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Influenza-like Illness Incidence Is Not Reduced by Influenza Vaccination in a Cohort of Older Adults, Despite Effectively Reducing Laboratory-Confirmed Influenza Virus Infections

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(See the editorial commentary by McElhaney and McNeil, on pages 399–401.)

Background. Data on the relative contribution of influenza virus and other respiratory pathogens to respiratory infections in community-dwelling older adults (≥60 years) are needed.

Methods. A prospective observational cohort study was performed in the Netherlands during 2 winters. Nasopharyngeal and oropharyngeal swabs were collected during influenza-like illness (ILI) episodes and from controls. Viruses and bacteria were identified by multiplex ligation–dependent probe amplification assay and conventional bacterial culture.

Results. The ILI incidence in the consecutive seasons was 7.2% and 11.6%, and influenza virus caused 18.9% and 34.2% of ILI episodes. Potential pathogen were detected in 80% of the ILI events with influenza virus, coronaviruses, rhinoviruses, human metapneumovirus, respiratory syncytial virus, parainfluenza viruses, and *Haemophilus influenzae* being the most common. Influenza vaccination reduced influenza virus infection by 73% (95% confidence interval [CI], 26%–90%) and 51% (95% CI, 7%–74%) in ILI patients. However, ILI incidence was similar between vaccinated (7.6% and 10.8%) and nonvaccinated (4.2% and 11.4%) participants in 2011–2012 and 2012–2013, respectively ($P > .05$).

Conclusions. Influenza virus is a frequent pathogen in older adults with ILI. Vaccination reduces the number of influenza virus infections but not the overall number of ILI episodes: other pathogens fill the gap. We suggest the existence of a pool of individuals with high susceptibility to respiratory infections.

Clinical Trials Registration. NTR3386.

Keywords. influenza virus; influenza virus infection; influenza-like illness; older adults; vaccination.

Influenza virus causes seasonal epidemics, resulting in 3–5 million severe cases and 250 000–500 000 deaths globally each year [1]. Elderly persons, individuals with certain medical conditions and children aged <2 years have the highest risk for complications. Vaccination is an important tool to prevent infection and to reduce morbidity and mortality [1]. In the Netherlands, individuals aged ≥60 years are offered the annual influenza vaccination. However, public acceptance of vaccination is moderate [2]. Vaccine effectiveness (VE) varies per season and depends on age and health of the recipients, and the antigenic match of vaccine strains with circulating strains [3–5]. Furthermore, there is scientific debate about the methodology of determining VE [5, 6]. These discussions reach the media and influence the general opinion on influenza vaccine benefit. Moreover, to the public, flu as caused by influenza virus is the same as influenza-like illness (ILI) caused by respiratory pathogens, against which influenza vaccination will not protect. Consequently, influenza vaccination is perceived to be ineffective and vaccine uptake is reduced. To counter this trend, data on the relative contribution of influenza virus and other respiratory infections to ILI in older community-dwelling adults are lacking and needed [7–10]. This group is underrepresented in the Dutch primary care sentinel surveillance system [10, 11] and by definition absent in the Dutch Sentinel Nursing Home Surveillance Network [12]. This is also the case in many other studies worldwide [7–9].

The aim of this prospective observational study was to determine the relative contribution of influenza virus and other

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respiratory pathogens to ILI in older adults (aged ≥60 years) in 2 consecutive seasons in the Netherlands. In addition, influenza VE was estimated in both seasons. Upon ILI, we determined the presence of potential pathogens in the pharynx of the participant within 72 hours of symptom onset. As a control, we analyzed samples of the same individuals taken after recovery (8 weeks) and in a subset of asymptomatic controls for the same potential pathogens.

METHODS

Study Design

This prospective observational study was conducted during 2 consecutive influenza seasons (from December 2011 to April 2012 [2011–2012] and from October 2012 to May 2013 [2012–2013]) in the Netherlands. Adults aged ≥60 years were recruited through their general practitioner or through the Civil Registry. For the second season, participants were reinvited and additional participants were recruited through the Civil Registry. We also started earlier to use the same monitoring period as in the Dutch sentinel surveillance system [11]. There were no exclusion criteria for the study. Influenza vaccination status was recorded (2009–2012). Participants were part of the study for the entire duration of each season and contacted at the end of season to verify participation. Written informed consent was obtained from all participants. All trial-related activities were conducted according to Good Clinical Practice, which includes the provisions of the Declaration of Helsinki. The study was approved by the acknowledged ethical committee METC Noord Holland (http://www.trialregister.nl; NTR3386).

Participants were instructed about ILI symptoms according to the Dutch Pel criteria, defined by fever (≥37.8°C) with at least 1 other symptom of headache, myalgia, sore throat, coughing, rhinitis, or chest pain [13] and to report ILI as soon as possible after onset. A research nurse performed a home visit within 72 hours of fever onset. During this acute phase, nasopharyngeal and oropharyngeal swabs were obtained and additional information on demographics and comorbidities was recorded. A second visit (recovery phase) was performed 8 weeks (±1 week) later, during which the same samples were collected. If a new ILI episode was reported, participants were visited again. In the second season, a control group of asymptomatic participants, equally distributed over the different age groups and season, was sampled and questioned.

Nasopharyngeal and Oropharyngeal Swabs

Nasopharyngeal and oropharyngeal samples were obtained with a sterile swab with a flocked nylon tip and stored separately in 1 mL modified liquid Amies transport medium (Eswab, Copan, Brescia, Italy). Samples were transported at room temperature to the laboratory and processed and stored at −80°C within 8 hours after sampling.

Analysis of Viruses and Subset of Bacteria by Multiplex Ligation-Dependent Probe Amplification Assay

DNA and RNA were isolated from 200 μL of both swabs by easyMag isolation and eluted in 25 μL of buffer (bioMérieux, the Netherlands). Five microliters was used for the detection of a panel of respiratory viruses and bacteria by a real-time polymerase chain reaction (PCR)–based multiplex ligation-dependent probe amplification (MLPA) assay (RespiFinder Smart 22 kit; Pathofinder, the Netherlands). All analyses were performed on a Roche Lightcycler 480. MLPA analysis was performed on both swabs separately. A participant was excluded from the analysis and considered missing if either of the swabs or data for a swab were missing. For MLPA data analysis, a participant was considered positive for a target if at least 1 swab of the participant was positive.

Influenza virus–positive samples were subtyped by real-time reverse-transcription PCR using the Roche LightCycler 480 system with slightly modified protocols as described previously [14, 15].

Bacterial Culture

Conventional culture of oropharyngeal swabs was performed for *Streptococcus pneumoniae* and *Haemophilus influenzae* according to standard procedures [16]. Discrimination of *H. influenzae* and *Haemophilus haemolyticus* was performed by matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) [17]. Participants without available oropharyngeal swabs were excluded from analysis and designated as missing.

Statistical Analysis

For analysis of the contribution of influenza virus, a sample size of 200 ILI cases was estimated to be required. Based on an expected ILI incidence of 7.5% and a drop-out rate of 5%, a cohort size of 2100 participants was calculated. Based on results of the first season, 2500 participants were included in the second season.

Pearson χ^2 testing and independent samples *t* test of the means was applied to analyze participant characteristics with SPSS 19.0 for Windows software. A *P* value ≤.05 was considered significant.

The incidence of different viruses or bacteria was calculated as the percentage of swabs positive with the potential pathogen of the number of ILI events during the season. Attack rates were calculated as percentage of detected pathogens per number of monitored participants.

Vaccine effectiveness was determined by test-negative design analysis of ILI positive participants in the influenza-active period [18]. The analysis is restricted to the period that influenza virus was circulating in the Netherlands for that particular season, defined by the national influenza surveillance weekly reports. Participants with <14 days between the date of vaccination and the date of home visit were excluded from the VE analysis, as it

is uncertain whether the vaccine already had any effect in this period. Second and third ILI periods were included in the analysis only if an earlier ILI period was influenza virus negative. For ILI participants, influenza virus positive was considered "case" and influenza negative "control." The VE is calculated as (1 – odds ratio [OR]) × 100% with 95% confidence interval (CI) and is calculated per influenza virus subtype or lineage. The following factors were regarded as potential confounders: period in the season (early and late season), sex, smoking, comorbidity, and age (natural smoothing spline, 4 degrees of freedom). The association between the potential confounders and influenza virus positivity (any subtype) was analyzed with univariate logistic regression. Variables with $P < .20$ were considered in the multivariable analysis. Variables that changed the OR by at least 5% are included in the final multivariable logistic regression model for any influenza subtype (backward selection). All analyses were performed with SAS version 9.4 software. Sensitivity analyses were performed in the VE analyses for other control groups (Supplementary Materials).

RESULTS

Study Cohort and ILI Incidence

In this prospective study, we observed an ILI incidence of 7.2% (143/1992) and 11.6% (275/2368) in 2 consecutive seasons (2011–2012 and 2012–2013, respectively) (Figure 1A; Table 1). The average age of vaccinated individuals was significantly higher than that of unvaccinated individuals (respectively, 70.4 vs 66.9 years in 2011–2012 and 71.9 vs 67.9 years in 2012–2013; Table 2). The asymptomatic controls from the second season were older and more often vaccinated compared with the overall cohort (Figure 1B; Table 2). Furthermore, participants who reported comorbidities were vaccinated significantly more often than participants who did not report comorbidities (Table 3). No significant differences were found between individuals with or without ILI with respect to sex, age, and chronic illnesses (Tables 1 and 3). Importantly, no differences were found in the incidence of ILI episodes between vaccinated and unvaccinated participants (Table 1).

Pathogen Distribution in Swabs and Contribution of Influenza Virus

In 79.1% and 78.0% of the acute ILI samples from the 2 seasons, at least 1 potential pathogen could be identified by MLPA or bacterial culture (Figure 2A and 2B; Supplementary Table 1*A*–*C*). Viruses were detected in the majority of samples (64.9% and 73.8%, in 2011–2012 and 2012–2013, respectively). In 16.2% and 17.0% of the samples from the acute phase, >1 potential pathogen was detected, but no specific combinations of viruses and/or bacteria were observed (data not shown). In recovery samples, 8 weeks after acute ILI, potential pathogens were detected in 27.0% and 24.8% of cases in 2011–2012 and 2012–2013, respectively. In asymptomatic control samples, similar potential pathogens were observed as in recovery samples (21.5%) (Figure 2C).

In 2011–2012, influenza virus was detected in 18.9% of the acute ILI samples, predominantly of the A(H3N2) subtype (96.3%) (Figure 3; Supplementary Table 1*A*). Influenza virus was not detected in the corresponding recovery samples in this season, suggesting that influenza virus was the actual cause of ILI. In 2012–2013, influenza virus was detected in 34.2% of the acute ILI samples, and all 4 circulating subtypes were detected: 43.6% A(H3N2), 25.5% A(H1N1)pdm09, 25.5% B/Yamagata lineage, and 5.3% B/Victoria lineage. In addition, influenza virus was detected at a very low level in both the recovery samples and in samples of asymptomatic controls (1.1% and 0.9%, respectively).

We investigated which other viruses and bacteria were detectable during ILI episodes. In 60.8% (2011–2012) and 44.7% (2012–2013) of ILI samples, potential pathogens other than influenza virus were detected (Figure 3; Supplementary Table 1). Coronaviruses of all 4 common human subtypes (18.2% in 2011–2012 and 11.3% in 2012–2013), human metapneumovirus (hMPV) (20.3% and 3.6%), rhinoviruses (8.4% and 21.1%), respiratory syncytial virus (RSV) (4.9% and 6.5%), and parainfluenza viruses (2.8% and 5.1%) were detected in >5% of the ILI samples in at least 1 season. hMPV and rhinovirus varied most between the 2 seasons. All viruses were detectable at low levels in recovery and control samples. Rarely, the same virus was observed during both the ILI event and the recovery sampling, except for rhinoviruses, which were detected frequently at both visits (8.3% in 2011–2012 and 17.2% in 2012–2013), but as our test only detected rhinovirus in general, we cannot exclude that these are different serotypes.

The attack rate of influenza virus was significantly higher in the second season compared to the first season ($P < .0001$; Table 4). Interestingly, the increased attack rate could be attributed to significant increases in the attack rates of H1N1, the B/Victoria-like subtype, and the B/Yamagata-like subtype ($P < .0001$, $P = .04$, and $P < .0001$, respectively), whereas the attack rate of the H3N2 subtype was not significantly different between these seasons. For the other viruses, we observed significant increased attack rates in the second season for rhinovirus ($P < .0001$) and parainfluenza viruses ($P = .04$), whereas hMPV attack rates were significantly lower in the second season ($P = .0004$). The other viruses had similar attack rates during the 2 seasons.

The only bacterial species detected by conventional culture in a significant number of acute ILI cases was *H. influenzae* (15.4% in 2011–2012 and 11.3% in 2012–2013), frequently as the sole pathogen, while presence of other bacteria such as *H. haemolyticus* and *S. pneumoniae* was low. *Haemophilus influenzae* was also detected frequently in recovery and control samples.

Vaccine Effectiveness

We evaluated whether influenza vaccination reduced the overall influenza virus infection incidence and whether this influenced the incidence of ILI. Although influenza virus

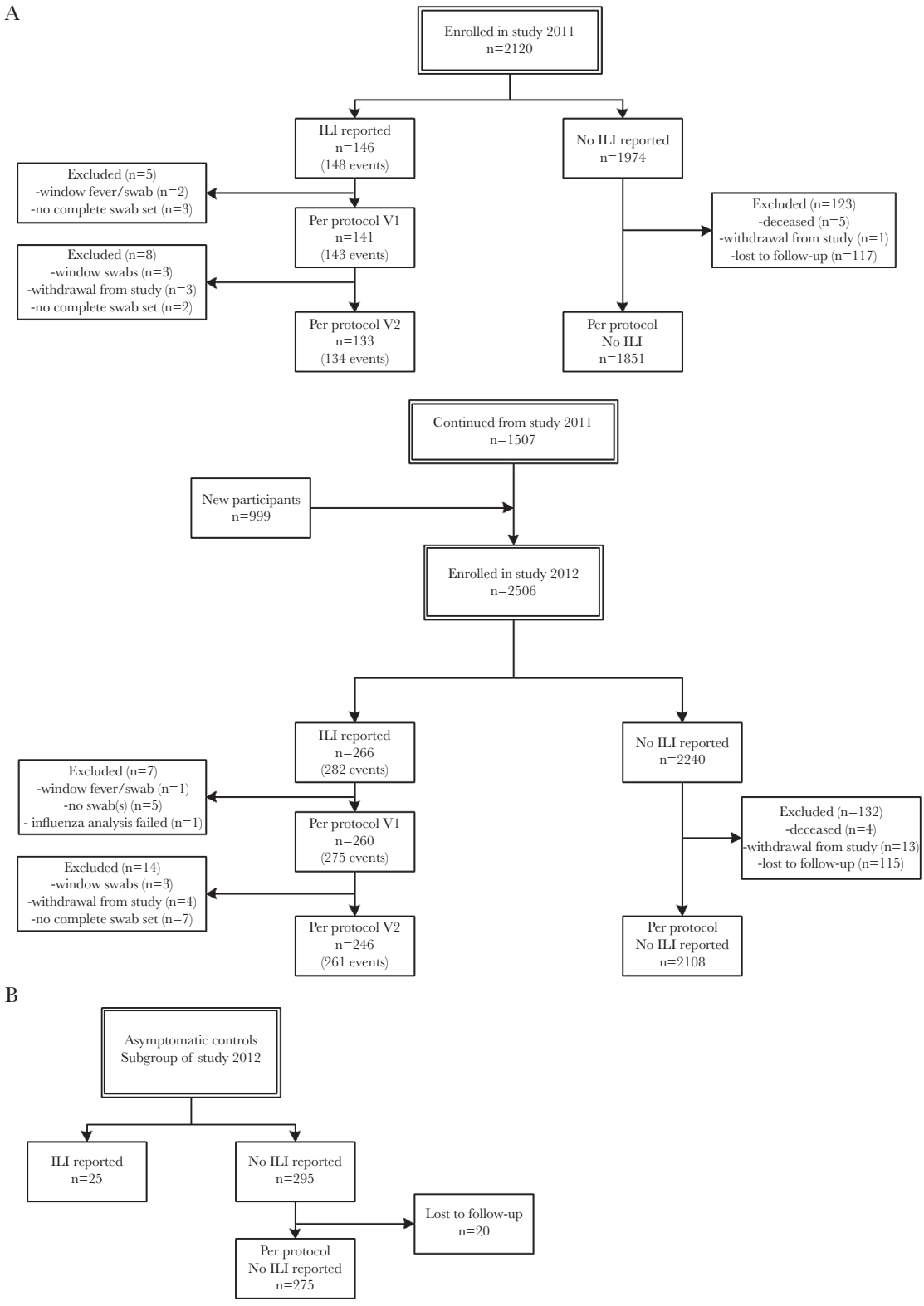

Figure 1. Flow diagram of enrollments and influenza-like illness (ILI) cases (2011–2012 and 2012–2013) (*A*) and the subgroup of asymptomatic controls (2012–2013) (*B*). A subject could have multiple ILI episodes per season. An ILI visit (V1) was considered "out of window" if the sample was taken >72 hours after start of fever. For the recovery visit (V2), the window was 7–9 weeks after ILI onset. Subjects were considered lost to follow-up if they did not respond to the end of study mailing and had no ILI visit (*A*). After the baseline visit had been performed, a subject could have an ILI event. Subjects were considered lost to follow-up if they did not respond to the end of study mailing and had no ILI visit (*B*).

Table 1. Demographic Characteristics of the Enrolled Participants

Characteristic		All (n = 1992)	ILI (n = 141)	No ILI (n = 1851)	*P* Value
2011–2012					
Male sex		992 (49.8)	61 (43.3)	933 (50.4)	NS[a]
Age, y, mean (range)		69.6 (60–93)	68.8 (60–89)	69.6 (60–93)	NS[b]
Influenza vaccination 2011–2012		1512 (75.9)	115 (81.6)	1396 (75.4)	NS[a]
Multiple ILIs					
2			2 (1.4)		
	Asymptomatic controls[c] (n = 340)	All (n = 2368)	ILI (n = 260)	No ILI (n = 2108)	*P* Value
2012–2013					
Male sex	155 (45.6)	1177 (49.7)	119 (45.8)	1058 (50.2)	NS[a]
Age, y, mean (range)	73.8 (61–93)	70.7 (60–95)	70.1 (60–89)	70.7 (60–95)	NS[b]
Influenza vaccination 2012–2013	261 (76.8)	1622 (68.5)	175 (67.3)	1448 (68.7)	NS[a]
Multiple ILIs					
2			14 (5.4)		
3			2 (0.8)		

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ILI, influenza-like illness; NS, not significant.

[a]Pearson χ^2 test.

[b]Independent samples *t* test of the means.

[c]Individuals in the asymptomatic subset were selected to be evenly distributed over the different age groups; therefore, the overall vaccination level was higher in the asymptomatic subset compared to the ILI and non-ILI groups.

infection incidence was significantly lower in influenza vaccinated than in unvaccinated individuals (Table 5), the incidence of ILI cases was not reduced by vaccination (Table 1).

Among participants with ILI, we observed a high VE of 73% (95% CI, 26%–90%) in 2011–2012 and a moderate VE of 51% (95% CI, 7%–74%) in 2012–2013 against influenza virus during the influenza-active period (Table 6). Furthermore, the VE for the predominant influenza virus subtype A(H3N2) in 2011–2012 was 71% (95% CI, 19%–90%). In 2012–2013, the VE against influenza virus type A(H3N2) was 67% (95% CI, 20%–86%). Additional sensitivity analyses for multiple ILIs, households with ILI, and the presence or absence of other virus infections did not affect this conclusion (Supplementary Table 2).

DISCUSSION

In this study in a cohort of community-dwelling older adults in the Netherlands, we show that influenza virus was present in 18.9% and 34.2% of ILI cases in 2 consecutive seasons and that influenza vaccination significantly reduced laboratory-confirmed influenza virus infection. In 60.8% and 44.7% of the acute ILI cases, potential pathogens other than influenza virus were detected. In addition, these pathogens were more often present during ILI than after recovery or in asymptomatic elderly persons. In 20% of the ILI cases, no potential pathogen was detected. The incidence of ILI cases was expected to decrease by a reduction in influenza virus–caused ILI through vaccination; however, this effect was not observed. Instead, the incidence of

Table 2. Age and Age Distribution in the 2011–2012 and 2012–2013 Cohorts in Relation to Vaccination Status

Cohort		Influenza Vaccination	No Influenza Vaccination	*P* Value[a]
2011–2012	Age, y, mean	70.4	66.9	.0001
2012–2013	Age, y, mean	71.9	67.9	.0001

	2011–2012				2012–2013				
Age Group, y	Age Distribution (n = 1992)		Vaccinated per Age Group		Age Distribution (n = 2368)		Vaccinated per Age Group		Age Distribution in the Dutch Population[b]
60–64	685	34.4%	443	64.7%	618	26.1%	331	53.6%	25.6%
65–69	496	24.9%	382	77.1%	687	29.0%	435	63.3%	24.1%
70–74	333	16.7%	273	82.0%	436	18.4%	329	75.4%	19.8%
75–79	279	14.0%	238	85.3%	313	13.2%	260	83.0%	12.9%
≥80	199	10%	175	87.9%	317	13.4%	270	85.2%	17.6%
Total		100%			100%				100%

Data are presented as No. (%) unless otherwise indicated.

[a]Independent samples *t* test of the mean.

[b]Source: Centraal Bureau voor de Statistiek, Den Haag/Heerlen, 1 January 2014.

Table 3. Comorbidities in Influenza-like Illness Cases and Asymptomatic Subgroup in Combination with Vaccination Status

	2011–2012	2012–2013	
Comorbidity	ILI Cases (n = 141)	ILI Cases (n = 260)	Asymptomatic Controls (n = 340)
Any chronic illness	58 (41.1%)	115 (44.2%)	152 (44.7%)
Chronic respiratory conditions	28 (19.9%)	35 (13.5%)	53 (15.6%)
Chronic heart failure	19 (13.5%)	41 (15.8%)	44 (12.9%)
Autoimmunity	7 (5%)	21 (8.1%)	33 (9.7%)
Diabetes mellitus	13 (9.2%)	31 (11.9%)	32 (9.4%)
Malignancy	9 (6.4%)	20 (7.7%)	33 (9.7%)
Vaccinated with any chronic illness	53 (91.4%)	129 (84.3%)	129 (84.9%)
Vaccinated without any chronic illness	62 (74.7%)	78 (53.8%)	132 (70.2%)
P value[a]	.012	.0001	.001

[a]Pearson χ^2 test.

ILI remained the same between the vaccinated and nonvaccinated individuals.

Influenza vaccination is offered to individuals 60 years and older in the Netherlands, as older adults are at increased risk for morbidity and mortality from influenza virus infections due to an aging immune system and age-related chronic illnesses [19, 20]. However, this policy is based on studies mostly performed in elderly persons in nursing homes, who are substantially older and more frail compared with community-dwelling elderly individuals. Studies in community-dwelling older adults are scarce [7–10], and only a restricted number of pathogens have been analyzed in these surveillance studies. To fill the gap in knowledge, we recruited participants through general practitioners and the Civil Registry, resulting in >99% of the participants living in the community. In line with the risk-based vaccination strategy in the Western world, older participants and participants with chronic conditions were more likely to be vaccinated [2]. The age distribution in the cohort was similar to that observed for those ≥60 years in the general Dutch population; only the oldest age group (>80 years) was underrepresented (Table 2). These elderly persons are often less likely to participate in studies. "Healthy user effect" or "frailty selection bias" is a well-known issue in observational influenza vaccine studies, as the very frail elderly persons are difficult to reach [21, 22].

We found that influenza virus is involved in 18.9%–34.2% of ILI cases in the 2 seasons studied. In addition, coronaviruses, rhinoviruses, hMPV, RSV, parainfluenza viruses, and *H. influenzae* were frequently observed as the sole detected pathogen in acute ILI cases, whereas they were low to absent in most of the recovery samples. However, rhinoviruses and the bacterium *H. influenzae* were also commonly detected in asymptomatic controls. The rhinoviruses may be of different subtypes, as we did not type these viruses. Viruses can often be

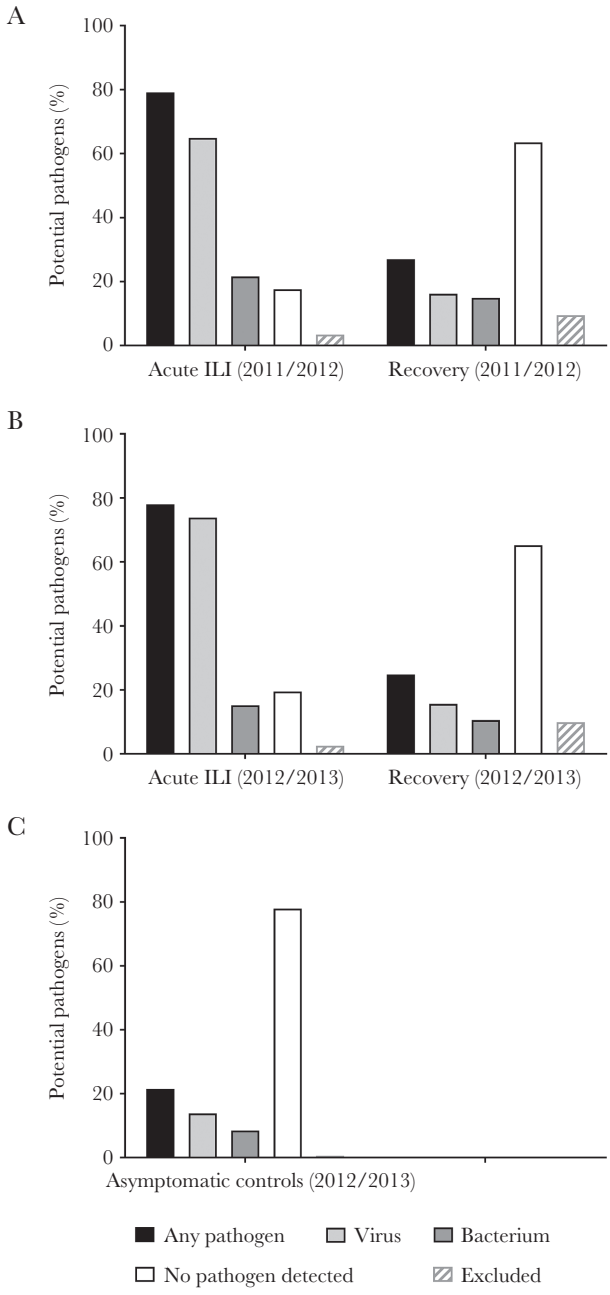

Figure 2. Distribution of detected viruses and bacteria per influenza-like illness (ILI) event. The incidence of virus or bacterium, or combination of both ("any pathogen") detected in the swab is depicted per ILI events in 2011–2012 (n = 143) (*A*), 2012–2013 (n = 275) (*B*), and asymptomatic controls (n = 340) (*C*). If a sample set was not complete, the event was excluded.

detected in individuals without clinical manifestations [7], but when they are found as the sole agent in the context of disease, they are commonly considered to be the cause of the disease. For bacteria, this is less clear as they are commonly carried in asymptomatic persons but may expand during respiratory viral infection or new acquisition. *Haemophilus influenzae* may induce an enhanced inflammatory state in the presence of other pathogens, as was shown in children [23]. This may lead to ILI.

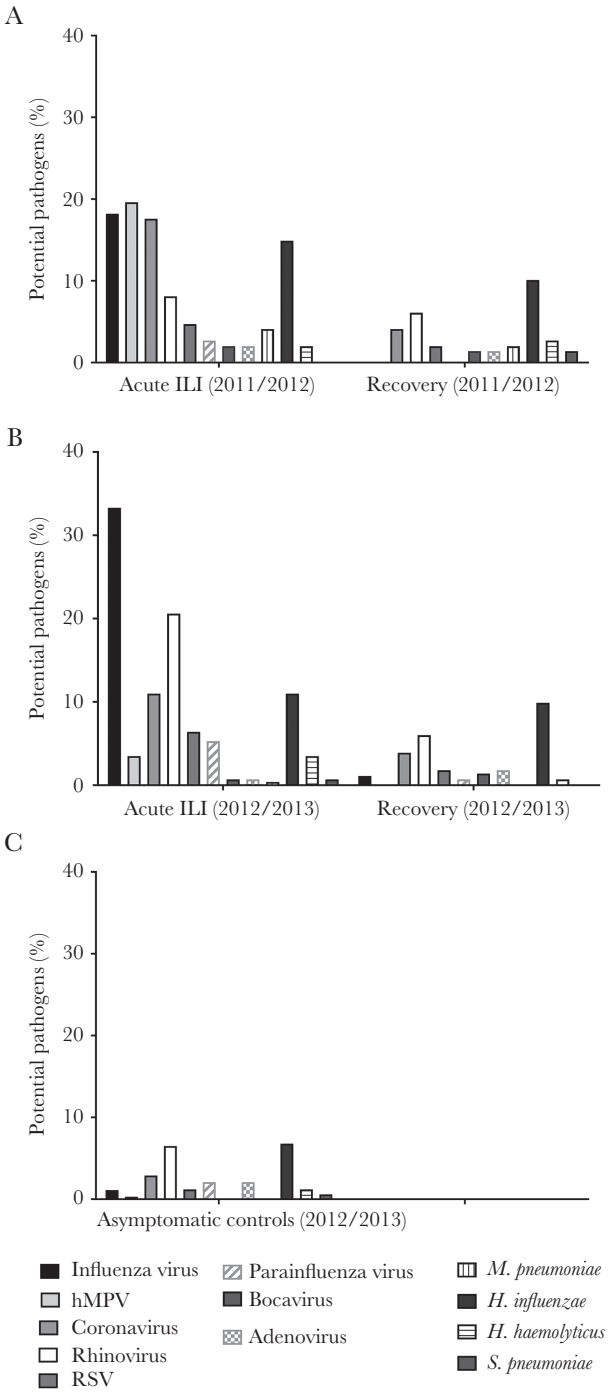

Figure 3. Viruses and bacteria detected in swabs of influenza-like illness (ILI) cases and samples of asymptomatic controls. Incidence per virus or bacterium detected in naso- and oropharyngeal swabs in 2011–2012 (n = 143) (*A*), 2012–2013 (n = 275) (*B*), and asymptomatic controls (n = 340) (*C*). The percentages were calculated per ILI event. Multiple pathogens could be detected in a single event and therefore contribute to the incidence for multiple pathogens. Abbreviations: hMPV, human metapneumovirus; ILI, influenza-like illness; RSV, respiratory syncytial virus.

However, in most ILI cases where we found *H. influenzae*, we did not find a second pathogen that could also explain the ILI symptoms.

Table 4. Attack Rate for Different Viruses in 2011–2012 and 2012–2013

Virus	2011–2012 (n = 2120)	2012–2013 (n = 2506)	*P* Value[a]
Influenza virus	1.3%	3.8%	<.0001
A(H3N2)	1.2%	1.6%	NS
A(H1N1)pdm09	0%	1.0%	<.0001
B/Victoria-like	0%	0.2%	.04
B/Yamagata-like	0.05%	1.0%	<.0001
Coronavirus	1.2%	1.2%	NS
hMPV	1.4%	0.4%	.0004
RSV	0.3%	0.7%	NS
Rhinoviruses	0.6%	2.3%	<.0001
Parainfluenza virus	0.2%	0.6%	.04
Bocavirus	0.1%	0.1%	NS
Adenovirus	0.1%	0.1%	NS

Abbreviations: hMPV, human metapneumovirus; RSV, respiratory syncytial virus; NS, not significant ($P > .05$).

[a]Pearson χ^2 test.

Influenza virus incidence in our cohort broadly matched the incidence reported in the Dutch sentinel surveillance system [11], where the 2011–2012 season proved to be mild and the 2012–2013 season was the longest influenza epidemic of the previous 20 years. The significant increase in attack rate for influenza virus could be attributed to the influenza virus subtypes A/H1N1pdm09 and influenza B. Influenza A/H3N2 was the predominant influenza virus subtype in both the 2011–2012 and 2012–2013 seasons, with similar attack rates. In contrast, the Dutch and European networks monitoring nursing homes

Table 5. Pathogens Detected in Acute Influenza-like Illness Events Relative to Vaccination Status

Influenza Season			
2011–2012	Vaccinated (n = 115)	Nonvaccinated (n = 26)	*P* Value[a]
Influenza virus	15 (13.0)	12 (46.2)	.0001
Coronavirus	22 (19.1)	4 (15.4)	NS
hMPV	24 (20.9)	4 (15.4)	NS
RSV	6 (5.5)	1 (3.8)	NS
Rhinoviruses	10 (8.7)	2 (7.7)	NS
Parainfluenza virus	4 (3.5)	0 (0)	NS
Haemophilus influenzae	19 (18.3)	3 (12.5)	NS
2012–2013	Vaccinated (n = 175)	Nonvaccinated (n = 85)	*P* Value[a]
Influenza virus	54 (30.9)	40 (47.1)	.011
Coronavirus	21 (12.0)	10 (11.8)	NS
hMPV	4 (2.3)	2 (2.4)	NS
RSV	12 (6.9)	6 (7.1)	NS
Rhinoviruses	43 (24.6)	13 (15.3)	.06
Parainfluenza virus	11 (6.3)	3 (3.5)	NS
Haemophilus influenzae	23 (13.1)	6 (7.1)	NS

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: hMPV, human metapneumovirus; RSV, respiratory syncytial virus; NS, not significant ($P > .05$).

[a]Pearson χ^2 test.

Table 6. Vaccine Effectiveness in the Influenza-Active Season

Influenza Virus Subtype	No.	Odds Ratio (95% CI)	VE, % (95% CI)[a]
2011–2012			
All influenza subtypes	122	0.268 (.097–.738)	73 (26 to –90)
Only influenza virus type A(H3N2)	121	0.288 (.103–.806)	71 (19 to –90)
2012–2013			
All influenza subtypes	206	0.493 (.262–.928)	51 (7–74)
Only influenza virus type A	178	0.423 (.211–.850)	58 (15–79)
Only influenza virus type A(H3N2)	154	0.330 (.137–.796)	67 (20–86)
Only influenza virus type A(H1N1)pdm09	137	0.466 (.179–1.215)	53 (–22 to 82)
Only influenza virus type B	141	0.570 (.203–1.600)	43 (–60 to 80)
Only influenza virus type B/Yamagata	136	0.935 (.286–3.056)	7 (–205 to 71)

For more details, see Supplementary Table 3.

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

[a]Corrected for the possible confounders age group, comorbidity, sex, and smoking. Data were calculated for the influenza-active period in the Netherlands as defined by the Netherlands Institute for Health Services Research [11].

reported a high ILI incidence and mortality in the 2011–2012 season [24, 25]. This underlines a potential difference between the generally healthy community-dwelling elderly persons and that of the generally more frail institutionalized elderly persons, who may overlap in age. It also shows that data acquired in one group do not necessarily apply to the other, including exposure and susceptibility to infection, as well as influenza VE.

We show that the incidence of influenza virus infection was reduced in individuals who received influenza vaccination and that VE to laboratory-confirmed influenza virus infection was high to moderate in the 2 seasons. The 95% CIs of the data are wide, probably due to the relatively small sample size, a common problem in similar studies. VE estimates are notoriously variable between studies [18], but the VE data from this study are in line with those reported by van der Hoek et al [18].

The most striking finding in this study was the similar incidence in ILI cases observed between vaccinated and the nonvaccinated individuals. This may be explained by assuming that a pool of people exists that is highly susceptible to respiratory infections. The reduction by vaccination in the number of cases caused by influenza virus infections is offset by a rise in the number of cases caused by infections by other pathogens. Cowling et al have described a similar increased risk of noninfluenza respiratory virus infection in influenza-vaccinated children [26]. However, we cannot attribute this effect to a specific pathogen. Influenza virus may take preference over other viruses and prevent them from filling the niche, possibly by inducing a prolonged antiviral state, as has been described for other viruses [23, 27]. When vaccination reduces influenza virus infections, the other pathogens can fill the gap.

It needs to be confirmed in other studies whether influenza virus vaccination has no effect on the total number of ILI cases. It would have important consequences for decisions on implementation of vaccination for community-dwelling older adults when looking at the overall disease burden and cost-effectiveness. However, a limitation of our study is that we did not directly monitor the duration and severity of disease in the ILI cases: Difference in disease or hospitalization was only registered in post-ILI questionnaires, and no significant events were reported. More detailed data on severity and duration of symptoms would allow assessing the relative risk posed by different pathogens, taking into account that influenza virus, unlike most other potential pathogens, can vary in pathogenicity between seasons.

In combination with other medical information, it may then be possible to assemble a profile of individuals potentially at risk for ILI or worse. Such a profile would be of great value to public health professionals.

A limitation of this study is the definition of ILI used, which differs between the World Health Organization, the European Centre for Disease Prevention and Control, and different countries, although most include fever and cough [28–30]. In this study we used the Dutch Pel criteria [13], which includes fever. It has been described that this specific ILI definition can affect the number and type of pathogens detected. Falsey et al showed that fever is more frequently associated with influenza virus infection in the elderly persons compared with other respiratory infections [7]. Cough is not a prerequisite in the Pel criteria, but as >80% of the participants with ILI and >90% of the participants with influenza virus–positive ILI reported coughing (data not shown), it is unlikely that cases were missed due to this difference in definition.

In summary, we show that influenza virus caused between 18.9% and 34.2% of ILI cases in community-dwelling older adults aged ≥60 years in 2 influenza seasons in the Netherlands, leaving the remainder caused by other pathogens. We also show that influenza vaccination was effective in reducing the incidence of influenza virus infections but did not reduce the ILI incidence, which may have important public health and healthcare consequences. Our data will also help to better

inform the public what to expect from influenza vaccination and how it will not protect against all cases of ILI, popularly seen as "flu."

Supplementary Data

Supplementary materials are available at *The Journal of 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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