THE UNIVERSITY of ADELAIDE

Healthy Development Adelaide 14th Annual Oration

Protecting our children against serious infectious diseases

Professor Helen Marshall

seek LIGHT

Robinson Research Institute
Healthy children for life.

Disclosure

- NHMRC Fellowship
- Member of the Australian Technical Advisory Group on Immunisation
- Investigator on sponsored vaccine studies (GSK, Pfizer, Novavax)
- B Part Of It study sponsored by The University of Adelaide
- Study funded by GSK
- No personal payments from Industry

Our Partners

Government of South Australia
SA Health

THE UNIVERSITY of ADELAIDE

Local Government Association of South Australia

Government of South Australia
Department for Education and Child Development

catholic education south australia

AISSA Association of Independent Schools of South Australia

SA PATHOLOGY

Robinson Research Institute
Healthy children for life.

SAHMRI
South Australian Health & Medical Research Institute

AHTA Adelaide Health Technology Assessment

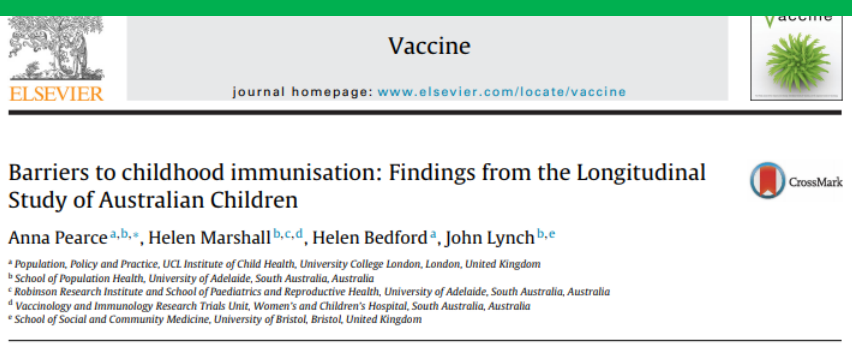
SA ACADEMIC HEALTH SCIENCE AND TRANSLATION CENTRE

Women's & Children's Hospital Foundation

Value of HDA in improving child health

9.3% underimmunised (only 16% had parents who disagreed with immunisation)

NHMRC Practitioner Fellowship 2019-2023
Targeted immunisation programs and tailored interventions



Vaccine

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

Barriers to childhood immunisation: Findings from the Longitudinal Study of Australian Children

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[e] School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom

The power of vaccines, still not fully utilised

- Vaccines prevented at least 10 million deaths between 2010-2015 and many more lives were protected from disease

Ultimate goal of immunisation is disease eradication: Small pox officially eradicated in 1980

http://www.who.int/publications/10-year-review/vaccines/en/

Game changer: Harnessing the extra benefits of immunisation to eradicate disease

- Individual (direct protection)
- Community protection (indirect benefits)
- “Two for one” benefits
- Protection against multiple diseases with one vaccine

1. Hib vaccination
2. Meningococcal vaccination
3. Maternal immunisation
4. HPV vaccination

Improving protection against life threatening diseases through herd immunity

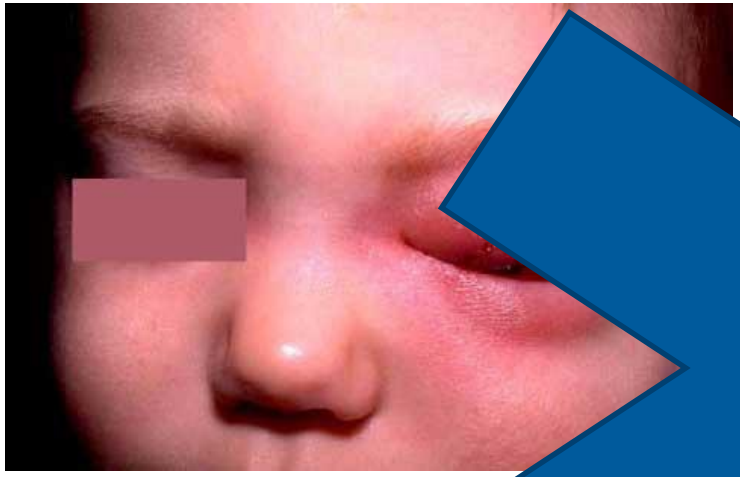
Haemophilus meningitis

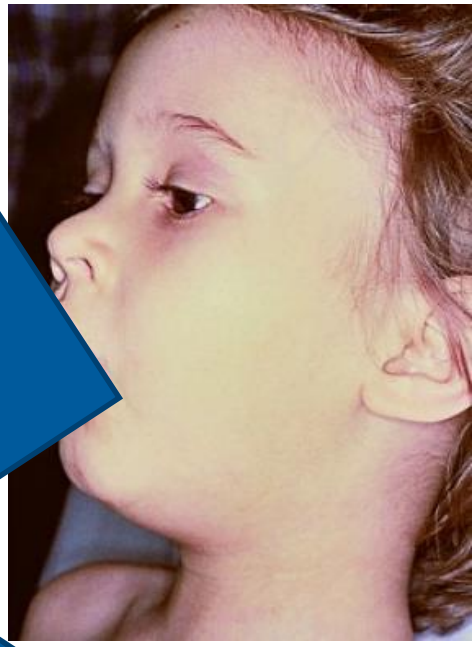
Haemophilus influenzae (Hib)

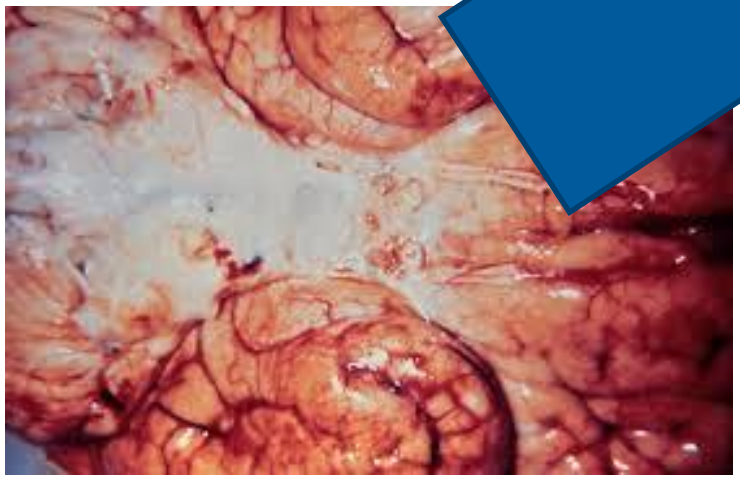
- A common cause of meningitis, epiglottitis and pneumonia prior to introduction of Hib vaccine
- Meningitis and epiglottitis are almost invariably fatal without treatment
- Most commonly affects children < 5 years
- 3% of children die from Hib meningitis and up to 30% have sequelae including deafness and brain injury
- 3-5% of healthy school-aged children carry Hib bacteria in their throat [1]

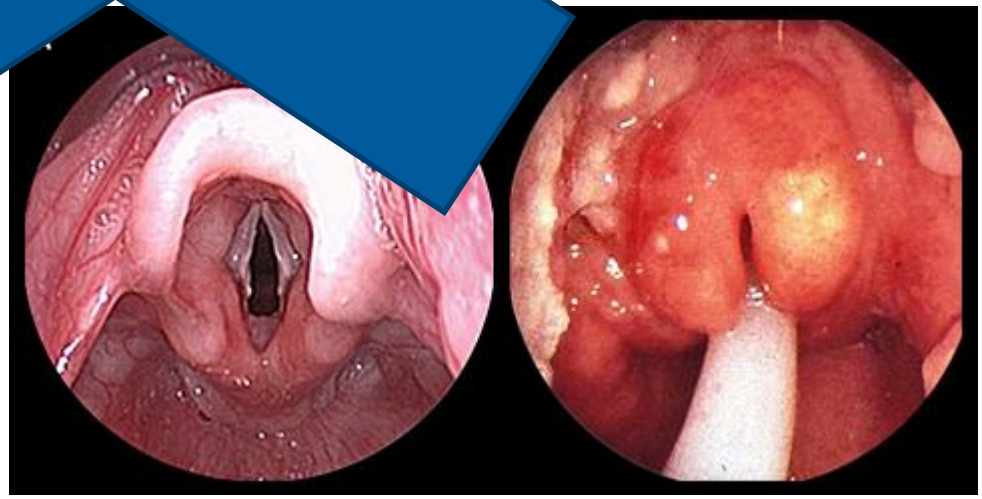
Barbour ML. Emerg Inf Dis 1996;2(3):176-82.

Meningitis, epiglottitis and orbital cellulitis are caused by *H. influenza and are now rare or eliminated diseases*



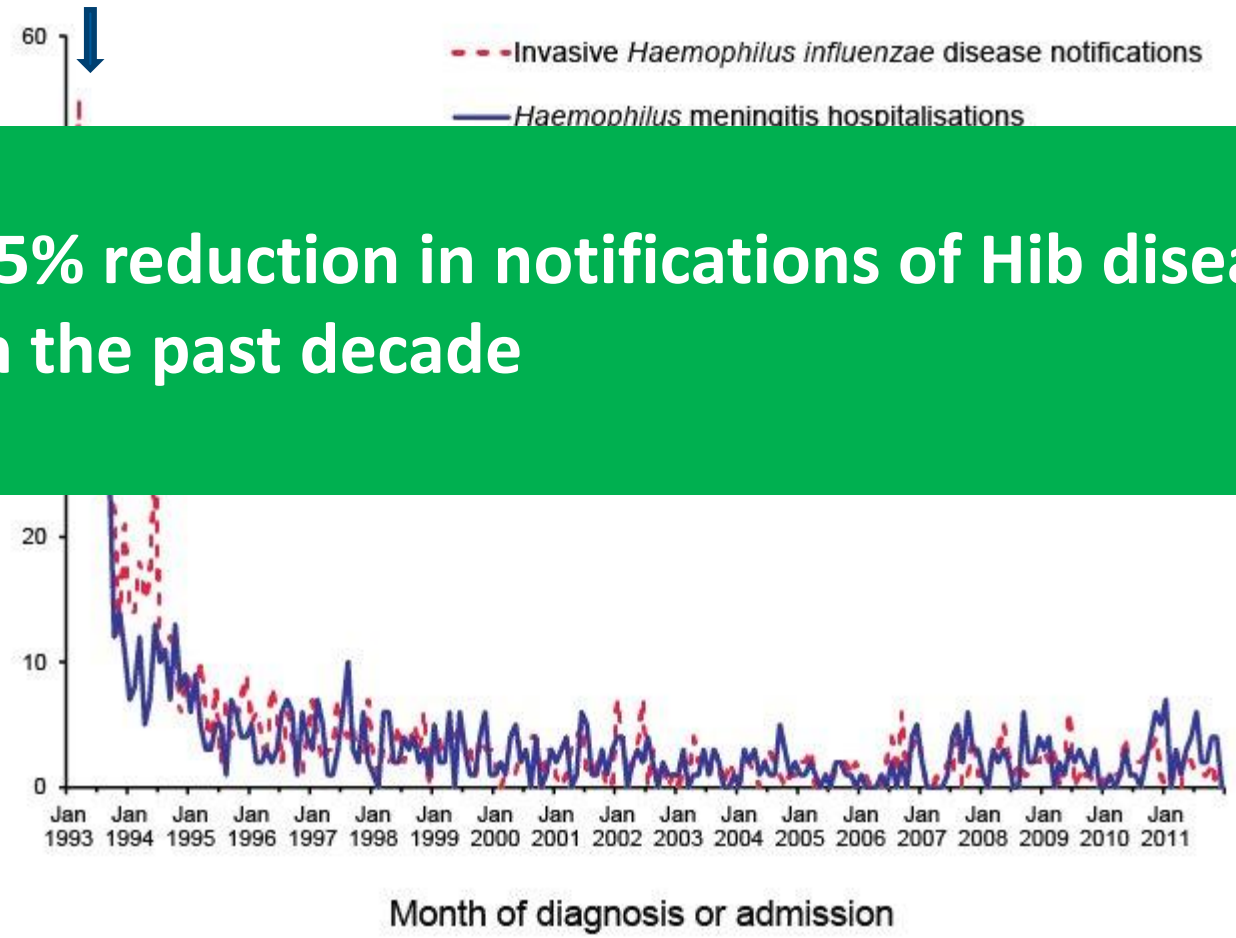






Impact of Hib vaccine on all Hib disease

- Introduced into the Australian Immunisation Program in July 1993
- Schedule 2,4,6 months with a booster vaccination at 12 months
- 549 cases in 1992 – 11 cases in 2013 (< 5 year olds)

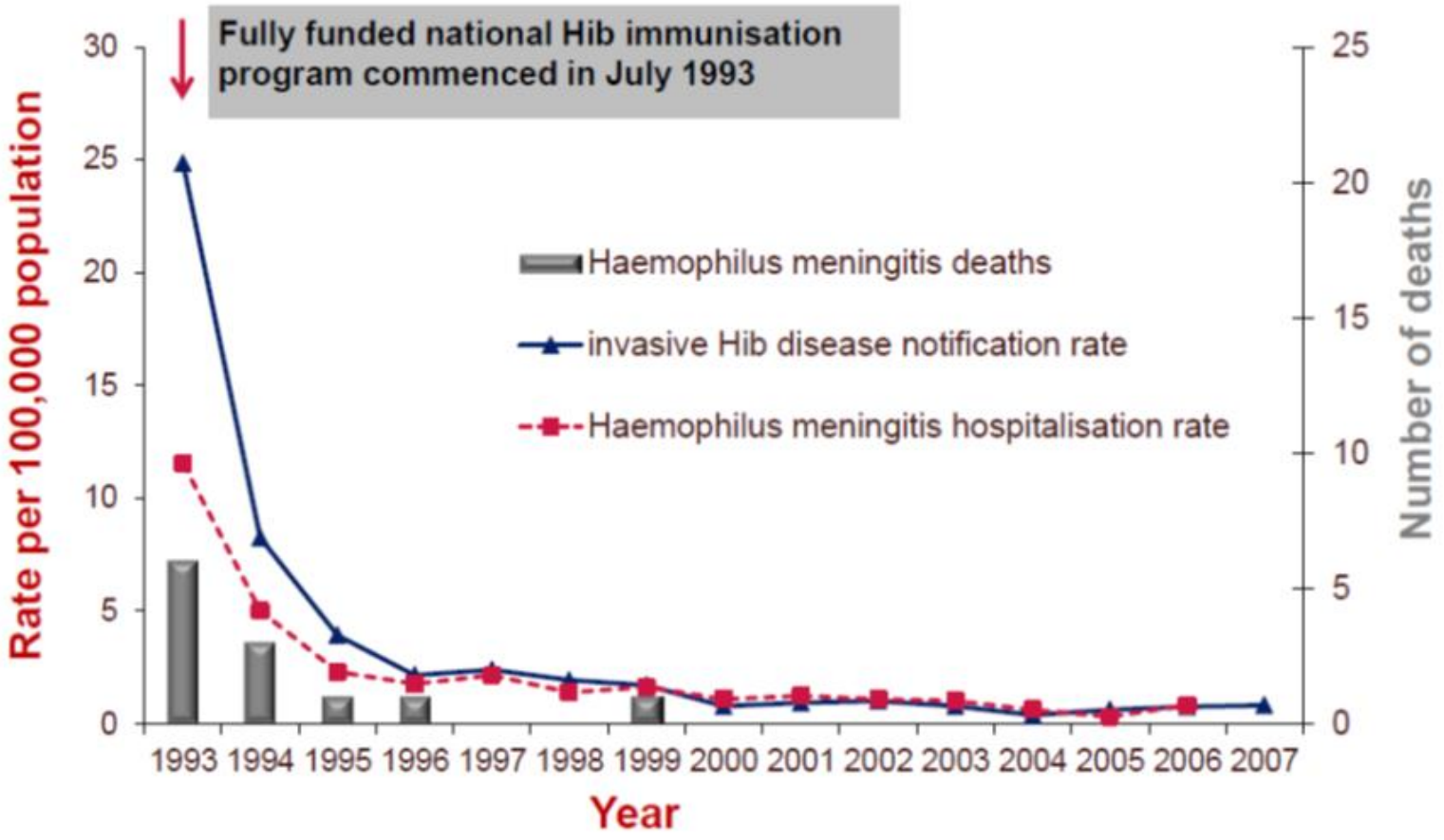


95% reduction in notifications of Hib disease in the past decade

Dey et al. CDI 2016:40
www.health.gov.au/internet/main/publishing.nsf/content/cda-cdi40suppl.htm

Impact of Hib vaccine on deaths and disease from invasive Hib disease

- Invasive *Haemophilus influenzae type b* disease notifications and Haemophilus meningitis hospitalisation rates and number of deaths† for children aged 0–4 years, Australia, 1993 to 2007



Chiu C et al CDI 2010;34:S17

Indirect (herd immunity) effects of Hib vaccination

↑ proportion of children immunised

↓

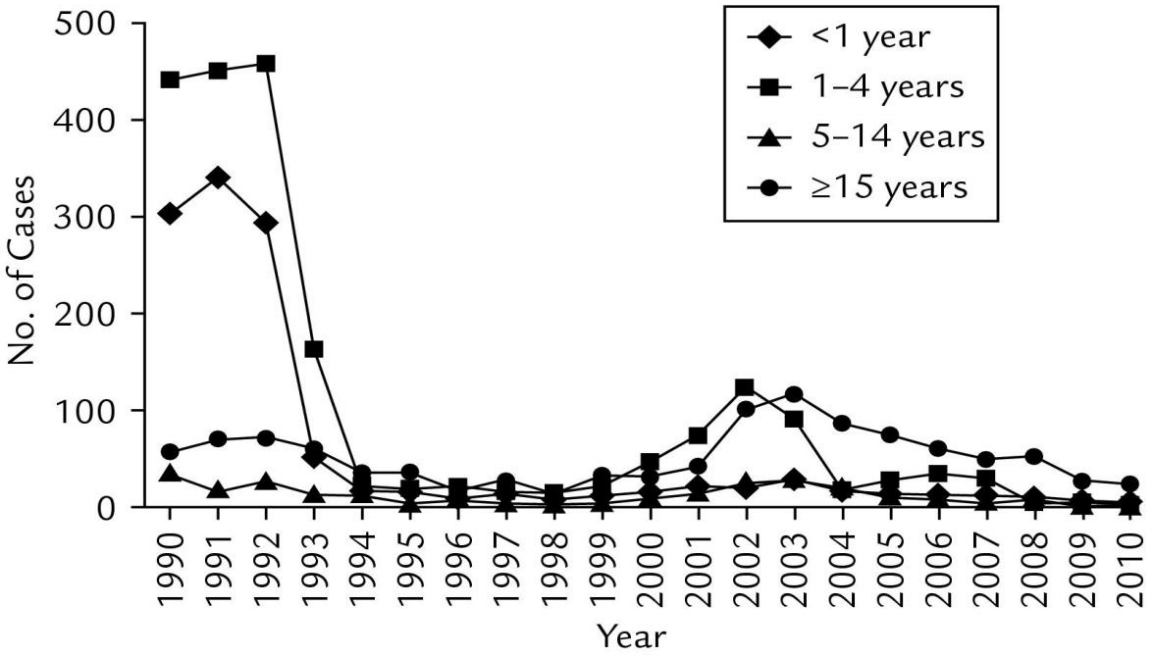
↓ carriage of Hib

↓

↓ transmission of Hib

↓

↓ Hib disease in unimmunised individuals



Hib notifications for all children in the UK

Ladhani SN. Clin Ther. 2012 Feb; 34(2):385-99

Elimination of meningococcal disease: is it possible?

Meningococcal disease

Meningococcal disease

Meningitis and septicaemia

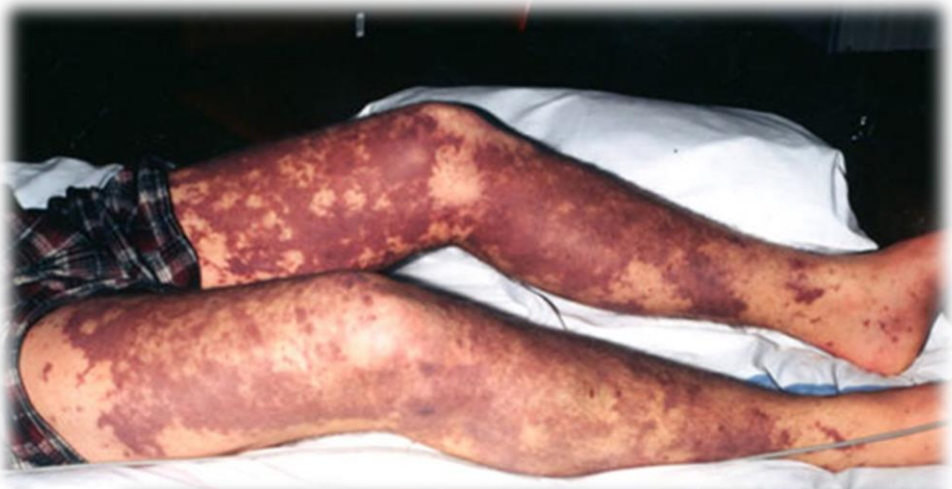
- Caused by different strains (groups) A,B,C,W,X,Y
- Approx. 240 cases per year in Australia
- Case fatality rate of 5-10%
- Bimodal pattern of disease
  - Children < 5 years of age, particularly infants < 6 months of age
  - Adolescents, 15-24 years of age
- Complications (sequelae)
  - Limb amputation due to limb ischaemia/gangrene, deafness, skin scarring [1]

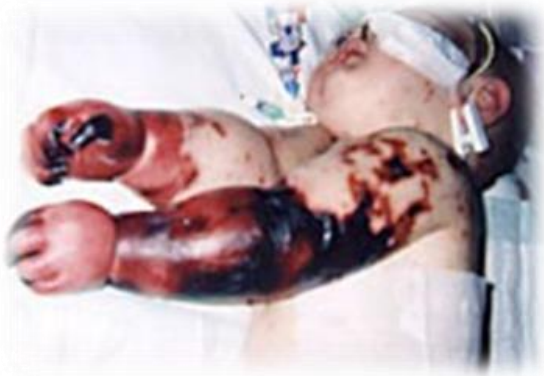
Carriage

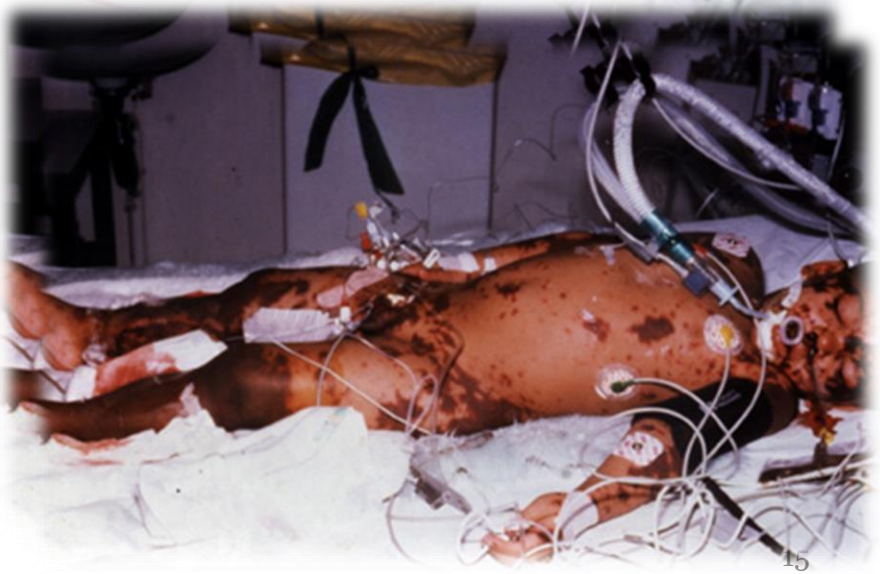
- 10% of people carry the meningococcus in their throat
- Most strains are harmless but hyperinvasive harmful strains are also carried and transmitted and don't discriminate

Wang B, Marshall H et al. PIDJ 2014;33(3):316-318

Invasive meningococcal disease







Meningococcal Vaccines

MenC vaccine at 12 months

- Extremely effective at protecting against group C disease
- Now superseded by MenACWY

MenACWY vaccine

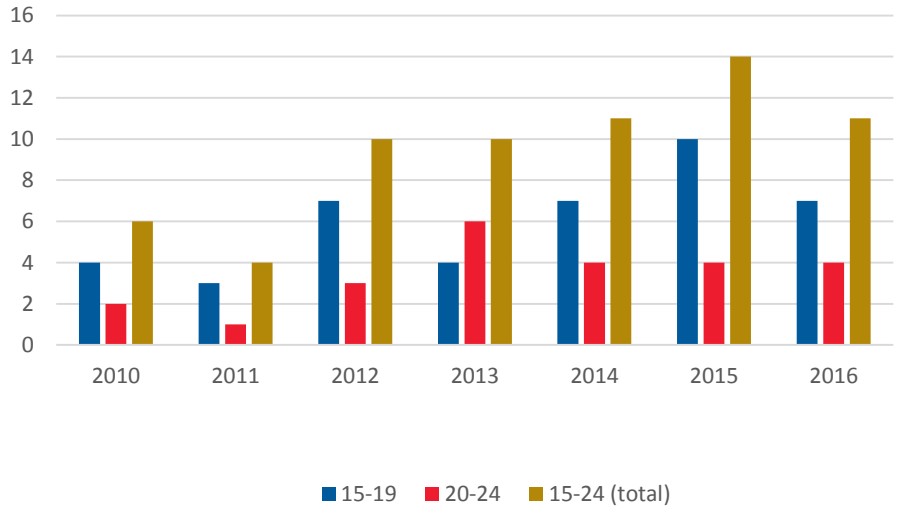
- Funded on the NIP at 12 months of age 01 July 2018
- Funded on the NIP from 15-20 years of age from 01 April 2018

Meningococcal B vaccine

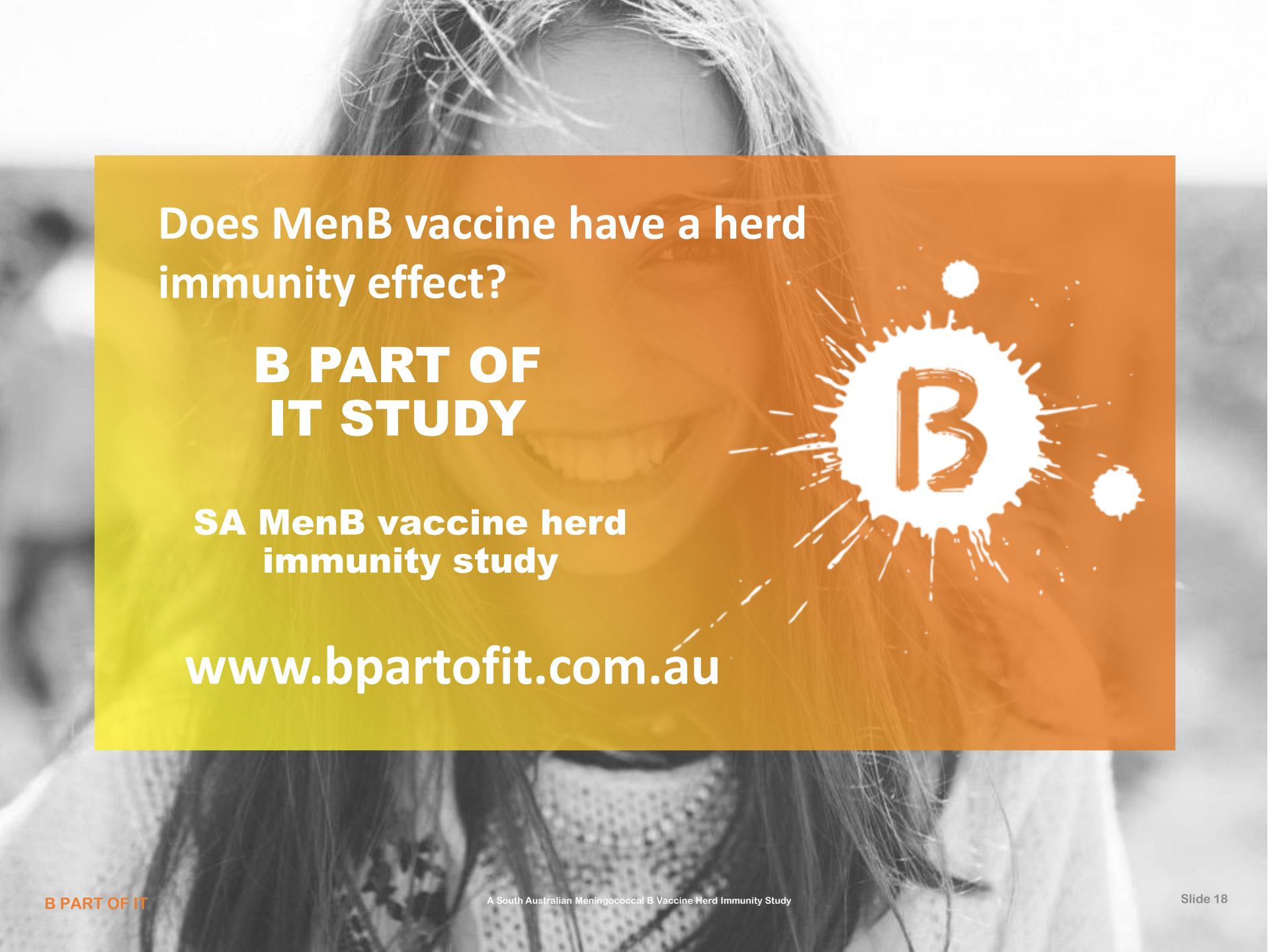
- Not included on the NIP due to unfavourable cost effectiveness estimates and uncertainty about herd immunity
- 84% effective in infant program in UK
- outer membrane protein vaccines
- Available on the private market
  - 2 licensed vaccines in Australia
    - 4CMenB (Bexsero®) - from 6 weeks of age
    - Menb:fHBP (Trumenba®) – from 10 years of age

Meningococcal B Disease in South Australia

- SA has the highest rate of IMD; 2.2/100,000 (4.4/100,000 in Aboriginal children)
- 88% due to serogroup B (2018 to date)
  - 85% of B cases are due to the hypervirulent NZ strain
- increase in adolescents notifications, serogroup B



IMD notifications in adolescents, SA



Does MenB vaccine have a herd immunity effect?

B PART OF IT STUDY

SA MenB vaccine herd immunity study

www.bpartofit.com.au

B Part of It study

- Study Design: Randomised controlled trial
- Potentially enrol ~40,000 high school students (24,000 year 10 and 11 students) **over a 3 month period**
- Offer free meningococcal B vaccine (2 doses) to every senior school student in SA
- Students to have throat swabs at 0 and 12 months
- Offer involvement to every school in SA – metropolitan, rural, remote
- Ensure students returned at 12 months

Involve the whole state in the study

19

Training in study processes, GCP and throat swab technique, transport of samples from rural and remote communities

4,990 kms travelled in Adelaide and country centres
Trained
- **>250 nurses**
- **35 admin staff**

20

Study population

All year 10, 11, 12 students attending any school in South Australia (SA), including metropolitan, rural and remote schools

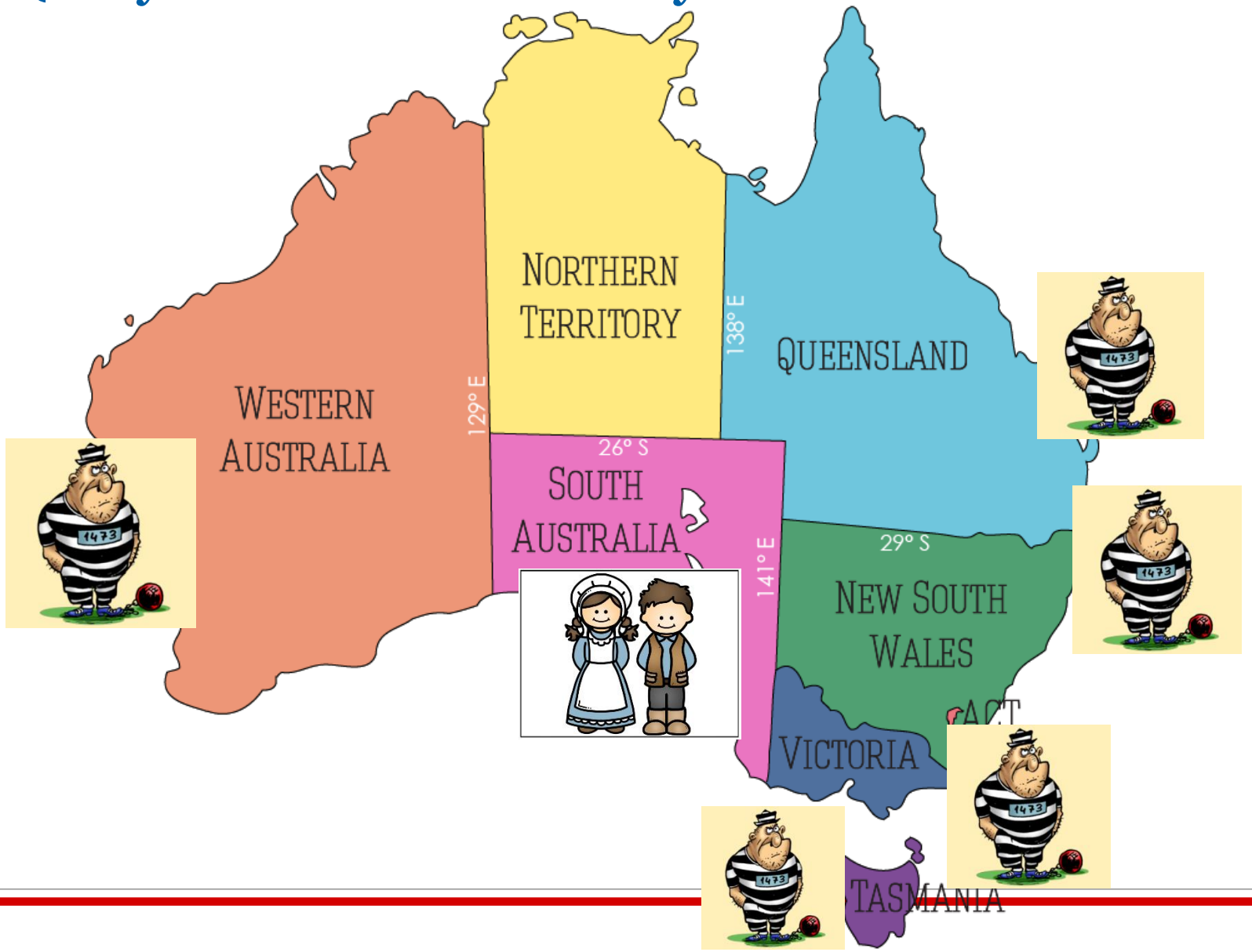
SA Pathology: Centralised pathology service and collection centres

Adolescent immunisation delivery through the school immunisation program

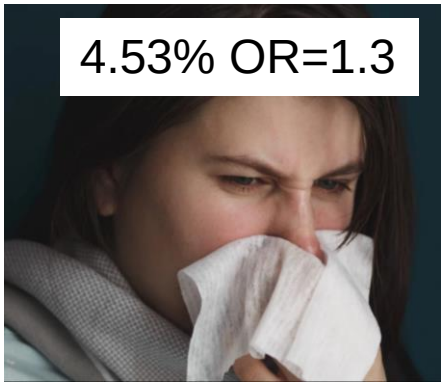
Stable population with low mobility

1.National Notifiable Disease Surveillance http://www9.health.gov.au/cda/source/rpt_4.cfm
2.Lahra M et al. CDI 2016;40(4):E503-511

Lower interstate mobility - SA is the safest state to live (only state not settled by convicts from the UK)



Risk factors for carrying the meningococcus in the throat



Study outcomes

- MenB vaccine protects against meningococcal B disease in adolescents but does not prevent acquisition of carriage of all invasive strains (A,B,C,W,Y) *
- To provide the best protection introduction of a MenB vaccine programs should focus on protection against age groups with the highest rates of disease

Future B Part Of It research

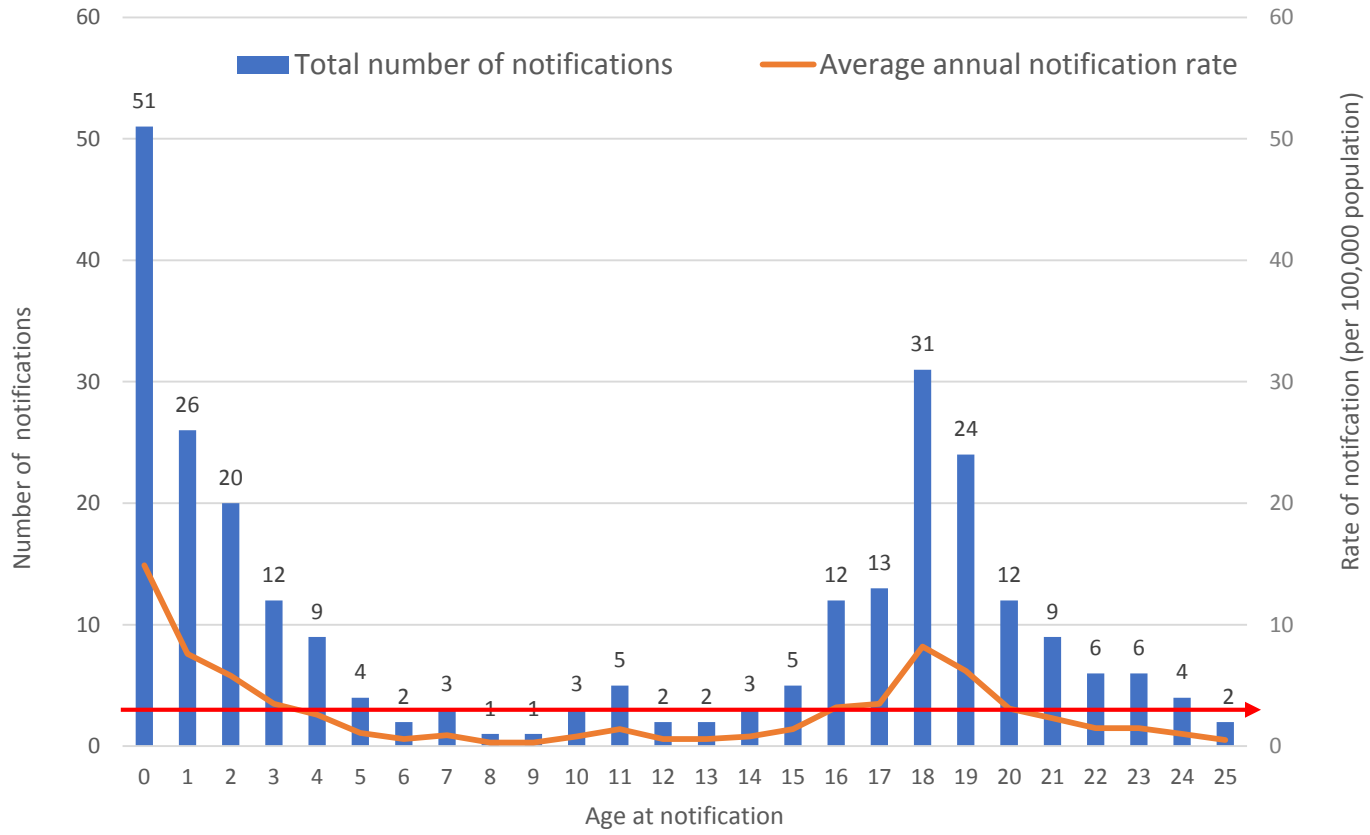
- * Does MenB vaccine prevent carriage of the hypervirulent strain causing disease in South Australia (close match to the vaccine)?
- Does MenB vaccine impact on density of the meningococcus being carried?

First in the world: Expanded MenB vaccine program in SA

Age	Program Category	Program start date	Program Availability
6 weeks - 12 months	Childhood Program	1 October 2018	Ongoing
>12 months - <4 years	Catch-up Childhood Program	1 October 2018	Ends 31 December 2019
15 and 16 years	Year 10 School Program	1 February 2019	Ongoing
16 and 17 years	Year 11 Catch-up School Program	1 February 2019	Ends 31 December 2019
17 - <21 years	Young Adult Catch Up Program	1 February 2019	Ends 31 December 2019

Elimination of meningococcal disease in children and young people in South Australia is possible

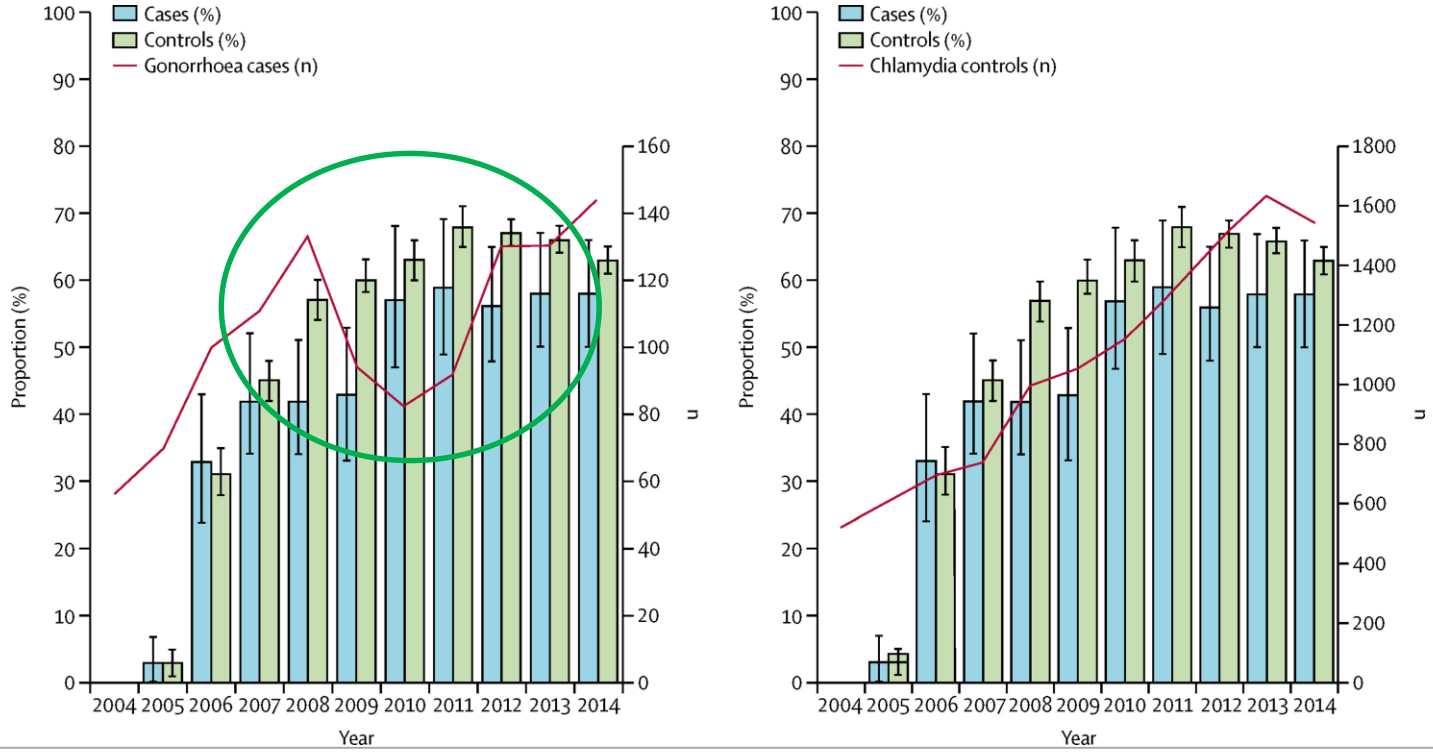
Age specific rates of meningococcal disease in SA



Extending the benefit of MenB vaccine: Potential effectiveness of MenB vaccine against *N. gonorrhoea*

Case control study of MeNZB

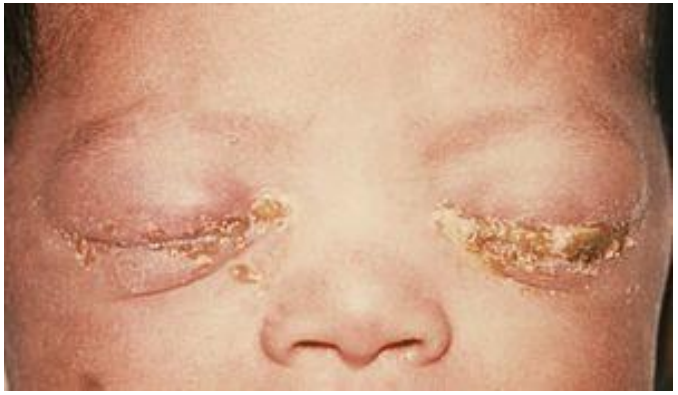
- VE of the 3+0 MeNZB™ against confirmed cases of gonorrhoea among adolescents and adults aged 15–30 years based on the odds ratio = 31% (95% CI 21–39%)



Petousis-Harris H et al. The Lancet 2017;390:1603-10

High burden of disease from *N. gonorrhoea*

- 106 million new infections annually [1]
- Disease impact is greatest on women and infants
- Complications include pelvic inflammatory disease and newborn infections



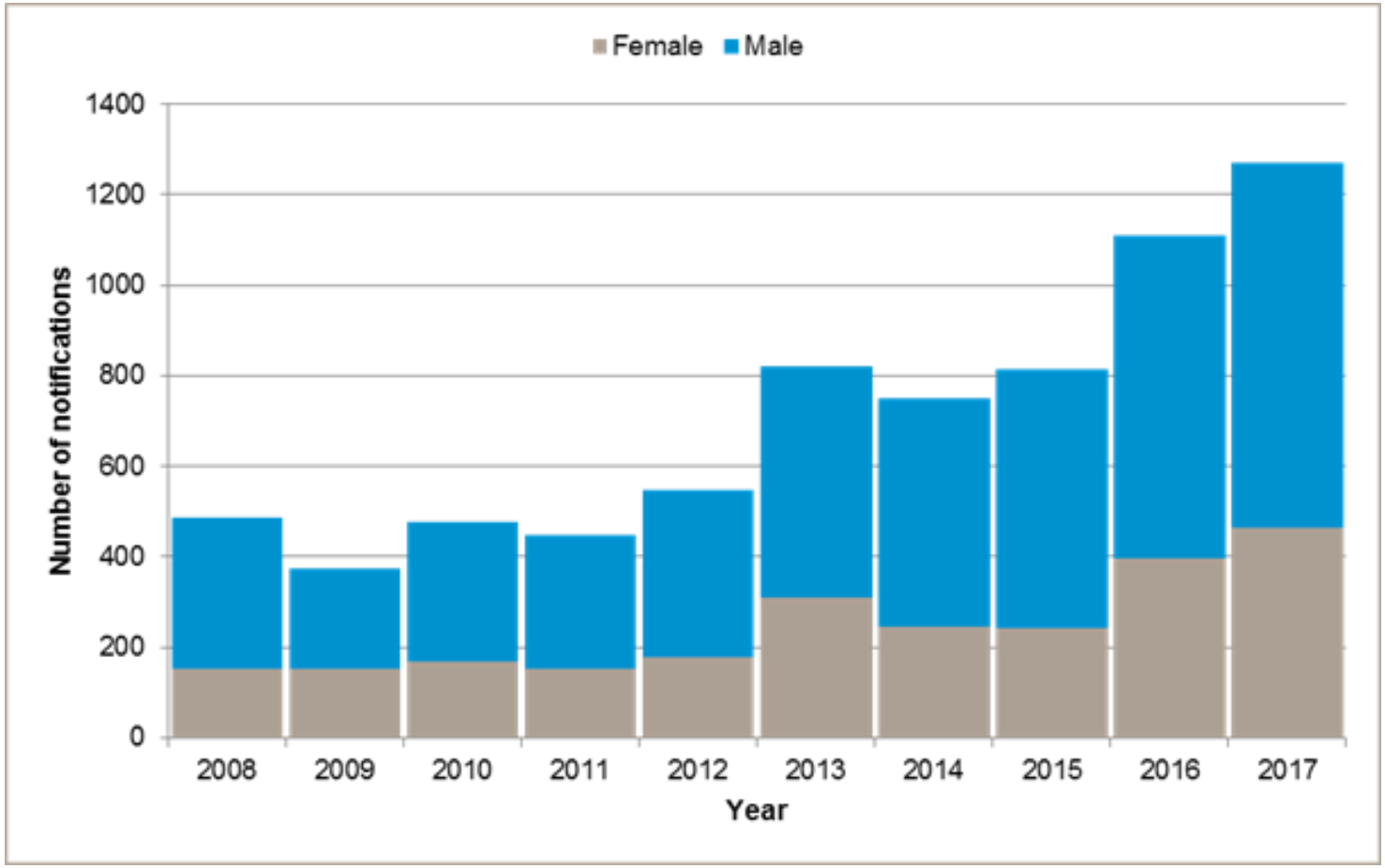
- > 50% risk of infertility if ≥3 infections

- Notification rate of 100/100,000 in Australia and increasing
- Rates in Aboriginal and Torres Strait Islander People (24 times risk)
  - 26.1 and 23.4 per 100 person years in 16-19 year old men and women respectively. [2]

- Increasing development of antibiotic resistance and difficulty treating infected adults.

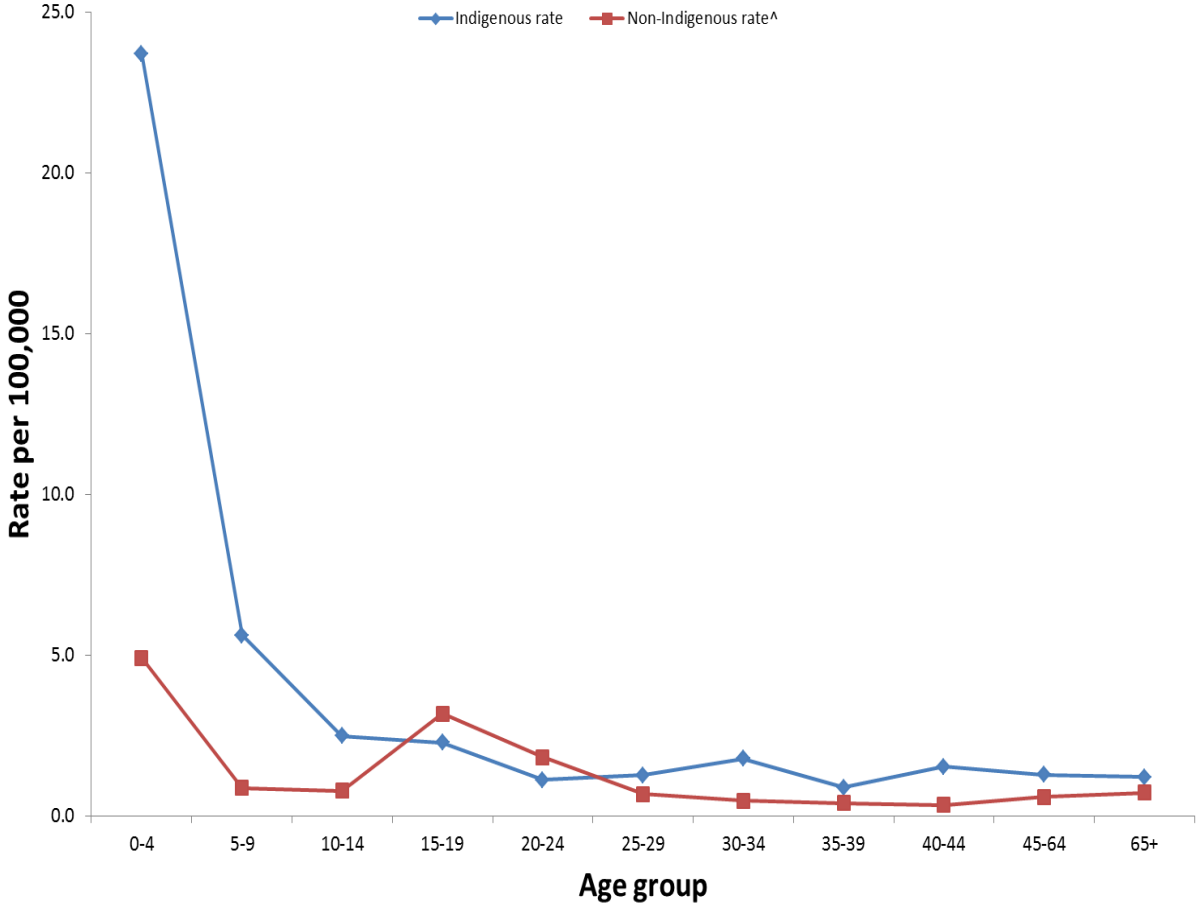
1. WHO Geneva; 2012 2. Silver BJ, et al. Sex Transm Infect 2015;91:135–141.

Increase in gonorrhoea infection in SA



Number of new diagnoses of gonorrhoea in South Australia by sex, 2008 to 2017

Closing the Gap: Potential to reduce meningococcal B disease in Aboriginal children



Notification rates of IMD, Australia, 2002 to 2018 YTD#, by Indigenous status and age group

30

NHMRC partnership grant: SA-NT MenB program evaluation

1. Assess the impact of the meningococcal B program in SA on meningococcal disease and gonorrhoea
2. Assess impact of a 4CMenB vaccine program in the NT on meningococcal disease, meningococcal carriage and gonorrhoea

Partners

- NT Health, SA Health, Commonwealth Government, GSK, AMSANT, SA-NT datalink, Women's and Children's Hospital foundation

Robinson Research Institute
Healthy children for life.

Government of South Australia
SA Health

Women's & Children's Hospital Foundation

Dual protection for both mother and infants

Maternal immunisation

Maternal immunisation: NHMRC recommendations (AIH)

Influenza vaccine:

- Recommended during any trimester of pregnancy
- Nationally funded program

Pertussis vaccine

Recommended in 3rd trimester

- Initially state/territory funded, national program announced
- Recommended for each pregnancy

The Hon. Greg Hunt MP
Minister for Health

MEDIA RELEASE

6 May 2018

Free whooping cough vaccine for every pregnant woman

The Turnbull Government will provide the whooping cough (pertussis) vaccine to every pregnant woman in the country, protecting both baby and mother from this life-threatening disease.

Maternal influenza vaccine effectiveness against influenza in infants to 6 months of age

Effectiveness of influenza vaccine in pregnancy

- 51% - 61% in the pregnant women[1]
- 86% of infants are protected at 8 weeks
- 30% at 6 months of age

(RCT influenza vaccination)[2]

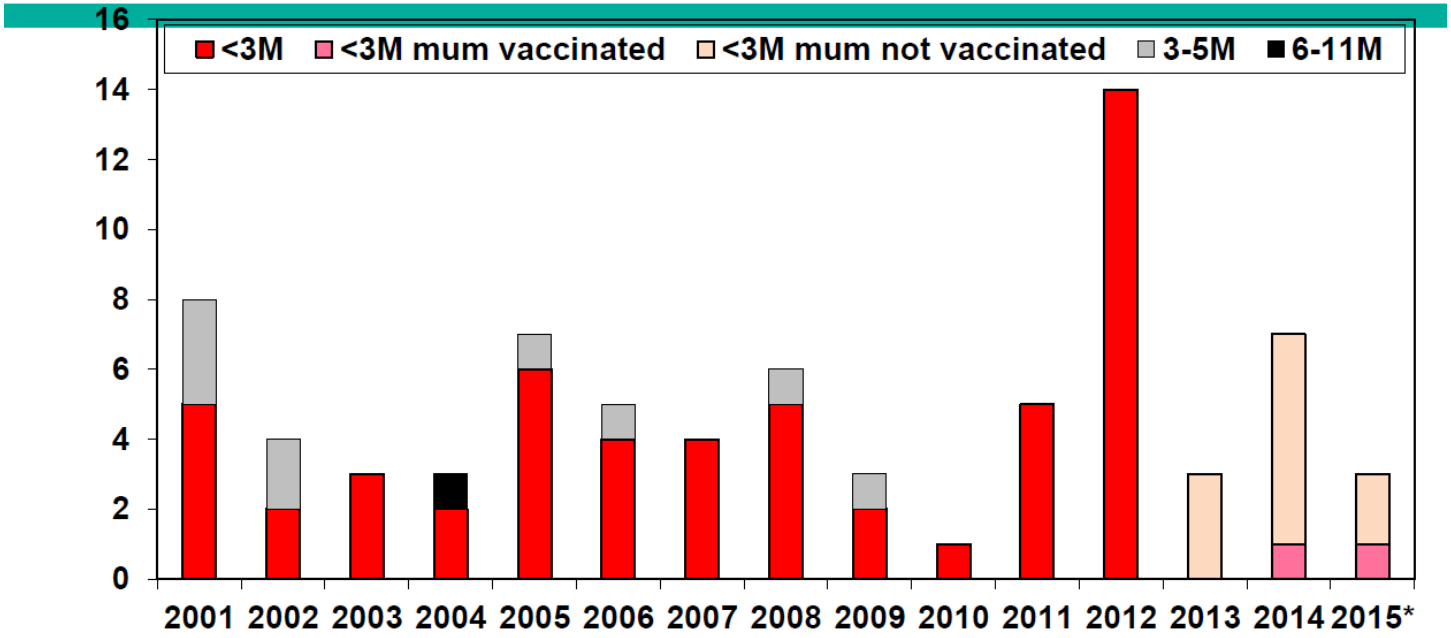
1.McMillan M, Kralik D, Porritt K, Marshall H. Influenza vaccination during pregnancy: a systematic review of effectiveness and safety. The JBI Database of Systematic Reviews and Implementation Reports. 2014;12(6): 281-381. 2.Nunes MC et al. JAMA Pediatr 2016

Pertussis vaccine effectiveness

No pertussis deaths reported in infants whose mothers were vaccinated ≥14 days prior to delivery (UK)

Public Health England

Reconciled deaths from pertussis in infants, England



Sources: lab confirmed cases, certified deaths, Hospital episode statistics, GP registration details, HPZone

UK evaluation [1]
VE=91%
(95%CI 84,95)

VE=95% (< 2 months)
(95%CI 87,95)

Gayatri Amirthalingam et al. Effectiveness of maternal pertussis vaccination in England: an observational. The Lancet 2014; 384: 1521–28

Safety of influenza vaccine in pregnancy

2 systematic reviews, same findings [1,2]

- No increased risk of fetal death
- No increased risk of premature delivery
- No increased risk of pregnancy complications

More recent studies have shown other pregnancy benefits beyond prevention of influenza

- 31% reduced risk of preterm birth associated with influenza vaccination
- 51% reduced risk of stillbirth if received influenza vaccine

1.McMillan M et al. The JBI Database of Systematic Reviews and Implementation Reports. 2014;12(6): 281-381.
2. Giles et al PHAA 2018 3. Mchugh et al Vaccine 2017;35:1403-09 4.Mchugh et al CID (accepted for publication)

Safety of pertussis vaccine in pregnancy

Systematic review of safety of pertussis vaccine in pregnancy, no increased risk of

- Preterm birth (< 37 weeks of gestation)
- Small for gestational age
- Stillbirth
- Neonatal death
- Low birth weight
- Congenital anomalies

McMillan et al. Obstet Gynecol. 2017 Mar;129(3):560-573. 1. Olsen SJ et al. Clin Infect Dis 2016;63:487–94.
2.Regan AK et al. Clin Infect Dis 2016;62:1221–7.

Factors associated with uptake of influenza vaccine among pregnant women

			Univariate logistic regression			Multivariate logistic regression		
Variable	Level	Received maternal influenza vaccine n (%)	Unadjusted odds ratio (OR)	95% CI	p-value	Adjusted odds ratio (AOR)	95% CI	p-value
Maternal age category	21-31	81/96 (84%)	1.00			1.00		
	32-43	55/83 (66%)	0.36	0.17-0.74	0.005	0.40	0.17-0.92	0.031
Country of birth	Australia	91/116 (78%)	1.00		0.763			
P								
P re re								
Midwife delivered maternal immunisation program	Prior	8/22 (36.3%)	1.00			1.00		
	Post introduction	128/156(82%)	8.00	3.06-20.9	<0.001	5.95	2.13-16.6	<0.001

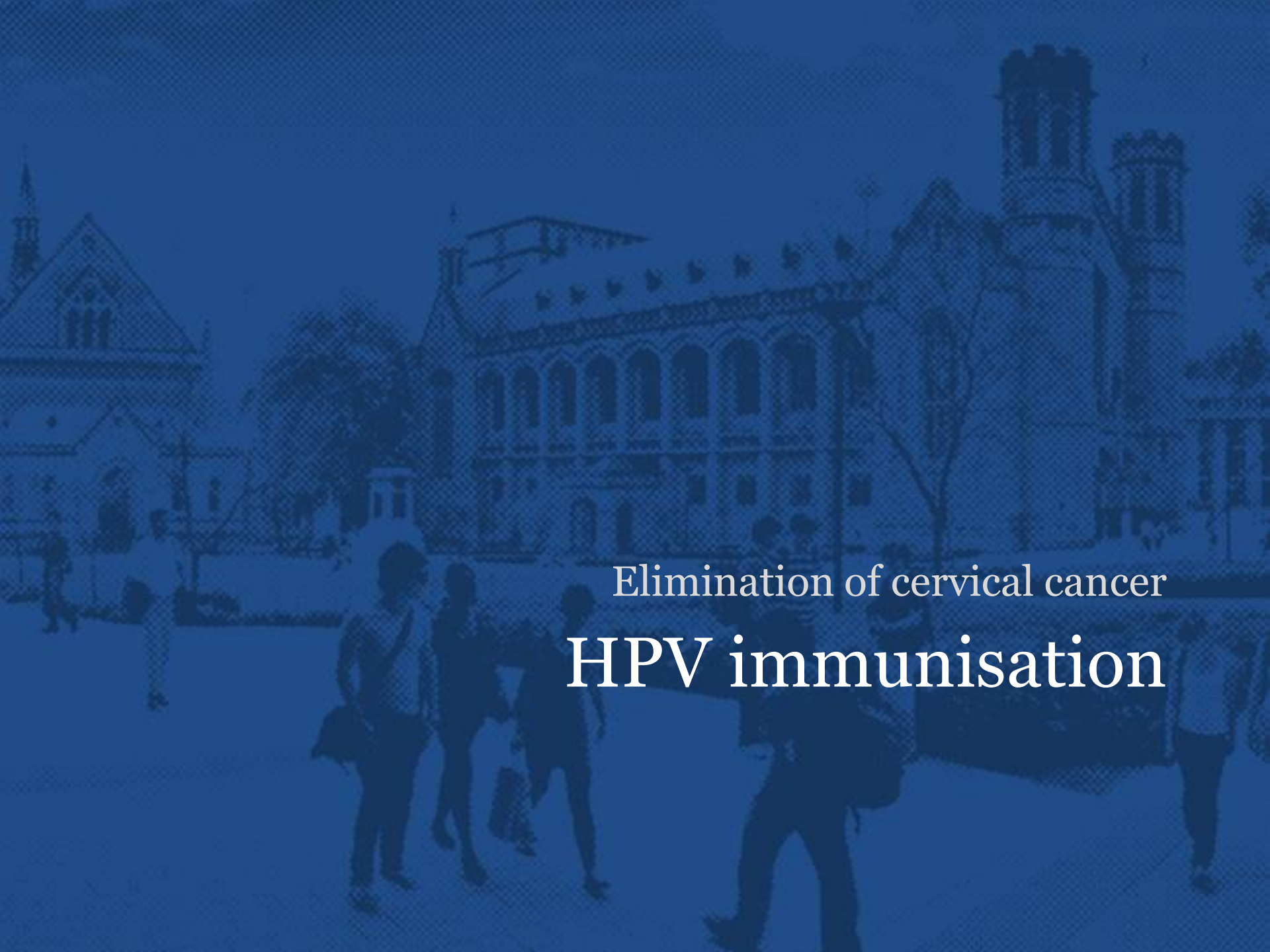
That's the whole idea of standard care, is that it gets picked up along the way. And if it doesn't become part of policy or a clinical guideline well then you open it up to being missed….and you know it would be common sense that if its severely going to affect morbidity and mortality that it would be part of standard care because our hospital would be liable in that situation [quote mid-wife]

The next generation of vaccines to protect pregnant women and infants

1. Group B streptococcus infection
- Uncommon, severe neonatal infection, causes meningitis in newborns
- GBS vaccines in clinical trial development

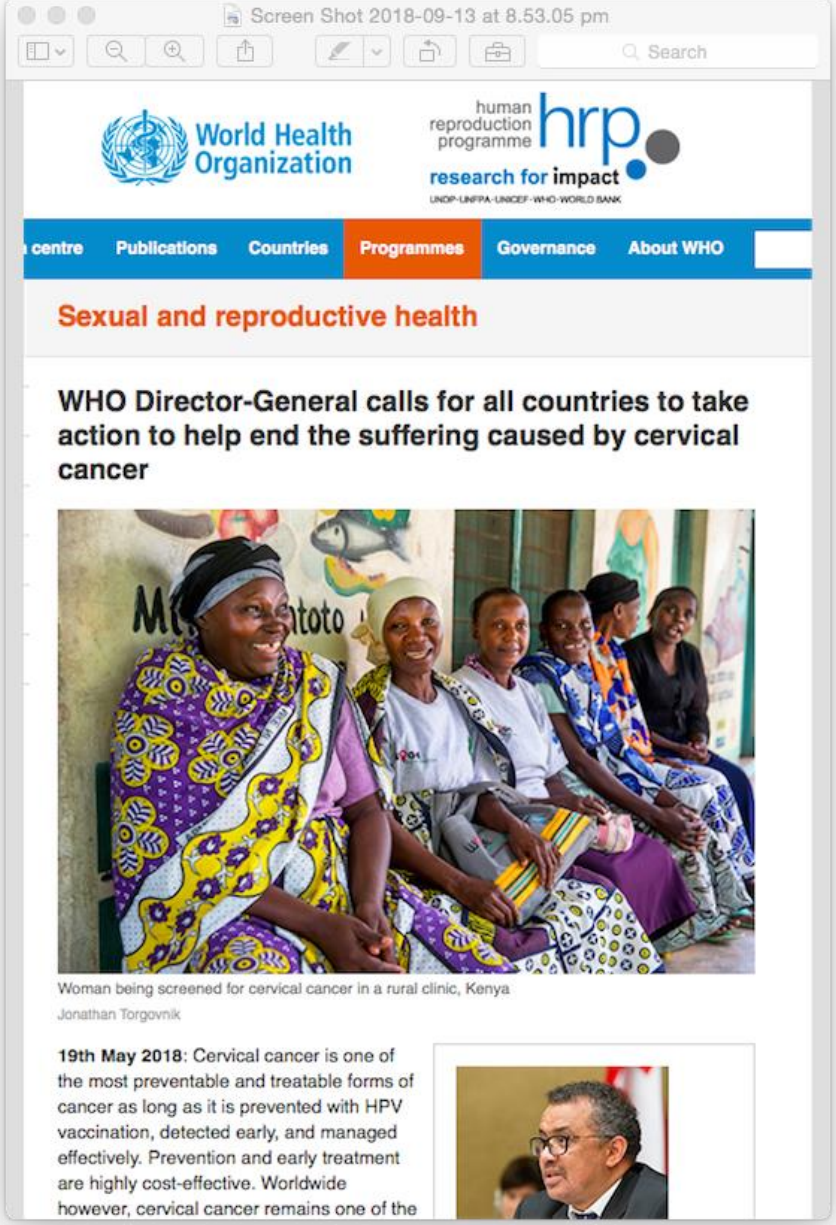
2. Maternal Respiratory Syncytial Virus (RSV)
- Common respiratory infection in infants
- Commonest cause of hospitalisation in infants
- RSV vaccine studies are being conducted in Australia

3. Zika virus
- Cause of microcephaly
- Virus transmitted by mosquitos
- Early vaccine development



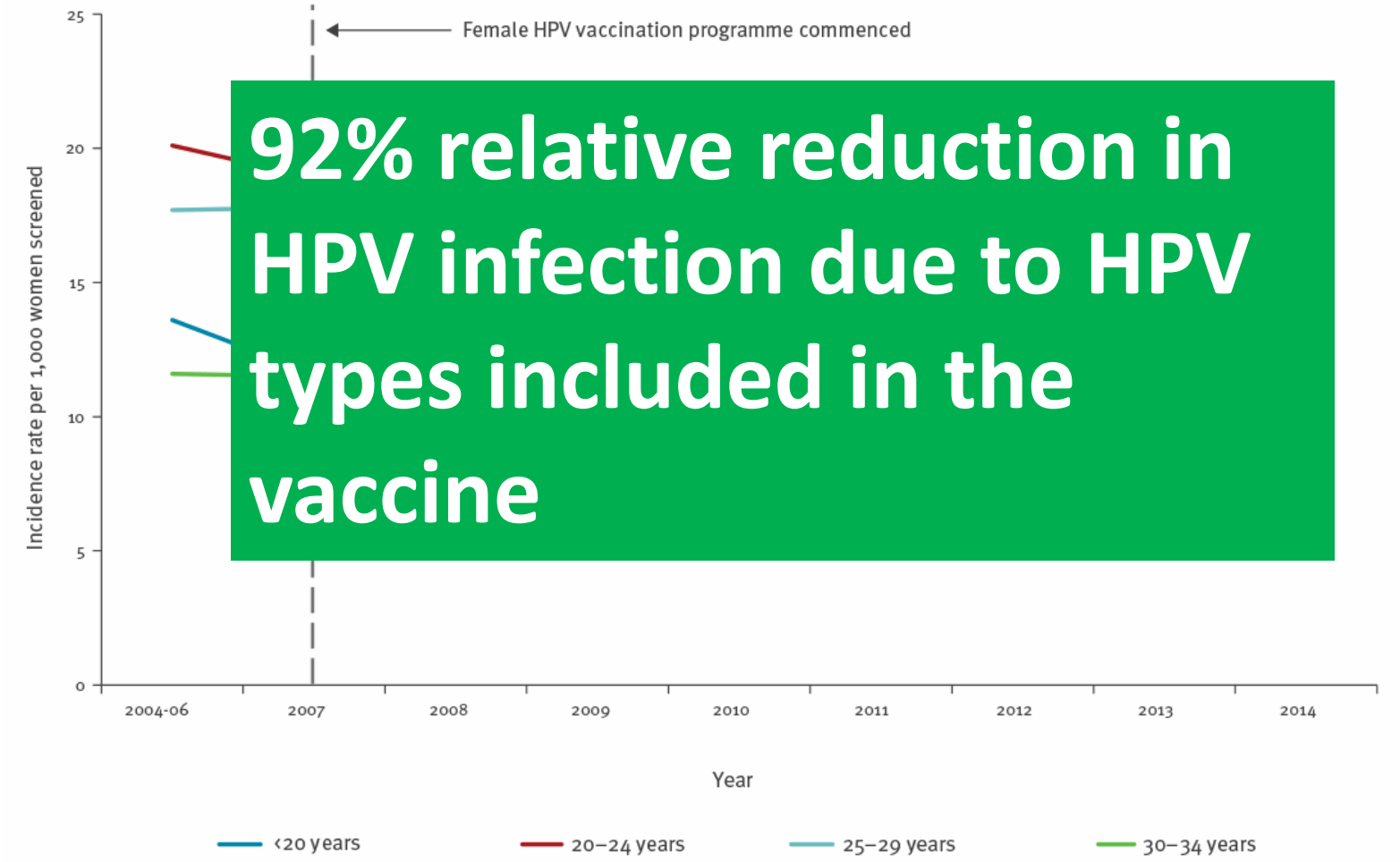
Elimination of cervical cancer

HPV immunisation



Dr Tedros Adhanom Ghebreyesus Director-General WHO calls for an end to cervical cancer, May 2018

Reduction in high grade cervical lesions following introduction of HPV (4vHPV) vaccine in Australia



Patel C.. Marshall H. Euro Surveillance 2018;23(41)

9vHPV vaccine program for boys and girls in Australia

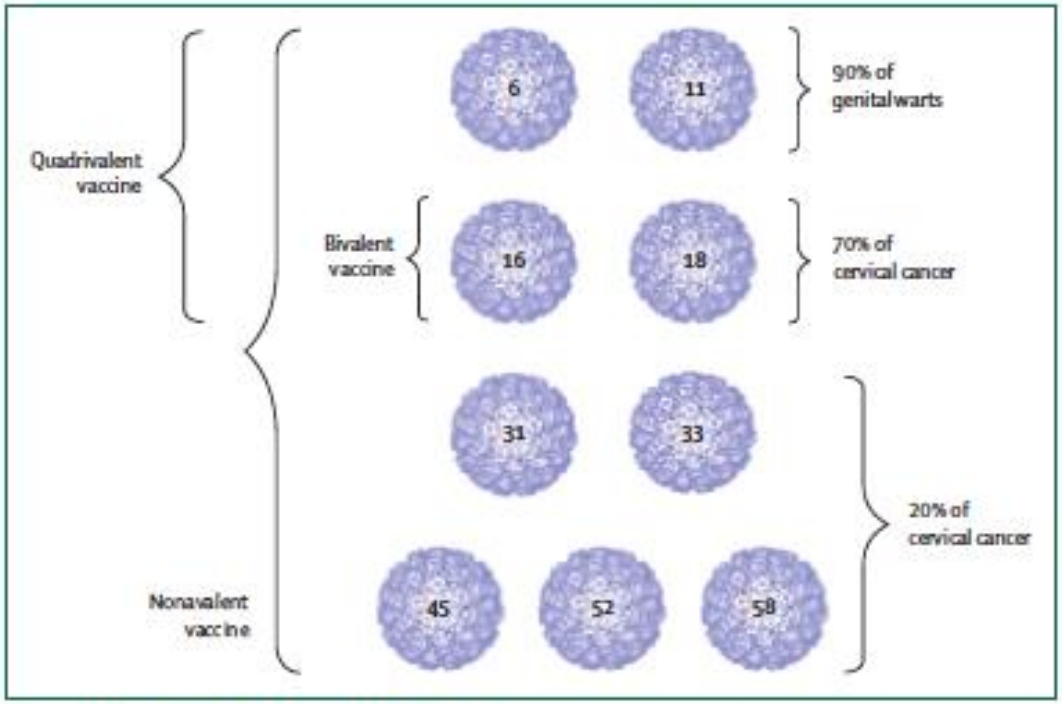


Figure 2: HPV VLP types in the nonavalent VLP vaccine
VLPs in the bivalent, quadravalent, and the nonavalent vaccines are shown with the proportion of neoplasistic disease attributed to each group. HPV=human papillomavirus. VLP=virus-like particle.

Gender neutral program to reduce transmission

Protection against 9 strains (instead of 4)

2 vaccine dose program (instead of 3 doses)

Australia has the highest uptake in boys in the world

Schiller & Muller. *Next generation prophylactic human papillomavirus vaccines*. Lancet Oncol. 2015 May;16(5):e217 - e225

The Australian Cervical Cancer Typing Study

Table 3. Distribution of genotypes placed in 4vHPV/2vHPV and 9vHPV targeted groups, 847 Australian cervical cancers, compared with results from Serrano *et al.*[17]

HPV type group	Number	% of total cases $n = 847$ (95% CI)	% of HPV positive $n = 787$ (95% CI)	% of HPV positive $n = 8,977$; Serrano *et al.* global data (95% CI)
16,18	607	71.8% (68.5–74.7%)	77.1% (74.0–80.0%)	70.8% (69.8–71.7%)
31,33,45,52,58	125	14.8% (12.4–17.3%)	15.9% (13.4–18.6%)	18.5% (17.7–19.3%)
Any 9vHPV	732	86.4% (83.9–88.7%)	93.0% (91.0–94.7%)	89.4% (88.8–90.1)
Other HPV	55	6.5% (4.9–8.4)	7.0% (5.3–9.0%)	10.6% (9.9–11.2%)
Negative	60	7.1 (5.4–9.0%)	NA	NA

Abbreviation: NA, not applicable.

Brotherton/Tabrizi et al. Int J Cancer 2017

Elimination of cervical cancer in Australia by 2035

Australia could become first country to eradicate cervical cancer

Free vaccine program in schools leads to big drop in rates, although they remain high in the developing world

● **Ian Frazer: Eliminating cervical cancer globally is within reach**

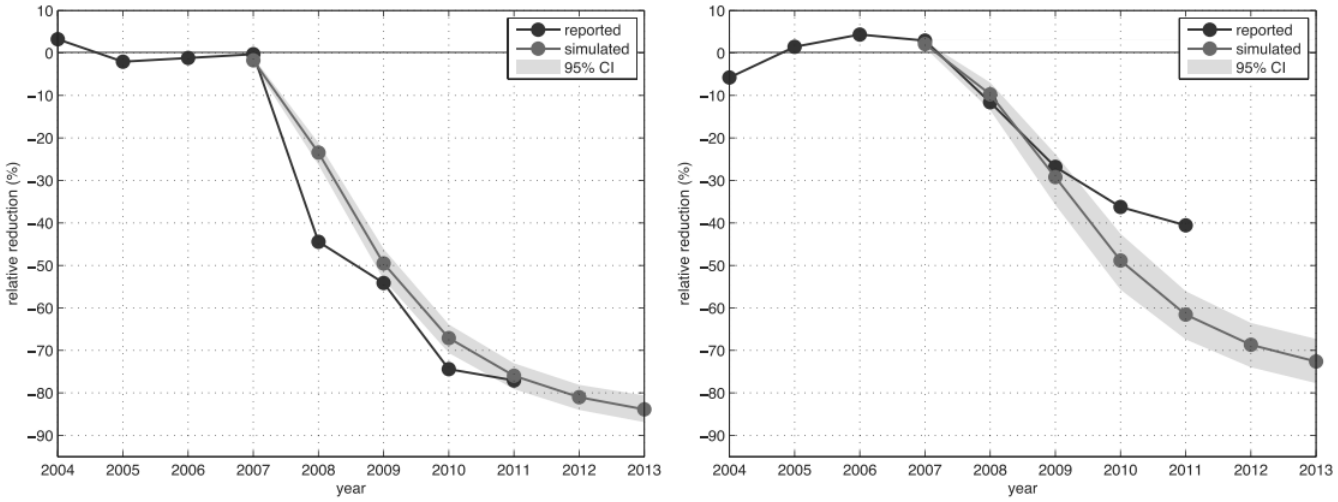
▲ Australia's free HPV vaccine program in schools has led to a dramatic decline in future cervical cancer rates. Photograph: Voisin/Phanie / Rex Features

Australia could become the first country to eradicate cervical cancer, according to an announcement from the International Papillomavirus Society.

Hall M, Frazer I et al. Lancet Public Health 2018

Reduction in genital warts (near elimination in Australia in 2018)

- Relative reductions in genital warts in females (left) and males (right) in those aged 12 to 26 years of age



Females

Males

Full impact of HPV vaccination on HPV-associated cancers is yet to be realised!
Additional HPV related cancers: Anal cancer, penile, vulval, vaginal and oral cancers

In conclusion

- The full impact of immunisation on disease is yet to be realised
- Harnessing the additional benefits of immunisation can lead to elimination of disease
- Measuring the impact of vaccine programs to improve and fine-tune out immunisation programs based on good evidence is essential
- Improving access for those most vulnerable and disadvantaged in the community is a priority to fully utilise the power of vaccines

WHO is now challenging international and national health leaders to make immunisation not only one of the biggest success stories of modern medicine but the greatest success story ever

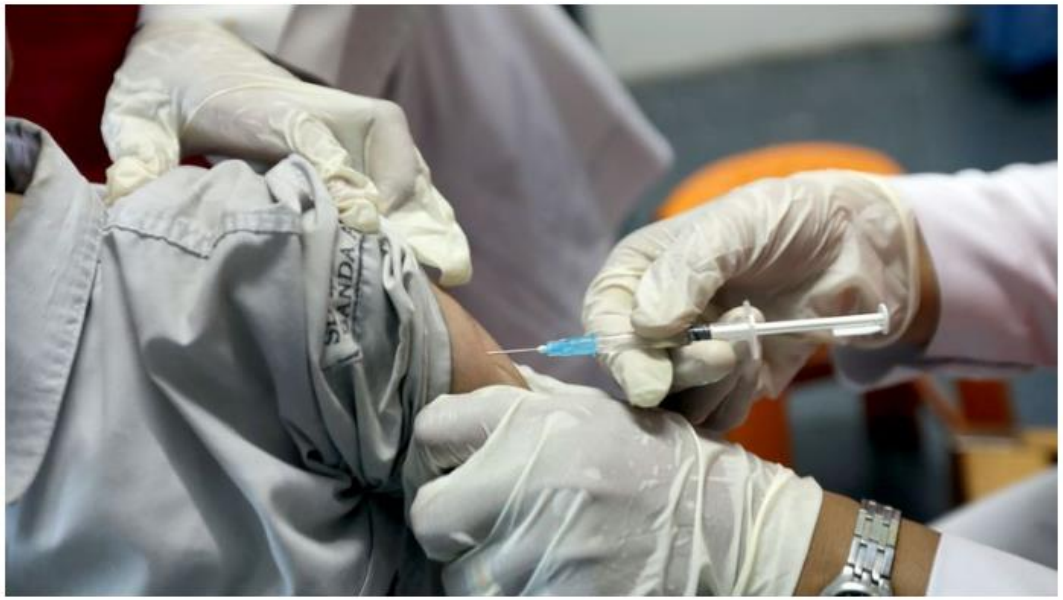
Technically this is entirely feasible. In a world where vast social inequalities create unrest and disturbing instability, the game-changing power of universal vaccination with safe, protective, and cost-effective vaccines ……is yet to be realised

Ten years of public health. WHO http://www.who.int/publications/10-year-review/vaccines/en/

Rubella eliminated in Australia, announced today!

Rubella disease eliminated in Australia, WHO declares

2:07am Oct 31, 2018



A file photograph shows an Indonesian school student being vaccinated against the Rubella virus at a school in Banda Aceh.

Rubella, the contagious disease that can cause pregnant women to miscarry or result in serious birth defects or stillbirth, has officially been eliminated in Australia.

From ME → WE

B Part of It Team

- Ms Susan Lee,
- Dr Pip Rokkas,
- Mr Mark McMillan,
- Ms Kate Riley,
- Mrs Leslie McCauley,
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- Mark Turra, SA Pathology
- A/Prof Ann Koehler, SA Health
- Mr Noel Lally, SA Health
- Mr Andrew Lawrence, SA Pathology
- Mr Tom Sullivan, AHTA, University of Adelaide
- Ms Melissa Peall, Melissa Cocca, Sara Almond, SA Health
- Ms Luda Molchanoff , Country Health
- Mrs Ann Marie Hayes, DECS
- Mrs Monica Conway, CESA
- Ms Carolyn Grantskaln, Bronwyn Donaghey, AIS
- Ms Sarah Scott, University of Adelaide
- Ms Lynette Kelly, University of Adelaide
- Council CEOs, immunisation coordinators and nurses
- VIRTU team

Scientific Advisory Committee

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- Professor Ray Borrow, Head, Vaccine Evaluation Unit, Public Health England
- Professor Adam Finn, Professor of Paediatrics and President ESPID, University of Bristol
- Associate Professor Charlene Kahler, Associate Professor, University of Western Australia
- Dr Shamez Ladhani, Paediatric Infectious Disease Consultant, Public Health England
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- Dr Jenny MacLennan, Clinical Researcher Virology, Microbiology, Immunology, University of Oxford
- Dr Caroline Trotter, Senior Lecturer in Epidemiology, Fellow of Hughes Hall, Cambridge University
- Dr Matthew Snape, Oxford University, UK

Reference group

- Professor Don Roberton (Chair) , Emeritus Professor, The University of Adelaide
- Professor Alastair Burt, Executive Dean, Faculty of Health Sciences, The University of Adelaide
- Ms Monica Conway, Assistant Director, Catholic Education South Australia
- Associate Professor Naomi Dwyer, Chief Executive Officer, Women's & Children's Health Network
- Ms Larissa Biggs and Ms Tahlia Riessen, Youth Advisory Group, Women’s and Children’s Health Network
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- Professor Paddy Phillips, Chief Medical Officer & Chief Public Health Officer, SA Health
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- Professor Steve Wesselingh, Director, South Australian Health & Medical Research Institute
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The VIRTU team

Paediatrician
Research medical officers
Research nurses
Scientists
Post-doctoral researchers
Paediatric trainees
Honours students
Masters students
Phd students

NHMRC “10 of the best” projects for 2016”

And the last word goes to….

Don’t put us at risk of serious infectious diseases