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MAJOR ARTICLE

Effectiveness of 2 Influenza Vaccines in Nationwide Cohorts of Finnish 2-Year-Old Children in the Seasons 2015–2016 Through 2017–2018

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Background. From 2015–2016 through 2017–2018, injectable, trivalent inactivated influenza vaccines (IIV3) and a nasal spray, tetravalent live-attenuated influenza vaccine (LAIV4) were used in parallel in Finland. To understand how well vaccination with each vaccine type protected children against influenza under real-life conditions, vaccine effectiveness in 2-year-olds was estimated for all 3 seasons.

Methods. Each season, a nationwide register-based cohort study was conducted. The study population comprised 60 088, 60 860, and 60 345 children in 2015–2016, 2016–2017, and 2017–2018, respectively. Laboratory-confirmed influenza was the study outcome. Seasonal influenza vaccination with either LAIV4 or IIV3 was the time-dependent exposure of interest. Vaccine effectiveness was defined as 1 minus the hazard ratio comparing vaccinated with unvaccinated children.

Results. From 2015–2016 through 2017–2018, the effectiveness of LAIV4 against influenza of any virus type was estimated at 54.2% (95% confidence interval, 32.2–69.0%), 20.3% (−12.7%, 43.6%), and 30.5% (10.9–45.9%); the corresponding effectiveness of IIV3 was 77.2% (48.9–89.8%), 24.5% (−29.8%, 56.1%), and −20.1% (−61.5%, 10.7%). Neither influenza vaccine clearly excelled in protecting children. The LAIV4 effectiveness against type B was greater than against type A and greater than the IIV3 effectiveness against type B.

Conclusions. To understand how influenza vaccines could be improved, vaccine effectiveness must be analyzed by vaccine and virus type. Effectiveness estimates also expressing overall protection levels are needed to guide individual and programmatic decision-making processes. Supported by this analysis, the vaccination program in Finland now recommends LAIV4 and injectable, tetravalent inactivated influenza vaccines replacing IIV3.

Keywords. vaccine effectiveness; influenza; children; cohort study; Finland.

For more than a decade, annual vaccination against influenza has been recommended to children aged 6–35 months in Finland [1]. Injectable, inactivated influenza vaccine has been given free of charge to all eligible children since 2007. To enhance vaccine uptake, the tetravalent live-attenuated influenza vaccine (LAIV4) administered as nasal spray was introduced in 2015 [2]. Since then, all 2-year-old children have been eligible for vaccination with LAIV4 or inactivated influenza vaccine without a recommended preference. As expected, vaccination coverage has increased steadily following LAIV4 introduction. While in 2014–2015 only 11% of children aged 6–35 months were vaccinated, 17%, 22%, and 24% were vaccinated in the 3 subsequent seasons (2015–2016, 2016–2017, and 2017–2018) [3].

Through 2017–2018, the 2 types of influenza vaccine provided by the vaccination program differed in valency as trivalent inactivated influenza vaccines (IIV3) always contained only 1 of the 2 influenza B components of LAIV4. Moreover, the vaccination program recommended 2 shots (at least 4 weeks apart) instead of only 1 if a child was to receive IIV3 and had not received either LAIV4 or 2 shots of IIV3 in previous seasons.

To understand how well vaccination protects against influenza under real-life conditions, vaccine effectiveness (VE) is estimated each season in Finland [4] as well as in many other countries [5]. However, VE appears to vary widely across seasons and countries. Known factors contributing to any true diversity in VE include differences in the circulating strains or in the age and vaccination history of the populations. It is thus apparent that genetic characterization of influenza viruses, power to stratify by age, and individual-level information on vaccination are required to better understand VE. The latter 2 of

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these demands can be met through studies utilizing population-based data from routine health registers [4].

In this article, we employ Finnish register data to estimate influenza VE in 2-year-old children by vaccine and influenza type. We focus on the 3 influenza seasons 2015–2016, 2016–2017, and 2017–2018, when LAIV4 was used in parallel with IIV3.

METHODS

We conducted 3 register-based cohort studies in Finland [4]. The study periods of interest were 3 influenza seasons—2015–2016, 2016–2017, and 2017–2018—each defined as starting at the first day of week 40 and ending at the last day of week 20.

Each season, the study population consisted of all 2-year-olds registered in the Population Information System [4]. We thus studied 3 partly overlapping cohorts of children alive at season onset and born November 2012–December 2013, November 2013–December 2014, and November 2014–December 2015, respectively. The exclusion criteria were history of residence abroad and residence outside the National Vaccination Register's (NVR's) [6] catchment area at season onset or in any previous season.

The outcome of interest was laboratory-confirmed influenza infection during the respective season, recorded in the National Infectious Diseases Register allowing distinction between cases of influenza A and influenza B [4]. The clinical presentation and severity of infection were unknown. As a proxy, however, we extracted hospitalization dates from the Care Register of Health Care [4] to count how many cases were hospitalized within 7 days since the influenza-positive specimen was sampled.

The exposure of interest was seasonal influenza vaccination with either LAIV4 or IIV3, recorded in the NVR [4]. Also, vaccinations given shortly before the respective season onset (ie, vaccinations from August through week 39) were included. We distinguished between 3 time-dependent exposure states: unvaccinated, partially vaccinated, and fully vaccinated. Until the first receipt of any influenza vaccine a child was considered unvaccinated and thereafter partially vaccinated until being fully vaccinated. A child was considered fully vaccinated with LAIV4 since day 15 after the first receipt of LAIV4. A child was considered fully vaccinated with IIV3 since day 15 after the second receipt of IIV3 or since day 15 after the first receipt of IIV3 if the child had already been vaccinated in previous seasons with LAIV4 or 2 shots of IIV3.

For each season, we conducted 2 separate analyses using vaccination with either LAIV4 or IIV3 as the exposure. Each child was considered to be at risk of the outcome of interest (influenza A, influenza B, or any influenza) from season onset until the first of the following events: outcome of interest, vaccination with an influenza vaccine other than the exposure, loss to follow-up (due to death or emigration outside the NVR's catchment area), or end of the study period [4].

The effect measure of interest was VE defined as 1 minus the hazard ratio comparing fully vaccinated children with unvaccinated children [4]. The hazard ratio was estimated using Cox regression with time since season onset as the underlying time scale. The validity of the proportional hazards assumption was checked visually by plotting nonparametric estimates of the hazards in the vaccinated and the unvaccinated children over time. In a sensitivity analysis, the estimation of VE was restricted to children not vaccinated against influenza in any previous season. Demographic and health-related background information was collected as listed in Supplementary Tables 1 and 2 to describe potential differences in influenza incidence and vaccine uptake.

Individual-level data from different registers were linked deterministically using the unique personal identity code assigned to all permanent Finnish residents [4]. All analyses were conducted in R 3.5.3 (R Foundation for Statistical Computing) [7].

RESULTS

Size of Study Population

In 2015–2016, the study population comprised 60 088 children of whom 1 child was excluded from the LAIV4 analysis due to vaccination with IIV3 before week 40, 2015 (Figure 1). In the subsequent 2 seasons, the study populations were 60 860 children (2016–2017) and 60 345 children (2017–2018). Seven children were excluded from the LAIV4 analysis in 2016–2017 and 8 were excluded in 2017–2018 (Figure 1).

Number of Influenza Cases

There were 309 influenza A and 79 influenza B cases in 2015–2016, 273 influenza A and 9 influenza B cases in 2016–2017, and 268 influenza A and 237 influenza B cases in 2017–2018. Repeated infections and coinfections were rare, occurring 6 times in 2015–2016 and 3 and 11 times in the subsequent 2 seasons. Only a few children were hospitalized: 61 influenza A and 12 influenza B cases in 2015–2016, 38 influenza A cases in 2016–2017, and 19 influenza A and 32 influenza B cases in 2017–2018.

Distribution of Vaccine Brands

Throughout the 3 seasons, Fluenz Tetra (AstraZeneca) was the only administered LAIV4 brand, while altogether, 4 IIV3 brands were used. The 2015–2016 IIV3 brands were Vaxigrip (Sanofi Pasteur) (99.8% of 6329 IIV3 doses), Influvac (Abbott) (0.2%), and Fluarix (GlaxoSmithKline) (0.0%; 2 children were vaccinated with Fluarix although this brand was recommended not to be used in this age group). The 2016–2017 IIV3 brands were Influvac (Abbott) (99.8% of 6938 IIV3 doses) and Vaxigrip (Sanofi Pasteur) (0.2%). In 2017–2018, children were vaccinated with Influvac (Abbott) (88.4% of 6494 IIV3 doses) and Agrippal (Seqirus) (11.6%). In each season, there was a small number of children receiving both LAIV4 and IIV3:

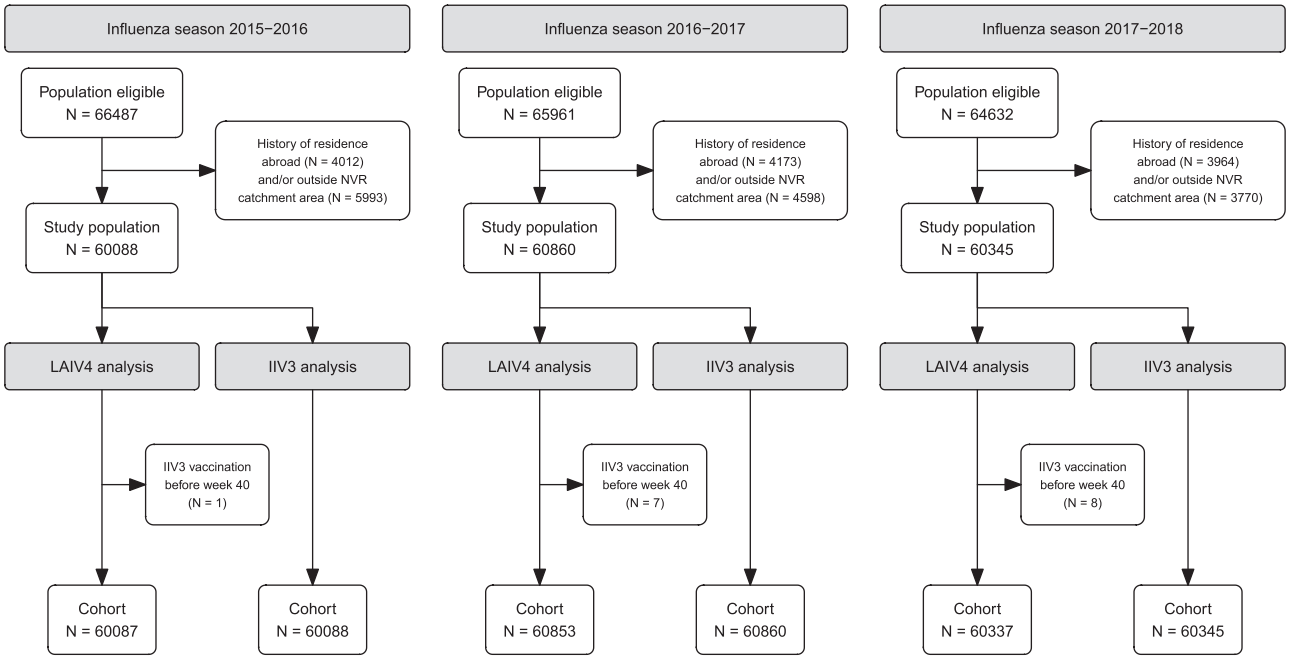

Figure 1. Enrollment of the study population (2-year-old children) into the cohorts: influenza seasons 2015–2016 through 2017–2018, Finland. Abbreviations: IIV3, trivalent inactivated influenza vaccine; LAIV4, tetravalent live-attenuated influenza vaccine; NVR, National Vaccination Register.

24 (2015–2016), 59 (2016–2017), and 87 (2017–2018). The majority of the children were vaccinated first with IIV3.

Timing of Influenza Epidemic and Vaccine Uptake

Supplementary Figures 1 and 2 show the timing of the influenza epidemic and the vaccine uptake in the study population. When the 2015–2016 influenza incidence reached its peak in week 4, 2016, most LAIV4 recipients had been fully vaccinated, but the number of children fully vaccinated with IIV3 was still increasing. In 2016–2017, the influenza incidence peaked already in week 52, 2016, when the vaccination campaign had not yet completed. Consequently, the percentage of children fully vaccinated with either LAIV4 or IIV3 was still increasing thereafter. When the 2017–2018 influenza incidence reached its peak in week 11, 2018, almost all vaccinations (LAIV4 and IIV3) had been administered. However, the epidemic had started early coinciding with the last weeks of the vaccination campaign.

Vaccination Coverage

In 2015–2016, 14% of the children were fully vaccinated with LAIV4 (Table 1, Supplementary Table 3) and 7% were fully vaccinated with IIV3 (Table 2, Supplementary Table 4) by the end of follow-up. These percentages increased to 20% (LAIV4) (Table 1) and 8% (IIV3) (Table 2) in 2016–2017 and 22% (LAIV4) (Table 1) and 9% (IIV3) (Table 2) in 2017–2018. Simultaneously, the proportion of children at season onset who were not vaccinated against influenza in any previous season decreased from 77.1% (2015–2016) to 70.5% (2016–2017) to 61.6% (2017–2018). In 2015–2016, no child had been previously vaccinated with LAIV4.

Vaccine Effectiveness

The VE of LAIV4 against influenza A and influenza B was estimated at 45.8% (95% confidence interval [CI], 32.2–69.0%) and 83.4% (32.3–95.9%) in 2015–2016 (Table 1, Figure 2). The corresponding figures for IIV3 were 90.3% (95% CI, 60.9–97.6%) and 34.6% (−79.5% to 76.1%) (Table 2, Figure 2). Restricting the analysis to children not previously vaccinated lowered the point estimates to 25.8%, 79.9%, 65.4%, and 22.4% and broadened the CIs, all of which contained the null hypothesis value of 0% (Supplementary Tables 5 and 6).

The VE of LAIV4 against influenza A and influenza B was estimated at 21.1% (95% CI, −12.1% to 44.4%) and 31.1% (−466.7% to 91.6%) in 2016–2017 (Table 1, Figure 2). Being fully vaccinated with IIV3 reduced the influenza A incidence rate by 23.1% (95% CI, −32.3% to 55.3%) (Table 2, Figure 2). There were no influenza B cases among those who were fully vaccinated with IIV3 (Table 2).

The VE of LAIV4 against influenza A and influenza B was estimated at −21.8% (95% CI, −62.4% to 8.7%) and 75.4% (57.7–85.7%) in 2017–2018 (Table 1, Figure 2). The corresponding figures for IIV3 were −42.0% (95% CI, −110.6% to 4.2%) and −0.2% (−55.9% to 35.6%) (Table 2, Figure 2). Restricting the analysis to children not previously vaccinated lowered the point estimates for LAIV4 against influenza B to 71.5% (95% CI, 23.1–89.4%) (Supplementary Table 5).

Baseline Differences in Influenza Incidence and Vaccine Uptake

The point estimates of the incidence of laboratory-confirmed influenza infection in unvaccinated children varied moderately

Table 1. Vaccine Effectiveness of LAIV4 Against Laboratory-Confirmed Influenza Infection in 2-Year-Old Children: Influenza Seasons 2015–2016 Through 2017–2018, Register-based Cohort Studies, Finland

Season and Influenza Virus Type	Unvaccinated			Fully Vaccinated			HR (95% CI)	VE (95% CI), %
	Cases,[a] n	Population,[a,b] n (%)	Incidence[c]	Cases,[a] n	Population,[a,b] n (%)	Incidence[c]		
2015–2016 (N = 60 087)								
Any	339	51 639 (85.9)	2.003	27	8442 (14.0)	1.354	0.458 (.310–.678)	54.2 (32.2–69.0)
A	277	51 639 (85.9)	1.636	26	8445 (14.1)	1.303	0.542 (.363–.811)	45.8 (18.9–63.7)
B	67	51 638 (85.9)	0.395	2	8445 (14.1)	0.100	0.166 (.041–.677)	83.4 (32.3–95.9)
2016–2017 (N = 60 853)								
Any	221	48 914 (80.4)	1.431	38	11 937 (19.6)	1.361	0.797 (.564–1.127)	20.3 (−12.7 to 43.6)
A	217	48 914 (80.4)	1.405	37	11 938 (19.6)	1.325	0.789 (.556–1.121)	21.1 (−12.1 to 44.4)
B	7	48 911 (80.4)	0.045	1	11 941 (19.6)	0.036	0.689 (.084–5.667)	31.1 (−466.7 to 91.6)
2017–2018 (N = 60 337)								
Any	354	47 270 (78.3)	2.369	75	13 056 (21.6)	2.445	0.695 (.541–.891)	30.5 (10.9–45.9)
A	171	47 269 (78.3)	1.143	64	13 062 (21.6)	2.085	1.218 (.913–1.624)	−21.8 (−62.4 to 8.7)
B	189	47 270 (78.3)	1.263	14	13 058 (21.6)	0.455	0.246 (.143–.423)	75.4 (57.7–85.7)

Abbreviations: CI, confidence interval; HR, hazard ratio; LAIV4, tetravalent live-attenuated influenza vaccine; VE, vaccine effectiveness.

[a]Vaccination status at the end of follow-up. See Supplementary Table 3 for cases and population partially vaccinated at the end of follow-up.

[b]Proportion of cohort size N.

[c]Per 10 000 person-weeks.

across the categories of the 20 considered baseline characteristics (Supplementary Table 7). However, the only 2 characteristics consistently associated with the incidence over the 3 seasons were "presence of acute disease between weeks 21 and 39" and "presence of underlying chronic conditions before season onset." The incidence among unvaccinated children with an acute disease or underlying chronic condition was 66.3% higher than the incidence among those without. The by far highest incidence of 29 cases per 10 000 person-weeks was observed in 2015–2016 in the 36 children born extremely preterm (before the gestational age of 28 weeks).

In each season under study, children born in November or December were more likely to receive IIV3 as their first influenza vaccine (Supplementary Tables 8–10). However, the estimated influenza incidence did not differ much by month of birth, except for children born in November or December, who had a slightly lower risk of laboratory-confirmed influenza infection in 2016–2017 (Supplementary Table 7).

In addition, residence and the number of well-baby clinic visits may have affected the vaccine uptake and influenza incidence. Children living in urban municipalities were more likely to be vaccinated than children living in rural municipalities, where the

Table 2. Vaccine Effectiveness of IIV3 Against Laboratory-Confirmed Influenza in 2-Year-Old Children: Influenza Seasons 2015–2016 Through 2017–2018, Register-based Cohort Studies, Finland

Season and Influenza Virus Type	Unvaccinated			Fully Vaccinated			HR (95% CI)	VE (95% CI), %
	Cases,[a] n	Population,[a,b] n (%)	Incidence[c]	Cases,[a] n	Population,[a,b] n (%)	Incidence[c]		
2015–2016 (N = 60 088)								
Any	339	54 872 (91.3)	2.003	6	4418 (7.4)	0.648	0.228 (.102–.511)	77.2 (48.9–89.8)
A	277	54 872 (91.3)	1.636	2	4418 (7.4)	0.216	0.097 (.024–.391)	90.3 (60.9–97.6)
B	67	54 869 (91.3)	0.395	4	4419 (7.4)	0.432	0.654 (.239–1.795)	34.6 (−79.5 to 76.1)
2016–2017 (N = 60 860)								
Any	221	54 967 (90.3)	1.431	14	5071 (8.3)	1.220	0.755 (.439–1.298)	24.5 (−29.8 to 56.1)
A	217	54 967 (90.3)	1.405	14	5071 (8.3)	1.220	0.769 (.447–1.323)	23.1 (−32.3 to 55.3)
B	7	54 966 (90.3)	0.045	0	5075 (8.3)	0.000	Not estimated	Not estimated
2017–2018 (N = 60 345)								
Any	354	54 435 (90.2)	2.369	50	5158 (8.5)	4.140	1.201 (.893–1.615)	−20.1 (−61.5 to 10.7)
A	171	54 434 (90.2)	1.143	29	5161 (8.6)	2.395	1.420 (.958–2.106)	−42.0 (−110.6 to 4.2)
B	189	54 435 (90.2)	1.263	22	5158 (8.5)	1.817	1.002 (.644–1.559)	−0.2 (−55.9 to 35.6)

Abbreviations: CI, confidence interval; HR, hazard ratio; IIV3, trivalent inactivated influenza vaccine; VE, vaccine effectiveness.

[a]Vaccination status at the end of follow-up. See Supplementary Table 4 for cases and population partially vaccinated at the end of follow-up.

[b]Proportion of cohort size N.

[c]Per 10 000 person-weeks.

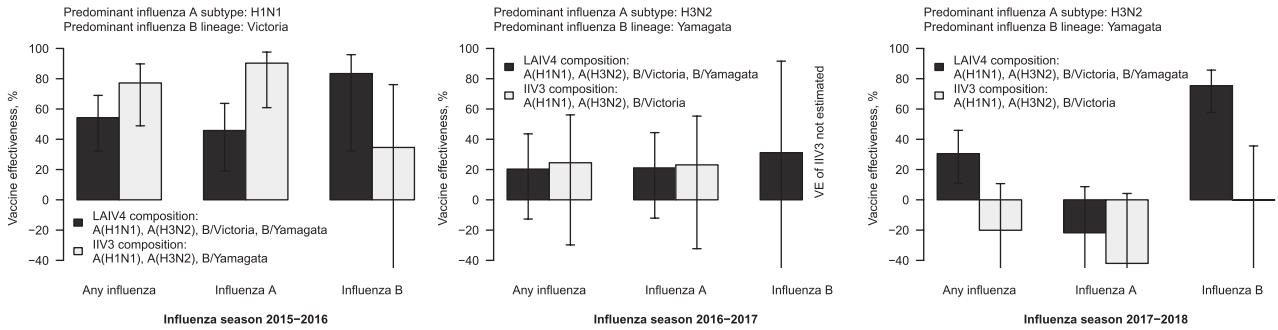

Figure 2. Vaccine effectiveness of LAIV4 and IIV3 against laboratory-confirmed influenza infection in 2-year-old children: influenza seasons 2015–2016 through 2017–2018, register-based cohort studies, Finland. The whiskers show the 95% confidence intervals. Abbreviations: IIV3, trivalent inactivated influenza vaccine; LAIV4, tetravalent live-attenuated influenza vaccine.

incidence among the unvaccinated was lower than in urban municipalities. Likewise, children who had visited well-baby clinics more than 17 times before the age of 2 years were more likely to be vaccinated than children who had visited well-baby clinics less than 12 times (Supplementary Tables 8–10). The influenza incidence in unvaccinated children who had visited well-baby clinics more than 17 times was higher than in unvaccinated children who had visited well-baby clinics less often (Supplementary Table 7).

DISCUSSION

In Finland, the influenza vaccine uptake among 2-year-olds has been steadily increasing. The VE, however, dropped from being initially high in 2015–2016 to rather low levels in 2016–2017 and 2017–2018. According to the presented register-based cohort studies, vaccination with LAIV4 or IIV3 reduced the influenza incidence rate by more than half in 2015–2016 but by less than one-third in the 2 subsequent seasons. The small number of hospitalized cases indicates that the majority of infections in children were detected and treated in primary care.

It is known from sentinel surveillance that the 2015–2016 influenza epidemic was predominated by A(H1N1)pdm09 and B/Victoria viruses, although the latter type circulated mainly towards the end of the season and to a much lesser extent [8]. According to our analysis, IIV3 provided better protection against influenza A than LAIV4. Since both contained A(H1N1)pdm09 virus antigen, the observed difference may be due to reduced replicative fitness of the A(H1N1)pdm09 component in LAIV4 [9]. Against influenza B, however, LAIV4 provided stronger protection than IIV3, which did not contain B/Victoria virus antigen in 2015–2016 and was thus mismatched with the circulating influenza B viruses. These findings are in line with results obtained in other studies on VE of LAIV4 and/or IIV3 in children from Canada [10], Israel [11], the United Kingdom [12, 13], and the United States [14]. Nevertheless, there have also been dissenting studies indicating lack of protection after vaccination with LAIV4, based on which the recommendation of using live-attenuated influenza vaccines was withdrawn in the United States [15].

The 2016–2017 epidemic in Finland was predominated by influenza A(H3N2) viruses [16], against which neither LAIV4 nor IIV3 was found to be efficacious. By contrast, a study conducted in the United Kingdom estimated VE of LAIV4 against influenza A(H3N2) at 57% [17], although the CI is wide and includes our point estimate. Focusing on IIV3, 3 studies in outpatient care did not show strong beneficial effects [18–20], while a fourth, hospital-based study did [11]. In general, VE against A(H3N2) strains has been consistently lower when compared with VE against other strains. Suggested reasons include the rapid evolution of wild A(H3N2) viruses, egg-based manufacturing of vaccines increasing the chance of antigenic mismatch due to egg adaption, and the complexity of human immune responses such as the imprinting effect of the first encountered infection [21, 22]. Due to the small number of influenza B cases among Finnish 2-year-olds it was not possible to estimate VE against influenza B in 2016–2017.

In 2017–2018, influenza A(H3N2) and B/Yamagata viruses co-circulated [23]. Neither LAIV4 nor IIV3 protected Finnish children against influenza A. Nevertheless, vaccination with LAIV4 was still beneficial due to its high effectiveness against influenza B. By contrast, the effectiveness of IIV3 against influenza B was estimated at 0%. Again, the trivalent vaccine composition mismatched with the circulating influenza B viruses. Our results regarding the effectiveness of LAIV4 are in agreement with results from the United Kingdom [24]. In contrast to our findings, a hospital-based Israeli study [11] found the children were protected after vaccination with IIV3, although this might be due to the different settings.

One strength of our register-based approach is the large size of the cohorts. We included essentially the whole population of Finnish children who were eligible for vaccination with LAIV4. Another strength is that we can distinguish between the brands of the vaccines recorded in the NVR. Consequently, the effectiveness of LAIV4 and IIV3 can be compared within the same population during the same season addressing the regulatory request for brand-specific VE [25].

In the present analysis, we revised our definition of children aged 2 years during an influenza season that was used in a previously conducted study [2]. Extending the inclusion criterion from children born in 2013 to children born November 2012–December 2013 increased the cohort size in 2015–2016 to over 60 000 despite the application of stricter exclusion criteria following a refinement of the NVR's quality assessment. Another difference from the previous analysis is the discrimination between fully and partially vaccinated children resulting in slightly higher VE estimates.

The general limitations associated with a register-based cohort study design have been described previously [4]. In particular, information bias and confounding may have affected the estimation of VE. Laboratory-confirmed influenza infection as recorded in the National Infectious Diseases Register does not describe the complete entity or spectrum of influenza disease in the Finnish population as many infections remain undetected, leading to outcome misclassification. Because the majority of patients tested for influenza are selected as part of routine clinical procedure, the representativeness of the recorded cases is unknown and ascertainment bias cannot be excluded. If the infection of an unvaccinated child is more likely to be confirmed than the infection of a vaccinated child, we expect to overestimate VE, and vice versa. Bias due to outcome misclassification, however, seems negligible if misclassification equally affects unvaccinated and vaccinated cases. In addition, we assumed that data in the NVR are complete, allowing unbiased estimation of VE, although we cannot exclude that some vaccinations were given without being registered in the NVR—for example, when administered in the private sector despite the free offer of vaccination in public health care centers.

Confounding due to demographic and health-related factors could have distorted our analyses. For instance, the higher IIV3 uptake and lower incidence among children born in November or December might have contributed towards an overestimation of IIV3 effectiveness in 2016–2017. Nevertheless, the current analyses were not adjusted for confounding because the propensity score and covariate adjustments performed so far in 2 similar studies [2, 26] did not reveal any major difference between crude and adjusted estimates. One possible explanation for such stability could be that 2-year-olds in Finland, a country with free public health care, form quite a homogenous group.

Great efforts are spent in motivating vaccine uptake prior to each influenza season. While the effectiveness by virus type is deemed the most important measure for vaccine manufacturers, for public health decision makers and individuals, such as parents of 2-year-old children at risk of influenza, the overall level of protection (effectiveness against any virus type) seems more relevant. The effectiveness of the nasal spray LAIV4 and the injectable IIV3 varied across the influenza seasons and neither of the vaccines clearly excelled. Supported by the present analysis, the vaccination program in Finland now equally recommends LAIV4 and injectable, tetravalent inactivated influenza vaccines replacing IIV3. Moreover, with the recent extension of the program to cover influenza vaccinations of children aged 3 to 6 years, we expect to conduct even better-powered studies in the future.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest: U. B. and H. N. are employees of the Finnish Institute for Health and Welfare, which has received funding from the European Commission and Sanofi Pasteur for the conduct of influenza vaccine effectiveness studies in the elderly. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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