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Influenza vaccine effectiveness by test-negative design – Comparison of inpatient and outpatient settings

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ABSTRACT

Background: Observational studies of influenza vaccine effectiveness (VE) are increasingly using the test-negative design. Studies are typically based in outpatient or inpatient settings, but these two approaches are rarely compared directly. The aim of our study was to assess whether influenza VE estimates differ between inpatient and outpatient settings.
Methods: We searched the literature from Medline, PubMed and Web of Science using a combination of keywords to identify published studies of influenza VE using the test-negative design. Studies assessing any type of influenza vaccine among any population in any setting were considered, while interim studies or re-analyses were excluded. Retrieved articles were reviewed, screened and categorized based on study setting, location and influenza season. We searched for parallel studies in inpatient and outpatient settings that were done in the same influenza season, in the same location, and in the same or similar age groups. For each of the pairs identified, we estimated the difference in VE estimates between settings, and we tested whether the average difference was significant using a paired *t*-test.
Results: In total 25 pairs of estimates were identified that permitted comparisons between VE estimates in inpatient and outpatient study settings. Within pairs, the prevalence of influenza was generally higher among patients enrolled in the outpatient studies, while influenza vaccination coverage among the test-negative control groups was generally higher in the inpatient studies. There was no heterogeneity in the paired differences in VE, and the pooled difference in VE between inpatient and outpatient studies was −2% (95% confidence interval: −12%, 10%).
Conclusions: We found no differences in VE estimates between inpatient and outpatient settings by studies using the test-negative design. Further research involving direct comparisons of VE estimates from the two settings in the same populations and years would be valuable.

1. Introduction

Influenza viruses are associated with a substantial disease burden of both medically attended ambulatory care and hospitalizations [1,2]. Vaccination is the best means of preventing influenza virus infections, but influenza vaccine effectiveness (VE) may differ from year to year and among different populations. Recently, there have been increasing numbers of studies estimating influenza VE using the test-negative design [3]. In this study design, patients are enrolled in outpatient clinics and/or hospitals based on a clinical case definition such as acute respiratory illness (ARI) or other syndromes consistent with influenza virus infections. Patients are then tested for influenza virus, and VE is estimated from the odds ratio comparing the odds of vaccination among patients testing positive for influenza versus those testing negative, adjusting for potential confounding factors. This study design is believed to be valid under a range of scenarios [4,5]. Importantly, this design is easy to implement in both inpatient and outpatient settings.

Estimates obtained from inpatient and outpatient settings in the same population may be expected to differ for several reasons. First, patients presenting to hospitals may present later in infection, may be older and may be more likely to be co-infected with another respiratory virus. There may therefore be a greater number of false negatives due to reduced viral shedding with time and

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Table 1
Comparison of study design between inpatient and outpatient settings from 14 publications.

Study	Country	Season	Setting	Case definition	Interval since onset	Dominant type/subtype[b]	Vaccine match[c]	Time in model	Comorbid in model	% with high-risk condition
Cheng et al. [12]	Australia	2010	Inpatient	Admission	Unrestricted	H1pdm	Yes	Fortnight	Yes	79%
Levy et al. [13]	Western Australia		Outpatient	ILI	≤4d			Week	No	NA
Fielding et al. [20]	Victoria, Australia		Outpatient	ILI	≤4d			Month	No	
Kwong et al. [14]	Ontario, Canada	2010–2011	Inpatient	Admission	Unrestricted	H3	Yes	Month	Yes	≥72.8%[d]
Skowronski et al. [15]	Canada		Outpatient	ILI	≤7d			Week	Yes	34.9%
Puig-Barberà et al.[a] [16]	Valencia, Spain	2011–2012	Inpatient	ILI	Not specified	H3	No	Week	No	88%
Jimenez-Jorge et al.[a] [17]	Spain		Outpatient	ILI	≤7d			Week (cat)	No	62.9%
Talbot et al. [18]	Tennessee, USA	2011–2012	Inpatient	ARI	≤10d	H3	No	Onset to admission	Yes	86%
Ohmit et al. [19]	USA		Outpatient	ARI	≤7d			Fortnight	Yes	25.4%
Cheng et al. [21]	Australia	2012	Inpatient	Admission	Not specified	H3	No	Not specified	Yes	83.2%
Sullivan et al. [22]	Australia		Outpatient	ILI	Not specified			Month	No	NA
Martinez-Baz et al. [10]	Narrava, Spain	2012–2013	Inpatient	ILI	≤7d	B	Yes	Month	Yes	NA
Martinez-Baz et al. [10]	Narrava, Spain		Outpatient	ILI	≤7d			Month	Yes	NA
Turner et al. [9]	Auckland, New Zealand	2013	Inpatient	SARI	≤7d	H3	Yes	Week	Yes	64.5%
Turner et al. [9]	Auckland, New Zealand		Outpatient	ILI	≤7d			Week	Yes	NA
Pierse et al. [23]	Auckland, New Zealand	2014	Inpatient	SARI	≤7d	H1pdm	Yes	Timing of the intervention to peak of season	Yes	51%
Pierse et al. [23]	Auckland, New Zealand		Outpatient	ILI	≤7d			Timing of the intervention to peak of season	Yes	26%

[a] Enrolled patients targeted for influenza vaccination. Cases were positive for influenza A(H3N2) virus.
[b] Information retrieved either from studies or the WHO website.
[c] Information retrieved either from studies or the WHO website.
[d] 72.8% was the percentage of subjects with chronic cardiovascular disease.