How can we know how safe COVID-19 vaccines will be?

Helen Petousis-Harris, PhD

Assoc Professor, University of Auckland

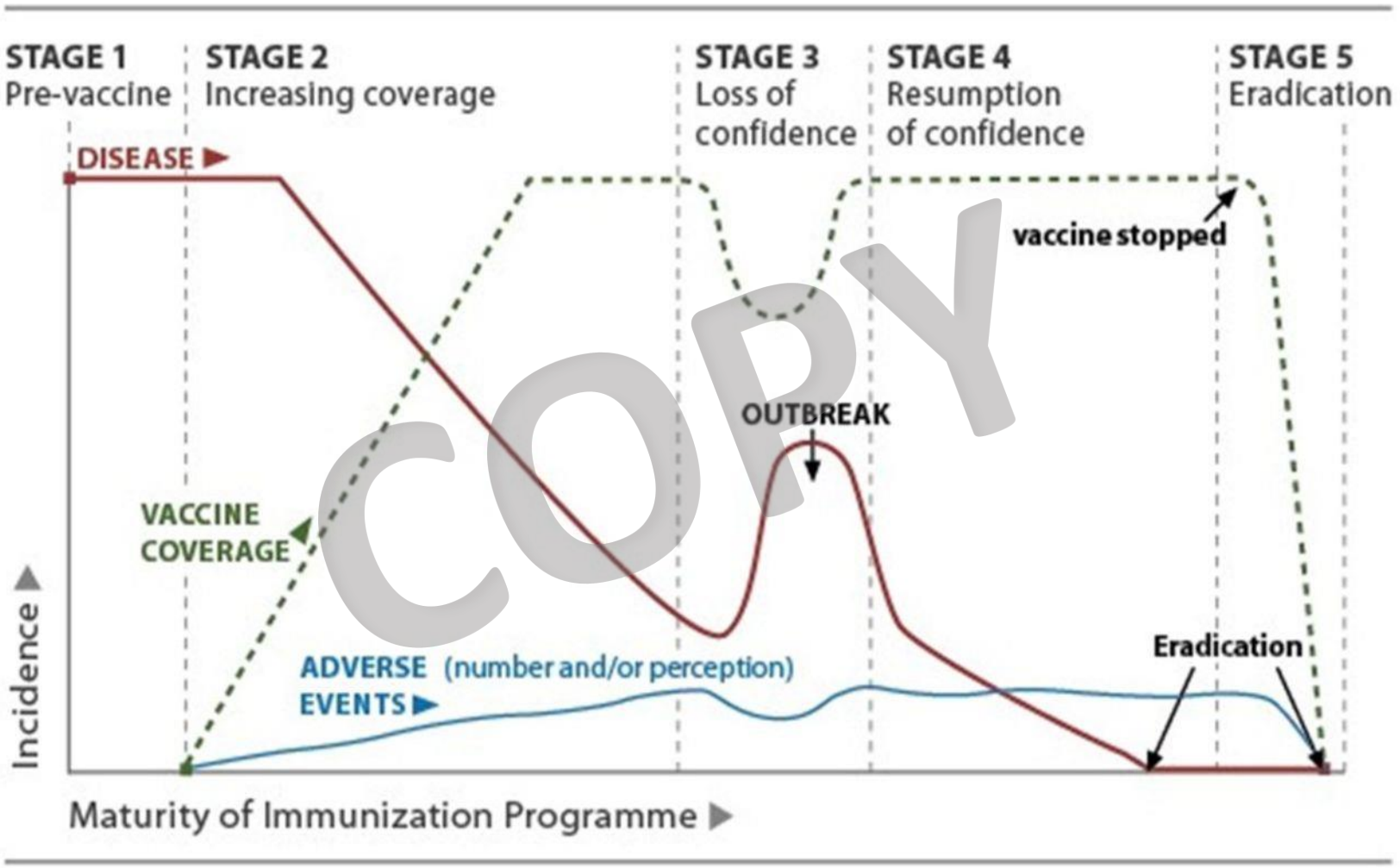
COVID-19 vaccines have been developed with unprecedented speed. How will we know how safe COVID-19 vaccines are?

- **The facets of vaccine safety monitoring**
  - **post-licensure monitoring**
- **Tools for assessing vaccine safety**
- **What we know and don’t know yet**

The challenges

History, public perception, rapid development

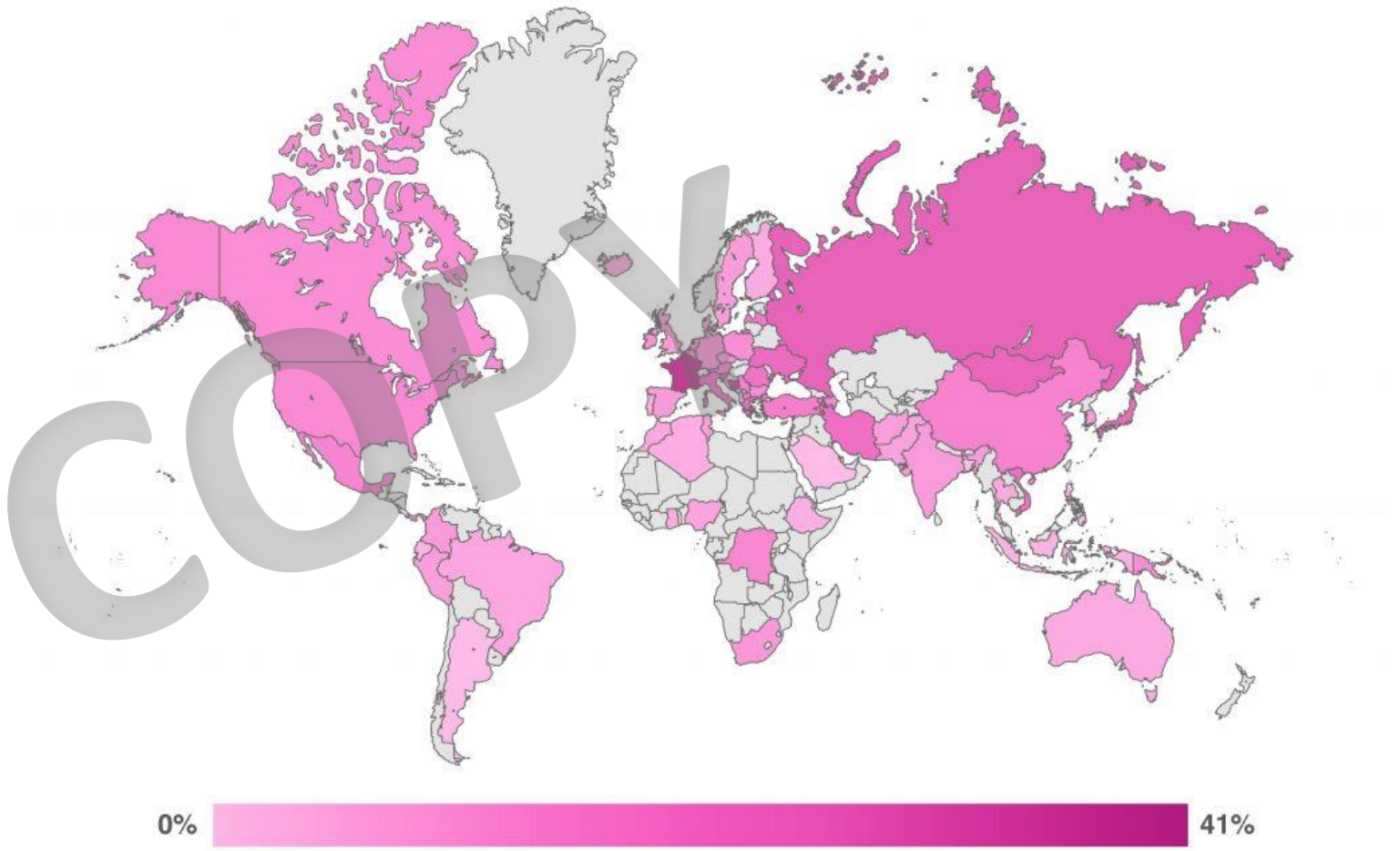
Potential stage in the evolution of an immunisation programme, vaccine safety.



Yonatan Moges Mesfin et al. BMJ Glob Health 2019;4:e001065

BMJ Global Health

Disagree- *"Overall I think vaccines are safe"*

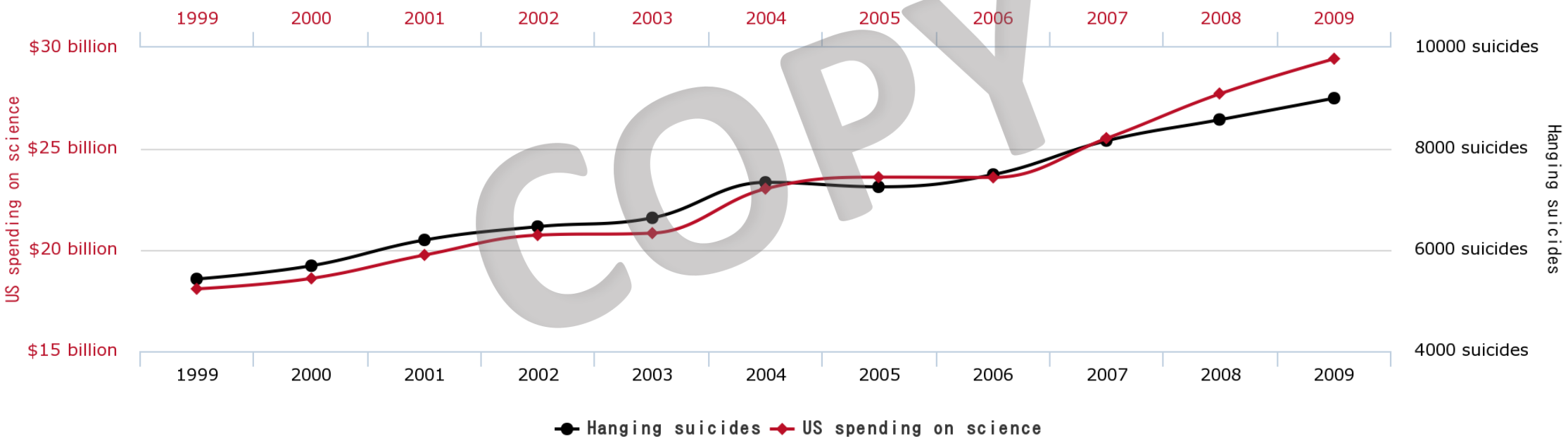


Vaccine Confidence Project 2016

US spending on science, space, and technology

correlates with

Suicides by hanging, strangulation and suffocation

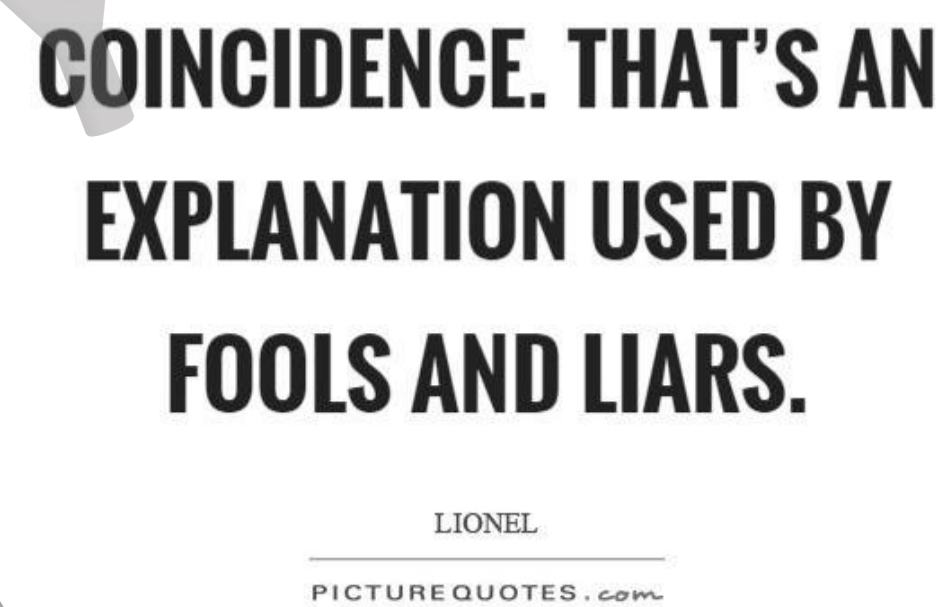


tylervigen.com

Separating legitimate events from coincidence

- If a cohort of 10 million individuals was vaccinated in the UK, 21·5 cases of Guillain-Barré syndrome and 5·75 cases of sudden death would be expected to occur within 6 weeks of vaccination as coincident background cases.
  - need >4million to detect a 2-fold difference
- In female vaccinees in the USA, 86·3 cases of optic neuritis per 10 million population would be expected within 6 weeks of vaccination.
- 397 per 1 million vaccinated pregnant women would be predicted to have a spontaneous abortion within 1 day of vaccination.

Vs.



Black, Steven, et al. "Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines." *The Lancet* 374.9707 (2009): 2115-2122.

Beyond rare events

Flu vaccines vary by:

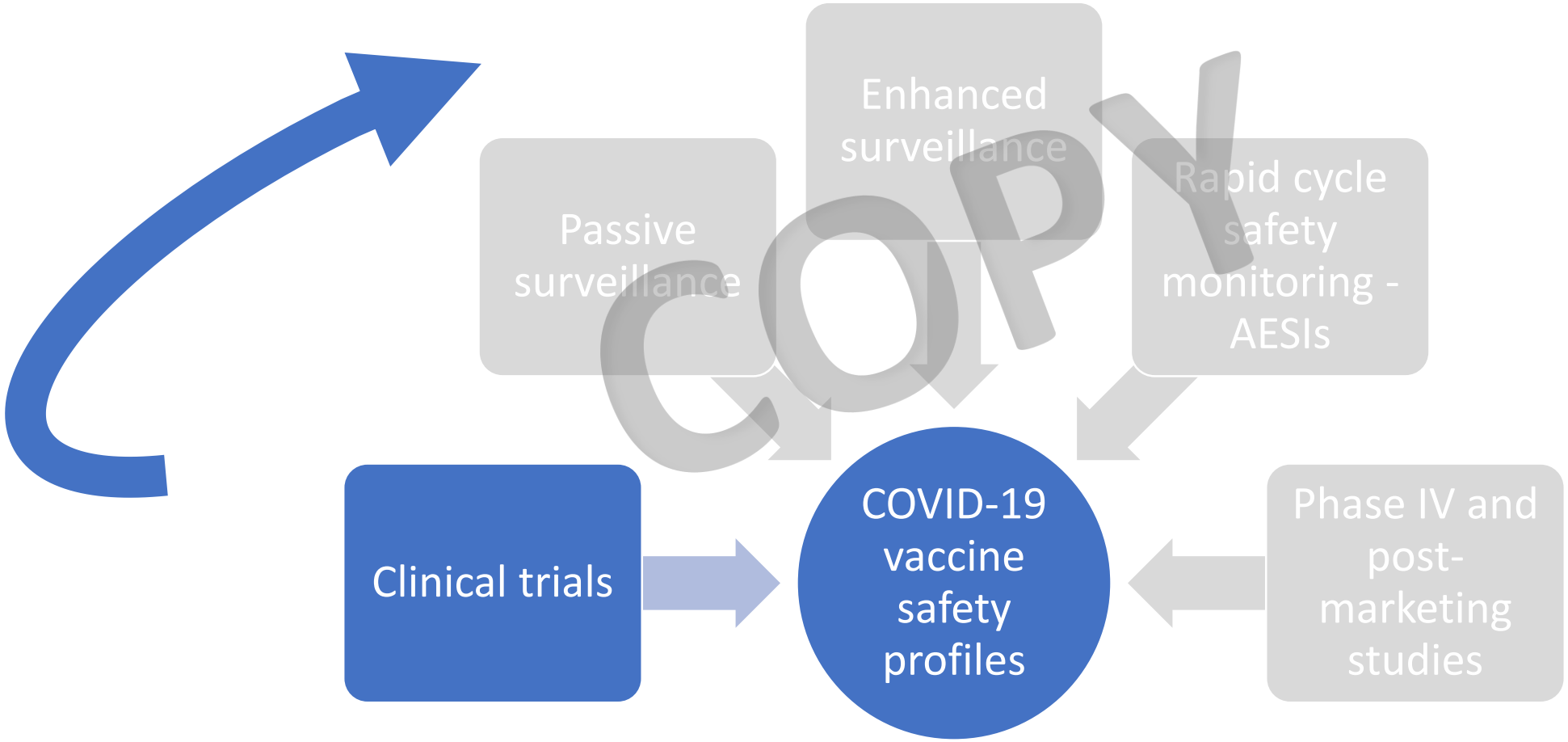
- Adjuvant: absent, present (type)
- Antigen(s): number, strain(s)
- Manufacturing: egg-based, cell-based
- Type: inactivated, live attenuated
- Match to circulating strains
- Effectiveness

Populations vary by:

- Genetic predisposition
- Healthcare delivery
- Seasonal effects

COVID-19 vaccine safety - what we know, what we don’t

Knowing the safety of COVID-19 vaccines

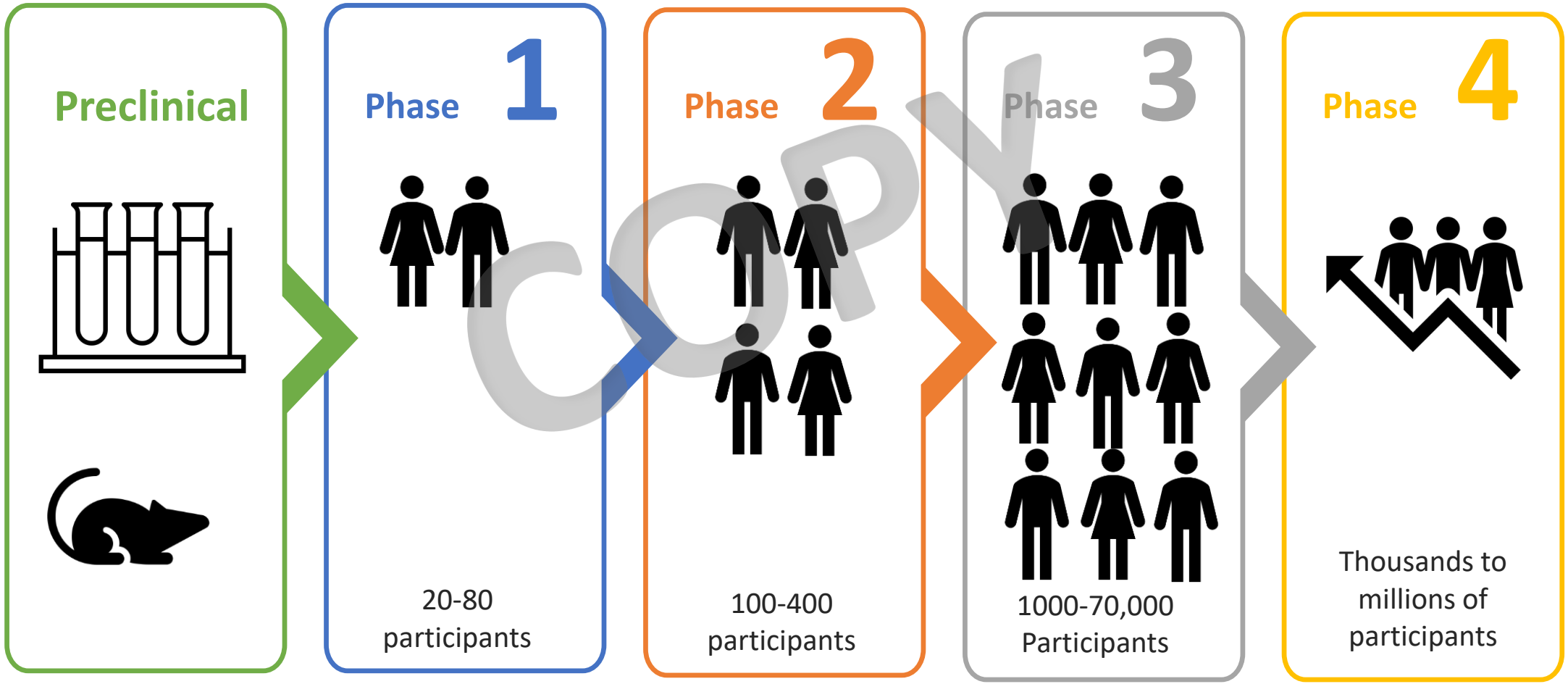


The body of knowledge

The standard process of testing vaccines 10-15 years

Approved for testing in humans

Submit for regulatory approval



Limitations of clinical trials

- Phase III trials need to be big enough to show efficacy – that the vaccine prevents the outcome.*
- To license a vaccine there needs to be sufficient evidence of safety.
- Need to be feasible!
  - $$$ □ □ □
- If an event occurs in 1 per 10,000, in a study with 20,000 people you might expect 2 cases, and in a study with 60,000 you might expect 6 cases.

If a vaccine increases the risk for these sorts of quite rare events then you would need some rather large numbers to exclude the possibility of the increased risk.

*Or immunogenicity if bridging data to correlate of protection

Limitations of clinical trials

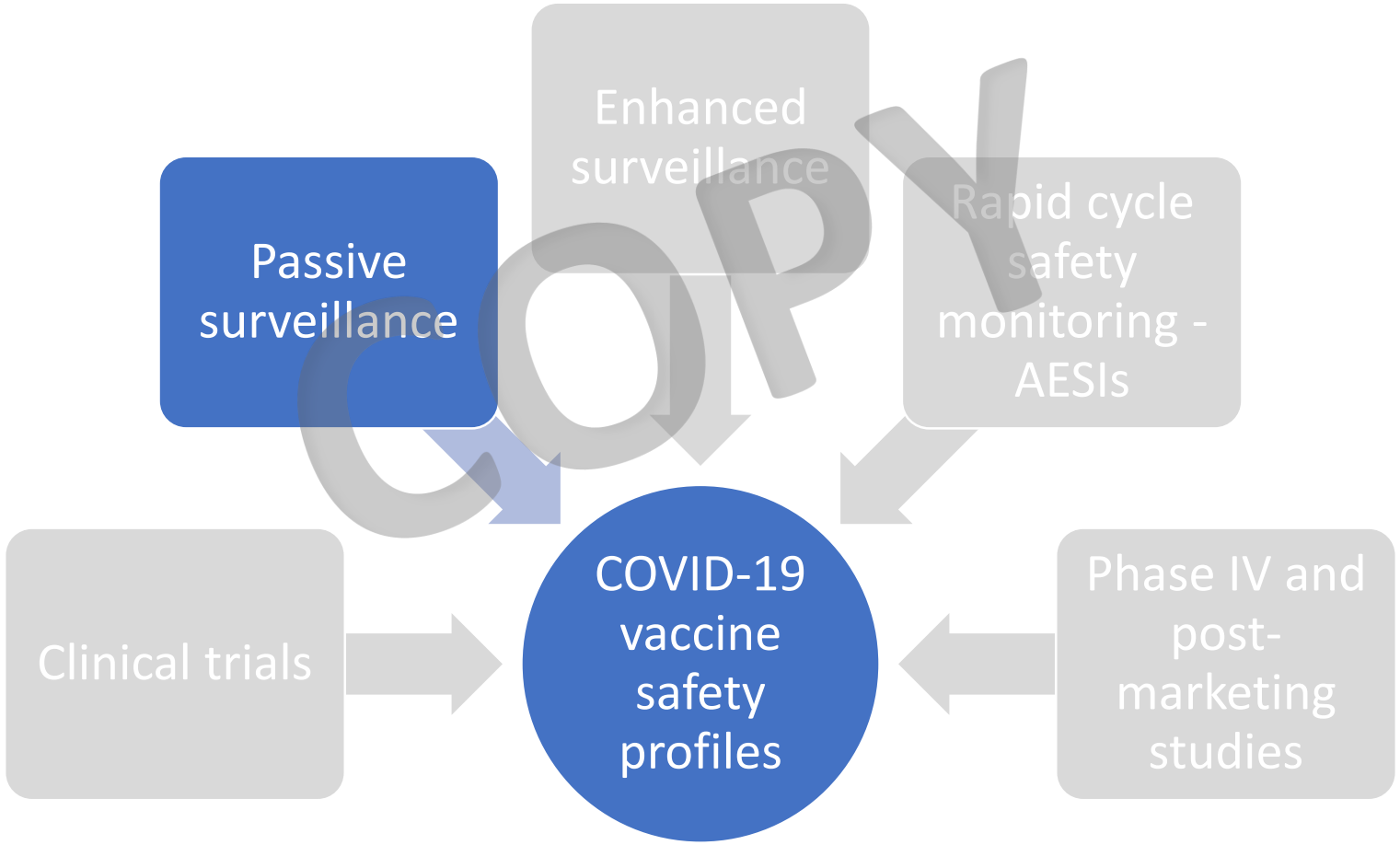
- Usually in healthy people at low risk for adverse events and most likely to make good immune response
- Cannot measure indirect effects
  - I.e community immunity, transmission
- Participants might not be genetically diverse

Q. What is the risk of neurological side effects / long term effects?

Solutions


adalet

Knowing the safety of COVID-19 vaccines



Spontaneous safety surveillance

- Passive safety surveillance (voluntary reporting of AEFI)
- Most countries have one
- Most contribute to the WHO Uppsala pharmacovigilance monitoring centre

✓Good for signal detection

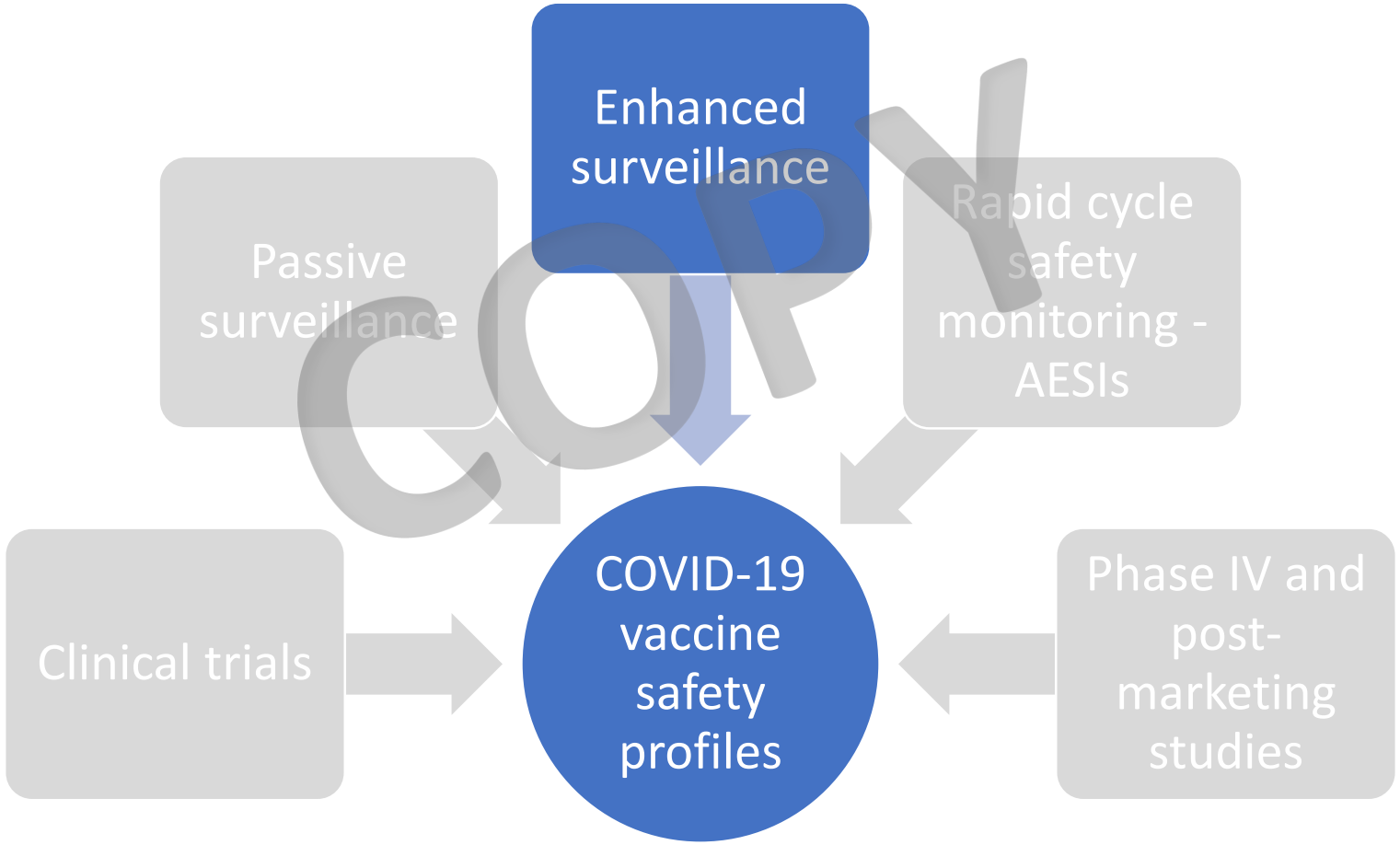
✗Cannot help with causality assessment

VAERS
Vaccine Adverse Event Reporting System

Australian Government
Department of Health
Therapeutic Goods Administration

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

Knowing the safety of COVID-19 vaccines



Enhanced monitoring

- E.g. Use of digital technologies to actively collect post vaccine adverse events
  - SmartVax
  - Vaxtracker
  - KiwiVax ☺

✓ Reveal events not picked up by GP visit

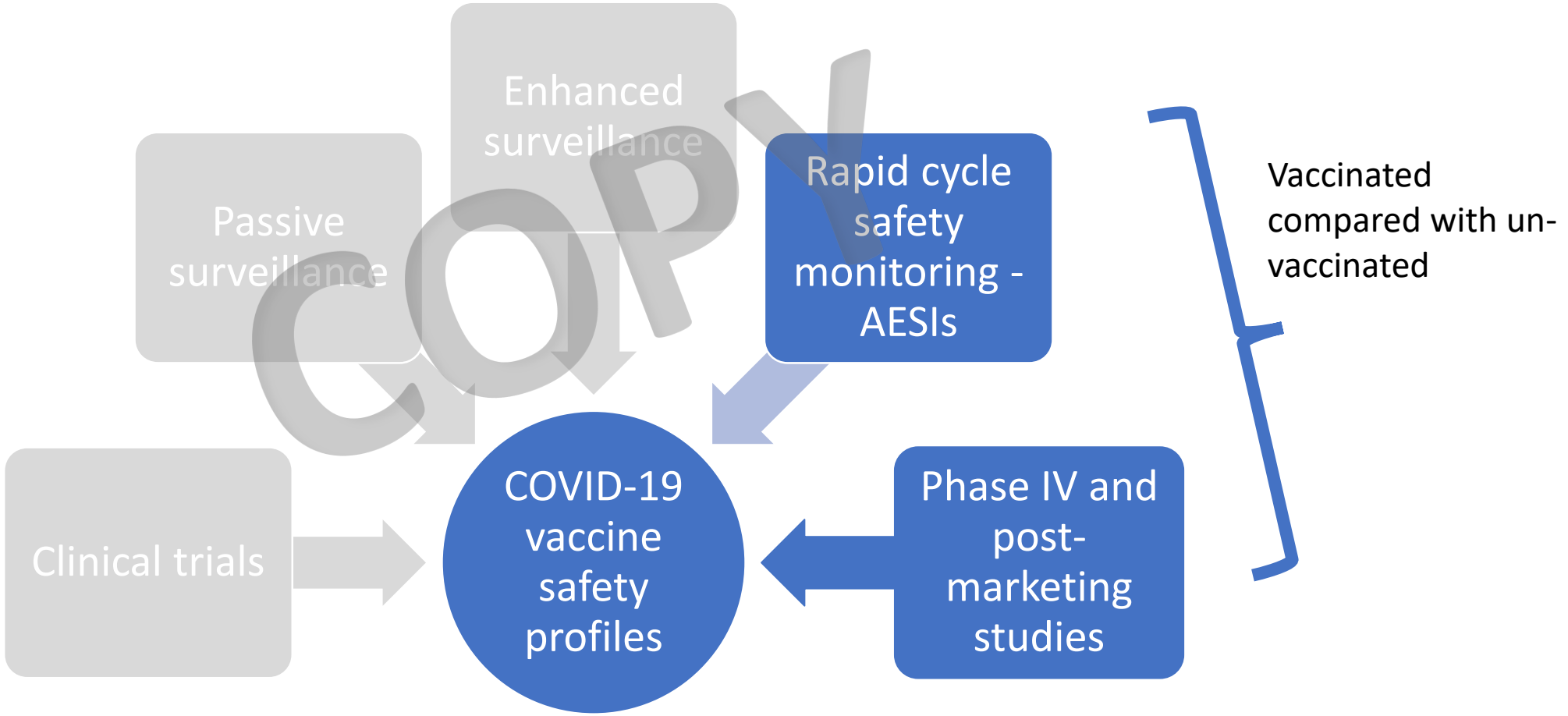
✓ Involve patients in pharmacovigilence

✓ SPEAC working group – standardisations and guidelines

✗ Cannot be used to infer causality of complex or rare events

✗ No unvaccinated for comparison

Knowing the safety of COVID-19 vaccines

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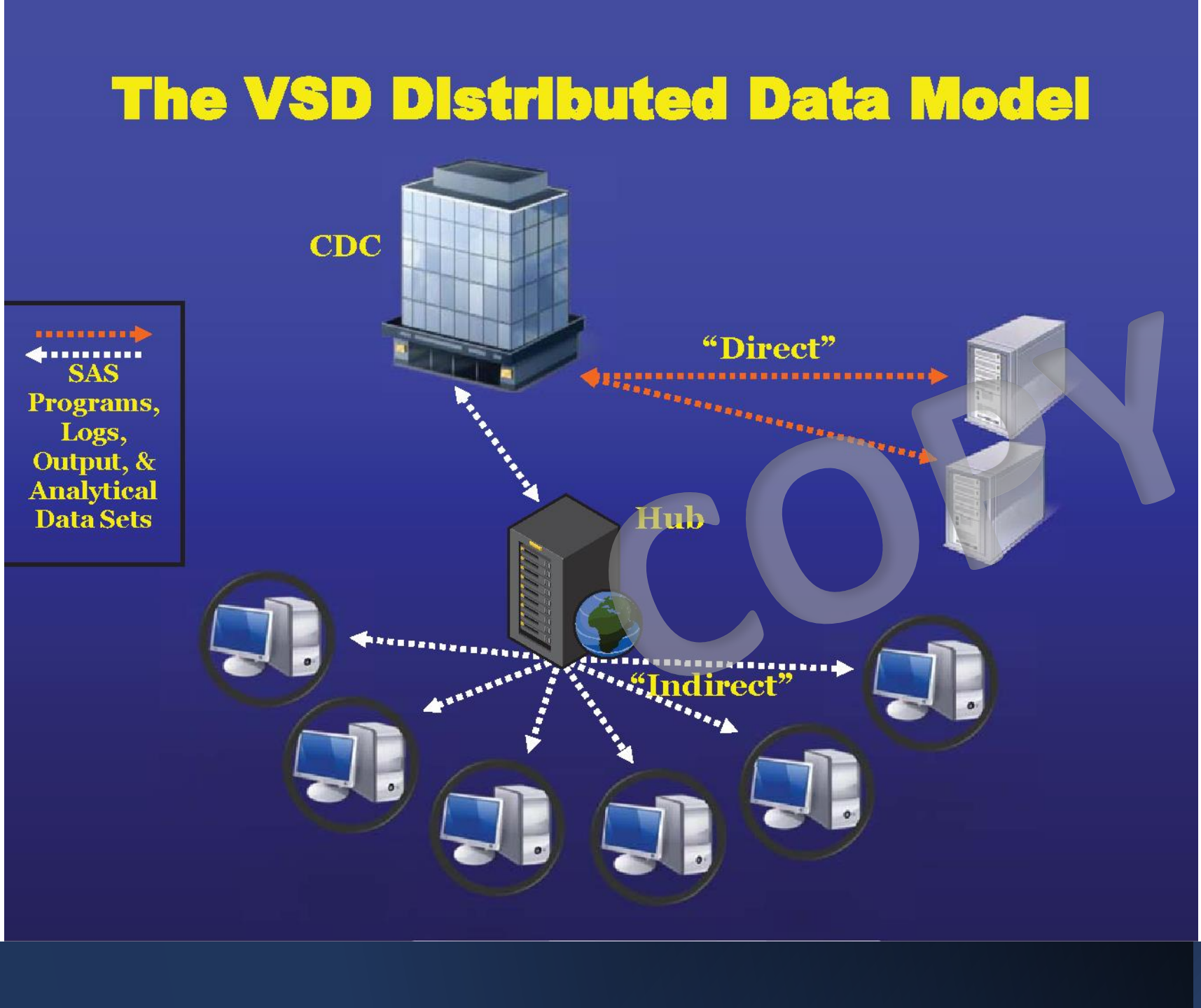


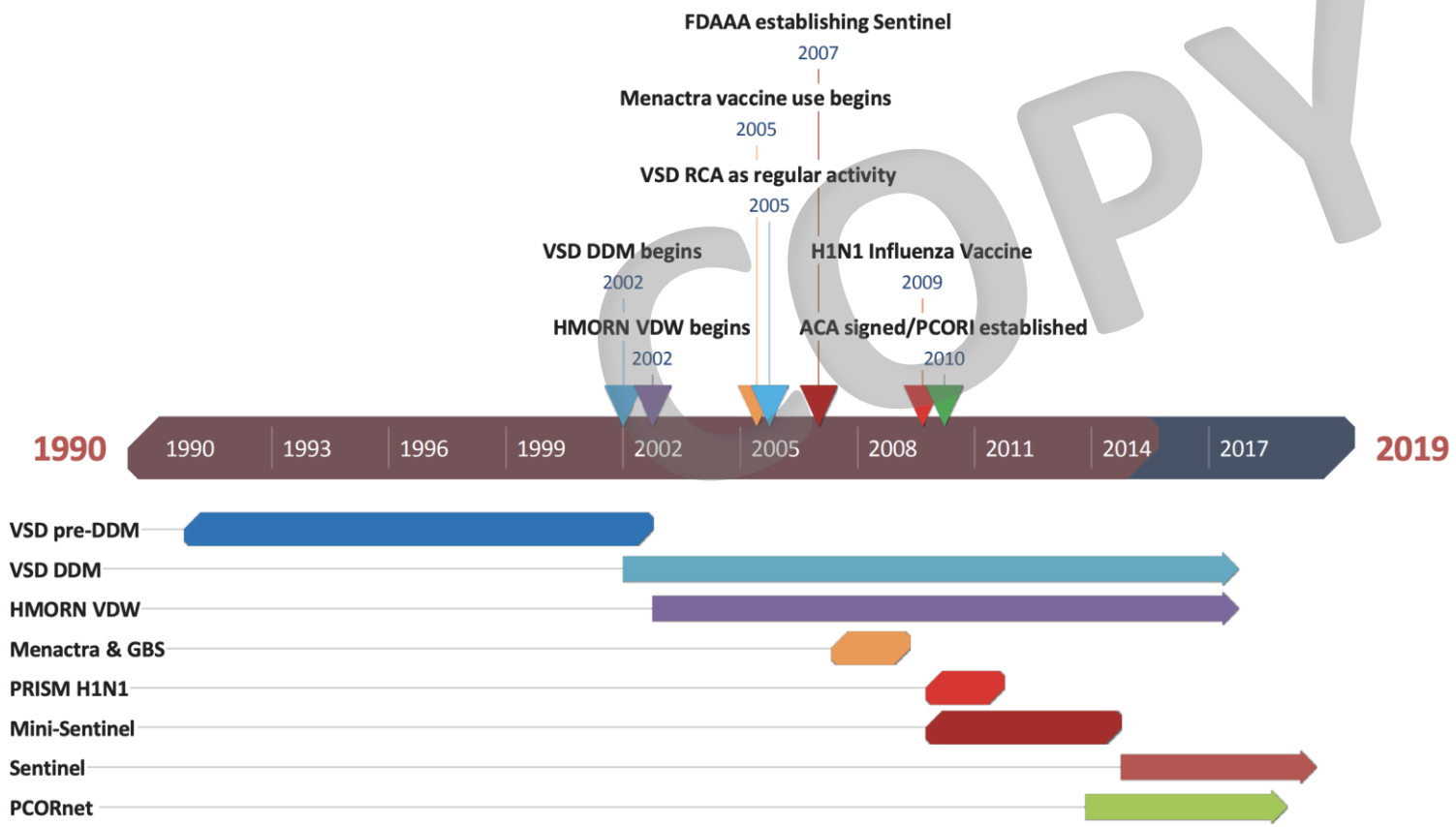
Using administrative data to answer big questions

- Electronic patient records
- Link vaccine exposure with health outcomes
- Compare vaccinated with unvaccinated
- Now we can really look for rare events

The US Vaccine Safety Datalink was the first imitative to use datalinkage for vaccines safety studies (1990). From centralized to distributed and 10m to 178m

Example – active vaccine safety monitoring in US

Figure 2. Timeline and Key Milestones of Selected Distributed Data Networks



Today up to 178million persons

Fahey KR. The Pioneering Role of the Vaccine Safety Datalink Project (VSD) to Advance Collaborative Research and Distributed Data Networks. eGEMs. 2015;3.


Cool tools and global collaborations
COPY

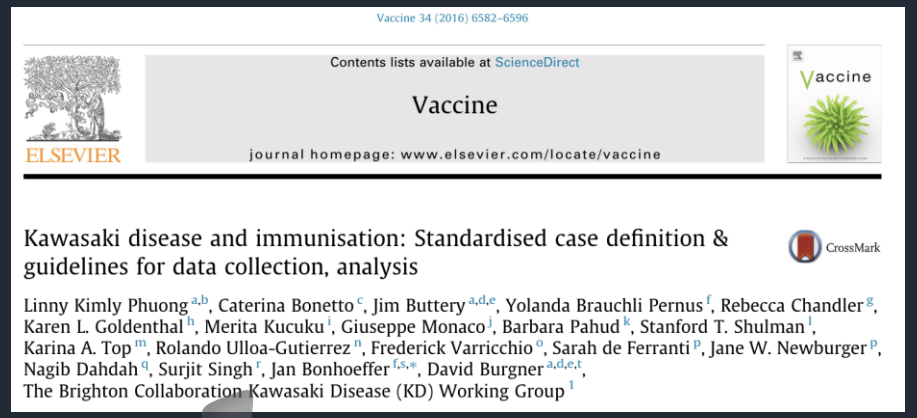
Brighton Collaboration

Est. 1999

Improving the quality of vaccine safety data

“Enhance the science of vaccine research, by providing standardized, validated and objective methods for monitoring safety profiles and benefit to risk ratios of vaccines.”

Over the years BC have developed many case definitions and guidelines – essential tools for assessing vaccine safety outcomes



Vaccine 34 (2016) 6582–6596

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Kawasaki disease and immunisation: Standardised case definition & guidelines for data collection, analysis

Linny Kimly Phuong [a,b], Caterina Bonetto [c], Jim Buttery [a,d,e], Yolanda Brauchli Pernus [f], Rebecca Chandler [g], Karen L. Goldenthal [h], Merita Kucuku [i], Giuseppe Monaco [j], Barbara Pahud [k], Stanford T. Shulman [l], Karina A. Top [m], Rolando Ulloa-Gutierrez [n], Frederick Varricchio [o], Sarah de Ferranti [p], Jane W. Newburger [p], Nagib Dahdah [q], Surjit Singh [r], Jan Bonhoeffer [f,s,*], David Burgner [a,d,e,t], The Brighton Collaboration Kawasaki Disease (KD) Working Group [1]

Available online at www.sciencedirect.com

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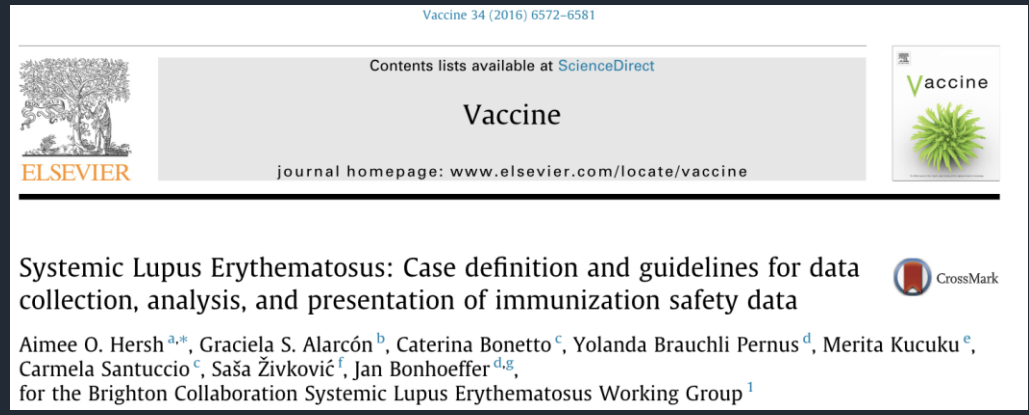
Vaccine 22 (2004) 551–556

Vaccine

www.elsevier.com/locate/vaccine

Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation

S. Michael Marcy [a], Katrin S. Kohl [b,*], Ron Dagan [c], David Nalin [d], Michael Blum [e], Marcy Connell Jones [f], John Hansen [g], Jerry Labadie [h], Lucia Lee [i], Bryan L. Martin [j], Katherine O'Brien [k], Edward Rothstein [l], Patricia Vermeer [m], The Brighton Collaboration Fever Working Group [n, o, l]



Vaccine 34 (2016) 6572–6581

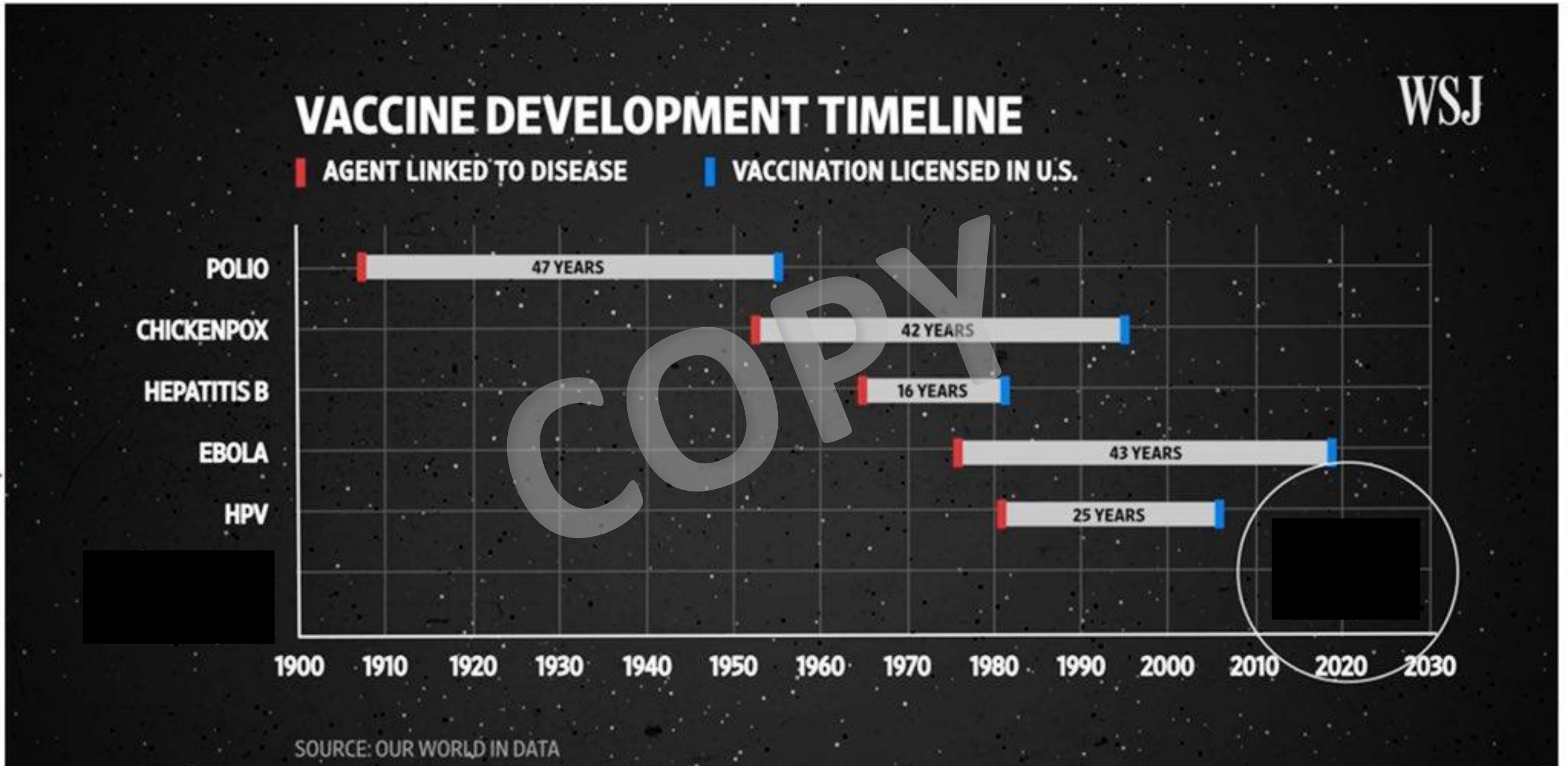
Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Systemic Lupus Erythematosus: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data

Aimee O. Hersh [a,*], Graciela S. Alarcón [b], Caterina Bonetto [c], Yolanda Brauchli Pernus [d], Merita Kucuku [e], Carmela Santuccio [c], Saša Živković [f], Jan Bonhoeffer [d,g], for the Brighton Collaboration Systemic Lupus Erythematosus Working Group [1]



The traditional vaccine development model was never going to serve us well in an emergency

CEPI is a global partnership founded in 2017 in Norway to advance innovations that could prepare us for emerging epidemics. By the end of 2019 they had invested in a range of vaccine technologies such as viral vector and RNA vaccine platforms so that they could progress faster.

New vaccine technologies pose new challenges for vaccine safety assessment from benchtop to first in humans…

SPEAC

Safety Platform for Emergency vACcines

CEPI partners with Brighton Collaboration to support safety assessment of vaccine candidates against emerging infectious diseases

Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/vaccine

The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of viral vector vaccines

Richard C Condit [a], Denny Kim [b], James S. Robertson [c], Jean-Louis Excler [d], Marc Gurwith [e], Thomas P. Monath [f], George Pavlakis [g], Patricia E. Fast [h,j], Jonathan Smith [j], Emily R. Smith [e], Robert T. Chen [e], Sonali Kochhar [k,l], For the Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology (BRAVATO) Working Group [1,*]

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of nucleic acid (RNA and DNA) vaccines

Denny Kim [a], James S. Robertson [b], Jean-Louis Excler [c], Richard C. Condit [d], Patricia E. Fast [e,f], Marc Gurwith [g], George Pavlakis [h], Thomas P. Monath [i], Jonathan Smith [j], David Wood [b], Emily R. Smith [g], Robert T. Chen [g], Sonali Kochhar [k,l], For the Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) [1]

Table 1
Brighton Collaboration.

Concatenated Version of Standardized Template for Collection of Key Information for Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines. For re						
1. Authorship	**2. Basic Vaccine information**	**3. Target Pathogen and Population**	**4. Characteristics of Vaccine Transgene and Expression**	**5. Delivery and Administration**	**6. Toxicology and Nonclinical**	**7. Hu and C Impo Infor**
1.1. Author(s)	**2.1** Vaccine name	**3.1** What is the target pathogen?	**4.1** Nature of the nucleic acid platform (**DNA** - synthetic, bacterial, plasmid, linear, >1 type/molecule, other; **RNA**- messenger, self-replicating, other)	**5.1** Describe how components of the vaccine formulation that facilitate stability* and delivery into cells (Section 2.4) impact the safety profile of the vaccine?	**6.1** What is known about biodistribution of the platform nucleic acid in its final formulation and mode of administration in animal models?	**7.1** W evide vaccir protec respo (e.g., passiv immu anima studie
1.2. Date completed/ updated	**2.2** Nucleic Acid Type: DNA, RNA, self-amplifying RNA	**3.2** What are the disease manifestations caused by the target pathogen in humans, for the following categories:	**4.2** Gene(s) incorporated into the vaccine (antigen, T-cell epitopes, antibiotic resistance factors, cytokines, other)	**5.2** Describe how the mode of vaccine delivery may impact safety?[1] (e.g., electroporation (please specify name of device), intradermal needle injection)	**6.2** How long does the RNA or DNA persist in vivo (may specify in tissue/ serum, proximal/ distal to site of administration)?	**7.2** De key in may i risk
	2.3 Adjuvant (if applicable)	• In healthy people	**4.3** Factors enhancing/controlling gene expression	**5.3** How might any co-administered components (e.g., adjuvants, cytokines, immunomodulatory molecules) impact the safety profile?	**6.3** What is the risk of integration of sequences from the platform nucleic acid into the host genome?	
	2.4 Final vaccine formulation components of formulation that may impact delivery into cells, stability, and safety (e.g., complexing with polymers, encapsulation within microparticles, liposomes)	• In immunocompromised people	**4.4** Non-expressed features impacting vaccine efficacy (CpG sequences, other)	**5.4** If applicable, describe the heterologous prime-boost regimen that this vaccine is a part of and the possible impact on safety	**6.4** What is the possible risk of autoimmunity or a harmful immune response?	
	2.5 Route and method of Delivery (e.g., intramuscular injection, gene gun, electroporation)	• In neonates, infants, children	**4.5** Other sequence features that may impact safety (e.g., sequences in DNA that might facilitate insertion or recombination)		**6.5** Do animal models for toxicity exist? Summarize results	
		• During pregnancy and in the fetus	**4.6** Is the transgene likely to induce immunity to all strains/genotypes of the target pathogen?		**6.6** Do animal models for immunogenicity and/or efficacy exist? Summarize results	
			4.7 What is known		**6.7** What is the	

Templates for new vaccines

What should we look for?

- Proven association with immunization
- Proven association with a vaccine platform and/or adjuvant relevant to CEPI vaccine development
- Theoretical concern based on immunopathogenesis
- Theoretical concern related to viral replication during wild type disease
- Theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms

Safety Platform for Emergency vACcines

D2.3 Priority List of Adverse Events of Special Interest: COVID-19

Body System	AESI
Neurologic	Generalised convulsion*
	Guillain-Barre Syndrome (GBS)*
	Acute disseminated encephalomyelitis
	Aseptic meningitis, Encephalitis / Encephalomyelitis*
Respiratory	Acute Respiratory Distress Syndrome (ARDS)
	Pneumonitis
Hematologic	Thrombocytopenia
Immunologic	Anaphylaxis*
	Vasculitides*
	Arthritis*
	Enhanced disease following immunisation
Other	Serious local/Systemic AEFI*
	Myocarditis
	Acute cardiac injury
	Arrythmia
	Septic shock-like syndrome
	Acute kidney injury

The most urgent immediate task for most countries is to establish the normal background rates for the adverse events of special interest.

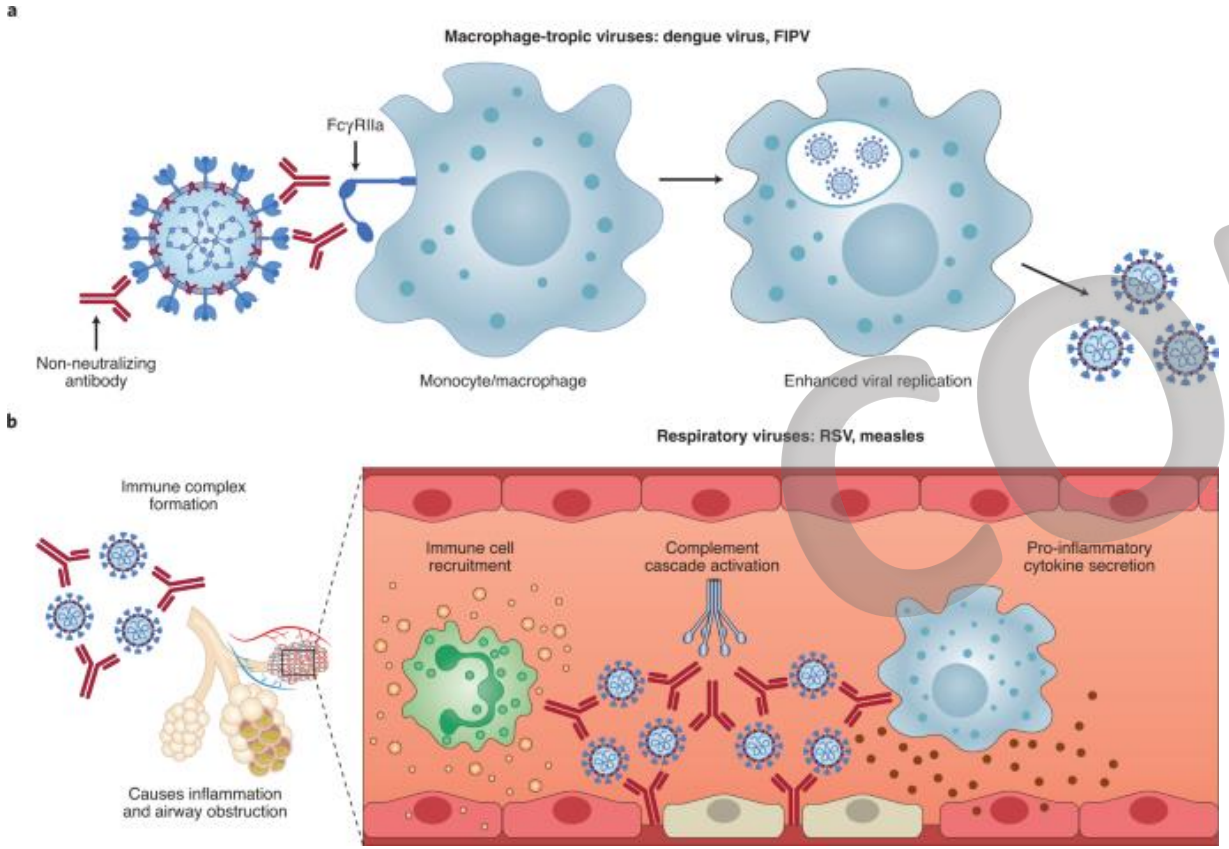
Q. What is the risk of neurological side effects/long term effects?

- A. Very low.
  - There are few examples of modern vaccines causing serious long-term adverse events
  - most recent is Yellow Fever/Dengvaxia and H1N1/Pandemrix
  - Biological plausibility lacking for many of the platforms
    - RNA, protein-based
  - Need to consider complications of COVID-19 and theoretical concerns, vaccine platforms, proven association a vaccine, theoretical from animal model

5 Dec 2020 - FOR LATE STAGE COVID CANDIDATES

- No signals from animal models
- No signals from Phase I/II immunogenicity data
- Pfizer and Moderna RNA combined ~75,000 participants to date, no signals
- Janssen and Ox/AZ viral vectors combined ~120,000

Q. What about enhanced disease?



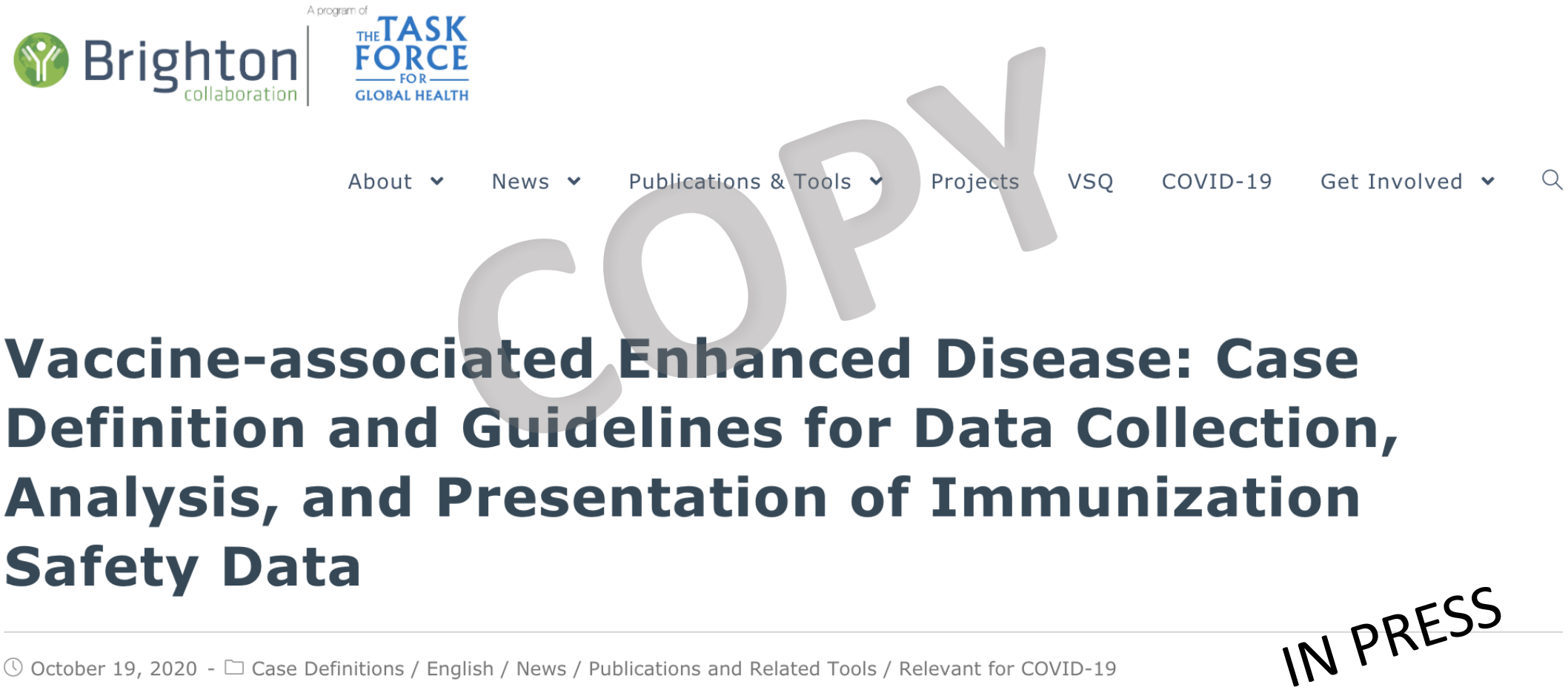
Having antibodies that do not actually neutralise the virus, or antibodies that form immune complexes can lead to enhanced disease

- Dengue fever
- Respiratory syncytial virus
- Animal model of unadjuvanted inactivated coronavirus vaccine

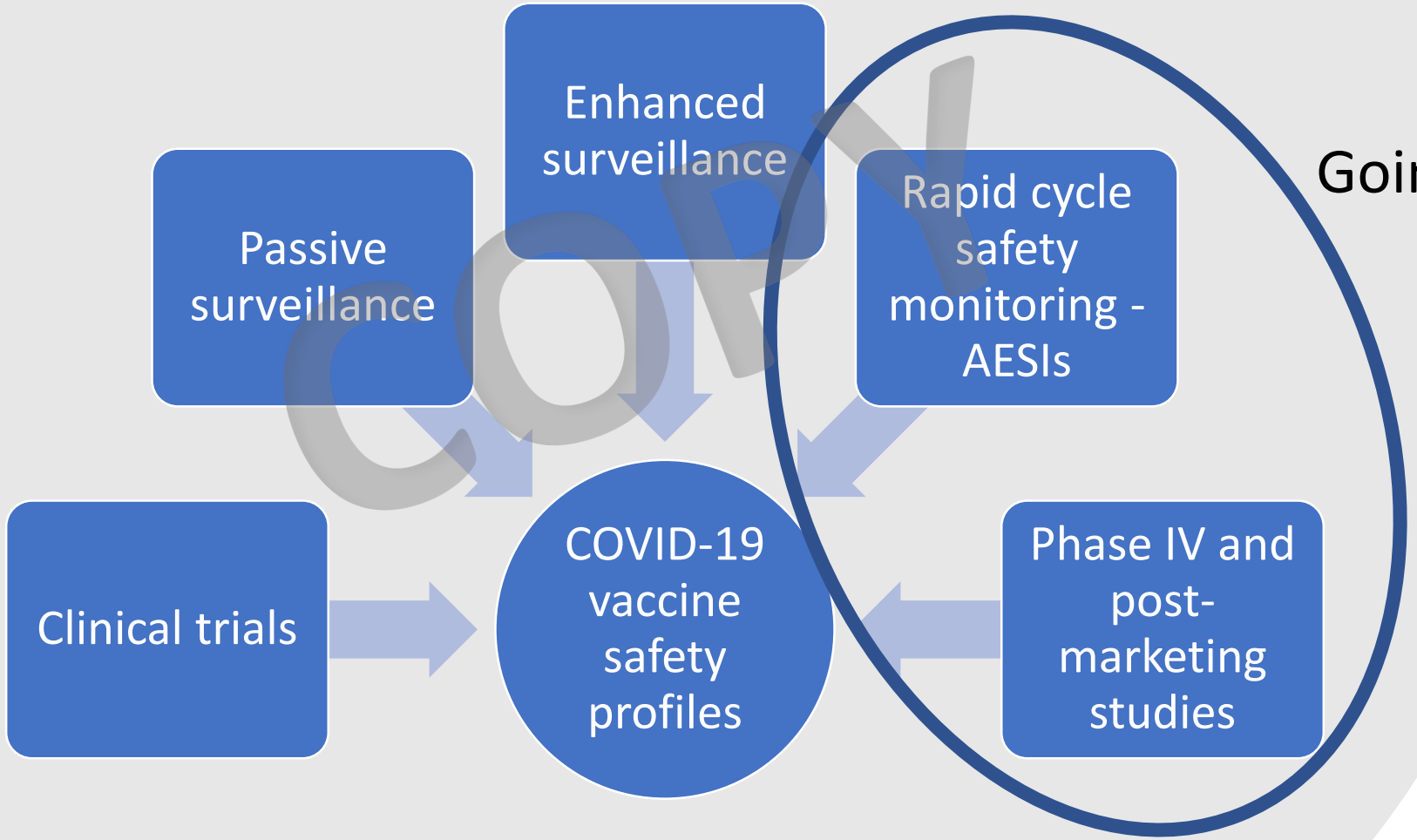
- Evidence against this so far for COVID vaccines
  - Not seen in animal models
  - Not seen in human immunogenicity studies
  - Not seen in people receiving convalescent sera
  - Not seen in the clinical trials…but early days

Nature Microbiol 2020

But this is being watched closely



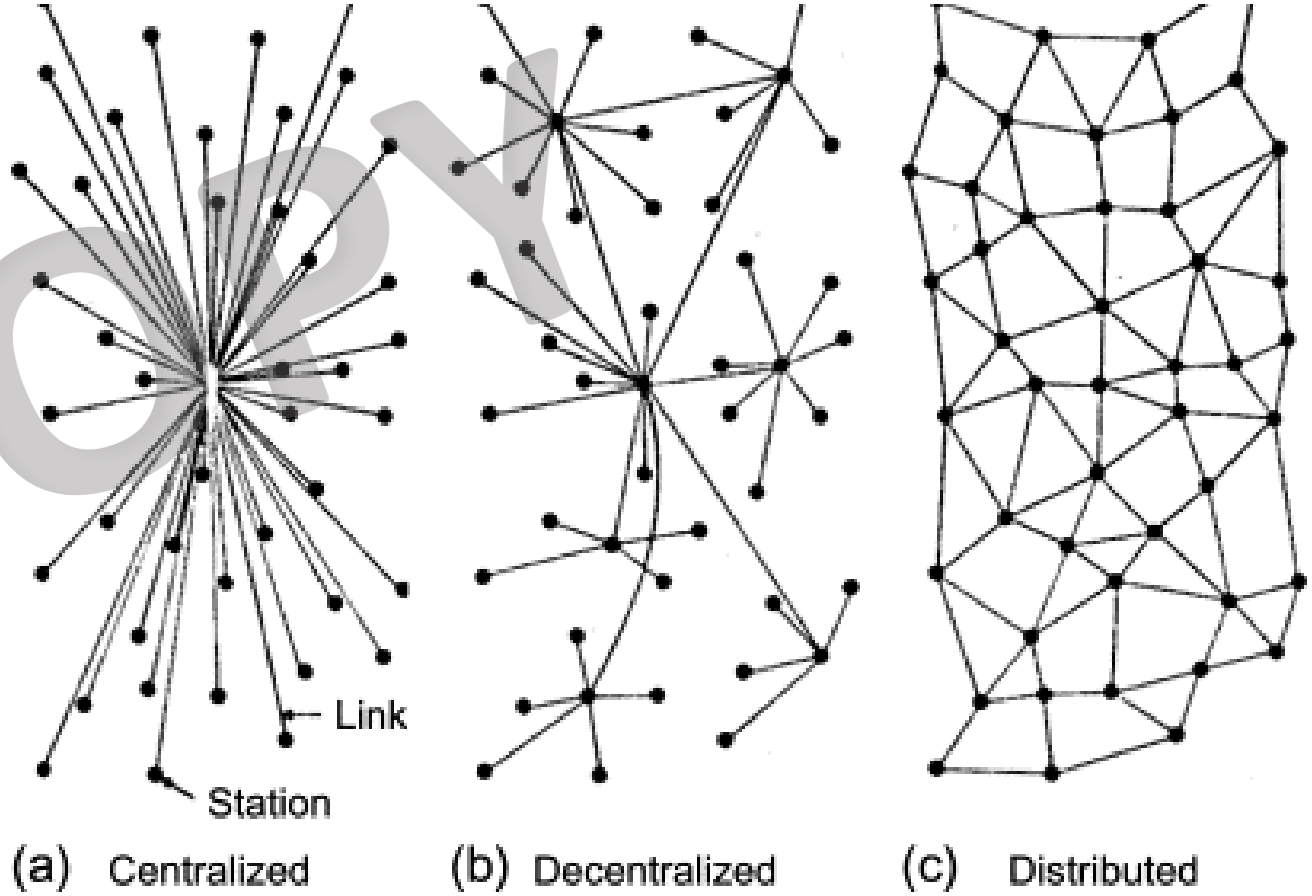
Knowing the safety of COVID-19 vaccines



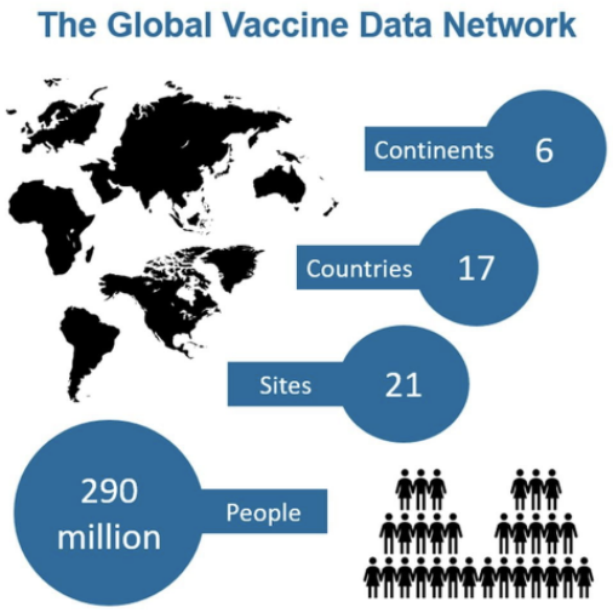
Going BIGGER!

Distributed networks

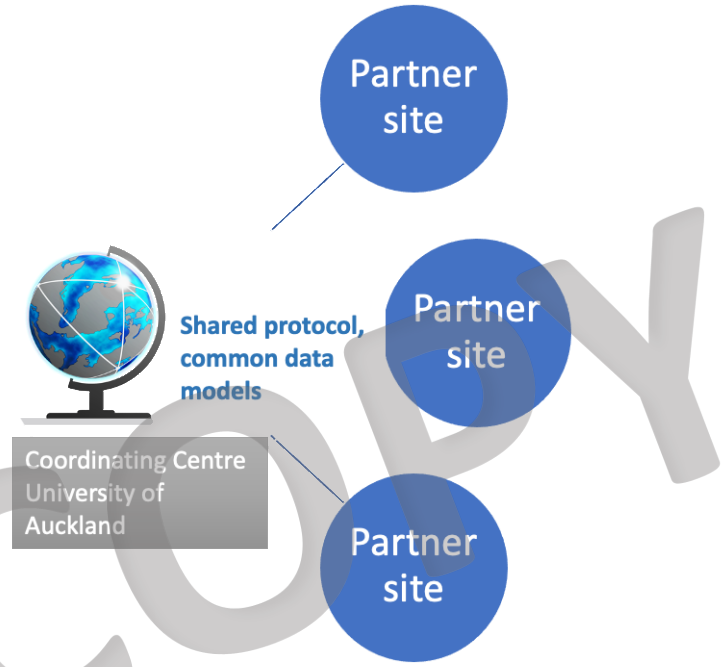
- Using common methods/protocols at different sites, different countries
- Combining outcomes in a kind of meta-analysis
- If everyone uses the same approaches, same definitions then we can combine findings



Distributed networks - Europe



The GVDN uses Big Data to assess vaccine safety and effectiveness across large and diverse populations around the world and over time.



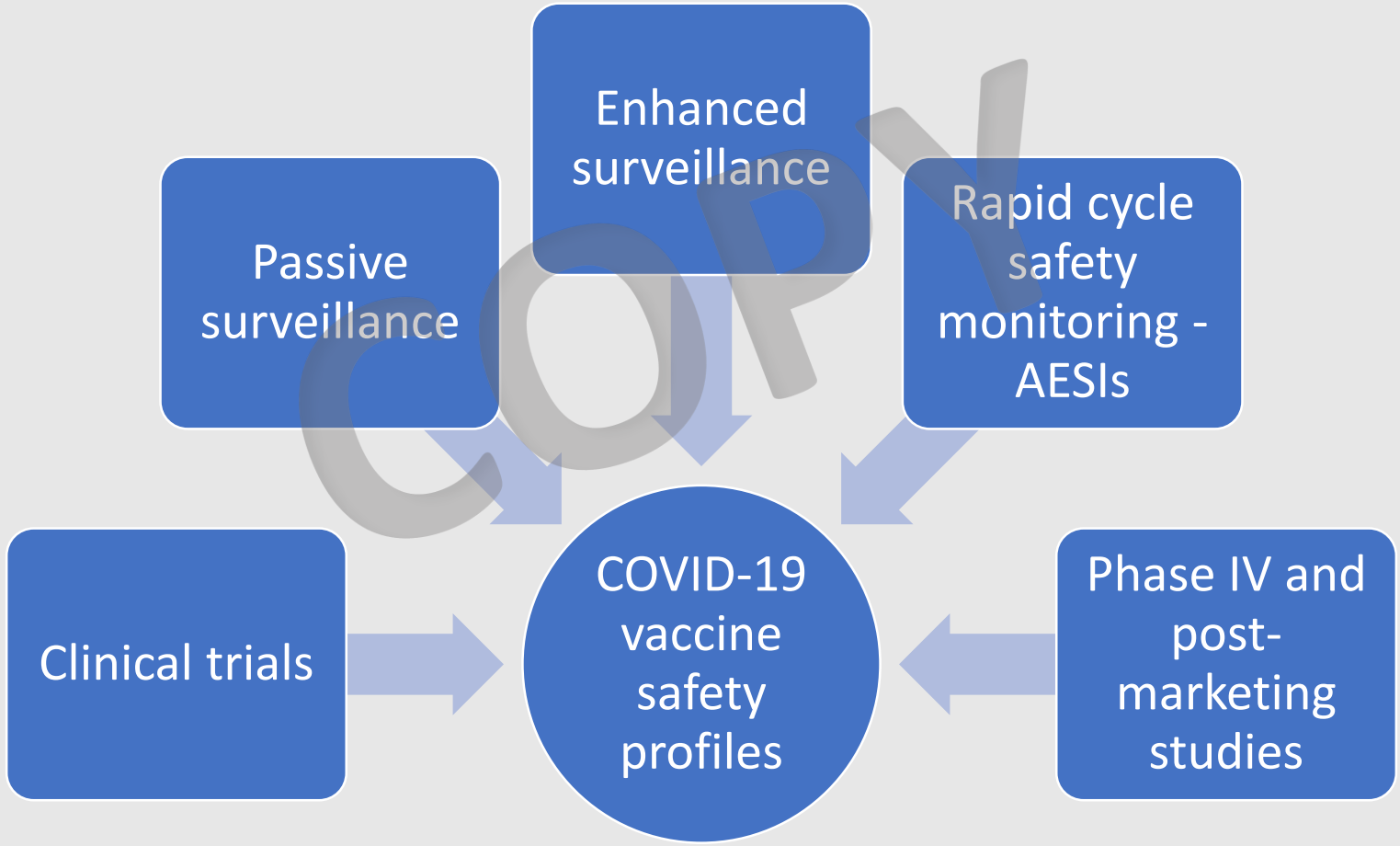
The Global Vaccine Data Network held its inaugural meeting at Fondation Merieux in Annecy on 29th and 30th January 2019, enabled by contributions from the Gates Foundation.

1. Argentina, Hospital de Niños Ricardo Gutierrez, Buenos Aires
2. Australia, Monash Health, Victoria
3. Australia, NCIRS Sydney Children's Hospitals Network, Sydney
4. Canada, British Columbia Provincial Health Services Authority
5. Canada, ICE, Ontario
6. China, School of Public Health, Peking University
7. China, Department of Epidemiology, School of Public Health, Fudan University, Shanghai
8. Denmark, Statens Serum Institut, Copenhagen
9. England Public Health England
10. Ethiopia University of Gondar
11. Europe Vaccine monitoring Collaboration for Europe
12. Finland, Finnish Institute for Health and Welfare THL, Helsinki
13. France, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris
14. Ghana Navrongo Health Research Centre
15. India, The INCLEN Trust International, New Delhi
16. New Zealand, General Practice and Primary Health Care, University of Auckland, Auckland
17. Scotland Public Health Scotland
18. South Africa, University of Witwatersrand, Chris Hani Baragwanath Hospital, Johannesburg
19. Taiwan, Health Data Research Center, National Taiwan University, Taipei
20. United States, Vaccine Safety Datalink, Centers for Disease Control and Prevention, Georgia
21. United States, Centers for Medicare & Medicaid Services, U.S. Food & Drug Administration, Maryland

Endorsements from Brighton Collaboration and CEPI

Distributed Networks - Global

Conclusions: The preclinical and clinical data gives us some optimism that COVID-19 vaccines will have a good safety profile. We will safety data beyond the clinical trials quickly and in diverse populations providing we use the tools at our disposal. We can detect and verify rare adverse events.



Thank you!

Share facts liberally ☺