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MAJOR ARTICLE

# Point-of-Care Influenza Testing Impacts Clinical Decision, Patient Flow, and Length of Stay in Hospitalized Adults

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***Background.*** Influenza is difficult to distinguish clinically from other acute respiratory infections. Rapid laboratory diagnosis can help initiate early effective antiviral treatment and isolation. Implementing a novel point-of-care test (POCT) for influenza in the emergency department (ED) could improve treatment and isolation strategies and reduce the length of stay (LOS).

***Methods.*** In a prospective, controlled observational cohort study, we enrolled patients admitted due to acute respiratory illness to 2 public hospitals in Bergen, Norway, one using a rapid POCT for influenza (n = 400), the other (n = 167) using conventional rapid laboratory-based assay.

***Results.*** Prevalence of influenza was similar in the 2 hospitals (154/400, 38% vs 38%, 63/167; $P = .863$). Most patients in both hospitals received antiviral (83% vs 81%; $P = .703$) and antibiotic treatment (72% vs 62%; $P = .149$). Isolation was more often initiated in ED in the hospital using POCT (91% vs 80%; $P = .025$). Diagnosis by POCT was associated with shorter hospital stay; old age, diabetes, cancer, and use of antibiotics, particularly broad-spectrum antibiotics, were associated with prolonged stay.

***Conclusions.*** POCT implementation in ED resulted in improved targeted isolation and shorter LOS. Regardless of POCT use, most influenza patients received antivirals (>80%) and antibiotics (>69%).

**Keywords.** influenza; point-of-care test; hospitalized adults; molecular assay; length of stay; antibiotics; isolation; neuraminidase inhibitor.

Acute (lower) respiratory tract infections are a leading cause of morbidity and mortality worldwide [1]. Influenza is one of the most commonly recognized viral pathogens [2, 3], and globally responsible for a significant burden on health care resources both in primary care and in hospitals. Influenza infection alone is estimated to cause up to 650 000 deaths annually [4–6]. Influenza may also pave the way for secondary bacterial pneumonia by reducing the effectiveness of alveolar macrophages [7, 8].

Clinically, influenza is difficult to distinguish from other respiratory tract infections of viral and bacterial origin [9]. Studies on the etiology of community acquired pneumonia (CAP) in hospitalized patients have found viral etiology to be common, as well as viral-bacterial coinfection, the last accounting for up to one-third of CAP infections [3, 10–14]

Initial misdiagnosis in hospital negatively impacts early treatment. In severe influenza disease, early onset of treatment with neuraminidase inhibitors (NAIs) is essential, as it reduces mortality, influenza-related pneumonia [15], and length of stay (LOS) in hospital [16–20]. Influenza diagnostics by laboratory-based reverse transcriptase polymerase chain reaction (RT-PCR) have long turn-around times (TATs) [21–23], limiting early NAI treatment. Antigen detection-based tests are limited by their low sensitivity. New point-of-care tests (POCTs) based on molecular assays like RT-PCR or similar nucleic acid amplification technologies generate results with high sensitivity and specificity in less than 30 minutes and the analysis can be performed at the bedside [24]. Their simplicity makes new POCTs easy to use in the emergency department (ED), outside laboratory facilities. Rapid tests in hospitals have logistical benefits and could potentially reduce the use of antibiotics [25]. Compared to traditional RT-PCR tests, studies suggest that POCT influenza diagnosis improves use of isolation, antibiotic stewardship, and antiviral use, reduces LOS, and results in overall health care savings [26–31]. However, these results need comparison to rapid laboratory-based influenza diagnostics. Upon the reorganization of the influenza diagnostic pathway in our hospital we hypothesized that the introduction of a novel

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POCT for influenza would improve logistics, NAI prescription, and overall antibiotic use during an influenza epidemic.

## METHODS

### Study Design

We conducted a prospective controlled observational clinical cohort study in 2 referral hospitals in Bergen, Norway, during the influenza season of 2018–2019. The 2 neighboring hospitals used different rapid influenza tests, Haukeland University Hospital used a novel POCT (hospital 1) and neighboring Haraldsplass Diaconess Hospital served as a control using a laboratory-based test (hospital 2). The inclusion period was December 2018 to March 2019, during the peak of influenza activity in Norway. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Western Norway (REK number 2018/1772), and the data collection conducted in accordance with the Declaration of Helsinki's principles of Good Clinical Practice (GCP). All enrolled patients provided written, informed consent. Adult patients fulfilling inclusion criteria were prospectively enrolled in the ED when admitted to hospital. The 2 study hospitals are cooperating teaching facilities providing equal services within the field of general surgery and internal medicine. They serve the unselected public in predefined geographical areas of Bergen. The hospitals differ in size and subspeciality expertise with hospital 1 being a referral and local hospital, and hospitals 1 and 2 serving public emergency care services for 500 000 and 145 000 people, respectively.

### Inclusion Criteria

Eligible patients were adults (aged ≥ 18 years) referred to the ED, and able to provide informed consent. Next of kin could provide consent, enabling inclusion of severely ill patients and elderly patients with cognitive impairment. Patients were prospectively included from the time of admission or within 2 days if ED inclusion was not feasible. Inclusion criteria were symptoms of acute respiratory illness lasting ≤7 days and 2 or more of the following symptoms: temperature ≥ 37.5°C, malaise, exacerbation of chronic obstructive pulmonary disease or asthma, dyspnea, sore throat, cough, myalgia, arthralgia, headache, or gastrointestinal symptoms.

Acute respiratory illness was defined as an episode of influenza-like-illness or upper or lower respiratory tract infection including CAP. Exclusion criteria was previous inclusion in the study.

### Molecular Diagnostic Assays

In hospital 1, the available influenza POCT was Abbott ID NOW Influenza A and B 2, an isothermal nucleic acid amplification-based assay targeting the polymerase basic gene 2 (PB2) for influenza A virus and polymerase acidic gene (PA) for influenza B virus. Test samples were obtained from the nostril. The manufacturers TAT was reported to be less than 15 minutes. The control, laboratory-based influenza test in hospital 2 was the Cepheid GeneXpert II, using the Xpert Xpress Flu/RSV and Xpert Flu test kit, real-time RT-PCR–based assays targeting influenza A matrix protein, PB2 and influenza A acidic proteins (PA), and influenza B matrix and nonstructural (NS) proteins. The assay provided results within 20 minutes with the Xpress test kit and 75 minutes for negative results with the ordinary Flu test kit using a nasopharyngeal swab for sampling. The producers report high sensitivities (81.6% and 94.9%, respectively, for POCT and the Xpert assay) and specificity (94.0% and 100%, respectively) when compared to reference standard RT-PCR [32, 33]. Between 10 and 18 March 2019 there was a shortage of the GeneXpert influenza/RSV tests (n = 12), and the Eplex Respiratory pathogen panel from GenMark Dx was performed instead.

### Research Staff

GCP-trained medical staff and students identified and included study patients admitted in the ED during the study period Monday to Friday 09:00–18:00. Outside these hours, consultants with ED duty included a small number of patients.

### Study Procedures

Patients received standard clinical care, with the responsible ED physician deciding if a nasopharyngeal test and a POCT influenza test was indicated, making the patient eligible for study inclusion. In hospital 1 the influenza POCT was generally supplemented by a laboratory-based RT-PCR including a broader respiratory panel (available after 24–48 hours; Supplementary Table 2). This was the exception in hospital 2. Baseline clinical and demographic characteristics were collected upon inclusion; subsequent clinical data was collected retrospectively from hospital records.

Narrow-spectrum antibiotics included phenoxy- and benzylpenicillins, aminopenicillins, and aminoglycosides. Broad-spectrum antibiotics included extended-spectrum agents such as piperacillin-tazobactam, second- and third-generation cephalosporins, quinolones, and carbapenems [34]. Resistance-driving antibiotics also included clindamycin, glycopeptide antibiotics, macrolides, and linezolid [35].

### Statistical Analysis

Proportions of patients were compared by $\chi^2$ test or Fisher exact test, while continuous variables were compared across groups using Wilcoxon rank-sum test (Mann-Whitney) or Student *t* test as appropriate. A *P* value ≤ .05 was considered significant. Multivariable analyses of explanatory factors associated with POCT was done using binary logistic regression. Outcome variables duration of hospital stay and duration of antibiotic use were assessed by Kaplan-Meyer survival analysis, log-rank tests, and Cox proportional hazards regression. Data analysis was performed in R (R Core Team; http://www.R-project.org/), IBM SPSS statistics version 24, and Prism version 8.1.2 (GraphPad Software).

## RESULTS

### Baseline Characteristics

Between December 2018 and March 2019, 625 patients were recruited (Figure 1A). Of these, 442 and 183 patients were recruited at hospitals 1 and 2, respectively. One patient withdrew from the study, and 57 patients (not fulfilling inclusion criteria) were subsequently excluded from analysis.

The age distribution of patients was similar at the 2 hospitals (Table 1 and Figure 1B), although there was a small but significant median age difference of 4 years, with older patients in hospital 2. Influenza was confirmed in 154 (38%) and 63 (38%) of patients in hospitals 1 and 2, respectively. The majority of patients had one or more comorbidities (85% and 90% in hospitals 1 and 2, respectively; Table 1). The most common

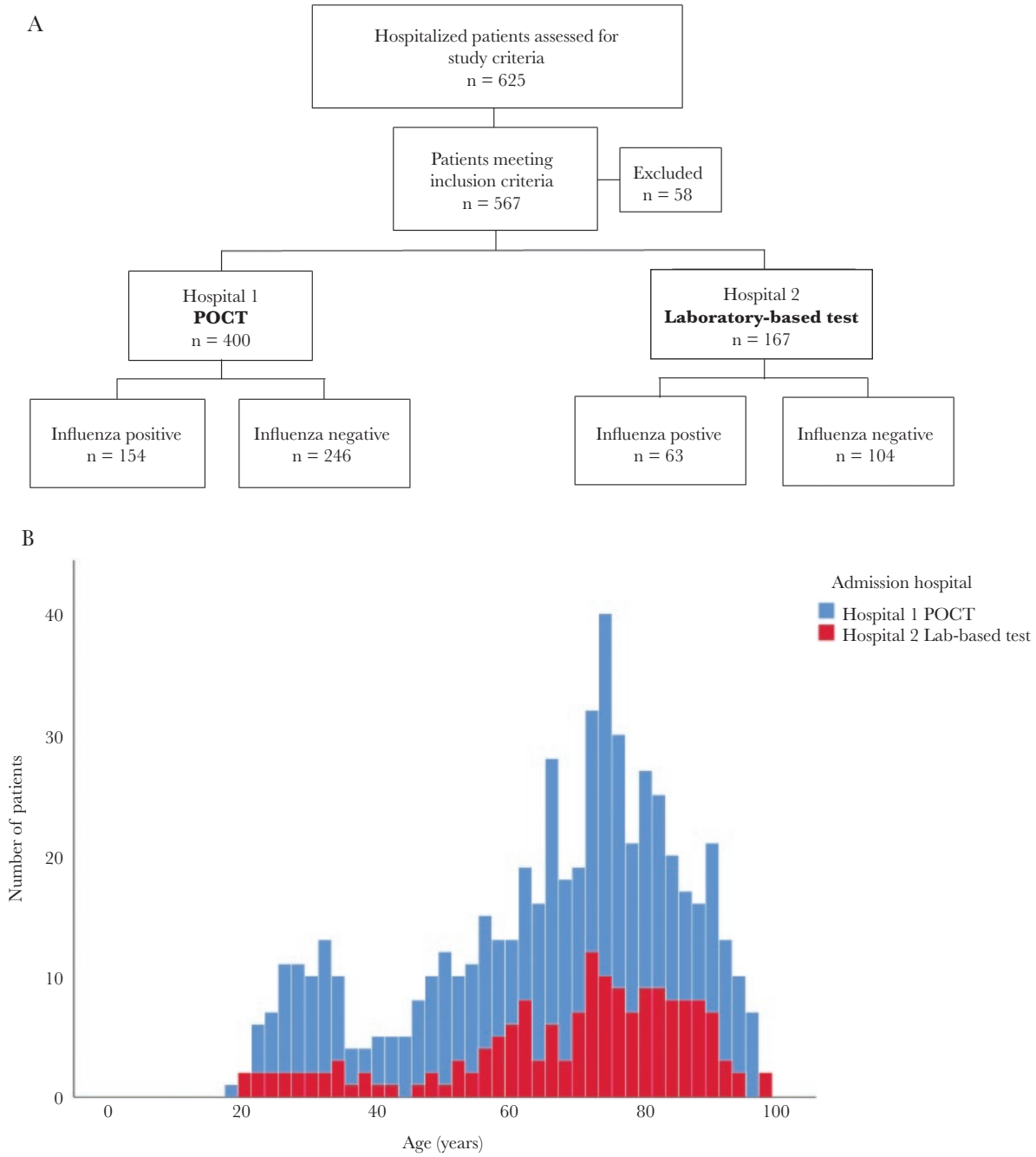


**Figure 1.** *A*, Study design. The study was designed as a prospective observational controlled study. All patients were tested for influenza upon admission. Participants were enrolled from 2 university referral hospitals in Bergen, Norway, between December 2018 and March 2019. The 2 hospitals differed in their rapid influenza diagnostic pathways. Forty-two patients at hospital 1 and 15 patients at hospital 2 were excluded as they did not fulfil inclusion criteria. One patient at hospital 2 withdrew from the study. *B*, Age distribution was similar in intervention hospital 1 and control hospital 2, with a peak of patients with ages between 65 and 70 years. Abbreviation: POCT, point-of-care test.

**Table 1. Baseline Patient Characteristics**

| Characteristics | Hospital 1 POCT (n = 400) | Hospital 2 Laboratory-Based Test (n = 167) | *P* Value |
|---|---|---|---|
| Age, y, median (IQR) | 68 (51–79) | 72 (60–82) | **.040** |
| Sex | | | |
| Female | 193 (52) | 86 (52) | .956 |
| Male | 207 (48) | 81 (48) | |
| Influenza vaccine | | | |
| 2018 | 185 (47) | 91 (56) | .051 |
| Last 5 years | 256 (65) | 115 (71) | .183 |
| Triage score upon admittance, mean (SD)[a] | 1.6 (0.73) | 1.6 (0.87) | .795 |
| Need for respiratory support | | | |
| Oxygen therapy | 160 (40) | 77 (46) | .186 |
| Noninvasive | 49 (12.3) | 10 (6.1) | **.029** |
| Invasive | 7 (2) | 0 (0) | .085 |
| Comorbidities | | | |
| None | 61 (15) | 16 (10) | .072 |
| Cardiovascular disease | 156 (39) | 81 (49) | **.032** |
| Respiratory disease | 179 (45) | 87 (52) | .110 |
| Diabetes mellitus | 60 (15) | 35 (21) | .083 |
| Hypertension | 137 (34) | 72 (43) | **.046** |
| Renal disease | 65 (16) | 26 (16) | .840 |
| Liver disease | 12 (3) | 0 (0) | **.024** |
| Neurological disease | 92 (23) | 45 (27) | .317 |
| Obesity (BMI > 30) | 86 (22) | 30 (18) | .341 |
| Active cancer | 49 (12) | 21 (13) | .895 |
| Immunocompromised[b] | 60 (15) | 24 (15) | .869 |
| Pregnancy | 6 (3) | 1 (1) | .366 |
| Other comorbidities[c] | 122 (31) | 57 (34) | .407 |
| Current smoker | | | |
| Yes | 66 (17) | 30 (18) | .708 |
| No[d] | 330 (83) | 137 (82) | |
| Additional diagnostics | | | |
| Influenza test | 400 (100) | 167 (100) | NS |
| Positive test | 154 (39) | 63 (38) | .863 |
| Respiratory panel | 325 (81) | 34 (20) | **<.001** |
| Positive pathogen other than influenza | 51(16) | 14 (41) | **.002** |
| Blood culture | 321 (81) | 152 (91) | **.002** |
| Positive culture | 24 (7) | 10 (7) | .724 |
| Urine pneumococcal antigen | 165 (42) | - | |
| Positive culture | 16 (10) | - | - |
| Chest X-ray | 341 (86) | 155 (93) | **.021** |
| Positive infiltrate | 118 (35) | 48 (31) | .426 |
| Duration of symptoms upon admittance, d, median (IQR) | 3 (1–4) | 2 (1–4) | **.011** |

Data are No. (%) except where indicated. *P* values are based on the $\chi_2$ test for differences in proportions for binary data and Mann-Whitney *U* test or Student *t* test as appropriate for continuous data. Bold font indicates a significant difference as defined by *P* value < .05.

Abbreviations: BMI, body mass index; DMARD, disease-modifying antirheumatic drug; IQR, interquartile range; POCT, point-of-care test; SATS, South African Triage Scale.

[a]Triage score: the Norwegian SATS emergency prioritization score is based on SATS and additional investigation. The score is presented as a color code. For calculation purposes, green = 0, yellow = 1, orange = 2, and red = 3

[b]The definition of immunocompromised patient includes:

1. Patients on regular oral prednisolone from 5 mg/d or prolonged courses (>10 d of elevated doses equivalent to 20 mg oral prednisolone or more), n = 28.
2. Patients treated with prednisolone in combination with DMARDs or biologic DMARDs, n = 16.
3. Patients receiving chemotherapy, n = 11.
4. Patients with organ transplants and immunosuppressive treatment, n = 7.
5. Patients on immune suppressive drugs for inflammatory bowel disease, n = 3.
6. Patients with acquired or innate immunodeficiencies, n = 8.
7. Other causes, n = 11.

[c]Other autoimmune diseases, rheumatological diseases, drug addiction, etc.

[d]Includes previous smokers.

were respiratory disease, cardiovascular disease, and hypertension, the latter 2 significantly more prevalent in hospital 2 (Table 1). While influenza-positive patients had less frequently comorbidities (79.6% vs 90.8%, $P < .001$) and fewer concomitant comorbidities (mean 2.0 vs 2.7, $P < .001$, Student $t$ test), they reported a higher symptom load than the influenza-negative patients (mean 6.4 vs 5.2 symptoms, $P < .001$). The most common symptoms were cough, temperature >37.5°C, malaise, and dyspnea (Supplementary Table 1).

Influenza-positive patients had shorter LOS than influenza-negative patients in both hospitals. Interestingly, intervention hospital 1 had shorter LOS (3 versus 4 days; Table 2), despite patients having a longer duration of symptoms before hospitalization (3 vs 2 days; Table 1). Oxygen therapy was provided to 40% and 46% of patients in hospitals 1 and 2, respectively ($P = .176$). The proportion of patients receiving noninvasive respiratory support was significantly higher in hospital 1 (12.3%) than in hospital 2 (6.1%, $P = .029$; Table 1), regardless of influenza status. Overall, only 7 patients needed ventilator treatment, all in hospital 1. Of these, 4 were influenza positive and all had comorbidities. None were pregnant and only one had received influenza vaccination.

Both hospitals use the Norwegian adaptation of South African Triage Scale (SATS) to assess patients according to severity of symptoms and signs in the ED. Patients are scored with a color code upon arrival with increasing severity from green, yellow, orange, to red (Supplementary Figure 1). The proportion of patients with combined mild (green, yellow) versus moderate/severe (orange, red) SATS scores were equal between the 2 hospitals.

Additional nasopharyngeal RT-PCR diagnostics for respiratory pathogens was performed in 81% and 20% of patients in hospitals 1 and 2, respectively. In hospital 1, the laboratory-based in-house RT-PCR yielded results within 24–48 hours (Supplementary Table 2), and detected 9 additional influenza cases. Altogether, 16% of conducted RT-PCR tests in hospital 1 detected respiratory pathogens other than influenza; comparably, hospital 2 detected other pathogens in 41% of patient samples. However, sampling in hospital 2 was restricted to those with a negative influenza test and suspicion of viral etiology.

**Table 2. Clinical Outcomes of the Patients**

| Clinical Outcomes | Hospital 1 POCT (n = 400) | Hospital 2 Laboratory-Based Test (n = 167) | 2-Sided *P* Value |
|---|---|---|---|
| Length of hospital stay, d, median (IQR) | 3 (1–5) | 4 (2–7) | **<.001** |
| Influenza positive | 2 (1–4) | 3 (1–6) | .075 |
| Influenza negative | 3 (2–5) | 4 (2–7) | **<.001** |
| Initial isolation | 159 (40) | 59 (37) | .507 |
| Influenza positive | 140 (91) | 47 (80) | **.025** |
| Influenza negative | 18 (7) | 12 (12) | .175 |
| 30-Days mortality | 13 (2) | 4 (3) | .204 |
| Influenza positive | 3(2) | 1 (2) | .512 |
| Influenza negative | 10 (4) | 3 (3) | .327 |
| Antibiotics all treatment | 303 (76) | 122 (73) | .469 |
| Influenza positive ($n^a$ = 154, $n^b$ = 63) | 110 (72) | 39 (62) | .149 |
| Influenza negative ($n^a$ = 246, $n^b$ = 104) | 193 (79) | 83 (80) | .777 |
| Antibiotics, broad spectrum and resistance driving | 131 (43) | 41 (34) | **.047** |
| Influenza positive ($n^a$ = 110 $n^b$ = 39) | 40 (36) | 14 (36) | .958 |
| Influenza negative ($n^a$ = 193, $n^b$ = 83) | 91 (47) | 26 (32) | .015 |
| Antibiotics, all treatment, duration, d, mean (SD) | 7.8 (5.3) | 6.9 (5.6) | .120 |
| Influenza positive ($n^a$ = 110, $n^b$ = 39) | 7.3 (4.9) | 4.5 (4.2) | **.002** |
| Influenza negative ($n^a$ = 193, $n^b$ = 83) | 8.1 (5.4) | 7.9 (5.9) | .877 |
| Antibiotics, all treatment, duration, d, median (IQR) | 7 (5–10) | 6 (3.5–9) | .120[c], **.046**[d] |
| Influenza positive | 7 (5–9) | 3.5 (1–8) | **.002**[c,d] |
| Influenza negative | 8 (6–10) | 7 (6–10) | .877[c], .621[d] |
| NAI treatment total | 136 (34) | 54 (32) | .673 |
| Influenza positive ($n^a$ = 154, $n^b$ = 63) | 128 (83) | 51 (81) | .703 |
| Influenza negative ($n^a$ = 246, $n^b$ = 104) | 8 (3) | 3 (3) | .847 |
| Time from triage to NAI treatment, h, mean (SD) | 6.2 (7.9) | 6.2 (6.0) | .985[c], .189[d] |
| Time from triage to NAI treatment, h, median (IQR) | 4 (2–7) | 5 (3–7.5) | .933[c], .189[d] |

Data are No. (%) except where indicated; median (IQR) or mean (SD) as appropriate according to the distribution of data. *P* values were calculated using appropriate comparison: $\chi^2$ for binary categorical variables and Mann-Whitney test or Student $t$ test for continuous variables. Bold font indicates a significant difference as defined by *P* value < .05.

Abbreviations: IQR, interquartile range; NAI, neuraminidase inhibitor; POCT, point-of-care test.

[a]Hospital 1.

[b]Hospital 2.

[c]$t$ test *P* value.

[d]Mann-Whitney *P* value.

#### Use of Isolation

In both hospitals a positive influenza test result was strongly associated with patient isolation. Nonetheless, a significantly higher proportion of influenza-positive patients were isolated immediately in the ED in hospital 1 using POCT (91%) than in hospital 2 (80%, $P = .025$). Isolation was largely restricted to influenza-positive patients, with only 7% and 12% of influenza-negative patients being isolated in hospitals 1 and 2, respectively. These patients were commonly isolated upon exhibiting gastrointestinal symptoms, not because of suspicion of contagious respiratory viral illness.

#### Antibiotic Treatment

Similar percentages of patients received antibiotics in the 2 hospitals, 76% (n = 303) in hospital 1 and 73% (n = 122) in hospital 2 ($P = .469$; Table 2). Overall, significantly fewer influenza patients compared to noninfluenza patients were prescribed antibiotics (69% vs 79%, $P = .008$). Interestingly, the length of antibiotic treatment in influenza patients was significantly shorter in hospital 2 compared to hospital 1 (median 3.5 vs 7 days, $P = .002$; Figure 2). Rapid antibiotic discontinuance (termination of initiated treatment the following day) was observed in 42.1% of influenza patients in hospital 2 compared to only 15.6% in hospital 1 ($P = .001$). In the influenza-negative patients, antibiotic treatment was terminated the following day in only 8% and 6% of patients in hospitals 1 and 2, respectively ($P = .651$). Of the 65 patients with a positive RT-PCR for respiratory pathogens other than influenza, 79% received antibiotics and no trend of antibiotic discontinuance upon other viral diagnosis was observed.

#### Neuraminidase Inhibitor Treatment

Importantly, the majority of influenza patients received NAI treatment (83% and 81% in hospitals 1 and 2, respectively). Mean treatment duration was 4.5 days and was comparable between the hospitals. Influenza patients were more likely to receive NAIs if symptom duration did not exceed 48 hours prior to hospitalization (89% vs 77%, $P = .023$). The use of NAI treatment in influenza-negative patients was low (3%) and treatment duration shorter (mean 3.3 days), suggesting that treatment was ended upon conclusive laboratory diagnostics. The mean time from triage in the ED to NAI treatment in influenza patients was equally rapid, 6.2 hours in both hospitals ($P = .985$; Table 2), with 69% receiving early NAIs (within 6 hours).

#### Mortality

The overall 30-day mortality rate was 2% among the influenza-positive patients in both hospitals, and 4% versus 3% for the influenza-negative patients in hospitals 1 and 2, respectively.

#### Turn-around Times

The mean time from swabbing to test result was 15 minutes for the POCT and 119 minutes (102–136 minutes) for the laboratory-based influenza test, and the mean difference between the time from test to result was 104 minutes (95% confidence interval [CI], 87–121 minutes) between the 2 hospitals. Furthermore, the effective TATs from triage to test result was 69 minutes (SD, 190 minutes) in hospital 1 for the POCT and 269 minutes (SD, 308 minutes) for the laboratory-based influenza test in hospital 2. To conclude, our results showed a mean time difference from triage to test result of 200 minutes (95% CI, 146–254 minutes).

#### Duration of Hospital Stay

We found that patients diagnosed with POCT, that is those admitted to hospital 1, had significantly shorter median duration of hospital stay than those admitted to hospital 2 (3 days vs 4 days, $P < .001$; Table 2 and Figure 3). Diagnosis by POCT was the only factor associated with shorter duration of hospital stay in both multivariable and univariable analysis (Table 3).

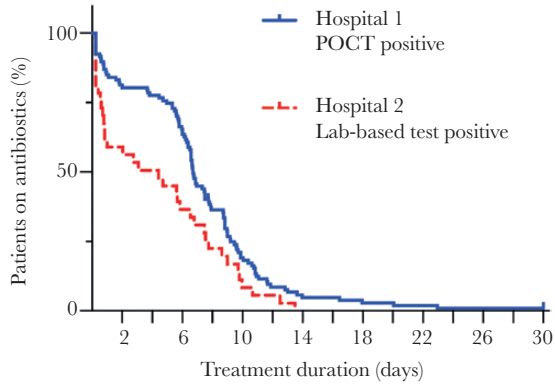


**Figure 2.** Duration of antibiotic treatment. Kaplan-Meyer curve demonstrating the duration of antibiotic treatment in influenza-positive patients admitted to hospitals 1 and 2. Log-rank test *P* value = .012. Antibiotic treatment length was set to a minimum of 0.25 days and prolonged antibiotic treatment >30 days was censored after 30 days for calculation purposes.

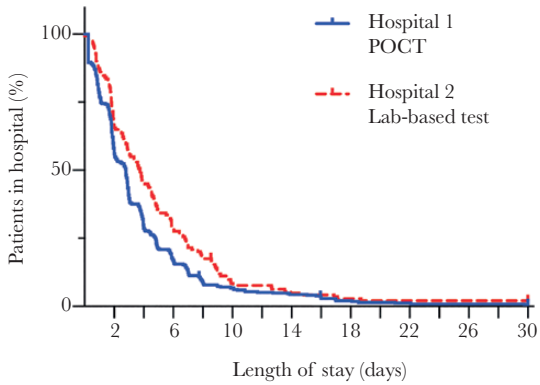


**Figure 3.** Length of hospital stay. Kaplan-Meyer curve demonstrating the overall length of stay of patients in hospitals 1 and 2. Log-rank test *P* value = .002. Hospital length of stay was set to a minimum of 0.25 days and prolonged hospital stay >30 days was censored after 30 days for calculation purposes.

**Table 3. Risk Factors for Prolonged Hospital Stay**

| Predictors | n | Length of Stay, d, Median (IQR) | Univariable Analysis *P* Value, Wilcoxon[a] | Multivariable Analysis *P* Value, Cox[c] |
|---|---|---|---|---|
| Overall | 566 | 3 (2–5) | NA | NA |
| Demographics | | | | |
| Age | | | | |
| Older, ≥ 70 y | 281 | 4 (2–6) | **<.0001** | .0975 |
| Younger, < 70 y | 285 | 2 (1–4) | | |
| Sex | | | | |
| Female | 274 | 3 (2–5) | .9155 | .1967 |
| Male | 292 | 3 (2–5) | | |
| Vaccination | | | | |
| Influenza vaccine | | | | |
| Vaccinated any time | 371 | 3 (2–5) | **.0355** | … |
| Never vaccinated | 183 | 3 (1–5) | | |
| Influenza vaccine 2018 | | | | |
| Vaccinated 2018 | 276 | 3 (2–6) | **.0032** | .7753 |
| Not vaccinated 2018 | 278 | 3 (1–5) | | |
| Influenza vaccine 2017 | | | | |
| Vaccinated 2017 | 251 | 3 (2–5.5) | **.0497** | … |
| Not vaccinated 2017 | 300 | 3 (1–5) | | |
| Influenza vaccine 2016 | | | | |
| Vaccinated 2016 | 229 | 3 (2–5) | .0621 | … |
| Not vaccinated 2015 | 322 | 3 (1–5) | | |
| Influenza vaccine 2015 | | | | |
| Vaccinated 2015 | 201 | 3 (2–6) | **.0130** | … |
| Not vaccinated 2015 | 348 | 3 (1–5) | | |
| Risk factors | | | | |
| Any underlying disease | | | | |
| Present | 486 | 3 (2–6) | **<.0001** | … |
| Absent | 76 | 1 (0–3) | | |
| Cardiovascular disease | | | | |
| Present | 236 | 3.5 (2–6) | **<.0001** | .4948 |
| Absent | 329 | 2 (1–5) | | |
| Hypertension | | | | |
| Present | 207 | 3 (2–6) | **.0015** | .1483 |
| Absent | 359 | 3 (1–5) | | |
| Respiratory disease | | | | |
| Present | 266 | 3 (2–6) | **.0026** | .9522 |
| Absent | 300 | 2 (1–5) | | |
| Smoking | | | | |
| Current | 95 | 4 (2–8) | **.0001** | .9249 |
| Previously or never | 467 | 3 (1.5–5) | | |
| Obesity, BMI >30 | | | | |
| Present | 177 | 3 (2–5) | .1993 | … |
| Absent | 300 | 3 (1–5) | | |
| Diabetes mellitus | | | | |
| Present | 95 | 4 (2–8) | **.0001** | **.0107** |
| Absent | 471 | 3 (1.5–5) | | |
| Renal disease | | | | |
| Present | 90 | 3 (2–6) | .0576 | … |
| Absent | 476 | 3 (2–5) | | |
| Liver disease | | | | |
| Present | 11 | 3 (1–5.5) | .6187 | … |
| Absent | 555 | 3 (2–5) | | |
| Neurological disease | | | | |
| Present | 136 | 3 (2–6) | **.0276** | .3749 |
| Absent | 430 | 3 (1.25–5) | | |
| Immunodeficiency | | | | |
| Present | 86 | 3 (2–5) | .2199 | … |

**Table 3. Continued**

| Predictors | n | Length of Stay, d, Median (IQR) | Univariable Analysis *P* Value, Wilcoxon[a] | Multivariable Analysis *P* Value, Cox[c] |
|---|---|---|---|---|
| Absent | 479 | 3 (2–5) | | |
| Cancer | | | | |
| Present | 68 | 4.5 (2.75–7) | **<.0001** | **.0153** |
| Absent | 497 | 3 (1–5) | | |
| Other comorbidities | | | | |
| Present | 177 | 3 (2–6) | .2779 | … |
| Absent | 388 | 3 (2–5) | | |
| Status on admission | | | | |
| Duration of symptoms | | | | |
| ≥ 3 d | 285 | 3 (2–5) | .8563 | … |
| < 3 d | 192 | 3 (2–5) | | |
| Triage score | | | | |
| 2–3 | 313 | 3 (2–6) | **.0004** | .7793 |
| 0–1 | 215 | 2 (1–5) | | |
| Diagnostics | | | | |
| Use of POCT | | | | |
| POCT, hospital 1 | 399 | 3 (1–5) | **<.0001** | **<.0012** |
| Laboratory-based test, hospital 2 | 167 | 4 (2–7) | | |
| Influenza test result | | | | |
| Positive | 217 | 2 (1–5) | **<.0001** | .7549 |
| Negative | 349 | 3 (2–6) | | |
| Blood culture | | | | |
| Pathogen recovered | 34 | 4 (2.25–7.75) | **.0333** | .2215 |
| No pathogen recovered | 530 | 3 (2–5) | | |
| Urine pneumococcal test | | | | |
| Positive | 16 | 3 (2–7.5) | .2414 | … |
| Negative | 547 | 3 (2–5) | | |
| Urine culture | | | | |
| Pathogen recovered | 15 | 3 (2–4) | .9722 | … |
| Negative or contaminated | 174 | 3 (2–5) | | |
| Chest X-ray | | | | |
| Infiltrate | 166 | 4 (2–6) | **<.0001** | .4300 |
| No infiltrate | 397 | 3 (1–5) | | |
| Interventions | | | | |
| Antimicrobial treatment | | | | |
| Received | 424 | 3.5 (2–6) | **<.0001** | <.2727 |
| Not received | 141 | 1 (1–3) | | |
| Longer antimicrobial treatment | | | | |
| >1 d | 362 | 4 (2–6) | **<.0001** | **.0002** |
| ≤ 1 d | 51 | 2 (1–4) | | |
| Broad-spectrum antibiotics | | | | |
| Received | 172 | 5 (2.75–8) | **<.0001** | **<..0001** |
| Not received | 394 | 2 (1–4) | | |
| Oseltamivir | | | | |
| Received | 191 | 3 (1.5–5) | .3695 | … |
| Not received | 372 | 3 (2–6) | | |
| Steroids | | | | |
| Received | 217 | 3 (2–6) | **<.001** | .0781 |
| Not received | 348 | 3 (1–5) | | |

Potential risk factors for prolonged hospital stay assessed in univariable analysis using Wilcoxon rank-sum test, and in multivariable analysis by both Poisson regression and Cox proportional hazards analysis. n = 566 (1 patient excluded due to missing data regarding comorbidities). Bold font indicates a significant difference as defined by *P* value < .05.

Abbreviations: BMI, body mass index; IQR, interquartile range; NA, not applicable; POCT, point-of-care test.

[a]Wilcoxon rank-sum test.

[b]Poisson regression.

[c]Cox proportional hazards analysis.

Comorbidity with diabetes or malignancy, use of broad-spectrum antibiotics, and duration of antibiotic use >1 day was associated with prolonged duration of hospital stay. In univariable analysis, prolonged hospital stay was also associated with older age, smoking, hypertension, cardiovascular, pulmonary, and neurologic disease.

History of influenza vaccination was associated with prolonged stay in univariable analysis, while actually having a positive influenza test was associated with shorter stay. Use of antibiotics, particularly broad-spectrum antibiotics, was strongly associated with prolonged hospital stay. Severity on admission (SATS score), positive blood cultures, infiltrate on chest X-ray, and use of steroids were associated with prolonged stay in univariable analysis only.

## DISCUSSION

Accurate and rapid laboratory diagnosis of influenza is essential to guide treatment and infection control. Clinical studies of the diagnostic accuracy of physician diagnosis of influenza report low sensitivity [9, 36].

This prospective, controlled clinical study is unique in studying the clinical and logistical effects of implementing a rapid influenza POCT in one hospital ED during the influenza season 2018–2019 and comparing it to a different rapid test, incurring specimen transport time, in the neighboring control hospital.

We found that use of POCT was associated with shorter LOS in both univariable and multivariable analysis. The finding that a history of influenza vaccination was associated with prolonged hospital stay is likely to have been because admissions for diseases other than influenza may be more severe and require longer treatment. Indeed, a positive test for influenza on admission was associated with shorter hospital stay. As expected, hospital stay was longer in older patient and those with underlying diseases, particularly diabetes and cancer. While triage severity of illness (SATS score) was similar in the 2 hospitals, it was associated with prolonged hospital stay within each hospital. The association between prolonged hospital stay and SATS score, positive blood cultures, infiltrate on chest X-ray, and use of antibiotics and steroids is not surprising as these factors all indicate more severe disease. While the particularly strong association with broad-spectrum antibiotic use could be attributed to severity of disease, it may reflect on other challenges such as risk of antibiotic-associated diarrhea and a lack of good peroral alternatives for tapering courses, both of which would lead to unnecessarily prolonged hospital stay. The interpretation of our results is limited by its observational character and by comparing 2 different hospitals. Hence, we cannot rule out that factors other than using POCT could explain the shorter LOS in hospital 1, including physicians' management preferences, discharge practices, bed occupancy rates, organization of patient flow, and complexity of patients' illnesses. Interestingly, hospital 1 is a referral hospital, which would be expected to increase rather than diminish the duration of hospital stay, but it receives the majority of patients as direct admissions. Importantly, both study hospitals had significantly shorter LOS compared to LOS reported in the global literature, despite older patients.

This study is unique in comparing 2 rapid tests. Others have not reported equally efficient TATs in both control and intervention groups; however, short TATs have been linked to improved antibiotic usage and early discharge. In our study, the POCT in hospital 1 was extremely rapid (15 minutes). The elimination of time-consuming test ordering and transport procedures lowered the threshold for rapid testing upon admission. In our cohort, 4/10 patients were regarded as mildly ill after the initial triage evaluation (Supplementary Figure 1) requiring further medical attention within 60 minutes. Interestingly, the median TAT from triage to test result of 69 minutes in hospital 1 shows that many patients had a rapid influenza POCT performed as part of the short initial triage assessment, despite a low initial SATS score. Early testing upon admission allowed incorporation of the influenza results into the ED clinician`s assessment, possibly influencing clinical management, emphasizing the importance of the close proximity of the test. The suggested benefits of rapid TATs are supported by Brendish et al's randomized controlled trial post hoc analysis on the impact of TAT on outcome with POCT, where they found a TAT below 1.6 hours was associated with improved clinical outcomes [37].

Our analysis confirmed a superiority in targeted use of isolation for influenza patients in hospital 1 where the new POCT was implemented, in agreement with previous findings [27]. The overall experience of implementing the rapid POCT was positive amongst health care workers and patients, and in line with the findings of a recent Dutch study, which demonstrated improved hospital patient flow after implementing an influenza POCT in the ED [26]. The use of POCT led to improved priorities for isolation facilities, and importantly avoiding prolonged unnecessary isolation of influenza-negative patients, which may save cost.

Antibiotic overuse due to the difficulties in diagnosis is common in adults with viral respiratory tract infections [38]. Bacterial coinfection is common with influenza [39], but antibiotic treatment is not indicated for viral infection alone. Furthermore, studies found that influenza-positive patients were more likely to receive treatment with antibiotics than with NAIs [27, 30]. Frequent prescription of antibiotics in both influenza-positive and -negative patients, without detection of bacteria, indicates that primary bacterial infection or coinfection is of great concern for the clinician. In our study, the presence of a rapid influenza POCT was not associated with a reduction in initial antibiotic prescription in patients with acute respiratory illness. Additional RT-PCR findings did not significantly change ongoing prescriptions. As influenza-positive patients presented to the ED with a high symptom load

(high SATS score), we speculate that the POCT result alone was insufficient for ED clinicians to rule out bacterial coinfection initially. However, antibiotic stewardship initiatives focus on reevaluating the choice of antibiotics after 24–72 hours. Consequently, we further investigated the effect of POCT on duration of antibiotic treatment. Our results demonstrated an earlier termination of antibiotics in influenza-positive patients in hospital 2, despite using the laboratory-based influenza test (Figure 2). This could be explained by differences in antibiotic prescribing culture and overall adherence to guidelines between the 2 hospitals, with perhaps the smaller hospital being better at antibiotic stewardship control. Furthermore, the small difference in TATs of the influenza POCT and the laboratory-based influenza test probably does not influence treatment choices from day 2 onwards. Hence, POCT could have greater impact in hospitals with higher antibiotic usage or standard laboratory-based RT-PCR yielding results in 24–48 hours.

Both hospitals exhibited high performance in targeted antiviral therapy, as NAIs were given to >80% of influenza-positive patients, and only 3% of influenza-negative patients. The mean symptom duration upon hospitalization was 2 to 3 days, comparable to the 2009 pandemic [40]. According to updated national guidelines, NAIs are recommended for influenza patients with a symptom duration <48 hours or when severely ill and in need of hospital admission. In severely ill influenza patients, NAIs have been shown to reduce morbidity and mortality even with later treatment onset [15, 17, 41]. NAIs are administered on the wards, not in the ED. However, our findings of a mean NAI treatment initiation only 6 hours after initial triage in both hospitals is encouraging, as rapid treatment is beneficial [15, 40, 42]. Time to NAI treatment in hospital 1, with POCT, could possibly be further shortened if NAIs were given in the ED.

Our study highlights the positive effects of a rapid influenza POCT in the ED on initial TATs, treatment decisions such as isolation procedures, initiation of antiviral therapy, and reduced LOS. Our findings support the implementation of POCT in the hospital setting. In light of the ongoing severe acute respiratory syndrome coronavirus 2 pandemic, there is currently an even greater demand for rapid and accurate feedback of test results, both regarding influenza and other respiratory pathogens. Randomized studies are needed to ascertain the benefits of using POCT. Future studies should aim to investigate the overall impact and cost-benefits from targeted use of isolation, and also the benefits of implementing molecular influenza diagnostics in primary health care facilities and outpatient clinics.

## Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

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## References

1. GBD 2015 LRI Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis **2017**; 17:1133–61.
2. Jain S, Williams DJ, Arnold SR, et al; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med **2015**; 372:835–45.
3. Jain S, Self WH, Wunderink RG; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization. N Engl J Med **2015**; 373:2382.
4. World Health Organization. Up to 650 000 people die of respiratory diseases linked to seasonal flu each year, **2017**. https://www.who.int/en/news-room/detail/14-12-2017-up-to-650-000-people-die-of-respiratory-diseases-linked-to-seasonal-flu-each-year. Accessed 9 November 2020.

5. GBD 2017 Influenza Collaborators. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. Lancet Respir Med **2019**; 7:69–89.
6. Iuliano AD, Roguski KM, Chang HH, et al; Global Seasonal Influenza-Associated Mortality Collaborator Network. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet **2018**; 391:1285–300.
7. McCullers JA. The co-pathogenesis of influenza viruses with bacteria in the lung. Nat Rev Microbiol **2014**; 12:252–62.
8. Ghoneim HE, Thomas PG, McCullers JA. Depletion of alveolar macrophages during influenza infection facilitates bacterial superinfections. J Immunol **2013**; 191:1250–9.
9. Dugas AF, Valsamakis A, Atreya MR, et al. Clinical diagnosis of influenza in the ED. Am J Emerg Med **2015**; 33:770–5.
10. Clark TW, Medina MJ, Batham S, Curran MD, Parmar S, Nicholson KG. Adults hospitalised with acute respiratory illness rarely have detectable bacteria in the absence of COPD or pneumonia; viral infection predominates in a large prospective UK sample. J Infect **2014**; 69:507–15.
11. Holter JC, Müller F, Bjørang O, et al. Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: a 3-year prospective study in Norway. BMC Infect Dis **2015**; 15:64.
12. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet **2011**; 377:1264–75.
13. Johnstone J, Majumdar SR, Fox JD, Marrie TJ. Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation. Chest **2008**; 134:1141–8.
14. Tatarelli P, Magnasco L, Borghesi ML, et al. Prevalence and clinical impact of viral respiratory tract infections in patients hospitalized for community-acquired pneumonia: the VIRCAP study. Intern Emerg Med **2020**; 15:645–54.
15. Muthuri SG, Venkatesan S, Myles PR, et al; PRIDE Consortium Investigators. Impact of neuraminidase inhibitors on influenza A(H1N1)pdm09-related pneumonia: an individual participant data meta-analysis. Influenza Other Respir Viruses **2016**; 10:192–204.
16. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med **2003**; 163:1667–72.
17. Muthuri SG, Venkatesan S, Myles PR, et al; PRIDE Consortium Investigators. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med **2014**; 2:395–404.
18. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet **2015**; 385:1729–37.
19. Lee N, Leo YS, Cao B, et al. Neuraminidase inhibitors, superinfection and corticosteroids affect survival of influenza patients. Eur Respir J **2015**; 45:1642–52.
20. Viasus D, Paño-Pardo JR, Pachón J, et al; Novel Influenza A(H1N1) Study Group of the Spanish Network for Research in Infectious Diseases (REIPI). Timing of oseltamivir administration and outcomes in hospitalized adults with pandemic 2009 influenza A(H1N1) virus infection. Chest **2011**; 140:1025–32.
21. Espy MJ, Uhl JR, Sloan LM, et al. Real-time PCR in clinical microbiology: applications for routine laboratory testing. Clin Microbiol Rev **2006**; 19:165–256.
22. Mahony JB. Detection of respiratory viruses by molecular methods. Clin Microbiol Rev **2008**; 21:716–47.
23. Mackay IM. Real-time PCR in the microbiology laboratory. Clin Microbiol Infect **2004**; 10:190–212.
24. Public Health England. Point of care tests for influenza and other respiratory viruses. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/762344/point_of_care_tests_for_influenza_and_other_respiratory_viruses.pdf. Accessed 9 November 2020.
25. Falsey AR, Murata Y, Walsh EE. Impact of rapid diagnosis on management of adults hospitalized with influenza. Arch Intern Med **2007**; 167:354–60.
26. Lankelma JM, Hermans MHA, Hazenberg EHLCM, et al. Implementation of point-of-care testing and a temporary influenza ward in a Dutch hospital. Neth J Med **2019**; 77:109–15.
27. Brendish NJ, Malachira AK, Armstrong L, et al. Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial. Lancet Respir Med **2017**; 5:401–11.
28. Martinot M, Greigert V, Gravier S, et al. Positive impact of a point-of-care molecular influenza test in the emergency department during the 2017-2018 seasonal influenza epidemic. Open Forum Infect Dis **2019**; 6:ofz312.
29. Benirschke RC, McElvania E, Thomson RB, Kaul KL, Das S. Clinical impact of rapid point-of-care PCR influenza testing in an urgent care setting: a single-center study. J Clin Microbiol **2019**; 57:e01281-18.
30. Akers IE, Weber R, Sax H, Böni J, Trkola A, Kuster SP. Influence of time to diagnosis of severe influenza on antibiotic use, length of stay, isolation precautions, and mortality: a retrospective study. Influenza Other Respir Viruses **2017**; 11:337–44.
31. Andrews D, Chetty Y, Cooper BS, et al. Multiplex PCR point of care testing versus routine, laboratory-based testing in the treatment of adults with respiratory tract infections: a

quasi-randomised study assessing impact on length of stay and antimicrobial use. BMC Infect Dis **2017**; 17:671.
32. Vos LM, Bruning AHL, Reitsma JB, et al. Rapid molecular tests for influenza, respiratory syncytial virus, and other respiratory viruses: a systematic review of diagnostic accuracy and clinical impact studies. Clin Infect Dis **2019**; 69:1243–53.
33. Jokela P, Vuorinen T, Waris M, Manninen R. Performance of the Alere i influenza A&B assay and mariPOC test for the rapid detection of influenza A and B viruses. J Clin Virol **2015**; 70:72–6.
34. Holen Ø, Alberg T, Blix HS, Smith I, Neteland MI, Eriksen HM. Bredspektrede antibiotika i norske sykehus. Tidsskr Nor Legeforen **2017**; 137:362–6.
35. Grave K, Helgesen KO, Hopp P. NORM NORM-VET usage of antimicrobial agents and occurrence of antimicrobial resistance in Norway, 2018. Tromsø/Oslo: Norwegian Surveillance System for Antimicrobial Drug Resistance, 2019.
36. Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does this patient have influenza? JAMA **2005**; 293:987–97.
37. Brendish NJ, Malachira AK, Beard KR, Ewings S, Clark TW. Impact of turnaround time on outcome with point-of-care testing for respiratory viruses: a post hoc analysis from a randomised controlled trial. Eur Respir J **2018**; 52:1800555.
38. van Houten CB, Cohen A, Engelhard D, et al. Antibiotic misuse in respiratory tract infections in children and adults-a prospective, multicentre study (TAILORED Treatment). Eur J Clin Microbiol Infect Dis **2019**; 38:505–14.
39. Klein EY, Monteforte B, Gupta A, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. Influenza Other Respir Viruses **2016**; 10:394–403.
40. Venkatesan S, Myles PR, Bolton KJ, et al; PRIDE Consortium Investigators. Neuraminidase inhibitors and hospital length of stay: a meta-analysis of individual participant data to determine treatment effectiveness among patients hospitalized with Nonfatal 2009 pandemic influenza A(H1N1) virus infection. J Infect Dis **2020**; 221:356–66.
41. Louie JK, Yang S, Acosta M, et al. Treatment with neuraminidase inhibitors for critically ill patients with influenza A (H1N1)pdm09. Clin Infect Dis **2012**; 55:1198–204.
42. Muthuri SG, Venkatesan S, Myles PR, et al; PRIDE Consortium Investigators. Impact of neuraminidase inhibitors on influenza A(H1N1)pdm09-related pneumonia: an individual participant data meta-analysis. Influenza Other Respir Viruses **2016**; 10:192–204.