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More targeted use of oseltamivir and in-hospital isolation facilities after implementation of a multifaceted strategy including a rapid molecular diagnostic panel for respiratory viruses in immunocompromised adult patients

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ABSTRACT

Background: Immunocompromised adults are more vulnerable to a complicated course of viral respiratory tract infections (RTI).
Objectives: Provide evidence on the effect of implementation of rapid molecular diagnostics for viruses on use of in-hospital isolation facilities, oseltamivir and antibiotic usage, and other clinical outcomes in immunocompromised patients.
Study design: A before-after study during two consecutive respiratory viral seasons, including immunocompromised adult patients presenting at a tertiary care emergency department with clinical suspicion of RTI. During the first season (2016/2017), respiratory viruses were detected using inhouse real-time PCR. The second season (2017/2018), we implemented a diagnostic flowchart including a rapid molecular test for 15 respiratory viruses (FilmArray®). We assessed the effect of this implementation on need for isolation, antivirals and empirical antibiotics.
Results: We included 192 immunocompromised adult patients during the first and 378 during the second season. Respiratory viral testing was performed in 135 patients (70%) during the first and 284 (75%) during the second season (p = 0.218) of which 213 (75%) using the rapid test. After implementation, use of in-hospital isolation facilities was reduced (adjusted odds ratio 0.35, 95%CI 0.19-0.64). Furthermore, adequate use of oseltamivir improved, with fewer prescriptions in influenza negative patients (0.15, 95%CI 0.08-0.28) and more in influenza positive patients (11.13, 95%CI 1.75–70.86). No effect was observed on empirical antibiotic use, hospital admissions, length of hospital stay or safety outcomes.
Conclusions: Implementation of rapid molecular testing for respiratory viruses in adult immunocompromised patients results in more adequate use of oseltamivir and in-hospital isolation facilities without compromising safety.

1. Background

Respiratory viruses are increasingly recognized as important causative pathogens in acute respiratory tract infections (RTI) in up to 50% of patients, depending on the season in which these viruses are detected [1–3]. Moreover, the number of immunocompromised patients is increasing due to ageing of the population, increased prevalence of chronic diseases as well as treatment with immunosuppressive agents [4,5]. Although immunocompromised patients have similar etiologies of acute RTI when compared to immunocompetent patients [6], they more often have a complicated course of the disease leading to high healthcare burden, especially in secondary and tertiary care settings [7,8]. Within the respiratory viral season, in-hospital isolation facilities are often falling short due to the high number of patients with suspected

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Table 1
Baseline characteristics (n = 570)[a].

Characteristics	2016/2017 (n = 192)	2017/2018 (n = 378)	*p*-value[b]
Age (years)	61.2 (48.9 - 69.4)	62.6 (50.7 - 70.8)	0.303
Male gender	95 (49.5%)	209 (55.3%)	0.189
Reason immunocompromised[c]			
Corticosteroid use > 700 mg cumulative last 6 months	110 (57.3%)	219 (57.9%)	0.883
Anti-CD20, biologicals[d] or anti-rheumatics last 6 months	39 (20.3%)	67 (17.7%)	0.453
Solid organ transplantation last 6 months	45 (23.4%)	114 (30.2%)	0.091
Stem cell transplantation last 6 months	8 (4.2%)	10 (2.6%)	0.326
Neutropenia (< 0.5 × 10 ^{9}/L)	12 (6.3%)	22 (5.8%)	0.838
CD4-penia (< 200 cells/mm^2)	5 (2.6%)	6 (1.6%)	0.521
Asplenia or hyposplenia	7 (3.6%)	9 (2.4%)	0.388
Primary immunodeficiency	2 (1.0%)	11 (2.9%)	0.236
Hypogammaglobinemia	7 (3.6%)	8 (2.1%)	0.281
Comorbidities[e]			
Cardiovascular disease	127 (66.1%)	271 (71.7%)	0.173
Active malignancy	64 (33.3%)	149 (36.4%)	0.156
Chronic Obstructive Pulmonary Disease	53 (27.6%)	173 (45.8%)	< .001
Diabetes Mellitus	49 (25.5%)	100 (26.5%)	0.810
Origin from other health institution or hospital	9 (4.7%)	18 (4.8%)	1.000
Admitted during past 90 days	58 (30.2%)	113 (29.9%)	0.938
Duration of symptoms (days)	3 (1 - 7)	3 (1 - 6)	0.949
Observations at Emergency Department			
Coughing	142 (74.0%)	305 (80.7%)	0.065
O^2 needed	101 (52.6%)	165 (43.7%)	0.043
Temperature (^{o}C)	37.9 (37.3 - 38.8)	37.7 (37.0 - 38.5)	0.018
Heartrate (beats per minute)	101 (89 - 115)	98 (85 - 110)	0.013
Systolic blood pressure (mmHg)	127 (110 - 143)	130 (114 -145)	0.062
Respiratory rate (beats per minute)	20 (16 - 24)	18 (15 - 24)	0.038
Diagnostic findings at the Emergency Department			
CRP (mg/L)	72 (29 - 140)	52 (18 - 108)	0.006
White cell count (x10^9/L)	9.7 (5.6 - 13.6)	9.6 (6.3 - 13.5)	0.885
Neutrophils (x10^9/L)	6.79 (2.57 - 11.03)	6.93 (3.14 - 11.21)	0.460
Lymphocytes (x10^9/L)	1.22 (0.61 - 2.28)	1.39 (0.66 - 2.87)	0.884
Infiltrate on chest X-ray at Emergency Department	86 (44.8%)	160 (42.3%)	0.572
Working diagnosis pneumonia at Emergency Department	107 (55.7%)	178 (47.1%)	0.051

[a] Binary variables are presented as absolute numbers and percentages, continuous variables are presented as median with interquartile range (IQR).
[b] *p-values* were calculated using Pearson's chi square test to compare proportions between groups and an independent sample *t*-test to compare means for normally distributed continuous variables and Mann-Whitney U test for non-normally distributed continuous variables.
[c] 363 patients have one reason to be immunocompromised, 174 patients have two reasons and 33 patients have three.
[d] Biologicals included: adalimumab, etanercept, golimumab, leflunomide, mepolizumab, nivolumab, nivolumab/ipilimumab, omalizumab, pembrolizumab.
[e] Comorbidities were defined as any cardiovascular disease or diabetes mellitus requiring medication and any active malignancy for which curative or palliative treatment was initiated. Obstructive pulmonary diseases were defined as asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) or cystic fibrosis (CF).

viral infections and immunocompromised patients with prolonged viral shedding [9,10]. Rapid and accurate detection of respiratory viruses by molecular diagnostics might lead to more targeted use of in-hospital isolation facilities [11] and improvement of other clinical outcomes due to more targeted antibiotic and antiviral therapy [12]. However, current evidence on the effect of implementation of rapid molecular testing on clinical outcomes and hospital resource use is heterogeneous and inconclusive. Most studies only focus on immunocompetent patients, do not specifically address the viral respiratory season, are of low quality due to their design or lack of proper adjustment for potential confounders [13–22], whereas randomized studies [11,23–26] evaluating effects within a research setting with perfect implementation of diagnostic assays, may lead to over-optimistic results.

2. Objectives

In the current study, we therefore aimed to assess the effect of rapid molecular diagnostic testing for respiratory viruses implemented in regular care presenting with suspected RTI in a tertiary University Medical Centre (UMC).

3. Study design

3.1. Study design and data collection

We performed an observational before-after cohort study. Patients were included at the emergency department (ED) of the UMC Utrecht, a 1042 bedded teaching hospital and a referral center for, among others, treatment of hematological malignancies, organ transplantation and HIV, located in the center of the Netherlands. Patients ≥18 years were included when they were immunocompromised at the time of presentation and presented with the clinical suspicion of a RTI, which was defined according to the definition of the World Health Organization, with measured fever of ≥38 °C, cough and onset within the last 10 days [27]. Pneumonia was defined as having visible new infiltrates at chest X-ray. Immunocompromised was defined as the use of corticosteroids (prednisone or equivalent, cumulative dose > 700 mg), anti-CD20 therapy, biologicals (TNF-alpha inhibitors, interleukin-5 inhibitors and monoclonal antibodies), methotrexate, azathioprine and/or mercaptopurine within the last 6 months, having received an autologous/allogenic stem-cell transplantation, having neutropenia (< 0.5 × 10^9/L), (functional) hypo/asplenia, CD4-penia (< 200 cells/mm^3), hypogammaglobinemia and/or having another primary immunodeficiency.

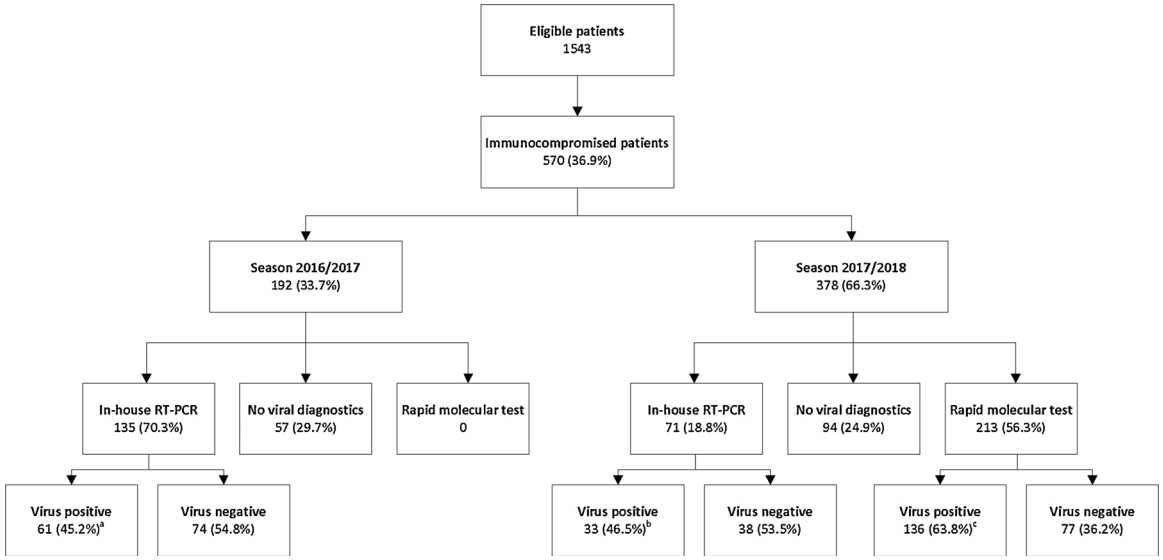

Fig. 1. Flowchart of included patients (n = 570).
[a]In 11 patients two viruses were detected and in one patient three viruses were detected.
[b]In 10 patients two viruses were detected.
[c]In one patient two viruses were detected.

Patients were included during two consecutive epidemic respiratory viral seasons (± 2 weeks), as determined by the National Institute for Public Health and the Environment. During the 2016/2017 season the inclusion period lasted from week 46 through week 12 (duration of 19 weeks) and during the 2017/2018 season from week 48 trough week 17 (duration of 22 weeks).

The primary endpoints were the use of antibiotics < 72 h after ED presentation, oseltamivir use and the use of in-hospital isolation facilities, e.g. private rooms with appropriate droplet precautions to avoid further circulation of respiratory viruses, in admitted patients. Secondary outcomes included hospital admissions, the duration of empiric antibiotic treatment (until switch or discontinuation), duration of oseltamivir treatment and the length of hospital stay and the length of stay inhospital isolation facilities in admitted patients. Furthermore, we assessed adverse outcomes – defined as 30-day mortality and/or intensive care admission (composite endpoint), representation at the ED and hospital readmission within 30 days – and potential disadvantageous effects, defined as length of ED stay, the use of additional common diagnostics for RTI, e.g. blood cultures, sputum cultures, *Streptococcus pneumoniae* urine antigen tests (PUAT) and *Legionella pneumophilia* urine antigen tests (LUAT), and > 1 chest X-ray within the first 72 h of admission.

Data were collected from the electronic patient files and the hospital clinical microbial system (GLIMS version 9.5). The study obtained ethical approval from the UMC Utrecht local ethics committee during both seasons (protocol numbers 16-692/C and 17-659/17–659/C).

3.2. Diagnostic procedures

During the first season, in-house real-time polymerase chain reaction (RT-PCR) was used for the detection of respiratory viruses [28]. Nucleic acids were extracted using the total nucleic acid protocol with the MagNA Pure LC nucleic acid isolation system (Roche Diagnostics, Basel, Switzerland). For detection of RNA viruses using the Universal Master Mix, cDNA was synthesized first using MultiScribe RT and random hexamers (Applied Biosystems, Foster City, CA). Detection of viral pathogens was performed in parallel, using laboratory developed RT-PCR assays specific for the following viruses: respiratory syncytial virus; influenza virus A and B; parainfluenza virus 1–4; rhinoviruses; bocaviruses; enteroviruses; adenoviruses; human coronaviruses OC43, NL63, and 229E; human metapneumovirus. Samples were assayed in a 25-μL reaction mixture containing 10 μL of cDNA/RNA, 12.5 μL of either TaqMan Fast virus 1-Step Master Mix, TaqMan Universal PCR Master Mix (Applied Biosystems), or 2.5 μL primer-probe mix. Amplification was performed using a Taqman 7500 instrument (Applied Biosystems) in two different protocols. For the targets detected with the Fast virus 1-Step Master Mix (influenza virus, RSV, rhinovirus, enterovirus, parainfluenza virus type 1 and 3) the amplification profile was 5 min 50 °C, 20 s 95 °C, 45 cycles of 3 s 95 °C, and 30 s 60 °C. For the other targets the amplification profile was 2 min 50 °C, 10 min 95 °C, 45 cycles of 15 s 95 °C, and 1 min 60 °C. To monitor for inhibition, a fixed amount of an internal control virus (murine encephalomyocarditis virus [RNA virus] and porcine herpesvirus [DNA virus]) was added before extraction [29]. The cut-off value for a positive result was set at a Cycle threshold (Ct) value < 45 [30]. Right before the second season we implemented a rapid molecular diagnostic test with a reported mean turnaround time of 2.3 h (SD 1.4 h) [11] - the FilmArray® respiratory viral panel version 1.7 (BioFire Diagnostics) - for simultaneous detection of a panel of respiratory viruses similar to the in-house RT-PCR. Additionally, the FilmArray® detects a couple of bacterial pathogens, *Bordetella pertussis, Bordetella parapertussis, Chlamydophila pneumoniae and Mycoplasma pneumoniae*, for which the assay however was not validated in our laboratory and results were neither reported for clinical practice nor for this study. The FilmArray® contains all needed reagents in a freeze-dried format for extraction, amplification, and detection steps. The FilmArray® test was performed according to the manufacturer's instructions. In brief, prior to run 1 ml of hydration solution and 300 μl of respiratory sample was added to the reagent pouch. The pouch was then placed on the FilmArray® instrument and the test performed using the FilmArray® system. After extraction and purification of all nucleic acids from the sample, a nested multiplex PCR is performed followed by an individual singleplex second-stage PCR reactions to detect the products from the first-stage nested PCR. The FilmArray® was available as diagnostic assay on weekdays between 8am-8pm and on weekend days and national holidays between 8–12 am. If samples were collected outside these opening hours, the rapid test was performed the following morning. Instructions on nasopharyngeal sampling were similar for the in-house RT-PCR and the FilmArray® and both tests were ordered by sending the sample plus application form to the clinical virology laboratory. All respiratory

Table 2
Detected viruses (n = 74)[a] and bacteria (n = 36)[b] during the 2016/2017 season and detected viruses (n = 180)[c] and bacteria (n = 51)[d] during the 2017/2018 season.

Respiratory viruses	2016/2017	2017/2018	*p*-value[e]
Adenovirus	–	1 (0.6%)	1.000
Bocavirus	3 (4.1%)[f]	–	0.024
Coronavirus	14 (18.9%)	18 (10.0%)	0.052
Human metapneumovirus	4 (5.4%)	10 (5.6%)	1.000
Influenza A	23 (31.1%)	30 (16.7%)	0.010
Influenza A H1/2009	–	10 (5.6%)	0.068
Influenza A H3	20 (27.0%)	13 (7.2%)	< .001
Influenza B	1 (1.4%)[g]	64 (35.6%)	< .001
Parainfluenza virus 1 - 4	3 (4.1%)	2 (1.1%)	0.150
Rhinovirus	11 (14.9%)	25 (13.9%)	0.841
Respiratory Syncytial Virus	15 (20.3%)	30 (16.7%)	0.493
Streptococcus pneumoniae	11 (30.6%)[h]	22 (43.1%)	0.239
Haemophilus influenzae	8 (22.2%)	11 (21.6%)	0.947
Pseudomonas aeruginosa	5 (13.9%)	8 (15.7%)	0.818
Other gram positive bacteria	6 (16.7%)[i]	4 (7.8%)[j]	0.202
Other gram negative bacteria	6 (16.7%)[k]	6 (11.8%)[l]	0.517

[a] During the 2016/2017 season (n = 192), 49 patients had a viral mono-infection, 11 had a viral coinfection and 1 patient had a viral triple infection, leading to a total number of 74 viruses (in 61 patients); 74 tested virus negative and 57 were not tested.

[b] During the 2016/2017 season (n = 192), 11 patients had a bacterial mono-infection, 15 had a viral-bacterial coinfection (of whom 1 with 2 bacteria), 3 had a bacterial coinfection and 1 had a bacterial triple infection, leading to a total number of 36 bacteria (in 30 patients).

[c] During the 2017/2018 season (n = 378), 158 patients had a viral mono-infection, 11 had a viral coinfection, leading to a total number of 180 viruses (in 169 patients); 115 tested virus negative and 94 were not tested.

[d] During the 2017/2018 season (n = 378), 26 patients had a bacterial mono-infection and 23 had a viral-bacterial coinfection (of whom 2 with 2 bacteria), leading to a total number of 51 bacteria (in 49 patients).

[e] *p-values* were calculated using a Pearson's chi square test or Fisher's exact test, as appropriate.

[f] Percentages of viruses were calculated using the viral denominator of that season (74 vs 180).

[g] There was only one Influenza B detection during the 2016/2017 season, which was in line with national trends in the distribution of Influenza A and B.

[h] Percentages of bacteria were calculated using the bacterial denominator of that season (36 vs 51).

[i] Other gram positive bacteria found during the 2016/2017 season: *Staphylococcus aureus* (n = 5), *Staphylococcus haemolyticus* (n = 1).

[j] Other gram positive bacteria found during the 2017/2018 season: *Staphylococcus aureus* (n = 3), *Enterococcus faecium* (n = 1).

[k] Other gram negative bacteria found during the 2016/2017 season: *Klebsiella pneumoniae* (n = 1), *Legionella pneumophila* (n = 1), *Neisseria meningitidis* (n = 1), *Stenotrophomonas maltophilia* (n = 1), *Citrobacter koseri* (n = 1) and *Morganella morganii* (n = 1).

[l] Other gram negative bacteria found during the 2017/2018 season: *Klebsiella pneumoniae* (n = 3), *Escherichia coli* (n = 1), *Moraxella catarrhalis* (n = 1), *Proteus mirabilis* (n = 1).

samples were collected in universal transport media and transported similarly, both the in-house RT-PCR and the FilmArray® were located in the clinical virology laboratory and handled in a standardized manner by trained technicians and all results were subsequently approved by a clinical virologist. Results of the rapid assay were directly reported to the treating physician by phone as were the positive test results of the in-house RT-PCR. In addition, results of both assays were reported in the electronic patient file.

During both seasons, the decision to perform microbiological procedures was left to the treating physician. Bacteria were defined causative when found in PUAT/LUAT, bronchoalveolar lavage culture, blood culture (in absence of another infection source) and/or accurately performed (< 10 squamous epithelial cells and > 25 neutrophils per low power field) sputum culture meeting pathogen-specific threshold criteria [31,32].

Furthermore, we enforced specific ED instructions for the management of patients presenting with a suspected RTI during the respiratory viral season (*Supplementary Text 1*). These instructions contained a flowchart and guideline for decision making on a (rapid) molecular diagnostic test performance, treatment with oseltamivir for (suspected) influenza and ribavirin [33,34] for respiratory syncytial virus (RSV) and application of in-hospital isolation facilities for (suspected) influenza virus, RSV, human metapneumovirus, adenovirus and/or parainfluenza virus. The implementation procedure consisted of plenary instructions for ED nurses and internal medicine and pulmonology physicians, distribution of pocket cards and a launch of all instructions on the internal hospital protocol website.

3.3. Statistical analysis

Analyses were performed using SPSS version 25 (IBM Corp, 2012). Multiple imputations were used to account for missing data. We used both determinants, confounders and outcome variables in the imputation model and we imputed missing values under the assumption of *missingness at random*. Differences between patients included during the first and second season were assessed by univariate analysis using a Pearson's Chi-square test or Fisher's exact test for differences in proportions for binary variables and Mann-Whitney *U* test for continuous variables, as appropriate. We compared outcomes between the two seasons using adjusted odds or risk ratios with a 95% confidence interval (CI) from multiple logistic or (log) linear regression, controlling for age, all covariates with an univariate *p*-value < 0.2 [35] and differences in viral prevalence for outcomes on antivirals and in-hospital isolation facilities. Stratified analyses were performed for influenza virus positive and negative patients for the use of oseltamivir. A *p-value* < 0.05 was considered statistically significant.

4. Results

During the two inclusion periods, 1543 patients presented with a suspected RTI, of whom 570 patients (36.9%) were immunocompromised. Patients had a median age of 62 years (interquartile range 50–70), 53.3% (n = 304) were male and 39.6% (n = 226) had a pre-existing chronic obstructive pulmonary disease (COPD) (Table 1). Of these 570 patients, 192 patients (33.7%) were included during the 19 weeks inclusion period within the 2016/2017 respiratory viral season and 378 patients (66.3%) were included during the 22 weeks inclusion period within the 2017/2018 season (Fig. 1). During the second season, more patients had COPD (45.8% vs 27.6%, p < 0.001). Both seasons had a comparable proportion of patients with signs of pneumonia, 86 patients (44.8%) vs 160 patients (42.3%) (p = 0.57). Overall, antibiotics were prescribed in 71.4% of patients, in 147 patients (76.5%) in first season and 260 (68.8%) in the second season. Overall, 61.7% received beta-lactam antibiotic monotherapy, e.g. amoxicillin, penicillin, amoxicillin-clavulanic acid, cefuroxime, ceftriaxone, cefotaxime, cefazolin or ceftazidime, and 9.6% beta-lactam antibiotics in combination with macrolides or fluoroquinolones. There were no differences between the two seasons in the proportion of patients who received narrow or broad spectrum antibiotic therapy or atypical coverage.

Of all patients tested during the first season (n = 135), 61 (45.2%) tested virus positive versus 169 (59.5%) patients during the second season (n = 284). Overall, influenza A and B virus were the most frequently identified viruses and accounted for 46.5% of all detected viral pathogens (Table 2). During the first season, influenza A(H3) virus was the predominant virus (27.0% of detected viral pathogens), while during the second season, influenza B virus was predominant (35.6% of detected viral pathogens). During the first season, 30 patients (15.6%) had bacterial infections, as compared 49 patients (13.0%) during the second season (p = 0.40) (Table 2), of which 15 and 23 viral-bacterial coinfections, respectively.

Table 3
Comparison of clinical outcomes (n = 570)[a].

Clinical outcomes	2016/2017 (n = 192)	2017/2018 (n = 378)	Unadjusted OR/RR (95%CI)	Adjusted OR/RR (95%CI)
Antibiotics given	147 (76.6%)	260 (68.8%)	0.68 (0.45-1.01)	0.83 (0.51-1.36)
Duration antibiotics until switch (days)[d]	3 (2-7)	4 (2-7)	1.16 (0.99-1.36)	1.05 (0.89-1.23)
Duration antibiotics until stop (days)[d]	7 (6-11)	7 (6-10)	0.98 (0.86-1.11)	0.99 (0.87-1.13)
Oseltamivir treatment given	80 (41.7%)	105 (27.8%)	0.54 (0.37-0.78)	0.25 (0.15-0.43)[b]
Oseltamivir given to influenza positives	17/24 (70.8%)	83/93 (89.2%)	3.42 (1.14-10.25)	11.13 (1.75-70.86)
Oseltamivir given to influenza negatives	63/168 (37.5%)	22/285 (7.7%)	0.14 (0.08-0.24)	0.15 (0.08-0.28)
Duration oseltamivir treatment (days)[d]	0 (0-2)	0 (0-2)	1.90 (1.54-2.36)	0.99 (0.78-1.26)[b]
Duration in influenza positives (days)[d]	5 (0-7)	5 (5-7)	0.87 (0.69-1.09)	0.79 (0.60-1.03)
Duration in influenza negatives (days)[d]	0 (0-2)	0 (0-0)	1.56 (1.08-2.24)	1.10 (0.78-1.79)
Admission to ward or HC unit	140 (72.9%)	240 (63.5%)	0.65 (0.44-0.95)	0.87 (0.54-1.41)
Length hospital stay if admitted (days)[d]	6 (3-10)	5 (3-10)	0.95 (0.79-1.14)	1.00 (0.83-1.21)
Admission in in-hospital isolation facility	79/140 (56.4%)	100/240 (41.7%)	0.52 (0.36-0.84)	0.35 (0.19-0.64)[c]
Duration isolation if admitted (days)[d]	1 (0-3)	0 (0-3)	1.40 (1.11 - 1.78)	1.22 (0.94-1.58)[c]
Blood culture taken at ED	145 (75.5%)	281 (74.3%)	0.94 (0.63-1.40)	1.95 (1.13-3.37)
Sputum culture taken at ED	53 (27.6%)	144 (38.1%)	1.64 (1.12-2.40)	1.56 (1.01-2.42)
PUAT and LUAT taken at ED	79 (41.1%)	124 (32.8%)	0.70 (0.49-1.00)	0.84 (0.54-1.29)
> 1 chest X-ray done < 72 h if admitted	46/140 (32.9%)	61/240 (25.4%)	0.70 (0.44-1.11)	0.68 (0.40-1.14)
30 day mortality and/or HC admission	43 (22.4%)	53 (14.0%)	0.57 (0.36-0.89)	0.86 (0.50-1.50)
Representation ED within 30 days	42 (21.9%)	83 (21.9%)	1.01 (0.66-1.53)	1.00 (0.64-1.56)
Readmission hospital within 30 days	35 (18.3%)	72 (19.0%)	1.06 (0.68-1.65)	1.00 (0.62-1.61)
ED length of stay (hours)[d]	3:43 (2:51 – 4:29)	4:01 (3:07 - 5:10)	1.08 (1.01-1.15)	1.08 (1.01-1.16)

ED, emergency department; HC, high care; OR, odds ratio; PUAT/ LUAT, *S. pneumoniae* and *L. pneumophilia* urinary antigen tests; RR, rate ratio.

[a] Binary outcome variables are expressed as number with percentage and continuous outcomes as median with IQR per season. From univariate and multivariate analysis, results are presented as OR for binary variables and RR for continuous outcomes. In multivariate analysis, ratios are adjusted for age and baseline characteristics with a p-value < 0.2 (gender, solid organ transplantation within the last 6 months, active malignancy, cardiovascular comorbidities, pulmonary comorbidities, coughing, O^2 need, temperature, heartrate, respiratory rate, SBP, CRP and signs of pneumonia at the ED).

[b] Additionally adjusted for differences in test result between the two seasons (n = 192 vs n = 378) for influenza virus (n = 24 vs n = 94).

[c] Additionally adjusted for differences in test results between the two seasons among admitted patients (n = 140 vs n = 240) for influenza virus (n = 16 vs n = 50), RSV (n = 11 vs n = 18), adenovirus (n = 0 vs n = 1), human metapneumovirus (n = 3 vs n = 5) and/or Parainfluenza virus (n = 2 vs n = 0).

[d] OR/RR calculated after conversion of continuous outcome to natural logarithm.

Implementation of the rapid molecular test and ED instructions led to a reduction in patients treated with oseltamivir (41.7% vs 27.8%, p < 0.001) (Table 3). When stratified, we observed that influenza virus positive patients received more oseltamivir prescriptions (70.8% vs 89.2%, p = 0.011) and influenza virus negative patients fewer (37.5% vs 7.7%, p < 0.001). Also, the number of admitted patients who needed in-hospital isolation facilities was significantly reduced (56.4% vs 41.7%, p = 0.001). We observed no significant effect on the proportion of patients who received empirical antibiotic treatment within 72 h of ED presentation (76.6% in the first season vs 68.8% in the second season, p = 0.458) or on the duration of antibiotics. Furthermore, we observed no effect on hospital admissions, length of hospital stay in admitted patients, the number of PUAT and LUAT taken at the ED, and the proportion of admitted patients receiving more than one chest X-ray within the first 72 h of admission. Also, there was no difference in any adverse outcomes between the two seasons. Significant disadvantageous effects were observed on the number of blood cultures taken at the ED (75.5% vs 74.3%, p = 0.017), the number of sputum cultures (27.6% vs 38.1%, p = 0.046) and length of stay at the ED (3:43 h vs 4:01 h, p = 0.020). When stratified based on admission, a significant increase in ED stay was only observed in non-admitted patients (p = 0.035) and not in admitted patients (p = 0.192).

5. Discussion

We assessed the effects of implementation of a rapid molecular diagnostic panel for respiratory viruses and specific ED instructions in immunocompromised adult patients presenting at the ED during the respiratory viral season. Implementation of these diagnostic interventions resulted in more targeted use of oseltamivir and in-hospital isolation facilities, without evidence of an increase in adverse outcomes. This is in line with a previous randomized study assessing the effect of rapid testing for respiratory viruses in mainly immunocompetent patients that observed an increase in oseltamivir use from 65% to 91% in influenza virus positive patients [11]. More targeted use of oseltamivir in influenza positive patients may not only lead to better individual patient outcomes [36], but may also lead to more rapidly decreased viral loads and thereby reduce secondary infections [37,38]. Additionally, the reduction of prescriptions in influenza virus negative patients (38% to 8%) may lead to less side effects [39]. A decrease in use of in-hospital isolation measurements, which is in line with the results of the same large randomized study [11], partially solves the recurrent logistical problem of a shortage in hospital beds during the crowded respiratory viral season. We did not perform an official costs-benefit analysis. However, based on the €hr concept [40] a substantial beneficial effect can be expected, since the rapid diagnostic test is as expensive as in-house RT-PCR in our setting and the implementation of specific instructions do not involve substantial costs, while the median turnaround time and isolation days are reduced considerably.

Rapid molecular testing for respiratory viruses did not reduce antibiotic prescriptions and the duration of antibiotic treatment in immunocompromised patients. The lack of significant results on these outcomes might be due to insufficient power of our study, and due to our vulnerable, immunocompromised patient population, in whom withholding or discontinuing antibiotic treatment is not according to (inter)national recommendations. Nevertheless, these results are in line with most former studies, mostly among immunocompetent patients, that also showed no reduction in antibiotic prescriptions [11,14,19,22,24,41,42]. Only two observational studies [15,16] showed a significant effect, but both validity and generalizability were problematic in these studies due to inadequate adjustment for potential confounders and specific patient selection [15]. The duration of antibiotic treatment was reduced in only one study among otherwise healthy children with uncomplicated acute RTI [14], whereas all studies among adult patients observed no effect [11,19,24–26,41,43]. Even though most studies show no effect on antibiotics, there might still

be potential for rapid molecular testing for respiratory viruses in antibiotic stewardship programs. This is supported by a randomized study that observed a significant reduction in single dose antibiotic prescriptions and antibiotics prescribed for less than 48 h [11]. Clear instructions or guidelines on whether to withhold antibiotics or to prescribe narrow spectrum antibiotics should however accompany the introduction of rapid molecular test for respiratory viruses to have maximum effect [43].

In contrast to similar studies, we were unable to show a reduction in the number of hospital admissions or length of hospital stay [11,41], which might also have resulted from our vulnerable patient population, a lack of power and the absence of 24/7 availability of the rapid molecular test, resulting in longer assay turnaround times overnight and during weekends. The absence of a difference in adverse events between the two seasons was similar to other studies [11,14,16,21,24,43]. The increase in the length of patient ED stay, especially in non-admitted patients, might be explained by waiting time for rapid viral test results, although we had no formal numbers on the proportion of patients for whom the rapid test result was available before leaving the ED, e.g. for clinical and bed management decision making. However, given the intense and crowded viral season of 2017/2018 with twice as many patients as during the previous season, this might also have resulted from overall longer ED turnaround times during the second season. Anyhow, rapid acquirement of respiratory samples, subsequent transportation to the laboratory and sufficient capacity of the rapid diagnostic test might reduce turnaround times of the results and thereby waiting times at the ED.

To our knowledge, this is the first study to assess the effect of regular care implemented rapid molecular testing for respiratory viruses in immunocompromised adult patients. Other studies have focused on immunocompetent patients, which make former results less applicable in tertiary care centers with a large proportion of immunocompromised patients. Furthermore, with our non-randomized design in which the implementation of the rapid diagnostics for respiratory viruses during the second season was not 100%, we provide a truthful reflection of daily practice. Our study also has several limitations. First, given the before-after design of the study, outcomes can be biased due to residual confounders. However, we thoroughly adjusted our analyses for differences at baseline using a liberal p-value to select confounding factors and differences in viral pathogens for certain clinical outcomes. We thereby reduced the effect of confounders more thoroughly than former before-after studies on rapid molecular testing [14–18,41]. Second, differences between the two seasons might also have been affected by trends in time not resulting from the diagnostic intervention per se. Adjustment for any possible trends in time with an interrupted time series analysis would have been appropriate. However, due to the short timeframe in this study and a limited number of patients per time point, this analysis was not feasible [44]. Also, we tried to maximize the potential effect of rapid testing by accompanying the implementation of this assay with specific instructions for the ED, by which we limited the possibility to distinguish the effect of the instructions and the rapid test as a sole intervention. Finally, our study was a single center study and clinical outcomes as antibiotic and antiviral prescriptions might be influenced by local protocols and guidelines, making results potentially less generalizable to other settings.

In conclusion, our study demonstrates that implementation of a rapid molecular test for the detection of respiratory viruses in adult immunocompromised patients who present at the ED with acute RTI, results in more targeted use of oseltamivir and in-hospital isolation facilities. The standard use of a rapid molecular test for respiratory viruses may therefore be recommended for these patients in daily practice.

Credit author statement

The diagnostic intervention was designed and implemented by LV, AR and JJO. LV designed the study and wrote the manuscript. LV and JW selected RSV screened patients for inclusion in the current study and collected clinical data of all included patients from the Electronic Patient Files. AH, KK and JJO were involved in clinical supervision. LV carried out the analyses of the data. All authors critically reviewed the manuscript and provided valuable comments.

Conflicts of interest

None of the authors have commercial or other associations that might pose a conflict of interest.

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Ethical approval

This study obtained ethical approval from the local ethics committee of the University Medical Center Utrecht, protocol numbers 16-692/C and 17-659/C.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.jcv.2019.04.003.

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