

Antimicrobial Resistance in a planet floating in an antibiotic solution

Rino Rappuoli

A European Tribute to the Life and
Career of Stanley Falkow

Paris May 28th 2019

Impact on the planet



131,000 tons of antibiotics used for animal food in 2013

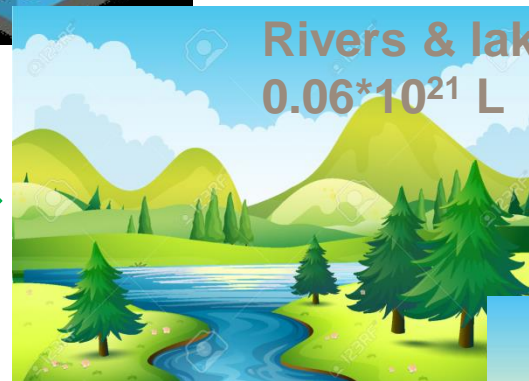
61,279 tons up to May 28 in 2019

The journey of antibiotics from land to oceans



animal feed etc.

Antibiotic resistance



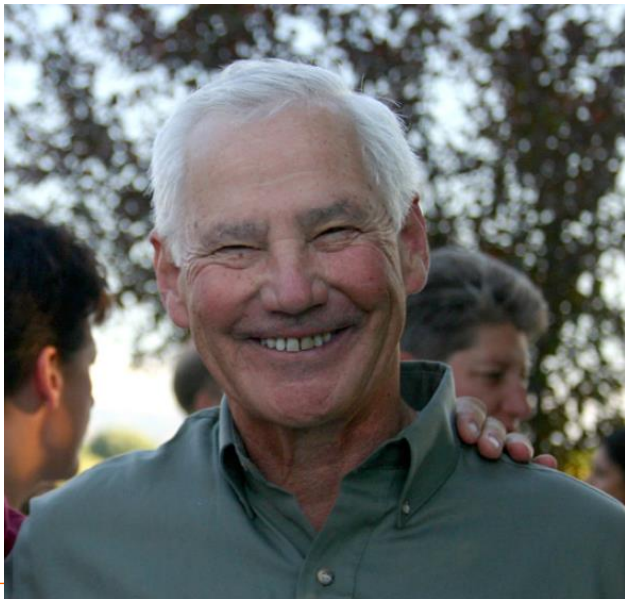
Stanley Falkow

Infectious Multiple Drug Resistance, 1975



“we owe to chemotherapy (antibiotics) the debt of reducing the high mortality rate of many bacterial infections” and to hygiene and vaccines the debt of preventing them, however **“in helping to solve some of the problems of infectious diseases, chemotherapy has created some problems of its own”**

The problem he was talking about was AMR



A photograph of a white rectangular sign with the words 'Infectious Multiple Drug Resistance' written in blue, bold, sans-serif capital letters. The sign is slightly tilted and has a soft shadow.

Economics of AMR

impact comparable to climate change

Predicted impact equal to 2 °C raise above preindustrial level of average surface temperature

Rope et al. Science 364, eaau4679, 2019



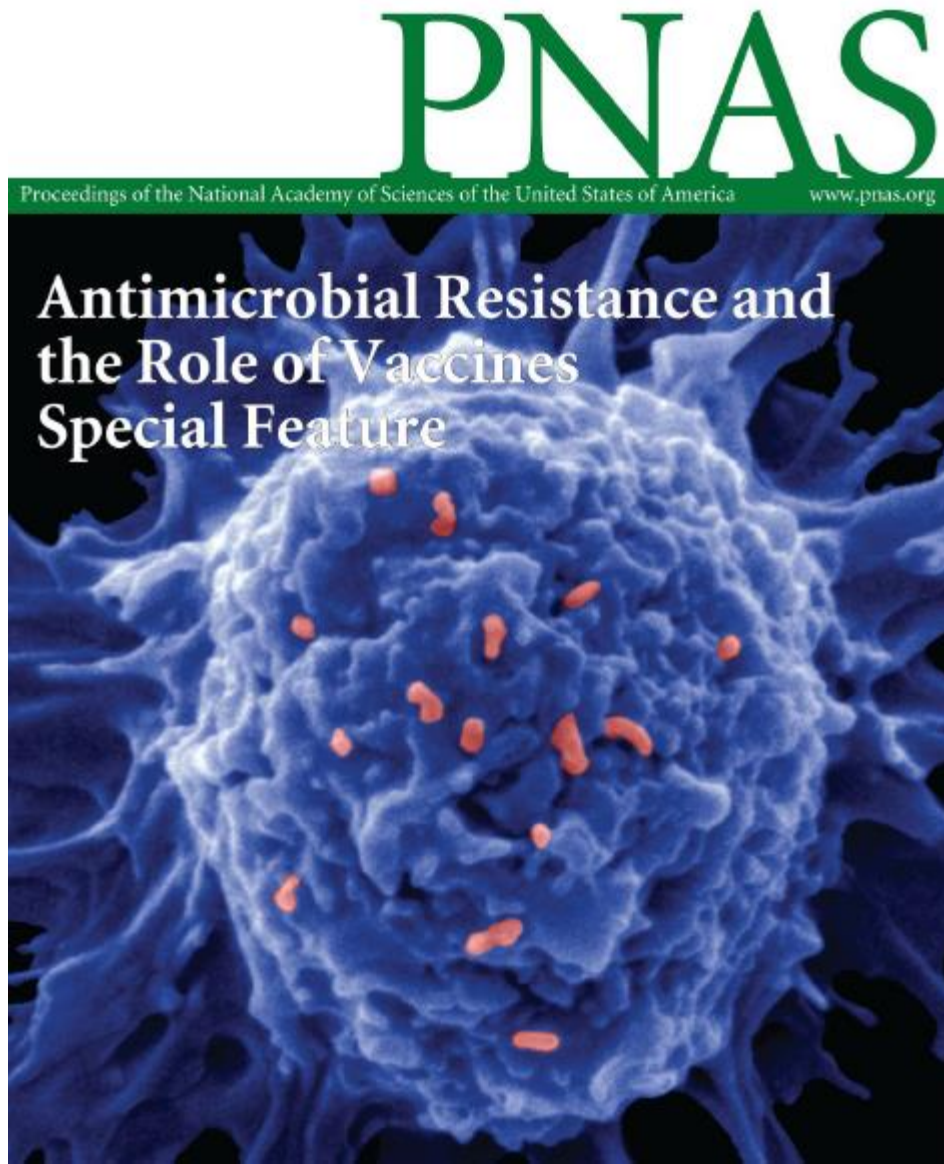
Antimicrobial resistance is a global crisis that threatens a century of progress in health and achievement of the Sustainable Development Goals.



There is no time to wait. Unless the world acts urgently, antimicrobial resistance will have disastrous impact within a generation.

Vaccines for AMR

A Special PNAS Feature dedicated to Stanley



- No resistant pathogens to vaccines
- Vaccines avoid microbiome disruption
- Vaccines bring greater return on investment for society

The problem of antimicrobial resistance

Economics of AMR

impact comparable to climate change

(Rope et al. Science 364, eaau4679, 2019)



- **Global tragedy of commons** (individuals acting rationally and according to their self-interest, collectively damage public goods)
- 100 trillion the cost of AMR up to 2050
- 3.4 trillion impact on GDP by 2030 (predicted impact of 2 °C raise above preindustrial level of average surface temperature is 3 trillion)
- So important to be discussed by the United Nations General Assembly
- Carbon tax for social cost of carbon (SCC) is being discussed, what about a tax for the social cost of antibiotics (SCA)

Infectious multiresistant plasmids colonizing the world, replacing the global microbiota...

...

THE GLOBAL MICROBIOME IS BECOMING AMR

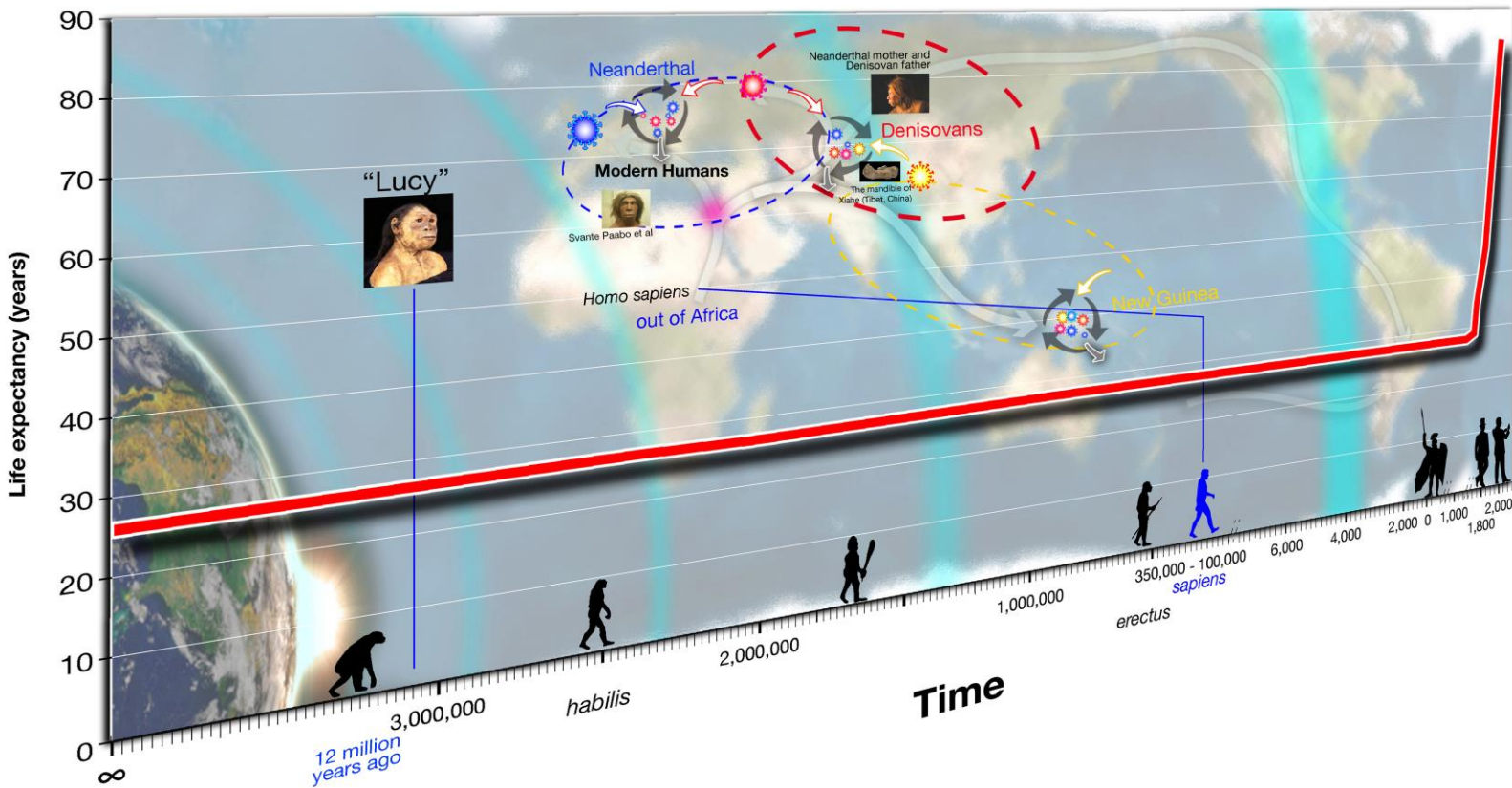
what is the consequence of living in a world where all microbes in water, soil, air, animals are antibiotic resistant? how close are we to the point of no return?

- **Bystander selection** of microbes that are not target of treatment is above 80%
- (PNAS 115, e11988-95, 2019)
- **Wastewater treatment plants in Europe:** 70-100% of samples contain AMR
- genes against most common antibiotics (Science advances 2019 eaau9124)
- **Vibrio Cholerae in the Bay of Bengal:** 100% resistant to 2 antibiotics,
- 17.2% resistant to 10 or more antibiotics (PNAS, 116, 6226-31, 2019)

-
- 700,000 deaths now, 10 M in 2050 (Cancer 8.2M)
 - Death from infection could follow from something as minor as a scratch
 - Cesarean sections, Joint replacement surgery, Chemotherapy, Organ transplant (4% of global GDP) more dangerous or prohibitive
 - Hospital infections untreatable

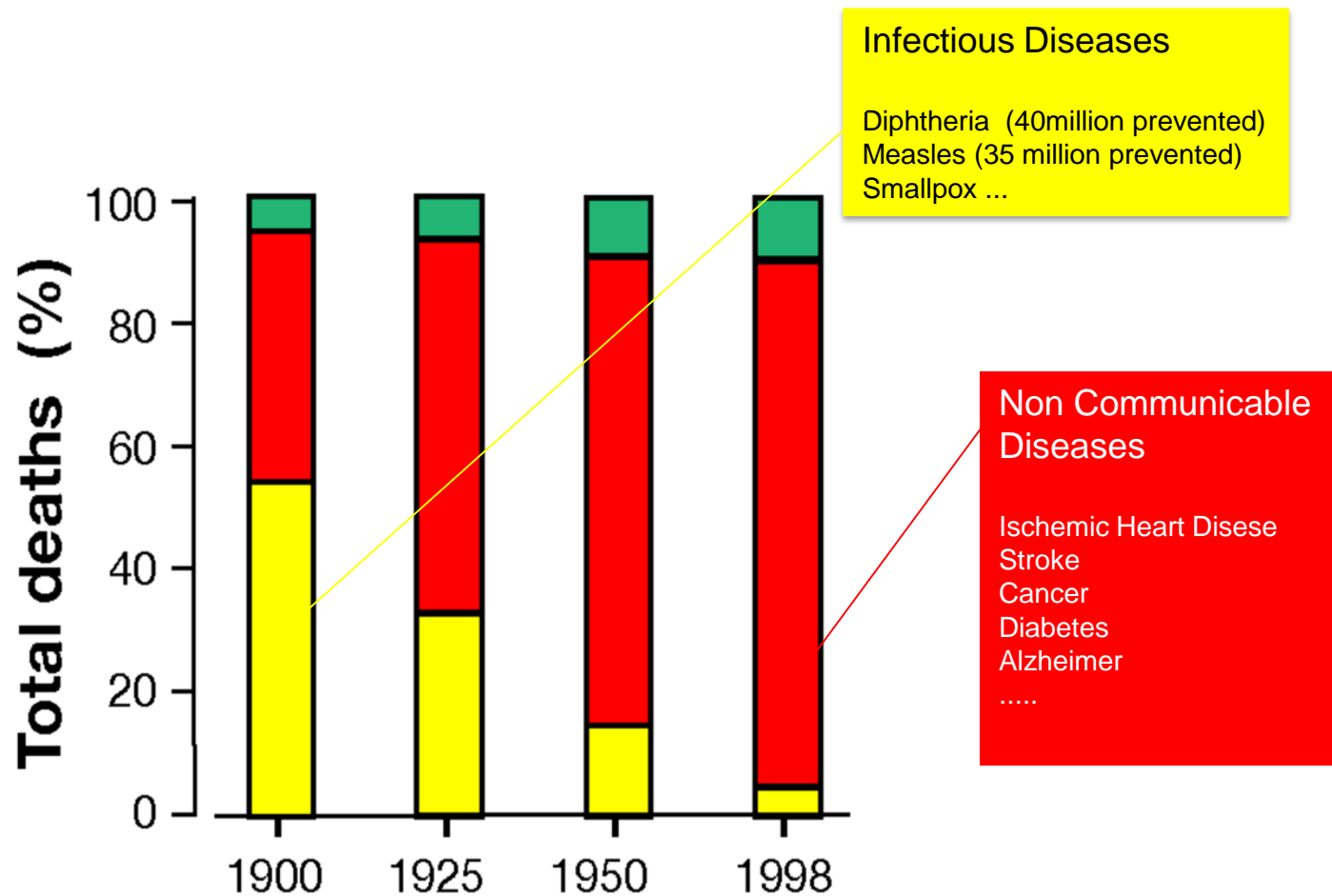
Human Evolution and Infectious Diseases

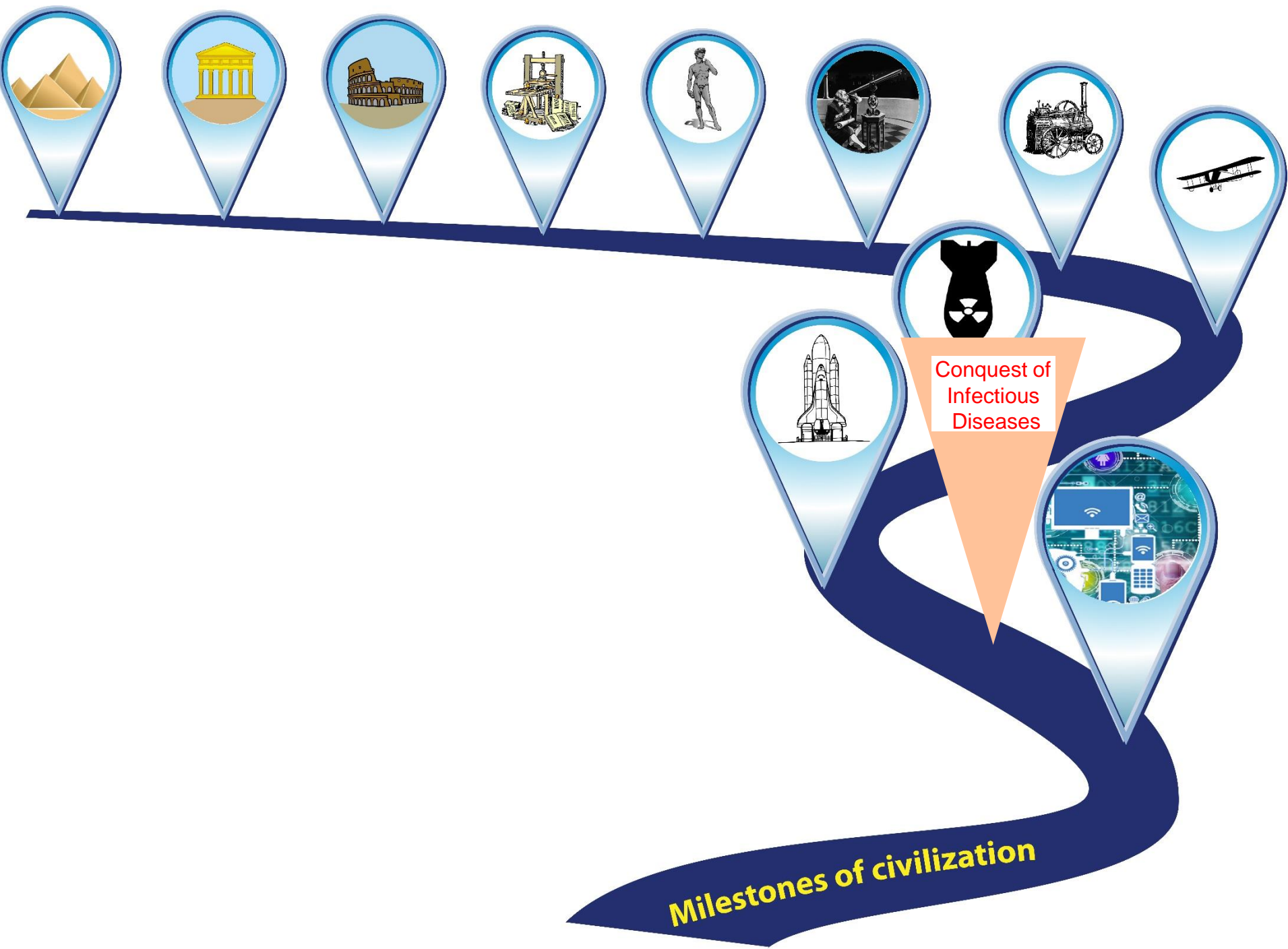
Improved health and increase of life expectancy an achievement of civilization



55 years gained since 1700
35 years gained since 1900

In 1900 in the USA people died of infectious diseases

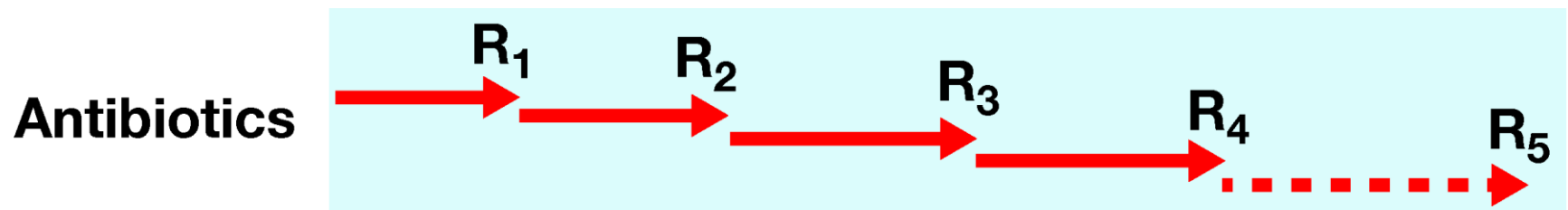




Vaccines, Antibiotics, Hygiene



Antibiotics generate resistance, become obsolete and need new antibiotics to control diseases



Vaccines

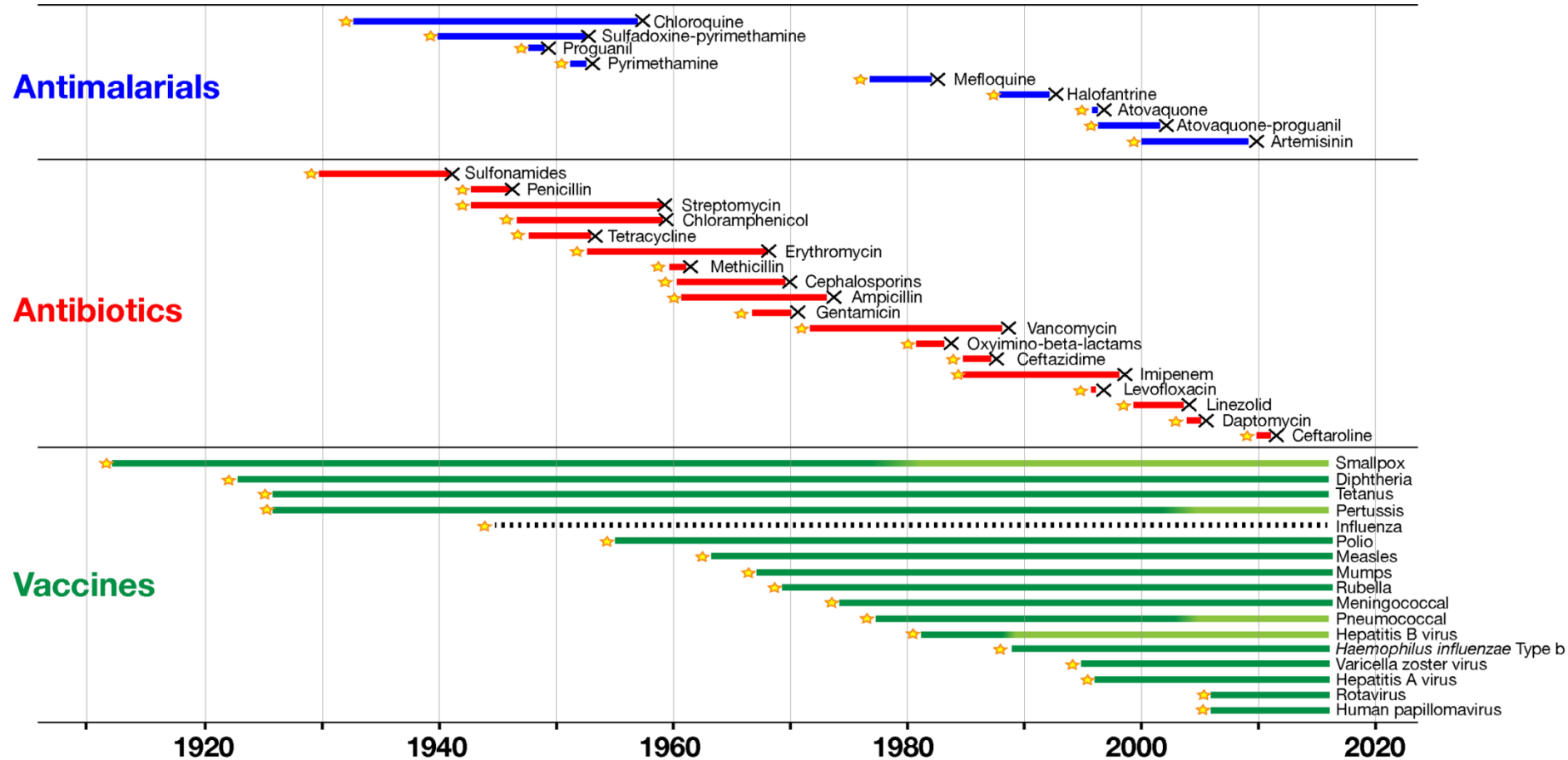
Vaccines control diseases quickly and for very long time, without generating major resistance

Hygiene

It works, however the time to introduce good hygiene and clean water in a low income country is several decades (40-50 years)

vaccines are evolution proof, drugs are not

Andrew Read



vaccines are evolution proof, drugs are not



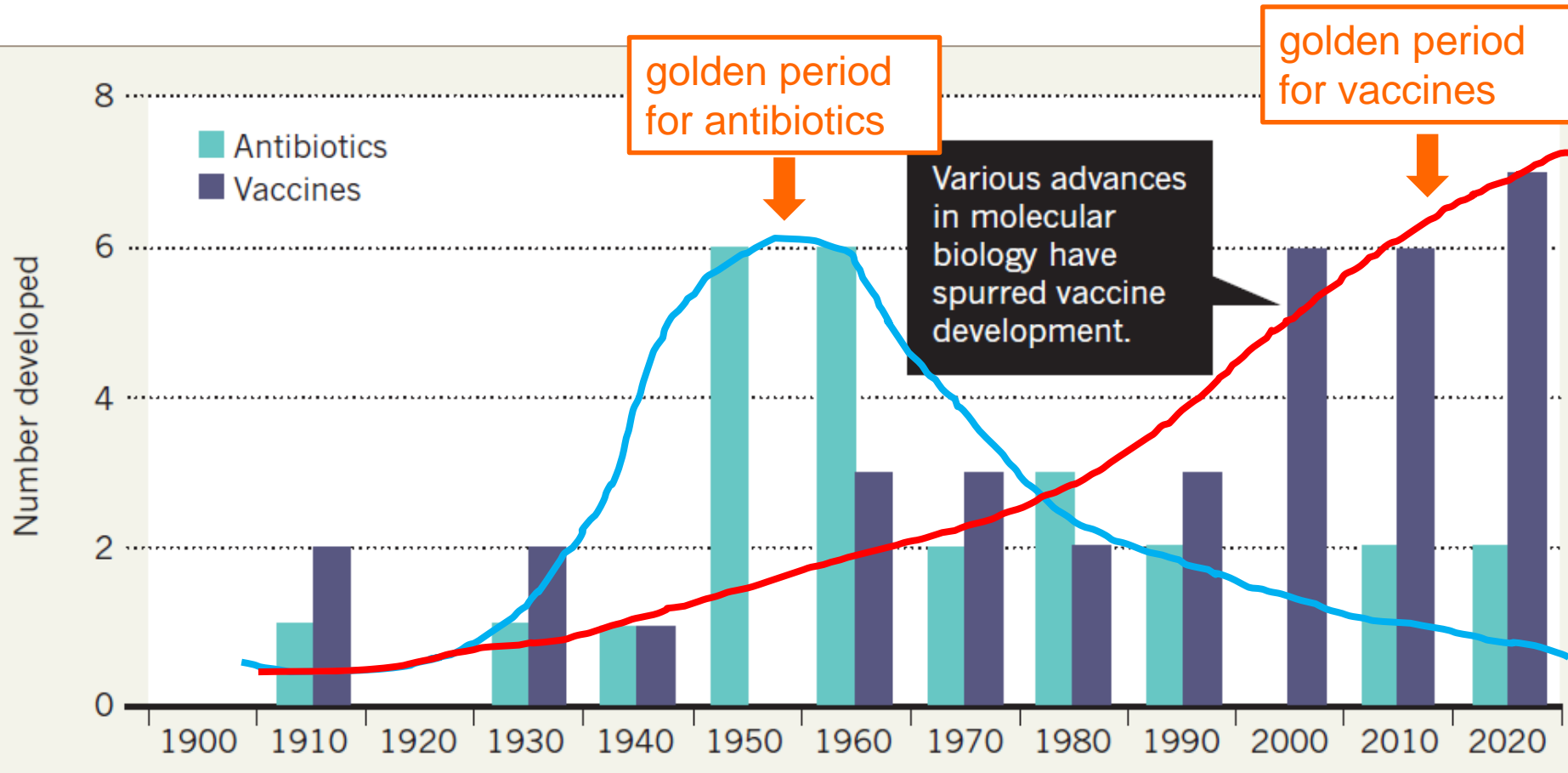
- Drugs

- one target
- work on a big bacterial population with high numbers to generate diversity and resistance

- Vaccines

- many targets /epitopes
- control a small bacterial population
- Resistance when the above rules are violated

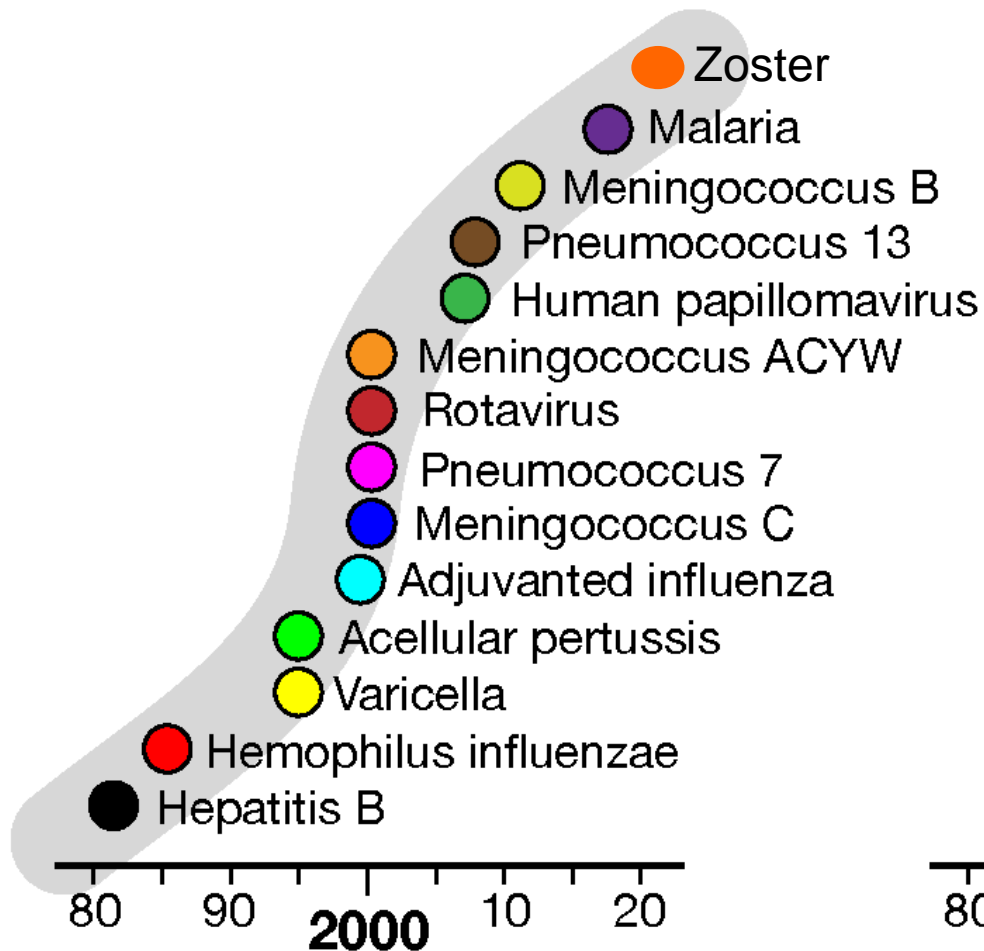
1950-70 golden period for antibiotics 1980-today golden period for vaccines



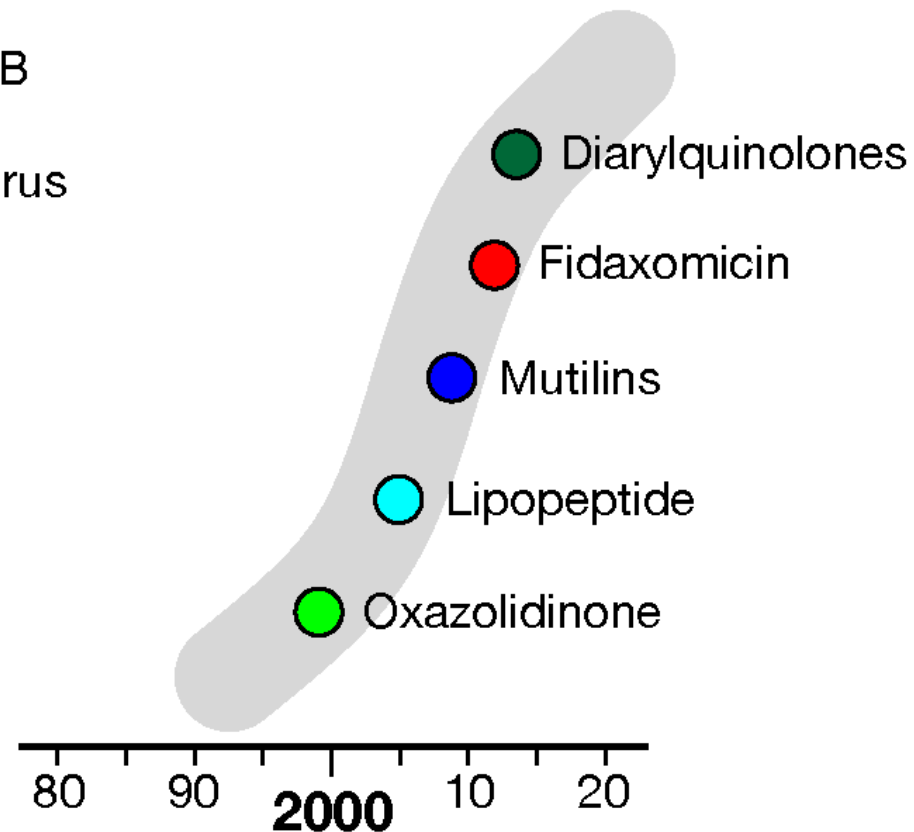
Licensed vaccines and antibiotics since 1980's



Vaccines



Antibiotics



Antimicrobial resistance (AMR)

700,000 deaths now, 10 M in 2050 (Cancer 8.2M)



Infectious multiresistant plasmids colonizing the world, replacing the global microbiota...

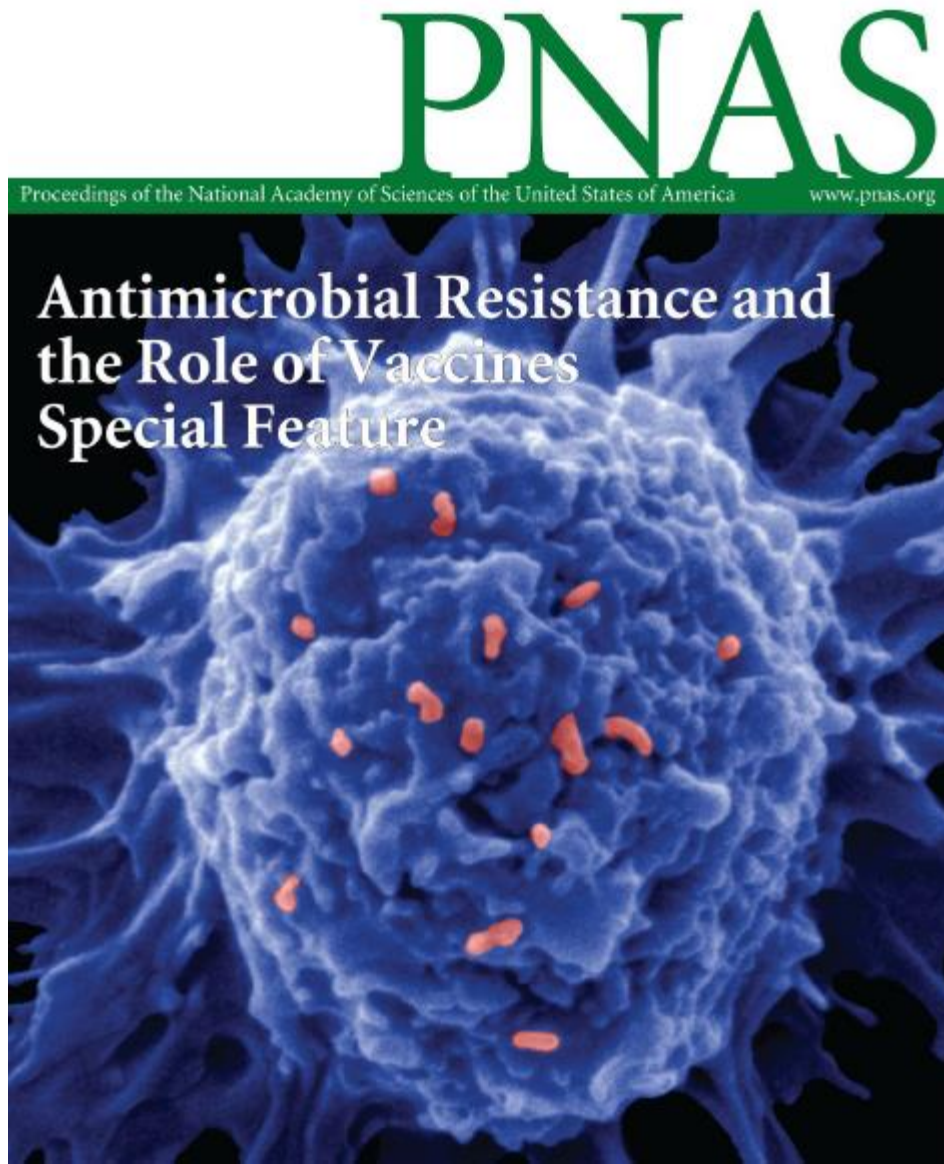


Vaccines can have an effect on antimicrobial resistance by reducing the number of ill people and avoiding unnecessary antibiotic prescriptions.

Deploy vaccines to fight superbugs

Immunizations combined with antibiotics could be our best shot at combating drug-resistant microbes, argue **Rino Rappuoli, David E. Bloom and Steve Black.**

Vaccines for AMR



- No resistant pathogens to vaccines
- Vaccines avoid microbiome disruption
- Vaccines bring greater return on investment for society

Diphtheria Venezuela

Emerg Infect Dis 25 (4) April 2019



2016 vaccination rates

DTP3

84%

DTP4

60%

Cases

Mortality

Cases

- 1990 – 2015

0

0

0

- 2016

324

17

5.5%

- 2017

1040

103

9.9%

- 2018

806

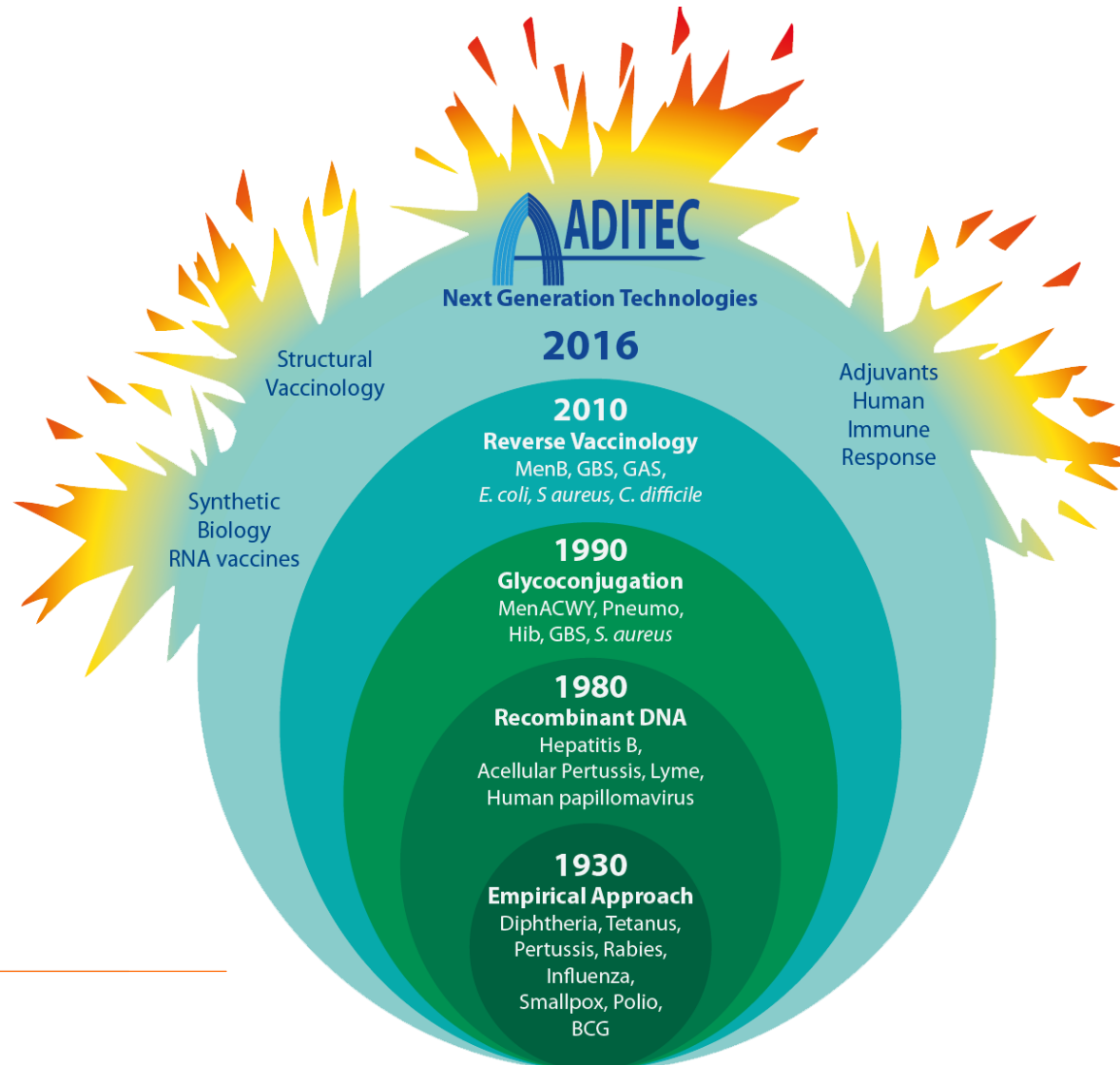
287

35.6%

Vaccines

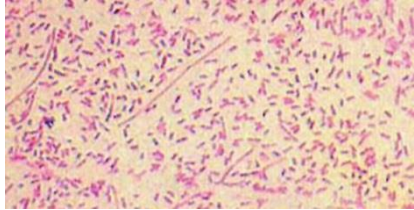
Vaccines

New technologies led to the development of new vaccines and to conquer new diseases



Capsular polysaccharides & Conjugates

Haemophilus influenzae type B (Hib)



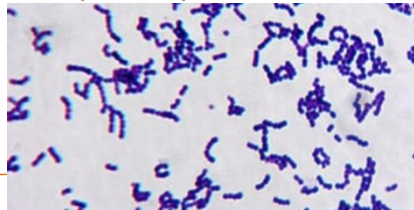
Pneumococcus



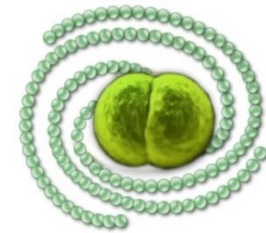
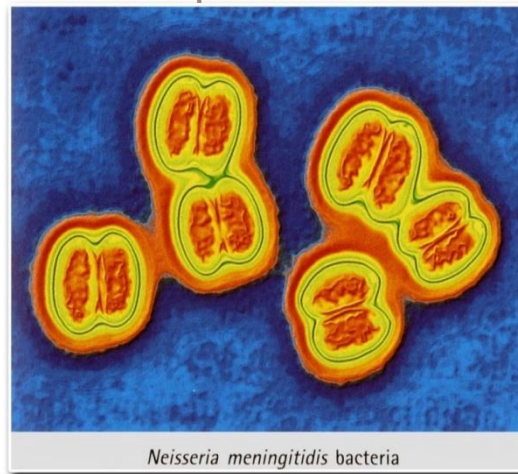
Meningococcus



Group B streptococcus



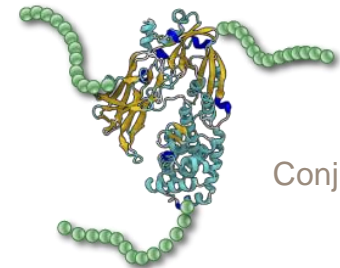
Capsule



Capsule

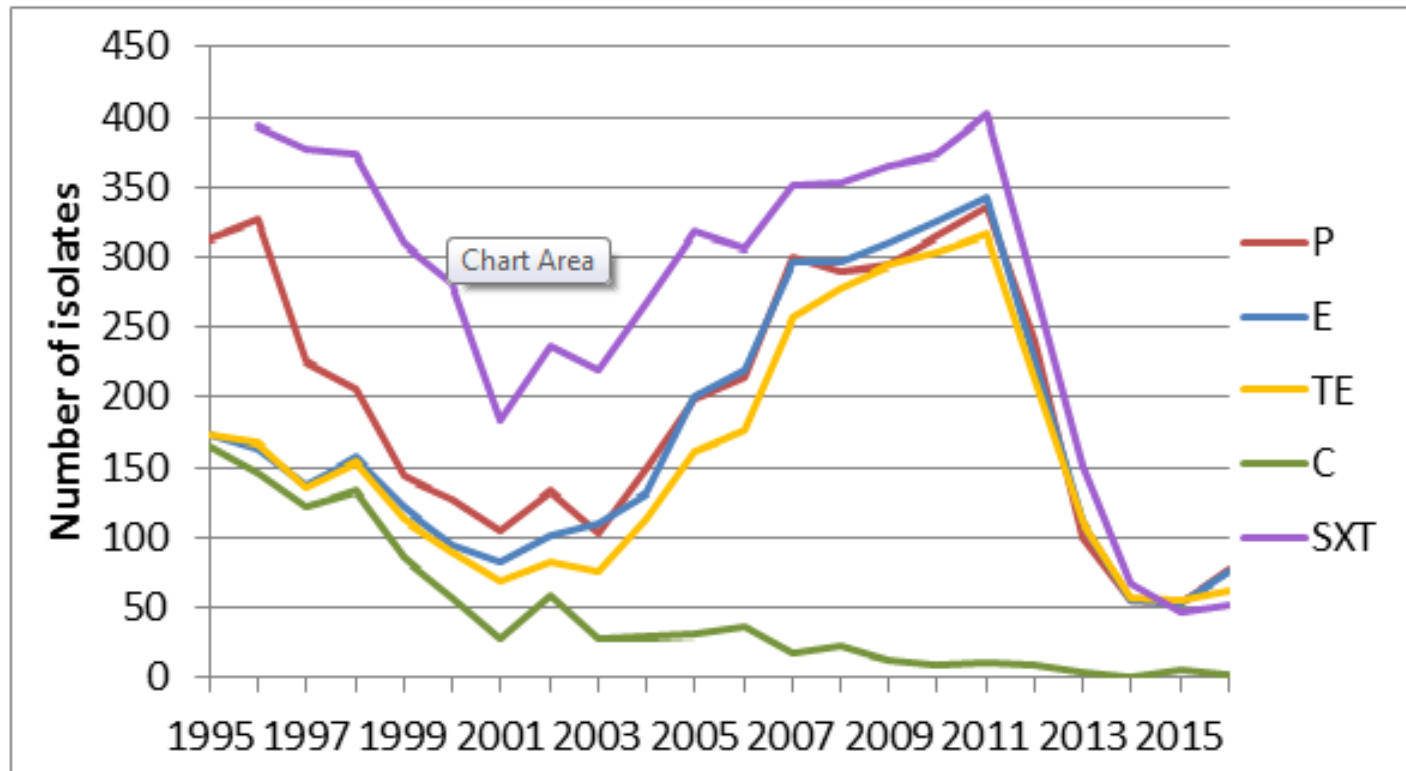


Polysaccharide



Conjugate

Effect of Pneumo 10 Vaccine in Iceland

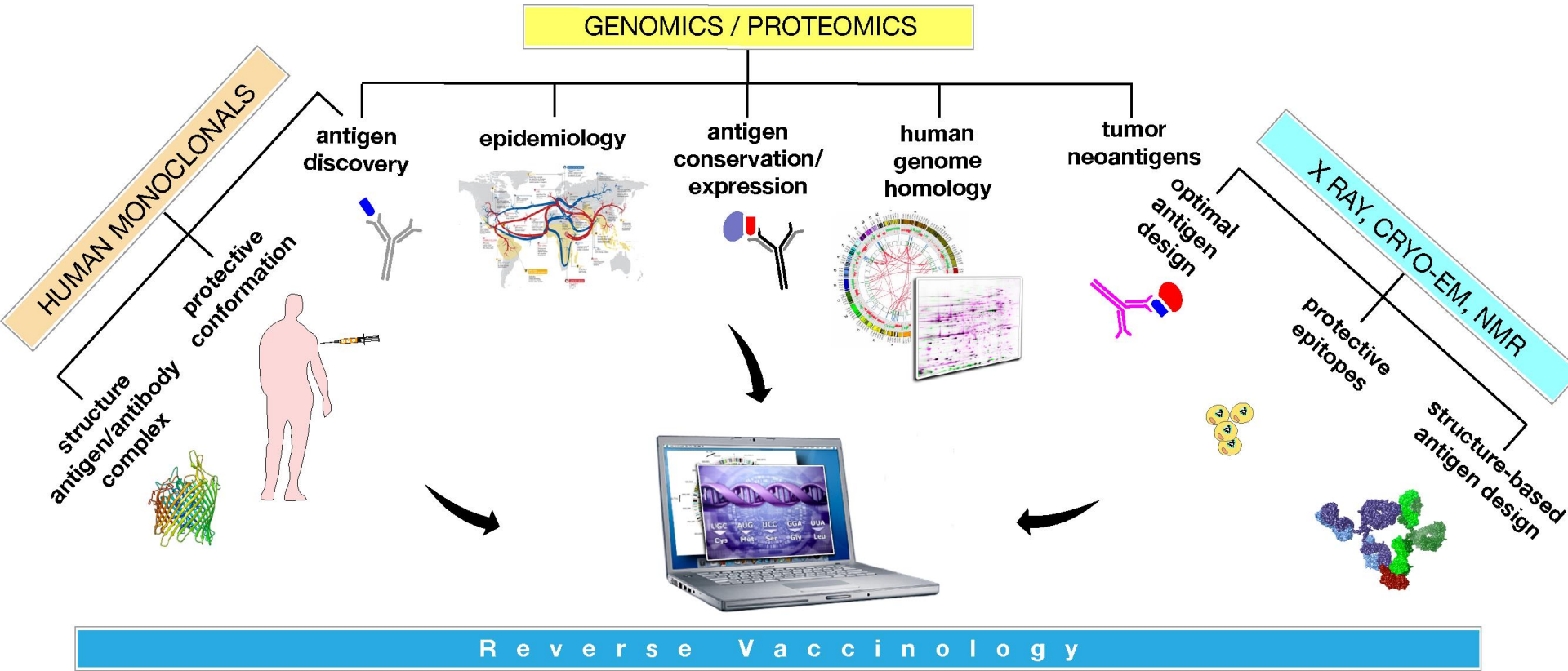


P=penicillin, E=erythromycin, TE= tetracycline, C=chloramphenicol, SXT=sulpha-trimethoprim

Reverse Vaccinology 2.0:

human immunology instructs vaccine antigen design

Rappuoli, Bottomley, D'Oro, Finco, De Gregorio *JEM* April 2016



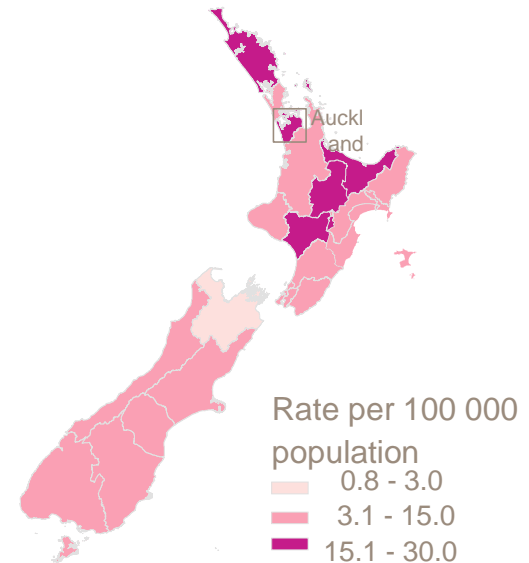
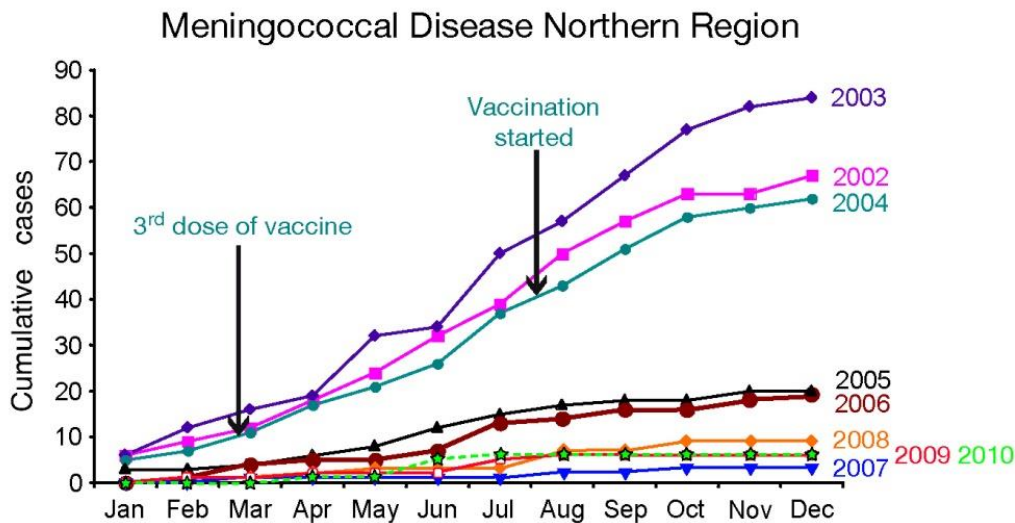
**information-based
vaccine design**

New Zealand experience

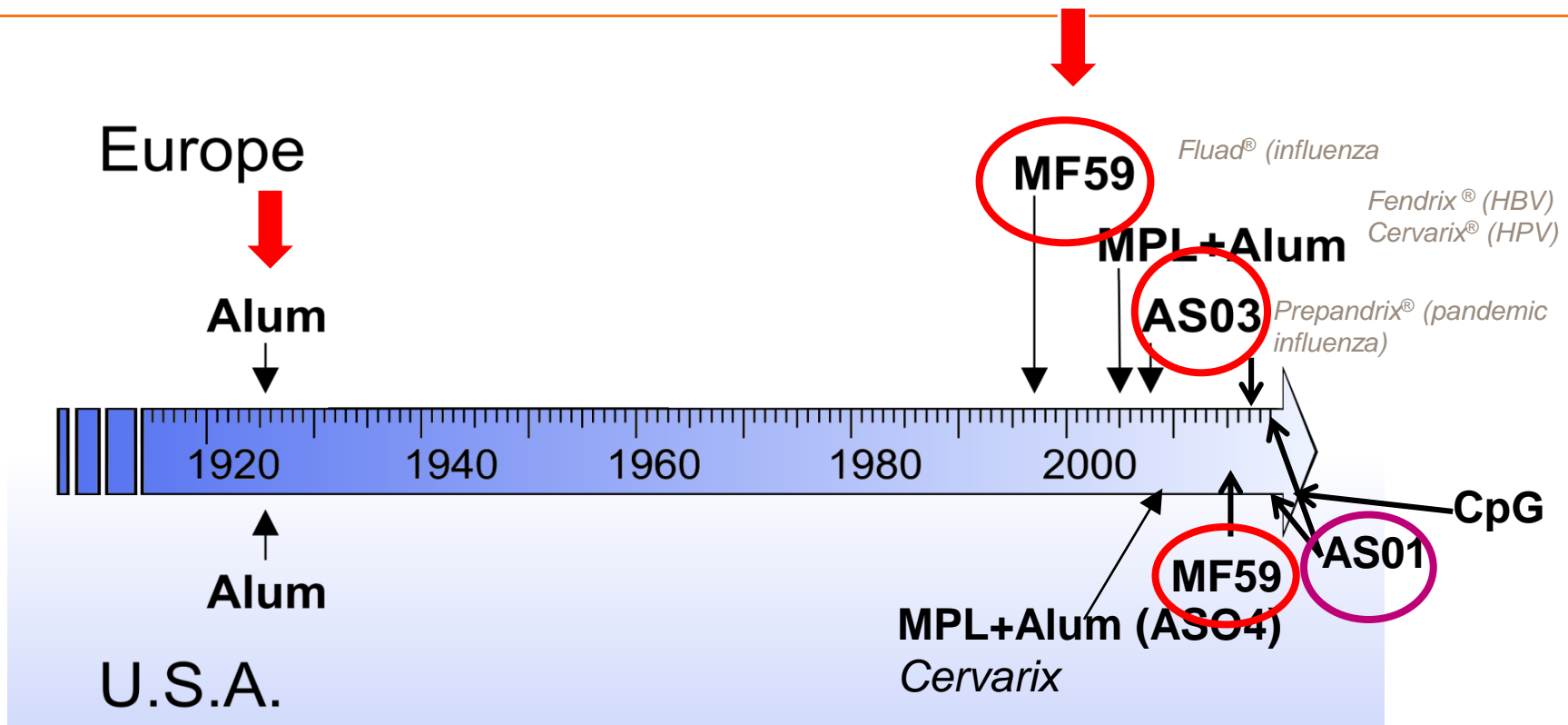
In 2004 an OMV vaccine was used in New Zealand



- Global vaccination campaign (5 wks-18yrs)
- Outer Membrane Vesicles successfully eliminated the MenB epidemic in New Zealand **and reduced gonococcal infection by 30%**



Adjuvant Development



- Many potent vaccine adjuvants have failed, due to safety concerns
- MF59 was a key innovation, first novel adjuvant in 70 years
- Alum and MPL (AS04®) are the only adjuvants currently approved in US

M72/AS01_E candidate vaccine (M72)



To induce a robust Th1 CD4⁺ T cell response against Mtb antigens

Mtb antigens
PepA (Mtb32A) and PPE18
(Mtb39A)

Adjuvant system
AS01_E

M72
candidate
vaccine

Liposome (carrier)

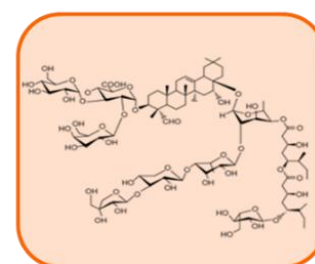
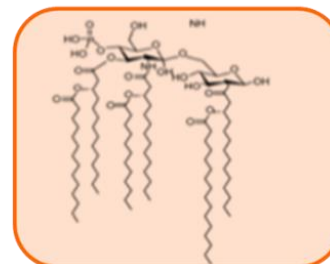
Antigens selection

[Skeiky, 1999; Dillon, 1999; Al-Attayah 2004]

- Lymphoproliferation - IFN- γ production
 - + Healthy PPD +
 - + TB patients
 - × PPD -
- No IL-10 production in TB patients

MPL

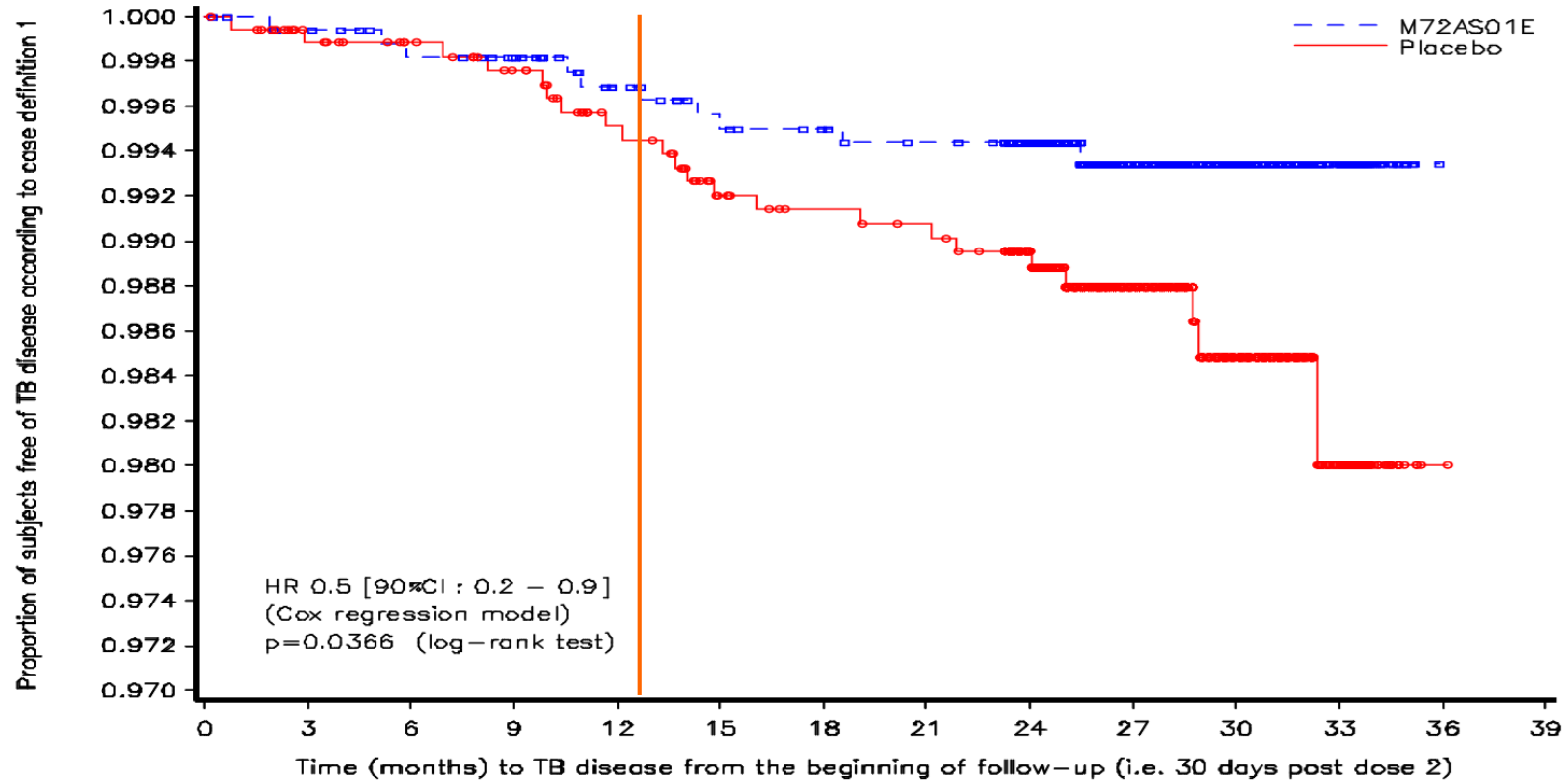
Saponin QS-21



A promising TB vaccine



Time	VE (case definition 1, ATP)		
	%	LL 90%CI	UL 90%CI
Period1 (≤ 1.12 years)	39.0	-42.5	73.9
Period2 (> 1.12 years)	66.5	13.3	87.0



Kaplan-Meier (ATP cohort for efficacy)

Van Der Meeren NEJM. 25 Sep 2018; DOI: 10.1056/NEJMoa1803484

Figure adapted from Van Der Meeren et al, presented at IDWeek, October 2018, San Francisco CA, Abstract 70677 <http://www.idweek.org>

Vaccines against poverty, an Institute to address the gaps in vaccine development



In the recent past, no mechanism was in place to develop vaccines needed only in developing countries



Novartis Vaccines Institute for Global Health (NVGH)

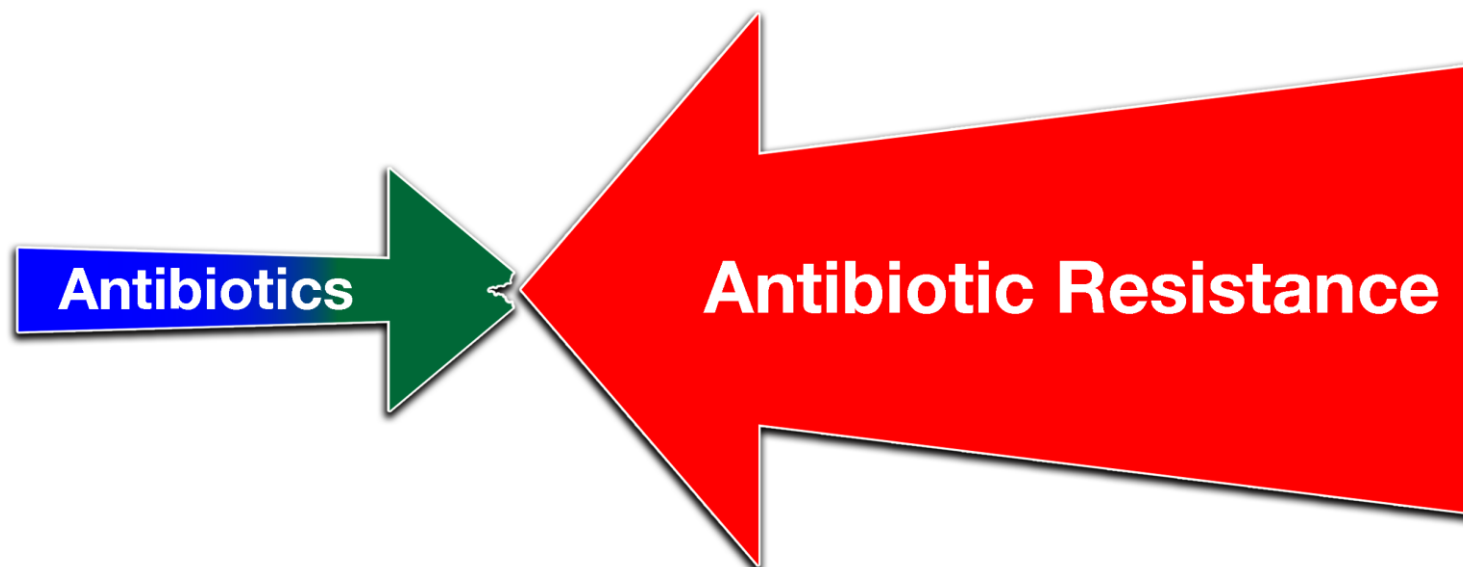
New name: **GSK Vaccine Institute for Global Health (GVGH)**

A new **non-profit** initiative
to develop effective and affordable vaccines for
neglected infectious diseases of developing countries



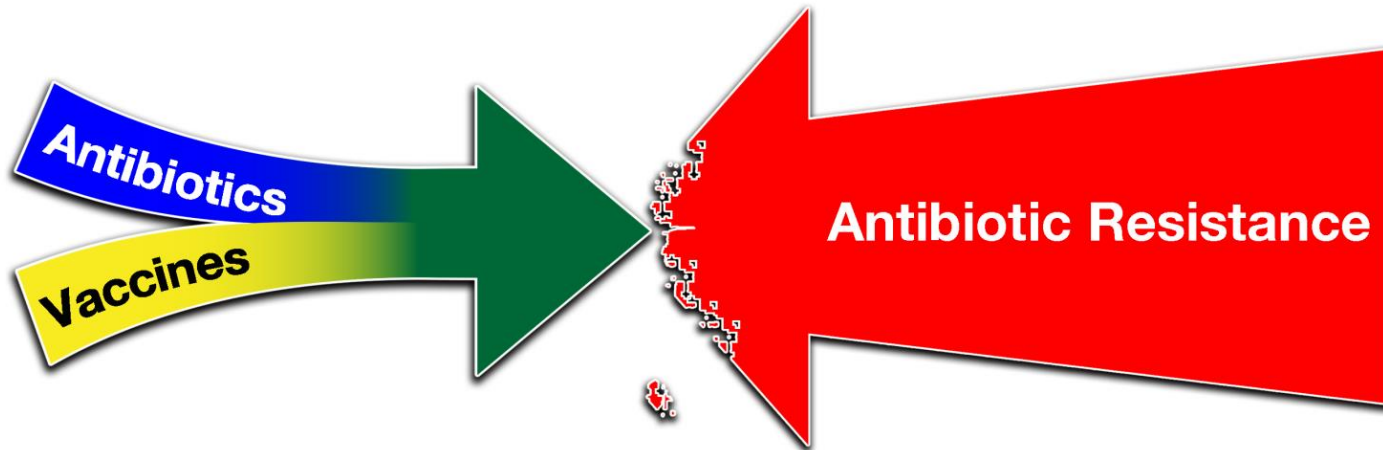
- Located in Siena , Italy
- Legal entity started in Feb 2007
- Allan Saul hired as CEO Sept 2007
 - Inauguration
Feb 22, 2008
- **Typhoid vaccine licensed to BioE
successful Phase III**
- **Shigella vaccine Phase I 2014**
- **iNTS Phase I 2020**

AMR is difficult for antibiotics alone



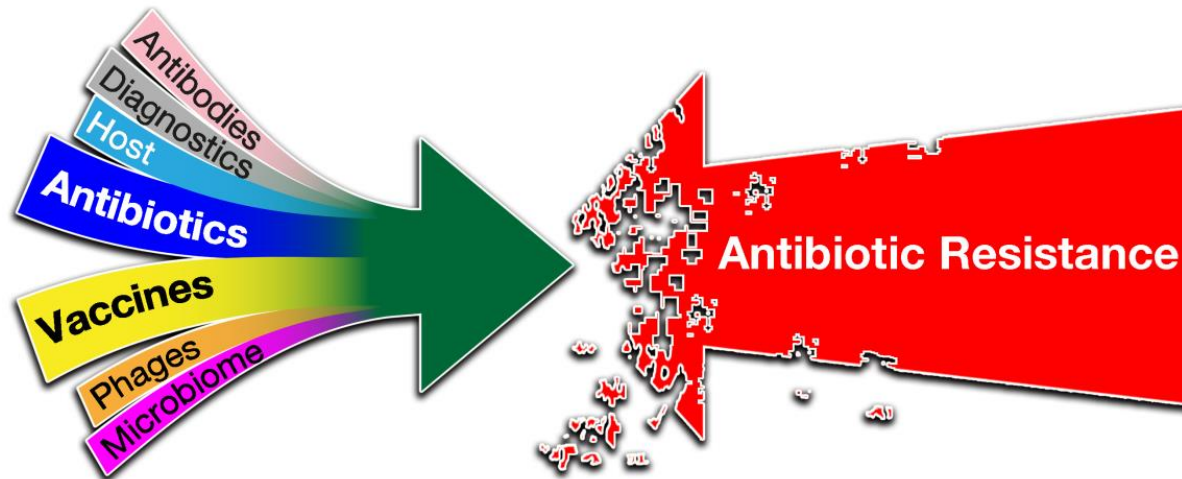
This figure was inspired by an early version of a manuscript by Elizabeth J Klemm, Vanessa K Wong and Gordon Dougan

Vaccines and Antibiotics together have a better chance to control AMR



This figure was inspired by an early version of a manuscript by Elizabeth J Klemm, Vanessa K Wong and Gordon Dougan

By joining forces we can control AMR



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Thank you