Challenges in the HPV Screening Landscape, Triage of Screening Positive Samples, and Screening in the Era of Vaccination.

Online meeting

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Objectives of the meeting (1)

- Landscape of HPV Screening - Discuss barriers to adoption and implementation of HPV testing
  - Review quality, validation and availability of HPV tests
  - Provide country examples of successful implementation of HPV testing
  - Discuss if we have enough options and supply needed for the global cervical cancer elimination
  - Review HPV screening and treatment challenges in different regions
  - Review challenges and opportunities to offer a complete system, from screening to treatment, in LMIC
  - Discuss the existing networks that support implementation of cervical cancer screening programs in LMICs.
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Objectives of the meeting (2)

- Triage: what are the best options.
  - Review current available triage, treatment and management algorithms
  - Discuss what are the best options for different situations
  - Review challenges and future opportunities
- Integration of Vaccination and Screening
  - How to organize cervical cancer screening in the era of vaccination
- Impact of COVID-19 on cervical cancer screening programs

The Landscape of HPV Screening; Where do we stand today?

Role of Screening in Cervical Cancer Elimination: What needs to be done at the level of vaccination, screening and treatment.

- Three pillars in cervical cancer control
  - Primary prevention – vaccine
  - Secondary prevention – screening
  - Tertiary prevention – treatment of precancerous lesions
- Vaccination alone will not get CC incidence below 4/100k before 2120
- Vaccination + screening will speed this up

Role of Screening in Cervical Cancer Elimination: What needs to be done at the level of vaccination, screening and treatment.

- Innovations on the horizon
  - Improved immunization schedules
  - Single dose HPV vaccine
  - Additional vaccine manufacturers
  - Self-collection devices
  - Artificial Inteligence-based screening
  - Lower cost HPV tests
  - Point-of-care screening technology

Role of Screening in Cervical Cancer Elimination: What needs to be done at the level of vaccination, screening and treatment.

- WHO can provide technical support at the regional level
- WHO cannot finance national plans for elimination
- Set up national plans with budget within the national budget

Quality Review, Validation and Availability of HPV tests

- 254+ commercial HPV assays (and 425+ variants)
- 60% of HPV tests without a single peer-reviewed publication
- 81% of HPV tests without published performance evaluation
- several clinically unvalidated HPV assays are used worldwide in daily practice
- serious COVID-19-related supply chain problems arising

Quality Review, Validation and Availability of HPV tests

- Validation criteria for HPV DNA assays established
- Different evidence levels of validation established, with a four * system
- mRNA tests – no validation guidelines yet
- mRNA tests:
  - Test based on 5 types: higher specificity but lower sensitivity
  - Aptima: higher specificity but slightly lower sensitivity for CIN2+, similar sensitivity for CIN3+
- Validation of self-obtained samples: similar sensitivity, lower specificity (using validated test)
- Validation workshop planned

WHO Prequalification of HPV diagnostic assays; pathway and recent developments

- Facilitate access to safe, appropriate and affordable IVDs of good quality
- Suitable to be used in resource-limited settings
- Specific emphasis on issues relevant to resource-limited settings, such as stability of products (heat / humidity); suitable specimen type; labelling of products; ease of use; training and materials
- Performance evaluation includes verification of analytical (e.g limit of detection, genotype detection, etc..) and clinical performance; and assessment of ease of use and operational characteristics

WHO Prequalification of HPV diagnostic assays; pathway and recent developments

- Technical Specifications Series (TSS-)4 describes the minimum requirements for HPV assays
- 2 prequalification (PQ) evaluation sites (the Scottish HPV Reference Laboratory and the National AIDS Research Institute, India)
- 3 HPV assays prequalified
  - Xpert HPV (Cepheid AB)
  - *care*HPV Test (QIAGEN GmbH)
  - Abbott *Real*Time High Risk HPV (Abbott GmbH&Co.KG)
- 2 HPV assays under assessment
  - Cobas 4800
  - Cobas HPV (6800/8800)
- Full assessment – 1 year
- If assessed by regulatory authority, abridged assessment by WHO – 3 mo

Experience from a prequalification reference lab: challenges and opportunities

- PQ evaluation labs are audited by WHO
- The labs are part of the performance evaluation
- Xpert and Care Assay evaluated in Scotland on analytical and virologic performance (not clinical performance)
- Current plasmid DNA standards limited to amplification and detection phase
- New standards, based on cell lines, more representative of clinical samples, in development
- More PQ evaluation labs needed (elimination -> more tests)
- Field testing remains of key value

Self-sampling; current situation and evolution in the future

- 45% of newly diagnosed CaCx in non-attenders
- 70% of non-attenders are just regular women
- Provide a test that is simple, easy and safe
- Opt-in and opt-out give comparable participation rates
- Opt-in is cheaper (and more environment-friendly, less waste)
- In DK, 28% of invitees for self-sampling were screened (17% via self-sampling, 11% by GP)
- High analytical stability of self-sampled material (i.e. useful in LMIC)
- Self-sampling enables screening outside the classical restraints of health care infrastructure (eg 7/11 in Indonesia)

Age at last screening and remaining lifetime risk of cervical cancer in older, unvaccinated women: a modelling study

- Benefits of screening are low below <25y and decline after >65y
- Screening efficiency highest between 30-60y
  - So, if screening only twice in a lifetime, ages 35 and 45 make sense
- Less residual risk after HPV-based screening compared to cytology
- Differences are in the value judgements & interpretation of model results by decision-makers
  - Below what threshold is cervical cancer risk sufficiently low not to screen?
  - How should we value harm outcomes vs benefit outcomes? Few women who screen will benefit, while many more will incur harms.

Discussion

- Will the elimination goal impact on the supply of HPV tests?
  - The increase in use of HPV tests will be slow, not Covid-like
  - However, the competition of Covid is fierce and may hamper production of HPV tests
- Will the elimination goal impact on follow-up and treatment?
  - The bottleneck is having sufficient equipment and qualified HCW
  - Industry has no business reasons to look at anti-virals for HPV

Discussion

- How will guidelines ensure tht women are handled and treated consistently and rationally?
  - ESGO is updating guidelines and sharing with WHO. However, this is for HIC. Resource-stratified guidelines are needed for LMIC
- Need to address the way (and timing) of communicating of updated guidelines to HCW
  - E-learning course for clinicians on new screening guidelines
  - WHO academy for training of HCW

HPV Screening and Treatment; Opportunities and Challenges in different regions.

Cancer screening and early diagnosis in low- and middle-income countries: Current situation

- Principles for Screening in LMICs
  - Needs space accessible to general population
  - Does not rely on highly trained doctors or lab personnel to perform
  - Results can be obtained fast, followed by immediate treatment
- Opportunities of HPV testing in LMIC:
  - Decreased risk of subjective interpretation
  - Easier to administer
  - Point-of-care with immediate results
  - Can be coupled with VIA for triage of HPV+

Cancer screening and early diagnosis in low- and middle-income countries: Current situation

- Challenges of HPV testing in LMIC:
  - Remains expensive
  - Requires equipment and supply chain
  - Access to treatment remains vital
- Despite HPV vaccines, screening remains essential to reduce incidence and mortality
- COVID-19 will likely impact screening and vaccination efforts for years to come

Review HPV Screening and treatment challenges in Eastern Europe Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Republic of North Macedonia, Hungary, Latvia, Lithuania, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia.

- Ten countries report organized cervical screening
- Only one country reaches coverage >70% - Slovenia
- Five countries have opportunistic cervical screening
- Lack of coverage data, lack of funding
- Cervical screening mainly based on conventional cytology
- National HPV-based organized cervical screening implemented in single country, but with extremely low coverage (Montenegro)
- Over-screening and under-screening: relatively high coverage in women below 40 and poor coverage in older women
- Many wrong perceptions concerning HPV-based cervical cancer screening in Central and Eastern Europe (e.g. mistrust in public health systems)

Review HPV Screening and treatment challenges in Eastern Europe Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Republic of North Macedonia, Hungary, Latvia, Lithuania, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia.

- Slovenia
- Effective screening program, with the three years coverage over 70%
- HPV vaccination integrated into NIP, free of charge, coverage over 60%
- Screening women 20-64 years, every three years, conventional cytology, HPV reflex testing for five indications
- Integration of cytology, histology and HPV-test results registry, population registry and cancer registry, all at national level

Review in Eastern European Countries and Central Asia Russia, Georgia, Belorussia, Ukraine, Moldova, Armenia, Azerbaijan, Uzbekistan, Kazakhstan, Kirgizstan

- The burden of HPV infection in women with normal cytology is high (ranging between 8 and 40% in general population)
- The incidence of HPV-related disease (AGW + all forms of cancer) is high
- Many HPV tests are licensed but not (fully) validated
- Pap test is free in several countries, whereas a free HPV test is available in only one country (Kazakhstan)
- HPV vaccine included in NIP in one country (Uzbekistan, since 2019)
- Organized cervical cancer screening and HPV vaccine in NIP are needed

Implementation of organized HPV-based screening programs; Strategies, Challenges and Successes.

- Netherlands
- Shift to HPV-based in 2017
- Detection rate has gone up, referral rate has gone up, PPV has gone down
- The shift is a long-term project: decision-making 2y; preparation 3.5 y; implementation 8 mo
- Further optimization:
  - Decrease unnecessary referrals (e.g. genotyping)
  - More self-sampling, non-responders + first-invited-women
  - Preparing for HPV-vaccinated women in screening program (as of 2023)
  - Lowering barriers for participation (2021)
  - Optimize vaccine promotion communication versus management HPV+’s
  - Dealing with consequences of the COVID19-pandemic

Implementation of organized HPV-based screening programs; Strategies, Challenges and Successes.

- Turkey
- HPV + Conventional Smear in each five years, for women aged 30-65 years old
- Up from 100,000 women in 2007 to 1,000,000 in 2016
- Through pilot studies, transitioning step by step
- Make screening easily accesible, free of charge and results given online, within 10 days
- Awareness and communication are the key, among public and HCW

Implementation of regional HPV-based screening; Challenges and way forward to national implementation

- Italy
- National guidelines for HPV-based screening are available, however, implementation is regional, now in 19 / 21 regions
- Implementation started with older women: year 1 55-64; year 2 45-54; year 3 34-44
- From 600,000 invitations (2015) to nearly 1.5M (2018)
- Higher coverage in North than in Central and South Italy
- All programs use validated HPV test
- Screening vaccinated women: significantly lower hr-HPV prevalence
- Lower rate of immediate referral for colposcopy in vaccinated women
- Impact of Covid-19

Road map to implementation of HPV-based screening; Halted implementation, Challenges and way forward.

- Belgium
- Complex situation – Federal – Regional
- Decision to switch taken in 2019
- HPV roadbook with 14 action points
- Six working groups
- Implementation date as yet unknown

Triage : Currently available options, future opportunities and challenges

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.

- Screening coverage is low in low- and lower middle income countries, around 15%
- Screening coverage is low in Sub-saharan Africa, Central and South Asia, and Oceania (except AUS/NZL)
- Deciding the screening strategy: restrict to 30-49; based on self-sampling; HPV test; triage by VIA+AVE / genotype restriction; treatment by thermal ablation as first line
- Performace of AVE algorithms
  - As screening: AUC 0.95
  - As triage of HPV+: AUC 0.87

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.

- Treatment
- Ideally, treatment should immediately follow the triage test, to avoid loss to FU
- Thermal ablation is the easiest to manage
- A considerable proportion may not be treatable because of large lesions or invisible TZ
- Do we need to limit the screening capacity based on treatment capacity (+/- 0.6% of triage positive)?

  - Do we need to guarantee that treatment is offered with no delays and with trained personnel?

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.

- A Cervical Precancer Planning Tool was developed for country decision-makers (PATH)
- To inform national cervical precancer screening and treatment strategies.
- To explore trade-offs for screening and treatment approaches
- Data monitoring is critical to evaluate impact and may increase performance.
- While under COVID, cervical screening should be undertaken within safe environments or delayed

Multicentric Study of Cervical Cancer Screening and Triage With Human Papillomavirus (HPV) Testing- ESTAMPA

- Latin America
- To investigate the performance of emerging cervical cancer screening and triage techniques among women 30 years and older
- To evaluate the feasibility of different approaches for implementation of organised HPV-based screening programmes
- Triage tests: Pap, LBC, p16/ki67 dual-stained cytology, VIA, HPV genotyping, methylation
- Pap sensitivity was significantly higher in lab with smears only from HPV+
- VIA sensitivity possibly due to examiners with large expertise
- Adding Pap ASCUS+ to triage by HPV non-16/18 positives increased the sensitivity by ~10-15%
- Repeat HPV-test may be considered to avoid clinical visits (self-sampling)
- No single triage test offers a final answer yet

HPV Screening, Triage and HIV positives.

- HIV+ women more frequently have (persistent) HPV infections, precursor lesions and cervical cancers
- HPV prevalence is at least twice as high in HIV+ compared to HIV- women regardless of age (except for 60+)
- CIN2+ develops more quickly in HIV+ women
- HPV-type restriction and more stringent cut-offs on the Xpert HPV (Cepheid) to define a positive test prior to treatment, in order to optimise specificity
- Xpert-HPV as POC: preloaded; limited skills required; fully automated; limited hands-on time
- Specificity for HIV-negative women was 93% and for HIV-positive women was 82%
- High-quality treatment remains critical -> thermocoagulator
- Overtreatment may not be such a big issue as it may increase longitudinal sensitivity

Existing networks supporting implementation of cervical cancer prevention and control in low resource settings.

Existing networks: Findings, Current Perspectives and Way forward - JHPIEGO

- 5-I framework
  - Innovation
  - Investment
  - Information
  - Influence
  - integration

Existing networks: Findings, Current Perspectives and Way forward - PATH

- Scale-up project
- Introduction of HPV testing + triage + treatment
- careHPV, results within 1 mo
- Recall needed, needs to be optimized
- Introduction in real life is more difficult than scale-up
- Often too costly
- Need for low-cost, reliable HPV test

Organizing cervical cancer screening in the era of vaccination

- Vaccination has reduced the incidence (and prevalence) of cervical precancers caused by vaccine-targeted HPV types
- In consequence, it is having an impact on screening performance and practices shifting the balance of benefits to harms
- Modelling studies: combining vaccination and screening is cost effective and good value for money but screening would have to start later in life, and be done less frequently
- Lesion management guidelines will also need to be relaxed: risk of cervical precancer post-LSIL is lower among vaccinated than among unvaccinated

Organizing cervical cancer screening in the era of vaccination

- With high vaccination coverage HPV transmission will be kept at a minimum.
- HPV-based tests may eventually lose its clinical utility in identifying disease that has become so rare
- Screening has immediate and long-term risks for women's reproductive health.
- Although today, such risks are far outweighed by the benefits of screening, will this balance change in the future?

- We need to define society's risk tolerance to decide in 30-40 years on abolishing cervical cancer screening or doing only once or twice during a lifetime.

Impact of Covid-19 on cervical cancer screening programs

- Globally, 88% of screening services suspended
- Results in delayed diagnosis
- Skin cancer diagnosis went down
- Catch up needed to overcome disruption
- Impact on CRC much bigger

- Although we are in a Covid-19 pandemic, we are also in an HPV pandemic. Universal vaccination is the way out. If it can be done for polio, it can be done for HPV.