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Eliyakim Hershkop
Touro College

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By Eliyakim Hershkop
Eliyakim Hershkop graduated in June 2015 with a B.S. Honors degree in Biology and is currently attending Technion School of Medicine.

Abstract
Influenza is a disease that has caused the deaths of tens of millions people in the last century alone. The influenza neuraminidase protein is essential in the mechanism infection. It enables the virus to leave the infected cell and proliferate. Antiviral neuraminidase inhibitor drugs can be used for treatment. The drug Tamiflu is the standard of care for both treatment and prophylaxis of influenza. The Cochrane reports of 2009 and 2014 conclude that evidence is lacking to support this. Numerous bodies disagree. Cochrane also question the accuracy and credibility of many studies and agencies in support of Tamiflu. This paper explores the issues.

Introduction

Influenza is a viral disease that routinely causes significant morbidity and mortality. Influenza pandemics have been responsible for the deaths of tens of millions of people in the last century alone. Science has been desperately searching for any agent to mitigate the effects of this infectious disease.

Tamiflu (a neuraminidase inhibitor) was brought to market in the last 20 years with great fanfare and hope. During the 2009 influenza pandemic government agencies and hospitals spent billions of dollars stockpiling the Tamiflu. It was widely touted by health professionals and the media as an effective "silver bullet" for the disease. In 2009 The Cochrane Report created a tremendous uproar with a British Medical Journal (BMJ) report that concluded that Tamiflu was not effective. Despite the controversy, Tamiflu continues to be recommended for use at clinics and hospitals as first line defense for treatment as well as prophylaxis (Zachary 2015).

Like any medication, use of Tamiflu involves financial and other costs i.e. side effects. Given that it is not a benign drug, it behooves us to explore the controversy in detail.

Methods

The information for this paper was obtained from many online resources. Many of the databases and journals used were accessed through the Touro library database and PubMed.gov. Much of the background information and pictures were accessed through Dr. Vincent Racaniello's (College of Physicians and Surgeons of Columbia University) "Virology 101" blog.

Background

Influenza is a viral infection that attacks the respiratory system (the nose, throat and lungs). It is caused by one of the three types of influenza viruses A,B and C. Influenza viruses can be spread by airborne droplets(aerosols) person-to-person contact, or contact with contaminated items (fomites). Airborne spread appears to be the most important mechanism. A single sneeze can generate up to 20,000 virus containing aerosol particles. Aerosolized particles produced by these activities are of different sizes. The largest droplets fall to the ground within a few meters and will transmit an infection only to those in the immediate vicinity. Smaller droplets can travel long distances determined by their size.

Onset of symptoms ranges from 1 to 4 days with an average of about 48 hours. Symptoms include sudden onset of chills, fever, cough, and generalized aches and pains. Severe Headache is common. In mild cases, many symptoms are like those of a common cold e.g. sore throat, runny nose, and mild conjunctivitis may also occur. After 2 to 3 days, acute symptoms rapidly subside, although fever may last up to 5 days. Cough, weakness, sweating, and fatigue may persist for several days or occasionally for weeks.

Influenza-related pneumonia is an important cause of increased morbidity or mortality in high-risk patients. Encephalitis, myocarditis, and myoglobinuria, sometimes with renal failure, develop infrequently after influenza A or B infection. Patients at higher risk are those with: underlying illness, acute respiratory distress syndrome, primary influenza pneumonia, or secondary bacterial pneumonia .These include: Children under the age of 4 years; adults over the age of 65 years; people with chronic medical disorders (e.g., cardiopulmonary disease, diabetes mellitus, renal or hepatic insufficiency, hemoglobinopathies, immuodeficiency); women in the 2nd or 3rd trimester of pregnancy and patients with disorders that impair handling of respiratory secretions (e.g., cognitive dysfunction, neuromuscular disorders, stroke, seizure disorders).

Aside from the use of antivirals such as Tamiflu treatment is symptomatic. This includes rest, hydration, and antipyretics as needed. Appropriate antibiotics are necessary for treating complicating bacterial infections. Antiviral drugs given within 1 to 2 days of symptom onset may decrease the duration of fever, severity of symptoms, and time to return to normal activity. The two main drug types are the neuraminidase inhibitors Oseltamivir and Zanamivir, and the adamantane drugs, Amantadine and Rimantadine. Neuraminidase inhibitors interfere with release of influenza virus from infected cells thereby halting the spread of infection. These will be discussed at length in this paper. Adamantanes block the M2 ion channel thereby interfering with viral uncoating inside the cell. They are effective only against influenza A viruses (influenza B viruses lack the M2

protein). Choice of antiviral drug is complicated by resistance of different influenza types and subtypes to different drugs (Pringle, 2014).

The influenza virus is unique in that it completely experiences changes in the characteristic of the antigens on its surface. Typically, small changes occur from one year to the next. This is known as "antigenic drift". Less frequently, there are significant changes in the surface antigens. This is known as "antigenic shift." Hosts who have been previously exposed to influenza generally have some residual immunity against viruses that have drifted antigenically. In contrast, there is little/no preexisting immunity against viruses that have shifted antigenically. The former is responsible for epidemics which tend to be milder in severity. The latter situation results in influenza pandemics, with high mortality e.g. The Spanish influenza of 1918 is thought to have caused 30-50 million deaths worldwide.

Influenza Type A can cause pandemics and epidemics and is our main concern. Type B can only cause epidemics. Type C can cause mild illness but does not cause pandemics nor epidemics. Influenza is often confused with "Influenza-like- illness" which may be caused by other factors but has similar symptoms.

Influenza is most common in the winter months. This is because the winter conditions are optimal for the spread of influenza. The transmission of infection is most effective at a humidity level of 20-35 degrees and colder temperatures. At these conditions virion particles are more stable and can travel further distances in droplets (Mubareka et al., 2009). Increasing levels of humidity of indoor air during the winter may be an effective way of decreasing the spread of influenza.

Pathophysiology

Influenza types

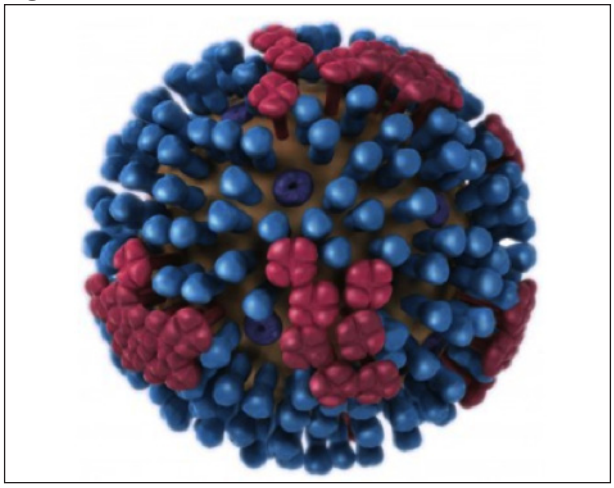
As noted above There are three types of Influenza A, B and C. Type A and type B cause the same spectrums of disease but type B can only infect humans and seals and therefore limits the reassortments in contrast to type A which has numerous hosts and numerous reassortments.

Influenza A Subtypes

Type A has 3 different membrane proteins, surface proteins hemagglutinin (HA), neuraminidase (NA). Matrix protein 2 (M2) traverses the membrane. As shown in figure 1. (Type B has the HA and NA proteins but does not have the M2 protein). (Tscherne and Garcia-Satre, 2011). The subtypes of influenza A are classified based on the HA and NA proteins. There are 18 HA types and 11 NA types. This means there are 198 possible combinations. The nomenclature of the virus describes the HA and NA subtypes for example a virus with HA type 11 and NA type 7 is called Influenza H11N7. Only a few types of influenza are pathogenic to humans. This depends on their ability to bind to Human sialic acid, as discussed later.

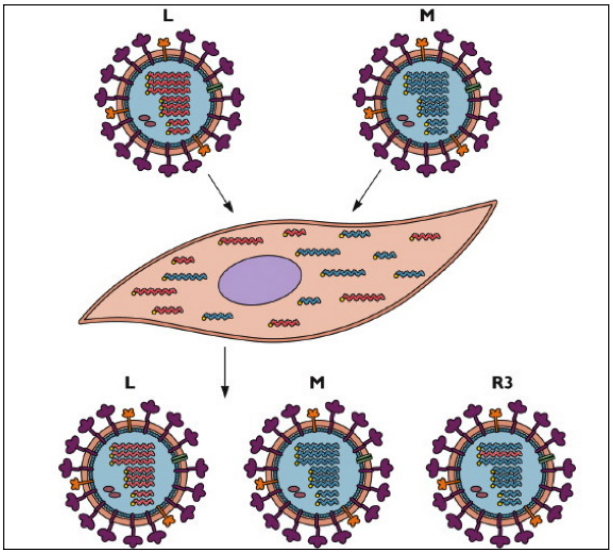
Antigenic drifts are minor mutations in preexisting HA and NA combinations resulting in new strains. This decreases the effectiveness of antibodies to the Influenza. Antigenic Shifts are new combinations of HA and NA proteins. Such as a change from H1N1 to H1N2. Antibodies produced against previous influenza strains are generally ineffective, thereby increasing its ability to infect and cause illness. These shifts often occur when two different influenza types infect one cell. When the viruses replicate the RNA can then combine and form a new "reassortant" type (see picture 3 below (Ranciello, 2013)).

Figure 1



HA (bl ue), NA (red), and M2 (purple) proteins (Ranciello 2013)

Figure 2



Influenza reassortment (Ranciello, 2013)

NA Structure

NA is a tetramer of four identical polypeptides each containing approximately 470 Amino Acids. It has four sections: A cytoplasmic sequence, a transmembrane sequence, a stalk and a globular head. There are two phylogenetic groups of NA, NA group 1 and NA group 2. Group 1 contains N1, N4, N5 and N8. Group 2 contains N2, N3, N6, N7 and N9. Group 1 has an additional cavity "150 loop" that is not present in group 2(Air, 2012).

Cell Invasion

Animal respiratory cell membranes contain Sialic acid molecules. These molecules are the binding site receptors of the influenza virus. (Gamblin, and Skehel, 2010). When viral HA proteins bind to sialic acid receptors on the host cells a sequence of events is set in motion resulting in the virus entering the cell.

Types of Sialic Acid

Sialic acid is a glycoprotein. It is typically linked to a galactose molecule. As stated, Sialic acid is linked to galactose. There are 2 main types of such linkages: 1. Alpha2, 3 linkage (pictured above), in which the carbon 2 of the acid is linked to the carbon 3 of galactose. 2. Alpha 2, 6 linkage, in which the carbon2 of the acid is linked to carbon 6 of galactose. Humans primarily have a2, 6 receptors. This means that viruses targeting this structure are more likely to infect these cells. The results of studies of early influenza virus isolates from the 1918, 1957, and 1968 pandemics suggest that these viruses preferentially recognized alpha (2, 6) linked sialic acids. In contrast, viruses targeting the a2, 3-linked structure are not very pathogenic for humans. In humans, these linkages are only found in ciliated epithelial cells, which are a minor population within the human respiratory tract. Nevertheless, these are the preferred receptors for the avian flu (Matrosovich et al., 2000).

Mechanism of infection

First the viral HA protein binds to the sialic acid receptors on the cell membrane. The virus is then engulfed by the cell through endocytosis. This causes the pH of the endosomal vesicle to drop to 5 which activates a conformation change on the HA protein which exposes a fusion peptide. The fusion peptide enables the viral envelope to fuse with the vesicle membrane wall. The viral RNA is then released into the cytoplasm. Viral RNA travels to the nucleus to initiate protein synthesis and assemble new viruses. The newly formed viruses travel back to the cell membrane. The virus interacts with the cell membrane causing it to bud off. The virus is released to infect other cells.

The mechanism of the virus leaving involves a potential problem. One would expect the viral HA protein to bind to the sialic acid receptors on the cell membrane as it leaves. This would result in the virus becoming trapped on the host cell. This is prevented by the NA protein which cleaves the sialic acid to allow the virus to escape (Wagner et al, 2002). NA also cleaves sialic acid molecules in mucus in the human respiratory tract (Cohen, et al., 2013). This increases viral infectivity.

Neuraminidase inhibitor drugs

In order to prevent viral infection the NA protein has been exploited by developing drugs that act as sialic acid analogs which bind to the NA active site. These are called NA inhibitors. These drugs disable the NA protein from cleaving sialic acid, leaving the virus trapped on the cell (Russel et al., 2006). Tamiflu (Oseltamivir) and Relenza (Zanamivir) are the two drugs which dominate the market. These have been stockpiled by governments and public health agencies (Jefferson et al., 2009) for the treatment of Flu and are recommended by the CDC.

Oseltamivir resistant strains

There have emerged strains of flu that are resistant to oseltamivir. This is due to a point mutation of histidine being switched for tyrosine (H274Y) in NA. This leads to decreased binding of the drug. Nevertheless this change is also detrimental for the virus as it leads to a decrease of surface NA reducing the virus replicating abilities and infectivity.

During the 2008-09 flu season oseltamivir resistant influenza H1N1 viruses with the H274Y change became more prevalent, and within a year they were found in most seasonal isolates. Two amino acid changes were identified that even in the presence of H274Y restore surface levels of NA. These are V234M and R222Q. These secondary mutations seem to balance the deleterious effects of the H274Y mutation, thus enabling it to spread (Bloom et al., 2010).

Discussion- The Tamiflu Controversy
Cochrane Report

At the height of the 2009 H1N1 influenza pandemic, the British Medical Journal (BMJ) released a Cochrane update (of a 2005 Cochrane meta-review) which shook the medical world. The report cast serious doubt on the usefulness of neuraminidase inhibitors (Nis) in influenza. Specifically concluding that, at best, NIs reduce symptoms by approximately one day- a moderate benefit.

They reviewed 1416 titles for neuraminidase inhibitors mostly on oseltamivir. They discarded all but 20 due to various problems. These included, variously, insufficient information, inaccessibility to data, poor description of methods, and issues of reliability. For example, some studies used a mixed population of healthy adults and those with comorbid complications. This

meant the studies weren't effective in properly determining outcome in healthy populations. They noted that, even this data may not be accurate as up to 80 percent of the studies may have not been "pure" influenza, rather "influenza like illness". This is because influenza was unconfirmed by laboratory tests.

Most importantly, according to Cochrane, there is insufficient data as to whether NIs are effective in reducing complications of lower respiratory tract infection as indicated by antibiotic use or hospital admissions. They also note that there is a significant risk of toxicity, especially of psychosis, in prophylactic treatment. They concluded "because of the moderate effectiveness of neuraminidase inhibitors, we believe they should not be used in routine control of seasonal influenza."

Kaiser et al (2003)published a meta-analysis of 10 studies of oseltamivir. They concluded that Oseltamivir was effective in reducing lower respiratory tract infections (LRTIs). The Cochrane 2005 report, which relied on this study also concluded that it was effective in reducing LRTIs.

Hayashi (Jefferson, et al, 2009) pointed out that the 2005 Cochrane report was flawed in that they didn't actually review the data of the individual studies themselves. In addition, he questioned the reliability of the Kaiser report as only 2 of these studies were actually published in peer reviewed journals (JAMA and Lancet). The other eight were not and were not available for review. He also notes a conflict of interest in that the authors of the Kaiser report included four employees and one paid consultant of F. Hoffman-La Roche (the manufacturer of oseltamivir). Hayashi also noted that in the two published studies, there was no significant difference between Oseltamivir and placebo in the incidence of LRTIs. He suggests that the only way to rely on the report is by a rigid appraisal of the other eight trials-which were not released by the drug company La Roche.

Cochrane was unable to obtain the data of the 8 unpublished studies for further analysis. This led Cochrane to conclude in 2009 that "paucity of good data has undermined previous findings for oseltamivir's prevention of complications from influenza. Independent randomized trials to resolve these uncertainties are needed." The question of a publication bias was also raised by Cochrane due to the fact that these results weren't published.

Doshi (2009), (a Cochrane author) goes so far as to suggest that oseltamivir is no better than NSAIDs, such as aspirin, in the treatment of influenza. He also notes the numerous contradictory reports in the clinical studies on the effectiveness of oseltamivir which casts doubts upon the reliability of the methods and information used to generate these reports. He criticizes the fact that government organizations have spent so much money on a drug before ascertaining the reliability of the data of its effectiveness. He notes that the Centers for Dis¬ease Control and Prevention (CDC) based their recommendations on the problematic Kaiser report.

The US government also partly based its national pandemic preparedness strategy on similar assumptions. As a result billions of dollars were spent building drug stockpiles, and oseltamivir was elevated to the status of a public health drug.

In 2014, Cochrane (published in BMJ 2014) released an update of a 5 year campaign it launched against Roche to obtain all the clinical study reports (CSRs)- which are extensive summaries of RCTs, on Tamiflu. Cochrane managed to pressure Roche into releasing all their data. They note that this is the first time all clinical study reports of trials in a manufacturer's program have been made available to readers without any restriction. The importance of this is the ability of researchers to assess the clinical trials for reliability, adherence to protocol, clarity of definitions and avoided reliance on conclusions of researchers who may have published biased material. It also allows for considerable more information on potential harms.

Cochrane notes that many discrepancies, problems and biases have been found in these trials. These include: Lack of clear definitions. For example there are eight definitions for laboratory confirmed influenza and no clear definition for influenza-like illness. Lack of reliability of the placebo. In many cases the placebo capsule had a different colored cap than that of the active capsule. This was not remarked on in the report. Many of the placebo capsules in oseltamivir trials contained dehydrocholic acid and dibasic calcium phosphate dihydrate. Both can cause gastrointestinal symptoms. Although the substances seemed to be in low doses, no discussion of their potential effects in people with fever was reported. Missing documents. This includes missing study protocols and amendments, study manuals of procedures and minutes of safety data monitoring committee meetings. Ghost authorship and lack of accountability. Authorship and accountability for the writing of many of the clinical study reports remains unclear. Some names on studies were redacted and no one seemed to claim responsibility for assembling and writing the reports. Missing data on duration and durability of symptom relief. Data on relapse after the five day treatment period were not reported in the clinical study reports.

There was also a mix-up with follow-up cards in a few of the trials which was not even reported in CSRs and only came to light from the FDA Summary Basis of Approval papers. There is ambiguity as to whether treatment of the flu shown through reduction of antibody titers was due to effectiveness of the viral

fighting activity of the drug or the immunosuppressant activity of the drug.

Cochrane 2014 concludes that oseltamivir is helpful for prophylaxis and modestly helpful in treatment (though they downplay its usefulness). In contrast to the assertion of various organizations Cochrane concludes that there is little evidence of significant benefits with regards to complications caused by influenza and viral transmission. Due to the above as well as the side effects, oseltamivir should be used cautiously. Due to all the discrepancies and poor quality of the studies, they question governmental sole reliance on this data to stockpile oseltamivir, its inclusion on the WHO list of essential drugs, and its use in clinical practice as an anti-influenza drug. This is especially true due to lack of sizeable benefits, and concerns of toxicity (Jefferson et al, 2014).

Cochrane study results

For Adults in Treatment trials: oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours-from seven days to 6.3 days. In treatment trials there was no difference in admissions to hospital.

For Adults in prophylaxis pre-exposure: oseltamivir reduced symptomatic influenza in participants by 55%. There was no significant effect on asymptomatic influenza (increase in antibody titers without symptoms). In post-exposure there are two components to interrupting transmissions of the virus. The reduction of viral spreading from nasal shedding and the prevention of onset of influenza in contacts.

Roche claims that it is effective, but there were serious flaws in the methods of the studies. This includes giving paracetamol which may have reduced viral shedding, and not checking antibodies in participants with potentially asymptomatic influenza. This leads to the conclusion that there is "no evidence of a reduction in transmission."

It is important to note that these studies specifically influenced WHO's policy of recommending this drug.

Harms for Treatment: increased the risk of nausea (risk difference 3.66%, 0.90% to 7.39%; number needed to treat to harm (NNTH) 28.) and vomiting (4.56%, 2.39% to 7.58%; 22, 14 to 42).

For Prophylaxis: oseltamivir increased the risk of psychiatric adverse events during the combined "on-treatment" and "off-treatment" periods (risk difference 1.06%, 0.07% to 2.76%; NNTH 94, 36 to 1538) and there was a dose-response effect on psychiatric events in two "pivotal" treatment trials of oseltamivir, at 75 mg (standard dose) and150 mg (high dose) twice daily (P=0.038).

Oseltamivir increased the risk of headaches on-treatment (risk difference3.15%, 0.88% to 5.78%; NNTH 32, 18 to 115).It increased renal events with treatment (0.67%,−0.01% to 2.93%), and increased nausea while receiving treatment (4.15%, 0.86% to 9.51%; NNTH 25, 11 to 116).

For child treatment it reduced influenza for otherwise healthy children by 12 to 47 hours with a mean difference of 29 hours. There was no effect in children with asthma. There was no significant difference in admissions to hospital. There was no significant effect on bronchitis, otitis media, sinusitis unverified pneumonia or any complication classified as serious or that led to study withdrawal. There was no significant difference in prophylaxis. In treatment of children, oseltamivir induced vomiting (5.34%, 1.75% to 10.29%; 19, 10 to 57).

Cochrane's call to governments

Compared with a placebo, taking Tamiflu led to a quicker alleviation of influenza-like symptoms of just half a day (from 7 days to 6.3 days) in adults, but the effect in children was more uncertain. There was no evidence of a reduction in hospitalizations or serious influenza complications; confirmed pneumonia, bronchitis, sinusitis or ear infection in either adults or children. Although when used as a preventative treatment, the drug can reduce the risk of people suffering symptomatic influenza, it is unproven that it can stop people carrying the influenza virus from spreading it to others.

Evidence from treatment trials confirms increased risk of suffering from nausea and vomiting. And when Tamiflu was used in prevention trials, there was an increased risk of headaches, psychiatric disturbances, and renal events.

Evidence also suggests that Tamiflu prevented some people from producing sufficient numbers of their own antibodies to fight infection.

Claims about the effectiveness of Tamiflu against complications were a key factor in decisions made by governments around the world to stockpile these drugs in case of a pandemic. The US has spent more than $1.3 billion buying a strategic reserve of antivirals, while in the UK the government has spent almost £424 million for a stockpile of about 40 million doses*.

It was initially believed that it would reduce hospital admissions and complications of influenza, such as pneumonia, during influenza pandemics. However, the original evidence presented to government agencies around the world was incomplete.

Along with the evidence of harms from the medication, it raises the question of whether global stockpiling of the drugs is still justifiable given the lack of reliable evidence to support the original

claims of its benefits. The BMJ and Cochrane issued a joint call to government and health policy decision makers the world over asking, in light of the latest findings from the Cochrane Review, would you make the same recommendations today, choosing to stockpile Tamiflu? (Breeze and Burns 2014).

Criticisms against the Cochrane reports

There are many that criticized the BMJ/Cochrane reports. The study was done in collaboration with channel 4 TV station in Britain. This may have led to a conflict of interests in overdramatizing a story for viewers. As Revere notes (Revere 2009) "Doing this in tandem with a media outlet whose objectives are not science but snagging viewers is unseemly at best and borders on the unethical".

An article in Nature (Noorden 2014) notes that it seems as if Cochrane, in their overzealousness to confront the big Pharmaceutical agencies have been "cherry-picking" the results to make them look worse for antivirals. Some of their statements have contributed to media misinterpretation that the drugs are 'ineffective' or 'useless'." For example: Cochrane writes " (oseltamivir) reduces symptoms of influenza by half a day" instead of the more precisely stating 18 hours for adults and 29 hours in children. In the 2009 report they also neglect to mention the prophylactic benefits. The Cochrane article obscures the therapeutic effect on decreased risk of diarrhea and cardiac system events by sandwiching them among the harms of the drug. A Cochrane author takes the extreme approach-not supported by evidence- of suggesting that Oseltamivir is no more effective than paracetamol.

It is important to note that Cochrane hasn't shown that antivirals didn't work for healthy people who got flu and were given a neuraminidase inhibitor to avoid more serious complications like pneumonia. It just alleged there was no "Cochrane-required-level-of-evidence" that they did prevent complications.

Cochrane only uses Randomized Controlled Trials (RCTs). These are studies in which volunteers are randomly assigned to get a treatment or a placebo and are considered the gold standard of evidence. Observational Studies that observe outcomes in people who receive a treatment don't make the cut because they are "unreliable for establishing treatment effects". However, often the observational studies are better at concluding the actual facts on the ground as opposed to the theory. For example, an observational study (Muthuri, 2014) of 30,000 people hospitalized during the 2009–10 swine-flu pandemic reported that neuraminidase inhibitors reduced mortality by 25%.

Although RCTs are considered the gold standard in of establishing effectiveness of a drug, they lack sufficient statistical power to allow reliable conclusions to be drawn about the effects on flu complications and hospitalizations- which are the key outcomes of interest during a flu pandemic. This is especially true noting that these small clinical trials were carried out to gain regulatory approval for Tamiflu as treatment and prophylaxis for seasonal flu. The trials were not designed to test for the severe outcomes that are most relevant to pandemics.

Additionally, The Metro (Branswell 2009) notes, sometimes it isn't possible to conduct randomized controlled trials. Sometimes observational data is the best evidence available.

For instance, it's unlikely any researchers could get permission to test Tamiflu against a placebo in people severely ill with H1N1. It would be considered unethical to withhold the drug from severely ill H1N1 patients if observational data suggested the drug might help.

Researchers worry that the Cochranes recommendation "we believe they should not be used in routine control of seasonal influenza" and the ensuing media storm of overly negative publicity risks undermining public confidence in this class of drug which will increase illness. Tamiflu is prescribed as the main treatment for serious cases of flu. Many experts say based on the observational data that these drugs work and have beneficial effects on severity of illness and preventing death. They are worried that we risk losing one of the few weapons we have. This is especially true based on the timing of the release and the lack of conclusive evidence that it doesn't work. "So here we are in the middle of a pandemic and the Cochrane folks, aided and abetted by the BMJ and television producers, are saying, "How do you know for sure that they will prevent pneumonia in an otherwise healthy person who gets flu?" There is evidence about this, even if the Cochrane zealots don't recognize it".

Evidence supporting the efficacy of Oseltamivir

It is hard to say that Oseltamivir is completely ineffective. One of the first human studies on the effectiveness of Tamiflu was published approximately fifteen years ago. In a 1999 study (Hayden et al) 117 healthy adult volunteers were inoculated with the influenza A virus. Two studies were conducted, one on prophylaxis where volunteers were given the drug 26 hours before inoculation and one on therapeutic treatment where they were given the drug 26 hours after inoculation. Treatment was continued for 5 days. In these trials, prophylaxis and early treatment with oral oseltamivir were both associated with significant antiviral and clinical benefits in experimental human influenza.

Prophylactic

Among the 12 evaluable placebo recipients, 8 (67%) had laboratory-confirmed infection and 6 (50%) had recovery of the virus from nasal washings. In contrast, of the 21 receiving oseltamivir

only 8 (38%) had laboratory confirmed infection and none of the 21 evaluable oseltamivir recipients had virus isolated.

The total symptom score area under the curve value was lower in the combined oseltamivir groups (n=21) compared with placebo (n=12); P=.02. Fourteen symptoms related to influenza were included in the score.

Therapeutic

Of the 69 with laboratory confirmed illness At 24 and 36 hours after initiating treatment, the median time to cessation of viral shedding was reduced from 107 hours in the placebo group to 58 hours in the combined oseltamivir group as shown in the graph. No virus was detected by 60 hours after infection. Effect of Oral Oseltamivir Treatment on Illness Following Experimental Influenza A/Texas/36/91(H1N1) Infection The total symptom score area under the curve value was lower in the combined oseltamivir groups (n=56) compared with placebo (n=13);

The total symptom score area under the curve value was lower in the combined oseltamivir groups (n=56) compared with placebo (n=13);

Dobson et al, 2015

In 2015 the Lancet published a study by Dobson et al. which shows that oseltamivir in adults with influenza accelerates time to clinical symptom alleviation, reduces risk of lower respiratory tract complications, and admittance to hospital.

The Cochrane reviews were based on meta-analysis of clinical trial study reports alone and not on individual patient data. In the Lancet study, Dobson et al did a meta-analysis of all available randomized treatment trials of oseltamivir-which includes both published and unpublished data (thereby overcoming previous concerns regarding potential publication bias). This analysis is first of its kind that reviewed individual patient data.

Nine trial studies were done between 1997 and 2001 involving 4328 participants. Participants were labeled as laboratory confirmed influenza-infected ("intention to treat infected") and Influenza-like ("intention to treat non- infected"). Participants were within 36 hours of feeling unwell- with a fever and at least two other influenza symptoms. They received 5 day regimens of Tamiflu with a 21 day follow up.

Limitations of these studies are that they weren't set up to test for relieving of respiratory complications As such, specific diagnostic tests were not used. Instead, in order to enhance reliable reporting of complications they incorporated "antibiotic use" in the definition of LTRIs. These tests were also not set up to determine prophylactic effects.

Effectiveness

Included are data from nine trials including 4328 patients. In the Influenza confirmed population (intention-to-treat infected population),

Alleviation of all symptoms for oseltamivir versus placebo recipients-21% shorter time of 25·2 h,

(The median times to alleviation were 97·5 h for oseltamivir and 122·7 h for placebo)

An estimated 44% reduction in risk lower respiratory tract complications requiring antibiotics more than 48 h after receiving oseltamivir (65 of 1544 participants given oseltamivir and110 of 1263 participants given placebo. Components were 56 versus 87 bronchitis, nine versus 21 pneumonia, and one versus four lower respiratory tract infections, respectively)

An estimated 63% risk reduction of admittances to hospital for any cause In the intention-to-treat (nine of 1591 participants had to be admitted to hospital for any cause versus 22 of 1302 participants given placebo). Participants given Oseltamivir had significantly less diarrhea, infections and infestations, and respiratory, thoracic and mediastinal disorders and fewer cardiac disorders. Regarding safety, increased the risk of nausea (9·9% oseltamivir vs 6·2% placebo), increased vomiting (8·0% oseltamivir vs3·3% placebo). No recorded effect on neurological or psychiatric disorders (although slightly higher with 150 mg). No serious adverse events.

Non-confirmed influenza (intention-to-treat non- infected population)

Oseltamivir was ineffective in non-confirmed influenza. This is consistent with the fact that Oseltamivir is an anti-viral. In some studies some researchers haven't distinguished between confirmed and non-confirmed influenza population. This will skew the results of efficacy of the drug being that it is not meant to treat non-confirmed influenza. Nevertheless, these results will more clearly resemble the effectiveness in real world situations where there is mix of these populations.

Conflict of interests

Dobson reveals that funding for his study was provided by the Multiparty Group for Advice on Science (MUGAS). They received an unrestricted grant from Roche but stipulated that Roche would not be involved in the actual review process in any way other than providing the requested data dictionaries and datasets. The results were not shared with Roche until the analysis was completed.

The author ASM reports fees from Biocryst and Roche outside of the submitted work. The author RJW reports fees as a board member of Gilead Sciences, funding for travel from Roche to attend an Influenza Resistance Committee meeting, and fees as Associate Editor of the Journal of Infectious Diseases.

CDC rejection of Cochrane Report

The CDC (CDC 2015) continues to promote antivirals such as Oseltamivir for treatment of the flu. The CDC promotes the "Take 3" campaign to fight the flu. Step 1 is to get vaccinated. Step 2 is taking preventative action to stop the spread of germs. Step 3 of the campaign encourages people to "take flu antiviral drugs if your doctor prescribes them."

In CDC (2014) an article entitled ""Have You Heard? CDC Recommendations for Influenza Antiviral Medications Remain Unchanged." The CDC addresses their recommendations and the Cochrane's criticism. Based on the observational studies published, the CDC says "treatment with a neuraminidase inhibitor antiviral drug was associated with a 25% reduction in the likelihood of death compared to no antiviral treatment. Early treatment with neuraminidase inhibitor antiviral drugs (i.e., within 48 hours of development of influenza illness) halved the risk of death compared to no antiviral treatment. This confirms findings from previous observational studies in hospitalized influenza patients that the clinical benefit of neuraminidase inhibitor antiviral treatment is greatest when started within two days of influenza illness onset."

The CDC states that their disregard for the Cochrane findings is because Cochrane did not consider any data from observational studies of oral oseltamivir. CDC adds that observational studies of antiviral treatment of seasonal influenza or influenza A (H1N1) pdm09 (2009 H1N1) have been conducted among hospitalized patients, including critically ill children and adults. Theses have consistently found that early oseltamivir treatment of influenza patients reduces the duration of hospitalization and risk of severe outcomes such as intensive care unit admission or death. CDC states that Cochrane RCT reviews of data on outpatients with clinically mild influenza-like illness is limited in by the narrow scope of participants. It is statistically underpowered and not designed to assess the effects of the medications on more severe influenza illness outcomes, such as hospitalizations, intensive care unit admissions, or deaths. RCT data is unavailable for those at highest risk for developing severe complications from influenza: hospitalized patients with severe influenza illness, the elderly, young children, pregnant women, and persons with underlying medical conditions such as chronic obstructive pulmonary disease (COPD), asthma, congestive heart failure and diabetes.

They conclude "available evidence for seasonal influenza and 2009 pandemic H1N1 virus infections consistently indicates that antiviral treatment, when initiated as soon as possible, can have clinical and public health benefits in reducing severe outcomes of influenza. Therefore, neuraminidase inhibitor antiviral medications continue to be recommended for treatment of influenza."

BMJ/Cochrane response to CDC and Lancet

In a response article written by the BMJ's Jeanne Lenzer "Why aren't the US Centers for Disease Control and Food and Drug Administration speaking with one voice on flu? " (BMJ 2015) Lenzer raises allegations regarding the reliability of CDC. She accusing them of being "more emotional than scientific" and notes that they are at odds with the FDA Who have said oseltamivir "has not been proven to have a positive impact on the potential consequences (such as hospitalizations, mortality, or economic impact) of seasonal, avian, or pandemic influenza." She considers the CDC's reliance on the Lancet review as unreliable. This is because the authors have not made their study protocol available for critique nor have they released an appraisal of the methodological quality of each study. She concludes by raising the concerns that the policies of the CDC and Lancet review have been influenced by funding from the Pharmaceutical companies. The CDC Foundation confirmed to The BMJ that the CDC received a directed donation from Roche for the campaign, stating, "Roche provided a grant of $198 000 to CDC Foundation [which] has an administrative fee of 13.5%, so $174 800 was provided to [the CDC to] support qualitative research into influenza prevention and treatment messaging." The CDC Foundation also receives funding from the pharmaceutical industry. A spokesperson said that over the past three years the foundation has received an average of around $6.3m annually from the industry, 21% of the foundation's overall funding. Some of the companies who have provided funds include Gilead, which holds the patent on oseltamivir, as well as Genentech and Roche, the drug's manufacturers. This greatly discredits the CDC's credibility as a nonbiased party.

The Lancet's Funding

The Lancet study itself was conducted through MUGAS which was funded by an open grant from Roche- as the study noted. Lancet asserts that neither they nor the study itself were influenced in any way by Roche. Additionally, neither MUGAS nor Roche saw the results of the study before publication.

Also two of the researchers note that they have had ties in the past to Roche. A third researcher, Stuart Pocock didn't list any conflict of interest on the research paper, but revealed to The BMJ that he has received funding from several drug companies for cardiovascular research, including Gilead and Genentech, but that none of his funding was related to the study of antivirals for flu.

Paul Roblin in his BMJ blog notes Although the name Multiparty Group for Advice in Science (MUGAS) might lead you to imagine an independent body bringing together representatives of a number of organizations to consider a range of issues, MUGAS is funded by Roche and is led by four scientists, three of whom are advisers to Roche. It appears to have been set up specifically as part of the attempt to counter the Cochrane's criticisms. He also notes that there is a complex set of inter-related organizations that supported the Lancet study and receive funding from Roche and Gilead. Also, one the Lancet authors and MUGAS have many more connections to the CDC, Roche and Gilead than they disclosed. One of the researchers for the Lancet article, Professor Richard J Whitley joined Gilead's board of directors in 2008 and works with/for the CDC.

Conclusion

All parties agree about the following: Oseltamivir is effective in reducing symptoms by at least 16 hours. Oseltamivir works reasonably well for prophylaxis. Oseltamivir has significant side effects including psychosis in prophylactic patients.

The main debate is whether it reduces secondary complications, hospitalizations and spread of disease. The debate also centers on whether it is justifiable to prescribe oseltamivir in the face of significant side effects. Also questioned is the wisdom of governmental stockpiling of billions of dollars of Tamiflu. The critics of oseltamivir, most prominently Cochrane/ BMJ point to the dearth of high quality evidence. Their opponents base their opinions on observational data, which is less rigorous, but compelling nonetheless. At the present, clinical practice favors action i.e. the use of oseltamivir for both prophylaxis and treatment. The clinical decision supporting resource "UpToDate" continues to recommend treatment with the anti-virals as per the recommendation of the CDC and the IDSA. This is based on the observational study data that shows its effectiveness. It seems that the current consensus in Hospitals is to give Tamiflu as a first line defense both for prophylaxis and for treatment. Although evidence shows it may not be as effective as we once thought, this is basically our only defense against influenza. In hospitalized patients with preexisting complications we wish to take all possible precautions. This author wishes to point out that such an approach is defensible only in an environment in which cost of treatment (financial and side effect) is not prohibitive. We wonder whether this calculus would be different elsewhere.

Many things can be learned from the Tamiflu controversy. Firstly, as demonstrated by Cochrane, one may err in assuming that because a paper is published in a peer reviewed journal all the evidence is reliable. Especially when an important decision must be made the data should be reviewed for accuracy, reliability of methods and lack of bias. Secondly, as suggested by Cochrane, the trustworthiness of decision making by government bodies should be questioned. In any situation, conflict of interest may be present. Thirdly, as suggested by their critics, was the Cochrane disingenuous in completely ignoring observational data supporting use of Tamiflu? And were the Cochrane writers sensationalists in their conclusions and media communications?

References

Air. (2012) Influenza neuraminidase. Influenza and Other Respiratory Viruses 6(4), 245–256.

Bloom JD, Gong LI, & Baltimore D (2010). Permissive secondary mutations enable the evolution of influenza oseltamivir resistance. Science (New York, N.Y.), 328 (5983), 1272-5 PMID: 20522774

BMJ 2014;348:g2545

BMJ 2015;350:h658

Branswell, Helen. "British journal, TV network question value of Tamiflu for seasonal flu." 9 11 2009. http://www.metro.us/. 15 06 2015 <http://www.metro.us/news/british-journal-tv-network-question-value-of-tamiflu-for-seasonal-flu/tmWili---9crzJOYS8kVzQ/>.

Breeze, Katie and Burns, Stephanie "Tamiflu & Relenza: how effective are they?" 10 April 2014. community.cochrane.org. 15 06 2015 <http://community.cochrane.org/features/tamiflu-relenza-how-effective-are-they?>.

CDC. "Flu View." 14 March 2015. http://www.cdc.gov/. 15 06 2015 <http://www.cdc.gov/flu/weekly/pdf/External_F1510.pdf>.

CDC. ""Have You Heard?"." 10 04 2014. http://www.cdc.gov/. 15 06 2015 <http://www.cdc.gov/media/haveyouheard/stories/Influenza_antiviral2.html>.

Cohen et al.: Influenza A penetrates host mucus by cleaving sialic acids with neuraminidase. Virology Journal 2013 10:321.

Dobson, Joanna, et al. "Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials." The Lancet 385.9979 (2015): 1729-1737.

Doshi, Peter. "Neuraminidase inhibitors--the story behind the Cochrane review." BMJ 339.dec07_2 (2009): b5164.

Flint, S. Jane, Lynn W. Enquist , Vincent R. Racaniello, Anna Marie Skalka. Principles of Virology. ASM Press, December 1, 2008.

Gamblin, Steven J., and John J. Skehel. "Influenza Hemagglutinin and Neuraminidase Membrane Glycoproteins." The Journal of Biological Chemistry285.37 (2010): 28403–28409. PMC. Web. 26 May 2015.

Hayden FG, Treanor JJ, Fritz R, et al. Use of the Oral Neuraminidase Inhibitor Oseltamivir in Experimental Human Influenza: Randomized Controlled Trials for Prevention and Treatment. JAMA. 1999;282(13):1240-1246. doi:10.1001/jama.282.13.1240.

Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. BMJ2009;339:b5106.

Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, Spencer EA, Onakpoya IJ, Mahtani KR, Nunan D, Howick J, Heneghan CJ. Neuraminidase inhibitors for preventing and treating influenza in adults and children. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD008965. DOI: 10.1002/14651858.CD008965.pub4.

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(14):1667-1672. doi:10.1001/archinte.163.14.1667.

Kimon C Zachary, MD. "Treatment of seasonal influenza in adults." n.d. www.uptodate.com. 14 June 2015

Matrosovich, Mikhail et al. "Early Alterations of the Receptor-Binding Properties of H1, H2, and H3 Avian Influenza Virus Hemagglutinins after Their Introduction into Mammals." Journal of Virology 74.18 (2000): 8502–8512. Print.

Mubareka, Samira, et al. "Transmission of influenza virus via aerosols and fomites in the guinea pig model." Journal of Infectious Diseases 199.6 (2009): 858-865.

Muthuri, S. G. Lancet Resp. Med. http://dx.doi.org/10.1016/S2213-2600(14)70041-4 (2014).

Noorden, Richard Van. "Report disputes benefit of stockpiling Tamiflu." Nature doi:10.1038/nature.2014.15022 (10 April 2014).

Pringle, BSc, PhD. Merck Manuals. April 2014. 26 05 2015 <http://www.merckmanuals.com/professional/infectious-diseases/respiratory-viruses/influenza>.

Racaniello, Vincent. "Influenza 101." 2013. Virology 101. 14 June 2015

Revere. "The Tamiflu doesn't work non-story." 10 11 2009. scienceblogs.com. 15 06 2015 <http://scienceblogs.com/effectmeasure/2009/12/10/the-tamiflu-doesnt-work-non-st/>.

Roblin, Paul. ""Paul Roblin on Dobson et al's Lancet Tamiflu re-analysis: an independent review group. Really?"." n.d. Blogs. BMJ.com.

Russell, Rupert J. Lesley F. Haire, David J. Stevens, Patrick J. Collins, Yi Pu Lin, G. Michael Blackburn, Alan J. Hay, Steven J. Gamblin & John J. Skehel. "The structure of H5N1 avian influenza neuraminidase suggests new opportunities for drug design." Nature (16 August 2006).

Tscherne, Donna M., and Adolfo García-Sastre. "Virulence Determinants of Pandemic Influenza Viruses." The Journal of Clinical Investigation 121.1 (2011): 6–13. PMC. Web. 26 May 2015.

Wagner, Ralf, Mikhail Matrosovich, and Hans-Dieter Klenk. "Functional balance between haemagglutinin and neuraminidase in influenza virus infections."Reviews in medical virology 12.3 (2002): 159-166.