**Supplement 1**

Theoretical considerations

Vaccination has an “all-or-none” effect if vaccination confers either full protection from infection or no protection at all. Let and denote successfully vaccinated and unvaccinated subjects susceptible to influenza at time . Vaccination may, however, alter the probability of hospitalization given influenza infection. The expected number of eligible vaccinated non-CP cases at time will be proportional to

(S1)

where . Similarly, the expected number of vaccinated CP cases

(S2)

Thus the total expected number of eligible vaccinated cases is

(S3)

and, similarly, the expected number of eligible unvaccinated cases

(S4)

The (expected) odds of vaccination among cases therefore is given by

(S5)

Note that the terms , representing the probability of not having acquired yet, cancel. If pre-existing immunity is independent of vaccination then this expression simplifies to

(S6)

As vaccination does not affect the risk of non-influenza ARI the vaccination, odds among controls will be

The resulting odds ratio is

(S7)

If both vaccination coverage and VE are equal for non-CP and CP subjects, this odds ratio simplifies to

(S8)

and (S9)

which is VE against hospitalization because of laboratory-confirmed influenza. Furthermore, if the probability of hospitalization is unchanged by vaccination, i.e. ,

(S10)

which is also VE against influenza infection. Note that expressions A2.9 and A2.10 are derived from the whole population. The resulting VE estimates therefore are generalizable to the whole population even though they are obtained only from hospitalized subjects.

If vaccine coverage varies by CP status, i.e. then expression A2.7 cannot be simplified and . Thus the resulting VE estimate will be biased for or : If both vaccination status and the study inclusion probability for non-influenza conditions is positively associated with CP status, the bias will be positive, i.e. too large VE estimates on average. In that case, only a stratified analysis can recover or . Specifically, among non-CP subjects

and VE is

Similarly, among CP subjects

and the VE in CP subjects is .

Sensitivity analysis

To assess the impact of deviations from core assumptions on resulting bias in CP-adjusted VE estimates we investigated the bias when each parameter assumed the lower and the upper bound of an assumed range (Table S1), while leaving the other parameters at default values. Bias was estimated as the median difference between the VE estimate and the true VE against hospitalization. When one extreme represented a default parameter value, such as the upper one for influenza test sensitivity (1.0), no bias was simulated, as no bias was known to result from the default setting. To maximize precision of the bias estimates, we did not restrict the sizes of the simulated studies to the target case and control numbers. Association of a parameter with bias was assumed if, at either extreme, the estimated bias was percentage points and did not decrease with increased numbers of simulations. If the bias estimate for a parameter value was , 10,000 simulations were run. If the estimated bias was then percentage points, that parameter value was deemed not to cause bias in the VE estimate.

All parameters that determined the accuracy of the assessment of influenza, vaccination or CP status, if they were not at their “ideal” value (perfect sensitivity/specificity) resulted in biased CP-adjusted VE estimates (Table S2). All other parameters were not associated with bias in the VE estimate (Table S2). Note that all the small deviations of the median differences between the estimated vs. the true VE against hospitalization (“bias”) that were observed with 1,000 simulations diminished to less than 0.1 with 10,000 simulations.

**Table S1** Assumed extreme values of parameters tested.

|  |  |  |
| --- | --- | --- |
| **Parameter Description** | **Parameter Symbol** | **Range** |
| Prev. of CP status |  | 0.1-0.4 |
| Vaccination uptake (non-CP) |  | 0.2,0.7 |
| Vaccination uptake (CP) |  | 1.2,8 |
| VE against infection |  | 0.1,0.8 |
| Prop. influenza hosp. prevented by vaccination, given infection |  | 0,0.2 |
| Inc. constant (max. daily influenza inc. rate per 1000 per day) |  | 0.002-0.006 |
| Scaling factor non-ARI incidence (non-CP)† | **-** | 2,10 |
| Scaling factor multiplier (CP)‡ | **-** | 2,10 |
| Testing probability of inpatients |  | 0.2,0.8 |
| Influenza test sensitivity |  | 0,0.2 |
| Influenza test sensitivity reduction (vaccinated) |  | 0.8,1 |
| Influenza test specificity |  | 0.9,1 |
| Vaccination status assessment sensitivity |  | 0.8,1 |
| Vaccination status assessment specificity |  | 0.8,1 |
| CP status assessment sensitivity |  | 0.7,1 |
| CP status assessment specificity |  | 0.8,1 |
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|  |  |  |
| Prob. of hosp. resulting from influenza (non-CP) |  | 0.01,0.1 |
| Influenza ARI hosp. odds ratio (CP vs. non-CP) | - | 1.5,10 |
| Prob. of hosp. influenza ARI (non-CP) |  | 0.01,0.1 |
| Non-influenza ARI hosp. odds ratio (CP vs. non-CP) | - | 1.5,10 |
| Prob. of hosp. non-ARI (non-CP) |  | 0.01,0.1 |
| Non-ARI hosp. odds ratio (CP vs. non-CP) | - | 1.5,10 |

†Incidence function for non-ARI events in non-CP subjects is defined as , where is the scaling factor

‡In CP subjects, the incidence function is , where is the scaling factor multiplier

**Table S2** Estimated biases of parameters at their extreme values (median difference, in percentage points, between VE estimates and the true VE against hospitalization) and the empirical distribution of these differences (2.5th and 97.5th percentile of difference), based on 1,000 or 10,000 simulations (see text). The other parameters were left at their default values. When an extreme value corresponded to their default value (e.g. ) no values are given (no bias).

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Low** | **High** |
|  | 0.09 (-4.37, 4.36) | 0.09 (-3.02, 3.21) |
|  | 0.04 (-4.47, 4.15) | 0.05 (-4.2, 3.72) |
|  | 0.07 (-3.87, 3.74)† | 0.09 (-4.51, 4.21)† |
|  | -0.09 (-7.92, 7.2)† | 0.02 (-2.28, 2.22) |
|  | -0.05 (-3.85, 3.86) | 0.03 (-3.26, 3.19) |
|  | -0.01 (-5.15, 4.66)† | 0.07 (-3.58, 3.4)† |
| Scaling factor non-ARI incidence (non-CP) | 0.07 (-3.88, 3.49) | -0.01 (-3.93, 3.64) |
| Scaling factor multiplier (CP) | 0.07 (-4.22, 4.21) | 0.05 (-4.19, 3.67) |
|  | 0.07 (-6.56, 5.8)† | 0.07 (-3.08, 2.94)† |
|  | -1.81 (-6.43, 2.45) | -‡ |
|  | -‡ | 9.03 (5.84, 11.9) |
|  | -13.42 (-17.83, -9.26) | -‡ |
|  | -9.85 (-15.05, -5.25) | -‡ |
|  | -8.34 (-13.21, -3.77) | -‡ |
|  | 7.86 (4.66, 10.7) | -‡ |
|  | 4.47 (1.28, 7.64) | -‡ |
|  | -0.02 (-4.85, 4.36) | 0.04 (-3.16, 3.03)† |
|  | 0.04 (-5.91, 5.29)† | 0.06 (-3.38, 3.17)† |
|  | 0.06 (-4.48, 4.15)† | 0.04 (-3.8, 3.65)† |
|  | 0.04 (-4.2, 3.83) | 0.03 (-4.03, 3.34) |
|  | 0.07 (-4.12, 3.78)† | 0.08 (-3.71, 3.95) |
|  | -0.03 (-4.41, 3.7) | -0.02 (-4.19, 3.73) |

†10,000 simulations

‡Parameter value corresponds to default value; no bias