Cervical cancer

Prevention, screening and treatment of pre-cancer, diagnosis and treatment of cancer Guidance for MSF Operations

Reproductive Health and sexual violence care Working Group

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Index

SUMMARY

Objective of this document

The present document responds to a **field demand** for a position on **MSF´s role in prevention, screening and treatment of cervical cancer**. The document is meant to discribe MSF's position on different screening options and treatment approaches[1], priority target groups and actions to be taken. The previous version (2012) has been updated in 2017 since that more data are available on screening methods and on HPV vaccines.

Conclusions and recommendations

Cervical cancer is one of the leading causes of cancer death in women in the developing world. While the screening and treatment of cervical cancer is **not a priority** in MSF operations**, there** are **opportunities** for MSF to implement preventative activities, screening and/or treatment of cervical (pre) cancer as part of ongoing activities in MSF projects. In a number of MSF projects, **screening and treating of pre-cancerous lesions** can be justified as a relatively simple means to impact on cervical cancer-related morbidity and mortality. **Visual inspection (VIA / VILI)** is the 1st choice screening method: it allows a one-visit screen and treats approach and can be implemented in MSF project conditions and through **mid-level health staff.** The **VIA / VILI is justified** in contexts where cervical cancer **prevalence is particularly high**.

HIV positive women are specifically at risk and selected pilot projects for "screen and treat" will prioritise this group. **MSF experience over the last 4 years**[2] shows the feasibility of cervical pre-cancer screening and treatment activities within MSF projects. **A progressive extension** of "screen and treat" procedure as a minor additional activity where MSF treats a critical mass of women in its SRH activities **should be considered for selected programmes with high cervical cancer prevalence**. In these programmes focus will be on a single visit screening and treatment approach for women aged 30-49 years (WHO minimum recommendation, 2013). **Screening without having access to treatment for precancerous lesions is not to be considered**. **HPV (human papilloma virus) vaccination of female adolescents** is recommended in MSF settings, particularly in countries where prevalence of cervical cancer is high.

[1] The vaccine and diagnostic working groups were consulted on their specific areas of expertise

[2] Refer to "16 06 MSF and Cervical Cancer Prevention - Capitalization Report" Dr. Severine Caluwaerts for the RH and SV care working group

1. INTRODUCTION

Cervical cancer is one of the **leading causes of cancer death** in women in the developing world and the second cause of cancer death in women worldwide. 528,000 new cases were diagnosed worldwide in 2012. and 266.000 women died of cervical cancer.[3]

In low income countries, cervical cancer **follows the more devastating causes of death amongst women in reproductive age** (HIV, maternal conditions, intentional and unintentional injuries, TB, cardiovascular diseases). In low and middle-income countries malignant neoplasms are part of the five most important causes of death amongst women of reproductive age.

In developed countries, cervical cancer deaths decreased by approximately 74% in the last 50 years, largely due to widespread Pap smear **screening and early treatment**. More recently new forms of screening (visual and HPV DNA testing) suited for use in low-resource contexts have been explored, as well as preventive measures, specifically **vaccination**. As of December 2015, over 65 countries have introduced a national HPV vaccination programme targeting adolescents, a number of others have started pilot or demonstration programmes[4].

Cervical cancer is the cancer with the most **Quality Adjusted Life Years** (QALY) lost for a woman, especially in vulnerable populations (women with no geographical, cultural or financial access to screening). An estimated 95% of women in developing countries have never been screened for cervical cancer. The cure rate for invasive cervical cancer is closely related to the stage of disease at diagnosis and with the availability of treatment. If left untreated, cervical cancer is almost always fatal.

In almost all cases the primary underlying cause of cervical cancer is infection with **human papillomavirus (HPV).** Genital human papillomavirus (HPV) is a very common sexually transmitted infection; almost all sexually active adults will be infected with HPV at some point in their lives. There are at least 200 serotypes of HPV, but only a few cause cancers. Most HPV infections do not cause symptoms or disease, but persistent infection with some types of HPV is a prerequisite for cervical cancer and is also responsible for a proportion of other less common anogenital and oropharyngeal cancers. 15 serotypes are classified as high-risk and another three as apparent high-risk (26, 53, and 66). Studies in developed countries reflect that HPV 16 and 18 are most likely responsible for at least 70% of the invasive cervical cancers. Little data is available on HPV viruses responsible for cervical cancer in developing countries.

Most HPV infections (up to 90%) resolve spontaneously; those that persist may lead to the development of pre-cancer and cancer. It usually takes 10 to 20 years for pre-cancer lesions caused by HPV to develop into invasive cancer.

Immuno suppressed women (in MSF working environment this is mainly related to HIV infection) are **more susceptible** to HPV infection and the development of invasive cancer can be accelerated because: (1) Suppression of the immune system renders the cell lining of the lower genital tract - vulva, vagina and cervix - more susceptible to infection, (2) There is less spontaneous clearance of HPV and (3) The progress from low-grade lesion to invasive cancer is much more rapid.

Over the years, MSF involvement in specific health care for women has increased significantly. Obstetrics, and specifically emergency obstetric care, is at the forefront of the activities. Cervical cancer is **not amongst the most urgent** health needs encountered amongst assisted populations. However, **its occurrence is increasing** and, in some contexts, described as striking by MSF staff. Official data[5] in Haiti estimates the incidence of new cervical cancer cases at 3.000 per year. Cervical cancer related death in Haiti is estimated at 54/100.000/year; 30 times higher than in the US. MSF operations present **opportunities to weigh in upon the early detection and treatment** of pre-cancer and referral for diagnosis and treatment of cancer and palliative care for advanced disease, specific opportunities can and should be explored when they arise in relevant missions.

[3] http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/cervical-cancer-statistics
[4] http://apps.who.int/iris/bitstream/10665/251909/1/9789241511544-eng.pdf?ua=1
[5] Partners in Health, August 2010 http://www.pih.org/news/entry/curbing-cervical-cancer-in-haiti/

2. PREVENTION, SCREENING AND TREATMENT OF CERVICAL (PRE-) CARCINOMA AS PART OF MSF ACTIVITIES

Below four key components of cervical cancer control are listed. Potential role and approach of MSF in each of them is discussed:

2.1. PRIMARY PREVENTION: HEALTH EDUCATION AND HPV VACCINATION

Primary prevention means prevention of HPV infection and cofactors known to increase the risk of cervical cancer and includes: education and awareness-raising to reduce high-risk sexual behaviours, and HPV Vaccination and treatment of pre-cancer lesions.

2.1.1. Health education

Health education should focus on condom use and prevention and treatment of STIs. Condom use protects partially against HPV and almost completely against other STIs (incl. Chlamydia and Herpes Simplex Virus (HSV) infections, which are possible co-factors for cervical cancer). STI detection and treatment might reduce persistent HPV infection.

Recommendation
- Continuously assure and reinforce message on condom use and access to condoms in MSF projects. (Note: condoms are included in the SRH core package. Dual protection is advised.)

2.1.2. HPV Vaccination

Two vaccines have been developed against HPV: one by GSK (Cervarix) and one by Merck (Gardasil). A third vaccine, protecting against 9 HPV serotypes (Gardasil Nano) has recently (January 2016) been FDA approved. Overall, HPV vaccine prices varied widely from 2007 to 2016. In industrialized countries, the price ranged from US$ 100 to US$ 233 per dose and in developing countries from US$ 30 to US$ 100 per dose. Full vaccine coverage requires 2 doses for immunocompetent adolescents < 15 years (WHO recommendation, at 0 and at 6 months), for girls > 15 years and known HIV positive adolescents 3 doses are recommended.[6]
For GAVI eligible countries (GDP < 1550 dollar) the HPV vaccine is available at 4.5 dollars per dose. Most countries where MSF works are GAVI eligible. The GSK vaccine offers partial protection against papilloma virus: it works against HPV type 16/18 and there is some cross reactivity with other oncogenic strains. The vaccine should prevent at least 70% of cervical cancer cases in developed countries. For most countries in Sub-Saharan Africa limited data from pilot studies on HPV types are available. From all studies data show that HPV 16 and 18 play an important role in cervical cancer (60-70% of all cervical cancers are related to any of the 2 infections)[7]. The Merck vaccine will in addition also protect against type 6 and 11; these types do not cause cervical cancer but anogenital warts.

[6] http://www.who.int/immunization/diseases/hpv/en/
[7] Firnhaber et al.(2011) Seroprevalence of HPV vaccine types 6, 11, 16 and 18 in HIV-infected women from South Africa, Brazil and Botswana. J Clin virol Nov;52(3):265-8. http://www.ncbi.nlm.nih.gov/pubmed/21908233
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HPV vaccination does not replace cervical cancer screening. Continued screening will be needed in sexually active women who never received HPV vaccine, as well as in vaccinated women to prevent cancer from HPV types not included in the current vaccines. The CDC recommends since 2015 HPV vaccination of victims of sexual assault.[8]

However, advantages of HPV vaccination are not unequivocally clear yet:

- Before effects of the vaccine become evident on population level, there is high coverage needed and there is only limited data on long term protection (scarce data about efficacy after 8 years).
- The long-term efficacy in HIV positive women is not yet assessed (studies are in progress).
- Vaccination is the only long-term protection against HPV infection and most effective in the target groups of girls age > 9 years and teenagers prior to their first sexual intercourse. They are however not a population group MSF has systematic contact with through the usual range of activities. In the future HPV vaccination of boys may become a preventive strategy in MSF as well.
- Vaccines do not appear to have a therapeutic effect on pre-existing infections.
- For both vaccinated and unvaccinated sexually-active women, there is need for continued cervical cancer screening.

Conclusion

- HPV vaccination is the only primary prevention promising long term protection.
- Knowledge on the HPV serotypes responsible for the development of pre-cancer lesions and cancer in developing countries is low and thus, potentially there may be a coverage gap for the existing vaccines. A better understanding of how HPV behaves in developing countries is needed.

Recommendations

- Gather samples for HPV serotyping prior to cervical cancer screening and treatment procedure (VIA/VILI) when support to WHO and/or MoH is feasible or in a setting of operational research as planned in Zimbabwe.[9]
- Consider piloting HPV vaccination in projects where MSF deals with children. Focus on vaccination (2 in a 6-month period) of girls starting age 9 years and teenagers preferably prior to first sexual contact.

2.2. EARLY DETECTION OF PRE-CANCER LESIONS, SCREENING TECHNIQUES

Three screening techniques will be discussed here: 1) cytology, consisting of conventional Pap smear and liquid-based Pap smear, 2) visual diagnostic techniques like colposcopy and VIA/VILI, 3) HPV DNA testing.

2.2.1. Cytology

Conventional Pap smear and liquid-based Pap smear are the most common screening techniques used worldwide. Both techniques are comparable in terms of logistic and laboratory requirements – liquid based even has a higher sensitivity and specificity. Taking samples for diagnosis can be done on the condition that reliable laboratory facilities with a trained pathologist are present in a mission country with (MSF) capacity for transport of material and specimens is adequate, and follow-up care and patient information management are well-organized. The time between sampling and results is approximately 1 week in developed contexts. In case of positive detection this involves a minimum of two visits (diagnostic and treatment).

[8] https://www.cdc.gov/std/tg2015/sexual-assault.htm (Note: MSF does not recommend systematic HPV vaccination for rape victims in all projects, but rather a context and project specific approach)

[9] A pap smear like of liquid-based sample can be taken and sent to a referral lab. Complete serotyping will require laboratory capacity MSF does not have. The objective would be to **contribute to ongoing efforts** (e.g. via WHO reference labs) rather than advance on this as MSF.

Recommendations

- Consider collecting Pap samples in contexts with existing (non-MSF) large-scale cervical cancer screening programmes with primary entrance point PAP screening and where laboratories with high quality histopathology facilities are available in the country.
- First consider the availability and quality of in-country laboratory facilities offering histopathological diagnosis.
- First assess availability and quality of in-country referral health facilities and their ability to handle cervical cancer, their quality of reporting and quality of patient recall systems.
- Start collecting Pap samples if quality of labs and health facilities assessed is satisfactory. Follow national guidance frequency of Pap smears.

2.2.2. Visual diagnostic techniques

Colposcopy

The standard practice for diagnosis of cervical (pre) cancer involves colposcopy, biopsy and endocervical curettage if necessary. Colposcopy allows a close inspection of an illuminated, magnified view of the cervix and the tissues of the vagina and vulva. It is used mainly for further investigation after an abnormal screening result. However, colposcopes are sophisticated, relatively expensive instruments. The technique requires specific training, experience, and equipment (magnifying device + light source); it can be used for diagnosis only.

Recommendation

- Not recommended in any current MSF context for reasons mentioned above

Visual inspection using acetic acid (VIA) and Lugol's iodine (VILI)

VIA and VILI[10] are promising alternatives to cytology where resources are limited. They do **not rely on laboratory services**[11] and can be performed by **mid-level providers**.

In research settings, VIA has been shown an average sensitivity for detection of pre-cancer and cancer of almost 77% (95% CI: 56-94) and a specificity of 86% (95% CI: 74-94). One study has shown that VILI can detect 92% of women with pre-cancer or cancer, a sensitivity considerably higher than that of either VIA or cytology. Its ability to identify women without disease is similar to that of VIA (85%) and only slightly lower than that of the conventional Pap smears[12]. Both, VIA and VILI, are **simple, painless procedures** with **immediate result** and **no specimen referral**.

VIA and VILI are currently being tested in large, cross-sectional, randomised controlled trials in developing countries. Initial feed-back on sensitivity and specificity are seen to be close to those observed in conventional Pap smears. The ongoing trials highlight the cost-effectiveness of VIA/VILI in low resource settings as well as the important advantage of the single visit screen-and-treat approach. WHO (2013) stresses the feasibility and importance of VIA/VILI cervical cancer screening particularly in countries with not enough resources to provide HPV testing as first entrance point for the test and treat cascade.

Advantages

- VIA and VILI are relatively simple and can be taught to nurses, nurse-midwives and other health workers (mid-level providers).
- Immediate result. There is no need for transport, laboratory personnel or equipment.
- Visual inspection with VIA/VILI offers the opportunity to provide immediate treatment in single-visit approach.
- Cost effective.

[10] Inspection of the cervix, which is swabbed either with iodine (affected areas will not absorb color in the same way health cell tissue does) or acetic acid (results in a whitish coloring of cells with a different cell structure than normal mucous lining of the vagina and cervix).

[11] **Necessary material**: Examination table, light source, Bivalved speculum, instrument tray, cotton swabs, examination gloves, 3-5% dilute acetic acid, Lugol's iodine solution, 0.5% chlorine solution, report-form for documentation of results.

[12] Examples of recent studies in the references. Diagnostic Value of VIA Comparing with Conventional Pap Smear in the Detection of Colposcopic Biopsy Proved CIN

Disadvantages

- The positive predictive value is slightly lower than that of a conventional Pap smear and in some studies not more than 20%. For both screening methods more than half of the women in a general population undergo treatment unnecessarily. However, in high prevalence population groups, the proportion of women undergoing unnecessary treatment is reduced.

Conclusion

- Visual inspection has diagnostic value comparable of that to a conventional Pap smear. The test allows and single visit screen-and-treat approach and the technique is suitable for cervical cancer screening in resource-poor settings.
- **Visual diagnosis** using VIA or VILI as part of a single-visit screen and treat approach seems most appropriate and feasible in the contexts where MSF is generally working.

Recommendations

- Start screening women in **HIV/AIDS programs**. They represent a priority target group due to their increased vulnerability to infection and cervical cancer development.
- **A progressive extension** of "screen and treat" procedure as a minor additional activity where MSF treats a critical mass of women in its SRH activities **should be considered for selected programmes with high cervical cancer prevalence**. In these programmes focus will be on a single visit screening and treatment approach for women aged 30-49 years (WHO recommendation).
- Any screening effort needs to be **accompanied by effective treatment** either as part of MSF care or through an accessible third party actor offering reliable/consistent quality of care.
- Pre-cancer screening and treatment should be offered on an outpatient basis whenever feasible.
- At the start up of screening activities in MSF programs, be prepared to find cases of **advanced stage cervical cancer** and related challenges: (1) absence of effective means of diagnosing, staging and treating cervical cancer in the country (2) the need for MSF capacity regarding surgical interventions and specifically oncology surgery (3) organization and follow-up of patients for treatment at tertiary level, (4) Palliative care for late stage cases where there are no other treatment options.
- Photographic **recording** is recommended to (1) document the diagnostic and (2) permit quality control of diagnostic and (3) teaching. Consent should be obtained for medical photography.

2.2.3. HPV-DNA testing

Currently, WHO recommends human papillomavirus (HPV) DNA as preferred entrance gate for screening if the health care system has enough resources to provide a HPV test.[13]
HPV DNA tests can be used as a primary screening method. Women testing positive with HPV DNA still need to undergo cytology or visual screening to confirm the diagnosis. HPV DNA-based screening should not begin before 25 years of age as in younger women there is a higher chance of spontaneous clearance of HPV. A cocktail hybrid HPV DNA test detects 13 high-risk HPV variants.

Over 15 studies have consistently shown that the use of HPV DNA tests as the primary screening method is significantly more sensitive than cytology-based screening (Pap) to detect cervical cancer or pre-cancer lesions. However, the disadvantage is that HPV DNA tests are less specific (8-12% loss of specificity compared to Pap smear). In addition, DNA based test are expensive (Belgium 25 euros per test).

Both VIA and primary HPV screening have been shown to be more cost-effective than PAP in low-resource settings. HPV is the most cost-effective method in a once-in a lifetime screening strategy. For other screening strategies (ie once every 3-5 years) data on most effective screening strategy are lacking or non-consistent.[14]

[13] http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf
[14] https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.30695

Advantages
- Significantly more sensitive than cytology-based screening as a primary screening method
- If a woman is tested HPV negative, the chance of her developing cervical cancer in the next 5-10 years is extremely low
- GeneXpert based HPV screening is feasible and already performed in pilot studies in several Sub-Saharan countries (South-Africa, Zambia). Results are available the same day (after 2-3 hours or even quicker).
- Possibility of self-swabbing and less provider dependent/time consuming than screening with VIA/VILI.

Disadvantages
- When HPV DNA testing is positive, visual inspection will still be needed if not there will be major overtreatment.
- HPV DNA Tests are relatively expensive and currently not widely available. Only 8 countries implemented (November 2016) HPV screening as a primary screening method and all are high or middle income[15].

Conclusion
- HPV DNA has high potential as a first line screening method and can be combined with a visual diagnostic and treatment in one visit if the health care system has enough resources to provide HPV testing

Recommendations
- Primary HPV screening is recommended as operational research/pilot project in some current MSF contexts
- Follow further development of HPV DNA rapid testing; specifically its potential for use in MSF projects

2.3. TREATMENT OF PRE-CANCER LESIONS

An alternative to first-world diagnosis and treatment (colposcopy, biopsy and endocervical curettage) consists of the **screen-and-treat** approach, where treatment decisions are based on the results of the screening test, without prior diagnostic test. The most practically feasible screening test *at the moment* for most resource-poor settings is VIA/VILI unless the healthcare system has enough resources to provide primary HPV screening.

Cryotherapy, electrosurgical loop excision procedure (LEEP) and cold knife conisation are suitable methods for treatment of lesions detected by VIA/VILI, depending on eligibility criteria and available resources. **Cryotherapy and LEEP are outpatient treatment options**. Cryotherapy is the easiest and least costly treatment method for pre-cancer as it does not require extensive of training and can be easily taught to midwives and other mid-level health providers. However, LEEP is the treatment of choice when the lesion is too large for the cryoprobe or involves the endocervical canal. The two methods have comparable effectiveness.

Advantages of screen-and-treat approach
- Infrastructure and equipment are simpler and less costly
- Screen and treat can be managed by mid-level health care providers
- Decreased loss to follow-up and treatment
- Lowers burden for women by reducing number of visits
- Highly acceptable to women and providers

Limitations of screen-and-treat approach
- No specimen available for later evaluation, unless biopsy taken before treatment
- Concerns of overtreatment and under treatment

[15] http://www.cervicalcanceraction.org/comments/comments2.php

Conclusion

- A **single visit screen-and-treat approach** is most appropriate and feasible in most contexts where MSF is usually working. Therefore, **visual diagnostics** (VIA and VILI) combined with treatment of pre-cancer lesions by **cryotherapy** should be favoured when pursuing cervical cancer screening and treatment is in MSF operations.

Recommendations

- Ensure treatment of pre-cancer lesions on an out-patient level whenever possible
- Train **mid-level health providers** in the use of cryotherapy
- Use **cryotherapy** as a primary treatment choice and electrosurgical loop excision for larger lesions or those involving the endocervical canal

2.4. DIAGNOSIS AND TREATMENT OF CERVICAL CANCER AND PALLIATIVE CARE

Health care providers at all levels should know the common symptoms and signs of (invasive) cervical cancer. If a woman consults with such symptoms, her cervix should be examined visually to determine whether further testing is needed. Referral to a validated tertiary structure if possible for curative radiotherapy and/or surgery, with or without chemotherapy. Potential cure is very closely related to stage of disease at moment of cancer diagnosis. Palliative care prior to referral should already be instigated at MSF project level. However in most MSF settings adequate referral options will not exist and care should be focused on palliation: pain management, treatment of infections and blood transfusion.

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