Health Advances' Insights:
SI Technology (formerly called "Core Shell")

- Single Injection (SI) technology has multiple applications and potential for huge impact
- Prioritization according to technical fit and unmet clinical need is essential to de-risked development – 50 vaccines were screened
- Rabies is the best first application and model drug for building out the technology platform
  - Strong technical fit and unmet need in low-and-middle-income-countries (LMICs)
  - Convert the lab scale process into commercially viable process with rabies before moving to more technically challenging, larger impact applications
- WHO Pre-Qualification helps make vaccines accessible in LMICs
  - Requires regulatory approval in US, Europe, India or other WHO designated countries

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Disclaimer

- The following deck was an independent analysis conducted by Health Advances on the potential applications of the single injection (SI) technology in 2018 and may not represent the current views of Particles for Humanity
  - Refer to the SI Development Plan for details regarding our team and timeline
- Health Advances work
  1. Examines burden of disease/ potential for impact, clinical need, value propositions, and technical fit with the technology for 50 vaccines that were screened
  2. Lays out the development and regulatory pathway for applications

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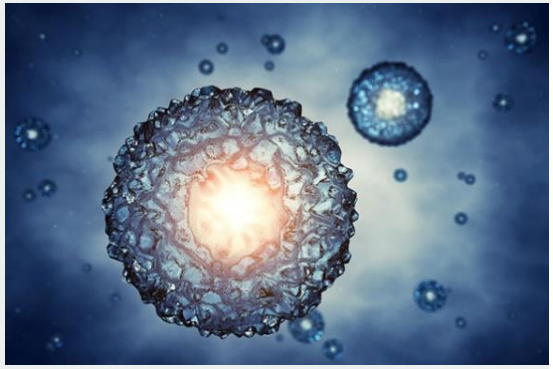
Strategy Consultants for the Healthcare Industry



Health Advances LLC
BOSTON | SAN FRANCISCO | ZUG
www.healthadvances.com

Presented to

Particles for Humanity

November 20, 2018

Background & Objectives

- The Gates Foundation is interested in funding innovative vaccine technology platforms for the developing world.
- Drs. Robert Langer and Ana Jaklenec have received grants from the Gates Foundation to develop drug delivery platform technology that can be used to accomplish the goal of improving vaccine delivery in the target populations.
  - The technology is being developed as a vaccine delivery platform that can deliver a multi-dose vaccine in a single injection, thus eliminating the need for patients to remember to obtain a second or subsequent booster shots, and thereby improving the vaccine coverage of the targeted populations.
- Health Advances supported Particles for Humanity – the start-up company developing this technology – in screening and prioritizing various applications for this platform technology.

Project Methodology

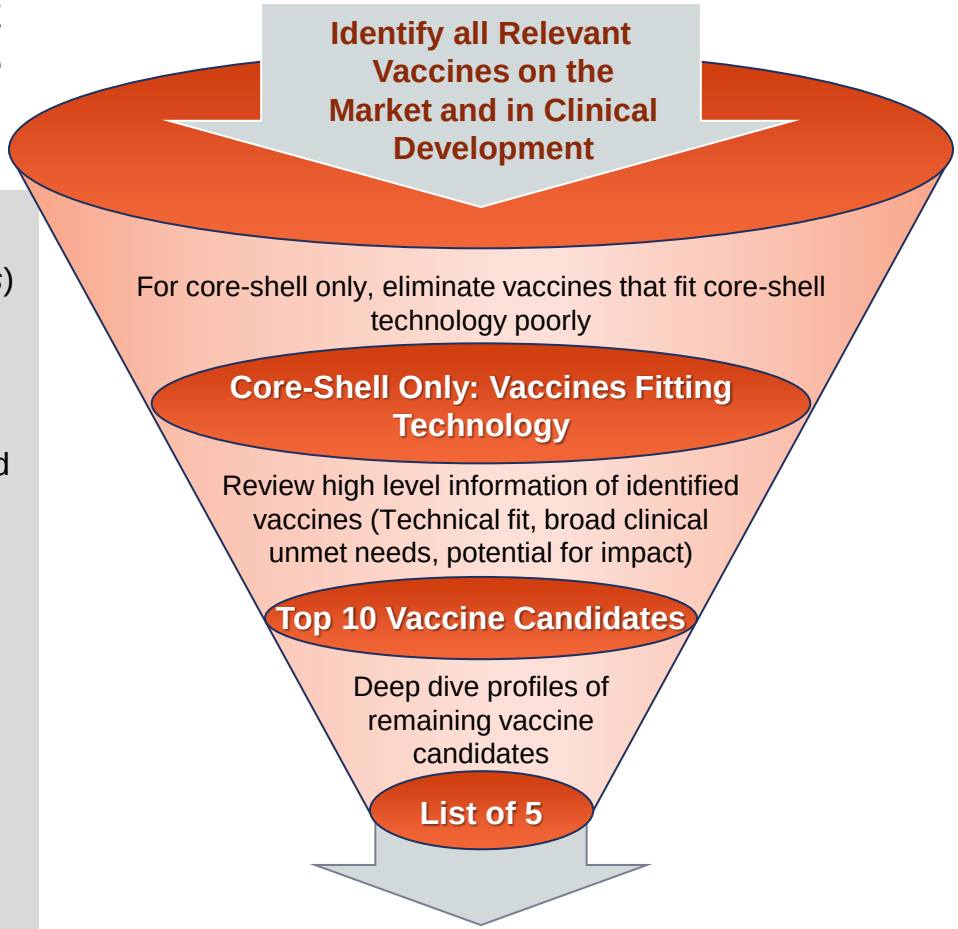
Health Advances conducted a sequential screening and prioritization assessment of various vaccines on the market and in development to help identify the vaccines that could provide both technical and clinical value demonstrations for the two technologies.

Key Criteria

(*Applied throughout the screening and prioritization process*)

- Technical fit
  - Exclude live vaccines, single shot regimens, oral/ intranasal ROAs
  - Other technical feasibility criteria: mass of vaccine and adjuvants, valency, pH and temperature stability
  - Ability of core-shell technology to address: overlap of vaccine regimen with normal vaccination schedules
- Clinical unmet need and potential impact
  - Global deaths due to disease
  - Disease contagiousness and deadliness
  - Compliance with vaccine regimen and impact of poor compliance
- Development path
  - Key geographies for development
  - Ease, timing, and cost of trials

Overview of Screening and Prioritization Process

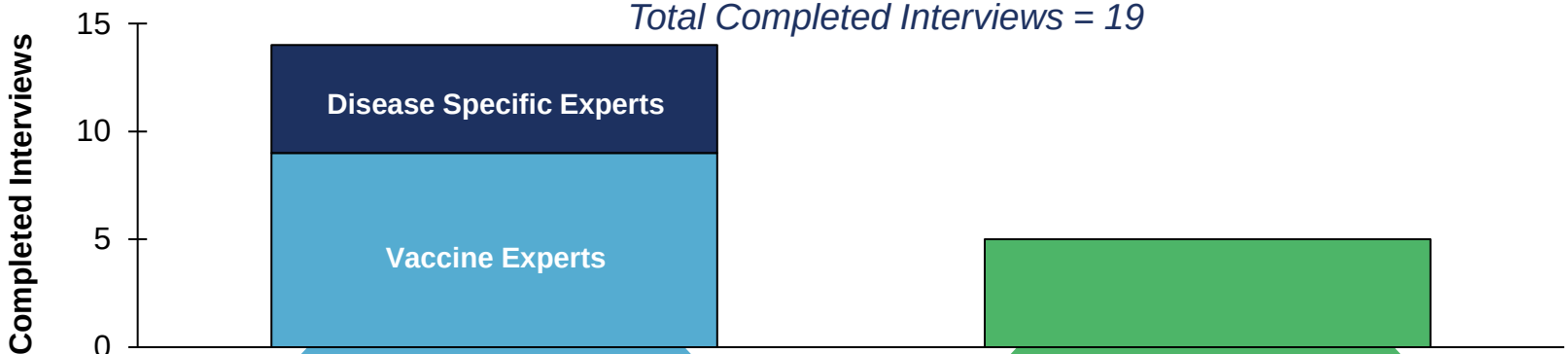


Primary Research Interviewees

In addition to extensive secondary research, Health Advances completed fourteen interviews with external vaccine experts, four of whom were experts in the prioritized diseases, plus four interviews with stakeholders at the Gates Foundation.

Health Advances Primary Research Program

Total Completed Interviews = 19



Example Institutions*

amp, AERAS, SANOFI, iavi International AIDS Vaccine Initiative, Middlebury, gsk, Gavi The Vaccine Alliance, NOVARTIS

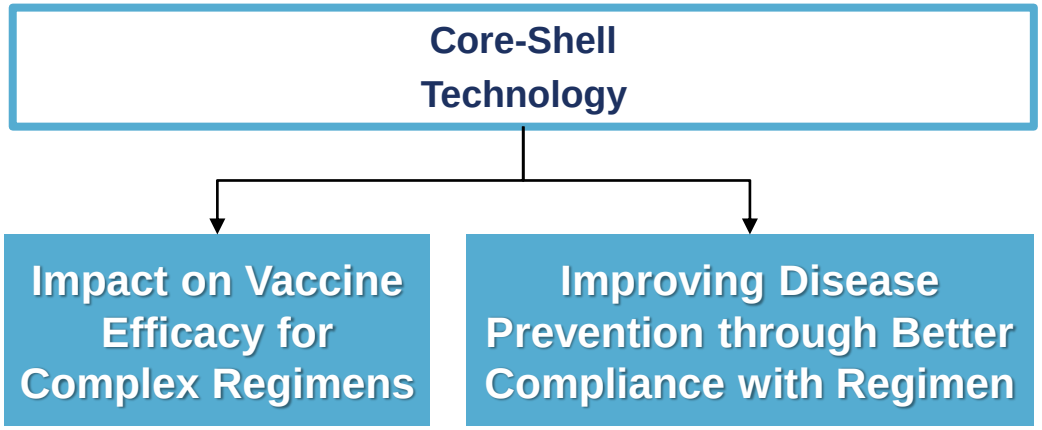
Name	Title
Shanda Boyle	Program Officer, Polio Program
Matt Hanson	Sr. Program Officer, Vaccine Delivery
Orin Levine	Director, Vaccine Delivery
Anita Zaidi	Director, Vaccine Development, Surveillance, and Enteric and Diarrheal Diseases programs and co-director, Maternal, Newborn & Child Health Discovery & Tools program
Peter Dull	Deputy Director, Integrated Clinical Vaccine Development

* Example institutions includes both current and previous institutions of interviewees.

Source: Health Advances interviews and analysis.

Value Propositions

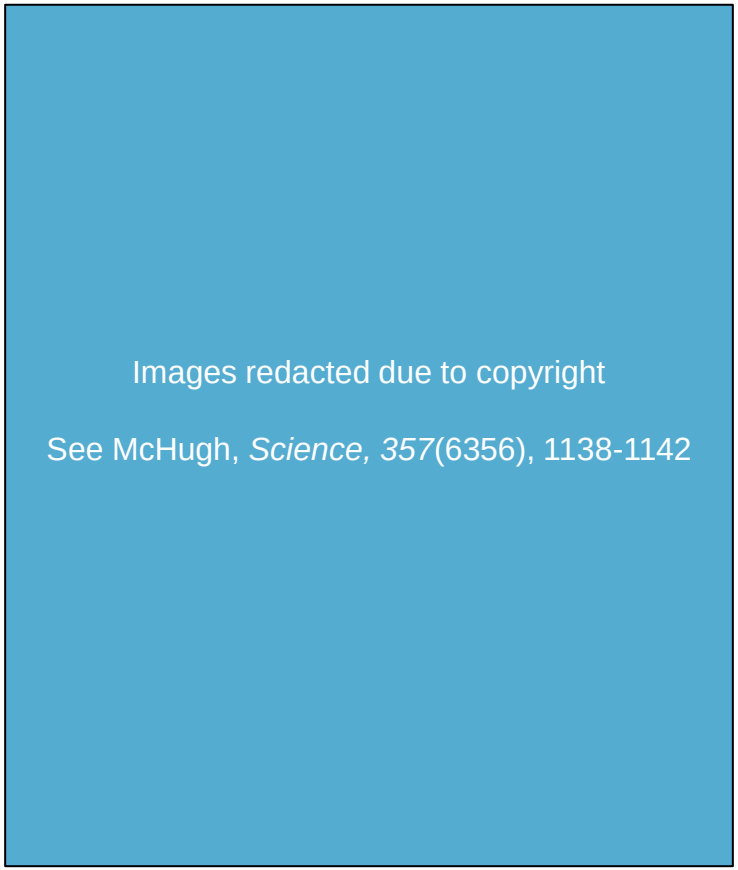
Technology Value Propositions



Source: Health Advances interviews and analysis.

Core-Shell Technology Overview

The core-shell technology encapsulates vaccine within engineered particles whose degradation kinetics can be manipulated to mimic multidose vaccine schedules.



Commentary

- Single injection of PLGA micromolded particles encapsulating vaccine
- Injection includes different particles to allow for different release times
- Using different dyes, the release kinetics can be visualized
- In this example, five different release time points are shown using different PLGA compositions and acid/ester caps
- In a rat model using inactivated polio vaccine, a single injection using the core-shell technology produced similar antibody titer levels to three bolus injections

Note: PLGA = poly(lactic-co-glycolic acid)
Source: Health Advances interviews and analysis, Langer Lab.

Vaccine Potential **Technical Fit & Clinical Impact** Summary

- Rabies and Meningococcus have significant unmet needs that could be addressed by the core-shell technology, particularly with respect to improving compliance with the full vaccine regimen to ensure higher protection levels.
- HIV/AIDS has the potential to be the most impactful application due to the potential for facilitating improved efficacy.

Application Prioritization	Technical Fit	Clinical Need	Value Proposition(s)
HIV/AIDS	+ Most pipeline vaccines are subunit-based and could be formulated into core-shell + Complex antigens and dosing schedule are thought to be necessary - Antigens and adjuvants are still in flux and may be challenging to reformulate	+ Huge global health burden with no approved vaccines	• Enable development and simplification of complex dosing regimens to achieve improved efficacy in HIV immunization • HIV vaccine development may also be a proof of concept for other development-stage vaccines that have been challenging due to complex dosing regimens
Rabies	+ Small mass and no adjuvants used + Can be lyophilized + Short-term dosing regimen makes stability in body less of an issue	+ Poor compliance with full regimen leads to still significant number of deaths in developing countries	• Improve compliance and reduce rabies-related fatality especially in the emerging world where some patients have a difficulty in accessing a full regimen of post-prophylaxis shots
Meningo-coccus	+ Small mass and no adjuvants used + Can be lyophilized	+ Significant unmet need for affordable C, W, Y, and X vaccines for meningitis belt - Limited need outside of Africa	• Enable more serotype vaccines to be delivered in one shot, improving compliance and reducing deaths from meningococcus
HPV (9-valent)	- 9-valent vaccine is heavy while lighter bivalent may not be used in the near future - Adjuvants could be omitted, but will cause regulatory challenges	+ Low compliance and coverage in developing world (and worldwide) + Target poorly compliant population - Single-shot trials showing modest loss of efficacy that could be an acceptable trade-off with cost	• Enhance compliance with simplified dosing schedule, and improve seroconversion rates by assuring full regimen is received • Over time, lower deaths due to HPV-meditated cancers, mainly cervical • Facilitate HPV vaccine campaigns

Note: Applications listed from most to least impactful. Assessment of impact assumes technical success.
Source: Health Advances interviews and analysis.

Prioritized Vaccine **Time-to-Impact** Summary

- Rabies would likely be fastest because it is less technically challenging and readily available.

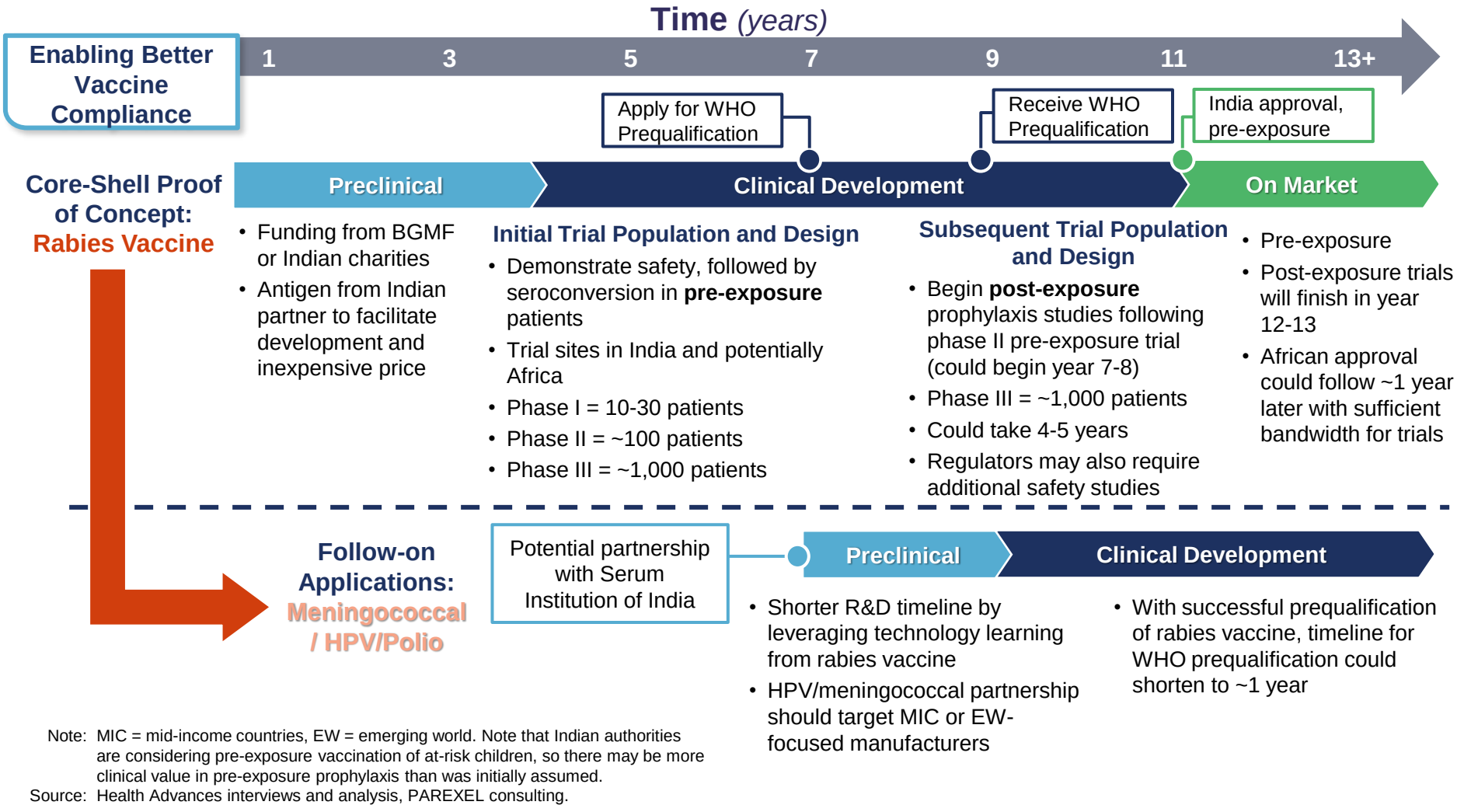
Application Prioritization	Development Timeframe	Partner	
		Potential Novel Vaccine Delivery Tech. Funders	Antigen Suppliers/Partners
Rabies	• Pre-exposure: ~11 years (~4 yrs preclinical, ~7 yrs development/ regulatory) • Post-exposure ~12-13 years • Slightly longer than MenAfriVac timeline (6 years development/ regulatory)	• BMGF • India-focused NGOs • Global Alliance for Rabies Control • Mission Rabies • End Rabies Now Campaign	• Multiple Indian manufacturers • Could also consider multinationals
Meningo-coccus	• ~10 years (~4 yrs preclinical, ~6 yrs development/regulatory) • However, development clock could not start until new conjugate meningococcal vaccines are developed, start of timeline unclear • Timeline once begun similar to MenAfriVac	• BMGF • GAVI • PATH	• Serum Institute of India (manufactures MenAfriVac)
HPV (9-valent)	• ~13 years (~5 yrs preclinical, ~8 yrs development/regulatory) • Longer due to expected technical challenges with larger vaccine, which will likely be necessary in the future • If Merck is uninterested, may need to wait for other 9-valent vaccines to progress	• BMGF • GAVI	• Indian and Chinese manufacturers have vaccines in development • Merck
HIV/AIDS	• ~18 years to market in developing world (~6 yrs research/ preclinical, ~12 yrs development/regulatory) • Assumes developed world would host first trials • Assumes partner demonstrates some efficacy with non-core-shell vaccine prior to development – Timelines would be longer if starting from scratch	• BMGF • NIH funds, either via vaccine developer or procured directly	• Partner interested in co-developing HIV core-shell vaccine from amongst those with HIV vaccines currently in development

Note: Assumes trials start as soon as possible. If considering a follow-on indication, preclinical timeline may shorten due to technology advancement. Applications are listed from fastest to slowest.

Source: Health Advances interviews and analysis.

Roadmap for Improving Compliance in Marketed Vaccines

Using rabies as a proof-of-concept for the core-shell technology could lead to market authorization in ~11 years for pre-exposure prophylaxis and 12-13 years for post-exposure. Follow-on applications could be considered once PfH applies for WHO prequalification.

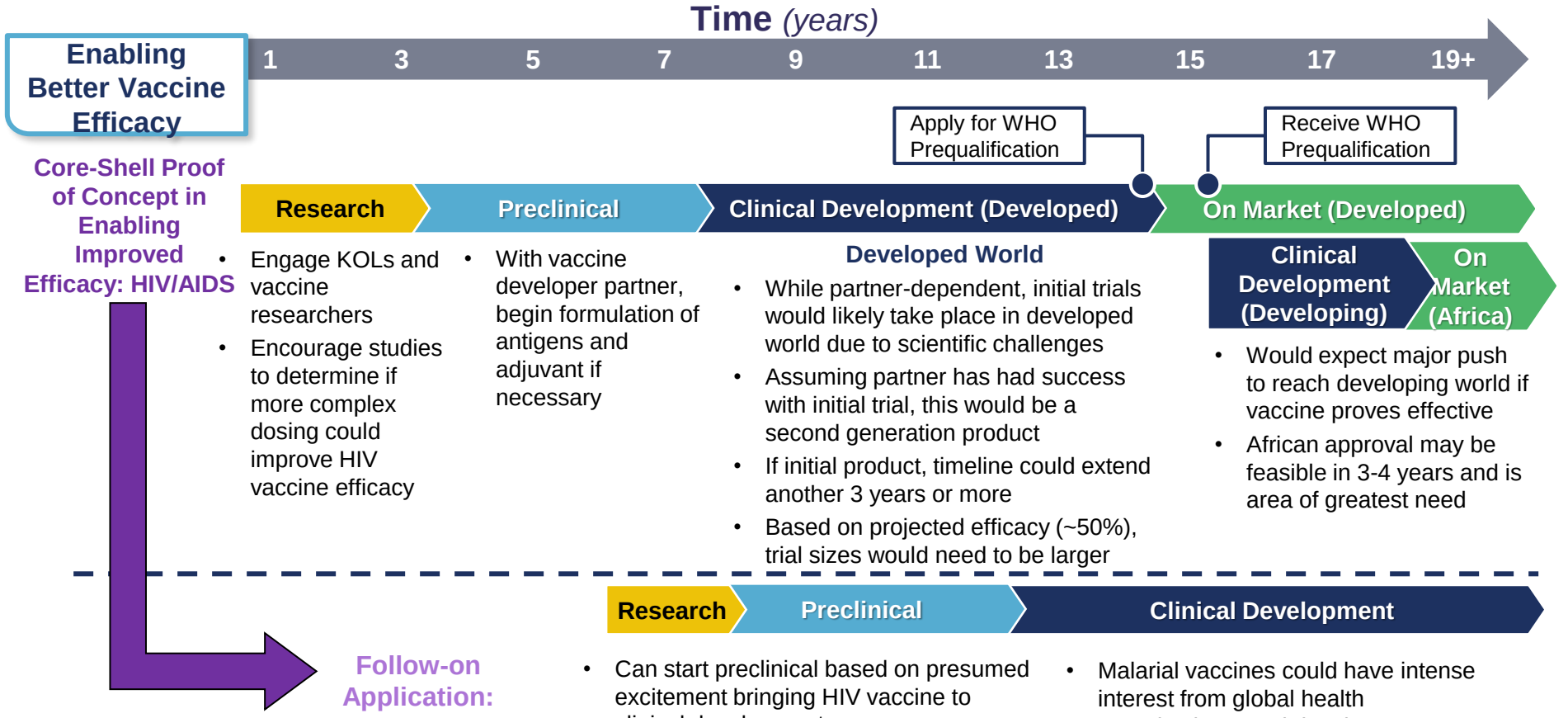


Note: MIC = mid-income countries, EW = emerging world. Note that Indian authorities are considering pre-exposure vaccination of at-risk children, so there may be more clinical value in pre-exposure prophylaxis than was initially assumed.

Source: Health Advances interviews and analysis, PAREXEL consulting.

Roadmap for Improving Efficacy of Pipeline Vaccines

To improve efficacy in HIV, at minimum another ~4 years of development would be expected to reach the developed world market, assuming a partner vaccine proves effective. Therefore, the developing world market approval would lag rabies market launch by ~8 years.



Note: MIC = mid-income countries, EW = emerging world, KOL = key opinion leader.
Source: Health Advances interviews and analysis.

Disease Profile (1 of 2)

Rabies virus is fatal if untreated, causing ~59,000 deaths annually. Most deaths occur in Asia and Africa where there is limited access to the vaccine.

Rabies Background

Pathogen Description	• Rod-shaped, single-stranded, negative-sense, unsegmented, enveloped RNA virus • The virus genome encodes five proteins • After infection, rabies virus may enter the peripheral nervous system – Typically migrates to the brain or may replicate in muscle tissue, prior to central nervous system invasion and replication – Then spreads to numerous other organs
Transmission	• 99% of cases caused by dogs in emerging countries • In the US, transmission is typically from other wild animals – bats, raccoons, skunks, etc.
Prevalence	• 59,000 human deaths annually in over 150 countries • 95% of cases occur in Asia/Africa
Fatality	• Untreated, the fatality rate is 99.9%
Contagiousness	• R_0 ~1.6

Symptoms and Treatment

Disease Progression	• Five general stages: incubation, prodrome, acute neurologic period, coma, and death • Virus infects the CNS, causing anxiety, confusion, convulsions, delirium and paralysis
Vaccines	• 3 monovalent vaccines available – One vaccine (Rabivax) only available in India • Used for pre-exposure and post-exposure prophylaxis
Therapies	• No specific anti-rabies agents are useful once clinical signs or symptoms develop • Post-exposure vaccine will abort the infection, if given shortly after animal bite, but there is no cure for clinical disease

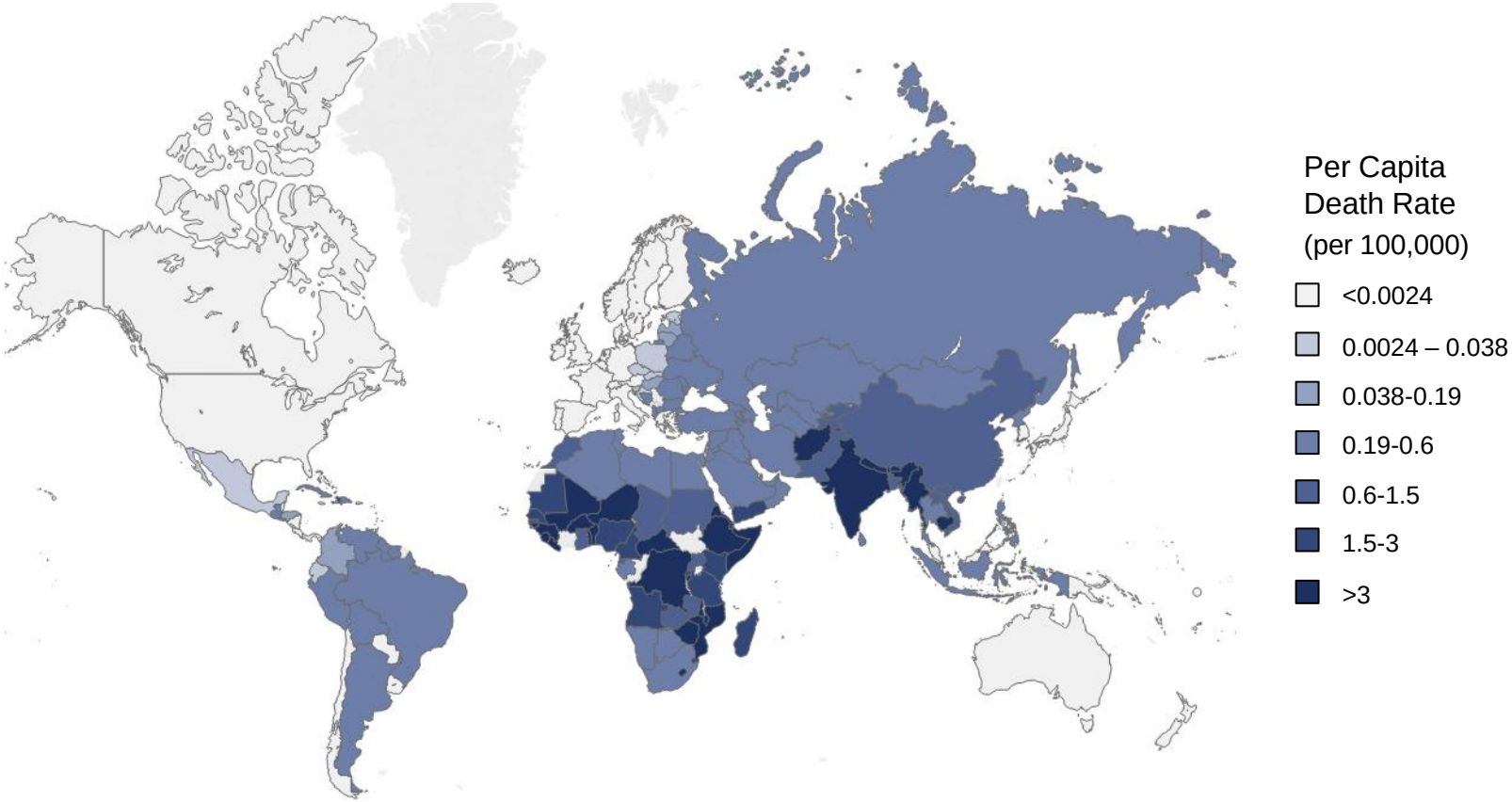
Source: Health Advances interviews and analysis, WHO, CDC, Medical Microbiology.

Disease Profile (2 of 2)

99% of rabies cases occur in Asia and Africa, with the highest per-capita deaths occurring in India, Afghanistan, Bangladesh, and a number of countries in sub-Saharan Africa.

Global Deaths from Dog-transmitted Rabies

Per Capita Death Rates, 2017



Source: Health Advances interviews and analysis, WHO.

Current Immunization Paradigm

The current rabies vaccines can be given prophylactically (3 doses) or therapeutically (4-5 doses). It is a highly effective vaccine if the full series is completed, but compliance with the full post-exposure regimen is poor in developing countries.

	Developed World	Emerging World
Recommendation	• CDC pre-exposure vaccination: people at high risk of exposure to rabies – 3 doses: at day 0, 7, and day 21 or 28 • CDC post-exposure vaccination: anyone who has been bitten by a rabid animal – 4 doses: day 0, 3, 7, and 14 days, in addition to immunoglobulin with the first dose	• WHO pre-exposure vaccination: those at high risk of exposure to rabies – 3 doses: day 0, 7, and day 21 or 28 • WHO post-exposure vaccination: anyone who has been bitten by a rabid animal – 5 doses: day 0, 3, 7, 14 and 28
Vaccine Used	• RabAvert and ImoVax are used interchangeably	• RabAvert and Rabivax supplied by GAVI/UNICEF – Rabivax supplied only in India
Compliance With Full Regimen	• ~85-90%	• ~60% – In general, patients are fairly compliant with the first 3 doses – Patients begin to stop returning upon 4th dose, and there is a dramatic drop off for the 5th
Immunization Rate	• RabAvert – Pre-exposure: when administered used in the recommended schedule, all subjects attain a protective titer – Post-exposure: when used in the recommended post-exposure WHO program protective titers of neutralizing antibody (>0.5 IU/mL) in 158/160 patients within 14 days and in 215/216 patients by day 28 • ImoVax – Pre-exposure: high titer antibody responses have been demonstrated in trials; seroconversion was often obtained with only one dose – Post-exposure: of 511 persons bitten by proven rabid animals and so treated, none developed rabies • Rabivax – Pre-exposure: in healthy volunteers all subjects attained a protective titer – Post-exposure: of 150 cases of suspected bites, 1 year later 84% of them had adequate rabies virus neutralizing antibody	

"There is no available data on the efficacy of a shortened course. This type of data is very difficult to obtain – we typically don't have easy access to patients, and we're not always sure if a patient was actually bitten by a rabid animal. Nevertheless, in most case reports, we see that an incomplete vaccine series is one of the culprits." – Rabies Vaccine KOL

Note: In 2010, the CDC shortened the post-exposure regimen to 4 doses to help prevent shortages and to cut down on side effects.
Source: Health Advances interviews and analysis, CDC, WHO, GAVI, FDA, Bariya J Immun 2014, Sullivan Annals of Emergency Medicine 2010, Sudarshan Hum Vaccin 2008.

Technical Characteristics of Current Vaccines

All rabies vaccines have a relatively light mass and no adjuvants, so they represent a good technical fit.

Feasibility

Key Products	RabAvert	ImoVax	Rabivax (India only)
Manufacturer	• GSK	• Sanofi	• Serum Institute of India
Valency	• Monovalent	• Monovalent	• Monovalent
Dosage	• Pre-exposure: day 0, 7, and day 21 or 28 • Post-exposure: day 0 (in addition to immune globulin), 3, 7, 14 and 28		
Active Ingredient	• 2.5 IU (~1.8 mcg)	• 2.5 IU (~1.8 mcg)	• 2.5 IU (~1.8 mcg)
Total Mass of Core Shell Vaccine	• International: 10 IU/~7.2 mcg (4 doses) • US:7.5 IU/~5.4 mcg (3 doses)	• International: 10 IU/~7.2 mcg (4 doses) • US:7.5 IU/~5.4 mcg (3 doses)	• International: 10 IU/~7.2 mcg (4 doses) • US:7.5 IU/~5.4 mcg (3 doses)
Lyophilized Form	• RabAvert and ImoVax are currently prepared in a lyophilized formulation • While Rabivax is not lyophiized, it is believed that there should be little difficulty preparing a lyophilized formulation of the rabies vaccine		
Allergenic Components	• Neomycin is present at ≤10 mcg, chlortetracycline at ≤200 ng, and amphotericin B at ≤20 ng per dose	• Contains <100 mg human albumin, <150 mcg neomycin sulfate and 20 mcg of phenol red indicator	• Thimerosal 0.01%

Dosing Limitations

Frequency of Dosing	• All doses are given within one month and could easily be condensed into a single core shell • Only challenge is ensuring the correct polymers to enable release at each specific time point

- The post-exposure prophylaxis regimen is challenging, as it consists of 5 doses within 28 days
  - *"The rabies vaccine is very efficacious, but for some people in rural China or India, it's not possible to go to the hospital five days in a month." – Rabies Vaccine KOL*

Note: No adjuvants are included in the rabies vaccine.
Source: Health Advances interviews and analysis, FDA, company websites, Ferguson J. Gen. Virol 1982.

Opportunities for Core-Shell

Rabies

Drivers and Barriers

Technical Fit	Clinical Unmet Needs
+Small mass +No adjuvants used +Complex regimen that could be simplified with core-shell	+Rabies is fatal once clinical symptoms develop +Poor compliance in emerging countries with full series due to difficulty accessing healthcare, which leads to deaths due to rabies + ~59,000 deaths globally
Development Path	
+Could follow similar strategy to MenAfriVac (Indian/African approval in 6-7 years)	+Initial studies should be done in pre-exposure prophylaxis, first step towards getting eventual post-exposure approval +Pre-exposure trials should be fast - Efficacy trials may be more difficult to recruit for life-saving treatment

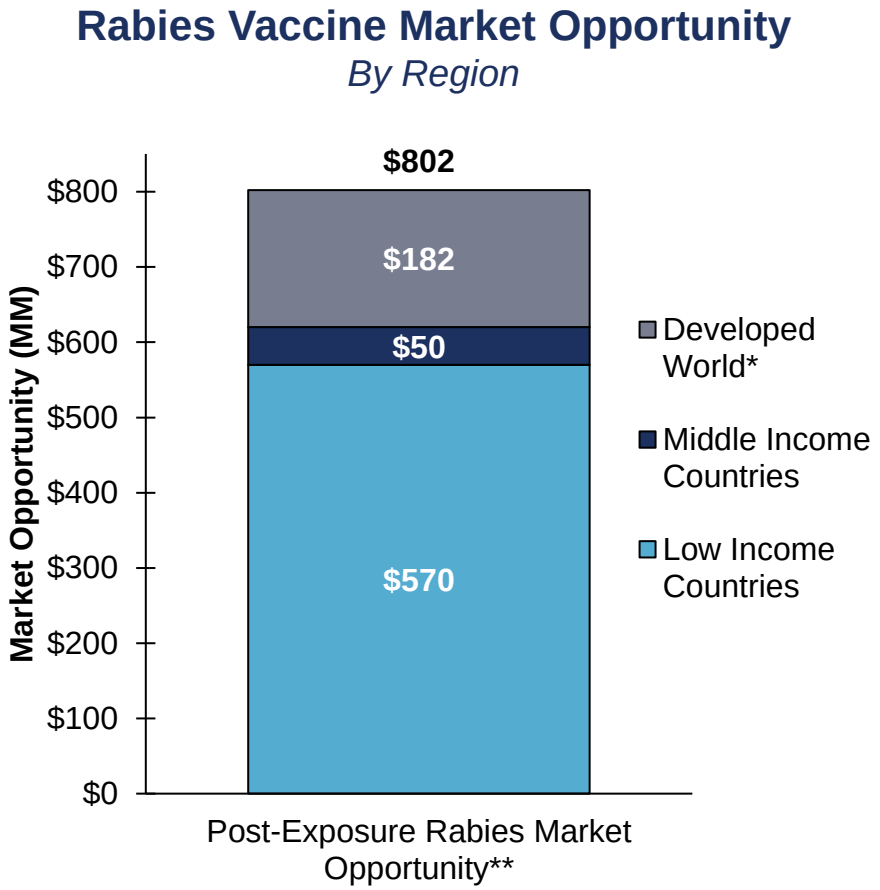
Value Proposition(s)	• Improve compliance with post-exposure vaccination with the goal of saving more individuals treated with the vaccines following exposure – Post-exposure rabies vaccination has compliance problems in emerging countries where patients may not be able to complete the full 5-shot vaccination series due to limited access to health care – Indian expert noted that India is considering pre-exposure vaccination of at-risk populations, so impact for pre-exposure labels could be higher than originally anticipated
Role in Platform Technology Development	• Rabies vaccine could serve as a proof of concept for the technology as it offers: – Relatively fast timeline to approval due to strong technical fit – Potential to demonstrate a clinically meaningful impact via improved compliance
Next Steps	• Obtain access to antigens for rabies vaccine – Both Indian (Serum Institute of India) and global partners (GSK, Sanofi) exist • While working to reformulate the vaccine into the core-shell technology, refine the clinical path to reach the market in target geographies (India, China, Africa)

Note: Drivers are denoted with a green plus sign while barriers are denoted with a red minus sign.
Source: Health Advances interviews and analysis.

Rabies Market Opportunity

Emerging markets represent a more significant opportunity compared to the US and other developed countries, due to the volume of vaccines administered.

	US	Middle Income	Low Income
Vaccination Target Population	• Target population consists of individuals **at risk of being exposed** to rabies or those who have **been exposed to rabies**		
People Immunized per Year	• ~50,000	• WHO reports 15MM • Used death rates to assume a 5/95 split between middle/low	
Units	• 50,000 x 4 doses = 200,000	• 750,000 x 5 doses = 3.75MM	• 14.25MM x 5 doses = 71MM
Price per Dose	• $400	• $13 (WHO data)	• $8 (UNICEF price)
Market Size (USD)	• $80MM	• $50MM	• $570MM



* Health Advances used the 2.27 scale up factor to scale up from the US market to the entire developed world.

** While pre-exposure vaccination represents additional market opportunity, there is less of a rationale for development and no clinical need as there is in post-exposure prophylaxis.

Source: Health Advances interviews and analysis, CDC, GAVI, UNICEF.

Disease Profile (1 of 2)

Meningo-coccus

Meningococcus bacteria cause highly fatal diseases such as meningitis, but such diseases are vaccine- preventable.

Neisseria meningitidis (meningococcus)

Pathogen Description	• Meningococcus causes multiple diseases such as meningitis, meningococcemia, and sepsis • Meningococcal diseases have a high mortality rate if untreated but are vaccine preventable • Classified according to the polysaccharide capsules: A, B, C, W135, X and Y account for most disease cases
Transmission	• N. meningitides is spread through saliva and respiratory secretion during coughing, sneezing, kissing, or sharing a source of water
Prevalence	• Observed worldwide but highest burden of the disease in the meningitis belt of sub-Saharan Africa (30,000 annual reported case)
Fatality	• Global death ~ 90,000 • Fatality ~50% (untreated, overall meningitis)
Contagiousness	• R_0 ~1.3

Meningitis

Diseases	• Meningitis is an acute inflammation that can be caused by virus, bacteria, or other microorganisms • A serious infection of the thin lining that surrounds the brain and spinal cord
Vaccines	• Polysaccharide vaccines used for outbreak in Africa (does not induce herd immunity) • Conjugate vaccines used in prevention and outbreak – longer lasting immunity and prevents carriage – Monovalent (A, C) – Tetravalent ACWY • Protein based vaccine for B
Therapies	• Requires immediate antibiotic treatment (penicillin, ampicillin and ceftriaxone)

Source: Health Advances interviews and analysis, WHO, CDC.

Disease Profile (2 of 2)

The African Meningitis belt region has the highest risk of meningitis epidemic. Most developed countries, including the US, have routine meningitis vaccination programs.

High Epidemic Risk Area for Meningitis

2017

Source: Health Advances interviews and analysis, WHO.

Current Immunization Paradigm

Meningo-coccus

Emerging countries, mainly in the African meningitis belt, have successfully implemented meningitis A vaccination campaigns, but do not have vaccination coverage for other serotypes.

Meningitis Vaccination Paradigm

	Developed World	Emerging World
Recommendation	• CDC recommends meningococcal ACWY vaccination all preteens and teens at 11 to 12 years old with a booster dose at age 16 • CDC recommends serogroup B meningococcal vaccination for age 10 or older at increased risk • ACWY vaccine labels recommend 4 doses for infant vaccination	• WHO recommends that countries with intermediate or high endemic rates* to vaccinate defined risk groups – Choice of vaccine depends on the locally prevalent serogroup(s)
Vaccine Used	• Conjugate ACWY: Menactra and Menveo • B: Bexsero, Trumenba	• Conjugate A: MenAfriVac • Polysaccharide vaccines : A, C, AC, ACW
Vaccine Coverage	• 85.1% (at least received one dose of ACWY)	• 77%-93% (coverage for campaign targets)
Compliance	• Most vaccinated at single dose regimen age	• Emerging countries campaign setting focuses on single dose Men A vaccine
Immunization Rate by Doses Received	• Conjugate multivalent vaccines require a booster for prolonged protection	• Conjugate A single dose has been successful in a campaign setting

* High endemic rate is defined by more than 10 cases per 100,000 population annually and intermediate rate is defined by 2-10 cases per 100,000 population annually.
Note: CDC recommends both serogroup B vaccines (Bexsero, Trumenba) and meningococcal conjugate ACWY vaccines (Menactra and Menveo).
Source: Health Advances interviews and analysis, CDC, WHO.

Introduction of Novel Meningococcal Vaccines in Africa

Meningo-coccus

Future meningitis vaccines for emerging countries will follow the steps MenAfriVac has taken, starting with a single dose mass vaccination campaign.

Meningitis Vaccination Paradigm

Vaccines in Development

- Vaccination has significantly reduced MenA cases, thus the focus is shifting to address other serotypes
- C and Y serotypes are higher priority, W is much less important
- X has no vaccine available

Vaccination Campaign

- Mass vaccination of under 29 population in high risk areas, i.e., meningitis belt countries
- Create herd immunity to severely cut down transmission

Routine Vaccination

- Inclusion of new serotype(s) to the routine immunization programs
- Infants will likely require more than a single dose for desired immunogenicity

- The MenAfriVac rollout will be used as a model for new Meningococcal vaccines
  - "*For any meningitis vaccines, it will start with campaigns targeting adults then will vaccinate infants. MenAfriVac was first used to vaccinate the 1-29 years old population and then targeting infants via routine immunization. So, it will be single dose campaign first, followed by a multidose regimen for infants.*" – *Vaccine Expert*

Source: Health Advances Interviews and analysis.

Technical Characteristics of Current Vaccines

Meningo-coccus

Meningococcus ACWY vaccines have a technical fit with core-shell, and novel monovalent or bivalent vaccines for emerging markets would likely have a similar profile.

Feasibility

Key Products	Menactra	Menveo
Manufacturer	• Sanofi	• Novartis
Valency	• 4 (Meningococcus A, C, W, Y)	• 4 (Meningococcus A, C, W, Y)
Dosage	• 2 doses 3 months apart (9 to 23 months old), age 2 or older single dose, booster at least 4 years after the prior dose	• 4 doses at (2,4,6, and 12 mos), 2 doses 3 months apart from 7 to 23 months old, age 2 or older single dose
Active Ingredients	• ~100 mcg	• ~100 mcg
Total Mass of Core Shell Vaccine	• 100 mcg	• 100mcg - 300 mcg
Adjuvant Mass	• No adjuvant	• No adjuvant
Lyophilized Form	• Not lyophilized	• MenA lyophilized, MenCYW-135 solution
Allergenic Components	• No preservatives, less than 2.66 mcg formaldehyde	• No preservative, less than 0.3 mcg residual formaldehyde

Dosing Limitations

Vaccine Fit with Schedule	• Menactra is not approved for infants; Menveo infant doses are all given within a year but other age group dosing schedules have longer timelines than 12 months

"In Africa, serotypes beyond A is the agenda. The final goal is to cover all serotypes, ABCWYX. Cost is a limiting factor, so the next step could be CW, maybe Y, and we'll pick off the serotypes one by one as vaccines become cheap enough for emerging countries." – Meningococcus Expert

Note: Meningococcus B vaccines are not technically feasible and were deprioritized in Phase 1.
Source: Health Advances interviews and analysis, FDA labels.

Opportunities for Core-Shell

Meningo-coccus

Drivers and Barriers

Technical Fit	Clinical Unmet Needs
+Size of vaccines are in line with core-shell criteria +No adjuvants used in meningococcal vaccines - Initial campaigns may be single shot (as in the case of MenAfriVac) and thus not a regimen that can be improved by core-shell	+Significant need for cheap C, W, Y, and X serotype vaccines for meningitis belt +Due to cost, serotype vaccines may be rolled out separately, leading to a complex multishot regimen that could be simplified via core-shell +~90,000 deaths globally +Given the anticipated rollout of inexpensive univalent or bivalent vaccines, the core-shell technology could help to simplify the regimen for childhood immunization

Development Path		
+Focus on Africa where WHO prequalification will be helpful	+Clear path to market illustrated by MenAfriVac (emerging market serotype A vaccine)	- Vaccines of interest are not on the market yet, and may not reach market if partners fail to develop cost-effective options for emerging markets

Value Proposition(s)	• Improve compliance to facilitate broader serotype coverage and herd immunity • Reduce number of shots for multi-vaccine regimens for meningococcus
Role in Technology Platform Development	• Meningococcal vaccines could be a valuable follow-up to a proof of concept, as once multiple serotypes are launched dosing could become complicated
Next Steps	• Gauge interest from Serum Institute of India (manufacturer of MenAfriVac), and understand timelines for launch of new meningococcal serotype vaccines

Note: Drivers are denoted with a green plus sign while barriers are denoted with a red minus sign.
Source: Health Advances interviews and analysis.

Meningitis Market Opportunity

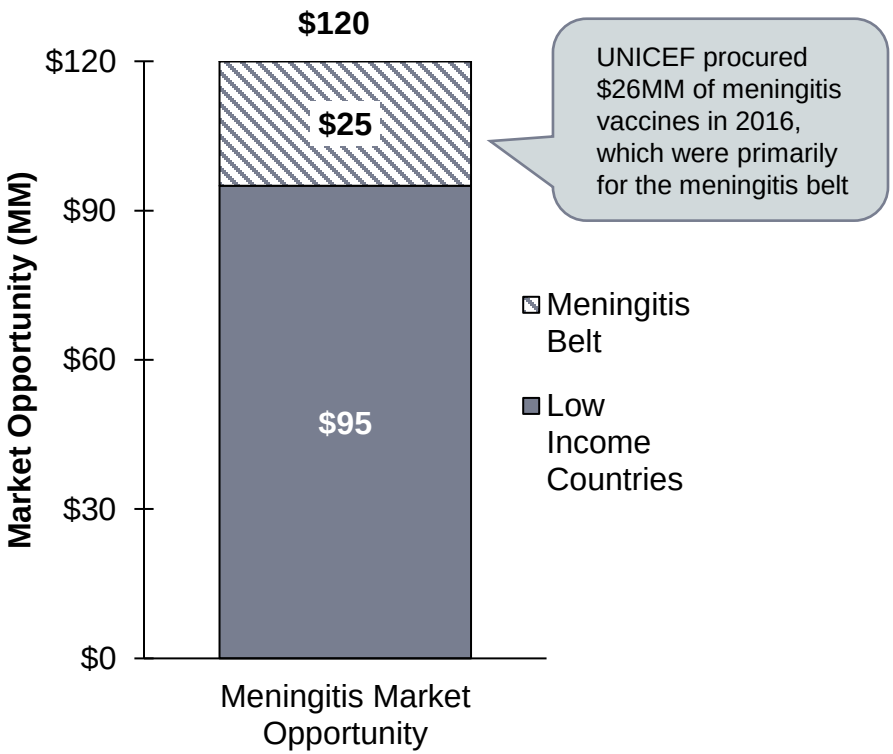
Meningo-coccus

Multivalent vaccines are in development for other serotypes in emerging countries. Routine immunization should be targeted for core shell as the campaigns are likely to use a single dose regimen.

	Low Income Countries (Includes Men. Belt)	Meningitis Belt[1]
Vaccination Target Population	• Infant Routine Immunization	• Infant Routine Immunization
	Age <1 Population[2] • 120MM	Age <1 Population[2] • 25MM
Units	• 120MM x 2 doses = 240MM	• 25MM x 2 doses = 50MM
Price per Dose	• $0.5 (MenAfriVac, MenA only)	• $0.5 (MenAfriVac, MenA only)
Market Size (USD)	• $120MM (per vaccine, multiple vaccines possible over time)	• $25MM (per vaccine, multiple vaccines possible over time)

Meningitis Market Opportunity

By Region, Per Vaccine



[1] The largest burden of meningococcal disease occurs in an area of sub-Saharan Africa known as the meningitis belt, which stretches from Senegal in the west to Ethiopia in the east. It consists of part of or all of Mauritania, Mali, Niger, Chad, Sudan, Eritrea, Ethiopia, South Sudan, Central African Republic, Nigeria, Cameroon, Burkina Faso, Benin, Togo, Ghana, Cote d'Ivoire, Guinea, Senegal, Guinea Bissau, The Gambia, Democratic Republic of Congo, Uganda, and Kenya.

[2] Infant <1 population calculation includes less developed countries population in US Census IDB.

Source: Health Advances interviews and analysis, US Census IDB, CDC, GAVI.

Meningococcus Vaccine Rationale for Core Shell

Meningococcal vaccines should be considered as a follow-on application despite complexity in the vaccination paradigm. Emerging countries typically use a meningitis A-only vaccine due to cost, but there is significant unmet need for vaccines covering the other serotypes.

Current Meningo-coccus A Vaccine Is Single-Shot

- The current meningococcus vaccine in use in GAVI countries covers the A serotype and, as a single-shot vaccine is not a fit for the core-shell technology
  - WHO estimates that menigococcus A is responsible for 80-85% of case of meningococcal epidemics in Africa
- Single-shot vaccines are in development from Chinese manufacturers

Significant Unmet Need Remains in Other Serotypes

- However, there is still significant unmet need in remaining serotypes relevant to the developed world (A/C/W/Y) vaccines
  - Use of the A/C/W/Y vaccines is currently limited by their cost, not need
  - GAVI maintains a stockpile of these vaccines for emergency use in Africa
  - As part of its ongoing vaccine investment strategy (for 2021-2025), GAVI is also considering supporting multivalent meningococcal vaccine use in the coming years

Current A/C/W/Y Vaccines Would Be a Good Fit

- A/C/W/Y vaccines appear to be a strong technical fit with the core-shell technology
  - Multivalent meningococcal vaccines are recommended for administration at 1-2 years of age, and are not used during infant vaccination due to poor efficacy in infants
  - The vaccine's mass is low, which would make loading the core-shell easier

Note: While meningococcal vaccines are administered in the developed world, they are frequently used as a single-dose
Source: Health Advances interviews and analysis.

Disease Profile (1 of 2)

Human Papillomavirus is the most common viral infection of the reproductive tract and causes a range of cancers.

Human Papillomavirus

Pathogen Description	• HPV is the most common sexually transmitted infection globally • HPV can be passed without any signs or symptoms and cancers often takes several years to develop after infection • Over 170 genotypes are known and 13 genotypes associated with high risk of cancers
Transmission	• HPV is commonly transmitted by having vaginal, anal, or oral sex
Prevalence	• Global prevalence ~11.7% (ranges 1.6-41.9%) • Highest in sub-Saharan Africa (~24%)
Fatality	• Global death ~ 270,000 • Fatality ~1%
Contagiousness	• R_0 ~1.0

HPV Diseases

Diseases	• Cervical cancer is the most common HPV-related cancer • HPV can cause vaginal, vulvar, penile, oropharyngeal and anal cancers • HPV can cause genital warts
Vaccines	• 3 prophylactic vaccines available • Bivalent, quadrivalent and nonavalent vaccines
Therapies	• No virus-specific treatment for HPV infection • Screening of pre-cancerous cervical lesions is highly effective in preventing progression to cervical cancer

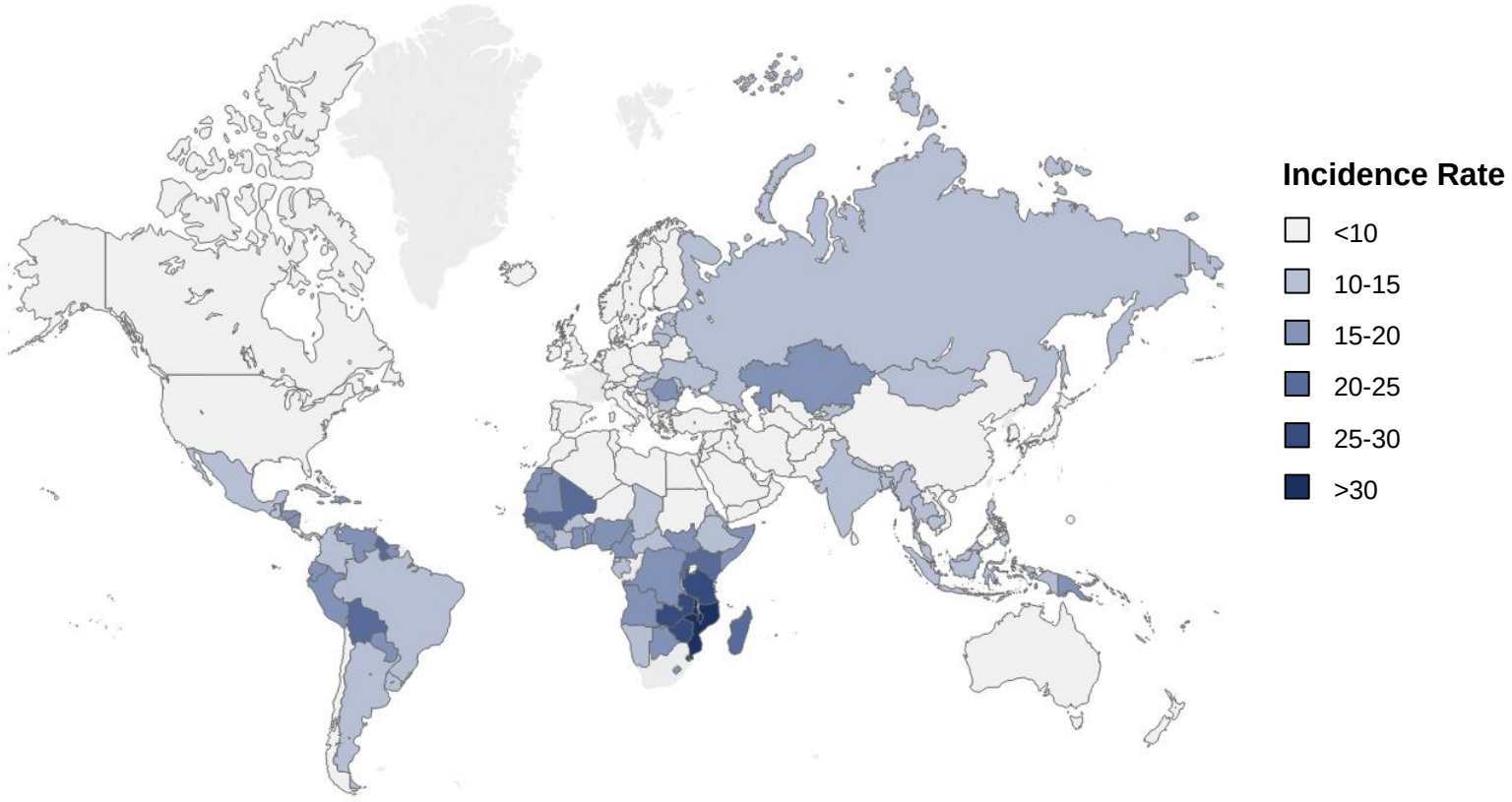
Note: HPV genotypes with high risk of cancers are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66.
Source: Health Advances interviews and analysis, WHO, CDC.

Disease Profile (2 of 2)

HPV is the most common viral infection of the reproductive tract across geographies. In particular, the Western, Central and Eastern Regions of Africa, and parts of South America have the highest incidence rates.

Global Incidence of HPV-related Cervical Cancers

Age standardized incidence rates (per 100,000)



Source: Health Advances interviews and analysis, de Martel 2017 Int Agency Res Cancer.

Current Immunization Paradigm

The developed world recommends vaccination of both female and male adolescent/young adults while emerging countries focus on female vaccination.

HPV Vaccination Paradigm

	Developed World	Emerging World
Recommendation	• CDC recommends vaccination of both male and female adolescent/young adults – 9-14 year-olds receive two dose of HPV vaccine at least 6 months apart – Teens/young adults who started the series later at age 15-26 years need 3 doses	• WHO recommends HPV vaccination of girls aged 9-14 – First dose under 15 years to follow 2 dose schedule (0,6 mos) – First dose older than 15 years to follow 3 dose schedule (0,2,6 mos)
Vaccine Used	• Gardasil 9 (nonavalent) is only HPV vaccine available in the US since 2016Q2 • Europe uses bivalent and quadrivalent vaccines	• Bivalent (Cervarix) and quadrivalent (Gardasil)
Vaccine Coverage	• 42.3% (at least received one dose)	• 3.0%
Compliance[1]	• 75.4% (31.9% complete full vaccination series)	• 90%[2] (2.7% complete full vaccination series)
Immunization Rate by Doses Received	• All approved HPV vaccines are highly efficacious in preventing HPV-related cancers • 2 dose series are considered non-inferior to 3 dose series • The dosing interval is critical (must be ~6 months) for immunogenicity achievement	
	• Gardasil 9 (nonavalent) is 100% effective in preventing cancers from all target HPV types	• Bivalent protects against two most common strain (16 and18 responsible for ~70% of cervical cancer)

[1] Compliance is calculated by compared the number of patients who complete the vaccine schedule with the number of patients who receive at least one dose. HPV vaccine completion rate is based on the average completion rate of female and male in bivalent and quadrivalent HPV vaccination study for 2014.

[2] Due to very low rates of coverage, compliance rate likely does not reflect the rate that would occur across the broader population.

Source: Health Advances interviews and analysis, CDC, WHO, Spencer 2018 AJPH, Bruni 2016 Lancet, GAVI.

Technical Characteristics of Current Vaccines

Higher valency HPV vaccines' heavy ingredients pose a significant challenge for the core-shell technology due to their mass, although the bivalent vaccine presents less technical challenge as it is much lighter.

Feasibility

Key Products	Gardasil 9	Gardasil	Cervarix
Manufacturer	• Merck	• Merck	• GSK
Valency	• 9 (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58)	• 4 (HPV 6, 11, 16, 18)	• 2 (HPV 16, 18)
Dosage	• 2-dose schedule (0, 6-12 mos) or 3-dose schedule (0, 1-2, 6-12 mos)		
Active Ingredient Mass	• ~300 mcg	• ~120 mcg	• ~40 mcg
Total Core Shell Mass	• 300 mcg (2nd dose)	• 120 mcg	• 40 mcg
Adjuvant Mass	• AAHS 500 mcg	• AAHS 225 mcg	• AS04 550 mcg
Lyophilized Form	• No (pre-filled syringe)	• No (pre-filled syringe)	• No (pre-filled syringe)
Allergenic Components	• No preservative/antibiotic		• Insect cell, viral protein <40ng, bacterial cell protein <150ng

Dosing Limitations

Fit with Schedule	• Approved for age 9-25, Gardasil 9 recently approved for adults to age 45 • Does not fit with the standard infant immunization schedule

- HPV vaccination has moved toward a two dose regimen to increase convenience and cost, while single dose regimens are under study with uncertain outcome
  - *"What's really fascinating is how the community will react to the single dose data. We'll need to balance the cost with perhaps a modest loss in efficacy or duration. In the next few years, we should have a better sense." – HPV Vaccine KOL*
- 9-valent vaccines under development will likely push out other vaccines in the long-term
  - *"Chinese and Indian manufacturers are working on the 9-valent vaccine. I'd say by 2025-2030 when core-shell technology would be relevant, we're likely living in a 9-valent world." – HPV Vaccine KOL*

Note: Total Core-shell mass calculation does not include the Initial dose. AAHS = amorphous aluminum hydroxyphosphate sulfate. AS04 has 500 mcg aluminum hydroxide and 50mcg 3-O-desacyl-4'monophosphoryl lipid A. Gardasil 9 and Gardasil are approved for both males and females while Cervarix is only approved for females. Originally approved for 3-dose, subsequently approved for 2-dose with immunogenicity data

Source: Health Advances interviews and analysis.

Opportunities for Core-Shell

HPV

Drivers and Barriers

Technical Fit	Clinical Unmet Needs
+9-valent vaccine will enjoy increasing demand globally while it will require further development to accommodate its large mass - Adjuvants are included, although not as critical to efficacy as other vaccines - Bivalent vaccine represents good technical fit but may not be relevant in a decade - Single dose regimen possible	+Mediocre compliance with two dose regimen in US (limited data in emerging markets) +Vaccines are highly efficacious if full regimen is received, but significantly less seroconversion is observed with two shots close together +~270,000 deaths globally +Simplified dosing schedule should improve compliance with vaccination regimen

Development Path	
+With WHO prequalification, African approval could be fast (requires only confirmatory Phase III)	- May be more difficult to demonstrate clinical effect of improved compliance given the long timeline of infection and oncogenesis

Value Proposition(s)	• Improve compliance with vaccine regimen in low-compliance population (adolescents) to improve real-world efficacy, coverage, and herd immunity
Role in Technology Platform Development	• HPV vaccines may make the most sense as a follow-on application to proof of concept – No clinical benefit to improved compliance will be immediately apparent – This would also give time to determine which vaccine would be used in the developing world and work out technical challenges for 9-valent vaccine
Next Steps	• Monitor evolution of the space in the next two years, especially around efficacy of one-dose vaccination • In the meantime, discuss with key stakeholders feasibility and interest in bivalent, quadrivalent, and 9-valent vaccine and gain access to appropriate antigens – Current marketed 9-valent vaccine is a poor technical fit due to its size, but technological improvements may overcome this limitation – Other 9-valent vaccines manufacturers in China and India may have smaller molecules

h a green plus sign while barriers are denoted with a red minus sign.
Source: Health Advances interviews and analysis.

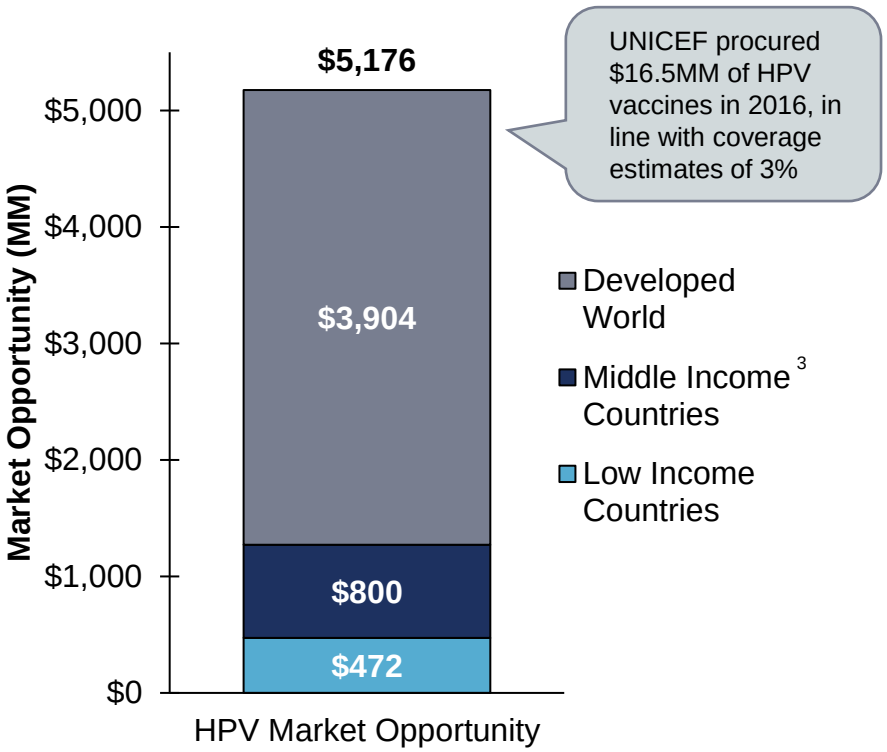
HPV Market Opportunity

HPV vaccines have a substantial market opportunity across most geographies, though interviewees have reported challenges with procurement, resulting in a relatively low market penetration.

	US	Low Income Countries
Vaccination Target Population	• Male and Female, ages 9-45[1]	• Female, ages 9-25
	Age 12 Population[2] • 2 MM (female), 2.3MM (male)	Age 12 Population[2] • 52.3 MM (female)
Public Health Target	• Closing the vaccination gap between rural and metropolitan area	• 30MM by 2020 (GAVI target)
Units	• 4.3MM x 2 dose = 8.6MM	• 52.3MM x 2 dose = 105MM
Price per Dose	• $200	• $14.10 (Most public sector) • $4.5 (GAVI procurement)
Market Size (USD)	• $1.72B	• $472MM

HPV Vaccine Market Opportunity

By Region



[1] Gardasil 9 was recently approved for adults up to age 45 in October 2018.
[2] Target population represents 12 years old population only. Developed World represents the US data and Emerging Markets segment includes 'Less Developed Countries' by the US Census IDB categorization.
[3] The middle income market size was scaled up from the low income market size, using the low income market as 11.5% and the middle income market as 19.5%.

Source: Health Advances interviews and analysis, US Census IDB, CDC, GAVI.

Disease Profile (1 of 2)

Patients with AIDS, caused by HIV infection, suffer from immune system failure and are therefore vulnerable to life-threatening opportunistic infection and cancers.

Human Immunodeficiency Virus

Pathogen Description	• HIV establishes chronic infections that persist for life • Without continuous, lifelong treatment, HIV leads to AIDS and death in most infected individuals
Transmission	• HIV can be sexually transmitted by sexual contact, transfer of blood, or during childbirth.
Prevalence	• Global prevalence ~36.7MM • US prevalence ~1.2MM • Highest in sub-Saharan Africa which increases mortality rate of other prevalent diseases such as malaria and tuberculosis
Fatality	• Global death ~ 1MM • Fatality ~80%, if untreated
Contagiousness	• R_0 ~3.5

AIDS

Diseases	• AIDS patients have an increased risk of developing various viral-induced cancers, including Kaposi's sarcoma, Burkitt's lymphoma, etc. • Opportunistic infections may be caused by bacteria, viruses, fungi, and parasites that are normally controlled by the immune system
Vaccines	• No licensed vaccines • Multiple vaccines in development
Therapies	• Combination of antiretroviral therapy suppresses viremia and halts disease progression and reduces virus transmission

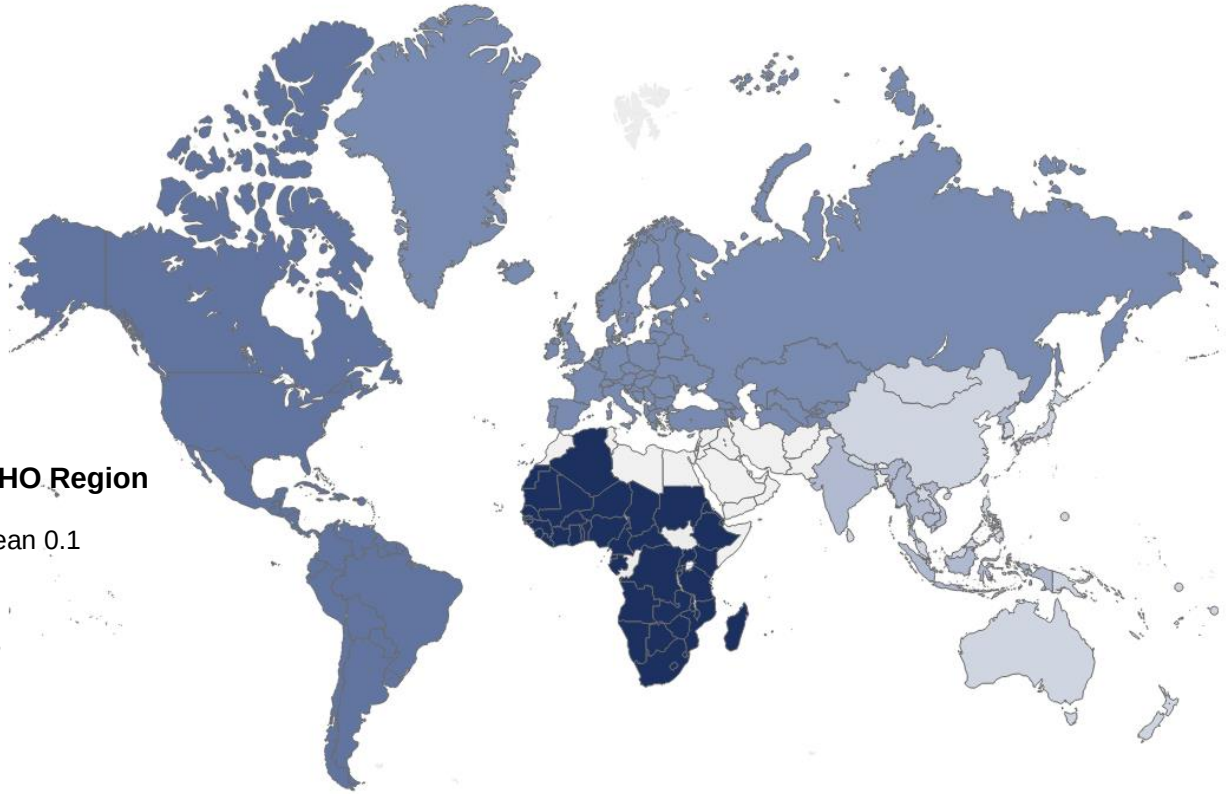
Note: HIV = human immunodeficiency virus, a lentivirus which is a type of retrovirus.
Source: Health Advances interviews and analysis, WHO, CDC, Korber 2017 Immunological Reviews.

Disease Profile (2 of 2)

The prevalence of HIV/AIDS is highest in Africa. While antiretroviral therapies have lowered the disease's fatality, prevention of transmission is a challenge even in developed countries.

Global Prevalence of HIV

2017, Prevalence % Among Adults 15 to 49



Prevalence (%) by WHO Region

- Eastern Mediterranean 0.1
- Western Pacific 0.1
- South-East Asia 0.3
- Europe 0.4
- Americas 0.5
- Africa 4.1

Source: Health Advances interviews and analysis, WHO.

HIV/AIDS Vaccine Development Paradigm

Current thinking is that multi-epitope, multi-injection vaccine development will be necessary to tackle HIV vaccine development challenges.

Challenges of HIV-1 Vaccine Development

Extraordinary diversity of HIV-1

- Four fairly distinct genetic groups (M, N, O, P)
- Most pipeline assets are multi-epitope approaches

Virus capable of evading immune response

- Early establishment of latent viral reservoirs
- Inability to induce broadly reactive antibody responses
- Lack of clear immune correlates of protection

Little pharmaceutical interest

- Lack of a small animal model, no existing method to elicit broadly reactive epitopes are significant challenges to R&D programs
- Existing antiretroviral therapies are effective and lucrative
- However, non-profit interest and investment is high

Most HIV/AIDS vaccines in development have complex components and dosing schedules, thus the core-shell technology can potentially provide value by facilitating compliance and efficacy

Source: Health Advances interviews and analysis, GAVI, WHO, Korber 2017 Immunological Reviews, Barouch 2018 Lancet, Barounch 2008 Nature..

HIV/AIDS Pipeline Vaccines

The majority of HIV/AIDS vaccines in development employ a multi-injection/multi-antigen approach in which the core-shell technology can provide significant value.

HIV/AIDS Vaccines in Development

Vaccine	Status	Prime	Boosts	Schedule	Developer and Strategy
HVTN702	Ph III	• ALVAC-HIV-C (vCP2438)	• 1: Bivalent Subtype C gp120/MF59	• **5 doses**: Prime at 0, 1 mos, Boost 1 at 3,6,12 mos	• GSK, Sanofi, BMGF • VV-pox, protein
HVTN 117	Ph II	• Ad26.Mos.HIV Trivalent	• 1: Ad26.Mos4.HIV • 2: gp140 C	• **4 doses**: Prime/Boost 1 at 0, 12 wks, Boost 2 at 24, 48 wks	• Curcell BIDMC IPCAVD • VV-adeno
HVTN 118	Ph II	• Ad26.Mos4.HIV	• 1: gp140 C • 2: Mosaic gp140	• **4 doses**: Prime at 0, 12 wks, Boost 1 or 2 at 24, 48 wks	• Janssen • VV-Adeno, Protein
RV 305	Ph II	• ALVAC-HIV vCP1521	• 1: AIDSVAX B/E	• **2 doses**: Prime/Boost 1 at 0, 24 wks	• USMRP-HIV • VV-Pox, Protein
RV 306	Ph II	• ALVAC-HIV vCP1521	• 1: AIDSVAX B/E	• **2 doses**: Prime at 0, 4 wks, Prime/Boost 1 at 12, 24 wks	• USMRP-HIV, NIAID • VV-Pox, Protein
HVTN 100	Ph I/II	• ALVAC-HIV-C (vCP2438)	• 1: Bivalent Subtype C gp120/MF59	• **2 doses**: schedule not determined	• NIAID, BMGF, Sanofi, Novartis • VV-Pox, Protein
HVTN 108	Ph I/II	• DNA-HIV-PT123	Bivalent Subtype C gp120+ • 1: AS01B • 2: MF59	• **4 doses**: Prime at 0,1,3,6 mos, Boost 1 or 2 at 3, 6 mos	• NIAID • DNA, Protein
IPCAVD009	Ph I/II	• Ad26.Mos.HIV Trivalent	• 1: gp140 C • 2: MVA mosaic	• **4 doses**: Prime/Boost 1 at 0, 12 wks, Boost 2 at 24, 48 wks	• Crucell, USMRP, BIDMC, IAVI • VV-Pox, Adeno, Protein

Note: Vaccines in stages Ph II and later with at least 1 or more boost shots are captured (8 out of 12 vaccines in the Ph 2 or later stage). NIAID = National Institute of Allergy and Infectious Disease. USMRP = US Military Research Program, BIDMC = Beth Israel Deaconess Medical Center. VV = viral vector

Source: Health Advances interviews and analysis, IAVI, clinicaltrials.gov.

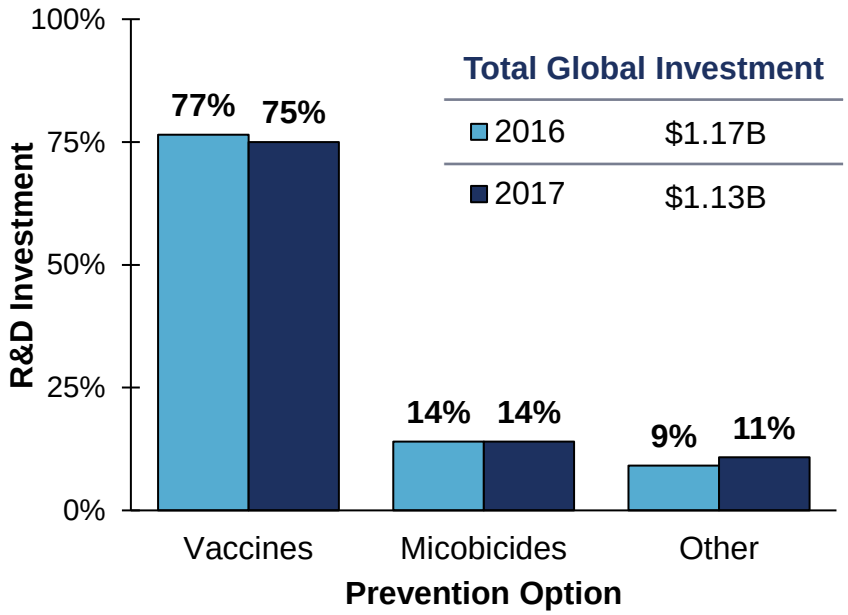
HIV/AIDS Market Opportunity

There are substantial funding resources for HIV/AIDS that could be used to develop core-shell technologies.

HIV/AIDS Global Funding

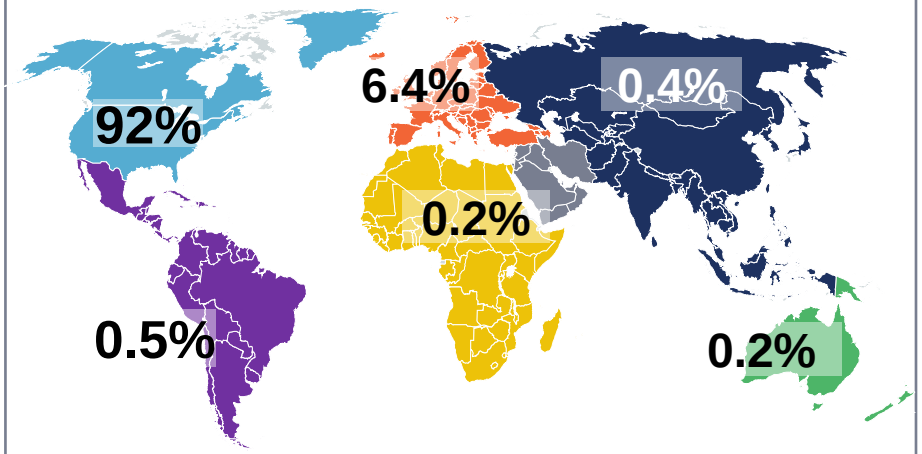
- UNAIDS estimates US$26.2B required for the global HIV response in 2020
- Overall funding for HIV prevention R&D is $1.17B in 2016: public (80%), philanthropic (15%), and commercial (5%)
- Top AIDS Vaccine Funders (2017):
  - NIH ($562MM), BMGF ($108MM), MHRP ($33MM), USAID ($30MM), Ragon institute ($10MM)

R&D Fund by Prevention Option



Public Sector Investment by Region

By Sector and Region, 2017



Note: MHRP = US Military HIV Research Program. Other preventative methods include prevention of vertical transmission, pre-exposure prophylaxis, treatment as prevention, voluntary medical male circumcision, female condoms.

Source: Health Advances interviews and analysis, US Census IDB, CDC, GAVI.

Opportunities for Core-Shell

HIV/AIDS

Drivers and Barriers

Technical Fit	Clinical Unmet Needs
+Core-shell technology could facilitate complex dosing regimens thought to be necessary for an HIV vaccine to be efficacious - Adjuvants are included in pipeline vaccines, although final formulations are unclear	+Core-shell could simplify regimens and improve trial and eventually real-world compliance +More complex regimens could potentially be developed with core-shell technology, leading in turn to greater efficacy +~1MM deaths globally +Technology could allow for the regimens that are necessary to successfully vaccinate against HIV

Development Path		
+Could potentially co-develop a product in US and emerging markets	+Over $800MM in funding annually for HIV vaccine development	- Unclear whether current vaccine candidates will prove effective - Long trial path likely

Value Proposition(s)	• Enable development and simplification of complex dosing regimens required to achieve efficacy in HIV immunization – The current scientific understanding is that the dosing regimen to immunize against HIV will likely be more complicated, including multiple antigens and more doses than is usual
Role in Technology Platform Development	• HIV/AIDS vaccines would be a long-term play in which we can demonstrate potentially (a) the ability to facilitate complex regimens and (b) significant clinical utility
Next Steps	• Forge partnership with interested vaccine developer to obtain funding for research • Sponsor or promote research into more complex vaccination regimens that could be unlocked by core-shell technology and improve HIV vaccination

Note: Drivers are denoted with a green plus sign while barriers are denoted with a red minus sign.
Source: Health Advances interviews and analysis.

Disease Profile (1 of 2)

Polio is a highly infectious disease affecting young children. Global eradication efforts have been successful in most countries.

Human Poliovirus

Pathogen Description	• Poliovirus is a highly infectious pathogen that mainly affects young children • There are three serotypes of human poliovirus that causes poliomyelitis
Transmission	• Poliovirus is spread through feces and saliva mainly in poor sanitation environments • The oral-oral route is common in a high hygiene settings
Prevalence	• Polio is eradicated in most of the world (remaining countries: Afghanistan, Pakistan, Syria, DRC)
Fatality	• N/A • Mainly result in permanent disabilities
Contagiousness	• R_0 ~6.0

Poliomyelitis

Diseases	• Poliomyelitis, known as infantile paralysis, is a disease of the central nerve system • Fewer than 1% develop paralytic disease following primary asymptomatic infection of the alimentary tract
Vaccines	• Two types: orally administered, live attenuated polio vaccine (OPV) and inactivated polio vaccines (IPV) for intramuscular (SQ) injection • Multi-disease vaccines: Pentacel (Dtap-Polio-hib), Pediarix (Dtap-HepB-Polio)
Therapies	• There is no cure and resulting paralysis is permanent

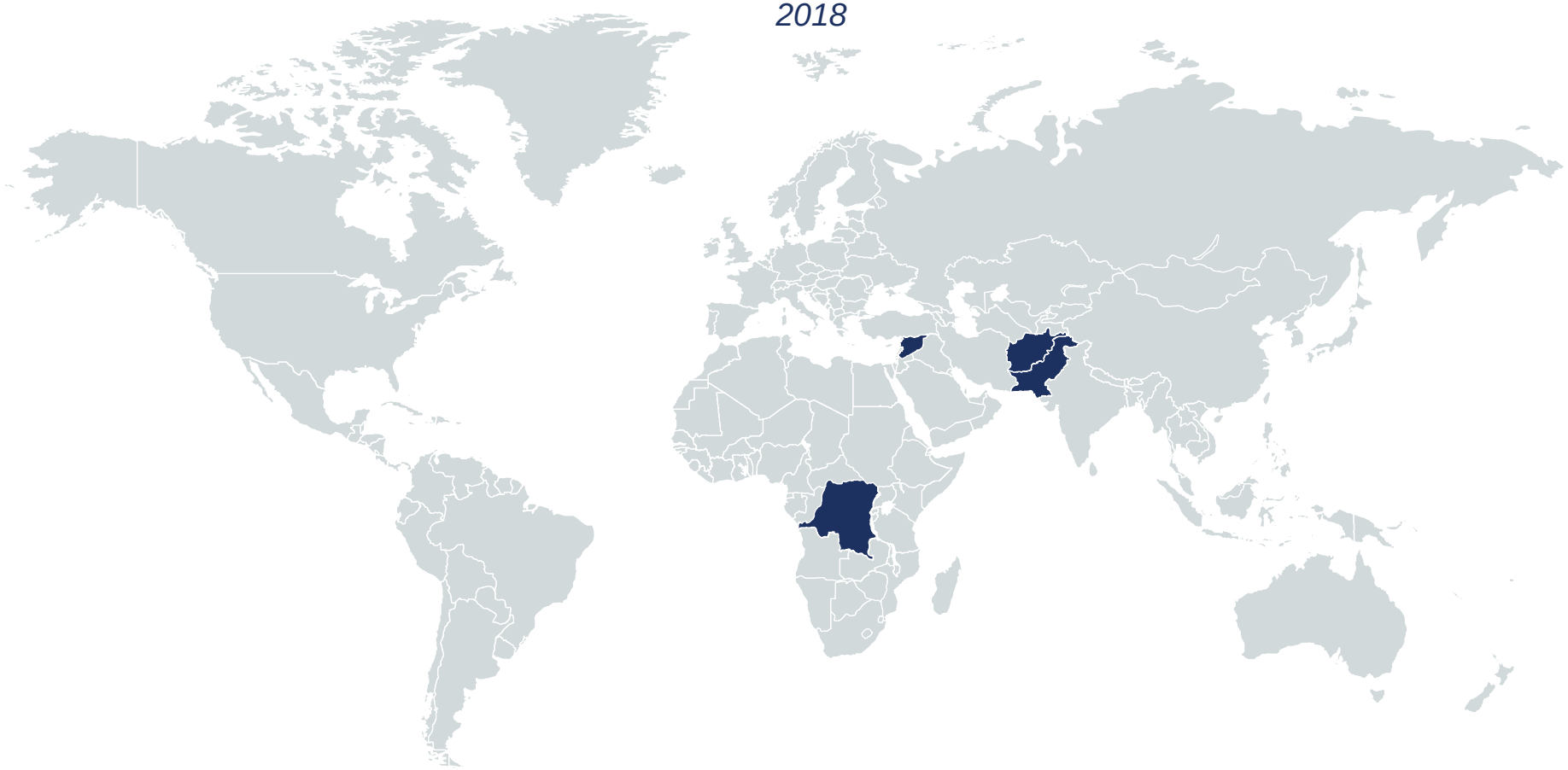
Source: Health Advances interviews and analysis, WHO, CDC.

Disease Profile (2 of 2)

Pakistan and Afghanistan remain as countries with naturally spreading polio. The interruption of immunization and circulating vaccine derived polio are responsible for Syria and DRC accordingly.

Countries with Active Polio Cases

2018



Source: Health Advances interviews and analysis, GPEI.

Current Immunization Paradigm

The developed world mainly uses IPVs while emerging countries mainly uses OPVs with the recommendation of at least of one dosing of IPV.

Polio Vaccination Paradigm

	Developed World	Emerging World
Recommendation	• CDC recommends that all children get four doses of polio vaccine – 3 doses: 2, 4, and 6 to 18 months old – 4th dose: between 4 through 6 years old	• For all countries using OPV, WHO recommends the inclusion of at least one dose of IPV in the schedule • In Polio endemic countries, bivalent OPV at birth followed by 3 doses at 2,4,6 months (one of them with IPV) • IPV only: 3 doses at 2,4, and 6 months then a booster with at least 6 month interval
Vaccine Used	• IPV is the only polio vaccine given in the US since 2000 • Polio vaccines are also combined with other diseases: Pentacel (Dtap-Polio-hib), Pediarix (Dtap-HepB-Polio)	• IPV and OPV are both used
Vaccine Coverage	• 94%	• 77%
Compliance	• ~71% (completion of full 4 doses)	• ~85%* (completion of at least 3 doses)
Immunization Rate by Doses Received	• Two doses are 90% effective and three doses are 99% to 100% effective • Booster dose is for prolonged protection	• OPV seroconversion is low but provides value in the control of transmission

* The compliance rate of oral vaccine differs greatly from that of IPV.

Source: Health Advances interviews and analysis, CDC, WHO, Baguune 2017 Archives Public Health.

Technical Characteristics of Current Vaccines

There are a number of IPV vaccine options, although they are all similar.

Feasibility

Key Products	IPOL
Manufacturer	• Sanofi
Valency	• 3 (Polio type 1, 2 & 3)
Dosage	• 3 dose at 2, 4, and 6-18 months • 4th dose at 4-6 years of ages
Mass of Single Vaccine Dose	• ~100 mcg*
Total Mass of Core Shell Vaccine	• 200 mcg (1st dose excluded)
Adjuvant Mass	• No adjuvant
Lyophilized Form	• Prefilled syringe, works with core-shell tech
Allergenic Components	• Less than 5 ng neomycin, 200 ng streptomycin, 259 ng polymyxin B

Dosing Limitations

Vaccine Fit with Schedule	• All doses are within a year but matches the regular infant dosing schedule

WHO Prequalified Polio Vaccines

Manufacturer	Vaccine Name
• Shantha Biotechnics (A Sanofi Company)	• ShanIPV • IPV
• GlaxoSmithKline Biologicals	• Poliorix • IPV
• Bilthoven Biologicals	• Polio Vaccine • IPV
• Sanofi Pasteur SA	• IMOVAX Polio • IPV
• AJ Vaccines A/S	• IPV Vaccine SSI • IPV
• Serum Institute of India	• Polio Vaccine • IPV
• Multiple partnership opportunities • ~30 WHO prequalified OPVs (monovalent, bivalent, and trivalent)	

Note: Active incredient mass is estimated from the components 40 D antigen unit of Type 1, 8 D antigen unit of Type 2, and 32 D antigen units of Type 3 poliovirus.
Source: Health Advances interviews and analysis, FDA labels, WHO

Opportunities for Core Shell

Stand-alone polio vaccination will see increasing competition due to the new hexavalent vaccine in development. Therefore the value of applying core shell to a post-eradication standalone IPV vaccine will not likely prove worthwhile.

Hypothetical Value Proposition(s)	• Core shell can improve logistics, affordability, and accessibility of the IPV vaccines, particularly the use in post-eradication era.

Drivers	Barriers
• Demand of the IPV vaccines which have more durable protection in post-eradication area • Initial studies have demonstrated feasibility in rodent models • Focus of key partners of Particles for Humanity, significant desire to eradicate disease	• **Hexavalent vaccines in development are a great competitive threat for a standalone polio vaccine** • **Consolidating only polio vaccine series does not provide logistical benefits for physicians and parents as it is tied in with regular infant vaccination schedule** • **Infants would be a harder population to recruit**

Possible Strategies	• Identify if there is a reasonable use case of an IPV-only vaccine for those with a contraindication to multivalent, multi-disease vaccines

Source: Health Advances interviews and analysis, Esposito 2014 Clin Microbiol Infect.

Polio Market Opportunity

The IPV vaccine will likely see significant competition from new hexavalent vaccines (DTaP + Hib + Hep B + IPV), which will limit the utility of the single vaccine.

	Emerging Markets
Vaccination Target Population	• Infant Routine Immunization Age <1 Population* • 120MM
Public Health Target	• 100% (eradication target) • Recommendation to include at least one IPV to 3 OPVs
Units	• 120MM x 3 dose = 360 MM
Price per Dose	• $1.2
Market Size (USD)	• $430MM

- *"Emerging countries will likely adopt the hexavalent vaccine that includes IPV. Even if you cover the whole series of IPV by a single injection, it is not going to compete against hexavalent use." – Vaccine Expert*

Development Path	• Hexavalent vaccine is in development and it poses a great threat to the use of polio only IPV vaccines

* Infant <1 population calculation includes less developed countries population in US Census IDB.
Note: GAVI projected vaccine support for polio is $200MM in 2019-2020. Current vaccination heavily rely on OPV which is much cheaper than IPV.
Source: Health Advances interviews and analysis, US Census IDB, CDC, GAVI.

Disease Profile

Malaria remains endemic in 91 countries, with a prevalence of over 200MM. While the fatality rate is relatively low, there are a still a significant number of deaths each year.

Malaria Background

Pathogen Description	• Caused by Plasmodium parasites • 2 parasites pose the greatest threat – *P. falciparum:* most common malaria parasite in Africa and responsible for most deaths globally – *P. vivax:* dominant parasite in most countries outside of sub-Saharan Africa
Transmission	• Parasites are spread to people through the bites of infected female *Anopheles* mosquitoes
Prevalence	• In 2016, there were an estimated 216MM cases of malaria in 91 countries (5% increase over 2015) • The WHO African Region carries a disproportionately high share of the global malaria burden – In 2016, the region was home to 90% of malaria cases and 91% of malaria deaths
Fatality	• Although fatality rate is <1%, deaths reached 445,000 in 2016
Contagiousness	• R_0 = ~115

Symptoms and Treatment

Disease Progression	• Symptoms usually appear 10–15 days after the bite • The first symptoms may be mild and difficult to recognize as malaria, but if not treated within 24 hours, can progress to severe illness • Children with severe malaria frequently develop one or more of the following symptoms: severe anemia, respiratory distress, or cerebral malaria • In adults, multi-organ involvement is also frequent
Vaccines	• RTS,S/Mosquirix – in pilot programs in Ghana, Kenya, and Malawi
Diagnosis and Treatment	• WHO recommends all suspected cases be confirmed before treating • WHO recommendations: – Artemisinin-based combination therapies (ACT) for the treatment of uncomplicated malaria – P. vivax infections should be treated with an ACT or chloroquine – Severe malaria should be treated with injectable artesunate for at least 24 hours and followed by a complete 3-day course of an ACT

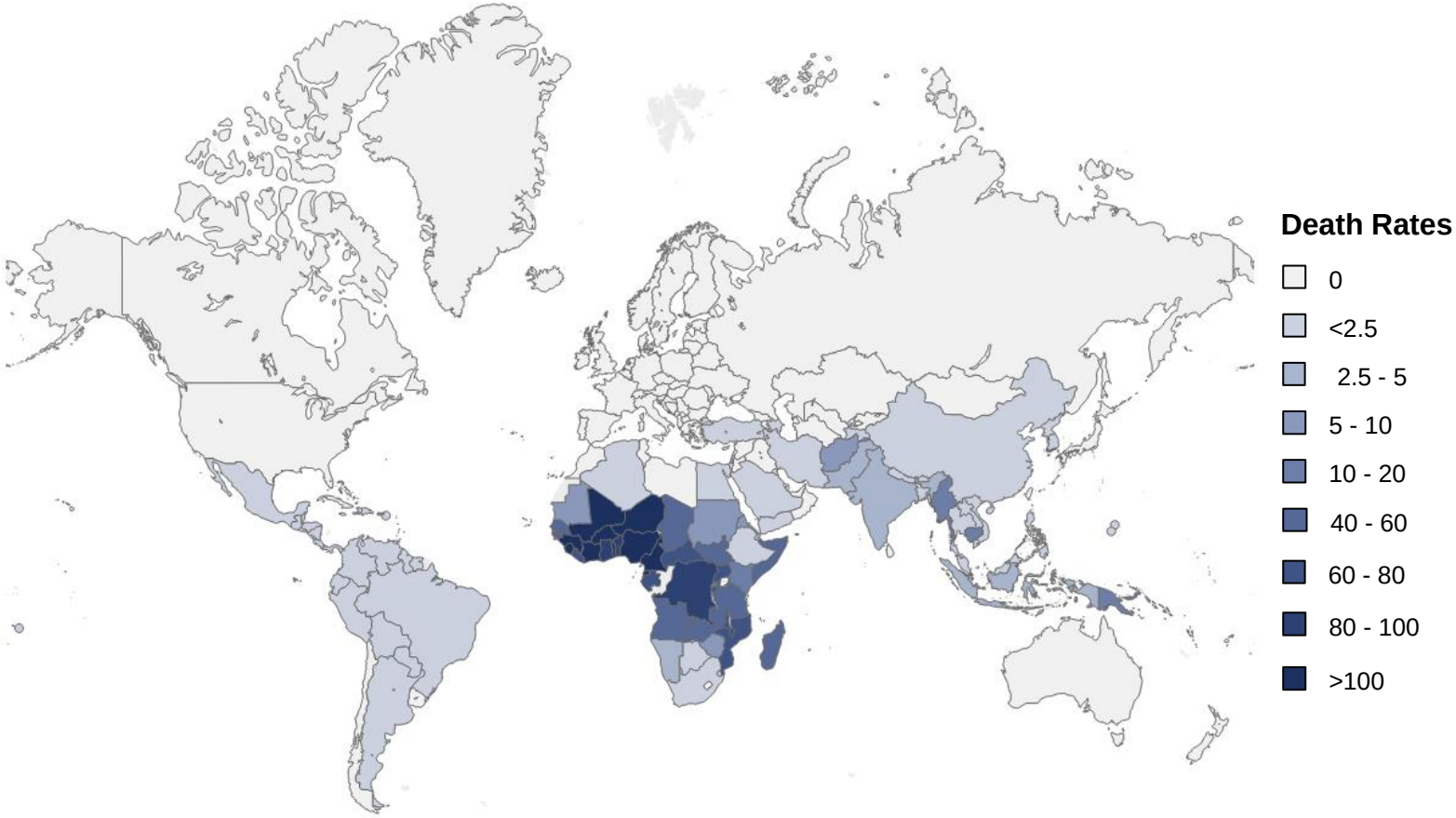
Source: Health Advances interviews and analysis, CDC, WHO, Smith PLOS Biology 2007.

Disease Profile (2 of 2)

Africa carries a disproportionately high share of the global malaria burden. In 2016, the region was home to 90% of malaria cases and 91% of malaria deaths.

Global Distribution of Malaria

Death Rates Per 100,000 Population, 2016



Source: Health Advances interviews and analysis, CDC.

Current Immunization Paradigm

Mosquirix is currently being deployed as part of a pilot program in Ghana, Kenya, and Malawi. Pending its success, it will eventually be rolled out to more African countries.

Malaria Vaccination Paradigm

	Emerging World	Developed World
Vaccine Recommendation	• Mosquirix (RTS,S) used in pilot programs in Ghana, Kenya, and Malawi • Starting at 5 months of age: 3 doses administered at 1-month intervals, fourth dose 15-18 months later	• Vaccine not recommended for use in the US/developed world • Antimalarial medications are recommended for travelers going to countries where malaria is endemic (chemoprophylaxis) – Starts 2-20 days before departure to a malarious area and continued for the duration of stay and for 1-4 weeks after return
Coverage and Compliance	• Pilot programs are just being rolled out in 2018, no data available yet on coverage/compliance • Experts believe there will be compliance issues – *"In trials we found that it was very difficult to get mothers to bring their babies back to the sites for all four doses. If you were able to give the vaccine in a single dose, that would remove the biggest barrier to efficacy." – Malaria KOL*	
Efficacy	• Ph III trial conducted from 2009-2014, enrolled 15,000 children 15-17 months in sub-Saharan Africa • In children who received 4 doses, the vaccine reduced malaria by 39% • The 4-dose vaccine schedule reduced severe malaria by 31.5% in this age group – Reductions also seen in malaria hospitalizations, all-cause hospitalizations and the need for blood transfusions • Among children who did not receive a fourth dose of the vaccine, the protective benefit against severe malaria was lost	

"Specifically, the MVIP will assess the feasibility of administering the required 4 doses of the vaccine in children; the vaccine's role in reducing childhood deaths; and its safety in the context of routine use. Data and information derived from the MVIP will inform a WHO policy recommendation on the broader use of the vaccine." – WHO

Note: MVIP = malaria vaccine implementation program.
Source: Health Advances interviews and analysis, CDC, FDA, Nelson Vaccine 2018.

Technical Characteristics of Current Vaccine

The active ingredient of the malaria vaccine is only 25 mcg, representing a good technical fit. However, the mass of the adjuvants is significant and efficacy is limited without them.

Feasibility

Key Products	Mosquirix/RTS,S
Manufacturer	• GSK
Valency	• Monovalent
Dosage	• 3 doses administered at 1-month intervals, fourth dose 15-18 months later
Active Ingredient	• 25 mcg RTS,S antigen
Total Mass of Core Shell	• 75 mcg (3 doses)
Adjuvant Mass	• 25 mcg MPL, 25 mcg QS-21
Lyophilized Form	• Antigen is lyophilized in current formulation
Allergic Components	• None

Dosing Limitations

Frequency of Dosing	• All doses can be given within 15 months and might be able to be be condensed into a single core shell injection (current limit ~12 months)

"I don't think there have been any trials that don't include the adjuvant. However, I believe that excluding them would lower the efficacy quite substantially, probably to the point of non-significant results." – Malaria KOL

Source: Health Advances interviews and analysis, FDA, CDC, Lino 1992 Vaccine.

Malaria Vaccine Summary

Malaria represents an area of high unmet need, a large market size, and strong potential funding from NGOs. However, the RTS,S vaccine's poor efficacy and need for adjuvants may cause technical challenges

Value Proposition(s)	• Current regimen consists of 4 shots, which could be condensed into one/fewer shots • High unmet need and significant funding from non-profits and government agencies • Although unproven, it may be possible to boost efficacy by increasing doses delivered while keeping total number of shots the same

Drivers	Barriers
• Very high disease prevalence and unmet need, with little preventative treatment • Very large (~$800MM) annual potential addressable market in emerging countries • Low fatality rate means clinical development may be simpler • 4 dose regimen showed low compliance, which could be improved with condensed regimen • Core-shell could unlock research on more complex regimens that could improve efficacy • Area of significant funding and support	• RTS,S vaccine has very low efficacy without adjuvants and mediocre efficacy overall • Covering the entire RTS,S schedule would require a core-shell that could last ~15 months • Current adjuvants are not pH stable and may not survive acidic environment during core-shell lysis • No evidence suggests that more complex dosing regimens will improved efficacy

Possible Strategies	• Work with GSK (RTS,S sponsor) to test the vaccine in a condensed regimen • Encourage studies to determine if extra doses lead to improved efficacy, which could facilitate need for core-shell solutions • Can leverage data in various African countries to seek approval elsewhere

Source: Health Advances interviews and analysis.

Malaria Market Opportunity

Clinical development for malaria has not proven to be logistically challenging, and the potential market opportunity is quite large, at around ~$800MM.

Development Pathway

- Despite large trial sizes, recruitment is not challenging due to unmet need
  - *"Because malaria is such a problem in sub-Saharan Africa, it was easy to get mothers to enroll their children in our Ph III studies. I don't anticipate any difficult enrolling our goal of 750,000 children in Ph IV." – Malaria KOL*
- Malaria is an area of high unmet need with significant financial and regulatory support
  - *"Total funding for malaria control and elimination reached an estimated $2.7B in 2016. Contributions from governments of endemic countries amounted to $800MM representing 31% of funding." – WHO*
  - *"Malaria is an area of significant unmet need. We ran the [RTS,S] trial with support from BMGF, and expect to see continued support from them and other organizations as the vaccine is rolled out." – Malaria KOL*
- Success in one African country does not guarantee approval in others
  - *"Development is not so simple as to say that success in one country would lead to automatic approval and acceptance in others. In our Ph III trial, we had 11 sites across 17 countries, and we worked with WHO to select 3 countries to pilot this program in. Pending the success of this trial and the position of WHO, we will begin to roll out this vaccine in other African countries." – Malaria KOL*

Market Opportunity

	Emerging Markets
Vaccination Target Population	• Will eventually be recommended for all children at 5 months in Africa[1]
People Immunized per Year	• ~39.5MM children (0-1 year old population, dose given at 5 months)
Units	• 39.5MM x 4 doses = 158MM units
Price per Dose	• $5
Market Size (USD)	• $790MM

[1] Mosquirix confers protection against *P. falciparum*, which is the most prevalent parasite in Africa. In Asia, the most prevalent parasite is *P. vivax*, against which this vaccine doesn't confer protection.

Source: Health Advances interviews and analysis, CDC, WHO, UNICEF, GAVI.

Disease Profile

Hepatitis A is not harmful if individuals are infected as children. However, adults with Hep A have a worse course of illness that can lead to chronic liver issues and occasionally death.

Hepatitis A Background

Pathogen Description	• Hepatitis A is a common water-borne pathogen • Infected children typically have no/limited symptoms, but adults can see a much worse course of disease with serious liver damage
Transmission	• Primarily spread when an uninfected (and unvaccinated) person ingests food or water that is contaminated with the feces of an infected person • Rarely spread through sexual contact
Prevalence	• In developing countries with poor sanitary conditions and hygienic practices, most children (90%) have been infected with the hepatitis A virus before the age of 10 – in these countries large-scale vaccination is not encouraged • 1.4MM cases globally each year, very few in developed world (~4,000 in US)
Fatality	• Rarely fatal, but can sometimes cause debilitating symptoms and fulminant hepatitis • Global deaths ~7,000 annually
Contagiousness	• R_0 = 1.3

Symptoms and Treatment

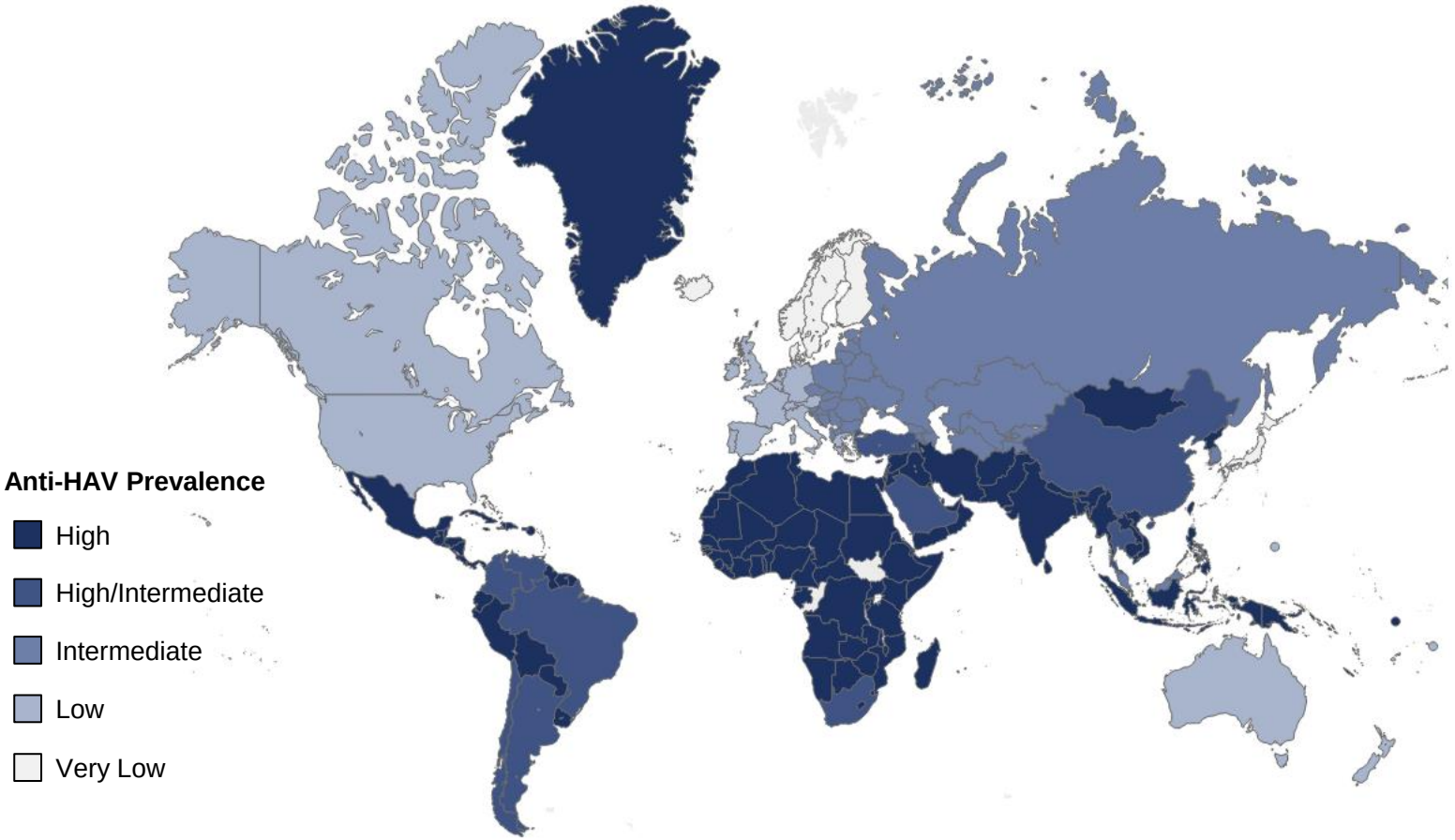
Disease Progression	• In endemic countries, children are asymptomatically infected with the virus which effectively prevents clinical hepatitis A in adolescents and adults • It can be most dangerous in unvaccinated, unprotected adults • Symptoms typically last less than 2 months and include fever, fatigue, nausea/vomiting, diarrhea, joint paint, and jaundice – In rare cases can cause liver failure in death (more common in people older than 50 with other liver diseases)
Vaccines	• Single antigen vaccines: Havrix, Vaqta, and Healive • Hep A/Hep B combo: Twinrix
Other Treatment	• No specific treatment • Therapy aimed at maintaining comfort and adequate nutritional balance (replacement of fluids that are lost from vomiting and diarrhea)

Source: Health Advances interviews and analysis, CDC.

Disease Profile (2 of 2)

In endemic countries, the majority of children have unknowingly been infected with Hepatitis A and thus develop immunity for the rest of their life. The countries with intermediate prevalence are where there is a high need for vaccination, as adults (without immunity) who contract Hepatits A are at most risk of severe consequences, including death.

Global Distribution of Hepatitis A Virus Infection



Source: Health Advances interviews and analysis, CDC.

Current Immunization Paradigm

Current immunization regimens consist of two doses, although it is believed that one dose is sufficient for seroconversion. The second dose is necessary for long-term protection.

Hepatitis A Vaccination Paradigm

	Developed World	Emerging World
Recommendation	• ACIP recommends that all children in the United States receive hepatitis A vaccine at 1 year – Havrix: month zero, 2nd dose 6-12 months later – Vaqta: month zero, 2nd dose 6-18 months later • Twinrix used in 18+ patients: 0, 1, 6 months	• In certain countries[1], recommended dosing ~1 year of age – Havrix: month zero, 2nd dose 6-12 months – Vaqta: month zero, 2nd dose 6-18 months – Healive: 0 months, 6 months
Vaccine Used	• Vaqta and Havrix have relatively equal market share (60/40 split) • Twinrix indicated for a different patient population	• Havrix and Healive are both WHO pre-qualified vaccines
Coverage and Compliance	• As of 2016, 73.9% of US adolescents ages 13-17 have received at least one dose • As of 2016, 64.4% of US adolescents ages 13-17 have received 2 doses • However, compliance in adults is low: only ~30% of adults initiating Hep A series receive both doses	• China: 2014 survey of Zhejiang province showed 89% coverage (1 dose regimen) • Israel: 2005 study showed 90% receive 1 dose, ~85% receive 2 doses • Brazil: 2006 study showed 90% received first dose, 85% receive 2 doses • Panama: 2015 study showed 70% coverage (1 dose regimen)
Efficacy	• All vaccines are inactivated vaccines, protecting against Hep A – Healive: seroconversion achieved in 99% of patients ~2 weeks after first dose – Havrix: 2 weeks after the first dose, ~94% of patients seroconverted; 1 month after the first dose, ~97% of patients seroconverted – Vaqta: seroconversion achieved in 99% of patients within 4 weeks of first dose • Despite seroconversion after 1 dose, 2 doses are recommended to ensure long-term protection	

"Countries may consider a 1-dose schedule as this option seems comparable in terms of effectiveness, and is less expensive and easier to implement. However, in individuals at substantial risk of contracting hepatitis A and in immunocompromised individuals, a 2-dose schedule is preferred." – WHO

1: The Hep A vaccine is included in immunization programs for the following countries: Argentina, Brazil, Chile, Colombia, Mexico, Paraguay, Panama, Uruguay, Iraq, Israel, Saudi Arabia, Bahrain, Kazakhstan, Romania, Russia, Slovenia, Turkey, Korea, and China.

Source: Health Advances interviews and analysis, CDC, FDA, Nelson Vaccine 2018.

Technical Characteristics of Current Vaccines

The Hepatitis A vaccines reflect a good technical fit, with a mass of only 0.4 mcg per core shell.

Feasibility

Key Products	Havrix	Vaqta	Healive	Twinrix
Manufacturer	• GSK	• Merck	• Sinovac	• GSK
Valency	• Monovalent	• Monovalent	• Monovalent	• Hep A/Hep B combo • Not considered for core-shell technology as Hep B is covered by pentavalent vaccine in GAVI countries
Dosage	• Initial dose followed by 2nd dose 2-6 months later		• Initial dose followed by 2nd dose 6 months later	
Active Ingredient	• 0.4 mcg	• 0.4 mcg	• 0.4 mcg	
Total Mass of Core Shell	• 0.4 mcg	• 0.4 mcg	• 0.4 mcg	
Adjuvant Mass	• 0.25 mg of aluminum as aluminum hydroxide	• 0.225 mg Al^{3+}	• 0.25 mg alum	
Lyophilized Form	• 1992 clinical trial of a lyophilized inactivated hepatitis A vaccine using an established cell line and HAV strain – Likely same HAV strain/active ingredient used in other Hep A vaccines, though can't directly correlate to the vaccines presented here			
Allergenic Components	• <40 ng/mL neomycin sulfate	• <10 ppb neomycin	• None	

Dosing Limitations

Frequency of Dosing	• Second dose is given within 12 months and could easily be condensed into a single core shell

Note: Werzberger NEJM 1992 reported the mass of the Hepatitis A antigen (25U) to be 0.4 mcg. Health Advances assumes a similar mass across all Hepatitis A vaccines.
Source: Health Advances interviews and analysis, FDA, CDC, Lino 1992 Vaccine.

Opportunities for Core-Shell

Hepatitis A represents a strong technical fit and a large market, however it is characterized by relatively low unmet need. The first dose of vaccine has strong efficacy which may limit interest in development.

Value Proposition(s)	• Current regimen consists of two shots, which could be easily condensed into one shot – However, the high efficacy of a single dose limits the value of this approach • Large market size and patient population

Possible Strategies	• Work with Chinese manufacturer and then use that data as support for approval in other countries (or stay in the Chinese market, which is very large)

Drivers	Barriers

• Very large ($1B+) annual potential addressable market, although in a limited set of countries that need the vaccine
• Low mass, could serve as a proof of concept for core-shell
	• Relatively low clinical unmet need, as very few patients experience severe complications
	• Some countries have condensed regimen into a single shot
	  – WHO suggests this approach if there are cost concerns
	  – China uses a single shot regimen
	• Vaccine is used primarily in middle-income countries and would receive limited support from non-profits
	  – People in low-income countries are often exposed as children, which confers immunity as an adult
	  – Vaccine used in countries of varying geographies with different regulatory systems, global approval may be challenging
	• Adjuvants included in current vaccines

Source: Health Advances interviews and analysis.

Hepatitis A Rationale for Core Shell

Hepatitis A should be considered for prioritization due to its technical fit and broad applicability. While Hepatitis A unmet need is lower than other diseases, there is still interest in supporting vaccination in emerging countries.

Hepatitis A Vaccine

Strong Technical Fit with Core-Shell

- Low mass vaccine
- Single antigen
- Not currently administered in infant vaccinations

→ **Hepatitis A vaccine presents limited feasibility concerns for core-shell technology**

Market Includes Both Developed and Emerging Markets

- Developed countries use Hepatitis A Vaccine for travelers and some at-risk patients
- Countries in South America, Asia, and Africa all have at least moderate risk and could use Hepatitis A Vaccines more broadly

→ **US and other developed countries could be used as a springboard to emerging markets**

Clinical Need is Moderate

- Worldwide deaths: ~10,000
- Case fatality rates can be as high as 4% (in the elderly population)
- GAVI does not currently support hepatitis A vaccine, but it is considering investing in hepatitis A vaccine in 2021-2025

→ **Clinical need is moderate, but sufficient to drive interest in novel vaccination approaches**

Source: Health Advances interviews and analysis, GAVI, WHO.

Hepatitis A Market Opportunity

Hepatitis A represents a large market opportunity, both in the developed world and in emerging markets.

Development Pathway

- Current vaccines have proven efficacy and with limited unmet need there is little motivation to develop an improved formulation unless it covers multiple diseases
  - *"Countries have had a hard time showing they have enough of a burden to get the government to sponsor the vaccine. If you put Hep A and Hep E together, that may be enough of an unmet need and create a business case." – Vaccine Expert (BMGF)*
- Vaccine will need to be inexpensive given the limited unmet need and success of current vaccines
  - *"People may show interest if you are able to make this product really cheap. The clinical unmet need isn't too bad, so the vaccine couldn't be very expensive. Plus right now one dose is pretty effective for immediate immunity, so there isn't too much of a need for a condensed schedule." – Hepatitis A KOL*

Market Opportunity

	Developed World (US)	Emerging Markets
Vaccination Target Population	• Included in routine immunization for children at age 1	• Included in routine immunization schedule at age ~1 in a subset of countries[1]
People Immunized per Year	• 4MM (1 year old population)	• ~28MM children[1] (1 year old population)
Units	• 4MM x 2 doses = 8MM units	• 28MM x 2 doses = 56MM units
Price per Dose	• $32	• $17
Market Size (USD)	• $256MM	• $952MM

[1] In highly endemic countries almost all persons are asymptomatically infected with HAV in childhood, which effectively prevents clinical hepatitis A in adolescents and adults. In these countries, large-scale vaccination programs are not recommended. The Hep A vaccine is included in immunization programs for the following emerging countries, which were included in this analysis: Argentina, Brazil, Chile, Colombia, Mexico, Paraguay, Panama, Uruguay, Iraq, Saudi Arabia, Bahrain, Kazakhstan, Romania, Russia, Slovenia, Turkey, Korea, and China.

Note: Developed world opportunity may be limited as a single dose is sufficient to protect travelers in the short term.

Source: Health Advances interviews and analysis, CDC, WHO, UNICEF, GAVI.

Disease Profile

Although there is a low case fatality rate, GBS bacteria is very common and therefore GBS causes 150,000 stillbirths and infant deaths worldwide each year.

Group B Strep Background

Pathogen Description	• Group B Streptococcus (group B strep, GBS) are bacteria that are naturally occurring in the body • Usually are not harmful, but can cause illness in people of all ages and is particularly dangerous in neonates
Transmission	• If a pregnant woman has the bacteria in her body, she can pass GBS to her baby during childbirth
Prevalence	• ~20% of pregnant women carry GBS bacteria – US: ~900 babies get GBS each year – Globally: 410,000 GBS cases – Africa has the highest burden: 54% of estimated cases of 65% of stillbirths and infant deaths
Fatality	• US: <50 newborn deaths per year • Globally GBS causes ~150,000 stillbirths and infant deaths
Contagiousness	• R_0 = 5.6

Symptoms and Treatment

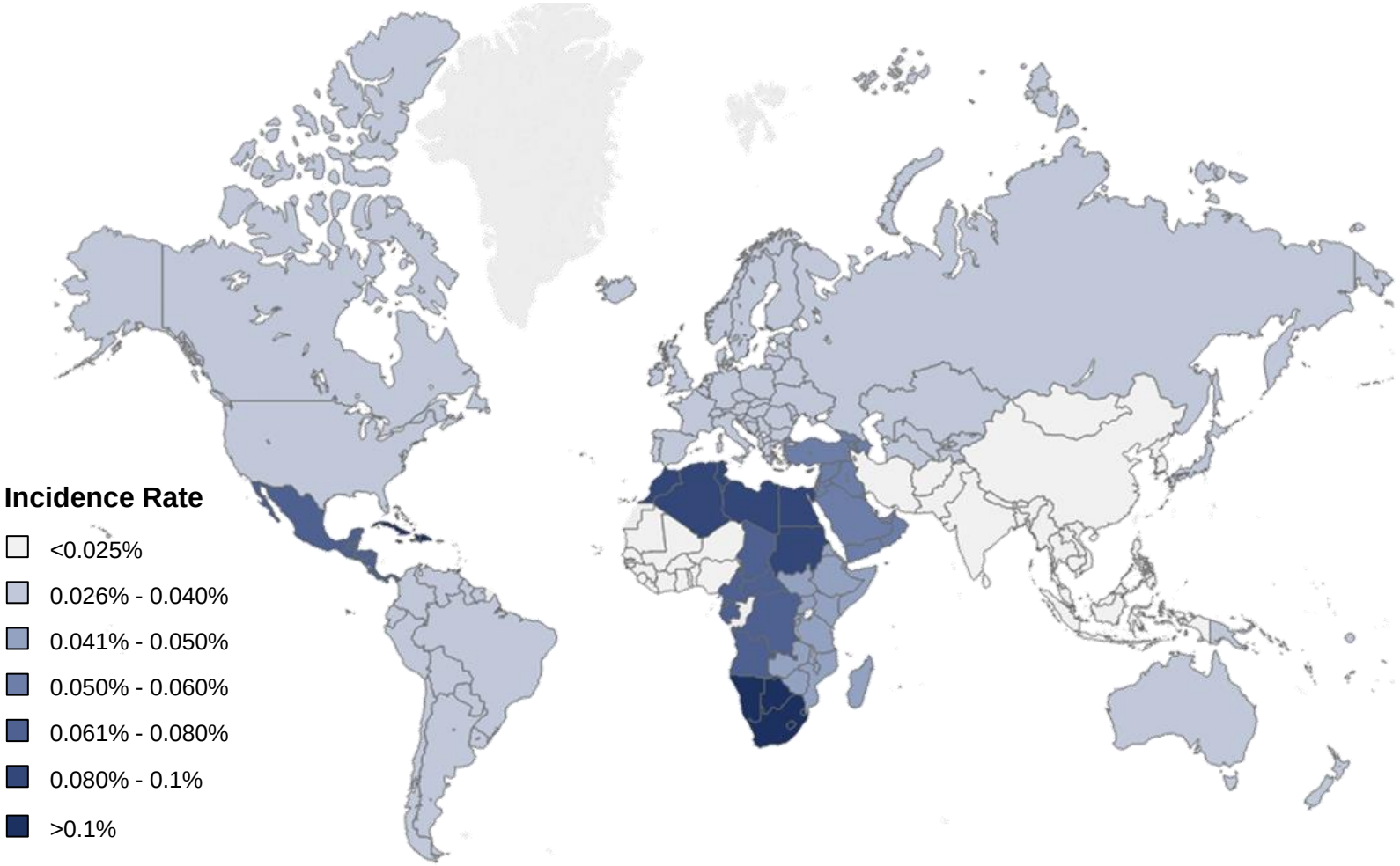
Disease Progression	• Symptoms include: fever, difficulty feeding, irritability or lethargy, difficulty breathing, blue-ish color • For early-onset disease in newborns (first week), GBS can cause severe complications: – Bacteremia and sepsis, pneumonia and meningitis • Similar illnesses are associated with late-onset GBS (first week through 3 months) – Meningitis is more common with late-onset GBS disease than with early-onset GBS
Vaccines	• None currently available • Pipeline vaccines from GSK, Pfizer in Phase II
Other Treatment	• IV antibiotics: e.g. penicillin or ampicillin • For babies with severe illness, doctors suggest additional procedures

Source: Health Advances interviews and analysis, CDC, WHO.

Disease Profile (2/2)

Infants are most affected by early onset GBS in Africa and Central America.

Incidence of Early Onset GBS



Source: Health Advances interviews and analysis, and Lawn, Clinical Infectious Disease 2017.

Group B Strep Pipeline Vaccines

GSK and Pfizer each have assets for GBS in clinical trials, however both have moved to single dose regimens.

Group B Strep Vaccines in Development

Vaccine	Status	Developer	Dosing Information	Notes
GBS vaccine	Ph II	• GSK (acquired from Novartis in 2015)	• Single dose • Two doses 2 and 6 weeks apart	• Trivalent vaccine - serotypes Ia, Ib, and III conjugated to CRM197 • Has been tested in pregnant women in the US
PF-06760805	Ph I/II	• Pfizer, BMGF	• Single dose	• Six valent vaccine (CPS – CRM197 conjugate) • Initial study in healthy adults 18 to 49 years of age with no history of a GBS infection, conducted in the US • Received a grant from the Bill & Melinda Gates Foundation to conduct a Phase 1/2 clinical trial in South Africa
GBS-NN vaccine MVX13211	Ph I	• MinervaX (based in Denmark)	• Two doses of 50 mcg given 4 weeks apart	• Single component, protein-only vaccine based on a fusion of highly immunogenic and protective protein domains from two surface proteins of GBS • Expected to protect against 95% of GBS isolates • Ph I trial in 240 healthy non-pregnant women – proven to be safe and highly immunogenic

"We looked at multidose regimens, but because there was sensitivity around vaccinating when the fetus was still developing. So you start in the third trimester, and we didn't see advantage to a second dose so close to the first." – GBS Expert

Source: Health Advances interviews and analysis, company websites, clinicaltrials.gov, PATH, WHO.

Group B Strep Vaccine Development Paradigm

There are multiple to challenges to GBS vaccine development, and most assets in development are a single dose, limiting the value of the core shell.

Group B Strep Vaccine Development

Challenges with Patient Population

- Pregnant women and newborn children are a difficult population to test in
  - *"A lot of times there are objections to vaccinating pregnant women, they are sensitive group to try experimental therapies on." – GBS KOL*
- Difficult to pick a time point that is safe for the baby and effective in preventing side effects of GBS
  - *"There are issues with timing of the vaccine, as we want to make sure we give it late enough so the fetus has enough time to develop, but early enough to prevent pre-term birth." – GBS KOL*

Complications with Development

- Current treatment consists of prophylactic antibiotics during birth
  - *"In the US and in some developing countries, there is prophylactic antibiotic use during birth. In these countries you can test for immunogenicity of the vaccine, but it will be very difficult to do an efficacy trial as you won't be able to see early onset disease." – GBS KOL*

Single Dose Regimen

- Most pipeline assets are single dose, limiting value add of core shell
  - *"We tried 2 doses, 2 and 6 weeks apart, but we didn't see much of an effect so we ultimately moved to a single dose regimen. I imagine most assets in development will continue to be a single dose." – GBS KOL*
  - *"Because there is such a tight timeline in which we are able to vaccinate the mother, a 2 dose regimen just isn't feasible." – GBS KOL*

Source: Health Advances interviews and analysis.

Group B Strep (GBS) Vaccine Summary

The group B strep vaccines in development are only a single dose and have proven to be difficult to develop.

Value Proposition(s)	• No clear value proposition: based on conversations with Novartis employee, GBS vaccines will likely be single shot despite multishot regimens in earlier phases
Possible Strategies	• Partner with company developing pipeline vaccine to reformulate into a single dose

Drivers	Barriers

• GBS can be fatal/lead to long-term consequences for newborns
• Current treatment can be a burden on the mother during childbirth
	• No technical fit: single shot regimen likely in Phase III of development
	• Pipeline vaccine that has challenges with clinical development
	  – Difficult timing of dosing
	  – Sensitive patient population (pregnant women and newborns)
	• Existing treatment in developed world and some emerging countries

Source: Health Advances interviews and analysis.

Vaccine Development in Selected Countries – Core Shell

Core-shell vaccine development for Africa can be expedited with WHO prequalification or FDA approval, while India will require trial data from Phase I to III with Indian subjects.

Africa

WHO Prequalification*

No → **Phase I** → **Phase II** → **Phase III** → **Approval Process**

- Trial timeline and size depends on new/existing vaccines' efficacy, and the impact of core-shell formulation

Yes → **Phase III** → **Approval Process**

- FDA approved vaccines can apply for WHO prequalification then gain access to the emerging country market with a single trial

India

WHO Prequalification /FDA Approval → **Phase I** → **Phase II** → **Phase III** → **Approval Process**

- **All vaccines** need Indian population Phase I trial
- New vaccine can be trialed in India, get WHO prequalification with the result, and then expand to Africa countries (similar to MenAfriVac development strategy)
- While FDA approval does not expedite the trial studies but can grant a faster review for clinical trial study protocols (2-4 wks vs. 8-12 wks)

* Clinical data from United States of America, Canada, Australia, Norway, Finland, France Denmark, Netherlands, Austria, Japan, EMA, Switzerland, Belgium, Germany, Italy, Ireland, UK, and WHO Prequalification Program are considered to be Stringent Regulatory Authority and can be accepted.

Source: Health Advances interviews and analysis.

WHO Prequalification

WHO prequalification is an essential step in the development of vaccines in India, Africa, and other parts of the developing world.

World Health Organization Prequalification Program

Regional Regulatory Experts Feedback

Aim

- To ensure vaccines to meet global standards of qualify, safety and efficacy

Implication

- The data submitted for dossier review, in conjunction with other procurement criteria, is used by UN and other procurement agencies for vaccine purchasing decision
- Many regulatory agencies of developing countries highly value WHO prequalification

- WHO prequal carries a scientific authority and can expedite clinical development and approval
  - *"Local authorities will accept data from other countries, provided it is scientific. WHO prequal has significant impact on the trial and approval process." – Africa Regional Regulatory Expert*
  - *"For a new manufacturer, pre-qualification is mandatory. Even for existing manufacturers, pre-qualification answers a lot of questions during the development process." – South Asia Regional Regulatory Expert*

Note: SRA = Stringent Regulatory Authority, EFMHACA = The Ethiopia Food, Medicine and Healthcare Administration and Control Authority, NAFDAC = National Agency for Food & Drug Administration & Control in Nigeria.
Source: Health Advances interviews and analysis.

WHO Prequalification Process

The WHO prequalification process consists of five steps: invitation, dossier submission, assessment, inspection, and decision.

Invitation

- Must be invited to apply for prequalification and meet one or more of following criteria
  - On WHO model list of essential medicines
  - Likely to meet criteria for inclusion based on need, effectiveness, and safety
  - Be recommended for use by current WHO treatment guide

Dossier Submission

- Manufacturer provides a comprehensive set of data about the quality, safety and efficacy of the product submitted for evaluation
- Bioequivalence data (can be from trials in healthy volunteers)
- A vaccine must be licensed in its country of manufacture as a prerequisite to prequalification

Assessment

- Team of assessors evaluates all data provided
- Team includes WHO staff and regulatory experts from various agencies

Inspection

- Verify the manufacturing sites comply with WHO good manufacturing practice
- Verify any CRO that conducted any clinical studies complies with WHO good clinical practice and WHO good laboratory practice

Decision

- If product is found to meet the specified requirements, and the associated manufacturing site(s) and CROs are compliant with WHO standards, the product is added to the WHO list of prequalified medicinal product
- Regular re-inspections take place to ensure products continue to meet standards

The long-term goal of WHO prequalification is to increase the availability of quality-assured medicines by assisting manufacturers to comply with WHO standards and supporting regulatory authorities to implement them.

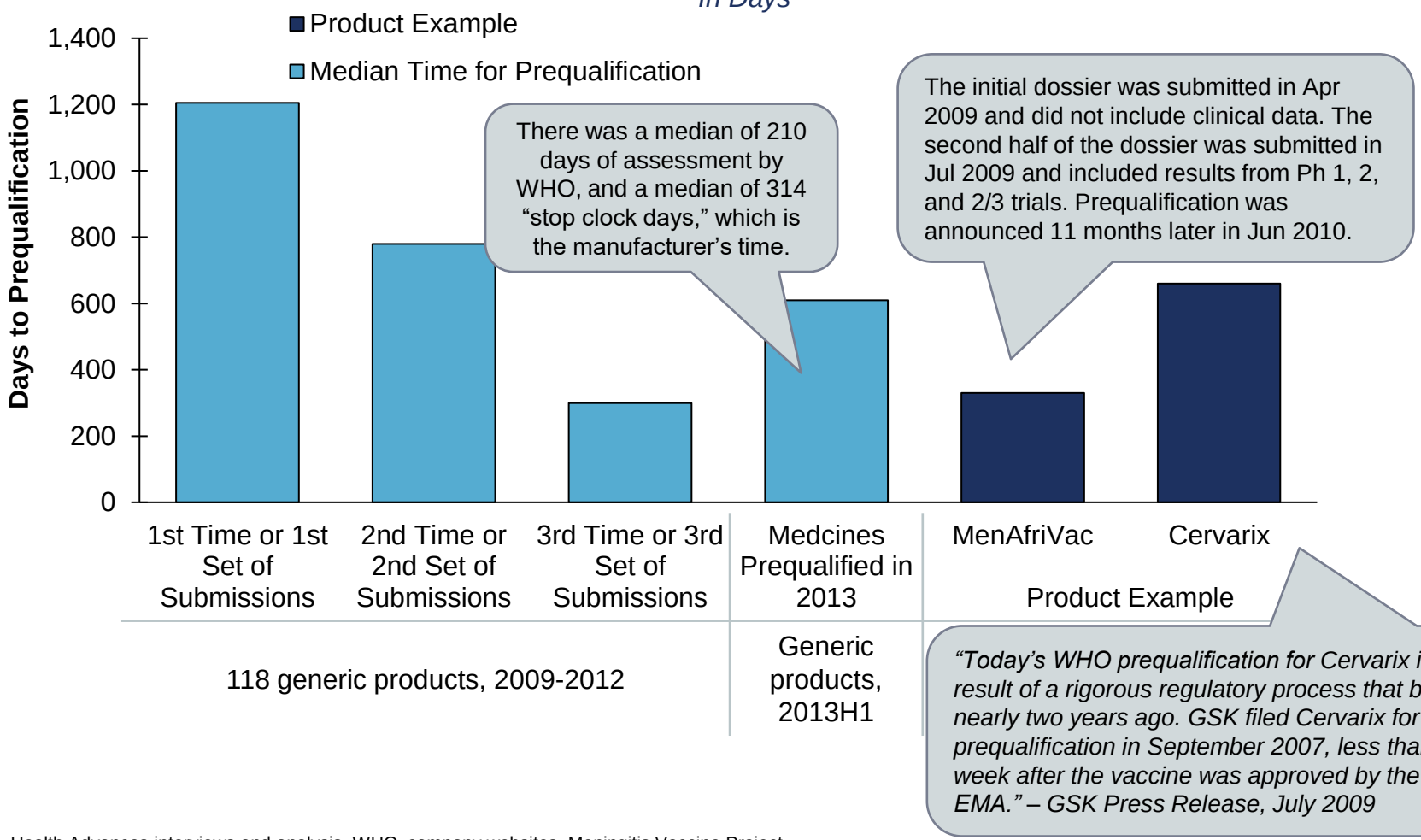
Note: A vaccine must be licensed in its country of manufacture as a prerequisite to prequalification.
Source: Health Advances interviews and analysis, WHO.

WHO Prequalification Timeline

The WHO prequalification process is typically quite rigorous and takes multiple years. The timeline can be expedited in instances of high unmet need and strong support, like MenAfriVac.

Time to WHO Prequalification

In Days



Source: Health Advances interviews and analysis, WHO, company websites, Meningitis Vaccine Project.

India: Clinical Trial Req'ts and Timeline – Core Shell

India requires the completion of Ph I, II, and III trials in India, in a similar manner to how trials are conducted in the United States.

Phase I

- First introduction of a vaccine into a human population for determination of its safety and biological effects including immunogenicity
- Includes study of dose and route of administration and should involve low risk subjects
- Drugs discovered in other countries phase I trials are not usually allowed to be initiated in India unless phase I data from other countries are available
  - However, such trials may be permitted even in the absence of phase I data from other countries if the drug is of special relevance to the health problem of India (may be the case for rabies)

Phase II

- Initial trials examining effectiveness (immunogenicity) in a limited number of volunteers
- Prophylactic vaccines can be given to normal subjects
- Therapeutic or curative vaccines may be given to patients suffering from particular disease

Phase III

- This focuses on assessments of safety and effectiveness in the prevention of disease, involving controlled study on a larger number of patients in multiple centers

The clinical development timeline and regulatory process are subject to many delays, and often take well over 5 years to complete.

Source: Health Advances interviews and analysis, PARXEXEL Consulting.

India: Potential Trial Delays – Core Shell

The Indian regulatory process and review by Drugs Controller General India (DCGI) is subject to many different delays.

Trial Applications	• Foreign sponsors must use a local agent to file all of the requisite applications relating to the conduct of a clinical trial – For protocols approved by EMA or regulatory agencies in the US, UK, Switzerland, Australia, Canada, Germany, South Africa or Japan, review approval is projected to take 2 to 4 weeks – Clinical trial applications that do not have prior approval of an acceptable foreign authority will take 8-12 weeks for approval – Will need to seek an Indian partner to initiate trials and clinical development
DCGI Interactions	• DCGI depends on external experts and other government agencies for advice on applications making the process subject to additional external delays
Biological Samples	• If biological samples are to be shipped out of India another license is required, this application process takes 2 to 4 weeks
Novel Technology	• Because the core-shell is a novel technology, review from Department of Biotechnology may be extended, resulting in ad additional 6 months of the approval timelines
Ethics Review	• There is no national ethics committee in India, ethics committees are situated regionally and/or associated with specific institutions • Ethics reviews can take 3 – 6 months

Source: Health Advances interviews and analysis, PAREXEL consulting.

Africa: Clinical Trial Req'ts and Timeline – Core Shell

Assuming WHO prequalification, a confirmatory Phase III trial in Africa is typically conducted over a time period of about 3 years, but can take longer if the ethics committee review is done after the regulatory authority review instead of in parallel.

Phase I

- Primarily for safety
- Countries will typically accept Ph I data from studies done in other countries provided it is scientific
  - Clinical data from the US, Canada, Australia, Norway, Finland, France, Denmark, Netherlands, Austria, Japan, EMA, Switzerland, Belgium, Germany, Italy, Ireland, UK, and those that have been prequalified by WHO can be accepted more quickly than data from other countries

Phase II

- Drugs that are already on the market can typically move directly to Phase II studies
- Tests for safety in the intended patient group and also tests efficacy

Phase III

- This focuses of safety and efficacy in the intended patient group, usually in multiple centers
- Ethics review is either conducted in parallel or following Ph III, and typically takes ~2 months
- Regulatory review and approval also takes ~2 months

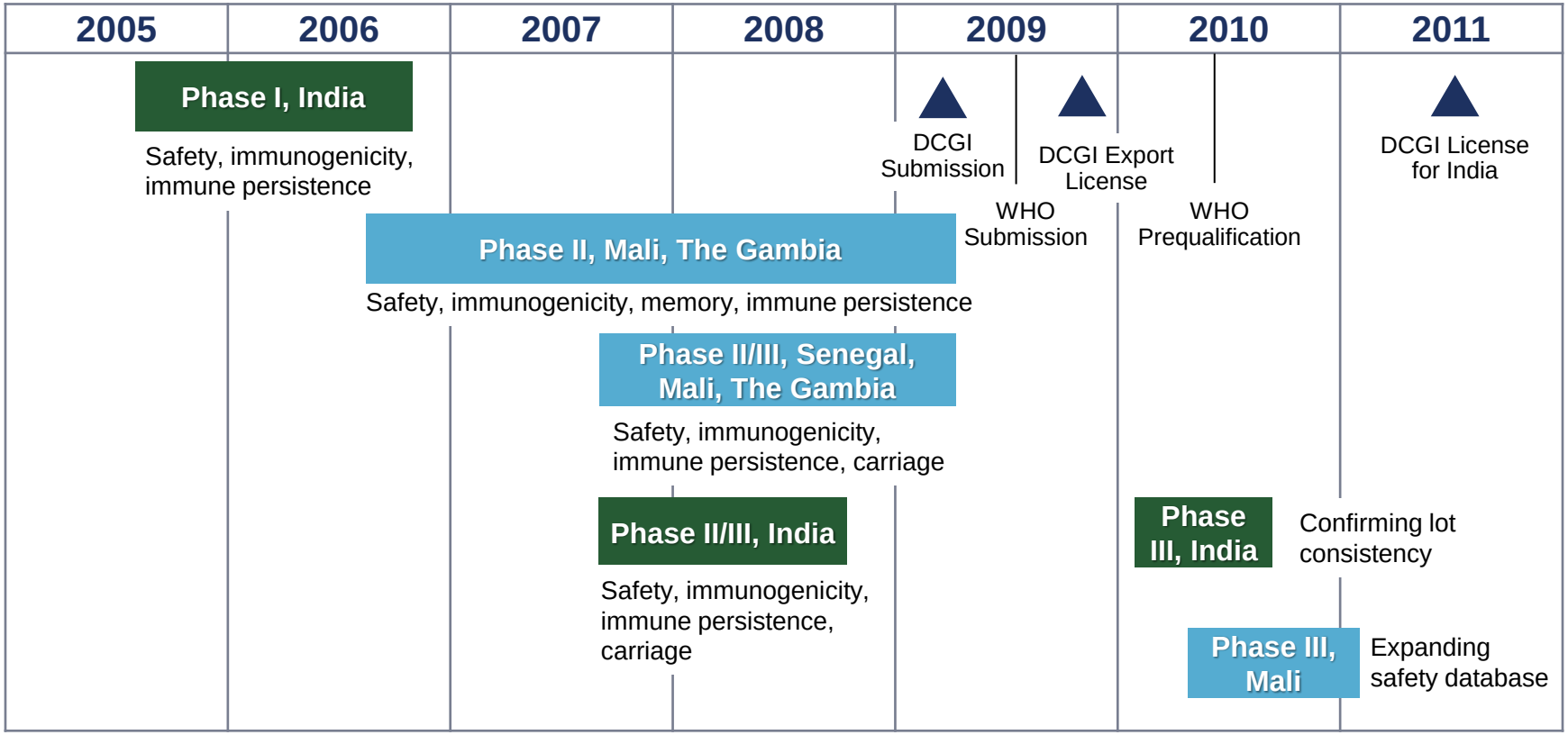
Phase I and II trials can be replaced by data from other countries or WHO pre-qualification data

- Through the Africa Vaccine Regulatory Forum (AVAREF Platform), a manufacturer can choose to conduct a trial in one of AVAREF member's states and seek joint approvals in other countries across Africa.

Source: Health Advances interviews and analysis, PAREXEL consulting.

Case Study: MenAfriVac Development Timeline

MenAfriVac was granted approval in India ~6 years after Ph I trials began in India, and the license for export (primarily to African countries) was granted in 2009, less than 3 years after trials began in Africa.



As MenAfriVac was the focus of an intense global health effort, clinical development was accelerated. Core-shell technology development may lag this timeline.

Source: Health Advances interviews and analysis, WHO, PAREXEL Consulting.

Indian trials | African trials

Trial Size Consideration – Core Shell

Larger trials are required for vaccines with low efficacy and/or low disease attack frequency. An HIV/AIDS vaccine trial will likely require a large population study due to the low expected efficacy.

Factors Determining Trial Size

Disease Attack Rate (Incidence Proportion)

- In general, the attack rate increases as R0 increases and is measured in 'at risk' population (defined as one that has no immunity to the attacking pathogen)
- If attack rates are **high**, the number of cases in the population of interest may be sufficient to measure VE accurately in a relatively small population and short time
- If attack rates are **low**, the enrollment and/or duration of follow up may need to be increased to detect sufficient cases for precise estimation of efficacy

Vaccine Efficacy

- The size of the trial depends on patient years of observation needed to accumulate the required number of cases in the unvaccinated group
- The number of endpoints required is inversely proportional to vaccine efficacy

Vaccine Efficacy	P=0.05 Power= 80%	P=0.05 Power=90%
20%	353	472
90%	12	14

	Rabies	Meningococcal	HIV/AIDS	HPV
Disease Attack Rate	• N/A (mostly by animal attack), R0=1.6	• ~1% (men. Belt), R0=1.3	• Varies by pop group, R0=3.5	• HPV 16 ~4.5%, vary by serotypes, R0=1.0
Vaccine Efficacy	• High efficacy	• High efficacy	• Expected to be low	• High efficacy
Relative Impact on Trial Size	• Smaller size: high efficacy/ attack rate	• Smaller size: high efficacy/attack rate	• Larger size: lower efficacy	• Moderate size: high efficacy but varied attack rate by serotype

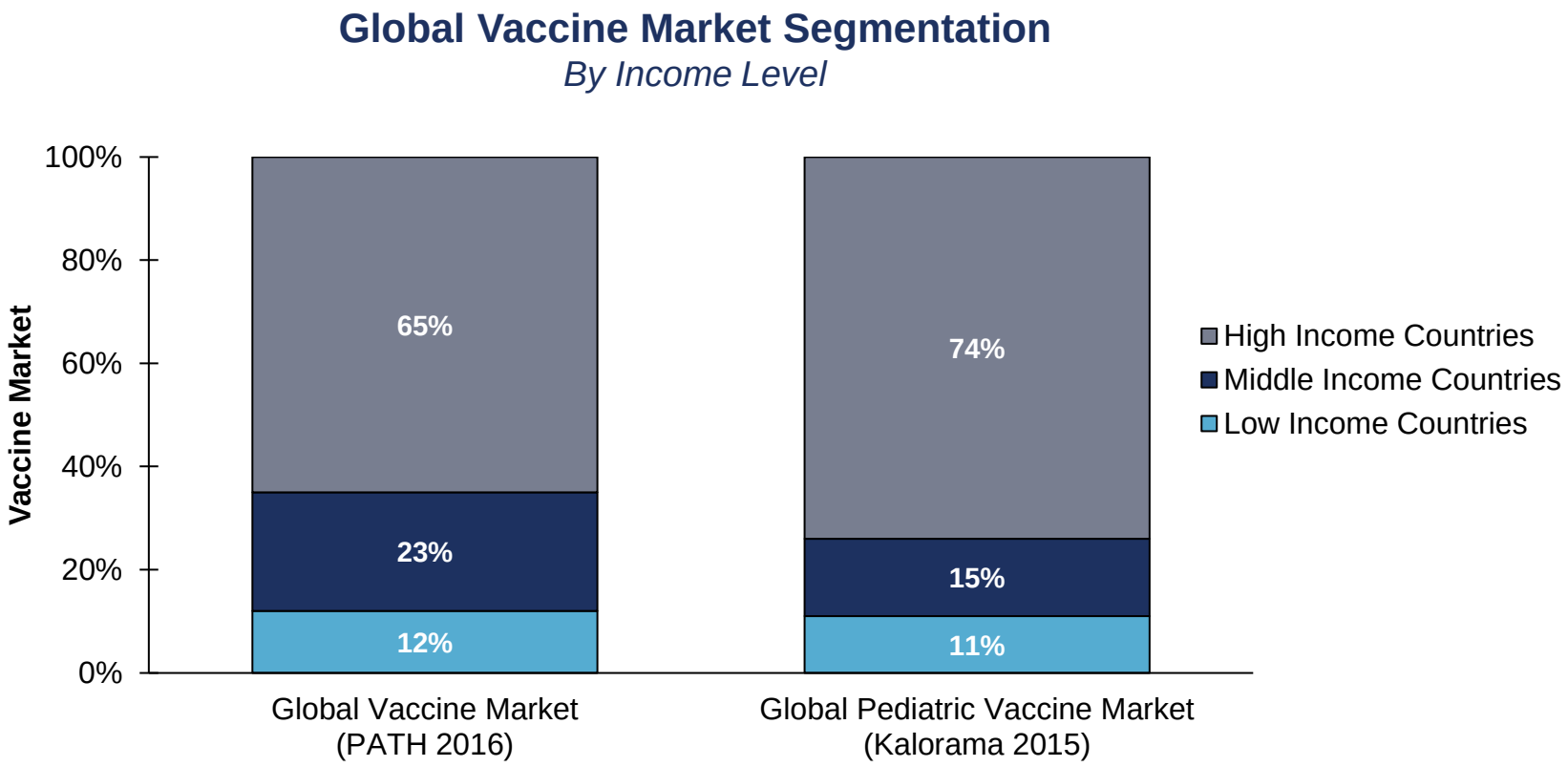
Note: R0= basic rate of reproduction, VE = vaccine efficacy, RR = the relative risks of vaccinated group, ARU = the disease attack rate (AR, frequency) among unvaccinated, ARV = AR among vaccinated.

Source: Health Advances interviews and analysis, WHO 2015 Guidelines on Clinical Evaluation of Vaccines.

$$VE(\%) = \frac{ARU - ARV}{ARU} \times 100 = 1 - RR$$

Vaccine Market Segmentation: Global, by Income Level

Using data from PATH and Kalorama, Health Advances estimated an average share split among high, middle, and low income countries to use for calculating market sizes.

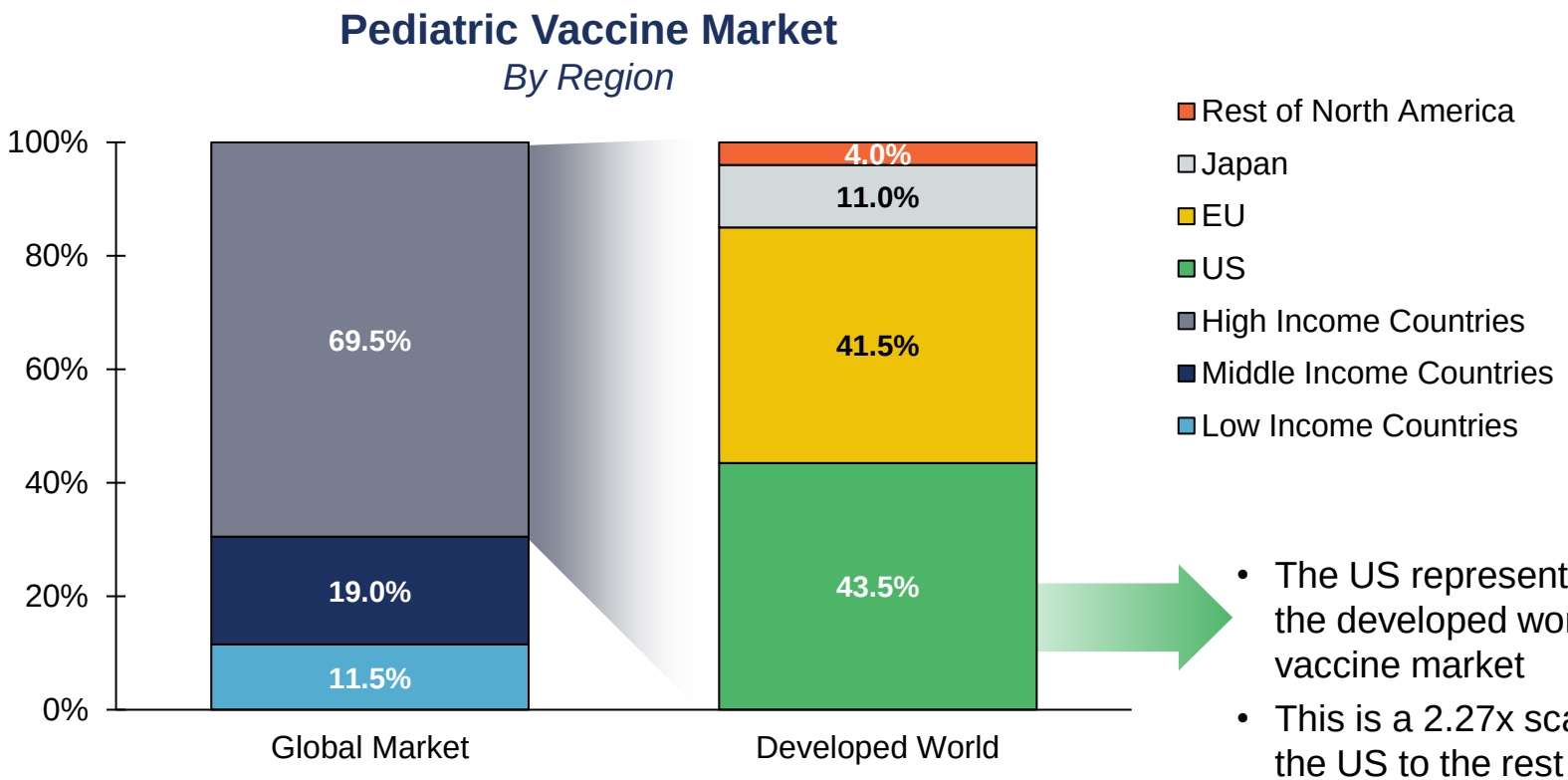


Health Advances used an average share split from these two sources to scale up and calculate relative market sizes: 69.5% for high income countries, 19% for middle income countries, and 11.5% for low income countries.

Source: Health Advances interviews and analysis, Kalorama 2015, PATH 2016.

Vaccine Market Segmentation: Developed World

The United States represents 44% of the pediatric vaccine market, which results in a scale up factor of 2.27x to the rest of the developed world.



- The US represents 44% of the developed world pediatric vaccine market
- This is a 2.27x scale up from the US to the rest of the developed world

Source: Health Advances interviews and analysis, Kalorama 2015.