



## *Let's Get Something Straight*

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## Not Waiting for Godot: Proactive Efforts to Find Potential Zoonotic Agents

In Samuel Beckett's play, "Waiting for Godot," the main characters, Vladimir and Estragon, wait in vain for Monsieur Godot under a tree; Godot never appears. Various interpretations of the meaning of this play have been put forth but the central fact is that Godot never appears. It can and should be asked why Vladimir and Estragon were waiting and who Godot is?

From time to time we are surprised when we discover the outbreak of a disease of which we never had heard, caused by a virus of which we never had heard. Since 2000 only (chosen for my convenience, reference 1), in addition to not unexpected cases, large or small clusters, outbreaks or epidemics of dengue, yellow fever, Japanese encephalitis, rabies, Newcastle disease, foot-and-mouth disease, undiagnosed respi-

ratory illnesses, norovirus illnesses, Congo-Crimean hemorrhagic fever, undiagnosed gastrointestinal illnesses, abalone (*Haliotis* sp) and lobster (*Homarus americanus*) die-offs, hepatitis A, B, C, D, and E, and unexplained deaths of hundreds of thousands of people, plus the remarkable extension of West Nile virus to and through the Western hemisphere, there have been re-emergences or emergences of other diseases:

**2000:** Kyasanur Forest disease, feline immunodeficiency virus disease (lions, *Panthera leo*), poliomyelitis, and nephropathia epidemica;

**2001:** More poliomyelitis, influenza virus A H5N1 in birds and humans ("avian influenza" or "highly pathogenic avian influenza," even "bird flu"), Ebola hemorrhagic fever, rabbit hemorrhagic disease, Ross River virus disease,

classical swine fever, a loggerhead turtle (*Caretta caretta*) die-off, and a human metapneumovirus, now recognized as an important cause of lower respiratory tract infections in children;

**2002:** Ebola and Marburg hemorrhagic fevers, recognition of human metapneumovirus in Australia, classical swine fever, Usutu virus extension (from Africa) to Europe, hantavirus pulmonary syndrome, Norwalk-like virus disease in Hong Kong (from Ireland), and Nipah virus disease in Bangladesh and India. In addition and notably, Severe Acute Respiratory Syndrome (SARS) was recognized in Asia and quickly spread there and essentially world-wide;

**2003:** More SARS and highly pathogenic avian influenza, human monkeypox, Ebola hemorrhagic fever, hemorrhagic fever

with renal syndrome, an equine herpesvirus, and the first report of a giant virus ("Mimivirus") of an amoeba (*Acanthamoeba polyphaga*), to which a small proportion of people with pneumonia have antibody;

**2004:** Still more highly pathogenic avian influenza and Ebola hemorrhagic fever, Bolivian hemorrhagic fever, equine herpesvirus, Koi herpesvirus in carp (*Cyprinus carpio*), hemorrhagic fever with renal syndrome, Lassa fever, Nipah encephalitis (2), African horse sickness, Rift Valley fever, tick-borne encephalitis and, after an absence of 35 years, O'nyong-nyong virus fever with rash;

**2005:** Marburg hemorrhagic fever, Chikungunya, highly pathogenic avian influenza (now moving globally), St. Louis encephalitis in Argentina, and a new human bocavirus discovered in Sweden;

**2006:** Yet more highly pathogenic avian influenza, Kyasanur Forest disease, chikungunya, African horse sickness, poliomyelitis, Ross River virus disease, Tasmanian devil (*Sarcophilus harrisii*) facial tumors (virus?), norovirus disease (on cruise ships; don't those people wash their hands?), bluetongue, bocavirus disease, epizootic hemorrhagic disease, Lassa fever, Marburg hemorrhagic fever, and Rift Valley fever;

**2007:** Sheep pox, Rift Valley fever, bluetongue, African horse

sickness, highly pathogenic avian influenza, Bolivian hemorrhagic fever, Marburg hemorrhagic fever, Ebola hemorrhagic fever, Newcastle disease, hemorrhagic fever with renal syndrome, poliomyelitis, porcine reproductive and respiratory syndrome, Lassa fever, Nipah encephalitis, Chikungunya (spreading and by now being imported just about everywhere), measles, Zika virus disease, viral hemorrhagic septicemia of fish, bovine ephemeral fever, equine influenza, epizootic hemorrhagic disease, cetacean morbillivirus, (bee) colony collapse disorder, classical swine fever, hand, foot and mouth disease, adenovirus-14 respiratory disease, and elephantid herpesvirus disease. [My teachers and, perhaps, the Editor of this Journal, will rap my knuckles for a sentence this long.]

We seem to not have learned much from repetitive occurrences of certain viruses. At the outset of an epidemic (or a cluster of cases of something "new"), newspapers and other popular media sources print headlines in large font and then this "disease of the week" disappears from public view and some other nonsensical writing takes center stage. That these diseases reoccur indicates that, at least at present, we cannot control them, that we are at the mercy of nature. To use the baseball analogy: "Nature always bats last." Nature has more time than we do.

That is, no matter what we seem to do, shy of preparing the rare vaccine that is effective, we are in the end always outsmarted by nature. Pessimistically, Voltaire said that "The art of medicine consists of amusing the patient while Nature cures the disease." I do not believe that. More accurately, I do not want to believe that. We cannot prepare vaccines for every disease and we could not apply them all even if we could prepare them. We could, and do, prepare and administer vaccines and use other measures for use against diseases that we consider important ones. Meanwhile, we develop treatments that are more effective than burying pigs' hearts by a full moon or replacing used parts with shiny new metal or plastic parts or, as do some dentists, drill holes in the bad parts and fill in with metals. All this is quite primitive, really.

There must be a way to get ahead of diseases, to foresee them, and to then do something in advance about diseases that are not-yet-a-problem. The practice of medicine has come a long way in the past relatively brief 1000 years and remarkable, even semi-miraculous, advances have been made. I read recently of a Taiwanese man who acquired a hantavirus infection in Inner Mongolia (China), had difficulty urinating, and was dialyzed at an Inner Mongolian hospital, after which his condition im-

proved; just like being at home! Eye surgery using lasers, replacement of hips and other joints, heart valve replacement, and many more advances in medicine have been huge successes.

Isaac Newton's logical mind led him to say that "Science consists in discovering the framework and operations of Nature, and reducing them, as far as may be, to general rules or laws – establishing these rules by observations and experiments, and thence deducing the causes and effects of things." If that is so, then what are we doing?

We observe, collect facts, total the numerators, reflect on all this, conduct experiments to verify the results of studies done under what we believe are controlled conditions, give lectures, teach what we think we know to classrooms of sleeping students, publish summaries, and then apply for grants to fund doing more of the same. Thus far, this logical system does not seem to be working, at least with respect to infectious disease emergence and psychiatric illnesses. If we are optimistic, we can look upon all these successes as incremental advances, so few and so laborious that we are not able to see what we have accomplished – relatively rapid progress seen in slow motion.

The ostensibly unrelated desire for personal power has its own deleterious effects on progress. Clearly wars, international

tensions (some few legitimate, most contrived), and economic realities are counterproductive. A nation without resources simply cannot care for its citizens. Is it not true that these so-called nations always seem to find enough money to purchase weapons of destruction but cannot seem to find enough money to determine what illnesses are present within their territories but certainly not be able to prevent illnesses among their citizens? What then is the definition of a "nation"?

Even so-called developed countries have difficulties keeping up with all these diseases. This is not unreasonable. For example, do Croatian diagnostic laboratories routinely test for infection with an ebolavirus? Of course not, and with good reason. There has never been a case of Ebola hemorrhagic fever in Croatia, so testing would be superfluous and expensive, money wasted, when it could be spent on diagnosis of recognized problems. Nonetheless, this means that Croatia is depending on human sentinels to detect the first (or second) ebolavirus infection, should it ever reach there. Croatia waits for Godot, as do most, if not all, other countries.

Nipah virus (family *Paramyxoviridae*, genus *Henipavirus*) was first recognized in Malaysia in 1999, when many adult, male, Chinese pig farmers and their pigs became ill, some with fatal

encephalitis. Fruit bats ("flying foxes," order Chiroptera, suborder Megachiroptera) soon were shown to be the natural hosts of this virus and the fascinating details of its natural history were documented quickly.

Thereafter, an outbreak of what was termed "measles encephalopathy," but what was, in actuality, Nipah virus disease, was reported in 2001 in Bangladesh and India. Note that (a) measles encephalopathy is rare; (b) outbreaks of measles encephalopathy are unknown; (c) there was no atypical measles virus circulating in the area where the cases occurred; (d) uninformed and not necessarily appropriate treatment with salicylates may at least as likely as a virus have been the etiologic agent of the reported instances of Reye's syndrome in some of these patients; (e) the laboratory documentation of the diagnosis of measles was incomplete, possibly inadequate, in these cases. The reported absence of rash in the presence of antibody was inconsistent with a diagnosis of measles. At the most, these could be considered measles virus infections, but they certainly should not have been considered measles cases. Measles without rash is like hemorrhagic fever without bleeding or government without taxes; and (f) cases were reported to having occurred in all age groups, which is unlikely to be consistent with measles in India, par-

ticularly where measles vaccine had been given on a regular basis over a long period of time and immunity to this virus anyway is extremely high. Some of the patients with this illness were in a nursing home, others were in medical personnel; these are inconsistent with the usual measles age-distribution. The field investigations clearly were incomplete or the reports from local epidemiologists were not received or were ignored. In sum, the outbreak was handled disastrously and the conclusions were nonsense. In 2003, researchers at the Delhi-based National Institute of Communicable Diseases contradicted the initial announcement by the Director of the Indian Council of Medical Research, which had stated that "the Siliguri outbreak was caused by measles." Their conclusion was based on the fact that "6 Siliguri samples were sent to [the U.S.] Centers of [sic] Disease Control, and they turned out to be of Nipah virus." The work on this virus could not continue because, once it was recognized what a dangerous agent they were dealing with, Indian investigators had to use it at the highest containment level, BL-4, and they did not have a BL-4 laboratory available; still don't. India? Not enough money to provide themselves with what they need? As are so many countries, India is not equipped properly and must rely on the compas-

sion and assistance (ie, charity) of others to protect its own citizens from natural phenomena.

Surely not every country in the world needs or can afford such a sophisticated facility as a BL-4 laboratory and the scientifically sophisticated people who manage them. Nonetheless, through the good offices of the World Health Organization, arrangements can be made to work with dangerous and exotic viruses so that, with arrangements made in advance, or arrangements made quickly, little or nothing need be lost in terms of time and human life.

It is not, however, a simple lack of funds and facilities that is most harmful, it is a lack of education. Time and again "outreach" efforts and contributions of visiting scientists must be used to educate and re-educate the populations of countries where, for examples, dogs should be vaccinated against rabies virus, people must be reminded to be vaccinated against influenza, as well as to avoid being fed upon by mosquitoes, to check themselves for ticks when they have been walking in the woods, to cross safely at intersections, to wear seat belts, to not drink and drive, to eat properly, etc. *ad nauseum*. This need for repetition is simply a flaw in human nature, I suppose, but when people have never heard of rabies, have never known of the need to vaccinate their dogs, and

have not known to stay away from dogs in areas where rabies is prevalent, it all looks rather hopeless, doesn't it? Darwinism in action! Swimming at the shallow end of the gene pool.

The 2003 experience with monkeypox in the US was enlightening in this regard (3). Someone legally imported (Ghana to Texas) monkeypox virus-infected Gambian giant rats (*Cricetomys* sp) and those rats subsequently contacted prairie dogs (*Cynomys* sp) in a pet shop in Illinois, transmitted the virus to them, and the prairie dogs transmitted the virus to people who must think that having a Gambian giant rat or a prairie dog is just like having a dog or cat, perhaps wanting to snuggle with them on cold nights or to take them on long walks. Fortunately, a very competent local clinic had provisionally identified the virus morphology as being consistent with that of a poxvirus in skin lesion tissue from a patient, from lymph node tissue from the patient's pet prairie dog, and from isolates of virus from culture of these tissues. Nevertheless, this recognition was too late to prevent secondary spread of the virus. Monkeypox virus and human cases of monkeypox were found not only in Illinois but in Wisconsin and Indiana.

In addition to the litany of emerging or re-emerging diseases noted above, there are "undi-

agnosed illnesses,” “undiagnosed deaths” (How difficult can death be to diagnose?), “undiagnosed die-offs,” “undiagnosed diseases,” and “undiagnosed fatal illnesses” (although such deaths also are not difficult to diagnose). Indeed, when I searched the word “undiagnosed” using ProMED’s search engine for 2000 through 2007 (1), I found 646 entries. These included “undiagnosed illnesses and deaths” in humans, livestock, wild birds, and fish. Many of the reports were from the same few places, repeatedly.

Why are diseases emerging or re-emerging now? Some are truly, if relatively, new but, principally, it is because we have not done a good job of looking for them. Old people die on a regular basis (not the same old people, of course), so when one dies the lazy diagnostician says, “She was old,” or “It appears to have been due to a stroke,” or “These things happen,” or “It was God’s will,” or some such. Nonsense. If disease and death, tornados and hurricanes, floods and fires, are God’s will, why do we take penicillin, build sea walls, put out fires, etc.? We thank God for sparing us from cancer, but whose idea was cancer? Godot’s? Fatalism can be fatal.

There is a cause for every death. Whereas it is true that one death does not, by itself, matter much (to the community) in this overpopulated world,

it matters objectively (personally and epidemiologically) and, worse, the cause of that person’s death might be the precursor of and evidence for the beginning of an epidemic, an “indicator case.” Recognition of such indicator cases results from increased awareness, increased recognition, and better diagnostics, but mostly because someone was paying attention, thinking “What is this?”

We are in an age of increasing ecologic disruptions, what we call “development” (Bumper sticker: “Destroy a work of art and you’re called a vandal. Destroy a work of nature and you’re called a developer.”), global climate change, earthquakes, fires, volcanoes, and the US Army Corps of Engineers, which believes it can repair the errors made by God. We impinge on natural areas, “improve” natural areas, are dependent on oil and other extractive industries, and we need increasing amounts of food to feed an increasing number of people.

And then there is politics. When the Soviet Union broke into pieces, it took a while (to at least now) to get reorganized properly. Former programs to control rodents and ticks, no matter how naïve and incomplete, were at least partially helpful. With the cancellation of such programs and a shifting of investment priorities to infrastructure and who knows what

else, increases in hemorrhagic fever with renal syndrome and tick-borne encephalitis have been observed, or now are being reported. Diseases are the price we pay for ignorance and for electing self-serving politicians. There should never be a human case of yellow fever, for example.

Improvements in recognition and diagnosis are near-term necessities for the individual patient, but it is long-term warnings that are needed for the population and for future populations. What that entails is a conscientious effort to not wait for Godot. If we are ever to be capable of predicting outbreaks we must become proactive, to search for Godot. This is much easier said than done, of course, but what alternative is there? For many decades field work was enthusiastically supported and funded by foresighted administrators, those who paid attention to what they were hired for, not to who was parking in whose space. When the idea arose that we already had enough information and now only needed to apply that information, support for field work collapsed, except as applied to post-epidemic studies so that what had happened could be described. Many numerators were collected; all very interesting but not at all predictive. Now we have young scientists who believe that viruses come from freezers, institutional memory

is being lost at a rapid rate, and history is irrelevant.

We speak of knowing what is what but we have not scratched the surface of the natural world and, now that recently emerged zoonotic diseases have reared their ugly heads, what always was needed and now is needed even more, are long-term (“longitudinal”; decades, not weeks) studies of nature. For example, until recently, bats (chiropterans) were essentially ignored, except by investigators interested in the peculiar biological characteristics of these fascinating mammals, and by those who study rabies virus. However, with the discovery of Hendra virus disease (4), Nipah encephalitis, and Severe Acute Respiratory Syndrome (5), and with the isolation or detection of these and other viruses in bats, scores of new viruses have been recognized. In addition, that RNAs of an ebolavirus (6) and a marburgvirus (7) recently have been detected in bats indicates that we may be close to finding the primary sources of these filoviruses, etiologic agents of tragic and frightening hemorrhagic fevers. There are 1116 species of bats, and viruses have

not been isolated from bats of 1032 species, so we have some work to do (8). Who will do this undoubtedly profitable work, other than those searching for what already is known? Who is routinely and longitudinally examining fleas (Siphonaptera), spiders (Arachnida), or ants (Formicidae)? Who is routinely and longitudinally examining healthy people, healthy plants, healthy house pets, healthy livestock, and healthy fish and other sea creatures?

We might simply wait for something to happen, for Godot to come along and then to respond, albeit too late, or we might better be advised to become proactive about all this. There is no question that the cost of prevention is a great deal less than the cost of control.

I am certain that many of those who read this will be in agreement with what is said here but I am equally certain that no one will do anything along these lines of thought. It has always been thus. In that case, we will continue to wait for Godot. Alternatively, you could go forth and learn to predict. You are our only hope for winning the war

against microorganisms and viruses.

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