Realising the Potential of Pharmacoepidemiology for Public Health Decision-Making

Studying the impact of medicinal products on populations: an essential tool for decision-making

Council for International Organizations of Medical Sciences (CIOMS)

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Foreword

This book summarizes, in five chapters, the collective and individual contributions of the members of the CIOMS XV Working Group. It sets out to tackle an ambitious challenge: analyzing how to make the most of the vast amount of data now available and the increasingly powerful tools of pharmaco-epidemiology to optimise the public health impact of medicinal products. In particular, by providing all the information needed to make the right decision at the right time.

At the level of the decision-maker, the questions that arise are: is a decision necessary? And, if so, what it should be and how it should be accompanied, particularly with regards to its consequences, which can sometimes be paradoxical and unexpected?

By documenting all interactions between medicinal products and populations (their use, justified or not, optimized or not, and all their direct and indirect effects) from the real world, the pharmacoepidemiological approach is also a valuable tool for anticipating and managing health crises in which medicinal products are, directly or indirectly, involved.

In fact, the main thrust of this book could be summed up as "*the proper use of pharmacoepidemiology to best serve population health and optimize decision-making in this field*."

Throughout the Group's work, one rule prevailed: to remain focused on the issues of decision-making and global health, while integrating the opportunities and constraints brought about by the upheavals of recent years: access to big data, artificial intelligence, new therapeutic paradigms (*e.g.*, biotechnology-derived products), pandemic threats, infodemics, *etc*.

Focusing on the situations that may or may not justify a decision being taken, and on the information that could best be used to make that decision, this book is deliberately not a technical manual or a methodological compendium. The aim was to focus on the decision, on whether or not the information needed at the time was available, and not to discuss the pros and cons of any particular methodological approach. Nor is this book intended to serve as a guideline or a collection of standardized procedures. While the methods and tools of pharmacoepidemiology are undoubtedly fascinating and continue to evolve rapidly, they have been extensively described elsewhere. Instead, it seeks to stimulate critical thinking and informed debate about how pharmacoepidemiological evidence is generated, interpreted, and ultimately used in decision-making processes.

Despite its inevitable limitations, if this book were to prove useful to decision-makers in the field of public health and pharmaceuticals, at least in certain respects, then we will have achieved our goal.

Summary of the CIOMS XV Report

Chapter 1: Pharmacoepidemiology: a major tool for public health

This chapter introduces pharmacoepidemiology as a scientific discipline essential to public health decision-making. It highlights the evolution of the field and its integration with epidemiology, pharmacology, and public health, alongside the growing use of large-scale real-world data. The chapter discusses the paradoxes of the discipline—its vast investigative potential contrasted with persistent gaps in addressing public health needs—and emphasises the importance of collaborative frameworks involving academia, industry, regulators, and patients. Finally, it calls for a new era in pharmacoepidemiology, harnessing advanced analytics and unified frameworks to maximise its impact on global health.

Chapter 2: Types of public health issues that can be addressed with pharmacoepidemiology

This chapter reviews the wide range of public health issues that pharmacoepidemiology can address, including medicinal product utilisation, equity and access, prescribing patterns, polypharmacy, misuse, and overuse. It illustrates how pharmacoepidemiology supports benefit-risk assessments, regulatory decision-making, and the optimisation of public health interventions. The chapter also explores the role of pharmacoepidemiology in supporting medicinal product development, promoting equitable access, and evaluating the impact of healthcare systems, policies, and regulatory actions. Ultimately, it underscores the discipline's value in identifying gaps, disparities, and opportunities for improving health outcomes.

Chapter 3: Evaluating existing pharmacoepidemiology evidence to support public health decision-making

This chapter outlines a structured workflow for assessing existing pharmacoepidemiological evidence before initiating new studies. It advocates for clearly defining public health issues, involving interdisciplinary experts, and synthesising available findings to identify evidence gaps. Examples from infectious disease management, chronic disease management, and label expansion illustrate how timely and actionable evidence can support rapid decision-making. The chapter emphasises the importance of clear communication, contextual interpretation, and proactive strategies to mitigate misinterpretation and misinformation, particularly during public health crises.

Chapter 4: Using pharmacoepidemiology to anticipate and manage public health crises

This chapter explores how pharmacoepidemiology can be used to anticipate, prepare for, and respond to public health crises and emergencies. It reviews the discipline's role in generating real-world evidence during crises such as pandemics, drug recalls, medicinal product misuse, resistance, shortages, and environmental disasters. The chapter outlines the ten stages of a public health crisis and the corresponding study types, emphasising the need for agile, pragmatic, and ethically sound research. It highlights the importance of timely interventions, robust data, and effective communication to safeguard public health. Key examples demonstrate how proactive pharmacoepidemiology can enhance crisis outcomes by informing policy, guiding public behaviour, and maintaining public trust.

Chapter 5: When pharmacoepidemiology may not be the best option for public health decision-making

This chapter outlines a structured workflow for assessing pharmacoepidemiological evidence prior to initiating new studies. It identifies situations such as duplication of existing research, the potential to delay critical decisions, the risk of exacerbating crises, lack of reliability or relevance, and limited generalisability. The chapter stresses the importance of prioritising resources, ensuring methodological rigour, and focusing on studies that provide meaningful and actionable insights for public health decision-making. It advocates for common sense and feasibility assessments to avoid inconclusive or unnecessary research.

Conclusion

The report concludes that pharmacoepidemiology is an irreplaceable tool for public health decision-making, providing comprehensive insights into how medicinal products are used and what effects they have in real-world populations. It calls for the optimal use of limited resources through the prioritisation of the most pressing public health issues and strengthened collaboration among stakeholders. By enhancing shared frameworks, data access and sharing, and clear communication, pharmacoepidemiology can play an even more central role in safeguarding and improving global public health.

Introduction

Pharmacoepidemiology[1] aims to appraise and understand the use and effects – both beneficial and adverse – of medicinal products in real-world settings. As such, it can be viewed as a bridging discipline that connects clinical pharmacology, epidemiology, public health, and social sciences. Although the systematic study of interactions between medicines and populations began to take shape in the late 1950s and early 1960s—galvanised by the thalidomide tragedy, which exposed the limits of pre-marketing evidence and underscored the need for population-based monitoring—pharmacoepidemiology may be regarded as a relatively young discipline. In the 40 years since its international recognition in the mid-1980s, it has become an indispensable component of modern medicinal product evaluation[2].

Initially heavily inspired by the concepts and methods of the epidemiology of diseases and environmental risks, pharmacoepidemiology has gradually established itself as a discipline in its own right thanks to the development of new concepts and original methodological approaches. These have ranged from classical field-based studies with limited sample sizes, culminating in refined analytical methods and bespoke approaches designed to address diverse needs. Moreover, the broad scientific community and other stakeholders now have greater access to large volumes of person-level medical, healthcare, and administrative claims data, as well as population-based healthcare databases. In some cases, it has become possible to conduct studies encompassing the entire population of a country or all users of a given medicinal product, rather than a sample of that population. This change in scale, and the possibility of exhaustive recruitment, have led to a shift in our perspective on a variety of classical epidemiological and statistical concepts, including selection biases, statistical power, confidence intervals, and statistical significance[3].

The World Health Organization defines public health as "*the art and science of preventing disease, prolonging life and promoting health through the organised efforts of society*". Medicinal products available today – whether older molecules with proven efficacy or innovative therapies that can prevent disease, treat illness, or modify prognosis – constitute public health tools with potentially major public health impact. Pharmacoepidemiological studies therefore provide invaluable information for those involved in public health and decision-making. Two central questions underpin this report: (1) does pharmacoepidemiology, even when it has the

[1] In the present book, it is used in its broadest sense, encompassing all approaches aimed at documenting the interactions between medicinal products and populations; in other words, finding out what the population does with the product (number of users, conditions of prescription and use, *etc.*) and what the product does in this population (referring to all effects and consequences, whether beneficial or undesirable).

[2] The term "medicinal product" will be used throughout this book because it has a broader meaning than « drug » or « medicine » (see the definition provided in the Glossary at the end of the book).

[3] For example, see the point made on these subjects by the American Statistical Association: https://www.amstat.org/asa/files/pdfs/p-valuestatement.pdf

means to do so, always generate the information required for public health decision-making? and (2) do decision-makers always make optimal use of this information?

While the pharmacoepidemiological approach – with its latest methodological developments and an almost unlimited sources of information – is now capable of exploring all aspects of the interactions between medicinal products and populations, it faces a series of new challenges. Indeed, over the past decade, new public health paradigms have emerged as a result of three key factors:

I. The popularisation of the One-Health[4] and other global health concepts, which makes it inappropriate not to consider, for a given medicinal product or a public health intervention, both the benefits and risks as a whole. Indeed, accounting for all the direct and indirect consequences of a public health intervention, *e.g.*, an immunisation campaign, can substantially alter our perception of the benefit/risk balance[5].

II. Increased awareness of emerging pandemic threats. The experience of COVID-19 in 2020-2022 has profoundly changed people's expectations regarding the healthcare interventions and conflicting demands concerning medicinal products: the fastest and widest possible availability while demanding absolute safety.

III. Advances in information technologies in statistics and computing, including the rise of "Big Data", artificial intelligence, and machine learning have led to a profound rethinking of the approaches used to date in pharmacoepidemiology, including the most recent ones.

Another challenge arises from the fact that, over the same period, conventional chemically derived drugs have been complemented, in many therapeutic areas, by biotechnology-derived novel agents whose mechanisms of action bear little or no resemblance to those of conventional pharmacology. As a result, core pharmacoepidemiological concepts such as dose, exposure density, and duration of exposure may be called into question and may require new approaches or types of analysis.

These profound changes call for a thorough re-examination of the concepts used to evaluate medicinal products. More than ever, the validity of therapeutic or preventive interventions must be assessed at the population level. Beyond – and in addition to – Evidence-Based Medicine (EBM), which has traditionally relied on the results of clinical trials, pharmacoepidemiology, in its open conception to the most recent advances, is increasingly becoming a cornerstone of public health decision-making. By reflecting, in real time, the overall impact of interventions on populations, it can also provide information on the consequences of this decision.

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[4] One Health' is an integrated, unifying approach to balance and optimize the health of people, animals and the environment. It is particularly important to prevent, predict, detect, and respond to global health threats such as the COVID-19 pandemic. See more at https://www.who.int/health-topics/one-health#tab=tab

[5] In this example, but also in many others, such as antibioresistance and nosocomial infections, the consequences may involve people who are not treated with the product in question.

It is this fundamental issue – the contribution and appropriate use of pharmacoepidemiology to inform public health decisions – that has been the central focus of the CIOMS XV working group, *Realising the Potential of Pharmacoepidemiology for Public Health Decision-Making*.

Chapter 1: Pharmacoepidemiology: a major tool for public health

The CIOMS XV document is intended to serve as a global reference for regulators, academic institutions, pharmaceutical and biotechnology companies involved in medicinal product development and marketing, as well as for health policy decision-makers at international, regional, and national levels. It is also relevant to researchers, academics, healthcare professionals, and patients. The guidance aims to:

- Encourage the implementation of well-designed studies that address critical public health questions related to medicinal products.
- Foster collaboration and knowledge exchange among regulatory authorities, industry, and scientific communities, thereby strengthening the role of pharmacoepidemiology in supporting meaningful research and improving global public health.
- Minimise unnecessary studies that do not contribute to informed decision-making and may even hinder or delay it—such as studies with questionable validity or those that fail to adequately address the intended public health issue.

Pharmacoepidemiology is a scientific discipline that applies epidemiological methods to evaluate the use, benefits, and risks of medicinal products and interventions in human populations (ISPE). More broadly, it can be described as the study of interactions between medicinal products and populations (Bégaud). Medicinal products are inherently public health tools, representing major advances in the treatment and prevention of diseases. Over recent decades, requirements for demonstrating their effectiveness and safety have become increasingly rigorous. As a result, decisions related to the development and delivery of medicinal products must now account for profound paradigm shifts in public health and regulatory expectations. It is therefore essential that decision-makers—the primary audience for this chapter—understand the meaning and importance of pharmacoepidemiology from the outset.

As noted in the Introduction, the emergence of novel therapeutic agents –such as gene therapy, biologics, and mRNA vaccines –whose modes of action and interactions with living organisms have very little in common with those of traditional chemically derived medicinal products, has called into question several classical principles of pharmacology, pharmacovigilance, and pharmacoepidemiology. These include concepts such as dose-effect relationship, drug-drug interactions, medicinal product-effect causation criteria, and the determination of medicinal product exposure. An additional challenge for post-marketing assessment of therapeutic effect and the generation of real-world evidence arises from the growing tendency toward accelerated market authorisation, particularly for innovative treatments targeting serious conditions. This trend disrupts the traditional product development paradigm –namely, the sequential phases I to IV clinical trials – that prevailed until recently.

In brief, conducting an in-depth assessment – wherever possible in real time – of the added value and associated risks of both innovative and older (*i.e.,* chemically derived) medicinal products would facilitate more informed selection and use. Such appraisal should consider the marked changes in outcomes that may arise from multiple factors, including age, sex, background disease incidence within a specific geographic area or population, and access to healthcare.

1.1 The paradoxes of pharmacoepidemiology

Pharmacoepidemiological research aims to generate valuable and robust evidence on the health effects of healthcare products, but its investigative potential does not always align with public health needs. Increasingly, pharmacoepidemiology is being leveraged to evaluate not only specific medicinal products and vaccine interventions, but also broader aspects of healthcare systems, population health behaviours, and policy responses. Pharmacoepidemiological approaches are also being applied to guide and support the clinical development of new medicinal products.

Paradoxes in pharmacoepidemiology include:

- The field's investigative potential is virtually unlimited, yet it does not always meet public health knowledge needs.
- There is a tendency toward technological and methodological development as an end in itself, sometimes at the expense of integrated, holistic approaches (such as One Health).
- The demand for immediate answers often conflicts with the time required for rigorous research.

Problems also arise when both the public and decision-makers increasingly expect immediate answers about medicinal product use and effects, often overlooking the time required for rigorous scientific research. The COVID-19 pandemic and the accompanying "infodemic" exemplified this challenge: a flood of narrowly focused studies on vaccine effectiveness and adverse events (such as myocardial infarction, thrombosis, myocarditis, and neurological effects) were released rapidly. Yet, comprehensive and real-time data on the overall benefit-risk remained scarce. This lack of global perspective allowed isolated risks to dominate public discourse, fuelling vaccine hesitancy as social media and influencers shaped opinion more than scientific evidence. At the same time, health authorities sometimes made hasty decisions and communications, neglecting the need for robust data and thorough epidemiological research, which ultimately undermined an objective assessment of vaccine benefit-risk balance.

But a "sliced" or fragmented approach to pharmacoepidemiology is not new; on the contrary, it has long been the rule for most of the debates that have animated pharmacoepidemiology in recent decades. Many studies – sometimes reaching contrasting conclusions – have focused on limited aspects of the population impact of a medicinal product, such as specific types of adverse events, without providing an overall assessment that would enable definitive conclusions to be drawn regarding the benefits and risks associated with a given product, and/or an appropriate decision to be taken about its use. Examples can be found even among the most widely used medicinal products. These include studies targeting the specific adverse effects of proton pump inhibitors or the effect of their long-term use on all-cause mortality (Xie). The same applies to the assessment of the overall benefit-risk balance of certain psychotropic drugs, mainly benzodiazepines, taking into account their well-documented and recognized adverse effects, but also their possible major effects from a public health perspective, which are subject to debate (Billioti de Gage).

Studies that do not appear to be a priority at first glance or that are unlikely to provide any responses to the questions concerning the interactions between medicinal products and public health, can even have effects that are contrary to public health objectives if they delay decision-making or lead to erroneous conclusions about risk or benefit and the real contribution of a medicinal product to public health.

1.2 Pharmacoepidemiology framework

The use of real-world clinical conditions upon commercialization is paramount to the assessment of the effects, both in terms of efficacy and safety, of medicinal products and serves dual purposes: optimizing individual patient care and evaluating broader population health impacts.

A framework in this context refers to a conceptual or structural guide that helps organize the methods, tools, and practices needed to address specific problems in pharmacoepidemiology and serves as a foundation for generating, analysing, and applying real-world evidence effectively and to ensure that research is scientifically sound, ethically conducted, and relevant to public health decision-making.

Advances in data infrastructure, computing power, and analytical methods now enable pharmacoepidemiologists to do more than assess benefits and risks. These tools help determine how to maximize therapeutic benefit, minimize harm, and optimize cost-effectiveness—both at the population level and specific subgroups.

The discipline is becoming even more central as regulatory agencies adopt adaptive medicinal product approval pathways aimed at improving timely access to innovative treatments. In parallel, the rise of learning health systems, which continuously analyse and apply internal data to enhance care delivery, underscores the strategic importance of pharmacoepidemiology in shaping the future of medicinal products and public health (Gagne and Avorn, 2019).

Collaborative efforts among academia, industry, healthcare systems, and government are essential to generate robust evidence and to support informed decision-making that benefits patients (Sabaté and Montané, 2023).

1.2.1. Academia

University researchers played a key role in the emergence of pharmacoepidemiology as a new discipline in the mid-1980s. They were responsible for most of its methodological developments, proposing innovative approaches that were subsequently applied to other areas of public health, such as self-controlled models, propensity scores, emulation of randomized trials, and improving confounding adjustment, bias minimization, and causal inference in observational studies. These contributions help enhance the validity and credibility of real-world evidence and are frequently at the forefront of addressing emerging challenges in study design and analysis.

The role of universities is, by essence, essential in the dissemination of knowledge, including through scientific publications and training.

Academic pharmacoepidemiology has also been essential in maintaining the integrity and transparency of evidence generation. Through open science practices, peer-reviewed publications, and independent replication of findings, academia helps safeguard public trust in evidence used for regulatory and policy decisions.

In summary, academia not only contributes to the technical advancement of pharmacoepidemiology but also strengthens its credibility, independence, and long-term sustainability as a discipline.

1.2.2. Pharmaceutical Industry

The pharmaceutical industry, through both internal resources and external collaborations or partnerships, plays a vital role in ensuring patient safety by conducting credible and timely pharmacoepidemiological research. Pharmacoepidemiological approaches are also used by researchers within the industry to guide and support the clinical development and approval of new products. This form of investigation has become an essential component in the development of pharmaceutical and biological products.

A key function of industry-led pharmacoepidemiology is the characterization of target medical conditions, including their occurrence, natural history, outcomes related to use, safety and effectiveness, associated costs, and the broader medical context in which they are managed. While some of these efforts are aligned with business objectives, most stem from a genuine commitment to better understand at-risk populations and from regulatory requirements for detailed information about medicinal product effects (Haas, 2019).

1.2.3. Regulatory

Regulatory agencies play a critical role in ensuring the safety, efficacy, and quality of medicinal products. Additionally, as part of government, they play a crucial role in influencing decision making with regard to public health policy. To fulfil their mandate, they rely heavily on pharmacoepidemiological data and studies to inform their decision-making throughout the lifecycle of medicinal products. Consequently, several regulatory initiatives have been launched in recent decades to generate and integrate real-world evidence (RWE) into regulatory frameworks in addition to regulatory guidance for the industry on conducting post-marketing studies (including Good Pharmacovigilance Practices).

1.2.4 The pharmacoepidemiology framework in the context of public health

This sub-section highlights the relevance and potential of pharmacoepidemiological frameworks in advancing public health initiatives and policymaking.

Pharmacoepidemiology lies at the intersection of epidemiology and pharmacology, the latter being the scientific discipline that characterizes pharmacotherapy as a population-level intervention. Similar population-level interventions—such as medical devices, environmental health actions, and diagnostic technologies—also rely on epidemiological principles.

Key public health applications of Pharmacoepidemiology frameworks include:

- Replicating successful collaborations between industry and regulators in other health domains (*e.g.*, medical devices, diagnostics, IT systems). This includes adopting practices such as risk management planning and requirements for post-marketing epidemiological studies.
- Adapting regulatory data systems for broader public health use. Public health authorities, HTA bodies, and other institutions can utilize platforms like Sentinel (US) and DARWIN (Data Analysis and Real-World Interrogation Network) EU® (EU) to conduct studies tailored to their needs.

For example, the DARWIN EU® data network is expected to expand access to interested parties like the European Centre for Disease Prevention and Control (ECDC) and national Health Technology Assessment (HTA) bodies, enabling them to conduct timely, reliable, and coordinated studies.

Similarly, the EMA framework contracts provide a model that public health agencies could adopt to access diverse data sources, academic expertise, and operational support for real-world research (Sabaté, 2023; Thaker, 2015)

Another example is the IMI-PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) project, a major European initiative and the first public-private partnership under the EMA umbrella focused on pharmacoepidemiological research on outcomes of therapeutics. It addressed key knowledge gaps and methodological limitations in pharmacovigilance and pharmacoepidemiological research, particularly around continuous benefit-risk monitoring across the product lifecycle.

The project developed innovative tools and methodological standards, enhanced the monitoring of medicinal product safety, and improved benefit-risk evaluation and communication strategies.

1.2.5. Patient involvement

Patient involvement is increasingly recognized as a critical component in the processes of the designing, conducting and interpreting pharmacoepidemiology studies either by industry or non-industry organizations. Involving patients in the early stages of pharmacoepidemiology research—such as defining study questions, selecting relevant outcomes, and interpreting findings—can enhance the relevance, acceptability, and impact of real-world evidence for public health decision-making. This approach ensures that studies reflect the lived experiences and priorities of the populations affected, thereby improving the utility of pharmacoepidemiological data in guiding regulatory and policy actions. Patient organizations and patient advocacy groups have increasingly become key players in private-public partnerships involving academia, industry, regulatory bodies, etc.

Several initiatives have demonstrated the value of structured patient involvement. The Innovative Medicines Initiative IMI-PREFER (Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle), a public-private collaborative research project, enabled the integration of patient preferences into benefit-risk assessments using tools such as Multi-Criteria Decision Analysis (MCDA) and Discrete Choice Experiments (DCE), highlighting the importance of aligning study outcomes with patient values, including treatment burden and quality of life (IMI-PREFER, 2024).

Despite these advances, patient involvement in pharmacoepidemiology remains fragmented and inconsistently applied. Studies often lack formal mechanisms or a framework to include patient perspectives, which can result in outcomes that fail to capture key issues such as treatment adherence, equity in access, and the acceptability of interventions. For example, pharmacoepidemiological research on anti-obesity medications has revealed disparities in access and off-label use, yet few studies have involved patients in shaping the research agenda or interpreting the implications for public health (Saxon et al., 2021; Chalasani *et al*., 2024).

To address these limitations, there is a pressing need for a unified, international, and precompetitive framework for patient involvement in pharmacoepidemiology. Such a framework should consolidate outputs from existing initiatives, including CIOMS report from Working Group XI on Patient involvement in the development, regulation and safe use of medicines (CIOMS, 2022), identify persistent gaps, and offer scalable models for implementation. As Hoos (2015) emphasized, embedding patient needs at the core of medicinal product development and lifecycle management requires active participation from all stakeholders—including patients, researchers, regulators, and industry—to ensure that evidence generation is inclusive, credible, and actionable.

1.3 An urgent need for a new era

It is commonly said, and rightly so, that randomized controlled trials remain the gold standard for validating and measuring the efficacy of healthcare products in the least biased way possible. It is also rightly pointed out that this approach does not operate under real-life conditions, and that the conduct of randomized clinical data can be cumbersome and costly.

The traditional comparison of the strengths and weaknesses of the experimental plan (clinical trial) and the observational approach must be revisited in light of the change of scale that pharmacoepidemiology has undergone in recent years:

- The data sources now available mean that pharmacoepidemiological studies can be conducted under real practice conditions on millions of people to provide, with relatively limited costs and resources, very detailed and reliable information in a timely manner.
- The new tools and resources available to researchers nowadays (new comparison designs, data linkage, emulation of controlled trials, machine learning, artificial intelligence, etc.) have radically changed the situation and circumvented many of the limitations inherent in the observational approach.

Pharmacoepidemiology has the potential to help generate evidence of the impact and efficiency, potential or measured, of any public health intervention, especially in the event of likely new treatment paradigms and public health challenges and help in the decision-making when related to difficult decisions.

However, these conceptual and technical developments make it more necessarily than ever to propose and adopt criteria and guidance to more precisely define the role and potential strengths of pharmacoepidemiology in assessing the contribution of medicinal products, including biologics, to meet global public health needs. Put alternatively, pharmacoepidemiology requires a new approach, to support strategy development and decision-making. This new approach would enable us to answer questions about when to conduct (or not) a study, on what, and using what data source(s).

1.4 Harnessing the potential of pharmacoepidemiology for public health

In the context of available data sources (administrative claims databases, electronic health care records, registries, population cohorts, *etc.*) and advances in this field such as "big data", tokenization, and, more recently, artificial intelligence, this guidance aims to:

- Define situations in which a comprehensive approach to the problem is necessary from a public health perspective; for example, a comprehensive assessment of the effects of a medicinal product and its benefits-risks balance for global public health.
- Help users to determine whether a study would be feasible and the best option; what is crucial in terms of resource optimization and management. The guidance will also facilitate prioritization of pharmacoepidemiological studies to be carried out according to their potential to produce meaningful results and address population impact.
- Develop an inventory of situations representing the challenges that the assessment of the impact of medicinal products on public health now entails and defining for each of them whether:
    - A pharmacoepidemiological study could be appropriate or should be conducted,
    - What information it should generate,
    - What would be the timeframe for setting up this study and obtaining relevant results what would be the study limitations and possible untoward consequences.
- A simpler and/or faster approach, always guided by common sense, should be adopted (e.g., medicinal product utilization data, meta-analysis of available data, modelling, could provide sufficient information on this issue).

More specifically, this guidance aims to define to what extent the paradigms of One-Health and global public health, and the launch of novel health products such as biologics, bring into question the applicability of some of the key-concepts and approaches of the current application of pharmacovigilance and pharmacoepidemiology. It has already been mentioned that confidence intervals and p-value may no longer be relevant when dealing with very large populations, in some cases approaching that of the geographical area studied.

The guidance also points out that pharmacoepidemiology, however effective it may be, is unable to provide a response to every question relating to medicinal products and public health. Several technical and conceptual reasons that account for this are listed and illustrated with practical examples. Fortunately, in many cases, such situations can be managed and an appropriate decision taken.

1.5 Conclusion

Pharmacoepidemiology is a critical discipline in modern public health, providing robust methods to evaluate the benefits and risks of medicinal products across populations. As therapeutic innovation accelerates and regulatory demands grow, pharmacoepidemiology enables informed decision-making and effective risk management.

This chapter has shown how the field bridges traditional pharmacology with real-world evidence, adapting to new therapies and evolving expectations for timely, reliable data. Persistent challenges remain, including fragmented research and the need for integrated frameworks that unite patient, academic, industry, and regulatory perspectives.

To maximize its impact, future efforts should focus on collaboration, advanced analytics, and transparent, patient-centred research. Unified frameworks and international guidance will be essential for generating actionable evidence and advancing global public health. By balancing scientific rigor with practical relevance, pharmacoepidemiology will continue to guide the safe and effective use of medicinal products for individuals and society.

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Chapter 2: Public health decisions that could be informed by Pharmacoepidemiology

The goal of this chapter is to review the situations for which pharmacoepidemiology can support public health decision-making—for example, by identifying, monitoring, and evaluating the use of medicinal products in addressing a specific public health concern.

Pharmacoepidemiology can be applied to a wide array of public health issues. It can assess the use, safety, and effectiveness of medicinal products in large populations, identify adverse medicinal product reactions including the most common ones and those that are tricky to detect, for example because their onset is very delayed, evaluate the efficacy and the effectiveness of medicinal products in routine clinical practice, and monitor patterns of misuse, overdose, or lack of adherence. Pharmacoepidemiology also plays a key role in guiding public health policy by informing regulatory decisions and evaluating the population-level outcomes of public health interventions. Ultimately, by evaluating medicinal product safety and effectiveness in real-world settings, pharmacoepidemiology helps improve health outcomes at scale and informs all levels of health strategies.

2.1 Utilisation of medicinal products

While medicinal products are vital for addressing public health concerns and have substantially contributed to life expectancy over the course of the 20th century (Bunker), their utilization can also contribute to public health challenges. One example is about the determination of *appropriate* versus *inappropriate* use of medicinal products, including misuse and overuse, and how to ensure that medicinal products are administered within the proper target population (WHO 2). It must be acknowledged that in a public health perspective, reviewing the use of medicinal products should take into consideration equity concerns related to access to treatments, recognizing the existing disparities in medication access across various demographic and socioeconomic groups.

<u>Equity and Access</u> are central from a public health perspective: Pharmacoepidemiology extends beyond simply evaluating medicinal product efficacy, effectiveness and safety—it can also support policymaking that addresses access and inequity.

<u>Pharmacoinequity</u> may stem from socioeconomic status, sex, age, ethnicity, geographic location, or off-label prescribing trends. Medicinal product utilization studies can uncover disparities in medication access across demographic and socioeconomic groups. Exploring possible public health consequences of these differences can lead to improved public health interventions and to a more efficient health care system. This would be the case, for example, with a vaccination campaign in which the most at-risk groups were, paradoxically, those in which the lowest coverage was achieved (Chalasani, Maldonado-Puebla, Essien, WHO 6).

Pharmacoepidemiology also tracks prescribing patterns and usage trends, including adherence to guidelines and off-label use. While off-label prescribing may be evidence-based in some contexts, it can carry risks when lacking robust support. Pharmacoepidemiology provides the data needed to evaluate these practices critically.

Polypharmacy, or the use of multiple medicinal products by one patient, is a growing concern, especially among the elderly (Morin). Although it is often necessary for managing complex chronic conditions, polypharmacy carries increased risks of adverse medicinal product reactions, medication errors, drug-drug interactions, and is associated with excess rates of fatal outcomes, hospitalization and healthcare costs. Prescription cascades—where side effects are mistaken for new conditions—further compound these risks (Rochon). Here too, pharmacoepidemiology is the tool of choice to identify these patterns and to define possible courses of intervention to achieve safer prescribing practices.

Overuse occurs when the number of medicinal products prescribed or consumed in a specific country or region significantly exceeds what is expected based on the epidemiology of a disease and recommendations for its prevention, management or treatment. This overuse may correspond to too many users, or/and excessive dosage, or/and excessive treatment durations.

Another type of misuse, which is just as problematic from a public health perspective, is the opposite situation: too few people are being treated, or treatments are being administered at too low a dose or for too short a period.

The role of pharmacoepidemiology is particularly valuable here in identifying these situations, describing the gaps between target populations and populations reached. Similarly, pharmacoepidemiology could explore gaps between what is recommended and what is done, identifying the factors that may explain these deviations, and studying their consequences in terms of public health (unjustified iatrogenesis in the first situation, cases of disease that are not prevented or are poorly treated in the second).

This overconsumption can generate or amplify a crisis context, for example, due to associated iatrogenesis. The most emblematic example of this situation is undoubtedly the opioid overuse epidemic in the United States, which led to a major health and media crisis between 2006 and 2010 and caused tens of thousands of deaths per year. Pharmacoepidemiological studies played a decisive role in monitoring the progression of the "epidemic" and studying its consequences. In particular, they have helped establish causal links between opioid use and the main adverse events observed, monitor consumption trends, identify risk factors for dependence, describe consumption patterns, and assess the efficacy and safety of medicinal products used to manage the main complications associated with this overuse (McHugh, Lam, Klaire, Santo).

Antimicrobial resistance is another public health threat associated with antibiotics misuse and overuse, with significant potential to cause public health crises. Infections caused by bacteria that have become multi-resistant to most antibiotics, even the most effective ones, are believed to cause nearly 2 million deaths worldwide each year (Anonymous 13). The main cause and prevention can be found in the widespread use of antibiotics, but above all in their use that does not comply with recommendations.

Apart from their use in humans, the widespread use of antibiotics in livestock farming for human consumption has also played a major role, either through the emergence of multi-resistant bacterial strains in these animals, which can then contaminate humans, or through the ingestion of antibiotic residues in the meat consumed. Although this widespread use in livestock farming remains high in some major producing countries, it has been declining overall in recent years (Ardakani).

A pharmacoepidemiological approach is crucial for studying patterns and trajectories of antibiotic use in the population and investigating the link between these patterns and the emergence of resistance, identifying and quantifying the health, social and economic consequences of multi-resistant bacterial infections. This information is essential for guiding antimicrobial management efforts and policy decisions. One example of where this has been implemented to support public health initiatives is within the UK. The Department for Health and Social Care, which now publishes prescribing trends for medicines by local primary care and wider area geographies to promote transparency of performance to share research on utilisation for the public as well as research community (UK Office for Health Improvement and Disparities).

The benefit-risk balance of a given medicinal product or public health action may be different in certain vulnerable populations from that which would be estimated in the general population. Physiological changes (pregnant or lactating women, children, older people, individuals with multiple comorbidities, etc.) can affect both medicinal product metabolism and pharmacological response with possible consequences on efficacy, and safety profiles. Here again, pharmacoepidemiology can make a valuable contribution by identifying these differences, providing a better understanding of their mechanisms and enabling therapeutic and regulatory strategies to be adjusted. For example, medication safety in pregnancy must account for potential effects on the foetus and the transfer of medicinal products through breast milk. In paediatric populations, where off-label use is common and sometimes unavoidable, pharmacoepidemiology helps fill evidence gaps due to the scarcity of paediatric trials (CDC, Mitchell, Werler, Adam).

Lastly, there may be medicinal product class specific questions about real-world use, such as anti-obesity medications. Despite eligibility, many patients do not receive these treatments due to inconsistent insurance coverage and systemic prescribing barriers (Saxon). Pharmacoepidemiological studies identify these gaps and support interventions that improve access and public health outcomes.

2.2 Effectiveness, safety, and benefit-risk balance of medicinal products

Assessing the safety and effectiveness of medicinal products is a cornerstone of public health. As mentioned above, pharmacoepidemiology plays a vital role in understanding how medicinal products perform across diverse populations, considering genetic, ethnic, socioeconomic, and cultural factors; as well as enabling the estimation of the population impact of adverse effects and consequences for the healthcare system. Pharmacoepidemiology also supports comparative effectiveness research, safety surveillance in vulnerable populations, cost-effectiveness analyses, and assessments of off-label or long-term use. By integrating real-world evidence, pharmacoepidemiology helps identify target or -at-risk populations, supports the design of inclusive clinical trials, and informs regulatory decisions for product approval. Post-approval, pharmacoepidemiology strengthens pharmacovigilance by identifying, evaluating, and managing adverse medicinal product reactions, thereby ensuring ongoing safety and effectiveness.

Current benefit-risk assessment frameworks typically rely on clinical trial data and periodic benefit-risk evaluation reports (PBRERs), which may not reflect population-level implications. These tools often fail to incorporate real-world perspectives, thereby limiting their utility in public health and decision-making contexts. Integrating pharmacoepidemiology findings into benefit-risk frameworks enhances relevance, inclusivity, and population-level impact. This integration involves better understanding of pharmacoepidemiology data, optimized guidance for benefit-risk assessments, and the prioritization of meaningful real-world evidence. Please refer to the Benefit-risk balance for medicinal products report from CIOMS working group XII (CIOMS).

All of these data can be used to optimize regulatory decisions, whether in terms of safety, market withdrawal, changes to indications, recommendations, or labelling. For example, the COVID-19 pandemic demonstrated the value of pharmacoepidemiology in benefit-risk assessment. Son *et al*. (Kyung-Hwa Son) conducted a multi-criteria decision analysis of COVID-19 vaccines by integrating clinical trial data, cohort study outcomes, and adverse event monitoring across diverse populations. Their work informed policy decisions and demonstrated how pharmacoepidemiology supports evidence-based assessments during public health emergencies.

Similarly, pharmacoepidemiological studies of the risk factors for MS patient for Progressive multifocal leukoencephalopathy (PML), allowed the voluntarily withdrawn product natalizumab, back on the market. Large national cohort studies were conducted, based on national registry, clinical trial and pharmacovigilance data, to analyse the infrequent occurrence of PMP, looking into JC-virus seropositivity status and duration of treatment with natalizumab (Bloomgren).

2.3 Pharmacoepidemiology to support medicinal product development

The epidemiology and natural history of disease provide the foundation for developing effective therapeutic interventions. By defining the population at risk and the progression of disease, pharmacoepidemiology helps identify unmet needs and informs endpoint selection for clinical trials and public health research. Additionally, real-world data can complement trial data as external comparator during product development, when randomization with a placebo would be unethical.

Pre-market trials often involve limited populations and may miss rare or long-term adverse effects. Pharmacoepidemiology addresses these gaps through post-marketing surveillance (Phase IV studies), evaluating safety in broader, more diverse groups. For example, the anti-inflammatory medicinal product Vioxx was withdrawn after pharmacoepidemiological studies revealed an increased risk of myocardial infarction (Sibbald).

A less intuitive, but equally important, contribution of pharmacoepidemiology to decision-making, concerns the early access to *a-priori* promising medicinal products for patients with unmet medical needs. Such as those with rare diseases, in emergency situations, and for the treatment, prevention, or diagnosis of debilitating or life-threatening diseases. Regulatory authorities have implemented expedited pathways to allow early access to such medicinal products provided that their effectiveness and safety are continued to be carefully assessed under real-world conditions of use, with a view to moving towards full approval (Maksimova). For example, pharmacoepidemiological studies have played a crucial role in improving access to bedaquiline for patients with multimedicinal product-resistant tuberculosis (MDR-TB) and extensively medicinal product-resistant tuberculosis (XDR-TB). Bedaquiline was made accessible in high burden tuberculosis countries, prior to completion of Phase 3 clinical trials. Several pharmacoepidemiological studies were then conducted including large multicounty studies as part of global initiatives. (CDC 26, WHO 27, WHO 28, Shaw, Kim, Koirala, Hewison, Huerga). Real-world evidence on effectiveness and safety (paying particular attention to cardiac adverse events, liver toxicity, and deaths) has helped to support the decision to get full authorization (FDA 34, EMA 35).

2.4 Understanding how access to medicinal products impacts public health

Equitable access to medicinal products and other health products is a fundamental human right and a global priority, as defined within the United Nations' Sustainable Development Goal 3.8 (SDG Target 3.8), which aims for the achievement of universal health coverage.

Pharmacoepidemiology, particularly drug utilization studies, is the tool of choice to assess and monitor access issues, such as geographic or economic barriers, and the unintended consequences of regulatory policies. The studies to be carried out as a matter of priority, obviously concern the most essential medicinal products. For example, in Brazil, access to diabetes and hypertension medications was found to be limited in certain geographic areas, prompting policy refinements (Miranda).

Even if access to large databases that accurately describe the use of medicinal products (who? why? and how?) is not possible, as it is the case in many countries where these problems of access are crucial, alternative and simpler approaches can, in most cases, provide sufficient information. For example, the WHO Health Action International (HAI) tool measures medicinal products prices, availability, affordability, and price components. Based on the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) system, this methodology provides a standardized way to measure and compare medicinal product utilization across different countries and regions (patterns and trends of medicinal product use, impact of interventions, *etc*.,). For example, the WHO/HAI tool identified significant gaps in the availability and affordability of essential antidiabetics in Ethiopia and has made it possible to develop appropriate strategies (Deressa).

The possible consequences, in terms of access or impact, of a decision or intervention should be systematically documented by an *ad-hoc* pharmacoepidemiological study. For example, in several European countries, restrictions on opioids have prevented misuse, but also limited legitimate use, impairing patient care, particularly in the management of pain associated with cancer (Vranken).

Shortages of essential medicinal products for prevention or treatment, which were rare a decade ago but are now more widespread and prolonged, are another major threat to public health and a constant cause of emergencies and crises that are sometimes difficult to manage.

Pharmacoepidemiology can make a significant contribution here, both in preventing and managing these high-risk situations. For example, by describing the levels and reasons for consumption of the medicinal product at risk of shortage. The first step is to combat unjustified use so that remaining stocks are available for the most urgent situations. But also, by looking at the efficacy and safety of possible therapeutic alternatives. Finally, by monitoring the decisions taken to ensure that feedback from the field is in line with the desired repositioning. Wagner and his colleagues describe mathematical modelling strategies for the distribution of the COVID-19 vaccine (Wagner). When COVID-19 vaccines were authorised for emergency use, production capacity and distribution logistics were limited, and priorities had to be set to minimise the burden of disease. They describe various mathematical models that incorporate disease-specific factors, such as transmission rates and age, to explore the optimisation of the distribution strategy.

To assess the effectiveness of a vaccine distribution strategy, Nicholas and colleagues (Nicholas) conducted a surveillance cohort study to evaluate the effectiveness of prioritising essential workers for COVID-19 vaccination to achieve racial/ethnic equity, taking into account racial/ethnic disparities in disease burden. Epidemiological data had already shown that Black, Latins, Native American, and Pacific Islander individuals were disproportionately affected by severe forms of COVID-19 and deaths related to the disease. At the same time, essential workers were at higher risk of infection, and frontline workers were more likely to belong to racial/ethnic minority groups. The Los Angeles Pandemic Surveillance Cohort was a longitudinal, community-based cohort study established to monitor the impact of COVID-19 infections. It collected data from surveys and blood samples from a representative sample of households on SARS-CoV-2 antibody status in relation to symptoms, testing and vaccination status, sociodemographic characteristics, and health-related behaviours. The study results suggest that prioritising essential workers in infectious disease vaccination campaigns is important, but not sufficient to reduce racial/ethnic disparities in early vaccine uptake.

2.5 Understanding the impact of healthcare systems, policies, and regulatory actions on public health

Pharmacoepidemiology contributes real-world evidence that supports and updates benefit-risk evaluations beyond clinical trials. As mentioned above, regulatory decisions, such as conditional approvals or market withdrawals, most often and, ideally, should always rely on pharmacoepidemiological evidence. The maturity of health care systems, how people have access to medicinal products and regulatory framework to facilitate funding and access impact the implementation of newly available interventions. Pharmacoepidemiology helps identify how these structures affect access, adherence, and outcomes

2.5.1 Connecting marketing authorizations to healthcare

Once a product is authorized, Health Technology Assessment (HTA) bodies use pharmacoepidemiological evidence to evaluate economic and clinical value to inform reimbursement decisions, pricing strategies, and clinical recommendations.

Pharmacoepidemiology also supports the creation of clinical guidelines, adapted to specific populations and healthcare contexts, ensuring regulatory decisions translate into equitable and effective healthcare delivery. These decisions affect patient access and real-world impact. Harmonizing pharmacoepidemiological efforts across regulators, HTAs, and healthcare providers maximizes public health benefits.

The patients W.A.I.T. (Waiting to Access Innovative Therapies) indicator is a real-world data tool the European Federation of Pharmaceutical Industries and Associations (EFPIA) has developed in 2004 to provide insights into availability and time to patient access. This tool has generated insights into the root cause for unavailability and delay to innovative medicines across the 27 EU nations (EFPIA).

2.5.2 The context of specific regulatory scenarios

Innovative therapies addressing unmet needs may qualify for expedited pathways, supported by real-world evidence. A weak regulatory framework can delay the adoption of effective medical interventions. Without decision-making bodies and strong regulation, evaluating and implementing new treatments can be inconsistent, limiting access to therapies that could improve patient outcomes. Pharmacoepidemiology plays a key role in post-authorization safety studies and in evaluating single-arm trials using real-world comparators. Such efforts help regulators and HTA bodies accelerate access to critical therapies (and unmet needs) such as in oncology.

Beakes-Read and her colleagues analysed the FDA's accelerated Approval Program performance through various real world data sources, to establish the time difference between the accelerated approval and the traditional approval. Looking at various aspects of the program, they provided real-world insights into the reliability and success of the program (Beakes-Read).

Wong and his colleagues looked at the effect of the same pathway on survival of patients with solid tumours. They identified cases for 3 solid tumours, for which accelerated treatment became available, and analysed the overall survival of patients in 3 cohorts (accelerated treatment, standard of care and no subsequent treatment). In their analysis they estimated the average survival gain among patients on the accelerated treatment as opposed to patients on previously available treatments and estimated that on a US population nearly 8000 life years were gained owing to the accelerated approval pathway (Wong).

2.5.3 The patients' perspective

Patients' perspectives are essential in public health decision-making. Effective communication strategies, including awareness campaigns and HCP engagement, ensure patients understand risks, benefits, and proper medicinal products use. Tools such as CIOMS WG XI guidelines (Patient involvement in the development, regulation and safe use of medicines) promote the integration of patient voices in benefit-risk assessments (CIOMS 45, EMA 46).

Specific patient reported outcomes (PROMs) can contribute to increase the quality of care. Data from these patient perspectives provide an opportunity for policy makers to get a comprehensive view of health status of population, identify health disparities, and assess the performance of health care systems in improving health outcomes. For example, PROMS required for advanced certification for total Hip and Knee Replacement ensuring compliance with patient-centred standards (Kendir).

2.5.4 The role of healthcare systems

Healthcare systems differ in funding and access models—ranging from publicly funded systems (UK, Spain) to insurance-based (France, Germany) and private systems (US). Mixed systems like Canada and Australia aim to balance these models.

The maturity of a healthcare system refers to its ability to provide high-quality, efficient, and sustainable care. A well-established infrastructure, robust regulatory framework, and ongoing innovations in care delivery. Emerging healthcare systems, particularly in low- and middle-income countries, may face poor health outcomes due to inconsistent use of evidence-based practices. Preventive services like vaccinations and screenings may be less available, leading to more preventable diseases. Health disparities among socioeconomic and demographic groups can worsen, increasing inequities in health and lifespan. In less mature systems, pharmacoepidemiology faces infrastructure and regulatory challenges. Capacity building, international collaboration, and health information systems are key to enabling meaningful research. Pharmacoepidemiology integration into national health policies helps improve healthcare equity and sustainability.

With growing healthcare costs, and equally increasing cost constraints Papanicolas and her colleagues compared health outcomes of the UK National Health Service (NHS) with other high income countries' health care systems through an observational study on real world data mostly from the Organization for Economic Cooperation and Development (OECD). Analysing 79 indicators across seven domains (including healthcare coverage and capacity among) they established that the UK NHS scored below average on patient safety and population health compared to US, Canada, Germany, Australia, Sweden, France, Denmark, the Netherlands and Switzerland (Papanicolas).

2.6 Optimization of implementation of public health interventions

For any intervention to be successful, effective implementation is important. Pharmacoepidemiology may be necessary to inform how public health interventions could be implemented. When planning the implementation of public health measures, insights from -the real-world can support various aspects, not limited to the feasibility of implementing the intervention, identification of populations that may benefit from an intervention (*e.g.*, demographic insights), where geographically interventions should be prioritized (*e.g.*, disease surveillance), or qualitative research into possible obstacles to implementation.

Case example: obesity requires long term treatment, and with the challenges of lifestyle interventions versus the cost of treatments, Ard, Lewis and Moore point out the importance of adjusting and combining interventions based on various individual characteristics to the effectiveness as well as the fairness of availability of treatment to resource-limited population (Ard).

Pharmacoepidemiology can also provide insights into operational aspects of interventions and identify opportunities for improvement. A survey may be done to assess the understanding of an intervention: If health care providers (HCPs) or patients do not understand how to apply an intervention, its impact may be suboptimal. A survey could also provide insights into understanding of implementation of the intervention and identify opportunities to maximize benefits of public health interventions.

Equally, pharmacoepidemiology may provide insights in other operational aspects, such as when to apply diverse strategies (e.g. different implementation methods over time).

Case example: Elong Ecambi *et al.* conducted a survey in Cameroon to understand self-medication and prescription of antibiotics in private pharmacies. Through the survey they established knowledge gaps and quantified the self-prescription of antibiotics; but also provided insights into the effects of common practice like prescription requirements. They drew conclusions on the need to develop guidelines for health care providers on the responsible use of antibiotics and specific health education targeting community members to address the high proportion of antibiotic use through self-prescription (Elong Ekambi).

Pharmacoepidemiology can also address the impact of regulatory actions (2.5.2), medication shortages (4.3.5), and evolving standards of care. It supports pandemic response through real-time monitoring of medicinal products' use and safety, please refer to Chapter 4. Additionally, pharmacoepidemiological studies may help to evaluate the effectiveness of risk mitigation measures and policy changes affecting medicinal product utilization and public health outcomes.

2.7 Conclusion

The listed examples in this chapter are not exhaustive. Pharmacoepidemiology stands as a cornerstone in public health decision-making, offering critical insights into the utilization, safety, effectiveness, and equitable access to medicinal products. Pharmacoepidemiology facilitates the assessment of benefit-risk balances, supports expedited access to innovative therapies, and guides the implementation of interventions tailored to diverse populations and healthcare contexts.

By systematically evaluating real-world patterns of drug use, adverse reactions, and prescribing trends, pharmacoepidemiology not only identifies gaps and disparities in healthcare delivery but also informs regulatory actions, policy interventions, and the optimization of public health strategies. Its role is especially vital in addressing complex challenges such as polypharmacy, misuse, overuse, and underuse of medicines, as well as in responding to crises like the opioid epidemic and antimicrobial resistance.

This chapter highlights the importance of integrating patient perspectives, real-world evidence, and health system maturity into public health frameworks. As healthcare systems evolve and face new challenges, the discipline's capacity to monitor, evaluate, and identify opportunities for medicinal product use remains essential for achieving public health goals across the globe and ensuring the sustainability of public health initiatives.

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Chapter 3: Appraisal of available pharmacoepidemiological evidence to support public health decision making

Public health decisions about medicinal products are not always contingent on the availability of pharmacoepidemiological data. For example, during the early phases of the SARS-CoV-2 pandemic, once vaccines became available, the urgency and scale of the public health threat warranted the rapid launch of immunization campaigns—particularly to protect high-risk groups—without waiting for real-world evidence to accumulate. Likewise, decisions to withdraw marketing authorization for a medication can be based on the precautionary principle, especially when the therapeutic value is limited, and serious adverse reactions are repeatedly observed.

Nevertheless, in most scenarios, pharmacoepidemiological data offer critical value in supporting public health decision-making**.** In the COVID-19 vaccine example, such data have played an essential role in the post-decision follow-up**,** enhancing the understanding of benefits and risks across different populations and contexts. This highlights the importance of evaluating existing pharmacoepidemiology evidence to determine how it may contribute to optimizing public health actions.

Pharmacoepidemiology can significantly inform public health decisions regarding medicinal products by offering data on real-world use, safety, effectiveness, and utilization of these products. Having timely, relevant, and actionable evidence is essential in the context of emerging health threats and policy changes. Evaluating existing evidence is an important first step before launching new studies. It is time-efficient, which is critical when decisions are needed rapidly, and cost-efficient, in particular by avoiding duplication of research. Overall, a thorough evaluation of existing pharmacoepidemiology evidence provides key information by determining whether additional data are truly needed or whether decisions can be supported with existing studies.

This chapter aims to:

- Provide a structured approach for evaluating existing pharmacoepidemiology evidence relevant to a public health issue.
- Emphasize the importance of assessing available evidence before commissioning new studies.
- Present worked examples to illustrate application of the proposed evaluation strategy
- Present how interpretation of pharmacoepidemiological evidence can support decision making in public health.

3.1 Workflow of evaluation of pharmacoepidemiology evidence

In the context of evaluating existing pharmacoepidemiology evidence to support public health decision-making, it is essential to consider various sources of information. These include peer-reviewed publications, conference abstracts, regulatory reviews, technical reports and grey literature, ongoing or unpublished studies (when accessible), and other relevant materials and data, including epidemiological surveillance data as needed. By systematically reviewing and synthesizing this evidence, decision-makers can ensure that their actions are informed by the most comprehensive and up-to-date data available

Appendix 1 includes examples of available tools to help support critical appraisal of pharmacoepidemiological evidence. An overview of the suggested flow of evaluation is discussed here.

Effective use of pharmacoepidemiology in public health decision-making begins with clearly defining the overarching issue and formulating focused questions. These questions should guide the type of evidence and expertise required, such as determining whether a medicinal product is safe, effective, appropriately used, or suitable for universal vaccination or screening programs.

Once the problem is defined, the next step is to identify the information needed to make informed decisions. This often involves consulting a broad range of involved parties—including healthcare providers, patients, caregivers, advocates, charities, academics, and experts from public and private sectors—who can offer diverse perspectives and highlight considerations that might otherwise be overlooked. Patients and their representatives, in particular, provide valuable insights into acceptable benefits and risks.

After gathering perspectives, it is essential to assess whether pharmacoepidemiological evidence can address the questions at hand. This typically involves an initial landscaping exercise to identify standard sources such as peer-reviewed studies, population-based surveys, surveillance systems, registries, and relevant grey literature or public assessment reports.

If time and resources allow, assembling a multidisciplinary team can strengthen the process. Experts such as pharmacoepidemiologists, statisticians, clinicians, pharmacists, pharmacologists, health economists, medical writers, public health practitioners, and librarians can collaborate to ensure comprehensive evaluation and interpretation of evidence.

The team should then conduct systematic or pragmatic literature reviews using appropriate databases to identify relevant pharmacoepidemiological studies. Each study must undergo critical appraisal to assess quality and potential biases, confounding, and effect modification. Standardized tools can support this process, often requiring agreement between reviewers on scoring. Pharmacoepidemiologists play a key role in contextualizing findings and determining their applicability to the public health question.

Following appraisal, the evidence should be synthesized, and gaps in knowledge identified. Consulting registries of ongoing or planned studies can help anticipate future evidence. Where gaps exist, decision-makers should consider whether new pharmacoepidemiological research is needed and whether commissioning such studies is feasible.

Finally, conclusions and recommendations should be formulated, including caveats and suggestions for additional research where appropriate. Communication strategies may be necessary to share findings with the public, using clear messaging and data visualization tools. As new evidence emerges, periodic reassessment ensures that decisions remain current and effective.

3.2 Examples of evaluation of existing pharmacoepidemiology evidence when addressing a public health issue

This section presents several examples illustrating how to evaluate existing pharmacoepidemiological data, sometimes collected or produced in a relatively short time frame, to support public health and medicinal product policy decisions.

3.2.1 Infectious disease management: the example of varicella vaccines

Infectious diseases offer examples of urgent public health issues, such as the COVID-19 pandemic, as well as long-term policy decisions, such as vaccine programmatic strategies (*e.g.*, which age groups to vaccinate, are boosters needed and how often, could it have a negative impact on the epidemiology of the disease). We provide an example illustrating how existing pharmacoepidemiology evidence can support national implementation of a varicella vaccine policy at a country level.

Varicella is an important vaccine-preventable disease causing a significant burden not only in childhood but throughout the lifespan, resulting in shingles in the elderly population. The effectiveness of vaccination varies from 83% for the single dose to 95% for the 2 doses, which clearly shows the association between the number of doses and public health benefits. In 1995, the United States was the first country to adopt a 1-dose varicella vaccine as a universal program. Since then, countries that introduced the varicella vaccine as a universal program have evaluated its effectiveness through a study of disease burden. However, some countries still have no universal varicella vaccine program for infants and selectively vaccinate only high-risk groups or healthcare workers. This is because healthy children often develop mild symptoms when infected with varicella; hence, the urgency lags behind that of other new vaccines (Lee).

Controversy around this issue meant that, in the UK, the decision to roll out varicella vaccine was taken almost 20 years after other countries had rolled out the vaccine. In such a case, the aforementioned small team should include vaccinologists, vaccine pharmacoepidemiologists, paediatricians and modellers, who would review the literature on varicella vaccine safety, effectiveness and use, the impact of vaccination programmes on children, and the epidemiology of zoster at all ages (Roderick, Amirthalingam). Key questions might be: Do you need boosters if you are in contact with individuals who have varicella, to maintain your level of immunity so that you do not develop zoster as an adult? If all children are vaccinated, would adults in their 20s, who had varicella when they were children, have varicella given that they are not boosted? Could this question be considered a pharmacoepidemiology gap? Thereafter the team would draw a conclusion and communicate to the public health decision-maker what it thinks is appropriate with respect to recommending this vaccine.

Evaluation of available literature on the vaccine from other countries was of key importance in the decision making to support a vaccine rollout. Bernal et al (2019) used pharmacoepidemiological methods through a surveillance study of data from all NHS hospitals in England to identify varicella admissions between 2004 and 2017 (Bernal). These data combined with numerous analyses of impact of vaccination programs in the UK, cost-effectiveness on NHS budget, parental acceptance among others contributed to decision making to roll out the program nationally (Akpo, Sherman).

3.2.2 Chronic disease management: the example of statins

Since their launch in 1987, statins have become established as a major agent in the prevention of cardiovascular events. They are among the most widely used drugs in the world, and the scientific literature on them (clinical trials, pharmacoepidemiological studies, modelling, etc.) numbers in the hundreds of publications and is undoubtedly one of the most extensive in the pharmacopoeia. Despite this abundance of information and the decades that have passed since their introduction, controversy and debate remain about the optimal prevention strategies and their risk-benefit balance in certain indications or population subgroups. Major questions remain unanswered. For example: Are these drugs mostly used at the appropriate dose or for a sufficient period of time given the initial level of risk? What is the benefit-risk balance of treatment in populations with low predicted cardiovascular risk? How does this balance change with the age of the person being treated? Is it the same regardless of whether LDL cholesterol levels are high or not? Finally, is the use of statins in primary prevention notoriously inadequate, as some experts claim (Xu)?

Controversies exist around the cardiovascular disease risk calculators used by clinicians to determine the best course of treatment for their patients (Cook). Risk calculators can over- or underestimate risk in different patient populations leading to inappropriate treatment decisions. They can sometimes be based on outdated data and may not account for relevant CVD risk factors. Furthermore, many have not been externally validated with their predictions not tested against pharmacoepidemiological data. The overestimation of CVD risk can lead to millions of people being prescribed long-term statin treatment without a clear benefit. Conversely, underestimation can lead to a failure to recommend necessary preventive therapy for individuals at risk of CVD events with the potential benefits not realised.

Pharmacoepidemiological studies suggest that, in primary prevention, statins may not achieve optimal LDL-cholesterol reduction in approximately half of treated patients within two years of initiation (Akyea). Potential explanations include early treatment discontinuation and suboptimal dosing. Increased utilisation of pharmacoepidemiology could help to understand the drivers for these findings and promote better public health strategies to ensure tailored treatments for patients so they get the maximum potential benefit.

For many years, concerns were raised regarding the risk of muscle-related adverse events associated with statin use, often fuelled by negative media coverage. A study including an observational open-label phase have shown these side-effects are likely to be caused by the nocebo effect where negative expectations around a medication cause people to experience such effects (Gupta). The earlier utilisation of pharmacoepidemiology may have helped to provide reassurance regarding the role of nocebo effects and prevented harmful effects of statin treatment cessation in patients.

Such questions, which are of major importance for public health and remain unanswered more than thirty years after this class of drugs became available, demonstrate that the investigative potential of pharmacoepidemiology has not been optimally exploited. Given that this is about preventing one of the leading causes of death worldwide, the questions listed above should have been answered clearly years ago to guide health decisions and policies. In this example, as in a few others, there are too many redundant or inconclusive studies, while major public health questions remain unanswered.

3.2.3 Label expansion

Approved medicinal products are sometimes prescribed outside their authorized indication, dose, regimen, route of administration, or target population (“off-label use”). Off-label prescribing may occur when there is unmet need (e.g., paediatric or other understudied populations), when clinical trials are ongoing, but access is limited, or when there is no approved indication and clinicians extrapolate from evidence in closely related conditions. . While off-label use is a legitimate aspect of clinical practice, it remains a prescriber-driven decision—at the discretion of the physician—and may entail greater evidentiary uncertainty and liability considerations than on-label use. Formal label updates (such as “label expansion” or “label change”) generally require a robust evidence package—often like initial approval—demonstrating that the benefit–risk profile supports the proposed change. Such label updates can take multiple forms: adding a new indication, extending use to a new population or subgroup (e.g., age, comorbidity, biomarker-defined group), revising dose/dosing frequency or route of administration, expanding or refining claims (including outcomes or endpoints), or updating warnings/precautions, contraindications, or limitations of use.

Increasingly, real-world data and real-world evidence contribute to these label changes—either as supportive evidence alongside with clinical trials or, in selected contexts, as a central component—by characterizing real-world utilization, outcomes, and safety; informing effectiveness in populations underrepresented in trials (such pregnant women or intellectual disabled individuals); providing external comparators or contextual benchmarks; and leveraging evidence from routine care, registries, or other structured real-world sources, including situations where off-label use has already generated informative clinical experience. That said, in recent years, real-world evidence has been used to support label expansion, evaluating data from off-label use as a key source. In 2019 the FDA approved extension of the label of palbociclib to include male patients with Metastatic Breast Cancer. Rarity of breast cancer in men limits the feasibility of large randomized controlled trials. During the four years after the approval for palbociclib male patients were treated off label. The real-world evidence derived from was three independent data sources: real-world data from insurance claims, a de-identified real-world data source derived from electronic health records (EHRs), and a global safety database. These were used to complement previous trial data (such as PK analysis) to confirm effectiveness and safety for male patients. The claims data was used to determine exposure (treatment patterns and duration). Using the electronic health records, researchers were able to establish real world effectiveness for male patients, and lastly the global safety database revealed no new safety signals associated with the off-label patient population (Wedam).

3.3 How interpretation of pharmacoepidemiological evidence can support decision making in public health

Section 3.1 outlined the importance and process by which existing pharmacoepidemiology evidence can be evaluated. However, the value of pharmacoepidemiology extends beyond evidence generation—its full potential is only realized through effective scientific interpretation and communication. Especially in times of crisis: clear, timely, and accurate interpretation of pharmacoepidemiological evidence is essential for informing policy decisions, empowering healthcare professionals (HCPs), and maintaining public trust.

In addition, pharmacoepidemiology studies often involve considerable complexity, both in their methodological design and data selection, but also in the interpretation of their results. Therefore, communication of complex findings must be clear, accurate, and non-misleading. Some key strategies and examples, to ensure accurate interpretation of evidence, are presented below:

- Include and explain confidence intervals, comparative data, and a frank articulation of the study's limitations alongside findings, such as uncertainty.
- Comparisons with existing data or known benchmarks.
- Provide absolute risks in addition to relative risks to contextualize potential harm or benefit.
- Clarify implications for individuals versus systems or populations.

3.3.1 Presenting risk in a meaningful way

Pharmacoepidemiological research often involves interpreting risk ratios, odds ratios, and other statistical measures. These must be conveyed in a way that is comprehensible to non-expert audiences.

- Absolute vs. Relative Risk: Relative risks (*e.g.*, "a 50% reduction in risk") can be misleading when presented alone. They should always be paired with absolute risks (*e.g.*, "*a decrease from 2 in 1,000 to 1 in 1,000*"), or better still, with an estimate of the number of cases prevented, to give a true sense of magnitude.
- Population-Level Metrics: Where findings are based on large population surveys, explain what they mean for the individual. For instance:
  "*Out of one million people vaccinated, 2 persons may experience a severe adverse events, while over 950,000 are protected from serious illness.*"
- Number Needed to Treat (NNT) / Harm (NNH): These statistics are helpful to contextualize benefit and risk:
  "*For every 100 people treated, 1 will benefit significantly, while fewer than 1 will experience a serious side effect*."
- Relatable Framing: Use plain language and familiar analogies to explain statistics. Rather than referencing "incidence rates," say:
  "*For every 10,000 people taking this medication, about 2 may experience this side effect*."

3.3.2 Explaining study strengths and limitations

The credibility of findings depends not just on what they say but on how clearly their reliability and limitations are communicated.

- Study Design: Explain the approach in lay terms:
  - "*This study followed thousands of people to see how often a side effect occurred after taking the medication*."
  - "*We analyzed health records to compare people who used the medication versus those who didn't*."

- Bias and Confounding: Acknowledge sources of uncertainty:
  - "*People taking the medication were generally healthier, which may partly explain the lower risk observed*."
- Communicating Uncertainty: Avoid overstatement by using intuitive language around confidence intervals:
  "We are 95% confident that the true risk is between 1 in 10,000 and 1 in 20,000."

3.3.3 Addressing study results in context

Pharmacoepidemiological findings are most informative when they are presented within an appropriate context, enabling audiences to better grasp their real-world relevance and significance. Isolated statistics can be misleading, whereas comparative framing enhances understanding and supports informed decision-making.

- Comparison With Baseline Risks
  Help audiences understand the magnitude of a risk by comparing it with familiar or baseline events.
  Example: "*The risk of this side effect is 1 in 10,000—lower than the annual risk of being struck by lightning.*"
- Relative Importance of Risks
  Frame the risk alongside other daily life risks to provide perspective.
  Example: "*This medication's side effect is ten times less common than developing serious complications from seasonal influenza*."
- Benefits Versus Risks
  Present a balanced view, highlighting both the therapeutic benefit and potential harms.
  Examples:
  • "*The medication reduces hospitalizations from 10% to 2% but carries a very small chance—1 in 50,000—of a serious allergic reaction*."
  • "*The vaccine prevents 95% of severe COVID-19 cases, while the risk of a serious side effect is less than 1 in a million*."

3.3.4 Addressing misinterpretations and misinformation

In times of public health crisis, pharmacoepidemiological data can be distorted—either unintentionally or deliberately—leading to public confusion, fear, or mistrust.

- Correcting Misunderstandings
  Clarify key distinctions between terms such as "association" and "causation," which are often misunderstood.
  Examples:

• "*This study identified a link between the medication and a side effect, but that doesn't prove the medication caused it. Other factors might be responsible.*"
• *"We observed a pattern, but further studies are needed to determine if there's a causal relationship."*

- Pre-empting Exaggerations
  Put findings into appropriate perspective to prevent alarmism.
  Example: "*Although the study found a doubling of risk, the overall risk remains extremely low rising from 1 in 100,000 to 2 in 100,000*."
- Providing Reliable Comparisons
  Reference findings from multiple trustworthy sources to reinforce scientific consensus.
  Example: "*These results are consistent with other studies, and regulatory authorities around the world have reviewed the data and continue to support the safety of this medication.*"

3.4 Conclusion

In summary, while urgent public health decisions may sometimes proceed without waiting for new pharmacoepidemiological data, these studies remain indispensable for evaluating real-world safety, effectiveness, and utilization of healthcare products. By systematically assessing existing evidence before commissioning new research, decision-makers can act swiftly, avoid unnecessary duplication, and ensure that policies are grounded in robust, timely insights—ultimately strengthening public health responses and optimizing patient outcomes.

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Chapter 4: Benefits of pharmacoepidemiology in anticipating and managing public health crises

This chapter provides an overview of how pharmacoepidemiological research can be used to anticipate, prepare for, and respond to public health crises or emergencies. It includes insights and use cases from past crises or emergencies where pharmacoepidemiology has played a role and offers recommendations to inform future public health planning and response strategies.

4.1 Pharmacoepidemiology in public health crises

It is important to ensure that the pharmacoepidemiological approach goes beyond purely scientific objectives, as a broader perspective is essential for effectively managing crises and supporting the rapid, informed decision-making required in these situations.

Pharmacoepidemiology plays, or, at least, should play, a critical role in public health crises by generating data-driven evidence about the use, safety, and effectiveness of medicinal products at the population level. During such crises, pharmacoepidemiological studies can help monitor the real-world impact of drugs and vaccines, detect adverse effects, and assess treatment outcomes across diverse populations. For instance, during the COVID-19 pandemic, pharmacoepidemiological studies were essential in tracking vaccine effectiveness, identifying rare side effects (like blood clot risks with certain vaccines), and guiding policy decisions on drug repurposing and vaccine and medicines evaluations and recommendations. This evidence supports regulatory bodies and public health authorities in making informed, timely decisions that can save lives and improve health outcomes (Wang, Sabate, Mohammadi, Zhou).

Pharmacoepidemiology can be pivotal particularly when the health of a population is significantly threatened by widespread disease, environmental hazards, natural or human-made disasters, or other large-scale health threats. These crises can have profound well-being, social, and economic impacts on individuals and communities (WHO). To strengthen global health resilience, stakeholders must prioritize integrating pharmacoepidemiological insights into emergency preparedness plans, policy frameworks, and rapid-response strategies.

In some cases, a public health crisis escalates into a public health emergency, which refers to an acute, immediate threat requiring urgent intervention. This designation is often officially declared by authorities to trigger governmental or institutional mobilization of resources, emergency response plans, and coordinated actions (WHO).

A range of contributing factors can trigger or exacerbate public health crises, regardless of whether they escalate to the level of declared emergencies. Examples include:

- Economic downturns and healthcare austerity policies that weaken healthcare infrastructures and services
- Deterioration of healthcare infrastructures and service, such as medicinal product shortages
- Armed conflicts, forced displacement, migrations
- Poverty, gender inequities, aging populations, and poor nutrition, unplanned urbanization, all of which may increase vulnerability to health threats (Kentikelenis, Page, Callaway, WHO).

4.2 Importance of timely, evidence-based interventions

During public health crises and emergencies, the ability to rapidly identify, implement, and evaluate health interventions is essential to anticipate a crisis, mitigating harm and protecting population health. Epidemiology and pharmacoepidemiology contribute essential real-world evidence to guide decision-making—especially when health interventions such as vaccines and therapeutics are deployed for prevention, symptom management, and mitigation of complications.

For example:

- MPOX (Monkeypox): the 2022 global MPOX outbreak highlighted the need for rapid deployment of smallpox-derived vaccines (*e.g.*, modified vaccinia Ankara, manufactured by Bavarian Nordic (MVA-BN)) and antivirals such as tecovirimat. Evidence from clinical trials and observational studies shows tecovirimat is generally safe, though its efficacy in lesion resolution remains limited; early administration may improve symptom relief in severe cases. Vaccination strategies continue to evolve to ensure equitable access and durability of protection (Karmarkar, Pipitò, Shabil).
- Anthrax: in bioterrorism or natural outbreaks, timely antibiotic prophylaxis (*e.g.*, ciprofloxacin, doxycycline) and adjunctive anti-toxin therapy are essential. CDC guidelines emphasise early initiation of antimicrobials and antitoxins to reduce mortality, particularly for inhalation anthrax and systemic disease. Systematic reviews confirm antitoxins improve survival in animal models and may benefit severe human cases (Bower, Hesse).
- Cholera: rapid implementation of oral cholera vaccines (OCVs) alongside aggressive rehydration therapy dramatically reduces case fatality rates. WHO and CDC guidance underscore oral rehydration solution (ORS) as the cornerstone of treatment, with mortality dropping from 30% to <1% when applied promptly. Preventive vaccination campaigns in high-risk regions complements these measures (CDC).

These examples illustrate that speed and evidence are inseparable during crisis response. Without robust, timely data, interventions risk being delayed, misallocated, or misused – therefore compromising public health outcomes.

4.3 Examples of public health crises and pharmacoepidemiology applications

Public health crises often expose vulnerabilities in healthcare systems and populations, creating urgent needs for evidence-based interventions. In this section, we describe some key scenarios where pharmacoepidemiology has/or can play a critical role by assessing medication use, safety, and outcomes during emergencies, informing strategies to mitigate risks and improve resilience.

4.3.1 Infectious Disease Outbreaks, Epidemics, and Pandemics

During disease outbreaks, epidemics or pandemics:

- Measles outbreaks: In 2023, an estimated 10.3 million people were infected with measles with measles outbreaks are happening in every region of the world (CDC measles)
- Meningococcal disease outbreak remains a critical public health concern due to its rapid onset, high case fatality rate, and potential for large-scale outbreaks (the Virginia Department of Health (VDH) outlines a structured response for meningococcal outbreaks, emphasising rapid case identification, immediate chemoprophylaxis, targeted vaccination campaigns and enhance surveillance and public health communication (VDH).
- Meningococcal disease epidemics:
  I. Meningitis caused 236,000 deaths globally in 2019, with Neisseria meningitidis as a leading bacterial aetiology. The highest burden occurred in low-resource settings, particularly in sub-Saharan Africa. Rising antimicrobial resistance threatens the effectiveness of standard prophylaxis and treatment, underscoring the need for continuous pharmacoepidemiological monitoring and adaptive treatment guidelines (Wunrow);
  II. Mazamay et al. provide a comprehensive review of meningitis epidemics in Africa from 1928 to 2018, highlighting: the “meningitis belt” across sub-Saharan Africa, where seasonal epidemics occur due to climatic and socio-economic factors; increasing reports of epidemics outside the belt, indicating shifting epidemiology and the need for broader surveillance; and vaccination campaigns (*e.g.*, MenAfriVac) (Mazamay).
- COVID-19 pandemic: the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began with an outbreak of COVID-19 in Wuhan, China, in December 2019. Soon after, it spread to other areas of Asia as an epidemic, and then worldwide in early 2020 constituting a pandemic) (CDC, MRF, VDH, WHO). Epidemiology and pharmacoepidemiology can be vital for the prediction of events, the rapid characterization of disease and disease outcomes, for the development of medicinal products and vaccines and its evaluation at the population-level. Among others, epidemiological and pharmacoepidemiological research allows the conduct of natural

history of disease studies, monitoring and evaluation of medicinal product/vaccine use, safety and effectiveness, repurposing of therapies, and the identification of adverse medicinal product reactions and medicinal product-medicinal product interactions in real world settings.

4.3.2 Medicinal product recalls and safety concerns

When serious safety concerns arise, pharmacoepidemiology offers a framework for assessing the public health impact of these events. It enables rapid evaluation of risk at the population level, supports evidence-based regulatory actions, and informs communication strategies to protect patients.

FDA Drug Recalls: The U.S. Food and Drug Administration maintain a comprehensive system for drug recalls, which may be initiated due to contamination, mislabelling, or safety risks. Recent recalls have included injectable products with sterility concerns and oral medications with undeclared impurities. Pharmacoepidemiological analysis helps quantify exposure, identify vulnerable populations, and guide mitigation strategies (FDA Drug recalls).

Withdrawal of Ranitidine (Zantac): In 2020, ranitidine-containing medicinal products were withdrawn globally after detection of N-nitrosodimethylamine (NDMA), a probable human carcinogen. The European Medicines Agency (EMA) referral process highlighted the importance of real-world utilisation data to estimate population exposure and inform risk-benefit decisions. (EMA).

These examples reiterate that pharmacoepidemiology is not only about scientific rigor but also about enabling swift, proportionate responses to safeguard public health when medicinal product safety is compromised.

4.3.3 Medicinal product misuse and overuse

Public health crises and emergencies may also arise from the use of psychotropic medicinal products, particularly in vulnerable populations such as individuals with dementia. Inappropriate or excessive use of antipsychotics, sedatives, and other psychotropic drugs in dementia care has been associated with serious safety concerns, including increased risk of falls, stroke, and mortality (Smith). These issues have led to national initiatives in the UK for instance to reduce unnecessary prescribing and improve monitoring (MHRA).

Chronic opioid use carries a significant risk of drug overuse and dependency, particularly when medications intended for short-term pain relief are used for extended periods. This can lead to tolerance, physical dependence, and, in some cases, misuse or overdose. The example of codeine, which is commonly prescribed for mild to moderate pain and cough suppression, illustrates the risk. While considered a “weak opioid”, prolonged or high-dose use can result in:

- Dependence and withdrawal symptoms upon discontinuation.
- Escalation to stronger opioids as tolerance develops.
- Serious adverse effects, including respiratory depression when combined with other CNS depressants.
- Public health impact, as codeine-containing products are widely available and sometimes misused outside prescription guidelines.

Policies on opioid use might not have an effect on opioid-related deaths, likely because of the illegal market (Béliveau, Goyer).

For the examples above, pharmacoepidemiology can play a key role enabling (among others):

- Monitoring of prescribing trends
- Identifying factors associated with overuse
- Causal analyses linking exposure to adverse outcomes
- Evaluation of harm-reduction interventions and treatment effectiveness

By analysing drug utilization and associated outcomes, it helps quantify risks, inform clinical guidelines, and design interventions to optimize medication use and improve patient safety.

4.3.4 Medicinal product resistance

Medicinal product resistance involves the reduction in effectiveness of a medication, such as an antimicrobials or an antineoplastic in treating a disease or condition. Examples of antimicrobial resistance include antibiotic resistances (*e.g.*, antibiotics resistance due to excessive human use or utilization in animal production and not respecting doses or intervals of use) or antiviral resistance. Antineoplastic resistance is the resistance of neoplastic (cancerous) cells, or the ability of cancer cells to survive and grow despite anticancer medicinal products. Here again, the contribution of pharmacoepidemiology can be crucial, in terms of preventing, understanding and managing medicinal product resistance, for example by analysing levels and patterns of use at population level and their association with specific resistance patterns (Chiang).

4.3.5 Medicinal product shortages

Shortages during outbreaks/pandemics may lead to reduced access or rationing with consequences, if the shortage lasts and is not counterbalanced by sufficient stocks, which can be dramatic in terms of public health medicinal products. Pharmacoepidemiology in these pre-crisis or crisis situations can, for example, quantify impacts of the shortage on population health, identify vulnerable groups that should be given priority, and evaluate alternative strategies, pharmacological or not (Santhireswaran).

4.3.6 Environmental disasters and climate emergencies

The link between pharmacoepidemiology and earthquakes, floods, hurricanes, extreme temperatures, or chemical and radiological exposures may seem a long way off, but these events can disrupt communities, displace vulnerable populations, hamper the delivery of continuous and coordinated healthcare, especially among persons with serious or chronic health conditions. In addition, extreme heat and air pollution can interact with medicinal product exposures to adversely impact health outcomes at the population-level. The intentional or unintentional release of chemical and/or radioactive agents to the environment may also result in public health crises and/or emergencies when affecting communities and human health.

4.4 How to anticipate, prepare for, and respond to public health crises and emergencies

For decision-makers involved in public health and medicinal products evaluation, there is a critical need for appropriate and robust evidence that can be used to lay the foundation to promptly and equitably prevent, respond, and mitigate a public health crisis or emergency.

Table I summarizes the 10 stages of a public health crisis or emergency, from the first warnings that could be drawn from experience and available information to the onset of the crisis itself or a health emergency. These stages are then compared with the three general objectives of the epidemiological studies, namely description, prediction and inference, showing how different types of pharmacoepidemiological studies can generate data to prevent, detect, monitor and assess the impacts of a crisis or emergency. The last section reviews a series of historical and current examples illustrating how pharmacoepidemiological evidence from all stages has been used to optimize decision-making and minimize the impact of the crisis or emergency.

Table I. Pharmacoepidemiological study types and objectives reported across the 10 stages of a public health crisis or emergency.

Stage of public health crisis or emergency	Broad Overview of Pharmacoepidemiology Study Objectives		
	Description	Prediction	Inference
1. Reflection and learning from past experiences	Burden of disease Disease profiling Case Reports Case Series Cross-sectional studies Medicinal product utilization		
2. Define unmet medical needs	Burden of disease Disease profiling Case Reports Case Series Cross-sectional studies Medicinal product utilization		
3. Detect the public health crisis or emergency and the population affected	Spontaneous reporting Disease Surveillance Public Health Surveillance		
4. Monitor the public health crisis or emergency	Geospatial analysis	Projections of disease based on predictive models	

Stage of public health crisis or emergency	Broad Overview of Pharmacoepidemiology Study Objectives		
	Description	Prediction	Inference
and estimate the magnitude			
5. Predict and pre-empt (and modelling)		Forecasting studies (transmission, uptake of medical interventions)	Simulation modelling of intervention impacts
6. Intervention development	Burden of disease (identification of high-risk populations)	Predictive models (identification of high-risk populations)	Uncontrolled trials Randomised controlled trials: a) Placebo-controlled trials with individual randomization b Individually randomized trials with delayed intervention as control group Pragmatic Clinical trials c) Placebo-controlled trials with cluster randomization d) Single-arm trials with historical external comparator Non-randomised trials Community trials
7. Intervention implementation and development	Monitoring Uptake		
8. Intervention monitoring and evaluation		Ecological study	Cohort study (prospective or retrospective) Case-Control Study

Stage of public health crisis or emergency	Broad Overview of Pharmacoepidemiology Study Objectives		
	Description	Prediction	Inference
			Case-Crossover Study Case-Time-Control Study Case-series Single-arm registry study with contemporaneous external comparator Test-negative case control effectiveness study Ecological study Survey Quasi-experimental study (e.g., controlled interrupted time series) Drug-drug interaction studies
9. Interpret & communicate the impact of RWE and science in public health crises or emergencies			Systematic Literature Review Meta-analysis Cross-Sectional Study
10. Contribute to assessment and harmonization of totality of evidence in public health crises or emergencies	Pharmacoepidemiological evidence can inform the development of guidelines and public health recommendations.		

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In public health crises or emergency contexts, the design of pharmacoepidemiological studies must be both agile and pragmatic. Rapid decision-making is essential, often requiring a balance between methodological rigor and the urgency of public health needs. Before initiating a study, it is crucial to assess the quality and appropriateness of data sources, evaluate feasible methodological approaches, and consider the time constraints that may influence study design and study conduct. The following table outlines the key stages and considerations in this process, providing a structured framework to guide study planning under public health crises or emergency conditions.

Table II: Key stages of study planning

Stage	**Description**
Preliminary Data Review	Search for historical or accessible data on disease, treatment, safety, alternatives, and population characteristics.
Feasibility and Approach Comparison	Compare feasibility, advantages, and limitations of study approaches including randomization or pseudo-randomization, considering situational constraints and available resources.
Time and Practicality Considerations	Consider time required to execute study; prioritize speed of results over internal validity if necessary.

4.5 Practical and ethical considerations in pharmacoepidemiological studies during public health crises or emergencies

There are several practical and ethical considerations that must be addressed when designing pharmacoepidemiological studies during such events.

4.5.1 Availability and types of data

One of the first questions to address is whether historical or real-time data are available on the key aspects of the public health problem. These aspects include:

- The disease or condition causing the crisis,
- The health intervention or treatment under study,
- The population characteristics, such as comorbidities, demographic profiles, and social determinants of health.

When existing data is not sufficient, researchers must assess whether prospective data collection during the crisis is feasible. This may involve establishing new surveillance systems or embedding data collection into clinical workflows—both of which are constrained by time and resources.

4.5.2 Feasibility and ethics of randomization

If prospective data collection is possible, it becomes important to consider whether randomized controlled trials (RCTs) can be ethically and practically implemented. In some situations, such as during early phases of an outbreak or when no standard treatment exists, randomization may be appropriate. However, in the context of widespread morbidity or mortality, the ethics of withholding treatment from a control group or delaying access may preclude an RCT. In such cases, non-randomized study designs may be more appropriate and ethically sound.

4.5.3 Timeliness of evidence generation

The urgency of public health decision-making often necessitates expedited evidence generation. While RCTs provide high internal validity, they typically require more time and controlled conditions that may not be compatible with the dynamic nature of crises. In contrast, observational studies—particularly those using real-time or near-real-time data—can yield more timely insights. These studies may sacrifice some control over bias and confounding, but offer faster answers to urgent questions, which can be more useful in guiding real-time public health responses.

In public health emergencies, interim results may need to be disseminated rapidly to inform urgent decisions. However, these must be clearly labelled as preliminary, framed with explicit explanations of what is known, what remains uncertain, and what the next steps are. This helps prevent premature conclusions or misinterpretation by the public and media.

4.6 Uses of pharmacoepidemiology in public health crises or emergencies

The widespread adoption of pharmacoepidemiological research over the past forty years, the availability of high-level expertise in this field, and the existence of particularly diverse and powerful investigative tools, which are now widely available, are extremely valuable assets for the prevention and optimized management of health crises and emergencies involving healthcare products. Although this potential is not often enough harnessed and, when it is, not always in a consistent and optimal manner, in many cases it has made a major contribution. Several examples of pharmacoepidemiological evidence are presented below to illustrate this point.

1.6.1 Data on the efficacy and safety of vaccines and medicinal products during the COVID-19 pandemic

Between December 2019 and May 2023, during the viral pandemic caused by SARS-CoV-2, pharmacoepidemiology played an essential role in optimizing public health policies aimed at protecting the global population as quickly and effectively as possible. The challenge was to assess, in real time and under real-world conditions the efficacy, safety and the benefit-risk of the medicinal products and vaccines proposed or used as they were administered to hundreds of millions of people.

A prime example was the vaccine efficacy study conducted between December 2020 and February 2021 using data from the Clalit Health Service, one of the largest health services in Israel, which was one of the first countries to opt for the most comprehensive immunization of its population. The study, which involved nearly 1.2 million people divided into two equal groups (vaccinated, one or two doses, and unvaccinated), confirmed (1) the efficacy of the main mRNA vaccine against symptomatic forms of COVID-19, particularly severe forms (hospitalizations and deaths), and (2) the benefit of a booster dose; with hospitalization rates reduced by 62% with one dose and 87% with two doses. These two key findings have been used to define or refine vaccination strategies in many countries (Dagan).

At the same time, several pharmacoepidemiological studies have helped to better characterize the SARS-CoV-2 pandemic, the conditions and the benefit-risk balance of treatments in this context, and the natural history of the disease, and to identify the sub-populations most at risk (Epi-Phare).

In synergy with pharmacovigilance systems, they have also made it possible to quickly identify and characterize several adverse effects associated with the treatments and vaccines used against COVID-19. First and foremost, those associated with vaccines, by far the most widely used medicinal products: anaphylactic reactions, thrombosis with thrombocytopenia syndrome (TTS), cases of myocarditis and pericarditis associated with mRNA vaccines (Comirnaty, Spikevax), etc. (Heidecker).

- Vaccine-induced immune thrombocytopenia (VITT) is a rare but serious immune reaction to adenoviral vector COVID-19 vaccines. Extreme activation of platelets and the coagulation system lead to a high risk of death from venous or arterial thrombosis or secondary haemorrhage (Greinacher, Schultz)
- Although generally benign, post-vaccination myocarditis can, in rare cases, be complicated by heart failure, mainly the left ventricle, or cardiac arrythmia. Pharmacoepidemiological studies have quantified this risk, described the progression of the condition and shown that the frequency of this complication varies greatly according to gender and, above all, age, with the highest rates observed in men aged 12 to 39 years. This information has been invaluable in better assessing the safety profile of vaccines in different population subgroups and in refining vaccination strategies.

1.6.2 Ebola epidemics: evaluation of treatments and vaccines

Ebola virus disease is associated with a high case fatality rate. It mainly affects populations in West and sub-Saharan Africa. The disease is transmitted through contact with the bodily fluids of an infected, sick or deceased person.

Following the major epidemic of 2013-2016 (28,000 cases and 11,000 deaths recorded) that affected West Africa (Guinea, Liberia and Sierra Leone) and the 2018-2020 epidemic in the Democratic Republic of Congo, two potential treatments were tested (PALM trial) and then approved:

- Inmazeb, comprising three monoclonal antibodies (atoltivimab, maftivimab and odesivimab-ebgn) and approved in the United States in October 2020,
- Ebanga, a human monoclonal antibody (mAb114) approved in the United States in December 2020 (FDA).

In addition, two vaccines specific to the Zaire Ebola virus were currently authorised in several countries based on non-traditional ring-vaccination trials, mimicking the public-health response in contrast to other individually randomized double blinded vaccine efficacy trials.

- Ervebo, a live recombinant vaccine administered in a single dose by intramuscular injection. More than 40,000 people were vaccinated with Ervebo in the DRC during the 2018-2020 outbreaks [32] (Henao-Restrepo).
- Zabdeno and its booster component Mvabea; recombinant vector vaccines, administered in two doses and authorised (marketing authorisation under exceptional circumstances) in the European Union in 2020 (Ishola).

Both Ervebo and Zabdeno are subject to regulatory risk management plans and ongoing efficacy and safety monitoring. However, beyond regulatory frameworks, epidemiological and pharmacoepidemiological studies have played a crucial role in improving our understanding of Ebola virus disease (EVD). These studies have helped characterize epidemic patterns, identify risk factors for transmission, and inform the development of transmission models critical to outbreak forecasting and control strategies.

Epidemiological investigations during major Ebola outbreaks—particularly the 2014–2016 West Africa epidemic and more recent outbreaks in the Democratic Republic of Congo—have shed light on disease dynamics, routes of transmission, and the role of community behaviours. These findings informed not only vaccine deployment strategies but also public health interventions such as contact tracing, isolation, and safe burial practices.

Pharmacoepidemiological studies, which focus on the use and effects of medical products in large populations, have been instrumental in evaluating the real-world effectiveness and safety of vaccines such as Ervebo (rVSV-ZEBOV) and the two-dose Zabdeno/Mvabea regimen. For example, the "ring vaccination" trial conducted in Guinea provided compelling evidence of Ervebo’s efficacy and helped shape emergency use protocols and later regulatory approvals.

Post-marketing surveillance and observational studies continue to monitor vaccine performance, adverse events, and long-term protection, contributing to risk-benefit assessments.

Ultimately, these studies have not only supported the licensure and rollout of Ebola vaccines but have also strengthened public health decision-making, improved outbreak response capabilities, and built a foundation for future epidemic preparedness (Henao-Restrepo, Ishola).

4.7 Environmental disasters, climate crisis, and healthcare access and outcomes

Pharmacoepidemiology offers a valuable lens through which to study and address the impact of environmental disasters and climate-related hazards on public health. This includes identifying vulnerable populations, describing the effects of environmental disruptions on healthcare delivery, and evaluating the interaction between climate stressors and medication use. Moreover, pharmacoepidemiological methods can support the evaluation of mitigation strategies aimed at reducing health risks linked to climate and environmental crises.

4.7.1 Heat waves

Certain populations, people under aged 5 or the elderly, particularly those with pre-existing conditions such as cardiovascular disease or diabetes, are more vulnerable to heat waves due to impaired thermoregulation and fluid or electrolyte imbalances. Furthermore, medications such as insulin or diuretics may exacerbate the risk of adverse health outcomes during periods of extreme heat.

Pharmacoepidemiological research has been instrumental in understanding these interactions. For example, Visaria conducted a time-stratified case-crossover study to evaluate the association between high heat index and the odds of hypoglycemia among older adults using insulin in the United States and Taiwan. The study found a statistically significant increase in hypoglycaemia risk during period of extreme heat in both countries (Visaria).

Additional studies further highlight the risks and interactions between climate extremes and medication use:

- Ou showed how maternal exposure to extreme heat events during early pregnancy has been linked to congenital heart defects (CHDs), and this study examined whether thermoregulation-related medications modify that risk. While most medications showed no significant interaction, drugs that alter central thermoregulation significantly increased CHD risk in the Southwest U.S., suggesting a need for further research. (Ou)

- Deters described how psycholeptics, psychoanaleptics, and cardiovascular drugs can affect heat tolerance when comparing poison centre data during heat years and non-heat years to assess overdose severity. While accidental exposures were more frequent during heat waves, severe symptoms were less common, though careful monitoring was advised as these drugs impair normal cooling mechanisms (Deters).
- Layton explained that heatwaves significantly increase heat-related hospitalizations among older adults with chronic conditions, and certain medications like diuretics, antipsychotics, and beta blockers further elevate this risk even without heatwaves. No strong synergistic interaction was found between heatwaves and these medications, but careful monitoring during summer months was recommended (Layton).

These findings underscore the importance of considering both environmental and pharmaceutical exposures in public health planning, especially as global temperatures continue to rise.

4.7.2 Severe weather events: Flooding and hurricanes

Severe weather events such as flooding and hurricanes can lead to public health emergencies by disrupting health systems, affecting access to essential treatments for chronic conditions like end-stage renal disease or cancer. Pharmacoepidemiological studies have examined the impact of these disruptions on healthcare utilization and long-term outcomes.

A notable study by Nogueira assessed the survival of U.S. patients undergoing radiotherapy for nonoperative locally advanced non–small cell lung cancer during hurricane-related disaster declarations. Using propensity score matching within the National Cancer Database, the study found that survival was significantly worse among those actively receiving treatment at the time of a hurricane disaster declaration compared to similar patients not exposed to such disruptions (Nogueira).

Other relevant investigations include:

- Remigio showed that inclement weather events such as rainfall, snowfall, hurricanes, and wind advisories were associated with an increased risk of missed haemodialysis appointments, with the strongest effects observed on the day of the event. These impacts persisted for several days, with hurricanes and wind advisories showing the highest cumulative risk over a week (Remigio).
- Rivera-Hernandez described how Hurricane Maria led to a significant increase in dialysis patients migrating from Puerto Rico to receive treatment elsewhere, while the number of patients dialyzed on the island dropped notably. However, mortality rates did not show significant changes, suggesting effective emergency preparedness and support for patients with kidney failure (Rivera-Hernandez).

- Fanny found that after Hurricane Harvey, paediatric emergency and urgent care visits showed increased odds of trauma, dermatological complaints, and toxicological emergencies compared to pre-hurricane and seasonal trends. These findings underscore the need for targeted paediatric disaster preparedness, including medication resources and public health education (Fanny).

These studies demonstrate how extreme weather events not only delay care but also may directly impact patient prognosis.

4.7.3 Earthquakes and tsunamis

Earthquakes and tsunamis pose unique challenges to healthcare continuity, particularly in regions with high disaster risk. For example, the 2011 Great East Japan Earthquake and subsequent tsunami significantly disrupted medical infrastructure and medicinal product supply chains.

Following this disaster:

- Patients with chronic diseases such as hypertension and diabetes experienced deteriorations in health due to impaired access to medicinal products and the loss of medical records.
- Pharmacists played an essential role in bridging gaps in care—supplying necessary medicinal products and assessing medicinal product needs during the subacute and chronic phases of the disaster response.

Studies exploring this include:

- In the review of health needs after the Great East Japan Earthquake, Ochi found that chronic conditions like hypertension and diabetes posed the greatest burden early on, worsened by loss of medications and records. Vulnerable groups included the elderly, disabled, and those with mental health issues, highlighting the need for better coordination and contingency planning for future disasters (Ochi).
- Hashimoto also described Pharmacists role. At Minamisoma Municipal General Hospital they played a critical role in maintaining drug supply and managing increased demand for chronic disease medications after the Great East Japan Earthquake, despite severe logistical and psychological challenges. The study emphasizes the importance of defining pharmacists' roles and establishing robust drug logistics systems for disaster preparedness, especially for vulnerable older populations (Hashimoto).
- Yakamoto describes how after the Great East Japan Earthquake, severe infrastructure damage disrupted medical services, and pharmacists played a vital role in disaster relief by managing medications, hygiene, and supporting self-care. The experience highlighted the need for coordinated disaster response systems and adaptive management strategies to address chronic disease care during large-scale emergencies.

These examples highlight the indispensable role of pharmacoepidemiology in disaster preparedness, continuity of care, and post-disaster recovery efforts.

4.8 Further Opportunities for Pharmacoepidemiology to serve Public Health

Despite its growing importance, pharmacoepidemiology has not yet achieved its full potential in informing public health decisions. The field has historically been shaped by the needs of the pharmaceutical industry, as well as regulatory and reimbursement authorities and public health agencies. In some instances, the use of pharmacoepidemiology by public health agencies (e.g. WHO, ECDC, CDC) assessing the effects of medicinal products such as vaccines, or public health interventions use pharmacoepidemiological methods and data sources however, they may not strictly refer to this research as "pharmacoepidemiology" but rather "epidemiology". Where pharmacoepidemiology is typically mentioned, much of the current evidence generation and decision-making infrastructure is geared towards:

- Regulatory submissions (*e.g.*, benefit-risk assessments)
- Safety monitoring and pharmacovigilance
- Market access and pricing
- Health technology assessments (HTAs)

This orientation often narrows the scope of research questions and outcomes, limiting their relevance to broader societal or population health priorities. There is a unique opportunity to apply pharmacoepidemiology to public health crisis.

4.8.1 Reframing policymakers

One fundamental gap lies in how we conceptualize “policymakers.” In a public health context, policy makers extend far beyond regulatory authorities and health agencies. They include:

- Patients and caregivers making medication decisions
- Health care providers and hospital managers
- Community leaders and advocacy groups
- Insurance providers and non-governmental organizations

Each of these actors influences health outcomes and resource distribution. To truly support public health, pharmacoepidemiological evidence must be accessible and meaningful to this wider spectrum of decision-makers.

4.8.2 Limitations in accessibility and usability

Even when robust studies are conducted, their results are often not readily accessible to those outside scientific, regulatory, or industry domains. This can limit:

- Patient and provider participation in shared decision-making
- Informed choices at the population level
- Trust in health interventions, especially during crises

The current framework too often assumes that downstream communication will bridge this gap—when in fact, study designs and outputs should be conceived with broader accessibility in mind from the outset.

4.8.3 Impact analysis: Quantifying the gaps

Several structural challenges illustrate how public health priorities can diverge from the industry-focused pharmacoepidemiology paradigm:

- Indication-Based Approvals vs. Societal Needs: Many medicinal products are approved for narrow indications, even when larger-scale public health applications might exist but lack economic incentives.
- Focus on Marketable Conditions: Pharmaceutical research tends to prioritize diseases with high return on investment, overlooking neglected conditions that disproportionately affect marginalized populations.
- Underutilized RWD for Population-Level Decisions: While real-world data (RWD) is increasingly used for regulatory purposes, its potential for addressing social determinants of health or disparities in care remains underexplored.

To close these gaps, pharmacoepidemiology must increasingly integrate public health equity, patient-centred outcomes, and context-sensitive communication into its core frameworks—expanding its relevance beyond regulatory compliance to real-world population impact.

4.9 Conclusion

Pharmacoepidemiology is a cornerstone for effective public health crisis management and prevention. By generating timely, real-world evidence, pharmacoepidemiological studies enable decision-makers to anticipate, prepare for, and respond to emergencies ranging from infectious disease outbreaks to medicinal product shortages and environmental disasters. The discipline's value is especially evident in its ability to monitor the health impacts of crises on vulnerable populations, such as patients with chronic diseases, who often experience deteriorations in health due to impaired access to medicinal products and loss of medical records during disasters. In these contexts, pharmacists play an essential role in bridging gaps in care—supplying necessary medicinal products and assessing patient needs throughout the subacute and chronic phases of disaster response.

Pharmacoepidemiology can support rapid, evidence-based interventions, guides resource allocation, and informs communication strategies that maintain public trust and optimize health outcomes. The chapter underscores the importance of agile, ethically sound research and cross-sector collaboration to safeguard public health. Ultimately, harnessing the full potential of pharmacoepidemiology strengthens resilience, improves crisis response, and ensures that public health actions are grounded in robust, actionable evidence.

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Chapter 5. When a pharmacoepidemiological study is not a good approach

5.1 Introduction

From the perspective of academic research, dismissing the opportunity to conduct a pharmacoepidemiological study may seem counterproductive, if not opposed to the very principle of the scientific approach. The aspiration to enhance knowledge, the drive or necessity to publish, the development of new methodological tools, and the incentives provided by an ever-growing number of scientific journals all explain the considerable and continually increasing volume of publications on medicinal products, which can make it difficult to tackle a particular subject.

From the perspective of scientific research and hypothesis testing, only mediocre studies with questionable results, or those that fail to adhere to ethical standards, should be censored, even if the ever-increasing competition in the publication market means this is not always the case. In practice, despite the policy promoted by some journals, the added value of a study and the potential public health impact of its results or conclusions are not always the most prioritized criteria.

From a public health perspective, and particularly at the level of decision-making, the situation may be different:

- (i) From a decision-maker's point of view, many published studies, even in respected journals, do not provide information that would be necessary to have an overall view of a problem. For example, if providing minimal new insights, focusing only on a narrow aspect of the problem (*e.g.*, studies conducted in sub-populations or assessments limited to a specific effect or risk), or lacking robustness in their results and conclusions.

- (ii) While certain topics are addressed by dozens of redundant studies, major questions remain unanswered or insufficiently explored. For example, hormone replacement therapy (HRT) during menopause is a pertinent case. To use or not to use an HRT and, if so, for how long is a debate that affects hundreds of millions of women, yet there is no comprehensive study that adequately balances the expected benefits (*e.g.*, symptoms associated with menopause, reduced risk of osteoporotic fractures) against the possibly associated risks (*e.g.*, increased probability of breast cancer and stroke). (NHS) Due to this difficulty of addressing the issue comprehensively, based on facts and objective measures, completely opposing positions are being taken, ranging from extreme caution due to a possible increased risk of breast cancer to recommendations for widespread use.

Similarly, while there is a consensus regarding the use of statins in people at high cardiovascular risk or for secondary prevention, numerous studies - of varying quality and with conflicting results - focused on the use of statins for cardiovascular prevention in low-cardiovascular risk individuals. In the absence of a large-scale and global study that has weighed up the benefits and adverse effects in such a population over the long term, rather than settling the debate, this plethora has generated confusion with controversies that have persisted for more than 35 years after these medicinal products were first marketed. This is particularly unfortunate given that this is a major public health issue, considering the burden of cardiovascular disease and mortality on one hand and, on the other hand, the disadvantages that could arise (adverse effects, cost) from exposing a much larger population whose baseline risk remains low (Abramson & Erratum, Zhang).

- (iii) In some cases, the publication of a study may not only fail to advance knowledge but may also make a situation more complex or provoke or worsen a crisis without providing the information necessary to address it effectively. This is particularly true for highly sensitive areas such as vaccines, oral contraception, and health issues in young children. The so-called "pill scare" following the announcement of an increased cardiovascular risk in women using third-generation contraceptives, reported in paragraph 5.2.3, is a good example. Even if the results and conclusions of the study that triggered the crisis are subsequently found to be inaccurate, exaggerated, or even downright fraudulent, the effects of the damage can take a very long time to disappear. A typical example are the fear and mistrust of vaccination that followed A J Wakefield's assertion of a link between autism and vaccination against MMR. (Wakefield) Despite a near consensus on the absence of causal relationship and the discovery of serious flaws in the initial publication that led to its retractation by the scientific journal, the rumour, based on what should be considered, until further notice, a spurious association or a fake, is far from dead and is still fuelling the anti-vaccine controversy.

More generally, such a situation can also be caused by studies set up under media or political pressure and therefore carried out in too short time or/and using recorded data that do not provide sufficiently reliable information to characterize exposure and, above all, the outcome making the situation even more tricky to manage.

5.2 Situations where a study could or should not be conducted

As outlined above, the following considerations pertain to the framework established by the CIOMS XV Working Group: optimizing the use of the pharmacoepidemiological approach to support public health and decision-making.

Within this context, the resources available - very limited relative to the breadth of issues to be addressed - must be optimized and, therefore, prioritized. From this point of view, it is not justified to invest time and resources in studies that, a priori, are unlikely to provide results that will advance our understanding of the problem, whether they are irrelevant or not very robust.

With this in mind, the first step is to consider situations where it is *a priori*, preferable not to pursue a pharmacoepidemiological study.

The most obvious situation, which will therefore not be detailed, is when the study that would be able to answer the question is simply not feasible. For instance, when the required data is unavailable, inaccessible, or too complex to analyse within a reasonable timeframe. This point, which obviously concludes the debate, will not be detailed in this chapter, which focuses on situations in which a study appears feasible but does not seem to be a good option or, at least, a priority. This issue has also been extensively addressed in a previous CIOMS publication.[6] It should simply be noted that situations in which it is technically impossible to conduct a study or modelling that could provide an answer are rare in practice.

For the reasons mentioned above, the present chapter only looks at the situation from the outset and addresses the two following questions: "*Is it really justified to set up a study*?" and, if so, "*What will be its limitations and what could be the adverse consequences?"* It is clearly beyond its scope to discuss here the reasons for preferring one type of study design or statistical analysis over another, and even less the major concern of fraud and misconduct.

The situations described below are given as examples and do not aim to provide an exhaustive review of a multifaceted, complex, and potentially contentious topic. Instead, they serve to illustrate this often overlooked yet critical aspect of good pharmacoepidemiological practice from the perspective of public health and decision-making.

In fact, these seven situations address different types of issues: those relating to the relevance of conducting a study in a given situation, those arising from the limitations and constraints that such a study would impose, and, finally, those relating to its feasibility.

5.2.1 The study would delay or complicate a decision when sufficient information is already available

Carrying out a study should not be used as a pretext for passing the buck and postponing a public health decision that could already be made based on existing information or simple common sense.

Suspending a public health decision until a study is completed assumes two critical conditions:

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[6] The various aspects of the feasibility of a pharmacoepidemiological study are, for example, extensively detailed in the CIOMS publication: Real-world data and Real-world Evidence in Regulatory Decision-making (Geneva 2024).

(i) The information needed to make a decision is not already available, either directly through existing studies or indirectly through modelling, or is not sufficiently complete or reliable, and

(ii) The planned study could, in principle, provide, within an acceptable timeframe, this information.

When these two conditions are not met, conducting such a study risks:

a. Wasting valuable resources and skills, which remain scarce.
b. Delaying critical decisions, due to the time required to design and carry out the study. This delay could have harmful public health consequences, such as postponing the availability of a promising health product, delaying the launch of a vaccination campaign or, conversely, maintaining a medicinal product on the market when its benefit/risk balance appears to be questionable.
c. Making the decision-making process even more complex if, for example, the study - after being presented as the oracle on which everything depends - proves inconclusive, or if the health or media landscape becomes more urgent or contentious during the delay. In most cases, reasoning grounded in common sense can determine whether the delay required to "find out more" is acceptable from a public health perspective. Rather than drawing on numerous historical examples, we can cite two recent issues:

- *Early availability of COVID-19 vaccines:* As it is often the case, clinical trials left some uncertainties, particularly regarding the safety profile of COVID-19 vaccines for certain rare events or the benefit for specific sub-groups. These fears led to questions and controversies. However, modelling based on clinical trial data, epidemiology of the disease and data from other vaccines could already lead to the conclusion that the potential negative impact was, in any case, unlikely to outweigh the expected benefits in terms of public protection (*e.g.*, the number of deaths and hospitalizations avoided). In this context, it would have been undoubtedly a mistake to delay vaccine availability to allow time for additional studies of potentially questionable added value. Instead, it was crucial to accompany the worldwide rollout of these vaccines with targeted surveillance to continuously reassess their benefit-risk balance.
- *Long-term use of benzodiazepines and risk of dementia:* A notable controversy concerns the potential increased risk of dementia among elderly benzodiazepine users. In June 2024, the PubMed database listed 47 studies on this topic, with contradictory findings, as well as four meta-analyses, none of which was able to resolve the debate definitively. In such cases, the added value of conducting yet another study is likely low or non-existent. However, common sense provides a clear basis for decision-making:

  Alzheimer's-type dementia is a serious and prevalent condition with no recognized effective treatment currently available studies that have reported an association between benzodiazepines and dementia point to prolonged use (over 6 months), which contravenes with international guidelines recommending a maximum duration of 12 weeks.

In this case, a medicinal product-utilization study, which could be implemented quickly, would suffice to estimate the proportion of benzodiazepine users in a specific country who fall into the potentially at-risk category by exceeding the recommended duration of use. This would allow for targeted interventions under the precautionary principle, without the need for additional, and probably inconclusive studies.

5.2.2 The study duplicates existing research without providing significant added value

In academic research, having multiple studies on the same topic can be valuable, particularly for gaining deeper insights, confirming or not a result or achieving more robust results through approaches like meta-analysis. "*Consistency of result on replication is perhaps the most important criterion in judgments of causality*".

This can also hold true in public health and decision-making, but *only if* the expected added value of the study is substantial enough to advance knowledge, resolve ambiguities, or provide conclusions robust enough to enable decision-making or the dissemination of critical information that was previously unattainable.

Otherwise, conducting such a study may result in wasting valuable resources - both skills and funding - that could be more effectively allocated to other pressing needs. Additionally, if its results are inconclusive or ambiguous, it could contribute to confusion, increase information "entropy", or delay critical decisions due to the time required for its completion without offering meaningful insights (see Point 5.2.1 above).

This remark also applies to some post-marketing studies requested by a health authority from a manufacturer when the information provided by the trials and studies carried out during the development phase seems, for the most part, to answer the question. If this is not the case, the missing information and weaknesses of the studies already carried out must be clearly identified in order to design a protocol capable of answering all the missing points and to supplement information available rather than duplicating what has already been done.

5.2.3 The study could trigger or exacerbate a public health crisis or obstruct public health action

As highlighted above, initiating a pharmacoepidemiological study without clear justification may, in some cases, make the management of a health or media crisis more complex, or decision-making more challenging. There are also instances where the study itself may generate a crisis or hinder, event prevent, beneficial public health actions. This may be the case, among many examples, of media coverage of a safety study conducted on a medicinal product without a reference group or time-window allowing comparison, or without the possibility of balancing the results with what would have happened in the absence of treatment.

For these reasons, before setting up a study project, it is essential to not only ask, "What could be the added value of this study?", but also systematically consider, "What are the potential harmful consequences, from a public health perspective, of conducting this study and/or publicizing its results?".

As a general rule, in a sensitive situation, any inappropriate or poorly designed study - or one with ambiguous conclusion – is likely to generate or worsen a crisis, foster suspicion, or hinder public health actions.

For instance, consider an immunization campaign launched in a context of significant vaccine hesitancy. In the absence of clear communication, a study designed to gather additional information on the real-world effectiveness or safety of a vaccine could be perceived not as a wise practice but as an admission that the clinical development process was incomplete, that many uncertainties remain as to the efficacy and safety of the vaccine and that the general population is in fact being used as experimental material.

Similarly, as mentioned above, when a study aims to identify, and further characterize an adverse event, it is crucial to have information that put this risk into context, for example by balancing it with a reliable and credible measure of the benefit that the medicinal product brings, or will bring, to the population. For example, this could involve comparing the frequency of adverse event with the number of cases of the disease expected to be prevented by a vaccination campaign.

The same principle applies to a study focusing solely on benefits without addressing any associated risks. Such an approach would not only hinder a comprehensive assessment of the benefit/risk balance of the intervention but could also undermine efforts to fully and objectively inform the public and healthcare professionals. Moreover, it might generate suspicion and fuel the spread of rumours about the safety of the product. Obviously, this should not be used as an excuse to refrain from conducting studies whenever the context is sensitive. On the contrary, these situations call for reliable and up-to-date data for effective management. However, before proceeding it is essential to return to the two key questions mentioned above:

- "What could be the added value of this study?", and
- "What could be the potential harmful consequence of conducting it and making it public?".

Indeed, sometimes it is not the study itself that can generate a misunderstanding or even a crisis, but the way in which its results or conclusions are interpreted or made public. For greater clarity and as mentioned in point 3.3 (Chapter 3), in terms of decision-making and communication in public health, results should be expressed, whenever possible, in absolute rather than relative values. Thus, rather than a relative risk that provides little information on the impact of the strategy, the chosen indicators should quantify the risk incurred by a person, or the number of cases prevented or induced in a population. Thus, to say that a treatment reduces or increases by a factor of 4 the probability of a disease occurring corresponds, depending on the value of the baseline risk, to a major or, on the contrary, negligible difference. Based on 100,000 people treated, this reduction by a factor of 4 equates to 75 cases prevented if the baseline risk is 1 per 1,000 for the period and 1,500 cases if the risk is 2 per 100.

In pharmacoepidemiology, the communication of results, as soon as the subject is sensitive, must always take into account the risk of misinterpretation and its possible consequences. For example, in the mid 90' in Europe, notably in the United Kingdom and Norway, the announcement of the results of a study showing a higher cardiovascular risk in women using so-called third-generation oral contraceptives caused a panic, a "pill-scare", that led to a significant number of unwanted pregnancies (Skjeldestad).

5.2.4 The study does not a priori provide the necessary guarantees to ensure the reliability or credibility of the results and conclusions

This restriction, which may relate to the scientific competence or intellectual independence of the authors, is obviously not exclusive to the public health and applies to all studies, observational or not, whatever the context. It does, however, constitute a fundamental prerequisite. The multifactorial and complex nature of the issues being addressed, the analysis of data often recorded for another purpose, as well as the challenges in analysing and controlling potential biases, necessitate that the study ensures the requisite expertise. This includes epidemiological, pharmacological, statistical, and clinical competencies, which are critical for designing the study appropriately, as well as for collecting, analysing and interpreting the necessary data.

Pharmacoepidemiology is a science requiring both theoretical and practical expertise, along with extensive experience in addressing its unique methodological challenges and potential pitfalls. Except for very straightforward investigations, one does not simply "become" a pharmacoepidemiologist. Even the disproportionality analyses carried out on pharmacovigilance report case databases, which appear to be quite straightforward, require a great deal of experience in controlling biases to avoid generating aberrant or irrelevant results (Fusaroli).

Moreover, the study's investigators or its scientific advisory board should include experts knowledgeable about the exposures (*i.e.*, health products) and the outcomes under investigation (*e.g.*, indications, clinical events) to minimize the risk of design flaws (*e.g.*, inappropriate study population, evaluation criteria, or time-windows) and interpretation errors.

These recommendations are essential for subjects at high risk of controversy (*e.g.*, vaccination) or in crisis or potential crisis situations (see Chapter 4). In such cases, it is crucial that if the decision is taken to carry out a study, it should be as irreproachable as possible, both in terms of methodology and analysis and in terms of the absence of any conflict of interest, whatever its nature. The slightest weakness detected by one of the parties involved would have every chance of being exploited to discredit the study and aggravate the suspicion.

Failure to provide these guarantees greatly increases the likelihood of generating situations that may prove difficult to manage such as inconclusive or questionable results, delayed or overly complicated decisions. It is also very likely to give rise to controversy and increase mistrust of researchers, funders and decision-makers.

5.2.5 The proposed evaluation criteria are irrelevant from a public health perspective

Many published studies, while scientifically valid, fail to contribute meaningfully to evaluating medicinal product-population interactions or supporting public health decisions because their evaluation criteria or results are difficult, if not impossible, to translate into a population impact.

From a public health perspective, the results should, wherever possible, be expressed as an attributable fraction of the risk in the population, or as the number of cases prevented or induced (see the examples given in Point 3.3 of Chapter 3). For example, when assessing the balance of benefits and risks of HRT in women aged 50 to 60, the relevant public health criterion would be the number of fractures prevented among treated women, rather than changes in bone density or another surrogate criterion (NHS (2023)).

Similarly, the public health benefit of vaccination in a population should, whenever feasible, consider herd immunity and outcomes at the populational level. These should be assessed using robust criteria such as the reduction in the number of hospital admissions and disease-related deaths, rather than surrogate or intermediate measures like biological (*e.g.,* viral load) or histological/anatomopathological findings alleged to be predictive of the studied outcome (*e.g.,* cervical cancer).

Except in rare cases where surrogate criteria are the only feasible option (such as a public health crisis), studies relying on these measures risk having their validity questioned or creating confusion, which can hinder public health actions.

From a public health perspective, when it comes to assessing the advantages/disadvantages of a strategy, the events studied should translate directly into measures of health impact and align with clear, binary, and unambiguous definitions (*e.g*., death, hospitalization, or measured disability). Composite criteria or scores that are relevant or validated should be avoided as far as possible.

5.2.6 The study fails to provide a comprehensive view of the problem or to provide generalizable results

This point highlights the key distinction between academic research and public health-focused studies. Academic research often prioritizes a focused view to gain a deeper understanding of specific mechanisms. In contrast, public health studies, particularly those intended to inform decision-makers, should adopt a more global and integrated approach to analysing the interaction between medicinal products and populations. This includes considering multiple facets of the interaction, such as direct and indirect consequences, beneficial and adverse effects, and patterns of use. For instance, during the SARS-CoV-2 pandemic, numerous studies examined vaccine efficacy in specific populations or focused on a particular type of adverse effects (*e.g*., myocarditis, pericarditis). However, paradoxically, there was a lack of large-scale, population-based studies that comprehensively weighed all identified adverse effects against the overall benefits - both at the population level and within specific subgroups - using comparable metrics such as the number of deaths or hospitalizations avoided or induced. It is very likely that this gap contributed to public uncertainty and fuelled the spread of misinformation (the so-called "infodemic") during this critical public health context.

Despite the growing accessibility of population databases, data linkage and advancements in artificial intelligence and *Big Data*, conducting such comprehensive studies remains challenging or even impossible in certain contexts. This may occur when estimating specific parameters requires an exceptionally long follow-up period (*e.g*., evaluating the long-term benefits of a prevention strategy such as vaccination against human papillomaviruses for preventing cervix cancer) or when access to a suitable reference population is unfeasible. In these cases, the solution is to integrate studies that have addressed different aspects of the issue and identify complementary approaches to document the missing piece(s) of the jigsaw, ultimately creating an integrated and balanced view of the topic.

Similarly, while recognizing the specificities that may vary across countries - such as differences in disease prevalence, prescribing practices, healthcare utilization, and population characteristics - the results and conclusions of a pharmacoepidemiological study should, from a global health perspective, be as broadly applicable as possible on a global scale. However, such differences may influence the magnitude of the population's impact and should be accounted for in the decision-making process. This is why it is important that the protocol and publication of the study detail how the different key variables and modifying factors affect the final results. In most cases, this can enable these results to be tailored to a given situation through modelling or sensitivity analysis.

The generalizability of results is all the more important because many of the countries involved often lack the resources to carry out specific high-quality studies.

5.2.7 The planned study has little chance of being conclusive and convincing

As already mentioned, in the field of public health and decision-making, a pharmacoepidemiological study should only be considered, funded, and conducted if it offers sufficient guarantees, from the outset, of significantly advancing knowledge on the subject. This advancement should enable the dissemination of clear and unambiguous information and, possibly, support informed decision-making.

At this stage, the two key questions that needs to be asked are:

- Is it realistically feasible, within the planned timeframe, to collect and analyse the data necessary to meet the study's objectives - particularly about statistical power (e.g., significance of a comparison or stability of an estimate, etc.)?
- Given the uncertainties associated with the real world, the statistical power required, and the measures provided in the protocol, does the study, considering the worst-case scenario, have a good chance of providing sufficiently robust results and answering the question asked unambiguously?

In any case, the study should allow for a sufficient safety margin to accommodate unforeseen challenges. If these conditions are unlikely to be met, the potential negative consequences are those outlined above: Wasted resources, possible controversies or suspicion induced by inconclusive or ambiguous results, and unnecessary delays in decision-making. Among the many examples one can cite:

- the difficulty of quantifying an association when the level of exposure is low or/and the outcome rare in the studied population,
- studies of the outcomes of exposed pregnancies, which often meet recruitment issues,
- studies requiring a very long follow-up in order to be conclusive as it is the case for the prevention of diseases with a long latency period or for delayed outcomes (*e.g*., cancer, renal or neurological consequences of diabetes).

One textbook example, in the years 1994-1998, was the suspicion of a link between vaccination against hepatitis B and the occurrence of a first episode of multiple sclerosis in the weeks following the injection of a dose of vaccine. Due to the significant number of cases reported to pharmacovigilance, the French health authorities asked for a study to be carried out. This field case-control study, conducted in a context of media crisis and, therefore, of time constraint, failed to achieve recruitment guaranteeing sufficient statistical power. It showed an increased risk (odds ratio around 1.2) but not statistically significant, which gave rise to completely opposing interpretations based on individual beliefs and a controversy that lasted for years (Touzé).

In all cases, to minimize the risk of non-conclusion, which means losing the benefit of having conducted a study and always complicating the communication of results and decision-making, a feasibility analysis, including worst-case scenarios, is highly recommended.

5.3 Conclusion

From a scientific point of view, in terms of generating new hypotheses and acquiring knowledge, the results and conclusions of a new study are always welcome, at least when that study can be considered credible.

When it comes to public health decisions, the issue is more complex and the requirements more restrictive.

Regardless of situations where information and conclusions are lacking in order to optimize a decision, prevent or manage a crisis (the subject of the two previous chapters), there are cases where it seems preferable, even if it may seem paradoxical, to refrain from conducting a study: Either because the study it is deemed unnecessary from the outset, as it is unlikely to provide any new information that could inform the decision; or because waiting for the results would delay a decision that could be made on the basis of already available information or simple common sense; or, finally, because in certain situations, the implementation of the study or the publication of its results could be likely to generate doubt or even crisis.

What should be called “the proper use of pharmacoepidemiology for public decision-making” is all the more important given that resources and high-level expertise in this field are limited and that it is therefore crucial to prioritize them, whenever possible, on major public health issues that remain incompletely explored.

References Chapter 5

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Conclusion

Formalized as a new scientific discipline and organization in 1984, pharmacoepidemiology has undergone incredible methodological and structural development over the past forty years. Now taught in over 100 universities worldwide and having developed a wide range of methods for data investigation and analysis, the field now has extremely powerful tools at its disposal, such as *big data* and artificial intelligence.

It is no exaggeration to say that it is now possible in many countries to study all aspects of the interaction between healthcare products and populations: their use and the resulting effects, whether beneficial to public health or, in some cases, untoward.

At a time of major global challenges and the need to think in terms of global health, pharmacoepidemiology clearly appears to be an irreplaceable tool for public health decision-making in all matters directly or indirectly related to health products. Not only does it inform decision-makers by providing them with a comprehensive picture of the situation, but it also alerts them well in advance before an anomaly can lead to a crisis or emergency and allows them to monitor the effects of a decision or non-decision.

The practical cases presented and discussed in this report show that pharmacoepidemiology has repeatedly been a valuable asset for decision-making in a wide variety of situations, but also for evaluating the safety and effectiveness of medicinal products in real-world settings, in emergency situations and health crises caused by medicinal product shortages, natural disasters, or medicinal product misuse.

Nevertheless, the resources available for pharmacoepidemiology are inherently limited and are not always used optimally: considerable resources are mobilized to conduct redundant studies that are not always justified and are sometimes doomed to be inconclusive. At the same time, major questions concerning medicinal products and global health remain unanswered. In six chapters, the CIOMS XV working group has attempted to lay the foundations for the proper use of pharmacoepidemiology in public health decision-making on medicinal products: What can it contribute? How to evaluate existing evidence? How can it be used in a health crisis? When is it better to refrain from conducting a study or program? And: How can effectively communication on pharmacoepidemiological evidence enhance the impact of evidence-based decisions making for public health? The future lies in strengthening partnerships among interested stakeholders, enhancing data sharing capabilities, and investing in the infrastructure needed to transform data into actionable knowledge. With these foundations in place, pharmacoepidemiology can move from answering questions retrospectively to enabling proactive, equitable, and globally scalable actions that protect—and measurably improve—public health.

Glossary

Determinant

1) A collective or individual RISK FACTOR (or set of factors) that is causally related to a health condition, outcome, or other defined characteristic. The concept is probabilistic, and thus the term does not imply a DETERMINISTIC philosophy of health, e.g., it does not embody genetic, environmental, or social determinisms. In human health -and, specifically, in DISEASES OF COMPLEX ETIOLOGY- sets of determinants often act jointly in relatively complex and long-term processes. They commonly operate both at aggregate (e.g., social, regional, global) and distal levels, as well as at the individual, personal level, i.e., across macro- and micro-levels, SYSTEMICALLY. See also CAUSALITY; CAUSES IN PUBLIC HEALTH SCIENCES.
A Dictionary of Epidemiology - 6th Edition (2014)

2) A collective or individual risk factor or set of factors that is causally related to a health condition, outcome, or other defined characteristic. The concept is probabilistic, and thus the term does not imply a deterministic philosophy of health; e.g., it does not embody genetic, environmental, or social determinisms. In human health—and, in particular, in diseases of complex aetiology—sets of determinants often act jointly in relatively complex and long-term processes. They commonly operate both at aggregate (e.g., social, regional, global) and distal levels, as well as at the individual, personal level; i.e., across macro- and micro-levels, systemically.
Dictionary of Public Health, Oxford University Press, New York), 2nd Edition, Online (2018)

3) Factor which influences the probability of the occurrence of an event or disease, or the state of health of a population.
Dictionary of Pharmacoepidemiology - Bernard Begaud (1995)

Evidence-based intervention

Interventions that have passed through evidence-based review process and provide guidance on translating evidence into practice, including implementation considerations and contextual adaptation within health programmes.
World Health Organization. (2024). Implementing WHO evidence-based interventions for adolescents and young adults living with and affected by HIV. WHO. ISBN 978-92-4-010041-1.

Evidence-based decision-making

Evidence-based decision-making is the systematic and transparent use of the best available evidence, combined with contextual considerations, expertise, and stakeholder values, to inform health policies, programmes, and interventions.
World Health Organization.
Evidence, policy, impact: WHO guide for evidence-informed decision-making. ***WHO; 2022.***

General population

1. All members of a human population, defined essentially on the basis of geographical location, as in a country, region, city, etc. All inhabitants of some given area. Everyone in the POPULATION being studied, irrespective of race, ethnicity, or professional status. Individuals admitted to hospitals, other health care facilities, and prisons are usually considered not to be part of the general population. The term is often used to underline the different results that studies tend to obtain in the general population and in specific populations, subgroups, or settings (e.g., in a working population, a hospitalized population). *A Dictionary of Epidemiology - 6th Edition (2014)*

2. Geographically defined population (e.g. the inhabitants of a city, region or country). This population is usually heterogeneous and can include subjects having very different characteristics. A risk, incidence rate or prevalence rate estimated in the general population can thus be very different from that would be measured in an ad-hoc reference group. *Dictionary of Pharmacoepidemiology- Bernard Begaud (1995)*

Global health

A term that became popular early in the 21st century to describe health problems that transcend national borders and services aimed at preventing or treating these conditions. It seems to have several meanings. Some agencies and organizations apply it to diseases that are prevalent mainly in tropical and subtropical regions (e.g. malaria); others use the term to allude to prevalent infections such as HIV/AIDS or to emerging epidemic diseases such as SARS; and others apply it to conditions associated with poverty and deprivation, as in low-income countries and urban slums. The Institute of Medicine has used the term to refer to health problems, issues, and concerns that transcend national boundaries, may be influenced by circumstances or experiences in other countries, and are best addressed by cooperative actions and solutions. Some commercial enterprises use the term to mean application of market methods to deal with health problems

at transnational level. In the absence of consensus on its meaning, all who use the term should define what they mean by it, but it may be preferable to adhere to established terms with universally agreed meanings and avoid using the term global health.
Dictionary of Public Health, Oxford University Press, New York), 2nd Edition, Online (2018)

Global public health goals

United States
CDC Global Health Strategy (last revised 2021)
Vision: The CDC aspires to create a world where people – in the United States and around the globe – live healthier, safer, and longer lives.
Mission: CDC's global health mission is to improve and protect the health, safety, and security of Americans while reducing morbidity and mortality worldwide.
Goals and Objectives:
Goal 1 – Health Security: Protect Americans and populations across the globe by strengthening global public health prevention, detection, and response
Objective 1.1: Strengthen the capacity to prevent and detect disease outbreaks and other public health threats
Objective 1.2: Strengthen the capacity for timely and effective response to disease outbreaks and other public health threats
Objective 1.3: Strengthen the capacity to build resilient public health systems to protect and secure essential healthcare services
Goal 2 - Health Impact: Save lives, improve health outcomes, and foster healthy populations globally
Objective 2.1: Reduce the morbidity and mortality of high burden diseases and conditions
Objective 2.2: Eliminate and eradicate priority diseases and other public health threats
Goal 3 - Public Health Science Leadership: Lead the advancement of global public health science and practice and serve as a leading source of credible scientific information
Objective 3.1: Develop and apply global public health scientific, laboratory, and programmatic expertise
Objective 3.2: Translate and disseminate evidence-based research and data into global health guidance, policy, and programs
Objective 3.3: Drive innovation to accelerate new, more effective tools, products, strategies, and technologies
Objective 3.4 Promote and ensure health equity as a central tenet across public health science, program and policy

https://www.cdc.gov/globalhealth/strategy/default.htm Accessed April 29, 2024

European Union

EU Global Health Strategy (last revised 2022)

1. Prioritise tackling the root causes of ill health, paying particular attention to the rights of women and girls, and to vulnerable populations and disadvantaged groups.
2. Improve equitable access to a full range of essential health services from health promotion to disease prevention and affordable quality treatment, rehabilitation and palliative care to fight communicable and non-communicable diseases.
3. Improve primary healthcare with built-in surge capacity and enhance core public health capacities to meet the requirements of the International Health Regulations.
4. Foster digitalisation as a fundamental enabler.
5. Boost global health research to develop the technologies and countermeasures which are necessary to improve health.
6. Address workforce imbalances and foster skills.
7. Strengthen capacities for prevention, preparedness and response and early detection of health threats globally.
8. Work towards a permanent global mechanism that fosters the development of and equitable access to vaccines and countermeasures for low- and middle-income countries.
9. Negotiate an effective legally binding pandemic agreement with a One Health approach and strengthened International Health Regulations.
10. Build a robust global collaborative surveillance network to better detect and act on pathogens.
11. Apply a comprehensive One Health approach and intensify the fight against antimicrobial resistance.
12. Link effectively all policies and measures that have an impact on global health within the Commission, EU agencies and EU financing institutions.
13. Better link and coordinate policies and measures of the EU and its Member States to speak with one voice and deliver effective action worldwide.
14. Support a stronger, effective and accountable WHO.
15. Steer the new global health governance by filling gaps and ensuring coherence of action.
16. Ensure a stronger EU role in international organisations and bodies.
17. Expand partnerships based on equal footing, co-ownership, mutual interest and strategic priorities.
18. Strengthen engagement with key global health stakeholders.
19. Enhance EU finance for global health with maximum impact.
20. Assess progress and ensure the accountability of the EU's global health action through permanent monitoring and assessment.

https://health.ec.europa.eu/document/download/25f21cf5-5776-477f-b08e-d290392fb48a_en?filename=international_ghs-report-2022_en.pdf
Accessed April 29, 2024

United Kingdom

UK Public Health England – Global Health Strategy 2019

"Global health: refers to health issues where the determinants circumvent, undermine or are oblivious to the territorial boundaries of states, and are thus beyond the capacity of individual countries to address through domestic institutions. Global health is focused on people across the whole planet rather than the concerns of particular nations. Global health recognises that health is determined by problems, issues and concerns that transcend national boundaries."

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/354156/Global_Health_Strategy_final_version_for_publication_12_09_14.pdf

Intervention

1. Intervention (cf constraints): any element imposed by a third party (usually the sponsor of a study) and planned beforehand (i.e., formalized by a protocol), capable of modifying usual care (e.g., regarding treatment allocation, type of surveillance or follow-up, benefits gained or risks incurred). The existence of a constraint should entail seeking subject's informed consent. See also: protocol, sponsor. *Dictionary of Pharmacoepidemiology - Bernard Begaud (1995)*

2. A general term covering any and all actions taken by health professionals aimed at preventing, curing, or relieving a health problem. *Dictionary of Public Health, Oxford University Press, New York), 2nd Edition, online (2018)*

Intervention strategy

A formally designed plan of action to deal with a health problem, usually at a community or population level. *Dictionary of Public Health, Oxford University Press, New York), 2nd Edition, online (2018)*

Joint population

Population actually benefiting from a public health action (e.g. the population of a country in which a diagnostic test has been carried out). In pharmacoepidemiology, this term usually designates the population actually treated with a given drug; this can be different from the target population as defined by the officially approved indications of this drug
Dictionary of Pharmacoepidemiology - Bernard Begaud (1995).

Medicinal product

Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; Any substance or combination of substances which might be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis. [ISO 11615] *(CIOMS ICH glossary)*

Pharmacoepidemiology

Pharmacoepidemiology is a scientific discipline that uses epidemiological methods to evaluate the use, benefits and risks of medical products and interventions in human populations. *(International Society for Pharmacoepidemiology, www.ispe.org)*

Population

All the inhabitants of a country or other designated region. In public health sciences, especially in epidemiology, many subsets of the entire population are identified and selected for intervention and study. Such a group is called a target population *Dictionary of Public Health, Oxford University Press, New York, 2nd Edition, Online (2018)*

Public health

Public health aims to improve the health of populations by keeping people healthy, improving their health and by preventing disease. *https://eurohealthobservatory.who.int/themes/health-system-functions/public-health Accessed April 29, 2024*

Real-world data

Data relating to patient health status and or the delivery of healthcare routinely collected from a variety of sources.
Examples of RWD include data derived from electronic health records (EHRs), medical claims and billing data; data from product and disease registries; patient-generated data, including from mobile devices and wearables; and data gathered from other sources that can inform on health status (e.g., genetic and other biomolecular phenotyping data collected in specific health systems) (source: CIOMS ICH Glossary, 9 Dec. 2025).

Real-world evidence
The clinical evidence about the usage and potential benefits or risks of a medicinal product derived from analysis of RWD (source: CIOMS ICH Glossary, 9 Dec. 2025).

Risk factor

1. Characteristic associated with an increased probability of occurrence of an event or disease. The characteristic can be inherent to the individual or sub-group (e.g. age, sex, genetic trait, etc.) or linked to a disease, environmental factor, diet, drug use, etc. The term risk factor does not necessarily imply the existence of a causal relationship between the presence of the factor and the occurrence of the event or disease. *Dictionary of Pharmacoepidemiology - Bernard Begaud (1995)*

2. A factor that is causally related to a change in the risk of a relevant health process, outcome, or condition. The causal nature of the relationship is established on the basis of scientific evidence (including, naturally, evidence from epidemiological research) and causal inference. The causal relationship is inherently probabilistic, as it happens in many other spheres of nature and human life. Risk factors for human health often have individual and social components; even when individual and social risk factors can be separated, they often interact. *A Dictionary of Epidemiology - 6th Edition (2014)*

3. A term first used in the 1950s in reports of results from the Framingham Study of heart disease, meaning an aspect of behavior or way of living, such as habitual patterns of diet, exercise, use of cigarettes and alcohol, etc., or a biological characteristic, genetic trait, or a health-related condition or environmental exposure with predictable effects on the risk of disease due to a specific cause, including in particular increased likelihood of an unfavorable outcome. Other meanings have been given to this term, such as a determinant of disease that can be modified by specific actions, behaviors, or treatment regimens. Risk factors may be divided into those directly related to disease outcomes (proximal risk factors), such as nonuse of seat belts and risk of injury in automobile crashes, and those with indirect effect on outcomes (distal risk factors). An example of the latter is the influence of ozone-destroying substances, such as CFCs, on the risk of malignant melanoma, mediated by increased exposure to solar ultraviolet radiation because of depletion of protective stratospheric ozone. *Dictionary of Public Health, Oxford University Press, New York), 2nd Edition, online (2018).*

Target population

This term has two different meanings, used to designate:

- A population addressed by a public health intervention, particularly one which is likely to receive a given treatment. The target population does not necessarily correspond to the population actually treated, called joint population.
- The population to which the results of a study or estimates made in a sample can be legitimately extrapolated.

Dictionary of Pharmacoepidemiology - Bernard Begaud (1995)

Appendix 1:Examples of tools to help support critical appraisal of pharmacoepidemiological evidence

Tool	Link	Description/Focus Area
Strengthening the Reporting of Observational studies in Epidemiology (STROBE)	https://www.strobe-statement.org/	Framework designed to improve the reporting quality of observational studies, including a checklist of 22 essential items that cover key aspects of study design, data collection, analysis and interpretation.
Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)	https://www.prisma-statement.org/	Widely used framework for enhancing clarity and transparency of systematic reviews and meta-analyses. Originally designed for RCTs, PRISMA has since been adapted for broader use including reviews of observational studies. The guidelines consist of a 27-item checklist and flow diagram.
Meta-analysis Of Observational Studies in Epidemiology (MOOSE)	Publication	Structured framework for reporting meta-analyses of observational studies. The framework compliments similar reporting guidelines (e.g., PRISMA) but specifically addresses the unique challenges of synthesizing data from observational studies.
Grading of Recommendations Assessment, Development and Evaluation (GRADE)	https://www.gradeworkinggroup.org/	A systematic approach to evaluating the certainty of evidence (assessed across domains like risk of bias, inconsistency, indirectness, imprecision and publication bias) and the strength of recommendations (graded as strong or weak based on the balance of benefits and harms, quality of evidence, values and preferences and resource use) in healthcare and public health.
Risk of Bias in Non-randomised studies - of Interventions (ROBINS-I tool)	https://www.riskofbias.info/welcome/home/current-version-of-robins-i	A tool for evaluating the risk of bias in non-randomized studies of interventions. Bias domains include confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of reported results. In its application it compared the study's results to a hypothetical

Tool	Link	Description/Focus Area
		ideal randomized control trial, assessing the overall bias and low, moderate, serious or critical.
Risk of Bias in Non-randomised studies - of Exposure (ROBINS-E tool)	https://www.riskofbias.info/welcome/robins-e-tool	This adapts ROBINS-I for exposure studies, where exposures are typically not randomized. Key considerations include bias from confounding, measurement bias, and temporal issues.
Critical appraisal tool for grey literature (AACODS)	https://canberra.libguides.com/c.php?g=599348&p=4148869	A checklist to critically appraise grey literature (material produced outside traditional publishing) ensuring its reliability and relevance, it focuses on 6 areas: authority, accuracy, coverage, objectivity, date, and significance.
CIOMS WG XIII	https://cioms.ch/working-groups/real-world-data-and-real-world-evidence-in-regulatory-decision-making/	Real-world data and real-world evidence in regulatory decision making - provides quality tools for RWE studies and reporting to support interpretation and reproducibility
ISPE Guidelines for good pharmacoepidemiological practice	https://onlinelibrary.wiley.com/doi/10.1002/pds.3891	Provides a framework for conducting and evaluating pharmacoepidemiological studies

Appendix 2: Pharmacoepidemiological tools and methodologies in public health

In the 1980s and 1990s, when the concepts of pharmacoepidemiology and real-world data were beginning to take hold, the implementation of a study was often cumbersome and costly because it usually required specific data collection in the field. Decisions were therefore most often based on pharmacovigilance data (spontaneous reporting), and for efficacy, on conclusions drawn from trials conducted during the medicinal product's clinical development. Currently, there seems to be no excuse for not making the pharmacoepidemiological approach the major resource for informing decisions on medicinal products and public health. The development of increasingly comprehensive and accessible databases, the arrival of new IT and statistical resources and the proliferation of data analysis methods have radically changed the environment.

Several pharmacoepidemiology tools, especially in developed countries, are available that enable researchers to assess the impact of effect on medications, including the safety and effectiveness, at a population level. This appendix describes some of the key pharmacoepidemiology tools and methodologies in assessing medicinal products at a population level and optimizing public health, as follows:

- Population-based Pharmacovigilance Systems: FDA's Adverse Event Reporting System (FAERS), European Medicines Agency's EudraVigilance and Japanese Adverse Medicinal Product Event Report database collect reports of adverse medicinal product reactions with medicinal products from HCPs, patients and consumers.
- Examples of population-based surveillance system that collect data on vaccine includes Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD) and FDA Biologics Effectiveness and Safety (BEST) in the US and surveillance data from vaccine-preventable diseases (VPD) in the EU. Data collected in these systems are used for detecting medicinal product and vaccine safety signals and monitoring post-marketing medicinal product safety.
- Large secondary databases including Electronic Health Records (EHRs) and Insurance Claims Databases. These databases containing patient health records or insurance claims provide real-world data on medicinal product usage and outcomes, which are used to study patterns of medication use, safety, and effectiveness in the general population.
- Disease or Product Registries: These registries collect prospective data over time on patients with certain conditions or those exposed to specific medicinal products. These are useful for acute and long-term outcome and monitoring the dosing, effectiveness and safety of new and established therapies.
- Design and Analytical Methods: Pharmacoepidemiology offer methods and analytical tools to estimate and quantify the relationships between intervention and risk factors and health outcomes at a population level. Population-based cohort and case-control studies are examples of PE study designs commonly used measures include population attributable risk (PAR), Number Needed to Treat (NNT), and Number Need to Harm (NNH). These

quantitative estimates are important for public health policies as they provide insights into the potential benefits and harms of treatments for populations.

- Predictive modelling of pre-emptive identification of (potential) public health issues is an emerging approach that leverages advanced analytics, machine learning and diverse secondary data sources to anticipate potential health issues before they escalate, enabling proactive prevention. This approach has been applied to various public health areas including infectious disease surveillance, chronic disease management, medicinal product safety monitoring, disaster preparedness, and socioeconomic and environmental determinants of health outcomes.