



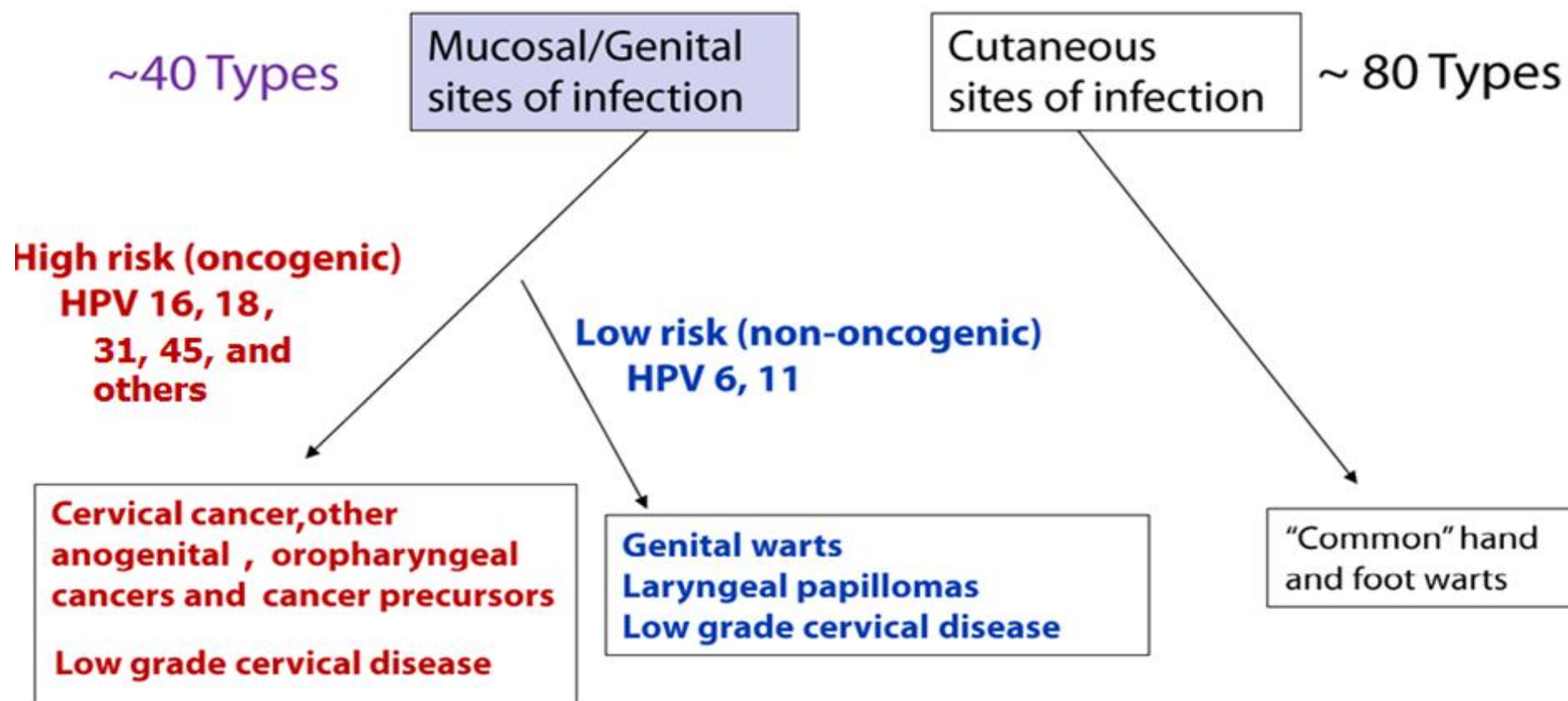
Cervical Cancer Burden and Options on HPV Vaccination

Dr. Deepa Gamage
Consultant Epidemiologist
Epidemiology Unit

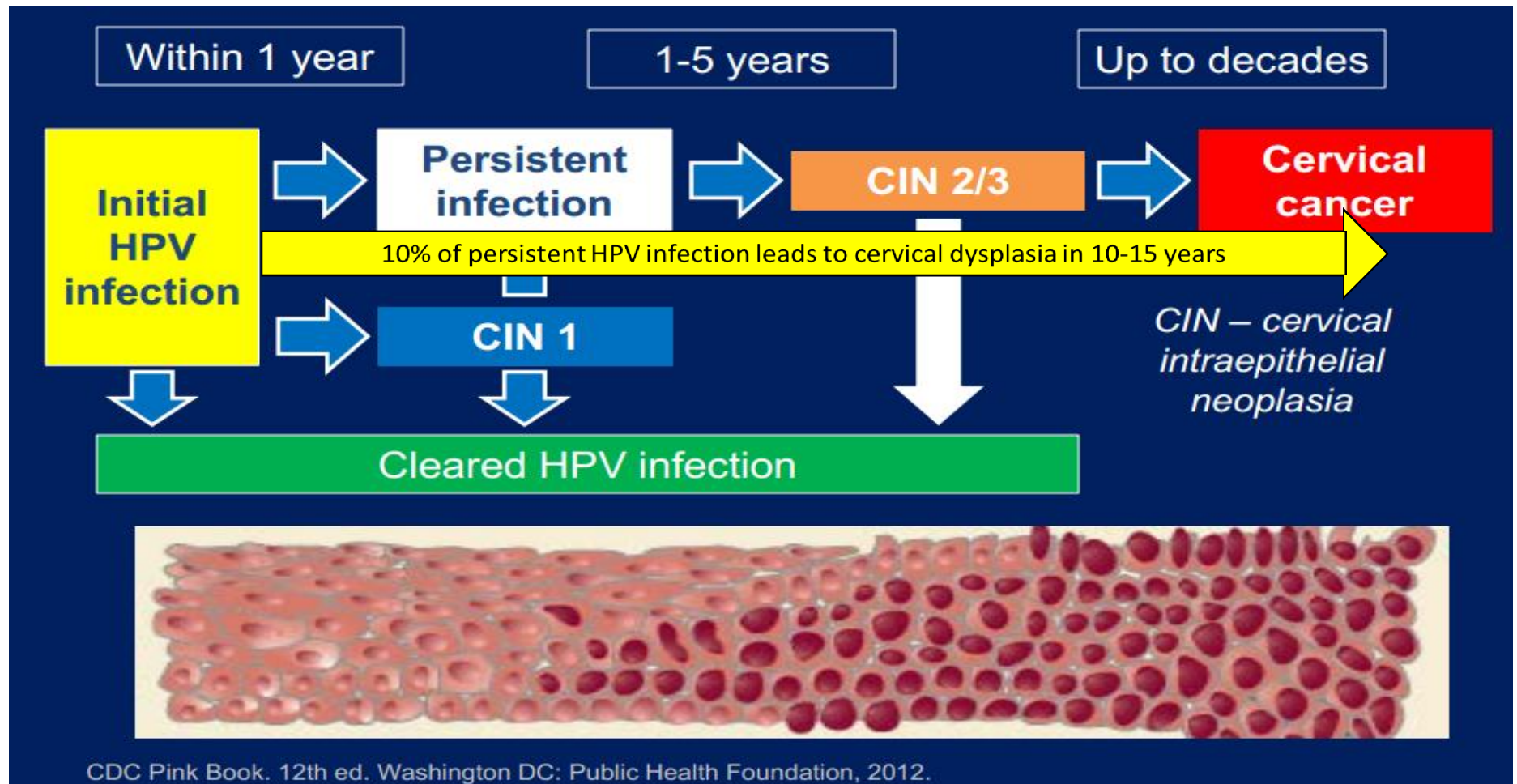
HPV infections

- “ Most HPV infections are asymptomatic and cleared within two years with no resultant diseases
- “ **If not cleared, clinical manifestations can include:**
 - “ anogenital warts,
 - “ recurrent respiratory papillomatosis (RRP),
 - “ cervical cancer precursors (cervical intraepithelial neoplasia = CIN),
 - “ cancer
 - “ **cervical,**
 - “ anal,
 - “ vaginal,
 - “ vulvar,
 - “ penile and
 - “ oropharyngeal)

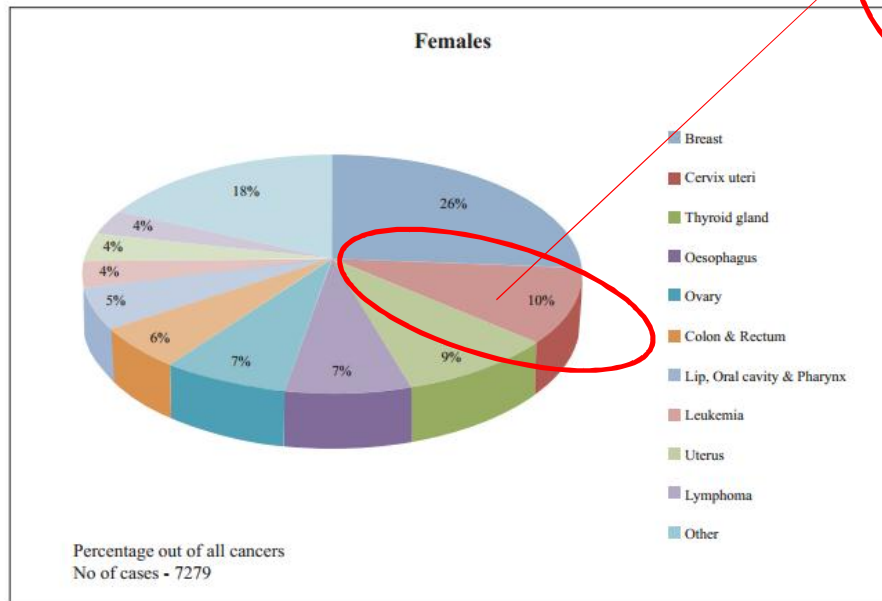
HPV types and disease association



Natural history of HPV cervical infection



Cervical Cancer burden : Sri Lanka



National Cancer Control Programme,
Cancer Incidence data 2007,

2nd most common
female cancers
2007 – 10% of all
female cancers are
cervical cancer

Global estimate : almost 12%
of all female cancers are cervical cancers

<http://globocan.iarc.fr/old/FactSheets/cancers/cervix-new.asp>

Globally, cervical cancer- 2nd common cause of cancer deaths, nearly 80% of deaths from developing countries.

1.4 million suffer from cervical cancer and nearly 450,000 new cases annually

Sri Lanka- nearly 850-950 with advanced disease each year admitted to government hospitals

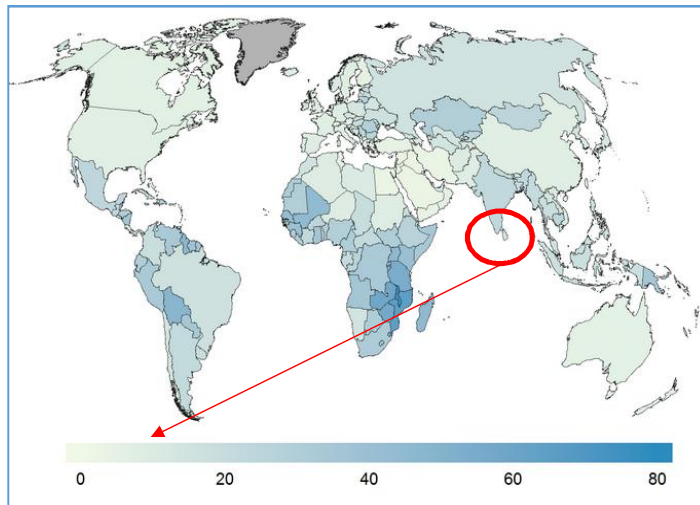
Cervical Cancer burden.....

Table 06: Leading cancer sites- 2007

Female				
Site	No.	CR	ASR	
Breast	1914	19.0	18.8	
Cervix uteri	732	7.3	7.4	
Thyroid gland	656	6.5	6.1	
Oesophagus	534	5.3	5.6	
Ovary	529	5.2	5.3	
Colon and rectum	405	4.0	4.1	

CR: Crude rate per 100,000 population
 ASR: Age standardized rate per 100,000 world population

Estimated Cervical Cancer Incidence Worldwide in 2012



Estimated age-standardised rates (World) per 100,000

<http://globocan.iarc.fr/old/FactSheets/cancers/cervix-new.asp>

Year	Total number of cervical cancer cases
2007	732
2008	850
2009 -2014	Still working on identifying duplicate cases

National Cancer Control Programme, Cancer Incidence data 2007, and on personal communication

- “ 9 treatment centres in Sri Lanka
- “ Data collection : hospital and laboratory based active collection
- “ 2012: “Population based cancer registry” started as a pilot project in Colombo district (hospital- government, privatet, laboratories, Death Registrars)

Prevention of cervical cancer

- “ Early detection and treatment

- “ cervical screening and management of precancerous stages and invasive cervical cancer stages

- “ Vaccination :

- “ for prevention of genital HPV infection due to High Risk (HR) genotypes

HPV prevalence

community prevalence and among cervical cancers: *Gamage et al, 2009*

HPV Community Prevalence study : Gampaha district

“ Community based descriptive cross sectional study, among 2000 married women between 20-59 years of age

“ Cluster sampling technique , proportional recruitment from each age category

“ Cervical swabs and pap smear samples were collected

HPV prevalence..... *Gamage et al*

- “ HPV-DNA was detected by PCR (40 cycles), using GP 5+/6+ primer system at Genetec Laboratory Sri Lanka
- “ Direct sequencing was done at the laboratory of Eton Bioscience North Carolina Branch, Research triangle park, NC, USA
- “ sequences were obtained in a form of electrogram and genotype identification was done at Genetec Lab. with the assistance of GenBank
- “ Pap smear testing : at Family Health Bureau laboratory

Prevalence-cervico vaginal HPV infection

	Total sample	HPV prevalence	95% CI
Overall prevalence	2000	3.3 % (66)	3.2-3.4
High risk genotype (16 &18)	2000	1.2% (24)	1.15 – 1.25
Cytologically normal women	1933	3.1% (59)	3.0-3.2

Geno types

31,33,35,39,45,51,52,56,58,59,68,73, 82 are also associated with CIN

HPV Geno type	no
" 16	- 22
" 18	- 2
" 31	- 1
" 33	- 1
" 35	- 2
" 42	- 7
" 45	- 1
" 51	- 1
" 56	- 4
" 62	- 5
" 66	- 4
" 73	- 2
" 81	- 2
" 83	- 1
" 87	- 2
" Total -	57

Distribution of HPV infection status by age

Age in years	HPV +ve	HPV -ve	Total
20-29	25[3.6%]	676[96.4%]	701[100%]
30-39	17[3.2%]	521[96.8%]	538[100%]
40-49	12[2.7%]	427[97.3%]	439[100%]
50-59	12[3.7%]	310[96.3%]	322[100%]
Total	66[3.3%]	1934[96.7%]	2000[100%]

Distribution of HPV status by pap smear result

Cytological abnormality	HPV +ve	HPV -ve	Total	<i>significance</i>
(r) Normal	59 [3.1%]	1874[96.9%]	1933[100%]	$\chi^2 = 8.9$ $df=1,$ $p=0.002,$ $OR=3.71$ $(1.37 - 8.59)$
CIN 1	2[16.7%]	10[83.3%]	12 [100%]	
CIN 2	1[50%]	1[50%]	2 [100%]	
Cervical malignancy	0[0%]	1[100%]	1 [100%]	
Infective / inflammatory changes	3[7.7%]	36[92.3%]	39 [100%]	
Endometrial cells above 40 years	1[7.7%]	12[92.3%]	13 [100%]	
Total	66[3.3%]	1934[96.7%]	2000 [100%]	

Progression of precancerous stages to invasive cervical cancer

Colposcopy and treatment of cervical intraepithelial neoplasia
-IARC, Sellors, JW and Sankaranarayan R
Meta analysis – studies 1950-1993
progress proportions into Invasive cervical cancer

- CIN 1 – 1%
- CIN 2 – 1.5%
- CIN 3 – 12%

Progression of CIN stages to invasive cervical cancer will be as follows

CIN 1 12 x 1/100 = 0.12 invasive cervical cancer/ 2000 women screened

CIN 2 2 x 1.5/100 = 0.03 invasive cervical cancer/ 2000 women screened

Total invasive cervical cancer detected at pap smear screening 1.15/2000

According to the study findings the total number needed to screen in future prevention of one cervical cancer is 1739 women (2000/1.15)

(if exclude women <35 yrs, the number needed to screen will be 1130)

Total number of women (above 35 years) needed to screen (at this HPV prevalence status) can be calculated in prevention of the total cervical cancers per year (850-900 cases)

Nearly 1 million women needs to be screened/year to prevent the total case burden

[Cervical cancer 850-900/year x number needed to screen above 35Y]

HPV prevalence among cervical cancers and risk attribution of HPV for cervical cancer : *Gamage et al*

Hospital based case control study

- “ 40 newly diagnosed cervical cancer patients : cases from Cancer Hospital Maharagama
- “ Controls 1:4 : age category and area matched, clinically normal women from the community

HPV status	Cases	Controls	
Positive	32(80%)	6(3.8%)	$\chi^2 = 116.6,$ $df=1,$ $p < 0.001,$ $OR = 102.67$ $(29.84 - 302.20)$
Negative	8(20%)	154(96.2%)	
Total	40(100%)	160(100%)	

HPV genotype	Cases	Controls	
Type 16	29(90.6%)	4(66.7%)	HR-VP
Type 18	2(6.3%)	0(0%)	HR-VP
Type 31	1(3.1%)	0(0%)	HR
Type 42	0(0%)	2(33.3%)	LR
Total	32(100%)	6(100%)	

Risk attribution... *Gamage et al*

	Adjusted Odds Ratio for HPV infection (by logistic regression)	Population Attributable Risk (PAR) %
All HPV geno types	<p>172</p> <p>172 times increased risk for development of invasive cervical cancer among those who have prevalent cervico vaginal HPV infection compared to normal women considering other possible risk factors in cervical cancer development</p> <p>(high parity, advancing age, social class, younger age at 1st pregnancy, number of life time sex partners, time since last delivery, age at 1st sex etc....)</p>	<p>85%</p> <p>if take 100 cervical cancer cases 85 are attributed to HPV infection</p>
Geno type 16 & 18	190.30	69%

Other HPV studies in Sri Lanka

2006:

Hospital based Case Control Study, 15 Cervical Cancer biopsy pathological specimens, compared with non Cervical Cancer pathological specimens

“ HPV genotype 16 positive : 73% among case specimens, and 20% among control specimens

“ HPV genotype 18 : 20% among case specimens and none among control specimens

De Silva et. al ,*Ceylon Medical Journal*, 2006 , vol. 51, no.3, pp.114-117.

2014

“ Among Invasive cervical cancers : overall prevalence of HPV infection : 84.7% ([95% CI: 76.0–91.2])

“ HPV genotype distribution among them :

“ HPV-16 : 67.3% [95% CI: 57.1–76.5] (66/98)

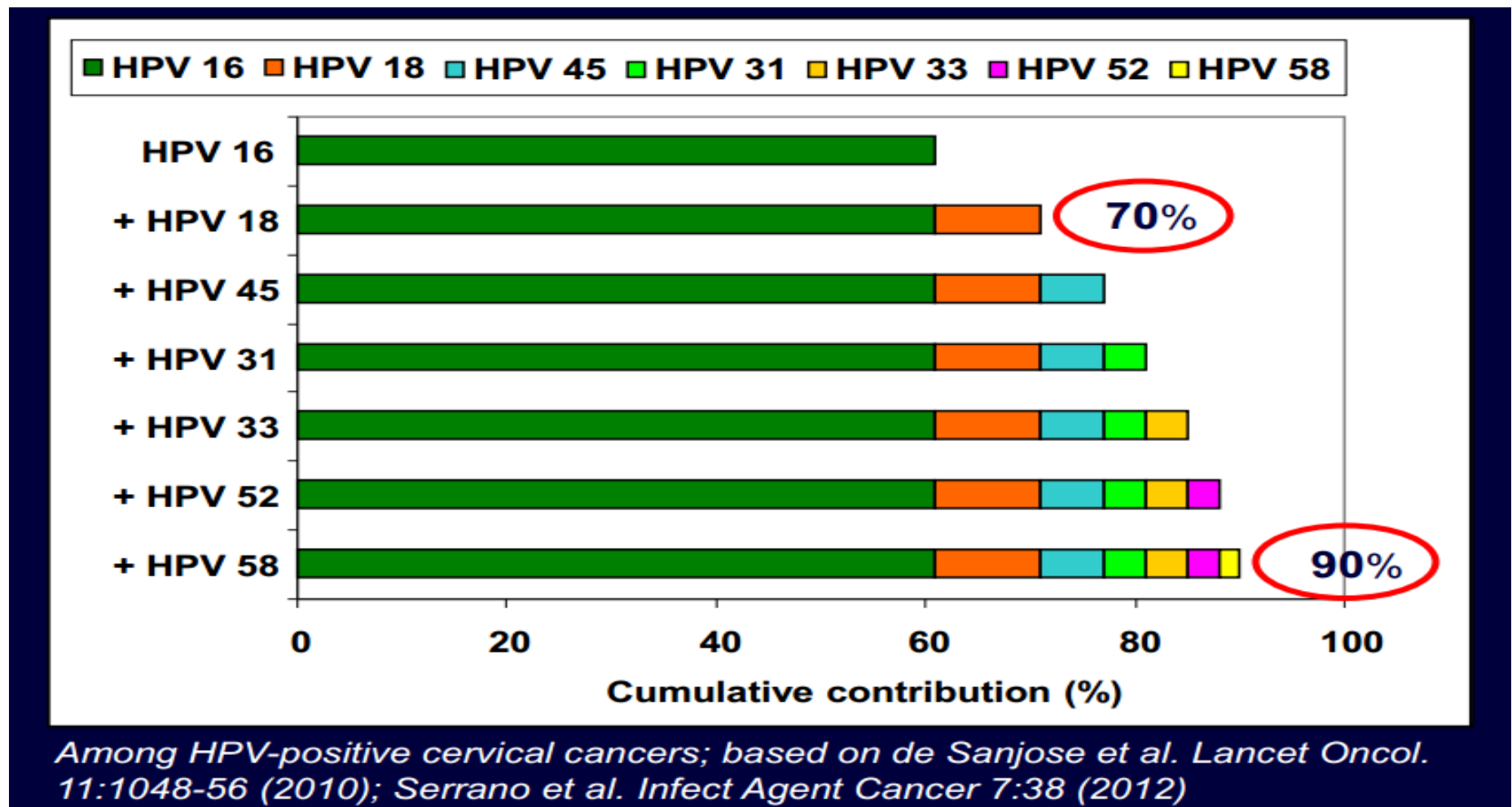
“ HPV-18 : 9.2% [95% CI: 4.3–16.7]

Karunaratne et. al. *BMC Cancer* 2014, 14:116
<http://www.biomedcentral.com/1471-2407/14/116>

HPV vaccine types

- “ **Quadrivalent HPV (HPV4) vaccine** (for prevention of 70% of cervical cancer cases)
 - Contains HPV types 16 and 18 (high risk) and types 6 and 11 (low risk)
 - Approved for females and males aged 9 through 26 Years
- **Bivalent HPV (HPV2) vaccine** (for prevention of 70% of cervical cancer cases)
 - Contains HPV types 16 and 18 (high risk)
 - Approved for females aged 10 through 25 years
- “ **Ninevalent HPV vaccine (9v HPV)** (for prevention of 90% of cervical cancers)
 - Contains HPV geno types 6, 11, 16, 18, 31, 33, 45, 52, and 58
 - for use in girls and young women 9 to 26 years of age
 - for the prevention of cervical, vulvar, vaginal, and anal cancers
 - pre-cancerous or dysplastic lesions genital warts caused by HPV types 6 and 11

Relative Contribution of HPV Types in 9vHPV Vaccine to Cervical Cancers Worldwide



Types of HPV vaccine

Bivalent	Quadrivalent	Ninevalent (new)
<ul style="list-style-type: none"> “ First licensed in 2007 “ HPV-VLP: genotype 16 & 18 “ schedule : 0-1-6 months “ No live biological products or viral DNA “ Liquid form “ intramuscular injections as dose of 0.5 mL Sero conversion 99-100% 	<ul style="list-style-type: none"> “ First licensed in 2006 “ Schedule : 0-2-6 “ No live biological products or viral DNA “ Liquid vaccine “ intramuscular injections as dose of 0.5 mL “ Sero conversion 99-100% 	<ul style="list-style-type: none"> “ Approved to use in USA, Canada :2014 December “ females ages 9 - 26 and males ages 9 – 15 “ to prevent <ul style="list-style-type: none"> “ cervical pre-cancers and cancers “ vulvar and vaginal pre-cancers and cancers “ anogenital warts

New recommendation of HPV vaccination: 2 dose schedule

Weekly Epidemiological Record (WHO) , WHO position paper : October 2014

Points for the discussion

- “ Should we introduce HPV vaccine
- “ If so what type of the vaccine
- “ Risk factor prevalence : what is different in Sri Lanka
- “ Need for collection of background disease burden data

Acknowledgement

- “ UNFPA for funding HPV studies
- “ PDHS, RDHS, MO/MCH and all MOOH in district of Gampaha
- “ Staff of Cancer hospital Maharagama
- “ FHB staff and Histopathologists and staff of FHB laboratory
- “ Staff of National Cancer control Programme
- “ Epid Unit staff and Supervisors of the study : Dr. Nihal Abeysinghe, Prof. Amala de Silva and Prof. Lalini Rajapaksa

Thank you