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The timing of respiratory virus molecular testing in emergency departments and its association with patient care outcomes

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Abstract

Objective: A rapid molecular diagnostic test (RMDT) offers a fast and accurate detection of respiratory viruses, but its impact on the timeliness of care in the emergency department (ED) may depend on the timing of the test. The aim of the study was to determine if the timing of respiratory virus testing using a RMDT in the ED had an association with patient care outcomes.

Design: Retrospective observational study.

Setting: Linked ED and laboratory data from six EDs in New South Wales, Australia.

Participants: Adult patients presenting to EDs during the 2017 influenza season and tested for respiratory viruses using a RMDT. The timing of respiratory virus testing was defined as the time from a patient's ED arrival to time of sample receipt at the hospital laboratory.

Outcome measures: ED length of stay (LOS), >4-hour ED LOS and having a pending RMDT result at ED disposition.

Results: A total of 2168 patients were included. The median timing of respiratory virus testing was 224 minutes (inter-quartile range,133-349). Every 30-minute increase in the timing of respiratory virus testing was associated with a 24.0-minute increase in the median ED LOS (95% confidence interval [CI], 21.8-26.1; P<0.001), a 51% increase in the likelihood of staying >4 hours in ED (odds ratio [OR], 1.51; 95% CI, 1.41-1.63; P<0.001) and a 4% increase in the likelihood of having a pending RMDT result at ED disposition (OR, 1.04; 95% CI, 1.02-1.05; P<0.001) after adjustment for confounders.

Conclusion: The timing of respiratory virus molecular testing in EDs was significantly associated with a range of outcome indicators. Results suggest the potential to maximise the benefits of RMDT by introducing an early diagnostic protocol such as triage-initiated testing.

Strengths and limitations of this study

- This is a retrospective observational study conducted across six EDs in Australia.
- It is the first study to assess the link between the timing of RMDT and patient outcomes in EDs.
- Data were obtained by linking the ED and laboratory information system datasets.
- Introducing an early diagnostic protocol such as ED triage-initiated testing may maximise the benefits of RMDTs.

Introduction

The accurate diagnosis of the cause of respiratory infections has over recent years depended on a molecular method using a multiplex polymerase chain reaction (PCR) panel testing. Multiplex PCR provides accurate diagnoses, but has been traditionally performed in a central laboratory with a lengthy test turnaround time (TAT), and with major repercussions for the efficiency of emergency department (ED) workflows and care processes.

ED overcrowding has been recognized as a growing problem in Australia and worldwide, contributing to deficits in the performance of the health system.[1-3] Delay in laboratory test results is often considered as one of many factors contributing to ED overcrowding and prolonged ED length of stay (LOS).[4-6] Fast result availability through the use of rapid diagnostic tests can potentially improve patient flow and lessen the burden of ED overcrowding.[7 8] Optimising patient flow is of particular importance given the 4-hour ED LOS target introduced in Australia in 2011 to improve the quality and timeliness of care across EDs.[9]

Diagnostic kits for the rapid diagnosis of respiratory viruses using a molecular PCR-based technology are now available for use in hospital-based laboratories. Existing evidence shows that RMDT in ED is associated with a significant decrease in hospital admissions [8 10], shorter TAT [8] and reductions in hospital resource utilisation.[11-13] However, evidence of the association between RMDT and ED LOS have been inconsistent.[8 14 15] Our previous study did not detect a significant association between RMDT use and ED LOS.[16] We hypothesised that this may be due to the fact that RMDT ordering took place a median of three hrs after a patient's ED arrival [16] suggesting that the impact of RMDT on ED LOS and other timeliness of care processes may depend on the timing of the test.

The aim of the study was to determine if the timing of respiratory virus testing using RMDT in ED is associated with indicators related to timeliness of patient care including ED LOS,

meeting the 4-hr ED LOS Australian emergency access target; having a pending RMDT result at ED disposition.

Method

Setting

A retrospective observational study was conducted across six public hospitals in New South Wales (NSW), Australia. All study sites provide 24-hour EDs: three principal referral hospitals (EDs A, B and D) with 76,228, 54,443 and 61,348 annual ED presentations respectively, two acute group A hospitals (ED C and ED F) with 50,025 and 38,039 annual ED presentations respectively and one public acute group A hospital (ED E) with 29,479 annual ED presentations (2016 data).[17]

Population

The study period was the 2017 influenza season, between 1 July and 31 October. The inclusion criteria were patients presenting to EDs with symptoms of respiratory infection and aged ≥18 years; Australasian triage scale categories of 3 (potentially life-threatening), 4 (potentially serious) or 5 (less urgent) and tested for respiratory viruses at a hospital-based laboratory using a RMDT. The RMDT used in this study was a Cepheid Xpert® Flu/RSV XC (Cepheid, Sunnyvale, CA). The Cepheid Xpert® Flu/RSV XC assay demonstrated a high sensitivity and specificity for rapid detection of influenza A, influenza B and RSV and RSV.[18]

Patients with triage categories of 1 (immediately life-threatening) or 2 (imminently life-threatening) were excluded from the current analysis as patients required urgent medical assessment and treatment. Relevant patient presentation characteristics and laboratory test data were obtained by linking the ED and laboratory information system datasets.[6]

Outcome measures

The primary outcome was ED LOS. ED LOS was defined as the length of time between ED arrival and patient disposition. The secondary outcomes included >4-hour ED LOS and having a pending RMDT result at ED disposition. A pending test result was defined as the unavailability of a verified RMDT result at the time of patient disposition from the ED.[19]

Statistical analysis

Descriptive statistics including medians with inter-quartile ranges (IQR) were reported. The RMDT TAT was defined as the time of sample receipt at the hospital laboratory to time of availability of RMDT result. The exploratory variable was the timing of respiratory virus testing using a RMDT, defined as the time from a patient's ED arrival to time of sample receipt at the hospital laboratory. For result interpretation purposes, the relationship between the timing of the RMDT and study outcomes were estimated for every 30-minute increase in the timing of the test.

The association between the timing of the RMDT and ED LOS was assessed using a median regression. As the ED LOS data were highly skewed, commonly used approaches such as ordinary least squares regression which models the conditional mean of the outcome variable was not appropriate methods.[20] Median regression is a special type of quantile regression which estimates the median of the outcome variable conditional on the values of the predictor variables.[21] It is robust to extreme values and therefore well suited for modelling such data.[22]

Binary logistic regression was used to assess the association between the timing of the RMDT and the secondary outcomes (e.g. >4-hour ED LOS, *yes/no*). The strength of the associations was measured using odds ratio (OR) with a 95% confidence interval (CI).

For all outcomes, the findings were reported for the overall sample and by study ED. Sub-group analyses by patient disposition and ED arrival time were also conducted. The baseline covariates included age, gender, triage category, arrival time, arrival day of week, mode of

arrival, patient disposition, overall number of tests ordered and number of test order episodes (tests ordered at one point in time during the ED stay). All analyses were adjusted for potential confounders – any variable having a significant association with a given outcome in a univariate analysis (P<0.05) was selected for the multivariate model. P-values were 2-tailed and P <0.05 was considered statistically significant. Analyses were conducted using Stata version 15 (StataCorp LP, College Station, TX).

Patient and public involvement

This study was conducted without patient and public involvement as it was a retrospective study conducted using pre-existing administrative data. The patients were not invited to comment on the study design and were not consulted to develop outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Baseline characteristics

A total of 2,168 patients were included in the study. Table 1 presents baseline characteristics. The median patient age was 74 years and 55.2% (n=1,196) were female (Table 1). Overall, there were 16,321 pathology tests ordered (i.e. RMDT and other tests combined) with medians of 3 test order episodes during the ED stay and 7 tests per patient. Analysis of RMDT results showed that 28.9% (n=626) were positive for either influenza A/B (n=617) or RSV (n=9). No patients tested positive for both influenza and RSV. The overall median TAT of RMDT was 183 minutes but this ranged from 104 minutes at ED A to 622 minutes at ED F.

Table 1: Baseline characteristics.

Variables	Result (N=2,168)

Gender, n (%)	
Male	972 (44.8)
Female	1,196 (55.2)
Age (years), median (IQR)	74 (56-84)
Triage scale, n (%)	
Category 3	1,777 (82.0)
Category 4/5	391(18.0)
Arrival time, n (%)	
0700hrs to 1900hrs	1,528 (70.5)
1900hrs to 0700hrs	640 (29.5)
Arrival day of week, n (%)	
Monday	356 (16.4)
Tuesday	294 (13.6)
Wednesday	327 (15.1)
Thursday	300 (13.8)
Friday	308 (14.2)
Saturday	257 (11.9)
Sunday	326 (15.0)
Mode of arrival, n (%)	
Private/public transport	906 (41.8)
State ambulance[1]	1,262 (58.2)
Study ED, n (%)	
A	723 (33.4)
B	193 (8.9)

C	301 (13.9)
D	530 (24.5)
E	239 (11.0)
F	182 (8.4)
Patient disposition, n (%)	
Admitted	1,567 (72.3)
Discharged	545 (25.1)
Other[2]	56 (2.6)
Test order episode, median (IQR)	3 (2-4)
Overall tests ordered, median (IQR)	7 (5-9)
Test result, n (%)	
Positive	626 (28.9)
Negative	1,542 (71.1)

ED, Emergency Department; [1]Fifteen patients arriving by either wheelchair, correctional services vehicle, helicopter rescue service or walked-in were combined with 'State ambulance'; [2]Transferred to another hospital or left ED at own risk.

The timing of respiratory virus testing

The median time from ED presentation to respiratory virus testing using the RMDT for all samples was 224 minutes (IQR, 133-349). There was considerable variation in the median time to RMDT across EDs which ranged from 173 minutes (IQR, 108-264) at ED B to 269 minutes (IQR, 178-444) at ED F (Figure 1).

Study outcomes

The overall median ED LOS was 533 minutes. ED B had the shortest and ED D had the longest median ED LOS. Overall, 88% (n=1,907) of patients stayed >4 hours in ED (range across EDs:

78.2% at ED B to 92.0% at ED A). RMDT results were pending for 38% (n=824) of patients at the time of ED disposition (range across EDs: 15.1% at ED A to 70.7% at ED E) (Table 2).

Table 2: Summary of study outcomes.

ED	N	Primary outcome	Secondary outcomes	
		ED LOS (minute), Median (IQR)	>4-hour ED LOS, N (%)	Patient with a pending RMDT result, N (%)
A	723	545 (358-953)	665 (92.0)	109 (15.1)
B	193	376 (257-549)	151 (78.2)	80 (41.5)
C	301	490 (342-859)	263 (87.4)	157 (52.2)
D	530	714 (366-1172)	457 (86.2)	186 (35.1)
E	239	455 (336-657)	208 (87.0)	169 (70.7)
F	182	700 (389-1177)	163 (89.6)	123 (67.6)
Overall	2,168	533 (338.5-975)	1,907 (88.0)	824 (38.0)

ED, Emergency Department; LOS, Length of Stay.

The association between the timing of respiratory virus testing and primary outcome

The results of univariate analysis describing the association between baseline characteristics and each study outcome are presented in *Supplementary* Table 1. All baseline variables except arrival day of week and test result were significantly associated with ED LOS (Table S1).

The timing of respiratory virus testing was strongly associated with ED LOS. After adjustment for potential confounders, every 30-minute increase in the time to RMDT was associated with a 24.0-minute increase in the median ED LOS (95% CI, 21.8-26.1; P<0.001). There were no major differences, in this association, by ED (Table 3).

Table 3: Median regression showing association between the timing of respiratory virus testing (every 30-minute increase) and ED LOS (minutes).

ED	N	Unadjusted	Adjusted†
		Coef. (95% CI)	Coef. (95% CI)
A	723	26.4 (22.2-30.5)	21.6 (16.5-26.7)
B	193	32.4 (27.1-37.7)	26.4 (20.0-32.8)
C	301	30.9 (26.4-35.4)	26.7 (22.3-31.2)
D	530	31.7 (26.1-37.3)	21.7 (17.7-25.8)
E	239	25.8 (21.0-30.7)	26.3 (21.5-31.0)
F	182	28.0 (19.8-36.1)	23.2 (14.6-31.8)
Overall	2,168	29.4 (27.5-31.2)	24.0 (21.8-26.1)

All analyses were highly significant with a *P-value* of <0.001. The coefficient indicates the median change in a given outcome (e.g. ED LOS) for every 30-minute increase in the timing of the RMDT. †Adjusted for gender, age, triage category, ED arrival time, mode of arrival, study ED, patient disposition, test order episode. ED, Emergency Department; LOS, Length of Stay.

A subgroup analysis by patient disposition and ED arrival time is shown in *Supplementary* Table 2. The association was more pronounced among patients who were subsequently discharged than for admitted patients and among patients who arrived to EDs between 0700hrs to 1900hrs than for patients arriving between 1900hrs to 0700hrs (Table S2).

The association between the timing of respiratory virus testing and secondary outcomes

The median time to RMDT was 113 minutes (IQR, 76-152) for patients with ≤4 hours ED LOS (n=261) and 250 minutes (IQR, 153-370) for patients staying >4 hours in ED (n=1,907). The median time to RMDT was 211 minutes (IQR, 122-336) for patients who received RMDT results before disposition (n=1,344) and 247 minutes (IQR, 151-364) for patients with pending RMDT results at disposition (n=824). Of the patients with pending RMDT results, the results of 30.3% (n=250) eventually came back positive for either influenza A/B or RSV.

The results of binary logistic regression are presented in Table 4 and show associations between the time to RMDT and secondary outcomes. The time to RMDT was positively associated with

both secondary outcomes. In the adjusted model, for every 30-minute increase in time to RMDT, the likelihood of staying >4 hours in ED (*versus* having ≤4 hours ED LOS) increased by a factor of 1.51 (OR, 1.51; 95% CI, 1.41-1.63; *P*<0.001). This is equivalent to a 51% increase in the likelihood of staying >4 hours in ED.

The association between the timing of the RMDT and having a pending test result at ED disposition was not as striking as with other outcomes. In the total sample, for every 30-minute increase in the time to RMDT, the likelihood of experiencing a pending RMDT result at ED disposition increased by a factor of 1.04 –a 4% increase – (OR, 1.04; 95% CI, 1.02-1.05; *P*<0.001) after adjustment for potential confounders. When the analysis was conducted separately by study EDs, the association was not statistically significant for EDs C, D and E (Table 4).

Table 4: Binary logistic regression showing association between the timing of respiratory virus testing (every 30- minute increase) and secondary outcomes.

ED	N	> 4-hr ED LOS		Patient with a pending RMDT result	
		Unadjusted	Adjusted†	Unadjusted	Adjusted††
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
A	723	1.58 (1.37-1.82)	1.51 (1.28-1.79)	1.04 (1.01-1.07)	1.06 (1.03-1.10)
B	193	1.74 (1.41-2.14)	1.70 (1.34-2.17)	1.06 (1.01-1.12)	1.16 (1.07-1.25)
C	301	1.51 (1.29-1.76)	1.48 (1.25-1.75)	0.99 (0.96-1.02)*NS*	1.02 (0.99-1.06)*NS*
D	530	1.69 (1.48-1.93)	1.64 (1.41-1.90)	0.99 (0.97-1.01)*NS*	1.02 (1.00-1.05)*NS*
E	239	1.40 (1.21-1.61)	1.39 (1.19-1.63)	1.00 (0.96-1.04)*NS*	1.02 (0.97-1.07)*NS*
F	182	1.63 (1.28-2.07)	1.90 (1.24-2.91)	1.01 (0.98-1.05)*NS*	1.05 (1.00-1.09)
Overall	2,168	1.54 (1.45-1.64)	1.51 (1.41-1.63)	1.02 (1.01-1.03)	1.04 (1.02-1.05)

All analyses, except those marked '*NS*', were significant with a *P-value* of <0.05. The coefficient indicates the likelihood of a given outcome for every 30-minute increase in the timing of the RMDT. †Adjusted for age, triage category, mode of arrival, study ED, patient disposition, test order episode and test result. ††Adjusted for gender, age, triage category, mode of arrival, study ED, patient disposition, test order episode. ED, Emergency Department; NS, Not Significant.

Discussion

The major finding of this study is that for every 30-minute increase in the time from ED arrival until respiratory virus testing there was a 24.0-minute increase in the median ED LOS. Moreover, an increase in the timing of respiratory virus testing was associated with a greater likelihood of experiencing an ED LOS greater than four hours and having a pending RMDT result at the time of disposition from the ED.

Previous studies have also reported a significant association between ED LOS and the time taken to obtain the results from laboratory testing in EDs.[6 23-25] However, unlike our study, the previous studies have been conducted in a context of broader patient populations visiting ED and, therefore, direct comparisons with other studies are not possible. For example, Li *et al*. conducted a retrospective study that included 123,455 ED presentations for all conditions across four EDs in NSW, Australia. That study assessed the relationship between ED LOS and TAT and found a 17-minute increase in ED LOS for each 30-minute increase in TAT.[6] In a recent large US study, Kaushik *et al*. evaluated the impact of reducing laboratory TAT on ED LOS using data from 486 hospitals with 4,483,169 ED presentations.[24] In that study, a 1-minute decrease in TAT was associated with a 0.50-minute decrease in ED LOS.[24] In another US study, Kocher *et al*. investigated the effect of diagnostic testing and treatment patterns on ED LOS using data from a large national study that included approximately 360 million ED presentations.[25] They found that, the ordering of a blood test was the most time consuming testing modality resulting in an adjusted marginal effect of a 72-minute increase in ED LOS and the likelihood of experiencing a >4-hour ED LOS increased by a factor of 2.29.[25]

The present study revealed a direct relationship between the timing of respiratory virus testing and a range of indicators of timeliness of patient care in ED. Delays in the ordering of RMDT had a negative impact on our selected ED outcomes. Our results suggest that earlier initiative of RMDT may result in reduced ED LOS. More systemic or procedural changes in the way healthcare is delivered (e.g. introduction of an early diagnostic testing protocol such as a triage-initiated testing) may be needed in order to maximise its benefits. Triage-based testing protocols have been shown to reduce wait times and ED LOS, decrease costs, reduces time to receiving medications and improve patient satisfaction in other conditions.[26-28] In an randomized controlled trial conducted in the US that including more than 1000 ED patients aged <3years, influenza testing at triage using a non-molecular antigen-based method led to significantly shorter ED LOS.[29] Future research should assess the potential impact of triage-initiated ordering of RMDT for patients presenting to ED with suspected respiratory viral infection on patient outcomes including the effect on ED LOS.

The current study showed that a delay in respiratory virus testing was associated with an increased likelihood of having a pending test result at ED disposition. The test results of 30.3% of patients with pending test results eventually came back positive for either influenza A/B or RSV. From an infection transmission perspective, patients who were discharged with pending results could potentially spread the infection, especially if appropriate management was not provided.

Strengths and weaknesses of the study

To the best of our knowledge, this is the first study to explore the relationship between the timing of respiratory virus molecular testing and ED outcomes among patients presenting with respiratory infections. Drawing from a large linked dataset in a multicentre study involving six hospital EDs further strengthened the generalizability of our findings.

Our study has some limitations. This study was conducted among adult patients (age>18 years). Given the impact of RMDT on ED LOS can be different among patients aged≤18 years [16], our findings may not be applicable to paediatric populations. It is important to note that, being an observational study, the findings of the current study do not imply a causal relationship. Our analyses were not adjusted for other factors which may have confounded the findings of this study. The input-throughput-output model [30] is commonly used in studies assessing factors affecting LOS and ED overcrowding.[25 31 32] Input factors are characteristics that contribute to the demand for ED services (e.g. patient demographics and ED presentation characteristics).[30] Throughput factors are characteristics related to ED care such as diagnostic evaluations and treatment.[25 30] Output factors are organisational or hospital capacity-related characteristics (e.g. access block).[30 32] Whilst our multivariable models were adjusted for a number of input variables, our current analysis did not consider the effect of several throughput and output/organisational factors due to lack of data. Previous studies have shown that throughput factors such as diagnostic imaging [25], clinical assessment [33] and treatment (administering a medication and performing a procedure) [25] and output/organisational factors [32 34 35] are important factors influencing ED LOS.

Conclusion

The timing of respiratory virus molecular testing in EDs was significantly associated with a range of outcome indicators. Results suggest the potential to maximise the benefits of RMDT by introducing an early diagnostic protocol such as a triage-initiated testing which warrants investigations in future studies.

Patient consent for publication: Not required.

Contributors:

AG, LL, MRD, RL, JT and JIW conceived the study and obtained research funding. NW and LL contributed to extraction, cleaning, linkage and analysis of data with input from other team members. NW, MRD, LL, JT, JIW and AG contributed to the interpretation of the results or drafting of the manuscript. All authors involved in the design of the study, critical revision of the manuscript and approved the final manuscript.

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Conflicts of interests: None declared.

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Figure's Legend

Figure 1: The time to RMDT by study EDs: Boxes represent the IQR (25th and 75th percentiles) with the median (50th percentile) value within the boxes, the mean value is represented as a '+' and the capped bars represent the 10th and 90th percentiles. The broken line indicates the overall median time to RMDT.

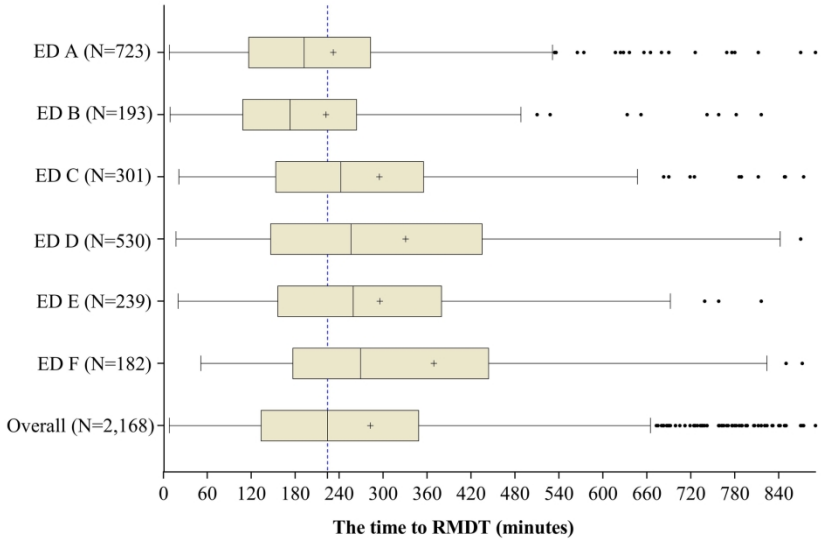

Figure 1: The time to RMDT by study EDs: Boxes represent the IQR (25th and 75th percentiles) with the median (50th percentile) value within the boxes, the mean value is represented as a '+' and the capped bars represent the 10th and 90th percentiles. The broken line indicates the overall median time to RMDT.

214x124mm (300 x 300 DPI)

Supplementary Data

Table S1: Univariate analysis showing variables associated with primary and secondary outcomes (N=2,168).

Variables	ED LOS (min)	> 4-hr ED LOS	Patient with a pending RMDT result
	Coef. (95% CI)	OR (95% CI)	OR (95% CI)
Female *vs.* Male	-75 (-119.6 to -30.4)	0.82 (0.63-1.07) *NS*	1.26 (1.06-1.51)
Age (for every 10-year increase)	51.2 (40.5 to 61.9)	1.38 (1.3-1.46)	0.86 (0.82-0.90)
Triage			
Semi-urgent *vs.* Urgent	-123 (-179.8 to -66.2)	0.43 (0.32-0.58)	1.66 (1.33-2.07)
Arrival time			
0700hrs to 1900hrs *vs*. 1900hrs to 0700hrs	-188 (-233.6 to -142.4)	0.75 (0.56-1.01) *NS*	0.97 (0.80-1.17) *NS*
Arrival day of week			
Weekdays vs. Weekends	8 (-39.8 to 55.8) *NS*	1.06 (0.80-1.42) *NS*	1.01 (0.83-1.22) *NS*
Mode of arrival			
Ambulance *vs.* private/public transport	224 (180.6 to 267.4)	3.76 (2.85-4.98)	0.63 (0.53-0.76)
Study ED			

A	Ref	Ref	Ref
B	-169 (-257.7 to -80.3)	0.31 (0.20-0.48)	3.99 (2.81-5.67)
C	-55 (-130.1 to 20.1)[NS]	0.60 (0.39-0.93)	6.14 (4.53-8.33)
D	169 (106.4 to 231.6)	0.55 (0.38-0.79)	3.05 (2.32-3.99)
E	-90 (-171.6 to -8.4)	0.59 (0.37-0.93)	13.60 (9.63-19.20)
F	162 (71.3 to 252.7)	0.75 (0.43-1.29) [NS]	11.74 (8.10-17.02)
Patient disposition			
Discharged *vs.* Admitted	-325 (-380.3 to -269.7)	0.17 (0.13-0.22)	2.41 (1.97-2.94)
Test order episode	120.6 (109.1 to 132.0)	2.58 (2.23-2.99)	0.83 (0.79-0.88)
No. of tests (for every 3 more tests ordered)	167.6 (149.5 to 185.7)	3.3 (2.78-3.93)	0.85 (0.78-0.92)
Test result			
Positive vs. Negative	-39 (-85.5 to 7.5)[NS]	0.71 (0.54-0.94)	1.12 (0.93-1.36) [NS]

ED, Emergency Department; RMDT, Rapid Molecular Diagnostic Test; LOS, Length of Stay; NS, Not Significant.

Table S2: Multivariate analysis showing the association between the timing of respiratory virus testing (every 30-min increase) with study outcomes by patient disposition and ED arrival time.

Variable	N	ED LOS (min)[†]	> 4-hr ED LOS[††]	Patient with a pending RMDT result[†††]
		Coef. (95% CI)	OR (95% CI)	OR (95% CI)
Patient disposition				
Discharged	545	28.0 (25.6-30.4)	1.68 (1.48-1.91)	1.09 (1.03-1.14)
Admitted	1,567	22.3 (19.4-25.2)	1.44 (1.32-1.58)	1.04 (1.02-1.05)
ED arrival time				
0700hrs to 1900hrs	1,528	26.6 (24.3-29.0)	1.49 (1.37-1.62)	1.03 (1.01-1.04)
1900hrs to 0700hrs	640	17.8 (13.4-22.0)	1.58 (1.37-1.81)	1.06 (1.03-1.09)

All analyses were significant with a *P-value* of <0.001. ED, Emergency Department; RMDT, Rapid Molecular Diagnostic Test; LOS, Length of Stay; [†]Adjusted for gender, age, triage category, mode of arrival, study ED, test order episode; [††]Adjusted for age, arrival day of week, mode of arrival, study ED and test order episode; [†††]Adjusted for gender, age, triage category, mode of arrival, study ED and test order episode.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	a=page 1 b=page 2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1=page 2 ('Setting) 1.2=page 2 ('Setting') 1.3=page 2 ('Setting')
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4		
Objectives	3	State specific objectives, including any prespecified hypotheses	Pages 4 and 5		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page 5		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Page 5.	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	The study was retrospective observational study as detailed in Page 5 Not applicable Separate reference was provided regarding the linkage process
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page 6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 5		

Bias	9	Describe any efforts to address potential sources of bias	Not described directly but effort was made to describe potential confounders		
Study size	10	Explain how the study size was arrived at	Page 5 –the study included all participants who fulfilled the inclusion criteria		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Pages 5 and 6		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Pages 5 and 6		

Data access and cleaning methods		.. Separate reference was provided regarding the data cleaning and linkage process.		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		.. Separate reference was provided regarding the data cleaning and linkage process.		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Page 7	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest	Pages 7 and 8		

		(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Pages 9 and 10		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 10-12		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Supplementary data		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page 13		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	Pages 14 and 15	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include	

		Discuss both direction and magnitude of any potential bias		discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 13 and 14		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 14		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 16		
Accessibility of protocol, raw data, and programming code		..	NA	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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The timing of respiratory virus molecular testing in emergency departments and its association with patient care outcomes: A retrospective observational study across six Australian hospitals

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The timing of respiratory virus molecular testing in emergency departments and its association with patient care outcomes: A retrospective observational study across six Australian hospitals

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Abstract

Objective: A rapid molecular diagnostic test (RMDT) offers a fast and accurate detection of respiratory viruses, but its impact on the timeliness of care in the emergency department (ED) may depend on the timing of the test. The aim of the study was to determine if the timing of respiratory virus testing using a RMDT in the ED had an association with patient care outcomes.

Design: Retrospective observational study.

Setting: Linked ED and laboratory data from six EDs in New South Wales, Australia.

Participants: Adult patients presenting to EDs during the 2017 influenza season and tested for respiratory viruses using a RMDT. The timing of respiratory virus testing was defined as the time from a patient's ED arrival to time of sample receipt at the hospital laboratory.

Outcome measures: ED length of stay (LOS), >4-hour ED LOS and having a pending RMDT result at ED disposition.

Results: A total of 2168 patients were included. The median timing of respiratory virus testing was 224 minutes (inter-quartile range,133-349). Every 30-minute increase in the timing of respiratory virus testing was associated with a 24.0-minute increase in the median ED LOS (95% confidence interval [CI], 21.8-26.1; P<0.001), a 51% increase in the likelihood of staying >4 hours in ED (odds ratio [OR], 1.51; 95% CI, 1.41-1.63; P<0.001) and a 4% increase in the likelihood of having a pending RMDT result at ED disposition (OR, 1.04; 95% CI, 1.02-1.05; P<0.001) after adjustment for confounders.

Conclusion: The timing of respiratory virus molecular testing in EDs was significantly associated with a range of outcome indicators. Results suggest the potential to maximise the benefits of RMDT by introducing an early diagnostic protocol such as triage-initiated testing.

Strengths and limitations of this study

- This is the first study to investigate the relationship between the timing of respiratory virus molecular testing and outcomes of patients presenting to ED with respiratory infections.
- This is a large multicentre study that involved six hospitals, enhancing the generalizability of our findings.
- Our findings may not be applicable to paediatric populations as this study did not include patients aged ≤18 years.
- Being an observational study, our findings do not imply a causal relationship.
- Our analyses were not adjusted for other relevant factors (e.g. access block) which may have confounded the findings of this study.

Introduction

The accurate diagnosis of the cause of respiratory infections has over recent years depended on a molecular method using a multiplex polymerase chain reaction (PCR) panel testing. Multiplex PCR provides accurate diagnoses, but has been traditionally performed in a central laboratory with a lengthy test turnaround time (TAT), and with major repercussions for the efficiency of emergency department (ED) workflows and care processes.

ED overcrowding has been recognized as a growing problem in Australia and worldwide, contributing to deficits in the performance of the health system.[1-3] Delay in laboratory test results is often considered as one of many factors contributing to ED overcrowding and prolonged ED length of stay (LOS).[4-6] Fast result availability through the use of rapid diagnostic tests can potentially improve patient flow and lessen the burden of ED overcrowding.[7 8] Optimising patient flow is of particular importance given the 4-hour ED LOS target introduced in Australia in 2011 to improve the quality and timeliness of care across EDs.[9]

Diagnostic kits for the rapid diagnosis of respiratory viruses using a molecular PCR-based technology are now available for use in hospital-based laboratories. Existing evidence shows that RMDT in ED is associated with a significant decrease in hospital admissions [8 10], shorter TAT [8] and reductions in hospital resource utilisation.[11-13] However, evidence of the association between RMDT and ED LOS have been inconsistent.[8 14 15] Our previous study did not detect a significant association between RMDT use and ED LOS.[16] We hypothesised that this may be due to the fact that RMDT ordering took place a median of three hrs after a patient's ED arrival[16] suggesting that the impact of RMDT on ED LOS and other timeliness of care processes may depend on the timing of the test.

The aim of the study was to determine if the timing of respiratory virus testing using RMDT in ED is associated with indicators related to timeliness of patient care including ED LOS,

meeting the 4-hr ED LOS Australian emergency access target; having a pending RMDT result at ED disposition.

Method

Setting

A retrospective observational study was conducted across six public hospitals in New South Wales (NSW), Australia. All study sites provide 24-hour EDs: three principal referral hospitals (EDs A, B and D) with 76,228, 54,443 and 61,348 annual ED presentations respectively, two acute group A hospitals (ED C and ED F) with 50,025 and 38,039 annual ED presentations respectively and one public acute group A hospital (ED E) with 29,479 annual ED presentations (2016 data).[17]

Population

The study period was the 2017 influenza season, between 1 July and 31 October. The inclusion criteria were patients presenting to EDs with symptoms of respiratory infection and aged ≥18 years; Australasian triage scale categories of 3 (potentially life-threatening), 4 (potentially serious) or 5 (less urgent) and tested for respiratory viruses at a hospital-based laboratory using a RMDT. The RMDT used in this study was a Cepheid Xpert® Flu/RSV XC (Cepheid, Sunnyvale, CA)[16 18]. The Cepheid Xpert® Flu/RSV XC assay demonstrated a high sensitivity and specificity for rapid detection of influenza A, influenza B and RSV.[19]

Patients with triage categories of 1 (immediately life-threatening) or 2 (imminently life-threatening) were excluded from the current analysis as patients required urgent medical assessment and treatment. Relevant patient presentation characteristics and laboratory test data were obtained by linking the ED and laboratory information system datasets.[6]

Outcome measures

The primary outcome was ED LOS. ED LOS was defined as the length of time between ED arrival and patient disposition. The secondary outcomes included >4-hour ED LOS and having a pending RMDT result at ED disposition. A pending test result was defined as the unavailability of a verified RMDT result at the time of patient disposition from the ED.[20]

Statistical analysis

Descriptive statistics including medians with inter-quartile ranges (IQR) were reported. The RMDT TAT was defined as the time of sample receipt at the hospital laboratory to time of availability of RMDT result. The exploratory variable was the timing of respiratory virus testing using a RMDT, defined as the time from a patient's ED arrival to time of sample receipt at the hospital laboratory. For result interpretation purposes, the relationship between the timing of the RMDT and study outcomes were estimated for every 30-minute increase in the timing of the test.

The association between the timing of the RMDT and ED LOS was assessed using a median regression. As the ED LOS data were highly skewed, commonly used approaches such as ordinary least squares regression which models the conditional mean of the outcome variable was not appropriate methods.[21] Median regression is a special type of quantile regression which estimates the median of the outcome variable conditional on the values of the predictor variables.[22] It is robust to extreme values and therefore well suited for modelling such data.[23]

Binary logistic regression was used to assess the association between the timing of the RMDT and the secondary outcomes (e.g. >4-hour ED LOS, *yes/no*). The strength of the associations was measured using odds ratio (OR) with a 95% confidence interval (CI).

For all outcomes, the findings were reported for the overall sample and by study ED. Sub-group analyses by patient disposition and ED arrival time were also conducted. The baseline covariates included age, gender, triage category, arrival time, arrival day of week, mode of

arrival, patient disposition, overall number of tests ordered and number of test order episodes (tests ordered at one point in time during the ED stay). All analyses were adjusted for potential confounders – any variable having a significant association with a given outcome in a univariate analysis ($P<0.05$) was selected for the multivariate model. P-values were 2-tailed and $P<0.05$ was considered statistically significant. Analyses were conducted using Stata version 15 (StataCorp LP, College Station, TX).

Patient and public involvement

This study was conducted without patient and public involvement as it was a retrospective study conducted using pre-existing administrative data. The patients were not invited to comment on the study design and were not consulted to develop outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Baseline characteristics

A total of 2,168 patients were included in the study. Table 1 presents baseline characteristics. The median patient age was 74 years and 55.2% (n=1,196) were female (Table 1). Overall, there were 16,321 pathology tests ordered (i.e. RMDT and other tests combined) with medians of 3 test order episodes during the ED stay and 7 tests per patient. Analysis of RMDT results showed that 28.9% (n=626) were positive for either influenza A/B (n=617) or RSV (n=9). No patients tested positive for both influenza and RSV. The overall median TAT of RMDT was 183 minutes but this ranged from 104 minutes at ED A to 622 minutes at ED F.

Table 1: Baseline characteristics.

Variables	Result (N=2,168)

Gender, n (%)	
Male	972 (44.8)
Female	1,196 (55.2)
Age (years), median (IQR)	74 (56-84)
Triage scale, n (%)	
Category 3	1,777 (82.0)
Category 4/5	391(18.0)
Arrival time, n (%)	
0700hrs to 1900hrs	1,528 (70.5)
1900hrs to 0700hrs	640 (29.5)
Arrival day of week, n (%)	
Monday	356 (16.4)
Tuesday	294 (13.6)
Wednesday	327 (15.1)
Thursday	300 (13.8)
Friday	308 (14.2)
Saturday	257 (11.9)
Sunday	326 (15.0)
Mode of arrival, n (%)	
Private/public transport	906 (41.8)
State ambulance[1]	1,262 (58.2)
Study ED, n (%)	
A	723 (33.4)
B	193 (8.9)

C	301 (13.9)
D	530 (24.5)
E	239 (11.0)
F	182 (8.4)
Patient disposition, n (%)	
Admitted	1,567 (72.3)
Discharged	545 (25.1)
Other[2]	56 (2.6)
Test order episode, median (IQR)	3 (2-4)
Overall tests ordered, median (IQR)	7 (5-9)
Test result, n (%)	
Positive	626 (28.9)
Negative	1,542 (71.1)

ED, Emergency Department; [1]Fifteen patients arriving by either wheelchair, correctional services vehicle, helicopter rescue service or walked-in were combined with 'State ambulance'; [2]Transferred to another hospital or left ED at own risk.

The timing of respiratory virus testing

The median time from ED presentation to respiratory virus testing using the RMDT for all samples was 224 minutes (IQR, 133-349). There was considerable variation in the median time to RMDT across EDs which ranged from 173 minutes (IQR, 108-264) at ED B to 269 minutes (IQR, 178-444) at ED F (Figure 1).

Study outcomes

The overall median ED LOS was 533 minutes. ED B had the shortest and ED D had the longest median ED LOS. Overall, 88% (n=1,907) of patients stayed >4 hours in ED (range across EDs:

78.2% at ED B to 92.0% at ED A). RMDT results were pending for 38% (n=824) of patients at the time of ED disposition (range across EDs: 15.1% at ED A to 70.7% at ED E) (Table 2).

Table 2: Summary of study outcomes.

ED	N	Primary outcome	Secondary outcomes	
		ED LOS (minute), Median (IQR)	>4-hour ED LOS, N (%)	Patient with a pending RMDT result, N (%)
A	723	545 (358-953)	665 (92.0)	109 (15.1)
B	193	376 (257-549)	151 (78.2)	80 (41.5)
C	301	490 (342-859)	263 (87.4)	157 (52.2)
D	530	714 (366-1172)	457 (86.2)	186 (35.1)
E	239	455 (336-657)	208 (87.0)	169 (70.7)
F	182	700 (389-1177)	163 (89.6)	123 (67.6)
Overall	2,168	533 (338.5-975)	1,907 (88.0)	824 (38.0)

ED, Emergency Department; LOS, Length of Stay.

The association between the timing of respiratory virus testing and primary outcome

The results of univariate analysis describing the association between baseline characteristics and each study outcome are presented in *Supplementary* Table 1. All baseline variables except arrival day of week and test result were significantly associated with ED LOS (Table S1).

The timing of respiratory virus testing was strongly associated with ED LOS. After adjustment for potential confounders, every 30-minute increase in the time to RMDT was associated with a 24.0-minute increase in the median ED LOS (95% CI, 21.8-26.1; P<0.001). There were no major differences, in this association, by ED (Table 3).

Table 3: Median regression showing association between the timing of respiratory virus testing (every 30-minute increase) and ED LOS (minutes).

ED	N	Unadjusted	Adjusted†
		Coef. (95% CI)	Coef. (95% CI)
A	723	26.4 (22.2-30.5)	21.6 (16.5-26.7)
B	193	32.4 (27.1-37.7)	26.4 (20.0-32.8)
C	301	30.9 (26.4-35.4)	26.7 (22.3-31.2)
D	530	31.7 (26.1-37.3)	21.7 (17.7-25.8)
E	239	25.8 (21.0-30.7)	26.3 (21.5-31.0)
F	182	28.0 (19.8-36.1)	23.2 (14.6-31.8)
Overall	2,168	29.4 (27.5-31.2)	24.0 (21.8-26.1)

All analyses were highly significant with a *P-value* of <0.001. The coefficient indicates the median change in a given outcome (e.g. ED LOS) for every 30-minute increase in the timing of the RMDT. †Adjusted for gender, age, triage category, ED arrival time, mode of arrival, study ED, patient disposition, test order episode. ED, Emergency Department; LOS, Length of Stay.

A subgroup analysis by patient disposition and ED arrival time is shown in *Supplementary* Table 2. The association was more pronounced among patients who were subsequently discharged than for admitted patients and among patients who arrived to EDs between 0700hrs to 1900hrs than for patients arriving between 1900hrs to 0700hrs (Table S2).

The association between the timing of respiratory virus testing and secondary outcomes

The median time to RMDT was 113 minutes (IQR, 76-152) for patients with ≤4 hours ED LOS (n=261) and 250 minutes (IQR, 153-370) for patients staying >4 hours in ED (n=1,907). The median time to RMDT was 211 minutes (IQR, 122-336) for patients who received RMDT results before disposition (n=1,344) and 247 minutes (IQR, 151-364) for patients with pending RMDT results at disposition (n=824). Of the patients with pending RMDT results, the results of 30.3% (n=250) eventually came back positive for either influenza A/B or RSV.

The results of binary logistic regression are presented in Table 4 and show associations between the time to RMDT and secondary outcomes. The time to RMDT was positively associated with

both secondary outcomes. In the adjusted model, for every 30-minute increase in time to RMDT, the likelihood of staying >4 hours in ED (*versus* having ≤4 hours ED LOS) increased by a factor of 1.51 (OR, 1.51; 95% CI, 1.41-1.63; *P*<0.001). This is equivalent to a 51% increase in the likelihood of staying >4 hours in ED.

The association between the timing of the RMDT and having a pending test result at ED disposition was not as striking as with other outcomes. In the total sample, for every 30-minute increase in the time to RMDT, the likelihood of experiencing a pending RMDT result at ED disposition increased by a factor of 1.04 –a 4% increase – (OR, 1.04; 95% CI, 1.02-1.05; *P*<0.001) after adjustment for potential confounders. When the analysis was conducted separately by study EDs, the association was not statistically significant for EDs C, D and E (Table 4).

Table 4: Binary logistic regression showing association between the timing of respiratory virus testing (every 30- minute increase) and secondary outcomes.

ED	N	> 4-hr ED LOS		Patient with a pending RMDT result	
		Unadjusted	Adjusted†	Unadjusted	Adjusted††
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
A	723	1.58 (1.37-1.82)	1.51 (1.28-1.79)	1.04 (1.01-1.07)	1.06 (1.03-1.10)
B	193	1.74 (1.41-2.14)	1.70 (1.34-2.17)	1.06 (1.01-1.12)	1.16 (1.07-1.25)
C	301	1.51 (1.29-1.76)	1.48 (1.25-1.75)	0.99 (0.96-1.02)*NS*	1.02 (0.99-1.06)*NS*
D	530	1.69 (1.48-1.93)	1.64 (1.41-1.90)	0.99 (0.97-1.01)*NS*	1.02 (1.00-1.05)*NS*
E	239	1.40 (1.21-1.61)	1.39 (1.19-1.63)	1.00 (0.96-1.04)*NS*	1.02 (0.97-1.07)*NS*
F	182	1.63 (1.28-2.07)	1.90 (1.24-2.91)	1.01 (0.98-1.05)*NS*	1.05 (1.00-1.09)
Overall	2,168	1.54 (1.45-1.64)	1.51 (1.41-1.63)	1.02 (1.01-1.03)	1.04 (1.02-1.05)

All analyses, except those marked '*NS*', were significant with a *P-value* of <0.05. The coefficient indicates the likelihood of a given outcome for every 30-minute increase in the timing of the RMDT. †Adjusted for age, triage category, mode of arrival, study ED, patient disposition, test order episode and test result. ††Adjusted for gender, age, triage category, mode of arrival, study ED, patient disposition, test order episode. ED, Emergency Department; NS, Not Significant.

Discussion

Key findings

The major finding of this study is that for every 30-minute increase in the time from ED arrival until respiratory virus testing there was a 24.0-minute increase in the median ED LOS. Moreover, an increase in the timing of respiratory virus testing was associated with a greater likelihood of experiencing an ED LOS greater than four hours and having a pending RMDT result at the time of disposition from the ED.

Interpretation and comparison with existing literature

Previous studies have also reported a significant association between ED LOS and the time taken to obtain the results from laboratory testing in EDs.[6 24-26] However, unlike our study, the previous studies have been conducted in a context of broader patient populations visiting ED and, therefore, direct comparisons with other studies are not possible. For example, Li *et al*. conducted a retrospective study that included 123,455 ED presentations for all conditions across four EDs in NSW, Australia. That study assessed the relationship between ED LOS and TAT and found a 17-minute increase in ED LOS for each 30-minute increase in TAT.[6] In a recent large US study, Kaushik *et al*. evaluated the impact of reducing laboratory TAT on ED LOS using data from 486 hospitals with 4,483,169 ED presentations.[25] In that study, a 1-minute decrease in TAT was associated with a 0.50-minute decrease in ED LOS.[25] In another US study, Kocher *et al*. investigated the effect of diagnostic testing and treatment patterns on ED LOS using data from a large national study that included approximately 360 million ED

presentations.[26] They found that, the ordering of a blood test was the most time consuming testing modality resulting in an adjusted marginal effect of a 72-minute increase in ED LOS and the likelihood of experiencing a >4-hour ED LOS increased by a factor of 2.29.[26]

The present study revealed a direct relationship between the timing of respiratory virus testing and a range of indicators of timeliness of patient care in ED. Delays in the ordering of RMDT had a negative impact on our selected ED outcomes. Our results suggest that earlier initiative of RMDT may result in reduced ED LOS. More systemic or procedural changes in the way healthcare is delivered (e.g. introduction of an early diagnostic testing protocol such as a triage-initiated testing) may be needed in order to maximise its benefits. Triage-based testing protocols have been shown to reduce wait times and ED LOS, decrease costs, reduces time to receiving medications and improve patient satisfaction in other conditions.[27-29] In an randomized controlled trial conducted in the US that including more than 1000 ED patients aged <3years, influenza testing at triage using a non-molecular antigen-based method led to significantly shorter ED LOS.[30] Future research should assess the potential impact of triage-initiated ordering of RMDT for patients presenting to ED with suspected respiratory viral infection on patient outcomes including the effect on ED LOS.

Implications of the study

The current study showed that a delay in respiratory virus testing was associated with an increased likelihood of having a pending test result at ED disposition. The test results of 30.3% of patients with pending test results eventually came back positive for either influenza A/B or RSV. This finding has significant patient safety implications. Pending test results at discharge are less likely to be followed-up and may lead to missed or delayed diagnosis and increased hospital representations. [31] [32] From an infection transmission perspective, patients who were

discharged with pending results could potentially spread the infection, especially if appropriate management was not provided.

Strengths and weaknesses of the study

Our study has some strengths. To the best of our knowledge, this is the first study to explore the relationship between the timing of respiratory virus molecular testing and ED outcomes among patients presenting with respiratory infections. Another strength of the study was that it is a multicentre study that involved six hospitals with a large sample size, enhancing the external validity (generalizability) of our findings.

The findings of the current study should be interpreted in the context of the following methodological limitations. Firstly, this study was conducted among adult patients (age>18 years). Given the impact of RMDT on ED LOS can be different among patients aged≤18 years [33], our findings may not be applicable to paediatric populations. Secondly, being an observational study, the findings of the current study do not imply a causal relationship. Thirdly, our analyses were not adjusted for other factors which may have confounded the findings of this study. The input-throughput-output model [34] is commonly used in studies assessing factors affecting LOS and ED overcrowding.[26 35 36] Input factors are characteristics that contribute to the demand for ED services (e.g. patient demographics and ED presentation characteristics).[34] Throughput factors are characteristics related to ED care such as diagnostic evaluations and treatment.[26 34] Output factors are organisational or hospital capacity-related characteristics (e.g. access block).[34 36] Whilst our multivariable models were adjusted for a number of input variables, our current analysis did not consider the effect of several throughput and output/organisational factors due to lack of data. Previous studies have shown that throughput factors such as diagnostic imaging [26], clinical assessment [37] and treatment

(administering a medication or performing a procedure) [26] and output/organisational factors [36 38 39] are important factors influencing ED LOS.

Conclusion

The timing of respiratory virus molecular testing in EDs was significantly associated with a range of outcome indicators. Results suggest the potential to maximise the benefits of RMDT by introducing an early diagnostic protocol such as a triage-initiated testing which warrants investigations in future studies.

Patient consent for publication: Not required.

Contributors: AG, LL, MRD, RL, JT and JIW conceived the study and obtained research funding. NW, LL, MRD, RL, RY, KC, JT, WV, JIW and AG have made substantial contributions to the design of the study. NW and LL conducted data extraction, cleaning, linkage and analysis. NW, LL, MRD, RL, KC, JT, JIW and AG involved in the interpretation of the results with input from RY and WV. NW, LL, MRD, JT and AG contributed to the drafting of the manuscript with input from RL, RY, KC and WV. All authors involved in the critical revision of the manuscript for important intellectual content as well as approved the final version to be published.

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Conflicts of interests: None declared.

Data sharing statement: The data that underline the results reported in this articles are available from the data custodians (South Eastern Sydney and Illawarra Shoalhaven Local

Health District), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The de-identified data however may be obtained from the corresponding author upon reasonable request and with permission of the data custodians.

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Figure's Legend

Figure 1: The time to RMDT by study EDs: Boxes represent the IQR (25th and 75th percentiles) with the median (50th percentile) value within the boxes, the mean value is represented as a '+' and the capped bars represent the 10th and 90th percentiles. The broken line indicates the overall median time to RMDT.

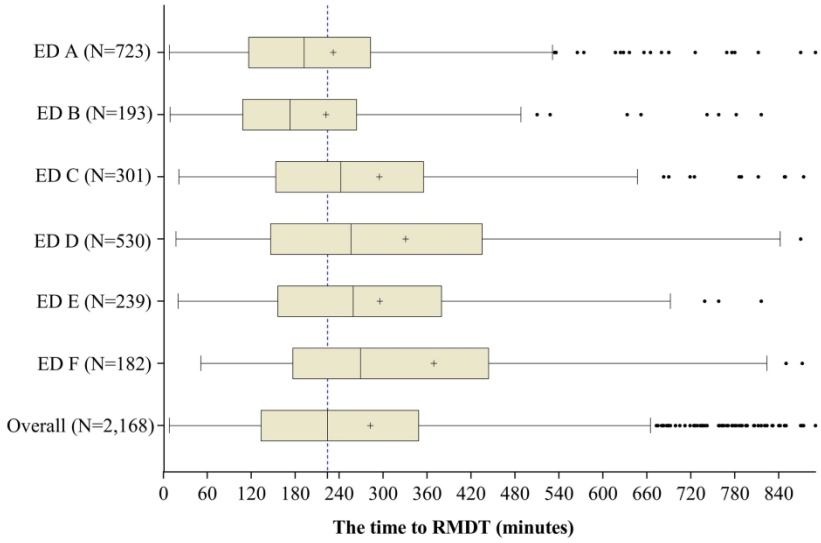

Figure 1: The time to RMDT by study EDs: Boxes represent the IQR (25th and 75th percentiles) with the median (50th percentile) value within the boxes, the mean value is represented as a '+' and the capped bars represent the 10th and 90th percentiles. The broken line indicates the overall median time to RMDT.

214x124mm (300 x 300 DPI)

Supplementary Data

Table S1: Univariate analysis showing variables associated with primary and secondary outcomes (N=2,168).

Variables	ED LOS (min)	> 4-hr ED LOS	Patient with a pending RMDT result
	Coef. (95% CI)	OR (95% CI)	OR (95% CI)
Female *vs.* Male	-75 (-119.6 to -30.4)	0.82 (0.63-1.07) *NS*	1.26 (1.06-1.51)
Age (for every 10-year increase)	51.2 (40.5 to 61.9)	1.38 (1.3-1.46)	0.86 (0.82-0.90)
Triage			
Semi-urgent *vs.* Urgent	-123 (-179.8 to -66.2)	0.43 (0.32-0.58)	1.66 (1.33-2.07)
Arrival time			
0700hrs to 1900hrs *vs*. 1900hrs to 0700hrs	-188 (-233.6 to -142.4)	0.75 (0.56-1.01) *NS*	0.97 (0.80-1.17) *NS*
Arrival day of week			
Weekdays vs. Weekends	8 (-39.8 to 55.8) *NS*	1.06 (0.80-1.42) *NS*	1.01 (0.83-1.22) *NS*
Mode of arrival			
Ambulance *vs.* private/public transport	224 (180.6 to 267.4)	3.76 (2.85-4.98)	0.63 (0.53-0.76)
Study ED			

A	Ref	Ref	Ref
B	-169 (-257.7 to -80.3)	0.31 (0.20-0.48)	3.99 (2.81-5.67)
C	-55 (-130.1 to 20.1)[NS]	0.60 (0.39-0.93)	6.14 (4.53-8.33)
D	169 (106.4 to 231.6)	0.55 (0.38-0.79)	3.05 (2.32-3.99)
E	-90 (-171.6 to -8.4)	0.59 (0.37-0.93)	13.60 (9.63-19.20)
F	162 (71.3 to 252.7)	0.75 (0.43-1.29) [NS]	11.74 (8.10-17.02)
Patient disposition			
Discharged *vs.* Admitted	-325 (-380.3 to -269.7)	0.17 (0.13-0.22)	2.41 (1.97-2.94)
Test order episode	120.6 (109.1 to 132.0)	2.58 (2.23-2.99)	0.83 (0.79-0.88)
No. of tests (for every 3 more tests ordered)	167.6 (149.5 to 185.7)	3.3 (2.78-3.93)	0.85 (0.78-0.92)
Test result			
Positive vs. Negative	-39 (-85.5 to 7.5)[NS]	0.71 (0.54-0.94)	1.12 (0.93-1.36) [NS]

ED, Emergency Department; RMDT, Rapid Molecular Diagnostic Test; LOS, Length of Stay; NS, Not Significant.

Table S2: Multivariate analysis showing the association between the timing of respiratory virus testing (every 30-min increase) with study outcomes by patient disposition and ED arrival time.

Variable	N	ED LOS (min)[†]	> 4-hr ED LOS[††]	Patient with a pending RMDT result[†††]
		Coef. (95% CI)	OR (95% CI)	OR (95% CI)
Patient disposition				
Discharged	545	28.0 (25.6-30.4)	1.68 (1.48-1.91)	1.09 (1.03-1.14)
Admitted	1,567	22.3 (19.4-25.2)	1.44 (1.32-1.58)	1.04 (1.02-1.05)
ED arrival time				
0700hrs to 1900hrs	1,528	26.6 (24.3-29.0)	1.49 (1.37-1.62)	1.03 (1.01-1.04)
1900hrs to 0700hrs	640	17.8 (13.4-22.0)	1.58 (1.37-1.81)	1.06 (1.03-1.09)

All analyses were significant with a *P-value* of <0.001. ED, Emergency Department; RMDT, Rapid Molecular Diagnostic Test; LOS, Length of Stay; [†]Adjusted for gender, age, triage category, mode of arrival, study ED, test order episode; [††]Adjusted for age, arrival day of week, mode of arrival, study ED and test order episode; [†††]Adjusted for gender, age, triage category, mode of arrival, study ED and test order episode.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	a=page 1 b=page 2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1=page 2 ('Setting) 1.2=page 2 ('Setting') 1.3=page 2 ('Setting')
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4		
Objectives	3	State specific objectives, including any prespecified hypotheses	Pages 4 and 5		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page 5		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Page 5.	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	The study was retrospective observational study as detailed in Page 5 Not applicable Separate reference was provided regarding the linkage process
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page 6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 5		

Bias	9	Describe any efforts to address potential sources of bias	Not described directly but effort was made to describe potential confounders		
Study size	10	Explain how the study size was arrived at	Page 5 –the study included all participants who fulfilled the inclusion criteria		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Pages 5 and 6		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Pages 5 and 6		

Data access and cleaning methods		.. Separate reference was provided regarding the data cleaning and linkage process.		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		.. Separate reference was provided regarding the data cleaning and linkage process.		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Page 7	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest	Pages 7 and 8		

		(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Pages 9 and 10		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 10-12		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Supplementary data		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page 13		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	Pages 14 and 15	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include	

		Discuss both direction and magnitude of any potential bias		discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 13 and 14		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 14		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 16		
Accessibility of protocol, raw data, and programming code		..	NA	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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The timing of respiratory virus molecular testing in emergency departments and its association with patient care outcomes: A retrospective observational study across six Australian hospitals

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The timing of respiratory virus molecular testing in emergency departments and its association with patient care outcomes: A retrospective observational study across six Australian hospitals

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Abstract

Objective: A rapid molecular diagnostic test (RMDT) offers a fast and accurate detection of respiratory viruses, but its impact on the timeliness of care in the emergency department (ED) may depend on the timing of the test. The aim of the study was to determine if the timing of respiratory virus testing using a RMDT in the ED had an association with patient care outcomes.

Design: Retrospective observational study.

Setting: Linked ED and laboratory data from six EDs in New South Wales, Australia.

Participants: Adult patients presenting to EDs during the 2017 influenza season and tested for respiratory viruses using a RMDT. The timing of respiratory virus testing was defined as the time from a patient's ED arrival to time of sample receipt at the hospital laboratory.

Outcome measures: ED length of stay (LOS), >4-hour ED LOS and having a pending RMDT result at ED disposition.

Results: A total of 2168 patients were included. The median timing of respiratory virus testing was 224 minutes (inter-quartile range,133-349). Every 30-minute increase in the timing of respiratory virus testing was associated with a 24.0-minute increase in the median ED LOS (95% confidence interval [CI], 21.8-26.1; P<0.001), a 51% increase in the likelihood of staying >4 hours in ED (odds ratio [OR], 1.51; 95% CI, 1.41-1.63; P<0.001) and a 4% increase in the likelihood of having a pending RMDT result at ED disposition (OR, 1.04; 95% CI, 1.02-1.05; P<0.001) after adjustment for confounders.

Conclusion: The timing of respiratory virus molecular testing in EDs was significantly associated with a range of outcome indicators. Results suggest the potential to maximise the benefits of RMDT by introducing an early diagnostic protocol such as triage-initiated testing.

Strengths and limitations of this study

- This is the first study to investigate the relationship between the timing of respiratory virus molecular testing and outcomes of patients presenting to ED with respiratory infections.
- This is a large multicentre study that involved six hospitals, enhancing the generalizability of our findings.
- Our findings may not be applicable to paediatric populations as this study did not include patients aged ≤18 years.
- Being an observational study, our findings do not imply a causal relationship.
- Our analyses were not adjusted for other relevant factors (e.g. access block) which may have confounded the findings of this study.

Introduction

The accurate diagnosis of the cause of respiratory infections has over recent years depended on a molecular method using a multiplex polymerase chain reaction (PCR) panel testing. Multiplex PCR provides accurate diagnoses, but has been traditionally performed in a central laboratory with a lengthy test turnaround time (TAT), and with major repercussions for the efficiency of emergency department (ED) workflows and care processes.

ED overcrowding has been recognized as a growing problem in Australia and worldwide, contributing to deficits in the performance of the health system.[1-3] Delay in laboratory test results is often considered as one of many factors contributing to ED overcrowding and prolonged ED length of stay (LOS).[4-6] Fast result availability through the use of rapid diagnostic tests can potentially improve patient flow and lessen the burden of ED overcrowding.[7 8] Optimising patient flow is of particular importance given the 4-hour ED LOS target introduced in Australia in 2011 to improve the quality and timeliness of care across EDs.[9]

Diagnostic kits for the rapid diagnosis of respiratory viruses using a molecular PCR-based technology are now available for use in hospital-based laboratories. Existing evidence shows that RMDT in ED is associated with a significant decrease in hospital admissions [8 10], shorter TAT [8] and reductions in hospital resource utilisation.[11-13] However, evidence of the association between RMDT and ED LOS have been inconsistent.[8 14 15] Our previous study did not detect a significant association between RMDT use and ED LOS.[16] We hypothesised that this may be due to the fact that RMDT ordering took place a median of three hrs after a patient's ED arrival[16] suggesting that the impact of RMDT on ED LOS and other timeliness of care processes may depend on the timing of the test.

The aim of the study was to determine if the timing of respiratory virus testing using RMDT in ED is associated with indicators related to timeliness of patient care including ED LOS,

meeting the 4-hr ED LOS Australian emergency access target; having a pending RMDT result at ED disposition.

Method

Setting

A retrospective observational study was conducted across six public hospitals in New South Wales (NSW), Australia. All study sites provide 24-hour EDs: three principal referral hospitals (EDs A, B and D) with 76,228, 54,443 and 61,348 annual ED presentations respectively, two acute group A hospitals (ED C and ED F) with 50,025 and 38,039 annual ED presentations respectively and one public acute group A hospital (ED E) with 29,479 annual ED presentations (2016 data).[17]

Population

The study period was the 2017 influenza season, between 1 July and 31 October. The inclusion criteria were patients presenting to EDs with symptoms of respiratory infection and aged ≥18 years; Australasian triage scale categories of 3 (potentially life-threatening), 4 (potentially serious) or 5 (less urgent) and tested for respiratory viruses at a hospital-based laboratory using a RMDT. The RMDT used in this study was a Cepheid Xpert® Flu/RSV XC (Cepheid, Sunnyvale, CA)[16 18]. The Cepheid Xpert® Flu/RSV XC assay demonstrated a high sensitivity and specificity for rapid detection of influenza A, influenza B and RSV.[19]

Patients with triage categories of 1 (immediately life-threatening) or 2 (imminently life-threatening) were excluded from the current analysis as patients required urgent medical assessment and treatment. Relevant patient presentation characteristics and laboratory test data were obtained by linking the ED and laboratory information system datasets.[6]

Outcome measures

The primary outcome was ED LOS. ED LOS was defined as the length of time between ED arrival and patient disposition. The secondary outcomes included >4-hour ED LOS and having a pending RMDT result at ED disposition. A pending test result was defined as the unavailability of a verified RMDT result at the time of patient disposition from the ED.[20]

Statistical analysis

Descriptive statistics including medians with inter-quartile ranges (IQR) were reported. The RMDT TAT was defined as the time of sample receipt at the hospital laboratory to time of availability of RMDT result. The exploratory variable was the timing of respiratory virus testing using a RMDT, defined as the time from a patient's ED arrival to time of sample receipt at the hospital laboratory. For result interpretation purposes, the relationship between the timing of the RMDT and study outcomes were estimated for every 30-minute increase in the timing of the test.

The association between the timing of the RMDT and ED LOS was assessed using a median regression. As the ED LOS data were highly skewed, commonly used approaches such as ordinary least squares regression which models the conditional mean of the outcome variable was not appropriate methods.[21] Median regression is a special type of quantile regression which estimates the median of the outcome variable conditional on the values of the predictor variables.[22] It is robust to extreme values and therefore well suited for modelling such data.[23]

Binary logistic regression was used to assess the association between the timing of the RMDT and the secondary outcomes (e.g. >4-hour ED LOS, *yes/no*). The strength of the associations was measured using odds ratio (OR) with a 95% confidence interval (CI).

For all outcomes, the findings were reported for the overall sample and by study ED. Sub-group analyses by patient disposition and ED arrival time were also conducted. The baseline covariates included age, gender, triage category, arrival time, arrival day of week, mode of

arrival, patient disposition, overall number of tests ordered and number of test order episodes (tests ordered at one point in time during the ED stay). All analyses were adjusted for potential confounders – any variable having a significant association with a given outcome in a univariate analysis ($P<0.05$) was selected for the multivariate model. P-values were 2-tailed and $P<0.05$ was considered statistically significant. Analyses were conducted using Stata version 15 (StataCorp LP, College Station, TX).

Patient and public involvement

This study was conducted without patient and public involvement as it was a retrospective study conducted using pre-existing administrative data. The patients were not invited to comment on the study design and were not consulted to develop outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Baseline characteristics

A total of 2,168 patients were included in the study. Table 1 presents baseline characteristics. The median patient age was 74 years and 55.2% (n=1,196) were female (Table 1). Overall, there were 16,321 pathology tests ordered (i.e. RMDT and other tests combined) with medians of 3 test order episodes during the ED stay and 7 tests per patient. Analysis of RMDT results showed that 28.9% (n=626) were positive for either influenza A/B (n=617) or RSV (n=9). No patients tested positive for both influenza and RSV. The overall median TAT of RMDT was 183 minutes but this ranged from 104 minutes at ED A to 622 minutes at ED F.

Table 1: Baseline characteristics.

Variables	Result (N=2,168)

Gender, n (%)	
Male	972 (44.8)
Female	1,196 (55.2)
Age (years), median (IQR)	74 (56-84)
Triage scale, n (%)	
Category 3	1,777 (82.0)
Category 4/5	391(18.0)
Arrival time, n (%)	
0700hrs to 1900hrs	1,528 (70.5)
1900hrs to 0700hrs	640 (29.5)
Arrival day of week, n (%)	
Monday	356 (16.4)
Tuesday	294 (13.6)
Wednesday	327 (15.1)
Thursday	300 (13.8)
Friday	308 (14.2)
Saturday	257 (11.9)
Sunday	326 (15.0)
Mode of arrival, n (%)	
Private/public transport	906 (41.8)
State ambulance[1]	1,262 (58.2)
Study ED, n (%)	
A	723 (33.4)
B	193 (8.9)

C	301 (13.9)
D	530 (24.5)
E	239 (11.0)
F	182 (8.4)
Patient disposition, n (%)	
Admitted	1,567 (72.3)
Discharged	545 (25.1)
Other[2]	56 (2.6)
Test order episode, median (IQR)	3 (2-4)
Overall tests ordered, median (IQR)	7 (5-9)
Test result, n (%)	
Positive	626 (28.9)
Negative	1,542 (71.1)

ED, Emergency Department; [1]Fifteen patients arriving by either wheelchair, correctional services vehicle, helicopter rescue service or walked-in were combined with 'State ambulance'; [2]Transferred to another hospital or left ED at own risk.

The timing of respiratory virus testing

The median time from ED presentation to respiratory virus testing using the RMDT for all samples was 224 minutes (IQR, 133-349). There was considerable variation in the median time to RMDT across EDs which ranged from 173 minutes (IQR, 108-264) at ED B to 269 minutes (IQR, 178-444) at ED F (Figure 1).

Study outcomes

The overall median ED LOS was 533 minutes. ED B had the shortest and ED D had the longest median ED LOS. Overall, 88% (n=1,907) of patients stayed >4 hours in ED (range across EDs:

78.2% at ED B to 92.0% at ED A). RMDT results were pending for 38% (n=824) of patients at the time of ED disposition (range across EDs: 15.1% at ED A to 70.7% at ED E) (Table 2).

Table 2: Summary of study outcomes.

ED	N	Primary outcome	Secondary outcomes	
		ED LOS (minute), Median (IQR)	>4-hour ED LOS, N (%)	Patient with a pending RMDT result, N (%)
A	723	545 (358-953)	665 (92.0)	109 (15.1)
B	193	376 (257-549)	151 (78.2)	80 (41.5)
C	301	490 (342-859)	263 (87.4)	157 (52.2)
D	530	714 (366-1172)	457 (86.2)	186 (35.1)
E	239	455 (336-657)	208 (87.0)	169 (70.7)
F	182	700 (389-1177)	163 (89.6)	123 (67.6)
Overall	2,168	533 (338.5-975)	1,907 (88.0)	824 (38.0)

ED, Emergency Department; LOS, Length of Stay.

The association between the timing of respiratory virus testing and primary outcome

The results of univariate analysis describing the association between baseline characteristics and each study outcome are presented in *Supplementary* Table 1. All baseline variables except arrival day of week and test result were significantly associated with ED LOS (Table S1).

The timing of respiratory virus testing was strongly associated with ED LOS. After adjustment for potential confounders, every 30-minute increase in the time to RMDT was associated with a 24.0-minute increase in the median ED LOS (95% CI, 21.8-26.1; P<0.001). There were no major differences, in this association, by ED (Table 3).

Table 3: Median regression showing association between the timing of respiratory virus testing (every 30-minute increase) and ED LOS (minutes).

ED	N	Unadjusted	Adjusted†
		Coef. (95% CI)	Coef. (95% CI)
A	723	26.4 (22.2-30.5)	21.6 (16.5-26.7)
B	193	32.4 (27.1-37.7)	26.4 (20.0-32.8)
C	301	30.9 (26.4-35.4)	26.7 (22.3-31.2)
D	530	31.7 (26.1-37.3)	21.7 (17.7-25.8)
E	239	25.8 (21.0-30.7)	26.3 (21.5-31.0)
F	182	28.0 (19.8-36.1)	23.2 (14.6-31.8)
Overall	2,168	29.4 (27.5-31.2)	24.0 (21.8-26.1)

All analyses were highly significant with a *P-value* of <0.001. The coefficient indicates the median change in a given outcome (e.g. ED LOS) for every 30-minute increase in the timing of the RMDT. †Adjusted for gender, age, triage category, ED arrival time, mode of arrival, study ED, patient disposition, test order episode. ED, Emergency Department; LOS, Length of Stay.

A subgroup analysis by patient disposition and ED arrival time is shown in *Supplementary* Table 2. The association was more pronounced among patients who were subsequently discharged than for admitted patients and among patients who arrived to EDs between 0700hrs to 1900hrs than for patients arriving between 1900hrs to 0700hrs (Table S2).

The association between the timing of respiratory virus testing and secondary outcomes

The median time to RMDT was 113 minutes (IQR, 76-152) for patients with ≤4 hours ED LOS (n=261) and 250 minutes (IQR, 153-370) for patients staying >4 hours in ED (n=1,907). The median time to RMDT was 211 minutes (IQR, 122-336) for patients who received RMDT results before disposition (n=1,344) and 247 minutes (IQR, 151-364) for patients with pending RMDT results at disposition (n=824). Of the patients with pending RMDT results, the results of 30.3% (n=250) eventually came back positive for either influenza A/B or RSV.

The results of binary logistic regression are presented in Table 4 and show associations between the time to RMDT and secondary outcomes. The time to RMDT was positively associated with

both secondary outcomes. In the adjusted model, for every 30-minute increase in time to RMDT, the likelihood of staying >4 hours in ED (*versus* having ≤4 hours ED LOS) increased by a factor of 1.51 (OR, 1.51; 95% CI, 1.41-1.63; *P*<0.001). This is equivalent to a 51% increase in the likelihood of staying >4 hours in ED.

The association between the timing of the RMDT and having a pending test result at ED disposition was not as striking as with other outcomes. In the total sample, for every 30-minute increase in the time to RMDT, the likelihood of experiencing a pending RMDT result at ED disposition increased by a factor of 1.04 –a 4% increase – (OR, 1.04; 95% CI, 1.02-1.05; *P*<0.001) after adjustment for potential confounders. When the analysis was conducted separately by study EDs, the association was not statistically significant for EDs C, D and E (Table 4).

Table 4: Binary logistic regression showing association between the timing of respiratory virus testing (every 30- minute increase) and secondary outcomes.

ED	N	> 4-hr ED LOS		Patient with a pending RMDT result	
		Unadjusted	Adjusted†	Unadjusted	Adjusted††
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
A	723	1.58 (1.37-1.82)	1.51 (1.28-1.79)	1.04 (1.01-1.07)	1.06 (1.03-1.10)
B	193	1.74 (1.41-2.14)	1.70 (1.34-2.17)	1.06 (1.01-1.12)	1.16 (1.07-1.25)
C	301	1.51 (1.29-1.76)	1.48 (1.25-1.75)	0.99 (0.96-1.02)*NS*	1.02 (0.99-1.06)*NS*
D	530	1.69 (1.48-1.93)	1.64 (1.41-1.90)	0.99 (0.97-1.01)*NS*	1.02 (1.00-1.05)*NS*
E	239	1.40 (1.21-1.61)	1.39 (1.19-1.63)	1.00 (0.96-1.04)*NS*	1.02 (0.97-1.07)*NS*
F	182	1.63 (1.28-2.07)	1.90 (1.24-2.91)	1.01 (0.98-1.05)*NS*	1.05 (1.00-1.09)
Overall	2,168	1.54 (1.45-1.64)	1.51 (1.41-1.63)	1.02 (1.01-1.03)	1.04 (1.02-1.05)

All analyses, except those marked '*NS*', were significant with a *P-value* of <0.05. The coefficient indicates the likelihood of a given outcome for every 30-minute increase in the timing of the RMDT. †Adjusted for age, triage category, mode of arrival, study ED, patient disposition, test order episode and test result. ††Adjusted for gender, age, triage category, mode of arrival, study ED, patient disposition, test order episode. ED, Emergency Department; NS, Not Significant.

Discussion

Key findings

The major finding of this study is that for every 30-minute increase in the time from ED arrival until respiratory virus testing there was a 24.0-minute increase in the median ED LOS. Moreover, an increase in the timing of respiratory virus testing was associated with a greater likelihood of experiencing an ED LOS greater than four hours and having a pending RMDT result at the time of disposition from the ED.

Interpretation and comparison with existing literature

Previous studies have also reported a significant association between ED LOS and the time taken to obtain the results from laboratory testing in EDs.[6 24-26] However, unlike our study, the previous studies have been conducted in a context of broader patient populations visiting ED and, therefore, direct comparisons with other studies are not possible. For example, Li *et al*. conducted a retrospective study that included 123,455 ED presentations for all conditions across four EDs in NSW, Australia. That study assessed the relationship between ED LOS and TAT and found a 17-minute increase in ED LOS for each 30-minute increase in TAT.[6] In a recent large US study, Kaushik *et al*. evaluated the impact of reducing laboratory TAT on ED LOS using data from 486 hospitals with 4,483,169 ED presentations.[25] In that study, a 1-minute decrease in TAT was associated with a 0.50-minute decrease in ED LOS.[25] In another US study, Kocher *et al*. investigated the effect of diagnostic testing and treatment patterns on ED LOS using data from a large national study that included approximately 360 million ED

presentations.[26] They found that, the ordering of a blood test was the most time consuming testing modality resulting in an adjusted marginal effect of a 72-minute increase in ED LOS and the likelihood of experiencing a >4-hour ED LOS increased by a factor of 2.29.[26]

The present study revealed a direct relationship between the timing of respiratory virus testing and a range of indicators of timeliness of patient care in ED. Delays in the ordering of RMDT had a negative impact on our selected ED outcomes. Our results suggest that earlier initiative of RMDT may result in reduced ED LOS. More systemic or procedural changes in the way healthcare is delivered (e.g. introduction of an early diagnostic testing protocol such as a triage-initiated testing) may be needed in order to maximise its benefits. Triage-based testing protocols have been shown to reduce wait times and ED LOS, decrease costs, reduces time to receiving medications and improve patient satisfaction in other conditions.[27-29] In an randomized controlled trial conducted in the US that including more than 1000 ED patients aged <3years, influenza testing at triage using a non-molecular antigen-based method led to significantly shorter ED LOS.[30] Future research should assess the potential impact of triage-initiated ordering of RMDT for patients presenting to ED with suspected respiratory viral infection on patient outcomes including the effect on ED LOS.

Implications of the study

The current study showed that a delay in respiratory virus testing was associated with an increased likelihood of having a pending test result at ED disposition. The test results of 30.3% of patients with pending test results eventually came back positive for either influenza A/B or RSV. This finding has significant patient safety implications. Pending test results at discharge are less likely to be followed-up and may lead to missed or delayed diagnosis and increased hospital representations. [31] [32] From an infection transmission perspective, patients who were

discharged with pending results could potentially spread the infection, especially if appropriate management was not provided.

Strengths and weaknesses of the study

Our study has some strengths. To the best of our knowledge, this is the first study to explore the relationship between the timing of respiratory virus molecular testing and ED outcomes among patients presenting with respiratory infections. Another strength of the study was that it is a multicentre study that involved six hospitals with a large sample size, enhancing the external validity (generalizability) of our findings.

The findings of the current study should be interpreted in the context of the following methodological limitations. Firstly, this study was conducted among adult patients (age>18 years). Given the impact of RMDT on ED LOS can be different among patients aged≤18 years [33], our findings may not be applicable to paediatric populations. Secondly, being an observational study, the findings of the current study do not imply a causal relationship. Thirdly, our analyses were not adjusted for other factors which may have confounded the findings of this study. The input-throughput-output model [34] is commonly used in studies assessing factors affecting LOS and ED overcrowding.[26 35 36] Input factors are characteristics that contribute to the demand for ED services (e.g. patient demographics and ED presentation characteristics).[34] Throughput factors are characteristics related to ED care such as diagnostic evaluations and treatment.[26 34] Output factors are organisational or hospital capacity-related characteristics (e.g. access block).[34 36] Whilst our multivariable models were adjusted for a number of input variables, our current analysis did not consider the effect of several throughput and output/organisational factors due to lack of data. Previous studies have shown that throughput factors such as diagnostic imaging [26], clinical assessment [37] and treatment (administering a medication or performing a procedure) [26] and output/organisational factors [36]

[38 39] are important factors influencing ED LOS. Finally, the current study did not consider the appropriateness of RMDT ordering practices. Reducing inappropriate or unnecessary respiratory virus testing could also have a considerable impact on reducing ED LOS.

Conclusion

The timing of respiratory virus molecular testing in EDs was significantly associated with a range of outcome indicators. Results suggest the potential to maximise the benefits of RMDT by introducing an early diagnostic protocol such as a triage-initiated testing which warrants investigations in future studies.

Patient consent for publication: Not required.

Contributors: AG, LL, MRD, RL, JT and JIW conceived the study and obtained research funding. NW, LL, MRD, RL, RY, KC, JT, WV, JIW and AG have made substantial contributions to the design of the study. NW and LL conducted data extraction, cleaning, linkage and analysis. NW, LL, MRD, RL, KC, JT, JIW and AG involved in the interpretation of the results with input from RY and WV. NW, LL, MRD, JT and AG contributed to the drafting of the manuscript with input from RL, RY, KC and WV. All authors involved in the critical revision of the manuscript for important intellectual content as well as approved the final version to be published.

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Ethical approval: Ethics approval was granted by the Human Research Ethics Committee of the South Eastern Sydney Local Health District (HREC/16/POWH/412).

Conflicts of interests: None declared.

Data sharing statement: The data that underline the results reported in this articles are available from the data custodians (South Eastern Sydney and Illawarra Shoalhaven Local Health District), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The de-identified data however may be obtained from the corresponding author upon reasonable request and with permission of the data custodians.

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Figure's Legend

Figure 1: The time to RMDT by study EDs: Boxes represent the IQR (25th and 75th percentiles) with the median (50th percentile) value within the boxes, the mean value is represented as a '+' and the capped bars represent the 10th and 90th percentiles. The broken line indicates the overall median time to RMDT.

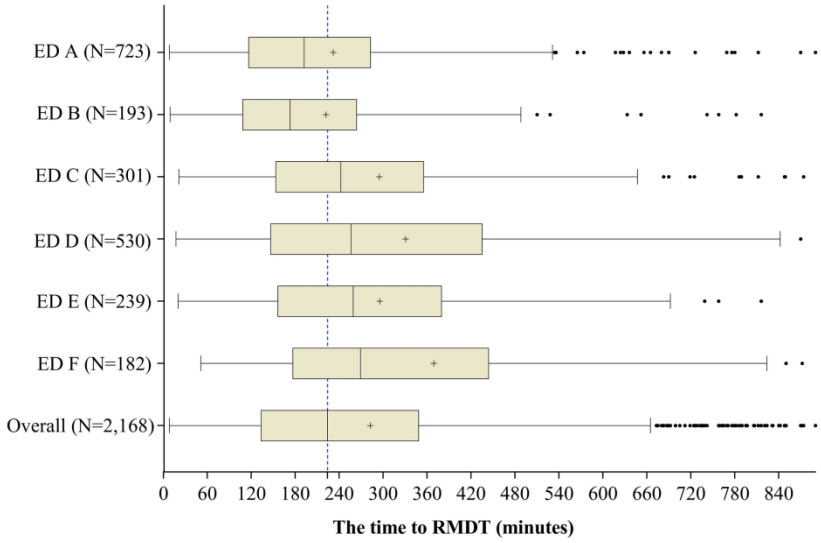

Figure 1: The time to RMDT by study EDs: Boxes represent the IQR (25th and 75th percentiles) with the median (50th percentile) value within the boxes, the mean value is represented as a '+' and the capped bars represent the 10th and 90th percentiles. The broken line indicates the overall median time to RMDT.

214x124mm (300 x 300 DPI)

Supplementary Data

Table S1: Univariate analysis showing variables associated with primary and secondary outcomes (N=2,168).

Variables	ED LOS (min)	> 4-hr ED LOS	Patient with a pending RMDT result
	Coef. (95% CI)	OR (95% CI)	OR (95% CI)
Female *vs.* Male	-75 (-119.6 to -30.4)	0.82 (0.63-1.07) *NS*	1.26 (1.06-1.51)
Age (for every 10-year increase)	51.2 (40.5 to 61.9)	1.38 (1.3-1.46)	0.86 (0.82-0.90)
Triage			
Semi-urgent *vs.* Urgent	-123 (-179.8 to -66.2)	0.43 (0.32-0.58)	1.66 (1.33-2.07)
Arrival time			
0700hrs to 1900hrs *vs*. 1900hrs to 0700hrs	-188 (-233.6 to -142.4)	0.75 (0.56-1.01) *NS*	0.97 (0.80-1.17) *NS*
Arrival day of week			
Weekdays vs. Weekends	8 (-39.8 to 55.8) *NS*	1.06 (0.80-1.42) *NS*	1.01 (0.83-1.22) *NS*
Mode of arrival			
Ambulance *vs.* private/public transport	224 (180.6 to 267.4)	3.76 (2.85-4.98)	0.63 (0.53-0.76)
Study ED			

A	Ref	Ref	Ref
B	-169 (-257.7 to -80.3)	0.31 (0.20-0.48)	3.99 (2.81-5.67)
C	-55 (-130.1 to 20.1)[NS]	0.60 (0.39-0.93)	6.14 (4.53-8.33)
D	169 (106.4 to 231.6)	0.55 (0.38-0.79)	3.05 (2.32-3.99)
E	-90 (-171.6 to -8.4)	0.59 (0.37-0.93)	13.60 (9.63-19.20)
F	162 (71.3 to 252.7)	0.75 (0.43-1.29) [NS]	11.74 (8.10-17.02)
Patient disposition			
Discharged *vs.* Admitted	-325 (-380.3 to -269.7)	0.17 (0.13-0.22)	2.41 (1.97-2.94)
Test order episode	120.6 (109.1 to 132.0)	2.58 (2.23-2.99)	0.83 (0.79-0.88)
No. of tests (for every 3 more tests ordered)	167.6 (149.5 to 185.7)	3.3 (2.78-3.93)	0.85 (0.78-0.92)
Test result			
Positive vs. Negative	-39 (-85.5 to 7.5)[NS]	0.71 (0.54-0.94)	1.12 (0.93-1.36) [NS]

ED, Emergency Department; RMDT, Rapid Molecular Diagnostic Test; LOS, Length of Stay; NS, Not Significant.

Table S2: Multivariate analysis showing the association between the timing of respiratory virus testing (every 30-min increase) with study outcomes by patient disposition and ED arrival time.

Variable	N	ED LOS (min)[†]	> 4-hr ED LOS[††]	Patient with a pending RMDT result[†††]
		Coef. (95% CI)	OR (95% CI)	OR (95% CI)
Patient disposition				
Discharged	545	28.0 (25.6-30.4)	1.68 (1.48-1.91)	1.09 (1.03-1.14)
Admitted	1,567	22.3 (19.4-25.2)	1.44 (1.32-1.58)	1.04 (1.02-1.05)
ED arrival time				
0700hrs to 1900hrs	1,528	26.6 (24.3-29.0)	1.49 (1.37-1.62)	1.03 (1.01-1.04)
1900hrs to 0700hrs	640	17.8 (13.4-22.0)	1.58 (1.37-1.81)	1.06 (1.03-1.09)

All analyses were significant with a *P-value* of <0.001. ED, Emergency Department; RMDT, Rapid Molecular Diagnostic Test; LOS, Length of Stay; [†]Adjusted for gender, age, triage category, mode of arrival, study ED, test order episode; [††]Adjusted for age, arrival day of week, mode of arrival, study ED and test order episode; [†††]Adjusted for gender, age, triage category, mode of arrival, study ED and test order episode.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	a=page 1 b=page 2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1=page 2 ('Setting) 1.2=page 2 ('Setting') 1.3=page 2 ('Setting')
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4		
Objectives	3	State specific objectives, including any prespecified hypotheses	Pages 4 and 5		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page 5		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Page 5.	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	The study was retrospective observational study as detailed in Page 5 Not applicable Separate reference was provided regarding the linkage process
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page 6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 5		

Bias	9	Describe any efforts to address potential sources of bias	Not described directly but effort was made to describe potential confounders		
Study size	10	Explain how the study size was arrived at	Page 5 –the study included all participants who fulfilled the inclusion criteria		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Pages 5 and 6		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Pages 5 and 6		

Data access and cleaning methods		.. Separate reference was provided regarding the data cleaning and linkage process.		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		.. Separate reference was provided regarding the data cleaning and linkage process.		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Page 7	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest	Pages 7 and 8		

		(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Pages 9 and 10		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 10-12		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Supplementary data		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page 13		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	Pages 14 and 15	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include	

		Discuss both direction and magnitude of any potential bias		discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 13 and 14		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 14		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 16		
Accessibility of protocol, raw data, and programming code		..	NA	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.