Influenza and common cold viruses in critically ill adults

van Someren Gréve, F.

Publication date
2024

2

SCOPING INTRODUCTION AND THESIS OUTLINE

EVOLVING INSIGHTS IN THE PATHOGENICITY OF COMMON COLD VIRUSES IN ADULTS

Traditionally, common cold viruses besides influenza virus were not regarded as clinically relevant by the physician on the adult Intensive Care Unit (ICU), except perhaps for severely immunocompromised patients. Pathogens such as respiratory syncytial virus (RSV), rhinovirus (RV), seasonal human coronavirus (hCoV), parainfluenzavirus (PIV), adenovirus (AdV) and human metapneumovirus (hMPV) were generally assumed to be only associated with mild disease, whilst their diagnostic detection was time consuming, costly and of no clinical consequence. During the last few decades however, there has been increasing attention for the role of these viruses as causes of severe disease in adults. This paradigm shift has been accelerated by the advent of nucleic acid amplification techniques (NAAT) such as real time polymerase chain reaction (RT-PCR), which made detection of respiratory viruses rapid, sensitive and more affordable.

Accumulating case series and cohort studies have indicated that the pathogenicity of common cold viruses in adults is not restricted to severely immunocompromised patients. Illustrative are reports of outbreaks among elderly nursing home residents, for example involving RSV[1–4], RV[5–8], hCoV[9–11], PIV[12–14], AdV[15–17] and hMPV[18–25], often associated with severe lower respiratory tract disease and fatal outcome. Also, PIV and AdV have long been known to cause outbreaks among previously healthy adults in institutional living conditions, such as military recruits and students, occasionally resulting in severe and even fatal pneumonia [26–32]. In hospitalized adults, in depth case series of, for example, hMPV infections with histopathological assessment of lung tissue, or careful assessments of the likelihood of diagnosed hMPV infections as the reason for respiratory failure and ICU admission, have indicated the potential of this virus to cause severe lower respiratory tract infections (RTIs) in patients without significant comorbidities or immunosuppression[33,34]. Larger epidemiological studies in hospitalized adults have shown that community acquired pneumonia (CAP) or severe acute respiratory infections (SARI) are associated with common cold viruses in 9-49% of cases[35–49], as also described in **Chapter 1**. In addition, these viruses are well-known causes of exacerbations of chronic cardiopulmonary disease [50–52], and are implicated in health-care associated or hospital acquired pneumonia (HAP)[36,53], bacterial co- or super-infections[54–56], and acute respiratory failure (ARF) as an umbrella syndrome[57–60]. Based on these evolving insights, the Centers for Disease Control and Prevention (CDC) in the United States of America (USA) have adjusted their clinical information sheets to indicate RSV, RV, PIV and hMPV as possible causes of severe disease in adults, particularly in the elderly and those with underlying medical conditions[61–64].

Disease burden is most accurately monitored for influenza viruses: in the USA there are an estimated 9-41 million cases annually, 140.000-170.000 hospitalizations and 12.000-52.000 influenza-related deaths[65]. Globally, the estimated respiratory

attributable mortality rate of influenza is between 291.000-646.000 deaths each year, with approximately 72.000 of these in the European region[66]. Similar efforts are increasingly conducted for RSV in adults, with estimates in the USA ranging between 60.000-160.000 hospitalizations and 6.000-10.000 deaths each year for those over 65 years old [67–73]. Apart from these viruses and and SARS-CoV-2, the disease burden of severe infections for other common cold viruses is still ill-defined.

CHALLENGES RELATING TO COMMON COLD VIRUSES IN CRITICALLY ILL ADULTS

As discussed in **Chapter 1**, in the adult ICU setting there also is increasing attention for the role of common cold viruses in critical illness. However, challenges remain regarding disease burden estimates, routine diagnostic practices, interpretation of NAAT results and clinical management of viral respiratory tract infections, as discussed below.

Estimating disease burden

While disease burden estimates for influenza and RSV are based on careful modelling using, amongst others, national influenza and RSV surveillance data and death certificates, several limitations remain. For example, estimates are only provided for respiratory illness, therefore likely underestimating the true influenza burden which includes non-respiratory disease such as exacerbation of chronic cardiopulmonary disease[74,75]. Also, these models typically use virus surveillance data of either non-hospitalized patients and/or retrospective test results from routine care in hospitalized patients, which likely suffer from a large testing bias as discussed in the next paragraph. For other common cold viruses such as RV, hCoV, PIV and hMPV, there is very limited aggregated data for estimates of total cases, attributable hospitalizations and associated deaths. In the adult ICU setting, as discussed in **Chapter 1**, most prospective epidemiological studies are also limited by small sample sizes, incomplete diagnostic work up, and crude mortality estimates without adjustment for confounders.

Who to test and how

While international influenza guidelines encourage clinicians to test all hospitalized adults with fever and respiratory symptoms for influenza viruses during the respiratory season[76], current Dutch national guidelines as well as international guidelines on CAP prior to studies of this thesis refrain from recommendations on diagnostic testing for influenza[77,78]. Furthermore, no recommendations for influenza testing are provided for patients with other clinical syndromes such as HAP[79]. Other common cold viruses are not mentioned in any of these guidelines, neither for the hospital or ICU setting, nor for specific risk groups. It remains challenging to define the clinical profile of which patients

to test: symptoms of influenza-like illness may be mild, non-specific or even absent in hospitalized patients with influenza or hMPV, including the absence of fever[80–83], and there is no clinical algorithm to clearly distinguish the microbiological cause of pneumonia without microbiological testing[84]. Furthermore, while there are indications that viral RTIs will be missed when relying only on upper airway sampling[85–87], guidelines remain unclear whether only upper airway samples suffice for virus testing, or whether lower airway samples should also be considered when available. Modelling studies suggest that we may miss up to 90% of predicted influenza cases in hospitalized adults[88], but there is no prospective data on how many viral RTIs are missed in adults.

Interpretation of NAAT results

In contrast to bacteria, common cold viruses need host cells to replicate, and therefore a positive NAAT indicates an active or recent infection. There is however a large spectrum of disease severity, and community - and healthy volunteer challenge studies have shown that asymptomatic infections can occur, even for influenza viruses[89–92]. It is therefore likely that epidemiological studies in the critically ill are affected by a background prevalence of intercurrent mild or asymptomatic infections unrelated to the direct cause of ICU admission. Studies with proper control groups to estimate the prevalence of coincidental mild infections in critically ill patients are lacking, complicating estimates of disease burden.

Clinical management

Diagnosing viral infections in the critically ill can have important implications for infection control measures, in addition to the rapid initiation of antiviral and/or immunomodulatory therapy in case of (suspected) influenza or COVID-19. However, there are large differences in national and international guidelines on whether and which infection control measures to implement for patients infected with the different common cold viruses[93–96], and it appears that evidence on transmission routes and impact is translated into policy and practice very slowly, if at all[97]. Also, decisions on the duration of infection control measures are complicated in the ICU setting. Normally, precautions are continued until 'clinical resolution of symptoms', but this is difficult to assess during invasive mechanical ventilation. A meta-analysis on influenza virus A(H1N1)pdm09 infections indicated that disease severity is associated with longer duration of shedding[98] . However, there is a paucity of data regarding virus shedding of seasonal influenza viruses and other respiratory viruses in the ICU setting, especially from the lower airways. Here it also remains challenging to distinguish replicating infectious virus from DNA or RNA remnants still detectable by RT-PCR. Regarding treatment of influenza, it remains unclear for how long treatment with neuraminidase inhibitors should be continued in the critically ill. The standard duration of 5 days originates from oseltamivir registration trials that were primarily performed in non-hospitalized patients with uncomplicated

influenza [99]. International, but not Dutch national treatment guidelines recommend to consider longer treatment in patients with severe influenza[78,100], however current data on viral shedding limits guidance on treatment decisions.

OUTLINE OF THIS THESIS

The general aim of this thesis is to gain further insights into the role of influenza and common cold viruses in adult critically ill patients, to advance estimates of disease burden, and guide diagnostics, treatment and infection control measures.

Chapter 3 describes the clinical practice of diagnostic testing for respiratory viruses in patients admitted to Dutch ICUs with suspected CAP or HAP. Also, the prevalence rates of viral RTIs from routine care test are reported, and the impact of these test results on antiviral treatment decisions.

In **Chapter 4**, the design and rationale of the COURSE study, a multicenter prospective observational cohort study in critically ill patients receiving IMV, are described. Results of this study are described in **Chapters 5 to 8**.

In **Chapter 5** we describe how many viral RTI were missed by comparing routine care virus testing to systematic screening for viruses during the feasibility period of the COURSE study.

Chapter 6 describes the prevalence of and clinical outcomes associated with viral RTI's in the COURSE study. Patients admitted because of a SARI are compared to a control group of those admitted because of other reasons (non-SARI), and diagnostic yield of upper and lower respiratory tract samples is assessed.

Viral RNA shedding dynamics in the upper and lower respiratory tract of RV, hCoV and RSV in COURSE participants are assessed in **Chapter 7**, while in **Chapter 8** the shedding dynamics of influenza viruses are studied in a combined cohort of influenza patients from the COURSE study and from a similar study in Hong Kong. In both chapters, shedding dynamics between SARI patients and non-SARI patients are compared, as well as between survivors and non-survivors, in order to explore differences in pathophysiology.

In **Chapter 9**, the findings of this thesis, and directives and future perspectives are discussed.

REFERENCES

1. Caram, L. B. *et al.* Respiratory syncytial virus outbreak in a long-term care facility detected using reverse transcriptase polymerase chain reaction: an argument for real-time detection methods. *J Am Geriatr Soc* **57**, 482–5 (2009).
2. Spires, S. S., Talbot, H. K., Pope, C. A. & Talbot, T. R. Paramyxovirus Outbreak in a Long-Term Care Facility: The Challenges of Implementing Infection Control Practices in a Congregate Setting. *Infect Control Hosp Epidemiol* **38**, 399–404 (2017).
3. Hababou, Y. *et al.* Molecular investigation of a RSV outbreak in a geriatric hospital. *BMC Geriatr* **21**, 120 (2021).
4. Beran, J. *et al.* Respiratory syncytial virus acute respiratory infections in ≥ 65-year-old adults in long-term care facilities in the Czech Republic. *Cent Eur J Public Health* **29**, 167–176 (2021).
5. Louie, J. K. *et al.* Rhinovirus outbreak in a long term care facility for elderly persons associated with unusually high mortality. *Clin Infect Dis* **41**, 262–5 (2005).
6. Longtin, J. *et al.* Rhinovirus outbreaks in long-term care facilities, Ontario, Canada. *Emerg Infect Dis* **16**, 1463–5 (2010).
7. Wald, T. G. *et al.* A rhinovirus outbreak among residents of a long-term care facility. *Ann Intern Med* **123**, 588–93 (1995).
8. Hicks, L. A. *et al.* Two Outbreaks of Severe Respiratory Disease in Nursing Homes Associated with Rhinovirus. *J Am Geriatr Soc* **54**, 284–289 (2006).
9. Falsey, A. R. *et al.* Long-term care facilities: a cornucopia of viral pathogens. *J Am Geriatr Soc* **56**, 1281–5 (2008).
10. Hand, J. *et al.* Severe Respiratory Illness Outbreak Associated with Human Coronavirus NL63 in a Long-Term Care Facility. *Emerg Infect Dis* **24**, 1964–1966 (2018).
11. Birch, C. J. *et al.* Human coronavirus OC43 causes influenza-like illness in residents and staff of aged-care facilities in Melbourne, Australia. *Epidemiol Infect* **133**, 273–7 (2005).
12. Jalal, H. *et al.* Molecular investigations of an outbreak of parainfluenza virus type 3 and respiratory syncytial virus infections in a hematology unit. *J Clin Microbiol* **45**, 1690–6 (2007).
13. Fiore, A. E. *et al.* Outbreak of pneumonia in a long-term care facility: antecedent human parainfluenza virus 1 infection may predispose to bacterial pneumonia. *J Am Geriatr Soc* **46**, 1112–7 (1998).
14. Civljak, R. *et al.* An Outbreak of Human Parainfluenza Virus 3 (Phylogenetic Subcluster C5) Infection among Adults at a Residential Care Facility for the Disabled in Croatia, 2018. *Intervirology* **62**, 174–181 (2019).
15. Kandel, R. *et al.* Outbreak of Adenovirus Type 4 Infection in a Long-Term Care Facility for the Elderly. *Infect Control Hosp Epidemiol* **31**, 755–757 (2010).
16. Klinger, J. R., Sanchez, M. P., Curtin, L. A., Durkin, M. & Matyas, B. Multiple cases of life-threatening adenovirus pneumonia in a mental health care center. *Am J Respir Crit Care Med* **157**, 645–9 (1998).
17. Sánchez, M. P., Erdman, D. D., Török, T. J., Freeman, C. J. & Mátyás, B. T. Outbreak of Adenovirus 35 Pneumonia among Adult Residents and Staff of a Chronic Care Psychiatric Facility. *J Infect Dis* **176**, 760–763 (1997).
18. Louie, J. K. *et al.* A summer outbreak of human metapneumovirus infection in a long-term-care facility. *J Infect Dis* **196**, 705–8 (2007).
19. Karimata, Y. *et al.* Clinical Features of Human Metapneumovirus Pneumonia in Non-Immunocompromised Patients: An Investigation of Three Long-Term Care Facility Outbreaks. *J Infect Dis* **218**, 868–875 (2018).
20. Liao, R. S., Appelgate, D. M. & Pelz, R. K. An outbreak of severe respiratory tract infection due to human metapneumovirus in a long-term care facility for the elderly in Oregon. *J Clin Virol* **53**, 171–3 (2012).
21. Spires, S. S., Talbot, H. K., Pope, C. A. & Talbot, T. R. Paramyxovirus Outbreak in a Long-Term Care Facility: The Challenges of Implementing Infection Control Practices in a Congregate Setting. *Infect Control Hosp Epidemiol* **38**, 399–404 (2017).
22. Hamada, N. *et al.* Performance of a rapid human metapneumovirus antigen test during an outbreak in a long-term care facility. *Epidemiol Infect* **142**, 424–7 (2014).
23. Chasqueira, M.-J. *et al.* Respiratory infections in elderly people: Viral role in a resident population of elderly care centers in Lisbon, winter 2013-2014. *Int J Infect Dis* **69**, 1–7 (2018).
24. Boivin, G. *et al.* An Outbreak of Severe Respiratory Tract Infection Due to Human Metapneumovirus in a Long-Term Care Facility. *Clinical Infectious Diseases* **44**, 1152–1158 (2007).
25. Honda, H. *et al.* Outbreak of human metapneumovirus infection in elderly inpatients in Japan. *J Am Geriatr Soc* **54**, 177–80 (2006).
26. Dudding, B. A. *et al.* Fatal Pneumonia Associated with Adenovirus Type 7 in Three Military Trainees. *New England Journal of Medicine* **286**, 1289–1292 (1972).
27. Bryant, R. E. & Rhoades, E. R. Clinical features of adenoviral pneumonia in Air Force recruits. *Am Rev Respir Dis* **96**, 717–23 (1967).
28. Park, J. Y. *et al.* Clinical Features and Courses of Adenovirus Pneumonia in Healthy Young Adults during an

Outbreak among Korean Military Personnel. *PLoS One* **12**, e0170592 (2017).
29. Wenzel, R. P., McCormick, D. P. & Beam, W. E. Parainfluenza pneumonia in adults. *JAMA* **221**, 294–5 (1972).
30. Centers for Disease Control and Prevention (CDC). Civilian outbreak of adenovirus acute respiratory disease--South Dakota, 1997. *MMWR Morb Mortal Wkly Rep* **47**, 567–70 (1998).
31. Sanchez, J. L. *et al.* Epidemic of adenovirus-induced respiratory illness among US military recruits: Epidemiologic and immunologic risk factors in healthy, young adults. *J Med Virol* **65**, 710–718 (2001).
32. Centers for Disease Control and Prevention (CDC). Two fatal cases of adenovirus-related illness in previously healthy young adults--Illinois, 2000. *MMWR Morb Mortal Wkly Rep* **50**, 553–5 (2001).
33. Sumino, K. C. *et al.* Detection of Severe Human Metapneumovirus Infection by Real-Time Polymerase Chain Reaction and Histopathological Assessment. *J Infect Dis* **192**, 1052–1060 (2005).
34. Hasvold, J., Sjoding, M., Pohl, K., Cooke, C. R. & Hyzy, R. C. The role of human metapneumovirus in the critically ill adult patient. *J Crit Care* **31**, 233–237 (2016).
35. Jain, S. *et al.* Community-acquired pneumonia requiring hospitalization among U.S. adults. *New England Journal of Medicine* **373**, 415–427 (2015).
36. Choi, S.-H. *et al.* Viral infection in patients with severe pneumonia requiring intensive care unit admission. *Am J Respir Crit Care Med* **186**, 325–32 (2012).
37. Karhu, J., Ala-Kokko, T. I., Vuorinen, T., Ohtonen, P. & Syrjälä, H. Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. *Clin Infect Dis* **59**, 62–70 (2014).
38. Wiemken, T. *et al.* Incidence of respiratory viruses in patients with community-acquired pneumonia admitted to the intensive care unit: results from the Severe Influenza Pneumonia Surveillance (SIPS) project. *European journal of clinical microbiology & infectious diseases* **32**, 705–10 (2012).
39. Falsey, A. R., Hennessey, P. A., Formica, M. A., Cox, C. & Walsh, E. E. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* **352**, 1749–59 (2005).
40. Cillóniz, C. *et al.* Community-acquired polymicrobial pneumonia in the intensive care unit: aetiology and prognosis. *Crit Care* **15**, R209 (2011).
41. de Roux, A. *et al.* Viral community-acquired pneumonia in nonimmunocompromised adults. *Chest* **125**, 1343–51 (2004).
42. Angeles Marcos, M. *et al.* The role of viruses in the aetiology of community-acquired pneumonia in adults. *Antivir Ther* **11**, 351–9 (2006).
43. Saito, A. *et al.* Prospective multicenter study of the causative organisms of community-acquired pneumonia in adults in Japan. *Journal of Infection and Chemotherapy* **12**, 63–69 (2006).
44. Johnstone, J., Majumdar, S. R., Fox, J. D. & Marrie, T. J. Viral infection in adults hospitalized with community-acquired pneumonia: Prevalence, pathogens, and presentation. *Chest* **134**, 1141–1148 (2008).
45. Jennings, L. C. *et al.* Incidence and characteristics of viral community-acquired pneumonia in adults. *Thorax* **63**, 42–8 (2008).
46. Hohenthal, U. *et al.* Aetiological diagnosis of community acquired pneumonia: Utility of rapid microbiological methods with respect to disease severity. *Scand J Infect Dis* **40**, 131–138 (2008).
47. Díaz, A. *et al.* Etiology of Community-Acquired Pneumonia in Hospitalized Patients in Chile. *Chest* **131**, 779–787 (2007).
48. Johansson, N., Kalin, M., Tiveljung-Lindell, A., Giske, C. G. & Hedlund, J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. *Clin Infect Dis* **50**, 202–9 (2010).
49. Luchsinger, V. *et al.* Community-acquired pneumonia in Chile: the clinical relevance in the detection of viruses and atypical bacteria. *Thorax* **68**, 1000–6 (2013).
50. Kujawski, S. A. *et al.* Rates of respiratory syncytial virus (RSV)-associated hospitalization among adults with congestive heart failure-United States, 2015-2017. *PLoS One* **17**, e0264890 (2022).
51. Falsey, A. R. *et al.* Respiratory syncytial virus–associated illness in adults with advanced chronic obstructive pulmonary disease and/or congestive heart failure. *J Med Virol* **91**, 65–71 (2019).
52. Cameron, R. J. *et al.* Virus infection in exacerbations of chronic obstructive pulmonary disease requiring ventilation. *Intensive Care Med* **32**, 1022–9 (2006).
53. Hong, H.-L. *et al.* Viral infection is not uncommon in adult patients with severe hospital-acquired pneumonia. *PLoS One* **9**, e95865 (2014).
54. Martin-Loeches, I., van Someren Gréve, F. & Schultz, M. J. Bacterial pneumonia as an influenza complication. *Curr Opin Infect Dis* 1 (2016) doi:10.1097/QCO.0000000000000347.
55. Lee, N. *et al.* High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. *Clin Infect Dis* **57**, 1069–77 (2013).
56. Thorburn, K., Harigopal, S., Reddy, V., Taylor, N. & van Saene, H. K. F. High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. *Thorax* **61**, 611–5 (2006).
57. Schnell, D. *et al.* Burden of respiratory viruses in patients with acute respiratory failure. *J Med Virol* **86**, 1198–202 (2014).
58. Ong, D. S. Y. *et al.* Respiratory syncytial virus in critically ill adult patients with community-acquired respiratory failure: a prospective observational study. *Clin Microbiol Infect* **20**, O505-7 (2014).

59. Carrat, F. *et al.* A virologic survey of patients admitted to a critical care unit for acute cardiorespiratory failure. *Intensive Care Med* **32**, 156–159 (2006).
60. Daubin, C. *et al.* Epidemiology and clinical outcome of virus-positive respiratory samples in ventilated patients: a prospective cohort study. *Crit Care* **10**, R142 (2006).
61. CDC. People at High Risk for Severe RSV Infection. https://www.cdc.gov/rsv/high-risk/index.html.
62. CDC. Common Colds: Protect Yourself and Others. https://www.cdc.gov/features/rhinoviruses/index.html.
63. CDC. Human Parainfluenza Viruses (HPIVs) - Symptoms and Illnesses. https://www.cdc.gov/parainfluenza/symptoms.html.
64. CDC - Human Metapneumovirus (HMPV). https://www.cdc.gov/surveillance/nrevss/hmpv/clinical.html.
65. CDC - Disease Burden of Flu. https://www.cdc.gov/flu/about/burden/index.html.
66. Iuliano, A. D. *et al.* Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *The Lancet* **391**, 1285–1300 (2018).
67. Thompson, W. W. *et al.* Mortality Associated With Influenza and Respiratory Syncytial Virus in the United States. *JAMA* **289**, 179 (2003).
68. Hansen, C. L., Chaves, S. S., Demont, C. & Viboud, C. Mortality Associated With Influenza and Respiratory Syncytial Virus in the US, 1999-2018. *JAMA Netw Open* **5**, e220527 (2022).
69. Zheng, Z., Warren, J. L., Shapiro, E. D., Pitzer, V. E. & Weinberger, D. M. Estimated incidence of respiratory hospitalizations attributable to RSV infections across age and socioeconomic groups. *Pneumonia* **14**, 6 (2022).
70. McLaughlin, J. M. *et al.* Rates of Medically Attended RSV Among US Adults: A Systematic Review and Meta-analysis. *Open Forum Infect Dis* **9**, (2022).
71. Branche, A. R. *et al.* Incidence of Respiratory Syncytial Virus Infection Among Hospitalized Adults, 2017–2020. *Clinical Infectious Diseases* **74**, 1004–1011 (2022).
72. Widmer, K. *et al.* Rates of Hospitalizations for Respiratory Syncytial Virus, Human Metapneumovirus, and Influenza Virus in Older Adults. *J Infect Dis* **206**, 56–62 (2012).
73. Matias, G. *et al.* Estimates of mortality attributable to influenza and RSV in the United States during 1997–2009 by influenza type or subtype, age, cause of death, and risk status. *Influenza Other Respir Viruses* **8**, 507–515 (2014).
74. Sullivan, S. Challenges in reducing influenza-associated mortality. *The Lancet* **391**, 1242–1244 (2018).
75. Li, L. *et al.* Heterogeneity in Estimates of the Impact of Influenza on Population Mortality: A Systematic Review. *Am J Epidemiol* **187**, 378–388 (2018).
76. Harper, S. A. *et al.* Seasonal Influenza in Adults and Children—Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America. *Clinical Infectious Diseases* **48**, 1003–1032 (2009).
77. Mandell, L. A. *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* **44 Suppl 2**, S27-72 (2007).
78. Wiersinga, W. J. *et al.* Management of Community-Acquired Pneumonia in Adults: 2016 Guideline Update From The Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT). *https://swab.nl/nl/cap* https://swab.nl/nl/cap (2016).
79. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. *Am J Respir Crit Care Med* **171**, 388–416 (2005).
80. Babcock, H. M., Merz, L. R. & Fraser, V. J. Is influenza an influenza-like illness? Clinical presentation of influenza in hospitalized patients. *Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America* **27**, 266–270 (2006).
81. Falsey, A. R., Baran, A. & Walsh, E. E. Should clinical case definitions of influenza in hospitalized older adults include fever? *Influenza Other Respir Viruses* **9 Suppl 1**, 23–9 (2015).
82. Lam, P.-P. *et al.* Predictors of influenza among older adults in the emergency department. *BMC Infect Dis* **16**, 615 (2016).
83. Hartman, L., Zhu, Y., Edwards, K. M., Griffin, M. R. & Talbot, H. K. Underdiagnosis of Influenza Virus Infection in Hospitalized Older Adults. *J Am Geriatr Soc* **66**, 467–472 (2018).
84. Ruuskanen, O., Lahti, E., Jennings, L. C. & Murdoch, D. R. Viral pneumonia. *Lancet* **377**, 1264–75 (2011).
85. Giannella, M. *et al.* Should lower respiratory tract secretions from intensive care patients be systematically screened for influenza virus during the influenza season? *Critical Care* vol. 16 R104 Preprint at https://doi.org/10.1186/cc11387 (2012).
86. Wurzel, D. F. *et al.* Respiratory virus detection in nasopharyngeal aspirate versus bronchoalveolar lavage is dependent on virus type in children with chronic respiratory symptoms. *J Clin Virol* **58**, 683–8 (2013).
87. Roa, P. L. *et al.* Diagnosis of Influenza in Intensive Care Units: Lower Respiratory Tract Samples Are Better than Nose–Throat Swabs. *Am J Respir Crit Care Med* **186**, 929–930 (2012).
88. Ortiz, J. R. *et al.* The Burden of Influenza-Associated Critical Illness Hospitalizations. *Crit Care Med* 2325–2332 (2014) doi:10.1097/CCM.0000000000000545.
89. Shaman, J. *et al.* Asymptomatic Summertime Shedding of Respiratory Viruses. *J Infect Dis* **217**, 1074–1077 (2018).

90. Jartti, T., Jartti, L., Peltola, V., Waris, M. & Ruuskanen, O. Identification of respiratory viruses in asymptomatic subjects: asymptomatic respiratory viral infections. *Pediatr Infect Dis J* **27**, 1103–7 (2008).
91. Peltola, V. *et al.* Rhinovirus transmission within families with children: incidence of symptomatic and asymptomatic infections. *J Infect Dis* **197**, 382–389 (2008).
92. Huang, Y. *et al.* Temporal dynamics of host molecular responses differentiate symptomatic and asymptomatic influenza a infection. *PLoS Genet* **7**, e1002234 (2011).
93. WIP-Richtlijn Indicaties voor isolatie - Rijksinstituut voor Volksgezondheid en Milieu. http://www.rivm.nl/Documenten_en_publicaties/Professioneel_Praktisch/Richtlijnen/Infectieziekten/WIP_Richtlijnen/Actuele_WIP_Richtlijnen/Ziekenhuizen/WIP_Richtlijn_Indicaties_voor_isolatie_ZKH.
94. Kimberlin, D. W., Brady, M. T., Jackson, M. A. & Long, S. S. *Red book : 2012 report of the Committee on Infectious Diseases.* (2021).
95. Siegel, J. D., Rhinehart, E., Jackson, M., Chiarello, L. & Health Care Infection Control Practices Advisory Committee. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings. *Am J Infect Control* **35**, S65-164 (2007).
96. Sharland, M., Butler, K. & Cant, A. *Manual of Childhood Infections: The Blue Book.* (2016).
97. Kutter, J. S., Spronken, M. I., Fraaij, P. L., Fouchier, R. A. & Herfst, S. Transmission routes of respiratory viruses among humans. *Curr Opin Virol* **28**, 142–151 (2018).
98. Fielding, J. E., Kelly, H. A., Mercer, G. N. & Glass, K. Systematic review of influenza A(H1N1)pdm09 virus shedding: duration is affected by severity, but not age. *Influenza Other Respir Viruses* **8**, 142–50 (2014).
99. Dobson, J., Whitley, R. J., Pocock, S. & Monto, A. S. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet* **385**, 1729–1737 (2015).
100. Uyeki, T. M. *et al.* Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. *Clin Infect Dis* **68**, e1–e47 (2019).