**REVIEW**

# Impact of multiplexed respiratory viral panels on infection control measures and antimicrobial stewardship: a review of the literature

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## Abstract

Multiplexed respiratory viral panels (MRVP) have recently been added to the diagnostic work-up of respiratory infections. This review provides a summary of the main literature of MRVP for patients with regard to 3 different topics. Can the results of MRVP reduce the inappropriate use of antibiotics, can they guide the use of appropriate antiviral therapy and do they have an added value with respect to infection control measures? Literature was searched for based on a defined search string using both the PubMed and Embase database. Twenty-five articles report on the impact of MRVP on antibiotic therapy. In all the articles where active antimicrobial stewardship was performed (e.g., education/advice on interpreting results of MRVP) ($N = 9$), a reduction in antibiotic therapy was shown (with exception of 2 studies). Three studies evaluating the effect of MRVP on antimicrobial use in a population that is not suspected of having bacterial pneumonia (e.g., absence of radiology suggestive for bacterial infection or low PCT) found a positive impact on antibiotic therapy. Eight studies with a short TAT ($< 7$ h) had a positive impact on use of antibiotic therapy. Eleven studies focused on the impact of MRVP on antiviral use. In contrast to antibiotic reduction, all studies systematically objectified improved antiviral use as a consequence of MRVP results. With regard to the impact of MRVP on infection control, eleven articles were withheld. All these studies led to a more accurate use of infection control measures by detecting unidentified pathogens or stopping isolation precautions in case of a negative MRVP result. MRVP don't reduce antibiotic therapy in all populations. Reduction seems more likely if the following factors are present: active antimicrobial stewardship, low likelihood of a bacterial infection, and a short turnaround time to result. With respect to antiviral therapy, all studies have an impact but the targeted use of antivirals is so far not that evidence based for all viral respiratory pathogens. Regarding infection control measures, the potential impact of MRVP is high because of the need of additional isolation precautions for many respiratory viruses, although logistical problems can occur.

**Keywords** Respiratory · Multiplex · Infection control · Antimicrobial stewardship

## Introduction

Respiratory infections are considered among the most important type of infections with an enormous impact on society [1]. This impact is reflected in the large number of hospital visits for both adults and children, where respiratory viral infections (RVI) are the most important reason to seek medical care [2, 3]. The diagnostic work up of these infections has changed tremendously over the last decades. With regard to laboratory diagnostics specifically, molecular methods have been added to the conventional laboratory diagnostics such as culture and antigen detection. Furthermore, the development of new molecular technologies has improved the capability to simultaneously detect multiple targets in a single run [4, 5]. Because these multiplexed respiratory viral panels (MRVP) are relatively new, the medical world is struggling with the proper actions to take based on the information yielded by these tests. The added value to improve insights into the epidemiology of RVI seems irrefutable [6]. However, the exact added clinical value of these tests seems less straight forward. This review tries to provide a summary of the main literature of

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MRVP with regard to 3 different topics. Can the results of MRVP reduce the inappropriate use of antibiotics? When is there a significant impact of MRVP on antiviral therapy? What is the added value of MRVP with respect to infection control?

## Methods

We performed a literature search on August 21th, 2021, using the PubMed and Embase database and included articles published before January 1st, 2021. The search strings that were used are provided in Table 1. The Pub-Med search resulted in 636 articles, and the Embase search resulted in 659 articles. After removal of duplicates, 1145 articles were withheld. These articles were subjected to the inclusion and exclusion criteria presented in Table 1. Additional articles were found using backward and forward citation tracking.

## Results

The results are presented in Table 2. Twenty-five articles ($N = 16$ for adults, $N = 5$ for children, $N = 4$ for mixed population) report on the impact of MRVP on antibiotic therapy. In all the articles where active antimicrobial stewardship was performed (e.g., education/advice on interpreting results of MRVP) ($N = 9$), a reduction in antibiotic therapy was shown (with exception of 2 studies). Three studies evaluating the effect of MRVP on antimicrobial use in a population that is not suspected of having bacterial pneumonia (e.g., absence of radiology suggestive for bacterial infection or low PCT) found a positive impact on antibiotic therapy. Eight studies with a short TAT ($< 7$ h) had a positive impact on use of antibiotic therapy.

Eleven studies ($N = 8$ for adults, $N = 3$ for mixed population) focused on the impact of MRVP on antiviral use. In contrast to antibiotic reduction, all studies systematically objectified improved antiviral use as a consequence of MRVP results.

With regard to the impact of MRVP on infection control, eleven articles ($N = 5$ for adults, $N = 4$ for children, $N = 2$ for mixed population) were withheld. All these studies led to a more accurate use of infection control measures by detecting unidentified pathogens or stopping isolation precautions in case of a negative MRVP result. An overview of respiratory viruses commonly included in MRVP, and their recommended isolation precautions is summarized in Table 3.

**Table 1** Search string, inclusion, and exclusion criteria

| Search string |
| --- |
| PubMed: |
| ("Adolescent, Hospitalized"[Mesh] OR "Child, Hospitalized"[Mesh] OR patient) AND ("Multiplex Polymerase Chain Reaction"[Mesh] OR "Multiplex Ligation Dependent Probe Amplification" OR "Multiplex Ligation-Dependent Probe Amplification" OR "PCR Multiplex" OR "Multiplex PCR") AND ("Infection Control"[Mesh] OR "infection control" OR "Hospitals, Isolation"[Mesh] OR "Patient Isolation"[Mesh] OR "Patient Safety" OR Safety OR isolation OR "Anti-Infective Agents"[Mesh] OR "Anti Infective Agents" OR "Antiinfective Agents" OR Antiinfective OR Microbicides OR Antimicrobial OR "Anti-Microbial Agents" OR "Anti Microbial Agents" OR "Anti-Bacterial Agents"[Mesh] OR Antibiotic OR Antibiotics OR "Anti-Bacterial Compounds" OR "Anti Bacterial Compounds" OR "Anti Bacterial Agents" OR "Antibacterial Agents" OR "Bacteriocidal Agents" OR Bactericides OR "Antiviral Agents"[Mesh] OR "Antiviral Drugs" OR Antivirals OR antiviral) AND (Respiratory OR "Respiratory Tract Diseases"[Mesh]) |
| Embase: |
| ('hospitalized adolescent'/exp OR 'hospitalized child'/exp OR patient) AND ('multiplex polymerase chain reaction'/exp OR "Multiplex Ligation Dependent Probe Amplification" OR "Multiplex Ligation-Dependent Probe Amplification" OR "PCR Multiplex" OR "Multiplex PCR") AND ('infection control'/exp OR "infection control" OR 'isolation hospital'/exp OR 'patient isolation'/exp OR "Patient Safety" OR Safety OR isolation OR 'antiinfective agent'/exp OR "Anti Infective Agents" OR "Antiinfective Agents" OR Antiinfective OR Microbicides OR Antimicrobial OR "Anti-Microbial Agents" OR "Anti Microbial Agents" OR "anti-bacterial agents" OR Antibiotic OR Antibiotics OR "Anti-Bacterial Compounds" OR "Anti Bacterial Compounds" OR "Anti Bacterial Agents" OR "Antibacterial Agents" OR "Bacteriocidal Agents" OR Bactericides OR 'antivirus agent'/exp OR "Antiviral Drugs" OR Antivirals OR antiviral) AND (Respiratory OR 'respiratory tract disease'/exp) |
| Inclusion and exclusion criteria: |
| (1) The study must report on the impact of MRVP on infection control measures and/or antimicrobial stewardship. |
| (2) The MRVP had to obtain information regarding at least 2 different viruses (and less than 6 bacteria.) |
| (3) Quantitative (non-)randomized studies, quantitative descriptive studies (including case reports), qualitative studies, (systematic) reviews and meta-analysis were all included provided that they were published in a peer reviewed journal. Conference proceedings and personal narratives were excluded. |
| (4) Studies written in English were considered. |
| (5) Studies conducted in developing countries were excluded. |

Table 2 Overview of studies reporting on the impact of MRVP on antibiotic use, antiviral therapy and infection control

| Reference | Population | Initial method | Evaluated method | Design | Time to result | Active antimicrobial stewardship? | Effect on antibiotic therapy |
|---|---|---|---|---|---|---|---|
| A. Antibiotic use | | | | | | | |
| [7] | Nonpneumonic LRTI hospitalized adults | Conventional + duplex PCR influenza/RSV (hospital PCR) | Initial + PCT + Film Array respiratory Panel (Biofire, Utah, USA) | RCT | Duplex PCR: 1–2 h after sample received FilmArray: 2–3 h after enrolment | Yes (text + email providing algorithm) | No significant effect on duration, presumably because of study effect |
| [8] | Adults and children in ED during influenza season | Not applicable | FilmArray respiratory Panel (Biofire, Utah, USA) | Prospective interventional | Not specified | Not specified (results communicated as soon as possible) | No significant effect on antibiotic prescription |
| [9] | Children with positive MRVP | Not applicable | FilmArray respiratory Panel (Biofire, Utah, USA) | Retrospective cohort | 3 h after order entry | Not specified | Longer treatment (> 2 days)/vancomycin more likely in influenza and hMPV positive patients compared to RSV positive patients |
| [10] | Admitted children | rapid antigen test | FilmArray respiratory Panel (Biofire, Utah, USA) | Retrospective | Not specified | No ASP implemented during study period | MRVP contributed to reduction in days of antimicrobial therapy for cephalosporins, macrolides and tetracyclines |
| [11] | Hospitalised adults with positive MRVP | Not applicable | in-house MRVP | Quasi-experimental before and after | Not specified | Yes (by phone in selected patient group with advice) | 1.3-day decrease in mean days of antibiotics postviral diagnosis |
| [12] | Adults in tertiary care referral centre | Not applicable | DFA and MRVP (not specified) | Retrospective observational cohort | Not specified | Not specified | Viral testing was not associated with significant reduction in antibiotic use |
| [13] | Children in tertiary care referral centre | Not applicable | In-house MRVP | Retrospective cohort | Approximately 24 h? | Not specified | Positive result was associated with shorter duration of IV antibiotics for patients with pneumonia/asthma |
| [14] | Adults with respiratory tract infection in tertiary care hospital | Not applicable | In-house MRVP | prospective, non-randomized | 6–24 h | Not specified (results communicated by phone/electronically) | Antibiotic management was most significantly correlated with radiographic suspicion of pneumonia and less so with results of the MRVP |

**Table 2** (continued)

| Reference | Population | Initial method | Evaluated method | Design | Time to result | Active antimicrobial stewardship? | Effect on antibiotic therapy |
|---|---|---|---|---|---|---|---|
| [15] | Children in ED prior to admission or inpatients within first 2 days of admission | Immunoassay/PCR for influenza and RSV (not specified); DFA for parainfluenza; adenovirus viral culture | FilmArray respiratory Panel (Biofire, Utah, USA) | retrospective cohort | 2–5 d vs 3 h after order entry | Not specified | Patients tested with MRVP were less likely to receive antibiotics for more than 2 days |
| [16] | Adults in ED and inpatients during influenza season with ILI | Not applicable | In-house MRVP | Retrospective cohort | <24 h? | Not specified | Unclear impact on antibiotics |
| [17] | Adult inpatients and outpatients | In-house MRVP | FilmArray POC testing (Biofire, Utah, USA) | Quasi-randomised trial | From admission: 39,5 h vs 19 h | No ASP implemented during study period | No difference in mean duration of antibiotics |
| [18] | ED and adult inpatients without pneumonia | Standard MRVP (not specified) | FilmArray POC testing (Biofire, Utah, USA) | RCT | Not specified | Yes (clinical and infection control teams were notified directly + results recorded in medical notes) | More patients received single dose or brief course of antibiotics |
| [19] | Adult outpatients with respiratory tract infection | Delayed in-house MRVP | Rapid in-house MRVP | RCT | After sample collection: 8–12 d vs 24–48 h | Not specified | Reduced antibiotic prescription at initial visit, no effect at follow-up |
| [20] | Adults and children in ED | IFA (Millipore/Chemicon, Temecula, CA) | FilmArray respiratory Panel (Biofire, Utah, USA) | Prospective randomized non-blinded | After sample collection: 26 h vs 1, 52 h | Yes (by telephone and electronic with questionnaire) | Decreased antibiotic prescription |
| [21] | Adults with lower respiratory tract infection without pneumonia | Commercial MRVP (Luminex, Texas, USA) | Rapid respiratory panel (Genmark diagnostics, California, USA) | Retrospective | 12 h–3 d vs 2–4 h | Not specified | Reduced antibiotic initiation in case of positive test for admitted patients without focal radiographic findings |
| [22] | Adult and paediatric inpatients and outpatients with ILI | FilmArray respiratory Panel (Biofire, Utah, USA) | FilmArray respiratory Panel (Biofire, Utah, USA) | Retrospective | After sample collection: a few hours | Yes (training provided) | Decrease in antibiotic use for children. Shorter duration of antibiotic therapy for adults and children after implementation of ASP |
| [23] | ED and inpatient adults positive for respiratory virus | Conventional methods + Influenza/RSV PCR (Gen-Probe, San Diego, USA) + standard MRVP (Luminex, Toronto, Canada) | FilmArray respiratory Panel (Biofire, Utah, USA) | Retrospective cohort | Median TAT for positive influenza: 7, 7 h vs 1, 7 h | Not specified (positive influenza and RSV by telephone) | Influenza positivity was associated with shorter duration of antibiotics |

**Table 2** (continued)

| Reference | Population | Initial method | Evaluated method | Design | Time to result | Active antimicrobial stewardship? | Effect on antibiotic therapy |
|---|---|---|---|---|---|---|---|
| [24] | Hospitalized children >3 months | Influenza/RSV PCR (*Focus Diagnostics, California, USA*) and PIV1-3 (*Hologic, California, USA*) | FilmArray respiratory Panel (*Biofire, Utah, USA*) | retrospective | Mean time: 18, 7 h vs 6, 4 h | Not specified | No difference in whether antibiotics were prescribed, but duration of antibiotic use was shorter after Filmarray implementation |
| [25] | Adults with negative PCT and positive viral PCR | not applicable | FilmArray respiratory Panel (*Biofire, Utah, USA*) | Pre-post, quasi-experimental study | Not specified | Yes (best practice alert in EMR) | Reduced length of antibiotic use without higher rate for re-initiation after discontinuation |
| [26] | Hospitalized adults | not applicable | PCR influenza/RSV (*Cepheid, California, USA*) + eSensor Respiratory viral panel (*Genmark diagnostics, California, USA*) | Retrospective quasi-experimental | Not specified | Yes (based on clinical decision support system) | No significant impact on de-escalation or antibiotic use |
| [27] | Patients for which respiratory panel + PCT was performed (age not specified) | Not applicable | Influenza/RSV first (*not specified*) + FilmArray respiratory Panel (*Biofire, Utah, USA*) | Retrospective | <24 h | Yes | Decrease in antibiotic duration, most profound with ASP intervention |
| [28] | Hospitalised adults with respiratory panel + PCT | Not applicable | FilmArray respiratory Panel (*Biofire, Utah, USA*) | Retrospective | <1 h after specimen obtained | No | Positive MRVP and low PCT results are infrequently associated with discontinuation of antibiotic therapy |
| [29] | Adults in ED | Anyplex II RV16 Detection with delayed results (*Seegene, Seoul, Korea*) | Anyplex II RV16 Detection with fast results (*Seegene, Seoul, Korea*) | RCT | After sampling 7 d vs <24 h (except Friday) | No | No reduction in length of antibiotic therapy |
| [30] | Hospitalized adults with LRTI | routine real-time PCR for ten pathogens (*not specified*) | FilmArray respiratory Panel (*Biofire, Utah, USA*) plus routine real-time PCR | RCT | ? vs 1 h after sample collection | Yes (results were reported and explained to physicians via telephone, text message or face-to-face) | Shorter duration of intravenous antibiotics. More de-escalation within 72 h and between 72 h and 7 d |

**Table 2** (continued)

| Reference | Population | Initial method | Evaluated method | Design | Time to result | Active antimicrobial stewardship? | Effect on antibiotic therapy |
|---|---|---|---|---|---|---|---|
| [31] | Adults in ambulatory cancer center | Not applicable | In-house MRVP, FilmArray respiratory Panel (Biofire, Utah, USA), Inlfuenza PCR (Cepheid) | Retrospective cohort study | About 24 h | Not specified | Viral testing on day 0 was associated with lower risk of antibiotic prescribing, though collinearity between viral testing and clinical service limited the ability to separate these effects on prescribing |
| **B. Antiviral therapy** | | | | | | | |
| [8] | Adults and children in ED during influenza season | Not applicable | FilmArray respiratory Panel (Biofire, Utah, USA) | Prospective interventional | Not specified | Not specified (results communicated as soon as possible) | More appropriate prescription of oseltamivir |
| [12] | Adults in tertiary care referral centre | Not applicable | DFA and MRVP (not specified) | Retrospective observational cohort | Not specified | Not specified | Positive sample associated with more antiviral use |
| [14] | Adults admitted for respiratory tract infection in tertiary care hospital | Not applicable | In-house MRVP | Prospective, non-randomized | 6–24 h | Not specified (results communicated by phone/electronically) | Influenza virus positivity was associated with appropriate antiviral management; positivity for viruses other than influenza was not correlated with significantly different outcomes |
| [16] | Adults in ED and inpatients during influenza season with ILI | Not applicable | In-house MRVP | Retrospective cohort | <24 h? | Not specified | Positive impact on antiviral management for influenza |
| [17] | Adult inpatients and outpatients | In-house MRVP | FilmArray POC testing (Biofire, Utah, USA) | Quasi-randomised trial | From admission: 39, 5 h vs 19 h | No ASP implemented during study period | Decrease in time to first dose of antiviral therapy |
| [18] | Adult ED and inpatients without pneumonia | Standard MRVP (not specified) | FilmArray POC testing (Biofire, Utah, USA) | RCT | not specified | Yes (clinical and infection control teams were notified directly+results recorded in medical notes) | Improved use of neuraminidase inhibitors |
| [20] | Adults and children in ED | IFA (Millipore/Chemicon, Temecula, CA) | FilmArray respiratory Panel (Biofire, Utah, USA) | Prospective randomized non-blinded | After sample collection: 26 h vs 1, 52 h | Yes (by telephone and electronic with questionnaire) | More accurate use of oseltamivir |

**Table 2** (continued)

| Reference | Population | Initial method | Evaluated method | Design | Time to result | Active antimicrobial stewardship? | Effect on antibiotic therapy |
|---|---|---|---|---|---|---|---|
| [26] | Hospitalized adults | Not applicable | PCR influenza/RSV (Cepheid, California, USA) + eSensor Respiratory viral panel (Genmark diagnostics, California, USA) | Retrospective quasi-experimental | Not specified | Yes (based on clinical decision support system) | Improved time to initiation of oseltamivir |
| [23] | ED and inpatient adults positive for respiratory virus | Conventional methods + Influenza/RSV PCR (Gen-Probe, San Diego, USA) in case of negative rapid antigen test + standard MRVP (Luminex, Toronto, Canada) | FilmArray respiratory Panel (Biofire, Utah, USA) | Retrospective cohort | Median TAT for positive influenza: 7, 7 h vs 1, 7 h | Not specified (positive influenza and RSV by telephone) | Similar rates of antiviral treatment for influenza. Longer median time to first dose for patients with a false negative rapid antigen test |
| [32] | Adult outpatient haemodialysis unit | In-house MRVP | Rapid influenza/RSV PCR (Roche, California, USA) | Retrospective cohort | After sample collection: 22.62 h vs 2.32 h | Positive results for influenza were directly communicated to healthcare provider | Tendency to reduced time of prescription of oseltamivir for influenza |
| [33] | Patients in acute ward, intensive care and paediatric ward | In-house MRVP | Rapid ePlex Respiratory Pathogen Panel (Genmark diagnostics, California, USA) | Retrospective | After sample reception: 27,1 h vs 3,4 h | Not specified (in-house in EMR, rapid by telephone) | More accurate use of oseltamivir |
| **C. Infection control** | | | | | | | |
| [15] | Children in ED prior to admission or inpatients within first 2 days of admission | Immunoassay/PCR for influenza and RSV (not specified); DFA for parainfluenza; adenovirus viral culture | FilmArray respiratory Panel (Biofire, Utah, USA) | Retrospective cohort | 2–5 d vs 3 h | Yes | MRVP testing increased likelihood of isolation for more than 2 days |
| [24] | Hospitalized children > 3 months | Influenza/RSV PCR (Focus Diagnostics, California, USA) and PIV1-3 (Hologic, California, USA) | FilmArray respiratory Panel (Biofire, Utah, USA) | Retrospective | Mean time: 18, 7 h vs 6, 4 h | Not specified | Decreased time in isolation |
| [33] | Patients in acute ward, intensive care and paediatric ward | In-house MRVP | Rapid ePlex Respiratory Pathogen Panel (Genmark diagnostics, California, USA) | Retrospective | After sample reception: 27, 1 h vs 3, 4 h | Not specified (in-house in EMR, rapid by telephone) | Decrease in isolation days in half of the patients |

**Table 2** (continued)

| Reference | Population | Initial method | Evaluated method | Design | Time to result | Active antimicrobial stewardship? | Effect on antibiotic therapy |
|---|---|---|---|---|---|---|---|
| [34] | Asymptomatic adult/paediatric haematology and oncology patients | Not applicable | RSV/hMPV r-gene (bioMérieux, Nürtingen, Germany) + RT-PCR influenza A/B | Retrospective data analysis | Not applicable | Electronic with recommendation including alert for infection control team | Additional isolation of asymptomatic patients with positive RSV or influenza test |
| [35] | Hospitalized children | Not applicable | FilmArray respiratory Panel (bioMérieux, Marcy l'Etoile, France) | Partly prospective | Not applicable | Not specified | Results affected infection control management in one-quarter of cases, directly related to number of isolation rooms available |
| [18] | Adult ED and inpatients without pneumonia | Standard MRVP (not specified) | FilmArray POC testing (Biofire, Utah, USA) | RCT | Not specified | Yes (clinical and infection control teams were notified directly + results recorded in medical notes) | Mean time to isolation for influenza positive patients was shorter. Mean time to de-isolation for patients isolated with suspected influenza (but negative test) was shorter |
| [36] | Adult patients with respiratory illness at ED | In-house MRVP | FilmArray respiratory Panel (Biofire, Utah, USA) | | After order entry: 36 h vs 3.23 h | Not specified | Isolation measures because of suspected RVI could be prevented in 56% admitted patients |
| [37] | Hospitalized adults during influenza epidemic | Not applicable | MRVP (not specified) | Retrospective | Not applicable | Not specified | Bed availability became critical and cohorting different viruses was necessary |
| [38] | Adult HSCT patients | Not applicable | COSMO respiratory-associated virus set targeting HRV, RSV, HCoV, influenza, adenovirus (Maxim Biotech, California, USA) and a combination of primer sets for PIV1-3, hMPV | Prospective | Not applicable | Not specified | Real-time monitoring of respiratory viral infections in the HSCT ward among patients with or without respiratory symptoms is required for the prevention of nosocomial RVI, especially of PIV3 infections |

**Table 2** (continued)

| Reference | Population | Initial method | Evaluated method | Design | Time to result | Active antimicrobial stewardship? | Effect on antibiotic therapy |
|---|---|---|---|---|---|---|---|
| [39] | Adult haematological patients | Not applicable | Molecular characterization of influenza, PIV and RSV (*Qiagen, Hilden, Germany; altona Diagnostics, Hamburg, Germany; Roche, Mannheim, Germany; Fast Track Diagnostics, Luxembourg; Applied Biosystems, Darmstadt, Germany; DNAstar, Madison, USA*) | Retrospective | Not applicable | Not applicable | Long-term viral shedding for more than 30 days was significantly associated with prior allogeneic transplantation and was most pronounced in patients with RSV infection with a median duration of viral shedding for 80 days |
| [40] | Children | Not applicable | FilmArray respiratory Panel (*Biofire, Utah, USA*)+partial sequencing of structural protein gene VP4-VP2 or VP1 region when panel positive for HRV/enterovirus | Not applicable | Not applicable | Not applicable | Early detection and awareness of emerging infections lead to proactive allocation of resources to manage an impending surge, instead of merely reacting to increased volumes |

*ASP* antimicrobial stewardship program; *CAP* community acquired pneumonia; *D* days; *DFA* direct fluorescent antibody test; *ED* emergency department; *EMR* electronic medical record; *h* hours; *HAP* hospital acquired pneumonia; *HCoV* human coronavirus; *hMPV* human metapneumovirus; *HRV* human rhinovirus; *HSCT* haematopoietic stem cell transplantation; *IFA* indirect fluorescent antibody test; *ILI* influenza like illness *LRTI* lower respiratory tract infection; *MRVP* multiplexed respiratory viral panel; *PCT* procalcitonin; *PIV* parainfluenza virus; *POC* point-of-care; *RCT* randomised controlled trial; *RSV* respiratory syncytial virus; *RVI* respiratory viral infection; *TAT* turnaround time; *VAP* ventilator acquired pneumonia

**Table 3** Recommended isolation precautions for different viruses when detected in respiratory samples

|  | CDC | WHO | LCI |
|---|---|---|---|
| Middle East respiratory syndrome coronavirus | S + C + A | S + C + A + (D) | S + C + A |
| Severe acute respiratory syndrome coronavirus | S + C + A + (D)[1] | S + C + A + (D) | S + C + A |
| Human coronavirus NL63 | NF | NF | NF |
| Human Coronavirus HKU1 | NF | NF | NF |
| Rhinovirus | S + D ± C[2] | NF | NF |
| Human parainfluenza virus | S + C[3] | NF | NF |
| Human metapneumovirus | S + C[4] | NF | NF |
| Respiratory syncytial virus | S + C + (D)[5] | NF | S + C + D |
| Cytomegalovirus | S[6] | NF | NF |
| Herpes simplex virus | NF | NF | NF |
| Seasonal influenza virus | S + D | NF | S + D |
| Adenovirus | S + D + C[7] | NF | S + D + C[8] |

[1]Airborne preferred, droplet if airborne unavailable

[2.]Contact precautions warranted if copious moist secretions and close contact likely to occur (e.g. young infants)

[3]Guidelines refer to infants/young children

[4]Route of transmission not established, assumed to be identical to RSV

[5]Guidelines refer to infants, young children and immunocompromised; mask according to standard precautions

[6]No additional precautions for pregnant healthcare workers

[7]Applicable for patients with adenovirus pneumonia

[8]Contact and droplet isolation precautions for children younger than 6 years old and for all ages in case of adenovirus pneumonia

*A*, airborne isolation precautions; *C* contact isolation precautions; *CDC* Centres for Disease Control and Prevention; *D* droplet isolation precautions; *LCI* Landelijke Coördinatie Infectieziektebestrijding; *NF* not found; *S* standard precautions; *WHO* World Health Organization

## Discussion

### Do MRVP reduce the use of antibiotics?

Inappropriate use of antibiotics in patients with RVI is a problem that concerns patients of all ages [41]. Antibiotic misuse not only leads to potential drug side effects, but is also associated with increasing prevalence of antibiotic resistance. Therefore, every tool that can lead to more appropriate use of antibiotics should be seized. The potential role of MRVP in this appears less straight forward than one might think. At a first glance, the results presented in Table 2 appear to be conflicting with some studies showing a reduction in antibiotic use and other studies failing to demonstrate this reduction. However, there are some interesting points to highlight. We therefore regrouped the studies according to the setting: presence of antimicrobial stewardship, patient's diagnosis as non-bacterial infection, and delay of MRVP result.

First, all the studies where active antimicrobial stewardship was performed (e.g., education/advice on interpreting results of MRVP) (N = 9) show a reduction in antibiotic therapy, with the exception of two studies. In the first study, 300 patients hospitalized with nonpneumonic

respiratory tract infections were randomly assigned at a ratio of 1:1 to receive standard care (bacterial and viral cultures and influenza/RSV duplex PCR) or procalcitonin (PCT)-guided care and MRVP (intervention group) [7]. Although there were no significant differences in antibiotic use or adverse events between intervention patients and those in the nonintervention group, subgroup analyses did reveal fewer subjects with positive results of viral testing and low PCT values who were discharged receiving antibiotics (20% vs 45%; $P = 0.002$) and shorter antibiotic durations among algorithm-adherent intervention patients versus nonintervention patients (2.0 vs 4.0 days; $P = 0.004$). Compared with historical controls (from 2008 to 2011), antibiotic duration in nonintervention patients decreased by 2 days (6.0 vs 4.0 days; $P < 0.001$), suggesting a study effect. The second study that failed to show an effect of active antimicrobial stewardship on antibiotic discontinuation used a clinical decision support system considering following factors: evaluation for concurrent bacterial infections of any source, antibiotic use for prophylaxis or an alternative indication (e.g., febrile neutropenia, chronic obstructive pulmonary disease exacerbation), noted concern for superimposed bacterial pneumonia on chart review, and type of virus isolated [26]. However, chest

radiography was not routinely included in the assessment and the study observed a low use of PCT. The reasons for the need of antimicrobial stewardship might be multiple. Interpretation of test results is complex, because multiple factors should be taken into account. For example, the same test result might need a different action for an immunocompetent patient in comparison to an immunocompromised patient. Also, the fact that many medical doctors are on a tight schedule might sometimes lead to a lack of time to thoroughly review all results and current antibiotic therapy. To conclude the section regarding the importance of antimicrobial stewardship, we would like to highlight the findings from the study of Moradi et al. They were able to attain a significant reduction in antibiotic therapy using an electronic medical record alert to question the need for antibiotics [25]. Patients were included if they had both a positive virus on MRVP and a PCT value < 0.25 ng/ml within 48 h of each other and at least one active systemic antibiotic. A big advantage of this method is that the alert can be automated to occur at all times, which doesn't require active intervention of the infection control team.

Second, three studies that evaluated the effect of MRVP in a population that is not suspected of having bacterial pneumonia (e.g., absence of radiology suggestive for bacterial infection or low PCT) found a positive impact on antibiotic therapy [18, 21, 25]. This seems intuitive, since the possibility of a bacterial component most likely undermines the results of a positive MRVP. However, a study of Timbrook et al. found that a positive MRVP and low PCT were infrequently associated with discontinuation of antibiotics [28]. A possible factor explaining the lack of antibiotic discontinuation in this study is the absence of an active stewardship program.

Last, another factor that seems to play an important role is the turnaround time (TAT) of the MRVP. The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America recommends the use of rapid viral testing for respiratory pathogens to reduce the use of inappropriate antibiotics (weak recommendation, low-quality evidence) [42]. With regard to MRVP in particular, we found that most studies reporting a short TAT (< 7 h) indeed report a positive impact on antibiotic therapy [15, 20–24, 30]. This seems intuitive, since testing closest to presentation of symptoms will most likely have the most impact on patient management. However, the study of Timbrook performed in hospitalized patients with a short TAT (< 1 h) of the MRVP failed to show a reduction in antibiotic therapy [28]. As mentioned before, the lack of antibiotic discontinuation in this study might be attributed to the absence of an active stewardship program.

To conclude, the result of MRVP on itself is unlikely to yield a positive effect on antibiotic use. A positive effect is more likely with active antimicrobial stewardship, a low suspicion of bacterial pneumonia and an actionable TAT.

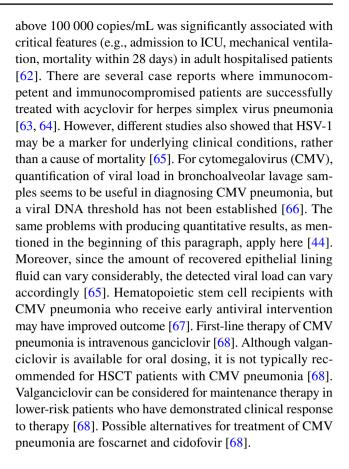## Can MRVP have a significant impact on antiviral therapy?

An important consideration to take into account when answering this question is to wander if MRVP are able to reveal the true aetiology of respiratory tract infections. The observation that respiratory viruses are detected in asymptomatic patients is evidence for the fact that the detection of a virus in symptomatic patients doesn't necessarily explain their etiological role for that patient. There are several explanations for this observation: detection of virus could represent the period of incubation before onset of symptoms, postinfectious shedding, or subclinical infection [43]. Furthermore, current laboratory practices generally report qualitative results for a MRVP, rather than determining a true viral load [44]. Of course, this also restricts the ability of the clinician to determine whether a retrieved viral pathogen is indeed the cause of the RVI. The currently available laboratory-developed viral load assays have multiple problems, including the lack of an international standard, lack of standardized technology, and lack of consensus on specimen types [44]. Additionally, the timing of specimen collection can influence viral load results [44].

Once the clinician concludes that the detected virus is indeed most likely the true pathogen, antiviral therapy can be considered. The benefit of determining the causative virus is limited by the low number of drugs that are available for the treatment of different RVI. Licensed drugs are available for influenza and respiratory syncytial virus (RSV). The CDC recommends antiviral treatment of influenza as early as possible for any patient with confirmed or suspected influenza who is hospitalized; has severe, complicated, or progressive illness; or is at higher risk for influenza complications [45]. For the first two groups, oral oseltamivir (neuraminidase inhibitor) is recommended, while other treatment options consist of other neuraminidase inhibitors (inhaled zanamivir, intravenous peramivir) and a cap-dependent endonuclease inhibitor (oral baloxavir marboxil) [45]. Importantly, decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza [46]. Thus, antiviral treatment should be initiated until results of MRVP are available. Impact on antiviral treatment can be expected in 2 situations: a patient started on antiviral therapy that tests negative and a patient that qualifies for therapy but wasn't suspected of having influenza. In contrast to antibiotic reduction, this improved antiviral use as a consequence of MRVP results was systematically objectified in all eleven studies focusing on the effect on antiviral use (Table 2). Hence, the effect on antiviral therapy seems to be less dependent

on antimicrobial stewardship, low suspicion of bacterial pneumonia, and short TAT. For treatment of RSV, the only licensed drug is ribavirin. Oral or nebulized ribavirin, alone or in combination with other interventions, may be useful for treatment of RSV in some immunocompromised individuals [47, 48]. However, it is not routinely recommended for treatment of RSV bronchiolitis in children, where supportive therapy remains the cornerstone of therapy [49].

For antiviral treatment of RVI, not caused by influenza and RSV, few options are available. Although supportive care remains the most important part of therapy for these infections, some data is available regarding antiviral treatment. However, in general, further research is needed to determine which groups of patients would benefit from antiviral therapy. Concerning adenovirus, there is limited published data available on the efficacy of cidofovir in immunocompromised patients. In lung transplant and hematopoietic stem cell transplant (HSCT) patients more specifically, cidofovir might contribute to clinical improvement and increased survival [50–52]. However, the prognosis of adenovirus pneumonia appears to remain poor despite the use of cidofovir, and there are concerns regarding nephrotoxicity of cidofovir [51, 53]. With regard to human metapneumovirus (HMPV), data on antiviral treatment is very scarce. The combination of oral and aerosolized ribavirin with polyclonal intravenous immune globulin (IVIG) seems an effective treatment for severe HMPV infections, but to our knowledge, no randomized controlled trials in humans have been performed. Despite this lack of good trials in humans, a lot of experience has been gained meanwhile in individual cases and small case series [54]. For pneumonia caused by parainfluenza viruses, case series show variable results for the use of ribavirin in transplant patients [55–58]. In contrast to ribavirin, DAS181 might be more suited for the treatment of parainfluenza virus infections in immunocompromised patients. DAS181 has been evaluated in different case series of transplant patients, but isn't available for clinical use at this moment [59]. Regarding human rhinovirus, there is no clear role for antiviral therapy in critically ill patients with rhinovirus pneumonia. This is also applicable for severe acute respiratory syndrome coronavirus (SARS-CoV), since severely ill ARDS-patients treated with ribavirin appear to benefit little from antiviral therapy [60]. With regard to middle eastern respiratory coronavirus (MERS-CoV), the combination of interferon alfa-2b and ribavirin showed a beneficial effect in a retrospective cohort study of 20 patients [61]. As for pneumonia caused by other viruses, diagnosing viral pneumonia by Herpesviridae remains a diagnostic challenge. Obtaining evidence of cytopathic effects is hard to obtain and not sensitive, while detection of Herpesviridae with viral culture or PCR doesn't differentiate active infection from asymptomatic shedding. For herpes simplex virus type 1 (HSV-1), a viral load in bronchoalveolar fluid

above 100 000 copies/mL was significantly associated with critical features (e.g., admission to ICU, mechanical ventilation, mortality within 28 days) in adult hospitalised patients [62]. There are several case reports where immunocompetent and immunocompromised patients are successfully treated with acyclovir for herpes simplex virus pneumonia [63, 64]. However, different studies also showed that HSV-1 may be a marker for underlying clinical conditions, rather than a cause of mortality [65]. For cytomegalovirus (CMV), quantification of viral load in bronchoalveolar lavage samples seems to be useful in diagnosing CMV pneumonia, but a viral DNA threshold has not been established [66]. The same problems with producing quantitative results, as mentioned in the beginning of this paragraph, apply here [44]. Moreover, since the amount of recovered epithelial lining fluid can vary considerably, the detected viral load can vary accordingly [65]. Hematopoietic stem cell recipients with CMV pneumonia who receive early antiviral intervention may have improved outcome [67]. First-line therapy of CMV pneumonia is intravenous ganciclovir [68]. Although valganciclovir is available for oral dosing, it is not typically recommended for HSCT patients with CMV pneumonia [68]. Valganciclovir can be considered for maintenance therapy in lower-risk patients who have demonstrated clinical response to therapy [68]. Possible alternatives for treatment of CMV pneumonia are foscarnet and cidofovir [68].

## Can MRVP significantly impact infection control measures?

The usefulness of molecular diagnostics for implementation of infection control measures is demonstrated by the widespread use of PCR for a numerous amount of pathogens (methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*, norovirus). Because asymptomatic shedding has been reported in a healthy population, it seems intuitive that MRVP could yield similar advantages [69]. Evidently, the impact of detecting respiratory viruses on isolation precautions is related to the necessity for additional infection control measures (next to standard precautions) for these viruses. An overview of respiratory viruses commonly included in MRVP and their recommended isolation precautions is summarized in Table 3 [45, 70–80]. In general, the same isolation precautions are recommended according to the different guidelines.

Two studies report that the results of MRVP affected infection control management, but also mention that logistical problems can limit their effect [35, 37]. Braybrook et al. found that infection control measures of hospitalized children were affected by MRVP in one-quarter of cases, but the value of testing was directly related to the number of isolation rooms available. On the other hand, Cunha et al. studied the infection control implications of MRVP in hospitalized

adults with influenza-like illness during the 2015 influenza A ($H_3N_2$) outbreak. They were able to provide single rooms for patients with influenza-like illness, but over time were forced to cohort different viral aetiologies.

Studies that compare the effect of rapid MRVP in comparison to standard (molecular) diagnostics appear to show mixed results. Subramony et al. reported an increased use of isolation precautions after implementation of a rapid MRVP, while other studies report a decrease in isolation time [15, 24, 33]. However, there are important differences in design: the study of Subramony compared the rapid MRVP to a combination of PCR (influenza and RSV) and conventional methods. For the study of Rogers (2015) and Van Rijn (2018), a standard MRVP was compared to a rapid MRVP. It may be possible that Subramony et al. compared a MRVP to a conventional method that is less sensitive, leading to a higher recovery rate of RVI and accordingly isolation requirement using a rapid MRVP.

Furthermore, there are different studies that show a beneficial effect of screening for respiratory viruses in immunocompromised patients. Importantly, this population is at risk of developing life-threatening pneumonia. Prolonged viral shedding is reported and might be a catalyser of nosocomial transmission [39]. In HSCT patients for example, the results of MRVP have shown to be useful for identifying asymptomatically infected patients with viral shedding [34, 38]. Baier et al. more specifically implemented a screening program for all patients lacking respiratory symptoms who were hospitalized on an adult and a paediatric haemato-oncological ward. The seasonal screening program enabled them to identify 23 (out of 251 tested patients) RSV or influenza infections in asymptomatic patients in a 4-month period. The authors concluded that this screening program proved useful for identifying asymptomatically infected patients with viral shedding, thus reducing the risk of transmission and potential nosocomial clusters of RSV and influenza virus on haemato-oncological wards. Kakiuchi et al. performed a 2-year prospective cohort surveillance study of symptomatic and asymptomatic RVI in hospitalized HSCT patients. For asymptomatic patients, the samples were subjected to cell culture-based viral isolation. If no pathogens were found with cell culture, the samples were then further tested with a MRVP. Symptomatic patients were tested using the MRVP. The parainfluenza virus type 3 (PIV3) accounted for 71% of the cases of RVI. Some PIV3 infections were asymptomatic and involved a longer virus-shedding period. The PIV3 was often detected from samples taken before the onset of respiratory disease and infections were attributed to nosocomial transmission. PIV3 infections before engraftment will more likely result in the development of lower respiratory tract infections and worse outcomes. Therefore, the authors recommend real-time monitoring of respiratory viral infections in the HSCT ward among patients with or without respiratory symptoms for the prevention of nosocomial RVI, especially of PIV3 infections.

Finally, MRVP can play a potential role in directing the public health response. For example, Shaw et al. highlighted the importance of syndromic surveillance in directing the public health response to an enterovirus D68 epidemic [40]. Early detection of the virus in the community informed decisions to activate hospital preparedness and emergency response teams and promoted proactive community and physician education aimed at avoiding unnecessary emergency department visits.

In general, all these studies led to a more accurate use of infection control measures by detecting unidentified pathogens or stopping isolation precautions in case of a negative MRVP result.

This study has several limitations. Although all studies cited were published in peer reviewed journals, we did not assess the quality of the different studies. We used an extensive search string on the PubMed and Embase database, but it seems likely that not all relevant articles were withheld. Also, because the selection of articles was performed by one person, selection bias is possible.

## Conclusion

MRVP recently have become part of routine diagnostic testing. Therefore, their impact with respect to antibiotic therapy use, antiviral treatment, and infection control is not fully understood. The effect on antibiotic therapy seems promising in combatting the global problem of antibiotic misuse and associated development of resistance. This effect might not be present in all populations and seems to be positively influenced by several factors: presence of an active antimicrobial stewardship program, low likelihood of a bacterial infection, and a short time to result.

The ability of MRVP to have an impact on antiviral treatment of RVI is most obvious for influenza. In contrast to the effect on antibiotic therapy, this effect seems to be less dependent on different factors (e.g., active antimicrobial stewardship, short time to result). Regarding treatment of RVI other than influenza and RSV, few options are available. Several studies report on a positive effect of antiviral therapy, although high-quality studies are needed in the future to further establish which drug, dose, route of administration, and indication should be used for these RVI.

With regard to infection control, the potential impact of MRVP is high because of the need of additional isolation precautions for many RVI. However, logistical problems can occur in the winter season. This impact is often more pronounced in an immunocompromised population, since RVI in this population are potentially life threatening and prolonged viral shedding occurs. Finally, MRVP have the

potential to adequately direct the public health response in case of an epidemic.

## Declarations

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