Journal of Clinical Virology 117 (2019) 27–32

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

# What is the role of rapid molecular testing for seniors and other at-risk adults with respiratory syncytial virus infections?

Steven J. Drews[a,*], Angela R. Branche[b], Ann R. Falsey[c], Nelson Lee[d]

[a] 2B1.03 WMC University of Alberta Hospital, 8440 112th St NW, Edmonton, Alberta, T6J 1L9, Canada
[b] University of Rochester, 601 Elmwood Avenue, Box 689, Rochester, NY 14642, USA
[c] 1425 Portland Avenue, Rochester General Hospital, Rochester, NY 14621, USA
[d] Division of Infectious Diseases, Department of Medicine, University of Alberta, Clinical Sciences Building (CSB), 1-124, 11350-83 Avenue NW, Edmonton, Alberta, T6G 2G3, Canada

ARTICLE INFO

*Keywords:*
Respiratory syncytial virus
Point-of-care testing
Polymerase chain reaction
Adult
Immunocompromised patient
Health resource

ABSTRACT

Lower respiratory tract infections are a leading cause of hospitalization and viruses are important causal pathogens, especially in the elderly, immunocompromised patients and those with respiratory or cardiovascular comorbidities. Respiratory syncytial virus (RSV) is recognized as comprising a substantial burden of morbidity and mortality in older and at-risk adults, and the emergence of rapid point-of-care molecular testing has made it possible to confirm an RSV diagnosis accurately, in a clinically actionable timeframe. RSV patients have significantly higher healthcare resource use (including hospital stays and emergency room/urgent care visits) than non-RSV matched controls, especially if aged ≥65 years, a longer length of hospitalization than those with influenza, and associated costs nearly three times higher. We found no direct clinical outcome data specific to rapid molecular testing for RSV in adults and very little in children. There is very limited evidence that prompt diagnosis may reduce hospital length of stay but this and other outcome parameters need confirmation in larger, prospective clinical trials. Regarding reducing inappropriate antibiotic prescribing, the picture is mixed and testing alone is unlikely to change entrenched habits. There is little incentive for clinicians to order routine RSV tests in adults given the absence of a specific antiviral therapy. However, with numerous vaccine and antiviral candidates in clinical development, we believe it is good practice to plan and start establishing standardized testing protocols – perhaps as part of outcome studies. For especially vulnerable patients, e.g., immunocompromised and transplant patients, prompt accurate RSV diagnosis may prevent disease spread and save lives.

## 1. Background

Lower respiratory tract infections (LRTIs) are a leading cause of hospitalization, especially in immunocompromised patients and those with respiratory or cardiovascular comorbidities, and viruses are commonly the causal pathogens. [1,2] Severe viral LRTIs, occur in vulnerable populations including patients who have undergone recent hematopoietic stem cell transplantation (HSCT), patients with hematologic malignancies, and patients who have undergone solid organ transplantation. Seniors, especially residents in long-term care facilities and/or those who have chronic cardiac or pulmonary disease, are also susceptible to severe viral LRTIs. For example, in the USA, over 75% of deaths due to respiratory syncytial virus (RSV) occur in the over-65 year age group, and despite diagnostic limitations at the time, RSV was estimated to result in 62,000 annual hospital admissions in this population nearly two decades ago [1,3]. With trends to an increasingly aging population, and more people having chronic diseases, it is likely that the burden of viral LRTIs will increase [1,4].

Development of molecular diagnostic tests has revealed that respiratory viruses make a substantial contribution towards the etiology of community-acquired pneumonia (CAP), suggesting that the viral pneumonia incidence may be underestimated [5]. Viruses are the most common pathogens in adults hospitalized with CAP [6], and respiratory viral pathogens are found in over a fifth of patients with hospital-acquired pneumonia (HAP) – and in up to 41% of patients with severe pneumonia of any origin requiring admission to ICU [1]. Moreover, viral LRTIs are associated with morbidity/mortality rates and healthcare utilization comparable to those associated with bacterial CAP and

* Corresponding author.
*E-mail addresses:* drews@ualberta.ca (S.J. Drews), angela_branche@urmc.rochester.edu (A.R. Branche), Ann.falsey@rochesterregional.org (A.R. Falsey), laishunn@ualberta.ca (N. Lee).

https://doi.org/10.1016/j.jcv.2019.05.010
Received 13 February 2019; Received in revised form 21 May 2019; Accepted 22 May 2019

HAP [7].

## 2. Epidemiology and burden of RSV in adults

RSV is one of the most important etiologic agents of acute RTI leading to hospitalization in infants < 2 years old [8]. While RSV is established as a major respiratory pathogen in infants, there has been a degree of inertia among healthcare providers for diagnosing RSV as a cause of respiratory disease in seniors and vulnerable adults, despite growing recognition of the burden of RSV in these patients. This is likely due to low and/or inconsistent sensitivity of culture and antigen-based tests (ABTs) in adults, as well as a lack of incentive for physicians to test for RSV when there are only symptomatic/supportive treatments available [9].

The sensitivity of viral cultures may be affected by relatively low viral loads in respiratory secretions, such as in older adults, and low suitability for transportation to a laboratory by more labile viruses, such as RSV versus the hardier influenza virus [10]. As such, rapid ABT can be insensitive to detecting influenza and RSV infections, leading to errors in diagnosis [10]. Rapid ABT sensitivity for influenza may be ≥43% depending on setting and on age versus molecular diagnostics such as polymerase chain reaction (PCR). Therefore, the US Food and Drugs Administration (FDA) has recently re-classified rapid influenza ABT systems from class I to class II devices, due to their poor diagnostic performance and low sensitivity [11]. For RSV, rapid ABT sensitivity is < 25% compared with molecular diagnostics (PCR) testing and thus, with such poor predictive benefit in older adults and low RSV infection prevalence, ABT is not recommended for general use [10,12]. However, patients with high viral loads, such as those immunocompromised or with respiratory failure, may be considered for ABT [13]. Rapid multiplex molecular assays that are more sensitive and specific and have the potential to rapidly and accurately identify respiratory viruses are commercially available to be operated in the laboratory or at the point of care, and are currently considered the test of choice [14, 15]. Molecular diagnostic assays for RSV among other respiratory viruses are increasingly used as their sensitivity improves compared with ABT and new tests are developed [12,16]. With increasing availability, especially in the point-of-care (POC) environment, such sensitive molecular diagnostics should enable more accurate and timely diagnoses of RSV in adults.

Nonetheless, despite use of rapid sensitive molecular methods in large, prospective studies reporting RSV incidence rates, disparities in study design with respect to case definitions, clinical settings and observation periods mean that estimates of RSV incidence in adults aged ≥50 years may underestimate the full burden of disease in this demographic [9].

Approximately 50% of RSV cases presenting to primary care have been estimated to occur in adults, in whom RSV is associated with a disease burden greater (and more consistent between seasons) than that of influenza [17]. RSV patients have significantly higher healthcare resource use (including hospital stays and emergency department [ED]/urgent care visits) than non-RSV matched controls across all age groups, especially those aged ≥65 years who have more visits to the ED/urgent care than their non-RSV counterparts [18].

Hospitalizations due to RSV in adults are increasing and are typically more severe than those for influenza, with mortalities of 6.3% and 3.0%, respectively [19]. In adults > 50 years old, hospitalization rates are similar for patients with RSV or influenza [20], but most RSV-related hospitalizations and mortality occur in seniors (79% and 93%, respectively); risk factors for severe RSV or influenza infection are similar [17]. Up to 31% of seniors with RSV require ICU admission compared with up to 12% of infants and young children [9,21]. With the caveat that more sensitive molecular diagnostic assays for RSV developed since the study was conducted in 2005 may impact the findings, a seminal prospective study of high-risk and elderly adults found that RSV infection was responsible for 11% of pneumonia hospitalizations, 11% for chronic obstructive pulmonary disease (COPD), 5% for congestive heart failure, and 7% for asthma – totaling nearly 200,000 patients annually in the US alone [22]. Patients with RSV have a longer hospitalization than those with influenza (mean 6.0 vs 3.6 days) and associated costs are nearly three times higher (mean 39,000 vs 14,500 USD) [19].

Patients with COPD are especially susceptible to RSV infection, which is an important trigger for exacerbations possibly via toll-like receptor 3-mediated antiviral immunity and inflammation, [23] leading to severe chronic airway inflammation [9]. COPD, conversely, is also a risk factor for severe RSV infection and mortality rates for RSV in COPD patients are even higher than those in RSV-infected patients after HSCT [1].

Another at-risk adult group comprises patients undergoing solid organ or HSCT. RSV is one of the respiratory viruses associated with the highest mortality in these patients, with limited management options [24]. Routine testing for respiratory viruses, including RSV, in symptomatic patients undergoing HSCT and delaying the procedure where feasible for patients who test positive, may help to improve outcomes [25].

## 3. Rationale and history of diagnostic testing for RSV

Non-molecular rapid laboratory testing reduces the number of ancillary tests, decrease antibiotic use, and shorten the hospitalization period in clinical pediatric practice; moreover, since RSV is highly contagious, rapid identification of infected infants is vital to initiate infection control measures and prevent nosocomial outbreaks [8,26]. ABTs are quick and easy with acceptable performance in young children, and are therefore used widely in clinical practice, but they have dramatically reduced sensitivity (as low as zero) in older children and adults, due to lower viral load and shorter duration of viral shedding [8]. Across all age groups, RSV rapid ABT pooled sensitivity and specificity are 80% and 97%, respectively. Sensitivity is much higher in children than adults (81% vs 29%, respectively) [26]. There are several commercially-developed rapid ABTs available for RSV diagnosis that are easy to perform, provide results in < 30 min, and several are suitable for POC use.

Molecular diagnostic tests are the most sensitive and specific methods for RSV detection, regardless of the patient population tested [8]. Reverse-transcriptase polymerase chain reaction (RT-PCR) has a much shorter turn-around time (hours) and superior analytic and clinical sensitivities compared with viral culture (which was previously the gold-standard test for RSV and other respiratory viruses) [8,26]. Although RT-PCR has superseded viral culture as the reference RSV diagnostic method, only ˜15% of clinical laboratories in the USA use this due to associated costs, specialized equipment, and expertise required [26]. With the advent of CLIA-waived molecular tests, POC application is possible, and is increasingly being utilized, although testing for influenza still predominates in adults [12,27]. POC testing has the potential for numerous benefits for the adult RSV patient population [14,27]. However, bias towards testing for influenza over RSV using rapid ABT may have been due to its morbidity and mortality across all ages, with testing for influenza in all age groups and for RSV more commonly in children. We believe that is likely also influenced by ordering behaviors resulting from the occurrence and profile of influenza pandemics, as well as a concern regarding influenza virus mutations playing a role [12]. Although in many institutions influenza and RSV molecular testing are duplexed, testing in adults is more common when influenza is active compared to RSV [28]. This practice may be due to the availability of influenza antiviral agents and issues of infection prevention in the healthcare setting surrounding a diagnosis of influenza. Thus, when peaks of influenza and RSV are temporally dissociated, RSV testing may be underutilized.

**Table 1**
Summary of findings with rapid molecular testing.

| Reference | Setting | Population studied | Type of tests performed | Major findings |
|---|---|---|---|---|
| Rogers et al. [23] | Hospitalised | Pediatric patients | Rapid respiratory panel with expanded multiplex PCR panel | After rapid respiratory panel test implementation, mean time to the test result was shorter (383 minutes versus 1119 minutes, P < 0.001), and % off patients with a result in the emergency department was greater (51.6% versus 13.4%, P < 0.001).<br>No differences in antibiotic prescription, but duration of antibiotic use was shorter after rapid respiratory panel test (P = 0.003); this was dependent on receiving test results within 4 hours. If test result was positive, the inpatient length of stay (P = 0.03) and the time in isolation (P = 0.03) were decreased after rapid respiratory panel test compared with before. |
| Mitchell et al. [24] | Emergency department | Pediatric patients | Rapid influenza A/B and RSV direct molecular assay | Rapid influenza A/B and RSV direct molecular assay improved emergency department oseltamivir use in pediatric patients. A reduction in overall oseltamivir use was reduced (31.0 % of the patients analyzed received oseltamivir compared to 61.5 %), duration of treatment was shortened in the post-implementation period (average duration of 3.24 days compared to 4.10 days). |
| Lee et al. [25] | Retrospective review of patient charts | RSV patients | Any | Early RSV diagnosis was associated with a shorter mean LOS. Patients who were diagnosed > 24 h post-admission had a longer mean [SD] LOS (9.8 [8.6] days; $n = 29$) than patients diagnosed < 12 h post-admission (6.2 [3.9] days; $n = 67$; $P = 0.006$), and patients diagnosed 12–24 h post-admission (7.4 [4.2] days; $n = 56$; $P = 0.038$). |
| Rogan et al. [26] | Emergency department | Pediatric emergency patients | PCR assay | A rapid turnaround of influenza and RSV PCR test results, by molecular point-of-care test, would have affected most cases when a pediatric ED physician ordered nasopharyngeal swabs for respiratory viral PCR panels during the management of patients. Of ED-initiated tests, physicians indicated in 39/61 cases (64%) patient management would have changed if bedside viral results were available. Physicians would have decreased ED LOS by 33 minutes, ordered 18% fewer tests (P < 0.001) with 17% fewer antibiotics among discharged patients (P = 0.043), and 13% increased appropriate antiviral use (P = 0.023). |
| Rappo et al. [27] | Tertiary care center | Adult patients | Multiplex PCR assay | Rapid turnaround time with a multiplex test may improve the evaluation and management of patients suspected of having respiratory virus infections. Multiplex testing decreased the time to diagnosis of non-influenza viruses (1.5 h versus 13.5 h, respectively; P < 0.0001). Multivariate logistic regression found that a diagnosis of influenza by multiplex test was associated with significantly lower odds ratios for admission (P = 0.046), LOS (P = 0.040), duration of antimicrobial use (P = 0.032), and number of chest radiographs (P = 0.005), when controlling for potential confounders. |
| Keske et al. [28] | Hospital (inpatient and outpatients) | Children and adults | Rapid molecular respiratory assay | By using MRT, inappropriate antibiotic use and, also, duration of inappropriate antibiotic use after the detection of virus was significantly decreased. Among hospitalized patients, in children, a significant decrease in antibiotic use (44.5% in 2015 and 28.8% in 2016, p = 0.009) was observed, but in adults the decrease was not statistically significant (72% in 2015 and 63% in 2016, p = 0.36). Duration of antibiotic use after the detection of virus was significantly decreased in both children and adults (p < 0.001 and p = 0.007, respectively). |
| Green et al. [29] | Hospital (inpatient and outpatients) | Children and adults | Multiplex PCR assay | The value of performing multiplex PCR panels for respiratory viruses in adult outpatients was unclear. Among adult outpatients, testing positive for non-influenza virus was not associated with receiving fewer antibiotic prescriptions.<br>There was no significant difference in antibiotic prescription rates between individuals who tested positive for a non-influenza virus and those who tested negative (48.6% and 49.3%, respectively, [chi-squared value, 0; $P = 1.0$]). |
| Semret et al. [30] | Hospitalised | Adults | 12-Virus respiratory panel. | Multiplex testing was associated with shorter durations of hospitalization and led to appropriate management decisions, including instituting antivirals and a trend toward antibiotic de-escalation. However, rapid testing for a broad array of viruses did not, per se, assist interventions among hospitalized adult patients, unless combined with other means of ruling out bacterial coinfections. A trend to discontinue antibiotics after an influenza virus–positive test result was seen in the univariate analysis, but this was no longer significant after adjustment for potential confounders (OR, 1.38 [95% CI, 0.89–2.16]). |

PCR, polymerase chain reaction.

## 4. Evidence for patient and/or system benefits from rapid molecular testing for RSV

A previous review was published regarding the impact of rapid testing in RSV and influenza on patient care and workflow, but data were mainly from ABTs and skewed towards influenza [27]. Our review summarizes the potential benefits of rapid molecular testing (RMT) for RSV and how this may contribute towards better patient outcomes and healthcare provision planning in older and at-risk adult populations. Performance metrics and technical aspects have been reviewed elsewhere [14]. We found very few studies showing a direct clinical outcome benefit specific to RMT for RSV in adults [29] or children [30–33] (Table 1). This is unsurprising, as there is no specific antiviral treatment for RSV and clinical management decisions may not be impacted discernibly following a positive diagnosis. Limited data from pediatric studies suggest that prompt laboratory molecular diagnosis of respiratory pathogens reduces duration of antibiotic use and inpatient length of stay (LOS), but does not alter the rate of antibiotic prescribing [30]. POC testing of children in the ED with a dual influenza/RSV assay facilitates more appropriate oseltamivir use, although this may have been achieved through testing for influenza alone [31].

Limited evidence shows that early diagnosis of adults with RSV may result in a shorter hospital LOS, with patients diagnosed ≤12 h of admission having a mean LOS of 6.2 days vs 9.8 days for patients diagnosed > 24 h from admission (P = 0.006). However, any benefit of a quicker diagnosis using molecular testing remains to be proven in prospective clinical studies [34]. In a prospective cohort study in pediatric patients presenting to the ED, physicians indicated that if they had received rapid POC results for RSV or influenza they would have changed their patient management strategy in 64% of cases [32]. Specifically, they would have decreased ED LOS (by an average 33 min), ordered 18% fewer tests (P < 0.001) with average per-patient charge savings of 669 USD, issued 17% fewer antibiotic prescriptions on discharge (P = 0.043), and increased appropriate antiviral use by 13% (P = 0.023). Hence, clinical and infection-control practice decisions may be similarly affected in an adult patient setting, in regard to a broad perspective of resource sparing, allowing for service infrastructure differences.

Proof-of principle for RMT comes mainly from influenza studies. Laboratory-implemented, multiplex-panel, RMT to diagnose influenza in a mixed-age adult ED patient population was associated with a significantly lower likelihood of hospital admission, shorter LOS, shorter duration of antibiotic use, and fewer chest radiographs, compared with conventional testing. There were some positive trends but no corresponding significant effects in patients with non-influenza LRTIs, likely due to a much smaller sample size [35]. Laboratory-implemented, rapid molecular respiratory multiplexed tests have also been shown to reduce both incidence and duration of inappropriate antibiotic prescribing in a hospital setting, although only the latter reached statistical significance in adults [29]. In a large study of adults (mostly outpatients, so unlikely to have severe disease), on-demand laboratory multiplex PCR panel testing reduced antibiotic prescribing only in relation to tests positive for influenza. There was no effect for patients who tested positive for non-influenza respiratory pathogens, leading to authors concluding that in this setting, testing only for influenza would be optimal and cost-effective [33]. Other studies have reached similar conclusions showing physicians adjusting antimicrobial prescribing in hospitalized patients in response to confirmed influenza LRTI but not to other viral pathogens [36]. This could be due to inertia and/or unwillingness to abstain from or limit antimicrobial prescribing because of a lack of treatments for viral LRTIs except influenza, as well as an inability to rule out bacterial coinfection.

Evidence for outcome benefits from RMT is sparse and conflicting, rarely altering patient management. This is the case with influenza, for which a treatment is available [37]. In one large, prospective, quasi-randomized study of patients ≥16 years with influenza-like illness, POC multiplex molecular testing done by trained ward staff was not associated with the LOS primary outcome or with most secondary outcomes, including readmission rates and mortality, when compared to outcomes associated with laboratory-based testing. There was, however, a shorter time to first dose of antiviral therapy after POC testing (median time to first dose reduced by 36 h), likely from a decrease in test turnaround time (19.0 vs 39.5 h; P < 0.001). POC testing also significantly improved antibiotics prescribing decisions (P < 0.001). Delays in requesting a test probably masked other benefits, demonstrating that the convenience and speed of a POC test does not guarantee optimal practice [38].

Another large, pragmatic, randomized trial assigned adults presenting to the ED or acute medical unit of a large UK hospital to a molecular POC test or routine clinical care. Routine use of molecular POC testing did not reduce antibiotic prescribing, though many patients were started on antibiotics before POC test results could be made available [39]. A liberal antibiotic prescribing approach for LRTIs appears to be entrenched in clinical practice due to concerns regarding bacterial co-infection, and strategies other than merely better and quicker testing methods are needed to improve antibiotic stewardship [37]. Timing of results probably also plays a part in failure to optimize antibiotic prescribing; a recent meta-analysis found that over a quarter of tests (of any type) designed to be used at the POC were actually evaluated in a laboratory, likely leading to unnecessary delays in the availability of results to physicians [15].

## 5. Future directions and conclusions

Although currently there is insufficient high-quality evidence to support routine testing of at-risk adults with RMT for RSV to guide decision making, there are sound clinical principles to encourage such testing. We strongly recommend the initiation of properly designed, randomized clinical trials to evaluate both the systemic feasibility and impact on patient outcomes of RSV RMT. Even a modest reduction in LOS and minimization of disease spread, especially nosocomial spread in high-dependency units, would likely have considerable economic and clinical benefits, given the contribution of older adults with RSV to the overall healthcare burden. Numerous antiviral treatments for RSV are in late-stage clinical development, so it makes sense to have testing protocols established in readiness; recent data estimate 49 RSV vaccine trials and 33 RSV antiviral trials are ongoing in the USA alone [40]. Testing for RSV could be integrated seamlessly via dual testing for influenza or in multiplexed respiratory viral panels, since seasons overlap in the northern hemisphere and these pathogens have similar profiles for vulnerability in adults [40].

More accurate testing of at-risk adults using molecular methods is needed to fill gaps in RSV epidemiology prior to the future introduction of vaccination programs [40,41]. Based on limited available outcome data, this could be achieved using dual RSV/influenza or multiplex viral panels, with results being used to guide antibiotic/antiviral prescribing and to gather RSV epidemiologic data. Unlike RSV, physicians respond to influenza test results when making clinical management decisions for hospitalized adults [36]. Research shows physicians do not consider RSV routinely in the differential diagnosis of influenza-like illness in nearly two-thirds of patients who present to the ED and are subsequently hospitalized – even in at-risk subgroups such as those who are immunocompromised or have predisposing comorbidities (e.g., COPD) [42]. These observations are unsurprising since confirmation of RSV infection appears unlikely to influence management strategy. However, the infection control practice of cohorting RSV-confirmed patients may be mandated in settings with a lack of single-bed rooms and where spread could have disastrous consequences, such as in immunocompromised individuals or those with underlying respiratory disease.

There are limitations of using routine viral testing to estimate disease burden for adult RSV patients. Specifically, utilizing duplexed or

multiplexed tests driven by influenza diagnosis when the temporal peaks of RSV and influenza do not coincide may result in underestimation of RSV cases [43]. Clear definitions and standardization of approach are required because accurate seasonality data can guide diagnostic testing, timing of clinical trials, future vaccination programs, and stockpiling of antivirals once available [44].

Syndromic testing via multiplex panels may be the most clinically relevant option for diagnosing LRTIs. However, these are expensive compared to routine laboratory molecular tests, (including POC options) and more pragmatic solutions may be required. One possibly could involve "targeting" multiplex assays to intrinsically more vulnerable patients, such as those immunocompromised or at risk because of underlying disease and in whom panel testing is most likely to be cost-effective [45]. More research from well-designed, prospective studies is needed to generate high-quality outcome data from RMT in at-risk adults with RSV LRTIs. Importantly, absence of evidence is not evidence of absence, and we do not know if there could be clinical, outcome and cost benefits (e.g., reduced LOS and improved infection control) from a quicker diagnosis in these patients irrespective of the availability of specific antiviral treatment. High-quality outcome data underpinning guideline recommendations would give physicians more confidence to order RSV molecular tests and argue for their clinical value despite costs [46].

## Funding

Medical writing support was funded by Janssen Pharmaceutica.

## Competing interests

None declared.

## Author contributions

All authors have contributed to the manuscript and approved the final version for submission.

## Ethical approval

None.

## CRediT authorship contribution statement

**Steven J. Drews:** Conceptualization, Data curation, Methodology, Formal analysis, Writing - review & editing. **Angela R. Branche:** Conceptualization, Data curation, Formal analysis, Methodology, Writing - review & editing. **Ann R. Falsey:** Conceptualization, Writing - review & editing. **Nelson Lee:** Conceptualization, Data curation, Methodology, Writing - review & editing.

## Acknowledgements

Medical writing support was provided by Chris Whittaker of Zoetic Science, an Ashfield company, part of UDG Healthcare plc.

## References

[1] J.M. Walter, R.G. Wunderink, Severe respiratory viral infections: new evidence and changing paradigms, Infect. Dis. Clin. North Am. 31 (2017) 455–474.
[2] E.E. Walsh, Respiratory Syncytial Virus infection: an illness for all ages, Clin. Chest Med. 38 (2017) 29–36.
[3] L.L. Han, J.P. Alexander, L.J. Anderson, Respiratory syncytial virus pneumonia among the elderly: an assessment of disease burden, J. Infect. Dis. 179 (1999) 25–30.
[4] A.R. Branche, A.R. Falsey, Respiratory syncytial virus infection in older adults: an under-recognized problem, Drugs Aging 32 (2015) 261–269.
[5] Y. Alimi, W.S. Lim, L. Lansbury, J. Leonardi-Bee, J.S. Nguyen-Van-Tam, Systematic review of respiratory viral pathogens identified in adults with community-acquired pneumonia in Europe, J. Clin. Virol. 95 (2017) 26–35.
[6] S. Jain, W.H. Self, R.G. Wunderink, et al., Community-acquired pneumonia requiring hospitalization among U.S. Adults, N. Engl. J. Med. 373 (2015) 415–427.
[7] C. Nguyen, S. Kaku, D. Tutera, W.G. Kuschner, J. Barr, Viral respiratory infections of adults in the intensive care unit, J. Intensive Care Med. 31 (7) (2016) 427–441.
[8] T. Popow-Kraupp, J.H. Aberle, Diagnosis of respiratory syncytial virus infection, Open Microbiol. J. 5 (2011) 128–134.
[9] A.D. Colosia, J. Yang, E. Hillson, et al., The epidemiology of medically attended respiratory syncytial virus in older adults in the United States: a systematic review, PLoS One (2017) e0182321.
[10] H.K. Talbot, A.R. Falsey, The diagnosis of viral respiratory disease in older adults, Clin. Infect. Dis. 50 (2010) 747–751.
[11] Food and Drug Administration (FDA). Microbiology Devices; Reclassification of influenza virus antigen detection test systems intended for use directly with clinical specimens. www.federalregister.gov 2017; 82 FR 3609:3609-3619.
[12] M.M. Azar, M.L. Landry, Detection of influenza A and B viruses and respiratory syncytial virus by use of clinical laboratory improvement amendments of 1988 (CLIA)-waived point-of-care assays: a paradigm shift to molecular tests, J. Clin. Microbiol. (56) (2018) e00367–18.
[13] C.B. Duncan, E.E. Walsh, D.R. Peterson, et al., Risk factors for respiratory failure associated with respiratory syncytial virus infection in adults, J. Infect. Dis. 200 (2009) 1242–1246.
[14] C.A. Hogan, C. Caya, J. Papenburg, Rapid and simple molecular tests for the detection of respiratory syncytial virus: a review, Expert Rev. Mol. Diagn. (2018) 1–13.
[15] A.H.L. Bruning, M.M.G. Leeflang, J.M.B.W. Vos, et al., Rapid tests for influenza, respiratory syncytial virus, and other respiratory viruses: a systematic review and meta-analysis, Clin. Infect. Dis. 65 (2017) 1026–1032.
[16] C.M. Midgley, A.K. Haynes, J.L. Baumgardner, et al., Determining the seasonality of respiratory syncytial virus in the United States: the impact of increased molecular testing, J. Infect. Dis. 216 (2017) 345–355.
[17] D.M. Fleming, R.J. Taylor, R.L. Lustig, et al., Modelling estimates of the burden of Respiratory Syncytial virus infection in adults and the elderly in the United Kingdom, BMC Infect. Dis. 15 (2015) 443.
[18] C. Amand, S. Tong, A. Kieffer, M.H. Kyaw, Healthcare resource use and economic burden attributable to respiratory syncytial virus in the United States: a claims database analysis, BMC Health Serv. Res. 18 (2018) 294.
[19] S.T. Pastula, J. Hackett, J. Coalson, et al., Hospitalizations for respiratory syncytial virus among adults in the United States, 1997-2012, Open Forum Infect. Dis. 4 (2017) ofw270.
[20] K. Widmer, Y. Zhu, J.V. Williams, et al., Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults, J. Infect. Dis. 206 (2012) 56–62.
[21] L. Bont, P.A. Checchia, B. Fauroux, et al., Defining the epidemiology and burden of severe respiratory syncytial virus infection among infants and children in Western countries, Infect. Dis. Ther. 5 (2016) 271–298.
[22] A.R. Falsey, P.A. Hennessey, M.A. Formica, et al., Respiratory syncytial virus infection in elderly and high-risk adults, N. Engl. J. Med. 352 (2005) 1749–1759.
[23] D. Liu, Q. Chen, H. Zhu, et al., Association of respiratory syncytial virus toll-like receptor 3-mediated immune response with COPD exacerbation frequency, Inflammation 41 (2018) 654–666.
[24] S. Abbas, J.E. Raybould, S. Sastry, O. de la Cruz, Respiratory viruses in transplant recipients: more than just a cold. Clinical syndromes and infection prevention principles, Int. J. Infect. Dis. 62 (2017) 86–93.
[25] A.P. Campbell, K.A. Guthrie, J.A. Englund, et al., Clinical outcomes associated with respiratory virus detection before allogeneic hematopoietic stem cell transplant, Clin. Infect. Dis. 61 (2015) 192–202.
[26] C. Chartrand, N. Tremblay, C. Renaud, J. Papenburg, Diagnostic accuracy of rapid antigen detection tests for respiratory syncytial virus infection: systematic review and meta-analysis, J. Clin. Microbiol. 53 (2015) 3738–3749.
[27] F. Ko, S.J. Drews, The impact of commercial rapid respiratory virus diagnostic tests on patient outcomes and health system utilization, Expert Rev. Mol. Diagn. 17 (2017) 917–931.
[28] S. Datta, E.E. Walsh, D.R. Peterson, A.R. Falsy, Can Analysis of Routine Viral Testing Provide Accurate Estimates of Respiratory Syncytial Virus Disease Burden in Adults? J. Infect. Dis. 215 (2017) 1706–1710.
[29] Ş Keske, Ö Ergönül, F. Tutucu, et al., The rapid diagnosis of viral respiratory tract infections and its impact on antimicrobial stewardship programs, Eur. J. Clin. Microbiol. Infect. Dis. 37 (2018) 779–783.
[30] B.B. Rogers, P. Shankar, R.C. Jerris, et al., Impact of a rapid respiratory panel test on patient outcomes, Arch. Pathol. Lab. Med. 139 (2015) 636–641.
[31] S.L. Mitchell, Y.C. Chang, K. Feemster, A.M. Cárdenas, Implementation of a rapid influenza A/B and RSV direct molecular assay improves emergency department oseltamivir use in paediatric patients, J. Med. Microbiol. 67 (2018) 358–363.
[32] D.T. Rogan, M.S. Kochar, S. Yang, et al., Impact of rapid molecular respiratory virus testing on real-time decision making in a pediatric emergency department, J. Mol. Diagn. 19 (2017) 460–467.
[33] D.A. Green, L. Hitoaliaj, B. Kotansky, S.M. Campbell, D.R. Peaper, Clinical utility of on-demand multiplex respiratory pathogen testing among adult outpatients, J. Clin. Microbiol. 54 (2016) 2950–2955.
[34] N. Lee, E.E. Walsh, I. Sander, R. Stolper, J. Zakar, V. Wyffels, D. Myers, R. Fleischhackl, Delayed diagnosis of respiratory syncytial virus infections in hospitalized adults: individual patient data, chart review analysis and physician survey in the USA, J. Infect. Dis. (2019), https://doi.org/10.1093/infdis/jiz236 [Epub ahead of print] PMID: 31070757.
[35] U. Rappo, A.N. Schuetz, S.G. Jenkins, et al., Impact of early detection of respiratory

viruses by multiplex PCR assay on clinical outcomes in adult patients, J. Clin. Microbiol. 54 (2016) 2096–2103.
[36] M. Semret, I. Schiller, B.A. Jardin, et al., Multiplex respiratory virus testing for antimicrobial stewardship: a prospective assessment of antimicrobial use and clinical outcomes among hospitalized adults, J. Infect. Dis. 216 (2017) 936–944.
[37] J.M. Walter, R.G. Wunderink, Testing for respiratory viruses in adults with severe lower respiratory infection, Chest. (2018) Jun 14. [Epub ahead of print].
[38] D. Andrews, Y. Chetty, B.S. Cooper, et al., Multiplex PCR point of care testing versus routine, laboratory-based testing in the treatment of adults with respiratory tract infections: a quasi-randomised study assessing impact on length of stay and antimicrobial use, BMC Infect. Dis. 17 (2017) 671.
[39] N.J. Brendish, A.K. Malachira, L. Armstrong, et al., Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial, Lancet Respir. Med. 5 (2017) 401–411.
[40] J.W. Tang, T.T. Lam, H. Zaraket, et al., Global epidemiology of non-influenza RNA respiratory viruses: data gaps and a growing need for surveillance, Lancet Infect. Dis. 17 (2017) e320–326.
[41] L. Kim, B. Rha, J.S. Abramson, et al., Identifying gaps in respiratory syncytial virus disease epidemiology in the United States prior to the introduction of vaccines, Clin. Infect. Dis. 65 (2017) 1020–1025.
[42] W. Binder, J. Thorsen, P. Borczuk, RSV in adult ED patients: do emergency providers consider RSV as an admission diagnosis? Am. J. Emerg. Med. 35 (2017) 1162–1165.
[43] S. Datta, E.E. Walsh, D.R. Peterson, A.R. Falsey, Can analysis of routine viral testing provide accurate estimates of respiratory syncytial virus disease burden in adults? J. Infect. Dis. 215 (11) (2017) 1706–1710.
[44] E.B. Rose, A. Wheatley, G. Langley, S. Gerber, A. Haynes, Respiratory Syncytial Virus Seasonality - United States, 2014–2017, MMWR Morb. Mortal. Wkly. Rep. 67 (2018) 71–76.
[45] P.C. Schreckenberger, A.J. McAdam, Point-Counterpoint: large multiplex PCR panels should be first-line tests for detection of respiratory and intestinal pathogens, J. Clin. Microbiol. 53 (2015) 3110–3115.
[46] A.M. Caliendo, D.N. Gilbert, C.C. Ginocchio, et al., Better tests, better care: improved diagnostics for infectious diseases, Clin. Infect. Dis. 57 (Suppl 3) (2013) S139–S170.