



COVID 疫苗 — 保護效力、安全性、採購及施打政策

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可能的利益衝突之揭露

- 我是一些醫療產品公司所贊助的觀察性研究的主持人，I only do public domain research and I have publication rights
- 我會提供個別公司的內部教育訓練，或公司贊助的 symposium，收取合理的講師費用，但不會為個別的產品代言 (not for the last 20 years)
- 我為一些醫療產品公司提供專業諮詢
 - 部分台灣公司免費
- 演講中會舉例，但並非推廣任何公司或產品



利益衝突之揭露

- 我 27 歲的兒子在 Moderna 公司工作五年
- 某 '前台大醫師' 為何用別名？
 - <https://news.ltn.com.tw/news/life/paper/1181660>
- I wrote two recent articles
 - <https://forum.ettoday.net/news/1933514>
 - <https://forum.ettoday.net/news/1995597>
- I have served on a TFDA committee



今天的大綱 -- COVID 疫苗

- 保護效力 (efficacy)
 - 安全性 (safety)
 - 採購 (procurement)
 - 施打政策 (roll-out and priority)
-
- 國際發展及現況 & 台灣
 - 科學 實証 為基礎 但不免會談到公共政策 及 國外政治考量



為甚麼要打疫苗？

- 根除 eradicate 疾病
- 降低 morbidity 及 mortality
- 降低傳染率

- For COVID in 2021 -- reduce morbidity and mortality
 - WHO Target Product Profile (April 29, 2020)
 - <https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines>
 - WHO Interim Guidance (March 17, 2021)
 - US FDA (May 25, 2021)
 - <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19>



Demonstration of Vaccine Efficacy

- Reduction / prevention of symptomatic COVID, especially severe cases
 - BNT162b2
 - mRNA-1273
 - AZD1222
 - Ad26.COVS.S (JNJ-78436735)
 - Inactivated COVID virus
 - Protein sub-unit (no approved product yet)
- Interim or final analysis of pivotal trials
- Large study size, clinical end point



Evidence-based medicine and regulatory science

- 生物理論 → 實証結果
 - translational medicine
- Surrogate marker 的概念
 - 流行病學及生物統計的重要



What about neutralizing antibody?

- It has been used as a surrogate marker for some vaccines (**Correlates of Protection, COP**)
 - Influenza, hepatitis A, pneumococcus, meningococcus, ...
 - After the first generation vaccine was developed, second generation vaccines could be evaluated in comparison with the first generation vaccine, using neutralizing antibody as end point (e.g. head-to-head comparison, non-inferiority design)
- Scientific basis – strong correlation between **antibody titer** and **vaccine efficacy**, based on
 - Long term follow-up of study subjects
 - Data from patients with natural infections



COVID-19

- A new disease with limited follow-up information
- Antibody data from the large trials are being analyzed
- More long term follow-up data the better
- Valid COP for COVID is important
 - Second generation vaccines
 - Wider vaccine supply for lower middle income countries
 - Heterologous prime-booster combination
 - Variants



COP for COVID vaccines

- WHO effort
 - <https://www.dcvmn.org/Webinar-WHO-COVID-19-vaccines-WHO-Meeting-on-correlates-of-protection>
- Neutralizing antibody is a very promising COP for COVID, but we are not there yet
- Some relevant topics
 - Antibody assay and reference lab
 - What is the antibody titer threshold for protection?
 - Comparator in head-to-head comparison?
 - Within the same platform?
 - Across platform?
 - Immuno-bridging study and non-inferiority margin



Published and ongoing data analysis

- <https://www.medrxiv.org/content/10.1101/2021.03.17.20200246v1>
- <https://doi.org/10.1038/s41591-021-01377-8>
- NIH (NIAID)-funded analysis of the large COVID vaccine trials in the US
 - https://figshare.com/articles/online_resource/CoVPN_OWS_COVID-19_Vaccine_Efficacy_Trial_Immune_Correlates_SAP/13198595
 - Will provide solid evidence
- No WHO guidance document yet



Human Challenge Trial

- 人體攻毒試驗
 - <https://www.cde.org.tw/Content/Files/Knowledge/81a45886-86ac-4213-b27f-0785b4ef9aec.pdf>
- Human Challenge Trial for COVID
 - 1daysooner.org
 - <https://ukcovidchallenge.com/covid-19-volunteer-trials/>
 - <https://www.imperial.ac.uk/news/218294/first-volunteers-covid-19-human-challenge-study/>



Scientifically, it's complicated

- *New England Journal of Medicine*, Correspondence
 - DOI: 10.1056/NEJMc2107808

“Since Covid-19 vaccines vary with regard to immunogenicity and immune specificity, we would encourage consideration of a vaccine boost from a T-cell–skewed vaccine after mRNA vaccination to boost T-cell responses and potentially to reduce the chance of breakthrough infection through the generation of cross-protective T-cell immunity. The prevention of vaccine failure due to variants is a critical part of pandemic management.”

Douglas F. Nixon, M.D., Ph.D.
Lishomwa C. Ndhlovu, M.D., Ph.D.
Weill Cornell Medicine, New York, NY



COVID 疫苗安全性



General concept for medical products – benefit-risk calculus

- 藥品 - 給病人使用，要接受一些風險
- 疫苗 - 給外觀正常的人用，但也要承擔一些風險
- “No risk” is NOT an option
- COVID vaccines
 - University of Cambridge, Winton Centre for Risk and Evidence Communication
 - <https://wintoncentre.maths.cam.ac.uk/news/latest-data-mhra-blood-clots-associated-astra-zeneca-covid-19-vaccine/>



Medical product safety

- Reactive?
- Proactive?
- Anticipatory! Safety signals
 - Signal detection / identification
 - Signal refinement
 - Signal evaluation



Preparing for the H1N1 vaccine in 2009

- First time in human history, tens of millions of people received a new vaccine in several months
- What would happen when millions of free living people were evaluated after vaccinations?
 - A lot of adverse events!
 - Need to differentiate signal from noise -- signal detection and signal refinement
 - Infrastructure was ready in 2009 and expanded in US and Europe afterwards, ready for COVID



https://www.biomedical.org.tw/webpage/front_news_view.aspx?flag=6EbPRJ5C078%3d&id=19AC3F4F-8ED6-4E0A-ACA4-A4961D22D1F0

2009/08/05, 建立疫苗監測機制！

聯合新聞網【聯合報／陳建煒／哈佛大學公共衛生學院兼任副教授（美國麻州）蒲若芳／台北醫學大學兼任助理教授（台北市）】

Lessons learned from the 2009 H1N1 flu vaccine, a more massive global vaccine roll-out in 2021



Different data and evaluation methods over a product's life cycle

- Non-human data
- Human data
 - Clinical trials
 - Traditional randomized control trials
 - Pragmatic trials
 - Observational / epidemiology methods
 - Spontaneous reports and safety signal detection
- Important considerations
 - High quality data
 - Data accessible on a timely basis
 - Large N and Real World (heterogeneous) Data for evaluation of rare events and risk factors
 - Valid design and analysis



Some concept / terminology

- Adverse events
 - Adverse Events of Special Interest (AESI)
 - Background rates of these events
- Adverse reactions
- https://www.cdc.gov.tw/Category/Page/V_XD8H6OSUpaTIMWgopkNg



Safety of COVID vaccines

- Inevitably there are safety signals
 - Vaccine-induced immune thrombotic thrombocytopenia (VITT)
 - Myocarditis among adolescents
 - Next???
- Is there a robust safety system in place?
- Epidemiology data
 - [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)00762-5/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00762-5/fulltext)
 - doi: <https://doi.org/10.1136/bmj.n1114>



Vaccine Safety Datalink (VSD)

- Sponsored by the US CDC
- Data from health plans with electronic medical records across different states
- *Pediatrics* 1997; 99: 765–73

Vaccine Safety Datalink Project: A New Tool for Improving Vaccine Safety Monitoring in the United States

Robert T. Chen, MD, MA*; John W. Glasser, PhD, MPH*; Philip H. Rhodes, PhD*;
Robert L. Davis, MD, MPH‡; William E. Barlow, PhD‡; Robert S. Thompson, MD‡;
John P. Mullooly, PhD§; Steve B. Black, MD||; Henry R. Shinefield, MD||; Connie M. Vadheim, PhD¶;
S. Michael Marcy, MD#; Joel I. Ward, MD¶; Robert P. Wise, MD, MPH**; Steven G. Wassilak, MD*;
Stephen C. Hadler, MD*; and the Vaccine Safety Datalink Team‡‡



Lancet 1998; 351: 611-2

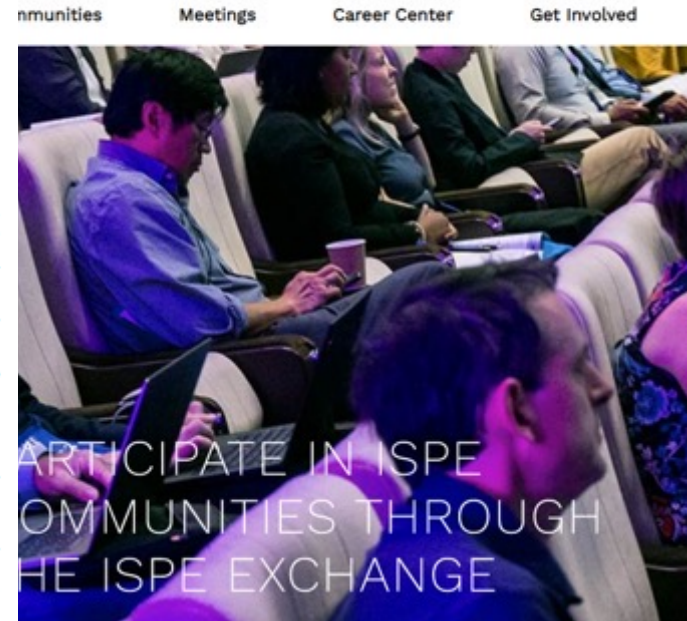
Vaccine adverse events: causal or coincidental?

See pages 637, 646

Although immunisations rank among the most important public-health measures, no vaccine is perfectly safe.^{1,2} Because vaccines are given to millions of healthy people, usually infants, extremely high standards for vaccine safety are demanded.³ It is therefore important to examine, critically and with an open mind, the report by Andrew Wakefield and colleagues of several children whose chronic bowel and behavioural abnormalities were linked by their parents and physicians to measles, mumps, and rubella (MMR) vaccination.

Robert T Chen, Frank DeStefano

Vaccine Safety and Development Activity National Immunization Program, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA



Meningococcal vaccine and Guillain Barre Syndrome (GBS)

- Vaccine was approved in January 2005
- I received an email from a senior epidemiologist of US CDC in September 2005

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; 21: 1350–1358
Published online 16 July 2012 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.3321

ORIGINAL REPORT

Study was sponsored by Sanofi Pasteur

Risk of Guillain–Barré syndrome after meningococcal conjugate vaccination

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<https://doi.org/10.1016/j.vaccine.2013.02.009>

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Contents lists available at SciVerse ScienceDirect

Vaccine

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



Algorithms for identification of Guillain–Barré Syndrome among adolescents in claims databases

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An excellent playbook in Taiwan

Vaccine 28 (2010) 7161–7166



Contents lists available at ScienceDirect

Vaccine

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

Design of a robust infrastructure to monitor the safety of the pandemic A(H1N1) 2009 vaccination program in Taiwan

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Huang et al. *Vaccine* 2010; 28: 7161-6

- Background incidence of diseases
- Monitoring vaccine utilization
- Voluntary reporting of programmatic errors
- Passive surveillance of adverse events following immunization
- Record-linkage surveillance for vaccine safety



COVID 疫苗採購

不要和生技產業發展搞在一起!!



疫苗採購 -- 國外、國內

- 殘酷的國際現況
- 2020 三月起 西方富有國家
 - 預購 超購
 - No one knows what vaccine(s) may work (somewhat like 亂槍打鳥)
- Now
 - 製造 COVID 疫苗是複雜的流程，一些疫苗的產能出了問題
 - 想買也買不到 買了也拿不到貨
- <https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-new-supply-agreement-philippines-7-million>
- <https://investors.modernatx.com/news-releases/news-release-details/unicef-and-moderna-announce-long-term-agreement-supply-vaccine>



疫苗

- 自行研發
- 外購
- 合作、代工

- 台大黃韻如教授的分析
 - <https://forum.ettoday.net/news/1917019>
 - <https://forum.ettoday.net/news/1917578>

- Not all COVID vaccine candidates have been proved to be efficacious
 - Inovio (still working on it), MSD, ...



COVID 疫苗施打政策



Roll out of COVID vaccines in Taiwan

- 第一線 的人員
 - Health care workers
 - 公車司機 警察 消防員 便利商店 超商 傳統市場 ...
- 長照機構
- ...
- 打疫苗的場所 及安排
- Cover more people with the first dose? vs.
- Reserve sufficient second dose?



Real World Evidence

- <https://www.nejm.org/doi/full/10.1056/nejmoa2101765>
- More data will be released to demonstrate vaccine effectiveness



- The best COVID vaccine is the first effective COVID vaccine available to you
- 向全國的第一線醫護人員 第一線工作人員致敬!!
- 敬祝各位身體健康
- hdrc.ntu.edu.tw

