Received: 18 May 2021 | Revised: 25 August 2021 | Accepted: 29 August 2021

DOI: 10.1002/hsr2.403

Health Science Reports Open Access WILEY

RESEARCH ARTICLE

Etiology of viral respiratory tract infections in hospitalized adults, and evidence of the high frequency of prehospitalization antibiotic treatment in Norway

Sara Debes[1,2] | Jon Birger Haug[3] | Birgitte Freiesleben de Blasio[4,5] | Christine Monceyron Jonassen[1,6] | Susanne Gjeruldsen Dudman[2,7]

[1]Østfold Hospital Trust, Center for Laboratory Medicine, Sarpsborg, Norway

[2]Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[3]Department of Infection Control, Østfold Hospital Trust, Sarpsborg, Norway

[4]Department of Methods Development and Analytics, Division of Infection Control and Environmental Health, Norwegian Institute of Public Health, Oslo, Norway

[5]Department of Biostatistics, Centre for Biostatistics and Epidemiology, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

[6]Department of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, Ås, Norway

[7]Department of Microbiology, Oslo University Hospital, Oslo, Norway

Correspondence
Sara Debes, Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway.
Email: sara.molvig.debes@so-hf.no

Funding information
Sykehuset Østfold, Grant/Award Number: Research Grant AB3417; Østfold Hospital Trust, Sykehuset Østfold, Grant/Award Number: AB3417

Abstract

Background and aims: Respiratory tract infections (RTIs) cause considerable morbidity and mortality in all age groups, but the epidemiology and role of several of the viral RTIs in the adult and elderly patients are still unclear, as is the extent of prehospitalization antibacterial drug use in this population.

Methods: We conducted a three-year (2015-2018) observational study of viral RTIs in hospitalized patients in a 500-bed hospital in Southeastern Norway, including all patients ≥18 years with RTI symptoms where one of the following viral agents was detected in a respiratory specimen (Seegene Allplex): Influenza A/B, RSV A/B, human metapneumovirus (hMPV), adenovirus and parainfluenza virus 1-4. Viral findings, demographical data, and information on prehospital antibiotic prescriptions were recorded.

Results: In 1182 patients 1222 viral infection events occurred. The mean patient age was 69.6 years, and 53% were females. Influenza virus A/B (63%), RSV A/B (15%) and hMPV (13%) were the most common agents detected. The proportional burden of influenza A H1 was found to be relatively high (65%) in the age groups <69 years, compared to older patients ($P = .001$, chi-square).

As many as 20% of the patients had been treated with antibiotics prior to admission, with the lowest rate for influenza A H3 group at 17% ($P = .036$, chi-square), and highest for the RSV group at 28% ($P = .004$, chi-square).

Oseltamivir was prescribed prior to hospitalization in only 3 cases (0.2%).

Conclusions: We found a high rate of prehospital antibiotic prescription in adults hospitalized with viral RTIs, warranting better stewardship programs to tackle the increasing antibiotic resistance problem.

KEYWORDS

adults, antibiotic, etiology, hospitalization, human metapneumovirus, influenza, respiratory syncytial virus, viral respiratory tract infection

Funding infomation: The funding source (Østfold Hospital Trust, Sykehuset Østfold, Research Grant AB3417) had no involvement in study design, collection, analysis, interpretation of data, writing of the report, or the decision to submit the report for publication.

1 | INTRODUCTION

The increasing antimicrobial resistance calls for accurate diagnostic methods, better treatment options, and infection control measures. Respiratory tract infections (RTIs) are causing considerable morbidity and mortality in all age groups. According to the Global Burden of Diseases, Injuries and Risk factors Study 2016, lower respiratory tract infection was in sixth place of cause of death in Norway.[1] Although bacterial agents are causing up to 50% of the RTIs, viral pathogens give rise to severe infections, outbreaks, and even pandemics.[2] It is vital to differentiate bacterial from viral RTIs, to reduce unnecessary antibiotic usage and limit multidrug antimicrobial resistance development. Reliable viral diagnostics and clinical data are needed to increase awareness about viral RTIs among health care personnel, especially in general practices where a sound patient education is of utmost importance.

In adults, respiratory viral infections (RVI) are implicated in 30% to 50% of community-acquired pneumonia (CAP), 80% or more of asthma exacerbations, and 20% to 60% of worsening of chronic obstructive pulmonary disease (COPD).[2] In addition, RVIs predispose those infected to a range of secondary bacterial infections, including otitis media, sinusitis, and pneumonia. RVIs can also cause severe worsening or complications of non-respiratory conditions (myocardial infarction, congestive heart failure, and diabetes) that contribute heavily to the burden of RVI-associated hospitalizations and mortality.[2]

Viruses causing Influenza-like illness (ILI) show different seasonality and consist mainly of influenza viruses A and B, respiratory syncytial viruses (RSV) A and B, human metapneumovirus (hMPV), human parainfluenza viruses (HPIV) 1-4, and adenoviruses. While both influenza A and B cause seasonal epidemics, influenza A may also cause pandemics after being introduced to the human population from animal reservoir species, thereby becoming a potential threat to global health. In Norway, on average, 1.7% of the population is diagnosed each season with influenza in primary care, with an average hospitalization rate of 48 per 100 000 population.[3]

Normally, RSV A and B circulate simultaneously, but one of the subtypes often dominates. RSV usually causes disease in late fall or early winter in temperate regions, with a peak between mid-December and early February.[4] As compared to influenza and RSV, hMPV tends to peak in the later winter months.[5] Among HPIVs, HPIV3 is the most common serotype encountered in symptomatic disease for all age groups. Illness related to HPIV4 infection is often mild and subclinical, and the virus is more difficult to detect.[6] For adenoviruses, which are non-enveloped viruses, most outbreaks occur in the winter or early spring, although infections occur throughout the year.[7]

While the epidemiology of viral respiratory infection in children is well established, especially for RSV and HMPV,[8-11] fewer reports exist on these viruses' role in adults and the elderly.

Despite the significant disease burden of viral RTIs, studies of these infections most often do not report the extent of related antibacterial drug use prior to hospitalization.

Based on sales data in Norway, around 84% of the human consumption of antibiotics is in patients outside health institutions, and usage in hospitals covers only 8% of the defined daily doses (DDD).[12]

Investigations on the extent of antibiotic treatment prior to hospitalization may help increase awareness of too extensive use, both among patients and doctors. Unnecessary prescription of antibiotics hampers diagnostics and renders further treatment more challenging, thereby increasing the risk that antibiotic treatment will continue during the hospital stay on a deficient basis.

This article investigates the viral epidemiology and prehospital antibiotic prescription in a countywide Norwegian hospital population of adults admitted with viral RTIs over three consecutive winter seasons.

2 | METHODS

We conducted a retrospective observational study over 3 years at Østfold Hospital Trust (SOHF), a 500-bed hospital in the South-east region of Norway, covering a population of 300 000.

Viral agents were detected using the multiplex polymerase chain reaction Seegene Allplex Respiratory Panel 1 and 2 assays (Seegene Inc., Seoul, South Korea), that targets influenza virus A RNA with subtypes influenza A H1 RNA (differentiating H1 strains that were circulating before 2009 from influenza A H1 pdm09 RNA (A H1pdm09 is hereafter named H1, as no older H1 strains were identified), influenza virus A H3 RNA, influenza virus B RNA, RSV A RNA, RSV B RNA, human metapneumovirus RNA, human parainfluenza 1, 2, 3, and 4 RNA, adenovirus DNA, and enterovirus RNA. Extraction of viral nucleic acids was performed using NucliSENS Easymag (bioMérieux) in 2015 to 2016 and thereafter MagNA Pure 96 Instrument (Roche) according to the manufacturer's instructions.

The inclusion criteria were hospitalized patients ≥18 years with one of the above-mentioned viral agents detected in a respiratory specimen during three (2015-2018) RVI season periods from week 40 to week 20. Patients were included from week 45 in the 2015/2016 season, when the hospital started using the multiplex diagnostics test. Laboratory data were retrieved from the laboratory information system (LIS) LVMS (Lab Vantage Medical Suite).[13] We omitted samples with more than one virus due to difficulty distinguishing a true infection from the asymptomatic carriage of the two viruses.

For all included patients, we examined the hospital's electronic patient journals (EPJ). We excluded hospital stays of <5 hours duration and patients without symptoms of a respiratory tract infection (RTI). An infection event (IE) was defined by at least one positive virus finding reported within 14 days before or after the hospital stay, together with symptoms consistent with a RTI. We included in the same IE all readmissions within a 14 days post-discharge period with an identical virus finding. In contrast, readmissions in the same period with a different virus finding were categorized as new IEs.

From the EPJ, we registered the following variables: gender, age, where the patient was admitted from (home or care facilities), and information on prehospital antibiotic prescription.

Pre-hospital antibiotic use was retrieved by investigating the EPJ. If the patient or referring physician reported having received antibiotic

treatment in a time period including 14 days prior to admission, or if the admission papers reported on this, the patient was listed as treated with antibiotics pre-hospital.

Total number of RTI admissions in the county with the ICD-10 codes J09-J18 *Influenza and pneumonia* and J20-J22 *Other acute lower respiratory tract infections* was taken from the Norwegian Patient Register.[14]

The discharge diagnoses (ICD-10 codes) were recorded.

The study was approved by the Regional Committees for Medical and Health Research Ethics (REK ref. 2017/1917 A). The hospitals privacy appeal board (public 17/05444) approved the study.

The Regional Committees for Medical and Health Research Ethics granted an exemption for patient consent statement.

2.1 | Statistical analysis

Descriptive patient data were analyzed using SPSS (IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp).

Categorical variables are presented as frequencies and percentages. Continuous variables are described as mean, median, SD and range.

Statistical analysis was performed using descriptive statistics with Pearson's Chi-square test, independent-samples *t* test, Welch robust test of equality of means, one-way ANOVA, and Poisson regression.

We tested the differences in antibiotics use between the different viral groups using the one-vs-everyone Chi-square test.

P values less than .05 were considered statistically significant for all analyses.

3 | RESULTS

3.1 | Viral RTIs

According to hospital records during the three-year study period, 1242 virus detections were identified, causing 1235 IEs in total.

In total, 2943 admissions due to RTI all causes (ICD-10 codes J09-J18 *Influenza and pneumonia* and J20-J22 *Other acute lower respiratory tract infections*) were recorded in the period from 2015 to 2018 in adults at the study hospital. Admissions due to viral RTI (the study population) in this period was of total 1310, thereby accounting for 45% of the total RTI admissions.

We excluded seven cases with two viral agents found in the same specimen and six cases of enterovirus infection due to the uncertainty concerning their clinical significance in the upper respiratory specimens.

After these exclusions, the study sample included 1222 IEs for the three seasons in 1182 patients. The number of viral RTIs increased during the study period with 209 (17%) IE from 208 patients in season 1, 462 (38%) IE from 454 patients in season 2, and 551 (45%) IE from 539 patients in season 3 (Table 1).

The total RTI-hospitalization (ICD-10 codes J09-J18 *Influenza and pneumonia* and J20-*J22 Other acute lower respiratory tract infections*) in the region was 857 admissions in 2015 to 2016, 1039 admissions in 2016 to 2017, and 1047 admissions in 2017 to 2018.

The viral RTI admissions comprised 26% of the total RTI admissions in 2015 to 2016, 48% of the total RTI admissions in 2016 to 2017 and 56% of the RTI admissions in 2017 to 2018.

By using Poisson regression, we found that the proportion of viral RTI admissions compared to total RTI admissions increased from the first to the last season ($P < .001$).

The total amount of respiratory virus testing in the Østfold County population, including children and outpatients, went from approximately 34.100 virus analyses in the 2015/2016 season to 63.250 in the 2016/2017 season and eventually 92.950 in the 2017/2018 season.

During the 2015/2016 season, the hospital tested 2.838 viral RTI samples and furthermore 5.271 samples in 2016/2017, with a positivity rate of 3% in both seasons. Finally, in 2017/2018, 7.751 samples were tested, with a positivity rate of 2.9%. In conclusion, we found no significant difference in positivity rate over the three seasons (overall positivity rate 2.9%), and the most common viral cause was Influenza B, accounting for 23% (Figure 1).

3.2 | Patient characteristics

In total, 574 (47%) males and 648 (53%) females were hospitalized with the main indication of suspected viral RTI. In seasons 1 and 3, there was a majority of hospitalized women, but in season 2, more males were admitted than females, although not statistically significant ($P = .062$, chi-square) (Table 1).

The mean age at hospital admission was 69.6 years (SD: 16.1), with a median of 72 years (range 18-103 years of age), with no difference in mean age for males (mean 69.3 years [SD: 15.6]) and females (mean 69.7 years, (SD: 16.6); $P = .659$, *t* test).

Mean age varied from 67.7 years in season 1 to 70.1 years in season 3, although not statistically significant ($P = .190$, ANOVA).

The age group with the highest number of admissions was between the age 70 to 79 years old (Figure 2).

About 30% of the admitted were <65 years of age, and 70% were ≥65 years of age.

The majority, 1110 (91%), were admitted from their homes while 66 (5%) were admitted from short-term and 46 (4%) from long-term care facilities.

3.3 | Causes of RTI

We identified influenza viruses A/B (63%), RSV A/B (15%), and hMPV (13%) as the most common agents among hospitalized adult patients (Figure 3 and Table 2).

In the 2015/2016 season, influenza viruses accounted for 41% of the total findings, and influenza A H1 dominated (65%). In addition,

TABLE 1 Baseline patient characteristics in virus-positive RTI infection events and hospital admissions, in three consecutive seasons

	Total number (%)			
	All seasons	**2015-2016**	**2016-2017**	**2017-2018**
Patients				
No. of patients	1182	208 (17.6%)	454 (38.4%)	539 (45.6%)
Patients in two seasons	19 (1.6%)			
Infection events (IE)				
Total viral infection events	1222	209 (17.1%)	462 (37.8%)	551 (45.1%)
Admissions				
Total admissions	1310	227 (17.3%)	498 (38.0%)	585 (44.7%)
Readmissions (% of total)	88 (6.7%)	18/227 (7.9%)	36/498 (7.2%)	34/585 (5.8%)
Gender				
Male	574/1222 (47%)	87/209 (41.6%)	235/462 (50.9%)	252/551 (45.7%)
Female	648/1222 (53%)	122/209 (58.4%)	227/462 (49.1%)	299/551 (54.3%)
Age, (y)				
Mean (SD)	69.6 (16.1)	67.7 (17.2)	69.8 (16.2)	70.1 (15.7)
Median (range)	72 (18-103)	71 (23-96)	73 (18-103)	72 (18-99)
<65 y	369 (30.2%)	75 (35.9%)	135 (29.2%)	159 (28.9%)
≥65 y	853 (69.8%)	134 (64.1%)	327 (70.8%)	392 (71.1%)

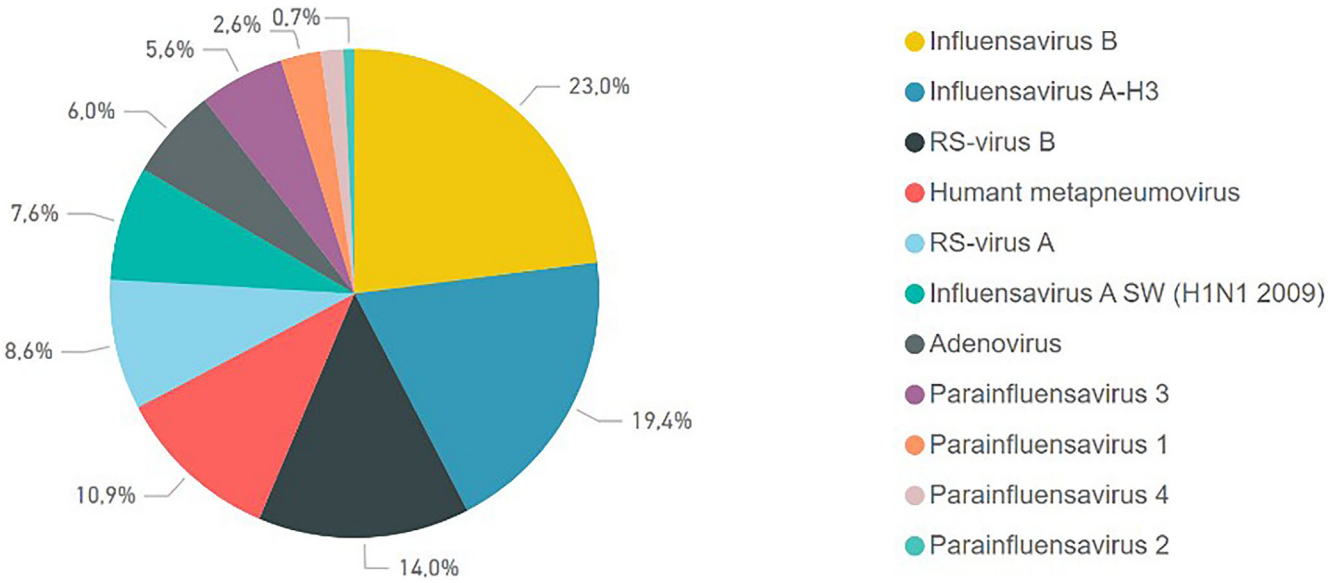

FIGURE 1 Distribution of viral etiology in patients with presumed respiratory tract infections in Østfold County during winter seasons 2015 to 2018

there was a large proportion of hMPV (31%), but only 17% RSV and 94% of the RSV infections in this season were due to RSV subtype B.

In the 2016/2017 season, 64% influenza virus were identified of which 92% were influenza virus A H3, while no cases of influenza A H1 were diagnosed. In this season, the percentage of diagnosed hMPV was only 4%, in contrast to RSV, which comprised 21% of all cases. Among the RSV positives, RSV subtype B was the most prevalent (72%).

The 2017/2018 season accounted for the highest percentage of total RTIs and included the most significant proportion of influenza cases (70%). Influenza virus B accounted for 64% of the influenza positives and nearly 45% of all hospitalized RTI patients with viral findings. In this season, contrasting the 2016/2017 season, HMPV comprised 13% of the IEs, while RSV only were detected in 9% of the events, out of which RSV B also was the most frequent subtype with 67% of all RSV cases.

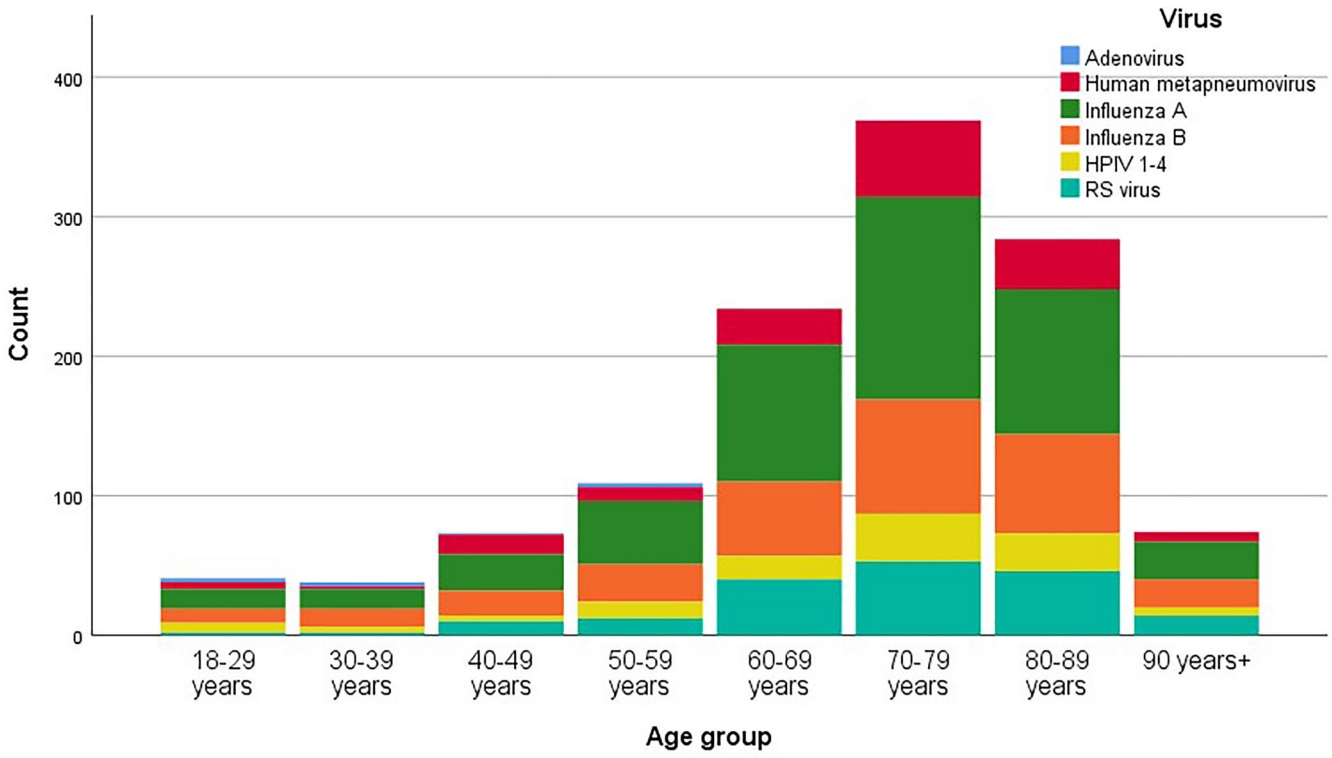

FIGURE 2 Age distribution of adults hospitalized with viral RTI, according to type of virus infection

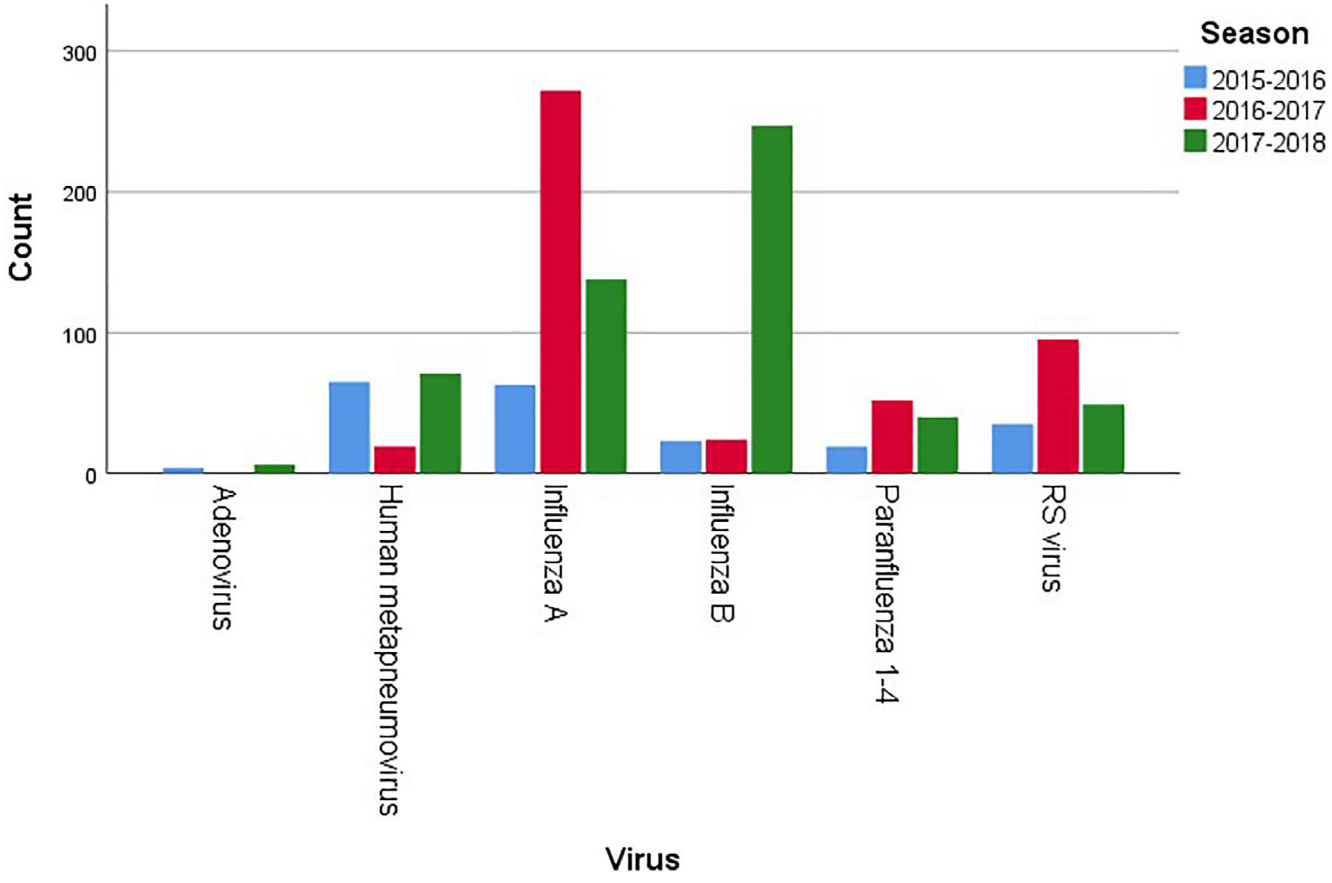

FIGURE 3 Number of virus detections in three consecutive winter seasons (2015-2018) in hospitalized adults, Østfold Hospital Trust

TABLE 2 Total number of hospital admissions with all cause respiratory tract infection in the county, and distribution and causes of viral respiratory tract infections over three consecutive seasons (2015–2018) in hospitalized adults

	All seasons	2015-2016	2016-2017	2017-2018
Total number of hospital admissions with all cause respiratory tract infection in the county	2943	857	1039	1047
Total number of respiratory virus findings	1222	209 (17.1%)	462 (37.8)	551 (45.1%)
Adenovirus	10/1222 (0.8%)	4/209 (1.9%)	0	6/551 (1.1%)
hMPV	155/1222 (12.7%)	65/209 (31.1%)	19/462 (4.1%)	71/551 (12.9%)
Influenza A group	473/1222 (38.7%)	63/209 (30.1%)	272/462 (58.9%)	138/551 (25.0%)
Influenza A no subtype	6/1222 (0.5%)	0	2/462 (0.4%)	4/551 (0.7%)
Influenza A H1	80/1222 (6.5%)	56/209 (26.8%)	0	24/551 (4.4%)
Influenza A H3	389/1222 (31.8%)	7/209 (3.3%)	271/462 (58.7%)	111/551 (20.1%)
Influenza virus B	294/1222 (24.1%)	23/209 (11.0%)	24/462 (5.2%)	247/551 (44.8%)
HPIV 1–4	111/1222 (9.1%)	19/209 (9.1%)	52/462 (11.3%)	40/551 (7.3%)
RSV AB	179/1222 (14.6%)	35/209 (16.7%)	95/462 (20.6%)	49/551 (8.9%)
RSV A	45/1222 (3.7%)	2/209 (1%)	27/462 (5.8%)	16/551 (2.9%)
RSV B	134/1222 (11%)	33/209 (15.8%)	68/462 (14.7%)	33/551 (6%)

TABLE 3 Age distribution of hospitalized patients with viral RTIs over three consecutive seasons (2015-2018), Østfold Hospital Trust

	Adeno	hMPV	Influenza A	Influenza B	HPIV 1–4	RSV A + B	Total
<65 y	10 (100%)	45 (29%)	143 (30%)	90 (31%)	37 (33%)	44 (25%)	369 (30.2%)
≥65 y	0	110 (71%)	330 (70%)	204 (69%)	74 (67%)	135 (75%)	853 (69.8%)
Age (y)							
Mean (SD)	39.5 (12.5)	70.0 (15.5)	69.5 (15.8)	69.3 (17.1)	68.7 (17.3)	72.0 (13.6)	
Median (range)	37 (24-58)	73 (19-94)	72 (18-103)	72 (18-99)	73 (19-96)	73 (27-100)	

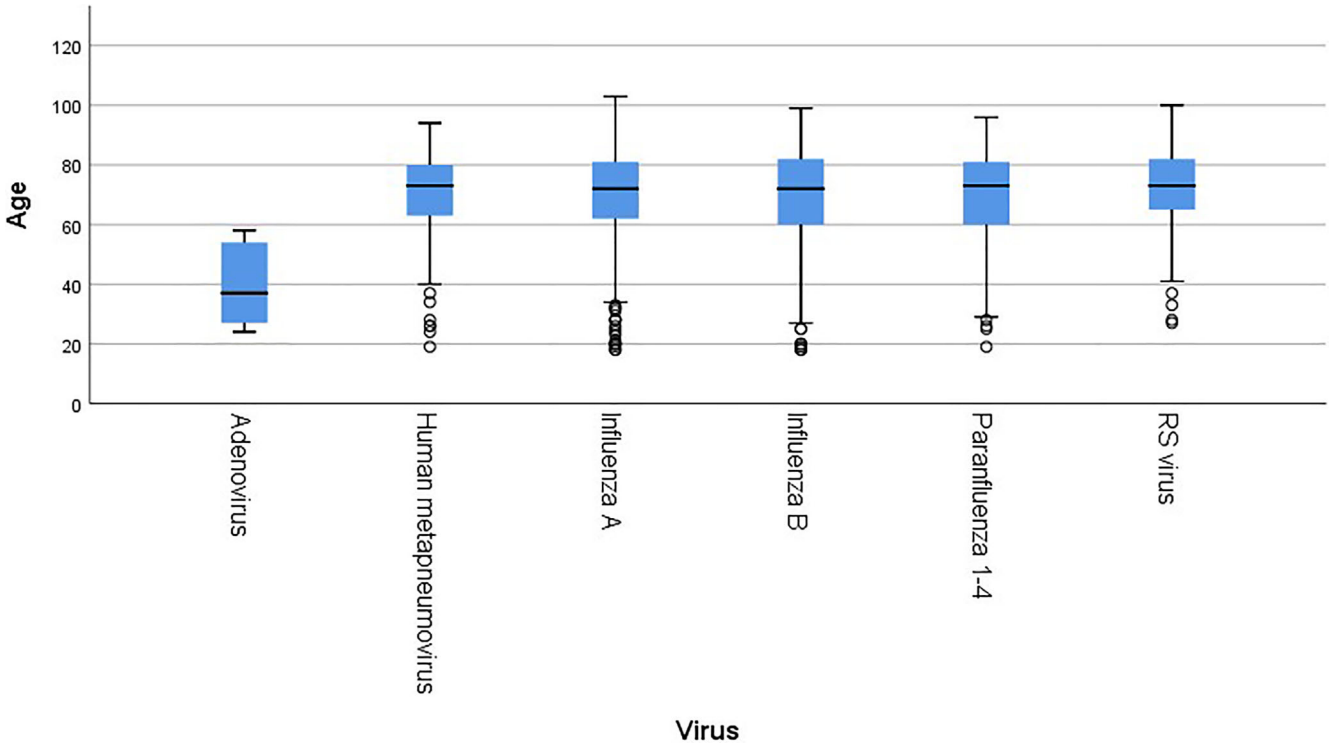

FIGURE 4 Mean age (CI) of hospitalized patients with viral respiratory tract infections, Østfold Hospital Trust 2015 to 2018

For all three seasons combined, based on Pearson's Chi-square test, the proportional burden of influenza A H1 was found to be relatively high (65%) in patients less than 69 years of age, and lower (35%) in patients ≥70 years old ($P = .001$).

Adenovirus accounted only for 10 IEs, with no cases detected in patients above the age of 60. The mean age in these cases was significantly lower than for patients with other virus infections ($P < .001$, Welch robust test of equality of means) (Table 3 and Figure 4).

HPIV was detected in 111 cases (9%) overall. We found a dominance of HPIV 3 (55%), while HPIV1 comprised only 23% of the cases. HPIV 2 and 4 accounted for much fewer IEs, 5% and 16%, respectively. The distribution of HPIV over the three seasons showed less temporal variation compared to the other viral agents.

In 1222 cases (99%) IEs, only one virus was detected. The seven co-infection cases that were excluded consisted of three cases with influenza A H3 and RSV B, one case with influenza A H3 and RSV A, one with influenza virus B and hMPV, one with influenza virus A and HPIV3, and one with hMPV and HPIV2.

3.4 | Antimicrobial treatment prior to hospital admission

In 244 (20%) of all viral RTIs, the patients had been treated with antibiotics within 14 days prior to admission (Table 4). After removal of treatment courses with agents for urinary tract infections, we found that 228 of the viral RTIs (19%) were treated with antibacterial agents before being hospitalized.

Season 1 had the highest prescription rate, with 23% of the patients receiving antibacterial treatment before hospitalization. A small decline was observed in the two following seasons, where 20% were treated in season 2, and 19% in season 3, although not statistically significant ($P = .463$, chi-square).

The pre-hospitalization antibacterial prescription rate was lowest among influenza A H3 patients, at 17% ($P = .036$,chi square), and highest for the RSV patient group, at 28% ($P = .004$, chi-square).

The prescription rate was significantly higher in the group of patients admitted from both short- and long-term care facilities compared to those admitted from their homes ($P < .001$, chi-square). We found no significant difference in the prehospital antibiotic treatment between the group <65 years of age and the group ≥65 years old, and no significant difference in male vs females ($P = .096$, chi-square).

Oseltamivir was prescribed prior to hospitalization in only three cases (0.2%), in whom influenza virus had been detected at admission. Two of the patients were admitted from home, and one admitted from a short-term stay in a care facility.

The mean length of hospital stay for the IEs was 5.4 (SD: 4.7), with median of 4 days (range 0-41 days). There was no significant difference in length of stay when comparing between the different virus groups.

The majority of the patients (69%) were discharged to home, 23% discharged to short-term facility care, and 3% to long-term facility care. 0.9% was transferred to another facility. There was no significant difference in the discharge status between the virus groups.

45 patients (3.7%) died during a hospital stay, with no significant difference when comparing the different virus groups.

TABLE 4 Antibacterial treatment prior to hospital admission in virus positive RTI patients, Østfold Hospital Trust (2015-2018)

	Total frequency	*P* value
Antibiotic treatment prehospital (%)	Of total infection events (N = 1222)	
No	978 (80.0%)	
Yes	244 (20.0%)	
Age (treated with antibiotics/total (% treated with antibiotics)		.376
<65 y	68/369 (18.4%)	
≥65 y	176/853 (20.6%)	
Viral agents (treated with antibiotics/total [% treated with antibiotics])		
Adenovirus (N = 10)	4/10 (40%)	
hMPV (N = 155)	37/155 (23.9%)	.193
Influenza A (N = 473)	80/473 (16.9%)	.034
Influenza A H1 (N = 80)	16/80 (20.0%)	.994
Influenza A H3 (N = 389)	64/389 (16.5%)	.036
Influenza B (N = 294)	52/294 (17.7%)	.262
Parainfluenza 1-4 (N = 111)	21/111 (18.9%)	.772
RSV (N = 179)	50/179 (27.9%)	.004
RSVA (N = 45)	14/45 (31.1%)	.057
RSVB (N = 134)	36/134 (26.9%)	.034
Admitted from (treated with antibiotics/total [% treated with antibiotics])		<.001
Admitted from home (N = 1111)	182/1111 (16.4%)	
Admitted from short-term care facility (N = 65)	44/65 (67.7%)	
Admitted from long-term care facility (N = 46)	18/46 (39.1%)	

4 | DISCUSSION

In this study, we have determined the etiology and rate of pre-hospitalization antibiotics use in a large population of adult patients hospitalized with viral respiratory tract infection during the influenza season October through May in 2015 to 2018.

The most common viral agents identified were influenza virus (63%), RSV A/B (15%), and hMPV (13%). These findings are in line with the results from the recent study by Cohen et al.[15]

The first season was dominated by hMPV, counting for nearly a third of the RTIs, in contrast to the subsequent two seasons where

influenza A H3, and B, accounted for 58.7% and 45% of all the virus findings, respectively.

Of the RSV cases, RSV subtype B dominated in all three seasons (75%).

We observed an increasing number of infection events during the three-year study period: the third season comprised 45% of the total events. By using Poisson regression, we also found that the proportion of viral RTI admissions compared to total RTI admissions increased from the first to the last season. One possible explanation could be that the multiplex assay was introduced to the hospital in November 2015 and potentially the clinicians were less aware of the new diagnostics, resulting in limited use at the beginning.

Another plausible explanation could be variations in the influenza virus circulation in Norway during these 3 years. According to the influenza report from the Norwegian National Institute of Public Health, 2015/2016 was a moderately severe influenza season dominated by influenza A H1.[16] Our results are in accordance with national data, as influenza A H1 accounted for 65% of all influenza cases in 2015/2016. According to data from both the national surveillance and the European sentinel system influenza A H1 was identified in 88% and 86% of all influenza cases, respectively. This season was also defined by a relatively low hospitalization rate compared to the 2016/2017 season (57 vs 95 per 100 000 population).[3]

The influenza report for 2016/2017 showed a high intensity of influenza in the eastern part of Norway,[17] with a dominance of influenza A H3, as observed in our study and reported in international data.[18]

According to the national influenza report for season 3 (2017/2018) the seroprevalence in the population against H3N2 was high, along with strong immunity against influenza A H1, but relatively low seroprevalence rate against influenza B, especially regarding the Yamagata lineage.[19] Our results showing a high number of influenza infections, especially influenza B, support the finding that the 2017/2018 season was unusually prolonged and extensive.

Norwegian surveillance data showed, as in our study, a significantly larger number of patients hospitalized with influenza this season compared to the previous three seasons. Estimates suggest 7.600 admissions in Norway in 2017/2018, compared to approximately 5.000 admissions in 2016/2017.[19]

Most of the influenza viruses circulating in 2017/2018 belonged to the Yamagata lineage, according to national data. The trivalent vaccine that season contained a B/Vitoria lineage component, and European studies showed a moderate effect against B- Yamagata between 36% and 54% for all ages, which is within what is expected for a trivalent inactivated influenza vaccine (30%-80%).[20]

We found the proportional burden of influenza A H1 high in those younger than 69 years and less common in the age groups ≥70 years old. This finding is consistent with previous reports and is probably due to protection in the older population from antibodies with cross-reactivity between pandemic H1N1 2009 and older H1N1 strains circulating before 1950.[21-23]

We also found that the mean patient age of the adenovirus group was significantly lower than for patients in the other virus groups. Although this study included only a few IEs with adenovirus, our results are in accordance with previous reports where adenovirus occurred more frequently at a younger age, owing to a lack of humoral immunity, and in crowded settings.[7,24]

In a study from the USA, hospitalization admittance due to RSV and hMPV in adults occurred at approximately the same frequency as influenza.[25] Another USA-based study showed individuals with RSV were admitted to the hospital later in their illness and had a higher median Charlson comorbidity index than those with influenza.[26]

In a study from France in adults hospitalized with ILI, where 777 patients were positive for at least one respiratory virus, RSV was detected in 8% of the virus cases and influenza virus in 73%.[27]

This study shows great discrepancy from our study, but may be explained by different study periods, as this study covered the influenza seasons from 2012 to 2015.

Consumption of antibacterial agents for systemic use in outpatients in Norway in 2019 showed that Østfold was the county with the highest prescription rate, and approximately 25% higher rate than in the lowest consumption area.[12]

Our study found that surprisingly many cases, one in five, had been prescribed antibiotic treatment within 14 days prior to admission.

The prescription rate was lowest in the influenza A H3 group, at 17% ($P = .036$), and highest in the RSV group, at 28% ($P = .004$). This result is in line with findings from studies from Spain, which found empirical antimicrobial therapy significantly more frequent in patients diagnosed with RSV than influenza during hospital stay.[28,29]

The higher rate of antimicrobial treatment in RSV patients might reflect that physicians may recognize the symptoms of influenza, but find this more difficult with RSV. Although there is an overlap in symptoms, several studies show that the presence of rhinorrhea and wheezing is suggestive of RSV, whereas fever above 38°C more frequently occurs with influenza infections.[28,30-35]

In a survey-based study from the USA, where 317 physicians were asked, 57% of the physicians responded that in patients ≥50 years with respiratory disease, they rarely consider RSV as a potential pathogen,[36] suggesting that awareness of RSV in adults is limited.

We found the prescription rate significantly higher in the group of patients admitted from both short-term care facilities and long-term care facilities, compared to those admitted from home. This may be because these patients have a high degree of comorbidity and severe conditions, but this also suggests a need for antibiotic stewardship programs in such institutions.

To our knowledge, this is one of the first studies to address pre-admission antibiotic prescription to hospitalized adult patients with laboratory-confirmed viral RTI.

A retrospective analysis of linked administrative health care data on inappropriate antibiotic prescribing for non-bacterial acute upper respiratory tract infections in primary care in Canada found that 46% of patients received an antibiotic prescription,[37] which is higher than the proportion in our study. The antibiotic stewardship has a long

tradition in Norway and may account for the lower prescription rate seen in our patients.

The improper use of antibiotic in patients with common non-bacterial respiratory infections is also described in a multicenter study from Israel and the Netherlands, where 83% of adults with viral RTI were prescribed antibiotics at the emergency department or during hospitalization.[38] Rampant misuse of antibiotics in viral infections not only puts the patients at risk of harmful side effects but also promotes antibiotic resistance.

In our study, only three patients (0.2%) received antiviral treatment prior to admission. This may be subject to underreporting, as the information is collected from the patients EPJ, and depend on information from the patient and admitting general practitioner (GP).

Even if there is a degree of underreporting, the extent of use of Oseltamivir in this population, with influenza virus being the most common, is surprisingly low.

According to the Norwegian Prescription Database, there is little difference in prescribing practices of Oseltamivir in this part of Norway, when comparing with the rest of the county in the years 2015 to 2018.[39] An explanation of the low amount of Oseltamivir treated patients may be that the referring practitioner in many cases assumed the cause to be bacterial and prescribed antibiotic treatment rather than antivirals.

The Norwegian Institute of Public Health recommends that patients with illness to the extent that they need admission to hospital, always should be considered for specific anti-influenza treatment. It is also urged that when handling patients in high-risk groups for severe influenza, it is important to initiate antiviral treatment as soon as possible, preferably within 48 hours, and the decision about starting treatment should not wait for laboratory confirmation.

This should be taken into consideration when communicating guidelines to GPs in the county, and further investigations should be done to consider to what extent the existing guidelines are known and interpreted in the pre hospital setting.

Our findings are subject to limitations.

Retrospective studies may have inaccuracies in the hospital records, both regarding the degree of documentation and missing data, but also to the later interpretation.

All data were collected by the same medical researcher, thereby securing consistency in interpreting the record files, and the final interpretation was done in collaboration with another medical researcher.

Our inclusion criteria of at least one positive virus finding reported within 14 days before or after the hospital stay, together with symptoms consistent with an RTI is broad. In some cases, we may have included patients with viral and bacterial co-infection[40] and secondary bacterial infections,[41] where the bacterial infection may have been the main reason for admission, and may also been a valid reason for initiation of pre-hospital antibiotic treatment. The broad time span may also lead to the inclusion of some nosocomial viral RTIs, in addition to the community-acquired viral RTI cases. We may also have included some patients with persistent viral shedding,[42,43] and in these cases, the symptoms and need for hospitalization may be independent of the virus found.

A weakness of the chosen method for collection of data on antibiotic treatment pre-hospital, is recall bias due to the retrospective design which can lead to underreporting. It is also a possibility that certain patient groups, for example elderly with dementia or critical ill may not remember having received treatment at home. Although it is standard procedure for referring physicians to report any medication prescribed prior to admittance to the hospital, this might also be prone to under-reporting.

This was a single-center analysis, and the features of the setting may not be representative of Norway as a whole.

5 | CONCLUSION

This study provides novel important results concerning the etiologies and prehospital antibiotic prescription in adults hospitalized with viral respiratory tract infection.

We describe a yearly seasonality in hospitalizations rate and differences related to etiology in patients with viral RTIs, with influenza being the main driver for hospitalization.

In this study, a large proportion of patient received treatment with antibacterial agents prior to hospital admission to treat viral infections. These results need to be disseminated to the general practitioners to help improve antibiotic prescribing and to combat antimicrobial resistance.

ACKNOWLEDGMENT

The authors would like to thank Sykehuset Østfold, Department of Research, for funding the study, and Jonas Christoffer Lindstrøm at Norwegian Institute of Public Health, for statistical guidance.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Sara Debes, Jon Birger Haug, Birgitte De Blasio, Christine Monceyron Jonassen, Susanne Gjeruldsen Dudman

Data Curation: Sara Debes

Formal Analysis: Sara Debes, Birgitte De BlasioFunding Acquisition: Sara Debes, Jon Birger Haug, Birgitte De Blasio, Christine Monceyron Jonassen, Susanne Gjeruldsen Dudman

Investigation: Sara Debes, Jon Birger Haug, Birgitte De Blasio, Christine Monceyron Jonassen, Susanne Gjeruldsen Dudman

Methodology: Sara Debes, Jon Birger Haug, Birgitte De Blasio, Christine Monceyron Jonassen, Susanne Gjeruldsen Dudman

Project Administration: Sara Debes, Christine Monceyron Jonassen, Susanne Gjeruldsen Dudman

Supervision: Jon Birger Haug, Birgitte De Blasio, Christine Monceyron Jonassen, Susanne Gjeruldsen Dudman

Validation: Sara Debes, Jon Birger Haug, Birgitte De Blasio, Christine Monceyron Jonassen, Susanne Gjeruldsen Dudman

Writing-Original Draft: Sara Debes

Writing-Review & Editing: Jon Birger Haug, Birgitte De Blasio, Christine Monceyron Jonassen, Susanne Gjeruldsen Dudman

All authors have read and approved the final version of the manuscript.

Sara Debes had full access to all the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

Sara Debes affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Sara Debes https://orcid.org/0000-0002-6342-2601

Susanne Gjeruldsen Dudman https://orcid.org/0000-0001-5047-4982

REFERENCES

1. Øverland S, Vollset SE, Kinge JM, et al. Disease Burden in Norway 2016. *Tidsskr Nor Laegeforen*. 2018;138(15):0274. https://doi.org/10.4045/tidsskr.18.0274
2. World Health Organization. Research needs for the Battle against Respiratory Viruses (BRaVe). Background document 2013. Available from https://www.who.int/influenza/patient_care/clinical/brave/en/. Accessed April 8, 2021.
3. Hauge SH, Bakken IJ, de Blasio BF, Håberg SE. Burden of medically attended influenza in Norway 2008-2017. *Influenza Other Respir Viruses*. 2019;13(3):240-247.
4. Borchers AT, Chang C, Gershwin ME, Gershwin LJ. Respiratory syncytial virus-a comprehensive review. *Clin Rev Allergy Immunol*. 2013;45(3):331-379.
5. Shafagati N, Williams J. Human metapneumovirus-what we know now. *F1000Res*. 2018;7:135.
6. Branche AR, Falsey AR. Parainfluenza Virus Infection. *Semin Respir Crit Care Med*. 2016;37(4):538-554.
7. Lynch JP 3rd, Kajon AE. Adenovirus: epidemiology, global spread of novel serotypes, and advances in treatment and prevention. *Semin Respir Crit Care Med*. 2016;37(4):586-602.
8. Smith DK, Seales S, Budzik C. Respiratory syncytial virus bronchiolitis in children. *Am Fam Physician*. 2017;95(2):94-99.
9. Shi T, Balsells E, Wastnedge E, et al. Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: systematic review and meta-analysis. *J Glob Health*. 2015;5(2):020416.
10. Divarathna MVM, Rafeek RAM, Noordeen F. A review on epidemiology and impact of human metapneumovirus infections in children using TIAB search strategy on PubMed and PubMed central articles. *Rev Med Virol*. 2020;30(1):e2090.
11. Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. *Lancet*. 2017;389(10065):211-224.
12. NORM/NORM-VET 2019. Usage of antimicrobial agents and occurrence of antimicrobial resistance in Norway; 2020; Tromsø/Oslo. Available from https://unn.no/fag-og-forskning/norm-norsk-overvakingssystem-for-antibiotikaresistens-hos-mikrober#rapporter. Accessed April 8, 2021.
13. Softwarepoint. Labvantage medical suite. Available from https://softwarepoint.com/solutions/labvantage-medical-suite. Accessed April 7, 2021.
14. The Directorate for e-Health. The Norwegian Patient Register. Available from https://helsedata.no/en/. Accessed August 23, 2021.
15. Cohen R, Babushkin F, Geller K, Finn T. Characteristics of hospitalized adult patients with laboratory documented influenza a, B and respiratory syncytial virus - a single center retrospective observational study. *PloS One*. 2019;14(3):e0214517.
16. Norwegian Institute of Public Health. Report 2016: Department of Influenza: Influenza season in Norway 2015–2016. Available from https://www.fhi.no/publ/2016/influensasesongen-i-norge-2015-16/. Accessed April 8, 2021.
17. Norwegian Institute of Public Health. Report 2017: Department of Influenza: Influenza season in Norway 2016–2017. Available from https://www.fhi.no/publ/2017/influensa-arsrapport-2016/. Accessed April 8, 2021.
18. Adlhoch C, Snacken R, Melidou A, et al. Dominant influenza A(H3N2) and B/Yamagata virus circulation in EU/EEA, 2016/17 and 2017/18 seasons, respectively. *Euro Surveill*. 2018;23(13):18-00146.
19. Norwegian Institute of Public Health. Report 2018: Department of Influenza: Influenza season in Norway 2017–2018. Available from https://www.fhi.no/publ/2018/influensasesongen-i-norge-2017-18/. Accessed April 8, 2021.
20. Rondy M, Kissling E, Emborg HD, et al. Interim 2017/18 influenza seasonal vaccine effectiveness: combined results from five European studies. *Euro Surveill*. 2018;23(9):18-00086.
21. Hsu JP, Phoon MC, Koh GC, et al. Comparison of neutralizing antibody and cell-mediated immune responses to pandemic H1N1 2009 influenza virus before and after H1N1 2009 influenza vaccination of elderly subjects and healthcare workers. *Int J Infect Dis*. 2012;16(8):e621-e627.
22. Hancock K, Veguilla V, Lu X, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med*. 2009;361(20):1945-1952.
23. Prevention CfDCa. Serum cross-reactive antibody response to a novel influenza a (H1N1) virus after vaccination with seasonal influenza vaccine. *MMWR Morb Mortal Wkly Rep*. 2009;58(19):521-524.
24. Lion T. Adenovirus infections in immunocompetent and immunocompromised patients. *Clin Microbiol Rev*. 2014;27(3):441-462.
25. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. *J Infect Dis*. 2012;206(1):56-62.
26. Malosh RE, Martin ET, Callear AP, et al. Respiratory syncytial virus hospitalization in middle-aged and older adults. *J Clin Virol*. 2017;96:37-43.
27. Loubet P, Lenzi N, Valette M, et al. Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France. *Clin Microbiol Infect*. 2017;23(4):253-259.
28. Martinez-Sanz J, Gilaberte Reyzabal S, Salillas J, et al. Respiratory syncytial virus infection among adults during influenza season: a frequently overlooked diagnosis. *J Med Virol*. 2019;91(9):1679-1683.
29. Kestler M, Munoz P, Mateos M, et al. Respiratory syncytial virus burden among adults during flu season: an underestimated pathology. *J Hosp Infect*. 2018;100(4):463-468.
30. Falsey AR, McElhaney JE, Beran J, et al. Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness. *J Infect Dis*. 2014;209(12):1873-1881.

31. Volling C, Hassan K, Mazzulli T, et al. Respiratory syncytial virus infection-associated hospitalization in adults: a retrospective cohort study. *BMC Infect Dis*. 2014;14:665.
32. Widmer K, Griffin MR, Zhu Y, Williams JV, Talbot HK. Respiratory syncytial virus- and human metapneumovirus-associated emergency department and hospital burden in adults. *Influenza Other Respir Viruses*. 2014;8(3):347-352.
33. Sundaram ME, Meece JK, Sifakis F, Gasser RA, Belongia EA. Medically attended respiratory syncytial virus infections in adults aged >/= 50 years: clinical characteristics and outcomes. *Clin Infect Dis*. 2014;58(3):342-349.
34. Branche AR, Falsey AR. Respiratory syncytial virus infection in older adults: an under-recognized problem. *Drugs Aging*. 2015;32(4):261-269.
35. Walsh EE, Peterson DR, Falsey AR. Is clinical recognition of respiratory syncytial virus infection in hospitalized elderly and high-risk adults possible? *J Infect Dis*. 2007;195(7):1046-1051.
36. Hurley LP, Allison MA, Kim L, et al. Primary care physicians' perspectives on respiratory syncytial virus (RSV) disease in adults and a potential RSV vaccine for adults. *Vaccine*. 2019;37(4):565-570.
37. Silverman M, Povitz M, Sontrop JM, et al. Antibiotic prescribing for nonbacterial acute upper respiratory infections in elderly persons. *Ann Intern Med*. 2017;166(11):765-774.
38. van Houten CB, Cohen A, Engelhard D, et al. Antibiotic misuse in respiratory tract infections in children and adults-a prospective, multicentre study (TAILORED treatment). *Eur J Clin Microbiol Infect Dis*. 2019;38(3):505-514.
39. The Norwegian Prescription Database. Statistics from the Norwegian Prescription Database. Available from http://www.norpd.no/Prevalens.aspx. Accessed August 21, 2021.
40. Bakaletz LO. Viral-bacterial co-infections in the respiratory tract. *Curr Opin Microbiol*. 2017;35:30-35.
41. Prasso JE, Deng JC. Postviral complications: bacterial pneumonia. *Clin Chest Med*. 2017;38(1):127-138.
42. Giannella M, Alonso M, Garcia de Viedma D, et al. Prolonged viral shedding in pandemic influenza a(H1N1): clinical significance and viral load analysis in hospitalized patients. *Clin Microbiol Infect*. 2011;17(8):1160-1165.
43. Na S, Chong YP, Kim MN, et al. Duration of viral shedding in patients admitted to hospital with pandemic influenza a/H1N1 2009 infection. *J Med Virol*. 2011;83(1):5-9.

How to cite this article: Debes S, Haug JB, de Blasio BF, Jonassen CM, Dudman SG. Etiology of viral respiratory tract infections in hospitalized adults, and evidence of the high frequency of prehospitalization antibiotic treatment in Norway. *Health Sci Rep*. 2021;4:e403. doi:10.1002/hsr2.403