Influenza and common cold viruses in critically ill adults

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GENERAL DISCUSSION

SUMMARY OF FINDINGS

The general aim of this thesis was to advance insights into the role of influenza virus and other respiratory viruses in critically ill adult patients, and the implications of these insights for clinical management and infection control measures. The main findings are:

Respiratory viruses are frequently detected in critically ill adults admitted to the ICU
We found that 34% of respiratory virus tests ordered by the attending staff were positive in patients admitted to the ICU with community acquired pneumonia (CAP) or hospital acquired pneumonia (HAP) during 3 consecutive winter seasons (**Chapter 3**). In a prospective cohort study, multiplex respiratory virus testing of systematically collected samples from both the upper and lower respiratory tract showed a prevalence of 29% in invasively ventilated adults admitted because of a severe acute respiratory infection (SARI) during the 2013-2014 winter season **(Chapter 6)**. In line with other reports in the literature (**Chapters 1 & 2**), these findings confirm a high prevalence of viral respiratory tract infections in adult critically ill patients in the ICU setting.

A proportion of detected common cold viruses may represent coincidental mild infections unrelated to ICU admission, but the burden of severe disease is likely substantial
Detection of respiratory viruses in adults admitted to the ICU does not in itself imply a causative role in critical illness. In **Chapter 1** and **Chapter 2**, evolving insights in the pathogenicity of common cold viruses in adults were summarized, highlighting their potential to cause severe disease, also in patients who are not severely immunocompromised. However, prevalence rates from epidemiological studies are likely confounded by background prevalences of unrelated mild infections. The case-control design of **Chapter 6** allowed for estimates of these coincidental infections, and showed significantly higher prevalences of RV and hMPV in patients admitted with a SARI compared to those admitted because of other reasons (non-SARI), and non-significant trends in the same direction for hCoV and RSV. While it remains challenging to attribute causality of a positive virus PCR for the presenting critical illness in individual cases, these findings indicate a substantial burden of common cold virus-associated severe disease in adults.

Viral respiratory tract infections are underdiagnosed in critically ill adults, and diagnostic reliance on nasopharyngeal (NP) swabs only will result in many missed infections
In **Chapter 3** we showed that the attending medical staff performed a test for respiratory viruses in only 46% of patients admitted to the ICU with a community acquired pneumonia (CAP) during the influenza season, and in only 13% of patients admitted with a hospital

acquired pneumonia (HAP). In 43% of patients, the influenza virus PCR results influenced antiviral prescription, i.e. empirical neuraminidase inhibitor treatment was discontinued after a negative test result, or treatment was initiated after a positive result. **Chapter 5** provided the first prospective data to assess how many infections are actually missed in the adult ICU setting: 71% of respiratory viruses were only detected by systematically collecting and testing of study samples, and were missed in routine clinical management as no test was ordered. Furthermore, of all patients with viral infections in the prospective cohort described in **Chapter 6**, 36% were exclusively detected in tracheobronchial aspirates (TA) and would have been missed if only a NP swab was tested. Taken together, these findings indicate that many viral respiratory tract infections, including influenza, are missed in the adult ICU setting, and including a sample from the lower respiratory tract greatly increases diagnostic yield.

Viral RNA shedding is prolonged in the critically ill, especially in the lower respiratory tract

By assessing daily obtained NP swabs and TA samples in our prospective cohort, we showed that influenza virus, RSV, RV and hCoV RNA shedding is prolonged in adult critically ill patients (**Chapters 7 & 8**). In the majority of patients viral RNA remained detectable throughout IMV. Also, viral RNA was detected for a significantly longer duration in TA compared to NP swabs. These findings may have implications for infection control measures and for clinical decisions on the duration of influenza antiviral treatment. Viral RNA levels and duration of shedding did not differentiate SARI from non-SARI patients with RSV, HRV or hCoV infections, but prolonged detection was associated with a fatal outcome.

CLINICAL IMPLICATIONS, DIRECTIVES AND FUTURE PERSPECTIVES

Estimating burden of disease

Findings in this thesis point to a substantial burden of severe common-cold associated illness in adults, and contribute to increasing needs and efforts to quantify this burden for the different respiratory viruses.

Most of these efforts are directed towards burden estimates for RSV and hMPV. RSV is associated with 60.000-160.000 hospitalizations and 6.000-10.000 deaths every year in people over 65 years old in the USA [1–7]. Two reports from a prospective study from the USA showed hospitalisation rates for RSV and hMPV of around 10 per 10.000 residents (>50 year old) per year, equal to estimated hospitalisation rates for influenza in that period[7,8].

Another approach which is increasingly used, is to compare clinical characteristics and outcomes of adults hospitalised with a common cold virus infection to those with

influenza. Several large international prospective studies indicate that - compared to adults hospitalised with influenza - those hospitalised with a RSV or hMPV infection have more severe lower respiratory tract symptoms, have an increased need for supplemental oxygen, and have comparable or even worse clinical outcomes [7,9–11]. However, prospective studies using systematic sampling and comprehensive multiplex testing for common cold viruses remain scarce. Also, surveillance and modelling studies based on retrospective data from routine care testing will likely underestimate the burden of common cold viruses in adults, as a substantial proportion of viral respiratory tract infections (RTIs) are missed in critically ill patients, either because viral diagnostics are not performed or because only the upper airway samples are tested. A recent report from an international cohort indicated an ongoing lack of diagnostic efforts for respiratory viruses, with less than 15% of hospitalized patients with CAP being tested[12]. Besides directly informing clinical decisions on treatment and infection control (see next paragraphs), diagnostic testing has an important role in national and international surveillance efforts to estimate the disease burden associated with respiratory virus infections. These surveillance efforts are essential to inform clinical, public health and research policy. For example, with currently two new RSV vaccines under approval [13], there is a need to identify risk groups for severe infection more precisely to guide a cost-effective vaccination strategy. Hence, there is a clear directive to improve diagnostic testing and viral SARI surveillance.

Who to test and how

There is clear room for improvement of diagnostic testing in the adult ICU setting. For influenza, as discussed in this thesis, using syndromic classifications such as influenza-like-illness as a test criterium in hospitalized adults will result in many missed infections[14–16] , amongst others illustrated by the absence of fever in a large proportion of one of our studied patient cohorts (**Chapter 3**). Therefore, the directive should be to test for the presence of influenza virus in all patients admitted to the ICU presenting with a suspected respiratory infection, irrespective of the absence of fever, and in those with exacerbation of chronic pulmonary or cardiac disease. While this is advised in the 2018 IDSA Influenza Guidelines[17], the Dutch CAP guidelines lag behind since these do not include a recommendation on influenza testing[18]. Likewise, the 2017 IDSA/ATS updated guidelines on the management of HAP and VAP do not mention influenza at all[19]. A further directive should be to include a sample from the lower airways for virus diagnostics whenever possible. In the ICU setting this can be a sputum sample for non-intubated patients, or a TA, mini-BAL or BAL for those receiving IMV. The latest IDSA Influenza virus guideline update from 2018 has indeed included this recommendation for patients receiving IVM[17] , but the Dutch national CAP guidelines and the 2019 update of international CAP guidelines have not[18,20].

If the burden and risk groups for severe disease of non-influenza respiratory viruses are comparable to influenza virus, it would be rational to implement a similar diagnostic

approach for these viruses. However, none of the abovementioned guidelines mention any non-influenza respiratory viruses, and awareness of evolving insights in the clinical importance of these viruses in adults remains low among medical professionals, e.g. illustrated by a survey among general practicioners[21]. In my view, sufficient evidence is available for RSV and hMPV to substantiate this approach, as is also advised by others, such as the Respiratory Syncytial Virus Consortium in Europe (RESCEU)[22,23] . A recent clinical practice guideline of the ATS from May 2021 also addresses this topic[24], and carefully advises to test for non-influenza viruses in adults admitted with severe CAP (which includes all patients receiving IMV). However, this guideline does not specify which viruses to test for, and only aspects of testing in relation to outcomes and costs are taken into consideration - not the protection of other patients and health-care workers by infection control measures.

Interpretation of nucleic acid amplification techniques (NAAT) results and disease classification

Attributing causality of detected common cold viruses to the presenting critical illness will remain challenging in individual patients. Therefore, there remains a risk of overestimating the burden of virus-associated severe disease in surveillance and etiological studies. Our approach of using a case-control design may contribute to adjust burden estimates, as it allows for correction of possible unrelated coincidental mild infections. A recent meta-analysis adopted a new approach for this correction, by calculating odds-ratios (OR) and virus-specific attributable fractions among the exposed (AFE) based on published case-control studies, to estimate etiological roles of specific common cold viruses in adults >65 years old with ARI[25]. These parameters for RSV (OR, 8.5 [95% CI, 3.9–18.5]; AFE, 88%) and hMPV V (OR, 9.8 [2.3–41.0]; AFE, 90%) were very similar to influenza (OR, 8.3 [4.4–15.9]; AFE, 88%). While this analysis should be interpreted with caution as the meta-analysis is performed on studies with severe methodological biases such as retrospective designs without systematic testing, it does offer a possible way forward to more precises estimates of the burden of common cold viruses.

To further advance clinical interpretation of test results and disease classification of common cold viruses, there is a clear need for a better understanding of the pathophysiology of severe disease. Ideally, a distinct set of host response markers should be identified to differentiate coincidental mild infections from severe infections. There is a growing body of data on transcriptomic profiles of viral respiratory tract infections, e.g. to identify markers of disease severity in COVID-19 [26] and differentiate bacterial from viral ARI based on host response analyses [27] . One approach may be to use unsupervised analysis of transcriptomic data to search for distinct clusters that may correlate with the different severity phenotypes. Another approach may be to search for markers of active virus transcription, to differentiate between an actively replicating virus and remnants of a recent but resolving infection. Subgenomic RNA is not contained in virions and only

transcribed in infected host cells, which may provide a useful approach in determining replication competence, as has been used in studies on SARS-CoV-2 infections [28,29].

Infection control measures

Given the evolving insights pointing to their clinical importance, it would be rational to implement infection control strategies similar to influenza for viruses such as RSV and hMPV. However, the 2014 Dutch national infection control guidelines advise contact plus droplet isolation measures for RSV and adenovirus only in hospitalized children under 6 years old and patients on hematological wards [30]. There is no indication in these guidelines for contact or droplet isolation measures for other common cold viruses. International guidelines contradict each other for non-influenza viruses such as RSV, hMPV, RV, hCoV, and PIV, ranging from contact plus droplet measures to no measures at all[31] . To better inform clinical practice guidelines, there is a clear need to reassess the burden of non-influenza respiratory viruses in relation to hospital-acquired infections in adults, including in those admitted to the ICU. Besides burden estimates, also risk groups, transmission routes and their relative contribution in different settings (e.g. with or without aerosol generating procedures) should be taken into account, as well as nosocomial spread via health care workers. Furthermore, in this thesis we provided evidence for prolonged RNA shedding of influenza virus, RSV, RV and hCoV in the critically ill, especially from the lower airways. Continued infection control measures until extubation or a negative NAAT therefore deserves consideration. The question remains if detection of low levels of viral RNA or DNA represent infectious virus or merely non-infectious remnants of nucleic acids. For SARS-CoV-2, virus culture studies were used to estimate PCR Ct- or Cp-value thresholds of virus infectivity[32]. While these likely provide reasonable estimations of infectivity, they should be interpreted with caution due to limited sensitivity of virus culture (especially for difficult to culture viruses such as hCoV and hMPV), lack of standardization between NAAT protocols, and sampling variation. Furthermore, low levels of viral RNA may also indicate early stages of the infection, as such representing replicating and infectious virus. As mentioned in the previous paragraph, detection of subgenomic viral RNA may provide a way forward.

Treatment

Currently, there are only registered antivirals for the treatment of influenza, as described in Chapters 1 and 2. Beside neurominidase inhibitors (oseltamivir, zanamivir, peramivir), these include baloxavir marboxil, an influenza polymerase inhibitor, which is currently not recommended for treatment of severe influenza [35]. A superiority RCT in hospitalized patients showed no benefit of treatment with baloxavir marboxil in combination with a neuraminidase inhibitor, compared to treatment with a neuraminidase inhibitor alone[33]. As prolonged influenza RNA shedding seems to be the rule rather than the exception in critically ill adults, there directive here is to consider continuing neuraminidase inhibitor

treatment beyond the standard duration of 5 days. Indeed, since the 2018 update, the IDSA Influenza treatment guidelines advise to consider longer treatment with neuraminidase inhibitors in immunocompromised and critically ill patients [17]. It seems rational to continue treatment at least for the duration of IMV, and to consider repeating influenza NAAT in those with prolonged IMV. Of note, in the absence of evidence from randomized clinical trials on neuraminidase treatment in hospitalised patients with severe influenza, clinicians will likely continue to question their effectiveness. The absence of such trials negatively impacts guideline development and compliance. Fortunately, a platform trial on oseltamivir treatment in the critically ill is ongoing, which includes arms of no treatment and 10-day treatment, and measurement of virological endpoints at selected sites [34]. In an ICU setting, there may be patients with active virus replication who will potentially benefit from antiviral treatment, while others may have severe disease due to immune dysregulation. In the latter patients, antiviral treatment may not lead to improved clinical outcomes, and immune modulation should be considered, as shown with dexamethasone treatment in severe COVID-19[35].

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