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Proof-of-principle of a technology transfer of a dried blood virus neutralisation assay to a Gavi-eligible country

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ABSTRACT

Background Global health clinical research is commonly led by high-income countries (HICs) as low- and middle-income countries (LMICs) face barriers to participate, including lack of financial and human capacity and lack of research environment. Respiratory syncytial virus (RSV) vaccine development is also led by HICs, while LMICs carry the burden of life-threatening disease. Representative trials and research capacity strengthening in LMICs are needed to ensure global vaccine access and equity. This study aims to transfer an RSV neutralisation assay, which uses live cells and virus with inherent high variation, to a country eligible to receive support from the Gavi, the Vaccine Alliance.

Methods Using a train-the-trainer approach, a Ghanaian researcher was trained in the Netherlands on the dried blood-based RSV neutralisation assay. Subsequently, a Dutch researcher visited Ghana to support the process of adapting the technique to the Ghanaian setting. In a previously validated RSV neutralisation assay on dried blood, Hep-2 cells were infected with a serial dilution of sample-virus mixture to determine the half-maximal inhibitory concentration. Fifty-one dried blood and serum samples were tested in parallel in both countries to assess concordance.

Results Training and technology transfer was deemed successful, which was defined as neutralisation measurements by the Ghana team and high concordance (Lin's concordance correlation coefficient (CCC)>0.8). Neutralising capacity measured in identical samples in Ghana and the Netherlands correlated highly (Lin's CCC=0.87; Spearman rho=0.89) but was systematically lower in Ghana than the Netherlands.

Conclusion We show successful transfer of an RSV neutralisation assay, thereby strengthening the laboratory research capacity in a Gavi-eligible country. Reliable measurement of RSV neutralising antibodies in a Gavi-eligible country and the use of dried blood can contribute to inclusion of LMICs in RSV vaccine development and access.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The global health research divide is evident in respiratory syncytial virus vaccine development, where vaccines are developed and available in high-income countries, despite low- and middle-income countries (LMICs) bearing the majority of the disease burden.

⇒ Representative trials and research capacity strengthening in LMICs are needed to ensure global vaccine access and equity.

WHAT THIS STUDY ADDS

⇒ In this newly established partnership, we used a train-the-trainer approach to transfer a low-tech dried blood live-virus neutralisation assay from the Netherlands to Ghana, a country eligible to receive support from Gavi, the Vaccine Alliance.

⇒ A sample panel measured in parallel in both countries showed high concordance and correlation despite the difficulties of running a bioassay with inherently high variability while using distinct materials.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The successful implementation of this low-tech virus neutralisation assay may facilitate local in-country participation in future trials, sample analysis and management of clinical trial samples.

⇒ The expertise and set-up would serve as a capacity strengthening platform for researchers in Ghana and other LMICs. The country's participation in trials can stimulate local manufacturing companies to produce current or future vaccines or monoclonal antibodies (mAbs), which ultimately can reduce barriers to equity in vaccine access and the ability to respond to pandemics.

INTRODUCTION

The global divide in resources, including research funding and scientific capacity, results in a research agenda set by high-income

countries (HICs).[1] Low- and middle-income countries (LMICs) experience substantial barriers to participate in clinical research, including lack of funding, lack of skilled personnel and lack of research environment (online supplemental file 1).[2] Equitable partnerships can facilitate research capacity strengthening by sharing knowledge, technology, expertise and funding to effectively address pertinent research questions and enhance self-sufficiency.[1 3]

The global research divide is visible in the respiratory syncytial virus (RSV) vaccine development: vaccines and immunisation are predominantly developed in HICs, where RSV is now a vaccine-preventable disease,[4–7] although more than 95% of RSV-associated hospitalisations and deaths occur in LMICs.[8] Registration trials included participants in LMICs, but sample and data analysis were performed in HICs. Consequently, no RSV vaccine or monoclonal antibody (mAb) is within reach in LMICs despite the high burden.[9 10] Representative clinical trials in LMICs are key to ensure global access and affordability of an effective RSV vaccine.[9 11] Trials largely monitor neutralising antibody (nAb) levels as a correlate of protection; however, a simple tool to measure protection after RSV vaccination is lacking in LMICs due to prohibitive costs and lack of research capacity.[12] Bioassays can measure nAbs with live cells and virus, but the live components inherently increase the complexity and the variation in results. Cell-based assays are recommended to have a target coefficient of variation (CV) of <50% with an average of 25%,[13] whereas industry guidelines are stricter with a CV <20%.[14] Capacity strengthening for vaccine trial research in Gavi-eligible countries, that is, LMICs that qualify for support from Gavi, the Vaccine Alliance to improve access to vaccines and immunisation services, could accelerate access to RSV vaccines while promoting research equity.

Serum obtained through venipuncture is generally considered the gold-standard sample to measure surrogates of vaccine-induced protective immunity.[15] Dried blood spots (DBSs) obtained through finger-prick offer attractive alternatives to serum antibody testing and have already been found to be appropriate tools for the antibody surveillance and/or diagnosis of other viral pathogens such as hepatitis C virus and HIV.[16 17] DBS samples provide numerous advantages over serum, as they are cheaper, less invasive and easy to (self-)collect in clinical and nonclinical settings. DBS do not require specialist equipment for processing and storage, have long-term stability, are readily transportable and hence may facilitate clinical trials in LMICs.[18 19] Our recently validated neutralisation assay using dried blood offers a patient-centric and financial solution to logistical barriers to immunisation research in LMICs.[20]

Here, we describe a technology and knowledge transfer of a dried blood-based RSV neutralisation assay as part of a new partnership to strengthen the research capacity in a Gavi-eligible country. The low-tech low-cost assay can be used to measure clinical trial endpoints in a low resource setting and can set a platform for future development of broader respiratory virus surveillance, vaccine impact and correlate of protection studies in LMICs.

METHODS

Site selection and training

The Virology Department of the Noguchi Memorial Institute for Medical Research (NMIMR) situated in Accra, Ghana, was selected as a site after a screening process involving ten sites within the international GOLD-III ICU network.[21] Thorough inquiry ensured availability of the required facilities to conduct the assay: cell and viral culture systems, biosafety level 2 cabinets (including lamina air flow hoods), fluorescence plate reader with required filters and available research staff experienced in cell culture and virus handling.

Using the train-the-trainer approach,[22] a researcher from NMIMR visited the University Medical Center Utrecht (UMCU), the Netherlands, for 1 month to be trained on the dried blood-based RSV neutralisation assay.[20] Subsequently a Dutch expert researcher visited Ghana for 1 month to support the process of adapting the technique to the Ghanaian setting (table 1). Successful training was defined as measurement of neutralising capacity in dried blood using the neutralisation assay by the Ghana team.

Sample panel preparation and handling

Individual samples for validation of the assay were obtained from healthy volunteers to be measured in parallel in both laboratories. Whole blood was either left blank or spiked with anti-RSV mAbs palivizumab and RSM01 (Bill & Melinda Gates Medical Research

Table 1 Distinct materials between the two laboratories

Distinct materials potentially increasing variation	Distinct materials unlikely increasing variation	Actions to reduce variation
Virus stocks cultured from the same master stock	Fluorescence plate reader	Triplicates rather than duplicates
HEp-2 cell stocks	Single-channel pipettes	WHO international standard
Culture medium	Non-critical reagents, for example, PBS	Verification of data analysis*
Multichannel with securely fitting tips	General laboratory equipment, for example, rocker, centrifuges, heat block	

*Raw data from Ghana was analysed in parallel by both Ghana and the Netherlands teams and compared with cross-validate the analysis methods.
PBS, phosphate-buffered saline.

Institute) at concentrations ranging 5–200 µg/mL. After 30 min on a rocker to mix, Mitra 20 µL volumetric absorptive microsampling tips (VAMS; Trajan Scientific, Neoteryx Clamshell, 20004) were touched to the whole blood sample surface to absorb the fixed volume and left to dry for 3 hours at room temperature.[20] The dried blood samples were packaged in zip-lock bags containing desiccant to allow further drying. Blood of eight healthy donors provided five unique samples per donor for a total of 40 dried blood samples. Additionally, four archived dried blood samples from a previous study,[20] four in-house serum pools and three commercially available serum pools (BEI Resources NR-4021, NR-4022 and NR4023) were added to the sample panel for a total of 51 samples. Samples were shipped to NMIMR on dry ice within 5 days and stored at −80°C until analysis. Prior to analysis on the neutralisation assay, dried blood samples were thawed for 30 min before opening the air-tight bag to prevent condensation. Dried blood was rehydrated by incubating VAMS tips in 200 µL of PBS in Eppendorf tubes overnight at room temperature on a shaker at 300 rpm.

Neutralisation assay

Neutralising capacity of the dried blood samples was tested using a neutralisation assay described previously.[20 23 24] Briefly, Hep-2 cells (ATCC CCL-23) were seeded at a concentration of 0.5×10^6 cells/well in 384-well black optical bottom plates (Thermo Scientific, 142761) and incubated for >4 hours. Dried blood eluate and serum controls, including the WHO 1st International Standard for Antiserum to RSV (NIBSC code:16/284),[25] were heat-inactivated at 56°C for 30 min. Dried blood eluate was then centrifuged at 15 000 g for 10 min to remove cell debris. Serum and dried blood eluate (1:10 during elution) were serially diluted in threefold from starting dilution 1:5 or 1:2 (total dilution 1:20), respectively, in Dulbecco's modified Eagle's Medium containing 10% foetal calf serum. Recombinant mKate-RSV-A2[26 27] was added 1:1 to the sample dilution series and incubated for 1 hour at 37°C before addition of 50 µL of the sample-virus mixture to the adherent Hep-2 cells. After 48 hours incubation at 37°C, relative fluorescence units were recorded using excitation at 584 nm and emission at 620 nm (FLUOstar OMEGA, BMG Labtech and Tecan SparkControl V3.2). The neutralisation curve and 50% inhibitory dilution (ID50) of samples were analysed using a log(inhibitor) versus response four-parameter nonlinear regression curve in GraphPad Prism V.8.3 or higher (GraphPad Software Inc., San Diego, CA, USA). International units (IU) were calculated according to manufacturer's instruction.[25] The bioassay using live cells and virus is inherently subject to high variability compared with non-biological assays, for example, ELISA, with <50% variance considered the target precision in cell-based assays.[13] Healthy adults were expected to have pre-existing anti-RSV antibodies detectable in the assay at baseline (ID50 of approximately 10^3) with an increase postspiking with palivizumab or RSM01.[28]

Sample size and statistical analysis

Results reported as IU/mL from both laboratories were compared using the Lin's concordance correlation coefficient (CCC) to test how well the pairs of observations conform relative to perfect concordance using DescTools package in R (V.4.4.1).[29] In case the data do not follow (near-to) normal distribution, Deming regression is performed using SimplyAgree package in R additional to Lin's CCC. Deming regression takes into account the measurement errors in both the dependent and independent variables simultaneously.[30] Additionally, Bland-Altman plots using the Log10 transformed data are used to describe the agreement between the two measurements.[31 32] A small bias is expected between the two laboratories due the live biological components of the assay resulting in a difference unequal to zero. Simulations performed in R using precision data previously obtained at the UMCU showed that a sample size of 50 samples would provide acceptable Lin's CCC values (≥0.9) and precision (CI width ≤0.1).[29] Successful technology transfer was defined as Lin's CCC >0.8. Assay precision was calculated as the percentage %CV of relative fluorescence units of sample duplicates (intra-assay precision) or %CV of the linear ID50 between runs (inter-assay precision). Plots were created in GraphPad Prism V.10.1.2.

Ethical approval

The use of blood samples from healthy adults from the UMCU healthy donor service was approved by the ethics committee of the University Medical Center Utrecht, reference number 07–125/O. The healthy volunteers provided informed consent before taking part of the healthy donor service.

Patient involvement

Patients were not involved in the design or conduct of the study. Interim study results were presented to the Respiratory Syncytial Virus Network patient advisory board.

RESULTS

Successful training was achieved within the planned time frame of 1 month of remote training of the trainer and 1 month on-site training of other personnel, according to the pre-specified definition of measuring neutralising capacity in dried blood using the neutralisation assay by the Ghana team. The RSV neutralisation assay performed in Ghana and the Netherlands detected neutralising activity in all blood samples of the sample panel including blank dried blood samples. Two samples gave unreliable ID50 values according to quality control criteria[20] on repeated measurements in Ghana and were therefore excluded from analysis. Lin's CCC was 0.87 (95% CI 0.80 to 0.92), which is above the defined value of 0.80 for a successful transfer (figure 1). As the data were minimally skewed, we also performed Deming regression resulting

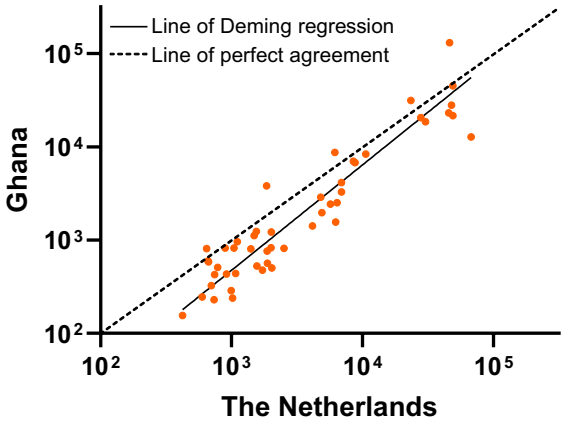

Figure 1 Scatter plot of respiratory syncytial virus (RSV) neutralising capacity in blood samples measurements in Ghana over measurements in the Netherlands. Scatter plot for Log_{10}-Log_{10} transformed RSV neutralising antibodies (ID50 in IU/mL) in dried blood measured in Ghana over measurements in the Netherlands (n=49 paired measurements). Deming regression (solid line) is compared with the line of perfect agreement (dashed line) to calculate the Lin's concordance correlation coefficient of 0.87. ID50, dilution factor with 50% viral neutralisation activity; IU/mL, international units per millilitre.

in the following equation: Ghana [IU/mL] = 1.13 x Netherlands – 2.37 (95% CI of slope 0.9795 to 1.280, 95% CI of Y-intercept −4.057 to −0.6775). Values in Ghana highly correlated with those in the Netherlands over the range of ID50 values (Spearman rho=0.89, 95% CI 0.81 to 0.94, p<0.0001) but were systematically lower. The measurement differences in RSV neutralising capacity in dried blood have a significant bias, better illustrated in the Bland-Altman plots (figure 2). The Log10 mean difference (Netherlands–Ghana) was 0.26 (figure 2), corresponding to a geometric mean difference of 1.81 with more bias seen in samples with lower neutralising capacity. Inter-assay and intra-assay precision were lower in Ghana than in the Netherlands (table 2).

DISCUSSION

We show successful strengthening of the laboratory research capacity in Ghana by implementing a virus neutralisation assay with dried blood. The neutralising antibodies in matched dried blood samples obtained at the laboratories in Ghana and the Netherlands had high concordance (Lin's CCC=0.87) and were highly correlated (Spearman rho=0.89) in the context of a biological assay with high expected variance due to the use of live virus and live cells. The reliable measurement of neutralising antibodies acts as proof-of-principle that knowledge and technology can be successfully transferred and thereby promote the participation of LMICs in RSV clinical trials.

The five recently available RSV vaccines and mAbs are only in use in HICs, despite the high burden in LMICs.[9] Urgent measures are needed to minimise the existing vaccine gap, including conducting representative trials and reducing pricing.[9 10] Notably, all phase 3 registration trials of the recently market approved RSV vaccines were also recruiting participants in upper middle-income

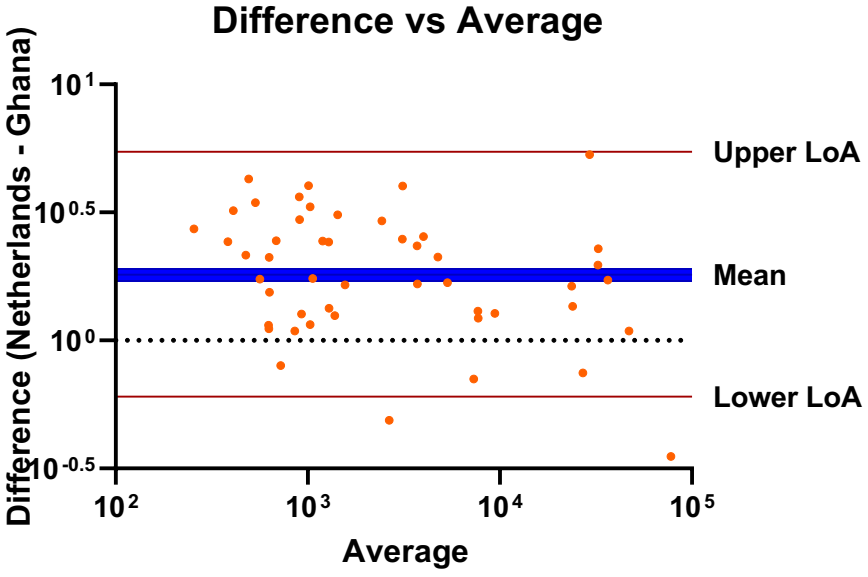

Figure 2 Bland-Altman plot of the agreement for respiratory syncytial virus neutralising antibody measurements between the Netherlands and Ghana. Scatter plot of difference between Log_{10} transformed neutralising antibodies (ID50 in IU/mL) in dried blood samples measured the Netherlands and Ghana versus the average of the two measurements. The mean difference (bias) with 95% CI in blue. Limits of agreement are calculated as mean bias±1.96*SD. ID50, dilution factor with 50% viral neutralisation activity; LoA, limit of agreement.

Table 2 Assay precision in the two laboratories

	Ghana	The Netherlands
Inter-assay precision (median, IQR)	35.6 (30.5–37.5)	23.6 (22.5–26.4)
Intra-assay precision (median, IQR)	12.9 (5.1–26.2)	3.5 (1.6–6.6)

Precision expressed as the %coefficient of variation (%CV) where lower %CV equals higher precision.
CV, coefficient of variation.

countries (UMICs),[5–7 33 34] yet these participants still lack post-trial access to these vaccines and no low or lower-middle income countries participate in the trials, except for the Gambia and the Philippines. To our knowledge, all trial samples are shipped to HICs for neutralising antibody measurements, further exposing the disparities and limited roles left for LMICs in addressing global health challenges posed by RSV. During the COVID-19 pandemic, LMICs played a crucial role in the genetic surveillance identifying mutants of concern.[35–37] However, vaccines developed in HICs tend to induce lower immune responses in LMICs,[38] underscoring the importance to conduct vaccine trials in LMICs. The research community shares the responsibility to include LMICs in global health research efforts, for example, by establishing partnerships.[1] The current assay set-up in Ghana, a Gavi-eligible country, and use of dried blood could facilitate clinical trials in LMICs, thereby ensuring access to effective vaccines and mAbs, as well as addressing other research priorities within the local research agenda. Dried blood sampling, more accepted than serum due to its common use in HIV testing,[17] is also more practical and safer for self-sampling or acquisition by field technicians and does not require cold-chain transportation, making it more suitable for LMIC settings. However, the lack of local production of VAMS devices and the price could pose a challenge in the procurement of VAMS for large-scale trials.

The current study had several strengths and limitations. The on-site training of the leading Ghanaian investigator in the Netherlands allowed an active practical hands-on experience and collaborative knowledge sharing. These fostered real time feedback, troubleshooting, seamless transfer of expertise between the two labs within a short time and contributed to the overall success of the tech transfer. By training the trainer, consistency in methodology and peer-to-peer learning was obtained in all Ghana trained personnel. Moreover, the use of the WHO international standard facilitated direct comparison of the assay results. Although identical methodology was used, certain critical reagents such as growth medium, virus and cell culture varied between the laboratories. The variations observed in the data were partly corrected by normalising the ID50 values to IUs with the international standard. In industry, it is commonly considered a best practice to acquire identical equipment and materials in the context of a technology transfer, which was not feasible in the current study. The lower resource setting in Ghana led to discrepancy in the availability of materials, such as a multichannel with securely fitting pipette tips (table 1). Inter-assay precision was higher in the Netherlands than in Ghana potentially due to higher quality of materials (table 2). Despite these limitations of using varying materials of varying quality with identical methodology, we were able to obtain a high correlation and concordance. A third limitation was the lack of cross-validation from Ghanaian samples shipped to the Netherlands, which is planned in a future study. The shipment of samples and consequently later measurement of samples in Ghana potentially caused the systematically lower neutralising capacity in Ghana than in the Netherlands. As there was no thawing during the shipment and antibodies are generally stable, we expect limited impact of the lack of cross-validation. Fourth, we transferred a neutralisation assay using RSV-A that cannot measure RSV-B neutralising antibodies. Assessment of protection against both RSV subtypes would require adaptation of the assay. Fifth, we observed a bias in measurements between the labs with higher measurement bias in samples with lower neutralisation capacity. As the number of observations is small for higher averages, the variation in bias could potentially be an artefact of lack of normal distribution in ID50 values. Cell-based bioassays typically target a variance below 50%, averaging around 25%,[13] so the observed 81% mean bias is likely partially attributable and within acceptable assay variation. As the neutralisation is best used to measure relative nAb differences in clinical trials, the lack of full agreement might be acceptable. Sixth, we acknowledge that technology transfers are more easily done to facilities with established research capacity (capacity strengthening) than facilities without any research capabilities (capacity building). The availability of the assay in the NMIMR research lab does not yet make the technology widely available to the entire country. Lastly, comprehensive assay validation is needed before the NMIMR can analyse samples for regulatory purposes, such as in vaccine trials.

The current research project has significantly impacted RSV clinical trial capacity in Ghana, establishing the laboratory as a research hub that can support other African countries. By successfully transferring the dried blood-based RSV neutralisation assay technology to Ghana, local researchers are now equipped and planning to analyse RSV clinical trial samples. Taking away some of the barriers to active participation of LMICs, especially Gavi-eligible countries in clinical trials, improves the access to vaccines where the disease burden is highest. This capacity strengthening not only enhances Ghana's

role in regional health research but also opens opportunities for expanding similar capabilities to labs in other regions and countries. Importantly, establishment of the neutralisation assay empowers Ghanaian scientists to participate in and lead research relevant to the population, ensuring that local health challenges are addressed with local expertise. Currently, intellectual property rights are predominantly owned by HICs often preventing local manufacturing of products, which could be resolved by active participation by LMICs. Localising research and development with this project contributes to decolonising global health by shifting the balance of research capabilities and decision-making power from HICs to LMICs through equitable partnerships with team engagement at all stages of the study. Consequently, it fosters a more equitable global health landscape where research and innovation are driven by those most affected by the diseases studied in order to achieve the 2030 sustainable development goals.[1]

Panel: Key next steps to LMIC participation in vaccine research and ultimate vaccine access

- Assay qualification and laboratory qualification for licensure (eg, good clinical laboratory practice).
- Obtain intellectual property rights, eg through voluntary licensing.
- Hubs for local manufacturing of vaccines or mAbs.
- Clarification of regulatory standards for registration trials in LMICs.
- Equitable partnerships between HICs and LMICs, including clinical research organisations based in HICs with existing research infrastructure in LMICs.

See also Partnerships for African Vaccine Manufacturing Framework for Action.[39]

CONCLUSION

We provide a proof-of-principle that a bioassay with inherently high variability can be transferred to resource limited settings such as in Ghana with limited time and financial investment. Strengthening research-capacity in LMICs offers a platform for future development of broader vaccine development, vaccine impact and correlate of protection studies in LMICs. The transfer of this assay is a key step in minimising the RSV vaccine gap between HICs and LMICs.

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Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee of the University Medical Center Utrecht (reference number 07-125/0). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

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