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Name of the University, Hospital, Research Institute, Academy or Ministry

Paul-Ehrlich-Institute (PEI)

Name of the Division, Department, Unit, Section or Area

Division of Haematology and Transfusion Medicine

City Langen **Reference Number** DEU-117

Title WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices

Report Year 07-2018 to 07-2019

1. Annual report on the agreed workplan

Describe progress made on the agreed workplan. For each activity, detail (1) the actions taken, (2) the outputs delivered, as well as (3) any difficulties that may have been encountered. Three responses are expected. [maximum 200 words per activity]. Indicate, if an activity has been completed previously, has not yet started or has been placed on hold.

Activity 1

Title: Development of an International Anti-Hepatitis E Reference Panel

Description: The diagnosis of HEV requires a variety of tests including the detection of IgM and IgG antibodies. Analysis of IgM antibodies is particularly useful for the confirmation of acute infection. Anti-HEV IgG may also be detectable during acute infection. Anti-HEV IgG is also a marker of past HEV infection and seroprevalence and anti-HEV and indication of previous exposure of different populations to HEV infection. Anti-HEV IgG assays vary in their performance and different studies have given widely different estimates of the seroprevalence of anti-HEV.

The importance of reference materials for the diagnosis of HEV infections was discussed at the WHO Expert Committee for Biological Standardization which asked for and also endorsed this important project.

Despite the establishment of an interim WHO International Reference Reagent (IRR, NIBSC code number 95/584) for antibodies to HEV in 1997, there are still wide discrepancies in the performance of anti-HEV assays. It was noted by the ECBS, at the time of establishment of the IRR that assays for anti-HEV were at an early stage of development and acknowledged that full assessment of new antibody assays requires panels of sera. Since the IRR was established, no international agreed unitage has been assigned to the preparation. In the original collaborative study, seven laboratories evaluated a range of mainly in-house developed assays and two commercial assays available at the time.

Fifteen years later, diagnostic sensitivities and specificities as well as inter-assay agreement have been shown to vary widely for different kits for the detection of both anti-HEV IgM and IgG. Anti-HEV IgM is the major serological marker of acute or recent HEV infection; however, the main problem with detection of this marker is specificity; this is further compounded by a lack of sensitivity. Significant underestimations of seroprevalence of HEV (IgG) have been the result of lack of sensitivity of available assays. These assay issues, compounded by the failure of many clinical diagnostic laboratories to test for HEV infection as an alternative diagnosis of acute hepatitis, have impacted on the surveillance of incident hepatitis E and understanding the extent of asymptomatic infection.

Different collaborators are already involved in the collection and preliminary testing of NAT-confirmed cases of hepatitis E – with genotype confirmation, and subsequent collection of sera/plasma samples prior to formulation of the panel and evaluation in an international collaborative study alongside the IRR. It may be possible to assign an internationally agreed unitage to the IRR.

Status: ongoing

The project was endorsed by the WHO Expert Committee on Biological Standardization (ECBS) in October 2015. Plasma has been obtained from recovered patients and donors with further units being screened. The period of sample collection/identification has been completed and materials are undergoing characterization prior to further processing and evaluation in a collaborative study.

The activity is led by Dr Sally Baylis.

Activity 2

Title: Development of the 1st International Chikungunya virus reference reagent for serology

Description: The mosquito-borne Chikungunya virus (CHIKV) is a member of the Alphavirus genus in the Togaviridae family. Chikungunya was first identified in Tanzania in the early 1950s. The disease occurs not only in Africa but also in Asia and the Indian subcontinent and, since 2013, has spread to the Americas, particularly central and Southern areas. Small outbreaks have also occurred recently in Europe.

The diagnosis of Chikungunya requires a variety of tests including detection of IgM and IgG antibodies. Co-circulation of Chikungunya virus with Dengue virus (DENV) and Zika virus (ZIKV) frequently occurs and infections cause by these viruses share common signs and symptoms in infected patients. Accurate diagnosis and discrimination of CHIKV from other virus infections is important for patient care. Analysis of IgM antibodies is particularly useful for the confirmation of acute infection. Anti-CHIKV IgG may also be detectable during acute infection. Anti-CHIKV IgG is also a marker of past CHIKV infection and seroprevalence and anti-CHIKV and indication previous exposure of different populations to CHIKV infection.

Anti-CHIK assays vary in their performance (for example, Niedrig et al. Clin Microbiol Infect. 2009;15:880 and Prat et al. Emerg Infect Dis. 2014;20:2129).

Status: ongoing

The proposal to establish a reference reagent was endorsed by the WHO ECBS in October 2016. Plasma was collected from blood donors as well as recovered patients, and the lead candidate material was evaluated in an external quality assurance study coordinated by INSTAND involving 39 participating laboratories using a variety of different methods. The candidate material was well detected by all participants.

The materials for the WHO collaborative study were lyophilized and aliquoted in 2018 and the collaborative study is scheduled to commence in Q3 2019.

The activity is led by Dr Sally Baylis.

Activity 3

Title: Development of the 1st International Standard for Chikungunya Virus (CHIKV) RNA for NAT-based

Description: Chikungunya virus is a blood borne pathogen transmissible by mosquitoes that has the potential to be transmitted by blood transfusion. The availability of an international standard for Chikungunya virus RNA would facilitate the development and quality control of new NAT assays for use in blood donor screening and in medical diagnostic testing. Such assays would significantly improve the safety of the blood supply worldwide. The topic was assigned high priority by the ECBS, and WHO was requested to provide these materials as soon as possible.

The International Standard for Chikungunya virus RNA will be used as a global standard for the development of assays for the detection of Chikungunya infections in blood donors. It may also be used as a reference standard to evaluate the performance of assays for detection of Chikungunya viral RNA. Users will be blood donor screening and diagnostic test developers, blood banks, hospitals, clinical laboratories and other establishments performing Chikungunya testing.

Status: ongoing

The candidate international standard (IS) was established by WHO ECBS in October 2017 as the 1st IS for CHIKV RNA for NAT- based assays with an assigned unitage of 2.5 million International Units (IU)/mL. Stability studies are ongoing and indicate that the preparation is stable and suitable for long-term use.

The activity is led by Dr Julia Kress.

Activity 4

Title: Development of the 1st International anti-HCMV IgG Standard

Description: Human Cytomegalovirus (HCMV) is spread worldwide with prevalence between 40% and 100%. The virus causes relatively mild and asymptomatic infections in immune competent persons, but can cause congenital disease and severe complications in those with immunodeficiency, e.g. immunological immaturity; acquired immunodeficiency or immunosuppression. Diagnostics of HCMV specific IgG and IgM antibodies and IgG avidity play a major role in prenatal care, blood transfusions and especially transplantation medicine. Current anti-HCMV assays differ considerably in their sensitivity, and there is no international reference material available at the moment. PEI anti-HCMV-IgG reference material has been available since 1982, which is frequently requested by manufacturers for calibration of their anti-CMV test kits. But this material is of limited supply and is weakly positive and not defined in international units. The proposed standard may serve for the calibration of the manufacturer's diagnostic kits, for quality control by competent authorities, and by users. WHO Expert Committee for Biological Standardization discussed the need for an international Standard expressed in IU/ml and endorsed the project.

In 2012 samples were sourced by PEI and tested for suitability for a possible candidate material as well as possible accompanying study samples selected. In April 2013 the project was shown to the WHO Collaborating Centre's meeting and the proposal provided to the ECBS was adopted in October 2013. A Collaborative Study was carried out between 2014 and 2016 to establish the candidate standard. Overall, a candidate anti-CMV IgG standard was developed with an assigned unitage of 46.4 units per mL and vial. In view of the variety of the anti-CMV tests, and their currently non-comparative performance, it is expected that the candidate standard will significantly facilitate comparability between the tests and make the results more reliable.

Status: ongoing

The 1st WHO International Standard for CMV IgG antibodies was adopted by the ECBS in October 2017. The first international WHO standard for anti-CMV IgG for serological assays is available from PEI (code 136616/17), with 46.4 International Units per mL assigned.

Stability studies are ongoing.

The activity is led by Dr Heinrich Scheiblauer.

Activity 5

Title: Extension of the WHO repository for Transfusion Relevant Bacteria Strains - Validation study for Red Blood Cell Relevant Reference Strains

Description: Bacterial contamination of blood components is one of the major threats in transfusion medicine. WHO has been approached by international organisations in the blood field to improve the situation of contamination testing by provision of international reference materials. The WHO Expert Committee for Biological Standardization discussed this issue and endorsed the project of bacteria repository and its expansion.

As a first milestone four Platelet Transfusion Relevant Bacteria Strains were validated in an international study and established in 2010 as the 1st WHO Repository of Platelet Transfusion Relevant Bacterial Reference Strains. The proposal to enlarge the repository was also endorsed by WHO ECBS in 2010. The report of the collaborative study was sent to WHO ECBS for endorsement/adoption at the ECBS Meeting in Geneva in October 2015.

In line with the strategy to establish Relevant Bacterial Reference Strains for all blood components and ATMPs the next step will be to establish a bacterial panel for Red Blood Cells (RBC).

The proposed list includes strains of the following transfusion relevant bacterial species:

Gram-positives: *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Micrococcus luteus*, *Streptococcus pyogenes*,

Gram-negatives: *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Pseudomonas fluorescens*, *Pseudomonas aeruginosa*, *Yersinia enterocolitica*, *Serratia marcescens*, *Serratia liquefaciens*, *Listeria monocytogenes*.

Status: ongoing

In 2017/18, frozen bacterial suspensions of the candidate strains *Listeria monocytogenes* PEI-A-199, *Serratia marcescens* PEI-B-P-56, *Serratia liquefaciens* PEIA-184, *Pseudomonas fluorescens* PEI-B-P-77, *Yersinia enterocolitica* PEI-A-105 and *Yersinia enterocolitica* PEIA-176 were shipped to 15 laboratories worldwide. The testing included the inoculation of RBC bags with a low concentration of bacterial cells and a weekly sampling to determine the number of colony forming units (CFU) for a total of 42 days. Analysis of the results revealed that except for *S. marcescens*, all strains showed good to excellent growth in RBC units. *S. liquefaciens*, *P. fluorescens* and the two *Y. enterocolitica* strains reached stationary phase with more than 109 CFU/mL between day 21 and 28. Growth kinetic of *L. monocytogenes* was significantly slower reaching concentrations of 106 CFU/mL at day 42. In contrast, *S. marcescens* only grew sporadically in one third of the inoculated RBC units.

Results were presented at the Transfusion Transmitted Infectious Diseases WP meeting (International Society of Blood Transfusion, ISBT, Basel) in June 2019. The finalization of the statistical analysis is to be expected in July 2019. The study report will be submitted in July/August 2019 and presented to ECBS in October 2019 for adoption of the 1st WHO International Reference Repository of Red Blood Cell Transfusion Relevant Bacterial Reference Strains.

The activity is led by Dr Oleg Krut and Dr Marcel Prax.

Activity 6

Title: Participation in the Blood Regulators Network (BRN)

Description: WHO recognized the need for rapid and reliable external advice in the field of blood and blood safety. The BRN is a working group of seven leading regulatory authorities in the field of blood products with the task of reacting rapidly to emerging risks, assessing new technologies, and providing advice to WHO. Current topics are support to continuous implementation of Resolution WHA63.12 and the BRN document "Assessment Criteria for National Blood Regulatory Systems"; ongoing revision of the existing WHO NRA (national regulatory agency) assessment tools to include the WHO assessment criteria for blood regulatory systems; BRN supports requests for assessment of blood regulatory systems, e.g. in the African region (ICDRA 2017 recommendation); evaluation of new developments such as pathogen inactivation technology for blood components, storage of red blood cells; discussion of opportunities for international convergence of regulations; proposed guidelines on recombinant DNA derived biotherapeutics; results of EBoV (Ebola Virus) clinical trials using convalescent plasma performed in Guinea; and discussions on national decision making on the MSM deferral (e.g. US FDA, impact of ART).

Status: ongoing

The BRN is a working group of seven leading regulatory authorities in the field of blood products with the task of reacting rapidly to emerging risks, assessing new technologies, and providing advice related to blood and blood regulation aspects to WHO.

Current topics are:

Ongoing support in development and validation of the WHO Global Benchmarking Tool (GBT) with integrated BRN criteria in selected African states; BRN supports requests for assessment of blood regulatory systems with specific focus on haemovigilance, e.g. in the African region (ICDRA 2018 recommendation); evaluation of the storage of red blood cells; discussion of opportunities for international convergence of regulations; and is currently drafting a position paper on HEV and is discussing a statement on the use of cryoprecipitate in bleeding disorders.

Dr Anneliese Hilger is chairperson of the BRN.

Activity 7

Title: Support for the project “Improving Access to Safe Blood Products through Local Production and Technology Transfer in Blood Establishments” (“Achilles Project”)

Description: WHO undertakes the project to enable LMICs to make use of blood components currently discarded as biological waste. “Improving access to medical products through local production and technology transfer” should increase access, especially for the poor in developing and least developed countries to medicines, vaccines and diagnostics of importance to public health, and especially for neglected diseases of the type II and type III categories as well as the specific needs of developing countries in relation to type I diseases.

The project was started with the workshop “Improving Access to Safe Blood Products in Low- and Middle-Income Countries (LMIC): A Framework to improve Public Health” at WHO Headquarters, Geneva, 14-15 June 2012. The initiative is an important element in the implementation of Resolution WHA63.12, which has been supported also by the WHO BRN, e.g. by elaborating the document “Assessment Criteria for National Blood Regulatory Systems”.

PEI experts/inspectors will contribute by facilitating meetings and training courses in several regions of the world.

Status: ongoing

During the recent reporting period, there were no direct WHO CC contributions for the Achilles project. However, under the umbrella of the GHPP “BloodTrain” (Global Health Protection Programme, initiated by the German Ministry of Health) project related activities were performed, e.g.: supporting the development of draft Terms of Reference for the African Blood Regulators Forum (November 2018), together with the partners WHO and NEPAD-AMRH (New Partnership for Africa's Development – African Medicines Regulatory Harmonization); training at PEI of regulators from African partner agencies in blood regulation (March 2019); organization of a training workshop on inspection of blood establishments in Harare, Zimbabwe (May 2019).

2. Annual report on other activities requested

Should WHO have requested activities in addition to the agreed workplan, please describe related actions taken by your institution [maximum 200 words]. Please do not include in this report any activity done by your institution that was not requested by and agreed with WHO.

2.1 68th Meeting of the Expert Committee on Biological Standardization (ECBS), Geneva, Switzerland, 29 Oct.-2 Nov. 2018

The president of the PEI, Professor Cichutek, acted as chairman of the ECBS.

Dr Micha Nübling and Dr Jens Reinhardt (rapporteur Blood Track) participated in the meeting.

The entire activities of the ECBS 2018 are laid down in the WHO Technical Report Series (TRS 1016).

2.2 18th International Conference of Drug Regulatory Authorities (ICDRA), Dublin, Ireland, 3-7 Sept. 2018

Dr Hilger participated in the WHO ICDRA's meeting 2018 as chair of the BRN. She gave a presentation about “Legal Framework for Haemovigilance in Europe”.

2.3 Cooperation with WHO in the area of WHO's Prequalification Programme (PQ) for in vitro Diagnostic Devices (IVD) and Procurement of IVDs

PEI IVD Laboratory continued to participate in the WHO Programme for the Prequalification of Diagnostics.

2.3.1 Review of product dossier submissions and on-site audits of in vitro diagnostic devices (IVDs) for the WHO Prequalification Programme (PQ)

Activities in collaboration with the WHO prequalification team in the WHO Essential Medicines and Health Products Department have now become routine. PEI-IVD Testing Laboratory (PEI-IVD, serology) and Section Molecular Virology (NAT) are regularly asked to review product dossiers and to accompany on-site audits as technical experts.

These evaluations/audits of PEI-IVD and Section Molecular Virology support WHO in the prequalification of IVDs for access to safe, appropriate and affordable good quality diagnostic devices in a fair manner.

In the past year, one on-site audit for three HIV NATs and one assessment of a change request for two HIV

NATs were performed as well as five inspections commissioned by WHO as part of the prequalification of HIV and HCV serological diagnostics.

2.3.2 Technical consultation on WHO prequalification requirements for Hepatitis C Rapid Diagnostic Tests (RDTs) and Enzyme Immunoassays, WHO HQ, Geneva, Switzerland, 29-30 Oct. 2018

Dr Heinrich Scheiblauer attended the consultation and contributed to the drafting of the corresponding technical specification series TSS-7.

2.3.3 5th Annual Meeting of WHO Prequalification of In Vitro Diagnostics Dossier Assessors and Inspectors, WHO HQ, Geneva, Switzerland, 13-15 November 2018

Dr Heiner Scheiblauer and Dr Annette Reissinger participated in the meeting.

These activities expand the WHO's assessment of tests used in developing countries around the world and also expand the scope for the PEI.

2.3.4 Technical Consultation on WHO prequalification requirements for nucleic acid tests for Hepatitis C and HIV, WHO HQ, Geneva, Switzerland, 27-29 May 2019

Dr Julia Kress participated in the meeting. The objective of the consultation was to review and finalize the proposed requirements for WHO prequalification of nucleic acid tests for Hepatitis C and HIV.

2.4 International Nonproprietary Names (INN) of blood products and monoclonal antibodies

From July 2018 to June 2019, Dr Weisser assessed 156 INN requests of biological and 136 INN requests of chemical substances. She attended two consultations of the INN expert group (67th and 68th consultation, October 2018 and April 2019, resp.) where new and outstanding applications were discussed and decisions on the selection of INNs were taken. At both consultations she was elected by the group to act as vice chair for Biologicals.

2.5 WHO Meetings and Workshops

WHO Meeting to Advance Diagnostics for Zika, Dengue, and Related Flaviviruses CICG, Geneva, Switzerland, 9-10 Oct. 2018

The meeting dealt with assessments of diagnostics for Zika, Dengue, and related flaviviruses. The intention was to identify key barriers for development and availability of sensitive and specific diagnostic assays; and to address key barriers for research. Dr Sigrid Nick participated in the meeting.

3. Resources

Indicate staff time spent on the implementation of activities agreed with WHO (i.e. those mentioned in questions no. 1 and no. 2 above). Do not include any data related to other activities done by your institution without the agreement of WHO. Please indicate staff time using the number of "full-day equivalents" – a day of work comprising 8 hours (e.g. 4 hours work per day for 7 days should be recorded as 3.5 full-day equivalents).

Number of staff involved (either partially or fully)

Senior staff	Mid-career staff	Junior staff, PhD students
19	13	0

Number of full-day equivalents, total for all staff involved

Senior staff	Mid-career staff	Junior staff, PhD students
240	250	0

Implementation of the agreed workplan activities (i.e. those mentioned in questions no. 1 and no. 2 above) normally require resources beyond staff-time, such as the use of laboratory facilities, purchasing of materials, travel, etc. Please estimate the costs of these other resources as a percentage of the total costs incurred (e.g. if you incurred costs of USD 100 and the value of your staff time was USD 50 which makes the total of USD 150, please report 33.3% and 66.7%).

Percentage of costs associated with staff time	Percentage of costs associated with other resources	Total
75.00	25.00	100.00

4. Networking

Describe any interactions or collaboration with other WHO Collaborating Centres in the context of the implementation of the agreed activities. If you are part of a network of WHO Collaborating Centres, please also mention the name of the network and describe your involvement in that network [maximum 200 words].

4.1 (WebEx) Meetings of WHO Collaborating Centres (CC) to support the development of WHO Biological Reference Preparations for Blood Products and in vitro Diagnostic Devices
Physical meetings of the WHO CC Network are scheduled for every other year. In between, WebEx meetings are performed for discussions on the ongoing activities.

4.1.1 Meeting by Teleconference of the WHO CCs to Support the Development of WHO Biological Reference Preparations for In Vitro Diagnostic Devices and Blood Products, 23 July 2018
Participants of PEI: Dr Sally Baylis, Dr Michael Chudy, Dr Micha Nübling, Dr Julia Kress.

4.1.2 2nd Teleconference in Follow-up to the April 2018, 6th Meeting of the WHO CCs to Support the Development of WHO Biological Reference Preparations for In Vitro Diagnostic Devices and Blood Products, 30 August 2018
Participants of PEI: Dr Sally Baylis, Dr Micha Nübling, Dr Barbara Schnierle.

4.1.3 Meeting by Teleconference of the WHO CCs to Support the Development of WHO Biological Reference Preparations for In Vitro Diagnostic Devices and Blood Products, 8 April 2019
Participants of PEI: Dr Annette Reissinger, Dr Julia Kress, Dr Hanna Roth, Dr Marcel Prax, Dr Michael Chudy, Dr Micha Nübling.

4.2 Participation in WHO collaborative studies for IVD

Section Molecular Virology of PEI participated in the collaborative study to establish the 6th WHO International Standard for HCV RNA for NAT-based assays. The study was organized by NIBSC, UK.