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Comprehensive Control of HPV Infections and Related Diseases in the Central and Eastern Europe and Central Asia Region

Guest Editor: F.X. Bosch
Co-Editors: M. Poljak, S.I. Rogovskaya, X. Castellsagué, M. Brotons and S. Syrjänen

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Review

Human Papillomavirus Prevalence and Type-Distribution, Cervical Cancer Screening Practices and Current Status of Vaccination Implementation in Russian Federation, the Western Countries of the former Soviet Union, Caucasus Region and Central Asia

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ABSTRACT

Limited data are available on the burden of human papillomavirus (HPV) and its associated diseases in the Russian Federation, the Western Countries of the former Soviet Union (Belarus, Republic of Moldova, Ukraine), the Caucasus region and Central Asia (Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan). Both the incidence and mortality rate of cervical cancer are higher in these countries than in most Western European countries. In this article, we review available data on HPV prevalence and type distribution in women with normal cytology, women from the general population, cervical precancerous lesions and cervical cancer, as well as data on national policies of cervical cancer screening and HPV vaccination initiatives in these countries. Based on scarce data from the 12 countries, the high-risk HPV (hrHPV) prevalence among 5226 women with normal cytology ranged from 0.0% to 48.4%. In women with low-grade cervical lesions, the hrHPV prevalence among 1062 women varied from 29.2% to 100%. HrHPV infection in 565 women with high-grade cervical lesions ranged from 77.2% to 100% and in 464 invasive cervical cancer samples from 89.8% to 100%. HPV16 was the most commonly detected hrHPV genotype in all categories. As the HPV genotype distribution in cervical diseases seems to be similar to that found in Western Europe the implementation of HPV testing in screening programs might be beneficial. Opportunistic screening programs, the lack of efficient call-recall systems, low coverage, and the absence of quality assured cytology with centralized screening registry are major reasons for low success rates of cervical cancer programs in many of the countries. Finally, HPV vaccination is currently not widely implemented in most of the twelve countries mainly due to pricing, availability, and limited awareness among public and health care providers. Country-specific research, organized nationwide screening programs, registries and well defined vaccination policies are needed.

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This article forms part of a Regional Report entitled "*Comprehensive Control of HPV Infections and Related Diseases in the Central and Eastern Europe and Central Asia Region*" Vaccine Volume 31, Supplement 7, 2013. Updates of the progress in the field are presented in a separate monograph entitled "*Comprehensive Control of HPV Infections and Related Diseases*" Vaccine Volume 30, Supplement 5, 2012.

1. Introduction

Human papillomavirus (HPV) infection, the main etiological factor of cervical cancer, has been extensively studied worldwide [1,2]. However, limited data are available on HPV genotype-specific distribution, prevalence, and incidence of its associated cervical diseases in different populations of the highly divergent regions of the Russian Federation, the Western Countries of the former Soviet Union (SU), the Caucasus Region and Central Asia. Since the early 1990's, when new independent former SU states were established, restructuring of the health care systems and changes in the economic situation have challenged the programs for cancer screening and primary prevention. In addition, the presence of concomitant risk factors, such as sexually transmitted diseases (STD), heavy tobacco smoking, and young age at first intercourse, combined with the lack of effective screening programs all contribute to the difficulty of reducing the burden of cervical cancer in this region of the world [3–8]. The incidence rates of cervical cancer in many countries of these regions (ranging from 6.7 per 100,000 women in Turkmenistan to 26.5 per 100,000 in Kyrgyzstan) and the mortality rates (ranging from 3.7 per 100,000 women in Turkmenistan to 13.4 per 100,000 in Kyrgyzstan) (Bray F *et al.*, Vaccine, this issue [9]) are higher than in Western European countries (incidence rates ranging from 2.1 per 100,000 women in Malta to 12.2 per 100,000 in Portugal; mortality rates ranging from 0.8 per 100,000 women in Iceland to 3.6 per 100,000 in Portugal) [10]. Approximately 25,700 women are diagnosed with cervical cancer and 12,700 die from this disease annually in these regions (Bray F *et al.*, Vaccine, this issue [9]).

This article outlines current cervical cancer screening practices and the implementation status of HPV vaccination in the Russian Federation, the Western Countries of the former SU (Belarus, Republic of Moldova, Ukraine) and the Caucasus region and Central Asia (Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan). Available data on HPV prevalence and type-specific distribution in women with normal cytology and from the general population, and cervical cancer and its precursor lesions in these 12 countries is also presented. A similar review for other Eastern and Central European countries is available in another article of this monograph (see Poljak M *et al.*, Vaccine, this issue [11]).

Data have been collected by a detailed review of published peer-reviewed literature through Medline/PubMed without language limitation performed through January 2012. Since published data in international and indexed medical journals are relatively scarce, additional data have been obtained from non-indexed national and local medical journals, key data source person(s) in each country who completed a questionnaire in Russian language and through the Black Sea Countries Coalition surveillance network. Persons who provided data are listed in the Acknowledgments.

2. The burden of HPV infection and HPV type distribution

The majority of HPV prevalence and HPV genotype distribution data in the region have been obtained from non-indexed medical journals. Undefined study populations, unknown underlying disease status of subjects who provided the samples tested and use of clinically non-validated HPV detection methods represented the main challenges in data analysis. To allow comparison of regional data with international data, the following inclusion criteria were applied: (i) cytology and/or histology results available, or general population study, (ii) use of Hybrid Capture®2 (HC2), Qiagen Gaithersburg, Inc., MD, USA (previously Digene Corp.) or polymerase chain reaction (PCR) for HPV detection, (iii) available description of HPV detection and genotyping methods used, and (iv) detection of high-risk HPV (hrHPV). In Russian Federation, 9 studies used AmpliSens® Real-Time PCR kit (InterLabService, Moscow, Russia) (AmpliSens) for HPV testing, which detects 12 different hrHPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59). Primers target HPV E1 and E2 genes. The method was recently compared with nested GP5+/6+ and MY09/11-PCR and HC2. AmpliSens® was found to be more sensitive (analytic sensitivity $1–5 \times 10^3$ GE/ml) and specific than the two other methods tested [12].

Key results of the studies dealing with the burden of HPV infection and HPV genotype distribution in the targeted countries are summarized in Tables 1–4.

2.1. HPV prevalence and type distribution in women with normal cervical cytology or in general population

Sixteen studies from Belarus, Georgia, Kazakhstan, Russian Federation and Uzbekistan were identified and are presented in Table 1 ([4,12–25], Stina Syrjänen, University of Turku, personal communication, March 2012, Nurzan Makhmutov, South-Kazakh Medical academy, personal communication, November 2010 and Tatyana Karatjuk, Omsk Medical Academy, personal communication, November 2011).

Seven studies conducted in Belarus ([13] and Stina Syrjänen, University of Turku, personal communication, March 2012), Georgia [14], and the Russian Federation ([13,17,22–24], Stina Syrjänen, University of Turku, personal communication, March 2012, Tatyana Karatjuk, Omsk Medical Academy, personal communication, November 2011), included women with normal cytology. In these seven studies, the hrHPV prevalence among 5226 women with normal cytology ranged from 0% (Tatyana Karatjuk, Omsk Medical Academy, personal communication, November 2011) to 48.4% [17]. This variation in HPV infection might result from different risk, age ranges and sample sizes of included populations, differences in HPV detection techniques and quality of cytological assessment. HPV16 was confirmed as the most common type in Belarus, with a prevalence range of 4.0–7.1%, and Russia, with a prevalence range of 2.7–14.1%. In Georgia, the most prevalent HPV type was HPV45 (1.6%).

The largest study among women with normal cytology in the region (INCO study) included a total of 3175 consecutive females attending six outpatient clinics in Moscow, Novgorod (Russian Federation), Minsk (Belarus), and Riga (Latvia) [13]. Three target populations were studied: (1) cervical cancer screening patients; (2) those attending gynecology outpatient clinics with different indications and (3) STD clinic patients. In total 6300 HC2 tests were performed of which 1511 were also tested with PCR (GP5+/6+ primers and subsequent hybridization with hr-oligo probe mixture (15 oligos), 3300 samples were analysed also with TaqMan® assays (Applied Biosystems Inc., Foster City, CA, USA) for the presence of HPV types 16, 18, 31, 33, 35, 39, 45, 52, and 58 [26]. Later, 190 samples were genotyped with Multimetrix test (Stina Syrjänen,

Table 1
Burden of high-risk HPV infection and HPV type distribution in women with normal cytology or in general population by country, study and population.

Country	Area	Reference	Population description	HPV test, Genotyping	Year of sample collection	N women	Mean age (range)	hrHPV pos (N)	hrHPV prev (%)	hrHPV types (%)													
										16	18	16/18	31	33	35	39	45	51	52	56	58	59
Belarus	Minsk	INCO study[a]	Gynecological outpatients	RT-PCR, inhouse	1998–2000	322	28.2 (15–63)	76	23.6	7.1	4.7[b]	–	1.9	4.0[c]	–[d]	0.6	4.7[b]	–	4.0[c]	–	4.0[c]	–
Belarus	Minsk	INCO study[a]	Attendants STD clinic	RT-PCR, inhouse	1998–2000	50	30.2 (16–48)	7	14.0	4.0	0.0	–	0.0	2.0[c]	–[d]	2.0	0.0	–	2.0[c]	–	2.0[c]	–
Georgia	Tbilisi	Alibegashvili T *et al.* 2011 [14]	General population	GP5+/6+ PCR, RLB	2007	1247	NR (15–59[e])	85	6.8	0.5	0.6	1.1	1.2	0.5	0.2	0.2	1.6	0.7	0.3	0.6	0.6	0.2
Kazakhstan	South	Buleshov MA *et al.* 2011 [15]; Makhmutov N[a]	Screening population[f]	HC2	NR	17,000	NR (35–60)	1870[g]	11.0	–	–	–	–	–	–	–	–	–	–	–	–	–
Russian Federation	Moscow	Kubanov AA 2005 [16]	General population[f]	PCR, genotyping by direct-SPH	1998–2003	8533	NR (NR)	1284[h]	15.0[h]	NR	NR	3.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Russian Federation	Moscow	Kuevda D *et al.* 2009 [12]	Attendants STD clinic[f]	RT-PCR, AmpliSens	2006–2008	571	27.2 (18–39.8)	121	21.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Russian Federation	Moscow	Komarova EV *et al.* 2010 [17][i]	Gynecological patients	RT-PCR, AmpliSens	2005–2010	352	32.1 (17–76)[e]	170[g]	48.4	36.3[j,k]	7.3[j,k]	NR	23.3[j,k]	13.0[j,k]	7.3[j,k]	8.9[j,k]	8.9[j,k]	8.1[j,k]	17.0[j,k]	10.5[j,k]	7.3[j,k]	7.3[j,k]
Russian Federation	Moscow	Bdaizieva ET *et al.* 2010 [18][j]	General population[f]	RT-PCR, AmpliSens	2008	33,112	NR (15–69)	8500	25.7	NR	NR	9.3	NR	NR	NR	NR	NR	–	NR	NR	NR	NR
Russian Federation	Moscow	Shipulina O *et al.* 2011 [19]	Adolescent[f]	RT-PCR, AmpliSens	2009	177	NR (13–19)	71	40.1	11.3[g]	6.8[g]	16.9[g]	11.9[g]	5.1[g]	4.0[g]	4.0[g]	2.8[g]	7.3[g]	10.2[g]	7.3[g]	5.1[g]	6.8[g]
Russian Federation	Moscow	Shargorodskaya AV *et al.* 2011 [20][i]	University students[f]	RT-PCR, AmpliSens	2010–2011	266	22 (18–30)	75[g]	28.2	7.5[g]	NR	NR	NR	NR	NR	5.6[g]	NR	NR	NR	6.8[g]	NR	NR
Russian Federation	Moscow	Goncharevskaya Z *et al.* 2011 [21]	CC Screening Patients[f]	RT-PCR, AmpliSens	2011	5182	45 (15–77)	695	13.4	4.4[g]	0.8[g]	NR	2.3[g]	1.1[g]	0.6[g]	1.1[g]	1.0[g]	1.4[g]	1.8[g]	1.7[g]	1.1[g]	0.8[g]
Russian Federation	Moscow and Novgorod	INCO study[a]	CC Screening Patients	RT-PCR, inhouse	1998–2000	833	35.6 (15.8–76.2)	216	25.9	7.1	3.4[b]	–	7.8	1.4[c]	–[d]	0.0	3.4[b]	–	1.4[c]	–	1.4[c]	–
Russian Federation	Moscow and Novgorod	INCO study[a]	Gynecological outpatients	RT-PCR, inhouse	1998–2000	75	31.3 (17.9–54.3)	27	36.0	14.1	4.0[b]	–	5.3	5.3[c]	–[d]	0.8	4.0[b]	–	5.3[c]	–	5.3[c]	–
Russian Federation	Moscow and Novgorod	INCO study[a]	Attendants STD clinic	RT-PCR, inhouse	1998–2000	469	28.2 (15.7–57.2)	170	36.2	10.4	4.3[b]	–	3.6	5.5[c]	0.2	0.6	4.3[b]	–	5.5[c]	–	5.5[c]	–
Russian Federation	Novgorod	Shevchenko EA *et al.* 2009 [4]	Attendants health center with no genital symptoms[f]	RT-PCR	2008	950	NR (18–45)	NR	NR	NR	NR	41.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Russian Federation	St. Petersburg	Alexandrova YN *et al.* 1999 [22][l]	Gynecological patients	MY09/11 PCR, RDB	1996–1998	309	30.2 (15–45)	NR	NR	7.4	1.9	NR	3.2	1.3	0.3	1.3	0.3	0.0	0.0	0.0	0.6	0.0
Russian Federation	St. Petersburg	Shipitsyna E *et al.* 2011 [23]	Gynecological outpatients	HC2, direct sequencing, RT-PCR	2008–2009	741	39.5 (30–65)[e]	73	9.9	2.7	0.5	NR	2.0	1.1	0.4	0.3	0.5	0.3	1.1	0.8	0.4	0.3
Russian Federation	Siberia,Tomsk	Karatjuk T[a]	Gynecological patients, control (healthy)	RT-PCR, AmpliSens	2008–2011	25	NR (19–45)	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Russian Federation	Ural, Ekaterinburg	Evstigneeva NP 2009 [24][i]	Attendants STD clinic	RT-PCR, AmpliSens	2008	803	NR (15–82[e])	212[g]	26.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Uzbekistan	Tashkent	Inamova ST *et al.* 2009 [25]	Gynecological patients[f]	PCR	2008	2295	NR (18–40)	869	37.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Amplisens: AmpliSens® (InterLabService, Moscow, Russia); CC: Cervical cancer; HC2: Hybrid Capture®2 (Qiagen Gaithersburg. Inc., MD, USA [previously Digene Corp.]); N: Number; NR: Not reported; pos: positive; prev: prevalence; RDB: Reverse dot-blot; RLB: Reverse line-blot hybridization; RT-PCR: Real time polychain reaction; SPH: solid phase hybridization; STD: Sexually transmitted disease; TS-PCR: Type-specific polychain reaction; "-": Not tested for the specific HPV type.

HPV type specific %: Percentage of type-specific infections among all analyzed samples; HPV16/18%: Percentage of infections with HPV16 and/or 18 among all analyzed samples.

[a] Personal communication. INCO study: Stina Syrjänen, University of Turku, personal communication, March 2012; Makhmutov N: Nurzan Makhmutov, South-Kazakh Medical academy, personal communication, November 2010; Karatjuk T: Tatyana Karatjuk, Omsk Medical Academy, personal communication, November 2011.

[b] HPV 18/45 reported as aggregated data.

[c] HPV 33/52/58 reported as aggregated data.

[d] HPV35 was only determined in 1451 samples of 3018 samples tested in the INCO study.

[e] Age information is related to the overall sample of the study.

[f] Study done in general population (no cytological result available).

[g] Not contributed by the authors of the study, but calculated using information from the authors.

[h] Includes low-risk types HPV6 and HPV11.

[i] Author provided additional data from their study for this review.

[j] HPV genotyping was performed in 124 HPV DNA positive patients with normal cytology.

[k] HPV type-specific distribution among HPV DNA positive samples.

[l] HPV type-specific distribution data were extracted from Bruni *et al.* JID 2010 meta-analysis database.

Table 2
Burden of high-risk HPV infection and HPV type distribution in women with low-grade squamous intraepithelial lesions (LSIL), atypical cells of undetermined significance (ASC-US) or cervical intraepithelial neoplasia (CIN) grade 1 by country, study and population.

Country	Area	Reference	Population description	HPV test, Genotyping	Year of sample collection	N women	Mean age (range)	Lesion	hrHPV pos (N)	hrHPV prev (%)	hrHPV types (%)												
											16	18	31	33	35	39	45	51	52	56	58	59	
Belarus	Minsk	INCO study[a]	Gynecological outpatients	RT-PCR, inhouse	1998-2000	106	28.9 (17.3-54.0)	ASC-US	31	29.2	12.3	0.9[b]	1.8	6.6[c]	-[d]	1.8	0.9[b]	-	6.6[c]	-	6.6[c]	-	
Belarus	Minsk	INCO study[a]	Attendants STD clinic	RT-PCR, inhouse	1998-2000	35	26.3 (16.0-36.6)	ASC-US	22	62.8	9.7	19.4[b]	3.2	9.7[c]	-[d]	5.6	19.4[b]	-	9.7[c]	-	9.7[c]	-	
Belarus	Minsk	INCO study[a]	Attendants STD clinic	RT-PCR, inhouse	1998-2000	4	22.2 (15.0-26.7)	LSIL	3	75.0	25.0	0.0	25.0	25.0[c]	-[d]	0.0	0.0	-	25.0[c]	-	25.0[c]	-	
Belarus	Minsk	INCO study[a]	Gynecological outpatients	RT-PCR, inhouse	1998-2000	2	28.5 (26.0-31.0)	LSIL	2	100	50.0	0.0	0.0	0.0	-[d]	50.0	0.0	-	0.0	-	0.0	-	
Russian Federation	Moscow	Komarova EV *et al.* 2010 [17][e]	Gynecological patients	RT-PCR, AmpliSens	2005-2010	329	32.1 (17-76)[f]	LSIL	171[g]	52.0	44.1[h,i]	12.5[h,i]	23.6[h,i]	15.3[h,i]	4.9[h,i]	15.3[h,i]	6.3[h,i]	10.4[h,i]	17.4[h,i]	9.0[h,i]	5.6[h,i]	5.6[h,i]	
Russian Federation	Moscow and Novgorod	INCO study[a]	CC Screening Patients	RT-PCR, inhouse	1998-2000	280	32.3 (17.4-72.0)	ASC-US	93	33.2	10.0	2.9[b]	6.4	3.9[c]	-[d]	0.3	2.9[b]	-	3.9[c]	-	3.9[c]	-	
Russian Federation	Moscow and Novgorod	INCO study[a]	Gynecological outpatients	RT-PCR, inhouse	1998-2000	27	29.2 (19.0-44.1)	ASC-US	12	44.4	25.9	7.0[b]	3.7	3.7[c]	-[d]	0.6	7.0[b]	-	3.7[c]	-	3.7[c]	-	
Russian Federation	Moscow and Novgorod	INCO study[a]	Attendants STD clinic	RT-PCR, inhouse	1998-2000	63	27.5 (16.3-45.2)	ASC-US	43	68.3	19.0	3.1	3.2	3.2[c]	15.9	1.6	1.6	-	3.2[c]	-	3.2[c]	-	
Russian Federation	Moscow and Novgorod	INCO study[a]	CC Screening Patients	RT-PCR, inhouse	1998-2000	19	33.2 (17.9-57.0)	LSIL	13	68.4	21.1	15.8[b]	10.5	5.3[c]	-[d]	5.3	15.8[b]	-	5.3[c]	-	5.3[c]	-	
Russian Federation	Moscow and Novgorod	INCO study[a]	Gynecological outpatients	RT-PCR, inhouse	1998-2000	2	34.3 (21.0-53.4)	LSIL	2	100	50.0	0.0	0.0	0.0	-[d]	50.0	0.0	-	0.0	-	0.0	-	
Russian Federation	Moscow and Novgorod	INCO study[a]	Attendants STD clinic	RT-PCR, inhouse	1998-2000	21	24.6 (18.6-40.6)	LSIL	17	81.0	14.3	9.5[b]	0.0	14.3[c]	0.0	4.8	9.5[b]	-	14.3[c]	-	14.3[c]	-	
Russian Federation	St. Petersburg	Shipitsyna E *et al.* 2011 [23]	Gynecological outpatients	HC2, direct sequencing, RT-PCR	2008-2009	76	39.2 (30-65)[f]	ASC-US/ LSIL	28	36.8	11.8	0.0	9.2	3.9	0.0	1.3	0.0	2.6	5.3	1.3	1.3	1.3	
Russian Federation	Siberia, Tomsk	Karatjuk T[a]	Gynecological patients	RT-PCR, AmpliSens	2008-2011	98	NR (19-45)	CIN1	NR	75.0	48.0	11.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	

Amplisens: AmpliSens® (InterLabService, Moscow, Russia); ASC-US: Atypical squamous cells of undetermined significance; CC: Cervical Cancer; CIN: Cervical intraepithelial neoplasia; HC2: Hybrid Capture®2 (Qiagen Gaithersburg, Inc., MD, USA [previously Digene Corp.]); LSIL: low-grade squamous intraepithelial lesion; N: Number; NR: Not reported; pos: positive; prev: prevalence; RT-PCR: Real time polychain reaction; STD: Sexually transmitted disease; "-": Not tested for the specific HPV type.
HPV type specific %: Percentage of type-specific infections among all analyzed samples.

[a] Personal communication. INCO study: Stina Syrjänen, University of Turku, personal communication, March 2012; Karatjuk T: Tatyana Karatjuk, Omsk Medical Academy, personal communication, November 2011.

[b] HPV 18/45 reported as aggregated data.

[c] HPV 33/52/58 reported as aggregated data.

[d] HPV35 was only determined in 1451 samples of 3018 samples tested in the INCO study.

[e] Author provided additional data from their study for this review.

[f] Age information is related to the overall sample of the study.

[g] Not contributed by the authors of the study, but calculated using information from the authors.

[h] HPV genotyping was performed in 144 HPV DNA positive patients with LSIL.

[i] HPV type-specific distribution among HPV DNA positive samples.

Table 3
Burden of high-risk HPV infection and HPV type distribution in women with high-grade squamous intraepithelial lesions (HSIL) or cervical intraepithelial neoplasia (CIN) grade 2 or 3 by country, study and population.

Country	Area	Reference	Population description	HPV test, Genotyping	Year of sample collection	N women	Mean age (range)	Lesion	hrHPV pos (N)	hrHPV prev (%)	hrHPV types (%)												
											16	18	16/18	31	33	35	39	45	51	52	56	58	59
Russian Federation	Moscow	Komarova EV *et al.* 2010 [17][a]	Gynecological patients with CIN2/3	RT-PCR, AmpliSens	2005-2010	208	32.1 (17-76)[b]	CIN2/3	207[c]	99.5	69.5[d]	9.0[d]	NR	17.6[d]	13.9[d]	2.7[d]	7.5[d]	4.8[d]	5.3[d]	6.4[d]	4.3[d]	5.3[d]	1.1[d]
Russian Federation	Moscow	Korolenkova LI *et al.* 2011 [27]	Pregnant women with HSIL	HC2, PCR	2006-2010	36	30.6 (22-45)	83.4% CIN2/3; 16.6% MIC	36	100	60.2	NR	83.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Russian Federation	Moscow	Korolenkova LI *et al.* 2011 [27]	Nonpregnant women with HSIL	HC2, PCR	2006-2010	248	32.2 (18-44)	85.9% CIN2/3; 14.1% MIC	246	99.2	63.3	NR	79.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Russian Federation	Siberia, Tomsk	Karatjuk T[e]	Gynecological patients	RT-PCR, AmpliSens	2008-2011	42	NR (19-45)	CIN2/3	42	100	69.0	14.3	4.7[f]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Russian Federation	Ural	Evstigneeva NP 2009 [24][a]	Gynecological patients with CIN1/2/3	RT-PCR, AmpliSens	2008	31	NR (15-82)[b]	CIN1/2/3	24[c]	77.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Amplisens: AmpliSens® (InterLabService, Moscow, Russia); CIN: Cervical intraepithelial neoplasia; HC2: Hybrid Capture®2 (Qiagen Gaithersburg, Inc., MD, USA [previously Digene Corp.]); HSIL: High-grade squamous intraepithelial lesion; MIC: Microinvasive carcinoma; N: Number; NR: Not reported; pos: positive; prev: prevalence; RT-PCR: Real time polychain reaction.
HPV type specific %: Percentage of type-specific infections among all analyzed samples; HPV16/18%: Percentage of infections with HPV16 and/or 18 among all analyzed samples.

[a] Author provided additional data from their study for this review.
[b] Age information is related to the overall sample of the study.
[c] Not contributed by the authors of the study, but calculated using information from the authors.
[d] HPV genotyping was performed in 187 HPV DNA positive patients with CIN2/3.
[e] Tatyana Karatjuk, Omsk Medical Academy, personal communication, November 2011.
[f] Coinfection of HPV16 and HPV18.

Table 4
Burden of high-risk HPV infection and HPV type distribution in invasive cervical cancer samples by country, study and cancer histology.

Country	Area	Reference	HPV test, Genotyping	Year of sample collection	N women	Mean age (range)	Lesion	hrHPV pos (N)	hrHPV prev (%)	hrHPV types (%)													
										16	18	16/18	31	33	35	39	45	51	52	56	58	59
Georgia	Tbilisi	Alibegashvili T *et al.* 2011 [14]	GP5+/6+ PCR, RLB	2007	91	45 (21-64)	95.6% SCC; 4.4% ADC	89	97.8	58.2	11.0	68.1	2.2	4.4	2.2	2.2	13.2	1.1	0.0	1.1	3.3	0.0
Russian Federation	Moscow	Kleter B *et al.* 1999 [28]	SPF10	1988-1994	129	NR	SCC	129	100	65.9	6.2	NR	3.9	1.6	1.6	0.0	8.5	0.0	1.6	3.1	2.3	0.0
Russian Federation	Moscow	Kleter B *et al.* 1999 [28]	SPF10	1988-1994	51	NR	ADC	51	100	60.8	17.6	NR	3.9	0.0	2.0	0.0	5.9	0.0	0.0	0.0	0.0	0.0
Russian Federation	Moscow	Zumbach K *et al.* 2000 [29]	GP60/124 PCR, TS-PCR 16,18	1995-1998	128	44 (18-74)	Carcinoma	115	89.8	87.0	15.7	100	-	-	-	-	-	-	-	-	-	-
Russian Federation	St. Petersburg	Zolotoverhkaya E *et al.* 2009 [30]	RT-PCR, AmpliSens	2008-2009	NA	NR	Carcinoma	92	NA	62.0	10.9	NR	9.8	8.7	1.1	0.0	6.5	NR	NR	1.1	NR	NR
Russian Federation	Tatarstan	Samoylova EV *et al.* 1995 [31]	TS-PCR 16,18	NR	21	NR	95.2% SCC; 4.8% ADC	21	100	95.2	14.3	100	-	-	-	-	-	-	-	-	-	-
Russian Federation	Ural	Evstigneeva NP 2009 [24][a]	RT-PCR, AmpliSens	NR	44	NR (15-82)[b]	Carcinoma	40[c]	90.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

ADC: Adenocarcinoma; Amplisens: AmpliSens® (InterLabService, Moscow, Russia); N: Number; NA: Not applicable; NR: Not reported; pos: positive; prev: prevalence; RLB: Reverse line-blot hybridization; RT-PCR: Real time polychain reaction; SCC: Squamous cell carcinoma; *SPF10: prototype research kit INNOLiPA HPV SPF10; TS-PCR: Type-specific polychain reaction;* "–": Not tested for the specific HPV type.
HPV type specific %: Percentage of type-specific HPV infections among HPV DNA positive cases; HPV16/18%: Percentage of infections with HPV16 and/or 18 among HPV DNA positive cases.

[a] Author provided additional data from their study for this review.
[b] Age information is related to the overall sample of the study.
[c] Not contributed by the authors of the study, but calculated using information from the authors.

Jniversity of Turku, personal communication, March 2012). HPV ntegration was analyzed with TaqMan®, targeting HPV16 E2 and E6 (464 samples). HPV follow-up data with colposcopy, cytology and/or histology were available for 887 women [26]. The data extraction from the original file showed that in Moscow, the hrHPV prevalence (real time PCR) among screening, gynecological and STD clinic patients with normal cytology was 25.9%, 36.0% and 36.2%, respectively (Stina Syrjänen, University of Turku, personal communication, March 2012). The hrHPV prevalence in Minsk (Belarus) in gynecologic and STD patients was 23.6% and 14.0%, respectively (Stina Syrjänen, University of Turku, personal communication, March 2012). High HPV prevalences in the INCO study may partly be explained by 1) young age of the cohort, 2) well trained gynecologists for optimal sampling, 3) high proportion of high-risk women (STD and gynecologic patients), 4) more sensitive and optimized HPV testing methods performed by expert technicians and 5) cytological classification differing from the Western European system in these countries.

The second largest study is a population-based HPV survey conducted by the International Agency for Research on Cancer and the local Institute of Morphology in Tbilisi (Georgia) from 2007 to 2010. In this study, HPV DNA detection in 1247 women with normal cytology using a GP5+/6+ PCR was 6.8% [13].

With respect to general population studies (no cytological result available), nine studies conducted in Kazakhstan ([15] and Nurzan Makhmutov, South-Kazakh Medical academy, personal communication, November 2010), Russian Federation [4,12,16,18–21], and Uzbekistan [25] were identified. The hrHPV prevalence in women from the general population ranged from 11.0% in an HC2-based screening study conducted in South Kazakhstan that included 17,000 women ([15] and Nurzan Makhmutov, South-Kazakh Medical academy, personal communication, November 2010) to 40.1% in adolescents in Moscow [19]. The only study identified in Uzbekistan among 2295 women who applied for routine gynecological care to the biggest obstetric and gynecologic clinical center in the country detected hrHPV infection in 37.9% of women [25].

To the best of our knowledge, there are no available HPV prevalence data for Armenia, Azerbaijan, Kyrgyzstan, Republic of Moldova, Tajikistan, Turkmenistan or Ukraine.

2.2. HPV prevalence and type distribution in women with low-grade cervical lesions

Only four studies from Belarus and Russian Federation were identified to describe HPV prevalence in women with low-grade cervical lesions (atypical squamous cells of undetermined significance [ASC-US], low-grade squamous intraepithelial lesion [LSIL] and cervical intraepithelial neoplasia grade 1 [CIN1]) (Table 2) ([13,17,23], Stina Syrjänen, University of Turku, personal communication, March 2012, Tatyana Karatjuk, Omsk Medical Academy, personal communication, November 2011). High-risk HPV prevalence in 1062 women with low-grade cervical lesions varied from 29.2% to 100%, although 100% prevalence was detected in populations that included only 2 women. The most common HPV genotype detected was HPV16.

In the INCO study, the hrHPV detection rate (real time PCR) in the screened population, gynecologic, and STD patients with ASC-US in Russian Federation (Moscow) was 33.2%, 44.4% and 68.3%, respectively. In Belarus (Minsk), the hrHPV prevalence among gynecologic and STD patients with ASC-US was 29.2% and 62.8%, respectively ([13] and Stina Syrjänen, University of Turku, personal communication, March 2012). Similar figures were also obtained in smaller studies from the region ([17,23], Tatyana Karatjuk, Omsk Medical Academy, personal communication, November 2011).

2.3. HPV prevalence and type distribution in women with high-grade cervical lesions

Four studies examining the HPV DNA prevalence in women with high-grade cervical lesions (high-grade squamous intraepithelial lesions [HSIL], CIN2 or CIN3) in the Russian Federation were identified (Table 3) ([17,24,27], Tatyana Karatjuk, Omsk Medical Academy, personal communication, November 2011]). The hrHPV prevalence in 565 women with high-grade cervical lesions ranged between 77.2% and 100%. A large study that reported HPV type-distribution among 187 CIN2/3 cases found that HPV16 was the most prevalent HPV genotype (69.5%), followed by HPV31 (17.6%), HPV33 (13.9%) and HPV39 (7.5%) [17].

2.4. HPV prevalence and type distribution in women with invasive cervical cancer

Six studies analyzing the HPV DNA prevalence in 464 invasive cervical cancer samples were identified [14,24,28–31]. As shown in Table 4, the prevalence of hrHPV infection ranged from 89.8% to 100%.

Three studies conducted in the Russian Federation [28,30] and Georgia [14] analyzed the HPV type distribution in at least 90 samples. Consistent with global estimates [32], in these three studies HPV16 was the most prevalent HPV type, varying from 58.2% among HPV-positive cases in Georgia to 65.9% in Russian Federation. The second most frequent HPV type was HPV18 (6.2–17.6%) or HPV45 (5.9–13.2%). The proportion of invasive cervical cancer cases positive for HPV16 and/or 18 was available in only three studies (range 68.1–100%) [14,29,31].

3. Cervical cancer screening practices

Cervical cancer screening in most of the Central Asian countries, the Caucasus region, the Russian Federation and the Western countries of the former SU is mainly opportunistic and characterized by cytology testing, using Romanowsky staining [33] and generally low or unreported coverage. Few examples of nationwide good coverage rates by opportunistic screening programs as described for Belarus, a country with a long history of cervical cancer screening, and Kazakhstan are very promising ([15,34,35], Nurzan Makhmutov, South-Kazakh Medical academy, personal communication, November 2010). Generally, the government covers expenses on cytology screening, biopsy and treatment. This is free of charge for residents in the majority of the countries (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Republic of Moldova, Russian Federation, Turkmenistan, Ukraine, and Uzbekistan). HPV testing is available on a self-payment basis in large cities. However, key challenges, such as as regional inequities in health financing, utilization of services, and health outcomes, have recently been described, for example, for Kazakhstan [36] and population health has not yet improved in the region.

3.1. Cervical cancer screening practices in the Russian Federation and Western countries of the former Soviet Union

In 1964, annual cytology screening was introduced in the former SU as part of routine cervical cancer screening programs. The first mobile cervical cancer prevention outreach program, intended primarily to screen women from the rural areas, was introduced in the Republic of Belarus in 1966. In 1976, the Ministry of Health (MOH) established centralized cytology laboratories in all regions and republics of the former SU to ensure quality control of cytology. Activities of opportunistic screening for cervical cancer performed by trained midwifes were integrated in polyclinic visits and are still performed to a certain extent in Belarus, Republic of Moldova, the

Table 5
Cervical cancer screening activities in Russian Federation and Western countries of the former Soviet Union.

Country	National protocols	Screening age	Screening interval	Screening methods	Screening units	Health care providers performing examination	Screening system	Registries	Coverage
Russian Federation	Order No.1253 (dated 30.12.1976) Order No.50 Order No.808	First intercourse or 18 years–No upper age limit	Annually	Pap test with basic Romanowsky or H&E staining	Primary level[a] and specialized ambulatory healthcare	Nurses and ob\gyns	Opportunistic; call-recall in few regions on irregular basis	National Cancer Registry, national and regional population registry	20–25%
Russian Federation Moscow	Order No.103 of the Moscow Committee of Health (dated 05.03.2002)	35–69 years	Every 3 years	Pap test with basic Romanowsky or MGG staining	Primary level[a], secondary level[a] and specialized ambulatory healthcare	Nurses and ob\gyns	Opportunistic screening program; call-recall in few regions on irregular basis	Moscow Cancer Registry, population registry	40–90%
Belarus	Minister's Order not available. Instruction for methodology of screening No.83-0904 (dated 03.02.2005)	18 years–No upper age limit	Annually	Pap test	Primary level, secondary level and specialized ambulatory healthcare	Nurses, ob\gyns	Opportunistic; no call-recall system	National Cancer Registry, population registry	75–80%
Republic of Moldova	Order No.68 (dated 10.03.2005)	20 years–No upper age limit	Every 2 years	Pap test	Upon visit at primary level, secondary level and specialized ambulatory healthcare	Midwives, ob\gyns and general practitioner	Opportunistic; no call-recall system	National population registry	Not available
Ukraine	Order No.503 (dated 28.12.2002) Order No.677 (dated 31.12.2004) Order No.48 (dated 03.02.2006)	18–65 years	Annually	Smear test with basic Romanowsky and Papanicolaou staining	Primary level and specialized ambulatory healthcare. Special cervical pathology cabinets on primary and secondary level	Nurses, ob\gyns and general practitioner	Opportunistic; no call-recall system	National Cancer Registry, national population registry; registration in a computerized system in two regions	20–30%

H&E: Hematoxylin and Eosin staining; MGG: May–Grünwald–Giemsa staining; Ob\gyns: Obstetrician\gynecologists.

[a] Primary levels (paramedical–obstetrical stations, paramedical stations, examination rooms, family doctor's out-patient facilities, district hospitals) and secondary levels (central regional hospitals, women's health centers, family planning).

Russian Federation and Ukraine [37,38]. The main features of current cervical cancer screening practices in the Russian Federation and Western countries of the former SU are summarized in Table 5.

Since 2009, 4330 offices have become involved in the Russian National Oncologic Program [39]. Guidelines advise annual prophylactic examinations for women over 18 years of age, along with free-of-charge Pap tests, as well as colposcopy, biopsy and treatment [33,37]. Usually, smears are first investigated by cytoscreeners (nurses or technical assistants) followed by an examination by the cytopathologist in the case of abnormal smears [33]. The coverage is generally estimated at 20–25% in the Russian territory (Elena Rudakova, Omsk Medical University, personal communication, September 2011). As a consequence, only 29% of women in Russian Federation diagnosed with cervical cancer have had a prior Pap smear; this proportion was 37.5% in the Central Federal Okrug and was lower in other regions, e.g., Khabarovsk (2.9%) and Kalmykia (3.1%) [39]. Currently, several professional societies and institutions including the Russian Medical Academy of Postgraduate Education are taking the initiative to develop colposcopy and cytology training programs for the Russian Federation and countries of the former SU.

Moscow is the first region in the Russian Federation to have implemented an opportunistic cervical cancer screening program with elements of a call-recall system in 2002, organized by the Moscow Public Health Department. The number of gynecologic examination rooms has doubled between 2001 and 2010. Centralized cytology laboratories have been set up in all administrative districts. Health information campaigns have been set up and screening services are accessible for 1,613,907 eligible women. A total of 327,500 women were screened in 2002, 499,824 in 2005, and 556,394 in 2010. However, as there is no centralized screening database, the exact coverage of the target population varies between 40–90%, according to different sources. The detection rate of CIN3 cases in Moscow increased from 0.04% in 2002 to 0.09% in 2010. Incidence of stage IV cancer decreased from 9.3 per 100,000 in 2001 to 5.8 per 100,000 in 2004. The proportion of stages I–II among all newly diagnosed cervical cancer cases increased from 57.3% in 2002 to 67.5% in 2010. The incidence to mortality rate ratio also increased, from 4.5 per 100,000 in 2001 to 8.3 per 100,000 in 2010. The carcinoma in situ versus invasive cervical cancer ratio shifted from 1:5.8 in 2001 to 1:3 in 2009 [39,40]. In spite of the program, the crude cervical cancer incidence rate increased from 12.0 per 100,000 in 2001 to 15.9 per 100,000 in 2010. A possible explanation might be an increase in detected stage IA lesions through increased screening activities, but there are no specific data to support this. The poor impact of the screening program might reflect insufficient coverage of the target population and the absence of a population-based invitation system [40].

In Ukraine, a program was implemented between 2005 and 2010 to increase numbers of skilled cytologists, gynecologists and midwifes. In parallel, reproductive health topics, including initiatives for cervical cancer screening, were advocated through campaigns. Some of the objectives could not be realized, mainly because of insufficient financial support. At present, annual cervical cytology testing is available in an opportunistic manner. A computerized evaluation system on the performance of cytological screening has been introduced in two Ukrainian regions [41,42]. Currently (and scheduled to continue until the end of 2015), Pap smear equipment is provided to cytological laboratories. Furthermore, the national cervical cancer prevention service aims to set up services for cervical lesion management units with specialists trained in colposcopy.

Annual gynecologic examination and Pap smear are available in Belarus. All completed tests and procedures are reported yearly to the district department of obstetrics and gynecology. In 2010, the Belarusian Cancer Registry database indicated that 28% of newly diagnosed cervical cancer patients are diagnosed during screening, of which 21% were in advanced stage [35,43–45]. An HPV test is offered to women with cervical lesions on self-payment basis. Since 2010, all pregnant women in Minsk are systematically tested for STDs, including HPV, free of charge.

Since 2005, the mandatory health insurance in the Republic of Moldova covers Pap tests, follow-up (colposcopy and biopsy) and treatment of resident women, including minority groups, in all regions [46,47]. The cervical cancer screening program is opportunistic. Guidelines for cervical cancer prevention have been developed within the 'National Strategy for Reproductive Health 2005–2015' and were approved by the MOH.

3.2. Cervical cancer screening practices in the Caucasus region and Central Asia

The main characteristics of cervical cancer screening programs in the Caucasus region and Central Asia are summarized in Table 6.

Since 2007, Armenia has had a cervical cancer prevention program including pelvic examination and Pap smear for all women visiting specially trained health care professionals for the first time. Cancer treatment is available free of charge for residents. Women are informed about cervical cancer screening services by nurses or midwives and counselled with additional information according to booklets that have been developed in cooperation with World Health Organization [47]. Pap smears are taken mainly by gynecologists, who also perform colposcopies. The results of examinations and treatments in these specialized centers are centrally recorded in a national database. Outreach programs are also available to women residing in rural regions of the country but the screening coverage rate is very low [48].

In Azerbaijan, Pap smears are performed at different levels of the health care system. Opportunistic prevention programs are free of charge for residents but are not widely accessible [47]. Outreach programs are also available and provided by oncologists. The National screening program is under development.

In Georgia (Tbilisi), the cervical cancer screening program was initiated in 2008, managed by the National Screening Center and endorsed by the Ministry of Labour Health and Social Affairs. The screening is provided with external quality control of the cytology diagnosis and is designed on an opportunistic basis with elements of a call-recall system. The screening is free of charge every 3 years for women between 25 and 60 years. One year after its implementation, 19.5% of the target population were covered, and in 2011 the cervical screening program was scaled up to other regions of the country [14,47].

A new national program of Kazakhstan for the period 2011–2015 devotes considerable attention and full financial support to early detection of preventable cancers [49]. Cervical cancer screening is recommended for women aged 30 to 60 years, at 5-year intervals [15,34]. Annual coverage of the target population is 72–75%, as reported by the MOH for the last years (Murat Kairbayev, Kazakh Research Institute of Oncology and Radiology, personal communication, October 2011). Launched by MOH, a pilot screening study was carried out in South Kazakhstan in 2008–2009 using conventional Pap test and HC2 (Nurzan Makhmutov, South-Kazakh Medical academy, personal communication, November 2010). Biopsy results are now recorded in a national statistical registry. The National Population Cancer Registry without individual identification has been active since 2003. Kazakhstan is presently launching several new screening projects.

Kyrgyzstan has no cervical cancer screening program. There are no data on the use of Pap smears or HPV testing at the national level [50].

Tajikistan had no cervical cancer screening program until the end of 2009. At that time, a national program on preventive

Table 6
Cervical cancer screening activities in countries of the Caucasus region and Central Asia.

Country	National protocols	Screening age	Screening interval	Screening methods	Screeening units	Health care providers performing examination	Screening system	Registries	Coverage (%)
Armenia	National Strategy of Early Diagnosis, Prevention and Treatment of Cervical Cancer 2006–2015	30–60 years	Every 3 years	Pap test	Polyclinics, specialized centers, health points in village	Ob\gyns	Opportunistic, management by local, regional and national health authorities, no call-recall system	Pap smear results centrally recorded in a national database	10–20%
Azerbaijan	National RH Strategy 2008–2015 (dated 2007) The national strategy on Cervical Cancer prevention is under development	Not available	Not available	Pap test	Polyclinics, women's welfare centers, National Oncologic Centers and Oncologic dispensaries in few regions	Ob\gyns, oncologists, cytologists, surgeons	Opportunistic screening	Not available	Not available
Georgia	National guidelines for CC screening elaborated and endorsed by MoLHSA	25–60 years	Every 3 years	Pap test	Screening centers, hospitals, national and private medical centers	Ob\gyns	Opportunistic with some elements of call-recall system	Not available	20%
Kazakhstan	Order No.607 (dated 15.10.2007) Order No.164 (dated 30.03.2009) Order No.685 (dated 10.11.2009) Order No.145 (dated 16 .03.2011)	30–60 years	Every 5 years	Conventional and liquid based Pap test	Primary level[a], secondary[a] and specialized ambulatory healthcare	Nurses, ob\gyns	Call-recall system in few regions on unregular basis	National Cancer Registry since 2003 and electronic databases (Medinform)	75%
Kyrgyzstan	No orders	Not available	Not available	Pap test and HPV test	Only in a private health center in Bishkek	Not available	No system established	Not available	Not available
Tajikistan	Act No.587 (dated 31.10.2009): Approval of the "National programme for the prophylaxis, diagnosis, and treatment of malignancies for the period of 2010–2015"	20 years- No upper age limit	Not available	Not available	Primary level and specialized ambulatory healthcare in few regions	Not available	Opportunistic screening	Not available	Not available
Turkmenistan	Saglyk National Programme in 2007–2011. Order No.413 (dated October 2010)	20 years - No upper age limit	Annually	Pap test	Primary level and specialized ambulatory healthcare in few regions	Not available	Opportunistic screening	Not available	Not available
Uzbekistan	Order No.312 (dated 03.11.2010) Act No.106 of the Cabinet of Ministers (dated 03.06.2010)	25–49 years	Not available	Pap test	Not available	Not available	Organized cervical cancer screening in four pilot regions (dated 2011)	Not available	Not available

CC: Cervical cancer; MoLHSA: Ministry of Labour Health and Social Affairs; Ob\gyns: Obstetrician\gynecologists; RH: Reproductive Health.

[a] Primary levels (paramedical–obstetrical stations, paramedical stations, examination rooms, family doctor's out-patient facilities, district hospitals) and secondary levels (central regional hospitals, women's health centers, family planning)

maintenance, diagnostics and treatment of malignant neoplasia was established and is undergoing extension planned from 2010 through 2015 [51].

In Turkmenistan, a national cervical cancer screening program was introduced in 2007, and annual cervical cytological tests and colposcopy were initiated in 2010. The population is poorly informed about cervical cancer screening and the coverage is unknown, but it is presumed to be very low (Chary Nazarov, Turkmenian Institution of Mother and Child, personal communication, July 2011).

In Uzbekistan, opportunistic screening with low coverage was originally in place in different regions. In 2010, organized cytological screening was initiated in the most densely populated part of the country (Fergana Valley) and in 2011 extended in other large regions of Uzbekistan (Tashkent, Navoi, Andijan, Nukus) (Said Sultanov, Research Centre of Obstetrics and Gynecology of the MOH of Uzbekistan, personal communication, December 2011). A total of 25,000 women aged 25–49 years are offered Pap tests, follow up for abnormal Pap smears, and treatment. As part of this pilot program, database building and equipment with screening devices (microscope, colposcope, coagulator) and office equipment, as well as training courses and educational material, are provided to general practitioners, gynecologists, and cytologists [52].

The limited data available underline the urgent need for country-specific nationwide research and health counseling of HPV infection, its risk factors and associated burden of diseases, as well as evidence-based prevention programs. With respect to high cervical cancer incidence and mortality rates, there is an obvious need for efficient call-recall systems, and quality-controlled cytology services and registration systems. Also, the standardized Papanicolaou staining of cervical smears should be adopted to allow utilization of international classification systems. A better infrastructure is present in Armenia, Belarus, Kazakhstan, the Russian Federation and Ukraine, compared to the other countries in the region. In countries with low quality cytological screening, HPV-based screening might be an alternative to consider. The treatment of pre-cancerous lesions and cancer identified during the screening is available free-of-charge according to orders of MOH in the majority of countries. However, the accessibility is limited in some regions of Kyrgyzstan, Tajikistan and Uzbekistan.

4. Current status of vaccination implementation

Current status of HPV vaccination implementation in the targeted countries is summarized in Table 7. There are 10 countries with at least one of two HPV vaccines licensed and the introduction of the vaccines is stated within pilot or regional immunization programs. Vaccines are generally available in the private sector and are not included in any of the National immunisation calendars.

In the Russian Federation, following the licensing of both HPV vaccines, Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) and Gardasil® (Merck & Co., Whitehouse Station, NJ USA), vaccination is now available in both state-run and private health centers [53]. HPV vaccines have been incorporated in some regional immunization programs. Over 20,000 girls have been vaccinated in the following regions: Moscow (2009), Moscow Region (2009), Ekaterinburg, Khanty-Mansiysk Okrug (2009), Perm (2009–2010), Smolensk (2010), Tyumen, Novosibirsk, Tomsk, Sakha, and Primorski Kray (2010–2011). In 2012, the programs were extended to Altay, Sakhalin and Kemerovo [53]. The experience gained from the implementation of other vaccines (such as hepatitis B) was used in implementation of the HPV vaccines. Vaccination is administered at children's polyclinics or in the school clinics. The general practice of vaccination at schools in the Russian Federation requires signed

Table 7
HPV vaccination status in Russian Federation, the Western Countries of the former Soviet Union (SU), the Caucasus region and Central Asia.

Regions	Countries	Regional projects for adolescents vaccination	Cervarix® date of licensure	Cervarix® population and age range (years)	Gardasil® date of licensure	Gardasil® population and age range (years)	Implementation of immunization program	Numbers of individuals vaccinated with any vaccine
Russian Federation and Western Countries of the former SU	Russian Federation	Yes	2008	Women (10–25)	2006	Men and women (9–45)	Regional programs	Over 20,000
	Belarus	No	2007	NA	2007	NA	None	Unknown
	Republic of Moldova	Yes	NA	Women (10–55)[a]	NA	Women (9–26)	Donation program	Unknown
	Ukraine	Yes	2007	Women (12-No upper limit)	2008	Men and women (9–45)	In the process of integration into the school-based vaccination program	Unknown
The Caucasus region and Central Asia	Armenia	No	2010	Women (15-No upper limit)	–	–	None	Unknown
	Azerbaijan	No	NA	Women (10-No upper limit)	–	–	None	Unknown
	Georgia	Yes	2010	Women (10-No upper limit)	2010	Women (10-No upper limit)	Pilot program	Unknown
	Kazakhstan	No	2008	Women (10-No upper limit)	2009	Men and women (9–45)	None	Unknown
	Kyrgyzstan	No	–	–	2009	Men and women (9–45)	None	Unknown
	Tajikistan	No	–	–	–	–	None	–
	Turkmenistan	No	–	–	–	–	None	–
	Uzbekistan	Yes	2009[b]	NA	2009	Women (13–15)	Donation program	Over 8000

Cervarix®: Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium); Gardasil®: Gardasil® (Merck & Co., Whitehouse Station, NJ USA); NA: No data available; in date of licensure it implies the HPV vaccine is licensed but date of licensure is not available; "–": Not applicable.

[a] Cervarix license ended in March 2013, GlaxoSmithKline applied for new registration for women aged 10–55 years.

[b] Cervarix was licensed in 2009 but is not on market.

parent's informed consent for all children's vaccinations, including HPV vaccination.

The initiation of the HPV vaccination program in Moscow region revealed a lack of knowledge about HPV among adolescents, parents and teachers. Vaccination was often negatively perceived by society as potential encouragement for adolescents to initiate sexual activity. When information was not provided, only 25% of parents gave their consent to vaccinate their daughters. The majority of the parents interviewed did not know that their children were already sexually active [6]. In Moscow and all other regions where the regional vaccination projects have been implemented, HPV vaccination is covered by local governmental public health funds free-of-charge for resident girls meeting the age criteria. One vaccine shot costs 150–200 United States dollars (USD).

In Belarus and Ukraine, vaccination with both HPV vaccines has been available in some regions, paid for by the individuals (Irina Kosenko, Research Centre of Oncology MOH Belarus, personal communication, July 2011). Vaccine implementation into the national vaccination program is currently under discussion. In Ukraine, HPV vaccination is now in the process of integration in the prophylactic school-based vaccination program. Public sentiment against vaccination arose from bad publicity generated by the unsuccessful measles immunization that has been widely discussed in the national media (Tatyana Tatarchuk, Research Centre of Pediatrics, Obstetrics and Gynecology of MOH Ukraine, personal communication, June 2011).

In the Republic of Moldova, the first 20,000 HPV vaccine doses have been donated and delivered free of charge through primary health care providers in vaccination clinics. Invitations are being sent directly to eligible girls or their parents, or persons who request HPV vaccination from the nurses. All family centers and some other clinics participate in the donor HPV vaccination program [47].

In Armenia and Azerbaijan, only Cervarix® is licensed at present and is available for all girls and women for a fee covered by the individual. No national or pilot HPV vaccination programs have been started [47].

In Georgia, a one-year project for HPV vaccination started in July 2010. It was aimed to cover 6400 girls in the age range of 11–13 years and Gardasil® was provided free of charge. Vaccination was carried out in vaccination network offices and a hotline was established in order to inform interested individuals about the location of the nearest vaccination office. Those who did not meet the criteria of the ongoing HPV vaccination project paid 380 USD for three doses of the HPV vaccine. In this case, the age limit of the patient was not specified. A proposal for the extension of the project for the upcoming years will likely be submitted [47].

In Kazakhstan and Uzbekistan, adult women are vaccinated in private vaccination units. In Uzbekistan in 2010, free-of-charge vaccination with donated Gardasil® was given to 8000 adolescent girls aged from 13–15 years (Said Sultanov, Research Centre of Obstetrics and Gynecology of the MOH of Uzbekistan, personal communication, December 2011).

In Kyrgyzstan Gardasil® is licensed and available for girls, boys and women for a fee, covered by each individual. No national or pilot HPV vaccination programs exist yet.

Tajikistan and Turkmenistan have no HPV vaccines available so far.

5. Conclusion

In conclusion, both the incidence and mortality rate of cervical cancer are higher in the evaluated 12 countries than in most Western European countries. HrHPV prevalence ranged from 0.0–48.4% in women with normal cytology and hrHPV infection in women with high-grade cervical lesions ranged from 77.2–100.0% and in cervical cancer from 89.8–100%. The most commonly detected hrHPV type was HPV16 in all categories. Cervical cancer screening in the targeted countries is mainly opportunistic. HPV vaccination is currently not widely implemented in the region reviewed here. No central recording system on HPV vaccination exists in any of the 12 countries and the exact numbers of vaccinated persons are virtually unknown. The educational health promotion programs for these populations are provided in some countries but need enhancement. Effective HPV-related cancer prevention will heavily depend upon universal geographical access, financial access and on the overall quality of the services provided. This requires national and local advocacy and the establishment of cancer screening, cancer and vaccination registries. Advocacy of the vaccine, including education of health officials, physicians, parents and teachers about the importance of the vaccine, should be conducted as much as possible globally [54]. Recommendations for cervical cancer prevention in the region are discussed in Poljak M *et al.*, Vaccine, this issue [55].

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