Surviving the 'Storm':
Expanding Public Health's Capabilities in Response to the Increasing Threats Posed by Novel, Pandemic Strain Viruses

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ABSTRACT

The recent emergence of two separate outbreaks of two new viruses has generated renewed interest in the threat of pandemics. For a significant portion of the total fatalities associated with these infections the cause of death was due to an over-reaction of an infected body's immune system. This research explores possible pharmaceutical interventions that would help expand the list of options public health could employ in a response. For inclusion in state stockpiles, medications must meet three specific criteria: medical efficacy, cost, and logistical considerations. We identified four medications that could be employed (three statins - atorvastatin, simvastatin, and gemfibrozil and an antiviral – ribavirin) and present options for their inclusion into state stockpiles. Through this research we have attempted to open a dialogue with other federal and state planners as they wrestle with the same challenges within their home agencies.

INTRODUCTION

While the Ebola crisis in Africa has recently captured the media's attention, influenza and other pandemic strain viruses remain by far the largest killer viruses facing the U.S. Seasonal flu-associated deaths in the United States have ranged from about 3,000 per season to about 49,000 per season.[1] Over the span of fifteen years public health has witnessed a series of pandemic viruses. In the late 1990s the world watched the emergence of the H5N1 avian influenza virus (that continues to smolder in Asia). In 2003 the SARS coronavirus erupted out of southeast China. And in 2009 the H1N1 influenza pandemic emanated out of Mexico. The recent emergence of two separate and concurrent outbreaks of two new viruses-- the H7N9 type-A influenza emanating from southeastern China and, the Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) coming out of northeastern Saudi Arabia-- has generated renewed interest in the threat of pandemics.[2] Science tells us that these naturally occurring pandemics are both normal, and to some extent, cyclical: it is not a matter of '*if*' humanity will see some sort of pandemic strain viral pandemic, but '*when*.'[3]

Although the 1918 Influenza and 2003 SARS Outbreak are separated by eighty-five years and decades of medical advances, the biological processes that take the lives of those who succumb to either of these illnesses are quite similar. Each of these infections is an invasion of a novel virus into the human body's respiratory system. For a significant portion of the total fatalities associated with each of these infections (some researchers have attributed as much as 50%), the cause of death was often described as 'viral pneumonia' as opposed to traditional bacterial pneumonia. In the intervening years since the 1918 event, physicians have developed a term for this pathological process that puts extreme stress on the lungs: Acute Respiratory Distress Syndrome (ARDS). Almost unique to each of these illnesses, this syndrome is an over-reaction of an infected body's immune system to contain and defeat an invading pathogen.[4] For this reason, we will consider novel influenza and novel pandemic strain viruses together in this manuscript since they pose a similar treatment conundrum.

Since the SARS outbreak in 2003, there has been a vast amount of research devoted to developing treatment strategies to combat ARDS. The literature on the effectiveness of these emerging treatment strategies is mixed

at best, but several of them may be useful for treating future novel viruses. Many states have existing stockpiles of medications originating from the CDC release in preparation for the 2009/2010 H1N1 epidemic.[5] Stockpiles are a difficult question for states to tackle because they are often for illnesses that may not yet exist (e.g. a novel strain that has yet-to-mutate), they require a sizeable investment of resources upfront, and they require sizeable time/effort/resources to properly maintain over long periods. While we do not address all of these state-specific fundamental issues, we do examine potentially useful options for a state wishing to supplement its existing stockpile of medications to provide some capabilities when confronting ARDS. This research is the first attempt to plan policy for this type of scenario.

Pandemics are of particular concern because disease is truly widespread, typically global, and frequently associated with a more virulent strain of virus (with the ensuing increase in fatality rates). Even if one of these novel influenza or pandemic strain viruses is only affecting a single country or state, there is still concern because the treatments required may quickly overwhelm existing capabilities. Depending on the ability to obtain supplies rapidly in an epidemic, it may become necessary to consider developing stockpiles. While the private sector health care system provides medical treatments, it is not required to maintain a stockpile of prescription medications or personal protective equipment. The private sector healthcare system may keep a few days' worth of supplies, but functions under the assumption that it can be readily resupplied. In case of a widespread disease, this assumption may no longer hold true, so the private sector healthcare system would suddenly need to rely on the state and federal public health resources to adequately resupply it with the needed medications and equipment.

The United States has invested significant time/energy/resources in preparation for a large-scale biological event. One of these investments in biosecurity led to the U.S. Centers for Disease Control and Prevention (CDC) creating and maintaining its Division of Strategic National Stockpile, which maintains a "$3.5B portfolio of antibiotics, medical supplies, antidotes, antitoxins, antivirals, vaccines, and other pharmaceuticals" in the strategic national stockpile (SNS).[6] A large proportion of the SNS is comprised of antibiotics and antivirals, so from a planning perspective, state and local public health agencies would likely be able to provide medications needed to treat bacterial pneumonia cases.[7] However it is unclear the extent to which those materials would be useful in countering the deadly effects of ARDS within patients during a pandemic. In order to be better prepared, a state may choose to supplement its existing stockpile to include medications that may prove useful in combatting ARDS. There are many options in various stages of development for such a stockpile, and the issue is how to identify good candidate medications. In particular, a good candidate medication would be one that has the greatest chance of having medical efficacy with a novel pandemic strain virus, one that is affordable to procure, and one that can be stored in existing stockpile facilities. Therefore, this paper will consider three specific criteria: medical efficacy, cost, and logistical considerations. Medical efficacy is considered in Section 1, Review of Medical Treatment Options. Cost, affordability, and logistical considerations are addressed in Section 2, Stockpile Considerations. Logistical considerations are limited to being able to incorporate the medication into existing stockpile facilities. Next, we estimate the approximate number of treatments (full courses of the medication) that would be required for the state and then determine the cost of this stockpile of medications using a widely available website. The State of Nevada is used as an example for these calculations, but other states can easily implement this methodology to obtain estimates for their situation. Next, the section explores what would be funding limits that could be considered as "affordable" by states. Section 3 provides the results of limiting medically efficacious therapies by the affordability constraint and the logistical stockpile constraint to provide a set of potential therapies that a state could consider including in their stockpile. Section 4 discusses the limitations of the analysis. The final section provides a discussion of possible options

available to states that decide to enhance and supplement their existing stockpiles to be able to combat ARDS.

Review of the Medical Treatment Options

The current body of knowledge surrounding potential treatment options for influenza and pandemic strain viruses appears to focus on two mechanisms to reduce disease in people who are severely ill: 1) limit virus replication in the host cell; and/or, 2) suppression of the body's hyper-immune response to inhibit ARDS. The literature revealed five classes of drugs that have demonstrated an ability to either inhibit virus replication, or to suppress the immune system: 1) antivirals; 2) statins; 3) interferons; 4) corticosteroids; and, 5) herbal/alternative medications. In the following sections, we discuss how each of these medications can have a beneficial effect in treatment and we provide a summary of the extent of the experimentation with their use. We do not consider potential side-effects as they are numerous, varied, and patient specific as to which will occur.

Antiviral Medications

When an invading virus approaches a possible host cell, it needs a 'key' to enter the host cell's outer wall. This process is achieved by a protein on the virus' surface called hemagglutinin (H or HA). Influenza viruses have sixteen (16) of these H proteins on their surface; so from the virus' perspective, they have sixteen possible 'keys' to try upon the host cell's outer wall. If the correct key is matched to the correct keyhole then the virus is allowed to open and pass through the cell's outer wall. Once that happens, the invading virus hijacks the host cell's replication system and makes thousands (to millions) of copies of itself, which usually results in the host cell's death. When that process is complete, those new copies of the virus once again need to pass through the outer wall of the host cell; except this time they need to go from the inside of the cell to the outside of the cell. In order to achieve that, each virus has another set of surface proteins called neuraminidase (N or NA). Influenza viruses have nine (9) of these N proteins on their surface; so from their perspective they have nine possible keys to try from inside the host cell's outer wall.[8]

Antivirals work either by blocking some/all of the sixteen H keyholes (hemagglutinin inhibitors) or by blocking some/all of the nine neuraminidase keyholes (neuraminidase inhibitors). This process helps to limit virus replication, thus lowering host cell infection. The current state stockpiles of Oseltamivir/*Tamiflu*® and Zanamivir/*Relenza*® are good examples of neuraminidase inhibitors.[9]

Statin Medications

Most of us would recognize statins for their traditional role in lowering cholesterol in the bloodstream. However, statins also have both an anti-inflammatory and an immune-modulatory effect. It is these additional benefits to statin use that authors like Fedson, Vandermeer, and Walsh discuss in relation to pandemic strain influenzas.[10] Statins do not impact virus replication, yet they do help to suppress the body's immune response. They are being explored as a potential treatment to ARDS.

Interferon Medications

Although interferons would technically be listed as antivirals, we have separated them from that class because of their unique mode of action. These naturally-occurring proteins are made and secreted by the cells of our body's immune system. They come in three classes: alpha (used to treat cancers and viral infections); beta (used to treat multiple sclerosis); and gamma (used for treating chronic granulomatous disease). The mechanism of action of interferons is not well understood, but this class of medications helps to modulate the body's immune system response to challenges from viruses, bacteria, cancers, and foreign substances that impact the body. Although interferon alphas do not directly kill viruses, they do help to boost the body's immune system, and to prevent a hyper response by that system.[11] Although interferon is more commonly discussed as a treatment

for diseases such as leukemia, AIDS-related Kaposi's sarcoma, or chronic hepatitis B and C, there is also an extensive literature about using it to enhance the body's immune system against pandemic strain influenzas, as well as novel HCo-Vs (specifically *interferon-α2b*).[12]

Corticosteroid Medications

This class of medication is similar to the natural hormones produced within our bodies that help to control many important functions such as blood sugar levels, salt levels, as well as our immune system's function. These medications are often used to help treat diseases that cause inflammation, which novel viruses would most likely cause within the human lung following infection.[13] This class of medication works by blocking substances within the human body that cause swelling. During the 2003/2004 SARS epidemic corticosteroids (generally) fell out of favor with the medical community because they suppressed the entire immune system: both the good and the bad components of that system's response.

Herbal / Alternative Medications

The literature often describes these medications as being "complementary" and "anti-inflammatory" in nature, with their effects primarily targeted on the host response rather than the virus replication. The Alleva et al. article includes a long list of Chinese herbs that are often described as 'adjunct treatment therapies' to antivirals.[14] Although these herbal medications are not currently licensed within the U.S., they do warrant further research and analysis.

Comparison

In order to be considered for a state stockpile, a medication needs to have demonstrated a baseline medical efficacy in treating and handling medical complications associated with novel pandemic strain viruses. Table 1 presents a summary of different therapy options discussed in the literature. The '*Uses*' columns describe the different uses for each therapy. The '*Medical Efficacy*' columns provide a synopsis of the therapy's expected medical impacts on patients ill with a pandemic strain virus. The next two columns, The '*Pros*' and *'Cons,'* provide a brief summary of positive and negative aspects associated with the therapy as discussed in the literature. As with almost any medication, long term immunity is not imparted upon the patient (as would be achieved through immunizations); so this is a *Con* for all listed therapies.

Table 1: Comparison of Different Therapy Options
- Pros - Positive aspects associated with the medication as discussed in the citations
- Cons - Negative aspects associated with the medication as discussed in the citations

Mono-Therapy *Class: Antivirals*

Oseltamivir (neuraminidase inhibitor)			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications	• Already in national/state stockpiles • Familiar to clinicians & public health • Easily stored long term • FDA licensed for influenza type A and B	• Possibly mismatched to virus strain • Drug Resistance • When used as prophylaxis, repeated regimens must be used

Citations - CDC[15], Beigel, Bray[16], Moscona[17], Cooper et al.[18], Treanor et al.[19], Nicholson et al.[20], Aoki et al.[21], Salomon et al.[22]

Relenza (neuraminidase inhibitor)			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications	• Already in national/state stockpiles • Familiar to clinicians & public health • Easily stored long term • FDA licensed for influenza type A and B	• Mismatched to strain • Drug Resistance • When used as prophylaxis, repeated regimens must be used

Citations - CDC[23], Moscona[24], Hayden et al.[25], Cooper et al.[26], Makela et al.[27], Salomon et al.[28]

Amantadine (adamantane drug)			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications	• Affordable • Easily stored long-term	• Only approved for influenza type A • Drug resistance problems

Citations - CDC[29]

Rimantadine (adamantane drug)			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications	• Affordable • Easily stored long-term	• Only approved for influenza type A • Drug resistance problems

Citations - CDC[30]

Ribavirin (nucleoside antimetabolite drug)			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications • Experimental	• Easily stored long-term • Generics Available	• Not in stockpiles • New to public health • Can induce anemia and/or toxicity issues

Citations - van Vonderen et al.[31], Hayden[32], Chan-Tack et al.[33], Salomon et al.[34]

Mono-Therapy Class: Statins

Atorvastatin (Lipitor®), Rosuvastatin (Crestor®), Simvastatin (Zocor®), Gemfibrozil (Lopid®)			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Treatment	• Lowers Immune Response	• Generics are affordable • Readily accessible • Familiar to care givers • Not virus-strain specific	• Some key data linked to animal-only studies

Citations - Fedson[35], Walsh[36], Kumaki et al.[37]

Mono-Therapy *Class: Interferons*

Interferon-α2b *Intron-A*			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Treatment	• Lowers Immune Response	• Provide a treatment option if drug resistance issues to AVs arise • Effective against a wide range of influenza viruses	• Expensive • Cold chain issues • Of the three types of interferons (alpha, beta, gamma) alpha primarily affects influenza viruses and beta affects HCo-Vs

Citations - Cinatl et al.[38], Katze et al.[39]

Interferon-α2b *PegIntron*			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Treatment	• Lowers Immune Response	• Provide a treatment option if drug resistance issues to AVs arise • Effective against a wide range of viruses	• Expensive • Cold chain issues • Of the three types of interferons (alpha, beta, gamma) only alpha affects influenza viruses and HCo-Vs

Citations - Cinatl et al.[40], Katze et al.[41]

Interferon-ß1a Avonex			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Treatment	• Lowers Immune Response • Experimental	• Provide a treatment option if drug resistance issues to other AVs arise • Effective against HCo-V	• Expensive • Cold chain issues • Of the three types of interferons (alpha, beta, gamma) beta impacts HCo-Vs • Small sample size of studies

Citations - Hensley et al.[42], Morgenstern et al.[43]

Interferon-ß1a Rebif			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Treatment	• Lowers Immune Response • Experimental	• Provide a treatment option if drug resistance issues to other AVs arise • Effective against HCo-V	• Expensive • Cold chain issues • Of the three types of interferons (alpha, beta, gamma) beta impacts HCo-Vs • Small sample size of studies

Citations - Hensley et al.[44], Morgenstern et al.[45]

Mono-Therapy Class: Corticosteriods

Prednisone			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Treatment	• Lowers Immune Response • Anti-inflammatory properties	• Easily accessible • Familiar to clinicians & public health	• Performed poorly against SARS • Limited efficacy overall

Citations - Con: Oba[46], Pro: Bernard et al.[47], Neutral: Stockman et al. [48]

Mono-Therapy Class: Herbal Medicines

Uses	**Medical Efficacy**	**Pros**	**Cons**
Treatment	• Lowers Immune Response • Experimental	• Useful adjunct treatments • Targets the host response rather than the virus itself	• Not FDA approved • Limited data

Citations - Alleva et al.[49], Li et al.[50]

Combo-Therapy

Oseltamivir + Relenza			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications • Experimental	• Synergistic effect • Already in national/state stockpiles • Familiar to clinicians & public health • Easily stored long term	• Possible drug resistance issues • When used as an ongoing prophylaxis stockpiles are consumed quickly • Animal models in many studies

Citations - Govorkova et al.[51], Barik[52]

Oseltamivir + Ribavirin			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications • Experimental	• Synergistic effect • Easily stored long term	• Limits virus replication, but has no impact on immune system's response • Ribavirin: causes hemolytic anemia in high doses, high toxicity, and has relatively small therapeutic index

Citations - Govorkova et al.[53], Barik[54]

Relenza + Ribavirin			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications • Experimental	• Synergistic effect	• Limits virus replication, but has no impact on immune systems' response • Ribavirin: cause hemolytic anemia in high doses, high toxicity, and has relatively small therapeutic index

Citations - Govorkova et al.[55], Barik[56]

Peramivir + Ribavirin			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications • Experimental	• Synergistic effect	• Limits virus replication, but has no impact on immune systems' response • Peramivir is approved in Japan and Korea only

Citations - Govorkova et al.[57]

Amantadine + Ribavirin			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications • Experimental	• Enhanced inhibitory effect • Synergistic effect	• Limits virus replication, but has no impact on immune system's response • Amantadine has been identified to have many drug resistance issues

Citations - Govorkova et al.[58], Barik[59]

Antivirals + Statins			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications • Lowers Immune Response • Experimental	• Addresses virus replication issues and immune system hyper response issues concurrently • Some AVs already in state/federal stockpiles • Statins are easily accessible and familiar to clinicians	• Still being researched and tested • Small sample size in some studies • Statins are not in SNS/state stockpiles

Citations - Govorkova et al.[60], Barik[61]

Interferon-α2b + Ribavirin, PegIntron/Rebetol Combo Pack			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications • Lowers Immune Response • Experimental	• Synergistic effect • Proven to have an effect against novel viruses • Provides another Tx option during pandemics • Each component is commonly used in clinic settings	• Comes as an injectable medication only • From SARS: "May improve outcome, but a definitive treatment regimen was not clearly established" (see Falzarano reference)

Citations - Falzarano et al.[62]

Interferon-α2b + Ribavirin, PegIntron/Rebetol Combo Pack			
Uses	**Medical Efficacy**	**Pros**	**Cons**
Prophylaxis Treatment	• Decreases Virus Replications • Lowers Immune Response • Experimental	• Synergistic effect • Proven to have an effect against novel viruses • Provides another Tx option during pandemics • Each component is commonly used in clinic settings	• Comes as an injectable medication only • From SARS: "May improve outcome, but a definitive treatment regimen was not clearly established" (see Falzarano reference)

Citations - Falzarano et al.[63]

Table 1 reveals many varying recommendations on whether/if these therapies should be used, and if so, whether as a treatment, as post-exposure prophylaxis, or as a combination of the two. Unfortunately, we cannot provide a measure of relative efficacy between these therapeutic options. This is due to the fact that the source information on the medication efficacy comes from the evidence of their use gathered during prior pandemic strain illnesses and/or in laboratory or experimental settings. This presents a two-fold issue: 1) a novel virus is by definition new, so we cannot be certain that the medications will provide the same benefits at the same levels as seen with existing viruses 2) there is no way to conduct comparative clinical trials of the medications so a true comparative efficacy cannot be established. The only two categories we will drop from further consideration are herbal remedies, as they are not FDA approved and there are no conclusive clinical studies on their efficacy, and Peramavir, as it is still in Phase II clinical trials in the US (and hence still several years from receiving FDA approval). All of the medications that we consider in this paper have shown at least baseline levels of efficacy in treating influenza and pandemic strain viruses and their complications.

Stockpile Considerations

Given a basic level of potential medical efficacy, the remaining medications are further screened in Table 2 to determine whether or not they are viable candidates for a state stockpile. The three criteria we consider are additional medical considerations, cost, and logistical considerations. Additional medical considerations include two categories which indicate whether the medication is known to be kept in the strategic national stockpile (SNS) and whether the medication is familiar to physicians. If medications are known to be

already in the SNS, then states are much less likely to spend scarce resources on medications that already may be obtainable from a federal source. In addition, many states already have some of these medications on-hand in smaller scale stockpiles left over from the 2009/2010 'push' of what the CDC released in preparation for the prolonged response to H1N1. Therefore, when we consider what the SNS already has in its inventory, matched with what states still have left over from H1N1, we assume that these medications would not be considered a good choice for a state stockpile. In addition to these issues surrounding existing accessibility to stockpiled medications, we also consider whether or not physicians are familiar with these medications. A strength of any stockpile would be not only its accessibility, but also its acceptability by clinicians to employ it. If stockpiled medications are unfamiliar to caregivers, then they may be less likely to call on them in times of need.

Since pandemics are, by definition, large in scale and wide-ranging, the amount of doses/regimens that would need to be procured for a state stockpile will be substantial. Given the fiscal limitations that states face, compounded with declining federal funds provided through various public health preparedness grants, the medication procurement costs would need to be affordable. While there is no set definition of "affordable", we chose to limit the price tag to a proposed recommendation of 1% of a state's total public health preparedness (PHP) annual budget. This percentage was chosen based on what the Nevada PHP program has retrospectively been able to afford. This percentage may vary by state.

State PHP programs will need to rely on their existing climate controlled bulk-storage warehousing capabilities that were developed during the 2009/2010 HIN1 response. To be considered as a viable pharmaceutical therapy for a state stockpile, the medication must be capable of being stored in climate controlled facilities long-term, and must have no cold-chain requirements.

Estimating Costs of Stockpile

While medical and logistical considerations are readily available online, the process to determine cost implications requires additional calculations and assumptions. It is important to highlight that these cost estimates are only rough estimates; more precise calculations would require exact treatment guidelines which will be developed only after the emergence of a specific novel virus.

To calculate the costs of a stockpile, we need to estimate two items: 1) the number of treatments that will be needed (i.e. how many people do we think may require treatment), and 2) the amount of medication that may be used in an individual treatment (which provides the amount of medication needed to complete a full treatment course for a single individual). To estimate the number of treatments needed, we relied on the CDC website's *FluAid 2.0* downloadable software to project a range (e.g., minimum (min), mean, and maximum (max)) of the number of individuals who will require treatment. The software provides three rates which can serve as a basis of the calculation: 1) the '*Gross Attack Rate*' (GAR), which measures how many people will become clinically ill from a novel influenza virus (clinical illness is defined as a case that causes some measureable economic impact) 2) the '*Hospitalization Rate*', which measures the number of people who fall clinically ill who would require hospitalization, and 3) the '*Mortality Rate*', which measures the number of clinically ill patients who will lose their lives.[64]

While the GAR gives estimates of the total number of people who may fall ill from a novel virus, the range of 'illness' can span anything from 'barely noticeable' to 'life threatening,' and hence, it may include too large a segment of our population to be of any real use. The hospitalization rate calculation narrows our focus to those patients for whom we would be most interested in providing potentially life-saving medications (i.e. to those who are ill enough to require hospitalization). This will be an underestimate of those seeking treatment, but given the limited response capabilities that

we project, it would not be unreasonable to restrict treatment to this group. The mortality rate calculations are useful in that they describe to us how many people we stand to lose if we do nothing, but they are too narrow for treatment planning. We would want/need to introduce these medications prior to knowing exactly which patients will succumb to the disease. An additional benefit of using the hospitalization rate as the basis for our calculations stems from the fact that it assumes that patients who will be treated will be in a clinical environment where potential intravenous drug therapies may be administered properly, if any such are found to be suitable for state stockpiles.[65]

Nevada has a total of 2,775,216 residents (as of October 1, 2013), with 766,414 of those falling within the 0-19 year old group, 1,656,765 in the 20-64 year old group, and 352,038 in the 65+ group.[66] These age groups were further split into high risk and non-high risk sub-groups using the Meltzer, Cox and Fukuda rates cited on the CDC's FluAid 2.0 website.[67] For the state of Nevada the software predicts the total number of hospitalizations to be 1,580 at minimum, with a mean of 4,970 and a maximum of 10,112 hospitalizations. Similar calculations can be done for every state or region considering adding to its stockpiles.

While the CDC *FluAid 2.0* software used in the previous section is specific to pandemic influenzas, without any comparable estimating techniques for other viruses such as novel HCo-V, we chose to use these estimates as a basis for any potential novel viruses.

To estimate the amount of medication needed in an individual treatment, we need to make some assumptions about the treatment regimen. Since we are considering strains of virus that may not yet even exist, we decided to use the standard multi-day therapy provided on the GoodRx website (www.goodrx.com). If the GoodRx website does not provide a specific multiday regimen, a generic '*one pill/capsule per day for ten days*' treatment regimen is applied.

We developed cost estimates for the min, mean, and max hospitalization rates for Nevada and the treatment regimens outlined above using the GoodRx website.

Estimating State Funding Limits

For many states, including Nevada, their state and local PHP programs are completely funded by an aligned federal grant formed by the Hospital Preparedness Program (HPP) and the Public Health Emergency Preparedness (PHEP) cooperative agreement.[68] The CDC publishes the amount of funding awarded to each state and territory.[69] According to the CDC's publication for Fiscal Year 2013, the state of Nevada receives approximately $9.7M in funding. The one percent funding limit for Nevada is therefore $97K.

Table 2 shows the additional medical considerations, the logistical considerations, and the cost considerations (based on Nevada's estimated costs) for each of the treatment options identified in Table 1. The first column identifies whether or not the therapy is known to be in the SNS and whether the therapy is familiar to physicians. The second column provides the cost associated with obtaining treatment to be able to handle the minimum, mean, and maximum estimated hospitalization rates. The final column identifies whether or not the therapy can be contained in existing bulk storage facilities. If the answer is "No", this implies that the therapy requires cold chain storage (i.e. it must be continuously refrigerated). The final row answers the question whether or not the specified therapy could be used to build a state-level stockpile. Examples of factors which would exclude a candidate therapy are: therapy is too expensive (e.g. more than one percent of the Nevada's annual PHP budget), therapy requires cold chain (the state can only handle bulk storage in a climate controlled warehouse), and therapy is already included and widely available through the Strategic National Stockpile (SNS).

Table 2: Candidate Therapy Selection (Using Nevada Cost Numbers)

Mono-Therapy *Class: Antivirals*

Oseltamivir (neuraminidase inhibitor)		
Medical Considerations	**Cost**	**Logistical Considerations**
Part of SNS Stockpile Familiar to Physicians	Min= $173K Mean = $544K Max = $1.1M	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Relenza (*neuraminidase inhibitor*)		
Medical Considerations	**Cost**	**Logistical Considerations**
Part of SNS Stockpile Familiar to Physicians	Min= $101K Mean = $319K Max = $649K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Amantadine (adamantane drug)		
Medical Considerations	**Cost**	**Logistical Considerations**
Not part of SNS Stockpile Not familiar to Physicians	Min = $3K Mean = $9K Max = $18K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Rimantadine (adamantane drug)		
Medical Considerations	**Cost**	**Logistical Considerations**
Not part of SNS Stockpile Not familiar to Physicians	Min = $45K Mean = $141K Max = $286K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Ribavirin (nucleoside antimetabolite drug)		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Not familiar to Physicians	Min= $20K Mean = $62K Max = $127K	Bulk Storage Possible
Recommendation: **Good choice for State Stockpile**		

Mono-Therapy Class: Statins

Atorvastatin (Lipitor)		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Familiar to Physicians	Min= $8K Mean = $24K Max = $49K	Bulk Storage Possible
Recommendation: **Good choice for State Stockpile**		

Rosuvastatin (Crestor)		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Familiar to Physicians	Min = $90K Mean = $282K Max = $575K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Simvastatin (Zocor)		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Familiar to Physicians	Min = $2K Mean = $5K Max = $11K	Bulk Storage Possible
Recommendation: **Good choice for State Stockpile**		

Gemfibrozil (Lopid)		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Familiar to Physicians	Min = $3K Mean = $11K Max = $22K	Bulk Storage Possible
Recommendation: **Good choice for State Stockpile**		

Mono-Therapy *Class: Interferons*

Interferon-α2b Intron-A		
Medical Considerations	**Cost**	**Logistical Considerations**
Not part of SNS Stockpile Not familiar to Physicians	Min= $3.2M Mean = $10.0M Max = $20.5M	Bulk Storage not Possible
Recommendation: **Poor choice for State Stockpile**		

Interferon-α2b PegIntron		
Medical Considerations	**Cost**	**Logistical Considerations**
Not part of SNS Stockpile Not familiar to Physicians	Min= $12.7M Mean = $40.0M Max = $81.4M	Bulk Storage not Possible
Recommendation: **Poor choice for State Stockpile**		

Interferon-ß1a Avonex		
Medical Considerations	**Cost**	**Logistical Considerations**
Not part of SNS Stockpile Not familiar to Physicians	Min= $18.0M Mean = $57.0M Max = $115.9M	Bulk Storage not Possible
Recommendation: **Poor choice for State Stockpile**		

Interferon-ß1a Rebif		
Medical Considerations	**Cost**	**Logistical Considerations**
Not part of SNS Stockpile Not familiar to Physicians	Min= $7.7M Mean = $24.6M Max = $49.9M	Bulk Storage not Possible
Recommendation: **Poor choice for State Stockpile**		

Mono-Therapy *Class: Corticosteroids*

Prednisone		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Familiar to Physicians	Min= $25K Mean = $78K Max = $159K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Combo-Therapy

Oseltamivir + Relenza		
Medical Considerations	Cost	Logistical Considerations
Part of SNS Stockpile Familiar to Physicians	Min = $274K Mean = $863K Max = $1.1M	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Oseltamivir + Ribavirin		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Not familiar to Physicians	Min = $193K Mean = $606K Max = $1.2M	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Relenza + Ribavirin		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Not familiar to Physicians	Min = $121K Mean = $382K Max = $776K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Amantadine + Ribavirin		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Not familiar to Physicians	Min = $22K. Mean = $71K Max = $144K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Combo-Therapy: Antivirals + Statins

Oseltamivir + Atorvastatin (Lipitor)		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Familiar to Physicians	Min = $181K Mean = $568K Max = $1.2M	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Oseltamivir + Rosuvastatin (Crestor)		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Familiar to Physicians	Min = $263K Mean = $826K Max = $1.7M	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Oseltamivir + Simvastatin (Zocor)		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Familiar to Physicians	Min = $175K Mean = $549K Max = $1.1M	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Relenza + Gemfibrozil (Lopid)		
Medical Considerations	Cost	Logistical Considerations
Not part of SNS Stockpile Familiar to Physicians	Min = $104K Mean = $331K Max = $672K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Ribavirin + Atorvastatin (Lipitor)		
Medical Considerations	**Cost**	**Logistical Considerations**
Not part of SNS Stockpile Not familiar to Physicians	Min = $27K Mean = $86K Max = $176K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Ribavirin + Rosuvastatin (Crestor)		
Medical Considerations	**Cost**	**Logistical Considerations**
Not part of SNS Stockpile Not familiar to Physicians	Min = $110K Mean = $345K Max = $702K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Ribavirin + Simvastatin (Zocor)		
Medical Considerations	**Cost**	**Logistical Considerations**
Not part of SNS Stockpile Not familiar to Physicians	Min = $21K Mean = $68K Max = $137K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Ribavirin + Gemfibrozil (Lopid)		
Medical Considerations	**Cost**	**Logistical Considerations**
Not part of SNS Stockpile Not familiar to Physicians	Min = $23K Mean = $74K Max = $149K	Bulk Storage Possible
Recommendation: **Poor choice for State Stockpile**		

Interferon-α2b + Ribavirin, PegIntron/Rebetol Combo Pack		
Medical Considerations	**Cost**	**Logistical Considerations**
Not part of SNS Stockpile Familiar to Physicians	Data not available on GoodRx website. Likely to cost more than individual PegIntron.	Bulk Storage not Possible
Recommendation: **Poor choice for State Stockpile**		

Results

As seen in Table 2, the only family of therapies that is not considered viable for a state stockpile due to logistical considerations are the Interferons, because they all require cold-chain storage (i.e. the medication requires continuous refrigeration) and cannot be stored in existing bulk storage warehouses. In terms of costs, Table 2 shows that the costs of medications can be much greater than 1% of a state's federal grant formed by the Hospital Preparedness Program (HPP) and the Public Health Emergency Preparedness (PHEP) cooperative agreement. For Nevada, the affordability limit is approximately $97,000. Average stockpile costs of these medications for Nevada run from the cheapest ($9,000) to the most expensive ($57,000,000). Combination therapies, on-patent medications, most antivirals and the interferons fall outside the affordability limit. In addition, there are several therapies listed in Table 2 that appear to be good choices for a state stockpile but are excluded because they are already included within the CDC's SNS.[70]

Of the remaining therapies, four were identified that met the cost consideration: ribavirin, atorvastatin, simvastatin, and gemfibrozil.

Limitations

This research was limited by several issues, most notably by the fact that it is attempting to plan for a virus that does not yet exist. Although the references used in this research provide a glimpse into what the global public health community is discussing, they do not provide us with a definitive protocol on how to treat novel influenza and novel pandemic strain viruses. This research was also limited by a lack of knowledge of the full range of medical therapies available in the nation's SNS. For security reasons the full list of what is included within the nation's stockpiles is not published openly.

The calculations shown here reflect only the Nevada resident population, and do not compensate for its additional population of visitors. Depending on the time of year, Nevada's overall population can swell by nearly twenty percent with the tourist population (e.g. New Years' Eve celebrations on the Las Vegas Strip, etc.). As an example for two of the state's largest cities: tourism data report that nearly forty million visitors came to Las Vegas in 2012, and nearly 4.1 million visitors are expected to see Reno each year. Other preparedness planning options are being developed to handle this issue.

We chose to use an online accessible (open source) pharmaceutical bulk price quoting website called *GoodRx* (www.goodrx.com). However, this is only a top-line estimate and is not fully reflective of what a health department may be able to negotiate if it did decide to proceed with a bulk purchase of medications. In addition, we did not attempt to address the maintenance issues associated with a stockpile (drug rotation, detailed logistical considerations including floor space, etc.) because most states are maintaining a current stockpile of medications from the H1N1 preparation and already have developed and implemented stockpile management plans.

Finally, influenza and MERs-CoV treatment is a vibrant, dynamic ever-changing research field. As new therapies become available, they will also need to be examined using the methodological framework developed in this paper.

Discussion

This research showed how expensive a potential state-level stockpile could become. Medical efficacy is not as significant a limiting factor as cost and logistical considerations. In this era of declining grant funds and an all-hazards approach, could/should these 'few options' even be considered as a possible investment in state-level prevention efforts?

An even bigger question is whether or not a state should carry an individual state-level stockpile. We do not address this question in depth in this paper because many states already have a state-level stockpile due to the medications they received from the CDC (which allocated it from the SNS) in preparation for the H1N1 virus in 2009/2010. Given that states

already have an existing stockpile, the next question is what it should include. Given the existing US strategic stockpile, it is unlikely that states would wish to allocate scarce resources to duplicating an existing federal resource. However, this does expose states to some risk as the SNS is not large enough to provide every state all needed medications in the worst case scenario. Also, in a slowly growing pandemic, the last states affected may also find fewer medications available. These scenarios are very unlikely. It is unclear what a state's role should be in supplementing the known stockpile by duplicating medications. In this manuscript, we assumed that a state would not wish to duplicate the SNS and would only consider medications that may not already be included in the SNS to augment their treatment options. The following paragraphs discuss four options for supplementing an existing state stockpile to provide additional treatment options for novel influenza and pandemic strain viruses based on the analyses conducted in this paper.

One option would be to expand the current state stockpile to include three statins (atorvastatin, simvastatin, and gemfibrozil) that can help limit the body's immune response within patients suffering from pandemic viruses. The observed medical benefit of reducing a physiological response to infection is particularly appealing because it is independent of a specific virus strain. From a medical efficacy point-of-view they are appealing for the synergistic effect they have when used in tandem with antivirals existing in state stockpiles. Although the scientific explanations behind these synergistic effects are still being studied, the literature makes a strong case for the use of antivirals and statins administered together as a complementary treatment option. These recommended statins are appealing for other reasons as well: they are affordable at bulk rates (even if all three are purchased at the maximum levels, the total purchase cost would be under the 1% limit); they are well known to both the public and healthcare providers; and they are easily stored long-term in climate controlled warehouses. The major drawback is that they are not useful as prophylaxis, only as a treatment. From a state planning perspective, to have a set of affordable and complementary therapies that work independently of a specific virus strain would be a welcomed addition to a state-level stockpile.

A second option would be to expand the state's existing stockpile of antivirals to include another, ribavirin, as well as adding statins. The research indicates that this additional antiviral therapy has significant medical efficacy when used as either a prophylaxis, or as a treatment. The research goes on to discuss the synergistic effect this medication has when used in conjunction with other antivirals (e.g. oseltamivir, relenza, etc.), as well as statins. While it would be possible to purchase the average levels of the three medications in a single purchase and remain below the 1% cut-off, it is not possible to purchase the maximum level. To have another prophylaxis and/or treatment option, that complements what is already in state stockpiles, would be a force multiplier within a public health response to pandemic.

Rather than purchase, maintain and rotate supplemental therapies within an existing state stockpile, a third option is for a state to create contracts with vendors that would be activated upon a pre-determined trigger. For example, a state may prepare a pre-written contract to purchase a given quantity of therapy '*A*' that would go into effect when a trigger (such as Stage 4, the first confirmed human case in North America). This option would provide a set of medical therapies that would expand the current list of options available to public health and clinical providers during a pandemic. The risk associated with this approach is the providers' ability to deliver on the contracts during a pandemic when all contracts of this nature will come due at the same time. For a state such as Nevada, this is a serious consideration as any pandemic that reaches the state will most likely have affected California first – and the county of Los Angeles has five times the population of the state of Nevada.

Finally, a fourth option would be to do nothing and continue to rely on existing state stockpiles and projected SNS materials.

Since the successful completion of the 2009/2010 response to the H1N1 pandemic,

many states have acquired and maintained state stockpiles of antiviral medications and PPE. As those same states prepare for future pandemics involving novel viruses, some state planners are looking to expand their current stockpiles to include more treatment and prophylaxis options. This manuscript identifies four such medications, an antiviral that could be used as a treatment option or as a prophylaxis option: ribavirin; and three statins that could be employed solely as treatment options: atorvastatin, simvastatin, and gemfibrozil.

In planning for pandemics that would involve viruses that may not yet exist, this ability to expand state stockpiles with more treatment/prophylaxis options may be a sound investment. Nearly all prevention efforts come with some kind of cost, be they in money, time, or space; yet these recommended medical therapies are preventative efforts against some of the most dangerous threats posed to humanity: pandemics. Through this research we have attempted to open a dialogue with other federal and state planners as they wrestle with the same challenges within their home agencies.

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Notes

1. http://www.flu.gov/pandemic/about/ .

2. World Health Organization [WHO], Global Overview of an Emerging Novel Coronavirus (MRS-CoV), Presentation to the World Health Assembly, May 23, 2013, http://www.who.int/csr/disease/coronavirus_infections/WHA_CoV_update_KeijiFukuda_23May13.pdf (accessed June 3, 2013); Avian Influenza A (H7N9) Virus, Centers for Disease Control and Prevention Website, http://www.cdc.gov/flu/avianflu/h7n9-virus.htm (accessed July 31, 2013); Middle East Respiratory Syndrome: Frequently Asked Questions/FAQs, Centers for Disease Control and Prevention Website, http://www.cdc.gov/coronavirus/mers/faq.html (accessed August 1, 2013); G. Khan, "A Novel Coronavirus Capable of Lethal Human Infections: An Emerging Picture," *Virology Journal* 10, (2013), 66, http://www.virologyj.com/content/10/1/66 (accessed August 26, 2013).

3. J.K. Taubenberger and D.M. Morens, "1918 Influenza: the Mother of All Pandemics," *Emerging Infectious Diseases* 12, no.1, (2006), http://dx.doi.org/10.3201/eid1209.050979 (accessed July 28, 2014);
M.I. Meltzer, N.J.Cox, and K. Fukuda, "The Economic Impact of Pandemic Influenza in the United States: Priorities for Intervention," *Emerging Infectious Diseases* 5, no.5 (1999): 659-671;
J.M Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History,* (New York: Penguin Books, 2004).

4. J.M Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History,* (New York: Penguin Books, 2004).

5. CDC Health Update: Swine Influenza A (H1N1) Update: New Interim Recommendations and Guidance for Health Directors about Strategic National Stockpile Material, Centers for Disease Control and Prevention Website, distributed via Health Alert Network/HAN on April 26, 2009 at 11:45 PM EST, http://www.cdc.gov/h1n1flu/HAN/042609.htm (accessed August 1, 2013).

6. The Division of Strategic National Stockpile (DSNS) Program: A Report from the Board of Scientific Counselors (BSC), 33, http://www.cdc.gov/phpr/science/documents/DSNS_Program_Review_Workgroup_Report_FINAL2.pdf. (accessed December 15, 2014).

7. A National Repository of Life-Saving Pharmaceuticals and Medical Supplies Centers for Disease Control and Prevention Website, http://www.cdc.gov/phpr/stockpile/stockpile.htm, Published October 2012, (accessed August 1, 2013); L.M. Alleva, C. Cai, and I.A Clark, "Using Complementary and Alternative Medicines to Target the Host Response during Severe Influenza, *Evidence-Based Complementary and Alternative Medicine* 7, no.4, (2013), http://dx.doi.org/10.1093/ecam/nep152 (accessed August 21, 2013).

8. Influenza Antiviral Medications: Summary for Clinicians, Centers for Disease Control and Prevention Website, http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm (accessed October 22, 2013).

9. Ibid.

10. D.S Fedson, "Pandemic Influenza: A Potential Role for Statins in Treatment and Prophylaxis," *Clinical Infectious Diseases* 43, no.2 (2006): 199-205;M.L Vandermeer et al., "Association between Use of Statins and Mortality among Patients Hospitalized with Laboratory-Confirmed Influenza Virus Infections: A Multistate Study," *Journal of Infectious Diseases* 205, no.1, (2012): 13-19; E.E. Walsh, "Statins and Influenza: Can We Move Forward?" *Journal of Infectious Diseases* 205, no.1 (2012): 1-3.

11. Interferon, MedicineNet Website, http://www.medicinenet.com/interferon/article.htm (accessed October 24, 1013).

12. D. Falzarano et al., "Inhibition of Novel β Coronavirus Replication by a Combination of Interferon-α2b and Ribavirin," *Scientific Reports* (2013):3, http://www.nature.com/srep/2013/130418/srep01686/full/srep01686.html (accessed July 28,2014).

13. A.C Poinier, and S.M Shoor, Corticosteroids, WebMD Website, http://www.webmd.com/hw-popup/corticosteroids, Published May 7, 2010, (accessed October 24, 2013).

14. Alleva, Cai, and Clark, "Complementary and Alternative Medicine."

15. What You Should Know About Flu Antiviral Drugs, Centers for Disease Control and Prevention Website, http://www.cdc.gov/flu/antivirals/whatyoushould.htm (accessed October 16, 2013).

16. J.Beigel, and M. Bray, "Current and Future Antiviral Therapy of Severe Seasonal and Avian Influenza," *Antiviral Research* 78, no. 1 (2008): 91-102. Published online 2008 February 4.

17. A. Moscona, "Neuraminidase Inhibitors for Influenza," *The New England Journal of Medicine* 353, (2005): 1363-1373.

18. N.J Cooper et al., "Effectiveness of Neuraminidase Inhibitors in Treatment and Prevention of Influenza A and B: Systematic Review and Meta-Analysis of Randomized Controlled Trials," *British Medical Journal* 326, no.7401 (2003): 1235.

19. J.J. Treanor et.al. , "Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza," *JAMA: The Journal of the American Medical Association* 283, no.8 (2000): 1016-1024.

20. K.G. Nicholson, et al., "Efficacy and Safety of Oseltamivir in Treatment of Acute Influenza: a Randomized Controlled Trial," *The Lancet* 355, no. 9218 (2000): 1845-1850.

21. F.Y Aoki, et al., "Early Administration of Oral Oseltamivir Increases the Benefits of Influenza Treatment," *Journal of Antimicrobial Chemotherapy* 51, no.1 (2003): 123-129.

22. R. Salomon, and R.G Webster, "The Influenza Virus Enigma," *Cell* 136, no.3 (2009) : 402-410.

23. What You Should Know About Flu Antiviral Drugs, Centers for Disease Control.

24. Moscona, "Neuraminidase Inhibitors for Influenza".

25. F.G Hayden, et al., " Efficacy and Safety of the Neuraminidase Inhibitor Zanamivir in the Treatment of Influenzavirus Infections," *New England Journal of Medicine* 337, no.13 (1997): 874-880.

26. Cooper et al., "Effectiveness of Neuraminidase Inhibitors".

27. M.J. Mäkelä et al., "Clinical Efficacy and Safety of the Orally Inhaled Neuraminidase Inhibitor Zanamivir in the Treatment of Influenza: A Randomized, Double-Blind, Placebo-Controlled European Study," *Journal of Infection* 40, no.1 (2000): 42-48.

28. Salomon and Webster, "The Influenza Virus Enigma".

29. Influenza Antiviral Drug Resistance, Centers for Disease Control and Prevention Website, http://www.cdc.gov/flu/about/qa/antiviralresistance.htm (accessed October 17, 2013).

30. Ibid.

31. M.G.A.Van Vonderen, et al., "Ribavirin in the Treatment of Severe Acute Respiratory Syndrome (SARS)," *Netherlands Journal of Medicine* 61, no.238 (2003): 42.

32. F.G Hayden, "Antivirals for Pandemic Influenza," *Journal of Infectious Diseases* 176 (Supplement 1) (1997): S56-S61.

33. K.M. Chan-Tack, J.S. Murray, and D.B Birnkrant, "Use of Ribavirin to Treat Influenza," *New England Journal of Medicine* 361, no.17 (2009): 1713-1714.

34. Salomon and Webster, "The Influenza Virus Enigma".

35. Fedson, "Pandemic Influenza: A Potential Role for Statins in Treatment and Prophylaxis"; D.S. Fedson, "Meeting the Challenge of Influenza Pandemic Preparedness in Developing Countries," *Emerging Infectious Diseases* 15, no.3 (2009): 365.

36. Walsh, "Statins and Influenza: Can We Move Forward?"

37. Y. Kumaki, J.D. Morrey, and D.L Barnard, "Effect of Statin Treatments on Highly Pathogenic Avian Influenza H5N1, Seasonal and H1N1pdm09 Virus Infections in BALB/c mice," *Future Virology* 7, no.8 (2012): 801-818.

38. J Cinatl, et al., "Treatment of SARS with Human Interferons," *The Lancet* 362, no.9380 (2003): 293-294.

39. M.G. Katze, Y. He , and M.Gale, "Viruses and Interferon: A Fight for Supremacy," *Nature Reviews Immunology* 2, no.9 (2002): 675-687.

40. J Cinatl, et al., "Treatment of SARS".

41. Katze, He, and Gale, "Viruses and Interferon".

42. L.E. Hensley, et al., "Interferon-β 1a and SARS Coronavirus Replication," *Emerging Infectious Diseases* 10, no.2 (2004): 317.

43. B. Morgenstern, et.al., " Ribavirin and Interferon-β Synergistically Inhibit SARS-Associated Coronavirus Replication in Animal and Human Cell Lines," *Biochemical and Biophysical Research Communications* 326, no.4 (2005): 905-908.

44. Hensley, et al., "Interferon-β 1a".

45. Morgenstern, et.al., " Ribavirin and Interferon-β".

46. Y .Oba, N. Lee, and J. Sung, "The Use of Corticosteroids in SARS," *New England Journal of Medicine* 348, no.20 (2003): 2034-2035.

47. G.R Bernard, et al. "High-dose corticosteroids in patients with the adult respiratory distress syndrome," *New England Journal of Medicine* 317, no.25 (1987): 1565-1570.

48. L.J. Stockman R. Bellamy, and P. Garner, "SARS: Systematic Review of Treatment Effects," *PLoS Medicine* 3, no.9 (2006): e343.

49. Alleva, Cai, and Clark. "Complementary and Alternative Medicine".

50. S. Li, et al., "Identification of Natural Compounds with Antiviral Activities Against SARS-Associated Coronavirus," *Antiviral Research* 67, no.1 (2005): 18-23.

51. E.A. Govorkova, and R.G. Webster, "Combination Chemotherapy for Influenza," *Viruses* 2, no.8 (2010): 1510-1529.

52. S. Barik, "New Treatments for Influenza," *BioMed Central [BMC] Medicine* 10, no.1 (2012): 104.

53. Govorkova and Webster, "Combination Chemotherapy".

54. Barik, "New Treatments".

55. Govorkova and Webster, "Combination Chemotherapy".

56. Barik, "New Treatments".

57. Govorkova and Webster, "Combination Chemotherapy".

58. Ibid.

59. Barik, "New Treatments".

60. Govorkova and Webster, "Combination Chemotherapy".

61. Barik, "New Treatments".

62. Falzarano et al., "Inhibition of Novel β Coronavirus".

63. FluAid 2.0 Pandemic Influenza Planning Resources, Centers for Disease Control and Prevention Website, http://www.cdc.gov/flu/pandemic-resources/tools/fluaid.htm (accessed October 17, 2013).

64. FluAid 2.0 Pandemic Influenza Planning Resources, Centers for Disease Control and Prevention Website, http://www.cdc.gov/flu/pandemic-resources/tools/fluaid.htm (accessed October 17, 2013).

65. Ibid.

66. J. Hardcastle, "Nevada County Age, Sex, Race, and Hispanic Origin Estimates and Projections 2000 to 2032: Estimates from 2000 to 2012 and Projections from 2013 to 2032," The Nevada State Demographer's Office Website, http://nvdemography.org/wp-content/uploads/2013/10/Nevada-Summary-Workbook-ASRHO-Estimates-and-Projections-2000-to-2032.pdf (accessed October 20, 2013).

67. Meltzer, Cox, and Fukuda, "The Economic Impact of Pandemic Influenza".

68. http://www.cdc.gov/phpr/coopagreement.htm (accessed December 15, 2014), http://www.phe.gov/Preparedness/planning/hpp/Pages/funding.aspx (accessed December 15, 2014).

69. Instructions for Preparing an Interim Progress Report, Catalog of Federal Domestic Assistance (CFDA) Number: 93.074 – National Bioterrorism Hospital Preparedness Program and Public Health Emergency Preparedness Program Funding Opportunity Announcement (FOA) Number: CDC-RFA-TP12-120102CONT13, Centers for Disease Control and Prevention Website, http://www.cdc.gov/phpr/documents/TP12-120102CONT13_AMENDMENT_03_25_13.pdf (accessed November 5, 2013).

70. http://www.cdc.gov/phpr/stockpile/stockpile.htm.

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