Salmonella Paratyphi A vaccine: Introduction

Adwoa Bentsi-Enchill

WHO HQ, Dept of Immunization, Vaccines & Biologicals

PDVAC meeting

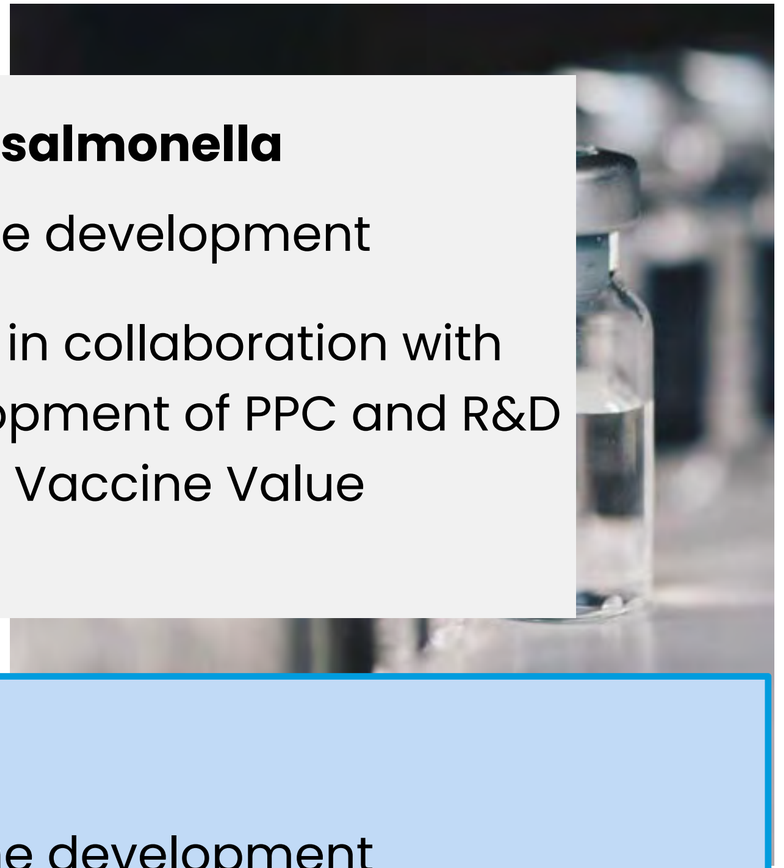
06 December 2022

Overview of WHO work on salmonella vaccines

Typhoid

Status: **licensed vaccines + WHO SAGE recommendation (2017)**

- Routine immunization: single IM dose at 9 mths or 2nd yr of life
- 2 typhoid conjugate vaccines (TCVs) prequalified; Bharat Biotech (Vi-TT) and Biological E (Vi-CRM_{197})
- Active pipeline of additional candidates
- SAGE evidence review planned (in ~2 years); incl. duration of protection and need for booster(s)



Non-typhoidal salmonella

- Status: Vaccine development
- Work ongoing in collaboration with IVI: incl. development of PPC and R&D Roadmap, Full Vaccine Value Assessment

Paratyphoid

- Status: Vaccine development
- Value proposition, use case and demand
- Bivalent typhoid/paratyphoid as a possible test case for Evidence Considerations for Vaccine Policy (ECVP)

Public health burden of typhoid & paratyphoid fever (Enteric fever)

- Acute non-specific febrile illness (clinically indistinguishable) caused by
  - *Salmonella enterica* serovar Typhi (*S.* Typhi)
  - *S.* Paratyphi (**serogroup A** > B > C)
- Fecal-oral transmission
- Treatment: appropriate antibiotics

Typhoid

- ~11-21 million cases/year
- ~128,000 to 161,000 deaths/year
- peak incidence in 5–19 yrs of age

Paratyphoid (mainly in S Asia)

- ~6 million cases/year
- ~54,000 deaths/year

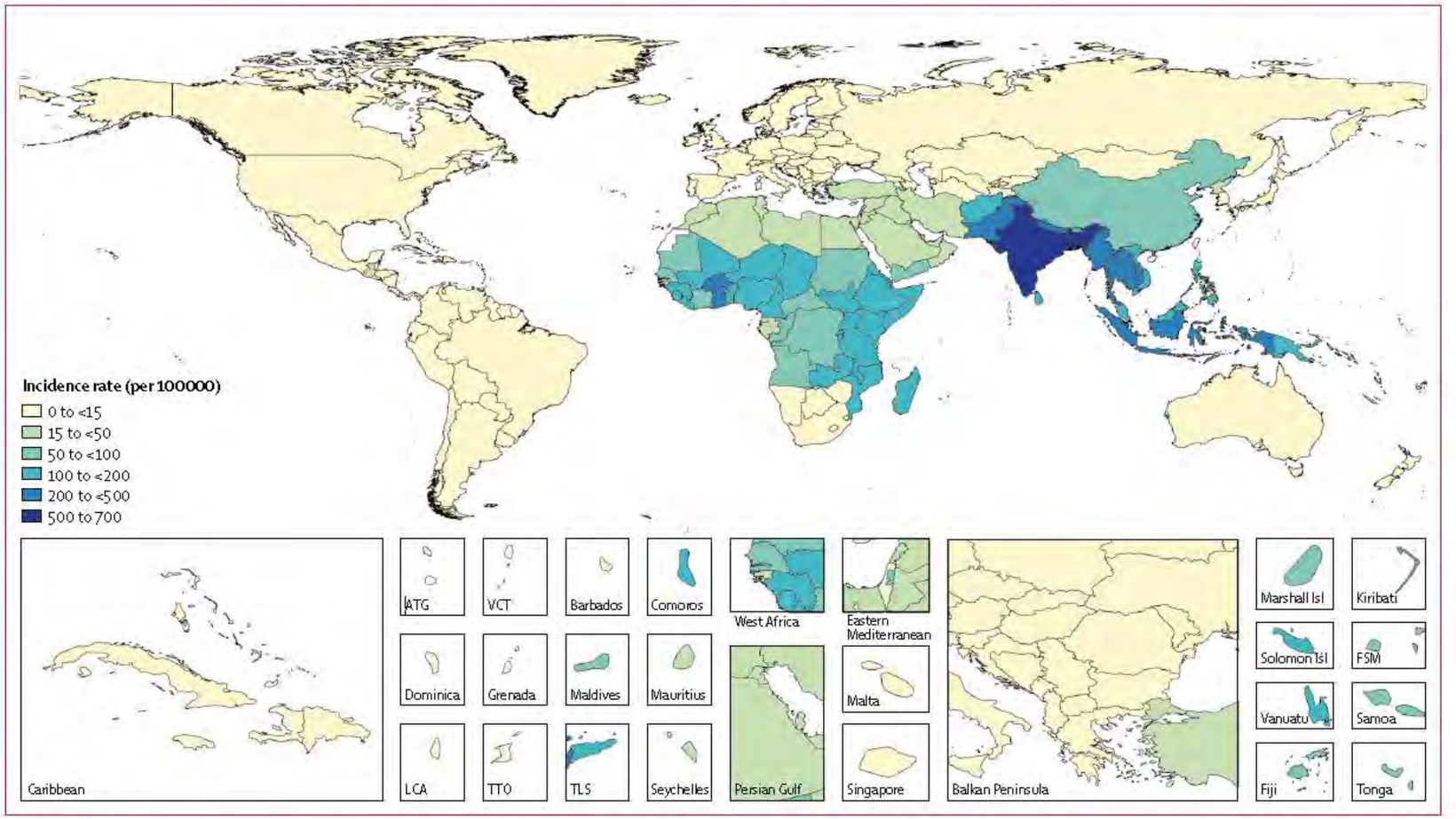


Figure 1: **Incidence rates (per 100 000) of typhoid and paratyphoid fevers, by country, in 2017**
Unfilled locations are those for which GBD does not produce estimates. The inset maps detail smaller locations. ATG=Antigua and Barbuda. FSM=Federated States of Micronesia. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. Isl=Islands. LCA=Saint Lucia. TLS=Timor-Leste. TTO=Trinidad and Tobago. VCT=Saint Vincent and the Grenadines.

GBD 2017 Typhoid and Paratyphoid Collaborators. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis 2019; 19: 369–81

Session outline

Presentations

- Status of paratyphoid vaccine pipeline and considerations for combination vaccine strategies
- Role of CHIM for licensure and policy

Questions to PDVAC

1. **Is there adequate data on strategies for a bivalent typhoid/paratyphoid vaccine to define a way forward for accelerating vaccine development?**
   - If not, what are the gaps and what data are required?
   - Is the framework for Evidence Considerations for Vaccine Policy (ECVP) an appropriate tool for the bivalent vaccine?
2. **What evidence will be required to support CHIM data for the regulatory and policy pathways for a bivalent typhoid/paratyphoid vaccine?**

Human Challenge: paratyphoid

Andrew J Pollard

Typhoid and Paratyphoid fever

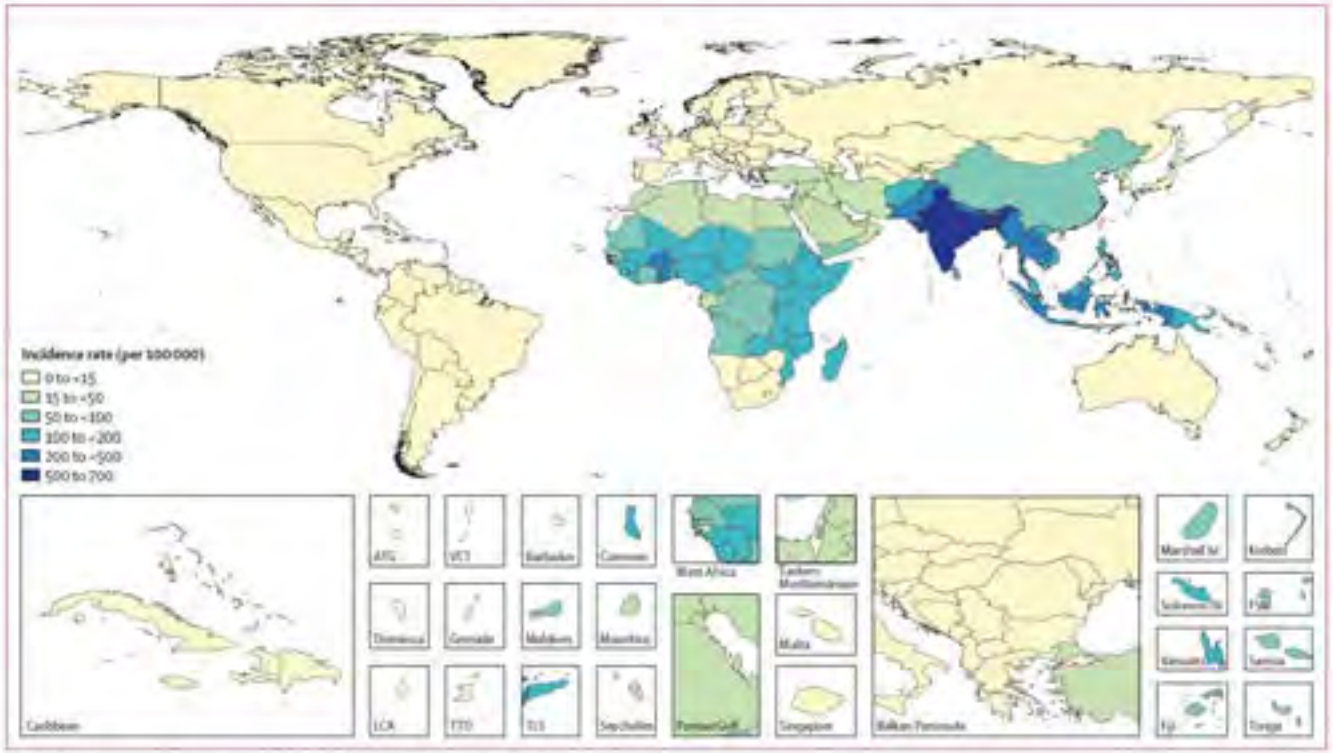


Figure 1: Incidence rates (per 100 000) of typhoid and paratyphoid fevers, by country, in 2017
Unfilled locations are those for which GBD does not produce estimates. The inset maps detail smaller locations. ATG=Antigua and Barbuda. FSM=Federated States of Micronesia. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. Isl=Islands. LCA=Saint Lucia. TLS=Timor-Leste. TTO=Trinidad and Tobago. VCT=Saint Vincent and the Grenadines.

IHME

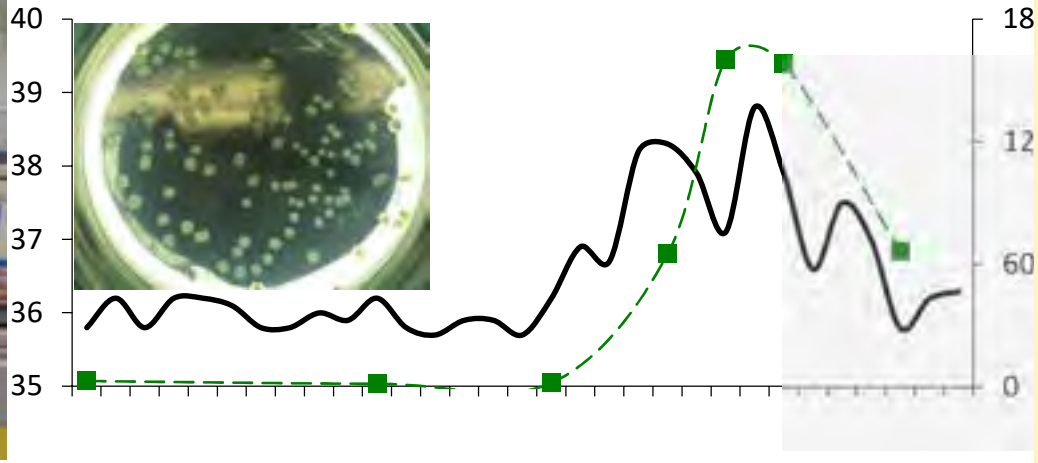
Human Challenge Model

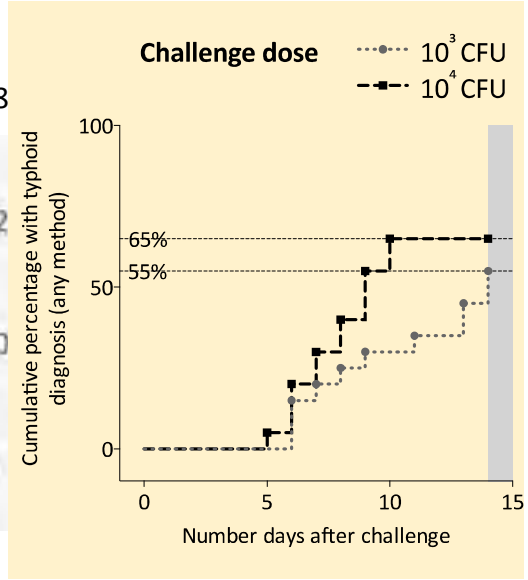
World Health Organization

FINAL
ENGLISH ONLY

Guidelines on the quality, safety and efficacy of typhoid conjugate vaccines:

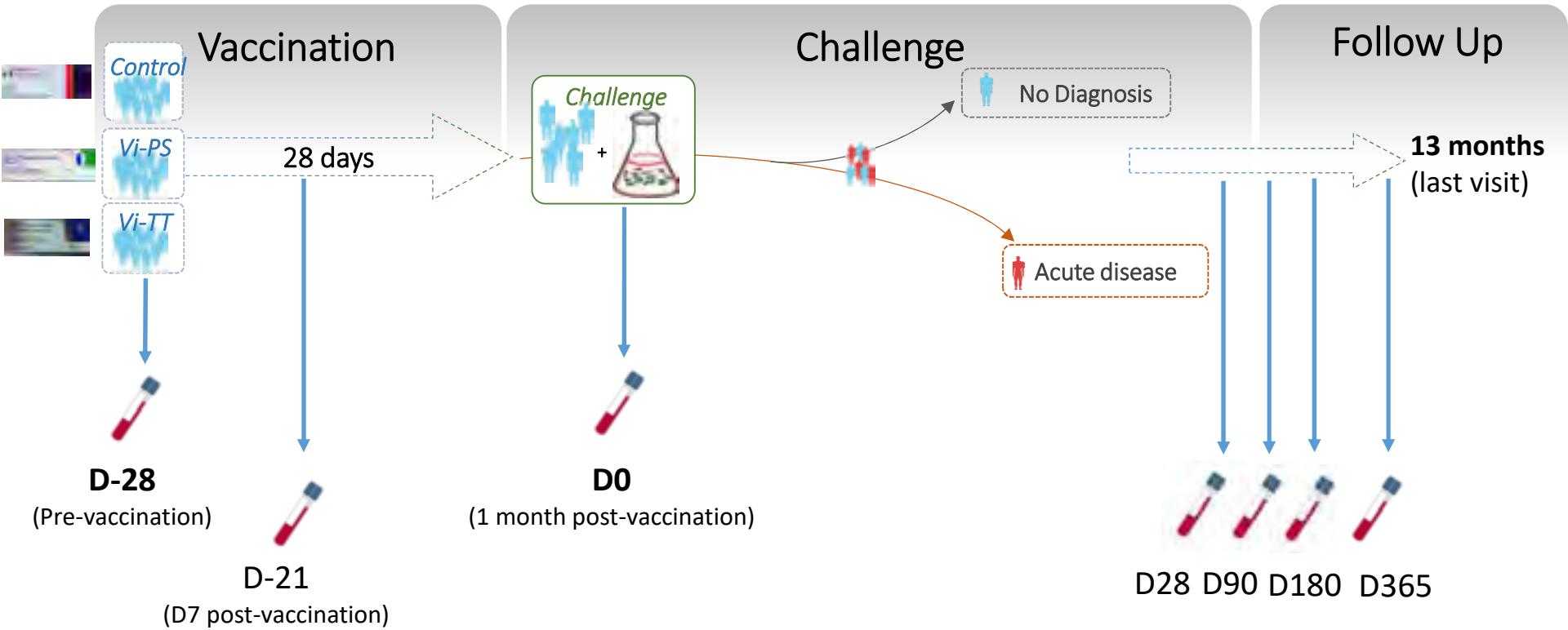
Nevertheless, successful typhoid challenge studies conducted in healthy adults using an appropriate and validated model (i.e. one in which some protective efficacy of unconjugated Vi vaccines is detectable) could provide considerable supporting evidence of the efficacy of a Vi conjugate vaccine. Human challenge studies may also provide at least limited information on the relationship between the immune response and various efficacy parameters. If, in consultation with


40
39
38
37
36
35
18
12
60
0


Challenge dose
10^3 CFU
10^4 CFU
100
50
0
65%
55%
Cumulative percentage with typhoid diagnosis (any method)
0
5
10
15
Number days after challenge

Vaccines Against *Salmonella* Typhi

Oxford typhoid fever
Controlled Human Infection Model (CHIM)



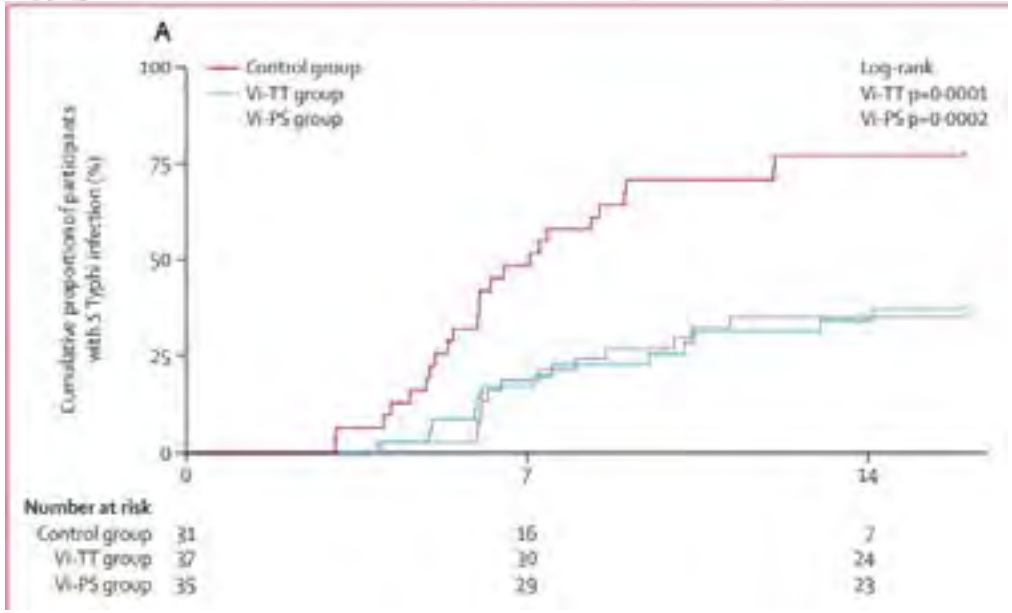
Typhoid Diagnosis **defined as fever ≥38°C for >12 hours or positive blood culture**

Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of *Salmonella* Typhi: a randomised controlled, phase 2b trial

Celine Jin, Malick M Gibani, Mitty Moore, Helena B Jones, Elizabeth Jones, James Meiring, Victoria Hill, Jonathan Cooper, Anna Nellyakina, Simon A Kerridge, Jennifer Hill, Stefanie Thanasekaran-Amaya, Christopher J Blohmke, Ly-Mee Yu, Robin Angus, Andrew J Pollard

Summary

Background *Salmonella enterica* serovar Typhi (*S* Typhi) is responsible for an estimated 20 million infections and 200 000 deaths each year in resource poor regions of the world. Capsular Vi-polysaccharide-protein conjugate vaccines (Vi-conjugate vaccines) are immunogenic and can be used from infancy but there are no efficacy data for the leading candidate vaccine being considered for widespread use. To address this knowledge gap, we assessed the efficacy of a Vi-tetanus toxoid conjugate vaccine using an established human infection model of *S* Typhi.



Vaccine use

WHO SAGE

Typhoid vaccines

SAGE noted the continued high burden of typhoid fever and the alarming increase in antimicrobial resistance of *Salmonella* Typhi (*S.* Typhi) in low- and middle-income countries. SAGE re-emphasized the importance of programmatic use of typhoid vaccines for controlling endemic disease. Following review of the available data, SAGE recommended the introduction of typhoid conjugate vaccine(TCV) for infants and children over 6 months of age as a single dose in typhoid endemic countries. Introduction of TCV should first be prioritized to countries with the highest burden of disease or a high burden of antimicrobial resistant *S.* Typhi. SAGE also recommended catch-up vaccination wherever feasible, with priority for catch-up in the youngest age groups (up to 15 years of age), depending on local epidemiology.

Typhoid vaccination is recommended in response to confirmed outbreaks of typhoid fever. Typhoid vaccination may be considered in humanitarian emergencies depending on risk assessment in the local setting.

REGULATION

WHO prequalification

POLICY

WHO SAGE recommendations

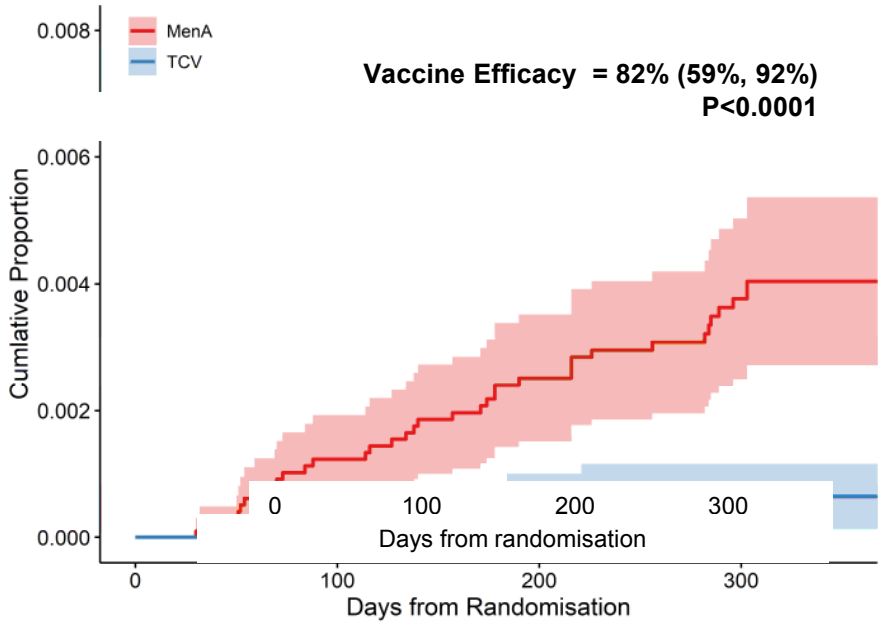
Dollars

Gavi funding

WHO prequalification


ORIGINAL ARTICLE
Setopati
Society
Trial of 'game-changer' typhoid vaccine in Nepal over 81% effective
Nepalis not made guinea pigs for the trial
Setopati
The news of success of the first field trial of a new typhoid
of a Typhoid Conjugate
alawian Children
fever
80% reduction in typhoid in children

Interim Vaccine efficacy



Shakya et al NEJM 2019

2 year efficacy

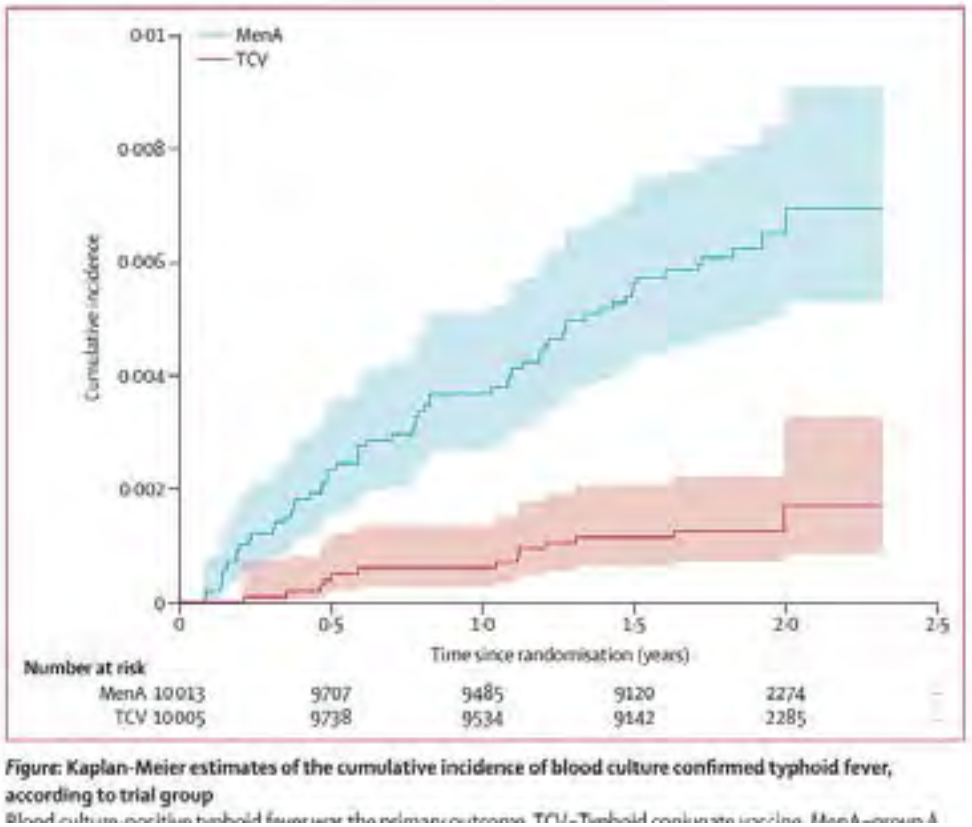


Figure: Kaplan-Meier estimates of the cumulative incidence of blood culture confirmed typhoid fever, according to trial group

Blood culture-positive typhoid fever was the primary outcome. TCV=Typhoid conjugate vaccine. MenA=group A

There were 13 cases of culture-positive typhoid fever in the TCV group and 62 cases in the MenA group,

protective efficacy of 79·0% (95% CI 61·9–88·5%; p<0·0001;

Shakya et al, Lancet Global Health

MORE Tuesday, 05 July 2022

The Himalayan

Kids Who Need It

HOME KATHMANDU NEPAL COVID-19 COVID CONNECT WORLD OPINION BUSINESS

Nepal

7.5 million children to be vaccinated against typhoid

By Rastriya Samachar Samiti
Published: 04:33 pm Apr 05, 2022

Ministry of Health and Population.

KATHMANDU, APRIL 5

Typhoid and Paratyphoid combined

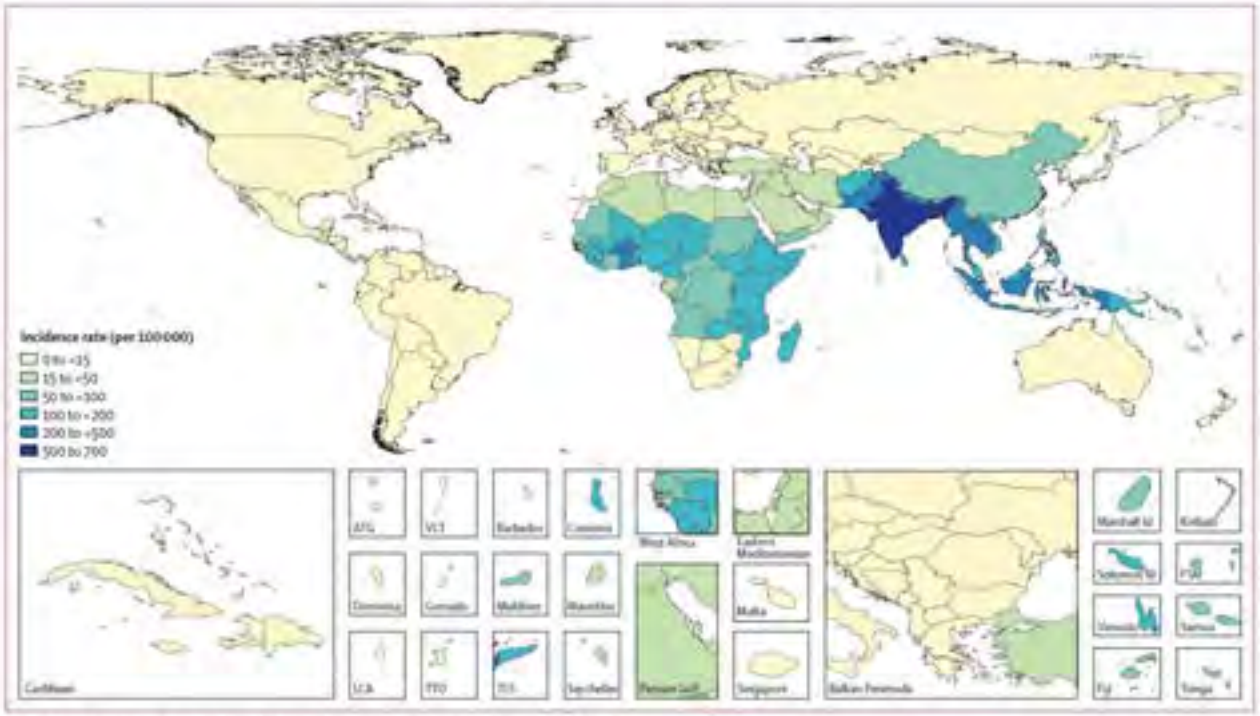
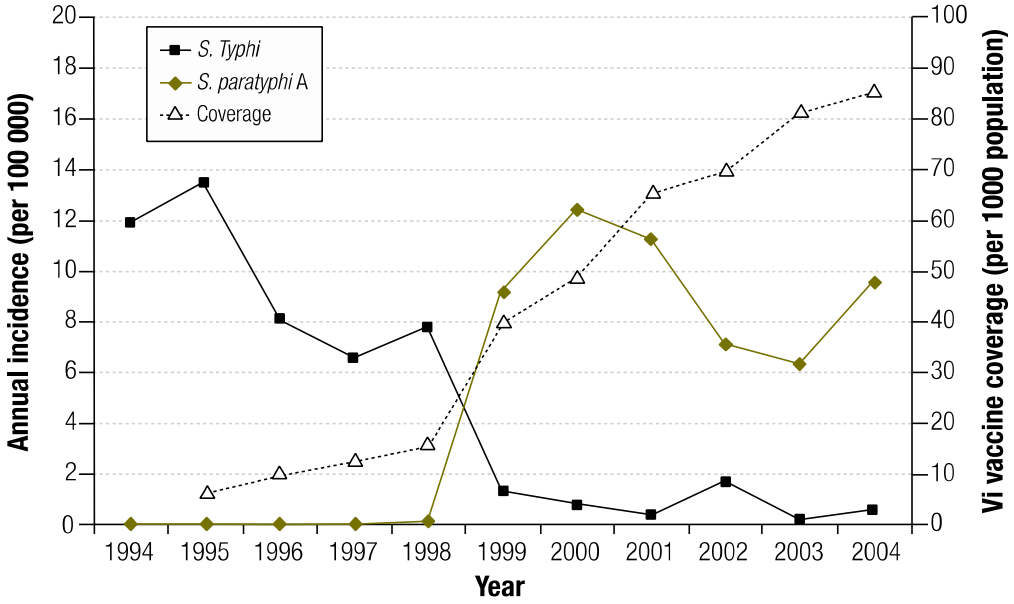


Figure 1: Incidence rates (per 100 000) of typhoid and paratyphoid fevers, by country, in 2017
Unfilled locations are those for which GBD does not produce estimates. The inset maps detail smaller locations. ATG=Antigua and Barbuda. FSM=Federated States of Micronesia. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. Is=Islands. LCA=Saint Lucia. TLS=Timor-Leste. TTO=Trinidad and Tobago. VCT=Saint Vincent and the Grenadines.

Paratyphoid

Fig. 2. **Estimated *Salmonella typhi* and *Salmonella paratyphi* A incidence with cumulative Vi polysaccharide immunization coverage in Guangxi province, China, 1994–2004**



Data from China's Notifiable Infectious Disease Reporting system, laboratory surveillance and outbreak investigation, Guangxi Centers for Disease Control and Prevention, Guangxi, China.

- Up to 50% of enteric fever in returning travelers
- Some areas of Asia, leading cause of enteric fever
- Most trial sites have lower rates ~10% of cases

Dong, B.D et al Bull World Health Organ , 2010 88(9), 689–96

Clinical Infectious Diseases
SUPPLEMENT ARTICLE

When it became apparent that typhoid casualties in France and Flanders were derived from 3 distinct infections (typhoid, paratyphoid A, and paratyphoid B), steps were also taken to prepare a new vaccine. Developed under David Harvey at the Royal Army Medical College, a combined TAB (typhoid plus paratyphoid A and B) vaccine was introduced in 1916. During the last 3 years of the war, >90% of British soldiers were inoculated

Postgraduate Medical Journal (February 1972) 48, 98–106.

CURRENT SURVEY

- TAB vaccine in travelers to Nepal was 95% protective against Typhi and 72-77% against Paratyphi (small numbers)

Assistant Professor of Pathology, Royal Army Medical College, Millbank, London, S.W.1

Schwartz et al, *Ann Int Med* 1990

Summary

The various preparations of TAB vaccines proposed in the past and/or available for use at present, together with the methods suggested for the vaccination procedures, are described.

The difficulties of interpreting the serologic diagnostic tests (Widal Test) and the possible dangers of vaccination during an epidemic (provocation typhoid) are discussed.

Introduction

The first attempts in this direction were made independently by Sir Almroth Wright (*Lancet*, 19 Sept. 1896) and by Pfeiffer & Kolle (*Deutsche Medicinische Wochenschrift*, 12 Nov. 1896) both of whom inoculated dead cultures of typhoid bacteria into man with no ill-effects and with the result that specific agglutinins and bactericidins made their appearance in the blood of the inoculated men.

In the years following these first attempts at active immunization of man against enteric fever, the

ponent consists of three str
while the *S. paratyphi* comp
strains each (HA6 and A1; HB3 and B1).

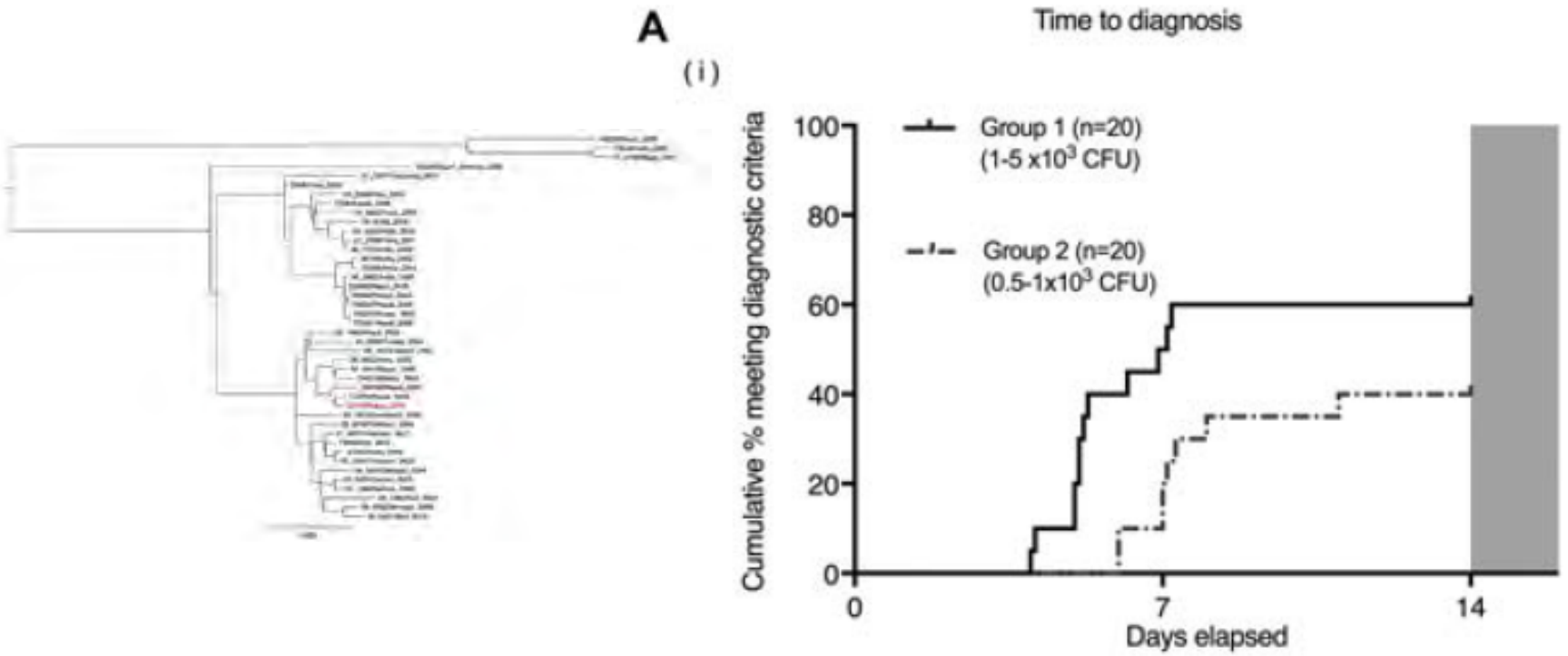
S. typhi Ty2 is the best known of these strains, and it is used on a world-wide scale in the preparation of typhoid vaccines everywhere—it was isolated originally from an epidemic of typhoid fever in Russia.

Each strain is cultured on solid trypsinized meat broth agar contained in special flasks (Roux bottles), and the resultant harvest of bacteria is killed by heating at 54°C for
scanned image of page 98
enol saline as a concentrated suspension until required for the production of the whole vaccine.

Vaccines are dispensed for use either in 0·5-ml ampoules or in 5-ml vials containing the following concentration of bacilli/ml: *S. typhi* (three strains ×660 millions); *S. paratyphi A* (two strains×750 millions); *S. paratyphi B* (two strains×750 millions); thus giving a total of 5000 million bacilli/ml preserved in 0·5% phenol saline.

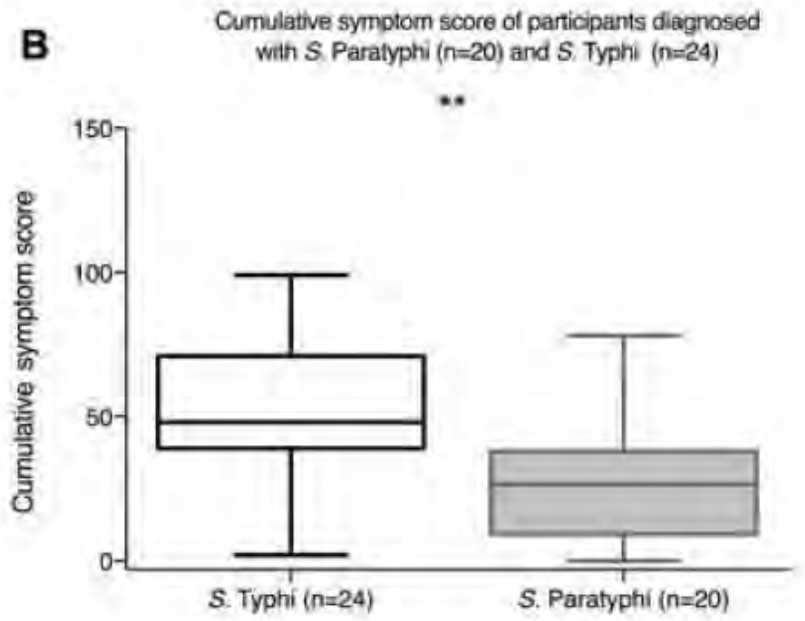
Paratyphoid attack rates in the human challenge model

Composite diagnosis



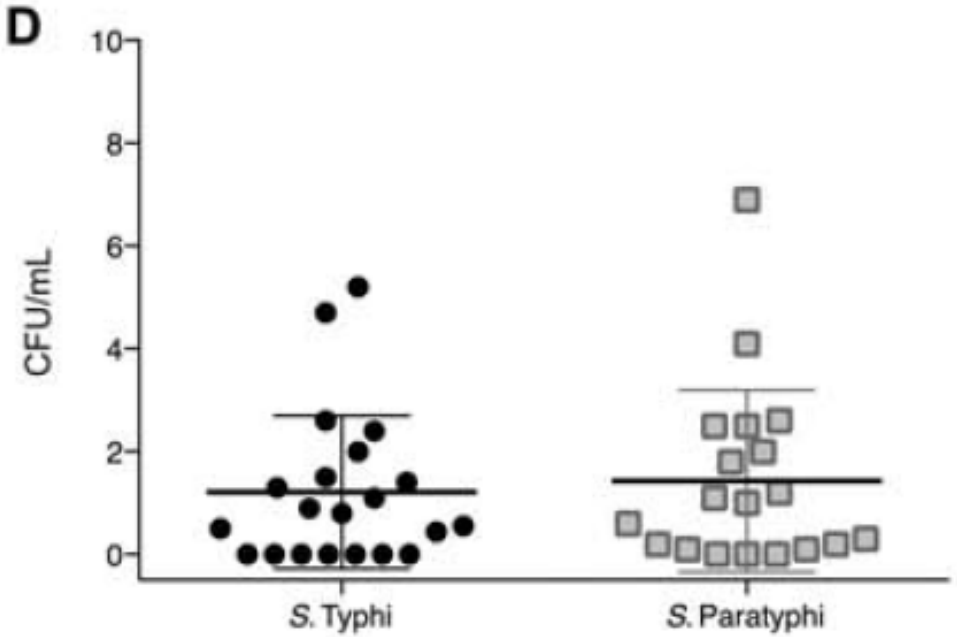
Dobinson et al, 2017

Less symptomatic than S Typhi

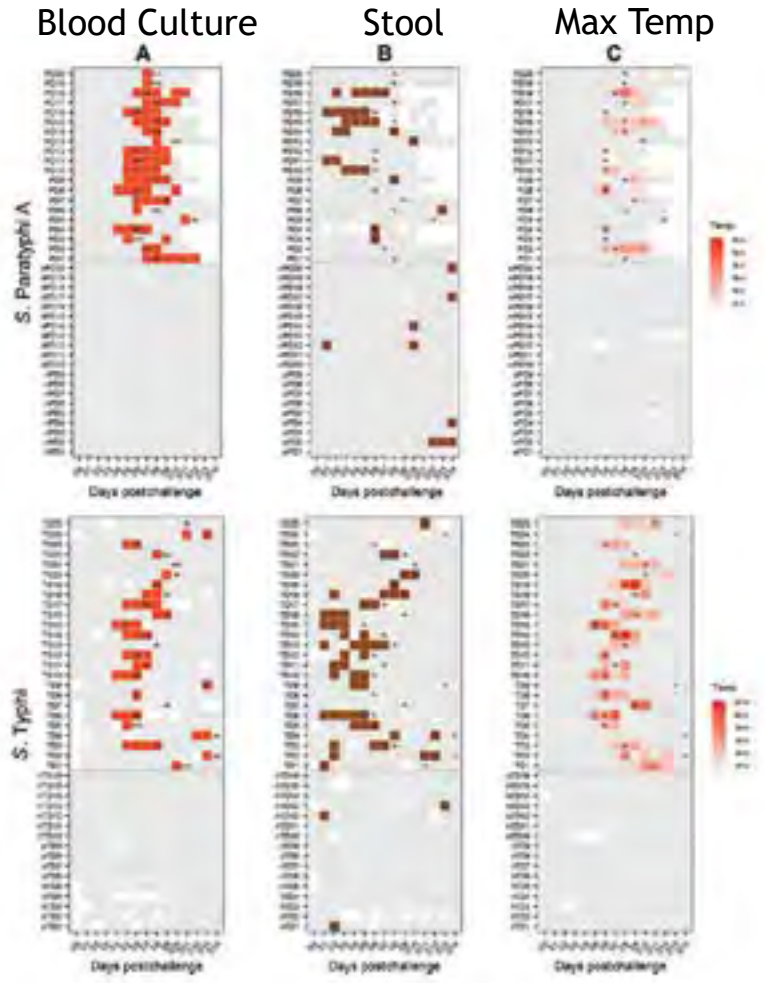


Dobinson et al, 2017

Similar level of bacteraemia S Typhi vs S Paratyphi CFU

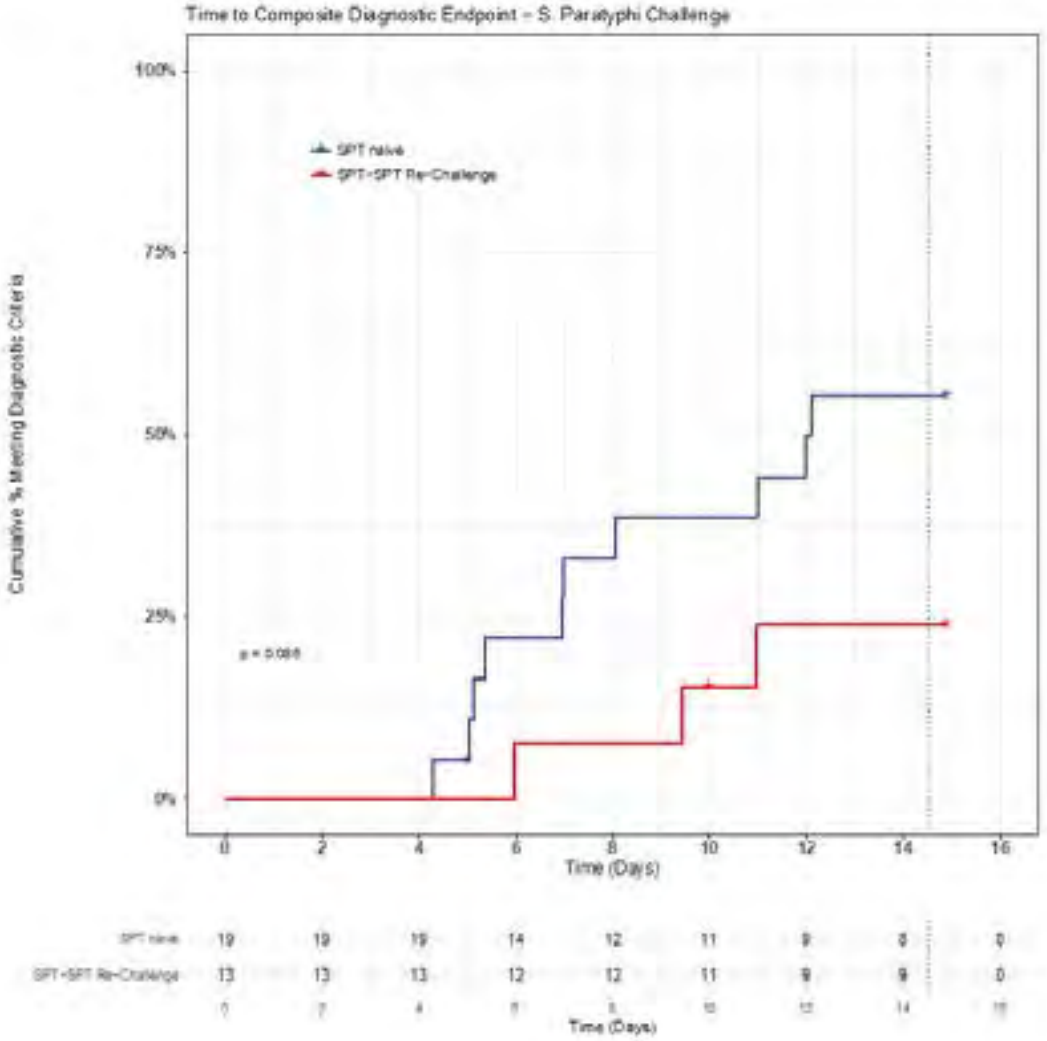


Dobinson et al, 2017

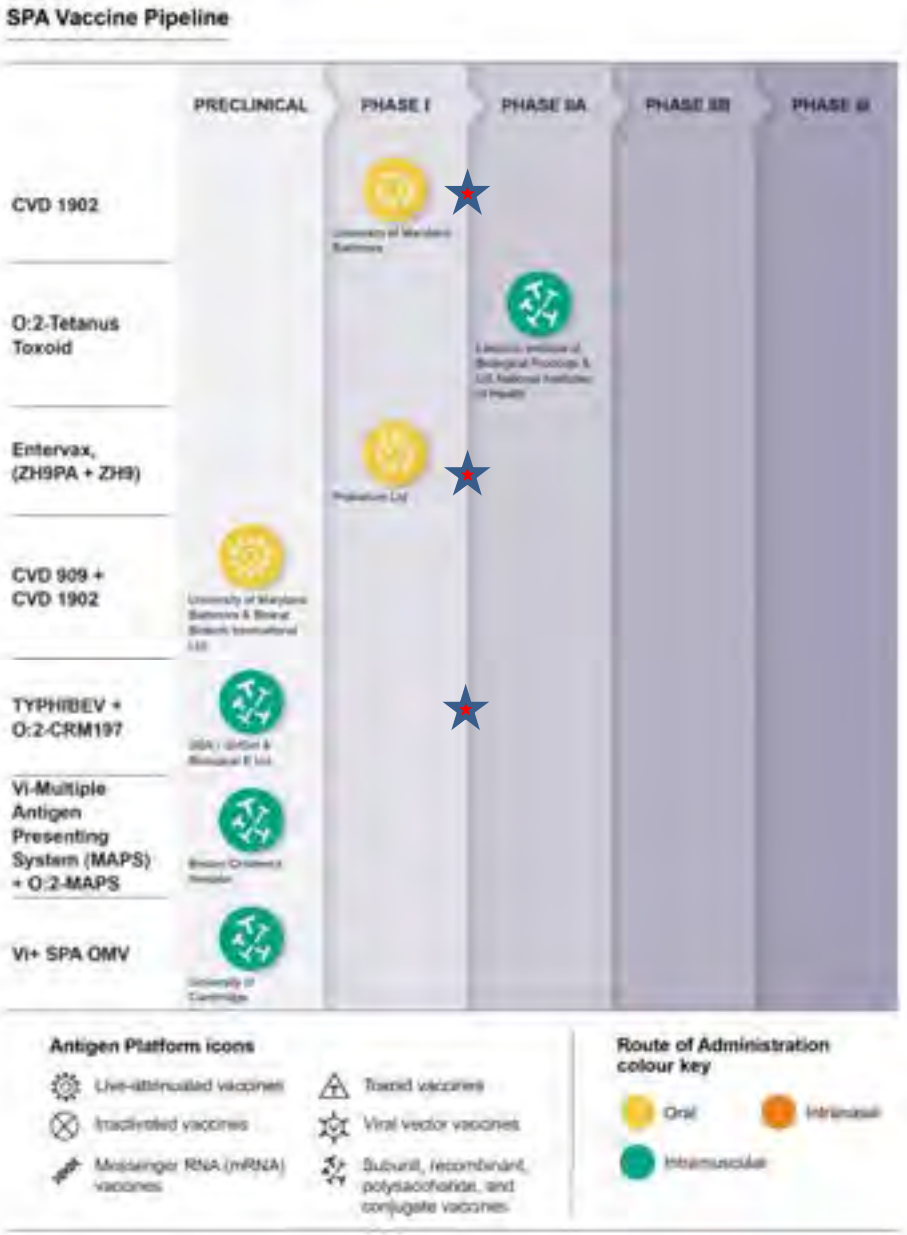


Dobinson et al, 2017

P vs
PP



Gibani et al



PDVAC, WHO

www.ovg.ox.ac.uk

Bivalent live oral vaccine to prevent enteric fever

CVD 909 – *S*. Typhi

- Derivative of wild type strain Ty2
- Δ*aroC*,Δ*aroD*, constitutive Vi expression
- Phase 1 & 2 trials completed

CVD 1902 – *S*. Paratyphi A

- Derivative of wild type strain ATCC 9150
- Δ*guaBA* – impedes guanine nucleotide biosynthesis (Wang J et al. Infect Immun 2001)
- Δ*clpXP* – encodes a multifunctional chaperone ATPase with regulatory properties (H Matsui et al 2003)
- Phase 1 completed

BBC AJP Home News Sport Weather iPlayer Sounds

NEWS

Home | Cost of Living | War in Ukraine | Coronavirus | Climate | UK | World | Business | Politics | Tech

England | Local News | Regions | Oxford

Human challenge tests for Oxford paratyphoid vaccine

26 April

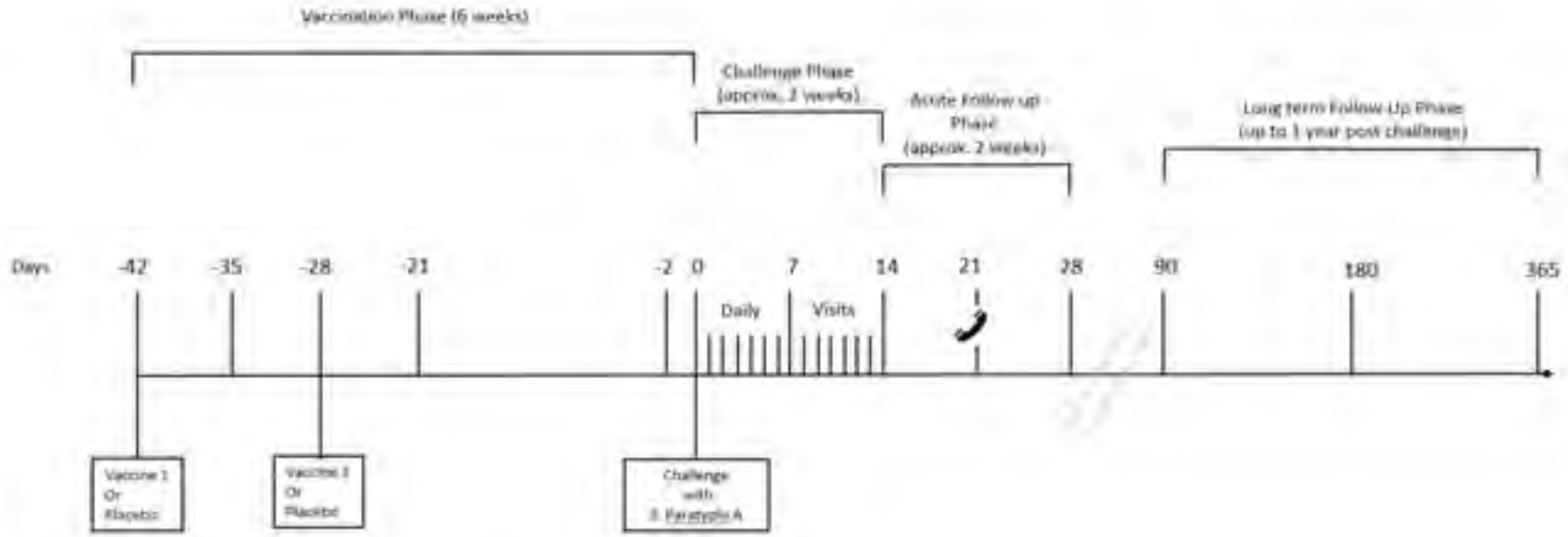
The first volunteers have received doses of vaccine, or a placebo, in Oxford

Volunteers are set to be infected with a highly contagious bacteria to test a new paratyphoid vaccine.

CVD1902 CHIM efficacy study

7.2. Figure 1: Visit Structure for whole study

Lines above timeline denote individual visits/study procedures



Licensure?

- Live attenuated vaccines
  - License on basis of VE in CHIM?
  - Field VE studies?
  - Plus field immunogenicity

- Conjugates
  - License on non-inferiority to licensed typhoid vaccines (on immunogenicity)
  - Added potential of paratyphoid component from field immunogencity plus evidence of protection in CHIM

- Paratyphoid efficacy trial….. Feasible?
  - 100,000-250,000
  - supporting data for paratyphoid component from CHIM

Acknowledgements

Oxford Vaccine Team

Trial Volunteers

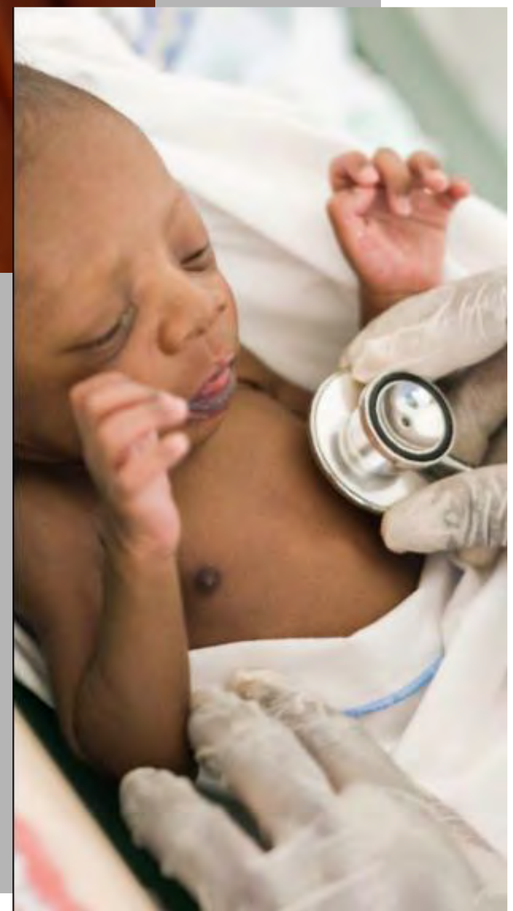
Trial site investigators and teams in UK, Nepal, Bangladesh and Malawi

Funders

NIHR | National Institute for Health Research

MRC
Wellcome
Bill & Melinda Gates Foundation

Update on progress towards immunization against Respiratory Syncytial Virus (RSV)



PDVAC meeting

6 December 2022

World Health Organization | IVB

RSV burden

Lower respiratory tract infections leading cause of child mortality worldwide

Estimated numbers of LRTI deaths-
0-27 days: 200,000 per year
1-59 months: 540,000 per year

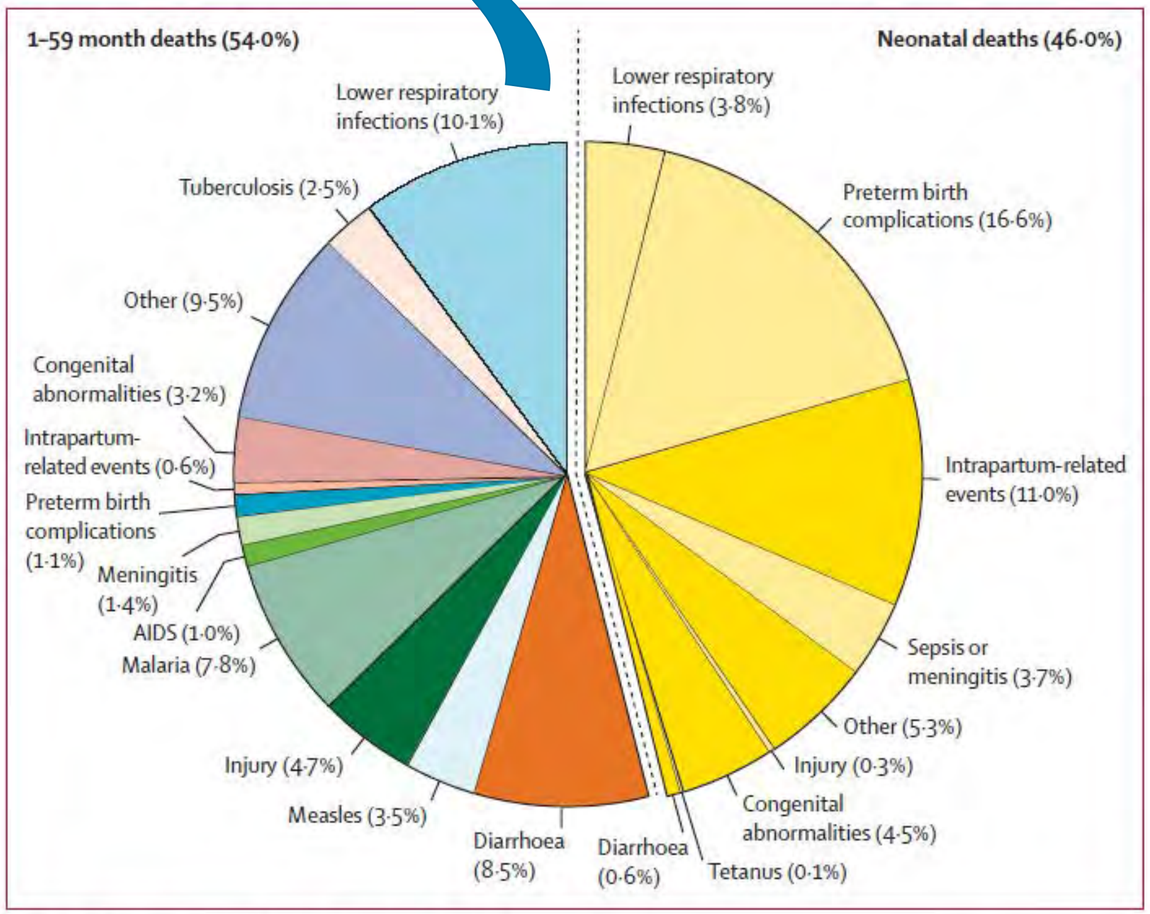
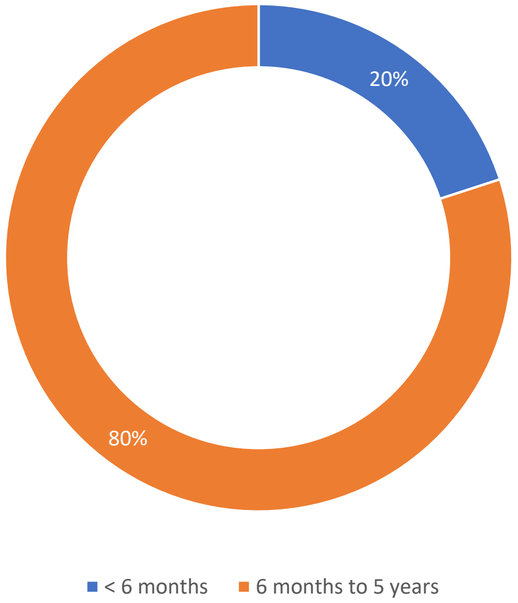


Figure 1: **Global causes of under-5 deaths in 2019**
Deaths of neonates (aged 0–27 days) are on the right-hand side and deaths of children aged 1–59 months are on the left-hand side.

From. Perin J, et al. Lancet Adolesc Child Health 2022. https://doi.org/10.1016/ S2352-4642(21)00311-4

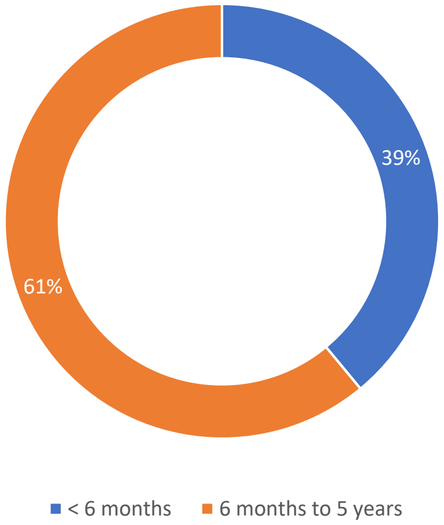
Considerable annual global morbidity and mortality

33,000,000 RSV-associated ALRI episodes in the community



Leading cause of ALRI in children

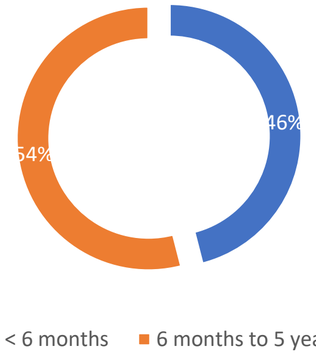
3,600,000 RSV-associated ALRI hospitalizations



Leading cause of pediatric hospitalization

Children under 6 months of age account for almost half of all RSV-associated deaths.

101,000 RSV-attributable deaths
229,000 RSV-associated deaths



2% of total global mortality burden

And 3.6% in children < 6 months old

Reference: *You Li, et al.* ***Lancet*** **2022; 399: 2047–64**.

Global disease burden of RSV in children under 5 years

- 4x as many deaths in community as in hospital in LICs

- 2.0% of total global deaths among children <5 years; 3.6% of deaths <6 months

From: *You Li, et al.* ***Lancet* 2022; 399: 2047–64**. *Slide courtesy of You Li and RESCEU*

New RSV burden Data: CHAMPS & Community Mortality

- **Findings from recently completed mortality surveillance studies reveal high unmeasured RSV mortality in community settings in LMICs, where infants might lack access to oxygen and supportive respiratory care**
- **RSV detected in 4–27% of all community deaths among infants <6 m in multiple countries**

Community mortality

RSV PCR of NP swab taken ≤48h of community death

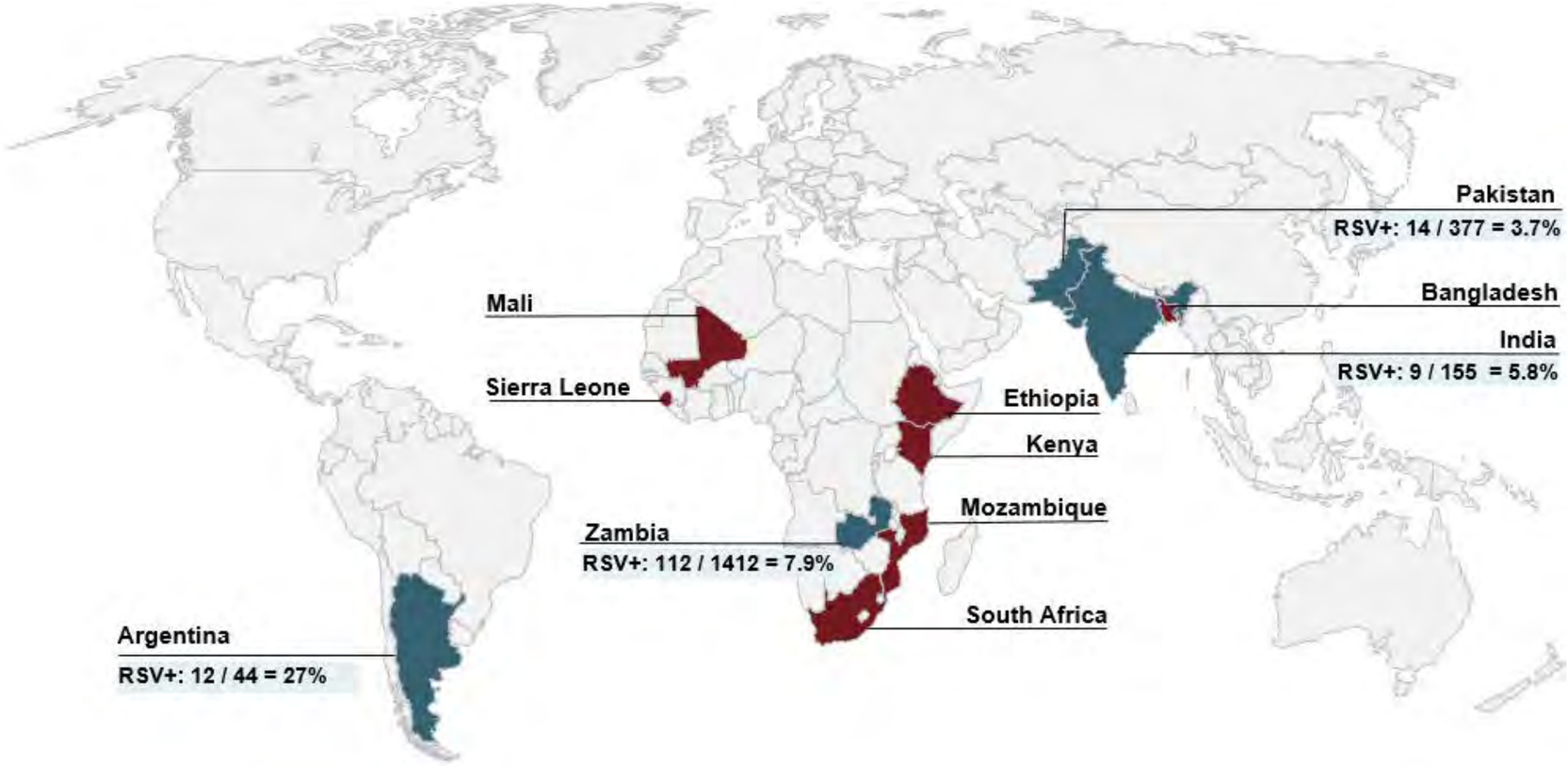
CHAMPS

RSV TAC of NP and lung, histopathology from MITS

RSV detected in 39/520 (7.5%)

Expert panel assigned cause of death

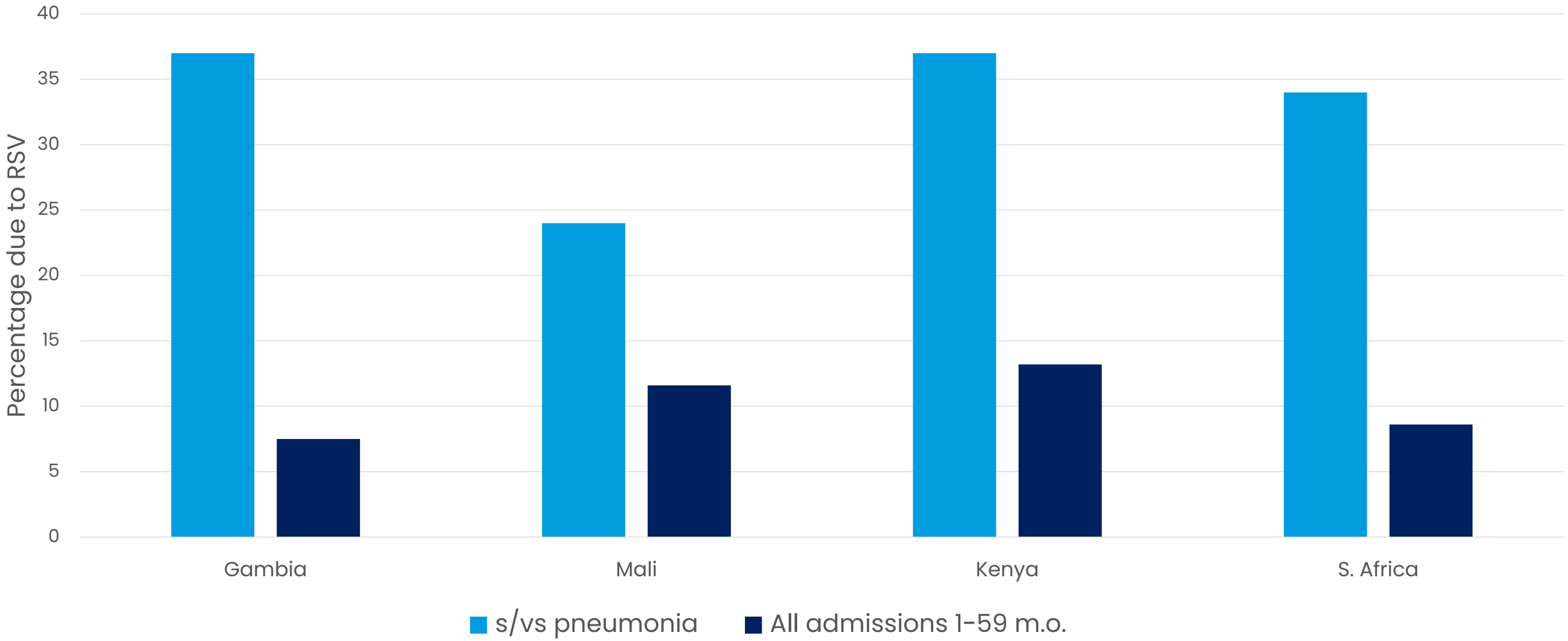
RSV determined to be in causal pathway or play a contributory role in 5% of all deaths in infants 7d – 6m



These data indicate global RSV-associated mortality in infants <6m may be as high as 100,000 deaths annually

Slide courtesy of Padmini Srikantiah, BMGF

Burden of RSV on the health care system in LMICs



PERCH investigators. *Lancet* 2019. http://dx.doi.org/10.1016/S0140-6736(19)30721-4.

RSV prevention on antimicrobial use.

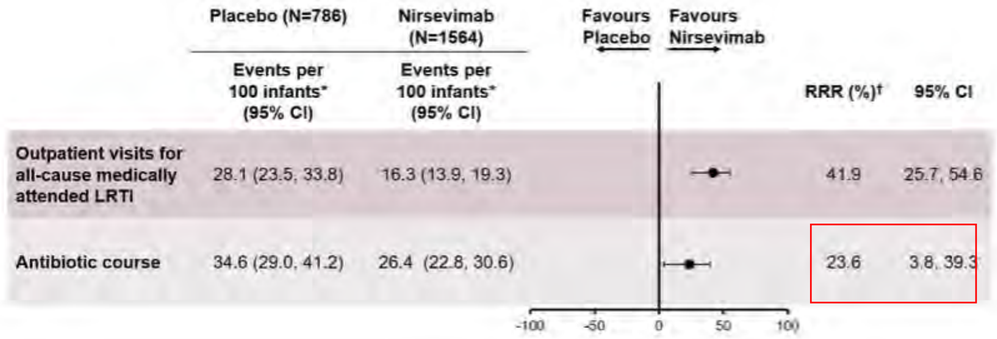
Novavax vaccine

Table 2. VE against antimicrobial prescriptions among infants within the ITT populatio

Setting and end point	Through 90 d from birth: RSV F vaccine, no. of events per 100 person-y (no. of events)	Through 90 d from birth: Placebo, no. of events per 100 person-y (no. of events)	Through 90 d from birth: VE (95% CI), %
All countries, person-y	730	379	
All antimicrobial prescriptions	133.7 (976)	148.7 (563)	12.9 (1.3–23.1)
All antimicrobial prescriptions for LRTI*	71.0 (518)	82.2 (311)	16.6 (1.4–29.4)
HICs	242	132	
All antimicrobial prescriptions	55.8 (135)	72.2 (95)	20.2 (–10.1–42.2)
All antimicrobial prescriptions for LRTI*	10.3 (25)	20.5 (27)	49.4 (3.5–73.5)
LMICs	488	247	
All antimicrobial prescriptions	172.3 (841)	189.5 (468)	10.9 (–2.1–22.2)
All antimicrobial prescriptions for LRTI*	101.0 (493)	115.0 (284)	12.8 (–3.6–26.7)

From Lewnard J, et al. PNAS, vol 119; 2002.

Nirsevimab monoclonal Antibody



From Simoes E et al, 12th International RSV symposium. Belfast. Oct 2022

WHO activities preparing for a policy decision

WHO activities to advance RSV vaccine/mAb development

- In 2016, SAGE requested preparations be made to support global policy-making for RSV maternal vaccines and mAbs.
- Some key activities undertaken by WHO:
  - PPCs for paediatric and maternal vaccines (2017), mAbs (2021)
  - R&D roadmap (2017)
  - Regulatory guidelines on RSV vaccines (2020), mAbs (2023)
  - Formation of a Technical Advisory Group for RSV (2017)
  - RSV surveillance as part of GISRS (including some LMICs)
  - Vaccine value profile for RSV mAbs and maternal immunization (accepted 2022)
  - Engagement with maternal, neonatal & child health programs
    - Vaccine safety in pregnancy, ANC visit timing and coverage, KAPs of MI
  - Increasing emphasis on country and regional outreach for decision making

RSV Roadshow

- Objective: To undertake a series of workshops and supplemental activities to increase knowledge about RSV and support LMICs in making decisions about introduction of future RSV prevention products

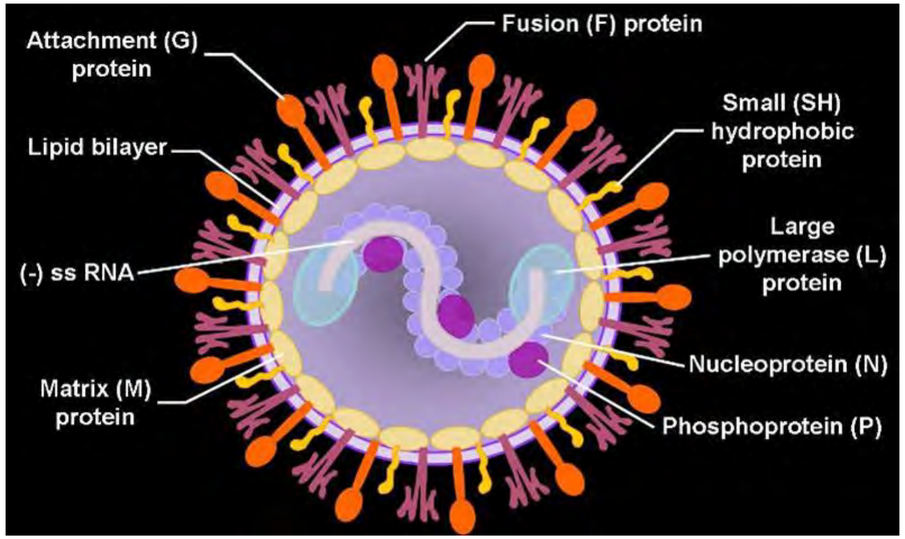
- Topics to be covered include: clinical, epidemiology, burden, seasonality, product characteristics, product choice

- Key policy decision makers and opinion leaders for new vaccines/products. “RSV Champions”

- Starting with opportunistic talks at EPI manager meetings, RITAG meetings, etc.

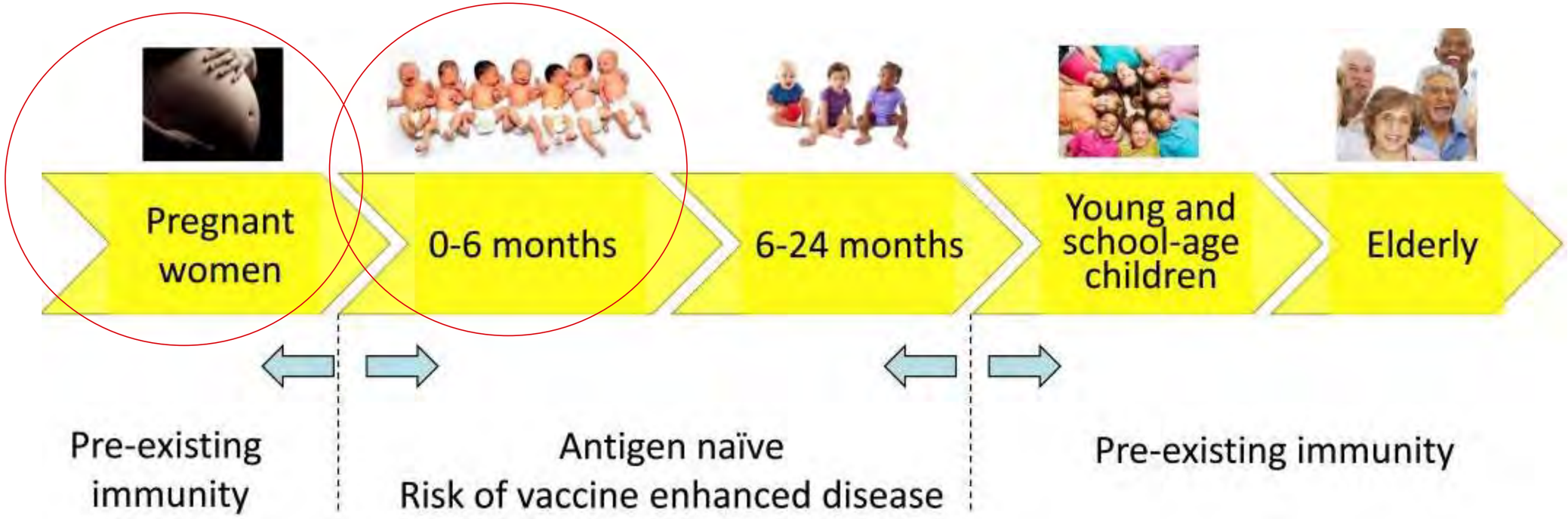
- Dedicated regional-led workshops starting in 2023

RSV product timeline



Potential Target Populations for RSV Vaccines

>20 candidates in clinical development*

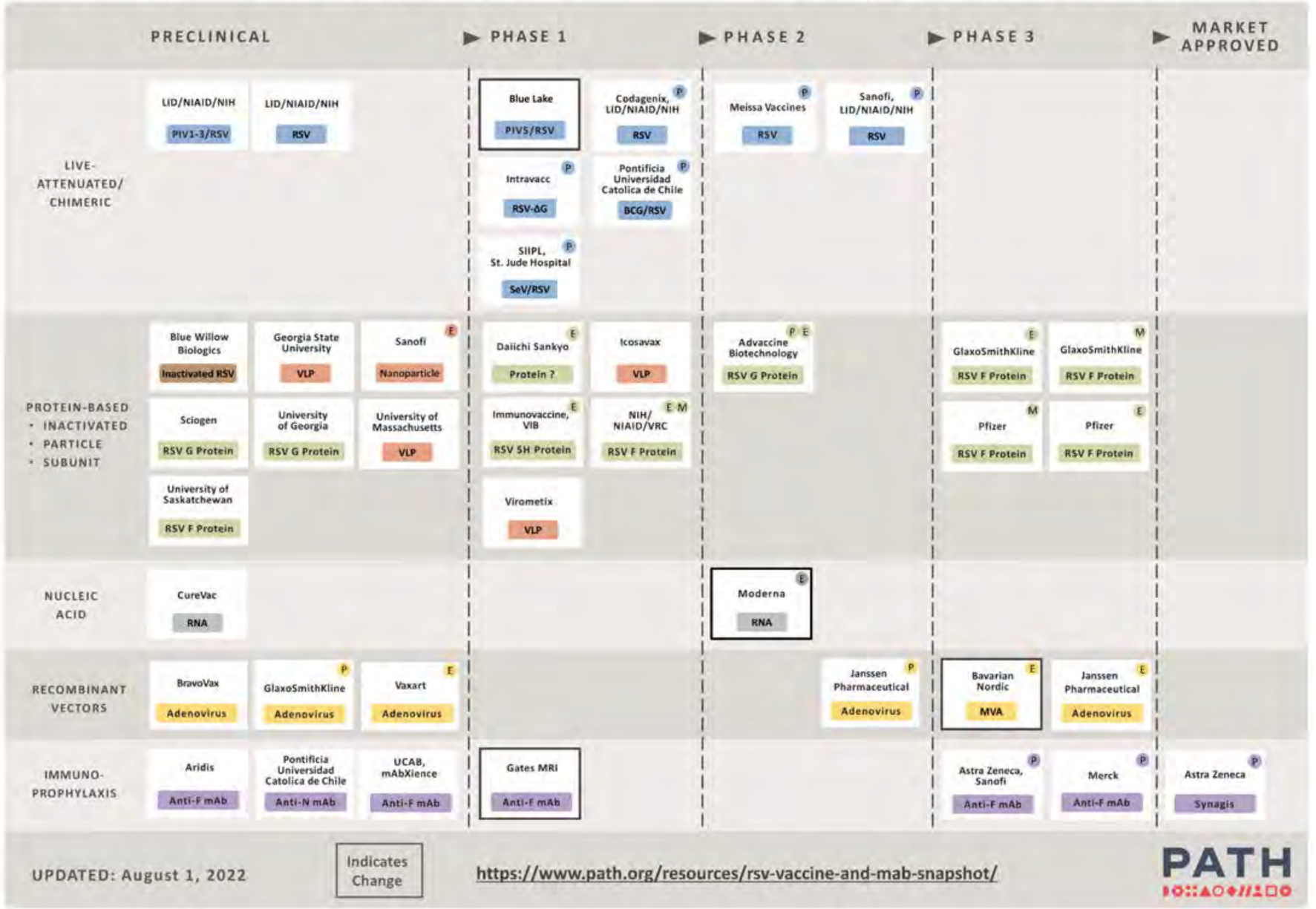


* https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/

Image from: Graham BS, Vaccine 2016

RSV Vaccine and mAb Snapshot

TARGET INDICATION: P =PEDIATRIC M =MATERNAL E =ELDERLY



UPDATED: August 1, 2022

Indicates Change

https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/

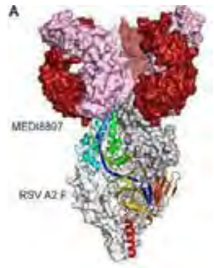
PATH

World Health Organization

World Health Organization

Monoclonal antibodies - overview

- Palivizumab, since 1990s, 5 monthly doses, costly, limited use in very high-risk children
- Nirsevimab from Astra-Zeneca and Sanofi
  - long-acting mAb due to engineered Fc portion (>5 months protection for entire RSV season)
  - **Approved by EMA** in November 2022 (FDA opinion Q2 2023) (results next slide)
- Other long acting mAbs:
  - Merck, Clesrovimab (ph2b/3), completed in 2024, potential licensure in 2025
  - Gates MRI, RSM01 (ph1)
- Administer soon after birth or at first EPI visit
- Seasonal dosing might be possible if RSV seasonality known (and if programmatically feasible)



Monoclonal antibodies – nirsevimab results

- Ph3 enrolled 3012 term & late pre-term infants, July 2019 – October 2021
- Phase 3 results[1], efficacy calculated on data from 1490 infants enrolled in 2019 in 20 NH countries and in 2020 in 1 SH country. UMIC: Bulgaria (5%), Russia (3.6%), **S. Africa (31%)**:
    - 74.5% efficacy against medically-attended RSV LRTI (95% CI, 49.6 to 87.1), 150 days
    - 62.1% efficacy against RSV-LRTI hospitalization (95% CI, -8.6 to 86.8), 150 days
    - Pooled analysis with ph2 data[2]:
    - **77%** (50.3 to 89.7) against hospitalization
    - **86%** (65.2 to 94.8)against very severe
    - Reduction in all-cause LRTI and antibiotic prescribing.
    - Analysis of full cohort will be available soon
- Product presentation – pre-filled syringe (not autodisable); price unknown

1. Hammitt L et al, Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. N Engl J Med. 2022 Mar; 2. Presentation by Simoes E at RSV symposium October 2022

Maternal vaccines - overview

- Pfizer, pre-fusion F, inducing higher neutralization titres (11-17 fold GMT *vs* 3 fold GMT than previous candidate Novavax), bivalent, interim phase 3 announced (next slide).
- GSK, stopped enrolment and vaccination due to a safety signal. Further analysis to better understand safety data from these trials is ongoing, and the relevant regulatory authorities have been informed.
- **Pfizer candidate now the only maternal vaccine in late stage development**

Maternal vaccines – Pfizer candidate

- Ph 3 interim analysis (7,400 pregnant women & their infants in 18 countries):
  - 69.4% (CI: 44.3%, 84.1%) against severe medically attended RSV-associated LRTI at 6 months (81.8%, CI: 40.6%, 96.3%, at 3 months)
  - Efficacy for MA-LRTI of 51.3% (CI: 29.4%, 66.8%) at 6 months
- Safety follow up birth until 1-2 years.
- Submission to FDA by end 2022, possible licensure by mid 2023
- LMICs: Argentina (11%); Brazil (1%); Gambia (1%); Mexico (1%); Philippines (1%); S.Africa (13%)
- Lyophilized single dose vial, MDV to be developed with BMGF co-funding, global access agreement with price and volume commitments for GAVI 72.

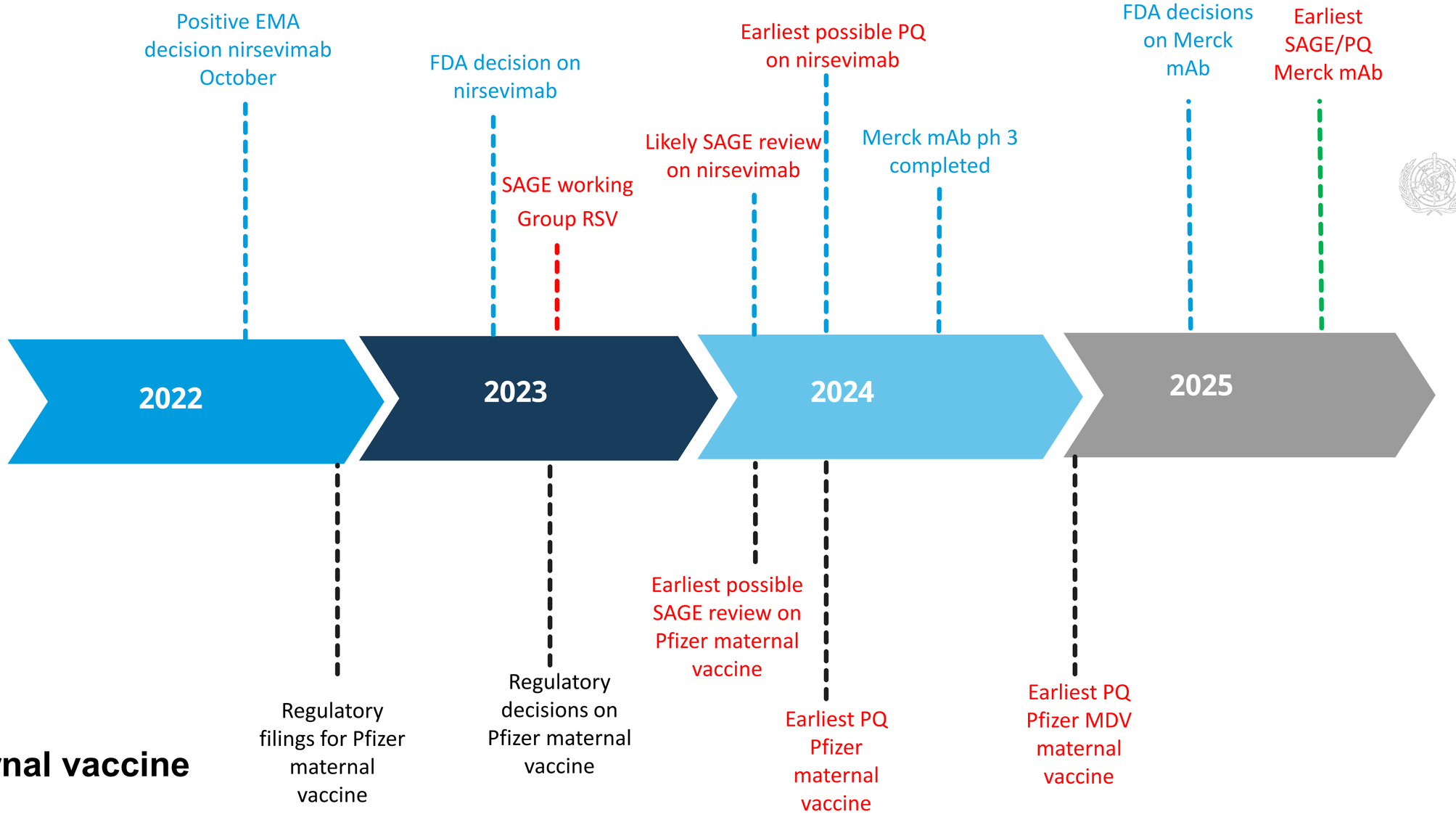
Press release Pfizer: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-data-phase-3-global

Timelines for lead RSV candidates aimed at protecting infants

World Health Organization

Monoclonals

WHO



World Health Organization

Maternal vaccine

TAG and SAGE discussion on data needs in LMICs for RSV preventive mAbs and maternal immunization

TAG discussions on data needs in LMICs

- 13 TAG members with diverse backgrounds
- Questions posed to TAG:
  1. How would these products perform in LMIC settings?
  2. What additional data might be needed from LMIC settings for these products?
- The discussion was *not* about:
  - Did the phase III trials have sufficient LMIC representation? (Consensus was No.)
  - Whether these products should be recommended in LMICs.
- 4 TAG virtual meetings from May – September with expert presentations on subject matter

TAG discussions on data needs in LMICs

- The WHO RSV vaccine technical advisory group reviewed available evidence on the performance and mechanism of action of the long-acting mAbs and maternal immunization and concluded that these products would likely work equally well in countries across income levels, despite the fact that HICs accounted for the majority of subjects enrolled in the clinical trials

SAGE discussion – October 2022

- Given huge global burden of RSV, SAGE recognized the enormous potential of these interventions and the need for vaccine equity to not delay introduction to LMICs.
- Will review clinical trial data when available for review.
- However, they also noted that there are many competing health priorities in countries and the current pivotal trials might not provide sufficient evidence for decision making in some countries.
- In parallel with the regulatory, policy & financing decisions, SAGE recommends an additional study in several LMICs that can define the full potential public health impact be conducted.
  - Initial discussions for an impact study will take place with TAG in December
- SAGE also suggested that market shaping (e.g through GAVI) be explored to make the mAbs affordable for LMICs.

Planned IVB activities

- Secondary effects journal article
- Input into design of impact study (sub-group of TAG)
- SAGE WG likely to be formed in 2023 to review maternal immunization and mAbs
- RSV roadshow
- Continued monitoring of pipeline

Thank you

Questions to PDVAC

- Confirmation on no need to develop an ECVP or FVVA – focus attention on impact paper and country outreach

Future malaria vaccines and monoclonal antibodies for prevention

6 December 2022

Lindsey Wu
Technical Officer, WHO Global Malaria Programme

Outline

- **For information**
  - MALVAC achievements and future plans
  - Malaria vaccine PPCs
  - Malaria vaccine R&D pipeline
- **For advice**
  - Monoclonal antibodies for malaria prevention
  - Multi-stage malaria vaccines

MALVAC history and achievements

- **First established in 2008**
  - Developed first WHO Preferred Product Characteristics (PPCs), published 2014
- **Reconvened with new members in 2019**
  - Updated malaria vaccine PPCs, published in November 2022
  - Technical consultation on Phase 3 trials for malaria vaccines to reduce morbidity/mortality*
  - Advised on malaria vaccine R&D pipeline dashboard
  - Input to WHO PPCs on monoclonal antibodies for malaria prevention
- **Future plans to discontinue MALVAC to reduce duplication of groups/processes**
  - Integrate activities into other WHO expert groups (e.g., PDVAC) and convene ad hoc technical consultations for specific topics

*https://www.who.int/news-room/events/detail/2021/04/12/default-calendar/who-working-group-on-late-stage-development-for-malaria-vaccines-to-reduce-disease-burden

MALVAC future plans

Previous MALVAC activities and proposed integration with other WHO processes and groups

MALVAC activity	Timeline	To be addressed by
R&D pipeline dashboard, bi-annual data update	Next in 2023	Call for data from experts via PDVAC, GMP, IVB, MPAG
R&D pipeline analysis report	Next in 2023, update every 2-3 years	Comments from experts in GMP, IVB, PDVAC, MPAG
Malaria vaccine PPCs, update every 5 years	Next in 2025/2026	Technical consultation with expert committee, input from PDVAC
Malaria mAbs PPCs, update every 5 years	Next in 2026	Technical consultation with expert committee, input from PDVAC
New malaria vaccine and/or mAbs technologies (e.g., multi-stage vaccines)	TBD 2023	Technical consultations with expert committee, input from PDVAC

Malaria vaccine PPCs (2022 update)

World Health Organization

Expanded set of strategic goals

- Vaccines to prevent blood stage infection (new)
  - Envisaged as high efficacy pre-erythrocytic antigens, but may include high efficacy blood-stage vaccines
- Vaccines to reduce morbidity and mortality
- Vaccines to reduce transmission at the community level

Clinical development considerations

- Evaluation and harmonization of endpoints, clinical development pathways, comparator arms

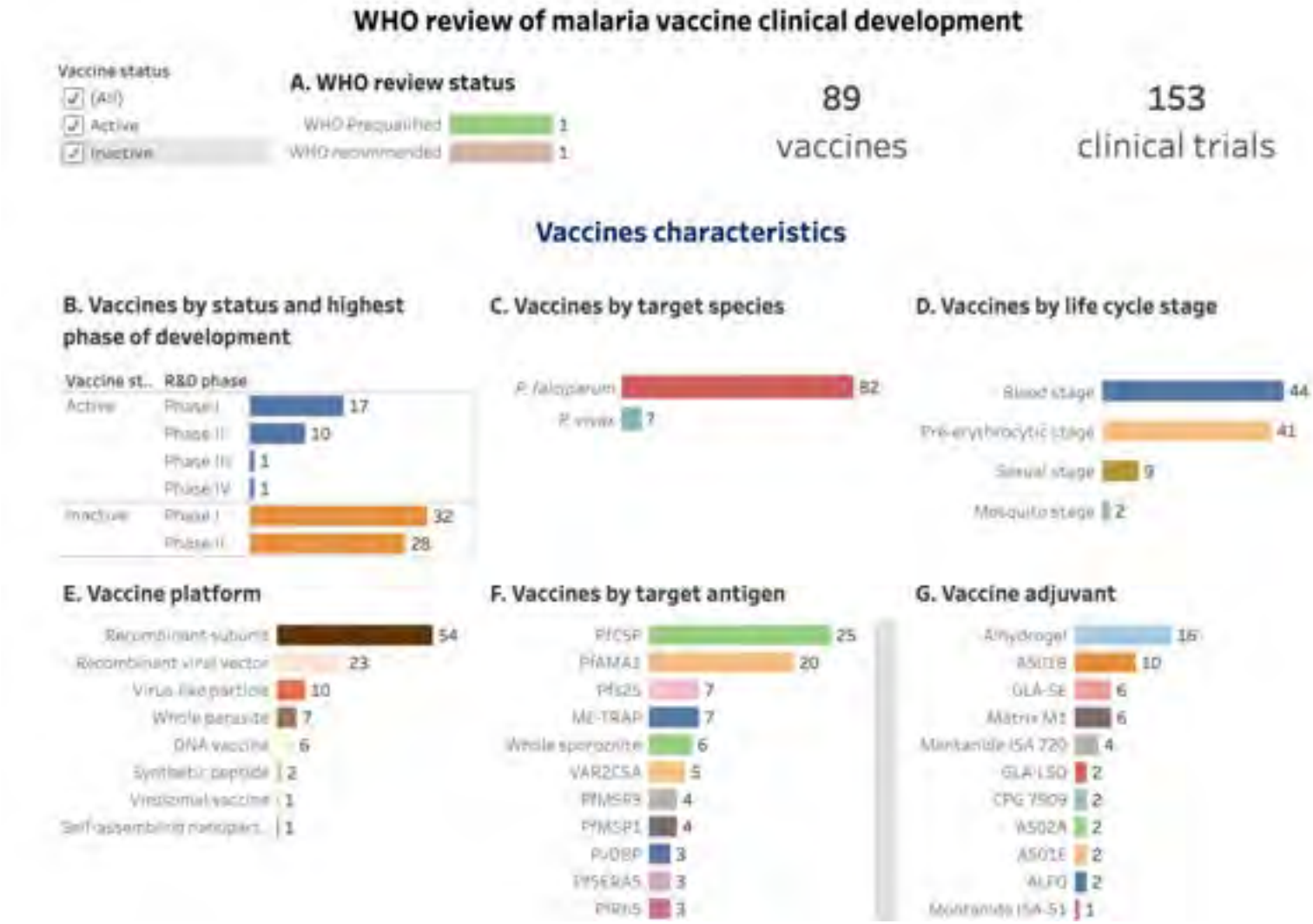
Update on the state of the art

- Functional assays, CHMI studies, adjuvants and delivery platforms

https://www.who.int/publications/i/item/9789240057463

Malaria vaccine R&D pipeline

World Health Organization



World Health Organization

https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/who-review-of-malaria-vaccine-clinical-development

Malaria vaccine candidates

World Health Organization

Pre-erythrocytic stage

P. falciparum		
WHO recommended	•	RTS,S/AS01 (circumsporozoite protein)
Phase 3	•	R21/MatrixM (circumsporozoite protein)
Phase 2	•	PfSPZ Vaccine (whole sporozoite) PfSPZ-CVac (PfSPZ challenge under chemoprophylaxis)
Phase 1	•	VLPM01 (virus-like particle) rCSP/AP10-602 (circumsporozoite protein) PfGAP3-KO (genetically attenuated whole sporozoite) FMP013 and FMP014 (self-assembling nanoparticles) PfSPZ-GA1 (genetically attenuated whole sporozoite) DNA-ChAd63 PfCSP (heterologous prime-boost)
P. vivax		
Phase 2	•	PvCSP (circumsporozoite protein) PvSPZ (whole sporozoite)

World Health Organization

Malaria vaccine candidates (2)

Blood-stage

P. falciparum	
Phase 2	• Rh5 (reticulocyte binding protein)
Phase 1	• BK-SE36 (PfSERA5 antigen)
P. vivax	
Phase 2	• PvDBP (Duffy-binding protein) • Pf7G8 (chemically attenuated whole parasite) • DNA-ChAd63 PfCSP PfAMA1 ME-TRAP (heterologous prime-boost)

Sexual, sporogonic, or mosquito stage (interrupting transmission)

P. falciparum	
Phase 2	• Pfs230D1M-EPA/AS01B (gamete surface antigen) • Pfs25M-EPA/AS01B (zygote/ookinete)
Phase 1	• Pfs25-IMX313/MatrixM (zygote/ookinete) • R0.6C (Pfs48/45)
P. vivax	
Phase 1	• Pvs25-IMX313/MatrixM

Malaria in pregnancy

P. falciparum	
Phase 1	• PRIMVAC (targeting VAR2CSA) • PAMVAC (targeting VAR2CSA)

Monoclonal antibodies for malaria prevention

- **Scientific Development Committee convened Nov 2021 to develop first PPCs***
- **Primary use case (immediate public health need)**
  - Reduction in morbidity/mortality in infants and children (age of highest disease burden)
  - Seasonal administration, single dose, duration of protection 3-6 months
- **Additional use cases for future consideration (for advice in later slides)**
  - Adults, particularly pregnant women
  - Pre-hospital discharge prophylaxis, children with severe anemia
  - Infancy, prior to receiving malaria vaccine (which is given at 5 months of age)
- **Potential advantages to other malaria prevention interventions**
  - Single-dose mAbs – improved adherence compared to 3-4 dose chemoprevention regimens
  - Immediate immune protection and reduced side effects & less reactogenicity compared to vaccines

*https://www.who.int/news-room/events/detail/2021/11/03/default-calendar/malaria-monoclonal-antibodies-for-malaria-prevention-preferred-product-characteristics-and-clinical-development

R&D challenges for malaria mAbs

- **Safety -** questions for advice in later slides
  - Repeat administration over multiple seasons – impact of anti-drug antibodies (ADAs) on safety and efficacy
  - Immune interactions between mAbs and vaccines co-administered or administered close in schedule – early studies needed to rule out risk?
- **Development challenges**
  - Potency and duration of protection (Fc modifications for half-life extension)
  - Achieving target efficacy at feasible dose volume
  - Cost of manufacturing/production - to have comparable cost-effectiveness to vaccines and chemoprevention drugs for LMICs
- **Delivery**
  - Infrastructure for effective seasonal administration
  - Currently being explored for malaria vaccines

Most advanced malaria mAbs candidates

- **CIS43LS and L9LS (US NIAID/NIH)**
  - Target sporozoites (CSP, similar to RTS,S)
  - Prevention of blood stage infection, reduction of disease

- **CIS43LS**
  - High protective efficacy in CHMI trials in healthy adults (Phase 1)[1]
  - Phase 2 – dose escalation, efficacy IV admin in adults (348 participants) in Mali[2]
    - Protection over malaria transmission season - 6 months follow-up
    - Endpoint – time to first infection (microscopy), AL at enrollment to clear parasitaemia
    - 40 mg/kg efficacy 88.2% (79.3 – 93.3%), 10 mg/kg efficacy 75% (61.0 – 84.0%)

[1] Gaudinski et al, NEJM 2021. https://www.nejm.org/doi/10.1056/NEJMoa2034031
[2] Kayentao et al, NEJM 2022. https://www.nejm.org/doi/10.1056/NEJMoa2206966

- **L9LS (US NIAID/NIH)**
  - Similar to CIS43, 3-fold increased potency
  - Phase 1 CHMI, safety and efficacy of IV and SC admin in healthy US adults[3]
  - Phase 2 studies, recruiting as of 2022
    - Children aged 6 -10 years, Mali (seasonal), single SC admin[4] (expected completion March 2023)
    - Children aged 5 months – 5 years, Kenya (perennial), two SC admins over 12 months[5] (expected completion April 2024)

- **TB31F, transmission blocking mAb**
  - Targets gametocytes to prevent human to mosquito transmission
  - Phase 1, safety and pharmacokinetics in healthy adults in Netherlands
  - >80% transmission reducing activity at 3.3 mg/mL

[3] Wu et al, NEJM 2022. https://www.nejm.org/doi/10.1056/NEJMoa2203067
[4] https://clinicaltrials.gov/ct2/show/NCT05304611
[5] https://clinicaltrials.gov/ct2/show/NCT05400655
[6] van der Boor et al, Lancet Inf Disease 2021. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00428-5/fulltext

Questions on mAbs

- **Repeat administration and ADAs**
  - How long should follow-up be to study impact of ADAs on efficacy/safety?
  - Repeat administration over 1 season (if more than one dose needed for duration of protection)
  - Evaluate over multiple seasons? How many seasons?
- **Immune interactions with vaccines**
  - Immunological basis for mAbs interference with malaria vaccines vs. non-malaria vaccines
  - What studies are required to demonstrate lack of interference?
  - Required only for first malaria mAbs or needs evaluation for all malaria mAbs?
- **Co-administration with vaccines**
  - How should the timing of administration with other vaccines (such as EPI vaccines) be specified?
  - Administered at same time, within 2 weeks, longer than 2 weeks of other vaccines?

Future considerations for malaria mAbs

Which of the following areas should be prioritized for future WHO discussion? Other use cases to be considered?

- **Pre-hospital discharge prophylaxis for children admitted with severe anaemia**
  - High risk of re-admission or death within 6 months of discharge
  - Several trials (Malawi, Kenya, Ghana, Gambia) show monthly post-discharge malaria chemoprevention (PDMC) with SP or ACTs substantially reduces risk
  - Updated WHO Malaria Guidelines recommend PDMC, based on systematic review/meta-analysis
- **Malaria in pregnancy**
  - IV administration in ANCs, feasibility data needed
  - Ensuring safety and access in first trimester
- **Early infancy prior to eligibility for malaria vaccine**
  - RTS,S only recommended from age 5 months, can mAbs provide protection in months before

Future considerations for malaria mAbs (2)

- **As part of mixed malaria intervention packages**
  - Alternative to seasonal malaria chemoprevention (SMC)
    - Or perennial malaria chemoprevention (PMC, formerly intermittent preventive treatment in infants IPTi)
    - Or can it be used alongside chemoprevention
  - Administered before malaria vaccine

Multi-stage malaria vaccines

Potential WHO technical consultation on clinical development pathways

- **Transmission blocking vaccines in the pipeline**
  - Pfs230D1-EPA/AS01 and Pfs25-EPA/AS01 - Phase 1 and 2, Mali (NIAID, MRTC Mali)
  - Pfs25-IMX313/MatrixM – Phase 1b, Tanzania (Oxford)
- **Potential combination with pre-erythrocytic stage or blood stage targets**
  - RTS,S/AS01; R21/MatrixM
  - Rh5 - Phase 2a, UK (with AS01); Phase 1b, Tanzania (with MatrixM)

Multi-stage malaria vaccines

Proposed questions:

- **What are the potential combinations and use cases?**
  - Transmission blocking vaccine/target (TBV) + seasonal administration of pre-erythrocytic vaccine/target (PEV)
    - Also with blood-stage vaccines/targets (BSV) to neutralise breakthrough infections after PEV
- **Which transmission settings? Which target age groups?**
- **What R&D stage is appropriate for testing combined vaccines?**
- **What needs to be demonstrated for individual components before combining?**
- **What are the best clinical endpoints?**
  - Role of transmission assays and surrogate endpoints
- **What can be demonstrated in phase 3 trials vs. post-licensure?**

Thank you

WHO

Mary Hamel (WHO IVB), David Schellenberg (former WHO GMP), Kate O'Brien (WHO IVB), Pedro Alonso (former Director GMP)

MALVAC members

Chetan Chitnis, Chair (Institut Pasteur); Edwin Asturias (University of Colorado); Philip Bejon (KEMRI); Katharine Collins (Radboud University); Brendan Crabb (Burnet Institute); Socrates Herrera (Institute of Immunology, Colombia); Miriam Laufer (University of Maryland); Regina Rabinovich (ISGlobal); Meta Roestenberg (Leiden University); the late Adelaide Shirley (John Snow Institute); Halidou Tinto (Institut de Recherche en Science de la Santé, Burkina Faso); Marian Wentworth (Management Sciences for Health)

Scientific Development Committee for mAbs

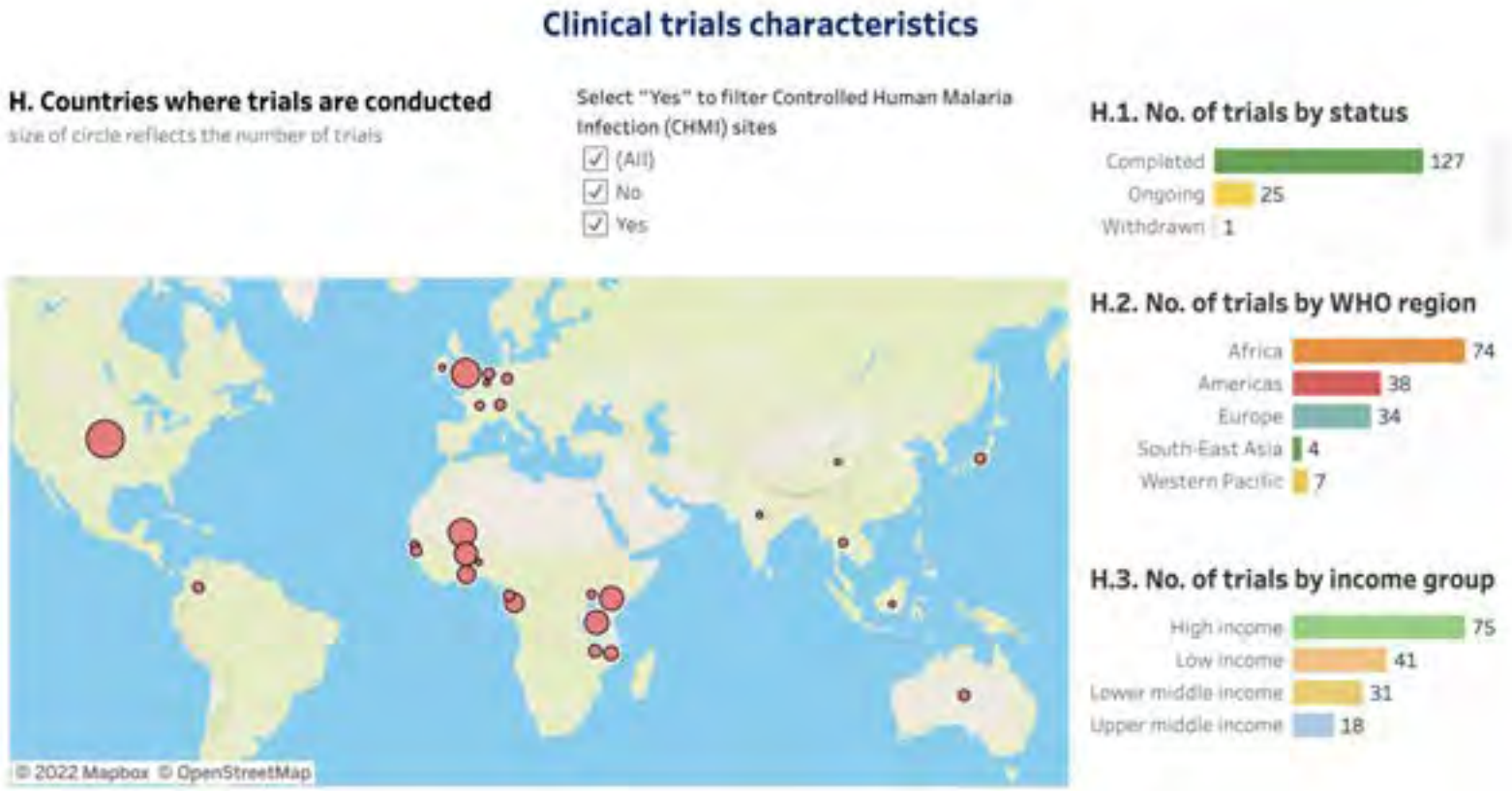
Francisco Saute, co-Chair (Manhiça Research Center); Kevin Marsh, co-Chair (Oxford University); Enrica Alteri (Independent Consultant); Subhash Chand (Indian MOH); Alasanne Dicko (University of Bamako); Jean Louis Ndiaye (UCAD, Senegal); Melissa Penny (Swiss TPH); Regina Rabinovich; Francisco Saute (Manhiça Research Center); Marian Wentworth

Additional reference slides if needed

World Health Organization

World Health Organization

Malaria vaccine R&D pipeline



https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/who-review-of-malaria-vaccine-clinical-development

Malaria vaccine R&D pipeline

World Health Organization

I. List of vaccine candidates and trials

(hover on last column for a popup window with more information)

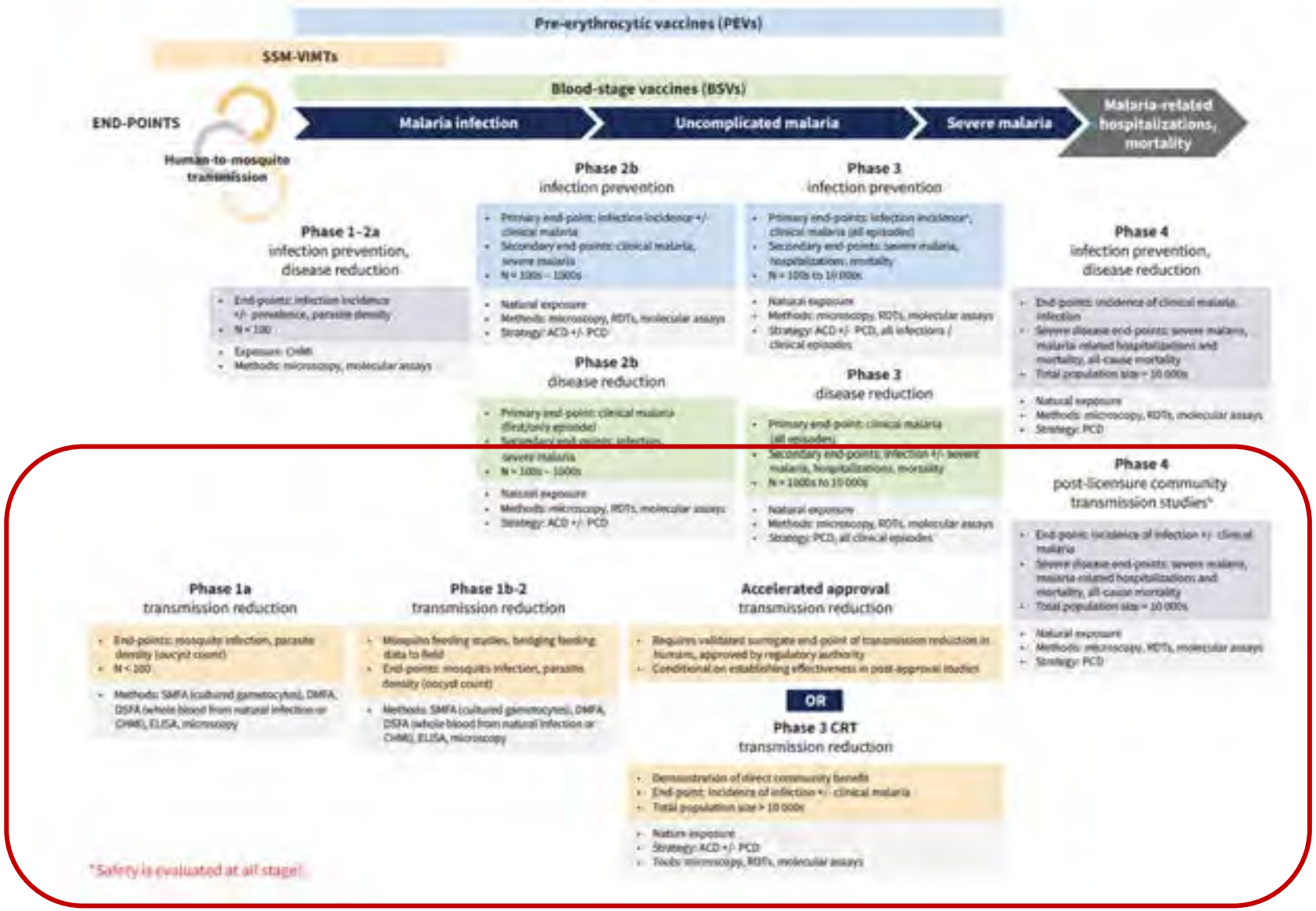
Product name	Vaccines status	Trial status	
Ad35.CS.01	Inactive	Completed	Phase I
			Phase I
Ad35.CS.01 + Ad26.CS.01	Inactive	Completed	Phase I/IIa
Ad35.CS.01 + RTS,S/AS01E	Inactive	Completed	Phase II
BK-SE36	Inactive	Completed	Phase I
BK-SE36/Alhydrogel	Inactive	Completed	Phase I
			Phase I
BK-SE36/CpG	Active	Completed	Phase I
			Phase I
			Phase I
BSAM2/Alhydrogel CPG 7909	Inactive	Completed	Phase I
ChAd63 PfAMA1;ChAd63-MVA PfAMA1	Inactive;Inactive	Completed	Phase I
ChAd63 PfAMA1;MVA PfAMA1;ChAd63 MSP1;MVA MSP1;ChAd63-MVA ME-T...	Inactive;Inactive;...	Completed	Phase I/IIa
ChAd63 PfAMA1;MVA PfAMA1;PfAMA1-C1/Alhydrogel;PfAMA1-C1/Alhydroge...	Inactive;Inactive;...	Completed	Phase I
ChAd63-MVA ME-TRAP	Inactive	Completed	Phase II

World Health Organization

https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/who-review-of-malaria-vaccine-clinical-development

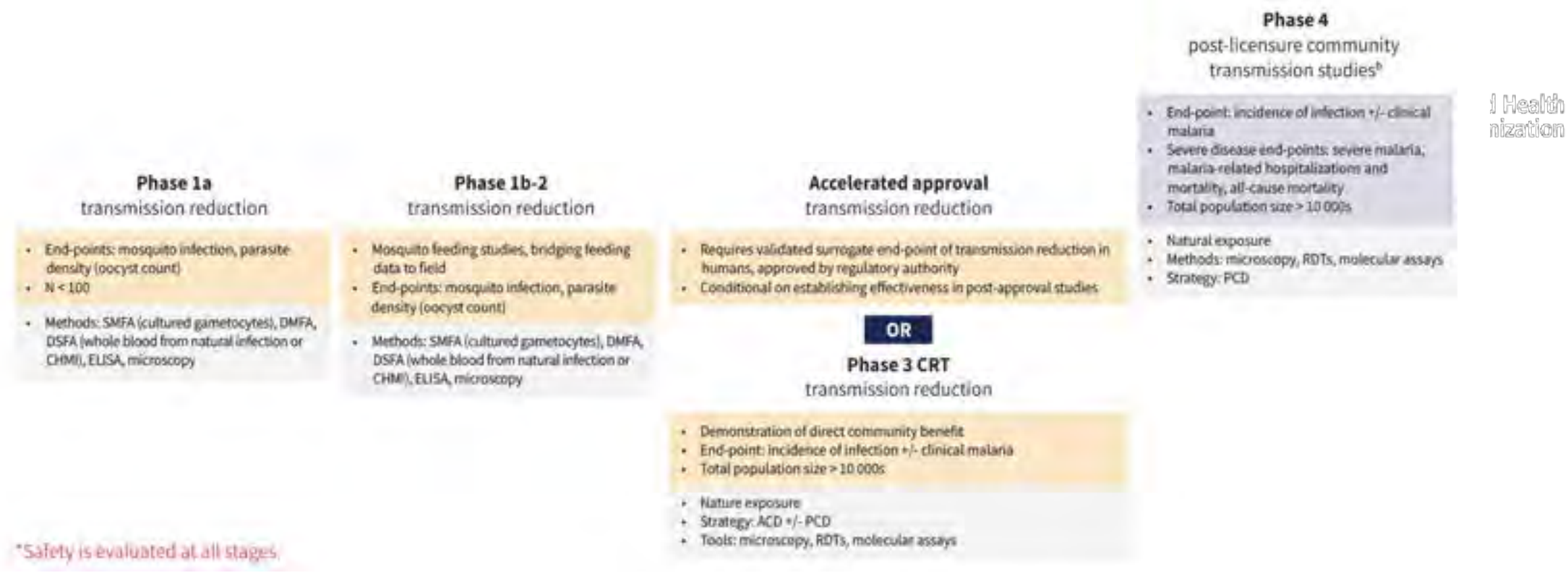
Malaria vaccine clinical development pathways

World Health Organization



World Health Organization

Malaria vaccine clinical development pathways



Vaccine Specific Session: Malaria

1. Update on Malaria Vaccine Introduction – Mary Hamel, IVB
2. Future Malaria Vaccines and Monoclonal Antibodies for Prevention – Lindsey Wu, GMP

WHO recommendation on use of the first malaria vaccine: Oct 2021

World Health Organization

WHO recommends the RTS,S/AS01 malaria vaccine be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO

- RTS,S/AS01 malaria vaccine should be provided in a schedule of 4 doses in children from 5 months of age for the reduction of malaria disease and burden.
- Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a 5-dose strategy in areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks.
- RTS,S/AS01 introduction should be considered in the context of comprehensive national malaria control plans.

Useful links

WHO malaria vaccine position paper
https://www.who.int/publications/i/item/who-wer9709-61%E2%80%9380

WHO Guidelines for malaria
PDF version:
https://www.who.int/publications/i/item/guidelines-for-malaria
MAGICapp Online platform:
https://app.magicapp.org/#/guideline/5701

Malaria Vaccine Implementation Programme
https://www.who.int/initiatives/malaria-vaccine-implementation-programme

NITAG Resource center
https://www.nitag-resource.org/

Pilot implementations to understand the vaccine feasibility, safety, impact in routine use (2019-2023)

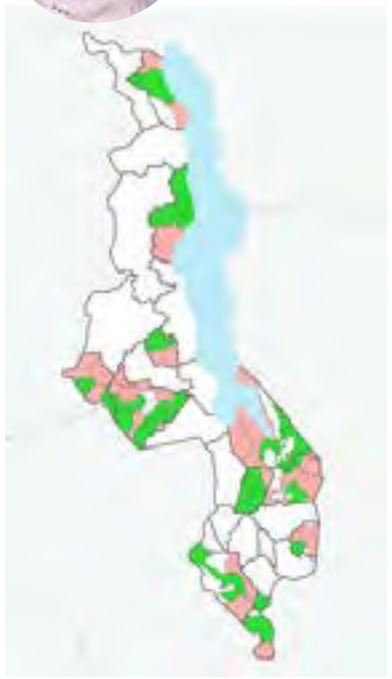
World Health Organization

Since April 2019: More than 3.7 million doses administered; more than 1.2 million children reached with at least 1 dose

Pilot vaccinating areas

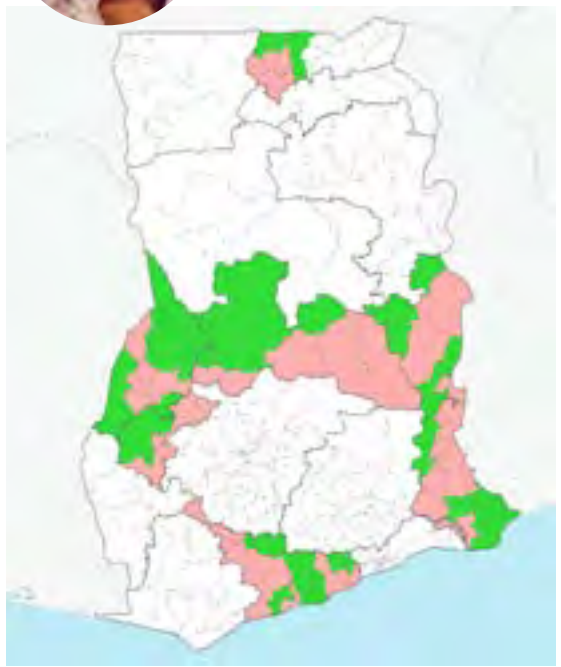
Pilot comparator areas (non-vaccinating)

Malawi



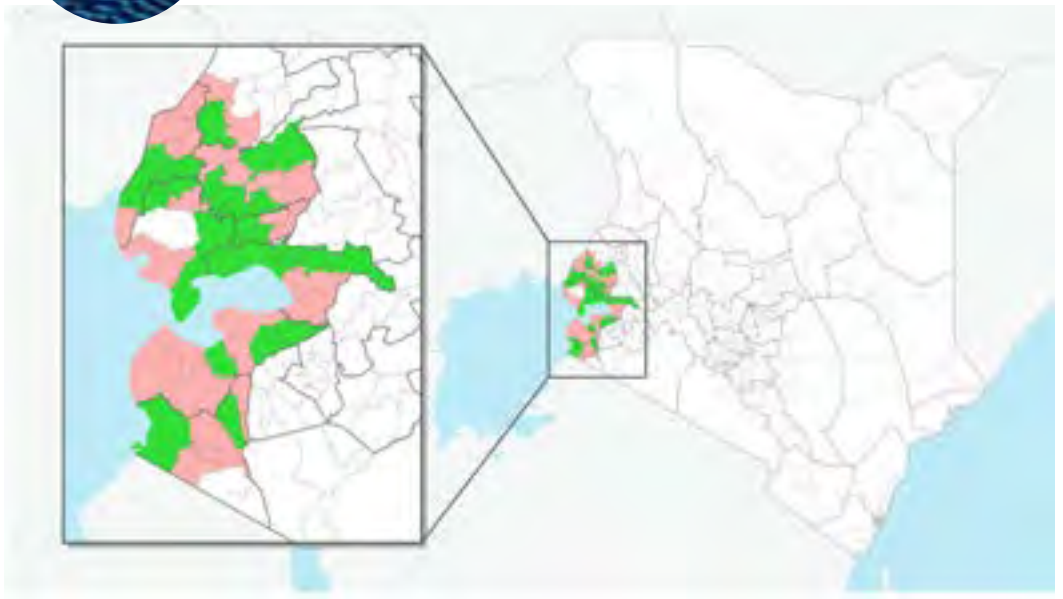
11 districts

Ghana



81 districts in 7 regions

Kenya



51 sub-counties in 8 counties

Summary findings from the MVIP: 24 months after first vaccination (April 2019 – April 2021)

1. **Feasibility:** Vaccine introduction is feasible, with good uptake and coverage through the routine systems, no impact on uptake of other vaccines, insecticide-treated bed nets (ITNs), care-seeking behavior

2. **Safety:** Vaccine is safe; no safety signals identified after over 3 million doses provided

3. **Impact:** Vaccine introduction resulted in a substantial reduction in severe malaria and all cause mortality *in children of the age that they could have received the vaccine*, even when introduced in areas with good ITN use and access to care. During 24 months after vaccine introduction:
   - 32% (95% CI 8, 46%) reduction in hospitalized severe malaria
   - 7% reduction in all-cause mortality (persisted through 36 months ~10%)

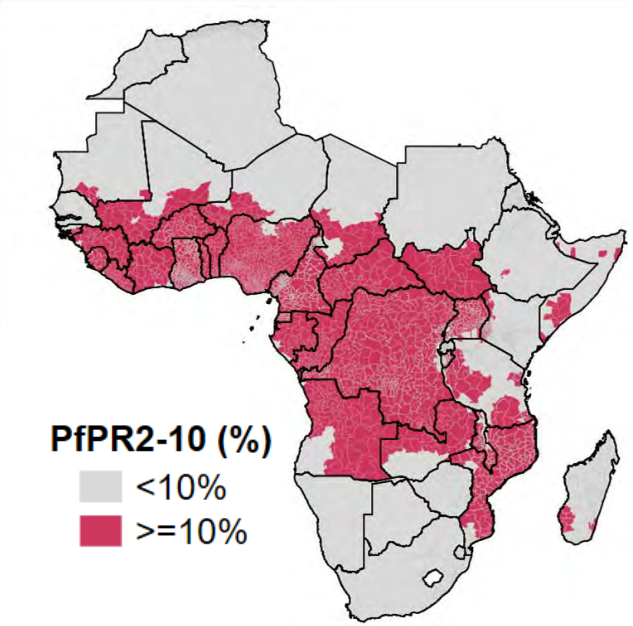
4. **Equity:** the vaccine is reaching children who are not using other forms of prevention such as insecticide-treated nets, increasing access to malaria prevention interventions to > 90%

Vaccine supply expected to be insufficient to meet demand in initial years

World Health Organization

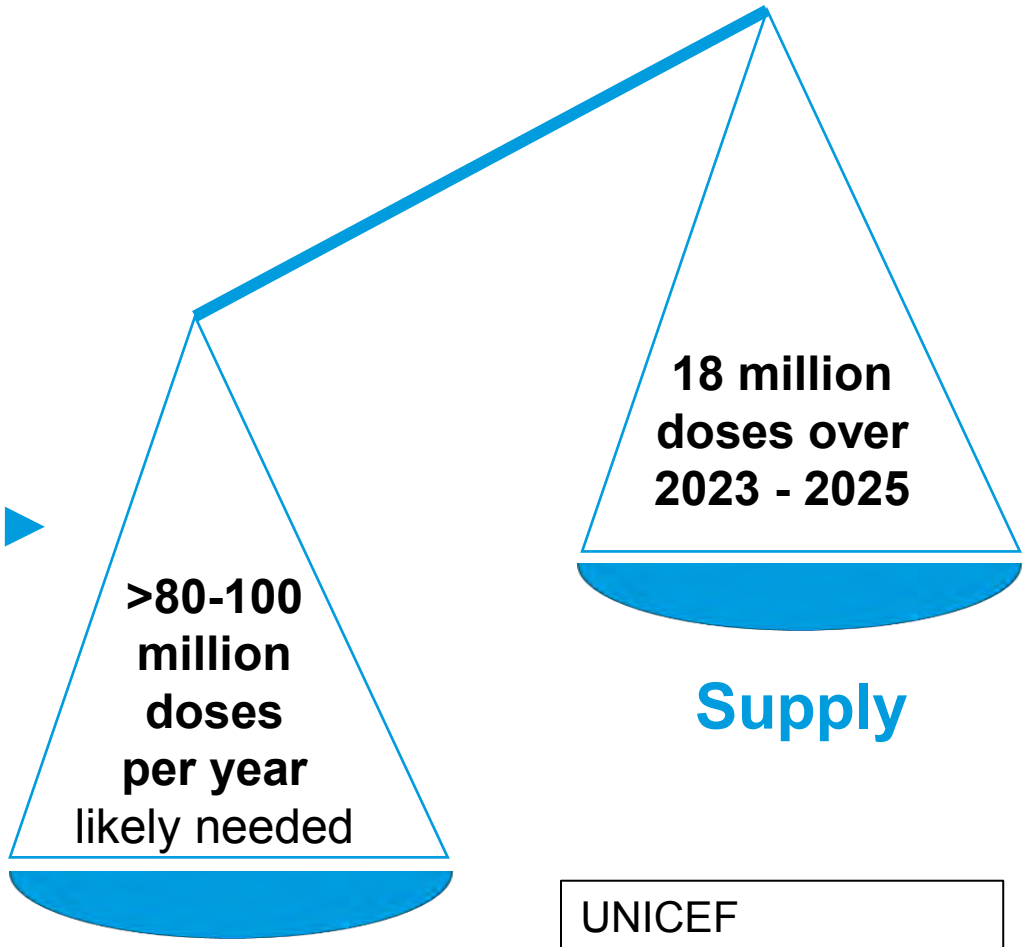
Over **25 million children** are born each year in regions with moderate to high malaria transmission

At least **27 countries** have already expressed interest in introducing the vaccine



P. falciparum parasite prevalence ($PfPR_{2-10}$) estimates, 2019.
Source: MAP 2019

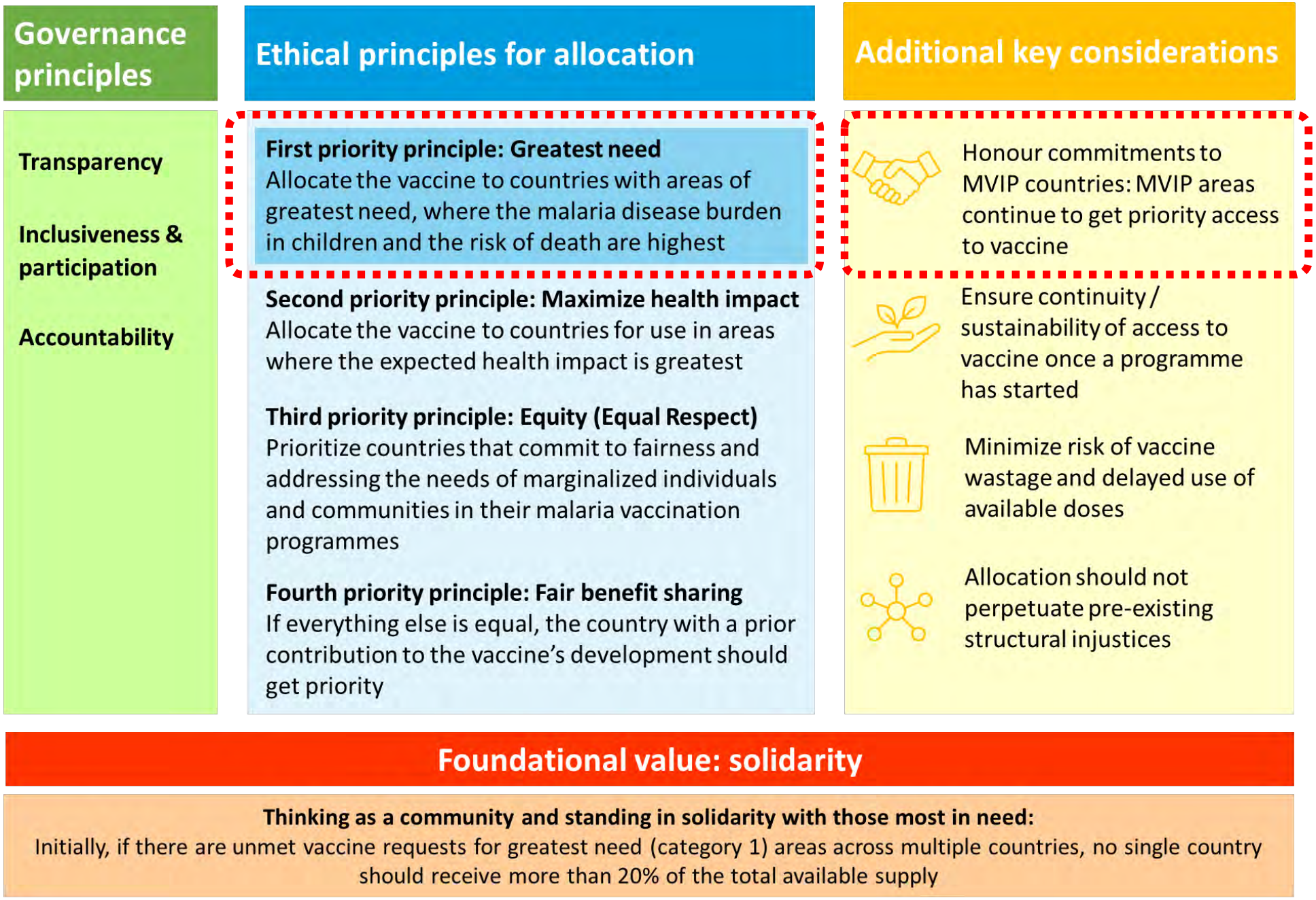
Pockets of moderate transmission outside Africa, mainly in PNG and possibly in India



UNICEF procurement
Cost: 9.30 Euro/dose

Framework for the allocation of limited malaria vaccine supply

Available on WHO website



Key implications of Framework for countries and partners

- All countries will have to consider a **phased approach** to vaccine implementation, starting in areas with highest need, with expansion after supply increases.
- Interested countries are **not guaranteed access to the malaria vaccine during the initial years of roll out, due to supply constraints.** The Framework aims to ensure that allocation of available doses adheres to values and principles of solidarity, greatest need, impact, and equity.
- It is an **ethical imperative to work on improving the supply situation** to ensure that all children in need have an opportunity to access additional protection from vaccination

Countries planning to submit applications to Gavi for malaria vaccine (as of 22 Nov)

≥27 countries with demonstrated interest in applying to Gavi for malaria vaccine introduction

Country	Gavi Expression of interest	Gavi application target
19-21 July workshop, Accra (6)		
Ghana	N/A – approved for MVIP cont.	Jan 2023
Malawi	N/A – approved for MVIP cont.	Jan 2023
Kenya	N/A – approved for MVIP cont.	Jan 2023
DRC	Submitted	Jan 2023
Uganda	Submitted	Jan 2023
Mozambique	Submitted	Jan 2023
20-22 Sept workshop, Accra (5)		
Burundi	Submitted	Jan 2023
Niger	Submitted	Jan 2023
Liberia	Submitted	Jan 2023
Zambia	Submitted	April 2023
Madagascar	TBC	July 2023

Country	Gavi Expression of interest	Gavi application target
18-20 Oct workshop, Nairobi (8)		
Benin	Submitted	Jan 2023
Cote d'Ivoire	Submitted	April 2023
Cameroon	Submitted	Jan 2023
Burkina Faso	Submitted	Jan 2023
Sierra Leone	Submitted	Jan 2023
CAR	Submitted	Jan 2023
Nigeria	Submitted	Jan 2023
Sudan	Submitted	Jan 2023
9 or 10 Nov workshop, virtual (6)		
Chad	Submitted	Jan 2023
Guinea	Submitted	Jan 2023
The Gambia	Submitted	Jan 2023
Ethiopia	Submitted	July 2023
Tanzania	Submitted	TBC
Togo	*[not yet received]*	TBC
Other countries that have indicated interest – not attending a workshop		
Congo	Submitted	Sep 2023
South Sudan	Submitted	April 2023
Mali	TBC	TBC

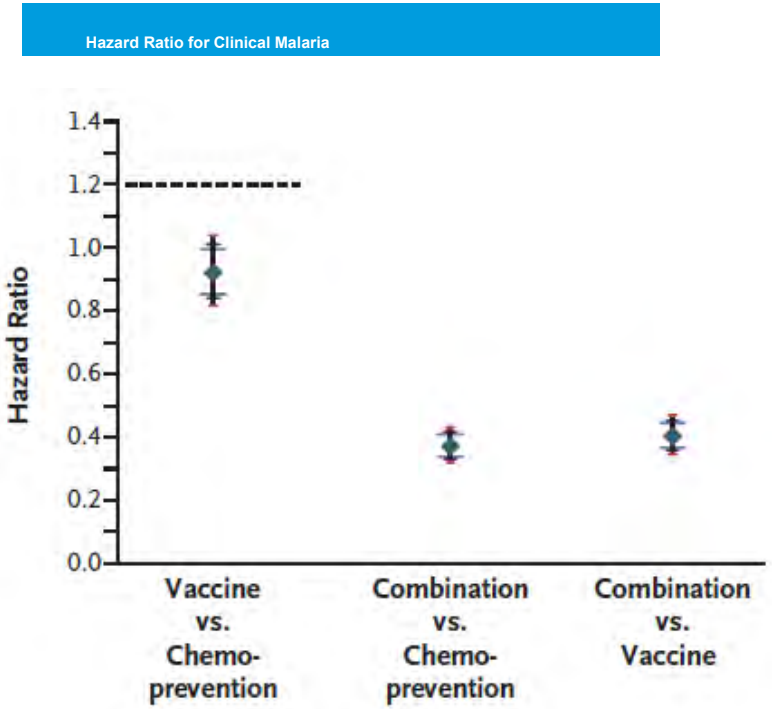
Market shaping efforts to increase supply/ decrease cost

- WHO, Gavi, UNICEF continue market shaping efforts as a priority, primarily through:
  - Increased RTS,S/AS01 supply
    - RTS,S product transfer to Bharat Biotech underway
    - GSK has committed 30M doses of AS01 to match antigen, without support for increased capacity
    - Potential fractional dosing; case control study to assess 3 vs 4 dose regimen
  - Second vaccine with similar or higher efficacy would reduce gap between demand and supply
    - Preparing for R21/MatrixM review – awaiting developer's timeline for submission of Phase 3 trial primary and secondary outcome measures so can plan review
      - Could see availability as early as 2024 for use in highly seasonal transmission settings
    - Presentation at ASTMH late breaker indicate may be as efficacious as RTS,S in areas of highly seasonal transmission
    - No data from high perennial transmission site
    - Will assess safety, efficacy, and duration of protection

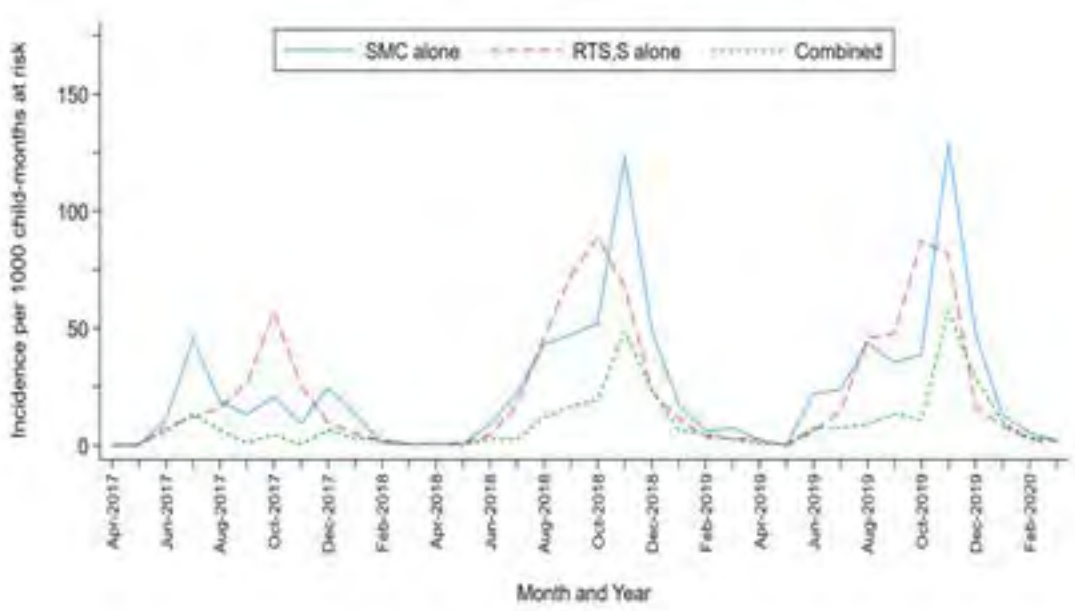
Thank you

Seasonal vaccination vs SMC

Seasonal vaccination non-inferior to 4 rounds of SMC



The 90%, 95%, and 99% confidence intervals for the hazard ratios all excluded the prespecified noninferiority margin of **1.20** (99% CI, 0.82 to 1.04)



Source: Chandramohan, D., Zongo, I., Sagara, I., Cairns, M., Yerbanga, R. S., Diarra, M., ..& Greenwood, B. (2021). Seasonal malaria vaccination with or without seasonal malaria chemoprevention. New England Journal of Medicine, 385(11), 1005-1017.

WHO recommendations for malaria vaccine schedule

Schedule (requires new vaccine visits)

- First dose administered from 5 months of age
- Minimum interval of 4 weeks between doses
- 3-dose primary schedule
- 4th dose approx. 12 – 18 months after 3rd dose to prolong duration of protection
- Flexibility in schedule to optimize delivery: as an example, to align 4th dose with other vaccines in second year of life
- Children who begin their vaccination series should complete the 4 dose schedule.

Optional schedule for settings with highly seasonal malaria or perennial malaria with seasonal peaks

- Maximizes impact by timing vaccination to the period of highest malaria transmission
- Primary 3-dose series provided monthly with additional doses provided annually prior to peak season (up to 5 doses total)
  - VE 12 months after dose 3 provided before peak in highly seasonal areas: **noninferior to seasonal malaria chemoprevention (75% efficacy)***
  - VE 12 months after dose 3 given age-based in perennial setting: **51% (95% CI 47–55)**

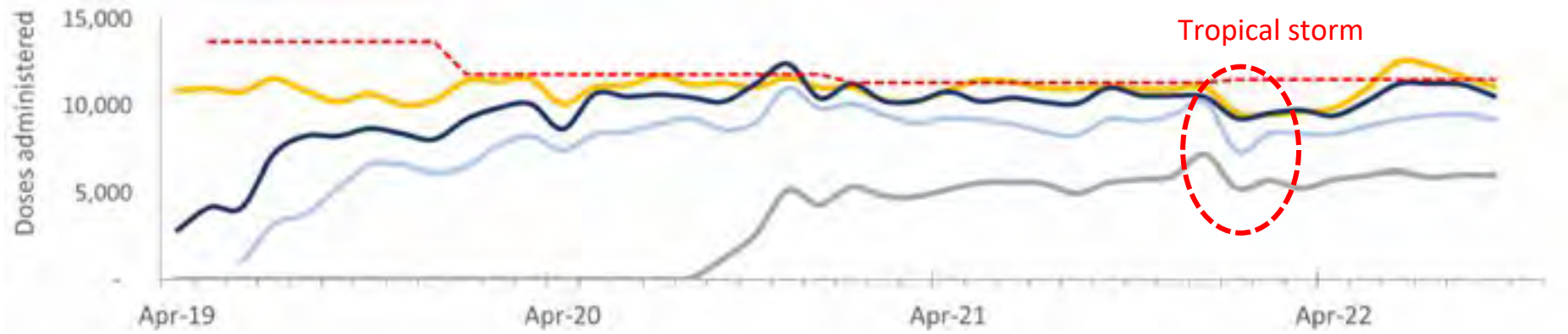
*Chandramohan *et al*, N Engl J Med 2021; 385:1005-1017
DOI: 10.1056/NEJMoa2026330

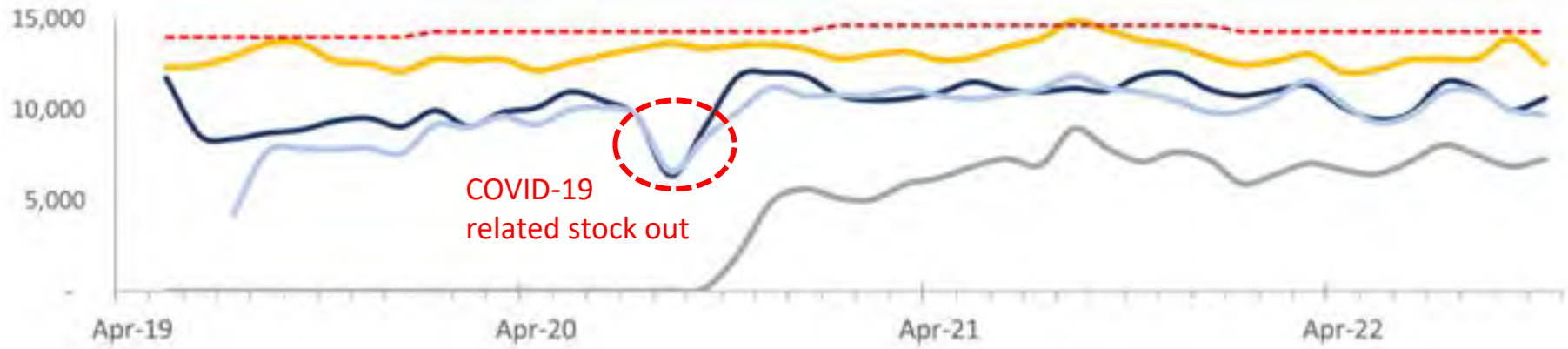
Immunization coverage in MVIP areas: monthly administrative data reports

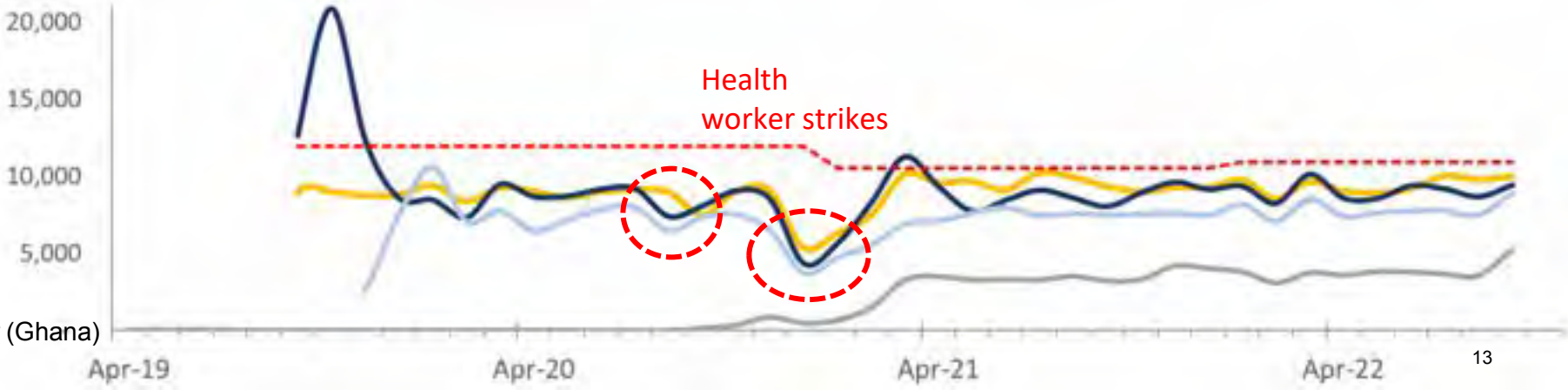
Malawi	2021	2022#
Penta-3	97%	94%
RTS,S-1	93%	89%
RTS,S-3	81%	76%
RTS,S-4		*69%

Ghana	2021	2022#
Penta-3	92%	89%
RTS,S-1	76%	74%
RTS,S-3	74%	72%
RTS,S-4		*71%

Kenya	2021	2022#
Penta-3	87%	87%
RTS,S-1	82%	83%
RTS,S-3	67%	72%
RTS,S-4		*54%







Data through Sept 2022 (Kenya, Malawi); October (Ghana)
* Among children who received RTS,S-3

WHO, Gavi, partners supported technical workshops to share MVIP lessons learned provide support for Gavi applications, including to identify areas of greatest need

- **Areas of greatest need**: those with highest malaria prevalence or incidence and highest child mortality across countries:
- Accra 19-21 July
  6 countries
- Accra 20-22 Sept
  5 countries
- Nairobi 18-20 Oct
  8 countries
- Webinars 9 & 10 Nov
  8 countries

Overview of Progress in STI Vaccines

Carolyn D. Deal, Ph.D.

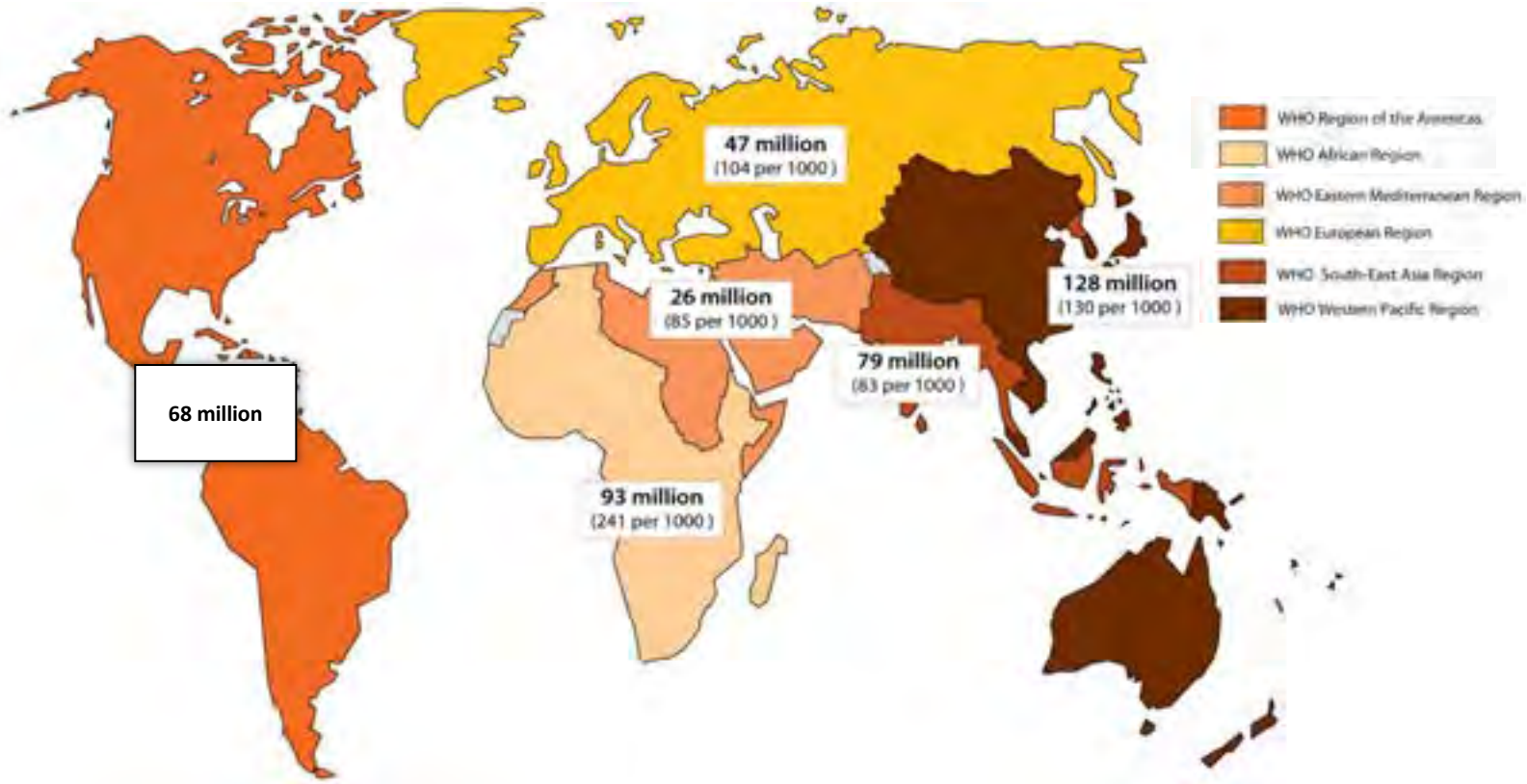
Chief

Enteric and Sexually Transmitted Infections Branch
NIAID, NIH, DHHS

December 6, 2022

National Institute of Allergy and Infectious Diseases

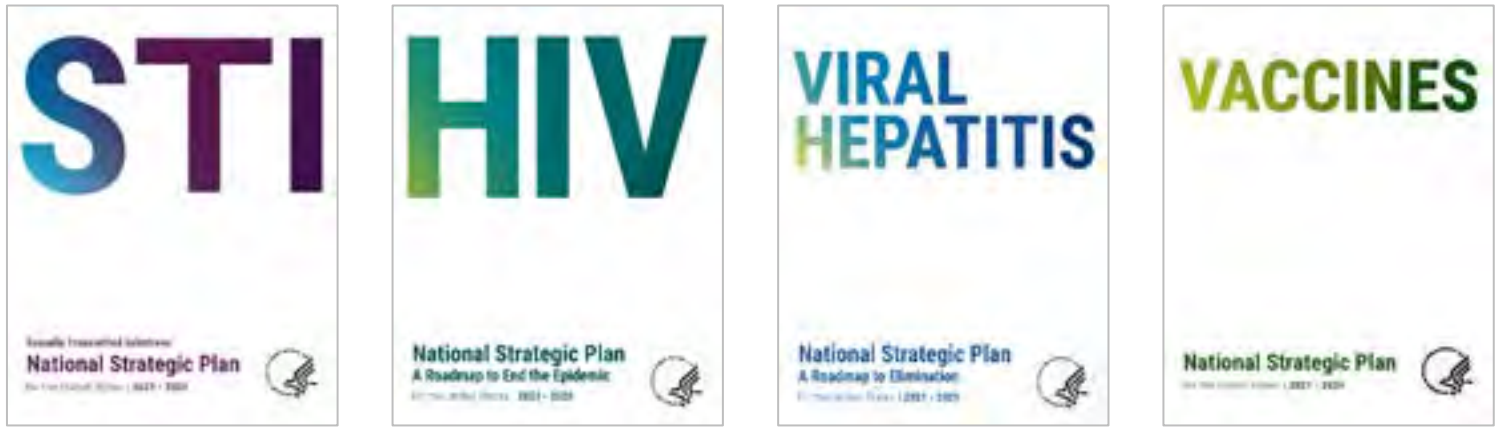
World Heath Organization
Global HIV, Hepatitis, and STIs Programmes

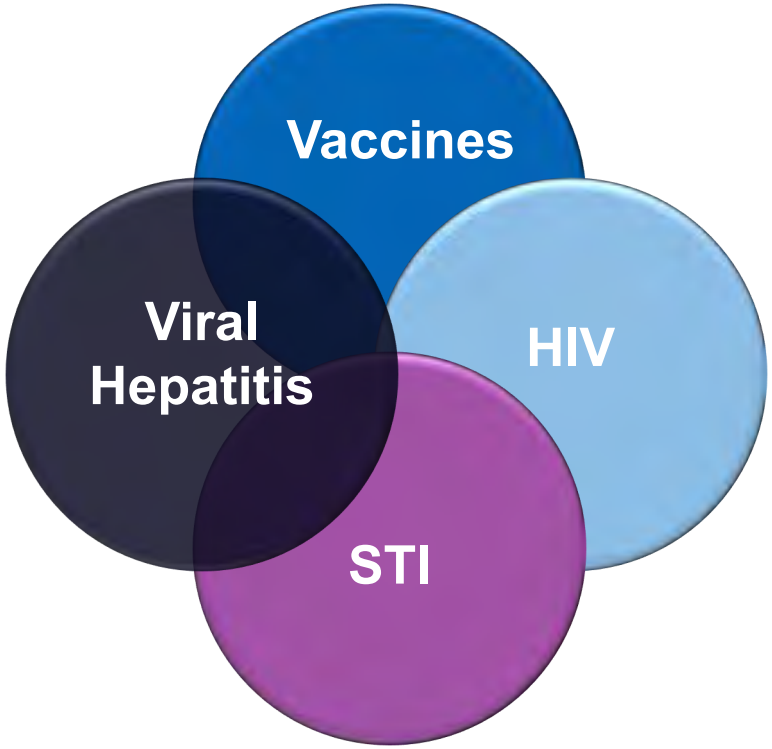


- More than 1 million STIs are acquired each day

NIH National Institute of Allergy and Infectious Diseases

Engaging the Syndemic Across National Strategic Plans



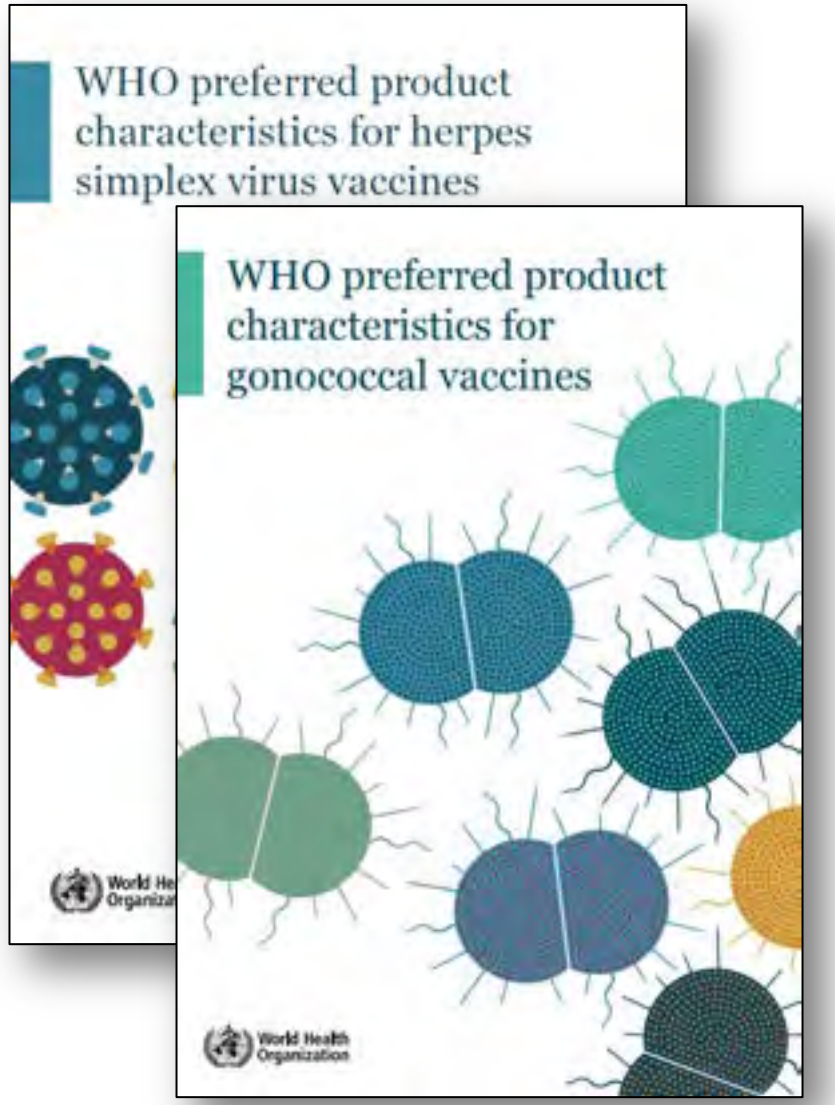


Stigma, discrimination, and social determinants of health are integral to addressing the syndemic

NIH National Institute of Allergy and Infectious Diseases

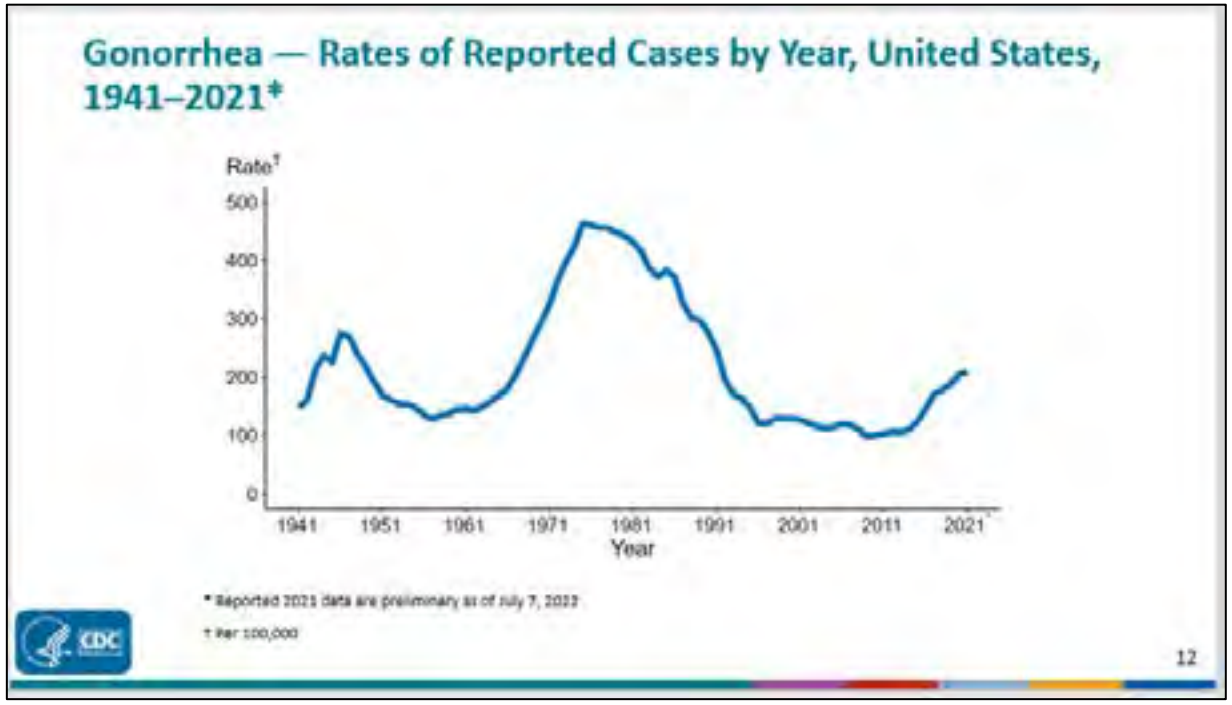
STI Vaccines - A Needed Intervention

- **Rationale:**
  - Despite diagnostics and treatment, epidemics of these diseases continue
  - Growing concern about antibiotic resistant *N. gonorrhoeae*
  - Limited commercial development (except for HBV & HPV)
- **WHO & NIAID developed an STI Vaccine Roadmap**
  - Collaboration with CDC & multiple international partners
  - Outlines need, development status, & future prospects for STI vaccines (HSV, *Chlamydia trachomatis*, gonorrhea, trichomanias, syphilis)
  - https://doi.org/10.1016/j.vaccine.2014.01.053
- **WHO Product Development Vaccine Advisory Committee**
  - HSV, chlamydia, & gonococcal infections highlighted at meetings
  - Published Preferred Product Characteristics (PPC) for HSV vaccines (https://www.who.int/reproductivehealth/publications/HSV-Vaccine-PPCs/en/)
  - Preferred Product Characteristics for Gonococcal Vaccines (https://www.who.int/immunization/research/ppc-tpp/Gonococcal_vaccine_PPCs_for-public-comment.pdf)



Neisseria gonorrhoeae

- **Importance**
  - Second most reported notifiable infection in the US;
  - 696,764 cases reported in 2021
  - Increasing over past 10 years
  - Control relies on prompt identification and treatment
- **Challenges with treatment**
  - History of resistance emerging as new antibiotics introduced
  - Currently showing resistance to most antibiotics commonly used for treatment
  - Antimicrobial resistance has increased interest in a vaccine
- **US CDC:** Urgent threat; **WHO:** Priority 2: High

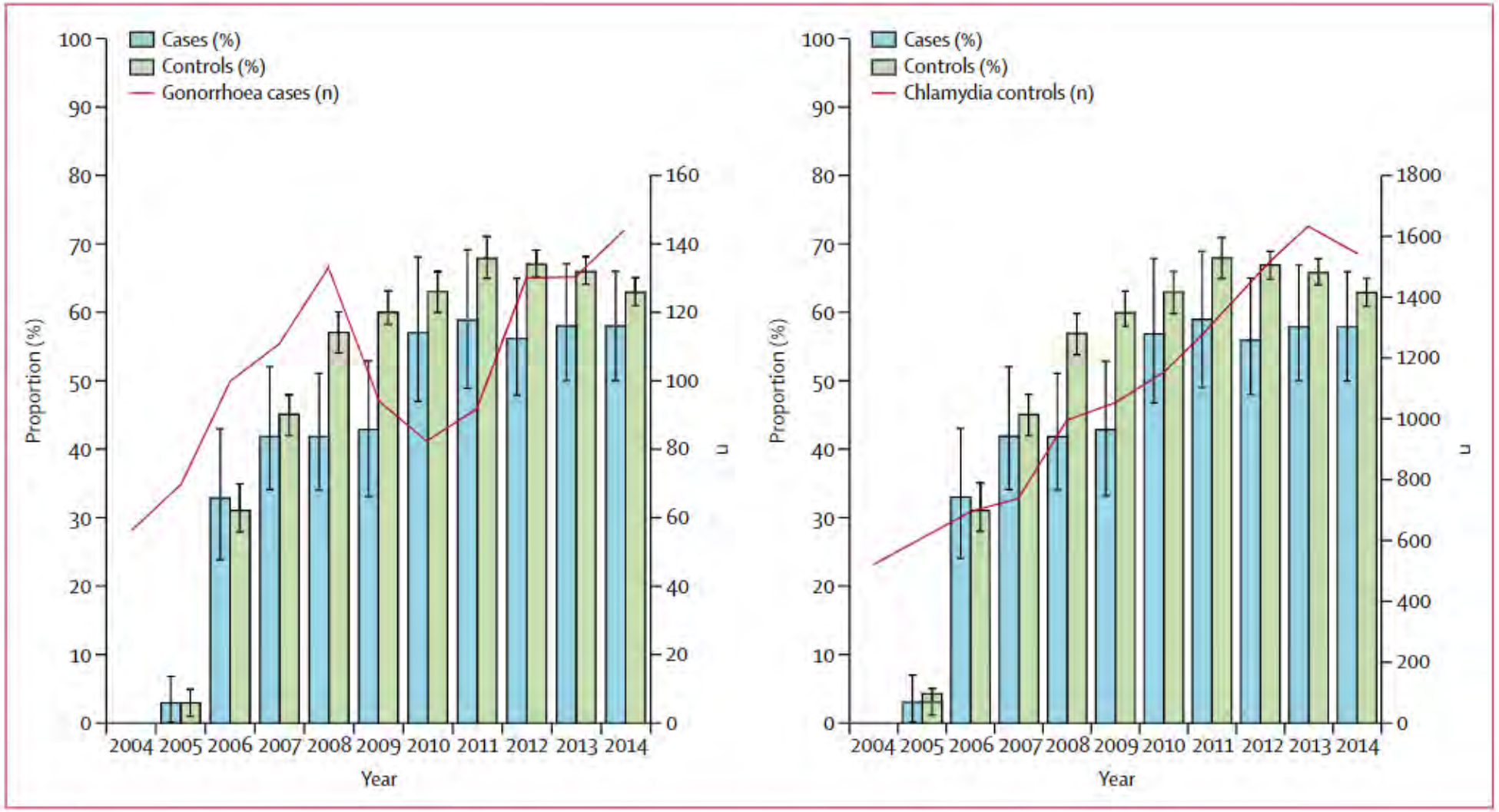


National Institute of Allergy and Infectious Diseases

N. gonorrhoeae Bexsero® (4CMenB) Clinical Trials

Gold Coast University Hospital	Time to first *N. gonorrhoeae* infection (urogenital, anorectal, or oropharyngeal) – n=130 (MSM)	Australia: study to be completed in 2024
Kirby Institute	Time to first *N. gonorrhoeae* infection (urogenital, anorectal, or oropharyngeal) – n=730 (MSM)	Australia: study to be completed in 2025
NIH National Institute of Allergy and Infectious Diseases	Incidence of *N. gonorrhoeae* infection (urogenital or anorectal) – n=2,200 (men/women)	USA/Thailand: study to be completed in 2024
UNC	Urethral challenge model of vaccinated men – n=140	USA: study to be completed in 2028
NIH National Institute of Allergy and Infectious Diseases	Characterize the rectal mucosal IgG antibody response to *N. gonorrhoeae* – n=50 (men/women)	USA: study to be completed in 2023

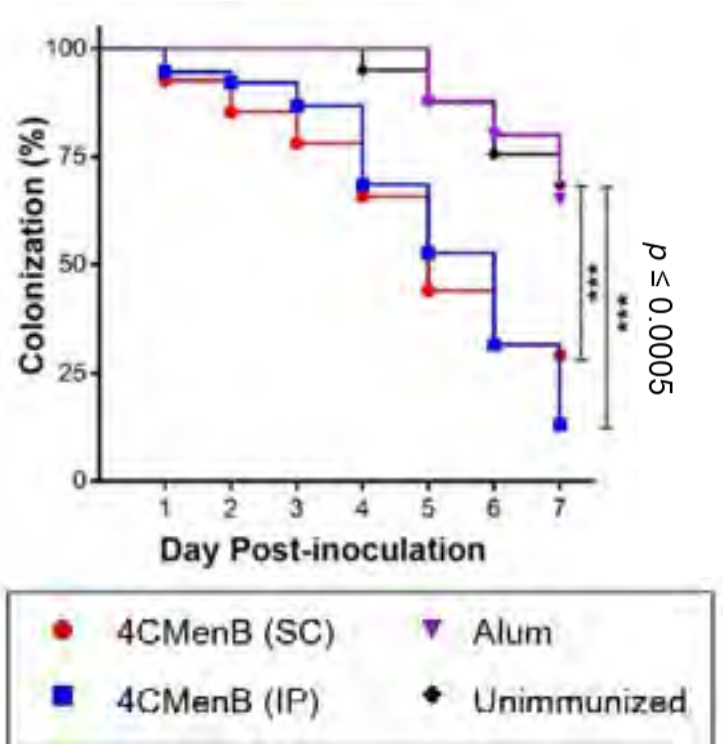
Effectiveness of a group B OMV meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

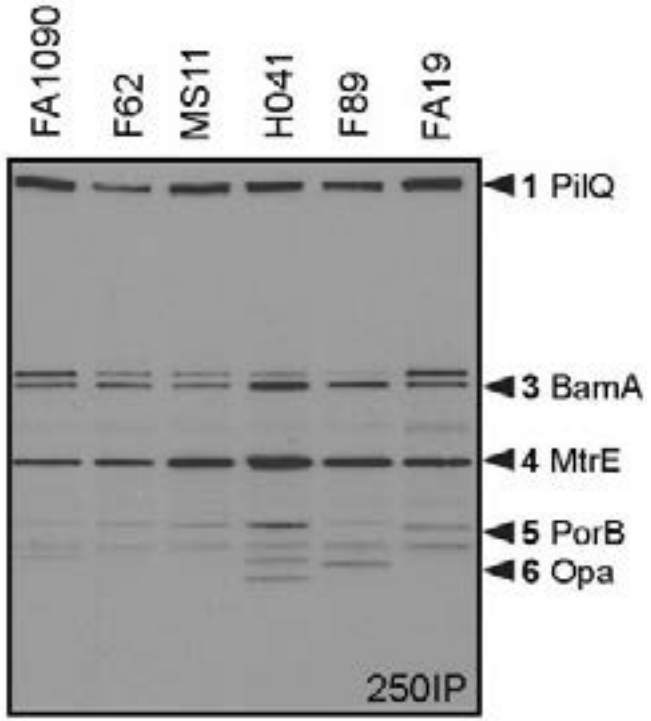


https://www.ncbi.nlm.nih.gov/pubmed/28705462

4CMenB in a Mouse Model

- In the gonococcal mouse model, 4CMenB immunization:
  - Reduced colonization
  - Immune serum recognized GC OMV proteins





n = 38-41/group

Leduc & Connolly, *et al.* 2020

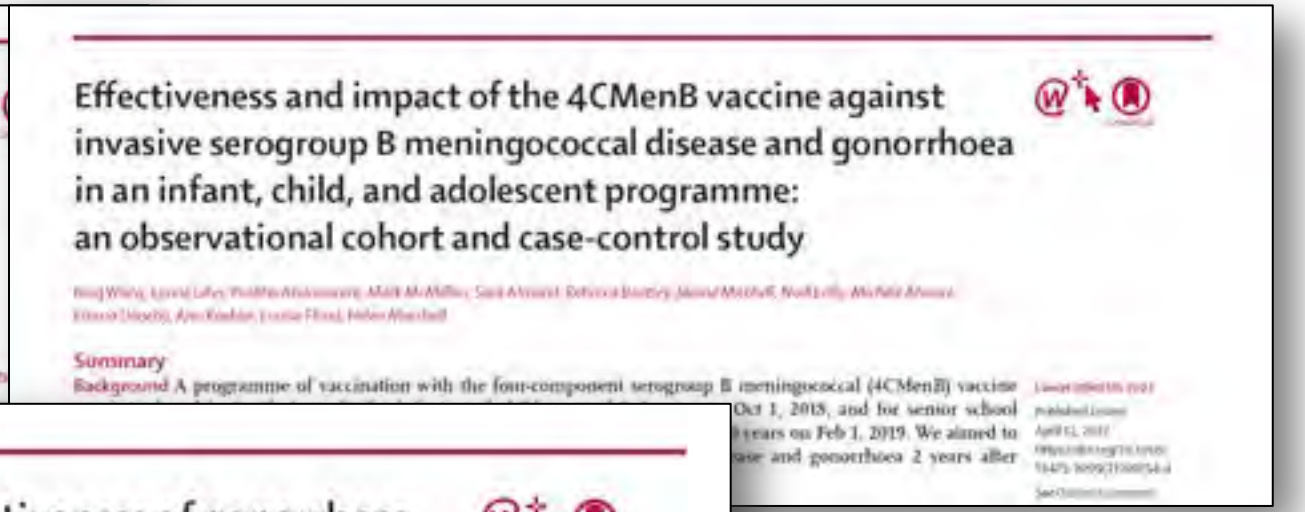
National Institute of Allergy and Infectious Diseases

Efficacy of Group B Meningococcal Vaccine in Preventing Gonorrhea

Effectiveness of a serogroup B outer membrane vesicle meningococcal vaccine against gonorrhoea: a retrospective observational study

Summary

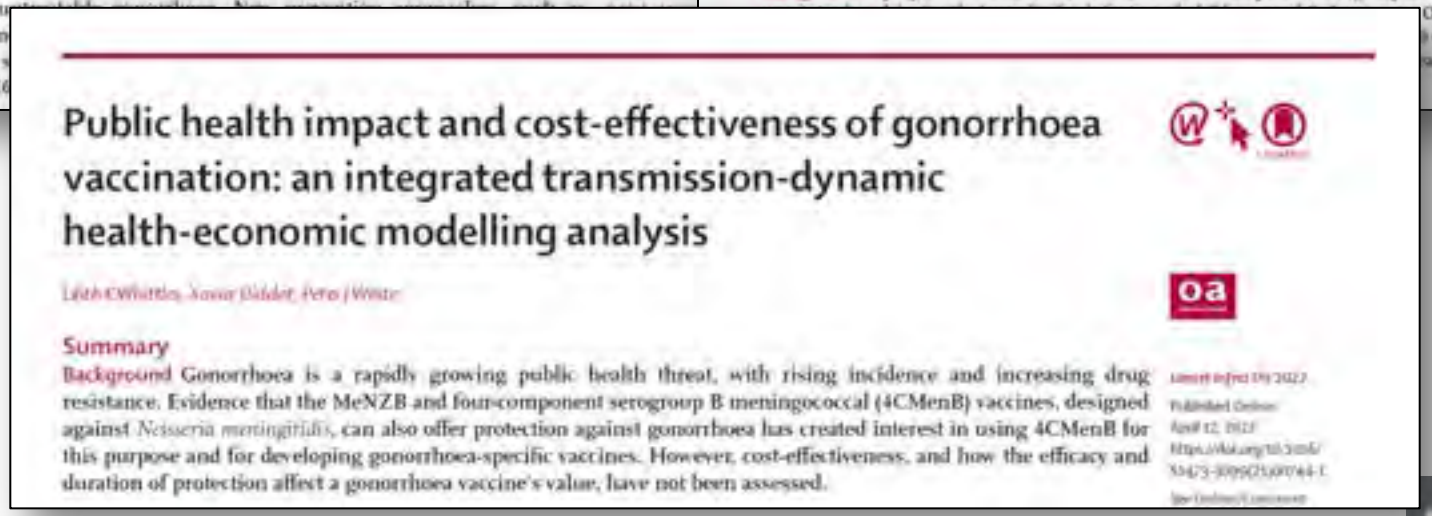
Background Declining antimicrobial susceptibility to current gonorrhoea antibiotic treatment and inadequate



Effectiveness and impact of the 4CMenB vaccine against invasive serogroup B meningococcal disease and gonorrhoea in an infant, child, and adolescent programme: an observational cohort and case-control study

Summary

Background A programme of vaccination with the four-component serogroup B meningococcal (4CMenB) vaccine



Public health impact and cost-effectiveness of gonorrhoea vaccination: an integrated transmission-dynamic health-economic modelling analysis

oa

Summary

Background Gonorrhoea is a rapidly growing public health threat, with rising incidence and increasing drug resistance. Evidence that the MeNZB and four-component serogroup B meningococcal (4CMenB) vaccines, designed against *Neisseria meningitidis*, can also offer protection against gonorrhoea has created interest in using 4CMenB for this purpose and for developing gonorrhoea-specific vaccines. However, cost-effectiveness, and how the efficacy and duration of protection affect a gonorrhoea vaccine's value, have not been assessed.

Lancet Infectious Diseases, April 12, 2022

NIH National Institute of Allergy and Infectious Diseases

The ANRS DOXYVAC Trial

European AIDS Treatment Group

October 24, 2022

Efficacy of a meningococcal B vaccine and a preventive antibiotic in reducing the risk of sexually transmitted infections

The ANRS DOXYVAC trial, conducted by a research team from the Paris public hospitals group (AP-HP), Université Paris Cité, Inserm and Sorbonne Université in collaboration with AIDES and Coalition PLUS, demonstrates the efficacy of both a meningococcal B vaccine in reducing the risk of gonorrhea infection and the use of doxycycline as preventive intervention for sexually transmitted infections when taken within 72h after sexual intercourse. In the wake of these results and taking into account the recommendations of the data and safety monitoring board, the scientific leaders and sponsor have decided to discontinue the trial and recommend the provision of both interventions to all its participants. This study is sponsored and funded by ANRS | Emerging Infectious Diseases in partnership with Roche (1).

Press release:
https://www.eatg.org/hiv-news/efficacy-of-a-meningococcal-b-vaccine-and-a-preventive-antibiotic-in-reducing-the-risk-of-sexually-transmitted-infections/

ClinicalTrials.gov:
https://www.clinicaltrials.gov/ct2/show/NCT04597424

NIH National Institute of Allergy and Infectious Diseases

Phase 2 Clinical Trial: Testing 4CMenB as a Gonococcal Vaccine

- **2015**: US FDA licensed rMenB+OMV NZ vaccine to prevent Group B meningococcal infection (Bexsero, Novartis/GSK)
- **2020**: Phase 2 trial initiated. A collaboration between NIAID, STI CTG, HPTN, Uniformed Services University (USU), WRAIR/AFRIMS and GSK
- Phase II, randomized, observer-blind, placebo-controlled, multi-site trial of the FDA licensed vaccine, 4CMenB (Bexsero)
- Objective: To demonstrate efficacy in prevention of urogenital and/or anorectal gonococcal infection https://clinicaltrials.gov/ct2/show/NCT04350138
- Approximately 2,200 participants are to be enrolled to achieve at least 202 evaluable cases. Participants: Men (MSW and MSM) and women
- 5 sites in the United States, 2 sites in Thailand
- Sponsor: National Institute of Allergy and Infectious Diseases

NIH National Institute of Allergy and Infectious Diseases

Additional studies of 4CMenB vaccination and gonococcal infection

- **Australia: 2 Phase 3 trials among MSM (Trial 1 =ACTRN12619001478101; Trial 2= NCT04415424)**
  - Trial 1: n=130; Trial 2: n=730; started/starting in 2020
  - Primary outcome: time to first *N. gonorrhoeae* infection (urogenital, anorectal, or oropharyngeal)
  - Sponsors: Trial 1, Gold Coast University Hospital; Trial 2, Kirby Institute (Australia)
  - Expected completion: 2023 and 2024

- **USA: Efficacy of immunization with 4C-MenB in preventing experimental urethral infection with *Neisseria gonorrhoeae* (NCT05294588; Phase 2)**
  - n=140 males (age 18-36)
  - Primary outcome: prevention; male urethral challenge model
  - Sponsors: University of North Carolina, Chapel Hill (USA)
  - Estimated completion: 2028

- **USA: Mucosal immunity against *Neisseria gonorrhoeae* after 4CMenB vaccination (NCT04722003; Phase 2)**
  - n=50 males and females aged 18-49 years
  - Primary outcome: characterize the rectal mucosal IgG antibody response to *N. gonorrhoeae* elicited by the 4CMenB vaccine as compared with placebo in healthy adults
  - Sponsor: NIAID
  - Estimated completion: 2023

NIH National Institute of Allergy and Infectious Diseases

Additional (non-RCT) studies of 4CMenB vaccination and gonococcal infection

- **USA: Gonococcal immune responses induced by 4CMenB (NCT04094883; Phase 4)**
  - n=15 young people (age 18-25)
  - Primary outcome: change in anti-*N. gonorrhoeae* OMV-specific IgG, IgM, IgA concentrations; change in frequency of CD4+ T cells expressing at least two different activation markers
  - Sponsors: University of North Carolina, Chapel Hill (USA); Completed September 2020

- **Kenya: Gonococcal immune responses to 4CMenB among key populations (NCT04297436)**
  - n=~ 50 males and females aged 18-25 years (with and without HIV infection)
  - Primary outcome: cross-reactive humoral and T cell responses against *N. gonorrhoeae*
  - Sponsor: University of Oxford (United Kingdom); Completed February 2022

- **Australia: Immunisation for adolescents against serious communicable diseases (NCT04398849)**
  - n=7,100 males and females aged 14-19 years (in the Northern Territory)
  - Primary outcome: surveillance data on gonorrhea and meningococcus following 4CMenB vaccination
  - Sponsor: University of Adelaide; Estimated completion 2024

Gonorrhea vaccine candidates under development

- **Outer membrane vesicle vaccines**
  - **Meningococcal (*Nm*) OMVs**
    - 4CMenB (Bexsero®, GSK)
    - MC58ΔABR (FDA/CBER)
  - **Gonococcal (*Ng*) OMVs**
    - With microencapsulated IL-12 and IL-10 (TherapyX, Inc.)
    - Genetically modified strains (Emory/USU)

Nm: Connolly *et al. JID.* 2021; Leduc & Connolly *et al. PLoS Pathogen*. 2020 (4CMenB)
Matthias *et al. JID.* 2022 (MC58ΔABR)

Ng: Reviewed in Rice PA, Shafer WM, Ram S, Jerse AE. *Annu Rev Microbiol*. 2017; Tran Ho *et al.* Poster 3687. *ASM Microbe*. 2022.

Slide courtesy of Ann Jerse, USU

- **Peptide vaccines**
  - 2C7 LOS epitope, peptide mimetic (UMass)
  - PorB and MtrE peptide/virus-like particles (UNM)
  - Nanoparticles with MtrE (UNC)
  - MtrE in Vesi-vax liposomal platform (Molecular Express, Inc.)

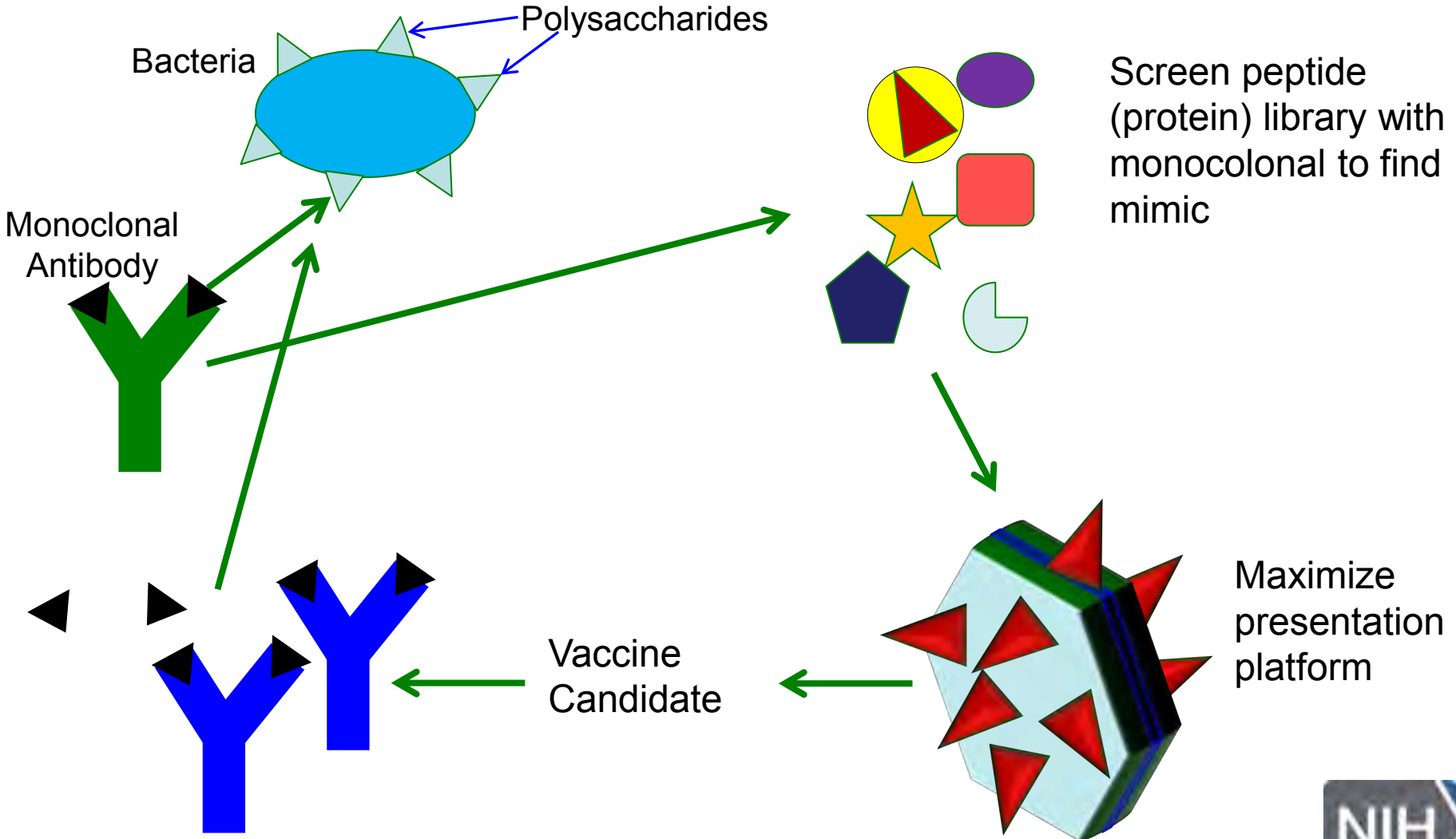
- **Purified Protein Subunit Vaccines**
  - **Antigens involved in physiology or metabolism**
    - TbpA,B – transferrin receptors (U of Toronto/Georgia State)
    - MetQ – methionine transporter (OSU; Griffith U)
    - MsrA/B – repairs oxidatively damaged proteins (Griffith U)
  - **Antigens involved in evasion of innate effectors**
    - MtrE – outer membrane channel of efflux pumps (USU/Emory)
    - SliC – lysozyme inhibitor (OSU)
    - Acp – lysozyme inhibitor (U of Southampton)
  - **Antigens involved in bacterial structure; identified by proteomics**
    - BamA – central component of the outer membrane protein assembly complex (OSU)

NIH National Institute of Allergy and Infectious Diseases

Gonococcal Vaccine Candidates Approaching Phase 1 Trials

- Novel TbpB antigens identified by analysis of transferrin-binding defective TbpB mutants (PI: Schryvers, R01)
- NGoXIM: gonococcal OMVs combined with sustained-release microspheres containing recombinant human IL-12 (Intravacc B.V., BAA)
  - This vaccine will be formulated for intranasal immunization with GneX12 (IL-12 containing microspheres) developed and produced by Therapyx Inc.
- dmGC_0817560: native Outer Membrane Vesicles (nOMV) isolated from gonorrhea (PI: A. Hill, CARB-X)

Peptide “mimic” vaccine



Gulati, S, Rice PA, et. al. Properdin Is Critical for Antibody-Dependent Bactericial Activity against Neisseria gonorrhoeae that Recruit C4b-Binding Protein. J Immunol. 2012 Apr 1; 188(7) 3416-25. PMID: 22368277

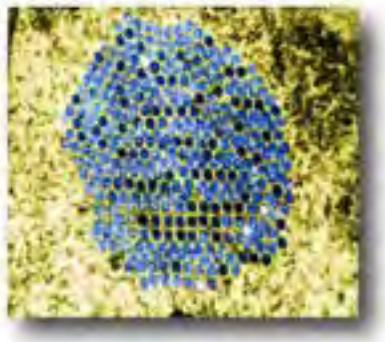
NIH National Institute of Allergy and Infectious Diseases

Questions going forward

- Future questions:
  - What other studies are needed to evaluate 4CMenB vaccines?
  - What would be the implications (for 4CMenB containing vaccines of a positive outcome of the phase II gonococcal studies with the 4CMenB vaccine?

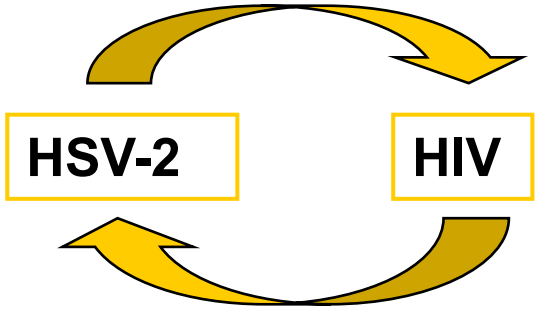
Herpes simplex virus

Leading cause of genital ulcer disease (GUD) worldwide

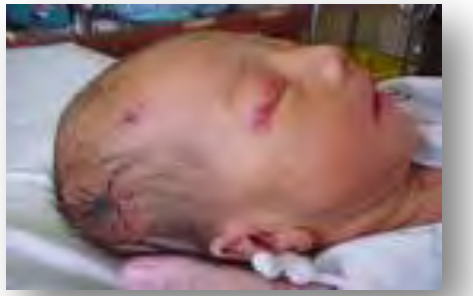


Impact on sexual and reproductive health (SRH)

HIV-1 acquisition and transmission



Neonatal herpes

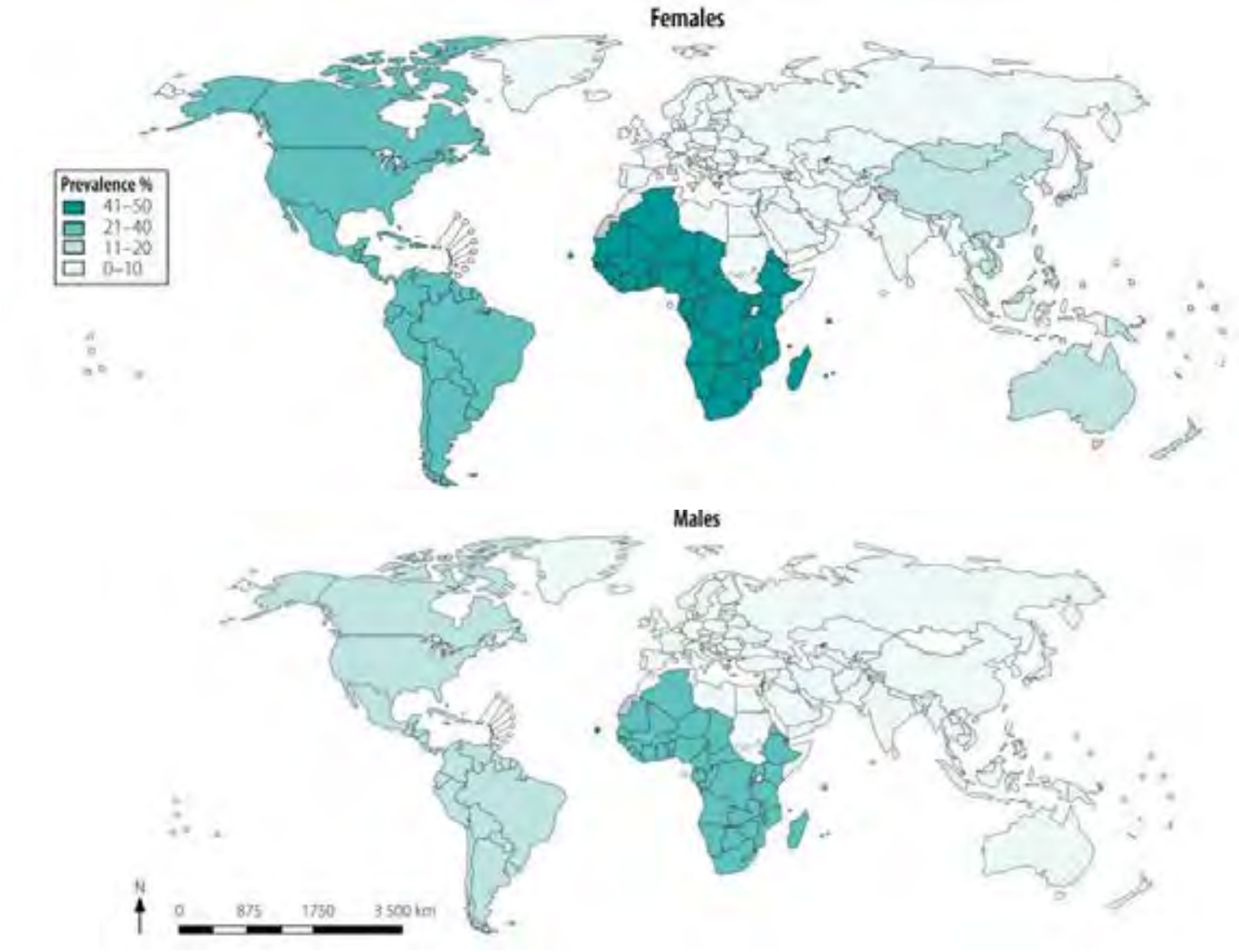


National Institute of Allergy and Infectious Diseases

Herpes simplex virus-2 Clinical Trials

Vaccines	Phase 1	Phase 2	Phase 3	
ANTERIS	COR-1			Stopped after Phase I/IIa trial (2017)
agenus	HerpV (AG-707)			
genocea	GEN-003			MTA & license to Shionogi in 2020
SANOFI	HSV529			Study to be completed in May 2024
Vical	VCL-HB01			
GlaxoSmithKline	Herpevac – Canada, USA			
BIONTECH	mRNA vaccine			Phase I starting soon

HSV-2 prevalence estimates: 491.1 million infections globally in 2016



Bull World Health Organ. 2020 May 1; 98(5): 315–329. Published online 2020 Mar 25. doi: 10.2471/BLT.19.237149

Large Global Burden of HSV-1 Infection, Increasing Role of Genital HSV-1

- An estimated 3583.5 million of the 5632.6 million global population 0–49 years of age were infected orally with HSV type 1, a prevalence of 63.6%.
- Genital HSV type 1 infection affected an estimated 192.0 million individuals 15–49 years of age worldwide, equivalent to a prevalence of 5.2%.
  - The number of people with genital HSV type 1 was highest in the Region of the Americas, followed by the European Region.
- Taken together, an estimated 596.0 million–655.7 million people, 16.0–17.6% of the world's population 15–49 years of age, had genital HSV type 1 or HSV type 2 or both.

Bull World Health Organ. 2020 May 1; 98(5): 315–329. Published online 2020 Mar 25. doi: 10.2471/BLT.19.237149

Basic Research & Pre-clinical HSV Vaccine Development

- Subunit vaccine based on glycoprotein D of HSV-2 (gD2), gC2 and gE2 (prophylactic vaccine)
  - University of Pennsylvania (PI: Friedman)
- Live attenuated HSV-2DgD vaccine (prophylactic vaccine)
  - Albert Einstein College of Medicine (PI: Jacobs)
- Recombinant vaccine based on gD2/gB2 in proprietary nanoemulsion for intranasal administration (therapeutic and prophylactic vaccine)
  - BlueWillow Biologics (formerly NanoBio, Inc.) (PI: Ganesan)
- mRNA vaccines based on two virion proteins and two ribonucleotide reductase subunit proteins (therapeutic vaccine)
  - University of California, Irvine. (PI: BenMohamed)
- Live-attenuated HSV-1 vaccine that demonstrates cross-protection against HSV-2 (prophylactic vaccine)
  - Thyreos, Inc.

Image source: CDC

NIH National Institute of Allergy and Infectious Diseases

Phase 1 Trial: RNA Vaccine for HSV

- Sponsored by BioNTech
- Vaccine: RNA vaccine administered as intramuscular injection
  - Developed by Harvey Friedman at the University of Pennsylvania
  - glycoprotein D of HSV-2 (gD2), gC2 and gE2

Questions going forward:

- How does the development of an mRNA based candidate affect the feasibility and potential value proposition for a HSV vaccine?
- Is there anything WHO should/could do to support this innovation?

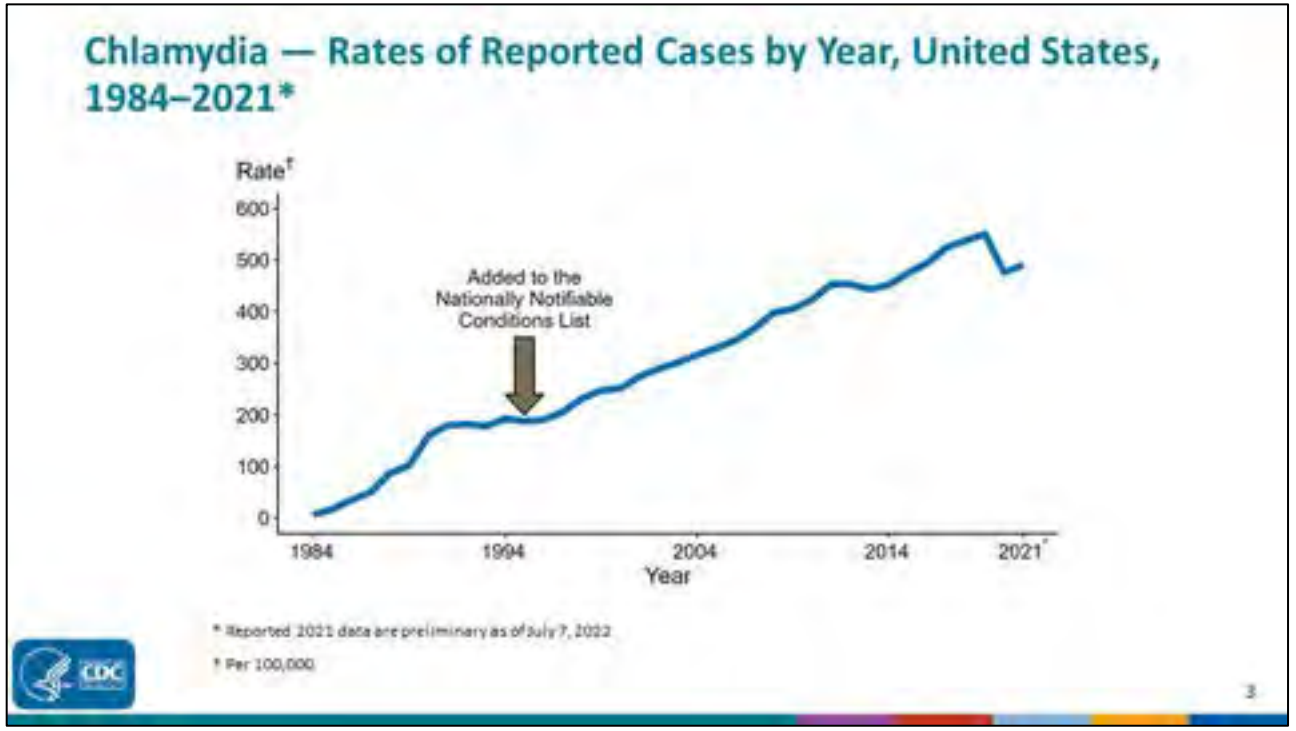
https://clinicaltrials.gov/ct2/show/NCT05432583

NIH National Institute of Allergy and Infectious Diseases

Chlamydia trachomatis

- **Importance**
  - Most common notifiable STI in the United States
  - 1,628,397 cases reported in 2021

- **Challenges**
  - Most common bacterial STI worldwide
  - Important cause of infertility, EP, chronic pelvic pain
  - Disproportionately affects adolescents
  - Control programs are hard to bring to scale



National Institute of Allergy and Infectious Diseases

Chlamydia trachomatis Clinical Trials

recombinant protein

Vaccines	Phase 1	Phase 2	Phase 3

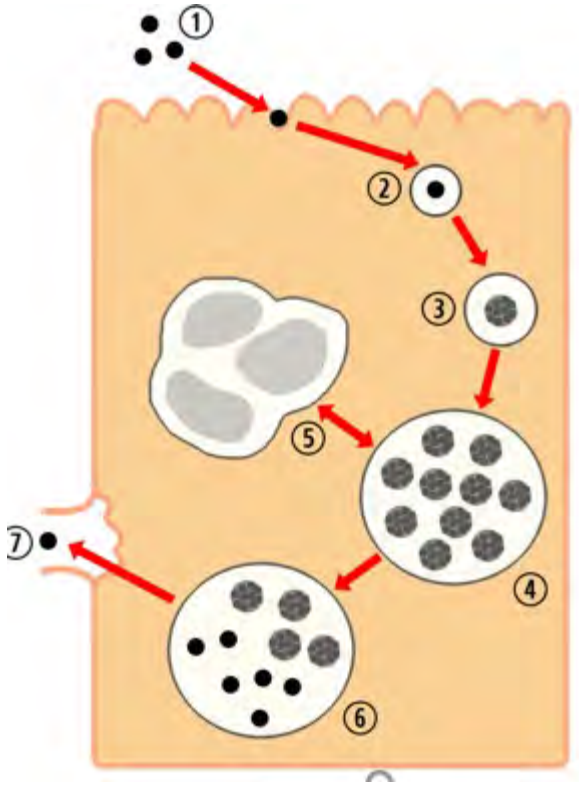
STATENS SERUM INSTITUT

CTH522

●●● *Study completed in February 2022*

Stages of the developmental cycle and vaccine targets

1. Extracellular EBs and attachment: MOMP, omcB, PmpD, PmpG
2. Endocytosis: TarP
3. Differentiation of EBs to RBs: Key proteins yet to be identified
4. Replication: Inc, MOMP, omcB, HtrA, NrdB, Pgp3, plasmid-encoded proteins, TarP
5. Persistence phase: Hsp60, HtrA
6. Differentiation of RBs to EBs: Key proteins yet to be identified
7. Exocytosis/Exit: Key proteins yet to be identified



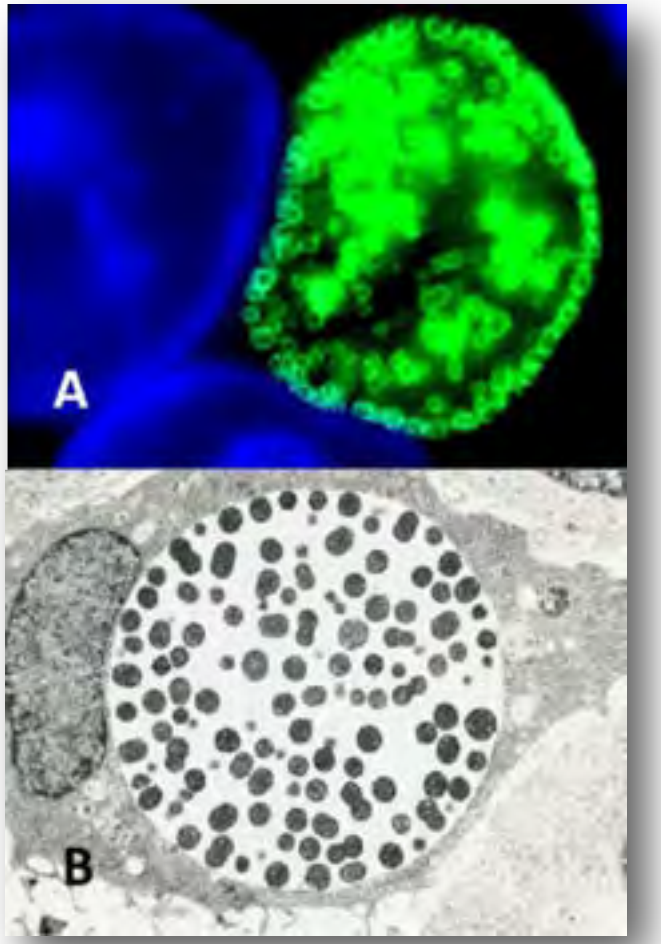
Chlamydial vaccine candidate now under clinical evaluation

- Vaccine based on the chlamydial MOMP (CTH522, SSI) completed Phase 1 trial
  - Recombinant protein containing several MOMP serotypes
  - Safe and induced significant levels of neutralizing antibodies
  - Robust cellular response and levels of vaginal IgG and IgA
  - CTH522:CAF01 superior to CTH522:Alum
  - Results published in Lancet Infectious Diseases: https://pubmed.ncbi.nlm.nih.gov/31416692/.
- Clinical Phase 1 dose response study of CTH522:CAF01 finished in February 2022 (NCT03926728)

Slide Source: Frank Follmann, Statens Serum Institut

Basic Research & Pre-clinical Chlamydia Vaccine Development

- Whole-cell inactivated *C. trachomatis* with or without multi-protein subunit mix (MOMP, CPAF, OmcB, and/or pgp3) developed in a novel swine model
  - NC State University (PI: Kaeser)
- Recombinant MOMP variable domains fused to *N. lactamica* carrier proteins
  - Tufts University (PI: Massari)
- Protein vaccine with MOMP and 4 Pmp antigens
  - University of Alabama (PI: Geisler)
- Nanoparticles containing MOMP and other outer membrane proteins
  - Lawrence Livermore Labs (PI: Coleman)

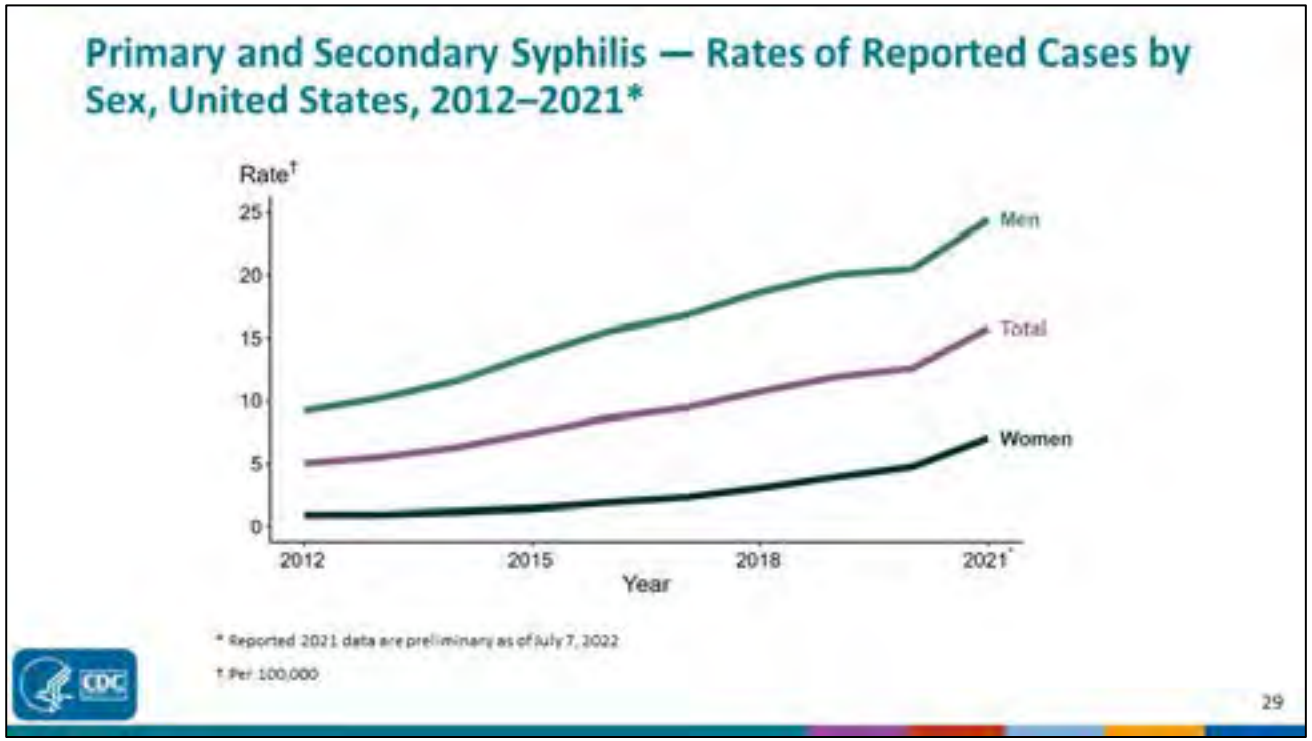


Chlamydia inclusion body image: Marrazzo & Suchland, 2014. *F1000 Prime Reports*

NIH National Institute of Allergy and Infectious Diseases

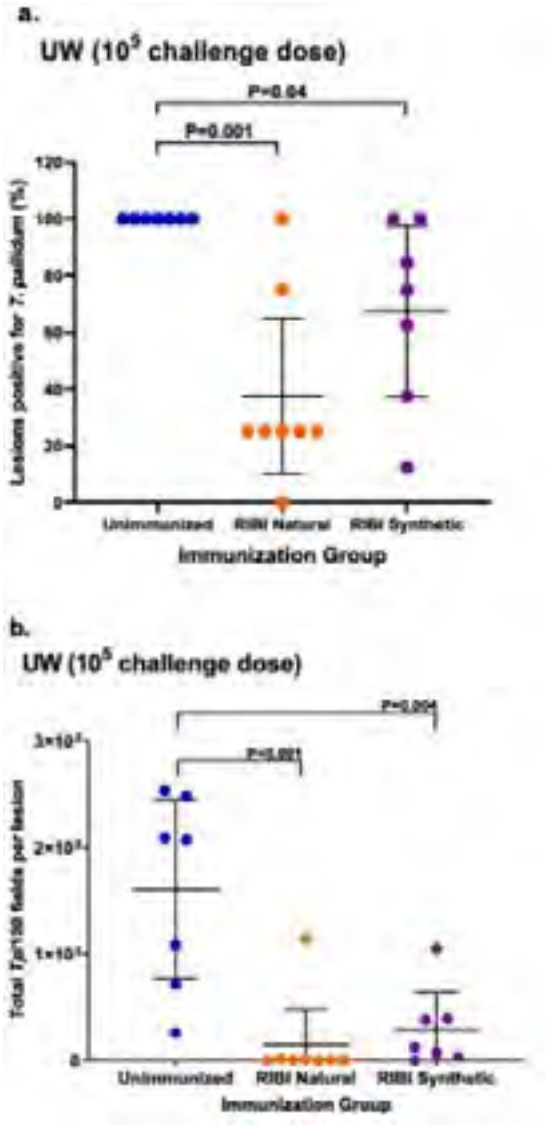
Treponema pallidum

- Syphilis case reports continue to increase since reaching a historic low in 2000 and 2001. In 2021, there were 171,074 new cases of syphilis (all stages).
- From 2017 to 2021, 46.3% of primary and secondary syphilis cases were among men who have sex with men.
- From 2020 to 2021, the number of cases among MSM increased 5.5% (17,786 in 2020 to 18,770 in 2021).
- Congenital syphilis continues to be a concern in the United States. Preliminary 2021 data show more than 2,600 cases of congenital syphilis.



National Institute of Allergy and Infectious Diseases

Tri-antigen Syphilis Vaccine



- Immunization with a TprC/TprK/Tp0751 tri-antigen cocktail protects animals from progressive syphilis lesions and substantially inhibits dissemination of the infection
- Both the number of positive lesions (a) and total treponemes recovered per lesion (b) were reduced in immunized rabbits compared to unvaccinated controls
  - Immunization groups included two different RIBI adjuvants, either natural or synthetic RIBI

Lukehart SA, *Vaccine,* 2022. https://pubmed.ncbi.nlm.nih.gov/36376214/

NIH National Institute of Allergy and Infectious Diseases

Supporting National Efforts to Control and Prevent Syphilis

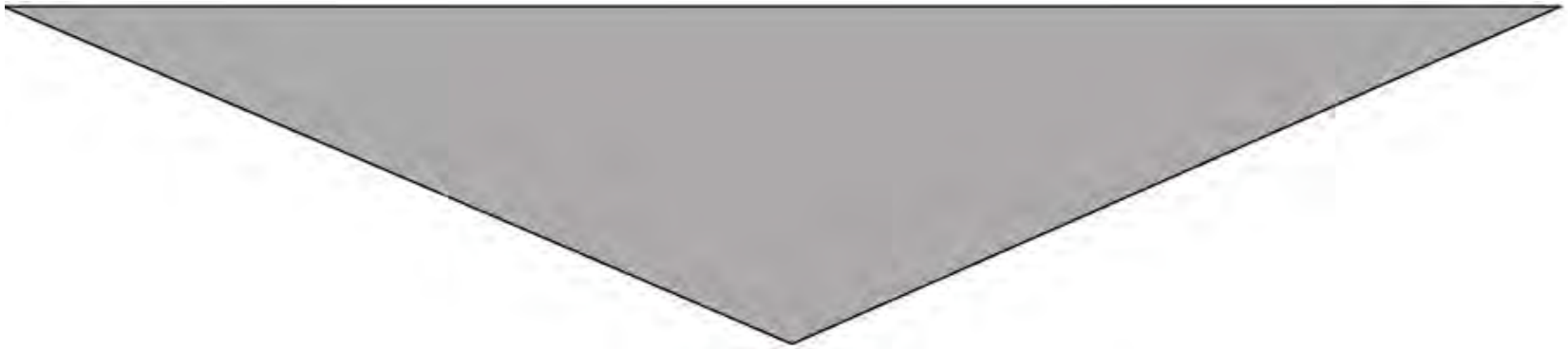
- Basic research advances
  - "Factors affecting long-term in vitro culture of *T. pallidum*" (P.I. Steven Norris)
  - Developed a method for long-term in-vitro culture of *T. pallidum* where bacterium remains viable, multiplies, and remains infectious
  - Potential to accelerate future research

Edmondson D, *mBio,* 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6020297/

Challenges and Opportunities

- Understanding pathogenesis
- Natural history of infection
- Exploring the human immune response
- Need to increase public health awareness
- Overcoming manufacturing challenges

- Research opening new avenues of understanding of STIs
- Early clinical trials provide insight to protective immune responses
- Opportunity for dialogue with policy makers in governments and NGOs
- Increasing vaccine manufacturing capability around the world



Vaccines to Control and Prevent STIs

NIH National Institute of Allergy and Infectious Diseases

Ongoing Public Health Needs: New Interventions for the Future!

Thank You

DMID/ESTIB/STI Section Team
Tom Hiltke, PhD
Jonathan Glock, MPH
Kimberly Murphy, MS
Peter Wolff, MHA
Krista Cato, RN
Melinda Tibbals, RAC, CCRA
Leah Vincent, PhD
Lori Newman, MD
Eleanore Chuang, PhD
Kristie Connolly, PhD

NIAID/DIR
Jeff Cohen, MD

NIAID/DMID
Amanda Coleman

PDVAC focused discussion:

Therapeutic HPV vaccines

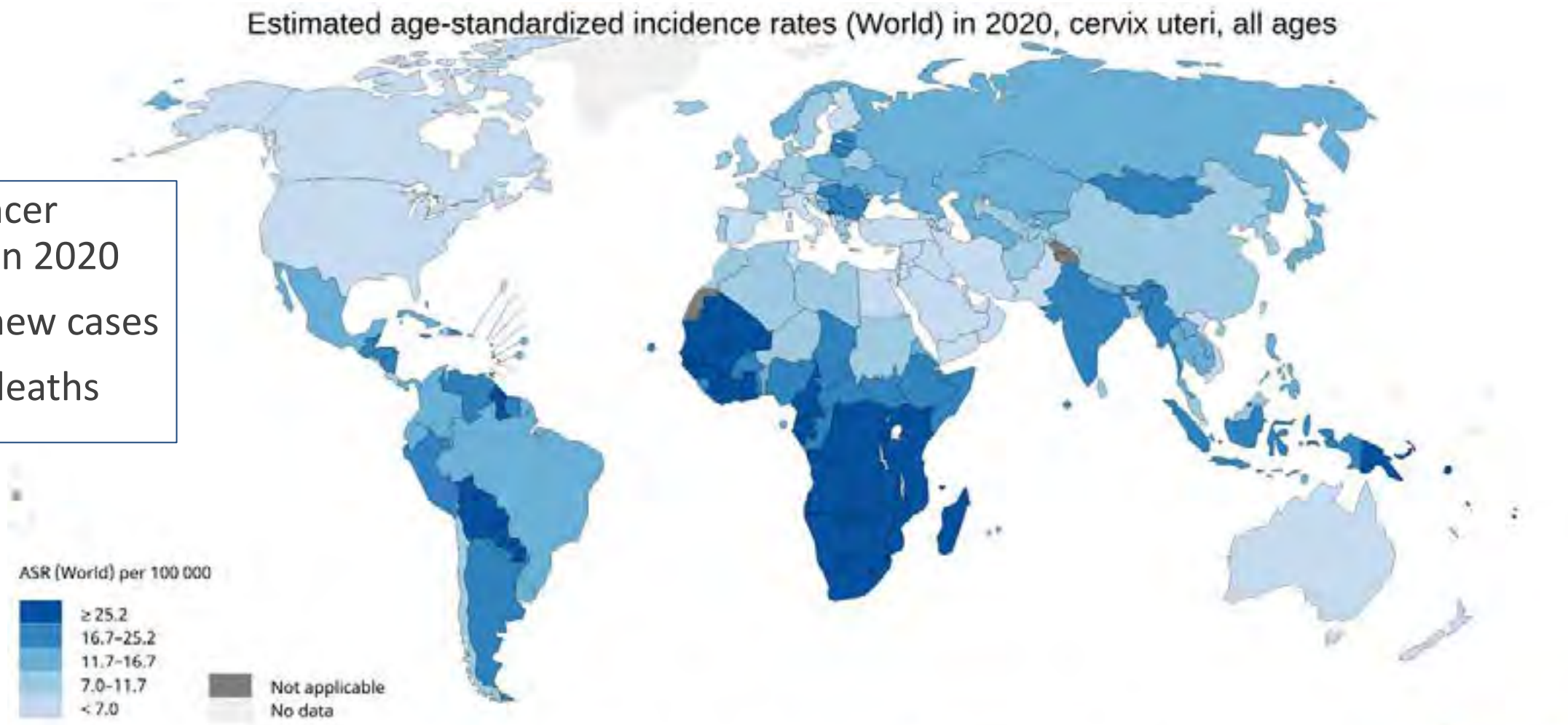

The Teal Sisters, Zambia, survivors and advocates for cervical cancer elimination

Dr Sami Gottlieb
World Health Organization
6 December 2022

Cervical cancer is a global health problem

Cervical cancer worldwide in 2020

- 604,000 new cases
- 342,000 deaths

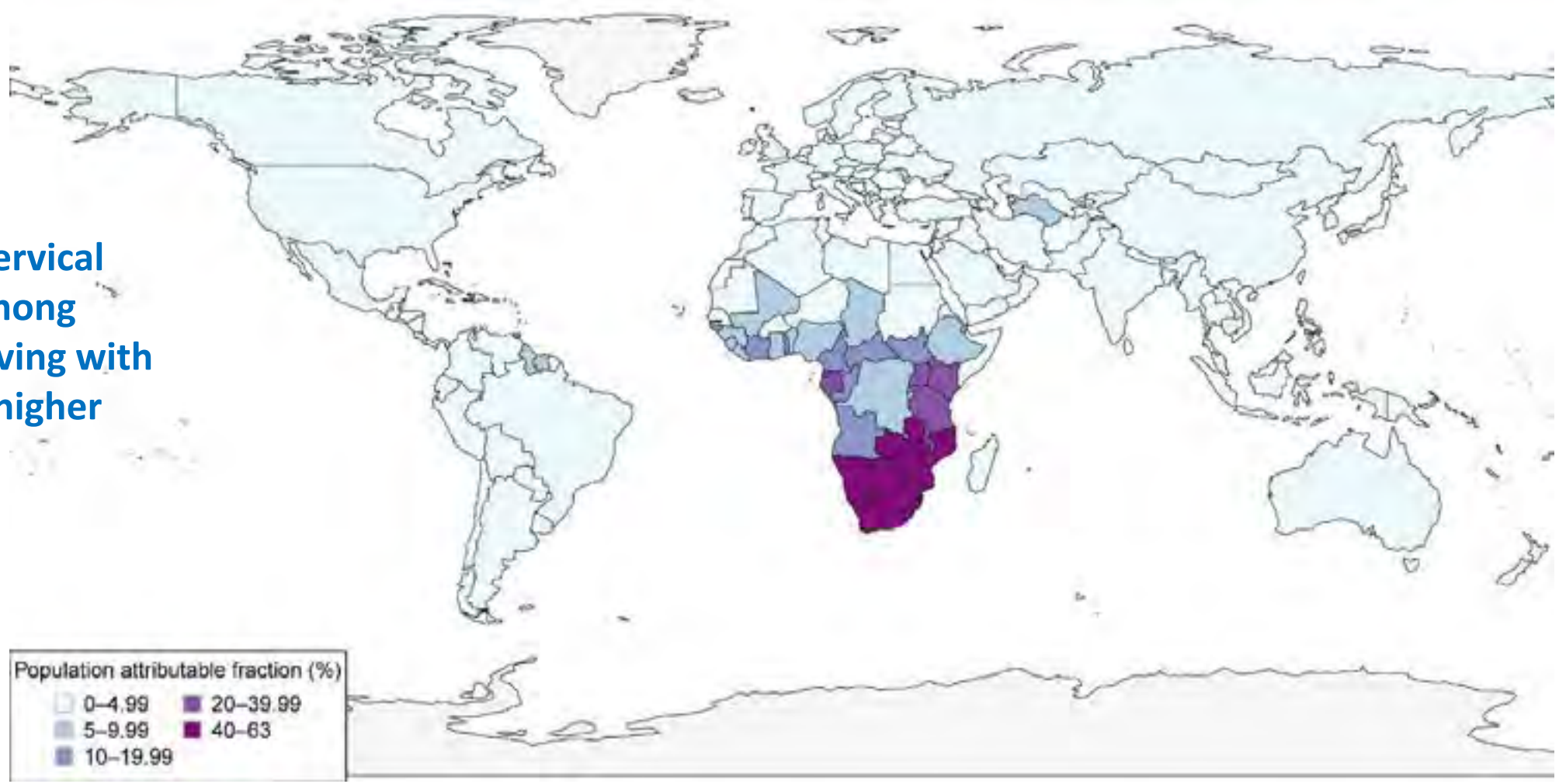


Data source: GLOBOCAN 2020
Graph production: IARC
(http://gco.iarc.fr/today)
World Health Organization

Cervical cancer and HIV

Population attributable fraction of women with cervical cancer living with HIV, 2018

Risk for cervical cancer among women living with HIV is 6x higher



Source: Stelzle D, Tanaka LF, Lee KK, et al. Estimates of the global burden of cervical cancer associated with HIV. Lancet Glob Health 2021; 9(2):e161-e169.

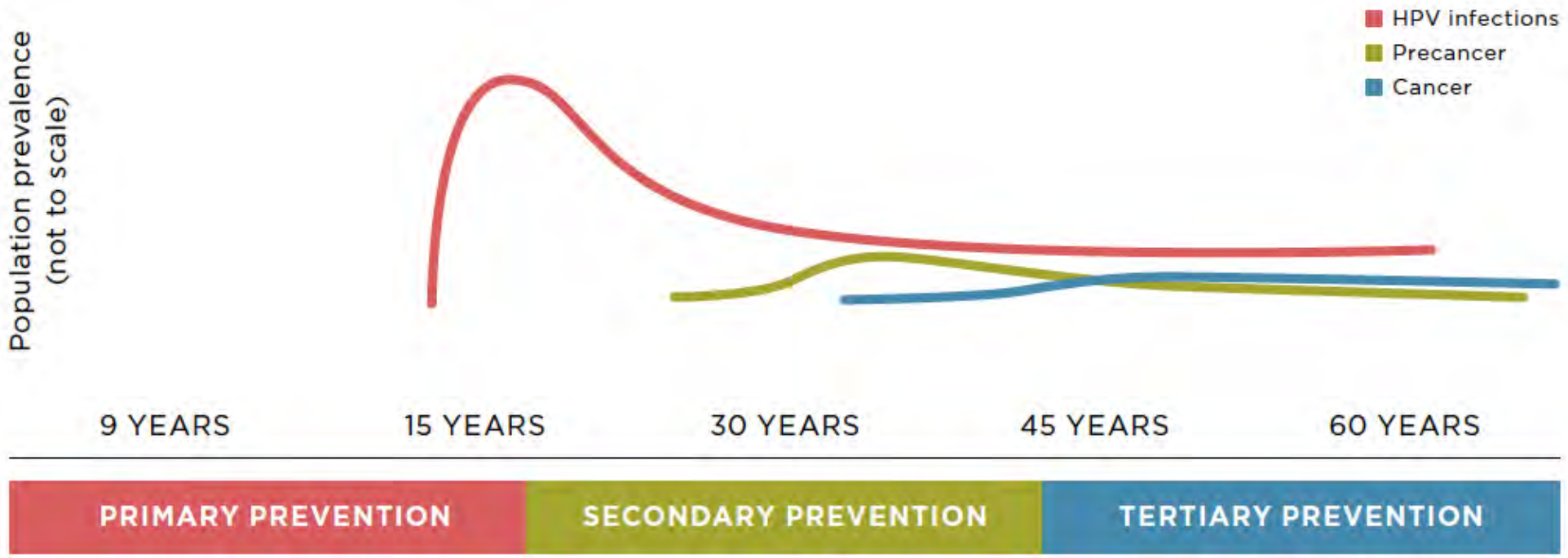
Global strategy to eliminate cervical cancer

- "One woman dies of cervical cancer every two minutes…Each one is a tragedy, and we can prevent it." (Dr. Tedros Adhanom Ghebreyesus, May 2018)

- Global strategy to eliminate cervical cancer launched in 2020

https://www.who.int/publications/i/item/9789240014107

WHO life-course approach to cervical cancer control



Girls 9-14 years

Prophylactic (Px) HPV vaccination

Women 30-49 years (WLHIV: 25-49 yrs)

Screening, preferably with HPV test

Treatment as needed, eg, thermoablation or cryotherapy

Women at any age

Treatment of invasive cervical cancer

Global strategy targets by 2030

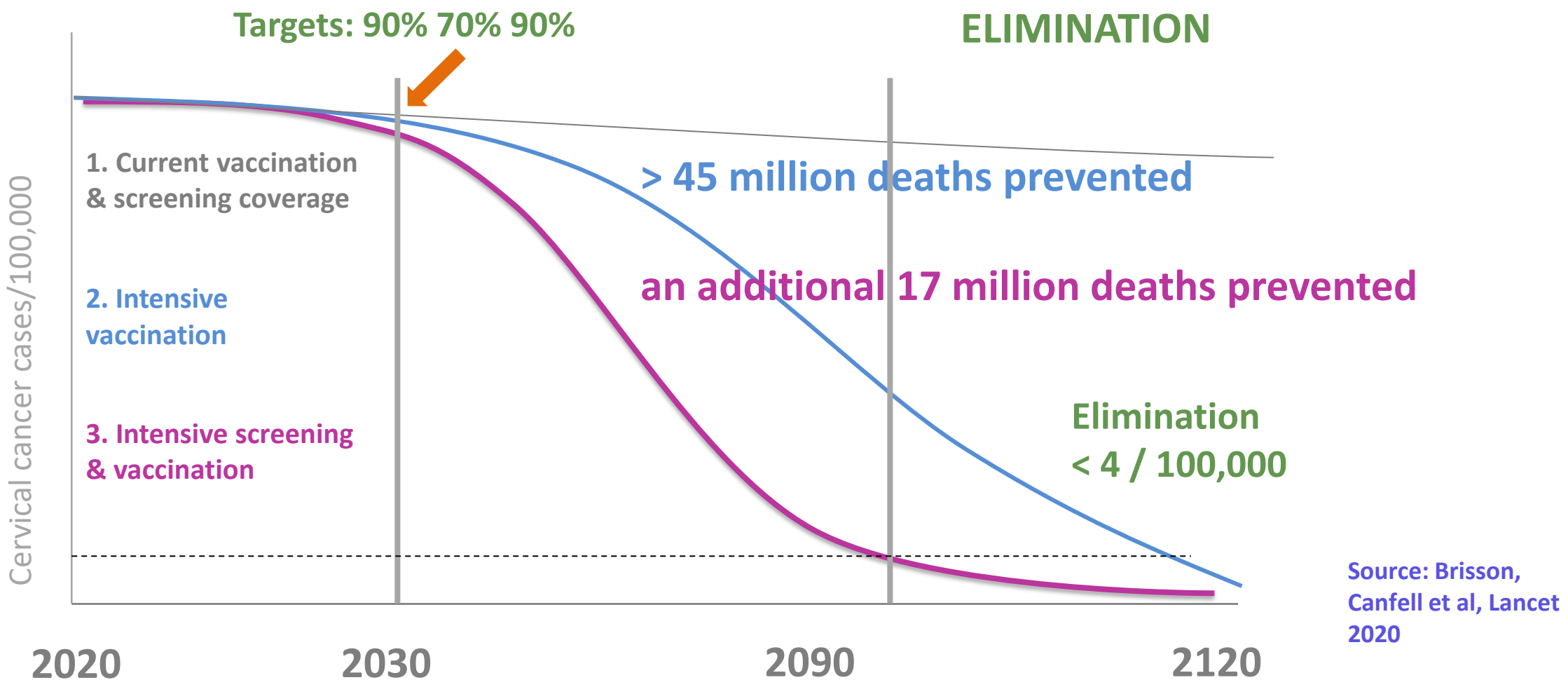
Threshold for elimination as a public health problem:
Age-adjusted incidence rate < 4/100,000 women

2030 Targets

SDG 2030 Target 3.4:
30% reduction in mortality from NCDs

Strategy to achieve elimination

- If 2030 targets met and sustained: can avert **62 million deaths** over next century



Source: Brisson, Canfell et al, Lancet 2020

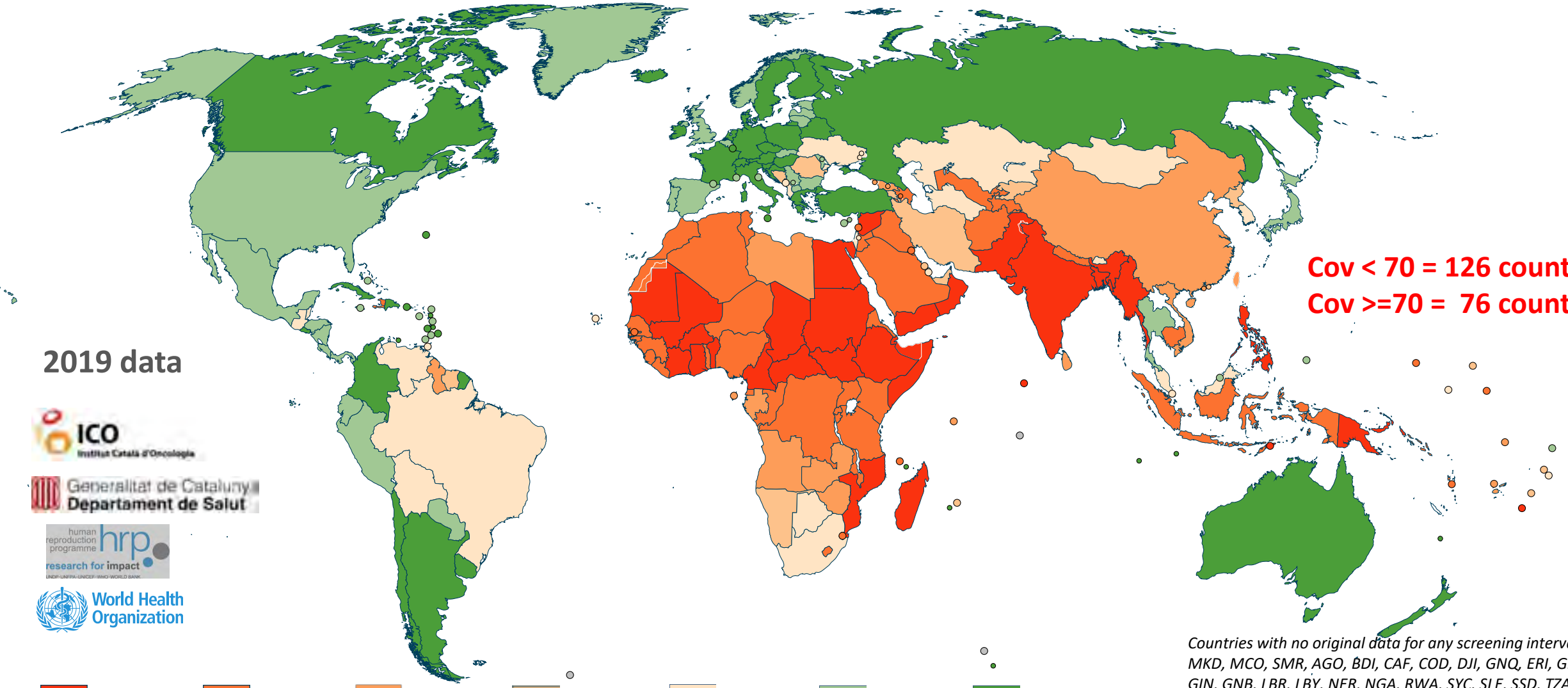
Inequity in Px HPV vaccine introduction

Countries with HPV vaccine in national immunization programme

- 70% of 9-14-year-old girls live in countries without programme
- Only 12% of girls in LMICs have received 2 doses

Bruni et al., Prev Med. 2021 Mar;144:106399. doi: 10.1016/j.ypmed.2020.106399.

Ever in lifetime screening coverage, women 30-49y



2019 data

Cov < 70 = 126 countries
Cov >=70 = 76 countries

0-9% 10-19% 20-34% 35-49% 50-69% 70-89% 90-100%

Countries with no original data for any screening intervals: MKD, MCO, SMR, AGO, BDI, CAF, COD, DJI, GNQ, ERI, GMB, GIN, GNB, LBR, LBY, NER, NGA, RWA, SYC, SLE, SSD, TZA, TGO, ATG, PAN, SUR, VEN, ASM, COK, NIU, WSM, VUT, AFG, BHR, KHM, PRK, PSE, YEM

Strategy challenges and new innovations

- Many **challenges in reaching targets** of cervical cancer (CxCa) elimination strategy by 2030
  - Critical to address gap for women who have not received prophylactic HPV vaccines
  - Complexity of HPV screening & treatment approaches has been a barrier in LMICs
- As we **scale up existing interventions**, also **scanning horizon for new innovations** that might enhance existing efforts or address specific gaps

Therapeutic (Tx) HPV vaccines

- Intended to work in people who already have infection, e.g., to clear HPV infection and/or cause regression of CIN2+ lesions
- Most of the clinical development over the past several years has focused on:
  - Targeting invasive cancer or high-grade precancers
  - VGX-3100: modest but significant efficacy in regression of CIN2+ and viral clearance
- Tx HPV vaccines targeting infection + low-grade precancers may be more feasible
  - Several candidates now in phase 1/2 trials

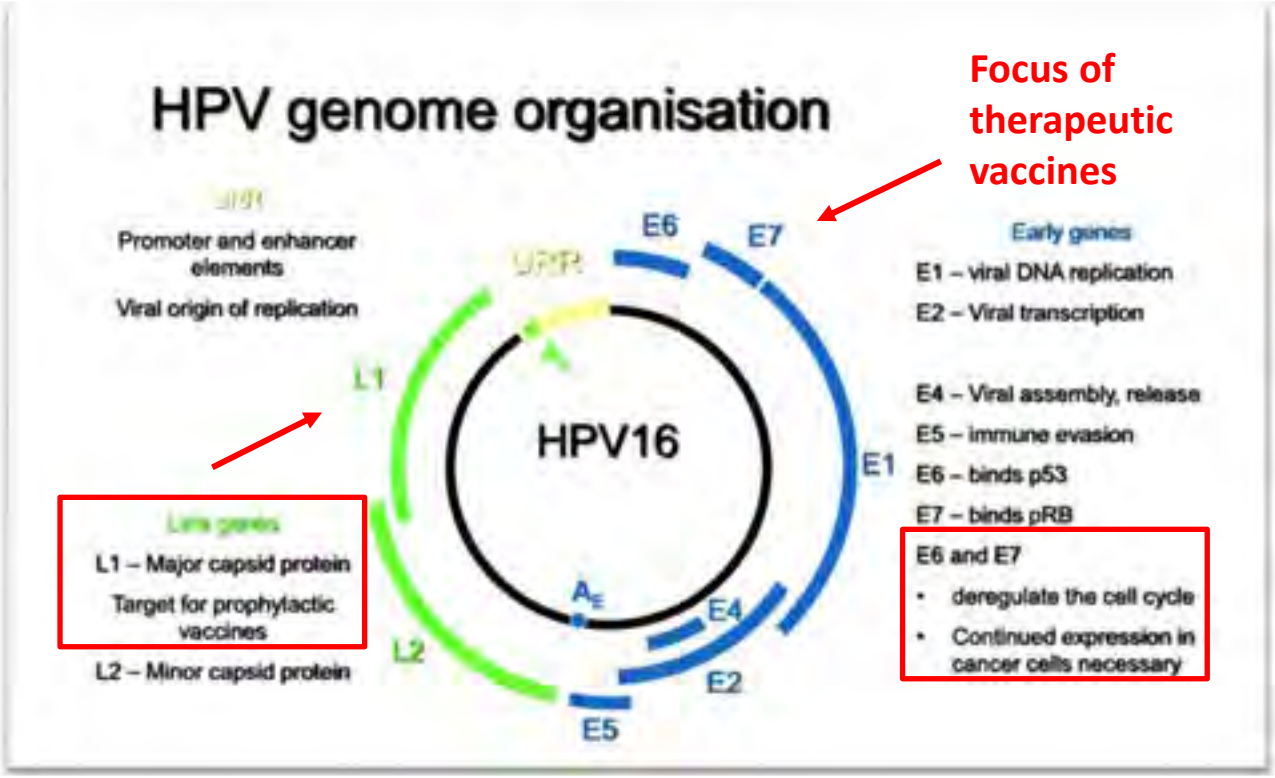


Figure courtesy of Margaret Stanley, Univ of Cambridge

Can Tx HPV vaccines address gaps?

- What is the **added value** of Tx vaccines, given likely **timelines to development relative to**:
  - scale-up of screening & treatment, and
  - aging of cohorts vaccinated in adolescence?
- How would Tx HPV vaccines be **used to address public health need?** How does this influence **the attributes that would optimize impact?**
- What are their **likely attributes**? How does this affect **potential value and optimal use?**

Full value of vaccines assessment

- What is the public health need the vaccine would address?
- How valuable would the vaccine be?

Preferred product characteristics

- What should the vaccine look like to maximize its benefits?
- Who will get it and how will it be used?

Global activities: value and PPCs of Tx HPV vaccines

- Oct 2021: **Initial consultation** to lay groundwork for understanding potential value and preferred characteristics of Tx HPV vaccines
- Public health need for Tx HPV vaccines: goal of **reducing CxCa deaths over next 30-40 years**

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

Understanding the public health value and defining preferred product characteristics for therapeutic human papillomavirus (HPV) vaccines: World Health Organization consultations, October 2021–March 2022

Holly J. Prudden, Sharon L. Achilles, Celina Schocken, Nathalie Broutet, Karen Canfell, Hiroki Akaba, Partha Basu, Neerja Bhatla, Z. Mike Chirenje, Sinead Delany-Moretlwe, Lynette Denny, Deepa G. Gamage, Rolando Herrero, Raymond Hutubessy, Luisa Lina Villa, Raul Murillo, John T. Schiller, Margaret Stanley, Marleen Temmerman, Fanghui Zhao, Gina Ogilvie, David C. Kaslow, Peter Dull, Sami L. Gottlieb, Therapeutic HPV Vaccine PPC Expert Consultation Group*

Waiting room of gynaecologic health outpatient department – Nepal

- **Modeling** to evaluate the impact of Tx vaccines under different scenarios guided by experts, IVIR-AC
- **End-user assessment** of women, providers, and programme managers being launched now
- Nov 2022: **Follow-up expert PPC consultation** convened in Nairobi

Aligning public health need and PPC approaches

Settings where some S&T scale-up, but costly/complex, large loss to follow-up before treatment	Settings where very difficult to scale up S&T at all
Need: alternative, simpler treatment following a positive test to increase overall proportion of women with precancers who are effectively treated	**Need**: way to reach women who haven't received Px HPV vaccine to reduce overall proportion who develop cervical precancers (and thus CxCa)
Most aligned Tx vaccine mechanism: regression of CIN2/3 lesions	**Most aligned Tx vaccine mechanism:** clearance of HPV infection

Aligning public health need and PPC approaches

Settings where some S&T scale-up, but costly/complex, large loss to follow-up before treatment	Settings where very difficult to scale up S&T at all
Need: alternative, simpler treatment following a positive test to increase overall proportion of women with precancers who are effectively treated	**Need**: way to reach women who haven't received Px HPV vaccine to reduce overall proportion who develop cervical precancers (and thus CxCa)
Most aligned Tx vaccine mechanism: regression of CIN2/3 lesions	**Most aligned Tx vaccine mechanism:** clearance of HPV infection
PPC table 1: Tx HPV vaccines used as treatment of cervical precancers	**PPC table 2:** Tx HPV vaccines used as treatment of HPV infections (to prevent cervical precancers)

Initial modeling efforts

- Use of well-validated model in 78 LMICs developed as part of CxCa Elimination Consortium
- Initial model: population-based vaccination with Tx HPV vaccine with high efficacy/coverage can have positive impact on CxCa cases/mortality if NO scale-up of existing interventions
  - Added benefits drop as background scale-up approaches CxCa strategy targets (90-70-90)
  - Deaths averted relatively modest versus 90-70-90 (e.g., 1.6-2.7m deaths vs 14.6m deaths by 2070)
  - Efficacy in regressing CIN2/3 and 'immune memory' influential
- Next: Additional analyses more closely aligning with PPCs & realistic background scale-up, e.g., delinking Px HPV vaccination from screening from treatment
- Analyses for women living with HIV
- Cost-effectiveness analyses

Aligning public health need and PPC approaches

PPC 1: focused on precancers	PPC 2: focused on HPV infection
Indication: Regression of high-grade cervical precancers due to HPV types 16, 18 (and 45?) Regression of precancers due to other types or clearance of additional HPV types would add benefit.	**Indication**: Clearance of HPV type 16, 18 (and 45?) infection Clearance of additional HPV types or regression of precancers would have added benefit
Target population: Women with a positive CxCa screening test according to current screening guidelines	**Target population:** Women ages 25 to 45(?) years in at-risk populations (e.g., high proportion who have not already received Px HPV vaccine nor CxCa screening)
Delivery strategy: Alignment with existing cervical cancer screening and treatment infrastructure. HPV testing and vaccination may occur outside of traditional settings.	**Delivery strategy:** Population-based delivery

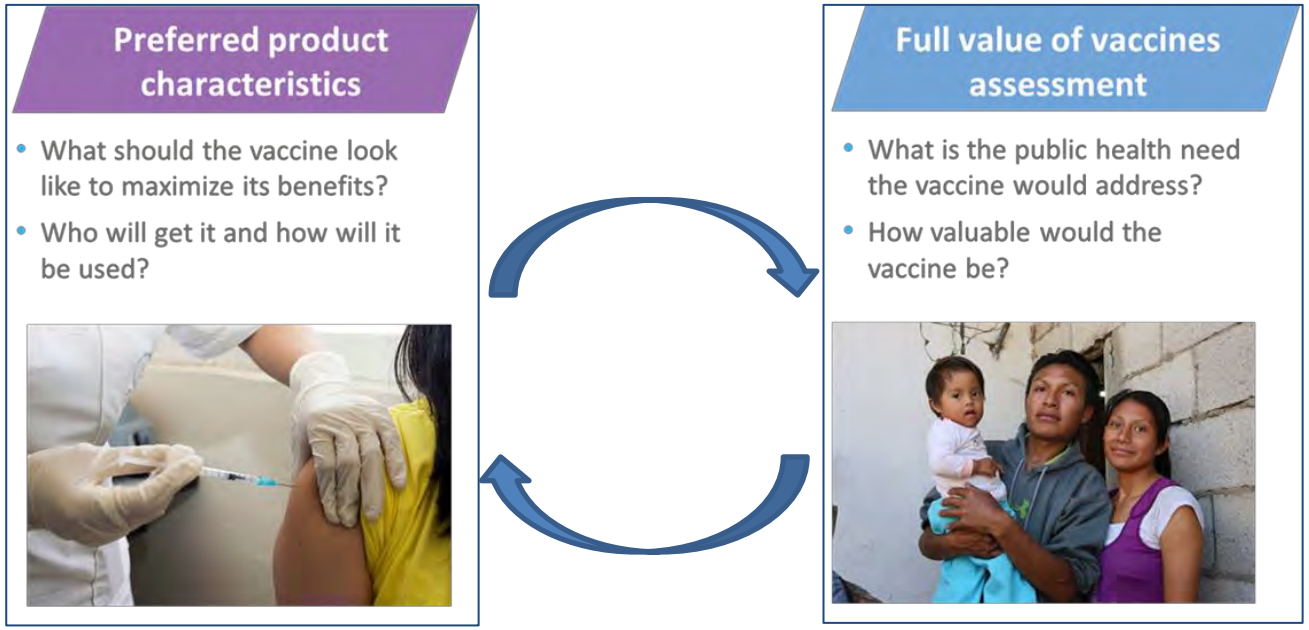
Questions for PDVAC

- Does PDVAC agree with approach of developing 2 sets of therapeutic HPV vaccine PPCs:

  PPC 1: for vaccines causing regression of high-grade cervical precancers targeted to women with a positive cervical cancer screening test

  PPC 2: for vaccines clearing oncogenic HPV infection targeted to adult women through population-based delivery?

- For both sets of PPCs: How to best approach the iterations between the PPCs with the full value of vaccines assessments?



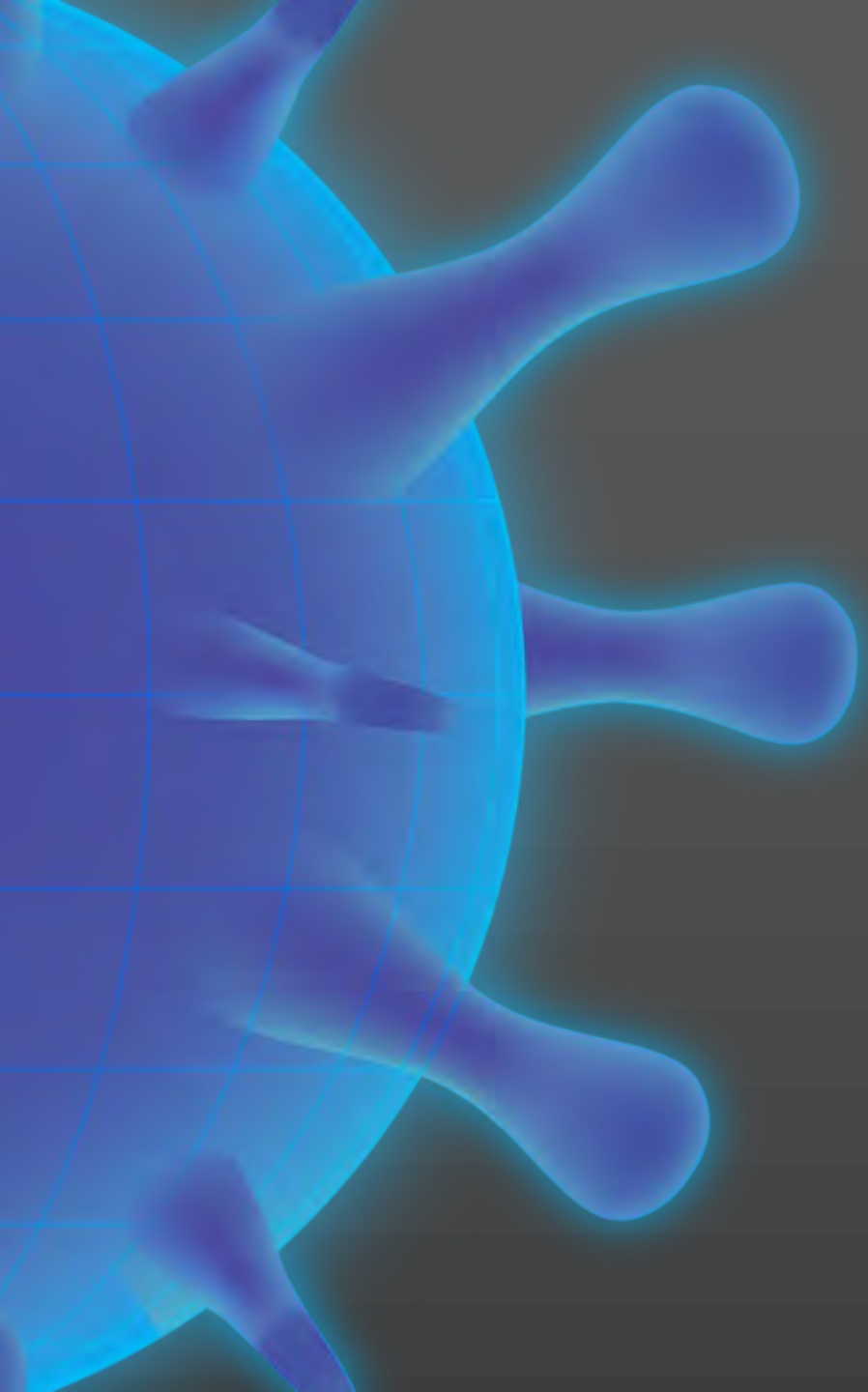
Thank you!

Many thanks to PDVAC, the many colleagues participating in these efforts, and the Bill & Melinda Gates Foundation for support

Holly Prudden
Celina Schocken
Sharon Achilles
Maribel Almonte
Margaret Stanley
Sinead Delany-Moretlwe
Karen Canfell & team
David Kaslow
Gina Ogilvie
Paul Bloem
Hiro Akaba
Partha Basu

and the

Therapeutic HPV vaccine expert consultation participants!



Improved influenza vaccines: Current pipeline and considerations for a revised PPC

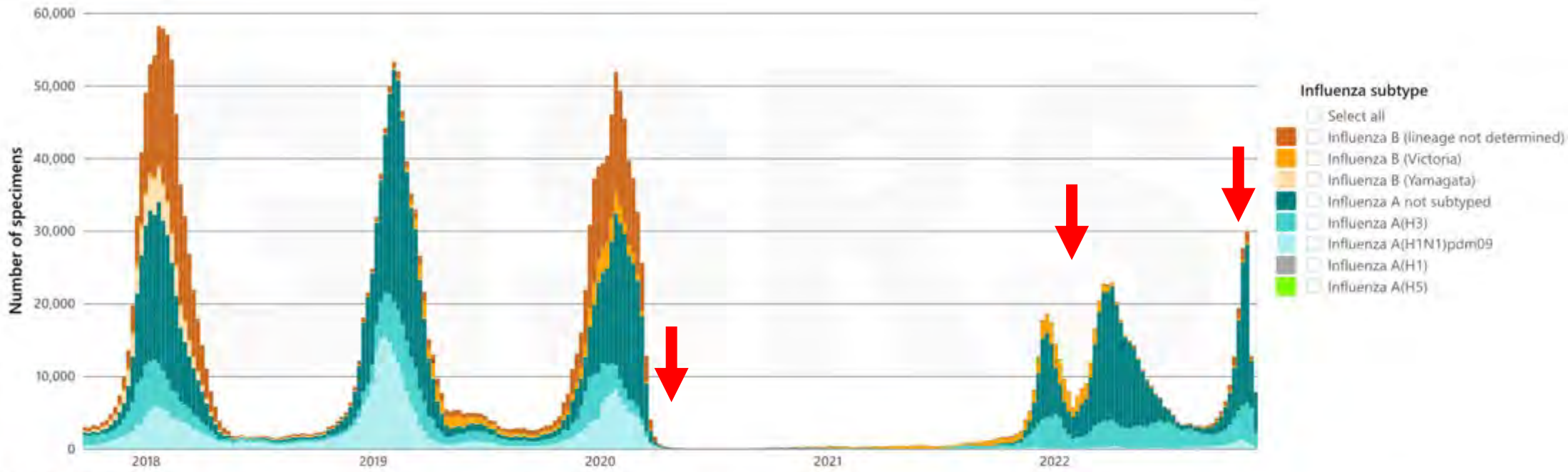
Chris Chadwick
Influenza Preparedness and Response
WHO Health Emergencies Programme

PDVAC Meeting
6 December 2022

Outline

- **Influenza vaccine R&D overview**
- **Global initiatives and activities**
- **WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines**
- **Questions for PDVAC**

Influenza virus detections: Sep 2017-Nov 2022



*Surveillance site type:

- **Non-sentinel**: Data obtained from non-sentinel systems as indicated by the reporting country. Data reported in this category may include outbreak investigation, universal testing, testing at point of care or other systems apart from sentinel surveillance.
- **Sentinel**: Data obtained from sentinel surveillance as indicated by the reporting country. Sentinel surveillance systems collect high-quality data in a timely manner systematically and routinely from sentinel surveillance sites representatives of the population under surveillance.
- **Type not defined**: Source of data not indicated by the reporting country neither as sentinel nor as non-sentinel surveillance. These data may include sentinel or non-sentinel surveillance sources or both.

Calendar type: ISO 8601

Data source: FluNet (https://www.who.int/tools/flunet)

Global guidance: Updated influenza vaccination position paper – May 2022

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

Contents

Sommaire

Vaccines against influenza: WHO position paper – May 2022

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale vaccination programmes. They summarize essential background information on diseases and vaccines and conclude with the current WHO position on the use of vaccines worldwide.

The papers are reviewed by external experts and WHO staff and endorsed by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization (www.who.int/groups/strategic-advisory-group-of-experts-on-immunization). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method is used to assess systematically the quality of the available evidence. The SAGE decision-making process is reflected in "evidence-to-recommendation" tables. The processes followed for the preparation of vaccine position papers are described at: www.who.int/publications/m/item/guidance-for-the-development-of-evidence-based-vaccine-related-recommendations. The position papers are intended for use mainly by national public health officials and managers of immunization programmes. They may also be of interest to international funding agencies, vaccine advisory groups, vaccine manufacturers, health professionals, researchers, the scientific media and the general public.

This position paper is concerned with vaccines and vaccination against seasonal (epidemic) influenza. In recent years, there have been important developments in the

Vaccins antigrippaux: note de synthèse de l'OMS – mai 2022

- **All countries recommended to consider implementing seasonal influenza vaccination programme**
- **Priority target groups: health workers, individuals with comorbidities/underlying conditions, older adults, pregnant women**
  - Children also considered an important target population
- **Addresses repeat vaccination**
  - VE found to be lower for those vaccinated in current and prior season vs those vaccinated in current season only
  - Vaccination in current + prior seasons provided better protection than not being vaccinated or being vaccinated in the prior season only
- **Research priorities identified, including:**
  - Development of improved, novel, and universal influenza vaccines
  - R&D by existing manufacturers in LMICs, including transitioning to enhanced and next-generation influenza vaccines

https://www.who.int/publications/i/item/who-wer9719

Influenza vaccine R&D overview

Currently approved seasonal influenza vaccines

- **Traditional influenza vaccines:**
  - Inactivated
  - Live attenuated
- **Enhanced/newer influenza vaccines[1]:**
  - Adjuvanted
  - Cell-based
  - High-dose
  - Recombinant

- **Global production capacities (2019)[2]:**

Breakdown of capacities	Seasonal	Pandemic
Total annual capacities		
Seasonal	1.48 billion doses	
Pandemic (moderate case)		4.15 billion doses
Pandemic (best case)		8.31 billion doses
By vaccine type		
IIV	89.6%	88.9%
LAIV	5.0%	3.4%
Recombinant	5.4%	7.7%
By substrate		
Embryonated eggs	84.5%	79%
Cell culture	15.5%	21%

1. As defined by the 2020 ECDC Systematic review of the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-systematic-review-efficacy-vaccines
2. Sparrow E, Wood JG, Chadwick C, Newall AT, Torvaldsen S, Moen A, et al. Global production capacity of seasonal and pandemic influenza vaccines in 2019. Vaccine. 2021;39(3):512-20.

Monitoring next-generation influenza vaccine R&D

- **CIDRAP has created a database of novel vaccine candidates in clinical or late preclinical development**
- **Funded by the Global Funders Consortium for Universal Influenza Vaccine Development**
- **Continuously updated as new information becomes available**
- **Tracks both active and inactive candidates**

Novel influenza vaccine candidates in *active* preclinical and clinical development

	Preclinical	Phase 1	Phase 2	Phase 3	Approved
Recombinant proteins	33	1	1	0	0
Recombinant influenza virus-based	10	3	2	0	0
Virus-vectored	21	2	1	0	0
Virus-like particles (VLP)	23	0	0	1	0
Non-VLP nanoparticles	23	3	1	1	0
Nucleic acid-based	20	3	0	2	0

Source: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Novel vaccine candidates in *active* clinical development

Recombinant proteins

ConserV Bioscience (UK), Imutex (UK)
FLU-v

Russian Academy of Sciences (Russia), VA Pharma (Russia)
M2e based recombinant fusion proteins

Recombinant influenza virus-based

FluGen (US)
RedeeFlu M2SR

Vivaldi Biosciences (US), Icahn School of Medicine at Mount Sinai (US)
deltaFLU

National Institute of Allergy and Infectious Diseases (US)
BPL-1357

Icahn School of Medicine at Mount Sinai (US), GSK (US)
cHA-based LAIV combinations

Codagenix (US)
CodaVax

Virus-vectored

Vaxart (US)
VXA-A1.1 oral tablet

Jenner Institute, University of Oxford (UK)
MVA/ChAdOx2-NP+M1

National Institute of Allergy and Infectious Diseases (US), Sanofi Pasteur (US)
Ad4-H5-VTN

Virus-like particles (VLP)

Medicago (Canada)
Quadrivalent VLP (QVLP)

Non-VLP nanoparticles

Novavax (US), Emergent BioSolutions (US)
Nano-Flu (qNIV)

Osivax (France)
OVX836

Emergent BioSolutions (US)
EBS-UFV-001

National Institute of Allergy and Infectious Diseases (US)
FluMos-v1

National Institute of Allergy and Infectious Diseases (US), Sanofi Pasteur (US)
Stabilized headless HA stem nanoparticles

Nucleic acid-based

Moderna (US)
Modified mRNA lipid nanoparticles

Pfizer (US), BioNTech (Germany)
Modified mRNA

CureVac (Germany), GSK (US)
mRNA vaccines

Pfizer (US)
Self-amplifying RNA

Sanofi Pasteur (US), Translate Bio (US)
mRNA NA

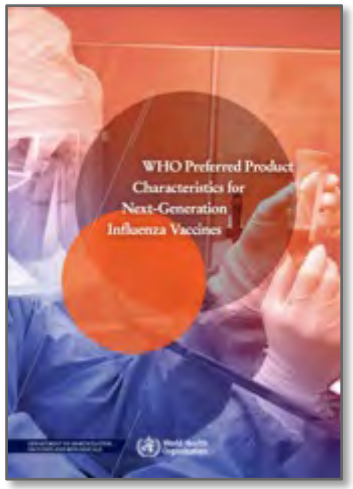
Phase 3

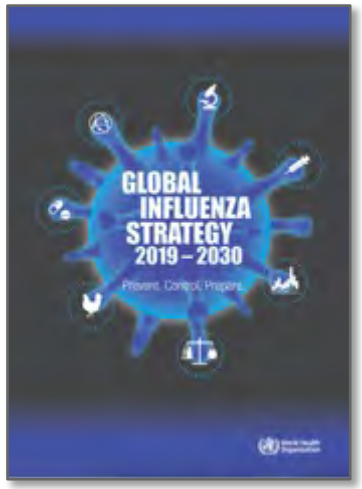
Source: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

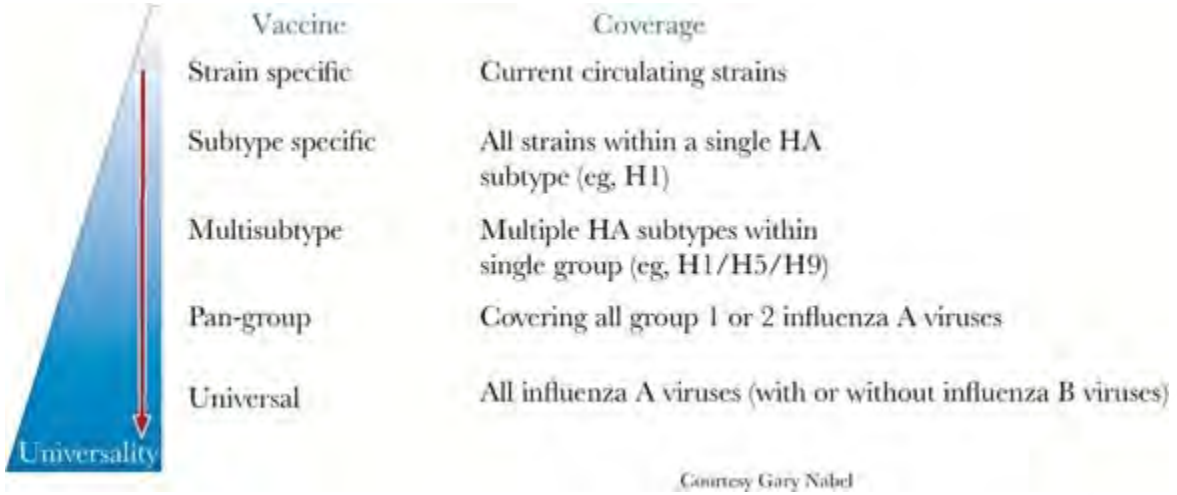
Global initiatives and activities

Global focus on next-generation influenza vaccines

- **WHO PPCs (2017):**
  - Strategic goal 1: Greater protection than compared to currently PQ'd vaccines, protection against severe influenza for at least 1 year (2022)
  - Strategic goal 2: Protection against severe diseases for at least 5 years, suitable for LMICs (2027)
- **NIAID strategy (2018): stepwise approach to universal influenza vaccines**
- **Global Influenza Strategy (2019):**
  - Increased breadth of protection, longer duration of protection, enhanced effectiveness against severe disease, decreased time for production
- **IVR Roadmap (2021): 10-year strategy to promote R&D for improved vaccines and broadly protective/universal vaccines**
  - Strategic priorities across virology; immunology and CoPs; vaccinology; animal models and human challenge studies; policy, financing, and regulation
- **Other initiatives:**
  - Global Funders Consortium, Sabin Influenzer Initiative, National Academy of Medicine consensus studies, US Government National Influenza Vaccine Modernization Strategy, BMGF/Flu Lab Grand Challenge for UIV Development, NIAID Collaborative Influenza Vaccine Innovation Centers, EU-India collaboration for next-generation influenza vaccines







IVR Roadmap

- **10-year plan for prioritizing and coordinating global influenza vaccine R&D**
  - Issues and barriers
  - 24 strategic goals
  - 113 milestones: 37 designated high-priority
  - Additional research priorities

- **2019**
  The Global Funders Consortium for Universal Influenza Vaccine Development initiated development of the IVR
- **2021**
  The Influenza Vaccines R&D Roadmap was launched
- **2022**
  IVR Monitoring, Evaluation, and Adjustment (ME&A) phase began

Advancing progress on global influenza vaccine R&D

Member States + WHO Expert Groups

IVR Steering Committee

Strategy → Roadmap → Implementation

Specific milestones for vaccinology of improved seasonal influenza vaccines

By 2023	**Milestone 3.1.a**: Assess the advantages and tradeoffs of new seasonal influenza vaccine technologies, including recombinant, cell-culture, and mRNA technologies, over current egg-based IIVs for their potential to enhance effectiveness and shorten production time while maintaining capabilities for reliable annual delivery of vaccines (Bartley 2021, Kis 2020, Rajaram 2020, Rosa 2021).
By 2024	**Milestone 3.2.d:** Establish partnerships for designing, funding, and conducting multiseason, product-specific comparative efficacy trials of seasonal influenza vaccines in, and suitable for, LMIC populations and different age-groups.
By 2024	**Milestone 3.2.e (High Priority):** Determine optimum methods for assessing the effectiveness of conventional egg-based and cell culture-based vaccines with new vaccine technologies, in coordination with regulatory agencies and using consistent end points, to allow data to be combined (WHO 2016a) as appropriate over multiple seasons and to allow better comparability of data across studies.
By 2025	**Milestone 3.3.d:** Based on outcomes of milestones 3.3.a, 3.3.b, and 3.3.c, develop a consensus approach on clinical trial methodologies for demonstrating vaccine effectiveness in preventing severe influenza disease in different geographical settings.

Specific milestones for vaccinology of broadly protective/universal influenza vaccines

By 2022	**Milestone 4.1.a:** Develop a set of preferred product characteristics (PPCs) for broadly protective and universal influenza vaccines, in collaboration with the WHO's efforts to revise its 2017 guidance on PPCs for next-generation influenza vaccines (WHO 2017).
By 2022	**Milestone 4.1.b:** Develop a summary analysis of influenza vaccine approaches for broadly protective or universal influenza vaccines, including intellectual property data, and create a mechanism to update this summary at least annually.
By 2022	**Milestone 4.1.c:** Develop a transparent process, such as an international consortium, for identifying the most promising influenza vaccine candidates that warrant further investigation (Epstein 2018).
By 2023	**Milestone 4.2.d:** Develop an approach for harmonizing clinical protocols (including defining clinical or immunologic end points) that deal with key issues, such as assessment of durability of broadly protective influenza vaccines over several years and assessment of broadly protective vaccines in special populations (e.g., pregnant women, young children, HIV-infected people). These efforts should focus on approaches that prioritize efficacy as a clinical trial end point as feasible.
By 2023	**Milestone 4.2.e (High Priority):** Develop consensus on streamlining clinical research for evaluating broadly protective influenza vaccines, drawing on COVID-19 vaccine experience.

Specific milestones for policy, financing, and regulation (1)

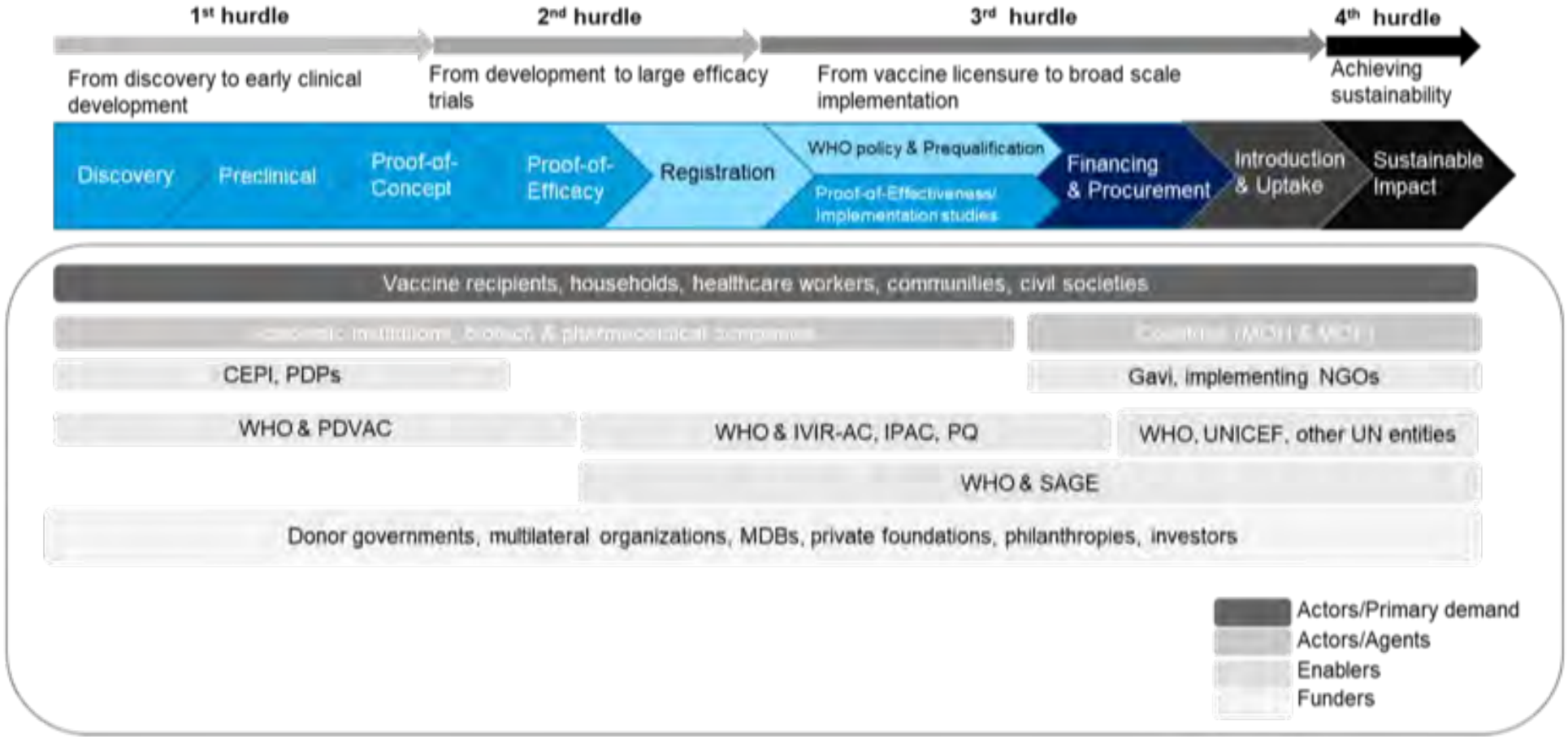
By 2022	**Milestone 6.1.a (High Priority):** Develop and disseminate a full value of vaccine assessment (FVVA) for improved seasonal and broadly protective, universal influenza vaccines that addresses different vaccine use cases and includes an assessment for LMICs (NASEM 2019).
By 2023	**Milestone 6.2.d:** Create a summary of critical evidence, as a basis for policy recommendations, relevant to the design of clinical trials for universal or broadly protective influenza vaccines and their outcomes, similar to the "evidence to recommendation" framework created by the WHO SAGE on Immunizations Working Group on COVID-19 Vaccines (WHO SAGE on Immunizations 2020).
By 2024	**Milestone 6.2.e:** Develop a global strategy that addresses health equity issues, encompasses the interests of LMICs—including the need for improved seasonal influenza vaccines—and is aimed at supporting country transitions from annual vaccination programs to use of more durable, broadly protective or universal vaccines.
By 2022	**Milestone 6.3.e:** Conduct mapping of intellectual property for improved influenza vaccines to identify synergies in approaches that may be used to develop new partnerships.
By 2023	**Milestone 6.3.f:** Develop a consensus vision for sharing intellectual property or proprietary technologies related to improved influenza vaccines that includes benefit sharing and equitable access for LMICs.

Specific milestones on policy, financing, and regulation (2)

By 2022	**Milestone 6.4.a (High Priority):** Conduct a workshop that includes regulators and vaccine manufacturers to: (1) clarify regulatory processes related to the development and evaluation of broadly protective or universal influenza vaccines, (2) develop a regulatory science agenda that anticipates the challenges of evaluating and licensing these new vaccines, (3) review the regulatory experience with COVID-19 vaccines and identify ways to streamline the process for new influenza vaccines, and (4) generate additional recommendations regarding how best to provide guidance on vaccine development, manufacture, approval, and delivery.
By 2023	**Milestone 6.4.b (High Priority):** Identify a framework to address post-marketing assessment of safety and effectiveness of new broadly protective or universal influenza vaccines.
By 2024	**Milestone 6.4.c:** Develop consensus on best practices for using CHIVIM studies in supporting licensure of new influenza vaccine products (Bresee 2019, Erbelding 2018, Innis 2019a).
By 2025	**Milestone 6.4.d:** Identify regulatory challenges associated with developing influenza vaccines that prevent severe disease but do not necessarily prevent infection (Berlanda Scorza 2016), such as defining clinical end points.

WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines

Full value of influenza vaccines assessment



"Should we invest in developing a universal flu vaccine?"

"Should we recommend/fund a universal flu vaccine?"

"Should we introduce a universal flu vaccine?"

Hutubessy, Raymond C.W. and Lauer, Jeremy Addison and Giersing, Birgitte and Sim, So Yoon and Jit, Mark and Kaslow, David and Botwright, Siobhan, The Full Value of Vaccine Assessments (FVVA): A Framework to Assess and Communicate the Value of Vaccines for Investment and Introduction Decision Making (May 7, 2021). Available at SSRN: https://ssrn.com/abstract=3841999

WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines (1)

	Improved influenza vaccines	Universal-type influenza A vaccines
Target date	2022	2027
Indication	Prevention of severe influenza illness	Same
Target population	Children aged 6-59 months	Persons aged 6 weeks and older belonging to a group at high risk of severe illness
Safety	Mild reactogenicity acceptable; Severe reactogenicity at a rate ≤ current PQ'd seasonal vaccines	Same
Co-administration	Absence of clinically important interference with concomitantly administered vaccines	Same
Duration of protection	Minimum of 1 year	Minimum of 5 years
Outcome measure	Severe lab-confirmed illness	Same
Efficacy	Better than that of current PQ'd seasonal vaccines for *vaccine-matched strains* **OR** for *circulating antigenically drifted strains*	Better than that of current PQ'd seasonal vaccines for *vaccine-matched strains* **AND** for *circulating antigenically drifted strains*

WHO Preferred Product Characteristics for Next-Generation Influenza Vaccines (2)

	Improved influenza vaccines	Universal-type influenza A vaccines
Immunogenicity	CoPs against severe illness are needed to minimize costs of trials and to promote innovation	If CoP against severe illness is identified for a specific class of influenza vaccine, immunogenicity studies will be adequate to demonstrate vaccine efficacy
Registration and PQ	Product should be PQ'd	Same
Programmatic suitability	WHO defined criteria for programmatic suitability of vaccine should be met	Same
Value proposition	Dosage, regimen, and CoGs should be compatible with affordable supply; vaccine should be cost-effective and price should not be a barrier to access	Same

Update of the PPCs

- **Need for review and update**
  - Renewed attention on global influenza vaccine R&D
  - Take stock of progress made towards 2022 target date
  - Planned workshops on CoPs, clinical trial design, human challenge studies
  - Multiple stakeholders have TPPs and desired characteristics
- **Process**
  - Follow harmonized approach for development/update of PPCs
  - Establish expert group to guide review and update
  - Updated draft open for public comment
- **Consideration**
  - FVIVA activities are based on the current PPCs
  - PPCs will be reviewed in parallel to the FVIVA, allowing for FVIVA outputs to inform PPC revision

Questions for PDVAC

- **Does PDVAC agree with the timing and approach for the review and update of the PPCs?**

- **Are there PDVAC members that would want to serve on the expert sub-group?**

- **Does PDVAC have any other recommendations for the PPC update or other issues for next-generation influenza vaccine R&D?**

Backup Slides

Novel vaccine candidates in active clinical development: Recombinant proteins

- **FLU-v**
  - Developer: ConserV Bioscience/Imutex (UK)
  - Approach: Peptide-based construct derived from conserved regions of internal proteins (M1, IAV-NP, IBV-NP, and M2) aiming to provide a broadly protective immune response against influenza A and B through viral clearance by cytotoxic T cell responses
  - Phase 2
- **M2e based recombinant fusion proteins**
  - Developer: Russian Academy of Sciences/VA Pharma (Russia)
  - Approach: Recombinant plant-produced protein (Flg4M2eHA2-1) based on the combination of 4 tandem copies of M2e and conserved fragments of HA2, fused to bacterial flagellin as an adjuvant for mucosal immunization; administered intranasally.
  - Phase 1

Source: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Novel vaccine candidates in active clinical development: Recombinant virus based (1)

- **RedeeFlu M2SR**
  - Developer: FluGen (US)
  - Approach: Novel single-replication (SR) platform for influenza A or B virus based on an otherwise wild-type influenza virus that does not express the M2 ion channel protein (M2-deficient); administered intranasally; aimed at eliciting cross-reactive antibodies against conserved HA stem and systemic and mucosal immune responses that block virus replication in the lung and provide cross-lineage protection against influenza virus
  - Phase 2
- **deltaFLU**
  - Developer: Vivaldi Biosciences/Icahn School of Medicine at Mount Sinai (US)
  - Approach: Self-adjuvanted, nonstructural protein 1 (NS1)-deficient, replication-deficient LAIV; administered as a nasal spray; aimed at stimulating interferon, mucosal cross-neutralizing IgA antibodies, systemic cytotoxic T-cell response (Th1) and B-cell response with cross-neutralizing antibodies and memory T-cell response
  - Phase 2
  - Note: Combination SARS-CoV-2 + universal influenza vaccine also in development

Source: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Novel vaccine candidates in active clinical development: Recombinant virus based (2)

- **CodaVax**
  - Developer: Codagenix (US)
  - Approach: LAIV generated through synthetic attenuated virus-engineering (SAVE); uses an algorithm to “de-optimize” the influenza HA and NA gene segments for reduced translation in human cells, resulting in virus attenuation while preserving the immunogenicity of wild-type virus; aimed at stimulating an immune response against influenza viruses from multiple seasons and multiple decades (e.g. influenza viruses from 1970s and 1930s)
  - Phase 1
- **cHA-based LAIV combinations**
  - Developer: Icahn School of Medicine at Mount Sinai (US)
  - Approach: Sequential combinations of chimeric (cHA) or mosaic (mHA) constructs (cHA-LAIV-LAIV and cHA-LAIV-IIV, M2e), consisting of “exotic” HA head domains (from avian influenza viruses) and a conserved stalk domain; sequential administration with cHAs with different head domains and the same stalk domain; aimed at focusing humoral immunity on the highly conserved HA stalk domain
  - Phase 1
- **BPL-1357**
  - Developer: NIAID (US)
  - Approach: A whole-virus vaccine, delivered intranasally or intramuscularly, made up of four strains of non-infectious, chemically inactivated, low-pathogenicity avian flu virus; intended to induce mucosal immunity similar to the immune response following influenza infection including cellular and B cell responses
  - Phase 1

Source: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Novel vaccine candidates in active clinical development: Virus-vectored

- **VXA-A1.1 oral tablet**
  - Developer: Vaxart (US)
  - Approach: Replication-defective adenovirus type-5 vectored construct that expresses HA; includes a novel toll-like receptor 3 (TLR3 ligand) agonist as an adjuvant; administered orally in tablets designed to release the virus in the ileum, with the potential to stimulate cellular and mucosal immunity and serum antibody
  - Phase 2
- **MVA/ChAdOx2-NP+M1**
  - Developer: University of Oxford (UK)
  - Approach: Two-dose heterologous viral vectored constructs: modified vaccinia virus Ankara (MVA) and the chimpanzee adenovirus ChAdOx2 expressing conserved influenza virus antigens, nucleoprotein (NP) and matrix protein-1 (M1); aimed at stimulating T-cell responses to influenza virus
  - Phase 1
- **Ad4-H5-VTN**
  - Developer: NIAID/Sanofi Pasteur (US)
  - Approach: Replication-competent adenovirus type 4 encoding influenza virus H5 HA (Ad4-H5-Vtn) administered as an oral capsule or via tonsillar swab or nasal spray, as a potential platform for inducing durable and systemic mucosal immunity against influenza glycoproteins
  - Phase 1

Source: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Novel vaccine candidates in active clinical development: Virus-like particles

- **Quadrivalent VLP**
  - Developer: Medicago (Canada)
  - Approach: Nicotiana benthamiana plant-derived (Proficia®) HA-bearing quadrivalent virus-like particle (QVLP); aimed at stimulating antibody and cellular immune responses
  - Phase 3

Source: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Novel vaccine candidates in active clinical development: Non-VLP nanoparticles (1)

- **Nano-Flu**
  - Developer: Novavax/Emergent BioSolutions (US)
  - Approach: Recombinant *Spodoptera frugiperda* (Sf9) insect cell or baculovirus system-derived, quadrivalent haemagglutinin nanoparticle influenza vaccine (qNIV), formulated with a saponin-based adjuvant, Matrix-M™
  - Phase 3
  - Note: Development of a combined pentavalent influenza/SARS-CoV-2 vaccine underway using same approach
- **OVX836**
  - Developer: Osivax (France)
  - Approach: Self-assembling nanoparticle with multiple copies of full-length NP antigens; aimed at stimulating antibodies, cytotoxic T cells, and T helper cells
  - Phase 2

Source: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Novel vaccine candidates in active clinical development: Non-VLP nanoparticles (2)

- **EBS-UFV-001**
  - Developer: Emergent BioSolutions (US)
  - Approach: Nanoparticle based vaccine that self-assembles during production and that displays a cross-reactive HA antigen for influenza virus A groups 1 and 2
    - Note: The self-assembling HA stabilized stem nanoparticle technology was developed by and licensed from NIAID
  - Phase 1
- **FluMos-v1**
  - Developer: NIAID (US)
  - Approach: Uses computationally designed nanoparticle immunogens that controllably display diverse HA trimers in an ordered array on self-assembling protein nanoparticles; aimed at eliciting both HAI activity and protective stem-directed neutralizing antibodies against heterosubtypic influenza viruses
  - Phase 1
- **Stabilized headless HA stem nanoparticles**
  - Developer: NIAID/Sanofi Pasteur (US)
  - Approach: Stabilized headless HA stem trimers on self-assembling nanoparticles; aimed at stimulating broadly protective immunity against novel viruses
  - Phase 1

Source: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Novel vaccine candidates in active clinical development: Nucleic acid-based (1)

- **Modified mRNA lipid nanoparticles**
  - Developer: Moderna (US)
  - Approach: Lipid nanoparticle-formulated modified mRNA vaccines encoding HA; aimed at eliciting robust germinal center and B cell responses
  - Phase 3
  - Note: Combination vaccines also under development – influenza + SARS-CoV-2 (Phase 1/2); influenza + RSV (Phase 1); influenza + SARS-CoV-2 + RSV (Phase 1)
- **Modified mRNA vaccine**
  - Developer: Pfizer (US)/BioNTech (Germany)
  - Approach: Next-generation mRNA seasonal influenza vaccine encoding WHO-recommended strains
  - Phase 3
  - Note: Combination influenza + SARS-CoV-2 vaccine also under development (Phase 1)

Source: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Novel vaccine candidates in active clinical development: Nucleic acid-based (2)

- **mRNA vaccine**
  - Developer: CureVac (Germany)/GSK (US)
  - Approach: Lipid nanoparticle-formulated, optimized mRNA vaccines encoding HA antigens
  - Phase 1
- **saRNA**
  - Developer: Pfizer (US)
  - Approach: Self-amplifying ribonucleic acid (saRNA) vaccine delivered intramuscularly
  - Phase 1
- **mRNA NA**
  - Developer: Sanofi Pasteur/Translate Bio (US)
  - Approach: Unmodified mRNA encoding full-length HA or full-length NA encapsulated in lipid nanoparticles (LNPs)
  - Phase 1

Source: https://ivr.cidrap.umn.edu/universal-influenza-vaccine-technology-landscape

Comparison of preferred characteristics/key features of broadly protective/universal influenza vaccines

Organization	Target viruses	Duration of Protection	Target Population
Bill & Melinda Gates Foundation	All influenza A and B viruses	Minimum of 3-5 years	All age groups
European Commission	Increased breadth of influenza strains	Improved duration of immunity	Different populations and LMICs
Global Funders Consortium for Universal Influenza Vaccines	Influenza A viruses and perhaps B viruses	More durable than current influenza vaccines	All age groups
National Institute of Allergy and Infectious Diseases	Group 1 and Group 2 influenza A viruses	Durable protection for at least 1 year	All age groups
Sabin-Aspen Vaccine Science & Policy Group	All influenza viruses	Lifelong	All age groups
WHO PPCs	Influenza A viruses	Minimum of 5 years	High-risk groups, especially in LMICs

Source: https://ivr.cidrap.umn.edu/sites/default/files/banner-download/IVR_Final_9_20_21.pdf

Novel delivery technologies and VIPS

Mateusz Hasso-Agopsowicz (WHO)
Marion Menozzi-Arnaud (Gavi)
Jean Pierre Amorij (UNICEF)
Courtney Jarrahian (PATH)

Session agenda and questions to PDVAC

Speaker	Talking Points	Allocated time
Marion	• VIPS and activities to accelerate the development of vaccine-MAPs	15′
Mateusz	• MR-MAP use cases and demand forecast • Results from country workshops	10′
JP	• iFVVA, value and investment	10′
Courtney	• Focus on broader pipeline	10′
PDVAC	• Discussion	15′

Questions to PDVAC

1. Are the mentioned activities appropriate to accelerate the development of vaccine MAPs?

2. How can we design a sustainable mechanism to engage with countries to inform product development and prepare for country uptake?

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

PDVAC – VIPS UPDATE

December 2022

Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

VIPS partners continue to work closely to accelerate three priority innovations for LMICs

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Gavi The Vaccine Alliance | World Health Organization | unicef | Bill & Melinda Gates foundation | PATH

Microarray patches

Heat-stable and CTC qualified vaccines

Barcodes

The VIPS Alliance has developed and is implementing **end-to-end roadmaps**[1], **aligned amongst partners, including 5-year action plans,** to accelerate development and uptake of each of the three VIPS prioritised innovation in LMICs.

[1] Roadmap for MAPs has been published: https://www.gavi.org/sites/default/files/about/market-shaping/VIPS-Alliance-Action-Plan-for-MAPS_Public-Summary.pdf; roadmaps for heat stable and CTC qualified vaccines and barcodes are still under development.

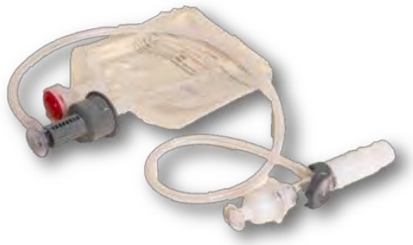
… and to monitor the innovation space

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

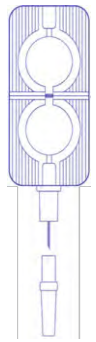
We continue to actively **monitor the vaccine product landscape for new innovations and new data on existing technologies**. If compelling data is identified, VIPS could expand the priority list; however, so far **VIPS remains focused on accelerating development and impact of the original three prioritised innovations**.

Primary containers

Delivery devices



Integrated containers and delivery devices



Formulations

Packaging

Labelling

Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

VPS priority innovation and today's focus is vaccine-MAPs

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Gavi The Vaccine Alliance | World Health Organization | unicef | BILL & MELINDA GATES foundation | PATH

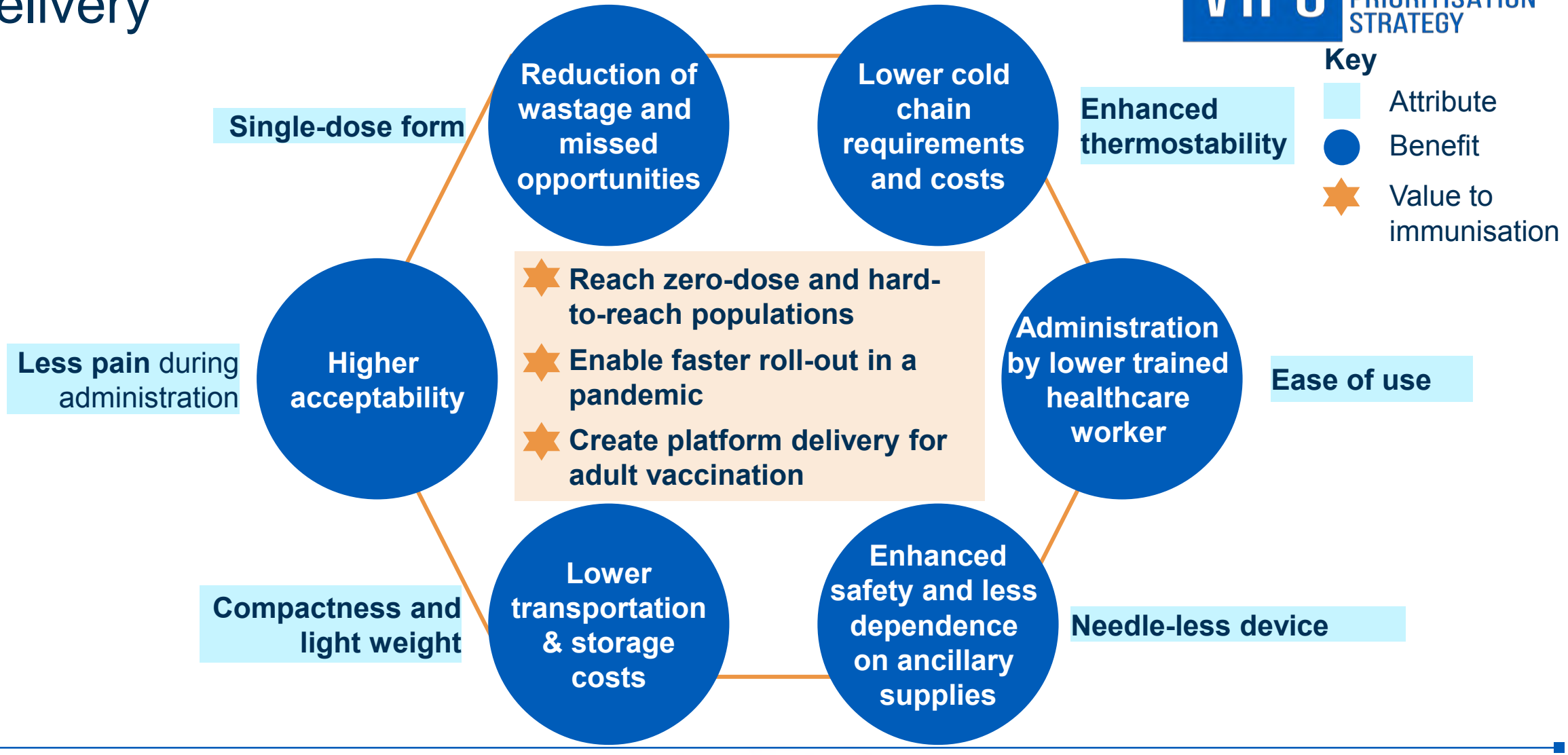
Microarray patches

Focus of discussion today

[1] Roadmap for MAPs has been published: https://www.gavi.org/sites/default/files/about/market-shaping/VIPS-Alliance-Action-Plan-for-MAPS_Public-Summary.pdf; roadmaps for heat stable and CTC qualified vaccines and barcodes are still under development.

Vaccine-MAPs could transform immunisation delivery

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY



Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

Across immunisation programmes, vaccine-MAPs can bring greater impact through increased equitable coverage and access

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

MR

Increase equitable coverage and contribute to MR elimination especially for HTR populations, due to (i) **enhanced thermostability** (ii) **application by lower-skilled individuals**, and (iii) **reduction of missed opportunities to vaccinate**

HPV

Increase access and coverage while reducing costs due to (i) **potential to train teachers to apply MAP** and to deliver to schools with other programs given **ease-of use** and (ii) the **potential for cheaper storage and distribution in outreach** settings

Pandemic preparedness and response

Enable broader access to and faster[1] rollout of vaccines in a pandemic due to (i) **enhanced thermostability**, (ii) **application by lower-skilled individuals**, and (iii) **less dependency on antigen and ancillary supply** in the event of shortages

Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

1. Assumes "final" MAP will be a platform technology, requiring similar development time to N&S

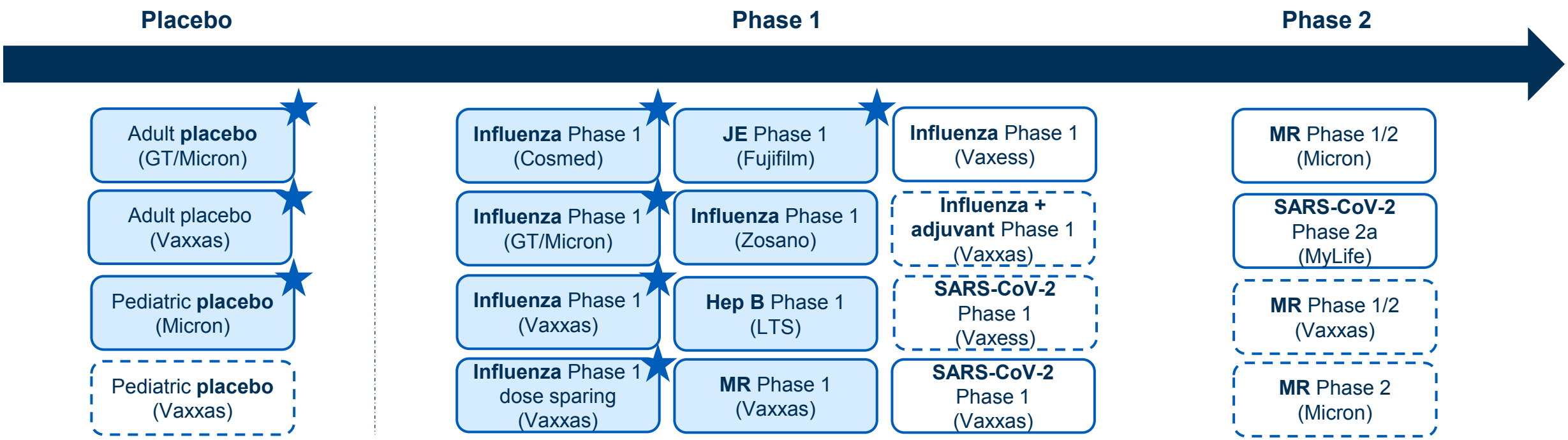
The clinical evidence base for vaccine-MAPs is expanding

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Results are published or anticipated for MR, Influenza, SARS-CoV-2, Hep B and JE in Phase 1, as well as Phase 2 studies for MR and SARS-CoV-2

Key

- Published ★
- In progress
- Completed
- Planned



Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

MR-MAP is the lead candidate for LMIC, with WHO PQ expected between 2029-2033 depending on the scenario

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

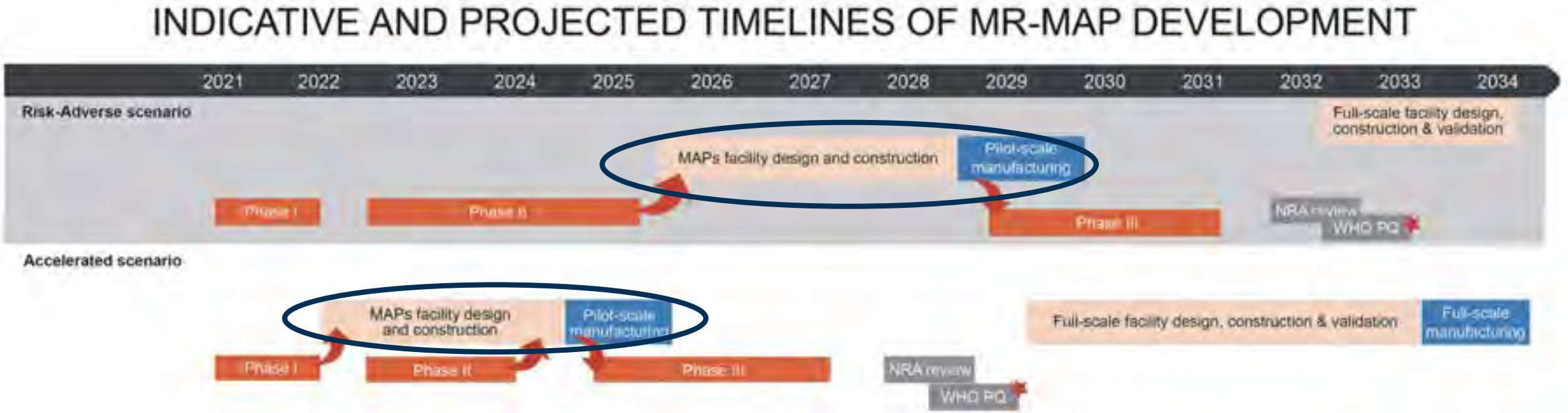


FIGURE 1 | Alternative timelines for MR-MAP development from phase one trial to WHO prequalification and product launch. Arrows indicate flow of data/materials between clinical and manufacturing activities. The timelines do not reflect a timeline for any MR-MAP product. The actual timelines may vary. *MR-MAP is ready to be used in LMICs. See assumptions behind the scenarios in Section 5.

Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

VIPS has identified 12 priority vaccine targets for vaccine-MAPs

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

	PRIORITY VACCINE LIST for vaccine-MAPs in alphabetical order
Priority 1	Hepatitis B virus
	Measles, rubella (MR)/ Measles, mumps and rubella (MMR) viruses
	Human papillomavirus
	Rabies virus
	Yellow Fever
	Influenza virus, seasonal and pandemic
	SARS-CoV-2
Priority 2	Group B streptococcus (GBS), S agalactiae
	Neisseria meningitidis A,C,W,Y,(X)
	Salmonella Typhi
	Streptococcus pneumoniae

PRELIMINARY

Upcoming for public consultation

Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

The VIPS Alliance is working to address the main challenges to accelerate vaccine-MAPs as a platform

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Demand uncertainty

- **Priority vaccines**
- **COGS** assessment and impact of **scale**
- **Use cases, demand sizing and global health impact** (FVVAs)
- **Pull mechanism**
- **Country engagement**

High upfront costs

- **Risk-sharing approaches for R&D** and **manufacturing**

Technical and regulatory risks

- **Regulatory**

Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

Several manuscripts are addressing some of the open questions related to vaccine-MAPs development

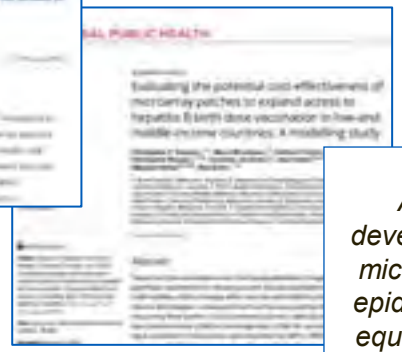
VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Progress and remaining challenges to accelerate MR-MAPs

https://doi.org/10.3389/fpubh.2022.809675

MR-MAP global demand

https://www.medrxiv.org/content/10.1101/2022.08.11.22278665v1.full



Hep-B birth dose cost-effectiveness

https://doi.org/10.1371/journal.pgph.0000394

Accelerating the development of vaccine microarray patches for epidemic response and equitable immunizat coverage requires investment in microa patch manufacturir facilities

Call for investments in MAPs manufacturing

MAP RWG

White paper on MAP quality attributes

Sterility manuscript

MAPs quality attributes

Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

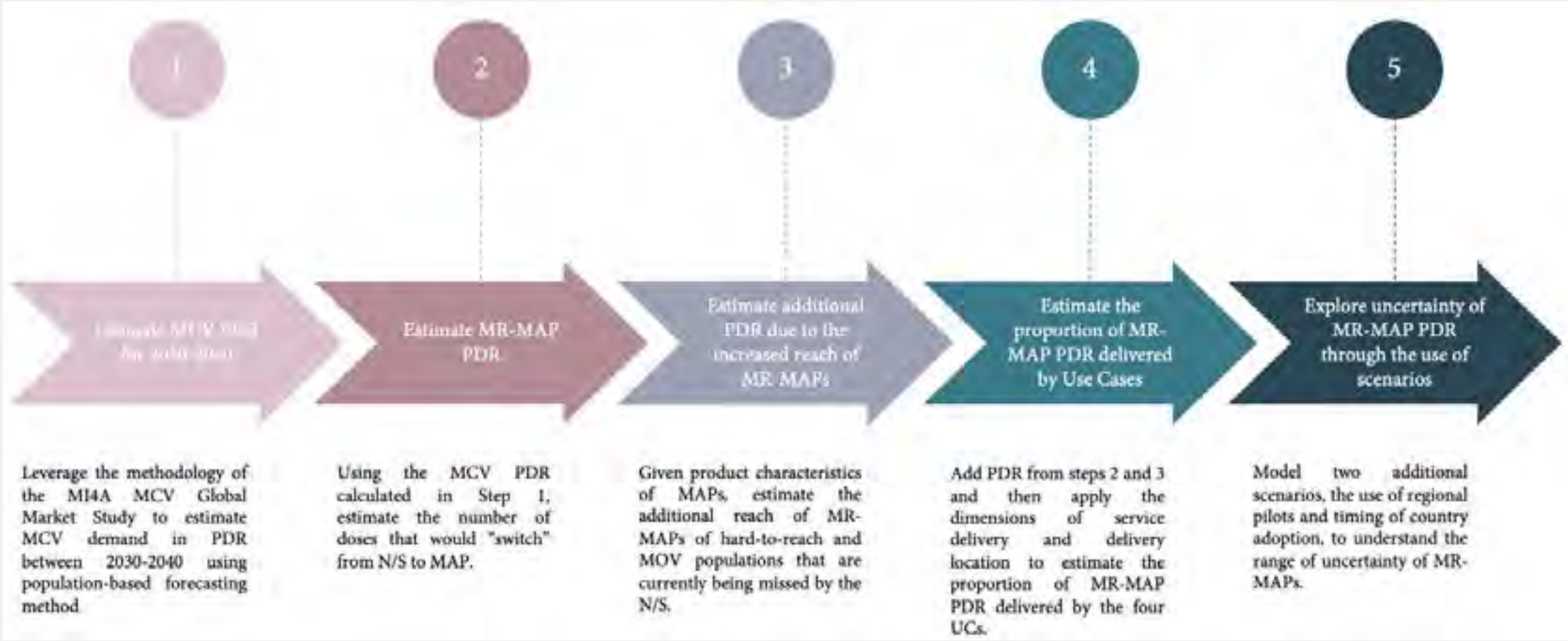
Update on MR-MAP use cases, demand forecast and country consultations

Mateusz Hasso-Agopsowicz, WHO

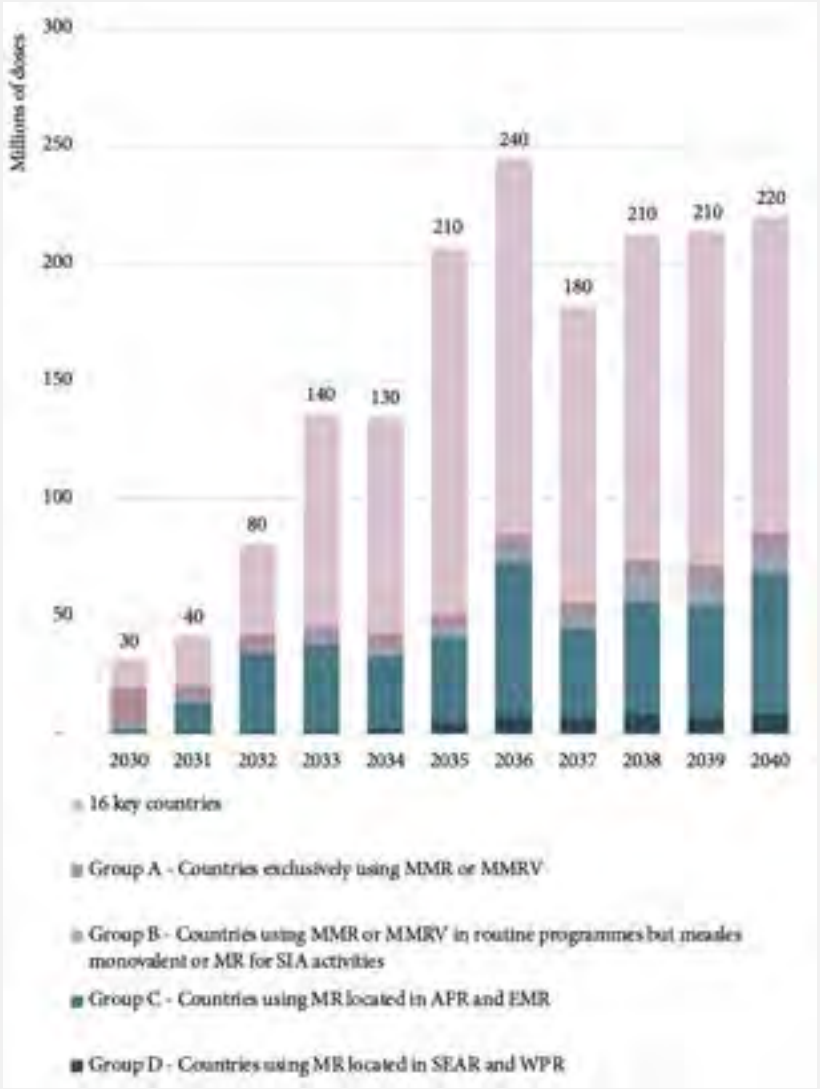
Final use cases identified for MR MAPs

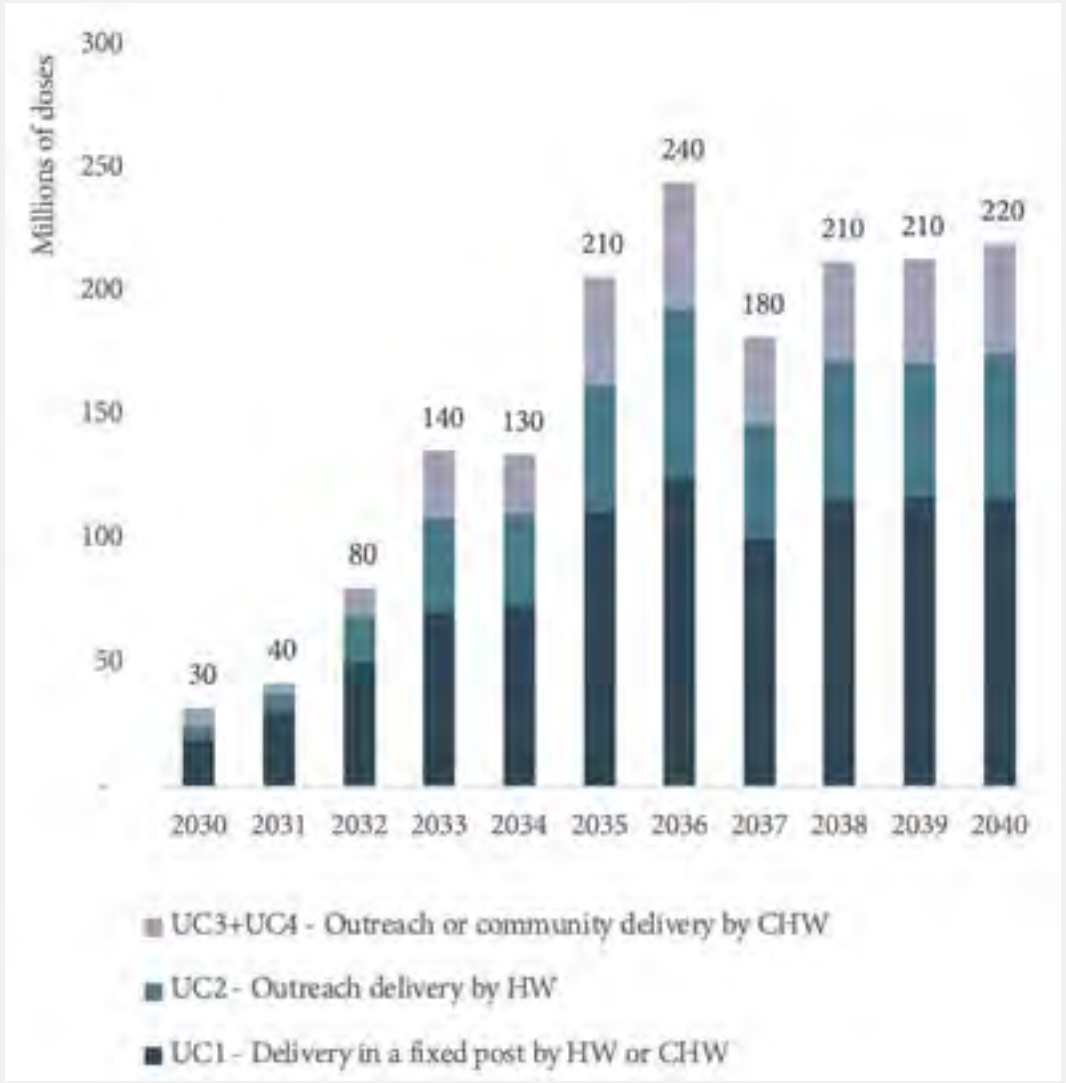
	Health Worker (HW)	**Community Health Care Worker** (CHW)	**Self administration**
Fixed Health Post (full cold chain capabilities)	1 **Delivery by HW or CHW in Fixed Post** Fixed health post is defined as a permanent structure which has full cold chain capabilities		5 **Self-administration with HW or CHW assistance** The MR-MAP is self-administered by the individual with the assistance or under supervision of HW or CHW, who is able to monitor for AEFI and record and report who has received the vaccination.
Outreach (reduced cold chain capabilities)	2 **Delivery by HW in outreach or other settings** Includes delivery in areas that do not have access to a fixed health post conducted by health workers and with reduced or no cold chain capacities.	3 **Outreach delivery by CHW** Includes delivery in areas that do not have access to a fixed health post conducted by community health workers and with reduced cold chain capacities.	
Other settings (no cold chain)		4 **Delivery by CHW in other settings** The CHW residing in a specific area is given a stock of MR-MAPs and can deliver them within their own community as needed.	6 **Self-administration without assistance** The MR-MAP is self-administered by the individual. The vaccination would be monitored and supervised by another individual who has received minimal training

Methods: demand forecast for MR-MAPs, 2030-2040



Results: demand forecast for MR-MAPs, 2030-2040





Country workshops to understand the use, demand and attributes for MR-MAPs

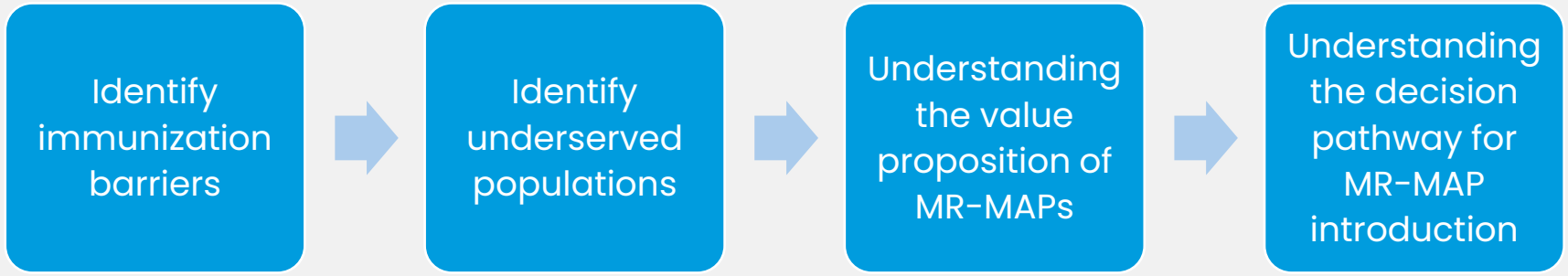
Workshop format:

- CAPACITI Innovation Framework
- 2 day in-person workshop in Indonesia and Ethiopia
- Participants from MoH, subnational EPI, NITAGs, regulatory, research institutes, local partners

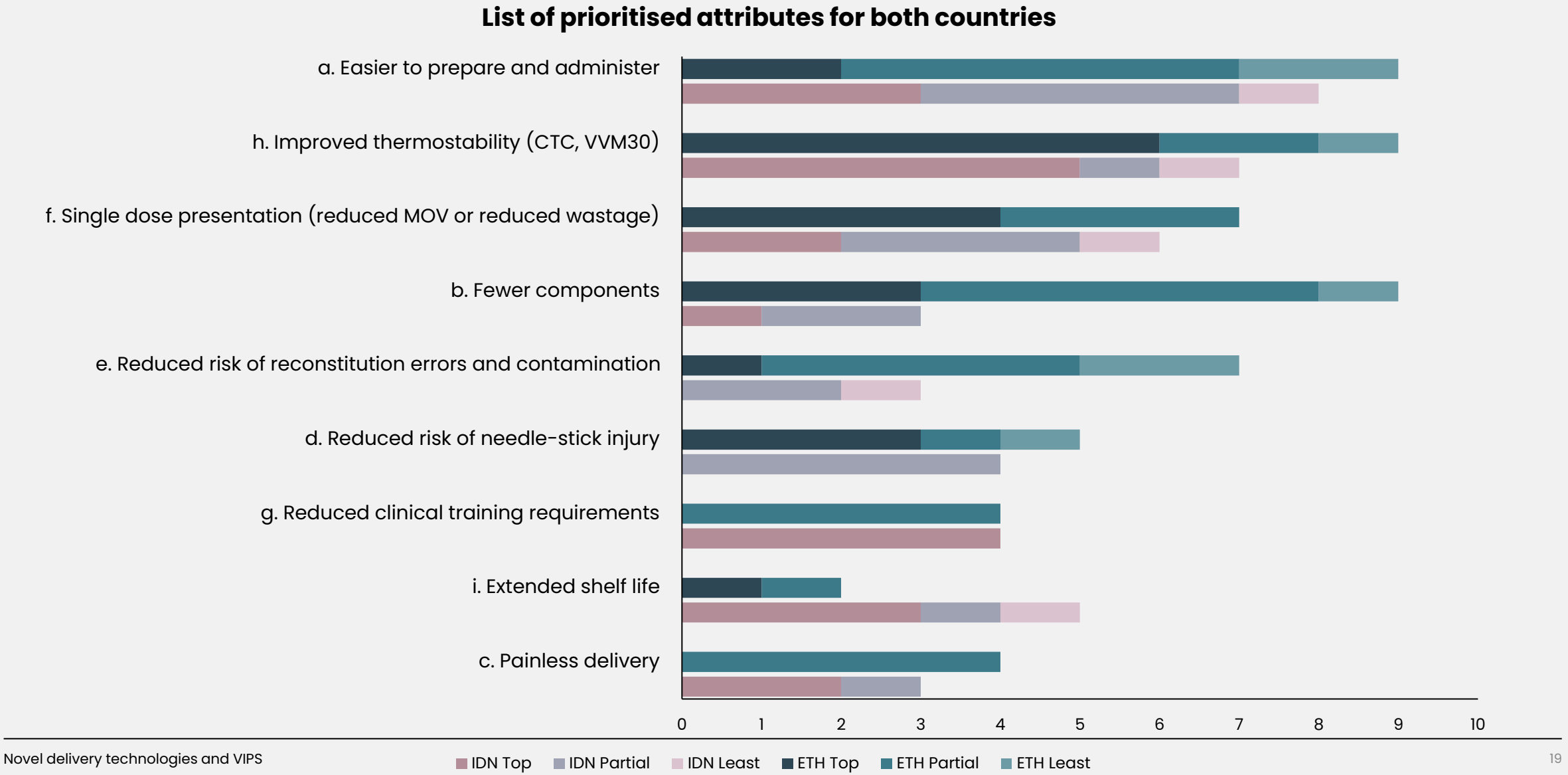
Research questions:

- What are the important attributes of MR-MAPs?
- How and where would you use MR-MAPs?
- What is the decision pathway and data packages required for the introduction of MR-MAPs?
- What is the feasiblity of mixed delivery of MAPs and N/S

Workshop steps:



Understanding desired attributes of MR-MAPs



Understanding the use of MR-MAPs

	Country A	Country B
1 Delivery by HW or CHW in Fixed Post	Yes, preferred delivery for pilot introduction	
2 Delivery by HW in outreach or other settings	Yes, especially in hard-to-reach areas and populations	
3 Outreach delivery by CHW	Maybe	Yes
4 Delivery by CHW in other settings	Maybe	Yes
5 Self-administration with HW or CHW assistance	Unlikely, needs research and policy considerations	
6 Self-administration without assistance	Unlikely, needs research and policy considerations	

Pathway to a decision to introduce MR-MAPs

Criteria

- Positive impact on coverage and equity
- Cost considerations (budget impact, cost effectiveness, cost per child)
- Cold chain needs
- Level of wastage
- Waste management implications
- Immunogenicity
- Community acceptance
- Supply stability; local production opportunities

When would you not consider MR-MAPs

- Does not meet WHO PPQ, regulatory or TPP
- Inferior immunogenicity or safety
- Disease burden for Rubella is low, would not consider MR
- Unsustainable global supply
- High cost beyond government ability to finance
- Community rejection

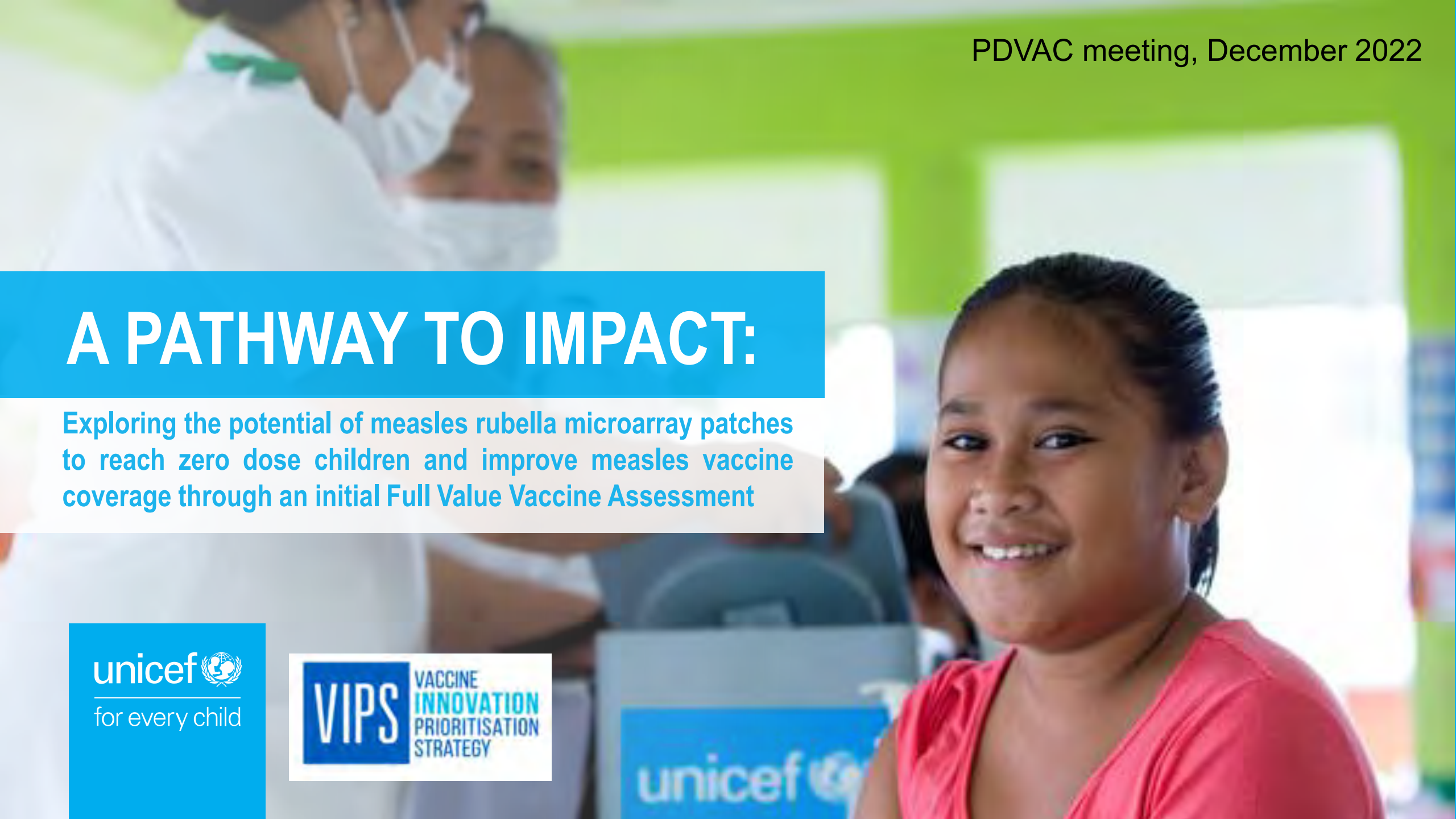
Evidence needed

- Cost benefit analysis
- BeSD surveys to understand community acceptance; health worker acceptance studies
- Immunogenicity
- Impact assessment on waste management needs
- Budget impact use case scenarios
- Projected supply availability
- Cold chain volume needs and availability
- Outcomes of pilot studies in varied geographic areas

PDVAC meeting, December 2022

A PATHWAY TO IMPACT:

Exploring the potential of measles rubella microarray patches to reach zero dose children and improve measles vaccine coverage through an initial Full Value Vaccine Assessment



unicef
for every child

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

The Measles-Rubella vaccine averts the highest number of vaccine-preventable deaths in children. It has the highest return on investment in public health.[1]

However, **immunization rates have stagnated**. When vaccination coverage for measles or rubella falls below the necessary threshold, **outbreaks** of measles and rubella **occur**.

To understand the potential value of MR-MAPs, UNICEF led an initial full value vaccine assessment (iFVVA)

Methodology

Desk review

- Identify barriers faced by MR programme
- Assess MR-MAP development timelines

Demand forecasts

- Assuming better reach of hard-to-reach populations and reducing missed opportunities for vaccination considering Use Cases

Financial analysis

- Price benchmarking analysis
- Discounted Cash Flow analysis

Consultations

- 34 experts across a wide range of topics

Cost, impact, and cost effectiveness

- PATH's Vaccine Technology Impact Assessment (VTIA) model
- LSHTM Dynamic Measles Immunisation Calculation Engine (DynaMICE) model

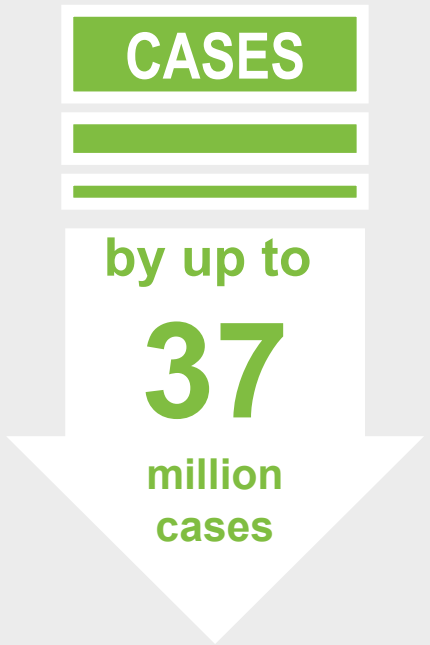
Expert Advisory Group

- 19 experts to discuss the methodology and assumptions used, and to endorse the key findings

The iFVVA demonstrates the strong potential of MR-MAPs to reduce measles morbidity and mortality

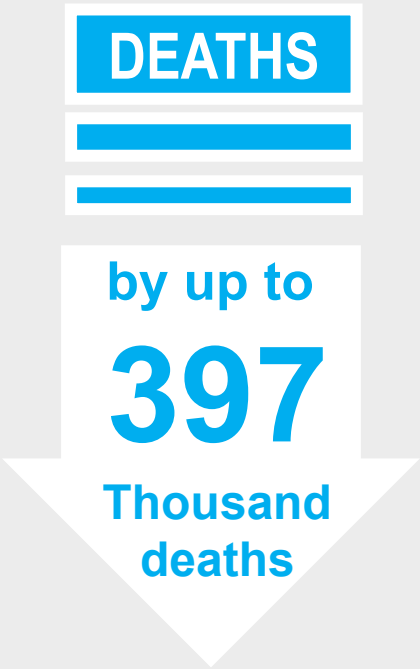
Results

Reduction in measles



35% reduction

Reduction in measles



35% reduction

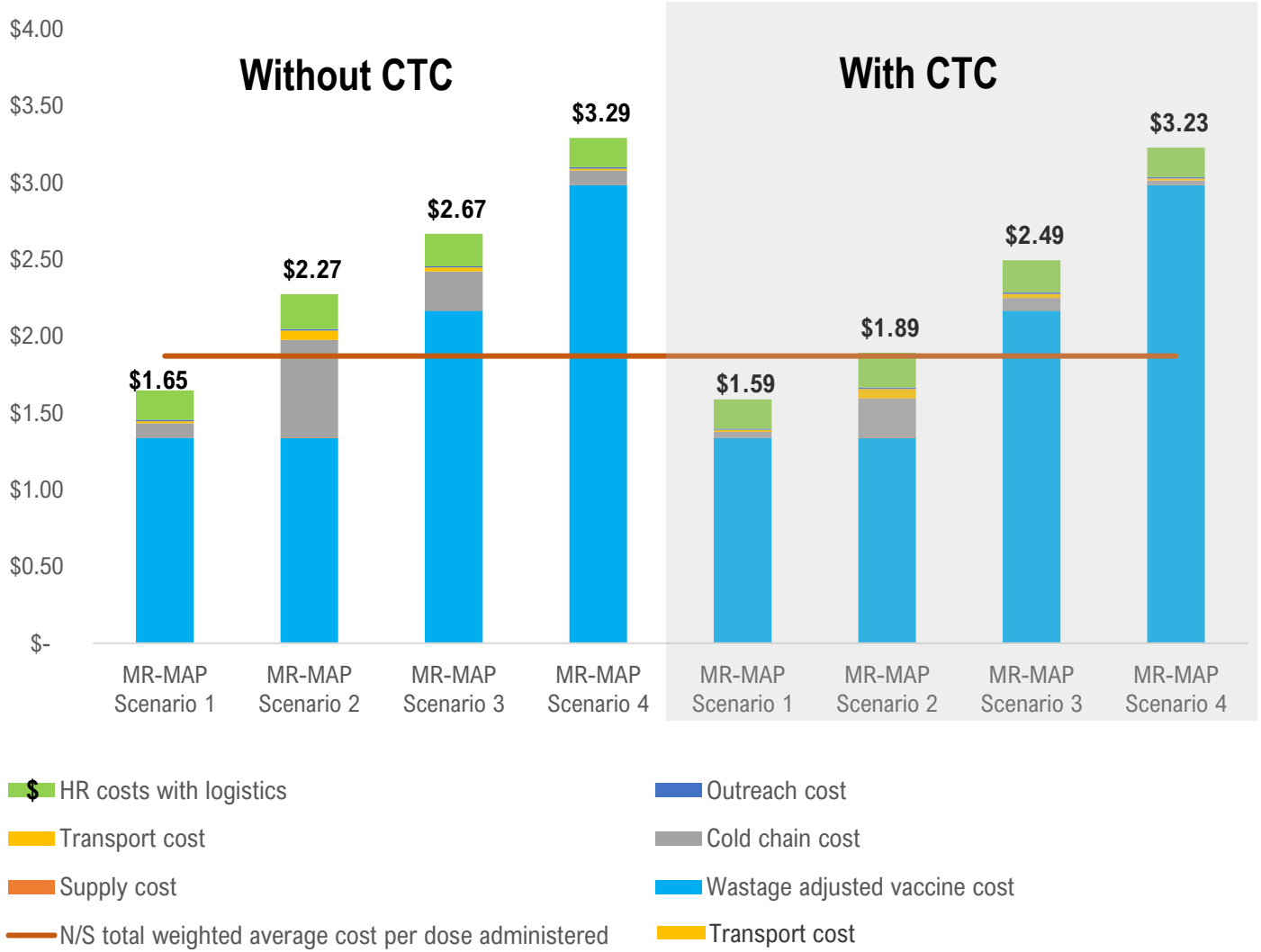
Reduction in measles-related

35% reduction

Increase MCV Coverage

MR-MAPs could reach an estimated **80 million more children (8%)** between 2030 and 2040 than would be reached using a needle and syringe presentation alone

MR-MAPs can be a cost-saving option for routine immunization



With the most optimal product characteristics, the costs related to **purchasing and delivering MR-MAPs would be lower than the same costs of the needle and syringe in LICs and LMICs**

Scenario	MR-MAP Price per dose ($USD)	Volume (cm^3)	HR time for administration (in seconds)
Scenario 1	$1.29	3	20
Scenario 2	$1.29	20	200
Scenario 3	$2.11	8	120
Scenario 4	$2.92	3	20

Introducing MR-MAPs has different cost effectiveness considering country types

		Scenario 3 High coverage growth MR-MAPs available in 2030	Scenario 4 Low coverage growth MR-MAPs available in 2030	Scenario 5 High coverage growth Accelerated intro in countries with greatest need in 2030	Scenario 6 Low coverage growth Accelerated intro in countries with greatest need in 2030	Threshold Health opportunity cost
		ICER	ICER	ICER	ICER	ICER
High income countries (n=12)	Low MR-MAP price	(106,711)	(118,106)	(92,222)	(110,808)	55,871 (5,845-180,794)
	High MR-MAP price	(102,109)	(116,597)	(85,219)	(108,987)	
Upper middle income countries (n = 16)	Low MR-MAP price	(1,766)	(648)	(2,192)	(1,026)	5,311 (581–14,152)
	High MR-MAP price	(581)	(92)	(825)	(270)	
Lower middle income countries (n = 33)	Low MR-MAP price	349	40	435	52	339 (116–7,043)
	High MR-MAP price	961	133	1,189	176	
Low income countries (n=20)	Low MR-MAP price	319	10	395	12	137 (72–432)
	High MR-MAP price	1,323	71	1,557	78	
Total	**Low MR-MAP price**	**22**	**(47)**	**149**	**(17)**	
	High MR-MAP price	**779**	**44**	**1,043**	**95**	

Values in red indicate cost effectiveness for the income group when compared against health opportunity costs

- Introducing MR-MAPs in HIC and UMIC will create significant savings due to the reduction of measles treatment costs rather than reduction of DALYs
- Introducing MR-MAPs in LMIC and LICs will increase total cost, but assuming a stagnation in MR vaccination coverage, it will be a cost-effective intervention regardless of the low or high price estimate

With the either the low or high estimates for MR-MAP prices and stagnant growth in coverage, introducing MR-MAPs would be a cost-effective strategy in all countries, based on relative comparisons of health opportunity costs.

Cost per DALY saved

IFVVA modeling* demonstrates that cost per DALY saved for LICs and LMICs ($85-$2,310) is comparable to the HPV ($91-$928), Rotavirus ($202-$428) and RSV maternal vaccines ($70-$270).

*Estimated doses from MR-MAP demand forecasting, estimated price from benchmarking analysis, and estimated DALYs from DynaMICE

The net present value for manufacturing MR-MAPs is positive under the right conditions.

The analysis highlights that the importance of (i) clarifying the **manufacturing partner** of choice and **manufacturing set-up** and related costs; and (ii) the critical influence of an appropriate **price** on manufacturer financial sustainability

Reaching additional children (HTR/MOVs) & additional benefits of MR-MAPs

- **Increase coverage and equity.**
  MR-MAPs are projected to reach additional **80-110 million children** that are in **hard-to-reach populations** or are part of the **missed opportunity for vaccination (MOV)** that cannot be reached by the current N/S presentation

- **Avoidance of reconstitution errors and** subsequent **impact.**
  From literature analysis: reconstitution errors and their impact were shown to significantly **impact immunization coverage** and one country witnessed a 40% decrease in coverage and 70 **deaths due** to a reconstitution **error**.

- **Decrease wastage**.
  If countries utilizing 10-dose vials were to adopt MR-MAPs, which will likely have a much lower wastage rate, they would experience **~39%** decrease in the number of doses to be purchased, while countries utilizing 5-dose vials could experience a decrease of **14%**

Committing to MR-MAPS:
Next steps with VIPS partners

- ❑ Communication of iFVVA results, including publication(s)
- ❑ Operational research to improve the accuracy of the demand forecast, better understand use cases and acceptability, and quantify the benefits and costs of MR-MAPs
- ❑ Answer technical questions on MR-MAP efficacy, safety, and immunogenicity
- ❑ Answer questions related to the financial sustainability of manufacturing (e.g., optimization of bulk and shareability of MAP lines across multiple antigens)
- ❑ Develop an appropriate regulatory pathway beyond first licensures for MR-MAPs
- ❑ Develop an approach and mechanisms for risk sharing the MAP develop and scale-up and implementation in LICs


unicef
for every child
Thank you.
unicef
© UNICEF/UN0216133

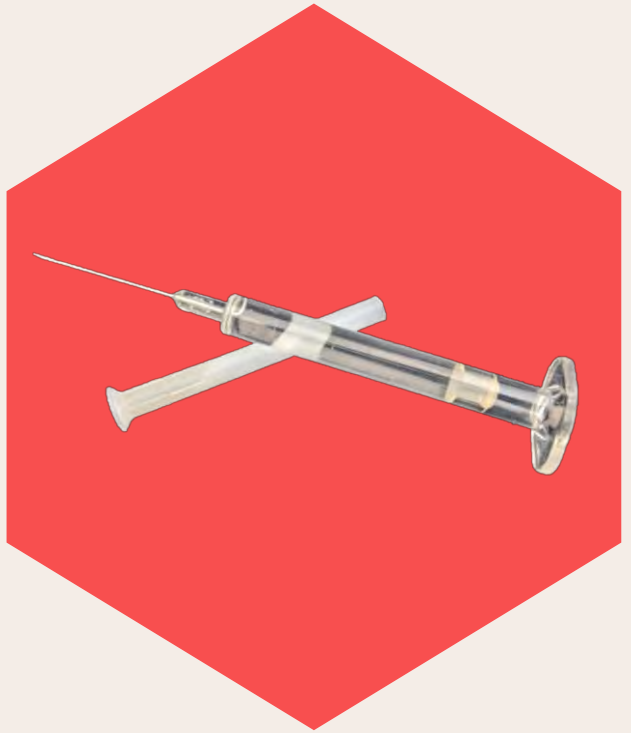
Vaccine product innovations

Update on pipeline of delivery technologies

PDVAC December 6, 2022

Courtney Jarrahian

Medical Devices and Health Technologies, PATH



Intranasal & inhalational delivery

Vaccines for respiratory delivery, including newly licensed COVID vaccines, have a variety of primary containers and delivery devices.

The device used impacts vaccine deposition in the respiratory tract, storage volume, ease of use, acceptability, and cost.

PATH and the International AIDS Vaccine Initiative (IAVI) are collaborating to assess the usability, acceptability, and programmatic fit of two nasal spray options (prefilled device and vial with syringe and spray attachment) in three countries.

Examples of vaccine product presentations

Prefilled syringe with attached nasal sprayer and dose divider

Image: PATH

– Medimmune/AstraZeneca (Influenza)[1]

Glass vial with intranasal OPV dropper

– Bharat Biotech (COVID)[2]

Image: Bharat Biotech

Glass vial with syringe, vial adapter, and nasal spray hub (dose divider)

Image: SIIPL

– Serum Institute of India (influenza)[1]
– Multiple pipeline candidates (COVID)[3]

Glass vial with vial adapter and oral syringe used as intranasal dropper

– Codagenix/Serum Institute of India Pvt. Ltd. (COVID)[3]

Glass vial and reusable vaporizing device with disposable cup for oral inhalation

– CanSino Biologics (COVID)[2]

Image: Aerogen/CanSino

1) WHO PQ; 2) Domestic authorization; 3) clinical development

PATH

Photo: PharmaJet

Jet injection

Reducing costs and stretching supplies of IPV:

WHO prequalified (PQ) PharmaJet Tropis device has been used to deliver approximately 3M doses of fractional, intradermal IPV (fIPV) in campaigns this year (7M doses total to date in Pakistan, Somalia, and Nigeria).

Stratified-pair, cluster-randomized study planned in 2023 to assess the impact on coverage, cost, and programmatic feasibility of the device for fIPV in routine immunization setting in Nigeria.

Improving efficacy of DNA vaccines:

COVID-19 clinical trial results published; Phase 2 studies in progress for cancer vaccines, including HPV.

PATH

Photo: MedInstill

Multidose vaccine pouch

Status

Institut Pasteur de Dakar is installing filling capacity for Intact Solutions MUSIC kit delivery for COVID or future liquid vaccines used in campaign settings.

Focus areas for development:

- Regulatory and PQ pathway.
- Human factors evaluation.
- Assessment of the acceptability, feasibility, and programmatic fit for LMIC immunization program.
- Training evaluation.
- Supply chain mapping of device components and accessories.

PATH

Pipeline compact prefilled autodisable devices (CPADs)

The **Injecto easyject device is the most advanced alternative** to Uniject and has an autodisable feature, is acceptable to users, and is **compatible with standard prefilled syringe filling equipment** with minor modifications.

Blow-fill-seal technology holds promise, but a **device with a WHO PQ-compliant autodisable feature must be developed**, validated, and assessed for usability, manufacturability, cost, and cold chain volume.

Prefilled syringe CPAD	Blow-fill-seal prefilled injection devices (non-AD)		
Injecto easyject	**Brevetti Angela Secureject**	**ApiJect™ prefilled injector**	**Unither Euroject™**
 Image: Injecto	 Photo: Brevetti Angela	 Photo: ApiJect	 Photo: Unither

PATH

Injecto easyject: User study

easyject evaluation

PATH aimed to evaluate the usability, acceptability, and programmatic feasibility of the easyject in comparison to the Uniject for contraceptive and vaccine delivery.

Summary of findings

In both countries, **participants highlighted that the device was easy to learn and use, easy to transport, and time-saving**.

Removing the cap and pressing down the plunger rod were challenging steps for several participants and have been addressed through design modifications.

Device preference was mixed between countries and cadres. However, **the majority of respondents in both countries were willing to use either device**: 100% of providers in Zambia, 95% of providers, and 86% of clients in Uganda.

Image: PATH

Immunization provider in Zambia practices a simulated injection with the easyject device.

PATH

Dual-chamber delivery devices

Glass dual-chamber prefilled syringe

Glass devices are currently available, but **cold chain volume and cost** may put them out of reach for low- and middle-income country vaccine markets.

Credence Companion®

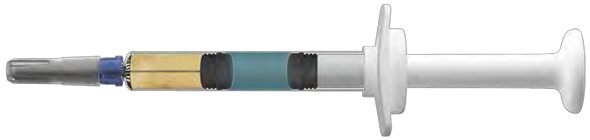


Image: Credence MedSystems

Frangible-seal dual-chamber delivery devices

Technology for injectable vaccines is in early-stage development, with key technical challenges to overcome, including identification of **materials with sufficient water vapor barrier** properties.

PATH Dualject

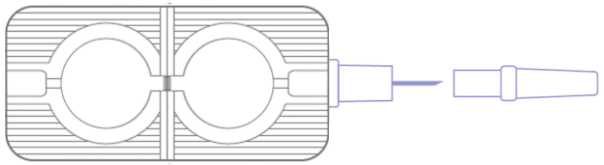


Image: PATH

PATH

Vaccines with non-standard dose volumes create major challenges for autodisable syringe supply logistics and countries

Autodisable (AD) syringes are exclusively supplied for vaccines by UNICEF, are fixed-dose and have fixed needles, so **vaccines must be paired with syringes with the same dose volume** and needle length.

Pre-COVID, **95% of syringes supplied by UNICEF were 0.5mL**.

Syringes have much longer shipping times than vaccines since they are usually shipped by sea due to their bulkiness (typically 2-3 months, up to 6-8 months recently).

The introduction of COVID vaccines with non-standard dose volumes posed **significant program challenges**:

- New AD syringe development and prequalification
- Significantly increased logistics costs and lead times, sometimes delaying vaccinations
- Pairing correct devices with vaccine at point of use

Recommendations for pipeline vaccines

1) Prioritize formulating new vaccines to match standard AD syringes (**0.5mL**, 0.1mL, 0.05mL)

If that is impossible…

1) Seek input early on programmatic suitability and syringe supply issues (PATH, UNICEF SD, WHO PQ, countries, etc.).
2) Formulate vaccines to match existing prequalified AD syringes (**0.3mL**, 0.25mL, 0.2mL)
3) Consider whether a CPAD presentation is suitable.

PATH

For more information contact:

Courtney Jarrahian
cjarrahian@path.org


PATH

Abbreviations

AD	autodisable
CPAD	compact prefilled autodisable
fIPV	fractional-dose inactivated poliovirus vaccine
HPV	human papillomavirus
IPV	inactivated poliovirus vaccine
LMIC	low- and middle-income country
OPV	oral poliovirus vaccine
PQ	prequalification
UNICEF SD	United Nations Children's Fund Supply Division
WHO	World Health Organization

Questions to PDVAC

1. **Are the mentioned activities appropriate to accelerate the development of vaccine MAPs?**

2. **How can we design a sustainable mechanism to engage with countries to inform product development and prepare for country uptake?**

Overview of preventative infectious disease mAbs in clinical development & WHO activities

World Health Organization

World Health Organization

Erin Sparrow, 6 December 2022

Licensed mAbs for prevention* of IDs

World Health Organization

Indication	Tradename, mAb name, manufacturer	Dose and route of Administration	Cost (US$)**
Pre-exposure prophylaxis of **COVID-19** (SARS-CoV-2)	Evusheld®, tixagevimab & cilgavimab, AstraZeneca	150 mg of each mAb intramuscularly	~$ 500
Pre-exposure prophylaxis of **COVID-19** (SARS-CoV-2)	Ronapreve®, casirivimab & imdevimab	600 mg of each mAb administered as a single intravenous infusion or by subcutaneous injection	~$ 850-2730
Prevention of recurrent **Clostridium difficile**	Zinplava™, bezlotoxumab , Merck	Intravenous infusion of 10 mg/kg	~$ 4,000
Emergency prophylaxis of inhalational **anthrax**	Abthrax, raxibacumab, GSK	Intravenous infusion of 40 mg/kg	~$ 2,000
Emergency prophylaxis of inhalational **anthrax**	Anthim®, obiltoxaximab, SFL Pharmaceuticals Deutschland GmbH	Intravenous infusion of 16 mg/kg	
Post-exposure prophylaxis for the prevention of **rabies**	Rabishield™, Serum Institute of India	3.33 IU/kg dose. Wound infiltration (as much of the dose as possible) and intramuscular for remaining dose. of 3.33 IU/Kg	~$ 25
Post-exposure prophylaxis for the prevention of **rabies**	Twinrab™, docaravimab & miromavimab, Zydus Vaxxicare	40 IU/Kg dose. Wound infiltration (as much of the dose as possible) and intramuscular for remaining dose.	~$ 25
Post-exposure prophylaxis for the prevention of **rabies**	Xunke, ormutivimab, North China Pharmaceutical Group	Not reported	
Prevention of **RSV** in high-risk infants and high-risk very young children	Synagis®, palivizumab, Astra Zeneca	15 mg/kg of body weight, given intramuscularly once a month during the RSV season.	~$3,500 (100mg/ml)
Prevention of **RSV in infants**	Beyfortus®, Nirsevimab, Sanofi Pasteur/Astra Zeneca	50mg dose for infants <5kgs 100mg dose for infants >5kgs	Unknown

*There are also mAbs currently approved for the treatment of Ebola, COVID-19 and HIV
**Based on information found in the public domain

Current pipeline of preventative mAbs in active clinical trials*

- Chikungunya (1 candidate, mRNA), ph1 completed
- Ebola (3 candidates), ph1-ph2a
- **HIV** (10 candidates) ph1-2
- Influenza (1 candidate) ph2
- **Malaria** (4 candidates) ph1-2
- **Rabies** (1 candidate) ph3
- **RSV** (3 candidates) ph1-3
- Staphylococcus aureus (1 candidate), ph3
- SARS-CoV-2 (2 candidates), ph1
- Yellow fever (1 candidate), ph1
- Zika (1 candidate), ph1

* Active was defined as trials that were registered from 1 January 2015 and that were not terminated, suspended or withdrawn. Does not include mAbs aimed at treatment nor trials for mAbs already authorized for prevention. Excludes trials that have an unknown status if trial registration was over 5 years ago.

Advantages and disadvantages of mAbs

Advantages/ potential:

- Quick protection (vaccines can take weeks and >1 dose to mount full immune response)
- May have fewer side effects than other drugs (chemoprophylaxis)
- Potential applications:
    - Prevention of disease during periods of high risk for diseases where vaccine development has been challenging
    - To help address AMR
    - Applications in epidemics/pandemics
    - Alternative to blood derived immunoglobulins (more standardized production)

Disadvantages:

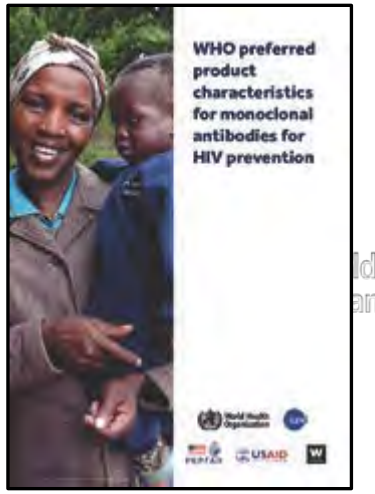
- Cost (more expensive to produce than vaccines and chemically synthesised drugs) – but new technologies are on the horizon...
- Short-lived (several months with extended half life)
- Administration by HCW required (injections, IV)
- Clinical development long/challenging for some pathogens

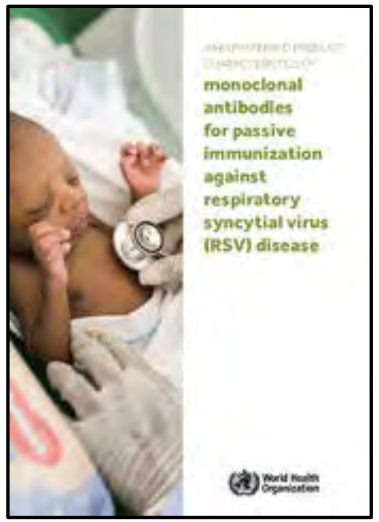
PQ of preventative ID mAbs

- If prequalified as medicines, there are two main issues that will need to be clarified:
- **Programmatic suitability**: The extent to which the programmatic suitability required for vaccines is applicable to mAbs used within the routine immunization programme.
- **Prequalification of originator mAbs by manufacturers not located in countries with an SRA**: Whether manufacturers in countries such as India (where vaccine prequalification is possible under an NRA with maturity level 3) could receive prequalification under the medicines pathway.

WHO preferred product characteristics (PPCs)

- WHO PPCs aim to encourage innovation & promote development of products for use in LMIC settings.
- They describe preferential attributes such as indications, schedule, target populations, use case(s), route of administration, programmatic suitability as well as preliminary consideration of data that should be collected for safety, efficacy and policy evaluation.





Developed for:

- mAbs for **HIV** prevention
  www.who.int/publications/i/item/9789240045729
- mAbs for passive immunization against **RSV** in infants
  www.who.int/publications/i/item/9789240021853

Under development for:

- Prevention of **malaria** (P. Falciparum) in infants and young children

WHO guidance on the quality, safety and efficacy of mAbs for infectious diseases

- Developed by the WHO Norms & Standards for Biologics Unit (NSB)
- First round of public consultation completed, second round soon.
- The document will be presented to the ECBS for adoption in March 2023.
- Disease specific supplements to follow: RSV, COVID (in 2023) and rabies, HIV, malaria (in 2024). To provide additional details relevant to the development and assessment of mAbs for a specific disease, e.g:
  - Information on the infecting agent, pathology, and variants
  - Epidemiology and transmission
  - International reference materials
  - Information on antigens and epitopes (e.g.neutralizing or enhancing epitopes)
  - In vitro models and assays
  - Animal models
  - Human challenge models
  - Information and data available on clinical evaluation of mAbs for the disease


World Health Organization

WHO/BS/DRAFT/19 August 2022
ENGLISH ONLY

WHO Guideline on the nonclinical and clinical evaluation of monoclonal antibodies and related biological products intended for the prevention or treatment of human infectious diseases.

PQ likely to follow the medicines pathway
(different requirements to vaccines)

Question to PDVAC

- Would a generic PPC for infectious disease mAbs be feasible to develop or are characteristics pathogen specific?
- Is there a need for technical documents/guidance on HIV mAbs for paediatric use to guide development (e.g. research roadmap) – to be discussed after HIV presentation.

World Health Organization

Thank you

World Health Organization

Overview of traditional production technologies and novel ways to bring down costs

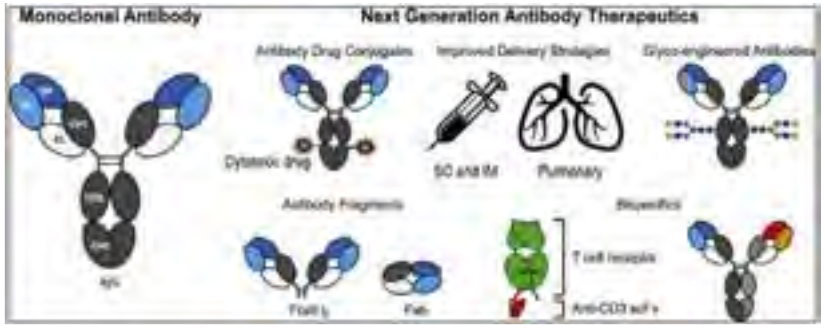
Veysel Kayser, PhD

Associate Professor
University of Sydney
Sydney School of Pharmacy

6 December 2022

WHO PDVAC meeting - Geneva

THE UNIVERSITY OF SYDNEY



mAb-Nanoparticle Conjugates

Outline

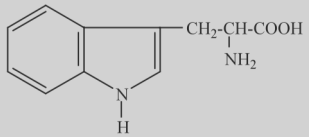
- Our research
- Therapeutic mAbs & market
  - Why are mAbs expensive?
- Differences between small molecules and mAbs
- Summary of mAb manufacturing
- New developments
  - Protein engineering
  - Novel formulation approaches
  - Different mAb formats
- Future outlook & concluding remarks

Current research in the lab

Theme I

Small molecule studies

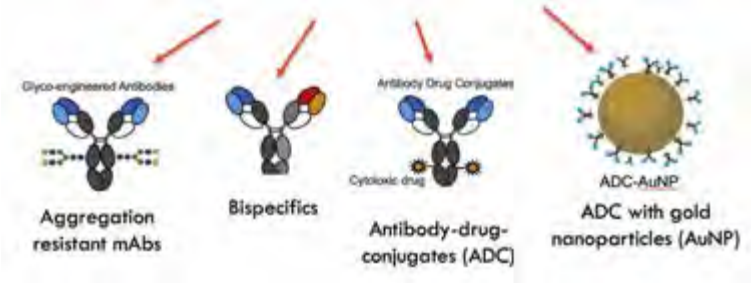
- MW: <500 Da
- Crystallization
- Nucleation
- Catalytic activity
- Anti-cancer properties
- Anti-viral / bacterial properties



Theme II

Biotech products / Biopharmaceuticals / **Biosimilars & Biobetters / mAbs / ADCs / bispecifics** / Antibody-NP / peptides / other therapeutic proteins

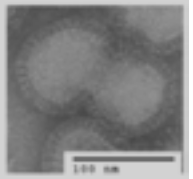
- Formulation
- Aggregation
- Protein-protein interactions
- Predictive tools
- Molecular level information



Theme III

Vaccines
(Flu, Rabies, COVID-19…)

- New vaccines
  - Traditional
  - Protein based
  - Nanoparticle
- Formulation
- Characterization
- Aggregation
- Particle size
- Predictive tools

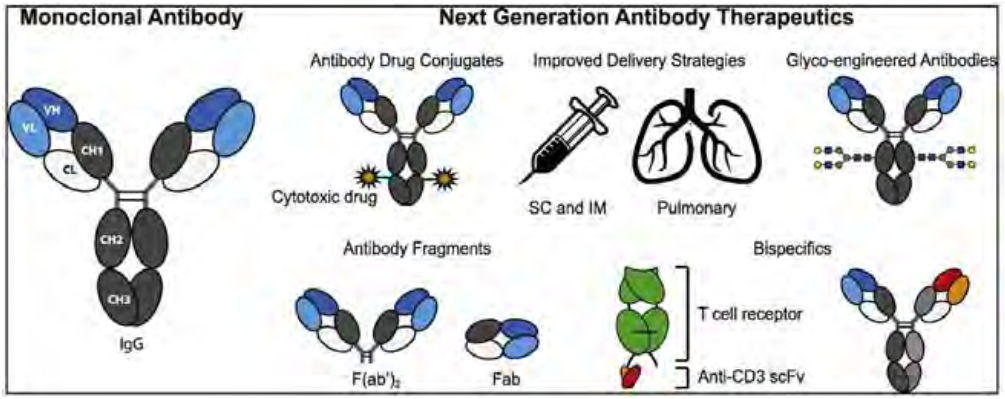


Theme II: Development of therapeutic mAbs

- Developing novel (e.g., ADC, bispecifics) and biosimilar antibodies (e.g., Herceptin®, Humira®)
- Developing biobetters with enhanced stability & affinity via bioengineering approaches – computational tools and experimental methods
- Developing new formulations and sensitive methods for biologics

Monoclonal Antibody-Directed Therapy
Veysel Kayser, Amita Datta-Mannan (Eds), 2022 MDPI

Therapeutic Monoclonal Antibodies and Antibody Products, Their Optimization and Drug Design in Cancers
Veysel Kayser (Ed), 2022 MDPI



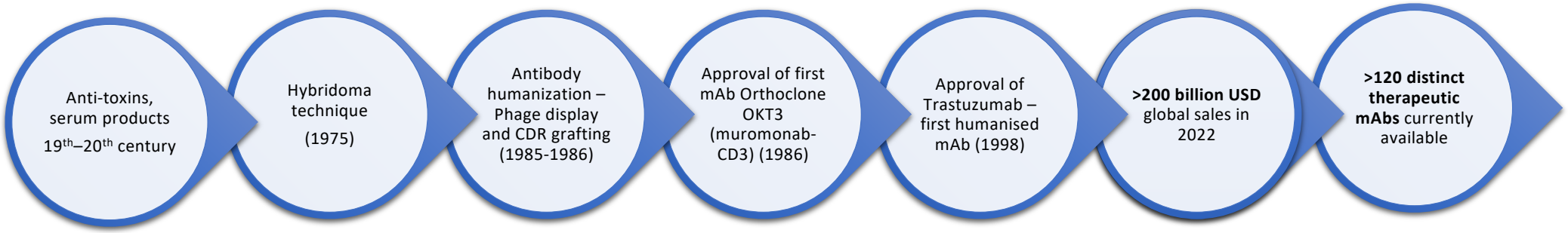
Conformational stability and aggregation of therapeutic monoclonal antibodies studied with ANS and Thioflavin T binding.
V Kayser, N Chennamsetty, V Voynov, B Helk, BL Trout
MAbs 3 (4), 408-411

The state-of-play and future of antibody therapeutics.
Z Elgundi, M Reslan, E Cruz, V Sifniotis, V Kayser
Adv Drug Deliv Rev 122, 2-19

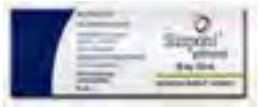
Recent publications:

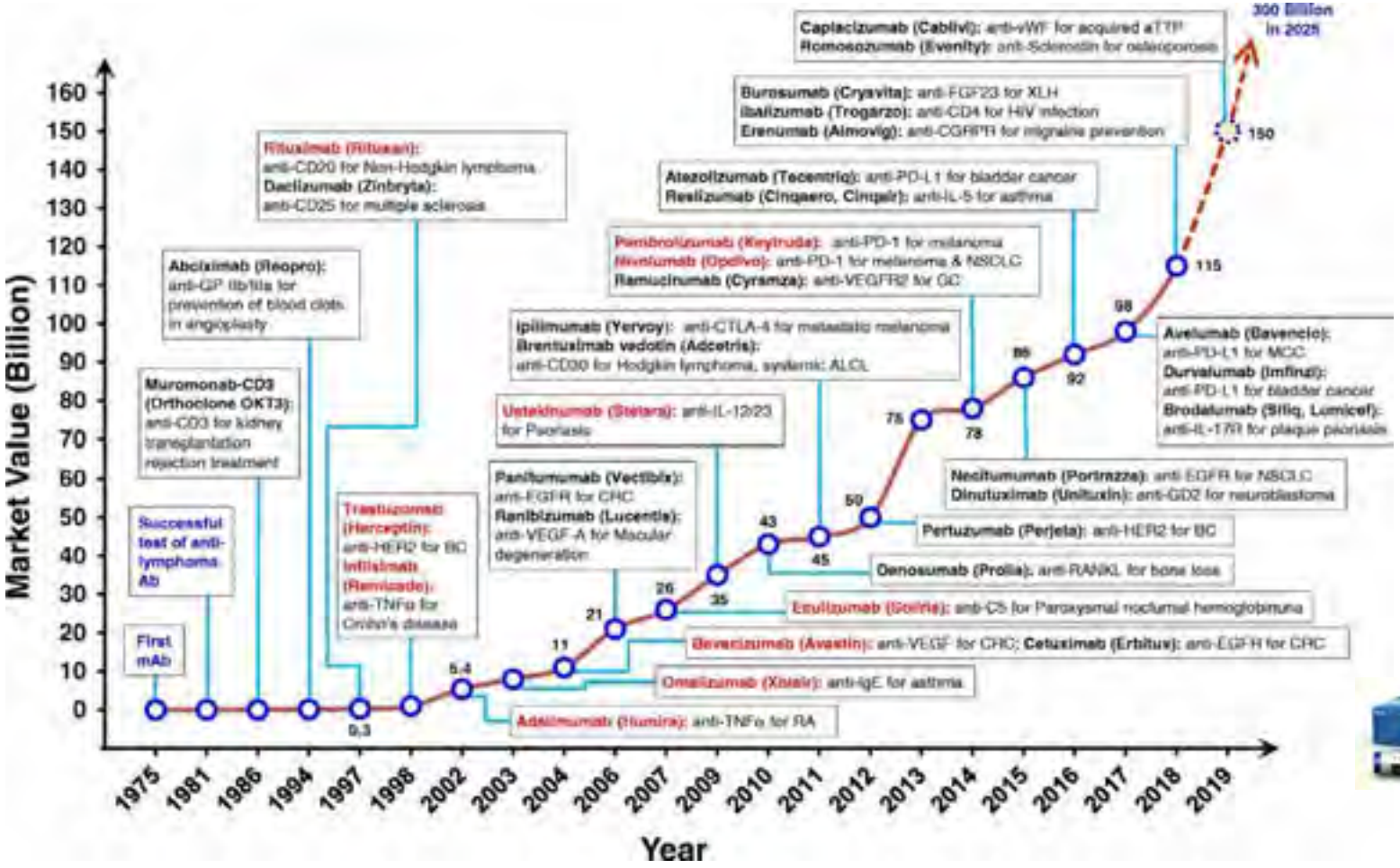
1. Cruz, E. *et al* (2021) *Pharmaceutics,* 13 (11), 1747
2. Mckertish, C. *et al* (2021) *Biomedicines* 9 (8), 872
3. Tarkistani, MAM. *et al* (2021) *Nanomaterials* 11 (5), 1227
4. Cruz, E. *et al* (2019) *Cancers,* 11(6), 1-22
5. Reslan, M. *et al* (2018) *Chem Comm*, *54*(75), 10622-10625
6. Sifniotis, V. *et al* (2019) Antibodies, 8(2), 36
6. Reslan, M., Kayser, V. (2018) Biophys Rev, 10(3), 781-793
7. Reslan, M.; Kayser, V. (2018) Pharm Dev Tech, 1-7
8. Elgundi, Z. *et al* (2017) *Adv Drug Deliv Rev*, 122, 2-19
9. Reslan, M. *et al* (2017) *Pharm Dev Tech*, 22(6), 785-791
10. Elgundi, Z. *et al* (2017) *JoVe*, 2017 (119), 1-8
11. Sahin, Z. *et al* (2016) *Eur J Pharm Sci*, 86, 115-124

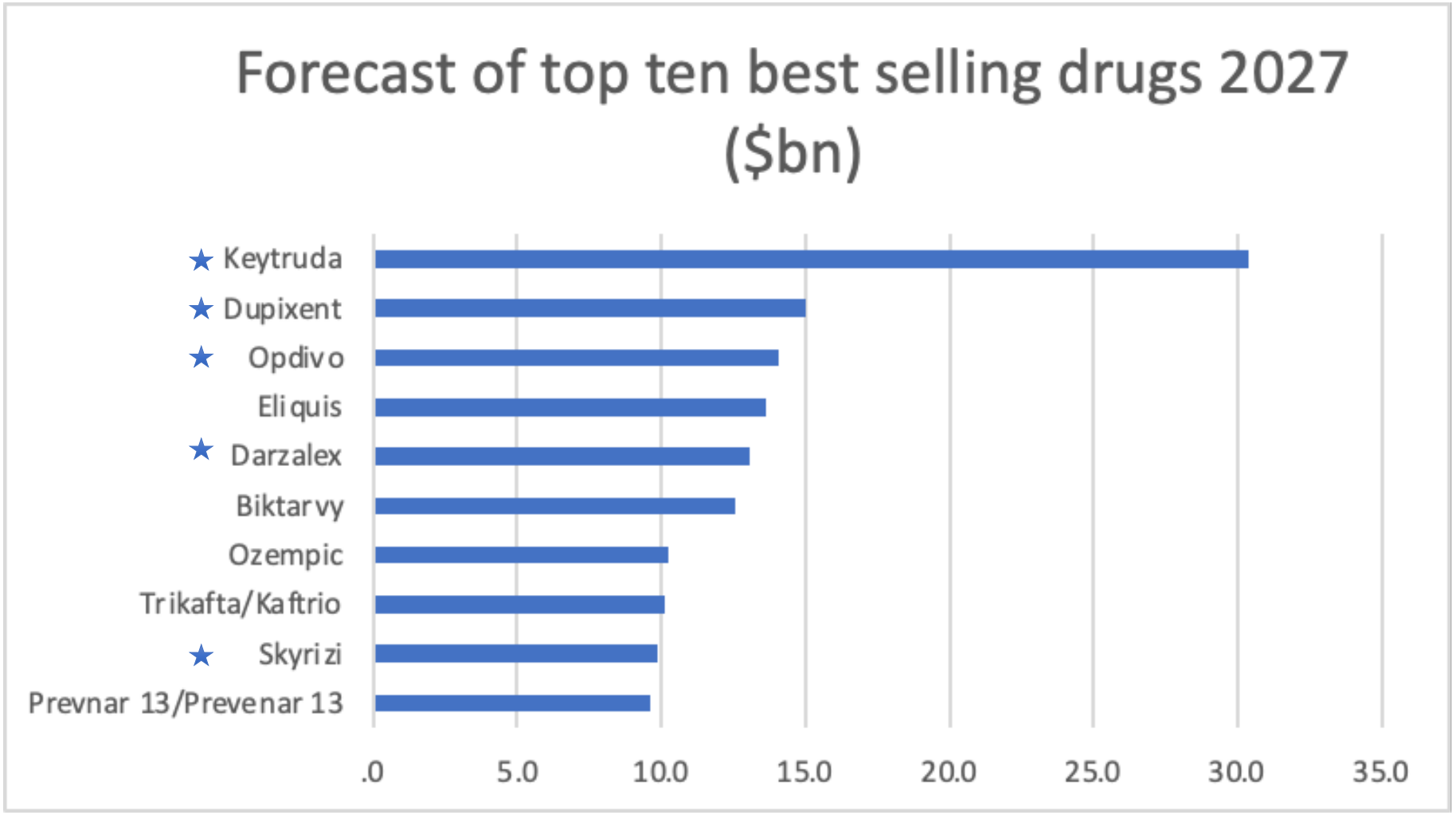
The antibody revolution



mAb market




Market Value (Billion)
Year
300 Billion in 2025
Caplacizumab (Cablivi): anti-vWF for acquired aTTP
Romosozumab (Evenity): anti-Sclerostin for osteoporosis
Burosumab (Crysvita): anti-FGF23 for XLH
Ibalizumab (Trogarzo): anti-CD4 for HIV infection
Erenumab (Aimovig): anti-CGRPR for migraine prevention
Atezolizumab (Tecentriq): anti-PD-L1 for bladder cancer
Reslizumab (Cinqaero, Cinqair): anti-IL-5 for asthma
Pembrolizumab (Keytruda): anti-PD-1 for melanoma
Nivolumab (Opdivo): anti-PD-1 for melanoma & NSCLC
Ramucirumab (Cyramza): anti-VEGFR2 for GC
Ipilimumab (Yervoy): anti-CTLA-4 for metastatic melanoma
Brentuximab vedotin (Adcetris): anti-CD30 for Hodgkin lymphoma, systemic ALCL
Avelumab (Bavencio): anti-PD-L1 for MCC
Durvalumab (Imfinzi): anti-PD-L1 for bladder cancer
Brodalumab (Siliq, Lumicef): anti-IL-17R for plaque psoriasis
Necitumumab (Portrazza): anti-EGFR for NSCLC
Dinutuximab (Unituxin): anti-GD2 for neuroblastoma
Pertuzumab (Perjeta): anti-HER2 for BC
Denosumab (Prolia): anti-RANKL for bone loss
Eculizumab (Soliris): anti-C5 for Paroxysmal nocturnal hemoglobinuria
Bevacizumab (Avastin): anti-VEGF for CRC; Cetuximab (Erbitux): anti-EGFR for CRC
Omalizumab (Xolair): anti-IgE for asthma
Adalimumab (Humira): anti-TNFα for RA
Rituximab (Rituxan): anti-CD20 for Non-Hodgkin lymphoma
Daclizumab (Zinbryta): anti-CD25 for multiple sclerosis
Abciximab (Reopro): anti-GP IIb/IIIa for prevention of blood clots in angioplasty
Muromonab-CD3 (Orthoclone OKT3): anti-CD3 for kidney transplantation rejection treatment
Ustekinumab (Stelara): anti-IL-12/23 for Psoriasis
Panitumumab (Vectibix): anti-EGFR for CRC
Ranibizumab (Lucentis): anti-VEGF-A for Macular degeneration
Trastuzumab (Herceptin): anti-HER2 for BC
Infliximab (Remicade): anti-TNFα for Crohn's disease
Successful test of anti-lymphoma Ab
First mAb
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
1975
1981
1986
1994
1997
1998
2002
2003
2004
2006
2007
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
0.3
5.4
11
21
26
35
43
45
50
75
78
85
92
98
115
150


Forecast of top ten best selling drugs 2027 ($bn)
Keytruda
Dupixent
Opdivo
Eliquis
Darzalex
Biktarvy
Ozempic
Trikafta/Kaftrio
Skyrizi
Prevnar 13/Prevenar 13
.0
5.0
10.0
15.0
20.0
25.0
30.0
35.0

Why are mAbs expensive?

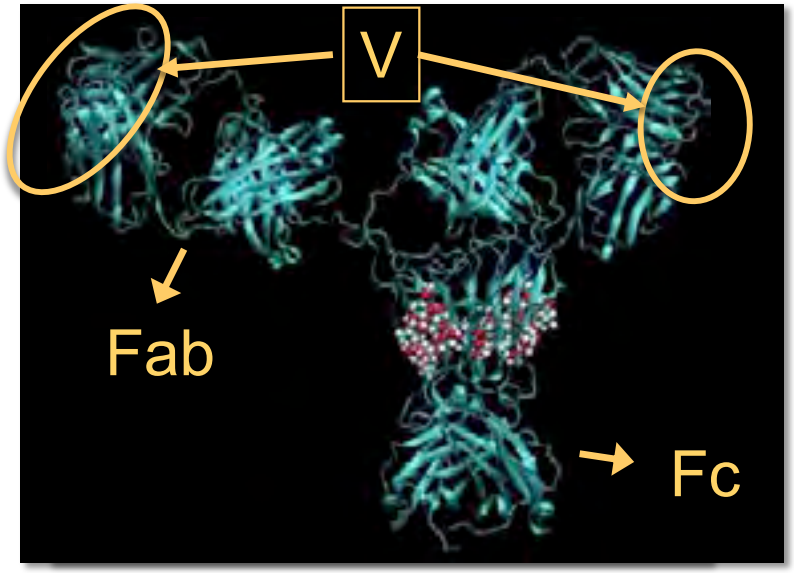
- High value proteins such as mAbs require high front-end investment
- Manufacturers desire timely return of their investment – before patent protection is ceased
- R&D phase is long, difficult, and complex
- Full size mAbs require mammalian cell line production due to PTMs

- Complicated and difficult to purify mAbs – affinity chromatography & and characterise
- Difficult to formulate
- Parenteral delivery
- High protein concentrations and multiple administrations are needed
- Cold-chain transport and long-term storage
- Lack of competitor products – biosimilars are 15-40% cheaper than originators
- … others?

What can we do to reduce the cost?

- High value proteins such as mAbs require high front-end investment
  - Consider cheaper front-end manufacturing technologies
- Manufacturers desire timely return of their investment – before patent protection is ceased
  - Put a cap in profit & consider changing patent duration
- R&D phase is long, difficult, and complex
  - Adapt novel methods to streamline R&D phases
- Full size mAbs require mammalian cell line production due to PTMs
  - Consider other expression systems, e.g., plants
  - Consider smaller Ab-formats, e.g., F_{ab} domain
- Complicated and difficult to purify – affinity chromatography & and characterise mAbs
  - Develop other ways to purify & characterise mAbs
- Difficult to formulate
  - Develop better, more stable formulations more rapidly
- Parenteral delivery
  - Consider other delivery methods
- High protein concentrations and multiple administrations are needed
  - Improve half-life & binding capability so lower protein concentration is sufficient
- Cold-chain transport and long-term storage
  - Invest in techniques aiming for room-temperature formulations
- Lack of competitor products – biosimilars are 15-40% cheaper than originators
  - Provide incentives for researchers and manufacturers including academics & small pharma to develop mAbs prior to need
- … others?

Structure & action of mAbs



- Monoclonal antibodies (mAbs) are targeted therapy agents – large proteins (>1000 aa) produced through genetic engineering. Antibodies have several features key to their action as therapeutics:
- **Bind antigen**. One end (variable domains) bind mAg through loops at its tips, and may block its action, or crosslink receptors (and lead to loss from cell surface or apoptosis).
- They usually have to be given IV or SC.
- Side effects can include reactions to non-human proteins.

- **Stays in serum for 14-28 days (half-life).** mAb escapes filtration in kidney (large size, 150 kD) and pinocytosis (binds to recycling receptor in cell).
- **Neutralise and/or Kill.** The other end (Fc) acts as flag leading to killing of agent by engaging C1q, TRIM21, neutrophils, macrophages & NK cells. Depends whether IgG1,2,3 or 4.

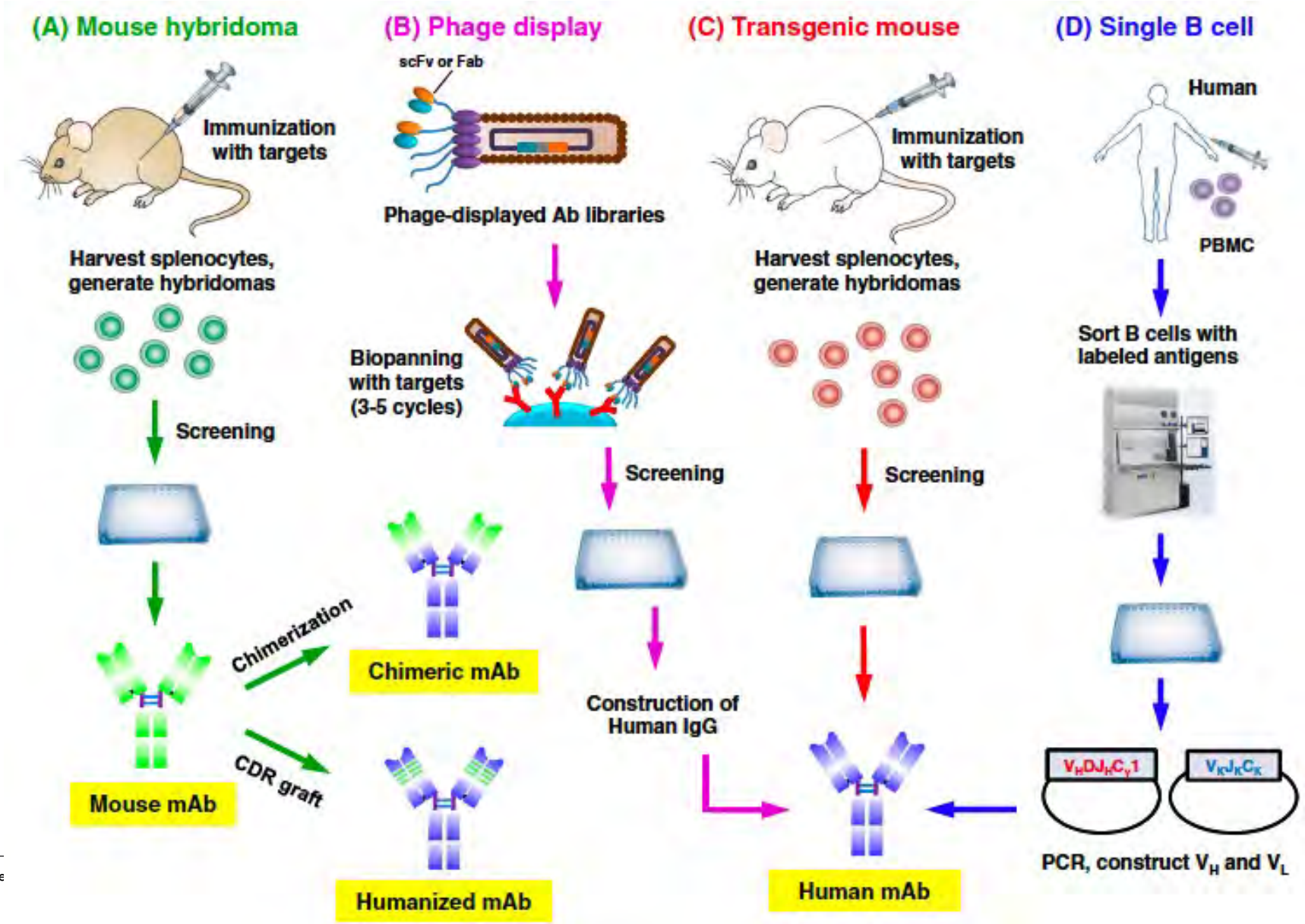
E. Cruz & V. Kayser, Chapter 4: "Major Classes of Biotherapeutics", in "Biologics, Biosimilars, and Biobetters: An Introduction for Pharmacists, Physicians and Other Health Practitioners" ed. Iqbal Ramzan. 2021 John Wiley & Sons, Inc. ISBN:9781119564652

Comparison of common characteristics of mAbs and small molecule drugs

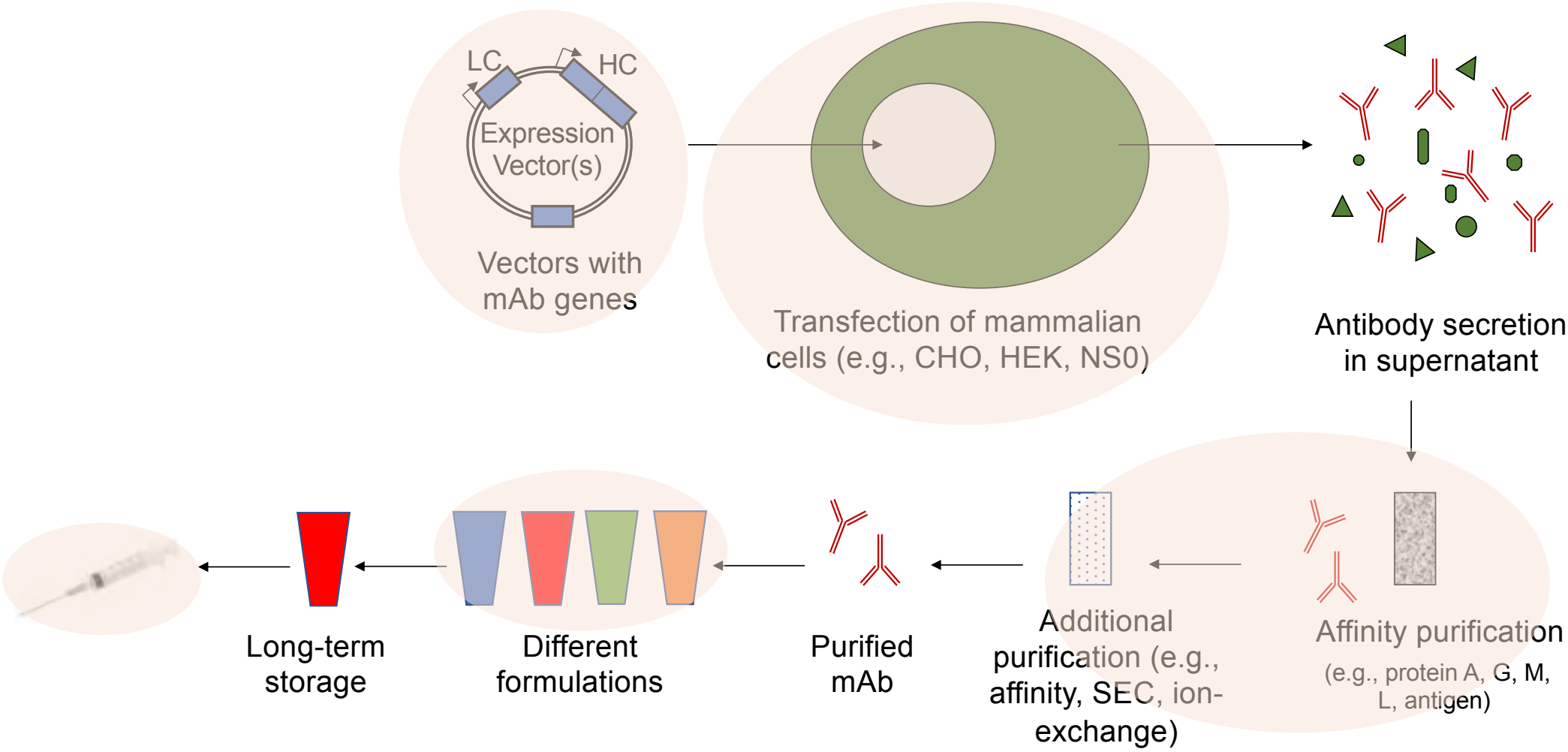
Characteristics	Antibodies	Small Molecule Drugs
Molecular weight	150,000 Daltons	< 500 Daltons
Physicochemical/biological properties	Complex	Less complex
Production method	Using living organisms/cells	Chemical synthesis
Critical process steps in manufacture	Many	Significantly less
Characterization	Difficult, often not well characterized	Relatively simple, well characterized
Physical/chemical stability	Poor – requires stabilizing excipients and low temperature storage	Relatively stable at room temperature
Administration	Limited - usually parenteral	Flexible – usually oral
Half-life	Days to weeks – dosing daily to monthly	Relatively short – dosing every few hours is common
Specificity/affinity for target	Very high	Relatively low – off-target effects more common
Safety profile	Less common side effects, but can be immunogenic	More common side effects, but less likely to be immunogenic
Cost	High production and treatment costs	Relatively lower production and treatment costs
Heterogeneity	High	Low or none

Kayser et al., "Pivotal Biology, Chemistry, Biochemistry and Biophysical Concepts of Biologics and Biosimilars", in "Biologics, Biosimilars, and Biobetters: An Introduction for Pharmacists, Physicians and Other Health Practitioners" ed. I. Ramzan. 2021 John Wiley & Sons

Techniques / platforms for mAb development



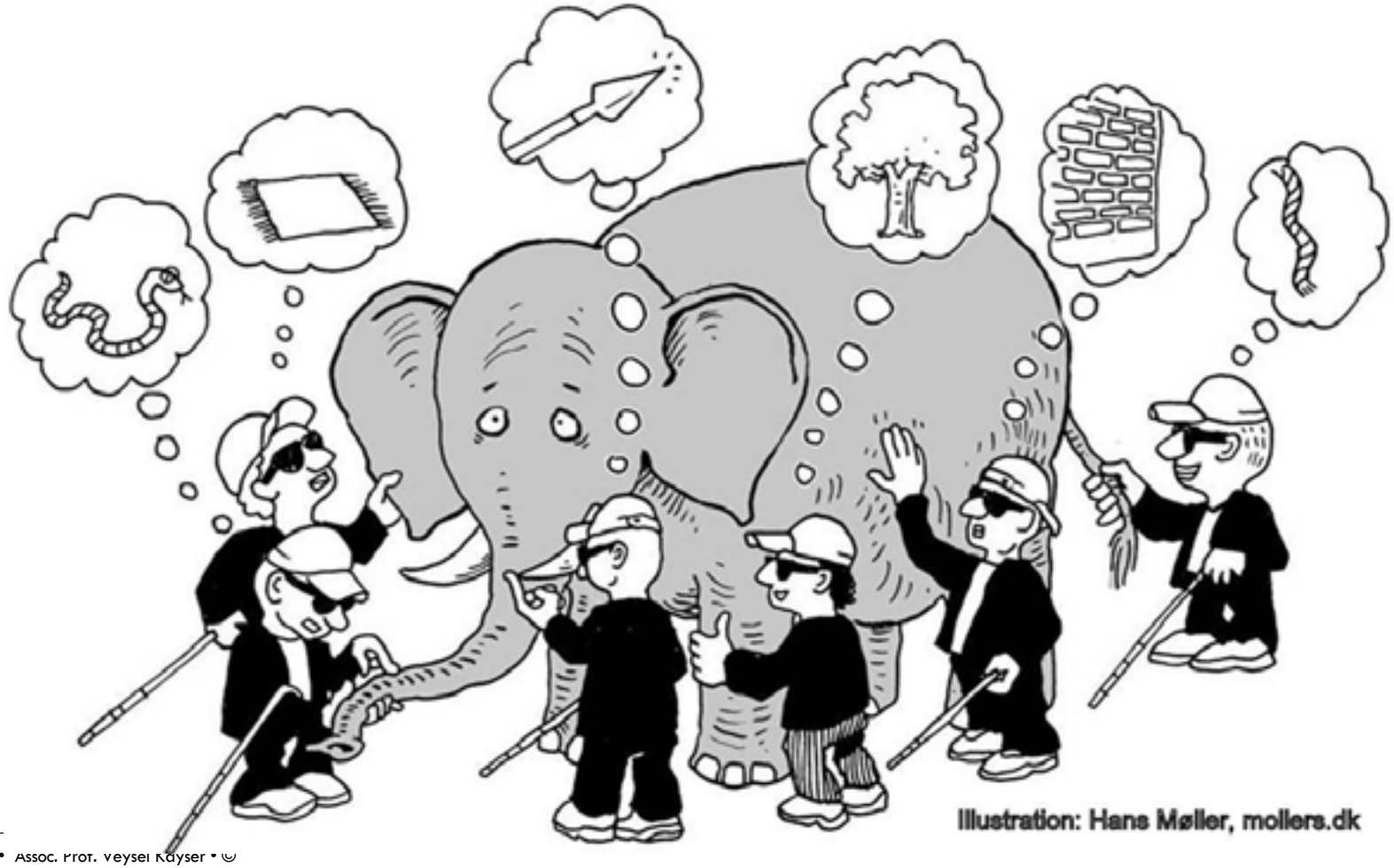
Lu et al. Journal of Biomedical Science (2020) 27:1


LC
HC
Expression Vector(s)
Vectors with mAb genes
Transfection of mammalian cells (e.g., CHO, HEK, NS0)
Antibody secretion in supernatant
Affinity purification
(e.g., protein A, G, M, L, antigen)
Additional purification (e.g., affinity, SEC, ion-exchange)
Purified mAb
Different formulations
Long-term storage

What are the new developments?

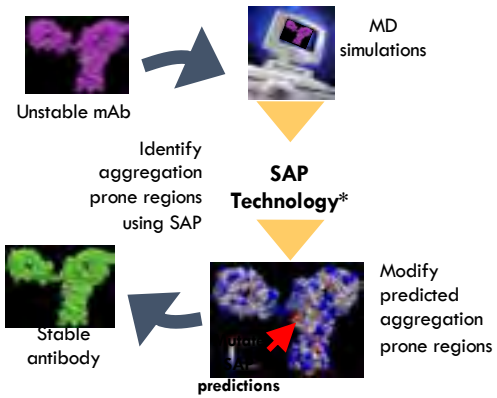
- **Formats:**
  - *Available:* full size mAbs & some other modalities exist for other indications such as cancer, e.g., ADCs, bispecifics.
  - *New:* mAb-nanoparticle conjugates, nucleic acid-encoded mAbs, Ab mimetics and other engineered proteins such as Fc-fusion, darpins, monobodies, nanobodies…
- **Formulations:**
  - *Available:* buffered liquid & lyophilised
  - *New:* room temperature & microneedle & inhalation & others?
- **Delivery methods & body systems:**
  - *Available:* SC & IV & IM
  - *New:* SC, IV, IM, and also solid dosage forms / oral / inhalation, microneedle…
- Biophysical **methods**:
  - *Available:* computational, spectroscopy (e.g., UV-Vis & fluorescence & DLS/MALS), separation (e.g., HPLC, electrophoresis), microscopy (e.g., optical)
  - *New:* includes abovementioned methods but more sensitive, *in situ* & high-throughput capabilities

Need for different methods for different aspects of the system



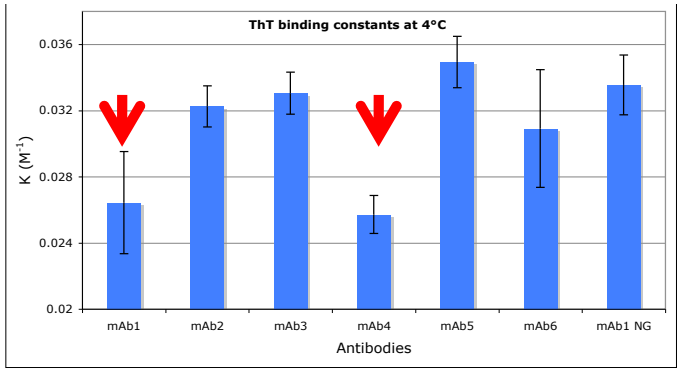
Characterisation of mAbs requires orthogonal methods

In silico prediction

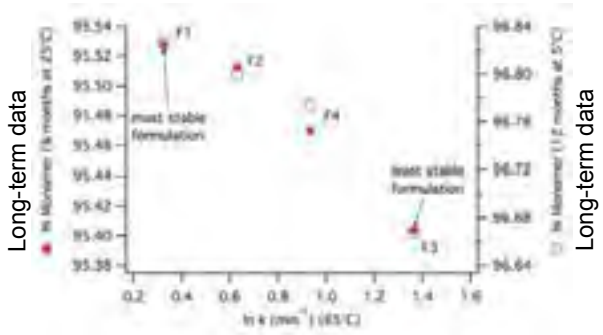


- Chennamsetty *et al.*, JMB, (2009)
- Chennamsetty *et al.*, PNAS, (2009)

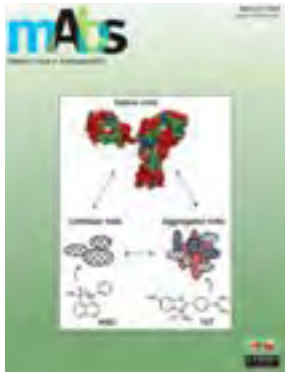
Candidate screening



Formulation ranking

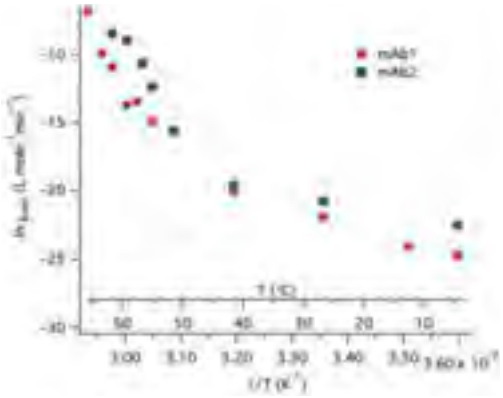


Kayser *et al.*, Biotech. J. (2012)



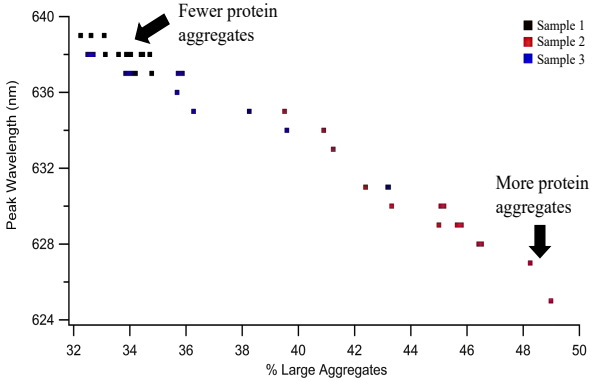
Kayser *et al.*, mAbs (2011)

Non-Arrhenius kinetics



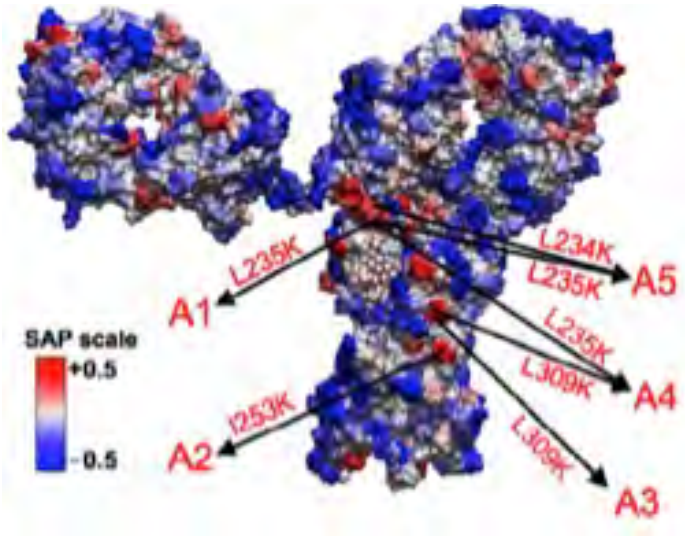
Kayser *et al.*, J. Pharm. Sci. (2011)

Formulation / lot screening

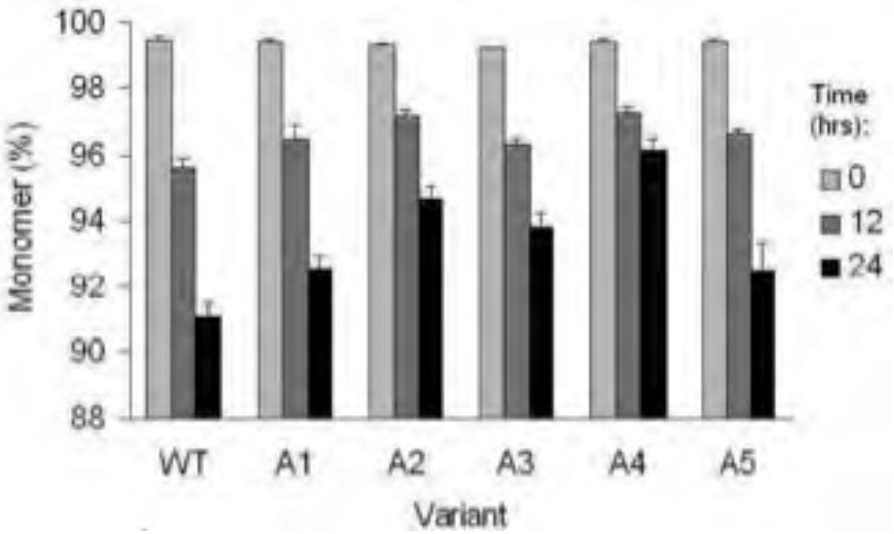


Sahin *et al.*, Vaccine, (2017)

Preventing aggregation via selected mutagenesis



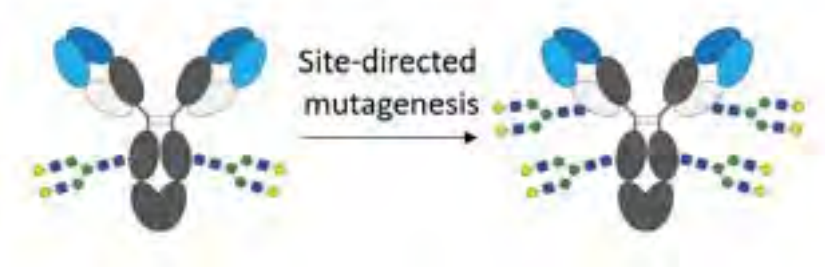
The sites chosen for mutation are indicated A1 – A5



Monomer loss of antibody wild-type and variants A1–A5 upon heat stress at 58 C (measured by SEC-HPLC)

Chennamsetty *et al.*, JMB, (2009) & Chennamsetty *et al.*, PNAS, (2009)

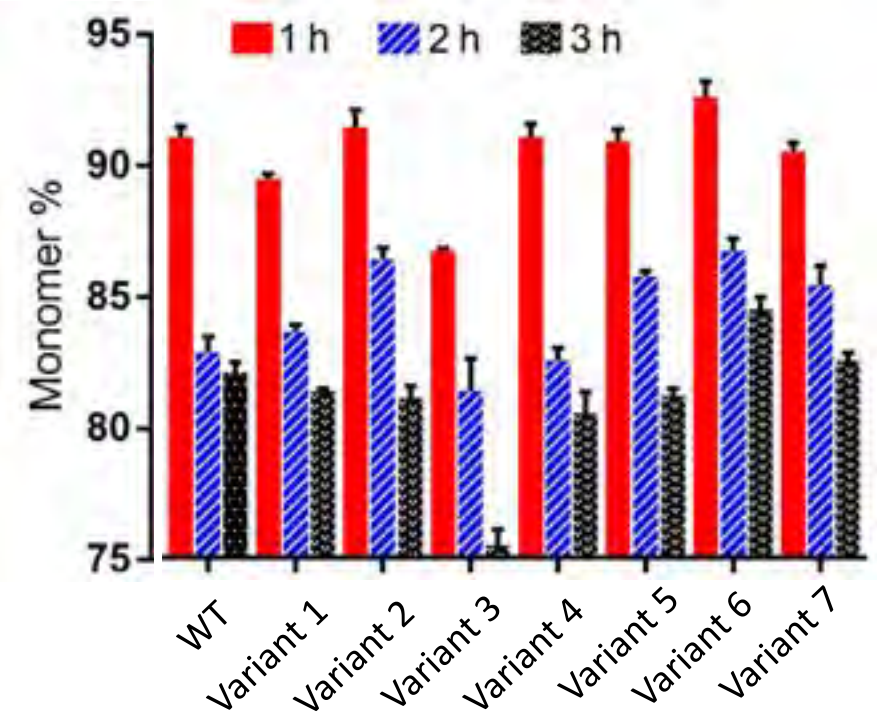
Hyperglycosylation: a new approach for preventing protein aggregation & enhance half-life: Addition of engineered glycosylation sites



Thermodynamic stability

mAb	T_m1 (°C)	T_m2 (°C)	T_{agg} @266 nm
WT	69.6 ± 0.5	82.0 ± 1.4	70.7 ± 0.1
Variant 1	69.6 ± 0.3	81.1 ± 1.4	71 ± 0.4
Variant 2	70.6 ± 0.2	**88.2 ± 2.2**	71.7 ± 0.1
Variant 3	70.1 ± 0.5	**88.3 ± 1.1**	**72.5**
Variant 4	69.9 ± 0.5	**89.3 ± 0.2**	**72.3 ± 0.3**
Variant 5	68.4 ± 0.6	83.5 ± 0.5	70.6 ± 0.3
Variant 6	69.7 ± 0.5	83.4 ± 0.7	71.8 ± 0.4
Variant 7	69.4 ± 0.2	82.7 ± 0.9	71.7 ± 0.5

Accelerated stability studies



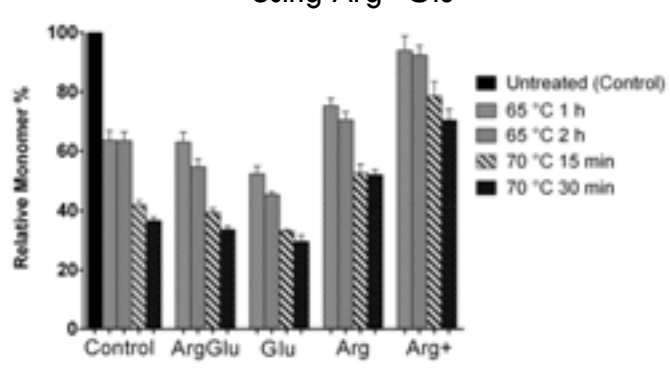
Monomer loss following incubation at 65 °C for 1, 2 and 3 hours

- Cruz, E. *et al* (2021) *Pharmaceutics*, 13 (11), 1747
- Reslan, M. *et al* (2020) *Int J Biol Macromol* 158, 189-196

A mAb (or vaccine) that is stable at room temperature and can be delivered orally or via inhalation???

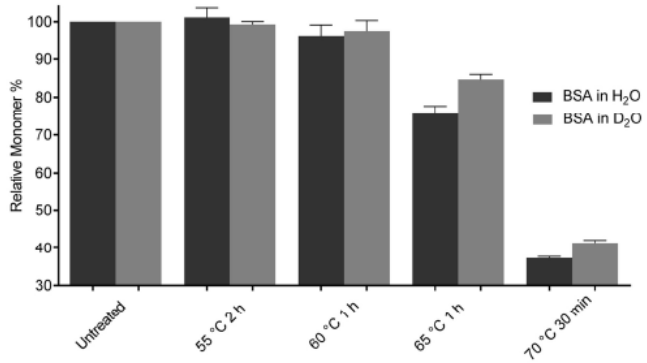
Formulation development

Using Arg+Glu

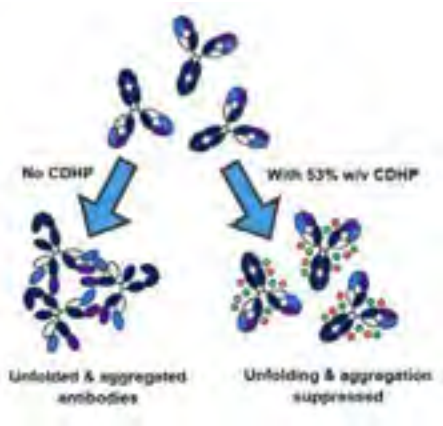


Reslan et al., Pharm Dev Technol. 2017;22(6):785-791

Using Deuterium

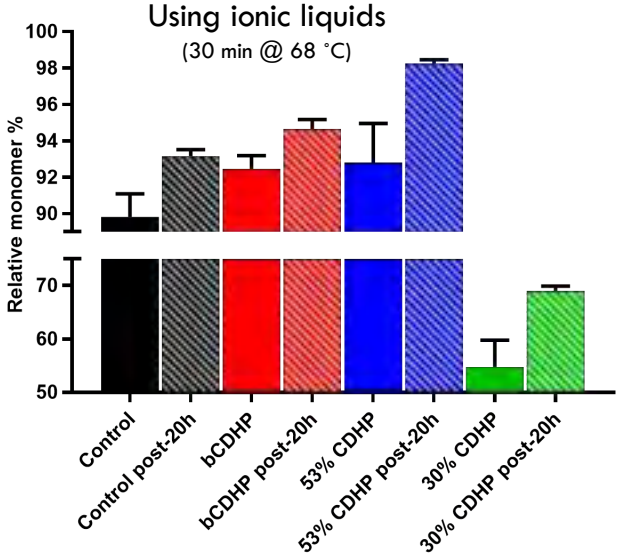


Reslan & Kayser, Pharm Dev Technol. 2018;23(10):1030-1036



Using ionic liquids

(30 min @ 68 °C)

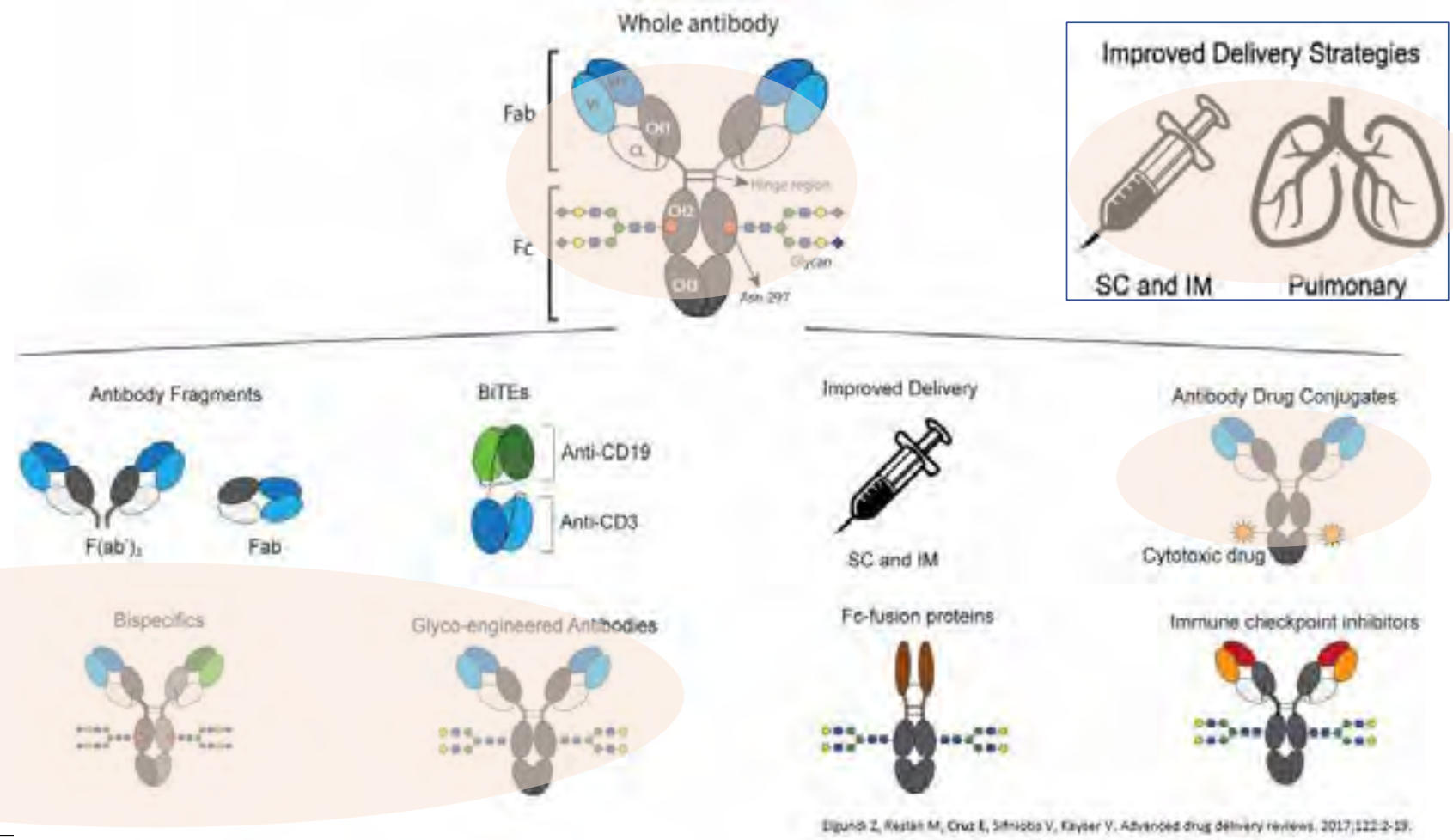


Reslan et al., Chem Comm, 2018;54(75), 10622-10625
Reslan & Kayser, V. Biophys Rev, 2018;10(3), 781-793

Ionic liquids: molten salts with unique properties:

- High thermal stability
- High tunability of ion pairing: 10^6 combinations

Next generation mAb therapies



Elgundi Z, Reslan M, Cruz E, Sifniotis V, Kayser V. Advanced drug delivery reviews. 2017;122:2-19.

Future outlook & concluding remarks

- High cost is a multifaceted issue for mAbs – requires input from all stakeholders
- More $$$ for basic research is a must
- **New formats** such as ADCs, bispecifics, mAb-NP complexes have great potential
- Antibody **engineering** can improve stability, solubility, half-life etc. of mAbs
- New **formulation** stability strategies, e.g., w/ ionic liquids, are promising
- New delivery approaches, e.g., inhalation, oral, microneedle, should be considered

Postnatal prophylaxis against HIV transmission and the role for monoclonal antibodies

December 6, 2022

Theodore Ruel MD
Professor and Chief
Division of Pediatric Infectious Disease
University of California, San Francisco, USA

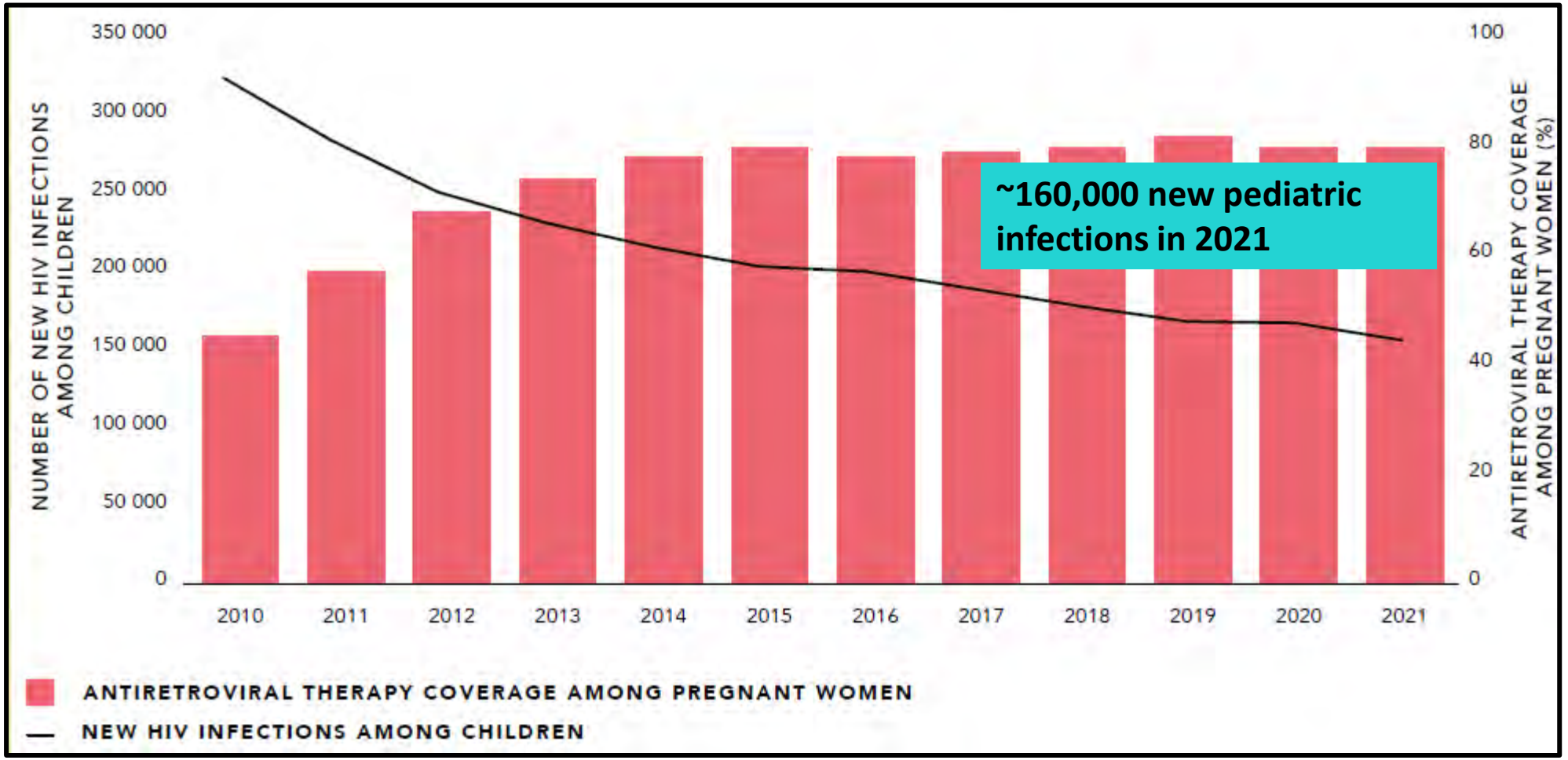
Shelly Malhotra MS
Executive Director, Global Access
International AIDS Vaccine Initiative (IAVI)
New York, NY, USA

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

World Health Organization

iavi Translating science into global health impact

Despite gains in antiretroviral coverage among pregnant women, new HIV infections continue to occur in children,

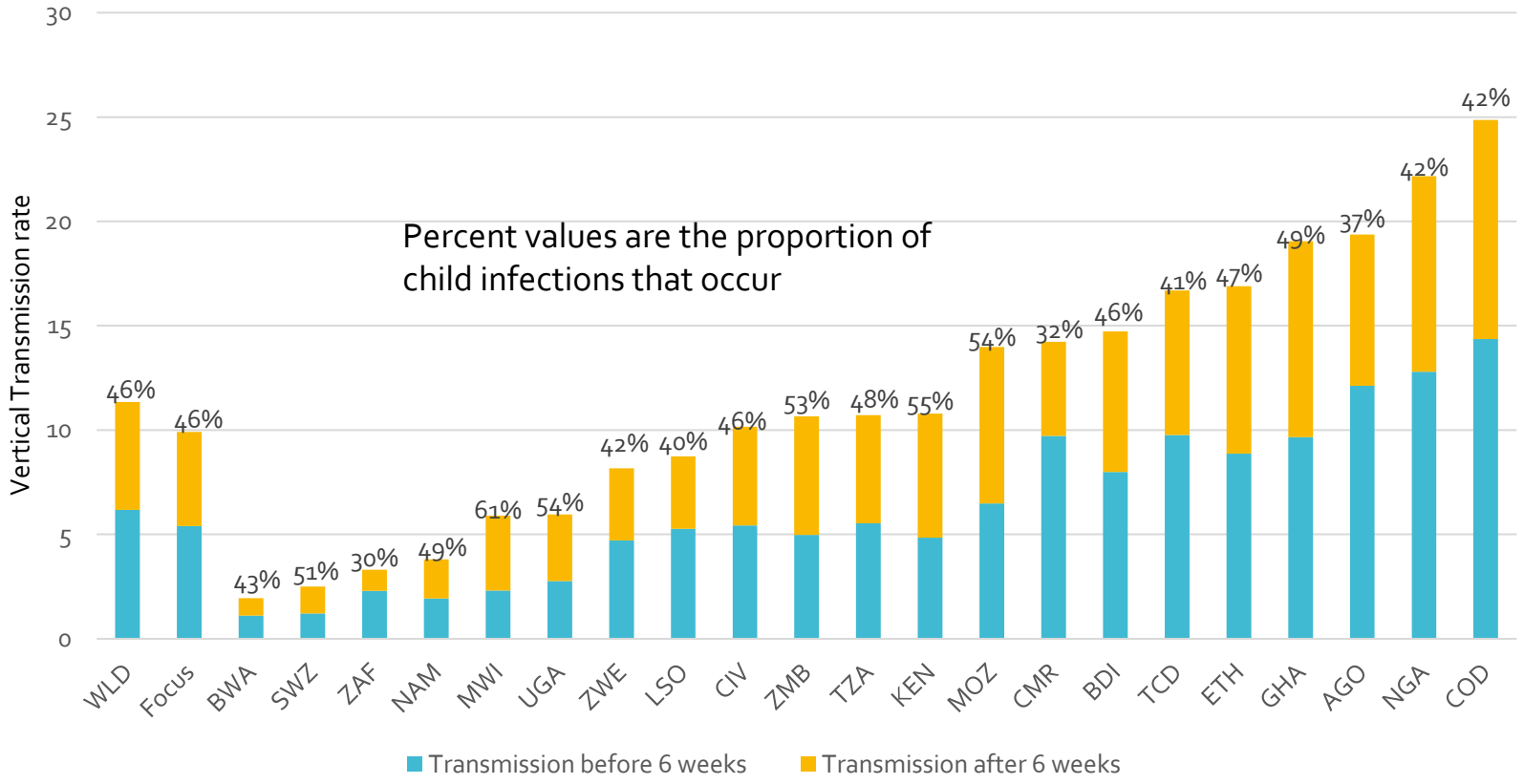


UNAIDS epidemiological estimates 2022: *aidsinfo.unaids.org*

Half of vertical transmission occurs during breastfeeding

46% (2019)

Vertical transmission rate and the percent occurring during breastfeeding, by country

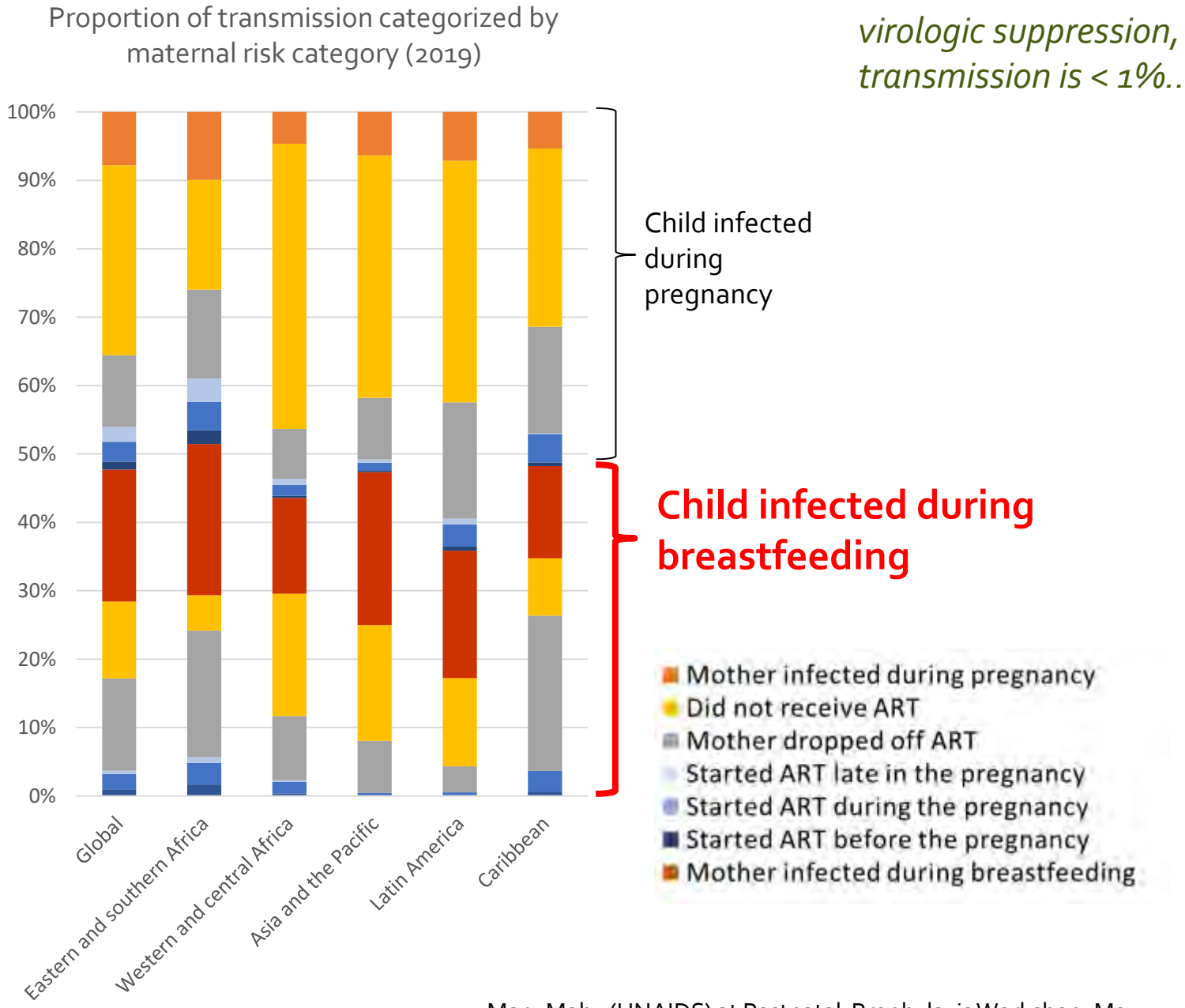


Mary Mahy (UNAIDS) and George Siberry (USAID) at PNP meeting 1, May 11, 2021

Source: UNAIDS 2020 estimates

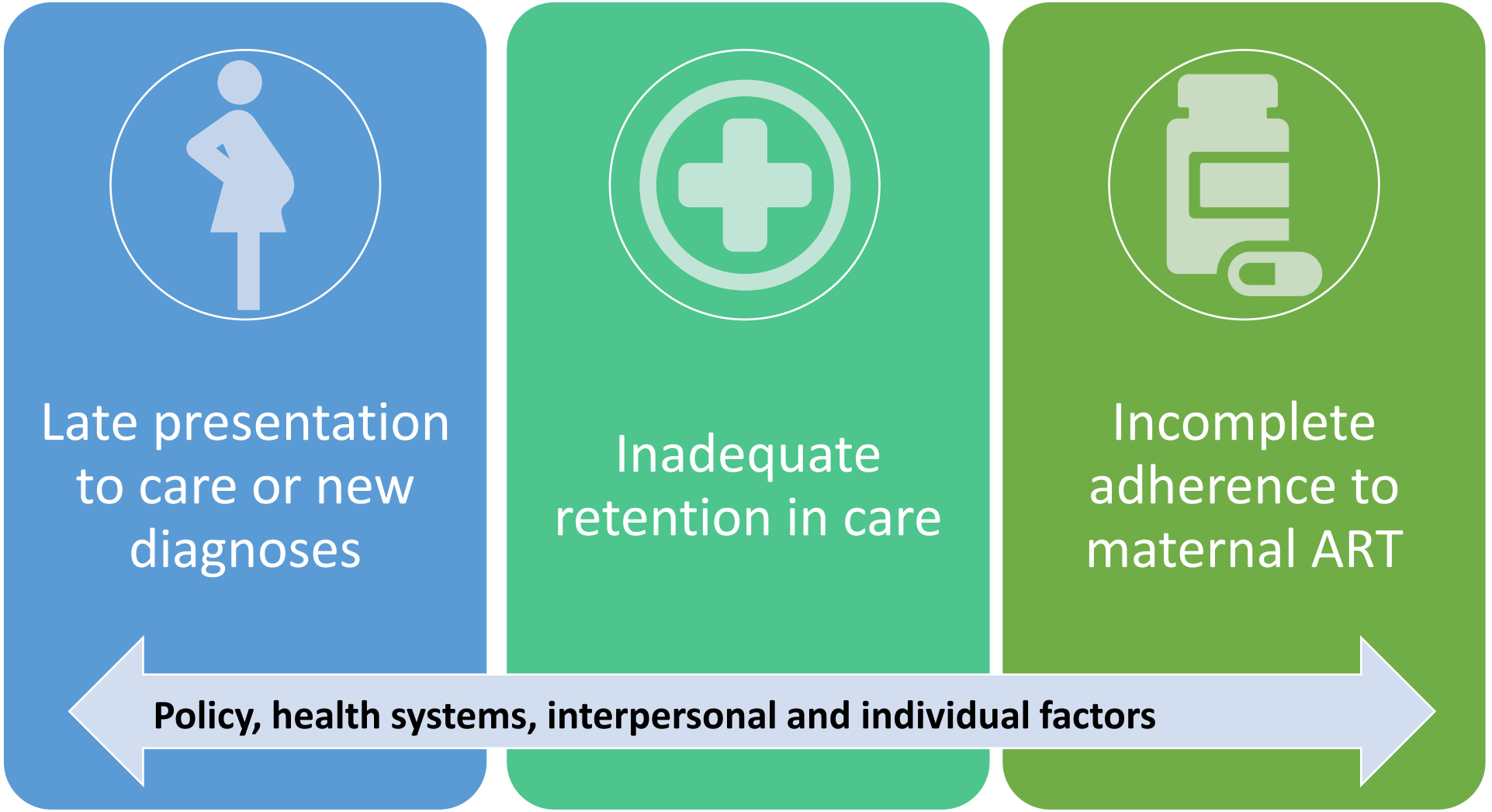
Half of transmission during breastfeeding is attributed to new infections in mothers (and half not)

If a mother with HIV is treated and achieves virologic suppression, risk of transmission is < 1%…



Mary Mahy (UNAIDS) at Postnatal Prophylaxis Workshop, May 11, 2021

Breakthrough cases occur due to gaps at many levels



The landscape of maternal treatment continues to shift …

- **Increasingly, women are entering pregnancy on treatment**
- **Progressive scale up of dolutegravir based treatment and viral load monitoring**
- **High rates of maternal viral suppression during pregnancy and breastfeeding**
- **Fewer new pediatric infections among babies born to women on suppressive antiretroviral regimens**

We must continue to expand and improve diagnosis and treatment of women with HIV …

… but until we have achieved perfect diagnostic and treatment coverage, some women will be viremic, and their infants will be at risk for transmission

What can we do to provide a safety net …

The toolbox to prevent paediatric HIV infections

Combination prevention for pregnant and lactating women

Antenatal and postnatal maternal HIV testing

Maternal treatment and adherence support

Differentiated service delivery and peer-support to improve retention

Postnatal Prophylaxis (PNP)

What do we know about the efficacy of PNP?

Single drugs can work as PNP, but these are old data about old drugs in a different era …

- NVP, 3TC, LPV/r given daily to the infant during breastfeeding demonstrated to reduce risk of postnatal infections, equivalent to suppressive maternal ART
- Several studies demonstrated no advantage to combination PNP, when combined with ZDV, to reduce risk of transmission during breastfeeding
- No studies have examined the added benefit of infant PNP during breastfeeding to mothers on ART

Lack of new agents for PNP means guidelines and countries struggle to advance care

Currently NO guidance on what to do if mothers continue to be unsuppressed or are detected as viremic during breastfeeding

Countries are implementing variable approaches to PNP

- Extended use of PNP, single and multidrug, through breastfeeding
- PNP to infants of mothers with viremia, until re-suppression or through breastfeeding

Limited armamentarium of ARVs agents currently used for PNP

- New pediatric agents have not been evaluated for PNP
- New agents and formulations are being tested for the treatment and prevention of HIV infection in adults

Key concepts for the study and development of new approaches to PNP

- Be agile and remain *current against evolving treatment landscape*
- Utilize novel *efficient trial designs* given low frequency of outcome to be prevented
- Generate *data that will change guidelines* = efficacy in real world settings

bNAbs for post-natal prophylaxis

Why infants are falling through the cracks with current post-natal prophylaxis strategies

- **Adherence challenges:**
  - Challenges with daily administration (6-12 weeks)

- **Stigma-related issues:**
  - Negative perceptions & stigma around giving ARVs to infants; confidentiality difficult to maintain with home administration in post-natal context

- **Gaps in capturing infants at risk:**
  - Current PNP strategies particularly a challenge for “high-risk” mothers who may themselves be facing adherence & access challenges.
  - Need for safe & effective strategies to address needs of infants of mothers newly infected during breastfeeding

- **Fragile market creates supply vulnerability**
  - PNP relies on old ARVs no longer used in adult therapy, contributing to supply insecurity and frequent stock outs.

- **Toxicities:**
  - Concern about toxicity with ARV-based options; risk stratification for ARV-based options presents further barrier to scale up.

**Based on interviews with community representatives, implementers, researchers, & experts conducted in Q1-2 2022 (n=20)*

Evidence highlights promising potential role of bnAbs in post-natal prophylaxis

Promising infant SHIV efficacy data/proof of concept in adults:

- Passive immunization with bNAbs shown to disrupt HIV transmission both as pre- and post-exposure prophylaxis in non-human primates when administered within 30–48 hours of oral SHIV exposure (Hessell, 2016; Shapiro, 2020)
- In adults humans, AMP trials found VRC01 given every 8 weeks reduced sexual transmission of HIV-1 for viral isolates that were VRC01 sensitive, providing proof-of-concept for passive immunization;

  → *however* combinations necessary given only 30% of the HIV strains circulating in the regions where the trials were conducted were sensitive to VRC01 (Corey, 2021)

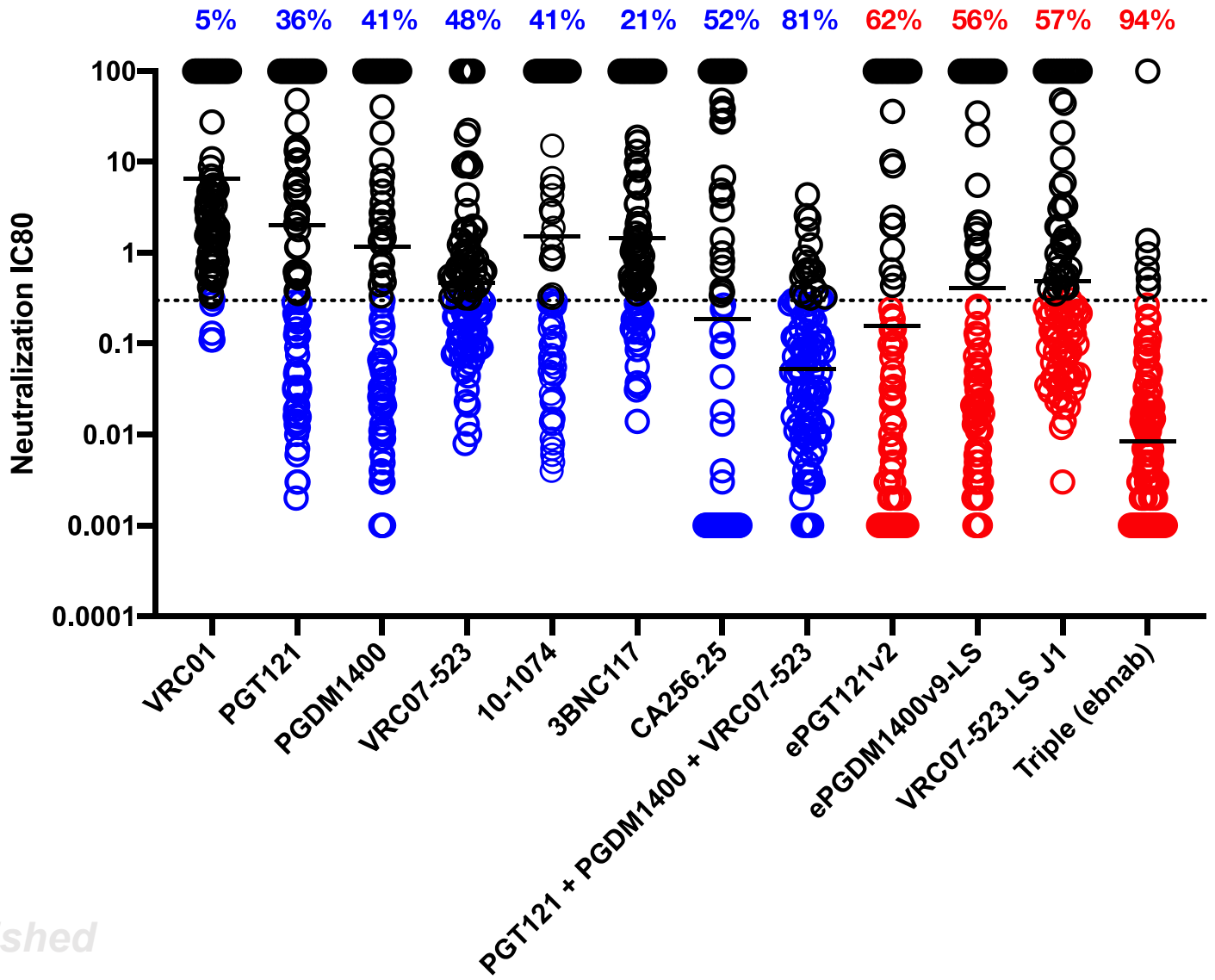
Growing evidence of safety of bnAbs for infant prophylaxis:

- All 3 bNAbs tested in infants (i.e., VRC01, VRC01LS, and VRC07-523LS) demonstrated good safety & tolerability in HIV-exposed infants at birth (Cunningham, 2020; Cunningham, 2020; McFarland 2021)

Potential for long-acting protection:

- Subcutaneous injection of VRC07-523LS to neonates -- with LS mutation for half-extension -- maintained levels for 12 weeks, suggesting potential for quarterly dosing (Cunningham, 2021)

Next generation enhanced antibodies show broader neutralization coverage at lower doses compared to parental antibodies on a clade C virus panel (n = 100)



0.3 ug/ml cut off

- *Combination of three ebnAbs covers 94% of different clade C viruses that are circulating in South Africa at stringent cut-off (vs only 5% with VRC01)*
- *High potently ebnAbs can enable lower dosing than earlier generation bnAbs*

Unpublished

Each circle represents a different virus, plotted values are neutralization IC80.

Exciting potential product profile for bNAbs in line with WHO preferred product characteristics

- Long-acting protection supports adherence (3 mo+. TBD)

- Promising safety profile could make bNAbs a viable candidate for broad vaccine-like implementation in the highest prevalence settings

- Discreet administration
- Potential alignment with routine immunization/well-baby visits

- Low dosing for infants supports lower cost of goods than in adults
- Infrequent dosing lowers delivery costs

- Subcutaneous injection (optimized formulations target volume of 1 mg/kg, .5 ML).

- Obviates risk of resistance to drugs critical to treatment (relevant for other pipeline PNP options)

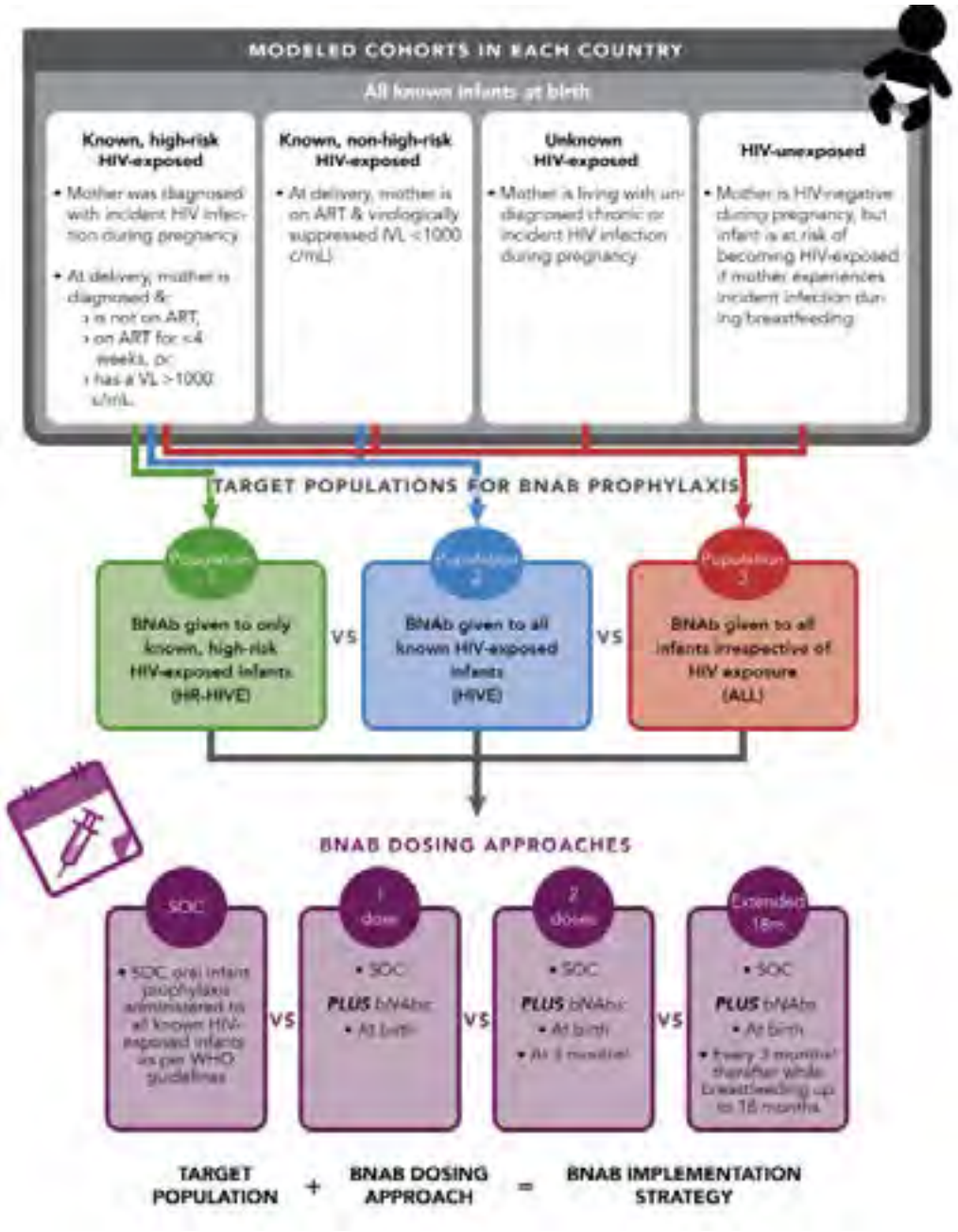
Key takeaways:

- bNAbs hold potential to address acceptability & stigma barriers.
- Promising product profile could support adherence & broader roll-out
- Lower volume & cost with pediatric indication can support feasibility

https://www.who.int/publications/i/item/9789240045729

Health & economic impact of bNAbs for PNP

Modeling in South Africa, Cote d'Ivoire and Zimbabwe, led by CEPAC, Mass General



Dugdale, IAS 2022, manuscript under review

- Under base case assumptions, modeling suggests adding bnAb infant HIV prophylaxis to WHO-recommended oral infant prophylaxis.
  - **Could reduce vertical HIV transmission by 24-42%** (depending on setting) relative to the standard of care alone, when used for the duration of breastfeeding for all infants known to be HIV-exposed at birth.

- Across a wide range of cost and efficacy combinations, bNAbs could be **cost effective**:
  - **For all HIV-exposed infants** in **Côte d'Ivoire** and **Zimbabwe**, for up to 18 months;
  - **For all infants**, irrespective of known HIV exposure, in **South Africa** for up to 18 months.

→ All-infant strategy makes sense in setting with maternal prevalence greater than 15%

A snapshot of bNAbs clinical development programs

Clinical Trials						
Sponsor/Trial	**bnAbs**	**Population**	**Phase**	**Status**	**Outcome**	**Country**
IMPAACT 2037	PGT121.414LS and VRC07-523LS	Infants Exposed to HIV-1	Phase 1	In Development	Protection when administered subcutaneously soon after birth in infants at high risk for peripartum or breastfeeding HIV transmission.	Brazil, Kenya, South Africa, and the United States
South African Medical Research Council, PACTR202205715278722	CAP256V2LS and VRC07-523LS	HIV-1 exposed uninfected neonates and infants	Phase 1	Date of first enrolment: 27/06/2022	Safety and Pharmacokinetics of subcutaneous administration	South Africa
IAVI/VRC/HVTN	ePGT121v2; ePGDM1400v9-LS; and VRC01.23.LS	Phase 1 in adults in 2023; plans for Phase 2 HIV-1 exposed uninfected neonates & infants in 2026	Phase 1	Date of first enrolment: Q3 2023	Safety and Pharmacokinetics of subcutaneous administration	TBD: South Africa, Uganda, U.S

What's next…

Ensuring the acceptability, feasibility, & regionally driven clinical development

Evaluating Feasibility & Acceptability

- Study kicking off to:
  - Learn about **mother's experiences & perceived acceptability** of using bnAbs for PNP
  - Identify **special considerations**, perceived benefits & feasibility/implementation considerations.
  - Understand **perspectives of community gatekeepers** (partners, mothers-in-law, providers, policy-makers) with respect to role of bnAbs in infant HIV prophylaxis

Stakeholder consultation on development plan

- To gather **regional perspectives** to further refine & gain consensus around potential **study design** and licensure considerations for the **clinical development** of bnAbs for infant prophylaxis in Africa.

- **Stakeholder consultation** -- including community representatives, civil society partners, clinical trial sponsors, regulators, ethicists, researchers and funders – to inform clinical development plan for bnAbs for infant HIV prophylaxis
- February 9-10

BUSINESS MODEL INNOVATION: Workshop on novel business models for mABs, 9-10 March 2023

affordable available

Novel partnership strategies are needed that address unique drivers of mAbs cost & advance an access paradigm for mAbs.

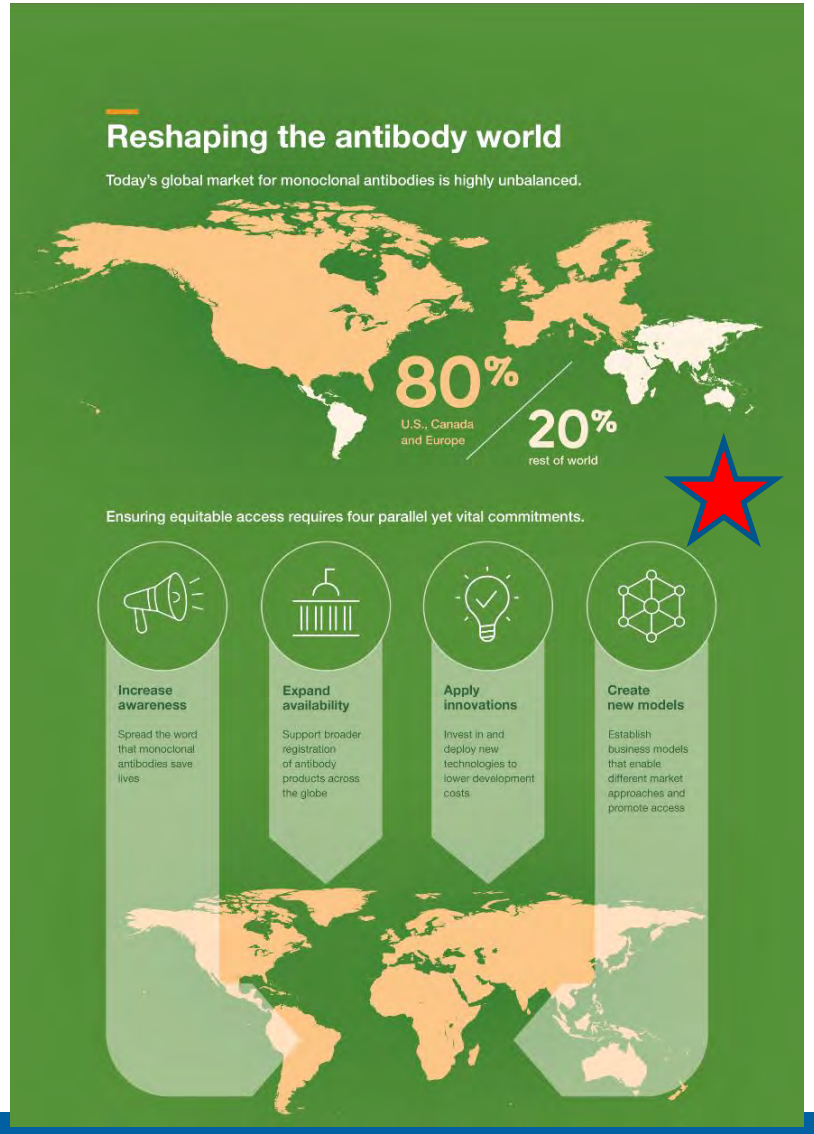
iavi Unitaid wellcome medicines patent pool

Approach:

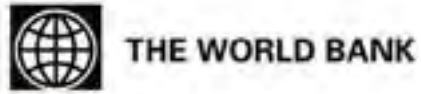
- Key partners will convene mAbs consultation to **identify novel business models for sustainable, scalable, affordable global mAbs access**.

Objectives:

- **Explore innovative partnership approaches & strategies** for a sustainable, affordable business model for mAbs access in LMICs.
- **Define set of priority interventions and enablers** (licensing, market-shaping, de-risking incentives, etc) to catalyze innovative business models for mAbs access in LMICs.



IAVI gratefully acknowledges the generous support provided by the following major funders



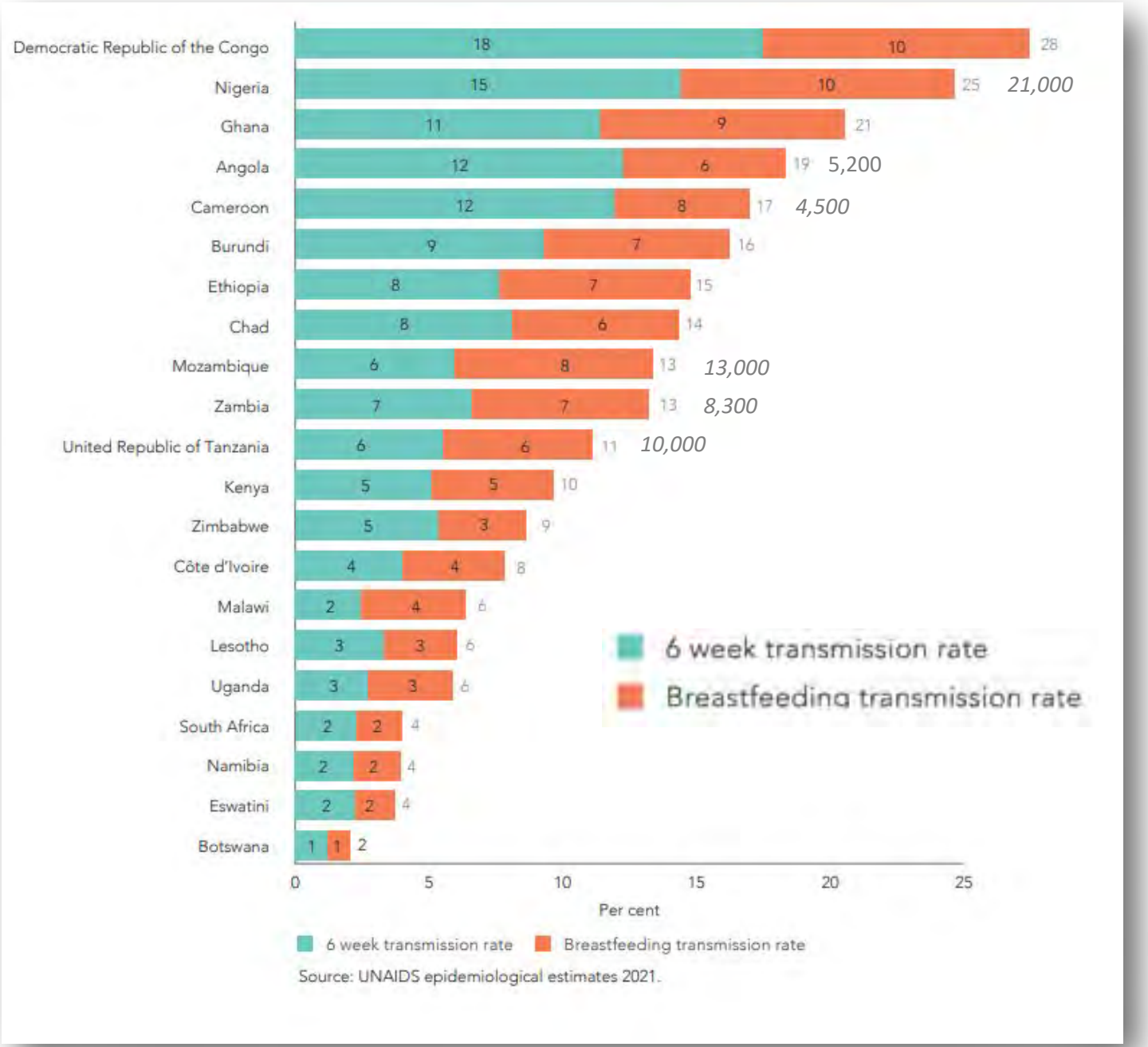
Biomedical Advanced Research and Development Authority (BARDA) | Foundation for the National Institutes of Health | National Institute of Allergy and Infectious Diseases | amfAR, The Foundation for AIDS Research | Broadway Cares/Equity Fights AIDS | Cancer Research UK | The City of New York, Economic Development Corporation | Congressionally Directed Medical Research Program (DoD) | GSK | The Hearst Foundations | Keith Haring Foundation | Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the USA and Canada)

And many other generous individuals and partners around the world

As of April 2022

Back up

“Real world” Vertical transmission of HIV, by timing of transmission, focus countries, 2020



The role of vaccines in reducing AMR

WHO strategy and priorities

Mateusz Hasso-Agopsowicz, MSc, PhD

Technical Officer, Vaccine Product & Delivery Research

Department of Immunization, Vaccines & Biologicals

World Health Organization

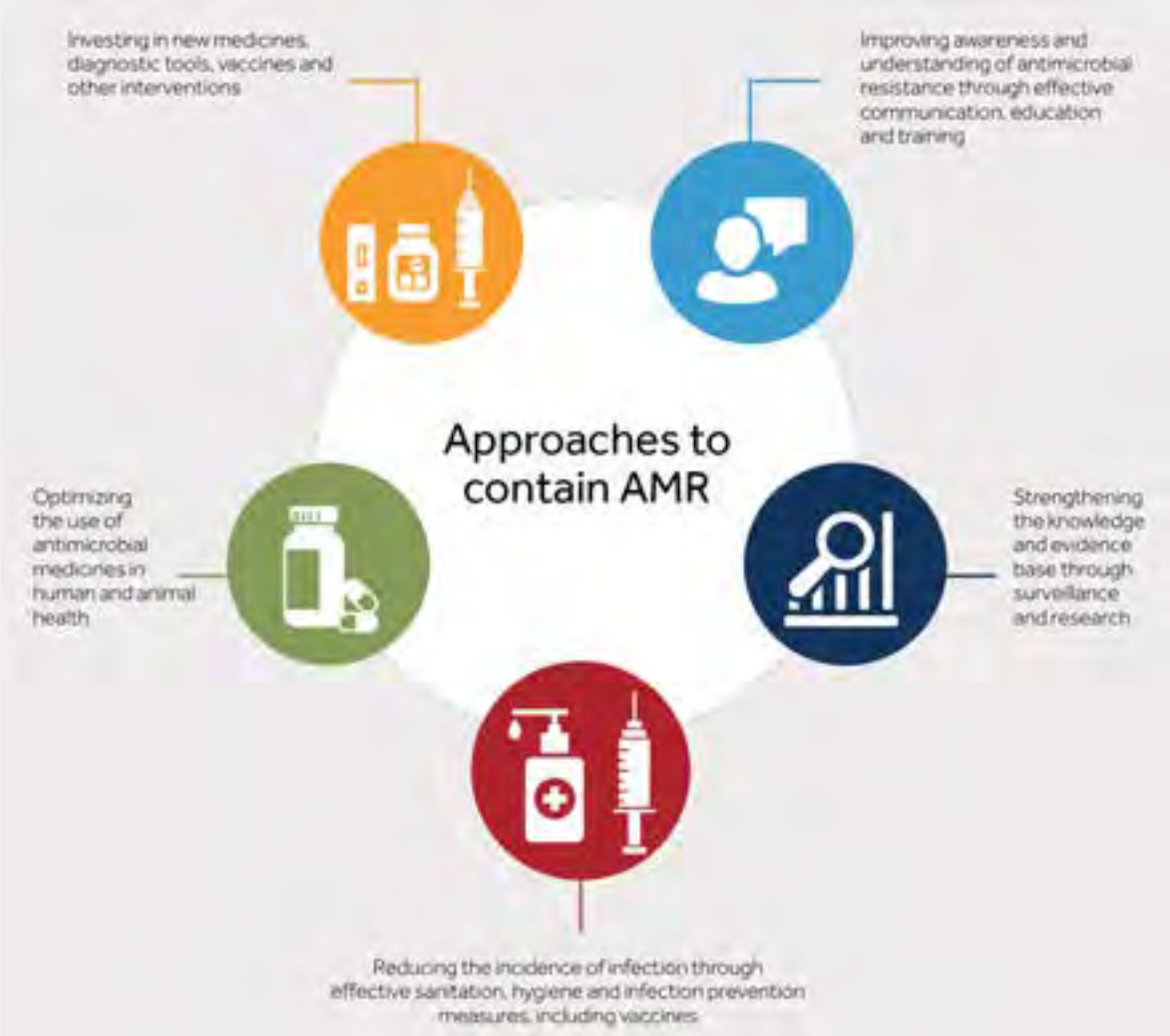
Orientation to the session

Speaker	Talking Points	Allocated time
Mateusz Hasso-Agopsowicz (WHO)	• The role of vaccines in reducing AMR: WHO priorities and workstreams	10′
Padmini Srikantiah (BMGF)	• Case study: *Klebsiella pneumoniae*	15′
PDVAC	• Discussion	20′

Questions to PDVAC

- Are the mentioned activities appropriate to articulate and leverage the role of vaccines in reducing AMR?
- What is an appropriate mechanism to build awareness and increase urgency of the burden of Klebsiella and need for a Klebsiella vaccine?

Global Action Plan on AMR



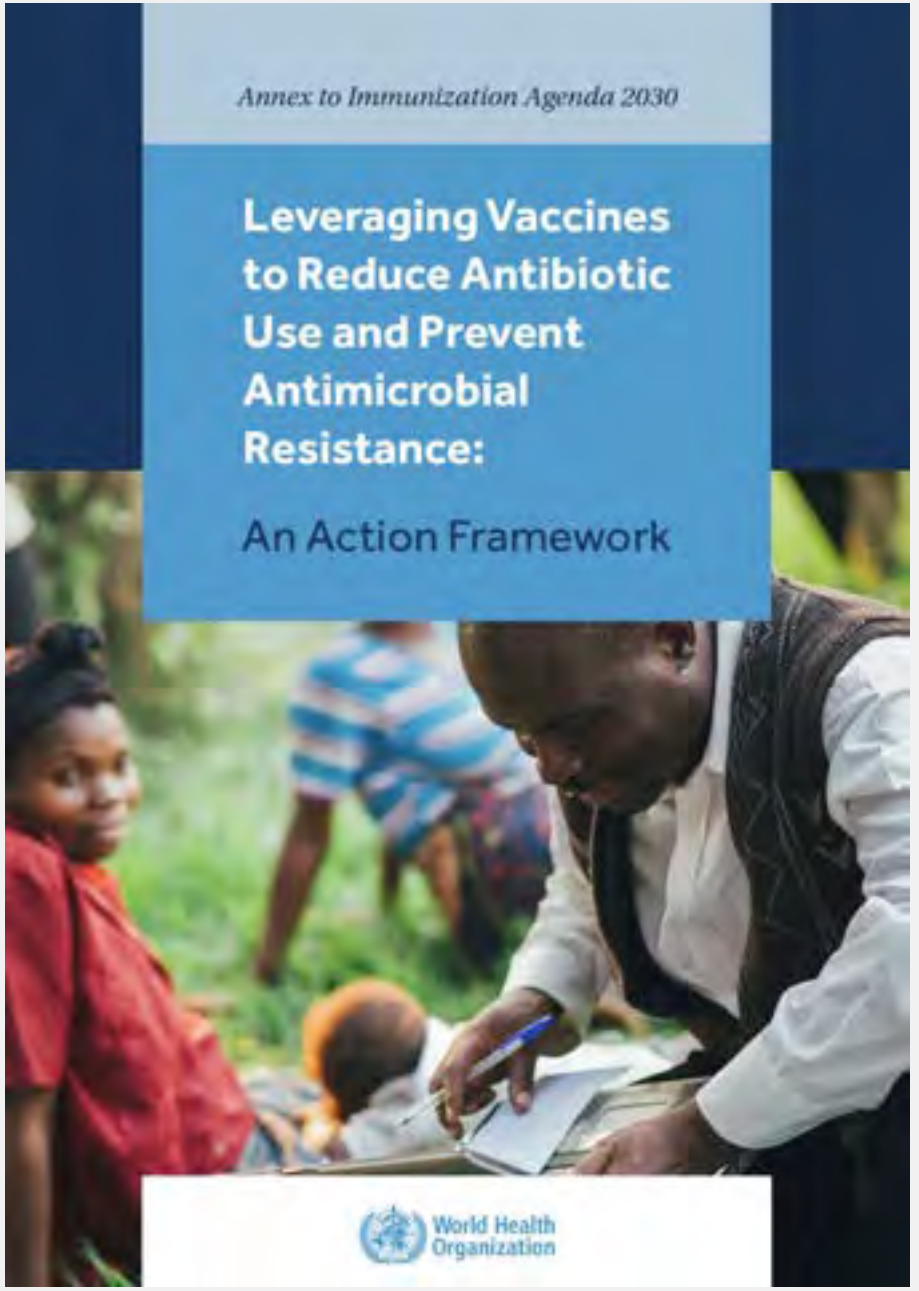
https://www.who.int/publications/i/item/9789241509763

The Action Framework to leverage vaccines against AMR and AMU

Expanding use of licensed vaccines to maximize impact on AMR

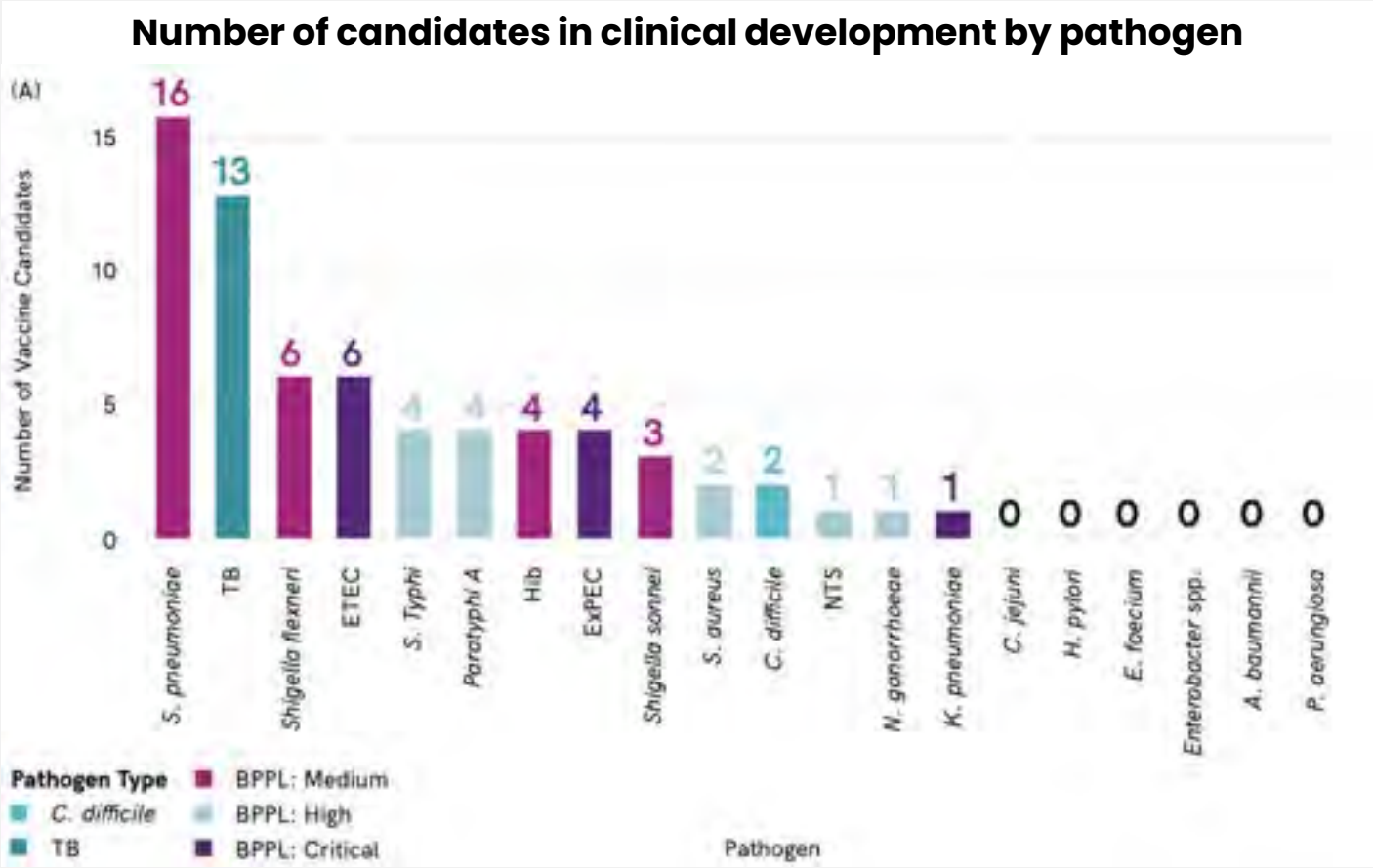
Develop new vaccines that contribute to prevention and control of AMR

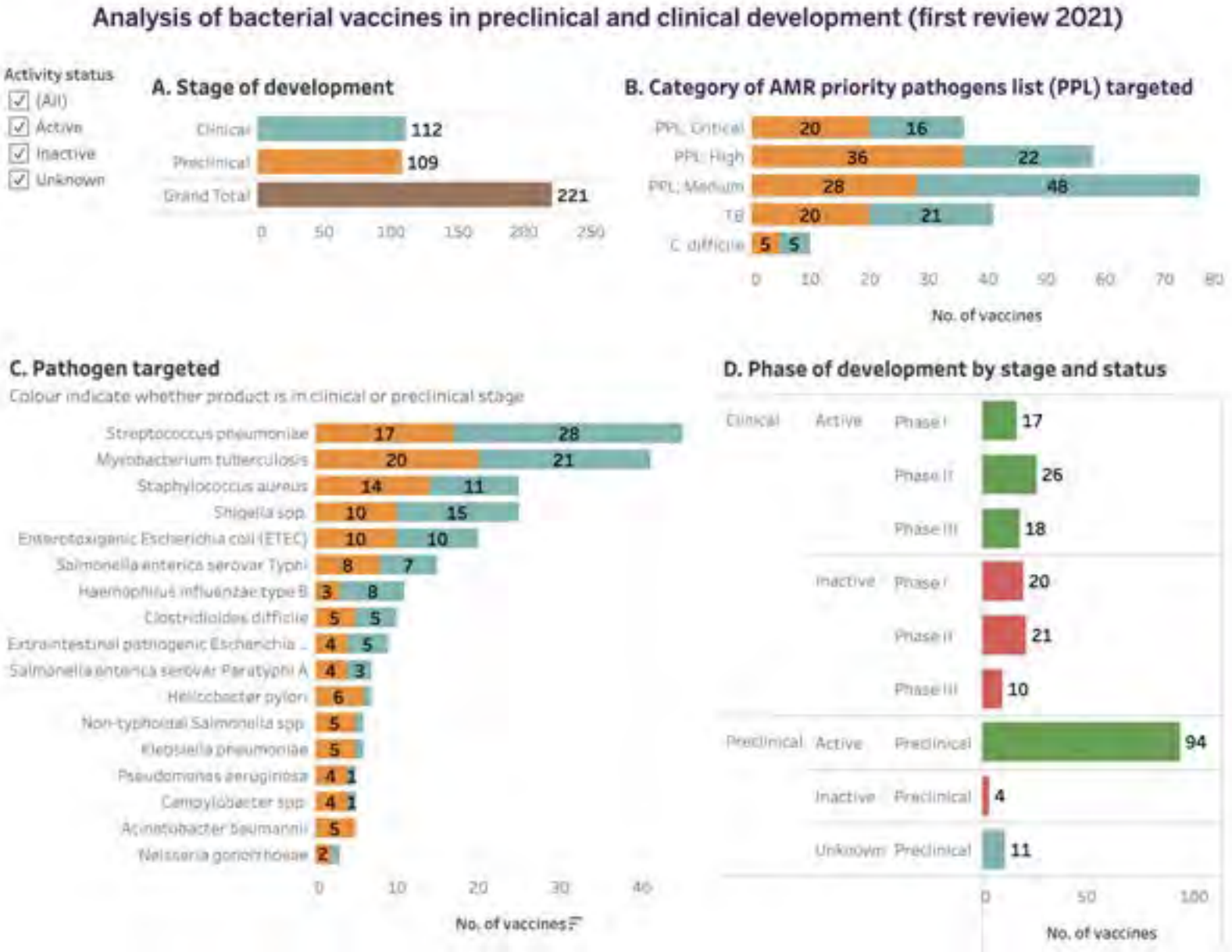
Expanding and sharing knowledge of vaccine impact on AMR



Bacterial vaccines in clinical and preclinical development 2021: clinical results

- **61 vaccines** in active clinical development identified (activity in the last 3 years, still list on company portfolio)
- **The highest number** of vaccine candidates for *S. pneumoniae*, TB, and *Shigella flexneri*
- **No candidates in clinical development**: *E. faecium*, *H. pylori*, *P. aeruginosa*, *A. baumannii*, *Enterobacter* spp, or *Campylobacter* spp.





https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/who-review-of-bacterial-vaccines-in-development-for-priority-pathogens

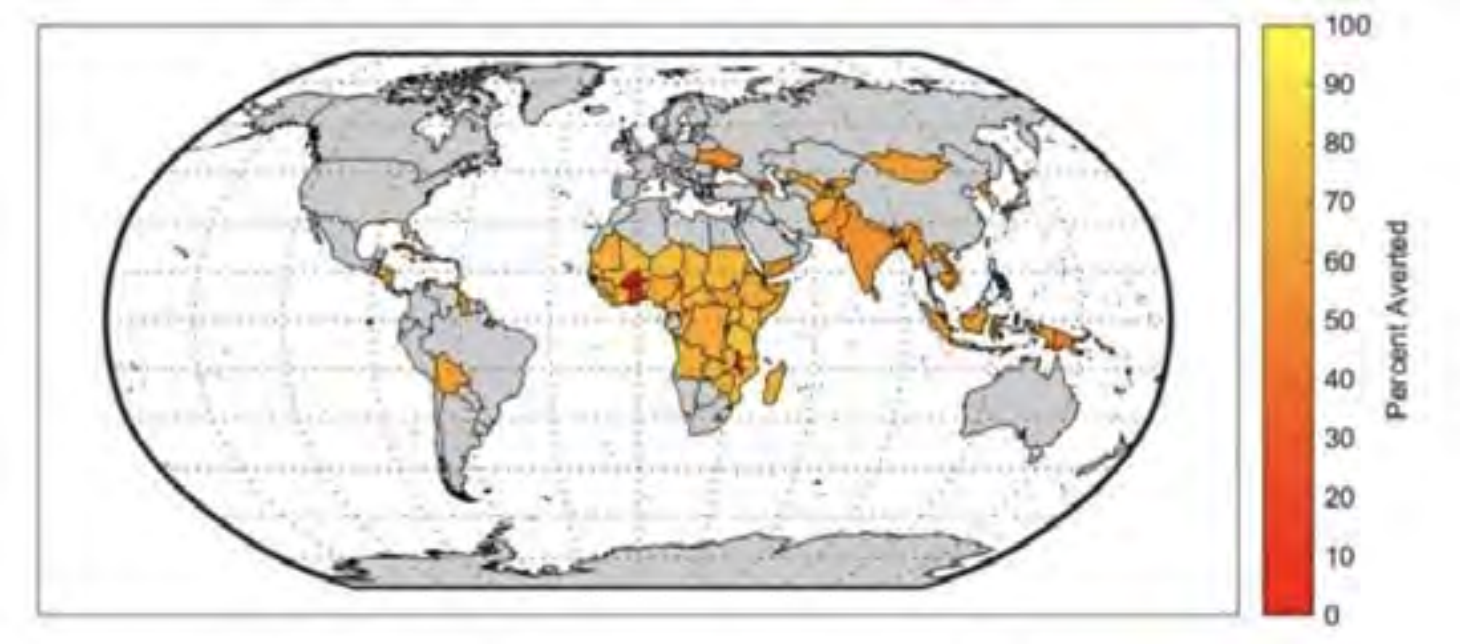
Bacterial vaccines in clinical and preclinical development 2021: conclusions

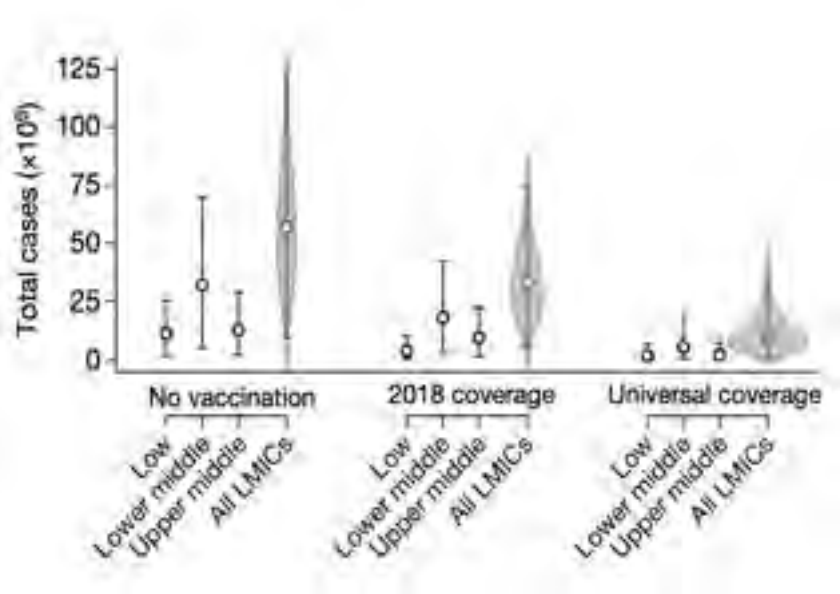
CLASS A: PATHOGENS WITH VACCINES THAT ARE ALREADY LICENSED	CLASS B: PATHOGENS WITH VACCINES IN LATE-STAGE CLINICAL TRIALS WITH HIGH DEVELOPMENT FEASIBILITY	CLASS C: PATHOGENS WITH VACCINES IN EARLY TRIALS OR WITH MODERATE TO HIGH DEVELOPMENT FEASIBILITY	CLASS D: PATHOGENS WITH A SMALL NUMBER OR NO VACCINE CANDIDATES IN AND LOW DEVELOPMENT FEASIBILITY
Streptococcus pneumoniae	*Neisseria gonorrhoeae*	*ETEC*	*Acinetobacter baumannii*
Hib	*ExPEC*	*Shigella* spp.	*Helicobacter pylori*
Salmonella enterica ser. Typhi	*Salmonella enterica* ser. Paratyphi	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*
	Clostridioides difficile	*Campylobacter jejuni*	*Staphylococcus aureus*
	Mycobacterium tuberculosis	NTS	*Enterococcus faecium*
			Enterobacter spp.
RECOMMENDATION	**RECOMMENDATION**	**RECOMMENDATION**	**RECOMMENDATION**
Increase coverage and accelerate introduction	**Accelerate development and prepare for introduction.**	**Continue development and expand knowledge of impact on AMR.**	**Focus on other prevention and control tools to prevent AMR.**

Assessment of the value of vaccines in preventing AMR

Criteria to evaluate the role of vaccines in preventing AMR:

- Vaccine averted AMR health burden
- Vaccine averted antibiotic use
- Vaccine averted economic burden
- Urgency of the AMR threat
- Pathogen impact on equity and social justice

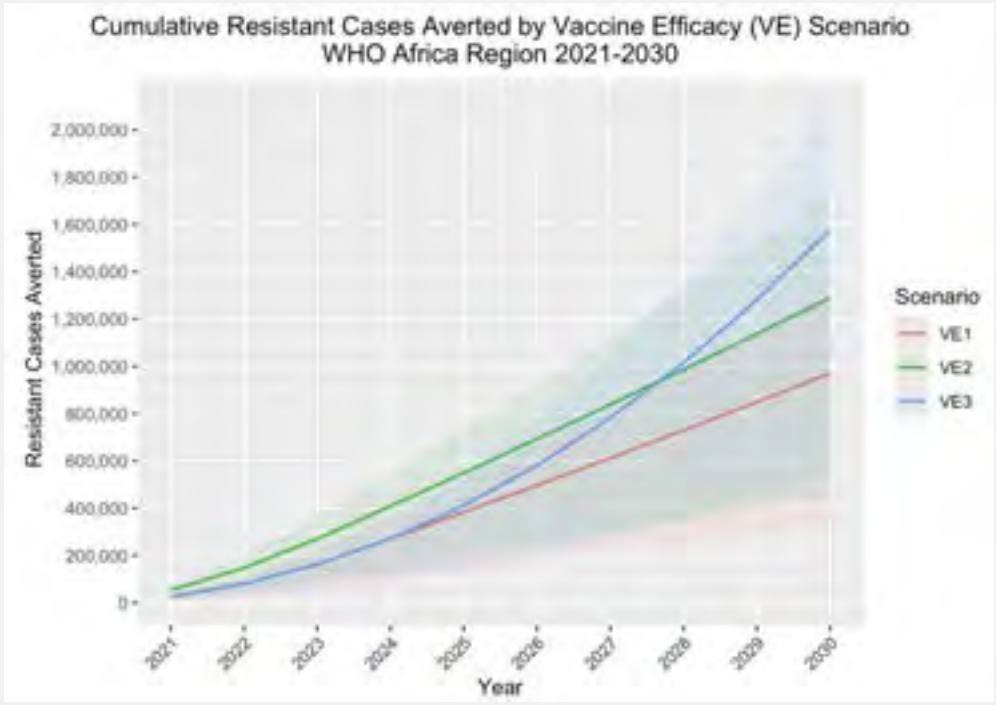


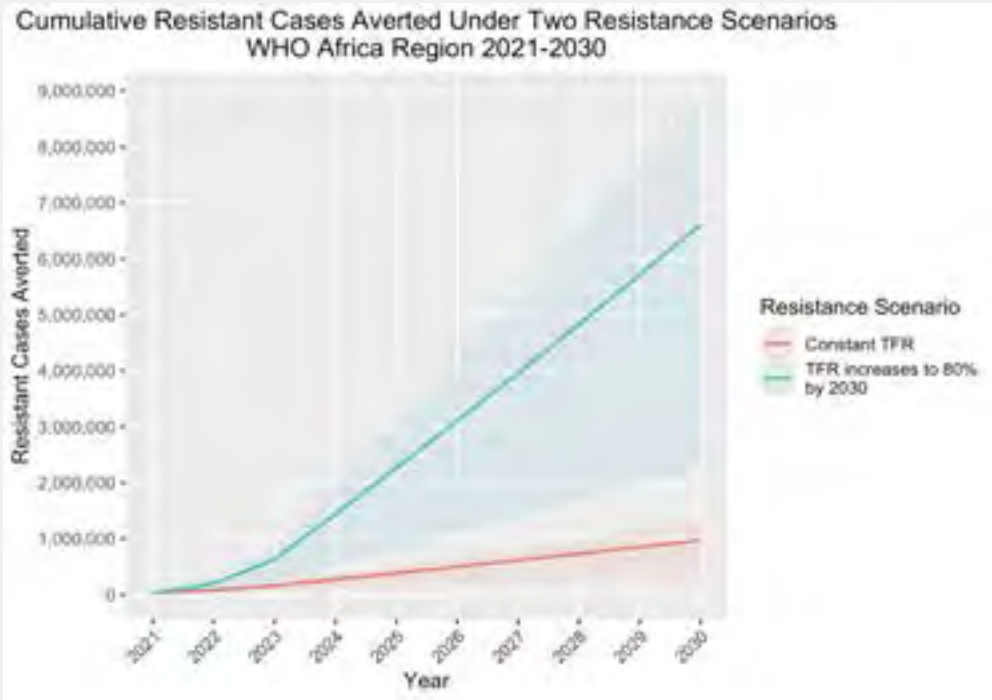


Malaria Vaccine Impact on Drug-susceptible and Resistant Cases and Deaths: A Modelling Study

preliminary results

- 123 million drug sensitive cases, **1.6 million drug resistant cases**, and 0.3 million deaths averted in Africa between 2021-2030
- VE 80% in first year, dropping 20pp each year
- With rapid increase in drug resistance **over 6.6 million resistant** cases averted.



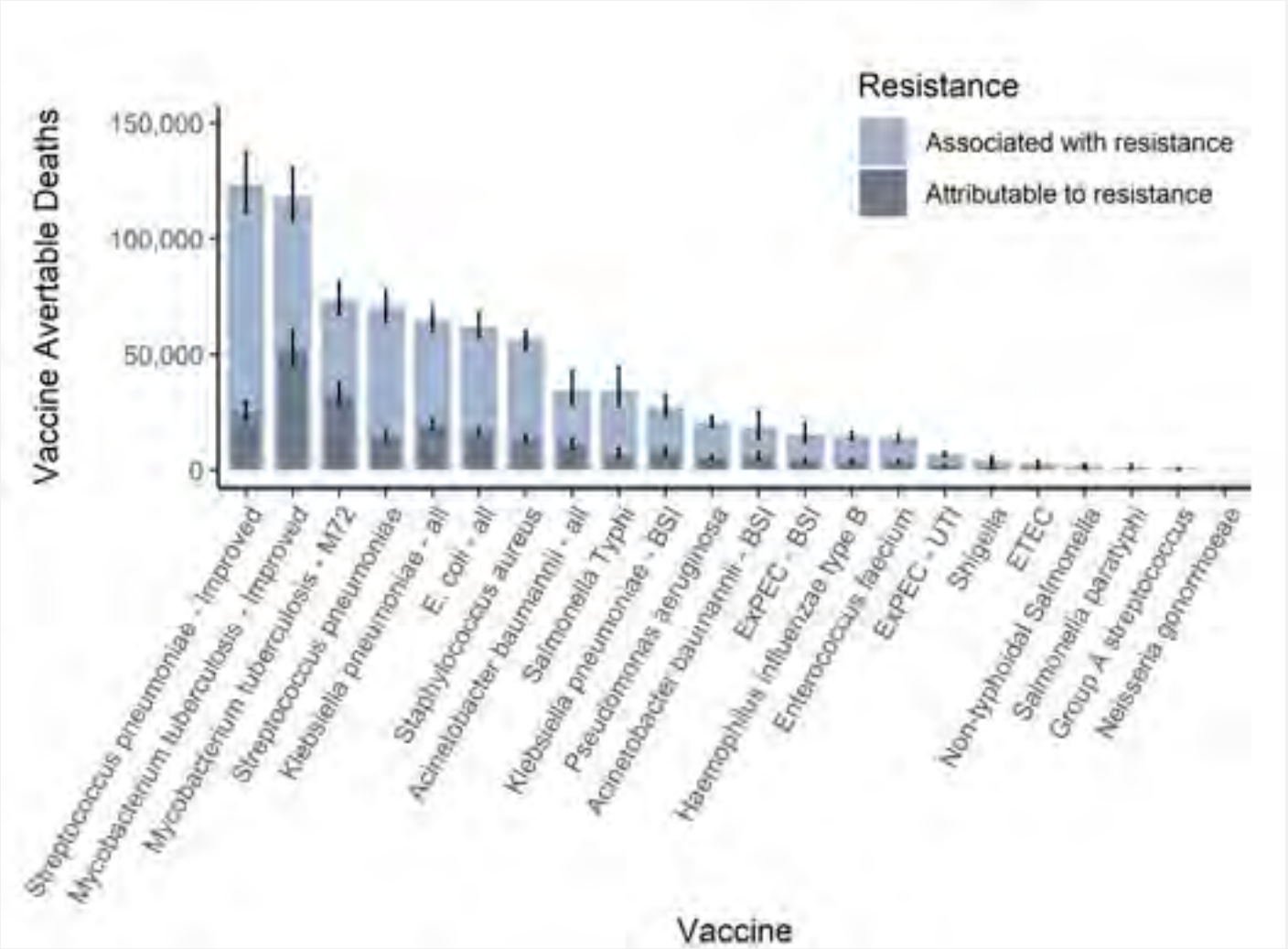


https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4231231

Vaccine avertible global health burden of AMR

preliminary results

- AMR is a global health threat with **1.27 million deaths attributable** to bacterial AMR and **4.95 million deaths associated** with bacterial AMR worldwide in 2019;
- *Streptococcus pneumoniae*: **123,526 (111,386 - 137,246)** deaths associated with resistance averted by a vaccine with 50% efficacy against LRI, 70% efficacy against other presentations and strains.
- *Mycobacterium tuberculosis*: **118,250 (107,668 - 130,801)** deaths associated with resistance averted by a WHO PPC vaccine with an 80% efficacy given to infants, with life long protection or boosting.



https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4105587

Mateusz Hasso-Agopsowicz

hassoagopsowiczm@who.int

https://www.linkedin.com/in/mateusz-hasso-agopsowicz/

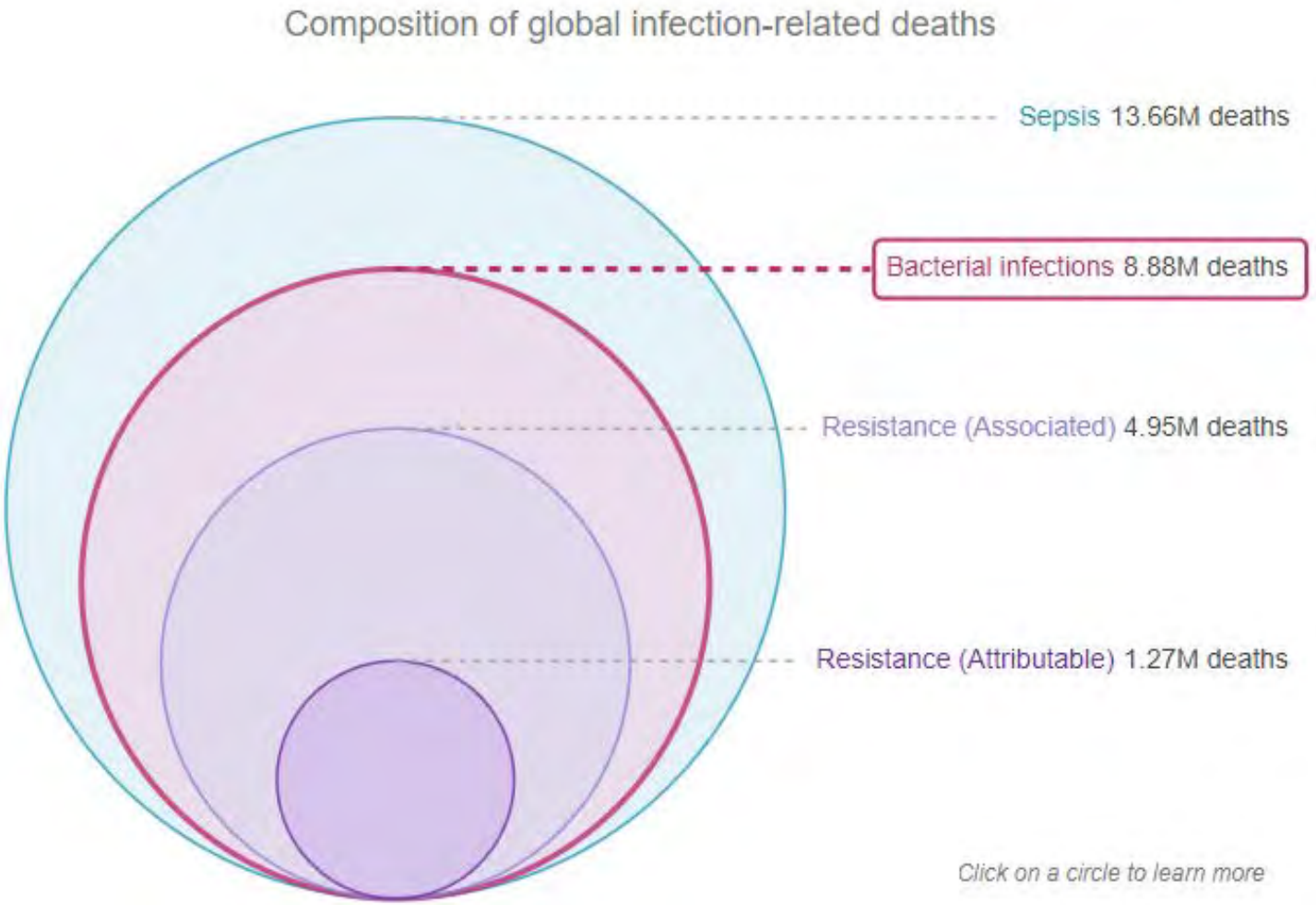
Klebsiella pneumoniae: Burden of disease and potential for vaccine development

Padmini Srikantiah, MD MPH
Deputy Director, Pneumonia Programs
Antimicrobial Resistance Strategy Lead
Bill & Melinda Gates Foundation
PDVAC, December 6, 2022

OUTLINE

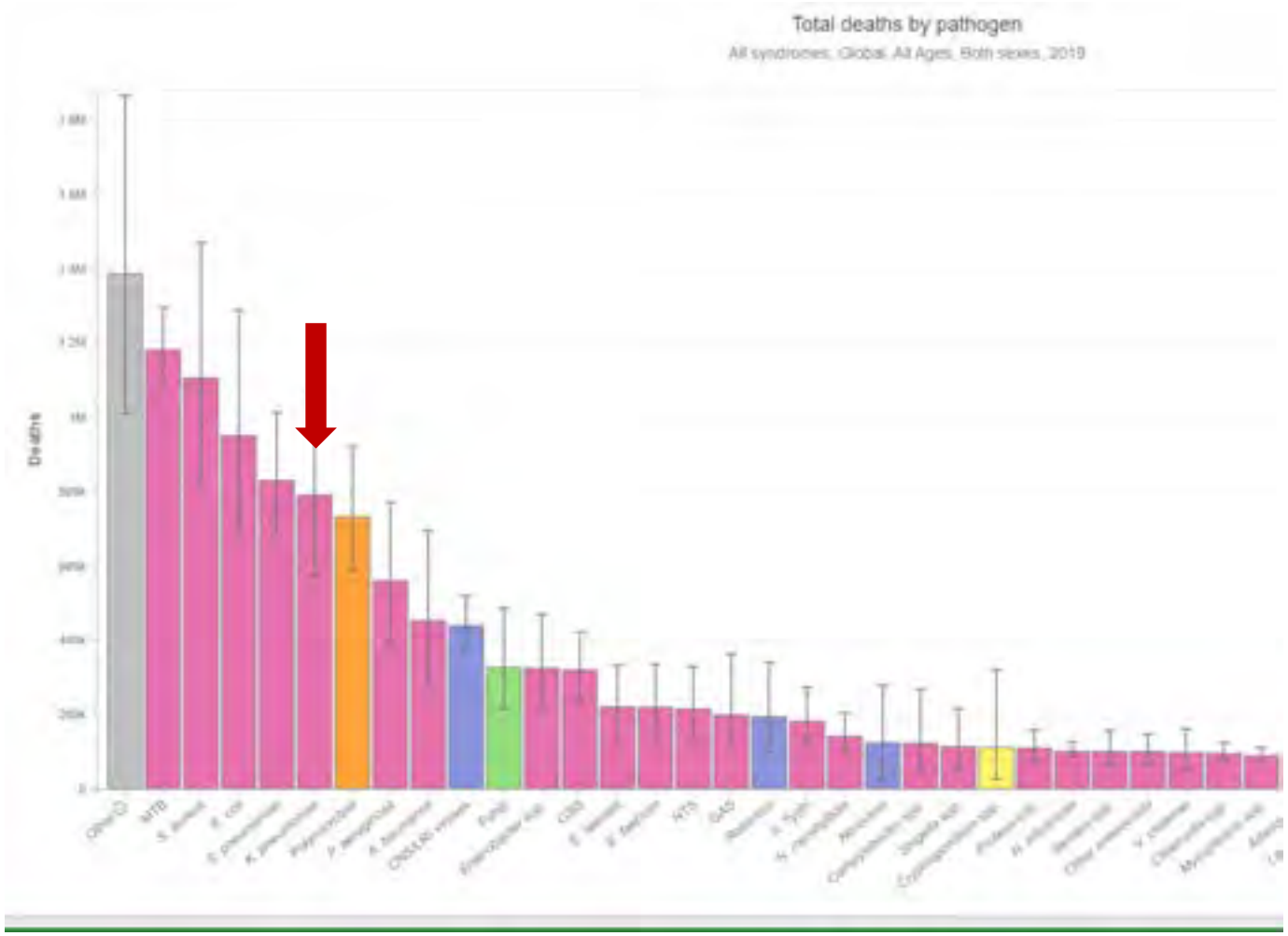
1. Global burden of bacterial infections: Role of *Klebsiella pneumoniae*
2. Global burden of AMR: role of *Klebsiella pneumoniae*
3. *Klebsiella pneumoniae* as a leading etiology of neonatal sepsis and related deaths
4. BMGF *Klebsiella pneumoniae* vaccine development strategy and activities

IHME GLOBAL BURDEN OF DISEASE: 8.9M DEATHS DUE TO BACTERIAL INFECTIONS IN 2019



Source: https://vizhub.healthdata.org/microbe/

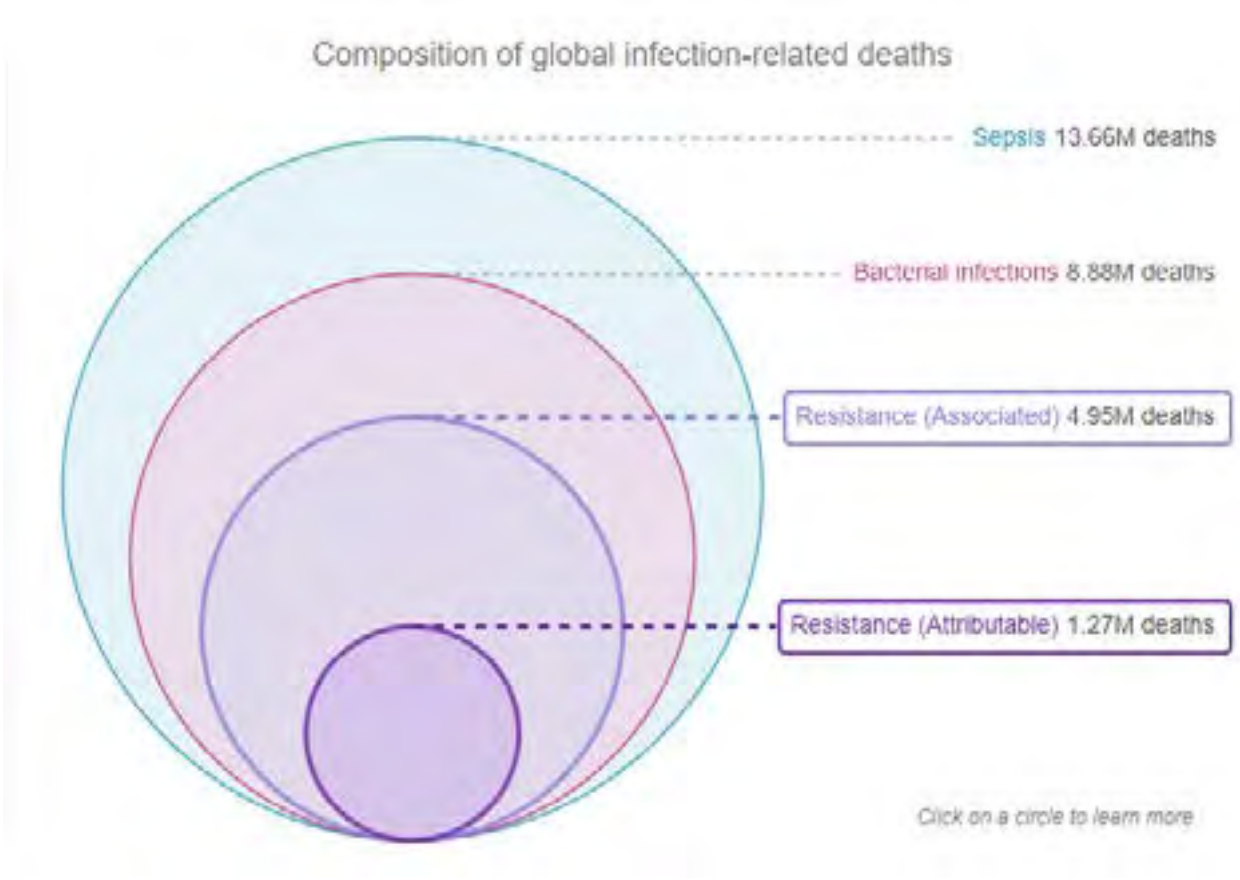
FIVE PATHOGENS ACCOUNT FOR >50% OF BACTERIAL INFECTIOUS DEATHS



- Five pathogens associated with 4.8M bacterial infectious deaths
  - *Mycobacterium tuberculosis*
  - *Staphylococcus aureus*
  - *Escherichia coli*
  - *Streptococcus pneumoniae*
  - ***Klebsiella pneumoniae***
- Globally, in 2019, *K. pneumoniae* associated with:
  - 789,903 global deaths
  - 10.2 deaths/100K population

Source: https://vizhub.healthdata.org/microbe/

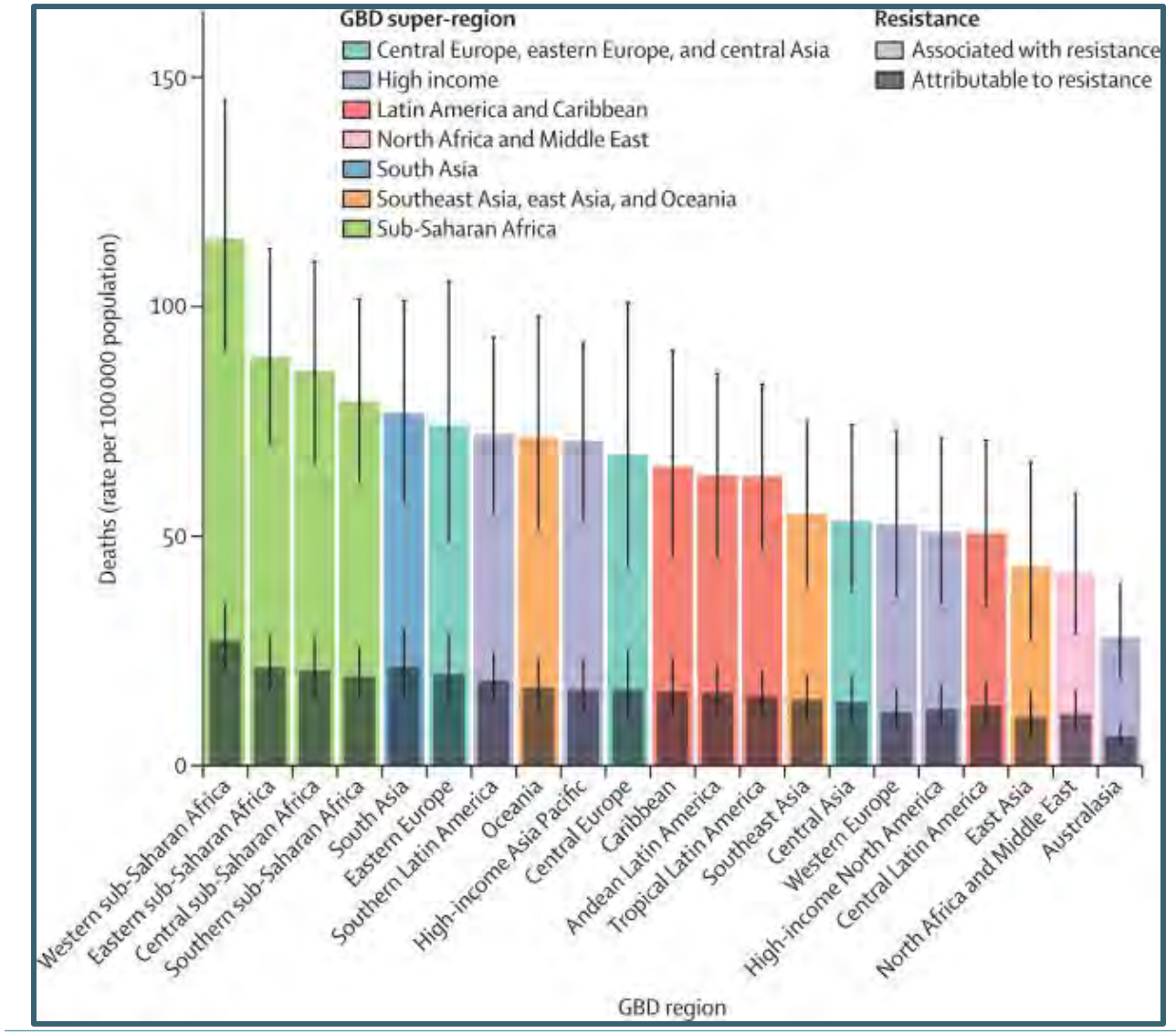
AMONG INFECTIOUS DEATHS, 4.95M ASSOCIATED WITH BACTERIAL ANTIMICROBIAL RESISTANCE (AMR)



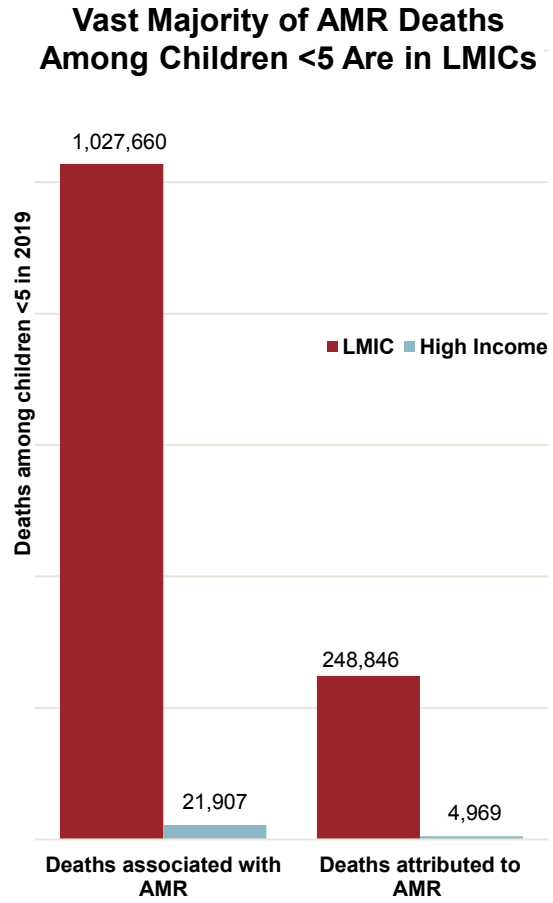
- 4.95 million (3.63-6.57) deaths associated with bacterial AMR
  - Bacterial AMR is the 3rd-leading underlying cause of death among GBD Level 3 causes, behind only ischemic heart disease and stroke
- 1.27 million (95% UI 0.911-1.71) deaths attributable to bacterial AMR
  - Bacterial AMR is the 12th-leading underlying cause of death among GBD Level 3 causes, ahead of HIV, TB, and malaria

Source: https://vizhub.healthdata.org/microbe/

AMR DEATHS BY GLOBAL BURDEN OF DISEASE (GBD) REGION



Highest rates of AMR deaths are in low- and middle-income countries globally and among those under 5 years of age



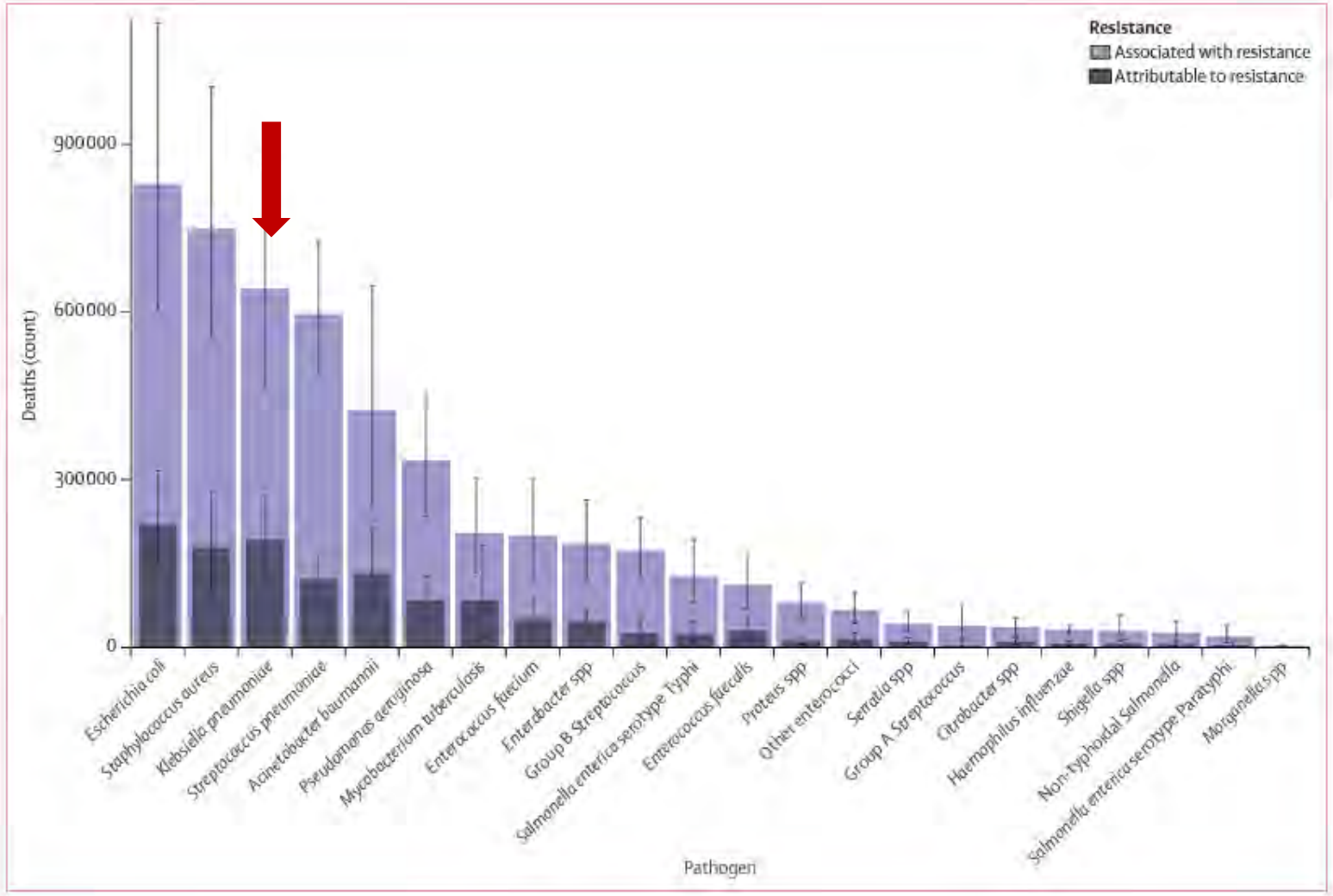
Antimicrobial Resistance Collaborators. GRAM Publication. *The Lancet*, February 12, 2022; 399 (10325).

ASSOCIATED AND ATTRIBUTABLE GLOBAL AMR MORTALITY

- Top six pathogens responsible for **929,000** (660,000-1,270,000) deaths attributable to AMR and **3.57** (2.62-4.78) million deaths associated with AMR in 2019

- Vaccines available for only two of these six pathogens

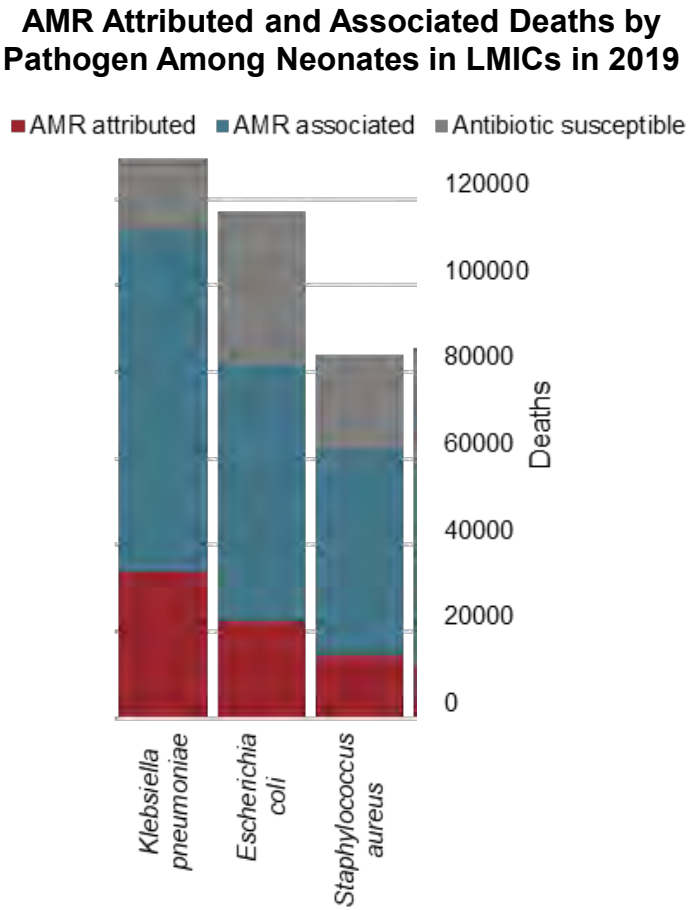
- ***Klebsiella pneumoniae*** accounts for **641,703 AMR associated deaths**
  - **192,590 deaths attributable to AMR**

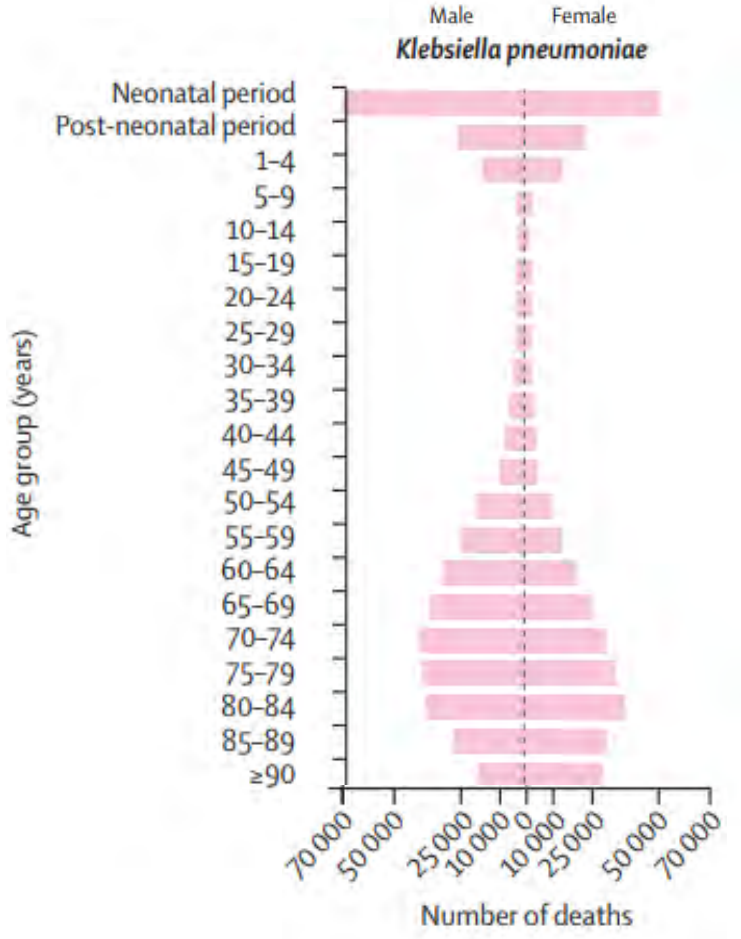


Antimicrobial Resistance Collaborators. GRAM Publication. *The Lancet*, February 12, 2022; 399 (10325).

KLEBSIELLA PNEUMONIAE IS LEADING CAUSE OF BACTERIAL INFECTIOUS DEATHS AMONG NEONATES

- *Klebsiella pneumoniae* is
  - Associated with 129,151 deaths among neonates in 2019
  - The majority (87%) of these deaths are AMR related
    - 78,802 *K. pneumoniae* AMR-associated deaths
    - 33,889 *K. pneumoniae* AMR-attributed deaths



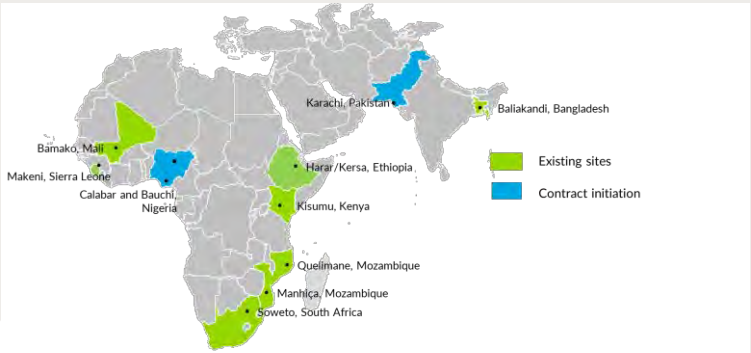


GBD 2019 Antimicrobial Resistance Collaborators.. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019 *The Lancet*, 2022).

KLEBSIELLA PNEUMONIAE IN THE CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) PLATFORM

CHAMPS Mortality Surveillance

- Combined analysis of clinical data, verbal autopsies, laboratory tests for multiples pathogens, tissue samples with molecular and pathology techniques
- Reviewed by expert panel to determine the specific causes of death in children under five in seven countries in Africa and Asia



K. pneumoniae Testing and Death Summary by Age in CHAMPS

Age Group	Tested	K. pneumoniae TAC positive*	K. pneumoniae in causal chain
Stillbirth (n=1159)	1098	122 (11%)	7 (0.6%)
Death within first 24 hours (n=540)	539	88 (16%)	28 (5%)
Early neonate (24 to <72hr) (n=329)	329	106 (32%)	51 (16%)
Early neonate (72hr to 6d) (n=201)	200	97 (49%)	71 (36%)
Late Neonate (7 to 27 days) (n=240)	239	132 (55%)	89 (37%)
Infant (28 days to less than 6 months) (n=281)	280	152 (54%)	100 (36%)
Infant (6 months to less than 12 months) (n=161)	161	96 (60%)	31 (19%)
Child (12-59 months) (n=407)	404	201 (50%)	88 (22%)
TOTAL n=3318 (%)	3250	994 (31%)	465 (14%)

https://champshealth.org/

KLEBSIELLA PNEUMONIAE CONTRIBUTES TO 45% OF ALL NEONATAL INFECTIOUS DEATHS IN CHAMPS

Neonatal Age Group (n=total MITS DeCoDed)	Infectious Cause in Chain	*K. pneumoniae* in Causal Chain (% of infectious)
Death within first 24 hours (n=540)	98 (18%)	28 (29%)
Early neonate(24to <72hr) (n=329)	107 (33%)	51 (48%)
Early neonate (72hr to 6d) (n=201)	139 (69%)	72 (52%)
Late neonate (7d to 27d) (n=240)	192 (80%)	89 (46%)
TOTAL Neonates (n=1310)	536 (41%)	240 (45%)

https://champshealth.org/

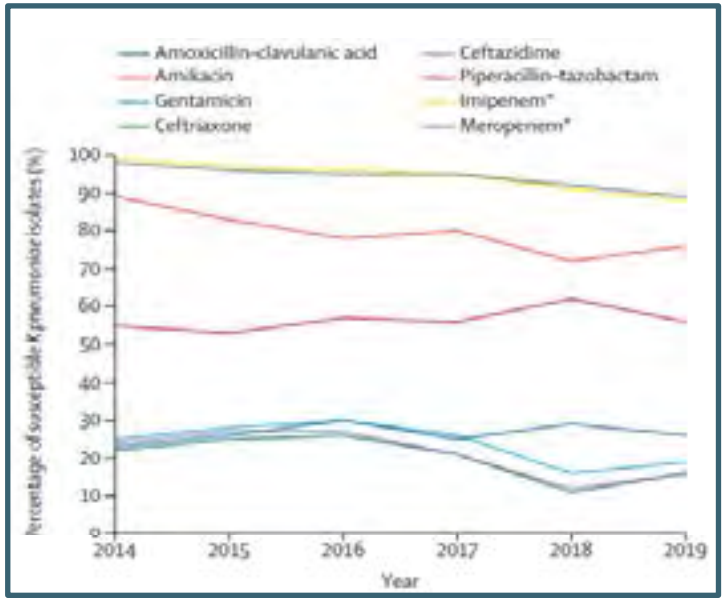
K. PNEUMONIAE IS LEADING ETIOLOGY FOR NEONATAL SEPSIS AT DIFFERENT LEVELS OF HEALTH FACILITIES: SOUTH AFRICA

	National central (n=13 366)	Provincial tertiary (n=7212)	Regional (n=18 599)	District (n=4261)
Gram-negative bacteria	8268 (62%)	4638 (64%)	9890 (53%)	2040 (48%)
Klebsiella pneumoniae	3745 (28%)	2221 (31%)	4302 (23%)	887 (21%)
Acinetobacter baumannii	2394 (18%)	1008 (14%)	2010 (11%)	274 (6%)
Escherichia coli	667 (5%)	386 (5%)	1124 (6%)	319 (7%)
Serratia marcescens	465 (3%)	265 (4%)	613 (3%)	103 (2%)
Enterobacter cloacae	341 (3%)	260 (4%)	561 (3%)	157 (4%)
Pseudomonas aeruginosa	235 (2%)	80 (1%)	268 (1%)	48 (1%)
Other Gram-negative pathogens	421 (3%)	436 (6%)	1012 (5%)	252 (6%)
Gram-positive bacteria	3668 (27%)	2211 (31%)	7623 (40%)	2093 (49%)
Staphylococcus aureus	1241 (9%)	690 (10%)	2547 (14%)	737 (17%)
Enterococcus faecium	834 (6%)	554 (8%)	1627 (9%)	419 (10%)
Enterococcus faecalis	726 (5%)	521 (7%)	1492 (8%)	406 (10%)
Coagulase-negative staphylococci	232 (2%)	61 (1%)	203 (1%)	69 (2%)
Group B Streptococcus	527 (4%)	317 (4%)	1347 (7%)	304 (7%)
Other Gram-positive pathogens	105 (1%)	757 (10%)	407 (2%)	158 (4%)
Fungi	1430 (11%)	363 (5%)	1086 (7%)	128 (3%)
Candida parapsilosis	599 (4%)	98 (1%)	305 (2%)	12 (1%)
Candida albicans	442 (3%)	148 (2%)	320 (2%)	55 (1%)
Candida auris	28 (0%)	1 (0%)	31 (0%)	0
Other yeasts	361 (3%)	116 (2%)	430 (3%)	61 (1%)

Data are n (%).

Table 3: Pathogens isolated from neonates with culture-confirmed bloodstream infections and meningitis by hospital tier

- *K. pneumoniae* most common identified etiology of blood culture confirmed neonatal sepsis in South Africa at central, regional, and district level facilities
- High and increasing percentage of resistance to broad spectrum antibiotics detected in *K.* pneumoniae suggests burden not likely to decrease in coming years



Mashau, et al. *Lancet Global Health* 2022; 10: e1170–78

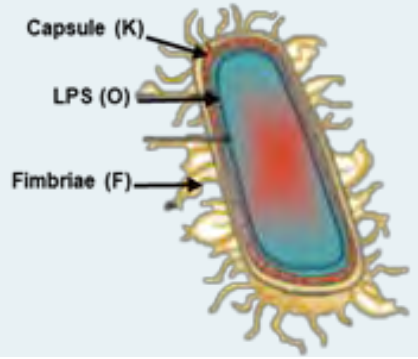
KLEBSIELLA PNEUMONIAE MATERNAL IMMUNIZATION STRATEGY

Prevention of *K. pneumoniae* neonatal sepsis: potential for a maternal conjugate vaccine approach

Lipopolysaccharide (LPS) O-antigens and capsular K antigens are potential targets for conjugate vaccines

K (capsular) antigens

- 77 defined serotypes but >140 K loci defined on the basis of gene content
- Preliminary analysis* estimate that the most common 20 K loci among neonatal sepsis isolates (adjusting for local clonal expansions) account for ~70% of neonatal sepsis cases
    - These serotypes account for ~50-60% of total *K pneumoniae* global sepsis cases (all ages)



O (LPS) antigens:

- Twelve distinct O loci
- Preliminary analysis* estimate the top 3 O loci account for ~90% of the sepsis cases

Considering a high valency O-Ag + K-Ag conjugate vaccine approach

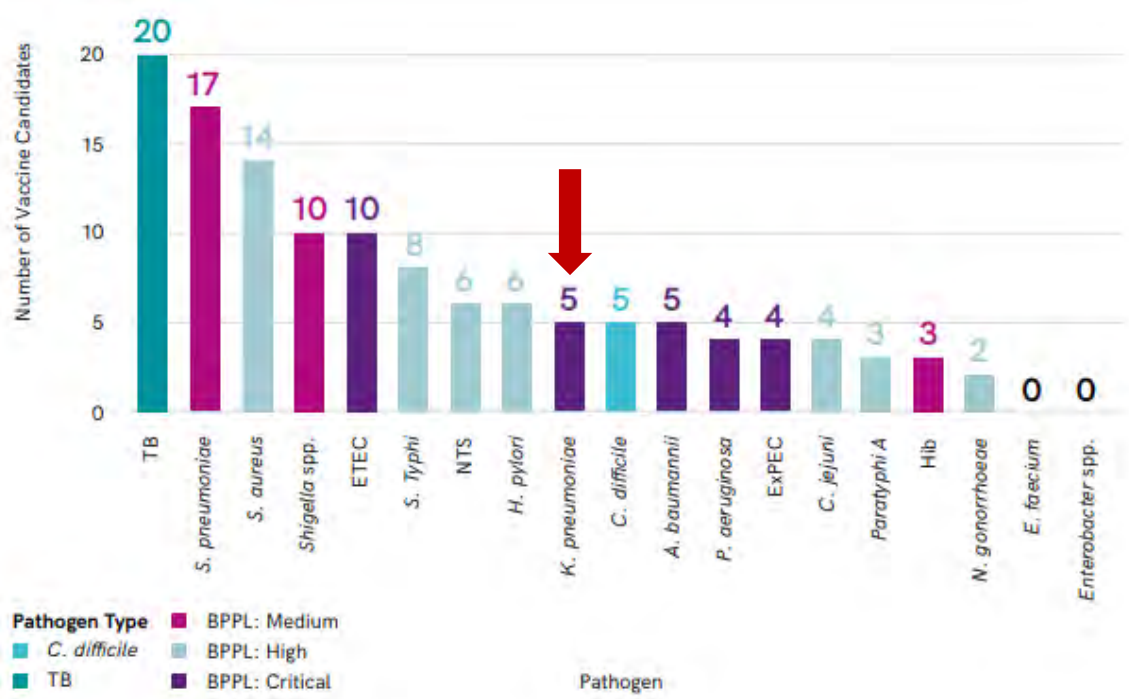
- 20+-valent conjugate vaccine which covers 60-70% of K-types, and majority of O-types

BMGF *K. pneumoniae* vaccine development activities

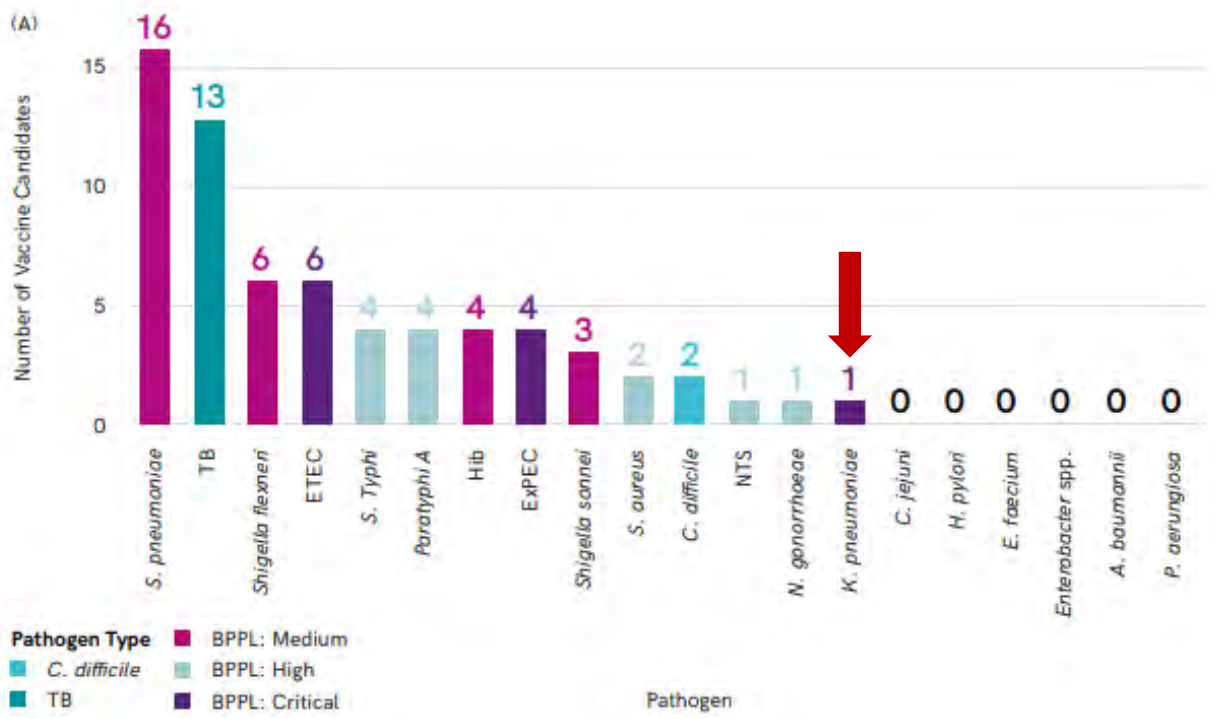
- More complete characterization of genomic and sero-epidemiology of *K. pneumoniae* neonatal sepsis
- Development of *K. pneumoniae* neonatal sepsis animal maternal immunization model
- Clarify whether serotype specific antibodies targeting K and O antigens confer protection, and work to develop *Kpn* correlate of protection

KLEBSIELLA PNEUMONIAE VACCINE DEVELOPMENT EFFORTS

Pre-clinical



Clinical



- *Klebsiella pneumoniae* vaccine development is prioritized in CARB-X
- Current funding cycle includes specific call for proposals targeting Gram negative neonatal sepsis pathogens

CARB-X

World Health Organization, 2022: Bacterial vaccines in clinical and preclinical development 2021

SUMMARY

- *Klebsiella pneumoniae* is a leading cause of bacterial infectious death globally, associated with >780K deaths in 2019

- *Kpn* is the leading cause of neonatal infectious deaths, with >120K deaths in 2019
  - High and rising antimicrobial resistance plays an important role in contributing to these deaths

- To prevent and reduce these deaths, BMGF has prioritized *Kpn* as a potential maternal vaccine target
  - Capsular and sub-capsular *Kpn* antigens are potential vaccine targets
  - *Kpn* included as priority pathogen in CARB-X AMR vaccine portfolio

  - ***Question for PDVAC:*** What is the most appropriate mechanism to build awareness about burden of K pneumoniae infections and increase urgency on need for a Kpn vaccine?

ACKNOWLEDGEMENTS

- BMGF
  - Keith Klugman, Kristin Savage, Angela Guo, Funmi Akeju, Nicki Benson
- IHME
  - Chris Murray, Mohsen Naghavi, Eve Wool
- CHAMPS
  - Diana Blau, Cyndy Whitney
- Baby GERMS
  - Nelesh Govender, Rudzani Mashau
- LSHTM and Monash University
  - Kat Holt, Kelly Wyres
- WHO
  - Mateusz Hasso Agopsowicz
  - Martin Friede

Questions for PDVAC

- Are the mentioned activities appropriate to articulate and leverage the role of vaccines in reducing AMR?

- What is an appropriate mechanism to build awareness and increase urgency of the burden of Klebsiella and need for a Klebsiella vaccine?