Epidemiology and burden of illness of seasonal influenza among the elderly in Japan: a systematic literature review and vaccine effectiveness meta-analysis

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INTRODUCTION

- Seasonal influenza causes considerable healthcare burden. Morbidity and mortality are concentrated among older adults, the very young, and people with chronic diseases.[1]
- In Japan, the influenza-associated respiratory mortality rate per 100,000 people has been estimated at 0.2, 3.5 and 27.5 among individuals aged <65 years, 65-74 years and ≥75 years, respectively.[2]
  - The population is aging and the burden in the elderly is therefore likely to increase.[3]
  - Detailed epidemiological data have been generated from individual studies with different methods and populations, but never synthesized.
- Annual vaccination is recommended for elderly and other high-risk Japanese population groups. Vaccine effectiveness (VE) is affected by virus type/subtype, antigenic match, age and health status of vaccine recipients and vaccination timing.[4]
- To describe the available evidence on influenza epidemiology and VE in adults in Japan, we conducted a systematic review and meta-analysis of VE, stratified by study characteristics.

METHODS

Literature review

- Systematic literature review of articles published in English or Japanese between January 1, 1997 and November 20, 2018 from PubMed, EMBASE, and ICHUSHI, and grey literature
- Search criteria:
  - Influenza[MeSH] AND *selection of epidemiological and/or health economic terms* AND elderly OR adult AND Japan AND published 1997 – 2018 AND English[lang] OR Japanese[lang]
- **Included**: systematic reviews, prospective or retrospective observational studies (evaluating at least 10 patients), randomized controlled trials and economic studies describing populations aged ≥18 years
- **Excluded**: animal studies, in vitro/ex vivo studies, gene expression/protein expression studies, laboratory studies, editorials, non-systematic reviews, conference minutes, and case studies/case series evaluating fewer than 10 patients

Meta-analysis

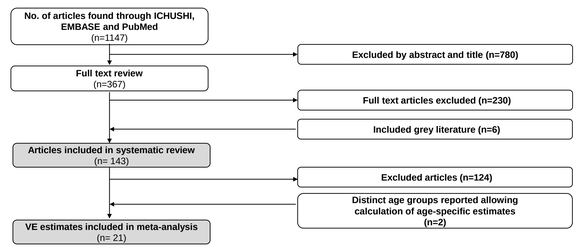
- Age-specific (three categories: < 65 years; mixed ages; ≥ 65 years) VE estimates or incidence rates of respiratory outcomes were extracted into a predefined data extraction template and converted to relative risks (RR).
- Random-effects meta-analysis estimated RR of outcomes in influenza vaccine recipients vs unvaccinated groups, and explored whether a) subject age; b) study setting, c) design or d) circulating influenza virus types were explanatory of RR[5]
- RR estimates were presented as a forest plot and used to estimate VE using the formula RR = 1-VE.

RESULTS

Epidemiology

- Reported incidence rates varied considerably depending on study design, season, study setting and, most importantly, case definitions.
  - Studies conducted at Long Term Care Facilities (LTCF) reported incidence rate ranging from 5% to 24%
  - From national surveillance data, 14,580,000 influenza cases were estimated in 2017/18 season, in which 9% were aged >70 years-old (overall attack rate: 8.03%)
  - Mild episodes of non-specific endpoints such as Influenza-Like Illness (ILI) were much more common than hospitalized or laboratory-confirmed cases.
- Influenza A viruses were the most common type (comprising 41.7% - 100% of isolates) in 21 of 24 publications between the 1998/1999 and 2017/2018 seasons.
- Over 60% of influenza hospitalizations occurred in people aged >60. Influenza patients with pneumonia were significantly older than patients admitted without pneumonia (mean age: 85.3 years vs. 71.4 years; p<0.05).
- Using an excess mortality approach, a peak of more than 35,000 influenza deaths was estimated during the 1998/1999 season in all ages but this has declined to <10,000 deaths since 2004/05.
- Data on comorbid populations were rare. End-stage renal disease requiring hemodialysis was the most commonly-studied comorbidity.

Figure 1 – PRISMA flow chart of studies included in the review and meta-analysis



Vaccine effectiveness meta-analysis

- Figure 2 shows overall VE was 19.1% (95% CI: 2.3% - 33.0%) with significant heterogeneity between studies (I^2: 89.1%). There was no evidence of significant publication bias from small studies (Egger's test: p = 0.327).
- Figure 3 shows study setting and population characteristics were not significantly predictive of VE, but a trend of decreasing VE with increasing age was observed (VE: 40.1% [-57.3 – 77.2] in the <65 group; 35.7% [2.0 – 57.8] in the mixed age group and 12.9% [-8.0 - 29.8] in those aged ≥65; p = 0.21).

Figure 2 – Forest plot of VE estimates and the overall pooled estimate from a random effects model without adjustments. Lines are 95% CIs and boxes are weighted by the inverse of the variance of each point estimate

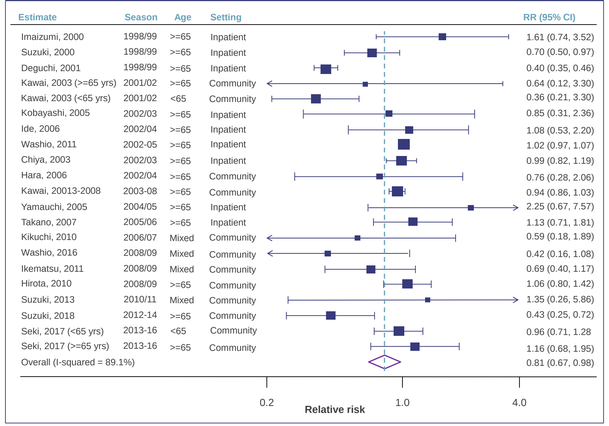
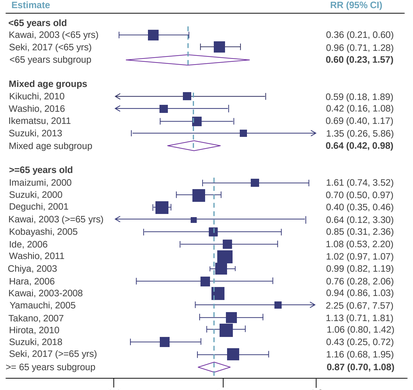


Figure 3 – Forest plot of VE estimates stratified by age



Discussion

- Study design, case definitions and setting were important determinants of epidemiological variation. More representative influenza surveillance, including outpatient settings, may benefit future epidemiological research.
- In common with other countries, the burden of hospitalization and deaths in Japan is highest in those individuals aged >60 who should be targeted for influenza vaccination. Additional research on risk factors for poor outcome, specifically including comorbid status, is warranted.
- Meta-analysis confirmed the value of influenza vaccination. The rather low overall VE was due to the high proportion of studies conducted in the elderly population in whom VE was lowest. This suggests better vaccines are needed for this group.

Limitations

- Studies were not excluded based on assessment of their methodological quality.
- Some relevant grey literature may have been overlooked during the search for reasons of feasibility.
- Observational cohort VE studies are vulnerable to confounding based on the baseline health status of individuals. This may have been compounded by the use of different case definitions incorporating results of point-of-care tests whose sensitivity is reportedly low in the elderly.[6]

CONCLUSION

The highest burden of influenza hospitalization in Japan is in the elderly population and while influenza vaccines are effective, VE is suboptimal in the elderly who are most at risk. In order to assess the burden of influenza more precisely, further study will be necessary.

DISCLOSURES

YH, JN and DT are employees of Sanofi Pasteur, who financially supported this study.

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