
VirtuaLAB
3er Congreso Virtual
de Bioquímica Clínica
2019

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3er Congreso Virtual de Bioquímica Clínica 2019

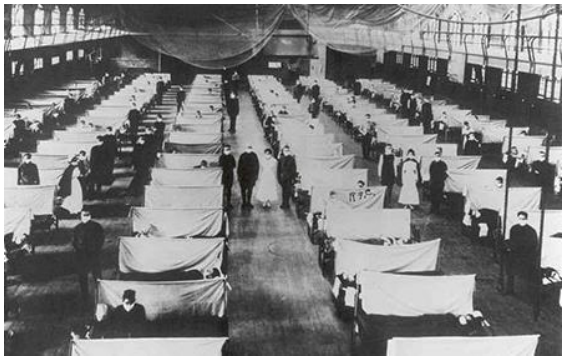
Vacunas: perspectiva histórica, avances y desafíos

Dra. Daniela Hozbor
VacSal-IBBM FCE UNLP CONICET

Las enfermedades infecciosas siempre han tenido un impacto devastador en la humanidad

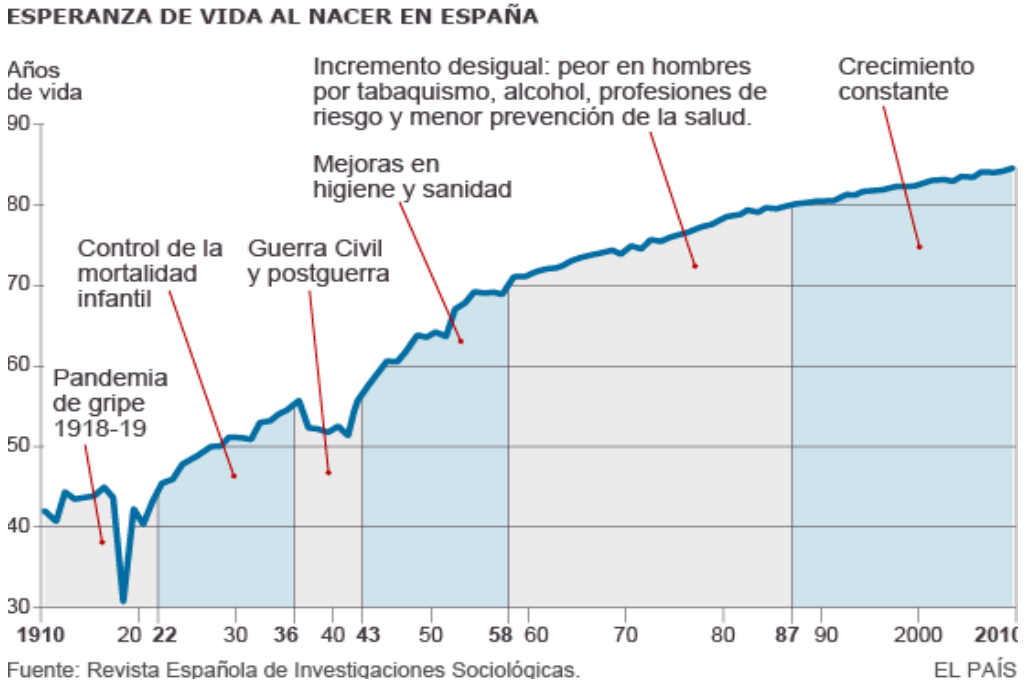
Algunas de las pandemias catastróficas:

- La plaga de Justiniano (542-546 dC), que tuvo una tragedia de 100 millones de muertes
- La peste bubónica (1347-50 dC), también conocida como la "Muerte Negra", que provocó la muerte de un tercio de toda la población humana
- La influenza "española" en 1918, que causó entre 50 y 100 millones de muertes en todo el mundo, reduciendo a la mitad la población europea. 500 millones de personas, o un tercio de la población mundial, se infectaron con este virus. La pandemia fue tan grave que, de 1917 a 1918, la expectativa de vida disminuyó en alrededor de 12 años, a 37 años para los hombres y 42 años para las mujeres.



En 1918 No se había identificado al agente causal. No había pruebas diagnósticas. No había antivirales, ni antibioticos para las infecciones secundarias. No había vacunas, higiene, cuarentena y cierre de lugares públicos.

Antes de la introducción de estrategias preventivas y terapéuticas efectivas, la esperanza de vida se estimaba en <50 años y las infecciones eran las que imponía este límite



Este escenario cambió con la introducción de tres medidas: Higiene, antibióticos y vacunación

Antibióticos: 1929 Penicilina. Su primer uso en humanos una década más tarde. Reducción dramática de la mortalidad causada por enfermedades infecciosa

1940 se documentó el primer caso de una cepa de E. coli resistente a la penicilina y, a fines de la década de 1960, más del 80% de las cepas de S. aureus adquirieron la misma resistencia.

En 1956, se aisló en japon *Shigella flexneri* resistente a estreptomicina, tetracicline, cloramfenicol y sulfonamidas.

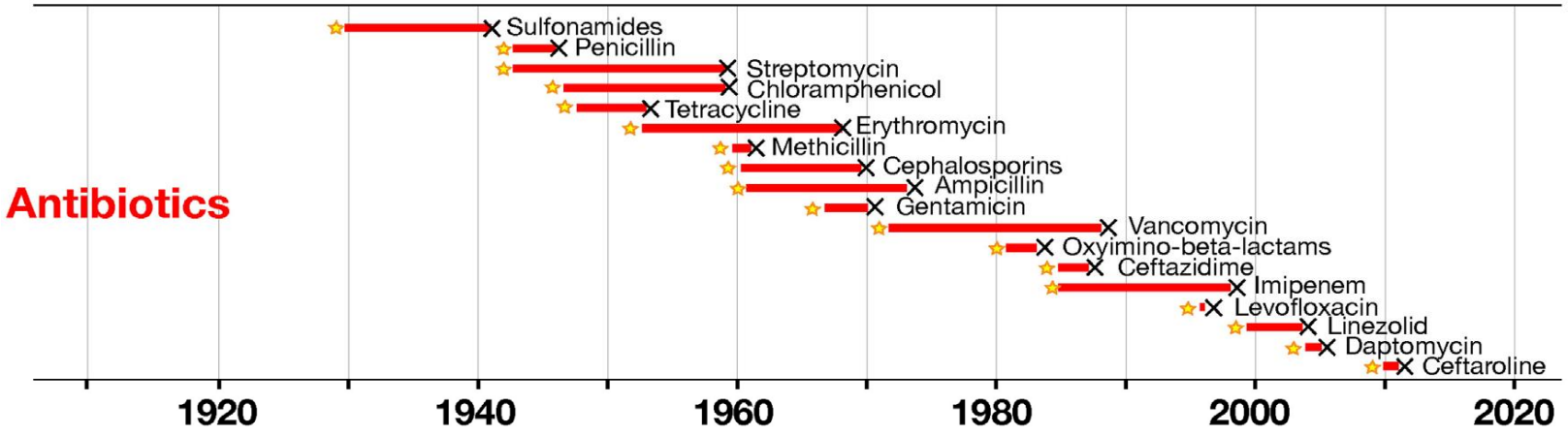
Table 1 Global antibiotic resistance levels associated with major bacterial pathogens

	Resistance rate				
Pathogen	United States	S. Africa	UK	India	Australia
S. pneumoniae	17–34	ND	7–8	ND	ND
S. aureus	0–45	0–29	0–11	2–94	0–18
E. coli	1–55	0–84	0–66	11–92	0–55
Enterobacter spp.	5–88	3–100	ND	ND	3–30
K. pneumoniae	8–22	2–68	0–14	2–80	0–9
P. aeruginosa	5–26	1–35	3–14	0–69	ND
A. baumannii	6–49	2–41	2–9	3–90	ND
M. tuberculosis	0–2.9	3–5.9	0–2.9	ND	0–2.9
N. gonorrhoeae	0.1–3	0.1–70	0–70	0.1–70	0.1–70

Antibiotic resistance data are presented from 2000–2014 and listed as the percentage of isolates tested that were resistant to each antibiotic class used for each pathogen. These antibiotics are pathogen specific. The table depicts the range of antibiotic resistance for each pathogen via available drugs and does not take into account the proportion of strains that are resistant to more than one antibiotic class. Data for all pathogens except *M. tuberculosis* and *N. gonorrhea* were obtained from the Center for Disease Dynamics, Economics and Policy (https://resistancemap.cddep.org/). Tuberculosis data were obtained from ref. 85. *N. gonorrhea* data were obtained from the WHO Gonococcal Antimicrobial Surveillance Programme (GASP), which covers strains analyzed between 2011 and 2014 (http://www.who.int/reproductivehealth/topics/rtis/gonococcal_resistance/en/). ND, no data provided.

Jansen et al 2018

VOLUME 24 | NUMBER 1 | JANUARY 2018 NATURE MEDICINE



It is estimated that by 2050, 10 million lives a year may be lost to AMR, exceeding the 8.2 million lives a year currently lost to cancer[5]. To put this number in perspective, currently, at least 700,000 people die of resistant infections every year globally, more than the combined number of deaths caused by tetanus, cholera and measles.


frontiers in Immunology

REVIEW

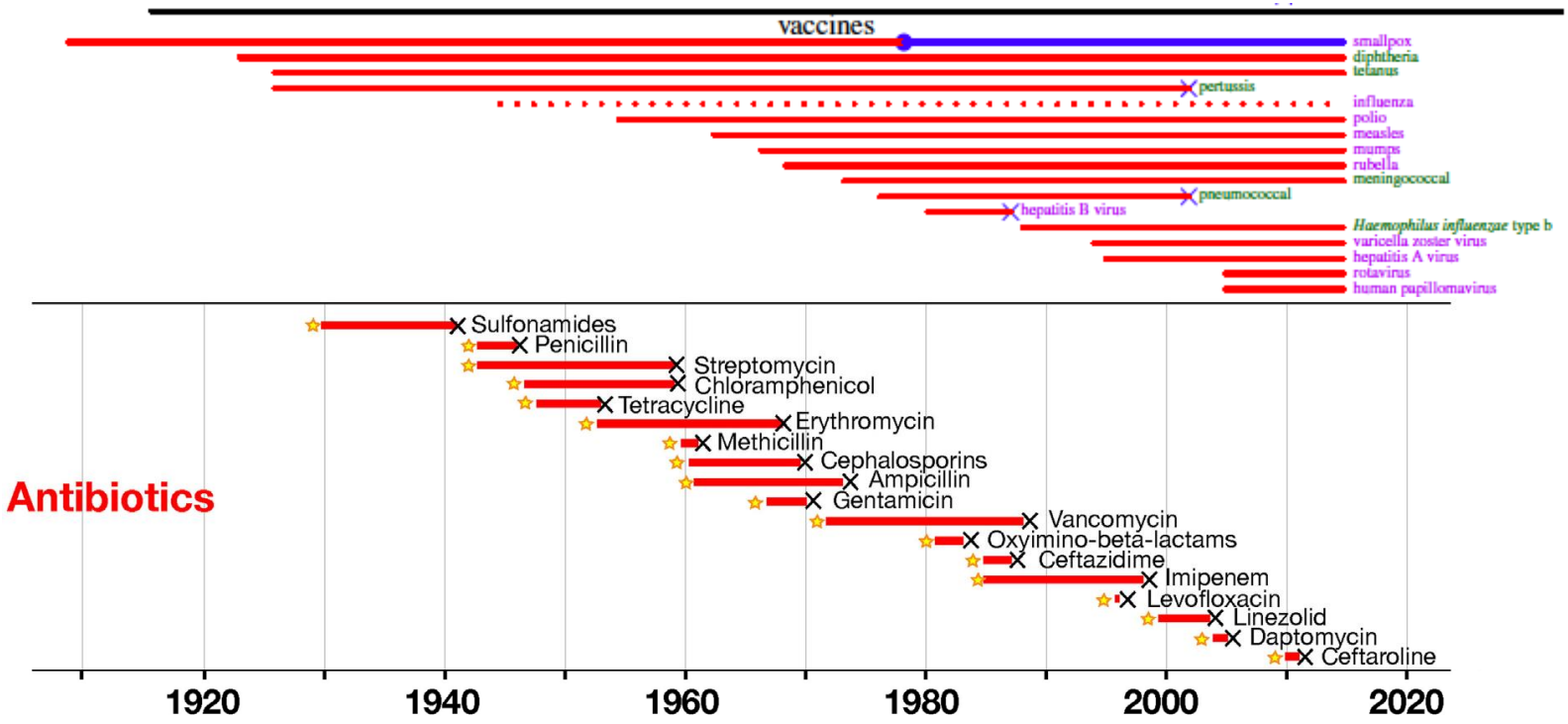
Changing Priorities in Vaccinology: Antibiotic Resistance Moving to the Top

Aldo Tagliabue and Rino Rappuoli

Esta alarmante situación llevó a llamar a la comunidad a desarrollar nuevos antibióticos.

2016, se asignaron alrededor de 500 millones de dólares a iniciativas nuevas y existentes que apuntan a acelerar el desarrollo de nuevos antibióticos…

Las vacunas, por otra parte, rara vez han demostrado inducen fenotipos resistentes



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REVIEW

Changing Priorities in Vaccinology: Antibiotic Resistance Moving to the Top

Aldo Tagliabue[1] and Rino Rappuoli[2]*

[1] Institute for Genetic and Biomedical Research, CNR, Cagliari, Italy, [2] GSK Vaccines, Siena, Italy

Vacunación

Desde la variolización (siglo XI) Jenner (1749-1823) a Maurice Hilleman (1919-2005) Stanley Plotkin (1936-contenporáneo) Rino Rappuoli (1952-contenporáneo)
Los datos recolectados muestran que la vacunación es intervención médica más efectiva jamás introducida

Table 1. Comparison of 20th century annual morbidity and current estimates vaccine-preventable diseases

Disease	20th Century annual morbidity (2)	2016 Reported cases (3)	Percent decrease (%)
Smallpox	29,005	0	100
Diphtheria	21,053	0	100
Measles	530,217	69	>99
Mumps	162,344	5,311	97
Pertussis	200,752	15,737	92
Polio (paralytic)	16,316	0	100
Rubella	47,745	5	>99
Congenital rubella syndrome	152	1	99
Tetanus	580	33	94
Haemophilus influenzae	20,000	22*	>99

**Haemophilus influenzae* type b (Hib) < 5 y of age.

Todas estas enfermedades se han reducido en más del 90% y muchas han sido eliminadas o han alcanzado reducciones del 99%.

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Author contributions: W.A.O. and R.A. wrote the paper.
See Perspective on page 4055.
[1]To whom correspondence should be addressed. Email: WORENST@emory.edu.

Hasta ahora se han salvado> 700 millones de casos de enfermedades, más de 150 millones de muertes

Durante 2011-2020 se espera que las vacunas salven
25 millones de muertes, 2.5 millones / año, 7000 / día
300 / hora y 5 muertes por minuto.

Se estima que se podrían evitar 1,5 millones de muertes adicionales si mejora la cobertura de vacunación global.

Percentage of target population vaccinated, by antigen
based on WHO-UNICEF estimates

	2018	2017	2016	2015	2014	2000	1990	1980
BCG	89	89	89	88	88	80	81	15
DTP1	90	91	91	90	89	83	88	30
DTP3	86	86	86	85	84	72	75	20
HepB_BD	42	41	37	37	35	5	-	-
HepB3	84	84	85	83	81	30	1	-
Hib3	72	72	71	63	55	13	0	-
IPV1	72	58	47	23	-	-	-	-
MCV1	86	86	86	85	84	72	73	16
MCV2	69	68	67	63	59	18	-	-
PCV3	47	45	43	38	32	-	-	-
Pol3	85	86	85	85	85	73	75	21
RCV1	69	52	48	47	45	21	8	3
rotac	35	28	25	23	19	-	-	-
TT2plus	72	73	72	70	67	62	55	9
YFV	49	48	46	42	43	11	-	-

Durante 2018, aproximadamente el 86% de niños menores de un año (116,3 millones) en todo el mundo recibieron tres dosis de la vacuna contra la difteria-tétanos-pertussis.

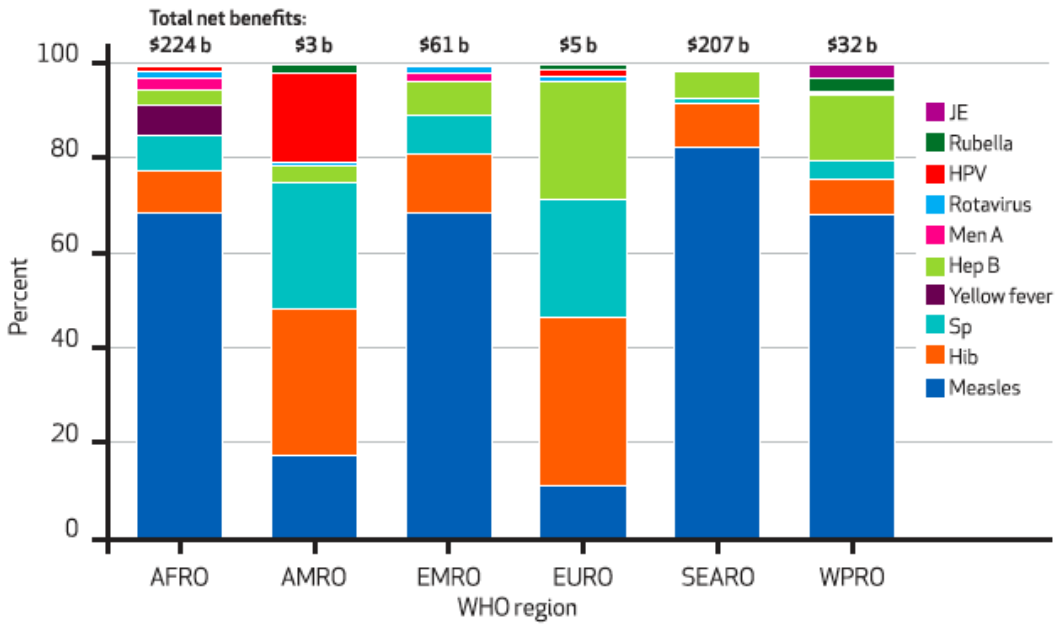
Pero... alrededor de 19,4 millones de niños menores de un año no recibieron vacunas básicas.
Cerca del 60% de esos niños viven en 10 países: Angola, Brasil, República Democrática del Congo, Etiopia, India, Indonesia, Nigeria, Pakistan, Filipinas y Vietnam.

By Sachiko Ozawa, Samantha Clark, Allison Portnoy, Simrun Grewal, Logan Brenzel, and Damian G. Walker

Return On Investment From Childhood Immunization In Low- And Middle-Income Countries, 2011–20

DOI: 10.1377/hlthaff.2015.1086
HEALTH AFFAIRS 35,
NO. 2 (2016): 199–207

Estimated Breakdown Of Net Benefits, By Antigen And World Health Organization (WHO) Region, Across 94 Low- And Middle-Income Countries, 2011–20

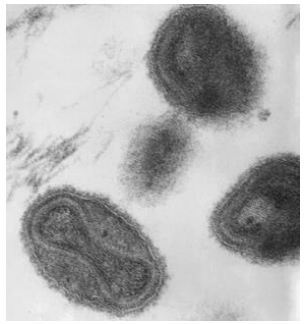


SOURCE Authors' analysis based on health impact estimates derived from Gavi's 2014 strategic demand forecast and dose estimates from Gavi's 2014 adjusted demand forecast (Notes 8 and 25, respectively, in text). **NOTES** Economic benefits are reported in billions of 2010 US dollars. AFRO is the African region. AMRO is the region of the Americas. EMRO is the Eastern Mediterranean region. EURO is the European region. SEARO is the South-East Asian region. WPRO is the Western Pacific region. JE is Japanese encephalitis. HPV is human papillomavirus. Men A is *Neisseria meningitidis* serogroup A. Hep B is hepatitis B. Sp is *Streptococcus pneumoniae*. Hib is *Haemophilus influenzae* type b.

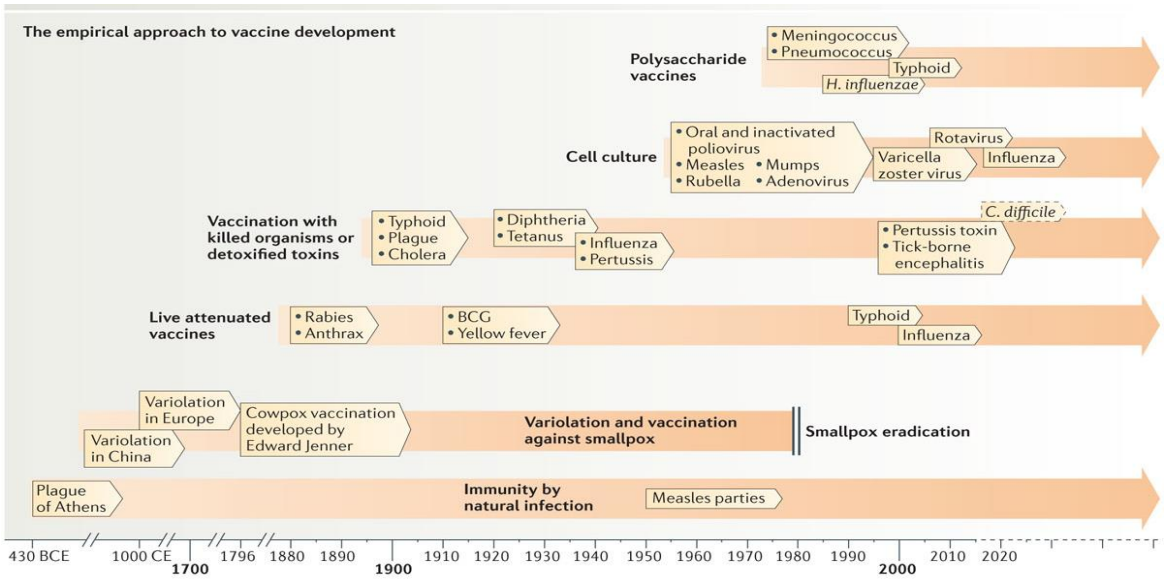
La primera evidencia escrita relacionada con los procesos de vacunación data del siglo XI y se encuentran en la literatura china

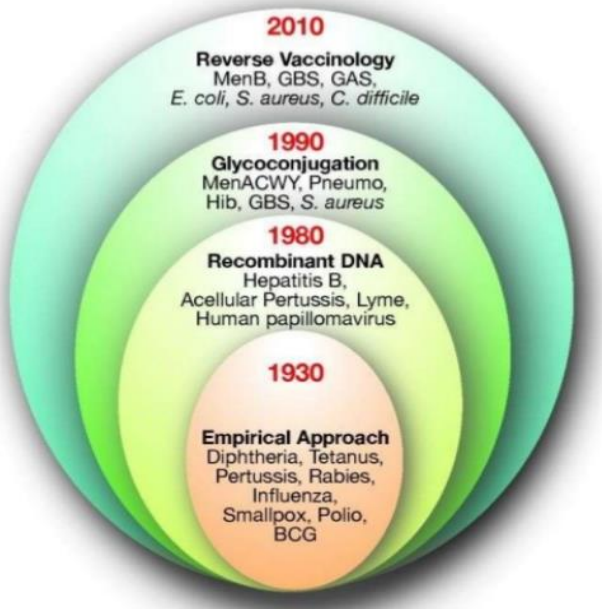
Viruela: una enfermedad infecciosa grave, contagiosa, causada por el Variola virus que podía provocar la muerte. El nombre viruela proviene del latín variŭs (variado, variopinto), y se refiere a los abultamientos que se presentan en la cara y en el cuerpo de una persona infectada.

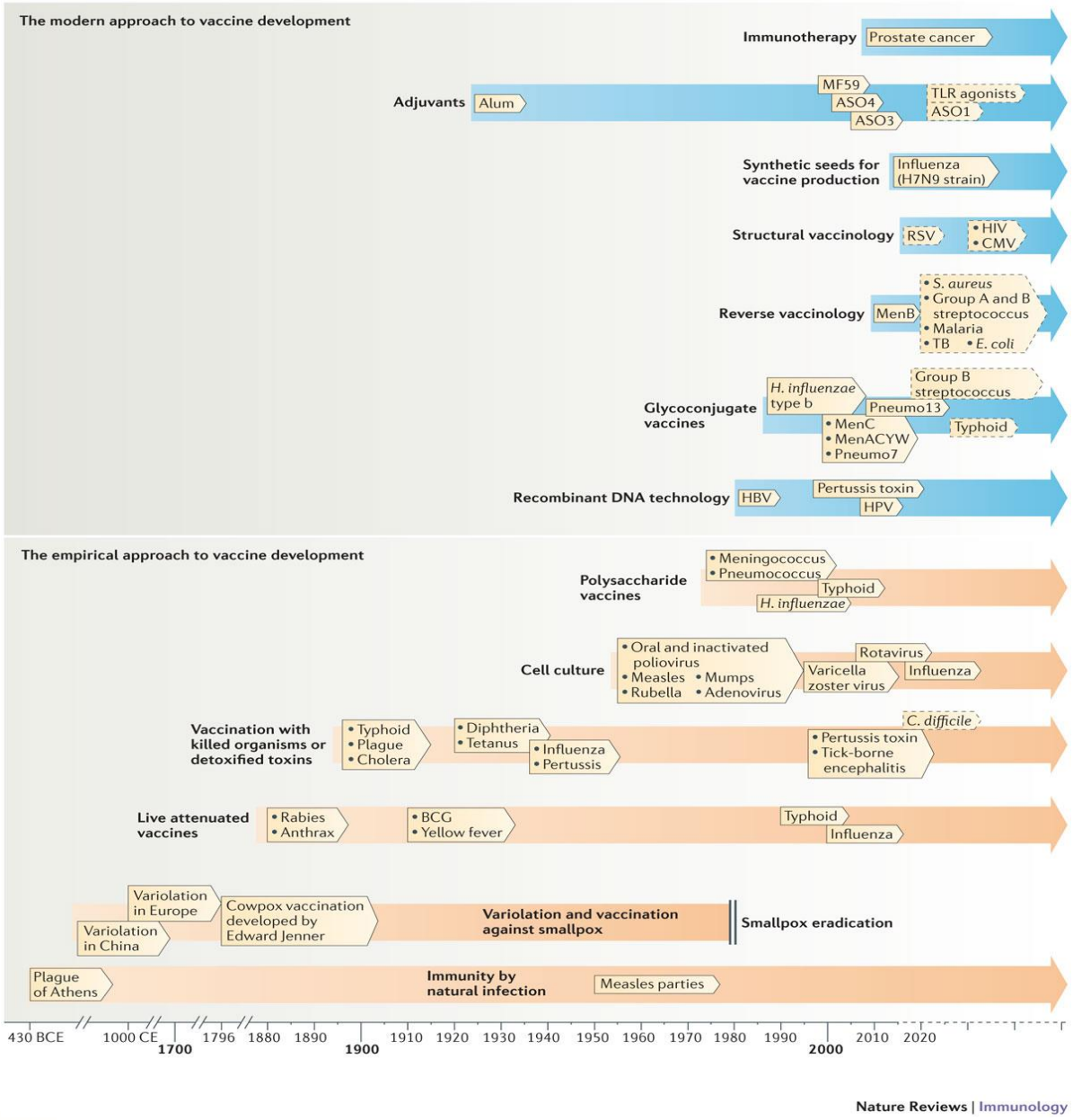
El trabajo de Edward Jenner representó el primer intento científico de controlar una enfermedad infecciosa mediante el uso deliberado de la vacunación. Estrictamente hablando, no descubrió la vacunación, pero fue la primera persona en introducir ciencia en el procedimiento y en la evaluación.



Micrografía electrónica de transmisión (TEM) representa una serie de viriones del virus de la viruela; Mag - aproximadamente 370.000x.







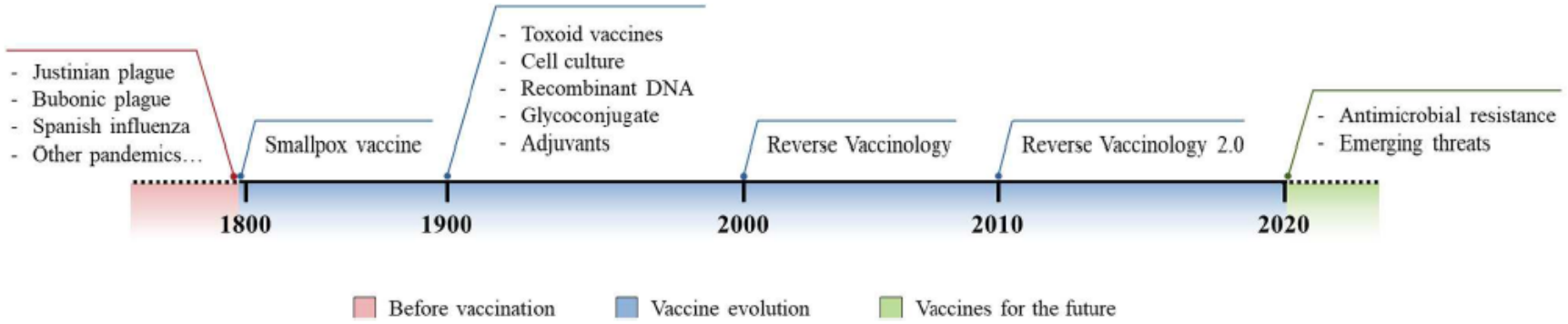


FIGURE 1 | Vaccine evolution. Schematic representation of the burden of infectious diseases before vaccination was introduced (red), technological and methodological advances in vaccinology following the introduction of the first vaccine (blue), and the future use and implementation of vaccine development to fight modern threats (green).

frontiers in Immunology

MINI REVIEW
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Reverse Vaccinology 2.0

JEM

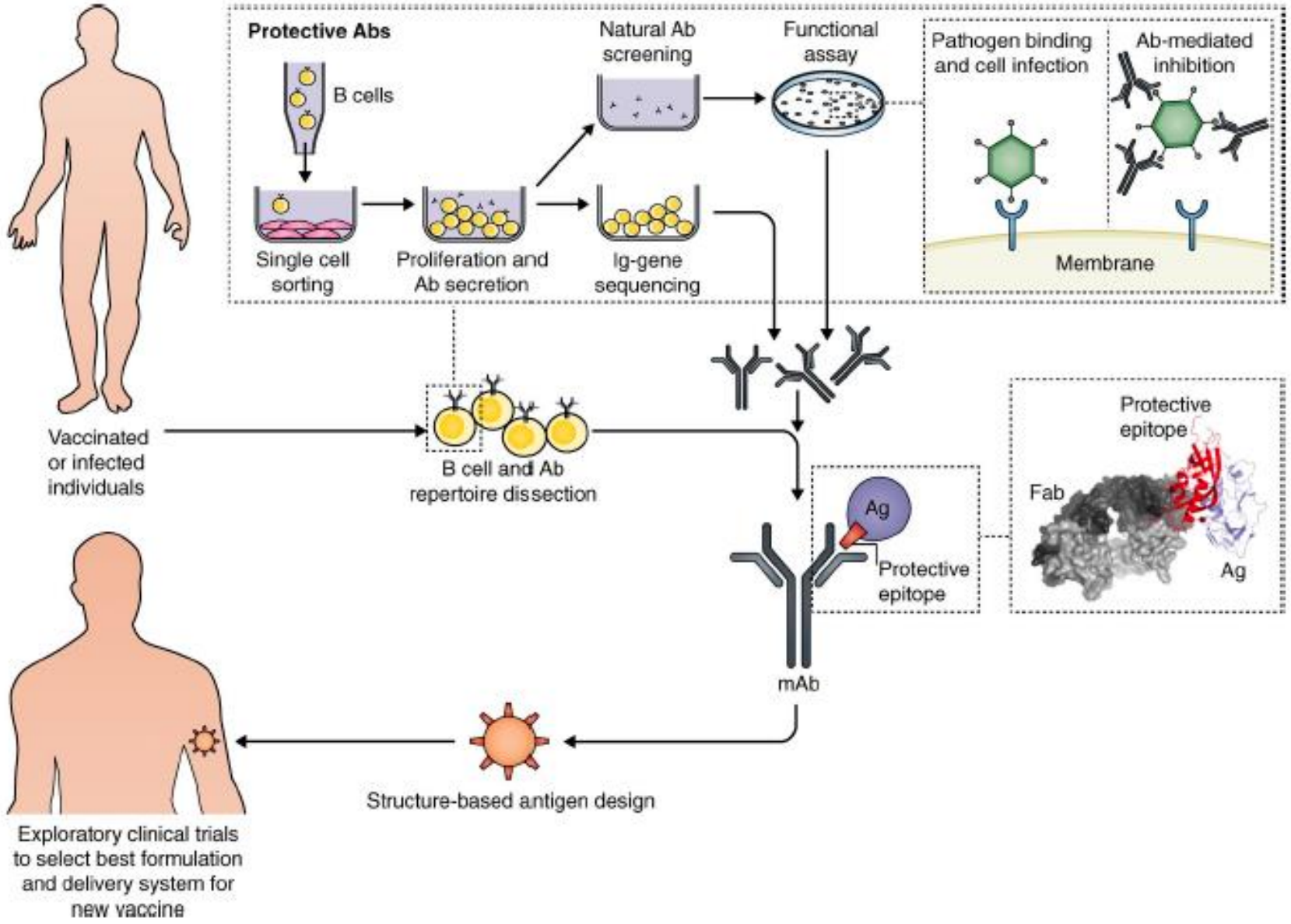
Perspective

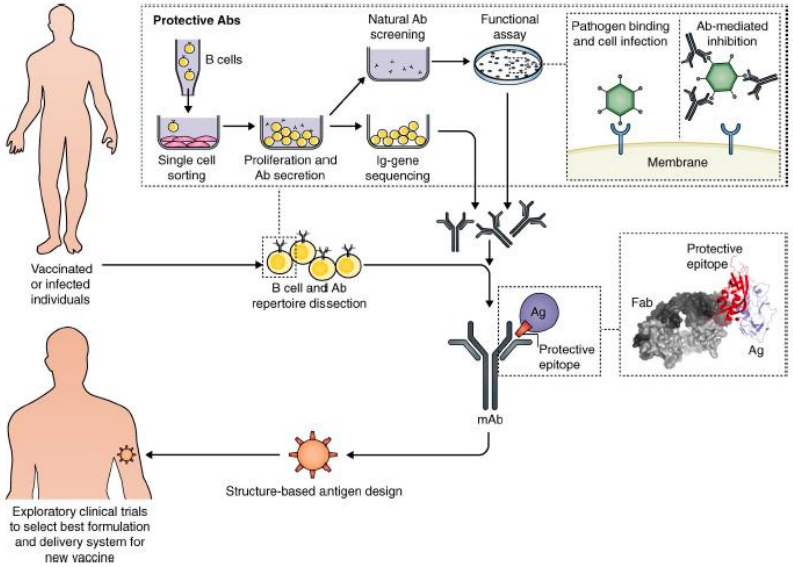
Reverse vaccinology 2.0: Human immunology instructs vaccine antigen design

Rino Rappuoli, Matthew J. Bottomley, Ugo D'Oro, Oretta Finco, and Ennio De Gregorio

GlaxoSmithKline Vaccines S.r.l., 53100 Siena, Italy

Traditionally, vaccines have been developed by cultivating infectious agents and isolating the inactivated whole pathogen or some of its purified components. 20 years ago, reverse vaccinology enabled vaccine discovery and design based on information deriving from the sequence of microbial genomes rather than via the growth of pathogens. Today, the high throughput discovery of protective human antibodies, sequencing of the B cell repertoire, and the increasing structural characterization of protective antigens and epitopes provide the molecular and mechanistic understanding to drive the discovery of novel vaccines that were previously impossible. We are entering a "reverse vaccinology 2.0" era.


Protective Abs
B cells
Natural Ab screening
Functional assay
Pathogen binding and cell infection
Ab-mediated inhibition
Single cell sorting
Proliferation and Ab secretion
Ig-gene sequencing
Membrane
Vaccinated or infected individuals
B cell and Ab repertoire dissection
Protective epitope
Fab
Ag
Protective epitope
Ag
mAb
Structure-based antigen design
Exploratory clinical trials to select best formulation and delivery system for new vaccine



HIV Estudios de mapeo de epitopes con estos Abs permitieron identificar otras regiones de Env con capacidad de inducir bNAbs.

RSV: es la principal causa viral de enfermedad grave del tracto respiratorio en niños de todo el mundo (Nair et al., 2010) y también afecta a adultos mayores e inmunocomprometidos (Falsey et al., 2005).

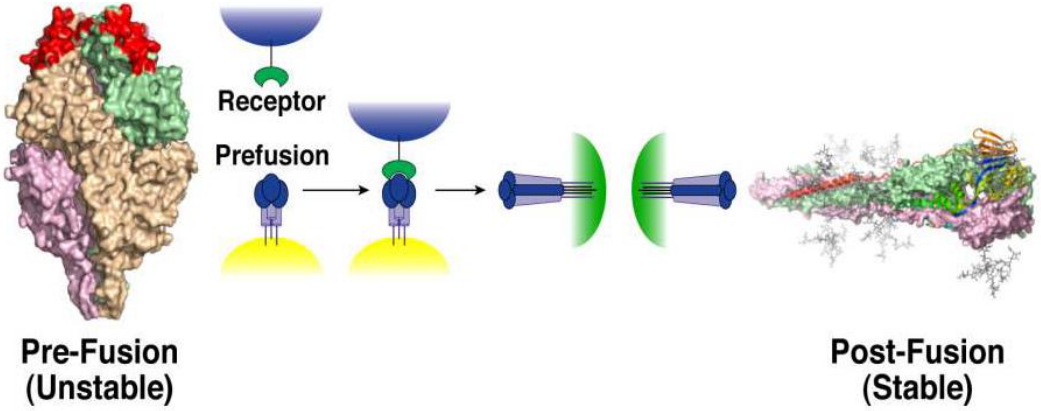
Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization from Respiratory Syncytial Virus Infection in High-Risk Infants

The IMpact-RSV Study Group

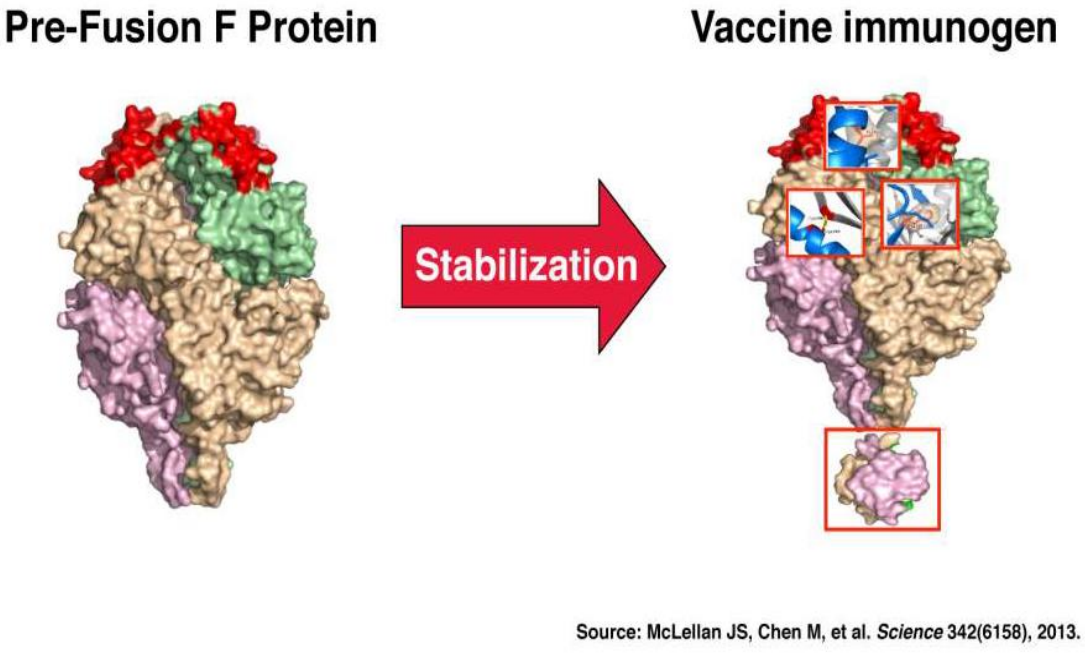
- Palivizumab is a monocolonal antibody vs. Fusion protein
- Used for periodic prophylaxis of severe RSV for premature infants
- Shown to reduce RSV hospitalizations by 82%

Co-cristalización de mAbs con la proteína de fusión (inestable, cambios conformacionales) y diseños computaciones permitieron mejoras pero no fue suficiente.

La proteína trimerica de fusión sufre cambios confomacionales desde una conformación prefusión metaestable hacia una postfusión más estable.

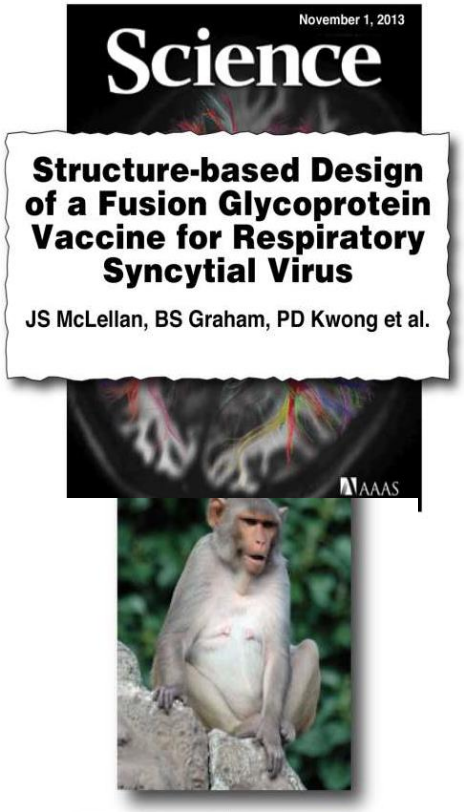


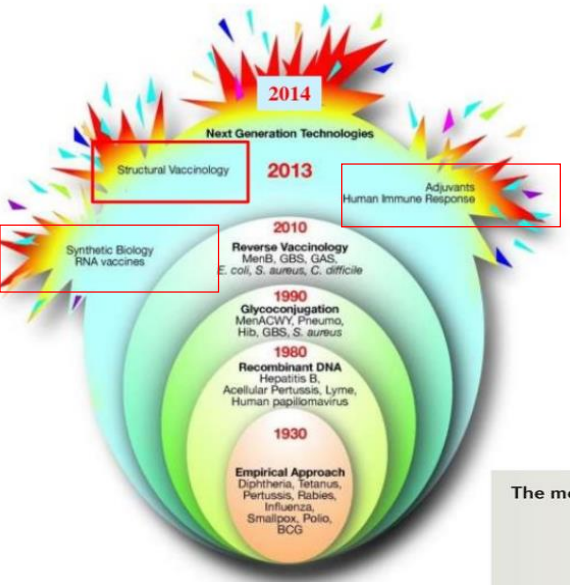
McLellan et al 2013 Proteína de prefusión. Co-cristalizaciones Identificó un anticuerpo (D25) que se pega y atrapa a la proteína en una conformación antes no observada. Identificó una estructura cuaternaria del trimero de la proteína.

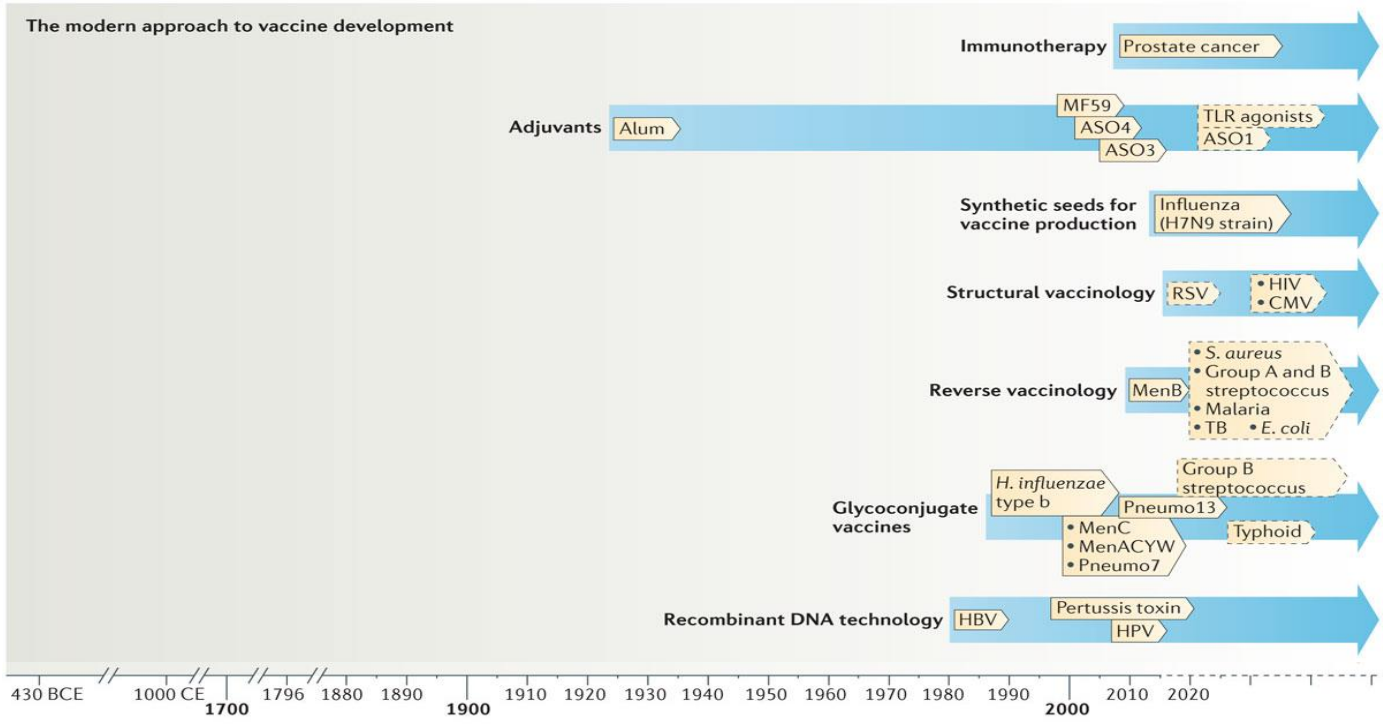


Source: McLellan JS, Chen M, et al. *Science* 342(6158), 2013.

Estabilizó al epitope introduciendo mutaciones



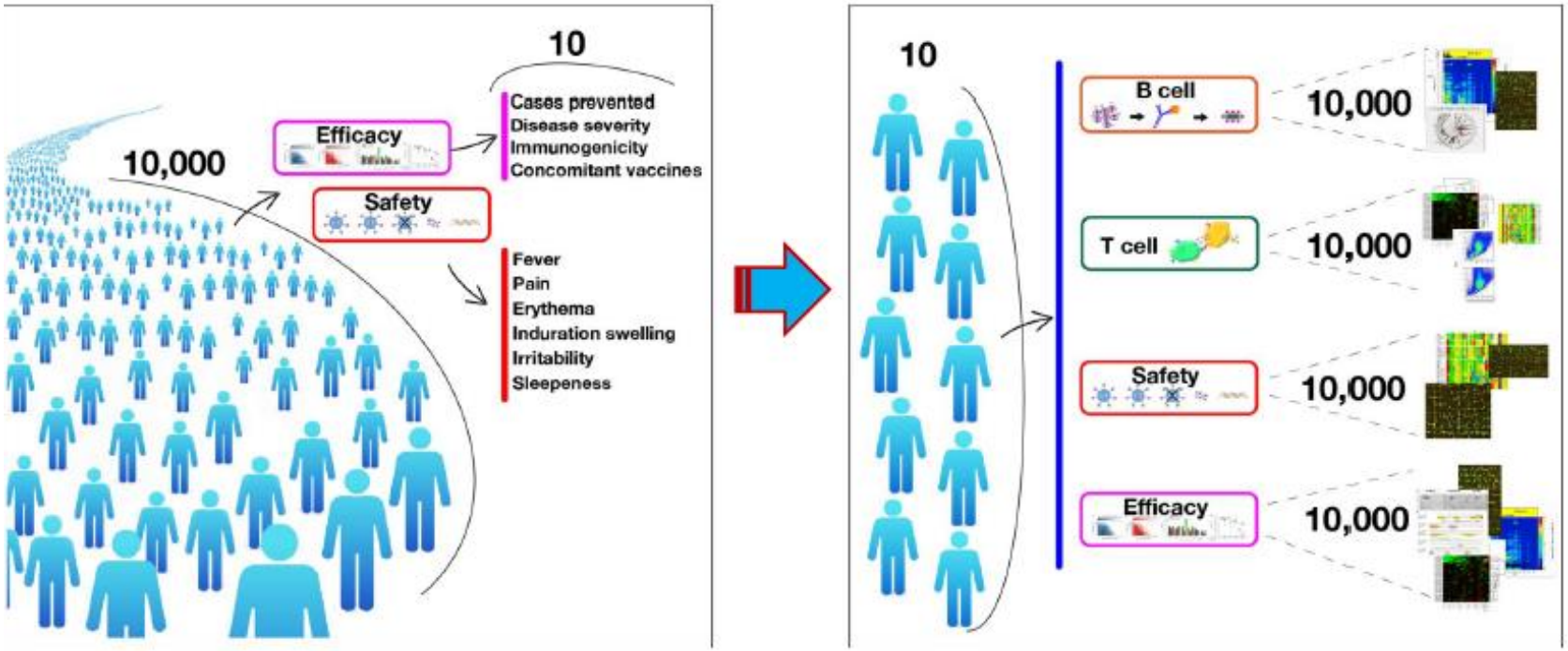




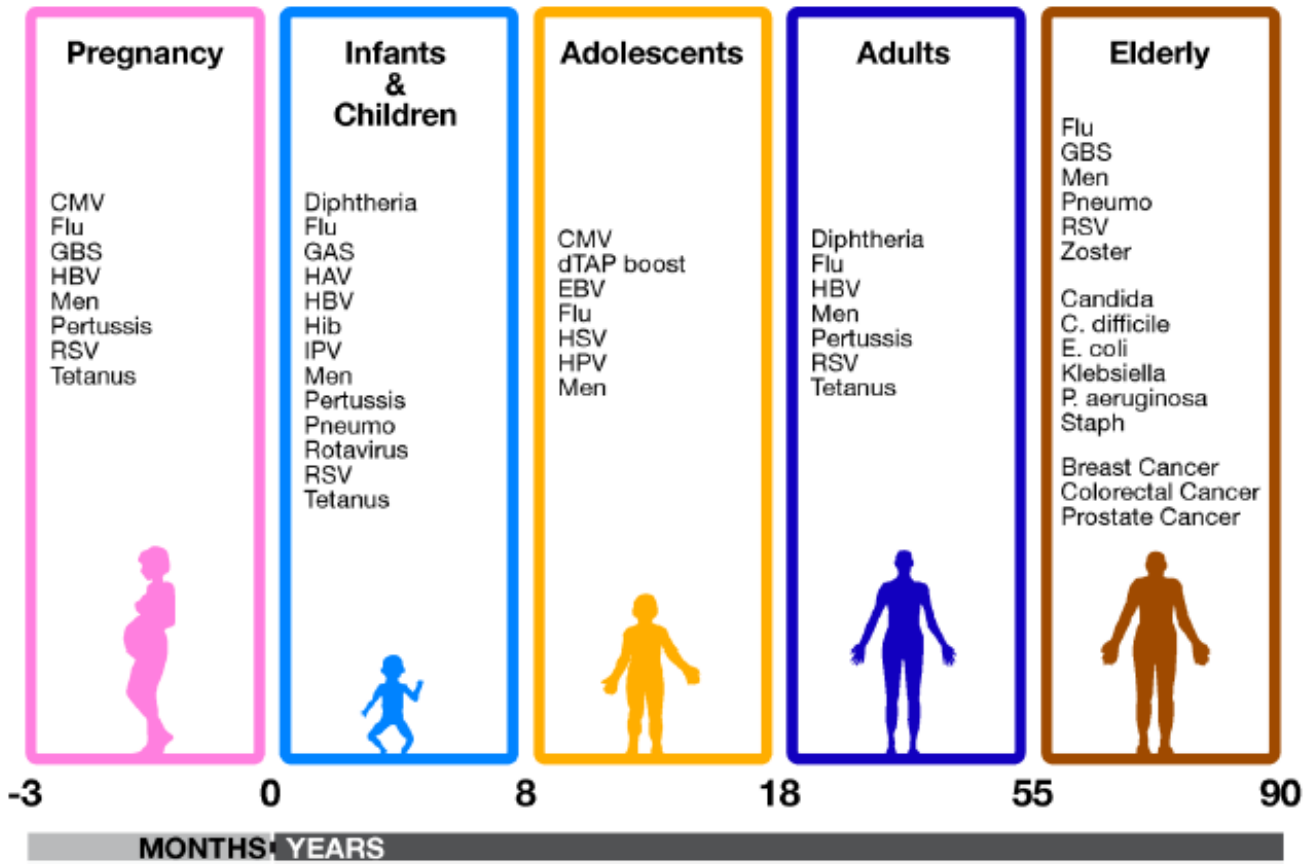
Nature Reviews | Immunology

Systems biology

From 10,000 people with 10 data each
to
10 people with 10,000 data each



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 today's society

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

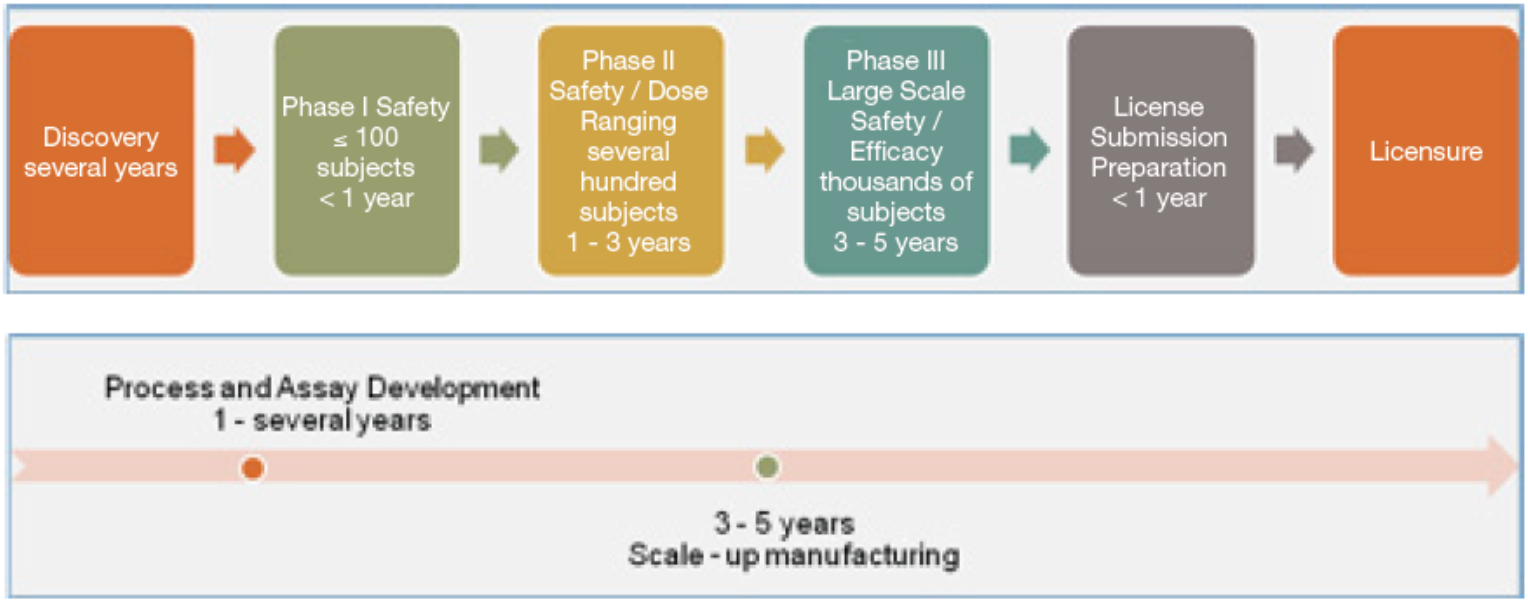
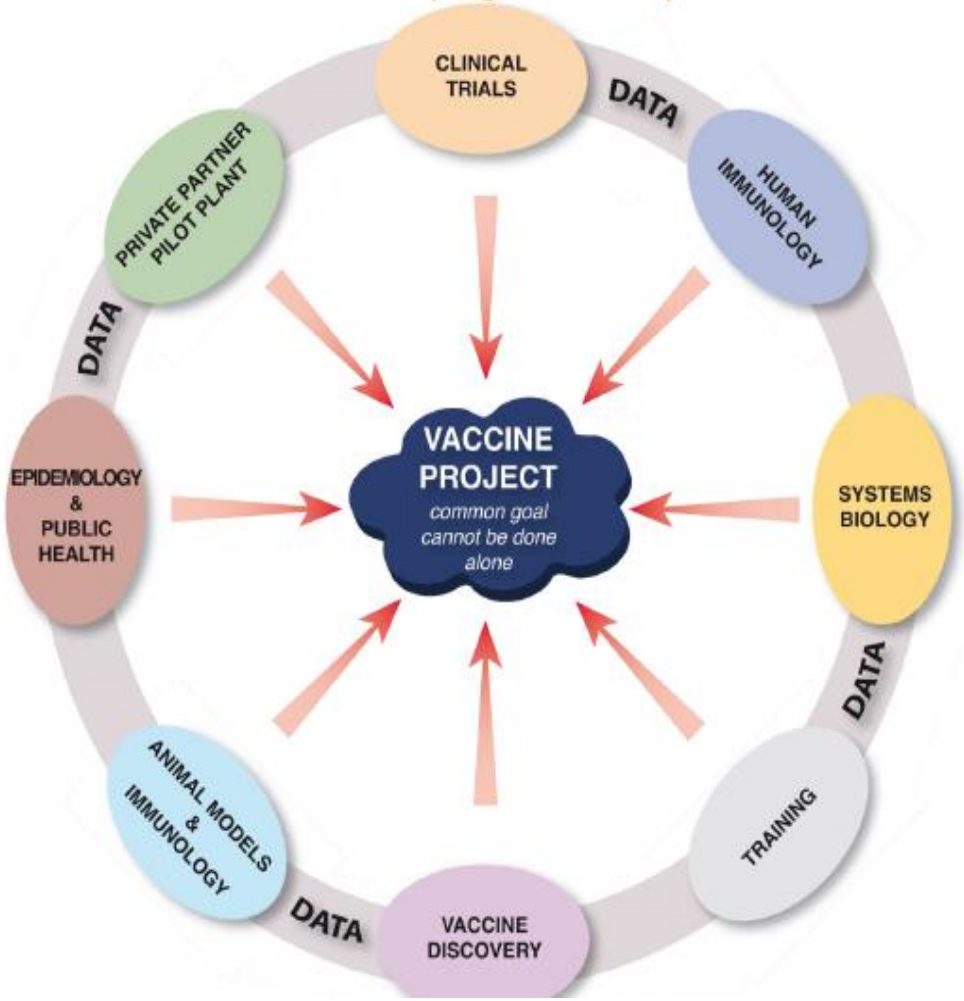


FIGURE 43. VACCINE DEVELOPMENT PROCESS OVER A PERIOD OF UP TO 15 YEARS AT A COST OF UP TO $1 BILLION

Collaboration of many partners is necessary for a vaccine development (Big science)



ADITEC is a collaborative research programme that aims to accelerate the development of novel and powerful immunisation technologies for the next generation of human vaccines. Scientists from 13 countries and **42 research** partners collaborate in the ADITEC project.

ADITEC comprises some of the most competitive European research groups from universities, research institutions and biotech companies together with top US groups on systems biology and adjuvants. Different aspects of vaccination, from basic research, new technologies to clinical trials and public health, are covered.

ADITEC started in October 2011, is a 5-year project and has received funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement No 280873.

Recently the European Commission approved a one year no cost extension postponing the end of the project to 30 September 2017.

ADITEC: 13 Clinical Studies

Partner / Sponsor Contact	Vaccine Population Objectives	Comments
UIBK	**Licensed Hepatitis B vaccine - alum** Elderly & young adults.	Ongoing recruitment Completes 2015
OXF UNTGE	**Licensed Influenza ± MF59 adjuvant** Infants Systems biology of adjuvanted vaccines in infants	Completed
SURREY NVD / ICL / UIBK	**Comparison of adjuvants in young and elderly with neoantigen (H5N1)**	In Planning
MPG	**Novel rBCG**	This trial is outside of ADITEC
SURREY	**Comparison of adjuvants prime-boost, matched neoantigens discordant adjuvants systems biology 36 young adults** **Licensed hepatitis B vaccines with alum (Engerix) or AS04** (MPL - Fendrix)	Ongoing recruitment
SURREY	**Heterologous route of immunisation prime-boost, breadth of CMI: IM TIV and nasal LAIV** Young adults	Start Q4 2014
NVD	**Characterisation of adjuvants** **Novel influenza / menB + novel adjuvants** Healthy adults	Novartis trials
SURREY	**Enhancing mucsal immune responses by targeted IM immunisation** 40 Adult women	Completes October 14
UGOT	**Licensed oral cholera / LAIV** Young adults: Sublingual immunisation with subunit / live vaccines versus intranasal and oral	Completed
UOXF NVGH	**Novel IM typhoid/paratyphoid; WT *S. typhi* challenge:** Young adults Systems biology of *S. typhil* oral challenge and vaccination	Model completed
NVGH SURREY	**Novel GMMA *Shigella sonnei* vaccine** 52 Young adults Phase 1 trial comparing IM / ID / IN (using device) immunisation, dose escalation, novel antigen	Recruitment ongoing
SURREY	Phase 1 Comparison of adjuvants with model antigen	Not yet selected
TBD	Novel technology developed in ADITEC	Not yet selected

Number	Patents	Applicant
CN105377879 A	Vaccines against Chalmydia sp	Statens Serum Institut
US2014112979 A1	Methods for producing liposomes	Statens Serum Institut
US2016244488 A1	Cholera Toxin A-Like Polypeptide useful as adjuvant component	University of Gothenburg
WO 2014139587 A1	Improved poxviral vaccines	Okairos Ag
US 9321829 B2	Antibodies directed against Influenza	Emory University
US9469685 B2	Antibodies directed against influenza	Emory University
WO2017108902 A1	Oil-in-water emulsions including retinoic acid	Novartis AG

Coverage in 8 Low Performing Countries

Solo sirven las conquistas científicas sobre la salud si éstas son accesibles al pueblo.

Ramón Carrillo
1906- 1956

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Muchas gracias por tu atención!!

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Vacunas: perspectiva histórica, avances y desafíos

Dra. Daniela Hozbor
VacSal-IBBM FCE UNLP CONICET