

# THE CHALLENGES OF EVALUATING INFLUENZA VACCINES

**The influenza virus is the only pathogen that we vaccinate for annually.**

Because the circulating strains of influenza virus may change from year to year, **annual reformulation and revaccination are required** to protect the public against influenza.<sup>1,2</sup> This means we need to evaluate influenza vaccines on an annual basis.<sup>3</sup>



**The complementary value of real-world evidence**

**Randomized controlled trials** (RCTs) are a well-established requirement for determining vaccine safety profiles and efficacy.

But influenza's variability presents a unique challenge, since RCTs follow specific patient populations in a highly specialized environment with specific timeframes.<sup>3-5</sup>

**Real-world evidence** (RWE) availability has been steadily increasing worldwide. Analysis of RWE can help in identifying unmet needs and in the assessment of drug outcomes.<sup>5,6</sup> For example, the US Center for Biologics Evaluation and Research employs monitoring and surveillance programs to evaluate influenza vaccines.<sup>7</sup>

# INFLUENZA HAS IMPACTED THE LIVES OF **MANY CANADIANS**

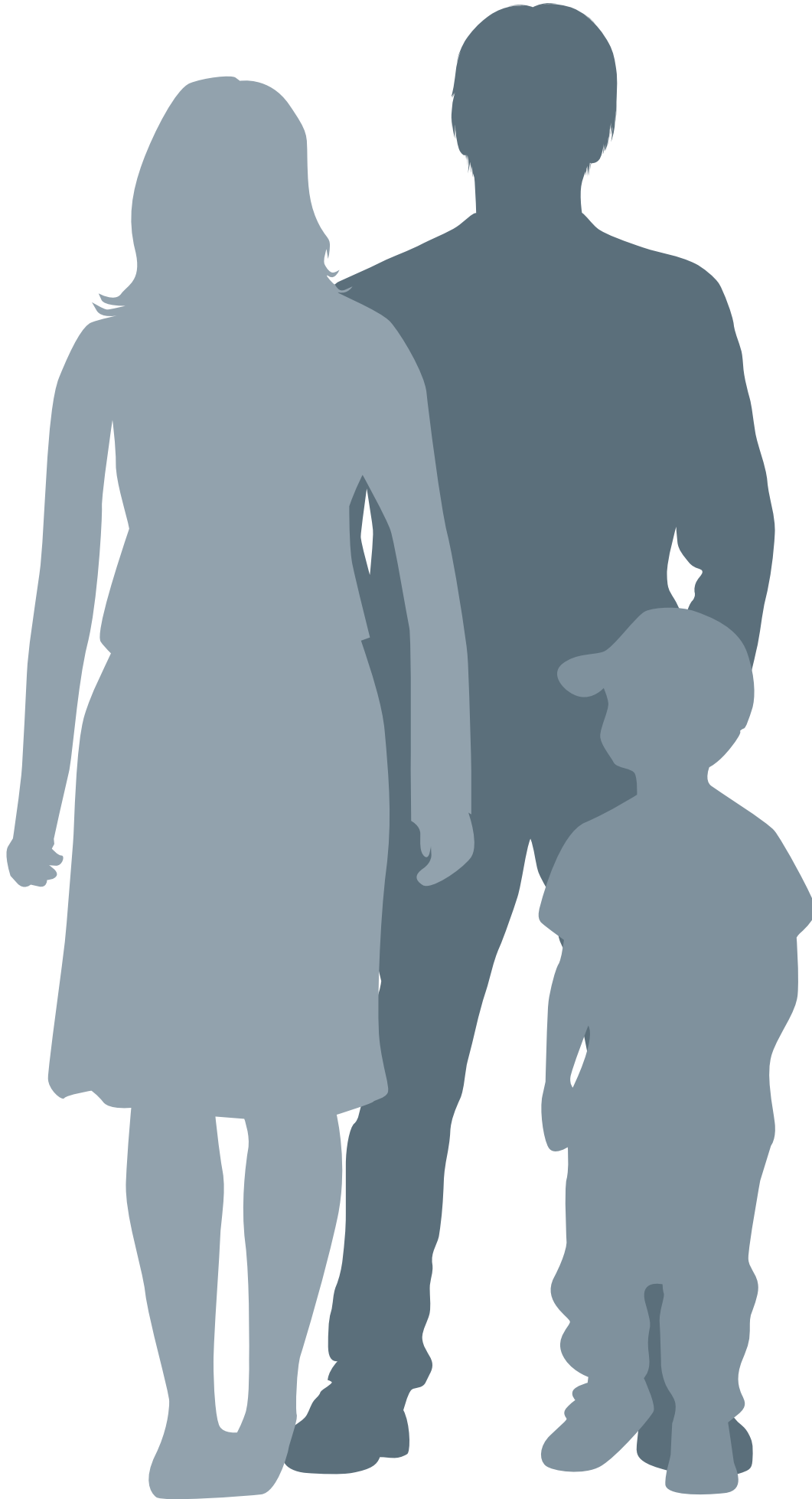
Influenza has been reported to have a high burden in hospitalizations and mortality<sup>2+</sup>

According to NACI 2020-2021, together, influenza and pneumonia are ranked among the top 10 leading causes of death in Canada.<sup>2</sup>

## **Influenza-related hospitalization and mortality in Canada** *Estimated averages per year*



**12,200**  
hospitalizations  
*Influenza-related  
all age groups*



**3,500**  
deaths  
*Influenza-related  
all age groups*



REAL-WORLD EVIDENCE MAY OFFER NEW OPPORTUNITIES TO GAIN INSIGHT INTO PUBLIC HEALTH ISSUES SUCH AS VACCINE UTILIZATION.<sup>4,5,8</sup>

† Influenza vaccines are not indicated to reduce morbidity or mortality following the onset of influenza.

# INFLUENZA VIRUSES AND THE EVER-PRESENT POSSIBILITY OF **ANTIGENIC DRIFT**<sup>1,2</sup>



Many factors may reduce influenza vaccine effectiveness<sup>2†</sup>

- **Strain mismatch** between the vaccine strains and the circulating influenza viruses
- **Type and subtype** of circulating viruses
- **Health and age** of the individual receiving the vaccine

IN RANDOMIZED CONTROLLED CLINICAL TRIALS, COMMERCIALIZED INFLUENZA VACCINES HAVE BEEN SHOWN TO BE EFFICACIOUS IN PROVIDING PROTECTION AGAINST INFLUENZA INFECTION AND ILLNESS. HOWEVER, THE EFFECTIVENESS OF THE VACCINE – THAT IS, HOW IT PERFORMS IN SETTINGS THAT ARE MORE REFLECTIVE OF USUAL HEALTH CARE PRACTICE – CAN VARY FROM SEASON TO SEASON AND BY INFLUENZA VACCINE STRAIN TYPE AND SUBTYPE.<sup>2</sup>

† Not an exhaustive list.

# RWE CAN PROVIDE KEY REAL-WORLD INFORMATION TO THE DRUG RESEARCH AND DEVELOPMENT PROCESS

## Examples of current uses of real-world evidence

- Claims data
- EMRs/EGRs
- Prospective observational data
- Medical claims and billing data
- Patient-generated data, including from in-home-use settings
- Surveillance
- Mortality database
- Primary and secondary care data
- Administrative data
- Disease and device registries
- Pharmacy data
- Cost studies
- Mobile devices
- Consumer data
- Social media

### Real-world evidence

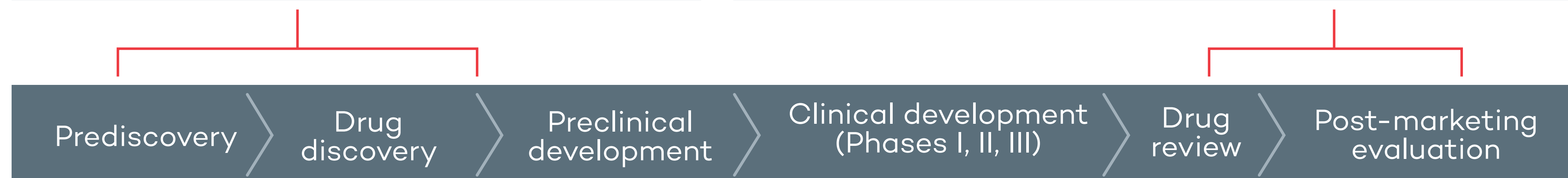
Identifying unmet needs

- Natural history
- Co-morbidities
- Burden of illness
- Incidence and prevalence
- Disease mechanisms
- Clinical practice patterns

### Real-world evidence

Informing clinical and policy decisions

- Usage patterns
- Outcome predictors
- Benefit/risk in subgroups
- Pharmacovigilance
- Population-level impact



Adapted from The National Academies of Science, Engineering, Medicine (USA) and the FDA<sup>6,7</sup>  
EHR = electronic health record; EMR = electronic medical record.

The potential to expand the role of RWE in the drug development process is an area of active investigation.<sup>6</sup>

# RWE & RCTs:

## COMPLEMENTARY BENEFITS

**RCTs:** the well-established requirement of clinical evidence<sup>4,7</sup>

- Research infrastructure is generally separate from routine clinical practice
- Designed to control variability and maximize data quality
- Restrictive eligibility criteria which aim to ensure that the participants in the RCT have the disease of interest or have characteristics which allow detection of a drug effect
- Usually are randomized, double-blind trials with pre-defined endpoints
- Limited generalizability to real-world settings

**RWE:** analysis of real-world data (**RWD**) that can build over time<sup>4,6,7</sup>

- RWD are data relating to patient health status and/or the delivery of health care which are routinely collected from a variety of sources
- RWE is the clinical evidence about the use and potential benefits/risks of a medical product based on an analysis of RWD
  - Has the potential for bias and other issues that may impact the robustness of the findings (e.g., confounding, such as body weight and age)
  - Examples of RWE are prospective and retrospective observational studies, meta-analyses, case-control studies, cohort studies, cross-sectional studies, case reports and disease registries

### Use of RCTs and RWE to evaluate influenza vaccines

RCTs continue to be the most valuable tools for providing evidence of the safety profiles and efficacy of seasonal influenza vaccines.<sup>3-5</sup> However, they can only assess these vaccines in controlled, specific patient populations and over a narrow, well-defined period of time. RWE can provide information about larger, more general groups, such as Medicare and Medicaid populations in the US.<sup>5,7</sup>

# VACCINATING AGAINST INFLUENZA **IS COMPLEX**<sup>1,2</sup>

- Influenza virus strains may change from year to year due to antigenic drift
- Annual reformulation is needed
- Vaccine effectiveness can vary

## **Real-world evidence contributes valuable information regarding influenza vaccines and their use to help guide decision-makers**<sup>4-7</sup>

- Based on real-world data which is timely and increasingly available
- Complements traditional randomized-controlled trials
- Can reflect the dynamics of actual healthcare systems

IN ADDITION TO DATA FROM RANDOMIZED CONTROLLED TRIALS, LOOK TO REAL-WORLD EVIDENCE FOR COMPLEMENTARY INSIGHTS THAT CAN INFORM PUBLIC HEALTH POLICY IN VACCINATING AGAINST INFLUENZA.<sup>7</sup> INFLUENZA VIRUS AND INFLUENZA VACCINES CHANGE WITH TIME.<sup>1,2</sup> RWE IS A VALUABLE TOOL THAT CAN EVALUATE INFORMATION ABOUT VACCINES IN A TIMELY WAY.<sup>5,7</sup>

**References:** **1.** Government of Canada. Vaccination for adults. <https://www.canada.ca/en/public-health/services/vaccination-adults.html#a5>. Published March 29, 2019. Accessed on September 13, 2020. **2.** Public Health Agency of Canada. An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI). Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2020–2021. <https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2020-2021.html>. Published May 2020. Accessed on September 13, 2020. **3.** Government of Canada. Access to the seasonal flu vaccine in Canada. How the flu shot makes its way from the laboratory to the doctor's office. [http://publications.gc.ca/collections/collection\\_2007/hc-sc/H164-47-2007E.pdf](http://publications.gc.ca/collections/collection_2007/hc-sc/H164-47-2007E.pdf). Published 2007. Accessed on September 13, 2020. **4.** Government of Canada. Elements of Real World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle. <https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html>. Published March 5, 2019. Accessed on September 13, 2020. **5.** Government of Canada. Optimizing the Use of Real World Evidence to Inform Regulatory Decision Making. <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/optimizing-real-world-evidence-regulatory-decisions.html>. Published April 16, 2019. Accessed on September 14, 2020. **6.** The National Academies of Sciences Engineering Medicine. Real-World Evidence Generation and Evaluation of Therapeutics: Proceedings of a Workshop. 2017. <https://www.nap.edu/catalog/24685/real-world-evidence-generation-and-evaluation-of-therapeutics-proceedings-of> (accessed Nov. 4, 2020). **7.** FDA. Framework for Real-world evidence program. 2018. **8.** PHAC. Seasonal influenza vaccine coverage in Canada. 2017–2018.



Seqirus Canada Inc.  
Kirkland, Québec  
[www.seqirus.ca](http://www.seqirus.ca)  
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