Effect of disease definition on perceived burden of acute respiratory infections in children –a prospective cohort study based on symptom diaries

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Introduction

Acute respiratory infections (ARI) are the most frequent childhood diseases in Western countries, and the most common reason for children to visit health care professional.[1-3] Still, most ARI in children resolve spontaneously and in about 50% of cases do not lead to consultation of a paediatrician.[4-6] As a consequence, assessing the full burden of these infections cannot solely be based on physicians' reports. Studies assessing the frequency of ARI in the population try to overcome this limitation by including other data sources. In the past, four different data collection methods have been used: (1) hospital visits every time the child has symptoms[7], (2) retrospective surveys via parent-administered questionnaires or interviews[8-11], (3) parent-administered prospective symptom diaries[5, 6, 12, 13], and (4) a combination of parent-administered prospective symptom diaries and interviews.[14, 15] However, a definition of ARI episodes for these additional data sources is more difficult to apply than simply to rely on physician reports. The proposed definitions also vary widely in the literature, as was recently shown by Roth et al. in a systematic review of studies in developing countries.[16] The main challenges include the question of which combination of symptoms constitutes an ARI and how different ARI episodes should be separated.

Our objective was to investigate the influence of different definitions on the disease burden of ARI through a prospective cohort study using symptom diaries.

Materials and Methods

Papers including ARI definitions based on symptom diary data were identified through a literature search that was primarily based on a systematic review regarding birth cohort studies on infectious diseases with a broad search strategy (Figure 1)

which was complemented by a search applying terms including “symptom or symptoms”, “diary or diaries”, and a collection of terms for ARI ((common cold*) OR ("respiratory tract infection") OR ("respiratory tract infections") OR ("respiratory infection") OR ("respiratory infections") OR ("respiratory illness")). We searched medline® using the PubMed® website and Embase®, restricting searches to publications from 1990 to June 2016. Only papers with a clear definition of ARI (including the symptoms required for an episode to start and the number of symptom-free days between ARIs) were included in the selection. Papers reporting definitions for upper respiratory infections only were excluded. We applied the identified definitions to a recently collected dataset consisting of parent-administered symptom diary data. This dataset was derived from the before mentioned feasibility study conducted between November 2013 and June 2014 in Braunschweig, Germany. Seventy-five parents of one- to three-year-old children were recruited in child care centers and were asked to fill in a symptom diary for respiratory and gastrointestinal infections over three months covering the following symptoms/sign: fever, wheeze, dry cough, wet cough, runny/blocked nose, chills, vomiting, loose stool, loss of appetite, increased sleep requirement, and clinginess.

Statistical analyses

We applied the different definitions of ARI in the dataset with daily symptom diary collection and determined for each definition the number and duration of ARI episodes for each study participant. We report for each definition overall parameters of disease burden in our dataset (total number of ARI episodes, total days with ARI, symptom-free days included in ARI episodes, mean duration of an ARI episode, median duration of an ARI episode, the minimum and maximum number of episodes per participant, and the minimum and maximum total days with ARI per participant).

In order to assess differences across disease definitions on these parameters of disease burden, we used Friedman tests.[18]

All analyses were performed with Stata for Windows, version 12 (StataCorp, College Station, TX).

Human subjects review

The study protocol was approved by the Ethics Committee of Hannover Medical School, and was reviewed by the Federal Commissioner for Data Protection and Freedom of Information. Written informed consent was obtained from all participants.

Results

Definitions of ARI episodes

In our literature search we identified six different ARI definitions in symptom diary studies which fulfilled the inclusion criteria (Table 1 and 2). In all definitions, a runny/blocked nose and cough were included (but not as a necessary requirement); in three definitions fever played a role.[12, 19, 20] In the definitions of Samet et al.[14] and Douglas et al.[12], new ARI episodes are only defined if symptoms occur on two consecutive days, whereas in all other definitions an episode starts on the first day when the required symptom/s occur.

A single day of runny/blocked nose as the only symptom is regarded as an ARI episode only in the definitions proposed by Kusel et al.[6] and Sarna et al.[21] In the definition proposed by Douglas et al.[12], at least two consecutive days of a runny/blocked nose are required. In the other definitions, a second symptom is required for an episode to start. Yet, in the definition proposed by Lambert et al.[19], once these requirements are fulfilled, the episode also includes previous days with a

single symptom, e.g. just a runny/blocked nose (personal communication S. Lambert[19]). According to von Linstow[20], days with a runny/blocked nose only were considered as an episode of ‘‘simple rhinitis” and were not classified as an ARI.

The number of symptom-free days between episodes required by the definitions ranged from two[14] to six days.[20] In the further text, ARI definitions are referred to by the last name of the first author of the corresponding publication.

Symptom diary data

Since ten of the original 75 participants provided less than 30 days of diary data, they were excluded from all analyses leading to a final sample size of 65. These participants provided symptom diary data for 5,516 days out of 5,850 theoretically possible days (94.3%).

The most common reported symptoms were a runny/blocked nose (2,090 days, 37.9% of all days), followed by cough (wet or dry) on 1,419 days (25.7%). Both symptoms together occurred on 1,121 days (20.3%). Fever occurred on 208 days (3.8%), chills on 27 days (0.5%). Cough with a runny/blocked nose combined with fever and chills occurred on 15 days (0.3%).

Disease burden of ARI

The total number of ARI episodes in our dataset varied from 139 (Samet[14]) to 235 (Kusel[6]), and the total number of days with ARI was between 1633 (Samet[14]) and 2491 (Douglas[12]). The mean duration of ARI episodes ranged from 10.0 (Kusel[6]) to 15.3 (von Linstow[20]) days. The median duration ranged from 7 (Kusel[6]) to 10 days (Samet[14]). ARI episodes lasted between one and 90 days. The proportion of participants with no episodes ranged from 1.5% (Kusel[6]) to 13.9% (Samet[14]). The

maximum number of episodes per participant ranged from four (von Linstow[20]) to eight (Douglas[12], Kusel[6], and Sarna[21]) (Table 3).

The number of episodes and days with ARI varied significantly across the applied definitions (for both comparisons: Friedman-test, $p<0.001$).

Detailed examination of special features of the definitions

ARI episodes consisting solely of days with just a runny/blocked nose were allowed in three definitions (Kusel[6], Douglas[12], and Sarna[21]). They contributed 42 out of 235 episodes (17.9%), 32 out of 213 episodes (15.0%), and 39 out of 227 (17.2%) episodes respectively. These episodes had durations between one (Kusel[6] and Sarna[21]: n=7) and 11 days (all three definitions: n=1). One of these episodes was included in an ARI episode according to Lambert[19] and von Linstow[20], one was included in an ARI episode only according to Lambert[19], further eight were included in ARI episodes only according to von Linstow[20], and none of them according to Samet[14], leaving 31 episodes consisting completely of days with just a runny/blocked nose that were not part of ARI episodes according to other definitions than Kusel[6], Douglas[12] or Sarna[21].

ARI episodes consisting solely of days with just fever are only possible when applying the definitions by Lambert[19] and Douglas[12]. They contributed five out of 189 episodes (2.6%) and one out of 213 episodes (0.5%) in these definitions, respectively. These episodes had durations between one and two days. None of these episodes were included in ARI episodes according to the other definitions.

The number of episodes with a duration of one day was zero for Samet[14] and Douglas[12], eight for von Linstow[20], 12 for Lambert[19], 18 for Sarna[21], and 21 for Kusel[6]. In total, there were 33 episodes which lasted one day according to at least one

definition. Of those, six episodes were unique to the definitions by Kusel[6] and Sarna[21] (meaning these days were not part of an episode according to any other definition) and were characterized five times by a runny/blocked nose only, and one time by dry cough. Seven episodes were unique to the definition by Lambert[19]: Four with fever only; one with increased sleep requirement and vomiting; one with increased sleep requirement, vomiting, and loss of appetite; and one with fever, loss of appetite, and increased sleep requirement (loss of appetite is not relevant for this definition).

Further one-day-episodes that were not part of an episode according to the other definitions, was one episode according to Lambert[19] and Sarna[21] (fever, moist cough, loss of appetite, increased sleep requirement), one episode according to Kusel[6], Lambert[19], and Sarna[21] (wheezing), one episode according to Kusel[6], von Linstow[20], and Sarna[21] (runny/blocked nose, loss of appetite), and two further according to Kusel[6], Lambert[19], von Linstow[20], and Sarna[21] (1: fever, runny/blocked nose, increased sleep requirement, 2: cough without specification, runny/blocked nose) (Table 4).

ARI episodes according to von Linstow[20] included thirty-seven occurrences of three to five consecutive symptom-free days, meaning that these episodes would be shorter and/or split into two, if a period of at least three instead of six symptom-free days would be considered in the definition.

Discussion

Symptom diaries are a useful tool to assessing the complete burden of ARI in children. Yet, we demonstrated that the application of different definitions for ARI episodes led to substantial differences in the reported number and duration of ARI

episodes. The total number of ARI episodes and the total number of days with ARI varied by a factor of 1.69 and 1.53, respectively, between the lowest and the highest.

These substantial differences have to be kept in mind when studies applying different definitions are compared with respect to incidence of ARI or disease burden of ARI. The discrepancies were mainly caused by differences in the definitions regarding the possibility of one day episodes, the number of symptom-free days, and the considered combinations of symptoms. For instance, five unique one-day-episodes defined by Kusel[6] and Sarna[21] and 26 episodes with a duration between two and eleven days defined by Kusel[6], Sarna[21] and/or Douglas[12] were days with a runny/blocked nose only. A runny/blocked nose only could, especially in summer, be due to allergic rhinitis.[22] On the other hand, a runny/blocked nose could have been caused by a respiratory virus fought by the immune system without causing other symptoms. Four unique one-day-episodes defined by Lambert[19] and one episode with a duration of two days defined by Lambert[19] and Douglas[12] were days with fever only. However, fever may not be specific enough, because fever in children can also be caused by vaccination, other infections, or inflammation processes (e.g. dentition). Another two unique one-day-episodes following the definition by Lambert[19] were days with increased sleep requirement and vomiting, symptoms that could as well have been caused by other illnesses (including gastrointestinal infections). It has to be noted, that the definition used by Lambert et al. [19] was a definition for influenza-like illness (ILI) from an efficacy study evaluating an influenza vaccine.

Further, five one-day-episodes according to two or more of the definitions by Kusel[6], Sarna[21], Lambert[19], and von Linstow[20] that were not part of an episode according to the other two definitions contained typical infectious diseases symptoms like fever and cough, fever and a runny/blocked nose, and cough and a runny/blocked nose,

which might have been infections fought quickly by the immune system that would be missed if two consecutive days with symptoms are required.

The number and duration of episodes further depend on the number of symptom-free days required for a new episode to start. In the definition by von Linstow[20], this was handled in the most extreme way (at least six days). In thirty-seven occurrences ARI episodes according to von Linstow[20] would have been split or ended if at least three consecutive symptom-free days would be required instead of six because they included three to five consecutive symptom-free days. The definition of an illness episode as "new" is problematic as the rules applied regarding the number of symptom-free days seem somewhat arbitrary. They are usually explained by the number of days of the latent phase, however, one could be infected by a second virus while still showing symptoms of an infection from an earlier virus, leading to no symptom-free days but two different ARI episodes as supported by proportions of reported co-infection (two or more viruses) of about 10%.[5, 23]

Taking our study results into account, we come to the following evaluation of the definitions: In the definition by Lambert[19] too many unspecific symptoms are considered and just fever for one day leading to an ARI episode seems questionable. The six symptom-free days required for a new episode to start in the definition by von Linstow[20] lead to very long episodes which might actually be several different infections, leading to an underestimation of the number of ARI episodes. In the definition of Samet[14] two days with at least two symptoms are required for an ARI which might lead to an underestimation of ARI because mild infections causing only one symptom a day are not considered. The definitions by Kusel[6], Douglas[12], and Sarna[21] are most sensitive, yet further research is needed to investigate the specificity especially regarding ARI episodes completely consisting of days with just a

runny/blocked nose (Kusel[6] and Sarna[21]: one day episodes possible, Douglas[12]: two consecutive days with the symptom required) which might actually be due to an allergy and regarding ARI episodes completely consisting of days with just fever (Douglas[12]) which might actually be caused by vaccination, other infections or inflammation processes (e.g. dentition). Regarding the number of symptom-free days between episodes at least three consecutive symptom-free days was the number supported by most of the identified definitions. Yet, further research is necessary to justify this number.

There are several limitations of our study. First of all, the sample size of our cohort study is limited; nevertheless the study was large enough to detect relevant differences between ARI definitions. Second, not all symptoms included in the identified definitions were assessed in our cohort study; identification of the ARI episodes could thus only be based on the symptoms available which could have biased our results. Nevertheless, only trouble breathing, hoarse/sore throat, shortness of breath, muscle aches, headache, irritability, tachypnea, and malaise were not covered in our symptom diary. As the study participants were children less than 3 years of age, items based on child self-reporting (headache, muscle aches, and sore throat) are considered to be not observable[24], therefore overall bias is estimated to be small. Finally, our dataset provided no possibility for validation of the ARI episodes. True validation of the different definitions is only possible using additional data collection tools. One possibility is the confirmation by a physician or nurse, as done in the study by Samet et al. 1993. In this study, only 31 out of 646 ARI episodes (4.8%) defined as such, based on symptoms, were not considered as ARI by the validating nurse who made a diagnosis based on the history of symptoms and a physical examination.[25] Another validation method might be, e.g. a nasal swab. Hence, the detection of a virus very much depends on the collection technique, the

days between the onset of symptoms and the obtainment, and on the days between the obtainment and the freezing/analysis[26] and is not necessarily a "proof" for an infection. The non-finding rate in community-based studies with nasal swabbing of children with respiratory symptoms lies between one quarter and one third.[5, 17, 23] Furthermore, Kusel[6] et al. also found viruses in 24.6% of samples obtained on days without symptoms.[23] Here the question arises if this still would be considered as an infection. Finally, the very small but existing proportion of bacteria as the causal agent for an ARI must be considered which are often not covered in analyses of nasal swabs.[27]

Conclusion

Applying different definitions for ARI episodes to the same cohort study dataset led to considerable differences in the number and duration of ARI episodes. Direct comparisons of study results obtained via different definitions seem therefore questionable. We propose the development of a standardized ARI definition for the use in upcoming cohort studies based on diary data. This process could be conducted using a Delphi survey with experts in this study field. Critical issues are the possibility of one day episodes, the considered combinations of symptoms for the initiation of an ARI episode (e.g. if just a runny/blocked nose or fever are considered as an ARI, or the importance of unspecific symptoms like increased sleep requirement or loss of appetite), and the number of symptom-free days between different ARI episodes.

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