Influenza

RIDTs (Rapid Influenza Detection Tests) 2017:
- CDC says: "RIDTs vary in terms of sensitivity and specificity when compared with viral culture or RT-PCR. Product insert information and research publications indicate that:
  Sensitivities are generally approximately 50-70%
  Specificities are generally approximately 90-95%"

Cost for Tamiflu for Kids:
- 1/17: for 20 kg kid, $300 for liquid, and $150 for 45 mg capsules (can sprinkle on applesauce)

Influenza Clinical Diagnosis by Score
2  fever plus cough
2  myalgias
1  duration <48 hours
1  chills or sweats.

0-2: 8% likelihood of influenza
3:  30%
4-6: 59%


INTRODUCTION: A clinical decision rule to improve the accuracy of a diagnosis of influenza could help clinicians avoid unnecessary use of diagnostic tests and treatments. Our objective was to develop and validate a simple clinical decision rule for diagnosis of influenza. METHODS: We combined data from 2 studies of influenza diagnosis in adult outpatients with suspected influenza: one set in California and one in Switzerland. Patients in both studies underwent a structured history and physical examination and had a reference standard test for influenza (polymerase chain reaction or culture). We randomly divided the dataset into derivation and validation groups and then evaluated simple heuristics and decision rules from previous studies and 3 rules based on our own multivariate analysis. Cutpoints for stratification of risk groups in each model were determined using the derivation group before evaluating them in the validation group. For each decision rule, the positive predictive value and likelihood ratio for influenza in low-, moderate-, and high-risk groups, and the percentage of patients allocated to each risk group, were reported. RESULTS: The simple heuristics (fever and cough; fever, cough, and acute onset) were helpful when positive but not when negative. The most useful and accurate clinical rule assigned 2 points for fever plus cough, 2 points for myalgias, and 1 point each for duration <48 hours and chills or sweats. The risk of influenza was 8% for 0 to 2 points, 30% for 3 points, and 59% for 4 to 6 points; the rule performed similarly in derivation and validation groups. Approximately two-thirds of patients fell into the low- or high-risk group and would not require further diagnostic testing. CONCLUSION: A simple, valid
clinical rule can be used to guide point-of-care testing and empiric therapy for patients with suspected influenza.

2012-13 Notes
- Tamiflu:
  + CDC says "
  - Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who:
    + is hospitalized;
    + has severe, complicated, or progressive illness; or
    + is at higher risk for influenza complications.
  - Persons at higher risk for influenza complications recommended for antiviral treatment include:
    + children aged younger than 2 years;*
    + adults aged 65 years and older;
    + persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), and metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopmental disorders (including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);
    + persons with immunosuppression, including that caused by medications or by HIV infection;
    + women who are pregnant or postpartum (within 2 weeks after delivery);
    + persons aged younger than 19 years who are receiving long-term aspirin therapy;
    + American Indians/Alaska Natives;
    + persons who are morbidly obese (i.e., body mass index is equal to or greater than 40); and
    + residents of nursing homes and other chronic care facilities." (from CDC website, 1/15)
  - By implication, it's not appropriate for others. Seems to me that for healthy people, in the first 24 hours of disease, it's likely that the benefits might outweigh the harms, but from 24-48+ hours, it's likely that the harms (vomiting, psychosis, acute renal failure) overwhelm the benefits.
  + "When indicated, antiviral treatment should be started as soon as possible after illness onset, ideally within 48 hours of symptom onset. However, antiviral treatment might still be beneficial in patients with severe, complicated or progressive illness and in hospitalized patients when started after 48 hours of illness onset, as indicated by observational studies. For example, antiviral treatment of pregnant women (of any trimester) with influenza A (2009 H1N1) virus infection has been shown to be most beneficial in preventing respiratory failure and death when started within less than 3 days of illness onset, but still provided benefit when started 3- 4 days after onset compared to 5 or more days (Siston, et al JAMA 2009). A larger
study reported similar findings and showed that starting oseltamivir treatment up to 4 days after illness onset provided benefit in reducing the risk of severe illness compared to later treatment of 2009 H1N1 (Yu, et al. Clinical Infectious Diseases 2011). Another study of critically ill patients and fatal cases with 2009 H1N1 virus infection reported that antiviral treatment with a neuraminidase inhibitor was associated with improved survival compared to untreated patients, and while early treatment conveyed the most benefit, patients who started antiviral treatment up to 5 days after illness onset had improved survival compared to untreated patients (Louie, et al. Clinical Infectious Diseases 2012). A meta-analysis of observational studies of oseltamivir for treatment of influenza concluded that treatment may reduce duration of symptoms, hospitalization, and mortality compared to no treatment (Hsu, et al. 2012). Another systematic review and meta-analysis of observational studies of neuraminidase inhibitor treatment of patients with 2009 H1N1 virus infection, primarily oseltamivir treatment, concluded that early initiation of treatment reduced the likelihood of severe outcomes compared to late or no treatment. This review found a 65% mortality reduction in early-treated versus untreated patients (Muthuri et al Clinical Infectious Diseases 2012).

+ "While influenza vaccination is the first and best way to prevent influenza, a history of influenza vaccination does not rule out the possibility of influenza virus infection in an ill patient with clinical signs and symptoms compatible with influenza."

+ "Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset."

‡ 2008-2009 Influenza
(NOTE: Magee Pharmacy recommends Relenza for pregnant patients with influenza)

Due to the high prevalence of oseltamivir-resistance among influenza A (H1N1) viruses identified to date during the 2008-2009 influenza season, the Centers for Disease Control and Prevention has issued revised recommendations for the use of antiviral drugs for influenza treatment and prophylaxis. These recommendations are described in detail below.

As expected at this time of year, influenza activity is increasing in Pennsylvania, although overall activity remains low. Although only a small number of viruses have been fully examined in Pennsylvania, so far all three seasonal influenza subtypes have been identified in the Commonwealth - influenza A (H1N1) (6 isolates), influenza A (H3N2) (4 isolates) and influenza B (2 isolates). Oseltamivir-resistance has been seen among the Pennsylvania influenza A (H1N1) viruses tested. Information on influenza surveillance in Pennsylvania is available on the Pennsylvania Department of Health’s website at http://www.dsf.health.state.pa.us/health/cwp/view.asp?a=171&q=246529.
These findings indicate there is still abundant time to vaccinate individuals at high risk of influenza complications and those wishing to reduce their risk of influenza in the coming months. Vaccination remains the single most effective measure to avoid influenza. The influenza A (H1N1) viruses exhibiting resistance are closely matched to the strain included in the 2008-2009 influenza vaccine.

The findings also reinforce the importance of diagnostic testing for influenza. When samples are taken, it is important to use a test that at the very least distinguishes between influenza A and B, since this will assist in decision making regarding treatment. It is also important to submit samples testing positive for influenza to reference laboratories for subtype identification. Sub typing is especially crucial in settings such as long term care facilities, health care, and other institutional settings where prophylaxis may be necessary. Such samples can be submitted to the state public health laboratory. Details concerning submission can be found at http://www.dsf.health.state.pa.us/health/cwp/view.asp?A=167&Q=243575

Throughout the United States, 98% of influenza A (H1N1) isolates have demonstrated oseltamivir-resistance. These H1N1 isolates remain sensitive to the other neuraminidase inhibitor, zanamivir (Relenza) and are also sensitive to the other class of influenza antiviral medications (the adamantanes rimantidine and amantadine). Adamantane drugs are not active against influenza B, and many other influenza A strains are resistant to these drugs. Therefore their use as single agents for therapy or prophylaxis should be reserved for situations where other options are unavailable.

On December 19, CDC issued the following interim recommendations regarding the use of antiviral agents. These recommendations may change as more data on antiviral resistance and circulating strains become available over the influenza season.

1. For those known to be infected with influenza B, either oseltamivir or zanamivir may be used.

2. If a patient tests positive for influenza A and the subtype is unknown, zanamivir should be used unless there are known contraindications (patient < 7 years of age, has chronic underlying airway disease, or cannot use the zanamivir inhalation device). As an alternative (or if zanamivir is unavailable), oseltamivir in combination with one of the adamantane drugs (rimantidine or amantadine) can be used.

Note the adamantane drugs (especially amantadine) are associated with balance difficulties and neuropsychiatric concerns. They should be used with caution in groups such as the elderly where balance may be an issue. Furthermore, data and experience regarding use of combination antiviral medication for influenza are limited.
3. If the patient tests positive for influenza A and the subtype is known, treatment should be based on the subtype results. For influenza A (H1N1), zanamivir could be used with oseltamivir in combination with an adamantane as the alternative recognizing the contraindications and cautions mentioned above. For influenza A (H3N2) either oseltamivir or zanamivir could be used.

4. For settings where prophylaxis may be indicating, selection of antiviral medications should be based on the resistance patterns of the virus causing disease or circulating in the community. For influenza A (H3N2) or influenza B, prophylaxis should use either oseltamivir or zanamivir. For influenza A (H1N1), prophylaxis should use zanamivir alone with rimantadine alone as an alternative.

þ Tamiflu Peds Dosing
(incorrectly BID in some literature; it's once daily for 10 days)
-15 kg, -33 lbs, 30 mg once daily, Rx 1 btl
15-23 kg, 33-51 lbs, 45 mg once daily, Rx 2 bottles
23-40 kg, 51-88 lbs, 60 mg once daily, Rx 3 bottles
>40 kg, >88 lbs, 75 mg once daily, Rx 4 bottles

þ Resistance to Amantadine
- More than 90% of influenza A viruses currently circulating in the United States are adamantane-resistant, which suggests that the antiviral drugs amantadine and rimantadine should not be used for the remainder of the 2006 flu season, according to an early-release study published online Feb. 2 by the Journal of the American Medical Association.
[Adamantane Resistance Among Influenza A Viruses Isolated Early During the 2005-2006 Influenza Season in the United States
Rick A. Bright, PhD; David K. Shay, MD, MPH; Bo Shu, MD; Nancy J. Cox, PhD; Alexander I. Klimov, PhD

þ Antivirals for Influenza
- if you combine oseltamivir with probenecid 500mg QID you can more than double the serum levels of oseltamivir

þ Influenza Testing at Mercy
Mercy Hospital of Pittsburgh
1400 Locust Street
Pittsburgh, PA 15219-5166
MEMORANDUM
DATE: January 22, 2001 TO: Medical Staff, Nursing Units
FROM: Charles L. Eperthener, Supervisor, Rapid Service Lab
Rosemary Edwards, M.D., Director, Rapid Service Lab
Dennis Borochovitz, M.D., Chairman
James Kuzycz, Director Department of Laboratory Medicine
SUBJECT: RAPID INFLUENZA TESTING

Effective January 22, 2001, the Rapid Service Laboratory will offer a rapid influenza assay to aid in the diagnosis of Influenza A and B viral infections.
ID-FLU.TXT

This assay is compares Mercy able to a 14-day viral culture. A positive result indicates the presence of Influenza A and/or B antigen. A negative result should be interpreted as the absence of Influenza A and/or B antigen. False negative results will occur in specimens improperly collected or where low levels of antigen are present. False positive results will not occur with patients who have received the influenza vaccine. The potential of interference from medications such as anti-virals, anti-microbials, interferon, intranasal steroids, and anti-asthmatics has not been established.

The sensitivity of the test is 95% and the specificity is 92%. The Positive Predictive Value is 86% and the Negative Predictive Value is 89%.

The specimens of choice are either nasopharyngeal swabs or throat swabs. Only swabs with plastic shafts and dacron tips should be used for specimen collection. If you wish to order a rapid influenza test, please contact the Rapid Service Laboratory at ext. 8044 to obtain the required swabs. This influenza test utilizes an antibody-antigen reaction not dependent on the presence of live influenza virus in the specimen. The use of specimens preserved in viral transport media is not recommended. The test may be ordered in Invision by accessing the RSL Miscellaneous screen and selecting "Rapid Influenza A & B".

Please call the Rapid Service Laboratory when sending a specimen for the Influenza testing. This will allow the reagents to warm to room temperature. Failure to notify the lab will result in a 15-minute delay in the reporting of the results.

Influenza testing received in the Rapid Service Laboratory between 4:00 a.m. and 7:00 a.m. will not be tested until after 7:00 a.m.

Please direct any questions to Charles Eperthener at ext. 7304. Thank you for your time and attention to this matter.

CE/RE/DEB/JK/kmf

> I am pleased to notify you that we are now ready to
> begin the Rapid Influenza A/B testing in the Rapid Service Laboratory.
> The test is available today, January 12, 2000, at 1:30 pm. We have chosen
> the BioStar Rapid Influenza kit because of its comparability to the 14
> day viral culture. The specimen of choice is either a throat or nasal
> swab. The swab must have a dacron tip and a plastic shaft. We receive an
> exact number of swabs with each kit. If your staff will call the Rapid
> Service Laboratory at ext. 8044 when they order the test, we will put a
> swab in the tube system and send it to the DEM. This will also allow us
> time to get the reagents out of the refrigerator. Any other type of swab
> or swabs in transport media cannot be used. The turn-around time is
> approximately 30 minutes. The test is ordered by accessing the RSL
> screen in Invision, clicking on the MISC. option, and selecting the test
> "Rapid Influenza A & B". A memo will be sent around shortly, but if you
> would share this with your staff, we can begin immediately.
>
> From: Eperthener, Charles
> Sent: Monday, January 15, 2001 9:35 AM
> To: MacLeod, Bruce
ID-FLU.TXT

Subject: RE: Influenza Testing

Dr. MacLeod,

Here is some of the information that you requested. BioStar Influenza -
sensitivity - 95%, specificity - 92%, PPV - 86%, NPV - 89%. This test
utilizes an antibody/antigen reaction. The test kit is impregnated with
antibodies to influenza A and B. We do not need to recover live virus
from the patient, just material containing the antigen. There is no
cross reactivity with a long list of both bacteria and viruses. False
positives do not occur with patients who have received the influenza
vaccine. The manufacturer is sending me some abstracts that should help
you in the interpretation of the test. I will pass them along as soon as
I receive them. Please let me know where your office is located and I
will deliver them myself. Thanks.

Influenza Vaccine
- avoid if:
  + hx of Guillain-Barre syndrome
  + females who might be pregnant
  + allergy to eggs, chickens, chicken feathers or chicken dander
  + currently "ill" or febrile
- if unsure if has had it, OK to give another dose (memo from Kate Werwie,
  Mercy DEM, 12/3/98)
- Give October through January
- highly recommended for high-risk adults and children. High-risk means:
  + chronic pulmonary, cardiovascular, or renal disease
  + diabetes
  + chronic severe anemia
  + immunologic impairment
  + nursing home or other chronic care facility residents
  + everyone 65 years or older
  + children and adolescents (6 months-18 years) on chronic ASA therapy
  + women in second or third trimester during flu season
  + household contacts of the above highrisk groups
  + healthcare workers
  + others who desire protection
- doses of vaccine (1999-2000):
  + 6-35 months: split virus only, 0.25 cc IM in thigh
    (repeat after 1 month if first < 9 years' age and first flu vaccine)
  + 3-8 years: 0.5 cc split virus only IM, 1-2 doses
  + 9-12 years: 0.5 cc split virus only IM in deltoid, 1 dose
  + > 12 years: 0.5 cc whole or split virus IM, 1 dose

ELISA Testing for Influenza:
- The assay is produced by Becton Dickinson and is the "Directigen (tm) Flu A
  Assay." There is an influenza B assay as well. The assay is very simple
  and makes the many thousands (probably during my Ph.D. work over 50,000)
  egg inoculations we did seem foolish. The other traditional method is a
nonspecific hemagglutination of red blood cells, which as much as culture is too laborious and not timely, the hemagglutination method is too crude and nonspecific.

- The Directigen ELISA assay uses conjugated monoclonal antibodies to the influenza type nonspecific nucleoprotein (two monoclonals are used). Because the nucleoprotein is very type specific the assay is very specific for influenza A and because the NP is not very prone to antigenic variation the assay is very sensitive and need not be optimized for each season's strain.
- The assay takes 15 minutes to run and a positive test result is indicated by a purple colorometric result (a triangle on the filter membrane).
- The nurses don't really like the procedure because you need to perform a nasal washing in which 2-3 cc of NS are instilled into one nares and blown into a specimen cup.
- Cost: $15 per assay. Charge: $35 per assay.
- One can certainly debate the use of an assay for an illness that most often can be diagnosed clinically and for which there is no universal treatment, although some may warrant rimantadine or amantadine treatment as has been discussed on the list.
- I think there is however a role for the assay to truncate potentially useless testing/treatment in the less clearcut cases. My hypothesis is that there may be a substantial quantity of needless testing and treatment during the influenza season and perhaps the test may have a role in eliminating some of this when applied prudently where clinical decision making may not suffice.
--Ian Cummings

Antivirals for Flu

- new drugs: neuraminidase inhibitors
  + selectively inhibit both influenza A and B
  + zanamivir (Relenza - intranasal)
  + oseltamivir (Tamiflu - oral): 75 BID for 5 days, or 75 daily for 5 days if renal insufficiency
  + ? effective, must be started within 30 hours (not 48 as per the marketing literature), will feel moderately horrible for 4 days instead of terrible for 5 days.
  + no studies vs. amantadine or rimantadine
  + may be effective for prophylaxis but not yet FDA approved for this.
- Amantadine 100 mg BID for 5 days is effective, but has many side effects, and should ideally be started within 24 hours. (4.4mg/kg/day up to max of 150 mg/day for peds, and 100 mg/day if over 65 years old.) Cost for this is $1.69 total for generic (per Med Ltr 39(1006) Aug 1 1997)
- Rimantadine (Flumadine) 100 mg BID, or 200 mg daily for 7 days (5 mg/kg/day up to 150 mg/day for peds, only 100 mg daily if over 65), is as effective or more so, and has less side effects, but costs more ($20.97 for the course) (per Med Ltr 39(1006) Aug 1 1997)
- Should decrease dosage of either drug to 100 QD for those over 65 or with renal insufficiency.
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- CDC (MMWR) says "out of concern for inducing resistance, treatment should be discontinued as soon as clinically warranted, generally after 3 - 5 days of treatment or within 24 to 48 hours after the disappearance of signs and symptoms."
- amantadine is recommended for both prophylaxis and treatment of IA in both adults and children (>=1 year).
- rimantidine is recommended for the prophylaxis and treatment of adults with IA but only prophylaxis in children.
- rimantidine may have fewer CNS side effects (dizzyness, anxiety etc.) than amantadine (6% vs 14%).
- GI side effects are about the same for both drugs (3%).
- Treatment should be initiated within 48 hours of symptom onset.
- Dosage Schedule as a function of age:

<table>
<thead>
<tr>
<th>Drug</th>
<th>1-9</th>
<th>10-13</th>
<th>14-64</th>
<th>&gt;64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>5 mg/kg/d (150 mg max)</td>
<td>100 mg BID</td>
<td>100 mg BID</td>
<td>&lt;=100mg/d</td>
</tr>
<tr>
<td>Rimantidine</td>
<td>same</td>
<td>same</td>
<td>same</td>
<td>100 - 200 mg/d</td>
</tr>
</tbody>
</table>


- Children older than 10 who weigh less than 40 kg should get the schedule for ages 1 - 9 instead.
- Therapy should be limited to 3 - 5 days OR 24 - 48 hours after symptom resolution to prevent development of resistance. CDC (MMWR) says "out of concern for inducing resistance, treatment should be discontinued as soon as clinically warranted, generally after 3 - 5 days of treatment or within 24 to 48 hours after the disappearance of signs and symptoms."
- In renal failure: amantadine dosage should be reduced for CrCl < 50 ml/min (see product insert) and rimantidine dosage should be reduced to 100 mg/d (adults) for CrCl < 10 ml/min.
- Patients with hepatic dysfunction should have the dose of rimantidine reduced to 100 mg/d. No increase in adverse reactions to amantadine have been seen with conventional doses.
- Amantadine may increase the frequency of seizures in patients with chronic seizure disorders. Rimantidine may do so to a lesser extent.
- More severe side effects such as delirium, hallucinations and seizures have been observed with amantadine in patients with renal failure, psychiatric disorders, seizures and the elderly.
- A recent review of rimantidine suggested that it may be the preferred drug in elderly and in those with mild to moderate renal insufficiency. The efficacy of these drugs (rimantidine is typical) is modest (time to 50% reduction in symptoms decreased by 1 - 3 days).
ID-FLU.TXT

Abstract: <ID-FluA.TXT -Wintermeyer>
- Whether this is enough justification to prescribe it and risk side effects has to be individualized. My practice is to rarely prescribe them. If you do it is important to remember that it has to be given early (< 48 hours) to be effective and that therapy should be limited to 3 - 5 days only. --H. Louzon MD
- In an article published in the NEJM in the mid-1980's it was shown that Amantadine is ineffective in prophylaxis against influenza A if the index case is being treated with the drug.
- This can have significance when one family member is immunocompromised... it is probably best NOT to treat the sick other member and instead prophylax the immunocompromised host. Rimantidine is marketed in a way that suggests that it should be used BOTH for the index case AND prophylaxis of other family members. Has anyone seen data to suggest that the same phenomenon that occurs with Amantadine doesn't occur with Rimantidine? --Woodrow Gandy MD
- There is no reason to believe that rimantadine is any different in this regard than is amantadine. Resistant strains develop after several days of therapy (5 to 7) and is one reason why treatment of the index case should be limited to as short a course as possible (3 - 5 days). Virus resistant to one drug is also resistant to the other. [Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996;45(No. RR-5):12-14.]
The bottom line is that an immunocompromised family member should have recieved the vaccine in the first place, and failing that, take chemoprophylaxis. If they are not and a family member becomes ill then the immunocompromised person should begin chemoprophylaxis. The question then becomes whether the index case should be treated at all out of fear that resistant strains will emerge. I don't think that there is any firm recommendation on this. However the product information for rimantadine reads: "Transmission of rimantadine resistant virus should be considered when treating patients whose contacts are at high risk for influenza A illness. A virus strain resistant to rimantadine can emerge during treatment and such resistant strains have been shown to be transmissible and to cause typical influenza illness." The implication is clear. Rimantadine does not appear to have a margin of safety over amantadine in this regard.
--H. Louzon MD
After reading the CDC recommendations on this I went back and found 2 interesting articles. One specifically adresses the issue of whether treating the index case with rimantadine would tend to result in spread of resistant strains to other family members. The answer (as I strongly suspected) is yes.
[Hayden FG, Belshe RB, Clover RD, Hay AJ, Oakes MG, Soo W. Emergence and apparent transmission of rimantadine-resistant influenza A virus in
The CDC document also suggested limiting the length of therapy in the index case to prevent the emergence of resistant strains.

What was not mentioned, however, is that these strains may develop in as short a period as 2 days.

Abstract: <ID-FluA.TXT -Sperber>

--H. Louzon MD