Vaccines: Health care workers, influenza, new developments

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Why vaccinate health care workers?

- Protects their patients by reducing their role as sources or transmitters of influenza
- Reduces their personal risk of becoming unwell.
- Reduces absenteeism, at least during seasons of moderate to high influenza activity
  - Preserves the workforce
  - Reduces disruption by avoiding the need to relocate staff away from patient care roles
  - Reduces costs to the system

Health Care Worker Vaccinations

- US
  - All - hepatitis B, measles, mumps rubella, varicella, tetanus, diphtheria, pertussis, meningococcus, **influenza**
- UK
  - All- hepatitis B, polio, measles, mumps, rubella, varicella, tetanus, diphtheria, pertussis, **influenza**
  - Selected – BCG, meningococcus ACW135Y, hepatitis A, Japanese encephalitis, cholera, smallpox, tick-borne encephalitis, typhoid, yellow fever
- Australia
  - All – hepatitis B, **influenza**, tetanus, diphtheria, pertussis, measles, mumps, rubella,
  - Selected – BCG, hepatitis A

Health care workers and influenza

- HCWs are at significantly higher risk of influenza infection and vaccination prevents it
  - Unvaccinated HCW 3.4 times as likely to experience an influenza infection as unvaccinated healthy adults
  - Unvaccinated HCWs 2.8 times more likely to get influenza than vaccinated HCWs
  - Rates of asymptomatic infections higher in HCWs
- HCWs give influenza to their patients
  - Long term residential care facilities
  - Neonatal units
  - Renal dialysis units

Kuster, S. P.,et al. Incidence of influenza in healthy adults and healthcare workers: a systematic review and meta-analysis. *PLoS One* 2011; 6(10):e26239.

Cunney RJ, *et al*. *Infect Control Hosp Epidemiol.* 2000;21:449–51.
Hall, C. *Pediatrics.* 1975.Vol 55(5), 673-77.
Tsagris V, et al. J Hosp Infect 2012;81(1): 36-40.
Malavaud S, *et al*. *Transplantation.* 2001;72:535–7.
Elder G, *et al*. *BMJ.* 1996;33:1241–2.

HCW influenza vaccination uptake

- The Australian experience[1]
  - 10 studies from 1997 to 2008 . Vaccination rates 16.3%–58.7%.
    - Physicians 29% to 58.3%
    - Nurses 19% to 56.4%
    - Allied health professionals 23% to 57.7%
    - Ancillary or support staff 18% to 66.7%
    - 2/3 hospitals with vaccination rate over 50% had active implementation of vaccination policies or interventions.
    - Free vaccine did not increase uptake.
- Why not?[2]
  - fear of adverse reactions, lack of concern, inconvenient delivery, lack of perceived personal risk, doubts about vaccine efficacy

1. Seale H, MacIntyre R. 2011. Seasonal influenza vaccination in Australian hospital health care workers: a review. Med J Aust 2011; 195 (6): 336-338.

2. Hollmeyer HG et al. Influenza vaccination of health care workers in hospitals—A review of studies on attitudes and predictors. Vaccine 27 (2009) 3935–3944

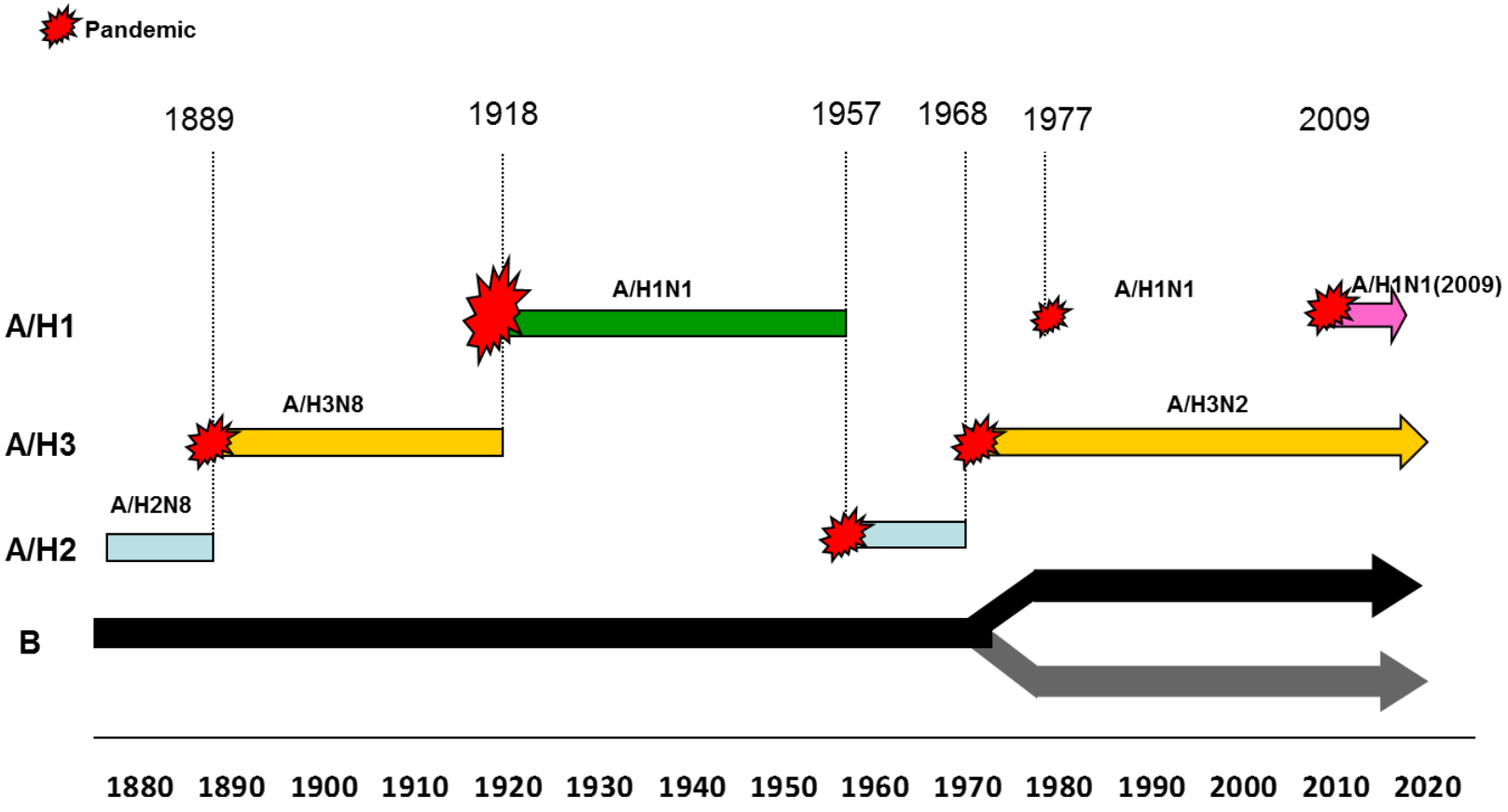
What if they don’t get vaccinated

- Encourage vaccination
  - Cost, accessibility, appropriate messages
- Discourage non-vaccination
  - Declination statements
  - Masks if not vaccinated
  - Restricted work opportunities
- Mandate vaccination
  - Effective and well accepted in many countries

Messages to HCWs

- You have a responsibility to your patients and co-workers to get influenza vaccination each year
- Side effects are minimal, serious side effects are rare
- There are few, if any, valid reasons why HCWs should not get vaccinated each year

Influenza: circulating types/subtypes



Some of the questions and controversies about influenza vaccine

- Does it prevent infection? **YES**
- Does it prevent mild disease? **YES**
- Does it prevent pneumonia, hospitalisation, severe disease, death? **YES**
- Does it protect contacts? **YES**
- Does it make you sick? Uncommonly and mild
- Is there any herd immunity? Possibly
- How long does protection last? Depends
- Which vaccine formulation should we use – quadrivalent versus trivalent? **QIV**
- When should we deliver the annual vaccine? Near as practical to the season
  - Is one vaccine a year enough?
  - Is one vaccine a year too many?
- Is protection following natural infection better than vaccine-induced protection? **YES (but at a cost!)**
- Is protection derived from live attenuated vaccines better than that from inactivated vaccines? **YES**

Solving these problems: the holy grail of influenza vaccines

- Single lifetime dose that elicits broadly cross protective immunity against current and evolving seasonal influenza antigenic drift variants
- Provides good responses to pandemic strains in naïve populations
- Not achievable, so how do we get closer to that?
  - Broader protection
  - Longer duration

Influenza vaccines: the current situation

- Egg-based inactivated split virion vaccines, with or without adjuvants
  - Most common vaccines in use
  - Long record of safety and effectiveness
  - Traditionally grown in eggs →3-6 month lead time
  - Can get problems with HA yield, egg supply
  - Adjuvants enhance responses and improve protection especially in those who respond poorly (elderly), and against novel subtypes (e.g H5)
- Cell culture based inactivated vaccines
- (Live attenuated vaccines – on their way)
  - Better and broader protection in children
  - Not good as seasonal vaccines for adults

Efficacy of influenza vaccination

- Prevention of influenza infection
  - Children: 50-90%
  - Adults < 60 years: 30% - 80%
  - Elderly > 60 years: 20% - 60%
- Prevention of illness and death
  - reduction of respiratory illness in the elderly
  - Prevention of exacerbation of underlying illness, e.g. reduces mortality due to myocardial infarction or congestive cardiac failure in patient with pre-existing cardiac disease
  - reduction of hospitalisation of elderly
  - reduction of mortality

Influenza A subtypes and vaccine effectiveness 2010-2012 WA

Levy A et al Vaccine 32 (2014) 6312–6318

Effectiveness against medically attended laboratory-confirmed influenza

	All years	Range
A/H1N1	74%	8-80%
A/H3N2	39%	-55-46%
B	56%	54-85%

Effectiveness varies across types and subtypes and is least predictable for A/H3N2

Influenza vaccine effectiveness

- **Personal level**
  - Case-control study - patients >=6 months with laboratory-confirmed influenza infection, effectiveness against hospitalisation for pneumonia
  - 2767 patients : **VE 56.7% (95%CI, 31.9%-72.5%).**
- **Population level**
  - Overall and indirect impact of vaccinating school age children
  - In primary school age pilot areas – reduced cumulative primary care influenza-like consultation, emergency department respiratory attendance, hospitalisation and excess respiratory mortality in target and non-target age groups
  - **Effective in reducing illness and impact of illness in vaccinees**
  - **Probable herd immunity effect**

Grijalvaln CG et al Association between hospitalization with community-acquired laboratory-confirmed influenza pneumonia and prior receipt of influenza vaccination. JAMA 2015;314(14):1488-97

RG Pebody et al. Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza a and b strains, England, 2014/15. Euro Surveill. 2015;20(39):pii=30029.

What can we do about it?

- Better coverage for existing vaccines
- Enhancing responses to existing vaccines
- Better vaccines
- Optimise delivery

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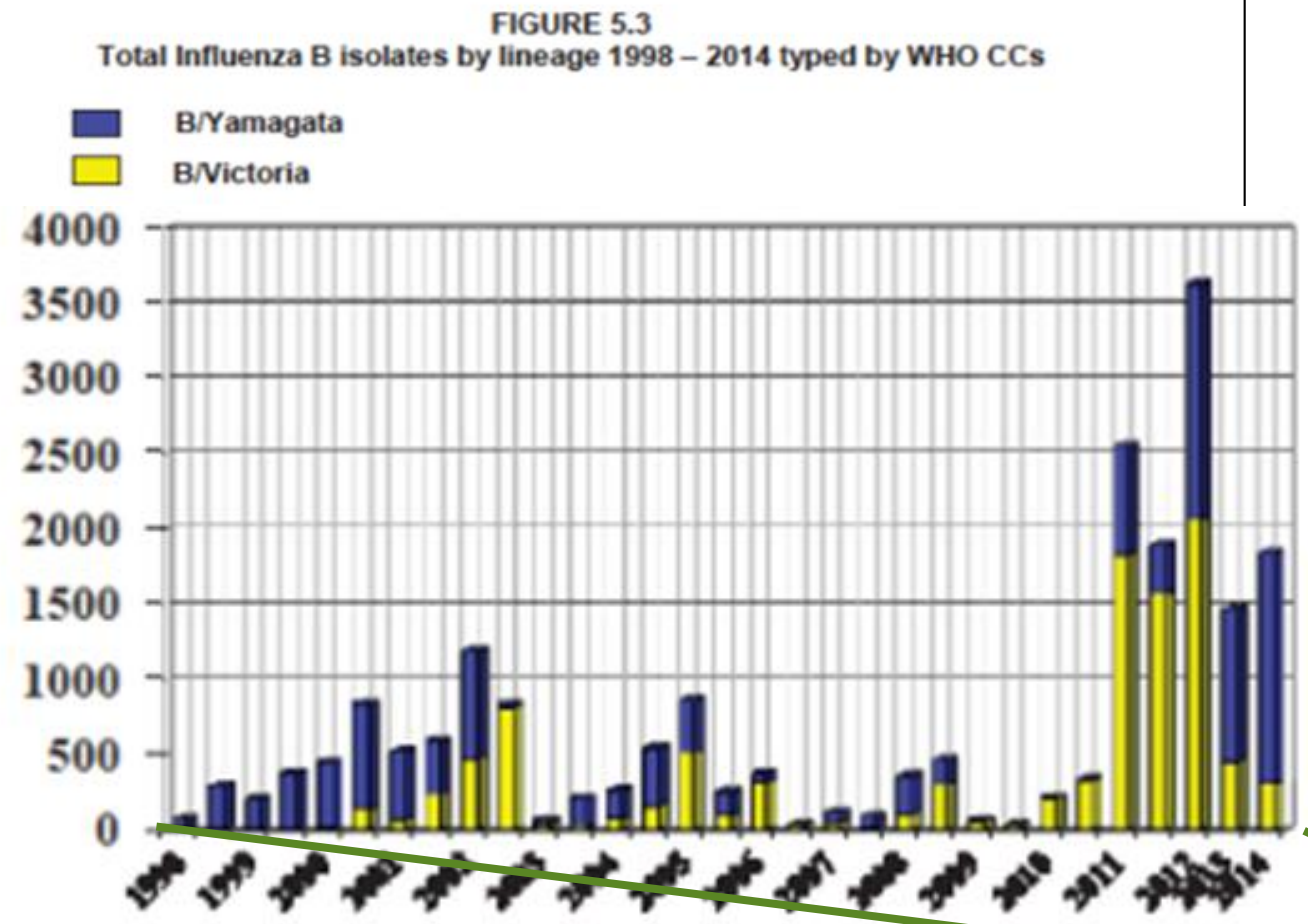
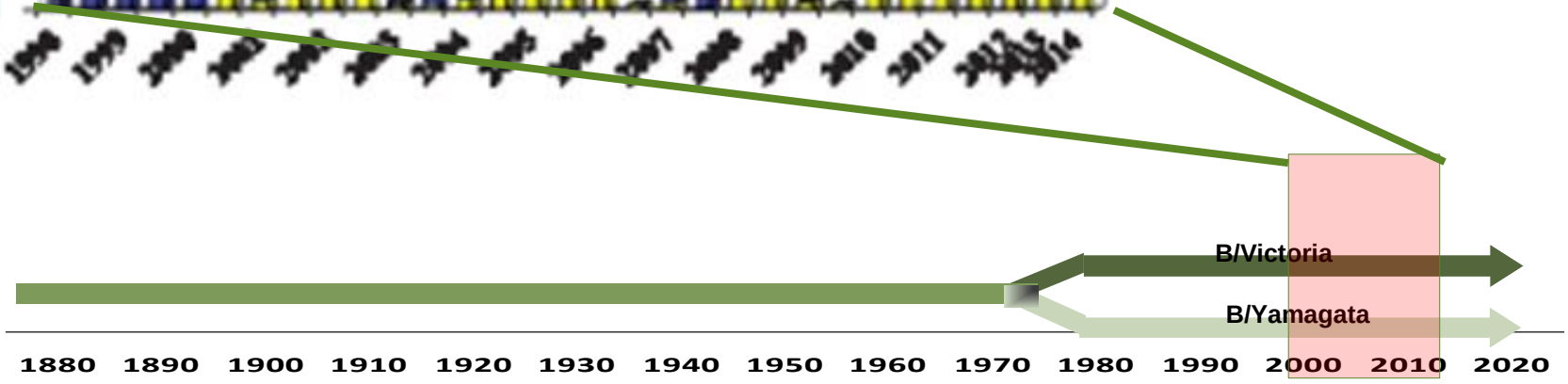
Back to Basics



- B lineages tend to switch every 3-5 years
- Patterns of lineages varies from country to country



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Quadrivalent vaccine

- Trivalent influenza vaccine (TIV) contains antigen from one influenza A/H1 strain, one influenza A/H3 strain and one influenza B strain from one lineage
- Therefore TIV can only contain antigen from one influenza B lineage
- Quadrivalent influenza vaccine (QIV) contains antigens from two influenza B strains representing the two lineages
- The WHO and the Australian Influenza Vaccine Committee currently provide recommendations for strains to put in the TIV, plus the additional influenza B strain for the QIV

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Why quadrivalent?

- QIV will offer more reliable protection against influenza B as it covers seasons where there is a mismatch between the lineage of the vaccine strain and the circulating strain, and seasons where both lineages circulate
- More flexible for use across countries with varying lineage distributions

Cost-effectiveness is also determined by:

- How often the lineage within the TIV is a mismatch with the circulating lineage
- How often there is significant circulation of both lineages
- The extent of cross-protection against the other lineage provided by the influenza B strain in the TIV
- The cost differential for the QIV versus TIV

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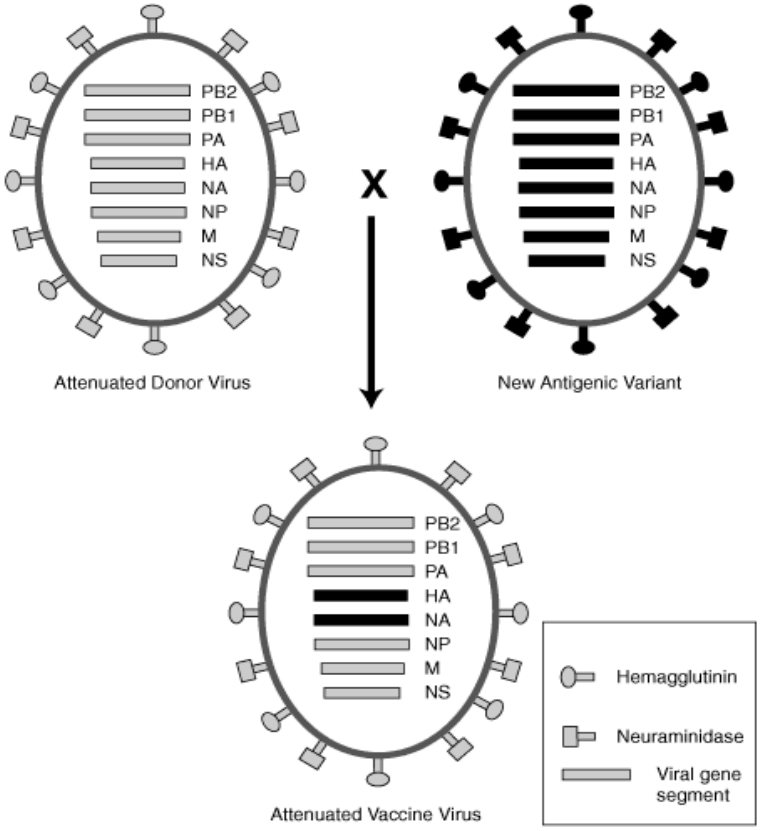
Live attenuated vaccines for influenza

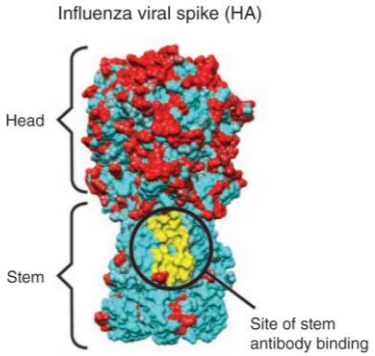


- Delivered intranasally
- Stimulate T-cell and B-cell responses
- Good efficacy in young children with broader cross-protection for drift variant compared with inactivated vaccines
- Less effective in adults due to attenuated replication
- Preferred vaccine for children in the USA and UK
- None yet licensed in Australia

Universal influenza vaccines

- Induce responses that are directed at highly conserved epitopes
- Haemagglutinin (HA) –

Stalk region more conserved than the globular head, but epitopes in head are immunodominant - standard vaccines do not induce good responses to stalk epitopes



Stalk antibodies provide more broadly protective neutralising antibodies and may also enhance antibody dependent cytotoxicity (ADCC), antibody dependent cell-mediated phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC)

- Neuraminidase (NA)
  - More conserved that HA therefore cross-strain protection more likely. May also enhance ADCC, ADCP, CDC
- T-cell responses recognise linear epitopes that are more highly conserved (HA, NP and matrix proteins)

Timing of influenza vaccines

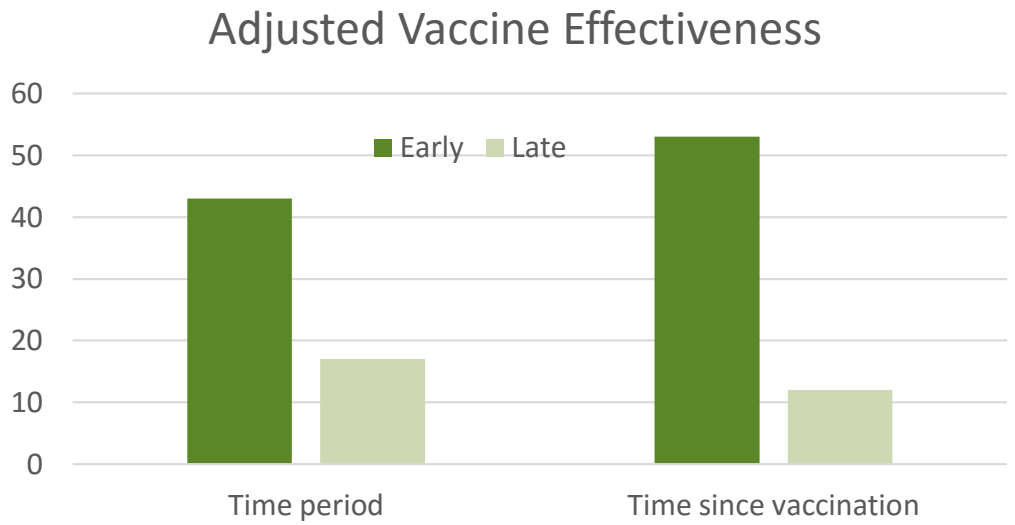
- When is the best time to deliver seasonal influenza vaccine?
- How long does protection last and is one dose a year enough?
- Is one dose a year too much?

Influenza vaccines – why a new one every year?

- Virus drifts antigenically between seasons
  - Varies from season to season, and between types and subtypes
  - Greatest drift between seasons generally seen
    - For H3N2
    - When there is a B lineage shift between seasons
- Duration of protection only lasts for a single season

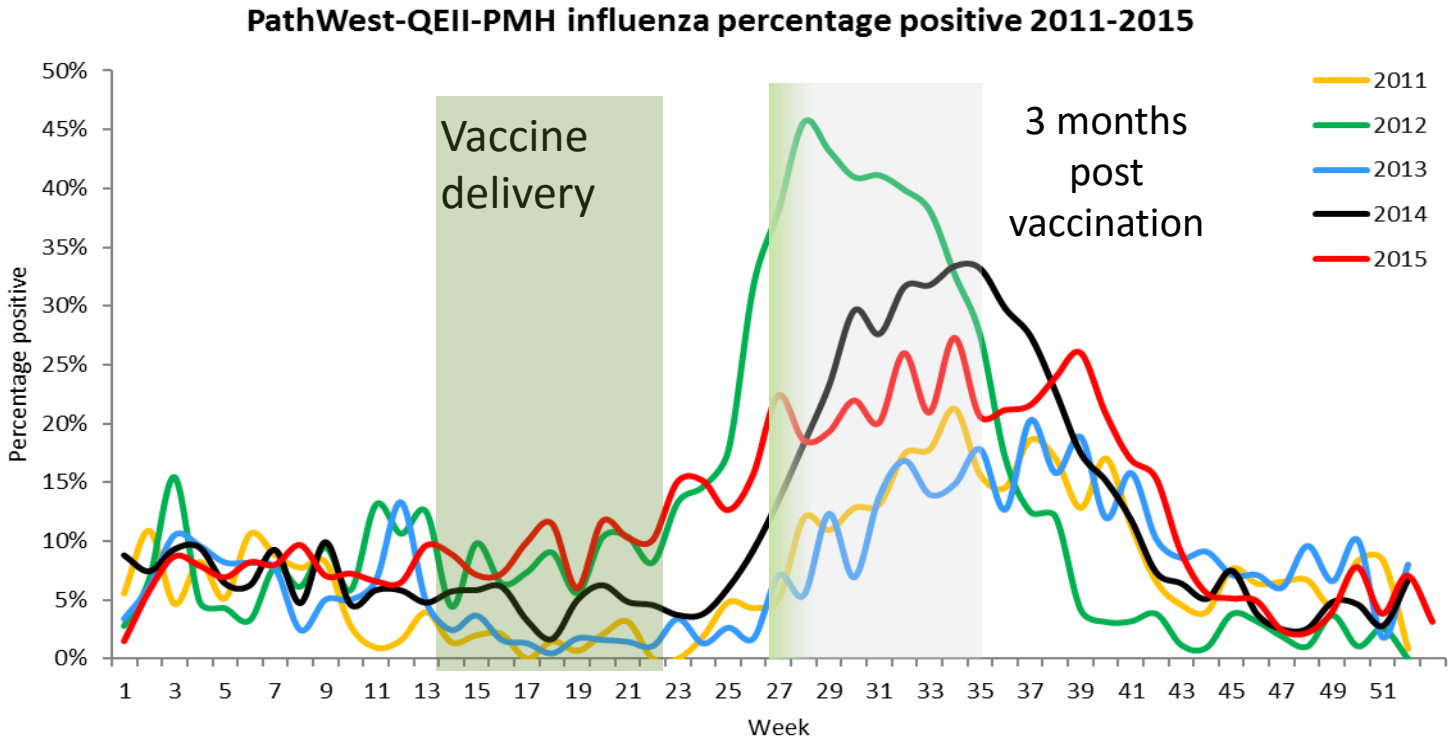
Annual influenza vaccination – not enough of a good thing?

- UK 2011/12 season[1] – protection against A/H3N2
  - Stratified analysis by time period - adjusted VE 43% for Oct to Jan, 17% Feb to Apr.
  - Stratified analysis by time since vaccination - adjusted VE of 53% for those vaccinated < 3m, and 12% for those vaccinated >= 3m.



1. Pebody RG et al. Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: evidence of waning intra-seasonal protection . Euro Surveill. 2013;18(5):pii=20389.

Do we give seasonal influenza vaccine too early?



- Current vaccine delivery timing means that many people may have declining protection before or during the peak of the influenza season

Annual influenza vaccination – too much of a good thing?

- Effects of repeated inactivated influenza vaccination among healthcare personnel on antibody response to A/H3N2 virus during 2010-11.
- Post-vaccination responses were inversely associated with the number of prior vaccinations
  - 2.3 among those with 4 prior vaccinations, 6.2 among HCP with zero prior vaccinations ($p<.0005$).
  - Titres >100 in 32% of HCP with 1 prior vaccination compared to only 11% of HCP with 4 prior vaccinations

Thompson MG et al. *Vaccine* 2016 Feb 10;34(7):981-8

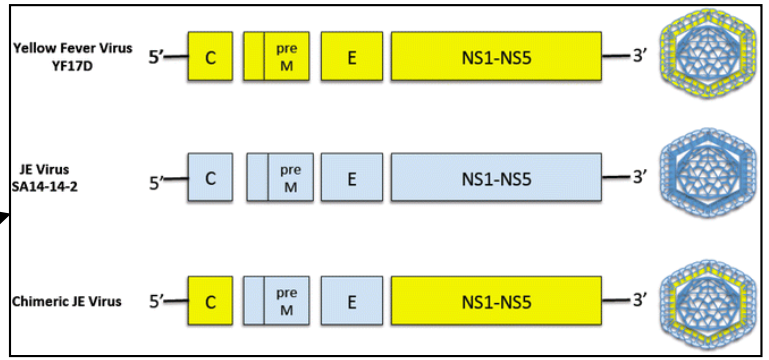
Prior vaccination and influenza VE: vaccine interference

- Vaccination provides protection against medically attended influenza infection, regardless of prior vaccination history.
- Vaccine interference is indicated if protection is lower in individuals who were vaccinated in both the current and previous season compared with those vaccinated in the current season only.
  - No evidence of vaccine interference from previous-season vaccination.
  - However, when 5 years of historical vaccination data was included, it suggested a significant reduction in current-season VE among frequent vaccinees compared with nonvaccinees.
- "Interference due to repeated prior vaccination is one possible explanation for this difference, but unmeasured confounding could also account for the observed differences"

McLean HQ et al. CID 2014:59;1375

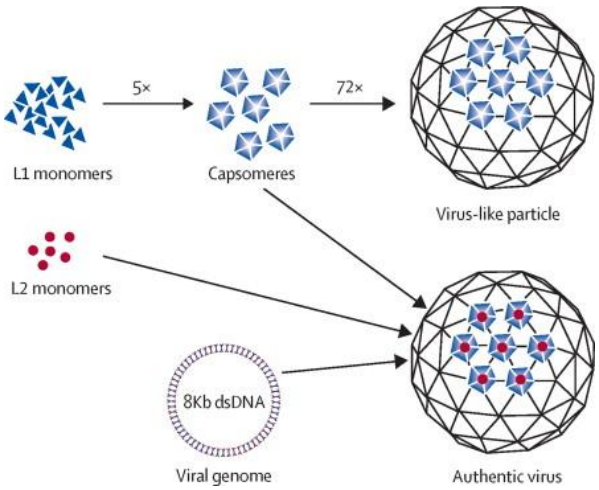
Other significant advances in vaccine delivery

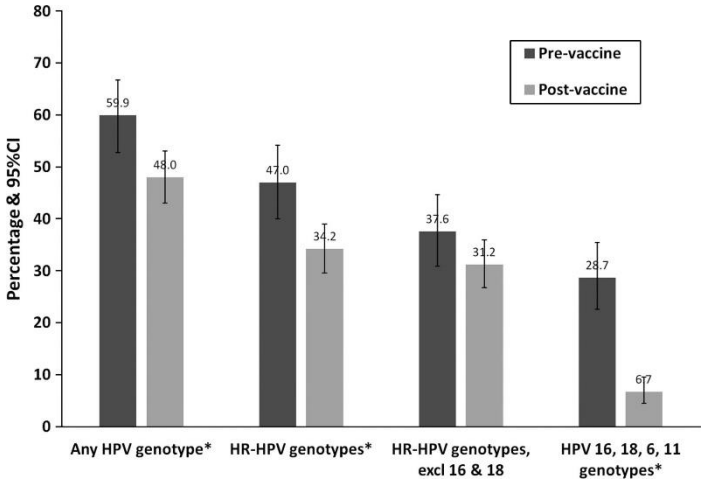
- Virus-like particles
  - Human papillomavirus
- Chimeric vaccines
  - JEV vaccine
    - Chimerivax – Japanese encephalitis virus sequences in YF backbone
  - Ebola
    - Two chimeric vaccines encoding the surface glycoprotein of *Zaire ebolavirus* (ZEBOV): one in vaccinia, one in adenovirus 3
    - Strong ZEBOV-specific neutralising antibody responses
    - Boosting of the ChAd3 with rVSV-ZEBOV increased virus-specific antibodies 12X, and increased glycoprotein-specific CD8+ T cells 5X
- DNA vaccines



Ewer K et al. A Monovalent chimpanzee adenovirus Ebola vaccine boosted with MVA. N Engl J Med 2016; 374:1635-1646

HPV vaccine





- Two types: Cervarix (HPV 16,18) and Gardasil (HPV 6,11,16,18)
- In HPV naive recipients
  - 90 to 100% effective at preventing persistent infection with vaccine genotypes and related cervical disease
  - 4vHPV vaccine also 100% effective against external anogenital and vaginal lesions due to vaccine genotypes

Sepehr N. Tabrizi et al. J Infect Dis. 2012;206:1645-1651

Value adding

- Herd immunity
  - large decline in vaccine-targeted HPV types in fully and partly vaccinated women and a smaller but significant decline in unvaccinated women,
  - suggests herd immunity in the Australian population
- Cross-protection against non-vaccine high risk types
  - 86% effective against vaccine-targeted HPV types for fully vaccinated women compared with unvaccinated women
  - 58% effective against non-vaccine-targeted but related genotypes (HPV 31, 33, and 45).

Tabrizi SN et al. **Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study.** The Lancet Infectious Diseases, Volume 14, Issue 10, 2014, 958 - 966