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H1N1 Resource Book



RUTGERS

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Introduction

You have already received training from your employer to familiarize you with a variety of issues surrounding the possibility of a future H1N1 pandemic. As a result of your participation in this training, you should have a basic understanding of the H1N1 virus, including what it is, how it is transmitted, how to reduce your likelihood of infection, and what to do should an infection occur. While understanding these topics is essential to protecting your health and the health of those around you, you may be looking for more in-depth information on one or more of the subjects included in the training.

This resource book has been compiled to serve as a succinct document to which you can refer in order to learn more about a variety of H1N1-related topics. Also included under each subject heading are a list of external references you may wish to access for additional information. Finally, given the constantly evolving state of our knowledge on H1N1, a brief list of websites maintained by the Centers for Disease Control and other governmental organizations is provided. These sites should be consulted regularly, as the recommendations and material contained throughout the training may be updated/revised as more information becomes available.

Natural Selection and Fitness

In the H1N1 training, we learned that new flu viruses are constantly evolving, creating the need to develop new vaccines annually; however, the “how” and “why” of this phenomenon were left largely unexplored. The truth is that in order to understand how new diseases come to be, you need to know a little about natural selection and genetics: the former is the process by which emerging diseases evolve, and the latter is the mechanism by which the necessary physiological changes occur.

There are a number of factors that determine an organism’s survival; however, only one can be passed from one generation to the next: genetic characteristics. Our genes are the blueprints for the construction of our physical bodies, and determine everything from how tall we are, to what color eyes we have, to whether we can efficiently metabolize certain nutrient sources. Sometimes these traits are inconsequential; for example, you might think blue eyes are prettier than brown, but the difference could hardly be described as life-altering. At other times, however, genetically-derived physical differences between organisms do make a difference in survival. Take, for example, a species of birds in which some members have large beaks and are able to open hard-shelled nuts while others have thinner beaks that cannot crack nuts. These differences would likely have no effect on survival if a variety of hard and soft food sources were available, but should a sudden storm or climatic shift obliterate the softer foods, the birds with the larger beaks would be able to survive, while those without them would perish.

Clearly, genetic characteristics can impact survival; and survival, in turn, is critical to reproduction, which is the process by which organism’s pass their unique genetic material on to future generations of their kind. “Fitness” is the term used to describe an individual organism’s reproductive success; the more

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surviving offspring that are produced, the greater the organism's fitness. Continuing with the bird example, should softer foods be eliminated, the small-beaked individuals would die (i.e. their fitness would be reduced), leaving their large-beaked counterparts to breed. Soon the species as a whole would look fundamentally different than before, as it would consist entirely of large-beaked individuals.

There was a time in our own history, for instance, in which early human ancestors likely knuckle-walked in much the same way we see chimpanzees and other apes do today. Somewhere along the line, however, individual organisms were born that were able to stand straighter, and eventually, to walk on two legs. These characteristics conferred a fitness advantage because they allowed the individuals who possessed them to spot predators farther away and (likely) allowed for the physiological changes necessary to facilitate speech. Because the less ape-like individuals reproduced more successfully than their relatives, the prevalence of those traits within our ancestral populations was amplified, and very gradually, these and other changes led to the development of the human race as we know it today.

So, by way of two simple examples, we have illustrated the basic processes behind evolution through natural selection. Simply put, individual organisms whose genetic characteristics make them better adapted to their environments enjoy enhanced fitness, and as such, will have a greater impact on the character of their species in the future through the continuation of their genetic heritage.

Birds and humans are one thing, but how does natural selection translate to diseases? The answer to this question comes in understanding that like other things, the microbes that cause disease possess genetic material on which the process of natural selection acts¹. If one viral particle contains genes that make it better able to infect a host, or less susceptible to the medications we develop to combat it, for example, that virus will likely have higher fitness, resulting in an amplification of its genetic traits in future generations of the disease. It is in exactly this way that we have seen the development of antibiotic-resistant bacteria such as MRSA, and it is this process that could potentially give rise to a second wave of H1N1 that might be more dangerous than the one experienced worldwide during the summer of 2009.

So, evolution favors organisms that are better adapted to their environments, and if these adaptations are genetically based, they may be expressed in increasingly high proportions in future generations. But where do these "better adapted" organisms come from? How did our first bipedal ancestor or the first antibiotic-resistant bacterium come to be in the first place? The answer to both questions is rooted in genetics and mutation, both of which are discussed in the following section.

For more information on evolution and natural selection, see:

<http://www.globalchange.umich.edu/globalchange1/current/lectures/selection/selection.html>

<http://www.nature.com/nature/newspdf/evolutiongems.pdf>

¹ Prions, the agents responsible for causing New Variant Creutzfeldt-Jakob Disease (i.e. mad cow disease), are unique in this respect as they are composed of malformed proteins and do not rely on reproduction to cause disease.

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Genetics and Mutation

As mentioned briefly before, the “construction” of every single living organism is guided by genetic instruction manuals. Amazingly, every one of these manuals, whether they code for the production of a human, a plant, a bacteria, or any other living thing, are written using the same basic alphabets, namely DNA or RNA. Most organism’s genetic material is contained in chromosomes, which are located in the nuclei of virtually every cell in their bodies.

Unlike a printed book on a shelf, however, genetic instructions are not static. Characters can be substituted and rearranged; in fact, these alterations are commonplace, and occur most often through mutation and sexual reproduction. Frequently, reordering genetic instructions has no discernable effect, and the organism created using the new code is indistinguishable from one built using the original instructions. Sometimes, however, the presence of a new code can reduce an organism’s fitness or even prove fatal, outcomes that typically limit fitness, and therefore the probability that the genetic alteration will be passed on to future generations. But sometimes, the new code that’s formed provides the instructions needed to create an organism that is better adapted to its environment than the other members of its population, members with whom it must compete for resources. In these instances, reproductive success (i.e. fitness) may be enhanced.

For more information on genetics and mutation, see:

<http://ghr.nlm.nih.gov/handbook>

<http://www.dnafb.org/15/concept/>

<http://www.dnai.org/>

Viruses

Viruses are small in size, and though they may appear elaborate, they are often little more than a packet of genetic material wrapped in a protein coat. The genetic material is what codes for the production of new viruses; while the protein is what enables the virus to enter a healthy cell, infecting it.

To understand the mechanism of viral infection, we need to know a bit about the structure of cells they’re targeting. Cells are encased in membranes (or in the case of plants, cell walls) that separate what’s inside the cell from what’s outside. These coatings offer the cell protection and allow it to maintain the specific chemical balance necessary to survive and reproduce. Despite their separation, however, no cell lives in isolation: neighboring cells must communicate with one another and things must be taken in and expelled as part of normal life processes. In order to facilitate these exchanges, cells rely on receptors within their membranes and walls. It is either by tricking these receptors, or by forcefully injecting their genetic material into the cell, that viruses gain access, causing infection.

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Once inside a susceptible host cell, the virus will “hijack” the cell’s internal structures, stopping their normal functioning and redirecting them for its own ends. The main activity assumed by an infected cell is the production of more virus particles, which are then released to infect other cells and repeat the process. For example, a single human cell can be made to produce 10,000 polio viruses, which then enter the body and repeat the process anew.

Infected cells often die, either because they fail to carry out the functions necessary for their own survival, or because the exit of the virus particles causes fatal structural damage. This process of cell death may actually cause some of the symptoms associated with a particular virus.

Perhaps the most important trait of viruses is that because they are not “whole cells,” they can afford to allow a much higher mutation rate during the course of reproduction. This is true, because the more complex an organism’s physiology, the more precise must be the transcription of its genes to ensure correct functioning. Also, because a virus does not expend any energy in its own reproduction (the host cell does everything), even if some offspring are nonviable due to harmful mutations, the virus itself has lost nothing.

This capacity to tolerate high rates of mutation is important, because as we learned earlier, mutation is the ultimate driver of evolution: the more mutations that occur, the higher the likelihood that a more fit strain of virus will emerge. Unfortunately, since “more fit” means greater levels of reproduction of disease-causing agents, mutations that prove beneficial for viruses are rarely good news for us, the susceptible host population.

For more information on viruses, see:

<http://www.livescience.com/viruses/>

<http://health.howstuffworks.com/virus-human.htm>

Creating a “New Flu”

Among members of the public health profession, it is widely believed that flu represents the greatest pandemic risk. One of the major reasons for this stems from the microbe’s genetic and physical characteristics, both of which make large numbers of potentially-devastating infections probable.

Composed of RNA, flu works like other viruses, by taking over the machinery of a healthy host cell and forcing it to reproduce copies of itself. As in other organisms, flu RNA acts as a template for the creation of “offspring;” and in theory, the replication process should create identical copies of the “parent” virus. The mechanics of flu reproduction are very approximate, however; and mistakes (i.e. mutations) are common. Although sometimes those mistakes prove fatal to the virus, they more often prove benign, or scarier, may lead to the creation of a new strain that is even more virulent than the original.

Once produced, a viable mutated form of a virus will likely prove resistant to vaccines developed to combat the original strain. This fact, combined with the steady mutation rate of flu, are why we are

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advised to get a flu shot annually, as opposed to once in a lifetime as we do in the case of many other diseases, including measles and mumps.

Zoonotic Infections:

Humans are not the only organisms that are susceptible to disease; in fact, microbes exist that are capable of sickening virtually every life form on Earth. (Bacteria, for example, are susceptible to some forms of viral infections.) As discussed in the training, diseases originating in animal populations are called “zoonotic diseases,” and are considered particularly concerning because they are not endemic to human populations, meaning that no natural immunity is likely to exist. Also, like human forms of influenza, zoonotic flu strains mutate frequently, a fact whose significance we will explore shortly.

But how do viruses that originated in animal populations cause illness in humans? To answer that question, we have to return to the mechanism of infection discussed under the “Viruses” heading above. As we already know, viruses often gain access to healthy cells by “tricking” them with the receptors in their protein coats. For the most part, cell receptors are unique to each species, a fact which usually prevents a flu that has developed in one kind of animal from causing disease in another. In some cases, however, interspecies similarities in cell receptors allow viruses to “jump the species barrier,” entering the cells of a new type of organism and causing infection.

Such novel infections typically remain isolated within the individual that has been affected, as transmission from the new host to another of their own species is unlikely. This phenomenon has been observed with bird flu, for example, a disease that can be spread to humans through close contact with infected birds, but has not been shown to pass between human hosts with any degree of regularity.

Of all the animal-borne flu strains, those that originate in swine are particularly likely to infect humans; this is because the receptors on human cells are very similar to those on the cells of pigs, increasing the likelihood of a virus jumping the species barrier. (It is interesting to note that these same similarities are what allow us to use pig hearts and other organs as transplants.) Because of cellular similarities with other, non-human species, swine may also act as intermediaries through which viruses originating in animal populations can infect people. Avian influenza, for instance, may be contracted by a pig, then passed on to a human host.

While human infections with zoonotic diseases are cause for concern when confined to particular individuals, it is the possibility that a mutation could lead to the creation of a zoonotic virus transmissible *between* people that causes the most concern among public health professionals. Such a scenario is particularly worrisome because it represents the introduction of a completely novel flu strain into human populations. Since the virus did not “co-evolve” with human hosts, existing levels of immunity can be expected to be minimal to nonexistent, increasing the likelihood of a pandemic.

For more information on zoonotic diseases, see:

<http://www.cdc.gov/Ncidod/dpd/animals.htm>

<http://www.who.int/zoonoses/en/>

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Reassortment:

In addition to mutation and zoonotic flu viruses, new strains of flu can be created when multiple viruses exchange genetic material within the body of a host organism. This can only occur when an animal is infected with more than one virus at the same time, but when it does; it can result in the production of a new virus with unpredictable, potentially devastating properties. As mentioned in the previous section, swine may become infected with endemic (swine) flu, avian flu and human flu. When multiple strains are present in one animal, it creates a virtual “living Petri dish” in which the various viruses could combine to create a new strain. If this were to occur, none of the species to which the original flu viruses were endemic could be expected to have any immunity to the new disease; therefore, all would be highly susceptible, with potentially devastating consequences.

For more information on reassortment, see:

http://www.hhmi.org/biointeractive/animations/subunit/sub_middle_frames.htm

<http://pathmicro.med.sc.edu/mhunt/genet.htm>

Epidemics

An epidemic is said to occur when infection rates within a population exceed normal background (endemic) levels. The number of cases needed to declare an epidemic varies from one disease to another, precisely because the endemic levels of diseases are unique. Smallpox, for example, is believed to have been eradicated worldwide. Therefore, the appearance of a single case would be declared an epidemic. HIV, in contrast, is far more common across the globe; and for this reason, a large number of new cases would have to be discovered before an epidemic would be said to be underway.

Clearly, existing diseases like smallpox and HIV have the potential to cause epidemics, but new or “emerging” disease represent perhaps a more worrisome threat in this regard. Whether arising as a result of a zoonotic disease crossing the species barrier, a significant mutation in a familiar human illness, or from some other source, emerging diseases, and their potential to cause epidemics, are cause for considerable concern. This is because, with no prior exposure, human populations can be expected to possess little to no natural immunity to such new diseases, a fact which increases the likely spread and the potential severity of illness. As mentioned previously, flu viruses mutate frequently, sometimes giving rise to new strains; a characteristic which increases the probability of an epidemic.

Epidemics are cyclic in nature. Once a disease takes hold in a population of vulnerable individuals, infection rates will be high as there is little natural resistance to its spread. After a period of time, infection rates will drop substantially, perhaps to the point where the disease appears to have been eradicated. This is because susceptible individuals have already been sickened or killed, leaving behind the more resistant members of the population. Depending on the nature of the disease and of the immunity, resistance may be passed to offspring, thereby ensuring high levels of continued resistance to the disease among future generations.

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But this is often not the end of the epidemic cycle; another outbreak will occur when one of two things happen. First, an epidemic can resurface as soon as enough non-resistant hosts are born to support another outbreak of the disease. What's more, changes in the disease itself (through mutation or other mechanisms) can occur, meaning that existing immunity offers little or no protection. For these reasons, despite modern medical advances, epidemics are still a major concern.

A number of factors affect whether and where an epidemic will occur, as well as its severity. Natural factors, such as climatic conditions and the occurrence of disasters affect the frequency and severity of epidemics. For example, many disease vectors, such as mosquitoes, thrive in warm, moist conditions. Gains in the incidence of mosquito-borne illnesses such as malaria have already been observed at increasingly high altitudes as a result of warming planetary temperatures. Many anticipate that as the process of global climate change continues, the regions impacted by these and other diseases will shift and expand as more and more territory becomes suitable habitat for vectors. Natural disasters such as hurricanes and floods can also create ideal conditions for disease transmission (i.e. poor sanitation, hygiene and nutrition, crowded shelters, etc.), and it is not surprising that after such events, disease levels typically skyrocket.

Manmade factors also impact epidemics. Modern travel, for instance, has created a situation in which infection can be spread globally in a very short period of time, potentially facilitating the occurrence of a pandemic before the initial threat is even recognized. One need only think of SARs, which developed in China, but spread to Hong Kong, Canada and elsewhere through travel by infected persons, to see the potentially devastating consequences of our ability to go anywhere anytime. Infectious diseases can also be used as weapons of terror, particularly if altered to increase their virulence or infectious properties. While the 2001 Anthrax attacks did not produce an epidemic, they provide a real life illustration of how biological agents can be used as weapons. Finally, the improper use of medical interventions (such as antiviral medications and antibiotics) may encourage the development of resistant strains of disease. Evidence of this outcome can be found in the development of MRSA and other antibiotic-resistant bacteria, and in the discovery that swine flu cannot be treated effectively with two of the four antiviral medications approved for use in the United States.

For more information on epidemics, see:

<http://library.thinkquest.org/11170/>

<http://www.amnh.org/exhibitions/epidemic/prologue/prologue.html>

<http://uhaweb.hartford.edu/bugl/histepi.htm>

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Finally, since our understanding of H1N1 is constantly evolving, recommendations related to necessary precautions and other information contained within the training may be updated and/or changed. For more information on novel H1N1 and to keep abreast of the latest government recommendations, see:

<http://flu.gov/>

<http://www.pandemicflu.gov>

<http://www.cdc.gov/H1N1FLU/>

<http://www.who.int/csr/disease/swineflu/en/>

<http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm150305.htm>

<http://www.flufinder.gov>