Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Impact of repeated influenza vaccinations in persons over 65 years of age: A large population-based cohort study of severe influenza over six consecutive seasons, 2011/12–2016/17

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A R T I C L E I N F O

Article history:
Received 18 April 2018
Received in revised form 14 July 2018
Accepted 22 July 2018
Available online xxxx

Keywords:
Seasonal influenza
Repeated vaccinations
Vaccine effectiveness
Older persons

A B S T R A C T

Background: A forty-year debate on the potential negative effects of repeated seasonal influenza vaccination has been inconclusive, with multiple observational studies of various design providing heterogeneous results too inadequate to inform vaccination policy.
Methods: A large population-based cohort study including over one-million observations in individuals over age 65 from six consecutive seasons (2011/12 –2016/17) in Stockholm County, Sweden. Current season vaccine effectiveness (VE) against severe, mostly hospital-attended, influenza was assessed using Cox multivariate regression analyses adjusting for demographic variables, comorbidities and previous seasonal influenza vaccination status.
Results: In none of the six seasons was VE significantly different in persons vaccinated in the current season only, compared to those who had been vaccinated in both the current and the previous season. Neither were there any differences in VE during the seasons 2014/15–2016/17 when comparing persons vaccinated during the current season only vs. those vaccinated during one-three or four-five previous influenza seasons. In contrast, persons only vaccinated during one or more previous years had no protection during the current season.
Conclusions: Persons above 65 years are the largest group at risk for severe or complicated influenza and policy should support their yearly seasonal influenza vaccination, which is to-date the best preventive measure available for all risk groups. No negative effects of repeated seasonal vaccination were seen in this large population-based cohort of older persons with severe influenza, which strengthens the recommendation that persons belonging to this age group should be vaccinated yearly.

1. Introduction

During the last forty years, there has been a debate whether protection from seasonal influenza vaccine may be attenuated by vaccination in prior seasons [1–14]. The major concern has been that prior vaccination or vaccinations may attenuate the effectiveness of the influenza vaccine during the current seasons, particularly for Influenza A(H3N2) and B strains [4,5,9,10], but also for influenza A(H1N1)pdm09 [4,13]. An often-used model for explaining the possible mechanism for such interaction is the antigen distant hypothesis (ADH), described by Smith et al in the late 1990s [15]. The ADH predicts that there may be negative interference from a prior season's vaccine on the current season's vaccine effectiveness, when the antigenic distance is small between the two vaccines but large between the prior vaccine and the current season's epidemic strain [15]. However, most recent studies indicating a negative interference of prior vaccinations have mainly included children, adolescents and non-elderly adults seeking outpatient care, and there is a lack of data on the possible impact in older persons with severe influenza.

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https://doi.org/10.1016/j.vaccine.2018.07.052
0264-410X/© 2018 Published by Elsevier Ltd.

In Stockholm County, a catchment area that encompasses 2.3 million individuals, seasonal influenza vaccination has been offered free-of-charge to persons 65 years and older since 2001, and data on all vaccine exposures for this age group have been recorded in a web-based vaccination register since 2009. We have previously shown that vaccine effectiveness (VE) is possible to estimate using population-based registers [16,17]. The aim of this study was to use this method to investigate the impact of prior vaccinations on the VE of seasonal influenza vaccine during six seasons, 2011/2012 to 2016/2017, in older persons (>65 years). In this age group the risk for severe influenza is substantial and, in Stockholm County, a majority of older persons with laboratory-confirmed influenza will be hospitalized.

2. Methods

2.1. Study population

Six annual closed cohorts each comprising all individuals ≥66 years of age (n ~ 300.000 persons yearly), registered in Stockholm at the start of each season, 2011/12–2016/17. In Stockholm County influenza vaccination is offered free-of-charge and entered in the vaccine register from 65 years, irrespective of whether the vaccination is performed by the county's primary health care, outpatient care, or in private vaccination clinics.

The present study included persons from 66 years of age, so that all those included could have received an influenza vaccination free-of-charge in at least one prior season. The influenza season was defined as starting on October 1 and ending on May 31 the following year.

2.2. Data sources

As has been described earlier [17], age, sex, diagnoses of influenza and comorbidities were collected using Stockholm County's central database (VAL) and the Stockholm Mosaic system [18] was used as a proxy for living conditions and socioeconomic status. Immigration and death dates were not available in VAL, necessitating the design of a closed cohort for each season.

VAL has over 99% coverage for inpatient care [19] and the validity of the diagnostic coding has been estimated to 85–95%, depending on the diagnosis [20]. The validity of VAL was confirmed for influenza by the present study, since 95% of inpatients discharged with an influenza diagnosis (International Classification of Diseases, 10th revision (ICD-10) J09-J11) had a laboratory-confirmed influenza (LCI) during the two seasons (2015/16 and 2016/17) when such data were available.

Comorbidities were extracted from VAL using ICD-10 codes for tumours (C00-D48), diabetes (E10–14), circulatory (I00-I99) and non-acute respiratory illness (J40-J99) registered for a period of up to three years before the start of the respective season.

Vaccinera, the County's vaccination register, contains all data on seasonal and pandemic influenza vaccination of persons ≥65 years of age, since the influenza pandemic in 2009 [21]. The regional coverage of the Vaccinera database can be assumed to be 100% as vaccination is free-of-charge for the patient, and registration is mandatory and required for reimbursements to the healthcare provider.

SmiNet is the national electronic surveillance system for the reporting of communicable diseases [22]. Since December 1, 2015, it is mandatory for all Swedish laboratories to report findings of influenza (reported as influenza A or B) to SmiNet.

Data from VAL, Vaccinera and SmiNet were linked using the same personal identification numbers (PIN).

2.3. Case definition

During 2011/12 to 2014/15 seasons, a case was defined as being treated in hospital with a clinical diagnosis of influenza (ICD-10 codes J09 - J11). These cases were obtained from VAL (see above).

During the 2015/16 and 2016/17 seasons, when it was possible to link to SmiNet, a case was defined as having been diagnosed with LCI by polymerase chain reaction (PCR). PCR is the only method used for influenza diagnoses in Sweden since 2009.

2.4. Vaccination status

Vaccination dates and vaccine types were derived from Vaccinera. Two tri-valent inactivated split-virus vaccines, Vaxigrip® (Sanofi Pasteur MSD) and Fluarix® (GSK) accounted for more than 99% of the vaccinations performed. No high-dose, adjuvanted, or quadrivalent vaccines were used.

During each "current" season, 2011/12–2016/17, individuals with influenza infection before vaccination, or up to 13 days post-vaccination, were considered to be unvaccinated, as were those who did not receive the seasonal vaccine. Those with influenza infection ≥14 days post vaccination were considered to be vaccinated.

During each "previous" season, 2010/11 to 2015/16, a person was defined as vaccinated (exposed) if at least one influenza vaccination was noted in the vaccine register during that previous season. We did not include the 2009/2010 seasonal vaccine in the analysis because about 60% of persons ≥65 years received the pandemic ASO4-adjuvanted monovalent influenza A(H1N1)pdm09 (Pandemrix®,GSK) vaccine during October – December 2009 [21], with much fewer later vaccinated with the 2009/10 seasonal vaccine. However, vaccination with Pandemrix® 2009–2010 was included as a covariate in the statistical analysis because this adjuvanted vaccine induced a better protection, and at least in children also a protection of longer duration, than ordinary seasonal vaccine [21,23].

2.5. Influenza epidemiology

The dominating circulating seasonal influenza strains and levels of influenza activity in Sweden during the six seasons are shown in Table 1. Mismatch between the vaccine strain and the dominating strain or strains was seen in 2011/12 (A(H3N2)), 2012/13 (B), 2014/15 (A(H3N2) and B), 2015/16 (B), and 2016/17 (A(H3N2)). During 2016/17, mutations in the egg-adapted vaccine for A (H3N2) as well as in the circulating 3C.2a1 and 3C.2a subclades resulted in mismatch [16,24–26].

2.6. Statistical analyses

Vaccine effectiveness (VE) was assessed using Cox regression analyses. Hazard rate ratios (HRR) were calculated comparing the hazard rates of influenza cases among vaccinated and unvaccinated individuals. VE was calculated as (1 – adjusted HRR) × 100 % and reported with 95% confidence intervals (CI). Vaccination status during the study season was modelled as a time-varying exposure, so individuals could contribute to both vaccinated and unvaccinated risk-time.

Two models were used [5]. In model 1, VE for each season was estimated for all combinations of vaccine exposure in the current and previous season: 1. Not vaccinated in either season (reference group), 2. vaccinated in the current season only, 3. vaccinated in the previous season only, and 4. vaccinated in both seasons.

In model 2, VE was estimated for the seasons 2014/15, 2015/16 and 2016/17 for all combinations of seasonal influenza vaccine exposure in the current season and 4-year (season 2014/15) or