World Health Organization

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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 9 to 10 December 2020

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 proposal contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Comments MUST be received by **3 December 2020** and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Technologies, Standards and Specifications (TSS). Comments may also be submitted electronically to the Responsible Officer: **Dr Ivana Knezevic** at email: knezevici@who.int.

Proposal (title)	1st WHO International Standard for SARS-CoV-2 Antigen		
Proposer (name of Institution)	e.g. NIBSC	**Principal contact**	Jacqueline Fryer
Rationale	Rapid and accurate detection of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is essential to support the clinical management of infected patients and infection control procedures. While NAT is the recommended method for virus detection it is generally reliant on expensive equipment and specialized operators and therefore has limited accessibility in low-resource settings. Rapid diagnostic tests detecting viral antigens (Ag-RDT) provide a relatively inexpensive means to quickly (within 30 mins) identify virus infected individuals away from a laboratory setting. However, analytical sensitivity of Ag-RDTs is lower than for NAT (as there is no amplification of the target). In addition, like NAT-assays the clinical sensitivity of Ag-RDTs is highly dependent on the characteristics of the test/product manufacture, the patient population and the quality of sampling and sample processing and has been reported to be highly variable. The WHO has published interim guidance on the use of antigen detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays. The assay landscape for detection of SARS-CoV-2 antigens is evolving rapidly with ~100 companies developing or manufacturing Ag-RDTs. The target analyte is most often the nucleocapsid (N) protein, although there are assays that also detect spike (S) protein as well as a combination of the two. Most tests have been evaluated for nasal or nasopharyngeal samples, although some are being developed for saliva. A common reference reagent for these Ag RDTs is needed to 1) facilitate development, assessment and comparability of assays, including determining the limit of detection and 2) to serve as the basis for calibration of secondary standards for quality control.		
Anticipated uses and users	Anticipated uses: • Comparative evaluation of SARS-CoV-2 antigen tests • Evaluation of analytical sensitivity (in terms of the IU) • Calibration of secondary references for SARS-CoV-2 antigen • Other regulatory and QA activities (post-market surveillance, EQA) End users include; regulatory authorities, manufacturers of assays and secondary references, reference laboratories.		
Source/type of materials	A pilot study is planned to investigate potential source materials for the candidate WHO International Standard because of the range of antigen targets and clinical specimen types that are in use. Pilot study samples will comprise: • Cultured virus: multiple strains (BetaCoV/Australia/VIC/01/2020 and other circulating strains grown in VERO SLAM cells), with virus inactivated by different methods (including gamma-irradiation, heat/acid treatment or other suitable methods). • Recombinant proteins: N and trimeric S protein (expressed in E. coli or		

	HEK293 cells). Samples will be formulated in buffer or synthetic/negative clinical samples (swab/saliva).		
Outline of proposed collaborative study	The collaborative study will involve ~15-20 laboratories worldwide, performing SARS-CoV-2 antigen assays, and representing control/reference laboratories, manufacturers, clinical and academic laboratories. The aim will be to assess the suitability of different preparations to serve as the International Standard for use in the harmonization of SARS-CoV-2 antigen assays.		
Issues raised by the proposal	The possible variability of N and S proteins between different SARS-CoV-2 strains and the effect of this variability on the performance of antigen assays is currently unknown. Commutability of cultured virus and recombinant proteins to clinical samples should be investigated where possible.		
Action required	ECBS to endorse proposal		
Proposer's project reference		**Date proposed:**	December 2020
CONSIDERATIONS FOR ASSIGNMENT OF PRIORITIES (TRS932)			
Approval status of medicine or in vitro diagnostic method	FDA has issued EUA for 7 Antigen Diagnostic Tests for SARS-CoV-2. Two rapid antigen tests are listed in the WHO EUL for In vitro diagnostics (IVDs) Detecting SARS-CoV-2. FIND is conducting prospective diagnostic evaluation studies on 12 SARS-CoV-2 Ag-RDTs.		
Number of products or methods	According to the FIND SARS-CoV-2 Diagnostic Pipeline 2020 (https://www.finddx.org/covid-19/pipeline/.) there are up to 100 companies developing or manufacturing Ag-RDTs.		
Public health importance	SARS-CoV-2 is the etiological agent of the Coronavirus Disease 2019 (COVID-19). COVID-19 presents with a range of symptoms of varying severity. Asymptomatic infection also occurs often although frequency is not defined. Of people who develop symptoms, current data indicate that 40% have mild symptoms, 40% have moderate symptoms and non-severe pneumonia, 15% have significant disease including severe pneumonia, and 5% experience critical disease with life-threatening complications.		
Global importance	The World Health Organization declared COVID-19 a Public Health Emergency of International Concern on 30th January 2020, and a Pandemic on 11th March 2020. As of 1 November 2020, nearly 46 million cases and 1.2 million deaths have been reported globally.		
Global need from regulatory & scientific considerations	A common reference material is needed to support individual assay and comparative evaluations (for regulatory approval and post market surveillance).		

ECBS outcome	[BLANK]