REAL-WORLD EVIDENCE AND RANDOMISED CLINICAL TRIALS FOR VACCINES

To ensure people are receiving the best protection against influenza, it is important to determine how effective influenza vaccines are.

HOW CAN WE DETERMINE VACCINE EFFECTIVENESS?

Both vaccine efficacy and vaccine effectiveness can provide an indication of how well a vaccine works.[1]

VACCINE EFFICACY[1]

The extent to which a vaccine provides a beneficial result under **ideal conditions**

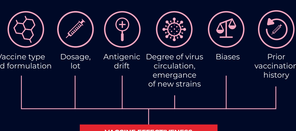
Measured in **randomised controlled trials (RCTs)**

VACCINE EFFECTIVENESS[1]

The extent to which a vaccine provides a beneficial result under **real-world conditions**

Measured using **real-world evidence (RWE)** studies (also known as observational studies)

As vaccine effectiveness is measured in real-world conditions, it can be influenced by a number of factors:[2-5]



RCTS AND RWE STUDIES HAVE DISTINCT PURPOSE AND METHODOLOGY:[5,6]

RCTs		RWE STUDIES
Demonstrate clinical efficacy and safety	**Purpose**	Demonstrate clinical safety and effectiveness in a real-world clinical practice setting
Yes	**Randomised**	Sometimes[1]
Optimal, controlled setting	**Study environment**	Uncontrolled, reflective of real clinical practice
Highly selected through well-defined eligibility criteria	**Study population**	Heterogeneous due to limited eligibility criteria
Alternative/placebo	**Comparator**	Single marketed drug or standard of care
Well-defined	**Endpoints**	Endpoints typically encountered in clinical care
Mandated testing and visit schedule	**Follow-up**	Testing and care based on usual/ real-world practice setting

[1]Pragmatic study designs can be randomised; non-interventional, observational studies are not randomised.

The choice for which study design to use will depend on the objective of the study as well as weighing up the **benefits and limitations** associated with each study type:[5-12]

RCTs

BENEFITS

- ✓ Low risk of bias
- ✓ Can determine vaccine efficacy
- ✓ Robust data

LIMITATIONS

- × Slower data output
- × Must be carried out over multiple seasons for influenza
- × Data may not be generalisable owing to strict eligibility criteria
- × Participants may be lost to follow up
- × Data may not be comparable between seasons

RWE

- ✓ Quick data output
- ✓ Potential for very large participant numbers
- ✓ Can be carried out over one season
- ✓ Can identify events that occur at a low rate
- ✓ Can determine effectiveness in populations not usually enrolled in RCTs (e.g. owing to low patient numbers or complex patient history)
- ✓ Can determine both direct and indirect protection against viruses
- ✓ No special attendance/ visits needed
- ✓ Reflective of real-world clinical practice

- × Not able to determine efficacy
- × May be subject to bias and confounding

Whilst randomised studies are considered the 'gold standard' when determining the efficacy of vaccines, data outputs are slow.[13] **RWE can allow for quick patient enrollment and rapid retrieval of data.**[14]

The **need for rapid data is particularly pertinent for influenza**, owing to the rapidly evolving nature of the virus, seasonal aspects and annual vaccine reformulation.[10]

A Cochrane review that investiagted the impact of study design on effect measured said that **"on average, there is little difference between the results obtained from RCTs and observational studies"** and **"no significant differences between effects of study designs were noted"**.

HOW HAS RWE BEEN USED TO INFORM DECISION MAKING?

The value of RWE for decision making was demonstrated during the COVID-19 pandemic.[15] Owing to the need for quick data turnaround, RWE studies were used to assess vaccine effectiveness and inform policy.

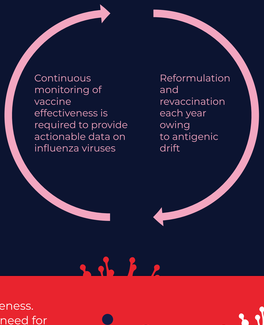
Test-negative case–control studies evaluated vaccine effectiveness against COVID-19, and helped to evolve the UK vaccination programme by:[17–21]

- evaluating effectiveness against symptomatic disease, hospitalisations and death
- evaluating effectiveness against antigenically drifted SARS-CoV-2 variants
- informing the need for booster doses, booster vaccine type and dosing intervals
- establishing effectiveness of booster doses against mild and severe disease
- identifying effectiveness in various at-risk populations

In the case of influenza, RWE is valuable tool for evaluating vaccine effectiveness owing to the need for timely information.[3,10,22]

Collection of RWE allows for retrospective annual evaluations to guide decision making by:[3,9,10,16]

- ✓ providing a timely and buildable data set to monitor and evaluate effectiveness;
- ✓ build comparable data year-on-year to identify trends;
- ✓ determining whether vaccine performance is affected by evolving influenza viruses.



The JCVI advocate for the generation of high-quality RWE, to support consideration of the relative effectiveness of the influenza vaccines.[23]

Both RCTs and RWE can provide important data on vaccine effectiveness. Owing to the evolving nature and seasonality of influenza there is a need for timely methods of gathering evidence.

Well-conducted RWE studies can gather evidence for vaccine effectiveness quickly, and enable year-on-year comparisons to be made, allowing for timely changes to public health policy.

COVID-19, coronavirus disease 2019; JCVI, Joint Committee on Vaccination and Immunisation; RCT, randomised controlled trial; RWE, real-world evidence; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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