What is needed for implementation of a complete system from screening to treatment in LMICs? Moving towards an organised cervical cancer screening, diagnosis and treatment in LMICs.

Simms et al. estimated that in the absence of further intervention, there would be 44.4 million cervical cancer cases (25M deaths) diagnosed globally over the period 2020-69, with almost two-thirds of cases occurring in low-HDI or medium-HDI countries (1).

WHO: Implementation of HPV-based screening twice per lifetime between 35 years and 45 years in all LMICs with 70% coverage globally will bring forward the effects of prevention and avert a total of 12.5-13.4 million cases in the next 50 years. HPV-based screening twice per lifetime in all LMICs with 70% coverage.

And we need to manage all screen positive!

HOW TO MAKE IT REAL?


The screening situation

Screening situation in 2020

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HOW TO MAKE IT REAL?

Planning

Deciding the screening strategy

- Identify population at risk
  - Age range
  - Screen history
  - HIV status
- Screening approach and test
  - Speculum exam or Self sampling
  - TRIAGE or TREAT
  - Self sampling HPV test
- Manage screen positive
  - Self sampling HPV test
- Treat the positives
  - VIA+AVE and/or HPV type restriction
  - Ablation & LLETZ
- Ensure treatment capacity
  - Thermal ablation as first line

Available strategies for triage of HPV-positive women in low resource settings

- Visual inspection after AA: Poor reproducibility and low accuracy in many settings. Leads mainly to under treatment (1)
- VAT: Visual evaluation for treatment: Overtreatment (2)
- Enhanced visual inspection (with digital images): Unclear benefit
- Visual inspection after AA with automated reading: AI-based Preliminary excellent results (3)
- HPV genotype restriction: Scientifically strong added value (4)
- Multiplex of virological and cellular markers (under evaluation) (5)

(1) Catarino et al. 2017, Wentzensen 2017
(2) Toliman et al. 2018
(3) Hu et al.
(4) Demarco et al. 2020
(5) Gizaw et al. 2019

A ‘test and treat’ algorithm based HPV would have appropriately treated 92% (33/36) of all women with high-grade disease (HSIL or worse); over-treated 13% (64/491) of women without disease; and would not have detected and treated 8% (3/36) of women with high-grade disease.

First Proof of Principle in Guanacaste Natural History Study
Guanacaste, Costa Rica, use of cervigrams at baseline and follow up for CIN2+ Automated Visual Evaluation (AVE)

- AVE severity score (0 to 1) to predict precancer
- Evaluation of AVE algorithm
  - ROC curves
  - AUC statistic
- Compared well with other tests: HPV, cytology, cervicography, colpocopic impression

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Use of VIA either as primary screening or as triage would have missed 48.5% of HSIL.
Performance of Automated Visual Evaluation (AVE) algorithms

Screening
AUC = 0.95

Triage of HPV positive
AUC = 0.87

HPV type restriction
Type-specific cumulative risk of progression to CIN3+ of single HPV infections

Screening
Treatment

Treatment of precancerous lesions

- Ideally treatment should follow the triage test, if possible, in the same visit to avoid lost to FU.
- Thermal ablation is the easiest to manage and has shown to overcome many structural issues of cryotherapy with similar performance (1).
- Still a considerable proportion may not be treatable because of large lesions (2) or not visible TZ.
- Issues:
  - Logistical: Women need to accept treatment, personnel may not be available at the time of confirmation, devices may not be ready.
  - Technical: Distinction between TZ1, TZ2 and TZ3 under VIA/AVE. Management of TZ2 and TZ3 need good referral system.

(1) WHO guidelines 2019, Holme et al 2020; Randal 2019, Pinder et al. 2020
(2) Gage et al. 2009

Key issues in management

- How many cervical cancer cases can be managed?
  - Do we need to limit the screening capacity based on the availability of managing invasive cervical cancer cases detected through the screening process (approx 0.6% of triage positive)?
  - Do we need to guarantee that treatment of precancerous lesions (about 1%) is offered with no delays and with trained personnel to run thermal ablation and LLETZ?
  - Should these 2 points be the very first questions to be answered before large scale screening is initiated?

Scenario with high accuracy, minimizing overtreatment and potential low cost

VAT Visual assessment for treatment
VIA Visual evaluation necked eye
AVE Automated visual evaluation
HIGH/HIGH 16,18,45,31,33,35,52,58
LOW-HIGH 39,51,56, 59,68
Data collection

- Minimal data collection can provide a basic measure of the impact and performance of the intervention.
- Ideally a cancer registry will be extremely useful.
- Low cost approaches are available (cell phone software designed for this, DHIS2.)
- Data collection, analysis and feedback based on results are critical to re-shape efforts when needed.

A Cervical Precancer Planning Tool was developed for country decision-makers.

- The purpose of the Tool is to inform national cervical precancer screening and treatment strategies.
- The Tool enables end-users to explore trade-offs for the following:
  - Screening approaches
    - Number of women correctly identified
    - Number of women missed
    - Number of women incorrectly referred
    - Costs
  - Treatment equipment deployment approaches
    - Loss to follow-up
    - Equipment utilization
    - Cost

In summary

- Impact of screening programmes may be limited by the availability of treatment facilities.
- Self-sampling and HPV testing are key elements for high coverage and high accuracy.
- Selection of a triage strategy remains unsettled in low resource settings, but new low-cost approaches are likely to increase accuracy and affordability.
- Data monitoring can be critical to evaluate impact and may increase performance.
- While under COVID, cervical screening should be undertaken within safe environments. Otherwise delay the intervention.

THANK YOU FOR YOUR ATTENTION

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