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ABSTRACT

Despite long standing immunisation programs, pertussis remains a challenging disease in Australia and globally, with young infants most at risk of death and severe disease. Globally, the emergence of pertactin negative strains of *Bordetella pertussis* has been observed, with implications unclear. Adults are a common reservoir of infection and a source of transmission to young infants, and vaccine coverage in this group is largely unknown. In this research program, we aimed to:

1. Describe the clinical severity of *Bordetella pertussis* infections in Australian children and investigate factors associated with severe disease;
2. Describe the impact of genotypic variants lacking pertactin expression on severity of pertussis infections in children; and
3. Assess community knowledge and awareness of pertussis infections and predictors of uptake of recent pertussis vaccination in the South Australian population.

Methods:

1. Medical, laboratory and vaccination records were reviewed for children admitted to hospital with a diagnosis of pertussis at any of eight participating tertiary paediatric hospitals around Australia. A severity scoring system was designed and used to determine predictors of severe pertussis disease in the enrolled children.
2. To assess the influence of emerging *B. pertussis* variants deficient in pertactin antigen, clinical details were collected from medical records of children presenting to, or admitted to one of three major paediatric hospitals in Australia (Women's and Children's Hospital, Adelaide, Princess Margaret Hospital, Perth, Children's Hospital at Westmead, Sydney) during 2008-2012 with a confirmed pertussis infection and an isolate available for determination of pertactin expression and genotyping.

3. A cross-sectional survey of randomly selected households was conducted in South Australia by Computer Assisted Telephone Interviews to ascertain pertussis (whooping cough) vaccination history and predictors of recent vaccine uptake (within previous five years) amongst South Australian adults. Knowledge, perceptions and attitudes towards pertussis infections and prevention were evaluated. Log binomial models were fit to assess predictors of awareness of adult pertussis vaccine availability

Results:

1. One hundred and twenty children who were hospitalised with pertussis were enrolled nationally. Over 40% of cases were in children less than two months of age. A pertussis severity score (PSS) was determined for all cases with the majority of children classified as not severe ($PSS \leq 5$). Young age (< 2 months, $p=0.014$), presence of fever at admission ($p=0.030$), presence of co-infection ($p=0.004$) and prematurity ($p=0.024$) were associated with more severe disease.

2. A total of 199 *B. pertussis* isolates collected during 2008-2012 were identified from children presenting to, or admitted to, one of the three participating hospitals. One third of these isolates (35.7%; 71/199) were pertactin deficient. Over one third of cultured cases were from children less than three months of age ($n=82/199$; 41.2%). Most severe disease occurred in young, unimmunised infants. Adjusting for pertussis toxin promoter allele, vaccination status and age category, Prn status was not associated with disease severity (Risk Ratio=0.97, 95%CI: 0.57-1.62, $p=0.90$).

3. From 3124 randomly sampled contactable households, 1967 interviews with individuals aged 18-93 years were conducted (participation rate 63%), including 608 parents of children aged < 18 years. Recent adult pertussis vaccine coverage was low, with only 10% of respondents reporting pertussis vaccination in the previous

five years. Predictors of recent pertussis vaccination included higher education, larger household size, perception of greater disease severity and discussion with a family physician about pertussis vaccination. The majority of respondents (97%) had heard of pertussis (whooping cough) and many (73%) considered whooping cough to be highly contagious and severe for infants (89%). Whilst 61% of respondents were aware of the availability of an adult pertussis booster vaccine, only 8% (n=154) reported their general practitioner had discussed it with them. If provided free, 77% agreed that they would be more likely to accept a booster pertussis vaccination.

Conclusion:

B. pertussis infections continue to pose a threat to Australian children, particularly infants too young to have received direct protection through vaccination. Children admitted to hospital with *Bordetella pertussis* and fever or co-infection should be closely monitored, particularly if they have a history of prematurity. The rapid emergence of pertactin negative *Bordetella pertussis* variants do not appear to be associated with any increased severity of disease for children, however the impact of strain evolution on vaccine efficacy and transmissibility requires further investigation. Whilst knowledge regarding transmission and severity of *Bordetella pertussis* was high in the general community, uptake of adult pertussis vaccination is remarkably low amongst South Australians. Improved awareness regarding the availability of a booster pertussis vaccine through general practitioners and/or provision of funded pertussis vaccination for adults has the potential to improve pertussis vaccine coverage and provide greater protection for vulnerable infants.

THESIS DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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PUBLICATIONS DURING CANDIDATURE

This thesis contains three manuscripts, which have been published by international peer-reviewed journals, 'Paediatric Infectious Diseases Journal'-published; 'Journal of Infection'- and 'Vaccine'.

- 1) Marshall H, Clarke M, Rasiah K, Richmond P, Buttery J, Reynolds G, et al. Predictors of disease severity in children hospitalized for pertussis during an epidemic. *The Pediatric Infectious Diseases Journal*. (Impact Factor 3.135)

- 2) Clarke M, McIntyre P, Blyth C, Wood N, Octavia S, Sintchenko V, Giles L, Quinn H, Hanly G, Hill V, H, Lan R, Marshall H. Impact of pertactin deficient *B. pertussis* variants on clinical severity of pertussis disease in Australian children. *Journal of Infection* (Impact Factor: 4.441)

- 3) Clarke M, Thomas N, Giles L, Marshall H. Community awareness and predictors of uptake of pertussis booster vaccination in South Australian adults. *Vaccine*. (Impact Factor: 3.492)

Statement of contribution to manuscripts

For the first manuscript, Michelle Clarke is second author, having contributed to data collection and the statistical analysis plan with Helen Marshall as lead author conceiving and leading the national research study. The manuscript was co-authored by Helen Marshall and Michelle Clarke with statistical input and guidance from Data Management and Analysis Centre (Tom Sullivan and Suzanne Edwards) and the Women's and Children's Hospital Public Health Research Unit (Kate Dowling and Peter Baghurst). Michelle completed the final presented statistical analyses and prepared reports of statistical tables for review and discussion with above named statistical advisors. Other national co-authors contributed to editing and review of the manuscript and the final data analysis plan.

For the second manuscript, Michelle Clarke collected data with regards to clinical outcomes for children enrolled at the Women's and Children's Hospital, prepared national data collection tools and collated and cleaned data from all three participating sites. Michelle Clarke designed the analysis plan and performed all statistical analyses with Lynne Giles guiding and advising for more complex statistical analyses. Michelle Clarke prepared the first draft of the manuscript with guidance from Helen Marshall and Lynne Giles. HM, LG and co-authors from sites in NSW and WA assisted with study design, and/or contributed to review and editing of the manuscript.

For the third manuscript, Michelle Clarke performed all statistical analysis with guidance from supervisors, Helen Marshall and Lynne Giles. MC prepared the first draft of the manuscript under the direct supervision of HM and LG. HM and NT assisted with study design, and contributed to, reviewed and edited the manuscript.

LG provided guidance and advice to MC for statistical analyses, and contributed to, reviewed and edited the manuscript.

I confirm that all three manuscripts have been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. I further confirm that the order of authors listed in the manuscript has been approved by all authors. I acknowledge the assistance of Chris Heath, Research Nurse and friend within the Vaccinology and Immunology Research Trials Unit (VIRTU) for her assistance with proof reading manuscripts and this thesis.

PRESENTATIONS DURING CANDIDATURE

During candidature, I presented work related to this Master's thesis at the School of Population Health Seminar series, the Robinson Research Institute Symposium (2014) and the National Public Health Association of Australia Communicable Diseases Conference (2015).

Oral presentations

- 1) Clinical severity comparisons between pertactin deficient and pertactin positive *Bordetella pertussis* variants. Communicable Diseases Conference, Brisbane, 01 June 2015
- 2) Community understanding of whooping cough and vaccine uptake in South Australian adults. University of Adelaide School of Population Health Seminar, 30 April 2015
- 3) Pertussis: a continuing challenge. Robinson Research Institute Symposium – invited oral presentation, 06 November 2014

Poster presentations

- 1) Community knowledge and uptake of booster pertussis vaccination – poster. Robinson Research Institute Symposium, Adelaide, 06 November 2014
- 2) Clinical severity comparisons between pertactin deficient and pertactin positive *Bordetella pertussis* variants. Florey postgraduate conference 24 September 2015 and Robinson Research Institute Symposium, Adelaide, 04 November 2014

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studies, providing endless emotional support and taking care of our family to allow me to achieve what I believe are important life goals. My children are a constant reminder of why I do what I do and why I will continue to strive to explore ways to improve protection for children against infectious diseases.

“There is no trust more sacred than the one the world holds with children. There is no duty more important than ensuring that their rights are respected, that their welfare is protected, that their lives are free from fear and want and that they can grow up in peace.”

-- Kofi Annan

LIST OF ABBREVIATIONS

ABS	Australian Bureau of Statistics
ACIR	Australian Childhood Immunisation Register
ACT	Adenyl Cyclase Toxin
ATAGI	Australian Technical Advisory Group on Immunisation
CATI	Computer Aided Telephone Interview
CI	Confidence Interval
CPAP	Continuous positive airway pressure
DNT	Dermonecrotic Toxin
DTP	Diphtheria-Tetanus-Pertussis
DTPa	Diphtheria- Tetanus-acellular Pertussis
DTwP	Diphtheria-Tetanus-whole cell Pertussis
FP	Family Physician
GCP	Good Clinical Practice
GP	General Practitioner
HDU	High Dependency Unit
HREC	Human Research Ethics Committee
ICD	International Classification of Diseases
ICU	Intensive Care Unit
Ig	Immunoglobulin
IQR	Interquartile range
IV	Intravenous
LOS	Length of stay
NIP	National Immunisation Program

NNDSS	National Notifiable Disease Surveillance System
NSW	New South Wales
OR	Odds Ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PCR	Polymerase Chain Reaction
PRN	pertactin
PROS	Population Research and Outcomes Studies
PSS	Pertussis Severity Score
PT	Pertussis Toxin
PTXP	Pertussis Toxin Promoter
RR	Risk Ratio
RSV	Respiratory Syncytial Virus
SA	South Australia
SD	Standard deviation
TCT	Tracheal Cytotoxin
UK	United Kingdom
US	United States
VIRTU	Vaccinology and Immunology Research Trials Unit
WA	Western Australia
WCH	Women's and Children's Hospital
WHO	World Health Organization