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# Duration of clinical symptoms in children with acute respiratory infection

**Running title: Duration of symptoms in children with acute infection**

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**Abbreviations:** PCR – polymerase chain reaction, RTI – respiratory tract infection, RSV – respiratory syncytial virus, SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2, ED – emergency department, SD – standard deviation

**Key words:** co-, pneumococcus, respiratory pathogen

**Key notes:**

- Only limited data are available the duration of symptoms after infection with common respiratory viruses

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- During acute respiratory infections, 20-30% of children experience clinical symptoms more than 14 days after the onset of infection, and 2-3% have symptoms lasting for more than 28 days.
- Viral and bacterial co-detection appeared to increase the duration of symptoms.


## Abstract

### Aim

To investigate duration of clinical symptoms associated with various respiratory viruses and with the co-detection of respiratory viral and bacterial pathogens.

### Methods

This prospective cohort study included 737 acutely ill children treated in a pediatric emergency department prior to the COVID-19 pandemic. Nasal swab samples were analyzed with multiplex PCR panels for 16 viral and 7 bacterial respiratory pathogens. Parents filled in a questionnaire about the symptoms at the time of the visit and 14 days afterwards.

### Results

Persistent symptoms 2 weeks after the onset of acute illness were common: 32% of the patients with a coronavirus 229E, NL63 or OC43 finding, 31% of those with human metapneumovirus and 25% of those with rhinovirus reported ongoing symptoms. At least one symptom lasting more than 4 weeks was observed in 3-4% of the children. Children with viral and bacterial co-detection had a longer duration of fever than those with only viral detection (3.3 d [SD 2.8] vs. 1.6 d [SD 2.4], $p < 0.001$).

### Conclusion

Symptoms lasting for more than 2 to 4 weeks appear to be relatively frequent in all respiratory viral infections in children. Viral and bacterial co-detection may increase the duration of illness.

## Introduction

Respiratory tract infection (RTI) is one of the most frequent indications for medical care and the prescription of antibiotics in children.[1] During the last decade, molecular diagnostic tools have become widely available for fast, accurate detection of respiratory pathogens associated with RTIs, and several studies using multiplex polymerase chain reaction (PCR) panels for the detection of respiratory pathogens have shown that respiratory viruses are found in 50-90 % of children with acute respiratory infection, including the most commonly detected viruses such as rhinovirus, respiratory syncytial virus (RSV), adenovirus and influenza viruses. Co-infections with multiple viruses and viral and bacterial co-infections have been reported to lead to a longer hospital stay for children.[2-8]

Numerous studies have recently reported that children may suffer from prolonged symptoms lasting for more than 4 weeks after the onset of COVID-19 infection,[9-11] the most commonly described being fatigue, insomnia, headache and respiratory symptoms.[10,11] Limited data are available, however, on the duration of symptoms after infection with other respiratory viruses, and few studies have reported the duration of clinical symptoms associated with various respiratory viruses,[12] as most previous studies have focused on a single pathogen such as influenza virus,[13] rhinovirus[14] or RSV.[15]

We report here on the duration of symptoms related to various respiratory viruses in a cohort study carried out at a pediatric emergency department (ED) during one epidemiological year before the COVID-19 pandemic. We also investigate the impact of viral and bacterial co-detection on the symptoms, using a multiplex PCR for the detection of viral and bacterial pathogens.

## Methods

### *Study design*

The population for this prospective study consisted of children under the age of 16 years examined due to a suspected acute RTI by triage assessment or fever (measured temperature ≥ 38.0 °C) at the pediatric ED in the Department of Pediatrics and Adolescent Medicine, Oulu University Hospital, Oulu, Finland, between September 1, 2014 and August 31, 2015. The frozen samples were analyzed in 2017-2018 and the medical records reviewed in 2019-2020. We did not exclude any children due to underlying disease or age and all the children attending to the ED were included to the study.

All the children with respiratory symptoms such as runny nose, cough or tachypnea or fever underwent nasopharyngeal swabs for respiratory pathogens, and the results of a multiplex PCR for respiratory viruses were available during the next office day as a part of routine clinical practice. Multiplex PCR for respiratory bacteria was performed later on frozen samples.

The parents filled in a questionnaire form during the ED visit regarding symptoms (fever, cough, dyspnea, ear pain, gastrointestinal symptoms, rash and changes in appetite) and their duration up to that time and were sent a follow-up e-mail questionnaire to fill in 2 weeks after the visit. Total duration of the symptoms was the calculated by adding duration of symptoms before the ED visit to duration of symptoms reported by parents in follow up questionnaire. The electronic records for each patient were reviewed manually to confirm the correct diagnoses, any hospitalization, and the laboratory results.

The Ethics Committee of the Northern Ostrobothnia Hospital District at Oulu University Hospital, Oulu, Finland, evaluated and approved the research plan, and the Finnish National Supervisory Authority for Welfare and Health approved the use of frozen samples for bacterial PCR (V/56413/2017). Only children whose parents gave their consent were enrolled in the study.

*Sample collection*

Nurses working at the pediatric ED were trained to collect nasopharyngeal specimens from the children, and an instruction sheet was prepared and distributed to them. Copan FLOQSwabs flocked swabs (Copan Diagnostics, Inc, California, USA) were used for the multiplex real-time PCR for respiratory viruses and bacteria. The nasopharyngeal swab was obtained from each child by passing it through the nostril to the nasopharynx and rotating it at least two or three times to collect epithelial cells. The swab was then inserted into a 3 ml transport medium tube (Universal Transport Media, UTM™; Copan Diagnostics, Inc, California, USA) at room temperature and sent immediately to the clinical microbiological laboratory at Oulu University Hospital (NordLab, Oulu, Finland) for analysis of respiratory viruses on the next office day. The samples were then stored at -80°C for later multiplex PCR analysis for respiratory bacteria.

*Pathogen detection*

The Anyplex™ II real-time PCR (Seegene Inc. Seoul, Korea) was used to test for 16 viral respiratory pathogens (Adenovirus, Influenzaviruses A&B, Parainfluenzaviruses 1-4, Rhinovirus, Respiratory syncytial viruses A & B, Bocavirus, Metapneumovirus, Coronaviruses 229E, NL63 and OC43 and Enteroviruses). The viruses were isolated using nucleic acid by means of the QIAsymphony DSP Virus/Pathogen Mini Kit (Qiagen, Hilden, Germany) and a QIAsymphony SP instrument (Qiagen, Germantown, USA). Correspondingly, the Allplex Respiratory Panel 4 (Seegene Inc. Seoul, Korea) used for bacterial detection was used to target seven respiratory pathogens: *Bordetella parapertussis, Bordetella pertussis, Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Mycoplasma pneumoniae* and *Streptococcus pneumoniae*.

*Statistical analysis*

We calculated median and mean durations and standard deviations (SD) to represent the duration of the selected symptoms in viral and bacterial infections and in co-detections. The results were presented as means and SDs, but the testing was based on ranks of symptom duration. Age-adjusted differences between the viral infections and co-detections were assessed with a non-parametric (Quade's) ANCOVA test, which allows adjustment for covariates when the group distributions are non-Normal.[16] We decided to use Rhinovirus as the most common finding as reference value for testing. The statistical analyses were performed with SPSS 27 software (SPSS Inc., Chicago, IL, USA).

**Results**

*Population*

During the year concerned we recruited 737 children whose parents had filled in the electronic questionnaire (Figure 1) and received follow-up data on 505 of these children. Frozen samples for bacterial PCR were available from 373 children and we received follow-up data for 244 them with a mean age of 34 months (SD 38), 55% of whom were girls. Altogether 201 (40%) children were hospitalized and two were admitted to the pediatric intensive care unit. The children admitted to hospital did not differ from the rest of the population in terms of age, gender or the pathogens detected.

*Detected respiratory pathogens*

Of the 505 children, 346 (69%) were positive for at least one respiratory virus, 56 (11%) for 2 viruses and 5 (1%) for 3 viruses. The most common viruses were rhinovirus (n = 157), adenovirus (n = 48), human metapneumovirus (n = 48) and RSV (n = 39). Of the 244 children with bacterial PCR results and follow-up data available (Figure 1), 118 (48%) had *S. pneumoniae*, the most common pathogen, while *H. influenzae* was identified in 56 (23%) children and *M. pneumoniae* in 2

(0.8%). We did not find any cases that were positive for *C. pneumoniae, L. pneumoniae, B. pertussis* or *B. parapertussis.* Viral-bacterial co-detection was observed in 117 (48%) children.

*Proportion of children with clinical symptoms*

The proportion of children with fever ranged from 54% in those with rhinovirus to 100% in those with the influenza virus (Supplementary Table S1). Dyspnea was most often reported in children with a positive rhinovirus finding (65%) and least common in those with enterovirus (13%).

Symptoms lasting for more than 2 weeks were common, as 32% of the patients with a respiratory virus had at least one persisting symptom 2 weeks after the onset of illness (Table 1). The proportion with persistent symptoms was highest in the children with a positive coronavirus finding (8/25, 32%), followed by those positive for human metapneumovirus (15/48, 31%) and or rhinovirus (46/157, 29%) (Table 1). Symptoms persisting for more than 4 weeks were less common, with only 3.8% of the rhinovirus-positive patients reported as having symptoms 28 days after the onset of illness.

*Duration of clinical symptoms dependent on a respiratory virus finding*

The mean duration of fever was shorter in the children with rhinovirus (1.4 days, SD 2.4) than in those with adenovirus (mean duration 4.0 days, SD 2.7, $p < 0.001$), human metapneumovirus (mean duration 4.0 days, SD 2.6, $p < 0.001$), influenza viruses (mean duration 4.0 days, SD 2.4, $p < 0.001$), coronaviruses (mean duration 2.4 days, SD 2.9, $p = 0.009$) or RSV (mean duration 2.1 days, SD 2.7, $p = 0.006$) (Supplementary figure S1).

The mean duration of dyspnea was significantly longer in children with rhinovirus (mean duration 3.4 days, SD 4.9) than in those with adenovirus (mean duration 1.4 days, SD 3.0, $p = 0.001$), influenza viruses (mean duration 0.7 days, SD 1.2, $p = 0.01$) or coronaviruses (mean duration 0.9 days, SD 1.1, $p = 0.027$). We did not find any significant differences between rhinovirus and the other viruses detected with respect to coughing.

The mean duration of rhinitis ranged from 5.5 (SD 5.2) days in the influenza-positive children to 13.2 (SD 7.6) days in the coronavirus-positive ones (Figure 2) and was longer in the patients with rhinovirus detected than in those with adenovirus (9.0 days, SD 7.0 vs. 5.8 days, SD 6.9, $p = 0.004$). The mean time over which a poor appetite was reported was significantly shorter in the patients with rhinovirus (mean duration 3.3 days, SD 4.0) than in those with adenovirus (mean duration 6.8 days, SD 5.5, $p < 0.001$) or human metapneumovirus (mean duration 5.1 days, SD 4.9, $p = 0.006$).

*Duration of clinical symptoms dependent on viral-bacterial co-detection*

A longer duration of fever was associated with viral-bacterial co-detection than with viral detection alone (mean duration 3.3 days, SD 2.8 days, vs. 1.6 days, SD 2.4 days, $p < 0.001$) (Figure 2), and co-detection was also associated with an increased mean duration of rhinitis (mean duration 9.1 days, SD 7.0 vs. 8.0 days, SD 6.9, $p = 0.029$) and of lack of appetite (5.3 days, SD 5.2 vs. 3.5 days, SD 3.9, $p = 0.024$) relative to the patients with a viral pathogen detected. The duration of symptoms in the viral-bacterial co-detection cases did not differ significantly from that in the cases with viral detection alone with respect to dyspnea or cough.

## Discussion

In this report on the duration of symptoms associated with the detection of nasopharyngeal viral and bacterial pathogens in 737 children attending a pediatric ED approximately 20-30% of the children experienced clinical symptoms more than 2 weeks after the detection of a respiratory virus and a number of them had symptoms lasting for more than 4 weeks. Viral and bacterial co-detection appeared to increase the duration of illness in the children.

Most previous studies of the duration of symptoms associated with respiratory viruses have focused on a single respiratory pathogen such as influenza virus,[13] rhinovirus[14], RSV[15], or SARS-CoV-2.[9-11] An earlier Finnish prospective cohort study reported the median duration of fever to be three days in

children with mild influenza and four days in children with moderate or severe influenza,[17] this was confirmed by the mean duration of four days observed here. Likewise, the median duration of symptoms in children with RSV infection has been reported to be 11 days when under three years of age and nine days when aged from three to six years.[18] While the clinical and socioeconomic burdens of RSV, rhinovirus and influenza have been well noted,[14,17-19] the differences relative to other respiratory viruses in terms of the duration of clinical symptoms were surprisingly small in the present study.

Symptoms lasting for more than two weeks were found to be common in children with a respiratory virus detected, and several of them had symptoms that lasted more than four weeks. The proportion of children with a symptom persisting for four weeks was 3.8% in the present rhinovirus-positive group, which appears to be somewhat similar to the figure of 4.4% reported by Molteni *et al.* in SARS-CoV-2 positive children, for instance.[20] We did not, however, obtain sequential nasopharyngeal samples during the study, so that there may have been sequential respiratory virus infections in these children, which could explain the total duration of symptoms. Our results support the finding of an earlier review that up to 10% of the children with acute respiratory tract infection still had a cough 25 days after the onset of symptoms.[21]

The proportion of children in our cohort who had viral-bacterial co-detections, 48%, is similar to the figure of 58% recently reported by a Korean retrospective study,[22] and the occurrence of viral-bacterial co-detection involving any virus together with *H. influenzae* or *S. pneumoniae,* was found to be positively associated with the duration of fever, rhinitis and lack of appetite to a greater extent than viral infection alone. Many specific virus-bacteria relationships have been observed in the pathogenesis of respiratory infections.[6] *S. pneumoniae* co-infection with influenza, rhinovirus or RSV, for example, has been reported to increase the risk of acute otitis media,[23,24] and pneumococcal colonization of the nasopharynx has been reported to increase the clinical severity of RSV infection in young children.[25] Only a few previous studies, however, have estimated the

clinical impact of co-detections by means of multiplex PCR testing. Colonization with respiratory bacteria, including *S. pneumoniae, H. influenzae* or *M. catarrhalis*, has been reported to increase in nasal wash samples during viral infections,[26] and even though bacterial co-infections have generally been reported to increase the severity of a disease,[27] pneumococcal co-infections have also been reported to reduce the clinical severity of viral infections.[23] On the other hand, although *M. pneumoniae* and *Chlamydophila pneumoniae* have been reported to be important pathogens in children hospitalized for acute respiratory tract infections,[28] we found only two patients with *M. pneumoniae* in our series and none with *C. pneumoniae.*

The main strength of this work lies in the use of multiplex PCR for both respiratory viruses and bacteria in a large cohort of pediatric ED patients with data available on the duration of their symptoms. The population was representative of acutely ill children presenting to a pediatric ED, and as most patients were not hospitalized on account of their illness, patients with less severe infections were also included. There were some limitations, however, the study setting may overestimate duration of symptoms as major part of the children with respiratory infection do not seek medical attention and the mildest infections are not included in the study population. Also, we focused our attention on the duration of symptoms as reported by parents and did not analyze complications such as acute otitis media. Follow up data was collected at one timepoint two weeks after the ED visit. Repeated follow up could have offered more accurate data. Furthermore, follow up of four weeks after the ED visit could have been beneficial. Also, asymptomatic carriage of bacterial pathogens is common in the first years of life, with incidences of up to 50% for *S. pneumoniae* and 30% for *H. influenzae*[29] and the role of asymptomatic carriage of nasopharyngeal bacteria or asymptomatic viral infections could not be assessed in this study. Also, DNA viruses i.e. adenovirus are capable to establish persistent infection or latency in lymphoid organs, such as tonsils, which could explain detection of the virus without active infection. Other limitations were that we did not have bacterial samples from all the patients, that the multiplex PCR

platform did not include *Moraxella catarrhalis*, and that the study was conducted prior to the SARS-CoV-2 pandemic.

**Conclusions**

The duration of clinical symptoms appeared to be fairly similar in children with different respiratory virus detections, and symptoms lasting more than two weeks were common. Viral-bacterial co-detection by multiplex PCR appeared to be associated with an increase in the duration of symptoms.

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Figure 1. Study flow chart

Figure 2. Median duration of certain symptoms associated with viral and bacterial detections and co-detections. Horizontal lines indicate the median duration of symptoms and each dot indicates one study participant. The groups are presented as: V-/B-: no pathogens detected, V-/B+: bacterial detection without any virus detected V+/B-: viral detection without any bacteria detected, V+/B+: viral-bacterial co-detection.

**Table 1. Proportion of children with symptoms persisting for more than 14 days**

| Virus | Rhinovirus | Adenovirus | Metapneumovirus | RSV[b] | Bocavirus | Parainfluenzavirus[c] | Coronaviruses[d] | Influenza -virus[e] | Entero - virus |
|---|---|---|---|---|---|---|---|---|---|
| N[a] | 157 | 48 | 48 | 39 | 32 | 31 | 25 | 23 | 8 |
| | Patients with persisting symptoms n (%) | | | | | | | | |
| Fever | 0 - | 1 (2.1) | 0 - | 0 - | 0 - | 0 - | 0 - | 0 - | 0 - |
| Cough | 28 (18) | 4 (8.3) | 9 (19) | 4 (10) | 2 (6.3) | 5 (16) | 5 (20) | 2 (8.7) | 1 (13) |
| Dyspnea | 7 (3.5) | 0 - | 0 - | 0 - | 0 - | 0 - | 0 - | 0 - | 0 - |
| Rhinitis | 34 (22) | 5 (10) | 11 (23) | 7 (18) | 4 (13) | 3 (9.7) | 7 (28) | 2 (8.7) | 3 (38) |
| Poor appetite | 6 (3.8) | 3 (6.3) | 3 (6.3) | 1 (2.6) | 0 - | 1 (3.2) | 1 (4.0) | 0 - | 0 - |
| Any symptom | 46 (29) | 10 (21) | 15 (31) | 8 (21) | 4 (13) | 5 (16) | 8 (32) | (8.7) | 3 (38) |

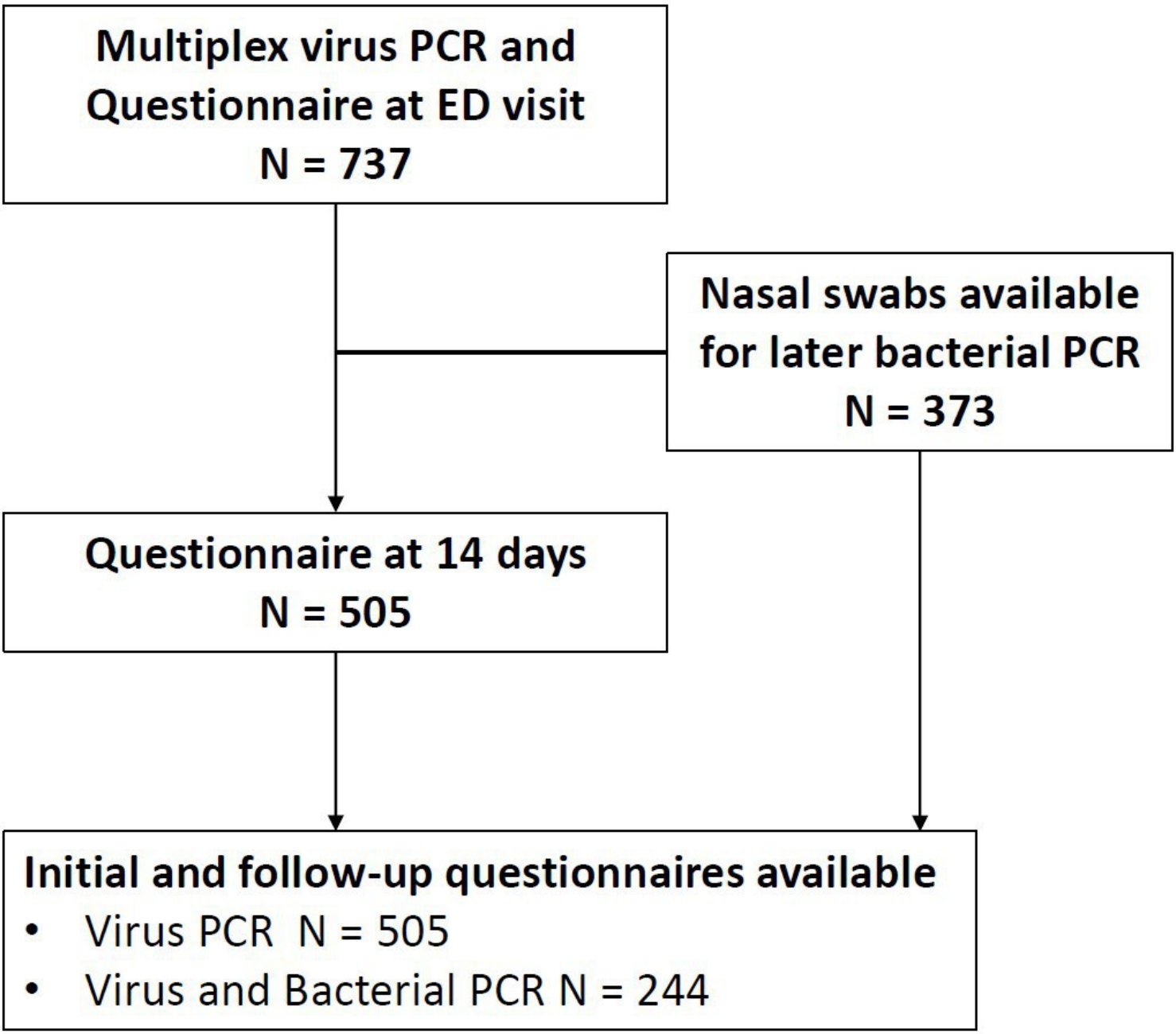
[a] Total of test-positive patients

[b] Combined positive results for Respiratory syncytial viruses A (25) and B (14)

[c] Combined positive results for Parainfluenzaviruses PIN1 (2), PIN2 (2), PIN3 (21) and PIN4 (6)

[d] Combined positive results for Coronaviruses 229E (0), NL63 (4) and OC43 (21)

[e] Combined positive results for Influenzaviruses A (13) and B (10). One patient tested positive for H1N1 virus

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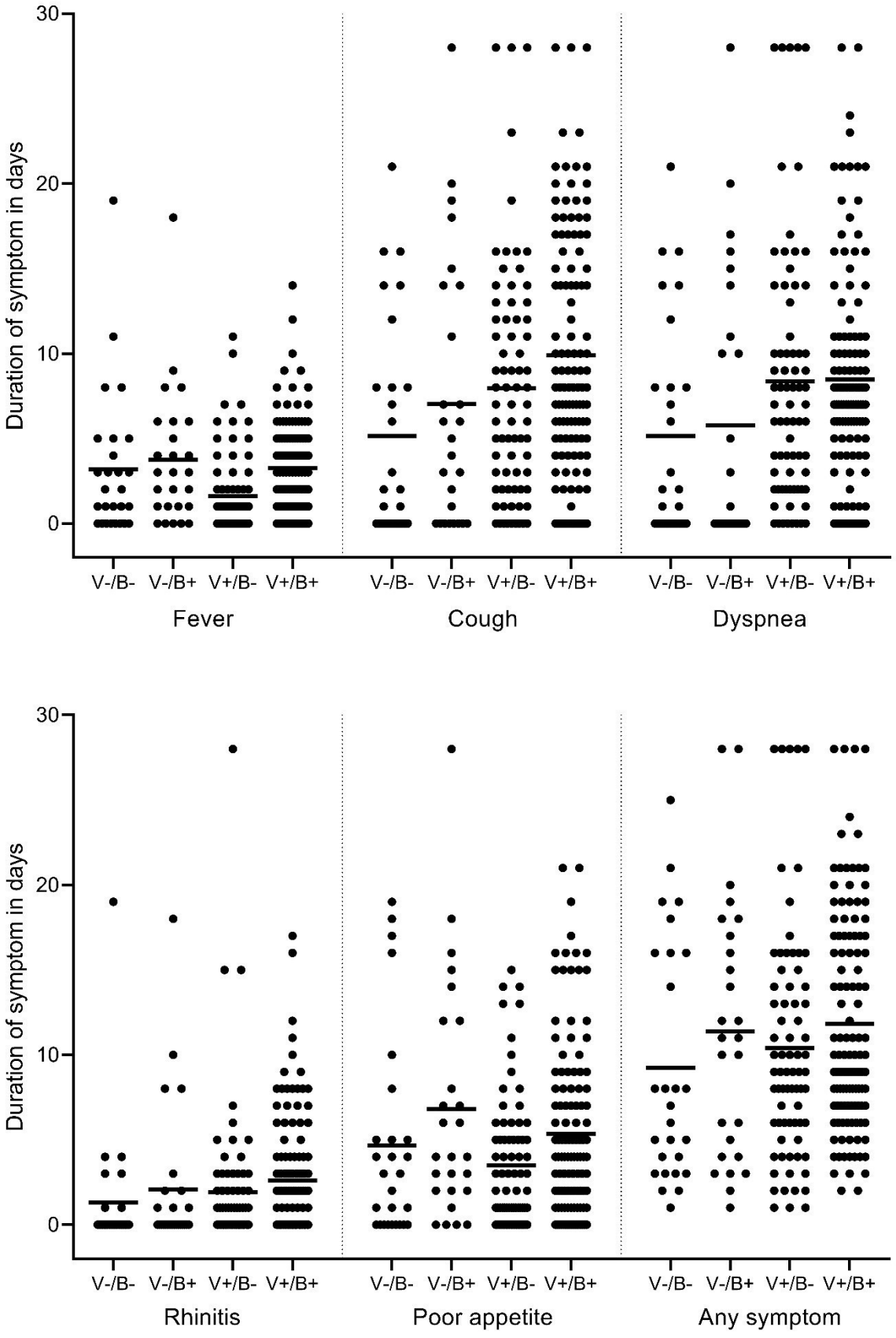


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