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Original article

Impact of multiplex respiratory virus testing on antimicrobial consumption in adults in acute care: a randomized clinical trial

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ABSTRACT

Objectives: Inappropriate use of antibiotics is associated with development of antimicrobial resistance. In respiratory infections it is often difficult to differentiate between viral and bacterial infections, and empirical treatment is common. Enhanced viral testing is expected to clarify clinical decision-making and reduce the prescription of antibacterial agents, but the impact of such information on patient care is unclear.

Methods: We conducted a (1:1) randomized controlled clinical trial involving 998 adults with respiratory symptoms, fever, chest pain or poor general condition in the emergency unit of a tertiary hospital. Multiplex PCR results for 496 patients were available in 24 hours (intervention group) and those for the remaining 502 patients were available in 7 days (control group). Our primary outcome measures were the duration of hospitalization and the consumption of antibiotics within 30 days of enrolment.

Results: In all, 841 of 998 (84%) patients had respiratory symptoms at study entry. A respiratory virus was detected in 175 (17.5%). The mean duration of hospitalization was 4.2 days (SD 5.4) in the intervention group and 4.1 days (SD 4.9) in the control group (difference 0.1, 95% CI –0.5 to 0.6, *p* 0.810). The mean days on antibiotics were 11.3 days (SD 12.6) in the intervention group and 10.4 days (SD 11.4) in the control group (difference 0.9, 95% CI –0.6 to 2.4, *p* 0.235).

Conclusions: Multiplex PCR testing for respiratory viruses with results available within 24 hours did not reduce the consumption of bacterial antibiotics or the length of hospital stay in adults presenting with respiratory symptoms, fever, chest pain or reduced general condition in acute care. **E. Saarela, Clin Microbiol Infect 2020;26:506**

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Introduction

Viral respiratory infections range from common colds to severe, life-threatening diseases, especially in immunocompromised individuals. Differentiation between viral and bacterial respiratory tract infections merely on the grounds of clinical symptoms and signs is challenging. This may lead to excessive use of antibiotics

and a risk of increasing antimicrobial resistance, costs and nosocomial infections, including *Clostridium difficile* [1,2].

Respiratory viruses play a role in the pathogenesis of pneumonia both independently and together with bacteria [3–5], and likewise viral infections can exacerbate asthmatic symptoms and chronic obstructive pulmonary disease [6–10]. Nucleic acid amplification-based methods have been shown to provide rapid, accurate and specific diagnoses of respiratory viral infections [11], but rapid viral diagnostics increase costs, so that these methods should have a clear clinical impact to justify their use [12].

Identification of the influenza virus can reduce the number of hospital admissions, the length of hospitalizations and the duration

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of antimicrobial medication [13], but the evidence regarding the impact of testing for other respiratory viruses is limited. We set out to test in a randomized controlled trial whether active use of multiplex respiratory virus PCR tests can reduce the use of antimicrobial medication in adult patients in acute care. Our hypothesis was that rapid viral diagnostics reduces antibiotic consumption and the length of hospital stay.

Methods

Study design

This randomized (1:1) clinical trial involving adults entering the Internal Medicine Emergency Unit was conducted at Oulu University Hospital from September 2014 to October 2015. This is a tertiary hospital with 800 beds and an emergency department working 24 hours a day. Before the study mainly antigen testing for influenza virus was used. We offered the opportunity to participate in the clinical trial in the emergency room to patients older than 16 years having (a) any respiratory infection symptom such as cough, rhinitis, shortness of breath or sore throat, (b) fever ($>38^{\circ}\text{C}$), (c) chest pain, or (d) poor general condition for an unknown reason. We did not apply any exclusion criteria.

Possible participants were informed about the study by a trained nurse working during office hours on weekdays. After obtaining informed consent, this nurse took nasal swabs for viral detection. The patients were randomly allocated into two groups upon enrolment: a rapid viral diagnostics group (intervention group) and a delayed viral diagnostics group (control group). The attending physician received the viral results for the intervention group within 24 hours, except for samples obtained on Fridays, the results for which were available on the next office day, whereas the viral results for the control group were received 7 days after sampling.

The patients were randomized by a biostatistician into these groups in permuted blocks of four to eight (Fig. 1). After sampling, an opaque envelope corresponding to the numerical order was opened to reveal the group to which the patient belonged. To detect the carriage rate of respiratory viruses we also collected nasal swabs from 75 patients entering the internal medicine emergency unit without respiratory symptoms.

The nasal swab samples, obtained using Copan Floq Swabs™, were analysed in the microbiological laboratory (Nordlab, Oulu) by the multiplex real-time PCR method Anyplex™ II RV16 Detection (Seegene, Seoul, Korea) to detect a range of 16 respiratory viruses: adenovirus, bocavirus, coronavirus OC43/NL63/229E, enterovirus, influenza A/B virus, metapneumovirus, parainfluenza 1/2/3/4 virus, rhinovirus and respiratory syncytial A/B virus. The attending clinicians had access to viral test results according to group (intervention or control) via the web-based system used for routine clinical work and they decided upon the treatment of the patients independently.

The protocol was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District, Oulu, Finland. The trial has the registered number NCT02538770 in the [ClinicalTrials.com](https://www.clinicaltrials.com) database.

Clinical data collection

The nurse collected systematic data from the patients on co-morbidities, current medication and symptoms at entry, and we followed this up 2 weeks later by means of a questionnaire on the duration of the symptoms and any additional medical care needed. We reviewed the medical records after the 30-day follow-up time and extracted data on co-morbidities, the course of the disease, the duration of antibiotic medication, the length of hospitalization and the duration of intensive care. All microbiological and radiological

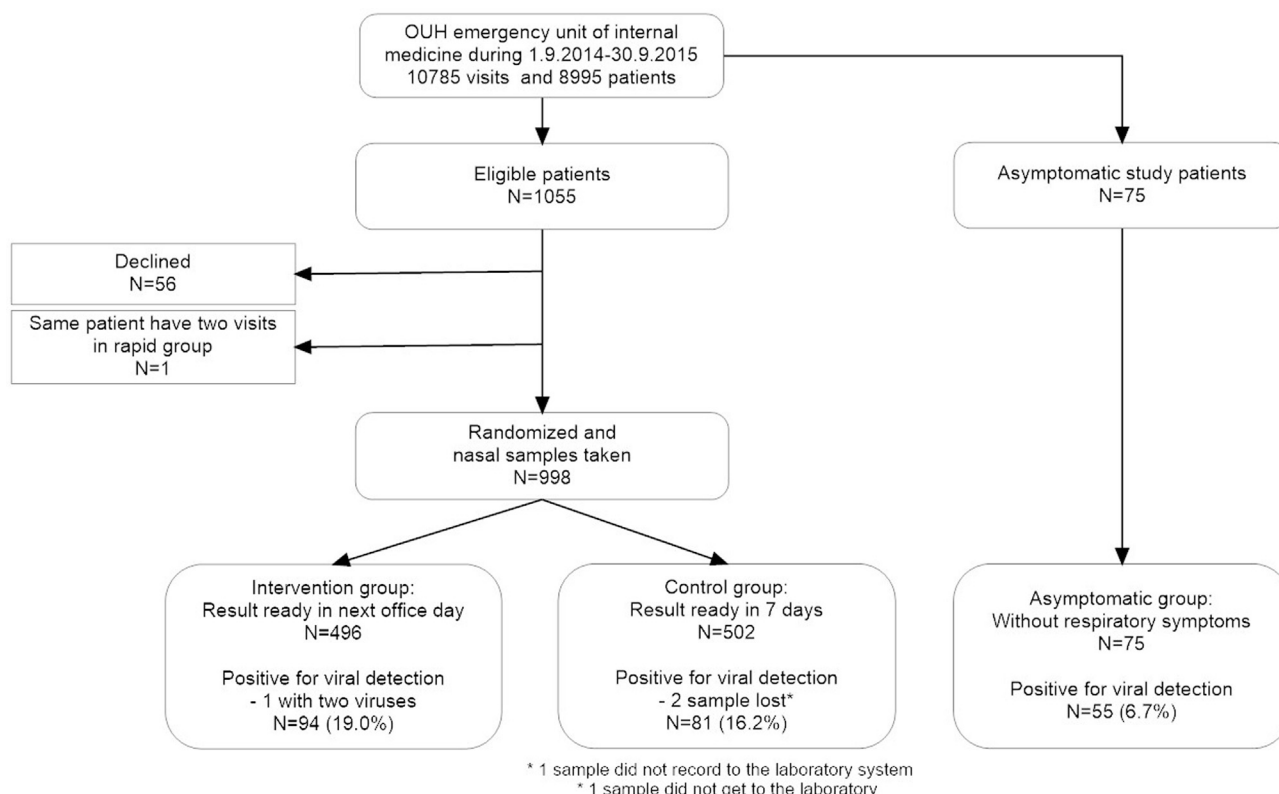


Fig. 1. Study design and flow chart.

findings were recorded, and the number of deceased participants was ascertained from the national population register (Statistics Finland). The total costs of patients' hospital stays were obtained from the hospital administration. The costs of using the multiplex PCR method for respiratory viral detection (€78 per test for the intervention group and €36 per test for the control group) were included in the hospital costs in the case of the intervention group, whereas the detection costs for the control group were covered from the research grants and were not included in the analysis.

Antimicrobial consumption was defined as the use of any antibacterial agent and was ascertained from the medical records, the national electronic prescription database, and information provided by the participants. In this way we knew the precise duration of 96.7% of the courses of antibiotic treatment. For the remaining 3.3% of the courses, we used the estimated duration of 10 days. Prophylactic antibiotics were excluded from the analysis.

Primary outcome

The primary outcome measures were duration of hospitalization and antibiotic consumption. Duration of hospitalization was defined as number of days in hospital within 1 month after randomization. Antimicrobial consumption was defined as the number of days on antibiotics and the number of defined daily doses of bacterial antibiotics within 1 month of enrolment. We also reported the proportion of patients receiving any antibiotic treatment within 30 days. This outcome was also analysed for the first 7 days when the viral results were available for the patients in the intervention group but not for the patients in the control group.

Secondary outcomes

The secondary outcome measures were the number of radiological examinations, the total costs of hospital treatment and the diagnostic procedures. Furthermore, we compared the number of patients requiring intensive care or dying during the 30-day follow up.

Sample size

The appropriate sample size was calculated using the proportion of patients receiving antimicrobial treatment during 30-day follow up as the primary outcome measure. The estimated proportion of these patients was 75%. We regarded a 10% absolute reduction in proportion of patients receiving antibiotics in the intervention group as a clinically significant change. To gain a power of 90% with a type I error of 0.05, one would need 920 participants, 460 in each group. To achieve this we decided to recruit 1000 participants.

Statistical analyses

Two proportions were compared using the Standardized Normal Deviate test and differences together with their 95% CIs were reported. The durations of antibiotic treatment were compared using Student's *t* test and mean differences with 95% CIs of the mean difference were reported. All the analyses were performed following the intention-to-treat principle using the IMB SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) and STATS DIRECT version 3.1.14 (StatsDirect Ltd, Birkenhead, UK) statistical programs.

Results

Population

A total of 998 eligible patients were included in our trial, of whom 496 were randomly allocated to the intervention group and

502 to the control group (Fig. 1). The groups were comparable in terms of age and co-morbidities (Table 1). In the intervention group 429/496 (87%) had at least one respiratory symptom on entry; in the control group this number was 412/502 (82%). One-third of the patients were immunosuppressed in both groups. From the 496 patients in the intervention group, 334 (67%) were hospitalized as were 350 (70%) of the 502 patients in the control group.

A respiratory virus was detected in 175 patients, 94 (19%) in the intervention group and 81 (16%) in the control group (Table 2). One patient had rhinovirus and coronavirus OC43 in his sample and all the others had only one virus. In the control group without respiratory symptoms, 5/75 (6.7%) patients had positive virus findings.

Primary outcome

A total of 684 (69%) patients were admitted to Oulu University Hospital, the mean duration of hospitalization being 4.2 days (SD 5.4) in the intervention group and 4.1 days (SD 4.9; difference 0.1, 95% CI –0.5 to 0.6) in the control group (Table 3). The mean duration of antibiotic treatment in all study patients within 1 month was 11.3 days (SD 12.6) in the intervention group and 10.4 days (SD 11.4) in the control group (difference 0.9, 95% CI –0.6 to 2.4). There was no statistically significant difference between the groups. Antibiotic consumption in mean defined daily doses was 0.38 (SD

Table 1
Background characteristics

	Intervention group (n = 496)	Control group (n = 502)
Age (years), mean (SD)	61.7 (17.0)	61.4 (17.6)
Male, n (%)	263 (53)	263 (52)
Any co-morbidity, n (%)	373 (75)	354 (71)
Chronic lung disease	167 (34)	153 (30)
Chronic heart disease	171 (34)	167 (33)
Chronic neurological disease	73 (15)	72 (14)
Diabetes	109 (22)	99 (20)
Immunosuppression ^a	152 (31)	143 (28)
Antibiotic treatment at entry ^b , n (%)	266 (54)	264 (53)
Symptoms at entry, n (%)		
Any respiratory symptom	429 (87)	412 (82)
Cough	281 (57)	253 (50)
Rhinitis	158 (32)	162 (32)
Sore throat	136 (27)	115 (23)
Shortness of breath	343 (69)	317 (63)
Other possible infection symptoms		
Fever (>38.0°C)	242 (49)	232 (46)
Chest pain	221 (45)	226 (45)
Poor general condition	428 (86)	415 (83)
Diagnostic procedures		
Blood culture obtained	276 (56)	279 (56)
Positive blood culture	8 (2.9)	17 (6.1)
<i>Escherichia coli</i>	2 (25)	8 (47)
<i>Streptococcus pneumoniae</i>	3 (38)	5 (29)
<i>Staphylococcus aureus</i>	2 (25)	0
Other	1 (13)	4 (24)
Urine culture obtained	238 (48)	256 (51)
Positive urine culture	41 (17)	49 (19)
Thoracic imaging, chest X-ray or CT	473 (95)	467 (93)
Point-of-care influenza testing performed	120 (24)	108 (22)
POC positive for influenza	21 (18)	8 (7.4)
Discharged home from ER	112 (23)	107 (21)

Abbreviations: ER, emergency unit; POC, point of care.

Data are n (%) of patients, unless otherwise indicated.

^a Defined as a previously or currently treated cancer (except skin cancer other than melanoma), immunosuppressive medication as a minimum 5 mg of daily prednisolone, primary immune deficiency requiring immunoglobulin treatment, human immunodeficiency virus infection, liver cirrhosis, organ transplantation, splenectomy.

^b Patients with antibiotic treatment before entry and those with antibiotic treatment started in the emergency unit included.

Table 2
Viruses detected in patients

	All patients (n = 998) I = 496/C = 502	Radiological pneumonia ^a (n = 180) I = 104/C = 76	COPD or asthma ^b (n = 64) I = 28/C = 36	>65 years old (n = 476) I = 246/C = 230	Immuno- suppressed (n = 295) I = 152/C = 143
Rhinovirus					
Intervention	41 (8.3)	10 (9.6)	9 (21.1)	13 (5.3)	9 (5.9)
Control	45 (9.0)	6 (7.9)	7 (19.4)	14 (6.1)	11 (7.7)
Influenza B virus					
Intervention	15 (3.0)	1 (1.0)	0	7 (2.8)	6 (3.9)
Control	5 (1.0)	0	0	1 (0.4)	2 (1.4)
Metapneumovirus					
Intervention	9 (1.8)	4 (3.8)	1 (3.6)	5 (2.0)	4 (2.6)
Control	10 (2.0)	2 (2.6)	0	4 (1.7)	3 (2.1)
Coronaviruses					
Intervention	5 (1.0)	1 (1.0)	1 (3.6)	3 (1.2)	2 (1.3)
Control	7 (1.4)	1 (1.4)	1 (2.8)	2 (0.9)	2 (1.4)
Influenza A virus					
Intervention	8 (1.6)	2 (1.9)	0	7 (2.8)	3 (2.0)
Control	3 (0.6)	0	1 (2.8)	2 (0.9)	2 (1.4)
RSV					
Intervention	6 (1.2)	2 (1.9)	0	3 (1.2)	1 (0.7)
Control	4 (0.8)	0	1 (2.8)	3 (1.3)	1 (0.7)
Parainfluenzaviruses 1–4					
Intervention	5 (1.0)	1 (1.4)	0	1 (0.4)	2 (1.3)
Control	5 (1.0)	0	1 (2.8)	3 (1.3)	4 (2.8)
Adenovirus					
Intervention	5 (1.0)	1 (1.0)	0	3 (1.2)	4 (2.6)
Control	2 (0.4)	1 (1.4)	0	0	0
Enterovirus					
Intervention	1 (0.2)	0	0	0	0
Control	0	0	0	0	0
Any virus					
Intervention	95 ^c (19.2)	21 (20.2)	11 (39.3)	42 (17.1)	31 (20.4)
Control	81 (16.1)	11 (14.5)	11 (30.6)	29 (12.6)	25 (17.5)

Abbreviations: COPD, chronic obstructive pulmonary disease; I, intervention group; C, control group; RSV, respiratory syncytial virus.

Bocavirus was also tested for, but not found.

Data are n (%) of patients.

^a Radiologically confirmed pneumonia.^b Patients with acute exacerbation of asthma or chronic obstructive pulmonary disease.^c One patient had two viruses in his sample.**Table 3**
Primary and secondary outcomes

	Intervention group n = 496	Control group n = 502	Difference (95% CI)	p value
Primary outcome				
Duration of hospitalization (days), mean (SD)	4.2 (5.4)	4.1 (4.9)	0.1 (–0.5 to 0.6)	0.810
Days on antibiotics within 30 days, mean (SD)	11.3 (12.6)	10.4 (11.4)	0.9 (–0.6 to 2.4)	0.235
Mean daily DDDs within 30 days (SD)	0.38 (0.42)	0.35 (0.38)	0.03 (–0.02 to 0.80)	0.235
Patients with antibiotic treatment in 30 days, n (%)	317 (64)	322 (64)	0 (–6.2 to 5.7)	0.895
Within 7 days	302 (61)	307 (61)	0 (–6.3 to 5.7)	0.897
Secondary outcomes				
Radiological examinations, mean (SD)	2.5 (3.3)	2.2 (3.0)	0.2 (–0.3 to 0.8)	0.407
Total costs of hospital treatment, mean (SD)	3539 (7303)	3339 (6664)	200 (–669 to 1069)	0.652
Radiological examinations, mean (SD)	262 (404)	223 (385)	39 (–14 to 92)	0.148
Laboratory costs, mean (SD)	440 (774)	374 (580)	147 (62–232)	0.001
Admitted to ICU, n (%)	27 (5.4)	33 (6.6)	–1.1 (–4.2 to 1.9)	0.429
Death within 30 days, n (%)	15 (3.0)	15 (3.0)	0.0 (–2.1 to 2.3)	0.999

Abbreviations: DDD, defined daily dose, ICU, intensive care unit.

Differences are either differences in proportions or differences in means, depending on the values concerned. Costs are reported in euros.

0.42) per day in the intervention group and 0.35 (SD 0.38) per day in the control group (difference 0.03, 95% CI –0.02 to 0.80). A total of 317/496 patients (64%) in the intervention group and 322/502 (64%) in the control group received antimicrobial treatment during the 30-day period (Fig. 2). During the first 7 days, 61% (609/998) of the patients in both groups received antibiotic treatment (Table 3).

Secondary outcomes

The mean number of radiological examinations was 2.5 (SD 3.3) in the intervention group and 2.2 (SD 3.0) in the control group

(difference 0.2, 95% CI –0.3 to 0.8). There was no statistically significant difference between groups. The mean of the total costs of hospital treatment per patient was higher (€3539 (SD €7303)) in the intervention group than in the control group (€3339 (SD €6664), difference 200, 95% CI –669 to 1069), as were the mean costs of the radiological examinations (€262 (SD €404) versus €223 (SD €385), difference 39, 95% CI –14 to 92). The laboratory expenses were also higher in the intervention group, but it should be remembered that the costs of multiplex PCR testing were included in the laboratory costs in the case of the intervention group but not in the control group.

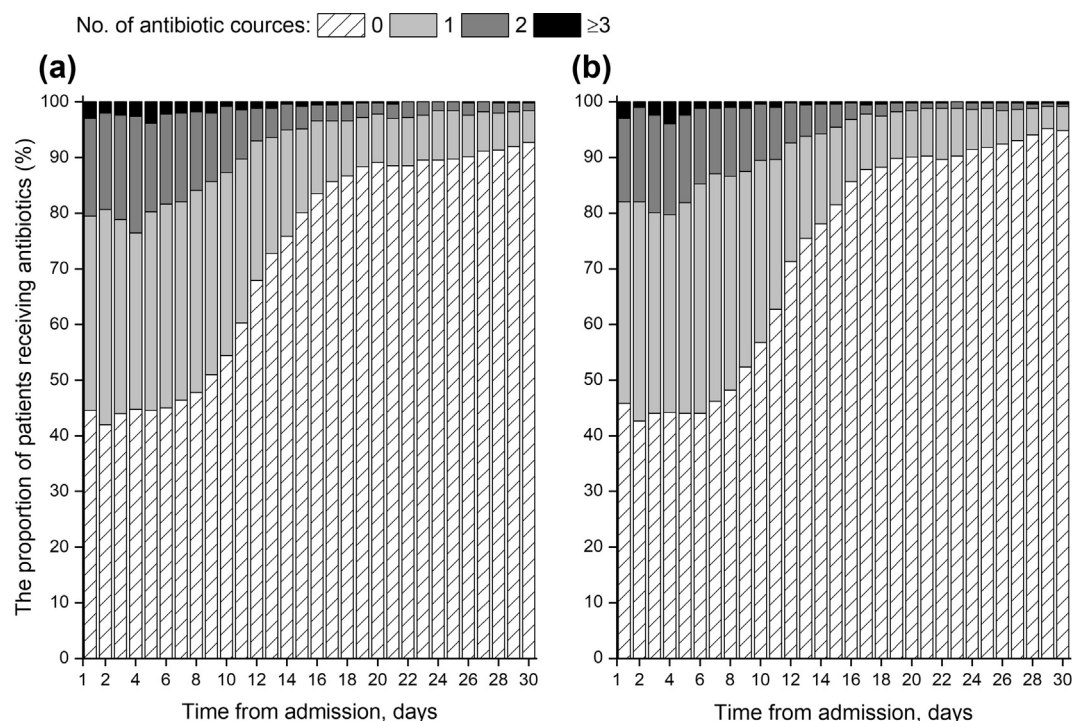


Fig. 2. The proportion of patients receiving antibiotics by day. In the intervention group (a) the results of viral testing were given in 24 hours and in the control group (b) the results were given in 7 days.

Altogether 5.4% ($n = 27$) of the patients in the intervention group and 6.6% ($n = 33$) in the control group required treatment in the intensive care unit and 30 participants (3.0%) died during the 30-day follow up, 11 of 15 receiving antibiotics in the intervention group and 13 of 15 in the control group (Table 3).

Discussion

Antibiotic resistance has been recognized as a major problem worldwide, and there is an urgent need to find ways of reducing the use of antibiotics and targeting them better to gain the best possible benefit with lowest risk to individuals and society. Active diagnosis of respiratory pathogens has been proposed as one potential solution to this problem. However, in our randomized controlled trial, the knowledge of the results of multiplex respiratory virus testing did not reduce antimicrobial consumption in adults in acute care. Sixty-four per cent of the participants in both the intervention and control group received antibiotics during the 30-day follow-up period and there were no differences in the antibiotic days, defined daily doses or duration of hospital care between the groups.

Several randomized studies aiming to reduce antibiotic consumption by means of improved diagnostics have been conducted in recent years. In one randomized controlled trial in the UK, adult patients presenting at hospital with acute respiratory illness or fever were randomized into two groups, for either a molecular point-of-care test for respiratory viruses or routine care. Over 80% of the patients in both groups received antibiotics and the mean duration of antibiotics remained unchanged [14]. Also, when viral detection was combined with serum procalcitonin (PCT) measurement and an algorithm for interpreting the PCT results was provided there was no significant difference in antibiotic use [15]. However, a subgroup analysis in this randomized controlled trial conducted with individuals with non-pneumonic lower respiratory tract infections in a US community hospital showed shorter duration of antibiotic treatment in the algorithm-adherent patients, and

fewer patients with positive viral testing and low PCT values were discharged with antibiotics. A large randomized trial of 1656 patients with suspected lower respiratory tract infection, covering 14 US urban academic hospitals obtained the same result. There was no difference in days on antibiotics or in adverse events between the standard care group and the intervention group, which had an additional viral testing and PCT measurement provided with graded recommendations for antibiotic use based on PCT levels [16]. In a Canadian quasi-experimental before-and-after study combining virology testing with an antimicrobial stewardship intervention, a 1.3-day decrease in mean days on antibiotics was noted compared with the previous year [17]. Without counselling, physicians seem to respond less to positive viral results other than influenza and rely more on radiographic findings when deciding on antibiotic treatment, as shown in a prospective observational study conducted in a Canadian tertiary hospital [18].

The reasons for interventions failing to reduce antibiotics in acutely ill adults may be due to clinicians' anxiety in the face of poor outcomes. Lower respiratory tract infections were the sixth most common cause of death in high-income countries in 2016 [19], and it is reported that influenza and pneumonia cause over 51 000 deaths annually in the USA [20]. In an observational study of Medicare patients aged ≥ 65 years, mortality among hospitalized individuals with community-acquired pneumonia was 11% [21]. The incidence of pneumonia rose five-fold and mortality was doubled as age increased from 65–69 years to >90 years [21]. A secondary analysis of the EPIC study, in which in-hospital deaths of pneumonia patients were evaluated, noted that only 2.2% of the patients died in tertiary hospitals but 63.4% of these were at least 65 years old and 61.5% had at least two co-morbidities [22]. Many patients in internal medicine emergency units belong to these high-risk groups.

The fact that the proportion of patients with a virus detected in their nasal swab was low, only 17.5%, can be largely explained by the definition of our population. We recruited patients with respiratory infection symptoms and also patients with chest pain

and poor general condition to see whether respiratory viruses play a role in these conditions and to evaluate whether viral testing should be part of the routine diagnostics. There were subgroups with more positive results, however, in that 34% of the patients tested for influenza had some respiratory virus detected. Influenza-like symptoms have been associated with more positive virus detections in other studies as well [23]. Even though 31%–39% of our participants with asthma or chronic obstructive pulmonary disease had a virus detected, this was true of only 6%–11% of the individuals with acute coronary syndrome, suggesting that targeting the testing to patients with respiratory infection symptoms or respiratory co-morbidities would probably be more beneficial.

We chose to test the impact of rapid viral diagnostics on reducing antimicrobial consumption in acutely severely ill adults in a tertiary hospital due to extremely high antibiotic consumption in these patients. Antimicrobial resistance is an increasing problem and at least in Europe the burden of infections with antibiotic-resistant bacteria is highest in infants and in people aged ≥ 65 years [24,25]. The threat of poor outcome is particularly present in the elderly [21,22].

The strengths of the study are the randomized study design, the large sample size, the broad panel of viruses and the high quality of data due to collection from different sites of information. Our large population provides statistical power for detecting differences between the groups, so that the series serves well to represent the real-life situation in an emergency room. The more convenient nasal sampling has shown no difference compared with nasopharyngeal swabbing in influenza virus detection [26]. The outcome measure of antibiotic consumption is clinically relevant and topical, and the Anyplex II multiplex PCR detection method represents the highest quality diagnostics available at the time, the sensitivity of the test being 95.2% [27].

One limitation of this study is that even in the intervention group, the viral detection results were received about 24 hours after sampling, so that this information was not available during the primary evaluation of the patient. This concerns particularly those individuals that were discharged home from the emergency room. The low number of viruses may also be considered as a limitation. Partially this was due to an exceptionally low incidence of viral epidemics during our study. Annual variation in the severity of viral outbreaks is a well-known phenomenon, which could only be controlled in a clinical trial by extending the study period to several years. As Finland is a country with fairly low antibiotic consumption, the effect might have been more prominent in a different setting.

In conclusion, multiplex respiratory virus testing with the results available within 24 hours did not reduce the consumption of antibiotics in this randomized controlled trial. It should be noted that point-of-care tests providing multiplex respiratory pathogen results directly in the emergency room were not used here but would be an interesting topic to investigate in the future.

Transparency declaration

The authors declare no competing interest related to the study. This work has been supported by the Research Foundation of the Pulmonary Diseases, Finland, and by grants from the Northern Ostrobothnia Hospital District, Finland.

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