



Optimising protection for pregnant women and their infants against serious infectious diseases

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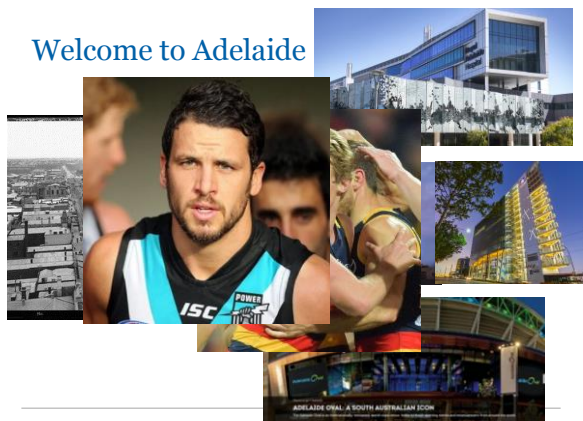
Disclosures

- Investigator on clinical vaccine trials sponsored by Industry
- Institution receives funding for Investigator led studies from Industry (GSK, Pfizer)
- Member of the Australian Technical Advisory Group on Immunisation, Australian Government

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Welcome to Adelaide



Maternal immunisation: NHMRC recommendations (AIH)

Influenza vaccine:

- Recommended during any trimester of pregnancy
- Nationally funded program

Pertussis vaccine: dTpa

- 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

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.

6 May 2018

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Presentation

How can we optimise protection for pregnant women and infants against influenza and pertussis?

Improving the effectiveness of maternal immunisation

- Increasing vaccine uptake in pregnant women, particularly vulnerable women
- Evidence of influenza and pertussis vaccine safety and identifying additional non-specific vaccine effects in pregnancy (pregnancy and infant outcomes) and effective communication of findings
- Optimising the immune response in pregnant women and in infants

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Maternal immunisation uptake in Australia

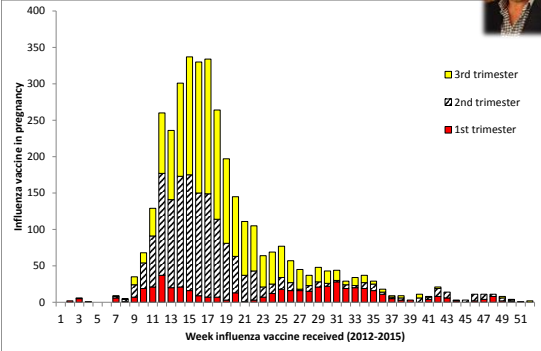


Uptake in Australia – ★★☆☆

State/territory	Influenza vaccine coverage (%)		Pertussis vaccine coverage (%)	
	2015	2016/2017	2015	2016/2017
NT	44.2	45.6	45.4	?
Qld	46.9	56.0	52.1	63
NSW	31.9	?	27.7	?
Victoria	39.7	61	31.8	82
SA	56.2	76	57.4	81
WA	53.2	55	63	80
Aboriginal and Torres Strait Islander (WA)	62		64	
Aboriginal and Torres Strait Islander (NT)		68.5		

FluMum study (personal communication Ross Andrews), Rowe et al. ESPID 2018 Data sourced from Clinical Council Unit, Safer Care Victoria. Data compiled by Health Protection Branch, Mohammad H. PlosOne (accepted for publication), Mak et al 2016, Peterson K 2016 (personal communication)

Flu vaccine in pregnancy is rarely given after Mother's day !



Gaps

- We can do better....
 - Limitations in data
 - likely bias from small sample sizes in estimating coverage and mostly measured in tertiary obstetric hospitals
- Goal > 90% for influenza and pertussis vaccine pregnancy**
- Data lacking on community and private obstetric services and hospitals
 - We need to use the whole calendar year to ensure better access to vaccines for pregnant women

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

- Effectiveness of influenza vaccine in pregnancy
- 51% - 61% in the pregnant women¹
 - 86% of infants are protected at 8 weeks and 30% at 6 months of age (RCT influenza vaccination)²



Influenza in infants up to six months of age that required hospital admission. (Case-control studies)

Study	Case group (n)	Control group (n)	Results
Benowitz et al. (2010)	Influenza test positive (91)	Influenza test negative (156)	Adjusted effectiveness 91.5% (95% CI: 61. to 98.1%) [†]
Poehling et al. (2011)	Influenza test positive (151)	Influenza test negative (1359)	Adjusted OR 0.52 (95% CI: 0.30 to 0.91) [†]

[†] Adjusted model retained, immunization of household contacts, and prematurity

[†] Adjusted model included age, sex, race/ethnicity, site, study year, tertile of the influenza season, smoke exposure at home, number of siblings, day care attendance, insurance status, and whether the infant was ever breast-fed.

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

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Influenza vaccine effectiveness in pregnant women (Australia)

PREVENT cohort study (Australia, USA, Canada, Israel)

- VE against laboratory confirmed influenza in pregnant women
- 40% (CI 12, 59) overall, 55% (1st/2nd trimester), 35% (3rd trimester)
- 55% overall for matched circulating strains



PAEDS partnership grant (PAEDS partnership grant and FluCAN)

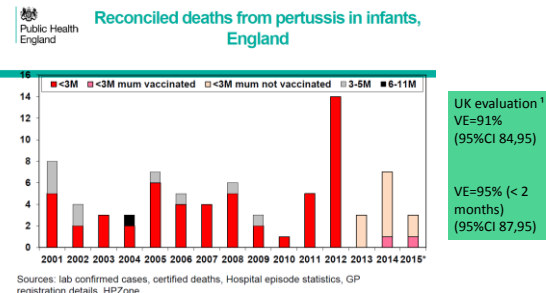
- VE against hospitalisation for confirmed influenza in infants
- 53% at 8 weeks of age
- 23% at 3 months of age
- 11% at 6 months of age



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Pertussis vaccine effectiveness

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



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

Pertussis vaccine effectiveness (Australia)

VE of maternal immunisation amongst infants

< 6 months hospitalised with pertussis using a test negative design, PAEDS

= 85.9% (48.2, 96.2)



Effectiveness of maternal pertussis vaccination in preventing infection and disease in infants: The NSW Public Health Network case-control study.

Nathan Sait^{1,2}, Kevin Wang³, Shigma Rag⁴, Heather Baldwin⁵, Kate Alexander⁶, Meena Chandra⁷, Jane Thomas⁸, Helen Quinn⁹, Vicky Sheppard¹⁰, Stephen Conaty¹¹

VE= 69% in under 3 month olds

VE = 94% against hospitalisation



1. FluMum

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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

Supported by more recent studies

Lisa McHugh et al (FluMum study)

- No difference in birthweight or gestation between vaccinated and unvaccinated³
- Or preterm births (HR 1.10; p=0.28); LBWT (HR 1.05; p=0.77); SGA (HR 0.99; p=0.94).⁴
 - There was no evidence of elevated risk by trimester of IIV.



1. McMillan M et al. The JBI Database of Systematic Reviews and Implementation Reports. 2014;12(6): 281-381-15
2. Gilles et al PHAA 2018 3. McHugh et al Vaccine 2017;35:1403-09 4. McHugh et al CID (accepted for publication)

Pertussis vaccine safety in pregnancy

Systematic review of safety of pertussis vaccine in pregnancy

- Preterm birth 0.47 to 1.50 (< 37 weeks of gestation)
- Small for gestational age 0.65-1.00
- Stillbirth 0.36-0.85
- Neonatal death 0.16-1.00
- Low birth weight 0.76-1.20 (less than 2,500 g)
- Congenital anomalies 0.20-0.91

Of three retrospective studies assessing chorioamnionitis after vaccination, one showed a small but statistically significant increase.

Objective rates of fever were low, $\leq 3\%$ and systemic events observed included headache, malaise, and myalgia.



McMillan et al. Obstet Gynecol. 2017 Mar;129(3):560-573.

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IMSafe study

Aim: To provide high level of evidence on safety of influenza and pertussis vaccine in pregnancy using a prospective cohort study design

- prospective cohort infant and maternal safety following maternal influenza and pertussis immunisation (n=1500)
- Healthy primips, enrol at < 20 weeks gestation
- Data collection:
 - Maternal
 - on lifestyle, education, SES, SEIFA, obstetric history, infections in pregnancy, BP
 - Immunisations during pregnancy – date, trimester, reasons for not receiving the vaccine
 - Investigations
 - detailed ultrasound – HC, biparietal diameter, abdominal circumference, femur length
 - Placental biopsies
 - Saliva, serum, plasma, urine
 - Infant
 - Infant measurements, foetal compromise, congenital anomalies, weekly weights



Maternal vaccination non-specific effects in pregnancy and infant outcomes

Several more recent observational studies of maternal influenza immunization

- Olsen et al observed a significantly reduced risk of preterm birth associated with influenza vaccination during a time period of high viral circulation (aRR: 0.69; 95% CI: 0.55–0.87)
- Regan et al reported a large risk reduction for stillbirth (adjusted hazard ratio [HR]: 0.49; 95% CI: 0.29–0.84)
- Current studies are assessing whether providing influenza vaccination before commencing an IVF cycle increases success rates by inducing immunological tolerance



1. Olsen SJ et al. The effect of influenza vaccination on birth outcomes in a cohort of pregnant women in Lao PDR, 2014–2015. Clin Infect Dis 2016;63:487–94. 2. Regan AK et al. Seasonal trivalent influenza vaccination during pregnancy and the incidence of stillbirth: population-based retrospective cohort study. Clin Infect Dis 2016;62:1221–7.

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Improving uptake of maternal immunisation

Interventions to improve uptake of pertussis vaccination in pregnancy: systematic review



Educational interventions focussed on pregnant women (RCTs)

- Tdap vaccine information statement
- Affective video messaging
- Cognitive messaging iBook

No association with uptake

Practice Interventions (observational)

- Midwife delivered immunisation program OR= 21
- Complex - vaccine champion, provider to patient talking points, educational brochures, posters
- iPads with patient centred tutorial 9-14%

Increased uptake of pertussis vaccine

Healthcare provider focussed interventions (observational)

- Best practice alert (electronic medical record) 97%
- ACOG toolkit – physicians received information via email and at regular faculty meetings 36 – 61%

Increased uptake of pertussis vaccine

Factors associated with uptake of influenza vaccine among pregnant women



Variable	Level	Received maternal influenza vaccine n (%)	Univariate binomial regression			Multivariable binomial regression		
			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					
	Other	32/42 (76%)	0.50	0.16-1.57	0.763			
Parity	Primiparous	69/82 (84%)	1.00					
	Multiparous	67/97 (71%)	0.42	0.20-0.87	0.021	0.43	0.19-0.99	0.048
Provider recommendation received	No	40/64 (63%)	1.00			1.00		
	Yes	96/115 (83%)	3.03	1.49-6.14	0.001	2.81	1.19-6.68	0.002
A midwife delivered maternal immunisation program	Prior	8/25 (32%)	1.00			1.00		
	Post introduction	128/155 (83%)	8.00	3.06-20.9	<0.001	5.95	2.13-16.61	<0.001

Factors associated with uptake of pertussis vaccination



Variable	Level	Received maternal pertussis vaccine n (%)	Univariate binomial regression			Multivariable logistic regression		
			Odds ratio (OR)	95% CI	p-value	Adjusted odds ratio (AOR)	95% CI	p-value
Maternal age category	21-31	85/96 (89%)	1.00			1.00		
	32-43	60/82 (73%)	0.35	0.18-0.78	0.010	0.39	0.130-1.11	0.078
Country of birth	Australia	102/116 (88%)	1.00					
	Other	32/42 (76%)	0.30	0.28-2.14	0.124			
Parity	Primiparous	70/82 (85%)	1.00					
	Multiparous	75/98 (77%)	0.53	0.24-1.18	0.116			
Awareness of maternal pertussis recommendation	No	37/64 (63%)	1.00			1.00		
	Yes	108/117 (92%)	7.78	3.31-18.2	<0.001	4.43	1.61-12.23	0.009
A midwife delivered maternal immunisation program	Prior	5/25 (20%)	1.00			1.00		
	Post introduction	140/155 (90%)	31.73	10.25-98.27	<0.001	21.17	6.14-72.95	<0.001

Pregnant women's views: qualitative study



In-depth interviews 17 pregnant women

- Most pregnant women were not aware of immunisation recommendations for pregnant women
- Endorsement by their health-care provider, perception of risk and benefit, and previous vaccination experience play a vital role in women's decisions whether or not to be immunised during pregnancy
- Although the role of healthcare provider was identified as vitally important, the majority of women had not been advised of recommended vaccines by their healthcare provider

Healthcare provider's views



2. Barriers to accessing immunizations
MMR... Its always done before they leave, even the early discharges have always had their MMR [shared care GP] I would say its nearly never forgotten because its part of what we do, its like getting up in the morning and brushing your teeth [midwife]
3. Being part of a structured or systematic process
"...I was just talking about this the other day with a group of GPs. And one person in the group had had to pick it up when [sic] MMR hadn't been done in the hospital, but everybody else said no it was always done before they leave, even the early discharges have always had their MMR, we don't have to do that, the hospital does it" GP2
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 because our hospital would be liable in that situation

MIMS: Maternal Immunisation Matters

Pilot study data

- Lower uptake of vaccines in pregnancy in women with English as a second language
- Women of CALD background and multiparous mothers less likely to have received pertussis vaccination (RR 0.24, $p = 0.01$)

MIMS

- RCT of a verbal and written information to women of non-English speaking backgrounds to assess uptake of influenza and pertussis vaccines

Influenza	English (151)	Non-English (32)	P value
Heard of influenza	141 (93%)	Yes 27 (84%)	Yes 0.092
10 (7%)	No 5 (16%)	No	
Influenza contagious	136 (91%)	Yes 27 (84%)	Yes 0.291
15 (9%)	disagreed 5 (16)	disagreed	
Awareness that pregnant women can be vaccinated against the flu	112 (74%)	Yes 17 (53 %)	Yes 0.018
39 (25%)	No 15 (46%)	No	
Believing the vaccine is safe during pregnancy	106 (71%)	Yes 16 (50%)	Yes 0.024
44 (29%)	No 16 (50%)	No	

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Maternal Immunisation; research to practice and policy

Pregnant women's views

Confidence in immunisation providers recommendations

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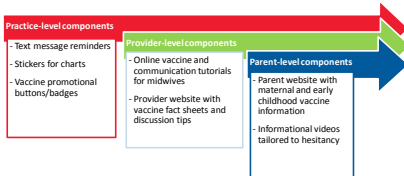
1. Webb H, Marshall J, Marshall J

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P3-MumBubVax: intervention to optimise midwife vaccination discussions

P3-MumBubVax: intervention to optimise midwife vaccination discussions

Components at 3 levels: the Practice-, Provider-, and Parent-levels



Project leads:
Dr. Angela Dwyer (Murdoch Children's Research Institute, University of Melbourne); Dr. Jessica Kaulman (Murdoch Children's Research Institute, University of Melbourne); Dr. Kate Morgan (Department of Primary Industries, Tasmania State Institute); Dr. Thomas Black (Curtin University, WA Health); Prof. Paul O'Keefe (University of Western Australia); Dr. Andrew Rogers (Curtin University, Tasmania State Institute)



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Optimising the immune response

Gaps: Evidence for optimal timing of maternal pertussis vaccination

- Earlier maternal pertussis immunisation [from 20 weeks gestation (UK)]
 - Increased antibody levels in infants¹
 - Increase in uptake in the UK from 60% to 70% since implementation
- Maternal pertussis vaccination suppression of primary infant responses – clinical relevance?

- Impact of DTPa with every pregnancy on maternal and infant antibody levels (NHMRC project grant application)

TABLE 2
Newborn cord blood antibody levels by groups

	Vaccinated 20–32 wk (N = 38)	Vaccinated 33–36 wk (N = 44)	Control group (N = 27)	P value ^a
Cord blood pertussis vaccination				
anti-PT	5.83 (0.93)	5.31 (1.17)	4.19 (1.04)	<.001
anti-PTx	5.18 (0.88)	5.03 (1.18)	4.21 (1.08)	<.001
anti-PTx2	4.18 (1.10)	3.58 (1.25)	2.80 (1.2)	<.001

anti-PT, IgG transplacental pertussis toxin; anti-PTx, IgG transplacental pertussis toxin; anti-PTx2, IgG transplacental pertussis toxin; anti-PTx2, IgG transplacental pertussis toxin.

^a Results of analysis for differences across 3 groups.

Woods et al. Vaccine 2016;34(12):2800–2806.



Email me

1. Naidu MA et al. AJOG 2016:e237

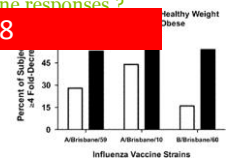
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OptiMum: does obesity in pregnancy affect influenza vaccine responses ? (WCH Foundation)

- 50 % of pregnant women in Australia are overweight or obese

- effect of obesity on influenza vaccine responses ?

- Pre
- Michelle Clarke P2-008
- Adults 1 2
- Obesity results in a greater decline of influenza antibodies post vaccination²



OptiMum study

- (H Marshall, M Clarke, S Lambert, I Barr, L Giles)

Aim:

- to investigate the impact of obesity and pro-inflammatory cytokines on influenza antibody levels post vaccination in pregnant women

1. Sheridan P et al. International J of obesity 2012;36(8):1072-7. 2. Sperling RS et al. Obstet Gynaecol 2012;119(3):631-9.

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In Summary: Improving effectiveness of maternal immunisation programs

- Effective communication for pregnant women AND immunisation providers about benefits and safety of maternal immunisation
- Assisting providers by NORMALISING immunisation as part of standard pregnancy care
- Better ACCESS to vaccines for pregnant women
 - Identifying vulnerable women, providing tailored immunisation strategies
 - Vaccinate past MOTHER'S DAY (influenza)
 - Consider recommendations for EARLIER DELIVERY of pertussis vaccine in pregnancy
- Evidence for scheduling of maternal vaccines to OPTIMISE immune response in infants and pregnant women

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Are we ready for the next generation of vaccines for pregnant women ?

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



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Maternal Immunisation Collaborators

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- A/Prof Julie Leask, University of Sydney
- Dr Annette Regan,
- Dr Margie Danchin, RCH, Melbourne
- A/Prof Michelle Giles, Melbourne, Vic

