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The European Journal of Public Health, Vol. 30, No. 2, 275–280

doi:10.1093/eurpub/ckaa016 Advance Access published on 14 February 2020

The Dutch influenza vaccination policy and medication use, outpatient visits, hospitalization and mortality at age 65

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Background: Our objective was to obtain estimates of the impact of the Dutch vaccination programme on medication use, outpatient visits, hospitalization and mortality at age 65. **Methods:** We linked population-wide mortality, hospitalization and municipality registries to identify influenza-related deaths and hospitalizations, and used health interview surveys to identify medication use and outpatient visits during 1996–2008. We applied a regression discontinuity design to estimate the intention-to-treat effect of the personal invitation for a free influenza vaccination sent to every Dutch inhabitant at age 65 years on each of the outcomes, separately in influenza-epidemic and non-epidemic months. **Results:** Invitation receipt for free influenza vaccination at age 65 led to a 9.8 percentage points [95% confidence interval (CI) = 3.5 to16.1; $P < 0.01$] rise in influenza vaccination. During influenza-epidemic months, it was associated with 1.5 fewer influenza/pneumonia deaths per 100 000 individuals (95% CI = −3.1 to −0.0; $P = 0.05$), a 15 percentage point lower probability to use prescribed medicines (95% CI = −28 to −3; $P = 0.02$) and 0.13 fewer General Practitioner (GP) visits per month (95% CI = −0.28 to 0.02; $P = 0.09$), while the association with hospitalizations due to influenza/pneumonia was small and imprecisely estimated (seven more hospitalizations per 100 000 individuals, 95% CI = −20 to 33; $P = 0.63$). No associations were found with any outcomes during non-epidemic months. **Conclusions:** Personal invitations for a free influenza vaccination sent to every Dutch inhabitant at age 65 took pressure off primary health care but had small effects on hospitalizations and mortality.

Introduction

Seasonal influenza may lead to excess healthcare use, severe illness and sometimes death among individuals aged 65 and older.[1] Most countries recommend annual seasonal influenza vaccination to reduce the burden of influenza in this age group.[2,3] However, the effectiveness of vaccination for people aged 65+ has come under scrutiny during the last decade. A meta-analysis of randomized controlled trials (RCT) concluded that good evidence of the impact of vaccines on pneumonia, hospitalization and mortality is lacking for this fragile age group,[1] and new RCTs are not feasible due to the near universal vaccination recommendation for people aged 65+.[1] This has led to a greater reliance on evidence from observational studies which are more prone to selection and confounding biases.[4–6]

Only few observational studies on vaccination effectiveness have addressed biases due to non-random treatment allocation and/or unobserved confounders. Applying the relatively new test-negative study design alleviates, but does not completely remove, concerns about these biases.[1,7–9] Studies applying instrumental variable (IV) analysis have been unsuccessful: using prevalence of chronic diseases[10,11] or vaccination coverage[11,12] as IV's do not account for confounding due to co-morbidities[11,13] or herd immunity.[14] Exploiting variation in influenza incidence over time[15,16] fails to correct for selection and confounding due to time variation in vaccination take-up and herd immunity.

The overall effect of a vaccination programme relates to the difference in incidence or health outcomes between a targeted population and a comparable non-targeted population.[17] It depends on vaccination effectiveness, vaccination coverage and herd immunity. Our objective was to obtain estimates of the overall effect of the Dutch vaccination programme on mortality and hospitalization for influenza/pneumonia and respiratory diseases, and medication use and physician visits from population-based registries (and representative survey data) that are not affected by confounding and selection biases. These biases may arise when comparing vaccinated with non-vaccinated individuals,[6–9] epidemic and non-epidemic periods[15,16] or imposing the untestable exogeneity assumption underlying IVs.[10–14] We used a regression discontinuity design (RDD)[18–20] that exploits the age eligibility rules of the Dutch free vaccination policy between 1996 and 2008 to estimate the intention-to-treat effect of receipt of a personal invitation for a free influenza vaccination sent to every Dutch inhabitant over 65 years. Separate estimation in epidemic and non-epidemic months provided an internal validity check of the identifying assumptions of RDD.

Methods

Setting

Before 1996, free influenza vaccination in The Netherlands was targeted to high-risk individuals, defined as people with chronic disorders, such as diabetes, cardiovascular and pulmonary conditions, renal disease, immune dysfunctions and HIV/AIDS patients. All other individuals had to pay the full cost of 40 euro (in 2018 purchasing power).

In 1996, the vaccination policy was reformed into a population-wide programme and all individuals aged 65 and above received a personalized invitation letter for free influenza vaccination. In addition, barriers to take-up vaccination were further reduced for programme-eligible individuals by providing GPs with their own stock of vaccines and by providing remuneration and supporting agencies to healthcare providers in charge of the vaccination programme. Receipt of an invitation letter in September/October depended on whether the individual would be 65 on May 1st of the next calendar year ('programme-age'). Hence, all individuals turning 65 between September/October and May 1st received the invitation letter when their actual calendar age was 64; thereby preventing that invitation receipt coincided with eligibility for other social programmes, such as pension benefits.

Between 1996 and 2008, vaccination rates of the target group reached 75–80% in The Netherlands and were among the highest in Europe.[21,22] Prescribed medicines, general and specialist physician services, and hospital care were available to everyone through comprehensive social health insurance.

Study design

RDD[18–20] exploits the insight that the receipt of a personal invitation for a free flu shot cannot be influenced as every individual inevitably becomes eligible for the free influenza programme when they turn 65. When invitation receipt leads to a discontinuous increase in vaccination behaviour at age 65, but no discontinuity in any other determinant of mortality and medical care use, RDD deals with confounding and selection biases (Supplementary appendix S4).[23–25] Individuals slightly younger and older than 65 can then be considered identical, except for the receipt of an invitation for a free flu shot. The lack of an incentive to postpone vaccination the year before turning eligible, as antibodies decline over time and the influenza virus mutates every year, further adds to the strength of the RDD research design.

We applied RDD separately in epidemic and non-epidemic months.[15,16] Existence of a discontinuity at 'programme-age' 65 in epidemic months and absence of a discontinuity in the other months is then indicative of the effectiveness of the free influenza vaccination programme for mortality, medical care and medication outcomes at age 65.

Study population and data sources

We used two datasets: annual cross-sectional health interview surveys (HIS) for 1997–2008 and linked administrative data sources from Statistics Netherlands for 1996–2008. As stipulated in the data agreement, Statistics Netherlands pre-viewed the findings of all analyses in this project prior to publication.

HIS informed on medication use, physician visits and vaccination behaviour. Prescribed and non-prescribed medicine uses during the last month were reported as binary variables. The number of GP visits and the number of visits to the medical specialist during the last 2 months were rescaled into monthly figures. Vaccination take-up was self-reported, and vaccinated individuals reported the reason for vaccination take-up.

The linked administrative databases included the mortality registry for 1996–2008, the hospital registry for 1996–2005, and the municipality registry for 1996–2008 which contained demographic information for all inhabitants of The Netherlands. We retrieved the timing of deaths related to influenza/pneumonia (ICD 10 codes J09–J19 for primary or secondary cause of death) and all respiratory problems (ICD 10 codes J00–J99 for primary or secondary cause of death) from the mortality registry, and the timing of hospitalizations due to influenza/pneumonia (ICD 9 codes 480–488) and due to all respiratory problems (ICD 9 codes 460–519) from the hospital registry.

In the HIS and the registries, actual date of birth was used to compute 'programme-age' at May 1st of any given year, and 'programme-age' was defined in years and months. The Imbens and Kalyanaraman[23] criterion and Lee and Lemieux[18] guidelines recommended removing individuals whose 'programme-age' was younger than 63 or older than 66 to ensure that included individuals were sufficiently close to the 'programme-age' threshold of 65 (Supplementary appendix S4).[23–25]

Influenza seasons were defined to start 1 September and end 31 August in the following year (1997/98–2007/08 in the HIS; 1996/97–2005/06 in the hospital registry; and 1996/97–2007/08 in the mortality register). We subdivided each influenza season into

epidemic and non-epidemic months using data from the National Institute for Public Health and the Environment. Epidemic months are defined as months in which there was at least 1 week with more than 5% of the year-round influenza incidence (Supplementary appendix S3).[14,26]

Every month, HIS collected approximately one-twelfth of the annual number of observations, and year, month of interview and recall period were used to assign individuals to influenza seasons and (non-)epidemic months within influenza seasons. The data construction was different in the hospital and mortality register data. In both registries, we considered for each influenza season all individuals that were alive at the start of that influenza season. In the hospital registry, the timing of admission was used to construct binary indicators of any hospitalization during the epidemic and non-epidemic months. Comparing epidemic with non-epidemic months in the mortality register leads to a mechanical effect as dying in the epidemic period makes it impossible to die again in the non-epidemic months thereafter. Therefore, the non-epidemic period covered mortality (binary variable) throughout the entire influenza season, and the epidemic period considered mortality (binary variable) during the epidemic months among individuals that were alive at the start of that epidemic period. The same mechanical effect might make it impossible to be admitted to the hospital in the months after death; but the estimates for the mortality outcomes will inform on the sign and magnitude of the bias. Since hospitalizations and mortality may occur in the month following the influenza infection,[27] we extended the epidemic period in both registries with 1 month.

More details are provided in Supplementary figures S1 and S2, and Supplementary appendices S1–S3.[14,26,28]

Statistical analyses

We used ordinary least squares (OLS) to model medication use, physician visits, hospitalization and mortality as a linear function of 'programme-age', a binary variable for 'programme-age' equal or older than 65, and an interaction between this binary variable and 'programme-age' to allow for differential trends at each side of the cut-off (RDD regression). The OLS coefficients of the binary indicator and its associated 95% CI and P values provided the intention-to-treat estimates of the receipt of an invitation for a free flu shot, i.e. the divergence in medication use/physician visits/hospitalization/mortality at opposite sides of, but very close to the 'programme-age' threshold of 65. The estimates for epidemic and non-epidemic months were directly comparable in the HIS as medication use and physician visits were measured/rescaled in monthly figures, but the estimates for the epidemic and non-epidemic months derived from the registries were only comparable after dividing by the (observation-weighted) average number of months in the (non-)epidemic period (Supplementary appendix S4).[23–25] Estimates of the relative magnitudes were obtained after dividing the intention-to-treat estimate by the predicted value of the dependent variable at 'programme-age' 65. In order to ease the interpretation of the intention-to-treat estimates, we further ran a pooled RDD regression to establish the discontinuity in vaccination take-up at 'programme-age' 65.

All RDD regression models were adjusted for the following potential confounders. In the HIS, we controlled for gender, education (primary, lower secondary, upper secondary and post-secondary), household composition (single, couple, household with children and other), the number of household members, influenza season, population density (inhabitants/km^2: below 500, between 500 and 2500 and above 2500), pre-existing medical conditions (asthma, heart disease, liver disease, kidney disease, diabetes, rheumatism and cancer), and presence of a long-term illness, infirmity or handicap. In the registries, data availability limited adjustment to gender and influenza season. The HIS-based analyses used the sample weights provided by HIS, and robust standard errors were clustered at the year-municipality level to mimic the sampling design. Analyses with the registries used robust standard errors clustered at the individual level.

We also carried out several sensitivity and robustness checks to assess the validity of the RDD. First, we checked for discontinuities in vaccination take-up at 'artificial' cut-offs and assessed whether behaviours, such as prevention, health behaviour and altruism, changed when becoming eligible for free influenza vaccination. We further tested for heaping bias,[24] discontinuities in the control variables, and re-estimated all RDD models with different windows around the 'programme-age' cut-off, alternative assumptions about the trends in vaccination take-up left and right of the cut-off, and assuming the logistic regression model. Finally, we checked whether missing data in the HIS could bias our estimates. Supplementary appendix S4 provides more details.[23–25]

Results

Subjects

We observed mortality and hospitalization for the entire Dutch population in the 'programme-age' bandwidth 63–66 during the course of respectively 12 and 10 influenza seasons. For this group, table 1 indicates that, on average, 7 out of 100 000 individuals died every month from influenza/pneumonia during the epidemic period, and 6 out of 100 000 during the non-epidemic period. These monthly numbers were higher for respiratory hospitalization: 80 and 56 out of 100 000. We also studied 3183 individuals in the HIS sample during 11 influenza-seasons and observed slightly more GP visits and medication use during epidemic as compared with non-epidemic months. In total, 40% decided to vaccinate against influenza (Supplementary table S1). Additional characteristics of the HIS sample and linked mortality and hospitalization registries are presented in Supplementary table S1.

Age discontinuity in vaccination take-up

Individuals whose 'programme-age' turned 65 were 9.8 percentage points (95% CI = 3.5 to 16.1; $P<0.01$) more likely to vaccinate (Supplementary table S2). We found a coinciding increase (decrease) in the relative frequency of written invitations from the GP (vaccination on own initiative; Supplementary table S2). Sensitivity analyses confirmed the validity of the RDD, i.e. no discontinuities in vaccination take-up at artificial 'programme-ages'; and prevention and health behaviour did not change when becoming eligible for free influenza vaccination (Supplementary table S2).

Impact of receiving a free influenza invitation on medication, medical care use and mortality

Table 2 shows the change in medication use, physician visits, hospitalizations and mortality after receiving an invitation for free influenza vaccination at 'programme-age' 65. We found no evidence for age discontinuities in medicine use and physician visits during non-epidemic months. During epidemic months, some discontinuities emerged: a 15 percentage point lower probability to use prescribed medicines (95% CI = −28 to −3; $P=0.02$) and 0.13 fewer GP visits (95% CI = −0.28 to 0.02; $P=0.09$) per month, corresponding to relative reductions of 20% and 26%.

The hospitalization indicators showed no evidence of an age discontinuity at 'programme-age' 65 in epidemic and non-epidemic months, and the same was true for respiratory deaths. Every month, 1.5 influenza/pneumonia deaths per 100 000 individuals (95% CI = −3.1 to −0.0; $P=0.05$) were averted during epidemic months—a 20% relative reduction—while the discontinuity was very small during non-epidemic months (−0.3 per 100 000, 95% CI = −1.0 to 0.4; $P=0.41$)—a 5% relative reduction.

Table 1 Characteristics of the Study Population in the HIS and the linked mortality and hospitalization registries during epidemic and non-epidemic months ('programme-age' bandwidth 63–66)

	Outcomes during epidemic months[a]		Outcomes during non-epidemic months[a]	
Characteristics	***n*[b]**	**%[c]**	***n*[b]**	**%[c]**
HIS[d] (1997/98–2007/08)				
Medication use				
Non-prescribed medicines	724	44	2459	40
Prescribed medicines	724	65	2459	64
Physician visits				
GP visits,[e] mean (SD)	984	0.37 (0.68)	2197	0.31 (0.49)
Medical specialist visits,[e] mean (SD)	984	0.17 (0.40)	2198	0.19 (0.47)
Hospitalization registry (1996/97–2005/06)				
Influenza/pneumonia hospitalization[e]	5 831 941	0.018	5 831 941	0.013
Respiratory hospitalization[e]	5 831 941	0.080	5 831 941	0.056
Mortality registry (1996/97–2007/08)				
Influenza/pneumonia deaths[e]	6 463 524	0.007	7 183 332	0.006
Respiratory deaths[e]	6 463 524	0.017	7 183 332	0.015

HIS, Health Interview Survey.

[a]Epidemic months are months in which there is at least 1 week in which >5% of the year-round influenza incidence occurs. The epidemic period is extended with 1 month for non-prescribed and prescribed medicine use and influenza/pneumonia and respiratory hospitalization; and with 2 months for GP and medical specialist visits. For influenza/pneumonia and respiratory deaths, the epidemic period is extended with 1 month; and the non-epidemic period coincides with the entire influenza season (Supplementary appendix S3).

[b]Number of observations. Every month, HIS collected one-twelfth of the annual number of observations, leading to a different number of observations in epidemic and non-epidemic months. In addition, the epidemic (non-epidemic) period was extended (shortened) with the length of the recall period—1 month for medication use and 2 months for physician visits—and there were some missing data (consult section Study population and data sources, Supplementary appendices S1 and S3, and Supplementary figure S1 for more details). In the epidemic and non-epidemics months of the hospitalization registry and the non-epidemic months in the mortality registry, the included observations are all individuals that were alive at the start of an influenza season. The observations in the epidemic months of the mortality registry coincide with all individuals alive at the start of the epidemic period (consult section Study population and data sources, Supplementary appendix S2, and Supplementary figure S2 for more details).

[c]Percentage, unless indicated otherwise.

[d]All percentages, means and standard deviations were calculated using the sampling weights provided by HIS. The number of observations is the actual unweighted number of observations.

[e]Rescaled to monthly figures (Supplementary appendix S4).

Table 2 Impact of invitation for a free flu shot on medication, medical care use and mortality at age 65 ('program-age' bandwidth between 63 and 66)[a,b]

	Epidemic period (95% CI)[c]	*P*-value	Non-epidemic period (95% CI)[c]	*P*-value
HIS (1997/98–2007/08)				
Non-prescribed medicines	−0.077 (−0.217 to 0.064)	0.28	−0.018 (−0.098 to 0.061)	0.65
Prescribed medicines	−0.151 (−0.278 to −0.025)	0.02	−0.050 (−0.119 to 0.019)	0.15
GP visits[d]	−0.131 (−0.283 to 0.021)	0.09	0.020 (−0.065 to 0.106)	0.64
Medical specialist visits[d]	−0.064 (−0.159 to 0.031)	0.18	0.020 (−0.065 to 0.104)	0.65
Hospitalization registry (1996/97–2005/06)				
Influenza/pneumonia hospitalization[d]	0.000007 (−0.000020 to 0.000033)	0.63	−0.000000 (−0.000013 to 0.000012)	0.98
Respiratory hospitalization[d]	0.000046 (−0.000010 to 0.000101)	0.11	−0.000012 (−0.000038 to 0.000013)	0.34
Mortality registry (1996/97–2007/08)				
Influenza/pneumonia deaths[d]	−0.000015 (−0.000031 to −0.000000)	0.05	−0.000003 (−0.000010 to 0.000004)	0.41
Respiratory deaths[d]	−0.000017 (−0.000041 to 0.000007)	0.16	−0.000002 (−0.000012 to 0.000009)	0.75

HIS, Health Interview Survey.

[a]Each row represents an age discontinuity obtained from a separate OLS regression. For HIS, sampling weights provided by HIS were used. We allowed for linear trends in 'programme-age' that can vary on each side of the 'programme-age' cut-off. All HIS analyses were controlled for differences in sex, being member of a risk group based on pre-existing medical conditions, education, household composition and size, influenza season, population density, and presence of chronic illness. Analyses on the registries were controlled for differences in sex and influenza season. The number of observations is presented in table 1. All age discontinuities are expressed as percentage point changes in probabilities per month, except for GP and medical specialist visits which are expressed as absolute changes in the number of visits per month.

[b]Epidemic months are months in which there is at least 1 week in which >5% of the year-round influenza incidence occurs. The epidemic period is extended (compressed) with 1 month for non-prescribed and prescribed medicine use and influenza/pneumonia and respiratory hospitalization; and with 2 months for GP and medical specialist visits. For influenza/pneumonia or respiratory deaths, the epidemic period is extended with 1 month; and the non-epidemic period coincides with the entire influenza season (Supplementary appendix S3).

[c]Adjusted for clustering at the wave-municipality level in the HIS and adjusted for clustering at the individual level in the registries.

[d]Rescaled to monthly figures.

Supplementary appendix S4 and Supplementary tables S3 and S4 confirm robustness of these estimates to the specification of the RDD models (window, functional form trends and logistic regression), heaping bias, discontinuities in the control variables and missing data.[23–25]

Discussion

We found that the Dutch policy to invite every individual aged 65 or above for free influenza vaccination was associated with reduced mortality from influenza and pneumonia, GP visits and prescribed medication use; but had no association with mortality from all respiratory diseases, hospitalizations, medical specialist visits and non-prescribed medication use. During an epidemic month, there were 1.5 fewer influenza/pneumonia deaths per 100 000 individuals (95% CI = −3.1 to −0.0; $P = 0.05$), a 15 percentage point lower probability to use prescribed medicines (95% CI = −28 to −3; $P = 0.02$) and 0.13 fewer GP visits (95% CI = −0.28 to 0.02; $P = 0.09$) at 'programme-age' 65, corresponding to relative reductions of 20%, 20% and 26%. During non-epidemic months, none of the outcome variables were associated with the receipt of an invitation for a free flu shot.

Influenza vaccination among individuals aged 65 and older is recommended in most developed countries[2,3] as previous studies have indicated that the flu shot protects the elderly from death during epidemic months.[1,4,5] We confirm that influenza and pneumonia deaths reduce after receipt of an invitation for free influenza vaccination, but the estimated mortality reduction is very small, also in contrast to previous findings.[29,30] The absence of an effect on influenza/pneumonia/respiratory hospitalizations, for which previously risk reductions between 21% and 32% have been reported using observational data,[31–33] is in line with modest levels of vaccination effectiveness at age 65; while the estimated reductions of GP visits and prescribed medicines suggest that the Dutch free vaccination policy primarily reduces primary care usage. The savings in terms of reduced GP visits alone, even without accounting for prescribed medicines, more than compensate for the cost of the Dutch influenza vaccination programme. A back-of-the envelope calculation for influenza season 2003/04, for example, indicates that the expected number of averted GP visits per individual (−0.131 during four epidemic months and + 0.020 during eight non-epidemic months) multiplied with a 20.20 euro savings per averted GP visit[34] outweighs the total cost of the influenza vaccination programme which equalled 12.40 euro per vaccinated individual[35] times the increased probability that an individual vaccinates (+0.098), leading to net savings of 6.14 euro per invited individual at age 65, i.e. 20.20 * [0.131 * 4–0.020 * 8] – 12.40 * 0.098 (table 2, Supplementary table S2 and Supplementary appendices S3 and S4).[14,23–26] In fact, all together, our findings suggest that earlier studies of likely suffered from residual confounding and selection biases, while our study of the impact of the Dutch vaccination programme stresses the additional importance of reduced primary care costs.

The most important strength of our study included the use of population-based registries for hospitalization and mortality outcomes in combination with a research design that allows overcoming confounding and selection biases.[36] To our knowledge, our study was the first to use an RDD approach to analyze a vaccination programme's effectiveness against health and healthcare outcomes; avoiding biases from comparing vaccinated with non-vaccinated individuals,[1–5,29–33] epidemic and non-epidemic months/influenza seasons,[15,16,33,37,38] the untestable exogeneity assumption underlying IVs,[10–14] or restricting to laboratory confirmed positive and negative cases of influenza.[7–9]

A possible limitation was that all estimates reflect the intention-to-treat effect of an invitation receipt for a free flu shot, as vaccination uptake was not available in the registries, and therefore identify the impact of the vaccination programme and not the impact of vaccination take-up.[39,40] Our estimated 9.8 percentage points (95% CI = 3.5 to16.1; $P < 0.01$) increase in vaccination take-up at age 65 can, however, be used to obtain an indication of the local average treatment effects of vaccination take-up as there was no evidence for corresponding discontinuities in the control variables or preventive, health and altruistic behaviour, and provided the HIS surveys accurately reflect the population in the administrative register data.[18,41] We further note that our estimates are local at 'programme-age' 65 and most likely upper bounds for those aged 65 and older since antibody response to influenza vaccination declines with age.[42,43]We neither can exclude that the absence of an effect on respiratory deaths and hospitalizations (ICD J00–J99 and ICD 9 460–519) derives from the inclusion of non-infectious deaths and hospitalizations, such as COPD, in these ICD codes. Finally, the absence of a mortality impact during the non-epidemic period, which includes months with low and high influenza incidence, indicates that attrition bias in the hospital register and the HIS surveys must be very small.

In conclusion, we find that the Dutch free vaccination programme led to considerable cost savings by taking pressure from primary health care and had a small to negligible effect on hospitalizations and influenza/pneumonia deaths at age 65.

Supplementary data

Supplementary data are available at *EURPUB* online.

Acknowledgments

This project has used data provided by Statistics Netherlands via a Remote Access facility. As stipulated in the data agreement, Statistics Netherlands pre-viewed the findings of this project prior to publication to ensure that privacy sensitive, individual-specific information is not revealed. The data from this study can only be applied for through a government data sharing portal of Statistics Netherlands (https://www.cbs.nl/en-gb/our-services/customised-services-microdata/microdata-conducting-your-own-research). This work was completed while Tom Van Ourti was a visiting scholar at the Milken Institute School of Public Health of the George Washington University The authors would like to thank two anonymous reviewers, Anne Gielen, Philippe Beutels, Adrian Bruhin, Geert Dhaene, Sam Harper, Tim Kanters, Hale Koç, Jürgen Maurer, Magne Mogstad, Owen O'Donnell, Erwin Ooghe, Samantha Rawlings, Erik Schokkaert, Isabelle Soerjomataram, Joost Timmermans, Hans Van Brabandt, Ellen Van de Poel, Hans van Kippersluis and GP Private Practice van Eerd for insightful comments and suggestions.

Funding

This work was supported by the Research Foundation–Flanders (FWO) [1174913N].

Conflict of interest: None declared.

Key points

- Convincing evidence on seasonal influenza vaccination effectiveness is lacking for individuals aged 65+.
- A regression discontinuity design showed that an invitation for free influenza vaccination was associated with lower prescribed medicine use, fewer GP visits and minor mortality reductions at age 65, but only during influenza-epidemic months.

- Invitations for free Influenza vaccination among the 65+ takes pressure off primary health care, but had small effects on hospitalization and mortality.

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The European Journal of Public Health, Vol. 30, No. 2, 281–285

doi:10.1093/eurpub/ckz238 Advance Access published on 29 January 2020

Rotavirus vaccination impact, Ireland, implications for vaccine confidence and screening

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Background: Rotavirus vaccine efficacy is well established. However, it is important to consistently demonstrate the positive impact of vaccination programmes in order to optimize uptake rates and combat vaccine hesitancy. **Methods:** Routine data were used to examine rotavirus vaccine effectiveness in Ireland, including changes in age-specific crude incidence rates (CIRs), hospitalizations and hospital length of stay. National intussusception incidence was interrogated. Vaccination status of vaccine-eligible cases of rotavirus infection was determined. **Results:** Nationally, a reduction in the CIR of rotavirus infection of 77.2% [95% confidence interval (CI) 57.8–88.5%, $P<0.001$] was observed post-inclusion of the rotavirus vaccine in the primary immunization schedule. A decrease in hospitalizations of 85.5% (95% CI 79.3–90.2%, $P<0.001$), 86.5% (95% CI 82.9–89.4%, $P<0.001$) and 78.5% (95% CI 74.7–81.9%, $P<0.001$) was observed in children aged <1, <2 and <5 years, respectively. Most hospitalizations occurred in infants too young to have been vaccinated. There was no significant difference in median length of stay for children hospitalized with rotavirus infection. Decreased CIRs and hospitalization rates in unvaccinated children aged between 2 and 5 years suggest community immunity. Vaccine non-protection was 0.13%. No increase in the national CIR of intussusception was observed. **Conclusions:** Inclusion of the rotavirus vaccine in the Irish primary immunization schedule has resulted in a significant reduction in the burden of rotavirus infection. However, vaccine hesitancy remains a concern. With new vaccination programmes, risk of vaccine harms should be considered and mitigated in order to protect individuals and the integrity of the programme.

Introduction

Rotavirus is a leading cause of acute gastroenteritis in paediatric populations, resulting in considerable morbidity and healthcare utilization.[1–3] Rotavirus crude incidence rates (CIRs) are high in Ireland with 2308 cases notified in 2017; a national CIR of 48.5/100 000 population.[4] There is significant geographical variation in CIRs, with the highest and lowest regional CIRs observed in the Midlands (78.0/100 000 population) and North-East (33.9/100 000 population), respectively.

Following a recommendation from the World Health Organization (WHO) in April 2009, 86 countries have included rotavirus vaccination in their national primary immunization schedules,[2] with associated reductions in rotavirus-attributable morbidity.[1,3,5,6] In December 2016, Ireland introduced the Rotarix™ vaccine for all infants born on or after the first of October 2016.[7] Rotarix™ is a live attenuated monovalent vaccine administered orally in two doses at 2 and 4 months of age.[7]

Inclusion of a new vaccine in the national immunization schedule is associated with financial and administrative challenges, including the cost of providing the vaccine and the need to define and address barriers to access. Vaccine hesitancy poses an additional challenge and may be exacerbated by vaccine controversy arising from misinformation, disinformation and genuine cases of vaccine harm. While the clinical effectiveness of the rotavirus vaccine is established,[2,8–10] historic and current vaccine controversies demonstrate that public opinion has a considerable impact on uptake rates.[11–15] It is, therefore, important that policymakers and health professionals act to combat vaccine hesitancy by consistently demonstrating and communicating the positive impact of population-level immunization. The integrity of immunization programmes can be further protected by ensuring potential vaccine harms are identified and the risk of such harms mitigated in so far as is practicable. For the rotavirus vaccine, potential harms include increased risk of intussusception and risk of severe iatrogenic vaccine strain infection if administered to an infant with an undiagnosed primary immunodeficiency disorder (PID).

The aims of the study were to:

(1) demonstrate the impact of inclusion of the rotavirus vaccine in the Irish primary immunization schedule, including vaccine effectiveness [defined as direct (vaccine induced) and indirect (population related) protection during routine use[16]] and incidence of intussusception; and
(2) consider how potential harms associated with rotavirus vaccination might be mitigated to protect individuals and public confidence in immunization programmes.

The objectives of the study were to:

(1) determine the vaccine effectiveness of the rotavirus vaccine following its inclusion in the primary immunization schedule. Measures of vaccine effectiveness examined include:
   - changes in age-specific CIRs of rotavirus infection,
   - changes in age-specific hospitalizations and bed days used (BDU) for rotavirus infection and
   - changes in rotavirus-attributable morbidity, using hospital length of stay (LOS) as a proxy;
(2) determine the vaccination status of vaccine-eligible cases of rotavirus infection in the Midlands region post-inclusion of the vaccine in the primary immunization schedule; and
(3) identify whether the national CIR of intussusception has increased post-inclusion of the rotavirus vaccine in the primary immunization schedule.