This is a peer-reviewed, author's accepted manuscript of the following encyclopaedia book chapter entry: Bennie, M., Kurdi, A., & Mueller, T. (2022). Using administrative data from public health and drug programs. In Z-U-D. Babar (Ed.), *Encyclopedia of Evidence in Pharmaceutical Public Health and Health Services Research in Pharmacy* (pp. 1-13). Springer. https://doi.org/10.1007/978-3-030-50247-8_61-1

Encyclopaedia of Pharmaceutical Public Health

Chapter: Using administrative data for Public Health and Drug Programs

This chapter presents an overview of how real world administrative data, routinely available as part of clinical practice within healthcare systems, can be used to generate real world evidence to inform regulators; support policy formation and monitoring; shape service delivery; and improve patient care. We outline in brief the methods that can be applied to these data, incorporating strengths, weaknesses, opportunities and challenges with the use of aggregate and individual level data, respectively. We complete with illustrations, from the authors own experiences, of how real world data can drive, both within countries and across countries, improvement in patient care as part of public health and drug programmes.

Introduction

Generation of real-world evidence (RWE) from real-world data (RWD) to inform decisions related to medicines regulation, drug programs, and public health more broadly is not a new concept. RWD is the "*data that are related to patients' health status and/or healthcare delivery that are collected/generated routinely from patients' use and contact with healthcare system through a variety of database sources; collected from a variety of sources, such as EHRs, claims and billing data, medical product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status (e.g., mobile devices)";* whereas, RWE is "*the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD*" (1). As stated in the definition, RWD could be gathered from a variety of sources which are usually large secondary databases, generated routinely for administrative purposes when patients are contacting healthcare systems seeking healthcare service. Briefly, these data are either aggregated-level or individual-level data; the former includes sales data from wholesalers which contains information about the total amount of drugs in the system without any information on individuals; the latter on the other hand includes electronic health records, prescribing/dispensing data, claims/reimbursement datasets, and patients/drugs registries which contains information about individual patients in terms of their demographics, disease, medication and treatment outcomes even though these may varies according to the type of the dataset (2). A key important feature is the ability to link records across different datasets which provides a comprehensive insight into patients and prescribers' profile, allowing researchers to assess appropriateness of drug use and treatment clinical outcomes (see subsequent sections for further details). In general, RWD can be used to generate RWE that are related to drug use pattern,

identification of early signals on inappropriate drug use and patient safety issue, effectiveness of drugs in extended populations, and help to design, develop, and evaluate healthcare interventions/policies/guidelines with the ultimate goal of achieving safe, effective and efficient healthcare delivery.

In fact, the regulatory agencies, such as the US Food and Drug Administration (FDA) and the European Medicines agency (EMA), have a long history of using RWD/RWE to evaluate the safety of medicinal drug products. For instance, in the early 2000s, RWE generated from the analysis of Medicaid databases helped to identify a safety issue signal about the increased cardiovascular disease risk associated with taking COX-2 inhibitors. However, recently, there has been an increased recognition of the potential use of RWD to generate evidence to inform and support healthcare and drug development decisions related to practice guidelines, coverage decisions, post-marketing safety and efficacy of therapeutic products (3). The FDA in particular has been required to establish a program of work to evaluate the potential role of using RWE to first, support approval of a new indication for an already approved drug; and/or second, to assist in satisfying post-approval study requirements as well as initiating activities to address key challenges and issues related to using RWE in regulatory decisions (3). Although the EMA has also used RWD for evaluation of benefit-risk and safety signals (4), both FDA and EMA have less experience of using RWE to support decisions related to efficacy for initial drug approvals except in a few instances primarily in oncology and rare disease settings where there is a high unmet clinical need (3). The potential role of using RWE to provide supporting material related to the effectiveness of drugs for regulatory decisions is attributed mainly to issues of external validity and generalisability of findings from randomised clinical trials (RCTs), as patients included in RCTs do not always reflect the heterogeneous patient population treated in routine clinical practice, especially those with advanced age or comorbidities (5); in these circumstances, RWD can be used to generate evidence to complement existing evidence about using a therapeutic product in these heterogeneous patients population that are often excluded from RCTs.

However, RWD has issues with internal validity that are associated with lack of randomisation and unrecorded/unmeasured confounders leading to biases in RWE generation; hence the concerns about whether RWD and RWE can be used to accurately assess effectiveness of drugs (6,7). Additionally, sources of RWD (both aggregated and patient level data), such as electronic health records, insurance claims, or drug and disease registries, have their own unique features, designs, and purpose, and thus they often do not capture all the necessary data elements required to answer a particular research question. Consequently, in order to use RWD to generate RWE to address a regulatory decision and inform clinical practice, the data and analysis should be reliable, credible,

and reproducible to ensure high-quality and regulatory-grade RWE (8), which could be achieved through strategies to advance RWD collection and analysis using advanced and robust study design and analytical methods. In this regard, several efforts and strategies have been undertaken. First, development of frameworks to highlight opportunities for using RWD to generate valid evidence to support regulatory decisions; these include FDA's RWE framework (9) (which takes into considerations whether the RWD are fit for purpose, whether the used methodologies are robust enough to provide adequate scientific evidence, and whether the used approach meets the FDA's regulatory requirements) and the SPACE framework (10) (A Structured Pre-approval and Post-approval Comparative Study Design Framework to Generate Valid and Transparent Real-World Evidence for Regulatory Decisions) which identifies the key design features, feasibility assessment and validity consideration necessary to generate a valid and transparent RWE. Second, evaluation of whether RWE can support causal relationship to support drug effectiveness by calibrating RWE studies against a known treatment effect from an RCT; this calibration and systematic replication approach, through using causal study designs and analysis methods, would help to understand whether and under what circumstances RWD can be used to generate RWE that are comparable and similar to those of RCTs. Furthermore, the key objective of this calibration of RWE against RCT is to identify the magnitude and direction of residual bias attributed to the lack of randomisation of real-world studies; in this regard, the FDA launched their RCT DUPLICATE initiative (Randomized, Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology) to compare findings of RCTs with the trial-design emulated non-randomised real-world studies (11). Results from the first phase of the RCT DUPLICATE initiative indicated key design aspects that are key to emulate RCT findings and enhancing the validity of RWE, including selection of the appropriate active comparator and availability of data/information on necessary inclusion/exclusion criteria, exposures, outcomes, and confounders, all of which would limit and determine the type of clinical questions that could be answered using RWD. Use and generation of RWE have seen a rapid growth in the recent years, especially the massive RWE on treatments for COVID-19 (12,13) and safety of COVID-19 vaccines (14); as RWD continue to mature, which enables greater access and reliability of RWD, further growth in generation of RWE is expected.

Methods and Scientific Base

Using administrative data for public health purposes – to inform policy, drive improvement, and advance patient care – requires an understanding not only of the data that is potentially available for analyses, but also of the methods suitable and appropriate for such analyses.

1. Understanding administrative data

Administrative data is data that is collected as a by-product of routine services and processes, and potentially offers a rich source of information; this is especially the case in areas where data is available in a digital format, which simplifies accessibility of datasets. Unsurprisingly, administrative data are used widely for official statistical publications (15). With the advent of advanced information technology, administrative data is increasingly being used in health-related research, including epidemiology, public health surveillance, and service planning/management (16).

Nevertheless, in order to use data appropriately and draw valid conclusions, it is crucial to keep in mind the original purpose of the data, the setting in which it has been collected, and the systems used to generate it. For instance, health records may serve a number of different purposes: to provide a summary of a patient's medical conditions, test results, and treatments, thereby supporting clinicians in providing further patient care; to enable the collation of information useful to detect infectious disease outbreaks, and possibly identify extremely vulnerable patients to be targeted for additional measures as was the case in the early phase of the COVID-19 outbreak (17); or to facilitate the generation of invoices to charge patients or insurance companies for services rendered (18), to name just a few. In addition, depending on context, data coverage may vary; whereas some countries capture health-related data for their entire populations, in other countries this is restricted to subgroups only, for example those included in specific health insurance schemes or within a certain age bracket; similarly, while some data such as demographics and coded procedures may be widely available in various data sources, other information might be sparse depending on the setting. Moreover, data may be available either on an individual patient level; or on an aggregate level, with implications for the type of study and analysis that can be undertaken.

For various reasons, all of these aspects have an impact on what kind of clinical and public health related research questions can be investigated and addressed; most importantly, data availability, coverage, and quality may affect the accuracy, reliability, and generalisability of findings. Considering further that different parts of a health service quite likely use different computer systems and procedures – resulting in an array of different storage systems, file formats, and coding conventions that are not necessarily obvious or compatible – it is always advisable to seek advice from those tasked with generating and curating the data; if available, meta-data as frequently provided by data controllers is a good starting point for any enquiry.

2. Aggregate data

Aggregate data on drug use is based on purchases and/or sales within a health care system and can be obtained from, for instance, manufacturers, wholesalers, pharmacies, and hospitals; these data

are reflective of the total amount of drugs supplied and distributed within a particular system, i.e. without providing any information with regards to the drugs used by individual patients (19).

Aggregate data can be used for a number of different purposes. Common applications include the description and forecasting of drug use, often with the aim to predict expenditure and facilitate planning; evaluating the impact of pharmaceutical policies to assess whether interventions have been successful; and conducting ecological studies, including those aimed at comparing drug use and prescribing trends between countries (20–22). To facilitate the latter, a technical unit of measurement – the Defined Daily Doses (DDDs), integrated into the Anatomical Therapeutic Chemical (ATC) classification system – has been developed and endorsed by the WHO (23). DDDs are defined as "*the assumed average maintenance dose per day for a drug used for its main indication in adults*" (24), and enable the comparison of drug use across different settings by providing a fixed unit independent of drug strength, package sizes, or retail prices (ibid).

Data access

As aggregate data is collected routinely in the majority of countries globally – although not necessarily to the same extent – a wide range of sources of aggregate data are available, many of which are freely accessible. For instance, both the Organisation of Economic Development (OECD) and the European Union (EU) offer a large variety of health-related datasets (25,26); the World Health Organisation, with its particular focus on global health, manages a number of datasets at the behest of its member states (27); and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) maintains a searchable database of data sources (28). In addition, several more specialised datasets are available, such as the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), providing reference data on antibiotic consumption for the majority of European countries coordinated by the European Centre for Disease Prevention and Control (ECDC) (29). Datasets can usually be directly accessed through an online interface, and/or downloaded in a standardised format (such as csv. files) for further use.

Data preparation and analysis

Information contained within aggregate level datasets is usually limited, but generally includes drug names and respective quantities and/or costs (19). It is advisable to inspect the data prior to conducting any analyses to become familiar with labels and the coding conventions used, if applicable; and to check the completeness of the data. If data stems from different sources, it is also vital to ensure that the measurements used are comparable across datasets.

Analyses that can be conducted using aggregate level data are usually limited to basic, mostly descriptive statistics, although more advanced methods such as interrupted time series analysis may be feasible depending on the range of data available. It needs to be kept in mind, though, that studies using aggregate data – sometimes called "ecological studies" – cannot be used to make inferences on individuals; although generation of hypotheses may be possible (30).

Main aspects to consider when using aggregate data

Strengths	**Weaknesses**
Easily obtainable, frequently free of charge	Offers limited information (e.g. absence of diagnosis or indication)
No ethical or information governance issues	Heavily curated, quality not easy to assess
Relatively easy to use	Not possible to link with other data
Opportunities	**Challenges**
Good way of getting a quick overview of a topic	Might not be up-to-date
Sufficient to answer a number of important questions related to public health	

3. Individual level data

Individual level data contains data that is related to individual patients, and can, for example, be obtained from electronic health records, pharmacy dispensing and reimbursement databases, patient registries, or health surveys (19). Individual level data is not available in many countries, primarily because of resource limitations or due to the way the health system was set up; furthermore, the extent and scope of available data – for instance with regards to population coverage – is variable across settings.

Nevertheless, when available, individual level data is much more detailed than aggregate level data, and facilitates a wide range of different study designs, including cohort and case-control studies (31). Hence, individual level data offers the opportunity to address a range of clinical research questions that can not sufficiently be addressed using aggregate data alone. Most importantly, individual level data can be used to investigate, in-depth, medication use – for instance prescribing trends among specific populations, or adherence to medicines; individual level data is also valuable for analysing outcomes of drug treatment, including their clinical effectiveness and safety to inform regulatory decisions and inform clinical practice. Individual level data can, potentially, also be used to evaluate cost-effectiveness of medicines, and may play an important role in medicines approval and health technology assessment procedures (as detailed in the introduction section of this chapter).

Data access

Access to individual level data is usually subject to strict approval processes, although details differ between countries and settings; furthermore, adherence to relevant information governance rules and guidelines is crucial in order to ensure the safety and security of any data accessed and, most importantly, the confidentiality of patients – after all, health records contain private and sensitive information, and protecting this information is paramount. To safeguard patients' privacy, individual level data is typically only made available in anonymised form, i.e. identifying information such as names, addresses, and dates of birth have been removed from the dataset; this is particularly vital if the focus is on a small group of patients, for example those with a rare disease, who might theoretically be identifiable based on the information obtained. In addition, depending on context and details, ethical approval may be required to guarantee that the work to be undertaken is in line with current standards of practice (32).

Data preparation

Once suitable data has been obtained, a crucial first step is to inspect the data to ensure that the content provided matches what was expected; and to evaluate the quality of the data, including its completeness and the accuracy of values. In a second step, data need to be converted into formats suitable for analyses; this might, for instance, comprise changing data structures, recoding values, or deriving additional variables based on existing variables (e.g. categorising patients into age groups based on age if provided as a continuous variable).

If no single dataset comprises all the information needed to address a particular question, record linkage – i.e. combining two or more different dataset containing data on the same patients – may be an option to circumvent this issue; however, there are a number of prerequisites to allow record linkage. First and foremost, linking individual patient's records requires the presence of, ideally, a unique patient identifier (deterministic linkage); or a number of variables suitable to determine if records do indeed belong to the same patient. Variables frequently used for this probabilistic linkage are name, date of birth, and address; crucially, in order for linkage to be successful and valid, datasets need to be accurate and should be updated regularly. Furthermore, since datasets are commonly provided to researchers in anonymised form, record linkage needs to be done early on in the process by the data provider themselves who have access to the required identifiable information; this task requires technical expertise as some manipulation of datasets (in terms of formatting, coding, etc.) may be necessary, and a good collaborative working relationship with the data provider is vital to enable this process to run smoothly.

Data analyses

Since individual level datasets are usually quite complex, obtaining meaningful and accurate results may also require complex analytical methods, including advanced statistical approaches to reduce risks of bias and confounding – i.e. the risk that results may have been affected by the way data was recorded; the circumstances of the data collection; and the population covered by the dataset. This is particularly true for attempts to make causal inferences based on routinely collected data (33). Detailed discussions of appropriate methods for analysing routinely collected, individual level data are, however, beyond the scope of this chapter; good starting points for further inquiries would be standard textbooks of, e.g., pharmacoepidemiology (34) and drug utilisation research (35).

Main aspects to consider when using individual level data

Strengths	**Weaknesses**
Detailed information available	Difficult to access (ethics, cost, time)
Potentially linkable to other data	
Opportunities	**Challenges**
Enables a wide range of study designs and the potential to answer important questions	Quality not always as expected
Complementary to clinical trials data, with the potential to support clinical decision making	Crucial information might not be available
Provides insights into clinical practice, useful for quality improvement and planning purposes	Expert input usually required – data controllers, clinicians, etc.

Examples of using RWD to generate RWE for drug programs and public health impact

This section provides a number of examples from the authors' experiences of using health system administrative RWD to generate RWE to: inform regulators; support policy formation and monitoring; shape service delivery and improve patient care through data-driven quality improvement initiatives, using Scotland's RWD capability and infra-structure.

Scotland has a long history of capturing and using routine health system data, including medicines data, to better understand the impact (intended and unintended) of health interventions provided through the comprehensive, publicly funded, healthcare system. From a *national* medicines data perspective data is routinely *digitally collected and collated*: at an aggregate level in primary/community care and in hospital/secondary care; and at an individual level in primary care (since 2010) and most recently from secondary care (since 2020) (36,37). Individual level data collation has been enabled through the longstanding use of a unique patient identifier – the Community Health Index (CHI) number – which is allocated to all residents when registering with the NHS Scotland health system (38)**.** This identifier is used each time a patient interacts with the healthcare system thus enabling a patient's journey to be mapped within and across complex health care organisational structures through record linkage across the various RWD sources. These

capabilities in Scotland (population of approximately 5.6million) allow the study of how medicines are being used in routine clinical practice across the life course, from cradle to grave, and understanding of their contribution and value to public health.

1. Building an Infection Informatics capacity for surveillance and action – a learning health system at scale

International landscape

Antimicrobial resistance (AMR) is a global public health issue with antimicrobial use a key contributor to AMR (39). Use of routine aggregate antimicrobial consumption data is a cornerstone of AMR surveillance and the foundation for antimicrobial stewardship programmes. By example, the European region has two major surveillance systems that collate and regularly report antimicrobial use: ESAC-Net (European Surveillance of Antimicrobial Consumption Network) and the WHO Europe Antimicrobial Consumption (AMC) Network. In developing countries, surveillance is more variable and the challenge is greater with less extensive digitalisation of health systems (40). The WHO, as part of the WHO Global Action Plan on AMR, has called for National Action Plans to stem raising AMR (39).

UK / Scottish landscape

In the context of the UK the response to the WHO included publication of the UK AMR Strategy (2013-2018) which called for "*better access to surveillance data*" and "*optimising prescribing practice through antimicrobial stewardship*". This was subsequently reinforced in the UK 2019-2024 Action Plan (41). In Scotland, this provided the leverage for the creation of an infection intelligence platform (IIP) acknowledging the importance of informatics to empower clinicians and healthcare systems to measure interventions to prevent and manage infections (42,43). The IIP enabled enhanced connectivity and linkage of multiple disjointed infection related datasets (including microbiology, medicines, hospital activity, and deaths) to produce a responsive informatics resource to allow rapid enquiry at a national level to inform clinical decisions and guide national policy. Similar endeavours are evolving internationally.

Data driven action

The clinical use of the IIP has been guided by the Scottish Antimicrobial Prescribing Group (SAPG), the recognised national clinical forum for antimicrobial stewardship. Outputs have included:

i) Annual publication of the *Scottish Antimicrobial Use and Resistance Report* (44) which uses both aggregate (drug use & geography) and individual level data (patient demographics) intelligence to highlight key areas of concern to inform public health policy direction.

ii) Regular reporting to the national clinical forum, SAPG, of antibiotic use in specific groups (e.g. children, elderly) and settings (e.g. nursing/care homes) and performance against nationally agreed quality prescribing indicators using both aggregate and individual level medicines data (45).

iii) Specific studies addressing important clinical questions investigating the intended and unintended consequences of antimicrobial stewardship and infection management interventions. For example, one study examined any potential change in severe upper respiratory tract infections presenting to hospital in relation to prior exposure to antibiotics in the community. The study identified that despite reduction in overall community antimicrobial use, prescribing in patients presenting to hospital had increased and mortality had reduced (39). This provided reassurance to the clinical community that the drive to reduce primary care prescribing was not adversely impacting patient care.

iv) Specific studies investigating infection risk factors and clinical outcomes which can be used to generate risk models to support tailored clinical decision support tools e.g.

- quantification of the temporal and cumulative association between community antimicrobial use and community acquired *Clostridioides difficile* (46)
- characterisation of patient risk factors in multidrug resistant urinary infection (47)

2. High Risk Medicines (HRMs) Stewardship

International / UK landscape

Recognising the potential harm from medicines, in 2017, the WHO Global Patient Safety Challenge: *Medication Without Harm* was launched, with the goal to reduce the level of severe avoidable harm related to medicines by 50% over 5 years, globally (48). Both internationally and in the UK there has been a long history of improving safety of medicines with multiple approaches being used to identify, quantify and manage harm. A key component has been the creation and use of prescribing safety/quality indicators at both aggregate and individual level to provide feedback to clinicians and enable health system monitoring (49). In the main these indicators are generated from routine administrative data systems with varying levels of complexity and scope, often determined by the level of digitalisation within the health system (50). However, there is now a recognition that simple audit/feedback and educational outreach is only part of the solution, and focus needs to turn to a

more systematic approach to the design of interventions, embracing behavioural change theories and implementation / improvement science if harm is to be minimise (51).

Data driven action

Scotland has used routine administration data on medicines, both at aggregate and individual level, to support policy and service monitoring but importantly also as components of multi-faceted interventions in both clinical trials and quality improvement initiatives:

i) <u>General practice setting</u>:

In 2010, using the newly available national administrative individual level prescribing dataset in primary care, we set out to explore how this new RWD could be used to provide feedback to clinicians to drive improvement in the safer use of medicines. Firstly, we brought together a group of Scottish clinicians to derive consensus on which high risk medicines (HRMs) to target, resulting in the selection of non-steroidal anti-inflammatory drugs (NSAIDs) and anticoagulants (52). These drug groups are recognised internationally as major contributors of adverse drug related hospital admissions and it was also feasible to identify and generate routine RWD reports at scale on their usage at a general practice geography level (53). Using an established 'feedback intervention' model for encouraging behavioural change, the team designed an intervention protocol with the aim of providing tailored information to General Practitioners to help them make more knowledgeable decisions about HRM prescribing (45). The resulting pragmatic three-arm cluster randomised EFIPPS (Effective Feedback to Improve Primary Care Prescribing Safety) trial tested the intervention protocol in 262 General Practices. The trial featured an educational intervention (in all 3 arms), feedback of performance for targeted indicators (arms 2 & 3), and a theory-informed behaviour change intervention (arm 3 only). The findings identified a 12-14% reduction in HRM prescribing among practices that received feedback (arm 2&3) compared to a simple educational intervention (arm 1) (54). This demonstrated that a simple, easy-to-deliver and nationally scalable provision of RWD with feedback performance on prescribing safety could effectively reduce usage of HRM. Translation of this RWE into routine healthcare systems has included: inclusion of the measures as part of national polypharmacy guidance (55); and integration into the established National Therapeutics Indicator (NTI) programme allowing a focus on patient safety issues covering all 944 General Practices in Scotland (56,57).

ii) <u>Community pharmacy setting</u>:

Building on the general practice HRM programme we describe in this example how RWD (using indicator measures) has been applied to monitor the impact of the contribution of community

pharmacy, adopting a quality improvement approach, to support HRM stewardship. Initially, 29 community pharmacies from across Scotland took part in an iterative learning model, the Breakthrough Series Collaborative model. An important focus was the co-design and use of an NSAID care bundle, comprised of two elements: the 'NSAIDs' Communication Care bundle' focussed on patient education, and the 'NSAIDs' Safer Care bundle' focused on the pharmacists' clinical assessment and feedback to GPs. Quality improvement process mapping techniques were used within participating pharmacies, to highlight the core steps to delivering the NSAID care bundle within routine community pharmacy practices to evolve an intervention that could be implemented at scale (58).

As a direct result of this quality improvement programme (co-design and programme testing), the NSAID care bundle has been scaled and fully implemented into all 1257 community pharmacies in Scotland as part of the NHS community pharmacy contract, and highlighted within the Scottish Government '*Achieving Excellence in Pharmaceutical Care, 2017"* publication (59). The measurement of impact of these endeavours is captured using RWD through the NTI programme. By example, the HRM measure 'Acute Kidney Injury' (i.e. percentage of people aged ≥65 years co-prescribed an NSAID and an ACE inhibitor/angiotensin receptor blocker and a diuretic) demonstrated that over the period April 2018 to June 2020, there was a 30% reduction in those patients exposed to this HRM combination across Scotland. Similarly, there has been a reduction of 16% in the volume of NSAIDs prescribed in Scottish General Practices for the period April 2018 to June 2020 (57).

iii) Cross-national collaborations

In addition to national activities supporting HRM stewardship in Scotland, a wider European network of researchers and clinicians has started to investigate the differential uses of oral anticoagulants in a number of European countries in order to better understand the respective patient populations, and to evaluate the drugs' safety and clinical effectiveness. Initial studies have focused on the use of direct oral anticoagulants (DOACs) in patients with atrial fibrillation, and first results showed, in general, high persistence and adherence to DOACs among patients in five countries – Denmark, Germany, Norway, Scotland, and Sweden (60). Further outcomes, including on the benefit of DOAC treatment in patients with atrial fibrillation at low risk of stroke, are being investigated, with potential implications on treatment guidelines in the future.

3. Generation of RWE in response to emerging pandemics and emergency health crisis

One of the key important applications of routinely collected administrative data is their use to generate rapid and speedy evidence in response to an unexpected emergent health crisis and

disease pandemic where conducting more rigorous experimental studies is either unethical or not feasible, especially when quick evidence to address urgent health issues is required. A very recent example is the use of RWD in the era of the COVID-19 pandemic which has been declared by the WHO as a public health emergency on 3rd January 2020 and then a global pandemic on 11th March 2020 (61). In response to this pandemic, rapid and large observational studies, using linked individual level datasets, were required not only to identify the clinical and epidemiological profile of COVID-19 but also to evaluate the effectiveness and safety of various preventive and curative pharmacological interventions such as vaccines and anti-viral therapies. In this context, several projects have been established in the UK whereby secure analytical platforms of routinely collected national administrative and clinical data have been created to be used to address COVID-19 related clinical questions in a very timely manner, including OpenSAFELY (62) and EAVE II (Early Pandemic Evaluation and Enhanced Surveillance of COVID-19) (63). The former platform has been used to generate timely RWE on various aspects related to the clinical profile of COVID-19 such as risk factors associated with COVID-19 related mortality (64), as well as the impact of certain chronic conditions (e.g. asthma, COPD, rheumatoid arthritis (65,66)) and medications (e.g. non-steroidal anti-inflammatory drugs and inhaled corticosteroids (65,67)) on COVID-19 clinical outcomes. Additionally, the EAVE II platform has generated RWE on COVID-19 vaccines use in a real-world setting including evidence on both vaccine effectiveness (68–70) and safety (71,72); further studies, including those investigating the in-hospital use of medication in patients with COVID-19, are ongoing (73). Furthermore, the EAVE II platform has been used to develop a risk prediction algorithm (QCOVID) to predict risk of COVID-19 related hospital admission and mortality (74). All these RWE have been essential in enhancing our understanding of the epidemiology and clinical prevention and management of COVID-19, all of which have been key in informing and shaping our public health policies and strategies to tackle the spread and management of COVID-19.

Conclusion

In summary, routinely collected, administrative data can be used for public health purposes in a number of ways. Depending on context, a wide range of aggregate and/or individual level data may be available, supporting research and auditing activities that may ultimately inform policy, drive improvement, and advance patient care. Nevertheless, limitations of the data need to be acknowledged, and methodological approaches need to be tailored to both the available data and the wider context.

References

1. Schurman B. The Framework for FDA's Real-World Evidence Program. Applied Clinical Trials. 2019;28(4):15–7.

2. Wettermark B, Elseviers M, Almarsdóttir AB, Andersen M, Benko R, Bennie M, et al. Introduction to drug utilization research. In: Drug Utilization Research [Internet]. John Wiley & Sons, Ltd; 2016 [cited 2021 Nov 7]. p. 1–12. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118949740.ch1

3. Ramamoorthy A, Huang S-M. What Does It Take to Transform Real-World Data Into Real-World Evidence? Clinical Pharmacology & Therapeutics. 2019;106(1):10–8.

4. Cave A, Kurz X, Arlett P. Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe. Clinical Pharmacology & Therapeutics. 2019;106(1):36–9.

5. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. Br J Cancer. 2014 Feb 4;110(3):551–5.

6. Slattery J, Kurz X. Assessing strength of evidence for regulatory decision making in licensing: What proof do we need for observational studies of effectiveness? Pharmacoepidemiology and Drug Safety. 2020;29(10):1336–40.

7. Schneeweiss S. Real-World Evidence of Treatment Effects: The Useful and the Misleading. Clinical Pharmacology & Therapeutics. 2019;106(1):43–4.

8. Miksad RA, Abernethy AP. Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality. Clin Pharmacol Ther. 2018 Feb;103(2):202–5.

9. ElZarrad MK, Corrigan-Curay J. The US Food and Drug Administration's Real-World Evidence Framework: A Commitment for Engagement and Transparency on Real-World Evidence. Clinical Pharmacology & Therapeutics. 2019;106(1):33–5.

10. Gatto NM, Reynolds RF, Campbell UB. A Structured Preapproval and Postapproval Comparative Study Design Framework to Generate Valid and Transparent Real-World Evidence for Regulatory Decisions. Clin Pharmacol Ther. 2019 Jul;106(1):103–15.

11. Franklin JM, Patorno E, Desai RJ, Glynn RJ, Martin D, Quinto K, et al. Emulating Randomized Clinical Trials With Nonrandomized Real-World Evidence Studies: First Results From the RCT DUPLICATE Initiative. Circulation. 2021 Mar 9;143(10):1002–13.

12. Pundi K, Perino AC, Harrington RA, Krumholz HM, Turakhia MP. Characteristics and Strength of Evidence of COVID-19 Studies Registered on ClinicalTrials.gov. JAMA Intern Med. 2020 Oct 1;180(10):1398–400.

13. Califf RM, Hernandez AF, Landray M. Weighing the Benefits and Risks of Proliferating Observational Treatment Assessments: Observational Cacophony, Randomized Harmony. JAMA. 2020 Aug 18;324(7):625–6.

14. Cai C, Peng Y, Shen E, Huang Q, Chen Y, Liu P, et al. A comprehensive analysis of the efficacy and safety of COVID-19 vaccines. Molecular Therapy. 2021 Sep 1;29(9):2794–805.

15. Office for Statistics Regulation. Administrative data (part 1) [Internet]. 2021 [cited 2021 Oct 12]. Available from: https://osr.statisticsauthority.gov.uk/guidance/administrative-data-and-official-statistics/quality-assurance-of-administrative-data-case-examples/administrative-data-part-1/

16. Virnig BA, McBean M. Administrative Data for Public Health Surveillance and Planning. Annual Review of Public Health. 2001;22(1):213–30.

17. Public Health Scotland. COVID-19 Shielding programme - COVID-19 data and intelligence - COVID-19 - Our areas of work - Public Health Scotland [Internet]. 2021 [cited 2021 Oct 12]. Available from: https://www.publichealthscotland.scot/our-areas-of-work/covid-19/covid-19-data-and-intelligence/covid-19-shielding-programme/

18. Thomas J. Medical records and issues in negligence. Indian J Urol. 2009;25(3):384–8.

19. Eriksson I, Ibáñez L. Secondary data sources for drug utilization research. In: Drug Utilization Research [Internet]. John Wiley & Sons, Ltd; 2016 [cited 2021 Nov 7]. p. 39–48. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118949740.ch4

20. Wettermark B, Persson ME, Wilking N, Kalin M, Korkmaz S, Hjemdahl P, et al. Forecasting drug utilization and expenditure in a metropolitan health region. BMC Health Serv Res. 2010 May 17;10:128.

21. Wen H, Schackman BR, Aden B, Bao Y. States With Prescription Drug Monitoring Mandates Saw A Reduction In Opioids Prescribed To Medicaid Enrollees. Health Affairs. 2017 Apr 1;36(4):733–41.

22. Robertson J, Iwamoto K, Hoxha I, Ghazaryan L, Abilova V, Cvijanovic A, et al. Antimicrobial Medicines Consumption in Eastern Europeand Central Asia – An Updated Cross-National Study and Assessment of QuantitativeMetrics for Policy Action. Frontiers in Pharmacology. 2019;9:1156.

23. WHO Collaborating Centre for Drug Statistics Methodology. WHOCC - History [Internet]. 2018 [cited 2021 Nov 7]. Available from: https://www.whocc.no/atc_ddd_methodology/history/

24. WHO Collaborating Centre for Drug Statistics Methodology. WHOCC - Definition and general considerations [Internet]. 2018 [cited 2021 Nov 7]. Available from: https://www.whocc.no/ddd/definition_and_general_considera/

25. Organisation for Economic Co-operation and Development. Health - OECD [Internet]. [cited 2021 Nov 7]. Available from: https://www.oecd.org/health/

26. Publications Office of the European Union. Datasets - data.europa.eu [Internet]. [cited 2021 Nov 7]. Available from: https://data.europa.eu/data/datasets?locale=en&categories=HEAL&page=1&query=medicine

27. Data collections - WHO [Internet]. 2021 [cited 2021 Nov 7]. Available from: https://www.who.int/data/collections

28. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Search Database [Internet]. 2021 [cited 2021 Nov 7]. Available from: http://www.encepp.eu/encepp/search.htm

29. European Centre for Disease Prevention and Control. Disease and laboratory networks [Internet]. European Centre for Disease Prevention and Control. 2021 [cited 2021 Nov 7]. Available from: https://www.ecdc.europa.eu/en/about-us/who-we-work/disease-and-laboratory-networks

30. Pearce N. The ecological fallacy strikes back. Journal of Epidemiology & Community Health. 2000 May 1;54(5):326–7.

31. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. ENCePP Guide on methodological standards in pharmacoepidemiology [Internet]. 2021 [cited 2021 Nov 22]. Available from: https://www.encepp.eu/standards_and_guidances/methodologicalGuide5.shtml

32. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [Internet]. 2021 [cited 2021 Oct 13]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

33. Hernán MA. The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data. Am J Public Health. 2018 May 1;108(5):616–9.

34. Strom BL, Kimmel SE, Hennessy S, editors. Pharmacoepidemiology. 5. ed. Chichester: Wiley-Blackwell; 2012. 953 p.

35. Elseviers M, editor. Drug utilization research: methods and applications. Chichester, West Sussex : Hoboken, NJ: John Wiley & Sons Inc; 2016.

36. Public Health Scotland. How we share data and intelligence - Sharing our data and intelligence - Our areas of work - Public Health Scotland [Internet]. 2021 [cited 2021 Nov 7]. Available from: https://publichealthscotland.scot/our-areas-of-work/sharing-our-data-and-intelligence/how-we-share-data-and-intelligence/

37. Alvarez-Madrazo S, McTaggart S, Nangle C, Nicholson E, Bennie M. Data Resource Profile: The Scottish National Prescribing Information System (PIS). Int J Epidemiol. 2016 Jun;45(3):714–715f.

38. Public Health Scotland. Community Health Index (CHI) Number | ISD Scotland | Data Dictionary [Internet]. [cited 2021 Nov 7]. Available from: https://www.ndc.scot.nhs.uk/Data-Dictionary/SMR-Datasets//Patient-Identification-and-Demographic-Information/Community-Health-Index-Number/

39. World Health Organization. Global action plan on antimicrobial resistance [Internet]. Geneva: World Health Organization; 2015 [cited 2021 Nov 7]. 28 p. Available from: https://apps.who.int/iris/handle/10665/193736

40. Godman B, Egwuenu A, Haque M, Malande OO, Schellack N, Kumar S, et al. Strategies to Improve Antimicrobial Utilization with a Special Focus on Developing Countries. Life. 2021 Jun;11(6):528.

41. UK Government. Antimicrobial resistance (AMR) [Internet]. GOV.UK. 2019 [cited 2021 Nov 22]. Available from: https://www.gov.uk/government/collections/antimicrobial-resistance-amr-information-and-resources

42. Bennie M, Malcolm W, Marwick CA, Kavanagh K, Sneddon J, Nathwani D. Building a national Infection Intelligence Platform to improve antimicrobial stewardship and drive better patient outcomes: the Scottish experience. Journal of Antimicrobial Chemotherapy. 2017 Oct 1;72(10):2938–42.

43. Public Health Scotland. Infection Intelligence Platform [Internet]. 2020 [cited 2021 Nov 22]. Available from: https://www.isdscotland.org/Health-Topics/Health-and-Social-Community-Care/Infection-Intelligence-Platform/About-IIP/

44. Health Protection Scotland. Scottish One Health Antimicrobial Use and Antimicrobial Resistance in 2019 [Internet]. 2021 [cited 2021 Nov 22]. Available from: https://www.hps.scot.nhs.uk/web-resources-container/scottish-one-health-antimicrobial-use-and-antimicrobial-resistance-in-2019/

45. Healthcare Improvement Scotland. Safeguarding antibiotics for Scotland, now and for the future [Internet]. Scottish Antimicrobial Prescribing Group. [cited 2021 Nov 22]. Available from: https://www.sapg.scot/

46. Kavanagh K, Pan J, Marwick C, Davey P, Wiuff C, Bryson S, et al. Cumulative and temporal associations between antimicrobial prescribing and community-associated Clostridium difficile infection: population-based case-control study using administrative data. J Antimicrob Chemother. 2017 Apr 1;72(4):1193–201.

47. Malcolm W, Fletcher E, Kavanagh K, Deshpande A, Wiuff C, Marwick C, et al. Risk factors for resistance and MDR in community urine isolates: population-level analysis using the NHS Scotland Infection Intelligence Platform. J Antimicrob Chemother. 2018 Jan 1;73(1):223–30.

48. World Health Organization. Medication Without Harm [Internet]. 2017 [cited 2021 Nov 7]. Available from: https://www.who.int/initiatives/medication-without-harm

49. Fujita K, Moles RJ, Chen TF. Quality indicators for responsible use of medicines: a systematic review. BMJ Open. 2018 Jul 1;8(7):e020437.

50. Campbell S, Wettermark B, Andersen M. Defining and developing quality indicators for drug utilization. In: Drug Utilization Research [Internet]. John Wiley & Sons, Ltd; 2016 [cited 2021 Nov 7]. p. 126–38. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118949740.ch12

51. Bennie M, Kurdi A, MacBride-Stewart S, Avery T. Medication safety in primary care-from measurement to action. Drug Ther Bull. 2021 Feb;59(2):24–8.

52. Barnett KN, Bennie M, Treweek S, Robertson C, Petrie DJ, Ritchie LD, et al. Effective Feedback to Improve Primary Care Prescribing Safety (EFIPPS) a pragmatic three-arm cluster randomised trial: designing the intervention (ClinicalTrials.gov registration NCT01602705). Implementation Science. 2014 Oct 11;9(1):133.

53. Howard RL, Avery AJ, Slavenburg S, Royal S, Pipe G, Lucassen P, et al. Which drugs cause preventable admissions to hospital? A systematic review. Br J Clin Pharmacol. 2007 Feb;63(2):136–47.

54. Guthrie B, Kavanagh K, Robertson C, Barnett K, Treweek S, Petrie D, et al. Data feedback and behavioural change intervention to improve primary care prescribing safety (EFIPPS): multicentre, three arm, cluster randomised controlled trial. BMJ. 2016 Aug 18;354:i4079.

55. Scottish Government. Polypharmacy Guidance Realistic Prescribing, 3rd edition [Internet]. 2018 [cited 2021 Nov 23]. Available from: https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/04/Polypharmacy-Guidance-2018.pdf

56. Scottish Government. National Therapeutic Indicators and Additional Prescribing Measures 2017/2018 [Internet]. 2018 [cited 2021 Nov 23]. Available from: https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2017/07/NTI-17-18-Early-release-document-v1.0.pdf

57. Public Health Scotland. National therapeutic indicators data visualisation [Internet]. 2021 [cited 2021 Nov 23]. Available from: https://publichealthscotland.scot/publications/national-therapeutic-indicators-data-visualisation/national-therapeutic-indicators-data-visualisation-data-to-june-2021/

58. Weir NM, Newham R, Corcoran ED, Ali Atallah Al-Gethami A, Mohammed Abd Alridha A, Bowie P, et al. Application of process mapping to understand integration of high risk medicine care bundles within community pharmacy practice. Research in Social and Administrative Pharmacy. 2018 Oct 1;14(10):944–50.

59. Scottish Government. Achieving excellence in pharmaceutical care: a strategy for Scotland [Internet]. 2017 [cited 2021 Nov 23]. Available from: http://www.gov.scot/publications/achieving-excellence-pharmaceutical-care-strategy-scotland/

60. Komen JJ, Pottegård A, Mantel-Teeuwisse AK, Forslund T, Hjemdahl P, Wettermark B, et al. Persistence and adherence to non-vitamin K antagonist oral anticoagulant treatment in patients with atrial fibrillation across five Western European countries. Europace. 2021 Nov 8;23(11):1722–30.

61. World Health Organization. Coronavirus disease (COVID-19) [Internet]. 2021 [cited 2021 Nov 23]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019

62. University of Oxford. OpenSAFELY: Secure analytics platform for NHS electronic health records [Internet]. 2021 [cited 2021 Nov 23]. Available from: https://www.opensafely.org/

63. University of Edinburgh. EAVE II [Internet]. The University of Edinburgh. [cited 2021 Jun 8]. Available from: https://www.ed.ac.uk/usher/eave-ii

64. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020 Aug;584(7821):430–6.

65. Schultze A, Walker AJ, MacKenna B, Morton CE, Bhaskaran K, Brown JP, et al. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. The Lancet Respiratory Medicine. 2020 Nov 1;8(11):1106–20.

66. Rentsch CT, DeVito NJ, MacKenna B, Morton CE, Bhaskaran K, Brown JP, et al. Effect of pre-exposure use of hydroxychloroquine on COVID-19 mortality: a population-based cohort study in patients with rheumatoid arthritis or systemic lupus erythematosus using the OpenSAFELY platform. The Lancet Rheumatology. 2021 Jan 1;3(1):e19–27.

67. Wong AY, MacKenna B, Morton CE, Schultze A, Walker AJ, Bhaskaran K, et al. Use of non-steroidal anti-inflammatory drugs and risk of death from COVID-19: an OpenSAFELY cohort analysis based on two cohorts. Annals of the Rheumatic Diseases. 2021 Jul 1;80(7):943–51.

68. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. The Lancet. 2021 May 1;397(10285):1646–57.

69. Grange Z, Buelo A, Sullivan C, Moore E, Agrawal U, Boukhari K, et al. Characteristics and risk of COVID-19-related death in fully vaccinated people in Scotland. The Lancet. 2021 Nov 13;398(10313):1799–800.

70. Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. The Lancet. 2021 Jun 26;397(10293):2461–2.

71. Simpson CR, Shi T, Vasileiou E, Katikireddi SV, Kerr S, Moore E, et al. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. Nat Med. 2021 Jul;27(7):1290–7.

72. Patone M, Handunnetthi L, Saatci D, Pan J, Katikireddi SV, Razvi S, et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med. 2021 Oct 25;1–10.

73. Mueller T, Kerr S, McTaggart S, Kurdi A, Vasileiou E, Docherty A, et al. Retrospective cohort study to evaluate medication use in patients hospitalised with COVID-19 in Scotland: protocol for a national observational study. BMJ Open. 2021 Nov 1;11(11):e054861.

74. Clift AK, Coupland CAC, Keogh RH, Diaz-Ordaz K, Williamson E, Harrison EM, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ. 2020 Oct 20;371:m3731.