

# Impact of a 24/7 Rapid Molecular Assay for Influenza Detection on the Prescription of Oseltamivir

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We assessed the impact of a rapid molecular assay for influenza detection whether outsourced or performed onsite 24/7 in a University Hospital in Paris, France. Shorter median time-to-results (16.8 vs 2.3 hours,  $P < .05$ ) and an increased rate of adequate prescription of oseltamivir (76.6% vs 95.3%,  $P < .05$ ) were observed.

**Keywords.** adequacy of oseltamivir prescription; flu; microbial diagnosis; time-to-result; Xpert Flu/RSV XC assay.

All countries are affected by yearly seasonal influenza epidemics (estimated at 5%–10%) with a high mortality rate, particularly in the elderly, young children, immunocompromised patients, and patients with chronic diseases [1]. During the epidemic season, clinical diagnosis has poor sensitivity and specificity in case of influenza-like illness [2]. Microbiological diagnostic tests were recommended if they were rapid, easy-to-use, easy-to-interpret, and exhibit good sensitivity and specificity [3]. Immunochromatography antigen-based assays displayed a low sensitivity (10%–80%) [2], whereas a sensitivity >95% was shown for molecular detection assays, such as the Xpert Flu/RSV XC assay [4]. The treatment of influenza by antiviral agents is debated [5], but it must be initiated as soon as possible for

patients with severe, complicated, or progressive illness or for those who require hospitalization [2].

Rapid influenza diagnostic testing has previously been shown to reduce patient turnaround time at the emergency department, the hospitalization rate, and antibiotic prescriptions [6–9]. However, its impact on antiviral therapy was questioned [6, 8–11]. In this study, we evaluated the impact of molecular influenza testing insourcing on the time-to-results and rates of adequate therapy with oseltamivir.

## MATERIAL AND METHODS

### Patient Consent Statement

The study was carried out in accordance with the Declaration of Helsinki. This study was a noninterventional study with no addition to standard care. Biological material and clinical data were obtained only for standard diagnostic following physicians' prescriptions (no specific sampling, no modification of the sampling protocol). Data analyses were carried out using an anonymized database.

### Study Design

This study was conducted retrospectively on data obtained for 2 consecutive influenza epidemics (seasonal epidemic 2015–2016 from week 47/2015 to week 18/2016, and seasonal epidemic 2016–2017 from week 47/2016 to week 18/2017) for patients consulting or hospitalized at Lariboisiere University hospital (Assistance Publique-Hôpitaux de Paris, Université de Paris, Paris, France).

The influenza molecular diagnosis was done for patients presenting influenza-like illness and who required hospitalization due to severe respiratory symptoms or at risk for degradation of pre-existent illness [2]. Detection of influenza viruses was performed using Xpert Flu/RSV XC assay (Cepheid, Sunnyvale, CA) on nasopharyngeal swabs (UTM swabs; Copan, Brescia, Italy). Results were transmitted through the hospital web intranet, and antiviral treatment with oseltamivir was dispensed 24/7 by the hospital pharmacy for patients with confirmed or suspected influenza cases.

During period 1 (from week 47/2015 to week 18/2016 and from week 47/2016 to week 51/2016), patient samples were shipped twice a day from Lariboisiere Hospital to Saint-Louis Hospital, located 3 km away. The assays were performed 6 days a week at opening hours (8:00 AM–6:00 PM on weekdays and 8:00 AM–3:00 PM on Saturday). During period 2 (from week 52/2016 to week 18/2017), the assays were performed 24/7 in the Lariboisiere Hospital microbiology laboratory.

The results of the Xpert Flu/RSV XC Assay (detection of influenza A virus, influenza B virus and respiratory syncytial virus

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[RSV]), the times of sampling and of results were extracted from the laboratory information System (Glims; MIPS, Gent, Belgium). Time-to-results was defined as the time between the sampling and the result of the assay.

Data on oseltamivir prescriptions were extracted from the pharmacy management software (CoPILOT; Maincare Solutions, Cestas, France). Prescription adequacy was defined as the proportion of patients who tested positive for influenza among those who had a prescription for oseltamivir.

Time-to results and adequacy of antiviral treatment were compared between the first and the second periods using *t* test and  $\chi^2$  test, respectively. Analyses were performed using R, version 3.1.3, and *P* < .05 were considered statistically significant.

## RESULTS

### Microbiological Diagnosis of Influenza During the Two Epidemic Seasons After Our Diagnostic Stewardship

Microbiological results are presented for the 2 periods in Table 1. The number of patients sampled increased 4-fold between the 2 influenza epidemic seasons (203 tests done during winter 2016 and 808 during winter 2017). This was in agreement with the dramatic rise in the hospitalization for influenza-like illness observed during the second winter throughout the country [12]. Consequently, with

regard to the 2 periods (period 1 when assays were outsourced, and period 2 when they were performed in-house), there were more patients tested during period 2 (658 patients tested from the last week of 2016 to the end of the flu epidemic in winter 2017) than during period 1 (353 patients tested during the flu epidemic 2015–2016 plus the beginning of the 2017 epidemic).

The positivity rate of the molecular test was similar for the 2 periods: 29.2% when the assay was outsourced and 24.5% when it was performed onsite (*P* = .10). With regard to virus detection, rates were similar for influenza A (20.1% vs 19.9%, *P* = .94) and for RSV (3.7% vs 4%, *P* = .93). However, they differed for influenza B (5.4% vs 0.6%, *P* < .05) due to the high prevalence of influenza cases due to the B virus during the season 2015–2016 (Supplementary Figure 1) [13]. The peak of influenza cases was observed between weeks 9 and 11 during season 2016, but earlier, between weeks 1 and 3, for season 2017 (Supplementary Figure 1), as observed for all of France by the French surveillance network [12, 13].

### Time-To-Results Due to Onsite 24/7 Implementation of Rapid Molecular Testing for Influenza

We compared the time-to-results of the Xpert Flu/RSV XC Assay whether it was outsourced (from week 47/2015 to week 18/2016, *n* = 353 tests) or performed onsite 24/7 (from week

**Table 1. Patients Characteristics, Molecular Assay Results, and Prescriptions of Oseltamivir When Influenza Molecular Testing (Xpert Flu/RSV XC Assay) was Outsourced or Performed Onsite 24/7**

Variable	Number of Patients			PValue
	All Periods <i>n</i> = 1011	Period 1 (Tests Outsourced) <i>n</i> = 353	Period 2 (Tests Performed Onsite 24/7) <i>n</i> = 658	
<b>Patient Characteristics</b>				
Mean age (years, SD)	64.2 (±21.7)	61.6 (±22.2)	65.6 (±21.2)	<.05
Female gender	526 (52%)	187 (53%)	339 (51.5%)	.66
Outpatients	50 (7.8%)	19 (7.7%)	31 (7.4%)	.61
<b>Department of Molecular Assay Prescription</b>				
Emergency room	621 (61.4%)	160 (45.3%)	461 (70.1%)	<.05
Intensive Care Units	194 (19.2%)	108 (30.6%)	86 (13.1%)	<.05
Internal medicine	74 (7.3%)	28 (7.9%)	46 (7.0%)	.58
Others <sup>a</sup>	122 (12.1%)	57 (16.1%)	65 (9.9%)	<.05
<b>Molecular Assay Results</b>				
Positive	264 (26.1%)	103 (29.2%)	161 (24.5%)	.1
Influenza A	202 (20%)	71 (20.1%)	131 (19.9%)	.94
Influenza B	23 (2.3%)	19 (5.4%)	4 (0.6%)	<.05
RSV	39 (3.9%)	13 (3.7%)	26 (4%)	.93
Negative	747 (73.9%)	250 (70.8%)	497 (75.5%)	.11
<b>Time-to-Results</b>				
Median time-to-results between sampling and laboratory result (IQR) (in hours)	3.0 (1.9–9.3)	16.8 (6.4–22.7)	2.3 (1.6–2.9)	<.05
<b>Management of Antiviral Chemotherapy</b>				
Prescriptions of oseltamivir	103 (10.2%)	39 (11.0%)	64 (9.7%)	.51
Proportion of oseltamivir prescription associated with assay positive for influenza virus	91/103 (88%)	30/39 (76.9%)	61/64 (95.3%)	<.05
Proportion of oseltamivir prescription dispensed after obtaining the molecular assay result	80/103 (77.7%)	20/39 (51.3%)	60/64 (93.8%)	<.05

Abbreviations: IQR, interquartile range; RSV, respiratory syncytial virus; SD, standard deviation.

<sup>a</sup>Other departments are cardiology, geriatrics, neurology, and maternity wards.

47/2016 to week 51/2016, n = 658). When performed in our hospital, the median time-to-result was markedly lower (2.3 hours) than when outsourced (16.8 hours,  $P < .05$ ) (Table 1, Supplementary Figure 2).

#### Oseltamivir Prescription and Xpert Flu/RSV XC Assay Result

During period 1, 39 of 353 (11.0%) patients were treated with oseltamivir, and 30 of 39 (76.9%) tested positive for influenza A (n = 22) or influenza B (n = 8) (Table 1). During period 2, 64 of 658 (9.7%) patients were treated with oseltamivir, and 61 of 64 (95.3%) tested positive for influenza A (n = 60) or influenza B (n = 1) (Table 1). Oseltamivir prescription adequacy was significantly higher during period 2 than period 1 (95.3% vs 76.9%,  $P < .05$ ) (Table 1).

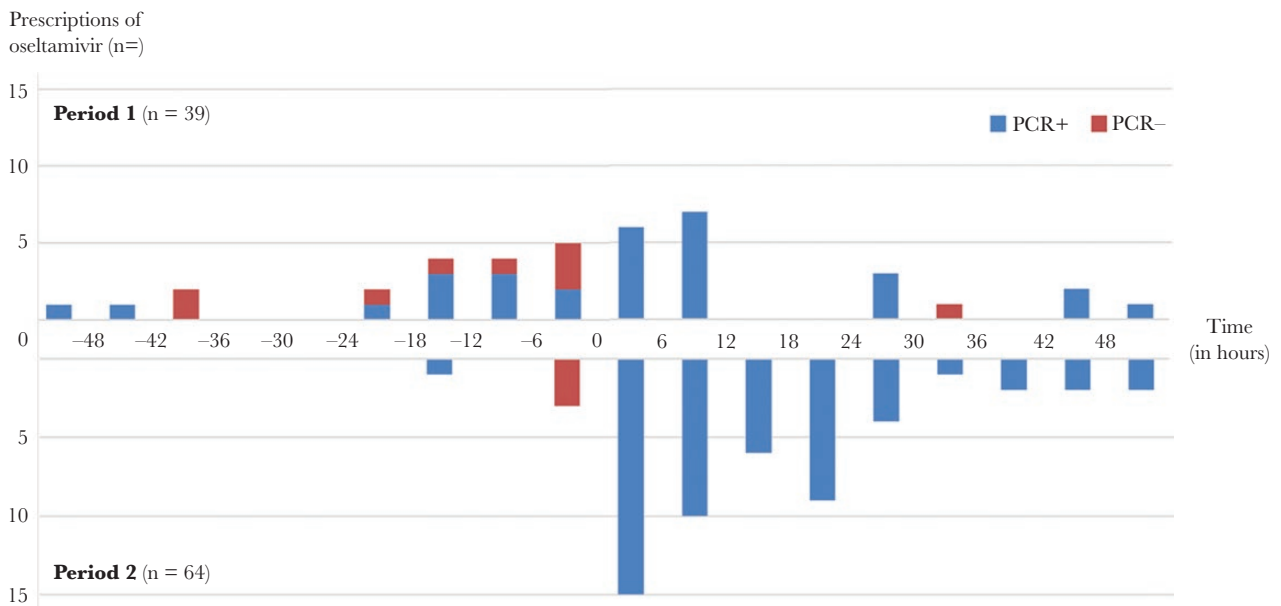
Oseltamivir was dispensed on the basis of a positive molecular assay result in 93.8% (60 of 64) during period 2 but only in 51.3% (20 of 39) of the cases during period 1 ( $P < .05$ ) (Table 1, Figure 1). For both periods, most inadequate oseltamivir prescriptions were those for which the first dose was dispensed before the molecular assay result, as shown in Figure 1.

Taken together, these results suggest that physicians prescribed oseltamivir before molecular assay result during period 1, due to the long time-to-results (16.8 hours). This observation probably explains the poor oseltamivir adequacy during period 1 (76.9%). In contrast, a short time-to-results observed during period 2 (2.3 hours) was compatible with an early dispensation of oseltamivir oriented by molecular assay result during period 2. This observation is in line with a higher oseltamivir prescription adequacy during period 2 (95.3%).

## DISCUSSION

In this study, we showed that implementing a molecular assay for influenza viruses in the hospital where the emergency room is located and running 24/7 significantly shortened the time-to-results and induced better adequacy of oseltamivir prescription in influenza cases. Our results showed that oseltamivir was mostly dispensed without molecular assay results when the test was outsourced, whereas oseltamivir prescriptions were guided by the molecular assay results when the test was implemented 24/7 onsite.

Few studies have evaluated the impact of influenza diagnostic testing on oseltamivir prescriptions [6, 8–11]. It is noteworthy that 3 studies were based on antigen-based diagnosis tests, which are known for their poor sensitivity [8, 10, 11]. Trabattoni et al [6] compared the impact of another rapid molecular diagnosis test (Alere i Influenza A and B Assay) when it was performed in the clinical ward or in the laboratory, and they did not find any difference in oseltamivir prescriptions. Dugas et al [9] suggested a strategy including a polymerase chain reaction (PCR)-based diagnostic test to initiate antiviral treatment for patients who met the Centers for Disease Control and Prevention (CDC) criteria [2]. The CDC recommends that patients with severe respiratory symptoms receive empirical influenza antiviral treatment despite a negative rapid influenza test result [2]. However, these recommendations were published in 2011 and focused on the antigen-based diagnostic tests, known to have low sensitivity. In 2020, the issue is different because the results of PCR-based assays are reliable and can be available within a few hours. In conclusion, because rapid molecular assays for



**Figure 1.** Time between results of Xpert Flu/RSV XC PCR Assay and dispense of the first dose of oseltamivir for the 2 periods. Oseltamivir prescriptions associated with a positive assay are indicated in blue, and those with a negative assay are indicated in red.

influenza viruses are now available, they should be implemented as point-of-care testing as close as possible to emergency rooms for a more accurate prescription of antiviral drugs.

## CONCLUSIONS

The limiting factors of our study are the following: (1) this study was retrospective and monocentric, and (2) the clinical impact of the microbial diagnosis was limited to the management of antiviral chemotherapy. It is interesting to note that our 2016 and 2017 epidemic data were concordant to that described by the French surveillance networks for flu epidemics, which suggests that our results would be similar in other hospitals [12, 13].

## Supplementary Data

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

**Supplementary Figure 1.** Results of Xpert Flu/RSV XC PCR Assay in Lariboisière Hospital during winters 2015–2016 (A) and 2016–2017 (B), per week. Negative results are represented in blue, and positive results for influenza A, influenza B, and RSV are in red, green and purple, respectively  
**Supplementary Figure 2.** Impact of the 24/7 in-hospital implementation of the Xpert Flu/RSV XC PCR Assay on time-to-results. Blue and red bars represent the time-to-result distribution when the assay was performed 24/7 in our hospital (Lariboisière hospital) and when it was outsourced (Saint-Louis hospital), respectively.

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**Potential conflicts of interest.** All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

## References

1. World Health Organization. A manual for estimating disease burden associated with seasonal influenza. Available at: [http://www.who.int/influenza/resources/publications/manual\\_burden\\_of\\_disease/en/](http://www.who.int/influenza/resources/publications/manual_burden_of_disease/en/). Accessed 7 September 2020.
2. Fiore AE, Fry A, Shay D, et al.; Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **2011**; 60:1–24.
3. World Health Organization. WHO recommendations on the use of rapid testing for influenza diagnosis. Available at: [http://www.who.int/influenza/resources/documents/rapid\\_testing/en/](http://www.who.int/influenza/resources/documents/rapid_testing/en/). Accessed 7 September 2020.
4. Salez N, Nougairède A, Ninove L, et al. Prospective and retrospective evaluation of the Cepheid Xpert Flu/RSV XC Assay for rapid detection of influenza A, influenza B, and respiratory syncytial virus. *Diagn Microbiol Infect Dis* **2015**; 81:256–8.
5. Leibovici L, Paul M. Should we recommend neuroaminidase inhibitors for influenza? *Clin Microbiol Infect* **2014**; 20:O979–80.
6. Trabattoni E, Le V, Pilmis B, et al. Implementation of Alere i influenza A & B point of care test for the diagnosis of influenza in an ED. *Am J Emerg Med* **2018**; 36:916–21.
7. Soto M, Sampietro-Colom L, Vilella A, et al. Economic impact of a new rapid PCR assay for detecting influenza virus in an emergency department and hospitalized patients. *PLoS One* **2016**; 11:e0146620.
8. Bonner AB, Monroe KW, Talley LI, et al. Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: results of a randomized, prospective, controlled trial. *Pediatrics* **2003**; 112:363–7.
9. Dugas AF, Coleman S, Gaydos CA, et al. Cost-utility of rapid polymerase chain reaction-based influenza testing for high-risk emergency department patients. *Ann Emerg Med* **2013**; 62:80–8.
10. Suryaprasad A, Redd JT, Ricks PM, et al. Effect of rapid influenza diagnostic testing on antiviral treatment decisions for patients with influenza-like illness: southwestern U.S., May–December 2009. *Public Health Rep* **2014**; 129:322–7.
11. Williams LO, Kupka NJ, Schmaltz SP, Barrett S, Uyeki TM, Jernigan DB. Rapid influenza diagnostic test use and antiviral prescriptions in outpatient settings pre- and post-2009 H1N1 pandemic. *J Clin Virol* **2014**; 60:27–33.
12. Équipes de Surveillance de la Grippe. Influenza activity in France, Season 2016–2017. *Bull Épidémiol Hebd* **2017**; 22:466–75.
13. Équipes de Surveillance de la Grippe. Influenza activity in mainland France, Season 2015–2016. *Bull Épidémiol Hebd* **2016**; 32-33:558–63.