INTERNATIONAL VACCINE INSTITUTE

The Landscape of Current and New Vaccines

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International Vaccine Institute

MISSION

Discover, develop and deliver safe, effective and affordable vaccines for global public health

DISCOVER

- Epidemiology
- Novel antigens
- Novel adjuvants
- New delivery mechanisms
- New routes of administration

DEVELOP

- Laboratory process development
- Assay development
- Technology transfer for large-scale production
- Clinical Development
- Regulatory support (WHO PQ)
- Data analysis

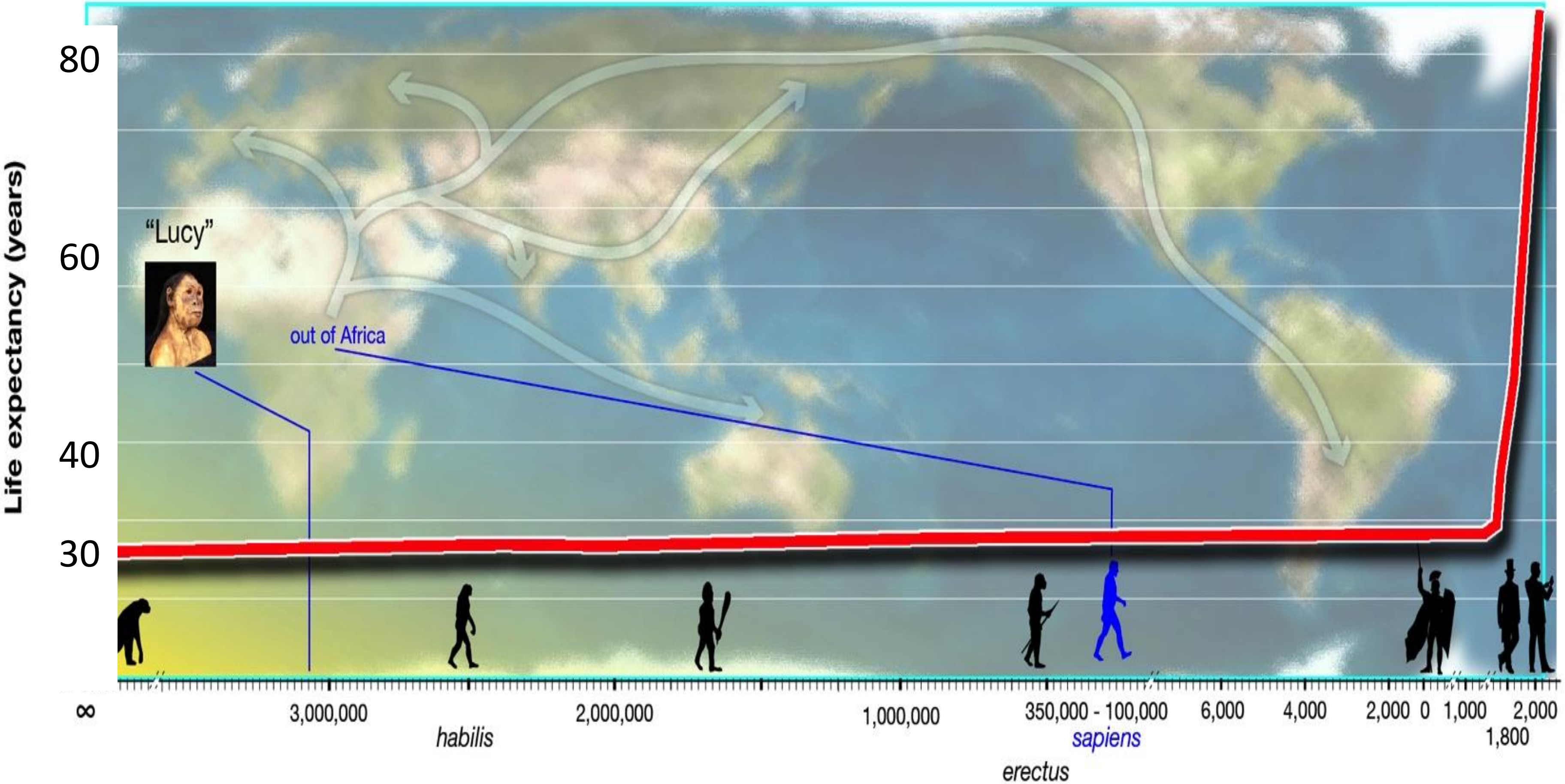
DELIVER

- Epidemiologic, socioeconomic and socio-behavioral studies
- Vaccine feasibility, acceptance, and field effectiveness studies
- Cost-effectiveness and impact analyses
- Vaccination campaigns

Rational and sustainable vaccine introduction

Until recently human life everywhere was nasty, brutish and short

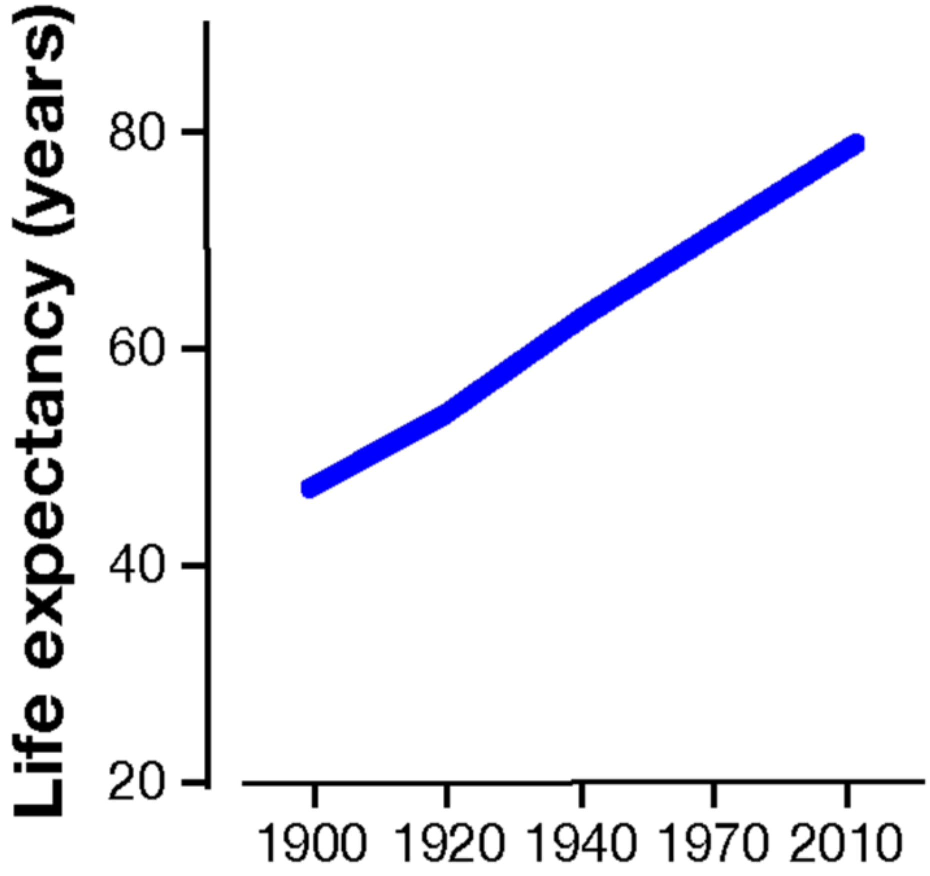
For 99.9% of the history of mankind, life expectancy has been < 30 years



Why? And How?

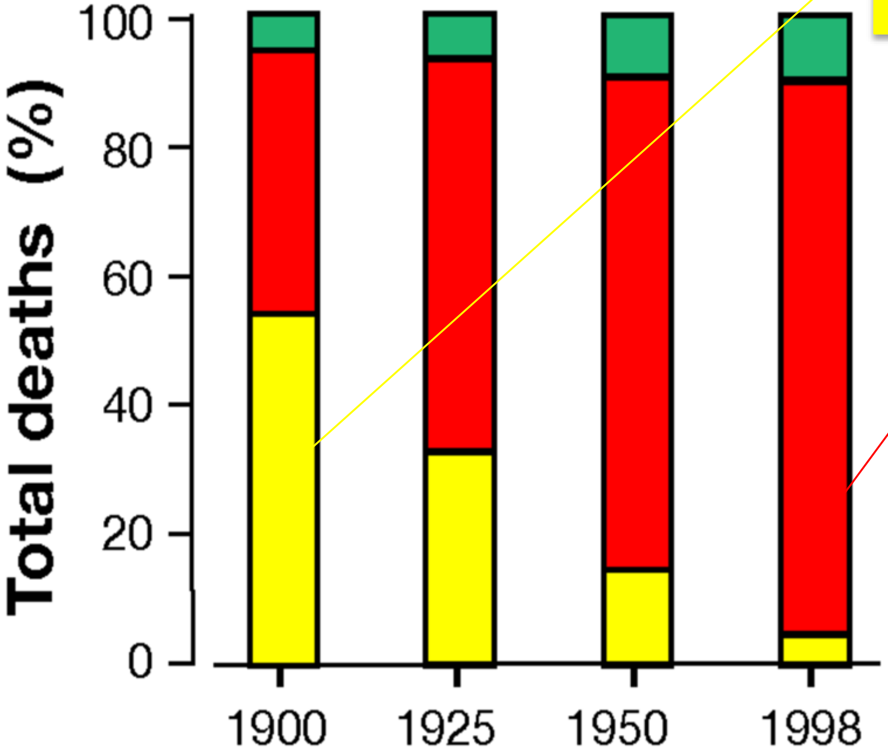

FEBRUARY 23 / MARCH 2, 2015
TIME
SPECIAL
HEALTH
DOUBLE
ISSUE
THIS
BABY
COULD
LIVE
TO BE
142
YEARS
OLD
Dispatches From the
Frontiers of Longevity
time.com

Starting in the 19th century life expectancy rose



Life Expectancy in the United States

Infectious disease mortality has decreased



Infectious Diseases

Diphtheria (40million prevented)
Measles (35 million prevented)
Smallpox ...

Non Communicable Diseases

Ischemic Heart Disese
Stroke
Cancer
Diabetes
Alzheimer
.....

Much of the decrease can be attributed to vaccination

- Vaccination has reduced cases by >3.0 billion

  >500 million deaths prevented
- From 2011-2020 vaccines will save
  - 25 million deaths
    - 2.5 million/year
    - 7000/day
    - 300/hour
    - 5/min

WHO Global Action Plan
http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/index.html)

Vaccines are cost effective

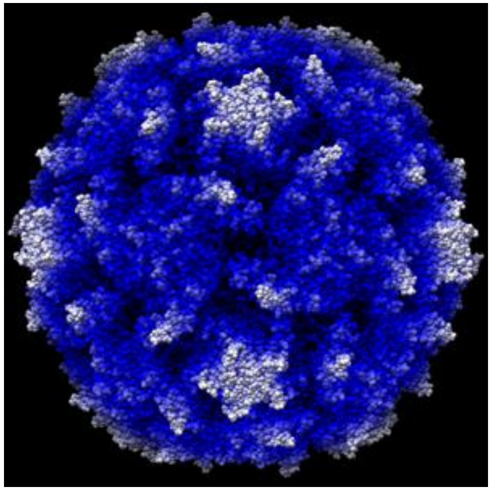
In the United States, from 1994 – 2013, the Centers for Disease Control and Prevention estimated that vaccination saved lives and reduced the cost of illness (MMWR 2014; 63:16).

Vaccines prevented
- 322 million illnesses
- 21 million hospitalizations
- 732,000 deaths

Vaccines saved:
- $295 billion direct costs
- $1.38 trillion in total societal costs

Until recently many vaccines followed a simple formula

Poliovirus, 2.9A resolution

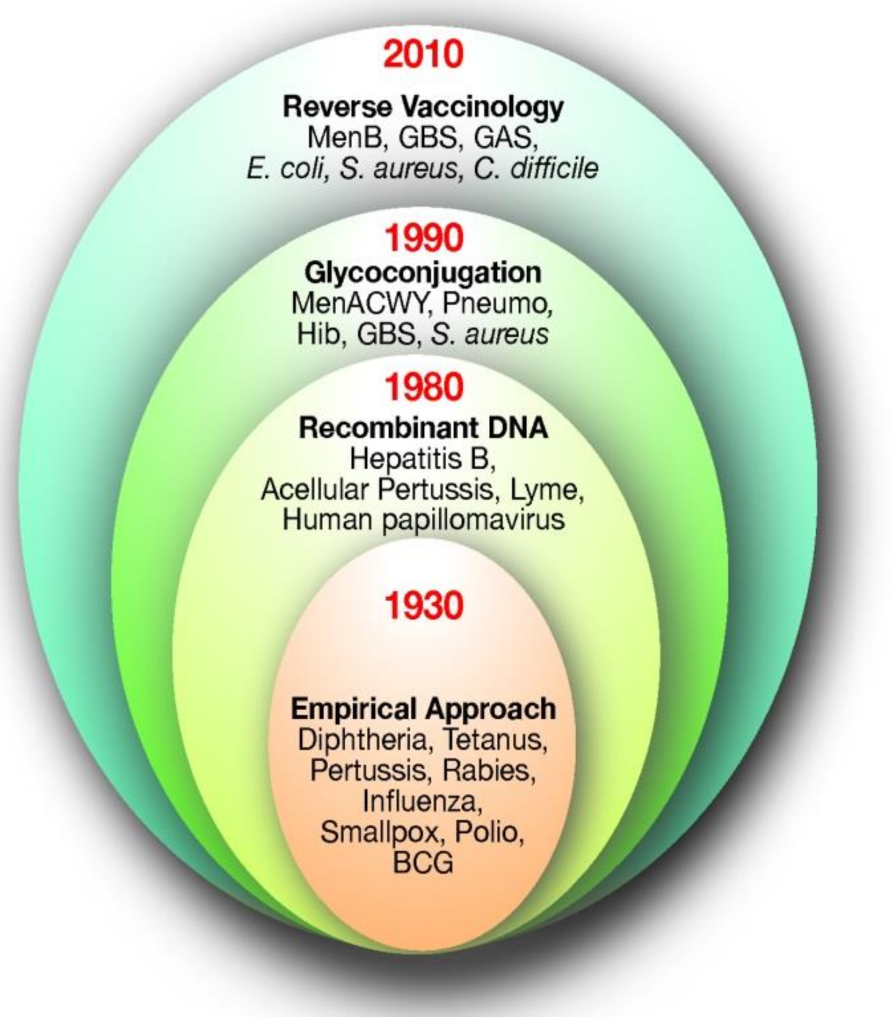


Isolate

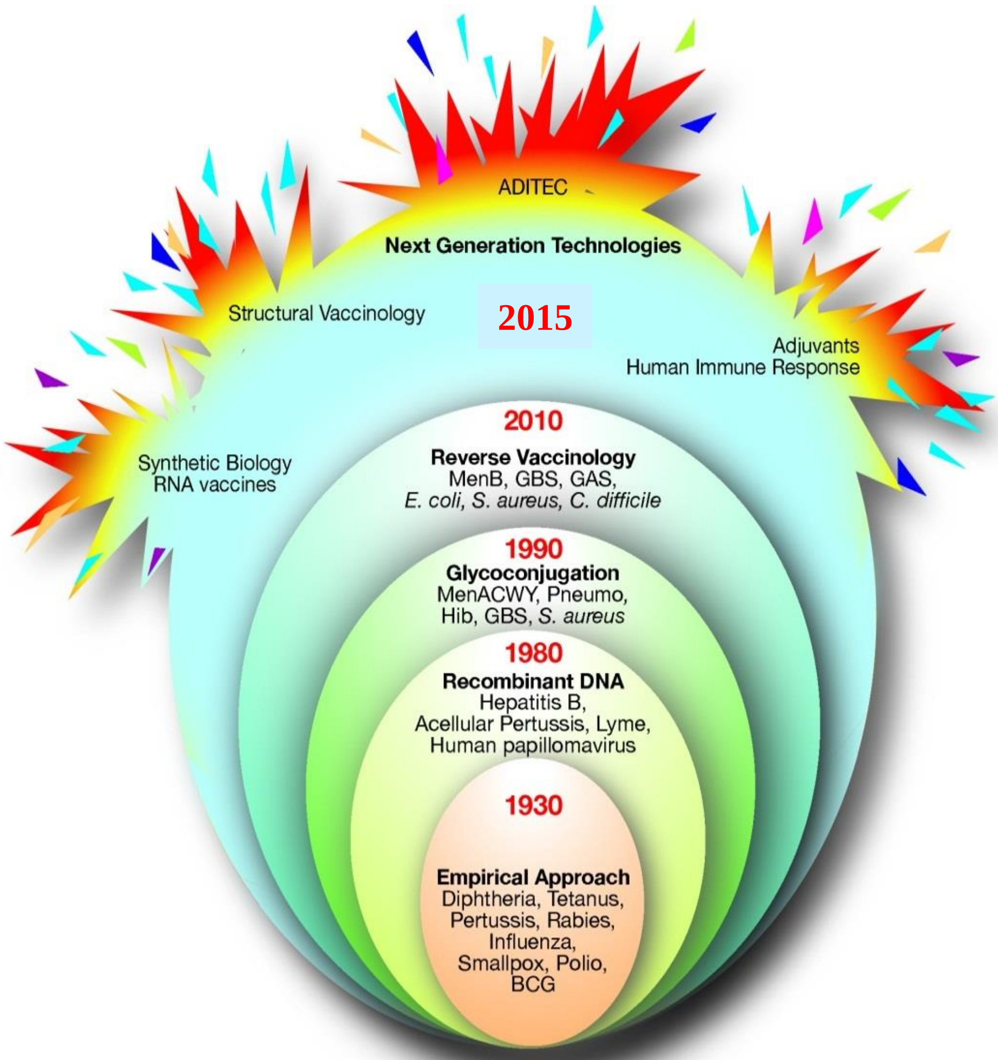
Inactivate / Attenuate

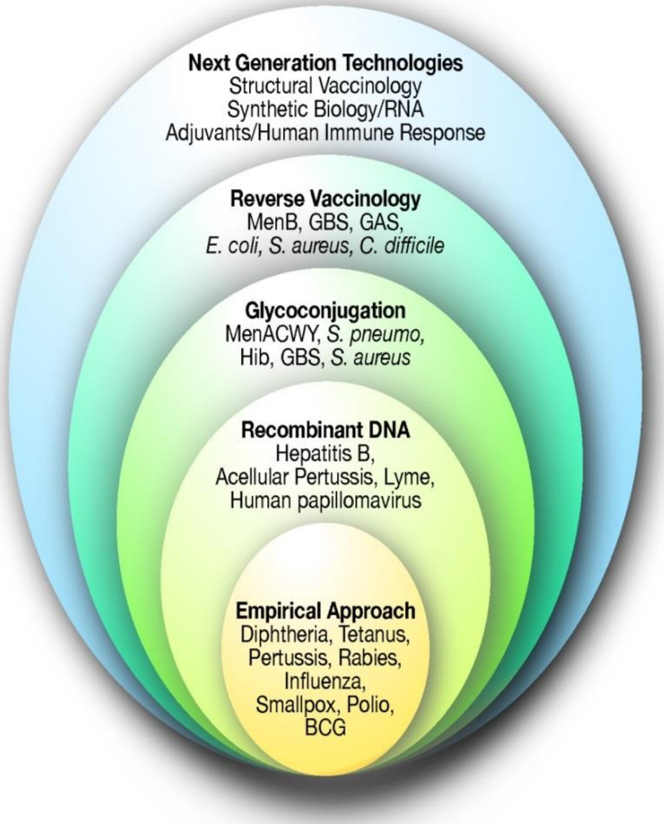
Inject the microorganism causing disease

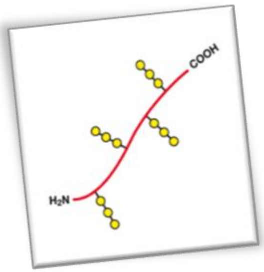
In the last 30 years, there has been a revolution in vaccine discovery



And there is greater promise in the future



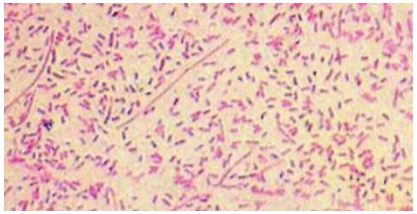




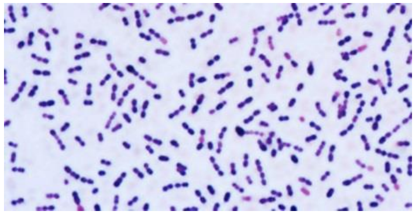
Conjugate vaccines

Capsular polysaccharides & conjugates

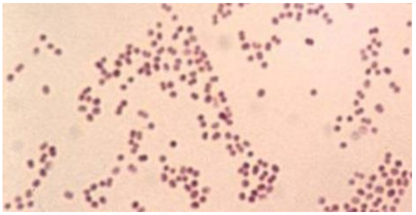
Haemophilus influenzae type B (Hib)



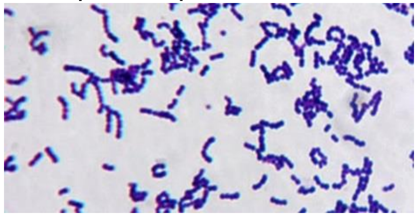
Pneumococcus



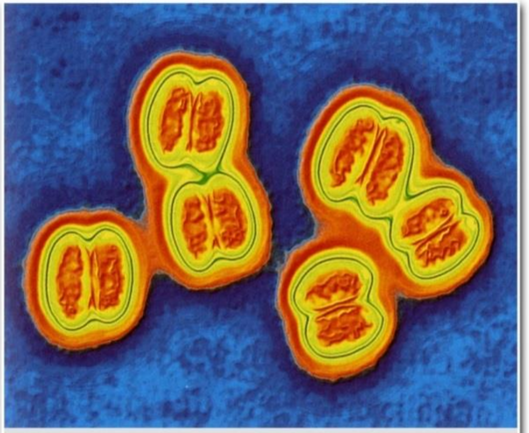
Meningococcus



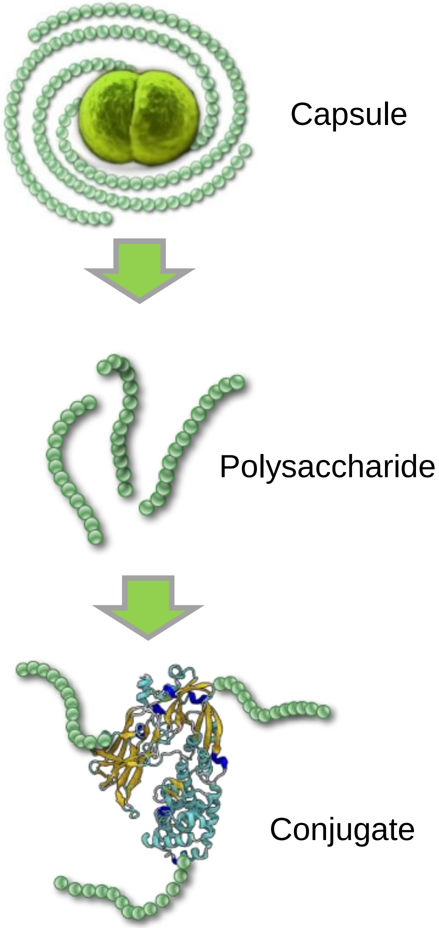
Group B streptococcus



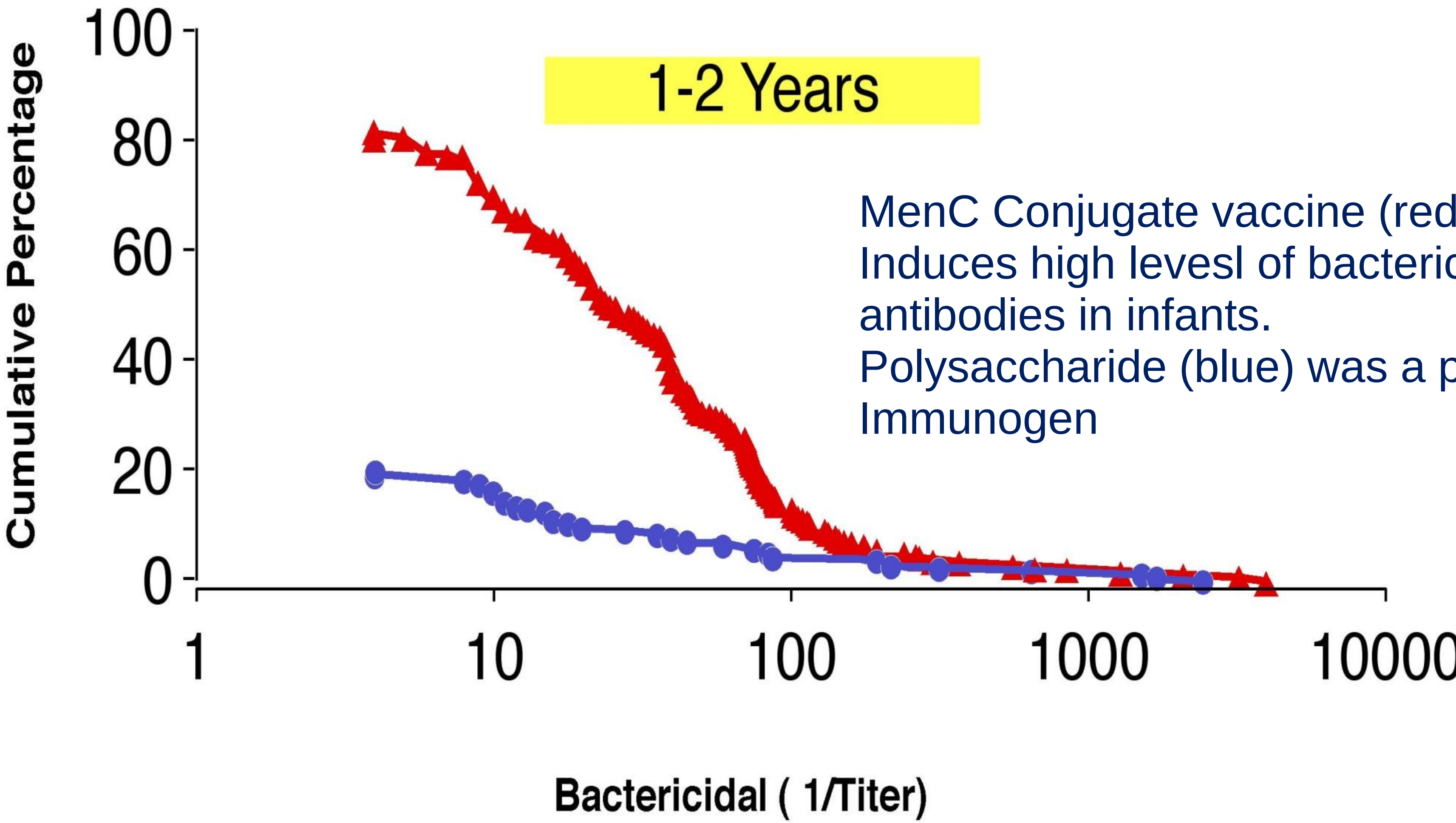
Capsule



Neisseria meningitidis bacteria



Conjugation of polysaccharide to protein improves immunogenicity in infants

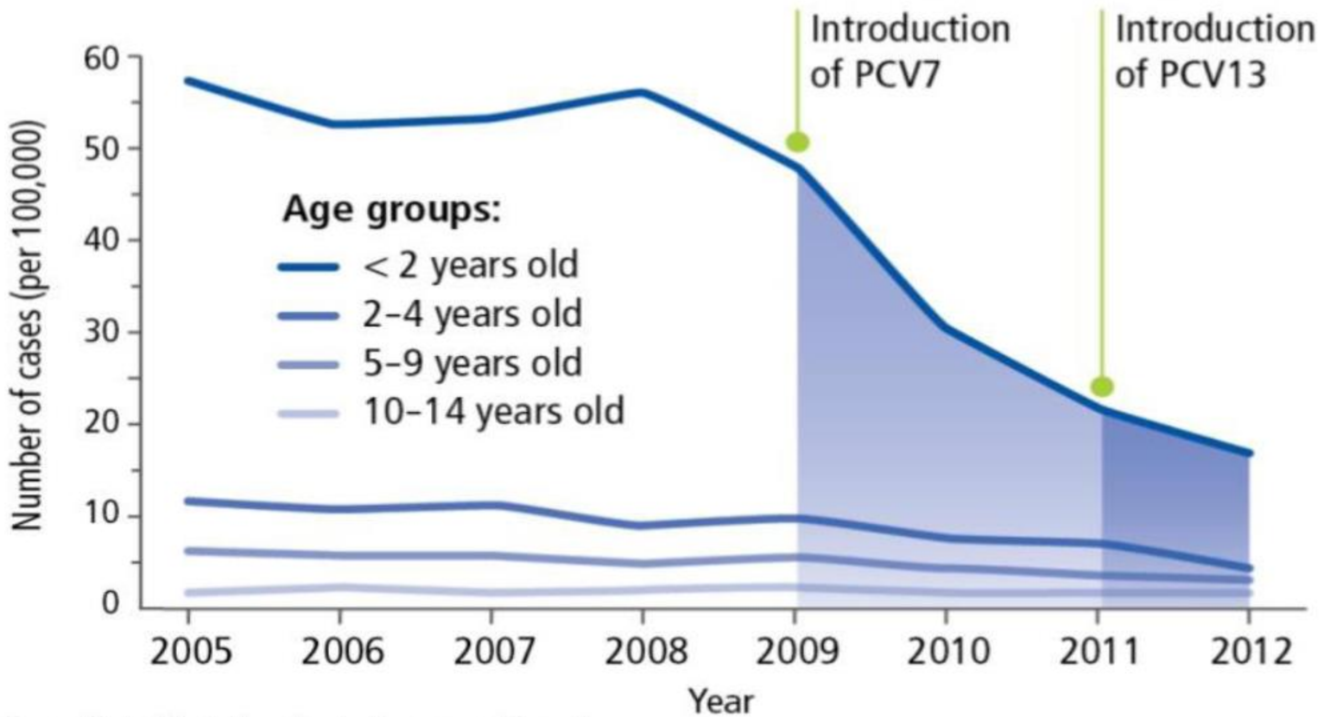


MenC Conjugate vaccine (red) Induces high levesl of bactericidal antibodies in infants.
Polysaccharide (blue) was a poor Immunogen

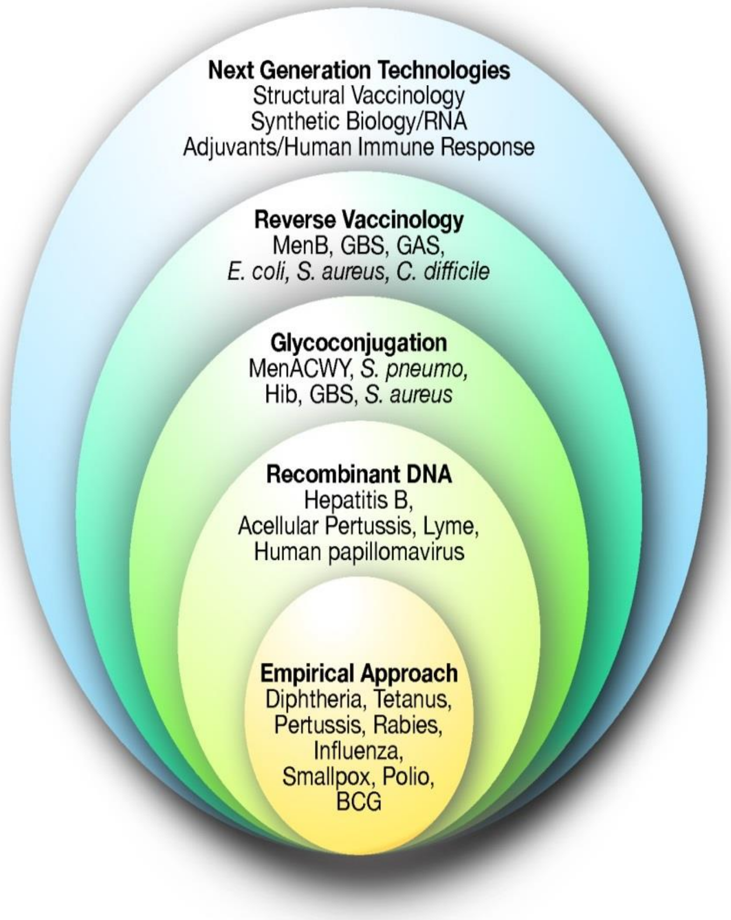
Impact of PCV: RSA

Substantial reduction in pneumococcal disease in South Africa thanks to vaccines

Invasive pneumococcal disease cases by age group



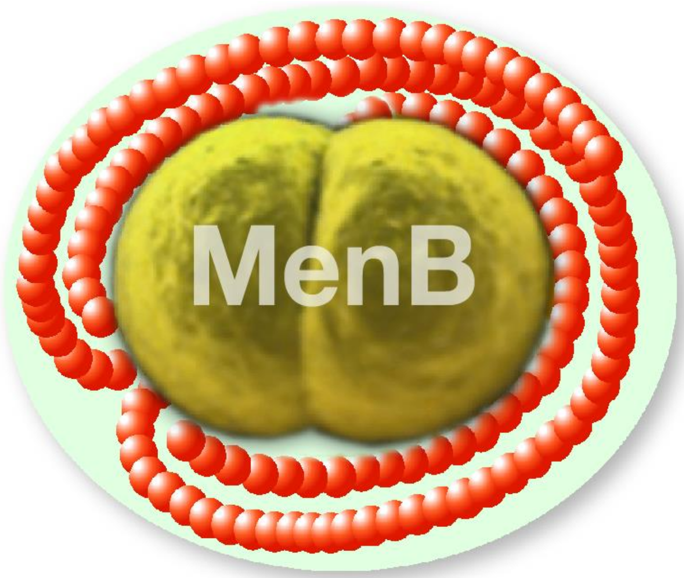
Source: Effects of Vaccination on Invasive Pneumococcal Disease in South Africa. *New England Journal of Medicine*, November 13, 2014.

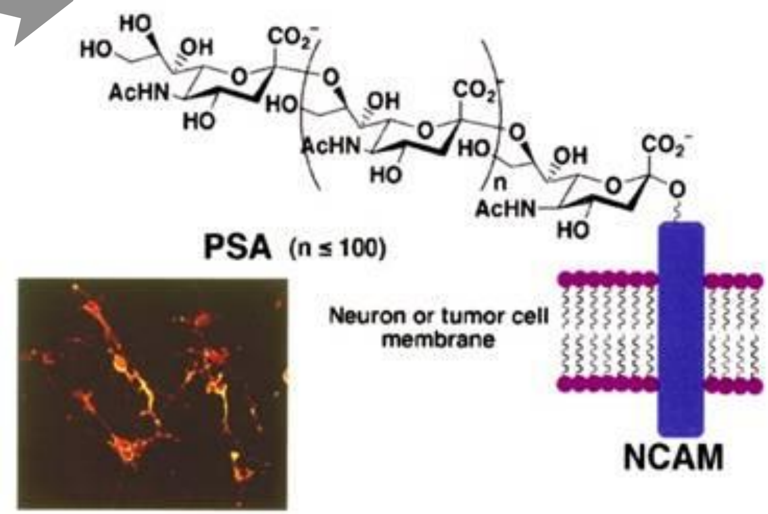


Reverse Vaccinology

and a vaccine for Meninigococcus B

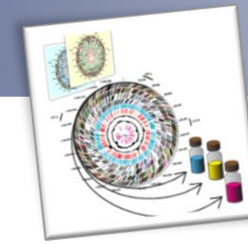
Meningococcus B capsule is a self antigen and cannot be used for vaccination

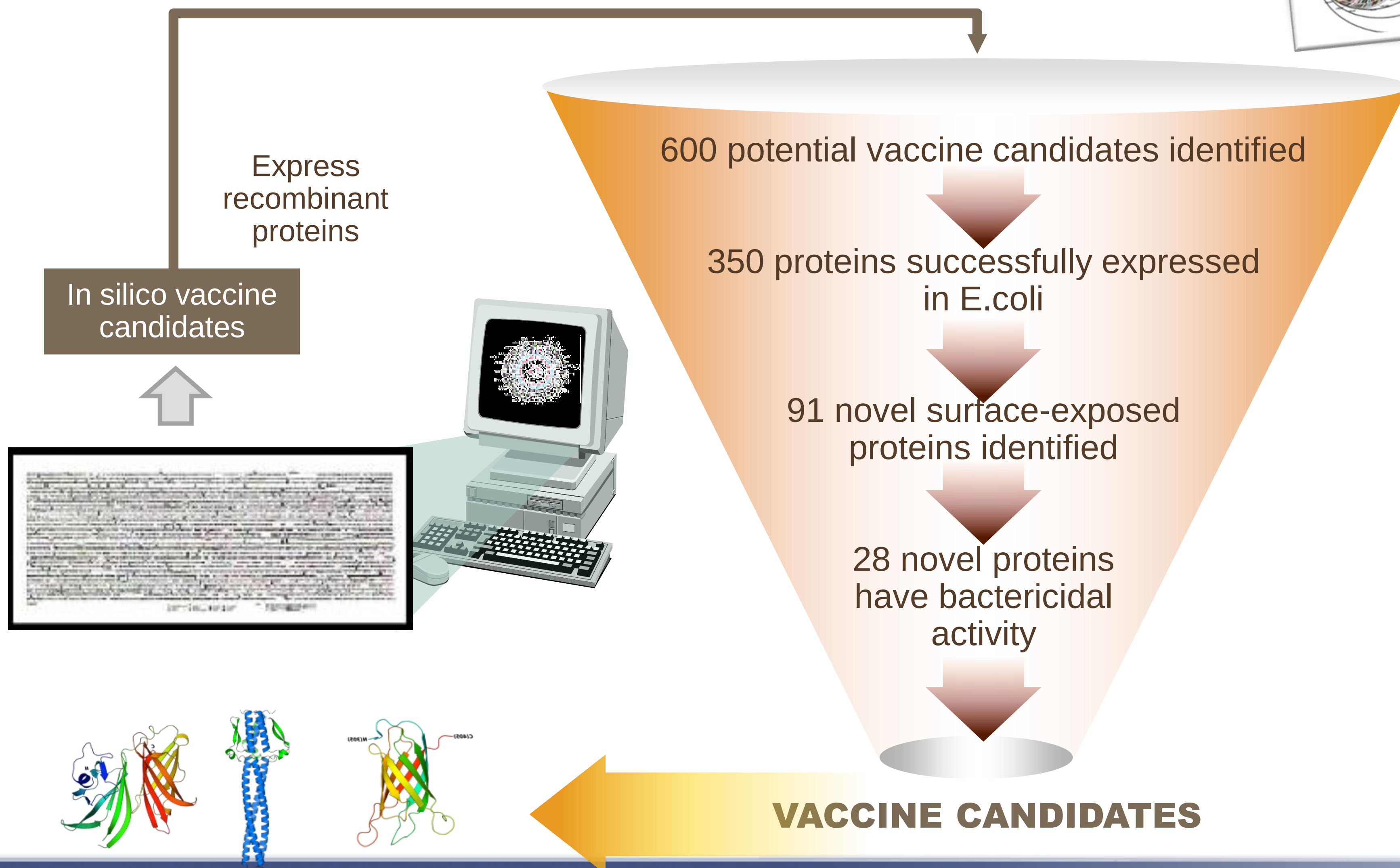


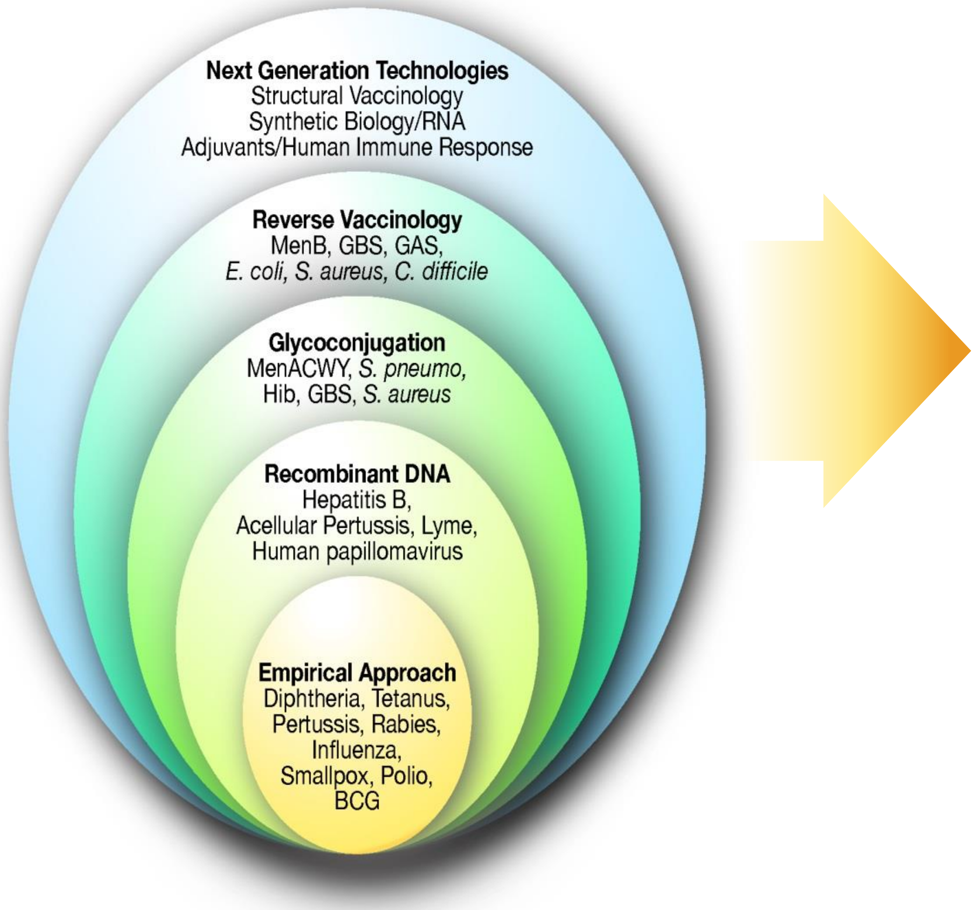


Men B capsule is structurally similar to human glycoproteins like NCAM, raising the risk of autoimmunity to the vaccine.

Reverse Vaccinology: genomic approach



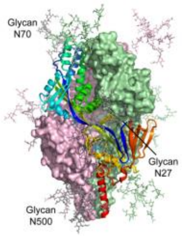




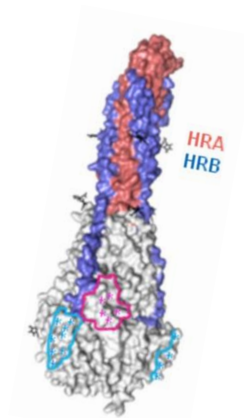
Structural Vaccinology

Structure-based antigen design

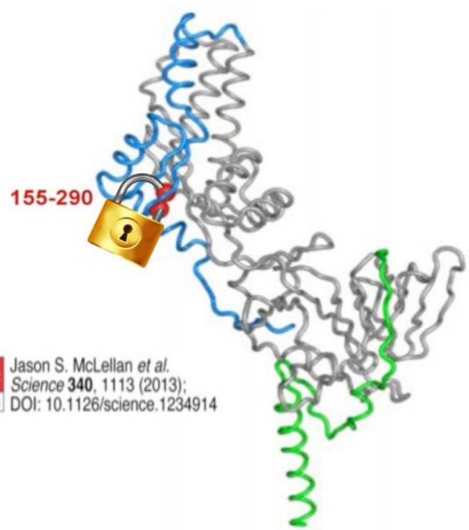
Structural Vaccinology: Respiratory syncytial virus

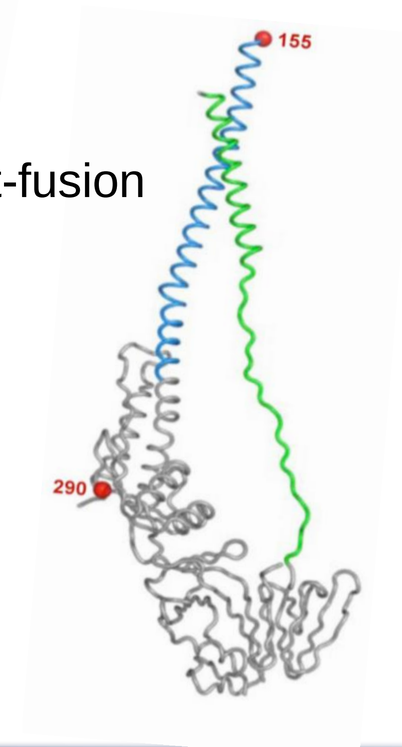


Pre-fusion

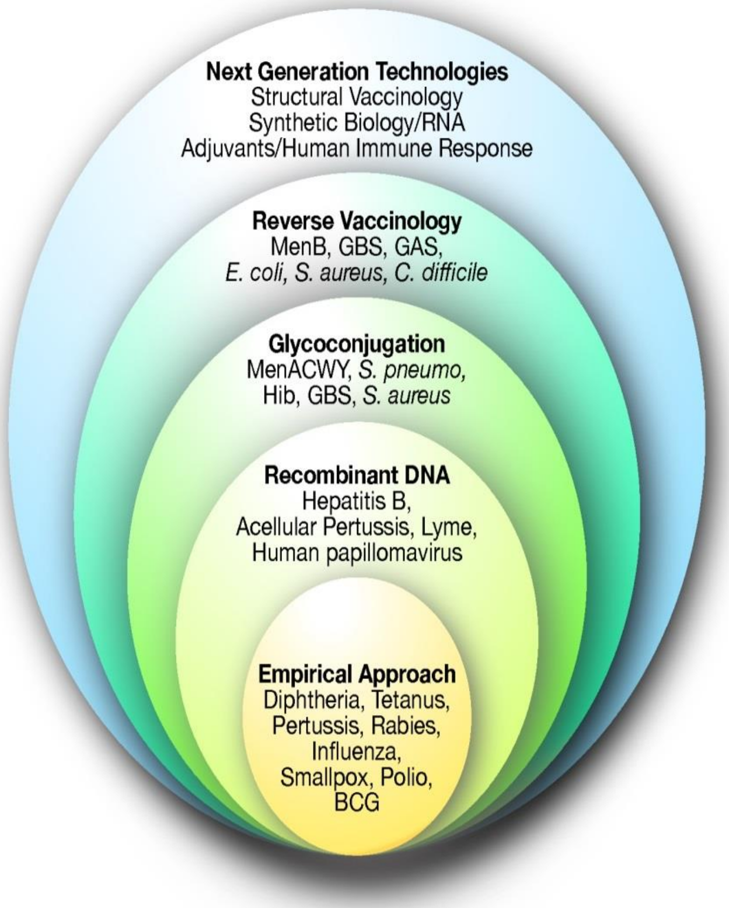


Post-fusion





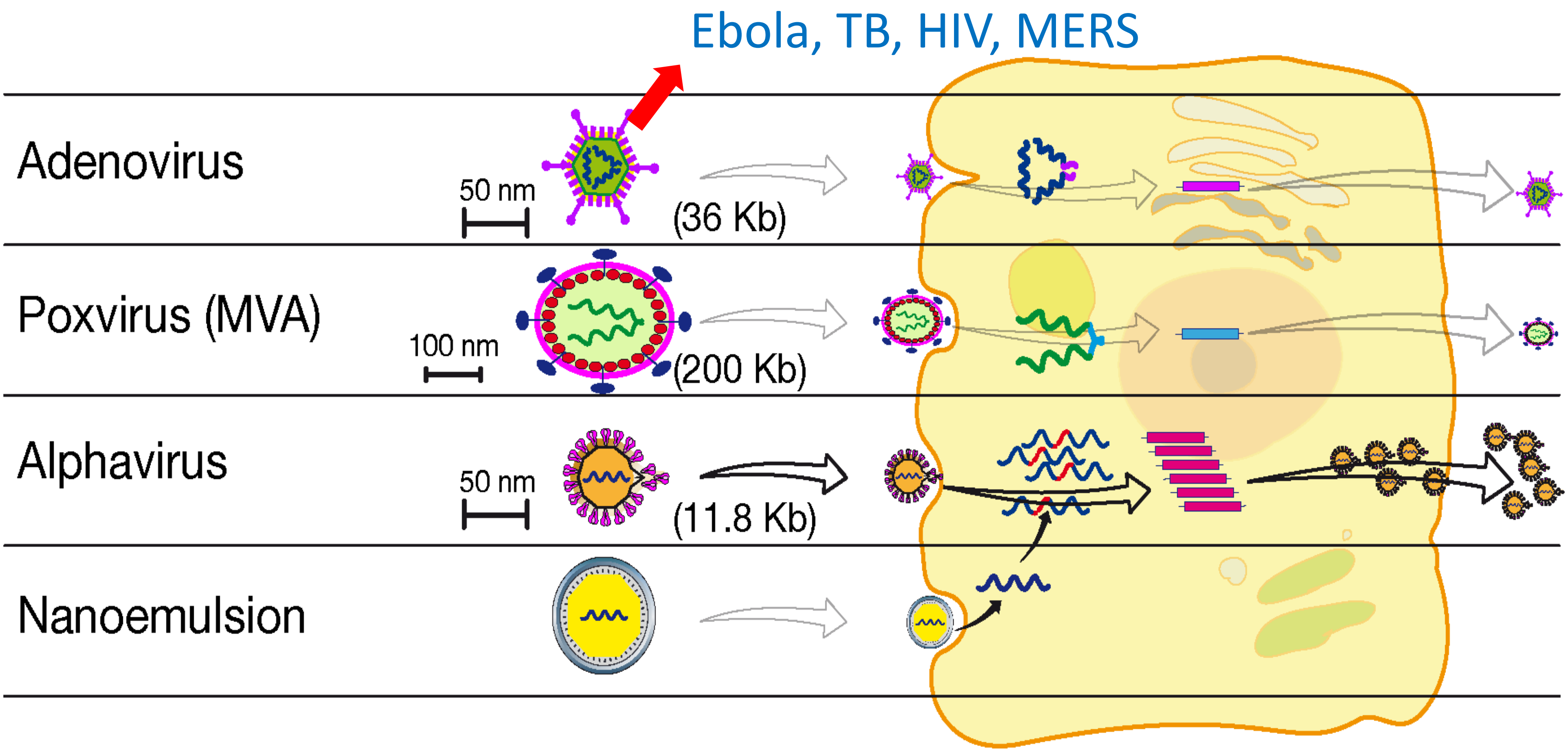
Science AAAS Jason S. McLellan *et al.*
Science **340**, 1113 (2013);
DOI: 10.1126/science.1234914



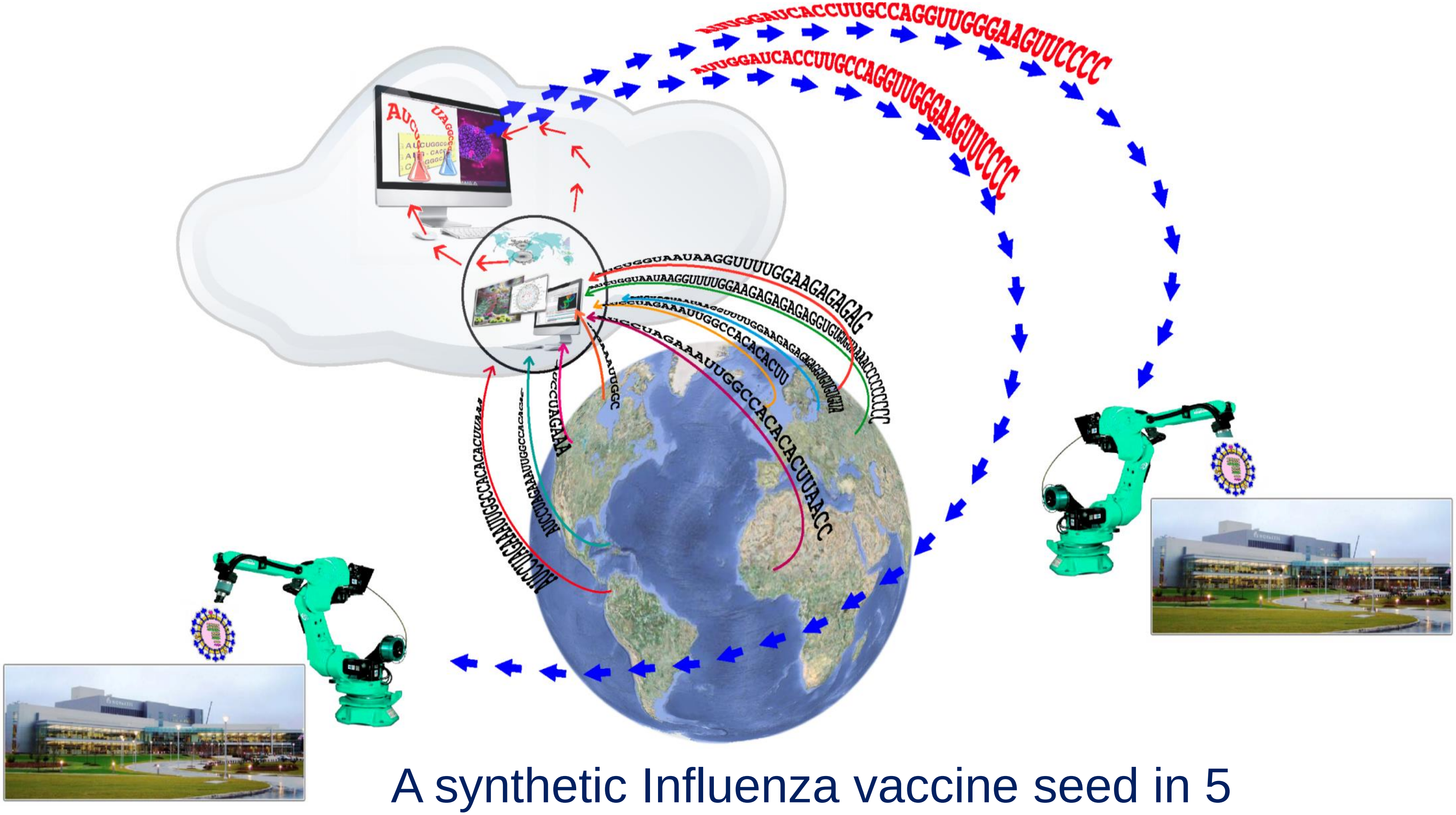
Synthetic biology

Synthetic vaccines: engineering viruses to express target antigens

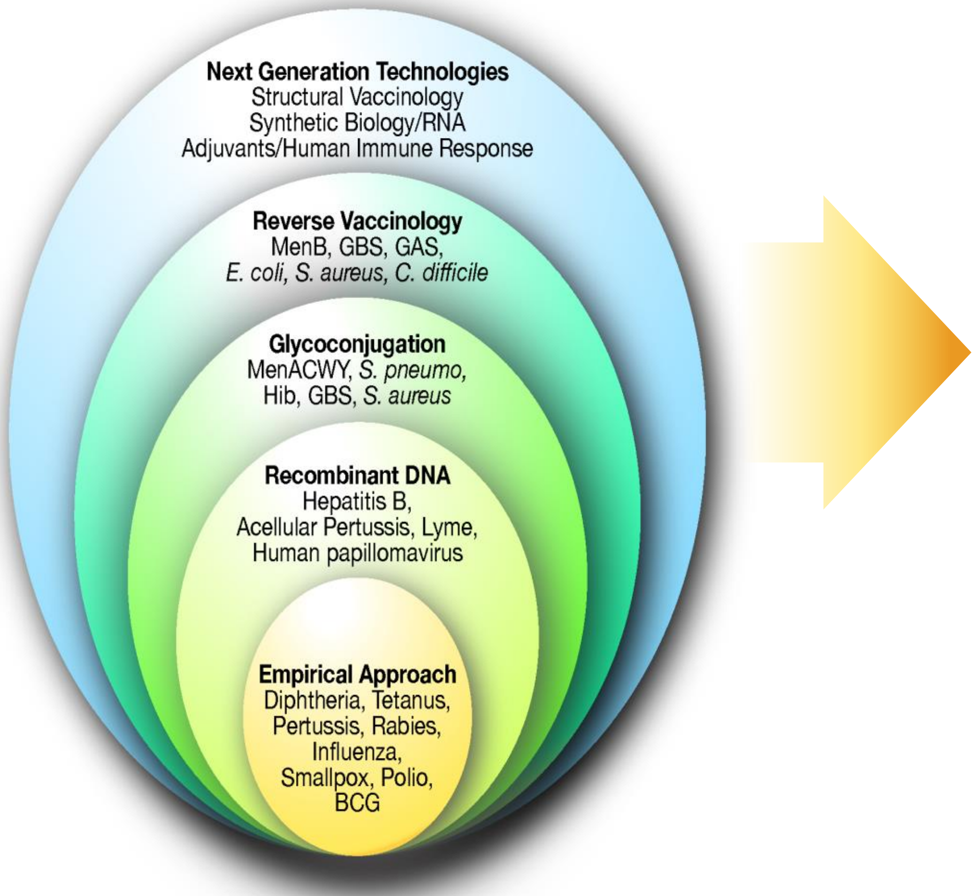
Using replicating and non replicating viral vectors to transfer genes to cells



Molecular techniques offer unprecedented speed

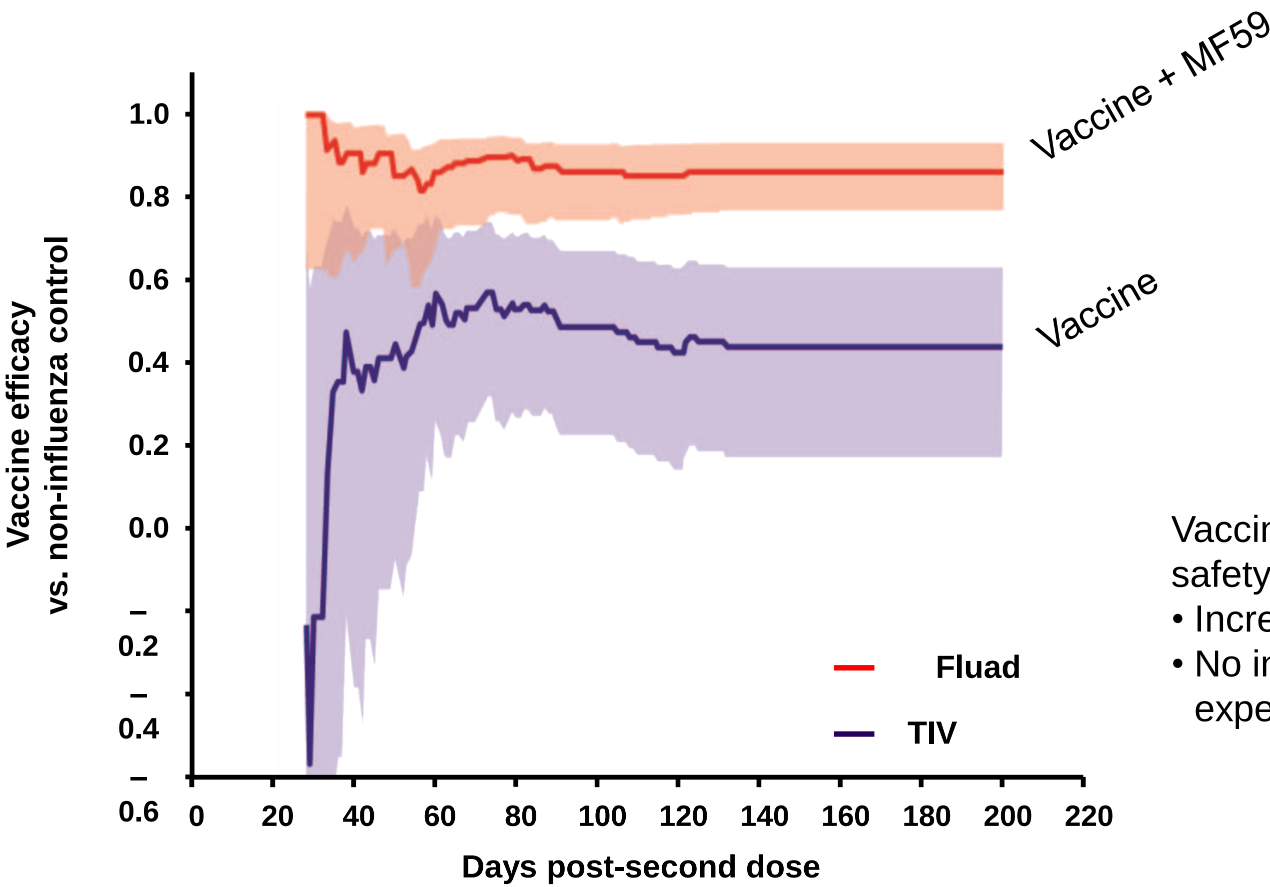


A synthetic Influenza vaccine seed in 5 days, a synthetic RNA vaccine in 10 days



Adjuvants: turning the dirty little secret into better, stronger, faster, longer vaccines

MF59 increases efficacy of influenza vaccine in children from 43 to 86%



Vaccine also showed satisfactory safety profile:

- Increased local reactogenicity
- No increase in serious adverse experiences vs. control

Vesikari T, *et al.* NEJM.

Vaccines in the news 2015 [1]

Malaria

Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial

*RTS,S Clinical Trials Partnership**

www.thelancet.com **Vol 386 July 4, 2015**

Zoster vaccine 97% efficacy in the elderly

Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults

N ENGL J MED 372;22 NEJM.ORG MAY 28, 2015

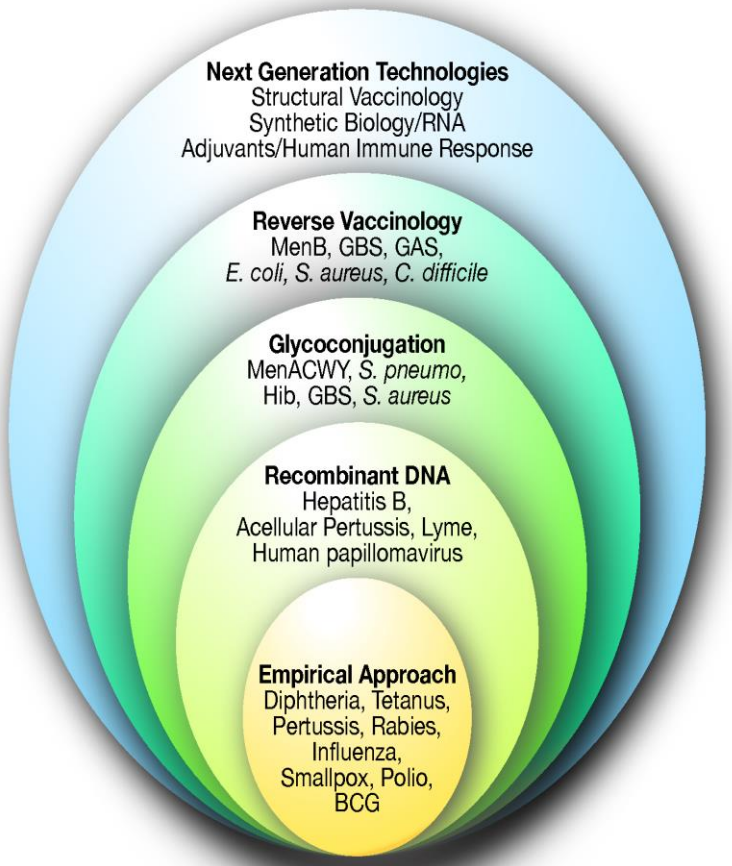
Ebola vaccine 100% efficacy

Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial

www.thelancet.com **Published online July 31, 2015**

Vaccines in the news 2015 [2]

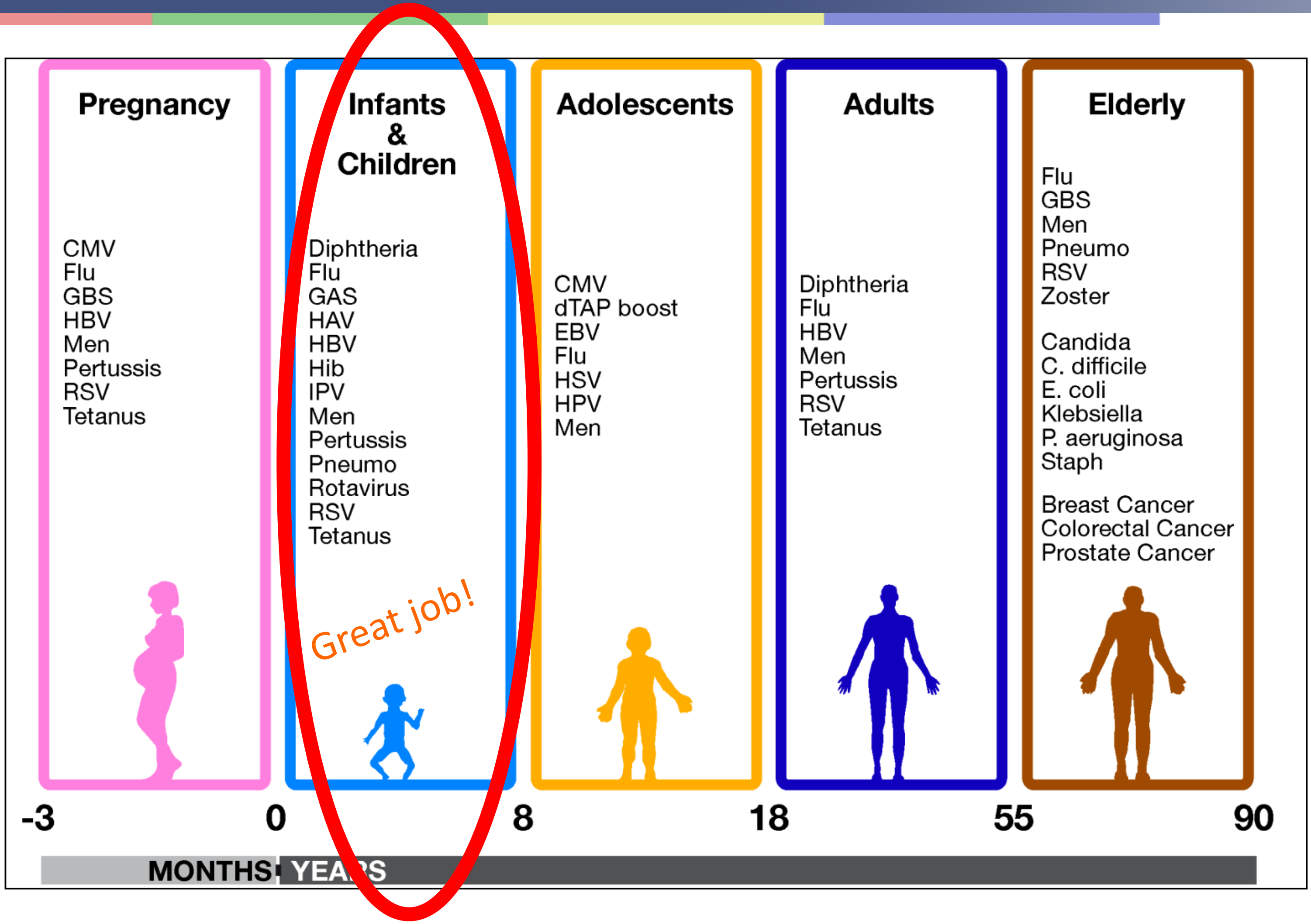
- Dengue
  - Sanofi Pasteur(Hadinegoro, NEJM 2015), Takeda, Butantan
- Clostridium difficile
  - Phase III ongoing
- High dose quadrivalent influenza
  - Targets elderly
  - Addition of 2d B strain (only correct 50% of time)



Next challenges

Translating science to impact

Vaccines for every age



INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

R.Rappuoli, C. Mandl, S: Black , E. De Gregorio
Nature Reviews Immunology | November 2011; doi:10.1038/nri3085

Vaccines for the challenges of the 21st century

Poverty

Cholera
Dengue
ETEC
HAV
HBV
HEV
Flu
JEV
Malaria
Men B
Parasitic infections
Paratyphoid
Rabies
Rotavirus
Salmonella
S. enterica
S. typhimurium
Shigella
TB
Typhoid fever

Emerging infections

AIDS
Anthrax
Avian influenza
Cholera
Diphtheria
Dengue
Ebola
EV71
Malaria
SARS
TB
Smallpox
West Nile
Yersinia

Travelers

Cholera
Dengue
ETEC
Flu
HAV
HBV
JEV
Malaria
Men
Paratyphoid
Rabies
Shigella
TB
Typhoid fever
Yellow Fever

Patients with Chronic diseases

CMV
Flu
Fungal infections
P. aeruginosa
Parainfluenza
RSV
Staph
TB

Immunotherapy/therapeutic vaccines?

Cancer
Antoimmune diseases
Alzheimer
Chronic infections
(HCV, HBV, HPV, HIV, ...)
Metabolic diseases
Allergy
Drug addiction

Vaccine scorecard (Plotkin et al, NEJM 2015)

Vaccine-Preventable Diseases and Infections and Targets Currently Uncontrolled by Vaccination.*

Diseases and infections with commonly used vaccines	
Diphtheria	Polio
Haemophilus influenzae type b	Pneumococcus
Hepatitis type A	Rabies
Hepatitis type B	Rotavirus
Human papillomavirus (HPV)	Rubella
Influenza types A and B (seasonal)	Smallpox
Japanese encephalitis	Tetanus
Measles	Tickborne encephalitis
Meningococcus	Typhoid
Mumps	Varicella (chickenpox)
Pertussis (whooping cough)	Yellow fever
Diseases and infections with limited-use vaccines	
Adenovirus types 4 and 7	Anthrax
Diseases and infections with no vaccines or only partially effective vaccines	
Campylobacter	Lyme disease
Cancer	Malaria
Candida	MERS
Chikungunya	Metapneumovirus
Chlamydia	Moraxella (for otitis)
Clostridium difficile	*Neisseria gonorrhoeae*
Cryptosporidium	Norovirus
Cytomegalovirus	Nosocomial bacteria
Dengue	Parainfluenza
Ebola and viral hemorrhagic fevers	Plague
Enterovirus including EV71, EV68, CA16	Rhinovirus
Epstein–Barr virus	RSV
Escherichia coli	*Salmonella paratyphi*
Helicobacter pylori	SARS
Haemophilus influenzae, nontypable	Schistosomiasis
Helminths (numerous)	Shigella
Hepatitis type C	Staphylococcus
Hepatitis type E	Tuberculosis
Herpesvirus type 6	Strep group A
Herpes simplex	Strep group B
HIV–AIDS	Toxoplasmosis
Influenza, universal	Trypanosomiasis
Influenza, avian types H5 and H7	West Nile virus
Leishmaniasis	

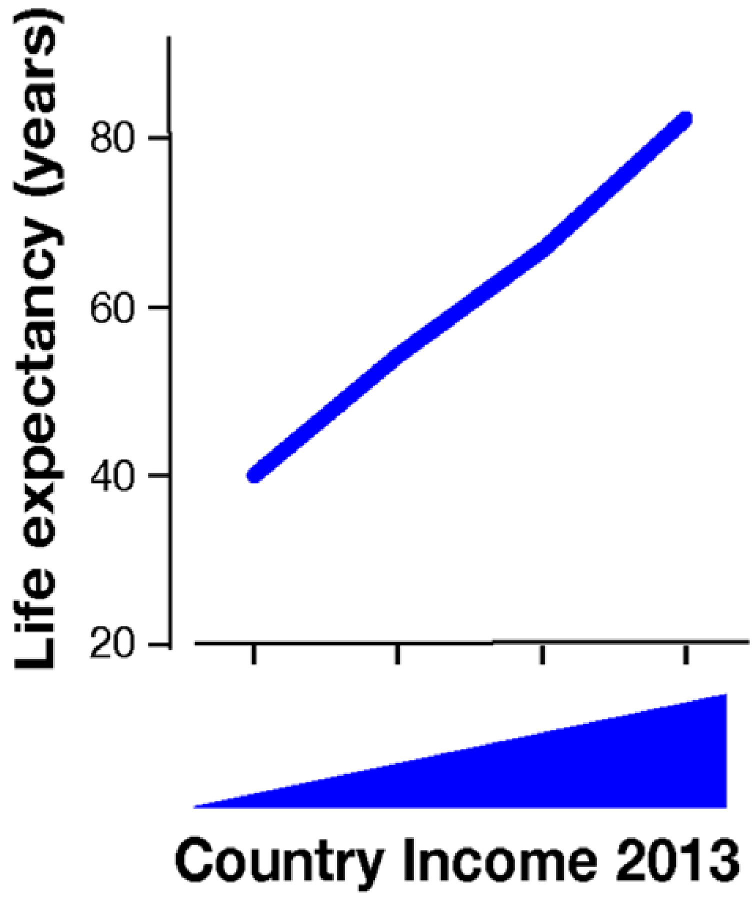
* Information is from the Foundation for Vaccine Research. MERS denotes Middle East respiratory syndrome, RSV respiratory syncytial virus, and SARS severe acute respiratory syndrome. Vaccines for some of the targets indicated above are in advanced development, but most are not.

Big Pharma

- Cost
  - $500M less complex vaccine
  - $1 B more complex vaccine
- Failure rate: only 7% of vaccines reaching preclinical development are licensed

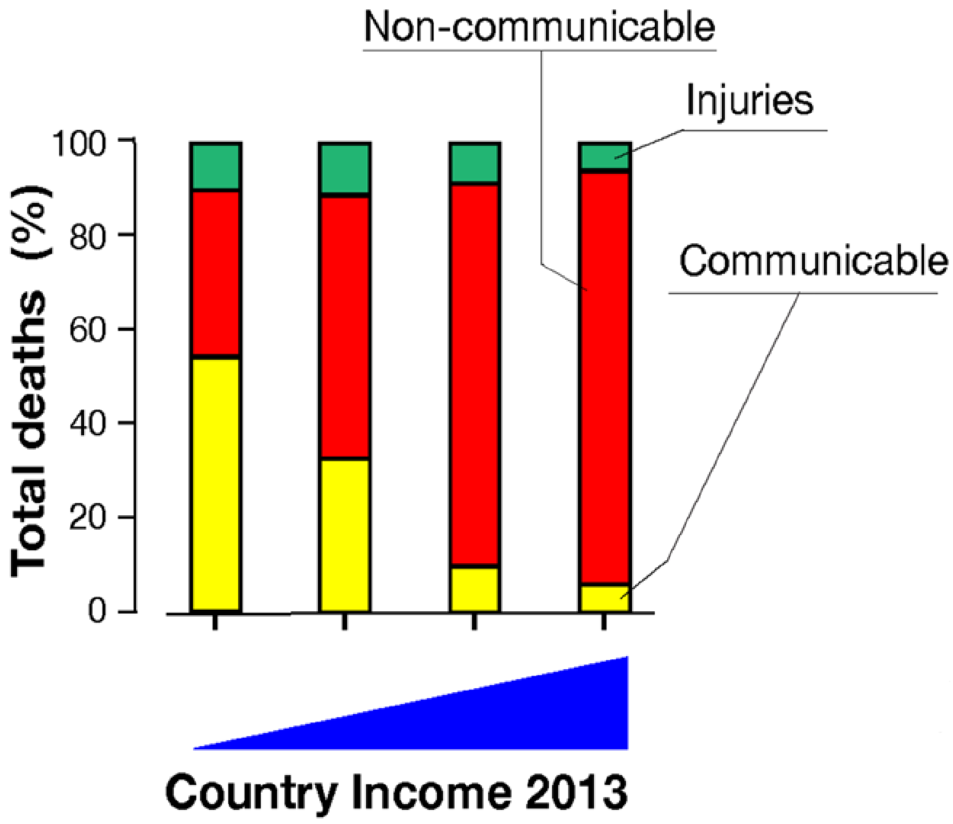
Vaccines for all

In low income countries life is still very short



Vaccines have the potential for greater impact in lower income countries

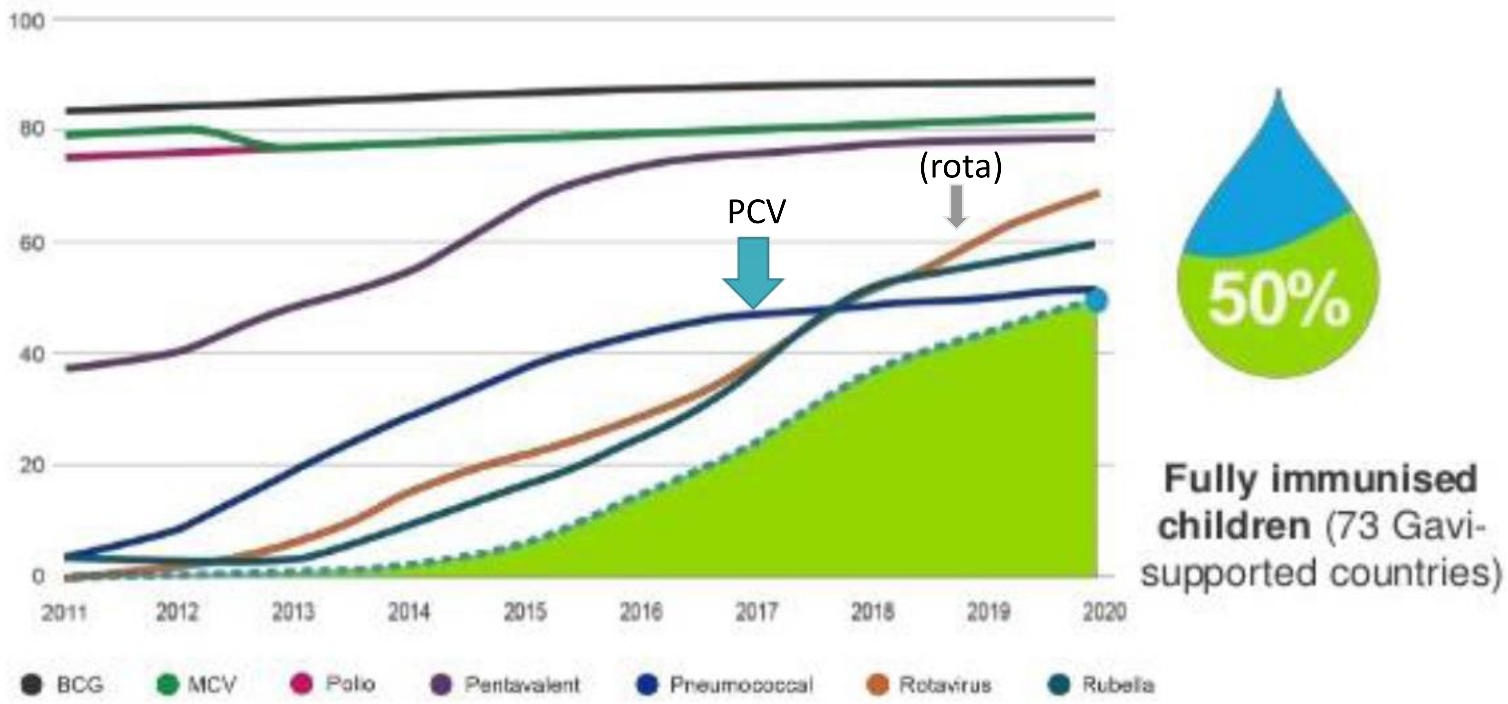
As income levels fall, infectious diseases have a greater impact on mortality.



GAVI: forecast costs and deaths averted

VACCINE	2011 to 2015			2016 to 2020		
	Expenditure in US$ millions	Number immunised	Deaths averted	Expenditure in US$ millions	Number immunised	Deaths averted
PNEUMOCOCCAL	2,462	80 M	400,000	2,789	190 M	~600,000
PENTAVALENT[a]	1,710	240 M	2,600,000	1,294	300 M	~3,000,000
ROTAVIRUS	374	40 M	60,000	955	150 M	~200,000
HPV	39	1 M	20,000	347	30 M	~600,000
MEASLES SECOND DOSE AND MEASLES-RUBELLA[b,c]	241	200 M	300,000	343	500 M	~700,000
YELLOW FEVER[c]	136	70 M	200,000	288	150 M	~300,000
TYPHOID	-	-	-	241	50 M	~20,000
CHOLERA[d]	26	-	-	89	-	-
MENINGITIS A[c]	202	240 M	-	85	100 M	~60,000
JAPANESE ENCEPHALITIS[c]	5	7 M	1,000	52	70 M	~8,000
TOTAL	US$ 5.2 billion		3.9 million	US$ 6.5 billion		5–6 million

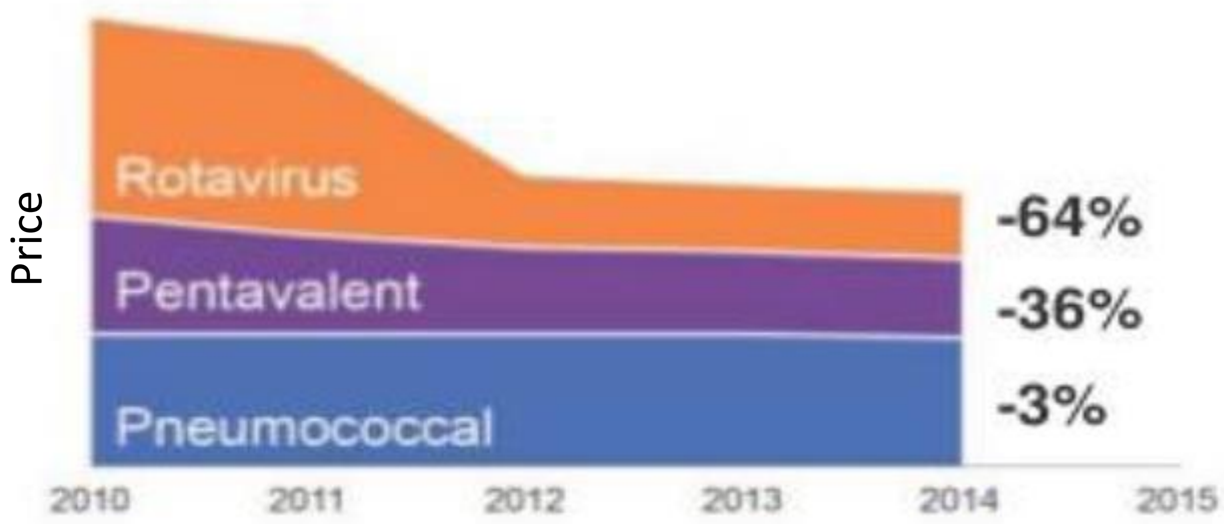
Immunization coverage, Gavi-supported countries



Source: Preliminary Gavi projections based on WHO/UNICEF coverage estimates and Strategic Demand

Success has a price

PCV accounts for a large % of spending



Unicef, 2015, Cost to fully immunize a child with rota, pentavalent, and pneumococcal vaccines

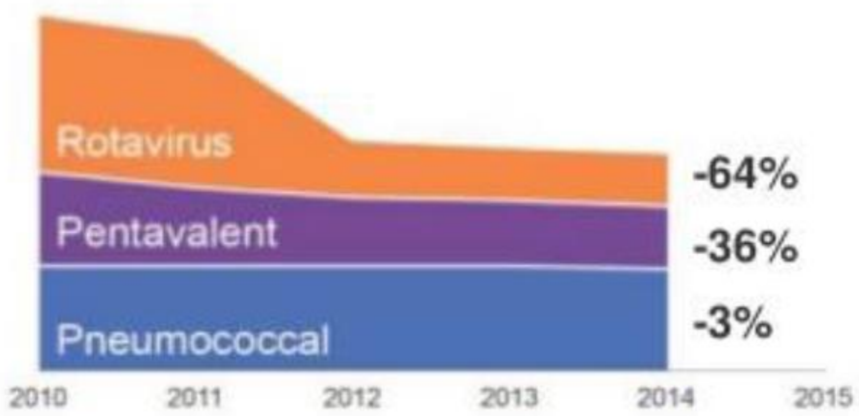
Pneumococcal conjugate vaccines for GAVI

- Duopoly: Pfizer (13 valent) & GSK (10 valent)
- $150 in developed countries, $7 in Gavi-supported countries (Adv Market Commitment: Gavi provides monetary compensation to companies to attract vaccine supply into market)
- Gavi 2016 -2020 (projected) 6.5B USD, PCV accounts for 2.8B USD (43%)

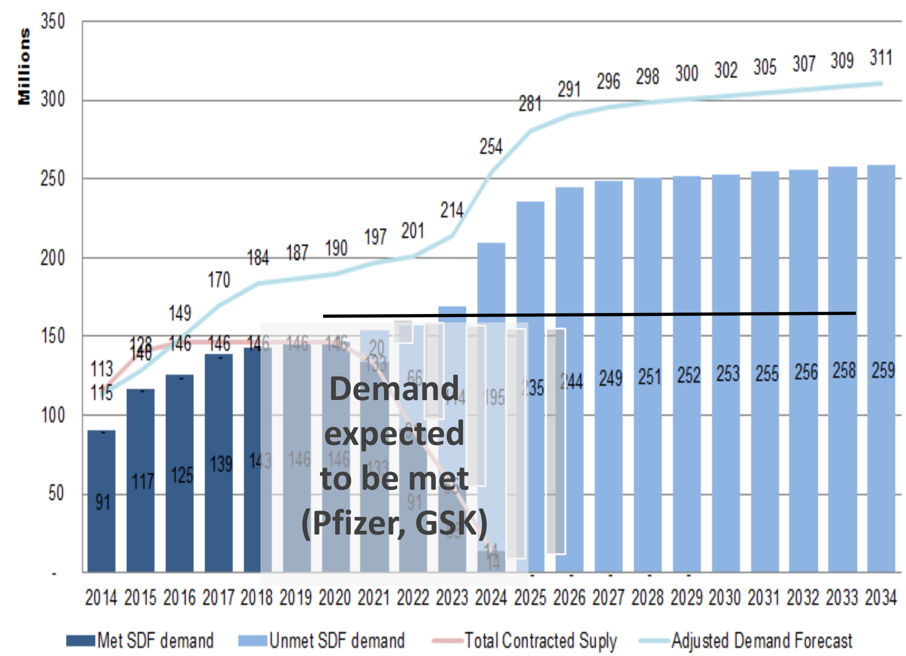
Unmet Demand for PCV – the challenge of supply

PNEUMOCOCCAL CONJUGATE VACCINE

NEEDED: *A LOW COST VACCINE FOR DEVELOPING COUNTRIES*



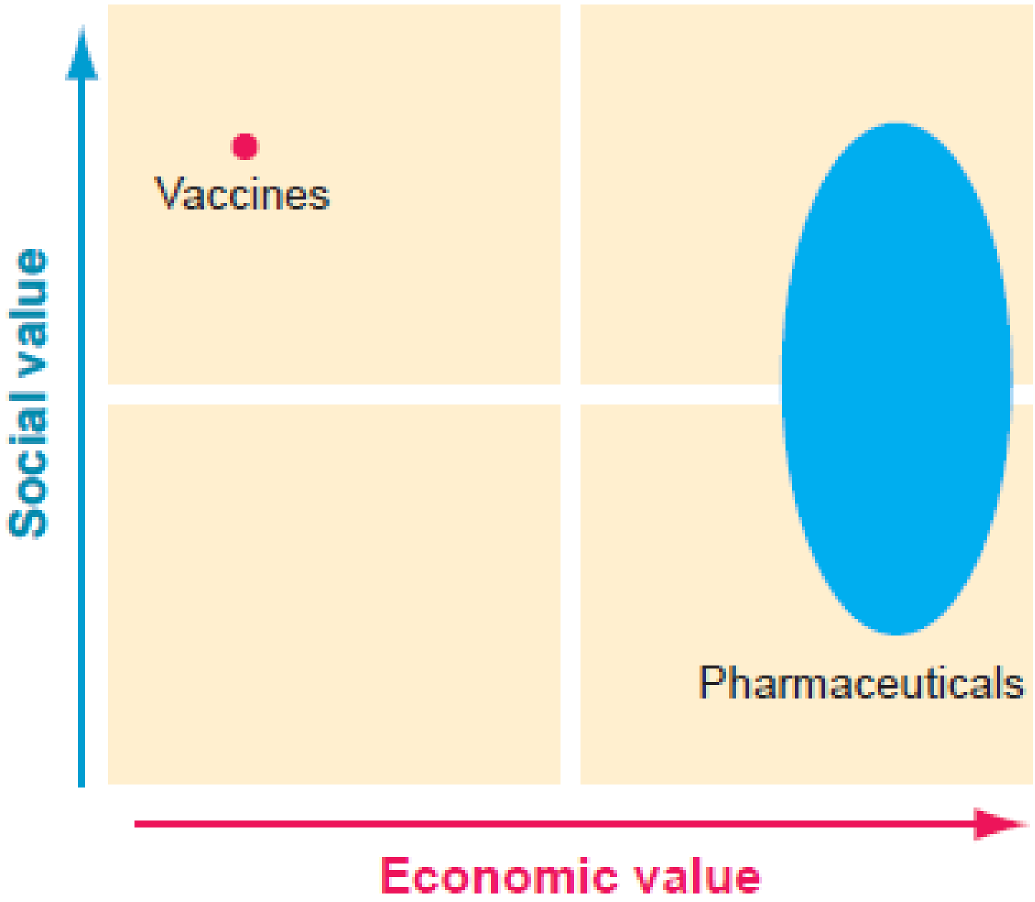
Unicef, 2015, Cost to fully immunize a child with rota, pentavalent, and pneumococcal vaccines



Rising to the challenge of supply

- Philanthropy
  - Bill and Melinda Gates
  - Wellcome Trust
- Governments
  - PDPs
  - Support for low cost manufacturers
- International organizations: Gavi, WHO, UNICEF, IVI
  - Policy
  - Purchase
  - Tech transfer/capacity building
- Markets
  - Alternative sources of supply from lower cost manufacturers
- New technologies

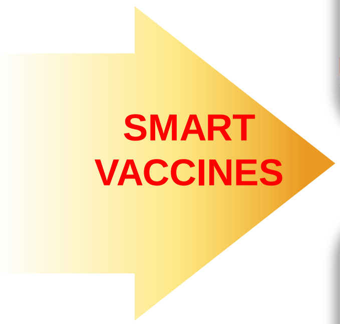
Changing the valuation of vaccines



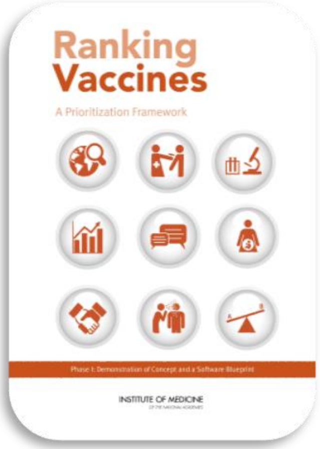
Earning money / saving lives: Should industry, government, charities invest in vaccines?

Why aren't vaccines correctly valued?

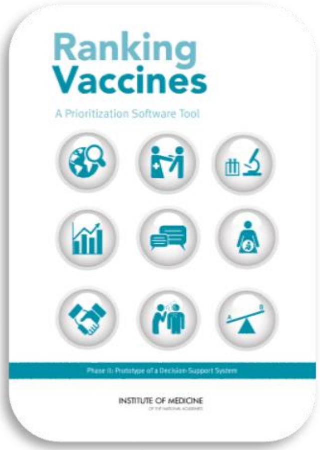
- **Visibility:** Immunization typically prevents diseases, so most people lack first-hand experience
  - How do you value a benefit you cannot see?
- **Vaccine value:** in a world of limited resources **cost-effectiveness** becomes important in decision making, but health economics not able to assign the right value to vaccines



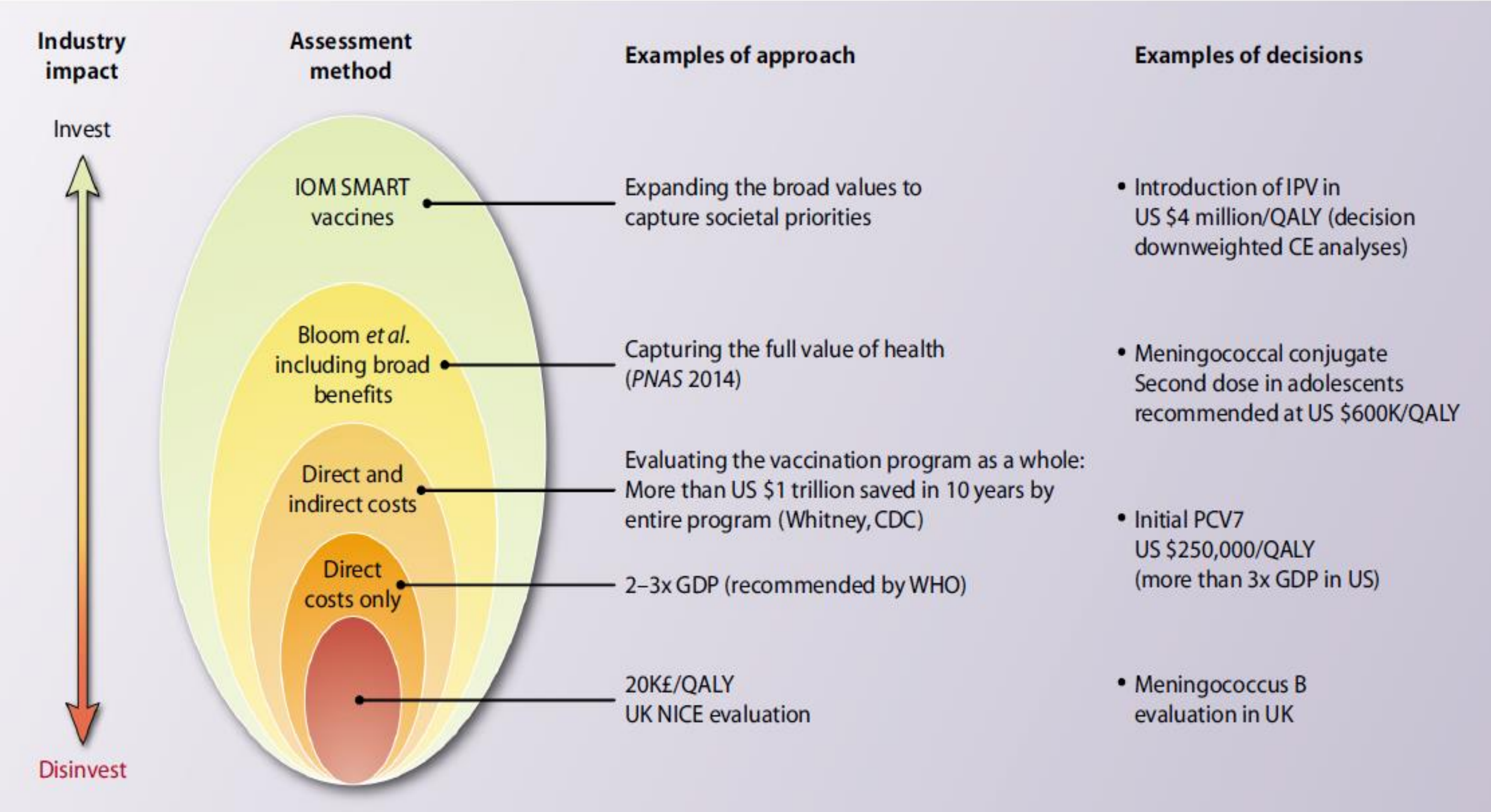
2012



2013



How to properly assign value to vaccines?



www.ScienceTranslationalMedicine.org 1 April 2015 Vol 7 Issue 281 281ps8

Comparison of Existing Global Health Funds and Proposed Vaccine-Development Fund.*

Variable	Global Fund to Fight AIDS, Tuberculosis and Malaria	GAVI	UNITAID Airline Tax	Proposed Vaccine Development Fund
Focus	HIV, tuberculosis, and malaria prevention, treatment, care, and support	Purchase and delivery of childhood vaccines	Purchase of HIV, tuberculosis, and malaria drugs	Accelerating discovery and development of new vaccines
Source of funds	Donor governments (95%); private foundations, corporate donors, and individuals (5%)	Donor governments (80%); private foundations (17%); International Finance Facility for Immunization (2%)	Airline solidarity levy	Donor governments (50%); private foundations and industry (50%) Options: financial transactions tax, tax breaks for industry donors
Eligibility	Middle- and low-income countries	Low-income countries	85% of funds must go to low-income countries	Scientists, institutions, and biotechnology companies engaged in vaccine discovery and development
Application process	Competitive country proposal	Facilitative country proposal	Funds distributed to implementing agencies and NGOs on a discretionary basis	Competitive proposal
Proposal review	Country proposals reviewed by independent technical review panel; board usually follows panel's recommendations	Country proposals facilitated by GAVI, reviewed by independent reviewers appointed by GAVI; decisions made by board	No proposals required	Proposals subject to rigorous scientific review by independent panel; board makes funding decision on the basis of scientific merit and available funds
Features	Performance-based model emphasizing results, transparency, accountability; hands-on monitoring by local fund agents and independent auditors; does not implement or fund research	Performance-based model emphasizing results, transparency, accountability; hands-off monitoring; does not implement or fund research	Does not implement or fund research	Performance-based model emphasizing results, transparency, accountability; independent auditors will monitor and assess performance; will not finance phase 3 clinical trials or conduct research
Governance	27-member international board representing donor and recipient countries, foundations, NGOs, industry, other stakeholders; 5 members are nonvoting representatives of WHO, U.N. agencies, and World Bank	28-member international board representing donor and recipient countries, private individuals, U.N. agencies, vaccine industry, foundations, other stakeholders	12-member executive board; 1 member is nonvoting WHO representative	Streamlined structure; medium-sized board whose majority of voting members represent donors; rest of composition to be determined
Funds disbursed through December 31, 2014	$25.8 billion	$7.8 billion	Approximately $2 billion	Goal: raise $2 billion initially

* Information is from the Foundation for Vaccine Research. GAVI denotes Global Alliance for Vaccines and Immunization, NGO nongovernmental organization, WHO World Health Organization, U.N. United Nations, and UNITAID Unity and AID.

A Global Vaccine Development Fund?

Proposed cost: $2 billion

The cost of failure?

- Ebola: est $8 billion
- Deaths: 20,000

Perspective

JULY 23, 2015

Establishing a Global Vaccine-Development Fund

Stanley A. Plotkin, M.D., Adel A.F. Mahmoud, M.D., Ph.D., and Jeremy Farrar, M.D., Ph.D.

Summary

- Vaccines are among the oldest effective medical interventions and have had a tremendous impact on mankind
- Vaccinology is vibrant and innovative and will continue to have a great impact on the society
  - Despite success in developing safe and effective vaccines, there are still diseases to overcome
- Cost-effectiveness alone undervalues vaccines, multi-criteria evaluation methods are needed to capture the full benefits of vaccination
- The next great challenge will be to get these vaccines to those in greatest need, through novel funding mechanisms, lower cost production, capacity building, and sustainable implementation

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