

# The Developing Threat of New Pandemic Influenza Strains

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## ABSTRACT

New influenza strains emerging in the world could cause a global pandemic comparable to the disastrous influenza pandemic of 1918. Current stocks of vaccine and antivirals are inadequate in quantity with variable effectiveness. Despite multi-billion-dollar federal expenditures, the contingency plans to distribute available vaccine or drug stockpiles, to care for the sick, or to maintain essential urban infrastructure are all seriously deficient, and mainly focused on maintaining continuity of government. Government guidance on personal protective measures has lagged years behind evidence of transmission through eye contact or aerosol. Although there are some promising developments in vaccine and antiviral development, at present local communities will be relying mostly on their own resources in a 1918-type pandemic.

## Forgotten History

In March 1918, a virulent viral strain from the influenza A genus (Orthomyxoviridae family), suddenly appeared in a rural area of Kansas. By late September this strain had transformed itself to cause a rampant pulmonary disease with severe overwhelming lung damage. Many victims turned purple from respiratory failure and died within a day of the onset of symptoms.

By November 1918 a lethal influenza pandemic gripped the world. It would claim more victims than the First World War. Roughly one of four U.S. citizens became infected, and in about six weeks it killed a half million Americans. The U.S. population was less than half of today's, or about 103,208,000. It has been cited as one of the most devastating epidemic in recorded world history, and it is stated that more people died of influenza in a single year than in four years of the Black Death (bubonic plague) from 1347 to 1351.<sup>1</sup>

It is feared that a 1918-type event could happen again, and there are disturbing signs that it may happen soon.

## New Influenza Strains

As shown in Figure 1, starting in 1990 there has been a worrying and progressive increase in the number of "micro-outbreaks" of new influenza A strains that could emerge into humans.

In March 2013, an H7N9 avian virus was first reported in humans in China as the result of a spillover event. These infections showed a tissue tropism and pathological, immunological, and clinical manifestations that distinguished it from the other influenza A strains and sub-types known to infect man.

Particularly alarming was the ability of this H7N9 Influenza strain to cause a serious lung pathology accompanied in many cases by the rapid development of a severe acute respiratory distress syndrome (ARDS) similar to the 1918 H1N1 pandemic.<sup>2</sup>

Over the last few years this H7N9 bird flu virus has sickened and killed several hundred people in China in small outbreaks characterized by a 40 percent mortality rate. While the current risk is low, the pandemic potential is worrying. Reportedly, it has developed resistance to currently stockpiled antiviral drugs.

In addition to new influenza strains, other types of animal RNA viruses will continue to emerge into human populations as previously unknown infections.

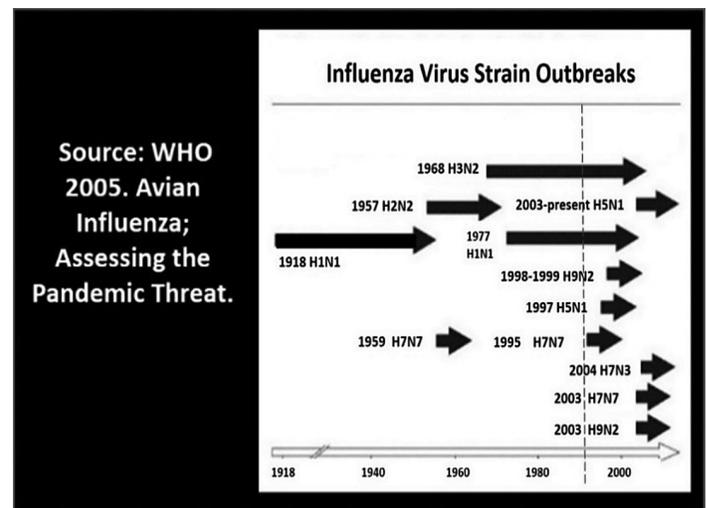


Figure 1. Increase in Influenza Outbreaks from New Strains

## The Problem of the "Vaccine Gap"

A human population that is properly immunized against a new strain of influenza A virus by an effective vaccine will not suffer serious illness or transmit the virus. However, a new vaccine cannot be made until after a new strain has appeared and a recognized pandemic has begun. This time delay between the start of a pandemic and the first, limited availability of a suitable vaccine is called the "vaccine gap." There has been an unacceptable vaccine gap during each of the last four major influenza pandemics.<sup>3</sup>

As witnessed during the lethal 1918 outbreak, most influenza deaths will occur during the time that it takes to make significant quantities of vaccine using classical production methods. While a recently revamped production

capability promises to decrease this gap, current production capability is still inadequate to quickly immunize the entire population of the U.S. Because there will be only a limited amount of any initial new vaccine, federal guidelines have been developed to identify which groups should receive the first immunizations. This process is based on a tiered list created by the Department of Health and Human Services (DHHS).<sup>4</sup>

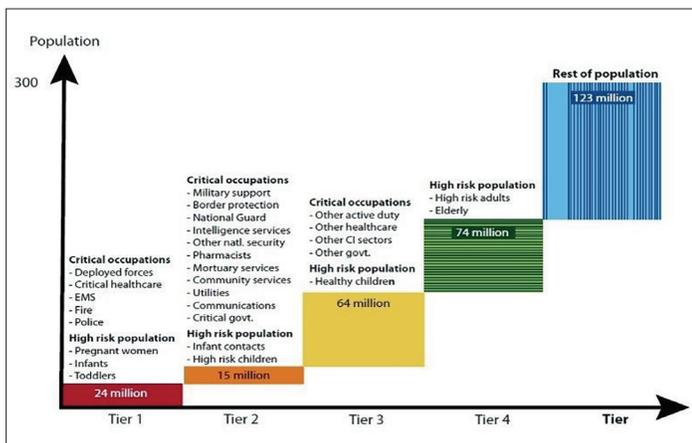
Tier 1 contains the most important groups that will receive the first vaccine supply, with an objective to protect the government and armed forces, and the critical medical, fire, and police forces of the 120 largest cities in the U.S. These tiers and groups are defined in Figure 2.

However, it is apparent that both the Department of Homeland Security (DHS) and DHHS have not properly addressed the vulnerabilities of the linked infrastructures that support high-density urban regions. For example, under the current guidance, millions of infants and toddlers will receive a new pandemic influenza vaccine well before the adult workers who are employed in maintaining the electricity, water supply, communications, and other critical infrastructures of any high-density metropolitan area.

There is also no consideration evident for the global just-in-time economy, which has neither surge production nor distribution capacity for many critical products and services. When considering vaccine and antiviral drug production, even a minor disruption to a single production reagent, packaging material, or distribution pathway means that a new vaccine or drug could quickly become unavailable.

Many scientists and public health experts believe that the current federal guidance for initial vaccine distribution is fatally flawed and that it will not minimize a pandemic-induced disruption of essential goods and services.<sup>5</sup>

Thus, there is an urgent need for a national prioritization of essential goods and services to ensure that these are maintained during a pandemic. This should be followed by an attempt to identify and assess the number of essential personnel necessary to maintain these critical supply chains and infrastructures.



**Figure 2.** Current Federal Tiers for Vaccine Distribution  
Source: U.S. Government Avian and Pandemic Flu Information

In past influenza pandemics, the groups at increased risk for serious illness and death have differed in both age and health status. In the 1918 pandemic, healthy young adults were an unexpected major high-risk group. It is assumed that in the next such pandemic this would be the same, but it is not certain. Therefore, any national vaccination guidance must be adaptable to different pandemic scenarios.

Another significant problem concerns the demonstrated poor effectiveness of current influenza vaccines for all population groups. The use of fertilized chicken eggs in the vaccine manufacturing process results in a drift of the vaccine strain more toward birds than humans. Continuing change to tissue culture-based vaccine production should help improve the efficacy of new vaccines. A Cochrane Review has also determined that the effectiveness of current influenza vaccines in the elderly is only modest at best, and urgent further research is needed.<sup>6</sup>

In any event, under the current federal plan, there will be no available vaccine for 123 million U.S. citizens (about 30 percent of the American workforce), many of whom work to ensure there is electricity, food on the supermarket shelves, gasoline, diesel fuel, spare parts, banking services, mass transportation, and the many other essential services necessary to maintain the nation's high-density urban populations.

### Influenza Risk for Disadvantaged Communities

When an influenza vaccine is in short supply, distributing it quickly and equitably among the different populations and communities presents a significant problem for effective pandemic planning, and the barriers to equitable vaccine distribution are formidable, even when vaccines are available.<sup>7,8</sup> People's willingness to be vaccinated may also vary.<sup>9,10</sup>

Both historical data and computer modeling suggest that to maximally reduce the level of influenza pandemic spread, it is the poor, low-resource communities that should be targeted with the first doses of vaccine. This is because of their high population density and other factors that promote transmission.<sup>11</sup> Additionally, living in poverty is an independent risk factor for influenza hospitalization, suggesting that poor communities should be specially targeted for vaccine outreach and other efforts to prevent infection and improve outcomes.<sup>12</sup>

### The Antiviral Drug Oseltamivir

To overcome the vaccine-gap problem, the U.S. has decided to stockpile oral antiviral drugs to issue to critical population groups until a vaccine can be made and administered. The main antiviral influenza drug selected for stockpiling is oseltamivir phosphate, brand name Tamiflu®, made by Hoffman-La Roche.<sup>13,14</sup> The standard 10-capsule protocol is one capsule twice a day for five days without missing a single dose. The drug is promoted both as treatment and prophylaxis following a possible influenza

virus exposure. Drug treatment must start within hours of the first initial symptoms, such as a spiking fever, chills, cough, and body aches.<sup>15</sup> It was envisioned that this national stockpile would be augmented with a contingency plan for rapid additional synthesis of more oseltamivir for the rest of the American population. This drug supply would also treat essential groups such as medical workers and emergency responders.

Seemingly overnight, oseltamivir was promoted as a wonder drug and the federal government rushed to purchase more than \$1.5 billion worth of this antiviral agent. While authorities proudly described how this would protect America, some perceptive doctors and scientists were uncertain whether oseltamivir was even worth taking at all.

During the stockpiling effort, the Cochrane Collaboration was tasked with conducting a systematic review to verify oseltamivir's clinical drug trials. In 2014, its final review was published,<sup>16</sup> and it severely questioned the drug's effectiveness. It did agree that oseltamivir could reduce the duration of symptoms by about a day, but only if it was taken at the very first sign of illness. Serious neuropsychiatric side effects have been reported in children, almost entirely in Japan.<sup>17</sup>

CDC continues to recommend oral oseltamivir as an important drug for influenza treatment.<sup>18</sup> In 2017, the European Center for Disease Prevention and Control (ECDC) reported on its own review of oseltamivir. Its report reaffirmed that there was evidence to support using oseltamivir to treat and prevent influenza A virus infections, but it agreed that more studies were needed. Treatment side effects were not considered.<sup>19</sup>

However, the need for sophisticated statistical methods to demonstrate its actual effectiveness shows that oseltamivir is certainly not the miracle medication it was initially reported to be. Even if the drug works and it can be delivered in time to the population, the mathematics of supply and demand are clear.

When fully in place, the federal stockpile will contain a total of 50 million doses, mainly of oseltamivir, with the rest made up of the inhalable antiviral drug zanamivir, marketed as Relenza<sup>®</sup> by GlaxoSmithKline. An additional 31 million doses will be held in state stockpiles currently holding 81 million doses of antivirals, for a U.S. population of more than 326 million. During the 1918 pandemic, about 28 percent of Americans became infected. Today, this figure would equate to more than 91 million people.

The Pentagon has already claimed priority for the stockpiled antiviral for use by its deployed operational forces.<sup>20,21</sup> The federal government will also prioritize oseltamivir for its list of essential federal employees out of about 1.26 million workers.<sup>22,23</sup> There are also more than 12 million private medical workers in the U. S., according to 2015 figures from the Bureau of Labor Statistics, and unless they are given prophylactic drugs, many may not go to work for fear of infecting their families.

In addition, there are approximately two million first

responders, such as police and firefighters, who are essential for the function of any city.<sup>24</sup>

The above issues could become moot because even a single small change in the influenza A virus's "blueprints" can create resistance to oseltamivir.<sup>25,26</sup> This was confirmed during the 2007–2008 and 2009 flu seasons. In 2013–2014, oseltamivir resistance was found in both H5N1 and H7N9 Influenza strains during treatment with the drug. Recent data from experiments on mice suggest the customary 5-day course of treatment may not be sufficient for all influenza strains.<sup>27</sup>

## The National Pandemic Response Plan

In 2005, the Bush Administration rushed to formulate a national strategy for pandemic influenza preparedness and response.<sup>28</sup> The plan had major deficiencies and left the task of caring for millions of sick Americans up to the individual states. A few months later, DHHS released its follow-on Pandemic Influenza Plan. An updated plan was released in 2017, which includes links to interim updates.<sup>29</sup> The Government Accountability Office (GAO), the investigative arm of Congress, has continued to forcefully criticize DHHS for its failure to develop a credible national pandemic plan. For the last seven years, a series of GAO reports has criticized all levels of pandemic preparedness. From my review of these documents, I observe that two large bureaucracies, DHHS and DHS, are required to work together to facilitate the national pandemic response. Not surprisingly, their plans differ in important respects. For example, the DHS strategy called for using antiviral drugs only for treatment, while the DHHS plan called for use of antivirals for both treatment and prophylaxis, with obvious implications for the size of the needed stockpile.

The role of the federal government would be limited to: support of overseas containment efforts; guidance to state and local authorities on protective measures; reviewing laws and regulations pertaining to a national pandemic response; coordinating response among federal, state, and local authorities and the private sector; mitigating the pandemic's economic impact; procurement and distribution of vaccine and antiviral medications to pre-determined priority groups; and accelerating research and development of vaccines and therapies for influenza.

## State and Local Preparedness

The Pandemic Influenza Plan emphasizes that that authorities of each state and each municipality are responsible for their own community responses to pandemic. DHHS has provided general guidance to the states and more than \$11 billion to foster this process, and has outlined programs to enhance emergency preparedness.<sup>30,31</sup> In addition, HHS has provided more millions in supplemental funding specifically for improving community preparedness for an influenza pandemic.<sup>32</sup> The FY 2017 Budget included \$915 million in total for CDC and the Assistant Secretary for Preparedness

and Response (ASPR) for preparedness capabilities of public health departments and healthcare facilities at a state and local level for all hazards, including chemical, biological, radiological, and nuclear threats, as well as other disasters, outbreaks, and epidemics.<sup>33</sup>

To enhance state and local readiness in the cities in the regions where more than half of Americans live, the 2004 Cities Readiness Initiative (CRI) was created. Starting with 21 cities, the CRI gradually expanded to include 72 cities with at least one CRI city in every state.<sup>34</sup>

Local authorities are responsible for pre-selection of buildings to be contracted for use as Alternate Care Sites, and for recruiting, training, and management of medical-surge personnel. They are responsible for making provisions for receiving and distributing antiviral drugs and vaccine to their communities, developing local mortuary surge capability, and making plans for continuity of local government and first responders. They are also responsible for disseminating home care and pandemic information to the public.

In February 2008, the DHHS Office of the Inspector General was asked to examine and evaluate 10 localities in five states for their medical surge capability. Despite the federal money supplied to these local authorities, OIG found that:<sup>35</sup>

- Fewer than half of selected localities had started to recruit medical volunteers, and none of the five states had implemented an electronic system to manage them. Only four localities had started to register and train medical volunteers, and all four had concerns about using volunteers.
- No locality had an effective electronic system for managing medical volunteers.
- All 10 localities had acquired limited caches of medical equipment, but many experienced difficulties with even the basic inventory tracking of equipment.
- Only three of the five states had implemented electronic systems to track available hospital beds during an emergency.
- Most localities had not completed selecting alternate care sites to alleviate hospital crowding, and few had signed formal agreements with building owners.
- No locality had plans for how their alternate care sites would be staffed, managed, and supplied.
- Nine localities had no guidelines for altering triage, admission, and patient care during a pandemic. Seven localities were concerned that they would be legally at risk if they were to alter their standards of care, and all nine reported that they wanted additional state or federal guidance.

While local public health departments had conducted medical surge exercises, none had consistently documented their “lessons learned.” Most of the exercises were simply discussion-based, not operations-based, and not one local authority consistently created after-action reports and improvement plans.

This inexcusable lack of community progress in response to federal funding is troubling but understandable.

Over the last 20 years, public health authorities have experienced severe budget cuts and a loss of 50,000 health officials. Despite guidance from CDC and DHHS, many local jurisdictions lack the staff that can effectively plan a community pandemic response. In addition, city managers do not seem to appreciate the true seriousness of the pandemic influenza risk, and difficulties often arise between city managers and their local public health authorities. This is amplified by the fact that most federal funding is “stove-piped” to either local emergency management or local public health, but not to both.

One other possible factor may be increasing reliance on the federal government to solve society’s problems. Whether from political, social, or intentional economic design, this increasing government dependency is unrealistic and fraught with potential disaster. Government is not, and never has been capable of meeting everyone’s needs simultaneously.<sup>36</sup>

Community managers must work with public health agencies to prepare and rehearse rational pandemic plans, and build community response up to county and state levels. This is key to a true national pandemic response.

Current national modeling suggests that a severe pandemic with a 35 percent attack rate would overwhelm existing resources during the first 12 weeks of an outbreak. Maximum hospital bed capacity, and available mechanical ventilators, would be exceeded during the first 2-3 weeks, with a peak intensive care bed requirement that is 461 percent of total U.S. capacity. Other beds would require a 191 percent increase in national capacity.<sup>37</sup>

Without effective antiviral drugs to cover the vaccine gap, local communities must try to limit their influenza infection rates to a level that can be managed by their medical-surge capability. In a world of high-technology medicine, these interventions are simple and basic, but they are all that will be left for the millions of Americans who will have no vaccine or drug treatment.

These measures are called non-pharmaceutical interventions or NPI, and they include cough and sneeze etiquette and hand hygiene; routine cleaning of frequently touched surfaces; voluntary home isolation when ill; voluntary home quarantine of exposed household members; use of surgical face masks in community settings; and other individual/municipal-mandated social-distancing measures.

It is important to note that these same NPI were introduced in 1918 to disrupt the spread of the virus, but they failed to reduce its transmission by the 60 percent needed to gain effective control of the pandemic.

### **Current HHS Influenza Protection Guidelines Are Still Inadequate**

U.S. medical workers must be assured that the protective measures they use will prevent them from contracting influenza infection. Loss of even a few workers or volunteers due to infection could have a domino effect, causing a volunteer surge-medical capability to vanish overnight.<sup>38</sup>

For influenza the ferret serves as the animal model for human

infection. Ferrets and humans share similar lung structures and function, and human and avian influenza viruses exhibit similar patterns of binding to the sialic acids in the respiratory tracts of both species.<sup>39</sup> Based on ferret and human data, it is acknowledged that the influenza virus may be transmitted to humans in three ways: (1) by direct contact with infected individuals; (2) by contact with contaminated objects (doorknobs, elevator buttons, work surfaces, etc.) and then touching the face, eyes, or mouth; (3) by inhalation of virus-laden aerosols.

The original 2006 DHHS Pandemic Influenza Plan recommended use of simple surgical masks as part of the personal protective equipment (PPE) for routine care of influenza patients. This recommendation ignored more than 50 years of data on the behavior of small particle aerosols, and more than 8 years of data concerning the viability of influenza and other viruses in such aerosols.<sup>40-46</sup> The advice was wrong in any medical care setting with dehumidified air and high concentrations of virus in the environment. Yet the DHHS did not update its Pandemic Influenza Plan to recommend the use of high-efficiency particulate air (HEPA) filtered N95 masks (respirators) until 2017.<sup>29</sup>

Experimental data now reveals that the new 2017 DHHS guidelines are still inadequate for complete protection against influenza in the enclosed medical setting, because scientists now realize that there is a fourth way to contract influenza: through the surface of the eye.<sup>47</sup> When the human eye contacts an influenza aerosol from an infected patient's cough or sneeze, surface tension draws the viral particles onto the outside of the eye, where they adhere. The eye's naso-lacrimal drainage system then translocates these viruses from the eye's surface through the tear ducts and into the inside cavity of the nose within 30 minutes.<sup>48</sup>

Human sneezing and coughing will generate a small-particle aerosol with some viral-laden particles that are one to five microns in diameter. These microscopic particles behave as a gas and can remain suspended in the air for hours. The influenza virus inside these micro-droplets can remain infectious for at least 2 hours.<sup>46</sup>

Experiments have shown that eye exposure alone to some influenza A virus strains is sufficient to cause a lethal infection in the surrogate ferret model and almost certainly in humans.<sup>47-50</sup> Therefore, airway protection alone is not a full countermeasure against influenza exposure, infection, or severe disease. For ease of use and safety, full protection ideally requires a sealed, full-face HEPA-filtered respirator, combined with alcohol-based wipe disinfection of both respirator and hands after use.

For a lethal 1918-type virus with no vaccine and no drug treatment, the safety of medical personnel must always err on the side of caution. Yet, just as biosafety data were ignored during the Ebola virus outbreak in 2014, DHHS seems oblivious to the scientific results for influenza A viruses and the eye.

### **Local Communities Will Have to Manage a Pandemic Themselves**

The strategy of the National Pandemic Influenza Response Plan is to first focus on protecting the federal government, the military, and the state governments by

rapidly distributing antiviral drugs until the first doses of vaccine can be manufactured. It is a top-down response with an emphasis on ensuring continuity of government, while trying to preserve the minimum basic infrastructures of the 120 largest U.S. cities. Whatever federal surge-medical personnel are available will be used at government levels first, with little left over. Smaller cities and towns are required to use their own planning and resources.

The current gaps and shortfalls in the national plan are manifold, despite multiple iterations of organizational change and the formation of entirely new federal agencies since 2001. More than a decade of ever-changing federal guidance on even the simplest issues, such as when to use simple protective surgical masks, indicates a dysfunctional bureaucracy.

In addition, a combination of increasing global population, increasing high-density urbanization, economic globalization, just-in-time inventories, and the complex supply and distribution chains for food, energy, and other basic infrastructure components have combined into a serious new set of problems that were not factors in 1918.

In 1996–2017, the U.S. spent a conservatively estimated \$79 billion toward a national biological defense, but DHS, DHHS, the defense department, and the 10-year-old Defense Threat Reduction Agency are unable to provide complete data, or to account for all one-time advance appropriations.<sup>51</sup> Actual spending could be much higher. From 2001–2008 the U.S. spent \$40 billion, and federal bioweapons-related funding has remained roughly steady at approximately \$6.6 billion/year since FY2004.<sup>52</sup> This federal funding purchased a biological defense system that was unable to properly implement a simple syndromic surveillance system at five U.S. airports and manage 11 cases of Ebola virus disease without major public alarm in 2014.

### **Hopeful Developments**

On the positive side, there is progress in development of new, more effective influenza vaccines and their faster production. Also, scientists are gradually moving toward a universal influenza vaccine effective against most strains of influenza A.<sup>53,54</sup> Progress is also being made in the development of a new class of highly effective antiviral drugs such as favipiravir (T-705 or Avigan), developed by Toyama Chemical Co., which Japan has already stockpiled for its own pandemic response.<sup>55</sup> Other new drugs seem promising.<sup>56</sup> These include an endonuclease inhibitor and new RNA polymerase inhibitors.

### **Conclusions**

In the event of a major 1918-type pandemic, at least 123 million Americans will not receive any antiviral medications or vaccines for weeks. The U.S. currently lacks the medical workforce and well-rehearsed local authority plans to take care of the millions of seriously ill cases. There will predictably not be enough antiviral drugs or vaccine for all Americans,

and we lack well-thought-out plans for prioritizing their use. Even if there were an adequate supply, many local authorities appear unable to distribute these essential items in time to make any difference to their communities. Local/regional hospitals would be quickly overwhelmed, and morgues would overflow.

As Americans watch their neighbors, co-workers, or family members become ill and some die around them, all there will be is federal advice to stay away from others, to wash hands frequently, and if sick, stay home from work and be nursed at home. Despite enormous amounts of federal spending, our situation is not much better than in 1918. Most communities will be on their own.

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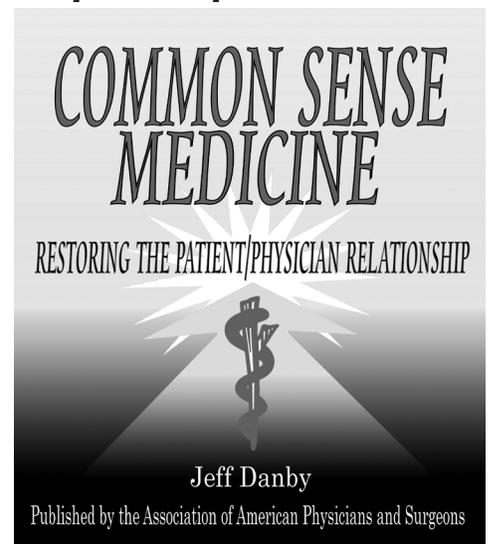
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