5th Pharmacoepidemiology Research Network Symposium

Wednesday 20 November 2019, 10:00am – 4:30pm

St Margaret's College

University of Otago

Dunedin

ABSTRACTS

Nationwide register-based studies on vaccination: the Danish experience 2001 – 2019

Anders Hviid

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In 1968, Denmark introduced a unique personal identifier for the whole population. This identifier is used in all national registers including demographic, socio-economic, and health registers. These registers represent a veritable gold mine for health researchers. We initiated a research programme in 2001 to take advantage of these unique resources to study the post-licensure epidemiology of vaccination. In the first part of this talk, I will describe the unique Danish setting for register-based research in the context of vaccination epidemiology. In the second part of the talk, I will present some of our work on human papillomavirus vaccine safety, highlighting different ways of using register-data and different study designs.

Towards a Global Vaccine Data Network

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The Global Vaccine Data Network (GVDN) is a newly formed group of experienced vaccine safety researchers from five continents, representing public research and public health institutions. The goal of the network is to develop capacity to perform collaborative vaccine evaluations using data linkage, initially focussed on vaccine safety and eventually extending to effectiveness and risk benefit using real world evidence, in a sustainable manner.

The first aim of the proposed data network is to develop and test a model for sustainable collaboration globally to generate robust and timely real-world evidence on vaccine effects. Through a proposed pilot study, we will investigate (1) the utility of the GVDN to assess vaccine safety signals by vaccine type and manufacturer, and (2) the ability to conduct genomic studies on the risk of adverse events following vaccination in a diverse global population.

This presentation will introduce the structure of a global distributed data network (the GVDN), potential common data models, and the role of New Zealand as the coordinating centre.

Using data linkage to investigate pertussis vaccination failure in New Zealand

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Background

Pertussis vaccination is an extremely successful measure for the prevention of pertussis morbidity and mortality. However vaccination results in imperfect immunity, and prevention of infection, transmission, and clinically significant disease without associated morbidity and mortality is not as successful. Vaccine effectiveness is responsive to national immunisation schedule changes (such as changing number and timing of doses, as well as establishing a different high risk schedule). Little is known about risk factors for pertussis vaccination failure and the existence or identity of groups at higher risk for pertussis vaccination failure. The identification of groups that are at higher risk enables targeting strategies to better prevent pertussis vaccination failure

Aims

This research aims to (1) describe pertussis vaccination failure in New Zealand, and (2) investigate risk factors for pertussis vaccination failure.

Methods

Information from six national administrative datasets (National Health Index, National Immunisation Register, Episurv, National Minimum Dataset, Maternity Collections, and Pharmaceutical Collections) were linked via an encrypted identifier (Figure 1). We identified 504,847 children aged less than 4 years old who were fully vaccinated between 1 January 2006 and 31 December 2016. We discuss one of the exploratory analysis methods used – search partition analysis (SPAN). SPAN develops classification rules using Boolean expressions; it outputs a combination of attributes (risk factors) that discriminate low from high risk of pertussis vaccination failure. SPAN was developed as an alternative to more well-known classification methods such

as classification and regression trees and searches globally so as to deal with the instability related to hierarchical searches.

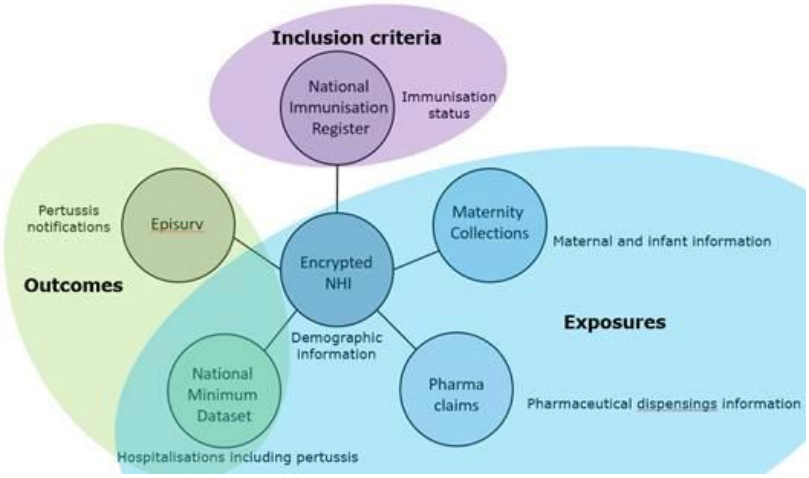

Figure 1. Administrative datasets used and their functions

Results

Our data indicates pertussis vaccination failure is a rare event (0.2%) and that vaccination protects well against the worst case scenario, death. Preliminary findings indicate ambulatory sensitive hospitalisations, high antibiotic use, recurrent wheeze, and respiratory hospitalisations are of interest for potential risk factors.

Conclusions

The volume and complexity of exposures obtained via data linkage provides exciting opportunities. SPAN is an exploratory method that can simplify some of this complexity.

Impact of human papilloma virus vaccination on rates of high grade cervical abnormalities in young New Zealand women: register data matching study

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Introduction

The New Zealand human papilloma virus (HPV) immunisation programme commenced in 2008. Between 2012 and 2015 there was a 20% decrease in high-grade cervical abnormalities in New Zealand women aged 20–25 years. The objective of this audit was to interrogate the National Cervical Screening Programme Register (NCSPR) and National Immunisation Register (NIR) to determine the impact of vaccination on the occurrence of high-grade abnormalities in vaccinated and non-vaccinated women.

Methods

Following ethical and National Kaitiaki Group approval, ~700,000 NSCPR records were accessed from women aged 20–25 between 2005 and 2015 and matched with vaccination records. A cohort study design was used. To be eligible for analysis, women needed to be born between 1990 and 1994 and have at least one smear recorded when aged 20–25. The outcome event was a high grade histology.

Results

A total of 104,313 women (376,402 person years of follow-up) were eligible for analysis. The incidence of high-grade cytology was lower in vaccinated women (at least one dose prior to 18 years) than in unvaccinated women (8.5 vs 11.3 per 1,000 person years [p1000py], incidence rate ratio [IRR] 0.75, 95% CI 0.70, 0.80, $p<0.001$). The incidence of high-grade histology was lower in vaccinated women than in unvaccinated women (6.0 vs 8.7 p1000py, IRR 0.69, 95% CI 0.64, 0.75, $p<0.001$). There was no evidence of a difference in the incidence of high-grade histology between European and Māori women overall or after taking vaccination status into account.

Discussion

It is important to understand the impact of the HPV immunisation programme on vaccinated and unvaccinated women for future cervical cancer prevention

in New Zealand. Data linkage between the NIR and NCSPR is essential and needs to occur at an early stage.

Using spontaneous reports to confirm the safety profile of vaccines

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Background

Medsafe routinely uses information from many different sources to monitor and confirm the safety profile of vaccines. An important source of information is the spontaneous reporting of vaccine adverse events from members of the public, including healthcare professionals and consumers, to the Centre for Adverse Reactions Monitoring (CARM). These reports are sometimes referred to as adverse events following immunisation (AEFI).

Recently, there was a community outbreak of meningococcal disease in Northland. A targeted programme using meningococcal ACYW vaccines started in December 2018 and ended in April 2019 to combat this outbreak. In addition, Bexsero (meningococcal B vaccine) was approved for use in New Zealand in July 2018.

This presentation provides an overview of spontaneous reports of vaccine adverse events to meningococcal vaccines and how these reports are used to confirm the safety profile of the vaccines.

Results

CARM received 93 case reports of AEFI for meningococcal vaccines between 1 July 2018 and 30 April 2019. There were 53 reports for meningococcal ACYW vaccines (Menactra and Nimenrix) and 46 reports for meningococcal B vaccine (Bexsero) during this time period. Some patients received more than one meningococcal vaccine so the number of case reports does not equal the sum of the vaccine reports.

The reports to meningococcal vaccines can be compared with the 4,373 reports of suspected adverse reactions to CARM during 2018 of which 1,473 reports were associated with vaccines.

Conclusions

There was an increase in AEFI reports to meningococcal vaccines during the period July 2018 to April 2019. It is not uncommon to see an increase in AEFI reports during mass vaccination campaigns or when new vaccines are introduced to the national immunisation schedule.

Using newly linked New Zealand Health Survey and pharmaceutical microdata to examine the extent that hazardous drinkers are prescribed medications with known alcohol interaction risks

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In order to develop and target new interventions, it is necessary to understand more about the use of prescribed medications that are known to interact with alcohol and the associated risks for different population groups.

A research collaboration between the Ministry of Health, the Health Promotion Agency/Te Hiringa Hauora (HPA), and the Health Quality & Safety Commission will use a newly developed dataset consisting of the New Zealand Health Survey linked to pharmaceutical dispensing data. This dataset is being analysed to inform the HPA strategic priority to help people who are drinking above HPA's low-risk levels to reduce their alcohol consumption through screening, brief intervention, and promoting awareness of risks.

The research will initially investigate the proportion of adults taking prescription medication stratified by drinking hazard level, ethnicity, sex, and age group. Depending on initial findings it may be possible to pool multiple years of survey data to investigate additional population socio-economic characteristics (e.g. unmet primary health care need, education attainment, and area based socio-economic deprivation). These results will be used to inform health care professionals and help them to have discussions about alcohol consumption when they are prescribing medicine to their patients.

Metformin adherence and persistence in people with type 2 diabetes: latest findings from the national study

Simon Horsburgh[1, 2], Lianne Parkin[1, 2], Dave Barson[1, 2], Katrina Sharples[1, 3, 4], Jimmy Zeng[1, 2], Lisa Te Morenga[5], Fa'afetai Sopoaga[6]

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It is estimated that around 197,000 New Zealanders aged 25 years or over (6.2% of that population) have been diagnosed with type 2 diabetes mellitus (T2DM). Pacific and Māori populations are particularly affected, with a three-fold and two-fold higher prevalence of T2DM compared to the non-Pacific and the non-Māori populations, respectively. Metformin is recommended as the first-line pharmaceutical treatment for T2DM. However, overseas research has found that many patients have suboptimal metformin adherence and persistence, reducing the effectiveness of metformin for achieving good levels of glycaemic control and increasing the risk of T2DM complications. We examined adherence and persistence in new metformin users nationally to quantify levels of adherence and persistence and to identify potential factors which might influence them.

We created a cohort of all New Zealanders with T2DM commencing metformin monotherapy between 1 January 2006 and 30 September 2014 using national data collections and followed them until the end of 2015. We obtained data on person- and health-related characteristics from these collections as well as information on medication use and health events from metformin initiation until dispensing of another antidiabetic, death, or end of follow-up (31 December 2015).

Adherence was measured using the Medication Possession Ratio (MPR), calculated annually, and discontinuation (defined as a possession gap of more than 90 days). We used a linear mixed spline model with a knot at the end of one year to examine changes in MPR by demographic and clinical factors and competing risk models were used to examine factors associated with

metformin discontinuation. Poisson regression models were used to model the rate of discontinuation.

After applying exclusion criteria, we arrived at a cohort of 85,066 individuals. Adherence increased with age at initiation and the number of non-diabetic medications dispensed prior to initiation, while Māori and Pacific ethnicity was associated with reduced adherence. Risk and rate of discontinuation followed similar patterns, with increasing age at initiation and number of non-diabetic medications dispensed prior to initiation associated with lower risk and rate of discontinuation, and Māori and Pacific ethnicity associated with greater risk and rate of discontinuation.

Collectively these findings are concerning, as they point to lower levels of metformin adherence and persistence in the groups most affected by T2DM burden.

What helps and hinders metformin adherence and persistence: views of people with type 2 diabetes

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Quantitative research in diverse settings has revealed considerable variations in adherence and persistence in relation to oral antidiabetic drugs, including metformin. Internationally, qualitative studies have provided valuable insights into the findings produced by quantitative studies of oral hypoglycaemic use, but it was unclear whether the findings of these investigations could be generalised to the New Zealand population. To complement our national quantitative study of metformin adherence and persistence, we undertook a qualitative study to explore New Zealand patients' views about what makes it easier, and what makes it difficult, for them to take metformin regularly.

A total of 10 Māori, 10 Pacific, and 10 non-Māori non-Pacific patients with type 2 diabetes who had started metformin monotherapy within the previous two years were recruited through mainstream general practices; a healthcare provider for Māori, Pacific, low income families and others who experience barriers to primary care; a Māori primary health organisation; and a Pacific healthcare provider.

We undertook face-to-face audio-recorded semi-structured interviews with participants, using the Theory of Planned Behaviour as a theoretical framework to explore factors that influenced metformin adherence and persistence. Te Whare Tapa Whā and the Fonofale models of health were also used to frame interviews with Māori and Pacific participants, respectively. The recorded interviews were transcribed and uploaded to NVivo to facilitate data organisation and analysis.

This presentation will outline some of the key findings from the study.

PHARMAC update on achieving medicine equity

Jason Arnold

Principal Analyst, Access Equity; PHARMAC, Wellington

In April 2019 PHARMAC published the paper *Achieving medicine access equity in Aotearoa New Zealand: towards a theory of change* which discusses medicine access equity: bringing together expert opinion and evidence to prompt action across the health system. This is summarised in a recent New Zealand Medical Journal digest *Inequities in access to medicines are too staggering to ignore.*

Research tells us there were 608,000 lost opportunities in 2012/2013 for Māori to access medicines which resulted in Māori not receiving 1.1 million medication treatments. This trend is continuing and potentially getting worse.

As the next stage in this work, PHARMAC commissioned the National Hauora Coalition (NHC) and Synergia to collaboratively develop and implement a medicine access equity outcomes framework. The framework will identify key outcomes and associated measures to enable PHARMAC to track change at three key levels:

1. Population level monitoring
2. The five key drivers of medicine access inequity, and
3. PHARMAC's internal capability

Jason Arnold from PHARMAC will guide you through the *Theory of change* paper and highlight the feedback received so far. Following this, he will talk about how PHARMAC plans to implement the new Framework which will monitor the health outcomes of Māori and Pacific priority populations experiencing the following priority health conditions:

1. Cardiovascular disease
2. Asthma
3. Chronic obstructive pulmonary disease
4. Gout
5. Diabetes

PHARMAC believes we can make a huge difference to New Zealand by addressing these issues and improving access to the medicines we already fund, but we can't do this alone – it needs commitment and collaboration across the whole health system.

Treatment escalation patterns in people with type 2 diabetes: a national follow-up study

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Guidelines in New Zealand and elsewhere recommend metformin monotherapy as first-line pharmacological treatment for type 2 diabetes, with subsequent stepwise intensification to other oral hypoglycaemics and insulin if required for glycaemic control. However, information about the real-life treatment escalation patterns in New Zealand is very limited.

The aims of this national cohort study were:

1. To describe the sequence in which unique therapeutic regimens were subsequently introduced in patients who initiated metformin monotherapy for type 2 diabetes
2. To describe the time to escalation of treatment from:
    a. Metformin monotherapy to a second therapeutic regimen (overall, recommended, "other");
    b. Recommended second therapeutic regimen to a third therapeutic regimen (overall, recommended, "other");
    c. "Other" second therapeutic regimen to a third therapeutic regimen (overall, recommended, "other")
3. To repeat the above analyses for the periods before, and after, the publication of type 2 diabetes management guidelines by the New Zealand Guidelines Group in June 2011

The study was based on an established cohort of 93,874 individuals who initiated metformin monotherapy for type 2 diabetes between 1 January 2006 and 30 September 2014. This cohort was derived using linked demographic, health, and pharmaceutical dispensing data from the Ministry of Health's National Collections. For each cohort member, the dates that antidiabetic drugs were dispensed, the types of drugs dispensed, and the number of days

supplied were used to generate a longitudinal record of episodes of use of mutually exclusive therapeutic regimens. Follow-up ended on 31 December 2015 or the date of death (if earlier). Sunburst plots were used to illustrate the sequence in which therapeutic regimens were introduced and whether those regimens were used in an order that was consistent with guidelines. Cumulative incidence curves were used to describe the time taken to escalate from one therapeutic regimen to another.

Some preliminary findings from this study will be presented.

Dispensing of medicines with potential for fetal harm during pregnancy in New Zealand

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Background
Medicines classified as Category D or X (D/X) have an increased risk of fetal harm if used during pregnancy. Use of these medicines during pregnancy in New Zealand has not been described.

Aims
This study describes the dispensing of potentially harmful medicines before and during pregnancy in New Zealand between 2005 and 2015.

Methods
Dispensing records in the Pharmaceutical Collection were linked with members of the New Zealand Pregnancy Cohort. Exposure to D/X medicines (using the Australian risk categorisation system) was examined from 270 days prior to conception through to the end of pregnancy. Outcomes of D/X-exposed pregnancies were also reviewed.

Results
874,884 pregnancies were included in the study. A Category D medicine was dispensed during 4.3% of pregnancies overall. Exposure to a Category X medicine occurred in 0.058% of pregnancies; once misoprostol dispensings were excluded X-exposure decreased to 0.035%. Generally, dispensings declined through the 270-day pre-pregnancy period and continued to decline throughout pregnancy. Dispensing of X medicines increased over the study timeframe whereas dispensing of D medicines increased to 2011 then declined slightly. D/X exposure during pregnancy was more likely in smokers than non-smokers, and less likely in Māori and Pacific women than European women. Pregnancies exposed to a D/X medicine had higher rates of termination than unexposed pregnancies.

Conclusion

Dispensing of potentially harmful medicines in pregnancy in New Zealand was low, particularly for Category X medicines, with exposure generally declining as pregnancy progressed. However, rising pregnancy exposure to isotretinoin over time may warrant intervention.

Balancing access and safety: stocks of paracetamol in urban New Zealand households

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Abstract not available

Cardiovascular medications and breast cancer outcomes in New Zealand

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Background

The burden of cancer in New Zealand is high, and is one of the leading causes of death. Concurrently, there has been a high and increasing prevalence of New Zealand adults medicated for cardiovascular indications over the last few years. Beta blockers, used for a range of cardiovascular indications, have been associated with improved cancer outcomes in overseas studies, but this association may not be directly applicable to New Zealand patients. Therefore, this study aimed to examine the association between the use of beta blockers and breast cancer outcomes in New Zealand women.

Methods

Various regional and national databases were linked to establish a cohort of breast cancer patients (9241 women) with their corresponding medication use, hospital records, and death records between 2007 and 2015. Cox proportional hazard models were used to assess the hazard of breast cancer specific death associated with beta blocker use.

Results

22% of patients used a beta blocker after diagnosis. The unadjusted hazard ratio for the association between beta blocker use and breast cancer death was 1.41 (95% CI 1.20–1.65), and 1.26 (95% CI 1.06–1.50) after adjustment for confounding variables. When considering subgroups however, the increased risk only remained in those with at least one cardiac condition, in patients under 80 years of age, and in those who were dispensed a beta blocker in the last periods of life. When excluding dispensings in the 6 months prior to death/last follow up, the hazard ratio between beta blocker use and breast cancer death decreased to 1.02 (95% CI 0.85–1.22).

Conclusion

The findings of our study do not support an association between the use of beta blockers and breast cancer death. Future research should explore this association further in order to establish a potential role for beta blockers as an anti-cancer agent.

Validated guidelines for pharmacological alternatives to currently prescribed medications with anticholinergic properties in older adults with dementia

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Background

Medications with anticholinergic properties are known to be associated with worsening of cognitive impairment in individuals diagnosed with dementia. With the aid of the international Resident Assessment Instrument-home care (interRAI-HC) tool, we observed a high prevalence of prescribing potentially inappropriate medications in older adults with dementia, especially the anticholinergic class of medications.

Methods

We formulated a guideline for prescribers, focussing on pharmacological alternatives to the currently prescribed anticholinergic class of medications for older adults with dementia presenting with co-morbidities, based on the current literature review of anticholinergic burden scales and serum anticholinergic activity of various medications. The guidelines were prepared referring to the medications listed in the New Zealand drug formulary, and the medications were classified according to the ATC-DDD Index 2019. Medications were sorted according to the high/moderate anticholinergic activity and their low/no anticholinergic activity substitutes.

Results

Of the 117 medications prescribed for ailments of the Central Nervous System, 38% were classified as medications with high or moderate anticholinergic activity (HOMAA), and 56% were observed to possess low or no anticholinergic activity (LONAA). Likewise, for the gastrointestinal, cardiovascular, respiratory, endocrine, genito-urinary system, and infections, we found that of all medications prescribed, those which were observed to have HOMAA constituted 28%, 3%, 46%, 0%, 5%, and 30% respectively, and the medications which possessed LONAA comprised 48%, 56%, 43%, 62%, 43%, and 70% respectively. The interRAI-HC dataset constituted 75,410

individuals, of which 12,983 older adults were diagnosed with dementia. We discovered that there could be a significant reduction (18%) in the anticholinergic burden in older adults with dementia when the guideline was incorporated using the interRAI dataset.

Conclusion

The application of the guidelines for prescribing alternatives to anticholinergic medications in this vulnerable population has the potential to reduce untoward effects associated with the prescription of anticholinergic medications, slow cognitive decline, and decrease the risk of mortality.