



Researching new prevention approaches for cervical cancer:

Methodological guidelines

Original source:

Alliance for Cervical Cancer Prevention (ACCP)
www.alliance-cxca.org

Objectives of a prevention program:

- To reduce incidence of and mortality from cervical cancer.

How? Minimum requirements:

- Detection of cervical precancer (early disease) using an appropriate test.
- Treatment of early disease to prevent progression to cancer.

Appropriate test to detect precancer:

- Low cost.
- Safe.
- Convenient and acceptable.
- Reliable.
- Good test performance characteristics.

Test reliability:

Ability of the test to be scored identically if performed again by the same or another provider.

- Reliability depends on:
 - Clinical manifestation of early disease.
 - The method of measurement (subjectivity of the test).
 - Skills of the test provider.
 - Number of steps in the test processing.
- Poor reliability = poor reproducibility.

Test characteristics:

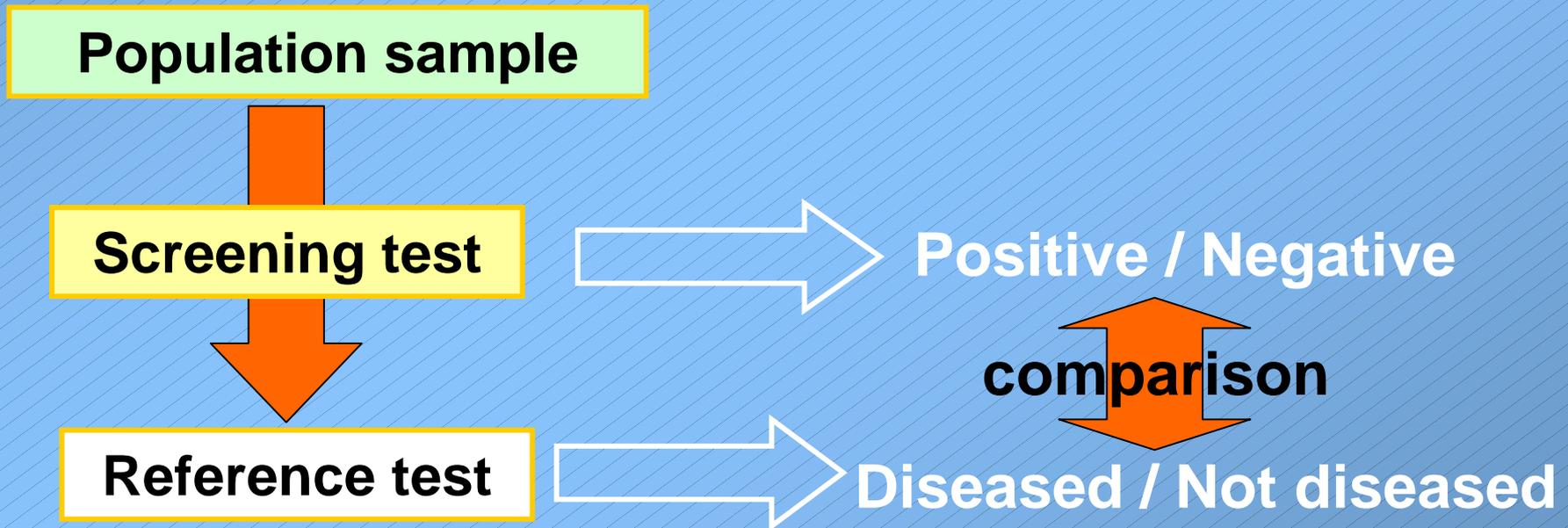
- **Accuracy: inherent characteristics of the test.**
 - **Sensitivity (Se):** proportion of women with actual disease who test positive.
 - **Specificity (Sp):** proportion of women without actual disease who test negative.

Test characteristics (continued):

- **Clinical utility: depends on the prevalence of disease.**
 - **Positive predictive value (PPV):**
probability of having disease, given a positive test.
 - **Negative predictive value (NPV):**
probability of having no disease, given a negative test.

Estimation of test characteristics:

Cross-sectional study



Test characteristics computation:

		Early disease		
		Present (+)	Absent (-)	
Test	+	a	b	a+b
	-	c	d	c+d
		a+c	b+d	

Accuracy

$$Se = a/a+c$$

$$Sp = d/b+d$$

Clinical utility

$$PPV = a/a+b$$

$$NPV = c/c+d$$

Internal validity:

■ Avoidance of misclassification bias:

- Accepted gold standard used as reference test; no time lag between new test and reference test.

■ Avoidance of information bias:

- Assessment of the different tests, independent of all relevant clinical information and other test results.

■ Avoidance of verification bias:

- The reference standard is applied to the full study population.

External validity:

- Characteristics of study participants (e.g., age, disease spectrum).
- Test cut-off point definition (test negative versus positive).
- Definition of disease.

⇒ **All affect generalizability and comparability between studies.**

Application:

- 100,000 individuals, prevalence of early disease=1%.
- **Se=90% and Sp=90%** means:
 - Detection of 900 of the 1,000 true cases.
 - Mislabeling of 9,900 healthy people.
 - **PPV=8.3%** (12 false-positives for every true positive).
- If prevalence decreases to 0.1%, **PPV=0.9%**.

Prevention program effectiveness:

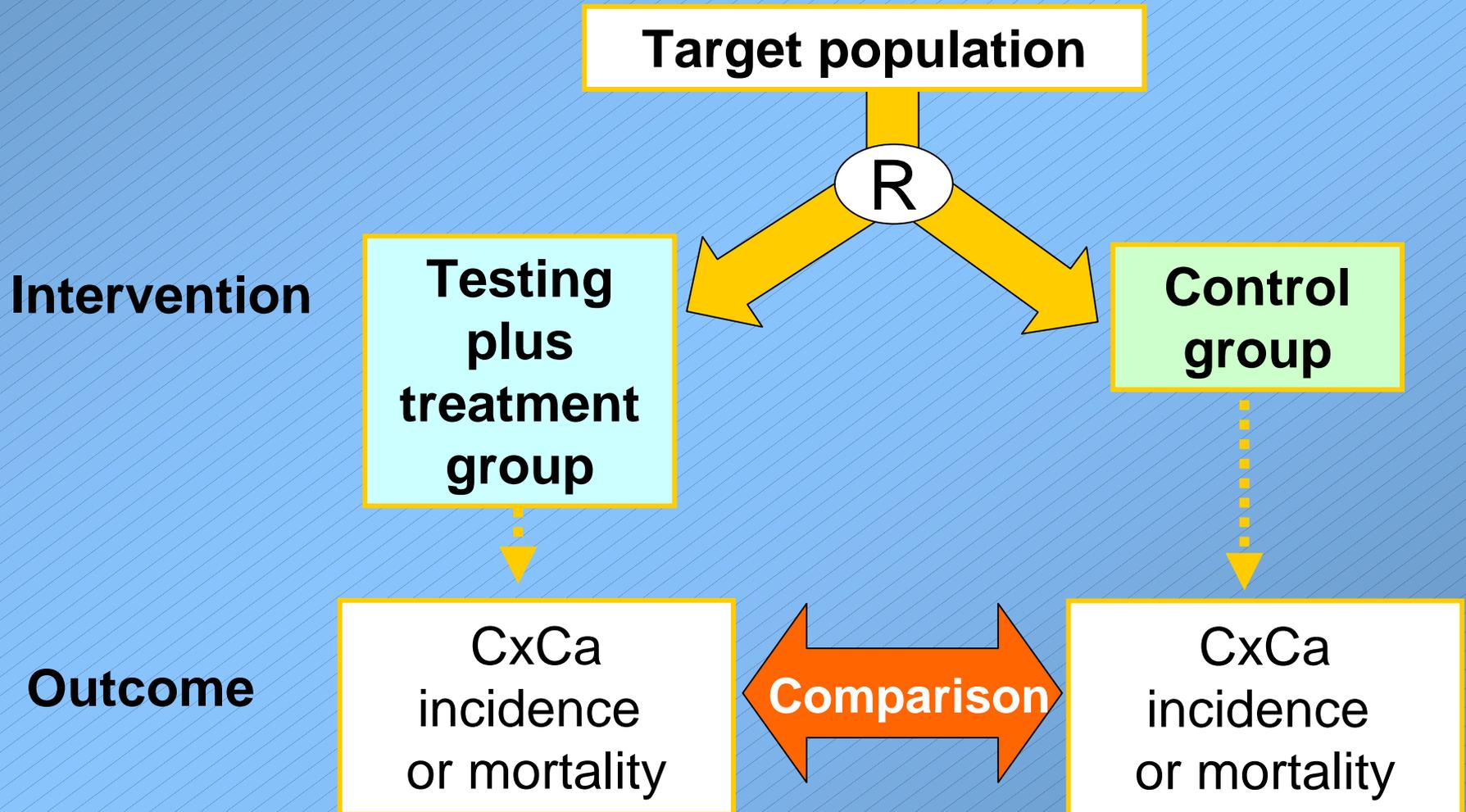
- **An appropriate test does not mean an effective program.**
- **You also need a effective service delivery system:**
 - Good test coverage.
 - Appropriate management of screen-positives (limitation of loss to follow-up).
 - Effective, acceptable, and reasonable cost of the treatment.

Measuring program efficacy and effectiveness:

Study designs:

- Experimental:
 - Randomized controlled trials (RCTs).
 - Nonrandomized controlled trials.
- Observational:
 - Cohort.
 - Case-control.
 - Ecological.

Randomized controlled trials (RCTs):



Randomized controlled trials (RCTs):

- Random assignment of people/communities to one group or another to ensure comparability.
- Standardization of the intervention—test **AND** treatment modalities—to ensure comparability and reproducibility.

Best methodology, but very labor intensive.

Effectiveness consideration:

Showing that a prevention program protocol is efficacious using a RCT does not mean it is effective under normal program conditions.

- **RCT outcome** = result of strict application of a standardized protocol under ideal conditions (efficacious).
- **Effectiveness** = expected improvements in health resulting from routine service delivery programs.

Alliance for Cervical Cancer Prevention (ACCP) work:

Usefulness of Pap test in reducing cervical cancer mortality is generally acknowledged in countries with well organized screening programs, but successful implementation is challenging in low-resource settings.

- In response to these challenges, ACCP is conducting:
 - **Cross-sectional studies** to estimate characteristics of low-cost tests in different settings.
 - **RCTs** to answer efficacy questions for these screening tests and treatments, integrated into specific service delivery approaches.
 - **Pilot projects** to assess the effectiveness of alternative prevention algorithms in routine practice.

Conclusions:

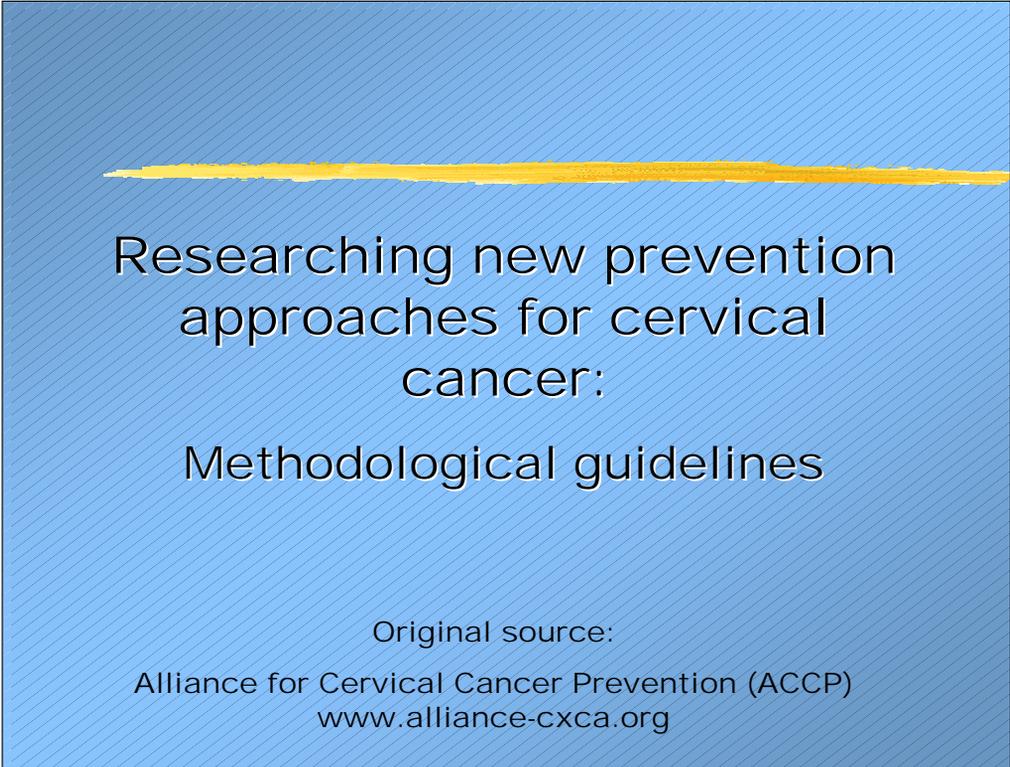
- Determining a test's characteristics requires a rigorous cross-sectional study design.
- Selecting a good test does not necessarily mean you will have an effective prevention program.
- RCT study designs are best for assessing program efficacy, but are very labor intensive.
- Evaluations of pilot projects and observational study designs are useful for assessing the effectiveness of chosen prevention strategies in routine settings.

References:

- Hulley SB, Cummings SR (eds.). Designing Clinical Research: An Epidemiologic Approach. Baltimore: Williams and Wilkins, 1988.
- Riegelman RK. Studying a Study and Testing a Test: How to Read the Medical Literature (2nd Edition). Boston: Little, Brown and Company, 1989.
- Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical Epidemiology: A Basic Science for Clinical Medicine. Boston: Little, Brown and Company, 1991.
- Weiss NS. Clinical Epidemiology: The Study of the Outcome of Illness. New York: Oxford University Press, 1986.

For more information on cervical cancer prevention:

- **The Alliance for Cervical Cancer Prevention (ACCP)**
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- **ACCP partner organizations:**
 - EngenderHealth www.engenderhealth.org
 - International Agency for Research on Cancer (IARC) www.iarc.fr
 - JHPIEGO www.jhpiego.org
 - Pan American Health Organization (PAHO)
www.paho.org
 - Program for Appropriate Technology in Health (PATH) www.path.org



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Slide overview: This presentation provides an overview of methodologies to assess the value of new approaches to preventing cervical cancer.

•*Notes:* The traditional cervical cancer prevention approach in many countries worldwide is cytology-based screening and referral of test-positive results to another facility, where diagnostic testing is available. With this approach, women testing positive on the second test get a biopsy and the specimen is sent to a pathology lab for confirmatory assessment of her disease status. The woman has to return to the facility a third time for her biopsy results and management recommendation, including treatment as appropriate—which may or may not require another clinic visit.

•*Notes:* New prevention approaches involve alternative tests other than cytology to detect early disease, and/or new ways of linking testing and the management of positive cases.

Objectives of a prevention program:

- To reduce incidence of and mortality from cervical cancer.

How? Minimum requirements:

- Detection of cervical precancer (early disease) using an appropriate test.
- Treatment of early disease to prevent progression to cancer.

Slide overview: A cervical cancer prevention program aims to reduce incidence of and mortality from cervical cancer.

•*Note for bullet 2:* The objective to reduce incidence and mortality can be reached only if three conditions are met:

- Use an appropriate test to detect cervical cancer precursors.
- Treat early disease.
- Follow-up test positive clients to limit drop outs between testing and treatment.

Appropriate test to detect precancer:

- Low cost.
- Safe.
- Convenient and acceptable.
- Reliable.
- Good test performance characteristics.

Slide overview: The first condition described in the previous slide was to have an appropriate test. There are number of factors influencing a test's appropriateness.

•*Note for bullet 1:* The cost of testing should be cheap enough that high coverage can be achieved in developing countries despite limited health budgets

•*Note for bullet 2:* The test should cause minimal pain and discomfort and no major complications

•*Note for bullet 3:* The test should be convenient, and acceptable to women and other community members in order to increase women's participation. This factor can be studied via community-based qualitative studies.

•*Note for bullets 4 and 5:* In addition to these three factors, the test should be reliable and have good performance characteristics to ensure accurate detection of early disease and clinical utility.

Test reliability:

Ability of the test to be scored identically if performed again by the same or another provider.

- Reliability depends on:
 - Clinical manifestation of early disease.
 - The method of measurement (subjectivity of the test).
 - Skills of the test provider.
 - Number of steps in the test processing.
- Poor reliability = poor reproducibility.

Slide overview: Reliability assesses the degree to which repeated measurements of a test (by the same provider/rater or different providers/raters) yield the same result.

- When variability exists between different raters independently performing the test for the same individual, this is called inter-observer variability.
- When the variability exists for repeat measures for the same individual by the same rater, this is called intra-observer variability.

■ *Notes for bullet 1:* Reliability depends on:

- The clinical manifestations of early disease (precancer)
- The method of measurement; a visual test is likely to be less reliable than a biological test because it is rater-dependant.
- The more skilled the test provider/rater, the better the test reliability. Standardized test procedure guidelines and training of providers to those guidelines minimizes variability.
- For tests involving many steps, risk of implementation errors is higher. The more steps involved, the less likely the test reliability.
- Test reliability is assessed through reproducibility studies.

■ *Notes for bullet 2:*

- If a test is not very reliable, its application in different settings and with different providers will likely yield different outcomes.

Test characteristics:

- **Accuracy: inherent characteristics of the test.**
 - **Sensitivity (Se):** proportion of women with actual disease who test positive.
 - **Specificity (Sp):** proportion of women without actual disease who test negative.

Slide overview: Test characteristics include how well the test reveals the true status of disease and how useful the test is in clinical practice in distinguishing between those likely and not likely to have disease.

•*Notes for bullet 1:* There are several measures traditionally used to assess how well a test detects the presence of early disease (precancer)

- Sensitivity and specificity measure the ability of a test to correctly identify diseased or non-diseased people, respectively.
- Sensitivity and specificity are considered inherent characteristics of the test because, in principle, they do not vary according to disease prevalence.
- Usually, if a proper methodology is used to estimate them, sensitivity and specificity values can be compared across different sites and different tests. This property makes sensitivity and specificity useful to those recommending policies regarding which test is most appropriate, given local constraints, demands and expectations.
- Sensitivity and specificity are usually inter-related. Increases in one yield corresponding decreases in the other.
- A test with low reliability cannot be expected to be very accurate. On the other hand, a test with high reliability may not be very accurate, if repeated measures are the same but incorrect.

Test characteristics (continued):

- **Clinical utility: depends on the prevalence of disease.**

- **Positive predictive value (PPV):**

- probability of having disease, given a positive test.

- **Negative predictive value (NPV):**

- probability of having no disease, given a negative test.

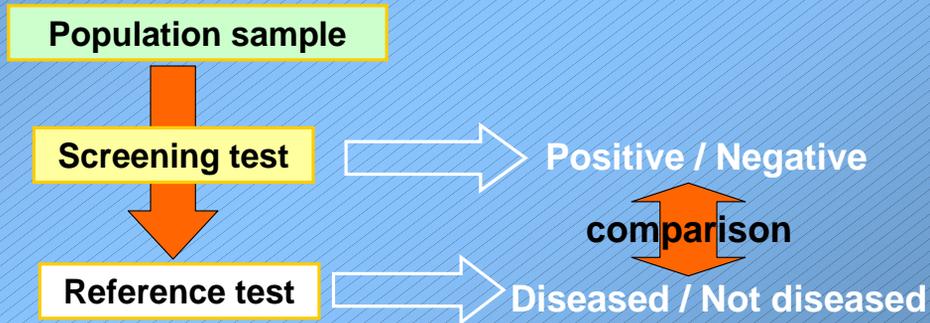
Slide overview: Clinical utility is another important test characteristic.

- *Notes:* Predictive value measures the test's ability to predict disease or non-disease given the underlying prevalence of disease in a target population. The higher the prevalence of disease in that population, the higher the test's positive predictive value when applied in that population.

- *Notes:* Differences in predictive values across study sites cannot be easily interpreted without knowledge of the underlying prevalence of disease in the population studied.

Estimation of test characteristics:

Cross-sectional study



Slide overview: To estimate test characteristics, one usually conducts cross-sectional studies. These studies aim to estimate how accurately the test detects early prevalent disease (e.g., precancer).

- *Notes:* With such designs, usually a representative sample of the target population (at risk of disease) independently undergoes 2 tests:
 - The first is the screening test you want to assess: the results are categorized as positive (suspicion of early disease) or negative (no early disease suspected).
 - The second is a reference test which “correctly” identifies the existence of early disease or non-early disease. The latter should be a test commonly accepted as being as close to the truth as possible, i.e, a “gold-standard”. These results are categorized as disease absent or present.
- *Notes:* A test’s characteristics are computed by comparing the screening test results to those considered as “truth” (via the reference or gold standard test).

Test characteristics computation:

		Early disease		
		Present (+)	Absent (-)	
Test	+	a	b	a+b
	-	c	d	c+d
		a+c	b+d	

Accuracy

$$Se = a/a+c$$

$$Sp = d/b+d$$

Clinical utility

$$PPV = a/a+b$$

$$NPV = c/c+d$$

Slide overview: This two-by-two table illustrates how the four measures—sensitivity, specificity and positive and negative predictive value—are traditionally calculated in test characteristic studies involving early disease (e.g., precancer).

- *Notes:* All four cells of the table must be filled completely. That is, everyone with a screening test result must also have a corresponding gold standard test result.
- *Notes:* The formulae on the bottom are standard for calculating direct estimates of the four test characteristics.

Internal validity:

- **Avoidance of misclassification bias:**
 - Accepted gold standard used as reference test; no time lag between new test and reference test.
- **Avoidance of information bias:**
 - Assessment of the different tests, independent of all relevant clinical information and other test results.
- **Avoidance of verification bias:**
 - The reference standard is applied to the full study population.

Slide overview: For test characteristic study results to be credible, studies must be internally valid. Otherwise the study may produce results that systematically depart from the true values; this is called bias. This slide provides a summary of some of the types of bias that can affect the validity of test characteristic study results.

•*Note for bullet 1:* Misclassification bias happens when the reference test is not totally accurate in detecting disease and people are “misclassified” into the wrong disease status category. For cervical precancer detection, a recognized “reference standard” is colposcopy followed by biopsy if the colposcopy reveals any abnormality – that is, a combined gold standard test. To avoid misclassification when measuring a new test’s ability to *detect* prevalent disease, both the new test and the reference test should be performed as close as possible in time before disease progression is likely.

-*Note for bullet 2:* Bias is potentially introduced if the reference standard results are determined with prior knowledge of either the new test’s results or any clinical information associated with disease risk; this is called information bias. Therefore, all reference standard test results must be determined independently of (blind to) previous results.

- *Note for bullet 3:* Verification bias occurs when only some of the participants receive the reference test (for example, only those with a positive screening test). This type of bias tends to result in overestimated sensitivity and underestimate specificity values because one is not “verifying” screened negative.

External validity:

- Characteristics of study participants (e.g., age, disease spectrum).
- Test cut-off point definition (test negative versus positive).
- Definition of disease.

⇒ All affect generalizability and comparability between studies.

Slide overview: External validity refers to the extent to which a study's results are applicable to the population to which the test will be applied.

▪ *Note for bullet 1:* Studies that include older, menopausal women may yield different results than studies on younger women because of physiological or anatomical differences that affect how a test performs. Interpreting differences in study findings, and the applicability of study findings to a particular clinical population, requires knowledge of relevant characteristics of the study population. If a test is to be used in the general population to identify early disease but studies have only been conducted on referral patients, (experiencing a more limited spectrum of disease) then the test may not perform in practice as assumed from study results.

▪ *Note for bullets 2:* Test classification schemes are not standardized and therefore cutoff points that distinguish between what is test-positive and test-negative in only one study may differ from those in another study. This may result in different study test characteristic estimates.

▪ *Note for bullets 3:* Disease categories from one study also may not necessarily match those of another study and they should always be clearly defined when reporting study results. For studies measuring the accuracy of a test to detect cervical disease leading to cancer, usually HSIL is the relevant precursor because of the higher probability of progression of HSIL to cancer. Grouping women who have cancer with those who have precancerous disease may artificially overestimate test accuracy since cancer is easier to diagnose than HSIL and these people may have been referred into the study from elsewhere (not from the general population).

▪ *Final note:* Differences in any of the above factors across studies will render

Application:

- 100,000 individuals, prevalence of early disease=1%.
- **Se=90% and Sp=90%** means:
 - Detection of 900 of the 1,000 true cases.
 - Mislabeling of 9,900 healthy people.
 - **PPV=8.3%** (12 false-positives for every true positive).
- If prevalence decreases to 0.1%, **PPV=0.9%**.

Slide overview: There are no universal standards for minimum or acceptable sensitivity or specificity values. Acceptable values depend on the relative importance of identifying true cases of disease versus the burden of falsely identifying a woman as diseased when she is not - and the prevalence of disease in that population.

■ *Notes:* For example, consider a target population of 100,000 individuals with a disease prevalence of 1% i.e. 1,000 true cases:

- A test with good test characteristics (Se and Sp = 90%) will detect 900 of the 1,000 true cases, but it will also be falsely positive for 9,900 healthy women.
- This yields a PPV of 8.3% i.e. 12 false positives (FP) for every true positive (TP) identified.
- If the prevalence of true disease were lower, 0.1%, sensitivity and specificity would theoretically remain the same but the PPV would decrease to 0.9% (i.e. 111 FP for every TP).
- If the prevalence of true disease on the other hand were higher, the PPV would correspondingly be higher and the number of FP would be lower relative to the number of TP identified.

■ *Additional note:* Other important considerations when comparing tests are the psychological impact of having a false-positive screening test, how false positive tests are managed, the relative cost to the health care system, the woman and society of false positive versus false negative findings and the relative benefits of identifying true disease versus identifying true non-

Prevention program effectiveness:

- An appropriate test does not mean an effective program.
- **You also need an effective service delivery system:**
 - Good test coverage.
 - Appropriate management of screen-positives (limitation of loss to follow-up).
 - Effective, acceptable, and reasonable cost of the treatment.

Slide overview: Various criteria other than a test's accuracy, clinical utility and reliability render early detection useful in yielding improved outcomes. Indeed, early detection—unlinked to treatment—does not result in health improvement.

•*Note for bullet 2:* For a program to effectively and efficiently reduce morbidity and mortality, other basic criteria related to the service delivery system must also be met:

- The proportion of women receiving the test (test coverage) should be high in order to identify the majority of prevalent precancerous cases in the population that could progress to cancer
- There should be an appropriate management protocol for test-positive women. This protocol should ensure that the majority of lesions detected are ultimately treated (limited loss to follow up).
- The treatment should be effective in curing precancer, acceptable, and available at reasonable cost (considering the limited health budgets of developing countries).

▪*Final note:* The extent to which these factors, in addition to test accuracy and reliability, affect overall program effectiveness needs to be assessed through appropriate study designs.

Measuring program efficacy and effectiveness:

Study designs:

- Experimental:
 - Randomized controlled trials (RCTs).
 - Nonrandomized controlled trials.
- Observational:
 - Cohort.
 - Case-control.
 - Ecological.

Slide overview: Cervical cancer prevention program efficacy is reduced morbidity and mortality under ideal program conditions; program effectiveness measures the same outcomes under normal service delivery conditions.

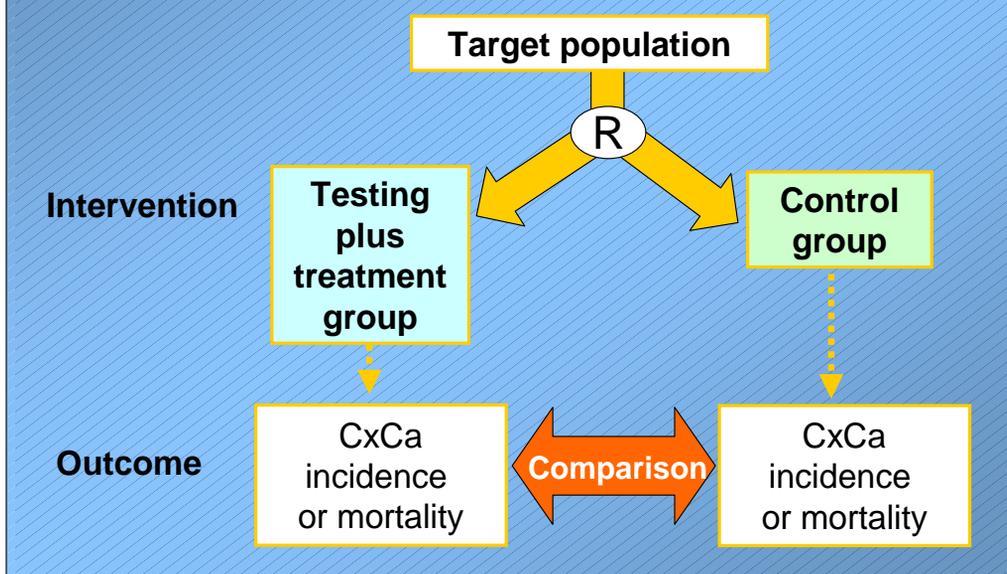
Note for bullet 1: To measure how well testing linked to treatment results over time in reduced morbidity and mortality, intervention or observational studies can be used. This slide lists types of studies within each of the two main categories of designs in order of study “rigor”. The more rigorous the study design, the stronger the conclusions that can be made from the studies.

In intervention or experimental studies, the investigators control how the intervention is implemented. In the case of cervical cancer prevention, the intervention involves detecting disease through testing, linking testing to treatment, and effectively treating appropriate precancerous cases. Such studies are designed to test a hypothesized cause-effect relationship by modifying the causal factor (in this case, prevention program).

In observation studies, the investigators do not manipulate how the intervention is applied to the population. Changes in outcomes are studied in relationship to differences in the program, and effort is made to reduce sources of bias that could affect interpretation of study results, but the investigators do not manipulate the intervention.

Detailed descriptions of the specific methodologies used in the above

Randomized controlled trials (RCTs):



Slide overview: In a randomized controlled trial, to maximize comparability, eligible people of the target population are *randomly* assigned to an intervention group (for example, testing plus treatment as appropriate) or to the control group (which may receive treatment if cancer is identified). These randomization groups are also called "arms".

Notes:

- This presentation focuses on the RCTs methodology because it is less susceptible to bias.
- Participants are followed-up for many years in order to monitor cervical cancer incidence or mortality (CxCa' on the slide is an abbreviation for cervical cancer)
- A comparison of these outcomes indicates whether the prevention program (testing plus treatment as indicated) was efficacious in reducing these outcomes.

Randomized controlled trials (RCTs):

- Random assignment of people/communities to one group or another to ensure comparability.
- Standardization of the intervention—test **AND** treatment modalities—to ensure comparability and reproducibility.

Best methodology, but very labor intensive.

Slide overview: Randomization serves to maximize the likelihood that relevant factors other than the intervention (program) itself equally affect all arms of the study. Thus, any observed differences in outcomes are more likely to reflect the effect of differences between the program arms.

- *Note for bullet 1:* Randomization can be performed at the level of the community rather than individuals to facilitate randomization and particularly to avoid contamination between arms.
- *Note for bullet 2:* When the maximum potential effect of the program is of interest (program efficacy), investigators should ensure that a standardized protocol is implemented in all arms to ensure reproducibility of the intervention modalities.
- *Additional notes:*
 - Randomized Controlled Trials (RCTs) usually require long term follow-up and a large sample size. Blinding of group status to reduce potential bias resulting from this knowledge is also ideal, but **rarely possible**.
 - While RCTs are considered the gold standard study design for determining the efficacy of early detection and treatment programs, to date, evidence supporting the effectiveness of the Pap test in reducing cervical cancer mortality has come from observational (case-control and cohort) studies.

Final Note: In randomized trials the research team controls as many aspects of the study as possible to maximize internal validity and thus credibility

Effectiveness consideration:

Showing that a prevention program protocol is efficacious using a RCT does not mean it is effective under normal program conditions.

- **RCT outcome** = result of strict application of a standardized protocol under ideal conditions (efficacious).
- **Effectiveness** = expected improvements in health resulting from routine service delivery programs.

Slide overview: It is important to understand what RCTs tell us and how results may differ in real-life circumstances.

■ *Note for bullet 1:* RCTs are efficacy studies investigating improvements in health that result from the strict application of a standardized protocol for early detection and treatment of identified cases. Such studies measure, under ideal circumstances, maximum health improvements that programs involving the use of a new test, linked to treatment, could expect to yield.

■ *Note for bullet 2:* As programs do not operate in a rigorous, standardized way in practice, there is interest in knowing the likely improvement in health that a program under normal operating conditions involving a new test linked to treatment would yield. This information is provided through effectiveness studies involving other designs than RCTs.

Alliance for Cervical Cancer Prevention (ACCP) work:

Usefulness of Pap test in reducing cervical cancer mortality is generally acknowledged in countries with well organized screening programs, but successful implementation is challenging in low-resource settings.

- In response to these challenges, ACCP is conducting:
 - **Cross-sectional studies** to estimate characteristics of low-cost tests in different settings.
 - **RCTs** to answer efficacy questions for these screening tests and treatments, integrated into specific service delivery approaches.
 - **Pilot projects** to assess the effectiveness of alternative prevention algorithms in routine practice.

Slide overview: The Alliance for Cervical Cancer Prevention (ACCP) is researching various alternative methods for preventing cervical cancer in low-resource settings.

•*Notes:* Pap smear is an acceptable screening test in good quality programs, but its associated service delivery system is not always effective in developing countries (multiple visits, no quality control procedure, etc). Moreover, its implementation using a good service delivery system may be expensive.

•*Note for bullets:* To respond to this challenge, ACCP has promoted studies to investigate various tests (VIA, VILI, HPV testing, good quality cytology) and ways to link testing with treatment.

- Accuracy and reliability of these tests are being assessed using multi-country cross-sectional studies.
- Efficacy is being assessed using large RCTs comparing various test and treatment algorithms. The results of these RCTs will be available over the next few years for morbidity, and over the next decade for their effect on mortality.
- Effectiveness is being evaluated through pilot programs in different settings.

Conclusions:

- Determining a test's characteristics requires a rigorous cross-sectional study design.
- Selecting a good test does not necessarily mean you will have an effective prevention program.
- RCT study designs are best for assessing program efficacy, but are very labor intensive.
- Evaluations of pilot projects and observational study designs are useful for assessing the effectiveness of chosen prevention strategies in routine settings.

Slide overview: To conclude, there are 4 steps to consider in researching new cervical cancer prevention strategies:

- Note for bullet 1:* A new test needs to be assessed through a rigorous cross-sectional study to determine its accuracy.
- Note for bullet 2:* The test needs to be linked to treatment in the context of a feasible service delivery system to assess its value in preventing cervical cancer.
- Note for bullet 3:* The choice of which testing and treatment algorithm is best should be made using RCTs, but this is very labor intensive.
- Note for bullet 4:* Pilot project evaluations and observational studies can provide evidence of the effectiveness of the selected service delivery algorithm in routine settings.

References:

- Hulley SB, Cummings SR (eds.). Designing Clinical Research: An Epidemiologic Approach. Baltimore: Williams and Wilkins, 1988.
- Riegelman RK. Studying a Study and Testing a Test: How to Read the Medical Literature (2nd Edition). Boston: Little, Brown and Company, 1989.
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