Incidence

Incidence refers to the occurrence of new cases of a disease (outcome) in a population over a period of time. It involves following a group of people who are **at risk for developing the developing the disease** and recording the outcomes that occur. Unlike prevalence, which is measured at a point in time, incidence requires a period of follow-up.

For example, one goal of the Framingham Heart Study (FHS)) was to observe the incidence of Coronary Heart Disease (CHD) among all participants and among participants with certain risk factor characteristics (e.g. smokers, non-smokers, …). The teaching data set for this class contains 4,434 participants who attended the 1956 biennial examination. However, 194 of them were previously diagnosed with CHD, leaving 4,240 participants who are at risk for developing a first CHD event during the 24 years of follow-up. The following results were observed for these 4,240 subjects:

- 1406 died from any cause
- 88,389.45 person-years were observed before subjects died or the study ended

- 824 died from non-CHD causes (no longer at risk of developing CHD),
- 32 lost-to-follow-up and had not developed CHD at their last contact,
- 2338 completed 24 years of follow-up and did not develop CHD,
- 1046 developed CHD during the 24 years of follow-up (including 582 deaths)
- 80,925.16 person-years were observed before subjects were lost-follow-up, died, developed CHD, or the study ended

If you only published that 1406 participants died during this study and gave no other information, then a reader could draw no conclusion about whether this is a large number of deaths (reflecting a high risk population) or a small number (reflecting a low risk population). A reference point is needed and two are available to report:

1. The size of the population at risk (1406 deaths occurred in 4420 subjects during 24 years of follow-up)
2. The amount of follow-up time observed (1406 deaths occurred during 88,389.45 person-years of follow-up)

These findings reflect the two types of calculations used by epidemiologists to measure the incidence of an outcome in a population:

1. **Cumulative Incidence**
2. **Incidence Rate**

C**umulative Incidence** is defined as the proportion of people who develop a disease (outcome) during a fixed period of follow-up. As a proportion, the value for the Cumulative Incidence can range for as low as 0.0 (when there are no deaths) and 1.0 (when everyone dies). The period of follow-up must also be specified. 1406 death occurred during 24 years of follow-up. Far fewer deaths would be expected during only 1 year of follow-up, and 4420 deaths would be expected during 100 years of follow-up. From the data given above, the value for the **24-year Cumulative Incidence of Death is:**

(# Deaths)/(# At Risk) =1406/4420 = 0.33

The direct calculation of the Cumulative Incidence as shown above requires knowledge of the mortality outcomes for all of the 4420 subjects who were followed. For example, if a subject were lost-to-follow-up, then his/her mortality outcome would be unknown and you would not know whether or not to include that person in the numerator of the calculation for the Cumulative Incidence. Fortunately, we have complete follow-up for mortality in these data. The investigators determined mortality status for all subjects, even those who failed to attend scheduled exams, by monitoring reported deaths through a search of a national death index. They contacted previously specified relatives and friends of any subject who was lost-to-follow-up. However, the above calculation could not be preformed to measures the 24-year Cumulative Incidence of CHD as there were 32 subjects who were lost-to-follow-up and had unknown CHD status after becoming lost. In addition, there were 824 other subjects who died from non-CHD causes and we would have no way to know if these subjects would have developed CHD during the remaining part of the 24-year follow-up time had they not died. In such instances where the Cumulative Incidence cannot be calculated directly and alternative measure of incidence, the **Incidence Rate**, is typically calculated.

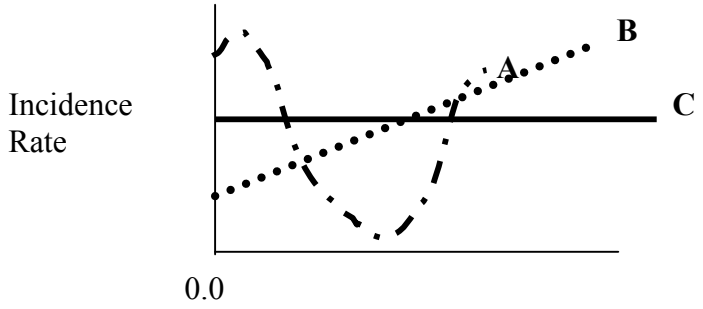
One limitation of the Cumulative Incidence is that is does not account for the timing of the outcomes during the follow-up period. The value for the Cumulative Incidence would be 0.33 if all 1406 deaths occurred at the very beginning of the follow-up period or at the very end of the follow-up period. On the other hand, the values for the Incidence Rate would differ under these two scenarios.

Finally, Cumulative Incidence is often labeled as the **Estimated Risk**, or the **Average Risk.** Risk refers to an individual's probability of developing an outcome. A risk for an individual is estimated by the Cumulative Incidence that is calculated for a group of people who are assumed to share the same common risk as the individual in question. As with the Cumulative Incidence, a risk requires a specification of a time period. My risk of dying in the next few moments is (hopefully) very small, but my risk of dying in the next 100 years is 100% (1.0).

An alternative measure of incidence is the **Incidence Rate** (also labeled as the **Instantaneous Risk**, **Hazard Rate**, or **Incidence Density**). It refers to the instantaneous risk of developing the outcome at a point in time during the follow-up period, among

those at risk at that time. The value for the Incidence Rate may be constant over the period of follow-up or may vary over time, showing periods of high and low values. This is depicted by the three Incidence Rate functions, IR(t), that are shown in the following figure:

Examples of Incidence Rate functions (IR(t)).



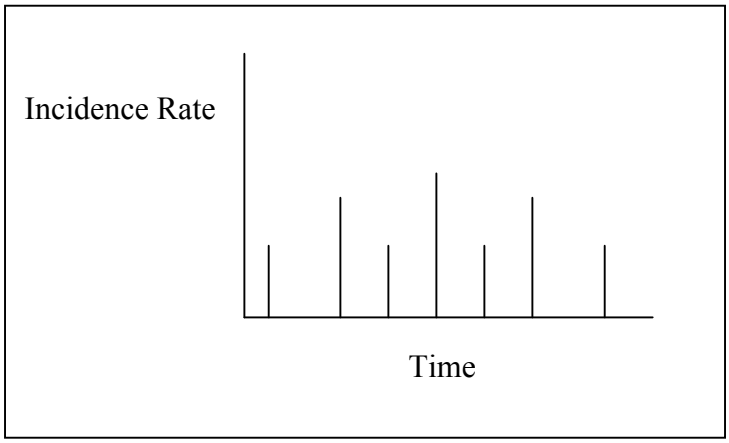
The Incidence Rate function depicted by the "roller-coaster" graph (A) may pertain to a study that records deaths among patients undergoing a major surgical procedure (e.g. coronary bypass surgery or transplant surgery). Patients may be at high risk of dying during and initially after the surgery, as depicted by the higher values for the Incidence Rate function. However, if patients survive this critical period, then they may go through a period of lower risk, as depicted by the lower values for the Incidence Rate function. Finally, as time elapses, these subjects will age and develop risk factors that may increase their risks of dying during subsequent periods, as depicted by the increasing values for the Incidence Rate function.

The Incidence Rate function depicted by the increasing line (B) might be expected from following subjects for a long period of time. As the follow-up time increase, the subjects at risk for developing an outcome at a point in time become older and are at higher risk for developing the outcome.

The Incidence Rate function depicted by the flat line (C) might be expected from a study with a short period of follow-up, where the risk of developing the outcome might not change over the period of follow-up.

As a measure of Instantaneous Risk, the value for the Incidence Rate could be estimated at each point in time during the follow-up by calculating the instantaneous Cumulative Incidence. However, because of the limited number of observed outcomes, values for the Cumulative Incidence would equal zero except for those times at which an outcome occurs. This would lead to a series of spikes to describe the Incidence Rate function as shown in the following figure. Spikes occur only at times when outcomes

occur and the height of each spike corresponds to the portion of outcomes that develop at that time among the subjects at risk. Although this accurately describes the data, the underlying Incidence Rate function is probably continuous in nature and better described by examining the outcome incidence during intervals of time.



The value for Incidence Rate function during an interval of time is estimated by the following formula

IR (# cases of disease during the interval)/(amount of person-time during the interval)

This expression is different from the formula for the Cumulative Interval in the denominator refers to the amount of person-time observed during the interval rather than the number of subjects at risk at the start of the interval. This accounts for the length of the interval. Suppose two investigators (A and B) wished to calculate the value for the Incidence Rate function at a time, t. Suppose that the Incidence Rate function was constant around that time. If investigator B's interval around t was half as wide as Investigator A, then she would expect two see roughly half as many outcome cases and half as much person-time during her interval as were seen by Investigator A. Hence their Incidence Rate calculations should provide similar values. However, this would not be true for calculations of Cumulative Incidence, which are dependent on the length of follow-up (length of the interval).

If the Incidence Rate function is constant during the follow-up period (Graph C in the above figure) then its value for any time, t, can be calculated by the following formula:

IR = (total number of cases of disease)/(total amount of person-time)

This assumption justifies treating 10 person-years of follow-up from following 10 subjects for 1 year as equivalent from following 1 person for 10 years. If the Incidence

Rate function varies over time (Graphs A and B in the above figure), then the value for the Incidence Rate from this formula is an average of the different values for the Incidence Rate function at different point in time. This is described by the data in the following table.

Year	Population A			Population B			Population C		
	# At Risk	# Deaths	Person-years	# At Risk	# Deaths	Person-years	# At Risk	# Deaths	Person-years
1	100	10	95	100	2	99	100	10	95.0
2	90	10	85	98	2	97	91	9	85.5
3	80	10	75	96	2	95	83	8	77.0
4	70	10	65	94	34	77	74	7	69.5
Total		40	320		40	368		34	327

Each population has 100 subjects at risk at the beginning of the study. 40 deaths occur in Population A and in Population B, leading to identical values for the 4-year Cumulative Incidence of Death

$$40/100 = 0.40$$

However, the Incidence Rate functions for Populations A and B differ markedly. If we assume that the deaths occurred at the midpoint of each year then the values for the Incidence Rate function (cases/1 person-year) for each year are shown in the following table

Year	Population A			Population B			Population C		
	# Deaths	Person-years	Incidence Rate	# Deaths	Person-years	Incidence Rate	# Deaths	Person-years	Incidence Rate
1	10	95	0.11	2	99	0.02	10	95.0	0.11
2	10	85	0.12	2	97	0.02	9	85.5	0.11
3	10	75	0.13	2	95	0.02	8	77.0	0.10
4	10	65	0.15	34	77	0.02	7	69.5	0.10
Total	40	320	0.13	40	368	0.44	34	327	0.10

The Incidence Rate function for Population A increases over time despite the constant number of deaths each year. The reason for the increase is the decreasing number of subjects who are at risk at the beginning of each year.

Although Populations A and B show a common value for the 4-year Cumulative Incidence of death, they show markedly different Incidence Rate functions. The Incidence Rate function for Population A increases slightly over time, where it is very low during the first three years for Population B and then increases dramatically during the fourth year of follow-up.

The Incidence Rate function for Population C is roughly constant of the four years of follow-up. The value for the constant Incidence Rate is

$$IR = 34/(327 \text{ person-years}) = 0.10(\text{cases/1 person year})$$

Similar calculations can be performed for Populations A and B but the resulting values ,(0.13cases/person-year) for Population A and (0.44cases/person-year) for Population B, are weighted averages for the different values for the Incidence Rate functions for these populations. The weights for these calculations are the amounts of person-time for each age-specific Incidence Rate. Mathematically, this is shown for Population B by the following equation:

40/368py = [99**(2/99py)** + 97**(2/97py)** + 95**(2/95py)** + 77**(34/7py)**]/ [(99+97+95+77)py]

It should be also noted that the dimension for an Incidence Rate is cases/person-time. This can be simplified to 1/time (by cancelling cases in the numerator with persons in the denominator). This implies that the value for the Incidence Rate depends on the chosen unit of time. For example:

1 case / 1 person year = 1 (cases/person year)

= 1 (cases/52 person-weeks) = 0.0192 (cases/person-week)

= 1 (cases/365 person-days) = 0.0027 (cases/person-day)

= 10 (cases/person-decade)

= 100 (cases/person-century)

This example underscores the meaningless for a reported Incidence Rate without the specification of the time period.

As expected, there is a mathematical relationship between the Cumulative Incidence for a period of time and the Incidence Rate function that exists during that period. For example, if the Incidence Rate is constant during a period of time and is equal to 1case/(100person-years), then 100 persons at risk at the beginning of that interval would approximately provide 100 person-years of observation and 1 case of the outcome if followed for 1 year. Hence the one-year Cumulative Incidence approximately would be 1/100 = 0.01. This is an approximation because the one subject who becomes a case would not provide a full year of follow-up (unless the case developed at the very end of the year) and the 100 subjects would provide slightly than 100 person-years of follow-up. In general, if the value for the Incidence Rate is small or the time period of follow-up is short, then the value for Cumulative Interval during this time period can be calculated from the following formula

$$CI \approx IR \times (\text{length of time period})$$

If the time period is not short or the Incidence Rate is not small this approximation does not hold. For example, the Incidence Rate for Population C is .10(deaths/person year). The previous formula would yield the following results when applied to different time periods

One-year CI = .10 x 1 = 0.1
Four-year CI = .10 x 4 = 0.4
Ten-year CI = .10 x 10 = 1.0
Twenty-year CI = .10 x 20 = 2.0

Although the One-year Cumulative Incidence listed above is similar to what would be calculated from the data in the above Table (10/100 = 0.10), the four-year cumulative incidence overstates what would be calculated from that data (34/100 =0.34). More importantly, the value for the 20-year Cumulative Incidence is mathematically not possible, since the value for a Cumulative Incidence cannot exceed 1.0. The overstated values listed in this calculation reflect a problem of not accounting for the diminishing size of the population at risk as subjects are followed over time. The following formula shows the general association between the Cumulative Incidence and the Incidence Rate when the latter is constant over time

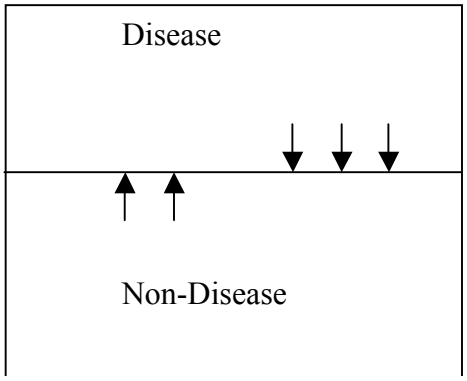
$$CI = 1 - e^{-IR \times (\text{time period})}$$

Using this general formula for Population C yields the following values for the Cumulative Incidence for the different time periods list above

One-year CI = $1 - e^{-.10 \times 1}$ = 0.10
Four-year CI = $1 - e^{-.10 \times 4}$ = 0.33
Ten-year CI = $1 - e^{-.10 \times 10}$ = 0.63
Twenty-year CI = $1 - e^{-.10 \times 20}$ = 0.86

The values for the one-year and four-year Cumulative Incidence (0.10 and 0.33, respectively) are very similar to those obtained from the data in the above Table (0.10 and 0.34, respectively).

There is also a mathematical relationship between the Prevalence of a disease and the Incidence Rate of that disease when we have a **steady state**. The steady state assumption implies that the Prevalence and the Incidence Rate of the disease are constant over a time period for a population of fixed size. This is depicted by the following figure:



If there are N people in the Population and P = the Prevalence of disease then at any time

diseased subjects = N(P)
non-disease subjects= N(1-P)

Suppose the disease in question is non-fatal and IR is the Incidence Rate that determines the number of new cases of disease that develop from the non-diseased group. To retain a steady state, this flow would need to be balanced by the number of cures of the disease that develop from the diseased group. If the D = average duration of disease, then the Cure Rate would equal 1/D. Thus for the steady state to remain, the following equation must hold

$$N(P)(1/D) = N(1-P)(IR)$$

This implies

$$P/(1-P) = IR \times D$$

It follows that is the Prevalence of disease (P) is small that

$$P \approx P/(1-P) = IR \times D$$

The important message from this calculation is not the mathematical relationship between Prevalence and Incidence in a steady state, but the general principal that Prevalence is function of Incidence and disease duration.