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Factors associated with vaccine reactogenicity in school aged children and young adults following administration of two protein-based vaccines

Helen Aspasia Petousis-Harris

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy, The University of Auckland, 2011
Abstract

**Aim** To identify or exclude factors associated with injection site reactions following immunisation.

**Methods** Literature review identifying key factors of gender, psychological stress, and exercise and injection technique. Study conducted involving secondary analyses of existing data from a clinical trial of outer membrane vesicle meningococcal (OMV) vaccines in children aged eight to 12 years including examination of factors associated with perceived pain at the time of injection, followed by a randomised trial of three injection techniques used to deliver the quadrivalent human papillomavirus vaccine in females aged 14-45 years and males aged 14-26 years. Data collected included stress variables and blood samples for evaluation of cytokines.

**Findings** In the first study vaccinator was the variable with largest effect on reactogenicity outcomes of injection site pain, erythema and induration. Ethnicity had an effect on injection site pain and erythema. Body mass index was associated with injection site pain. Baseline antibody did not affect injection site reactions but reactogenicity effected antibody levels measured after dose two. Perceived pain on injection was most strongly effected by vaccinator and vaccine formulation. These outcomes informed the design for the prospective study.

This trial found the three injection techniques did not affect injection site reactogenicity. Females tended to experience more reactogenicity. Perceived stress, social support and atopy were not associated with reactogenicity outcomes and exercise showed little effect. No cytokine functional groups nor individual cytokines were associated with reactogenicity outcomes. No variables, including injection technique, were associated with wide variation in perceived pain on injection. Case-by-case observational data suggest some variations in anatomical site may be important.

**Conclusions** This thesis demonstrated factors that can ameliorate both reactogenicity and pain on injection. Injection technique plays an important role in both reactogenicity and perceived pain on injection following OMV vaccines. Why vaccinator effects on pain on injection was not elucidated from the trial but anatomical site may be a factor, which has implications for vaccinator education. Ethnic differences in injection site reactions requires further research. Calling reactogenicity an adverse event may be a
misnomer since it correlates positively with antibody response, a finding which could improve confidence in immunisation.
Dedication

I would like to dedicate this work to my Mother for her unconditional love and support throughout all my endeavours, and who is not here to see the finish of this one.
Acknowledgements

This thesis would not have been possible without the following people.

Thank you to my supervisors and advisors who have each brought their unique skills and experience to the table. Gregor Coster who guided me through the complex administrative process and always provided supportive and encouraging words, this would never have got off the ground without him; Diana Lennon who provided her experience with the Meningococcal B studies and brilliance, and provided permission to use the NZ meningococcal B clinical trial data; Felicity Goodyear-Smith who picked up where Gregor left off and brought her fabulous academic rigor and editorial skills as well as friendship, and Joanna Stewart who provided statistical guidance with the patience of a saint. Special thanks to Sarah Young who provided advice for the cytokines and who supervised the assays.

Special thanks to my dear friend Nikki Turner who insisted I should do a PhD and held my hand enthusiastically all the way.

Thank you to all of those, of whom there are many, who contributed to the meningococcal B school based trials and provided the data for the secondary analysis presented in this thesis. In particular thank you to Catherine Jackson who assisted in the provision of information and provided excellent advice and helpful feedback.

The FAR trial could not have happened without the innovation, passion and fantastic skills of Tracey Poole who did everything humanly possible to find and recruit participants and for efficiently coordinating so much of the collection and management of the data. You gave so much more than I could ever have asked for.

Thank you to the Immunisation Advisory Centre (IMAC) for supporting me throughout this thesis as I continued to work full time. You are a most special and treasured organisation.

Also, to all the IMAC staff vaccinators who gave their time freely: Brenda Gerard, Ben Soe, Karin Batty, Leeann Knight, Lisbeth Alley, Gary Reynolds, Meri Ormsby, Linda Hill, Michelle Tanner and Nikki Turner. Also special thanks to Linda O'Conner. Thanks to Erin Lockett who meticulously arranged the FAR trial procedural documents and negotiated the administrative network.
I am indebted to all of the participants in the FAR trial who were such a willing and
great bunch of people.

Thanks to the generosity of the sponsors who donated prizes and gifts for the FAR trial
participants: New Zealand Jewellers, Hell Pizza, Napoleon Perdis Cosmetics, CSL,
Angela Daniel Jewellery, Teddytime, Silver Ribbon Foundation, Dymock, Hoytes, U by
Kotex, and Vodafone NZ.

Finally, much love and thanks to my family Vaughan, Jason, Danyon and Alexander for
their continuing support and who have endured my end of thesis absences without
complaint.
Publications and presentations arising from this research

Published paper


Oral presentations


Further articles

The following article is in preparation
Helen Petousis-Harris, Catherine Jackson, Joanna Stewart, Gregor Coster, Nikki Turner, Diana Lennon. Vaccinator matters: Factors associated with reactogenicity to an OMV meningococcal B vaccine in children aged 8-12 years.

Further manuscripts are planned on other aspects of this thesis, in particular:

- injection site and perceived pain on injection
- the reactogenicity of quadrivalent human papillomavirus vaccine following administration with three different injection techniques
- stress, social support and associations with cytokines.
Research contribution

The first study presented in this thesis is a secondary analysis of existing data. I was responsible for obtaining ethical approval, management of all data and the analysis and interpretation. Joanna Stewart provided statistical guidance.

The second study is a prospective clinical trial. I was responsible for study design, obtaining ethical approval and study conduct. The day to day coordination and ongoing data collection was undertaken by Tracey Poole. The vaccinations were delivered by authorised vaccinators. Phlebotomy was undertaken by the vaccinators, Tracey Poole and I. The cytokine assays were undertaken by Immunologists at the University of Otago department of Pathology in Dunedin. The FAR trial analyses were undertaken by me with the exception of the logistic regression with repeated measures which was provided by Joanna Stewart. The follow up of participants with induration and swelling was carried out by clinician Dr Alison Vogel.
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### Abbreviations

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<th>Description</th>
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<tbody>
<tr>
<td>ADCC</td>
<td>Antibody Dependant Cellular Cytotoxicity</td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse Event Following Immunisation</td>
</tr>
<tr>
<td>APC</td>
<td>Antigen Presenting Cell</td>
</tr>
<tr>
<td>AS03</td>
<td>Adjuvant System 03 GSKs proprietary oil-in-water emulsion adjuvant</td>
</tr>
<tr>
<td>AS04</td>
<td>Adjuvant System 04 GSKs proprietary adjuvant</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CD</td>
<td>Cluster of differentiation</td>
</tr>
<tr>
<td>CDC</td>
<td>Centres for Disease Control</td>
</tr>
<tr>
<td>CGRP</td>
<td>Calcitonin gene related product</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
</tr>
<tr>
<td>COSTART</td>
<td>Coding Symbols for a Thesaurus of Adverse Reaction Terms</td>
</tr>
<tr>
<td>CV</td>
<td>Chiron Vaccine</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>DAMP</td>
<td>Damage Associated Molecular Patterns</td>
</tr>
<tr>
<td>DT</td>
<td>Diphtheria-Tetanus</td>
</tr>
<tr>
<td>DTH</td>
<td>Delayed-type Hypersensitivity</td>
</tr>
<tr>
<td>DTP</td>
<td>Diphtheria-Tetanus-Pertussis</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme Linked Immunosorbent Assay</td>
</tr>
<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric Mean Titre</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C Virus</td>
</tr>
<tr>
<td>HPA</td>
<td>Hypothalamic-Pituitary-Adrenal</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papillomavirus</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization of Technical Requirements for Registration for Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>IFNγ</td>
<td>Interferon Gamma</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
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<tr>
<td>IPV</td>
<td>Inactivated Polio Vaccine</td>
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ISR  Injection Site Reaction
LPS  Lipopolysaccharide
MedDRA  Medical Dictionary for Regulatory Activities
MeNZB™  New Zealand tailor made meningococcal B vaccine
MF59  Novartis' proprietary oil-in-water emulsion adjuvant
MHC  Major Histocompatibility Complex
MMF  Macrophagic myofasiiitis
MMR  Measles Mumps and Rubella
MoH  Ministry of Health
MOOSE  Meta-analysis of Observational Studies in Epidemiology
mRNA  Messenger RNA
NGF  Nerve Growth Factor
NIH  National Institutes of Health
NIPH  National Institute of Public Health (Norway)
NIR  National Immunisation Register
NK  Natural Killer
NO  Nitrous Oxide
OMP  Outer Membrane Protein
OMV  Outer Membrane Vesicle
PAMP  Pathogen Associated Molecular Patterns
PBMC  Peripheral Blood Mononuclear Cells
PCR  Polymerase Chain Reaction
PMN  Polymorphonuclear granulocytes
PSQ  Perceived Stress Questionnaire
PSS  Perceived Stress Scale
QUORUM  Improving the Quality of Reports of Meta-Analysis of Randomized Controlled Trials
ROS  Reactive Oxygen Species
RSV  Respiratory Syncytial Virus
SAS  Statistical Analysis Software
SBA  Serum Bactericidal Antibody
SC  Subcutaneous
SES  Socioeconomic Status
SISS  Single Item Social Support
SLE  Systemic Lupus Erythematosus
TGF  Transforming Growth Factor
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th1</td>
<td>T-helper cell type 1</td>
</tr>
<tr>
<td>Th2</td>
<td>T-helper cell type 2</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll like receptor</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour Necrosis Factor</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>VLP</td>
<td>Viral-like particle</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WHO-ART</td>
<td>World Health Organization Adverse Events Reaction Terminology</td>
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## Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Adjuvant</td>
<td>Substance that enhances immunogenicity. Until the late 1990’s Aluminium salts were the only adjuvants licensed for human use.</td>
</tr>
<tr>
<td>Antibody</td>
<td>Protein produced by B-plasma cells specific for single molecular shape. Also called immunoglobulin or Ig. Part of adaptive immunity.</td>
</tr>
<tr>
<td>Antigen</td>
<td>Usually protein or sugar that initiates a specific immune response.</td>
</tr>
<tr>
<td>B-cell</td>
<td>Belong to group of white blood cells called lymphocytes. Part of specific immunity.</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Small peptides that facilitate leukocyte trafficking into tissues</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Key mediators in the control of the inflammatory response.</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>Antigen presenting cells. Activated after uptake of foreign material and migrate to lymph nodes to present antigen to T and B cells.</td>
</tr>
<tr>
<td>Eccentric exercise</td>
<td>External resistance resulting in lengthening of muscle</td>
</tr>
<tr>
<td>Granuloma</td>
<td>Spherical mass of cells, usually walling off foreign substances. Consist largely of macrophages.</td>
</tr>
<tr>
<td>IL-10</td>
<td>Activator of B-cells and anti-inflammatory.</td>
</tr>
<tr>
<td>IL-13</td>
<td>Activator of B-cells and anti-inflammatory.</td>
</tr>
<tr>
<td>IL-1α and β</td>
<td>Produced mainly by monocytes and macrophages, but also by endothelial cells, fibroblasts and epidermal cells in response to stimuli such as bacterial lipopolysaccaride (LPS) and other microbial products. Secreted IL-1 is involved in inflammation with associated vasodilation, and cramps.</td>
</tr>
<tr>
<td>IL-4</td>
<td>Potent activator of B-cells. Anti-inflammatory cytokine, suppresses pro-inflammatory cytokines such as IL-1 and TNF.</td>
</tr>
</tbody>
</table>
IL-6  Pro-inflammatory cytokine secreted by T cells and macrophages, often in response to trauma. Becomes elevated in response to muscle contraction. Important mediator of fever and of the acute phase response. IL-6 can be secreted by macrophages in response to specific microbial molecules.

IL-8  A chemokine, attracts neutrophils.

Innate  Cells and mechanism that protect host in a non-specific manner, discriminates 'self' from 'non-self'

Lymphocyte  White blood cells that include the T-cell, B-cells and natural killer cells

Macrophage  “Big eaters” Large white blood cells derived from monocytes. They have phagocytic functions and stimulate both innate and adaptive immunity.

Monocytes  White blood cells capable of differentiating into macrophage and dendritic cells

Phagocyte  “eating” cell - white blood cells that ingest cellular debris and foreign material. Include neutrophils, monocytes, macrophage, dendritic cells and mast cells.

T-cell  Belong to group of white blood cells called lymphocytes. Part of specific immunity

TGF-β  Affects processes that include cellular differentiation and growth to inflammation and wound healing. TGF-β can act both synergistically and antagonistically with other cytokines depending on the context.

TNF-α  Primarily produced by macrophages and promotes inflammation. It attracts neutrophils, stimulates phagocytosis, and production of inflammatory agents. A local increase in TNF concentration causes the key symptoms of inflammation to occur - heat, swelling, redness and pain. It attracts monocytes and neutrophils. TNF-α is produced at all inflammatory sites.

Toxoid  A bacterial toxin that has been chemically modified to remove toxicity.