Vaccinations for Special Risk Groups

A Clinical update

Dr Nicole Gilroy

Senior Staff Specialist, Infectious Diseases

Westmead Hospital, NSW

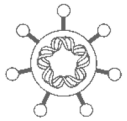
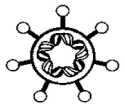
THE UNIVERSITY OF SYDNEY

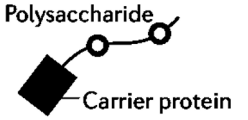
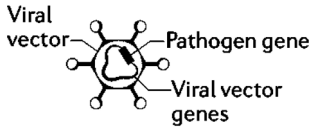
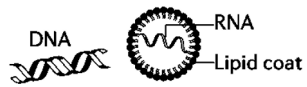
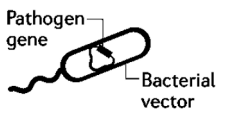
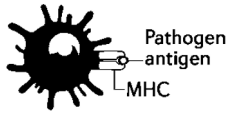
NSW GOVERNMENT Health Western Sydney Local Health Network

Overview

- Types of vaccine
- Special Risk Groups
- Funding for vaccinations in Special Risk Groups
- Strategies to improve immunogenicity
  - Protein conjugates, novel adjuvant vaccine, dosage, site of adminstration
- Recommendations

Types of vaccines

Type of vaccine		Examples
Whole organism live-attenuated (weakened but can replicate)		Measles, Mumps, Rubella Yellow Fever, oral polio, oral typhoid, rotavirus Varicella Zoster, BCG Japanese encephalitis *(Imojev*)
Killed whole organism		Rabies Inactivated polio (*IPOL*) Hepatitis A Japanese encephalitis *(Jespect)*
Toxoid		Diphtheria, tetanus
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, Hepatitis B, polysaccharide pneumococcal (*Pneumovax 23*) and meningococcal vaccine (*Mencevax*) , typhoid
Virus-like particle		Human papillomavirus

Type of vaccine		Examples
Outer-membrane vesicle		Meningococcal B Vaccine *(Bexsero, Trumenba)*
Protein-polysaccharide conjugate		Hib Pneumococcus (*Prevenar13)* Meningococcus (*Meningetec, Menveo, Nimenrix)*)
Viral vectored		Ebola SARS CoV-2 (*Astra Zeneca*)
Nucleic acid vaccine		SARS-CoV2 (*Pfizer, mRNA*)
Bacterial vectored		Experimental
Antigen-presenting cell		Experimental

Pollard Aj et al Nature reviews Immunol 2020

Those at risk of VPDs & complications

A heterogeneous population

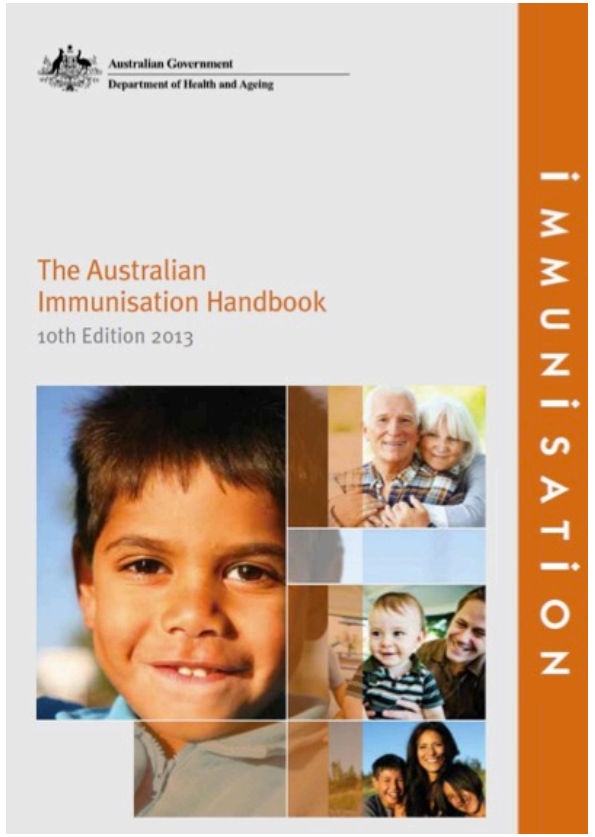
- Chronic diseases
  - *Diabetes, Cardio-respiratory, CKD & Chronic Liver Disease*
- Auto-immune/ inflammatory diseases/ immunosuppression
  - *Eg RA, SLE, Inflammatory Bowel Diseases*
- HIV
- Cancer
- Transplants
  - *Solid Organ Transplants (SOT) & Haematopoietic Stem Cell transplants (HSCT)*
- Splenectomy
- Indigenous
- Incarcerated
- Migrant populations
- Pregnancy, extremes of age

Special risk groups
What makes them special?

- Loss of immune memory from previous vaccination
  - *Immunocompromised (eg HSCT), elderly*
- Reduced vaccine efficacy
  - *Immunocompromised, ESRD, elderly*
- Increased risk of acquiring a VPD
  - *Social determinants*
    - *Poverty, nutrition, travel/migration, indigenous, PWID, occupation, aged & disability care*
  - *Immunocompromised*
- Increased risk of complications from VPDs
  - *Immunocompromised, splenectomy, pregnancy, chronic diseases*
- Increased risk of adverse events
  - ***Live vaccines** in the immunocompromised, pregnancy*

The vaccination history
Risk factors for VPD, optimising safety & efficacy

- Vaccination status?
- Vaccination status of close/ household contacts?
- Risk factors & vaccine indications?
  - Social / demographic/pregnancy
  - Immunodeficiency
  - Chronic Disease, Cancer
  - Surgeries (eg splenectomy)
  - Medications/ immunosuppression
- Vaccine contraindications?
  - Seek advice when in doubt
- Optimising vaccine use
  - What vaccine? what dose? what time?
- Barriers to vaccine uptake?
  - Hesitancy, fear, misinformation, cost



AUSTRALIAN IMMUNISATION HANDBOOK
NHMRC
https://immunisationhandbook.health.gov.au

Vaccination
Funding

- National Immunisation Program
  - Primary Childhood Immunisation Schedule
  - Adolescent vaccine (dTpa, HPV, Men ACWY)
  - Adult vaccines for at risk (eg age >65, indigenous status, pregnancy, comorbidity, splenectomy)
- State-funded
  - Eg Japanese encephalitis (Torres Straits); Rabies (post-exposure); HBV in at risk populations (immunosuppressed, HCW, PWID, sex workers, household contact with HBV etc)
- Pharmaceutical Benefit Scheme
  - Diphtheria-Tetanus booster-adT booster (Prescriber bag)
- Private-out of pocket

National Immunisation Program (NIP)

- Federally funded

- Covers 17 infectious diseases

  - 6 Bacterial diseases
    - Pneumococcus, Haemophilus, Meningococcus, Diphtheria, Tetanus, Pertussis
  - 8 Viral diseases
    - Rotavirus, Hepatitis B, MMR, polio, VZV, HPV

  - + additional funding Hep A (indigenous)
  - + additional funding Influenza (at risk)

    + Staged population roll out (adults, <18 yrs TBA)
  - COVID-19

NATIONAL IMMUNISATION PROGRAM (NIP) –AUSTRALIA

July 2020

	Birth	2 mo	4 mo	6mo	12 mo	18mo	4yr	10-13	14-16	>65
Hep B	×	×	×	×						
DTPa		×	×	×		×	×	**dTpa**		
Hib		×	×	×		×				
Polio (IPV)		×	×	×			×			
Pneumococcus		13vPCV[1]	13vPCV	13vPCV risk factors or Indigenous (WA, NT, SA, QLD)	13vPCV		23vPPV risk factors or Indigenous (WA, NT, SA, QLD			13vPCV (>70)
Rotavirus		×	×							
MMR					×	×				
Meningococcus		Men B Indigenous	Men B Indigenous	Men B Indigenous with risk factors	Men ACWY Men B Indigenous				Men ACWY	
Varicella Zoster						×				 × (70-79 yrs)
HPV								× **2 doses**		
Influenza[3]				>6 months & medically at risk (inc immunocompromised, indigenous, pregnancy) All non-indigenous children > 6 months and <5 years						x

1. Indigenous Australians also recommended for Hep A (12 months) Prevenar 13 followed by pneumovax23 (>50 yrs)) Influenza (all >6 months) Men B (all at 2,4,12 months)
2. Pregnant women funded for influenza and pertussis vaccination
3. Splenectomy patients funded to receive(Men B, Men ACWY, Prevenar13, Pneumovax23, Hib)
4. Meningococcal and pneumococcal vaccination in high risk groups

What is recommended*, is not always funded

- Herpes Zoster vaccination
  - Recommended ≥60yrs
  - Funded ≥70 yrs

- Haematopoietic stem cell transplants
  - Recommended childhood reimmunization post transplant
  - Few vaccines are funded

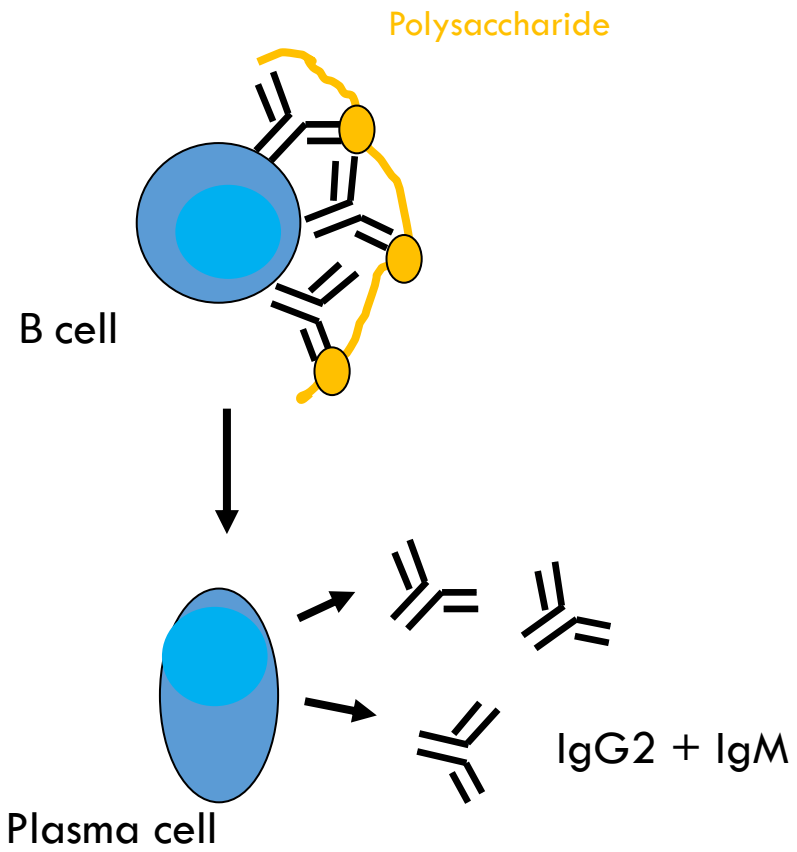
*AUSTRALIAN IMMUNISATION HANDBOOK (NHMRC)
https://immunisationhandbook.health.gov.au

Strategies to improve immunogenicity

Protein conjugate vaccines

- **Principle**- Using a polysaccharide vaccine and conjugating this to a protein (eg tetanus toxoid) increases T cell-dependent immune response and improves immune memory
  - Pneumococcus- Prevenar13
    - 15 valent and 20 valent vaccines in Phase III trials
  - Meningococcus- 4vMCV (ACWY)
  - Haemophilus influenzae type B-Hib

Polysaccharide vaccines (PV)
23 PPV (Pneumovax 23), 4vMPV (Mencevax)

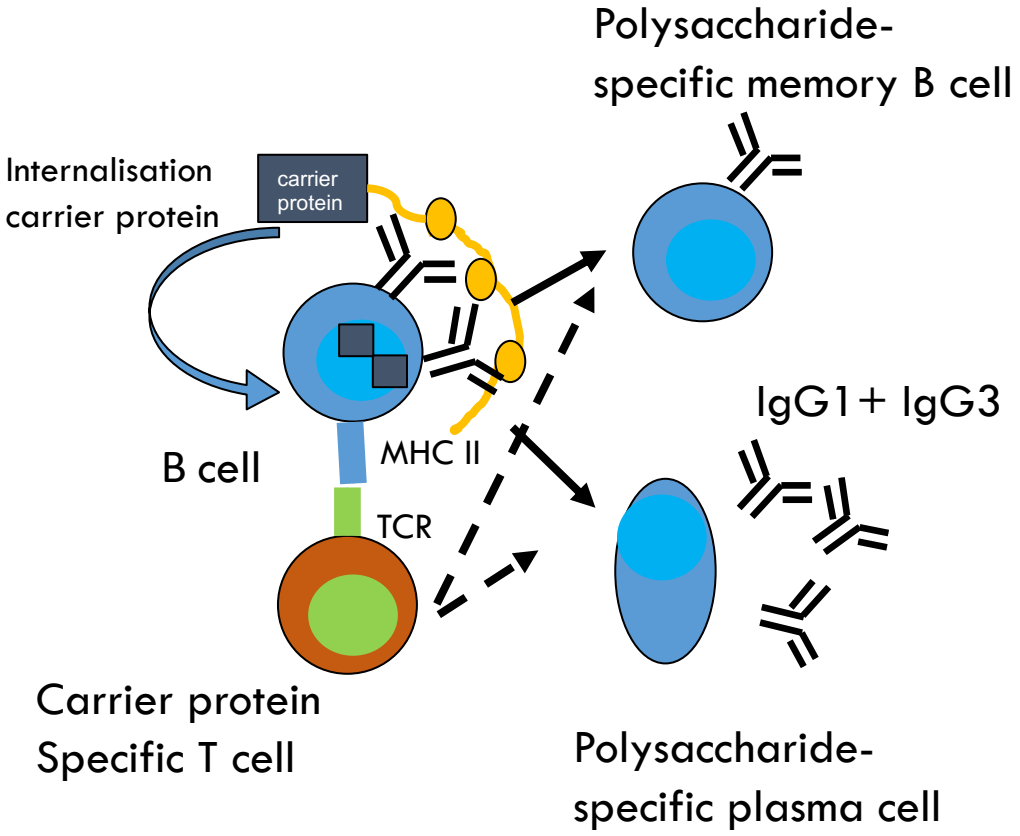


- T cell independent
- Ab production short-lived
- No memory B cells
- No affinity maturation
- Elicits no, or poor, immune response
  - <2 yrs
  - Immunocompromised

Pollard AJ et al Nature reviews Immunology (2020)
Siber et al N ewEngl J Med (1980)
Stevens R et al J Clin Immunol (1983)

Protein-conjugate vaccine (CV)

13v PCV (pneumococcal) , 4vMCV (meningococcus) Haemophilus (Hib)



- T cell dependent
- Memory B cells
- Affinity maturation
- Improved immunogenicity
- Mucosal immunity
  - blocks colonization
- Herd immunity

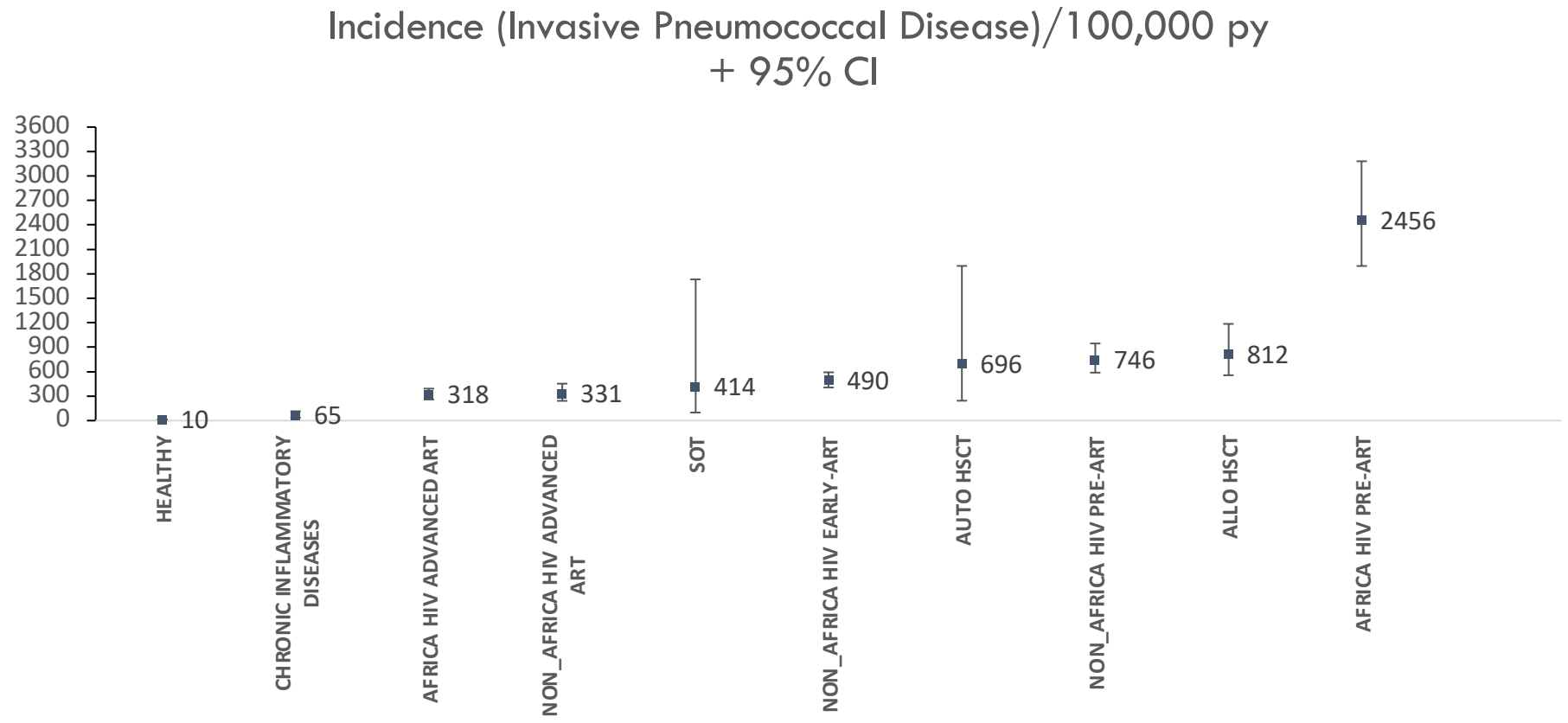
Pollard AJ et al Nature reviews Immunology (2020)
Siber et al N ewEngl J Med (1980)
Stevens R et al J Clin Immunol (1983)

Asplenia and hyposplenia vaccinations

Funded under NIP since July 2020

Baseline (at least 14 days post splenectomy)	2months	5 yearly boosters	Annual
Meningococcal B *Bexsero*	Meningococcal B *Bexsero*		
Men ACWY (conjugate) *Nimenrix,*	Men ACWY (conjugate) *Nimenrix*	Men ACWY (conjugate) *Nimenrix*	
Pneumococcal (conjugate) *Prevenar13*	Pneumococcal (polysaccharide) *Pneumovax 23*	Pneumococcal (polysaccharide) *Pneumovax 23* * Up to a maximum of 2 boosters per lifetime	
Haemophilus influenzae type B *Act-Hib*			
Influenza (to coincides with influenza season)			Influenza

Invasive Pneumococcal Disease
Immunocompromised populations



Adapted from Van Aalst et al Travel Medicine & Infect Dis (2018)

Pneumococcal vaccinations
Recommendations & funding

Recommended, NIP funded

- >70 yrs (Prevenar13)
- Previous episode of invasive pneumo disease
- Congenital or acquired immunodeficiency
- Haematological malignancies **
- Transplants**
- HIV
- Cochlear implants, CNS shunts(with proven suspected leak)
- Relapsing or persisting nephrotic syndrome
- CKD (eGFR <15), dialysis

Recommended vaccines:
Prevenar 13, followed 8 weeks later by Pneumovax 23 (“Prime-boost”)
If Pneumovax 23 administered first, wait 12 months before giving Prevenar 13
Up to 2 further doses of Pneumovax 23, at 5 yr intervals (maximum 2 boosters per lifetime)
** For patients receiving rituximab, defer vaccination for at least 6 months

Pneumococcal vaccinations

Recommendations & funding

Recommended, NIP funded	Recommended, not NIP funded
• >70 yrs (Prevenar13) • Previous episode of invasive pneumo disease • Congenital or acquired immunodeficiency • Haematological malignancies ** • Transplants** • HIV • Cochlear implants, CNS shunts(with proven suspected leak) • Relapsing or persisting nephrotic syndrome • CKD (eGFR <15), dialysis	• Immunosuppressive therapies **(incl anticipated IS) • Non haematological cancers receiving chemoradiotherapy, or planned for therapy • Diabetes • Chronic Liver Disease • Chronic resp disease (CF, bronchiectasis, Severe asthma, COPD, fibrotic lung disease) • Cardiac disease (Congenital, ischaemic, failure) • Smokers • CKD (eGFR 15-<30)- Stage 4 disease

Recommended vaccines:

Prevenar 13, followed 8 weeks later by Pneumovax 23 (“Prime-boost”)

If Pneumovax 23 administered first, wait 12 months before giving Prevenar 13

Up to 2 further doses of Pneumovax 23, at 5 yr intervals (maximum 2 boosters per lifetime)

** For patients receiving rituximab, defer vaccination for at least 6 months

Meningococcal vaccinations
Recommendations & funding

Recommended, NIP funded
Men ACWY (Nimenrix)
Men B (Bexsero)

- Asplenia, hyposplenia
- Complement deficiency
- Eculizumab

Meningococcal vaccinations
Recommendations & funding

Recommended, NIP funded Men ACWY (Nimenrix) Men B (Bexsero)	Recommended, not NIP funded Men ACWY (Nimenrix, Menveo, Menactra) Men B (Bexsero, Trumenba)
• Asplenia, hyposplenia ** • Complement deficiency** • Eculizumab**	• HIV, regardless of CD4 count** • HSCT** • Laboratory workers- Men ACWY(1 dose) Men B (2 doses) • Traveller (Hajj)- Men ACWY(I dose) only • Young adults/ adolescents close quarters- Men ACWY(1 dose) Men B (2 doses) • Young adults/ adolescents who smoke-Men ACWY(1 dose) Men B (2 doses)

Recommended vaccines:
For immunocompromised adults **:
2 doses Men B (Bexsero), 8 weeks apart; 2 doses of Men ACWY, 8 weeks apart
3 doses Men B (Trumenba) 0, 1-2 months, 6 months; 2 doses Men ACWY, 8 weeks apart
** For patients receiving rituximab, defer vaccination for at least 6 months

Strategies to improve immunogenicity

Adjuvants

- **Principle-** Adjuvants (aluminium, oil in water emulsions, TLR agonists, nanoparticles, virosomes, liposomes etc) combined with vaccine antigens enhance the immune response
  - Immune cell recruitment at the site of administration
  - Enhanced antigen presentation
  - Enhanced transport to regional lymph nodes

  Examples
  - MF59- Influenza vaccine (Seqiris, Fluad)
  - $AS01_B$-Recombinant Zoster Vaccine (RZV, Shingrix)
  - AS04- Human papillomavirus vaccine (Cervarix)
  - CpG-Hepatitis B (Heplisav-B)

Recombinant Zoster Vaccine
Shingrix

- Inactive subunit vaccine (HZ/su) for prevention of shingles
- Two dose schedule (0, 2 months)
- VZV glycoprotein E(gE) + $AS01_B$ adjuvant
  - $AS01_B$
    - MPL (stimulates innate immunity, cytokine release)
    - QS-21(antibody and T-cell mediated immunity)
- Phase III studies demonstrating high efficacy in > 50 yo (97.2%) and >70 yo (89.8%), 3-4 yrs f/up

James SF et al Ann Pharmaco therapy 2018

Recombinant Zoster Vaccine
Shingrix

- TGA registered product (2018), not marketed until 2021
- More immunogenic than Zostavax (the live attenuated vaccine)
    - Efficacy >90% cf 50%, with more durable immune responses
- Indications:
    - For patients > 50 yrs, including those planned for immunosuppression
- Theoretical risks with immune stimulation
    - Autoimmune disease
    - Transplants
        - *Await more safety data from clinical trials*

Recombinant Zoster Vaccine
Immunocompromised Host

- A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in **autologous hematopoietic cell transplant recipients**

  Stadmauer et al Blood 2014

- Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine **in HIV-infected adults**: a phase 1/2a randomized, placebo-controlled study.

  Berkowitz et al J Infect Dis 2015

- Cellular and humoral responses to gE were significantly higher for at least a year when compared to saline placebo

- No safety issues

Recombinant Hepatitis B vaccine
Heplisav b

- New generation Hepatitis B vaccine (not TGA licensed)
- Adjuvant (CpG1018)- TLR 9 agonist
- FDA-approved for use in adults Nov 2017
- 2 dose schedule (0 and 4 weeks)
- Significantly higher sero-protection rates in adults (18-70 yrs) and those with type 2 diabetes compared to Engerix B (using 3 doses; 0,1,6)
- Can complete vaccination course by 1 month cf 6 months

Medical letter Drugs & Therapeutics JAMA 2018; 319: 8:822

Strategies to improve immunogenicity

Hepatitis B-High antigen doses or intradermal administration

- Hepatitis B vaccination ESRD
  - Dialysis formulation 40 mcg (0, 1, 6 months) or 2 x20 mcg each arm (0,1,6 months)
- Hepatitis B vaccination HIV, post HSCT
  - Children receive adult formulation
  - Adults receive 2x20 mcg dose each arm (0,1,2 and 6 months)
- Non-responders
  - ~10% Hep B vaccinees do not attain an antibody titre ≥10 mIU/ml
  - Administer a booster dose→recheck sero-status
  - If negative sero-response after booster, give another 2 doses one month apart
  - If non-response, intradermal vaccination an option

    Eg 0.25 ml (5ug/ dose) x4 doses i.d, 2weeks apart

Playford et al Infect Control and Hospital Epidemiol (2002)

Influenza

Recommendations 2021

- For adult <65 yrs & paediatric population
  - Inactivated quadrivalent vaccine
    - 2 A subtypes (H3N2 + H1N1) +
    - 2 B lineages (Victoria +Yamagata)

- For ≥ 65 yr olds
  - Inactivated adjuvant quadrivalent vaccines (aQIV) with enhanced immunogenicity
    - Adjuvant (MF59) vaccine (*Fluad quad*)
    - High dose (4 x standard antigen) (*Fluzone High dose*)- not in use 2020, 2021

Influenza vaccination

Adjuvanted & High dose in transplant recipients

- Randomized Controlled Trial of **Adjuvanted Versus Non-adjuvanted Influenza Vaccine** in Kidney Transplant Recipients

Kumar D et al Transplantation 2015

- MF-59 adjuvant not associated with increase in allo-antibodies
- Higher immunogenicity in 18-64 year olds
- Those on MMF had esp poor responses

- Standard-dose Versus **High-dose Flu Vaccine** in Solid Organ Transplant.

Kumar D et al Poster ID Week San Diego 2017

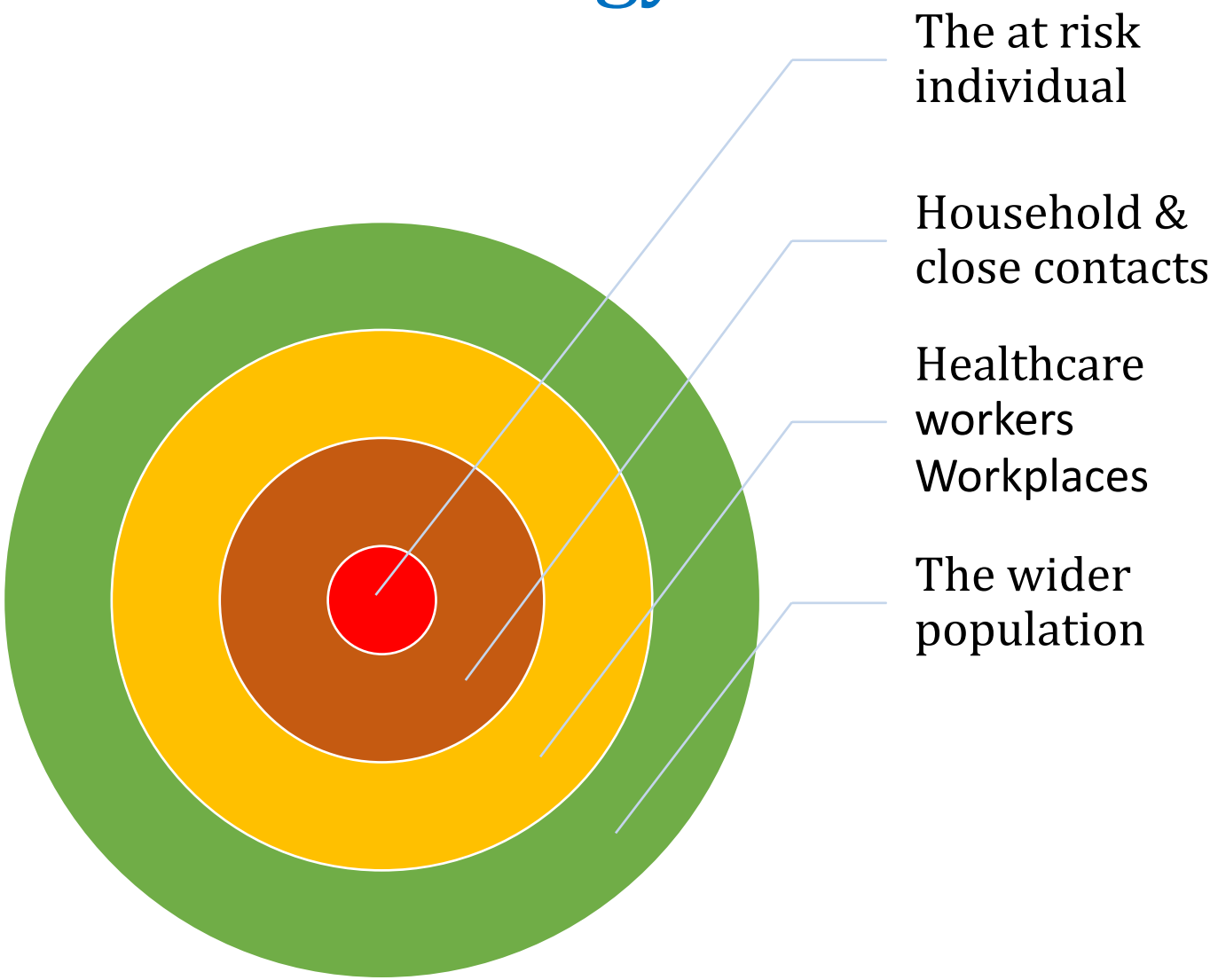
- High dose influenza vaccine demonstrated higher seroconversion rates to all 3 influenza antigens
- Higher Geometric mean titres
- No significant increase in biopsy proven rejection

Live-attenuated vaccines
Contraindicated in the immunocompromised or pregnancy

- **Measles Mumps Rubella (MMR)**
  - Exception: HIV with CD4 ≥200/ uL
  - Exception: BMT recipient, > 24 months post transplant, no disease relapse, no GVHD, immune reconstitution
- **Varicella Virus vaccine (VAR)**
  - Exception: HIV with CD4 ≥200/ uL (if non-immune or IgG negative)
- **Zoster vaccine (Zostavax)**
  - Exception:BMT recipient, > 24 months post transplant, no disease relapse, no GVHD, immune reconstitution
  - Exception: low level immunosuppression (pred ,20mg for <14 days; MTX <0.4mg/kg/ week; azathioprine <3mg/kg/ day; 6 MP <1.5 mg/kg/day
- **Rotavirus (in children)**
- **BCG**
- **Yellow fever***
- **Japanese encephalitis vaccine (Imojev; not JEspect)**
- **Oral typhoid**
- **Oral polio (no longer marketed in Australia)**

** People with a contraindication to yellow fever vaccine require a letter stating that the yellow fever vaccine is contraindicated on medical grounds & should display the YF vaccination centre's official stamp provided by the state or territory health authority*

Ring vaccination strategy



A word on the herd

- High levels of vaccination uptake in contacts of those with immunocompromise will prevent acquisition and onward transmission of infection
- Especially important for diseases for which an immunocompromised person may be non-immune & suffer severe complications

Herd Immunity thresholds

- The proportion of a population that need to be vaccinated (V_c) to prevent transmission

$$V_c = (1 - 1/R_0) / E *$$

- R_0=number of secondary cases from each case of infection
- E=vaccine efficacy

Herd immunity thresholds

$$V_c = (1 - 1/R_0) / E \ *$$

Theoretical example: **Measles**

R_0=number of secondary cases from each measles case =12

E= vaccine efficacy~95%

Where R_0=12 $V_c = (1 - 1/12) / 0.95 =$ 96%

Conclusion: >95% of the population need to be vaccinated to prevent community transmission of measles (in a randomly mixing, homogeneous population)

* Fine P et al Clin Infect Dis 2011; 51:911

Close contacts
of immunocompromised

- Household member >6 months old
  - Recommend influenza vaccine annually (in addition to childhood vaccinations)
- Live attenuated vaccines are safe in contacts

  (exception is oral polio, no longer marketed Australia)
  - MMR negligible transmission risk
  - VZV -secondary transmission~6 /56 million doses
  - Zostavax for contacts >=50yrs – very low risk of secondary transmission
  - Rotavirus (in children)-contact precautions for ~4 weeks
  - Travel vaccinations (Yellow fever, typhoid) as required

1. CDC MMWR 2007;
2. Rubin LG et al Clin Infect Dis 2013

In conclusion

- Take a vaccination history
  - Ascertain indications, contraindications for vaccination
  - Recommend vaccinations in household/close contacts
- Promote uptake of NIP/state-funded vaccinations (the “low hanging fruit”)
  - Influenza, pneumococcal, HPV, Hepatitis B and meningococcal vaccinations, age-based recommendations for Zostavax …refer to GP or via hospital-based clinic for vaccination
- Safety and efficacy of new adjuvanted vaccines hold promise
  - Shingrix as an alternative to Zostavax; ?Heplisav as an alternative to Engerix / H-B-VaxII
  - More evidence is needed in immunocompromised populations
- Use opportunities (incl hospitalization, clinic encounters) to administer recommended vaccines esp in marginalized populations
- Identify and address barriers to vaccine uptake

Questions?