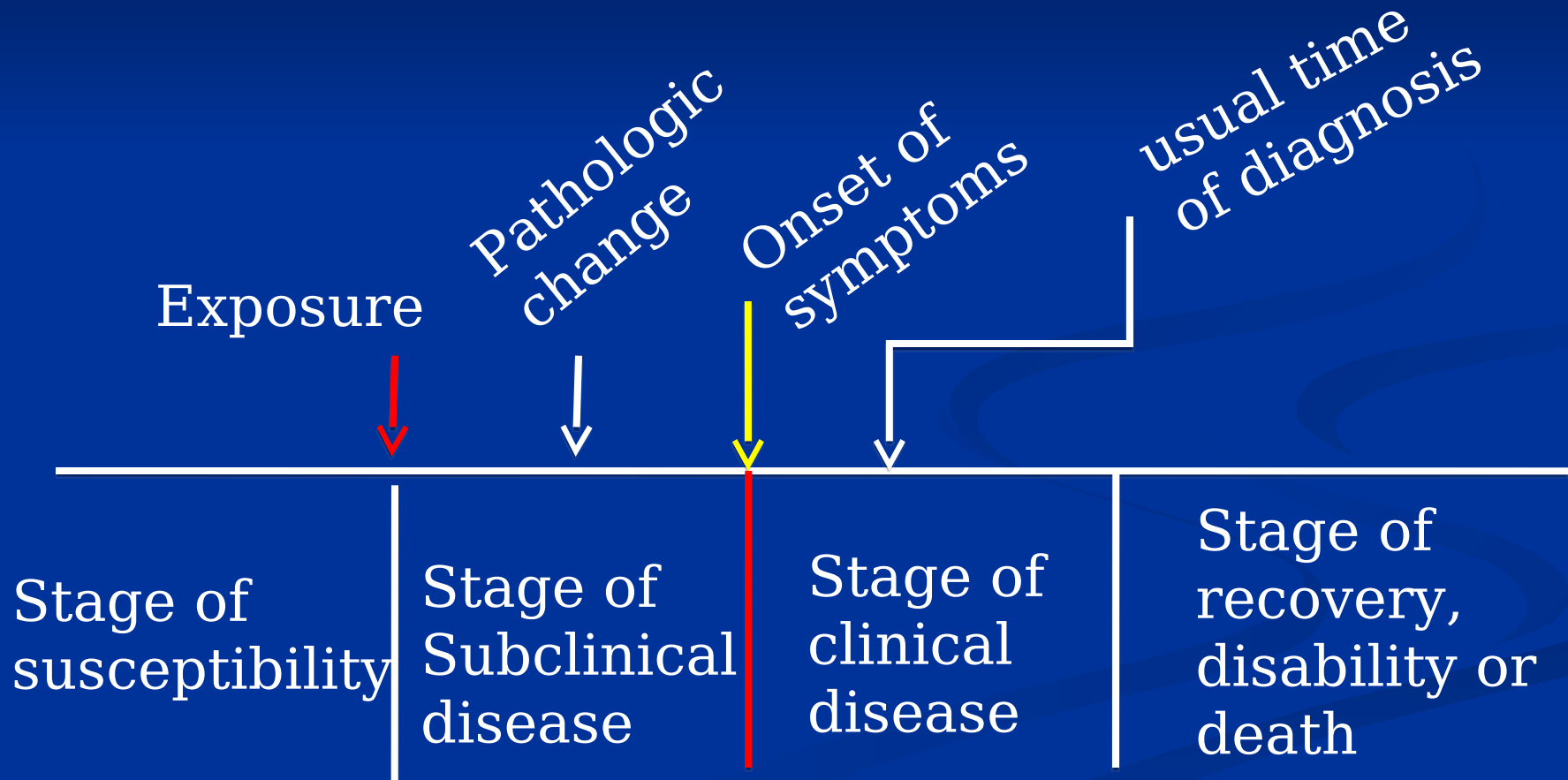


Diagnostic and Screening tests

Brain storming questions

- What does mean screening?
- Screening : Why ?When? How?
- Describe implementation approach of screening
- What are measures for a screening test?
- What are the potential source of bias in Screening?

Natural course: stages of progression



Definitions:

- **Diagnostic** tests: tests performed in persons with a symptom or a sign of an illness
- **Screening** test: tests that are done in individuals with no such symptoms or sign
 - the presumptive identification of **unrecognized** disease by application of **rapid tests** or examinations,
 - ‘The examination of **asymptomatic** people in order to **classify** them as **likely or unlikely** to have the disease of interest.’

Aims of screening

- To **alter** the natural course of disease for a better outcome for individuals affected.
- To reduce morbidity & mortality through early detection & treatment (prevention)
- Protect the society from contagious d/s by early detection & management
- Reduce economic cost from managing overt disease and epidemics

Implementation approach of screening

- **Selective screening**—Tests are used to detect a specific disease, or predisposing condition, in people who are **known to be at high risk of having, or of developing**, the condition.
 - ✓ Single disease screening, e.g. chest X-rays for pneumoconiosis
 - ✓ Multiphasic screening, e.g. antenatal examinations
- **Mass screening**—Large numbers of people are tested for the presence of disease or a predisposing condition **without specific reference** to their individual risk of having or developing the condition.
 - ✓ Single disease screening, e.g. cervical screening
 - ✓ Multiphasic screening, e.g. biochemical profiles on hospital patients

Conti....

■ Opportunistic screening

- Some screening only occurs when the opportunity arises, for example blood pressure screening for hypertension in **general practice**, or cervical smears on women using an oral contraceptive. This is of use because up to 90% of people will see their general practitioner over a 2-year period, so that it is a cost-effective way of reaching a large proportion of the population.

Rationale of planning screening tests

Judgment requires about few critical issues like,

- What kind of illness to be checked?
- What kind of person to be tested?
- How is the costs of
 - Illness (monetary and physical)
 - Costs of the tests.
- What level of test accuracy is required etc

Criteria for instituting a screening program

1. Disease	■ High magnitude i.e. prevalence ■ Serious (disability & fatality); ■ Known natural history (i.e. recognizable & long preclinical (asymptomatic) stage & time b/t Dx to overt disease
2. Test	■ Sensitive and specific ■ Simple and cheap ■ Safe and acceptable ■ Reliable
3. Diagnosis &	■ Facilities are adequate ■ Effective, acceptable and safe Rx/ rehabilitative methods available

Definitions of summary measures for a screening test

1. **Sensitivity(Se):** proportion of true positives that are correctly identified by a screening test
2. **Specificity(Sp):** proportion of true negatives that are correctly identified by a screening test
3. **Positive predictive value (PV+):** is the probability of the presence of the disease in a person with a positive (abnormal) test result
4. **Negative predictive value (PV-):** is the probability of not having the disease

VALIDITY OF A screening TEST

- A central issue in evaluating a test is its validity, or the ability to **differentiate accurately** between those who have the disease and those who do not have.
 - The validity of the test refers to the extent to which the test is capable of correctly diagnosing the presence or absence of the disease concerned.
- These two aspects,
 - 1) **Sensitivity:**
 - 2) **Specificity**

Validity can be illustrated by 2 x 2 table

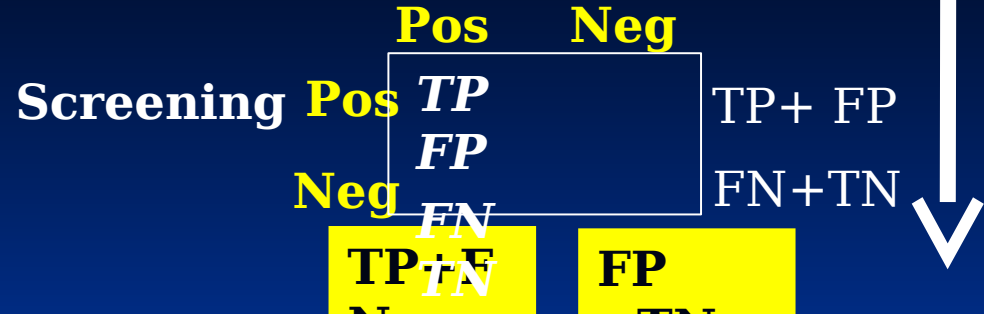
		True disease (golden standard test)		Total
		Positive	Negative	
Screening or diagnostic test	Positive	a (True positive)	b (False Positive)	a + b
	Negative	c (False negative)	d (True negative)	c + d
Total		a + c	b + d	a + b + c + d

What can be calculated to check the accuracy of a screening test against Gold standard”

- 1. SENSITIVITY** of the screening test (validity)
- 2. SPECIFICITY** of the screening test (validity)
- 3. POSITIVE PREDICTIVE VALUE** of the screening test (Yield)
- 4. NEGATIVE PREDICTIVE VALUE** of the screening test

Confirmatory test Gold standard

<i>a</i>	
<i>b</i>	
<i>c</i>	
<i>d</i>	



$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}}$$

$$\text{Sensitivity} = \frac{a}{a + c}$$

Probability of a positive test in people with the disease

$$\text{Specificity} = \frac{d}{b + d}$$

Probability of a negative test in people without the disease

Prevalence = TP + FN

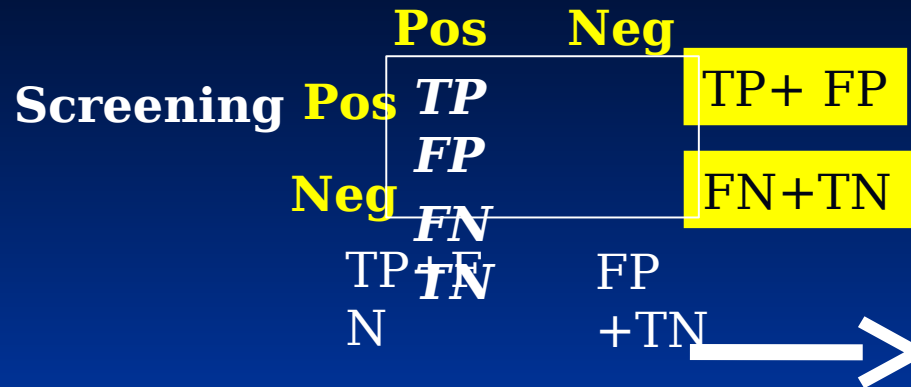
Study population = TP + FN
+ FP + TN

		Confirmatory test Gold standard		
		Pos	Neg	
Screening	Pos	a	b	a + b
	Neg	c	d	c + d
		a + c	b + d	

Sensitivity = $\frac{\text{Persons with the disease who are positive by the test}}{\text{Total number of persons with the disease}} \times 100$

Specificity = $\frac{\text{Persons without the disease who are negative by the test}}{\text{Total number of persons without the disease}} \times 100$

Confirmatory test Gold standard



$$PVP = \frac{TP}{TP + FP}$$

$$PVN = \frac{TN}{TN + FN}$$

$$\text{Prevalence} = \frac{TP + FN}{TP + FN + FP + TN}$$

$$\text{Prevalence} = \frac{TP + FN}{TP + FN + FP + TN}$$

Positive Predictive value of test = $\frac{a}{a + b}$.

Probability of a person having the disease when the test is positive

Negative Predictive value of test = $\frac{d}{c + d}$.

Probability of a person not having the disease when the test is negative

- **Relationship between sensitivity, specificity, prevalence and predictive values are as follows:**

PV(+) = $\frac{P \times Sn}{(P \times Sn) + ((1 - P) \times (1 - Sp))}$.

PV (-) = $\frac{(1 - P) \times Sp}{((1 - P) \times Sp) + (P \times (1 - Sn))}$.

Where P is the prevalence of disease
 Sn is the sensitivity and Sp the specificity

These equations can be used to calculate predictive values for different combinations of test sensitivity, specificity and disease prevalence.

**True disease
(golden standard test)**

		Positive	Negative	Total
Screening or diagnostic test	Positive	380	20	400
	Negative	320	1280	1600
	Total	700	1300	2000

Sensitivity

Specificity

PPV

NPPV

$$= \frac{380/700}{380/400}$$

$$= \frac{1280/1300}{1280/1600}$$

=

$$= 54.3\% \\ = 80 \%$$

$$= 98 \%$$

$$= 95 \%$$

Example

- **Considering a diagnostic test has a sensitivity of 95 % and specificity of 80 % and calculate the Positive and negative predicative value when the prevalence of the disease is:**
 - 1) 20 %?
 - 2) 1%?

1a. Prevalence 20 %

$$PV(+) = \frac{P \times Sn}{(P \times Sn) + ((1 - P) \times (1 - Sp))}$$

$$= \frac{0.2 \times 0.95}{(0.2 \times 0.95) + ((1 - 0.2) \times (1 - 0.8))}$$

$$= 0.54 \text{ or } 54 \%$$

- This means that of all the positives found by the screening test only 54 % are true positives.

1b. Prevalence 20 %

$$\begin{aligned}\frac{PV(-)}{Sp} &= \frac{(1 - P) \times Sp}{((1 - P) \times Sp) + (P \times (1 - Sn))} \\ &= \frac{(1 - 0.2) \times 0.80}{((1 - 0.2) \times 0.80) + (0.2 \times (1 - 0.95))} \\ &= 0.98 \quad \text{or} \quad 98 \%\end{aligned}$$

- This means that of all the negatives found by the screening test 98 % are true negatives.

2a. Prevalence 1 %

$$PV(+) = \frac{P \times Sn}{(P \times Sn) + ((1 - P) \times (1 - Sp))}$$

$$= \frac{0.01 \times 0.95}{(0.01 \times 0.95) + ((1 - 0.01) \times (1 - 0.8))}$$

$$= 0.045 \quad \text{or} \quad 4.5 \%$$

This means that of all the positives found by the screening test only 4.5 % are true positives.

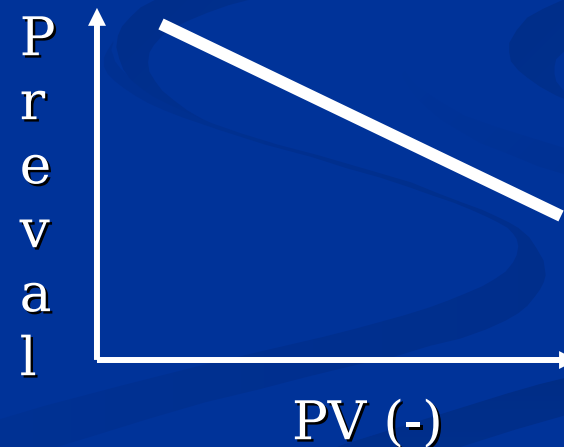
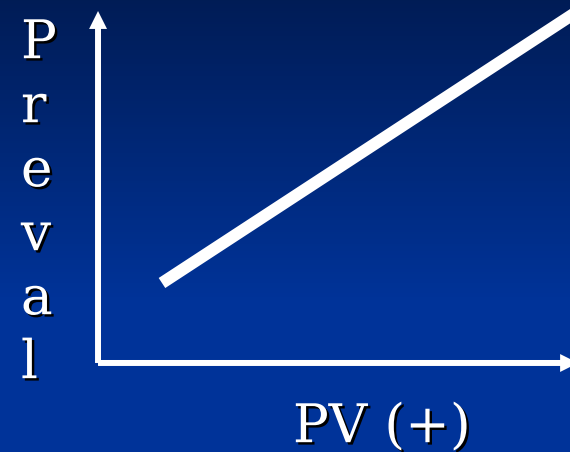
2b. Prevalence 1 %

$$\begin{aligned} \text{PV}(-) &= \frac{(1 - P) \times \text{Sp}}{((1 - P) \times \text{Sp}) + (P \times (1 - \text{Sn}))} \\ &= \frac{(1 - 0.01) \times 0.80}{((1 - 0.01) \times 0.80) + (0.01 \times (1 - 0.95))} \\ &= 0.999 \quad \text{or} \quad 99.9 \% \end{aligned}$$

This means that of all the negatives found by the screening test almost all are true negatives.

Relationship between Prevalence and predictive values

- PPV (when the sensitivity & specificity is constant) is directly related to the prevalence of a disease in a community.
- NPV (when the sensitivity & specificity is constant) is inversely related to the prevalence of a disease in a community.



Potential Source of Bias in Screening

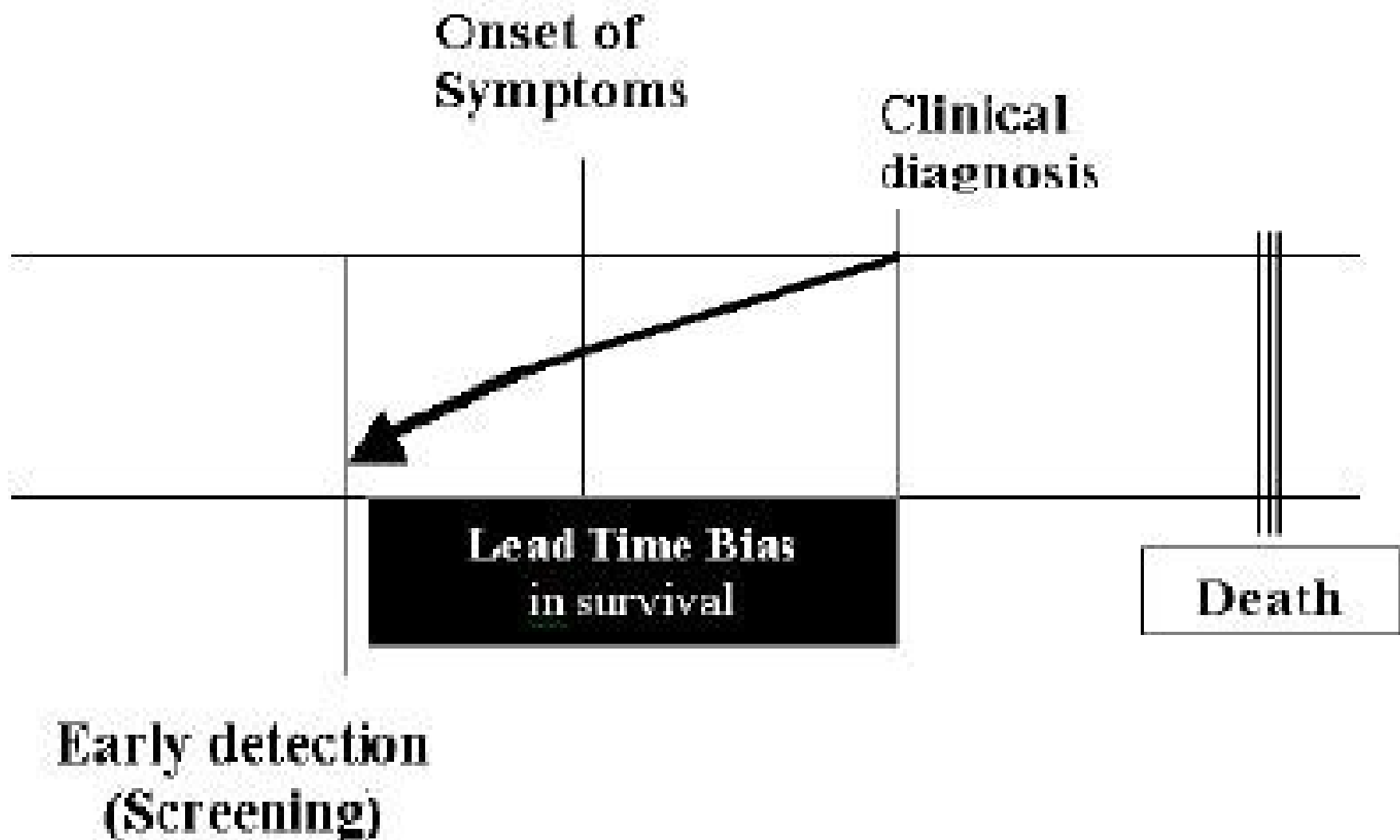
- Self-selection (volunteer) bias
- Lead time bias (early diagnosis)
- Length Bias (chronicity and progression)

Self-selection (volunteer) bias

- **Volunteers:** better health, lower mortality rates, more likely to adhere to prescribed medical regimens
- Therefore, observational study comparing the screened group with the general (unscreened) population, may lead to **lower mortality rates** among screened irrespective any effect of screening or
- The worried one with greater risk as a result of medical or family history. These group will have **greater mortality rate** irrespective of screening
- Therefore ,the direction of this bias is unpredictable.

Lead-Time bias

- The interval between the diagnosis of a disease **at screening** and when it would have been detected due to development of **symptoms**
- It is simply the amount of time by which the diagnosis has been advanced as a result of screening
- Interval screening is more likely to identify **slowly progressive cases** whose prognosis is significantly better than individuals with **aggressive disease**.
- Consequently, **cases identified by screening will appear to have a better prognosis than those who have been identified following the appearance of symptoms.**
- In such circumstances, the overall mortality in the population may be unaltered because the **screening programme has missed many of the people with aggressive disease.**



- **Example:** Take two women, A and B, whose biological onset of breast ca was at age 35 years
- Woman A: screen at age **41** and detected as having breast Ca, died at age **46** (Survived 5 years)
- Woman B: was not screened, diagnosed with breast ca at age **43** and died at age **46**
- Conclusion???
- Lead time bias could be controlled by taking age specific mortality rates or if the lead time of a disease could be estimated, this could be taken into account

Length bias

- Over representation among screen-detected cases of those with a **long preclinical phase of disease** and thus a **more favorable prognosis**
- Diseases tend to be heterogeneous with respect to their natural history; **prevalence depends on duration**
- Those with **long preclinical phase** are readily detectable on screening compared to those with **short preclinical phase** Length bias may lead to an erroneous conclusion that **screening was beneficial** when, in fact, observed differences in **mortality** were a result merely of less rapidly fatal cases through screening
- Difficult to quantify

Onset of Symptoms

