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RESEARCH LETTER

Virus interference and estimates of influenza vaccine effectiveness from test-negative studies

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CONFLICTS OF INTEREST

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To the Editor:

Placebo-controlled randomized controlled trials provide the most convincing data on the protection against infection and illness conferred by influenza vaccines, but are not always feasible.[1] Despite the presence of technical difficulties including antigenic variations of the virus, non-measurable confounders, and typically mild disease presentation with non-specific symptoms, observational studies can provide ongoing evidence that influenza vaccines retain effectiveness.[1]

One observational study design for estimating vaccine effectiveness (VE) involves identifying medically-attended acute upper respiratory tract infections (URTIs) and attributing them to influenza or other etiologies using laboratory tests.[1-8] Vaccination coverage is then compared between influenza-positive patients (cases) and influenza-negative patients (controls), adjusting for potential confounders. An apparent advantage of the use of controls with acute URTI is that it reduces the risk of bias due to health-care seeking behavior, if vaccinated individuals were more likely to seek care when ill.[3-5]

An assumption required for this 'test-negative' case-control study design to be valid is that the risk of illness associated with non-influenza infections must be independent of receipt of influenza vaccination.[3] However, it has been hypothesized that a respiratory virus infection confers immunity against the same and other respiratory viruses for a short time, perhaps a few weeks, associated with the innate immune response to viral infection including

interferons which have broad protective effects against a range of viruses.[9,10] This biological mechanism, known as temporary non-specific immunity, has been proposed as the cause of epidemiological 'interference' between respiratory virus epidemics in which an epidemic of one virus appears to affect epidemics of other viruses at the ecologic level.[11-13] Here we discuss the implications of virus interference via temporary non-specific immunity on VE estimates from test-negative studies.

In Figure 1, cases that test positive for influenza are classified by vaccination status. Within the controls it is possible to separate those that test positive for a non-influenza respiratory virus from those that test negative for all viruses. Odds ratios (ORs) can be estimated using either or both control groups (OR_1, OR_2 and OR_3 in Figure 1), and the calculations are illustrated with data from a published study.[2] In that study, influenza vaccination appeared to be associated with an increased risk of non-influenza respiratory virus infections, which is consistent with temporary non-specific immunity. In a separate placebo-controlled trial of influenza vaccination, we reported that recipients of influenza vaccine had significantly higher risk of non-influenza respiratory virus infections.[14]

Temporary non-specific immunity would lead to a higher risk of non-influenza respiratory virus infections among vaccine recipients, i.e. in general we might expect $B_1/D_1 > B_2/D_2$, and $OR_2 < OR_1 < OR_3$. If VE were estimated as 1–OR, the inclusion of individuals who test positive for other respiratory viruses would tend to increase the VE estimate. It is unclear whether OR_3 would provide an unbiased estimate of VE. A negative test for respiratory viruses in a patient with

acute URTI does not exclude a respiratory virus etiology, since the test may lack perfect sensitivity particularly for lower viral loads, the specimen may have been incorrectly collected from the patient, or for other reasons.[2]

There are some caveats to this discussion. First, ORs from case-control studies should be adjusted for potential confounders that may relate both to being vaccinated and to experiencing a URTI associated with influenza, although adjustment may not affect the ordering of OR_1, OR_2 and OR_3. Non-specific immunity cannot easily be directly measured, and the same problem may extend to conditional evaluation methods in transmission studies.[15] Second, we have not discussed other potential biases in test-negative studies which are explored in detail elsewhere.[3,5] Finally, if influenza incidence is low or temporary non-specific immunity is weak, there should not be substantial differences between OR_1, OR_2 and OR_3.

Selection of the control group can be a weak point of case-control studies,[15] and as discussed here can be affected by transmission dynamics including interference. More detailed investigations including simulation approaches are warranted into of the interpretation of VE estimates from test-negative studies.

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FIGURE LEGEND

Figure 1. Schematic table of a test-negative case-control study illustrated with data from a published study.

Figure 1. Schematic table of a test-negative case-control study illustrated with data from a published study*.

Influenza vaccination status	Case patients with influenza	Control patients	
		A non-influenza respiratory virus detected	No respiratory virus detected
Vaccinated	A = 14	$B_1 = 90$	$B_2 = 24$
Unvaccinated	C = 34	$D_1 = 81$	$D_2 = 46$

* For the purposes of this illustration, we extracted data from Kelly et al.[2] including the patients recruited from emergency departments as well as from general practices, and the fully vaccinated individuals are considered to be "vaccinated" while other individuals are considered to be "unvaccinated".

The crude odds ratio (OR) from this study, including all controls, would be estimated as $OR_1 = (A \times [D_1 + D_2]) / ([B_1 + B_2] \times C) = 0.46$.

Restricting controls to the group who tested positive for a respiratory virus, the crude odds ratio would be $OR_2 = (A \times D_1) / (B_1 \times C) = 0.37$.

Restricting controls to the group who tested negative for all viruses, the crude odds ratio would be $OR_3 = (A \times D_2) / (B_2 \times C) = 0.79$.

ORs should be adjusted for confounders, and presented with confidence intervals, although this is unnecessary for the present illustration.