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EDITORIAL

NJCC goes viral

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In this edition of the Netherlands Journal of Critical Care (NJCC) viral infections take centre stage. The influenza season is upcoming and the first warnings in the media have been posted. Although most viruses can be detected year-round, they typically show seasonal epidemic peaks. The consequence for the intensive care unit (ICU) varies strongly each year. Immunocompromised patients are always at risk. The vulnerability of people not belonging to the defined 'risk groups' seems to depend on the circulating influenza strains.

Seasonal influenza is an acute respiratory infection caused by influenza viruses which circulate in all parts of the world. There are three types of seasonal influenza viruses, types A, B, and C. Influenza type A viruses are further classified into subtypes according to the combinations of two different proteins, the haemagglutinin (H) and the neuraminidase (N), located on the surface of the virus. The subtypes of influenza A viruses currently circulating among humans are influenza A/H1N1 and A/H3N2 subtypes. Only influenza type A viruses are known to have caused pandemics. Circulating influenza B viruses can be divided into two main groups (lineages), referred to as B/Yamagata and B/Victoria lineages. Influenza B viruses are not classified into subtypes. Influenza type C virus is detected much less frequently and usually causes mild infections, thus resulting in a less significant burden on public health. Influenza A and B viruses circulate and cause outbreaks and epidemics. For this reason, relevant strains of influenza A and B viruses are included in seasonal influenza vaccines. Seasonal influenza is characterised by a sudden onset of fever, cough (usually dry), headache, muscle and joint pain, severe malaise, sore throat and a runny nose. The cough can be severe and can last two or more weeks. Most people recover within a week without requiring medical attention. But influenza can cause severe illness, with respiratory failure, multiple organ failure and death, especially in individuals at high risk. Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths. Epidemics can result in high levels of work and school absenteeism, and productivity losses. Clinics, hospitals and ICUs can be overwhelmed during peak illness periods. Seasonal influenza spreads easily, with rapid transmission in crowded areas including schools and nursing homes. When an infected person coughs or sneezes, droplets containing viruses are dispersed into the air and are spread to individuals in close proximity who breathe in these droplets. The virus can also be spread by hands contaminated with influenza viruses. The incubation period is about two days.[1]

It is not possible to predict exactly when the influenza season will start and whether the epidemic will be serious. However, the influenza activity in the southern hemisphere sometimes gives an indication of what to expect. Compared with past years, Australia suffered a severe influenza season mainly caused by influenza A/H3N2 and influenza B/Yamagata.[2] Clinical severity, as measured through the proportion of patients admitted directly to the ICU and deaths attributed to influenza, however, was deemed low to moderate and was in the lower range reported in recent years. There were a number of deaths reported due to influenza and pneumonia, the majority of which were among the elderly, which is consistent with a season predominated by influenza A/H3N2.

In this edition of the NJCC, Wuister and Koeman[3] describe the characteristics of critically ill influenza patients of the influenza epidemic of the 2015/2016 season, mainly caused by influenza A/H1N1, in the ICU of a Dutch, non-academic hospital. It clearly illustrates the possible fulminant outcome of influenza, in this case particularly in young, male patients without comorbidities. The paper also raises awareness for the upcoming season. Interestingly, in this study 20% of patients developed a superinfection with *Aspergillus* spp., associated with high mortality. This finding is relatively new and an increasing number of studies have been published during the last five years reporting

Aspergillus spp. superinfection or co-infection with influenza A/H1N1, especially in non-immunocompromised, young patients.[4] Further studies to unravel this association are being performed.

The World Health Organisation (WHO) advises risk groups to get their vaccinations since it is the most effective means of influenza prevention available. Among healthy adults, influenza vaccine provides protection even when circulating viruses may not exactly match the vaccine viruses (i.e. vaccine mismatch). Among the elderly, influenza vaccination may be less effective in preventing illness but reduces the severity of disease and incidence of complications and deaths. Annual vaccination is recommended for individuals with an increased risk of complications, such as pregnant women, age above 65 years, chronic illness (diabetes, chronic heart, kidney, hepatic or lung disease), immunocompromised patients, children aged between 6 months to 5 years or people who live with or care for high-risk individuals.[1] The larger part of patients described in the study by Wuister and Koeman, however, did not belong to a risk group and 25% had severe infection despite vaccination.[4]

Influenza vaccination is most effective when circulating viruses are well-matched with viruses contained in vaccines (i.e. vaccine match). Due to the constant evolving nature of influenza viruses, the WHO Global Influenza Surveillance and Response System (GISRS) – a network of National Influenza Centres and WHO Collaborating Centres around the world – continuously monitors the influenza viruses circulating in humans and updates the composition of influenza vaccines twice a year.[1] In the Netherlands, influenza vaccine effectiveness (IVE) has been studied recently and it was concluded that IVE was approximately 50% in case of a vaccine match and low when there was a vaccine mismatch in circulating viruses and viruses contained in the vaccine. Moreover, when influenza A/H3N2 was the dominant influenza subtype, IVE was low.[5] The 2017/2018 trivalent vaccine in the Netherlands contains fragmented, inactivated virus of the subtypes influenza A/N1H1, influenza A/H3N2 and influenza B/Brisbane (from the influenza B/Victoria lineage). In the tetravalent vaccines used abroad, influenza B/Phuket (from the influenza B/Yamagata lineage) is added to the former three, all according to the WHO recommendations.[6]

This edition of NJCC also contains a review of respiratory viral infections in the ICU by Van Someren Gréve and Ong.[7] Of relevance for the coming winter season, the authors highlight the issue of underdiagnosing of viral infections. The authors also present an overview of respiratory viruses that are prevalent in the adult ICU. Next to influenza these are mainly human rhinovirus, respiratory syncytial virus, parainfluenza virus and coronavirus. There is no doubt that influenza has pathogenicity. For the other viruses, unfortunately, the clinical significance in critical illness remains unclear. Treatment options are limited to neuraminidase inhibitors in the early phase of influenza infection although some new antivirals are in clinical development. For the other viruses there are no registered treatment options. Awareness of bacterial or fungal co-infections is crucial and needs to be incorporated in the diagnostic approach and in early pre-emptive therapy. Especially in the patients who show no or delayed recovery.

Current national isolation guidelines advise droplet isolation only for influenza and adenovirus infections until resolution of clinical symptoms.[8] This leaves the decision to stop isolation measures at the discretion of the intensivist while duration of viral shedding may vary and transcend clinical cure. In the era of real time semi-quantifiable PCR methods for the diagnosis of infections, this technique should also be validated to predict safe termination of isolation measures after viral infections in the ICU.

Forewarned is forearmed. So be prepared in your ICU for the patient with a respiratory viral infection in the next few weeks. Have your medical and nursing staff vaccinated in time and be clear about your local isolation guidelines. Consider viral infection during the season in every patient with respiratory failure of infectious origin and follow the diagnostic guideline. Isolate the patient and start neuraminidase inhibitors as soon as influenza is suspected. Provide the supportive care needed and try to avoid steroids. Have a high suspicion of bacterial or fungal co-infection, especially *Aspergillus* spp., also in 'non-high risk' patients. Start pre-emptive antibiotic or antifungal treatment. If the recent influenza activity in the southern hemisphere is predictive for our season, it might be mainly influenza A/H3N2 and influenza B/Yamagata circulating, which is fortunate because this would mean no occurrence of influenza A/H1N1, known for its poor outcome and association with *Aspergillus* spp. Moreover, there would be a vaccine match this season, although the influenza vaccine effectiveness is low for influenza A/H3N2. Hopefully, we will keep the infections in our ICUs from going viral.

References

1. World Health Organization. Influenza (seasonal). Fact sheet November 2016. (http://www.who.int/mediocentre/factsheets/fs211/en). (Accessed October 22, 2017)
2. Australian Government Department of Health. Australian Influenza Surveillance Report No.10: 16 – 29 September 2017 (http://wwww.health.gov.au/flureport). (Accessed 22 October2017).
3. Wuister AMH, Koeman M. Characteristics of critically ill influenza patients in an Intensive Care Unit in the Netherlands. Neth J Crit Care. 2017;25:205-209.
4. van de Veerdonk FL, Kolwijck E, Lestrade PPA, et al. Influenza-associated aspergillosis in critically ill patients. Am J Crit Care Med. 2017; Apr 7 [doi:10.1164/rccm.201612-2540LE].
5. van Doorn E, Darvishian M, Dijkstra F, et al. Influenza vaccine effectiveness in the Netherlands from 2003/2004 through 2013/2014: the importance of circulating influenza virus types and subtypes. PLoS One 2017; 12: eo169528.
6. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2017-2018 northern hemisphere influenza season. (http://www.who.int/influenza/vaccines/virus/recommendations/2017_18_north/en/). (Accessed 22 October 2017).
7. van Someren Gréve F, Ong DSY. Seasonal respiratory viruses in adult ICU patients. Neth J Crit Care. 2017;25:198-204.
8. Rijksinstituut voor Volksgezondheid en Milieu. WIP-richtlijn Indicaties voor isolatie 22 september 2014 (http://www.rivm.nl/dsresource?objectid=6642621a-52da-4cd0-96c7-58bea053b380&type=org&disposition=inline). (Accessed 22 October 2017).