HPV Epidemiology and WHO HPV LabNet

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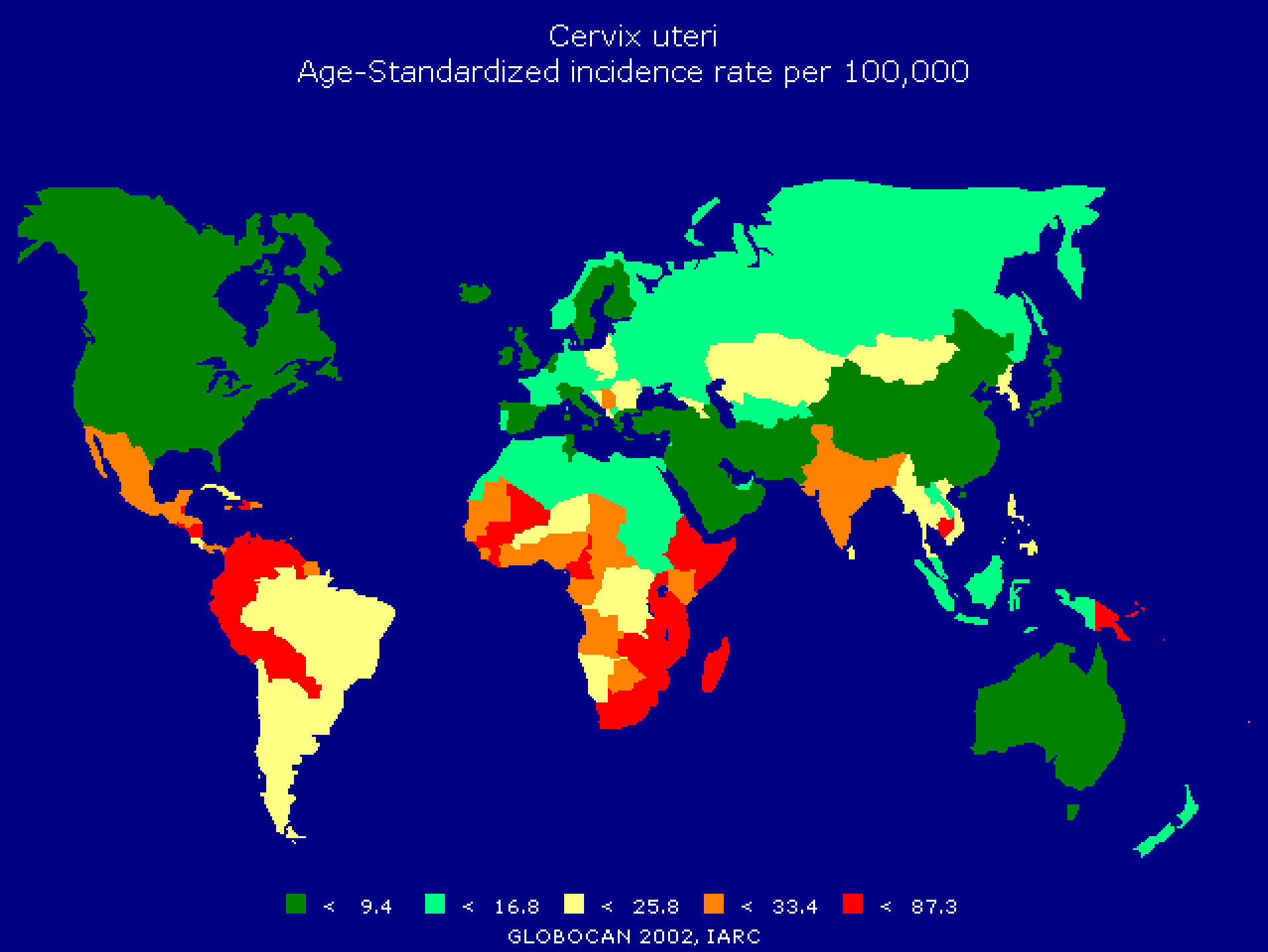
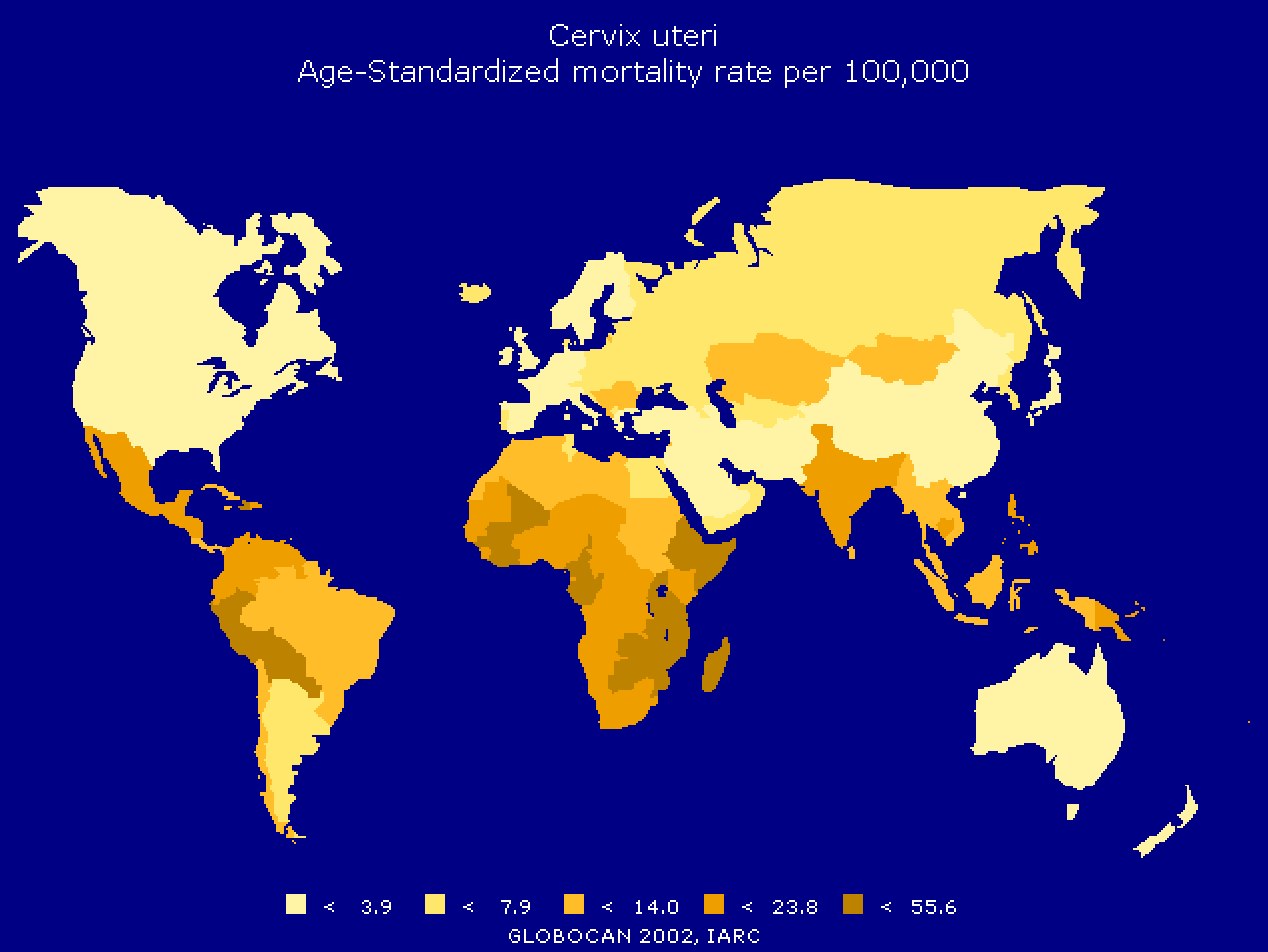
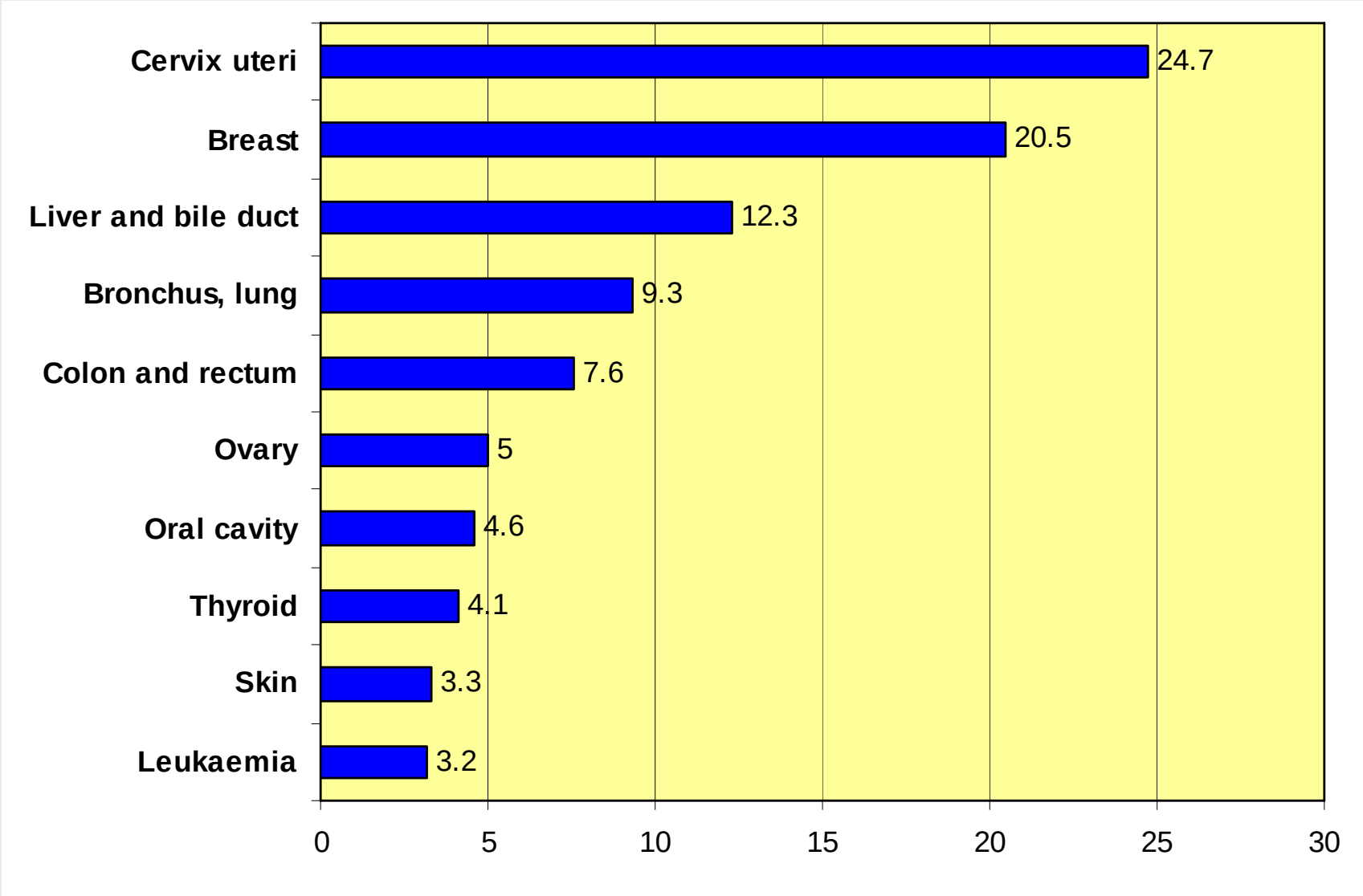

Cervix uteri
Age-Standardized incidence rate per 100,000
< 9.4
< 16.8
< 25.8
< 33.4
< 87.3
GLOBOCAN 2002, IARC


Cervix uteri
Age-Standardized mortality rate per 100,000
< 3.9
< 7.9
< 14.0
< 23.8
< 55.6
GLOBOCAN 2002, IARC

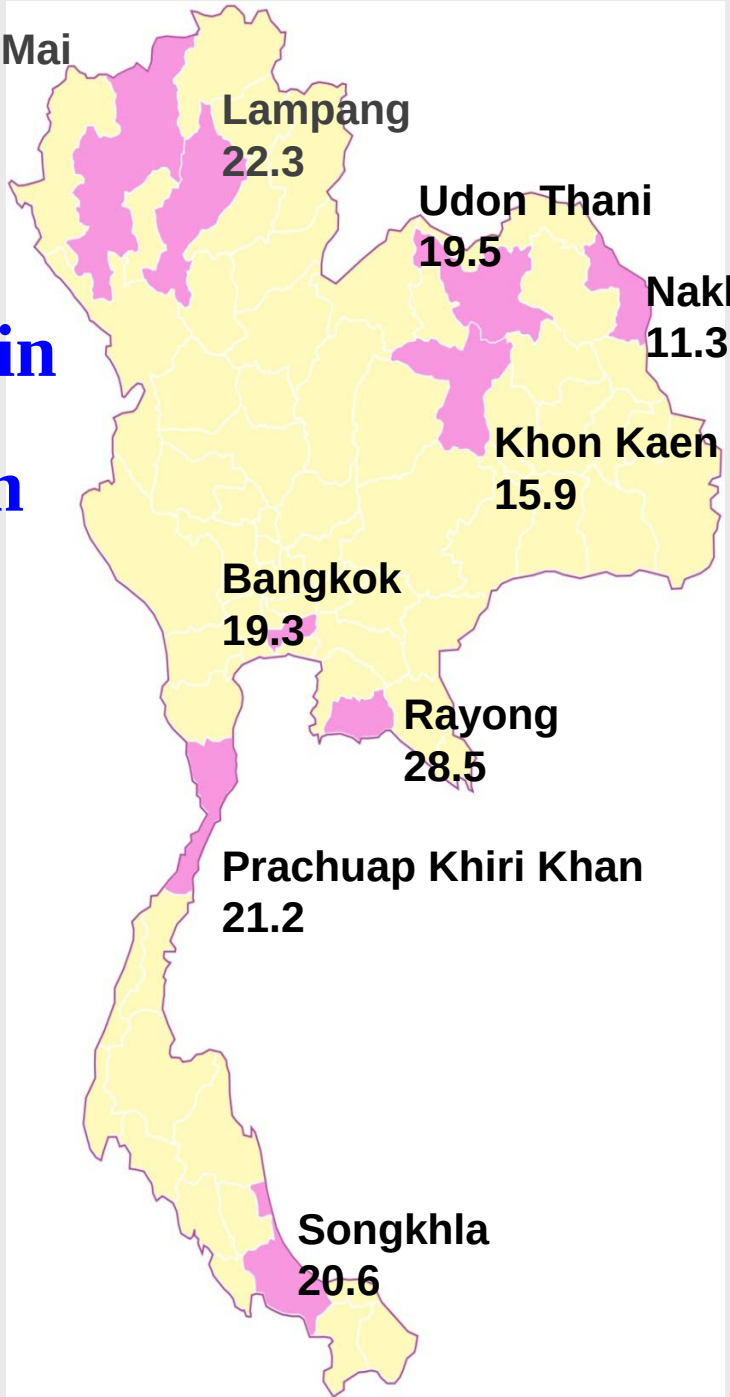
Cervical Cancer is top leading cancer in Thai Female



Cancer in Thailand Vol. IV, 1998-2000

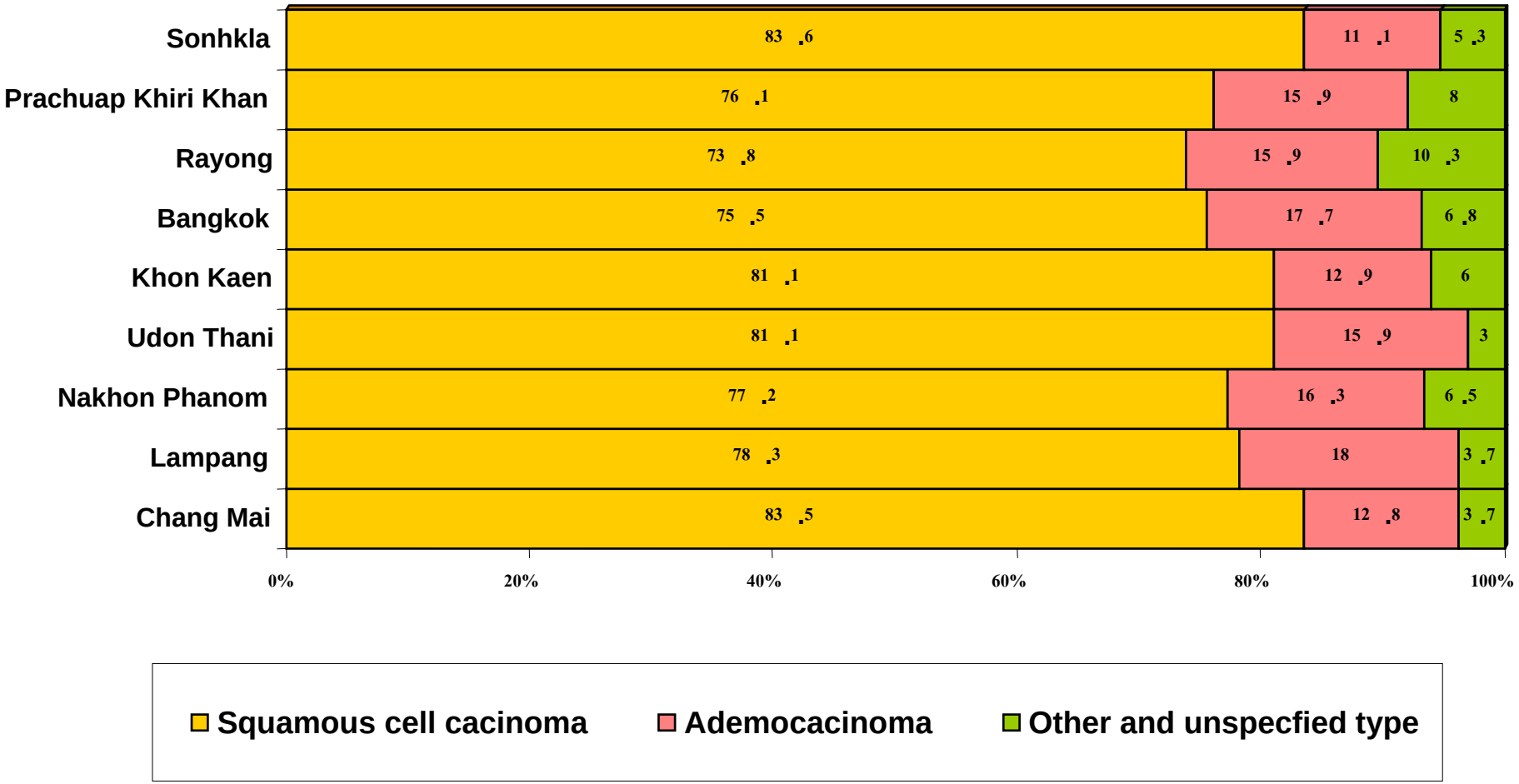
Incidence Cervical in different regions in Thailand

Thailand 24.7



Cancer in Thailand Vol. IV, 1998-2000

Cervical cancer : percentage distribution of histological type among microscopically verified cases ,1998 -2000



Human Papillomavirus

Human papillomavirus (HPV)

HPV is sexually transmitted

- Approximately 40 different types of HPV infect the epithelial lining of the anogenital tract.
- There are oncogenic and non-oncogenic types of HPV.
- Oncogenic HPV is a necessary but not sufficientcause of invasive cervical cancer.
- Most infections caused by oncogenic HPV resolve spontaneously.
- Persistent infections may progress to pre-cancerous lesions.
- Oncogenic HPV has been implicated in other cancers.

IARC Evaluation February 2005

Anogenital tract :

Sufficient evidence for carcinogenicity for types

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66

Some studies also point to

a possible role of HPVs 6, 11, 26, 30, 68, 73, and 82, which are rarely found in human cancers.

Epidemiologic Classification

High risk type: Based of type specific odds ratio

16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, 68, 73

: Based on prevalence among patients and control

39, 82

Probable high risk: Based on prevalence among patients and control

26, 53, 66

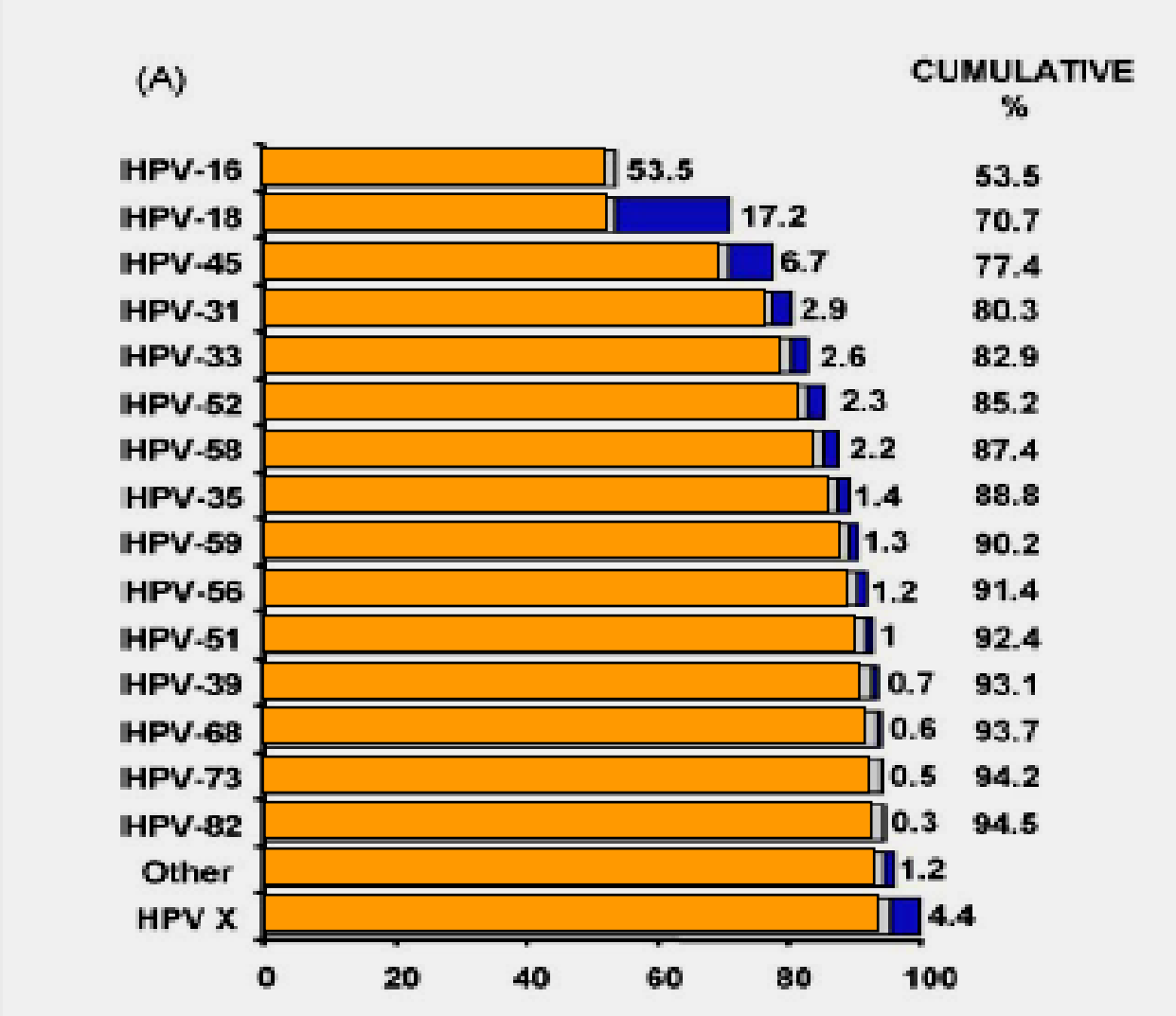
Undetermined risk: Based on none of detection of the sample

34, 57, 83

Munoz et al, N Engl J Med 2003

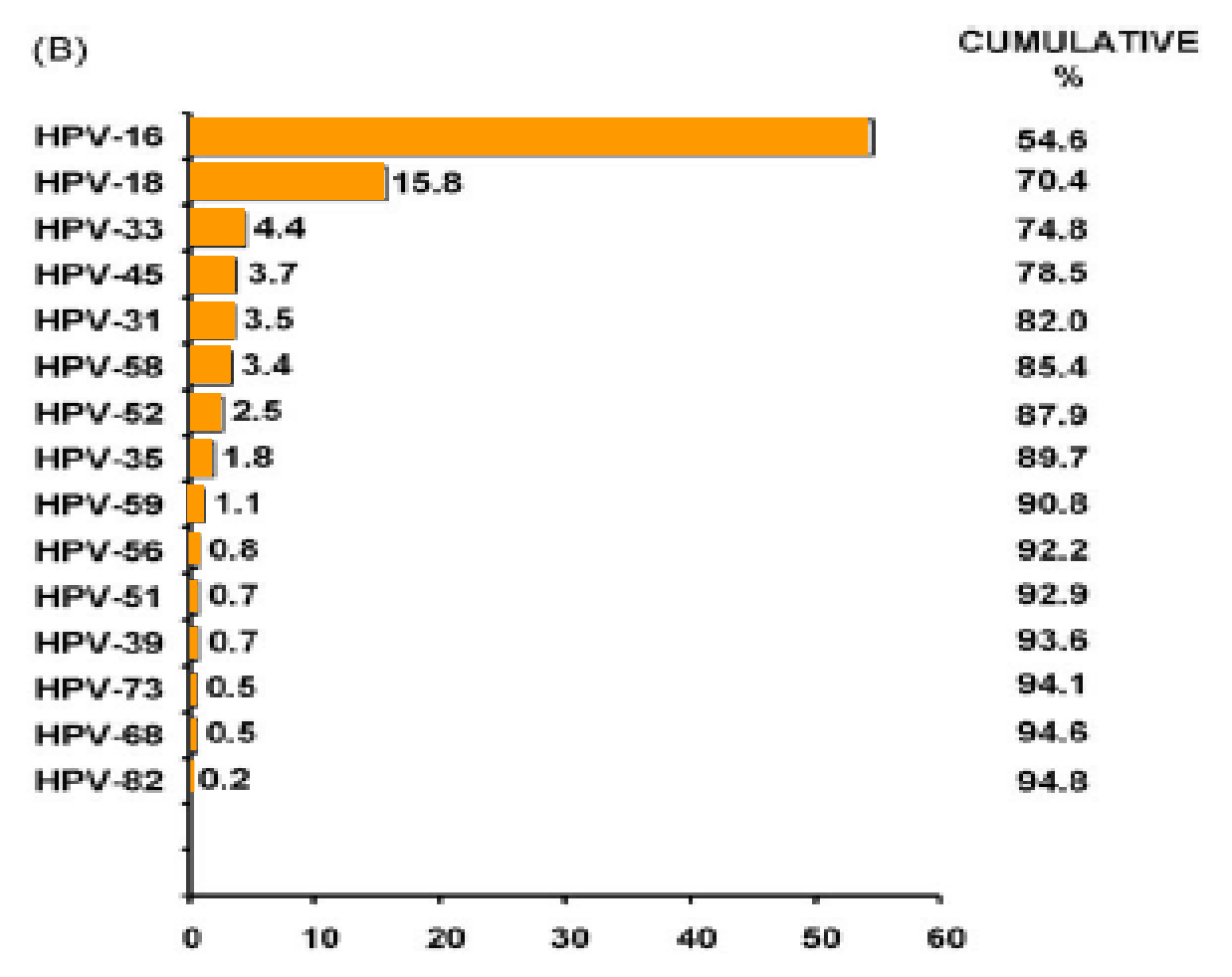
Type of cancer	Papillomvirus types involved	Percent HPV-positive
Cervical cancer	**16**, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 (26, 68, 73, 82)	>95%
Vulva carcinoma		
basaloid	16, 18	>50%
„warty“	16, 18	>50%
keratinizing	16	<10%
Penile carcinoma		
basaloid	16, 18	>50%
„warty“	16, 18	>50%
keratinizing	16	<10%
Vaginal carcinoma	16, 18	>50%
Anal cancer	16, 18	>70%
Oral cavity and tonsils	16, 18, 33	~25%
Nail bed	16	~70%

Percentages of cervical cancer cases attributed to the most frequent HPV types in all world regions combined, as estimated form the IARC pooled analysis of 3085 cases



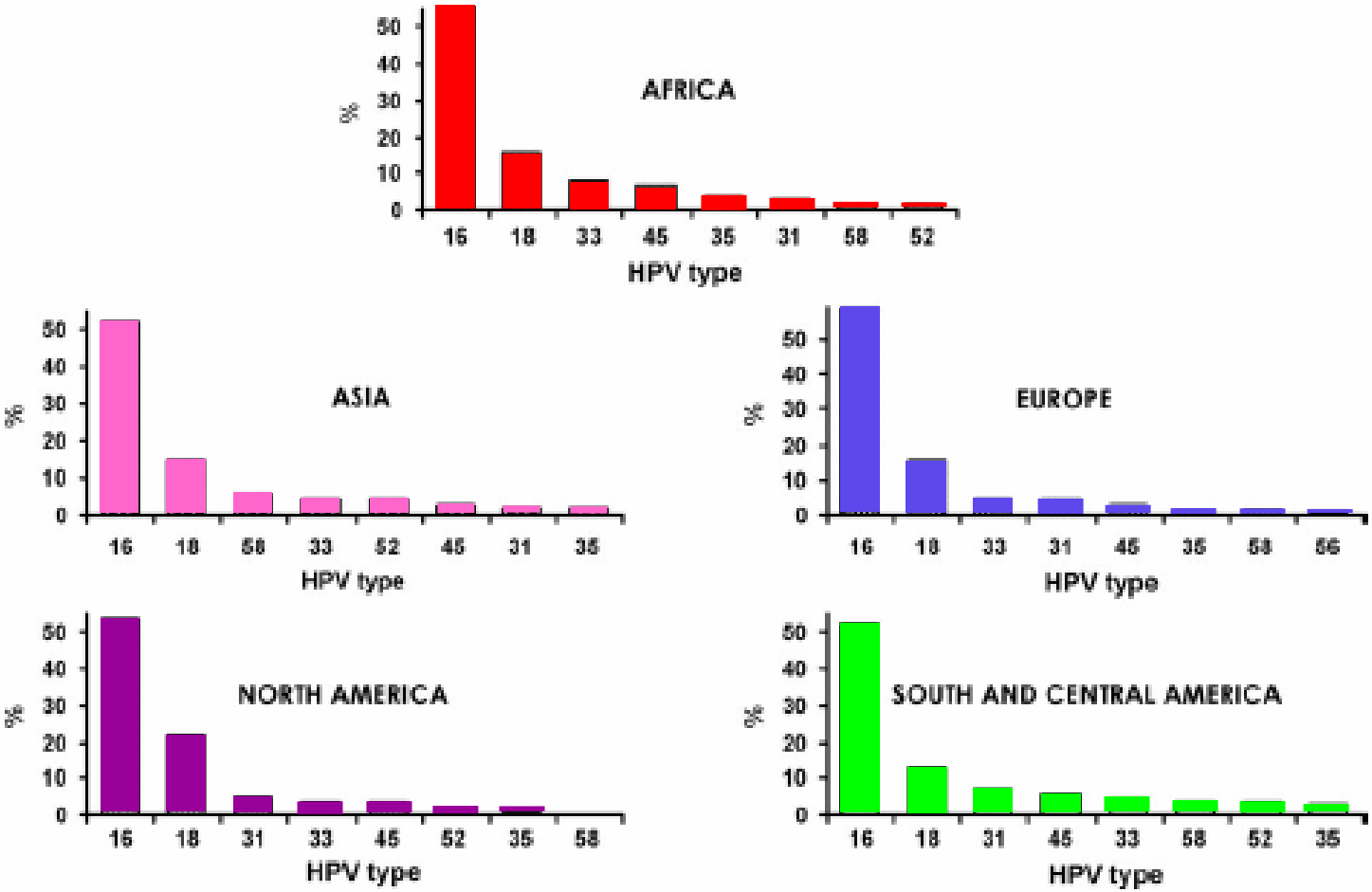
Munoz N et al. Int J Cancer 2004

Percentages of cervical cancer cases attributed to the most frequent HPV types in all world regions combined, as estimated form Meta-analysis of more than 14,500 cases



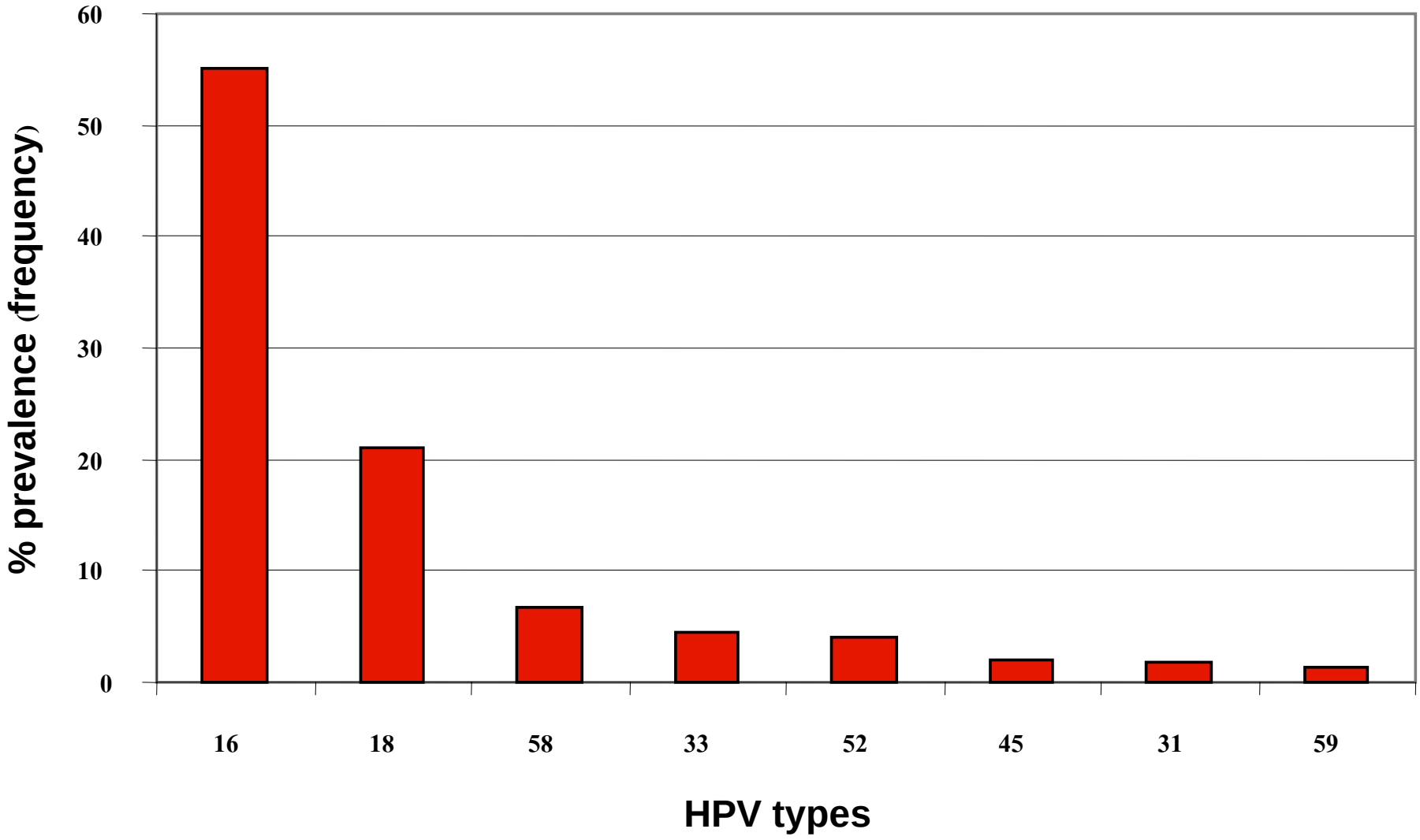
G.Clifford et al. Vaccine 2006

Eight most common HPV types in more than 14,500 cervical cancer cases, by region



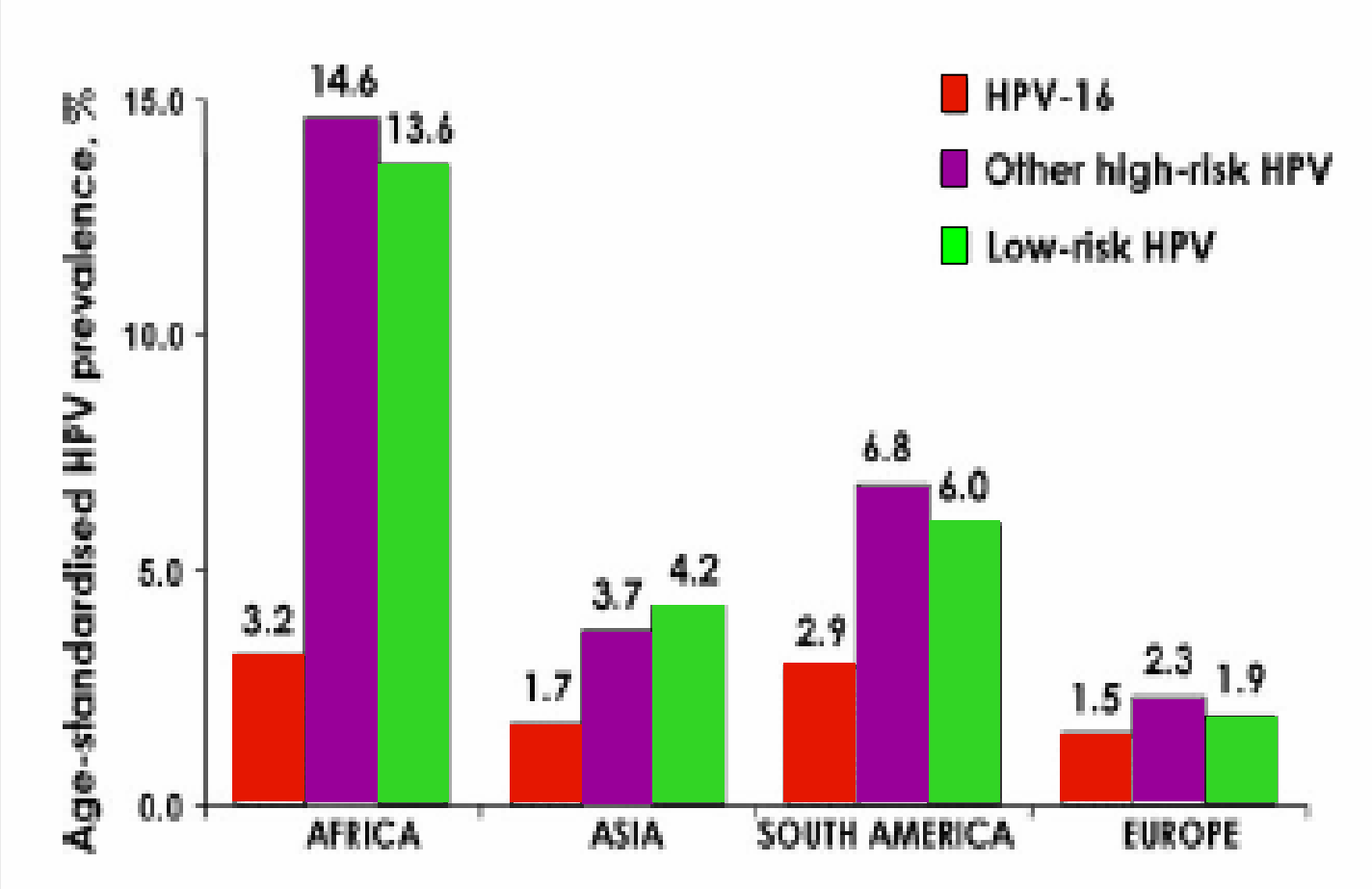
Clifford GM.et al. Vaccine 2006

Eight most common HPV types in 738 Cervical cancer cases , in Thailand



Chichareon S et al, J Natl Cancer Inst 1998, Sriamporn S et al Int J Gynecol Cancer 2006, Sukvirach S NCC8, 2005

Age-standardised HPV prevalence in the IARC pooled analysis among women without cervical abnormalities by region



G.Clifford et al./Vaccine 24S3 (2006) S3/26-S3/34

Population-based HPV prevalence in Lampang and Songkla, Thailand

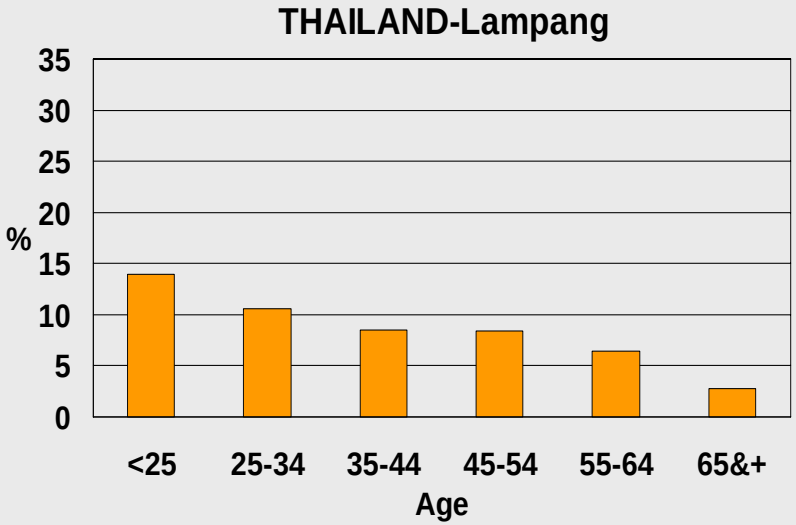
Prevalence of HPV infection

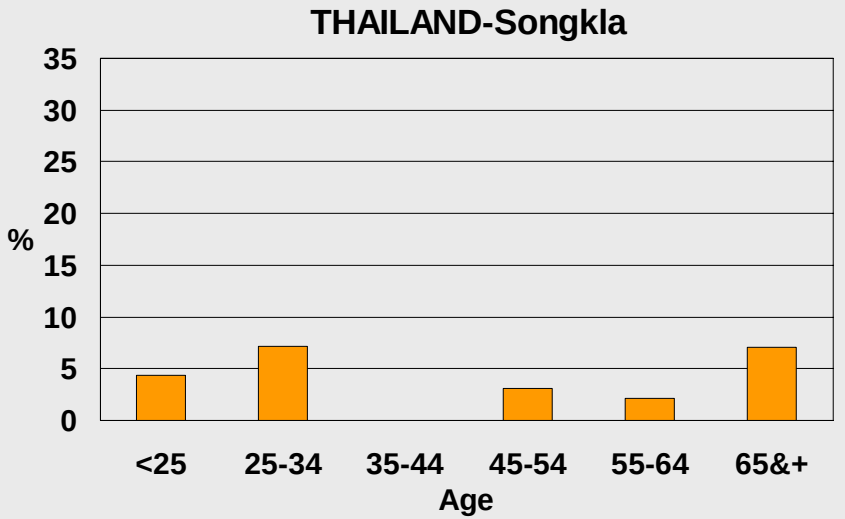
	LP (n=1035)	SK (n=706)	overall (n=1741)
Age-standardized HPV prevalence (world standard population)	9.1%	3.7%	6.3%
Prevalence of HR-HPV types	5.8%	2.3%	
Prevalence of LR-HPV type	2.1%	1.6%	
Abnormal cytological finding	4.9%	2.4%	

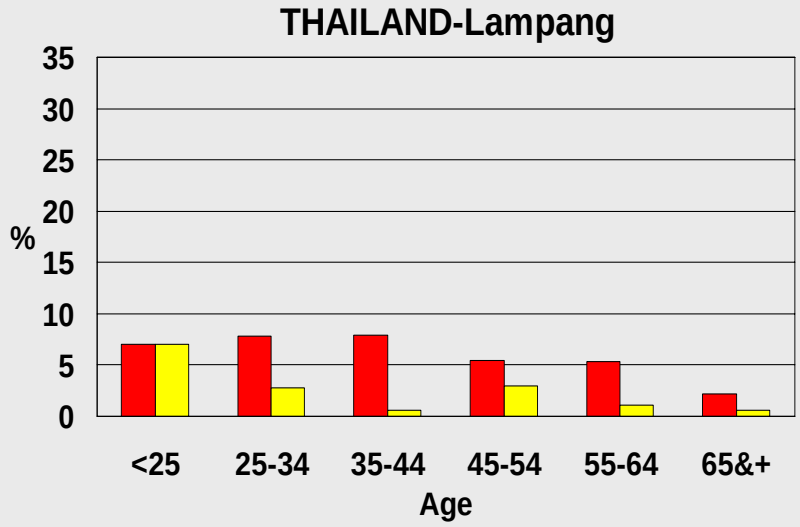
HPV specific type distribution

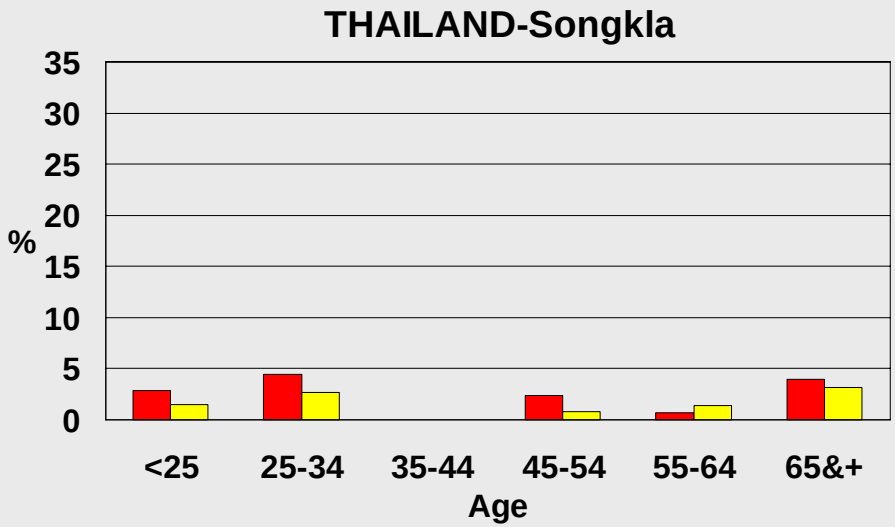
- 28 different HPV types were detected
- The 3 most common types in all women surveyed were HPV 52, 72, 16
- The 3 most common types in women without abnormality were HPV 72, 16, 70
- HPV 52 was the most common type among 68 women with abnormal cytology in this study.

Prevalence of cervical HPV-DNA by age in Lampang and Songkla

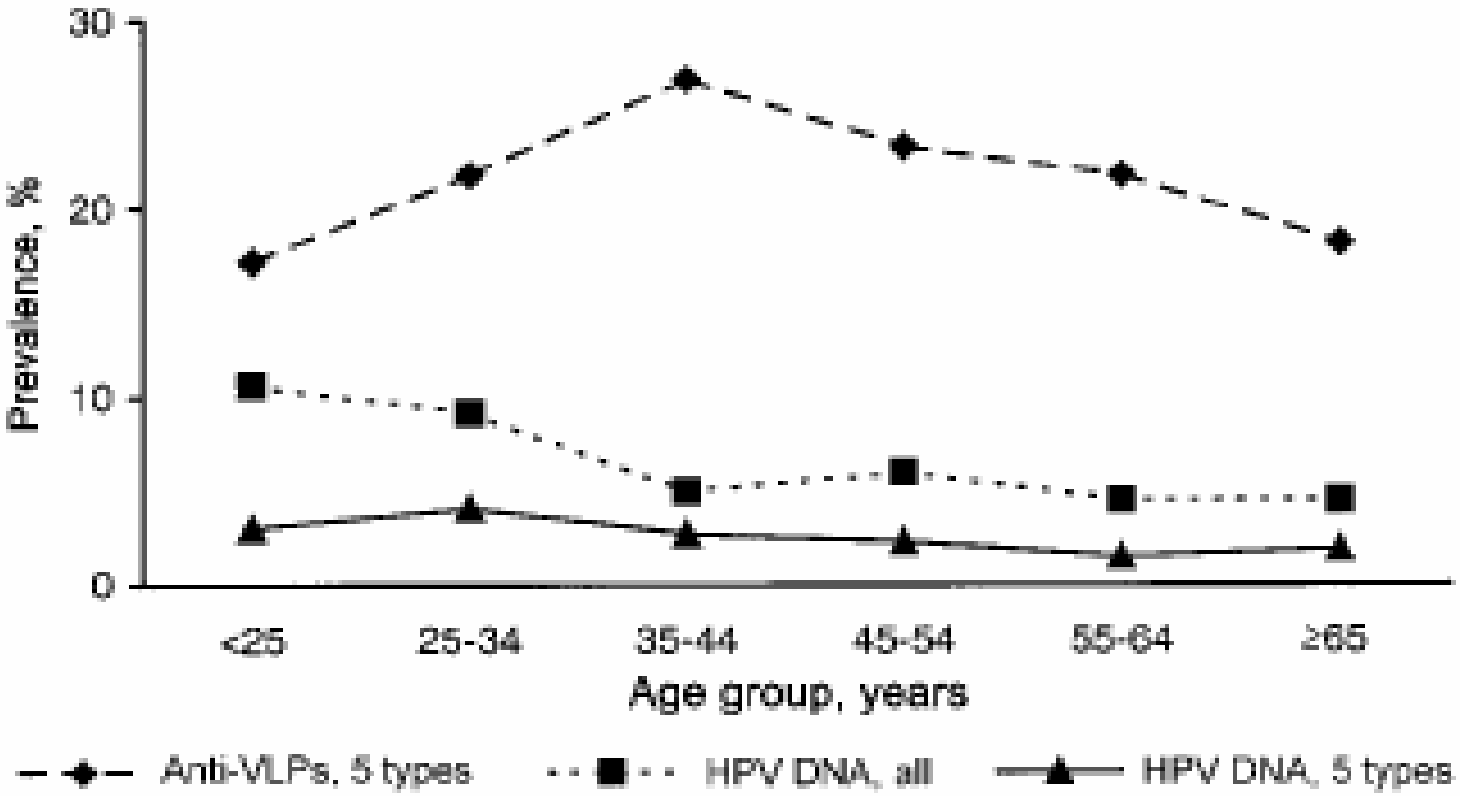






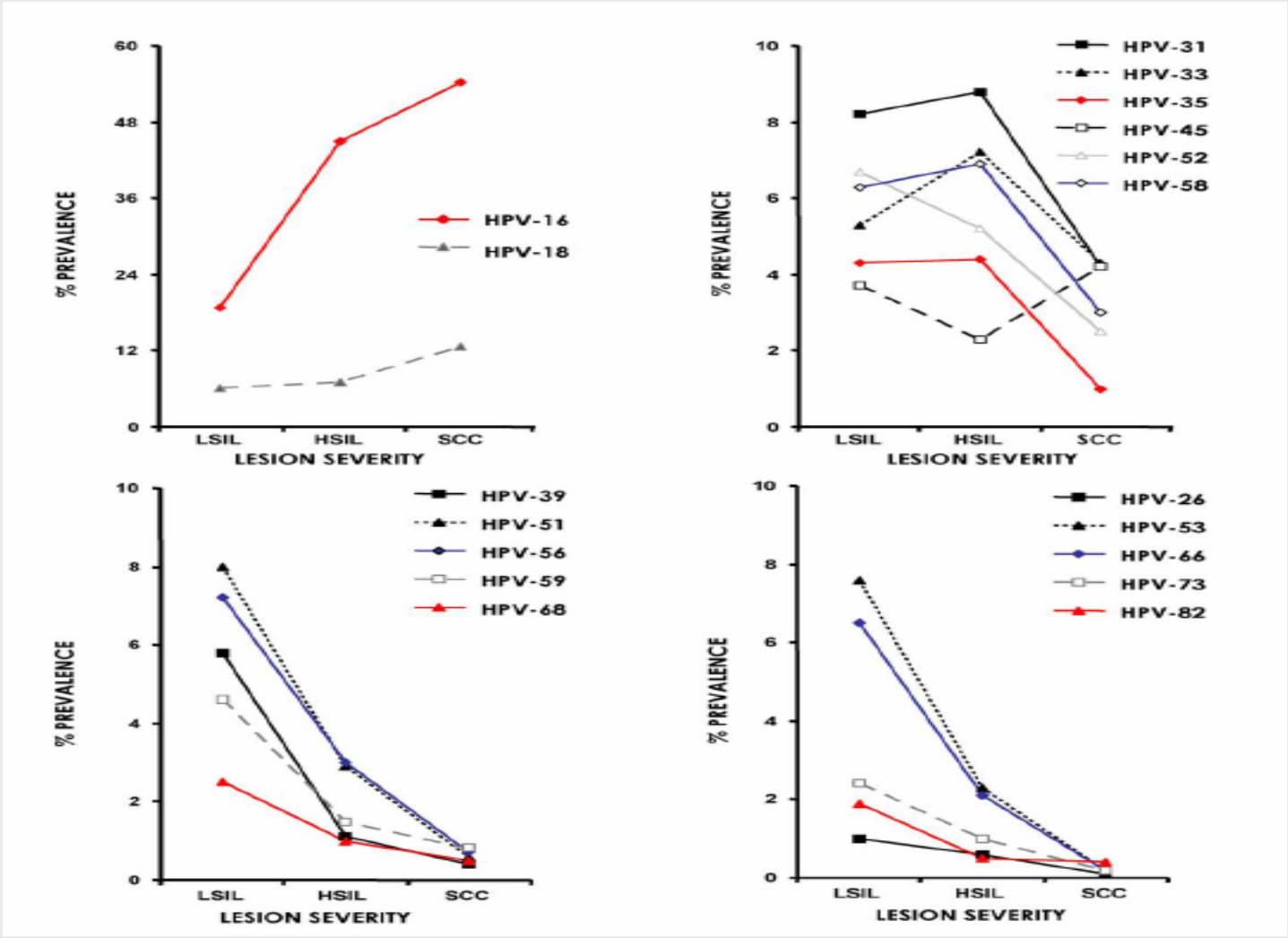


Prevalence of antibodies against virus-like particles (anti-VLPs) of human papilomavirus (HPV) types 16, 18, 31, 33, and 58 and HPV DNA of these 5 HPV types and of all types.



Sukvirach S. et al, JID 2003

HPV type-specific prevalence from meta-analyses of low-grade squamous intraepithelial lesions (LSIL), high-grade intraepithelial lesions (HSIL), squamous cell carcinoma (SCC)



Clifford GM. Vaccine 2006

The WHO global HPV LabNet

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Kei Kawana, Japan

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Background

Establishment of WHO Global HPV LabNet recommended by expert group in 2005.

Call for applications for member laboratories announced on WHO website. International peer review + site visit of candidate laboratories.

2 Global Reference Laboratories and 7 Regional Reference Laboratories appointed during 2006-2007.

Why do we need a global HPV LabNet ?

”Lack of widespread availability of reliable and internationally standardised methods for measuring HPV and immunity to HPV is one of the most important obstacles for the progress in the global eradication of HPV-associated cancers”

Such standardisation has been accomplished for a number of other vaccine-preventable diseases by launching WHO LabNets

Mission Statement by the WHO

The mission of the WHO Global HPV LabNet is:

To contribute to improving quality of laboratory services for effective surveillance and monitoring of HPV vaccination impact, through enhanced, state-of-the-art laboratory support.

Support 1) the introduction of HPV vaccines
and 2) surveillance of disease and infection.

Support for clinical diagnosis or screening could run concurrently with this effort but should not be the major focus of the network at this stage.

Major vaccine-related uses of HPV assays:

- Clinical trials (phase IV/V; second generation vaccines): Defining susceptible populations (serology & HPV DNA); defining endpoints (HPV DNA); defining immunogenicity (serology).
- HPV immunity persistence over time and assessing vaccine coverage/population immunity: Serology
- Assessing efficiency of the eradication strategy chosen, including checking for “escape mutants” and ”type replacement”: HPV DNA tests
- Understanding epidemiology for design of vaccination trials and designing programs: Serology & HPV DNA

Int. J. Cancer: **118**, 1508–1514 (2006)

Results of the first WHO international collaborative study on the standardization of the detection of antibodies to human papillomaviruses

Morag Ferguson[1]*, Alan Heath[2], Suzanne Johnes[2], Sonia Pagliusi[3] and Joakim Dillner[4]
On behalf of the collaborative study participants†

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[4]*Department of Medical Microbiology, Lund University, Malmo University Hospital, S-20502 Malmö, Sweden*

Results from HPV 16 immunoassays

		Laboratory									
	HPV serotype	1	2	3	4	5	6	7	8	9	10
NIB-01	16										
NIB-03	6+11+16+18 #										
NIB-04	Vaccine										
NIB-05	Vaccine										
NIB-07	Vaccine										
NIB-08	16 #										
NIB-09	6+11+16+18										
NIB-10	Vaccine										
NIB-12	Negative										
NIB-13	18 #										
NIB-14	Vaccine										
NIB-16	6+11 #										

=sera contributing to pool ## Reactive +/-

Intitally wide range of titres in HPV 16 immunoassays

		Range of titres
NIB-01	HPV 16 natural infection	100-640
NIB-03	Pool HPV 6+11+16+18 #	<100-640
NIB-04	Vaccine	100-2560
NIB-05	Vaccine	384-2560
NIB-07	Vaccine	400-2560
NIB-08	HPV 16 natural infection #	<20-160
NIB-09	Natural HPV 6+11+16+18	<20-80
NIB-10	Vaccine	1600-10240
NIB-12	Negative	-
NIB-13	HPV 18 natural infection #	-
NIB-14	Vaccine	5381-40960
NIB-16	HPV 6+11 natural infection #	-

Including the same reference standard serum in the assay resulted in low interlaboratory variation- even without any attempts at assay standardisation (results given in PLL-calculated Units of HPV antibody levels)

	Laboratory												
Sample	1	2	3	4	5	6	7	8 *	9	10 *	Mean potency	%GCV	Neutralisation
08	0.24	0.45	0.37	0.37	0.54	0.50	0.42	0.40	0.68	0.74	0.43	33	0.4
09	0.09	0.54	0.41	0.27	0.36	0.29	0.16	0.10	-	0.30	0.24	91	0.3
03	0.07	1.10	0.20	0.22	0.29	0.26	0.11	0.25	0.19	0.26	0.22	111	0.2
04	4.93	6.70	4.04	5.13	4.45	5.21	6.71	9.95	8.24	3.26	5.91	35	16
05	2.05	4.03	3.91	3.32	2.35	3.11	3.67	1.79	4.63	2.20	3.06	39	4
07	4.14	3.88	5.06	4.79	5.12	4.15	6.19	6.65	7.24	2.92	5.13	25	54
10	16.44	18.10	16.28	16.54	12.76	10.20	29.99	17.40	24.23	3.03	17.2	37	102
14	24.68	53.85	74.21	40.07	26.14	55.02	91.51	25.03	59.30	3.13	45.10	63	870

Antibody Unit Standardisation

- **Simply relating measurements to the same international Standard greatly reduced interlaboratory variability (Ferguson et al, 2006 IJC).**

- **Definition of internationally standardised Units will allow comparing HPV antibody levels between different studies and different vaccines**

- **Meaningful definition of level of antibodies required for protection will require internationally standardised Units.**

HPV DNA standardisation

Global WHO collaborative effort-

29 laboratories worldwide, testing the same samples.

J Clin Microbiol, 44,571, 2006

Assay variability much greater than expected (up to 5 logarithms differences in sensitivity!! False positive results common also in ”expert” laboratories.)

Promoting adequate Quality Assurance will be important.

Standardising Measurements

- All results must be reported in internationally standardised Units and traceable to an internationally recognized biological standards preparation.
- First candidate **standard**: HPV16 Antibodies. Large serum pool from women verified to have HPV16 antibodies in multiple laboratories worldwide. Several years of testing/stability studies.
- Standard approved by the WHO Expert Committee for Biological Standards in October 2007 as a WHO reference reagent and assigned a definition of 5 WHO Units/ampoule.
- Maintained at the WHO collaborating centre National Institute for Biological Standards and Controls (NIBSC) in UK.
- Not every lab needs an aliquot of the International Standard!
- Regional/national reference laboratories will receive an aliquot. Other labs can establish traceablity to the International Standard by exchange of serum samples with a reference laboratory.
- Reviewers should be aware of the importance of reporting

Standardising Procedures or Standardising Quality Indicators and how they are measured?

- Standardising the SOPs used is not always a good idea.
  - Takes very long time and efforts to agree on details.
  - Stops development work/improvements. New SOPs that give even better quality will not be discovered.
- But **common standards/quality indicator measurements** will **promote progress** by enabling sharing/comparing results/experiences.

Quality Indicators

- Should not change over time- Same quality indicators should work also for new methods, decades later.
- Primarily based on purpose- the results should have a quality corresponding to the intended use.
- We would need to have consensus and enforce use of the same quality indicators.

WHO Proficiency Panel as Quality Indicator: HPV DNA testing and typing

- An HPV DNA test could be said to have a quality corresponding to the intended use if it can correctly classify HPV types of interest for HPV vaccination, when present at levels that would be medically relevant for an HPV vaccination monitoring program.
- Proficiency panel tests only ONE step in the analysis chain. Other essential steps are e.g.:
  - Epidemiological design of surveillance sampling
  - Sample handling- Transportation, pre-treatment, safety measures against mix-up.
  - Data handling

Considerations for composition of the 1st WHO HPV DNA proficiency panel

- HPV types: 14 oncogenic and 2 benign HPV types (most likely everything that will be of interest for HPV vaccination for the foreseeable future).
- Sensitivity requirement: High requirement for HPV16 and 18, less important for other types.
- Should be able to detect multiple infections.
- High capacity to detect wrong typing (cross-hybridisation et c): Related HPV types systematically separated into different pools.
- Should work for all HPV DNA detection systems known today (and as far as possible also for conceivable improvements)

A quality indicator based on proficiency panels

- Sensitivity and specificity should be evaluated at least annually using a blinded proficiency panel issued by the WHO HPV Lab Net. Results should at least conform to what is considered useful for the intended purpose (HPV surveillance)
- Proficiency for the intended purpose:
  - Mis-typing and false positives: None allowed.
  - Sensitivity: 50 genome equivalents for HPV16 and 18 (GE to be replaced with the corresponding amount of IU, when available), 500 genome equivalents for other HPV types.

Progress so far

- **International standards:**
  - Candidate standard for unit of HPV16 ABs: Approved as WHO reference reagent with 5U/ampoule by WHO ECBS
  - Candidate standard for amount of HPV16DNA and HPV18 DNA: Prepared, under international evaluation
  - Candidate standard for unit of HPV18 ABs: In preparation.
- **Proficiency panel for HPV DNA testing and typing –** Prepared, under international evaluation.
- **The WHO HPV Laboratory Manual** (Guidelines on Standards and Quality Indicators, examples of SOPs found to work): In progress. First draft to be discussed at international hearing in January 2008.

Thank you