



From bench to bed: where are we (lost?) in translation

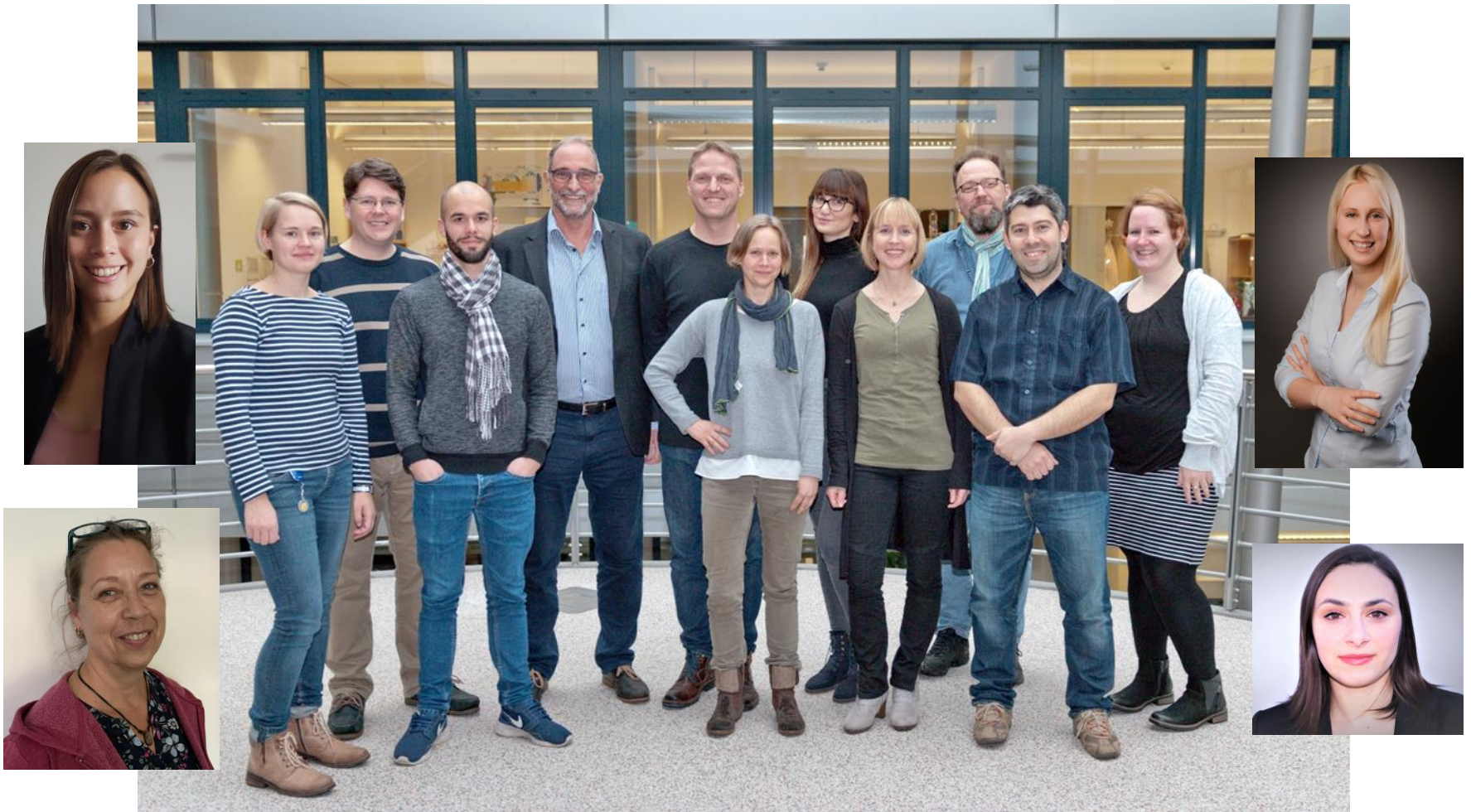
Carlos A. Guzman, HZI – Department of Vaccinology and Applied Microbiology

Kolloquium GSI - 20.10.2020

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HZI HELMHOLTZ
Zentrum für Infektionsforschung

The Team



Infectious diseases spread...



❑ Mobility & Tourism

❑ High risk (elderly and newborn)

❑ Nosocomial infections and antibiotic resistance

❑ Zoonosis (influenza)

Infections: a major actual challenge

NEWS

DR Congo Ebola outbreak spreads to Mbandaka city

17 May 2018

f t w Share



Twenty-three people are known to have died

The Ebola outbreak in DR Congo has spread from the countryside into a city, prompting fears that the disease will be increasingly hard to control.

NEWS

Health

Zika outbreak: What you need to know

31 August 2016 Health

Zika virus outbreak

Share



Dejailson Arruda and his daughter Luiza, who was born with microcephaly

The World Health Organization has declared the Zika virus a global public health emergency.

Zika virus

Infections: a major actual challenge 2019/2020

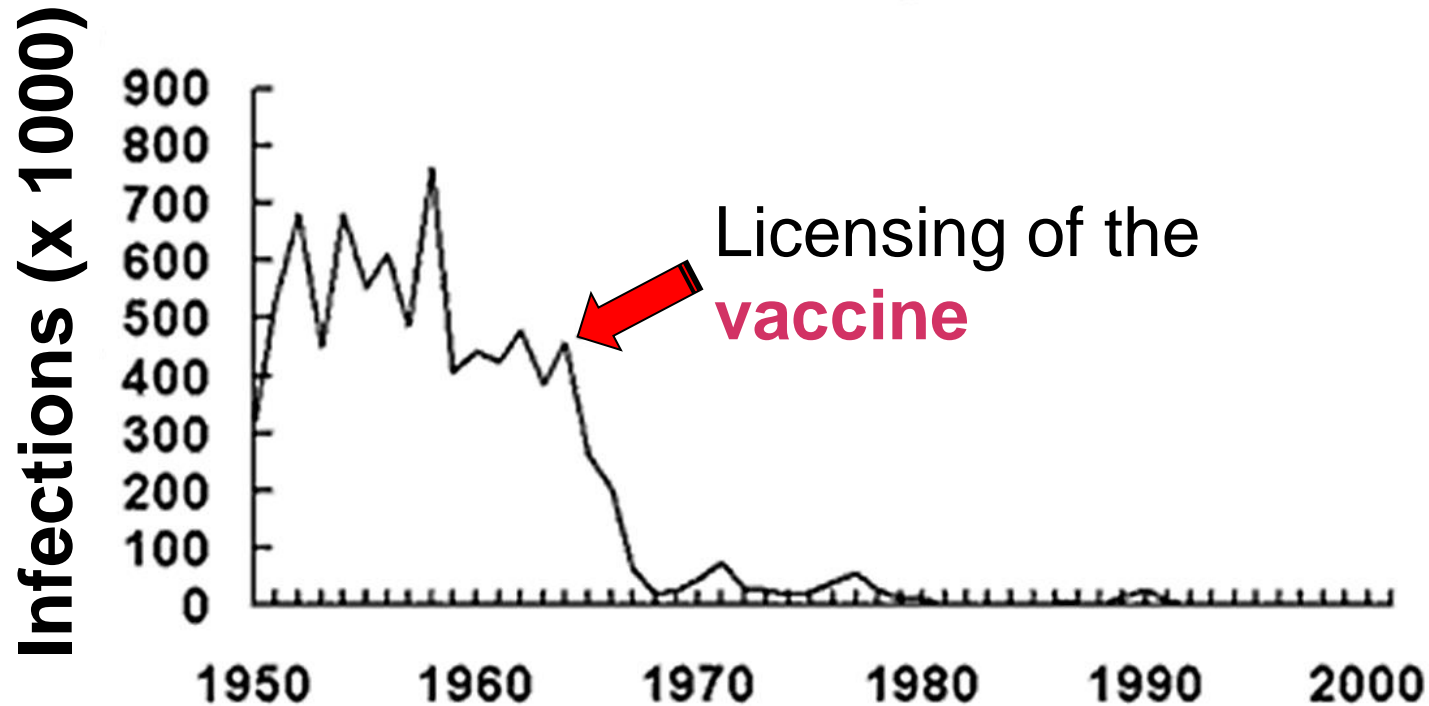


New approaches to **prevent** infectious diseases are urgently needed

- ❑ prevent disease-related suffering is **social duty**
- ❑ reduce disease-associated costs is a **pressing need**
- ❑ vaccination is the **most cost-effective** prevention tool

What are the benefits of vaccination?

Measles in the USA, 1950-2001



Source: CDC

- Measles: **2.6 million** deaths in 1980 versus **122,000** in 2012 (84% coverage)

Some numbers

- ❑ Eradication of **smallpox... measles** and **polio** realistic targets
- ❑ Maternal **pertussis** vaccination program UK: **-79% infant deaths**
- ❑ 18 years **HBV** vaccine Italy: prevalence **-99%**, **€ 580 million** saved
- ❑ **Influenza** EU: **€ 250 M saved** per year... reduction in deaths for co-morbidities:
-28% diabetics, **-50%** heart attack, **-24%** stroke in chronic lung diseases
- ❑ **HPV** UK: predicted **-86% cervical cancers** with 70% coverage

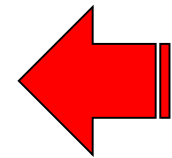
Source: Vaccines Europe – Vaccines a tool for spending SMART

Suboptimal vaccine implementation

- ❑ lack of opportunity: **competing priorities**
- ❑ **erosion** due to success of vaccines
- ❑ **public perception** (efficacy and safety)
- ❑ **socio-cultural** issues - alternative health beliefs
- ❑ hesitant (**25%**) and rejecters (**5%**)

Some factors affecting the overall efficacy of a vaccination campaign

- ❑ **intrinsic efficacy of the vaccine**
- ❑ **storage** & cold-chain
- ❑ fulfilment of vaccination **schedule** (number of doses)
- ❑ lack of **access** - economic factors
- ❑ vaccine **rejecters** & **anti-vaccine** groups



A long way from Jenner's initial efforts...



Smallpox vaccination!

Vaccine rejecters



What Led to the Nigerian Boycott of the Polio Vaccination Campaign?



UN agency declares global health emergency to stem potential resurgence of polio

WHO declares polio an international public health emergency

Published May 06, 2014 · Associated Press



Polio infected countries

- Afghanistan
- Cameroon
- Equatorial Guinea
- Ethiopia
- Iraq
- Israel
- Nigeria
- Pakistan
- Somalia
- Syria
- Source: WHO



Credits +

Global polio eradication initiative applauds WHO African region for wild polio-free certification

Support from national governments and global donors critical to the region's success against wild polio and must continue to achieve a polio-free world

25 August 2020 | News release | GENEVA

[العربية](#) [中文](#) [Français](#) [Русский](#) [Español](#)

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Polio:
> 10 years lost!!!

Media Contacts

Pro/against vaccination groups

... an ongoing very emotional debate

Never inject them.
There are **NO** safe vaccines!

Shaken Baby Syndrome
Chronic Ear Infections
Death
SIDS
Seizures
ADD
Allergies
Asthma
Autism
Diabetes

DO NOT VACCINATE!!

"It's a Smallpox world"

Why would my kids be a threat vaccinated kids, sure that vaccines work?

your eCards

Ja gem

PBS NEWS

THE SUNDAY TIMES
Revealed: MMR research scandal

ST investigation exposes scientist's 'fatal' conflict of interest

PBS NewsHour
Taking Shots

MMR a job too far

NO NEED FOR THE NEEDLE
NUMBER OF CONSCIENTIOUS OBJECTION

Greater Manchester	795
Merseyside	708
Southern Coast	660
Gold Coast	632
East North Queensland	532
Darling Downs - SW Queensland	279
West Moreton Only	356
Townsville Marjuly	274
White Water	500
Central Queensland	900
Central and NW Queensland	13
QUEENSLAND TOTAL:	4121

Source: Queensland Health

W news

Anti-Vaccination Movement

VACCINES ARE TOXIC.
PROTECT OUR CHILDREN

DANGER
CHILD VACCINE
(TOXIC WASTE)

Outside of medical exceptions, should unvaccinated children be allowed in public schools?

No 79%

Yes 21%

Sermo Physician Poll • July 2014 • 3,114 Voters • blog.sermo.com

Tells parents that risks of vaccination outweigh the benefits

Gets vaccinated before traveling abroad

Twice as many diseases protected against, **97% LESS** load on the immune system

DEADLY CHOICES

HOW THE ANTI-VACCINE MOVEMENT THREATENS US ALL

PAUL A. OFFIT, M.D.

DEADLY CHOICES

HOW THE ANTI-VACCINE MOVEMENT THREATENS US ALL

PAUL A. OFFIT, M.D.

The case for vaccines vs **The case against**

Whoooping cough

Perennially the scourge of childhood, whooping cough was a major cause of school in the United States before widespread vaccination efforts began in the 1940s.

Measles Cases and Outbreaks

644 outbreaks

23 Outbreaks

NEW ENGLAND PATRIOTS: YOU JUST WON THE SUPER BOWL! WHAT DID YOU DO NEXT?!

MMR a job too far

WHOOPIING COUGH

Wall of Shame for Pro-Vax Claims

Whoooping cough

Perennially the scourge of childhood, whooping cough was a major cause of school in the United States before widespread vaccination efforts began in the 1940s.

And the evil Mr. Vaccine played his role of never getting pulled or stung even again, during the children's escape to the town of Noddy's Hollow.

Wall of Shame for Pro-Vax Claims

Comparison of 20th Century Annual Morbidity and Current Morbidity: Vaccine-Preventable Diseases

Disease	20th Century Annual Morbidity	2008 (est.)	Percent Reduction
Diphtheria	45,152	0	100%
Tetanus	175,385	0	100%
Measles	52,392	0	100%
Mumps	112,390	4,084	96%
Pertussis	147,271	15,632	89%
Polio (paralytic)	162,918	0	100%
Rubella	42,740	11	99%
Chicagoland Rubella Syndrome	83	1	99%
Fetuses	1,241	41	96%
Neurological Infections	26,890	267	98%

Number of Preventable Diseases

118010

From June 3, 2007 To June 22, 2013

Number of Preventable Deaths

1170

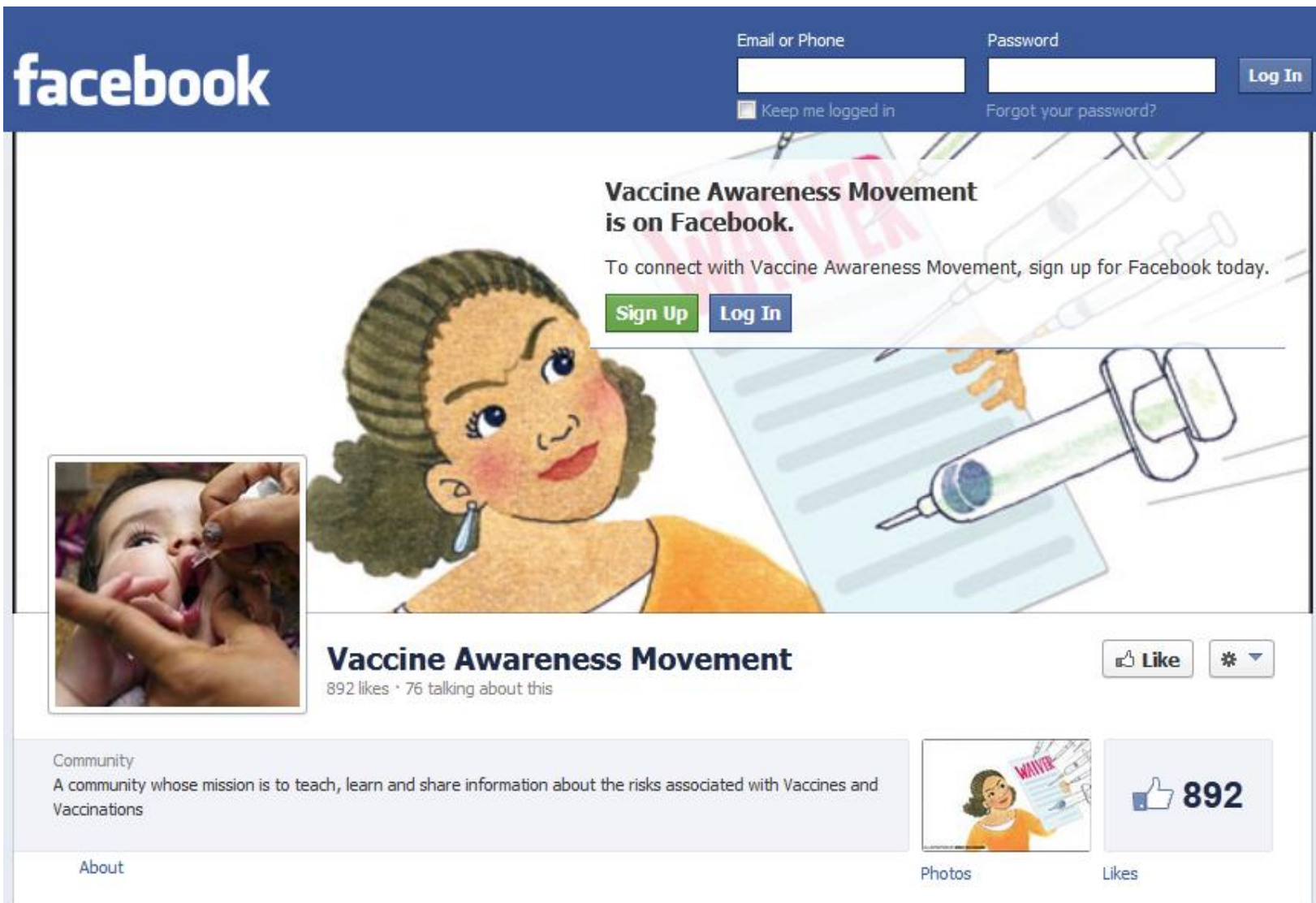
From June 3, 2007 To June 22, 2013

Number of Adverse Diagnoses Substantially Linked to Vaccinations

0

From June 3, 2007 To June 22, 2013

Anti-Vaccination campaigns



The image shows a screenshot of a Facebook page for the "Vaccine Awareness Movement". At the top, the Facebook logo is on the left, and the login section is on the right, featuring fields for "Email or Phone" and "Password", a "Log In" button, and checkboxes for "Keep me logged in" and "Forgot your password?". The main content area has a blue header with the text "Vaccine Awareness Movement is on Facebook." and a sub-header "To connect with Vaccine Awareness Movement, sign up for Facebook today." Below this are "Sign Up" and "Log In" buttons. The background features a cartoon illustration of a woman with curly hair and a yellow top, with a syringe and a document labeled "WAVE" overlaid. On the left, there is a small photo of a baby being vaccinated. Below the main header, the page name "Vaccine Awareness Movement" is displayed with "892 likes · 76 talking about this". To the right are "Like" and "Settings" buttons. Below this, there is a "Community" section with the text "A community whose mission is to teach, learn and share information about the risks associated with Vaccines and Vaccinations". At the bottom, there are "About", "Photos", and "Likes" (showing 892 likes) buttons.

facebook

Email or Phone

Password

Log In



Keep me logged in

[Forgot your password?](#)

Vaccine Awareness Movement is on Facebook.

To connect with Vaccine Awareness Movement, sign up for Facebook today.

[Sign Up](#) [Log In](#)



Vaccine Awareness Movement

892 likes · 76 talking about this

Like

Community

A community whose mission is to teach, learn and share information about the risks associated with Vaccines and Vaccinations

About

Photos

Likes **892**

Vaccines & Autism

The way to hell is paved with good intentions...

- ❑ **Andrew Wakefield – Lancet 1998**
 - No control group, relied on people memories, no statistics, ethical issues
 - Lancet refute the paper: “falsified facts” (2004)
- ❑ **No links established (studies analyzing over 25,000,000 vaccinees)**
- ❑ **25% American parents believe some vaccines cause autism...**

Source: *Vaccines Europe – Vaccines a tool for spending SMART*

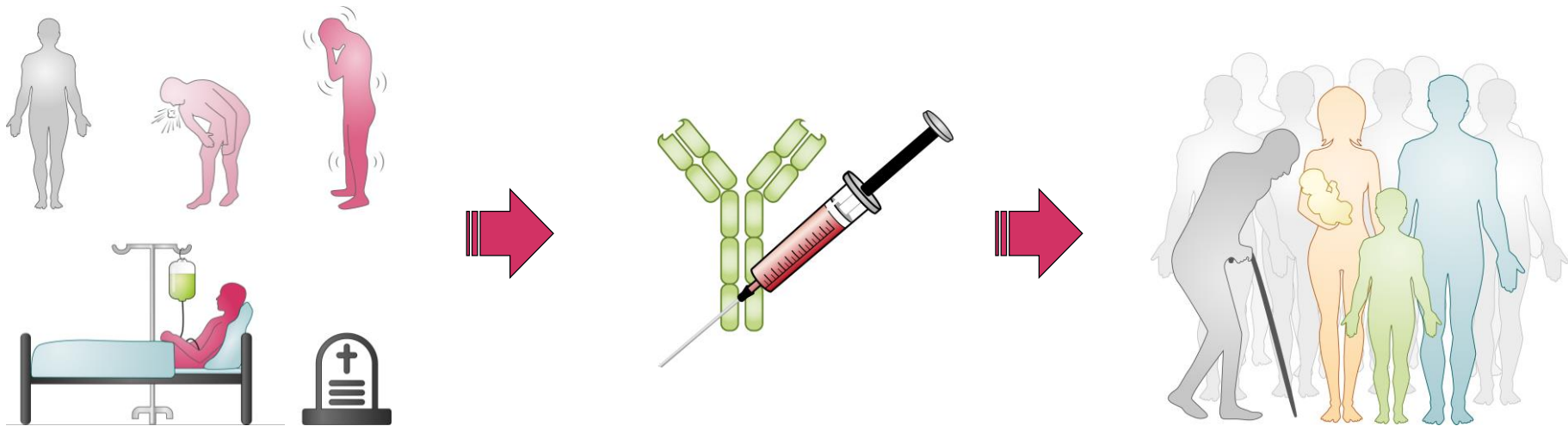
Current roadblock:

Many diseases for which vaccines are **not available**

or the available vaccines are **suboptimal...**

Main bottleneck...

... we are not all equal



The ideal vaccine

- ❑ **Single** dose
- ❑ **Effective** in all... even newborns, elderly, patients with co-morbidities
- ❑ **100% safe** - no side effects
- ❑ **Lifelong** protection
- ❑ **Cheap...**



Don Urban

Vaccinology – Quo vadis?

- ❑ Enhanced antigen selection – increased **safety/efficacy**
- ❑ Improved **acceptance** – needle free vaccines
- ❑ **Individualized** interventions – only those who benefit
- ❑ New diagnostics - efficient **prediction** of vaccine efficacy

How knowledge/technologies can help us to do better?

Classical vaccine development (one by one)

Immune Responses
in Convalescents

Pathogenesis
Studies



Target selection



Production/formulation



Immunogenicity



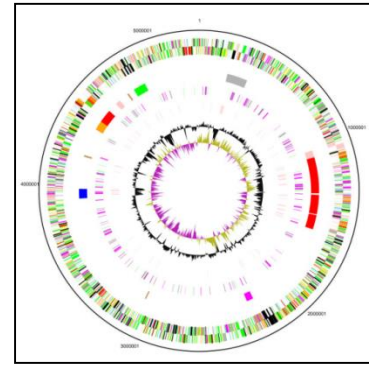
Efficacy

Many weakness
&
time consuming...

One step at the time



Reverse vaccinology



Genome

In vivo Gene Expression:
proteomics/transcriptomics



"In silico"
Antigen Selection

Conservation

Production/formulation

HTP Screening - immunogenicity/efficacy/safety

Many primary targets & rapid!!!!



Jump!!!!

Reverse vaccinology: a success story

REPORTS

Identification of Vaccine Candidates Against Serogroup B Meningococcus by Whole-Genome Sequencing

Mariagrazia Pizza,^{1*} Vincenzo Scarlato,^{1*} Vega Massignani,¹
Marzia Monica Giuliani,¹ Beatrice Aricò,¹ Maurizio Comanducci,¹
Gary T. Jennings,¹ Lucia Baldi,¹ Erika Bartolini,¹
Barbara Capecchi,¹ Cesira L. Galeotti,¹ Enrico Luzzi,¹
Roberto Manetti,¹ Elisa Marchetti,¹ Marirosa Mora,¹
Sandra Nuti,¹ Giulio Ratti,¹ Laura Santini,¹ Silvana Savino,¹
Maria Scarselli,¹ Elisa Storni,¹ Peijun Zuo,¹ Michael Broecker,²
Erika Hundt,² Bernard Knapp,² Eric Blair,³ Tanya Mason,³
Hervé Tettelin,³ Derek W. Hood,⁴ Alex C. Jeffries,⁴
Nigel J. Saunders,⁴ Dan M. Granoff,⁵ J. Craig Venter,³
E. Richard Moxon,⁴ Guido Grandi,¹ Rino Rappuoli^{1†}

10 MARCH 2000 VOL 287 SCIENCE www.sciencemag.org



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Novartis Global Communications
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<http://www.novartis.com>

MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG

Novartis Bexsero[®] vaccine approved by FDA for the prevention of meningitis B, the leading cause of bacterial meningitis in the US



News & Events

Home > News & Events > Newsroom > Press Announcements

FDA News Release

FDA approves a second vaccine to prevent serogroup B meningococcal disease

For Immediate Release

January 23, 2015

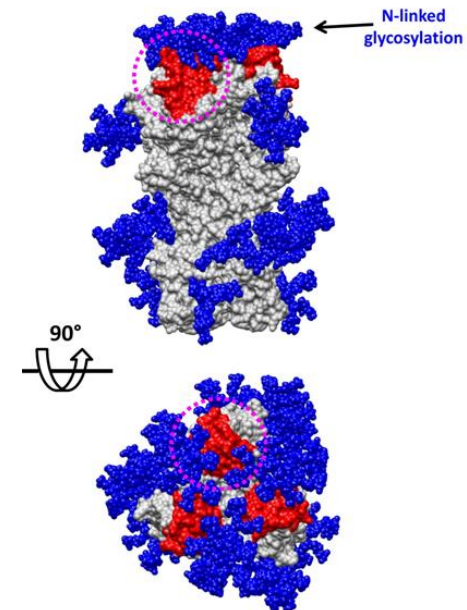


Structural Vaccinology

- ❑ Antigen atomic-level **structural** information
- ❑ Functional properties structural **domains**
- ❑ **Rational design** optimized immunogens

Influenza virus

- ❑ **Segmented** genome
- ❑ Prone to **mutations**
- ❑ **Hemagglutinin** mediates virion fusion - major target
- ❑ **Many** serotypes (e.g. H1N1, H3N2)
- ❑ Immunity **serotype-specific**

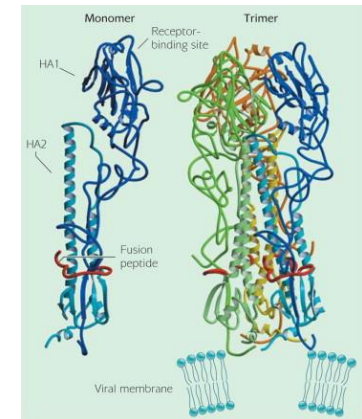


RESEARCH ARTICLE

VACCINES

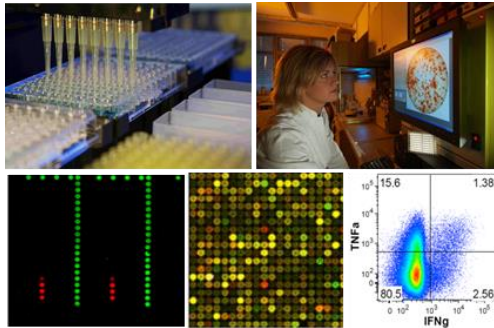
A stable trimeric influenza hemagglutinin stem as a broadly protective immunogen

Antonietta Impagliazzo,^{1*}† Fin Milder,¹‡§ Harmjan Kuipers,¹‡§ Michelle V. Wagner,²‡||
Xueyong Zhu,³‡ Ryan M. B. Hoffman,³‡ Ruud van Meersbergen,¹§ Jeroen Huizingh,¹§
Patrick Wanningen,¹§ Johan Verspuij,¹§ Martijn de Man,¹§ Zhaoqing Ding,²||
Adrian Apetri,¹† Başak Kükrer,¹† Eveline Sneekes-Vriese,¹ Danuta Tomkiewicz,¹†
Nick S. Laursen,³¶ Peter S. Lee,³ Anna Zakrzewska,¹§ Liesbeth Dekking,¹§
Jeroen Tolboom,¹§ Lisanne Tettero,¹§ Sander van Meerten,¹§ Wenli Yu,³
Wouter Koudstaal,¹† Jaap Goudsmit,¹† Andrew B. Ward,³ Wim Meijberg,¹§
Ian A. Wilson,^{3*} Katarina Radošević¹#



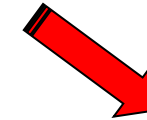
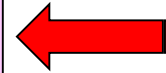
SCIENCE sciencemag.org

Vaccine Technologies – our activities



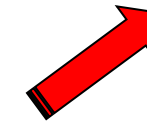
Biomarkers

Human response to vaccination



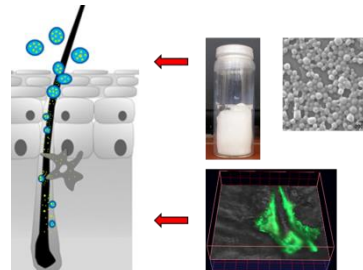
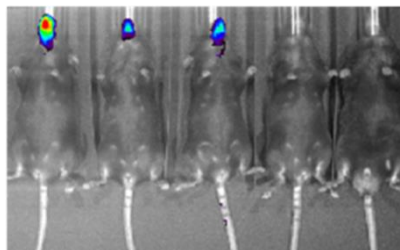
Adjuvants

**Vaccine candidates
(Influenza & Hepatitis)**



Mechanisms of action & effector functions

**Combination with other technologies
(Nanocarriers/Vectors)**



Challenges in vaccinology

- ❑ Technologies to stimulate the **“right” type** of (protective) response
- ❑ Vaccines that protect **all subpopulation groups**
- ❑ Needle-free strategies to increase vaccination **acceptance**

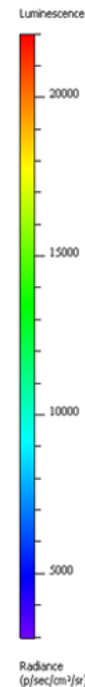
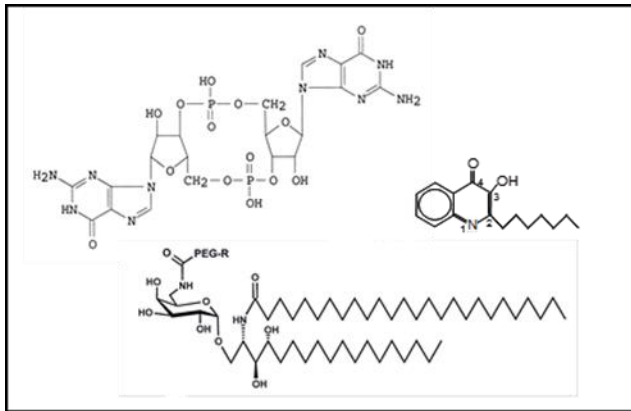
How to stimulate what is needed?

Using adjuvants

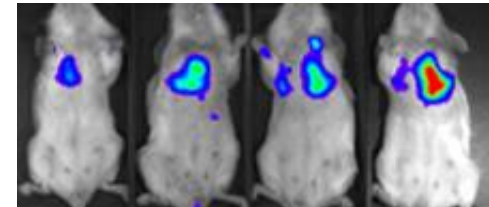
- ❑ Improve the **strength** of the immune response
- ❑ Enable to **modulate** the quality of elicited response
- ❑ Antigen **sparing**, **speed** responses, improved **memory**
- Only a **few adjuvants** licensed for human use
- Virtual **monopoly** by the industry

New adjuvants with well-defined molecular targets

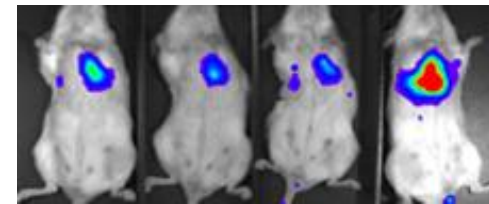
- Active by parenteral and **mucosal** routes
- Modulate humoral and **cellular** responses



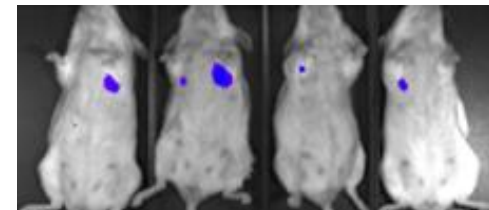
Control



Vaccine



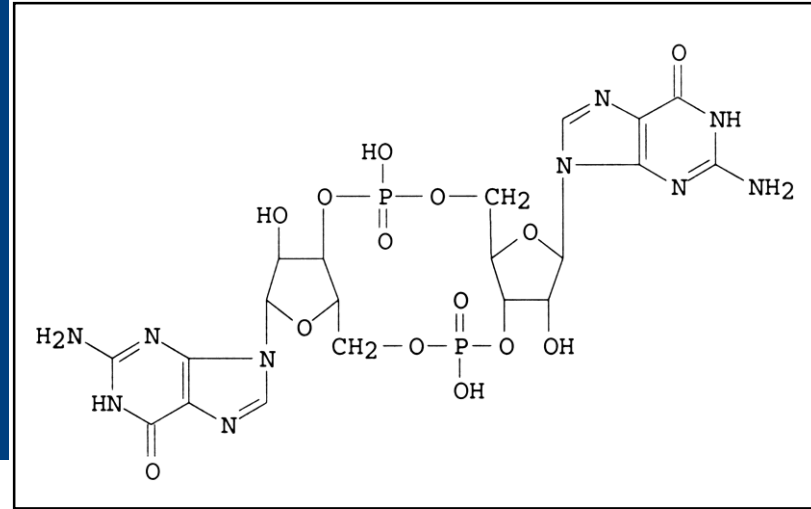
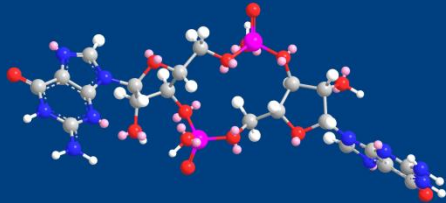
Vaccine +
adjuvant



Rueckert *et al.* (2017) **FASEB J**
Škrnjug *et al.* (2014) **PLoS One**
Riese *et al.* (2015) **Eur J Immunol**
Ebensen *et al.* (2017) **Front Immunol**

Lirussi *et al.* (2017) **eBioMedicine**
Sanchez Alberti *et al.* (2017) **NPJ Vaccines**
Schulze *et al.* (2017) **Nanomedicine**
Volckmar *et al.* (2017) **Sci Rep**

CDN – new promising immune modulators



- ❑ **Known molecular target** - via *STING-TBK1* activation
- ❑ **Activation key immune cells** - DC, M Φ & NK
- ❑ **All effector functions** (antibodies, Th & CTL)
- ❑ **Active in poor responders** (old, young, sick)

Ebensen *et al.* **Vaccine** 2007 and 2011;
Ebensen *et al.* **Clin Vaccine Immunol** 2007;
Madhun *et al.* **Vaccine** 2011;
Pedersen *et al.* **PLoS One** 2011;
Sanchez *et al.* **PLoS One** 2014;
Škrnjug, Rueckert *et al.* **PLoS One** 2014;
Škrnjug *et al.* **PLoS One** 2014;
Rueckert, Rand *et al.* **FASEB J** 2017;
Lirussi *et al.* **EBioMedicine** 2017

T. Ebensen



K. Schulze



P. Riese



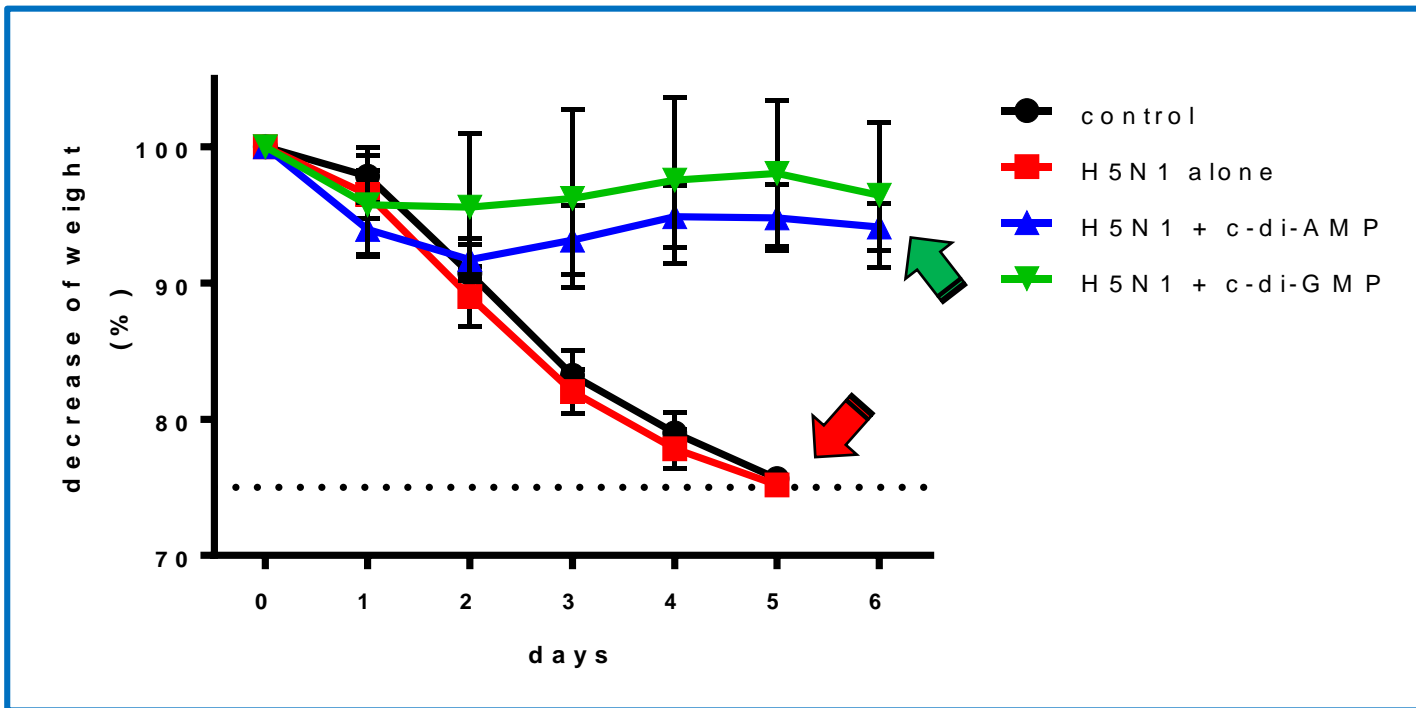
C. Rückert



I. Škrnjug



Sublingual vaccination against **influenza H5N1** with virosome-based formulations



Similar results in models for **senescence**, **metabolic dysfunction** and **neonatal** vaccination!!!

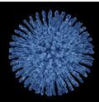
T. Ebersen



K. Schulze



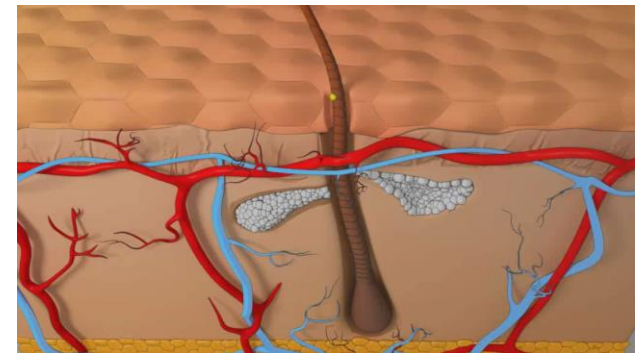
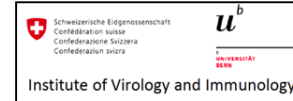
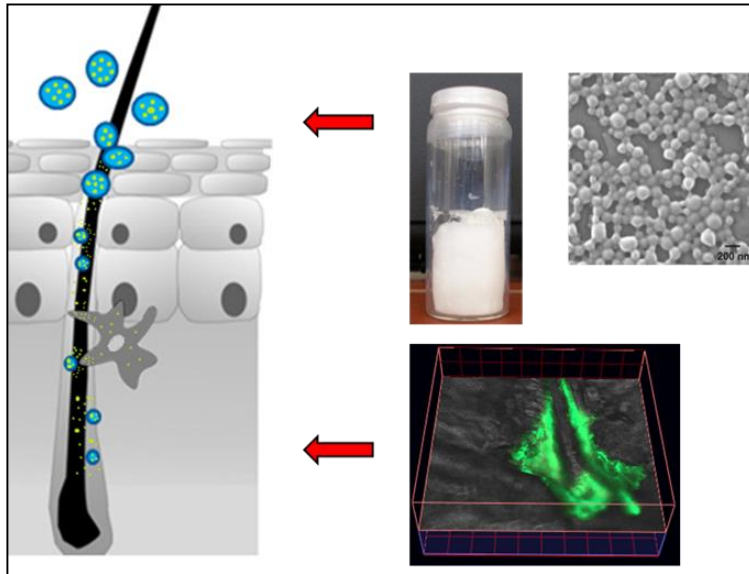
PanFluVac





Novel nanocarriers for needle-free vaccines

- ❑ Mucosal and trans-follicular delivery
- ❑ Conventional antigens and RNAs



Mittal *et al.* (2013) **Vaccine**
 Mittal *et al.* (2014) **Nanomedicine**
 Mittal *et al.* (2015) **J Control Rel**
 Démoulin *et al.* (2016) **Nanomedicine**
 Démoulin *et al.* (2017) **J Control Rel**
 Schulze *et al.* (2017) **Nanomedicine**

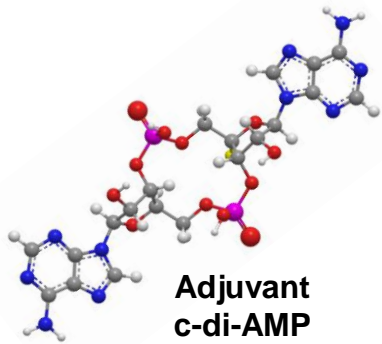


C. Guzmán



C.-M. Lehr

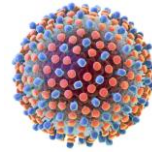
Clinical development – coming 1-3 years



Phase I-II



HCV



HELMHOLTZ-ALBERTA
INITIATIVE

HelmholtzZentrum münchen
German Research Center for Environmental Health

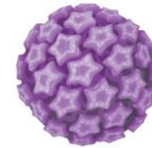
HBV



TherVacB DZIF
German Center
for Infection Research

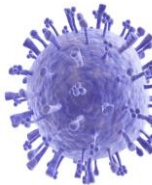


HPV



dkfz. GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

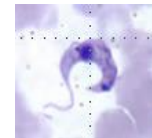
Flu



INCENTIVE - Indo-European
Consortium for Next Generation
Influenza Vaccine Innovation



Chagas

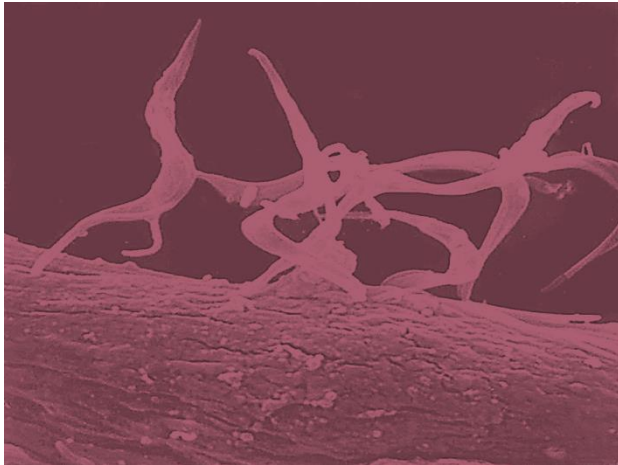


cruziva



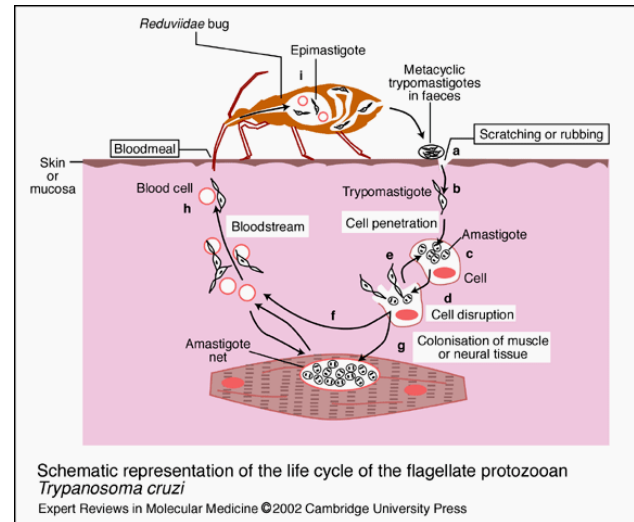
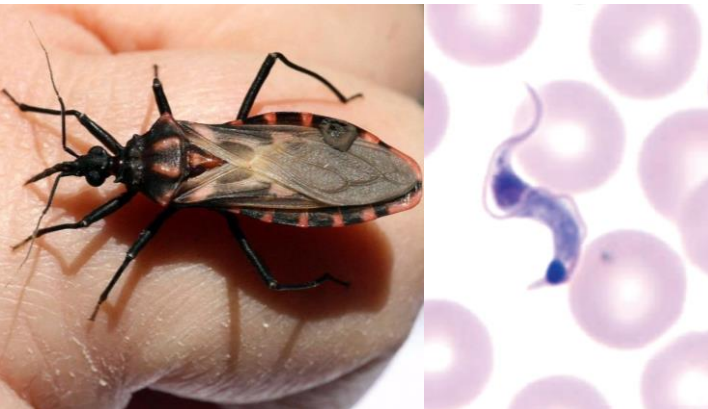
HUMAN
VACCINES
PROJECT

Case study - Chagas disease



Trypanosoma cruzi

- ❑ Classical transmission
- ❑ Organ transplantation
- ❑ Transfusion
- ❑ Perinatal

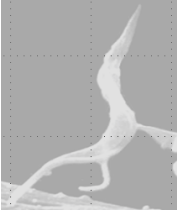


Chagas disease... a global problem



21 **endemic** and 19 **non-endemic** countries

Case study: Chagas disease

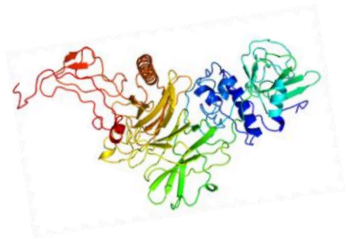


- ❑ **~10 million** infected individuals who will progress to chronicity
- ❑ **30-40%** chronically infected develop **life-threatening** clinical forms
- ❑ Disability adjusted life-year (DALYs): **252,000/year**
- ❑ Huge financial burden (annual **costs > EUR 6 billion**)
- ❑ Drugs only active in **early infection**, **lengthy** and **highly toxic**
- ❑ **No vaccine** available

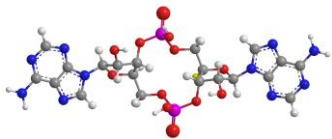
CRUZIVAX Project

Development an **intranasal** needle-free vaccine against *T. cruzi* infection

CRUZIVAX™



- ❑ Chimeric trivalent synthetic antigen - Traspain – IPR (N-CZ+iTS+C-ASP2)



- ❑ HZI's new adjuvant c-di-AMP - IPR



CRUZIVAX Project

C.A. Guzmán



M. Carrondo



C.A. Guzmán



G. Santos-Gomes



I. Novák



L. Grode



E. Sicuri



Development of vaccine components

GLP & GMP production of the vaccine components

Preclinical validation of the vaccine in different animal models

Toxicology

Preparation and implementation of a clinical phase I trial

Health economics studies and demand assessment



E. Malchiodi



A. Cordes



E. Malchiodi



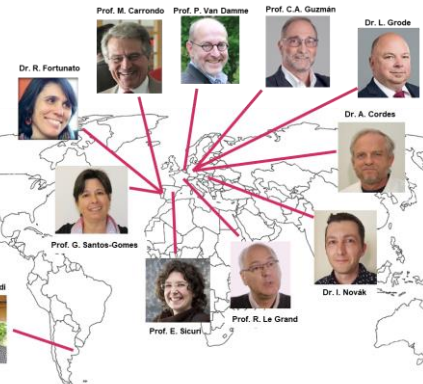
R. Le Grand



C.A. Guzmán



P. Van Damme

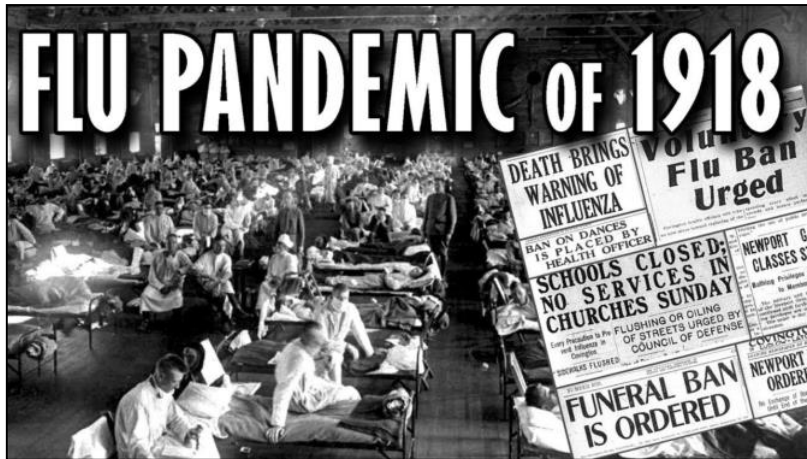


Responsiveness to vaccines

- we are not all equal -

What are the underlying mechanisms and potential biomarkers for poor responsiveness?

Influenza is a major threat to human health

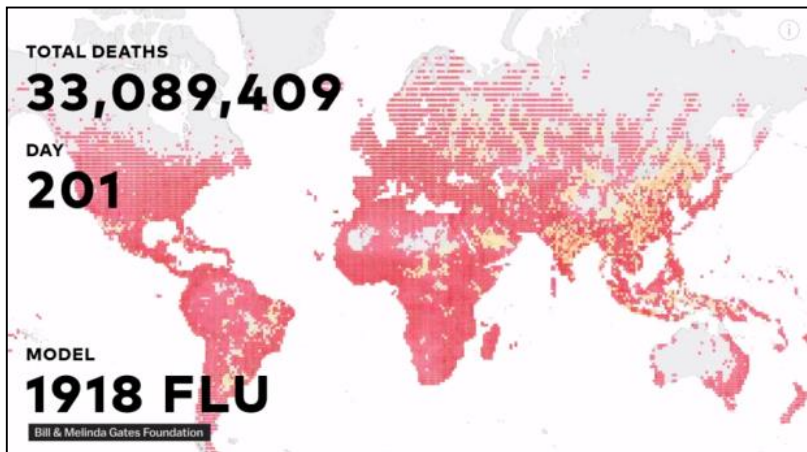


❑ Deaths (~ 650,000)

❑ Influenza-related **medical visits**

❑ Influenza-related **work absences**

❑ Different **high risk groups**

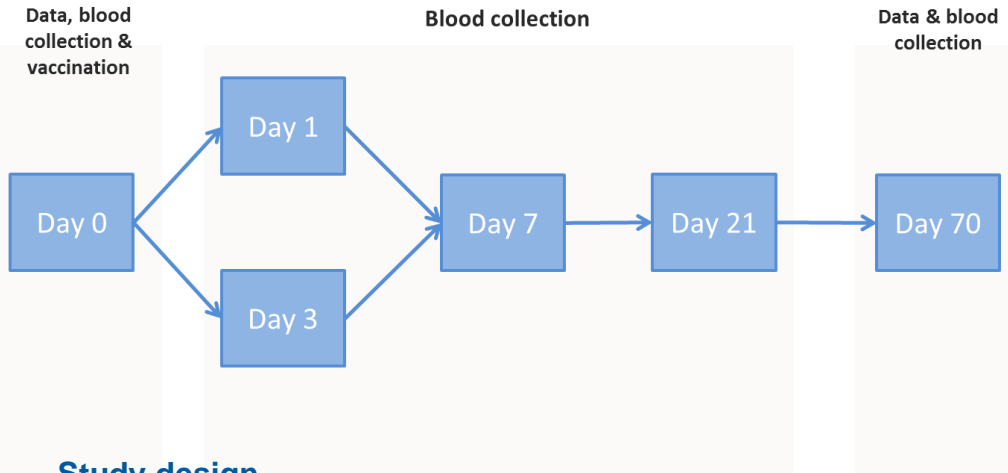


Efficacy influenza vaccines:

○ <65 years old 60% 😊

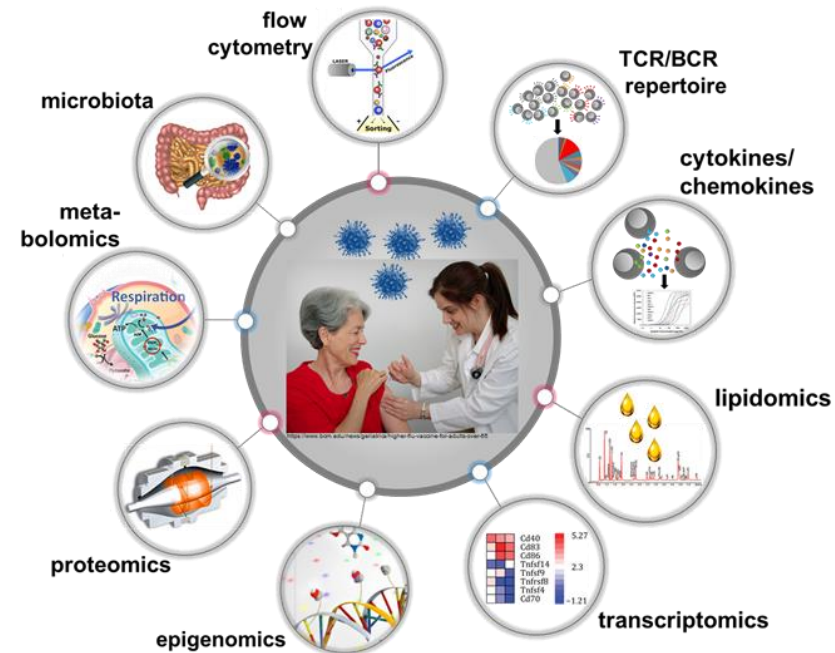
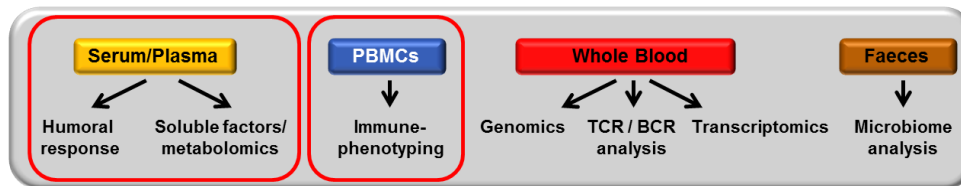
○ >65 years old 19% 😞

Prospective cohort over an influenza season - a Systems Vaccinology approach based on 2 studies -



Study design

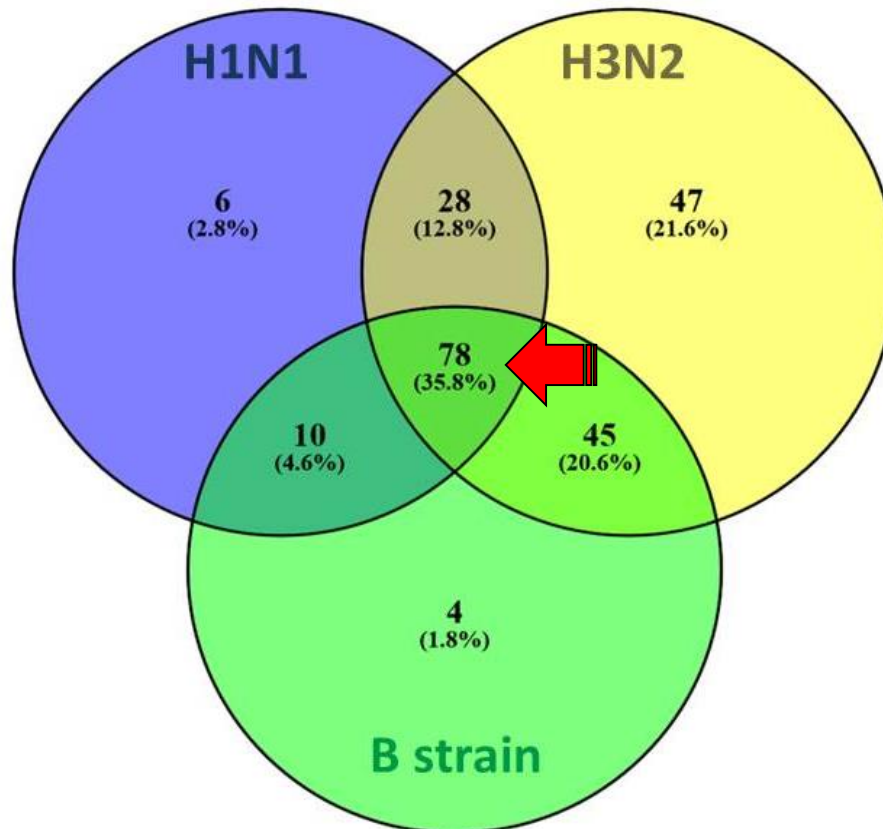
- Volunteers ≥ 65 years of age (n=234)
- Vaccine: TIV Fluad® (seasons 2014/15 & 2015/16)
- Sample collection: day 0, 1/3, 7, 21 and 70



Responsiveness to influenza vaccination in the elderly

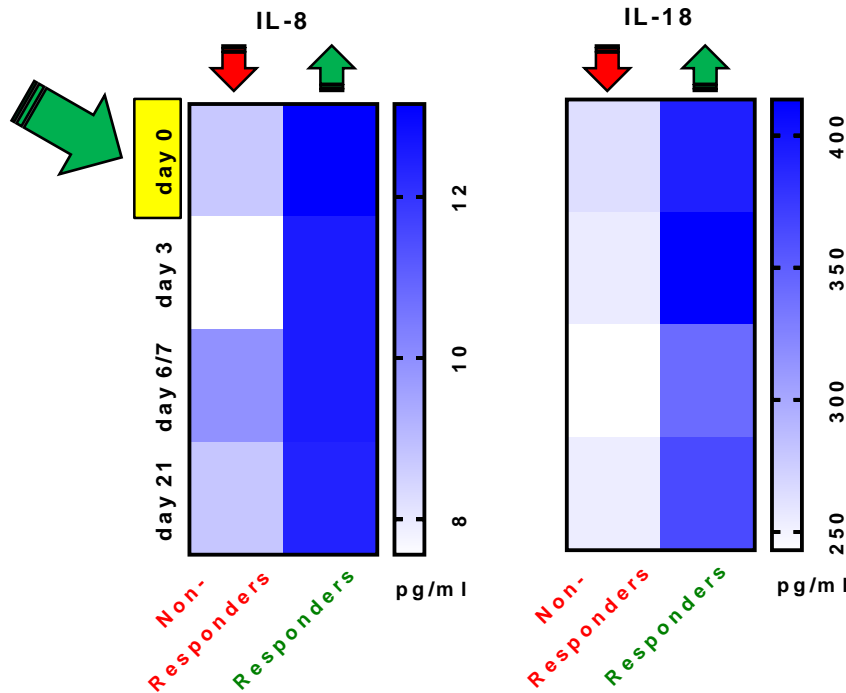


Responders



32 plasma proteins differ globally between responders and non-responders

IL-8 & IL-18 levels correlate with responsiveness



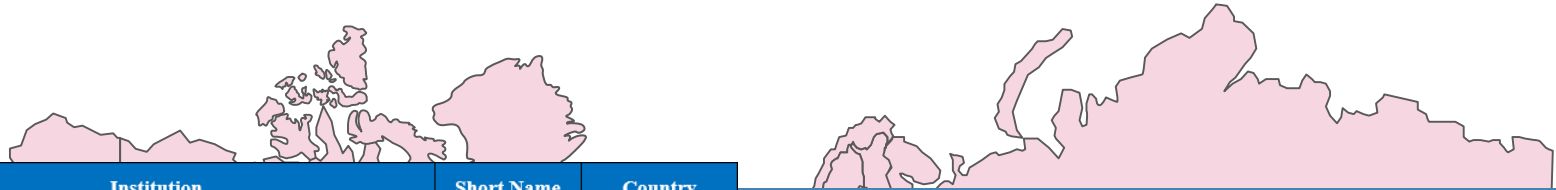
Area under the ROC curve 0.86 (on day 0)



F. Pessler

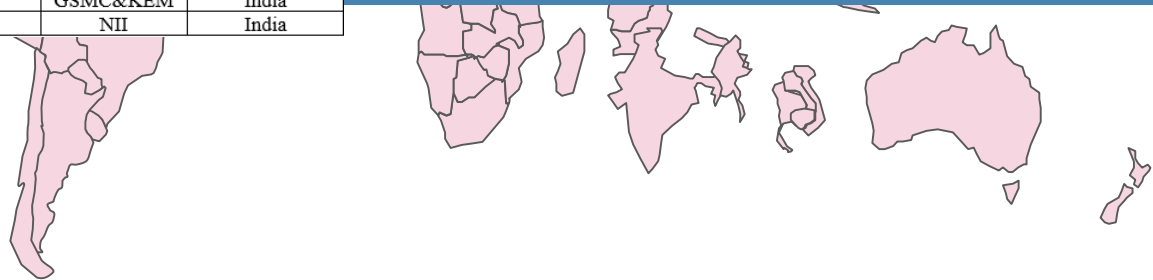
Indo-European Consortium for Next Generation Influenza Vaccine Innovation –

INCENTIVE - ~ € 20 million



Part Nr.	Institution	Short Name	Country
1	Helmholtz-Zentrum fuer Infektionsforschung	HZI	Germany
2	Public Health Foundation of India	PHFI	India
3	Translational Health Science and Technology Institute, India	THSTI	India
4	Université Libre de Bruxelles	ULB	Belgium
5	University of Bergen, Norway	UiB	Norway
6	University of Oslo, Norway	UiO	Norway
7	Universiteit Antwerpen	UA	Belgium
8	Academisch Ziekenhuis Leiden	LUMC	the Netherlands
9	Institut Pasteur	IP	France
10	ASA Spezialenzyme GmbH	ASA	Germany
11	Fundacion Privada Instituto de Salud Global Barcelona	ISGlobal	Spain
12	Bioaster Fondation de Cooperation Scientifique	Bioaster	France
13	University of Georgia Research Foundation, Inc	UGARF	United States
14	Stichting Human Vaccines Project Europe	HVP Stichting	the Netherlands
15	EuroVacc Foundation	EVF	Switzerland
16	Human Vaccine Project, Inc	HVP Inc	United States
17	Indian Institute of Technology Madras	IITM	India
18	Seth GS Medical College & KEM Hospital, Mumbai	GSMC&KEM	India
19	National Institute of Immunology	NII	India

A partnership of 19 institutions from Europe, India and the US, with leading scientists in the fields of influenza, immunology, vaccinology, clinical science, biostatistics and social-economics.



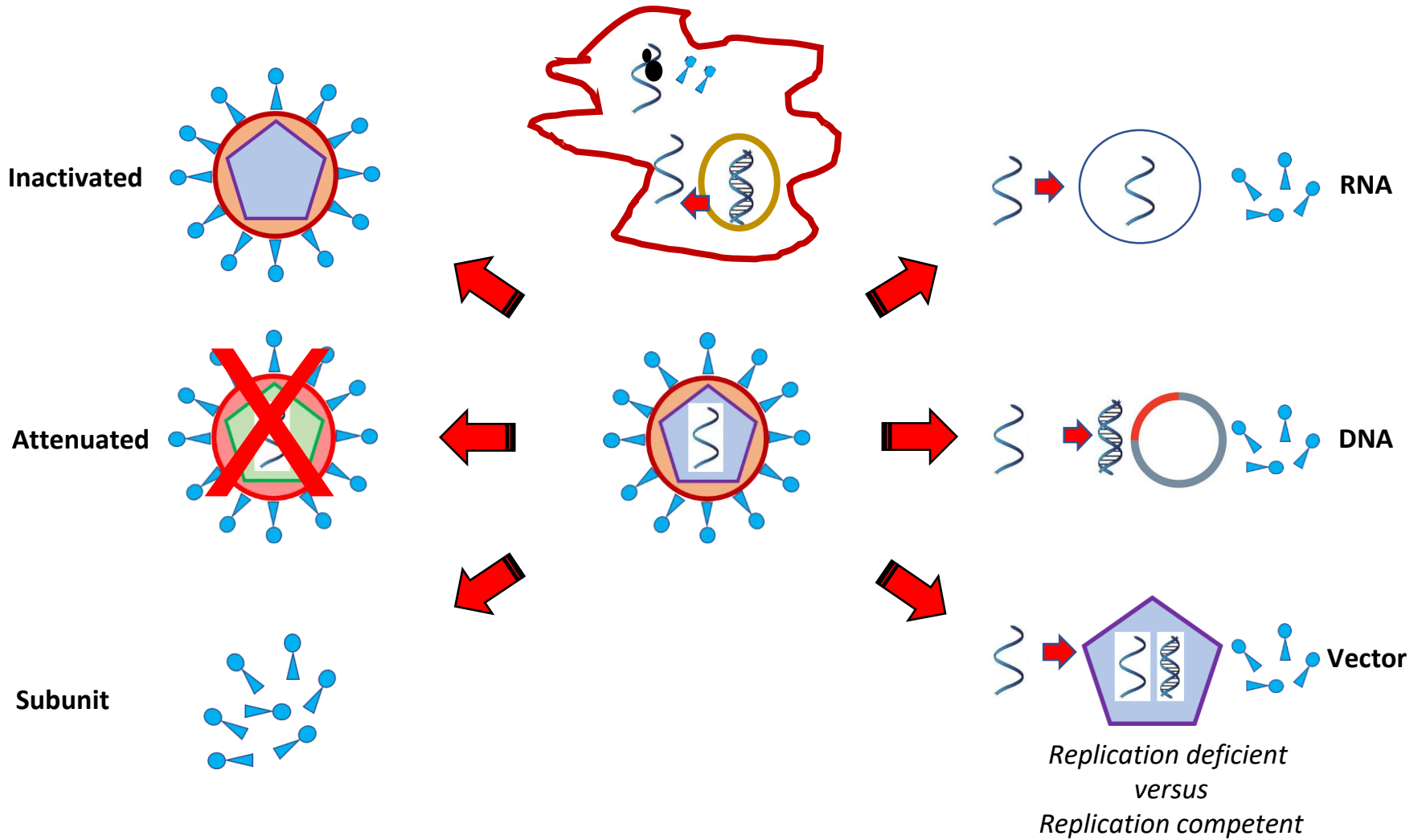
Contact:

carlos.guzman@helmholtz-hzi.de

What offers the future in terms of COVID-19 vaccines?

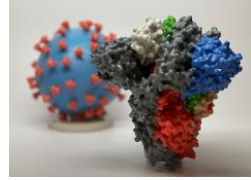


Types of vaccines



Landscape COVID-19 candidate vaccines

19 October 2020

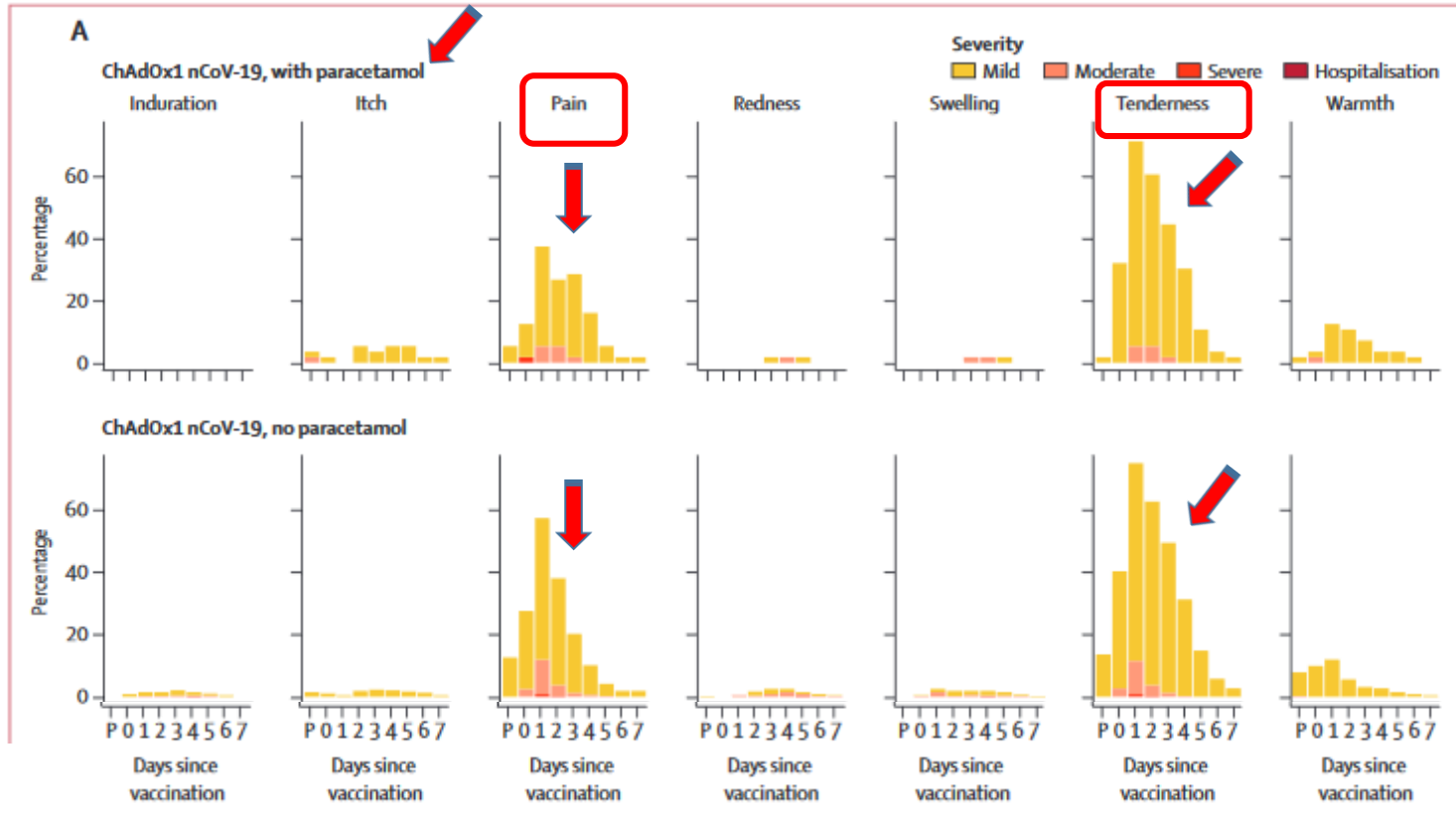


- ❑ 44 vaccine candidates in clinical evaluation
- ❑ Phase 3 (10), phase 2/2b (2), phase 1/2 (11), phase 1 (21)... 2 rolling review
- ❑ Technologies: protein 16 (1 trimer, 1 dimer RBD, 1 RBD, VLP 2), virus inactivated 7, NR adenoviruses 7 (2 simian), RNA 6, DNA 4, R measles 1, R VSV 1, R Flu 1, NR MVA 1
- ❑ 37 im, 2 id, 1 sc, 1 oral, 1 im/mucosal
- ❑ Adjuvants: GSK, MF59, CG, Matrix M, Advax, etc.
- ❑ Phase 3: Oxford/Astrazeneca (Ad), CanSino Biological Inc. Inc./Beijing Institute of Biotechnology (Ad), Gamaleya Research Institute (Ad), Janssen (Ad), Sinovac (inact), Wuhan Institute of Biological Products/Sinopharm (inact), Beijing Institute of Biological Products/Sinopharm (inact), BioNTech/Fosun Pharma/Pfizer (RNA), Moderna/NIAID (RNA), Novavax (Prot)

154 vaccine candidates in preclinical evaluation



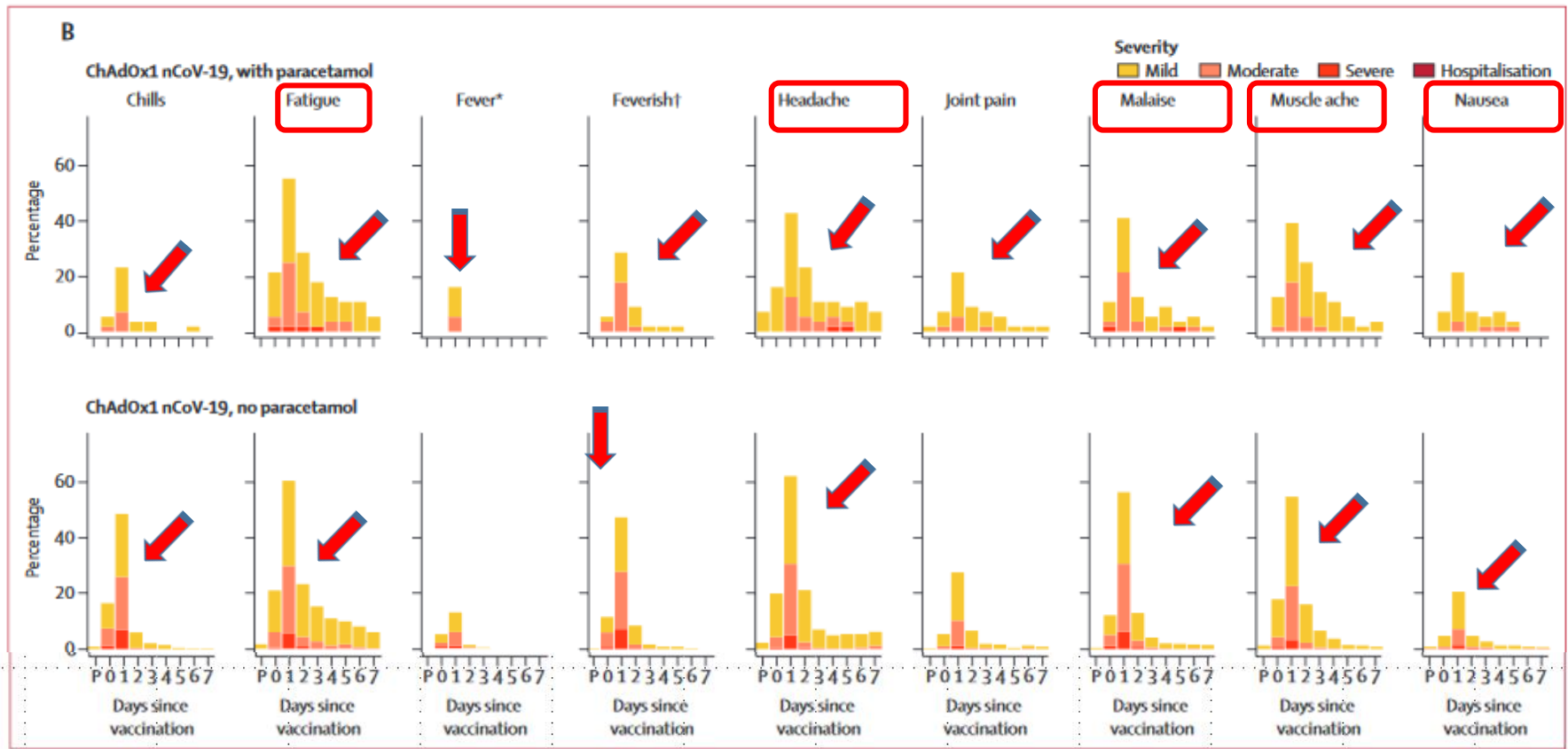
Oxford/AstraZeneca ChAdOx1 (AZD1222) nCoV-19 (5x10¹⁰) - local effects -



www.thelancet.com Published online July 20, 2020
[https://doi.org/10.1016/S0140-6736\(20\)31604-4](https://doi.org/10.1016/S0140-6736(20)31604-4)

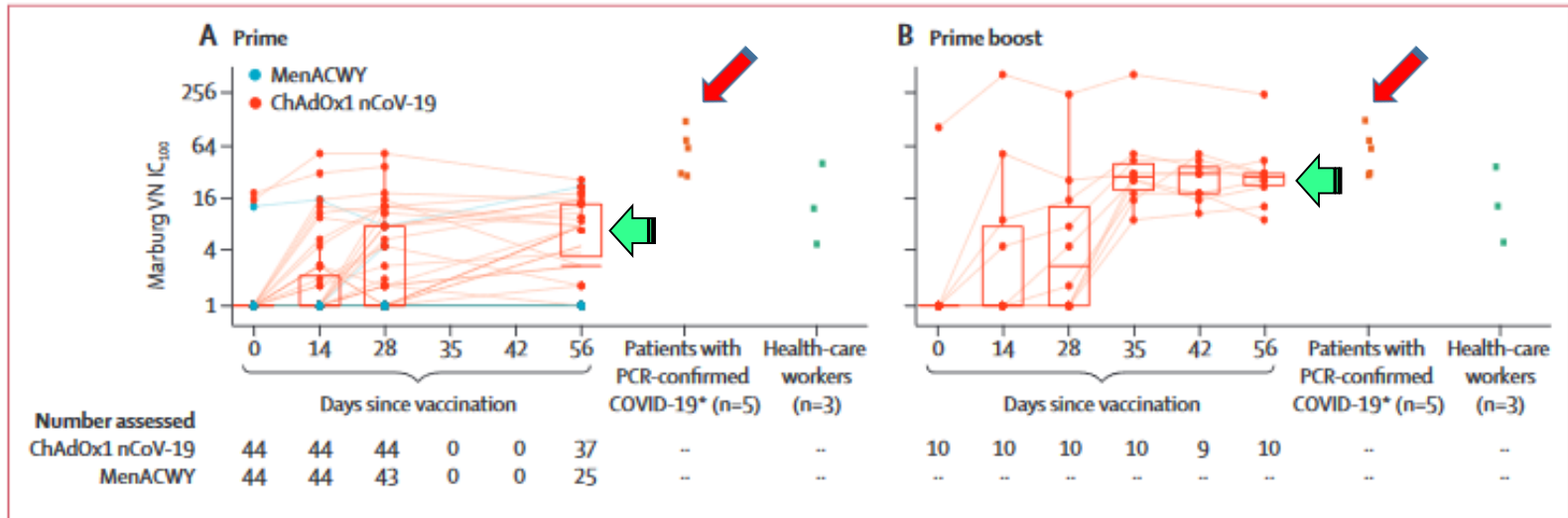


Oxford/AstraZeneca ChAdOx1 nCoV-19 - systemic effects -





Oxford/AstraZeneca ChAdOx1 nCoV-19 - Immunogenicity -



Not wowwww, but large study ~ 1000!!

- ❑ Temporary paused in July 2020 due to 1 SAE/neurological symptoms: continue after determining that it was a **MS**
- ❑ Temporary paused (still in USA) due to SAE (09.20): **transverse myelitis**
- ❑ **Johnson & Johnson** - Adeno26 paused (10.20) due to **unexpected illness**



rAd26 & rAd5 vector-based prime-boost COVID-19 vaccine phase 1/2 (Gamaleya, Russia)

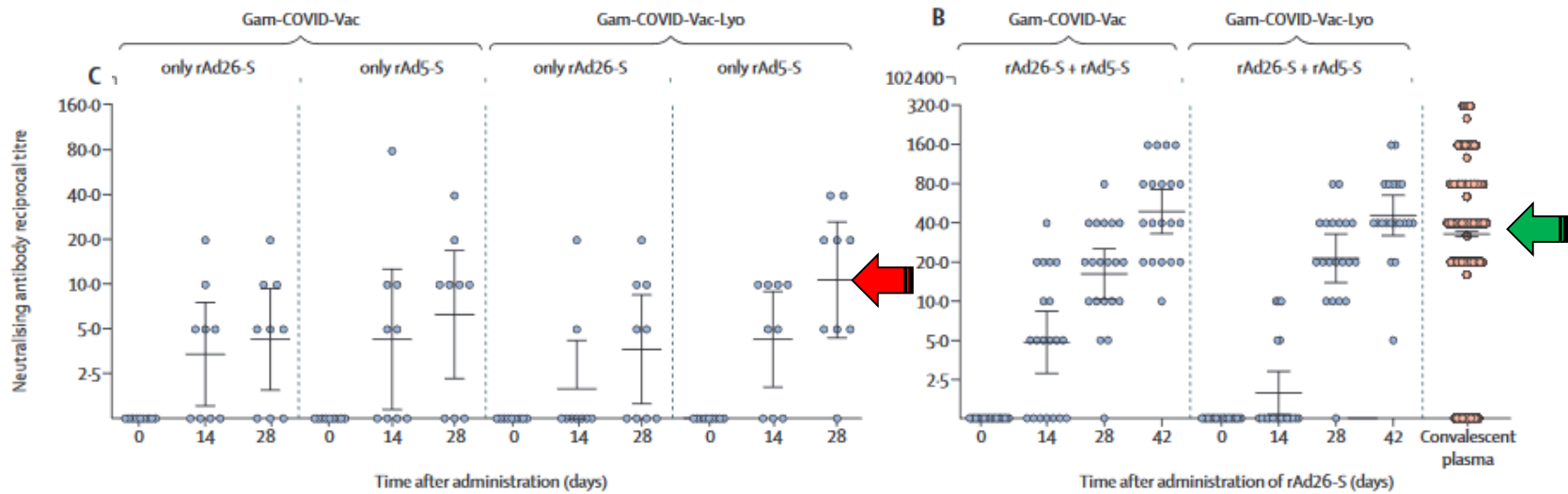
76 (**38 + 38**); 9 rAd26-S, 9 rAd5-S (phase 1), 20 rAd26-S/rAd5-S (phase 2)

Pain [58%], hyperthermia [50%], headache [42%], asthenia [28%],
and muscle and joint pain [24%]

Neutralizing antibodies 49 (frozen
formulation) & 45 lyophilized formulation



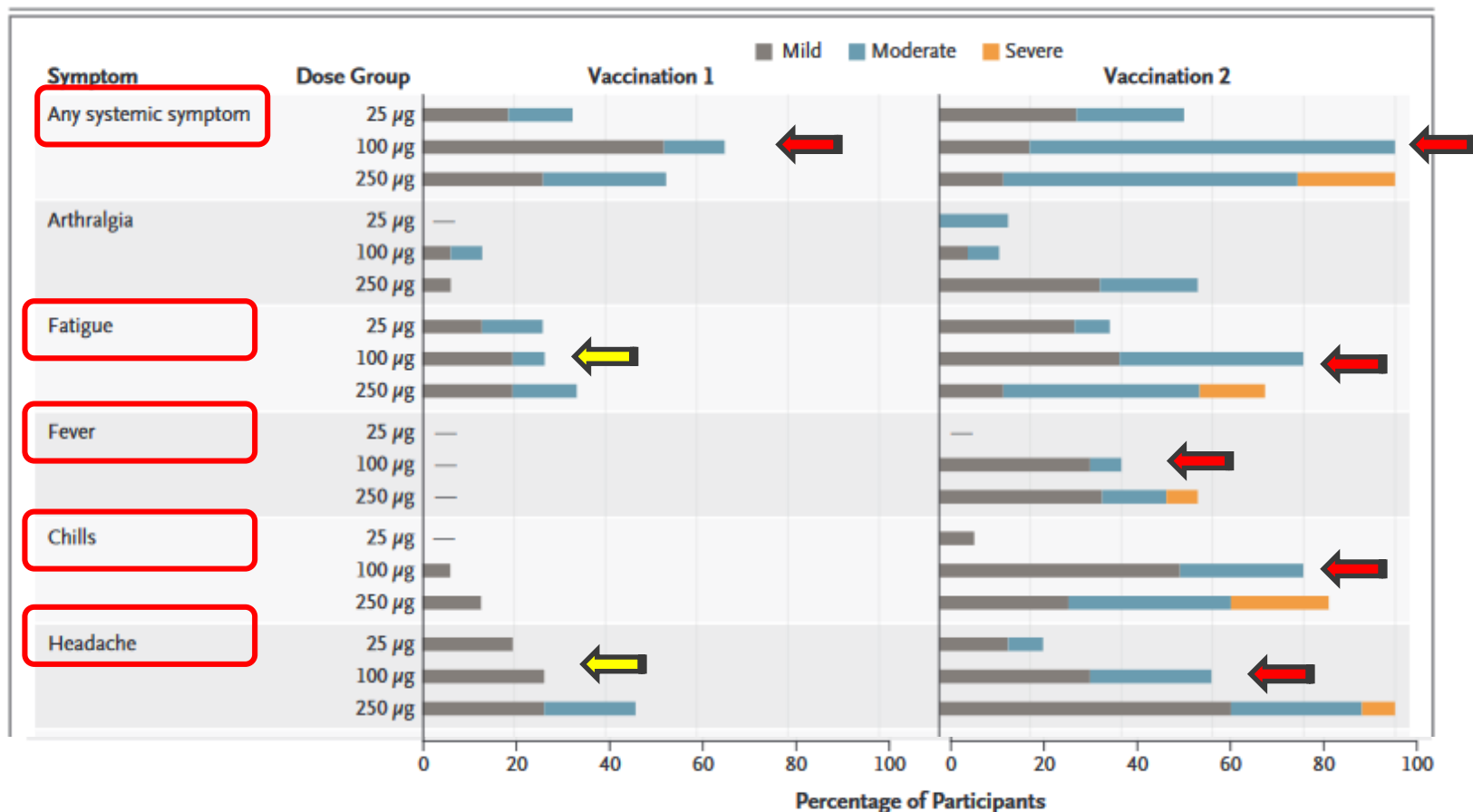
rAd26 & rAd5 vector-based prime-boost COVID-19 vaccine phase 1/2 (Gamaleya, Russia)



Modest numbers of volunteers enrolled, young/white, ~70% males, low titers, booster needed, lyophilized vaccine better performance, not very well-tolerated

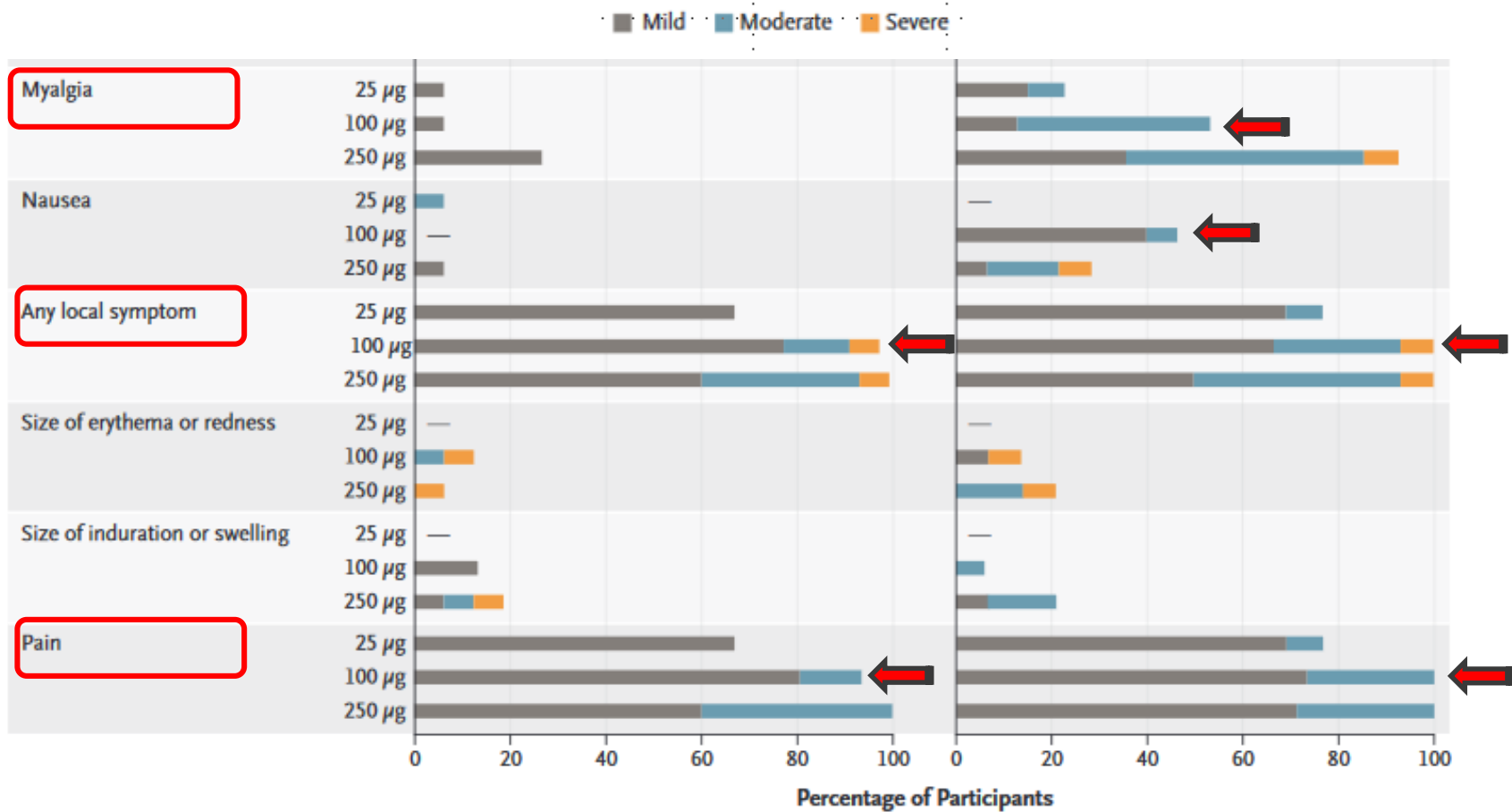


Moderna – Phase 1 trial – on phase 3 RNA 100 µg





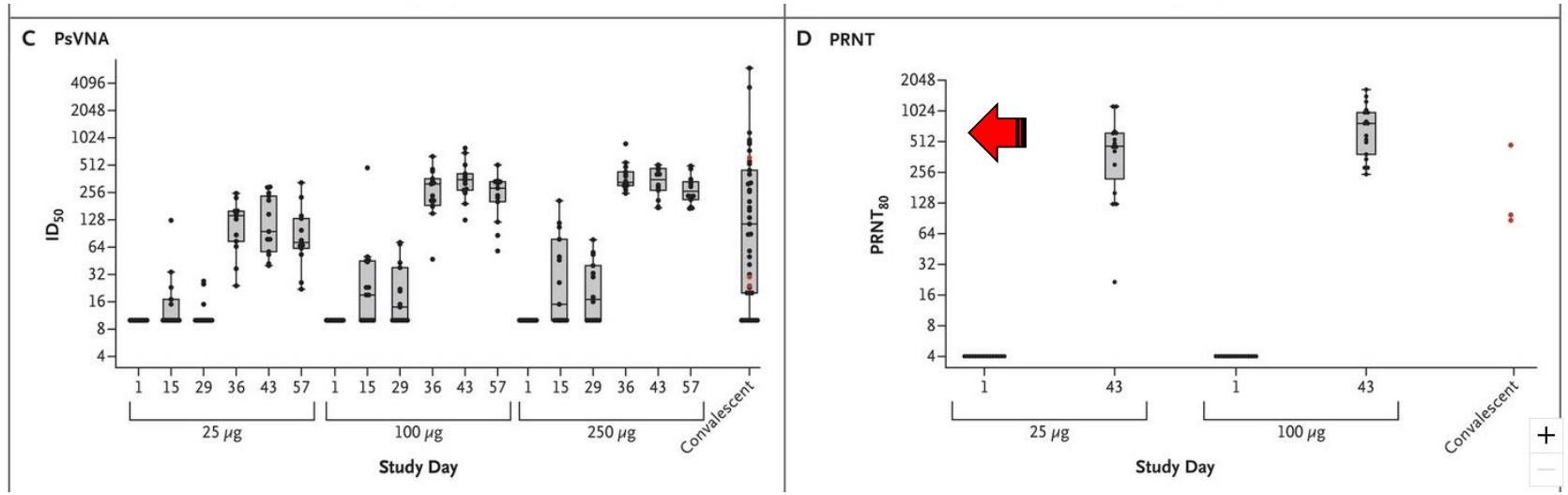
Moderna – Phase 1 trial – on phase 3 100 µg





Moderna – Phase 1 trial – on phase 3 100 µg

Not bad!!!





Biontech BNT162b1

Local Reactions Reported within 7 days after Vaccinations 1 and 2

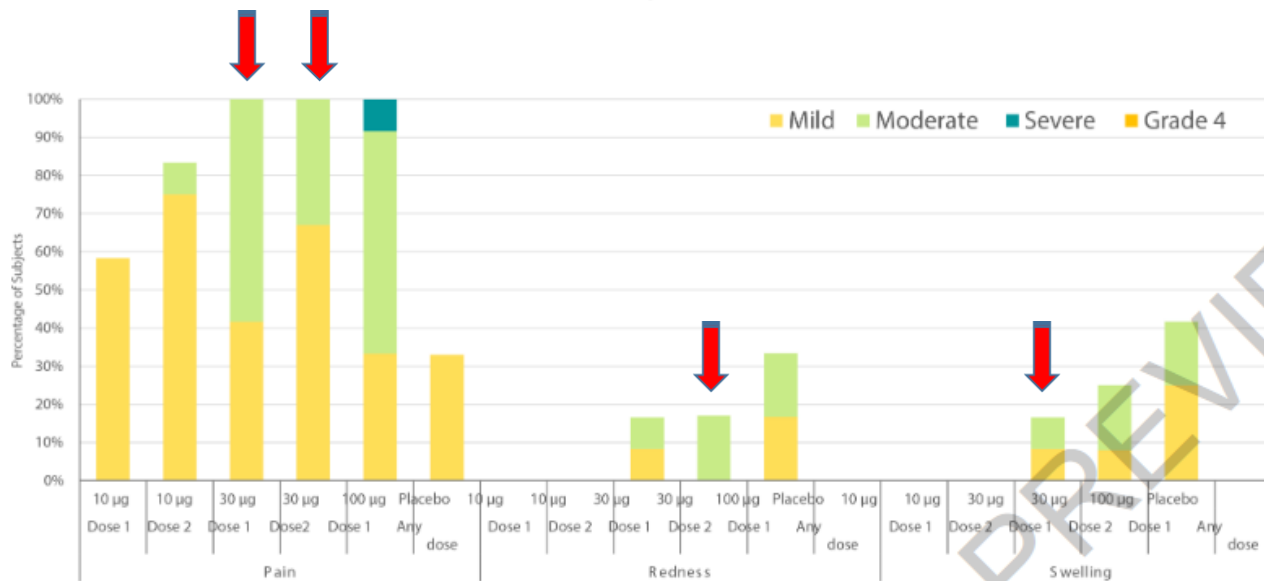


Figure 2 | Local reactions reported within 7 days of vaccination for all dose levels. Solicited injection-site (local) reactions were: pain at injection site (mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization) and redness and swelling (mild: 2.0 to 5.0 cm in diameter;

moderate: >5.0 to 10.0 cm in diameter; severe: >10.0 cm in diameter; Grade 4: necrosis or exfoliative dermatitis for redness, and necrosis for swelling). Data were collected with the use of electronic diaries for 7 days after each vaccination.



Systemic Events Reported within 7 days after Vaccination 1

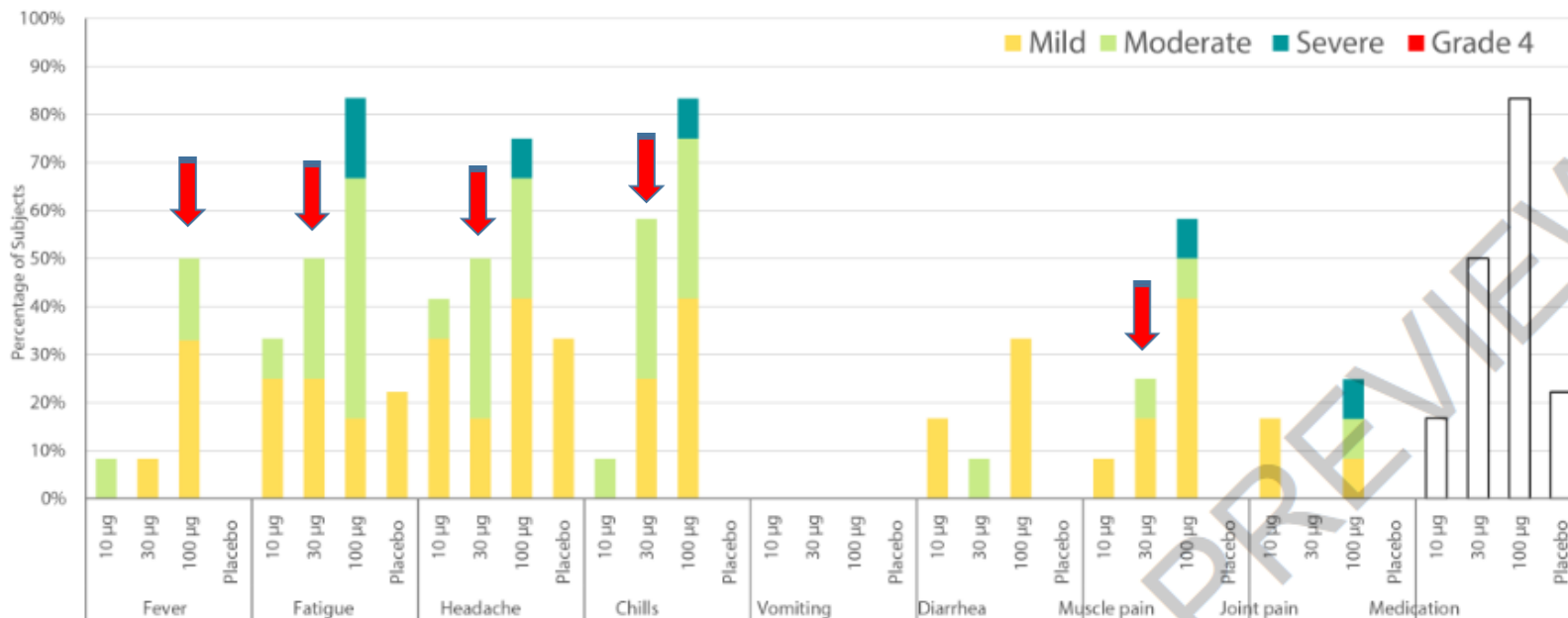


Figure 2 | Local reactions reported within 7 days of vaccination for all dose levels. Solicited injection-site (local) reactions were: pain at injection site (mild: does not interfere with activity; moderate: interferes with activity; severe: prevents daily activity; Grade 4: emergency room visit or hospitalization) and redness and swelling (mild: 2.0 to 5.0 cm in diameter;

moderate: >5.0 to 10.0 cm in diameter; severe: >10.0 cm in diameter; Grade 4: necrosis or exfoliative dermatitis for redness, and necrosis for swelling). Data were collected with the use of electronic diaries for 7 days after each vaccination.

Biontech BNT162b1



Systemic Events Reported within 7 days after Vaccination 2: 10 µg & 30 µg

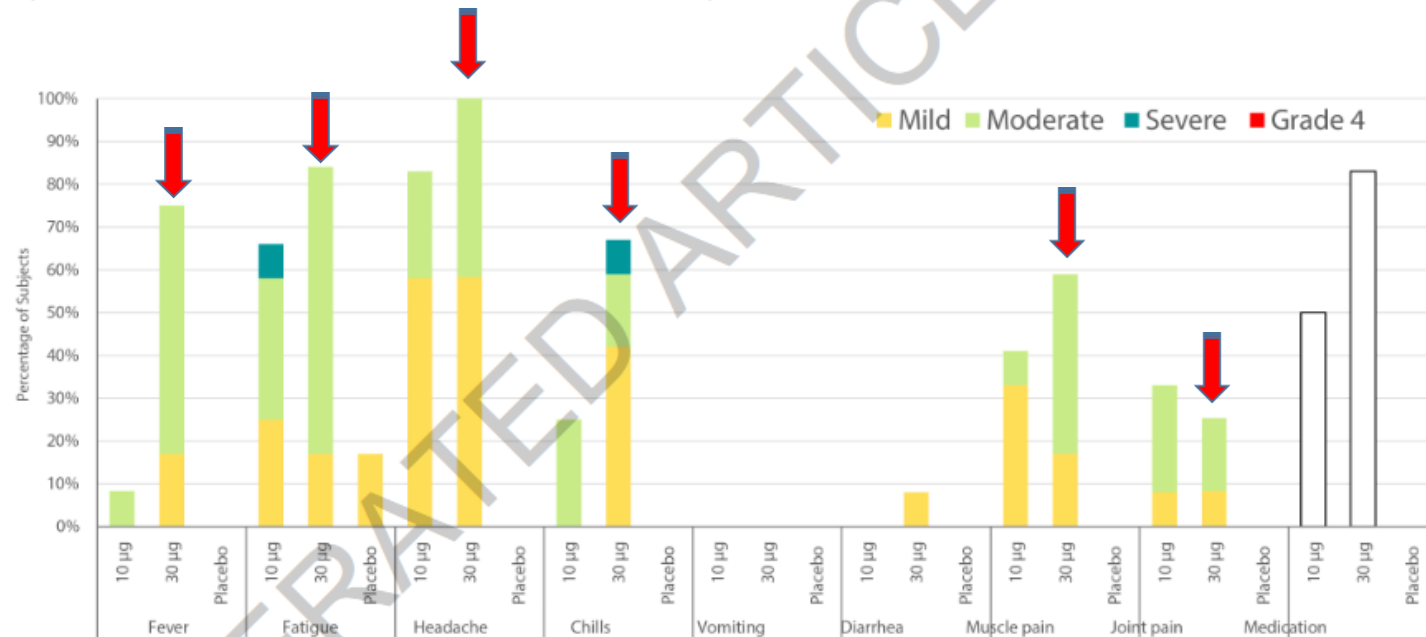


Figure 3 | a. Systemic events and medication use reported within 7 days after Vaccination 1 for all dose levels and b. After Vaccination 2 for the 10-µg and 30-µg dose levels. Solicited systemic events were: fatigue, headache, chills, new or worsened muscle pain, new or worsened joint pain (mild: does not interfere with activity; moderate: some interference with activity; severe: prevents daily activity), vomiting (mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; severe: requires intravenous hydration),

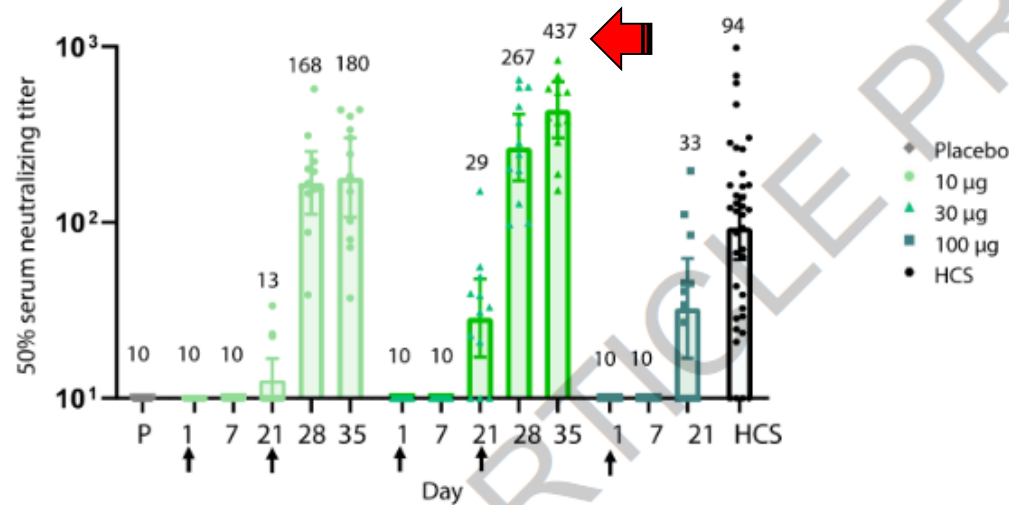
diarrhea (mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; severe: 6 or more loose stools in 24 hours); Grade 4 for all events: emergency room visit or hospitalization; and fever (mild: 38.0 °C to 38.4 °C; moderate: 38.5 °C to 38.9 °C; severe: 39.0 °C to 40.0 °C; Grade 4: >40.0 °C). Medication: proportion of participants reporting use of antipyretic or pain medication. Data were collected with the use of electronic diaries for 7 days after each vaccination.



Biontech BNT162b1

Looks **good!**

But, why **changing horses** in the middle of the race???



These results showed that BNT162b1 stimulates neutralizing antibodies. However, **BNT162b2** was selected to advance to a Phase 2/3 study *"based on the totality of available data from our preclinical and clinical studies, including select immune response and tolerability parameters"*

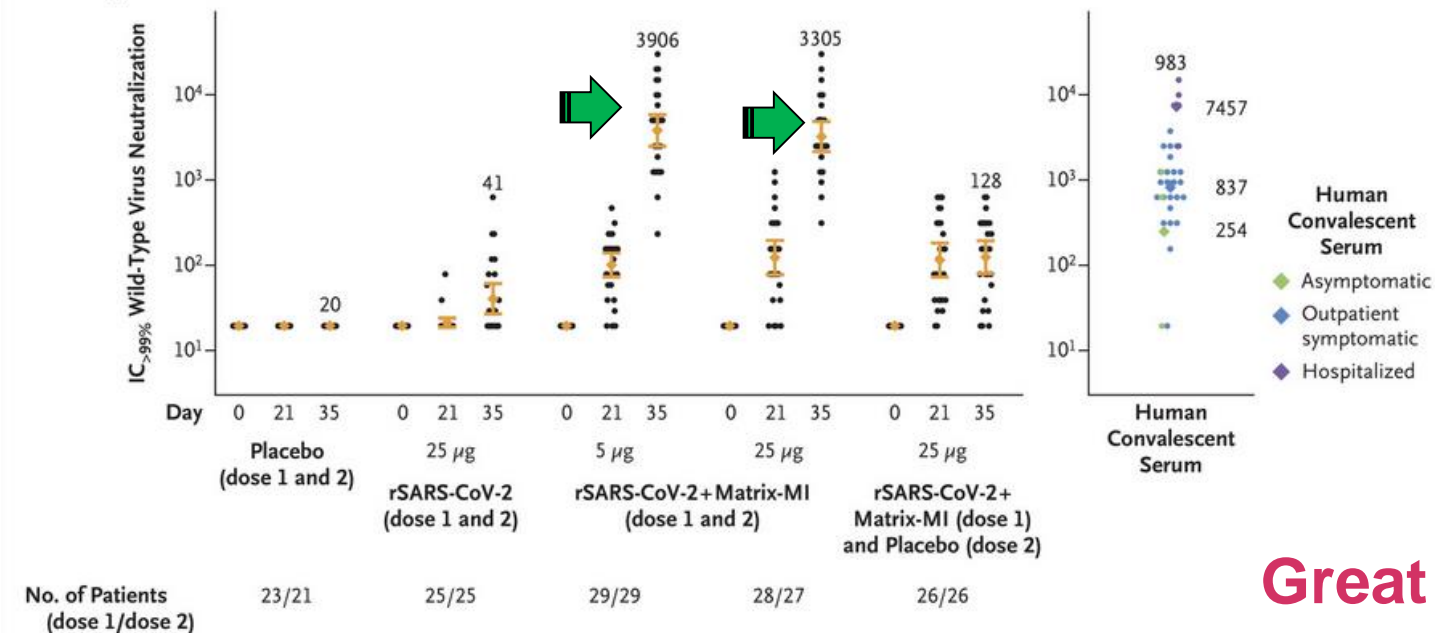


Novavax – phase 1

Vaccine Regimens

Vaccine Group	No. of Participants		Day 0		Day 21 (+5 days)	
	Randomized	Sentinel	rSARS-CoV-2	Matrix-M1 adjuvant	rSARS-CoV-2	Matrix-M1 adjuvant
A	25	—	0	0	0	0
B	25	—	25 μ g	0	25 μ g	0
C	25	3	5 μ g	50 μ g	5 μ g	50 μ g
D	25	3	25 μ g	50 μ g	25 μ g	50 μ g
E	25	—	25 μ g	50 μ g	0	0

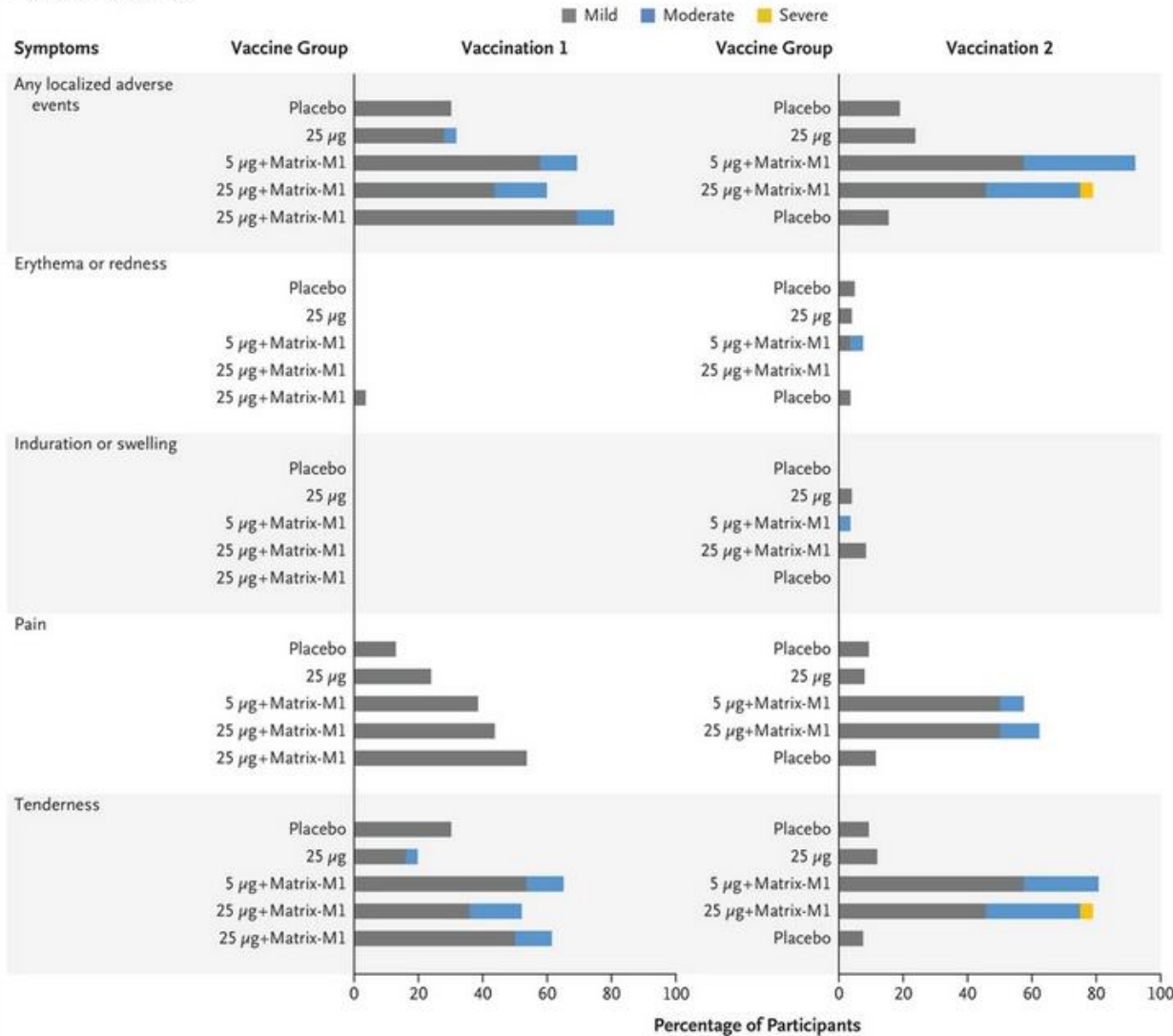
B Wild-Type SARS-CoV-2 Microneutralization





Novavax – phase 1

A Localized Symptoms



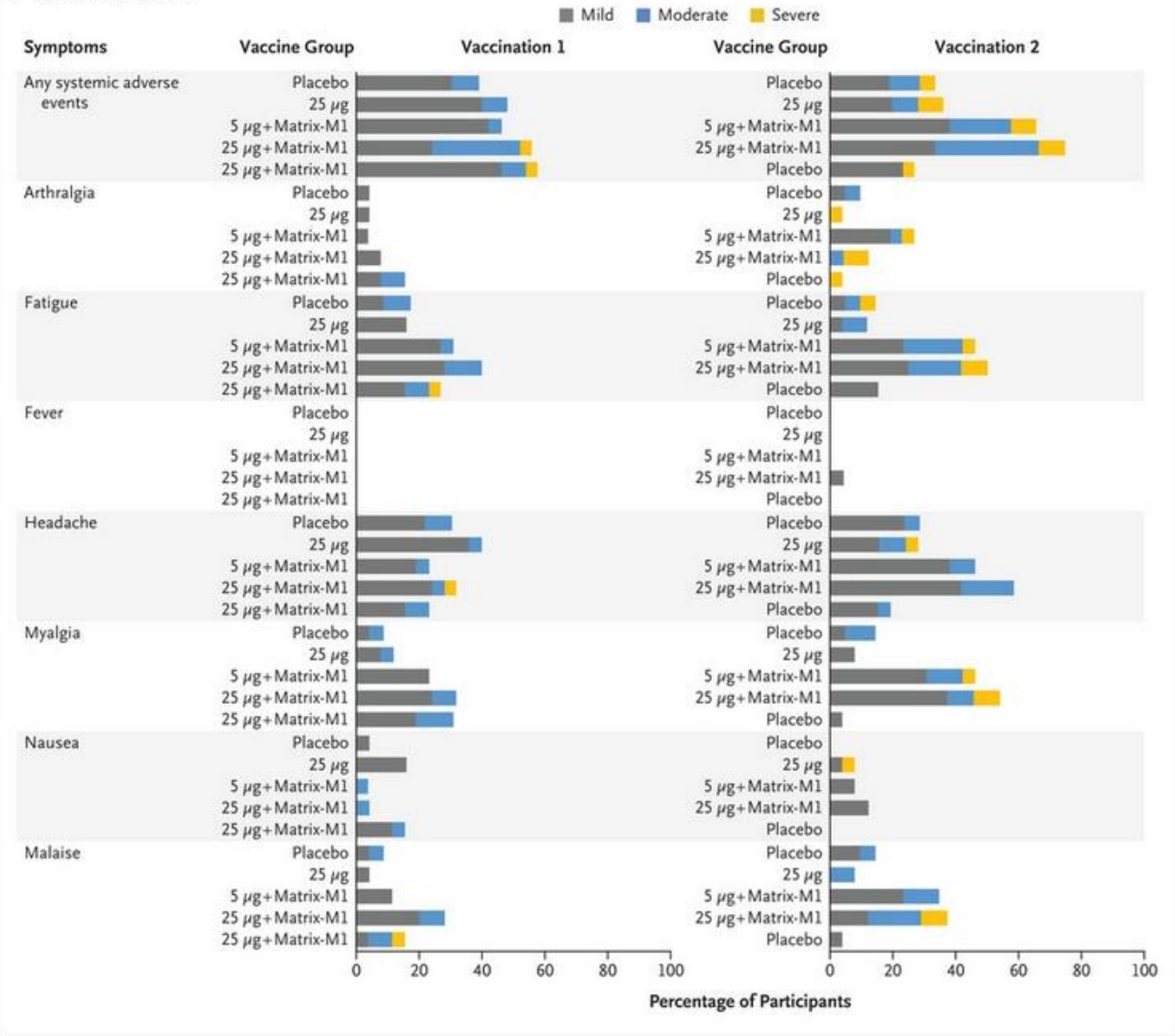
Not so well-tolerated!!

Matrix-M??



Novavax – phase 1

B Systemic Symptoms



Not so well-tolerated!!

Matrix-M??



Inactivated Vaccine Against SARS-CoV-2 Wuhan Institute of Biological Products/Sinopharm

96 participants (2.5, **5**, and 10 µg/dose) and alum (n = 24 in each group), 3x im days 0, 28, and 56.
Phase 2, # **224** adults 5 µg/dose in 2 schedule groups (days 0 and 14 [n = 84] vs alum only [n = 28],
and days 0 and 21 [n = 84] vs alum only [n = 28])

AE: 6.0% vaccinated and **14.3%** alum controls (protocol days 0 and 14);
and **19.0%** vaccinated and **17.9%** alum controls (protocol days 0 and 21)

Seems very well-tolerated!!!

Shengli Xia; Kai Duan; Yuntao Zhang; et al

JAMA. Published online August 13, 2020. doi:10.1001/jama.2020.15543



Inactivated Vaccine Against SARS-CoV-2

Wuhan Institute of Biological Products/Sinopharm

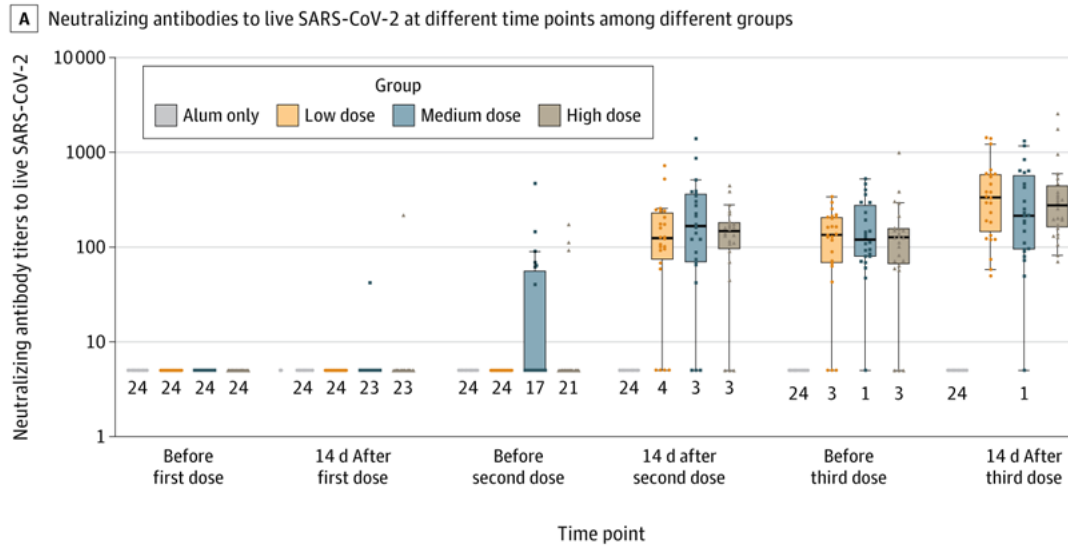
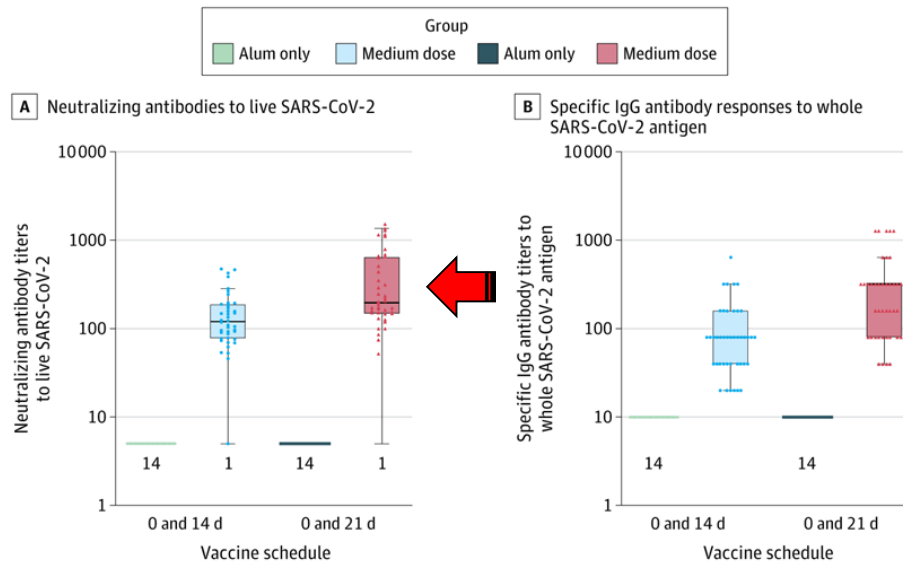
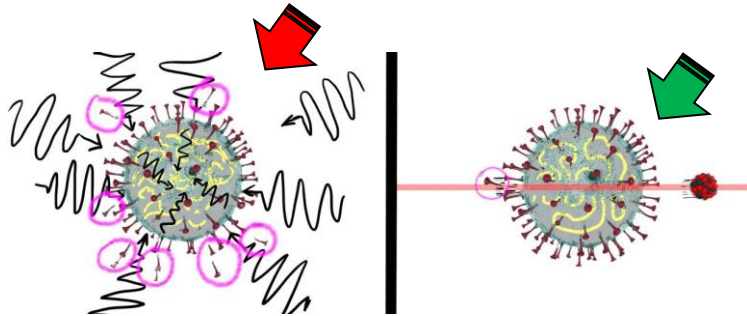


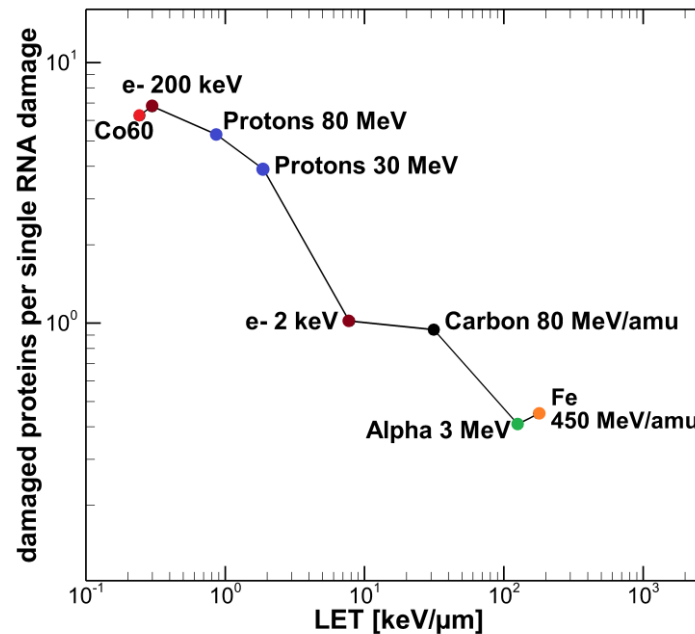
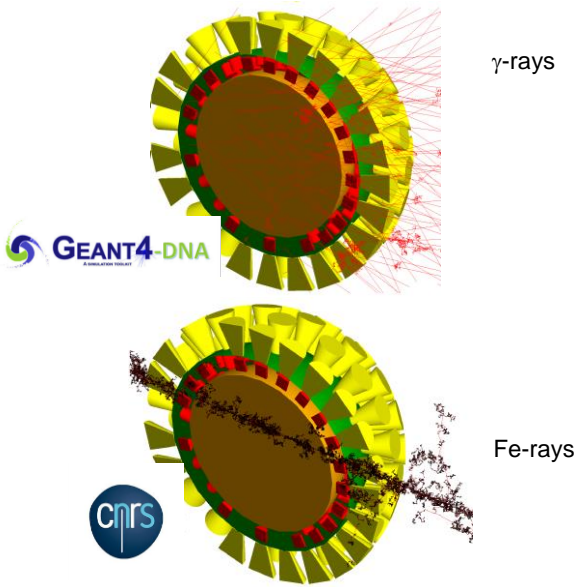
Figure 3. Antibody Responses 14 Days After the Second Dose in the Phase 2 Trial



Can heavy ions contribute to the inactivation of COVID-19 and other viruses for vaccine development?



Virus inactivated by **heavy ions** (rather than chemicals or γ -rays) have **less damage** to membrane epitopes and are therefore expected to produce **more effective protective responses**



Beamtime approved by the Bio-PAC 2020, first test in Spring 2021

Durante et al. (2020) *Frontiers Physics*

COVID-19 – Vaccines some issues...

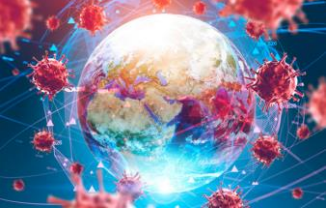


❑ What we know from ongoing trials

- All candidates are immunogenic
- No SAE were reported – Phase 1/2

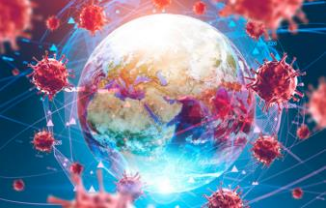
❑ Gaps/issues

- Antibody titers required for protection **unknown!!!**
- Direct comparison among vaccines **not possible** 😞
- Innovative technologies seem to be **less well-tolerated** than conventional ones
- Paucity of safety/efficacy data in COVID-19 high risk individuals – **upcoming!!!**
- **No information** on how long last immunity/memory – **No needed for approval!!!**



COVID-19 – Vaccines some issues...

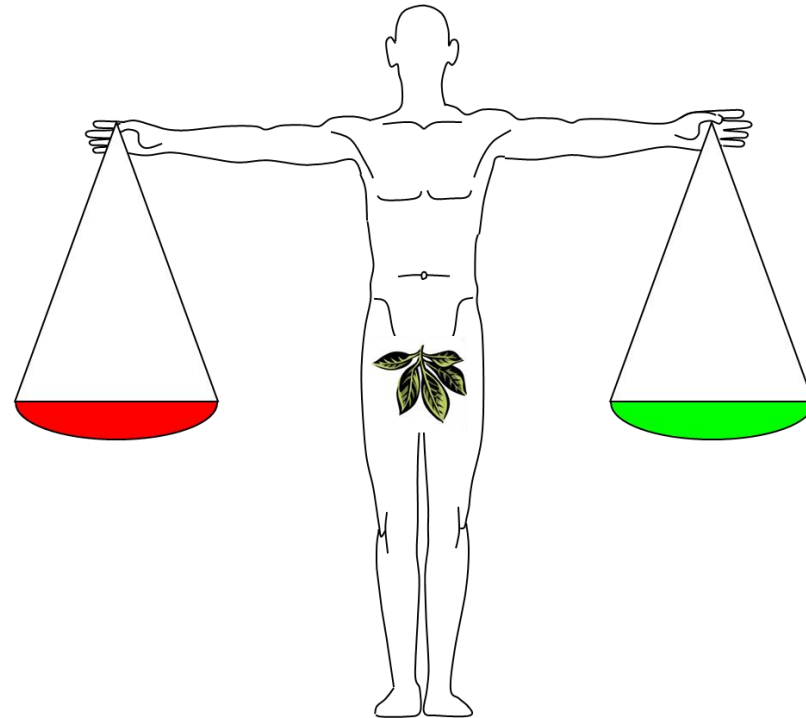
- ❑ Can spike/RBD evolve making vaccines ineffective?
- ❑ Contribution of cellular immunity unknown - 81% naive has CD4/CD8 T cells
- ❑ Who should be vaccinated?
- ❑ Who should be vaccinated first? ... An ongoing discussion – Staggered?



COVID-19 – Vaccines

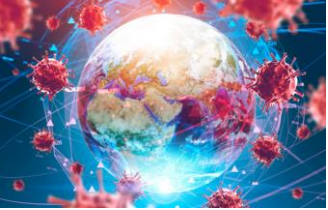
key open issues... in principle simple

Disease:
deaths,
suffering
& costs



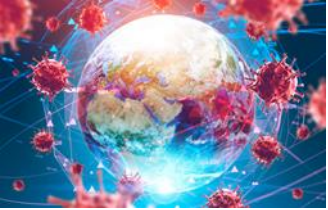
Vaccines:
risks,
benefits
& costs

Cost-benefit balance:
might differ in **subpopulation groups** & for **different vaccines**



COVID-19 – Vaccines open issues...

- ❑ To which extent are efficacy/safety phase 3 studies powered?
- ❑ What about vaccine-dependent enhancement???
- ❑ **Final safety & efficacy of vaccines in different subpopulation groups!!!**
- ❑ **Is cost-benefit acceptable? For which vaccine? For which group?**
- ❑ **Which vaccine to choose? Who should be vaccinated?**
- ❑ Can delayed/rare AE be missed due to short clinical development times and size trials?
- ❑ Can interim analysis of trial data mislead on true efficacy/safety?????
- ❑ Vaccines for everybody – 2022/2023???
- ❑ Will boosters be required? How often? Vaccination pass - makes sense?



The New York Times

Opinion

Big Pharma May Pose an Obstacle to Vaccine Development

Concerns about profits and liability have often kept them from moving quickly enough.

By Gerald Posner

Mr. Posner is the author of the forthcoming "Pharma: Greed, Lies and the Poisoning of America."

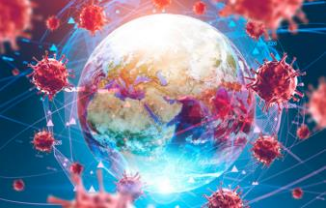
March 2, 2020



Artem Egorov/iStock, via Getty Images Plus

COVID-19 – Vaccines Liability issues: Is a good sensor for the degree of confidence of producers on their own products?

Profits & liability issues potential roadblocks
(i.e. swine [influenza in 1976](#) when MSD, Wyeth, Merrell and Parke-Davis refused to sell 100 million doses until they got full liability indemnity and guaranteed profit – **100 million \$ on damages paid**)

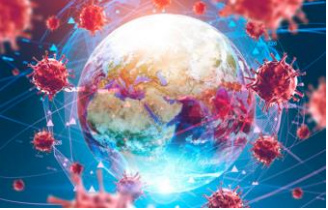


COVID-19 – Vaccines

as for any medical intervention side effects are unavoidable...
we only aim at reducing and managing the risk

“The speed and scale of development and rollout do mean that it is impossible
to generate the same amount of underlying evidence that normally would be
available through extensive clinical trials and healthcare providers building
experience,” ... this creates “inevitable risks”

European Federation of Pharmaceutical Industries and Associations



COVID-19 – Vaccines

Liability issues: contradictions, views & thoughts

the European Commission stated...

“Liability still **remains** with the companies”...

...“to compensate for such high risks, the Advanced Purchase Agreements provide for member states to **indemnify** the manufacturer for liabilities incurred under certain conditions,”...

Which ones???

Contract information will not be disclosed!!!!

Yannis Natsis, an elected member in charge of patient representation on the board of the European Medicines Agency, said that an exemption from civil liability would create

“a dangerous precedent”

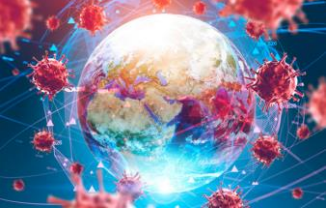
... he was also concerned about the

“lack of transparency in the negotiations”...



Yannis Natsis

Policy Manager, EPHA - EMA MB member - European Health
Forum Gastein Board member



COVID-19 – Vaccines

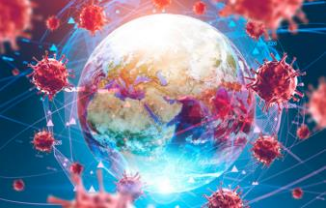
Liability issues: some thoughts

The public sector is already essentially paying for "research and development, production and distribution of a vaccine we don't even know about" (e.g. 1 billion \$ from BARDA for AstraZeneca, 300 millions D for Curevac, etc.)

For certain stakeholders it is "unacceptable" that the costs for potential damages caused by a new coronavirus vaccine should be shouldered by European taxpayers, rather than the pharma industry

Some thoughts:

- not every company receives overwhelming support
- not every company expects a significant profit
- important to know if public funds were wisely used, if support reflects access and price structure, and who pays for what in case of civil processes... particularly under EUA



COVID-19 – Vaccines

In a nutshell

Unprecedented speed!!!! 😊

Immunogenic/no SAE/protective (?)

(too?) Many candidates 😊

Cost-benefit???

Huge potential 😊

Many first in class

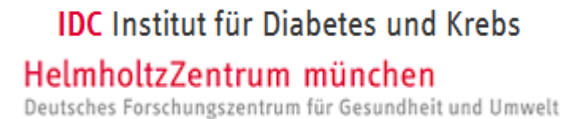
Great expectations/reliance 😞

Political/public pressure 😞

Transparency (lack thereof?)

Acknowledgements

- ❑ Yang Li, Bowen Zhang, Ulrich Kalinke, Frank Pessler (Twincore, Hannover)
- ❑ Thomas Illig, Christoph Schindler (MHH, Hannover)
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