Basic terms:

**Prevalence** = Number of existing cases of disease at a point in time / Total population.

Notes:
- Numerator includes old and new cases
- Prevalence is cross-sectional and cannot be used to infer causation
- Useful in determining the burden of disease.

**Incidence** = Number of new cases in a fixed time period / Number of people at risk.

When asking 'Is this association a valid one?' Assess the effect of chance and bias:

**Chance** error results from random variation that occurs from sample to sample and can be assessed by the p-value.

**Bias or systemic error** is when an error is introduced due to the design or the conduct of a study. Several types of bias exist (see box below).

**Validity:** how closely the results of a measurement correspond to the actual value that was being measured. Failures of validity are mainly concerned with systematic errors, or bias.

**Reliability:** how reproducible the results are if you were to repeat the measurement. E.g., Intra-rater reliability = agreement between repeated results obtained by the same interviewer; Inter-rater reliability = agreement between results obtained by two or more different interviewers. Unreliability is mainly due to random, or chance variations.

The validity of a screening test can be assessed by looking at its sensitivity, specificity, positive predictive value and negative predictive value.

**Sensitivity:** the probability of having a positive test when the disease really is present; it is equal to the true positives divided by the sum of the true positives and the false negatives. A negative result on a highly sensitive test helps rule disease out (SNNOUT).

**Specificity:** the probability of having a negative test when the disease is not present; it is equal to the true negatives divided by the sum of the false positives and the true negatives. A positive test result on a highly specific test helps rule in the disease (SPPIN).
Positive predictive value: the probability of the person having the disease when the test is positive; is equal to the true positives divided by the sum of the true positives and the false positives. Decreases when disease is rare.

Negative predictive value: the probability of the person not having the disease when the test is negative; it is equal to the true negatives divided by the sum of the true negatives and false negatives.

Forms of Bias that can influence screening results:

lead-time bias = the apparent lengthening of survival due to earlier diagnosis in the course of disease without any actual prolongation of life

length-time bias = the tendency of screening to detect a larger number of cases of slowly progressing disease, but miss aggressive disease due to its rapid progression.
1. Observational Designs

**Case reports:** description of an individual patient; often intriguing but not necessarily representative

**Case-series:** descriptive/observational study of a series of cases.

**Cross-sectional surveys** (aka prevalence studies): a snapshot of health data, such as exposure and disease, assessed simultaneously in a population. Often uses a representative sample and can suggest links between risk factors and disease.

**Case-control study:** a type of observational study designed to identify (but not prove) risk factors or causal influences. People are selected according to whether they have a particular disease (cases) or do not have the disease (controls). The groups are then compared with respect to the presence or absence of the exposure now, or in the past. Indicator of risk is the odds ratio (OR).

**Cohort study:** a type of prospective observational study in which people are selected according to the presence or absence of exposure (e.g., putative causal factors) and followed over a period of time to investigate outcomes. Indicator of risk is based on incidence of disease among exposed and unexposed people. Calculate the relative risk (RR).

2. Experimental Designs

**Randomized Controlled Trial (RCT):** a study in which people are randomly assigned to different exposures or interventions and the outcome of each group is measured and compared.

<table>
<thead>
<tr>
<th>Design</th>
<th>Case reports/Case series</th>
<th>Surveys</th>
<th>Case-Control*</th>
<th>Cohort*</th>
<th>RCT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Formulation of hypotheses</td>
<td>Prevalence of disease; associations of risk factors with health outcomes</td>
<td>Identifying risk factors in rare diseases or diseases with long latency periods; evaluation of multiple exposures</td>
<td>Provides estimates of incidence, relative &amp; attributable risk good for evaluating multiple effects of one exposure</td>
<td>Strongest evidence for the effect of a treatment without the effect of confounders (randomness of exposure)</td>
</tr>
<tr>
<td>-</td>
<td>Results usually come from one patient or from one center</td>
<td>Causality cannot be inferred</td>
<td>Recall bias due to exposures in the past</td>
<td>Selection Bias due to losses to follow-up</td>
<td>Lack of generalizability, need to assess compliance, the effect of small samples and losses to follow-up</td>
</tr>
</tbody>
</table>

*Causality criteria:* These are the elements that suggest a causal relationship between a factor and the onset of disease; they include Temporal sequence, Biologic plausibility, Strength, Consistency, Dose-response, Reversibility (TeBSConDoR)
Issues in interpreting study results:

External validity or generalizability: can the results from this study be applied to other groups not part of the study? Mainly reflects quality of sampling.

Internal validity refers to how well the study was undertaken: were there biases, losses to follow-up, etc? A study that is not generalizable does not necessarily mean that it is not internally valid.

Confounding occurs when another factor, the confounder, produces an apparent association between an exposure and a disease. E.g., in assessing the association between coffee drinking and myocardial infarction, smoking may be a confounder, if the coffee drinkers also smoke. Confounding variables can be handled either by using randomized or stratified study designs, or by measuring the confounder and analyzing its effect using regression.

Efficacy: a measure of the benefit resulting from an intervention for a given health problem under ideal conditions (e.g., all patients took all of the medication prescribed) vs. Effectiveness: a measure of the benefit resulting from an intervention for a given health problem under usual conditions of clinical care for a particular group. In an RCT, ‘intention to treat’ analyses include patients who did not adhere to the treatment as though they did, making this a study of effectiveness.

Clinical versus statistical significance: A result is classified as statistically significant if it is unlikely to be due to chance alone (i.e. the p value obtained upon statistical analysis is less than the critical alpha value, usually 0.05). An outcome is clinically significant if it is meaningful in the clinical setting (i.e. the difference would lead you to change your management). Note: statistical significance increases with sample size, so results can be statistically significant without being clinically significant.

Number needed to treat (NNT): A measure of clinical significance. The NNT is number of patients who need to be treated in order to prevent one adverse outcome.
**Normal distribution**: characterized by a bell-shaped and symmetrical curve, with scores more concentrated in the middle than in the ends. It is described by the mean and the standard deviation.

**Mean**: a measure of central tendency for continuous variables. It is the sum of the scores divided by the number of cases.

**Median**: a measure of central tendency for a continuous variable, but used when the distribution is not normal. It is the score above and below which 50% of the observations fall.

**Mode**: a measure of central tendency for a discrete variable (e.g., eye color). It is the most frequent score in the population (e.g., brown eyes are most common).

**Variance**: a measure of the dispersion among the scores in a given population. First calculate the mean of the scores, then measure the amount that each score deviates from the mean and square each deviation (by multiplying it by itself). Add these squared deviations. The variance equals the average of the squared deviations from the mean.

**Standard deviation**: the square root of the variance. Used to characterize the dispersion among the scores in a given population.

**Standard error**: it is the standard deviation divided by the square root of the number of data values. This gives a measure of the variability of the mean (e.g., if the study were to be repeated).

**Hypothesis testing**: statistical tests used for answering the question ‘Is the mean/median/proportion of this group statistically different (i.e., more than expected by chance) from the value of another group?’

<table>
<thead>
<tr>
<th>For continuous measures</th>
<th>For discrete proportions</th>
<th>For medians</th>
<th>Non-parametric methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>z-test and t-test</td>
<td>ANOVA</td>
<td>Chi-square</td>
<td>Non-parametric</td>
</tr>
<tr>
<td>Statistical tests used to determine whether a mean differs from the theoretical value or from another mean. Z-test for n&gt;30 and t-test for n&lt;30</td>
<td>Statistical test to determine if there are significant differences between variances of multiple samples</td>
<td>Statistical test to determine whether an observed association between 2 categorical variables differs from the theoretical value or from each other</td>
<td>Used when data do not follow a normal distribution. Examples: Wilcoxon Rank test, Mann-Whitney U Test</td>
</tr>
</tbody>
</table>
Other statistics often mentioned in clinical studies:

**Correlation**: a statistical measure of the association between two variables (“if you know one, how accurately could you predict the other?”). Pearson’s correlation is designated as r, and ranges from -1 to 1 with r = 0 being defined as no correlation. Note that correlation does not necessarily imply causation.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Disease</th>
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<tbody>
<tr>
<td>+</td>
<td>a</td>
</tr>
<tr>
<td>-</td>
<td>c</td>
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</table>

**Odds Ratio**: the odds of having been exposed if you have the disease versus if you do not, often derived from a case-control study; OR= ad/bc

**Relative Risk**: the probability of developing the disease if you are exposed versus if you are not; RR= (a/(a+b)) / (c/(c+d)). A RR of 1.0 indicates no effect, RR=2.0 indicates double the risk; RR=0.5 half the risk. RR can be calculated from a cohort study.

**Regression Analysis**: used to estimate the influence of one or more independent variables on a dependent variable and allows us to control for confounders. Types of regression used are based on the type of data and include: logistic regression for a discrete dependent variable, linear regression for a continuous dependent variable, Poisson regression for certain types of count data, or survival analysis for a continuous dependent variable that records the time to an event.

CheatSheets™ Seminars on Manuscripts Revolutionizing Therapies (SMRT) Club and Elective, Faculty of Medicine, University of Ottawa, 2005, 1st edition

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Acknowledgements: Thanks to the many volunteers of the SMRT elective who made this creation possible!