

# **Chapter 1: SARS - Steroid and Ribavirin Scanda I**

*“Thought is an infection. In the case of  
certain thoughts, it becomes an epidemic.”*

— Wallace Stevens

*The Infectious Myth* is a book project by David Crowe that is currently under development. It examines the lack of evidence for viral causes of disease or, in the case of Mad Cow and related diseases, the evidence for and against prions. It also examines the evidence that all of these diseases have environmental causes, if our environment is broadly defined to include the water we drink the air we breath, the food we eat, and the chemicals we consume as drugs, or expose ourselves to as cosmetics, pesticides, pharmaceutical drugs, recreational drugs and more.

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## SARS - Steroid and Ribavirin Scandal



SARS rose from the depths of China in November of 2002, bringing with it coughing, fever and patchy infiltrates on X-Rays. Sweeping into Singapore, Hong Kong, Taiwan and Vietnam in February, 2003 it barely paused before jumping the Pacific Ocean, landing in the United States, Australia, the Philippines and most especially Canada, where it homed in on the metropolis of Toronto. By the end of May, cases had been found in 29 countries around the world. The epidemic spread on a wave of fear leaving a severe and acute economic chill wherever it took hold.<sup>1</sup>

The World Health Organization was heavily criticized for ignoring a warning in November of 2002 that a highly infectious and dangerous new disease was sweeping through Guangdong. After the SARS crisis broke early in the next year nobody could even remember the name of the Chinese scientist who reported this while attending a WHO sponsored conference on influenza in Beijing.<sup>2</sup>

The SARS panic did not start until a rumor was disseminated on a discussion forum hosted by the medical surveillance website ProMedMail.org intended to help public health workers exchange news of outbreaks of disease all around the world. Stephen Cunnion, MD wrote:

*“Have you heard of an epidemic in Guangzhou? An acquaintance of mine from a teacher’s chat room lives there and reports that the hospitals there have been closed and people are dying.”<sup>3</sup>*

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The resulting email trail included a reassuring report that the Hong Kong Secretary for Health, Welfare and Food, Dr. Yoh Eng-kiong, was in hot pursuit of this new infectious disease, working with mainland China authorities in the province of Guangdong. He called on the public not to be unduly concerned, words that were obviously not heeded considering the fear storm that soon tore around the world.

It was realized later that SARS had stewed quietly for several months within Guangdong's more than 75 million inhabitants but as soon as word leaked out, the disease also spread, almost at the speed of email, as if it was the internet carrying the infection.<sup>4</sup>

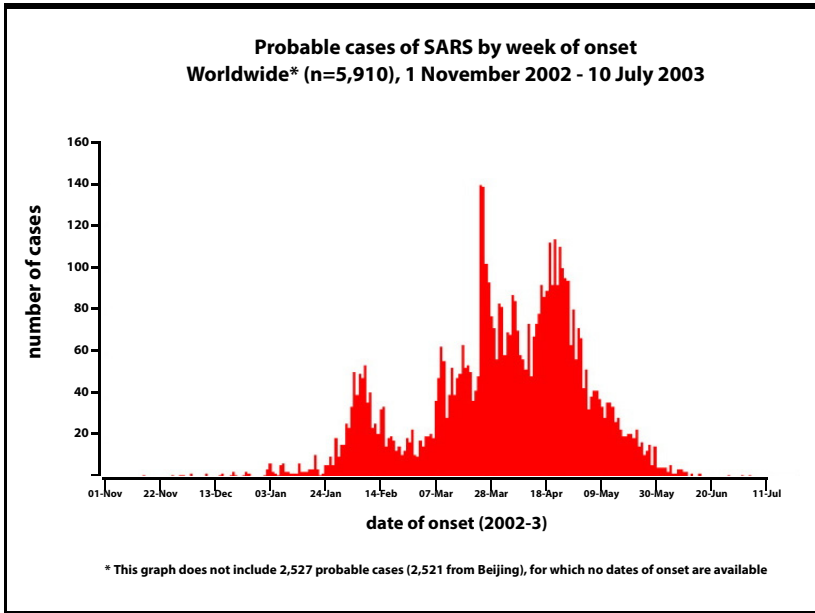
On February 15<sup>th</sup>, less than a week later, Hong Kong became the second country hit with the first of its eventual 1,755 cases. Within the next ten days the three other countries that would end up being hardest hit had their first cases, Canada on February 23<sup>rd</sup> and Taiwan and Singapore two days later.

The economic damage was severe, with reduced travel to and from affected areas. Major metropolitan centers in Asia were under siege for weeks – Hong Kong, Singapore and Taipei in particular. In the North American epicenter, Toronto, twenty-five thousand people were quarantined, 438 were diagnosed with SARS and 44 deaths were registered as SARS between February and August of 2003.<sup>5</sup>

Hotels in the city emptied as tourists and convention goers canceled. Fear among local residents left theaters, shopping malls and restaurants empty. Nobody wanted to travel to Toronto and no other airport wanted flights from there either. Total economic damage was estimated at hundreds of millions of dollars.<sup>6</sup>

Strangely enough, however, there was little impact on any other major city in North America, even those like Vancouver, San Francisco and Los Angeles, with large Asian immigrant populations, a great deal of tourism, and many daily flights to and from Asia.

Three months into this time of incredible, worldwide panic and fear, researchers announced that a previously unknown coronavirus had been proven to cause SARS, leading to the hope of vaccines and diagnostic tests. But only two months later, in July, the disease disappeared. Despite predictions of an annual recurrence, a possible small outbreak of less than 10 cases in China in early 2004, and a few false alarms, it sank without a trace.



**Figure 1. The Rise and Fall of the SARS Epidemic<sup>7</sup>**

## What was SARS?

Almost as inexplicable as the rapid rise and fall of the SARS epidemic is its definition. According to WHO a *suspect* case of SARS was highly constrained in both space and time but the only symptom required was a fever:

- Presentation after November 1, 2002,
- High fever (over 38C – 100.4F) and
- Being in a SARS-affected area within the last 10 days or having close contact with a person with SARS.

A *probable* case also required X-Ray evidence of lung infiltrates, a positive coronavirus test (after it was decided that a coronavirus was the cause) or an autopsy revealing evidence of respiratory distress without any other known reason.<sup>8</sup>

The CDC definition of a suspect case for the United States was only slightly more stringent, requiring a finding of lower respiratory tract illness such as a cough or shortness of breath. The Canadian definition additionally required that no other cause of respiratory illness be found.<sup>9</sup>

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A definition used in Hong Kong was similar, although it contained some exclusions:

*“fever of 38°C or higher, radiological infiltrates compatible with pneumonia, and two of: chills, new cough, malaise, and signs of [lung] consolidation. We excluded patients who had known pathogens, radiological evidence of lobar consolidation, or who responded to antibiotics within 48 [hours]. Exposure to the virus was defined as coming within 0.91m (3 feet) of an index patient with symptoms of SARS when providing care. Infected hospital staff were those who acquired SARS 2-7 days after exposure, with no exposure to cases outside the hospital.”<sup>10</sup>*

These definitions are remarkable because vague symptoms – mild illness commonly found in the population – are combined with very specific criteria of time and space to produce a new illness.

The definitions ensured that only people who had been recently in contact with others with SARS were themselves diagnosed, enhancing the belief that this was a contagion. People who had not been in contact with earlier SARS victims could not be diagnosed themselves – no matter what their symptoms. The inclusion of time limitations in some of the definitions emphasized the origins in China. The CDC, for example, would not accept cases before February 1, 2003 preventing a skeptic from scanning through old medical records and finding old cases in other countries matching the definition, overturning the disease’s creation myth.

One constant with all these definitions was the presence of a fever, a body temperature of at least 38C (100.4F) *one* degree Celsius higher than the commonly referred to ‘normal’ body temperature of 37C (98.6F). Public health officials generally referred to 38C as a *high* fever in their definitions but it clearly is not. It may not even constitute a low fever for everyone.

In a 2003 study of 130 healthy adults one person had a temperature this high and three others had temperatures within half a degree. If this research holds for the general population, then we could expect that a large number of people a few will meet this lax, 38C, definition of fever, especially health care workers who have been exposed to a patient with SARS are under emotional stress from the fear that they will get infected, and may be forced to wear extra layers of protection while working.<sup>11</sup>

Outside the context of SARS, medical advice often calls 38C a low grade fever and recommends against treatment. The author and pediatrician Dr. Sears implies that fevers below 38.4C are “low-grade” and that even those above 40C do not require medical treatment as long as they quickly come down. An American pediatric clinic uses 38.9C as the upper limit for a low grade fever. A British cancer society advises that “low grade” fevers, those under 38C, “may not always need treatment”. US clinical guidelines from the Department of Health and Human Services define a high fever as

being at least 39C. Harrison's *Principles of Internal Medicine*, virtually a doctor's encyclopedia, defines an afternoon oral temperature of 37.8C as the lowest fever temperature (or a rectal temperature of 38.2C or a morning oral temperature of 37.3C). Yet, for SARS, 38C was defined as a high fever requiring immediate and drastic action.<sup>12</sup>

People trying to refine the definition and diagnosis of SARS had a problem – there simply was not much overlap between the symptoms of different people assumed to be SARS cases. A survey of Hong Kong patients found that the only symptoms common to a majority of patients were also common in other less exotic illnesses. The only universal symptom was fever, but that was because the original definition of SARS required it. Apart from that, the best they could come up with was that each of the following symptoms occurred in the majority of patients, although none occurred in more than three-quarters:

- Chills or rigors;
- Muscle pain;
- Cough;
- Headache;
- White blood cell deficiency (lymphopenia);
- Elevated lactate dehydrogenase levels.

A study of Canada's first ten patients produced similar findings and also found X-Ray evidence for lung infection in most patients.<sup>13</sup>

Clearly many of these people were sicker than just a temperature of 38C would indicate but it is hard to conclude from this that they were all sick with the same illness and that the cause, in all cases, was the same virus.

The definition created a significant bias in favor of a diagnosis of SARS at the height of the panic and a bias away from diagnosing it after the epidemic was declared over (when contact with a SARS patient was unlikely). This may have been why one girl in China who really had pulmonary tuberculosis was diagnosed with SARS and placed with SARS patients. Tragically, the drugs she was given for SARS caused liver damage. In Taiwan, authorities eventually decided that half the deaths they had counted as SARS were not, causing the WHO to drop the worldwide death toll from 916 to 774.<sup>14</sup>

## **Transmission like Magic**

Most health care workers accepted that SARS was one of the most infectious pathogens ever known to medical science, with superman-like powers, able to leap tall buildings and travel between continents at the speed of an intercontinental

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jetliner. There was often very weak evidence for contact between a new infection and a previous SARS case but this just increased the apparent infectivity of the unknown virus believed to be its cause. Scientists reporting in the middle of the epidemic on a cluster of cases in Hong Kong found that some of the cases had only had “minimal” contact with previous cases, but did not let this prevent them from concluding that “SARS appears to be infectious in origin.”<sup>15</sup>

The case of a man, the so-called “index patient”, who is believed to have brought SARS to Hong Kong and infected 9 other people before dying, is a good illustration. His closest contact with these people was through staying on the same floor of a hotel as one of them although this man had no recollection of meeting the index patient, not even of passing him in the hallway. The index patient did have close contact with his wife, as they came from China to Hong Kong together and stayed in the same room, but she remained uninfected and well. The conclusion of these authors was not that infectivity remained unproven but that “exposure (however trivial) to source patients and fever [are] the most important pointers to the diagnosis of SARS”.

This same hotel was supposedly the place where transmission to two other people occurred, one who came to Vancouver and started an epidemic there, and one who traveled to Toronto and started that city’s crisis. Again, however, there is no evidence for any contact other than being in the same hotel.<sup>16</sup>

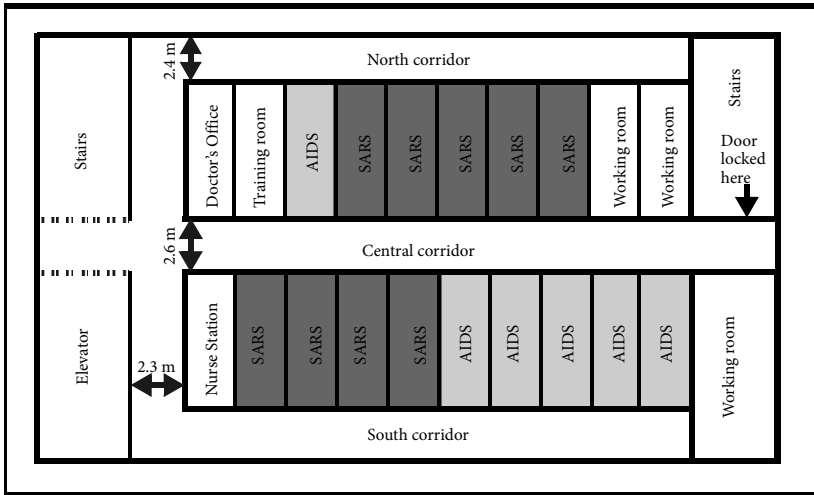
Paradoxically, the lack of evidence for contact between SARS patients heightened the fear of transmission. Obviously whatever the SARS virus was (and for some time there was debate over which virus it was) it must be extraordinarily infectious. This belief led to the exclusion of consideration of non-infectious causes: “The clusters in Toronto, Canada, and Hong Kong, in which the index cases apparently stayed on the same floor of the same hotel, together with the high number of health care workers that became infected, made the hypothesis of an environmental non-infectious cause unlikely after the first reports were known.”<sup>17</sup>

Two months after the epidemic had emerged from China scientists were already concluding that SARS was a “deadly infection”, that it had “already become a global health hazard, and its high infectivity is alarming.”<sup>18</sup>

## The Accidental Experiment

A good test for the infectivity of SARS would have been to put several SARS patients in close contact with immune-compromised patients, perhaps people with AIDS. Obviously such an experiment would be completely unethical but a Chinese hospital performed this exact experiment by mistake.





**Figure 2. Map of a Guangdong Hospital SARS and AIDS Wards<sup>20</sup>**

At the SARS epicenter, in the city of Guangzhou, in the province of Guangdong, one hospital inadvertently put 95 SARS patients on the same floor as 19 AIDS in-patients between February and May 2003, the entire duration of the SARS epidemic (Figure 2). Many out-patients were also exposed, but they were not included in the study as their exposure was harder to quantify.<sup>19</sup>

There was a corridor between the wards for hospital staff. While it was closed to patients, it had open windows on both sides, allowing unrestricted airflow between the wards. There were corridors at both ends of the wards that were open to all patients where the two groups “had contact over short distances”. All the AIDS patients had opportunistic infections and most had low CD4 cell counts normally taken to indicate severe immune suppression. While all the SARS patients wore masks only one AIDS patient did. Making matters worse, one AIDS patient was misdiagnosed with SARS and settled in among people with this deadly respiratory infection for a week before being rediagnosed and moved to an AIDS ward.

Despite all this contact not a single AIDS patient became ill with SARS, and none even had antibodies to the coronavirus that eventually became accepted as the probable cause. While the seriously immune-compromised AIDS patients appeared to be immune to SARS several health care workers at this hospital were diagnosed with the disease.

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## Route of Transmission

Most people accepted that the disease originated in Guangdong (as well as being infectious). Therefore, there be some route of infection, either directly between patients or through some kind of 'vector', such as an animal that could harbor the infection, perhaps without symptoms, and transmit it to people.

Direct transmission between people seemed unlikely as almost two-thirds of the 1,511 Guangdong SARS victims had no contact with any of the other victims including all 13 'index' cases – those blamed for the original outbreak.<sup>21</sup>

Animal transmission seemed more plausible because eleven of the early cases had jobs involving contact with live animals. This belief strengthened after the coronavirus theory took hold and a CDC investigation of people in Guangdong found that while only 1.2 percent of healthy adults surveyed were positive for the virus, 3.9 percent of 508 animal traders tested were positive and fully 72.7 percent of 22 civet traders. There was a small problem, however – not a single animal trader surveyed had SARS and only two of the SARS patients in this study were animal traders. Thus the theory morphed into the belief that SARS had long circulated among animal traders, leaving them immune, but had somehow broken out into the general population in late 2002.<sup>22</sup>

This theory runs into a big problem though, as animal traders are far from hermits. They earn their living by moving around and interacting with farmers and customers, and must have done so for years. And, like most other people, at least some must have friends and neighbors who are not normally exposed to animals. The theory clearly requires a co-factor, something that stimulated the transmission of the virus to humans for the first time, or from animal traders for the first time. In other words, to maintain the infectious theory of SARS it is necessary to admit that an infectious agent by itself was unlikely to have been the sole cause. The only way out is to assume that a non-pathogenic virus suddenly mutated into something deadly without changing enough that animal traders lost their immunity.

But, if the SARS virus had mutated into something highly pathogenic, it must have quickly mutated back into something that could not cause disease. A survey found that 80 percent of civet cats being sold in a market in Guangdong between June 2003 and January 2004 were infected. But this was after the epidemic had burned out in China, so far not to recur.<sup>23</sup>

The lack of proof for the theory that civet cats were the reservoir for the virus was did not stop authorities from killing thousands of them (but not until several months after the epidemic had already ended) and banning their sale for several months. If the cats were responsible, one would assume that the virus was circulating

on the farms where many animals were kept in close quarters. But surveyors of the Guangdong market had also surveyed farms and noted that, “no indication of civet infection was seen on most farms during the same period.”<sup>24</sup>

For a while Hong Kong also tried to blame animals, but they picked on the lowly and despised cockroach as an explanation for how 300 people at the Amoy Gardens apartment building in Kowloon (clearly not the best address in town) came down with SARS even though many of them had no direct contact with any other victims. This theory eventually died due to lack of scientific evidence. Although it made the world news, not a single scientific paper was published on the topic.<sup>25</sup>

Despite the lack of evidence that SARS was transmissible, in the end the Chinese accepted the blame. Two medical professors from the Guangzhou Institute of Respiratory Diseases concluded in a bout of self criticism in the *British Medical Journal* in 2006, worthy of the Cultural Revolution, that their epidemic was due to secrecy, the consequent slow reaction to an infectious threat, careless infection and transmission control procedures and also because of their propensity to eat animals such as civet cats.<sup>26</sup>

## **Fear only Fear Itself**

What is not considered in any of the medical papers on SARS is the possibility that the disease was spread by fear. Fear is transmitted most effectively by words which can travel at the speed of light through a fiber optic cable or over radio waves. The spread of fear was slowed by the need for at least one sick person to arrive but, given the vague symptoms that defined SARS and the need for contact with previous cases, a single elderly person with serious pneumonia (who had recently been in China or Hong Kong) could spread panic to millions of people after their arrival in another country.

It is notable that Canada was one of the countries hardest hit by the panic, but the United States was almost immune from both the panic and cases of the disease. When SARS was just starting its offensive from China to the rest of the world in February 2003, the United States was massing 100,000 troops in Kuwait for the war on Iraq that everyone knew was to come. And indeed, on March 20<sup>th</sup>, US troops crossed the border into Iraq. Canada managed to avoid participation in the war without offending their neighbor by claiming (with some justification) that their military was fully committed to the war in Afghanistan which had started earlier, shortly after September 11<sup>th</sup> 2001.<sup>27</sup>

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While Toronto (from which you can see the United States across Lake Ontario on a rare clear day) was soon locked down by fear of SARS, Americans were much more worried about their friends and neighbors being sent to fight, and about the threat of terrorism which many believed was due to the Weapons of Mass Destruction of the soon-to-be deposed, and later executed, dictator of Baghdad – Saddam Hussein.

Americans might have been preoccupied, but health authorities everywhere, with the backing of governments, moved quickly to emphasize the importance of taking SARS seriously (and the serious consequences of disobeying). China threatened to execute people or jail them for life if they broke quarantine orders. One Beijing nurse with symptoms resulted in 171 people being closely watched. Malaysia quarantined 203 people who had visited a produce market frequented by a SARS case. In Nanjing, 10,000 were quarantined. In Hong Kong over a thousand people were quarantined and a “human rights advocate” advocated banishing the families of SARS patients to quarantine camps in surrounding hills. In the greater Toronto area an order by the province’s health minister gave public health officials legal powers and they used them – 25,000 were quarantined.<sup>28</sup>

The World Health Organization declared SARS a “Worldwide Health Threat” a week before the invasion of Iraq. Not long after, US President George W. Bush took time out from fighting the Iraq war to sign an executive order adding SARS to a list of diseases for which quarantine could be imposed on healthy people because they had been exposed to someone with the disease.<sup>29</sup>

Dr. Matt Irwin, a skeptical medical doctor based in the Washington, DC, area wrote in May, 2003 that they were used to viral pneumonias and saw nothing to fear because they saw nothing new:

*“Viral pneumonias are relatively common, and in children the majority of cases of pneumonia are viral. Viral pneumonias normally resolve on their own and are thought to usually have milder symptoms than most bacterial pneumonias. They are probably under-diagnosed for a number of reasons, one of which is that there is no treatment for a viral pneumonia but everyone with bacterial pneumonia gets treated with antibiotics. Since you don’t really know which one the person has, you just presume it is bacterial to justify the antibiotic prescription. It is very difficult to identify a pathogen in most cases of pneumonia, even if it is bacterial. People use the term “atypical” pneumonia when someone presents with mild symptoms. Atypical pneumonias are thought to include some less virulent bacteria as well as viruses. On our own service at Howard we have had four cases of atypical pneumonias in the past week alone. I have been joking with our team and calling them all “SARS” cases.”<sup>30</sup>*

Obviously he and his colleagues did not share the fear, panic and desperation arising from the belief that SARS was a novel disease caused by a deadly and exceedingly infectious virus. Doctors almost universally recommended the use of high doses of broad spectrum drugs to counter the perceived danger, most notably high dose steroids and the antiviral drug ribavirin. As Hong Kong scientists wrote in 2004:

*“Ribavirin was chosen as an empiric antiviral agent for SARS therapy in the dire situation of a major outbreak of a life-threatening infection, before the etiologic [causative] agent was even identified. Ribavirin was the antiviral agent with the broadest spectrum of activity that was commercially available then, when SARS was thought to be caused by a novel virus.”<sup>29,31</sup>*

Treatment with corticosteroids was also “empiric”. This word normally means that treatment decisions are based on previous experience rather than from recommendations derived from controlled clinical trials. But in the case of SARS there was no relevant experience to draw on. The term appears to be used as a euphemism for “flying by the seat of your pants”. Others referred to SARS treatment as “experimental”, with a meaning closer to “unproven” than being studied in a controlled clinical trial, preferably randomized and double-blinded.

## **Hit Hard with Steroids, Ribavirin and Whatever**

Hong Kong led the way in defining the treatment for SARS. By May, 2003 they reported that their protocol included an antibacterial drug usually followed by ribavirin and the steroid methylprednisolone, depending on the patient’s symptoms. Both drugs were often given intravenously resulting in faster action and more drug in the bloodstream, compared with oral dosing. In severe cases the patient’s breathing was assisted with mechanical ventilation.<sup>32</sup>

The CDC in the United States reported the use of similar protocols, although the steroids chosen differed and sometimes oseltamivir, from the American drug company Gilead, was used instead of ribavirin. Singapore used a similar protocol. Toronto doctors reported after the epidemic that the empirical therapy in their first ten cases also included antibiotics along with both oseltamivir and ribavirin, without steroids.<sup>33</sup>

Although there are many defenders of the approach that was taken, it is now clear that it was at best ineffective and at worst, fatal. Even in cases where people were not killed, many were seriously disabled. In a situation like this it is very difficult to determine how good the therapy was afterwards because it is not known what would

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have happened without it. Randomized clinical trials are required to find this out and when a disease has disappeared they are impossible. Further, even if SARS returned, the use of a placebo would probably be banned as unethical, meaning that research would be more likely to compare two different steroids or oseltamivir versus ribavirin, rather than doing nothing. Yet there is no proof that only providing supportive treatment is not the best option.

Treatment decisions were defended by assuming that SARS would have had an enormously high death rate without drugs. At the Prince of Wales Hospital in Hong Kong they defended the use of both steroids and ribavirin, even though 11% of SARS cases at their hospital died. Because their treatment was not performed in an experimental context, there was no group of untreated people with SARS to compare this with, so it is not known whether this death rate would have been higher or lower without treatment.<sup>34</sup>

### Steroids

Steroids were the better understood arm of the SARS regimen, as these drugs have been used for many years for a variety of conditions, compared to ribavirin which is newer and previously used only for a few relatively rare conditions such as Hepatitis C or Hantavirus. Steroids were used to prevent lung damage, although they are known to be immuno-suppressive and to have several other adverse effects, especially when used at high doses.

It is therefore not surprising that considerable damage from the high doses of these drugs was found. A psychiatrist who screened more than a hundred SARS patients in Hong Kong found that more than half were still experiencing neurological problems, such as difficulty concentrating, after being declared cured of SARS. It was also found that the total dosage of the steroid prednisolone was the leading risk factor for osteonecrosis, the destruction of bones within the body. When it occurred it was about a hundred days after steroid therapy was terminated and often involved major bones such as the hips and femur. One study found that more than 30 percent of SARS patients experienced this devastating disorder and another found it in over 40 percent.<sup>35</sup>

Another complication was a reduction in some classes of immune system cells although, because this is also a complication of ribavirin treatment, it is not possible to lay the blame entirely on steroids. Chinese doctors reported one patient who died of the fungal infection aspergillosis after prolonged treatment with corticosteroids, a clear sign of severe immune suppression. When the patient looked like he was dying, one of the treatments given in desperation was even higher doses of methyl-

prednisolone. One month after being quarantined with chills and a fever he was dead with fungus spread throughout his body.<sup>36</sup>

The bottom line for patients was survival, and there were reports that this was lower in patients who were dosed with steroids. No hard conclusions can be drawn because SARS treatment was as far as from a controlled clinical trial as can be imagined. Instead of randomizing patients to drug treatments they were assigned based on the judgment of doctors, introducing both the doctor's opinion and the initial condition of the patient as uncontrolled variables.

If sicker patients were more likely to be given steroids, then some of the survival disadvantage could have been due to their condition, not the drugs. However, an analysis of the factors associated with death in SARS patients showed that those who received pulsed doses of methylprednisolone had the highest excess risk – these patients were twenty-six times more likely to die than those who did not receive this therapy. By contrast SARS patients admitted to a hospital suffering from shortness of breath were only four times more likely to die than those who did not have this symptom at admission. Another study showed that the half of a group of forty SARS patients who were infused with serum from recovered patients instead of pulsed prednisolone had a lower mortality. Among children, the risk of severe illness was twenty-seven times higher when methylprednisolone was used (after statistical adjustment for severity of initial illness).<sup>37</sup>

After the SARS panic of 2003 had waned there were cautious words about the use of steroids, although few doctors wanted to come right out and claim that they had killed many people. Hong Kong doctors recommended waiting for one day if the patient's condition was deteriorating or for two if the patient's condition was stable (but not improving) before starting steroids. Japanese doctors, reacting to reports of many cases of osteonecrosis among Chinese SARS patients agreed that this was a recognized side effect of steroids but merely recommended that "To determine the optimal timing, dosage, and duration of steroid treatment, randomized controlled trials should be done."<sup>38</sup>

In a letter to the *New England Journal of Medicine* during the epidemic American doctor Yuji Oba was more blunt:

"The use of systemic corticosteroids in patients with the severe acute respiratory syndrome (SARS) is of serious concern...Early treatment with corticosteroids in patients with ARDS [acute respiratory distress syndrome] is highly controversial and is not a standard of care, at least in North America. Although ribavirin has activity against coronaviruses and human metapneumoviruses in vitro, there are no antimicrobial agents with proven effectiveness for the treatment of SARS at this point. And the use of corticosteroids with possibly inef-

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fective antiviral agents in patients with viral-induced pneumonitis or ARDS can be hazardous.”<sup>39</sup>

Some Hong Kong doctors defended their position with the statement that “SARS is a serious disease with a rapid downhill course.” They obviously did not think that their use of steroids might have given their patients the downhill push. Two Hong Kong doctors did consider this disturbing possibility, saying “The natural history of untreated SARS in both adults and children remains unclear...the probability of spontaneous recovery could not be ascertained.” Their analysis of the experience of children diagnosed with SARS led them to caution “The use of corticosteroids in viral infections is controversial and is potentially hazardous.” although they did agree that it could be useful in patients facing respiratory failure.<sup>40</sup>

### Ribavirin the Nuke

Ribavirin is a nucleoside analog just like AZT (azidothymidine), the first and most controversial drug claimed to kill HIV. Nucleosides are the four ‘beads’ used to create chains of DNA from four base molecules – Adenine, Cytosine, Guanine and Thymidine. When three phosphate groups are added to a nucleoside it can be inserted into a growing chain of DNA. The nucleoside, which retains one of the phosphates, is then known as a nucleotide and, unless it is at the end of a DNA chain, another molecule will soon be added, like another bead on a chain.

Nucleoside analogs, sometimes ironically known as ‘nukes’, are molecules that behave much like a true nucleoside (Guanine in the case of ribavirin). But there is a difference – while they can join a growing DNA or RNA chain they do not allow the addition of another nucleotide, thereby terminating the chain. The theory to support the use of compounds with such a potentially deadly activity is that since viruses need to construct DNA or RNA chains every time they divide, interfering with this will stop viral replication. The problem with this theory is that several types of human cells continually divide, including those that produce white and red blood cells, muscle, our hair and nails, so these will be damaged by nucleoside analogs.

Less well-known is the impact on mitochondria. These organelles are found in every living animal cell and are responsible for the regulation of energy within the cell. Without mitochondria, life would be impossible. Mitochondria have their own DNA but do not have the sophisticated DNA repair mechanisms of the cell nucleus, so are particularly susceptible to damage from nucleoside analogs. In addition, the energy currency of cells that mitochondria bank is a reserve of phosphate molecules, so drugs that bind them will also affect mitochondria. Mitochondrial damage results in widespread and serious damage to muscle (including heart muscle), nerves, bone



marrow, the pancreas, liver and also can result in an excess of lactic acid in the blood. But all cells that use energy are susceptible.<sup>41</sup>

Cell division is necessary for the replenishment of both white and red blood cells and ribavirin, as expected, does cause serious anemias, especially in people who already have heart disease:

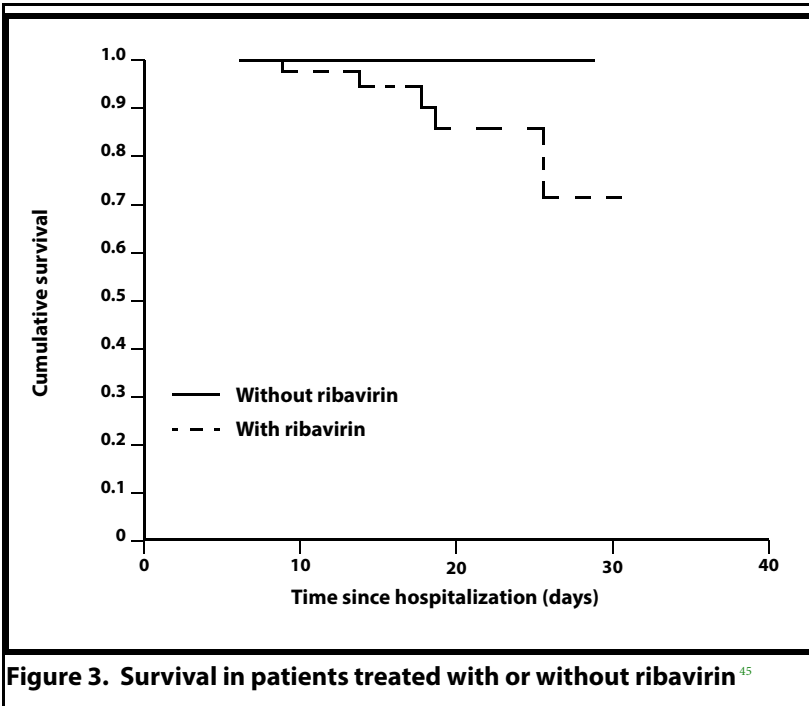
*“Systemic use of ribavirin (intravenous or oral administration) may cause dose-dependent anemia due to hemolysis [red blood cell destruction] and bone marrow suppression, both of which are reversible. Hemolytic anemia usually occurs after 10 days of therapy but may appear as early as 3 to 5 days after initiation of the drug; it is usually observed with doses of 1–2 g [per day] or higher. Patients with pre-existing cardiac disease in whom anemia develops are at increased risk of deterioration of cardiac status.”<sup>42</sup>*

The danger of the drug should have been known because of previous experiences published in scientific journals. It was approved for investigational use against the hantavirus pulmonary syndrome in the United States in 1993 and 1994 but the results were not encouraging. 71% of recipients became anemic and the fatality rate was 47%. Yet, because this was, yet again, not a randomized clinical trial (there was no placebo group not receiving the drug), it was possible to salvage ribavirin’s reputation by postulating that the people taking the drug were already at risk for the serious illness (and death) found only after starting to take it. In other words, the researchers imagined a similar group of people not taking the drug and somehow knew that more than 71% of them would become anemic and more than 47% would die.<sup>43</sup>

In Canada the amount of ribavirin used was certainly more than enough to cause the serious adverse effects associated with doses over a gram a day. A group of 21 Toronto MDs and scientists reported in JAMA at the tail end of the epidemic that their patients had greatly exceeded the danger zone, being infused with four grams a day for the first four days of treatment, followed by three days at 1.5 grams. They noted that, “The use of ribavirin was temporally associated with significant toxicity”, including significant decreases in hemoglobin levels and signs of hemolysis (blood cell destruction).<sup>44</sup>

Seven doctors and scientists from Taiwan writing in the journal *Chest* noticed similar problems with the administration of ribavirin, although their patients were only given between 1.0 and 1.2 grams per day, and they took it orally rather than intravenously. They still noticed hemoglobin decreases starting about three days after the start of therapy and they found that this was associated with “a significantly higher mortality rate”. Patients who were suffering from a lack of oxygen (which ribavirin may exacerbate by killing red blood cells) had a 29% death rate on ribavirin. Their conclusion was that, “Unless ribavirin can be shown to be effective against SARS-

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coronavirus, the risk of anemia posed by this drug argues against its use in SARS patients”, although one has to wonder how such toxicity would be acceptable even if it could kill the coronavirus.<sup>46</sup>

They apparently eventually concluded that ribavirin couldn’t even kill the coronavirus (or stop whatever was causing SARS) because one of the authors wrote to me later, in response to questions about their study, saying that “Anemia was observed in almost every patient receiving ribavirin which did not seem to stop disease progression.”<sup>47</sup>

It is interesting to compare the amount of ribavirin given every day to the number of targets for it – the number of chromosomes in the human body. If we take an upper estimate of the number of cells in the average human, of about  $100 \times 10^{12}$  (one hundred trillion) and multiply this by the number of chromosomes in each cell, 46, we can estimate that there are about  $4.6 \times 10^{15}$  (4.6 quadrillion) chromosomes. Ribavirin is a molecule with a molecular weight of 244.206, using the weight of a single hydrogen atom or proton as the reference (molecular weight 1). We know that 1 gram of hydrogen has about  $6.022 \times 10^{23}$  atoms (Avogadro’s constant), meaning that each gram of ribavirin has about  $2.46 \times 10^{21}$  atoms. Dividing this by the number of

chromosomes, we can estimate very roughly that a dose of one gram of ribavirin provides about half a million molecules for every chromosome in the body. Clearly there is a large potential for genetic damage and for interference with the cell division that regularly occurs in many types of human cells with such massive doses.<sup>48</sup>

Several doctors from Hong Kong, where ribavirin was used on all SARS cases, rose to the defense of ribavirin after this criticism from Taiwan. They raised some legitimate uncertainties: doctors may have assigned patients to take ribavirin because they were sicker, and the patients who became hypoxemic (had low blood oxygen) might have been sicker without the doctors realizing it. It is true that none of the ribavirin studies were randomized controlled trials. But there is no evidence to say that their interpretation is right, and serious blood deficiencies are clearly associated with the use of this drug.<sup>49</sup>

Other Hong Kong doctors stated, quite incredibly, that “limited data suggest that, at least in adults, dosages of about 2 g/day might be effective while not causing severe adverse reactions. Such doses should be considered for further studies. Doses lower than 1 g/day appear ineffective.”<sup>50</sup>

The defensiveness of the Hong Kong doctors may have derived not so much from scientific conservatism but from fear of embarrassment – that an intervention for which they literally defined the protocol and which was so vigorously applied by them actually might have killed many of their patients.<sup>51</sup>

The best argument for ribavirin was that it, while a double-edged sword, could be wielded carefully enough to hurt the purported SARS virus more than the patient. But this did not hold any water as Hong Kong researchers were forced to admit that several studies showed that the drug was ineffective against the virus. Researchers using high doses in mice even found that it increased some measures of the presence of the virus in lungs.<sup>52</sup>

Not every doctor in Hong Kong was a ribavirin enthusiast. Dr. S. T. Lai writing in a European medical journal put the problem succinctly, “Ribavirin is a controversial drug with low efficacy and significant toxicities.” Singapore doctors wrote that “It is highly unlikely that ribavirin alone has any significant clinical benefits in the treatment of SARS”, perhaps using the word “alone” to carefully open the door for the use of ribavirin in combination with other drugs. This is a strategy that has been used profitably in diseases like AIDS and cancer, where the market value of an ineffective drug can be preserved by claiming some mysterious synergistic effect with other drugs that have also suffered in ignominy after being found to be useless (or worse) by themselves.<sup>53</sup>

There are some doctors and researchers who do believe that ribavirin can be safe and effective but contradictions between their statements indicate that a safety margin

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might not exist. Ribavirin was used for Hepatitis C before SARS came along. For this disease researchers reported 0.8 grams per day as safe but 1.0 or more as putting the patients at a significantly higher risk of anemia. A Chinese doctor, reviewing several reports on the use of the drug against SARS, concluded that 1 gram per day would be ineffective, 4 grams would cause serious adverse effects but that 2 grams “might not” cause severe adverse reactions.<sup>54</sup>

Despite those who believe in the drug, a cold hard look at the data shows that higher doses of ribavirin really were deadly. In Canada, where it was used most enthusiastically, 61% of a group of 110 patients had hemolytic anemia, a condition where blood cells literally break apart, and a similar number had unusually low calcium and magnesium levels. They concluded that the drug was neither safe nor effective, and warned that patients who had taken it should be followed up because of its teratogenic potential (ability to produce malformations in growing body parts, particularly a concern with any SARS patients who might later get pregnant).<sup>55</sup>

In China, the death rate from SARS was much lower than in Canada and significant side effects from ribavirin were not observed. This may have been because the dosage was lower (0.8 grams per day in Guangzhou) and the drug was given orally rather than intravenously. Similarly, fewer side effects were observed in children, but they were also given the drug orally. It has been estimated that only about half of a dose of ribavirin taken orally is actually absorbed.<sup>56</sup>

## Ventilation

Many people with SARS did have difficulty breathing, a problem that often worsened as treatment progressed. Supplemental oxygen was then required and could either be provided invasively, through tubes inserted through the patient’s nose into their airway, or non-invasively, usually through a mask over the mouth and nose connected to an oxygen tank. If conditions worsened further, intubation might be used. This is a tracheotomy, a hole in the throat, through which oxygen is pumped.<sup>57</sup>

While more than 90 percent of SARS patients in Hong Kong were invasively ventilated, with only one hospital deciding to use non-invasive ventilation, doctors later concluded that:

*“Compared to invasive mechanical ventilation, non-invasive ventilation as initial ventilatory support for acute respiratory failure in the presence of severe acute respiratory syndrome appeared to be associated with reduced intubation need and mortality...neither patients nor [health care workers] would be well-served should intubation and [invasive mechanical ventilation] remain endorsed as the only mode of ventilatory support for SARS...Since specific therapy is lacking in*

*this disease, early [non-invasive ventilation] application may provide safe and effective support for [acute respiratory failure] while waiting for the disease to abate spontaneously or respond to immunomodulatory therapy.”<sup>58</sup>*

It was not just Hong Kong, Japanese medical researchers found that, “Noninvasive positive pressure ventilation was commonly employed in many Chinese hospitals and was found to avert the need for intubation and invasive ventilation in up to two-thirds of SARS patients with deterioration.”<sup>59</sup>

One of the reasons for the use of invasive ventilation is that it protects health care workers from the breath of patients with what was believed to be a highly infectious virus. The fear was great but afterwards the risk was determined to be quite low. The Hong Kong report on ventilation found not a single case of transmission to a health care worker due to the use of non-invasive ventilation.<sup>60</sup>

It is reasonable to suspect that the greater success of non-invasive ventilation was merely an artefact of these people being less sick upon admission. However, the one hospital in Hong Kong that used only non-invasive ventilation also reported that on two measures, the level of lactic acid in the blood, and X-Ray findings, their patients were sicker at the time of admission than those admitted to hospitals relying on invasive ventilation. Not only were health care workers not at risk, but patients in this hospital did better, even though they started off in worse shape.<sup>61</sup>

A Canadian study of SARS victims that examined their recovery up to a year after discharge from hospital reported that, “All SARS survivors who were mechanically ventilated reported muscle wasting and weakness at the time of hospital discharge.” The researchers also found other complications in some patients.<sup>62</sup>

## **Traditional Chinese Medicine**

Traditional Chinese medicine was associated with a relatively low death rate in 77 SARS patients treated with integrated Chinese and Western medicine at a hospital in Guangdong, even though many of the cases were diagnosed as severe. It is impossible to tell, however, whether this is due to the benefits of Chinese medicine or simply less exposure to Western medicine as the patients were still given antibiotics, steroids and the anti-flu drug oseltamivir, although none were given ribavirin, and the aggressiveness of the drug treatment was less.<sup>63</sup>

## **Future Drugs**

Ribavirin, being a nucleoside analog, fits within the first generation of AIDS drugs, so naturally some proposed the use of a protease inhibitor, the second

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generation of AIDS drugs. For some reason the combination of the two Abbott protease inhibitors lopinavir and ritonavir packaged together by Abbott as kaletra seemed most popular. This may be simply because protease inhibitors are less toxic than nucleoside analogs, so when they are compared head to head you can conclude that protease inhibitors are better. But, without randomized trial with a proper placebo, it is impossible to conclude that either active therapy is safe or effective (let alone safe *and* effective). Protease inhibitors are hardly without side effects, severe metabolic abnormalities are commonly found with them including lypodystrophy (fat redistribution), extremely high cholesterol levels, heart disease, liver failure, diarrhea and kidney stones.<sup>64</sup>

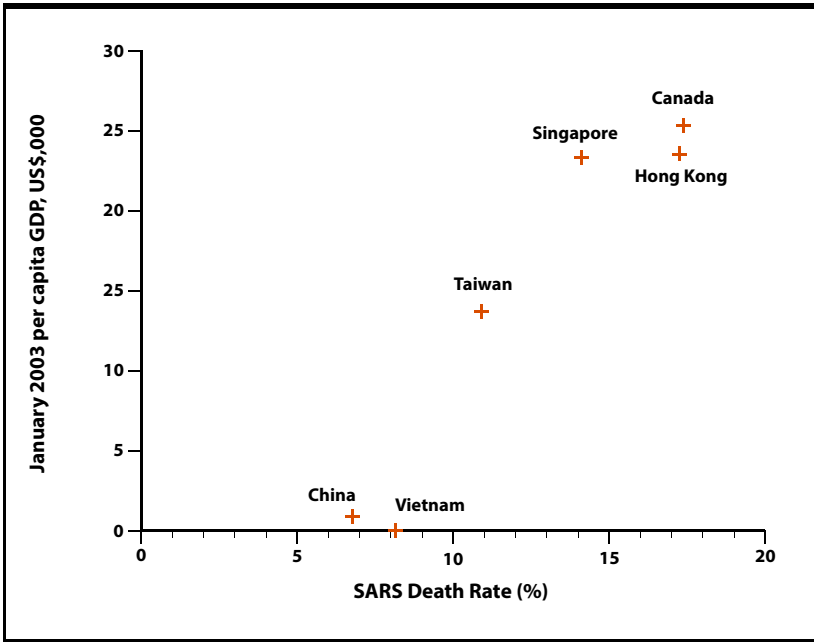
But while kaletra or other protease inhibitors designed for use in AIDS might be the front runners for use on victims of the next SARS epidemic, if one is ever declared again, there are many others in the running, some already in existence, some being just ideas still on the drawing board – EICAR (a similar drug to ribavirin but scarily considered to be 10 to 100 times more potent), anti-Helicases, Fusion Inhibitors, Endonucleases, Human monoclonal antibody, Human interferon, RNA interference drugs, Valinomycin, Glycyrrhizin (found in liquorice), the malaria drug Chloroquine and the blood thinner Pentoxifylline.<sup>65</sup>

### Life got Worse after SARS

The over-reaction to the perceived SARS crisis by doctors around the world, but especially in Hong Kong, had tragic consequences in the lasting side effects from the aggressive treatments used. Luckily the crisis burned itself out quickly or the hundreds of victims might have ballooned into the thousands. The disease's rapid exit was probably due to the disease's definition, requiring contact with a SARS victim. This critical portion of the definition may have both artificially created the crisis, and caused it to peter out. Once severe isolation and quarantine were put in place it became very difficult to come in contact with someone with SARS. Therefore, regardless of symptoms, a diagnosis of SARS was impossible.

Aggressive treatment for SARS has left a legacy of bone degeneration due to steroids, sudden kidney failure probably caused by ribavirin, and long-lasting muscle weakness probably caused by both classes of drug as well as by mechanical ventilation and intubation. During treatment, patients suffered from liver damage and serious anemia, which resolved slowly, if at all, afterwards. Even those who escaped such serious side effects were found to have reduced physical capacity and quality of life a year later.<sup>66</sup>

Roughly, the richer the country, the more aggressive the therapy. This translated into more than double the death rate in Canada than in mainland China. The



**Figure 4. Per capita GDP versus SARS Death Rate**<sup>67</sup>

Canadian death rate by April 2003 was 11 percent, but in China, where the epidemic had started almost three months earlier, the death rate was only 4 percent. After the epidemic was over the World Health Organization compiled statistics and found that the death rate in China was 7 percent of all SARS cases, 8 percent in Vietnam, 11 percent in Taiwan, 14 percent in Singapore, but 17 percent in both Hong Kong and Canada. Figure 4 shows a good correlation between higher income and a higher death rate from SARS.<sup>68</sup>

Doctors could be accused of performing a giant experiment on their patients in their panic to do something and not sit idly by. But it was far worse than a poorly thought out experiment – it was not an experiment at all. For all the pain, agony, fear and death that resulted, there was no unambiguous data collected. Patients were assigned to treatment by the whim of their doctor or hospital, rather than by randomization. This made it difficult to extract meaning from the data that was collected and reported.

One of the important questions that remains unanswered, due to the lack of experimental evidence, is whether patients would have fared better with only traditional nursing and not aggressive doctoring. If patients had been kept comfortable, properly hydrated and, if needed, given supplemental oxygen in the least

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intrusive way would they have fared better? Even if controlled clinical trials are funded in the future they will likely only be to test drug A against drug B, not drug treatment versus no or minimal treatment.

### Personal Stories

During and following the SARS crisis many stories of individuals who were diagnosed surfaced. They suffered greatly, if they even survived, and illustrate the devastating effects of the drugs that were prescribed to them. A good sign that a disease is non-infectious is the lack of cases among health care workers, but SARS was a major exception to this rule – often the majority of cases were among nurses and doctors. This was largely due to the definition, as contact with a SARS victim was necessary to be diagnosed with SARS, and with hospitals closed to visitors, often only health care workers had contact with SARS patients.

A case report in the *Hong Kong Medical Journal* describes the experience of a medical officer who developed flu-like symptoms (fever, headache, muscle pain etc.). Despite no evidence of lung infection he was treated for SARS for 21 days, enduring ribavirin, prednisolone and intravenous methylprednisolone, as well as many other drugs. In a similar report in *Lancet*, this time written by the victim himself, Dr. Eugene Wu from Hong Kong described how he was prescribed corticosteroids and ribavirin then, after his first recovery, was dosed with a second round of drugs, after which his condition deteriorated and he was re-hospitalized.<sup>69</sup>

These doctors were lucky, they at least survived the panicky onslaught of pharmaceuticals unlike Dr. Carlo Urbani of *Medicins sans Frontiers* who earned the dubious honor of becoming the SARS martyr after he treated the first SARS patient in Vietnam, was then diagnosed himself and, after eighteen days in hospital, died on March 29, 2003. His treatment was probably similar to the standard treatment in Vietnam which the CDC describes as including a “wide range of antibiotics” (but admits that they were, “not observed to be clinically beneficial”). Early SARS patients, probably including Urbani, were given oseltamivir when it was believed that the disease was caused by a flu virus although this recommendation was changed to ribavirin later (the CDC also admits that, “Neither oseltamivir nor ribavirin was observed to have any clinically beneficial effect on the course of illness”). Urbani was likely also given steroids like most other Vietnamese patients. The CDC made no judgment about whether this therapy was of any benefit.<sup>70</sup>

Another compelling story was of the Toronto nurse Susan Sorrenti, described in several Canadian papers. Like many health care workers she was exposed to a SARS patient, consequently banished into quarantine at her own home where she was supposed to monitor herself for a 38C or higher fever, or any signs of respiratory



illness. She woke up on the morning of March 28, 2003 with a temperature of 38.1C and immediately checked herself in as a SARS patient. The reporters noted that, at this time, she was still feeling fine.

Doctors put Sorrenti on antibiotics and steroids. As her temperature climbed and her condition worsened she was put on ribavirin. Now she was short of breath and nauseous. Her steroid dose was increased. She now needed oxygen and developed a cough. She was now not only nauseous but also constipated. Apart from SARS drugs she was also taking tranquilizers to deal with her depression, anti-emetics to try unsuccessfully to reduce her nausea and acetaminophen with codeine to ease her aches and pains. Eventually her condition stabilized although several weeks after leaving the hospital she still had difficulty walking. She described the side effects of ribavirin as “just horrible”.<sup>71</sup>

### **Mostly Dire Post Mortems**

The authors of a systematic review on SARS treatment commissioned by the World Health Organization Expert Panel on SARS Treatment concluded:

*“Despite an extensive literature reporting on SARS treatments, it was not possible to determine whether treatments benefited patients during the SARS outbreak. Some may have been harmful. Clinical trials should be designed to validate a standard protocol for dosage and timing...Of patients treated with ribavirin 36%–61% developed haemolytic anaemia, a recognised complication with this drug, although it is not possible to rule out the possibility that SARS-CoV infection caused the haemolytic anaemia, as there is no control group. One study noted that over 29% of SARS patients had some degree of liver dysfunction indicated by ALT levels higher than normal, and the number of patients with this complication increased to over 75% after ribavirin treatment”<sup>72</sup>*

On the other hand, a good example of how scientists could miss the stunningly obvious was the observation by twenty eight doctors and scientists that, for forty-nine patients who had experienced severe SARS, “The mean time between onset of symptoms and worsening [for nineteen] was 8.3 days. Intravenous ribavirin 8 mg/kg every 8 h for 7–10 days and steroid was given in 49 patients at a mean of 6-7 days after onset of symptoms.” Yet, despite their finding that, on average, symptoms worsened less than two days after starting steroid therapy, the researchers stated, presumably with straight faces, that “Severe complicated cases are strongly associated with underlying disease and delayed use of ribavirin and steroid treatment.” They simply could not comprehend that their aggressive treatment could have been the trigger for the worsening of symptoms after a week. Nor did they apparently consider that the

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reason symptoms did not resolve within the first week might have been because of initial dosing with a variety of anti-bacterials and the antivirals oseltamivir and amantadine.

Doctors writing in *JAMA*, contradicted this optimism:

*“Treatment strategies have included empirical antibiotic therapy, intravenous and oral ribavirin, corticosteroids, and intravenous immunoglobulin. However, no compelling evidence exists that these strategies improve clinical outcome, and use of ribavirin has been associated with significant toxic effects.”*<sup>73</sup>

Doctors who worked in Toronto during the SARS crisis reported numerous health problems during and after treatment: <sup>74</sup>

*“67% reported alopecia [hair loss]; it resolved in most patients by 6 months and was not significantly associated with ribavirin administration in this limited sample...*

*Fatigue (64%, 54% and 60%) and difficulty sleeping (47%, 50%, and 44%) were commonly reported at the 3-, 6-, and 12-month time points, respectively. Patients also frequently mentioned shortness of breath (44%, 49%, and 45%)...*

*Only 12%, 18% and 13% of patients stated that they were asymptomatic at the 3, 6, and 12-months visits...*

*All SARS survivors who were mechanically ventilated reported muscle wasting and weakness at the time of hospital discharge. 3 patients had new reactive airways disease. 2 patients had entrapment neuropathies, 2 patients had hoarseness after prolonged intubation, and 1 patient had heterotopic ossification and discomfort at old chest tube sites...*

*A reduced walking distance was present in 31% of patients at 3 months and in 18% at 1 year. There was no relationship between 6-minute walk distance and exposure to steroids, burden of comorbid illness, preexisting pulmonary dysfunction, or degree of weight loss.”*

Despite this list of problems that occurred in a large fraction of patients, and persisted for a long time, note how the doctors tried to minimize the role of the medications, “not significantly associated with ribavirin” and “no relationship [with] exposure to steroids”.

In Hong Kong fingers were pointed at health authorities, starting in the major scientific journal *Nature* in May 2003, in the middle of the epidemic, when it was discovered that many people who had died after being diagnosed with SARS (and dosed with ribavirin and high dose corticosteroids) showed evidence of damage to organs other than the lungs, including the lymph and spleen.<sup>75</sup>

A treatment protocol, however, is rather like the Titanic, steaming on until the patient's voyage through life is abruptly terminated as these Hong Kong doctors document:

*“Ribavirin therapy was begun around day 6, and therapy with pulsed steroids was begun around day 9. The radiographic appearance of SARS in the patients in whom it was fatal continued to deteriorate until the point at which the worst radiograph was acquired (the fourth milestone) at the end of the 3rd week.”<sup>76</sup>*

Sadly, the result of this tragedy was not to persuade researchers to question whether drug therapy was necessary but just a race to find new drugs. The ancient doctor's motto, “First do no harm”, appears to have been forgotten.

An investigation into the response of the Hong Kong health authorities was expected by some to name the names of people responsible for the tragedy but it merely retreated into bureaucratic suggestions for better communications and reporting structures, as if medical decisions had nothing to do with the size and intensity of the disaster. One suspects that even if the report had been more scathing it would have criticized doctors for not acting aggressively enough, it is highly unlikely that it would have criticized them for being too aggressive.<sup>77</sup>

Fifteen medical professionals from Hong Kong were repentant, confessing in 2004 that, “In retrospect, we do not think that ribavirin alone has any significant effect in arresting disease progression. Corticosteroids are also probably unnecessary for patients who do not develop significant respiratory compromise. With hindsight, the use of corticosteroids in less severe SARS cases and for the early management of SARS during the phase of active viral replication was probably inappropriate.”<sup>78</sup>

## **Coronavirus as Cause**

SARS almost certainly broke the world record for the shortest time between breakout and widespread acceptance of the causative agent – a coronavirus.

There was early and widespread agreement that SARS was infectious based on the presence of clusters of cases, reinforced by an early editorial in the prestigious and influential *New England Journal of Medicine*:

*“It is becoming quite clear that SARS is an infectious disease. Case clusters in Canada and Hong Kong, as reported in [the New England Journal of Medicine] make a noninfectious environmental cause highly unlikely and implicate a novel coronavirus and a novel metapneumovirus in its pathogenesis.”<sup>79</sup>*

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This evidence did eliminate the environment as the sole cause but showed a distinct lack of imagination, as the possibility that the panic caused by the first case outside China (based more on the location of the victim rather than anything unusual about the symptoms) could cause a massive over-reaction by doctors and massive over-medication, particularly severe in richer countries, was not even considered.

### Koch's Postulates

Koch's postulates are the simple logical rules laid down by German bacteriologist Robert Koch in the 1800s. They have been stated in many different ways but essentially they require that before a germ can be accepted as the cause of the disease it must be shown to be present in every case of the disease, must be isolated and injected into another organism where it must cause the same disease and finally must once more be isolated from these secondary cases. In a speech to a medical conference in 1936 (published in 1937), the famous virologist Thomas Rivers quoted the even more famous Koch speaking at a medical conference in 1890 that:

*"If it can be proved:*

***first** that the parasite occurs in every case of the disease in question, and under circumstances which can account for the pathological changes and clinical course of the disease;*

***secondly**, that it occurs in no other disease as a fortuitous and non-pathogenic parasite; and*

***thirdly**, that it, after being fully isolated from the body and repeatedly grown in pure culture, can induce the disease anew;*

***then** the occurrence of the parasite in the disease can no longer be accidental, but in this case no other relation between it and the disease except that the parasite is the cause of the disease can be considered."*<sup>80</sup>

Note that these are logical postulates, not scientific. They are based on the idea that a cause must come before a consequence, and that the cause must be present to cause a consequence. Thus it is unlikely that they will become outdated as more scientific data comes available. The problem for virologists was succinctly expressed by Rivers: "It is obvious that Koch's postulates have not been satisfied in viral diseases."

This is a problem for all viruses. I am unaware of a single virus that has satisfied Koch's postulates. Rivers' caution is as true today as in 1936. While I could discuss Koch's postulates with any virus, they play a particularly important role with SARS.

In particular Rivers did not like the *habeas corpus* (“bring the body”) requirement of Koch. Like many other virologists, he wanted to rely on immunologic reactions (e.g. antibody tests) or other highly indirect methods of detection. They abhor the necessity to actually produce, through purification, the virus. Now, virologists are leaving immunological evidence behind, relying more on genetic evidence obtained with PCR, the Polymerase Chain Reaction.

Much more recently, the journal *Nature* allowed Dutch researchers to claim “Koch’s postulates fulfilled for SARS virus” in May of 2003 by allowing the phrase in the title. We will see that this was clearly not true and provides simply amazing evidence that the claims of virologists are not examined critically, but simply accepted on the basis of faith or consensus.<sup>81</sup>

### **Thomas Rivers’ Postulates**

The Dutch authors cited Rivers’ speech in some of their papers, something very unusual in a scientific world where anything over ten years old is suspect. Soon we will get to what these authors said that Rivers said, but this is what Rivers actually said:

- “(a) A specific virus must be found associated with a disease with a degree of regularity.*
- (b) The virus must be shown to occur in the sick individual not as an incidental or accidental finding but as the cause of the disease under investigation.”*

This is stunning in its simplicity, and in its stupidity. The first condition relies on the prestige of the virologist who declares that an association between a virus and disease occurs “with regularity”, something undefinable that clearly allows cases of disease without the virus. And the second is a clear example of a tautology, circular reasoning.

### **What the Dutch said Rivers said**

In three different papers the Dutch authors describe Rivers’ 1936 postulates as:

- 1) isolation of virus from diseased hosts;*
- 2) cultivation in host cells;*
- 3) proof of filterability;*
- 4) production of comparable disease in the original host species or a related one;*
- 5) re-isolation of the virus; and*
- 6) detection of a specific immune response to the virus.*<sup>82</sup>

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This is not even close to what Rivers said, and they repeated it. How could they have read Rivers' paper and completely misinterpreted them? I first wrote to the Dutch researchers, but received no response, which is unfortunately quite common. But I got my first clue when I read the third paper, published in *Lancet*, and this time, for the same list of six postulates, saw that they didn't reference Rivers but *The Dictionary of Virology*.

Sure enough, the dictionary contained a restatement of Koch's postulates with an escape clause for viruses followed by the six ersatz postulates, also erroneously referencing Rivers:

*“Koch's Postulates: Criteria for determining whether a particular microorganism is the etiological agent of a disease. They are: (1) The microbe is regularly found in lesions of the disease. (2) It can be grown in pure culture in vitro. (3) When such a pure culture is inoculated into experimental animals, a similar typical disease results. (4) The microbe can be re-isolated from the experimentally induced disease in animals.”*

*“These postulates were modified for application to virus diseases by Rivers (1937) to read: (1) Isolation of virus from diseased hosts. (2) Cultivation in experimental hosts or host cells. (3) Proof of filterability (to exclude larger pathogens). (4) Production of a comparable disease in the original host's species or in related ones. (5) Reisolation of the virus. (6) Detection of a specific immune response to the virus. Rivers TM (1937) J Bacteriol 33,1.”<sup>83</sup>*

This leads to the conclusion that the Dutch researchers never read Rivers' 1937 article, even though it is not difficult to find – it is even available online. Perhaps the Dutch felt that a reference to the original paper was more prestigious than a reference to a dictionary, a vanity that would have lain undiscovered if the dictionary had quoted Rivers accurately.

With this new clue I was able to track down the editor of the dictionary, Dr. Brian Mahy, in the middle of preparing a new edition. He admitted that he had never verified this entry – that it had been written by another editor, who had unfortunately died a few years before. He responded in defense of his past colleague stating that the six conditions were probably a restatement of what Rivers wrote, just not a direct quote (although the dictionary implies they are a direct quote by using the verb “read”). I pointed out restatement was an unlikely explanation for a number of reasons, including that several of the critical words in the dictionary ‘quotation’ are completely missing from Rivers' speech (e.g. “isolation”, “diseased hosts”, “filterability” and “production”), not even words based on the roots of these words are present. Even stronger evidence is a direct contradiction between the dictionary's postulate six (“Detection of a specific immune response to the virus”) and Rivers who makes it

clear that he believes that immune responses to viruses are often not present and are not essential to prove causation.<sup>84</sup>

The most charitable explanation is that the now-deceased editor was stating what he thought he remembered and never got around to checking. But how exactly the words arose is not the big problem – it is the fact that virology has no agreed standard for verifying that a virus is cause of a disease. Koch's postulates are alternately rejected or embraced by virologists depending on what is convenient at a particular moment. The papers by Dutch researchers that started my investigation are a perfect illustration of this. Two of the three papers include the phrase "Koch's postulates fulfilled" in the title yet the claim in the body of the papers morphs to, "Koch's postulates, as modified by Rivers for viral diseases". Adding to the confusion, the original 1937 paper, which seems to be commonly cited but rarely read, explicitly rejects the postulates ("It is obvious that Koch's postulates have not been satisfied in viral diseases. Moreover, it is equally evident that proof of the etiological significance of viruses has been obtained without their satisfaction...Koch's postulates as proposed by him do not have to be fulfilled in order to prove that a virus is the cause of a disease...now it is possible to bring excellent evidence that an organism is the cause of a malady without the complete satisfaction of the postulates").

Rivers finished his trashing of Koch's postulates by claiming that time and progress had passed them by, "At the time when they were formulated Koch's postulates were essential for the progress of knowledge of infectious diseases; but progress having left behind old rules requires new ones which some day without doubt will also be declared obsolete. Thus, in regard to certain diseases, particularly those caused by viruses, the blind adherence to Koch's postulates may act as a hindrance instead of an aid."<sup>85</sup>

This set of six new postulates might have arisen as a false memory in the mind of a dictionary editor, and they can be criticized for not insisting that a virus be purified, but it is important to know whether they were met by the Dutch researchers and the authors of four previously published papers, three from the *New England Journal of Medicine* and one from *Lancet*. The Dutch claimed that these earlier papers had satisfied the first three postulates and that their research, described compactly in less than a single page, established the last three. And they were not the only scientists to claim to have found a causative association between a coronavirus and SARS.

## **#1 – Carlo Urbani Paper**

One of the papers from the May 15, 2003 issue of the *New England Journal of Medicine* included the deceased Carlo Urbani as a co-author although he likely was not alive to have written a word of it. The authors claim in their abstract that, "a novel

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coronavirus was isolated from patients who met the case definition of SARS” and, in addition, that the virus was shown to kill cells because, “Cytopathological features [evidence of diseased cells] were noted in Vero E6 cells inoculated with a throat-swab specimen”. They also claim that electron microscope pictures show particles typical of coronaviruses and that a stable portion of the “consensus” coronavirus genome was used to extract the RNA of this novel virus. Based on this they claimed that, “the evidence indicates that this virus has an etiologic [causative] role in SARS”.<sup>86</sup>

These authors must have hoped that nobody would ever critically read their research and discover just how thin the evidence was, and how flawed their experiments. They imply that they isolated this coronavirus from many of the nineteen people they had samples from. Actually they only achieved isolation, according to their definition, in samples from four of those people. And in two of the cases where they had multiple samples from different parts of the body, only one from each of the cases resulted in successful isolation.

Antibody tests were not much more successful, only 7 of 17 people tested produced positive results. Their conclusions relied heavily on the genetic PCR (Polymerase Chain Reaction) test for the coronavirus genome even though this is not, by their standards, isolation. PCR was, however, positive in 15 out of 17 samples tested.

They achieved 100 percent correlation by lumping the three tests together. The two people for which PCR was negative and the two for which PCR was not done were also negative by isolation but did have positive antibody tests. Abracadabra! Everyone with SARS was now positive, although nobody was positive on all tests.

Remember this trick – you will soon come across it again.

### #2 – German Study

Another *New England Journal of Medicine* by a group of German scientists made the modest claim that “The novel coronavirus might have a role in causing SARS.” After developing a genetic test based on material fished out of cell cultures (not from purified virus) they claimed that all five patients with probable SARS tested positive on samples mostly taken from their lower respiratory tracts. So did three of thirteen with probable SARS, but for these people they used samples of mucus from their noses. They also found that none of 21 healthy contacts were positive, but for these people they used fecal samples.

The accuracy on a very small number of people with or without SARS is impressive, but if the test is accurate for “probable SARS” it indicates that doctors had been severely over-diagnosing the condition. This is a common problem that occurs



with diagnostic tests, when there is a disagreement between two tests or between a test and clinical diagnosis, there is no 'gold standard' to sort it out, no completely accurate yardstick by which to compare the two competing methods. Often diagnostic tests win out over diagnosis because a test seems more scientific and less biased, but that does not mean that they are necessarily more accurate.

A clearer problem occurred when they studied a number of samples from the patient from whom the test was developed and less than half of the samples were positive. Of the two cases blamed on close contact with him, one person was negative on all samples that were genetically tested, and the other was negative on 16 out of 21 tests.<sup>87</sup>

### **#3 – The Canadians**

Canada, which had sacrificed the economy of Toronto to SARS, obviously did not want to get left out of the scramble to claim the discovery of the cause of this disease. In the third *New England Journal of Medicine* paper, scientists from Toronto and Vancouver studied samples from the first ten cases diagnosed in Canada. They were unable to detect any virus by viral culture, electron microscopy and a number of specific viral tests, but they did detect genetic material that they claimed matched a human metapneumovirus and a new coronavirus. The coronavirus was detected using probes from scientists in Hong Kong and at the US Centers for Disease Control although only five out of the nine patient samples were positive on this test. At another laboratory, tests were performed on samples from four of the patients and two of those were positive. It is hard to understand how this paper was described as meeting any reasonable criteria for "isolation of virus from diseased hosts, cultivation in host cells, and proof of filterability".<sup>88</sup>

### **#4 – The Hong Kong Paper**

The last paper referenced by the Dutch researchers in *Nature* was published in the prestigious British medical journal *Lancet* whose editors claimed that it provided, "strong evidence that SARS is associated with a novel coronavirus" which, if read carefully, is clearly not a claim that the coronavirus is the cause of SARS, just a claim that they often hang around together.

Unfortunately, this paper's authors, all from Hong Kong hospitals, also used tricks to try to boost a weak association to the level of a causative association. They found the RNA that they believed was from a new coronavirus in only half the nose swab specimens tests (22 out of 44) and in just over half (10 of 18) of the stool samples from fifty Hong Kong patients. They also found antibodies in 35 out of 50 samples

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(but because at least 32 of the 50 patients had at least two antibody tests, this actually only represents about half of the total number of patients).

Even after lumping all three tests together, and taking a leap of faith, they only claimed hesitantly that, “If seropositivity to human pneumonia-associated coronavirus in one serum sample *or* viral RNA detection in the nasopharyngeal aspirates or stools is deemed evidence of infection with the coronavirus, 45 of the 50 patients have evidence of infection.” The authors and the *Lancet* editors made much of the fact that none of these tests were positive in 80 other hospital patients (not all with respiratory diseases), nor in 200 blood donors. This is not terribly comforting because a test that had a false positive rate of 1:1000 would probably not be positive in 200 people, but would produce about 300,000 false positives if used on, for example, all Americans.<sup>89</sup>

### #5 – The Last Three Postulates

The Dutch scientists in *Nature* claimed to fulfill the last three of the mysterious six conditions to prove causality using two (2) macaques. The monkeys were inoculated with impure materials taken from a cell culture believed to contain the SARS coronavirus. The paper does not indicate whether the materials were put into the macaques directly into the brain (as is often done), under the skin or, more realistically, into their noses, and did not respond to requests for clarification. Another limitation is that the animals were only monitored for six days before being killed.

One of the two macaques suffered “respiratory distress” but the other only suffered from a skin rash and tiredness. The scientists claimed to have detected viral RNA in their nose and throat two to six days after the injection. Antibodies were found in two other macaques who were allowed to live for 16 days, although no information on the health of these monkeys was provided.

An autopsy of the two macaques found severe lung disease in one of them (presumably the one suffering from respiratory distress) and unusual large cells (syncytia) that they claimed were indistinguishable from those found in lung tissue of human SARS victims.

The scientists claimed that the virus cultured from the monkeys was visually identical to the virus inoculated into them, but only provided the ‘after’ electron microscope photograph, not the ‘before’ picture.

This data was used to support the claim that they had produced a comparable disease to SARS (although they only claimed that they had done this in one of the four

macaques), that they had re-isolated the virus, and that they had detected a “specific immune response” (but not in the one monkey that had the SARS-like disease).

There were no controls in this study, no macaques injected with materials produced in the same way differing only in the absence of the virus. There was no evidence provided that the monkeys were exposed to the virus in the same way that humans must be. And there was no consideration that injecting foreign cells and the chemicals used to culture them into a monkey could cause allergic or other toxic reactions, perhaps the source of the rash that both monkeys experienced.

Their claim of ‘isolation’ is based on a debased definition used by virologists, bearing no resemblance to the dictionary or chemical definitions which mean to separate one thing from everything else, derived from the Latin/Italian word ‘isola’ meaning island. They claimed to have pictures of the virus, but without purification there is no way to tell if the particles shown under the electron microscope are actually the source of the RNA that is claimed to be from a coronavirus. There is no way to know, in fact, just from electron micrographs, that the particles are even a virus at all.

The sloppiness of the coronavirus science is hard to understand until you realize that the search never really was for the cause of SARS, it was for the virus most closely associated with SARS, even if the association wasn’t very good. Think of it like the World Cup, which is not a tournament to find the best sports team in the world, but is limited to finding the best soccer team. Nobody would expect a hockey team to win when only soccer teams are allowed to play. The winner was indeed the best virus theory but what’s best is not always good.

[#5710 – Other 4 monkeys](#)

[#5711 – Later paper on aetiology](#)

## **The Coronavirus Theory In Practice**

If a coronavirus was the cause then the symptoms of the disease should peak in parallel with the amount of virus in the body. A Taiwanese study on eight patients with SARS found instead that the coronavirus RNA (‘viral load’) peaked and started to decline 3.5 to 5 days *before* the major symptoms of the disease reached their worst levels. The authors of this study noted that “SARS progresses after the viral loads decrease” implying that something else was driving disease progression.<sup>90</sup>

One of the top virologists in Canada during the time of SARS was Dr. Frank Plummer, scientific director of the Canadian National Microbiology Laboratory in Winnipeg, a man who was often in the news when journalists wanted scientific information during the Canadian SARS epidemic. If only he had critically examined

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the papers claiming virus causation, as a senior scientist should have, he would have been prepared to find that only a minority of people might test positive if a single SARS test was used (rather than using multiple tests and declaring a positive if any one of them was positive). He said, in late April 2003, that the SARS coronavirus had only been found in 40 percent of recent cases in Canada. This was an even lower fraction than in the five out of nine of the first cases in Canada, those most convincingly connected to Hong Kong, who tested positive. Plummer pointed out that because all of the SARS victims being tested were linked to the original case transported from Hong Kong, they should all have the same virus, implying that, if this was not the case, the virus could not possibly be the cause of the disease.<sup>91</sup>

Plummer pointed out another problem for the coronavirus theory was that the virus was found in low quantities early in the disease when people were believed to be most infectious, and higher quantities later. Yet even he was trapped within the belief that it had already been proven that SARS was infectious, he just held out for a different virus, although all other plausible candidates had been eliminated by the coronavirus.

It is not only important for a test to be positive in people with the condition the test is searching for, it is equally important – perhaps even more important – that the test not react in samples from people who do not have the condition. Although the coronavirus researchers found few positive tests in the small number of people they tested who did not have SARS and were not exposed to someone with SARS, Plummer found it in 20 percent of such people. Although Plummer had not tested a random sample neither had the coronavirus researchers.

When Hong Kong researchers tried to rectify this they found that 0.48 percent of people in Hong Kong survey tested positive for the coronavirus without having any symptoms of SARS. This means that, out of the 6.9 million in Hong Kong at that time, just over 33,000 people were likely positive but only 1,728 ever were diagnosed with SARS. That is, about 5 percent of the people who had the SARS virus according to the test they used showed symptoms of SARS, which would certainly change the perception of the SARS virus as incredibly dangerous.

This research illustrated the danger of claiming that something is absent in a large population through testing only a small group of people. If something is really only present in half of one percent of a population you would have to test about 460 randomly selected people to be 90 percent sure of stumbling across at least one case, something that the original coronavirus researchers did not come even close to doing.<sup>92</sup>

Infectious disease specialists can wave this problem away by describing these people as asymptomatic carriers. But this only raises more questions. If so many people were ‘silent’ carriers of the disease and the SARS virus was believed to be

highly infectious, why did it not spread far and wide? If healthy people testing positive were not infectious, what was different about them? What co-factor gave the 1,728 people in Hong Kong SARS that was not present in the other 33,000 or so people who had the virus but never got ill? What value would there be in a test that would only show a 5% chance of future illness? Perhaps the greatest omission was that there was no proof that these healthy people would not have reacted positive to the test prior to the SARS epidemic. If this was the case then clearly the test is of no value, even if it does sometimes react correctly, and even if the coronavirus is the cause of SARS.

A US CDC survey in Guangdong, the epicenter of the original epidemic, was intended to find out if animal traders were at higher risk of exposure to this coronavirus. It did find that 13 percent of the 508 traders tested did have antibodies, which was much higher than the 2.9 percent of hospital workers involved in SARS control, the 1.6 percent of Guangdong CDC workers tested and, most importantly, higher than the 1.2 percent of 84 healthy adults tested. However, that latter figure, although small, if extrapolated to the entire province of Guangdong which had a population over 86 million in 2000 would indicate that there had been more than one million silent infections, something that is very difficult to believe.<sup>93</sup>

Another implication of this data is that if there were such a large number of people with infections but no symptoms, and if these people were infectious, then quarantining sick people would be of absolutely no value. The only alternative would be to test 86 million people and quarantine about one million of them, something that obviously would be impractical and that would probably cause more disease and illness through the crowding of so many people into medical concentration camps.

Another problem that these surveys reveal is that a much smaller percentage of silent infections became overt SARS in China than in Hong Kong. There were 1,511 cases among an estimated one million or so SARS antibody positive people in Guangdong. In other words less than 0.2 percent went from infection to disease. Yet in Hong Kong, where people are generally richer than in mainland China, and presumably better fed, the rate was about 5 percent, more than twenty five times *higher*.

There has not been a random survey of people in Guangdong province, so it is possible that the rate of antibody positivity was much higher in the CDC sample than in the general population. However, if a disease could spread rapidly throughout the population of Hong Kong, nobody was doing anything that could have stopped it from spreading among the population of Guangdong during the several months between the initial outbreak in November 2002 (in Guangdong) until the rest of the world became aware of it in February of the next year. It was only when the disease caught the attention of the world outside China that a serious response, including quarantine, began.

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The growing belief in the SARS coronavirus, or at least the tests for it, suffered another blow from Canada when a large number of elderly people with cold-like symptoms in Surrey, British Columbia tested positive for the virus genome. Shortly after it was concluded that it was a false alarm, perhaps a relatively harmless related virus. Perhaps, considering the shoddiness of the science behind the rushed indictment of the coronavirus, it was a perfectly good test, it just was not a test for the cause of SARS.<sup>94</sup>

## Other Respiratory Causes

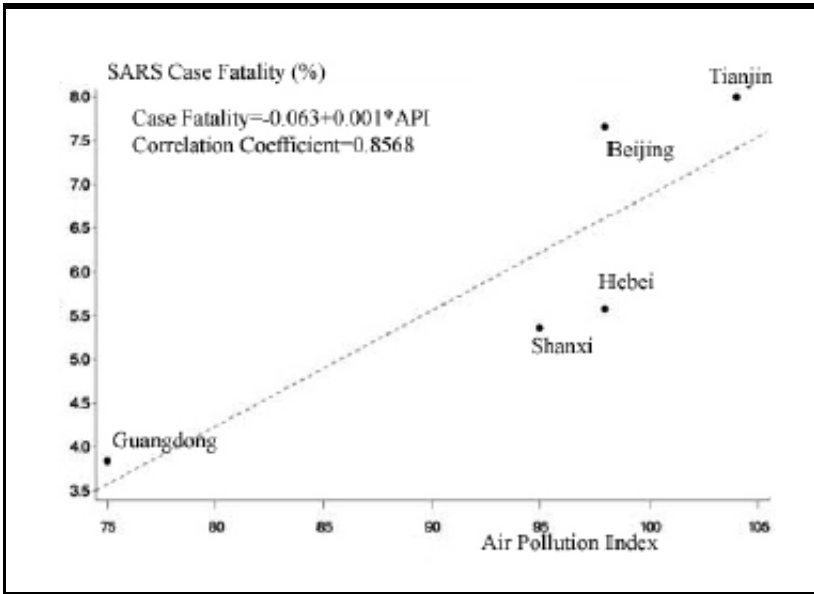
Perhaps there is a parallel Earth where environmental contamination gets the blame for everything, no matter whether it is really the cause or not. Perhaps on that planet emails are sent blaming a new, but unknown, chemical, when a few cases of disease with unusual symptoms are found, even though the real cause is some kind of germ. This is certainly not the planet we live on. Here, even when it is known that the epicenter of a *respiratory* disease suffers from extraordinarily high levels of *air pollution*, no attention is given to this obvious fact.

In 1997, almost exactly five years before the SARS epidemic, Mark Hertsgaard wrote in *Atlantic Monthly* that:

*“Sixty to 90 percent of the rainfall in Guangdong, the southern province that is the center of China’s economic boom, is acid rain. Since nearly all the gasoline in China is leaded (Beijing switched to unleaded gas in June [1997]), and 80 percent of the coal isn’t ‘washed’ before being burned, people’s lungs and nervous systems are bombarded by an extraordinary volume and variety of deadly poisons. One of every four deaths in China is caused by lung disease, brought about by the air pollution and the increasingly fashionable habit of cigarette smoking.”<sup>95</sup>*

Things had not got any better by 2002, just two months before the November, 2002 outbreak the *South China Morning Post* reported that, “Hong Kong was shrouded in thick smog for the second time in less than a week.” Although much of the pollution was generated by vehicles and industry in Hong Kong, a lot also came across the border from Guangdong, with offshore typhoon Sinlaku stopping the polluted air from escaping. The combination of high levels of emissions, still air and hot temperatures was reaching “dangerous levels.”<sup>96</sup>

In a look back at the epidemic in China, researchers concluded that the death rate was higher in cities with worse air pollution (Figure 5). The authors concluded that, “SARS patients from regions with moderate APIs [air pollution indexes] had an 84% increased risk of dying from SARS compared to those from regions with low



**Figure 5. SARS Fatality Rate and Air Pollution Index**

APIs. Similarly, SARS patients from regions with high APIs were twice as likely to die from SARS compared to those from regions with low APIs...the possibility of a detrimental effect of air pollution on the prognosis of SARS patients deserves further investigation”<sup>97</sup>

The Toronto area might be clean compared to China but it is hardly pristine. The *Toronto Star* newspaper wrote about an asthma sufferer, in April 2003 right in the middle of the SARS epidemic:

*“Smog has never forced her into hospital, as it has tens of thousands of others...Health Canada says smog is responsible for 7.7 percent of all the premature deaths in Toronto, Hamilton, Ottawa, London and Windsor...The Ontario Medical Association estimates that this year, polluted air will kill 2,030 people across Ontario, including 530 in Toronto and 360 in the rest of the GTA [Greater Toronto Area]...It will also lead to 47,810 emergency visits to Ontario hospitals and 14,090 admissions. Health-care costs and lost productivity will combine for a price tag of nearly \$1.25 billion.”<sup>98</sup>*

By comparison with the 890 estimated annual deaths from air pollution in the Toronto area, SARS was blamed for only 44 deaths by local doctors, although even

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that number might be too high – Statistics Canada reported only 30 deaths for the entire epidemic.<sup>99</sup>

### Lessons Not Learned

Doctors decided that SARS was caused by a virus right from the first email that brought it to the attention of the world outside China. Not knowing what the virus was they threw their most potent drugs at the patients – broad spectrum antibiotics, corticosteroids and broad spectrum antivirals, most fatally ribavirin.

The belief that SARS was highly contagious was strengthened by definition – by requiring that SARS only be diagnosed in people who had contact with a previous SARS case. This also made it much more likely that health care workers would be diagnosed. It also meant that evidence that the disease was not transmissible was misinterpreted as evidence that the virus had almost supernatural powers of transmission. Virus particles could exit a person via a cough or sneeze, land on a door handle or elevator button, and hours later infect someone who touched the same object.

While doctors were overdosing their patients with drugs, virologists were searching for the virus with the best link to the disease. The best that was found was a new coronavirus, although the evidence that they were indeed working with a virus is weak. But, more importantly, the weak association between this supposed new virus and the disease was not considered to be the mortal blow to the viral causation theory.

Sadly, the tragedy has not been recognized as iatrogenic (caused by medical treatment) and, while ribavirin is unlikely to be used if similar circumstances arise in the future, the same basic approach will be taken, perhaps with lower doses of steroids, and a different drug, perhaps the AIDS protease inhibitor Kaletra.

Virus hunters have proven once again that they will always interpret scientific data in a way that bolsters their viewpoint and have shown that they are incapable of thinking outside the viral envelope.

The only positive thing about SARS is that its flawed definition that brought it to prominence so rapidly might have sealed its doom. Since it is now impossible for a person to have recent contact with someone with SARS, it now appears impossible for anyone to ever be diagnosed again.



## Chapter 2 – SARS - Steroid and Ribavirin Scandal

pg	#	Notes
51	1	Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. WHO. 2004 Apr 21.
51	2	Dead silence. CBC Disclosure. 2003 Nov 18. <a href="http://www.cbc.ca/disclosure/archives/031118_sars/whoknew.html">http://www.cbc.ca/disclosure/archives/031118_sars/whoknew.html</a>
51	3	Pneumonia - China (Guangdong) : RFI. ProMedMail.org. 2003 Feb 10. Drexler M. Safety net. TJOLS. 2008 Apr 2. <a href="http://www.tjols.com/printer_article-611.html">http://www.tjols.com/printer_article-611.html</a>
52	4	A 2002 population estimate for the registered population of Guangdong was 76.49 million. Because of China's registration system there may have been millions more people registered to other places in China but living in Guangdong because of the economic opportunities. <a href="http://www.thegprd.com/about%5Ceconomic.html">http://www.thegprd.com/about%5Ceconomic.html</a>
52	5	Mazzulli T et al. Severe acute respiratory syndrome: overview with an emphasis on the Toronto experience. Arch Pathol Lab Med. 2004 Dec; 128(12): 1346-50.

## The Infectious Myth

pg # Notes

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- 52 6** The economic impact of SARS. CBC News. 2003 Jul 8.  
<http://www.cbc.ca/news/background/sars/economicimpact.html>
- 53 7** Epidemic curves - Severe Acute Respiratory Syndrome (SARS). WHO. 2007 Mar [accessed].  
<https://www.who.int/csr/sarsepicurve/epiindex/en/>  
At the time of writing the links on this page were broken. The text of the graph was redrawn, and simplified for clarity.
- 53 8** Case Definitions for Surveillance of Severe Acute Respiratory Syndrome (SARS). WHO. 2003 May 1.  
<http://www.who.int/csr/sars/casedefinition/en/print.html>
- 53 9** Severe Acute Respiratory Syndrome (SARS) and Coronavirus Testing --- United States, 2003. MMWR. 2003 Apr 11; 52(14): 297-302.  
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5214a1.htm>  
Severe Acute Respiratory Syndrome (SARS) case definitions. Health Canada. 2003 Apr 2.
- 54 10** Mackowiak PA et al. A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. JAMA. 1992 Sep 23-30; 268(12): 1578-80.
- 54 11** Seto WH et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). Lancet. 2003 May 3; 361(9368): 1519-20.
- 55 12** <http://www.askdrsears.com/html/8/t082100.asp>  
<http://www.cancerhelp.org.uk/help/default.asp?page=12850>  
*Refers to fevers up to 38C as "low grade" and advises that it "may not always need treatment".*  
[http://guideline.gov/summary/summary.aspx?doc\\_id=5613&nbr=3783](http://guideline.gov/summary/summary.aspx?doc_id=5613&nbr=3783)  
*Indirectly defines a high fever as at least 39C.*  
[http://www.ramsdellpediatrics.com/ArticlePage.aspx?Article\\_id=185](http://www.ramsdellpediatrics.com/ArticlePage.aspx?Article_id=185)  
*Defines low grade fevers as those under 38.9C (102F).*  
Harrison's Principles of Internal Medicine. McGraw-Hill. 2005.

**55 13** Lee N et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med.* 2003 May 15; 348(20): 1986-94.  
Poutanen SM et al. Identification of Severe Acute Respiratory Syndrome in Canada. *N Engl J Med.* 2003 Mar 31; 348(20).

**55 14** Wong CY et al. Tuberculosis in a SARS outbreak. *J Chin Med Assoc.* 2004 Nov; 67(11): 579-82.  
Taiwan revises data on SARS; total toll drops. *NY Times.* 2003 Oct 5.  
<http://query.nytimes.com/gst/fullpage.html?res=9F00E4DB123CF936A35753C1A9659C8B63>

**56 15** Tsang KW et al. A Cluster of Cases of Severe Acute Respiratory Syndrome in Hong Kong. *N Engl J Med.* 2003 May 15; 348(20): NEJMoa030666.

**56 16** Poutanen SM et al. Identification of Severe Acute Respiratory Syndrome in Canada. *N Engl J Med.* 2003 Mar 31; 348(20): NEJMoa030634.

**56 17** Selmi C et al. The search for a practical approach to emerging diseases: the case of severe acute respiratory syndrome (SARS). *Dev Immunol.* 2002 Sep; 9(3): 113-7.

The publication date is before the SARS epidemic because of a long delay in publishing this journal issue. The article was not actually written and the issue not published until 2003.

**56 18** Lee N et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med.* 2003 May 15; 348(20): 1986-94.

**57 19** Chen XP et al. Lack of severe acute respiratory syndrome in 19 AIDS patients hospitalized together. *J Acquir Immune Defic Syndr.* 2003 Oct 1; 34(2): 242-3.

**57 20** ibid

**58 21** Prevalence of IgG Antibody to SARS-associated coronavirus in animal traders - Guangdong province, China, 2003. *MMWR.* 2003 Oct 17; 52(41): 986-7.

He JF et al. [An epidemiological study on the index cases of severe acute respiratory syndrome occurred in different cities among Guangdong province]. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2003 May; 24(5): 347-9.

## The Infectious Myth

pg # Notes

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**58 22** Prevalence of IgG Antibody to SARS-associated coronavirus in animal traders - Guangdong province, China, 2003. MMWR. 2003 Oct 17; 52(41): 986-7.

He JF et al. [Severe acute respiratory syndrome in Guangdong Province of China: epidemiology and control measures]. Zhonghua Yu Fang Yi Xue Za Zhi. 2003 Jul; 37(4): 227-32.

**58 23** Tu C et al. Antibodies to SARS coronavirus in civets. Emerg Infect Dis. 2004 Dec; 10(12): 2244-8.

**59 24** ibid

**59 25** China under pressure over Sars. BBC News. 2003 Apr 9.  
[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details\\_term=cockroach%20AND%20sars](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=cockroach%20AND%20sars)

**59 26** Zhong N et al. What we have learnt from SARS epidemics in China. BMJ. 2006 Aug 19; 333(7564): 389-91.

**59 27** [http://en.wikipedia.org/wiki/2003\\_invasion\\_of\\_Iraq](http://en.wikipedia.org/wiki/2003_invasion_of_Iraq)  
Severe acute respiratory syndrome - SARS. The Business Development Group. 2003 Apr 11.

**60 28** Timeline: SARS virus. BBC News. 2004 Jul 7.  
<http://news.bbc.co.uk/2/hi/asia-pacific/2973415.stm>  
SARS timeline. CBC. 2003 Dec 15.  
<http://www.cbc.ca/news/background/sars/timeline.html>  
<http://www.rediff.com/news/2003/apr/24sars1.htm>  
[http://.cbc.ca/stories/2003/05/06/sars\\_china030506](http://.cbc.ca/stories/2003/05/06/sars_china030506)  
<http://www.cbsnews.com/stories/2003/04/15/eveningnews/main549528.shtml>

Mazzulli T et al. Severe acute respiratory syndrome: overview with an emphasis on the Toronto experience. Arch Pathol Lab Med. 2004 Dec; 128(12): 1346-50.

- 60 29** Timeline: SARS virus. BBC News. 2004 Jul 7.  
<http://news.bbc.co.uk/2/hi/asia-pacific/2973415.stm>  
Executive order on quarantinable diseases. 2003 Apr 4.  
<http://www.hhs.gov/news/press/2003pres/20030404a.html>  
Fact sheet on legal authorities for isolation/quarantine. 2005 May 3.  
<http://www.cdc.gov/ncidod/sars/factsheetlegal.htm>
- 60 30** Irwin M. SARS critique. Personal correspondence. 2003 May.
- 61 31** Leung CW et al. Severe acute respiratory syndrome among children. *Pediatrics*. 2004 Jun; 113(6): e535-43.
- 61 32** So LK et al. Development of a standard treatment protocol for severe acute respiratory syndrome. *Lancet*. 2003 May 10; 361(9369): 1615-7.
- 61 33** Preliminary clinical description of Severe Acute Respiratory Syndrome. *MMWR*. 2003 Mar 28; 52(12): 255-6.  
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5212a5.htm>  
Poutanen SM et al. Identification of Severe Acute Respiratory Syndrome in Canada. *N Engl J Med*. 2003 Mar 31; 348(20): NEJMoa030634.  
Hsu L-Y et al. Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. *Emerg Infect Dis*. 2003 Jun; 9(6).
- 62 34** Sung JJ et al. Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. *Thorax*. 2004 May; 59(5): 414-20.
- 62 35** Luck A. SARS patients 'suffer brain damage' from steroid cocktail. *Daily Telegraph*. 2003 Jun 1.  
Hong N et al. Avascular necrosis of bone in severe acute respiratory syndrome. *Clin Radiol*. 2004 Jul; 59(7): 602-8.  
Cinatl J Jr et al. High-dose hydrocortisone reduces expression of the pro-inflammatory chemokines CXCL8 and CXCL10 in SARS coronavirus-infected intestinal cells. *Int J Mol Med*. 2005 Feb; 15(2): 323-7.

## The Infectious Myth

pg # Notes

**63 36** Zhang Z et al. Longitudinal alteration of circulating dendritic cell subsets and its correlation with steroid treatment in patients with severe acute respiratory syndrome. *Clin Immunol.* 2005 Sep; 116(3): 225-35.

Wang HJ et al. Death of a SARS case from secondary aspergillus infection. *Chin Med J (Engl).* 2004 Aug; 117(8): 1278-80.

**63 37** Tsang OT et al. Coronavirus-positive nasopharyngeal aspirate as predictor for severe acute respiratory syndrome mortality. *Emerg Infect Dis.* 2003 Nov; 9(11): 1381-7.

Soo YO et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect.* 2004 Jul; 10(7): 676-8.

Leung CW et al. Severe acute respiratory syndrome among children. *Pediatrics.* 2004 Jun; 113(6): e535-43.

**63 38** Tsang K et al. Severe acute respiratory syndrome: scientific and anecdotal evidence for drug treatment. *Curr Opin Investig Drugs.* 2004 Feb; 5(2): 179-85.

Fujii T et al. Current concepts in SARS treatment. *J Infect Chemother.* 2004 Feb; 10(1): 1-7.

**64 39** Oba Y et al. The use of corticosteroids in SARS [letter and response]. *N Engl J Med.* 2003 May 15; 348(20): 2034-5.

**64 40** *ibid*

Leung CW et al. Clinical picture, diagnosis, treatment and outcome of severe acute respiratory syndrome (SARS) in children. *Paediatr Respir Rev.* 2004 Dec; 5(4): 275-88.

**65 41** Brinkman K et al. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as a common pathway. *AIDS.* 1998 Oct 1; 12(14): 1735-44.

Koren G et al. Ribavirin in the treatment of SARS: A new trick for an old drug? *CMAJ.* 2003 May 13; 168(10): 1289-92.

**65 42** Koren G et al. Ribavirin in the treatment of SARS: A new trick for an old drug? *CMAJ.* 2003 May 13; 168(10): 1289-92.

**65 43** Loutfy MR et al. Interferon alfacon-1 plus corticosteroids in Severe Acute Respiratory Syndrome. *JAMA*. 2003 Dec 24; 290(24): 3222–8.

**65 44** Booth CM et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA*. 2003 Jun 4; 289(21): 2801–9.

**66 45** Chiou HE et al. Adverse effects of ribavirin and outcome in severe acute respiratory syndrome: experience in two medical centers. *Chest*. 2005 Jul; 128(1): 263-72.

Followed up by an email exchange with one of the authors, Dr. Y.T. Lu, in May, 2007.

**66 46** ibid

**66 47** ibid

**67 48** Molecular weight of ribavirin is 244.206:

<http://en.wikipedia.org/wiki/Ribavirin>

Number of cells in the human body is estimated as about 100 trillion:

[http://en.wikipedia.org/wiki/Human\\_biology](http://en.wikipedia.org/wiki/Human_biology)

**67 49** Chu CM et al. Ribavirin should be tested in clinical trials in combination with other antiviral agents for severe acute respiratory syndrome. *Chest*. 2005 Dec; 128(6): 4050.

**67 50** Leung CW et al. Clinical picture, diagnosis, treatment and outcome of severe acute respiratory syndrome (SARS) in children. *Paediatr Respir Rev*. 2004 Dec; 5(4): 275–88.

**67 51** Chu CM et al. Ribavirin should be tested in clinical trials in combination with other antiviral agents for severe acute respiratory syndrome. *Chest*. 2005 Dec; 128(6): 4050.

So LK et al. Development of a standard treatment protocol for severe acute respiratory syndrome. *Lancet*. 2003 May 10; 361(9369): 1615–7.

**52** Hui DS. An overview on severe acute respiratory syndrome (SARS). *Monaldi Arch Chest Dis*. 2005 Sep; 63(3): 149–57.

Barnard DL et al. Enhancement of the infectivity of SARS-CoV in BALB/c mice by IMP dehydrogenase inhibitors, including ribavirin. *Antiviral Res*. 2006 Aug; 71(1): 53–63.

## The Infectious Myth

pg # Notes

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---

**67 53** Lai ST. Treatment of severe acute respiratory syndrome. *Eur J Clin Microbiol Infect Dis.* 2005 Sep; 24(9): 583–91.

Leong HN et al. Investigational use of ribavirin in the treatment of severe acute respiratory syndrome, Singapore, 2003. *Trop Med Int Health.* 2004 Aug; 9(8): 923–7.

**68 54** Chang CH et al. Meta-analysis: ribavirin-induced haemolytic anaemia in patients with chronic hepatitis C. *Aliment Pharmacol Ther.* 2002 Sep; 16(9): 1623–32.

Zhaori G. Antiviral treatment of SARS: can we draw any conclusions? *CMAJ.* 2003 Nov 25; 169(11): 1165–6.

**55** Knowles SR et al. Common adverse events associated with the use of ribavirin for severe acute respiratory syndrome in Canada. *Clin Infect Dis.* 2003 Oct 15; 37(8): 1139–42.

Koren G et al. Ribavirin in the treatment of SARS: A new trick for an old drug? *CMAJ.* 2003 May 13; 168(10): 1289–92.

**56** Wu W et al. A hospital outbreak of severe acute respiratory syndrome in Guangzhou, China. *Chin Med J (Engl).* 2003 Jun; 116(6): 811–8.

Chiu WK et al. Severe acute respiratory syndrome in children: experience in a regional hospital in Hong Kong. *Pediatr Crit Care Med.* 2003 Jul; 4(3): 279–83.

**68 57** Hillberg RE et al. Noninvasive ventilation. *N Engl J Med.* 1997 Dec 11; 337(24): 1746–52.

**69 58** Yam LY et al. Non-invasive versus invasive mechanical ventilation for respiratory failure in severe acute respiratory syndrome. *Chin Med J (Engl).* 2005 Sep 5; 118(17): 1413–21.

**59** Fujii T et al. Current concepts in SARS treatment. *J Infect Chemother.* 2004 Feb; 10(1): 1–7.

**69 60** Yam LY et al. 2005.

**61** Yam LY et al. 2005.



**69 62** Tansey CM et al. One-Year Outcomes and Health Care Utilization in Survivors of Severe Acute Respiratory Syndrome. *Arch Intern Med.* 2007 Jun 25; 167(12): 1312–1320.  
<http://archinte.ama-assn.org/cgi/content/full/167/12/1312>

**69 63** Lin L et al. A retrospective study on clinical features of and treatment methods for 77 severe cases of SARS. *Am J Chin Med.* 2003; 31(6): 821–39.

**70 64** Tsang K et al. SARS: pharmacotherapy. *Respirology.* 2003 Nov; 8 Suppl: S25–30.

Zeldin RK et al. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. *J Antimicrob Chemother.* 2004 Jan; 53(1): 4–9.  
<http://rethinkingaids.com/quotes/haart-Pls.html>

**70 65** De Clercq E. Potential antivirals and antiviral strategies against SARS coronavirus infections. *Expert Rev Anti Infect Ther.* 2006 Apr; 4(2): 291–302.

Bermejo Martin JF et al. Pentoxifylline and severe acute respiratory syndrome (SARS): a drug to be considered. *Med Sci Monit.* 2003 Jun; 9(6): SR29–34.

Wu Q et al. Photolabeling probes of ribavirin and EICAR. *Nucleosides Nucleotides Nucleic Acids.* 2005; 24(5-7): 999–1008.

## The Infectious Myth

pg # Notes

- 70 66** Lyn TE. Bone disease worry for former SARS patients. Reuters. 2003 Oct 10.
- Wu VC et al. Renal hypouricemia is an ominous sign in patients with severe acute respiratory syndrome. *Am J Kidney Dis.* 2005 Jan; 45(1): 88–95.
- Cui HJ et al. Serum hepatic enzyme manifestations in patients with severe acute respiratory syndrome: retrospective analysis. *World J Gastroenterol.* 2004 Jun 1; 10(11): 1652–5.
- Chu WC et al. Thin-Section CT 12 Months After the Diagnosis of Severe Acute Respiratory Syndrome in Pediatric Patients. *AJR Am J Roentgenol.* 2006 Jun; 186(6): 1707–14.
- Leung CW et al. Severe acute respiratory syndrome among children. *Pediatrics.* 2004 Jun; 113(6): e535–43.
- Tansey CM et al. 2007.
- 71 67** Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. WHO. 2004 Apr 21. (URL no longer functioning) [http://www.who.int/csr/sars/country/table2004\\_04\\_21/en/print.html](http://www.who.int/csr/sars/country/table2004_04_21/en/print.html)
- Global Economic Indicators. CEIC Data. 2020 Jan [accessed]. Per capita GDP in US dollars was obtained for January 1, 2003. <https://www.ceicdata.com/en/countries>
- 71 68** ibid
- 72 69** Wong RS. Severe acute respiratory syndrome in a doctor working at the Prince of Wales Hospital. *Hong Kong Med J.* 2003 Jun; 9(3): 202–5.
- Wu EB et al. Haemorrhagic-fever-like changes and normal chest radiograph in a doctor with SARS. *Lancet.* 2003 May 3; 361(9368): 1520–1.
- 72 70** Reilley B et al. SARS and Carlo Urbani. *N Engl J Med.* 2003 May 15; 348(20): 1951–2.
- Vu HT et al. Clinical description of a completed outbreak of SARS in Vietnam, February–May 2003. *Emerg Infect Dis.* 2004 Feb; 10(2): 334–8.

**73 71** Nuttall-Smith C. SARS survivor fought for every breath. *Calgary Herald*. 2003 May 2; A3.

Howard-Ruben J. Canadian nurse recovers from SARS as government plagued by criticism. *Nursing Spectrum*. 2003 Oct 1.

<http://community.nursingspectrum.com/MagazineArticles/article.cfm?AID=10550>

Picard A. Mommy, are you going to die? *Globe & Mail*. 2003 Apr 5.

**73 72** Stockman LJ et al. SARS: Systematic Review of Treatment Effects. *PLoS Med*. 2006 Sep 12; 3(9).

**74 73** Loutfy MR et al. Interferon alfacon-1 plus corticosteroids in Severe Acute Respiratory Syndrome. *JAMA*. 2003 Dec 24; 290(24): 3222–8.

**74 74** Tansey CM et al. One-Year Outcomes and Health Care Utilization in Survivors of Severe Acute Respiratory Syndrome. *Arch Intern Med*. 2007 Jun 25; 167(12): 1312–1320.

<http://archinte.ama-assn.org/cgi/content/full/167/12/1312>

**74 75** Cyranoski D. Critics slam treatment for SARS as ineffective and perhaps dangerous. *Nature*. 2003 May 1; 423(6935): 4.

**75 76** Antonio GE et al. Radiographic-clinical correlation in severe acute respiratory syndrome: study of 1373 patients in Hong Kong. *Radiology*. 2005 Dec; 237(3): 1081–90.

**75 77** Marshall SJ. Expert Committee finds little fault in Hong Kong's response to SARS. *Bull World Health Organ*. 2003; 81(11): 848.

**75 78** Leung CW et al. Severe acute respiratory syndrome among children. *Pediatrics*. 2004 Jun; 113(6): e535–43.

**75 79** Drazen JM. Case Clusters of the Severe Acute Respiratory Syndrome. *N Engl J Med*. 2003 Mar 31; 348(20): e6–7.

**76 80** Rivers TM. Viruses and Koch's Postulates. *J Bacteriol*. 1937 Jan; 33(1): 1–12.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC545348/>

**77 81** Fouchier RA et al. Aetiology: Koch's postulates fulfilled for SARS virus. *Nature*. 2003 May 15; 423(6937): 240.

## The Infectious Myth

pg # Notes

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- 77 82** Osterhaus AD et al. The aetiology of SARS: Koch's postulates fulfilled. *Philos Trans R Soc Lond B Biol Sci.* 2004 Jul 29; 359(1447): 1081-2.  
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1693394/>  
Kuiken T et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *Lancet.* 2003 Jul 26; 362(9380): 263-70.  
Fouchier RA et al. Aetiology: Koch's postulates fulfilled for SARS virus. *Nature.* 2003 May 15; 423(6937): 240.
- 78 83** Mahy BWJ. *A dictionary of virology*, 2nd ed. Academic Press. 1997.
- 79 84** Email exchange between David Crowe and Dr. Brian Mahy. 2007 Jul.
- 79 85** Rivers TM. Viruses and Koch's Postulates. *J Bacteriol.* 1937 Jan; 33(1): 1-12.  
[pubmedcentral.nih.gov/picrender.fcgi?artid=545348&blobtype=pdf](http://pubmedcentral.nih.gov/picrender.fcgi?artid=545348&blobtype=pdf)
- 80 86** Ksiazek TG et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med.* 2003 May 15; 348(20): 1953-66.
- 81 87** Drosten C et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med.* 2003 May 15; 348(20): 1967-76.
- 81 88** Poutanen SM et al. Identification of Severe Acute Respiratory Syndrome in Canada. *N Engl J Med.* 2003 May 15; 348(20): 1995-2005.  
Fouchier, 2003.
- 82 89** Peiris JSM et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet.* 2003 Apr 5; 361(9364): 1319-25.
- 83 90** Wang WK et al. Temporal relationship of viral load, ribavirin, interleukin (IL)-6, IL-8, and clinical progression in patients with severe acute respiratory syndrome. *Clin Infect Dis.* 2004 Oct 1; 39(7): 1071-5.

- 84 91** Clennell A. China closes schools in Beijing as SARS world death toll hits 235. *The Independent*. 2003 Apr 23.  
[http://news.independent.co.uk/world/science\\_technology/article116268.ece](http://news.independent.co.uk/world/science_technology/article116268.ece)
- Altman LK. Virus Proves Baffling, Turning Up in Only 40% of a Lab's Test Cases. *NY Times*. 2003 Apr 24.
- Walgate R. Cause of SARS disputed. *The Scientist*. 2003 Apr 11.
- Poutanen SM et al. Identification of Severe Acute Respiratory Syndrome in Canada. *N Engl J Med*. 2003 May 15; 348(20): 1995–2005.
- 84 92** Woo PC et al. Relative rates of non-pneumonic SARS coronavirus infection and SARS coronavirus pneumonia. *Lancet*. 2004 Mar 13; 363(9412): 841–5.  
[http://en.wikipedia.org/wiki/Demographics\\_of\\_Hong\\_Kong](http://en.wikipedia.org/wiki/Demographics_of_Hong_Kong)
- 85 93** <http://www.unescap.org/esid/psis/population/database/chinadata/guangdong.htm>
- 86 94** Acute respiratory syndrome - Canada (British Columbia). [www.promedmail.org](http://www.promedmail.org). 2003 Aug 19.  
[http://www.promedmail.org/pls/askus/f?p=2400:1001:3812668426576991518::NO::F2400\\_P1001\\_BACK\\_PAGE,F2400\\_P1001\\_PUB\\_MAIL\\_ID:1000,22593](http://www.promedmail.org/pls/askus/f?p=2400:1001:3812668426576991518::NO::F2400_P1001_BACK_PAGE,F2400_P1001_PUB_MAIL_ID:1000,22593)
- 86 95** Hertsgaard M. Our real China problem. *Atlantic Monthly*. 1997 Nov; 280(5).
- 86 96** Benitez MA. Environmentalists are demanding action after thick smog again shrouds the SAR Does HK deserve a brighter future? *South China Morning Post*. 2002 Sep 7.
- 87 98** Gorrie P. Smoggy forecast for Ontario's future. *Toronto Star*. 2003 Apr 4.
- 88 99** Mazzulli T et al. Severe acute respiratory syndrome: overview with an emphasis on the Toronto experience. *Arch Pathol Lab Med*. 2004 Dec; 128(12): 1346–50.
- Deaths. *Statistics Canada*. 2003; 84F0211XIE.