Milestones for HPV vaccines introduction

Training in Reproductive Health Research
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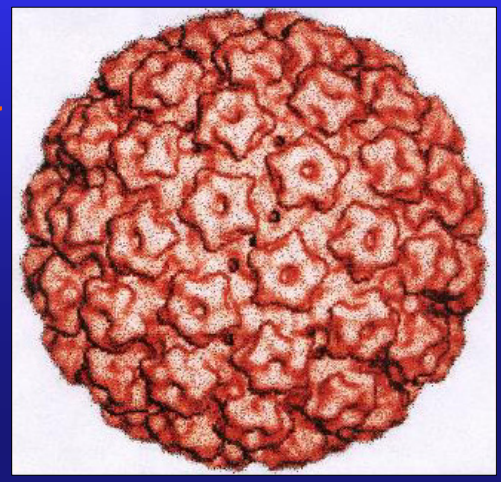
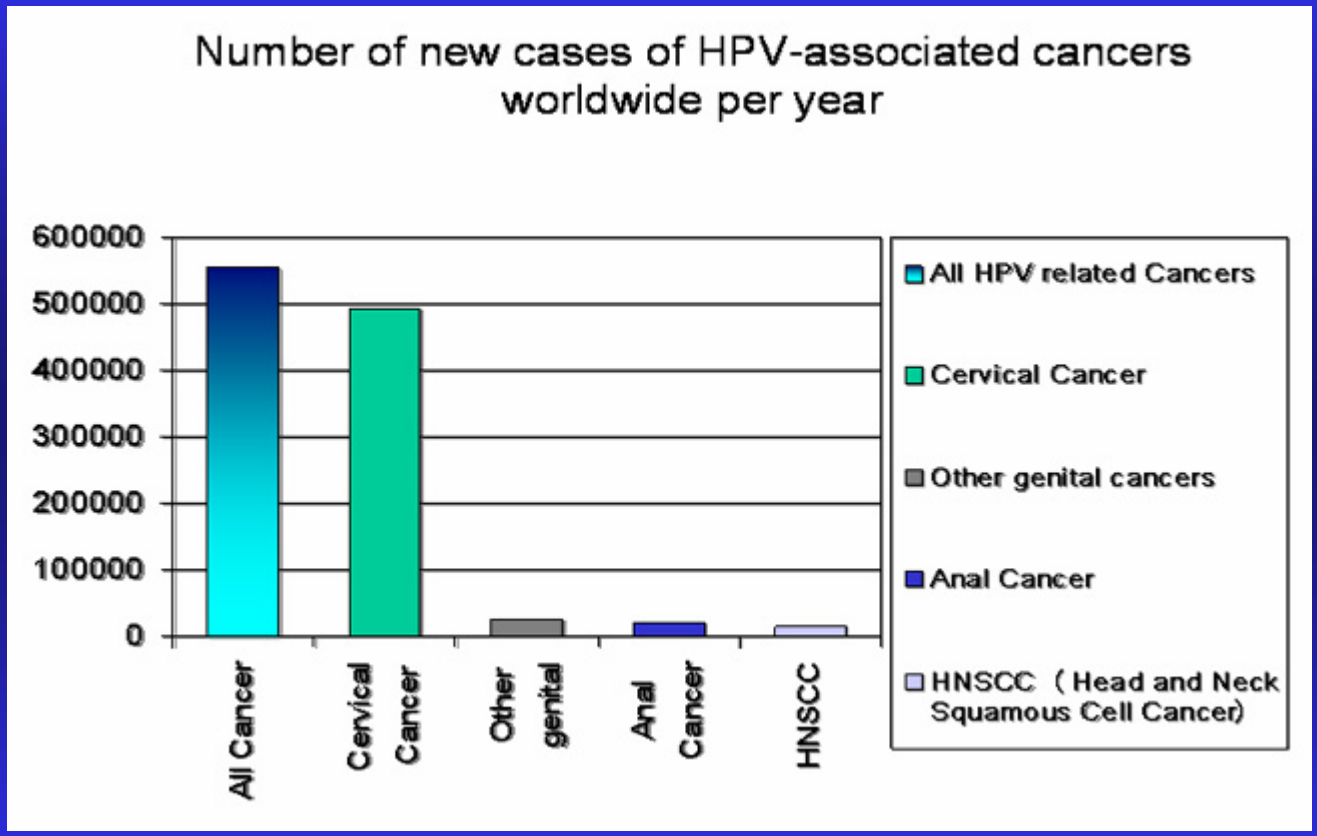
Papillomaviruses and Human Diseases

SITES	DISEASES
Anogenital	Anogenital warts Cervical neoplasias and carcinoma Anal carcinoma, Penile carcinoma, Vulvar carcinoma
Skin	Common warts, deep plantar warts Mosaic warts, flat warts, etc Melanomas
Respiratory	Juvenille laryngeal papillomatosis Laryngeal, sinusial, tonsillar and oro-pharyngeal squamous cell carcinomas
Others	Conjunctival papillomatosis, carcinoma and keratosis in epidermodysplasia verruciformis, HNSCC Carcinomas associated with immune deficiency

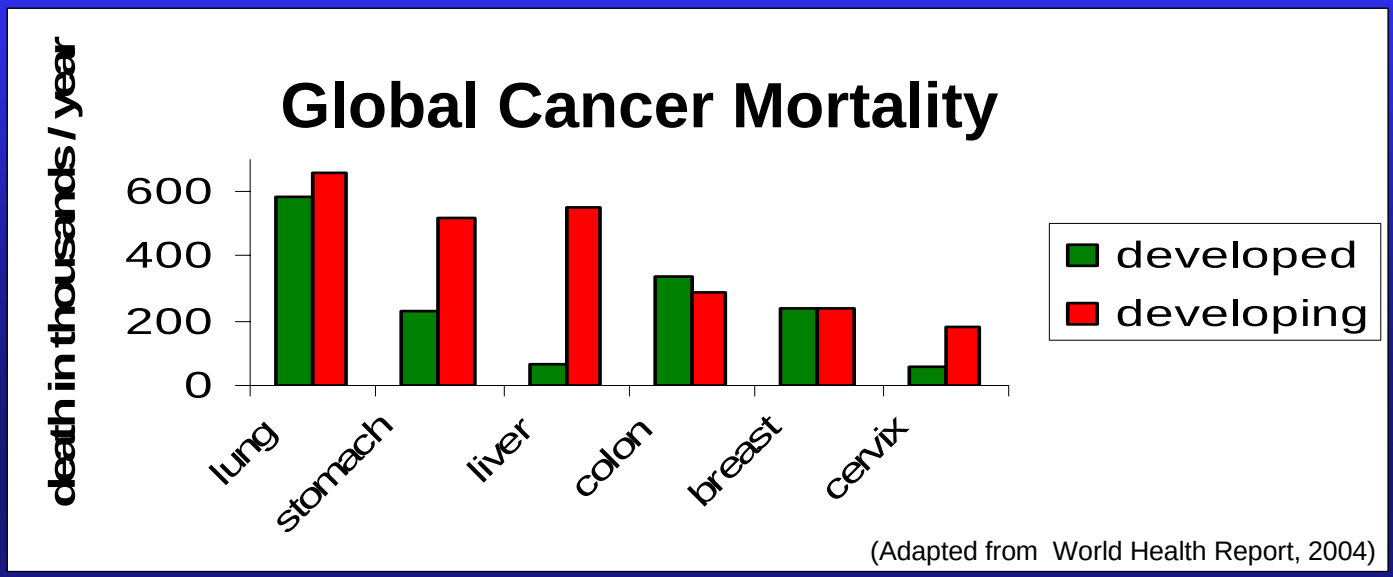


Cervical cancer represents 90% of HPV associated global disease burden

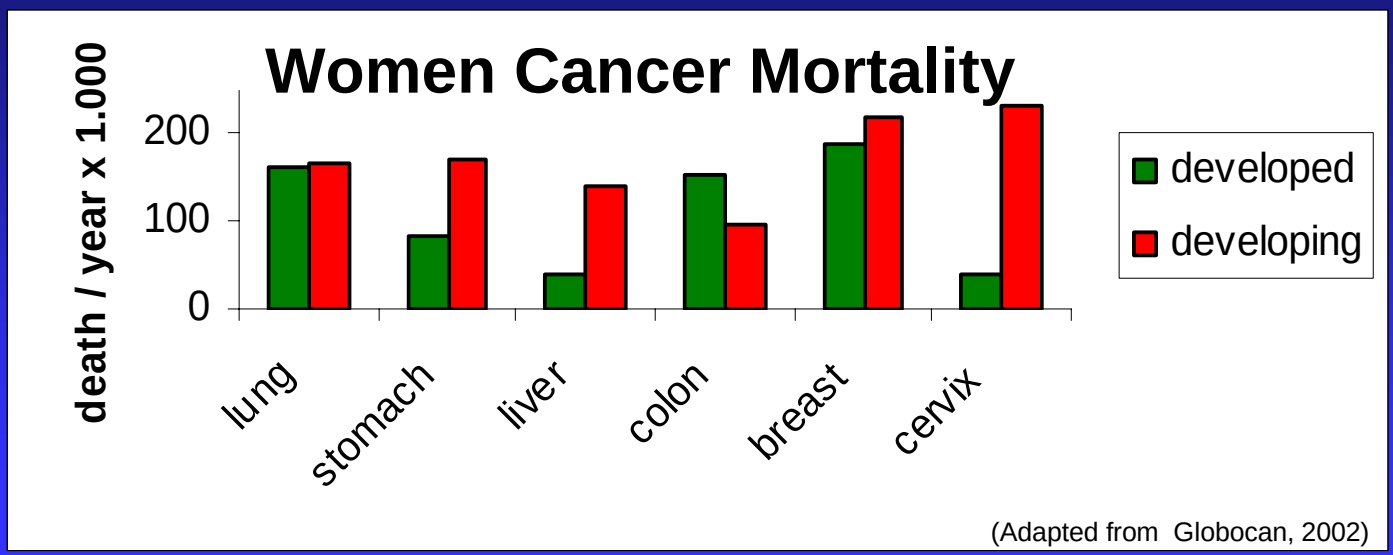


(from Pagliusi et al. 2005)

Cervical cancer is the foremost cause of women cancer mortality in developing countries

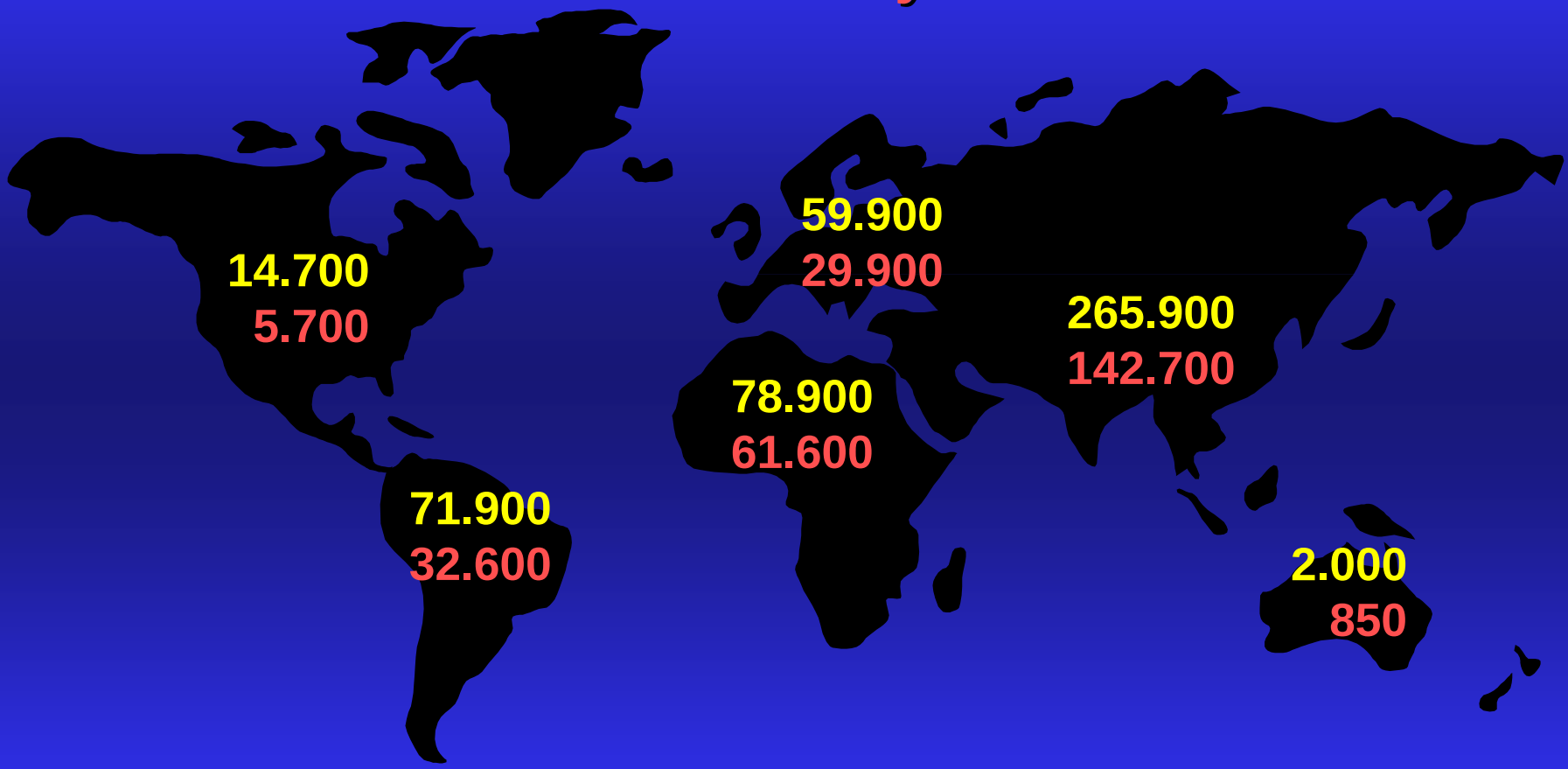


(Adapted from World Health Report, 2004)



(Adapted from Globocan, 2002)

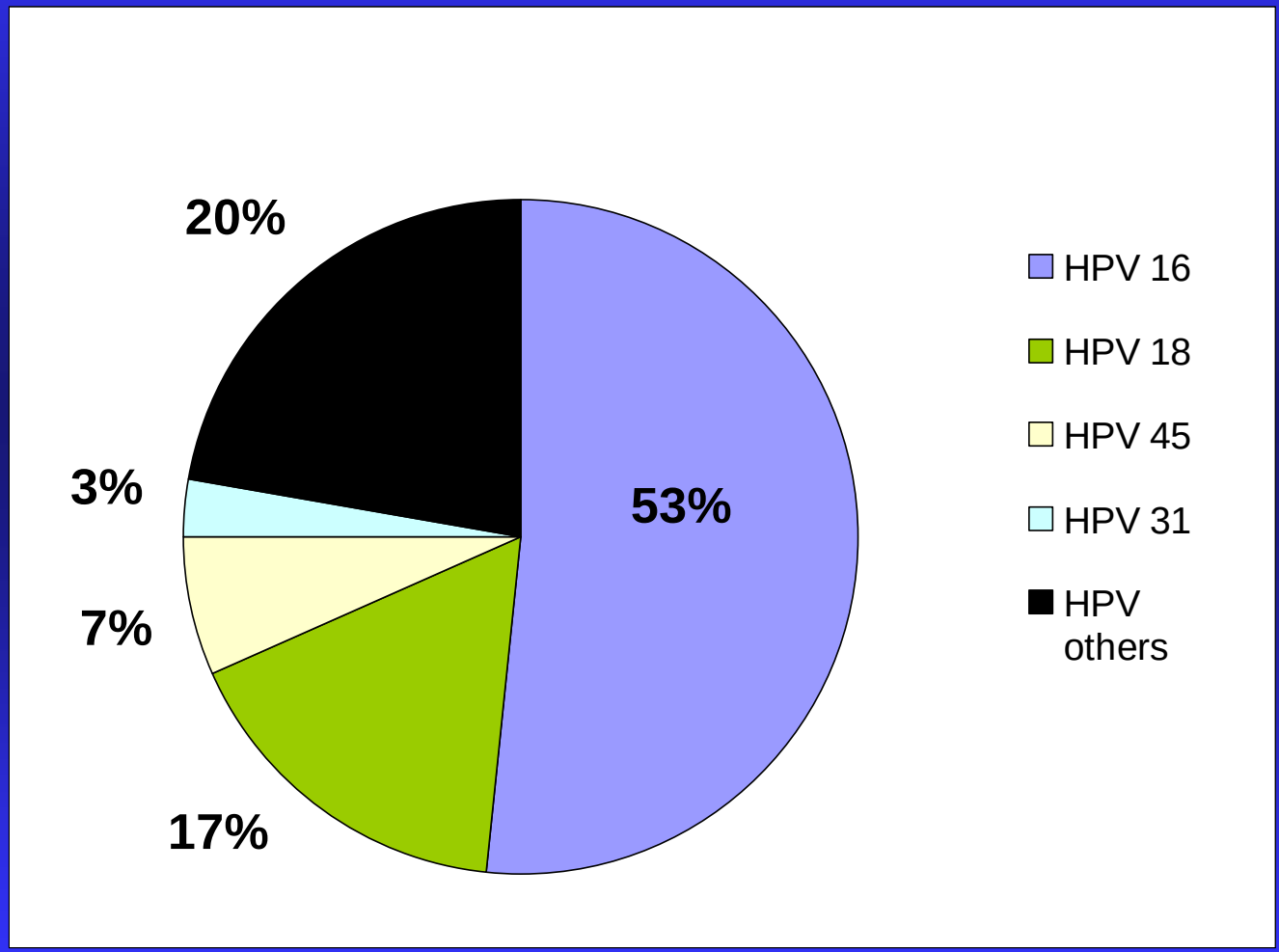
Global distribution of annual number of new cervical cancer cases and mortality



Asia accounts for about half of all cases

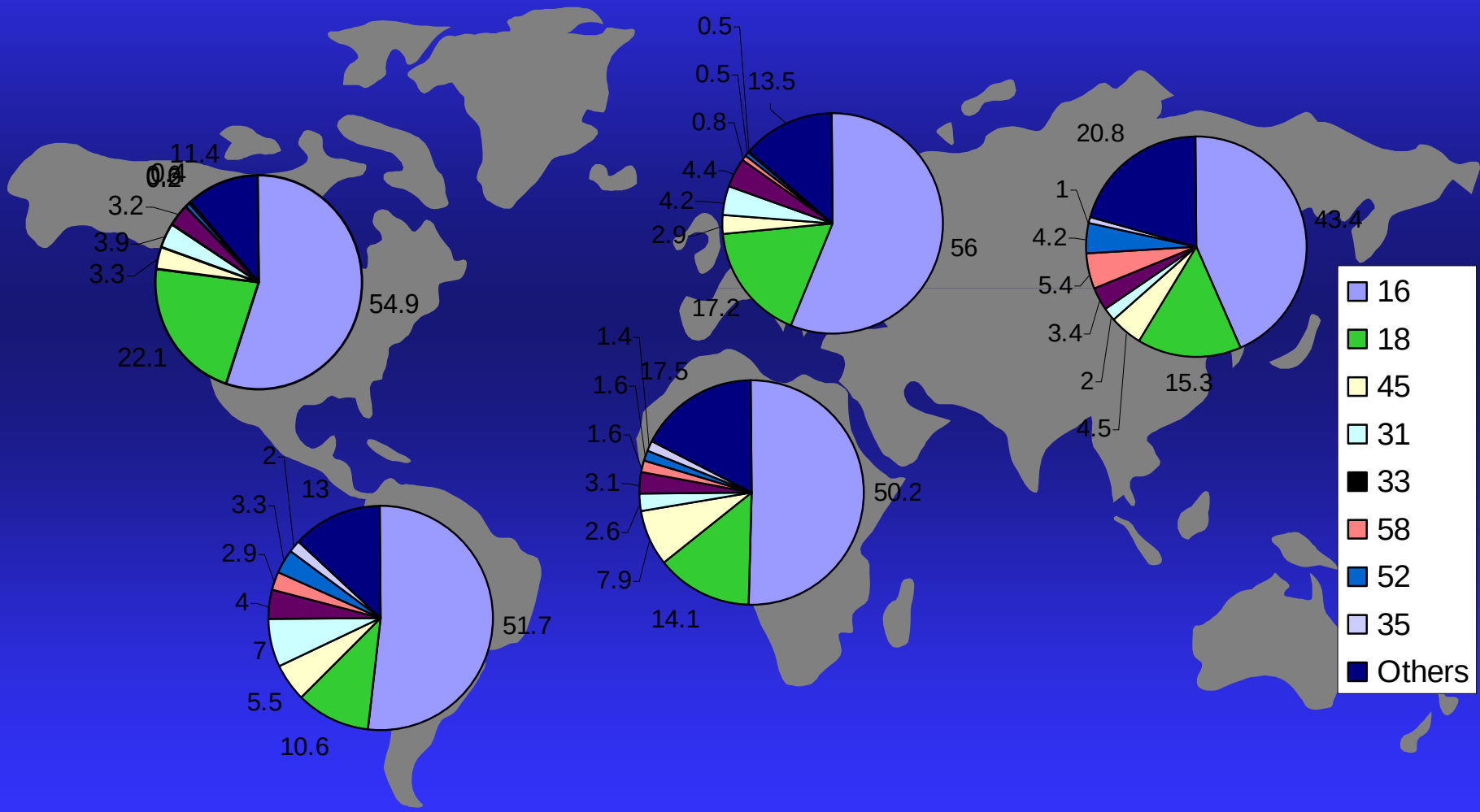
(global incidence ~493.000 and mortality ~273.000 cases, adapted from Globocan 2002)

Four HPV types are significantly associated with cervical cancer worldwide



(Adapted from Munoz et al., 2004)

Regional distribution of HPV type prevalence in cervical cancer (% of all cases analysed)



Fom Pagliusi and Aguado 2004

HPV vaccine candidates are becoming available

Prophylactic vaccine candidates are being developed: Recombinant L1 proteins self-assemble into VLPs

- **Safe, immunogenic and well tolerated (Harro et al. 2001)**
- **Complete protection against persistent HPV infections in vaccinated women has been demonstrated in independent studies (Koutsky, 2002; Harper et al. 2004; Villa et al. 2005)**

*courtesy from Nieland

Summary of two independent phase IIb studies

	Merck (16)	GSK (16+18)
ATT cohort analysis	1533 subjects	721 subjects
Safety Collection	14 days post vax	7 days post vax
Safety Data		
% w/any AE	93% (V) vs. 92% (P)	96% (V) vs. 93% (P)
% w/injection site AE	86% (V) vs. 82% (P)	95% (V) vs. 86% (P)
Seroconversion	99.7%	100%
Efficacy criteria		
• Persistent Infection (Per-Protocol)	100% (HPV 16)	100% (HPV 16/18)
• Persistent Infection (Intention-To-Treat)	93% (HPV 16)	84% (HPV 16/18)
• Transient or Persistent Infection (Per-Protocol)	91% (HPV 16)	87% (HPV 16)
•CIN	100% (9 women)	100% (6 women)
	Koutsky et al. 2002	Harper et al. 2004

Results of Merck phase III study

- 12,167 women aged 16-26 yrs in North and South America, Europe and Asia
- 3 doses at day 1, month 2 and month 6
- No cases of HPV 16/18-related CIN 2/3 or adenocarcinoma in situ in the completely vaccinated group
- 21 cases in the placebo group
- Efficacy 100% in those vaccinated according to protocol and 97% including partially vaccinated women

Choice of endpoints for vaccine efficacy trials

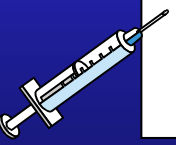
- Objective is to measure the level of protection conferred by vaccine against cervical cancer
- Primary endpoint for efficacy should be a specific measurable outcome
- Outcome should represent a beneficial effect on illness, symptoms or quality of life
- Primary endpoint determines the study design and sample size
- Secondary endpoints can be assessed in sub-studies, e.g. by staging of disease

Endpoints for HPV vaccine efficacy

What public health authorities would like to know to be convinced of the efficacy of HPV vaccines against cervical cancer?

1. **Desirable to have a globally-agreed measurable efficacy endpoint**
2. **Time and ethical considerations make it necessary to use surrogate endpoint, rather than invasive cervical cancer**
   - **Malignancies develop slow and cancer as outcome or endpoint requires very large and lengthy studies**
   - **State-of-art clinical management requires that premalignant stages are treated immediately**

The etiology of cervical cancer and opportunities for prevention



~1 year

Transient infection

HPV infection

> 2 years

Persistent infection

2-5 years

Low grade dysplasia

4-5 years

High grade dysplasia

9-15 years

Invasive cancer

Lab parameters: Virology:

- **–Incident HPV infections**
- **–Persistent HPV infections**

Clinical and lab parameters: Cytology/Histology :

- **–LSIL and/or HSIL**
- **CIN 1 and/or CIN2-3**

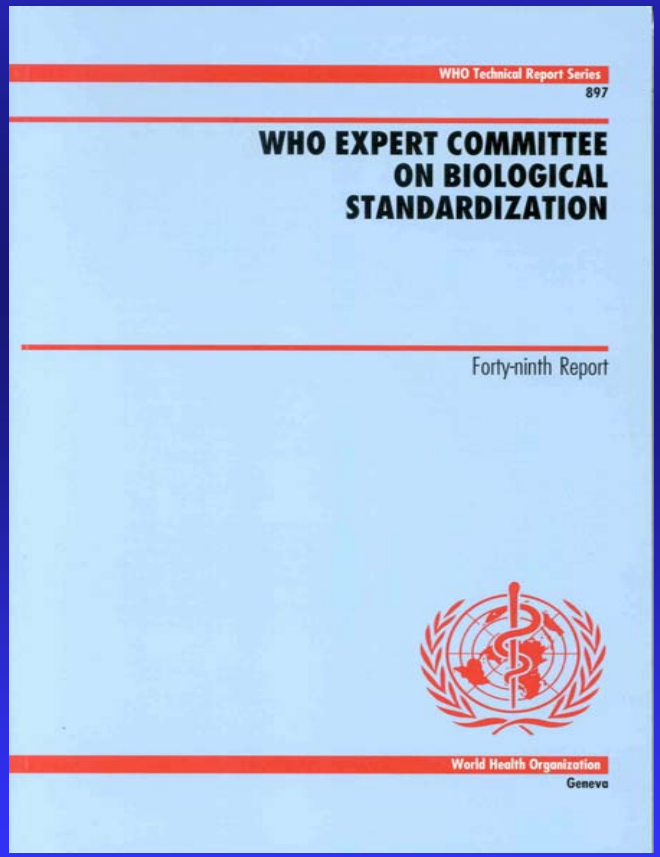
Surrogate endpoints for HPV vaccine efficacy

An international group of experts recommended that:

- CIN of moderate and high grade combined with virological data be used as primary endpoint for proof of efficacy of HPV vaccines, and cancer as secondary endpoint
- Maintain long-term follow up to document breakthrough cases, and reveal correlates of protection
- In future HPV vaccine trials in developing countries issues of including a control group need to be appropriately addressed
- Once the endpoint is demonstrated, vaccination should be offered to control group

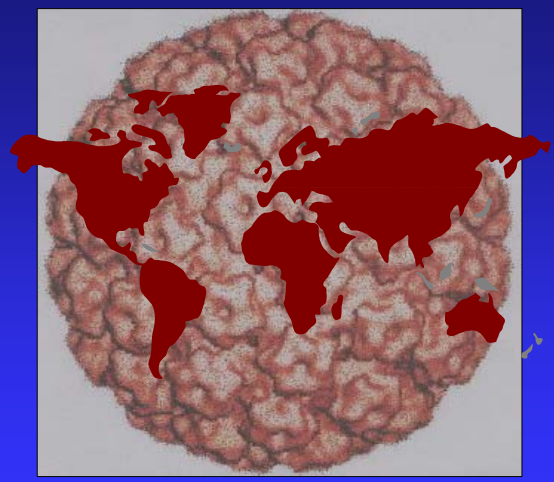
Immunization, Vaccines & Biologicals
Vaccine quality standards
WHO products

Global written standards



Global measurement standards

Support for the science base by developing a HPH lab network



Conclusion

- Safety and immunogenicity profile of HPV vaccine candidates appear satisfactory, and there is evidence that types 16 and 18 will target the majority of cases worldwide
- Recommended endpoint for efficacy of a cervical cancer vaccine is CIN of moderate or high grade, and if proven, vaccination may have an impact in public health problem
- In a post vaccination era it is desirable to monitor vaccine performance and survey the epidemiology of HPV and cancer
- Ideally, preventive programmes should include both primary and secondary prevention activities, including environmental, educational, technology and vaccination components