Editor-in-Chief's Note

Pharmacoepidemiology

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Although measles was declared eliminated in the United States in 2000, it has reemerged in the United States and abroad. In the first nine months of 2019, a total of 1249 cases of measles were reported in the United States—the highest number on record since 1992 and nearly double the number of cases seen in any year in the past decade.[1,2] In the Democratic Republic of the Congo, a striking 4000 deaths were attributed to measles in 2019, and more than 200,000 measles cases have been reported year to date.[3] Efforts to vaccinate Congolese children and supply medicines are ongoing as health authorities attempt to gain control of the epidemic.[4]

In the United States, the resurgence of measles has been attributed to reduced vaccination rates driven by vaccine hesitancy and misinformation.[5,6] Fear of vaccines rose in 1998 in response to the now widely discredited claim that the MMR vaccine causes autism.[7] Readers are referred to my June Note,[8] within which I described ways to engage with those who remain opposed to vaccination to help mitigate their concerns. Last month, infectious diseases experts participated in a global "Twitterstorm" during IDWeek to advocate for vaccination and spread accurate information using the hashtag #WhyIVaccinate.[9] In addition to these efforts, we turn to pharmacoepidemiologists to supply objective, rigorous scientific evidence about vaccine usage and safety, to disseminate this information to the public, and to counter misinformation.

Strictly speaking, pharmacoepidemiology refers to the study of the use, effectiveness, and safety of pharmacologic agents (ie, drugs, biologics, vaccines) in large, well-defined populations. Pharmacoepidemiology focuses on groups rather than on individuals. Studying pharmacologic agents under real-world conditions in sufficiently large samples or populations should yield inferences about their effectiveness, tolerability, and safety that are more convincing and reproducible.

Whenever one reads a case report or even the results of a well-designed and carefully executed clinical trial, certain questions tend to surface: Is this finding truly representative or generalizable? In a given trial, has randomization adequately equated the limited samples or has it inadvertently introduced random or sampling errors? When groups are compared, were the sample sizes really large enough to remove the impact of any relevant differences? Clearly, the larger the sample size, the less likely it is that sampling or random errors will affect inferences.

Currently, many pharmacoepidemiological studies utilize data from electronic health records, registries, and other databases. These sources are usually chosen because the information they contain is available and bounded by defined time periods. Some obvious limitations of data from such sources are that data collection and entry were not intended for research purposes. Most often, available data were entered by different people and usually for administrative or medical billing purposes. Important data may be missing from the records, especially highly relevant clinical information as to why a treatment was prescribed or whether an intended course of treatment was completed.

Pharmacoepidemiology has many applications, particularly when it would be impractical or impossible to randomize a treatment, or when an outcome of interest is rare. A valuable example is as follows: Hormone replacement therapy (HRT) for postmenopausal women became increasingly popular during my medical school years. Initially, HRT consisted of estrogen obtained from pregnant horses. By 1975, several facts became apparent: (1) unopposed estrogen caused proliferation of the endometrium; and (2) when progestins (synthetic progesterone) were added to estrogens in HRT, endometrial cancer prevalence was reduced.[10,11] These "before and after" historical comparisons are an unquestionably useful type of pharmacoepidemiological study. Similar real-world

observational studies confirmed the role of nicotine in addiction to cigarettes, smoking as a risk factor for lung cancer,[12] and folic acid in preventing spina bifida and other neural tube defects.[13]

Other potential uses are population-based comparative effectiveness studies. Although randomized trials provide evidence for drug approval, head-to-head comparisons of two or more available treatments provide data on which agents produce superior outcomes in real-world clinical settings, while minimizing side effects.[14] For example, the treatment of nosocomial pneumonia due to methicillin-resistant *Staphylococcus aureus* (MRSA) is complex and, because of antimicrobial resistance, limited to few medications. Conflicting results from efficacy studies of linezolid and vancomycin provided the rationale for comparing effectiveness in a real-world, national cohort of patients infected with MRSA pneumonia. Over a 9-year period, 5271 adults with MRSA pneumonia were admitted to VA hospitals in the United States. Propensity for treatment-adjusted hazard ratios revealed similar mortality at 30 days but superior clinical success and earlier discharge in patients treated with oral or intravenous linezolid compared with intravenous vancomycin.[15] Another approach is the use of meta-analyses to compare two different treatments. These studies compare different populations. A good example is a study comparing outcomes from coronary artery bypass surgeries performed both with and without pumps.[16] This study concluded that outcomes from both were comparable. The journal that published this study in 2017 stopped publishing in September 2018.[17] I could find no explanation for Dove Press's decision to discontinue this journal.

Another use is in signal detection in postmarketing pharmacovigilance studies. It is only from very large populations that infrequent adverse events can be detected (eg, 1/10,000). Registries are sometimes used to make these determinations. Unfortunately, registries have inherent limitations: (1) submissions are voluntary and by clinicians, and quality, accuracy, and completeness cannot be assured; (2) there may be issues with transparency because registries are financed, maintained, and analyzed by product sponsors, and public access is usually not allowed; (3) because more than one agent may be available to treat a condition, disease-focused registries may be preferable to agent-focused ones[18]; and (4) a given agent may be used for more than one condition, and other agent—disease problems may be overlooked. In addition, patients may be using more than one agent, making the attribution of any untoward or positive effects to a specific one difficult. Despite these limitations, valuable information can be gleaned from registries. We should not throw out the baby with the bath water.

I am unaware of any pharmacologic agent that achieves the same outcomes in all persons exposed. There are always some who do not benefit at all, some whose benefit is comparable to what a placebo would have accomplished, and others whose benefit is compromised by unwanted pharmacologic effects. Factors such as diet and genetics may also contribute to variability. One can only trust that using a large population will address these concerns and reveal patterns that small samples are not able to detect. But, how large is really large enough? There is no answer to this last question—the sample size used is always governed by the numbers available.

Having access to large sample sizes is a luxury in science. I believe they provide an opportunity that I have never seen explored in pharmacoepidemiology. I staunchly believe in replication. In that regard, I have not come across replications of pharmacoepidemiological findings. I would like to offer a suggestion that stems from my experience with assessments of test—retest reliability and internal consistency. Would it not strengthen confidence in a finding from a large population if the finding was replicated in two cohorts created by randomly dividing the whole sample into two parts? This split-half reliability approach would not work for rare events. I would like to know what statisticians would suggest as the minimum prevalence needed to make this split approach useful. I have learned from several colleagues about the "Rule of Three."[19] According to this rule, one would need three times the sample size to pick up one event with statistically significant confidence. In other words, to find an event that occurs in 1 in 1000 persons, one would need a population of 3000. Therefore, to conduct a split-half reliability assessment, one would need a minimum of 6000 persons.

Here is a bit of humor, inspired by and modified from an incompletely documented source[20]: A chemist, a physicist, and an epidemiologist were walking down a hallway when they noticed smoke coming from a closet that contained cartons of health records. Opening the door, they saw flames coming from one carton. The chemist wondered what reagents would quickly stop oxidation to put out the fire. The physicist wondered about how much energy would have to be removed from the fire to stop the combustion. Meanwhile, the epidemiologist was setting

fire to all of the other cartons. Startled, the other two asked: "Why on earth are you doing this?" The epidemiologist quickly answered: "Don't we need a complete sample to extrapolate and then solve this problem properly?"

As I see it, pharmacoepidemiology is an evolving science. It is our hope that *Clinical Therapeutics* will contribute to the growth of this field by publishing and disseminating scholarly written and well-refereed contributions.

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