Serosurveillance Summit Meeting Report

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Foreword

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A special thanks to our hosts at the Johns Hopkins University Bloomberg School of Public Health for their leadership in organizing this Summit on Integrated Multiplex Serosurveillance; and to all participants for attending and bringing their remarkable technical expertise to this gathering. These are exciting times in building collaborative and integrated disease surveillance platforms in low-resource settings and it'll be important to leverage new technologies for improved public health protection.

Infectious diseases remain a major cause of morbidity and mortality globally. Integrated multi-pathogen serosurveillance is an important complement to event-based clinical surveillance, providing insights simultaneously into human exposure and immunity to multiple pathogens including asymptomatic or undetected infections. Routine population-representative serosurveys can help identify immunity gaps, detect antibody signatures of emerging infectious diseases, estimate the prevalence and sometimes incidence of key infections, and identify priority populations for disease control, including targeted vaccination programs.

The COVID-19 pandemic has highlighted the inadequacy of many routine surveillance systems and the inability for data to be linked across platforms to inform timely public health decision-making. In the current landscape of global health programs, surveillance systems are often disease-specific, creating siloed and rigid systems that are not well coordinated, leading to parallel and redundant reporting, especially in low-resource settings.

Technological advances are providing new tools to better understand population-level exposure and susceptibility to human pathogens. Advances in multiplex bead assay testing, sample collection, and computational modeling have the potential to transform integrated multi-pathogen serosurveillance into a powerful tool for responding to infectious disease threats and for effective public health program design. To fully harness the potential of multiplex technologies, we need to coordinate better across health risks, create opportunities for resource-sharing and build upon existing and successful vertical disease programs. Country ownership based on locally accepted public health priorities should be the foundation of the design and implementation of any population-representative serosurveillance program. The optimal timing and frequency of serosurveys will depend on the specific use cases and biomarkers available.

In the words of Ambassador John Nkengasong: 'Given the tremendous advancements in the capabilities of laboratory systems across low- and middle-income countries over the past decade, it is crucial for all of us to build upon that platform to help promote a fully integrated, multiplexed, and networked surveillance and response system for public health. National public health institutions especially will have a unique role to play in the design, implementation and constant innovation in these efforts.'

This Serosurveillance Summit (March 7-8, 2023) Meeting Report represents a significant contribution to identifying remaining challenges and potential solutions for building serosurveillance programs across stakeholders. Defining the public health use cases for multiplex serosurveillance is essential to demonstrate the value of this approach to public health decision makers, complementary to other available surveillance metrics. We must prioritize public health use cases that lead to clear demand for services and public health action, and then build the system from there. As discussed in the Use Case Scenarios Working Group Summary, integration provides the potential to exploit economies of scale. Being able to integrate into existing surveys or surveillance systems would make multi-pathogen serosurveillance more sustainable, though it may not work for all public health use cases. Population-based multi-pathogen serosurveillance conducted at regular intervals (e.g., every 2-3 years) in a representative and sufficiently powered sample, ideally at both national and sub-national levels, will provide the most useful data for improved public health decision-making.

This summit brought together technical experts, epidemiologists, country implementors, multilateral organizations, private industry, and funders who are paving the way for more standardized and robust use of novel integrated serosurveillance platforms. The Bill and Melinda Gates Foundation aims to generate more evidence to make integrated multi-pathogen serosurveillance a powerful, useful, and accessible tool, especially for resource-limited settings. We thank each of the organizers, chairs, co-chairs, and note-takers for all their efforts in representing the collective thinking in this detailed Meeting Report and encourage the expansion of integrated serosurveillance so it can be a valuable instrument for future public health decision-makers.

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Acronyms

AFRO	African Region
BMGF	Bill and Melinda Gates Foundation
BSA	Bovine Serum Albumin
BSPH	Bloomberg School of Public Health (Johns Hopkins University)
CDC	Centers for Disease Control and Prevention
CMOS	Complementary Metal Oxide Semiconductor
COVID-19	Coronavirus Disease 2019
DBS	Dried Blood Spots
DENV	Dengue Virus
DTP	Diphtheria, Tetanus, and Pertussis
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
GST	Glutathione S-Transferase
HIV	Human Immunodeficiency Virus
IgA/G/M	Immunoglobulin A/G/M
IVD	In Vitro Diagnostic
KEMRI	Kenya Medical Research Institute
LMIC	Low- and Middle-Income Country
LSTMH	London School of Hygiene and Tropical Medicine
MBA	Multiplex Bead Assay
MDA	Mass Drug Administration
MFI	Median Fluorescence Intensity
MR	Measles and Rubella

MSA	Multiplex Serological Assay
NIBSC	National Institute for Biological Standards and Control
NTD	Neglected Tropical Disease
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PRNT	Plaque Reduction Neutralization Tests
RIVM	National Institute for Public Health and the Environment (Netherlands)
RUO	Research Use Only
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
VPD	Vaccine-Preventable Disease
WHO	World Health Organization
ZKV	Zika virus

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Use Case Scenarios: Christopher Drakeley, Emily Gurley, Thomas Jaenisch, Kondwani Jambo

Supply Chain: Richelle Charles, May Chu, Daniel Leung

Seroepidemiology: Andrew Azman, Sonia Hegde, Eunice Wangeci Kagucia, Nicole Walter

Laboratory Assays: Christopher Heaney, Gerco den Hartog, Diana Martin, Rosemary Rochford

Data Analytics: Isabel Rodriguez, Henrik Salje, Saki Takahashi, Amy Winter

Sustainable Implementation: Martha Idali Saboya-Diaz, Fiona van der Klis, Sammy Njenga, Amy Wesolowski

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Executive Summary

The Johns Hopkins Bloomberg School of Public Health hosted an in-person workshop on integrated, multiplexed serosurveillance March 6-7, 2023. Almost 90 experts from different fields participated, including researchers (e.g., CDC, Institut Pasteur, LSHTM, RIVM, and academicians), multilateral organizations (e.g., CDC AFRO, PAHO, WHO), private industry (e.g., Luminex, Tetracore), funders (e.g., BMGF, Global Fund), and country partners (e.g., Bangladesh, India, Kenya, Malawi, Mozambique, Papua New Guinea, Sierra Leone, Uganda). Participants were divided into 6 working groups to identify key challenges and potential solutions for integrated serosurveillance using multiplex bead array (MBA) technology. Building upon the varied experiences of technical experts, the workshop established a community of practice.

Use Cases for Multiplexed Serosurveillance:

1. **Burden and distribution of infections** to complement or fill in gaps of existing surveillance systems
2. Identification of **emerging and reemerging infections**
3. Identification of **vaccine program reach or gaps**, geographic or demographic gaps
4. Assessing **changes in pathogen exposure due to behavioral, environmental, or pharmaceutical interventions or environmental changes**
5. Monitoring **peri- and post-elimination** settings for diseases with elimination goals
6. **Research** to improve the application of integrated serosurveillance

Key Challenges Discussed in Each Working Group

Working Group	**Key Challenges**
Supply Chain	Procuring and maintaining appropriate platform technology, producing and procuring quality-assured beads and assays, commercializing kits, maintaining the cold chain, understanding and addressing country-specific limitations to importation, and limited human and technological capacity to anticipate and avoid supply chain issues
Sero-epidemiology	Selecting sample populations and sample sizes, establishing the frequency of serosurveillance, identifying and validating less resource-intensive sampling strategies, defining sampling approaches that answer multiple questions, determining core individual- and household-level data to collect, linking serosurvey antigens and study design for programmatic impact
Laboratory Assays	Supporting technology transfer and training, sharing best practices and protocols, standardizing antigen use across countries, defining quality control standards
Data Analytics	Standardizing and cleaning raw laboratory data, translating cleaned data into useful epidemiologic inference, and developing analytical/visualization pipelines for target audiences
Sustainable implementation	Demonstrating added value for initial engagement, generating buy-in across national health systems, ensuring adequate laboratory capacity and procurement, and interpreting data and integrating results for decision making

Cross-Cutting Solutions Identified

Create an electronic platform for information sharing

All groups advocated for a digital platform to share information across experts. A Github, Slack, or website could be a forum to share lists of supplies, existing protocols, antigens that have or have not worked for assay development, and quality control procedures. R code and apps could also be shared for data cleaning and analysis as well as comparing models that have been developed for data analytics.

Build local capacity

Research institutions that have been conducting multiplex serology in LMICs have been conducting training in a similar manner. Many working groups suggested building in-country capacity for a variety of topics, and this was further highlighted in the sustainable implementation group. This could include for example: supply chain logistics and equipment maintenance (supply chain), sampling (seroepidemiology), bead coupling and running the assay (laboratory), and data analysis (data analytics).

Develop quality control or standardization process

As countries develop multiplex assays, quality control and standards for evaluating the performance of an assay are needed. This could include a panel of standard positive/negative controls or some other evaluation kit to maintain high quality of the assay, laboratory testing procedures, establishment of cutoffs for seroprevalence, etc. While ensuring quality is important, this should also be balanced with flexibility for countries to customize assays to meet their needs based on use cases and interest.

Establish laboratory network

A network of laboratories could facilitate information sharing, developing harmonized protocols, sharing of materials, and implementing training and quality control procedures. The structure could include regional hubs that support surrounding countries with regards to training, supplies, etc. This network could be modeled off SeroNet in the US or other global laboratory networks, such as for polio or measles and rubella.

Generate political buy-in for multiplex serosurveillance

Political will is needed to sustainably integrate serosurveillance into the surveillance system and ensure findings are useful for programmatic decision making. Involving ministries of health early in the process and demonstrating the value of multiplex serosurveillance can generate buy-in from governments, funders, and implementers. Policy briefs and use case examples can generate interest among additional funding agencies to invest in serological surveillance as a complementary surveillance mechanism.

Next steps

This meeting created a community of practice to carry forward the work to be done in terms of building platforms for data sharing, laboratory protocol comparisons, data analytic tools and lessons learned to move towards routine serosurveillance implementation globally. Each working group will continue meeting to work on the proposed solutions and next steps identified. A follow-up meeting will be held in 2024.

Introduction

Serological surveillance or "serosurveillance" involves the collection and analysis of serum samples, dried blood spots, or oral fluid to measure antibodies (typically IgG antibodies) to estimate population levels of exposure or immunity to infectious diseases [1]. Serological surveillance is a tool that complements traditional public health surveillance for infectious diseases. This includes identifying population immunity gaps against vaccine-preventable diseases (VPDs), monitoring exposure to malaria, tracking neglected tropical disease (NTD) elimination, and identifying exposure and immunity to enteric diseases, vector-borne diseases, and emerging infectious diseases. Interest in serological surveillance has increased in the past couple of years due to the COVID-19 pandemic highlighting the importance of monitoring population immunity to provide policy makers with better information to guide public health policies and programs [2]. Going forward, this continues to include guiding vaccination strategies and continued monitoring for future emerging pathogens. The swift investment in infrastructure created during the pandemic for laboratory and methodological support can now be used to support serosurveillance for multiple pathogens.

Technologies used to conduct serosurveillance range from single antigen-antibody combination or 'monoplex' assays, including enzyme-linked immunosorbent assays (ELISAs), to multiple antigen-antibody combination multiplex serological assays (MSAs) including multiplex bead assays (MBAs) [3]. The ability of multiplex serological assays to test for exposure to and immunity against several diseases at the same time holds powerful implications for measuring disease burden, identifying immunization gaps [4,5], and tracking the impact of interventions or intervention cessation (e.g., following cessation of MDA azithromycin programs for trachoma) [6,7] while increasing the speed of analysis and lowering costs.

Multiplex serological assays have been developed and used to detect immunity and/or exposure to vaccine-preventable diseases such as measles, mumps, rubella, and varicella [8,9]; respiratory illnesses [10]; neglected tropical diseases including trachoma [6,7,11], onchocerciasis [12], and Chagas disease [13]; malaria [14,15]; sexually transmitted infections like HIV, syphilis, and herpes [16]; emerging infectious diseases [17]; and, more recently, SARS-CoV-2 [18]. Despite the rich data that MSAs can produce, many limitations to their broader adoption and use exist, including challenges related to product characteristics, supply chains and affordability, data analysis and interpretation, use of analyses to guide health interventions, and implementation.

Although these challenges are formidable, MSAs have been used for integrated serosurveillance in several settings, though primarily for research or pilot-level activities [19]. As technical and implementation-related questions arise and are answered through pilot

activities, concerted efforts must be taken to understand the strengths, limitations, and broad applicability of these technologies across a range of geographical and epidemiological settings.

In 2016, the Pan American Health Organization (PAHO) and the U.S. Centers for Disease Control and Prevention (CDC) established an integrated serological surveillance initiative using the Luminex MBA platform in the Region of the Americas [19,20]. Some countries, with support from the CDC, have expanded their laboratory capacity to allow for integrated surveillance to be streamlined within national ministries of health, but challenges to incorporate multiplex serology into public health decision-making remain. As part of their efforts in capacity building, they developed a Toolkit for Serosurveillance of Communicable Diseases in the Americas to support program managers and teams involved in the control and elimination of communicable diseases who are interested in incorporating integrated serological surveillance into their surveillance systems [20].

In 2018, an expert group met to perform a landscape analysis of approaches that support an integrated serosurveillance platform. Their work cataloged the pathogens available to be included in a multiplex serological assay at the time, laid out objectives for an integrated platform, and started to identify potential use cases [21]. They also discussed community and stakeholder engagement, ethical considerations, and advocacy. The report summarizes the group's insights and proposed roadmap for implementation, including objectives, technical requirements, ethical issues, logistical considerations, and monitoring and evaluation.

Serosurveillance Summit

Building on the roadmap laid out by this previous integrated serosurveillance platform meeting, a serosurveillance summit was developed to bring together technical experts to follow up on several issues. On March 6-7, 2023, the Johns Hopkins Bloomberg School of Public Health hosted an in-person workshop in Baltimore, MD, USA on integrated, multiplexed serosurveillance Almost 90 experts from different fields participated, including researchers (e.g., CDC, Institut Pasteur, LSHTM, RIVM, and academicians), multilateral organizations (e.g., CDC AFRO, PAHO, WHO), private industry (e.g., Luminex, Tetracore), funders (e.g., BMGF, Global Fund), and country partners (e.g., Bangladesh, India, Kenya, Malawi, Mozambique, Papua New Guinea, Sierra Leone, Uganda). Participants were divided into six working groups with each participant belonging to two working groups. The working groups met twice during the meeting. The objectives of the workshop were to identify key challenges and potential solutions for integrated serosurveillance using MBA technology and to establish a community of practice of technical experts.

The welcome remarks highlighted the vision for the meeting with comments provided by William Moss from BSPH, May Chu from the University of Colorado, Eunice Kagucia from KEMRI, Ambassador Dr. John Nkengasong (U.S. Global AIDS Coordinator and Special

Representative for Global Health Diplomacy), and Marc Bulterys from BMGF. KEMRI provided an in-country perspective of leveraging resources during the pandemic to set up a serosurveillance system. Kenya has established five geographically representative sites, conducted cross-sectional surveys, developed an anti-spike SARS-CoV-2 IgG assay, and been developing additional panels for VPDs, arboviruses, Rift Valley fever, and RSV. The objective of this work is to have laboratory assays that are relevant to different stakeholders both nationally and globally based on a priority pathogen list.

Partner remarks recognized that sustainable integrated multiplex serosurveillance is a multidisciplinary endeavor that requires bringing more partners to the table to establish a cooperative framework and build consensus to fill the identified gaps. It was acknowledged that serosurveillance serves as one pillar of integrated surveillance, which includes traditional surveillance systems, wastewater surveillance, and mortality surveillance. The call to the group was to strengthen serosurveillance systems in all countries, especially in low-resource settings, to support disease surveillance and serve as an early warning for the next pandemic. The objectives for the meeting were for each of the working groups to:

- Discuss experiences with establishing integrated multiplexed serosurveillance systems with a focus on multiplexed bead assays
- Discuss challenges in establishing integrated multiplexed serosurveillance systems
- Discuss opportunities to expand integrated multiplexed serosurveillance systems
- Identify research needs for integrated multiplexed serosurveillance systems
- Establish a community of practice for integrated multiplexed serosurveillance systems

Discussions from the six working groups are summarized in this report:

- **The Use Case Scenarios Working Group** looked at use cases for serosurveillance across antigens in terms of how serology informs programmatic decision making, building off epidemiological scenarios for integrated serosurveillance.
- **The Supply Chain Working Group** discussed issues including multiplex bead array assay availability, antigen-bead coupling, reagent availability, equipment, and opportunities for technology transfer.
- **The Seroepidemiology Working Group** looked at epidemiologic considerations such as study design, sampling strategies, handling different target populations, and ways to address biases.
- **The Laboratory Assays Working Group** addressed thresholds for seropositivity, standardization, control panels, methods and tools for processing, and considerations for improving assays for certain antigens (cross-reactivity, antibody kinetics, etc.).

- **The Data Analytics Working Group** assessed analytical approaches to seroprevalence data, how to combine modeling with seroprevalence data, approaches to data triangulation, and tools to support in-country analysis.
- **The Sustainable Implementation Working Group** focused on country issues related to implementation, policy implications, and the sustainability of serosurveillance systems. This includes dissemination and translation of results to policymakers and challenges in establishing integrated serosurveillance systems.

Use Case Scenarios Working Group Summary

Objective and Overview

This working group focused on defining the use cases for multiplex serological surveillance. A use case is the context in which multiplex serosurveillance could be useful. This includes what types of epidemiological or public health questions could be answered. Defining the use cases helps demonstrate to public health decision makers the value of serology in providing complementary information to other surveillance metrics. Because use cases may differ by antigen, there can be scenarios where they overlap within a population. For example, one national serosurvey may provide monitoring for the elimination of one disease while providing a baseline seroprevalence for another.

Methodology/Approach

The starting point for this group was the epidemiological scenarios for integrated serosurveillance as defined in the PAHO toolkit: (1) areas where epidemiological surveillance systems are fragile or in epidemiological silence; (2) areas where interventions have been implemented and must be monitored to assess progress toward programmatic goals; and (3) areas where diseases are close to elimination, or where they have been eliminated and post-elimination surveillance is needed. The working group co-leads had a pre-meeting where they reviewed these scenarios and discussed an initial seven use case scenarios which were more detailed than PAHO's three categories. The working group meetings comprised of iterative discussions to define the use case scenarios, including what public health questions could be answered by each of these scenarios, what examples would fall into each of these use case scenarios, and how group members' experiences could be used as examples. The second day refined the use case scenarios and created a table with examples of the use case or objectives that would fall into that use case, sampling considerations (e.g., target population and survey design), example pathogens, and challenges for that use case.

There were a few overarching goals in the development of the scenarios. This included keeping the scenarios more generalizable by not delving too deeply into a particular pathogen or scientific question to be answered. They also aimed to be parsimonious in the number of use case scenarios. The working group also considered what the public health action would be based on the findings of each use case and its intended audience. Since multiplex serosurveillance would be part of public health surveillance, the end user was considered to be the government, which could take public health action after identifying intervention areas.

The final list of use cases proposed by the group is shown in Table 1 and is discussed in more detail below. There is an example case from a published paper provided for each use case in the description that follows.

Table 1: Use Cases, respective sampling strategy/survey design, and example pathogens

	Use Case	Survey design/sampling strategy	Example pathogen(s)
1	Burden and distribution of infections	National or subnational cross-sectional surveys	*Campylobacter*, Chagas, chikungunya, cholera, *Cryptosporidium*, cysticercosis, *Giardia*, neglected tropical diseases, *Plasmodium* species (some), strongyloidiasis, yaws, HIV
2	Identification of emerging and re-emerging infections	Convenience samples (e.g., blood donors), residual samples from facility-based surveillance (e.g., acute febrile illness), targeted sampling of risk groups (e.g., healthcare workers)	Ebola, Lassa, Marburg, Mpox, SARS-CoV-2, Zika,
3	Identification of vaccine program reach or gaps	Targeted sampling according to prior information (spatial, age, sex); national surveys, subsets of populations in a survey	Measles, polio, rubella, SARS-CoV-2, yellow fever
4	Assessing infection changes due to behavioral, environmental, or pharmaceutical interventions or environmental changes	Repeat cross-sectional surveys; longitudinal cohort; national surveys or subset; targeted sampling; may need to oversample children to get naïve population; residual samples may be possible but needs further operational research	Chikungunya, dengue, malaria, PCV13 (must be able to distinguish between vaccine- and infection-derived immunity), Typhoid
5	Monitoring peri- and post-elimination surveillance settings	Young children (1-5 or 1-9 years); targeted sampling where or in whom transmission last occurred; facility-based residual samples	Guinea worm, human African trypanosomiasis, Lymphatic filariasis, malaria (sub-national levels), onchocerciasis, trachoma, visceral leishmaniasis, yaws
6	Research		

Use Cases

1. Burden and distribution of infections

This use case was originally about capturing infections that may have been missed by facility-based surveillance. This would provide additional information to clinic-based surveillance, where there may not be good surveillance. It was highlighted how serosurveillance captures a truer estimate of the number of infections because it measures antibodies regardless of whether a case is symptomatic or asymptomatic. This can also be used to inform policymakers about the ability of the health system to identify cases.

> *There was an example of a study in Mombasa city in the coastal region, where dengue was known to have outbreaks from time to time. The counties in Kenya are decentralized, so each county is responsible for their health. The county did not have the capacity to test for dengue in facilities except at the hospital and had run out of tests. They were using clinical diagnosis aside from the rapid test if available (if the case presented was not malaria, then it was dengue). When they performed a dengue antibody test, they found 80% seropositivity.*

It was noted that this could provide an estimate of the number of infections for some pathogens, which could be used as a baseline. This estimate could be used to calculate other disease transmission parameters including incidence of infection for some pathogens. There was some discussion around whether serology was estimating cases or infections, but the working group ultimately agreed it would estimate infections because cases require clinical signs and/or symptoms which cannot be measured in a serostudy.

Example paper for this use case: Henrik Salje, Kishor Kumar Paul, Repon Paul, Isabel Rodriguez-Barraquer, Ziaur Rahman, Mohammad Shafiul Alam, Mahmadur Rahman, Hasan Mohammad Al-Amin, James Heffelfinger, Emily Gurley (2019) Nationally-representative serostudy of dengue in Bangladesh allows generalizable disease burden estimates eLife 8:e42869. https://doi.org/10.7554/eLife.42869

2. Identification of emerging and reemerging infections

This use case most often referred to SARS-CoV-2 serological surveillance, but also included Zika, Mpox, Ebola, Lassa, and Marburg. There was some debate about distinguishing emerging infections from reemerging ones. Emerging pathogens pose a unique challenge because novel pathogens are harder to detect because they have not been identified for surveillance and a new assay is required. The availability of well-developed targets for a new pathogen also poses difficulties. There may also be political challenges with identifying new or reemerging pathogens in terms of having to declare new outbreaks.

There was also an acknowledgement that as transmission increases, pathogens may shift from being emerging pathogens to endemic and no longer fall into this use case. Serosurveillance could be used for estimating population-level attack rates, identifying areas or demographic groups at high risk to target clinical surveillance, identifying variations by season, changes in variants or strains for pathogens, characterizing the immunologic landscape, or looking at antibody type. Serosurveillance can also be used to guide vaccines for emerging pathogens. This includes looking at the duration of vaccine immunity, as compared to natural infection, and the design of vaccines, such as what strains to include.

Example paper for this use case: Basto-Abreu, A., Carnalla, M., Torres-Ibarra, L. et al. Nationally representative SARS-CoV-2 antibody prevalence estimates after the first epidemic wave in Mexico. Nat Commun 13, 589 (2022). https://doi.org/10.1038/s41467-022-28232-9

3. Identification of vaccination coverage or gaps

Vaccination coverage monitors a vaccine program's reach and could be assessed if it is possible to distinguish between vaccine- induced immunity, as compared to immunity from infection with available antigens, such as SARS-CoV-2. Gaps in coverage were described as specific issues related to a vaccine program's reach within geographic or sociodemographic groups, including groups which differed by age, sex, ethnicity, or religion. There was some discussion around whether to describe this use case more generally as identifying immunity gaps; however, the working group decided to narrow the focus to vaccines. The example provided involved assessing measles and rubella seroprevalence after an immunization campaign. While a clear action, vaccination, can be taken based on serological findings, challenges remain. These include difficulties in being able to distinguish vaccine-induced immunity from infection-induced immunity, such as for measles; collecting samples from children being more challenging than collection from adults; and developing consensus on the threshold of seroprevalence that warrants a vaccination response, and what precision is needed around that estimate.

Example paper for this use case: Murhekar MV, Gupta N, Hasan AZ, Kumar MS, Kumar VS, Prosperi C, Sapkal GN, Thangaraj JWV, Kaduskar O, Bhatt V, Deshpande GR, Thankappan UP, Bansal AK, Chauhan SL, Grover GS, Jain AK, Kulkarni RN, Sharma SK, Chaaithanya IK, Kharwal S, Mishra SK, Salvi NR, Sharma S, Sarmah NP, Sabarinathan R, Duraiswamy A, Rani DS, Kanagasabai K, Lachyan A, Gawali P, Kapoor M, Shrivastava AK, Chonker SK, Tilekar B, Tandale BV, Ahmad M, Sangal L, Winter A, Mehendale SM, Moss WJ, Hayford K. Evaluating the effect of measles and rubella mass vaccination campaigns on seroprevalence in India: a before-and-after cross-sectional household serosurvey in four districts, 2018-2020. Lancet Glob Health. 2022

Nov;10(11):e1655-e1664. doi: 10.1016/S2214-109X(22)00379-5. PMID: 36240831; PMCID: PMC9579355.

4. Assessing infection changes due to behavioral, environmental, or pharmaceutical interventions or environmental changes

This use case proposes to use serology to measure changes in infection due to intervention use in the population or a change to a population's environment that was not a targeted intervention for that population (e.g., deforestation or a dam being put in place). Interventions had to have large-scale implementation with plans to be integrated into the health system, so this would not include small randomized clinical trials.

One of the most compelling examples of this use case was to assess the effectiveness of an intervention such as vaccines. Whereas vaccination coverage is captured above in use case #3, vaccine effectiveness studies would be captured here. One example provided was monitoring the vaccine effectiveness of PCV13 in Malawi using seroincidence.

A second noted example was the impact of other interventions such as antimalarials or water, sanitation, and hygiene (WASH) interventions on seroprevalence. This could include vector control approaches, such as bednet distribution or indoor residual spraying. These interventions often have an impact on multiple infections, such as malaria, lymphatic filariasis, dengue, and chikungunya. Serology could be used to calculate seroprevalence or seroincidence for some pathogens.

Example paper for this use case: Plucinski MM, Candrinho B, Chambe G, Muchanga J, Muguande O, et al. (2018) Multiplex serology for impact evaluation of bed net distribution on burden of lymphatic filariasis and four species of human malaria in northern Mozambique. PLOS Neglected Tropical Diseases 12(2): e0006278. https://doi.org/10.1371/journal.pntd.0006278

5. Monitoring peri- and post-elimination surveillance settings

This use case is intended to capture pathogens for which there are elimination targets. This includes progress towards elimination, certifying or validating elimination, and monitoring post-elimination. It was originally proposed to have two separate use cases, one for certification of elimination and one for continuing to monitor after elimination; however, it was decided to keep these together because it would apply to the same pathogens, depending on the phase of elimination.

It was clarified that for NTDs there are some specific definitions around elimination that must be taken into account, including formal certification processes. Elimination refers to the elimination of transmission at a national level rather than elimination as a public health problem. Once a country enters peri-elimination, it no longer conducts mass drug administration. There are also different processes for certification of elimination depending on the pathogen, for example, polio elimination requires the absence of identified wild virus types for 3 years. For NTDs, there is not yet guidance on post-verification surveillance, but there are four proposed strategies for lymphatic filariasis:

1) Post-verification surveillance for 10 years with periodic surveys
2) Sentinel sites for blood collection and testing, such as antenatal care clinics
3) National seroprevalence platforms to do periodic testing, such as is done with HIV/AIDs
4) Xenomonitoring (i.e., the detection of human pathogens in arthropod vectors)

One key challenge is identifying the appropriate antibodies to monitor. If an antibody is cumulative or long-lasting, it will be difficult to see a change using serological surveillance. Monitoring for an antibody that decays rapidly would allow changes to be seen more easily. For NTDs there is also a challenge in identifying biomarkers that work well in low transmission.

Example paper for this use case: Oguttu D, Byamukama E, Katholi CR, Habomugisha P, Nahabwe C, Ngabirano M, Hassan HK, Lakwo T, Katabarwa M, Richards FO, Unnasch TR. Serosurveillance to monitor onchocerciasis elimination: the Ugandan experience. Am J Trop Med Hyg. 2014 Feb;90(2):339-45. doi: 10.4269/ajtmh.13-0546. Epub 2013 Dec 16. PMID: 24343885; PMCID: PMC3919245.

6. Research

This use case was added on the second day of the meeting and was conceptualized as being a methodological use case. This use case could answer operational research questions related to, e.g., identifying negative and positive controls or estimating epidemiological parameters. This use case could improve the application of multiplexed serosurveillance.

7. Other use cases considered

There was originally a use case to identify population levels of susceptibility; however, this was instead split into estimating burden of disease (use case #1), population immunity gaps to vaccine-preventable diseases (#3), and monitoring for elimination (use case #5). This included monitoring geographic heterogeneity in seroprevalence and outbreak risk. There was also a concern raised about antibody levels being equated with immunity when this is not the case for all pathogens.

The group originally considered a use case for hard-to-reach populations; however, it was decided that these populations likely constituted an example of a subgroup that would be a target across a number of use cases. This was envisioned to include highly mobile populations such as nomadic, pastoral, or border populations. It could also potentially include displaced populations or socially hard-to-reach populations, though they would have a different set of considerations. Using multiplex serology in this case is an efficient way to get a baseline across several pathogens. It can also identify specific geographic areas or priority populations that face a multi-pathogen burden.

> *One example was an integrated serological survey in Guyana which included several diseases with different objectives. The survey included ten different pathogens (lymphatic filariasis [a target for elimination], malaria, diseases for which they did not have much data available [e.g., toxoplasmosis and others], and four VPDs) in hard-to-reach populations. It was important to understand the gaps and what interventions need to be designed.*

Study Designs for Use Cases

On the second day of the meeting, the group discussed which kind of survey design was most appropriate for each of the use cases.

1. Burden and distribution of infections

This use case was believed to best be served by national or subnational cross-sectional surveys that included all ages, such as demographic health surveys. There are many pathogens that could be used in this use case, including NTDs, enteric pathogens, malaria, and arboviruses. The challenges for this use case are the same as across other use cases. These include needing a well-functioning assay; a commitment to using the serology data in some amanner, such as implementing an intervention; and translating results for decision-making.

2. Identification of emerging and reemerging infections

For this use case, the speed with which it is possible to detect the new pathogen is critical. Therefore, sampling strategies could include taking residual samples from blood donors or facilities or targeting specific risk groups of interest such as healthcare workers or mine workers.

3. Identification of vaccine program coverage or gaps

Sampling for this use case would be targeted at potential risk groups, which could be geographic or sociodemographic, and could be done through surveys. The age group for this use case is typically children, particularly those less than five years of age. This age group is

often under-sampled in national surveys designed for adult diseases; therefore, multiplex study designs would need to ensure that sufficient children are included. It can be difficult to collect blood samples from younger children, so considerations for ensuring they are included would be important for this use case.

4. Assessing infection changes due to behavioral, environmental, or pharmaceutical interventions or environmental changes

For this use case to assess a change after an intervention, the sampling design would need to be either a longitudinal cohort or repeated cross-sectional surveys before and after the intervention. The challenges here would be those involved with any longitudinal analysis: dropout, ascertaining effectiveness due to the intervention rather than other influences or temporal trends, and distinguishing an appropriate antigen. To see a change in prevalence after a behavioral or environmental intervention could take a substantial amount of time, particularly for long-lasting antigens that do not wane. One solution is to use a control group such as younger age groups that may not have been exposed before the intervention, or another comparable population that does not receive the intervention.

5. Monitoring peri- and post-elimination surveillance settings

Sampling considerations for this use case focused on being able to identify the appropriate population. One approach could be to focus sampling in an area where transmission last occurred or where there is a signal identified due to xenomonitoring or environmental surveillance. Convenience samples, such as from children at antenatal care visits with their mothers or facility-based residual samples, could also be used to monitor progress towards elimination. Targeting high-risk populations may also prove beneficial, like focusing on men for some diseases or people who go to the forest, for spatially focused infections. It is also possible to use national surveys like those conducted for HIV/AIDS. For neglected tropical diseases, it was emphasized that appropriate age groups for inclusion may differ. For example, the antigens for trachoma will cross-react with antibodies for genital chlamydia because both diseases are caused by *Chlamydia trachomatis*; therefore, they are not suitable for surveillance of adults.

Additional Considerations

Some other discussion points that arose from the conversations include differences between country and donor priorities, integration, and overlap with other working groups.

It was noted that there may be some use cases for pathogens that are high priorities globally but that may not be a priority for a specific country. This could include detection of a pathogen in a new country, such as Zika in countries where it has not been previously found. There is also interest globally for some countries to include pathogens on their multiplex panel that allow for

country comparisons, positive or negative controls, or cross-reactivity. In some ways this tied back to the operational research question but centered more on which pathogens to include in testing.

There was some discussion around defining "**integration**." In general, there was consensus that integration applied across a number of aspects because it provides economies of scale. It was noted that integration could occur across use cases, sampling approaches, and pathogens on the assay. If specimen collection approaches can be similar across use cases, this is more efficient than requiring a different sampling approach for each use case. Similarly, being able to integrate into existing surveys or surveillance systems would make multiplex serosurveillance more sustainable, though it may not work for all use cases.

There was a fair amount of overlap with issues addressed in the Seroepidemiology Working Group. This group considered the use cases and thought through the approaches to sample collection as well as challenges to these approaches.

The definition of the use cases on the first day was helpful to guide the practical considerations for multiplex serology for the other groups on the second day. Discussions from this group helped frame the Seroepidemiology and Data Analytics Working Groups' thinking on the second day. Having defined use cases allowed these groups to walk through specific scenarios.

Conclusions and Next Steps

The working group will further refine these use cases, identifying additional examples for each and building out Table 1 in terms of pathogens and the most compelling use for each. Additional consideration may be given to the study design for each of these use cases. These use cases provide a foundation for implementing stakeholders interested in conducting serological surveillance, policymakers who would make decisions based on these findings, and funding agencies to see the value in investing in serological surveillance.

Supply Chain Working Group Summary

Objective and Overview

The objective of the Supply Chain Working Group was to identify challenges, solutions, and good practices associated with procuring reagents, antigens/antigen-coupled beads, and platform technology to conduct MBAs. Supply chain bottlenecks were reported to contribute to month- and even year-long delays to conducting MBAs. The Supply Chain Working Group comprised researchers, supply chain experts, and manufacturers to represent a diversity of expertise and opinions and to allow for the identification of cross-cutting challenges and solutions.

Over the course of the Serosurveillance Summit, this Working Group identified several challenges broadly categorized under the following themes:

1. Platform technology challenges
2. Bead- and assay-related challenges
3. Kit commercialization challenges
4. Cold chain challenges
5. Country-specific limitations and considerations
6. Human and technological capacity challenges

Methodology/Approach

The co-leads of the Supply Chain Working Group met once before the Serosurveillance Summit to develop and discuss a preliminary list of supply chain challenges. To ensure that other Working Group members were able to contribute topics for discussion before the Summit, the Co-Chairs requested that members respond to the following prompts:

1. Currently, what supply chain issues hinder serosurveillance efforts, including the collection and laboratory analysis of samples? Which of these issues have you personally experienced?
2. In addition to current issues, what supply chain issues do you anticipate arising in the future?

The additional challenges identified from other members of the working group were combined with challenges discussed in the pre-meeting and discussed over the first and second days of the Serosurveillance Summit. During these sessions, members were invited to share personal experiences as they related to supply chain challenges and solutions and to continue to contribute new ideas that had not been identified in the pre-meeting or responses to prompts. On the second day, solutions to key challenges were developed as a group then presented in the plenary session.

Challenges and Solutions

1. *Platform Technology Challenges*

On April 1, 2021, the Luminex Corporation ceased the sale of their MAGPIX Research Use Only (RUO) Instrument [22], in part due to the discontinuation of a critical camera component by one of their suppliers. Since then, Luminex is now using a complementary metal oxide semiconductor (CMOS optics) image sensor in their MAGPIX IVD instruments. Working Group members underscored the convenience and ease of use of the MAGPIX instrument which utilizes a camera read-out which is more practical in resource-constrained settings, due to its smaller size, ease of installation, and durability of its optical elements. Some laboratories in resource-limited settings do utilize laser flow-based Luminex instruments due to their superior performance compared to the MAGPIX. However, the sensitivity of the lasers requires specialized installation and maintenance, which limits access and use of these instruments widely in resource-constrained areas.

Several challenges exist beyond the discontinuation of the MAGPIX RUO instrument. The absence of local subsidiaries has led to difficulties purchasing, selling, and servicing instruments located in low- and middle-income countries (LMICs). Individuals and organizations in high-income countries often purchase and transport the MAGPIX RUO Instrument to LMIC laboratories themselves, with the purchasers holding the responsibility of organizing equipment servicing. End-users have faced issues locating quality, timely, and local maintenance services. Following the 2021 acquisition of Luminex by DiaSorin [23], a depot is being developed in Italy which could facilitate the procurement and maintenance of machines in more countries. However, Luminex remains the sole authorized seller of MAGPIX instruments despite partnerships with MilliporeSigma, ThermoFisher, Bio-Techne, and BioRad, contributing to issues with procuring these instruments locally. Furthermore, the COVID-19 pandemic has exacerbated supply chain weaknesses and contributed to the shortage of plastics [24].

Potential Solutions

- **Identifying the most appropriate platform technology by setting:** Establishing the typology of each market by location, regulatory and technological infrastructure, and volume of labs and instruments could be used to determine the best platform technology for a given location and provide Luminex with data on the market potential for MAGPIX RUO. Luminex can sell MAGPIX IVD instruments in countries without regulatory requirements for the use of IVD instruments. In settings where flow cytometers are used, these could be investigated as alternative platform technologies for running multiplex bead assays.
- **Identifying the needs and demand for the platform technology and associated maintenance services:** Determining the scope of existing MAGPIX instruments by

number of instruments, number of laboratories, and where these are located can aid in developing repair/maintenance plans and expanding coverage, particularly in remote areas. Forecasting the demand for MAGPIX instruments across these same variables can facilitate an understanding of the need for a MAGPIX RUO instrument or possible alternatives. Coverage may be expanded upon completion of the new Luminex depot in Italy.

- **Exploring the possibility of licensing the MAGPIX to another IVD manufacturer:** The working group briefly discussed if Luminex would not make or service an RUO MAGPIX, if it would be possible to arrange for licensing of the manufacturing and service to another entity (e.g., a WHO-approved in-vitro diagnostic manufacturer in an LMIC).

2. Bead and Assay-Related Challenges

The coupling of antigens to beads and procurement of antigen-coupled beads can be time- and resource-intensive steps. Bottlenecks along the supply chain including outsized demand for antigen-coupled beads, differences in distributor speeds can pose significant challenges to performing MBAs, and halted shipments due to missing reagents.

The number of laboratories coupling antigens to beads is often eclipsed by the number of laboratories which use them. This can introduce opportunity costs by allocating human resources away from conducting and publishing research and toward bead coupling. When purified proteins are readily available for purchase or procurement, this process can be expedited. However, the limited availability of these proteins, particularly for antigens related to neglected tropical diseases, require labs to generate, purify, and validate their own proteins or to rely on others who do. Some laboratories are taking on the role of suppliers, producing beads in 2-4 weeks minimum and shipping them out themselves.

Standardization issues also exist: where multiple laboratories are producing the same proteins—or where proteins are procured from multiple commercial sources—slight deviations could have important implications for comparing assay results between settings. Reference controls are needed to address this issue as well as standardized approaches to coupling beads and performing assays. While the production and procurement of antigen-coupled beads poses clear challenges, some participants reported substantial delays in procuring uncoupled beads or microplates, including months-long delays when purchasing from a Luminex partner instead of Luminex itself.

Other procurement challenges related to non-bead reagents were also flagged as causing long delays. Some suppliers do not ship orders until they are complete, meaning that shortages of a single product could create a bottleneck for the shipment of the remaining items in the order. When shortages of certain materials are known ahead of time, this issue can sometimes be

averted, but only when researchers know which reagents and products can be substituted without affecting the quality of the assays. This was reported as a key knowledge gap. Others have experienced delays of non-substitutable products like sheath fluid.

Potential Solutions

- **Standardizing and validating antigens:** Establishing a common source for given antigens, whether through commercial or non-commercial suppliers, could remedy issues stemming from variations between antigens. Additionally, having validated reference controls can aid comparability where these variations do exist and provide quality control measures while validating suppliers can assure quality.
- **Creating a central repository for antigens and other knowledge:** The creation of a knowledge repository which includes lists of which purified antigens or antigen-coupled beads are available and from whom, as well as standards associated with these antigens and antigen-coupled beads, was viewed as a promising solution for connecting users to suppliers. Early in the pandemic, UK Research and Innovation and the Wellcome Trust partnered to establish the COVID-19 Protein Portal: a resource for UK-based scientists to search for and request proteins free-of-charge for research purposes. [25] A similar portal specific to MBAs could help to pool demand and streamline production and procurement processes while also democratizing access which currently may require the establishment of individual collaborations with bead-producing laboratories. In conjunction with this repository, establishing a collaborative network to identify reliable and expedient distributors by country/region, share knowledge of substitutable and critical components (e.g., through creation of a GitHub repository of protocols), and find products could help to overcome several supply chain hurdles.
- **Forecasting demand for key reagents and products:** Predicting the quantity of product required based on current and anticipated usage can allow laboratories to plan ahead and avoid stockout-related delays in the future. Producing this knowledge could also rationalize the creation of more local warehouses to hold these products, further shortening shipment times.
- **Exploring commercialization:** If some purified proteins or protein-coupled beads were commercialized, this could allow researchers to focus their efforts on other activities while also shortening the time to receive these products. Commercialization of kits which included everything to complete MBAs—or the development of non-commercial kits which included everything except antigen-coupled beads—would dramatically shorten the list of products which laboratories need to procure, but this requires further exploration.

3. Kit Commercialization Challenges

The potential of commercializing kits in the future was discussed throughout the Working Group sessions. Commercialization could standardize assays, allowing for the same reagents to be used across laboratories, and several participants thought it could potentially ensure sustainability by shifting responsibilities to procure reagents, produce antigen, and couple beads to commercial suppliers. In doing so, the small number of groups which currently produce these beads could focus their efforts on other activities including conducting serosurveillance and building capacity to use these kits. By introducing greater manufacturing capacity, commercialization could also extend the reach and access to this technology for resource-limited settings which have been unable to procure them at all or in sufficient quantity. Additionally, kits were viewed to be one approach to simplify and reduce shipping costs as cold chain requirements could be standardized.

The distinction between "commercial" versus "home-brew" or "laboratory-developed tests" is important to detail. While some commercial kits are approved for use by, e.g., the US Food and Drug Administration (including emergency use authorization or 510K predicate), tests used for surveillance do not fall under FDA rule. In this summary, a commercial kit refers to kits assembled by a commercial entity for RUO/surveillance use that does not require FDA clearance. This challenge overlaps with the Laboratory Assay Working Group and will require joint discussions moving forward.

Although commercialization has many benefits, there are some potential consequences to harmonizing efforts. Shelf-life limitations, temperature requirements, and shipment delays were viewed to be challenges for the procurement of existing MBA reagents and kits. Commercialization would likely require large-scale purchases to provide sufficient commercial incentive to manufacturers and potentially increase the overall cost of performing the assays. It could also limit the customizability of these kits—which was prioritized by many in attendance. Additionally, any antigen added to the common panel would need to be validated. Furthermore, cost control measures and ownership of kits remain uncertain. This area of work also intersects with the Laboratory Assays Working Group, further underscoring the need for coordination between groups.

Potential Solutions

- **Pooling demand for commercial kits:** Establishing a common panel based on common priorities could allow for laboratories to pool demand, generating sufficient commercial incentive for manufacturers to produce these kits and allowing for larger manufacturing volumes and a subsequent lowering in price compared to more customized kits. However, establishing these common priorities could prove challenging.
- **Developing multiple commercial kits:** This approach could avoid the pitfalls associated with developing a single common panel by providing options that could better meet

different users' unique needs. This approach would likely require different reagents and standards for each kit.

- **Preserving the customizability of commercial kits:** Two options were discussed which could allow for commercial kits to be customized to users' needs. The first option would allow purchasers to select which antigens were included in kits, though this approach could be more expensive in comparison to purchasing more uniform kits. The second involved masking bead regions in standardized kits, allowing users to not collect data on certain antigens. Any additional antigens added to the common panel would need to be validated to ensure there are no impacts to the performance of the antigen added or the antigens in the kit.
- **Pursuing non-bead alternatives:** Producing a "bundle" which included all common reagents necessary to conduct an MBA except antigen-coupled beads would allow purchasers to use their own, fully customized beads while easing the burden of procuring all other reagents separately. Creating these bundles could prove challenging or unappealing for manufacturers which would need to source products from other companies. Contracting with a supply chain management organization to produce these bundles could be feasible and leverage these organizations' familiarity with diverse supply chains and their unique requirements, though involving these organizations would add additional costs.

4. Cold Chain Challenges

Cold chain requirements for reagents, antigens, antigen-coupled beads, specimens, and kits pose additional challenges. When cold chains are interrupted, the quality and validity of these components cannot be guaranteed, and logging when and to what extent these interruptions occur is not standard practice. Some courier services do not replenish or replace cooling agents like dry ice or gel packs, posing issues when long shipment and customs clearance times occur. The costs of interrupted cold chains can fall on both customers, who may accept products which no longer meet quality standards, and suppliers, if customers refuse to accept products which were not properly stored upon arrival.

Potential Solutions

- **Making temperature logs and internal controls standard practice:** Using temperature loggers for temperature-sensitive shipments can allow recipients to determine when, at what temperature, and for how long shipments have exited the cold chain. Stability testing and knowledge sharing can allow recipients to gauge the viability of these materials, and internal controls can provide additional quality control measures.

- **Modifying packaging and labeling practices:** Packaging and transporting boxes with accessible or removable cooling materials can allow for their replenishment by couriers without opening the primary shipment container (available with select courier services). Labeling temperature-sensitive packages with storage instructions can also help to ensure that the cold chain is not interrupted.
- **Exploring non-cold chain or new approaches:** Some approaches, such as lyophilization of antigen-coupled beads could be explored, though it will necessitate stability testing for each type of antigen. For specimens, using dried tube specimens [26] or dried blood spots [27] could reduce reliance on cold chains. These approaches could lower the costs of including cold materials like dry ice. Furthermore, exploring new developments in cold chain maintenance equipment that sustain low temperatures without replenishment (e.g., from Stirling/VWR in Basel, Switzerland) could offer additional alternatives.

5. Country-Specific Limitations and Considerations

Differences in customs procedures, shipping schedules, and regulations between countries can be challenging for suppliers and users to navigate. Some countries receive infrequent shipments of commercial products, and the COVID-19 pandemic further reduced the ability to utilize commercial airlines for the transportation of products. Customs-related delays are common due to improper labeling or misunderstanding related to the contents of shipped materials. Some attendees noted that bureaucratic issues could further contribute to delays in processing goods through customs. Together, these delays can contribute to situations where daily holding rates in customs can outpace the costs of the shipment.

Beyond issues related to products sitting in customs, country-related restrictions requiring certification for in vitro diagnostics and equipment can restrict the use of such technologies in the country. For countries with limited manufacturing capacity, most or all products may need to be imported, relying on external manufacturers and supply chains. Unexpected changes in currency exchange rates can further complicate procurement when international payments take time to be cleared.

Potential Solutions

- **Building forecasting knowledge, involving partners, or partnering with supply chain experts:** Forecasting can allow suppliers and procurers to anticipate the frequency and duration of delays and to better plan for alternate transportation methods, delays, and changes in currency exchange rates. Understanding the frequency of shipments to a country, how long products will be held in customs, and what cooling materials can be used would allow suppliers and recipients to plan ahead, including choosing when a

supplier ships. Checklists for specific countries and regions could be shared between organizations to facilitate knowledge sharing. The involvement of all partners including manufacturers and receiving laboratories in this process is critical; partnerships with supply chain experts can facilitate this.

- **Establishing partnerships between local distributors and foreign manufacturers:** While some countries have limited local manufacturing capacity, partnerships with foreign manufacturers can allow for more streamlined procurement processes where a distributor, rather than the end-user, manages issues related to importation and local transport.
- **Exploring standardized approval processes for importation of key products:** The successful importation of materials and equipment necessary for MBAs can vary from country to country. By establishing a standardized approval process for importation of certain products, akin to the Collaborative Procedure for Accelerated Registration of WHO prequalified IVDs, [28] could facilitate the importation by approving products across several countries at once. This process could potentially be overseen by the Africa Centres for Disease Control and Prevention for African Union member states.
- **Ensuring clear labeling of biological products:** Discrepancies in labeling the contents of antigens, antigen-coupled beads, or specimens could lead to substantial delays due to confusion regarding whether a shipment contained pathogenic materials. Establishing protocols to clearly label shipments as non-infectious and non-living and additional information (e.g., why the materials are thought to be non-infectious or how materials were made to be non-infectious [29]) can avoid suspicion and unnecessary holds on materials. Having these standards in place at the research/facility level before shipment could help to avoid downstream issues. However, some participants noted that they avoided using certain antigens entirely due to country-specific prohibitions and restrictions (e.g., tetanus toxoid)

6. Human and Technological Capacity Challenges

Limitations in human and technological capacity to not only perform MBAs but also to produce or procure materials and to plan/forecast supply and demand and stockouts were viewed as significant supply chain obstacles. Knowledge gaps were common along the supply chain: end-users may experience frustration due to a lack of familiarity with supply chain issues, manufacturers may be uncertain of the overall demand for products, and supply chain/logistics service providers may not know the type and quantity of services and goods required for a given order. Tools that adequately assess and fulfill demand and determine the most cost-effective approaches to procuring materials are needed.

Potential Solutions

- **Securing funds for procurement up front:** Shipping delays may emerge when a request for materials is made but payment is not immediately available. Some service providers may only act on requests if funds have been secured, necessitating a robust understanding of information and funding flows between users and service providers.
- **Training users on supply chain logistics:** By building researcher and laboratory capacity through supply chain logistics training, these individuals and organizations can develop a deeper understanding of the best practices associated with ordering, shipping, and receiving materials. This insight can allow them to anticipate need and order accordingly to avoid bottlenecks, shorten delays, and limit wastage. Early planning with Ministries of Health to provide training to employees and implementing training of trainer programs were thought to support the sustainability of this endeavor in the face of budget constraints and brain drain. Other training areas discussed included training users on instrument use and routine maintenance protocols to sustain high instrument performance and minimize downtime and costly repairs, the optimal use of kit assays to reduce wastage, and coupling beads locally to reduce burden on supply laboratories.
- **Sharing information and developing a "playbook" and tool for projecting need and costs:** While transportation requirements and regulations may differ between countries and sites, working group members expressed the need for a general playbook and forecasting tool that can be adapted for site-specific needs and characteristics. This playbook and tool could help to better harmonize efforts between sites and enable them to accurately predict what materials are needed, the costs to procure these materials, and how to effectively clear these materials through customs. More advanced forecasting tools could anticipate swells in demand and help avert shortage delays.

Conclusions and Next Steps

Supply chain challenges affected all types of Supply Chain Working Group members from researchers to manufacturers and supply chain logistics experts. The discussion of these challenges revealed the need for both general and context-specific approaches. Knowledge sharing, capacity building, communication, collaboration, and forecasting were consistent themes across solutions. Innovations in product design and packaging that could address supply chain challenges were considered, in addition to caveats and trade-offs (e.g., cost versus customizability of commercial kits) that could emerge from pursuing these innovations. While continued efforts are needed to address these issues, this discussion may serve as a springboard for the development of knowledge and material sharing initiatives like playbooks and antigen repositories; collaborations between researchers, manufacturers, and supply chain experts; and the development of tools that allow users to anticipate and avoid issues that could lead to critical delays in research and serosurveillance.

The Supply Chain Working Group will continue to meet to discuss these challenges and to begin to investigate and implement some of the solutions described in this summary. Notable targets for future work include determining which countries would be appropriate settings for the MAGPIX IVD instrument, developing an information-sharing platform, and investigating commercial and non-commercial approaches to address multi-product supply chain challenges.

Seroepidemiology Working Group Summary

Objective and Overview

Seroepidemiology entails the design and implementation of the collection of antibody signatures from serologic samples to support the accurate interpretation and application of serological data for public health decision making. It includes all epidemiologic investigations involving the identification of antibodies developed in response to pathogen-specific antigens in populations. For the serosurveillance summit, however, the working group defined seroepidemiology as only those methods relevant to multiplexed serological surveillance and considered the following attributes to be included:

1. Sampling strategies
    - The administration of cross-sectional versus longitudinal serosurveys for surveillance
    - The development of a sampling strategy at the community- versus household-level
    - The use of residual biorepositories (i.e., leveraging existing serum surveys like DHS or healthcare facility specimens)
    - The implementation of surveys at the national versus subnational administrative level
2. Survey design
    - The selection of a target populations by demographic characteristics across antigens
    - The calculation of sample size to address different use cases for different pathogen-specific antigens

The goal of the Seroepidemiology Working Group was to identify key challenges related to population sampling strategies and survey design for multiplexed serosurveillance, to share solutions to the key challenges that investigators are currently engaging in, and to propose new solutions.

Methodology/Approach

The working group co-leads initially drafted a list of perceived challenges within the study and practice of seroepidemiology, as defined above, from which the full working group narrowed this down to identify a set of six primary challenges. Working group members then tackled one challenge at a time to first share solutions they were currently using or had learned about from the existing literature, and then postulated new potential solutions and the necessary next steps to help further the field of seroepidemiology.

The working group members also identified a framework within which seroepidemiology operates in order to structure the identified challenges and solutions (Figure 1). As it became clear that the preferred solutions for each challenge were dependent on the intended policy-relevant use case, outlined in the use case chapter (i.e., to assess the effectiveness of interventions, quantify the burden and distribution of infections, etc.) as determined by local

health agencies, two general use cases were selected on which to base the discussed current and novel solutions: (1) to quantify the burden and distribution of infections and (2) to identify the coverage or gaps in vaccine programs.

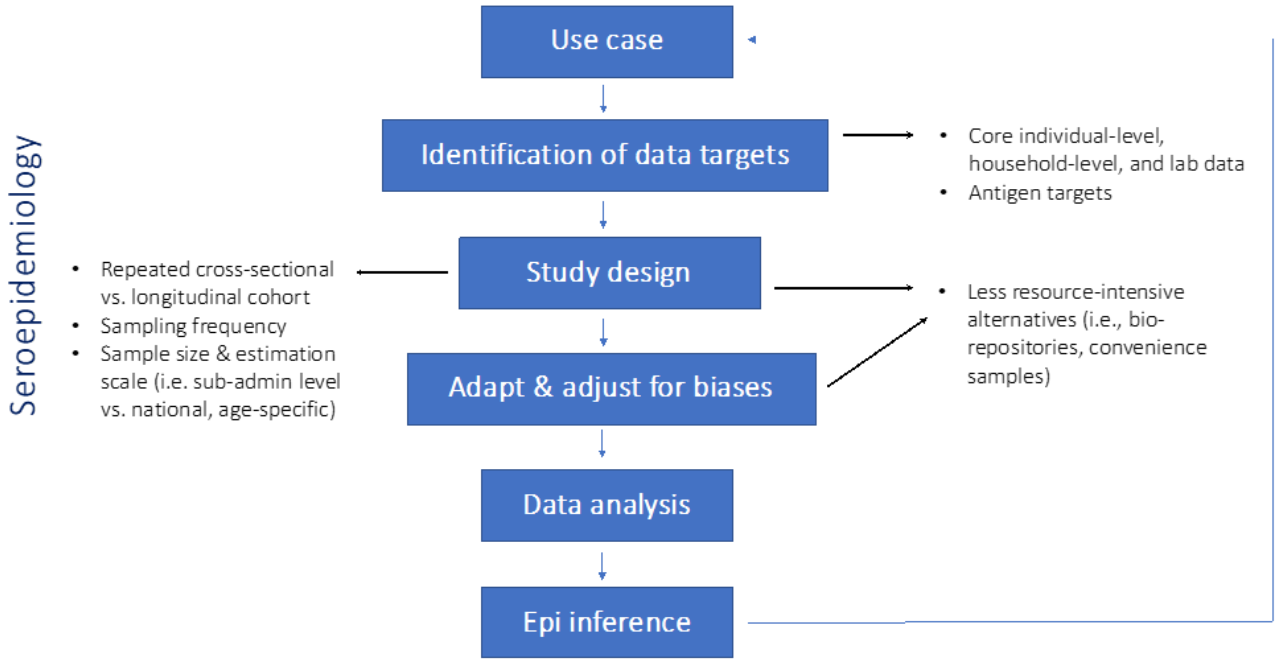

Figure 1. Process diagram of the practice of multiplexed serological surveillance and where seroepidemiology exists in the process. The black arrows and text indicate the identified primary challenges in seroepidemiology.

Challenges & Solutions

1. **What factors influence the tradeoffs between conducting repeated cross-sectional surveys (sampling different individuals each round) versus a longitudinal cohort (sampling the same individuals each round)?**

When deciding whether to conduct repeat cross-sectional versus longitudinal serosurveys for multi-pathogen surveillance, there is no *one-size-fits-all* or standard solution. Rather, the choice is context-dependent and often influenced by policy needs (i.e., use cases) and funding. To conduct surveillance, either repeat cross-sectional surveys or longitudinal cohorts are generally chosen. Longitudinal surveys may present added advantages in terms of an ability to estimate seroincidence and antibody waning. However, enrolling a longitudinal cohort to conduct long-term surveillance can be costly and labor-/time-intensive. Repeated cross-sectional surveys may be less resource-intensive but may present little public health value in a stable state, though this requires a further literature review. For example, one participant reported that conducting repeat cross-sectional serosurveys in the same clusters (or resampling the same

communities within short intervals – e.g., 1-2 years) to ascertain population-level seroprevalence found similar estimates over time. Therefore, when opting to implement repeat cross-sectional surveys, informed decisions on the sampling frequency should be made (see Challenge 2). Alternatively, the surveys could be administered in different settings/areas, though biases due to population and temporal differences should be considered. In addition, cohorts may be nested within repeated cross-sectional surveys.

Adopting an adaptive study design thus surfaced as the optimal choice, whereby once a core serosurvey design was selected, it could be adapted as needed to fit changing needs (e.g., adopting a cross-sectional survey design and implementing a nested cohort to answer different/specific questions). Sometimes overall seroprevalence may be the preferred population metric to measure from the data versus seroincidence, and, similarly, age-specific estimates or geospatially resolute estimates may be preferred depending on the questions of interest. As such, an adaptive design could also mean increasing the sample size of specific population groups of interest to further interrogate detected signals.

Potential Solutions

- Repeat cross-sectional, national surveys with a representative cluster-based sample, with informed decisions about sampling frequency, or changing clusters each round
- Adaptive study design with nested longitudinal cohort (cohort alone is not sustainable for long-term surveillance)

Next steps

- Development and use of protocols that allow for adaptive strategies and ethical amendments

2. What factors should drive the decision on how frequently to sample a population?

When choosing the sampling frequency for repeat cross-sectional or longitudinal serosurveys for multi-pathogen surveillance, there is no standard solution: the choice is again context-dependent (i.e., dependent on funding, use cases, and pathogens of interest). Thus, the frequency of surveys should be guided by both programmatic goals and disease-specific attributes including antibody kinetics and force of infection. For most pathogens, this frequency will be in the ~2-5-year range. If an existing national survey or previously collected samples are being leveraged to implement the multiplex serosurveillance (see Challenge 3), the frequency of sampling will be dependent on that of the survey being leveraged. Available funding is an important practical consideration.

Like the choice of study design, an adaptive design can be employed whereby more frequent surveys are added as needed based on prior survey results and dependent on pathogen attributes, e.g., seasonality for influenza. Another option may be to sample random clusters at

different time periods within a year to capture different seasons, particularly when the seasonality of a pathogen is unknown, or the pathogens of interest have seasonality patterns that span across the year. Further, the necessary survey frequency across pathogens can be determined by using existing surveillance platform repositories, if available, which may capture different seasons and time periods.

Potential Solutions

- Consensus of serosurvey frequency of ~2-5 years for most pathogens
- Adaptive design whereby one adds more frequent surveys as needed
- Within a year, sample random clusters at different time periods to capture different seasons
- Leverage existing surveillance platform repositories to determine necessary frequency

Next steps

- Identify optimal frequency for serosurveys if funding were available

3. **What are less resource-intensive alternatives to population-representative sampling that may lead to suitable precision for policy making or adaptive sampling strategies to account for biases (i.e., convenience samples, bio-repositories)? How do we evaluate their validity over space, time, and antigen choice?**

The costs associated with nationally representative integrated serosurveillance could be minimized through the use of less resource-intensive alternatives to de novo population representative sample collection, such as leveraging convenience samples from healthcare facilities (e.g., residual clinical samples) and schools or existing biorepositories. These samples can be particularly useful when sampling gaps or biases exist in the intended survey design, and they can be used to supplement data when the timeliness of results is required for policy-relevant questions. While research teams should consider leveraging other surveillance, research, and diagnostic projects to access existing biorepositories for the sharing of blood specimens, the informed consents given in the original study may not allow for future testing and sample quality/volume would need to be examined. Importantly, use of existing samples would be subject to ethical approval. Prospectively, programmatic and research activities entailing collection of samples that could be potentially leveraged for serosurveillance can include provisions for future sample testing during the informed consent process if supported by ethical review committee guidelines. Additionally, even if access and testing is granted, we have yet to understand and quantify the biases that exist when using convenience samples as compared to population representative samples.

Furthering the concept of an adaptive study design, the use of convenience samples or biorepositories, if available, can thus be used as part of an adaptive strategy to help answer

policy-relevant questions. Existing national surveys may be most useful when establishing a multiplex serosurveillance platform to help guide the study design or to help supplement data as these would already have a population-representative sampling frame. Sub-national surveys, residual research study samples, hospital-based residual samples, and the active collection of convenience samples (e.g., school-based surveys, modified health-facility surveys) may also prove useful as supplemental data or as an adaptive strategy to account for sampling biases (e.g., low sampling of children in the original study design). Convenience samples, however, still need to be validated with representative samples to quantify the biases incurred in order to ensure the proper epidemiologic inference is made.

Potential Solutions

- Leverage existing surveys initially or as an adaptive strategy
- Use residual sub-national survey, research study, or clinical residual samples, or actively collect convenience samples as supplemental data or take an adaptive strategy to account for sampling biases

Next steps

- Validate convenience samples with representative samples to quantify biases
- Share a scoping review of biases incurred
- Establish documentation of existing repositories

4. **How do we determine sample sizes and sampling approaches (e.g., number of clusters if multi-stage sampling, stratified sampling by age or geography) when we have multiple questions and antigens of interest? What are the trade-offs between trying to estimate a single number for the entire target population (e.g., national seroprevalence), district-specific estimates, age-specific seroprevalence, etc.?**

There is no *one-size-fits-all* or standard solution for determining an adequate sample size for multi-pathogen serosurveillance. As different pathogens may have different population prevalence and use cases may vary from quantifying disease burden to detecting emerging infections to estimating vaccine effectiveness, the sample size needed to answer different questions may vary by pathogen and age groups. Therefore, the chosen sample size should be powered to answer questions for the pathogens of key interest, and the sampling frame should be based on the lowest geographic unit needed for decision-making (e.g., district vs. sub-district level). After calculating the sample size for each pathogen-specific use case, the lowest common denominator should be selected to maximize estimation power and validity. For example, for pathogens where the use case is to quantify the burden of infection, the sample size should be powered to estimate seroprevalence or seroincidence with reasonable precision for each pathogen of interest, and the chosen sample size should ensure the pathogen with the lowest population prevalence has reasonable precision. Conversely, when the pathogen-

specific use case is to test vaccine coverage, the sample size calculation should be based on hypothesis testing of the presence of antibodies (or that adequate coverage is reached) versus the null.

For burden identification specifically or in a use case where geographically representative samples are important, an adaptive design could be implemented like the *run-in* method, which is often used in the clinical trials field, whereby a small sample is visited initially and, based on initial analyses or geospatial maps produced, the sample size is increased if needed [30]. To help further the standardization of these methods for sample size calculation and enable the comparison between different localities and datasets, there should be a sharing of simulation and sample size estimation tools.

Potential Solutions

- Power sample size for pathogens of key interest and based on the lowest administrative unit needed for decision-making
- Adapt sample size for burden identification (e.g., through use of the *run-in* method)

Next steps

- Optimize and share sample size tools and estimators
- Learn from the clinical trials field with regard to adaptive strategies

5. What core individual- or household-level and lab data should be collected from participants to allow for the broad use of samples?

Developing time-efficient and meaningful structured questionnaires that accompany serum data collection to help answer questions across pathogens and use cases can prove to be difficult. Maintaining consistency in the data collected across surveillance systems though is critical for making comparisons and global inference, thus a minimum core dataset was identified. A key consideration for the core minimum variables was minimization of the time burden to respondents. Age, sex (for some pathogens of interest), location, and date of specimen collection were identified as essential variables to include. Together with serologic data, data on these key variables can be used to estimate core metrics like the force of infection and seroprevalence, and to generate geospatial maps. Other data in the minimum core dataset that are critical but not essential to include are vaccination history (particularly for assessment of gaps/reach of vaccination programs), HIV status, and the reason the sample is being collected. In the context of secondary data use, e.g., when leveraging existing samples, protection of personally identifiable information will be important.

Importantly, there should be more overlap between seroepidemiology and the lab assay design, and when considering the essential data that should be collected, lab data should form part of the discussion. Raw lab data is important for both analyses and result interpretation,

including epidemiologic inference. These data are linked to (or dependent on) the populations or sub-populations sampled as selecting the appropriate negative and positive controls for the multiplex assay and ascertaining assay sensitivity and specificity directly influences analyses and results. Therefore, there should be harmonization of the data collected across surveillance systems, which should include the minimum core dataset in questionnaires, assay specifications, and raw lab data.

Potential Solutions

- Harmonize data collection across surveillance systems:
    - Age, location, sex, date of specimen collection
    - Response, participation rate (to help with bias estimation)
    - Assay specifications (sensitivity + specificity)
    - Raw lab data

Next steps

- Borrow and develop data harmonization and standards from other fields to make data sharing easier

6. How do we pair antigens of interest with clear scientific, policy-relevant, and answerable questions and appropriate study designs? Can we create a taxonomy of questions, antigens, and study population requirements to help with this?

Real-time data is important for public health action and policy decision-making. Though multi-pathogen surveillance has the ability and promise to provide real-time data, several gaps still exist in expediting the entire process to produce results in a timely, policy-relevant fashion. For seroepidemiology specifically, creating a taxonomy of how antigens (often multiple antigens are necessary for one pathogen and thus they provide different information about an infection) pair with clear scientific, policy-relevant questions and appropriate study designs would help standardize and craft a more efficient process. Also, creating a taxonomy would further support the involvement of epidemiologists in the lab assay design by outlining the specific use cases of antigen targets to harmonize with policy and articulating how increasing the number of pathogen-specific antigens can increase assay performance, like increasing specificity. Additionally, standardization of some antigens would allow for comparison of findings across studies and country settings.

Though there was limited time to truly articulate solutions for this challenge, the working group agreed creating this taxonomy is a necessary next step. It will be important to align the taxonomy with key use cases for serosurveillance [Use Cases Working Group Summary].

Next steps

- Create a taxonomy of paired pathogen-specific antigens with scientific, policy-relevant questions, and study design

It was noted several times that there is no *one-size-fits-all* or standard solution for determining an adequate study design or sample size for multi-pathogen serosurveillance and that this will vary by use case. The practical consideration of the cost of the study design or sample size came up as relative, but more information is needed to evaluate different study designs. Tied to the Data Analytics Working Group, it was noted that sharing seroepidemiology data analysis tools such as the Excel spreadsheet that is used by Johns Hopkins team to calculate seroincidence from serology data and other groups' R packages would be useful.

Conclusion and Next Steps

While there is much work to be done to further elucidate, discuss, and solve for challenges in seroepidemiology, the working group identified some key priorities based on this initial meeting including the creation of a toolkit that will include: the core protocols detailed above, epidemiologic tools like sample size and force of infection calculators, statistical bias assessment for convenience sampling, and data harmonization across data types (i.e., lab, field) and sites.

Table 2: Description of the discussed current and novel solutions in the working group by primary challenge in seroepidemiology. The shaded regions indicate what was not discussed.

	What are potential new solutions to this challenge?	Short, medium, or long term?	What are the next steps/considerations to help address this challenge?	What are the limitations of the current approaches to this challenge?
1	• Either repeat cross-sectional surveys in different settings/areas or cohort of the same individuals repeatedly sampled • Adaptive design – core serosurvey design that can be adapted as needed	Short/medium term	• Longitudinal not sustainable • Repeated cross-sectional, national surveys with each survey in different areas • Representative cluster-based sample, changing clusters with each round • Adaptive study design with inbuilt longitudinal cohort	• Ethics consideration for adaptive strategies - master protocol with subsequent ethics amendments (needs governance structure)

2	• Should be guided by antibody kinetics and force of infection for each pathogen • Should be guided by programmatic goals	Long term	• Do year-round surveys but change areas/clusters • Use existing platform as starting point • Depends on pathogen and seasonality of pathogen • Adaptive design - add in more frequent surveys as needed • Minimum would be based on existing platforms (about 2-5 years)	• Limited options if using convenience sampling • If leveraging existing national surveys, frequency will be dependent on that of the survey being leveraged
3	• Leveraging other surveillance/research/diagnostic projects for sharing of blood specimens (need to consider biases, ethics, timeliness, sample quality)	Short term	• Use hospital-based residual samples or actively collect samples • Compare convenience samples with results from representative samples • Conduct modified health-facility studies and/or school-based surveys • Leverage national surveys	• Healthcare-seeking behavior bias; bias from symptomatic population • Validation needed compared to representative samples individuals • Leveraging existing national surveys is dependent on whether funding is available for those platforms (e.g., national HIV prevalence surveys in some countries are funded by donors)
4	• Working groups online sharing of seroepidemiologic resources (like simulation and sample size tools)	Short term	• Challenges with sample size in children – supplement important age groups • Often guided by budget • Calculate sample size for each pathogen and select lowest common denominator (or lowest unit needed for decision-making like district/sub-district)	• May miss key population for future analyses

			• Consider with respect to programmatic interventions • Learn from clinical trial field with regard to adaptive strategies	
5	• Age, sex, and location most important • Sampling date, reason for sample being collected • Vaccination history, HIV status, etc. useful • Raw lab assay data is critical	Short term	• Age, location, sex, date of specimen collection • Additional suggestions to support pooled analyses: assay specifications (sensitivity + specificity), denominator, actual seroprevalence estimates, sampling frame or estimate of participation rate	• Data harmonization and standards for data sharing • Useful to know response/participation rate for calculations - at different cluster levels • Need to balance time spent on data collection and that needed to harmonize interpretation of findings from different settings
6	• Involvement of epidemiologists in lab assay design • Select antigen targets to harmonize with policy	Medium term		

Laboratory Assay Working Group Summary

Objective and Overview

The laboratory assay working group was tasked with considering issues related to the laboratory assay and testing including thresholds for seropositivity, standardization, control panels, methods and tools for processing, considerations for improved assays for certain antigens (to address cross-reactivity, antibody kinetics, etc.).

Methodology/Approach

During a pre-meeting, the co-leads outlined four challenges to address. The focus of discussion at the meeting was the four challenges:

1) How do we support technology transfer?
2) How do we share best practices?
3) How do we provide standardization across country?
4) How do we define the Quality Control Protocols?

The group also outlined the steps to consider for assay development:

1. Determine the question of interest
2. Identify candidate antigens and their characteristics (immunogenicity, whether involved in protective immunity, whether vaccine antigens, availability)
3. Identify control materials (reference standards, positive samples, negative samples)
4. Test whether antigens conjugate well to the beads, with low background (MFI signal)
5. Test whether MFI signal follows dilution steps (linearity)
6. Test whether reference standards run parallel to samples (parallelism)
7. Assess interferences between antigens to determine whether it can be multiplexed
8. Determine assay reproducibility (intraassay and interassay variability)
9. Create validation panels (characterize assay performance: sensitivity, specificity) This may vary based on infection rate and vaccination background from population to be investigated
10. Determine long-term stability of beads and outcomes

It was acknowledged that there was some overlap with other working groups, therefore the group developed a schematic on day 2 to depict how these challenges overlay between the working groups (Figure 2). For example, challenges related to reagent delivery, regulatory agencies, importation of beads and reagents in a timely manner, support for equipment, and capacity for equipment management were deemed to fall under the Supply Chain Working Group's remit. The usefulness of serosurveys and how the data are used to guide decision-making was decided to be part of the Use Cases Working Group. The need to have all partners fully invested in serosurveillance work across countries or regions was noted as being a key

topic for the Sustainable Implementation Working Group. For some issues that arose, there was an intentional choice to keep those separate and not discuss, while others did come up naturally in the discussion.

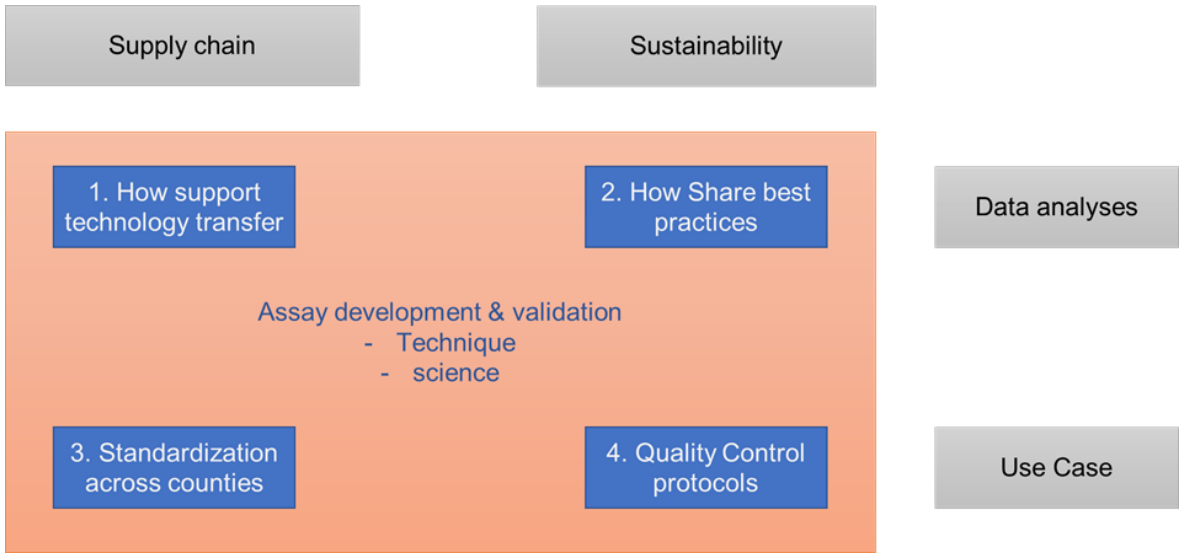

Figure 2. Challenges overlapping with other working groups

Challenges and Solutions

1. How do we support technology transfer?

Many of the groups represented (CDC, LSTMH, RIVM, JHU, CU) discussed their approaches to technology transfer and training and found that many were using similar approaches. This included bringing personnel to their labs, train-the-trainer approaches, and going in-country to provide supportive supervision. If possible inviting trainees to their laboratory allowed them to observe how everything is properly standardized. Countries could bring a subset of their panels to serve as a 10% quality assurance as a reference. There would then be a validation platform assay to assess competency. This would include reagents to reproduce the data in their own laboratories. There could also be reference materials from WHO, NIBSC or CDC. It is also possible that supervisory visits could be conducted in countries.

Although not traditionally thought of as technology transfer and more applicable to supply chain, the issue of support for the MAGPIX machines used for the Multiplex Bead-Based Assay (MBA) in serosurveillance was discussed. It was noted that the MAGPIX Research Use Only (RUO) machine is the currently favored instrument for LMICs because it does not use a laser and is easier to install, maintain, and repair in the field than other Luminex instruments. However, many working group members were concerned about the MAGPIX RUO being discontinued, leaving only an IVD option in this class of instruments. This issue was discussed with Luminex representatives who joined the 2nd day of discussions.

Potential Solutions

Short-term solutions include developing written protocols to share among groups as a best practice in performing MBA. Long-term solutions include the creation of networks to support training and monitor quality control, and to provide support for the MAGPIX equipment and engagement of governmental agencies in training and support of staff.

- **Regional hubs or train-the-trainer networks:** Representatives from Institut Pasteur, CDC, and LSTMH described how they use train-the-trainers approach. It was noted that it is important to consider who would be a good trainer and to realize that training goes both ways: trainers from laboratories can also learn from the trainees. Developing a directory of in-country sites with trained individuals who are willing and able to train others in the region through a formalized process could facilitate these efforts. Furthermore, sharing documents between sites on how to conduct trainings would be helpful. Establishing a regional laboratory network could enable closer collaboration and sharing of SOPs and samples within these regions. It was suggested that this could capitalize on resources and could be supported by BMGF or the Wellcome Trust.
- **Monitor the effectiveness of training programs:** Proposals to develop and expand training programs and to share documents between laboratories seek to improve the quality and capacity of laboratories. Monitoring the effectiveness of these approaches using a validation panel after training has concluded could help to ensure that these efforts were successful.
- **Involve governmental agencies in training**: It is important to work with governmental agencies, in particular ministries of health, for the sustainability of integrated serosurveillance. This could help address issues of staff turnover and distribution of resources. Within countries, district- and regional-level laboratories that have equipment could be better integrated into systematic thinking at the national level. Involvement of the government also ensures the ability to impact policy or program change.
- **MAGPIX machine support**: At the instrument-level, Luminex has trained individuals in-country on basic maintenance and troubleshooting and can provide virtual training through online modules. While there are not Luminex representatives in every country, one potential solution could involve connecting people who have received this training to support others in LMICs. Working group members advocated for its continued production and support by demonstrating demand for the instrument. There was a note about the machines already in use and continuing to support them. It was also brought up that there may be instances when the laser-based systems may be a better fit than the MAGPIX. Although this would be location dependent, perhaps it could be feasible in central locations where Luminex could provide set-up and tech support. Although basic

troubleshooting can be done by the user, if this has been explored and the machine is still broken, Luminex does not provide service coverage for laboratories in remote areas. They are in the process of establishing a depot in Italy, where machines could be sent for repair.

2. How do we share best practices?

Similar to the challenge above, it was noted that there was much expertise to share from groups who have been conducting integrated serosurveillance. A common theme in terms of solutions for sharing best practices across these issues was the need to develop a platform for networking and sharing information. It was highlighted that surveillance needs formal government buy-in and clear links to use and implementation. An information sharing platform could facilitate early formalized engagement with the government.

Potential Solutions

Platform to share protocols: Many experts in this working group have already developed SOPs on equipment maintenance, assay techniques, assay development, etc., but these resources have not been centralized. A well-developed and maintained central repository should be made for these documents, which should ideally be available in multiple languages. This repository could be hosted on a platform like GitHub, with users signing up for access and citing use of the repository in publications.

A component of **questions and answers** with experts is needed to address issues that may not have been included in original training. This could include a Slack as a way of sharing information quickly. As issues evolve, being able to communicate in a defined network that agrees on how to work together will allow adaptations to be made while ensuring assays maintain their quality. It was suggested that this group be made more formal with a name and a structure to provide legitimacy and facilitate acquiring funding. It was noted that to make the case for BMGF funding, it would need to clearly link back to supporting LMICs.

Serological network for multiplex serology: The information and resource sharing and ability to interact with other experts described above lend themselves to establishing a network of laboratories working on integrated multiplex serosurveillance, like the polio or measles laboratory networks or SeroNet for COVID-19. This network could have a coordinating center housed in an existing organization and could develop methods to engage local governments and establish capacity across countries. It could also facilitate material (reagents, controls, etc.) and intellectual sharing more seamlessly, which could hasten the signing of MOUs for those within the network.

Some challenges to a data sharing system were noted, including the need for data-sharing agreements between countries. A central, digitized, and regional approach could provide more

stability. Data sharing agreements could include defined outcomes, data quality checks, and more. This could model existing systems such as the one at PAHO to support countries' engagement with each other. This could also help to integrate serosurveillance into the surveillance system at the regional level.

3. How do we provide standardization across countries?

Issues in this challenge spanned several areas including assay development, antigen discovery and validation, identifying controls, and implementation.

Assay development issues included determining which antigens to use for which pathogens, sharing information on which antigens work in the MBIA and which don't work, and for which application or use-case. It was noted that the antigen target could vary by setting. Consideration should also be given to deciding how many antigens should be on a multiplex assay: the ability to multiplex hundreds does not necessarily mean it should be done.

There is extensive discussion of the critical need to establish standards for what is involved in evaluating the performance of an assay, particularly when control materials are not available for every assay. This includes quality control, establishing cut-offs for seroprevalence, and dilutions for combining pathogens. Automating the data processing and analysis steps with standardized scripts could help to address some of these issues. This issue overlaps with the Data Analysis Working Group.

It was noted that while there is a need to have quality control standards to ensure high-quality assays, this needs to be balanced with customizability to countries' needs. It was suggested that the pre-coupled beads could include the most requested antigens that have available positive controls and standards, such as for vaccine-preventable diseases. Having a common panel would allow comparisons across countries, and antigens not relevant in one country could serve as negative controls, but countries would want the flexibility to add antigens as well. A list of commonly used and prioritized antigens could be created to optimize sharing a base panel assay across countries that could be further customized and individualized to meet the countries' needs.

There was a fair amount of discussion of the cost implications for assay production. Some participants believed that having a common panel commercially made could be cost-effective. Rolling out the same panel across multiple countries would also provide a larger data set for post hoc analyses, so the cost-benefit for information would increase. However, it was also noted that having to purchase both external beads and controls for assay development could become expensive.

Potential Solutions

- **To create a working group that would identify, develop, and validate appropriate antigens.** For many of the pathogens, MBA assays are already being used with well characterized antigens. Sharing data on antigens and source of antigens for bead-coupling would a value to the community. Some thought to which antigens should be targeted toward history of exposure rather than protection, the latter of which is what vaccine developers are most interested in. For new/emerging pathogens where there is little information on antigens, proteome discovery was listed as a quick, yet expensive, first-pass approach to identify antigens. Other options include the company Serimmune, which can focus on identifying human immune responses.
- **Positive and negative controls** of serum are needed to standardize across platforms and sample types. For many studies, samples from young children (one year of age) are being used as negative controls, but these are not easily obtained and shared. For positive controls, pooled samples from populations that are exposed to many different pathogens are needed. However, it was noted that local controls are also important to consider for context and potential cross-reactivity. A panel of **monoclonal antibodies** for positive and negative controls was discussed as a long-term solution. Well-characterized specimens from longitudinal cohorts could serve as controls, but they tend to be limited in volume. Specimens from blood banks are more abundant. An up-to-date list of gold standard reference kits could be used to validate new assays and establish controls and cut-off values. **Standards from the National Institute for Biological Standards and Control (NIBSC)** could be used as a gold standard to validate in-country controls for wider availability. However, some pointed out that getting NIBSC standards can be a slow and tedious process. Bringing them to the table could facilitate provision of a central stock of agreed-upon supplies to facilitate customs and procurement.
- A challenge in controlling for bead-conjugation was also raised as an issue in standardization. Sharing protocols to validate the MBA assay **when transitioning between batches** of conjugated beads was discussed. In addition, **establishing panels of pre-coupled beads** could be a cost-effective way to scale-up production of the assays. Having a single source for antigens bead by any company could introduce significant trade-offs between convenience and cost.

4. How do we define quality control protocols?

Quality control protocols include topics addressing inter-assay variability, linearity and parallelism, buffer optimization, standardized control samples, calibrating new references; diagnostics or multiple applications; and evaluating in-house control materials. Many laboratories have existing standard quality control protocols, but these have not been shared to

a centralized source. It was noted that these protocols would differ depending on whether they were for assay validation or tracking assay performance over time.

- **Establishing a repository for common quality control targets** could allow for the sharing of existing and robust standard quality control protocols. Developing a checklist of quality control best practices for every step of the assay would create a starting point for laboratories to share protocols and identify where such protocols do not exist. This could create a minimum set of quality standards and help to identify critical components and steps.
- **Developing SOPs:** Assay development was viewed to be a labor-intensive process, taking an estimated 300-5,000 hours per assay. On the contrary, preparing a lab to use the new assay was estimated to take a few weeks. To these ends, SOPs would need to be drafted by individuals with specific competencies and a familiarity of original protocols, otherwise the assay quality could devolve as reagents and antigens were substituted. There was some concern that the credibility of the assay would further deteriorate if one cited the assay but did not adequately follow all of the steps. Although the same set of standards should ideally be used when optimizing an assay, flexibility may be warranted for different use cases, requiring additional specification for issues like dilutions, incubation times, etc. Having a single global protocol could stymie groups' abilities to optimize assays, so the repository of protocols should be viewed as a starting point that can be adapted.
- **Tools to ensure quality control:** One suggestion for ensuring quality control in assays was to use the same control panel on every plate and to have a quality control script assess variability. If values were to fall within 2 standard deviations, this script could standardize for variability using a standardized reference curve. These quality control scripts are coded in R and are being transformed into RShiny. It would be valuable to make these readily available.
- **Including disease experts in assay and SOP development early:** It was noted that disease experts will need to be involved throughout the entire process, from study design and assay development to data analysis and interpretation. These experts can help identify distinctions based on the use case, such as for age-dependent antigens including those related to Yaws, which cross-react with syphilis in an age-dependent manner. There also needs to be agreement on how the data will be used. Distinguishing exposure versus infection, natural infection versus vaccination, and seroprevalence versus seroprotection would require different mechanisms to be considered.

Additional Considerations

Some items were tabled for discussion by the group. This included sample types (DBS vs. serum, local pandemic samples vs. storage differences, and use of a Mitra device for specimen

collection), consideration for using other non-Luminex brand instruments, and rate-limiting factors in the laboratory that prevent high-throughput processing and data collection.

There was also consideration for whether the assay should be conceptualized as an openly sourced public good or one procured from commercial partners. While commercialization can be a narrow road, it could be impactful for scale-up. Government entities like the CDC and RIVM cannot operate on a commercial scale.

Table 3. Description of the discussed short and long-term solutions in the working group by challenge

Challenges	Short term solutions	Long-term solutions
How do we support technology transfer?	• Write training procedure for best practices and monitor effectiveness of training programs	• Machine support Luminex from Italy • Create train-the-trainer local networks/regional hubs • Build quality control network • Involve governmental agencies in training activities
How do we share best practices?	• Create platforms to share protocols (i.e., GitHub or a "SeroNet" equivalent center)	• Create sero expertise network • Embed network in organization
How do we provide standardization across country?	• Identify and validate antigens • Identify positive and negative controls • Share protocol to calibrate in-house reference against e.g., NIBSC • Engage NIBSC for discussion on standards	• Consider panels of pre-coupled beads • Can we use monoclonals for common antigens as standardized controls (or reference)
How do we define the Quality Control Protocols?	• Create working group to create agreement on quality control standards needed	• Reach agreement on QC standards • Publish standards on shared platform • Joint publication on quality control standards for global multiplex bead assays

Conclusions and next steps

In general, there was more agreement than disagreement on approaches to address the challenges. It was noted that many laboratory groups in attendance were tackling similar issues, and it was positive to hear that this was being done using similar approaches. The key to

continuing to move multiplex bead assay serosurveillance forward is information sharing to identify best practices. This includes a repository for sharing existing materials; creation of a laboratory network that allows peer-to-peer learning and supports quality control and standardization; and continued meetings of the working group to move forward the long-term solutions.

Data Analytics Working Group Summary

Objective and Overview

This working group focused on identifying, appraising, and synthesizing analytical approaches to multiplexed serosurveillance data; key challenges that complicate the interpretation of serologic data; approaches to combine mathematical and statistical modeling with data; and the tools and visualizations needed to support in-country data analysis.

Methodology/Approach

The part of the pipeline that this working group focused on began with the output of the raw laboratory data and ended with the epidemiological interpretations of these data. First, the working group co-leads had a pre-meeting where they generated a framework for the working group discussions (**Figure 3**). Three main challenges in this area were identified: (1) standardizing and cleaning raw laboratory data; (2) translating cleaned data to useful epidemiologic inference; and (3) developing analytical and visualization pipelines. On Day 1, the working group discussed each challenge, as well as sub-challenges and important considerations therein, and shared various approaches taken to tackle these challenges. On Day 2, the working group discussed additional considerations for each challenge as well as existing knowledge gaps, brainstormed potential solutions to meet these challenges, and identified key areas to make progress. Broadly, the challenges that were raised by working group members working across pathogen systems involved issues of cross-reactivity and other factors that complicate interpretation of serological data, as well as the need for paths forward for antigens that are relatively poorly characterized or have little gold standard validation data. In addition, several research areas identified in the working group were inherently linked to issues raised in the Laboratory Analysis and Seroepidemiology Working Groups. A summary of the discussions for each challenge is below.

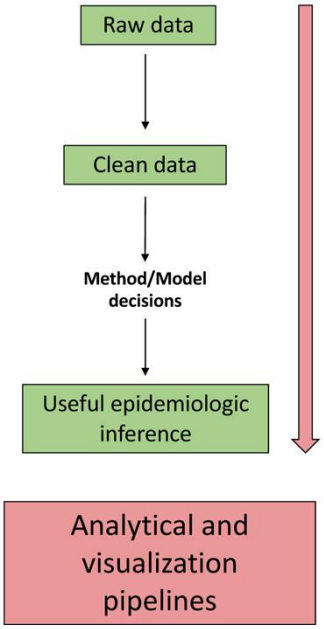

Figure 3: *Framework for discussion and the challenges identified for Data Analytics.*

Challenges and Solutions

1. **Standardizing and cleaning raw laboratory data**
    - **Performing quality control & data standardization within and between labs.** In general, a set of standard steps are taken at the start of an analysis, including background correction (i.e., subtracting MFI of empty wells) and removing samples with low bead counts (i.e., less than 50). The importance of tracking batches and bead lots to account for batch effects was also discussed. One suggestion was to look at the full

distribution of fluorescent intensities from the machine (not just summary metrics like mean or median, which is commonly done) as a source of additional data.

- **Identifying appropriate negative controls.** While there was a consensus that negative controls should (or could) be specific to a location, an open question was, how transferable are negative controls in different populations? An additional question was what is the extent to which the age distribution of negative controls matters? For instance, samples from young children may not be adequate negative controls for adults.
- **Running serial dilutions of a positive pool to generate standard curves.** The working group discussed how these serial dilutions can be used to correct for batch effects (normalization), to provide information on the dynamic range of the assay, and to interpret the quantitative results (i.e., is an MFI value in the linear portion of the standard curve or not?). A key question was on the appropriate positive pools to use for such dilution series. Based on the discussions, these could be pooled sera that are known to have high antibody levels for many antigens (ideally close to a universal control), and serial dilutions should ideally span the range of expected MFIs. It was raised that it is important to verify that these positive pools are not degrading over time and to compare replicability of standard curves. Discussion also focused on the frequency at which to run serial dilutions of a positive pool. Approaches taken by groups included a dilution series on every plate or at the start and end of each batch, depending on a variety of factors including expected precision. During the discussion, the possibility of using different models, including the logistic model, to fit the standard curve was raised.
- **Defining appropriate sample-level, internal controls for normalization.** Approaches taken include using bovine serum albumen (BSA) or glutathione S-transferase (GST) antigens to assess background reactivity, and VPD antigens as potential candidates to account for sample-level variations in immune responses (with caveats including if VPD titers vary or have waned). Some assay protocols already include individual-level tags for this purpose.
- **Implementing data standardization and normalization procedures.** The first question raised was on defining criteria that can be used to determine if normalization steps, as described above, worked. The working group members discussed how population distributions should be similar between plates, post-normalization, and how replicates should be similar between plates, post-normalization. It was discussed how in theory, performing the steps above should be sufficient to get rid of most batch effects. Different research groups have their own internal R scripts and/or Excel templates to perform these steps. A need for standardized R packages and/or sharing protocols for

these steps was raised. The working group noted that if data are not normalized in the same way, this can lead to substantially different answers from the same data set.

2. Translating cleaned data to useful epidemiologic inference

Deciding how to analyze the cleaned serologic data. The working group discussed two ways to analyze the data: as binary serostatus (i.e., seronegative vs. seropositive) or quantitative results (i.e., MFIs).

- **Analyzing binary serostatuses:** One key challenge identified was in establishing a cut-point for seropositivity. There are ultimately two questions to be answered with binary data: whether antibody levels in the blood are indicative of past vaccination or infection and whether they indicate protection against future infection. There are two approaches that are commonly used to create binary serologic data. The first approach is to use gold standard data on well-characterized negative and positive controls (and for the latter, with known time since infection or known protection from infection). Longitudinal, post-infection data are key: these control samples are used to determine a cut-point and test performance characteristics associated with that cut-point. A question was raised on what to do when infections cannot be observed directly (i.e., due to asymptomatic infections or lack of diagnostic testing availability). In that case, data from neutralization (gold standard) serologic assays could be used to generate validation sets and to determine cut-points. The second approach, taken when only negative controls are available, classically establishes a cutoff by using a cut-point defined as ~3 standard deviations over the mean of the negative controls. From here, the working group discussed how cut-points for the population can change over time. For instance, if a serosurvey is conducted near the peak of an epidemic, most individuals will have been recently infected and have higher antibody levels. However, if a serosurvey is conducted years after an epidemic, most individuals will have been infected long ago and have lower antibody levels.

  Additional ways in which cut-points may currently fail to account for population-level changes in prevalence (i.e., less natural boosting with VPDs in the post-vaccine era). It was also discussed how additional testing of samples in the indeterminate range may need to be done to reduce uncertainty. Overall, it was discussed how there are clear, established methods for modeling binary serostatus data, such as using the serocatalytic model and its variants. While there are some R packages to implement these models, bespoke scripts are more often used. The need for well-established, user-friendly tools to implement these standard models was discussed. A key limitation of binarizing serological data was also discussed, which is that uncertainty is often ignored with this

approach of determining and using a single cut-point. This can ignore factors such as individual heterogeneity in the immune response, measurement error, and cross-reactivity.

- **Analyzing the data as quantitative MFIs (or concentrations/titers):** The approach of using quantitative MFIs avoids biases introduced from converting MFIs into a binary serostatus. There are some established methods for modeling quantitative titer data, the most common being mixture models and antibody acquisition models. Analyzing quantitative MFIs can potentially address key issues such as cross-reactivity and can provide a way forward when validation data sets are not available, and the analyses are unsupervised (separate sections below). This approach can also be used to propagate uncertainty resulting from binarizing serological data forward in models used to estimate parameters such as time since infection or cumulative incidence of infection.
- **Stepping through a test case:** The working group briefly discussed how to analyze serological data from a specific use case identified during the summit on using serosurveillance to characterize pathogen burden (assuming serial, cross-sectional population-based serosurveys for a specific pathogen). The key branching point was whether a cut-point was known for that antigen. If a cut-point is available, then the analyst can assign serostatuses, obtain some useful metrics (seroprevalence, seroincidence), and fit versions of the serocatalytic model. If a cut-point is not available, then the analyst can take several approaches, including fitting mixture distributions, incorporating information on cross-reactivity if known, and conducting extensive sensitivity analyses. Ideally, multiple orthogonal approaches would converge on similar results and boost confidence in the findings. It was also discussed how unsupervised clustering of multiplexed antibody responses could be performed to obtain a better understanding of structure in the data. Furthermore, analysts may want to apply seroprevalence data from one spatial or temporal unit or scale, and smooth or predict it at others. The ability to borrow information from other units was identified as a strength, and the need for key meta-data that can be used to cluster individuals (e.g., age, sex, location) was raised. The working group also discussed how estimating jointly across geographic or socio-demographic groups can provide better information.
- **Accounting for cross-reactivity.** Several key questions were raised, including what antigens should be included on a panel. The working group discussed how including a mix of cross-reactive and non-cross-reactive antigens could help, where the correlation structure is driven by different factors to provide additional information. For example, having two DENV antigens that are cross-reactive could help disentangle distinct and overlapping responses. The group discussed the need for the balance of sources of correlation to be informative. On the extreme end, if correlation between two antigens

is extremely high, then the second antigen provides little new information, and it may be appropriate to drop one. Questions and approaches related to cross-reactivity may vary by pathogen. To name some examples discussed:

- Chikungunya and Mayaro virus: analysts can leverage information on quantitative titers to both pathogens to delineate all possible infection histories with the two pathogens.
- Influenza: analysts can leverage knowledge on strains going extinct over time to characterize cross-reactivity versus true exposure.
- Dengue, Zika, and Yellow Fever: as yellow fever sero-reactivity also results in DENV and ZKV sero-reactivity, the absence of yellow fever sero-reactivity can increase confidence in not having had exposure to the other two pathogens.
- SARS-CoV-2: populations that received mRNA-based vaccinations and have not experienced natural infection should only have antibodies to the Spike protein and not the Nucleocapsid protein.
- NTDs: high levels of cross-reactivity between antigens are likely, and the correlation structure is not yet well-understood; cross-reactivity may also be region-specific.

Several modeling approaches to account for cross-reactivity that are being developed, including by researchers in this working group, were discussed (i.e., multivariate Gaussian mixture models that integrate over all possible combinations of exposure histories to the [cross-reactive] antigens on the panel). It was also discussed how laboratory approaches, including antigen discovery for proteins that are more specific to the target pathogen, will be complementary for better accounting for issues on cross-reactivity.

- **Leveraging insights afforded by computer simulations (with caveats).** It was discussed how simulation frameworks, which take in levels of pathogen transmission and simulate multiplex assay data with various levels of noise, could be used to determine the ability of quantitative models to pick up the desired signal. It was discussed how simulations can also be powerful to look at different kinetics to evaluate infection history and cross-reactivity, and how simulation frameworks could help understand correlation structure of the data and cross-reactivity. This allows researchers to ask questions such as: “What would be an optimal antigen panel?”, “What are the characteristics of an additional antigen that would allow the researcher to disentangle hypotheses about cross-reactivity?”, or “What is the ratio of signal to noise in this assay?”. The working group also discussed how simulations are difficult in unsupervised scenarios (i.e., where researchers have less guidance on a cut-point or antibody kinetics).
- **Assessing the extent to which analytical approaches are generalizable across pathogens.** This issue was also discussed for cross-reactivity (see above). Broadly, the

working group discussed the "order of operations," i.e., when it may be important to incorporate factors such as antibody kinetics or cross-reactivity, and how this may depend on the pathogen. It was discussed how, for some pathogens, it is very important for factors to be standardized (i.e., for trachoma, to be reported to ministries of health and other decisionmakers/stakeholders). For other pathogens, where researchers are still trying to pinpoint the public health use cases, this will vary over time (i.e., in a decade, the discussions around DENV could look very different). The importance of engaging with global programs was raised.

- **Feeding data analyses back into the study design and data collection process.** These issues include potentially measuring multiple isotypes simultaneously to gain more insights, depending on the question(s) of interest (i.e., measuring IgA vs. IgG vs. IgM); analyzing multiple antigens jointly, including MR or DTP (i.e., antigens with shared exposure via vaccines); and collecting matrices beyond serum/DBS (i.e., paired specimens could be useful for determining cross-reactivity).

3. **Developing analytical and visualization pipelines**
    - **Recognizing the different analytical and visualization pipeline needs between programs and researchers.** The working group discussed the importance of knowing one's audience, regarding the level of complexity and detail that needs to be communicated and how the presentation should be standardized. A point raised was on building complexity: for example, an analytical pipeline could start with simple metrics such as seroprevalence, add covariates and trends, and then ultimately make connections to disease incidence. Due to time constraints, the working group was not able to discuss this important challenge in further detail.
    - **Developing and annotating Shiny (or similar) apps for programmatic use.** It was discussed how there are multiple successful examples of these apps being developed for specific projects and partners. A typical pipeline involves the steps between importing raw Luminex data and epidemiological inference (i.e., predicting binary serostatuses). The working group discussed how in no-code/low-code platforms there can be a lack of clarity about what is going on "under the hood." Depending on the intended use case, it may be necessary to ensure that the data and information meet certain minimum quality standards to ensure robust inference. One example of this which was discussed was how a user may want to input or select appropriate negative controls from the local epidemiologic setting. Different users may have different levels of interest in understanding what is going on under the hood.
    - **Generating useful visualizations.** It was discussed how spatial maps are generally well-received. An open area of inquiry is how to demonstrate uncertainty on maps (i.e., in some places it may be possible to say something definitive while this is less true in other places).

Conclusion and Next Steps

1. **Create centralized repositories of information and sharing of analytic methods/pipelines, standards, controls, and data.**
    - There is currently no serological equivalent to GenBank—the working group can look to pathogen genomics as a model for sharing.
    - While code to perform bioinformatics and data analytics exists, there are benefits to having standardized code for programmatic use cases (as compared to developing and applying frameworks for researchers).
    - A platform for sharing real-world multiplexed serologic data sets for testing and comparing models is needed.
    - More crosstalk between laboratory and analytics working groups would be beneficial to inform each other.
2. **Catalog quantitative models by user-friendliness and complexity.**
    - A menu of models (and corresponding analytical code) could be established, starting with serocatalytic models and increasing in complexity. These code bases would need to be regularly maintained to ensure compatibility.
3. **Catalog antigens by how interpretable/well-characterized they are.**
    - How can researchers think about where antigens lie on the path of interpretability? This question was also raised in the Seroepidemiology Working Group. The best-characterized antigens, with respect to positive controls, would have sera from individuals with PCR-confirmed infections in the same population as the serosurvey (ideal) or other validation data (e.g., data from PRNT assays). Optimal positive control sample sets would include paired acute-convalescent sera or longitudinal samples post-infection. The best-characterized antigens, with respect to negative controls, would ideally have sera from individuals known to not have had prior exposure in the same population as the serosurvey.

Sustainable Implementation Working Group Summary

Objective and Overview

The Sustainable Implementation Working Group explored case studies, challenges, and possible solutions to promoting the introduction and sustainability of integrated serosurveillance. This group consisted of individuals from research organizations, academic institutions, public health laboratories, multilateral organizations, funders, and supply chain experts.

Methodology/Approach

The co-leads for the Sustainable Implementation Working Group began by presenting a guiding structure for the session, beginning with an introduction to the topic and goals of the session as well as an overview of the agenda. A working definition of sustainability was provided to guide discussion over the two-day summit: "A country has incorporated **integrated serological surveillance** into its national surveillance system as a **complementary tool** for making better public health **programmatic** decisions. To this end, the country has established clear methods and procedures for the interprogrammatic collection, analysis, and utilization of data and handles all aspects, including costs, logistics, capacity, and infrastructure."

Throughout the summit, the definition of sustainable implementation expanded to include observations and comments from members of the Working Group. Importantly, sustainable implementation was thought to require continued, but not necessarily continuous (e.g., continuous collection of samples), efforts going beyond a single round of surveillance. This could mean that a country which is not currently conducting serosurveillance has the equipment and knowledge necessary to do so should the need arise. For different settings, sustainability may look very different depending on histories of collaboration, surveillance structures, and resources.

Four key challenges were identified at the start of the session which were further schematized into a flow-chart with guiding questions. The four challenges were:

1. Demonstrating added value for initial engagement,
2. Buy-in from across national health systems,
3. Laboratory capacity and supply chain/procurement/sustainability of funds, and
4. Serosurveillance approaches and data analysis for decision making.

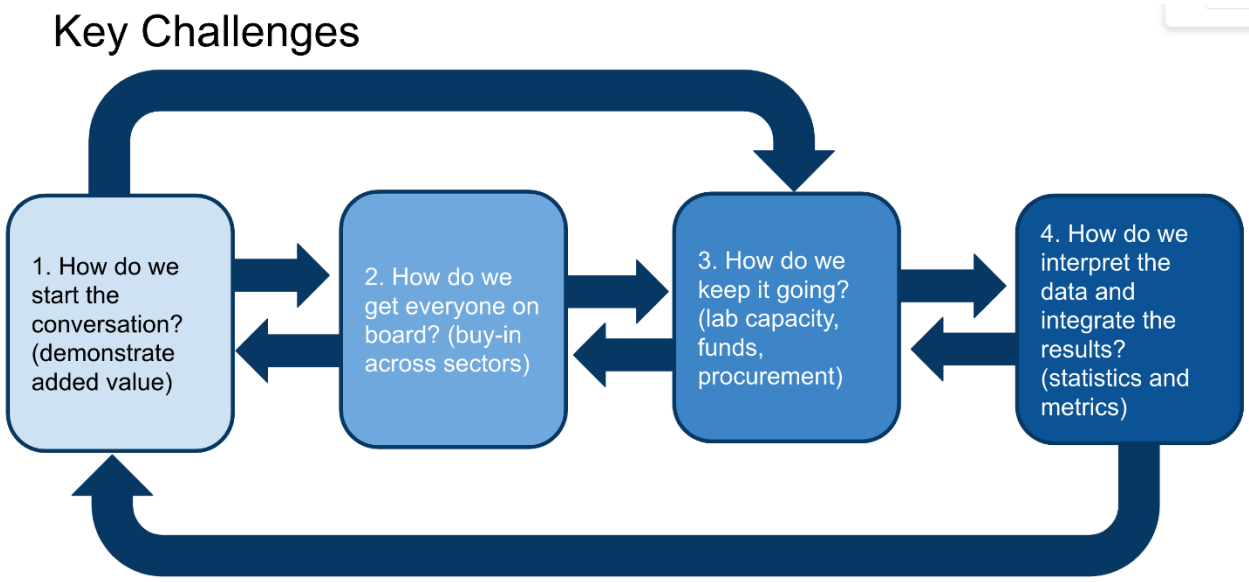

Figure 4. Outline of the key challenges and guiding questions identified in the Sustainable Implementation Working Group

Within these challenges, several details relevant to each challenge were presented, followed by case studies of countries within the Americas Region [19] and Africa [31] which have conducted serosurveillance. Following these case studies, an open discussion was facilitated to allow for the identification of additional challenges, context, case studies, and solutions to these challenges. On the second day, four sub-groups were formed to discuss approaches and solutions for sustainability as they related to political buy-in; lab training capacity, procurement, and assays; sample collection and biorepositories; and analysis and interpretation of results. The Working Group reconvened, and members of each sub-group reported the findings back, followed by discussion to synthesize the final recommendations.

Challenges and Solutions

1. Demonstrating Added Value

There are no clear recommendations and standardized methodologies established by WHO for integrated serosurveillance. Additionally, serosurveillance is viewed by many as a scientific exercise rather than a tool that can help to guide and support public health programmatic decisions. The added value and way serosurveillance can be complementary to current tools needs to be clearly articulated and outlined. Furthermore, the existence of several competing priorities necessitates clearer advocacy for wider uptake. Part of this broader challenge entails the need to clearly delineate the uses of serosurveillance, for example it is not considered a diagnostic test and intended for non-clinical support as well as additional benefits of helping strengthen surveillance systems.

Potential Solutions

- **Identifying how integrated serosurveillance can complement existing systems:** Establishing use cases for serosurveillance can help decision makers to understand the situations in which serosurveillance can serve as a complementary tool to existing approaches. For example, serology can provide baseline epidemiological data for several diseases in areas where surveillance is weak or inefficient; it can help to assess the impact of interventions; and it can provide information on the post-elimination surveillance phase. Clarifying the difference between serosurveillance and case surveillance and creating ongoing conversations with countries is important for establishing buy-in. Allowing countries to establish their own priorities, including target populations, geographies, and diseases can further support ownership. Messages should be tailored to countries based on their unique priorities, needs, and resources.
- **Articulating what "good" looks like:** Shifts in donor priorities from vertical to horizontal disease programming could open the door for greater funding for integrated serosurveillance. However, this approach is relatively newer to collaborative integrated surveillance discussions. Establishing good practice and use cases for integrated serosurveillance could encourage donors to fund this approach though it is important to acknowledge that good practice can vary depending on the setting and context.

2. Generating Buy-in from across National Health Systems

One important challenge to developing buy-in across sectors was the need to integrate work across disease-specific areas that have historically worked separately but which have shared surveillance challenges. Both technical and financial support is needed from influential international partners in public health including the WHO, foundations, the Global Fund, Gavi, and others. At the same time, these initiatives should be led by in-country partners including high-level decision makers that share an understanding of the needs and benefits of working together on integrated serosurveillance. As in the first overarching challenge, the perception that serosurveillance is best suited for research rather than integration into functional surveillance systems to guide programmatic decisions was highlighted. Furthermore, there is a need to focus on identifying the benefits and attaining the consent of the communities which provide specimens for serosurveillance to ensure sustainability.

Potential Solutions

- **Creating policy briefs and technical documents to describe key information:** Developing and approving protocols and approaches for serosurveillance can be a time-consuming process, particularly when multiple teams are involved. The creation of *plain-language* policy briefs for ministers of health and high-level government figures

can help to convey the purpose, process, benefits, and limitations of integrated serosurveillance. They can also help to establish the implications of being involved in terms of funding, resources, and logistics. Technical documents describing some of the same information as well as laboratory-specific information (e.g., sensitivity/specificity, barriers, and laboratory technology and reagent requirements), expectations, and available resources can help to bring technical teams on board. These documents should be provided in individuals' native languages where possible and build upon previous successes and failures. Understanding how other countries have been able to use integrated serosurveillance can provide motivating examples for new countries to participate.

- **Leveraging and integrating with regional networks:** Promoting partnerships and collaborations among countries, WHO regional offices, and research groups that are implementing integrated serosurveillance (e.g., PAHO, the Africa and US Centers for Disease Control and Prevention, among others) can help to expand and reinforce capacities, share data and experiences, find solutions and overcome challenges, disseminate information, etc., to expand the use of integrated serosurveillance as a tool for guiding public health interventions.
- **Highlighting, describing, and generating an evidence base:** Case studies of countries which have used serosurveillance and acted upon results, with examples for multiple diseases, are needed. This will help countries to better understand the utility of serosurveillance as a tool for making programmatic decisions.
- **Identifying common goals and objectives for serosurveillance:** While the COVID-19 pandemic has helped to demonstrate the utility of serosurveillance for public health purposes, establishing common goals and objectives between different groups working within a country has proven challenging. Conversations must be facilitated between groups that do not typically work together to identify opportunities for collaboration and knowledge and resource sharing. A scoping exercise by members of these groups to identify clear use cases, needs, and priorities, as well as how serosurveillance can and cannot complement ongoing efforts can help to establish common ground. Several members of the Working Group emphasized the importance of identifying key questions that integrated serosurveillance could answer.
- **Explaining the benefits and limitations of serosurveillance:** Expectations of what serology can do, including the available tests, number of antigens to test against, and knowns and unknowns, among others, should be appropriately managed.
- **Establishing target product profiles to meet public health needs:** Establishing target product profiles (TPP) for MBAs that meet identified public health needs can help to shift perspectives on serosurveillance from a research and data generation activity to a tool that can help to guide decision making. Developing MBAs which meet the

specifications laid out in these TPPs can support the generation of high-quality data with specific foci.

- **Identifying and communicating benefits to community participants:** Clearly articulating the benefits that serosurveillance can provide to participating communities is critical to sustaining serosurveillance efforts. Without this communication, individuals may see no incentive to participate and refuse to provide specimens for serosurveys. However, this communication must carefully balance demonstrating added value while not overselling the benefits of this tool. Training teams to explain serology and its focus on community- rather than individual-level results to participating individuals through discussions and consent forms can help to avoid confusion and improve adherence. Furthermore, detailing a process to return the results of serosurveys to communities in Standard Operating Procedures (SOPs) can further build community trust and buy-in. At a participant-level, providing health services (e.g., measurements for non-communicable diseases, tests for communicable diseases, etc.) at the time of specimen collection can greatly increase acceptance.

3. Building and Sustaining Laboratory Capacity and Supply Chain/Procurement/Funding

Several cross-cutting issues were identified relevant to sustaining integrated serosurveillance systems once they are established. In general, there are issues with implementation and continual processing of samples including lack of skilled laboratory staff with high turnover rates and limited ability for machine maintenance services and acquiring/producing antigen-coupled beads locally or without the support of international partners (such as the CDC). Controls are limited, and there is no systematic protocol, limiting comparability between laboratories. Following data generation, issues remain about the analysis and interpretation of these results which require support across aspects of Ministries of Health (including statistical support) and more advanced computational training than commonly found at many ministries.

Potential Solutions

- **Communicating across steps:** Breaking siloes between and within programs is essential for ensuring sustainable implementation. Laboratory, epidemiology, and programmatic teams are often separated from one another, which can hinder analysis efforts and understanding. By creating opportunities for these teams to work and communicate with one another, misunderstandings and disagreements can be addressed. Training laboratory personnel to understand the entire process from specimen collection to analysis can help to streamline awareness and functions. Clear protocols and training on how to run tests should be developed for laboratory personnel.

- **Clearly outlining laboratory needs:** Laboratory personnel can develop lists of materials required in the lab including essential items and substitutable items. This can help to minimize risk, identify alternate sources, and enable laboratory personnel to communicate with procurements to establish clear steps regarding order placements. Checklists for good quality standards for running MBAs should also be developed. Beyond laboratory materials, quality service maintenance for MBA instruments can be difficult to find in some countries. Manufacturers can help to identify suitable local and regional service agents. Challenges to specimen storage include adequate freezer and refrigerator space as well as power backups. Continuous investment in storage as well as the use of equipment such as uninterruptible power supply (UPS) units can aid laboratories in meeting storage and quality needs over time.
- **Developing resources/a network for support and troubleshooting:** A heavy dependency on external partners for tasks including identification of suitable antigens, coupling of antigens to beads, and quality control can limit sustainability. Identifying and sharing capacity for some of these tasks at a regional and subregional level would reduce this dependency. Help desks can allow users to troubleshoot issues across instruments, discuss challenges, and determine if tasks must be recompleted. Global and regional biobanks to store quality control standards can further facilitate comparison of results across laboratories.
- **Focusing on on-site training:** In the past, more experienced laboratories (e.g., from the CDC and RIVM) have invited researchers from national laboratories to visit with their own samples to carry out initial sample analysis for training purposes. This training can prove beneficial to the individuals who are able to attend but pairing these efforts with follow-up implementation in local laboratories can help to further build capacity. On-site training can also allow trainers to identify necessary adjustments based on available material and to train more individuals. The development of a regional lab network can allow for more lab staff to be trained and improve opportunities for troubleshooting. Online courses and train-the-trainer initiatives can also support laboratory capacity and sustainability. These training efforts should support seamless integration back into home laboratories by minimizing backlogged work upon return and providing reagents to begin serosurveillance immediately.
- **Addressing supply chain issues:** Building the capacity for countries to produce their own antigen-coupled bead panels could reduce countries' reliance on the small number of groups producing these beads. Developing this capacity could allow countries to provide antigen-coupled beads to other countries within their network. Other supplies are often imported from other countries. Collaborating with manufacturers to identify reliable local and regional agents can help to ensure timely delivery of supplies and allow serosurveys to move ahead when they are needed.

- **Sharing machine capacity:** Some countries own Luminex machines but restrict use of these instruments to a single disease area or team. Understanding how teams can work together to share instrument use can address this issue.
- **Considering options beyond Luminex:** One key concern for sustainability was the reliance on Luminex instruments and beads to conduct MBA. Luminex's egress from this space could lead to serious issues in sustaining serosurveillance efforts. Anticipating shifts in supply and changes in technologies and approaches, including consideration of alternate platforms, may be essential for ensuring sustainability.
- **Incentivizing the market for laboratory materials:** Few MBAs are commercially available, in part due to a lack of commercial incentive to manufacture and sell them. As a result, laboratories procure these assays from limited, non-commercial sources. Identifying well-established assays could enable a contract company to develop and provide these assays, though licensing fees apply for commercial use. Alternate approaches discussed include building antigen-bead coupling capacity or considering a role for entities like the African CDC to provide these assays to member states.

4. Interpreting Data and Integrating Results

Triangulation of information and analysis for each disease and group of diseases to define overlapping target population groups and evaluation units can be challenging, particularly due to differences in the epidemiological context and immunology of diseases as well as in the interventions required to treat each one. Additional evaluations clearly mapping results onto public health decision making regarding interventions is needed. Population-specific disease patterns and history of disease transmission are also important factors to consider. Further, data generated from serosurveys require more complicated data analytic pipelines than are available in many programs. This task is further complicated when several programs are simultaneously carrying out serosurveillance. Partnerships between public health programs and academics and researchers are needed to better understand programmatic needs and work to develop pipelines easing the pathways to interpreting results.

Potential Solutions

- **Facilitating efforts to produce straightforward outputs:** To build buy-in, more straightforward outputs are needed from well-characterized antigens. This could include age- and space-specific characteristics for vaccine-preventable diseases (VPDs). Uncertainty in the data should be communicated alongside these results, and data governance structures should be built into these efforts with additional clarity on what different indicators measure.

- **Leveraging existing serosurveys for quick wins:** The timely generation of evidence from existing and ongoing serosurveys can serve as "quick wins" where data is needed to demonstrate the value of integrated serosurveillance.
- **Building statistical analysis pipelines:** Sharing resources between programs in for a such as Stack Overflow can help to build researcher capacity to first generate R scripts then eventually critically interpret serosurveillance results. Such a forum could be internationally owned and crowdsourced to allow for questions to be asked and answered with free tools provided.
- **Mapping existing efforts and leveraging existing work:** Understanding the data capabilities and responsibilities within a country is important to establishing context-appropriate solutions. Partnering with existing government-funded organizations which are adept at analyzing large-scale datasets and sharing results for public health decision-making processes can help where capacity is limited. Partnering with local academic institutions could enable countries to meet these needs more efficiently. Well-equipped regional groups could perform analyses for others that are unable to do so themselves.
- **Developing training and general resources for analysis and interpretation:** Data analysis and interpretation for serosurveillance could be built into existing training platforms such as the US CDC's Field Epidemiology Training Program (FETP). Seconding postdoctoral researchers and graduate students to in-country locations can create positive environments for these skills to develop. Partnering with WHO Collaborating Centers can also be beneficial.
- **Developing SOPs for the analytical pipeline for common tasks and goals:** Mapping desired outputs can help data analysts to understand meaningful ways to interpret and present serosurveillance results. Building the appropriate level of interpretation into SOPs can help to standardize practice including developing an understanding of the minimum descriptive analysis needed for others to understand these results.
- **Integrating serological and programmatic data:** Considering serological and programmatic data together can ensure that valuable contextual information including history of outbreaks and administrative vaccination coverage are incorporated into the analysis and presented results.

5. Sample collections and biorepositories

Sustainable approaches to sample collection and the creation and use of biorepositories were discussed in detail by a subgroup on the second day of the Serosurveillance Summit. Five axes to consider sustainability were considered, ranging from less sustainable to more sustainable approaches. These axes are presented in Figure 5 below. Some approaches considered by this group were noted to be more sustainable but less useful, and vice versa. For example, while

biorepositories were thought to be useful for serosurveillance, the costs and labor associated with managing them were viewed to make them less sustainable. While steps can be taken to support sustainability—including using serum bank samples, collecting dried blood spots (DBS), and integrating serology into existing processes such as national surveys (e.g., Multiple Indicator Cluster Surveys, Demographic and Health Surveys, nutrition, neglected tropical disease nutrition surveys, etc.)—these approaches have been limited, and standardization as well as the establishment of community benefits and sample ownership are needed.

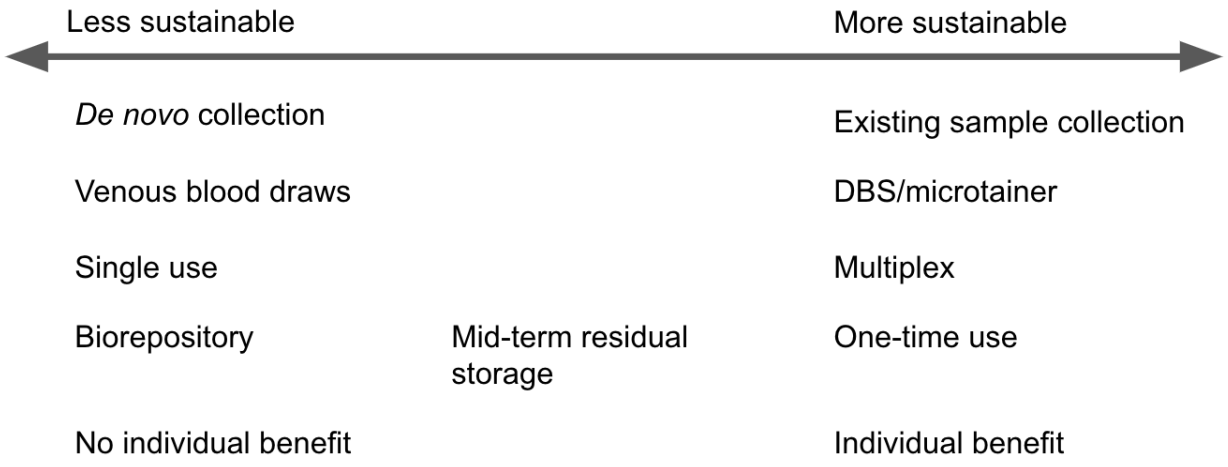

Figure 5. Examples of sample collection and biorepository practices for serosurveillance along a continuum of sustainability.

Conclusion and Next Steps

Building upon the discussions across the key challenges, five high-priority recommendations on sustainability were communicated to Serosurveillance Summit attendees:

1. **Create a repository of existing resources that demonstrate and explain serosurveillance:** This repository would include use cases, pros and cons to using serosurveillance, added benefits, instances of successes and failures, and evidence of cost-effectiveness for integrated serosurveillance (e.g., a serosurvey conducted in Paraguay cost $50,000 to collect and process 1,200 samples). This information should be presented in simplified language for general use and understanding by different levels of decision makers and members of technical teams. By communicating to both political leaders and technical teams, integrated serosurveillance programs will be more resistant to change due to political turnover.
2. **Conduct a mapping exercise of existing analytic capacity to guide training efforts:** By mapping the analytic capacity within a country, different training options can be considered to best fit the needs and resources of the target country. These options include seconding

postdoctoral researchers and graduate students, partnering with regional/national universities and WHO Collaborating Centers, developing online courses, etc. While these training programs can aid in building a competent workforce, turnover remains a pressing concern.

3. **Foster higher-level regional and international support to provide clear guidance on recommendations for implementation/use:** Having regional and international support for countries to implement integrated serosurveillance can support ongoing efforts even following setbacks. Developing proof-of-concept evidence at the regional level can enable organizations like WHO to make recommendations and issue guidance, but recommendations on sustainability will require leveraging organizations which are already conducting serosurveillance.
4. **Achieve commercial-caliber levels of resources for implementation:** Commercialization of key products like antigen-coupled bead assays could help to address supply chain bottlenecks that have emerged due to a reliance on a small number of organizations creating small batches of antigen-coupled beads. Building commercial caliber across the continuum of resources needed to implement integrated serosurveillance from sourcing of materials to data management can support sustainability.
5. **Create networks to share resources and use case successes and failures and to develop cross-laboratory collaborations:** Knowledge sharing between laboratories can help to build capacity and develop evidence in support of integrated serosurveillance. Partnerships between laboratories can leverage the strengths and capabilities of one group to support laboratories which lack capacity in certain areas.

Sustainable implementation of integrated serosurveillance requires close coordination at every level. Stakeholder-specific documents which clearly outline the purpose, benefits, and limitations of serosurveillance can help to build buy-in from high-level government officials to technical experts. Use cases across disease areas and geographies are needed to further build this support, with both successes and failures providing valuable information for future efforts. Commercialization of materials needed for MBAs can address supply chain bottlenecks while networks to share knowledge and promote collaborations can build capacity and contribute to the collective evidence pool. Critical to these efforts is the need for well-trained laboratory personnel and data analysts. Addressing these issues and garnering support from national and supranational bodies would pave the path for wider adoption of integrated serosurveillance, though measures of successful implementation and sustainability will vary from setting to setting.

Conclusion

The serosurveillance summit facilitated information sharing amongst participants who were all confronting similar issues. Overall, there was relative consensus on the next steps and continued needs to move the field of multiplex integrated serosurveillance forward. Potential solutions identified by the groups were similar in nature. Some solutions could be implemented in the short-term while others require additional research, long-term collaboration, and consensus-building. There was a substantial amount of overlap among the working groups because the issues are heavily intertwined (Figure 6).

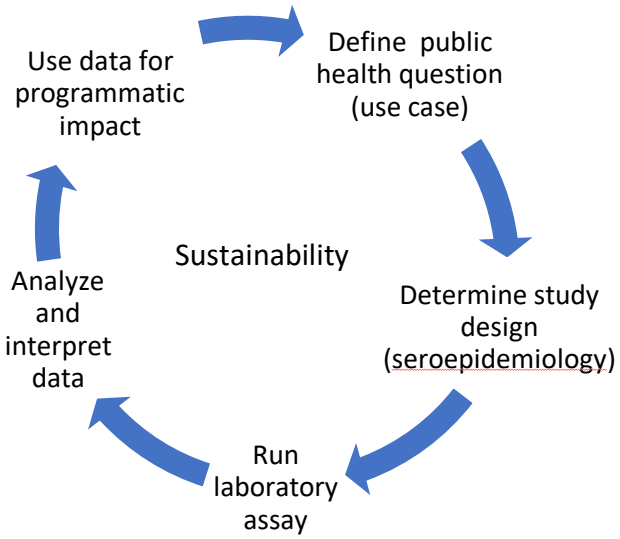

Figure 6. Multiplex serosurveillance cycle

Cross-Cutting Topics Discussed

Although each working group was provided with a separate set of topics, there was some natural overlap in the discussions due to the nature of the content as well as the fact that participants belonged to two working groups and attended multiple working group sessions. Below are the salient overlapping points that were discussed in multiple working groups.

There is a **need for data analytic tools and methods** given the complex nature of multiplex serological data. Data analytic pipelines that translate laboratory data and triangulate with other data sources (e.g., surveillance, vaccination coverage, and other health program data) would shorten the time frame from specimen collection to interpretation. The clear communication of results in a concise manner would allow for the timely use of data by health program decisionmakers.

Concerns with **supply chain constraints** continuously arose. Of particular concern is the ability to purchase and maintain the technology platform, given that Luminex had ceased sale of the

research use only MAGPIX, which was simplest to use in resource-limited settings. There were also concerns about the scarcity and procurement challenges for other reagents, particularly for the development of bead panels. The scarcity of appropriate controls with sufficient volumes for standardization was also an issue.

Finally, the **interplay between defining a use case to guide the objectives of serosurveillance and seroepidemiology to identify the appropriate study design** was discussed in multiple groups. The sustainability of a particular study design was also mentioned multiple times, in terms of whether residual specimens could be used to answer the question of interest versus having to collect new specimens. The complexities to define target populations across multiple antigens also arose several times.

Cross-Cutting Solutions

While each working group identified a set of next steps to address or a list of continued discussion topics (Appendix 2), there were a number of solutions generated that were cross-cutting. Coordination will be needed across working groups to facilitate integration of these solutions to serve the needs of multiple working groups.

Create an electronic platform for information sharing

All groups advocated for a digital platform to share information across experts. A GitHub, Slack, or website could be a forum to share lists of supplies, existing protocols, antigens that have or have not worked for assay development, and quality control procedures. R code and apps could also be shared for data cleaning and analysis as well as comparing models that have been developed for data analytics.

Build local capacity

Research institutions that have been conducting multiplex serology in LMICs have been conducting training in a similar manner. Many working groups suggested building in-country capacity for a variety of topics, and this was further highlighted in the sustainable implementation group. This could include for example: supply chain logistics and equipment maintenance (supply chain), sampling (seroepidemiology), bead coupling and running the assay (laboratory), and data analysis (data analytics).

Develop quality control or standardization process

As countries develop multiplex assays, quality control and standards for evaluating the performance of an assay are needed. This could include a panel of standard positive/negative controls or some other evaluation kit to maintain high quality of the assay, laboratory testing procedures, establishment of cutoffs for seroprevalence, etc. While ensuring quality is important, this should also be balanced with flexibility for countries to customize assays to meet their needs based on use cases and interest.

Establish laboratory network

A network of laboratories could facilitate information sharing, developing harmonized protocols, sharing of materials, and implementing training and quality control procedures. The structure could include regional hubs that support surrounding countries with regards to training, supplies, etc. This network could be modeled off SeroNet in the US or other global laboratory networks, such as for polio or measles and rubella.

Generate political buy-in for multiplex serosurveillance

Political will is needed to sustainably integrate serosurveillance into the surveillance system and ensure findings are useful for programmatic decision making. Involving ministries of health early in the process and demonstrating the value of multiplex serosurveillance can generate buy-in from governments, funders, and implementers. Policy briefs and use case examples can generate interest among additional funding agencies to invest in serological surveillance as a complementary surveillance mechanism.

Next Steps

This meeting created a community of practice to carry forward the work to be done in terms of building platforms for data sharing, lessons learned, and data analytic tools to move towards routine serosurveillance implementation globally. Unfortunately, there was limited participation from low- and middle-income country national public health agencies and national laboratories due to the delay in visa processing from the pandemic. Additional countries working on multiplex serosurveillance can be included in the working groups moving forward.

To leverage the momentum generated, participants will continue to serve on the working groups that interest them. Working groups will meet on a quarterly basis to implement the solutions and next steps as identified during the meeting and laid out herein. Johns Hopkins University will facilitate the information-sharing initiatives suggested by working groups. Where further research or collaboration is required, additional funding will be sought to fill these needs. The countries being supported by BMGF in Africa will serve as additional test cases for the scale-up of multiplex serosurveillance in LMICs. A follow-up meeting will be set for 2024 in one of the LMIC countries implementing integrated serosurveillance.

The COVID pandemic provided a focus on serosurveillance and how important it was to measure population immunity to track new pathogens and guide public health programs. The lessons learned in terms of serosurveillance study designs, laboratory capacity, and use of data for public health decision making provide an opportunity to expand beyond SARS-CoV-2 to additional pathogens of epidemiological interest. Leveraging the investment in serosurveillance is vital for continued preparedness and response to future pandemics.

Appendices

Appendix 1. Agenda

Serosurveillance Summit 2023

Bloomberg School of Public Health, Baltimore, Maryland
March 7 - 8, 2023

Working Groups

Overview

Each meeting day is broken into two sessions, during which discussion will be conducted regarding the thematic areas. The overall purpose of these working groups are:

1. To identify the general challenges in multiplex integrated serological surveillance related to each topic area with a focus on existing technologies, particularly multiplex bead arrays.
2. To establish a community of practice to tackle issues for multiplex serology going forward.

Everyone has been placed into two working groups that focus on a thematic area, with the consideration of your preferences and experiences. The leaders of your working groups should reach out to you before the summit with a list of key challenges identified related to the group's thematic area. Please review these challenges for feedback and think about cross-cutting, as opposed to pathogen-specific, solutions & approaches to discuss during the summit.

Group Descriptions

Supply Chain

This group will focus on supply chain issues including multiplex bead array assay availability, reagent manufacturing, equipment, and opportunities for technology transfer.

- Availability of antigen coupled beads
- Barriers to commercial manufacturing of assay reagents
- Assay and antigen validation
- Opportunities for technology transfer
- Affordability and economic considerations

Laboratory Assays

This group will address thresholds for seropositivity, standardization, control panels, methods and tools for processing, considerations for improved assays for certain antigens (cross reactivity, antibody kinetics, etc.).

- Ensuring quality standards
- Establishing thresholds for seropositivity
- Assay validation across antigens
- Standardization across countries to ensure comparability
- Access to positive and negative control panels

- Improved assays for selected antigens (addressing cross reactivity, antibody kinetics, etc.)

Seroepidemiology

This group will look at epidemiologic considerations such as study design, sampling strategies, handling different target populations, and ways to address biases.

- Survey design for multiplexed serosurveillance
- Specimen sampling strategies (residual, cross-sectional, longitudinal)
- Target populations by demographic characteristics across antigens
- Sample size issues for each antigen
- Addressing potential biases

Data Analysis

This group will assess analytical approaches to seroprevalence data, combining modeling with seroprevalence data, approaches to data triangulation, and tools to support in-country analysis.

- Standardized analytical approaches to analyzing seroprevalence data across antigens
- Combining modeling with seroprevalence data
- Approaches to data triangulation
- Data sharing and platforms for collaborations
- Tools for supporting in-country analysis

Use Case Scenarios

This group will look at use cases for serosurveillance across antigens in terms of how serology informs programmatic decision making, building off epidemiological scenarios for integrated serosurveillance.

- Use cases across antigens for programmatic decision making
- Pan-national issues
- Pathogen priority list
- PAHO's epidemiological scenarios for integrated serosurveillance

Sustainable Implementation

This group is focused on country issues related to implementation, policy implications and sustainability of serosurveillance systems. This includes dissemination and translation of results to policymakers, and challenges in establishing integrated serosurveillance systems.

- Dissemination and translation of serosurvey results to policy makers
- Training and resource needs
- Challenges and opportunities in establishing sustainable, integrated serosurveillance systems
    - PAHO experience: political engagement, technical involvement, innovative planning
    - Regional laboratory networks
    - South-south collaboration

Group Members *Participants attending via Zoom

	Sustainable Implementation	Lab Assay	Seroepidemiology
Leads	Martha Idali Saboya-Diaz	Christopher Heaney	Eunice Wangeci Kagucia
	Fiona van der Klis	Diana Martin	Andrew Azman*
	Sammy Njenga	Gerco den Hartog	Sonia Hegde
	Amy Wesolowski	Rosemary Rochford	Nicole Walter
Notetaker	Julia Poje	Lindsay Avolio	Shahjahan Ali
Members	Alison Jones	Bharat Parekh*	Andrea Carcelen
	Amy Winter	Catriona Patterson	Arthur Menezes
	Ard van Dongen	Daniel T. Leung	Ben Arnold
	Bryan Grenfell*	Fiona Angrisano*	Cheryl Cohen*
	Emily Gurley	James Nyagwange*	Christopher Drakeley
	Hellen Gelband	Jill Ray	Derek Cummings
	Gretchen M Cooley*	Kevin Tetteh	Eric Rogier
	Ibrahim Bob Swaray	Kokou Nouwame	Godfrey Bigogo
	Jonathan Jasson Mandolo	Kondwani Jambo	Henrik Salje
	Juliet Bryant*	Makhtar Niang	Isaac Ssewanyan
	Leanne Robinson*	Mattie Cassaday	Isabel Rodriguez
	Upendo Lisa Mseka	Nora Pisanic	Ivo Mueller*
	Mairead Whelan	Ramee Saleh	Jordan Tappero
	Manoj Vasant Murhekar	Rhea Longley*	Kirsten E. Wiens*
	May Chu	Richelle Charles	Kristen Aiemjoy
	Megan O'Driscoll	Ross Kedl	Kristin Savage
	Melissa Richard-Greenblatt*	Samantha Dolan	Shazia Ruybal*
	Yannik Roell	Sophie Berube	Thebora Sultane
		Taufiqur Rahman	Thomas Jaenisch
		Wilhelmina Strasheim	William Moss

	Supply Chain	Data Analysis	Use Cases
Leads	May Chu	Saki Takahashi	Thomas Jaenisch
	Daniel T Leung	Amy Winter	Kondwani Jambo
	Richelle Charles	Henrik Salje	Emily Gurley
		Isabel Rodriguez	Christopher Drakeley
Notetaker	Alex Kong	Mattie Cassaday	Natalya Kostandova
Members	Alexandra Morel	Andrew Azman*	Alison Jones
	Aloysius Bingi	Ben Arnold	Cheryl Cohen*
	Ard van Dongen	Bryan Grenfell*	Diana Martin
	Catriona Patterson	Christopher Heaney	Eric Rogier
	Bharat Parekh*	Derek Cummings	Eunice Wangeci Kagucia
	Blake Puneky	Gerco den Hertog	Isaac Ssewanyan
	Eddie Alberado	Godfrey Bigogo	Jordan Tappero
	Fiona Angrisano*	Gretchen M Cooley*	Juliet Bryant*
	Fiona van der Klis	Ibrahim Bob Swaray	Kristen Aiemjoy
	Hellen Gelband	Kirsten E. Wiens*	Leanne Robinson*
	Jill Ray	Kristin Savage	Mairead Whelan
	Jonathan Jasson Mandolo	Manoj Vasant Murhekar	Makhtar Niang
	Julia Poje	Megan O'Driscoll	Martha Idali Saboya-Diaz
	Kevin Tetteh	Nicole Wolter	Melissa Richard-Greenblatt*
	Kokou Nouwame	Ross Kedl	Sammy Njenga
	Ramee Saleh	Sophie Berube	Shazia Ruybal*
	Rhea Longley*	Taufiqur Rahman Bhuiyan	Sonia Hegde
	Rosemary Rochford		Upendo Lisa Mseka
	Samantha Dolan		Yannik Roell
	Shahjahan Ali		
	Thebora Sultane		
	Timothy Meehan		
	Wilhelmina Strasheim		

Agenda

Objectives

Discuss experience with establishing integrated multiplexed serosurveillance systems
Discuss challenges in establishing integrated multiplexed serosurveillance systems
Discuss opportunities to expand integrated multiplexed serosurveillance systems
Identify research needs for integrated multiplexed serosurveillance systems
Establish community of practice for integrated multiplexed serosurveillance systems

Day 1: Discussing Solutions & Approaches

Tuesday, March 7, 2023

8:30 AM – 9:00 AM **Check In**
Bloomberg School of Public Health, East Monument Street entrance
Meet at the East Monument Street entrance to check-in, receive your badge, and locate the meeting room.

9:00 AM – 10:00 AM **Welcome Address**
Feinstone Hall | Zoom Link – Meeting ID 91692618844 (Passcode 570946)
Organizers will give a welcome address, followed by introductions and setting the objectives of the workshop.
Dr. William Moss, Johns Hopkins University, *Welcome & Goals*
Dr. May Chu, University of Colorado, *Center for Global Health Consortium*
Dr. Eunice Kagucia, Kenya Medical Research Institute (KEMRI), *Country Perspective on Setting up Integrated Serosurveillance*
Dr. Marc Bulterys, Bill and Melinda Gates Foundation, *Vision for Integrated Serosurveillance*
Ambassador Dr. John Nkengasong, U.S. Department of State
Dr. Andrea Carcelén, John Hopkins University, *Meeting Overview & Objectives*

10:00 AM – 10:30 AM **Break & move to working group meeting rooms**

10:30 AM – 12:30 PM **Morning Working Session - Part 1**
Seroepidemiology - Room W2017 | Zoom Meeting 94531017769 (Passcode 171471)
Lab Assay - Room E9519 | Zoom Meeting 92491075304 (Passcode 113842)
Sustainable Implementation - Room W3031 | Zoom Meeting 94113538479 (Passcode 291028)
Working groups will meet to review the key challenges identified in their thematic areas by the co-leads and make any additions. Attendees will discuss how groups have addressed these challenges in the past and describe the context in which they were used. Attendees will also brainstorm new potential alternative solutions that address these challenges. The

rapporteur will take minutes of the discussion, particularly the lessons learned and solutions, and should keep a list of the resources named during this session. Discussion will be synthesized into approaches and solutions to challenges using a template.

12:30 PM – 1:30 PM **Lunch Break**
Feinstone Hall

1:30 PM – 3:30 PM **Afternoon Working Session - Part 1**
Supply Chain - Room E9519 | Zoom Meeting 97270138502 (Passcode 491863)
Data Analysis - Room W3031 | Zoom Meeting 97170883881 (Passcode 458858)
Use Case Scenarios - Room W2017 | Zoom Meeting 94107817980 (Passcode 026280)
During this session, individuals will join a different working group. Working groups will discuss the same as above.

3:30 PM – 3:45 PM **Break & return to main room**

3:45 PM – 5:00 PM **Working Group Reports**
Feinstone Hall | Zoom Link – Meeting ID 91692618844 (Passcode 570946)
Working groups will present on progress, challenges, overlap with other working groups, and key takeaways from the day (10 min each).

5:30 PM **Social Event (optional)**
Ministry of Brewing
1900 East Lombard Street
Baltimore, MD 21231

Day 2: Developing a Plan

Wednesday, March 8, 2023

8:30 AM – 9:00 AM **Check-In & Coffee**

Feinstone Hall

Arrive at Bloomberg School of Public Health for coffee and muffins. Badges provided on the first day should permit building entry for both days.

9:00 AM – 10:00 AM **Welcome & Instruction**

Feinstone Hall | Zoom Link – Meeting ID 91692618844 (Passcode 570946)

After an overview of the previous day, key objectives for the second day will be outlined.

10:00 AM – 10:15 AM **Group Photo**

Wall of Wonder

10:15-10:30 **Break & move to working group rooms**

10:30 AM – 12:30 PM **Morning Working Session - Part 2**

Seroepidemiology - Room W2017 | Zoom Meeting 94531017769 (Passcode 171471)
Lab Assay - Room E9519 | Zoom Meeting 92491075304 (Passcode 113842)
Sustainable Implementation - Room W3031 | Zoom Meeting 94113538479 (Passcode 291028)

Working groups will meet to review the challenges and potential solutions identified during day 1. The goal is to develop an agenda for next steps to move multiplex serosurveillance forward. They will also prepare the summaries of challenges, solutions, and gaps to report to the larger group in the wrap-up session. Specific objectives during this session will be to:

1. Review list of potential new solutions defined during first working group session and identify whether these are short-term or long-term solutions based on their feasibility
2. Evaluate the challenges and prioritize approaches currently being used and proposed solutions to determine the next steps to address these challenges. This could include scaling up approaches already being used, implementing a proposed solution, or defining additional needs.
   Conceptualize next steps as an advocacy pitch or setting a research agenda.
3. Review list of approaches described during first working group session and describe their limitations. *(If time allows)*

12:30 PM – 1:30 PM **Lunch Break**

Feinstone Hall

1:30 PM – 3:30 PM **Afternoon Working Session - Part 2**

Supply Chain - Room E9519 | Zoom Meeting 97270138502 (Passcode 491863)
Data Analysis - Room W3031 | Zoom Meeting 97170883881 (Passcode 458858)
Use Case Scenarios - Room W2017 | Zoom Meeting 94107817980 (Passcode 26280)
During this session, individuals will join their second working group. Working groups will discuss the same as above.

3:30 PM – 3:45 PM **Break & return to main room**

3:45 PM – 4:45 PM **Working Group Reports**

Feinstone Hall | Zoom Link - Meeting ID 91692618844 (Passcode 570946)
Each working group will take 10 minutes to report out on their findings and solutions from the summit and identify key next steps.

4:45 PM – 5:00 PM **Closing Remarks**

Feinstone Hall | Zoom Link - Meeting ID 91692618844 (Passcode 570946)

Appendix 2. Next steps categories identified by working group

Categories	Use Case Scenarios	Supply Chain	Seroepidemiology	Laboratory Assay	Data Analytics	Sustainable Implementation
Resource Development and Information Sharing	Refine use cases through, e.g., further consideration of use case study designs	Create an information-sharing platform including a central repository of antigens and standards, best practices, and a supply chain "playbook" (e.g., cold chain and labeling requirements, substitutable reagents, etc.) with the ability to share information on specific countries Develop a tool that can project need and costs of materials for MBA	Establish documentation of existing repositories Optimize and share sample size tools and estimators Borrow and develop data harmonization and standards from other fields to make data sharing easier Develop and pilot protocols that allow for adaptive strategies and ethical amendments	Develop a platform (e.g., GitHub) and laboratory network to share protocols, best practices, materials, and ideas, and to provide additional technical support following trainings Develop a repository for common quality control targets, protocols, scripts/apps, and checklists	Develop standardized data, data analytic packages, and procedures (e.g., approaches that can be used to establish cut-offs) Create centralized repositories of information and sharing of analytic methods/pipelines, standards, controls, and data Establish data analytics hub to support development of data analysis materials	Create a repository of existing resources that demonstrate and explain serosurveillance including use cases, evidence, and subsequent actions in the form of both policy briefs and technical documents Generate an evidence base of case studies where countries have used serosurveillance and acted upon results Develop SOPs and training resources
Capacity Building and Training		Develop supply chain forecasting capacity to anticipate shortages at a researcher and local government level	Learn from the clinical trials field with regard to adaptive strategies	Develop regional hubs and/or train-the-trainer networks to perform MBAs and provide MAGPIX machine support		Explore on-site training, online initiatives, and train-the-trainer initiatives to build laboratory capacity Develop capacity of countries to produce or procure their own beads

Research	Identify additional examples of pathogens and the most compelling use for each use case	Determine the most appropriate instrument for each setting based on capabilities (e.g., which countries could use and maintain MAGPIX IVD instruments) Explore alternative technologies to maintain the cold chain and new approaches that do not require cold chain maintenance	Identify optimal frequency for serosurveys based on multiple pathogens Validate convenience samples with representative samples to quantify biases	Establish a working group to identify, develop, and validate appropriate antigen and positive/negative controls	Identify appropriate controls Catalog quantitative models by user-friendliness and complexity Catalog antigens by how interpretable/well-characterized they are and develop standard curves Explore resources for data analysis, including computer simulations and methods to model quantitative titer data, and compare approaches across pathogens	Establish target product profiles based on public health needs

Building and Strengthening Partnerships		Investigate possibilities of partnerships to: 1. License the MAGPIX Research Use Only instrument to another manufacturer 2. Develop and commercially manufacture a "common panel" 3. Procure all necessary materials except antigen-coupled beads through a procurement service 4. Allow for local manufacture or provision of materials typically provided by foreign manufacturers only		Involve disease experts in assay and SOP development early on Explore commercial development of panels with pre-coupled beads Engage with the UK National Institute for Biological Standards and Control for discussions on standards	Perform quality control and data standardization within and between labs	Leverage and integrate with regional networks including exploration of opportunities to leverage existing technologies and expertise at other institutions to meet needs Achieve commercial-caliber levels of resources for implementation Create networks to share resources and use case successes and failures, and to develop cross-laboratory collaboration

Advocacy and Political Buy-In		Explore standardized approval processes for importation of key products	Create a taxonomy of paired pathogen-specific antigens with scientific, policy-relevant questions, and study design	Involve governmental agencies in training initiatives	Develop analytical and visualization pipelines	Foster higher-level regional and international support to provide clear guidance on recommendations for implementation/use Identify ways that integrated serosurveillance can complement existing systems and establish good practices and use cases for engagement with decision makers Identify and communicate benefits to community participants

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