Response to Reviews for the EDL Submission of Influenza Rapid Molecular Diagnostic Tests

Pre-submission ID Number: 93
Full Submission ID Number: 42

REVIEWER 1:

1. **Price on the device (instrument)**
   
   See pre-submission. Price of instruments currently on the market ranges from approx. $12 000 to $24 000 per instrument.

2. **Information on calibration**
   
   An examination of the instrument user’s manuals for the Alere I Instrument, mentioned as an example in the submission, showed that it is factory calibrated and no further calibration is necessary. If the instrument is moved, it is recommended to run positive and negative controls to ensure proper functionality. A user’s manual was not available online for the cobas LIAT platform. Other products may vary depending on quality and information provided by the manufacturer.

3. **Information on robustness**
   
   The two product examples provided in the submission both have components that must be stored at 2 – 8°C. No information is provided in package inserts regarding shelf life at these or other temperatures, except to say that kits are stable until the expiry date in the packaging. This is typically 18 to 24 months. No information is provided regarding performance in different humidity conditions. Robustness of other products which may be available in the market in the future will have to be tested by the user/country as part of a prequalification assessment to ensure quality and reliability of results.

4. **Information on the usage of not-well calibrated precision pipette if users need to use own Micropipettes (e.g., for swab eluted in viral transport media)**
   
   The two product examples provided in the submission do not require pipetting of samples. Nasal swabs or nasopharyngeal swabs are placed directly into the provided sample receptacle. That being said, if appropriately calibrated precision micropipettes are specified in the test protocol of a given product, reliable results cannot be guaranteed without them. All products must be used according to manufacturer’s instructions as stated in the package inserts.
5. **Availability of typical medicines (drugs) and cost of medication per person**

The Model Essential Medicines List includes Oseltamivir “for severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients.” No information was found on the availability and cost of this drug worldwide.

**REVIEWER 2:**

1. **Not clear whether the submission is aimed only at rapid, POC molecular tests (or all NAATs, including centralized lab tests)**

   It is true that the submission does not explicitly state that the molecular influenza tests being advocated for are for the point-of-care or near patient care setting. For clarity all of the information provided in the submission is focussed on small, self-contained cartridge-based, rapid molecular platforms.

2. **Proposed (new/adapted) text for the EDL: this important section is left blank**

   See pre-submission.

3. **No background on influenza, current access to tests, importance.**

   Brief information on the burden of influenza disease was provided in the pre-submission using the US CDC as a reference. In February 2018, WHO published a collection of freely available published articles describing the disease burden of influenza in LMIC’s. See https://www.who.int/influenza/surveillance_monitoring/bod/BOD_IORV_collection/en/

   According to the introduction to this publication, information on disease burden in LMIC’s if often missing and many of the papers presented described methods for estimating the disease burden in countries like India, China, Indonesia and many others. According to WHO, 290 000 to 650 000 deaths are associated with respiratory diseases and seasonal influenza every year.

   The Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota, USA published an article in December 2017 in their online newsletter entitled Studies Spotlight Heavy Burden of Severe Flu in Developing Nations. In it they discussed one review which found that the risk of hospitalisation and poor outcomes in general was not different between HIC’s and LMIC’s but the risk is significantly higher for children under 5, pregnant women, people with HIV/AIDS and kids with neurologic conditions in LMIC’s. While noting that the scarcity of data in LMIC’s makes it difficult to prioritise risk groups, the authors recommended that governments and WHO consider prioritising these groups for vaccination and treatment. Link: http://www.cidrap.umn.edu/news-perspective/2017/12/studies-spotlight-heavy-burden-severe-flu-developing-nations. Additionally, the following WHO publication discusses the WHO position on vaccines against influenza: https://www.who.int/wer/2012/wer8747.pdf?ua=1

   Influenza diagnostics in LMICs are mainly laboratory based molecular, virus isolation and immunological assays implemented by the National Influenza Centres (NICs) as part of the WHO Global Influenza Surveillance and Response System (GISRS):
No publications could be found describing the status of access to influenza diagnostics in LMIC’s. Given the lack of investment even in influenza surveillance in LMIC’s mentioned by the CIDRAP authors above, it may be true that the use of influenza diagnostic tests is not prioritized in LMIC’s.

4. **Clinical impact of flu rapid tests is not reviewed, and meta-analysis does not provide that either.**

Please see the information presented in response to this question in the RIDT submission. With regard to rapid molecular point-of-care tests, it was noted in the section of the submission that requested data on clinical impact that “no recent studies could be found showing that the enhanced performance of rapid molecular assays with results delivered in 15 to 20 minutes will lead to improved clinical outcomes and better antimicrobial stewardship.”

Despite this, all of the guidelines reviewed made explicit recommendations to use molecular tests for influenza diagnosis.

**National Institute for Communicable Diseases of South Africa:**
Influenza NICD recommendations for the diagnosis, prevention, management and public health response. April 2018

“molecular diagnostics (real-time multiplex PCR for influenza A and B virus or GeneXpert for influenza A and B virus) are currently the method of choice for influenza virus detection.”


**Ministry of Health and Family Welfare, Government of India**
Clinical Management Protocol for Seasonal Influenza

“Confirmation of seasonal influenza (including H1N1) infection is through:

- Real time RT-PCR or
- Isolation of the virus in culture or
- Four-fold rise in virus specific neutralizing antibodies.”

https://mohfw.gov.in/sites/default/files/49049173711477913766.pdf

**The Infectious Disease Society of America (IDSA):**
Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza

- Clinicians should use rapid molecular assays (ie, nucleic acid amplification tests) over rapid influenza diagnostic tests (RIDTs) in outpatients to improve detection of influenza virus infection
Clinicians should use reverse-transcription polymerase chain reaction (RT-PCR) or other molecular assays over other influenza tests in hospitalized patients to improve detection of influenza virus infection.

Clinicians should use multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses, in hospitalized immunocompromised patients.

Clinicians can consider using multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses, in hospitalized patients who are not immunocompromised if it might influence care (e.g., aid in cohorting decisions, reduce testing, or decrease antibiotic use).

Clinicians should not use immunofluorescence assays for influenza virus antigen detection in hospitalized patients except when more sensitive molecular assays are not available, and follow-up testing with RT-PCR or other molecular assays should be performed to confirm negative immunofluorescence test results.

Clinicians should not use RIDTs in hospitalized patients except when more sensitive molecular assays are not available, and follow-up testing with RT-PCR or other molecular assays should be performed to confirm negative RIDT results.


5. WHO policy on influenza test that is included is from 2005! WHO urgently needs to update its policy guidance!

WHO published another guidance on the use of influenza rapid diagnostic tests in 2010: https://apps.who.int/iris/bitstream/handle/10665/44304/9789241599283_eng.pdf;jsessionid=19E491714E72C3B61C8F028B46148315?sequence=1, and in 2011, WHO published the Manual for the laboratory diagnosis and virological surveillance of influenza, which has a section on RIDTs. In this section, the manual mentions that: “Rapid tests are useful for rapidly establishing the presence of influenza in certain circumstances such as outbreak situations, remote locations and areas where there is no access to laboratory facilities. However, WHO recommends that where possible tests such as IFA, culture or RT-PCR should be used to confirm and extend the results”. The WHO information on molecular diagnosis of influenza virus is updated on yearly basis and available at: https://www.who.int/influenza/gisrs_laboratory/molecular_diagnosis/en/

Finally, WHO is currently in the process of developing new guidelines for the clinical management of influenza infections: https://www.who.int/influenza/resources/documents/influenza-meeting-conclusion-27042018.pdf?ua=1

6. Cost-effectiveness in a LMIC context: no data shown

No data was found.

7. WHO PQ status of flu molecular dx is not indicated

Influenza testing is not currently covered by the WHO prequalification programme for in vitro diagnostics.
8. **Link between diagnostics and influenza treatment and EML** is missing.

Rapid testing for influenza is linked to treatment in two key ways. First, they can be used as a guide to support antiviral treatment and second, they may help reduce the use of antibiotics.

During the 2009 pandemic, the WHO guidelines for pharmacological management of pandemic influenza A(H1N1) 2009 and other influenza viruses strongly recommended that “Treatment should be started as soon as possible. Laboratory confirmation of influenza virus infection is not necessary for the initiation of treatment and a negative laboratory test for H1N1 does not exclude the diagnosis in all patients, therefore early, empiric treatment is strongly recommended. The evidence from clinical trials in uncomplicated seasonal influenza suggests most patients benefit from antiviral treatment commencing within 48 hours of onset of symptoms, but experience from use in patients with H5N1 virus infection and severe lower respiratory tract disease suggests that later initiation of treatment may also be effective, whenever viral replication is present or strongly suspected”.

https://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf?ua=1

**Antiviral Treatment:**

The Model Essential Medicines List includes Oseltamivir “for severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients”. As noted in the reviewer’s comments, this drug may be removed from the EML in the future “unless new information supporting its use in seasonal and pandemic outbreaks is provided.”

The South African and Indian guidelines currently both recommend treatment using neuraminidase inhibitors such as oseltamivir and zanamivir. This may change if these drugs are removed from the WHO EML.

The Infectious Disease Society of America (IDSA) published its updated guidelines in 2018 in Clinical Infectious Diseases and the detail with which they address the topic is useful and copied below. They recommend treatment with Oseltamivir or a selection of other antiviral agents for patients with confirmed or suspected infection and identify a broader list of patients for treatment than is specified in the WHO EML.

**Treatment Recommendations:**

Clinicians should start antiviral treatment as soon as possible for adults and children with documented or suspected influenza, irrespective of influenza vaccination history, who meet the following criteria:

- Persons of any age who are hospitalized with influenza, regardless of illness duration prior to hospitalization.
- Outpatients of any age with severe or progressive illness, regardless of illness duration.
- Outpatients who are at high risk of complications from influenza, including those with chronic medical conditions and immunocompromised patients
- Children younger than 2 years and adults ≥65 years
- Pregnant women and those within 2 weeks postpartum

Clinicians can consider antiviral treatment for adults and children who are not at high risk of influenza complications, with documented or suspected influenza, irrespective of influenza vaccination history, who are either:

- Outpatients with illness onset ≤2 days before presentation
• Symptomatic outpatients who are household contacts of persons who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised.
• Symptomatic healthcare providers who care for patients who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised.

Patients recommended for testing are as follows:

**Outpatients (including emergency department patients).**

1. During influenza activity (defined as the circulation of seasonal influenza A and B viruses among persons in the local community):

   Clinicians should test for influenza if the result will influence clinical management in the following patients:

   • High-risk patients, including immunocompromised persons who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (e.g., cough without fever).
   • Patients who present with acute onset of respiratory symptoms with or without fever, and either exacerbation of chronic medical conditions (e.g., asthma, chronic obstructive pulmonary disease [COPD], heart failure) or known complications of influenza (e.g., pneumonia).

   Clinicians can consider influenza testing for patients not at high risk for influenza complications who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (e.g., cough without fever) and who are likely to be discharged home if the results might influence antiviral treatment decisions or reduce use of unnecessary antibiotics, further diagnostic testing, and time in the emergency department, or if the results might influence antiviral treatment or chemoprophylaxis decisions for high-risk household contacts (see recommendations).

2. During low influenza activity without any link to an influenza outbreak:

   • Clinicians can consider influenza testing in patients with acute onset of respiratory symptoms with or without fever, especially for immunocompromised and high-risk patients.

**Hospitalized Patients.**

1. During influenza activity:

   Clinicians should test for influenza on admission all patients:

   • Requiring hospitalization with acute respiratory illness, including pneumonia, with or without fever on admission.
   • With acute worsening of chronic cardiopulmonary disease (e.g., COPD, asthma, coronary artery disease, or heart failure), as influenza can be associated with exacerbation of underlying conditions.
   • Who are immunocompromised or at high risk of complications and present with acute onset of respiratory symptoms with or without fever, as the manifestations of influenza in such patients are frequently less characteristic than in immunocompetent individuals.
Clinicians should test for influenza in all patients who, while hospitalized, develop acute onset of respiratory symptoms, with or without fever, or respiratory distress, without a clear alternative diagnosis.

During periods of low influenza activity:

Clinicians should test for influenza on admission in all

- patients requiring hospitalization with acute respiratory illness, with or without fever, who have an epidemiological link to a person diagnosed with influenza, an influenza outbreak or outbreak of acute febrile respiratory illness of uncertain cause, or who recently travelled from an area with known influenza activity.

Clinicians can consider testing for influenza in patients with acute, febrile respiratory tract illness, especially children and adults who are immunocompromised or at high risk of complications, or if the results might influence anti-viral treatment or chemoprophylaxis decisions for high-risk household contacts.


Antimicrobial Stewardship:

Several studies have shown that the use of influenza diagnostics tests have helped to reduce inappropriate antibiotic use – see response to review question for the RIDT submission. Used in combination with PCT results to indicate the presence or absence of a bacterial infection, rapid molecular influenza tests have been used to reduce inappropriate antimicrobial therapy.

The following poster was presented at the ID Week Conference in October 2018*:

Impact of Antimicrobial Stewardship Interventions Using Rapid Molecular Testing on the Appropriate Use of Antiviral Therapy and Reduction of Unnecessary Antibiotic Therapy for Patients Admitted with Acute Influenza

Session: Poster Abstract Session: Antimicrobial Stewardship: Impact of New Diagnostics
Saturday, October 6, 2018

Background: Rapid molecular tests combined with Antimicrobial Stewardship Program (ASP) interventions have provided opportunities to optimize patient outcomes and reduce unnecessary antimicrobial use. Our institution currently uses an FDA approved influenza/respiratory syncytial virus polymerase chain reaction (PCR) assay and multiplex respiratory panel. In addition, our institution commonly utilizes procalcitonin (PCT) levels. The ASP at Summa Health System – Akron Campus (SHS-AC) routinely recommends use of these rapid diagnostic tests to assist with antimicrobial and antiviral usage, including the discontinuation of antibiotics in influenza positive patients in the absence of a concurrent bacterial infection.

Methods: A retrospective review of all ASP interventions on influenza positive patients at SHS-AC was performed from December 2017-March 2018. The ASP reviewed all patients on broad spectrum antibiotics > 48 hours and all influenza positive patients without Infectious Disease consultation. The appropriateness of antimicrobial and antiviral therapy was assessed, including assessment of culture and PCR results, PCT levels, indication of therapy, and renal function. For patients with a positive influenza PCR and low PCT without evidence of bacterial infection, the

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recommendation was to discontinue antibacterial use. Data collected included: intervention type, acceptance rate, PCT levels, and influenza subtype.

**Results:** 233 total recommendations were made by the ASP on influenza positive patients, with a 96.6% acceptance rate. Interventions included the following: obtain PCT level (54/233), de-escalate or stop antibiotics based on culture, PCR, and PCT results (116/233), obtain influenza or respiratory PCR (8/233), initiate oseltamivir (37/233), and other (18/233).

**Conclusion:** ASP intervention combined with PCT levels and PCR results contributed to the reduction of unnecessary antibiotic use, and the initiation of oseltamivir therapy in influenza positive patients.

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* This poster is cited despite not having been through full peer review because it shows the combined use a nucleic acid-based test for influenza with procalcitonin to improve antimicrobial stewardship, which is a stated high priority for WHO. Typically, however, WHO would want to see peer reviewed studies to further support this approach.