  As a truly mad scientist, it has become my prerogative as Dr. Madness to create a bioweapon that is capable of death and chaos on a scale that has never been reached by a single act of terror. To that end, I will need to create my own novel weapon. No one biological agent could create the sort of terror that I am seeking to spread. I need something new - something mad. I will need to combine something that is highly infectious with something that is deadly. I will need a long incubation period but no possibility for a cure. I will combine the influenza virus with prions. The infectious nature of the influenza virus will spread my deadly combination and I will bring the world to its knees!

            As I want to be nowhere nearby during development, let me explain the details. A prion is simply a protein that exists in the brain. Every human body has in excess of ten million proteins at any given moment, doing an enormous variety of work. Proteins build, destroy, encode, decode, pack, unpack, hydrate, regulate, and have thousands of functions besides. These proteins are large and complex, as they have to perform very complex work to make a human function. The key to any protein’s complexity is in how it folds. Proteins have four layers of folding – primary, secondary, tertiary, and quaternary – in increasing complexity. Prions are interesting, as they have a normal state – the folding state that allows the protein to function in a healthy human being, and a misfolded state – the folding state that changes how the protein functions entirely. Many proteins have multiple folding states, but what is interesting about the misfolded state of prion proteins is that the misfolded state is much more favorable.

According to Aguzzi (2008) in a biological system, this favorability results in the prion protein acting as a template, guiding normal proteins into the misfolded state. As more misfolded prion proteins are introduced to the body, the process increases exponentially. The unique misfolding of prion proteins leads to formation of amyloid aggregates. These aggregates grow at their ends until they break at the center to double the number of aggregates. This continual growth and breakage leads to degeneration of the brain of the host. The brain will develop holes that will cause rapid mental deterioration and ultimately death.

While a few methods have been hypothesized and described in academic journals to treat prion disease, such as anti-prion antibodies that could cross the blood-brain-barrier and target cytosolic prion proteins, described first by Jones et al. (2010), there remains no actual treatment that could prevent aggregation and death in any patient, should infection occur. The only reason that this disease does not receive the full attention that it should deserve is that it is nearly impossible to contract. According to Ridley et al. (1986), human prion disease – generally in the form of Creutzfeldt-Jakob disease – occurs almost always as a spontaneous misfolding of prion-proteins in humans or it is in inherited disease. The only other way to contract the disease currently is by consumption of food contaminated with prions, but this happens incredibly infrequently with modern food standards.

How then will use of prions as my vector for death and chaos be successful? I am going to force prions to use a new vector. By utilizing the very infectious influenza virus, I will spread prions to the global population. The influenza virus operates using a single strand of viral RNA with a complement of proteins. How will I introduce prions using influenza, you might ask? As a misfolded protein, prions are encoded by a gene. I will sequence this gene from an infected individual with the inherited defective gene – illegally obtained of course – and include the gene sequence into the center of the RNA sequence of the influenza virus. Is it really that simply done? It really is. In fact, Heier et al. (2017) modified an adeno-associated virus (AAV) to deliver a cancer-killing protein to very particular targets in the body. Using modern technology, it is incredibly simple to synthesize RNA sequences that encode for just about anything. My particular combination will yield all the virality of the influenza virus with the delayed onset and inevitable death of prion disease.

            The delivery of this attack will be simple. I intend to release my biological weapon in every major world airport at the beginning of flu season. Influenza is spread by direct transmission, airborne aerosolization, and contact with contaminated surfaces. I will infect world travelers across the globe and spread my disease without having to do the hard work. According to Carrat et al. (2008), a person infected with the influenza virus is infectious from one-half day after initial infection to up to 9 days after infection, with an average duration of 5 days. For longer flights leaving the airports, this means a potential plane full of vectors spreading my disease. Every surface that they touch, every person that breathes the air that is coated with millions of virus particles – my disease will spread. As the primary reservoir of the influenza virus, human beings will spread my virus worldwide. There will be no country that remains unaffected. In fact, contrary to common thought, according to Lowen et al. (2007), the influenza virus thrives in the cold, surviving on surfaces and staying aerosolized longest at temperatures beneath 41°F.

There are no demographics that are resistant to infection, only those populations that have been immunized, but we will discuss how we will also affect those individuals without exception. The poor, the old, young, and the weak will be especially devastated by my disease, however. According to Sloan et al. (2015), these groups are disproportionately affected by influenza hospitalizations. Influenza tears through crowded households. The poor are forced into crowded households by necessity. Children are coddled by parents while they are sick. The old are either taken care of by their children or put into a nursing home where they infect all the other patients. All of these groups are much more likely to be vectors and spread my virus. Regardless of the favorability in these particular demographics, the influenza virus still ravages the wealthy and the healthy. My virus will spread globally across all demographic lines.

The World Health Organization has a department that is specifically devoted to monitoring and responding to the influenza virus – the Global Influenza Surveillance and Response System (GISRS). This group is responsible for monitoring the evolution of influenza viruses and providing recommendations to the world in case of pandemic potential. So why release my virus at the beginning of the flu season, you might wonder? I do not care if epidemiologists find my virus. In fact, I want them to find it. They will take a good long look at the RNA sequence when they isolate it and say to themselves, “we found a new subtype of the influenza virus! Good for us!” They will celebrate themselves and they will treat the virus like they treat every flu virus. They will vaccinate individuals and they will use standard procedures to prevent infection.

Meanwhile, if a person gets one single copy of the influenza virus in their body, the chain reaction of prion production is started. That is all that it takes. One single misfolded prion protein needs to be produced and a runaway reaction will begin that will result in death an average of six months later, according to Gambetti (2003). The genius of this is that immunization against influenza does not prevent infection. According to Demicheli et al. (2014), an influenza vaccine works by producing antiviral antibodies that reduce the amount of influenza-like symptoms in populations. The actual infection rate is as high as ever, the only difference is that the body can fight off the infection much more quickly than if it had to use naturally-acquired immunity alone. Thus, even though the influenza is defeated, the chain reaction of prion aggregation that results in death has been set in motion in every infection.

            According to Nicholson et al. (2003), 20% of children and 5% of adults develop symptomatic influenza each year, worldwide. The key word in that sentence is symptomatic. A healthy person can easily fight off a large number of infections, so viruses like influenza are not always symptomatic. In fact, according to Carrat et al. (2008), a full third of all influenza cases are non-symptomatic. This would imply that 30% of all children and 7.5% of all adults globally are infected by influenza each year. There are 1.9 billion children on Earth right now and a whopping 5.6 billion adults. My virus at its upper limit will reach 570 million children and 420 million adults on initial infection. If the virus performs as it has been programmed to do without immediate and drastic response, nearly 1 billion people will die within six months, or a little over 13% of the Earth’s current population.

            Let’s discuss the possible limitations to my civilization-ending weapon. Prion disease is so atypical of a disease that clinicians do not screen for it unless clinical symptoms are present – primarily a rapidly progressing dementia due to the breakdown of the brain. Once symptoms are present, there are a number of screens that can be performed to identify prion disease. In fact, Orrú et al. (2014) have recently found a non-invasive technique to effectively detect prion proteins in humans, so kudos to those do-gooders. However, if prion disease is not screened for until clinical symptoms present, which generally occurs after two to three months have already lapsed, the pandemic would have spread worldwide already and research could not produce a cure or treatment quickly enough to save lives. Post-mortem visual examinations of brain matter could easily reveal the tell-tale holes in the brain that are the result of prion aggregate growth, but identifying the problem will not be enough to save anyone in their limited time left alive.

A cure will immediately begin to be researched once the severity of the problem is realized. Cures for devastating emergent diseases are not a small feat. In fact, according to Singhal et al. (2015), although Ebola vaccines candidates had been developed in the years prior to the Ebola outbreak in West Africa, there remains no approved vaccine, only models that are in clinical trials, even three years later. Not to mention the fact that targeting specific proteins without devastating side effects is near impossible with our current understanding of pharmacodynamics. If I were given a choice, I would not hold out for a cure.

 The timeline will be this – flu season occurs and the normal amount of people get sick, some 1 billion people worldwide within the span of six months. Within three months, physicians will notice that there is an extreme increase in prion disease worldwide. This will be reported to global health organizations immediately, and epidemiologists will begin investigating. Definitively tying a sudden worldwide pandemic of prion disease with a vector jump in the form of the influenza virus would take precious time that epidemiologists would just not have. All of the initial victims will eventually be tied to their travel plans, so some sort of travel ban will be issued. Perhaps some researchers will accelerate research on some sort of preventative for contracting prion disease in the panic that will follow, but it is unlikely.

National borders will become physical lines as every country enacts martial law. Within a year, as the death toll rises to the billionth death, when public health officials are struck with the inability to respond, panic and rioting will ensue among the population that is healthy enough to do so. This will result in a secondary infection among the human vectors that are still harboring the active virus in their body. There can be no estimation of the toll that this secondary infection will have on the human population, as there will only be fragments of civilization left where there were once countries.  A global collapse of civilization would be imminent, as the diseases that humanity once conquered resurface due to infrastructure collapse and medical services becoming overwhelmed and eventually non-existent. Within five years my tiny island nation, with self-sustaining agriculture and energy production, isolated from the very beginning, will become the only government that remains. History will be written not by who was right, but by who was left.