of medicine or in vitro diagnostic method	Licensed mRNA-LNP products exist for COVID-19 and there is widespread development of other mRNA-LNP medicines
Number of products or methods	Analytical methods include separation assays for purity/integrity, encapsulation assays, cell based potency assays
Public health importance	mRNA based medicines are likely to be developed at pace in coming years to help tackle a wide range of infectious and non-infectious disease, including those with high burden in low and middle income settings
Global importance	Efforts to expand capability for production of mRNA vaccines (for example via the global mRNA technology transfer hub) will enhance global capability in mRNA technology
Global need from regulatory & scientific considerations	The availability of a WHO reference reagent will facilitate assay development and control and support troubleshooting or investigations into out of specification or invalid results
ECBS outcome	

Proposal (title)	First WHO International Standard for anti-Monkeypox virus antibodies		
Proposer (name of Institution)	MHRA	**Principal contact**	Giada Mattiuzzo
Rationale	Mpox (or monkeypox) disease was first described in humans 1970 and it is currently endemic in West and Central Africa countries. Outbreaks have occurred in the past linked to international travel or export of animal from endemic regions. The largest outbreak started in May 2022 and as of 19th December 2022 almost 83000 cases have been recorded in 110 countries, with 66 deaths. The WHO declared Mpox a Public Health Emergency of International Concern on 23rd July 2022. Monkeypox virus is a member of the *orthopoxvirus* genus which includes smallpox and cowpox. There are 2 clades: Clade I, previously known as the Congo basic (Central African), and Clade II, previously know as the West African clade. The latter is also divided in two subclades, IIa and IIb. Clade IIb includes variants largely circulating in the current (2022) global outbreak. Smallpox vaccines are available and offer a degree of protection against Mpox ,85% efficacy based on observational studies. There are 3 vaccines available for Mpox. ACAM2000 vaccine is approved in the USA for smallpox and made available for Mpox under the Expanded Access Investigational New Drug protocol. JYNNEOS vaccine, modified Vaccinia Ankara from Bavarian Nordic, is approved for both Mpox and smallpox in USA and Australia, as well as in Canada under the name of Imvamune, and in Europe as Imvanex. In Japan, LC16 KMB vaccine was approved for smallpox and Mpox. New vaccines are in preclinical phase including those based on a horsepox virus and mRNA technology. Availability of serological assays to compare immune responses elicit by vaccination will help evaluate current and new vaccines. Also, clinical symptoms associated with Mpox are often missed or confused with chickenpox making it difficult to understand epidemiology and real burden of this disease. Sero-epidemiology is also complicated by the cross-reactivity between orthopoxviruses. The availability of an International Standard will support the development and harmonisation of methods for the detection of antibodies to Mpox.		
Anticipated uses and users	National reference/control laboratories, vaccines and kit manufacturers, research groups. The standard will be used for the development and calibration of assay detecting anti-monkeypox virus antibodies to investigate immune responses following infection or vaccination, sero-epidemiological study,		
Source/type of materials	In collaboration with the Coalition for Epidemic Preparedness Innovation, a working reagent was prepared in November 2022. The preparation is a pool of convalescent plasma from100 Mpox recovered individuals from Democratic Republic of Congo, collected in 2022. The preparation was freeze-dried at the South Mimms		

	Laboratories of the MHRA using a well-established procedure. We have prepared approximately 2000 ampoules, which will be considered the candidate standard. We would like to collect material from the recent outbreak to compare convalescent plasma from a different Mpox clade infection. Such material if in adequate amount could be used as second candidate or included in the collaborative study.		
Outline of proposed collaborative study	10-15 laboratories worldwide with a neutralisation or binding assay for smallpox, vaccinia or Mpox. We would like to add convalescent plasma/serum from clade IIb infected individuals, as well as vaccinee plasma or serum To characterise the working reagent 22/218 a small pilot study was organized. We were able to recruit 4 laboratories. Analysis of the results from this study is underway and will inform on the design of the WHO collaborative study.		
Issues raised by the proposal	Global cases of Mpox are in decline Not many assays have been developed, and it is unclear how many laboratories will join the collaborative study. Cross-reactivity between orthopoxviruses complicates the interpretation of the results.		
Action required	ECBS to endorse proposal		
Proposer's project reference		**Date proposed:**	22/12/2022
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	3 vaccines approved in different regions. The antiviral tecovirimat (TPOXX) is approved in several countries as treatment for smallpox, cowpox and Mpox, although only safety clinical trials, no efficacy, have been conducted.		
Number of products or methods	No commercial assays are available for the detection of antibodies to Mpox, but there are several methods published in the literature for binding and neutralising antibody detection.		

Public health importance	The World Health Organization declared Mpox a Public Health Emergency of International Concern on 23rd July 2022. Whilst the number of cases is declining, Mpox is endemic in West and Central Africa country where it has a rate fatality between 0-11%.
Global importance	In the current, 2022 outbreak, 110 countries globally have reported cases of Mpox. The first outbreak outside endemic African states was recorded in 2003 in USA. Six states reported 47 confirmed and probable cases. Monkeypox has also been reported in travelers from Nigeria to Israel in September 2018, to the United Kingdom in September 2018, December 2019, May 2021 and May 2022, to Singapore in May 2019, and to the United States of America in July and November 2021.
Global need from regulatory & scientific considerations	During the WHO R&D consultation held on 2nd-3rd June 2022 the following research priorities were identified: Characterization of immune responses to identify biomarkers that could predict protection – the availability of a WHO International Standard is critical for the comparison of vaccine and immunological studies to identify what surrogate of protection can be identified. Epidemiology to understands knowledge gaps such as transmission dynamics, role of possible endemic circulation in Europe, reason behind the large 2022 outbreak.
ECBS outcome	[BLANK]

Proposal (title)	Third International Standard for Anti Hepatitis B Surface Antigen Immunoglobulin		
Proposer (name of Institution)	MHRA	**Principal contact**	Mark Hassall
Rationale	Replacement of 2nd International Standard for Anti Hepatitis B Surface Antigen Immunoglobulin (07/164) We have a stock of 442 vials of the 2nd IS left, which will be depleted by the middle of 2024.		
Anticipated uses and users	This standard is used in the accurate measurement of Hepatitis B antibody levels in immunoglobulin preparations and to assess immunity and vaccine responses. It is intended for Intended for calibration of secondary reference standards as well as harmonising and controlling assay performance. The target users are Clinical and public health laboratories, Vaccine manufacturers, Assay Kit manufacturers and Research laboratories.		
Source/type of materials	The current IS was produced using bulk immunoglobulin, so this would be the preferred material. However, plasma or serum may be suitable for the candidate standard as it is commutable, and closely represents clinical samples. We aim to produce a minimum of 5000 vials, depending on the volume of starting material that is obtained.		
Outline of proposed collaborative study	A collaborative study incorporating between 6 and 10 participants running bioassays will be set up to calibrate a new candidate to the 2nd IS and assign IU to the immunoglobulin standard.		
Issues raised by the proposal	Sourcing enough reactive material to produce a large enough batch of the IS to last for approximately 10 years.		
Action required	ECBS to endorse proposal		
Proposer's project reference		**Date proposed:**	January 2023
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			

Approval status of medicine or in vitro diagnostic method	Licensed safe and effective vaccines that offer 98% to 100% protection against hepatitis B available worldwide as well as diagnostic kits and Immunoglobulins therapies.
Number of products or methods	There are both single and combination vaccines available a number of antibody based diagnostic kits and immunoglobulin prophylaxis.
Public health importance	Provision of a new IS will provide continued support to the standardization of the potency of HBV vaccines globally and aid NCL's in the control of HBV vaccines. This will ensure the safety of the vaccine for use in disease control and prevention. Preventing hepatitis B infection averts the development of complications including chronic disease and liver cancer.
Global importance	Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It is a major global health problem. It can cause chronic infection and puts people at high risk of death from cirrhosis and liver cancer. The burden of hepatitis B infection is highest in the Western Pacific and Africa, where 116 million and 81 million people, respectively, are chronically infected. Sixty million people are infected in the WHO Eastern Mediterranean Region, 18 million in the WHO South-East Asia Region, 14 million in the WHO European Region and 5 million in the WHO Region of the Americas In highly endemic areas, hepatitis B is mostly spread from mother to child at birth or through horizontal transmission. Hepatitis B is also spread by needlestick injury, tattooing, piercing and exposure to infected blood and body fluids. Hepatitis B infection acquired in adulthood leads to chronic hepatitis in less than 5% of cases, whereas infection in infancy and early childhood leads to chronic hepatitis in about 95% of cases. This is the basis for strengthening and prioritizing infant and childhood vaccination.
Global need from regulatory & scientific considerations	Provision of the IS will support the standardization of the potency of HBV vaccines globally and aid NCL's in the control of HBV vaccines, as well as helping to accurately monitor antibody levels in immunoglobulin preparations and help calibrate controls for diagnostic kits.
ECBS outcome	[BLANK]

Proposal (title)	Third WHO International Standard for Anti Hepatitis A Immunoglobulin		
Proposer (name of Institution)	MHRA	**Principal contact**	Mark Hassall
Rationale	Replacement of 2nd International Standard for Anti Hepatitis A Immunoglobulin (replacement for 97/646). We have a stock of 332 vials of the 2nd IS left, which will be depleted by the end of 2024.		
Anticipated uses and users	This standard is used in the accurate measurement of Hepatitis A antibody levels in immunoglobulin preparations and to assess immunity and vaccine responses. It is intended for calibration of secondary reference standards as well as harmonising and controlling assay performance. The target users are Clinical and public health laboratories, Vaccine manufacturers, Assay Kit manufacturers and Research laboratories.		
Source/type of materials	Liquid bulk 16% Immunoglobulin which was used for the 2nd IS is available to produce a new candidate material. There is 3000 mL available that was donated by the Netherlands Red Cross. We aim to produce a minimum of 5000 vials.		
Outline of proposed collaborative study	A collaborative study incorporating between 6 and 10 participants running bioassays will be set up to calibrate a new candidate to the 2nd IS and assign IU to the immunoglobulin standard.		
Issues raised by the proposal			
Action required	ECBS to endorse proposal		
Proposer's project reference		**Date proposed:**	January 2023
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			

Approval status of medicine or in vitro diagnostic method	There are Licensed vaccines available worldwide, as well as diagnostic kits and Immunoglobulins used as a therapeutic treatment.
Number of products or methods	There are several licensed single Hepatitis A vaccines, as well as combination vaccines. available internationally which provide similar protection from the virus and have comparable side effects. In China, a live attenuated vaccine is also available, however no vaccine is licensed for children younger than 1 year of age. There are also a number of Immunoglobulin based diagnostic kits in use, and immunoglobulin therapies available for treatment.
Public health importance	Provision of a new IS will provide continued support to the standardization of the potency of HAV vaccines globally and aid NCL's in the control of HAV vaccines. This will ensure the safety of the vaccine for use in disease control and prevention. It will also help standardise HAV antibody levels in the Immunoglobulin preparations used therapeutically.
Global importance	Hepatitis A virus (HAV) causes a disease which is symptomatic of mass inflammation of the liver. The virus is primarily spread when an uninfected (and unvaccinated) person ingests food or water that contains contaminated faeces. Infections are common in low- and middle-income countries with poor sanitary conditions and hygienic practices, and in these regions most children have been infected with the virus before the age of 10. Outbreaks occur sporadically worldwide, with a tendency for cyclic recurrences. Epidemics related to contaminated food or water can arise incredibly quickly, and can also be prolonged, affecting communities for months through person-to-person transmission. Hepatitis A viruses persist in the environment and can withstand food production processes routinely used to inactivate or control bacterial pathogens.
Global need from regulatory & scientific considerations	Provision of the IS will support the standardization of the potency of HAV vaccines globally and aid NCL's in the control of HAV vaccines, as well as helping to accurately monitor antibody levels in immunoglobulin preparations and help calibrate controls for diagnostic kits.
ECBS outcome	[BLANK]

Running Title: Third WHO International Standard for Anti Hepatitis A Immunoglobulin (replacement for 97/646)

Proposal (title)	Second International Standard for Anti Varicella Zoster Virus Immunoglobulin		
Proposer (name of Institution)	MHRA	**Principal contact**	Mark Hassall
Rationale	Replacement of 1st International Standard for Anti Varicella Zoster Virus Immunoglobulin (W1044) We have a stock of 264 vials of the 1st IS left which will be depleted by the end of 2024.		
Anticipated uses and users	This standard is used in the accurate measurement of Varicella Zoster antibody levels in immunoglobulin preparations and to assess immunity and vaccine responses. It is intended for Intended for calibration of secondary reference standards as well as harmonising and controlling assay performance. The target users are Clinical and public health laboratories, Vaccine manufacturers, Assay Kit manufacturers and Research laboratories.		
Source/type of materials	The current IS was produced using bulk immunoglobulin, so this would be the preferred material. However, plasma or serum may be suitable for the candidate standard as it is commutable, and closely represents clinical samples. We aim to produce a minimum of 5000 vials, depending on the volume of starting material obtained.		
Outline of proposed collaborative study	A collaborative study incorporating between 6 and 10 participants will be run to assign IU to the immunoglobulin standard.		
Issues raised by the proposal	Sourcing enough reactive material to produce a large enough batch of the IS to last for approximately 10 years.		
Action required	ECBS to endorse proposal		
Proposer's project reference		**Date proposed:**	January 2023
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			

Approval status of medicine or in vitro diagnostic method	Licensed safe and effective vaccines are available worldwide as well as diagnostic kits and Immunoglobulins therapies.
Number of products or methods	Current varicella vaccines are attenuated vaccines based on the Oka VZV strain. Varicella vaccine has also been included in a combination vaccine with measles mumps rubella (MMRV). A vaccine which contains higher levels of the virus has also been developed for the prevention of shingles in the elderly. Antibody based diagnostic kits are available, and Immunoglobulin therapy is used in immunosuppressed patients to control infection.
Public health importance	Provision of a new IS will provide continued support to the standardization of the potency of VZV vaccines globally and aid NCL's in the control of VZV vaccines. This will ensure the safety of the vaccine for use in disease control and prevention.
Global importance	Varicella-zoster virus (VZV) is a member of the herpesvirus family, causing Chickenpox. Following infection, the virus remains latent in neural ganglia and in about 10-20% of cases it can be reactivated to cause herpes zoster, or shingles. Transmission occurs via droplets, aerosols, or direct contact with respiratory secretions, and almost always produces clinical disease in susceptible individuals. In childhood it mostly causes mild disease but tends to be more severe in adults. In neonates and immunocompromised people, it can be fatal. Disease is usually characterized by an itchy, rash most often starting on the scalp and face and accompanied by fever and malaise. The rash gradually spreads to the trunk and other extremities. Vesicles gradually dry out, scab over and disappear over a period of one to two weeks. Occasionally complications such as pneumonia or encephalitis can occur, at times with serious or fatal consequences.
Global need from regulatory & scientific considerations	Provision of the IS will support the standardization of the potency of VZV vaccines globally and aid NCL's in the control of VZV vaccines as well as helping to accurately monitor antibody levels in immunoglobulin preparations and help calibrate controls for diagnostic kits.
ECBS outcome	[BLANK]

Proposal (title)	4th WHO International Standard for Inactivated Polio Vaccine		
Proposer (name of Institution)	MHRA	**Principal contact**	Mark Hassall
Rationale	Replacement of 3rd International Standard for inactivated Polio Vaccine (IPV) based on wild type strains (replacement for 12/104). We have a stock of 513 vials of the 3rd IS left, which will be depleted by 2026.		
Anticipated uses and users	This standard is for use with IPV derived from wild type polio virus strains and is suitable for determining the antigenic content by in vitro assays. It is intended for Clinical and public health laboratories, Vaccine manufacturers and national control laboratories (NCL) for calibration of secondary reference standards as well as harmonising and controlling assay performance.		
Source/type of materials	There are 2 possible candidate materials already which were tested in conjunction with the 3rd IS. These are prepared from commercially available lots of IPV donated by European manufacturers		
Outline of proposed collaborative study	A collaborative study incorporating both candidate materials with up to 10 participants running bioassays for D-antigen content will be set up to identify the best candidate and to calibrate to the 4th IS.		
Issues raised by the proposal			
Action required	ECBS to endorse proposal		
Proposer's project reference		**Date proposed:**	January 2023
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	IPV is the vaccine of choice in the world with increasing usage across the globe considering the WHO Global Polio Eradication Initiative (GPEI). Multiple IPV products have been licensed in the world and prequalified by the WHO.		
Number of products or methods	IPV is used for routine vaccination and can be administered singly or as part of a multiple vaccine programme.		

Public health importance	Provision of a replacement IS will provide continued support to the standardization of the potency of IPVs globally and aid NCL's in the control of these. This will ensure the safety of the vaccine for use in disease control and prevention.
Global importance	Most of the world is free of Polio, but there is a continued need for vaccines in the drive to eradicate it fully. Therefore, there is a need to be able to access suitable reference materials to assess the quality of vaccines and ensure there is enough available to meet the current and future needs.
Global need from regulatory & scientific considerations	Provision of the IS will support the standardization of the potency of IPV and aid manufacturers and NCLs in the control of IPVs globally, and ultimately contribute to the global polio eradication programme.
ECBS outcome	[BLANK]

Running Title: 4th WHO International Standard for Inactivate Polio Vaccine (replacement for 12/104)

Proposal (title)	1st WHO Reference Reagent for control of RNA extraction, PCR and nanopore sequencing for direct detection of polio virus		
Proposer (name of Institution)	MHRA	**Principal contact**	Javier Martin, Manasi Majumdar, Erika Bujaki
Rationale	One of the major goals of WHO Polio Eradication Strategy 2022–2026 (https://polioeradication.org/gpei-strategy-2022-2026/) is to improve detection and response to detected polioviruses through sensitive surveillance. NIBSC is a global specialized lab for poliovirus detection, research and development and therefore plays an important role in supporting the Global Polio Laboratory Network (GPLN) that carries out routine surveillance of polioviruses from clinical and environmental samples. Rapid, direct methods of poliovirus detection are required to support the endgame of poliovirus eradication, facilitating swift responses to outbreaks, and permitting greater containment of poliovirus in diagnostic laboratories through the removal of the cell-culture step. Recently, we have been working on a nested PCR approach and sequencing the VP1 PCR product (commonly used for genetic characterization of polioviruses by the GPLN) via the Direct Detection by Nanopore Sequencing (DDNS) protocol. This method allows poliovirus confirmation in as little as 3 days after samples arrive at a laboratory, producing a full-length VP1 sequence required for identification of vaccine-derived and wild-type polioviruses. A pilot of the DDNS protocol has been carried out in Pakistan, DRC, and Oman. Following the training activities, a need for a positive control for the RNA extraction, PCR and nanopore sequencing steps has been identified. Therefore, we propose to develop 1st WHO Reference Reagent for control of RNA extraction, PCR and nanopore sequencing steps for direct detection of poliovirus. The reference reagent will be useful to help setting up the method as well as a run control to be used on a routine basis when carrying out DDNS protocol to detect poliovirus.		
Anticipated uses and users	The reference reagent will be used by the GPLN as a positive control for performing DDNS for poliovirus and will act as a run control for the RNA extraction, PCR, and sequencing steps.		
Source/type of materials	The reference materials will be made from Coxsackievirus A20 isolates grown in cell culture (source materials available at NIBSC)		
Outline of proposed collaborative study	The candidate identified will be initially tested at NIBSC. The preparation will be included in a collaborative study for characterization by several GPLN laboratories that currently detect poliovirus on a regular basis and other clinical/research organizations. Participants in the collaborative study will be asked to run the candidate reference material through the DDNS workflow and report the sequencing data. Based on the sequencing results from the collaborative study a decision will be made on the suitability of the reference reagent to be used as a positive run control.		

Issues raised by the proposal	None		
Action required	ECBS to endorse proposal		
Proposer's project reference		**Date proposed:**	16 Jan 2023
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES			
Approval status of medicine or in vitro diagnostic method	Various molecular diagnostic methods exist for poliovirus. However, nanopore sequencing of poliovirus is a relatively new technology and therefore there is a need to develop a positive control that can go through the steps of RNA extraction, PCR and nanopore sequencing and generate an expected sequence.		
Number of products or methods	DDNS for poliovirus is a relatively new method and therefore there is a need to develop a positive control that can test the complete workflow starting from RNA extraction and ending up with generation of a sequence. Therefore, this study is proposed to identify such a candidate.		
Public health importance	One of the major goals of WHO Polio Eradication Strategy 2022–2026 (https://polioeradication.org/gpei-strategy-2022-2026/) is to improve detection and response to detected polioviruses through sensitive surveillance. Detection and reporting of polioviruses are routinely done by 146 WHO accredited laboratories and the process is lengthy and complex. NIBSC being a global specialized polio laboratory has collaborated with Imperial College London to develop a protocol for direct detection of polioirus that can generate a poliovirus sequence within 3 days of receipt of a stool sample using nanopore sequencing. This method significantly decreases the turnaround time for reporting a poliovirus sequence from a clinical sample, this could accelerate poliovirus outbreak response, reducing their size and the cost of outbreak response. This method also cuts out the cell culture amplification step for detection of poliovirus from the clinical samples therefore can be a useful tool to roll out in GPLN labs many of which will not be able to host a polio essential facility.		
Global importance	Polio eradication remains one of the top global priorities of WHO. Methodology described here aligns with the major goals of WHO Polio Eradication Strategy 2022–2026 i.e., to improve detection and response to detected polioviruses through sensitive surveillance.		
Global need from regulatory & scientific considerations	During the pilot testing of DDNS at the GPLN labs a need for a positive run control which will undergo RNA extraction, PCR amplification and nanopore sequencing was deemed useful. This reference material can be useful to help setting up the method as well as a run control to be used on a routine basis when carrying out DDNS protocol to detect poliovirus and will help strengthening poliovirus surveillance strategies in GPLN labs.		

ECBS outcome	[BLANK]

Proposal (title)	First WHO International Standard for anti-SARS-CoV-1 Immunoglobulin G		
Proposer (name of Institution)	MHRA	**Principal contact**	Emma Bentley
Rationale	SARS-CoV-1 was responsible for an outbreak in 2002-2004 which resulted in an estimated 8000 infections and more than 700 deaths. Cases were reported in 25 countries, across 5 continents before the outbreak was brought under control. In recognising the future outbreak potential and the need to develop vaccines and therapeutics, SARS was listed as a priority pathogen by the WHO R&D Blueprint in 2015. In the on-going response to the recent COVID-19 pandemic, efforts are refocussing on preparedness for potential future coronavirus (re-)emergence. This includes availability of vaccines and therapeutics affording protection against SARS-CoV-1. The Coalition of Epidemic Preparedness Innovations (CEPI) is supporting the development of pan-coronavirus vaccines. The availability of a WHO International Standard for SARS-CoV-1 will support these efforts.		
Anticipated uses and users	Standardisation of serological assays detecting anti-SARS-CoV-1 antibodies (e.g. ELISA, neutralisation assays) used by: - National control / public health laboratories - Vaccine manufactures - Therapeutic Ab producers (e.g. mAb therapies) - Assay kit manufacturers - Research laboratories		
Source/type of materials	The candidate standard will be prepared from a donation of 500mL of purified immunoglobulin G manufactured under GMP for therapeutic use, and provided by the NIH, USA. The product was prepared in 2007, from pooled plasma collected from convalescent individuals from Hong Kong following the 2002-4 SARS outbreak. The material will be provided under MTA and the IRB ethics approval/patient informed consent shared with MHRA. Additional source material to include in the study has been donated by Duke NUS, Singapore. This includes convalescent serum samples collected from 30 individuals from Singapore, recovered from the 2002-2004 SARS outbreak.		
Outline of proposed collaborative study	The collaborative study will involve 15-20 laboratories worldwide, performing a range of serological assays for the detection of anti-SARS-CoV-1 antibodies. The range of laboratories will include representatives from national control, vaccine manufacturers, clinical and academic		

	laboratories. To evaluate performance of the standard and provide an assessment of commutability, the study panel will include convalescent serum/plasma samples of differing potencies from convalescent individuals unrelated to the candidate IS. The aim will be to assess the suitability of the candidate preparation to serve as an International Standard, with an assigned unitage, for use in the harmonisation of SARS-CoV-1 serological assays by: - Characterising the reactivity/specificity in different assay systems - Evaluating the potency/readout in a range of typical assays performed in different laboratories - Assess the extent to which the candidate is suitable to serve as a standard for a variety of different samples (i.e. commutability)		
Issues raised by the proposal	As the source material is IVIG, this may present an issue of commutability compared to clinical samples. Different formulations of the material, such as spiking into negative plasma, will be investigated and potentially two candidate materials included within the study.		
Action required	ECBS to endorse proposal		
Proposer's project reference		**Date proposed:**	March 2023
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	No diagnostic kits or vaccines are currently licensed; however several vaccines are undergoing development. This includes 13 platforms which are being funded by CEPI towards developing a pan-coronavirus vaccine; 12 candidates are preclinical and one is in phase 1 trials.		
Number of products or methods	In-house assays are available and have been published, these include ELISA and neutralisation assays.		
Public health importance	The 2002-2004 outbreak of SARS-CoV-1 had an overall case fatality rate of 9%, which was far higher in patients >60years old (reaching approximately 50%). The pandemic potential was demonstrated during this outbreak, with cases identified across 25 countries within a matter of weeks. The isolation of closely related coronaviruses from possible reservoir and intermediary hosts means the threat of future spill-over events is ongoing.		
Global importance	As above		

Global need from regulatory & scientific considerations	Standardised and calibrated assays will be vital for the accurate evaluation and development towards regulatory approval of treatments, including vaccines and therapies, and for the development of licensed serological diagnostics. This includes efforts towards defining correlates of protection.
ECBS outcome	[BLANK]

Running Title: **First WHO IS SARS-CoV-1 IgG**

Proposal (title)	1st WHO International Standard for Anti-tTG IgA and IgG autoantibodies		
Proposer (name of Institution)	MHRA/JRC	**Principal contact**	Dina Vara
Rationale	Coeliac disease is a major public health problem worldwide. A 2020 meta-analysis shows the incidence of coeliac disease has increased an average of 7.5% per year over the past several decades, with the incidence highest in females and children. The pooled global prevalence of coeliac disease has been reported at 1.4% based on serologic tests, with prevalence values at 0.4% in South America, 0.5% in Africa and North America, 0.6% in Asia, and 0.8% in Europe and Oceania. The diagnosis is usually made on the basis of coeliac-specific serology combined with duodenal biopsy findings. IgA and IgG autoantibodies against tissue transglutaminase (anti-tTG) in human serum are the most important biomarkers and variations in their levels are also used in management monitoring of this disease. Quantitative, commercially available diagnostic test kits have been developed for the measurement of these autoantibodies; however, controls and calibrators supplied with these kits have arbitrarily assigned unitage (usually U/mL). Consequently, quantitative values from different test kits are not comparable, and cut-off values for a positive outcome significantly vary. Several studies have also shown that the manufacturer-recommended assay cut-offs are not optimal for the majority of the anti-tTG IgA and IgG assays Calibration with an International Standard would improve the comparability of results from different tests, facilitating the use of anti-tTG IgA and IgG autoantibodies as diagnostic markers of coeliac disease, and would improve the monitoring of the disease management.		
Anticipated uses and users	An anti-tTG IS would be used by diagnostic kit manufacturers to calibrate their internal standards and by research institutions. Commercially available assays for anti-tTG IgA and IgG are used on a global scale and in the NHS clinical laboratories in the UK.		
Source/type of materials	The anti-tTG IgA and IgG starting material was a serum produced from plasmapheresis material obtained from one consenting patient with coeliac disease. The material was obtained at Trina Bioreactives (Nänikon, Switzerland). It was tested and found negative for all major pathogens (Hepatitis B surface antigen, HIV 1&2, HIV antigen, Hepatitis C antibodies. The JRC intend to establish this material as a Working Standard made available from their catalogue. A proportion of the material will be established as the 1st WHO International Standard with units assigned in IU/vial.		
Outline of proposed collaborative study	In a first collaborative study the suitability of the candidate IS for calibration of the diagnostic assays will be evaluated. The lyophilized candidate IS material will be distributed to manufacturers of diagnostic assays along with		

	purified anti-tTG IgA and IgG. International Units (IU) will be assigned to the candidate standard based on the outcome of the study. In a second collaborative study the commutability of the candidate IS with individual patient samples will be assessed.		
Issues raised by the proposal	Producing a commutable standard. The material was prepared using the argon method of drying and preserving lyophilized products. Thus, there may be challenges in measuring the oxygen headspace.		
Action required	ECBS to endorse proposal		
Proposer's project reference	TBC	**Date proposed:**	17/01/2023
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	FDA cleared and CE-marked in vitro diagnostic kits are commercially available, some of which are designed for automated platforms		
Number of products or methods	6 ELISA assays (INOVA, AESKU, Euroimmun, Orgentec, Eurospital, IBL) and 3 automated platforms (INOVA, Phadia, Biorad)		
Public health importance	High. The measurement of anti-tTG IgA and IgG in patient blood is used in the diagnosis of coeliac disease, and for regular monitoring of the disease management.		
Global importance	The global pooled seroprevalence of coeliac disease is 1.4%. The pooled incidence rates in women and men are 17.4 and 7.8 per 100 000 persons per year, respectively.		
Global need from regulatory & scientific considerations	An anti-tTG IS would allow global harmonisation of unitage for anti-tTG IgA and IgG measured in the serum of patients with coeliac disease.		
ECBS outcome	[BLANK]		

Anti-tTG (1st IS)

Proposal (title)	Proposed 1st International Reference Reagent for anti-Ross River Virus (Immunoglobulin G) Neutralizing Antibodies		
Proposer (name of Institution)	Paul-Ehrlich-Institut (PEI)	**Principal contact**	Sally Baylis Barbara Schnierle
Rationale	Ross River virus (RRV) is a zoonotic member of the *Alphavirus* genus in the *Togaviridae* family and is transmitted by a variety of mosquito vectors including *Aedes* and *Culex* species. Ross River fever caused by RRV is the most common vector-borne disease in Australia; however, RRV has been reported in Papua New Guinea and other Pacific regions including Fiji, the Cook Islands, American Samoa, New Caledonia, Wallis and Futuna, French Polynesia. Occasionally, RRV infections occur in travelers returning from endemic regions, and such importations may pose a potential risk of becoming established elsewhere - similar to other emerging arboviruses such as chikungunya virus and Zika virus. There are a large number of potential vertebrate hosts of RRV including both domestic and wild animals. With macropods such as kangaroos and wallabies seem to be the most important reservoirs of RRV, however, infections have been identified in cats, dogs, horses, bats and possums and human-mosquito-human transmission also occurs due to high levels of viraemia in people. The disease that is caused by RRV is characterized by rash, fatigue and polyarthralgia, which can last for weeks or months or even years – similar to closely related virus infections such as chikungunya fever.		
Anticipated uses and users	Uses include standardization of immunoassays for detection and/or quantification of anti-RRV (neutralizing) antibodies. Users of the reference material will include research laboratories and organizations developing RRV vaccines, IVD manufacturers and clinical laboratories, particularly arbovirus reference laboratories.		
Source/type of materials	Anti-RRV-positive plasma sourced through international collaborations; additional samples include negative plasma and plasma to evaluate Alphavirus cross-reactivity. All materials tested and confirmed negative for the presence of pathogenic blood borne viruses. ~3,000 vials of lyophilized plasma have been prepared from a plasma pool for anti-RRV antibody positive blood donors.		
Outline of proposed collaborative study	Candidate reference reagent evaluation in an international collaborative study investigating potency and reactivity/specificity. Participating laboratories include: reference and academic laboratories, vaccine manufacturers, test kit		

	providers and competent authorities using a range of RRV neutralization and immunoassays.		
Issues raised by the proposal	None.		
Action required	ECBS to endorse proposal.		
Proposer's project reference		Date proposed	January 2023
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or *in vitro* diagnostic method	As there are no specific treatments are available for RRV infections, patients are usually given supportive care and prescribed analgesics and anti-inflammatory drugs to treat symptoms. There are currently no licensed vaccines available for human use; one inactivated vaccine has completed phase III clinical trials. Prevention of RRV infections relies on mosquito control and avoidance of bites.		
Number of products or methods	Very few commercial diagnostics tests are available; diagnosis outside of endemic regions is performed by specialist reference laboratories.		
Public health importance	Ross River fever can result in significant morbidity due to long-lived polyarthralgia in patients.		
Global importance	RRV is endemic to Australia, Papua New Guinea and elsewhere in the Pacific region and has epidemic potential being competent for a wide range of mosquito species even in the absence of preferred enzootic hosts.		
Global need from regulatory & scientific considerations	Disease burden and RRV infections are not well understood since infections may be mild or asymptomatic; standardized assays are important for sero-surveillance. Similar to chikungunya, reference materials for neutralizing antibodies for RRV will be important for comparison of clinical data, and, ultimately the determination of antibody titres that inform about protection against RRV infection where clinical trials designed to evaluate efficacy are not feasible.		
ECBS outcome	[BLANK]		