

# An overview of pharmacoepidemiology in New Zealand: medical databases, registries and research achievements

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## ABSTRACT

Pharmacoepidemiology is an eclectic blend of epidemiology, clinical pharmacology and biostatistics. In New Zealand there have been recent advances in pharmacoepidemiology to examine drug utilisation, monitor adverse drug events and complement pharmacovigilance. This paper attempts to describe the past, present and future of pharmacoepidemiology, particularly in the area of translational research with a particular focus on medicine use and safety. New Zealand is well-positioned globally to make significant contributions to the knowledge base of drug safety in real-world settings.

Pharmacoepidemiology is an evolving area of research and was recognised as a distinct discipline in the early to mid-1980's. An interface between clinical epidemiology and pharmacology, pharmacoepidemiology benefits from methodology derived through epidemiology to examine drug effects in populations. Pharmacoepidemiology encompasses themes including pharmacovigilance, drug policy, post-marketing assessment of effectiveness and safety of medicines, cost-effectiveness and rationale use of medicines among other themes of research.<sup>1</sup>

There is growing interest in pharmacoepidemiology because randomised controlled trials (RCTs) used for registration purposes are typically underpowered to reveal safety signals for rare events. Furthermore, for operational or ethical reasons, it may not be feasible to conduct RCTs in special populations such as the very old and the very young, and for a duration long enough to capture all safety end points. Advances in pharmacoepidemiology have not only overcome the boundaries of generalisability but also extended the time for follow-up to study rare adverse events.<sup>1</sup>

## History of data collections and pharmacoepidemiology in New Zealand

Prior to national electronic data collections and registries in New Zealand, there was little pooled health data available on a national scale to conduct pharmacoepidemiological studies.

Before the Second World War, the Department of Statistics was accountable for compiling mortality data. The information ascertained in death registration forms (known as BDM28) was used by government for analysis and planning. In 1948 the responsibility of registering deaths was transferred to the Ministry of Health (MoH) and the mortality collection was later assigned a National Health Index (NHI) by MoH in 1988.<sup>2</sup>

Registries such as the New Zealand Cancer Registry (NZCR) is managed by New Zealand Health Information System (NZHIS) and achieved a nationwide success of over

90% coverage in 1972.<sup>2</sup> Health Benefits Limited (HBL), through the MoH, managed procurement and supply-chain data before the introduction of Pharmaceutical Management Agency Limited (PHARMAC).<sup>3</sup>

Roberts and Norris published findings based on the HBL data, which showed variations and changes in antidepressants dispensing in New Zealand between 1993 and 1997.<sup>4</sup> Subsequently, Nishtala and colleagues have published several drug utilisation studies analysing the pharmaceutical collections (Pharms) supplied by PHARMAC.<sup>5</sup>

### Pharmacovigilance in New Zealand

Pharmacovigilance is a unique area of pharmacoepidemiology concerning monitoring and reporting of adverse effects of medicines and therapeutic devices. The New Zealand Pharmacovigilance Centre (NZPhvC) is the epicentre for monitoring adverse reactions in New Zealand. The NZPhvC currently operates two main programmes: (1) Centre for Adverse Reactions Monitoring (CARM) and (2) Intensive Vaccine Monitoring Programme (IVMP).

The Intensive Medicines Monitoring Programme (IMMP) based in Dunedin was a branch of the CARM from 1977 until 2013.<sup>6</sup> IMMP established cohorts from prescription data, collected event information and developed a unique methodology known as Prescription Event Monitoring (PEM). PEM cohorts contained information, supplied by pharmacies, from prescriptions for medicines that have been selected for monitoring. MoH superintended IMMP coordination through CARM, however, some dispensing data entries were recorded retrospectively and affected collations as pharmacists were provided with hand-written forms to enter information on dispensed prescriptions, and these were to be returned through pre-paid postage envelopes.<sup>6</sup> IMMP made several significant contributions to pharmacovigilance in New Zealand, performing in-depth epidemiological investigations relating to the safe use of medicines and introduced programmes such as the Medication Error Reporting Programme (MERP).<sup>7</sup>

## New Zealand's national collections

Several national collections held by governmental organisations provide significant epidemiological data useful for population studies. Big data coverage in New Zealand comprises a nationwide collection of prescription claims or reimbursement data, industry-based and wholesale or supplier warehouse databases. Data holdings can also be medical, hospital or administrative records and events or disease-based registers. Table 1 displays a list of New Zealand databases used in population-based research.

## Methodological considerations

Pharmacoepidemiological studies are observational in nature, and hence suffer from confounding and bias. In the last few decades, advances in pharmacoepidemiology has encouraged novel methods of adjusting for confounding and bias.<sup>9</sup> In New Zealand, studies have progressed from examining trends in medicine utilisation to using apposite statistical models to examine health outcomes such as mortality, hospitalisation and use of primary care services. Access to advanced statistical software has encouraged use of predictive models and propensity score matching or inverse propensity score weighting, which to some extent mimics the process of randomisation in retrospective cohort studies.

In most observational studies, confounding variables typically include socioeconomic variables, time independent (sex, ethnicity etc.) and time varying cofounders (frailty etc.) and multi-morbidity.<sup>10</sup> Propensity scores (PS) are now increasingly being used to ensure distribution of confounding variables is the same in the exposed (treated) and the unexposed group (untreated). In propensity weighting, weights are applied to the exposed ( $1/PS$ ) and the unexposed ( $1/(1-PS)$ ) so that the overall distribution of the PS scores is the same in both groups. Individuals with a

**Table 1:** National collections and registers relevant to pharmacoepidemiology research.

Name	Alternative nomenclature	Brief description
<b>National claims and collections</b>		
Mortality collection	Mortality database	Confirmed deaths managed by the New Zealand Ministry of Health (MoH) and was first assigned National Health Index (NHI) in 1988.
New Zealand Health Information System data warehouse	NZHIS	Maintains datasets including Mortality data, NMDS, NZCR.
National Minimum Dataset	NMDS	NMDS is a national collection of public and private hospital discharge information, including coded clinical data for inpatients and day patients.
New Zealand Cancer Registry	NZCR	NZCR provides data for cancer incidence and survival studies, public health research, monitoring screening programmes and policy formulation.
General Medical Subsidy Claims	GMS	GMS claim holds information on subsidies paid to reduce consultation cost with general practitioners for children under 15 years of age or subsidy/community card holders.
Medicines Monitoring database	M2	Medicines and safety data held by New Zealand Medicines and Medical Devices Safety Authority (Med-safe).
Pharmaceutical Claims Collection (Pharmaceutical Management Agency (PHARMAC) collects and manages data through MoH)	Pharms Datamart	Holds dispensing data on medicines claims for prescribed dispensings that are subsidised by PHARMAC.
Primary Health Organisation enrolment database	PHO	Holds individuals' data for primary healthcare (Primary Care visits).
Laboratory Collection	Labs	Holds data on laboratory test carried out in individuals. Labs data reporting was enforced from July 1994.
National Non-Admitted Patient Collection	NNAP	Maintains data on non-institutionalised cases in healthcare facilities.
National Maternity Collection	NMC	Holds data on maternal deliveries.
Programme for the Integration Of Mental Health Datamart	PRIMHD	Holds data on mental health status of those accessing healthcare.
Intensive Medicines Monitoring Programme (Part of New Zealand Pharmacovigilance Centre (NZPhvC) or Programme with Centre for Adverse Reaction Monitoring (CARM) including Prescription Event Monitoring)	IMMP database	CARM held dispensing data for signal detection for more than three decades (1977–2013).
Client Claims Processing System	CCPS	The CCPS holds data which accounts for disability support events in community dwelling older people.
<b>Events and disease-based registers</b>		
Births, Deaths and Marriages Register	BDM	Held by MoH.
Virtual Diabetes Register	VDR	Specific algorithm is used to extract VDR data from NMDS database.
National Immunisation Register	NIR	Holds individual level data on immunisation.
National Cervical Screening Programme Register	NCSP	Cervical cancer screening database which holds data and some clinical information on females signed up to the Programme.
Australian & New Zealand Hip Fracture Register	Hip Fracture Register	Piloted in New Zealand.
<b>Electronic medical (health) records</b>		
Hospital Medical Records	HMR	A keep of medical records including those prescribed for hospitalised patients.
Medication Error Reporting Programme (MERP)	MERP database	Online reporting system maintained by NZPhvC which holds core information on the medicine, medication error and detail characteristics on factors that precipitated the recorded outcome.
<b>Administrative databases</b>		
Aotearoa New Zealand Health Tracker	ANZHT	Administrative data used in research work to estimate prevalence of common public health diseases like gout in population studies.
EpiSurv records (maintained by the Institute of Environmental Science and Research)	ESR	Mandatory reporting of notifiable diseases that have been reported to Medical Officers in the healthcare sector.
New Zealand Deprivation (NZDep) dataset	NZDep index	NZDep index is a composite deprivation score, extracted independently from information contained in census data, which compares socioeconomic positions of small area mesh-blocks between 60–110 people based on their location within a given time frame. Score of 1 (least deprived) to 10 (most deprived). <sup>8</sup>

high PS score have covariates that favour the use of the treatment, and lower PS scores suggest that individuals are drawn away from the treatment. Therefore, in order to achieve the covariate-balancing, the PS-weighting method is designed to weight down data from over-represented individuals and vice versa for data from under-represented individuals.

## Pharmaco-epidemiological studies in New Zealand

### Drug safety studies

Several drug safety studies have been conducted using the routinely collected national data in New Zealand, and have been able to associate medicine used with health outcomes at a population level.

Winnard et al utilised the Aotearoa New Zealand Health Tracker (ANZHT) population data to examine the overall prevalence of gout, and identified a high prevalence in the entire Aotearoa New Zealand population, particularly among Māori and Pacific people.<sup>11</sup> Similarly, a high co-prevalence of gout, diabetes and cardiovascular disease in the same population was identified in a later study.<sup>12</sup> A nationwide nested case-control study by Blank et al used data linkage over four years and identified that the use of a proton pump inhibitor was associated with a significantly increased risk of acute interstitial nephritis.<sup>13</sup> Another nested case-control study using data linkage investigated the association of statin and risk of rhabdomyolysis and highlighted that the absolute risk of rhabdomyolysis in a general population of simvastatin users is very low.<sup>14</sup> In 2009, Mehta et al examined the optimal clopidogrel therapy with the help of national health databases and concluded that clopidogrel coverage following percutaneous coronary intervention improved by 7% across sociodemographic groups after funding restrictions ceased.<sup>15</sup>

The Research in Pharmacoepidemiology (RiPE) group,<sup>16</sup> has published copious studies covering drug safety using Pharms dataset and other datasets such as the NMDS, Primary Care visits, Mortality collection and NZDep index for older individuals aged

65 years and above. Among these were some landmark studies, which examined the impact of Drug Burden Index (DBI), a measure of exposure to anticholinergic and sedative medications, on geriatric adverse drug events including falls, and another study which compared the haemorrhage-risk associated with anticoagulants in older New Zealanders on a propensity score matched, population-level cohort.<sup>17,18</sup> The later study concluded that the risk of any haemorrhage and intracerebral haemorrhage was lower in dabigatran users compared to warfarin users.<sup>18</sup>

### Drug utilisation studies using national health collections data

Literature search in Ovid MEDLINE and EMBASE identified 19 studies that have recently been published on pharmacoepidemiology using national health collections data. These studies are listed in Supplementary Table 1 (page 59). In addition to these, several other studies have examined utilisation patterns of various medicines, which can potentially guide future policy directions.

In 2005/6 Norris et al conducted a cross-sectional study using dispensing data linked with national datasets to investigate equity in statin utilisation among different ethnic groups and found that in contrast to results from other previous studies, statin use approximately matched the pattern of need.<sup>19</sup> Another study on health services utilisation by ethnicity variations was conducted by Wheeler et al, using the NZHIS via the Patient Information Management System (PiMS also known as iPM).<sup>20</sup> This study highlighted the variations in psychiatric inpatient representation, diagnosis and compulsory treatment across ethnic groups and socioeconomic status. Using toxicological and coronial databases between 2001 and 2005, Gallagher et al concluded that restricted access to work-related chemicals and stricter prescription/dispensing controls for antidepressants such as tricyclic antidepressants may reduce self-poisoning in New Zealand.<sup>21</sup>

In 2001, two studies reported the use of HBL data supplied by PHARMAC on subsidised dispensing of antidepressants between 1993 and 1997, and examined the regional differences<sup>4</sup> and changes<sup>22</sup> in the prescribing of antidepressants in New Zealand. The first

study concluded that regional differences in anti-depressant prescribing are large, and later highlighted that the use of newer agents was contributing to increased overall use of anti-depressant medication and government expenditure in New Zealand. The earliest direct national estimates of diagnosed congestive heart disease prevalence (2008), by sociodemographic status was undertaken in New Zealand in 2011.<sup>23</sup> Following this, a recent study examined the current epidemiological trends of leprosy in New Zealand for a 10-year period (2004 to 2013) to raise awareness among the health professional community and used the EpiSurv national surveillance database, administered by the Institute of Environmental Science and Research (ESR).<sup>24</sup>

### Registry-based studies

Population-level registry-based studies are a newer approach to pharmacoepidemiological studies in New Zealand, in particular the Cancer Registry. The incidence trends for 18 adult cancers, by ethnicity and socio-economic status was examined and found disparities between the different cancers among ethnic groups.<sup>25</sup> Another recent study examined the prevalence of statin discontinuation in individuals aged 75 years and older with a diagnosis of cancer, in the last year of life.<sup>10</sup> This study revealed that statins are more likely to be discontinued in older individuals with a diagnosis of cancer compared to those without cancer. This association hints at a plausible trend that having cancer is a more legitimate reason for discontinuing statins compared to other life-limiting conditions, knowing that the end-of-life is more predictable for individuals with cancer than individuals with other life-threatening diagnoses.

The National Cervical Screening Programme Register (NCSP-R) was used to identify women aged 20–69 years of age with an index high grade cytology report from 2009–2011, investigating pre-vaccination benchmark prevalence for Māori and non-Māori women, and identified long-term effects of vaccination to be similar in the two groups.<sup>26</sup> Additionally, Grant et al identified associations between parental intentions and the subsequent timeliness of infant immunisation using the National Immunisation Register.<sup>27</sup>

The Virtual Diabetes Register was used to

compare the prevalence of diagnosed and undiagnosed diabetes and prediabetes in New Zealand. In this study, the authors have summarised and compared regional and national diabetes prevalence surveys undertaken in New Zealand since the late 1960s.<sup>28</sup>

### interRAI (international Resident Assessment Instrument)

From 1<sup>st</sup> July 2015, it has been mandatory that all residential care facilities start using the suite of health and support needs assessment tools known as interRAI, in particular the interRAI Long-Term Care Facilities Assessment System (LTCF).<sup>29</sup> It targets people over the age of 65 years who require needs assessment for access to long-term publicly funded services. A recent study highlighted the user experience of interRAI assessment tools in New Zealand and explored clinicians' perceptions and experience of using interRAI electronic assessment tools, highlighting some barriers that need to be overcome prior to adopting the tool.

## Challenges and opportunities in New Zealand for pharmaco-epidemiological research

### Challenges

In 2006, Gauld & Goldfinch highlighted noteworthy limitations with the New Zealand health data collections. Concerns were raised regarding the standardisation of data collection systems, difficulties with information exchange and insufficient governance of information maintaining systems.<sup>30</sup>

While population-based datasets eliminate cost and time constraints, completeness and validity of the datasets are of a global concern. The New Zealand administrative databases are frequently utilised, and their accuracy and completeness has been tested in few observational studies.

### Opportunities

The New Zealand health sector holds and maintains rich observational health care data that are valuable for evaluation of health outcomes. Health care data describe

large patient populations and provide promising research opportunities for proactive, longitudinal surveillance of the safety and effectiveness of medicines. New Zealand can make major contributions to the knowledge base of medicines use and health outcomes in real-world settings. Appropriate quality and relevant data for monitoring health-related outcomes will enable opportunities for pharmacoepidemiological research and developments in policies, services, practices and quality of life for all individuals accessing healthcare in New Zealand.

## Conclusions

Pharmacoepidemiology is an evolving scientific discipline that offers a number of advantages to evaluate medication safety in a large population for a long period of follow-up, with good generalisability. New Zealand is well-positioned globally to make

significant contributions to the knowledge base of outcomes on the quality of medicine use in real-world settings. There is an increased recognition by various stakeholders, including Medsafe and PHARMAC, that a rapid increase in the quantity, diversity and accessibility of patient data will provide unprecedented opportunities for rapid assessment of drug safety, monitoring pharmaceutical policies, examining healthcare utilisation and decision-making relevant to all individuals accessing healthcare in New Zealand. This viewpoint article highlights the scope for methodological advances for performing pharmacoepidemiological studies in New Zealand. In conclusion, the future of pharmacoepidemiology in New Zealand requires an integrated development of models to capture outcome data, particularly on safety endpoints, and the integration of statisticians and epidemiologists on the need to improve designs and methodology in

### Competing interests:

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Supplementary Table 1: Summary of studies using claims dataset in New Zealand.

Author, year	Study design	Setting/ participants	Mean (SD) age (years)	Study duration	Outcome(s) studied	Conclusion	Statistics
Ndukwe et al, 2015 <sup>1</sup>	Open cohort	Population-based, ≥65 years (n=9,684)	79.4 (6.6)	3 years	Utilisation changes measured yearly in DDD/ TOPD by different weights of Donepezil	Donepezil utilisation increased from 5.2 to 8.2 DDD/TOPD between 2011 and 2013, while donepezil and beta-blockers concomitant use decreased (17.9% to 5.1%) of total users	ANOVA and Student t-tests
Ndukwe et al, 2016 <sup>2</sup>	Inception cohort	Population-based, ≥65 years (n=1,999)	79.5 (6.4)	3 years	TTFD (months), adherence (VMPR) and persistence (by patient visits and dispensing's)	Median TTFD = 12.4±0.6 months. Adherence (using VMPR) was 89.6% for gap of ≤31 days. Donepezil non-adherents discontinued 2.2 times faster than adherents	Survival curves and Cox regression
Ndukwe et al, 2014 <sup>3</sup>	Retrospective cross-sectional study	Population-based, ≥65 years	75.4 (0.1)	9 years	Utilisation changes measured yearly in DDD/DOPY	Utilisation rates and CV measures across DHBs. Between 2005 and 2013, Tairāwhiti DHB had the widest CV (20.5%)	CV and Gamma regression
Ndukwe et al, 2016 <sup>4</sup>	Retrospective cross-sectional	Population-based, ≥65 years	75.4 (0.1)	9 years	Utilisation changes measured yearly in DDD/TOPD	Increased utilisation (from 159.4 to 195.3 DDD/TOPD)	Linear regression
Nishtala et al, 2015 <sup>5</sup>	Cross-sectional	Population-based, ≥65 years	78.1 (7.8)	9 years	Utilisation of PPI	Overall PPI utilisation showed a 26.7% increase from 2005 to 2013	Trend analysis
Nishtala et al, 2014 <sup>6</sup>	Population-based study	Population-based, ≥65 years	74.7	1 year	Impact of DBI on fall-related hospitalisations, GP visits and all-cause mortality	Polypharmacy and exposure to DBI drugs are independently associated with an increased risk of fall-related hospitalisations, frequency of GP visits and mortality	Negative binomial regression, Survival analyses
Nishtala et al, 2014 <sup>7</sup>	Population-based study	Population-based, ≥75 years	-	-	Exploring potentially inappropriate medicines use	Potentially inappropriate medicines were identified in 42.7% of study participants	Poisson regression
Nishtala et al, 2015 <sup>8</sup>	Cross-sectional	Population-based, ≥65 years	-	9 years	Utilisation of analgesic medications	Analgesic utilisation increased by 5.44% from 2005 to 2013	Trend analysis
Nishtala et al, 2015 <sup>9</sup>	Cross-sectional	Population-based, ≥65 years	-	9 years	Prevalence and trends of polypharmacy and hyperpolypharmacy	Polypharmacy and hyperpolypharmacy were found to be higher in 2013 compared to 2005 (polypharmacy: 29.5 vs 23.4%, p<.001; hyperpolypharmacy: 2.1 vs 1.3%, p<.001)	Chi-squared test, multinomial regression
Nishtala et al, 2016 <sup>10</sup>	New user design cohort	Population-based, ≥65 years	Warfarin cohort: 77.4 (6.6) Dabigatran cohort: 77.3 (6.4)	6 months	Real world bleeding risks with warfarin and dabigatran	Risk of any haemorrhage and intracerebral haemorrhage was lower in dabigatran users compared to warfarin users	Propensity score matching, Cox regression
Salahudeen et al, 2015 <sup>11</sup>	Population-based study	Population-based, ≥65 years (n=537,387)	74.7 (7.6)	1 year	Anticholinergic scales are associated with global adverse health outcomes such as hospital admissions, falls, length of stay and GP visits	Anticholinergic burden scores obtained from each of the scales were associated with adverse clinical outcomes of interest	Negative binomial regression



Supplementary Table 1: Summary of studies using claims dataset in New Zealand (Continued).

Author, year	Study design	Setting/ participants	Mean (SD) age (years)	Study duration	Outcome(s) studied	Conclusion	Statistics
Salahudeen et al, 2015 <sup>12</sup>	Population-based study	Population-based, ≥65 years (n=2,248)	79.0 (8)	1 year	Predict adverse anticholinergic-type events using patient characteristics	Anticholinergic burden was found to be a significant independent predictor for developing an anticholinergic event	Logistic regression
Metcalfe et al, 2013 <sup>13</sup>	Population-based study	Population-based, age groups; 0–14, 15–24, 25–44, 45–64 and ≥65 years	-	1 year	Variations in dispensing of specific medication groups by ethnicity	Variable but sizeable differences in medicines dispensed to Māori compared with non-Māori, and likely differences for Pasifika populations	Descriptive analysis
Metcalfe et al, 2014 <sup>14</sup>	Population-based study	Population-based	Median: category A = 48 years (30–63) category E = 71 years (61–78)	1 year	Actual dispensing's of publicly funded blood glucose test strips (SMBG) according to severity of disease	183,000 patients were dispensed diabetes medicines during 2011 and found variations in the use of SMBG between treatment groups	Descriptive analysis
Smith et al, 2010 <sup>15</sup>	Population-based study	Population-based—age groups; 0–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, ≥75 years	-	2 years	Diabetes prevalence and utilisation of healthcare services	Substantial differences in the prevalence of diabetes and in hospitalisation rates by ethnicity	Descriptive analysis
Narayan et al, 2013 <sup>16</sup>	Retrospective cross-sectional study	Population-based, ≥65 years (n=537,387)	74.7 (7.6)	1 year	Anticholinergic exposure using anticholinergic drug score, drug burden index and acetylcholinesterase inhibitors	Significant proportion of older people are exposed to medicines with anticholinergic properties, including those dispensed acetylcholinesterase inhibitors	Student t-test
Narayan et al, 2015 <sup>17</sup>	Cross-sectional study	Population-based, ≥65 years (n=537,387)	74.7 (7.6)	1 year	Prevalence of PIMs	40.9% of older people were prescribed PIMs with approximately half dispensed ≥2 PIMs in 2011	Trend analysis
Narayan et al, 2016 <sup>18</sup>	Cross-sectional study	Population-based, ≥65 years	-	9 years	Utilisation of preventive medicines from 2005 to 2013	Utilisation of selected antithrombotics such as low-dose aspirin, clopidogrel, dabigatran and statins increased over the 9-year-study period and utilisation of dipyridamole, warfarin and bisphosphonates decreased	Poisson regression
Narayan et al, 2015 <sup>19</sup>	Cross-sectional study	Population-based, ≥80 years	84.9 (4.3)	10 years	Utilisation of antihypertensive medicines	75.31% of individuals were prescribed one or more antihypertensive medicines in 2005, compared with 78.75% in 2014	Poisson regression

ANOVA analysis of variance; CV coefficient of variation; DDD/TOPD defined daily dose per thousand older people per day; DHB District Health Board; DDD/DOPY defined daily dose per DHB-older population per year; TTFD Time-to-first discontinuation; PPI proton pump inhibitors; DBI drug burden index; VMPPR variable medication possession ratio; GP general practitioner; PIMs potentially inappropriate medicines.

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