Received: 14 April 2020 | Revised: 28 April 2020 | Accepted: 2 May 2020

DOI: 10.1002/pds.5029

WILEY

REVIEW

Considerations for pharmacoepidemiological analyses in the SARS-CoV-2 pandemic

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has triggered several hypotheses regarding use of specific medicines and risk of infection as well as prognosis. Under these unique circumstances, rapid answers require quick engagement in data collection and analyses; however, appropriate design and conduct of pharmacoepidemiologic studies are needed to generate valid and reliable evidence. In this paper, endorsed by the International Society for Pharmacoepidemiology, we provide methodological considerations for the conduct of pharmacoepidemiological studies in relation to the pandemic across eight domains: (1) timeliness of evidence, including the need to prioritise some questions over others in the acute phase of the pandemic; (2) the need to align observational and interventional research on efficacy; (3) the specific challenges related to "real-time epidemiology" during an ongoing pandemic; (4) what design to use to answer a specific question; (5) considerations on the definition of exposures; (6) what covariates to collect; (7) considerations on the definition of outcomes; and (8) the need for transparent reporting.

KEYWORDS

bias, COVID-19, methodology, pharmacoepidemiology

1 | INTRODUCTION

During the ongoing pandemic with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there is growing interest in how exposure to certain medicines affect the risk of SARS-CoV-2 infection as well as the clinical course of coronavirus disease 2019 (COVID-19). For example, non-steroidal anti-inflammatory drugs (NSAIDS)[1] and angiotensin converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs)[2,3] have been suggested to lead to worse outcomes in COVID-19. Meanwhile, hydroxychloroquine[4] has been suggested to be beneficial in treatment of COVID-19 patients based on anecdotal information or heavily criticised studies,[5,6] leading to an uncertain benefit/risk balance[7] and potential harm in patients.[8] Well-designed randomised clinical trials are required for assessment of efficacy of potential drugs to treat COVID-19[9]; however, for hypotheses related to the impact from concomitant use of medications, either on the risk of infection or on prognosis, high-quality pharmacoepidemiological analyses are urgently needed. Such studies hold specific challenges related to, for example, our currently limited knowledge of COVID-19 and the intensive care setting unfamiliar to most epidemiologists. Poorly designed studies may amplify public concern and promote wrong decisions based on flawed evidence rather than deliver the desired rapid public health support. In an attempt to support researchers, regulators and clinicians, we therefore provide methodological considerations for the conduct of pharmacoepidemiological studies in relation to the SARS-CoV-2 pandemic.

This commentary received endorsement from the International Society for Pharmacoepidemiology (ISPE).

2 | CONSIDERATION #1: TIMELINESS OF EVIDENCE

Each phase to the handling of the SARS-CoV-2 pandemic has its specific needs in term of evidence. Some epidemiological studies will have higher priority in the acute phase of the pandemic, whereas others will provide knowledge that is useful in later phases, for example, during a second wave of infections or for long-term follow-up of those infected. As an example, data analysis that leads to identification of hospitalised patients most likely to develop complications, and thereby support triage of patients with COVID-19, is of high importance in the acute phase, where health care systems are easily overwhelmed. With limited resources available, the most urgent study questions should be prioritised to maximise public health impact at a given time in the pandemic. The epidemiologic and clinical communities are urged to develop such research agenda including priorities to guide investment of resources and capacity. Other questions should be answered in a more informed manner, that is, at a time when our understanding of SARS-CoV-2 has improved and/or when increased sample size may allow more precise answers. Lastly, additional time will allow multinational collaborations to be established, something that should be prioritised to facilitate the replication and confirmation of findings with greater generalisability and thus greater potential impact.

3 | CONSIDERATION #2: OBSERVATIONAL AND INTERVENTIONAL RESEARCH ON EFFICACY

Large randomised trials assessing the efficacy of selected drugs in the treatment of COVID-19 are currently being conducted, for example, in the DISCOVERY (NCT04315948) and the SOLIDARITY (NCT04321616) trials testing remdesivir, lopinavir/ritonavir, interferon beta-1A, and chloroquine/hydroxychloroquine. In the context of an ongoing pandemic, observational assessment of the same hypotheses as those currently tested in trials is unlikely to add significant value in the short term, considering the sizable potential for bias in the assessment of efficacy related to in-hospital outcomes. At best, an epidemiological study will provide similar effect estimates as those obtained from the randomised controlled trial. Even if such estimates are available days or even weeks prior to the trial evidence, it is unlikely to inform clinical and regulatory decision-making on efficacy. Conversely, if the observational and interventional evidence does not align, the observational will not only create uncertainty for patients and physicians but might even lead to additional trials being performed at the expense of other and more important assessments. Observational studies on efficacy may, however, be useful in providing hypotheses of promising candidate drugs to be tested in interventional designs provided their exploratory nature is made very clear.

Key Points

- Consideration #1: Study questions needing urgent answers in the acute phase of the pandemic should be prioritised over those better answered at a later stage where our understanding of SARS-CoV-2 has improved and/or when increased sample size may allow more precise answers.
- Consideration #2: Observational studies to assess efficacy are, in the context of an ongoing pandemic, unlikely to add significant value in the short term. If performed, their hypothesis generating nature should be made clear.
- Consideration #3: The conduct of real-time epidemiology comes with specific challenges related to for example, lag in data availability and delay in coding of in-hospital outcomes, requiring close collaboration with both registry holders and clinicians to ensure valid analyses.
- Consideration #4: A core challenge is the identification of the underlying source population from which study subjects are identified given the considerable potential for bias, for example, related to changing thresholds for testing and admittance. Care must be taken to ensure that study subjects are all "at risk" of the outcome being studied.
- Consideration #5: Ascertainment of exposure generally follows standard pharmacoepidemiological principles. Rapid changes to prescribing practices during the pandemic and the analysis of in-hospital drug use comprise specific challenges.
- Consideration #6: Selecting useful covariates for risk studies are challenging as these are largely unknown or unmeasured (eg, adherence to quarantine regulations). For studies of COVID-19 prognosis, measures of frailty are particularly valuable. However, particular care must be taken as to not adjust for intermediates, for example, lab values obtained upon hospital admission or treatments after study inclusion.
- Consideration #7: The temporal and geographical variation in testing strategies and thresholds for hospitalisation and intensive care admission, as well as the delay from infection to admission and death, must be taken into account when ascertaining outcomes in COVID-19 patients
- Consideration #8: In the face of an ongoing pandemic, rapid assessment of evidence is important. This can be greatly facilitated by transparent reporting, including the use of checklist and design diagrams, as well as public registration of study protocols.

4 | CONSIDERATION #3: CHALLENGES OF REAL-TIME EPIDEMIOLOGY

There are several unique challenges related to the conduct of epidemiological studies of a currently ongoing pandemic. Exposure to chronically prescribed drugs and their relationship with certain outcomes (eg, hospital admission or fatality) will usually be assessed based on claims databases. The speed with which prescription information and hospital data is made available to researchers varies between countries and data sources, with some providing only annual updates[10] while others have lag times of only a few days.[11] In some countries, data availability is currently being accelerated, in order to provide the most recent, although often unvalidated, data to researchers. Importantly, even with very frequent data updates, information on patients with long-term stays in intensive care may only be available upon discharge or death. If a study is done before all data is available on all patients, recovered and unrecovered, the results may be skewed towards more favourable outcomes. In some countries with overwhelmed health care systems, death prior to hospitalisation or even diagnosis might occur. Challenges such as these are not commonly encountered by epidemiologists who are used to analyse historical data. Close collaboration with registry holders, that is, those with a deeper understanding of the data structure, is therefore essential to ensure proper analysis of near real-time data. Similarly, it will be important to collaborate with clinicians, to ensure an understanding of not only recording and coding practices (eg, intensivists) as well as prescribing practices (eg, specialist prescribers) but also the course of COVID-19 (eg, infections disease specialists).

Some data will not be available or incomplete in clinical or administrative databases. This includes self-medication, be it for pain or fever (NSAIDs, paracetamol), or in the hope of preventing or treating the disease (chloroquine), as well as clinical information such as the time of onset of symptoms or the measured vital parameters at presentation to the emergency department. Collection of such information can potentially be achieved by obtaining data from electronic health records or be done at the time of patient identification, for example, through questionnaires, medical chart review, and/or blood samples. The careful planning of such data acquisition is important, considering feasibility in a situation where the health care system is strained from the handling of the pandemic. For routinely collected parameters, this makes access to electronic health records particularly valuable. However, the documentation in such data will need to be interpreted in light of the stressful and novel situation in which clinical care was provided, thus perhaps not following typical coding conventions.

5 | CONSIDERATION #4: WHICH DESIGN FOR WHICH QUESTION?

In general, the design and analytical choices of a pharmacoepidemiological study need to be tailored to the specific research question,[12] with due consideration of both pharmacological aspects as well as the rapidly evolving clinical experience. Regarding the latter, including specialised clinicians will be particularly important in studies of COVID-19 as the proper analysis of outcomes such as intensive care unit (ICU) admission or mechanical ventilation requires considerable insights into clinical and coding practices.

A core challenge in epidemiological studies of COVID-19 lies with the identification of the underlying source population, that is, the population from which study subjects are identified. As further discussed below (see Consideration #7), variation in testing availability creates a considerable potential for bias, and great care must be taken to ensure that study subjects are all "at risk" of the outcome being studied. To this end, restriction, for example, to those with positive SARS-CoV-2 polymerase chain reaction (PCR) test or those admitted due to COVID-19, might be useful. However, such restriction will also drive the underlying research question. As an example, consider a study assessing the association between a given drug and COVID-19 prognosis. If subjects are selected from the general population based on a clinical diagnosis instead of those with a positive SARS-CoV-2 test, the estimates of the drug's association with poor as compared to favourable prognosis, may suffer from bias due to non-testing. This can be partly remedied by restricting to those admitted due to COVID-19. However, as being admitted in itself requires moderate to severe disease, the study question changes accordingly from the risks of severe over non-severe disease to the association between very severe (eg, death or ICU admission) over severe disease, which holds considerable implications for the interpretation of the study findings. As such, results from studies restricted to hospitalised patients may not be applicable to the non-hospitalised and less ill patients, and thus the risk of selection bias should be considered if results are generalised to all COVID-19 patients.

The choice of study design will ultimately depend on both the study question and data availability. Cohort studies will be particularly useful as they readily provide estimates of absolute risks. Nested case-control studies may also be useful if the main interest is in the difference in relative risk between users of related drugs, for example, ACE-inhibitors and users of other antihypertensive drugs. Finally, self-controlled designs such as case-crossover studies and self-controlled case-series are, in this context, less suitable, mainly due to their high sensitivity to information bias,[13] which is problematic in terms of the lack of in-hospital exposure data and the fact that the exact onset of COVID-19 disease or worsening of symptoms will in most databases be difficult to identify.

Finally, the use of active comparators should be considered.[14] This is particularly important for the assessment of associations where confounding by indication might be a threat to validity. Take as an example a study to assess the association between use of ACE-inhibitors and the prognosis of COVID-19. This would typically be designed as a cohort study, with estimation of the incidence of outcomes such as ICU admission, mechanical ventilation, or death. An appropriate comparator group has to be defined, for instance users of other antihypertensive drugs, to avoid confounding by indication or severity. As several chronic diseases have been linked to worsening of prognosis in COVID-19, it will be of particular importance to consider

the differences in underlying cardiovascular diseases when comparing users of different antihypertensive drugs.

6 | CONSIDERATION #5: HOW TO DEFINE EXPOSURE?

Measurement of exposure is a constant pre-occupation in pharmacoepidemiology. In the present context, three main scenarios can be described.

First, some drugs are used regularly for existing conditions, for example, ACE inhibitors in hypertension or hydroxychloroquine for autoimmune disease. Use of these medicines will be captured in electronic medical records and claims databases. The determination of the exposure status at a given date or period of time (before hospital admission, at the presumed time of infection) will depend on amount dispensed and usual usage pattern and can generally follow accepted epidemiological measurement practice. Even if very recent prescription data is not available, it is often reasonable to assume that they are continuously used in patients that consistently claim prescriptions in a time window before onset of infection.

Second, some drugs are used sporadically although often obtained via prescription, for example, ibuprofen or other NSAIDs and nitrates. Modelling exposure at a given time with such drugs is inherently difficult[15] and often requires extensive sensitivity analyses. Particular care must be taken to avoid reverse causation bias, that is, the inclusion of treatment of symptoms that are only later recorded and mistaken as outcome (eg, upon hospital contact), which will create a spurious association between exposure and outcome. This might for some associations warrant a time-window leading up the time of for example, hospital admission in which exposure is disregarded. Relevant to the study of COVID-19, this has previously been shown to be a particular concern in the association between recent use of NSAIDs and pneumonia complications.[16,17] Similar patterns could be hypothesised for, for example, other analgesics, antibiotics, and inhaled glucocorticoids.

Finally, some drugs are not recorded in health insurance databases, for example, drugs bought over-the-counter or via the internet. The only way to ascertain the use of these drugs is via patient questionnaires[18] or from blood samples, depending on drug pharmacokinetic characteristics and time from last ingestion.[19]

In the face of an ongoing pandemic, changes to prescribing practices occur at an accelerated pace and traditional indications are dissolving. As examples, some patients might be switched to alternative antihypertensive medication due to fear of complications with use of ACE inhibitors, while others might receive off-label medications like chloroquine prophylactically or for the treatment of mild symptoms. Such patterns make observational assessment very difficult and needs to receive particular attention in the design of studies.

In studies of hospitalised COVID-19 patients, in-hospital drug exposure data will allow studies of the prognosis of patients associated with specific drugs used in hospital. The lack of in-hospital drug use data is, however, a common limitation of databases based on outpatient prescribing or dispensing databases. Even when such data is available, prescriptions may change very rapidly in intensive care, becoming very difficult to trace even if electronically recorded. Further, care needs to be taken to avoid immortal time bias due to assessment of exposure after start of follow-up and classifying the time until start of exposure incorrectly as exposed,[20] as for example, seen in a recent study on use of ACE-inhibitors in COVID-19 patients,[21] leading to large and spurious protective effects. In the absence of data on individual patient prescribing, ascertainment of the in-hospital exposure may have to rely on manual exploration of hospital data, and especially of nursing documents, which are often the most precise source of in-hospital drug use.

7 | CONSIDERATION #6: WHAT COVARIATES TO COLLECT?

Covariates in studies of COVID-19 are used to describe the study population and to handle confounding, as in any other non-randomised pharmacoepidemiological study. Potential confounders include any risk factor for the outcome of interest that is present at start of follow-up and distributed unequally in exposed and unexposed. The choice of covariates thus not only depends on the exposure under study but also on whether the study outcome is risk of COVID-19 infection or prognosis.

The choice of covariates for confounder control in studies of infection risk is challenged by the currently limited data on risk factors for infection, as well as its dependence on largely unmeasured individual characteristics such as recent travel and adherence to quarantine regulations.

Data on risk factors and prognostic factors for COVID-19 are sparse, but patients who get severely ill or die from COVID-19 are reported to be more often elderly, male, and have comorbidities, including diabetes mellitus, cancer, hypertension, and other cardiovascular diseases, as compared to patients with less severe COVID-19.[22-28] Age, sex, and comorbidities are therefore crucial covariates in studies of COVID-19. Studies of ICU admitted patients, including patients with severe COVID-19, are further challenged by the presence of both the acute and chronic diseases, often unknown functional level before critical illness, and the frequent use of several concurrent interventions. This should, if possible, all be described by the covariates. Measures of frailty or functional level are particularly valuable in studies of risk and prognosis in an ICU setting, as they influence both the decision to admit and the treatment level when admitted.

Severity of illness or organ dysfunction scores is often used to summarise severity of the illness in studies of ICU patients with COVID-19. In addition, specific covariates in patients with COVID-19 admitted to the ICU include bedside measurements (eg, temperature and oxygen saturation), lab measurements (eg, infection parameters including lymphocytes, liver enzymes, and markers of kidney function), and imaging (eg, chest radiography and computed tomography). As COVID-19 is primarily a disease of the lower respiratory tract, the

severity of respiratory dysfunction can be described by the ratio between the partial pressure of oxygen in arterial blood to the inspired oxygen fraction (PaO_2/FiO_2 ratio) and the need for respiratory support (eg, oxygen supplementation, non-invasive ventilation, or mechanical ventilation). In addition, critically ill COVID-19 patients may develop other organ dysfunctions that can be described either by lab measurements or by relevant organ-supportive treatments.

Although the risk factors discussed above are of interest, not all of them act as confounders, that is, are unevenly distributed between users of two otherwise comparable drugs. Rather, they will mainly serve to describe the study population. Importantly, covariates like severity of illness, laboratory findings, and treatments for COVID-19 during hospitalisation will potentially be intermediate steps in the causal pathway between the preadmission use of a drug of interest and the outcome of COVID-19. Care should therefore be taken when adjusting for any such covariates measured after the point of exposure to the drug under scrutiny, as their inclusion in for example, regression analysis will potentially bias causal estimates.

8 | CONSIDERATION #7: HOW TO DEFINE OUTCOMES?

When defining outcomes, temporal as well as geographical variation in the testing for SARS-CoV-2, hospitalisation, and ICU admission of patients with COVID-19 should be considered.

The changing threshold for testing for SARS-CoV-2 are important both in studies on risk and prognosis of COVID-19. The WHO recommends different test strategies in countries without reported cases, with clusters of cases, and with community transmission.[29] In addition to these temporal changes in recommended testing strategy as the disease spreads, there is large geographical variation in the number of tests performed both between and within different countries. Such variation needs to be considered in studies of COVID-19, for example, by stratification or matching on place and time of COVID-19 testing. It is of particular concern, if the drug itself or its indication influences the chance of being tested. Such non-random testing may lead to milder COVID-19 cases being identified in exposed patients, which may lead to information bias in studies on risk of infection and to selection bias in studies of the prognosis of COVID-19 as the exposed cohort will include COVID-19 cases that would otherwise have been undiagnosed.

The threshold to admit a patient to a hospital may also change over time. Initially, imported cases were in many countries hospitalised and isolated to minimise the spread of COVID-19. Later, when COVID-19 started to spread in the community, hospital admission was reserved to patients with severe illness requiring in-hospital care. Such temporal changes need to be considered in hospital-based studies of COVID-19 prognosis, for example, by exclusion of those (few) patients admitted during the early phases and/or matching on time of admission as well as region.

The threshold for ICU admission and mechanical ventilation pose specific challenges. Several studies of COVID-19 prognosis have included ICU admission and/or mechanical ventilation as a proxy for critical illness.[26,30,31] However, ICU admission and treatment with mechanical ventilation reflects not only the severity of the illness, but also the national and/or regional organisation of health care which may impact the decision to admit the patient to the ICU and initiate treatment with mechanical ventilation. During usual routine clinical care, and in particular during a pandemic, ICU capacity is limited and admission is prioritised to the patients who are expected to benefit the most.[32,33] Consequently, factors influencing triage include among others a patient's preferences, low functional level before illness, low or very high severity of acute illness (and thereby probability of dying), high age, and severe chronic diseases with short life expectancy. This might lead to a paradoxically increased risk of ICU admission in users of preventive medication, for example, statins, which may not be prescribed to the same extent in the oldest and most frail populations.[34] Again, both geographical and temporal variation should be considered when comparing risk and prognosis of ICU admission, as there is considerable geographical variation in the number of ICU beds per inhabitants[35] and as the COVID-19 pandemic may lead to shortage of ICU beds and mechanical ventilators.[36]

Finally, in defining and handling outcomes in COVID-19, the lag from transmission to onset of symptoms and to the potential need for hospitalisation needs to be considered. This includes an estimated 5 to 6 days from the time of infection to onset of symptoms[37] and reports of for example, 7 days from onset until admission[38] or 11 days from onset of symptoms until mechanical ventilation.[22] Such delays need to be considered in the assessment of exposure and covariates in order to avoid reverse causation bias. Further, this holds implications for the choice of statistical model. Considering the large variation between patients in the delays reported above, use of time-to-event analysis (eg, Cox regression) will upweight patients with shorter delays compared to those with longer. Use of logistic regression, and thereby dichotomisation of outcomes such as "ICU admission within 30 days" (yes/no), seems more suited to identify factors associated with worse prognosis.

9 | CONSIDERATION #8: REPORTING

Under the current unique circumstances there is a high need for rapid assessment of hypotheses. Although, it may be tempting to quickly engage in data collection and analyses to provide rapid answers, it is important to adhere to existing guidance on the appropriate design and conduct of pharmacoepidemiologic studies to generate reliable and reproduceable evidence. Such resources include the ISPE guidelines for Good Pharmacoepidemiology Practices[39] and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.[40] Additionally, registration of study protocols and transparent reporting of study results will be particularly important in order to facilitate quick and efficient assessment of new evidence as well as replication. To this end, ENCePP and the European Medicines Agency have called for registration of all COVID-19-related

protocols in the EU PAS Register (www.encepp.eu). Furthermore, transparent reporting using for instance the RECORD-PE checklist[41] and the use of design diagrams[42] is highly encouraged.

10 | CONCLUDING REMARKS

In the face of an ongoing global pandemic, the pharmacoepidemiology community has a compelling duty to dedicate time and efforts and foster collaborations to generate valid and reliable evidence. Refocusing activities to the research questions with the highest potential public health impact will support regulatory decision makers and clinicians to provide care for patients with COVID-19. This will require an open-minded community willing to share data, methods and expertise to confront public health emergencies like the one experienced now.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

ACKNOWLEDGEMENTS

The authors are grateful to Peter Arlett, Marco Cavaleri, and Hans-Georg Eichler (The European Medicines Agency), Henrik Toft Sørensen (Aarhus University), Jesper Hallas, Kasper B. Kristensen and Mette Reilev (University of Southern Denmark) and Almut Winterstein, Krista Huybrechts and Alison Bourke (The International Society for Pharmacoepidemiology) for valuable input to the manuscript.

CONFLICT OF INTEREST

The views expressed in this article are the personal views of the authors and may not be understood or quoted as reflecting the views of their respective institution.

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How to cite this article: Pottegård A, Kurz X, Moore N, Christiansen CF, Klungel O. Considerations for pharmacoepidemiological analyses in the SARS-CoV-2 pandemic. *Pharmacoepidemiol Drug Saf*. 2020;1–7. https://doi.org/10.1002/pds.5029