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Burden of medically attended influenza infection and cases averted by vaccination – United States, 2013/14 through 2015/16 influenza seasons

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ABSTRACT

Background: In addition to preventing hospitalizations and deaths due to influenza, influenza vaccination programs can reduce the burden of outpatient visits for influenza. We estimated the incidence of medically-attended influenza at three geographically diverse sites in the United States, and the cases averted by vaccination, for the 2013/14 through 2015/16 influenza seasons.

Methods: We defined surveillance populations at three sites from the United States Influenza Vaccine Effectiveness Network. Among these populations, we identified outpatient visits laboratory-confirmed influenza via active surveillance, and identified all outpatient visits for acute respiratory illness from healthcare databases. We extrapolated the total number of outpatient visits for influenza from the proportion of surveillance visits with a positive influenza test. We combined estimates of incidence, vaccine coverage, and vaccine effectiveness to estimate outpatient visits averted by vaccination.

Results: Across the three sites and seasons, incidence of medically attended influenza ranged from 14 to 54 per 1000 population. Incidence was highest in children aged 6 months to 9 years (33 to 70 per 1000) and lowest in adults aged 18–49 years (21 to 27 per 1000). Cases averted ranged from 9 per 1000 vaccinees (Washington, 2014/15) to 28 per 1000 (Wisconsin, 2013/14).

Discussion: Seasonal influenza epidemics cause a considerable burden of outpatient medical visits. The United States influenza vaccination program has caused meaningful reductions in outpatient visits for influenza, even in years when the vaccine is not well-matched to the dominant circulating influenza strain.

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1. Introduction

Influenza is unique among vaccine-preventable diseases, in that maintaining immunity requires frequent re-vaccination due to the ongoing antigenic drift of influenza viruses [1]. In practice, this is accomplished through yearly influenza vaccination programs, which represent a multi-billion dollar investment of public health resources annually [2]. The effectiveness of seasonal influenza vaccines, and the impact of influenza vaccination on the burden of disease due to influenza, can vary considerably year to year [3]. A number of factors contribute to this variability, including the dominant virus types/subtypes and the antigenic match between the virus strains included in the vaccines and the circulating virus strains [4,5]. Systems to monitor influenza vaccine effectiveness (VE) have been established in a number of countries (e.g. [6–9]), contributing to a growing understanding of sources of variability in influenza VE. These studies can also identify unexpected problems with influenza vaccines, such as reduced effectiveness of certain vaccine virus strains from specific vaccine products or due to egg adaptation [4,10].

Although annual VE estimates serve many scientific and public health purposes, of perhaps greater interest to policy makers are

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estimates of the impact of influenza vaccination programs on cases, deaths, or medical encounters averted by vaccination. These estimates have been more difficult to obtain due to underdiagnosis of influenza in most clinical settings [11]. Many systems for estimating influenza VE through test-negative sampling are not equipped to estimate the incidence of influenza, which is needed to assess vaccine impact. One exception is the United States Influenza Vaccine Effectiveness (US Flu VE) Network [6]. Several study sites within the US Flu VE Network are able to provide population-based estimates of influenza incidence as well as VE. We have previously used the US Flu VE Network to demonstrate that ambulatory care visits averted by influenza vaccination can vary even when VE is relatively consistent, due to differences in influenza attack rates [12]. In this paper, we report the impact of influenza vaccination in the US on ambulatory care visits for influenza for the 2013/14 through 2015/16 influenza seasons, during which influenza VE varied considerably.

2. Methods

Details of the US Flu VE Network have been published previously [5,6,10,13]. In brief, the US Flu VE Network consists of five geographically distinct sites in the United States: Kaiser Permanente Washington in western Washington State (KPW, formerly Group Health Cooperative); the Marshfield Clinic in Marshfield, Wisconsin (MC); Baylor Scott and White Health in Temple, Texas (BSW); the University of Michigan and the Henry Ford healthcare systems in Ann Arbor and Detroit, Michigan; and the University of Pittsburgh partnered with the UPMC (aka, the University of Pittsburgh Medical Center) in Pittsburgh, Pennsylvania. These sites conducted active surveillance for medically attended influenza at ambulatory care clinics. For the present paper, estimates of influenza incidence were taken from the KPW, MC, and BSW sites, for which enumerated population cohorts could be defined and which have demographic and healthcare utilization data available through linked databases. The study was approved by institutional review boards at each participating site and the Centers for Disease Control and Prevention (CDC).

2.1. Source populations

We defined population cohorts as of September 1st of each study year (2013–2015). For KPW, the source population was drawn from enrollees in KPW's integrated group practice. These members receive healthcare coverage through KPW and receive medical care from KPW providers at KPW medical centers. Influenza surveillance was conducted at five (2013/14, 2015/16) or seven (2014/15) KPW medical centers. For estimating influenza incidence, we restricted the source population to KPW members whose primary healthcare provider was at one of the influenza surveillance clinics. The MC population consisted of (a) persons with at least 12 months of residency (or since birth for those <12 months old) in the central Marshfield Epidemiology Study Area (MESA), a 14 zip code region centered around Marshfield, Wisconsin (all seasons), and (b) non-MESA residents who have had ≥2 encounters within the 3 prior years at the main MC campus in Marshfield, affiliated hospital, or two adjacent satellite clinics (aged 6 months through 17 years in 2014/15 and all ages in 2015/16). MC captures at least 93% of all medical visits from MESA residents [14]. Influenza surveillance was conducted at primary care clinics located at the Main MC campus and one satellite clinic that serves MESA residents. The BSW population consisted of persons who had seen a BSW primary care provider for any reason within the 3 prior years and who lived in the Temple Population Research Area of East Bell County (defined by zip codes 765xx, excluding 7654x); BSW's market share among this population covers approximately 72% of all outpatient visits (MG, personal communication). Influenza surveillance was conducted at seven BSW primary care and urgent care clinics in East Bell County.

We defined covariates on all subjects in the source populations using administrative healthcare databases as previously described [12]. Subjects were classified according to age on September 1st of each season (6 months to 8 years; 9 to 17 years; 18 to 49 years, 50 to 64 years; and 65 years or older) and receipt of current season's influenza vaccine, as defined from administrative healthcare databases and state immunization registries [15]. We identified all ambulatory care visits for presumptive medically attended acute respiratory illness (ARI) based on International Classification of Diseases, Version 9, Clinical Modification (ICD-9, for encounters prior to 1 October 2014) and Version 10 (ICD-10, for encounters on or after 1 October 2014) codes (Supplemental Appendix).

2.2. Influenza surveillance and laboratory testing

At each surveillance clinic, trained staff reviewed appointment schedules and consulted with clinical staff, as needed, to identify patients seeking care for ARI, defined as respiratory illness with cough of less than eight days' duration [13]. Eligible patients were those with ARI who were ≥6 months of age as of September 1st (and thus eligible for current season's influenza vaccination). Study staff collected combined nasal and oropharyngeal (nasal only on children <2 years of age) swabs from eligible and consenting patients. Swab specimens were tested for influenza A and B viruses using real-time reverse transcriptase polymerase chain reaction (RT-PCR), with probes and primers provided by CDC. Specimens testing positive were further tested for virus subtype (influenza A) or lineage (influenza B). For the present study, US Flu VE enrollees who were not members of the site's source population were excluded from the analyses. Influenza cases were defined as patients seeking outpatient care with a positive test for any influenza virus.

2.3. Analysis

We estimated the cumulative incidence of medically attended influenza in our study populations by extrapolating the total number of influenza cases in the populations from the number of influenza cases among the US Flu VE enrollees [12]. For this, we stratified the source populations into mutually exclusive groups based on study site *s*, age group *a*, vaccination status *v*, and number of medically attended acute respiratory illness (MAARI) visits *m*. Each US Flu VE enrollee was then assigned a sampling weight. US Flu VE enrollees with zero MAARI visits were assigned a sampling weight of 1.0; the weight for other enrollees was the total number of subjects in the enrollee's (*s, a, v, m*) stratum divided by the number of US Flu VE enrollees in that stratum. Using the sampling weights, we estimated the total number of medically attended influenza cases in each (*s, a, v, m*) stratum. Confidence limits were calculated by bootstrapping from the source populations and the US Flu VE enrollees. To account for the fact that some influenza cases occurred before or after active surveillance at each site, we up-weighted the number of influenza cases at each site by the inverse of the proportion of influenza cases detected by state surveillance (Texas, Washington, and Wisconsin) that occurred during enrollment periods.

After calculating the cumulative incidence of influenza, we estimated the number of outpatient influenza visits averted by vaccination as previously described [12]. Age-specific estimates of influenza VE were taken from the US Flu VE Network. For each year and within each age stratum, we assumed influenza VE to be con-

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