Human Papillomavirus Vaccines as a Potential Novel Tool for Global Prevention of Cervical Cancer in Women

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1. Disease burden
2. Prevention strategies
3. Vaccine development and introduction

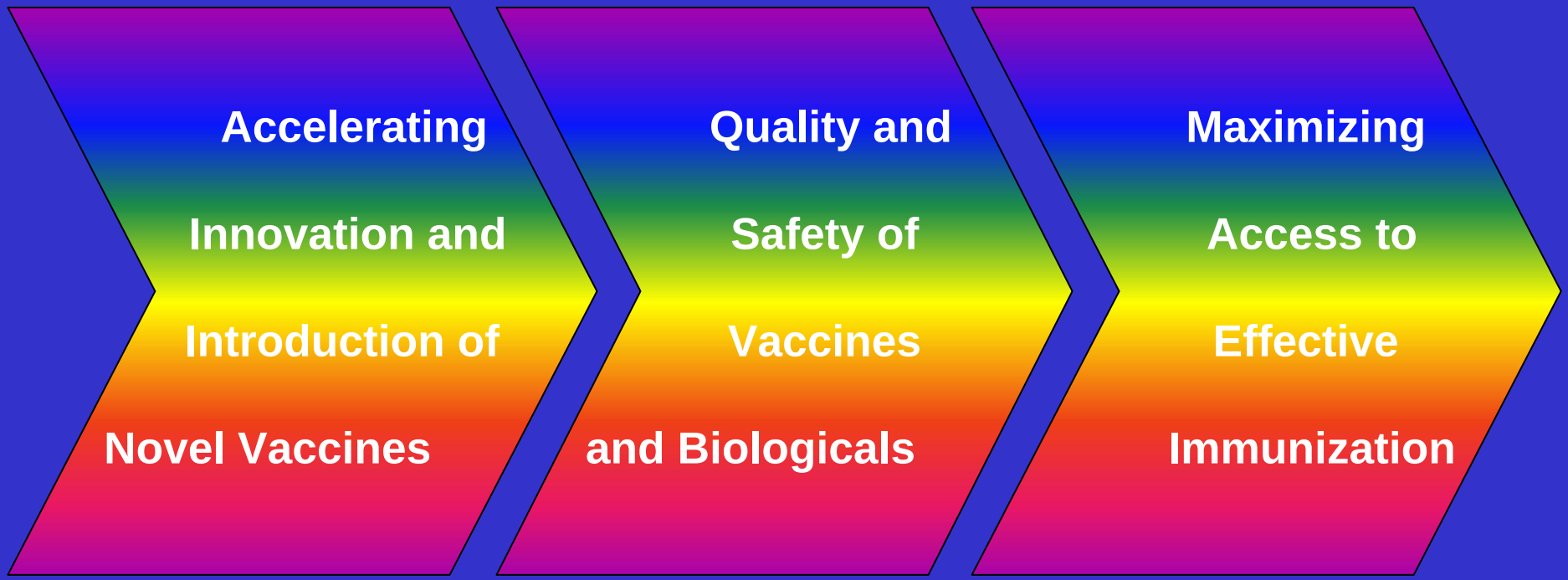
The role of WHO in HPV vaccine development and introduction

Mission

A world in which all people at risk are protected against vaccine-preventable diseases

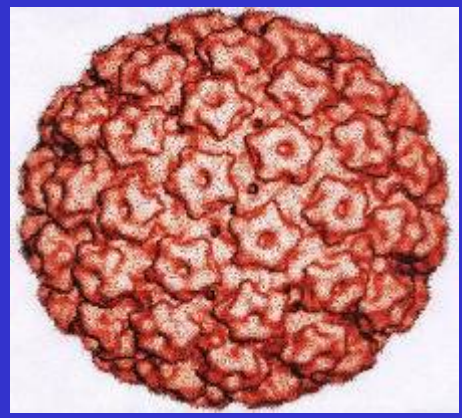
Cervical cancer to become a vaccine preventable disease

Dealing with the spectrum of a vaccine continuum

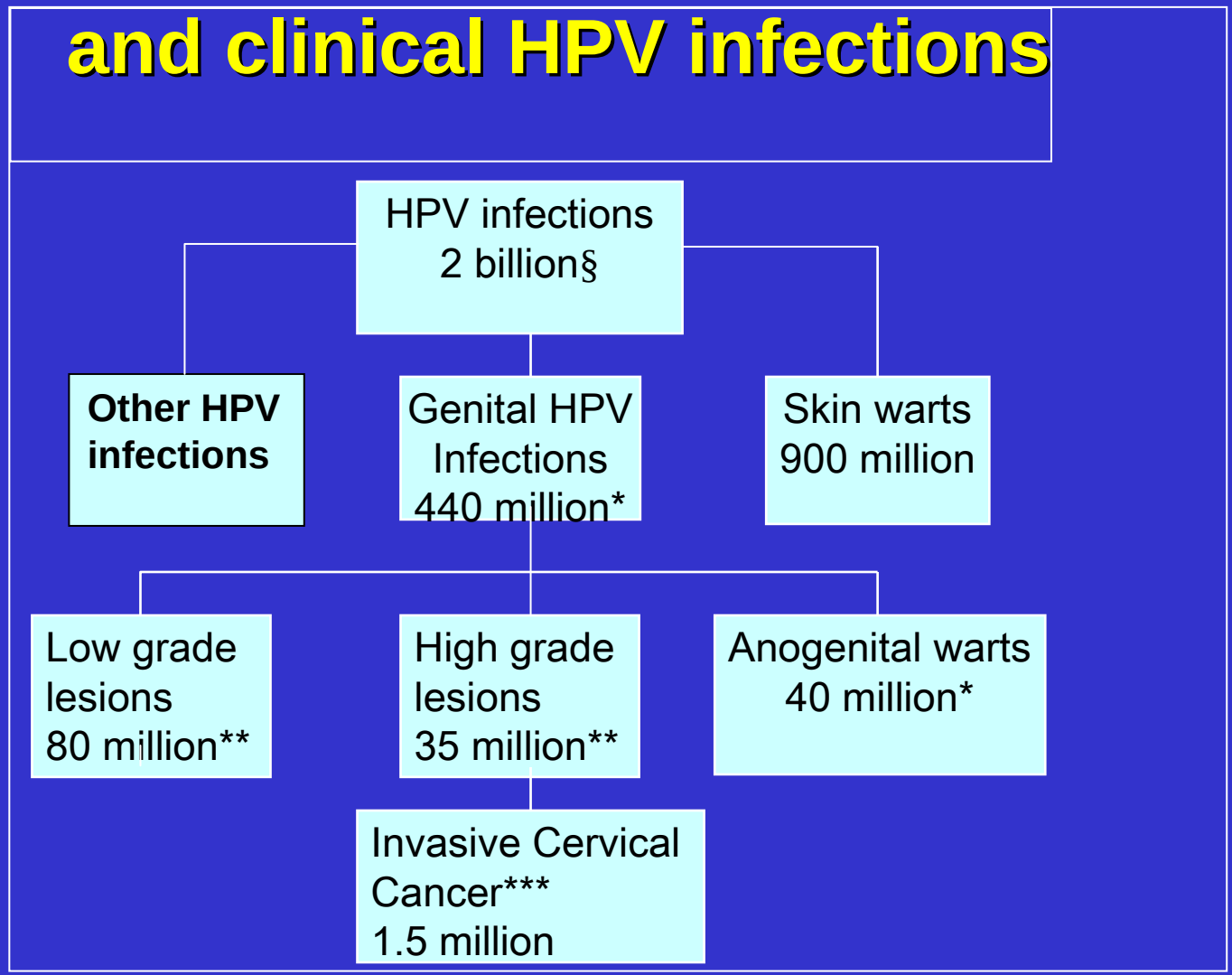


Papillomaviruses and Human Diseases

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

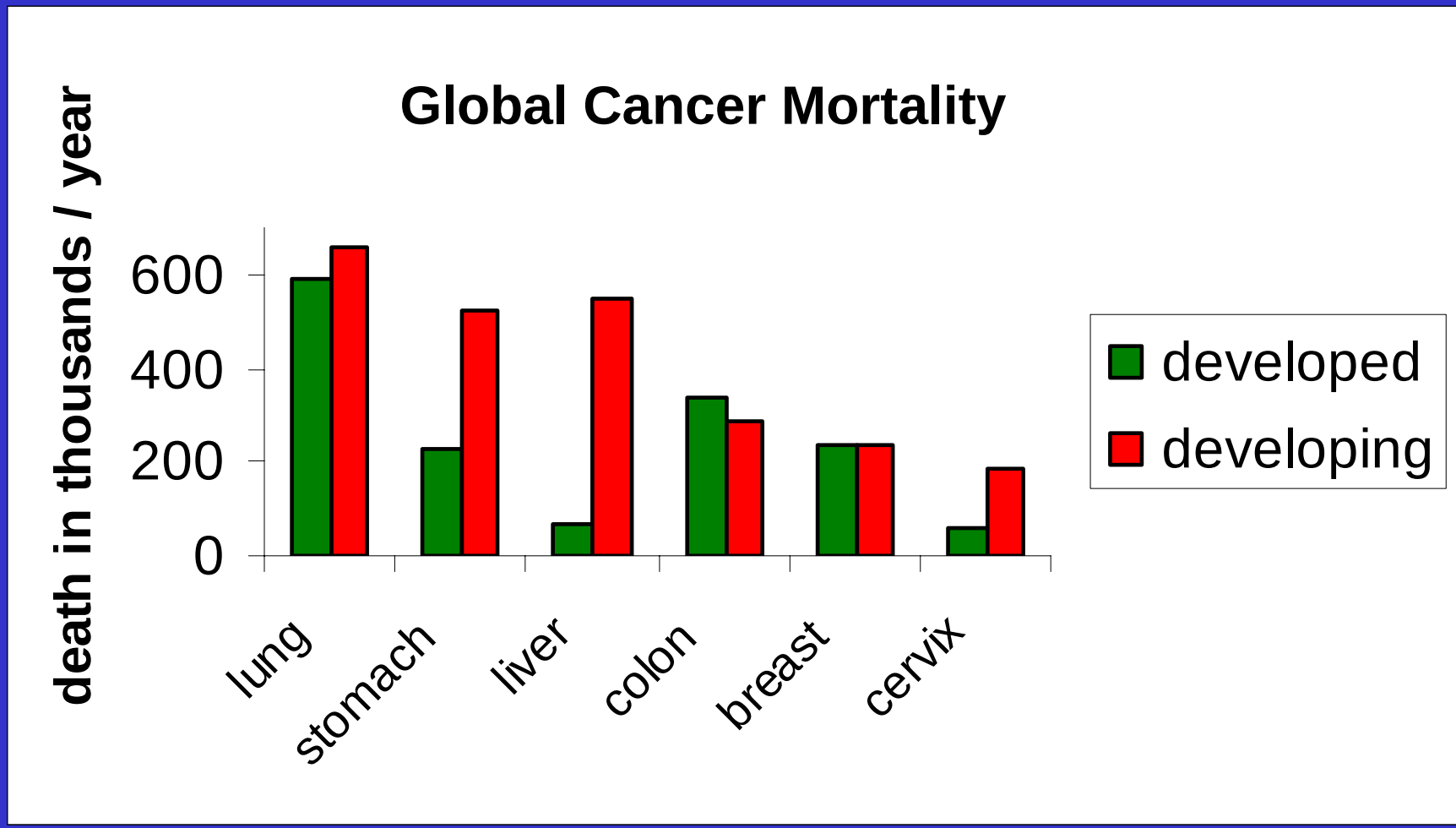


Estimated world prevalence of subclinical and clinical HPV infections



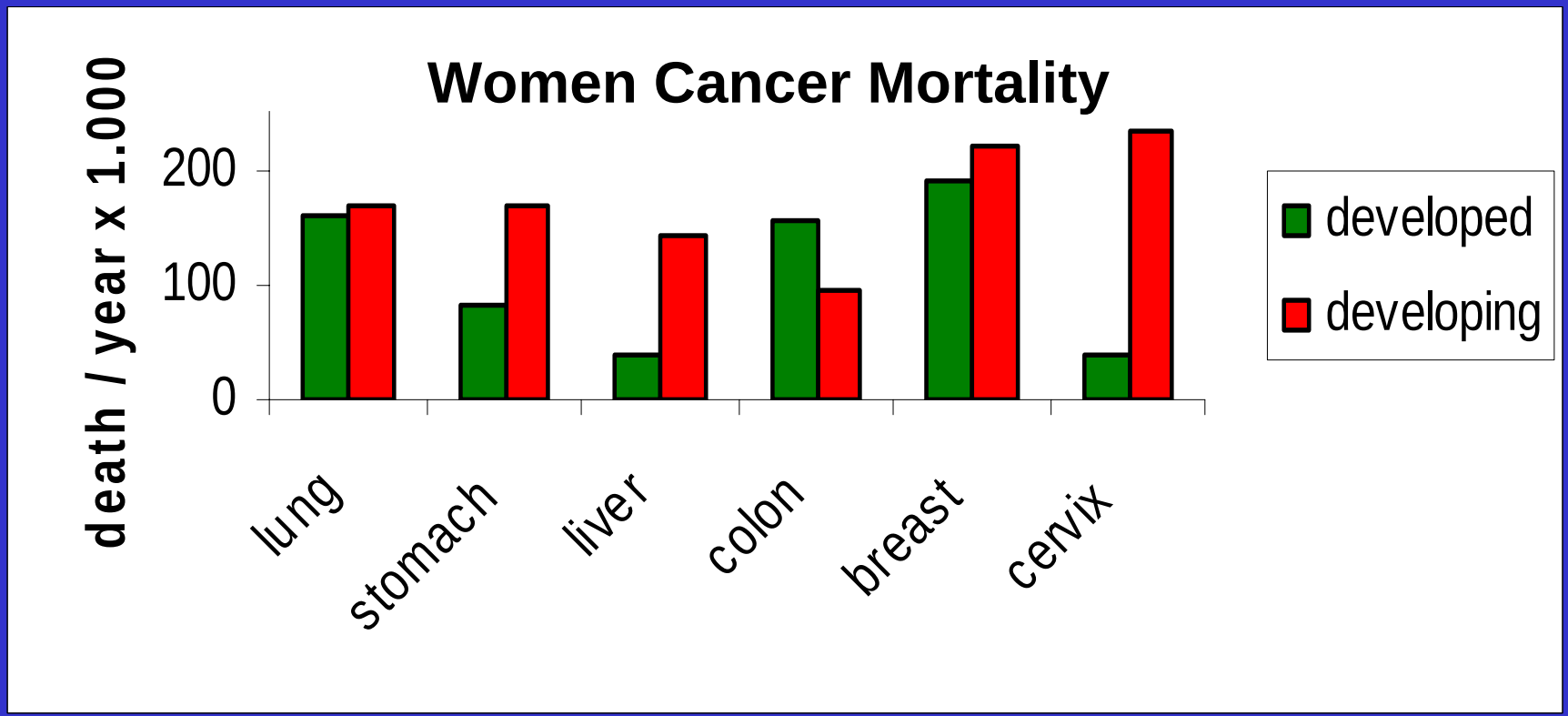
. Based on world population of 6.271.698.000 (World Bank) and surveys among subjects at reproductive age (15-50 years old)
*Koutsky 1997, § seroprevalence or *DNA prevalence **Herrero et al. 2000, 1997;**Sankaranarayanan et al. 2004; ***Parkin et al. 2001)

Cancer prevention and control are among the most important scientific and public health challenges of this era



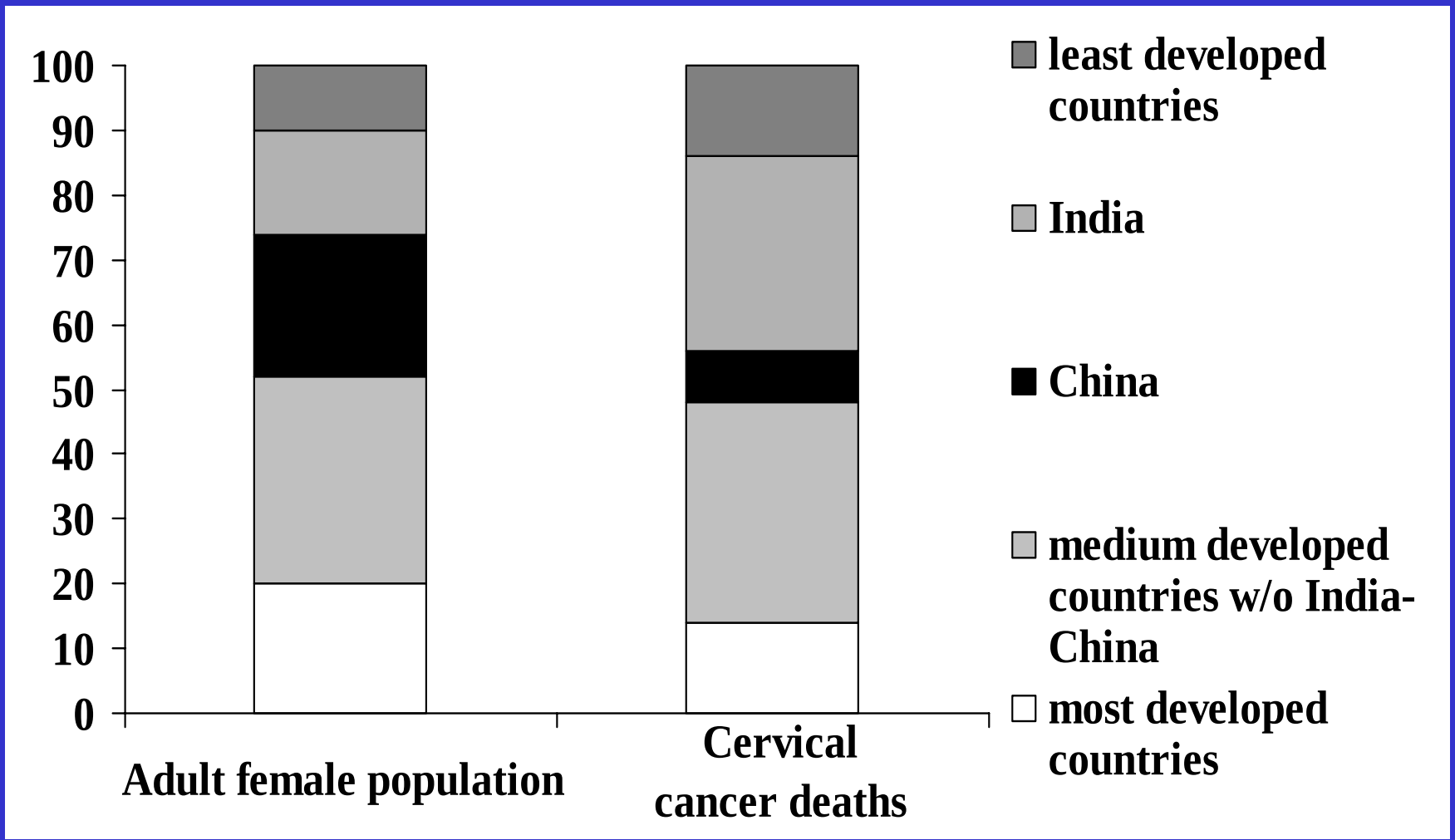
(Adapted from World Health Report, 2004)

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



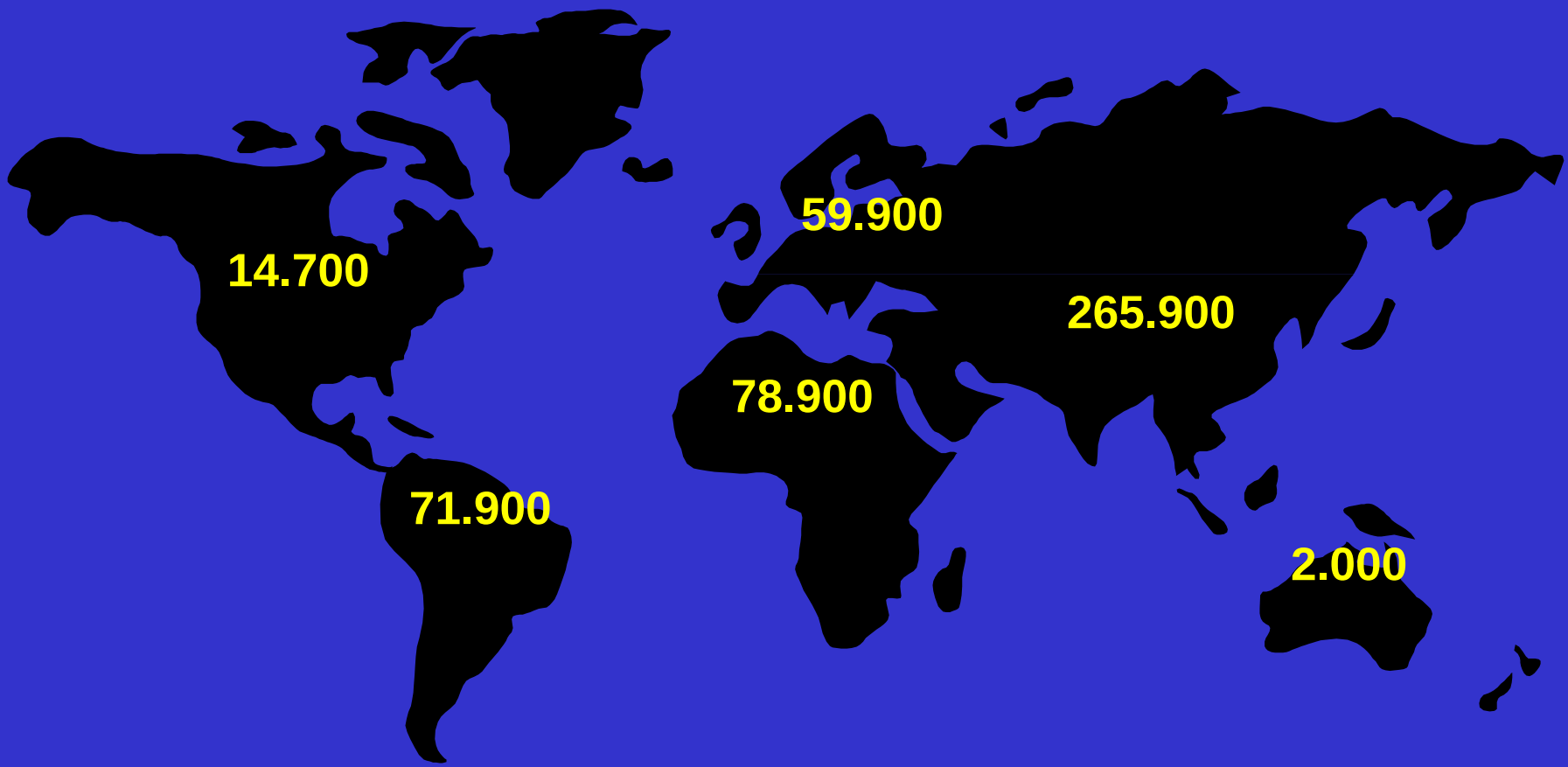
(Adapted from Globocan, 2002)

Distribution of adult female population and deaths due to cervical cancer in %



UNDP 2000 (adapted from Drain, 2002)

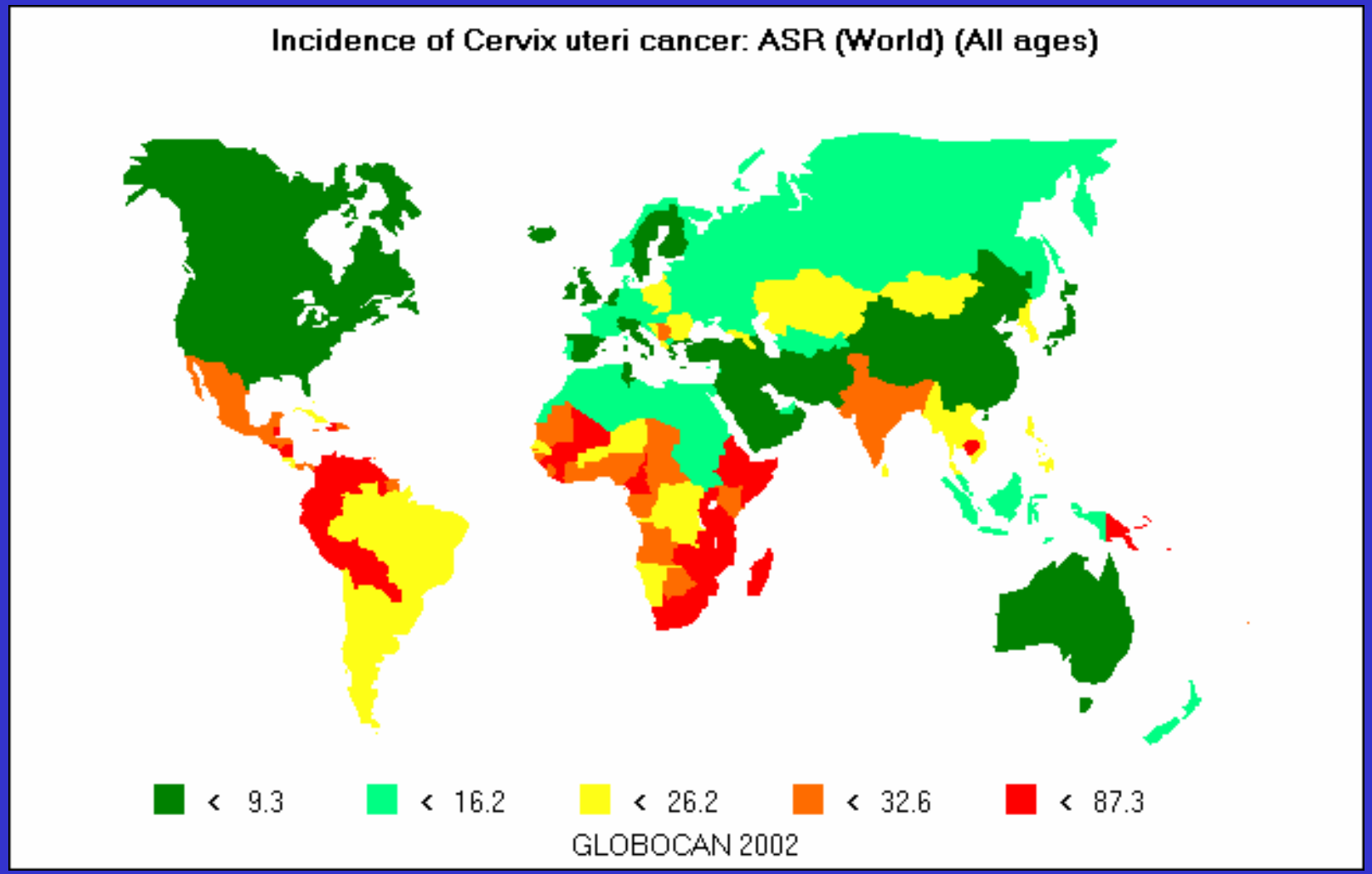
Global distribution of total number of new cervical cancer cases per year



Asia accounts for about half of all cases

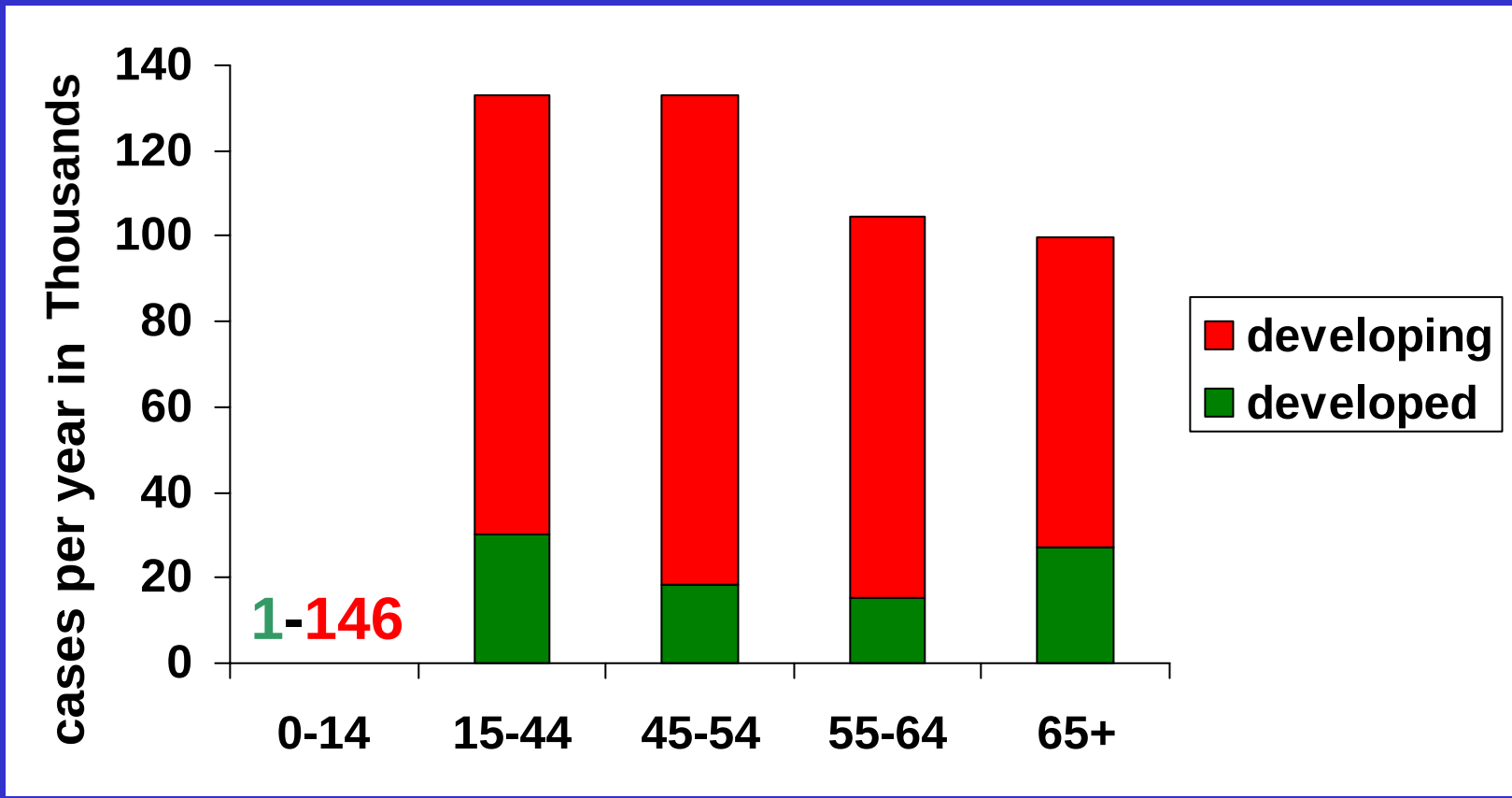
(adapted from Globocan 2002,)

Regional distribution of incidence rates* of new cervical cancer cases per year worldwide



* Per 100.000 women

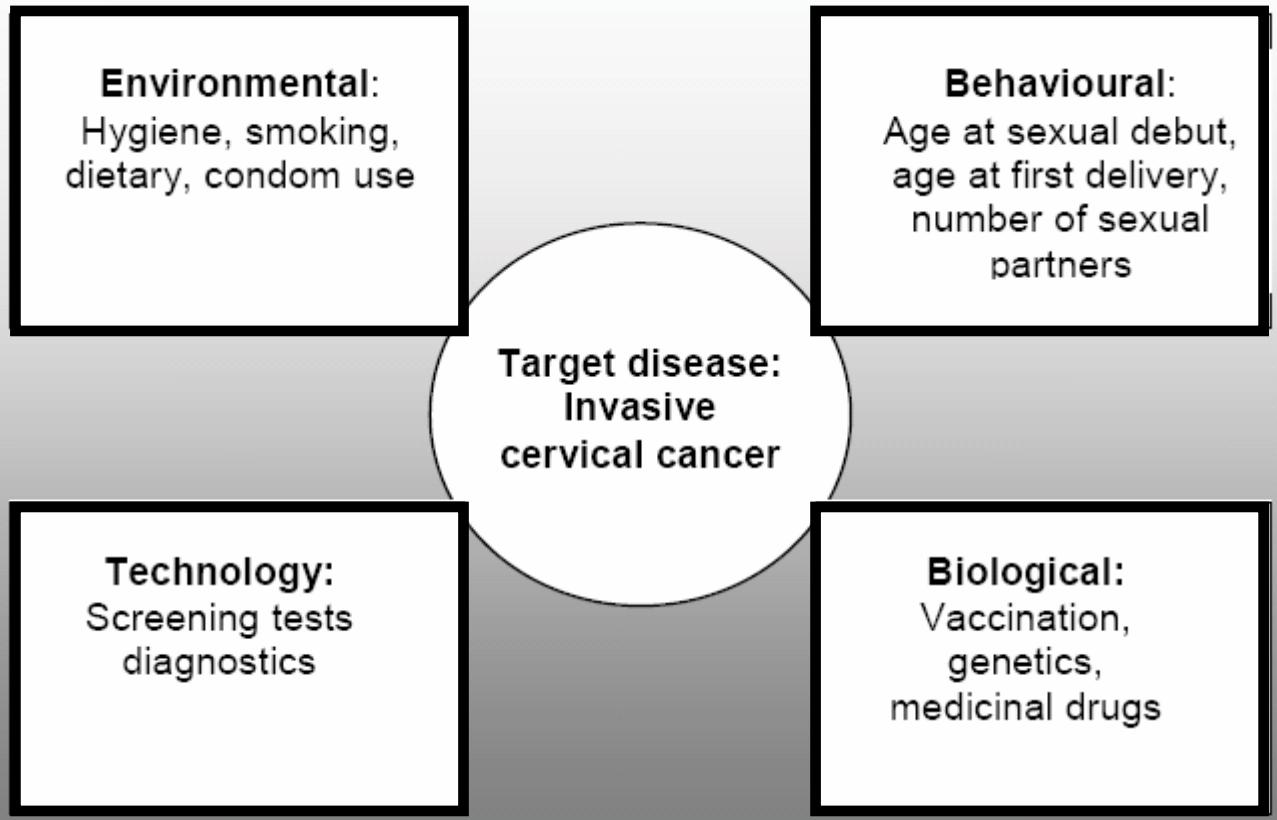
Age distribution of new cervical cancer cases



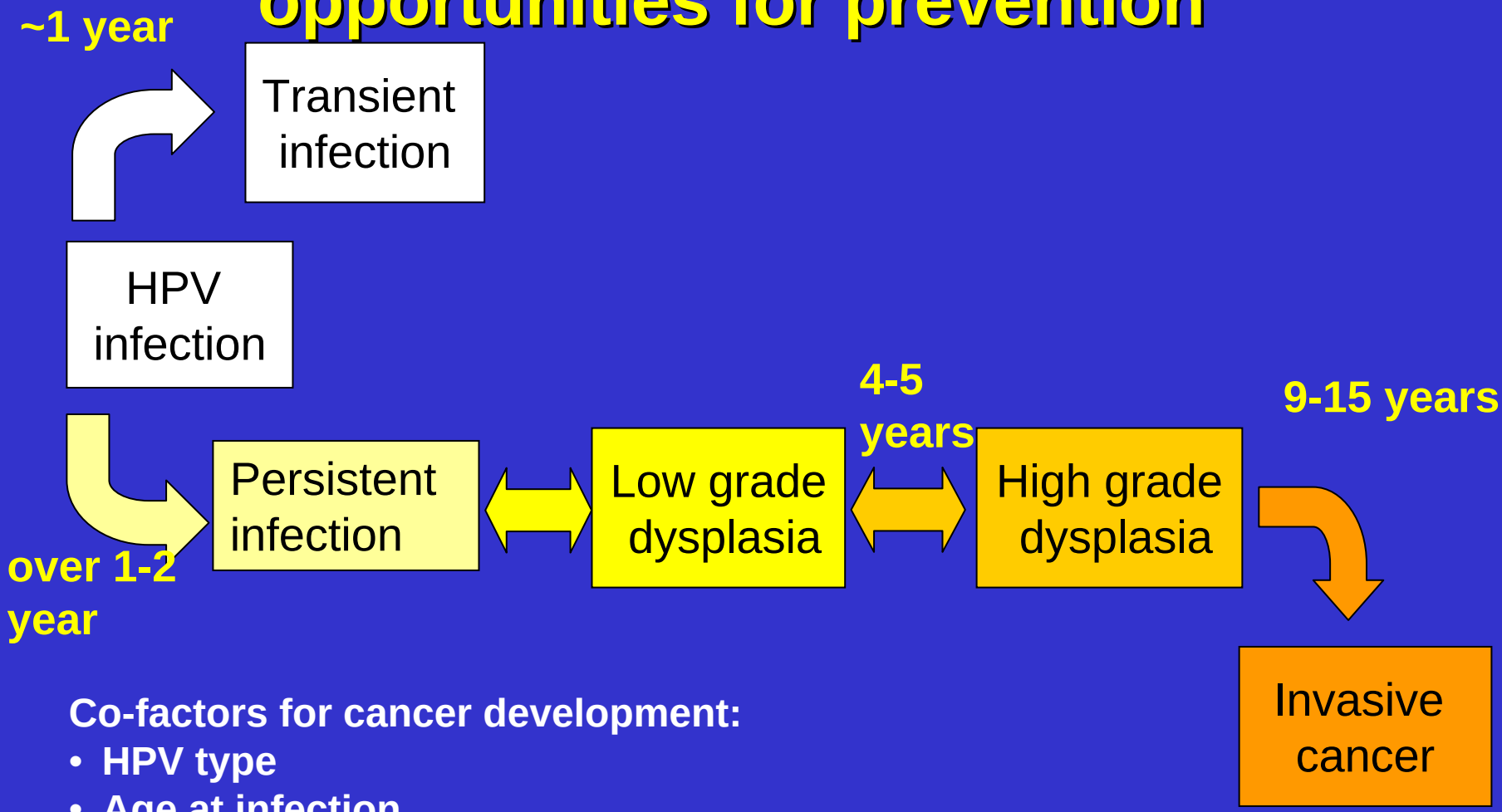
Age group	0-14	15-44	45-54	55-64	65+
developing	146	102673	114522	89338	72474
developed	1	30320	18568	15399	27163

(adapeted from Globocan, 2000)

CHANGES THAT IMPACT UPON DISEASE BURDEN



The etiology of cervical cancer and opportunities for prevention



Co-factors for cancer development:

- **HPV type**
- **Age at infection**
- **High parity**
- **Immune deficiency**
- **Chronic Chlamydia infection**
- **Hormonal, genetic, and environmental factors...**

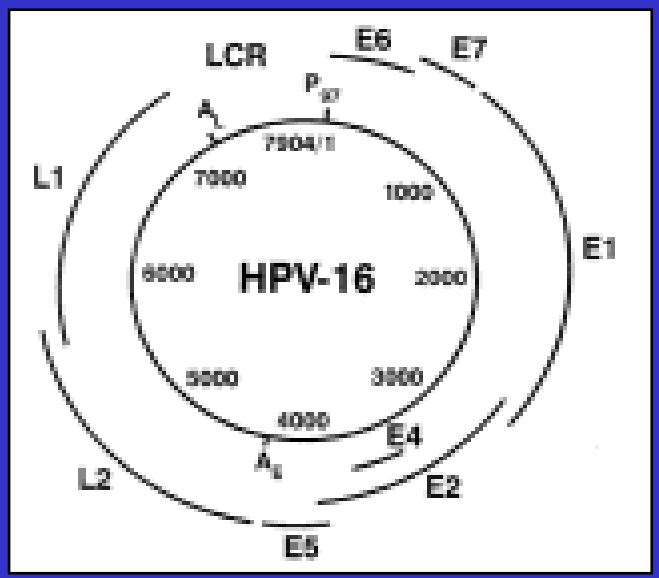
Natural History of CIN

Lesion	Regress	Persist	Progression to CIN 3	Progression to Invasion
CIN 1	57%	32%	11%	1%
CIN 2	43%	35%	22%	5%
CIN 3	32%	<56%	-	>12%

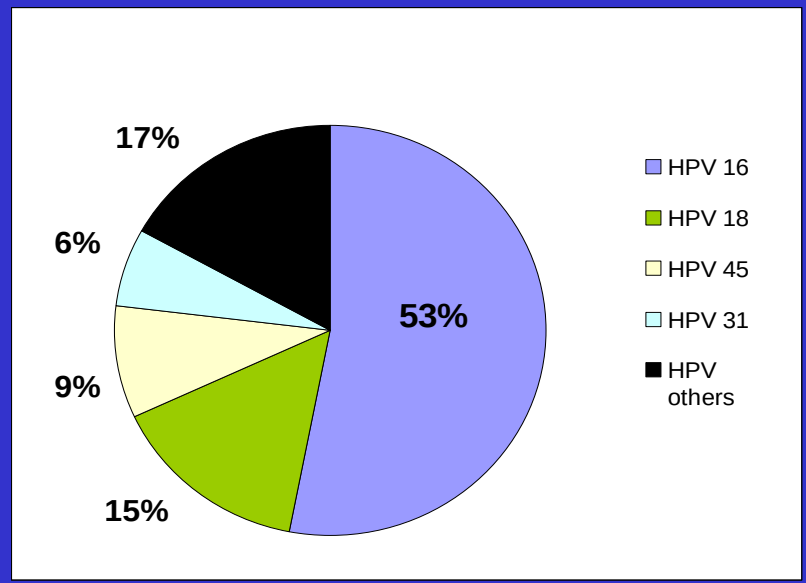
Modified from Östör AG: Natural history of cervical intraepithelial neoplasia: A critical review Int. J Gynecol. Pathol. 12:186-92, 1993. (Review)

Molecular basis for HPV vaccines

- HPV is a small circular dsDNA non-enveloped epitheliotropic virus
- Family includes more than 120 types,~30 cause genital infections*
- Four types that cause the greatest burden of cervical cancer*
- Sexually transmitted HPV virus DNA are associated with over 99% of cervical cancer cases*

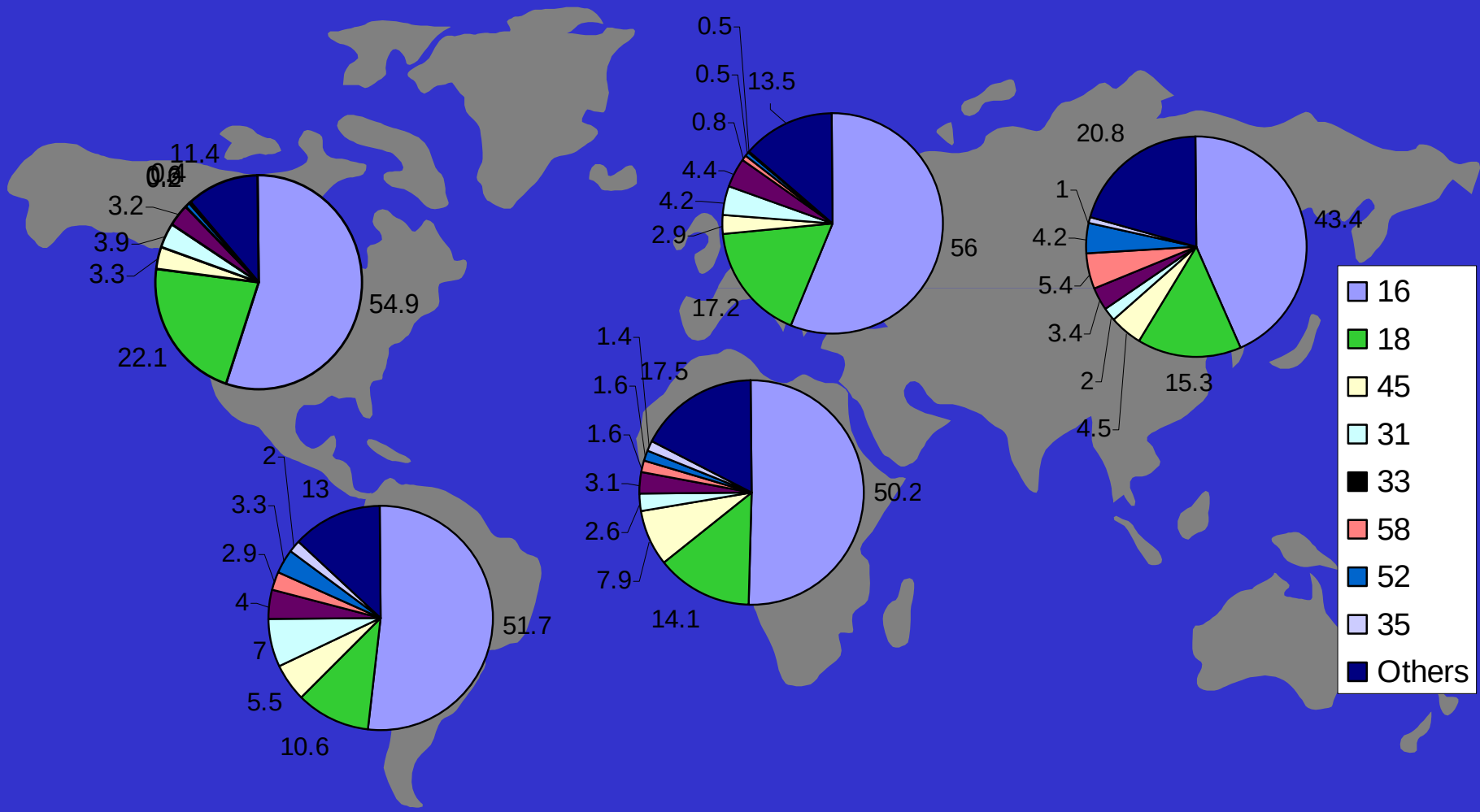


HPV 16 genome map



*(zur Hausen; Bosch et al., 1995; Walboomers et al. 1999)

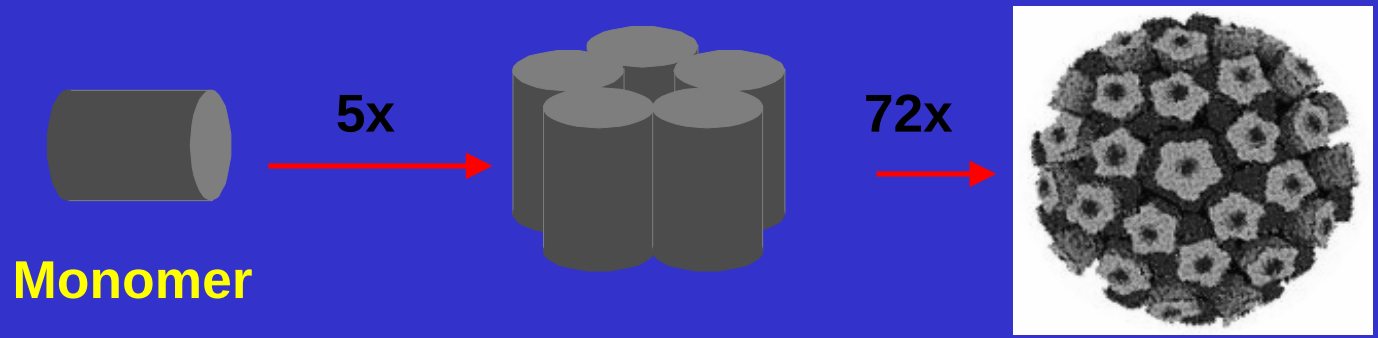
Regional distribution of HPV type prevalence in cervical cancer (% of all cases analysed)



Adapted from Clifford et al. 2002

HPV 16/18 vaccine candidates are becoming available

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



- Safe, immunogenic and well tolerated

- Complete protection against persistent HPV infections in vaccinated women has been demonstrated in two independent studies (Koutsky, 2002; EUROGIN 2003)

*adapted from Nieland

Milestones for HPV vaccines introduction

- Safety,immunogenicity,
- Efficacy
- Effectiveness
  - Epidemiology
  - Delivery-coverage
- Cost-effectiveness
- Impact on cervical cancer prevention

Summary of two independent phase IIb studies

	Merck	GSK
Candidate	HPV 16 VLPs	HPV 16/18 VLPs
Sample size	2392 subjects	1113 subjects
Study population	16 to 25 year olds with <6 lifetime sexual partners	15 to 25 year olds with ≤6 lifetime sexual partners
Inclusion criteria	Includes baseline positives	Excluded baseline positives
Primary Endpoint	Persistent HPV16 infection or HPV 16-related CIN	Transient or persistent HPV 16/18 infection

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%	99.8%
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)	n.a.

Milestones for HPV vaccines introduction

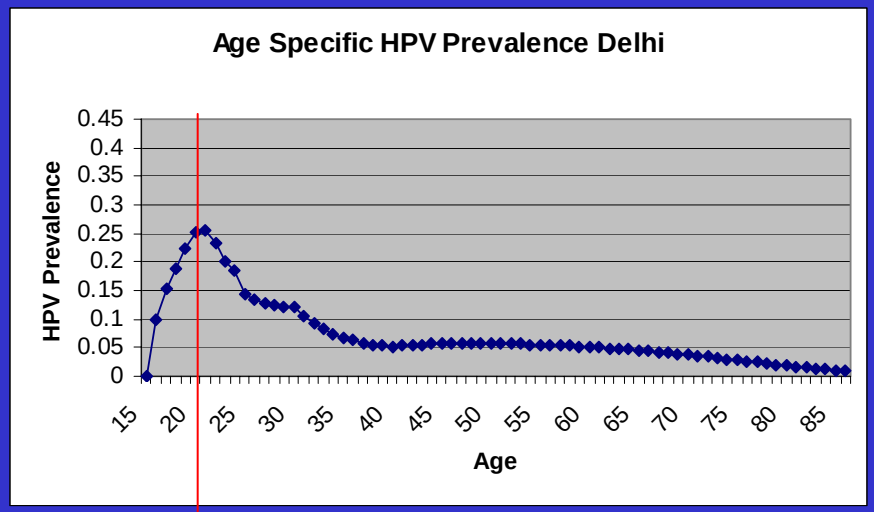
- **Efficacy: Desirable to have a globally-agreed measurable endpoint**
  - **Ethical and time considerations make it necessary to use surrogate endpoints, rather than invasive cervical cancer**
  - **Recommend CIN of moderate or high grade as primary endpoint, and cancer as secondary endpoint**
  - **Once this surrogate endpoint is validated, virological or immunological correlates of protection may be considered for future evaluation and product development**
  - **Document breakthrough cases following long periods**
  - **100% Efficacy against HPV 16 and 18 would prevent about 70% of cervical cancer cases**

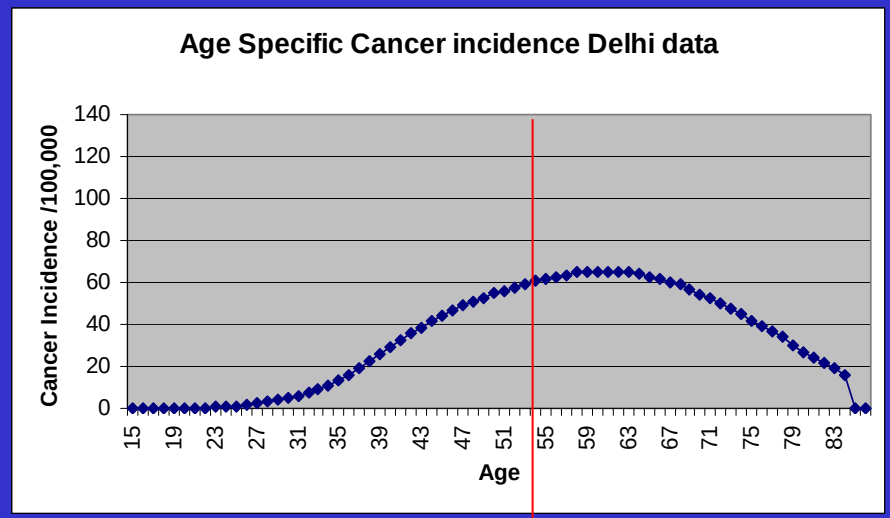
Milestones for HPV vaccines introduction

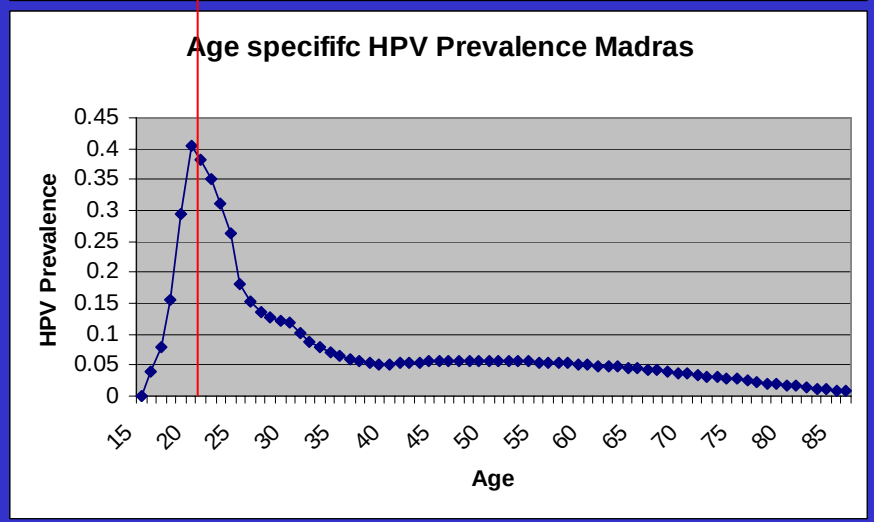
- **Effectiveness: Malignancies develop slowly and are relatively infrequent in a given population and therefore cancer outcomes require very large and lengthy studies**
  - **Duration of protection**
  - **Demonstration project**

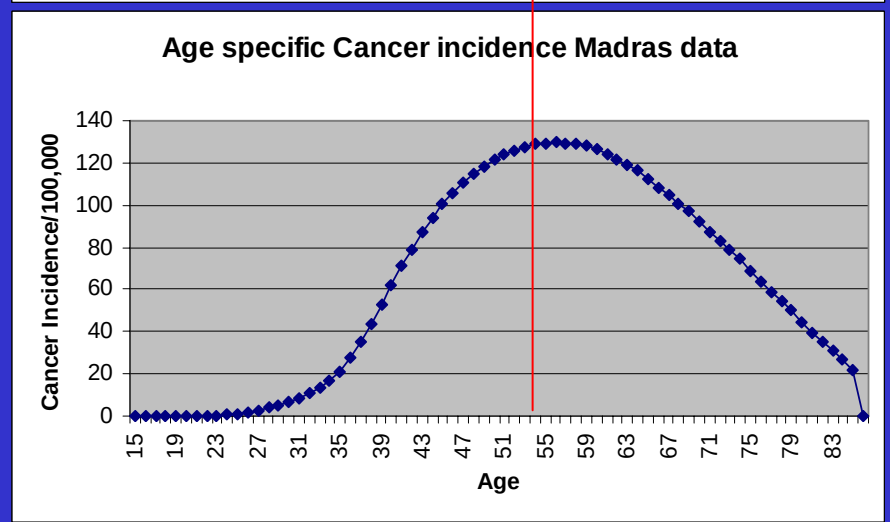
  - **Modelling**
  - **A model calibrated to Indian specific data by Shalini Kulasingam and colleagues (Duke university), using parameters in an existing model**

Age-specific HPV prevalence curves









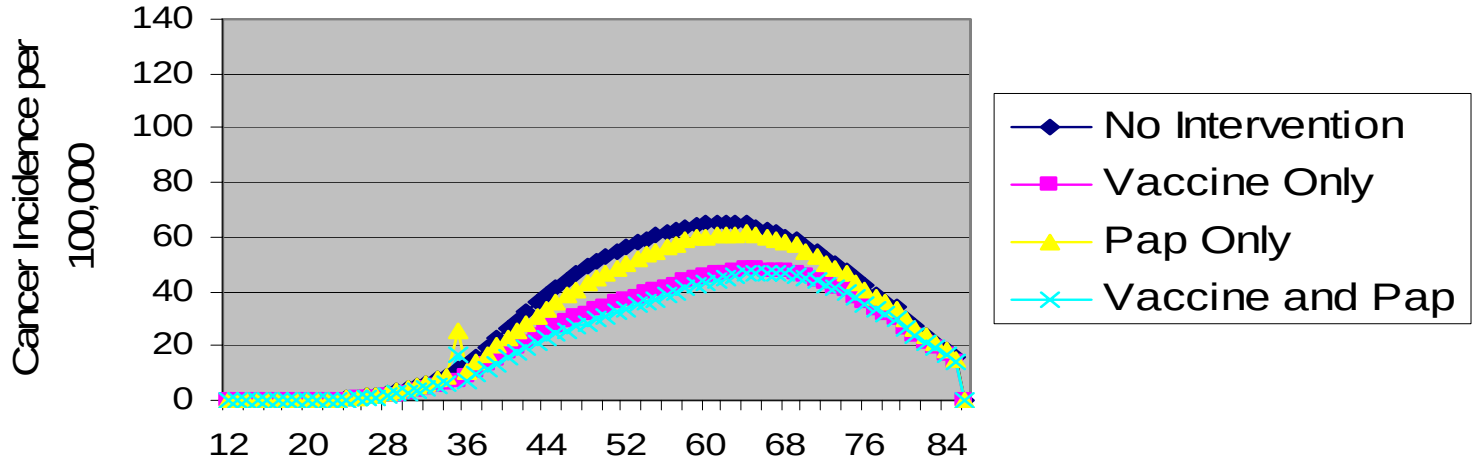
Two different models were developed using data from New Delhi and from Madras

With permission of Kulasingam et al.

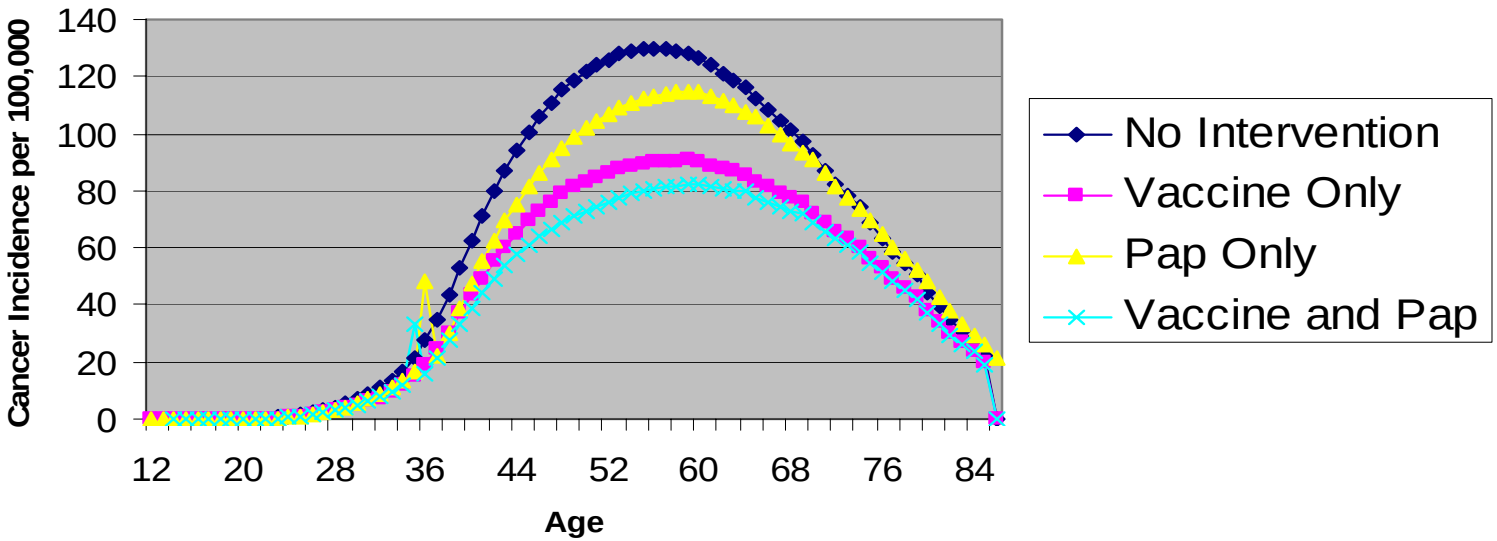
Baseline assumptions Vaccine

- Age of Vaccination is 12
- Vaccine efficacy is 90% (8) (lower bound of 95%CI from Koutsky et al. NEJM, 2002)
- Vaccine duration is 30 years- assumed
- Proportion of HPV types covered is 70% (9,10)
- Vaccine coverage is 70%- assumed

Age-Specific Cancer Incidence
New Delhi Model



Age-Specific Cancer Incidence
Madras Model



With permission of Kulasingam et al.

Outstanding issues

- Effectiveness in field conditions, immunodeffiency
- Duration of protection:
  - Infections later in life
  - Latent infections
- HPV type replacement in disease
- Role of male vaccination in disease burden
- Impact of vaccination on invasive cancer

Additional research for HPV vaccine evaluation relevant for public health use

- Immunogenicity and safety in immunocompromised subjects
- Feasibility of vaccinating adolescents
- Monitor the prevalence of HPV types in vaccinated populations by periodic sampling surveys
- Monitor the occurrence of invasive cervical cancer in specific early age groups to accelerate evaluation of impact of vaccination on cancer

Conclusion

As impact of vaccines on cancer is not yet empirically demonstrated, and health professionals still need to prevent cancers not related to the vaccine types:

- **For the next decades, combinations of primary and secondary prevention strategies will be needed, and the modalities of these combinations may change over time, depending on many factors that are likely to be country specific.**