National Vaccine Advisory Committee meeting Sept 17-18, 2019

Agenda item: Vaccines for Uncommon Diseases and Small Patient Populations

Topic: Vaccines and Antimicrobial Resistance

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National Vaccine Advisory Committee Member

National Vaccine Advisory Committee. Sept 17, 2019

Disclosure

Employed by GSK where I am a vaccine research physician scientist

Presentation at the invitation of the Office of Infectious Disease Policy, National Vaccine Advisory Committee

Presentation is for educational purposes only; this is not a sales, marketing or promotional presentation

Content of presentation will not include unapproved or investigational uses of products or devices

Vaccines and Vaccination Programs

- Enable individuals to experience healthier lives
- Benefit global society:
  - increased economic health and strong healthcare systems
- Investment in vaccines and disease prevention:
  - proven, effective public health strategy

Driving the potential of new vaccines to transform human health

Scientific knowledge advances and modern vaccine technologies offer great potential for new vaccine development:

- uncommon and/or emerging diseases imparting significant morbidity & mortality
- patient populations small in number yet at risk of clinically important medical and healthcare-associated infections
- personalized vaccines based on subpopulation or individual genetic information
- AMR-relevant vaccines aimed at preventing target pathogens likely to drive antimicrobial use and resistance

New vaccines need to be discovered, developed through to commercialization, and implemented through evidence-based vaccination policy recommendations

Need for comprehensive approach to realize full potential and impact

Discovering innovative technologies and developing new vaccines:
time, human and capital resource intensive, risky

Formulating vaccine policy decisions:
consider broad view, beyond direct health and economic benefits

Evaluate:

- Moral, social, and ethical impact of vaccines, integrated alongside other societal health interventions and programmatic synergies beyond vaccines
- Impacts related to reduced antibiotic use and antibiotic resistance.
- Health equity and justice, community health gains and improved healthcare system function, and societal economic health

Evolution of the current paradigm is needed optimize how we value new vaccines

Without considering full benefits and contribution to society of vaccines, stakeholders may not adequately value the next generation of vaccines, and policy recommendations may result in underutilization at the detriment of patients and public health

Key considerations:

- **Rapid development of new vaccine technologies enabling vaccines for vaccines targeted to less common diseases with significant impact**
- **Innovative clinical trial designs**
- **Role of real world evidence (i.e. post-licensure effectiveness) to adapt recommendations in real-time**
- **Improved collaboration and data-sharing**
- **Increased transparency throughout the development lifecycle**
- **High barriers to entry**

https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/refueling-the-innovation-engine-in-vaccines

Antibiotics

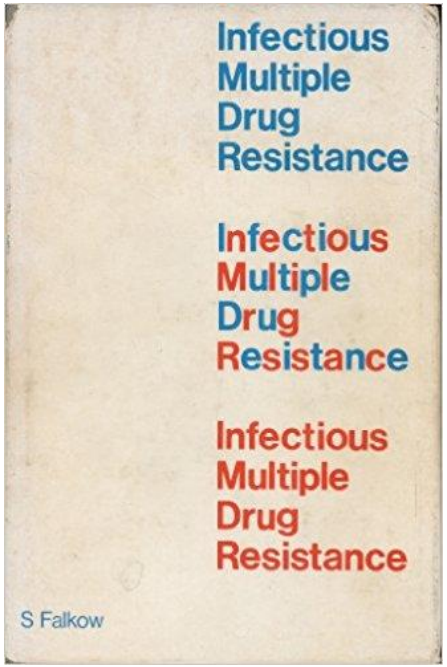
The discovery of antibiotics is one of the greatest medical advances of the 20th century

Modern medicine is made possible by our ability to treat, and prevent, infection: transplantation, neonatal care, complex surgeries, joint replacement, caesarian sections, oncology treatment, sepsis …

Antibiotics

Unfortunately, their use has created an evolutionary response from microbes, and these gains in healthcare are under threat from AMR

These events were predicted



Stanley Falkow (1934-2018) discovered the molecular mechanisms through which bacteria cause disease and predicted the rise of *multidrug-resistant* bacteria

By the 1970s he predicted that overuse of antibiotics would soon lead to drug resistance and the loss of their utility

Falkow already had plenty of evidence to base his predictions on

His recommendation to stop the use of antibiotics in animals was not implemented by the US authorities

Science 08 Jun 2018:Vol. 360, Issue 6393, pp. 1077 http://science.sciencemag.org/content/360/6393/1077

The Issue
Antibiotic-Microbial Resistance (AMR)

Multidrug resistant organisms increasingly common, extremely difficult to treat

Now encountering infections that are untreatable

Major contributor: over-prescription of current antibiotics in animals and humans

AMR
Why should we be worried?

Serious, growing threat to public health and economy

Deaths annually global, current:

- 60,000 tetanus 120,000 cholera 130,000 measles
- 1.2 M road accidents 1.4 M diarrheal dis 1.5 M diabetes
- 8.2 M cancer
- ***drug resistant infections: 50,000 US/EU; globally >700,000***

If current trend holds: by 2050, ~10 million AMR deaths globally, world GDP reduced up to 2-3.5%

O'Neill J. The review on antimicrobial resistance (2016). https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

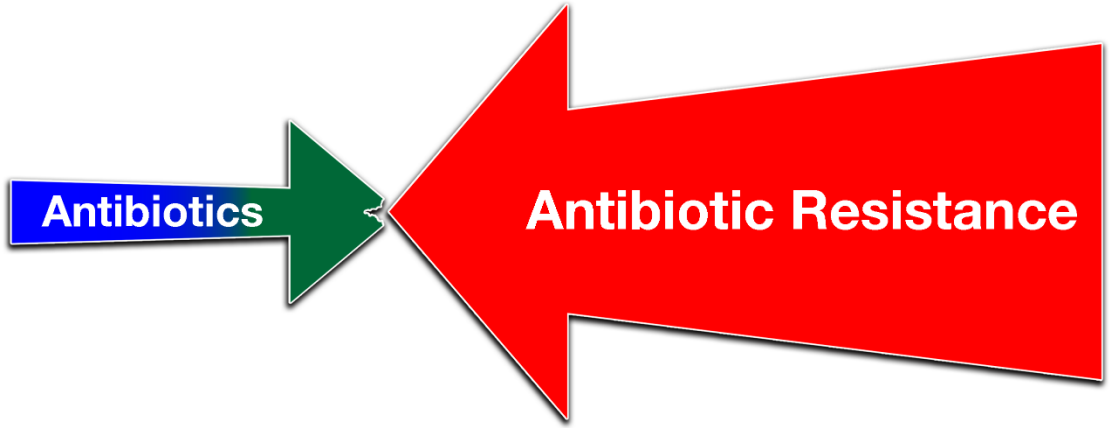
Worst case scenario: “post antimicrobial era”

Problem attracting global attention

Most proposed solutions focus on development of new technologies:

- Antibiotics
- Rapid diagnostic tests
- Vaccines

AMR is difficult for antibiotics alone

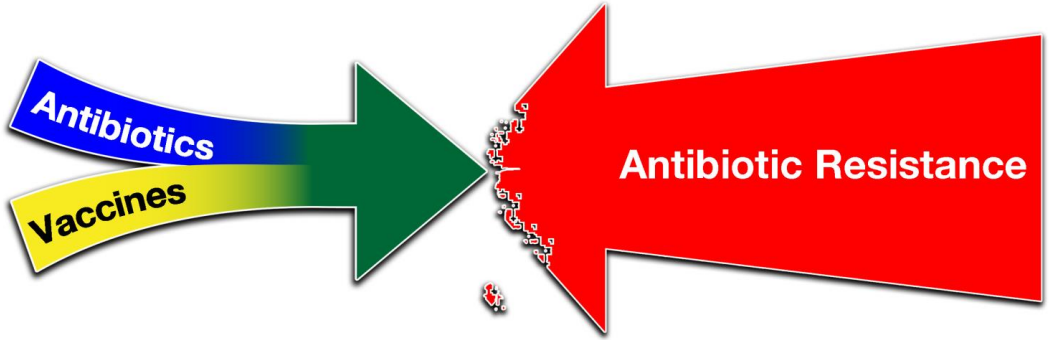


Bloom, Black Salisbury and Rappuoli. PNAS 2018:115;12869

Worst case scenario: “post antimicrobial era”

Problem attracting global attention; most proposed solutions focus on development of new technologies: antibiotics, rapid diagnostic tests, and vaccines

Role of vaccination in controlling AMR frequently acknowledged, yet not led to concrete changes in policy or resourcing



Bloom, Black Salisbury and Rappuoli. PNAS 2018:115;12869

Preventing infections to reduce society's dependence on ABX

Bacterial infections are major drivers of antibiotic prescribing

Vaccines to prevent bacterial infections reduce antibiotic use

– vaccines for diphtheria, meningitis, pneumonia and pertussis have protected tens of millions of individuals from these bacterial infections

Non-bacterial infections can trigger inappropriate use of antibiotics

– vaccines for non-bacterial infections, such as influenza and rotavirus, avoid diseases that can trigger inappropriate use of antibiotics

Increase awareness of role of vaccines in addressing AMR

Requires collaborative global response from all stakeholders:

- scientific community
- pharmaceutical sector
- policy-makers
- healthcare funders

A Call for Greater Consideration for the Role of Vaccines in National Strategies to Combat Antibiotic-Resistant Bacteria: Recommendations from the National Vaccine Advisory Committee

Approved by the National Vaccine Advisory Committee on June 10, 2015

National Vaccine Advisory Committee

The emergence of a novel virus receives widespread attention in the news media and among the public. However, the greatest threat to public health in the United States is unlikely to be an exotic disease but, rather, the mounting threat of antibiotic resistance in commonly acquired bacterial infections. The human and economic costs of this growing crisis are notable.[1,2] In the 2013 report by the Centers for Disease Control and Prevention (CDC), *Antibiotic Resistance Threats in the United States*, it is estimated that more than two million people contract an antibiotic-resistant infection each year in the United States, and approximately 23,000 die as a result of their infection.[2] The escalating rate of resistance among bacterial pathogens is being facilitated by the abundant (and often inappropriate) use of antibiotics, and concern is rising that the arsenal of effective products to treat bacterial infections will soon run out.[3] For example, it is now estimated that 6,700 (13%) of the 51,000 health-care–associated *Pseudomonas aeruginosa* infections that occur in the United States each year are resistant to at least three classes of antibiotics, and some strains show resistance to nearly all classes of antibiotics.[2] The lack of effective antibiotic therapy will have a significant impact in nearly all areas of medicine, but especially in surgery, oncology, intensive care, and transplant medicine.

In September 2014, the White House released the President's National Strategy to Combat Antibiotic-Resistant Bacteria[4] concurrently with the President's Council of Advisors on Science and Technology (PCAST) report and recommendations to the president on combating antibiotic resistance.[5] Together, these reports identify priorities and guide coordination across U.S. government agencies to (*1*) better prevent and respond to the spread of antibiotic resistance through improved prevention and stewardship of antibiotic use; (*2*) increase surveillance of emerging antibiotic resistance in humans, animals, and the environment; (*3*) improve capabilities for detection and diagnostics; (*4*) accelerate development of new products, including new classes of antibiotics, therapeutics, and vaccines; and (*5*) enhance international collaboration.[4] The federal commitment to addressing this issue was further emphasized by Presidential Executive Order 13676,[6] which calls for the development of a five-year National Action Plan[7] that proposes concrete activities and milestones for achieving the goals outlined in the National Strategy and a presidential budget request to Congress for $1.2 billion.[8]

PREVENTING INFECTIONS AND THE SPREAD OF ANTIBIOTIC RESISTANCE

Highlighting the role of vaccines and prevention in antibiotic stewardship

The PCAST report, the National Strategy, and the National Action Plan strongly emphasize that practical and measurable actions can and should be accomplished toward the goals of improved antibiotic stewardship and the development of new products to treat antibiotic-resistant infections. We particularly welcome Objective 4.3 of the National Action Plan,[7] which would intensify research and development into new human vaccines to prevent infections, thereby reducing the development of bacterial resistance and the general overuse of antibiotics.

However, although vaccines are mentioned as one component of the overall cadre of new products needed to combat emerging antibiotic resistance in human medicine, their potential to significantly reduce antibiotic use and thereby contribute to the overarching goal of "increasing the longevity of current antibiotics

RECOMMENDATIONS FOR INCENTIVIZING THE DEVELOPMENT OF VACCINES, DIAGNOSTICS, AND THERAPEUTICS TO COMBAT ANTIBIOTIC-RESISTANCE

SEPTEMBER 2017

PACCARB

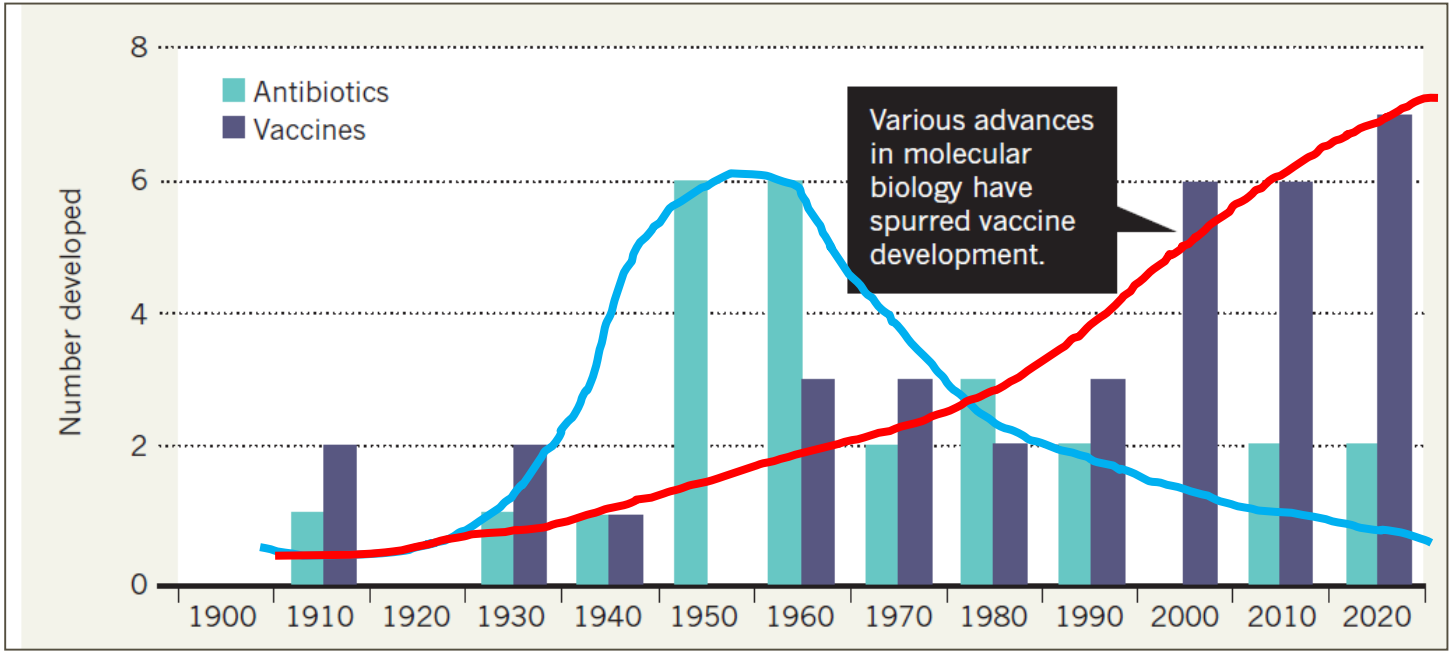
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Developing innovative AMR-relevant vaccines

Develop innovative AMR-relevant vaccines aimed at preventing infections where target pathogens are likely to drive antimicrobial use and resistance (e.g. Shigellosis, Tuberculosis, Malaria, Meningococcal Meningitides, Pneumococcus, COPD, RSV, Flu Universal, MRSA, Gonorrhea, HSV, candidiasis, *C. difficile, Klebsiella, Pseudomonas*)

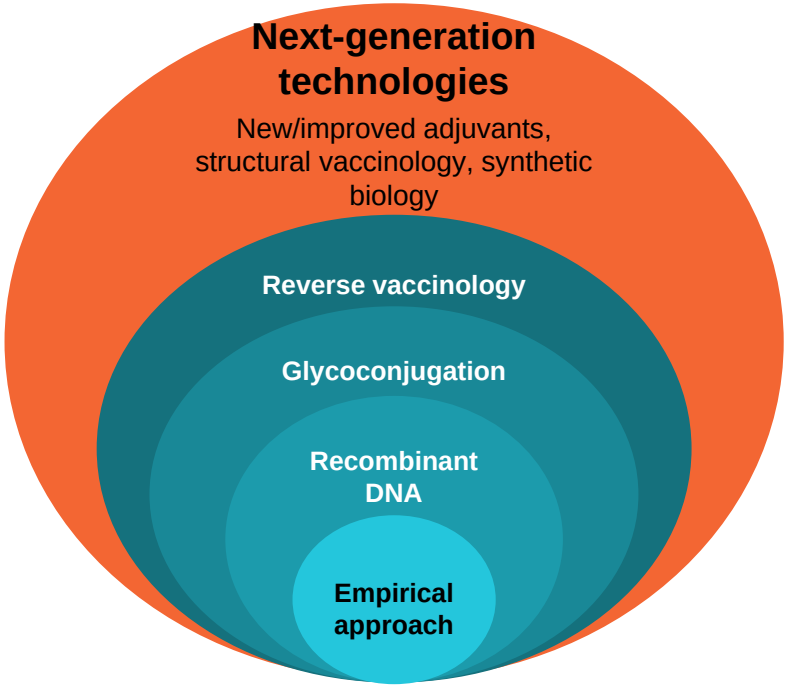
New, global initiatives for R&D of new drugs and vaccines being deployed

1950-70 golden period for antibiotics
1980-today golden period for vaccines



Bloom, Black Salisbury and Rappuoli. PNAS 2018:115;12870

Vaccine technology has been revolutionised in the past 30 years



Waves of new technologies have enabled the development of vaccines that were **previously not possible** and led to improvements in vaccine safety

Potential vaccine game-changing technology

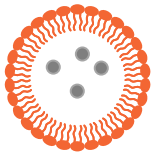
Adjuvant Systems

Synthetic vaccines (DNA/RNA)

Adenoviral vectors

Reverse vaccinology

Structural vaccinology



Platform Technologies

VACCINES FOR AMR PIPELINE

Pathogen name	Research / Preclinical	Phase I	Phase II	Phase III	Marketed	Total
Acinetobacter baumannii	0	0	0	0	0	0
Campylobacter	3	1	0	0	0	4
Enterobacteriaceae	0	0	0	0	0	0
Enterococcus faecium	0	0	0	0	0	0
Escherichia coli (enteric)	11	2	3	1	1	18
Escherichia coli (urinary)	1	1	1	0	0	3
Haemophilus influenzae	8	1	2	3	46	60
Helicobacter pylori	9	1	0	0	0	10
Klebsiella pneumoniae	3	0	0	0	0	3
Mycobacterium tuberculosis	25	4	8	2	13	52
Neisseria gonorrhoeae	4	0	0	0	0	4
Pseudomonas aeruginosa	4	0	0	0	0	4
Salmonella (non-typhoidal)	5	0	0	0	0	5
Salmonella Paratyphi	2	1	0	1	0	4
Salmonella Typhi	6	2	2	2	20	32
Shigella	15	2	2	0	0	19
Staphylococcus aureus	23	2	2	0	0	27
Streptococcus pneumoniae	31	7	8	3	7	56

https://vaccinesforamr.org/review-of-pathogens/vaccine-pipeline-information/ accessed May 5, 2019

Technologies to develop vaccines for AMR:	Not the major challenge
Sustainability of vaccine development for AMR:	The major challenge

Value of vaccines as tool for antimicrobial stewardship

- Collaborate across healthcare, research and policy community to:
  - Expand, strengthen evidence-base on vaccines and AMR
  - Present results via publications, scientific presentations
  - Produce, distribute educational materials
- Support expansion of AMR-sensitive economic models for vaccines accounting for the value of reduced antibiotic use, both in mass vaccination and targeted settings
- Include AMR value-add aspects of vaccines into larger attribution framework used by health authorities; explore potential for changes to vaccine labels to include how appropriate vaccines can impact AMR

Call to action:

- Prioritize vaccination, allocate funding, broaden points of access (e.g. pharmacy), encourage greater use of existing vaccines, and raise awareness amongt decision-makers of the role of vaccines in preventing AMR
- Incentivize development of AMR-relevant vaccines by:
    - Considering AMR-related benefits in regulatory submissions and HTA assessments
    - Developing new funding models such as public-private partnerships that share risk and costs of development where commercial viability is low
- Build body of data on vaccines and AMR through surveillance and research to facilitate decision-making by policy makers

A Call for Greater Consideration for the Role of Vaccines in National Strategies to Combat Antibiotic-Resistant Bacteria: Recommendations from the National Vaccine Advisory Committee

Approved by the National Vaccine Advisory Committee on June 10, 2015

Public Health Reports / January–February 2016 / Volume 131

Recommendation 1
NVAC recommends that the Assistant Secretary for Health (ASH), as the Director of the National Vaccine Program, work with agencies of the U.S. Department of Health and Human Services (HHS) and other federal and nonfederal partners to develop a stakeholder engagement plan to ensure that both vaccine and immunization stakeholders, as well as antibiotic stewardship stakeholder efforts, include information on the role of existing vaccines in minimizing antibiotic use. These communication efforts should include information on vaccines against bacterial pathogens that may currently be or may potentially become antibiotic resistant, and viral vaccines that, by preventing viral illnesses, decrease the inappropriate use of antibiotics for viral infections as well as decrease bacterial superinfections leading to needs for antibiotics.

Recommendation 1.1
These efforts should include a comprehensive analysis modeling the reduction in disease burden due to antibiotic-resistant bacterial strains, the potential reduction in antibiotic prescribing and health-care encounters, and the anticipated cost savings to the health-care system expected from increased uptake of recommended vaccines in all age groups. Vaccines under development may also be included to support those vaccine development efforts.

Recommendation 1.2
These efforts should also tie into surveillance efforts to determine the effects that vaccine uptake has produced on minimizing disease burden due to antibiotic resistant strains in all age groups, and on the ecology of infections caused by both vaccine and non-vaccine strains. When possible, surveillance efforts also should inform on the effects that vaccine uptake, and the reduction in disease caused by vaccine, has had on the prevalence of antibiotic-resistant strains.

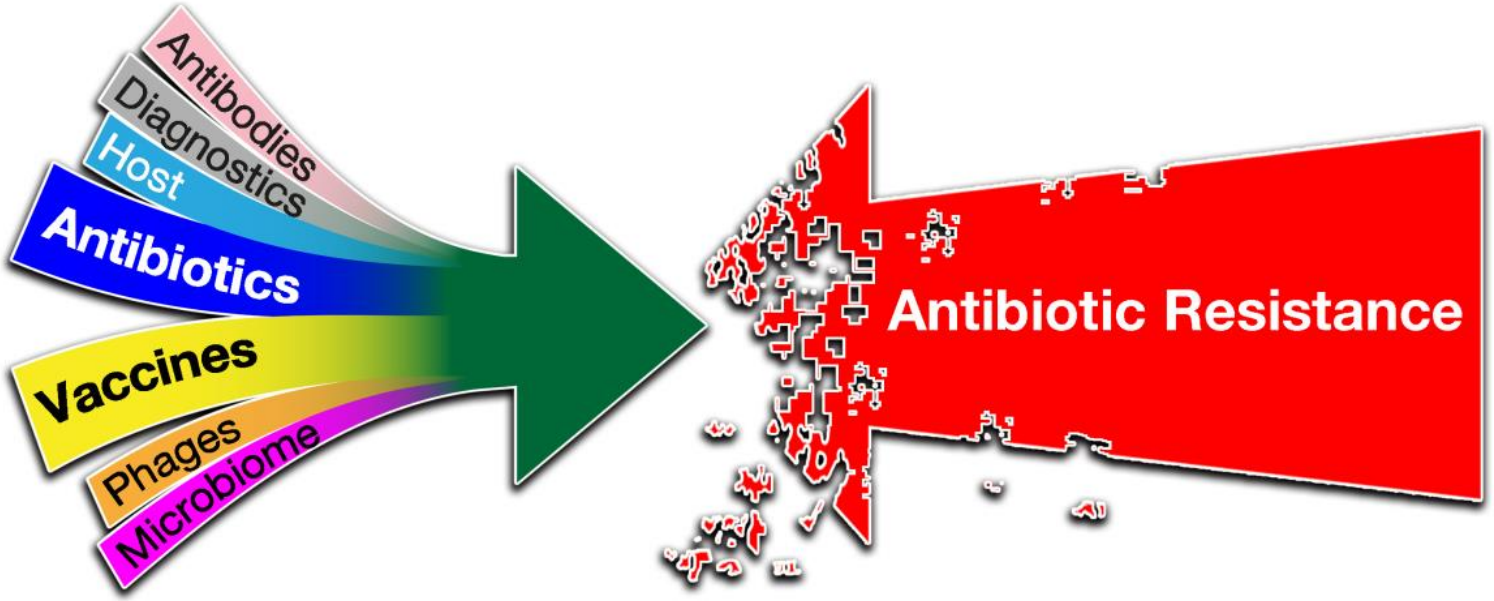
Recommendation 2
The NVAC strongly recommends that the ASH ensure NVAC remains regularly informed of efforts to address antibiotic resistance by revising the NVAC charter to include a liaison representative from the President's Advisory Council on Combating Antibiotic Resistant Bacteria on the NVAC. The NVAC also encourages the ASH to support the future inclusion of an NVAC representative on the President's Advisory Council on Combating Antibiotic Resistant Bacteria to provide knowledge of vaccines and the immunization system to their discussions. Cross-representation on committees maximizes the use of subject matter expertise and stakeholder input to better harmonize departmental efforts.

Recommendation 3
The NVAC strongly encourages the ASH to communicate to the HHS Secretary and the CARB Economic Incentives Working Group that incentives proposed to stimulate antibiotic development must also be evaluated for their utility to accelerate the development of vaccines and other novel prevention strategies. Proposed incentives must be flexible enough to apply to a range of diverse technologies to ensure that we continue to move toward long-term solutions to antibiotic resistance. When incentives are not found to be cross-cutting, additional alternative incentives should be proposed and analyzed to promote a more robust and comprehensive pipeline that includes vaccines.

Recommendation 3.1
Once appropriate economic incentives are identified, the NVAC recommends that the ASH work with relevant federal and nonfederal stakeholders to prioritize promising vaccine candidates to ensure programmatic resources support for vaccine candidates with the greatest potential impact for combating antibiotic resistance and reducing the use of antibiotics in health-care and community settings.

Recommendation 4
The NVAC recommends that the ASH work with FDA and vaccine manufacturers (including pre-commercial-stage biotechnology companies) to encourage early discussion of appropriate regulatory pathways and clinical trial design requirements for the development of vaccines targeting antibiotic-resistant bacteria and vaccines that decrease the use of antibiotics.

Recommendation 5
The NVAC requests that the National Vaccine Program Office provide an annual update on the progress made in supporting the role of vaccines in strategies to combat antibiotic-resistant bacteria.



Bloom, Black Salisbury and Rappuoli. PNAS 2018:115;12869

Evolution of the current paradigm is needed optimize how we value new vaccines

Key considerations:

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- **Innovative clinical trial designs**
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https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/refueling-the-innovation-engine-in-vaccines

HIV VACCINE
TRIALS NETWORK

Perspectives on Progress in Developing a Globally Effective HIV Vaccine

Larry Corey, MD

Principal Investigator, NIAID supported HIV Vaccine Trials Network (HVTN)

Past President and Director, Fred Hutchinson Cancer Research Center

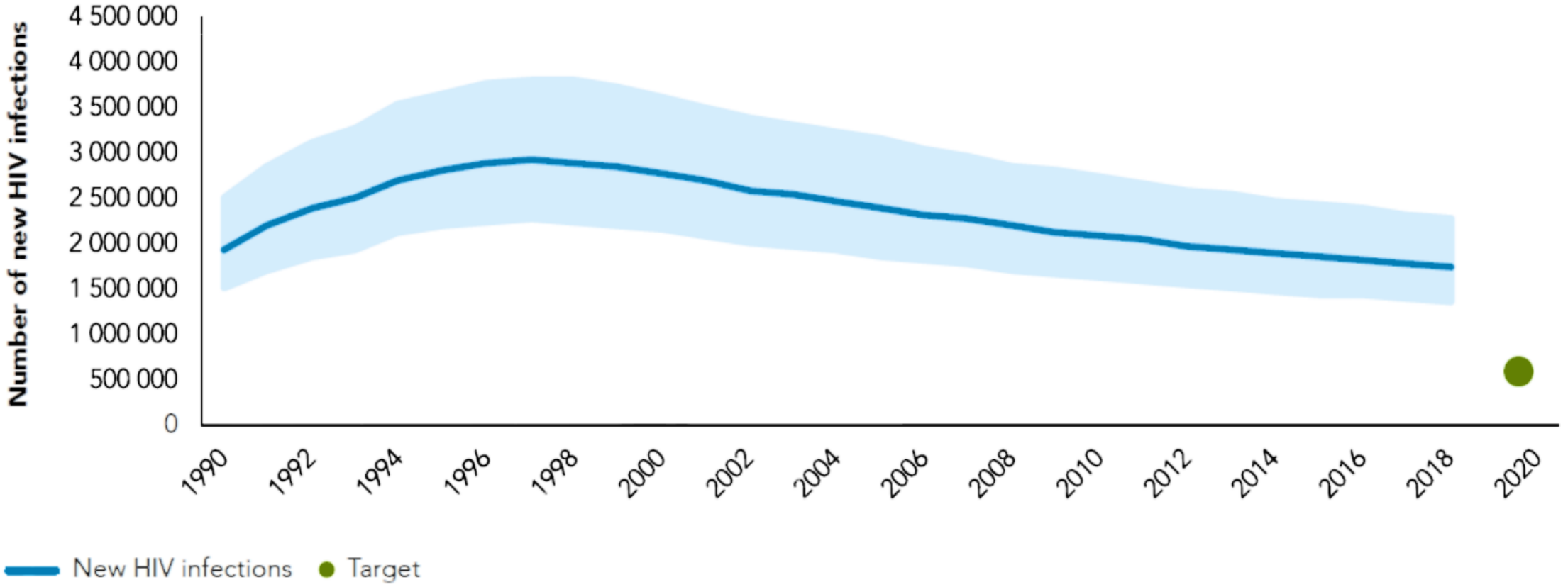
Member, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center

Professor, Laboratory Medicine and Medicine, University of Washington

HIV is Unfortunately Alive and Well Throughout the World

- Globally there are 1.4 million new infections yearly
  - This is 5,000 acquisitions a day
- 180,000 infants a year still infected
- 37 million people living with HIV (76 million since the epidemic started)
- 770,000 HIV related deaths in 2018
- US has “tolerated” 35,000 - 40,000 new infections a year

ADULTS AND CHILDREN NEWLY INFECTED WITH HIV: 1990–2018

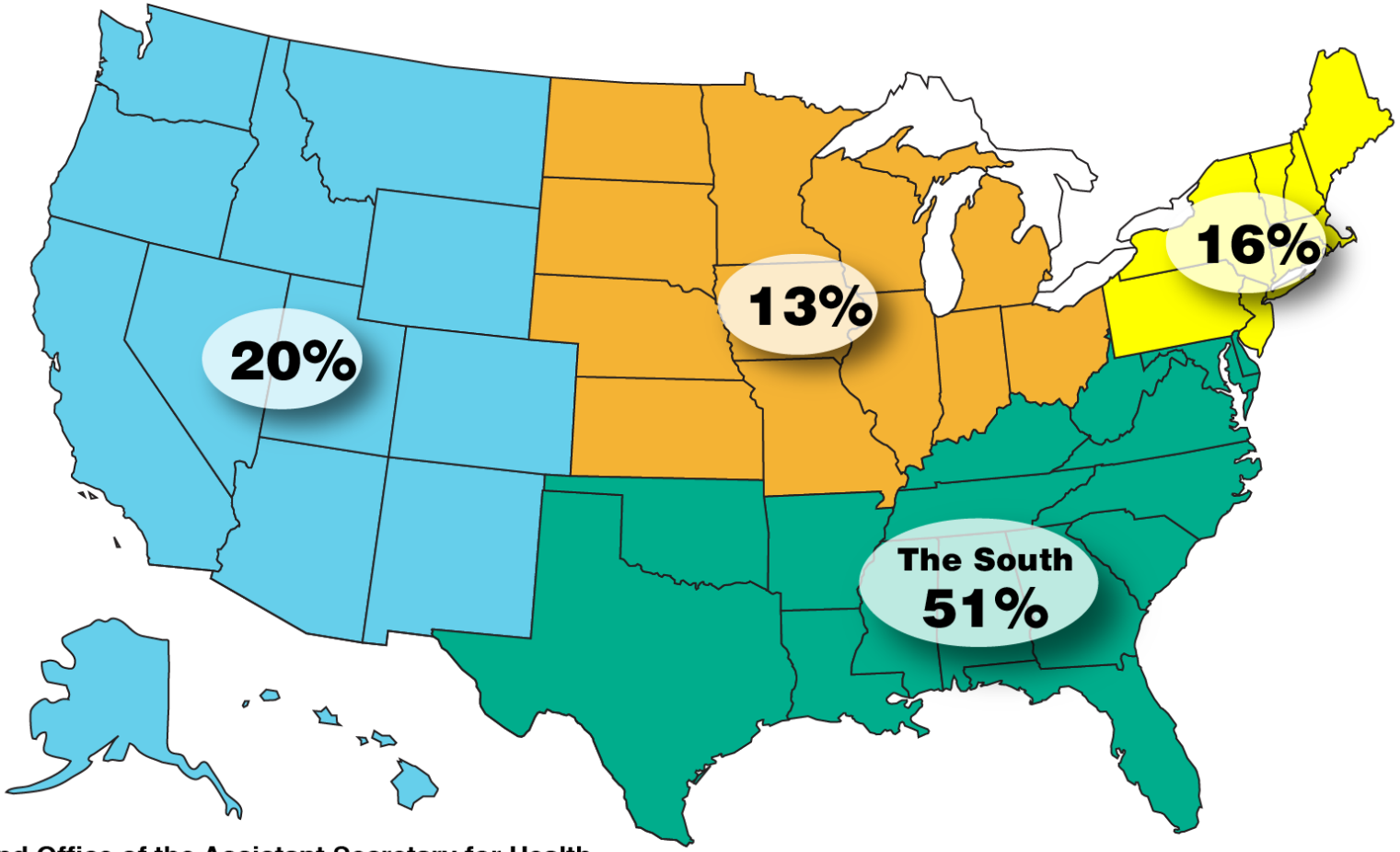


Source: UNAIDS 2019 estimates.

HIV VACCINE TRIALS NETWORK

Source: UNAIDS 2019

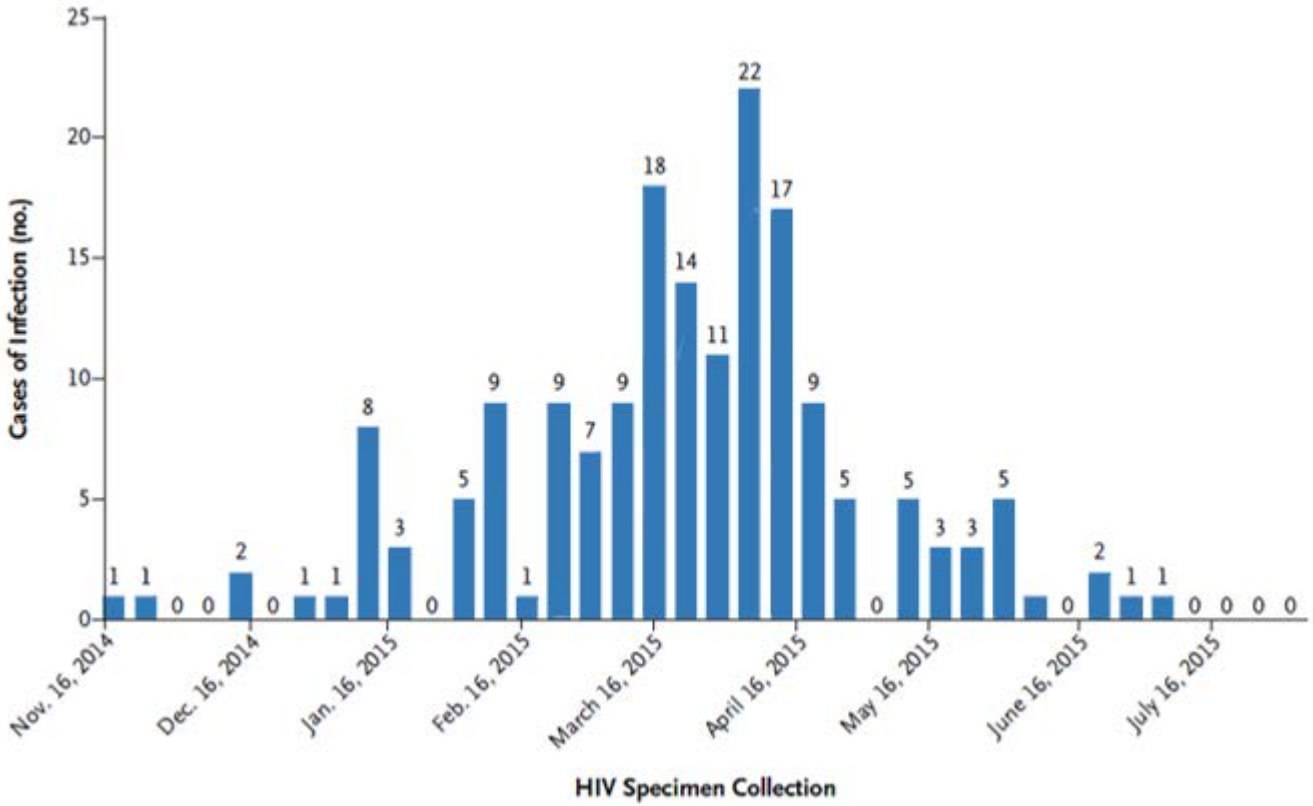
Relative Percentage of New Diagnoses in the United States by Geographic Region, 2016



Source: CDC and Office of the Assistant Secretary for Health

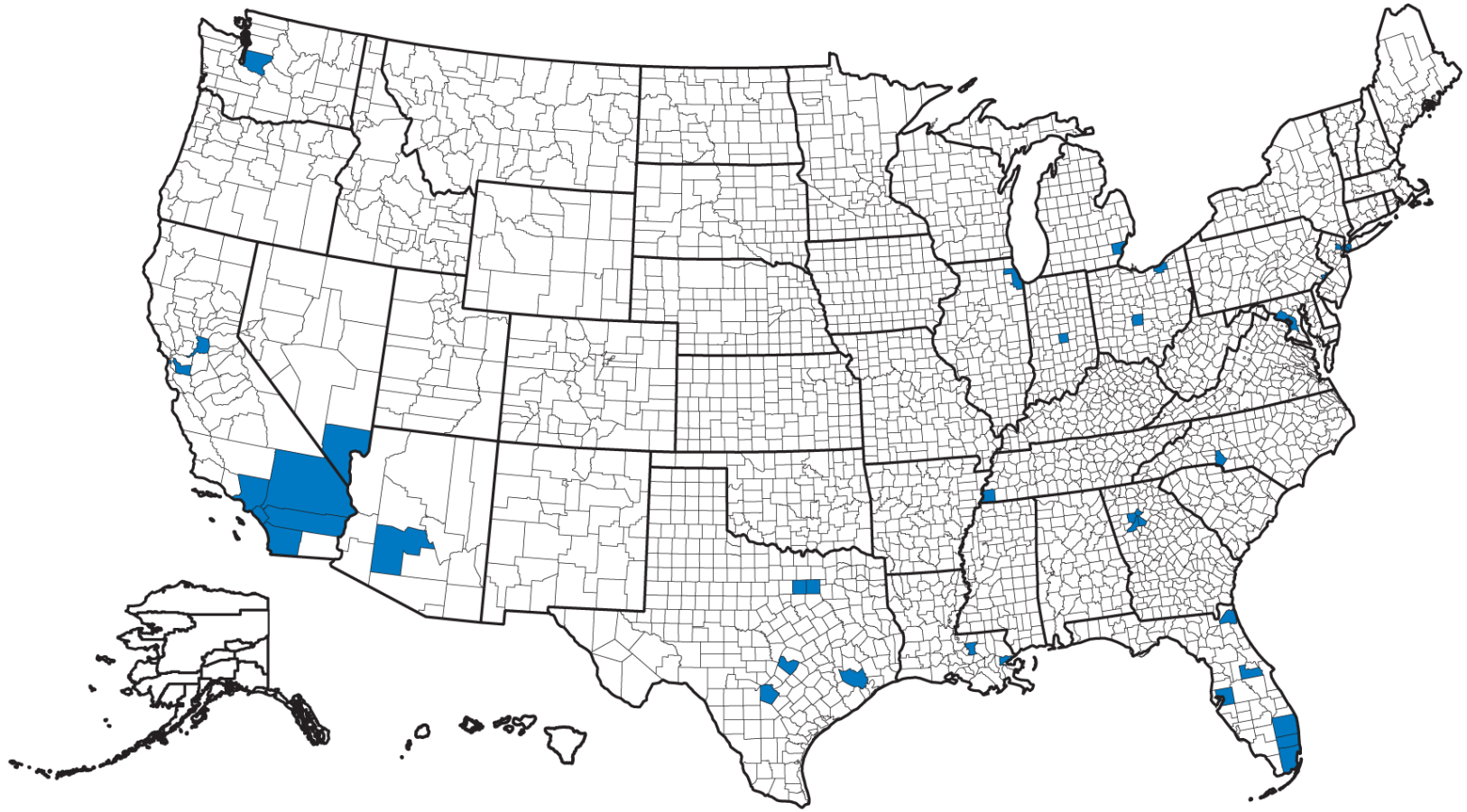
Indiana HIV Outbreak: Geographic Distribution

Scott County pop. 24,000; Austin, IN pop. 4,200



Adams, NEJM 2015;373:1379-1380

46 Counties Account for 50.3% of New HIV Diagnoses, 2016



Source: CDC and Office of the Assistant Secretary for Health

The Need for an HIV Vaccine

- With asymptomatic acquisition, prolonged subclinical infection, and sexual transmission, getting to an *AIDS Free Generation* will require a biologically based primary prevention modality with prolonged durability; preferably an effective HIV vaccine.

- Larry's definition of an *AIDS Free Generation*; 95% reduction in incident cases annually:
  - USA < 2,500 cases yearly
  - Globally < 100,000 cases yearly

The Need for an HIV Vaccine

- Test and treat is an important strategy for individual health and can have an effect on transmission.
- U=U is correct.
- However, long term adherence and prompt identification of HIV infection is just not translatable and scalable on a large scale.
  - It has not eliminated mother to child transmission, which has a very definable exposure.

ORIGINAL ARTICLE

HIV Testing and Treatment with the Use of a Community Health Approach in Rural Africa

D.V. Havlir, L.B. Balzer, E.D. Charlebois, T.D. Clark, D. Kwarisiima, J. Ayieko, J. Kabami, N. Sang, T. Liegler, G. Chamie, C.S. Camlin, V. Jain, K. Kadede, M. Atukunda, T. Ruel, S.B. Shade, E. Ssemmondo, D.M. Byonanebye, F. Mwangwa, A. Owaraganise, W. Olilo, D. Black, K. Snyman, R. Burger, M. Getahun, J. Achando, B. Awuonda, H. Nakato, J. Kironde, S. Okiror, H. Thirumurthy, C. Koss, L. Brown, C. Marquez, J. Schwab, G. Lavoy, A. Plenty, E. Mugoma Wafula, P. Omanya, Y.-H. Chen, J.F. Rooney, M. Bacon, M. van der Laan, C.R. Cohen, E. Bukusi, M.R. Kamya, and M. Petersen

ORIGINAL ARTICLE

Universal Testing, Expanded Treatment, and Incidence of HIV Infection in Botswana

J. Makhema, K.E. Wirth, M. Pretorius Holme, T. Gaolathe, M. Mmalane, E. Kadima, U. Chakalisa, K. Bennett, J. Leidner, K. Manyake, A.M. Mbikiwa, S.V. Simon, R. Letlhogile, K. Mukokomani, E. van Widenfelt, S. Moyo, R. Lebelonyane, M.G. Alwano, K.M. Powis, S.L. Dryden-Peterson, C. Kgathi, V. Novitsky, J. Moore, P. Bachanas, W. Abrams, L. Block, S. El-Halabi, T. Marukutira, L.A. Mills, C. Sexton, E. Raizes, S. Gaseitsiwe, H. Bussmann, L. Okui, O. John, R.L. Shapiro, S. Pals, H. Michael, M. Roland, V. DeGruttola, Q. Lei, R. Wang, E. Tchetgen Tchetgen, M. Essex, and S. Lockman

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2019 VOL. 381 NO. 3

Effect of Universal Testing and Treatment on HIV Incidence — HPTN 071 (PopART)

R.J. Hayes, D. Donnell, S. Floyd, N. Mandla, J. Bwalya, K. Sabapathy, B. Yang, M. Phiri, A. Schaap, S.H. Eshleman, E. Piwowar-Manning, B. Kosloff, A. James, T. Skalland, E. Wilson, L. Emel, D. Macleod, R. Dunbar, M. Simwinga, N. Makola, V. Bond, G. Hoddinott, A. Moore, S. Griffith, N. Deshmane Sista, S.H. Vermund, W. El-Sadr, D.N. Burns, J.R. Hargreaves, K. Hauck, C. Fraser, K. Shanaube, P. Bock, N. Beyers, H. Ayles, and S. Fidler, for the HPTN 071 (PopART) Study Team

The HIV prevention field needs something that is disruptive!

HIV Vaccine

Vaccines can bring infectious diseases under-control

THE PROGRESS OF NATIONS 1996

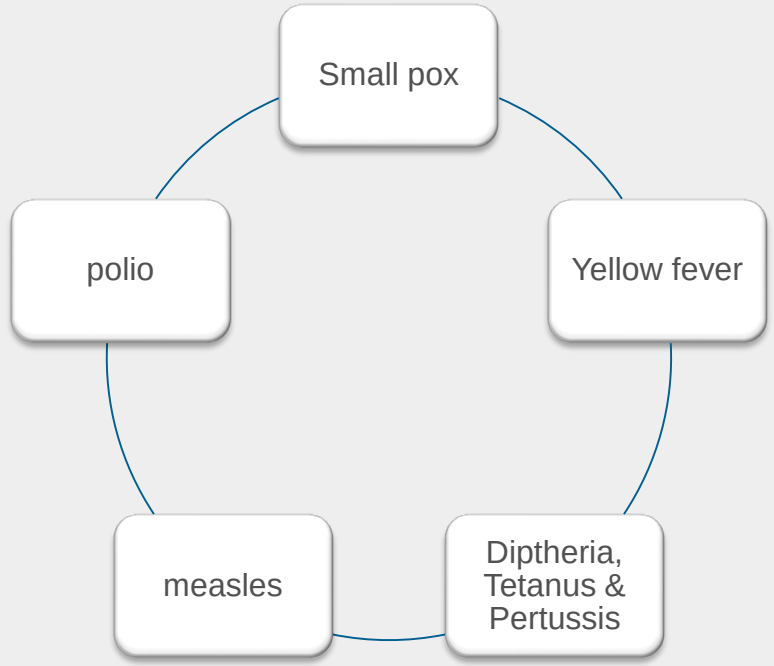
HEALTH

unicef

Vaccines bring 7 diseases under control

Two hundred years after the discovery of vaccine by the English physician Edward Jenner, immunization can be credited with saving approximately 9 million lives a year worldwide. A further 16 million deaths a year could be prevented if effective vaccines were deployed against all potentially vaccine-preventable diseases.

So far only one disease, smallpox, has been eradicated by vaccines, saving approximately 5 million lives annually.



saMRC advancinglife

CELEBRATING 50 YEARS

unicef

Why Has It Been So Hard to Develop an HIV Vaccine?

- Science issues:
  - Genetic diversity of the virus is greater than any other pathogen.
  - Envelope is less immunogenic than any other virus envelope protein; perhaps because of its' glycan shield.
  - The gp160 envelope trimeric structure is unique, hard to simulate and there are fewer trimers on the surface than most viruses.
  - Animal models are expensive and non-predictive of vaccine efficacy.
  - There are no human cures of HIV and hence there are no models to mimic (0 of 72 million and counting).

An exciting time to be in vaccine discovery…

The Science is advancing through clinical trials

- Four pivotal HIV vaccine related efficacy trials are underway. (AMP/Uhambo/Imbokodo)/Mosaico)
- These trials will define if either or both neutralizing and/or non-neutralizing antibodies can be tweaked to provide reasonable vaccine efficacy in high risk regions of the world.

Scientific advances are fueling vaccine discovery

- Antibody isolation and characterization has revolutionized our understanding of the immune response.
- Technologic advances allow researchers to understand where antibodies target the virus in unprecedented detail.
- Stabilization of the HIV Env trimer allows for engineering of trimeric mimics.
- Have shifted from empiric approaches to hypothesis-driven approaches.

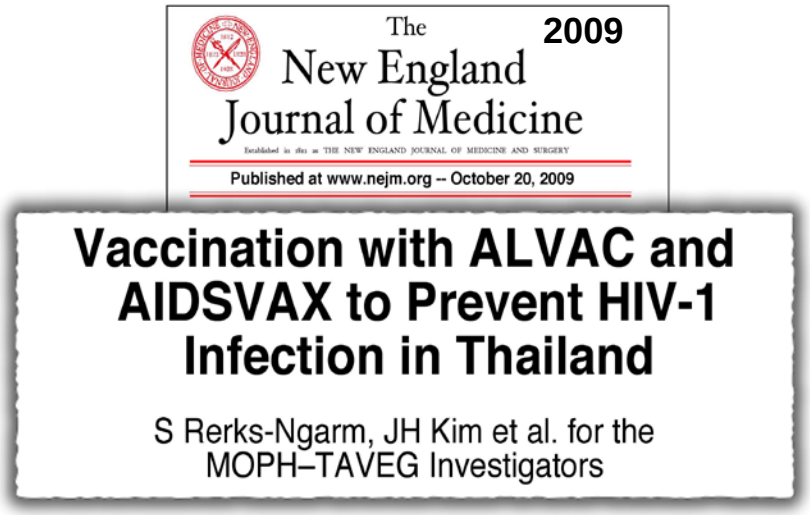
Next Generation Vaccines are entering the clinic

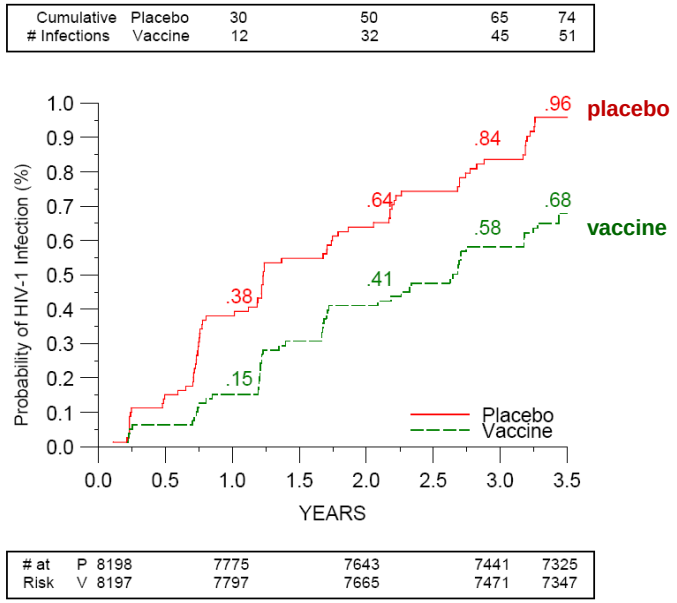
- Native-like trimers meant to resemble HIV's Env spike.
- Germline-targeting approaches generated using structure-based vaccine design.

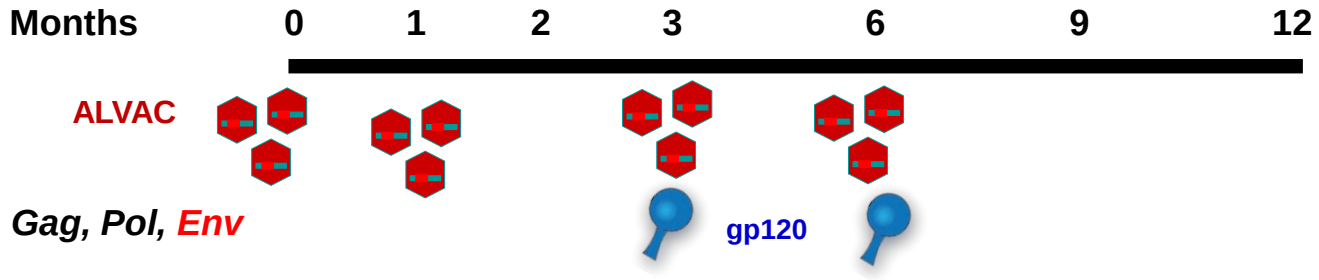
Questions remain:

Do bnAbs protect?
Potency and durability?
HIV variability?
bnAab maturation?

RV144: ALVAC prime, gp120 boost Vaccine Efficacy (31%)

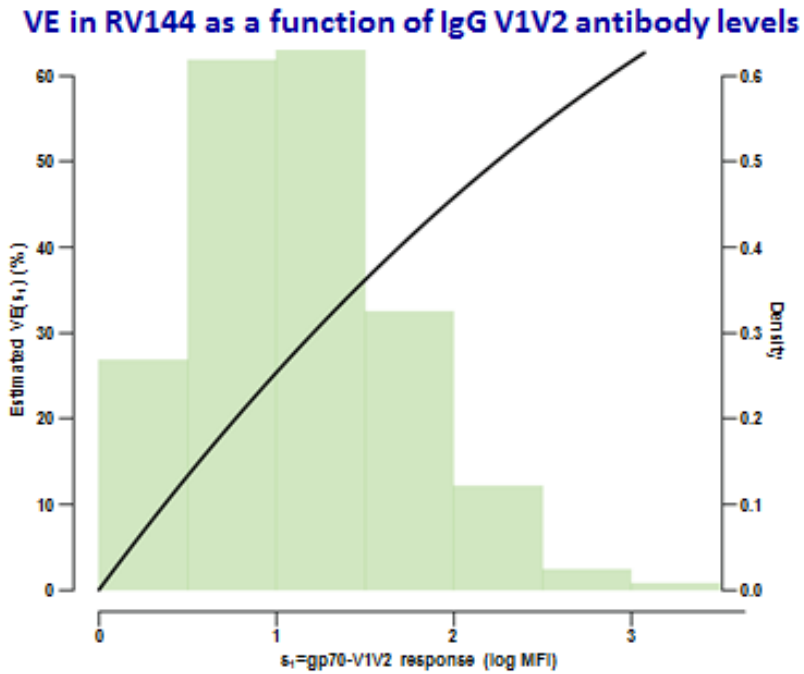






Correlation Between Antibodies to the V1V2 Loop and Vaccine Efficacy in RV144

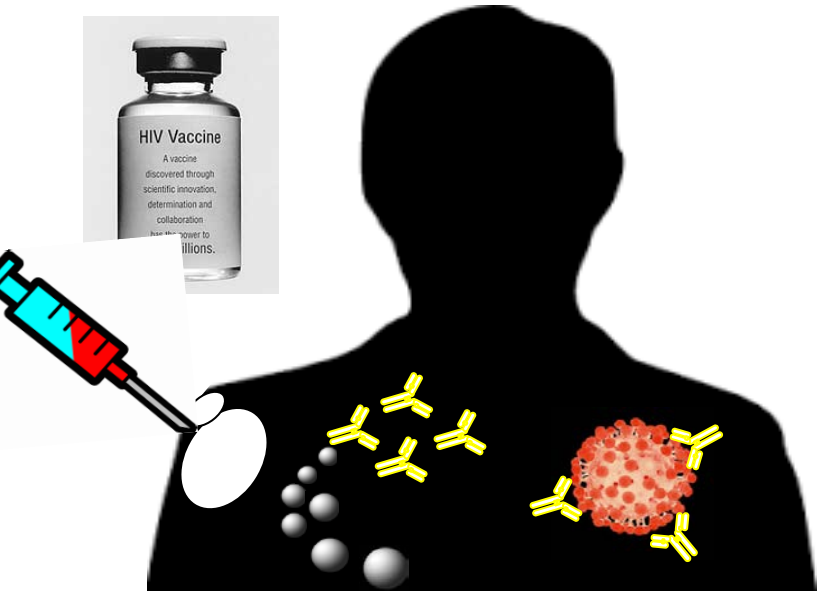
- Antibodies to the conserved region of V2, previously almost completely ignored by the HIV vaccine field, were highly correlated with efficacy.



Estimated vaccine efficacy in RV144 as a function of the level of IgG binding antibody to gp70-scaffolded V1V2 (black line) and the distribution of IgG levels among vaccinees (histogram)

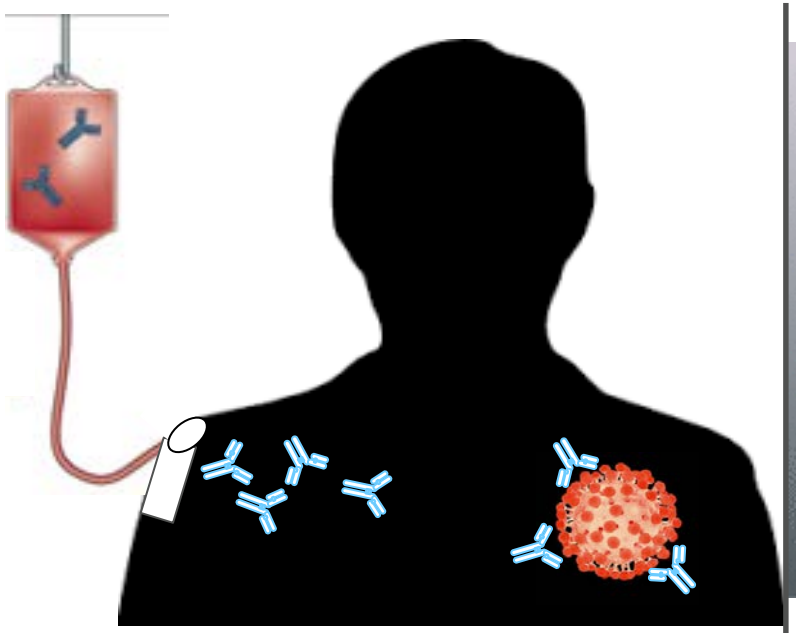
CURRENT HVTN APPROACHES IN THE CLINIC

1. Active Immunization to induce binding antibodies



Vaccination to stimulate binding antibodies previously shown to correlate with reduced risk of HIV infection in RV144 or in NHP challenge models. This is being tested in the large efficacy trials: **HVTN 702, HVTN 705, HVTN 706**

2. Passive Immunization (POC)



Pre-formed broadly neutralizing antibody e.g. VRC 01, a neutralizing antibody targeting the CD4 binding site. This is being tested in the **HVTN POC 703 (AMP trial). Other NABs targeting other sites on the env are being evaluated in phase 1.**

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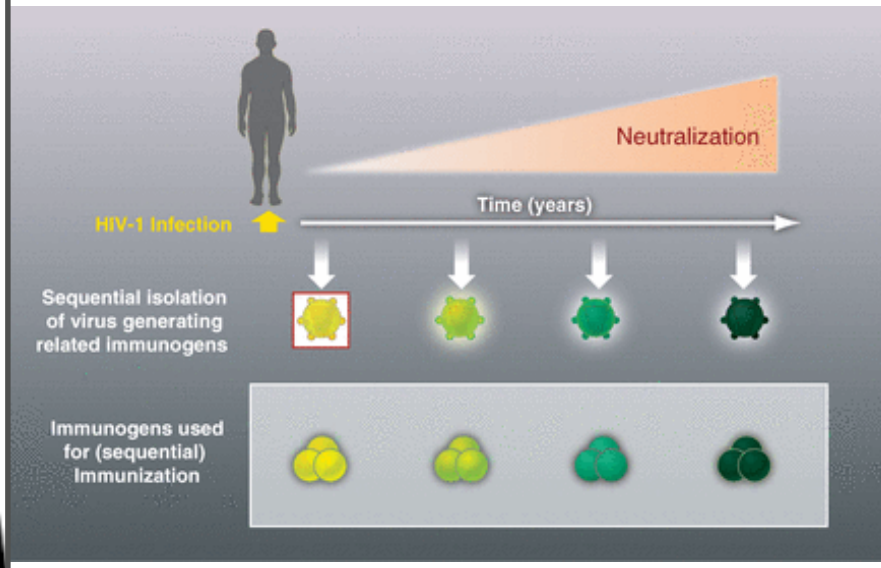


Coaxing the immune system to develop broadly neutralizing antibodies with immunogens e.g. lineage based vaccine design, germline targeting or epitope based vaccine design.

Current Phase 2B/3 HIV Vaccine Efficacy Trials

AMP (POC)
HVTN 703/704

Uhambo
(Phase 2B/3)
HVTN 702

Imbokodo
(Phase 2B POC)
HVTN 705

MOSAICO
(Phase 3)
HVTN 706

AMP
ANTIBODY · MEDIATED · PREVENTION
STUDY

uhambo

IMBOKODO

MOSAICO
HVTN 706/HPX3002

Ongoing HVTN Vaccine Efficacy Studies

Trial	Products	N	# of sites	Population	Countries	Public/Private Partnership
HVTN 702	ALVAC/gp120	5400	14	70:30 split women & men	South Africa	P5
HVTN 705	Ad26/gp140	2600	24	Women	Malawi, Mozambique, South Africa, Zambia, Zimbabwe	Janssen/J&J and NIAID/HVTN
HVTN 706	Ad26/gp140	3800	55	MSM, TG	Argentina, Brazil, Italy, Mexico, Peru, Poland, Spain, US	Janssen/J&J and NIAID/HVTN

2010 Formation of the P5 Partnership

Purpose:

To build on RV144 data and ultimately license a pox-protein based HIV vaccine with the potential for broad and timely public health impact.

Strategy:

- Developed a partnership to extend the RV144 concept to Clade C regions of the world.
- Use expert committees to select the strains and then use company expertise to manufacture these vaccines for immunogenicity, safety and efficacy.

gsk NOVARTIS

MHRP U.S. MILITARY HIV RESEARCH PROGRAM

HIV VACCINE TRIALS NETWORK

BILL & MELINDA GATES foundation

National Institute of Allergy and Infectious Diseases

SANOFI PASTEUR

MRC SOUTH AFRICA SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

Immune Correlates – Phase 2b

HVTN 702: opened in Oct. 2016

ALVAC prime, gp120 boost

NIH National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

FOR IMMEDIATE RELEASE
November 27, 2016

First New HIV Vaccine Efficacy Study in Seven Years Has Begun

South Africa Hosts Historic NIH-Supported Clinical Trial

- HVTN 702, modified RV144 prime-boost regimen
  - HIV Clade C; ALVAC-HIV + gp120 protein subunit vaccine with MF59 adjuvant
- Target n = 5,400 men and women aged 18-35 years

HVTN 705: opened in Nov. 2017

rAd26 prime, gp140 boost

NIH National Institutes of Health
Turning Discovery Into Health

FOR IMMEDIATE RELEASE
November 30, 2017

News Release

NIH and Partners Launch HIV Vaccine Efficacy Study

IMBOKODO
Imbokodo ("the rock" in Zulu)

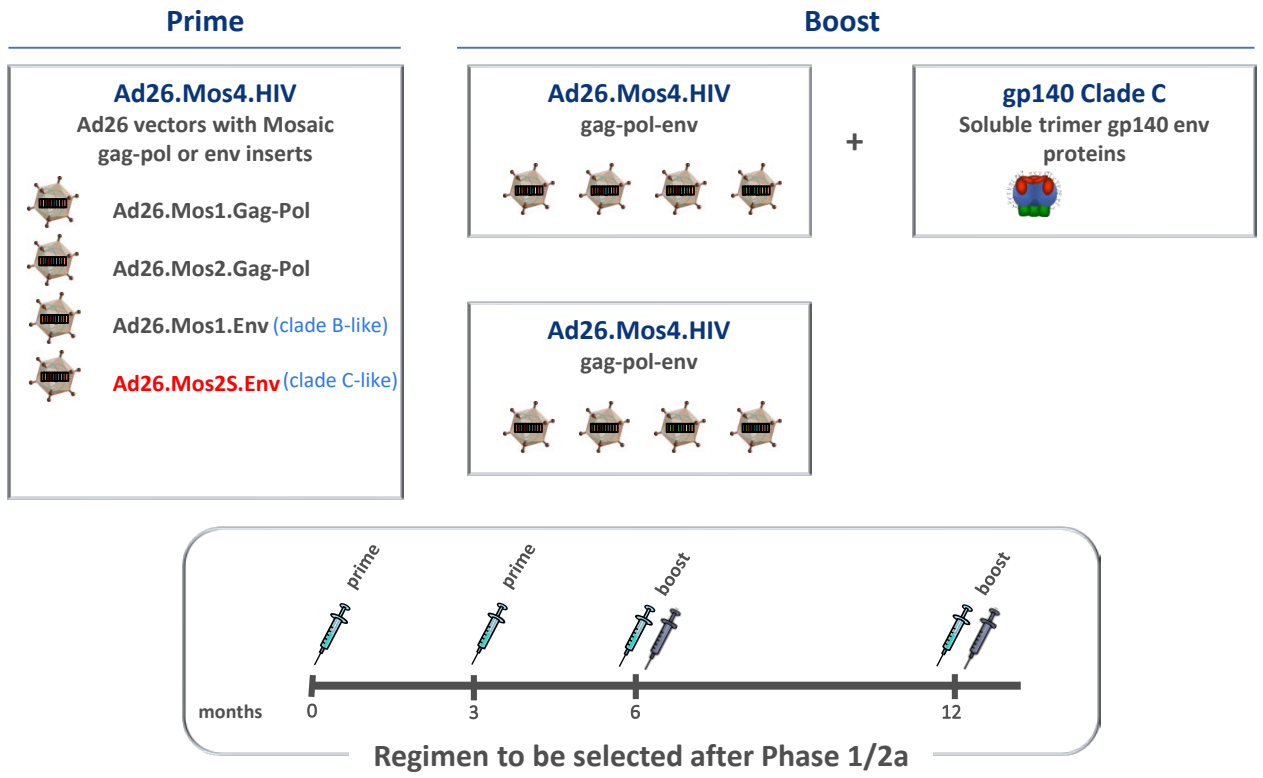
- Imbokodo trial (HVTN 705/HPX2008)
- Phase 2b; target n= 2,600 HIV-negative women in sub-Saharan Africa
- Quadrivalent, Ad26-vectored mosaic vaccine + recombinant clade C HIV gp140

HVTN 702 Schema:
5400 South Africans (18-35 yrs)

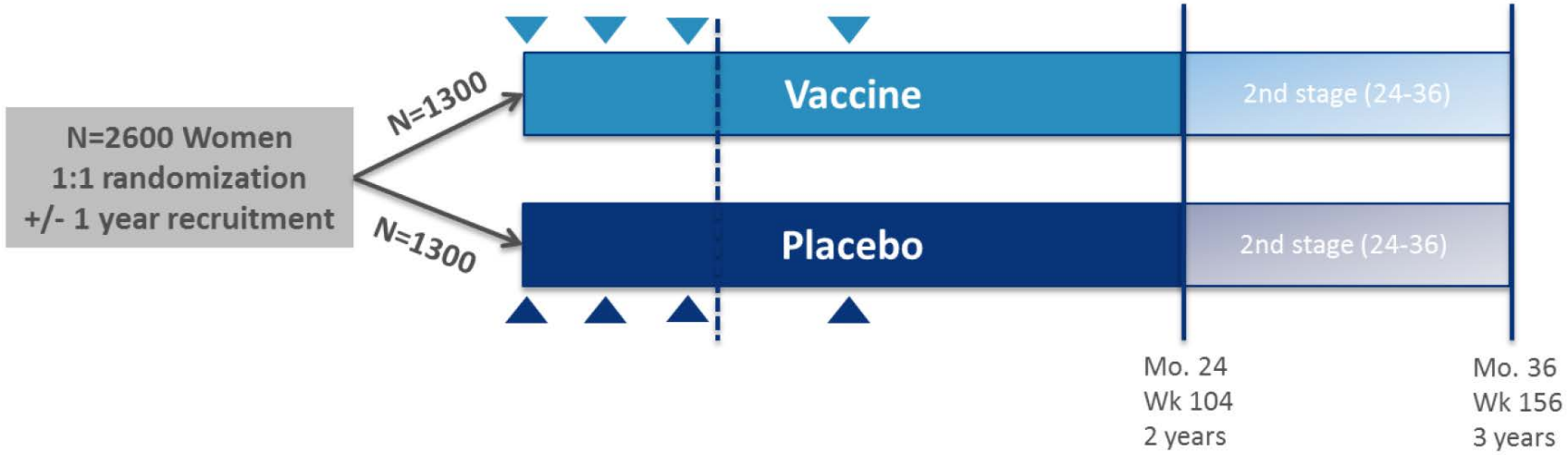
uhambo

Group	N*	Primary vaccine regimen				Boosters	
		Month 0	Month 1	Month 3	Month 6	Month 12	Month 18
1	2700	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438)+ Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59
2	2700	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo
Total	5400						

APPROACH (Ph 2):
Mixture of 4 mosaic Ad26 constructs + gp140 Clade C boost

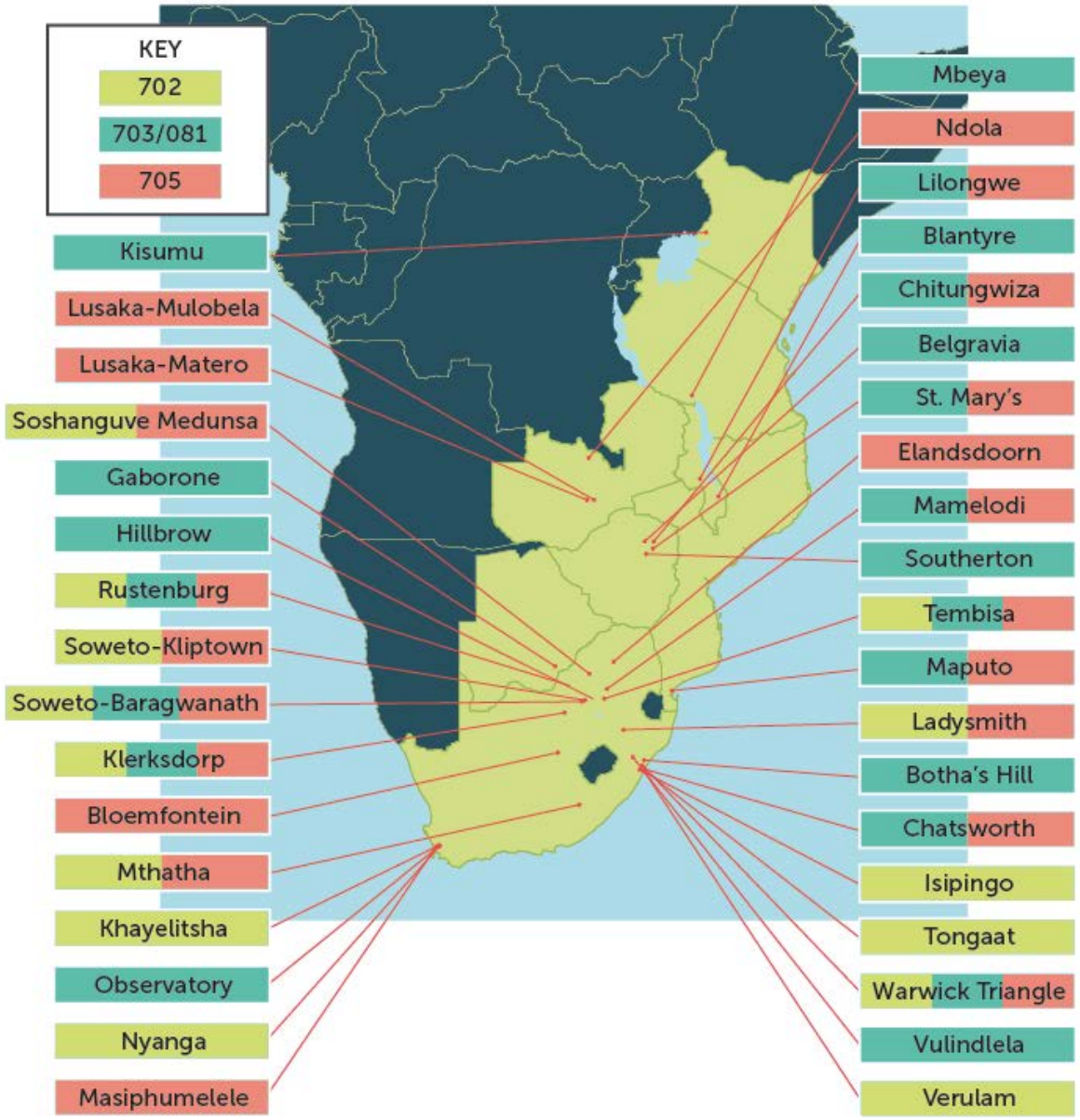


Study Schema: HVTN 705/Imbokodo



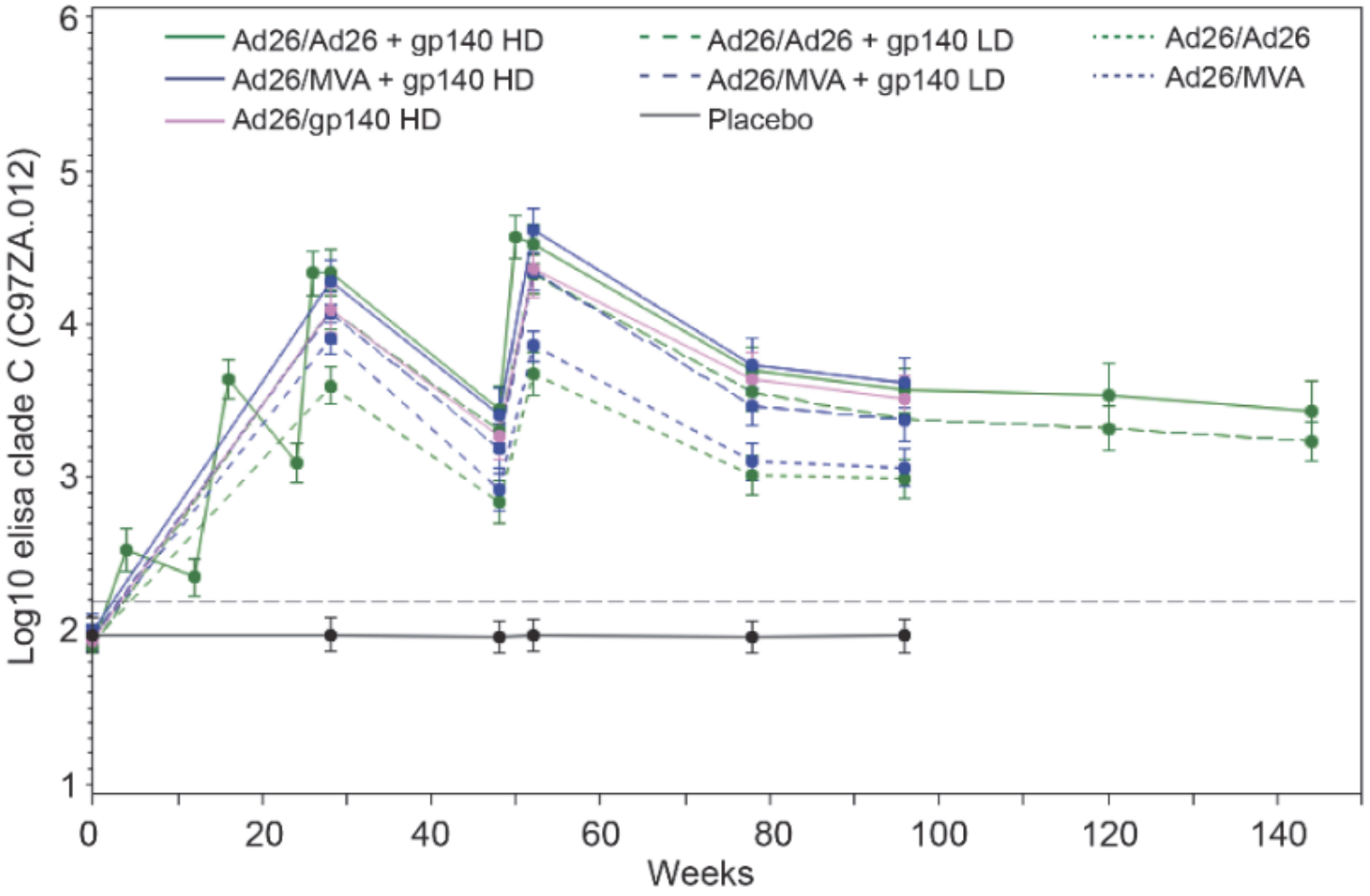
Chairs: Glenda Gray,
Co-chairs: Susan Buchbinder, Kathy Mngadi and Frank Tomaka

HVTN efficacy trial locations in sub-Saharan Africa

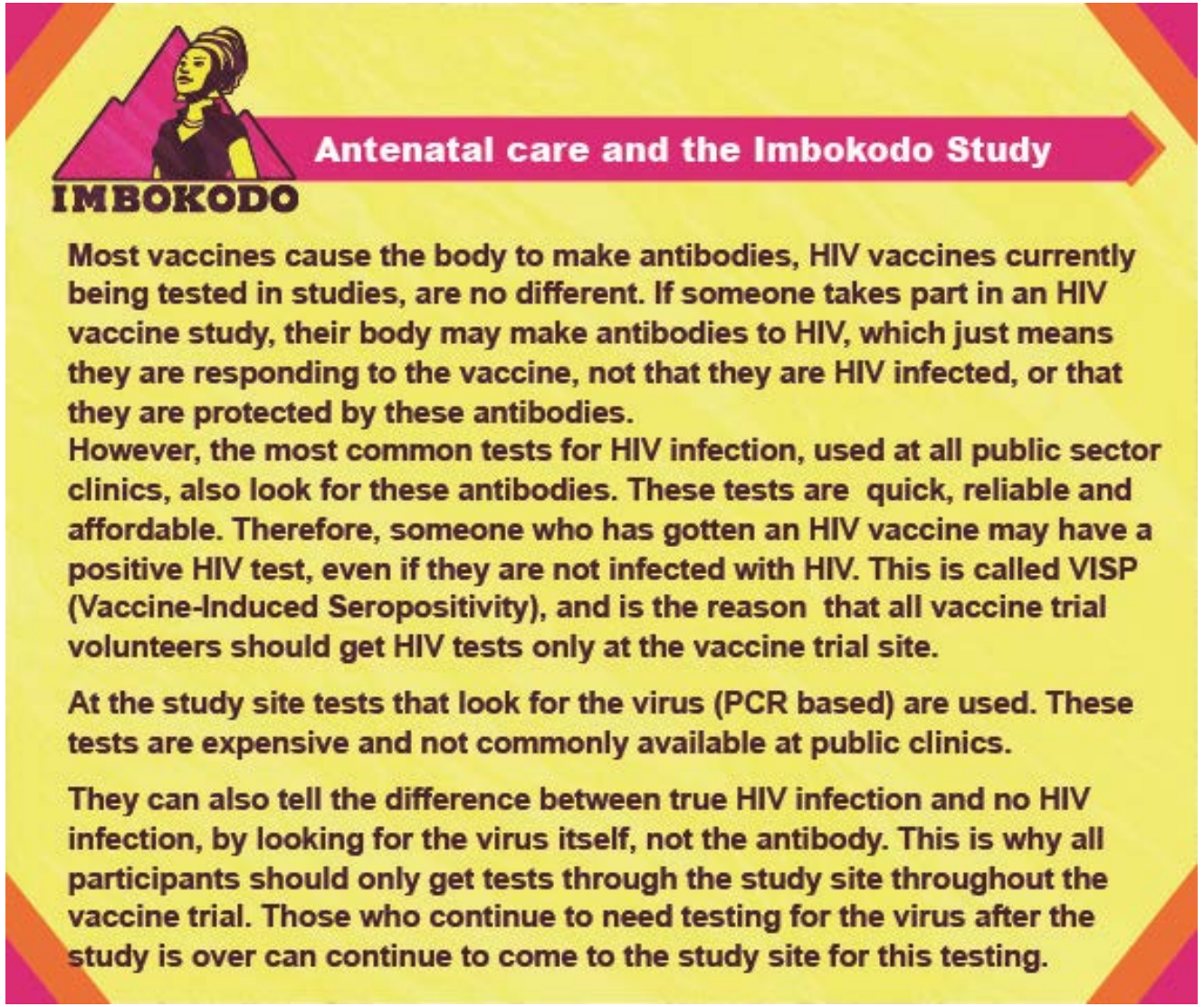


Durability of ELISA responses in HVTN 117, the Ad26/gp140 phase 2 qualifying trial.

Top line is HVTN 705 regimen Ad26/gp140 (HD = high dose)



Partial depiction of instructional flyer given to women in HVTN 705



HVTN 706 Schema

MOSAICO
HVTN 706/HPX3002

Table: Vaccination Schedule

Group	N	Month 0	Month 3	Month 6	Month 12
1	1,900	Ad26.Mos4.HIV	Ad26.Mos4.HIV	Ad26.Mos4.HIV + Clade C gp140, Mosaic gp140, adjuvanted	Ad26.Mos4.HIV + Clade C gp140, Mosaic gp140, adjuvanted
2	1,900	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo

Total dose of Ad26.Mos4.HIV is 5x1010 viral particles (vp)/0.5 mL injection.
Clade C gp140, Mosaic gp140, adjuvanted: adjuvanted protein formulation with a dosage strength of 80 mcg Clade C protein, 75 mcg Mosaic protein and 425 mcg aluminum (as aluminum phosphate adjuvant). Note: previously the dose of Clade C gp140 and/or Mosaic gp140 was reported as mcg of glycoprotein: 125 mcg Clade C gp140 and 125 mcg Mosaic gp140 glycoprotein correspond with 80 mcg and 75 mcg of protein, respectively.

Proposed 2020 configuration of HVTN CRSs in the US and Latin America

Non-neutralizing Approaches to HIV Vaccine Design

- Two non-neutralizing strategies are being undertaken:
  - 1 based upon RV144 correlates data and the other based upon correlates in NHP challenge experiments.
  - Both approaches suggest correlates relate to both binding/functional antibodies (ADCP and ADCC), as well as some T cell response (CD4 envelope and the other ELISPOT data).
  - We shall see whether these presumed correlates are shown to be consistent in human efficacy trials.
  - We shall see if any NHP challenge studies are predictive of vaccine efficacy.
  - In the end it may take both neutralizing and non-neutralizing antibodies to achieve success.

CURRENT HVTN APPROACHES IN THE CLINIC

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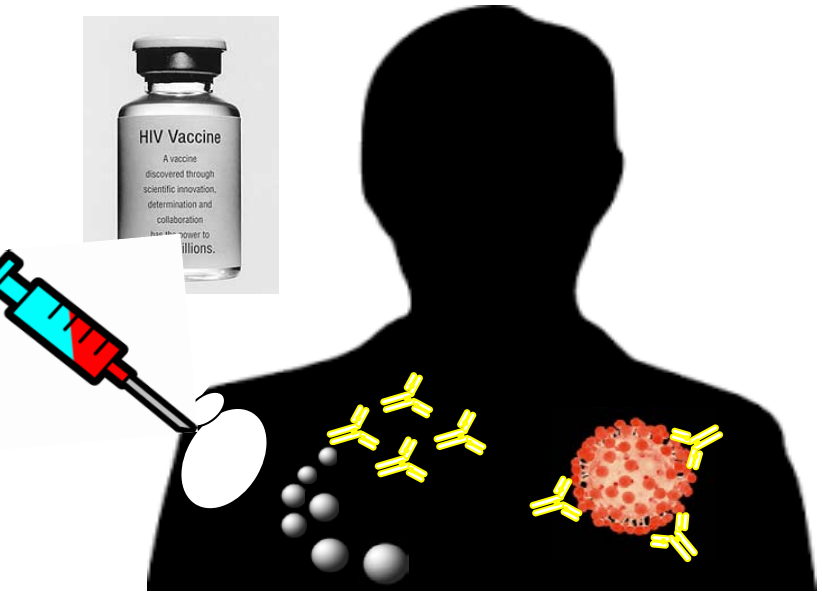

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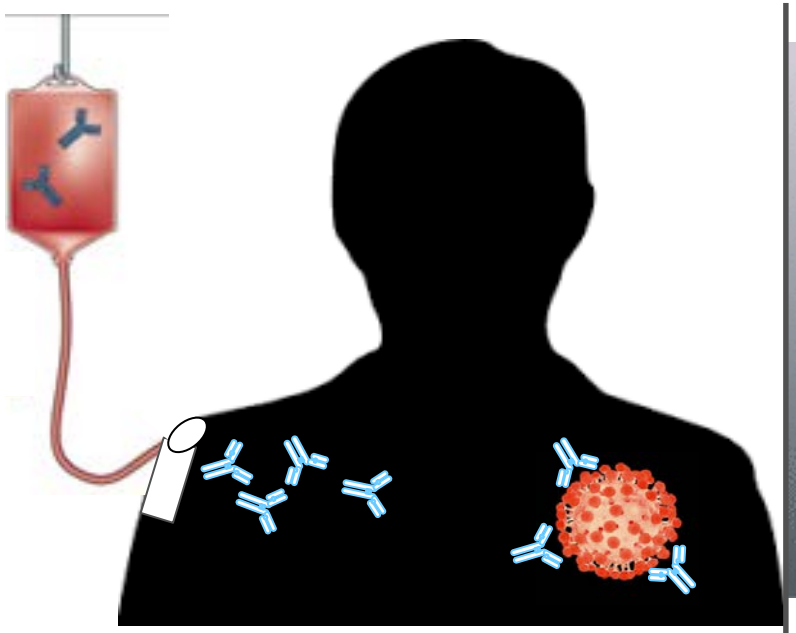

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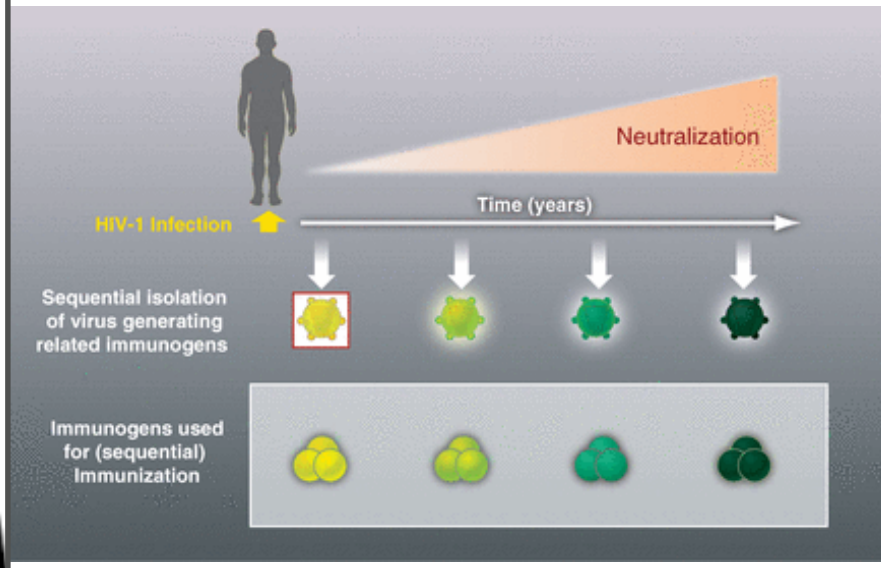


Coaxing the immune system to develop broadly neutralizing antibodies with immunogens e.g. lineage based vaccine design, germline targeting or epitope based vaccine design.

Broadly Reactive Neutralizing Antibodies Discovered since 2009

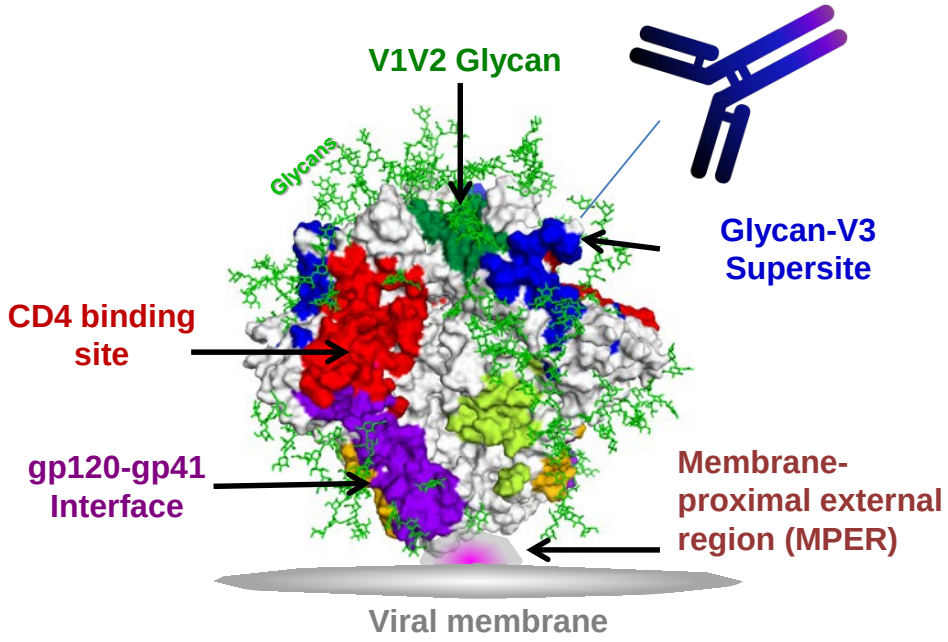


Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

- Isolated from HIV-infected individuals
- Penetrate glycan shield
- Potently neutralize most strains of HIV-1

Passive Antibody Prevention
Phase IIB Efficacy Studies

AMP = Antibody Mediated Prevention

Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults: MSM in Americas & heterosexual women in sub-Saharan Africa

- **Placebo controlled trial of VRC01 mAb (IV), given on 8 weekly schedule**
- **Two cohorts:**
  - **2,400 MSM + TG in North & South America (HVTN 704/HPTN 085)**
  - **1,900 Women in sub-Saharan Africa (HVTN 703/HPTN 081)**

- Both trials opened in April/May 2016
- 703/081 Accrued September 20, 2018 (End Jan 2021)
- 704/085 Accrued October 5, 2018 (End Oct 2020)

Chairs: Lawrence Corey, HVTN
Mike Cohen, HPTN
Co-chairs: Srilatha Edupuganti
Nyaradzo Mgodi

Cohorts for the AMP Studies

Cohorts	Antibody (VRC01) 10mg/kg	Antibody (VRC01) 30mg/kg	Placebo Saline	Total Population
HVTN704/HPTN085: 900 MSM & TG persons (Clade B) United States, Peru, Brazil & Switzerland		900	900	2,700
HVTN703/HPTN081: 634* Heterosexual women (Clade C) Sub-Saharan Africa – 7 countries		634*	634*	1,900
* Due to the randomization scheme, the numbers of vaccine and control recipients may differ slightly.				
Total	**1,534**	**1,534**	**1,534**	**4,600**

Study Schema for the AMP studies

AMP
ANTIBODY · MEDIATED · PREVENTION
STUDY

INFUSION SCHEDULE (WEEKS)

[A = VRC01 infusion; C = Control infusion]

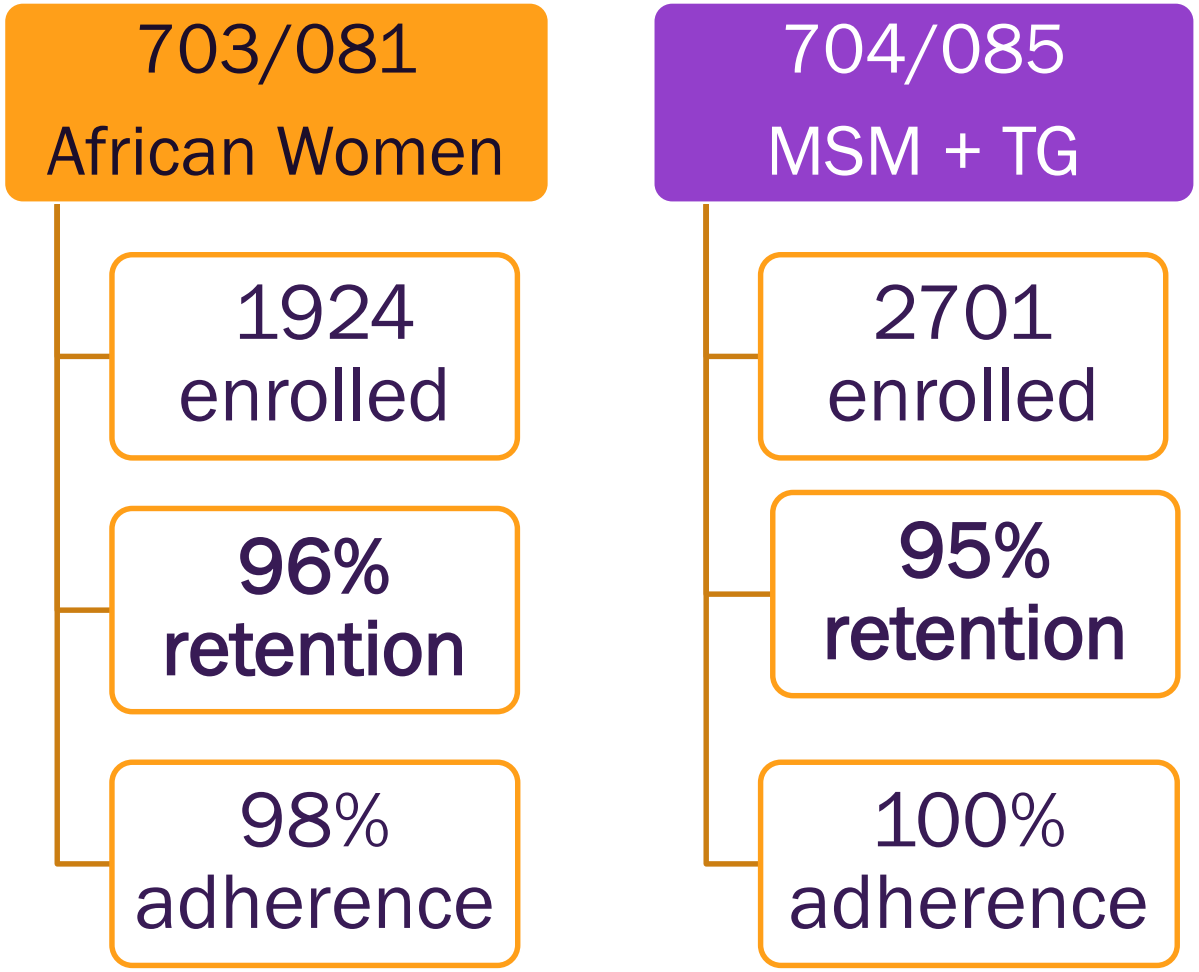
	Treatment: VRC01	N	0	8	16	24	32	40	48	56	64	72	80*	92**
Group 1	10 mg/kg	900 634	A	A	A	A	A	A	A	A	A	A		
Group 2	30 mg/kg	900 634	A	A	A	A	A	A	A	A	A	A		
Group 3	Control	900 634	C	C	C	C	C	C	C	C	C	C		

2700 (1900) for the MSM + TG (WSM) group; (1/3 VRC01 30 mg/kg; 1/3 VRC01 10 mg/kg; 1/3 control

***Week 80: last study visit to evaluate efficacy – primary end point**

****Week 92: final study visit to evaluate safety and tolerability; co-primary end point**

Enrollment and Retention Updates

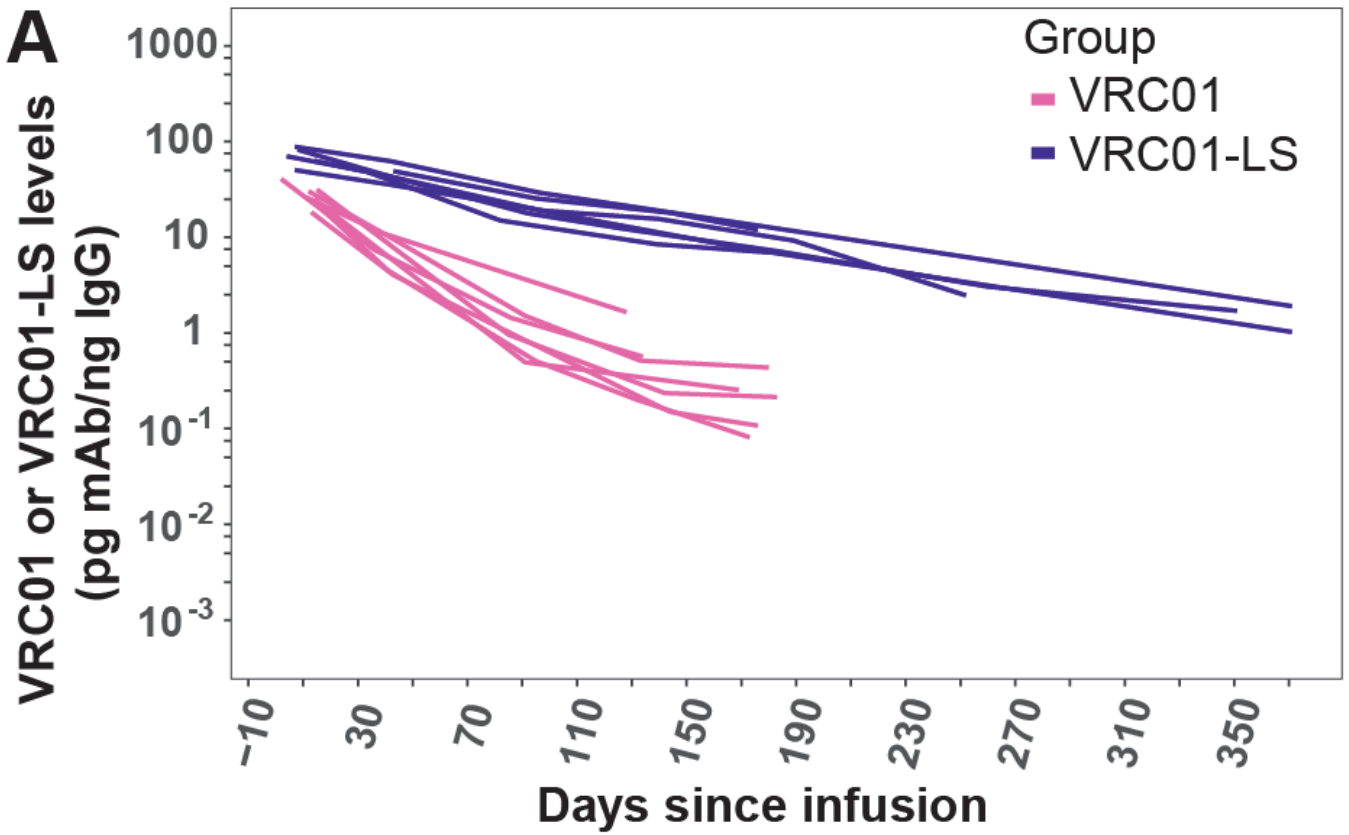


Moving to Self Administered Subcutaneous Injections

Extended Half Life preparations

Safety will be discussed next presentation

Enhanced half-life and augmented antibody levels in cervical biopsies of VRC01-LS vs. VRC01 in HVTN 116



Relative concentrations of antibody extracted from cervical biopsy tissue.
Note the much higher and more stable mAb levels with the LS mutation (purple lines) vs. parental (pink lines).

Summary

- If any of the HIV vaccines or antibodies in efficacy trial testing are effective, it will unleash an enormous explosion in scientific inquiry to improve, adapt and most importantly - bring to the world a new form of HIV prevention.

- An HIV vaccine will be the most complex vaccine ever designed:
  - Yes, the regimens will be an implementation challenge.
  - Vaccination may disrupt the way we diagnose HIV.
  - Vaccines will, however, overcome the current barriers to population based control of HIV and provide a tool that could get us to an HIV free generation; a reality that is not, present with the current tools.

- And yes, the science behind such a vaccine will have additional spin offs.

Acknowledgements

All the study staff,

the community engagement teams,

and most of all,

the participants who join the journey!

Acknowledgments

HVTN Lab Program
Julie McElrath, Georgia Tomaras, Nicole Frahm, John Hural, David Montefiori, Steve DeRosa, Erica Andersen-Nissen, Lynn Morris

USMHRP
Nelson Michael, Robert O'Connell

Bill and Melinda Gates Foundation
Emilio Emini, Nina Russell and team

Sanofi Pasteur
Jim Tartaglia, Sanjay Gurunathan, Sanjay Phogat

Janssen
Frank Tomaka, Maria Pau, Hanneke Schuitemaker, Paul Stoffels

HVTN Core, SDMC, EMT
Jim Kublin, Peter Gilbert, Glenda Gray, Susan Buchbinder, Scott Hammer, Gepi Pantaleo, Shelly Karuna, Nicole Grunenberg, Carter Bentley
Site Investigators
Study Volunteers

CHAVI ID
Bart Haynes, Larry Liao and colleagues

DAIDS Vaccine Research Program
Carl Dieffenbach, Mary Marovich, Dale Hu, Phil Renzullo, Pat D'Souza, Paul Kitsutani, Mary Allen, Jim Lane, Mike Pensiero

Collaborators - Africa

- Glenda Gray
- Linda Gail-Bekker
- Gita Ramjee
- Cheryl Louw
- Kathy Mngadi
- Graeme Meintjes
- Craig Innes
- Nicole Hunt
- Phillip Kotze
- Francis Martinson
- Jani Ilesh
- Stewart Reid
- Leonard Maboko
- Maphoshane Nchabeleng
- Lungiswa Mtingi
- Dumezweni Ntshangase
- William Brumskine
- Zvavahera Chirenje
- Mookho Malahlela
- Modulakgotla Sebe

Collaborators - U.S., South America and Europe

- Mark Mulligan
- Paul Goepfert
- Ray Dolin
- Lindsey Baden
- Ken Mayer
- Richard Novak
- Benigno Rodriguez
- Spyros Kalams
- Scott Hammer
- Beryl Koblin
- Ian Frank
- Michael Keefer
- Susan Buchbinder
- Julie McElrath
- Gepi Pantaleo
- Jorge Sanchez
- Martin Casapia
- Robinson Cabello

Need for and Challenges with Hepatitis C Vaccine Development

Andrea L. Cox, MD,PhD

Professor of Medicine and Oncology
Viral Hepatitis Center

JOHNS HOPKINS
MEDICINE

No Conflicts of Interest

HCV is a serious blood born infection

- ~70 million infected world-wide

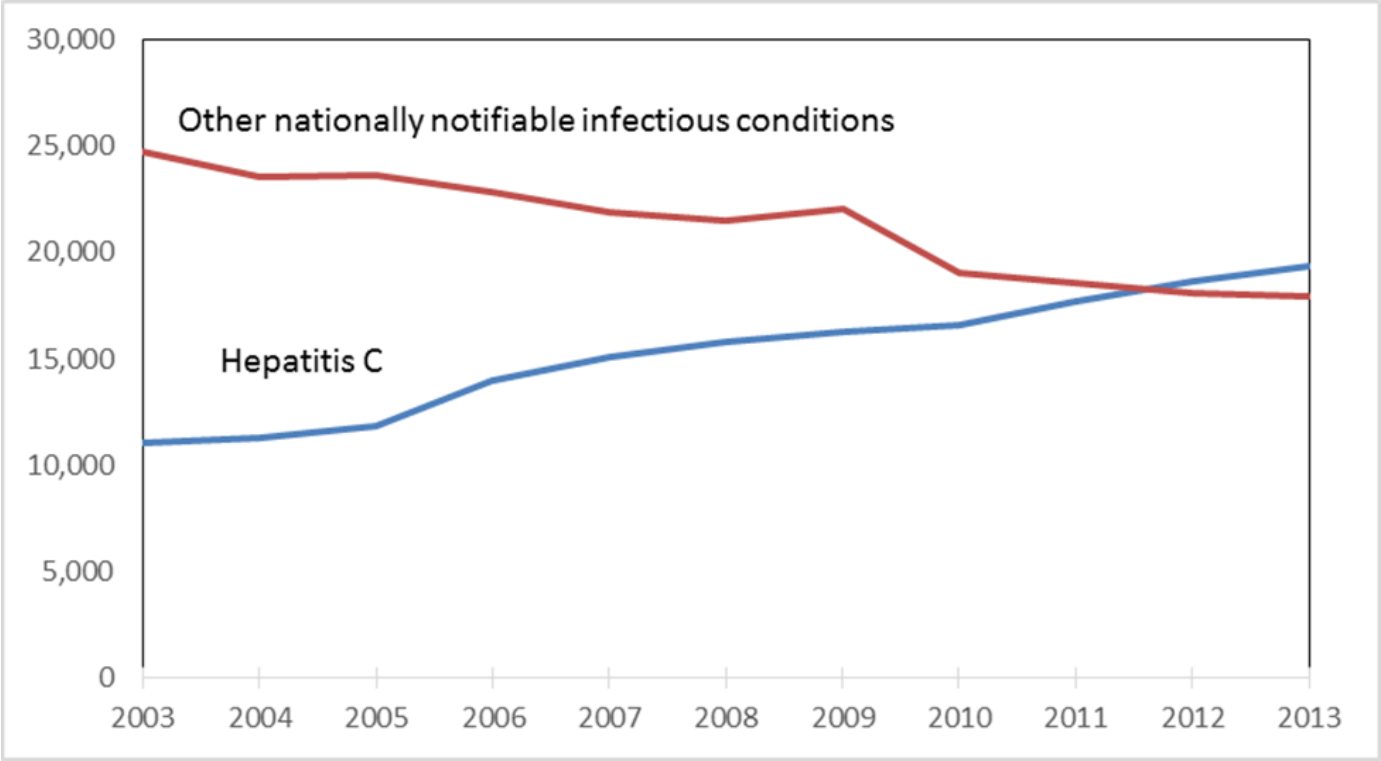
HCV is a serious blood born infection

- ~70 million infected world-wide
- Leading cause of end stage liver disease (ESLD) and hepatocellular carcinoma (HCC) in US and many other countries

HCV is a serious blood born infection

- ~70 million infected world-wide
- Leading cause of ESLD, HCC in US and many other countries
- HCV kills ~20,000 Americans annually

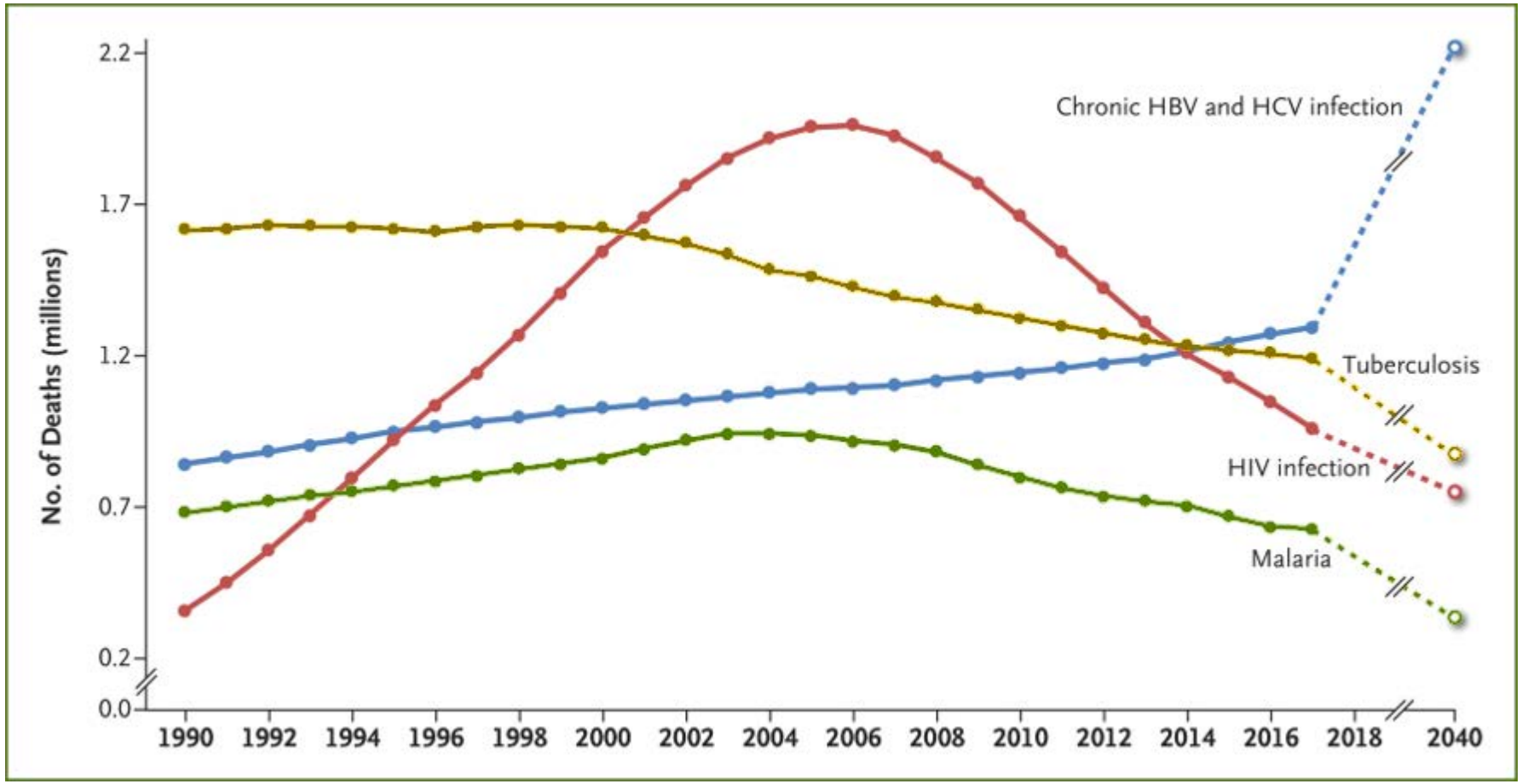
HCV Deaths Now Exceed Deaths from the Other Nationally Notifiable Infectious Diseases* combined



* HIV, TB, Hepatitis B and 56 other infectious conditions reported to CDC

Ly K, et al. Rising Mortality Associated with Hepatitis C Virus in the United States, 2003-2013 *Clin Infect Dis.*

Worldwide Deaths from HBV and HCV High and Rising



Thomas, DL, Global Elimination of Chronic Hepatitis, N Engl J Med 2019; 380:2041-2050

WHO Called for Viral Hepatitis Elimination by 2030

- Vaccines against HAV, HBV, and HEV
- Antiviral medications suppress HBV

WHO Global Health Sector Strategy on Viral Hepatitis 2016–2021
Towards Ending Viral Hepatitis

WHO Called for Viral Hepatitis Elimination by 2030

- Vaccines against HAV, HBV, and HEV
- Antiviral medications suppress HBV
- Direct acting antivirals (DAAs) cure HCV- termed sustained virologic response (SVR)

WHO Global Health Sector Strategy on Viral Hepatitis 2016–2021
Towards Ending Viral Hepatitis

WHO 2030 Targets for Viral Hepatitis Global Control

Achieve a:

- 90% reduction in new infections
- 90% of infected patients diagnosed
- 80% of infected eligible patients treated
- 65% reduction in liver-related deaths

WHO Global Health Sector Strategy on Viral Hepatitis 2016–2021
Towards Ending Viral Hepatitis

WHO 2030 Targets for Viral Hepatitis Global control- on target?

- 2019 Study assessed the progress made in 45 high-income countries (HIC) in meeting WHO 2030 HCV elimination targets

Razavi H., et. al. 2019. J Hepatol 70, 1, Supplement, page e748

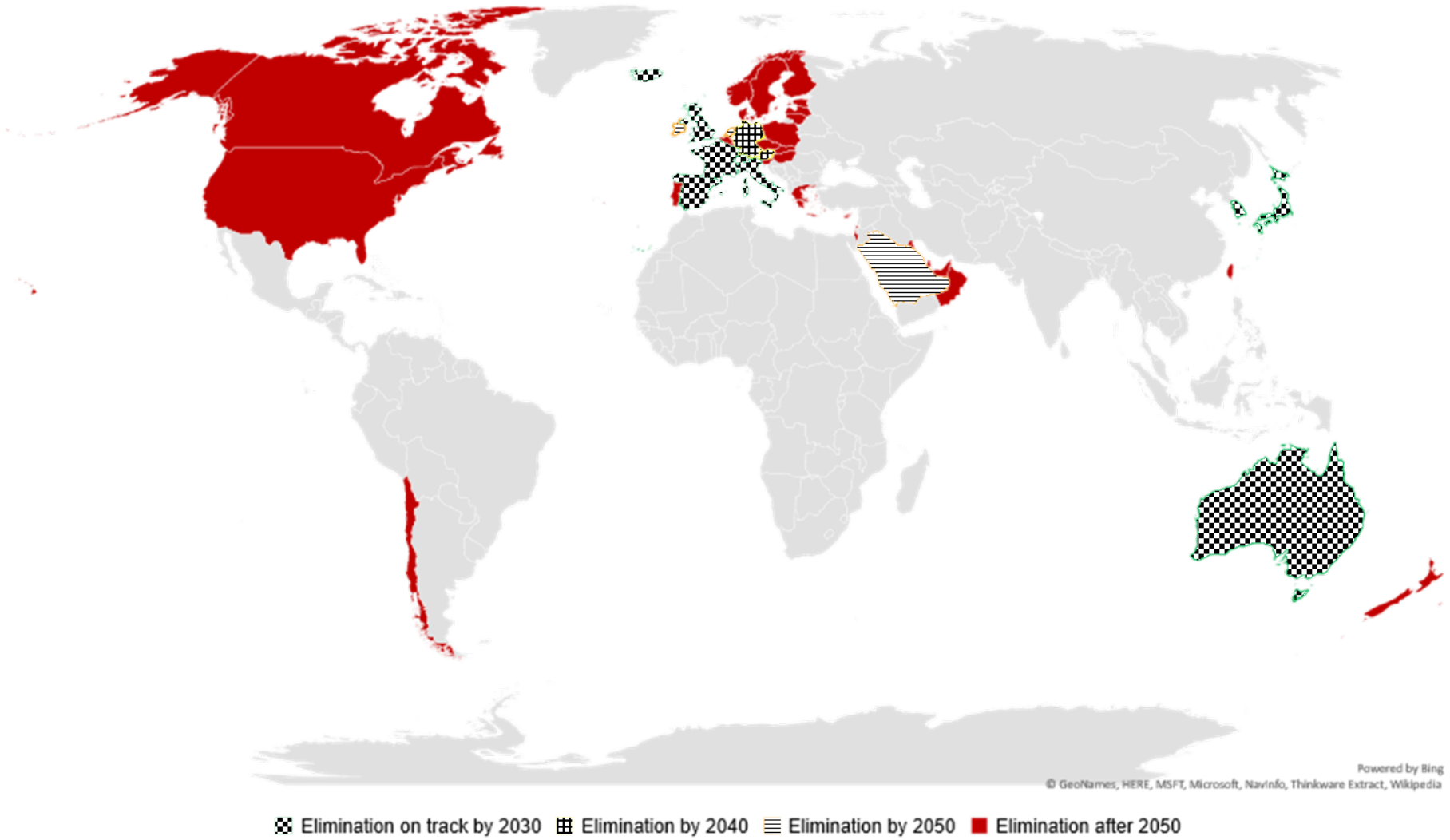
Results

80% not on track for 2030

67% off by >20 years

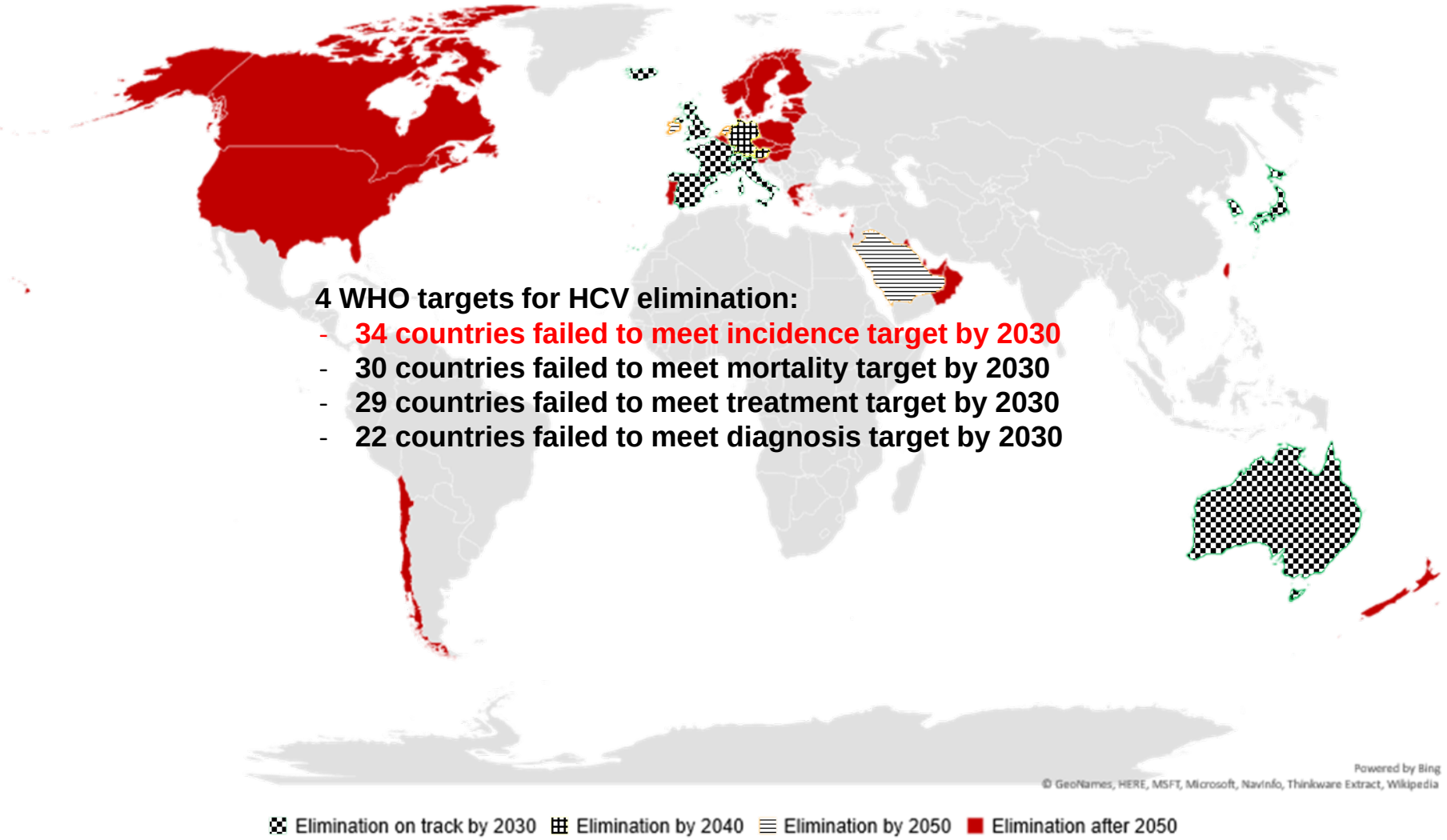
Razavi H., et. al. 2019. J Hepatol 70, 1, Supplement, page e748

Progress report on 45 HIC with data



Slide Courtesy of Homie Razavi of the Center for Disease Analysis

Progress report on 45 HIC with data



Slide Courtesy of Homie Razavi of the Center for Disease Analysis

2015 HCV incidence: 1.75 million and highly variable

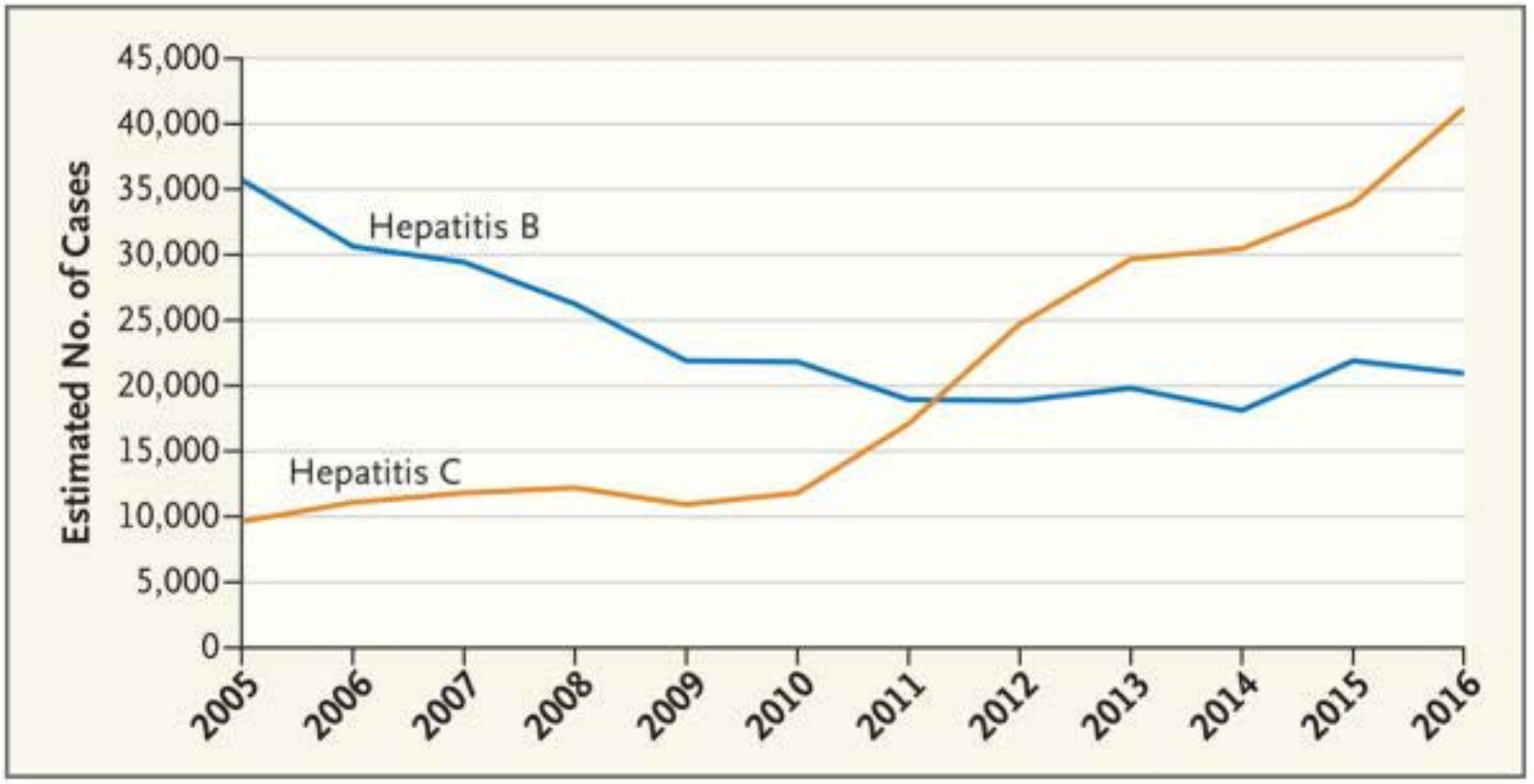
WHO region	Estimated incidence	Uncertainty (X1000)
African	309,000	222-544
Americas	63,000	59-69
Eastern Mediterranean	409,000	363-426
European Region	565,000	460-603
South-East Asia Region	287,000	243-524
Western Pacific Region	111,000	104-124
Global	**1,751,000**	**1,572-2,210**

WHO Global Hepatitis Report 2017

Epidemiological data for 2016 were extracted from national reports, publications and the Polaris Observatory. There were 91/210 countries with data on SVR, HCV-related deaths and new infections available for analysis; 109 countries had net change in epidemic size projected from the regional prevalence of HCV, extrapolated to their population size. 'Net cure' was defined as the number of people with SVR, minus new HCV infections, plus HCV-related deaths in 2016. Results: For the 91 countries analysed, there were 57.3 million people with chronic HCV infection in 2016. In the remaining 109 countries, the projected epidemic size was 12.2 million, giving a global epidemic size of 69.6 million. Across the 91 countries, there was a fall from 57.3 to 56.9 million people in 2017, a 0.7% reduction. The projected global net change was from 69.6 to 69.3 million, a 0.4% reduction. Ten countries had at least five times more people reaching SVR than new HCV infections, including Egypt and USA. In 47/91 countries, there were more HCV infections than SVR in 2016. Conclusion: Very few countries are on target to achieve elimination of HCV as a public health problem by 2030. While the North American, North African/Middle East and Western European regions have shown small declines in prevalence, the epidemic is growing in sub-Saharan Africa and Eastern Europe. Far higher rates of DAA treatment are required for worldwide elimination of HCV.

An epidemic of opioid use and overdose in the US

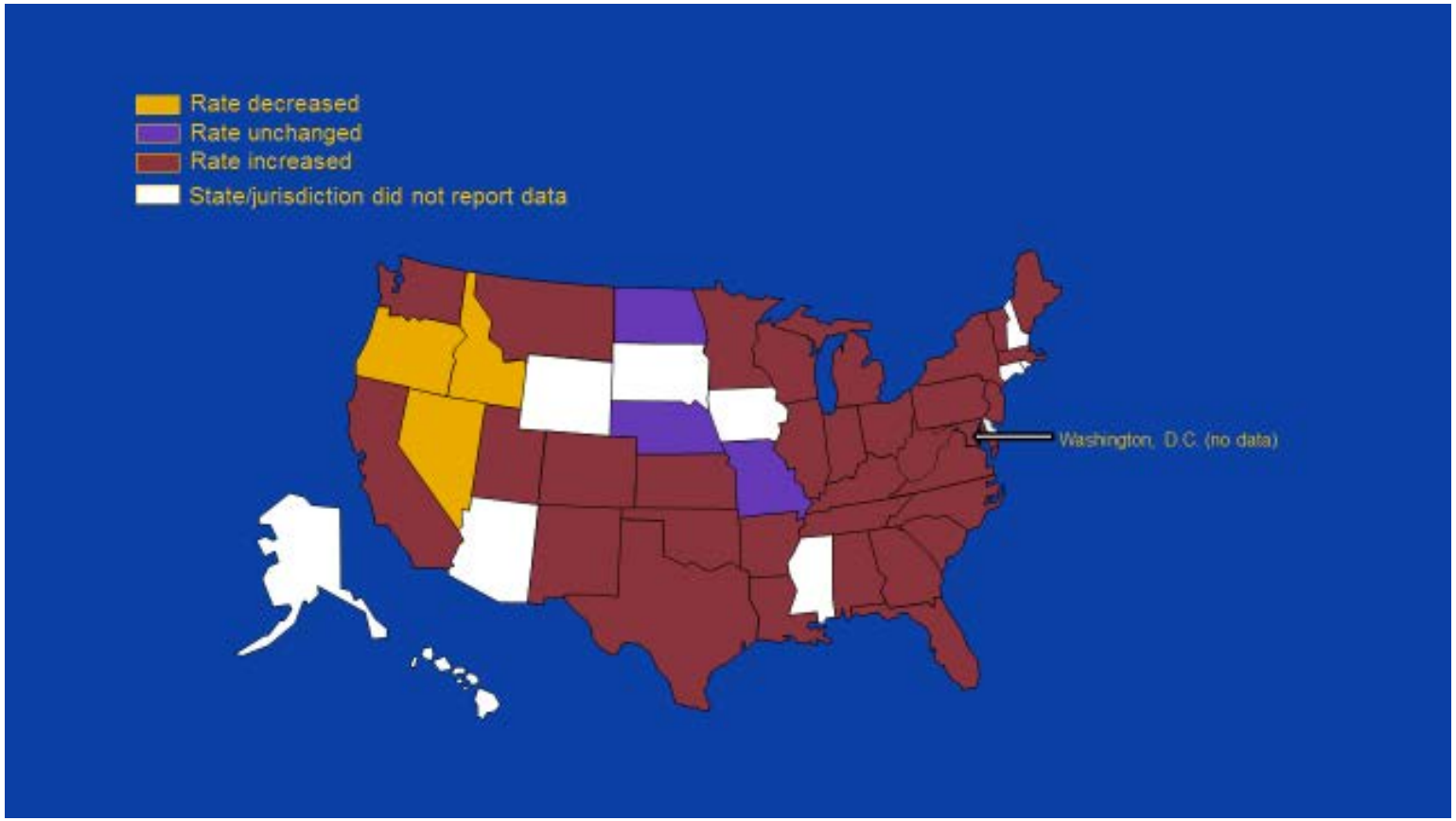
Increasing incidence of acute HCV infection, US 2005-2016



T. Jake Liang and John W. Ward, N Engl J Med 2018; 378:1169-1171

- 2x more in nonurban than urban
- Strongly correlated with IDU
- From 2000-2002, incidence rates for acute hepatitis C decreased among all age groups, except for persons aged 0–19 years; rates remained fairly constant among all age groups from 2002-2010.
- In 2013, the rate of acute hepatitis C increased among all age groups, except for persons aged ≥60 years, compared with rates in 2010. The largest increases were among persons aged 20–29 years (from 0.75 cases per 100,000 population in 2010 to 2.01 cases per 100,000 population in 2013) and persons aged 30-39 years (from 0.60 cases per 100,000 population in 2010 to 1.36 cases per 100,000 population in 2013).
- In 2013, among all age groups, persons aged 20–29 years had the highest rate (2.01 cases per 100,000 population) and persons aged ≥60 years had the lowest rate (0.10 cases per 100,000 population) of acute hepatitis C.

Changes in Rates of New HCV Cases Reported by State 2010-2014



Focus has been more on diagnosis/cure than prevention

Cure

New infection prevention

Challenges to cure

- Treatment remains expensive

Challenges to cure

- Treatment remains expensive
- We have already treated many of those easiest to treat- ~$60 billion on DAAs 2014-2017, but numbers of new patients initiating DAAs declining

Challenges to cure

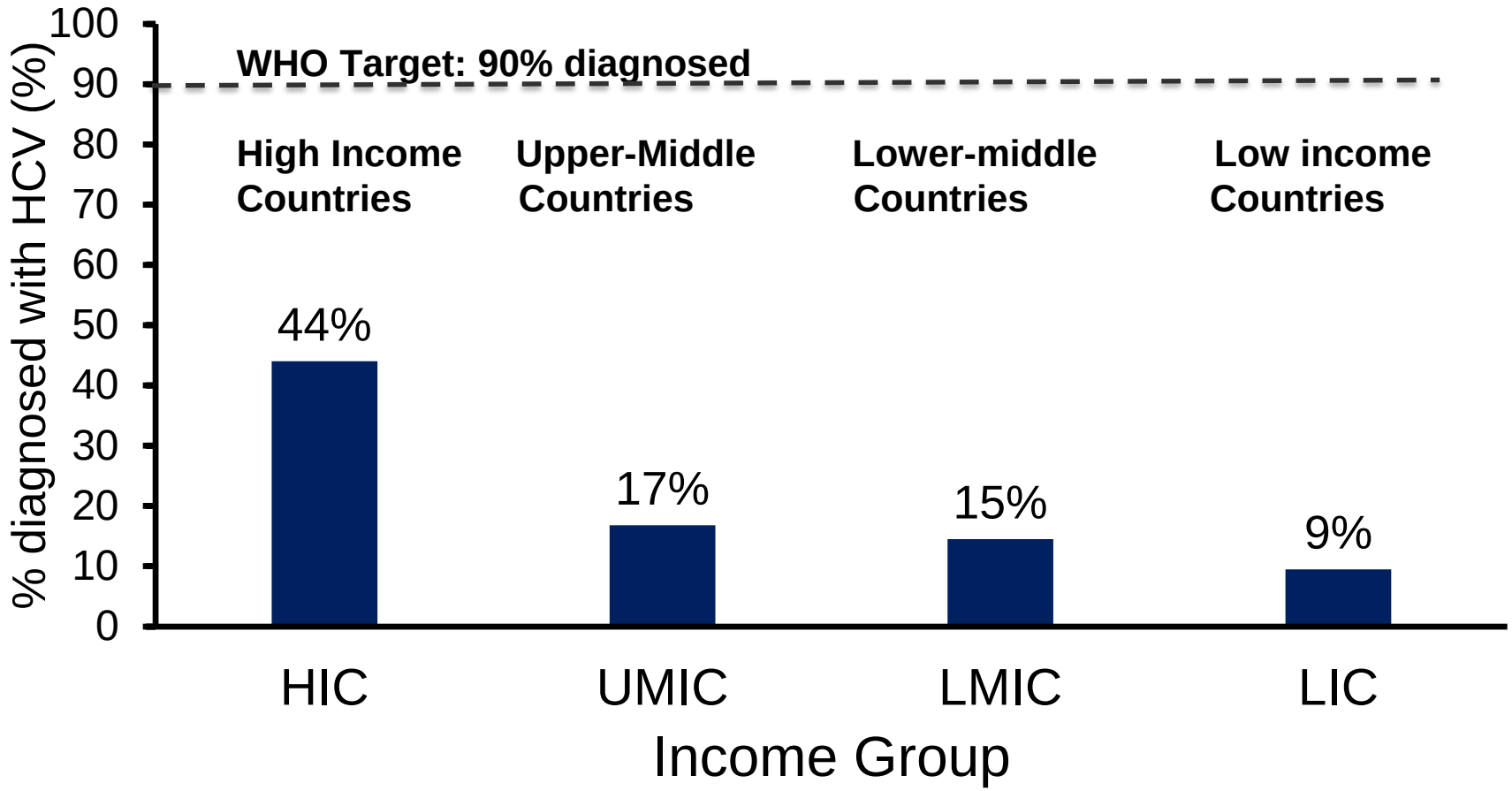
- Treatment remains expensive
- We have already treated many of those easiest to treat
- Finding the people who need treatment remains challenging

Identification of HCV Infected people is challenging

- Infection usually silent until ESLD present
- Highest risk groups are marginalized
- Knowledge of infection status limited

Centers for Disease Control and Prevention MMWR Recomm. Rec. 47 (RR-19), 1-39 (1998), Nature Outlook Hepatitis C vol 474, 7350, S2

Percent of HCV Diagnosed Globally 2016



Data from Polaris database, Andrew Hill

Challenges to cure

- Treatment remains expensive
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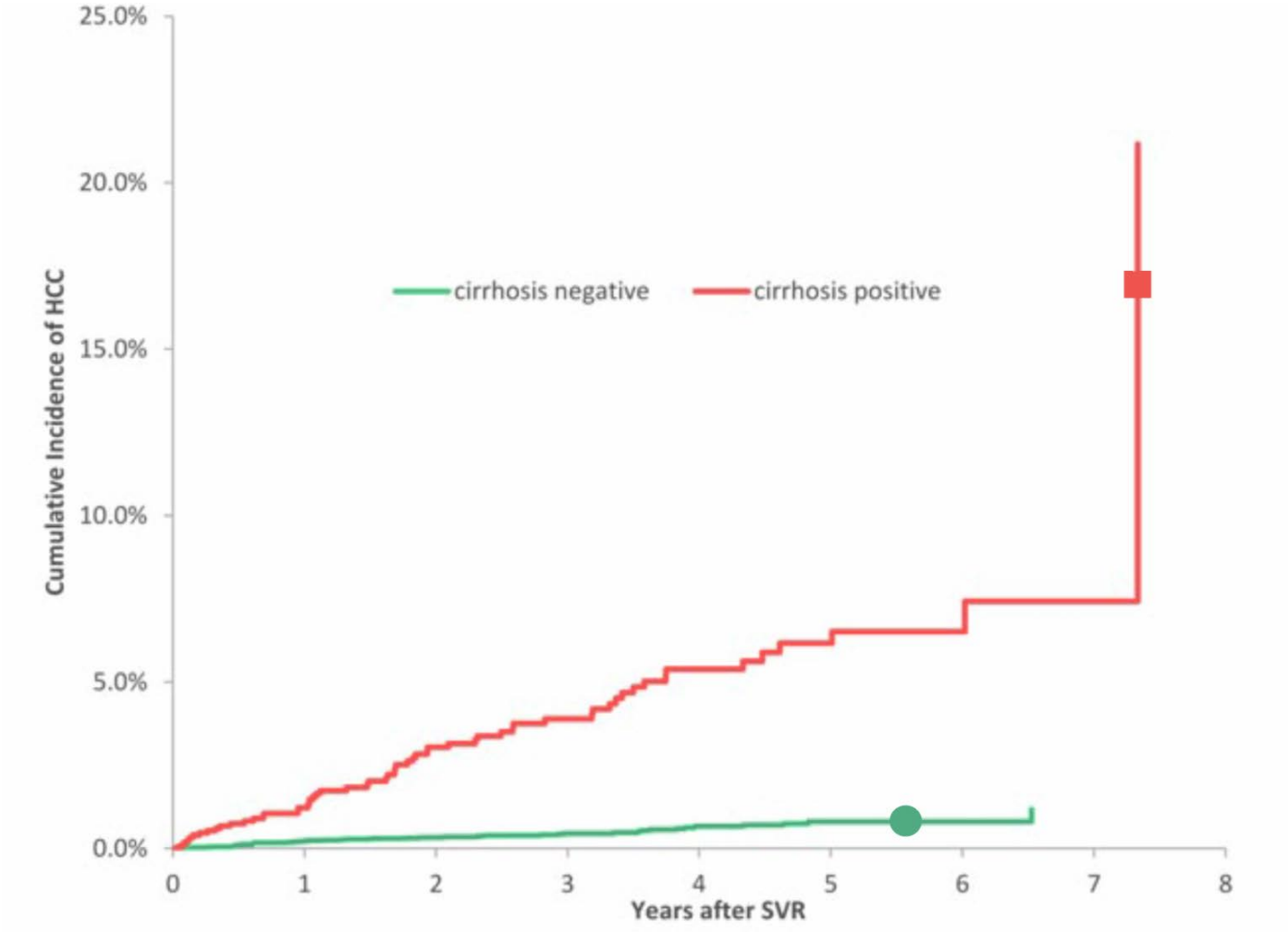
Challenges to cure

- Treatment remains expensive
- We have already treated many of those easiest to treat
- Finding the people who need treatment remains challenging
- Drugs do not provide protection against reinfection
- Treatment in the later stages doesn’t reverse all disease

Incidence of HCC after SVR is high in cirrhotics.



El-Serag, et. al. Risk of Hepatocellular Carcinoma after SVR in Veterans with HCV Infection, Hepatology, 2016 Jul;64(1):130-7.

Consider some additional focus on prevention…

Cure

New infection prevention

Is protective immunity possible?

Baltimore Before and After Acute Study of Hepatitis (BBAASH)

Enrolled: 18-35yo People Actively Injecting
HCV Ab & RNA negative

Anti-HCV Ab = black bar **HCV RNA = red bar**

Persistent Infection (73%)

Spontaneous Clearance (27%)

We are able to study the natural history of HCV infection using the BBAASH cohort, a group of young injection drug users in Baltimore who are followed prospectively beginning while they are HCV negative. Despite counselling, some of these individuals continue to inject and some of them become infected with HCV. These donors are then followed longitudinally with regular blood sampling during acute infection and then during HCV clearance or chronic infection.

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Spontaneous clearance of reinfection in 83%

Osburn et. al. Gastroenterolgy 2010;138:315–324

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HCV- Can we make an effective vaccine?

HCV- considerations for creating a vaccine

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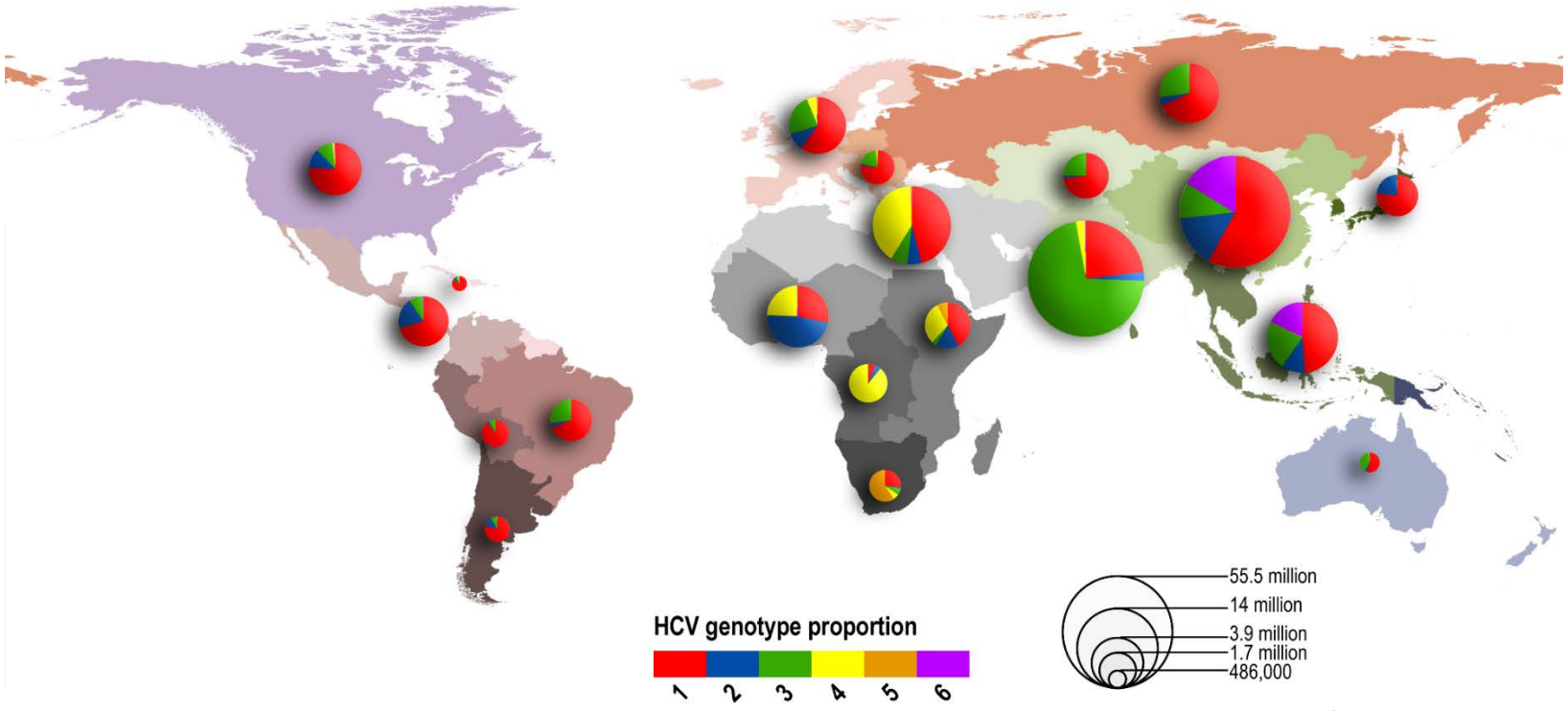
- Virulence factors unknown
- Correlates of protective immunity not completely known
- Viral diversity

Genetic Diversity of HCV is a challenge



The issue

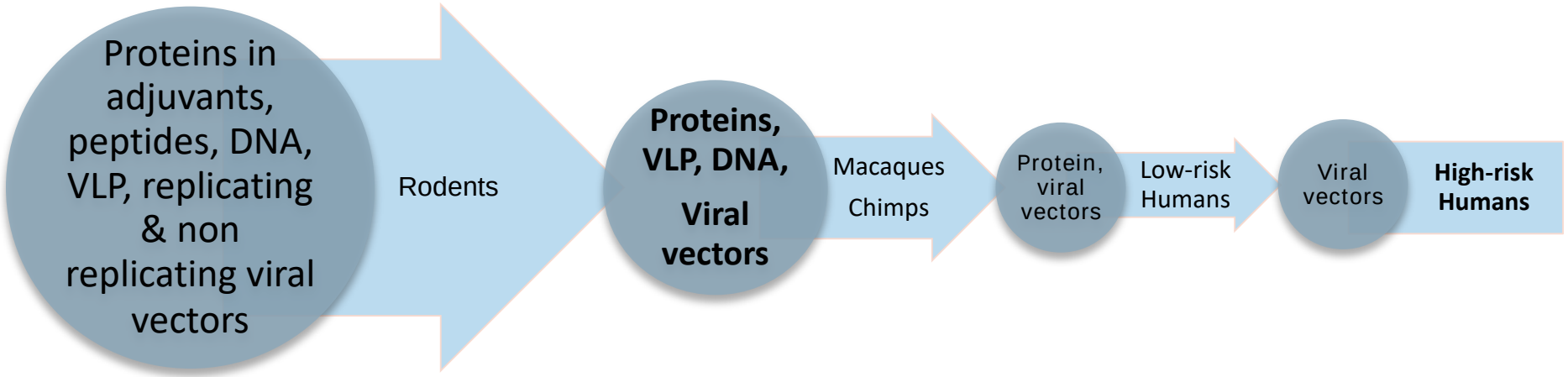
HCV- considerations for testing a candidate vaccine

- No animal model

HCV- considerations for testing a candidate vaccine

- No animal model
- Only predictably high incidence group without high HIV rates is people who inject drugs (PWID)

Efforts to develop a prophylactic HCV vaccine



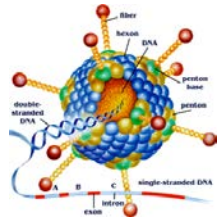
Cox AL, Vaccines for Hepatitis C, 25 Years After the Discovery of Hepatitis C, Springer, 2016

HCV- Can we make an effective vaccine?

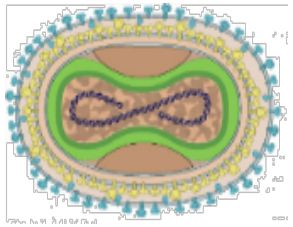
- Use vectors to deliver HCV antigens in a system that induces robust innate and adaptive immune responses

Prophylactic vaccine based on viral vectors to generate T cell immunity

- Prime: Low seroprevalence chimpanzee derived Adenovirus – ChAd3

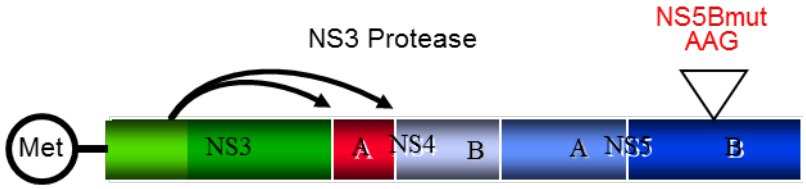


- Boost: attenuated strain of modified vaccina Ankara (MVA)



Prophylactic vaccine based on viral vectors to generate T cell immunity

- Vectored HCV antigen: Nonstructural proteins of HCV, not envelope (targets of neutralizing Ab)



VIP: Vaccine is Prevention

- **Design:** Double blind, randomized, placebo controlled at JHU, UCSF, UNM

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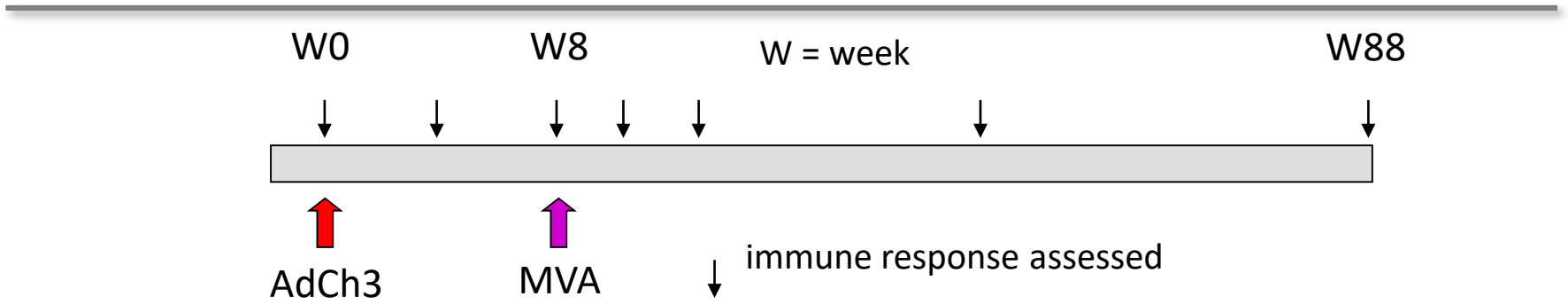
- **Population**: 18-45 yo PWID actively injecting at high risk for but not infected with HCV at screening
- **Enrollment completed in 2016:** 545
- **Goal:** assessment of safety, induction of HCV specific immune responses, and efficacy in preventing chronic HCV infection

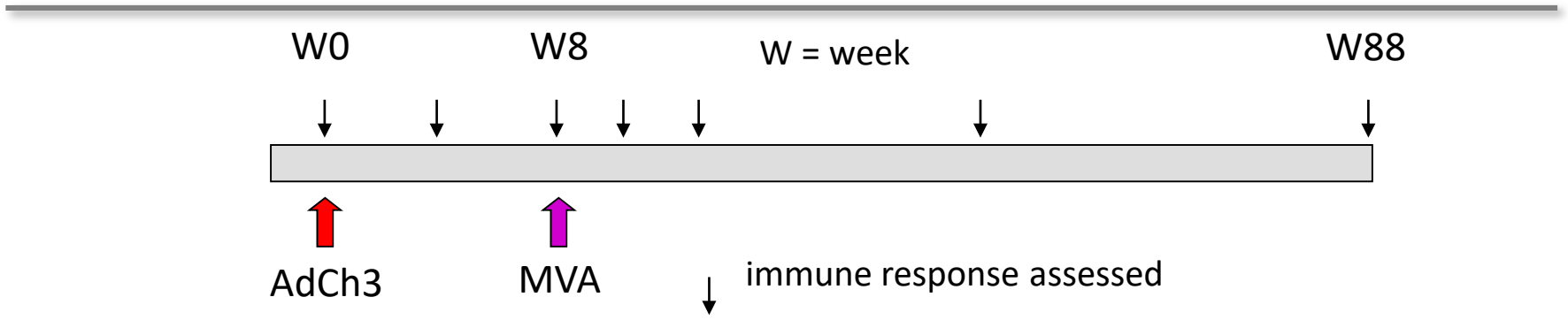
VIP Design

- **Two injections administered at 0 and 8 weeks:**
  AdCh3NS & MVA-NS
- Immune responses assessed



VIP Design

- **Two injections administered at 0 and 8 weeks:**
  AdCh3NS & MVA-NS
- Immune responses assessed
- HCV RNA tested monthly



VIP Results

- Vaccine induced robust T cell responses and was safe, but did not reduce progression to chronic infection.

Conclusions

- A prophylactic HCV vaccine is needed.

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  - Comprehensive strategy

Conclusions

- A prophylactic HCV vaccine is needed.
  - Comprehensive strategy
    - Prevention, harm reduction
    - Diagnosis
    - Treatment

Conclusions

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- Protective immunity likely exists *in vivo*.

Conclusions

- A prophylactic HCV vaccine is needed.
- Protective immunity likely exists *in vivo*.
- New prophylactic vaccine development efforts needed.

Acknowledgements

William Osburn
Michael Melia
Justin Bailey

Kimberly Page
Katherine Wagner

Carolyn Deal
Peter Wolfe
Rajen Koshy

Our Study Subjects

Stefania Capone
Antonella Folgori
Alfredo Nicosia
Elisa Scarselli

Paula Lum
Ellen Stein

Questions

- Thank you for your attention!

Vaccines for Uncommon Diseases: The Issue of Cost

H. Cody Meissner, M.D.
Professor of Pediatrics
Tufts University School of Medicine

NVAC
September 17-18, 2019
Washington DC

Disclaimers/Disclosure

- I have no financial relationship with the manufacturer(s) of any commercial product(s) discussed in this presentation

- I may discuss the use of vaccines in a manner not consistent with the Package Insert, but all recommendations are in accordance with recommendations from the ACIP & AAP

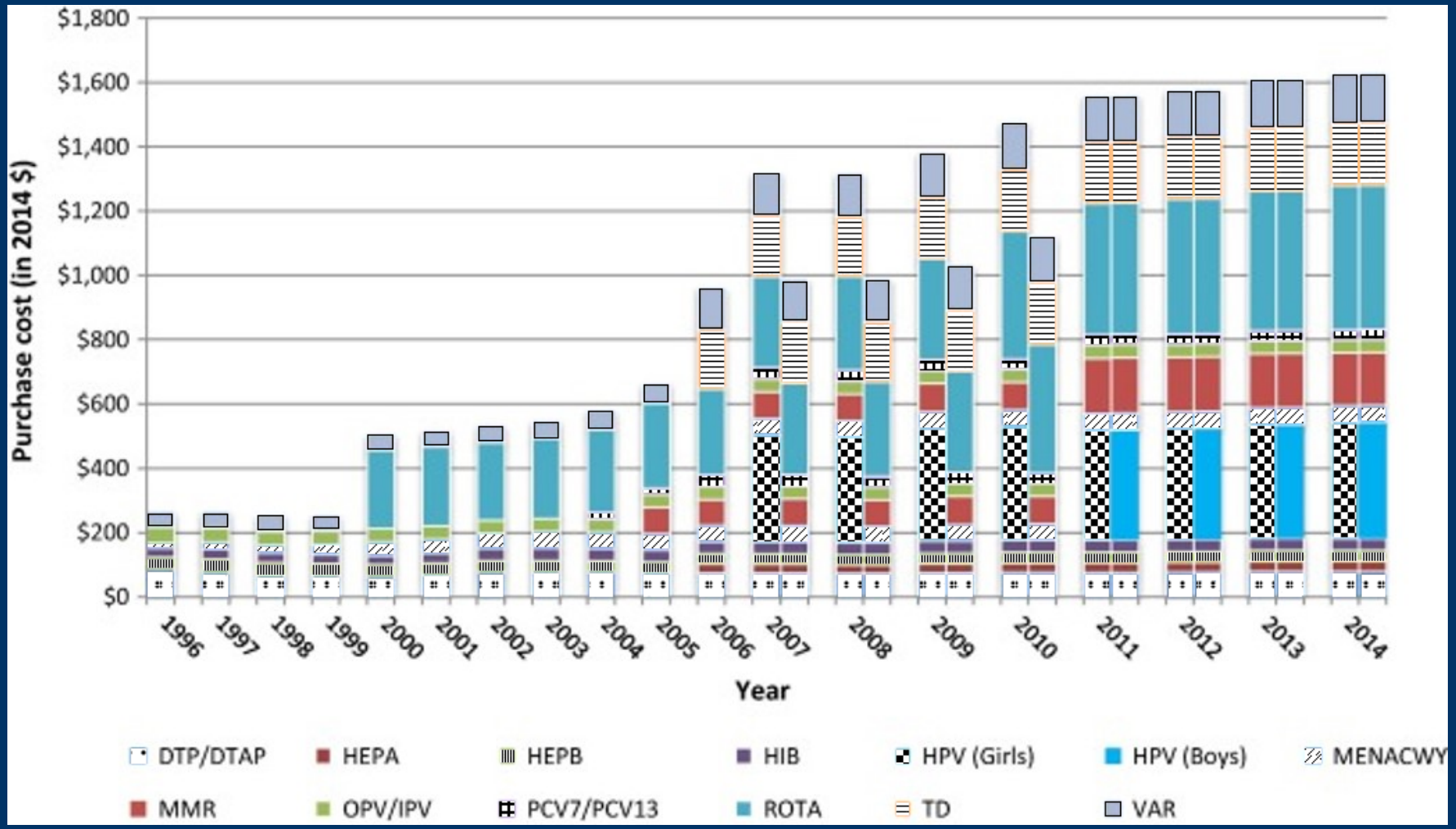
Opening & Closing Questions

- Can a safe & effective vaccine ever be too expensive?
  - What does “too expensive” mean?
  - A vaccine for a limited population will have similar development costs as a routine vaccine
  - Are quality adjusted life years saved the most appropriate measure of cost?
    - Is this equitable?
    - Is this sustainable?
  - Is the responsibility of pharmaceutical industry only to stockholders or to both community & stockholders?

2018 Figures for United States

Gross Domestic Product (GDP)	$20.9 trillion
Health Care Spending (HCS)	$3.7 trillion (17.7% GDP)
Total $ spent/year on vaccines (birth to <19 yrs)	$11.4 billion (0.3% HCS)
Total $ spent/person on vaccines (birth to <19 yrs)	$2,850

Purchase Costs of Recommended Vaccines, Ages 0 - <19 years, 1996-2014



Chen W, Messonnier M, Zhou F. Vaccine 2016;34(39):4706

Vaccines For Selected Populations

In Development

1. *C. difficile*
2. Dengue
3. HIV
4. GAS
5. Lyme
6. Norovirus
7. *S. aureus*
8. West Nile virus
9. Zoonotic influenza viruses
10. Pregnancy
    - RSV
    - GBS

WHO Priority

1. Crimean-Congo hemorrhagic fever
2. Ebola & Marburg virus disease
3. Lassa fever
4. MERS-CoV, SARS
5. Nipah virus (henipaviral diseases)
6. Rift Valley Fever
7. Zika
8. Disease X

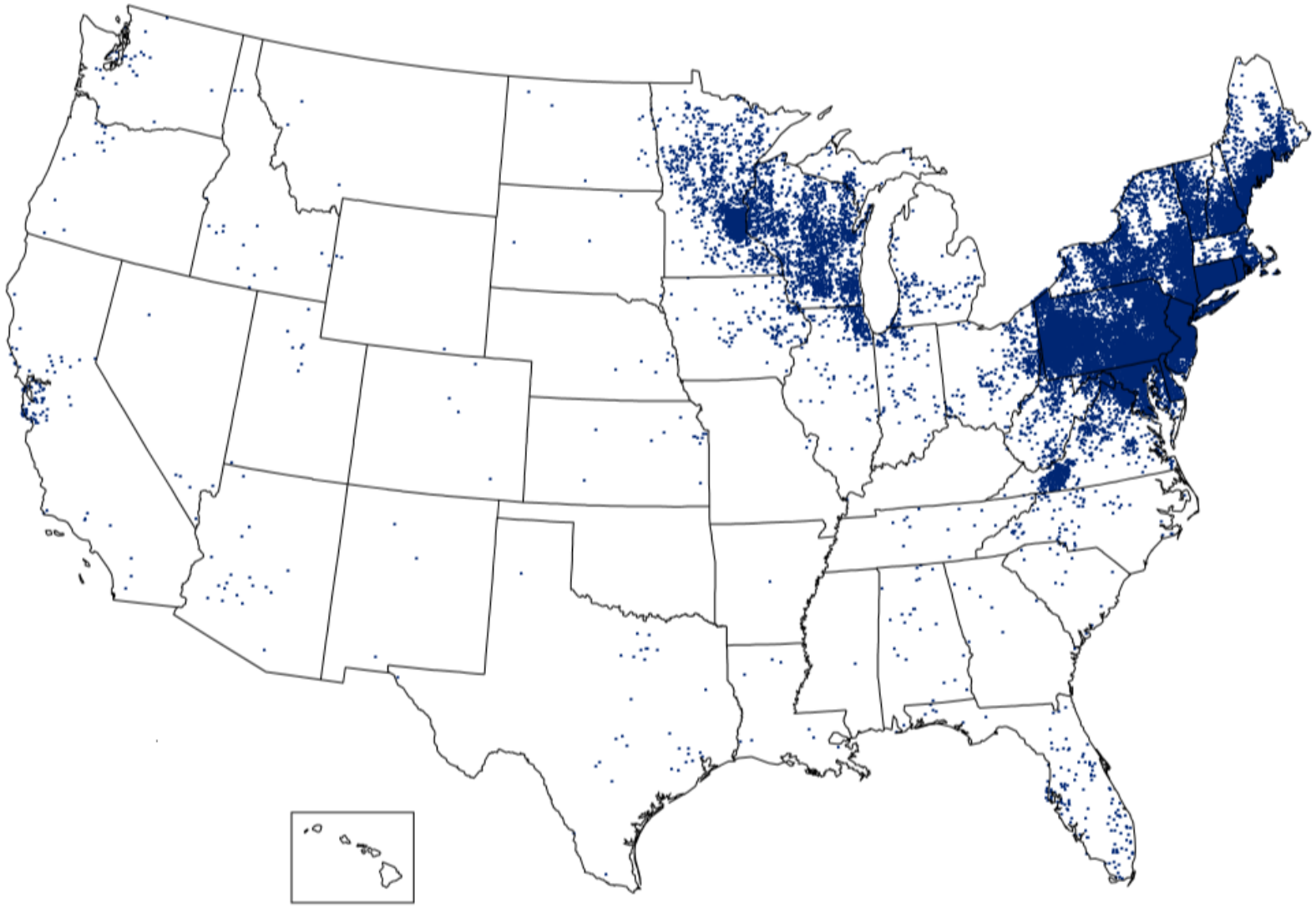
Questions

The value of a vaccine should be based on reduction in illness, pain, disability, mortality & reduction in (direct & indirect) health care costs

But how should a vaccine's value be balanced against pharmaceutical profit?

Are QALYS the best assessment of society's willingness to for a specific intervention (vaccine)?

Reported Cases of Lyme Disease -- United States, 2017



1 dot placed randomly within county of residence for each confirmed case

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First International Conference on Measles Immunization, Nov 1961

Courtesy of Sam Katz, M.D.

In 1941 in the United States, 894,134 people were reported to contract measles

In 2018, more people reached the summit of Mount Everest (807) than contracted measles in a whole year in United States (372)

Thank You

Albert Sabin, Jonas Salk & Basil O’Connor, 1961

Courtesy of March of Dimes

Modeled Costs of 2 Programs for Polio Vaccination & Prevention of VAPP,1994

Schedule	Total Program Cost (millions)	Cases of VAPP Prevented	Total Benefits (millions)	Net Incremental Cost (millions)	Cost per Case of VAPP Prevented
4 OPV	$375	0	$0	Reference	Reference
4 IPV	$416 (+$41)	9.5	$11.4	$28.1	$3.0 M ($1.7 to $11.2)

Miller MA, Sutter RW, Strebel PM, Hadler SC
JAMA 1996;276(12):967