Trivalent Rotavirus P2-VP8 Subunit Vaccine and its Public Health Value Proposition

Product Development Vaccine Advisory Committee
World Health Organization

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Bill Hausdorff, Fred Cassels
NRRV Team
ROTAVIRUS DISEASE

Rotavirus remains a leading cause of severe diarrhea among children <5 yrs worldwide

• Current disease burden:
  >250 million cases of diarrhea annually
  129,000 diarrheal deaths in 2016
  (declined from >500,000 in 2000).

• Four live attenuated oral rotavirus vaccines: WHO PQ
  Rotarix, GSK; RotaTeq, Merck;
  Rotavac, Bharat; RotaSiil, Serum Institute.

• Vaccination well established globally:
  • All settings observed a real impact (high, middle and low income settings)
  • Significant reduction in rotavirus related mortality, severe rotavirus diarrhea and all cause diarrhea in countries vaccine introduced.

Despite major progress, rotavirus disease continues to impact on child health.
Live Oral Rotavirus Vaccines

**Discovery & Preclinical**
- DCVMs include:
  - Bharat Serum
  - BioFarma Hilleman
  - Polyvac Wuhan
  - Shantha Butantan
  - Lanzhou

**Phase 1**
- Liquid BRV Butantan, Brazil
- RV3 – BB BioFarma, Indonesia

**Phase 2**
- Heat-stable pentavalent Hilleman MSD, India

**Phase 3**
- ROVAVIN (liquid) POLYVAC, Vietnam
- ROTAVIN (liquid) POLYVAC, Vietnam
- ROTAVIN 5D (liquid) Bharat Biotech, India
- ROTAVIN (liquid) Serum Institute India
- RotaTeq Merck, USA
- ROTAVIN-M1 (frozen) POLYVAC, Vietnam

**Market**
- RotaVAC 5D (liquid) Bharat Biotech, India
- ROTASIIIL (frozen) Bharat Biotech, India
- ROTAVAC (frozen) Serum Institute India
- ROTAVIN-M1 (lyo) Serum Institute, India

**WHO PQ**
- ROTAVAC (liquid) Bharat Biotech, India
- RotaTeq Merck, USA
- ROTAVAC (frozen) Bharat Biotech, India
- ROTAVAC 5D (lyo) Bharat Biotech, India
- ROTAVIN (liquid) Serum Institute India
Rationale for Considering an NRRV Vaccine

Limitations of current live oral rotavirus vaccines:

- Offer great benefit to populations in resource-limited countries but have reduced efficacy in those populations compared to other populations
  - Potential reasons include inference by maternal antibodies, coinfection with other pathogens, enteropathy, co-administration of OPV, nutrient deficiency and host genetics
- Cost compared to other EPI vaccines is high

NRRV candidates:

- Parenteral administration could avoid several intestinal barriers that oral vaccines must overcome, and thus may provide superior efficacy in target populations
- Projected to be relatively inexpensive (<<$1 per dose)
- May be added to EPI vaccines (co-formulated), facilitating delivery (and further decreasing cost)
Trivalent Rotavirus P2-VP8 Subunit Vaccine and its Public Health Value Proposition

Next Generation Rotavirus Vaccines--Non Replicating

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Licensure</th>
<th>WHO PQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expressed VP6 protein</td>
<td>U Tampere</td>
<td>IRV CDC-9 CDC/SII</td>
<td>VLP VP2/6/7 Mitsubishi/ Medicago</td>
<td>NRRV (P2-Vp8*) PATH</td>
<td>mRNA vaccine VP8* CureVac</td>
<td></td>
</tr>
<tr>
<td>IRV CDC-9 Zhifei Lvzhu</td>
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<td>mRNA vaccine VP8* CureVac</td>
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<tr>
<td>IRV 116E Bharat</td>
<td></td>
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<tr>
<td>VLP VP2/4/6/7 Baculo Baylor</td>
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<tr>
<td>Combo- VP6 with norovirus CCHMC</td>
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</tbody>
</table>

**Potential benefits include:**
- Lower COGs
- Higher efficacy profile
- Decreased signal intussusception
- Potential for use in combination vaccine
- Potential for alternative dosing schedules
Characteristics of the P2-VP8 Subunit Vaccine

- Developed at US NIH by Dr. Yasutaka Hoshino
- Comprised of recombinant truncated VP8 ~ 21kDa
  - Expressed in *E. coli*
  - Simple three step column chromatography process
  - Liquid formulation, adsorbed to aluminum hydroxide
- The trivalent P2-VP8 subunit vaccine is made by combining three VP8 subunit proteins expressing P[4], P[6] and P[8] serotypes, each fused to the P2 T-cell epitope of tetanus toxin
- Elicits immunoglobulin G (IgG) and immunoglobulin (IgA) binding antibodies as well as rotavirus neutralizing antibodies in pre-clinical studies; protection from disease in neonatal piglet model
- No unexpected toxicity observed in GLP toxicology studies on rabbits and guinea pigs following administration of four doses (4 X human dose) of vaccine at two week intervals
- Two dose vial without preservative, each 0.5 ml dose contains 90 ug of antigen (30 ug per serotype)
### Target Product Profile (TPP)

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Prevention severe rotavirus gastroenteritis</td>
</tr>
<tr>
<td><strong>Target Population</strong></td>
<td>Infants (6-12 weeks old) during primary EPI series (for co-administration)</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>IM</td>
</tr>
<tr>
<td><strong>Presentation / Formulation</strong></td>
<td>2 dose vial, liquid, 2-8 C. Formulated with aluminum hydroxide, ea 0.5 mL dose 90 ug P2-VP8 antigen (30 ug ea P[4], P[6], P[8])</td>
</tr>
<tr>
<td><strong>Dosing Schedule</strong></td>
<td>3 doses at 4 week intervals, starting 6-8 weeks of age</td>
</tr>
<tr>
<td><strong>Vaccination strategy</strong></td>
<td>Routine (+ penta/hexa)</td>
</tr>
<tr>
<td><strong>Expected Efficacy</strong></td>
<td>&gt; 75% in Phase 3 trial</td>
</tr>
<tr>
<td><strong>Price per Dose</strong></td>
<td>~ $0.68 / dose</td>
</tr>
<tr>
<td><strong>Manufacture</strong></td>
<td>SK bioscience, Seoul, manufacturing stand-alone vaccine for Phase 3 trial. Additional manufacturing partner(s) envisioned for combination vaccine development.</td>
</tr>
<tr>
<td><strong>Product Registration</strong></td>
<td>Korea is anticipated first country of licensure (for export).</td>
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<tr>
<td><strong>WHO Prequalification</strong></td>
<td>Yes, 2H 2024</td>
</tr>
<tr>
<td><strong>Manufacturing Capacity</strong></td>
<td>65 million doses per year 2-dose presentation</td>
</tr>
</tbody>
</table>
End to End Clinical Development Plan

Preclinical 2010-2013

- Phase I (monovalent)
  First-in-human Dose-escalation
  **Completed OCT 2013**

- Phase I/II (monovalent)
  Descending-age, Dose-escalation
  **Completed OCT 2015**

- Phase I/II (Trivalent P2-VP8)
  Descending-age, Dose-escalation
  (Adult, toddler, infant)
  Dose-ranging in infants
  **Completed DEC 2017**

- Pivotal Phase III
  2 active arms
  Trivalent P2-VP8 & licensed RVV

- Expanded Safety
  EPI Interference
  Lot-to-lot Consistency

- **BLA Preparation & Submission**

- **PSF Preparation & Submission to WHO for PQ**
End to End Clinical Development Plan

Phase I VAC 009
Monovalent P[8]

Phase I/II VAC 013
Monovalent P[8]

Phase I (monovalent)
First-in-human Dose-escalation
Completed OCT 2013

Phase I/II (monovalent)
Descending-age, Dose-escalation
Completed OCT 2015

Phase I/II (Trivalent P2-VP8)
Descending-age, Dose-escalation
(Agent, toddler, infant)
Dose-ranging in infants
Completed DEC 2017

Pivotal Phase III
2 active arms
Trivalent P2-VP8 & licensed RVV

Expanded Safety
EPI Interference
Lot-to-lot Consistency

2013

2024

Ethics consultation for head-to-head trial
Assay qualification
Thimerosal stability

BLA Preparation & Submission
PSF Preparation & Submission to WHO for PQ

Phase I/II VAC 041 Trivalent P[4], P[6], P[8]

- Safety & tolerability in South Africa healthy adults, toddlers, infants
- 15, 30, 90 ug IM 28 days apart
- Impact Vxn on shedding Rotarix

Results
- All dosage levels safe & well tolerated
- Robust anti-P2-VP8 IgG against all three P types
- Three doses better responses than two
- Significant decrease shedding Rotarix
- Greatest impact shedding with 90 ug dose (30 ug each serotype)
Assessment of Efficacy of the Standalone TV-P2-VP8

CVIA 061

A double-blind, randomized, active comparator-controlled, group-sequential, multinational trial to assess the safety and efficacy of a trivalent P2-VP8 subunit rotavirus vaccine in prevention of severe rotavirus gastroenteritis in healthy infants
CVIA 061 Key Study Characteristics (1)

- Two arm, double-blind, group-sequential, double-dummy trial (1:1)
  - TV P2-VP8 vaccine
  - Rotarix

- Multinational
  - To include 3 countries in Africa and sites in India

- Dose-level/regimen: 3 monthly doses of 90 µg of TV-P2-VP8, administered monthly with EPI vaccines at 6, 10 and 14 weeks of age

- Follow-up through 2 years of age (unless futility criteria met)
CVIA 061 Key Study Characteristics (2)

• Group sequential trial with two stages
  • Stage 1 ~3,500 infants, with interim assessment of futility
  • Stage 2 – if do not meet futility criteria at interim analysis, proceed to enroll balance of full study population (~8,200)

• Assessment of lot-to-lot consistency of 3 lots of vaccine
• Exploration of immune correlates of risk
• Assessment of interference with response to EPI
• Anticipated initiation – Q3 2019
Double-Dummy Study Design

**A**

TV P2-VP8 (90µg) + Oral Placebo  
N=4100

**B**

Rotarix® + IM Placebo  
N=4100

Screen/Enroll

Active Gastroenteritis Surveillance (Weekly Participant Contact)

1st dose at 6-8 weeks of age; subsequent doses 4 weeks (28 days) later from previous dose

Oral placebo: ORS; IM placebo: Normal saline

Lot-to-lot consistency  
N=1200; 400/lot

UIP Non-interference  
N= 800; 400/group
CVIA 061 Study Outline

Stage 1 Enrollment
3,500 infants
4-6 months

Interim analysis
once accrue
>30 cases SRVGE

Futility Criteria
Not Met

Futility Criteria Met

Close enrollment
Crossover vaccination of TV P2-VP8 infants
Study closure

Stage 2 Enrollment
4,700 infants
6-8 months

Primary analysis
once accrue >99 cases SRVGE or all reach 2 years of age

Final analysis after all participants reach 2 years of age
TV-P2-VP8 Future Development

• Assessment of efficacy of standalone vaccine

• Potential exploration of mixed regimens of live, oral RV vaccines and P2-VP8 vaccine

• Development of co-formulated vaccine, combining other EPI vaccines and P2-VP8 in a single injection

• Should efficacy results warrant, licensure and WHO prequalification of standalone and/or co-formulated vaccine for global availability
Maximizing impact of Rotavirus vaccines: NRRV value proposition

Bill Hausdorff, PhD
Lead, Public Health Value Proposition
CVIA/PATH
Washington, DC
The solution to the problem is…

…a next generation, parenterally administered rotavirus vaccine!!

But what, exactly, is the problem?
Isn’t THIS the problem?
NRRV should have intrinsically higher efficacy in primary series against severe disease in LICs.

Efficacy of live, oral rotavirus vaccination on severe rotavirus diarrhea, by region
Box represents percent efficacy; whiskers represent upper and lower bounds for the 95% confidence interval

Do we even need a Value Proposition?

A Systematic Review of the Effect of Rotavirus Vaccination on Diarrhea Outcomes Among Children Younger Than 5 Years
Lamberti, Laura M.; Ashraf, Sania; Walker, Christa L. Fischer; Black, Robert E. The Pediatric Infectious Disease Journal35(9):992-998, September 2016.doi: 10.1097/INF.0000000000001232
Yet NRRV has several other potential advantages over live oral vaccines

- Lower cost of goods/dose
- Could form part of mixed schedule with oral vaccine for higher efficacy
- Could serve as a booster to oral vaccine to prevent waning in 2\textsuperscript{nd} year of life
- Could be combined with DTP penta (or hexa) and/or IPV to minimize cold chain burden
- No intussusception

Which of these are “nice to have,” and which as “must haves”? Is higher efficacy itself a “must have”? Alternatively, do we even have to choose among these advantages?
Yes. We have to make some choices. We can’t do everything. Choices shape clinical program & recommending body/market interest

<table>
<thead>
<tr>
<th>Primary Theoretical Advantage</th>
<th>Clinical Endpoint Needed</th>
<th>Recommending Body/Market Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Higher VE in LICs</strong></td>
<td>Demonstrate NRRV’s clinical efficacy superiority</td>
<td>Strong selling point to SAGE &amp; LICs but perhaps not to MICs?</td>
</tr>
<tr>
<td><strong>Lower COGs/dose</strong></td>
<td>Demonstrate efficacy non-inferiority</td>
<td>Do LICs care if GAVI is paying? Is current price an important barrier for MICs?</td>
</tr>
<tr>
<td><strong>As part of mixed schedule or booster to counteract waning of current VE</strong></td>
<td>No need to demonstrate any efficacy after primary series; need to demonstrate heightened efficacy after mixed/boost</td>
<td>COGs advantage lost; is preventing incremental late disease sufficiently interesting to SAGE &amp; countries?</td>
</tr>
<tr>
<td><strong>Combinable with DTP combos or IPV</strong></td>
<td>Efficacy non-inferiority followed by work with one manufacturer to demonstrate immuno non-inferiority</td>
<td>Delayed time to market; plus would this allow single manufacturer to dominate DTP combo field?</td>
</tr>
<tr>
<td><strong>No intussusception</strong></td>
<td>Efficacy non-inferiority (impossible to demonstrate lack of intussusception pre-licensure)</td>
<td>Has US/Euro/Oz intussusception been a barrier to uptake in LICs or MICs? Is this a selling point?</td>
</tr>
</tbody>
</table>
And alignment of key stakeholders’ perception of the vaccine value is strongly desirable

- **PATH**: Ensure clinical development program will deliver “actionable” results
- **BMGF**: mitigate risks and costs of programmatic twists and turns
- **WHO SAGE**: will ultimately want them to recommend it
- **End Users** (e.g., including NITAGs and EPI program mgrs): they will ultimately choose among multiple products, and perhaps even pay for it
- **GAVI**: will want GAVI to be planning to buy vaccine
- **WHO PQ**: need to ensure we’ve done what is necessary to satisfy
- **Regulators**: need to ensure they appreciate the purpose of the product
- **Others?**
Public Health Value Proposition

- Critical, evidence-based process to ensure our efforts align with need and capacity for intended beneficiaries
  - Communicate value using the lens of stakeholders
  - Consider alternative solutions available to beneficiaries
- Inform planning for evidence generation during vaccine development
- Guide requirements for successful vaccine introduction
  - Identify and develop information required to support policy recommendations and uptake

In current WHO lingo: “Full Public Health Value of Vaccines”
Value Proposition Develops Over Project Lifecycle and Complements Other Project Documents

Explore/Early Stage Value Proposition

Learn/Mid-Stage Value Prop.

Confirm/Late-Stage Value Proposition

Gap analysis and plan to address

TPP Template

Integrated Product Development Plan Template

BMGF Uptake Planning Tool

BMGF Delivery Plan Template

LCS: Lead Candidate Selection
PCD: Pre-Clinical Dev.
FIH: First in Human
EP1: End of Phase 1
EP2: End of Phase 2
DTF: Decision to File
PO/LR

Discovery | Pre-Clinical | Phase 1 | Phase 2 | Phase 3 | Registration | Introduction

Discovery | Pre-Clinical | Phase 1 | Phase 2 | Phase 3 | Registration | Introduction

EP1: End of Phase 1
EP2: End of Phase 2
DTF: Decision to File
PO/LR
PATH’s Main NRRV Activities

NRRV Value Proposition*

- Primary research – acceptability and feasibility
- Impact and CE analysis
- NRRV vaccine development
- Evaluate the full public health value of a new injectable non-replicating rotavirus vaccine

*Supported by a 2-year grant from BMGF
For NRRV, how are we going to do it?  Project overview

- Develop detailed work plan for VP
- Do Lit Review to Assess Scientific Need for Various Desired Vaccine Characteristics
- Develop potential use cases
- Update models and conduct economic analyses
- Conduct feasibility & acceptability research
- Refine use cases & assumptions in analyses to generate impact and CE estimates
- Inform demand forecasts, value estimates, introduction strategy
- Finalize VP document
How do we align with stakeholders? VP as a living document

Develop detailed work plan for VP

Do Lit Review to Assess Scientific Need for Various Desired Vaccine Characteristics

Develop potential use cases

Update models and conduct economic analyses

Conduct feasibility & acceptability research

Refine use cases & assumptions in analyses to generate impact and CE estimates

Inform demand forecasts, value estimates, introduction strategy

Finalize VP document

Sharing with “both sides” of BMGF (periodically)

Work with WHO’s TSE methodology to get additional NRRV feedback

Discuss periodically with clinical development team and other stakeholders (e.g., WHO SAGE? GAVI?)

Present & discuss results at scientific fora
Acceptability & feasibility of introducing NRRV

A Mixed-Method Study to Assess Future Demand

**Overall objective:** Ascertain country preferences for RV products including NRRV
Based on anticipated health or economic advantages, within a range of RV vaccine options and in different country contexts

**Specific components:**
- *key informant interviews with global stakeholders*
- *scenario-based interviews with national stakeholders*
  - Sri Lanka, Myanmar, Malawi, Kenya, Ghana, Senegal, Peru
- *semi-structured interviews with health providers administering vaccines*
Development of RV vaccine use-case scenarios

Option 1: Oral Vaccine Scenario
Efficacy, storage, cost, presentation attributes of licensed LORVs, as well as RV3-BB (neonatal dose), are provided

Option 2: NRRV Scenario
NRRV as a co-administered intramuscular vaccine requiring three doses starting at 6-8 weeks during primary EPI series.
Efficacy may be higher or similar to LORVs
Cost and storage assumptions provided
May be standalone, part of a DTP-combination, and/or co-administered with LORVs

Essentially, a series of forced choices:
Which option would you prefer if NRRV looked like this? Or like this? Or this?
One early output of the NRRV Value Proposition
(Example of an Ad hoc focused analysis)

Critical assessment of the potential value of a booster dose of NRRV
The problem: Oral RV VE in some settings reported to wane by 20% or more in 2nd year of life (Rogawski JID 2018)

- Underlying explanation not clear
  - Could be waning immunological protection and/or a methodological artefact due to increased natural immunity in control group with age
- Could a heterologous booster dose of NRRV at 9 or 12 months be a solution?

<table>
<thead>
<tr>
<th>LORV Efficacy Study</th>
<th>Waning: Percent decrease between 1st and 2nd year efficacies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madhi</td>
<td>36.9%</td>
</tr>
<tr>
<td>Armah &amp; Tapia</td>
<td>35.1%</td>
</tr>
<tr>
<td>Colgate</td>
<td>42.2%</td>
</tr>
<tr>
<td>Armah &amp; Sow</td>
<td>23.7%</td>
</tr>
<tr>
<td>Cunliffe &amp; Madhi</td>
<td>31.8%</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>33.9%</strong></td>
</tr>
</tbody>
</table>

Is this an important avenue of research to prioritize?

Value Proposition Approach: Slow down, take a critical look at the potential public health value of a Booster Dose
Results I

A significant portion of the “waning” would be “unfixable” by NRRV as it is due to age-related accumulation of naturally protected controls.

Magnitude of natural protection estimated by looking at VE in efficacy trial controls who had experienced symptomatic RV episodes (Rogawski JID 2018)

<table>
<thead>
<tr>
<th>Study</th>
<th>Waning: Percent decrease between 1st and 2nd year efficacies</th>
<th>How much higher 2nd year efficacy should be (based on symptomatic RV)</th>
<th>Percentage of “waning” that is artefactual* (Hausdorff calculations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madhi</td>
<td>36.9%</td>
<td>5.8%</td>
<td>16%</td>
</tr>
<tr>
<td>Armah &amp; Tapia</td>
<td>35.1%</td>
<td>10%</td>
<td>28%</td>
</tr>
<tr>
<td>Colgate</td>
<td>42.2%</td>
<td>15.5%</td>
<td>37%</td>
</tr>
<tr>
<td>Armah &amp; Sow</td>
<td>23.7%</td>
<td>14.8%</td>
<td>62%</td>
</tr>
<tr>
<td>Cunliffe &amp; Madhi</td>
<td>31.8%</td>
<td>18%</td>
<td>57%</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>33.9%</strong></td>
<td><strong>12.8%</strong></td>
<td><strong>40%</strong></td>
</tr>
</tbody>
</table>

This percentage of artefactual waning likely underestimated, since (unmeasured) sub-clinical RV infection in controls further contributes to natural protection (Lopman JID 2018).
Results II
A highly effective NRRV booster dose at 9 or 12 mos. is too late for major incremental impact on RV mortality

(Model-based analysis by Burnett Vaccine 2017)

Estimates based on: RV mortality by age, plus assumption of 65% & 45% VE for LORV in 1st & 2nd yrs of life

NOTE: assumes all reported waning is due to immunological failure (i.e., not artefactual)

Other Assumptions
Waning can occur in abrupt step-wise fashion [highly unlikely], linearly, or logarithmically

In best case scenario, boosting increases VE by 50%

<table>
<thead>
<tr>
<th>Region</th>
<th>Linear waning</th>
<th>Logarithmic waning</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths occurring in ABSENCE of boost despite high oral RV coverage</td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>62,466</td>
<td>62,382</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>28,507</td>
<td>27,838</td>
</tr>
<tr>
<td></td>
<td>Deaths preventable by 12 mo. booster increasing VE by 50% (%)</td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>2,658 (4.3%)</td>
<td>4,035 (6.5%)</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>2,153 (7.6%)</td>
<td>3,269 (11.7%)</td>
</tr>
</tbody>
</table>
A boost at 9 and/or 12 months is not likely to make a major impact because

1. a significant portion of “waning” appears artefactual

2. even a highly effective NRRV dose at 9 months would come too late to make a major impact, at least on RV mortality

Similar VE and epidemiological considerations would also greatly attenuate magnitude of impact on serious RV disease
A few conclusions

- The NRRV Value Proposition is already helping us to garner insights on where there is—and isn't—significant public health value for an effective next generation rotavirus vaccine.

- The NRRV VP is most useful if it is
  - A critical, rather than promotional, assessment
  - Has outputs that are disseminated as they are generated to help inform strategy, clinical trial design, vaccine development rather than bunched together years later

- Tangible outputs include
  - Presentations at international meetings
  - Peer-reviewed publications
  - A summary report
Variety of expertise utilized to develop NRRV Value Proposition

- **PATH**
  - Overall guidance; use case scenario development; cost-effectiveness analyses; vaccine stakeholder and user interviews; project management

- **London School of Hygiene and Tropical Medicine**
  - Contribute to use case scenario development and undertake impact and cost-effectiveness modeling

- **Linksbridge SPC**
  - Contribute to use case scenario development, demand forecasting, market analytics and ensuring alignment between feasibility and acceptability research and market analysis needs; technical content and perspective, market analysis in final report

- **Vaccine Developer**
  - Awareness of and input into Value Proposition

- **In-country partners**
  - Conducting some of the stakeholder surveys & interviews

Plus potentially: WHO (TSE), others?
Collaborators/Funding

- Commercial Manufacturing Partner: SK Bioscience, Seoul, South Korea

- Serological Analysis: Cincinnati Children’s Hospital Medical Center: Serology

- Biochemical/Biophysical Characterization of Vaccine Antigens: Kansas University

- Phase I/II Clinical trials:
  - Johns Hopkins University, Baltimore MD USA
  - South African Clinical Research Centers:
    - RMPRU, Soweto / Shandukani, Johannesburg / FAMCRU, Tigerburg

- Phase III Clinical trial:
  - Africa:
    - CIDRZ, Lusaka, Zambia / Dodowa Health Research Center, Ghana / MLW, Blantyre, Malawi
  - India:
    - CHRD-SAS, New Dehli / KEM Hospital Research Centre, Pune / NICED, Kolkata

Funding Provided by Bill and Melinda Foundation