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Diagnostic Microbiology and Infectious Disease 91 (2018) 331–335

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

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

Clinical Studies

Impact of a multiplex PCR point-of-care test for influenza A/B and respiratory syncytial virus on an acute pediatric hospital ward☆

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ARTICLE INFO

Article history:
Received 3 November 2017
Received in revised form 22 February 2018
Accepted 20 March 2018
Available online 4 April 2018

Keywords:
Respiratory syncytial virus
Influenza virus A
Influenza virus B
Point-of-care technology
Rapid diagnostic tests

ABSTRACT

Patients with respiratory infections are often managed presumptively until confirmation of infection status. We assessed the impact of introducing the Enigma® MiniLab™ FluAB-RSV point-of-care test (POCT) on patients admitted with a suspected respiratory virus driven illness in an acute pediatric ward. This utilized a before and after design (respiratory viral seasons 2013/14 versus 2014/15). Following POCT implementation, oseltamivir prescribing increased in patients with influenza (OR = 12.7, $P = 0.05$, 95% CI [1.0, 153.8]). A reduction in the average reimbursement charges without a change in the length of stay was observed. Modeling suggested that laboratory test cost savings could be achieved if the POCT cost £30 and was used for screening, followed by the respiratory viral panel for RSV and influenza negative patients. A rapid POCT for influenza A/B and RSV infections in pediatric inpatients may improve oseltamivir prescribing, strengthen antimicrobial stewardship, reduce reimbursement charges and decrease laboratory costs.

1. Introduction

Influenza and respiratory syncytial viruses (RSV) are common causes of respiratory infections and can be particularly severe in children resulting in significant mortality (Nair et al., 2010). In the United Kingdom (UK), children aged under 15 years comprise 37% of all influenza-attributable hospital admissions (Cromer et al., 2014). The estimated hospital admission rate for influenza in previously healthy children aged under five years reaches 1.9 per 1,000 annually in England and is more than five times greater in children aged 5 to 14 who have comorbidities (Cromer et al., 2014). Influenza-like-illness (ILI) places a significant burden on healthcare systems (Rudan et al., 2005). In the United States, over 600,000 life years are lost, at a cost of $87.1 billion every influenza season (Molinari et al., 2007).

To reduce risk of hospital transmission, it is recommended that patients suspected of having either influenza or RSV infection are presumptively isolated in a side room or are cohorted with other patients, until confirmatory testing is available (Guy's and St. Thomas' NHS Foundation Trust, 2015; Public Health England, 2016a). Patients with confirmed influenza or those presenting during active influenza season should be offered antiviral treatment within 48 hours of symptom onset (Public Health England, 2016b). However, the prescribing of antivirals remains low in hospitalized children with only 9.3-11% of those eligible receiving these medications (Seale et al., 2011; Wilkes et al., 2009).

Centralized laboratory testing of respiratory samples can be slow (Douthwaite et al., 2016); reducing turnaround time may enable earlier appropriate treatment and / or improved cohorting and isolation strategies to prevent transmission. While enzyme immunoassay based point-of-care tests (POCTs) for influenza and RSV have been available for several years, a health technology appraisal found little benefit of using these devices in a near-patient setting (Nicholson et al., 2014). Moreover, these tests have lower sensitivities compared to PCR-based devices (Boku et al., 2013; DiMaio et al., 2012; Goldenberg and Edgeworth, 2015). A new multiplex PCR-based POCT, Enigma® MiniLab™ FluAB-RSV PCR assay (Enigma Diagnostics Ltd, Salisbury, UK), became available in 2015. The performance characteristics of a commonly used laboratory based respiratory pathogen panel (xTAG®)

☆ **Acknowledgments:** This study was funded by Enigma Diagnostics, and supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust. The study, data analysis and discussion were independently carried out by the study team, and all analysis and discussion are the authors' own.We would like to thank all of the staff at St Thomas' Hospital who collected the data for this study, in particular the staff on Mountain Ward (acute pediatric inpatient ward). Certain people provided extra help and advice: Charlotte Walker, Victoria Felton, Lorraine Colthurst, James Ross, David Taylor, Phillip Li, Jane Tozer, John Roberts, Jamie Crocker, Paul Wade, Nuria Martinez-Alier, and Karen Stein. Thanks to Daniel Gibbons for useful comments.

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https://doi.org/10.1016/j.diagmicrobio.2018.03.013
0732-8893/

and the POCT assay are summarized in **Table A1** (**Appendix 1,** Supplementary Data) (Lopes et al., 2012; Luminex Molecular Diagnostics, 2011; Perez-Ruiz et al., 2012).

We undertook a real-world evaluation to assess the impact of introducing the Enigma® MiniLab™ FluAB-RSV POCT in a pediatric ward compared to current care using just the laboratory test. This evaluated the length of stay, electronically recorded drug prescriptions including oseltamivir and antibiotics, laboratory tests, associated costs of drug prescriptions and laboratory tests, and reimbursement charges.

2. Materials and methods

2.1. Population and study design

The evaluation was conducted on the acute pediatric ward of the Evelina London Children's Hospital (Guys and St Thomas NHS Foundation Trust) in patients with suspected ILI (with typical symptoms of fever, headache, myalgia, cough, coryza and pharyngitis) or bronchiolitis (with typical presentation of one of more of the following; fever, rhinitis, cough, increased work of breathing and wheeze). Inpatient admission data was collected during the main influenza season between November 1 and February 28 of two consecutive years, for patients having a Respiratory Viral Panel (RVP) (xTAG® RVPfast2, Luminex Corp, Austin, TX) ordered within 72 hours of admission. Patients admitted during the 2013/14 season when only the RVP was used (period 1) were compared (with data collected retrospectively) to those during the 2014/15 season, in which both the POCT and the RVP were used in parallel (period 2). In period 2, the POCT was available for use 24 hours a day, 7 days a week for any patient admitted to Mountain Ward who required a swab taken for respiratory virus diagnostic testing. The final sample size was 274 (period 1) and 300 (period 2) (see **Appendix 2** for details, Supplementary Data). Staff were encouraged to act on the POCT result although no formal protocol was introduced. Study outcomes are presented from the perspective of the National Health Service (NHS). Research Ethics Committee approval was waived as this was classified as a service evaluation. The manufacturer of the POCT funded the study but did not have any role in analysis or reporting of findings.

2.2. Outcomes

Four outcomes were used to assess the impact of the POCT: length of stay, drug utilization (oseltamivir and antibiotics) and overall drug costs, ancillary laboratory test utilization and costs, and tariff reimbursement charges for both the total inpatient admission and the reimbursement for attributable time spent on the acute pediatric ward.

2.3. Drugs

Patient level prescribing data that was available in the electronic patient records was obtained for the entire hospital stay, including costs of pharmacy supplied items. All admissions in which oseltamivir, antibiotics, and immunoglobulins were prescribed were identified. The costs of all medications (for that prescribing year, converted to 2014/15 drug price) were determined to estimate the average total drug costs per admission. Drugs administered from ward stock were not captured in the electronic patient data; these potentially relevant antibiotics included amoxicillin, benzylpenicillin, cephalexin, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, clarithromycin, clindamycin, co-amoxiclav, erythromycin, flucloxacillin, gentamicin, metronidazole, trimethoprim, and vancomycin.

2.4. Laboratory tests

For each admission, the number of laboratory tests were obtained (12 admissions had no test data and were excluded from the analysis of test costs). Prices from the hospital's 2014/15 laboratory provider were used (unpublished).

2.5. Reimbursement charges

Reimbursement charges represent the payments made to the hospital from payors for completed patient admissions. These estimate the standard associated care costs (staff, hotel, indirect/overheads, standard diagnostics, medications, and procedures).

Reimbursement charges for admissions in the NHS are coded as Health Care Resource Groups (HRG), which are groupings of activities based on the International Classification of Disease version 10 (ICD-10) diagnostic codes, and specific procedures and interventions performed during an admission (NHS Digital, 2013). For a given code, factors including admission type (elective or emergency presentation), complications, length of stay, and specialized top-up services determine the final reimbursement charge. HRG codes and reimbursement charges from 2014/15 were used for both periods in the analysis (NHS Digital, 2013).

2.6. Data analysis

Descriptive statistics were reported for all eligible admissions during both periods. These included age (in months), sex, complications during admission, 'relevant conditions', being discharged with a respiratory HRG code, admission to the High Dependency Unit (HDU), total length of stay, length of stay on the acute pediatric ward, proportion of admissions where oseltamivir, antibiotics and immunoglobulin were prescribed, average total drug costs per admission, average number of laboratory tests per admission and per day, average total test cost, average total reimbursement charge and average acute pediatric ward reimbursement charge.

A 'relevant condition' is defined as an ICD-10 diagnostic code that is either an indication for receiving influenza vaccination (Public Health England, 2016c) or is clinically associated with a respiratory infection (see **Appendix 3**, Supplementary Data). This was included to control for conditions that could increase the risk of potential complications resulting from, and thereby the cost of, treating an influenza- or RSV-related infection. Certain HRG codes were distinguished as being 'with complications' as determined by patient acuity and we created a variable to control for that. We also created a variable for admissions that were discharged with a respiratory HRG code (see **Appendix 4**, Supplementary Data).

The proportion of positive results for each virus detected by the RVP in both periods was determined. Bivariate tests (χ^2 and t tests for categorical and continuous variables respectively) were conducted on all variables to determine whether there were statistically significant differences between periods.

To examine the effect of the use of POCT on the outcome of oseltamivir and antibacterial prescribing, we used the admission period as a proxy to estimate the odds ratio (OR) using logistic regression. The regression model is shown in **Appendix 2**, Supplementary Data. We also conducted multivariate linear regression analyses to explore the impact of the period on average reimbursement charges, and cost of drugs and laboratory tests. Regression analyses were controlled for potentially confounding patient characteristics: age, sex, having a relevant condition, having a complication, and HDU admission.

The effect on costs of laboratory tests was modeled if the POCT was used as a 'gatekeeper' screening test that was always performed before an RVP, i.e. patients with a positive POCT would require no further investigation whereas a follow-up RVP would be performed for those with a negative POCT. To analyze this, we removed the costs of the RVP tests performed in period 2 for patients who tested positive for

RSV and / or influenza A/B on POCT (see **Appendix 5,** Supplementary Data). We used an assumed cost of £30 for the POCT test.

To account for the skewed distribution of costs, a logarithmic transformation of cost was utilized as the outcome, which is a widely used strategy for analyses with non-normal distributions (Altman et al., 1983; Duan, 1983; Garrido et al., 2012; Manning and Mullahy, 2001). See **Appendix 2** (Supplementary Data) for additional information. All analyses were performed in Stata 11 for Windows (STATACorp, College Station, TX) and statistical significance was assumed at $\alpha = 0.05$.

3. Results

3.1. Descriptive statistics

Descriptive statistics are presented in Table 1. Patients in period 1 were significantly younger (median 19 vs. 26 months, $P < 0.01$) and had a higher occurrence of complications (22.3% vs. 13.0%, $P < 0.01$). The prescribing of oseltamivir and antibiotics between the two periods did not significantly differ from each other without controlling other potential confounders. There was also no evidence of significant differences for the other variables.

There was no significant difference between the periods for the total length of stay (median = 2 days for both periods, $P = 0.23$), or length of stay on the acute pediatric ward (median = 2 days for both periods, $P = 0.91$). The average reimbursement charges were not statistically different between periods. There was a slight increase in the number of respiratory HRGs in period 2, although it was not significant (51.1% vs. 59.0%, $P = 0.06$).

The proportion of positive results for the nine viruses included in the RVP was similar in both periods (Table 2), suggesting that overall burden of infection was similar between years.

Table 1
Descriptive statistics of the eligible admissions for periods 1 and 2.

	Period 1 ($n = 274$)	Period 2 ($n = 300$)	*P*-value
Patient characteristics			
Age – months (median, range)	19 (0-209)	26 (0-224)	<0.01
0–11 months (n, %)	102 (37%)	73 (24%)	
12–59 months (n, %)	123 (45%)	150 (50%)	
≥60 months (n, %)	49 (18%)	77 (26%)	
Female sex (n, %)	110 (40.1)	114 (38.0)	0.60
With a complication (n, %) [a]	61 (22.3)	39 (13.0)	<0.01
With a relevant condition (n, %) [b]	94 (34.3)	103 (34.3)	0.99
With a respiratory HRG (n, %) [c]	140 (51.1)	177 (59.0)	0.06
Requiring hospitalization in the High Dependency Unit (HDU) (n, %)	16 (5.8)	25 (8.3)	0.25
Length of Stay			
Length of stay – days (median, range)	2 (0-36)	2 (0-116)	0.23
Length of stay on the acute pediatric ward – days (median, range)	2 (0-36)	2 (0-56)	0.91
Drug Utilization and Costs			
Admissions with antivirals prescribed (n, %)	15 (5.5)	23 (7.7)	0.29
Admissions with oseltamivir prescribed (n, %)	12 (4.4)	23 (7.7)	0.10
Admissions positive for influenza with oseltamivir prescribed (n, %)	2 (13.3)	8 (40.0)	0.08
Admissions with antibiotics prescribed (n, %)	97 (35.4)	101 (33.7)	0.66
Admissions with immunoglobulins prescribed (n, %)	7 (2.6)	4 (1.3)	0.29
Average total drug cost (£, mean ± SD)	145 ± 470	136 ± 318	0.78
Laboratory Tests Utilization and Costs			
Number of laboratory tests per admission (n, mean ± SD)	24 ± 16	23 ± 17	0.41
Number of laboratory tests per admission day (n, mean ± SD)	13 ± 8	12 ± 8	0.11
Average total test cost (£, mean ± SD)	1,251 ± 373	1,219 ± 367	0.31
Reimbursement Charges			
Average reimbursement charge for the entire admission (£, mean ± SD)	1,468 ± 2,081	1,444 ± 2,484	0.90
Average reimbursement charge on the acute pediatric ward (£, mean ± SD)	1,355 ± 1,289	1,399 ± 2,421	0.79

[a] Complication defined as per the HRG discharge code.
[b] *ICD-10* codes for relevant conditions (C92, D57, D70, D73, D84, G12, G80, G93, I42, I50, I67, J18, J20, J44, J45, P27, P28, Q02, Q20, Q21, Q22, Q23, Q25, Q31, Q32, Q62, Q90, Z99). Full names can be found in **Appendix 3,** Supplementary Data.
[c] Respiratory HRGs: PA19A, PA14E, PA12Z, PA11Z, PA15A, PA14C, PA19B, PA65A. Full names can be found in **Appendix 4,** Supplementary Data.

3.2. Prescriptions for oseltamivir and antibiotics

Controlling for other potential confounding factors, the OR of oseltamivir prescription was 12.7 ($P = 0.05$, 95% CI [1.0, 153.8]) for admissions that were positive for influenza in period 2 compared to period 1 with marginally statistical significance. We did not observe significant differences in non-influenza and non-RSV patients (Table 3). There were no significant differences in the OR of antibiotics prescribed between periods in those positive for influenza and negative for both influenza and RSV.

3.3. Costs

For patients with a negative influenza and RSV test, we found reductions in the average reimbursement charge for both the entire admission and the stay on the acute pediatric ward (reductions of £165, $P = 0.05$, 95% CI [-£2, £332] and £148, $P = 0.05$, 95% CI [£1, £295], respectively); the cost saving effects remained when we look at all patients (reduction of £134, $P = 0.04$, 95% CI [£4, £265] and £126, $P = 0.03$, 95% CI [£10, £242], respectively) (Table 4). There was no change in reimbursement for patients with proven influenza or RSV infection. There was a small but significant increase in the cost of drugs electronically recorded between periods 1 and 2 for admissions in which the patients were positive for influenza and/or RSV (£12 increase, $P < 0.01$, 95% CI [-£21, -£3]).

Using simple modeling techniques, savings in the costs of laboratory tests could be realized if the POCT were to be used as a screening gateway test followed by an RVP for negative influenza/RSV results only, based on a POCT cost £30. The average estimated savings would be £44 ($P < 0.01$, 95% CI [£34, £53]) for all admissions, with the biggest difference in cost savings in positive influenza/RSV patients (saving of £105, $P < 0.01$, 95% CI [£93, £117]).

4. Discussion

This is the first evaluation to use a PCR-based POCT for influenza and RSV in a pediatric inpatient ward setting. Although not a randomized control trial, this before and after study suggested an increase in more accurate oseltamivir prescribing for patients with influenza following the introduction of the POCT, which may be due to improved compliance with clinical guidelines (NICE, 2009). Modeling of the data to

Table 2
Proportion positive of infections according to the respiratory viral panel result, by period [a].

Viral panel results	Period 1 (n = 274)	Period 2 (n = 300)	*P*-value
Influenza A (%)	15 (5.5)	18 (6.0)	0.79
Influenza B (%)	0 (0.0)	2 (0.6)	0.18
Respiratory syncytial virus (%)	65 (23.7)	75 (25.0)	0.74
Metapneumovirus (%)	10 (3.6)	8 (2.7)	0.50
Coronavirus (%)	15 (5.5)	13 (4.3)	0.52
Enterovirus (%)	106 (38.7)	116 (38.7)	0.97
Adenovirus (%)	10 (3.6)	11 (3.7)	1.00
Bocavirus (%)	10 (3.6)	14 (5.3)	0.55
Parainfluenza (%)	13 (4.7)	13 (4.3)	0.81
No evidence of viral infection (%)	74 (27.4)	73 (24.3)	0.46

[a] There are cases with multiple viral infections, so total number and percentages do not sum to 100%.

Table 3
Odds ratios of prescriptions of oseltamivir and antibiotics between the two periods (period 2 compared to period 1) [a].

	Admissions positive for influenza		Admissions negative for influenza and RSV	
	Odds ratio [95% CI]	*P*-value	Odds ratio [95% CI]	*P*-value
Admissions with oseltamivir prescribed	12.7 [1.0, 153.8]	0.05	0.7 [0.3, 2.0]	0.54
Admissions with antibiotics prescribed	0.4 [0.1, 2.7]	0.38	1.0 [0.6, 1.5]	0.79

[a] Controlling for age, sex, having at least one relevant condition, having a complication, and requiring hospitalization in the high-dependency unit; only showing the odds ratios for the variable 'period'. For complete model output, please see **Appendix 6**, Supplementary Data.

account for differences in the patient groups between periods 1 and 2 suggested reduced reimbursement charges for patients without influenza or RSV despite no observed change in length of stay. We also noted reduced costs of laboratory tests for all patients when the POCT was implemented, assuming the POCT was £30.

Our results are consistent with prior research showing that a POCT can increase appropriate oseltamivir use in a pediatric hospital (Bonner et al., 2003). This may be because confirmation of diagnosis was achieved on admission, thereby allowing clinicians to prescribe oseltamivir within 48 hours from the onset of symptoms, when it has greatest therapeutic effect (NICE, 2009). In period 1, over 85% of patients with influenza did not receive oseltamivir, which could have had negative consequences for patient care; a POCT could enable more timely and effective care for these patients.

While we did not observe a significant reduction in oseltamivir prescribing in patients who tested negative for influenza and RSV in period 2, an OR of 0.7 indicates a tendency towards decreased prescribing. In our real-world evaluation, this observation might be due to clinicians being unfamiliar and thus less trusting of the POCT and therefore continuing to prescribe oseltamivir if there are ongoing signs and symptoms of ILI.

While the result of antibiotic prescription in influenza positive patients did not reach statistical significance, the odds of prescribing antibiotics were estimated to halve for those positive for influenza in period 2. This compares with a study that evaluated the impact of a rapid diagnostics of influenza in the pediatric emergency department setting that detected a significant reduction in antibiotic prescription in the group which clinicians were informed of the positive results of the flu rapid test (Bonner et al., 2003). However, in our study, many antibiotics could have been administered directly through the ward supply and data on their use was unavailable to us in the electronic patient records. Hence, we do not know if there was a true change in antibiotic use across the time periods, or about the small observed increases in drug costs in period 2 for those with influenza and/or RSV. We would hope that a POCT might facilitate better antimicrobial stewardship in patients with suspected respiratory viral infection, but further studies are needed to assess this.

The average number of laboratory tests ordered remained unchanged between the periods. As the estimated test costs decreased in period 2, less expensive follow-up tests may have been requested following the POCT result, despite no changes in testing guidelines. This change in practice has been observed previously (Bonner et al., 2003). This suggests that a POCT could function as a gateway or screening test to prevent the use of additional or more expensive tests, with the benefit of providing a faster result. This could be seen if a POCT is implemented in other settings, as performing fewer expensive tests could be cost-saving for any healthcare provider treating patients during respiratory season. We could reasonably expect results of a similar or greater magnitude to those observed in this study if the POCT was deployed in the Emergency Department and tests were performed before patients arrived on the ward.

During period 2, reimbursement charges for the entire admission and for the stay on the acute pediatric ward decreased for patients who had negative results for both influenza and RSV. As we controlled for all known complications, any resultant residual confounding or effect modification should be minimized. There was no observed change in length of stay between the periods, suggesting that the changes in the reimbursement are not due to the different length of hospital admissions. However, reimbursement charges are determined by a range of variables, and it is difficult to specifically attribute the reduction in reimbursement to the POCT, although it may have been a factor.

It should be noted that there were differences in the epidemiology of influenza infections in 2013/14 and 2014/15. In a report from Public Health England, the peak rate of hospitalization (all ages) in 2014 to 2015 (1.9/100,000) was higher than the peak seen during 2013 to 2014 (0.8/100,000) (Public Health England, 2015). However, UK sentinel hospital surveillance indicated that the proportion of confirmed Influenza A confirmed hospitalized cases in those under the age of 17 years was lower in 2014/15 than 2013/14 (22% and 27% respectively). Excess all-cause mortality in all age groups increased from 0.2% in 2013/14 to 5.4% in 2014/15. Despite these differences, we did not observe any significant differences in the distribution of respiratory viruses during the study periods (Table 2). Conversely, we observed a greater rate of recorded complications (22.3% vs. 13.0%, $P < 0.01$ for 2013/14 and 2014/15 respectively) in the study population.

Furthermore, the rate of national uptake of live attenuated influenza vaccine in 2- and 3-year olds was lower in 2014/15 (38.5% and 32.9% respectively) compared to 2013/14 (42.6% and 39.5% respectively). Overall vaccine effectiveness may also have been different for the two periods (Caspard et al., 2017). It is not known what these differences may have had on the study findings. For example, it is possible that the change in oseltamivir prescribing was influenced by the increasing incidence of influenza A and/or increase in all cause excess mortality over the two periods. However, as these are national data and these parameters were not measured for the study population, it is not possible draw any definitive conclusions.

Table 4
Average reimbursement charge, and drug cost and laboratory test cost savings by type of patient for period 2 compared to period 1[a].

	Patients with influenza and/or RSV		Patients without influenza and RSV		All patients	
	Savings [95% CI]	*P*-value	Savings [95% CI]	*P*-value	Savings [95% CI]	*P*-value
Reimbursement for total admission (£)	50 [-204, 304]	0.70	165 [-2, 332]	0.05	134 [4, 265]	0.04
Reimbursement for stay on the acute pediatric ward (£)	74 [-162, 311]	0.53	148 [1, 295]	0.05	126 [10, 242]	0.03
Cost of drugs (£)	-12[b] [-21, -3]	<0.01	0 [-11, 10]	0.94	-3 [-11, 5]	0.47
Modeled costs of lab tests (£) (with assumed POCT cost of £30)	105 [93, 117]	<0.01	13 [1, 24]	0.03	44 [34, 53]	<0.01

[a] Controlling for age, sex, having at least one relevant condition, having a complication, and requiring hospitalization in the high-dependency unit.
[b] Negative savings imply an additional cost in the second period with regard to the first period.

There are several limitations of this study. First, there are potential unobserved factors which might influence the results. For instance, as a before and after evaluation, we did not control for unobservable time-varying factors; also, the study was performed while the hospital was attempting to improve its coding practices, which may have independently contributed to the results.

Second, because of unfamiliarity with the POCT test, clinicians may have still relied on the RVP results to make clinical decisions. We believe our results are likely to underestimate the true effect that the implementation of the test could have once the test has become embedded and trusted by clinicians.

The study was undertaken in one center and findings may not be generalizable. However, in terms of resource utilization, we believe that the impact of a POCT in other pediatric inpatient wards may be similar to what we observed in this study, given similar patterns of influenza and RSV.

Lastly, we were unable to determine whether patients were placed on cohorted or general wards, or in isolation beds. This information is not reliably recorded in the patient record, so we are unable to assess the impact of a POCT on bed management. Results from a questionnaire conducted at the time of the study suggested that ward staff felt the test improved bed management (results available upon request from the authors). We recommend conducting a time and motion analysis to capture other cost drivers, such as staff time. Further studies should also explore a packaged antimicrobial stewardship intervention involving an influenza/RSV POCT, including staff training on best prescribing practice following the POCT result. This study demonstrates that POCTs may have the potential to improve the appropriateness and efficiency of management of ILI in pediatric patients and strengthen antimicrobial stewardship practice.

Compliance with ethical standards

Conflict of interest

SD reports grants from Enigma Diagnostics Ltd, during the conduct of the study; previous grants from Beckton Dickinson. At the time of the study, EJA, AIVO, CYC, REG and CM were employed by Aquarius Population Health who receive project funding from Cepheid, Atlas Genetics, and other organizations with POCTs and government NIHR funding unrelated to this work. SG reports grants from Enigma Diagnostics Ltd, during the conduct of the study; personal fees from Becton Dickinson, grants and personal fees from Luminex Corp, grants and personal fees from Astellas, personal fees from Abbott, personal fees from Merck, personal fees from Qiagen, grants from Bio-Rad, grants from GenMark Diagnostics, outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diagmicrobio.2018.03.013.

References

Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J (Clin Res Ed) 1983;286(6376):1489–93.

Boku S, Naito T, Murai K, Tanei M, Inui A, Nisimura H, et al. Near point-of-care administration by the attending physician of the rapid influenza antigen detection immunochromatography test and the fully automated respiratory virus nucleic acid test: contribution to patient management. Diagn Microbiol Infect Dis 2013;76(4):445–9.

Bonner AB, Monroe KW, Talley LI, Klasner AE, Kimberlin DW. Impact of the Rapid Diagnosis of Influenza on Physician Decision-Making and Patient Management in the Pediatric Emergency Department: Results of a Randomized, Prospective, Controlled Trial. Pediatrics 2003;112(2):363–7.

Caspard H, Mallory RM, Yu J, Ambrose CS. Live-Attenuated Influenza Vaccine Effectiveness in Children From 2009 to 2015–2016: A Systematic Review and Meta-Analysis. Open Forum Infect Dis [Internet] 2017;4(3). [cited 2018 Jan 15, Available from: https://academic.oup.com/ofid/article/4/3/ofx111/4004900].

Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D, Miller E. The burden of influenza in England by age and clinical risk group: A statistical analysis to inform vaccine policy. J Infect 2014 Apr;68(4):363–71.

DiMaio MA, Sahoo MK, Waggoner J, Pinsky BA. Comparison of Xpert Flu rapid nucleic acid testing with rapid antigen testing for the diagnosis of influenza A and B. J Virol Methods 2012;186(1–2):137–40.

Douthwaite ST, Walker C, Adams EJ, Mak C, Ortiz AV, Martinez-Alier N, et al. Performance of a Novel Point-of-Care Molecular Assay for Detection of Influenza A and B Viruses and Respiratory Syncytial Virus (Enigma MiniLab) in Children with Acute Respiratory Infection. J Clin Microbiol 2016;54(1):212–5.

Duan N. Smearing Estimate: A Nonparametric Retransformation Method. J Am Stat Assoc 1983;78(383):605–10.

Garrido MM, Deb P, Burgess JF, Penrod JD. Choosing Models for Health Care Cost Analyses: Issues of Nonlinearity and Endogeneity. Health Serv Res 2012;47(6):2377–97.

Goldenberg SD, Edgeworth JD. The Enigma ML FluAB-RSV assay: a fully automated molecular test for the rapid detection of influenza A, B and respiratory syncytial viruses in respiratory specimens. Expert Rev Mol Diagn 2015;15(1):23–32.

Guy's and St. Thomas' NHS Foundation Trust. Clinical Guideline - Chapter 31: Seasonal respiratory viruses, including influenza. London: Guy's and St Thomas' NHS Foundation Trust; 2015.

Lopes E, Merante F, Himsworth D, Ginocchio D, Qian Y. Clinical Performance of the xTAG® Respiratory Viral Panel FAST v2 with Subtyping Capability of Influenza A 2009 H1N1 Non-seasonal Variant. 22nd European Congress of Clinical Microbiology and Infectious Diseases; 2012. [London].

Luminex Molecular Diagnostics. Performance Characteristics of the xTAG® Respiratory Viral Panel FAST. Toronto: Luminex Molecular Diagnostics; 2011.

Manning WG, Mullahy J. Estimating log models: to transform or not to transform? J Health Econ 2001;20(4):461–94.

Molinari N-AM, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E, et al. The annual impact of seasonal influenza in the US: Measuring disease burden and costs. Vaccine 2007;25(27):5086–96.

Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010;375(9725):1545–55.

NHS Digital. HRG4 2014/15 Consultation Grouper [Internet]. [cited 2015 Oct 28], Available from: www.hscic.gov.uk/article/3590/HRG4-201415-Consultation-Grouper, 2013.

NICE. Amantadine, oseltamivir and zanamivir for the treatment of influenza [Internet]. NICE; 2009 [Feb cited 2017 Apr 19, Available from: https://www.nice.org.uk/guidance/ta168?unlid=724409635201613117303].

Nicholson KG, Abrams KR, Batham S, Medina MJ, Warren FC, Barer M, et al. Randomised controlled trial and health economic evaluation of the impact of diagnostic testing for influenza, respiratory syncytial virus and *Streptococcus pneumoniae* infection on the management of acute admissions in the elderly and high-risk 18- to 64-year-olds. Health Technol Assess 2014;18(36):1–274. [vii–viii].

Perez-Ruiz M, Pedrosa-Corral I, Sanbonmatsu-Gamez S, Rodriguez-Granger J, Navarro-Mari J. Preliminary evaluation of the new version of Luminex® Respiratory Viral Panel (xTAG® RVP Fast v2). 15h Annual Meeting of the European Society for Clinical Virology; 2012. [Madrid].

Public Health England. Surveillance of influenza and other respiratory viruses in the United Kingdom: winter 2014 to 2015 [Internet]. London, UK: Public Health England; 2015 [Report No.: PHE publications gateway number: 2015046. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/429617/Annualreport_March2015_ver4.pdf].

Public Health England. Infection control precautions to minimise transmission of acute respiratory tract infections in healthcare settings. London: Public Health England; 2016a.

Public Health England. PHE guidance on use of antiviral agents for the treatment and prophylaxis of influenza [Internet]. London: Public Health England; 2016b [cited 2015 Aug 5, Available from: www.gov.uk/government/uploads/system/uploads/attachment_data/file/400392/PHE_guidance_antivirals_influenza_2014-15_5_1.pdf].

Public Health England. Flu Plan - Winter 2016/17. London: Public Health England; 2016c.

Rudan I, Lawn J, Cousens S, Rowe AK, Boschi-Pinto C, Tomašković L, et al. Gaps in policy-relevant information on burden of disease in children: a systematic review. Lancet 2005;365(9476):2031–40.

Seale AC, Toussaint FS, Finn A, Fraser JI. Prescribing in a pandemic: best use of oseltamivir in paediatric intensive care. Arch Dis Child 2011;96(9):902–3.

Wilkes JJ, Zaoutis TE, Keren R, Desai B, Leckerman KH, Hodinka RL, et al. Treatment with oseltamivir in children hospitalized with community-acquired, laboratory-confirmed influenza: review of five seasons and evaluation of an electronic reminder. J Hosp Med 2009;4(3):171–8.