DANISH MEDICAL JOURNAL

Original Article

Dan Med J 2021;68(8):A11200858

Viral pneumonia in Danish children

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Dan Med J 2021;68(8):A11200858

ABSTRACT

INTRODUCTION: Viral pneumonia is a common cause of hospital admission among Danish children. However, it remains unknown how many admissions among Danish children may be ascribed to viral pneumonia overall.

METHODS: Based on data drawn from the National Patient Register and the Danish Microbiology Database, hospital admissions for viral pneumonia and asthma-like disease were investigated among Danish children and adolescents < 18 years. Testing of admitted patients for respiratory syncytial virus (RSV) and influenza virus was also considered.

RESULTS: A total of 5,218 admissions with a diagnosis of viral pneumonia were identified among Danish children and adolescents < 18 years from 2012 to 2016. During the same period, 63,731 tests were conducted during hospital admission for RSV or influenza virus, which produced 9,933 positive tests for RSV and 3,287 for influenza. In addition, 43,213 admissions were due to asthma-like disease.

CONCLUSIONS: The present study documented overlapping age and seasonal epidemiological patterns of different measures of viral pneumonia among Danish children and presented how the collection of data from different sources (diagnoses and diagnostic tests) yielded a more complete picture of the burden of hospital contacts among Danish children and adolescents caused by viral pneumonia. Viral pneumonia is a very common cause of hospital admission among Danish children and adolescents.

FUNDING: No specific funding was available for the present project.

TRIAL REGISTRATION: not relevant.

Globally, pneumonia is the most frequent cause of death among children below five years of age [1]. A US-based clinical multicentre study from 2015 including 2,638 children and adolescents found that pneumonia requiring hospital admission was most often caused by viral infection of the airways [2]. A total of 66% (1,472 of 2,222 who had samples taken) had one or more viral infections of the airways as the most likely cause of their symptoms, respiratory syncytial virus (RSV) being the most frequent stand-alone cause (n = 622, 30%) followed by rhinovirus (n = 606), human metapneumovirus (n = 285), adenovirus (n = 248), para-influenza virus (n = 151), influenza virus (n = 149) and coronavirus (n = 110) as other frequent viral pathogens of the airways [2].

In Denmark, 2.9% of children below two years of age were admitted to the hospital with RSV [3] from 1997 to 2003, and the proportion was 2.5% from 2010 to 2016 [3]. In the study covering 1997-2003, we found that risk factors for hospital admission with RSV among Danish children in particular were previous admissions with asthma-like disease, having chronic disease, having siblings, attending day care and being born pre-/immaturely [4]. A similar profile of risk factors applies to some extent for RSV in other countries.

Infection with viral airway pathogens in general and rhinovirus in particular in children (and adults) may lead to

asthma-like disease, which was seen in 15% [5] to 40% [6] of Danish children, depending on the definition of the condition used. The association is complex because the risk of having a serious airway infection is increased among children with asthma-like disease [7]. Simultaneously, a serious viral airway infection comes with an increased risk of subsequent asthma-like disease [8] and bacterial infection [9].

The effect of the ongoing pandemic with SARS-CoV-2 on the prevalence of viral airway infection among children remains unknown. However, currently no clinical suspicion or evidence suggests that children and adolescents in general will become severely ill if infected with SARS-CoV-2. The number of children admitted to hospital with SARS-CoV-2 infection is low globally, even in geographical areas where the prevalence is high [10]. In Denmark, only few children have been admitted with SARS-CoV-2 infection, none of them have been in intensive care and none have died [11]). On rare occasions, SARS-CoV-2 infection may lead to severe multisystem inflammatory syndrome in children (MIS-C) [12].

The purpose of this article was to present and provide perspectives on the prevalence of viral pneumonia among Danish children and adolescents.

METHODS

Aiming to introduce different data sources of use in the presentation of a more complete picture of the burden of hospital contacts caused by viral pneumonia in children, data on both relevant admissions and microbiological tests were obtained and presented in four figures. The figures were based on the National Patient Register (NPR) [13] and the Danish Microbiology Database (MiBa) [14]. As presented in the **online supplement (https://ugeskriftet.dk/files/a11200858_-_supplementary.pdf)**, relevant admissions were defined using the International Classification of Diseases tenth version (ICD-10) diagnoses for pneumonia; the subgroup of pneumonias was coded specifically as viral pneumonia and asthma-like diseases. Admissions in the NPR included contacts defined as hospitalised patients, including main and secondary diagnosis codes but excluding referral diagnoses and administrative diagnoses. The data from the NPR were accessible from 1994 onwards, which defined the study period. When investigating microbiological tests during admissions among children and adolescents below 18 years of age, we followed the cohort from 2012 through 2016 as data on RSV and influenza virus were available from the MiBa for this period. A child may have undergone repeated admissions or have repeated tests performed. In case the same event occurred several times on the same date, it was counted only once.

The focus on RSV was selected based on knowledge of the clinical impact of RSV infections and due to the fact that vaccines for pregnant women against RSV in their newborns and vaccines to infants are currently being investigated and are expected to become available shortly [15]. The focus on influenza virus was selected because the infection may potentially be prevented as vaccination against influenza infection may be given to pregnant women and to children ≥ 6 months of age.

Trial registration: not relevant.

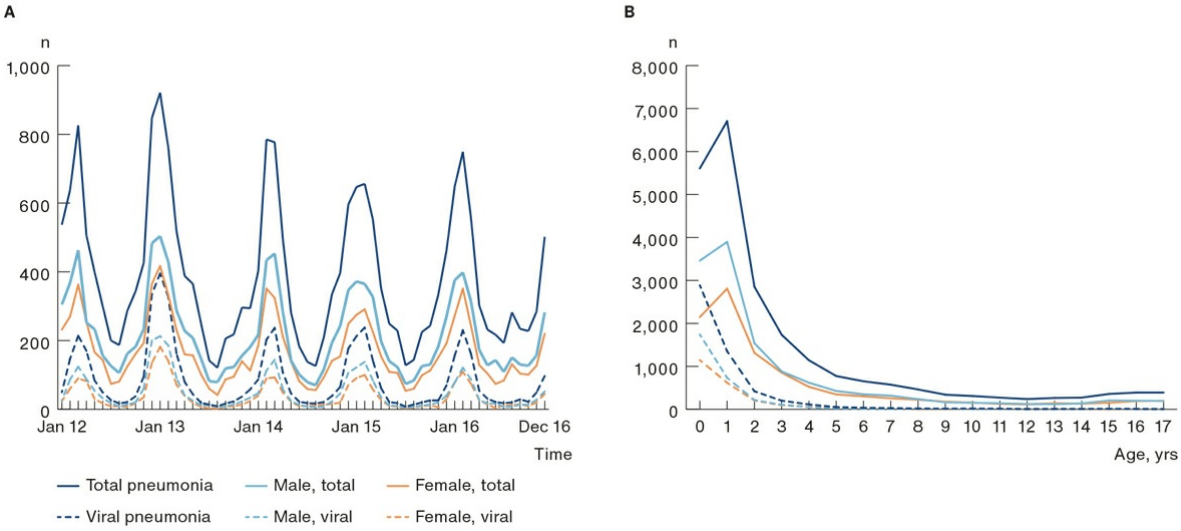
RESULTS

Pneumonia and viral pneumonia

In the study period (2012-2016), a total 604,014 admissions were found in the complete study population < 18 years of age. Among these, 23,349 (3.87%) admissions were due to pneumonia, and viral pneumonia was the cause for admission in 5,218 cases (0.86%).

A pronounced seasonal variation was found, i.e. a high prevalence during wintertime and a low prevalence during summertime in all admissions of children and adolescents and for the subgroup of admissions due to viral pneumonia (**Figure 1**). Admissions due to pneumonia did, however, occur throughout the year, whereas admissions due to viral pneumonia largely did not occur during the summertime.

FIGURE 1 Pneumonia. The number of hospital admissions from 2012 to 2016 in the National Patient Register among Danish children and adolescents < 18 years with International Classification of Diseases tenth version (ICD-10) diagnoses for pneumonia and the subgroup of pneumonias coded specifically as viral pneumonia. ICD-10 codes for pneumonia and the subgroup viral pneumonia relevant for the figure were defined as stated in the Online Supplement. **A.** The number of admissions over time, 2012-2016. **B.** The number of admissions as a function of age.



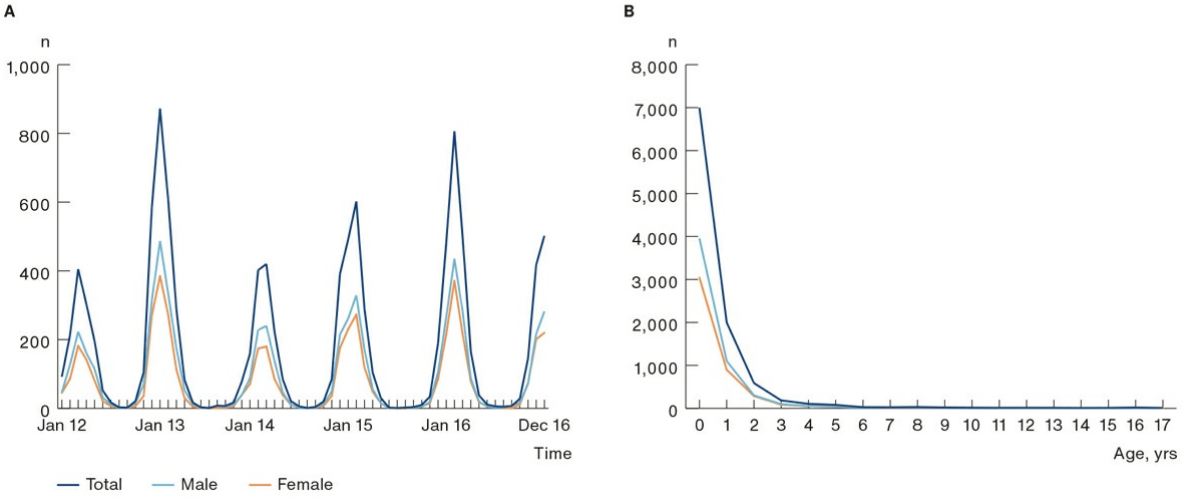
More boys than girls were admitted with a diagnosis of pneumonia. This finding was repeated consecutively every year during the study period. For the complete group of pneumonias, the curve based on age showed a high and increasing prevalence during the first two years followed by a declining prevalence through to seven years of age, after which the prevalence stabilised below 500 annual admissions.

For the subgroup of children who were admitted with viral pneumonia, the age pattern was slightly different. The prevalence was highest early in life and dropped to a very low prevalence around the age of four years.

Respiratory syncytial virus

In the study period, a total of 34,765 tests for RSV were performed in admitted children and adolescents; 9,933 (28.57%) tests were positive. A pronounced seasonal variation was seen with sharply defined peaks of RSV-positive tests in admitted Danish children each year in December, January and February – and largely no positive tests during summertime (**Figure 2**). Furthermore, considerable variation was found in the annual prevalence from one year to the next. For the age distribution, the prevalence was high among infants followed by a sudden drop within the first two years, as expected. Hence, the prevalence of RSV was low from two years and onwards and negligible from the age of four years. During the first two years, slightly more boys than girls were admitted with RSV and this finding was more pronounced in the peak season from December through February.

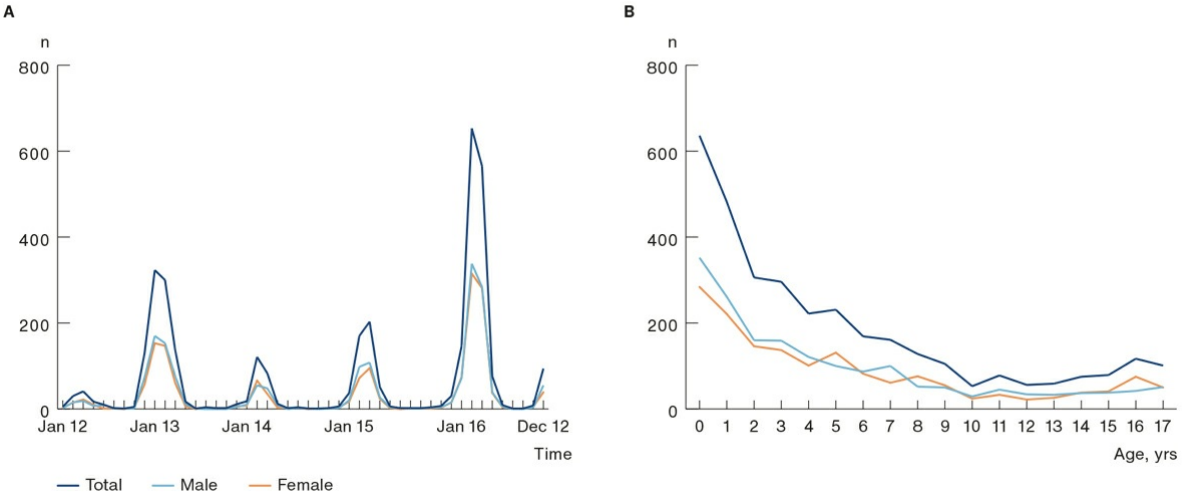
FIGURE 2 Respiratory syncytial virus (RSV). The number of airway secretion samples among admitted patients < 18 years who tested positive for RSV (including all subtypes) at the departments of microbiology in Denmark in 2012-2016. **A.** The number of RSV-positive tests over time. **B.** The number of RSV-positive tests as a function of age.



Influenza

In the study period, 28,966 tests for influenza virus were performed in admitted children and adolescents; 3,287 (11.35%) tests were positive. A similar pattern as for RSV was seen, including pronounced seasonal variation, notwithstanding that fewer children were typically admitted with the flu than with RSV (**Figure 3**). The variation in prevalence was even more pronounced than for RSV as the children admitted with the flu peaked in 2013 and 2016, which by recall were two winter seasons with severe flu epidemics. The age distribution differed from that of RSV infections by having a larger spread on all age groups despite peaking in infants and during the first two years. The flu also seemed to be increasing slightly among teenagers. The prevalence was similar for boys and girls.

FIGURE 3 Influenza. The number of airway secretion samples among admitted patients < 18 years who tested positive for influenza virus (including all subtypes) at the departments of microbiology in Denmark in 2012-2016. **A.** The number of influenza-positive tests over time. **B.** The number of influenza-positive tests as a function of age.



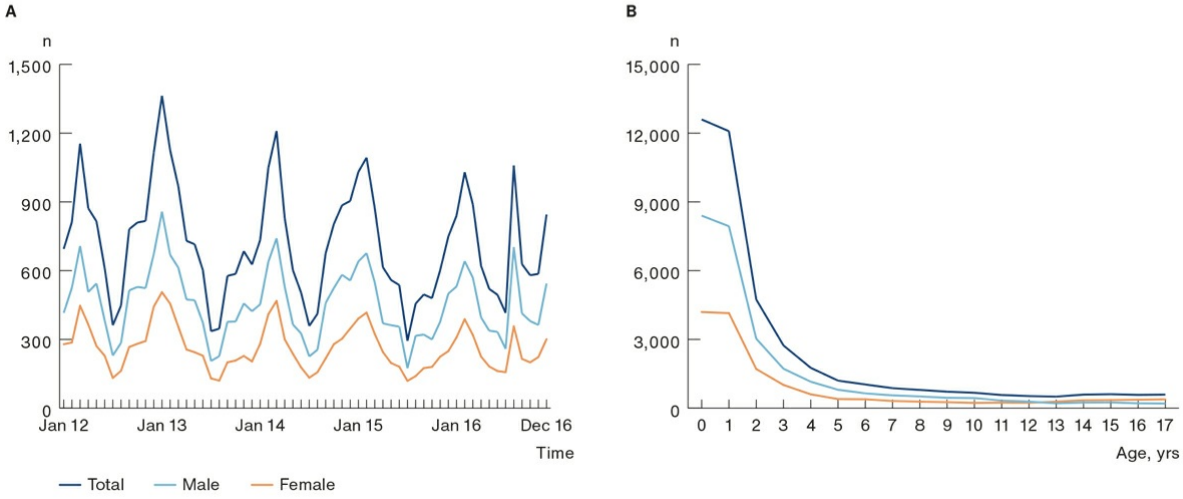
A large overlap was seen between children and adolescents who were tested for RSV and influenza virus. In total, 27,793 different children and adolescents were tested during the study period for RSV or influenza virus during admission.

Asthma-like disease

In the study period, admissions due to asthma-like disease represented 7.15% (n = 43,213) of the total number of admissions (n = 604,014) among children and adolescents < 18 years.

Figure 4 demonstrates pronounced seasonal variation for admissions due to asthma-like disease among Danish children and adolescents with many admissions during the wintertime and fewer admissions during the summertime. Even so, admissions for asthma-like disease did occur throughout the year as was the case for admissions due to pneumonia (Figure 1). The prevalence was considerably higher among boys than among girls and dropped from a high prevalence during the first two years of age to a low prevalence from 5-6 years and onwards.

FIGURE 4 Asthma-like disease. **A.** The number of hospital admissions in 2012-2016 in the National Patient Register among Danish children and adolescents < 18 years with International Classification of Diseases tenth version (ICD-10) diagnoses for asthma-like disease. ICD-10 codes for asthma-like disease used in the figure were defined as stated in the online supplement. **B.** The number of admissions as a function of age.



Extending the period between events from one day to seven days had little impact on the number of events during the study period: pneumonia 23,349 versus 22,103; viral pneumonia: 5,218 versus 5,034; asthma-like disease: 43,213 versus 40,669; RSV: 9,933 versus 9,637; influenza: 3,287 versus 3,098. It was not possible to determine changes in prevalence over the years (**Table A, online supplement https://ugeskriftet.dk/files/a11200858_-_supplementary.pdf**).

DISCUSSION

The study presented herein demonstrated that viral pneumonia is a frequent cause of hospital admission in infants and toddlers. This finding implies that researchers investigating disease burden will benefit from enclosing more data sources such as a combination of data on relevant admissions and testing for airway pathogens in order to get the full overview.

The prevalence was particularly high among infants and toddlers, which is a well-known fact [3, 4]. A recent epidemiological study from Sweden completed in parallel to the present study found that from the age of six years, the prevalence is low like in adults, whereas it increases again in the elderly [16].

Through five study years (2012-2016), we found 5,218 admissions of Danish children and adolescents with a diagnosis code of viral pneumonia. During the same period, 63,731 tests for RSV and/or influenza virus were performed during admission, presumably due to clinical symptoms indicating a viral pneumonia, although other

indications should also be considered. Among these, 13,220 tests were positive. Hence, the actual prevalence of viral pneumonia is much higher than what is suggested from ICD-10 diagnosis coding. As this study did not include comprehensive testing for other viral pathogens than RSV and influenza, a full overview of viral airway pathogens in Danish children and adolescents cannot be established.

It is well established that viral infections may trigger exacerbation of asthma-like disease, which likely contributes to the explanation of the observed seasonal variation with RSV, influenza virus and admissions for asthma-like disease. A UK study from 1995 detected airway virus in 80-85% of 9-11-year-old children with asthma exacerbation compared with the detection of airway virus in 12% of asymptomatic controls [17]. In a literature review from 2018, Zheng et al found that rhinovirus, RSV, metapneumovirus and enterovirus were the types of airway viruses that most frequently caused asthma exacerbation in children and adolescents. The study reported herein found 43,213 admissions due to asthma-like disease. However, we were unable to determine how many of these were caused by viral infections. That diagnoses of asthma-like disease and pneumonia were found also during summer seasons illustrates other causes of these disease entities than viral airway infections like RSV and influenza, which were found to be absent during summer seasons.

Throughout the analyses, more boys than girls were admitted with viral pneumonia and asthma-like disease. This may imply that boys tend to become more severely affected by airway infections and other conditions with pronounced airway inflammation. A study from China published in 2015 found a boy:girl ratio of 2.3:1 for children in intensive care units for RSV-infection [18]. Additionally, it has previously been shown that among Danish and Swedish children, boys have a higher risk of asthma-like disease than girls [4, 5, 19]. The reason for this remains unknown, but a series of factors, e.g. anatomical, physiological, inflammatory and sex hormonal factors, may contribute.

Finally, it the impact of the COVID-19 pandemic on the prevalence of viral pneumonia in Danish children and adolescents remains unknown. No evidence suggests that co-infection with several airway viruses leads to more severe disease courses [20]. Hopefully, vaccination and increased public awareness and alertness around hygiene and distancing will contribute to an overall decrease in the prevalence of viral pneumonia. Future studies will pursue this.

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Accepted 4 May 2021

Conflicts of interest none. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2021;68(8):A11200858

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