

Principles and Practice of Vaccine Development

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Conflicts of interest

- GSK Adjuvant Advisory Board (previously)
- Expert witness in a court matter (ongoing)
- No funding received from any companies whose products mentioned
- Acknowledge the provision of slides from GSK, Dr. Birgit Beisner (these slides should be obvious)

Outline

- Vaccine Development 101
 - Costs and other parameters of drug and vaccine development
 - <https://www.australianclinicaltrials.gov.au>
 - opportunities
- What is new(ish)?
 - Adjuvants – “danger” (Matzinger), “immunologists dirty little secret” (Janeway)
 - Checkpoint inhibitors – a new dawn for cancer vaccines
 - Tissue resident memory
 - New vaccines – Shingrix™
- Where are we heading?
 - Multivalency – improving efficacy or marketing?
 - Anti-Vax lobby

Drug (and vaccine) development

- Very expensive (some exc e.g. influenza)
- Tufts Uni do periodic costing – weight R&D costs against FDA-approved products, ie. "failure incorporated"
- R&D costs of 106 randomly selected new drugs obtained from 10 pharmaceutical firms
- Journal of Health Economics 47: 2016, 20-33
- US\$ 2013 \$2.6B pre-approval + \$300M post-approval

= \$2.9B/approved product

=> Vaccine (like drug) development is limited to 'deep pocketed' companies

R&D investment recovered via pricing

- “Differential pricing” – buyin from vaccine Pharma
- GAVI post-EPI getting the vaccines to the poorest countries, but countries “graduate each year”
- Vaccines – volume tends to be less of an issue (to-date)
- What if there is insufficient volume?
- Niche vaccines for e.g. hospital infections
- Vaccines for Indigenous Australians
- Will need a high price driven by development costs to counter volume impact - who would pay?

Highest Orphan Drug Prices

Four orphan drugs cost more than \$70,000 per month this year.
There are 33 orphan drugs that cost at least \$28,000 per 30-day supply.

2016 Price Per 30-Day Rx

Brand Name

Primary Indication

>\$70K



CEPROTIN

Protein C deficiency

STRENSIQ

Hypophosphatasia

VIMIZIM

Mucopolysaccharidosis IVA
(enzyme deficiency)

MYALEPT

Leptin deficiency in lipodystrophy

\$50-\$70K



RUCONEST

Hereditary angioedema

NAGLAZYME

Mucopolysaccharidosis IVA
(enzyme deficiency)

XURIDEN

Hereditary orotic aciduria

\$40-\$50K



CINRYZE

Hereditary angioedema

IMPAVIDO

Leishmaniasis

YERVOY

Metastatic melanoma

Source: Express Scripts

30 day script
costs in US in
2016

Data from Express
Scripts (US PBM)

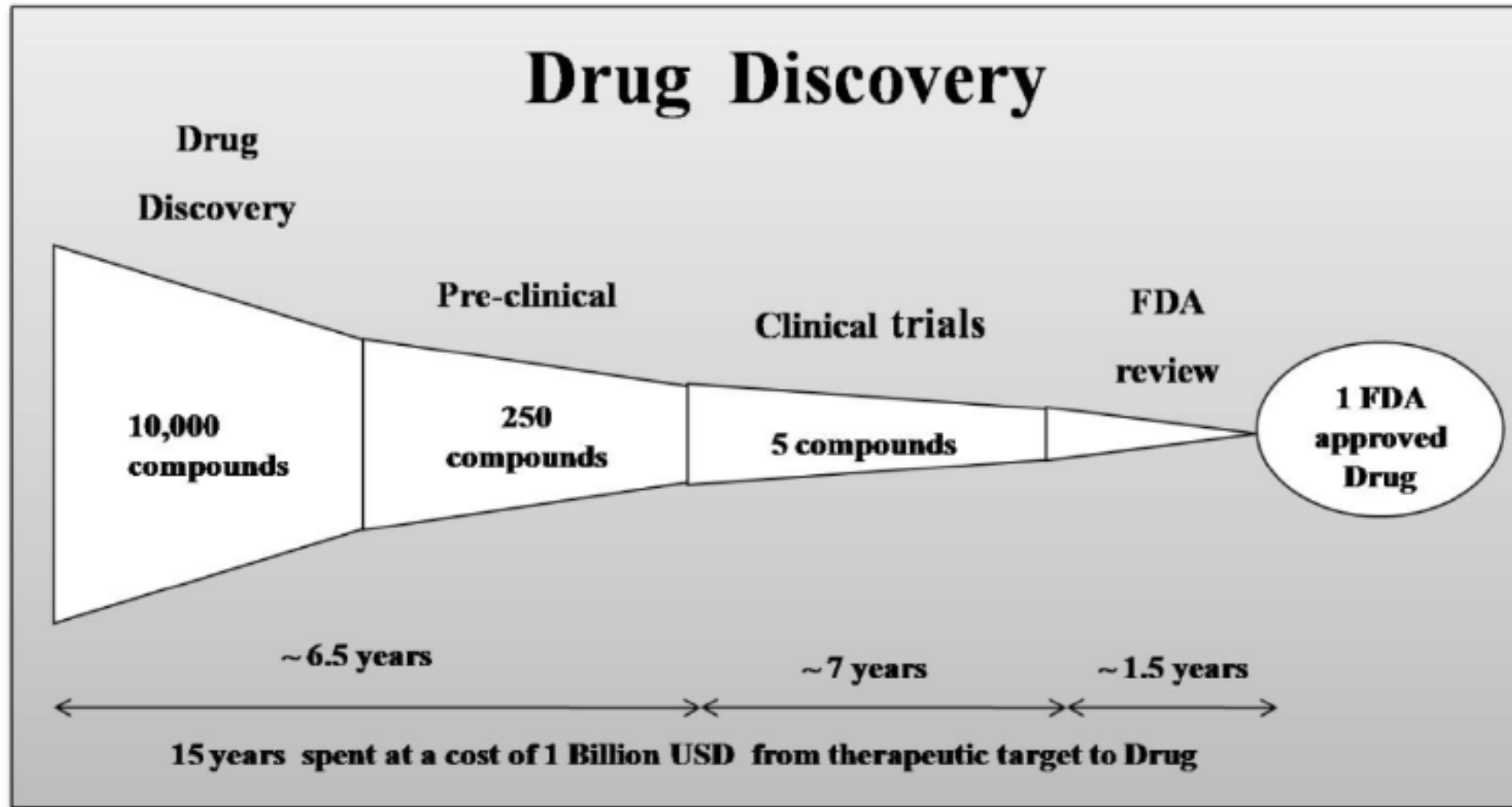
What is a vaccine that
prevents e.g. a CMV or
a KPC infection in a
cardiac transplant
patient worth?

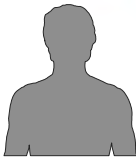
<http://lahealthexchange.com/blog/category/fda/page/2/>

Vaccine development 101

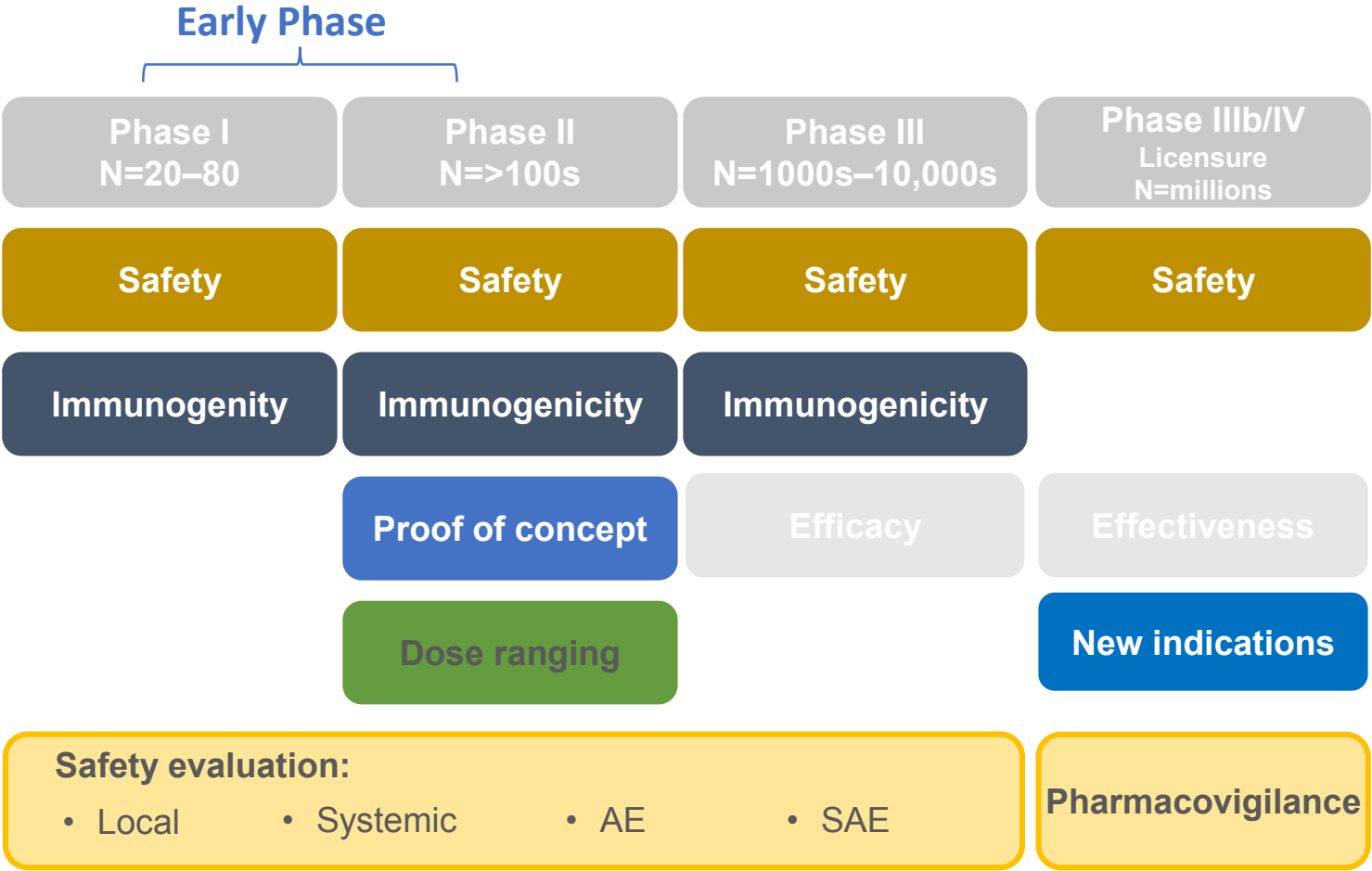
- Years of laboratory work 10-25+ post etiology, phylogeny
- Gather resources – VC, MRCF.... need health informatics
- Pre-clinical studies – toxicology, immunogenicity, seed lots..
- **Phase 1** – safety, dose escalation (1a/1b, immunogenicity?)
- **Phase 2** – proof of concept - immunogenicity
- Correlate of protection fundamental – human challenge?
- **Phase 3** – field studies (can be 1000->50,000) = pivotal trial
- Case definition important, infrastructure for diagnosis....
- **Phase 4** – post-marketing surveillance

Attrition major issue in drug development





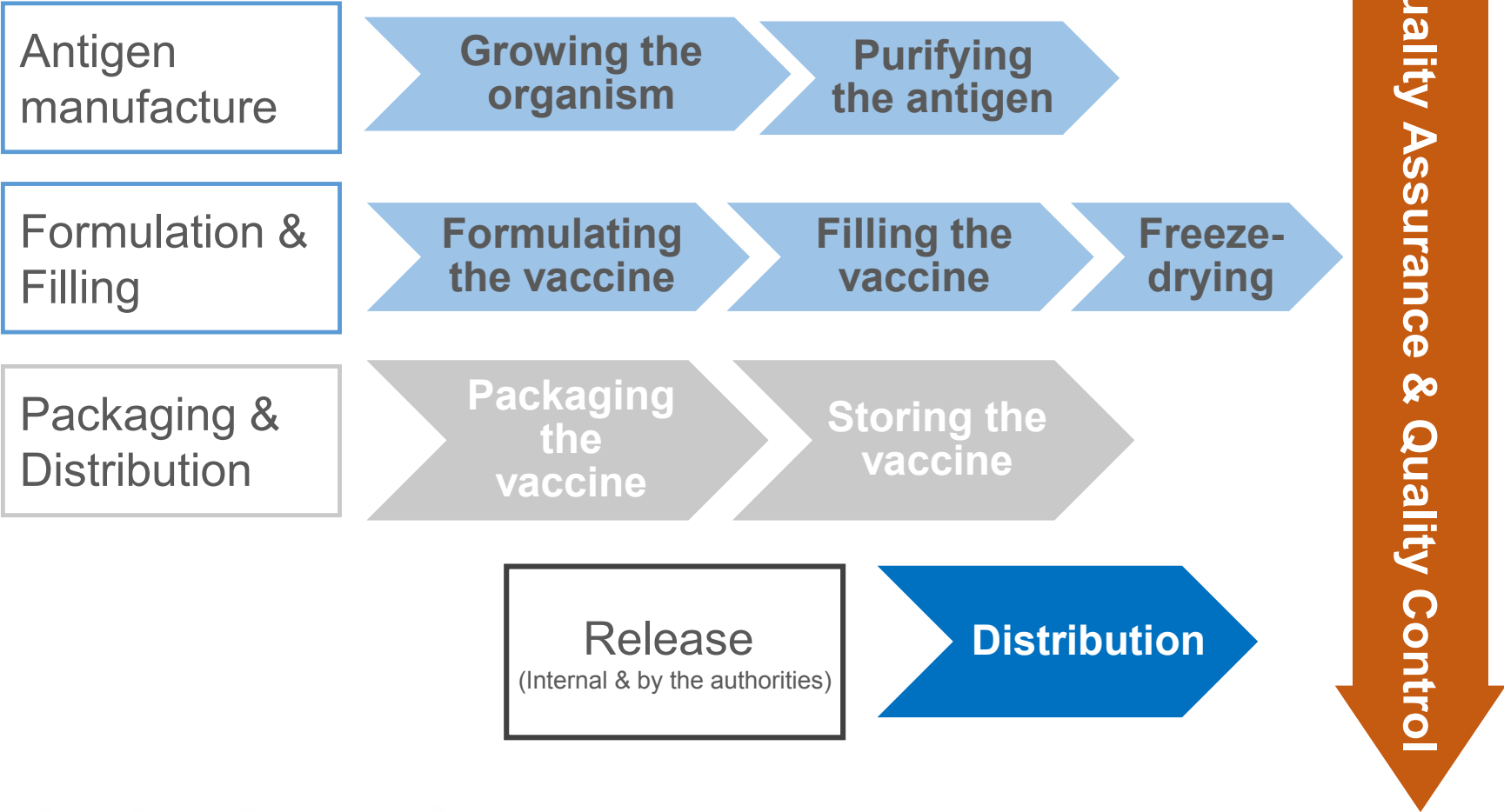
Clinical studies



AE, adverse event; SAE, severe adverse event

Leroux-Roels *et al.* Chapter 5 in: Garçon *et al.* Understanding Modern Vaccines, Perspectives in Vaccinology, Vol 1, Amsterdam, Elsevier, 2011, pp. 115–150; Douglas, Samant *et al.* Chapter 3 in: Plotkin *et al.* Vaccines, 6th edition, Philadelphia, Saunders, 2012, pp. 33–43; Baylor, Marshall. Chapter 73 in: Plotkin *et al.* Vaccines, 6th edition, Philadelphia, Saunders, 2012, pp. 1427–46

Vaccine manufacture is a multi-step process



Leroux-Roels *et al.* Chapter 5 in: Garçon *et al.* Understanding Modern Vaccines, Perspectives in Vaccinology, Vol 1, Amsterdam, Elsevier, 2011, pp. 115–50; International Federation of Pharmaceutical Manufacturers and Associations. The complex journey of a vaccine. Available at: http://www.ifpma.org/fileadmin/content/Publication/2014/IFPMA_Complex_Journey_Vaccine_Publication_2014.pdf?epoch=1394545293169 (accessed February 2014)

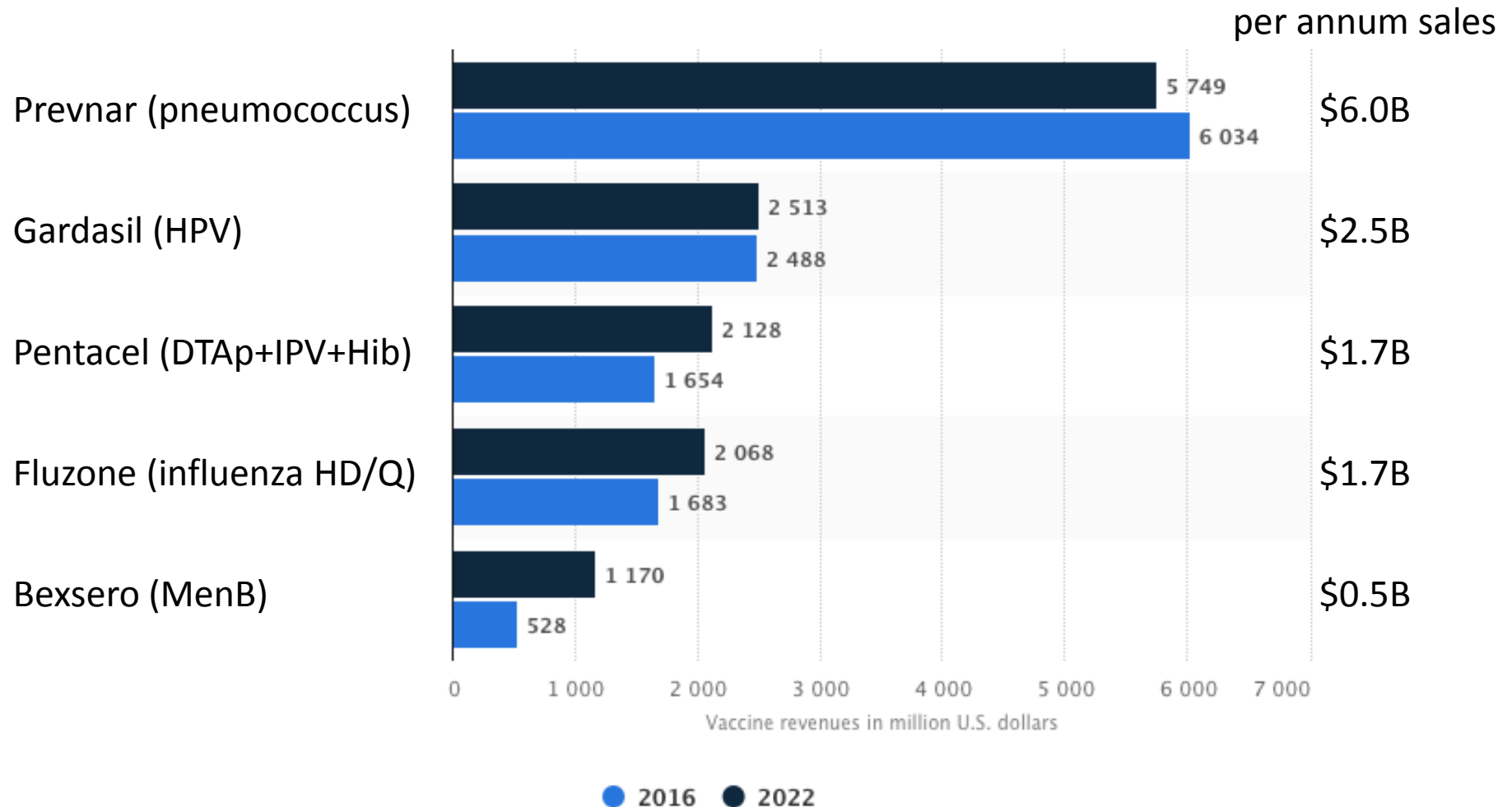
Do vaccine clinical trials happen here?

- <https://www.australianclinicaltrials.gov.au/>
- Search revealed 25 "vaccine" trials occurring, inc:
 - The B-VAX Project: Providing hepatitis B vaccinations through assertive outreach to people who inject drugs
 - ...effect of 10-valent pneumococcal-*Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV, Synflorix™) on the frequency of non-typeable *Haemophilus influenzae* (NTHi) infection
 - Human Papillomavirus (HPV) infection in young men who have sex with men
 - Optimising Rotavirus Vaccine in Aboriginal Children
- Opportunities, vaccine companies (4 large = Sanofi, GSK, Merck and Pfizer, 20-25% \$)



<https://www.statista.com/>

After all this - is there money in vaccines?



Adjuvants



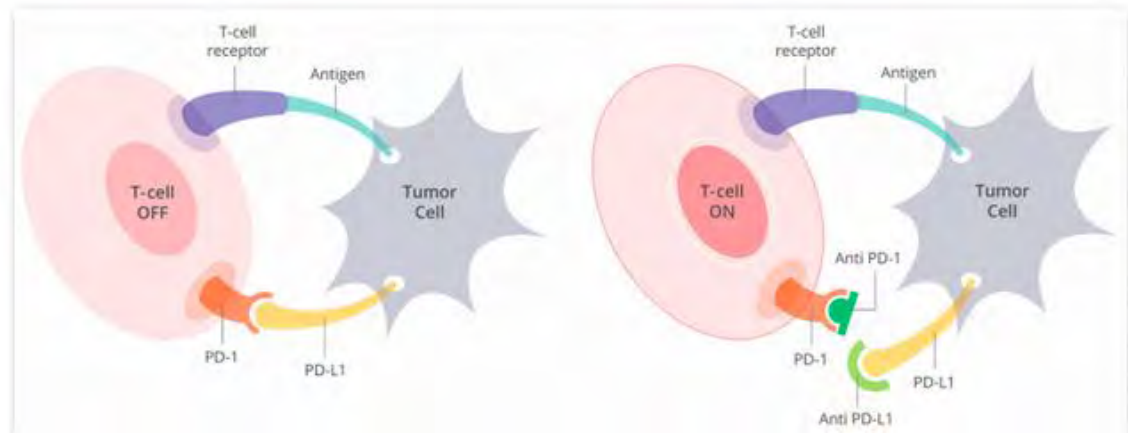
- Polly Matzinger and the “danger” hypothesis c.1994
- Paradigm shift – self vs non-self -> recognizing “danger”
- Created nexus between innate immune system -> inflammation and adaptive immune system (inflammation licensing of DCs.. -> T cells)
- “Danger” is seen as product(s) of pathogens (or cells under stress) that are detected by a growing network of sensors
 - Toll like receptors (TLRs)
 - NOD-like receptors and inflammasomes
 - https://www.adipogen.com/pub/media/Catalogs/PDFs/Inflammasome-1_2010_final_1.pdf?store=kr
- **Adjuvants work by activating innate sensors**, even Alum (+ depot)
- Li H, Nookala S, Re F. Aluminum hydroxide adjuvants activate caspase-1 and induce IL-1beta and IL-18 release. J Immunol. 2007 178(8):5271-6 and others

Adjuvants

- “Immunologists dirty little secrets” (Charles Janeway)
- New understanding of innate signaling – new adjuvants triggering TLRs, inflammasomes.... **create better danger**
- Hard to divorce potency from inflammation
- Used to ‘dose spare’ during epidemic e.g.H1N1
- Opportunities for increasing deployment, elderly use....
- e.g. MF59, AS03 = squalene, oil-in-water (o/w) emulsions
- Antigen reduction, potency has stimulated anti-Vax lobby

Checkpoint inhibitors

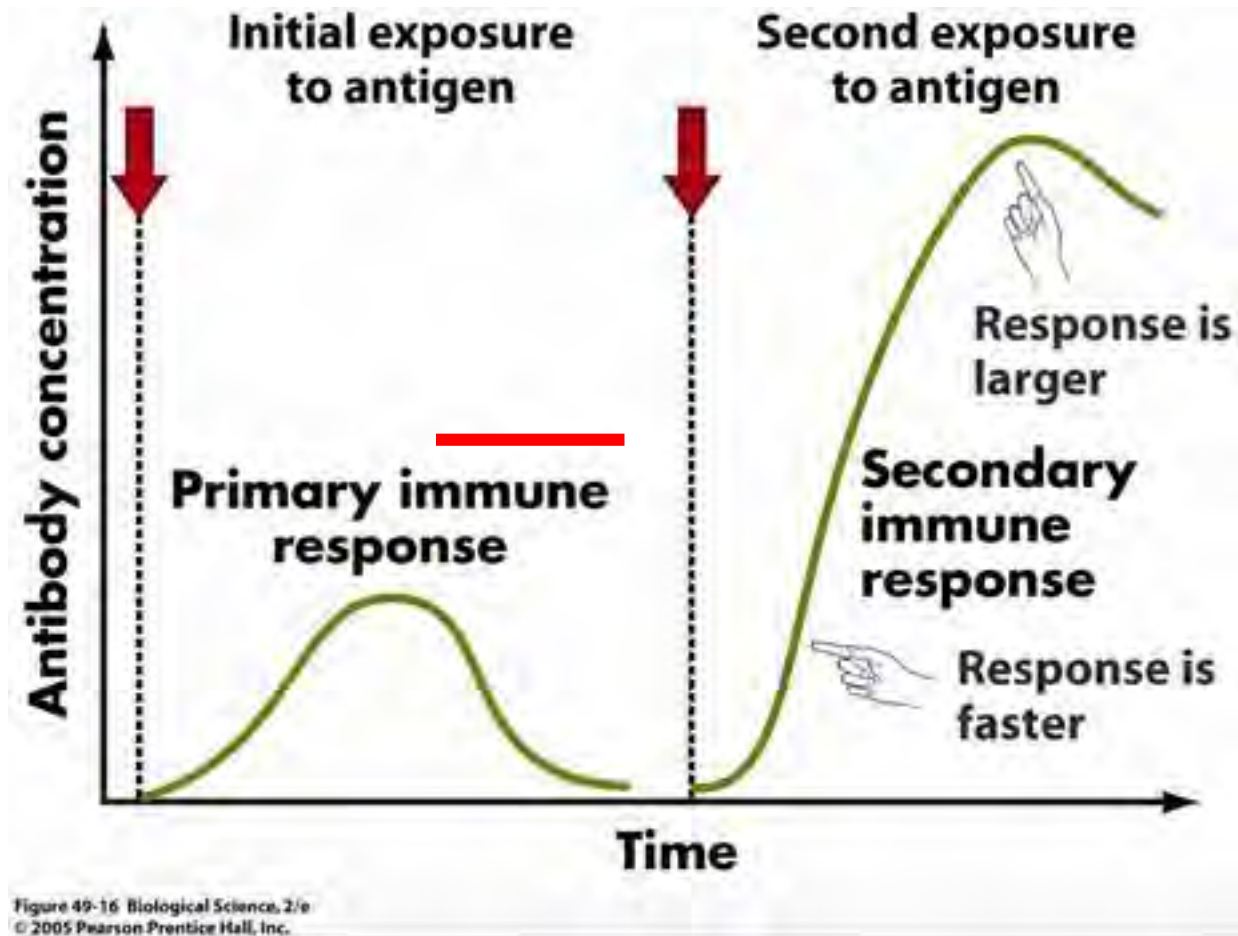
- US clinical trials.gov > Keytruda, Opdivo et al. >1300 trials
- What do they do?
 - Observation: period of activity, the immune system is regulated
 - This 'natural' regulation (or checkpoint) reduces immunopathology but also limits immune control of esp. cancer
 - Regulation mediated through ligands (e.g. PD-L1) and receptors (e.g. PD-1)
 - If antibodies can block
 - T cells keep working



Checkpoint inhibitors

- Rely on the development of an immune response
- New dawn for cancer vaccines, to be used in tandem
- Link between viruses and cancers
- Viral antigens may (again) become cogent cancer targets
- Therapeutic vaccine opportunities more generally
- Risks – autoimmunity, immunopathology

Immunological memory



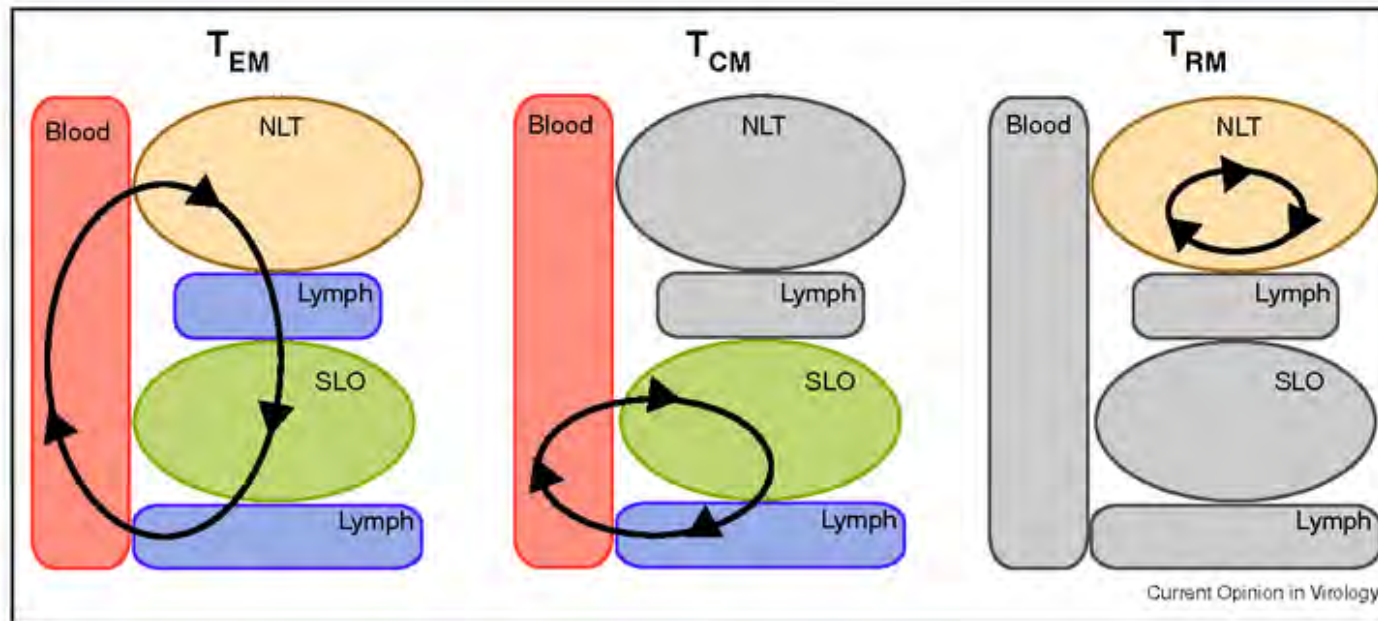
Phenomenon mediated by adaptive immune system, through engagement, activation, then clonal expansion (then contraction) of specific T and B cells

Some of the specific cells persist through the contraction phase – these cells are memory cells (esp. memory T cells)

Memory is programmed by transcription factors

Immunological memory

- Vaccines, with a **few exceptions** (e.g. tetanus) rely on immunological memory, which persists for years
- Memory no longer simple – effector memory (EM), central memory (CM) and tissue resident memory (RM)



Rosato et al.
Current Opinion
in Virology 2017

Immunological memory

- Parabiosis can establish which is most important – T_{RM} are being linked with protection inc. viruses
- One mouse immunized then joined to naïve animal
- Share T_{EM} and T_{CM}
- **Don't share T_{RM}**
- Separate and test immunity
- Can attribute role to T_{RM}



New vaccines

- Recombinant DNA-based biotechnology was supposed to solve most of problems with vaccine development e.g. pathogens that can't be grown (easily) 1980s
- “Malaria vaccine within 5 years” c.1985
- HepB vaccine, HPV vaccines, RTS-S but progress slow
- **ShingrixTM**
- ...”is lyophilized varicella zoster virus glycoprotein E (gE) antigen component with the accompanying **AS01_B** adjuvant suspension component” FDA product insert
- **AS01_B is a new adjuvant QS-21 + MPL** (LPS derived), drives T+B Diderlaurent *et al.*, 2017 Expert Reviews in Vaccines 16:55-63
- Produced in Chinese Hamster Ovarian (CHO) cells

New vaccines

ORIGINAL ARTICLE

Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older

Anthony L. Cunningham, M.B., B.S., M.D., Himlal Lal, M.D., Martina Kovac, M.D., Roman Chlibek, M.D., Ph.D., Shinn-Jang Hwang, M.D., Javier Diez-Domingo, M.D., Ph.D., Olivier Godeaux, M.D., Myron J. Levin, M.D., Janet E. McElhaney, M.D., Joan Puig-Barberà, M.D., M.P.H., Ph.D., Carline Vanden Abeele, M.Sc., Timo Vesikari, M.D., Ph.D., *et al.*, for the ZOE-70 Study Group*

RESULTS

In ZOE-70, 13,900 participants who could be evaluated (mean age, 75.6 years) received either HZ/su (6950 participants) or placebo (6950 participants). During a mean follow-up period of 3.7 years, herpes zoster occurred in 23 HZ/su recipients and in 223 placebo recipients (0.9 vs. 9.2 per 1000 person-years). Vaccine efficacy against herpes zoster was 89.8% (95% confidence interval [CI], 84.2 to 93.7; $P < 0.001$) and was similar in participants 70 to 79 years of age (90.0%) and participants 80 years of age or older (89.1%). In pooled analyses of data from

Vaccine trends

- Historical live, attenuated vaccines both highly efficacious and effective, can be single dose, adjuvants not required
- Increase in immunodeficiency – some contrived, HIV etc.
- General trend towards subunit, multiple doses
- OPV -> IPV
- Live attenuated zoster -> recombinant gE (longevity?)
- Plasma HBV vaccine -> recombinant yeast vaccine
- Some of this is around manufacturing and characterization, but reversion is a theoretical or real (OPV) risk – **adjuvants enable different immune correlates**

Vaccine trends

Multivalency to address serodiversity

- Individual vaccines – **conjugated pneumococcal vaccine**
 - 7-valent
 - 13-valent
 - 15-valent in development
 - 20-valent in development

Combination vaccines – 5-in-1, MMR....

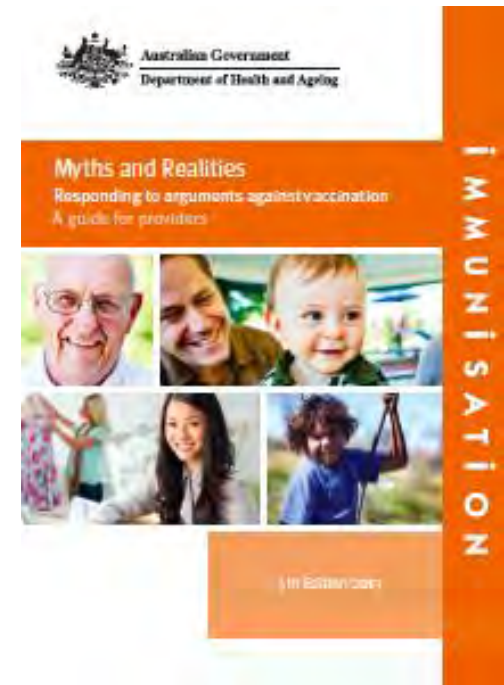
- Reduction in immunizations with new vaccines coming
- Potential for interactions, new hurdle for introduced vaccines

Anti-vaccination lobby

- Few areas of medicine have received such aggressive pushback, obstetrics?
- Largely driven off "fake news", "alternative 'facts'", "post truth"

...before these were made fashionable

- Debate provides oxygen
- Best approach - read Myths & Realities
...but it is 92 pages



Anti-vaccination messages start subtle



Andrew Wakefield - MMR, and autism

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Early Report

RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

Dr AJ Wakefield, FRCS, SH Murch, MB, A Anthony, MB, J Linnell, PhD, DM Casson, MRCP, M Malik, MRCP, M Berelowitz, FRCPsych, AP Dhillon, MRCPsych, MA Thomson, FRCP, P Harvey, FRCP, A Valentine, FRCR, SE Davies, MRCPsych, JA Walker-Smith, FRCP

Published: 28 February 1998

 PlumX Metrics

DOI: [https://doi.org/10.1016/S0140-6736\(97\)11096-0](https://doi.org/10.1016/S0140-6736(97)11096-0)

[Article Info](#)

RETRACTED

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Andrew Wakefield

Andrew Wakefield's 'dishonest and irresponsible' research into the causes of autism led to his being struck off by the General Medical Council. That would have ended most doctors' careers. Instead, the MMR 'martyr' moved to the US - and into reality TV



▲ Andrew Wakefield called for the suspension of the MMR, which caused widespread panic. Photograph: Getty Images

Wakefield trying to impact Houston election

Disgraced anti-vaxxer Andrew Wakefield aims to advance his agenda in Texas election

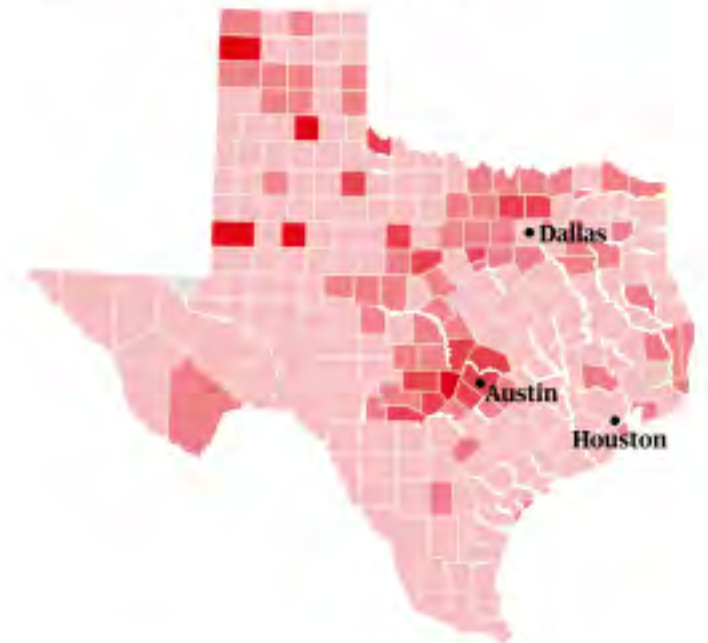
Wakefield sees Houston primary as a new start after his anti-vaccine theories were debunked and medical license revoked



The rate of Texas students who opted out of at least one vaccine doubled in seven years

2016-2017 Average of 0.97%

● No data ● < 1% ● 2% ● 3% ● >4%



Where the successful candidate will join another anti-Vaxxer



▲ Republican candidate Donald Trump during the Republican debate on Wednesday. Photograph: Justin Sullivan/Getty Images

Donald Trump blames a link to vaccines for causing autism. But he can't blame vaccines for his own apparent memory problem.

Trump GOP Debate 2015

The Republican presidential frontrunner **told the GOP debate** on Wednesday about one particular case. “People that work for me, just the other day, two years old, beautiful child went to have the vaccine and came back and a week later, got a tremendous fever, got very, very sick, now is autistic.”

Some very disturbing trends in the US

Outline

- Vaccine Development 101
 - Basic parameters of drug and vaccine development
 - <https://www.australianclinicaltrials.gov.au>
 - opportunities
- What is new(ish)?
 - Adjuvants – “danger” (Matzinger), “immunologists dirty little secret” (Janeway)
 - Checkpoint inhibitors – a new dawn for cancer vaccines
 - Tissue resident memory
 - New vaccines – Shingrix™
- Where are we heading?
 - Multivalency – improving efficacy or marketing?
 - Anti-Vax lobby

Summary - vaccination and vaccines

- Many new vaccines in the pipeline, and new uses
- Profitability, lack of patent exposure – gaining R&D attention, but some pushback from ant-vaxxers
- Hurdles for approval/use being reassessed
 - WHO Working Group 2016-2017 Typhoid vaccination
 - Changed guidelines to increase vaccine use (SAGE Oct 2017)
 - GAVI allocated funds to support expanded vaccine (Dec 2017)
 - New vaccine (Indian supplier) pre-qualified by WHO (Jan 2018)
 - Published evidence was limited, extensive immunogenicity
 - Human challenge study showing efficacy
 - Jin et al, Lancet 390:10111:2472-80 2017
- Model for other new vaccines?

It takes many years to develop a vaccine

Despite what you read on NHMRC grant proposals.....



- Safety surveillance continues indefinitely
- Additional clinical and epidemiological studies may be carried out for new indications or to assess impact and safety