TITLE: EVALUATION OF THE ROCHE COBAS LIAT FLU/RSV ASSAY FOR MANAGEMENT OF INFLUENZA IN THE ED

PI: Larissa May, MD, MSPH, MSHS, Director of ED Antibiotic Stewardship, UC Davis
Co-PI: Nam Tran, PhD, Associate Director, Point of Care Testing Center for Teaching and Research, UC Davis

Version: October 24, 2018

A. Objective

Roche Cobas Liat Flu/RSV POC Assay and procalcitonin testing as part of a stewardship intervention optimizes antiviral treatment and reduces antibiotic treatment for ED patients (under 50 years of age) with suspected influenza or RSV v. standard care using a prospective, patient-randomized design. In addition to the primary outcome, we will evaluate secondary outcomes including aggregate physician adherence to CDC guidelines for the treatment of influenza, antibiotic duration, hospital admission, and emergency department (ED) return visits within 30 days for patients diagnosed with influenza and RSV. Additional secondary outcomes would include time to resolution of symptoms, return to school/work, and subsequent healthcare utilization (e.g. doctor visits) obtained through patient self-report.

Hypothesis: The rapid waived POC assay and procalcitonin, as part of a stewardship intervention will lead to reduced antibiotic treatment by 20 percentage points compared to the control group for antibiotic non-responsive conditions including ILI and nonspecific URI and will increase appropriate antiviral treatment of patients with influenza at high risk recommended to receive treatment by 20 percentage points.

B. Background and Significance and Preliminary Studies

Influenza and Respiratory Syncytial Virus (RSV) impose a serious disease burden in terms of morbidity and mortality. In the US alone, these illnesses are estimated to contribute to mean annual 51,203 and 17,358 deaths, respectively[1]. RSV infections are estimated to result in approximately 1 of 334 all hospitalizations in children under the age of 5 years each year in the U.S[2]. There is no effective antiviral treatment for RSV, and nosocomial RSV outbreaks are mainly controlled by isolation of infected cases[3], indicating the need for rapid diagnosis. Those especially at risk of complications from influenza include children who are under 2 years of age, adults 65 years or older, and those with immune suppression and underlying cardiopulmonary disease[4 5]. Antiviral treatment has been shown to decrease risks of influenza-related complications in both of these age groups, with treatment most effective if administered within two days of diagnosis[6, 7]. However, previous lack of an accurate AND rapid point of care test for influenza makes prompt diagnosis of influenza a challenge, leading to significant over- and under-treatment with antiviral drugs[8].

The Centers for Disease Control and Prevention (CDC) currently recommend antiviral treatment for any patient with suspected influenza who is hospitalized or has severe or complicated illness[9]. In outpatients, antiviral treatment is recommended for patients at high risk of

complications due to age or chronic medical conditions[9]. However, the use of antivirals without any test result leads to not only unnecessary treatment, but also the risk of antiviral resistance[10]. Furthermore, physician adherence to these guidelines is low[8,11], likely due to knowledge of these risks.

Antiviral under-treatment can be attributed to the poor sensitivity of current rapid diagnostic tools. For one, influenza-like illness (ILI) is defined by the CDC as the presentation of fever (temperature of 100°F [37.8°C] or greater) and cough or sore throat[12]. These non-specific symptoms contribute to the low sensitivity and specificity of clinical diagnosis, which are approximately 64% and 67%, respectively[13]. This sensitivity drops even further for those who meet the CDC criteria of patients at high risk for influenza-related complications. An observational cohort study found that the sensitivity of ILI reached only 31% for adult patients who met the CDC's criteria for antiviral treatment, likely due to these patients' dulled immune response[8]. Thus, sensitivity of clinical diagnosis may be lowest for those who need antiviral treatment the most. Rapid influenza antigen tests are more specific, easy to use, and only take 15 to 30 minutes, but have a low sensitivity comparable to provider diagnosis[13, 14]. Procalcitonin has been demonstrated in multiple clinical trials to provide value in guiding antibiotic use particularly in respiratory infections for both adults and pediatric patients[15,16,17].

Unfortunately fewer than 40% of patients who are recommended to receive treatment for influenza receive it in the ED[18]. There are a variety of reasons for poor compliance with guidelines, including lack of awareness, poor understanding of the potential severity of influenza, and lack of accurate rapid diagnostic tests. There is great potential for rapid, accurate PCR-based influenza and RSV testing to increase prompt antiviral treatment in high risk-patients, decrease antibiotic use in virally infected patients, and improve infection control. CLIA waived rapid, accurate testing could guide better diagnosis and management and improve patient outcomes.

C. Study Population

Inclusion criteria: Patients <50 who are evaluated by the clinician for suspected influenza, including symptoms of ILI (fever >38°C and cough or sore throat) or non-specific URI for whom the clinician suspects RSV or influenza or lower respiratory infection (with or without ordering a chest xray).

Exclusion criteria: Patients who are pregnant, prisoners, or are unable to give informed consent in English or Spanish. Patients with influenza-like illness and upper respiratory symptoms for whom the provider is unwilling to wait for procalcitonin results.

Sample size: We plan to enroll 100 patients in each arm over a 12 month period (influenza season), which will have 80% power to detect a true 20 percentage point reduction in antibiotic use and 20 percentage point increase in adherence to guideline recommendations for antiviral treatment.

D. Study Timelines

Each subject will participate actively participate in this study for 4 weeks. Additionally, after 30 days, each subject's medical record will be queried for information as described below in SectionWe anticipate that it will take us one year from study implementation to enroll the required number of subjects. We anticipate that the primary analyses will be completed 2 years after beginning the study.

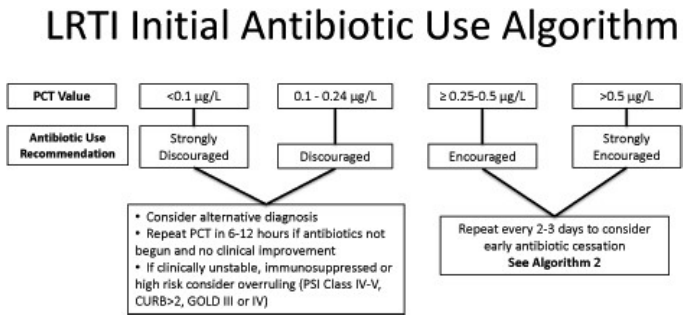
E. Study Endpoints

The primary study endpoint is the determination of whether use of the Roche Liat Flu/RSV Assay and procalcitonin testing, as part of a stewardship intervention optimizes antiviral treatment and reduces antibiotic treatment for ED patients with suspected influenza. The secondary study endpoints are aggregate physician adherence to CDC guidelines for the treatment of influenza, antibiotic duration, hospital admission, ED return visits within 30 days for patients diagnosed with influenza and RSV, time to resolution of symptoms, return to school/work, and subsequent healthcare utilization (e.g. doctor visits) obtained through patient self-report.

F. Research Design and Methods

This will be a prospective, patient-oriented, pilot randomized clinical trial to evaluate (in aggregate) both the use of the Flu/RSV Assay, procalcitonin, and the use of pharmacist-led education for providers in the interpretation of these test results. Children and adults <50 years of age who present to the pediatric ED of the UC Davis Medical Center with influenza-like illness (ILI),upper or lower respiratory infection (URI) will be eligible to participate.

Consented patients in the pediatric ED will be randomized into two arms: The intervention arm will receive procalcitonin with a patient specific stewardship intervention during the ED visit. The intervention will be pharmacist-led and include direct delivery to clinicians of information about interpreting test results and recommendations for antiviral-treatment for high-risk patients, and infection control precautions for patients being hospitalized with a positive RSV or influenza test and avoidance of antibiotics where not indicated. Clinician adherence to treatment guidelines with and without the educational intervention will be compared. Patients randomized to this arm will also have 1 ml of blood drawn for procalcitonin (PCT) analysis to identify bacterial infections. This sample will be taken at the time of a blood draw for standard clinical labs, or from an IV if one is in place. If no blood draw is ordered for standard of care and/or no IV is placed, patients will be given the option to consent to an extra needle stick for the purpose of research if both the clinician and patient agree to wait for the test result. Interpretation of the procalcitonin where obtained will be included in the intervention by the ED pharmacist. We will use the following protocol to guide clinicians in recommendations for antibiotic therapy. Procalcitonin will be an adjunct to guiding decision making for antibiotic use and will provide added value for both patients diagnosed with RSV and flu, as well as promote reduced antibiotic use for patients who do not have diagnosed flu or RSV and help guide appropriate treatment for those patients suspected of having LRTI. We will use a conservative protocol in both infants and older children similar to the figure attached but with a cutoff of 0.5 for recommendation of initiation of therapy in patients suspected of having LRTI.



The second arm will be standard care.

Physicians and patients will not be blinded to test type. Tests will be performed on a real-time basis in the ED. All results will be delivered via standard of care through the EMR.
For each of these groups, data of the frequency and duration of antibiotic administration, antiviral use, adherence to evidence based guidelines for treatment of influenza, disposition, concomitant diagnoses, isolation, hospitalizations, and unscheduled return visits or readmissions within a 30 day period will be collected and compared. In addition, we will compare procalcitonin levels for patients diagnosed with RSV or influenza by the Roche LIAT in the test arm compared to those found to have evidence of bacterial infection based on chest xray, blood culture, and other ancillary tests. Where not recommended, reason for antibiotic use will be documented by the pharmacist and abstracted from chart review.

Research coordinators will contact patients and/or parents at 1 and 4 weeks after enrollment for self-reported secondary outcomes including symptom resolution, return to school/work, and follow up healthcare visits, medication adherence (to antibiotics and/or antivirals), and adverse events.

G. Data Management and Confidentiality

All members of the researcher team will be trained in the ED EMR and HIPAA according to IRB and hospital policy. All records will be stored on a password protected computer or UCD encrypted shared drive, or locked in a file cabinet, accessible only to researchers. All data will be coded and the linking code will be kept separate from the main data analysis file.

H. Withdrawal of Subjects

Subjects may be withdrawn from the study without their consent if:

- Their treating physician feels it is no longer prudent for the patient to participate in the study.

I. Risks and Side Effects

For the primary subjects we will be using identifiable protected health information, therefore there are inherent possible confidentiality risks. However, all identifiable data is accessible only to trained users and clinicians who have passwords to the EMR system. Any confidentiality risks are minimal. Identifiable information will be stored in a password-protected database,

where patients will be assigned code numbers. Medical information will be stored in a separate password-protected database, sorted by code numbers. At the completion of the data analysis all identifiers will be erased from the records.

In addition, we plan to analyze aggregate clinical practice patterns through structured data forms. No identifiable data on the clinician will be recorded on research forms. No information on staff members will be recorded, thus we expect no risk to clinician or staff members' employment.

This study also presents several possible physical risks to the subjects randomized to Arm 1 of this study. Risks related to venipuncture for those who consent to an extra needle stick include pain, bruising, bleeding, or infection at the blood drawing site. The total volume of blood obtained for this study in the ED will not exceed 1 mL.

J. Benefits

This study may benefit the general public by improving clinical diagnosis and management of influenza.

K. Provisions to Protect the Privacy Interests of Subjects

Patients being considered for enrollment into this study will be approached in their ED rooms to assess their interest and willingness to participate in this study. Patients may request that those present step outside or remain in the room during the informed consent process and discussion.

L. Costs To Subjects

Procalcitonin testing will be provided at no cost to the subjects and funded by Roche. Patients will not be charged for the procalcitonin testing and it will not be submitted for insurance reimbursement.

M. Subject Compensation

Subjects will receive a $10 gift card for their participation in the study.

N. Facilities and Equipment

Drs. May and Tran are both graduates of NIH-supported clinical research training programs (e.g., K30, K12/KL2) with extensive experience conducting clinically-oriented translational research and emerging national reputations in their respective areas. We collectively feel that clinical outcomes studies are an essential and much needed step to demonstrate the real value and impact of molecular testing. Dr. May was recruited specifically to UC Davis to direct the first ED based antibiotic stewardship program in the nation to our knowledge and will leverage her expertise in translating rapid molecular diagnostic testing to improve clinical outcomes in the ED setting. UC Davis is also an up-and-coming research institution nationally and the UC Davis Department of Emergency Medicine is among the most highly respected academic and research-oriented emergency departments in the United States. The pediatric ED is a member of the national Pediatric Emergency Care and Research Network, which has been funded by NIH for many years and participated in numerous pediatric clinical trials including a focus on infectious diseases. The UC Davis Department of Emergency Medicine is well suited for this project, having demonstrated broad and sustained growth in its research program and productivity over the past decade. The Department demonstrates its support for research with a robust research

infrastructure, which includes a Vice Chair for Research, two Research Managers (one focused on multicenter research), and four full-time clinical research coordinators.

O. Devices

I confirm that all investigational devices will be labelled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.

P. Statistical Analysis

We will use standard descriptive statistics to summarize patient characteristics at randomization; mean and standard deviation (SD) for continuous variables and frequency and proportion for categorical variables. We will indicate the count of missing data for each variable. For the comparison of the primary outcomes, we will use frequency and proportions by arm, and compute a point estimate for the difference along with 95% confidence interval (CI) and p-value. We will stratify analysis based on flu status. For primary analyses (unstratified), we will use a Chi-square test (and Fisher exact test), and for stratified analyses, we used Mantel-Haenszel method. Secondary outcomes will be performed similarly. Statisticians and other investigators will remain blinded to treatment identity (e.g., data analyses with A/B coding). For all analyses, we will use SAS 9.4 (SAS Institute, Cary, NC).

Q. References & Literature Cited

[1] Thompson WW, Shay DK, Weintraub E, et al. Mortality Associated With Influenza and Respiratory Syncytial Virus in the United States. JAMA. 2003;289(2):179-186.

[2] Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360(6):588-598.

[3] Homaira N, Sheils J, Stelzer-Braid S, Lui K, Oie J-L, Snelling T, Jaffe A, Rawlinson W. Respiratory syncytial virus is present in the neonatal intensive care unit. J. Med. Virol. 2015

[4] Zhou H, Thompson WW, Viboud CG, Ringholz CM, Cheng PY, Steiner C, Abedi GR, Anderson LJ, Brammer L, Shay DK. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993-2008. Clin Infect Dis. 2012 May;54(10):1427-36

[5] CDC. Children, the Flu, and the Flu Vaccine. (2015, August 21). Retrieved October 26, 2015, from http://www.cdc.gov/flu/protect/children.htm

[6] Lizheng S, Loveless M, Spagnuolo P, Zhang M, Liu S, Liu J, Xu Y, Chen E, and Han J. Antiviral Treatment of Influenza in Children: A Retrospective Cohort Study. Advances in Therapy Adv Ther. 2014;31(7) 735-50.

[7] CDC. Use of Antivirals. (2015, February 25). Retrieved October 26, 2015, from http://www.cdc.gov/flu/professionals/antivirals/antiviral-use-influenza.htm

[8] Dugas AF, Valsamakis A, Atreya MR, Thind K, Manchego PA, Faisal A, Gaydos CA, and Rothman RE. Clinical Diagnosis of Influenza in the ED. The American Journal of Emergency Medicine. 2015. n. pag.

[9] CDC. Use of Antivirals. (2015, February 25). Retrieved October 26, 2015, from http://www.cdc.gov/flu/professionals/antivirals/antiviral-use-influenza.htm

[10] Li TCM, Chan MCW, Lee N. Clinical Implications of Antiviral Resistance in Influenza. Hagedorn C, ed. Viruses. 2015;7(9):4929-4944.

[11] Dugas AF, Monteforte B, Puri A, Awad M, Hsieh Y, Rothman R. ED Compliance with Influenza Antiviral Recommendations. The American Journal of Emergency Medicine. 2014;32(12): 1550-552.

[12] CDC. Overview of Influenza Surveillance in the United States. (2015, October 13). Retrieved October 26, 2015, from http://www.cdc.gov/flu/pdf/weekly/overview.pdf

[13] Petrozzino JJ, Smith C, Atkinson MJ. Rapid diagnostic testing for seasonal influenza: an evidence-based review and comparison with unaided clinical diagnosis. Journal of Emergency Medicine 2010; 39(4): 476-490.e1.

[14] Stein J, Louie J, Flanders S, Maselli J, Hacker JK, Drew WL, Gonzales R. 2005. Performance characteristics of clinical diagnosis, a clinical decision rule, and a rapid influenza test in the detection of influenza infection in a community sample of adults. Ann. Emerg. Med. 46:412–419.

[15] Rhee C.Using Procalcitonin to Guide Antibiotic Therapy.Open Forum Infect Dis. 2016 Dec 7;4(1):ofw249.
[16] Schuetz P1, Albrich W, Mueller B.Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future.BMC Med. 2011 2;9:107.
[17] Baumann P1, Baer G1, Bonhoeffer J2, Fuchs A3, Gotta V3, Heininger U1, Ritz N1,3, Szinnai G4, Bonhoeffer J1.Procalcitonin for Diagnostics and Treatment Decisions in Pediatric Lower Respiratory Tract Infections. Front Pediatr. 2017

[18] Dugas AF, Valsamakis A, Atreya MR, Thind K, Alarcon Manchego P, Faisal A, Gaydos CA, Rothman RE. Clinical diagnosis of influenza in the ED. Am J Emerg Med. 2015;33(6):770-5.