Death and Disease

Shifting the focus from Mortality to Morbidity

The COVID19 pandemic brought to the forefront questions regarding what our public health focus should be on. Commentary along the lines of 'if it doesn't kill me why should I care', and debate as to how cause of death is documented highlight critical misunderstanding and failures in communication about how epidemiology informs approaches to public health.

Topics: Immediate Cause of Death — Underlying Cause of Death — Mortality Rate — Survivorship Bias — Natural History Perspective of Disease — Morbidity Rate — Iceberg Principle of Disease Presentation — Triad of Epidemiology

Immediate Cause of Death — The final disease or condition which resulted in death. [National Vital Statistics System]

Underlying Cause of Death — The disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury. [World Health Organization]

Beyond their purposes for insurance, inheritance, and other legal matters, certificates of death are an important source of mortality information. These certificates specifically require the cause of death to be classified according to categories identified by the International Classification of Diseases (ICD). When death results from a single determinant (cause), this classification is straightforward. However, a persistent issue has been how to properly classify the cause of death when the individual has multiple comorbid (simultaneously present) determinants. Starting in 1948, the ICD set the precedent that the single cause of death to be used as the basis for routine mortality statistics should be the **underlying cause which initiated the cascade most directly leading to death**, but also allowed listing up to 20 additional multiple causes. Within the US, the National Vital Statistics System also provides legal mandates for the minimum required information included within certificates of death, which also allows for differentiating the underlying cause of death from the immediate cause of death.

> Consider the situation of an individual with diabetes who experiences a hypoglycemic (low blood sugar) event, causing them to lose consciousness (pass out). Since the event occurred while driving, they are involved in an accident, causing a massive loss of blood and subsequent death.

Although the massive loss of blood was the most immediate cause of death, the underlying cause of death would be the diabetes, as it initiated the train of events leading to the hypoglycemic event and subsequent accident resulting in death.

> However, consider the situation of an individual with congestive heart failure, which they have struggled with for 10 years, who dies after developing viral pneumonia.

In this case, although the congestive heart failure placed the individual at greater risk of death, the actual underlying cause of death was viral pneumonia, and the immediate cause of death would most likely have been respiratory failure. The congestive heart failure would be viewed as a significant condition that contributed to their death but not as a cause. Causes of death on the death certificate represent a medical opinion that might vary among individual physicians. In signing the death certificate, the physician, medical examiner, or coroner certifies that, in their medical opinion, the underlying cause is the one that most specifically initiated the train of events leading directly to death.

Mortality Rate — $\frac{Number\ of\ Deaths}{Population}$

The National Vital Statistics System, run by the National Center for Health Statistics at the Centers for Disease Control and Prevention, also compiles cause–of–death information from statewide electronic death registration systems, processing over 2 million records each year. This system provides publicly available data on mortality across all causes each year and quarterly estimates of mortality for the 15 leading causes of death. This database provides an important source of public health information to understand key factors related to mortality.

Cause of Death	Number of Deaths	Mortality Rate	Percent of Deaths
Cardiovascular Disease	2,706,931	0.20%	28.7%
Cancer	2,406,438	0.18%	19.7%
Respiratory diseases, Influenza, and Pneumonia	815,828	0.06%	6.5%
COVID-19	767,724	0.06%	6.1%
Stroke	620,969	0.04%	5.0%
Diabetes	378,075	0.03%	3.0%

Data from 2018 to 2021.

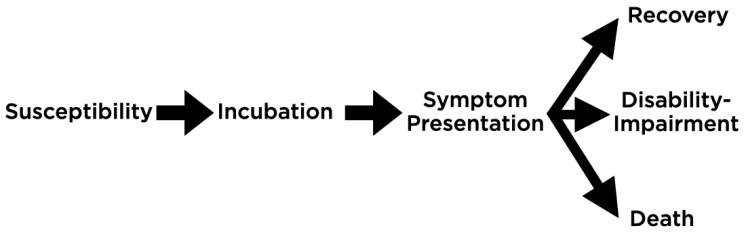
Data from the National Vital Statistics System paint a clear picture that cardiovascular disease and cancer represent nearly half of all deaths in the US — accounting for 48.4% of all deaths — representing a particularly important area of focus for efforts to enhance public health. Although cardiovascular disease and cancer have represented the leading causes of death since the 1940s, it is important to point out that public health efforts and improvements in medical care have reduced the mortality rate of cardiovascular disease by over 70% and cancer by over 30%.

Mortality rates provide a key starting point for descriptive epidemiology — a field that attempts to identify patterns in populations to understand variations in disease frequency — but by themselves can often be misleading. A key point is that just because there is a 0.18% mortality rate associated with cancer does not mean that you have a 0.18% chance of dying or even developing cancer in a given year. To get that information, we would need to turn to the field of actuarial science, which applies statistical methods incorporating demographic characteristics, environmental considerations, and various risk factors to predict the probability that you might contract and/or die from a given disease, disorder, or circumstance, given your past history, your family history, where you live, etc. This is how insurance and financial companies assess risk.

Survivorship Bias — A form of selection bias where erroneous conclusions are drawn by focusing only on individuals, groups, or cases have passed some selection process.

Natural History Perspective of Disease — A given disease or disorder will follow a standard progression from 1) Susceptibility to 2) Incubation to 3) Symptom presentation to 4) Resolution. But that resolution of the disease or disorder has only three possible outcomes: Recovery, Disability–Impairment, or Death.

Figure: Natural History Perspective of Disease.



Morbidity Rate — $\frac{Number\ of\ Clinically\ Ill}{Population}$

While mortality rates give us some sense of which parts of our physiological systems are likely to result in our death when they fail, focusing public health efforts only on mortality factors reflects a reversed form of survivorship bias (only focusing on the things that we do not survive) that ignores the Natural History Perspective of Disease. Specifically, just because an individual might survive a disease or disorder, does not mean that they will be free from experiencing long–term impairments in their health and aspects of wellbeing. An ongoing debate, in particular, is in regards to the observed reduction in mortality rates associated with cardiovascular disease and cancer. If current efforts are causing such reductions, is it really necessary to continue to spend hundreds of millions of dollars each year on prevention of cardiovascular disease and cancer? Examination of the morbidity rate of cardiovascular disease over the past 20 years indicates relatively minimal change in the number of patients diagnosed with cardiovascular disease and an increase in cancer diagnosis. So our public health efforts have not solved cardiovascular disease and cancer, they have just made us less likely to die from these diseases. Thus, while we may be less likely to die from these diseases we may still have to live with their negative effects, ultimately compromising health and aspects of wellbeing.

Iceberg Principle of Disease Presentation — The smallest percentage of individuals with a given condition/disease will present as clinically apparent cases. The largest percentage of individuals with a given condition/disease will present as latent, subclinical, undiagnosed and carrier states. Condition/disease severity is not always associated with clinical appearance.

The other issue with focusing primarily on mortality rates is that we may be missing out on addressing larger public health needs that could help improve societal health and aspects of wellbeing. Mortality as a public health metric of diseases/dysfunctions has the benefit of being an easily identified objective criteria — despite debate over the diseases/dysfunctions being an immediate cause, underlying cause, or contributing factor. Morbidity is a substantially more difficult measure as individuals with a disease/disorder may not always be aware of it. The iceberg principle of disease presentation characterizes this issue. The majority of individuals within a community who have a given disease or disorder will present as asymptomatic, or exhibit pre/subclinical states. In such instances, the individual may be aware that they have an issue, but due to the absence of symptoms or the minimal symptomatic burden they do not actively seek treatment. Alternatively, the individual may not even be aware that they have the disease or disorder. In either case, there would be no public health record which would allow us to easily and accurately assess morbidity. In such instances we would have to turn to more general approaches such as waste–water assessments or sales of over–the–counter medications in hopes that they might provide insight.

Problematically, however, the iceberg principle of disease presentation also notes that the clinical appearance of a disease or disorder is not always associated with the severity of the condition or disease; nor does the lack of clinical appearance minimize the potential comorbid impacts. Many of the most prominent diseases/disorders exhibit comorbidities with other prominent diseases/disorders; where the presence of one increases the risks of developing or the risks associated with the other. So even a subclinical presentation of heart disease may place that patient at greater risk of death due to stroke or respiratory diseases.

Triad of Epidemiology — The distribution of a disease in a given population occurs at the intersection of the agent (the necessary component of the disease), the host (the individual), and the environment (the things that contribute to the disease process).

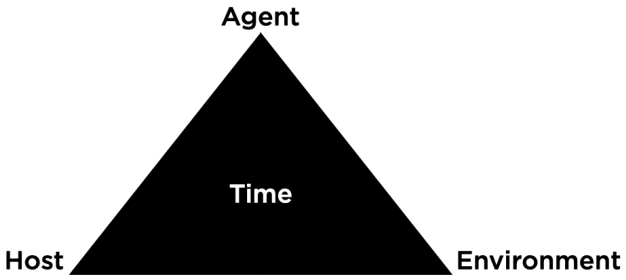
The fundamental assumption of epidemiological research is that diseases do not distribute randomly in populations, but rather distribute when the right accumulation of risk factors or determinants (causes) exists. Understanding the conditions necessary for the risk factors or determinants (causes) to result in the individual developing a disease/disorder is critical for trying to prevent its occurrence as well as to mitigate its effects. The Triad of Epidemiology framework suggests that the agent, host, and environment form a triangle and that in order to prevent the continuation of a disease/disorder it is necessary to break the connection on at least one side of the triangle. This framework is classically oriented towards infectious diseases, so conceptualizations of the **Agent** generally revolve around nutrients, poisons, allergens, radiation, or microbes. Without being exposed to the agent the individual does not develop the infectious disease. Outside of specific infectious diseases, the characterization of the **Agent** typically focuses on the internal physiological mechanisms but at times characterizations of behavior are also appropriate.

The **Host** is the human or animal that acquires the disease/disorder, recognizing that there is wide variation in the host's sensitivity to the agent given their genetics, immunologic state, age, prior medical conditions, lifestyle behaviors etc. The Host's genetics, immunologic state, age, prior medical conditions, and individual behaviors would be considered as individual level risk factors that might alter their sensitivity. The **Environment** refers to the surroundings and conditions in which the agent and host exist. Given the classical orientation towards infectious diseases, this might be conceptualized to reflect seasonal variations in the spread of the disease; but such concepts can similarly be applied to how environment alters behavioral choices. Environmental risk factors are those that are non-specific to the individual and reflect the surroundings and conditions in which the agent and host exist.

The final component of the Triad of Epidemiology framework is **Time**. Time sits in the middle of the triangle as although the conditions necessary for a disease/disorder might present (the agent, host, and environment); the amount of time in which all 3 conditions are present relates to the likelihood of contracting the disease/disorder. A sensitive host, in a facilitating environment, but only exposed to the agent for a

brief period of time is unlikely to be affected.

Figure: Triad of Epidemiology.



An epidemic — outbreak or occurrence of a disease in excess of the usual level of expectancy in a specific region — occurs when the agent, host, and environment are not in balance. This can be due to the emergence of a new agent, such as in the case of COVID-19 or due to changes in existing agents. From an infectious disease perspective this could be changes in the infectiousness or virulence of the agent. But could also encompass changes in the metabolic availability of relevant physiological components. The exposure to other diseases/disorders and changes in behavioral patterns (getting less sleep, experiencing high levels of continuous stress, being less physically active) may alter the sensitivity of hosts within the population, making contracting the disease/disorder of interest more likely. Finally, environmental changes may alter the spread of the disease/disorder. For instance, societal changes in transportation may alter the behavioral patterns of the host. Again because this framework is classically oriented towards infectious diseases, the idea of disease transmission can seem awkward for diseases such as diabetes and cardiovascular disease. But when considered alongside evidence for social influences in behavioral patterns, the framework still holds true.

Additional Resources:

International Classification of Disease, https://icd.who.int/browse11/l-m/en

Department of Health and Human Services (2003). Physicians' Handbook on Medical Certification of Death. Centers for Disease Control and Prevention. National Center for Health Statistics. https://www.cdc.gov/nchs/data/misc/hb_cod.pdf

How Do We Determine

Cause of Death

- 1948 - Word Health Organization codifies causes of death to enable global comparisons.
  - This codification became the International Classification of Disease.
  - This system set the precedent that single cause of death to be used as the basis for routine mortality statistics should be the **underlying cause which initiated the cascade most directly leading to death.**

The intent of this system is to eliminate attributing the cause of death to unspecific, intermediary-causes, or context that are impossible to have resulted in death. 'Garbage'-event coding masks potential public health threats and hinders the ability to identify changes in mortality.

INTERNATIONAL FORM OF MEDICAL CERTIFICATE OF CAUSE OF DEATH

Cause of death			Approximate interval between onset and death
I Disease or condition directly leading to death*	(a)	Immediate cause	
	due to (or as a consequence of)		
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)	Intermediate causes	
	due to (or as a consequence of)		
	(c)	Intermediate causes	
	due to (or as a consequence of)		
	(d)	Underlying cause	
II Other significant conditions contributing to the death, but not related to the disease or condition causing it			

*This does not mean the mode of dying, e.g. heart failure, respiratory failure. It means the disease, injury, or complication that caused death.

Leading

Causes of Death

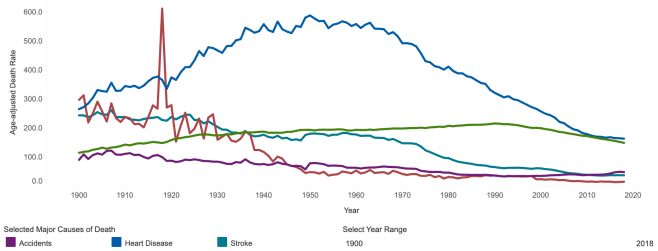
The National Vital Statistics System run by the National Center for Health Statistics at the Centers for Disease Control and Prevention provides publicly available data on mortality.

- All-cause mortality is provided yearly.
- The 15 leading causes of death are provided quarterly.

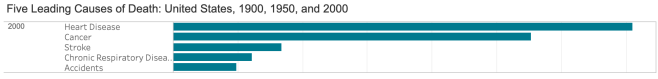
Mortality Rate

$$\frac{Number\ of\ Deaths}{Population}$$

Age-adjusted Death Rates† for Selected Major Causes of Death: United States, 1900 to 2018‡‡‡



Five Leading Causes of Death: United States, 1900, 1950, and 2000



Leading

Causes of Death

Mortality Rate does not equate to:

Risk of Death

Risk of Developing Disease

Mortality Rate is about what happened.

To determine what COULD happen, we turn to Actuarial Science.

SOCIETY OF ACTUARIES®

Mortality Rate

$$\frac{Number\ of\ Deaths}{Population}$$

Beyond Leading

Causes of Death

Morbidity Rate

$$\frac{\textit{Number of Clinically Ill}}{\textit{Population}}$$

Changes in **morbidity** tell us if we reduce the number of people who **get** the disease.

Mortality Rate

$$\frac{\textit{Number of Deaths}}{\textit{Population}}$$

Changes in **mortality** tell us if we reduce the number of people who **die** from the disease.

Iceberg Principle of Disease Presentation

The majority of individuals within a community who have a given disease or disorder will present as asymptomatic, or exhibit pre/subclinical states.

Aware of Condition, but Not Seeking Treatment

Multiple potential causes including lack of symptom presentation, subclinical symptom burden, negative perceptions/stigma.

This can also result from insufficient care facilities to address needs, financial implications of treatment, social burdens.

Unaware of Condition

Either due to lack of insight, lack of symptom presentation, insufficient health burden.

Individuals may not be aware that they are experiencing disordered health/wellbeing.

Iceberg Principle of Disease Presentation

The majority of individuals within a community who have a given disease or disorder will present as asymptomatic, or exhibit pre/subclinical states.

The clinical appearance of a disease or disorder is not always associated with the severity of the condition or disease.

Masking behaviors can suppress symptomatology.

Disease/disorder may have uncommon presentation.

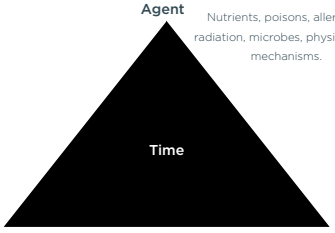
The clinical appearance of a disease or disorder is not always associated with the potential comorbid impacts.

The underlying biological processes can increase the risks associated with developing and suffering from other diseases/disorders

The fundamental assumption of epidemiological research is that:

Diseases do not distribute randomly in populations, but rather distribute when the right accumulation of risk factors or determinants (causes) exists.

Triad of Epidemiology



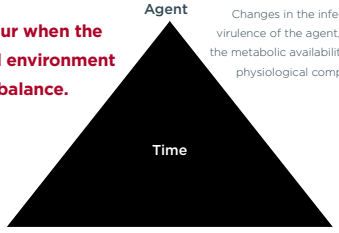
Agent: Nutrients, poisons, allergens, radiation, microbes, physiological mechanisms.

Host: Genetics, immunologic state, age, prior medical conditions, lifestyle behaviors would be considered as individual level risk factors that might alter sensitivity to the Agent.

Environment: Environmental risk factors are those that are non-specific to the individual and reflect the surroundings and conditions in which the agent and host exist.

Triad of Epidemiology

Epidemics occur when the agent, host, and environment are not in balance.



Agent: Changes in the infectivity or virulence of the agent, changes in the metabolic availability of relevant physiological components,

Host: Exposure to other diseases/disorders, changes in behavioral patterns.

Environment: Societal changes in transportation, social influences in behavioral patterns