

National Vaccine Advisory Committee
February 2, 2016

Aligning science, policy and partners to
create an enabling environment for vaccine
development

Mark Feinberg, MD, PhD
International AIDS Vaccine Initiative

Diverse challenges for vaccine innovation

- Challenges to vaccine development for prevalent diseases (eg, **CMV**, RSV, Group A Strep, etc)
- Challenges to vaccine development for emerging diseases (eg, **Ebola**, MERS, Zika, etc)
- Challenges to developing improved versions of available vaccines (eg, pertussis, influenza, etc)
- Challenges to applying scientific advances to develop new vaccines and improve existing vaccines (eg, novel adjuvants, combination vaccines, novel delivery routes, greater thermostability, etc)

The imperative to think and do differently.....

“To raise new questions, new possibilities, to regard old problems from a new angle, requires creative imagination and marks real advance in science.”

Albert Einstein

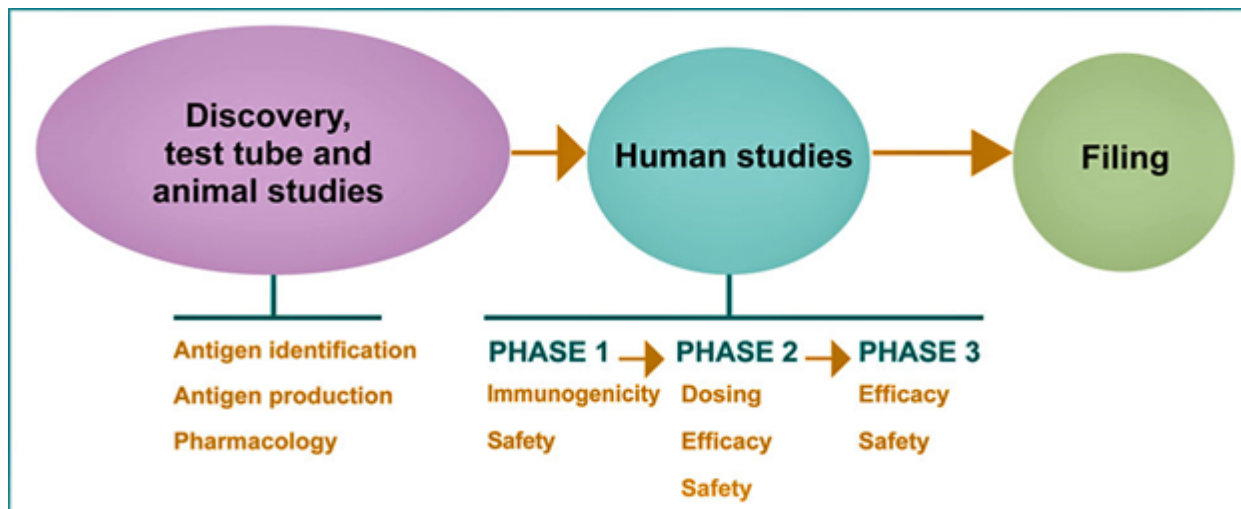
As quoted in the 2010 National Vaccine Plan, NVPO/DHHS

The imperative to think and do differently.....

Unless we find new ways of approaching vaccine development through greater mutual understanding and the proactive “end to end” alignment of private and public sector stakeholders to fill gaps and share risks, then promising scientific progress will not be effectively translated into public health progress and our ability to prepare for, and respond to, emerging public health threats will be greatly compromised.

Vaccine development has long been a long, complex and expensive process

- Vaccine development can take from 15 to 20 years and cost as much as USD^a 800 million or more.¹
 - Including costs to build a vaccine manufacturing facility and maintain equipment, that figure can rise to well over USD 1 billion.²
- Clinical development involves a large number of subjects.
 - Vaccines must meet a high threshold of efficacy and safety.
- Manufacturing processes must meet stringent quality control criteria.
- Final filing initiates an in-depth evaluation by governmental regulatory authorities.



Data from FDA Vaccine Approval Process.³

^a USD = US dollars.

1. Plotkin SA. *Health Aff.* 2005;24(3):631–634.

2. Center for Global Development. *Making Markets for Vaccines: Ideas to Action*. Center for Global Development; 2005.

3. US Food and Drug Administration. Available at: <http://www.fda.gov/cber/vaccine/vacappr.htm>. Accessed Nov 1, 2007.

Elements and Typical Timelines for Vaccine Development

15 to 20 Years

Typical timeline to develop a vaccine.

- Scientific opportunity
- Translation and feasibility
- Definition of desired target product profile (TPP)
- Clarity on anticipated vaccine demand and economic/public health value
- Definition (and enforcement) of key milestones and “go/no go” criteria
- Process Development
- Dose Selection
- Establishment of proof of concept
- Additional Phase II evaluation
- Manufacturing/supply solution for affordable production
- Phase III demonstration of safety/efficacy
- Licensure (informed by broad and deep evidence base)
- Generation of evidence to guide policies and recommendations
- Demonstration of feasibility and impact of introduction
- Provision of affordable, appropriate, reliable and sustainable supply

2016

2031+

Future vaccine development efforts face even greater uncertainties as well as higher risks, complexity and costs

- Biological risks/uncertainties (e.g., complex natural histories, incompletely understood pathogenesis, lack of natural immunity to natural infection, lack of available immune correlate of protection, safety concerns [e.g. immunopathologic potential], etc.)
- Development risks/uncertainties (e.g., populations, pathways, endpoints, duration and scope of clinical trials needed to support licensure)
- Programmatic risks/uncertainties (e.g., lack of “line of sight” from discovery to development to licensure to recommendation to reimbursement to implementation to in-use monitoring/follow-up [safety and duration of efficacy] to population impact demonstration)
- Resource constraints, opportunity costs and competing priorities

Typical portrayal doesn't communicate many of the key determinants for investment

- Long timelines for development exacerbate impact of uncertainties (eg, changing epidemiology or priority placed on prevention by policy makers and the public)
- Significant upfront investment at risk needed (eg, efficacy trials, manufacturing facilities before efficacy is demonstrated and probability of licensure de-risked)
- Investments in new vaccines compete, in a very resource constrained environment where significant pressures exist for maximizing pipeline productivity and value, with other projects with higher and faster potential return on investment (eg, novel biologics). In this environment, the impact of opportunity costs is often greater than those of direct costs.
- When policy makers and payers are not willing to pay higher prices for improved vaccines (eg, enhanced efficacy, combination, improved presentation, delivery), there is no possibility of realizing a return on investment in any traditional commercial model

Health Economics (HECON) studies and programmatic costs increasingly important to ACIP

- ACIP Charter
 - “When considering recommendations for use of a vaccine...deliberations should include consideration of vaccine efficacy as well as cost/benefit and risk/benefit analyses”
- Recent trend towards increased emphasis on economic studies, as well as overall impact to immunization programmatic costs by the ACIP (and CDC and DHHS)
- Such assessments are now major contributors to strength and breadth of ACIP recommendations

Guidance for Health Economics Studies Presented to the Advisory Committee on Immunization Practices (ACIP) – Nov07

<http://www.cdc.gov/vaccines/recs/acip/downloads/economics-studies-guidance.pdf>



Cost-Effectiveness of Meningococcal Vaccination Strategies for Adolescents in the United States*

Ismael Ortega-Sanchez, PhD
National Center for Immunization and
Respiratory Diseases

Cost-effectiveness of male HPV vaccination in the United States

Harrell Chesson, PhD
NCHHSTP
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices

Changes in the Cost-Effectiveness of Meningococcal Vaccination Strategies in the United States *

Ismael Ortega-Sanchez, PhD
National Center for Immunization and

Cost-Effectiveness of Quadrivalent HPV Vaccination of Adult Women

Harrell Chesson, PhD
NCHHSTP
Centers for Disease Control and Prevention

Advisory Committee on Immunization Practices
February 24, 2010



With a growing focus on vaccine price itself, rather than cost-effectiveness and public health value....

The development and availability of newer vaccines since VFC began 17 years ago has expanded the prevention impact of our programs, but most newer products and new formulations of old products have come at substantially higher prices. ***We have also seen prices rising after initial federal contracts were set, and prices failing to fall when vaccine schedules are compressed or a second vaccine manufacturer enters the market. These are not things that we would expect under normal economic conditions.***

At a time when budgets are under intense review, ACIP considerations and the public value and risk-benefit ratios of various vaccine recommendations are made even more difficult with the rising prices of vaccines. While the budget pressures I mentioned are not unique to CDC or to immunization, I know that ACIP members have been wrestling with complex policy decisions. ***Certainly, if vaccine prices were coming down instead of going up or were responding as we would expect them to under market conditions, there would be an easier set of decisions.***

Tom Frieden, MD, MPH

Director, Centers for Disease Control and Prevention

Comments to ACIP February 23, 2011



Barriers to Vaccine Development: Cytomegalovirus (CMV) Vaccine Case Study

- 1985 IOM Report¹: CMV identified as a candidate for accelerated vaccine development ... “success was reasonably foreseeable within the next decade”
- 1999 IOM Report²: CMV placed in the Most Favorable Category I with a vaccination strategy that could save money; report “assumed development is feasible and that licensure can occur within 7 years”
- Each year in the US, 30,000 children continue to be born with congenital CMV infection and CMV causes more long-term problems and childhood deaths than Down syndrome, fetal alcohol syndrome, and neural tube defects (>200 newborn deaths, >5,000 infants with permanent disability, >\$2 billion annual healthcare burden)
- Despite the efforts of many stakeholders over the years, there have been only a limited number of phase I and phase II CMV vaccine candidates, and none to date, with compelling promise or evident momentum towards licensure

1. IOM Report: New Vaccine Development: Establishing Priorities Vol I: Diseases of Importance in the United States, 1985, p.4.

2. IOM Report: Vaccines for the 21st century: a tool for decision making, 1999, p. 5.

3. CDC CMV website <http://www.cdc.gov/cmvp/index.html>, accessed April 25, 2011.

Scientific Challenges for the Development of an Effective CMV Vaccine

- Due to strict species specificity, relevant animal models to study vaccine safety and efficacy are limited, and none accurately recapitulate pathogenesis and potential protection from human congenital CMV disease
- Unknown immune correlate(s) of protection against congenital CMV infection
- While a live viral vaccine might elicit both desirable humoral and cellular immune responses, balance between vaccine attenuation and immunogenicity has not been achieved via traditional approaches
- Uncertain if recombinant subunit vaccines will be able to protect against a complex pathogen that establishes persistent infection and antagonizes host antiviral immune responses
- ***Clinical development path leading to licensure is exceptionally complicated with numerous uncertainties about the best age group and indication to target and the nature of clinical data needed to support favorable licensure and policy decisions***

Potential Target Populations Influence Clinical Trial Endpoint Choices

Adult Women

CMV seronegative

Prevention of cCMV infection or disease
Reduction of CMV viremia
Prevention of 1° CMV infection
Prevention of 1° CMV infection during pregnancy

CMV seropositive or seronegative

Prevention of cCMV infection or disease
Reduction of CMV viremia

Adolescent Girls

Immunologic bridging to adult population

- Inclusion of adolescent girls in pivotal efficacy studies of a cCMV vaccine will be challenging due to the long time frame between vaccination and pregnancy and the ability to assure follow-up of the infant many years after the subject entered the study
- Strategy will be necessary to bridge adolescent girls to the adult population

Toddlers and Young Children

CMV seronegative

Decrease horizontal transmission and subsequent prevention of cCMV (herd immunity)

Demonstration of VE: Number of Subjects (*CMV Seronegative*) Required to Accrue Required Primary Endpoint Cases (*Primary CMV Infection*)

Required Cases	Attrition (per year)	Infection Rate (per year)	Probability of becoming a case (per year)	Total Subjects to Enroll and Followed at the Indicated Duration to Acquire the Required Cases		
				2 years	3 years	4 years
44 [Power = 91% when VE = 75%]	15%	1%	0.01	3,823	2,761	2,238
		2%	0.02	1,920	1,393	1,134
		4%	0.04	969	709	582
		10%	0.10	399	299	251
		20%	0.20	210	164	143

Paula Annunziato, Merck, FDA-NIH Workshop on CMV Vaccines January 2012

Demonstration of VE: Number of Subjects (*CMV Seronegative*) Required to Accrue Required Primary Endpoint Cases (*Congenital CMV Infection*)

Attrition (per year)	Pregnancy Rate (per year)	Infection Rate [†] (per year)	Transmission Rate [‡] (per year)	Probability of becoming a case (per year)	Total Subjects to Enroll and Followed at the Indicated Duration to Acquire the Required Cases		
					2 years	3 years	4 years
Required cases = 44 [Power = 91% when VE = 75%]							
15%	10%	1%	30%	0.0003	126,864	91,246	73,670
			40%	0.0004	95,153	68,440	55,260
		2%	30%	0.0006	63,441	45,635	36,849
			40%	0.0008	47,585	34,232	27,644
	15%	1%	30%	0.0005	84,582	60,839	49,123
			40%	0.0006	63,441	45,635	36,849
		2%	30%	0.0009	42,300	30,432	24,576
			40%	0.0012	31,729	22,830	18,439
† Among CMV seronegative women; ‡ Among CMV seronegative women with primary infection.							

Paula Annunziato, Merck, FDA-NIH Workshop on CMV Vaccines January 2012

Demonstration of VE: Number of Subjects (*CMV Seronegative and Seropositive*) Required to Accrue Required Primary Endpoint Cases (*Congenital CMV Infection*)

Attrition (per year)	Pregnancy Rate (per year)	Infection Rate [†] (per year)	Transmission Rate (per year)	Probability of becoming a case (per year)	Total Subjects [¶] to Enroll and Followed at the Indicated Duration to Acquire the Required Cases		
					2 years	3 years	4 years
Required cases = 44 [Power = 91% when VE = 75%]							
15%	10%	1%	30% [‡] ; 1% [§]	0.0003 [‡] ; 0.00001 [§]	302,056	217,249	175,401
			40% [‡] ; 1% [§]	0.0004 [‡] ; 0.00001 [§]	229,282	164,914	133,153
		2%	30% ; 1%	0.0006 ; 0.00002	151,048	108,652	87,733
			40% ; 1%	0.0008 ; 0.00002	114,661	82,486	66,610
	15%	1%	30% ; 1%	0.0005 ; 0.00002	201,384	144,851	116,956
			40% ; 1%	0.0006 ; 0.00002	152,868	109,962	88,791
		2%	30% ; 1%	0.0009 ; 0.00003	100,712	72,453	58,511
			40% ; 1%	0.0012 ; 0.00003	76,454	55,009	44,429
†Assuming common infection rate among both CMV seronegative and seropositive women; ‡Among CMV seronegative women with primary infection; § Among CMV seropositive women with primary infection; ¶Assuming 40% are CMV seronegative and 60% are CMV seropositive.							

Demonstration of VE: Number of Subjects (*CMV Seronegative*) Required to Accrue Required Primary Endpoint Cases (*Congenital CMV Disease*)

Pregnancy Rate (per year)	Infection Rate [†] (per year)	Transmission Rate [‡] (per year)	Disease Rate [§] (per year)	Probability of becoming a case (per year)	Total Subjects to Enroll and Followed at the Indicated Duration to Acquire the Required Cases		
					2 years	3 years	4 years
Required cases = 44 [Power = 91% when VE = 75%] ; 15% attrition (per year)							
10%	1%	30%	10%	0.00003	1,268,486	912,237	736,440
		40%	10%	0.00004	951,369	684,184	552,337
	2%	30%	10%	0.00006	634,252	456,131	368,234
		40%	10%	0.00008	475,693	342,104	276,183
15%	1%	30%	10%	0.00005	845,663	608,166	490,970
		40%	10%	0.00006	634,252	456,131	368,234
	2%	30%	10%	0.00008	422,840	304,095	245,499
		40%	10%	0.00012	317,135	228,078	184,132
† Among CMV seronegative women ; ‡ Among CMV seronegative women with primary infection. § Among infected infants.							

Paula Annunziato, Merck, FDA-NIH Workshop on CMV Vaccines January 2012

Summary of FDA-NIH-NVPO Workshop on CMV Vaccine Development (January 2012)*

- “Pre-licensure studies using prevention of cCMV disease as a clinical endpoint to demonstrate vaccine efficacy are impractical given the complexity, number of participants needed and years of follow-up needed to detect hearing loss (the most common cCMV manifestation)”
- “Resolution of uncertainties regarding study endpoints likely to be acceptable to regulatory agencies could increase the likelihood of investment by manufacturers in development of CMV vaccines”
- “Prevention of cCMV infection is considered to be the most relevant and practically achievable endpoint for Phase III efficacy trials to support licensure of a vaccine indicated for prevention of cCMV disease”

*Krause et al, Priorities for CMV Vaccine Development
Vaccine, 32, 4-10, 2014

Filling the Gaps Impacting CMV Vaccine Development

Will prevention of congenital infection be sufficient to support licensure with a congenital disease prevention indication?

Will a safe and efficacious vaccine that is licensed for prevention of congenital CMV infection garner a broad and strong routine ACIP recommendation for girls and women?

What are the key drivers/assumptions of “value” for ACIP? What health economic analyses/budget impact will be needed?

- What are the policy expectations for demonstration of cost effectiveness and disease burden in relation to public health value to warrant widespread adoption of the vaccine?
- How do the expectations vary based on target population for vaccination?

How would the vaccine be handled in the National Vaccine Injury Compensation Program if the vaccine is indicated for women of child-bearing age and benefits the unvaccinated child?

Suggested approaches to reduce barriers and encourage development of prioritized vaccines

Ways in which HHS agencies and their partners can work together to reduce uncertainty around development, licensure and adoption pathways:

- **Prioritization**: develop a transparent, ranked list of vaccine priorities for key pathogens based on public health burden (current and emergent)
 - Coordinated among DHHS agencies to reach a consensus view from NIAID, CDC and FDA
 - Updated at appropriate and useful intervals to reflect changes in national goals
- **Biology and Epidemiology**: advance understanding of epidemiology and biology of prioritized diseases to fill in knowledge gaps, develop essential enabling tools (eg, case definitions and validated assays) and contribute to robust vaccine design and clinical trial design
- **Target Product Profiles**: develop desired product profiles that clearly describe target population and subpopulations segments, potential indications, key product attributes, etc.
 - Informed with input from scientific leaders and vaccine policy makers (e.g. ACIP, WHO)
 - Programmatic aspects like stability, ease of use and packaging are getting significant attention as priorities for WHO and several national regulatory agencies. Some standardization of FDA requirements with the emerging global needs could simplify and perhaps accelerate improved formulations and packaging.

Suggested approaches to reduce barriers and encourage development of prioritized vaccines (continued)

Ways in which HHS agencies and their partners can work together to reduce uncertainty around development, licensure and adoption pathways:

- **Basis for Licensure:** Identify the potential basis for licensure and clinical endpoints that will be used by regulators to assess vaccine efficacy, and the regulatory considerations for novel vaccine innovations
- **ACIP Policy Recommendation:** provide a reasonable expectation for a favorable recommendation and public sector funding if the target vaccine is developed
 - Private insurance reimbursement and public sector funding in the US are significantly impacted by the strength of ACIP recommendations
 - Greater transparency about the key drivers/assumptions of “value” for prioritized targets will guide development of appropriate health economic studies, budgetary impact and other analyses
- **Novel Development Partnerships:** where gaps exist, support and participate in creative new partnership models between public and private sector entities to advance vaccine innovation and accelerate public health impact
- **Alignment:** develop and facilitate a transparent process for alignment of science, policy, reimbursement, and regulatory stakeholders EARLY in the development process for prioritized vaccines, before key program decisions are made

Accepting and responding to the “new normal”

“Who would have predicted that the end of the last millennium would see the emergence of new pathogens and epidemics, when the medical world thought it had it all under control—at least in the wealthier part of the world? ...The story of new viruses is also not over, and it is safe to predict that more pathogens will emerge and affect us in always faster and more global ways.”

--Peter Piot*

**No Time to Lose: A Life in Pursuit of Deadly Viruses, 2012*

Enablers of Private Sector Engagement in Ebola Vaccine Development

- Appreciation of public health imperative and opportunity to contribute in a valuable, and in some instances unique, ways to the accelerate development of a promising vaccine candidates
- Recognition and ready acceptance of the fact that Ebola vaccine development is not an attractive commercial opportunity
- Expectation that vaccine development efforts would be advanced in collaboration with public sector partners to pool expertise, to share costs and risks, and to manage uncertainties
- Stated commitment of donor/funding organizations (eg, GAVI, UNICEF) to procure and deliver an Ebola vaccine should it prove efficacious and safe

Partnerships and Alliances Advancing Merck's rVSV-ZEBOV Vaccine Development Program



Public Health
Agency of Canada

Public Health Agency
of Canada (PHAC)



NewLink Genetics (Bio-
Protection Systems Corporation)

Phase I Studies

WHO Clinical Consortium/

Wellcome Trust

wellcome trust



- **Switzerland:** University Hospitals of Geneva
- **Germany:** University Medical Center Hamburg/Clinical Trial Center North
- **Gabon:** Centre de Recherches Medicales de Lambarene/University of Tuebingen
- **Kenya:** Kenya Medical Research Institute
- Marburg Laboratory

- **CCV** – Halifax, Canada
- US Department of Defense (WRAIR, JVAP, USAMRIID, DTRA)
- **NIAID/NIH**
- **NewLink Genetics**
- **BARDA**

II/III

Phase II/III Studies

Liberia: Liberia –

NIH Partnership (NIAID)



Sierra Leone: CDC/

Sierra Leone Medical
School, BARDA



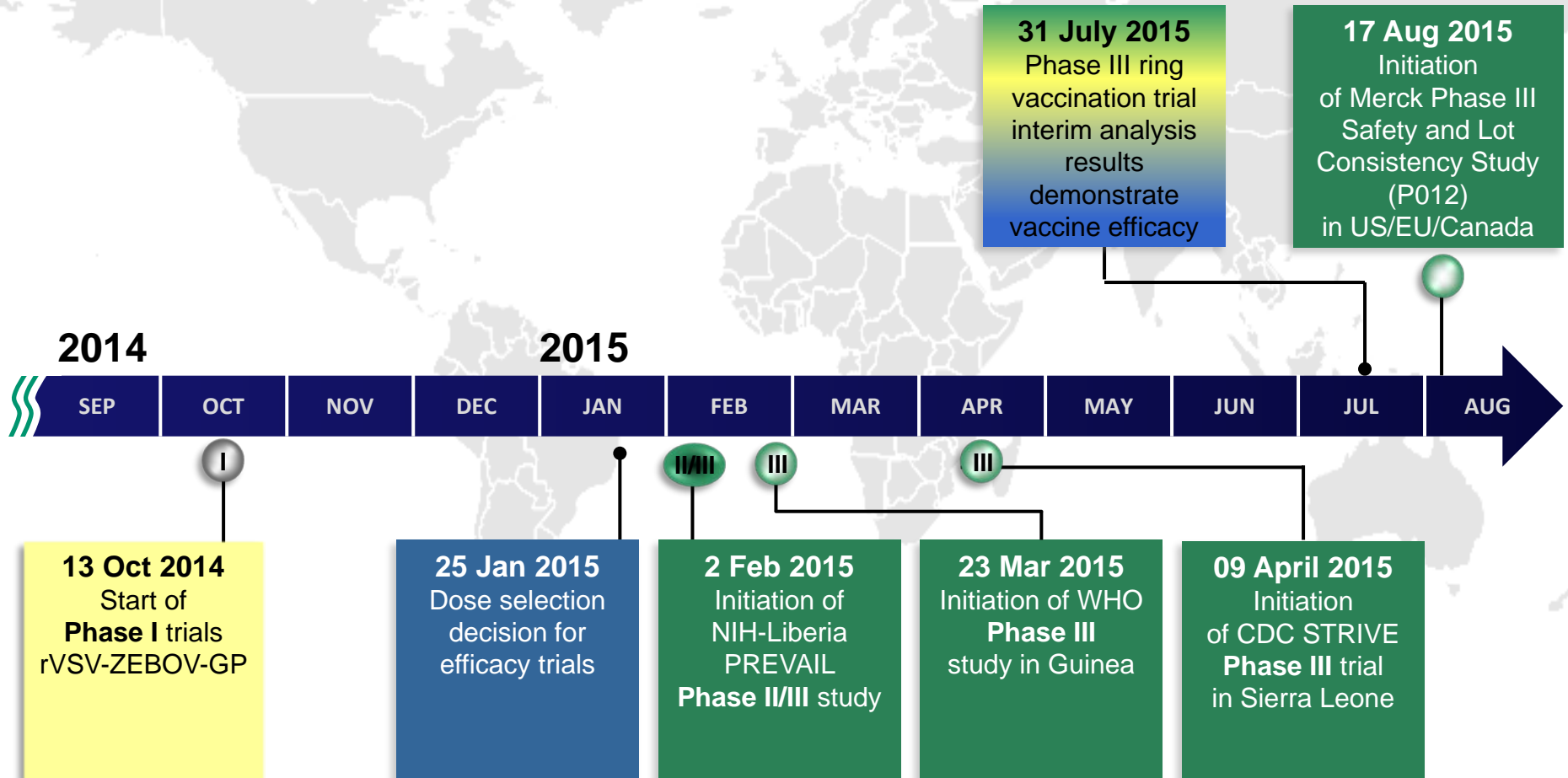
Guinea: WHO/Norwegian Institute of Public
Health//MSF/HealthCanada

**US Department of Defense (WRAIR, JVAP,
USAMRIID, DTRA)**



rVSV-ZEBOV-GP Vaccine Milestones, 2014-2015

Accelerated timeline to develop the Ebola vaccine.



Over 13,000 volunteers vaccinated to date



Conclusions

- The extent to which public and private sector partners work together in sharing risks and responsibilities in addressing this Ebola outbreak will have major implications for engagement in future outbreaks.
- Manufacturers need to have public sector partners who are willing to be transparent about projected demand forecasts and who are willing to share risks for the accelerated production of doses that might not end up being used.
- It is important for the global health community to stay committed to the development of Ebola vaccine candidates. If the global health community does not see the vaccines through to actual approval and deployment (or stockpiling), it will be more difficult to mobilize collective efforts to address future emerging infectious disease threats.
- Therefore, we need to recognize that the precedent set by the nature and ultimate success of the current response will inform and influence the global health community's response to future emerging infectious disease outbreaks

Will and what will we actually “learn from Ebola”?

- **Both** public and private sector partners, working **proactively** in **strategic** partnerships, will be essential to ensure effective public health preparedness
- Need to develop solutions/vaccines for specific disease targets, and proof of concept for those innovations targeting specific virus families (eg, coronavirus)
- Need to develop platform technologies that enable rapid product development and scalable production
- Need to develop consensus on clinical development approaches and regulatory frameworks optimal for use in outbreak settings
- Need to develop and sustain manufacturing solutions for products needed with unpredictable timing and magnitude

*We need good basic science and R&D approaches, but most importantly, we also need a new discipline to enable **trusting**, effective, efficient and proactive multisector partnerships*

Identified gaps/areas for improvement in partnership models

1 Challenge

2 Solution

3 Future implications

Time required to get clinical studies started and contracts signed between partners

Pre-approved templates

- Study protocols
- Clinical trials agreements
- Data /Material transfer agreements
- Ex-US liability insurance agreements

Public health community engagement/consensus on who will put templates into place (i.e. developers, FDA, WHO, other entity)

No known correlate of protection and no validated assays for measurement of immunogenicity

Collaborations to develop validated assays for use across companies engaged in vaccine development

Agreements should ensure regulatory requirements are met / different assays may be required for different vaccine constructs

Time required to solicit, secure and manage funding across multiple agencies with different requirements

Flexible, streamlined and harmonized funding processes across multiple USG agencies including more liberal use of “OTAs”

Efficient, accelerated funding pathways available to respond to evolving public health emergencies

Identified challenges / issues for improvement in partnership models (continued)

1 Challenge

2 Solution

3 Future implications

Unclear regulatory pathways in terms of pre-and post-licensure requirements due to changing epidemic situation

Predefined regulatory frameworks for accelerated pathways and/or emergency use authorization

Regulatory frameworks vetted across regulatory bodies and to include interface with WHO prequalification process

Greater need for manufacturing scale up capacity in tight time frame

Identification of external capacity for process development, scale-up and initial lot development

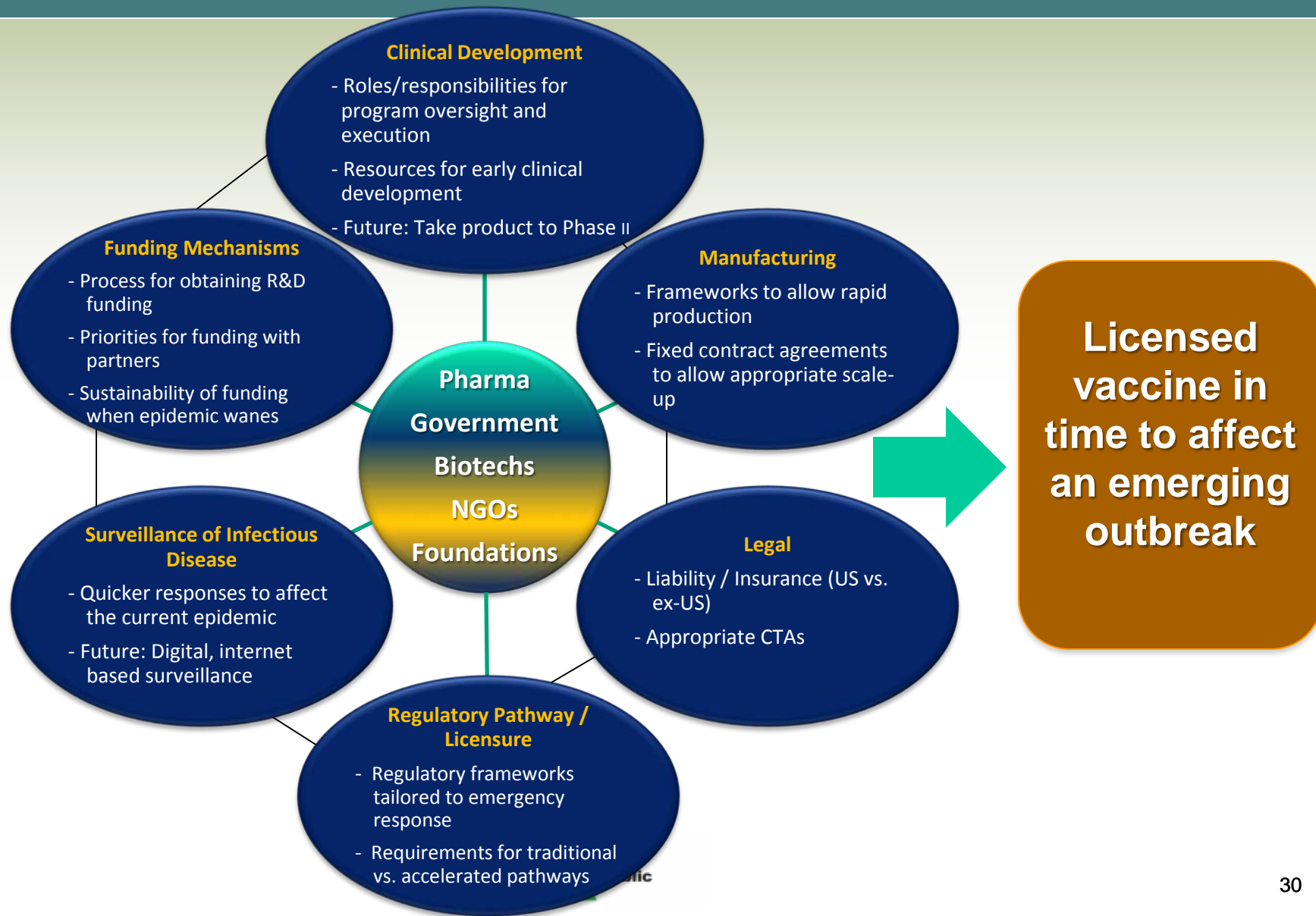
Need for surge capacity (on-call option), and funding / ownership for this option also needs to be determined

No target product profile, procurement of vaccine supply or deployment plan in advance beyond government stockpiles

Guidelines on desired vaccine image, how much vaccine needed, when, and how vaccine to be delivered prior to pre-qualification

Partnership with external funders (e.g. GAVI, country governments) to determine total doses (immediate deployment vs. long term)

Components of Future Partnership Models





Cecilia Kamura, Age 6, Robertsport, Liberia

Thanks very much.....

**....for your efforts to facilitate vaccine
innovation and improve public health....**