Ministry of Health of the
Republic of Moldova

National Society of
Pathology of Moldova

Assessment of Cervical Cytology Services in the Republic of Moldova and Recommendations for their Reorganisation to Comply with International Evidence-Based Standards

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Abbreviations:

AGUS	Atypical Glandular Cells of Undetermined Significance
ASCH	Atypical Squamous Cells cannot exclude High-grade
ASC-US	Atypical Squamous Cells of Undetermined Significance
BNS	Biroul Naţional de Statistică al Republicii Moldova / National Bureau of Statistics of the Republic of Moldova
CIN	Cervical Intraepithelial Lesion
CME	Continuing Medical Education
CNAM	Compania Nationala de Asigurari in Medicina / National Medical Health Insurance Company
CRIO	Cancer Registru din IMSP Institutul Oncologic / Cancer Registry of the Institute of Oncology
CSP	Cervical Screening Programme
DoM	Date of Manufacture
EECA	Eastern Europe and Central Asia
FIGO	International Federation of Obstetrics and Gynaecology
FTE	Full Time Equivalent (Full Time Salaried Position)
HSIL	High-grade Squamous Intraepithelial Lesion
ICCPA	International Cervical Cancer Prevention Association
IO	Institute of Oncology
LSIL	Low-grade Squamous Intraepithelial Lesion
MoH	Ministry of Health
MHO	Ministry of Health Order
NSPM	National Society of Pathology of Moldova
PHC	Primary Health Care
QA	Quality Assurance
RDC	Republican Diagnostic Centre
RM	Republic of Moldova
SOPs	Standard Operating Procedures
TBA	To be added
UNFPA	United Nations Population Fund
USMF	Universitatea de Stat de Medicina si Farmacie “Nicolae Testemitanu”/ State University of Medicine and Pharmacy “Nicolae Testemitanu”

Executive Summary

In 2015, cervical cytology laboratories in the Republic of Moldova (RM) reported processing 236,579 Pap tests, which is enough to screen about 72.3% of the target population. Well organised cervical screening programmes with 70% or more coverage of the target population in Western Europe have achieved reductions in cervical cancer rates of up to 80%. Therefore, similar reductions should be seen in RM but the data presented in this report instead show that cervical cancer incidence and mortality rates increased steadily from 2000 until 2011 when they plateaued at very high levels and have since shown no improvement whatsoever.

Therefore, the main issue with cervical cancer prevention in RM is not whether there is enough money to provide cervical screening (as the services already being paid for would be sufficient to screen 72.3% of the target population), but rather why all the resources that are currently being expended on these services are not producing any results.

The reason for this has been explained to the Ministry of Health many times: cervical screening in RM is being conducted opportunistically without proper staff training, standardisation of procedures, coordination of the component health services, effective patient management or quality assurance (QA). It therefore will not reduce cervical cancer rates but instead increase the harms and costs of screening.

The solution to this has also been explained to the Ministry of Health many times: effective measures need to be taken to organise cervical screening, with a key priority being the cervical cytology services because they currently have no evidence-based, nationally approved:

- Training curricula, standards or certification criteria,
- Working practice recommendations,
- Performance indicators, performance standards or QA procedures,
- System to monitor and evaluate cervical cytology and ensure compliance with international, evidence-based recommendations.

As a result, there are no mechanisms to:

- Ensure the people screening Pap tests (cyto-screeners) have the skills to do their job properly,
- Ensure cervical cytology laboratories comply with evidence-based best practice recommendations,
- Objectively measure the performance of cytology laboratories and cyto-screeners,
- Identify and improve suboptimal performance.

The impact this has on the cost-effectiveness of cervical screening is clearly demonstrated by the simple fact that *it is not having any effect on cervical cancer rates*. In addition, 10 of 18 laboratories reported processing a number of Pap tests that would be sufficient to screen between 75% and 374% of their catchment populations. Considering that coverage rates of 70% or more have only been achieved by well organised screening programmes in high-income countries, the rates reported in RM likely reflect the screening of women outside the recommended age range of 25-61 years, screening women more frequently than the recommended 3-year interval and/or over-reporting the number of Pap tests screened. These are serious concerns because the screening age range and interval are set to optimise the balance between the benefits and harms of screening, so screening women outside the recommended age range or interval will not improve cervical cancer rates but will increase the harms caused to the women being screened and increase the cost of screening.

The quality of the cervical cytology in RM is also of serious concern as evidenced by large variations in the proportions of Pap test results between laboratories. Among the 7 largest laboratories, the proportions of abnormal results varied 19 times from 0.32% to 6.06% and unsatisfactory results varied from 0.0% to 5.70%, while the proportions of equivocal, low-grade and high-grade results varied by 16 times, 118 times and 105 times respectively. Given that cervical disease rates will be similar across RM, these large variations in Pap test results will be due to equally large variations in service quality. Finally, the rates of high-grade results were too low and indicate that a substantial amount of high-grade pre-invasive cervical disease is being missed so it will not be treated and many of these women will go on to develop invasive cervical cancer.

The current situation with cervical cytology in RM is unethical and unsustainable. Therefore, it is now essential to reorganise these services to improve their quality, safety and cost-effectiveness.

The most important issue to be addressed is the urgent closure of the 18 cervical cytology laboratories that could not comply with even the most basic international recommendation that laboratories should screen a minimum of 15,000 Pap tests per year to ensure cyto-screeners are regularly exposed to the full range of cytology abnormalities needed to maintain their recognition skills. In this regard, the mean and median number of Pap tests processed by these 18 laboratories in 2015 were 3,803 and 4,683 respectively, which are both far below the recommended minimum number.

In addition, the other priority issues that must be addressed are:

- Strengthen capacities to continuously monitor and evaluate the remaining 7 cervical cytology laboratories to ensure they comply with international recommendations and encourage compliance with these recommendations through the use of performance-based payments.
- Progressively change from Romanowsky staining to Papanicolaou staining during the course of 2017.
- Enforce the cervical screening age range and interval.
- Prepare and approve an evidence-based training curriculum for cervical cytology screening.
- Designate cervical cytology screening as a distinct laboratory specialty with defined training standards and certification criteria.
- Prepare and approve an evidence-based working practice recommendations.
- Prepare and approve an evidence-based cervical screening laboratory facility and equipment specifications.
- Prepare and approve an evidence-based QA programme with performance indicators and standards.

Finally, the 7 laboratories that do meet the recommended minimum of 15,000 Pap tests per year should be given a period of 2 years to comply with the new training and certification requirements, working practice recommendations and performance standards specified in the QA programme. Then, any laboratories that do not achieve these criteria should be closed and their Pap tests redirected to the laboratories that can.

1. Introduction

Globally, cervical cancer is the 3rd most common cancer among women with more than 530,000 new cases and 275 000 deaths every year.[1] Most cases occur in low and middle-income countries where there are no cervical cancer prevention programs. In Europe, about 60,000 women develop and 30,000 women die from cervical cancer every year. Eastern Europe has substantially higher rates of cervical cancer than Western Europe and this is primarily due to the extensive opportunistic screening or nationally organised cervical screening programs in Western Europe.[2]

Cervical screening works by detecting *pre-cancerous* cervical lesions that can be removed using simple, effective and inexpensive outpatient procedures so the invasive cancers do not develop. Cervical screening will also detect invasive cancers but, by definition, these will be asymptomatic cancers and therefore in the earlier stages when treatment is less invasive, less expensive and more effective than for cervical cancers identified on the basis of clinical symptoms. Cervical screening programmes can reduce both the incidence as well as the mortality of cervical cancer by up to 80%. However, reductions of this magnitude will only be produced by well organised programmes in which a large proportion (70% or more) of the target population is regularly screened, all the component services are of high quality, all the services are efficiently coordinated and all women with a positive screening test are properly followed-up and any clinically relevant disease is treated.[3]

An important consideration with cervical screening programmes is that while they can provide substantial benefits, they can also cause a wide range of harms (see Table 1).[4] These harms are rare in well-organised programmes, but screening is applied to populations so the number of people affected can still be very large. Because of this, the European Guidelines for Quality Assurance in Cervical Screening (the European Guidelines) recommend that cervical screening should be delivered only through organised programmes.[5]

Table 1: Harms Inherent in Cancer Screening Programmes	
1	False negative screening test results leading to delays in cancer diagnosis or treatment.
2	False positive results leading to unnecessary stress, anxiety and invasive diagnostic procedures that carry a risk of complications.
3	Over-diagnosis through the identification of disease with no true malignant potential or that would not become clinically relevant during the individual's lifetime.
4	Over-treatment through the treatment of disease with no true malignant potential or that would not become clinically relevant during the individual's lifetime.
5	Unnecessary adverse sequelae such as premature membrane rupture and premature delivery in women who have been treated for cervical intraepithelial neoplasia (CIN).
6	Unnecessary costs arising from all of the above, which take health care resources away from services that could otherwise provide greater benefits for the population.

A report prepared for the United Nations Development Programme RM found the incidence of all cancers has steadily increased with cervical cancer found to be the most common cancer among women in 2011 when it accounted for 39.3% cases, the proportion of cervical cancers diagnosed in the late stages (FIGO stages 3 & 4) increased from 36.8% in 1990 to 56.1% in 2011, and the proportion of women surviving for 5 years or more decreased from 70.4% in 2000 to 61.5% in 2011.[6] In addition, data from the newly re-established Moldovan National Cancer Registry indicate that crude cervical cancer incidence and mortality rates are very high and have remained stable at 16.4 and 8.7 per 100,000 (average) respectively from 2009 to 2015.[7] These data show that the cervical screening conducted in RM is not effective so most cervical cancers are diagnosed on the basis of clinical symptoms that only appear in the late stages of this disease.

Recognising the seriousness of this situation, the United Nations Population Fund (UNFPA) RM Country Office began advocating for the implementation of a national organised cervical screening programme (CSP) in 2008, with the European Cervical Cancer Association (now the International Association for Cervical Cancer Prevention – ICCPA) participating from 2010. The UNFPA and the ICCPA have since remained actively involved, providing financial support and technical assistance at key junctures to guide activities and maintain progress.

One of the significant achievements of this process was the preparation and publication in February 2014 of a consensus agreed action plan to build the health service capacities needed to deliver the organised CSP.[8] A key element of this action plan the undertaking of a detailed assessment of cervical cytology capacities in RM to obtain the data required for reorganising these services to optimise their cost-effectiveness and bring their quality into line with international recommendations, including the European Guidelines. The outcomes of this assessment are now presented in this report.

2. Cervical cytology

2.1 Cervical cytology screening vs. cytopathology

Cervical cytology screening vs. cervical cytopathology:

- Cervical cytology screening is the process of examining Pap tests to find any abnormal cervical cells that may indicate the presence of clinically relevant cervical pre-cancer or cancer. In most of Western Europe, cervical cytology screening is conducted by specially trained laboratory technicians (cyto-screeners) who sign-off Pap tests when no abnormal cells are found and refer Pap tests with abnormal cells to a cytopathologist.
- Cervical cytopathology is the process of examining and classifying the abnormal cells that have been found by the cyto-screeners and proposing appropriate procedures to follow-up the women. This will be conducted by medically qualified doctors who have undertaken a cytopathology residency programme.

2.2 Cervical screening working practice recommendations

The test most commonly used for cervical screening is cervical cytology (the Pap test). Here it is essential to recognise that the use of cytology for screening is completely different from its use for diagnosis. Cervical screening is applied to asymptomatic women so the vast majority (about 90%) of Pap tests will be negative. Therefore, the objective of the cyto-screener is to identify the few specimens that have cytological abnormalities indicating the presence of clinically relevant cervical disease.

Screening cervical cytology specimens is a mentally tiring process so the European Guidelines have set working practice recommendations designed to ensure cyto-screeners will be alert when they are screening so their performance will not be compromised (see Table 2). In addition to these, many countries also limit the number of Pap tests that can be screened by each cyto-screener per day to between 40/day and 80/day, depending on the country.

Table 2: European Guidelines working practice recommendations for cervical cytology laboratories

- Each period of continuous screening should be ≤2 hours,
- Total time spent on primary screening/day should be ≤6 hours,
- Each laboratory should process ≥15,000 Pap tests/year so cyto-screeners continuously see a full range of abnormal cytology results,
- Each laboratory should have ≥4 cyto-screeners to enhance collaborative learning and ensure service provision during holidays, sick-leave, etc.

2.3 Cervical cytology processing techniques

There are 3 main cervical cytology techniques: conventional cervical smears processed by the Romanowski technique, conventional cervical smears processed by the Papanicolaou technique, liquid based cytology (LBC)

2.3.1 Conventional cervical smears – the Romanowsky vs Papanicolaou technique

The majority of cervical cytology in RM is currently processed using conventional cervical smears stained using Romanowsky technique. The use of this technique for cervical screening is largely restricted to the countries of the former Soviet Union and most cervical cytology in rest the world is stained by the Papanicolaou technique.

These 2 techniques use completely different staining processes so the cytological interpretation is also different and laboratories specialised in one technique cannot train cyto-screeners to work in laboratories using the other. This is very important for RM because, as clearly demonstrated by the wide variation in the proportions of abnormal Pap tests between laboratories, there is an urgent need to improve the quality of cervical cytology here. This can be most cost-effectively achieved through training exchanges with countries that have high quality cervical cytology but all these countries use the Papanicolaou staining technique. Therefore, continuing to use the Romanowsky staining technique in RM will prevent cervical cytology laboratories here from achieving internationally recognised evidence-based standards.

2.3.2 Conventional cytology vs liquid-based cytology

For conventional cervical cytology, cells collected from the cervix are spread on a glass microscope slide, preserved with a fixative liquid and the slide is then sent to the laboratory. In contrast, for liquid-based cytology (LBC), the cells collected from the cervix are placed directly into a vial of fixative liquid and the vial is sent to the laboratory where the cells are used to prepare a monolayer on the glass microscope slide.

The performance of conventional cytology vs LBC has been extensively studied with the conclusion being that the sensitivity and specificity are the same. However, these studies also concluded that LBC:

- Facilitates screening and interpretation by the uniform presentation of cervical cells on the glass slide.
- Reduces the number of inadequate specimens in environments where this is a problem,
- Reduces the time required to screen each specimen by ≤30%,
- Allows additional testing to be conducted without having to recall women (HPV, chlamydia, etc.).

All these characteristics can improve the cost effectiveness of cervical screening. However, the cost of the LBC reagents and equipment are higher than for conventional cytology so a cost-benefit analysis is needed to see if the savings achieved by the efficiencies would be sufficient to offset the higher costs.

3. Methods

In order to facilitate this report, a partnership was established between the National Society of Pathology of Moldova (NSPM) and the Italian Society for Pathology and Cytopathology (Società Italiana di Anatomia Patologica e Citologia – SIAPEC).

Population data for 1 January 2016 stratified by sex, age and region were obtained from the Biroul Naţional de Statistică al Republicii Moldova (BNS).[9] The annual cervical cytology screening requirement was then calculated by dividing the total number of women aged 25-61 by 3 (for the 3-year screening interval) and multiplying by the expected maximum coverage of 75% plus 15% for repeat and follow-up Pap tests.

All public sector cervical cytology laboratories were identified through the database of the RM National Health Insurance Company (Compania Naţională de Asigurări în Medicină – CNAM) which, as the organisation with responsibility to pay for these services, has complete records. In addition, all private sector cervical cytology laboratories were identified either through the CNAM database if they had contracts with public institutions or though the NSPM whose members work in these laboratories.

A comprehensive questionnaire was prepared to ensure uniform collection of data from each laboratory on the number of Pap tests processed together with the Pap test results, the number and qualifications of staff, the capacities and condition of facilities, and the types and condition of equipment. This questionnaire was approved by the Ministry of Health (MoH) and sent to all laboratories for completion under Ministerial Order.

The proportions of Pap test results across the 7 largest laboratories were compared using the Chi-square test for equality of proportions. Year to year changes in cervical cancer incidence and mortality were evaluated by fitting a linear model to the respective rates and calculating the p-values for the slopes.

Twenty-five of 28 laboratories were visited from 14-18 March 2016 to collect the completed questionnaires, verify the data and resolve inconsistencies in the datasets. Three laboratories did not participate.

4. Results

4.1 Cervical cancer rates and stage at diagnosis

Data from a report prepared for the United Nations Development Programme RM shows the incidence of all cancers increased steadily from 2000 to 2011, when cervical cancer was found to be the most common cancer among women, accounting for 39.3% cases.[10] Meanwhile, data from Moldovan National Cancer Registry show that cervical cancer incidence and mortality have remained high and without any statistically significant improvement since 2009 (see Table 3 and Figure 1).[7] In addition, the proportion of late stage diagnoses (FIGO stages III & IV) has remained very high and stable at about 50% over the period from 2009-2015 (see Figure 2). Here it should be noted that the denominators for the incidence and mortality rates are estimates based on the 2004 census and the true at-risk population may be smaller due to persistent high levels of emigration. Therefore, the actual rates may be even higher.[11]

Table 3: Cervical cancer incidence and mortality

	2009	2010	2011	2012	2013	2014	2015	P-value
Incidence	16.8	15.5	17.2	16.8	16.3	16.5	15.6	0.509
Mortality	8.7	10.4	8.0	8.2	8.7	9.2	8.1	0.585

Figure 1: Cervical cancer incidence & mortality

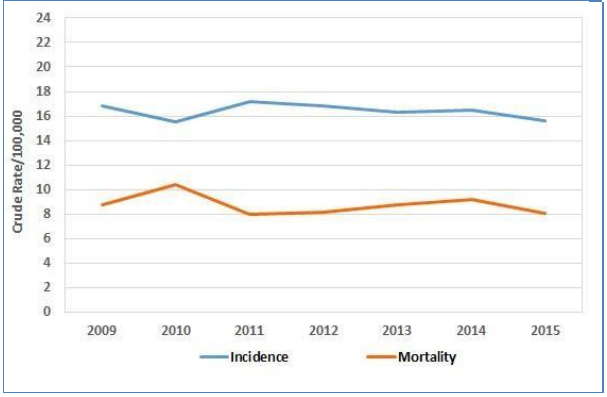
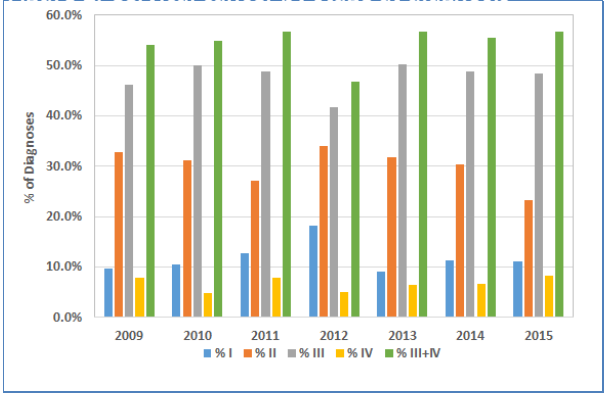


Figure 2: Cervical cancer by stage at diagnosis



4.2 Cervical screening target population

Data obtained from the BNS indicated there were ≈982,093 women aged 25-61 (inclusive) in RM as of 1 January, 2016.[9] This leads to an estimated total annual cervical screening requirement of 282,352 women based on the calculation: 982,093 ÷ 3-year screening interval x 75% anticipated maximum coverage + 15% for repeat and follow-up Pap tests (see Appendix 1).

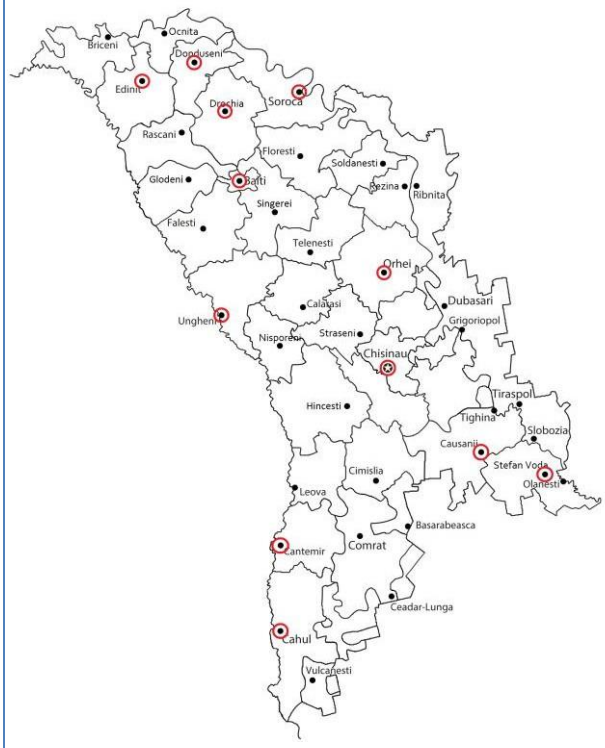
4.3 Number & location of cervical cytology laboratories

The consultation with CNAM and NSPM identified a total of 28 laboratories (22 public sector and 6 private sector) that provide cervical cytology screening services in RM (see Table 4 and Figure 3).

Table 4: Laboratories processing Pap tests in RM

	Laboratory	Paps/Yr
Northern region		
1	Balti - Immunotehnomed (Public-Private-Part.)	21,470
2	SR Donduseni	3,803
3	SR Drochia	2,345
4	CS Drochia	3,663
5	CS Edinet	7,682
6	SR Edinet	23,773
7	CS Soroca	8,590
Central region (including Chisinau)		
8	SR Orhei	3,745
9	SR Ungheni	17,900
10	Chisinau - AMT Botanica	18,230
11	Chisinau - AMT Centru	22,285
12	Chisinau - AMT Ciocana	TBA
13	Chisinau - AMT Riscani	11,622
14	Chisinau - Hospital of the State Chancellery	668
15	Chisinau - Policlinic of the State Chancellery	543
16	Chisinau - Institutul de Medicina Urgenta	1,084
17	Chisinau - CM Galaxia (private)	7,035
18	Chisinau - CM Pro Sano (private)	282
19	Chisinau - CM Sf. Pantelemon (private)	2,267
20	Chisinau - Morformed Service (private)	TBA
21	Chisinau - Neomedica Grup (private)	TBA
Republican facilities		
22	Institute of Oncology	29,267
23	Republican Diagnostic Centre	37,000
24	Institute of Mother & Child	845
Southern region		
25	CS Cahul	13,043
26	SR Cantemir	4,100
27	SR Causeni	6,710
28	CS Stefan Voda	5,523

Figure 3: Geographical distribution of cervical cytology laboratories in RM



4.4 Cervical cytology laboratory staff

This analysis found that 28 cytopathologists and 33 laboratory technicians were involved in the provision of cervical cytology screening services in RM.

Table 5: Cervical cytology laboratory staff

Cervical cytology laboratory		Cyto-pathologists	Laboratory technicians		Cervical cytology laboratory	Cyto-pathologists	Laboratory technicians
Northern Region				15	State Chancellery Policlinic	1 x FTE	-
1	Balti - Immunotehnomed	1 x FTE	4 x FTE	16	Institutul Medicina Urgenta	1 x FTE	2 x FTE
2	SR Donduseni	1 x FTE	1 x FTE	17	CM Galaxia	0.25 x FTE	1 x FTE
3	SR Drochia	1 x FTE	-	18	CM Pro Sano	1 x FTE	-
4	CS Drochia		-	19	CM Sf. Pantelemon	1 x FTE	1 x FTE
5	SR Edinet	1 x FTE	1 x FTE	20	Morformed Service	TBA	TBA
6	CS Edinet	1 x FTE	1 x FTE	21	Neomedica Grup	TBA	TBA
7	CS Soroca	1 x FTE	1 x FTE	**Republican Facilities**			
Central Region				22	Institute of Oncology	3.25 x FTE	4 x FTE
8	SR Orhei	1 x FTE	1 x FTE	23	Republican Diagnostic Centre	1.25 x FTE	3.5 x FTE
9	SR Ungheni	1 x FTE	1 x FTE	24	Institute of Mother & Child	3 x FTE	2 x FTE
10	AMT Botanica	0.5 x FTE	2 x FTE	**Southern Region**			
11	AMT Centru	0.5 x FTE	3 x FTE	25	CS Cahul	1 x FTE	1 x FTE
12	AMT Ciocana	-	-	26	SR Cantemir	1 x FTE	-
13	AMT Riscani	1.25 x FTE	1.5 x FTE	27	SR Causeni	1 x FTE	-
14	State Chancellery Hospital	2 x FTE	2 x FTE	28	CS Stefan Voda	1 x FTE	-

Within Chisinau, it was common for cytopathologists and laboratory technicians to work at more than 1 laboratory and in these cases, the full-time equivalent (FTE) per person was attributed to each laboratory in proportion to the annual number of Pap tests it processed (see Table 5).

These data indicate the total number of laboratory technicians would be more than sufficient to meet the screening requirements of a fully operational cervical screening programme in RM with 75% coverage of the target population and using the limit of 67 Pap tests/cyto-screener/day set previously by MHO № 68 of 10 March 2005 (282,352 Pap tests/year ÷ 67 Pap tests/cyto-screener/day x 240 working days/year = 18 full-time cyto-screeners), depending on the amount of work these people are required to do for other health services.

4.5 Cervical cytology staining techniques

All cervical cytology laboratories reported they currently stain Pap tests using the Romanowsky method.

4.6 Cervical cytology laboratory equipment

As all RM laboratories use the Romanowsky staining technique, only simple manual slide staining equipment is used to prepare Pap tests for microscopic examination. In addition, a total of 50 microscopes were reported. The date of manufacture (DoM) was not specified for 15 microscopes but all of the remaining 35 were manufactured since 2001 with most being inexpensive but serviceable makes/models with an appropriate range of objectives. The microscopes and other equipment reported by the laboratories are listed in Table 6.

Table 6: Cervical cytology laboratory equipment

	Cervical cytology laboratory	Microscopes	IT equipment	Other equipment
Northern Region				
1	Balti - Immunotehnomed	4 x Leica DM1000 (2015)	Soohoo PC (2015)	
2	SR Donduseni	1 x Max-Bino II (2007); 1 x Max II (2008)		
3	SR Drochia	1 x Nikon (DoM/model not specified)		
4	CS Drochia	1 x Biolam (DoM/model not specified)		
5	SR Edinet	1 x ERMA EZ-232; 1 x XSZ-20 (DoM not specified)		
6	CS Edinet	1 x Nikon YS100 (2007)		
7	CS Soroca	2 x KRUSS MBL2000 (2005)		
Central Region				
8	SR Orhei	2 x Nikon YS100 (2001 & 2004)	2x HP DX 2200	
9	SR Ungheni	1 x Biolam S13 (1980); 1 x XSZ-20 (2007)		
10	AMT Botanica	1 x binocular (DoM/model not specified)		
11	AMT Centru	1 x Ningbo XS-910 (2009)	PC workstation	1 x Fume hood; 1 x Reagent cabinet; 1 x Archive cabinet
12	AMY Ciocana	TBA	TBA	TBA
13	AMT Riscani	1 x ERMA-1502 (2004) 1 x Ceti Magnum B (2010)	ACER PC	
14	State Chancellery Hospital	2 x LOMO Micmed-6 (DoM not specified)		
15	State Chancellery Policlinic	1 x ERMA EZ-232 (2007)		
16	Institutul Medicina Urgenta	1 x Olympus BX41 (2002)	ASUS PC (2013)	
17	CM Galaxia	1 x ERMA EZ-232 (2005)	LG PC	
18	CM Pro Sano	1 x XSZ-107BN (2001)	Hantol PC (2014)	
19	CM Sf. Pantelemon	1 x KOZO XJS301 (2015)		
20	Morformed Service	TBA	TBA	TBA
21	Neomedica Grup	TBA	TBA	TBA
Republican Facilities				
22	Institute of Oncology	4 x T-Bota XSZ-158 (2014) 2 x KRUSS MBL2000 (DoM not specified) 5 x Binocular (DoM/model not specified)		
23	Republican Diagnostic Centre	4 x Olympus CX22LED (2014) 1 x Leica (2010/model not specified)	ASUS PC (2014)	1 x BD LBC Prepstain
24	Institute of Mother & Child	1 x Nikon (2001/model not specified) 1 x Micros MCX51 (DoM not specified)	AVM PC (2012)	1 x Fume hood
Southern Region				
25	CS Cahul	1 x XSZ-47 (2005)	Philips PC (2011)	
26	SR Cantemir	1 x ERMA EZ-232 (2008)	ASUS PC	
27	SR Causeni	1 x binocular (2006/model not specified)		
28	CS Stefan Voda	1 x Pro-Way PW-BK5000 (2008)		

4.7 Number of Pap tests processed relative to the target screening population

Twenty-five laboratories reported processing 236,579 Pap tests, enough to screen 72.3% of the target population. However, as coverage rates of 70% or more have only been achieved by well organised programs in high-income countries, this number is unlikely to reflect the true situation in RM. To investigate this, the number of Pap tests processed was compared to the estimated annual screening requirement for each of the 18 laboratories reporting these data (see Table 7 & Appendix 2). These data show the number of Pap tests reported by 10 laboratories would have been enough to screen from 80% to 374% of their respective target populations and indicate the screening age range and frequency were not being followed, and/or the number of Pap tests processed was over-reported.

Table 7: Estimated screening requirement vs reported № of Pap tests

Cervical Cytology Laboratory	№ Women Aged 25-61	Annual Reqirement[1]	Reported № Pap Tests/Yr	Coverage of Population
Balti - Immunotehnomed	69,827	23,275	21,470	92.25%
SR Donduseni	17,748	5,917	3,803	64.28%
SR & CS Drochia	19,319	6,440	6,008	93.30%
SR & CS Edinet	58,010	19,336	31,455	162.68%
CS Soroca	27,693	9,231	8,590	93.06%
SR Orhei	9,765	3,255	3,745	115.05%
SR Ungheni	64,237	21,411	17,900	83.60%
AMT Botanica	35,654	11,885	18,230	153.38%
AMT Centru	121,932	40,646	22,285	54.83%
AMT Riscani	54,781	18,261	11,622	63.64%
Institute of Oncology	142,119	47,373	29,298	61.85%
Republican Diagnositic Cent.	225,890	75,294	37,000	49.14%
CS Cahul	10,465	3,488	13,043	373.94%
SR Cantemir	17,199	5,733	4,100	71.52%
SR Cuaseni	25,506	8,502	6,710	78.92%
CS Stefan Voda	19,326	6,442	5,065	78.62%
Totals:	**982,093**	**327,364**	**236,579**	**72.27%**

1. Based on a 3-year screening interval

4.8 Compliance of cervical cytology services with the European Guidelines

The cervical cytology screening services provided by the 25 laboratories reporting the number of Pap tests processed were compared to the recommendations of the European Guidelines for:

- The minimum number of Pap tests (15,000 or more/year) that should be processed to ensure cyto-screeners are regularly exposed to the full range of cytology abnormalities needed to maintain their recognition skills.
- The minimum number of cyto-screeners (4 or more/laboratory) required to ensure collaborative learning, service provision during holidays, sick-leave, etc.

Only 3 laboratories (Balti Immunotehnomed, Institute of Oncology, Republican Diagnostic Centre), processing 38.0% of Pap tests in 2015, complied with both recommendations, while another 4 laboratories (SR Edinet, SR Ungheni, AMT Botanica, AMT Centru) processing 32.5% of Pap tests in 2015, complied only with the minimum number of Pap tests.

Table 8: Laboratory compliance with the European Guidelines

	Cervical Cytology Laboratory	№ Pap tests/year	№ lab technicians[1]	≥15,000 Paps/year[2]	≥ 4 Cyto-screeners[2]
Northern Region					
1	**Balti - Immunotehnomed**	**21,470**	**4 FTE**	**Yes**	**Yes**
2	SR Donduseni	3,803	1 FTE	No	No
3	SR Drochia	2,345	0 FTE	No	No
4	CS Drochia	3,663	0 FTE	No	No
5	**SR Edinet**	**23,773**	**1 FTE**	**Yes**	**No**
6	CS Edinet	3,841	1 FTE	No	No
7	CS Soroca	8,590	1 FTE	No	No
Central Region					
8	SR Orhei	3,745	1 FTE	No	No
9	**SR Ungheni**	**17,900**	**1 FTE**	**Yes**	**No**
10	**AMT Botanica**	**18,230**	**2 FTE**	**Yes**	**No**
11	**AMT Centru**	**22,285**	**3 FTE**	**Yes**	**No**
12	AMT Ciocana	TBA	TBA	TBA	TBA
13	AMT Riscani	11,622	1.5 FTE	No	No
14	State Chancellery Hospital	668	2 FTE	No	No
15	State Chancellery Policlinic	543	0 FTE	No	No
16	Institutul Medicina Urgenta	1,084	2 FTE	No	No
17	CM Galaxia	7,035	1 FTE	No	No
18	CM Pro Sano	282	0 FTE	No	No
19	CM Sf. Pantelemon	2,267	1 FTE	No	No
20	Morformed Service	TBA	TBA	TBA	TBA
21	Neomedica Grup	TBA	TBA	TBA	TBA
Republican Facilities					
22	**Institute of Oncology**	**29,267**	**4 FTE**	**Yes**	**Yes**
23	**Republican Diagnostic Cent.**	**37,000**	**3.5 FTE**	**Yes**	**Yes**
24	Institute of Mother & Child	845	2 FTE	No	No
Southern Region					
25	CS Cahul	13,043	1 FTE	No	No
26	SR Cantemir	4,100	0 FTE	No	No
27	SR Causeni	6,710	0 FTE	No	No
28	CS Stefan Voda	5,523	0 FTE	No	No

1. No data were provided on proportions of laboratory technician time available for cervical screening.
2. European Guidelines: ≥15,000 Pap tests/laboratory/year & ≥4 cyto-screeners/laboratory.

The remaining 18 laboratories, together responsible for processing 29.5% of Pap tests in 2015, did not comply with either recommendation. The mean and median number of Pap tests processed by these laboratories in 2015 were 3,803 and 4,683 respectively, which are far below the threshold of 15,000 Pap tests/year recommended in the European Guidelines.

4.9 Quality of cervical cytology services

As no performance indicators, standards or QA procedures are applied to cervical screening in RM, there are no mechanisms to objectively assess quality of these services. Therefore, to obtain an indication of service quality in the 7 laboratories processing 15,000 or more Pap tests/year, the distribution of non-normal cervical cytology results (excluding endocervicosa, inflammation and trichomonas) was compared between laboratories.

Given that socio-economic conditions across RM are fairly uniform and all of these 7 laboratories processed Pap tests from multiple regions, there should not be much variation in cervical disease rates between their respective catchment populations. Therefore, any significant inter-laboratory variations in the proportions of abnormal Pap test results would indicate a lack of standardisation in training, specimen preparation, specimen interpretation, service quality, etc. As a benchmark, the RM laboratory results were also compared to those from the Irish National Cervical Screening Programme during its first full year of operation (September 2008 to August 2009) when the target population was still largely unscreened.

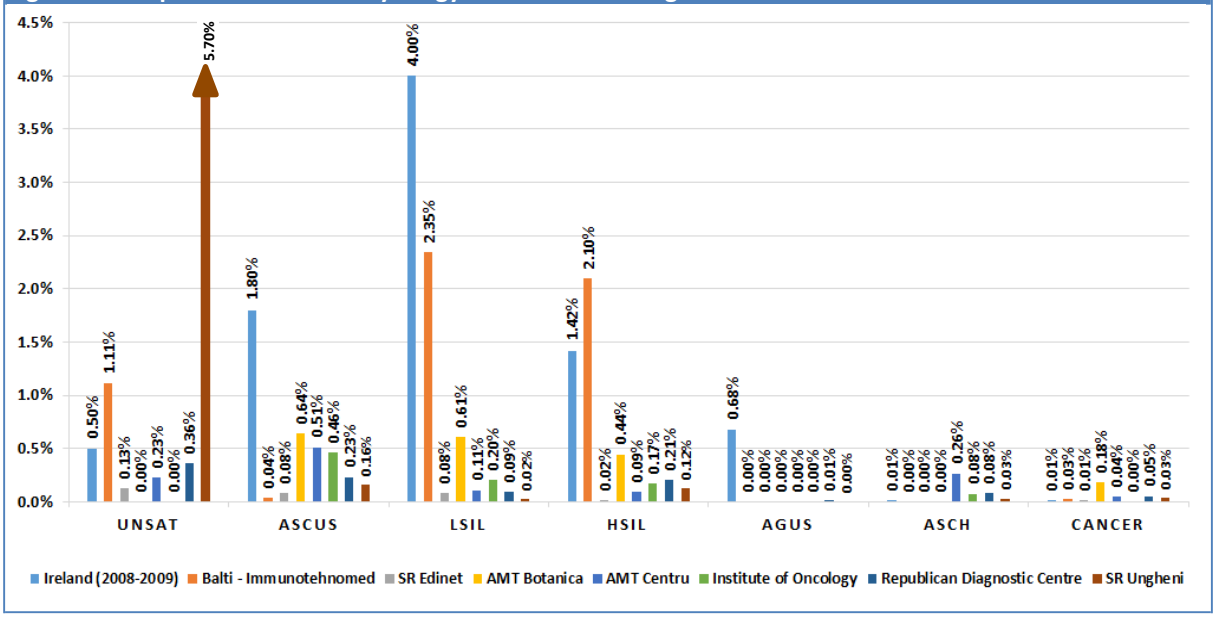
The data presented in Table 9 and Figure 4 show there were statistically significant variations in the proportions of cytological abnormalities between these 7 laboratories as well as between RM laboratories and the Irish cervical screening programme. The proportions of non-negative results showed a difference of 19 times between laboratories from a low of 0.32% (SR Edinet) to a high of 6.06% (SR Ungheni), while the proportions of unsatisfactory results ranged from a low of 0.0% (AMT Botanica) to a high of 5.70% (SR Ungheni). In addition, the proportions of ASC-US, LSIL and HSIL also showed substantial inter-laboratory variations of 16 times, 118 times and 105 times respectively, with the HSIL rates reported by 6 of the 7 laboratories being unusually low, even in comparison to well screened Western European populations.

Table 9: Comparison of cervical cytology results in the 7 largest RM laboratories

	Non-Neg %	Unsat %/№	ASC-US %/№	LSIL %/№	HSIL %/№	AGUS %/№	ASCH %/№	Cancer %/№
Ireland (2008-2009)	8.42%	0.5%/1,521	1.8%/5,130	4.0%/11,338	1.4%/4,005	0.7%/1,923	0.01%/28	0.01%/32
(Total RM:Ireland) *p* value:	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	*	*	*
Balti - Immunotehnomed	5.62%	1.11%/238	0.04%/8	2.35%/504	2.10%451	0.00%/0	0.00%/0	0.03%/6
SR Edinet	0.32%	0.13%/30	0.08%/19	0.08%/20	0.02%/4	0.00%/0	0.00%/0	0.01%/2
AMT Botanica	1.87%	0.00%/0	0.64%/116	0.61%/111	0.44%/81	0.00%/0	0.00%/0	0.18%/33
AMT Centru	1.25%	0.23%/51	0.51%/114	0.11%/24	0.09%/20	0.00%/0	0.26%/59	0.04%/10
Institute of Oncology	0.91%	0.00%/0	0.46%/136	0.20%/60	0.17%/50	0.00%/0	0.08%/22	0.00%/0
Republican Diagnostic Centre	1.04%	0.36%/132	0.23%/86	0.09%/34	0.21%/76	0.01%/5	0.08%/31	0.05%/19
SR Ungheni	6.06%	5.70%/1,020	0.16%/28	0.02%/4	0.12%/22	0.00%/0	0.03%/5	0.03%/6
(RM Laboratories) *p* value:	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	*	*	*

*Small numbers of AGUS, ASCH and cancer results prevented comparison across laboratories.

Figure 4: Comparison of cervical cytology results in the 7 largest RM laboratories



4.10 Cervical cytology working practice recommendations

RM has no working practice recommendations for cervical cytology screening. In the past, Ministry of Health Order (MHO) № 68 of 10 March 2005 set a limit of 67 Pap tests/cyto-screener/day. However, this order was subsequently replaced by MHO № 722 of 16 July 2012 that did not specify any limit.

4.11 Standard operating procedures

RM does have standard operating procedures (SOPs) for cervical cytology laboratories but as there are no mechanisms to monitor and evaluate laboratory performance or encourage laboratories to implement the SOPs, most laboratories do not comply.

4.12 Quality assurance

RM has no QA programme with performance indicators and standards for any aspect of cervical cytology screening. As a result there is no mechanism to monitor and evaluate the quality of these services or, more importantly, to identify sub-optimal performance so it can be improved.

4.13 Record keeping and IT systems

All laboratories reported using paper-based record keeping systems. A few laboratories reported they also had parallel electronic systems but these were only for internal use. Also, there were no electronic links between laboratories or between laboratories and other health services.

4.14 Training for cervical cytology laboratory staff (cytopathologists and cyto-screeners)

For the training of cytopathologists, a mandatory cytopathology residency programme was established in 1998 so people subsequently entering the field will have completed this residency, while those entering at an earlier date will have undertaken an internship programme.

For the training of cyto-screeners, RM has no nationally approved training curriculum or programme so the people currently providing this service will have been trained in general laboratory techniques with subsequent on-the-job training in cytology. Cyto-screener performance is highly dependent on their initial training and CME so the lack of an evidence-based training programme with training standards will compromise the safety and cost-effectiveness of cervical screening.

A related problem is that RM does not recognise cervical cyto-screening as a distinct laboratory speciality with defined training and certification requirements so there is no mechanism to ensure the people doing this job have been trained to the level required for them to provide a safe and cost-effective service.

5. Conclusions

In 2012, RM laboratories reported processing 365,676 Pap tests, which would have been enough to screen about 70.9% of the annual target population based on the 2-year screening interval recommended at that time.[8] Now, this assessment found that a total of 236,579 Pap tests were reported in 2015 which would have been enough to screen about 72.3% of the target population based on the new 3-year screening interval. Well organised cervical screening programmes with more than 70% coverage of the target population in Western Europe have achieved substantial reductions in cervical cancer rates. The same should be seen in RM but the data presented in this report show that cervical cancer rates rose steadily from 2000 to 2011 when they plateaued and have since shown no improvement whatsoever.

These data indicate that substantial health care resources are being expended on cervical screening in RM but they are not producing any results. The reason for this has been presented to the Ministry of Health many times: cervical screening in RM is being conducted opportunistically without proper staff training, standardisation of procedures, coordination of the component health services, effective patient management or QA. Therefore, it will not reduce cervical cancer rates but instead will be harming the women who are being screened and will be wasting health care resources.

Cytology is a key component of cervical screening and the data presented in this report show these services currently have no:

- Training curricula, training standards or certification criteria for cyto-screeners,
- Working practice recommendations,
- QA programme with performance indicators and standards,
- System for monitoring and evaluating cervical cytology services.

Because of these issues, there are no mechanisms to: ensure cyto-screeners have the knowledge and skills to do their job properly, ensure laboratories comply with evidence-based best practice recommendations, objectively measure the performance of cytology laboratories or cyto-screeners and most importantly, to identify and improve suboptimal performance. As a result, this assessment found that:

- Women outside the recommended age range are being screened and/or women are being screened too often, neither of which will contribute to reducing cervical cancer rates but instead will increase the harms and costs of screening.
- Only 3 of 25 cervical cytology laboratories comply with two basic recommendations from the European Guidelines for, a) the minimum number of Pap tests that should be processed to ensure cyto-screeners are regularly exposed to the full range of cytology abnormalities needed to maintain their recognition skills, and b) the minimum number of cyto-screeners required to ensure collaborative learning, service provision during holidays, sick-leave, etc. and only 4 more laboratories comply with the recommendation for the minimum number of Pap tests processed. Therefore, 18 of 25 cervical cytology laboratories in RM cannot comply even with these 2 basic recommendations from the European Guidelines.
- The quality of cervical cytology services is of serious concern, as evidenced by the proportions of Pap test results that vary widely from one laboratory to the next. Given that cervical disease rates would have been similar within the populations served by these laboratories, these wide variations in Pap test results will be due to equally wide variations in the quality of their services.
- The rates of high-grade Pap test results are too low, indicating that a substantial amount of high-grade pre-invasive cervical disease is not being detected so it is not being treated and many of these women will go on to develop invasive cervical cancer.

6. Recommendations

The current situation with cervical cytology in RM is unethical and unsustainable so it is now essential for the Ministry of Health to implement the policies and support the actions that are required to improve the quality, safety and cost-effectiveness of these services. The priority issues to be addressed are:

6.1 Close cervical cytology laboratories that do not comply with any international recommendations.

Eighteen cervical cytology laboratories do not comply with even the most basic international recommendation that laboratories should screen a minimum of 15,000 Pap tests per year to ensure cyto-screeners are regularly exposed to the full range of cytology abnormalities needed to maintain their recognition skills. In this regard, the mean and median number of Pap tests processed by these 18 laboratories in 2015 were 3,803 and 4,683 respectively, which are both far below the recommended minimum number.

Eighteen of 25 laboratories in RM do not comply with any international recommendations simply because they are too small. These laboratories should be closed and their Pap tests transferred to the 7 larger laboratories.

6.2 Strengthen capacities to continuously monitor and evaluate cervical cytology services.

Continuous monitoring and evaluation of cervical cytology laboratories is essential to ensure they comply with the international evidence-based recommendations and provide services that are safe and cost-effective. The monitoring and evaluation of cervical cytology requires cytology results to be correlated with data coming from other health services such as colposcopy and biopsy results. Therefore, the simplest solution is to incorporate this function into the cervical screening registry that is required to manage the overall cervical screening programme.

A working group of national and international experts must be convened to prepare the criteria for monitoring and evaluating the cervical cytology services and to prepare a service specification for its incorporation into the cervical screening registry.

6.3 Progressively change from Romanowsky staining to Papanicolaou staining

The majority of cervical cytology in RM uses conventional cervical smears stained by the Romanowsky technique. The use of the Romanowsky technique for cervical screening is restricted to the countries of the former Soviet Union and most cervical cytology in the rest world is stained by the Papanicolaou technique.

These 2 techniques use completely different staining processes so the cytological interpretation is also completely different and laboratories specialised in one technique cannot train cyto-screeners to work in

laboratories using the other. This is very important for RM because, as clearly demonstrated by the wide variation in the proportions of abnormal Pap tests between laboratories, there is an urgent need to improve the quality of cervical cytology here. This can be most cost-effectively achieved through training exchanges with countries that have high quality cervical cytology but all these countries use the Papanicolaou staining technique. Therefore, continuing to use the Romanowsky staining technique in RM will prevent cervical cytology laboratories here from achieving internationally recognised evidence-based standards.

RM must start the process of changing from the Romanowsky technique to the Papanicolaou technique by training cyto-screeners and cytopathologists throughout 2017 and updating selected laboratories with the objective of completing the change-over by the end of the year.

The process of switching from Romanowsky to Papanicolaou staining has already started by creating a nucleus of expertise in Chisinau. Two cytopathologists (one person from the Republican Diagnostic Centre and another from the USMF Nicolae Testemițanu) completed a 1-month training course in Papanicolaou cervical cytology at La Sapienza University Hospital in Rome during September 2016.

It is now necessary to:
- Institutionalise the new knowledge and skills by incorporating them into the pathology residency programme at the USMF Nicolae Testemițanu.
- Disseminate the new knowledge and skills through CME courses for cyto-screeners and cytopathologists that will be held at the USMF Nicolae Testemițanu throughout 2017.

The incorporation of the new knowledge and skills in the pathology residency curriculum as well as the preparation and holding of CME courses can be supported by experts from Western European countries where they have high quality cervical screening programmes, and experts from the British Association of Cytopathology have agreed to come to RM in March, 2017.

6.4 Enforce the cervical screening age range and interval

The screening age range and interval are set to optimise the balance between the benefits and harms of screening and thereby also maximise cost-effectiveness.

RM must act now to enforce compliance with the recommended cervical screening age range and interval to improve the balance between the harms and benefits of screening, and to maximise cost-effectiveness.

The simplest way to achieve this is for CNAM to change its contracts with PHC clinics and hospitals/institutes that have cytology laboratories by adding a clause specifying that it will only pay for Pap tests that comply with recommended screening age range and interval. A policy like this was implemented when Norway launched its organised cervical screening programme and the number of Pap tests dropped by 35% in the first year while cervical cancer rates declined, thereby demonstrating that the additional Pap tests were unnecessary and a waste of money.

6.5 Training curriculum for cyto-screeners

As noted above, cervical cyto-screeners must be properly trained in order to provide safe and cost-effective services. RM currently does not have an evidence-based curriculum for the screening of cervical cytology so the cyto-screeners are trained 'on the job' with the quality of training entirely dependent on the quality of the laboratory in which the training is done. This is not sufficient to ensure that all cyto-screeners are properly trained, as clearly demonstrated by the enormous variation in Pap test results between laboratories.

A working group of national and international experts must be convened to prepare and approve an evidence-based national curriculum for cervical cytology screening that will be delivered as a module within the laboratory technician training programme at the RM National College of Medicine and Pharmacy 'Raisa Pacalo'.

Model evidence-based training curricula for cyto-screeners can be obtained from Western European countries where they have high-quality cervical screening programs, together with support for the adaptation of the curricula to RM.

6.6 Designate cervical cyto-screening as a distinct laboratory specialty

Safe and cost-effective cervical screening requires high quality cervical cytology services and this cannot be achieved unless all cyto-screeners have the required knowledge and skills.

Cervical cyto-screening must be designated as a distinct laboratory speciality with a defined training curricula and certification criteria, and with certification being mandatory to work in the field.

6.7 Working practice recommendations

Evidence-based working practice recommendations for all aspects of cervical cytology screening are essential to ensure laboratory staff can comply with international best practice recommendations. RM currently does not have these.

A working group of national and international experts must be convened to prepare and approve evidence-based working practice recommendations for cervical cytology screening.

Model evidence-based working practice recommendations for cervical cytology screening can be obtained from Western European countries where they have high-quality cervical screening programs, together with support for the adaptation of the recommendations to RM.

6.8 Cervical screening laboratory facility and equipment specifications

The laboratory facilities and equipment are important factors influencing the quality of cervical cytology screening so all cervical cytology laboratories in RM must comply with international best-practice recommendations for their facilities and equipment.

A working group of national and international experts must be convened to work with the RM National Council for Evaluation and Accreditation in Health to prepare and approve facility and equipment specifications for cervical cytology laboratories.

Model facility and equipment specifications for adaptation to RM can be obtained from Western European countries where they have high-quality cervical screening programs, together with support for the adaptation of these specifications to RM.

6.9 QA programme, performance indicators and standards

QA programmes with appropriate performance indicators and standards are critical for the safe and cost-effective operation of cervical screening programmes. RM does not have a QA programme for any aspect of cervical cytology processing, screening or diagnosis.

Two performance indicators for PHC clinics/staff were implemented in January 2015: the proportion of women in the target population that have been screened and the number of women that have attended colposcopy, as measured by the number of women that bring their colposcopy clinic discharge form back to the referring family physician.

However, there are several problems with these performance indicators:

- They both rely on PHC clinics to submit the data (as there is no IT system that would allow independent data collection) so it will be subject to over-reporting. CNAM does audit a small number of PHC clinics every year (approximately 50 per year), and while the auditors can verify the number of women that attended colposcopy by checking for the colposcopy clinic discharge forms, there currently is no way to verify the number of women that have been screened.
- Both performance indicators are purely quantitative and their use without accompanying measures of quality, such as the proportion of inadequate Pap tests or the proportion of women referred to colposcopy that have clinically relevant cervical disease, will encourage PHC staff to meet the numerical targets at the expense of quality.
- The number of women attending colposcopy is influenced by many factors that are beyond the control of PHC clinics. Therefore, this indicator unlikely to have a positive influence on PHC staff behaviour.

These examples demonstrate that setting cervical screening performance indicators and standards is very complicated and requires careful consideration by experts who fully understand the entire screening process to avoid setting targets that will encourage unwanted actions, such as sacrificing quality to meet numerical objectives. Further, it is essential to recognise that cervical screening QA must apply to all the health services

involved in the programme because the sub-optimal performance of any one service will compromise the effectiveness of the entire programme, while setting performance indicators for only one part of the process will encourage people to focus on that part to the detriment of others. Therefore, cervical cytology QA cannot be considered in isolation and instead must be designed as an integral part of the overall cervical screening QA programme.

A working group of national and international experts must be convened to design a QA programme with performance indicators that are appropriate for the RM health system and encourage behaviours that will effectively improve the safety and cost-effectiveness of cervical screening.

This process can start by considering the QA recommendations, performance indicators and standards specified in the European Guidelines (see Appendix 3), and continue by adapting those that would be most appropriate for RM in the short, medium and longer terms.

6.10 Reorganise cervical cytology services

The primary objective of reorganising the cervical cytology services must be to bring them into compliance with international, evidence-based recommendations, including the European Guidelines. Therefore, the first steps must be to prepare and approve the evidence-based training curriculum for cervical cyto-screening and designate cervical cyto-screening as a distinct laboratory specialty with defined training and certification criteria, the cervical screening working practice recommendations, the cervical screening laboratory facility and equipment specifications, and the QA programme with performance indicators and standards. Then, laboratories should be given 2 years to comply.

The 7 laboratories that do meet the basic minimum standard of 15,000 or more Pap tests/year specified in the European Guidelines should be given a period of 2 years to implement the new training and certification requirements, working practice recommendations and performance standards specified in the QA programme. Then, any laboratories that do not achieve these criteria should be closed with their work redirected to the ones that can.

Appendix 1: Estimated cervical screening target population and annual № Pap tests					
	Total population	Total female population	Women 25-61 (inclusive)	Annual screening target[1]	Annual № Pap tests/year[2]
Total Republic of Moldova	3,369,100	1,853,005	982,093	327,364	282,352
Municipality of Chisinau	779,000	428,450	227,079	75,693	65,285
Chisinau	639,000	351,450	186,269	62,090	53,552
Codru	15,800	8,690	4,606	1,535	1,324
Cricova	10,700	5,885	3,119	1,040	897
Durlesti	19,300	10,615	5,626	1,875	1,617
Singera	8,500	4,675	2,478	826	712
Vadul lui Voda	4,900	2,695	1,428	476	411
Vatra	3,600	1,980	1,049	350	302
Chisinau all suburbs	77,200	42,460	22,504	7,501	6,470
Northern Region					
Balti	127,300	70,015	37,108	12,369	10,669
Briceni	74,200	40,810	21,629	7,210	6,218
Donduseni	41,800	22,990	12,185	4,062	3,503
Drochia	82,600	45,430	24,078	8,026	6,922
Edinet	80,000	44,000	23,320	7,773	6,705
Falesti	87,300	48,015	25,448	8,483	7,316
Floresti	83,800	46,090	24,428	8,143	7,023
Glodeni	56,800	31,240	16,557	5,519	4,760
Ocnita	53,000	29,150	15,450	5,150	4,442
Riscani	64,300	35,365	18,743	6,248	5,389
Singerei	85,100	46,805	24,807	8,269	7,132
Soroca	95,000	52,250	27,693	9,231	7,962
Central Region					
Anenii Noi	82,000	45,100	23,903	7,968	6,872
Calarasi	72,500	39,875	21,134	7,045	6,076
Criuleni	73,500	40,425	21,425	7,142	6,160
Dubasari	35,200	19,360	10,261	3,420	2,950
Hincesti	116,200	63,910	33,872	11,291	9,738
Ialoveni	100,600	55,330	29,325	9,775	8,431
Nisporeni	60,500	33,275	17,636	5,879	5,070
Orhei	112,700	61,985	32,852	10,951	9,445
Rezina	48,200	26,510	14,050	4,683	4,039
Soldanesti	38,700	21,285	11,281	3,760	3,243
Straseni	89,100	49,005	25,973	8,658	7,467
Telenesti	66,400	36,520	19,356	6,452	5,565
Ungheni	106,700	58,685	31,103	10,368	8,942
Southern Region					
Basarabeasca	27,400	15,070	7,987	2,662	2,296
Cahul	117,200	64,460	34,164	11,388	9,822
Cantemir	59,000	32,450	17,199	5,733	4,945
Causeni	87,500	48,125	25,506	8,502	7,333
Ceadir-Lunga	19,500	10,725	5,684	1,895	1,634
Cimislia	57,100	31,405	16,645	5,548	4,785
Comrat	23,600	12,980	6,879	2,293	1,978
Gagauzia (villages)	93,900	83,710	44,366	14,789	12,755
Leova	50,700	27,885	14,779	4,926	4,249
Stefan Voda	66,300	36,465	19,326	6,442	5,556
Taraclia	39,200	21,560	11,427	3,809	3,285
Vulcanesti	15,200	8,360	4,431	1,477	1,274
Totals:	3,369,100	1,853,005	982,093	327,364	282,352

1. Screening interval of 3 years
2. Estimated screening coverage of 75% + 15% for repeat and follow-up Pap tests

Appendix 2: Estimated cervical screening target population and annual № to be screened						
Cervical Cytology Laboratory	Region	Principal Facility	Est. № Women Aged 25-61	Annual Screening Reqirement	Reported Pap Tests/ Year	Coverage of Target Population
Balti - Immuno-tehnomed	Balti	CMF Balti	37,108	12,369		
	Drochia	CS Pelinia	1,586	529		
	Glodeni	CS Glodeni	2,915	972		
		CS Ciuciulea	3,411	1,137		
		CS Sturzovca				
	Singerei	CS Singerei	3,760	1,253		
		CS Singereii Noi	10,072	3,357		
		CS Radoaia				
		CS Draganesti				
		CS Bilicenii Vechi				
		CS Pepeni				
		CS Biruinta	904	301		
		CS Copaceni	10,072	3,357		
		CS Chiscareni				
		CS Cubolta				
		CS Flaminzeni-Coscodeni				
		CS Cotiujenii Mici				
		Totals:	**69,827**	**23,275**	**21,470**	**92.25%**
SR Donduseni	Donduseni	CS Donduseni	2,711	904		
		CS Taul	9,474	3,158		
		CS Sudarca				
	Ocnita	CS Otaci	2,390	797		
	Drochia	CS Mandic	3,173	1,058		
		CS Zgurita				
		Totals:	**17,748**	**5,917**	**3,803**	**64.28%**
SR Drochia & CS Drochia	Drochia	CS Suri	7,931	2,644		
		CS Sofia				
		CS Hasnasenii Mari				
		CS Tarigrad				
		CS Chetrosu				
CS Drochia		CS Drochia	5,043	1,681		
		CS Gribova	6,345	2,115		
		CS Nicoreni				
		CS Maramonovca				
		CS Ochiul Alb				
		Totals:	**19,319**	**6,440**	**6,008**	**93.30%**
SR Edinet	Briceni	CS Briceni	2,449	816		
		CS Lipcani	19,181	6,394		
		CS Larga				
		CS Corjeuti				
	Ocnita	CS Ocnita	2,624	875		
		CS Frunza	10,436	3,478		
SR & CS Edinet	Edinet	CS Edinet	5,364	1,788		
CS Edinet		CS Cupcini	17,956	5,985		
		Totals:	**58,010**	**19,336**	**31,455**	**162.68%**
CS Soroca	Soroca	CS Soroca	10,261	3,420		
		CS Soroca Noua	17,432	5,811		
		CS Cosauti				
		CS Racovat				
		CS Cainarii Vechi				
		CS Badiceni				
		CS Vadeni				
		CS Vasilcau				
		CS Parcani				
		CS Slobozi-Cremene				
		CS Nimereuca				
		CS Rublenita				
		CS Rudi				
		CS Visoca				
		Totals:	**27,693**	**9,231**	**8,590**	**93.06%**
AMT Botanica	Municipality of Chisinau	AMT Botanica	15,247	5,083		
		CS Bacioi	15,247	5,083		
		CS Singera	2,478	826		
	Anenii-Noi	CS Floreni	2,682	894		
		Totals:	**35,654**	**11,885**	**18,230**	**153.38%**
AMT Centru	Municipality of Chisinau	AMT Buiucani	15,247	5,083		
		CS Durlesti	5,626	1,875		
		CS Ghidighici	15,247	5,083		
		CS Truseni	15,247	5,083		
		CS Vatra	1,049	350		
		AMT Centru	15,247	5,083		
		CS Budesti	15,247	5,083		
		CS Vadul lui Voda	1,428	476		
		CS Ciorescu	15,247	5,083		
		CS Cricova	3,119	1,040		
	Ialoveni	CS Bardar	19,226	6,409		
		CS Razeni				
		CS Tipala				
		CS Milestii Mici				
		CS Horesti				
		CS Costesti				
		CS Rusestii Noi				
		Totals:	**121,932**	**40,646**	**22,285**	**54.83%**

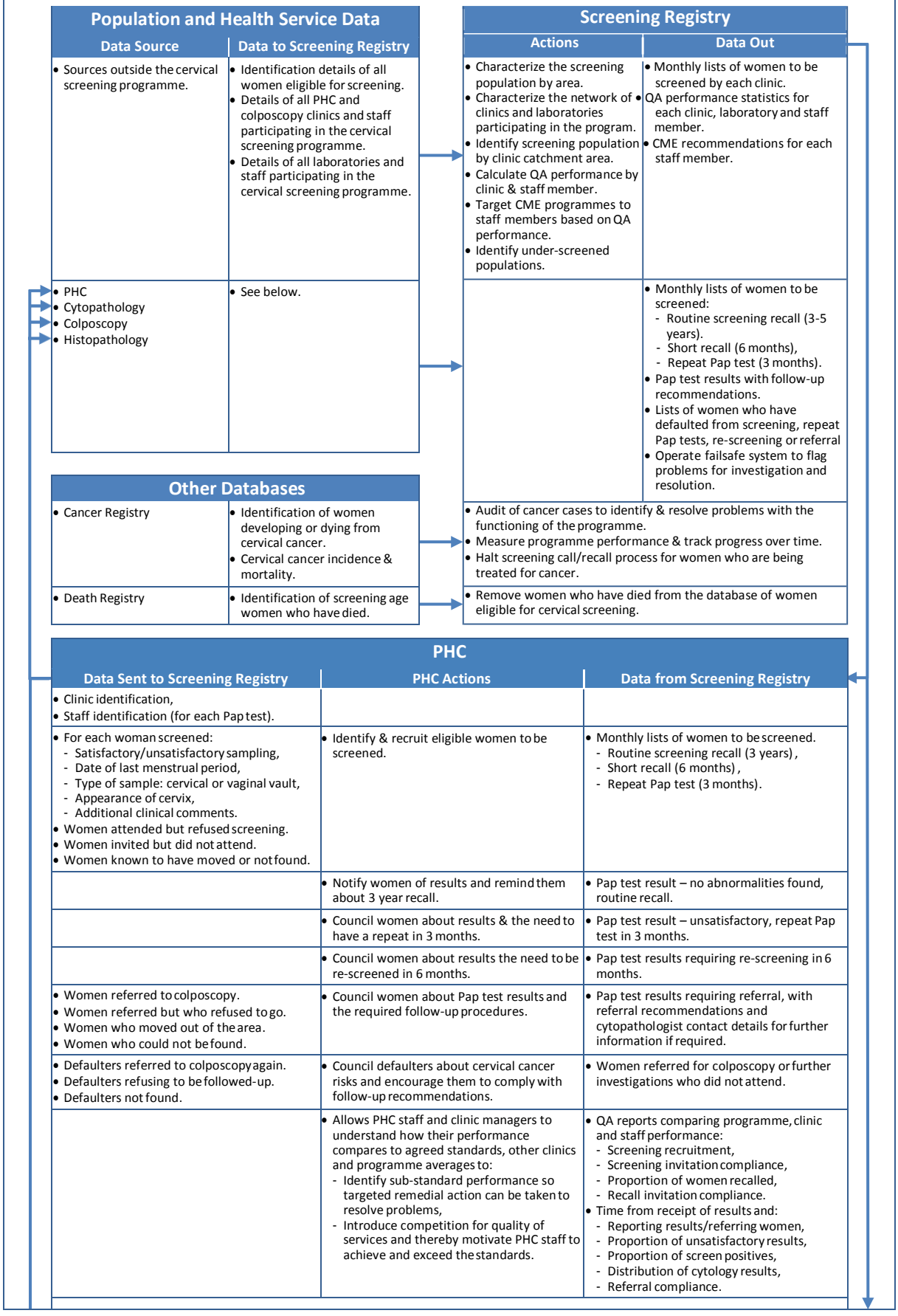
Appendix 2: Estimated cervical screening target population and annual № to be screened						
Cervical Cytology Laboratory	Region	Principal Facility	Est. № Women Aged 25-61	Annual Screening Reqirement	Reported Pap Tests/ Year	Coverage of Target Population
AMT Ciocana	Municipality of Chisinau	AMT Ciocana	15,247	5,083		
		CS Bubuieci	15,247	5,083		
		CS Colonita	15,247	5,083		
		Totals:	**45,742**	**15,248**	**TBA**	**TBA**
AMT Riscani: SCM Arhanghel Mihail	Municipality of Chisinau	AMT Riscani	15,247	5,083		
		CS Gratiesti	15,247	5,083		
		CS Stauceni	15,247	5,083		
	Criuleni	CS Magdacesti	4,832	1,611		
	Orhei	CS Peresecina	1,953	651		
	Straseni	CS Micauti	2,254	751		
		Totals:	**54,781**	**18,261**	**11,622**	**63.64%**
Institute of Oncology	Anenii-Noi	CS Roscani	8,045	2,682		
		CS Mereni				
		CS Bulboaca				
	Calarasi	CS Varzarestii-Noi-Pitusca	5,636	1,879		
		CS Bravicea				
	Criuleni	CS Criuleni	2,099	700		
		CS Hrusova	9,663	3,221		
		CS Balabanesti				
	Dubasari	CS Dubasari	10,261	3,420		
	Hincesti	CS Sarata - Galbena	9,814	3,271		
		CS Bobeica				
	Ialoveni	CS Ialoveni	4,606	1,535		
		CS Puhoi	5,493	1,831		
		CS Vasieni				
	Soldanesti	CS Soldanesti	1,749	583		
		CS Cotiujenii Mari	4,766	1,589		
		CS Raspopeni				
	Straseni	CS Straseni	5,684	1,895		
		CS Micleuseni	13,525	4,509		
		CS Codreanca				
		CS Cojusna				
		CS Vorniceni				
		CS Lozova				
		CS Zubresti				
	Basarabeasca	CS Basarabeasca	3,148	1,049		
		CS Sadaclia	2,420	807		
	Ceadir-Lunga (UTA Gagauzia)	CS Ceadir-Lunga	5,684	1,895		
		CS Cazaclia	10,265	3,422		
		CS Copceac				
		CS Tomai				
	Comrat (UTA Gagauzia)	CS Comrat	6,879	2,293		
		CS Avdarma	17,108	5,703		
		CS Dezghingea				
		CS Cioc-Maidan				
		CS Chirsova				
		CS Congaz				
	Leova	CS Leova	2,915	972		
		CS Filipeni	5,276	1,759		
		CS Borogani				
		CS Iargara	1,283	428		
	Taraclia	CS Taraclia	3,790	1,263		
		CS Musaitu	2,011	670		
		Totals:	**142,119**	**47,373**	**29,298**	**61.85%**
Republican Diagnositic Centre	Falesti	CS Falesti	4,431	1,477		
		CS Glingeni	21,017	7,006		
		CS Iscalau				
		CS Ciolacu Nou				
		CS Marandeni				
		CS Chetris				
		CS Bocsa				
	Floresti	CMF Floresti	3,848	1,283		
		CS Cuhurestii de Sus	20,580	6,859		
		CS Sanatauca				
		CS Trifanesti				
		CS Prodanestii Noi				
		CS Ciutulesti				
		CS Tirgul- Vertiujeni				
		CS Marculesti				
		CS Ghindesti				
	Glodeni	CS Fundurii Vechi	10,232	3,410		
		CS Balatina				
		CS Iabloana				
		CS Limbenii Vechi				
		CS Hijdieni				
		CS Cobani				
	Riscani	CS Riscani	3,148	1,049		
		CS Vasileuti	15,566	5,189		
		CS Saptebani				
		CS Zaicani				
		CS Varatic				
		CS Costesti				
		CS Recea				
		CS Mihailenii Vechi				
		CS Corlateni				

Appendix 2: Estimated cervical screening target population and annual № to be screened						
Cervical Cytology Laboratory	Region	Principal Facility	Est. № Women Aged 25-61	Annual Screening Reqirement	Reported Pap Tests/ Year	Coverage of Target Population
	Anenii-Noi	CS Anenii Noi	2,449	816		
		CS Tintareni	10,727	3,576		
		CS Hirbovat				
		CS Varnita				
		CS Speia				
	Hincesti	CS Hincesti	4,402	1,467		
		CS Bujor	14,721	4,907		
		CS Lapusna- Pascani				
		CS Ciuciuleni				
	Orhei	CS Orhei nr. 1	7,462	2,487		
		CS Orhei nr. 2				
		CS Cucuruzeni	13,672	4,557		
		CS Ivancea				
		CS Chiperceni				
		CS Susleni				
		CS Braviceni				
		CS Ciocilteni				
		CS Pelivan				
	Rezina	CS Rezina	3,615	1,205		
		CS Ignatei	10,436	3,479		
		CS Ciniseuti				
		CS Pripiceni- Razesi				
		CS Mateuti				
	Soldanesti	CS Vadul - Rascov	4,766	1,589		
		CS Oliscani				
	Telenesti	CS Telenesti	2,070	690		
		CS Chistelnita	17,286	5,762		
		CS Brinzenii Noi				
		CS Cazanesti				
		CS Saratenii Vechi				
		CS Mindresti				
	Basarabeasca	CS Bascalia	2,420	807		
	Cahul	CS Gavanoasa	21,066	7,022		
		CS Crihana Veche				
		CS Zirnesti				
		CS Larga Noua				
		CS Colibasi				
		CS Bucuria				
		CS Moscovei				
		CS Giurgiulesti				
	Cimislia	CS Cimislia	3,615	1,205		
		CS Gura Galbenei	13,030	4,343		
		CS Javgur				
	Leova	CS Sarateni	5,276	1,759		
		CS Sarata Noua				
	Taraclia	CS Corten	4,023	1,341		
		CS Valea Perjei				
		CS Tvardita	1,603	534		
	Vulcanesti (UTA Gagauzia)	CS Vulcanesti	4,431	1,477		
		Totals:	**225,890**	**75,294**	**37,000**	**49.14%**
SR Orhei	Orhei	CS Bulaiesti	9,765	3,255		
		CS Isacova				
		CS Ghetlova				
		CS Peresecina				
		CS Teleseu				
		CS Morozeni				
		Totals:	**9,765**	**3,255**	**TBA**	**TBA**
SR Ungheni	Calarasi	CS Calarasi	4227	1409		
		CS Sipoteni	11,271	3,757		
		CS Oniscani				
		CS Pirjolteni				
		CS Valcinet				
	Nisporeni	CS Nisporeni	3,352	1,117		
		CS Bolduresti	14,284	4,761		
		CS Milesti				
		CS Grozesti				
		CS Seliste				
	Ungheni	CS Ungheni	9,532	3,177		
		CS Cetireni	21,571	7,190		
		CS Napadeni				
		CS Manoilesti				
		CS Cornesti				
		CS Valea Mare				
		CS Pirlita				
		CS Petresti				
		CS Cioropcani				
		CS Sculeni				
		CS Danuteni				
		CS Costuleni- Macaresti				
		CS Radenii Vechi				
		Totals:	**64,237**	**21,411**	**17,900**	**83.60%**

Appendix 2: Estimated cervical screening target population and annual № to be screened						
Cervical Cytology Laboratory	Region	Principal Facility	Est. № Women Aged 25-61	Annual Screening Reqirement	Reported Pap Tests/ Year	Coverage of Target Population
SRL Morfomed Service	Criuleni	CS Dubasarii Vechi	4,832	1,611		
SRL Neomedica Grup	Straseni	CS Sireti	4,508	1,503		
		CS Panasesti				
	Hincesti	CS Crasnoarmeiscoie	4,907	1,636		
		Totals:	**14,247**	**4,749**	**TBA**	**TBA**
CS Cahul	Cahul	CS Cahul	10,465	3,488		
		Totals:	**10,465**	**3,488**	**13,043**	**373.94%**
SR Cantemir	Cantemir	CS Cantemir	1,458	486		
		CS Gotesti	15,741	5,247		
		CS Ciobalaccia				
		CS Baimaclia				
		CS Cociulia				
		Totals:	**17,199**	**5,733**	**4,100**	**71.52%**
SR Cuaseni	Causeni	CS Causeni	5,130	1,710		
		CS Tanatari	20,376	6,792		
		CS Tocuz				
		CS Cainari				
		CS Firladeni				
		CS Salcuta				
		CS Taraclia				
		CS Copanca				
		Totals:	**25,506**	**8,502**	**6,710**	**78.92%**
CS Stefan Voda	Stefan-Voda	CS Stefan-Voda	2,186	729		
		CS Antonesti	17,140	5,713		
		CS Talmaza				
		CS Olanesti				
		CS Crocmaz				
		Totals:	**19,326**	**6,442**	**5,065**	**78.62%**
	Cahul	CS Slobozia Mare	2,633	878		
		Totals:	**982,093**	**327,364**	**236,579**	**72.27%**

Appendix 3: Performance indicators for cervical screening		
	Indicator	Calculation
1	Programme extension/coverage calculated regionally and nationally	Nº targeted women in catchment area / Nº targeted women in the region or country
2	Programme recruitment during the screening interval, stratified by 5 year age groups	Nº women screened in the screening interval / Nº targeted women living in catchment area
3	Compliance to invitation (within six months after the end of the screening interval)	Nº invited women screened / Nº women invited
4	Proportion of eligible women recalled within the screening interval	Nº women recalled / Nº women eligible for recall
5	Compliance to recall invitation (within six months of the end of the screening interval)	Nº recalled women screened / Nº women recalled
6	Time (in working days) between: • screening test and reporting of result to patient • positive screening test result and offer colposcopy appointment • colposcopy appointment and reporting of results to patient • colposcopy/biopsy result and offer of appointment for treatment	
7	Pap tests/woman screened (include only the initial Pap test, not repeat tests such as those conducted after unsatisfactory tests or for follow-up)	Nº Pap tests in the interval / Nº women screened in the interval
8	Proportion of women requiring repeat Pap tests (calculate for initial screening appointment & recall screening appointment)	Nº women requiring repeat Pap / Nº women screened
9	Compliance with repeat Pap testing (calculate for the initial screening appointment & recall screening appointment)	Nº women having repeat Pap / Nº women referred for repeat Pap
10	Proportion of screen positive women (calculate for the initial screening appointment & recall screening appointment)	Nº women with a positive Pap / Nº women screened
11	Distribution of cytology results (calculate for the initial screening appointment & recall screening appointment)	Nº of each cytological diagnosis / Nº women screened
12	Referral rate to colposcopy (calculate for the initial screening appointment & recall screening appointment)	Nº women referred to colposcopy / Nº women screened
13	Compliance with referral to colposcopy (Calculate for 3 months after referral, 6 months after referral and by referral cytology)	Nº women attending colposcopy / Nº women referred to colposcopy
14	Biopsy rate (calculate for the initial screening appointment & recall screening appointment)	Nº women having a biopsy / Nº women having colposcopy
15	Proportion of women treated after screen detected CIN1	Nº women with CIN1 treated / Nº women with CIN1
16	Proportion of women treated after screen detected ≥CIN2	Nº women with CIN2/3 treated / Nº women with CIN2/3
17	Proportion of women having a hysterectomy after screen detected CIN	Nº women with CIN having a hysterectomy / Nº women with CIN
18	Positive predictive value of colposcopy referral (Calculate overall and for referral cytology, initial screening appointment, recall screening appointment & for grade of CIN)	Nº women with ≥ CIN1 / Nº women referred to colposcopy
19	Distribution of histology results (Calculate for histology result, initial screening appointment & recall screening appointment)	Nº women with CIN+ / Nº screened women
20	Cancer incidence after normal cytology (Calculate for interval from index cytology and by cancer morphology)	Nº women having cancer after normal cytology / Nº person-years of screened women for same period after normal cytology

Appendix 4: Cervical Screening Registry Data Requirements and Pathways



Cervical Screening Registry Data Requirements and Pathways

Cytology Screening & Cytopathology

Data Sent to Screening Registry	Use	Data from Screening Registry
• Laboratory identification. • Staff identification (for each Pap test). • Specimen type. • Squamous cell results. • Endocervical cell results. • Other/non-cervical cell analysis. • Follow-up recommendations.	• Anticipate sample receipt and initiate tracing of Pap tests that do not arrive at lab. • Investigate and resolve failsafe notices. • Allows laboratory staff and managers to understand how their performance compares to agreed standards, other laboratories and programme averages to: - Identify sub-standard performance so targeted remedial action can be taken to resolve problems, - Introduce competition for quality of services and thereby motivate laboratory staff to achieve and exceed the standards.	• Pap tests taken and date sent to lab. • Previous Pap test results. • Date of last menstrual period. • Type of sample: cervical or vaginal vault. • Appearance of cervix. • Additional clinical comments. • Failsafe notices to be investigated. • QA reports comparing programme, laboratory and staff performance: - Time from receipt of Pap test to reporting of results, - Proportion of unsatisfactory results, - Proportion of positives, - Distribution of cytology results.

Colposcopy & Cervical Surgery

Data Sent to Screening Registry	Use	Data from Screening Registry
• Clinic identification. • Colposcopist identification. • Appointment attendance. • Extent of lesion. • Colposcopic opinion. • Biopsy taken (yes/no). • Biopsy result. • Follow-up recommendations.	• Anticipate patient appointment and initiate tracing of defaulters. • Ensures access to referral Pap test result and related clinical information. • Investigate and resolve failsafe notices • Allows colposcopy staff and clinic managers to see how their performance compares to agreed standards and other clinics: - Identify sub-standard performance so targeted remedial action can be taken to resolve problems, - Introduce competition for quality of services and thereby motivate staff to achieve and exceed the standards.	• Women referred and date of referral. • Referring clinic/clinician identification. • Referral Pap test result and/or clinical indications. • Pap test history. • Additional clinical comments. • QA reports for colposcopy clinic and staff performance: - Time from referral to appointment, - Biopsy rate, - Proportion of women treated after screen detected CIN1, - Proportion of women treated after screen detected ≥CIN2, - Proportion of women having a hysterectomy after screen detected CIN, - Positive predictive value of colposcopy referral, - Distribution of histology results, - Cancer incidence after treatment for CIN.

Histopathology

Data Sent to Screening Registry	Use	Data from Screening Registry
- Specimen adequacy - Margin status - Histology result - Pathologist's follow-up recommendations	• Anticipate patient appointment and initiate tracing of defaulters • Ensures access to required clinical information • Investigate and resolve failsafe notices • Allows laboratory staff and managers to understand how their performance compares to agreed standards, other laboratories and programme averages to: - Identify sub-standard performance so targeted remedial action can be taken to resolve problems - Introduce competition for quality of services and thereby motivate laboratory staff to achieve and exceed the standards	• Specimen type and date of referral • Referring clinic/clinician identification • Colposcopic opinion and clinical details • QA reports: - Time from receipt of sample to reporting of results - Proportion of unsatisfactory results - Proportion of positives - Distribution of histology results

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