Epidemiology

Terminology
Definition of Terms
A Riddle to Be Solved

Some History
John Snow
Typhoid Mary

Terminology

Epidemiology is the scientific study of the occurrence, distribution, and control of diseases and unusual health states in populations and subpopulations for the purpose of prevention or influencing health care policy. Terris has expanded this definition with the following four points.

1. Discover the agent, host, and environmental factors that affect health, in order to provide the scientific basis for the prevention of disease and injury and the promotion of health.
2. Determine the relative importance of causes of illness, disability, and death, in order to establish priorities for research and action.
3. Identify those sections of the population that have the greatest risk from specific causes of ill health [and benefit from specific interventions], in order that the indicated action may be directed appropriately.
4. Evaluate the effectiveness of preventive and therapeutic health programs and services in improving the health of the population.

To these, Schoenbach and Rosamond have added:

5. Study the natural history of disease from its precursor state through its manifestations and clinical course.
6. Conduct surveillance of disease and injury occurrence in populations and of the levels of risk factors—passive (receive reports), active (poll practitioners, conduct surveys).
7. Investigate outbreaks (e.g., hospital acquired infections, disease clusters, food-borne and water-borne infections) to identify their source and controlling epidemics (e.g., measles, rubella, coronary heart disease, overweight).

Unlike physicians, who are primarily concerned with diagnosis and treatment of disease states in the individual patient, epidemiologists focus almost exclusively on subpopulations or populations. They may, at times, diagnose disease in an individual as part of their need to develop data on the population, but they rarely treat patients.

There is a variant, which combines several of the above goals, called shoe-leather epidemiology, wherein scientists must find every case of the disease, trace every contact with the victims and the contacts’ contacts. This requires going door-to-door, even when there are no doors, for as long as it takes to find the cause and control the disease—which may take weeks, or even months. Once the disease is controlled it may be necessary to analyze all of the collected records to determine the so-called index patient, from whom all other infections sprung. Once the index patient is found, then the search begins for the origin of the disease. As an example, a large outbreak of Marburg hemorrhagic fever occurred in northwestern Angola during the spring of 2005. DNA analyses of the viral strains found in various individuals indicated a single source. This provided the opportunity to test the hypothesis that the disease resides in bats once it has burned through a region. No results were available at the time of this writing.

We have left undefined the critical term disease. Different sources give different definitions. The simplest definition would be “an absence of wellness,” but that begs the question. Brock Biology of Microorganisms provides a very succinct definition:

Disease is damage or injury to the host that impairs host function.

On the other hand, Stedman's Medical Dictionary for the Health Professions and Nursing gives two short definitions for disease:

1. An interruption, cessation, or disorder of body functions, systems or organs. 2. A morbid entity characterized usually by at least two of these criteria: recognized etiologic agent(s), identifiable group of signs and symptoms, or consistent anatomic alterations.

Taber's Cyclopedic Medical Dictionary is more expansive and it says disease is:

A condition marked by subjective complaints, a specific history, and clinical signs, symptoms, and laboratory or radiographic findings. The concepts of disease and illness differ in that disease is usually tangible or measurable, whereas illness (and associated pain, suffering, or distress) is highly individual and personal. Thus, a person may have a serious but symptom-free disease (e.g., hypertension) without any illness. Conversely, a person may be extremely ill (e.g., post-traumatic stress syndrome) but have no obvious evidence of disease.
Suffice it to say, there are complications, unusual cases, and debatable points amongst all these definitions. Consequently, the study of disease, and epidemiology, in particular, may lead to different conclusions by different authors.

Returning to epidemics, some of which were described in the previous chapter, there are two major transmission routes of infectious diseases that can develop from outbreaks into epidemics: common source and host-to-host. **Common source** outbreaks arise from a contaminated source, such as water or food, while **host-to-host** infections are transmitted from one infected individual to another via various, perhaps indirect, routes.

Common source outbreaks usually produce more new cases earlier and faster than host-to-host epidemics. Picture the case of people eating contaminated food at a restaurant; a large number of people will become infected in a short time. Once the infected source is closed, sealed, or removed, the common source epidemic usually abates rapidly.

Host-to-host diseases are usually slower to grow and slower to diminish\(^1\). Suppose a disease is passed by aerosol droplets through coughing or sneezing. Transmission will require a sneeze directed at or near another person. That person will be no danger to others until the causative agent has reproduced sufficiently for the victim to be in an infectious state. Only then can that person transmit the disease.

\[\text{Incidence rate as a function of time for outbreaks and/or epidemics}\]

The CDC employs numerical criteria to define when an outbreak is an epidemic. In the figure below, five years worth of weekly data from 122 cities were collected and “smoothed” to determine a seasonal baseline for deaths due to pneumonia and influenza between 1999 and 2003. The baseline is given as a percentage of all deaths, which you can see range from 6% to 8% for these diseases. The epidemic threshold is defined to be 1.645 times the standard deviation of the weekly death rate. For those who have had any statistics, this means that when the death rate exceeds the 95\(^{th}\) percentile of the baseline distribution, there is an epidemic.

\[^1\] The spread of influenza in 1918 is an obvious exception.
It should be clear from the graph, that there were flu epidemics during the first months of the years 1999, 2000, and 2002.

Epidemiologists regularly monitor morbidity (state of being diseased) and mortality (death) in a population or subpopulation in an effort to identify unusual trends and patterns.

The control of the great epidemic diseases of the twentieth century, such as cholera, smallpox, yellow fever, and typhoid came about, in large part, through the efforts of the medical community, public health officials, and epidemiologists working together. These diseases devastated human populations until epidemiological principles were applied to identify the factors that influenced their spread. Contaminated water supplies were found to be the problem in the spread of cholera, mosquitoes carry yellow fever, rodents can harbor fleas that transmit typhus and/or Plague, and deer mice carry ticks that are infected with the bacteria that cause Lyme disease—all epidemiological discoveries.

The eradication of smallpox as a naturally occurring disease agent was also due primarily to epidemiological intervention, continuous surveillance, and an aggressive immunization program. Through careful investigative study, epidemiologists were able to elucidate critical factors and, when these factors were controlled, the world was able to halt the progress of those epidemics.

Germ Theory

Finding the causative agent of a disease was no small feat. Historically, the notion of germs is of relatively recent origin—just about 150 years old. The ancient Romans believed disease resulted from the imbalance of the four bodily humors: blood, phlegm, cholera or yellow bile, and black bile. If you had a fever and rosy cheeks, it was clear that you suffered from an excess of blood. The obvious (to them) solution was to withdraw blood by attaching leeches to your body or making an incision (in your forearm) for the purpose of bleeding you. An excess of yellow bile called for a diuretic to induce urination.

Convincing medical science of the validity of the germ theory was no small task. Unsuccessful attempts were made (at least indirectly) by Ignaz Semmelweiss, Florence Nightingale, John Snow, and many others. John Grove’s 1851 book *On the Nature of Epidemics* was the first to present the germ theory.

Early in his career, Robert Koch had the good fortune to be in India studying an outbreak of anthrax, a bacterial disease usually infecting cattle and sometimes humans. Koch sought to establish a closed chain of experiments that would provide unequivocal and irrefutable proof that a specific agent was responsible for a certain disease. In an 1876 paper, he published the following short list of requirements, now appropriately called Koch’s Postulates.

1. The microbe must be present in every case of the disease;
2. The microbe must be isolated from a diseased host and grown in pure culture;
3. The disease must be reproduced when the microbe grown in pure culture is introduced into a nondiseased susceptible host;
4. The microbe must be recoverable from an experimentally infected host.
Proving that an outbreak of disease has a specific cause requires extracting the causative agent from every infected individual tested. That common agent then has to be grown in sterilized “pure culture,” which is usually agar (seaweed extract), beef broth, milk protein, soybeans, or other “nutritious” (to the infecting agent) material. Then either someone (or some animal) must volunteer to be infected with the agent. This sequence closes on itself, insofar as Postulate 4 brings us back to Postulate 1. Establishing this chain of events for a microbe is considered to be proof of causation.

Currently, the Centers for Disease Control and Prevention (www.cdc.gov) and the National Institutes of Health (www.nih.gov) are the federal agencies responsible for overseeing such research. While Koch’s chain sufficed for many of the run-of-the-mill bacterial diseases of the nineteenth century, modifications had to be made in order to include diseases caused by viruses, some unusual bacteria, and/or prions. For instance, no known virus can be isolated and “grown” in “pure culture.” Some disease agents are so mutable that precisely the same organism cannot be recovered from different experimentally infected hosts, e.g., HIV. Even for bacterial diseases, there are dose/response curves that are functions of the characteristics of the state of the host and the state of the infectious agent. Such curves predict the extent of symptoms in terms of the number of microbes introduced into the individual. For some people, extremely large numbers are needed to cause disease, while others will develop symptoms from a much smaller dose. Since all individual characteristics have neither been isolated nor thoroughly studied, this forces a random character on infection and disease causation. Thus, it is reasonable to substitute the following requirements to make a set of Extended Koch’s Postulates (also called the Bradford Hill Postulates):

1. **Strength of statistical association**: the relation between exposure to the causative agent and the appearance of disease symptoms should have a highly statistically significant positive correlation: the greater the exposure, the more likely the disease.
2. **Consistency**: the exposure/symptoms cycle should be repeatably consistent across researchers, time, location, and methodology.
3. **Specificity**: exposure to a given microbe should result in the development of appropriate symptoms that are specific to infection by that microbe.
4. **Temporal sequence**: symptoms should follow risk/exposure within a reasonable and broadly predictable period of time.
5. **Dose/response or biological gradient**: higher exposure doses should result in an increased probability of developing symptoms.
6. **Biological plausibility**: there should be some explainable mechanism by which the body experiences disease symptoms as a result of exposure and infection.
7. **Coherence**: the hypothesized model should be a good fit with all available data.
8. **Experiment**: randomized clinical trials with appropriate controls are necessary for inferring causality.
9. **Analogy**: we are more likely to accept arguments that are similar to other arguments that we have accepted.

It is not necessary that all of these postulates be fulfilled exactly. You should also notice that these postulates are heavily based on probability and statistics to account for the many random factors that contribute to the disease processes.

The following table shows the extent of variability in the symptoms as various diseases arise. It is *not* common for a microbe to produce *exactly* the same disease in all infected hosts. Many other factors must be considered, e.g., infecting dose, entry point of infection, presence or absence of other microbes, age, sex, genetic makeup, nutritional status, general health of the host, and many others. From the table below, you see that many diseases need not present themselves in all their classical glory. Thus isolating a patient or enforcing quarantine may have little effect when there are many asymptomatic individuals walking around and generously sharing their infectious cargo.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>Wide range of symptoms</td>
</tr>
<tr>
<td>Measles</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Dengue Fever</td>
<td>Severe with varying intensity</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>HIV</td>
<td>Mild to severe</td>
</tr>
</tbody>
</table>

It is important to note that not all diseases exhibit this variability, and some diseases may have a more predictable outcome. This variability highlights the complexity of disease causation and the need for careful investigation and research to understand the underlying mechanisms.
### Frequency of Clinically Apparent Symptoms

<table>
<thead>
<tr>
<th>Infection</th>
<th>Approximate % with clinically apparent disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poliomyelitis (child)</td>
<td>0.1–1.0</td>
</tr>
<tr>
<td>Epstein-Barr virus (1–5 yr old child)</td>
<td>1.0</td>
</tr>
<tr>
<td>(young adults)</td>
<td>30–75</td>
</tr>
<tr>
<td>Rubella</td>
<td>50</td>
</tr>
<tr>
<td>Influenza (young adult)</td>
<td>60</td>
</tr>
<tr>
<td>Pertussis (whooping cough)</td>
<td></td>
</tr>
<tr>
<td>Typhoid</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Malaria</td>
<td></td>
</tr>
<tr>
<td>Anthrax</td>
<td></td>
</tr>
<tr>
<td>Gonorrhea (adult male)</td>
<td>99</td>
</tr>
<tr>
<td>Measles</td>
<td></td>
</tr>
<tr>
<td>Rabies</td>
<td>100</td>
</tr>
<tr>
<td>HIV (?)</td>
<td></td>
</tr>
</tbody>
</table>

### Further Definitions of Terms

A **host** is any organism capable of supporting the nutritional and physical requirements of another. For most of this book, we are the hosts.

A **microbe** is a microscopic organism.

The presence and multiplication of an organism on or within a host is called **colonization** or **infection**. Colonization can occur without symptoms of disease, but infection is accompanied by disease symptoms. A host that is colonized by a microbe is called a **carrier**.

All living organisms play host to other organisms. Even such lowly creatures as bacteria have their own collection of infecting critters.

We refer to the colonization of one organism by another as **symbiosis**. If the symbiotic relationship benefits both organisms, it is called **mutualism**. **Commensalism** is a symbiotic relation in which one organism benefits and the other is not harmed. **Parasitism** occurs when the infecting organism benefits and the host is harmed. If the host sustains injury or pathological changes in response to the parasite, the process is called an **infectious disease**.

The diagram below shows the continua along which symbiosis exists. It is not so cut-and-dried as the previous paragraph may have indicated. Microbes can change their relation to the host by decreasing or increasing their numbers or by relocating to other parts of the body. Also, the sizes of the circles do not indicate the extent of each form of symbiosis. In fact, among all living things, parasitism is the most prevalent form.

Any microbe causing tissue damage or a disease is termed a **pathogen**. There are many agents of infectious diseases: prions, viruses, bacteria, rickettsiae, chlamydiae, fungi, protozoa, and helminths. More about these in a later chapter.

As if the epidemiologist’s job isn’t hard enough, an **idiopathic** disease is one with no known cause. Some altered health states are so complex that modern medicine has yet to determine the causative agent(s), e.g., chronic...
fatigue syndrome, fibromyalgia, schizophrenia, etc.

A **portal of entry** is the process by which a pathogen enters the body, gains access to susceptible tissue, and causes disease.

1. The pathogen can do this by **penetration** of the skin or mucous membranes. This route is taken by: rabies, warts, staphylococci (boils), typhus, streptococci (impetigo), cutaneous anthrax, syphilis, Plague, ringworm, athlete’s foot, hookworm, and the **arboviruses** (viruses that are **arthropod borne**—carried by mosquitoes, fleas, ticks, etc.).

2. Disease can also be caused by **direct contact**, such as physical or sexual contact (**horizontal transmission**, no pun intended—really) or by **vertical transmission** (inheritance, as is the case in childbirth). Sexually transmitted diseases (STDs), rubella, herpes simplex virus (HSV), and chickenpox are all spread by direct contact.

3. Pathogens can be **ingested**, passing through the oral cavity into the gastrointestinal tract, e.g., cholera, typhoid fever, dysentery, food poisoning by *Salmonella* or other microbes, traveler’s diarrhea, hepatitis A, and polio.

4. The **most efficient** form of transmission for pathogens infecting the upper respiratory system is **inhalation**, whereby the microbes are inhaled on aerosol droplets and deposited on the respiratory tissue, e.g., influenza, common cold, measles, mumps, chickenpox, various pneumonias, pneumatic Plague, tuberculosis, and meningitis.

5. Some diseases can also be spread by the deposit of pathogens on inanimate objects, called **fomites**, from which they may be conveyed to the next organism coming in contact with the object before the organism dies². Some examples of fomites are: eating utensils, furniture, bedding, shared toothbrushes, shared razors, telephones, and incompletely sterilized surgical instruments.

6. Lastly, we have the unfortunate case of accidental injection of a pathogen; a deep needle stick of a health care worker, transfusion of unknowingly tainted blood, etc.

Once a disease has been introduced into a population, there is a need to find the process by which the causative agent leaves the body of a carrier and is transmitted to another host, called the **portal of exit**. Clearly, this may be different for common source and host-to-host transmissions.

Diseases acquired while hospitalized are said to be **nosocomial**. Such hospital-acquired infections are not as rare as one might think. Complete data are currently available only up to the year 2003. Researchers who analyzed these data arrived at an annual figure of 103,000 hospital deaths of which 75,000 could have been prevented by such simple measures as hand-washing, adequate sterilization of surgical instruments, and proper cleaning of hospital facilities. They claim the implementation of a strict hand-washing policy alone could save 20,000 lives every year! Current CDC policies governing health and safety carry no penalties, are strictly advisory, and seem to be regularly honored in the breach as much as in the observance. It seems that hospitals may not be the best places for sick people, but there are very good reasons for that. A recent study has found male doctor’s ties to be one source of infection!

### Most Common Nosocomial Pathogens

<table>
<thead>
<tr>
<th>Category</th>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>Coagulase-negative staphylococci</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td></td>
<td>Enterococci</td>
</tr>
<tr>
<td></td>
<td><em>Candida</em> and other fungi</td>
</tr>
<tr>
<td></td>
<td><em>Enterobacter</em> species</td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>Lower Respiratory Tract Infection</td>
<td><em>P. aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td></td>
<td><em>Enterobacter</em> species</td>
</tr>
<tr>
<td></td>
<td><em>Acinetobacter</em> species</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td>Surgical Wounds</td>
<td>Enterococci</td>
</tr>
<tr>
<td></td>
<td>Coagulase-negative staphylococci</td>
</tr>
<tr>
<td></td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td></td>
<td><em>Enterobacter</em> species</td>
</tr>
<tr>
<td></td>
<td><em>P. aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td><em>Candida</em> species</td>
</tr>
</tbody>
</table>

² Rhinoviruses, which are one of the causes of the common cold, can survive on a fomite for as long as 24 hours.
Any diseases or conditions induced by word or action of a physician or health care worker are said to be iatrogenic. Although this sounds like a rare occurrence, it most certainly is not. As reported in a survey article in the year 2000, estimates for the number of deaths in the US in this category per year are:

1. 12,000 due to unnecessary surgery
2. 7,000 due to medication errors made in hospitals
3. 20,000 due to “other” errors made in hospitals
4. 106,000 adverse reactions to correctly given drugs

Not to put too fine a point on it, the October 10, 2002 issue of the New York Times reported that a nurse-anesthetist in the pain treatment clinic of a Norman Oklahoma hospital used the same syringe to give sedatives to a large number of patients. Of the 300 patients treated at the clinic during 2002, 52 were found to be positive for hepatitis C. The hospital advised another 500 people treated at the clinic since 1999 to be tested for that disease.

Diseases that arise over a very short period of time are said to be fulminant, whereas those that are slow to develop are said to be insidious. As examples, Plague is fulminant and cancer tends to be insidious.

Once a pathogen has found its way into an organism (called causation), its development usually proceeds in several phases.

1. The latency period is when the infecting organism has entered the host, but not begun active replication.
2. During the initial incubation period, the pathogen begins active replication without producing recognizable symptoms.
3. We then advance to the prodromal stage with the initial appearance of symptoms, although the clinical presentation may be no more than a vague sense of malaise.
4. At the acute stage, the host experiences the maximum impact of the infectious process.
5. If the infection is contained, the host passes to the convalescent stage wherein there is a progressive elimination of the pathogen, damaged tissue is repaired, and associated symptoms are resolved. Once the pathogen has been totally eliminated and there are no residual signs or symptoms of disease, the host has reached resolution.

A host that does not reach the convalescent stage may continue in the acute stage until death or be maintained in a chronic disease state. The following table lists normal ranges of these times for several common diseases.

<table>
<thead>
<tr>
<th>Infectious disease</th>
<th>Latency period</th>
<th>Incubation period</th>
<th>Infectious period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>6–9</td>
<td>8–13</td>
<td>6–7</td>
</tr>
<tr>
<td>Mumps</td>
<td>12–18</td>
<td>12–26</td>
<td>4–8</td>
</tr>
<tr>
<td>Pertussis</td>
<td>21–23</td>
<td>6–10</td>
<td>7–10</td>
</tr>
<tr>
<td>Rubella</td>
<td>7–14</td>
<td>14–21</td>
<td>11–12</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>14–21</td>
<td>2–5</td>
<td>2–5</td>
</tr>
<tr>
<td>Varicella</td>
<td>8–12</td>
<td>13–17</td>
<td>10–11</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>13–17</td>
<td>50–110</td>
<td>19–22</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>1–3</td>
<td>7–12</td>
<td>14–20</td>
</tr>
<tr>
<td>Influenza</td>
<td>1–3</td>
<td>1–3</td>
<td>2–3</td>
</tr>
</tbody>
</table>

In the simplest case, there is infection by some microbe, a latency period, followed by the incubation period, and then the infectious period. Be forewarned, this order may change for some diseases and distinguishing between latency and incubation periods is not easily done. In fact, for chickenpox, if the virus is not completely eliminated from the host, it enters a latency period and can reappear as shingles years later.

There is more to an epidemic than the biology of the infectious agent. We need to consider the ecological triad

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3 This contributes to health care being the third leading cause of death in the US today.
of host-agent-environment. Changes in any one of the three can break, enhance, or retard the chain of infection.

Certainly, there are organisms that are more contagious than others, but factors other than the infectiveness of a diseases-causing agent often determine whether an epidemic occurs or not. The virulence of a disease is due to many factors. For the causative agent, there are:
1. pH susceptibility of the agent,
2. interaction of the agent with food and the environment,
3. immunological “uniqueness” of the agent, potential for damage and/or stress of the microbe,
4. interactions with other organisms (especially normal flora [see the chapter on the Immune System]),
5. variability of gene expression of multiple pathogenic mechanism(s),
6. portal of entry, and others.

For the host, we need to consider
1. age,
2. general health,
3. nutritional status and amount and type of food consumed,
4. gastric acidity,
5. immune competence,
6. occupation,
7. medications being taken,
8. surgical history,
9. metabolic and organ disorders (e.g., alcoholism, drug addiction, etc.),
10. genetic makeup (including anomalies), and others.

The environment frequently determines which pathogens survive and which do not. Tropical diseases, such as malaria and dengue fever, are rarely found in cool temperate or cold climates. Arid climates can cause desiccation of animal feces or urine so that they can become airborne, e.g., Hantavirus in mouse excrement. Moist and humid regions can allow easy transmission by liquids, e.g., Bolivian hemorrhagic fever from mouse urine.

Generally, a disease that can be transmitted from an animal to a human is called a zoonosis. There are more than 250 organisms known to cause such infections, some of which are resident on (or in) common household pets. It has been estimated that fully 70% of all human diseases originated in animals.\(^4\)

Descriptive epidemiology attempts to collect data on health conditions using various population, geographic, and temporal variables. The data regularly presented by the CDC and published in the Morbidity and Mortality Weekly Report (MMWR) are examples of the results of such studies.

Analytical epidemiology attempts systematic analyses of possible relationships between/among available variables. It employs two basic approaches to the interpretation of data, case control and cohort studies. Case control studies compare a group in which infection is present to a matching control group in which it is absent, hence, such a study is retrospective, or after-the-fact. Most cohort studies are prospective, or before-the-fact, insofar as they monitor the appearance of infection in carefully predefined groups over a period of time by comparing subjects exposed to the risk factors to those not exposed.

The usual gold standard for research is the randomized clinical trial (RCT), wherein volunteers are randomly assigned to either the exposure categories or treatment modalities being compared. Frequently, these are simply “exposed to a pathogen” versus “not exposed” or treatment versus placebo, which is a medically inactive substance. Testing infectious diseases is possible, but finding volunteers willing to be infected may not be the easiest task. How many people do you know who would have been willing to be infected with HIV or hepatitis for the sake of the advancement of scientific knowledge?

\(^4\) One author attributes 265 human diseases to dogs, 50 to cattle, 46 to sheep and goats, 42 to pigs, 35 to horses, 32 to rodents, and 26 to poultry.
Beyond the medical aspects of such studies are the statistical analyses from which we can infer causation. Some cases are easier to make than others. Establishing smoking as one of the main causative agents of cardiovascular disease and lung cancer required very extensive research over several decades before the inferences were well established and generally accepted. On the other hand, showing that pellagra was not a communicable disease took Joseph Goldberger a mere three months.

A Riddle to Be Solved (Pretend you’re an epidemiologist)

The following tables, drawn from a single retrospective observational study, illustrate an incidence of excess mortality at a period of time in history. Deaths for this population are categorized by economic status and gender, and then by economic status and age. The three rightmost columns listing of deaths per 100 are just the percentages of those exposed that died.

<table>
<thead>
<tr>
<th>Economic Status</th>
<th>Population Exposed to Risk</th>
<th>Number of Deaths</th>
<th>Deaths per 100 Exposed to Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td>Both</td>
<td>Male</td>
</tr>
<tr>
<td>I (high)</td>
<td>180</td>
<td>145</td>
<td>325</td>
</tr>
<tr>
<td>II</td>
<td>179</td>
<td>106</td>
<td>285</td>
</tr>
<tr>
<td>III (low)</td>
<td>510</td>
<td>196</td>
<td>706</td>
</tr>
<tr>
<td>Other</td>
<td>862</td>
<td>23</td>
<td>885</td>
</tr>
<tr>
<td>Total</td>
<td>1731</td>
<td>470</td>
<td>2201</td>
</tr>
</tbody>
</table>

This case of excess mortality is quite unusual insofar as it affected males at a far higher rate than females, 80% versus 27%. Additionally, there seems to be a relation between economic status and survival rates, e.g., the highest economic status had the lowest overall mortality rate, 38%, while the lowest economic status had a mortality rate of 75%—nearly double the lowest rate.

If we use Adult/Child as a variable instead of Gender, we have the following table.

<table>
<thead>
<tr>
<th>Economic Status</th>
<th>Population Exposed to Risk</th>
<th>Number of Deaths</th>
<th>Deaths per 100 Exposed to Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Economic Status</td>
<td>Adult</td>
<td>Child</td>
<td>Both</td>
</tr>
<tr>
<td>I (high)</td>
<td>319</td>
<td>6</td>
<td>325</td>
</tr>
<tr>
<td>II</td>
<td>261</td>
<td>24</td>
<td>285</td>
</tr>
<tr>
<td>III (low)</td>
<td>627</td>
<td>79</td>
<td>706</td>
</tr>
<tr>
<td>Other</td>
<td>885</td>
<td>0</td>
<td>885</td>
</tr>
<tr>
<td>Total</td>
<td>2092</td>
<td>109</td>
<td>2201</td>
</tr>
</tbody>
</table>

Only children in the lowest economic status category III died, but at the fairly high rate of 48%.

What was the risk to which these people were exposed? What was the cause of death? Over what period of time do you think this happened? Clearly the mortality rate is very high and the total number that died, 1490 out of 2201, is also quite high at 68%.

Some History

At the end of the 1400s, after the major global attack of Plague, the intelligentsia of the time arrived at the conclusion that a full causation of epidemics was as follows:

1. Such a disease as the Plague was highly contagious, spreading from sick to well by contact (according to some authorities of the time by the glance of the eye); and infection was associated with objects and places used or occupied by the sick.
2. The infection consisted in a corruption of the air (of what we should call a chemical nature).
3. This corruption of the air arose from decomposing organic matter, unburied bodies of the dead, marshy and putrid waters, and the like; and was favored by certain meteorological conditions, such as heat, dampness, and southerly winds.

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5 Of course, convincing the establishment he was right took several years. By the way, pellagra is caused by a deficiency or failure to properly metabolize the B vitamin niacin.
4. The basic factor that made possible the generation of a particularly virulent corruption (such as characterized a great and unusual pandemic) was a malign conjunction of the planets and fixed stars. To be more precise: "A conjunction of Saturn, Jupiter, and Mars in the 40th degree of Aquarius at 1:00 p.m. on March 20, 1345. This caused hot, moist conditions, which forced the earth to exhale a virulent sulfurous miasma." Such a conjunction was apt to be associated with other unusual earthly and heavenly phenomena such as unseasonable weather, earthquakes, "falling stars," thunderstorms, and the like; but these were "signs" of an epidemic constitution of the atmosphere rather than "causes" of such a condition.

6. Individual predisposition played a considerable part in determining which particular persons were stricken in the course of an epidemic.

Far though it may be from the truth of the matter, it was a start. Besides, medicine had advanced little beyond the Greek "physician" Galen (130–201 CE) until Lister, Koch, and Pasteur did their pioneering work on the Germ Theory of Disease in the mid-to-late 1800s.

The working class neighborhoods of the large European cities of the early 19th century were impoverished, crowded, and filthy beyond belief. They were a breeding ground for all manner of microbes. Diseases that previously afflicted populations as visitors from elsewhere, were now being incubated in the streets of these metropolises. In England, Chadwick’s Poor Law Commission collected data on the health(?) of the working class. Their shocking conclusions were that the average age of death for laborers was 16 years, tradesmen – 22 years, and gentry – 36 years.

John Snow

Others made progress toward understanding the causes of infectious disease without knowing the underlying responsible mechanisms/organisms. Prior to the discovery of the Germ Theory of Disease, an English physician (in fact, anesthetist to Queen Victoria during childbirth), John Snow, spent many years studying the incidence of cholera.

He plotted the locations of cholera deaths on maps of London and, in 1849, found an unusually high mortality rate (500 fatal cases within ten days in August and all within a circle of radius 250 yards centered on the Broad Street pump) on Broad Street, Golden Square, near Soho. His earlier theories were that something in the water was, somehow, associated with the disease. Snow asked the local officials to remove the pump handle from the local well, which was done on September 7. Within the week the cholera epidemic, although already slowing, all but disappeared from this area.

The following illustration is a copy of Snow's original map of the area. Each little darkened rectangle (coffin) represents a cholera death in the geographical region he studied. Pay special attention to the decrease in mortality as you move away from the Broad Street pump.

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6 Although the categories have changed slightly, the relationship between mortality and economic status continues to this day, the poor die younger than the rich.
Circles along streets are labeled as Pumps from which water was drawn for the use of the residents. In the upper left quadrant is Broad Street. At various locations there are dark rectangles, each of which represents a death at that location. Notice the relation between deaths and the proximity to the Broad Street pump. (This is Snow’s original map.)

Additional follow-up showed that a workhouse in the area was more than three-fourths surrounded by houses in which cholera deaths occurred, but only 5 cases had appeared amongst its 535 inmates; no doubt due to the fact that the house had its own private well. Also, a gentleman from Brighton visited his brother, who had died of cholera, drank the local water, and came down with cholera in his distant home the next evening. Even more remote was the case of a woman who had not visited the district in months but who had once lived there and had a special taste for the Broad Street water. Daily a carter brought a supply, filled at the Broad Street pump, to her house in Hampstead. On August 31, she too was stricken. A niece who happened to visit the woman also drank from the supplied water and returned to her home in far off Islington to die of cholera. Neither of these two communities had any other cases of cholera.

After the epidemic abated, other investigators opened the Broad Street well, and found the main drain from No. 40 Broad Street was only 2'6” from the well and 9'2” above the water level. Discolored soil and a washed appearance of the surrounding gravel indicated a high level of pollution, no doubt containing infected fecal matter from one or more carriers of cholera.

In the year 1854, Snow analyzed a much larger area south of the Thames River, across from Westminster Abbey and the Parliament Buildings, where water was supplied by competing companies, the Southwark & Vauxhall Company and the Lambeth Company. In parts of this area, each company enjoyed a monopoly, but for a majority of the customers, the companies competed head-to-head, each having installed pipes along the same streets. In this totally unregulated free market, residents enjoyed the option of connecting to either supplier and the distribution of houses between the companies appeared to be random. Customers of the Southwark & Vauxhall
Company credited their water with having a “full bodied flavor,” possibly due to the high salt content of 38 grains per gallon. The results of Snow’s detailed survey of all cholera deaths in the area showed that in one four week period, the Southwark & Vauxhall customers had 71 deaths per 10,000 houses and the Lambeth customers 4, while the overall rate for the rest of London was 9. In total, there were 315 deaths per 10,000 houses supplied by Southwark & Vauxhall, and 37 per 10,000 houses supplied by Lambeth. The death rate for the rest of London was 59 per 10,000 houses. These figures persisted across the areas of monopoly and the areas of competition. Snow concluded that the water Southwark & Vauxhall withdrew from the heart of London (Battersea Fields), containing the excrement and emissions of cholera victims, was the source of infection. The Lambeth Company withdrew its water considerably upstream of the city at Thames Ditton, which, at that time, was fairly pristine. Snow’s reportage of this is worth repeating:

The experiment, too, was on a grand scale. No fewer than three hundred thousand people of both sexes, of every age and occupation, and of every rank and station, from gentlefolk down to the very poor, were divided into two groups, without their choice, and, in most cases, without their knowledge; one group being supplied with water containing the sewage of London, and, amongst it, whatever might have come from cholera patients, the other group having water quite free from such impurity.

Despite this quite convincing numerical display, evangelical reformers like Edwin Chadwick who had preached the so-called Sanitation Doctrine, wherein disease was thought to arise from dirt (and dirt alone), held sway. Their solution was to scour and scrub the great unwashed of London, while giving no consideration to their, possibly infected and unwashable innards. In a similar vein, William Farr preached the miasma theory, whereby clouds of diseased effluvia were thought to arise from the city’s sewers and cesspools to infect any and all that came in contact with these menacing, but invisible, nebulosities. Farr’s work culminated in the start of the so-called Sanitation Movement, whereby sewers were enclosed, garbage was removed from the streets, and washing was strongly encouraged.

Although the Sanitation Movement was in full swing when the 1849 epidemic struck, little effect was felt, other than by the removal of the Broad Street pump handle. Nevertheless, Snow’s work was disregarded; the main criticism being that he was unable to identify the causative agent in the water. This remained a mystery until the publication of the germ theory of disease and the isolation of Vibrio cholerae by Koch 29 years later in 1883.

Strangely, in the twentieth century, as the germ theory of disease took hold, some officials embraced the new explanation with such vigor that they rejected any connection between dirt and disease. Thus relegating the collection of garbage and street cleaning to the newly formed public works departments, outside the venues and control of public health officials.

Typhoid Mary

Moving ahead in time, we come to the twentieth century and the classic first well-known case in North America of an identified carrier (an asymptomatic infected person), so-called Typhoid Mary.

Mary Mallon served as a cook (reputedly a very good one) to several households and institutions in New York City and Long Island. After a typhoid outbreak in a rented summer home in Oyster Bay, New York, the owner, Mr. George Thompson, in the interests of removing any stigma attached to his rental property, hired Dr. George Soper in 1906 to investigate. Soper earned his doctorate in sanitary engineering and had extensive experience in the epidemiological analyses of typhoid outbreaks. After sifting through all available evidence, he hit upon the fact that the family had changed cooks just prior to the outbreak. One of the cook’s specialties was an ice cream dessert served with sliced fresh peaches, an ideal medium for the growth of the causative microbes. Further investigation led to the employment agency that placed her. Of the eight families that had previously employed Mary, seven had instances of typhoid fever. In the last instance, the daughter of Henry Warren of Park Avenue contracted typhoid and died, the first death to be attributed to Mary. To Soper, this indicated that Mary Mallon was the likely source of contamination. He confronted her at the Warren household and asked, as diplomatically as he could, considering the

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7 The water was so “full-bodied” that it had a brown color with a bit of a head whenever the Thames was low and the ocean pushed saltwater as far as London. Water left in a pot took on a slimy coating and had a rather unpleasant odor. When a tap was covered with cloth to filter water for a pot of tea, it was not unusual to extract a tablespoon of “foreign materials.”

8 It didn’t help that he died of a stroke in 1856 and was thus unable to personally defend his theory.

9 Between 1900 and 1907 Soper tracked a total of 22 cases (fourteen servants and eight family members) of the fever to Mary. More interestingly, every one of these cases had been previously investigated and explained to be the result of other sources of infection. As a comparison, anywhere from 300 to 4500 cases were reported each year in New York City.
intensely personal nature of the request, for samples of her blood, urine, and feces. Claiming not to ever have had typhoid, Mary, menacingly displaying a carving fork and using rough language to the effect that she never had typhoid fever, promptly showed Soper the door. Undeterred, he and a colleague went to her home. Both were physically ejected by the suspect, this time using even coarser language and another, undoubtedly equally sharp, carving fork. Since Soper was independently employed, he had no authority to compel Mary to provide the requested samples. He turned to the city health department and the official health inspector, Dr. S. Josephine Baker. With police assistance in the five-hour search of the Warren residence, Dr. Baker took Mary into custody (going so far as restraining her by sitting on her in the police car) and obtained the requested samples. In the interests of “protecting the public health,” Mary was imprisoned in a cottage on North Brother Island.

At this time a similar case arose in upstate New York where an Adirondack mountain guide was identified as the source of an outbreak among 38 tourists, two of whom died (a higher rate than that attributed to Mary). The state health department, claiming no legal authority to do so, did not detain him. This left Mary as a singular prisoner of the public health system.

Bacteriological analysis by the health department of Mary’s feces revealed a high titer of Salmonella typhi, the bacterium causing typhoid, although of 163 samples taken between March 20, 1907 and June 16, 1909, fully 43 were negative. Her urine never tested positive. Public health authorities postulated that she had remained a carrier for several years because her gallbladder was infected. (Remember, at this time typhoid could not be cured with certainty.) The drugs hexamethylenamin and utropin were given, but with no change in her infective status. They offered to remove her gallbladder, but she refused and was in most ways totally uncooperative. In June of 1909 she sued for release, but the writ of habeas corpus was denied. The following year, upon the arrival of a new commissioner of health, after having been incarcerated for nearly three years, in February of 1910 she was released on the condition that she not cook or handle food for others and that she report to the health department every three months. Three months later she complained to the New York City Board of Health that she had been unjustly deprived of her means of earning a living. For a few years she worked as a laundress but then departed for parts unknown. Under the assumed name of Mrs. Brown, she returned to her vocation of choice and left a swathe of typhoid behind her. As a result of an investigation of an outbreak of twenty-five cases (including two deaths) at the Sloan Hospital for Women in Manhattan, after five years of freedom, Mary was rearrested and reimprisoned in 1915. She remained in custody on North Brother Island for 23 years and died in 1938, 32 years after first being identified as a chronic typhoid carrier. A total of forty-seven cases, including four deaths, were attributed to her. The state laboratory’s bacteriologic analysis of her feces between 1915 and 1936 yielded 207 positives and 23 negatives.

By comparison, Alphonse Cotils was a baker, restaurant owner, and carrier of typhoid who had been prohibited from preparing food in either of his establishments. Nevertheless, he continued to work in his bakery and was brought up on charges. The judge refused to imprison him since that would have been illegal, because he was not ill (For him, but not for Mary?). Besides Alphonse, there were several hundred other carriers who were not singled out for isolation. In 1922 one Tony Labella, a carrier as diagnosed by the New York authorities, was found in New Jersey and an outbreak of 87 cases and two deaths were laid at his doorstep. A further 35 cases and three deaths were also attributed to him. The inconsistency of having Mary Mallon isolated on North Brother Island for a first offense and then permanently put away for a second offense, while Cotils and Labella, who were also repeat offenders, remained free and uncharged did not seem untoward to any of the officials concerned.

How was all this viewed by the public? The July 7, 1909 issue of the British humor magazine Punch carried this bit of doggerel:

The Germ Carrier by O.S.
In the U.S.A. (across the brook)
There lives, unless the papers err,
A very curious Irish cook
In whom the strangest things occur:
Beneath her outside’s healthy gloze
Masses of microbes seethe and wallow
An everywhere that MARY goes
Infernal epidemics follow.

10 At that time Mary, although single, was living with Mr. A. Breihof (or Breshof).
11 Mary had arranged for an outside lab, the well-known Ferguson Laboratories, to test her urine and feces. Of the ten specimens, not one tested positive. This contradicted eight of the city’s results. The specimens had been secreted off the island by Breihof.
12 At no time was Mary informed of the danger of this surgery, nor of its poor record for altering the typhoid carrier state.
And it continues with the usual English disparagement of the Irish.

1910 was the year of publication of a work of fiction, *The Silent Bullet*, by Arthur Reeve wherein a villainous lawyer arranges the death of a rich man by inserting the Irish cook Bridget Fallon, who is a carrier, into the household so as to infect all and sundry with typhoid.

The May 18, 1915 issue of the august publication *Scientific American* carried the following less than compassionate statement:

*The great trouble with Typhoid Mary has been her perversity, exceeding even that which obtains in her most temperamental of callings. She has never conceded herself a menace; she has not obeyed the sanitary directions given her; she would not wash and disinfect her hands as required; she will not change her occupation for one that in which she will not endanger others; under an assumed name she had competed with the Wandering Jew in scattering destruction in her path.*

Neither Alphonse Cotils nor Tony Labella received such censure in the popular press of their time, even though they were responsible for similar, or worse, acts and outcomes. Whenever the *New York Times* referred to Labella it was as an “alleged” carrier, despite the certainty of that diagnosis in the eyes of health department officials. Oh, but for some equity and justice!

Often an epidemiological investigation must be carried out, whereby all relevant (and some irrelevant) data are collected with an eye to identifying the infectious agent, the mode(s) of transmission, and the possible measures for control. An epidemiologist must be a good (and possibly brave) detective. After the 1918 influenza pandemic, members of public health departments interviewed and checked the medical records of more than a hundred thousand people so as to better understand the deadly nature of the disease.

What was mankind’s greatest (and first) achievement that significantly reduced disease? The easiest problem to attack was the common source epidemic and the most efficient first tool was the development of adequate sewer systems and water treatment. This led to the establishment of trustworthy sources of clean (but not necessarily pure) water. Once clean water was available, the notions of sepsis, such as handwashing, lead to even more improvement in the health of the population. The introduction of sepsis into surgery, as argued by Semmelweiss and Nightingale, caused a steep decline in iatrogenic deaths at the (biologically filthy) hands of surgeons.

As a final word on the tabular mortality data: the unusual excessive mortality was due to the sinking of the *Titanic* on April 15, 1912. Economic status I and II were cabin classes, and III was steerage. The Other category refers to the crew, hence, there were no children in this group. Remember: “Women and children to the lifeboats first.” Not to put too fine a point on it, but two dogs survived the sinking. Henry Sleeper Harper’s pekinese (Sun Yat Sen) accompanied him on lifeboat no. 3 and Miss Margaret Hayes’ pomeranian left with her on lifeboat no. 7. Both boats left in the first wave of departures.

### Some Simple Epidemiological Models

The very simplest model of the spread of disease considers only Susceptible and Infected people, the so-called SI model. It assumes the relative rate of transmission remains constant. The prediction for the number of infected people that it generates is

\[ N(t) = N_0 (R_0)^{t/T}, \]

where \(N_0\) is the initial number of infected hosts, \(R_0\) is the so-called multiplier, \(t\) is the time elapsed, \(T\) is the average incubation period of the causative agent, and \(N(t)\) is the number of infected at a time \(t\) units later. This is called exponential growth when \(R_0 > 1\) and exponential decay when \(R_0 < 1\).

Estimates for the smallpox multiplier are \(3 \leq R_0 \leq 20\) and \(11 \leq T \leq 14\) days. In the most conservative scenario, we would take the highest value for \(T\) and the lowest value for \(R_0\), so that \(R(t) = 3^{t/14}\), when \(t\) is measured in days. Starting with one infected person, the “index case,” who is assumed to be mobile, after two weeks (14 days) we’d expect 3 cases, after 4 weeks \(3^2 = 9\) cases, after 6 weeks \(3^3 = 27\) cases, etc. The worst-case scenario would use \(R_0 = 20\) and \(T = 11\) days. The following table tells the tale of the damage.

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>11</th>
<th>22</th>
<th>33</th>
<th>44</th>
<th>55</th>
<th>66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number infected</td>
<td>20</td>
<td>400</td>
<td>8000</td>
<td>160,000</td>
<td>3,200,000</td>
<td>64,000,000</td>
</tr>
</tbody>
</table>

13 The similarity in the last names is unlikely to have been coincidental because Reeve was meticulous with details.
Need more be said?

In an actual case of a single smallpox-infected male housed in the Walberg Krankenhaus in Mershede Germany in 1970, the multiplier $R_0$ was 17. The patient’s room was “isolated,” but not to the standards required today. Many of those infected had no face-to-face contact with the index case. In fact, some of them were hospital patients whose rooms were two floors above his room!

In one of the unexpectedly late cases of SARS in Toronto Canada, 32 people were infected by a single “super spreader” patient and there have been others with even higher values of $R_0$. And this occurred well into the epidemic when public health officials knew of the extent of the transmissibility of the disease. Unfortunately, hospital officials felt the disease was on the wane and let their guard down, ever so slightly—but, clearly, more than enough for the causative coronavirus to take advantage of the opening.

More complex epidemiological models are available. The simplest is called the SIR model.

Here all people are classified as Susceptible, Infected, or Recovered/Removed. Such a model would be appropriate for smallpox or outbreaks of similar diseases. Of course, the mathematics gets much more complicated and the possibilities more numerous. For HIV, the number of alternatives is increased and the resulting diagram and the mathematics are even more complex and the resulting dynamics is much more complicated.

References
See [http://www.epidemiolog.net/evolving/TableOfContents.html](http://www.epidemiolog.net/evolving/TableOfContents.html)
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