Medical Screening

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Objectives of this presentation

After reading this presentation the student will:

- have an understanding of the concept of screening and the rationale for its use in prevention and early detection of disease.

- be aware of the importance of screening in sexual and reproductive health.

- be able to define and calculate sensitivity, specificity and positive and negative predictive values, and understand their implications.

- understand the criteria for implementing a screening programme.

- have considered how these criteria apply to the implementation of specific screening programmes in sexual and reproductive health.

Course outline

- Pre-course warm-up: some examples of screening in sexual and reproductive health

- Definition(s) of screening

- Essential concepts
  - False positives and false negatives
  - Sensitivity and specificity (test characteristics)
  - Positive predictive value, negative predictive value

- Criteria for implementation of screening programmes

- Case histories

  - Toxoplasmosis in pregnant women

  - HIV testing

Pre-course warm-up

• What does screening mean to you? (is it different to diagnosis? In what way?)

• What screening programmes have you come across (as a professional or as a patient)?

• Think about screening programmes related to sexual and reproductive health in your country:
   • For men
   • For women (and for pregnant women)
   • Fœtal and newborn screening

• Why do you think these programmes exist?

• Why is there screening for certain conditions in some countries and not others?

Write down all the screening programmes that come to mind

Some examples of screening in sexual and reproductive health

MEN

- *Prostate cancer*
- *HIV and other STIs*
- *Genetic screening*

**WOMEN
during pregnancy**

- *Gestational diabetes*
- *Toxoplasmosis and other infections*
- *Group B Streptococcus*
- *Genetic screening*

ANTE-NATAL (foetal)

- *First trimester screening (nuchal translucency/hCG/PAPP-A)*
- *Second trimester screening (AFP)*

WOMEN

- *Breast cancer*
- *HPV/cervical cancer*
- *HIV and other STIs*

NEWBORN

- *Physical examination (including hip dysplasia)*
- *Blood-spot (heel-prick) test*
- *Hearing*

Chose one of these screening programmes and keep it in mind when reading the next slide

- As we have seen, there are many screening tools used in sexual and reproductive health.
- Of the 11 screening programmes listed by the NHS (England and Wales), all but 3 are related to sexual and reproductive health:

  - abdominal aortic aneurysm programme
  - bowel cancer screening programme
  - breast screening programme
  - cervical screening programme
  - diabetic eye screening programme
  - fetal anomaly screening programme
  - infectious diseases in pregnancy screening programme
  - newborn and infant physical examination screening programme
  - newborn blood spot screening programme
  - newborn hearing screening programme
  - sickle cell and thalassaemia screening programme

So, what is screening?

According to the *Journal of Medical Screening* "there is no universally accepted definition of medical screening, but there is general agreement that the activity contains three elements"*

- Screening is a process of *selection* to identify individuals at *high risk* of a specific condition, often preceding a *diagnostic test* or *preventive action.*
- Screening is offered *systematically* to a population who have not sought medical attention and are *asymptomatic*. It is generally *initiated by medical authorities* not by the patient.
- The purpose of screening is to benefit the *individuals being screened* (in contrast for example to prevalence surveys for the purposes of research or surveillance).

These elements are encapsulated in the following statement:

> Screening is the *systematic* application of a test or inquiry, to identify individuals at sufficient *risk* of a specific disorder to *benefit* from further investigation or direct preventive action, among persons who have *not sought medical attention on account of symptoms* of that disorder.

* These elements are summarized here: for full text see http://msc.sagepub.com/content/15/1/50.full

Definition II

The National Health Service (England)* offers a simpler definition:

- Screening is the process of identifying people who appear healthy but may be at increased risk of a disease or condition.

- The screening provider then offers information, further tests and treatment. This is to reduce associated risks or complications.

This image* illustrates the concept nicely, representing the screening test as a sieve. We will come back to the analogy of sieves later in the presentation.
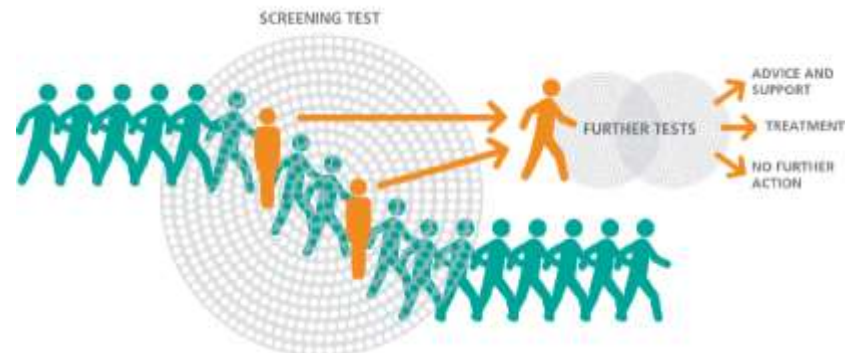
Let's consider a screening for HIV infection among pregnant women in the light of the first definition:

> Screening is the systematic application of a test or inquiry, to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action, among persons who have not sought medical attention on account of symptoms of that disorder.

- In most settings pregnant women are systematically tested for HIV infection.

- By testing for HIV we can identify those women who are (a) at risk of developing AIDS and whose babies risk contracting HIV through mother-to-child transmission.

- Both the infected woman and her unborn child can benefit from treatment. Depending on the setting, the mother will also be given advice about exclusive breastfeeding to reduce the chance of other infections and of HIV transmission.

- The woman has presented because she is pregnant – she does not have symptoms of HIV, but was screened as part of routine ante-natal care.

To understand the rationale for implementing screening programmes, we need to define some terms used for all tests (screening and diagnostic)

- **Imagine we have a population of 100 000 individuals**

- **20 000 of these individuals have a particular disease. The <u>prevalence</u> is the number of people with the disease divided by the population:** 20 000 **per 100 000)**

- **We have a diagnostic test which is pretty good but not perfect (no test is).**
  - **Our test will give a positive result for most (but not all) individuals who have the disease**
    - **Individuals with the disease but with negative results are the <u>false negatives</u> –** c **in the table below (2 thousand individuals in our example)**
  - **Our test will give a negative result for most (but not all) healthy individuals**
    - **The healthy individuals with positive results are the <u>false positives</u> –** b **in the table below (5 thousand individuals in our example)**
  - **The <u>true positives</u>, a, and the <u>true negatives</u>, d, make up the rest of our population so**
    - **a + c = 20 000 diseased individuals**
    So a = 20 − 2 = 18 thousand
    - **b + d = 80 000 healthy individuals**
    So d = 80 − 5 =75 thousand

thousands of individuals	WITH Disease	HEALTHY	
Positive	a = 18	b = 5	a + b = 23
Negative	c = 2	d = 75	c + d = 77
	a + c = 20	d + b = 80	100

For all tests we can define the sensitivity and specificity

Here's our table again:

thousands of individuals	WITH Disease	HEALTHY	
Positive	a = 18	b = 5	a + b = 23
Negative	c = 2	d = 75	c + d = 77
	a + c = 20	d + b = 80	Total = 100

Sensitivity describes how good the test is at finding diseased individuals, defined as follows:

- **The number of diseased individuals who test positive as a percentage of all diseased individuals**

Sensitivity = a / (a + c) x 100.

In our case 18/20 x 100 = 90 %

Specificity describes how good the test is at excluding disease in healthy individuals, defined as follows.

- **The number of healthy individuals who test negative as a percentage of all healthy individuals**

Specificity = d / (d + b) x 100.

In our case 75/80 x 100 = 93.75 %

For a given test in a given population we can define the positive predictive value (PPV) and the negative predictive value (NPV)

Here's our table again:

thousands of individuals	WITH Disease	HEALTHY	
Positive	a = 18	b = 5	a + b = 23
Negative	c = 2	d = 75	c + d = 77
	a + c = 20	d + b = 80	Total = 100

PPV describes how likely it is that an individual who tested positive is actually diseased:

- The number of individuals who test positive and who are diseased as a percentage of all individuals who tested positive

  PPV = a / (a + b) x 100.

  In our case 18/23 x 100 = 78.26 %

NPV describes how likely it is that an individual who tested negative is actually healthy:

- The number of individuals who test negative and who are healty as a percentage of all individuals who tested negative

NPV = d / (d + c) x 100.

In our case 75/77 x 100 = 97.40 %

Now look what happens if we take the same test and apply it in a population with a much lower prevalence. We'll call it population B.

Here's the new table for population B, where the prevalence is 5 000 per 100 000 population:

thousands of individuals	Diseased	HEALTHY	
Positive	a	b	a + b
Negative	c	d	c + d
	a + c = 5	b + d = 95	Total = 100

We calculated the <u>sensitivity</u> of the test two slides back (90%).

So a / (a + c) x 100 = 90

and a + c = 5 (thousands of diseased individuals)

So, a = 0.9 x 5 = 4.5

We calculated the <u>specificity</u> of the test two slides back (93.75%).

So d / (b + d) x 100 = 93.75

and b + d = 95 (thousands of healthy individuals)

So, d = 0.9375 x 95 = 89.0625

Now we can complete our table and calculate the *positive* and *negative* predictive values.

Here's our new table :
- We can fill in a and d from the previous slide
- We can then calculate b and c as shown in the table

thousands of individuals	Diseased	HEALTHY	
Positive	a = 4.5	95 − 89.0625 b = 5.9375	*4.5 + 5.9375* *= 10.4375*
Negative	5 - 4.5 c = 0.5	d = 89.0625	*0.5 + 89.0625* *= 89.5625*
	a + c = 5	b + d = 95	total = 100

Now the *positive predictive value is*

  PPV = a / (a + b) x 100

    = 4.5 / 10.4375 x 100

    = 43.11%

And the *negative predictive value* is

  NPV = d / (d + c) x 100

    = 89.0625 / 89.5625 x 100

    = 99.44%

Let's put these two populations side by side

thousands of individuals	WITH Disease	HEALTHY	
Positive	a = 18	b = 5	a + b = 23
Negative	c = 2	d = 75	c + d = 77
	a + c = 20	d + b = 80	Total = 100

thousands of individuals	WITH Disease	HEALTHY	
Positive	a = 4.5	b = 5.9375	a + b = **10.4375**
Negative	c = 0.5	d = 89.0625	c + d = **89.5625**
	a + c = 5	d + b = 95	Total = 100

Population A

prevalence 20 000 per 100 000

- Sensitivity = 90 %
- Specificity = 93.75 %
- PPV = 78.26 %
- NPV = 97.40 %

Population B

prevalence 5 000 per 100 000

- Sensitivity = 90 %
- Specificity = 93.75 %
- PPV = 10.4 %
- NPV = 99.44%

Sensitivity and specificity are characteristics of the test, not the population, so they don't change

In this population, of individuals with a positive test only 1 in 10 has the disease. The rest are *false positives*.

What does it all mean? Why does it matter?

- Imagine a disease which is rare (as in our example B above).

- Imagine the disease has a measurable but minor effect on those who suffer from it.

- Imagine the treatment is effective, but has unpleasant side-effects.

- Would you treat all of the individuals who tested positive, knowing that only 1 in 10 was truly diseased and the other 9 are false positives?

The acceptability of a test depends not only on the characteristics of the test but also on the characteristics of the population.

How can the PPV be improved?

The positive predictive value of a test can be improved by choosing a sub-population with a higher prevalence of the condition in question, for example

- Testing for HIV infection among TB patients or sex-workers

- Testing for diabetes among individuals over a certain BMI.

You could equally think of this approach as using to screens – the first (for example measuring BMI) having poor specificity (many people with high BMI are not diabetic) but being non-invasive and relatively inexpensive to administer.

Criteria for implementation of screening programmes ▯ warm-up

- Think about a disease or condition which you know well
  - How important is it to detect cases early?
  - If a patient has a positive result in the screening test, what is the next step?
  - What are the implications of not treating someone with the condition?
  - What are the consequences of treating someone who does not have the condition?
- In what situations would it be important to have a high <u>positive predictive value</u> (i.e. a low proportion of false positives)?
- In what situations would it be important to have a sensitive test?

Write down a list of factors which would influence the decision to use a particular test to screen a particular population (then look at the next slide to see if we agree).

Using the questions on the previous slide to guide you, write down a list of factors which would influence the decision to use a particular test to screen a particular population (then look at the next slide to see if we agree). It might help to think about a screening programme which you know well.

Factors influencing the decision to implement a screening programme

Disease characteristics

- the morbidity and mortality caused by the disease

Population characteristics

- the prevalence of disease (which, together with the test characteristics, will influence the positive predictive value)

Test characteristics:

- The cost of the test (and of administering it)
- Its acceptability to individuals tested (e.g. giving a saliva sample vs. a sample of spinal fluid or a biopsy)
- Its sensitivity and specificity

Treatment characteristics

- Cost
- Effectiveness
- Side-effects

Nature of possible preventive measures

These concepts are very clearly discussed on the following website: www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme

Case History – toxoplasmosis in pregnant women

In Switzerland until late 2008 it was common practice for pregnant women to be screened for toxoplasmosis immunity. Those who were found to be non-immune were then re-tested regularly. When recent infection was suggested by seroconversion the mother would be treated and amniocentesis would be performed. If fœtal infection was diagnosed, treatment or termination of the pregnancy were considered. Non-immune women were also advised to avoid contact with cats and their feces, and with soil, and not to eat under-cooked meat.

Toxoplasmosis in pregnant women, continued

In 2008 the Swiss Public Health Office recommended that screening for toxoplasmosis stop, for the following reasons

- The prevalence of toxoplasmosis in Switzerland had decreased, making new infections unlikely during pregnancy.

- The likelihood of congenital infection is lower than had previously been estimated.

- The efficacy of antibiotic treatment is limited.

- The practices recommended to prevent infection should not be restricted to women non-immune to toxoplasmosis.

In summary, the *benefits* of screening were small given

- the very few cases of congenital toxoplasmosis (few new infections in pregnant women and limited transmission to the fœtus)

- the limited efficacy of treatment

And insufficient to justify the *risks* and *costs* associated with screening

- the financial cost of tests

- the risk of spontaneous abortion following amniocentesis

- the high risk of false positives (low PPV) given the low prevalence of the infection

Case History – HIV testing

Consider how the case for HIV testing has changed over the last decades in light of the following

• The increase in availability of ARV to treat HIV

• The availability of rapid tests which use saliva rather than blood.

• The availability of therapies to prevent mother-to-child transmission of HIV

Summary

Screening is the *systematic* application of a test or inquiry, to identify individuals at sufficient *risk* of a specific disorder to *benefit* from further investigation or direct preventive action, among persons who have *not sought medical attention on account of symptoms* of that disorder.

- Screening plays an important role in sexual and reproductive health.
- It allows us to identify individuals *at risk* of disease or with sub-clinical disease.
- These individuals may benefit from further investigation, preventive measures and/or treatment.
- Characteristics of the disease, of the population, of the test and of the interventions or treatment all contribute to deciding if the benefits of a screening programme justify the costs and risks involved.

Further reading

Wald NJ. Guidance on terminology. J Med Screen. 2008 Jan 3;15(1):50-50. Available from: http://msc.sagepub.com/content/15/1/50.long

Evidence review criteria: national screening programmes - Publications - GOV.UK. Available from: https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes

Lesson 10: Interventional Studies (1) Diagnostic Tests, Disease Screening Studies | STAT 507. Available from: https://onlinecourses.science.psu.edu/stat507/node/17

Department of Health & Human Services, State Government of Victoria, Australia. Newborn screening. Available from: https://www.betterhealth.vic.gov.au:443/health/conditionsandtreatments/newborn-screening

Boubaker K, Raeber PA, Vaudaux B, Bucher HC, Garweg JG, Hoesli I, Kind C, Hohlfeld P, Swiss Working Group on congenital Toxoplasmosis. Toxoplasmosis during pregnancy and infancy. A new approach for Switzerland. Swiss Med Wkly. 2008 Dec 13;138(49-50 Suppl 168):1-8.