WHO Consultations on RSV Vaccines and Passive Immunization

Vasee Moorthy/ Birgitte Giersing/ Johan Vekemans

Wenging Zhang & Team

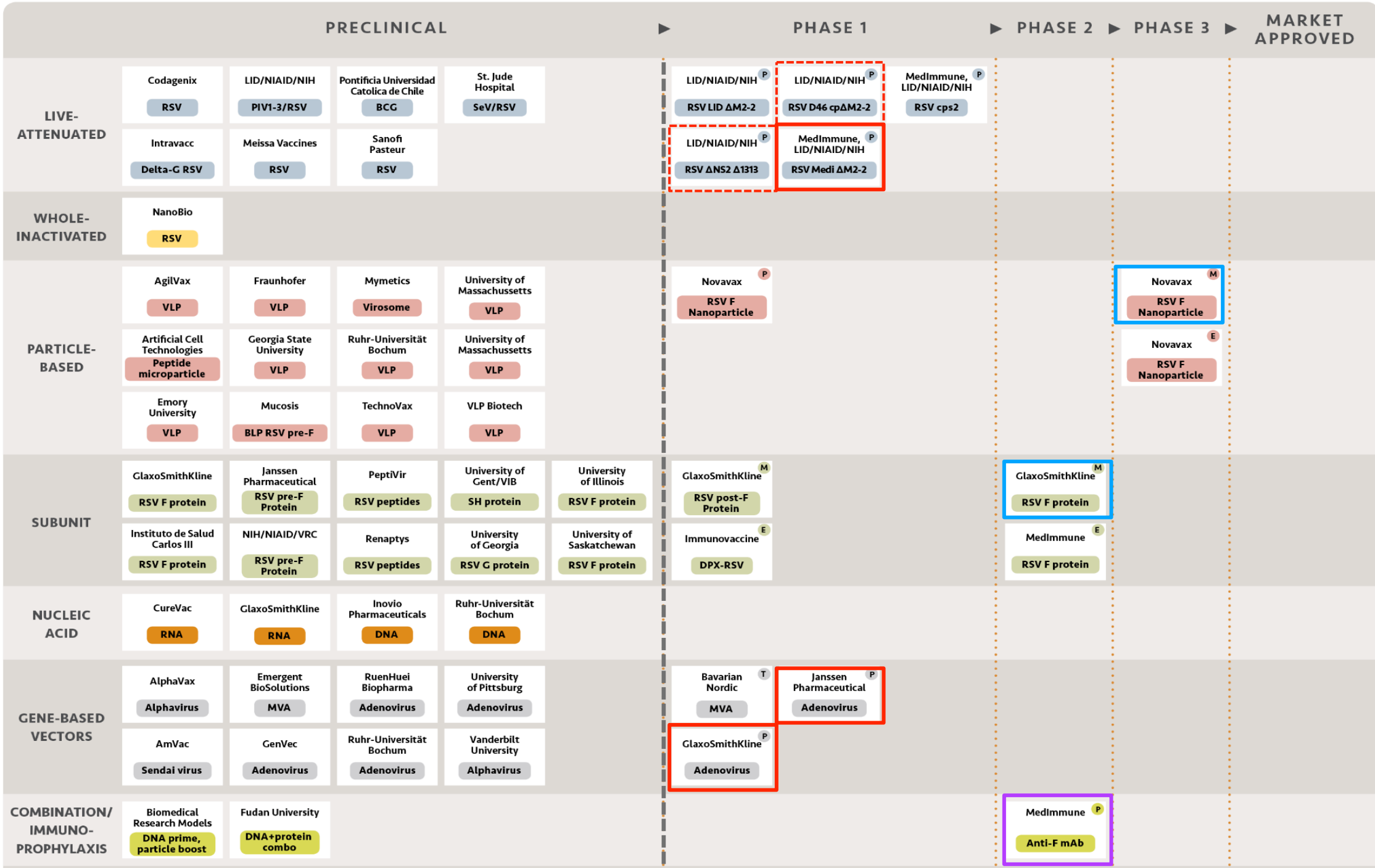
Mike Ward/ Ahmed Bellah

Ivana Knezevic/ Kai Gao

RSV Vaccine Snapshot

62 candidates total;16 in clinical trials

TARGET INDICATION: (P) = PEDIATRIC (M) = MATERNAL (E) = ELDERLY (T) = TBD



UPDATED: DECEMBER 15, 2015

http://sites.path.org/vaccinedevelopment/respiratory-syncytial-virus-rsv/

PATH

Summary of WHO activities

- Developing scientific consensus on development and testing pathways – first IVR consultation on RSV in March 2015
- A RSV vaccine R&D roadmap to identify key knowledge and capacity gaps so that further work can attempt to address these - IVR
- A Preferred Product Characteristics document is in development – IVR
- RSV surveillance – consultations in 2015 and Feb 2016 (HSE cluster)
- Regulatory Networks – DCVRN 2015 (EMP/RSS)
- RSV immunogenicity assays and standard reagents – first consultation Feb 2016 (EMP/ Norms and Standards)

Strategic Goals for RSV vaccine development

1. Maternal immunization/passive immunization to prevent RSV disease in infants less than 6 months of age.
2. RSV vaccines for active paediatric immunization to prevent RSV disease in infants and young children once protection afforded by maternal immunization wanes.

Geographical settings for clinical trials

- Efficacy trials are likely to be conducted in both high income and LMICs.
- Regulators and policymakers from different settings will be looking for data relevant to their own settings, and importance of defining endpoints relevant to target populations
- Desirable to construct widely applicable endpoints with objective criteria that can be applied in a standardised way across different settings to define severe RSV

Geographical settings for clinical trials

- Collaborations between northern and southern hemisphere trial sites could accelerate timelines because of complementarity in RSV seasonality
- Avoiding a scenario where safety and effectiveness is demonstrated partly through testing in LMIC, and vaccine then becomes available only for high income countries
- As disease burden is focused on LMIC, there is a major onus on developers & funders to work towards ensuring access and availability in LMIC

Global Development and Testing Pathway for Maternal & Paediatric Immunization

Gained consensus at IVR consultation on the pathway for clinical trials leading up to efficacy trials in pregnant women for protection of infants

Pathway for active paediatric immunization highlights caution in progressing from seropositive to seronegative children. This has lengthened timelines up until now.

The field has seen rapid progress with one of the maternal immunization approaches now in Phase 3.

Some/most manufacturers are considering different products for maternal vs paediatric immunization

Clinical case definitions for RSV vaccine efficacy trials – LMIC focus

- Included clinical features considered to be objective, standardizable and generalizable across settings, and generally accepted markers of severity
- It was proposed that the candidate case definitions agreed at the meeting were piloted in ongoing and planned epidemiological studies as well as in vaccine efficacy trials
- Further IVR consultation later in April to review progress

Gaps/issues highlighted by IVR scoping

- Very little health economic evaluation
- More impact modelling would be desirable
- Controversy about the impact of prevention of RSV in early life, and possible reductions in recurrent wheeze later in life: if confirmed this would affect the value proposition for the vaccine, and cost-effectiveness predictions

Gaps highlighted by IVR scoping: pathways to use in LMIC for long-acting mAbs

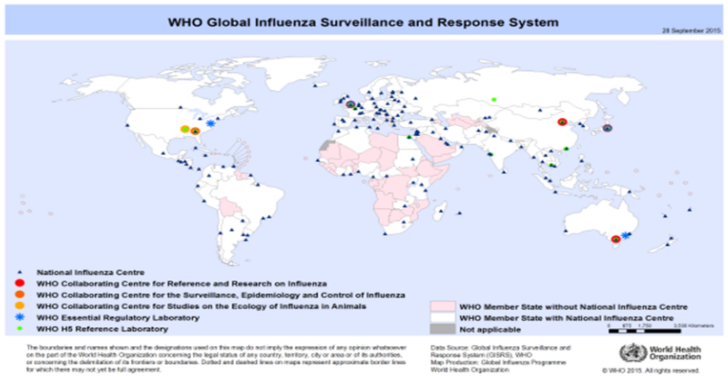
- The advent of single dose mAbs that persist at therapeutic levels for over 4 months is a major technology shift, relevant beyond RSV alone
- Chances for technical/regulatory success with the mAb approach look high, given existing licensed mAb
- Questions about pathways to use in low and middle income countries

RSV surveillance / background

- Objectives – through ***continuous*** monitoring and surveillance to
  - Understand epidemiologic and virological features of RSV circulation globally
  - Generate evidence for introduction of RSV vaccines including seasonality, risk groups and burden of disease

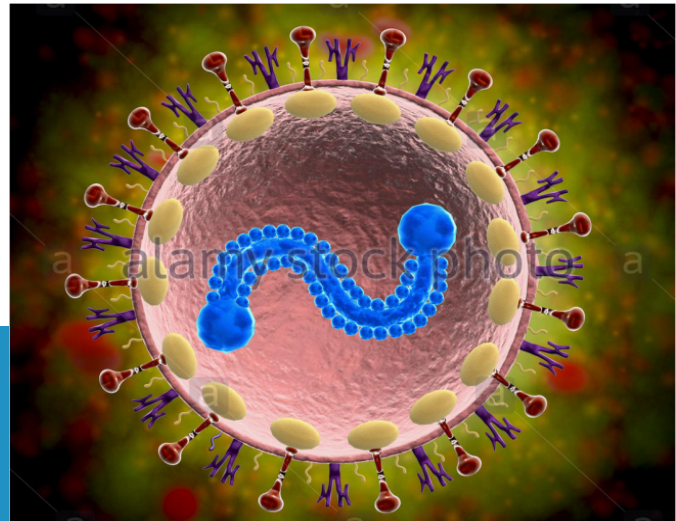
- Strategy: based on global influenza platform: WHO Global Influenza Surveillance and Response System (GISRS), fully functioning since 1952
  - 150 institutions in 113 countries – ***the*** national labs for influenza, MERS, SARS-CoV ...
  - Extensive sub-national sentinel networks → GISRS
  - >1.5 million respiratory specimens tested per year → highly efficient as required for influenza epidemics and pandemic

- Implementation:
  - Additions of components for RSV to GISRS
    - Case definitions, sentinel sites, sample size, lab testing algorithms
  - Lab testing protocols, reagents and quality assessment
  - Reporting
  - Coordination and reference labs
  - Roll-out plan and sustainability



RSV surveillance / status

- Buy-in from WHO ROs and countries
  - Experience from countries testing RSV along influenza surveillance reviewed
  - 14 countries from 6 ROs nominated for pilot – to be roll out in June 2016
- Lab testing
  - Reference labs identified
  - Lab platforms of pilot countries reviewed
  - Testing protocols validated
  - Testing algorithms being developed
  - Proficiency panels being prepared
- Surveillance protocols
  - Case definitions for pilot and sampling size being finalized
  - Practical guidance on sentinel site selection or addition being developed
- Reporting
  - Fields of reports being defined
  - Platform (FluNet/FluID) being tested
- Coordination mechanism
  - Global coordination mechanism being developed
  - Sustainability issues under review



Regulatory networks to support NRAs on RSV issues

AVAREF membership: 23 countries which includes Botswana, Burkina Faso, Cameroon, the Central African Republic, Ethiopia, Kenya, The Gambia, Ghana, Gabon, Guinea, Uganda, Tanzania, Mali, Malawi, Mozambique, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, South Africa, Zambia, and Zimbabwe.

DCVRN Current membership: Brazil, China, Cuba, India, Iran, Indonesia, Korea, South Africa and Thailand

Joint Review processes: MenAfriVac™; Phase II and II-III of the conjugate meningitis A vaccine manufactured by the Serum Institute of India.

Phase III study of the RTS, S/ AS01 malaria vaccine candidate, manufactured by GlaxoSmithKline (GSK) Biologicals.

Dec 2014 to June 2015, multiple Joint Reviews conducted for several Ebola vaccine manufacturers in Phase 1-3 for clinical trial authorisation in west and east Africa

Immune response to RSV vaccines: current understanding

- Protective effect of neutralizing antibody is supported by epidemiologic observations and intervention studies.
- Serum neutralizing activity is the most important serological endpoint for evaluation of many RSV vaccines.
- Binding to unique surfaces of pre-fusion F also may be a surrogate endpoint. Epitope-specific assays for binding or neutralization may reveal correlates of immunity.
- The role of mucosal and cell-mediated immunity largely depends on the type of vaccine and, therefore, these issues should be considered in the context of specific RSV vaccines.

Way forward with RSV measurement standards and assay standardization

1. WHO Measurement standard:

- IS (serum, adult plasma or Ig from healthy volunteers) for neutralization assays is priority
- Feasibility for developing a standard for epitope-specific assays, such as PCA is being explored
- A need for other standards should be revisited as we go along vaccine development

2. Standardization of the assays

- Manual/SOP

- Key reagents and parameters

3. Proposed timeline

- Develop collaborative study protocol

- Identify the source of right material, prepare IS candidates and sample panel for study.

- Confirm participating laboratories : Selection of labs – those that successfully completed PATH study would be eligible to take part in WHO collaborative study; in addition, other labs would be considered.

- Distribution of samples, Conduct of the study: 2016 – 2017. Progress report to the ECBS 2016

Conclusion

- Great momentum in development and testing of RSV vaccines
- A pathogen where the case may be focused more on morbidity than mortality
- First Decision session for RSV could be in 4 to 5 years time
- Would SAGE like to comment on further needed activities to support evidence-based decision making in that time-frame?

World Health Organization