Non-influenza respiratory viruses in adult patients admitted with influenza-like illness a 3-year prospective multicenter study

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Non-influenza respiratory viruses in adult patients admitted with influenza-like illness: A three-year prospective multicenter study

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ABSTRACT

Purpose To describe the burden, and characteristics, of influenza-like illness (ILI) associated with non-influenza respiratory viruses (NIRV).

Methods We performed a prospective, multicenter, observational study of adults admitted with ILI during 3 influenza seasons (2012-2015). Patients were screened for picornavirus, respiratory syncytial virus (RSV), coronavirus, human metapneumovirus, adenovirus, bocavirus, parainfluenza virus, and influenza, by PCR on nasopharyngeal samples. We excluded patients coinfected with NIRV and influenza.

Results Among 1421 patients enrolled, influenza virus was detected in 535 (38%), and NIRV in 215 (15%), mostly picornavirus (n=61), RSV (n=53), coronavirus 229E (n=48), and human metapneumovirus (n=40). In-hospital mortality was 5% (NIRV), 4% (influenza), and 5% (no respiratory virus). As compared to influenza, NIRV were associated with age (median, 73 years *vs.* 68, *P*=0.026), chronic respiratory diseases (53% *vs.* 45%, *P*=0.034), cancer (14% *vs.* 9%, *P*=0.029), and immunosuppressive drugs (21% *vs.* 14%, *P*=0.028), and inversely associated with diabetes (18% *vs.* 25%, *P*=0.038). On multivariable analysis, only chronic respiratory diseases (OR 1.5 [1.1-2.0], *P*=0.008), and diabetes (OR 0.5 [0.4-0.8], *P*=0.01) were associated with NIRV detection.

Conclusions NIRV are common in adults admitted with ILI during influenza seasons. Outcomes are similar in patients with NIRV, influenza, or no respiratory virus.

Keywords Influenza-like illness; Influenza; picornavirus; respiratory syncytial virus; coronavirus; human metapneumovirus

Introduction

Non-influenza respiratory viruses (NIRV) are responsible for a substantial proportion of influenza-like illness (ILI), and pneumonia [1,2], although epidemiological data on their burden are scarce. The pathogenicity of viruses recently discovered, such as human metapneumovirus in 2001, or bocavirus in 2005 [3,4], remains poorly characterized. Even NIRV discovered earlier (e.g. parainfluenza virus, respiratory syncytial virus (RSV), or adenovirus), have attracted limited clinical interest thus far, as a result of the absence of rapid tests routinely available, and the lack of vaccine or antiviral treatment with proven clinical efficacy [1,2,5,6]. The advent of highly sensitive and specific point-of-care tests for simultaneous detection of the main respiratory viruses is an opportunity to investigate the role of NIRV in common acute respiratory febrile illness, including the risk factors for, and the characteristics of, NIRV-associated ILI. These data may have important implications, including i) screening and early implementation of respiratory isolation for patients with NIRV to prevent nosocomial transmission; ii) identification of the major NIRV that should be targeted for development of antivirals or vaccines. We aimed to determine the characteristics of, and the risk factors for NIRV among adults admitted with ILI during influenza seasons in France.

Methods

Study design and population

We analyzed cases of laboratory-confirmed NIRV infection during three consecutive influenza seasons (2012/2013, 2013/2014, and 2014/2015), in a post-hoc analysis of patients hospitalized with community-acquired ILI, and enrolled in the FLUVAC study. FLUVAC is a prospective observational study of influenza vaccine efficacy conducted in six university

hospitals in France (Cochin Hospital, Paris; Bichat Hospital, Paris; Pontchaillou Hospital, Rennes; Dupuytren Hospital, Limoges; Montpellier University Hospital; Edouard Herriot Hospital, Lyon). Patients were invited to participate during periods of influenza circulation (from December to March). We collected data on non-institutionalized adults (>18 years), who were hospitalized for at least 24 h with ILI, with symptoms onset less than 7 days prior to sampling, through an active surveillance system staffed by trained healthcare professionals. ILI was defined as a combination of two criteria: (i) at least one of the following symptoms: fever (≥38°C), headache, myalgia or malaise, and (ii) at least one of the following respiratory symptoms: cough, sore throat, or shortness of breath (dyspnea) [7]. The characteristics and outcome of patients with influenza [8,9], and RSV [10] in this cohort have been previously reported.

Clinical data

We collected data on demographic, chronic underlying diseases, hospital admission during the previous 12 months, smoking status, hospitalization ward, and main characteristics of current ILI, including date of onset, date of admission, length of hospital stay, and outcome (i.e. complications, and in-hospital mortality). Data were collected on a standardized questionnaire from medical records, and face-to-face interviews with patients.

Virology

Tests for respiratory viruses were performed in nasopharyngeal swabs from all patients by means of multiplex reverse transcription-polymerase chain reaction (mRT-PCR). Bronchoalveolar lavage fluid samples and tracheal aspirates ordered by the physician in charge were also tested. Samples were initially tested in the virology laboratory of each participating hospital by means of real-time influenza A & B PCR. All samples were then sent to the French National Influenza Reference Center (CNR-Lyon) for confirmation. RNA and

DNA were extracted with the automated Easymag system from BioMérieux (Marcy l'Etoile, France), and influenza viruses were detected with an in-house real-time RT-PCR protocol [11]. Samples were also screened for a panel of NIRV: adenovirus (52 serotypes), human bocaviruses 1-4, human coronaviruses (229E, NL63, OC43, HKU1), human metapneumoviruses 1-4, parainfluenza viruses 1–4, picornavirus, and RSV, by real-time PCR, using the Respiratory Multiwell System (MWS) r-gene® on an ABI 7300 analyzer.

Ethics

The FLUVAC study (clinicaltrials.gov NCT02027233) respected Good Epidemiological and Clinical Practices in clinical research and the Declaration of Helsinki, and was approved by institutional review board. All study participants provided informed consent for respiratory viruses testing and data collection.

Statistical analysis

We first described the characteristics of all patients hospitalized with ILI who tested positive for at least one NIRV. Results were expressed as mean and standard deviation (SD), or median and interquartile range (IQR) for quantitative variables, and n (%) for qualitative variables. Missing data for each variable were excluded from the denominator. Factors associated with NIRV infection were analyzed by using two different comparison groups: i) patients with negative tests for both NIRV and influenza; ii) patients with documented influenza. The Wilcoxon rank sum test or Fisher's exact test was used, as appropriate, for univariable comparisons. For multivariable analysis, we used a backward stepwise logistic regression model, using NIRV test results (positive/negative) as the dependent variable. Covariables tested in the multivariable model were all variables with a *P*-value <0.2 in the univariable analysis. Results were expressed as odds ratios (OR) and adjusted OR (aOR) with 95% confidence intervals (CI). A *P*-value of 0.05 or less was considered statistically

significant. All analyses were performed using R software (v3, R Foundation for Statistical Computing, Vienna, Austria) [12].

Results

Characteristics of patients with influenza-like illness, and virus distribution

Overall, 1452 patients hospitalized with ILI were enrolled. Median age was 70 years [IQR, 54-82], 780 patients were male (54%), 1155 (80%) had at least one chronic underlying disease (mostly respiratory or heart diseases), 661 (46%) had been hospitalized in the previous 12 months, and 644 (44%) had been vaccinated against influenza. Among the 1452 patients tested, 781 (54%) were positive for at least one respiratory virus. We excluded the 31 patients (2% of total), who had simultaneous detection of influenza virus, and NIRV. Among the 1421 remaining patients, influenza virus was detected in 535 (38%), and NIRV in 215 patients (15%), including 7 with two NIRV. The NIRV detected were picornavirus, n=61 (27%), RSV, n=53 (24%), coronavirus 229E, n=48 (22%), human metapneumovirus, n=40 (18%), adenovirus, n=12 (5%), and bocavirus, n=8 (4%). No parainfluenza virus was detected. Flow chart is presented in Figure 1. The proportion of positive tests for influenza and for NIRV remained similar during the two first influenza seasons; a significant increase of influenza cases was noted in 2014-2015 winter (Table 1).

Characteristics of patients with non-influenza respiratory viruses (Table 2)

The 215 patients with at least one NIRV detected, had a median age of 73 years [60-83], 116 (54%) were male, and 174 (81%) had at least one chronic underlying disease, mostly respiratory (n=114, 53%), or heart diseases (n=90, 42%). Fifty-two patients (24%) were current smokers, 44 (21%) were taking immunosuppressive drugs, and 4 were pregnant (27%

of women less than 50-year-old). Mean duration of ILI at the time of admission was 3.0 days [2-4]. Main symptoms were fever (78%), cough (78%), dyspnea (74%), weakness or malaise (26%), headache (22%), and myalgia (21%). Ninety-four patients developed at least one complication during hospital stay, including pneumonia, n=68 (32%), and respiratory failure, n=47 (22%). Median length of stay was 8 days [5-17]. ICU admission was required for 16 patients (11%). Eleven patients died during hospitalization (5%).

Comparison of patients who tested positive for non-influenza respiratory viruses, and i) patients with influenza; ii) patients with no respiratory virus detected (Table 2)

Patients who tested positive for NIRV were older than patients with influenza (median, 73 years versus 68, *P*=0.026), more likely to have chronic respiratory diseases (53% versus 45%, *P*=0.034), solid cancer (14% versus 9%, *P*=0.029), and to be on immunosuppressive drugs (21% versus 14%, *P*=0.028), but less likely to have diabetes (18% versus 25%, *P*=0.038). Fever was less common with NIRV than influenza (79% vs 90%, *P*<0.001). Outcomes were similar, including complications, median length of stay, and in-hospital mortality. On multivariable analysis, only chronic respiratory disease (OR 1.5 [1.1-2.0], *P*=0.008), and diabetes (OR 0.5 [0.4-0.8], *P*=0.01), were significantly associated with NIRV.

When compared to patients with no detection of respiratory virus, patients who tested positive for NIRV were more likely to have chronic respiratory diseases (53% versus 44%, *P*=0.024), to be pregnant (27% versus 5%, *P*=0.021), and on immunosuppressive drugs (21% versus 15%, *P*=0.041), but less likely to have diabetes (18% versus 27%, *P*=0.011). Weakness was less common in patients with NIRV than in patients who tested negative for all respiratory viruses (26% vs 33%, *P*=0.047). Regarding outcome, pneumonia was more common in patients who tested positive for NIRV (32% vs 24%, *P*=0.019).

Discussion

In this prospective multicenter study performed during three influenza seasons in France, at least one NIRV was found in 15% of patients admitted with ILI, the major players being picornavirus (27%), RSV (24%), coronavirus 229E (22%), and human metapneumovirus (18%). NIRV were more common in patients with chronic respiratory diseases, and less common in patients with diabetes, whatever the comparison group (patients with influenza, or patients with no respiratory virus), and these associations remained significant in multivariable analysis. Although patients with NIRV were more likely to develop pneumonia than patients with no respiratory virus, mortality was similar in patients with NIRV, in patients with influenza, and in patients with no respiratory virus, at 4-5%.

Few studies have evaluated the epidemiology of NIRV in patients with symptoms suggestive of acute respiratory tract infection. Tanner *et al.* performed a prospective study during the 2009-2010 winter season in Central England, both in hospitals, and in general practitioner offices [13]. The two main NIRV were RSV (31%), and picornavirus (24%), as in our study, but the authors did not test for coronavirus, and bocavirus. Ambrosioni *et al.* conducted a two year-prospective study in one referral centre in Switzerland [14], and their findings were in line with ours, with two main differences: i) coronaviruses were more heterogeneous, and included 229E, NL63, OC43, and HKU1 strains; ii) human metapneumovirus was rare, at around 5%, with no significant difference between upper and lower respiratory tract samples, and between adults younger than 65 years, and elderlies.

Previous studies have identified age >65 years as a risk factor for NIRV, as well as chronic respiratory diseases [1,6,14,15]. For the latter, experimental studies suggested that NIRV may trigger acute exacerbation of chronic obstructive pulmonary diseases (COPD)

[16–18]. Interestingly, chronic respiratory diseases remained associated with NIRV in our study, even when the comparison group was patients with influenza, and even in multivariable analysis. This suggests a specific pathogenicity of NIRV in this population, that may be more prone to decompensate during NIRV infection than during influenza. Treatment with immunosuppressive drugs was also associated with NIRV in our study, whatever the comparison group, but the association was no longer significant on multivariable analysis, which suggests that confounding factors are involved. The lower prevalence of diabetes mellitus in patients with NIRV, as compared to patients with influenza, and to patients with no respiratory virus, in our study, was not expected. Diabetes has been associated with a broad range of infectious diseases [19,20], including upper respiratory tract infection in some studies [19], but not all [21]. Although the lower prevalence of diabetes in patients with NIRV as compared to patients with influenza could be related to stronger association between diabetes, and influenza, than between diabetes, and NIRV, we have no explanation for the lower prevalence of diabetes in patients with NIRV as compared to patients with no respiratory virus.

Our study has limitations. Firstly, we have no data to support causality between the presence of NIRV in upper respiratory samples, and the ILI that required admission. Other pathogens may be involved (e.g. bacteria), and NIRV may merely be a bystander infectious agent with no role in the symptoms reported. The lack of a control population with no respiratory symptoms is another limitation that precludes any conclusion on the pathogenicity of NIRV. Secondly, we only performed systematic tests for influenza, and a selection of NIRVs, although other pathogens have been associated with acute respiratory infections [22]. Thirdly, our study was limited to influenza seasons, in one country, and its findings may not apply to other settings. However, our study has strengths, including its prospective, multicentre design, and the standardization of viral tests for all adult patients admitted with

predefined ILI, during three consecutive influenza seasons. These strengths, and the limited number of missing data, reduce the risk of potential biases. Our study adds another brick in the wall by contributing to better characterization of the burden of NIRV in adult patients with suspicion of acute respiratory tract infections. The identification of transmissible, NIRV, in 15% of adult patients admitted with ILI would advocate for more systematic testing of these patients, especially those with chronic respiratory diseases. This would allow early respiratory isolation, as to prevent nosocomial transmission of NIRV, which may have severe consequences on patients with chronic respiratory diseases, and patients on immunosuppressive drugs.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interest related to the study. O Launay is an investigator for clinical trials sponsored by Janssen and other companies and received travel support to attend scientific meetings from pharmaceutical companies.

Appendix

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Fig. 1 Flow chart of patients hospitalized with influenza-like illness, and viruses detected in respiratory sample

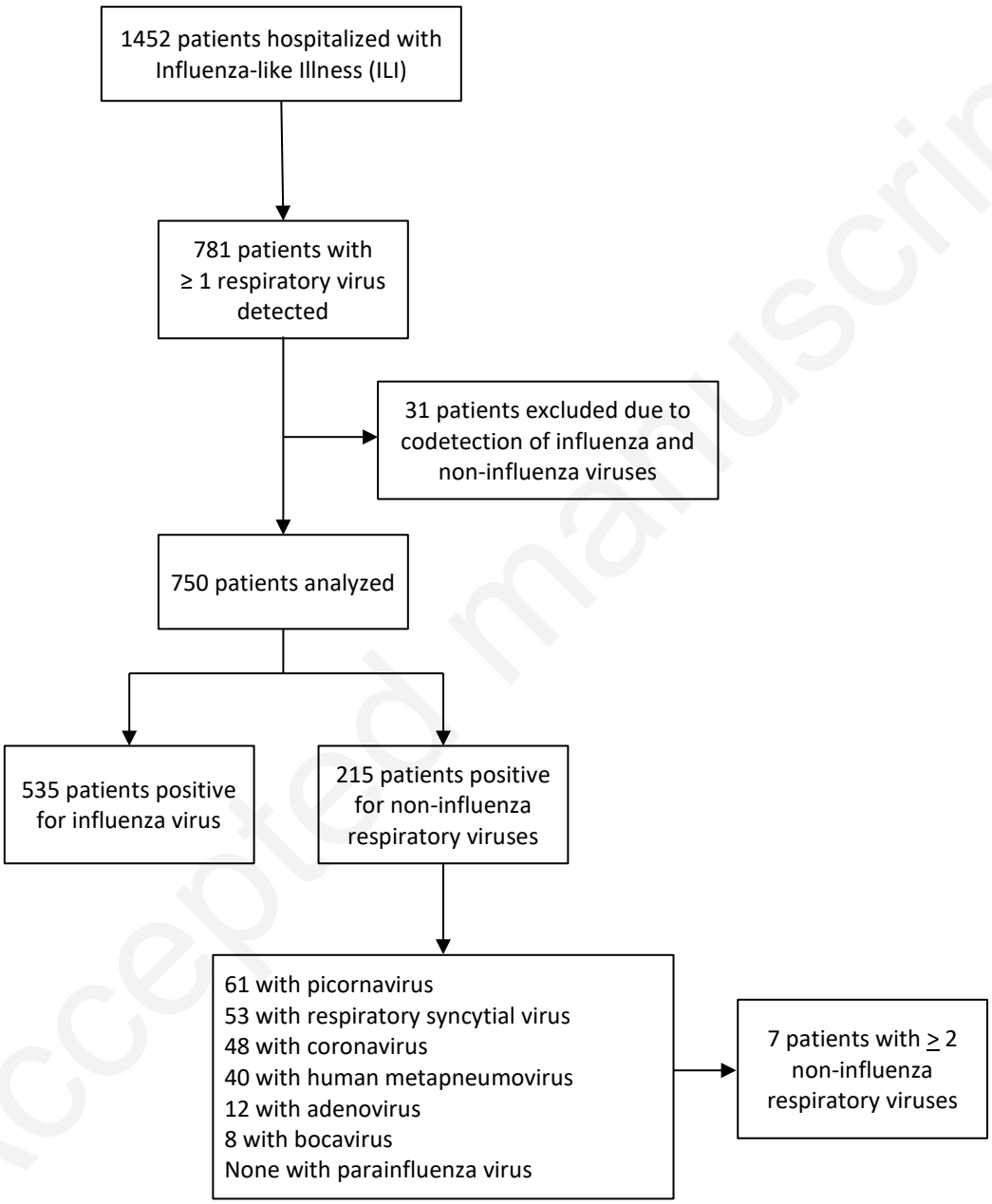

Table 1 Number and percentage of patients hospitalized with influenza-like illness who tested positive for non-influenza respiratory viruses, and for influenza, by year**.**

Influenza season	Non-influenza respiratory virus (NIRV), n (%)	Influenza, n (%)	Co-infection influenza + NIRV, n (%)	No respiratory virus, n (%)	Total
2012/2013	64 (14%)[ref]	149 (33%)[ref]	13 (3%)[ref]	222 (50%)[ref]	448
2013/2014	76 (19%)[NS]	101 (25%)[NS]	11 (3%)[NS]	219 (54%)[NS]	407
2014/2015	75 (13%)[NS]	285 (48%)**	7 (1%)*	230 (38%)**	597
Total	215 (15%)	535 (37%)	31 (2%)	671 (46%)	1452

Chi square test was done to compare the evolution, with 2012/2013 as the reference season.

[Ref], reference; [NS], non significant; *, $P<0.05$; **, $P<0.001$;

NIRV, non-influenza respiratory virus

Table 2 Comparison between patients who tested positive for non-influenza respiratory virus (NIRV), patients with influenza, and patients with no respiratory virus

	NIRV n=215 (15%)	**Influenza** n=535 (38%)	***P*-value for comparison between NIRV and influenza**	**No respiratory virus** n=671 (47%)	***P*-value for comparison between NIRV and no virus**
Men	116 (54%)	269 (50%)	0.36	380 (57%)	0.47
Median age, years (IQR)	73 (60-83)	68 (53-81)	**0.026**	70 (54-83)	0.11
Age >= 65 years	141 (66%)	310 (58%)	0.053	398 (59%)	0.10
Median BMI, kg/m2 (IQR)	24.5 (21-28)	24.9 (22-28)	0.25	24,8 (21-29)	0.32
Chronic diseases	174 (81%)	423 (79%)	0.56	537 (80%)	0.77
Chronic respiratory disease	114 (53%)	237 (45%)	**0.034**	296 (44%)	**0.024**
Chronic heart disease	90 (42%)	222 (42%)	0.93	287 (43%)	0.81
Cancer	31 (14%)	48 (9%)	**0.029**	84 (13%)	0.48
Diabetes	39 (18%)	135 (25%)	**0.038**	179 (27%)	**0.011**
Immunosuppressive drugs	44 (21%)	75 (14%)	**0.028**	98 (15%)	**0.041**
Pregnancy	4 (27%)	8 (16%)	0.45	3 (5%)	**0.021**
Current smokers	52 (24%)	121 (23%)	0.38	138 (21%)	0.16
Median time from symptoms onset to admission, days (IQR)	3.0 (2-4)	3.5 (2-4)	0.46	3.0 (2-5)	0.27
Symptoms					
Fever (≥38°C)	169 (79%)	480 (90%)	**<0.001**	520 (78%)	0.78
Weakness/Malaise	55 (26%)	165 (31%)	0.14	219 (33%)	**0.047**
Headache	47 (22%)	134 (25%)	0.33	167 (25%)	0.32
Myalgia	44 (21%)	116 (22%)	0.66	153 (23%)	0.44
Cough	167 (78%)	434 (81%)	0.28	506 (76%)	0.54
Dyspnea	160 (74%)	393 (73%)	0.78	517 (77%)	0.36
Complications	94 (44%)	248 (47%)	0.50	266 (40%)	0.28
Pneumonia	68 (32%)	152 (29%)	0.96	160 (24%)	**0.019**
Respiratory failure	47 (22%)	125 (23%)	0.69	135 (20%)	0.54
ARDS	20 (9%)	55 (10%)	0.78	50 (7%)	0.38
Heart failure	30 (14%)	78 (15%)	0.85	80 (12%)	0.41
ICU admission	16 (11%)	26 (10%)	1.0	39 (9%)	0.50
Median length of stay, days (IQR)	8 (5-17)	10 (4-23)	0.15	8 (3-16)	0.47
Mortality	11 (5%)	23 (4%)	0.69	32 (5%)	0.85

NIRV, non-influenza respiratory virus; BMI, Body mass index; IQR, Interquartile range; SD, Standard deviation, ARDS; Acute respiratory distress syndrome; ICU, intensive care unit

Refernces

[1] Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet Lond Engl 2011;377:1264–75. doi:10.1016/S0140-6736(10)61459-6.

[2] Luchsinger V, Ruiz M, Zunino E, Martínez MA, Machado C, Piedra PA, et al. Community-acquired pneumonia in Chile: the clinical relevance in the detection of viruses and atypical bacteria. Thorax 2013;68:1000–6. doi:10.1136/thoraxjnl-2013-203551.

[3] van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RAM, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719–24. doi:10.1038/89098.

[4] Allander T, Tammi MT, Eriksson M, Bjerkner A, Tiveljung-Lindell A, Andersson B. Cloning of a human parvovirus by molecular screening of respiratory tract samples. Proc Natl Acad Sci U S A 2005;102:12891–6. doi:10.1073/pnas.0504666102.

[5] Pavia AT. What is the role of respiratory viruses in community-acquired pneumonia?: What is the best therapy for influenza and other viral causes of community-acquired pneumonia? Infect Dis Clin North Am 2013;27:157–75. doi:10.1016/j.idc.2012.11.007.

[6] Galván JM, Rajas O, Aspa J. Review of Non-bacterial Infections in Respiratory Medicine: Viral Pneumonia. Arch Bronconeumol Engl Ed 2015;51:590–7. doi:10.1016/j.arbr.2015.09.015.

[7] European Centre for Disease Prevention and Control. Influenza case definitions n.d. http://ecdc.europa.eu/en/healthtopics/influenza/surveillance/Pages/influenza_case_definitions.aspx.

[8] Rondy M, Puig-Barbera J, Launay O, Duval X, Castilla J, Guevara M, et al. 2011-12 seasonal influenza vaccines effectiveness against confirmed A(H3N2) influenza hospitalisation: pooled analysis from a European network of hospitals. A pilot study. PloS One 2013;8:e59681. doi:10.1371/journal.pone.0059681.

[9] Loubet P, Samih-Lenzi N, Galtier F, Vanhems P, Loulergue P, Duval X, et al. Factors associated with poor outcomes among adults hospitalized for influenza in France: A three-year prospective multicenter study. J Clin Virol 2016;79:68–73. doi:10.1016/j.jcv.2016.04.005.

[10] Loubet P, Lenzi N, Valette M, Foulongne V, Krivine A, Houhou N, et al. Clinical characteristics and outcome of respiratory syncytial virus infection among adults

hospitalized with influenza-like illness in France. Clin Microbiol Infect 2017;23:253–9. doi:10.1016/j.cmi.2016.11.014.

[11] Bouscambert Duchamp M, Casalegno JS, Gillet Y, Frobert E, Bernard E, Escuret V, et al. Pandemic A(H1N1)2009 influenza virus detection by real time RT-PCR : is viral quantification useful? Clin Microbiol Infect 2010;16:317–21. doi:10.1111/j.1469-0691.2010.03169.x.

[12] R: The R Project for Statistical Computing n.d. https://www.r-project.org/.

[13] Tanner H, Boxall E, Osman H. Respiratory viral infections during the 2009-2010 winter season in Central England, UK: incidence and patterns of multiple virus co-infections. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol 2012;31:3001–6. doi:10.1007/s10096-012-1653-3.

[14] Ambrosioni J, Bridevaux P-O, Wagner G, Mamin A, Kaiser L. Epidemiology of viral respiratory infections in a tertiary care centre in the era of molecular diagnosis, Geneva, Switzerland, 2011-2012. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2014;20:O578-584. doi:10.1111/1469-0691.12525.

[15] Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults. N Engl J Med 2005;352:1749–59. doi:10.1056/NEJMoa043951.

[16] Zwaans W a. R, Mallia P, van Winden MEC, Rohde GGU. The relevance of respiratory viral infections in the exacerbations of chronic obstructive pulmonary disease—a systematic review. J Clin Virol Off Publ Pan Am Soc Clin Virol 2014;61:181–8. doi:10.1016/j.jcv.2014.06.025.

[17] Gunawardana N, Finney L, Johnston SL, Mallia P. Experimental rhinovirus infection in COPD: Implications for antiviral therapies. Antiviral Res 2014;102:95–105. doi:10.1016/j.antiviral.2013.12.006.

[18] Mallia P, Message SD, Gielen V, Contoli M, Gray K, Kebadze T, et al. Experimental rhinovirus infection as a human model of chronic obstructive pulmonary disease exacerbation. Am J Respir Crit Care Med 2011;183:734–42. doi:10.1164/rccm.201006-0833OC.

[19] Shah BR, Hux JE. Quantifying the Risk of Infectious Diseases for People With Diabetes. Diabetes Care 2003;26:510–3. doi:10.2337/diacare.26.2.510.

[20] Pearson-Stuttard J, Blundell S, Harris T, Cook DG, Critchley J. Diabetes and infection: assessing the association with glycaemic control in population-based studies. Lancet Diabetes Endocrinol 2016;4:148–58. doi:10.1016/S2213-8587(15)00379-4.

[21] Muller LM a. J, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AIM, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis Off Publ Infect Dis Soc Am 2005;41:281–8. doi:10.1086/431587.

[22] Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. N Engl J Med 2015;373:415–27. doi:10.1056/NEJMoa1500245.