

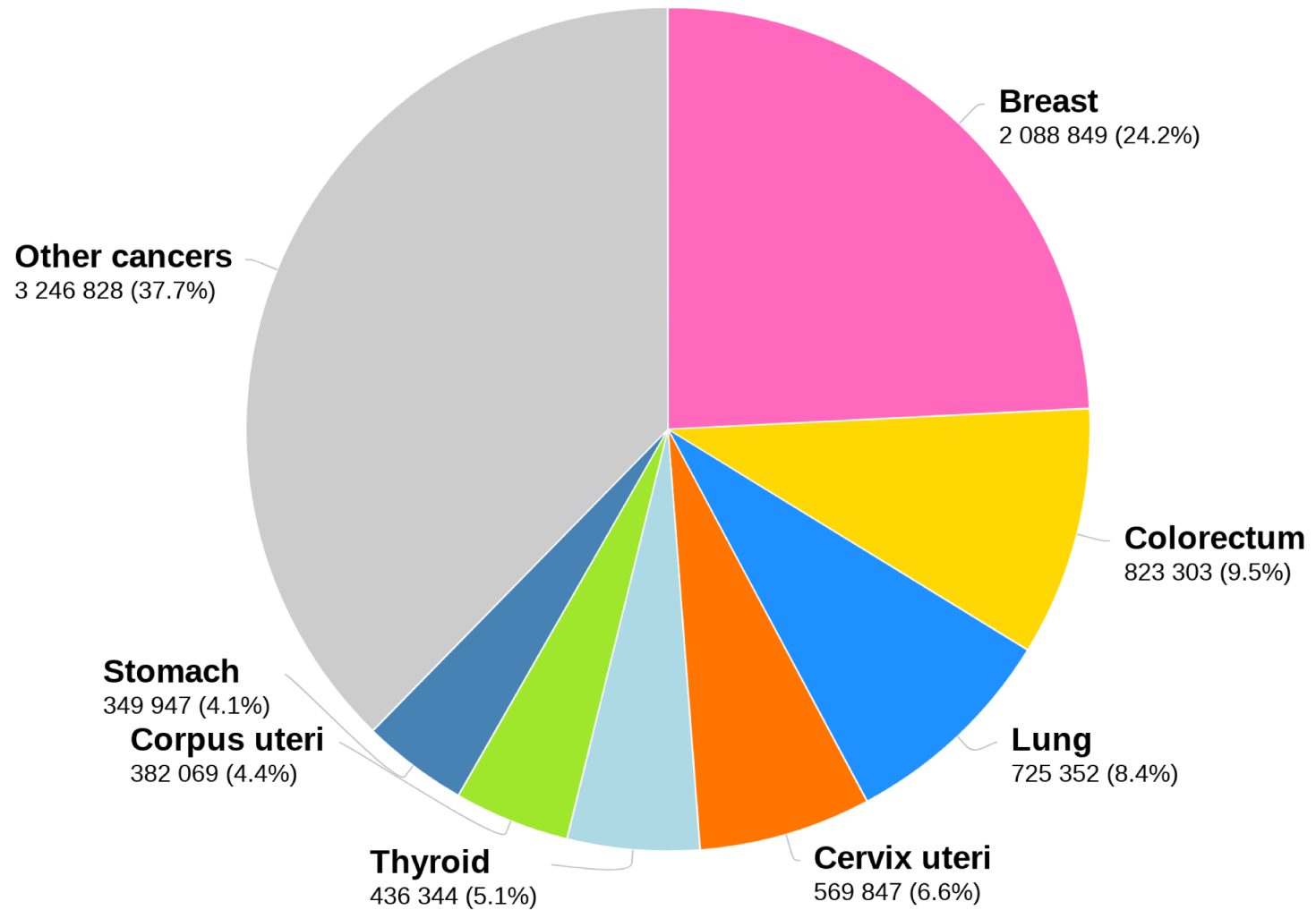
Overview of the evidence regarding HPV immunization effect on different disease outcomes

SAGE meeting, 23-25 October 2018

Purpose

- Review data in light of current SAGE recommendations
- Consider what HPV vaccine offers towards elimination goals for **cervical cancer** as a public health problem

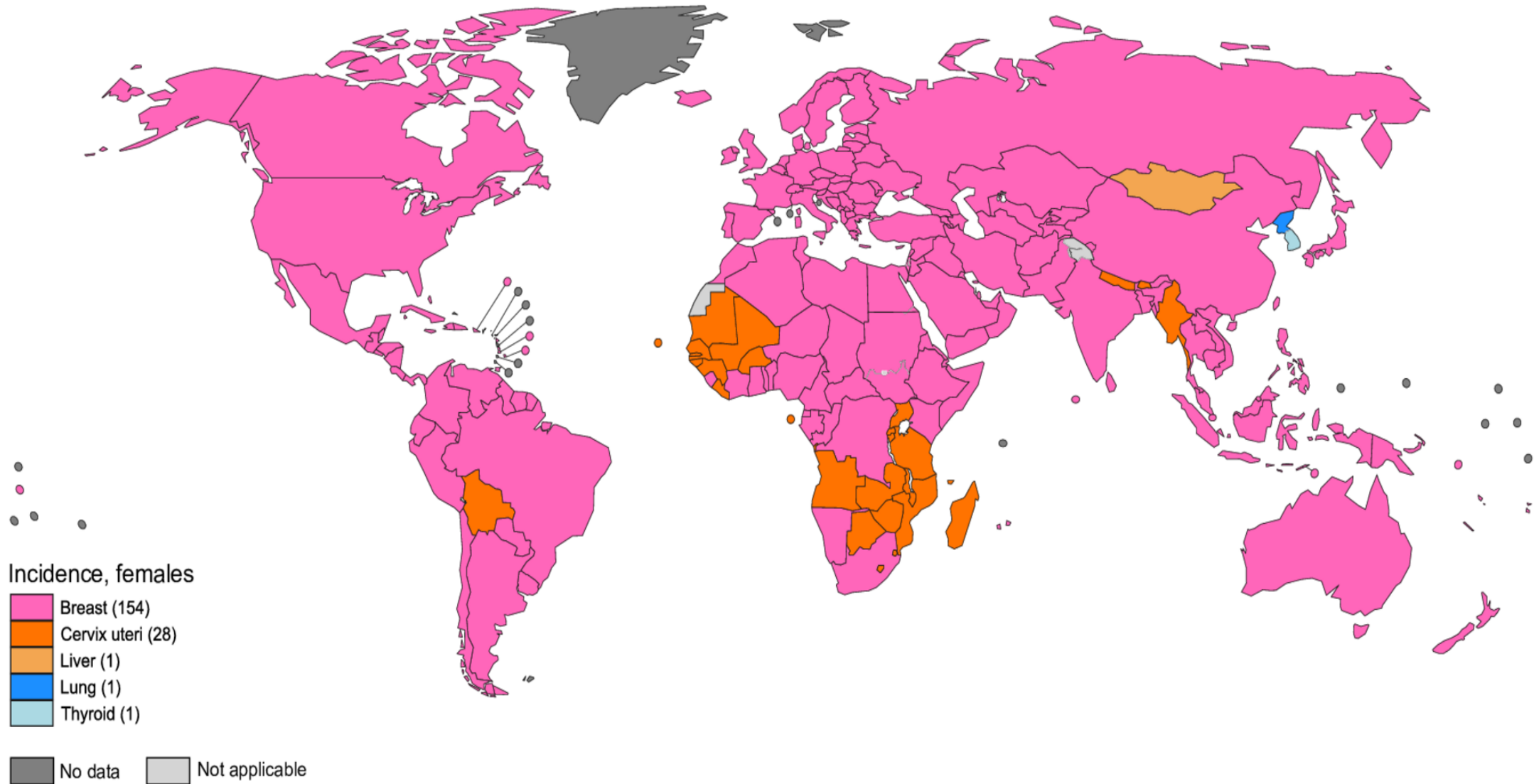
Estimated number of new cases in 2018, worldwide, all cancers, females, all ages



Total : 8 622 539



Most common cancer by country, females 2018



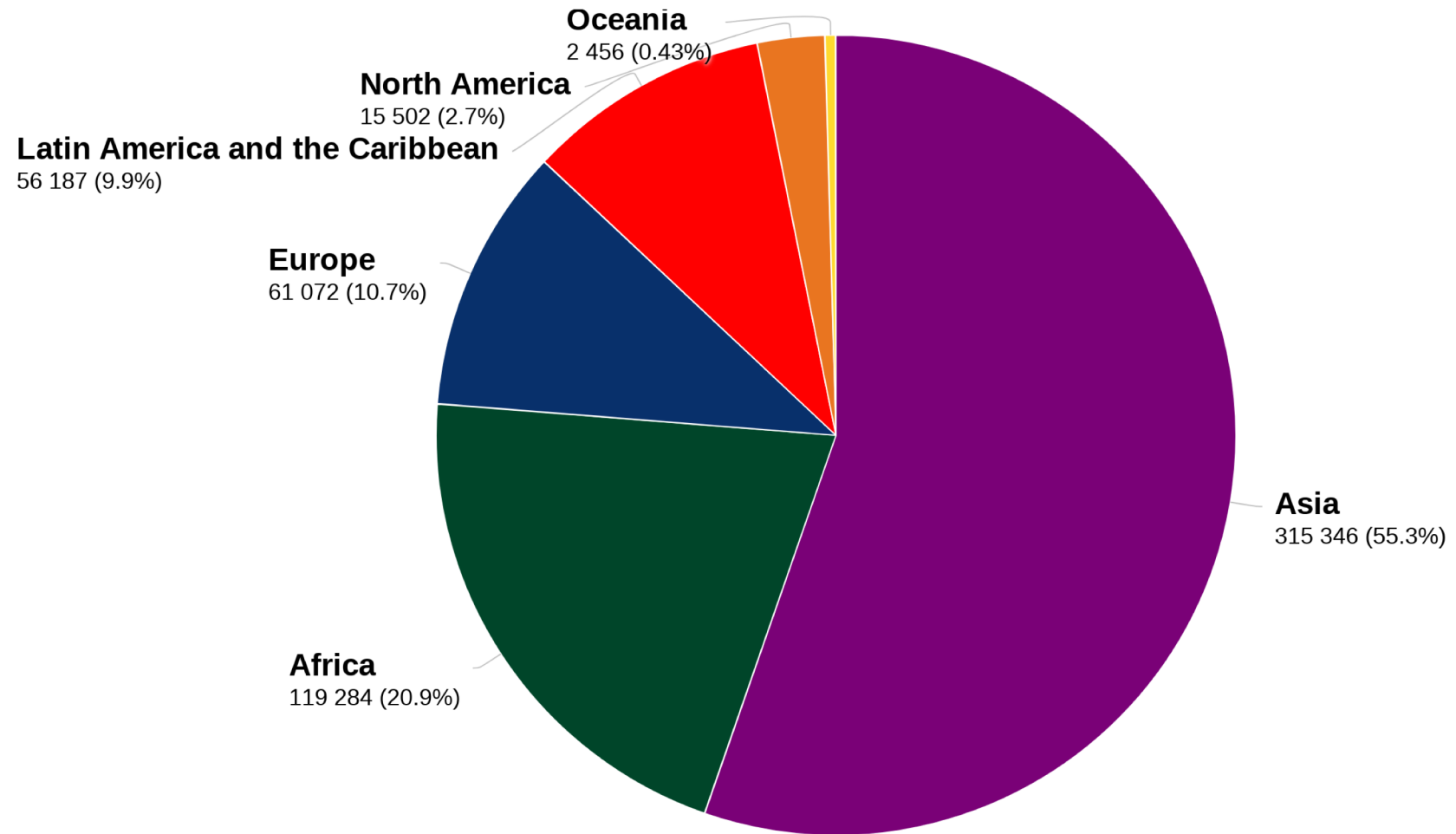
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: Globocan 2018
Map production: IARC
World Health Organization



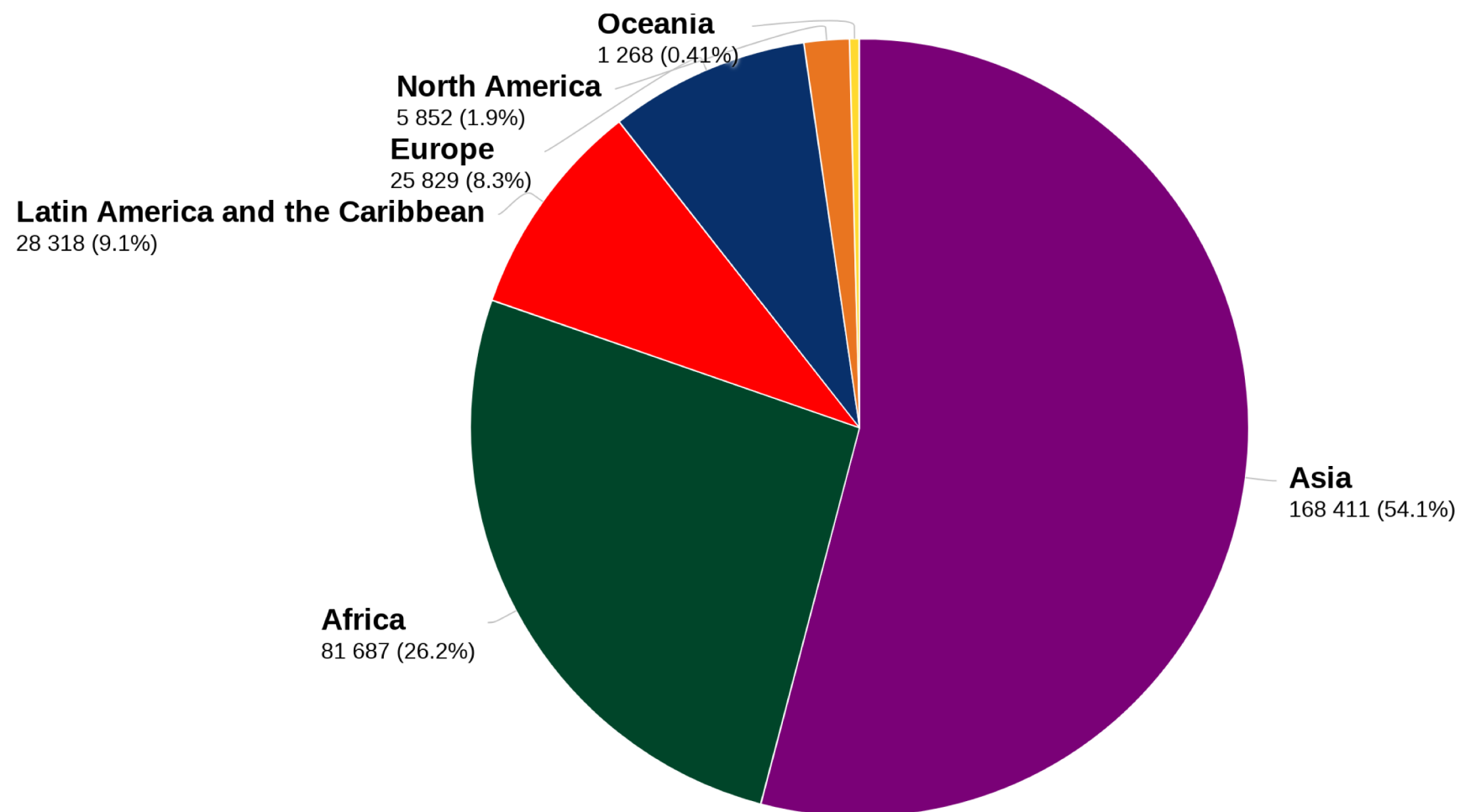
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Estimated number of new cases in 2018, cervix uteri, all ages



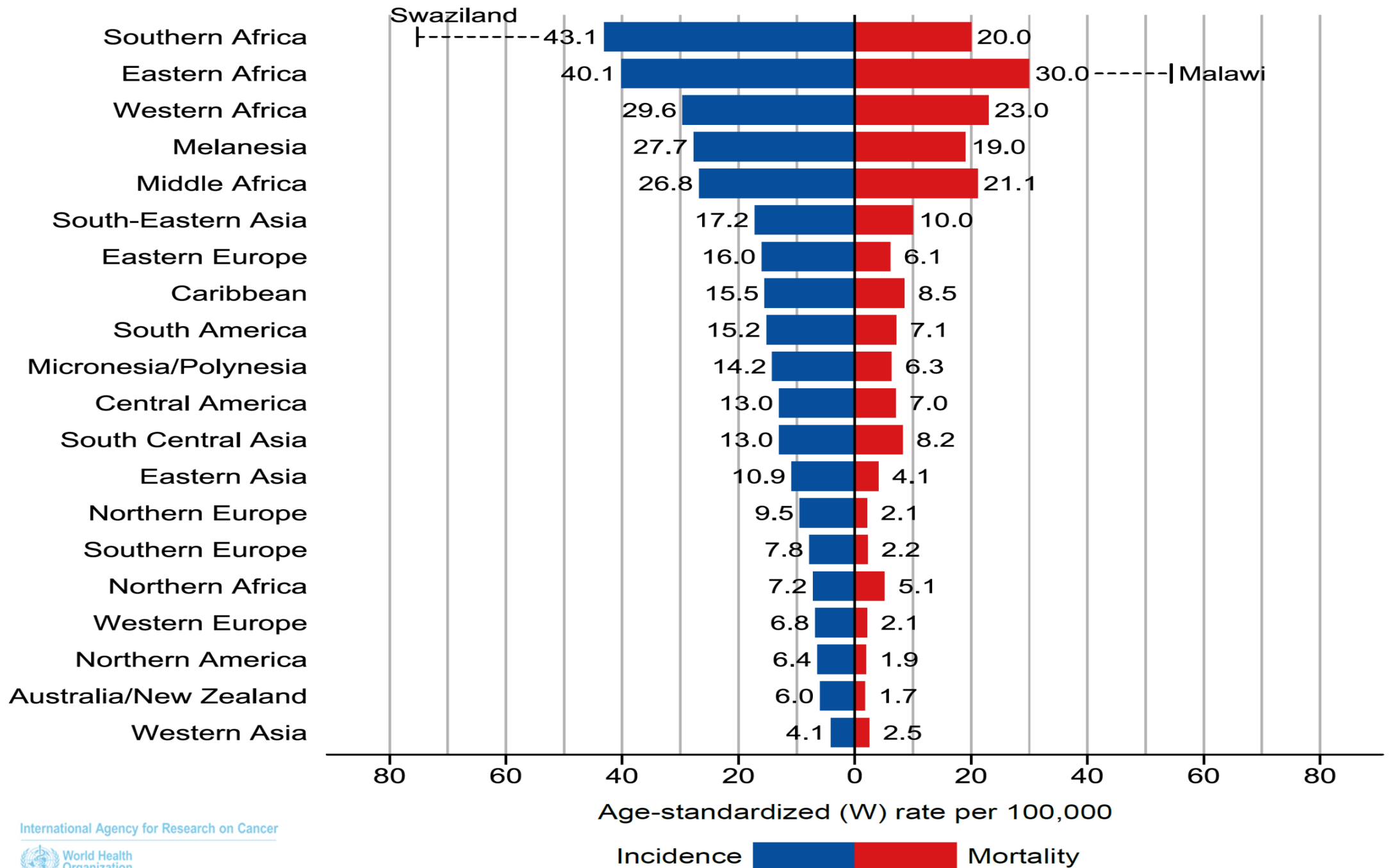
Total : 569 847

Estimated number of deaths in 2018, cervix uteri, all ages

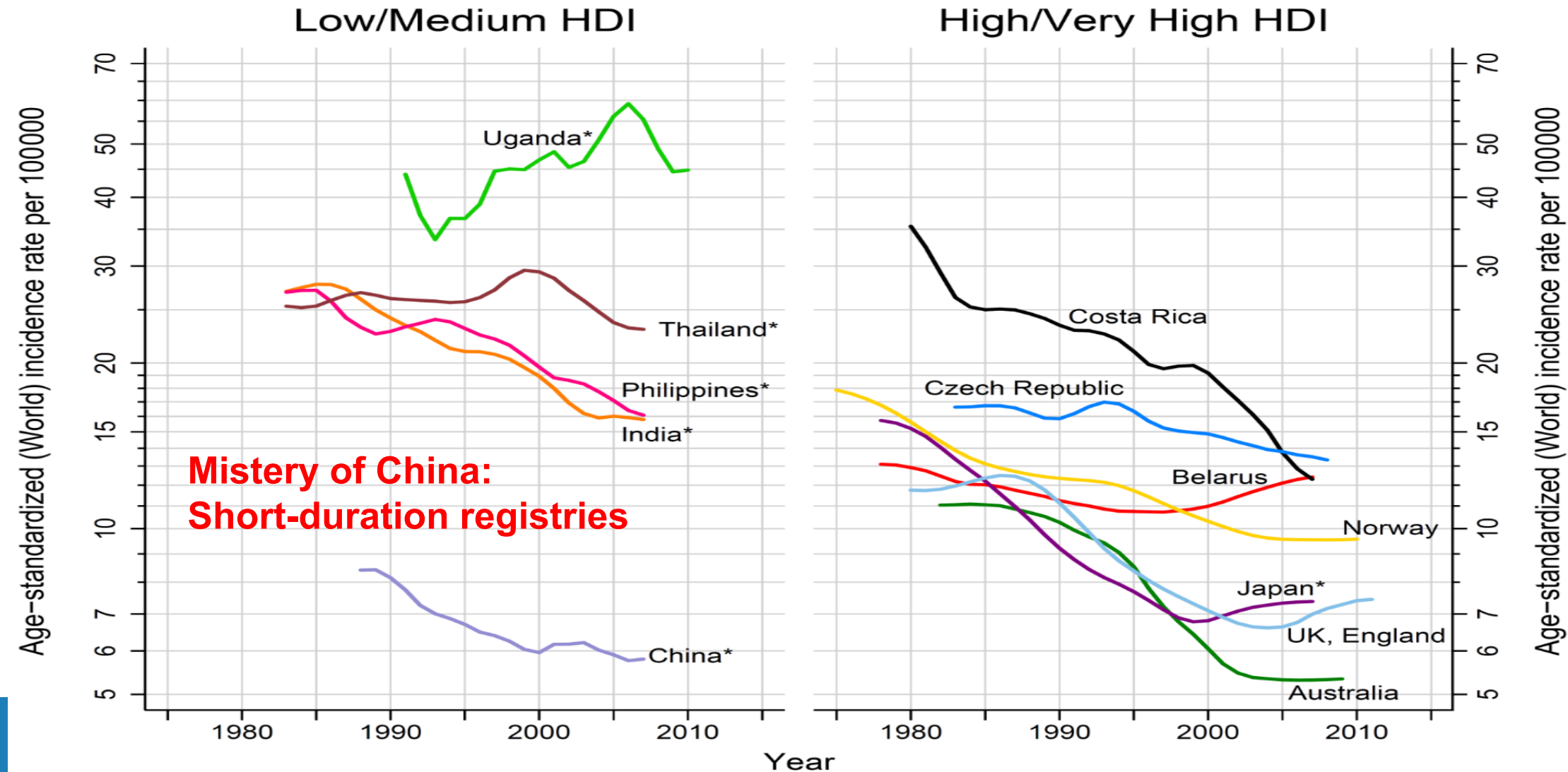


Total : 311 365

Estimated cancer cases attributable to HPV, by regions, 2018

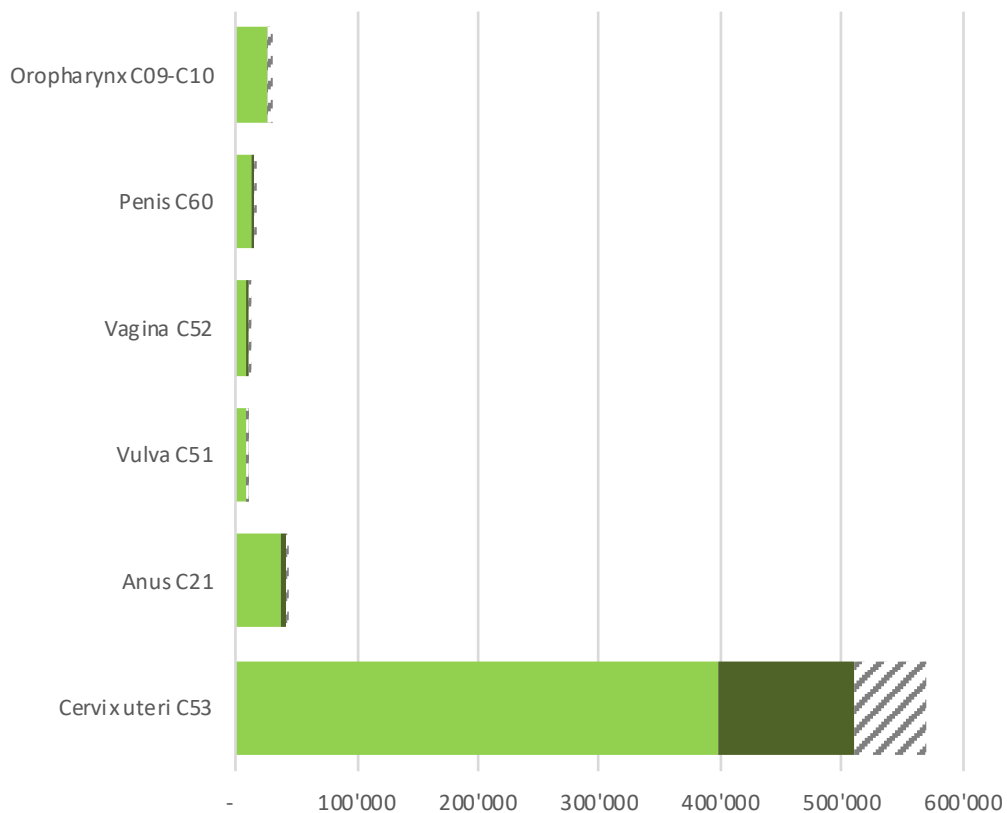


Age-standardized (World) incidence rates per 100 000 by calendar year for selected populations: Cervical Cancer 1975–2012

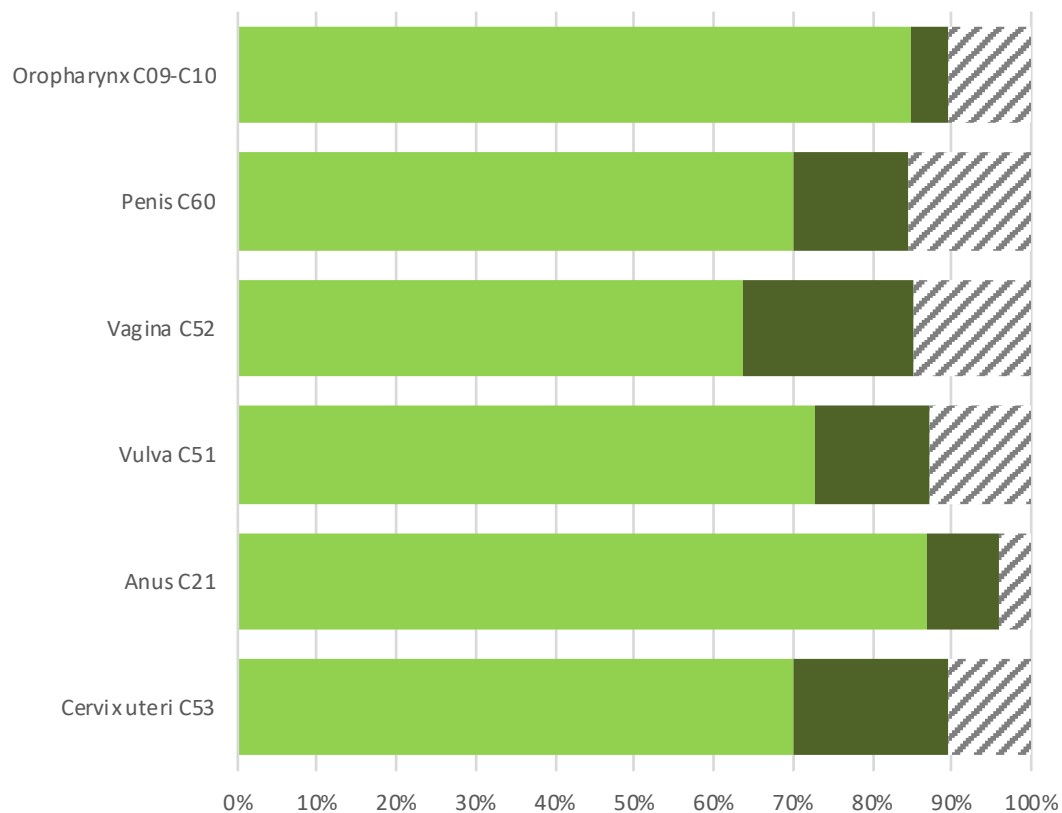


Relative contribution of HPV 16/18 or HPV 6/11/16/18/31/33/45/52/58 to HPV+ cancers by site

Number of cases by type



Percentage of cases by type



	Cervix uteri C53	Anus C21	Vulva C51	Vagina C52	Penis C60	Oropharynx C09-C10
16/18	398'700	37'154	7'994	8'739	12'097	25'325
6/11/31/33/45/52/58	111'066	3'801	1'596	2'964	2'481	1'432
Others	59'805	1'751	1'421	2'016	2'654	3'072

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NB: Base of tongue (C1), Oral Cavity (C02-C06) and Larynx (C32) are not presented in this table

Source: Globocan 2018, and modified from de Martel et al. 2017

Summary

- Very substantial burden
- Largest number of cases in Asia and Africa

Immunogenicity, efficacy and effectiveness of HPV vaccines

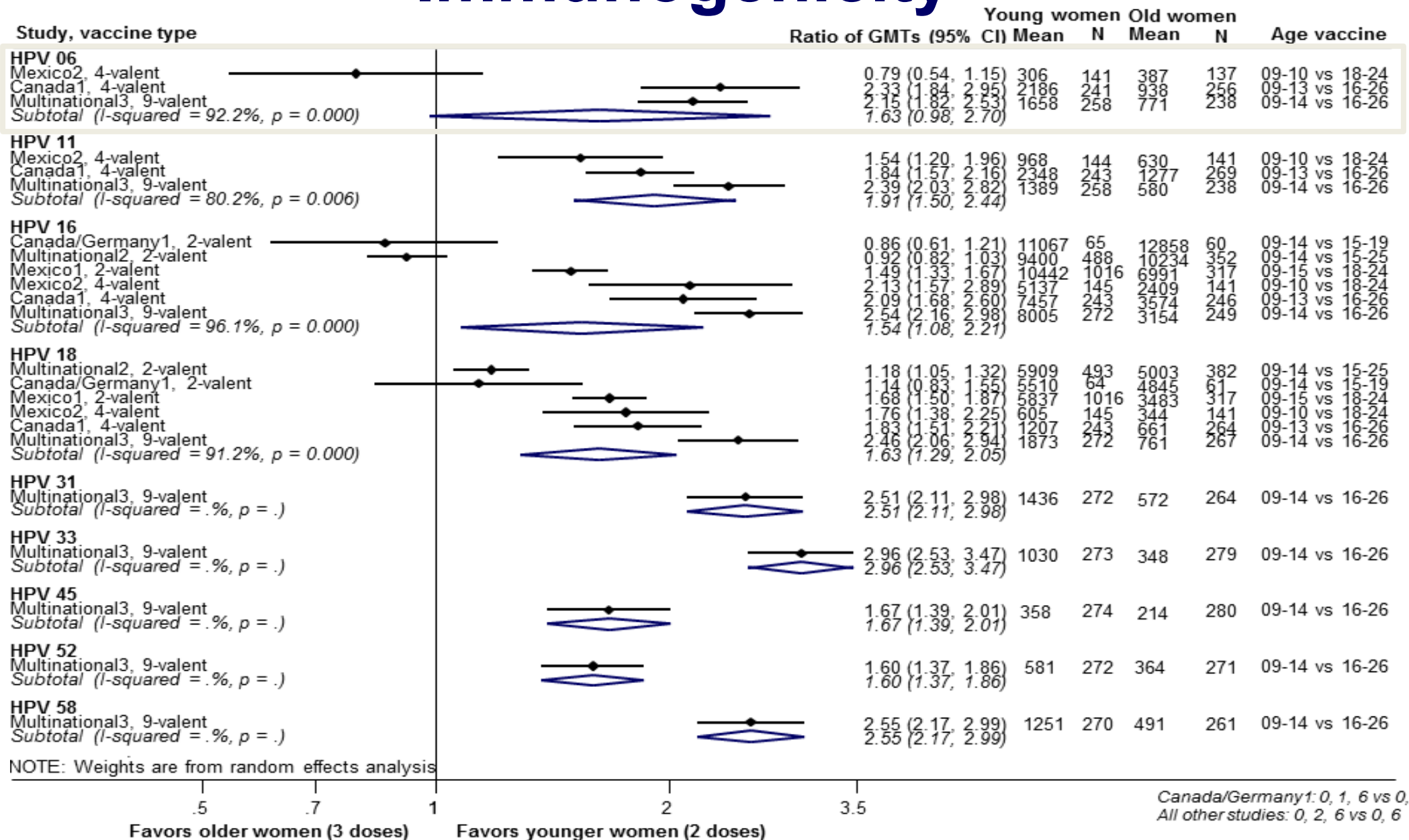
Systematic review on efficacy and immunogenicity of licensed vaccines 2018

Outline

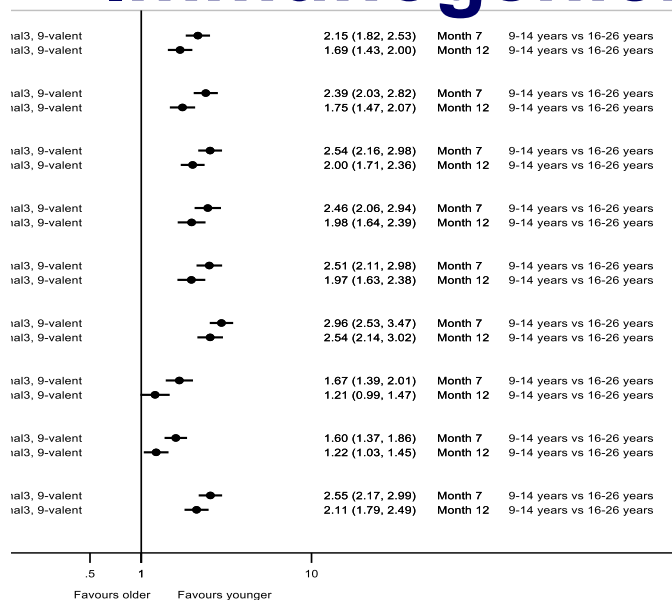
- **Comparison of two doses vs three doses HPV vaccine**
- Efficacy and immunogenicity in females with HIV
- Comparison of interval between doses (two-dose schedule)
- Efficacy of one dose of HPV vaccine
- Efficacy and immunogenicity in males with HIV and men who have sex with men (MSM)

Younger females (2 doses) vs Older females (3 doses) all vaccines, GMTs **one month** after last dose

Immunogenicity



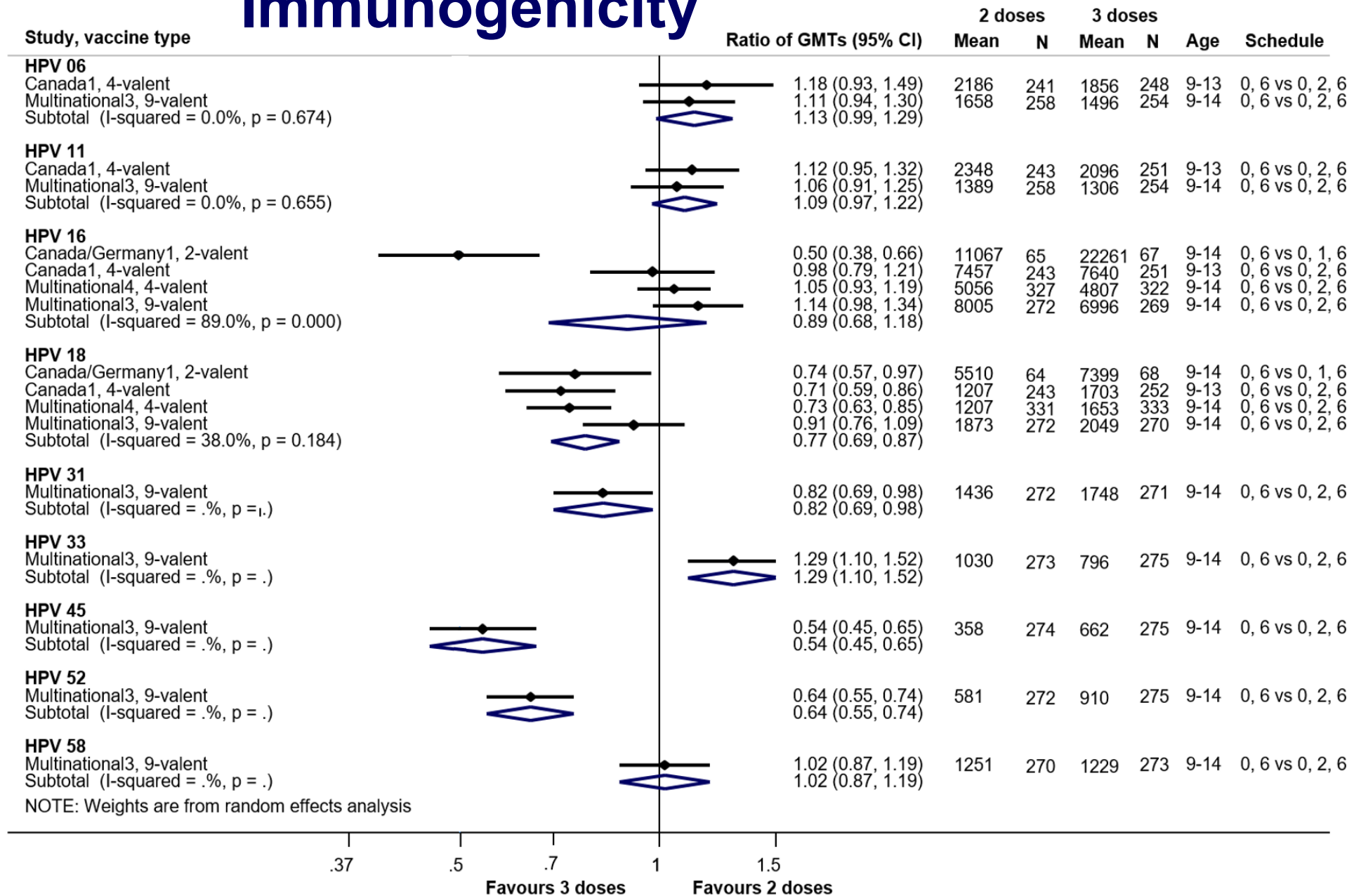
Younger females (2 doses) vs Older females (3 doses) – nonavalent vaccine, **long term follow-up** **Immunogenicity**



2 versus 3 doses in younger females (9-14 years)

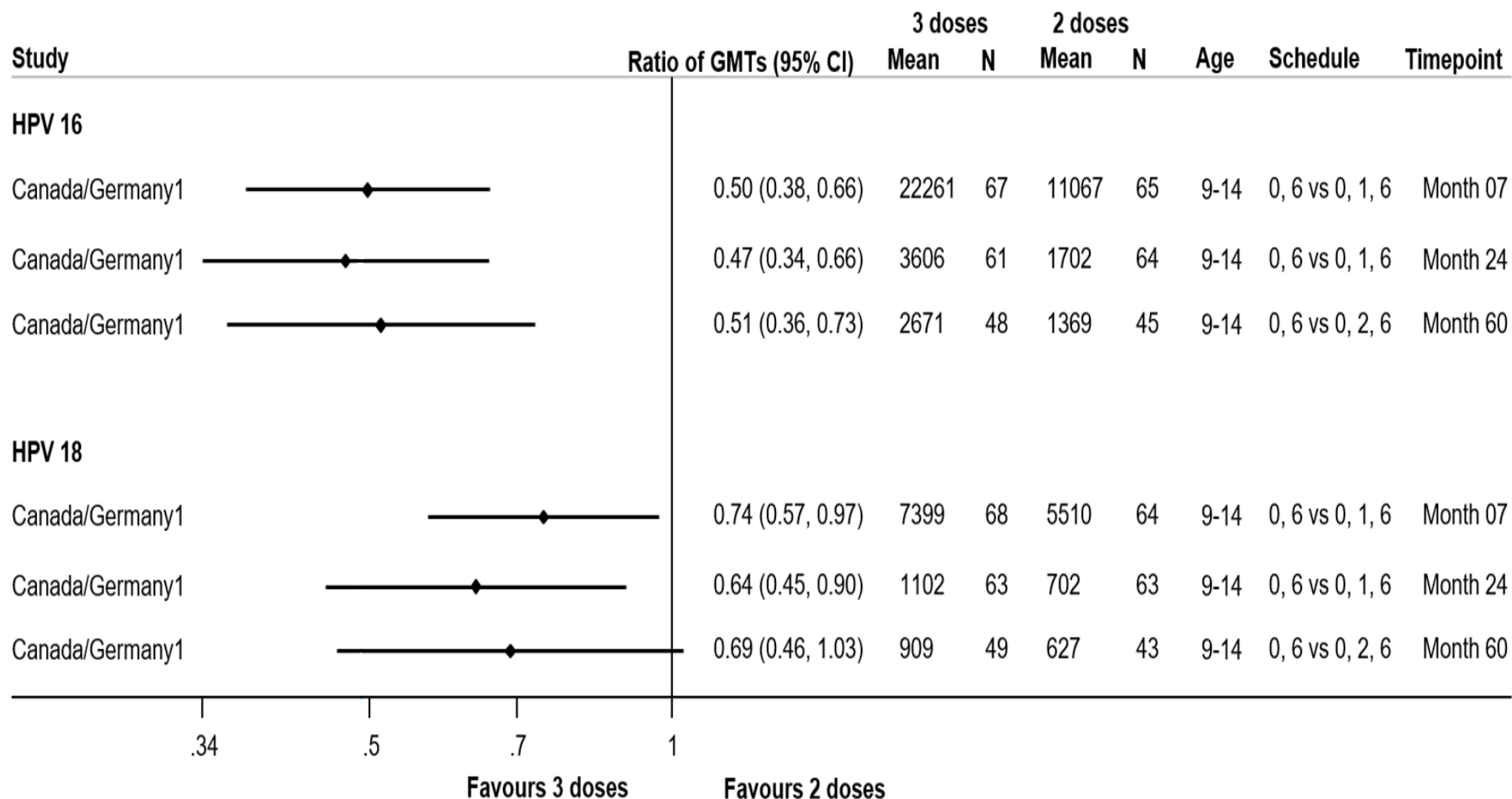
all vaccines; GMTs **one month** after last dose, RCTs

Immunogenicity



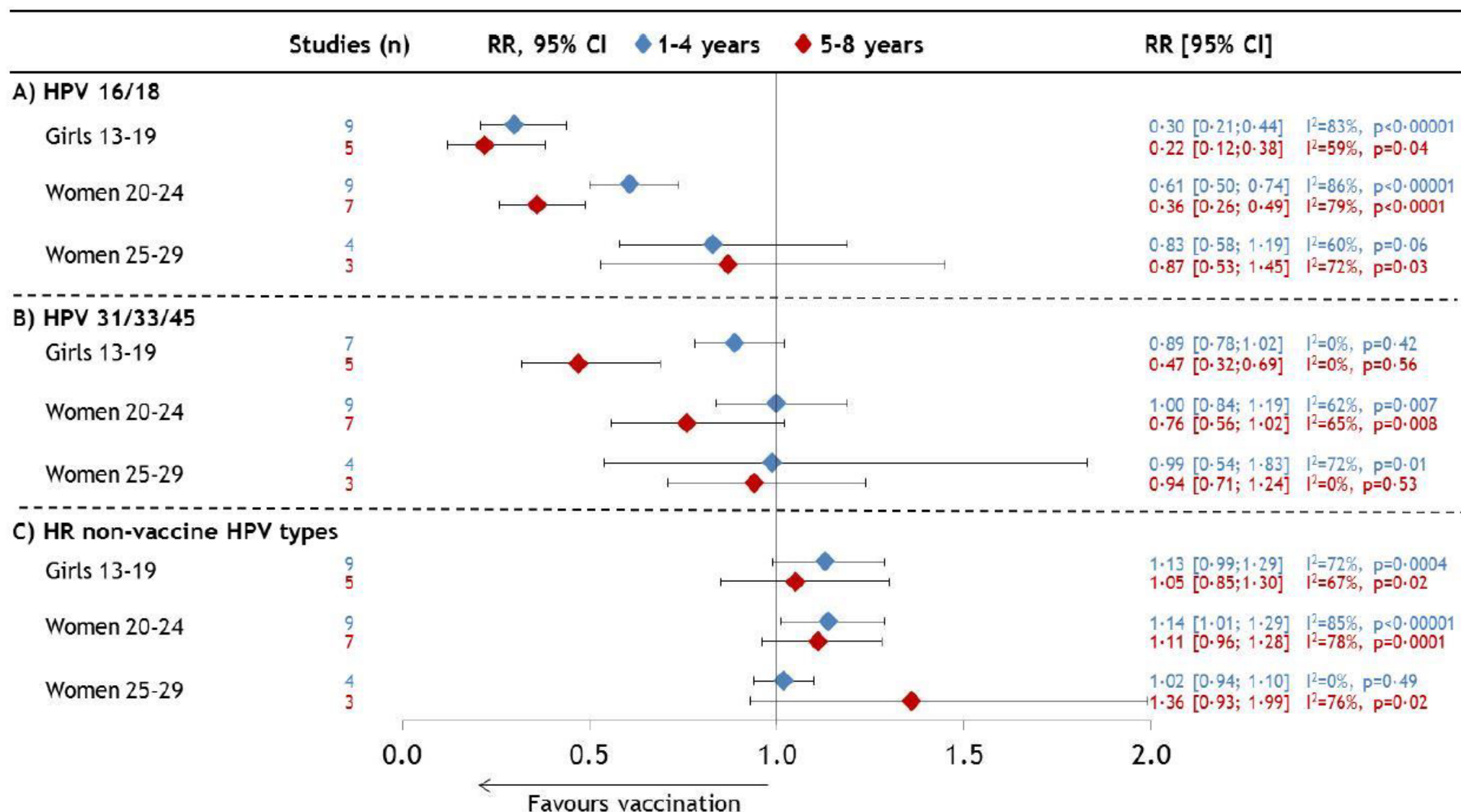
2 versus 3 doses in younger females (9-14 years) bivalent vaccine; **long term** follow-up, RCTs

Immunogenicity



HPV effectiveness (infection prevalence)

Figure 2. Changes in the prevalence of HPV infections between the pre-vaccination and post-vaccination periods (1-4, 5-8 years)



Summary

- Immunogenicity of 2 doses is good but lower than 3 doses
- Immune response persists with 2 and 3 doses
- Increasing evidence of effectiveness
- Early signals can be gained of impact towards elimination goals from studying infection

Outline

- Comparison of two doses vs three doses HPV vaccine
- **Efficacy and immunogenicity in females with HIV**
- Comparison of interval between doses (two dose schedule)
- Efficacy of one dose of HPV vaccine
- Efficacy and immunogenicity in males with HIV and men who have sex with men (MSM)

HIV+ vs HIV- (3 doses, females)

Immunogenicity (bivalent)

13

Comparison: 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) in HIV-positive females versus 2-valent HPV vaccine (3-doses (Day 0, Month 1, Month 6)) in non-HIV-positive females

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs follow-up: 7 months	<p>Study, vaccine type</p> <p>HPV 16</p> <p>South Africa1, bivalent</p> <p>Ratio of GMTs (95% CI)</p> <p>Female HIV+ Mean N Female HIV- Mean N</p> <p>0.44 (0.30, 0.63) 3558.2 42 8168.8 22</p> <p>HPV 18</p> <p>South Africa1, bivalent</p> <p>0.53 (0.32, 0.86) 1945.8 42 3703 22</p> <p>Favours female HIV- Favours female HIV+</p>	<p>⊕⊕⊕⊕ LOW</p> <p>⊕⊕⊕⊕ LOW</p>

CI= confidence interval; GMT= Geometric mean titre; HPV= human papilloma virus; HIV= human immunodeficiency virus

Forest plot for seroconversion not shown, as all participants in both groups seroconverted.

3 doses 4-valent VE

Forest plots: 4-valent HPV vaccine versus placebo in ≥18-year old HIV-positive females, males, and MSM with or without anogenital warts or HSIL

Participants: ≥18-year old HIV-positive males, females, and MSM, some participants had anogenital warts or high-grade squamous intraepithelial lesions (HSIL) at baseline

Setting: USA (including Puerto Rico) and Brazil

Comparison: 4-valent HPV vaccine (3-doses (Day 0, Month 2, Month 6)) versus placebo vaccine (3-doses (Day 0, Month 2, Month 6))

Outcome	Forest plots	Certainty of the evidence (GRADE)																																																										
High-grade AIN* follow up: 1 to 4 years	<table><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">4-valent</th><th colspan="2">Placebo</th><th rowspan="2">Weight</th><th>Risk Ratio</th><th>Risk Ratio</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>M-H, Random, 95% CI</th><th>M-H, Random, 95% CI</th></tr><tr><td>USA/Brazil1 (1)</td><td>46</td><td>288</td><td>45</td><td>286</td><td>100.0%</td><td>1.02 [0.70, 1.48]</td><td rowspan="5"></td></tr><tr><td>Total (95% CI)</td><td></td><td>288</td><td></td><td>286</td><td>100.0%</td><td>1.02 [0.70, 1.48]</td></tr><tr><td>Total events</td><td>46</td><td></td><td>45</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Not applicable</td></tr><tr><td colspan="7">Test for overall effect: Z = 0.08 (P = 0.94)</td></tr><tr><td colspan="8"><u>Footnotes</u> (1) 3 doses (0, 8, 24 weeks) in HIV-positive females and MSM with and without HSIL >27 years</td></tr></table>	Study or Subgroup	4-valent		Placebo		Weight	Risk Ratio	Risk Ratio	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI	USA/Brazil1 (1)	46	288	45	286	100.0%	1.02 [0.70, 1.48]		Total (95% CI)		288		286	100.0%	1.02 [0.70, 1.48]	Total events	46		45				Heterogeneity: Not applicable							Test for overall effect: Z = 0.08 (P = 0.94)							<u>Footnotes</u> (1) 3 doses (0, 8, 24 weeks) in HIV-positive females and MSM with and without HSIL >27 years								⊕⊕⊕⊕ LOW
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Anogenital warts (persistence or recurrence)** follow up: 18 months	<table><tr><th rowspan="2">Study or Subgroup</th><th colspan="2">4-valent</th><th colspan="2">Placebo</th><th rowspan="2">Weight</th><th>Risk Ratio</th><th>Risk Ratio</th></tr><tr><th>Events</th><th>Total</th><th>Events</th><th>Total</th><th>M-H, Random, 95% CI</th><th>M-H, Random, 95% CI</th></tr><tr><td>USA7 (1)</td><td>1</td><td>7</td><td>1</td><td>5</td><td>100.0%</td><td>0.71 [0.06, 8.90]</td><td rowspan="5"></td></tr><tr><td>Total (95% CI)</td><td></td><td>7</td><td></td><td>5</td><td>100.0%</td><td>0.71 [0.06, 8.90]</td></tr><tr><td>Total events</td><td>1</td><td></td><td>1</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Not applicable</td></tr><tr><td colspan="7">Test for overall effect: Z = 0.26 (P = 0.79)</td></tr></table>	Study or Subgroup	4-valent		Placebo		Weight	Risk Ratio	Risk Ratio	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI	USA7 (1)	1	7	1	5	100.0%	0.71 [0.06, 8.90]		Total (95% CI)		7		5	100.0%	0.71 [0.06, 8.90]	Total events	1		1				Heterogeneity: Not applicable							Test for overall effect: Z = 0.26 (P = 0.79)							⊕⊕⊕⊕ VERY LOW								
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Summary: HIV+ females

- Lower immunogenicity of 3 doses in HIV+ females
- Few studies and evidence of protection limited

Outline

- Comparison of two doses vs three doses HPV vaccine
- Efficacy and immunogenicity in females with HIV
- **Comparison of interval between doses (two dose schedule)**
- Efficacy of one dose of HPV vaccine
- Efficacy and immunogenicity in males with HIV and men who have sex with men (MSM)

Two doses vs two doses comparing interval **bivalent** vaccine; 2 months vs 6 months

Study, vaccine, age at administration		GMTs (95% CI)	Schedule	timepoint
HPV 16				
Canada/Germany1, 2-valent, 9-14 years		2.06 (1.60, 2.64)	0, 2 vs 0, 6	Month 7
Canada/Germany1, 2-valent, 15-19 years		2.15 (1.62, 2.84)	0, 2 vs 0, 6	Month 7
Canada/Germany1, 2-valent, 20-25 years		1.73 (1.26, 2.36)	0, 2 vs 0, 6	Month 7
Canada/Germany1, 2-valent, 9-14 years		1.94 (1.44, 2.62)	0, 2 vs 0, 6	Month 24
HPV 18				
Canada/Germany1, 2-valent, 9-14 years		1.60 (1.22, 2.10)	0, 2 vs 0, 6	Month 7
Canada/Germany1, 2-valent, 15-19 years		2.06 (1.52, 2.81)	0, 2 vs 0, 6	Month 7
Canada/Germany1, 2-valent, 20-25 years		1.54 (1.06, 2.24)	0, 2 vs 0, 6	Month 7
Canada/Germany1, 2-valent, 9-14 years		2.18 (1.54, 3.07)	0, 2 vs 0, 6	Month 24

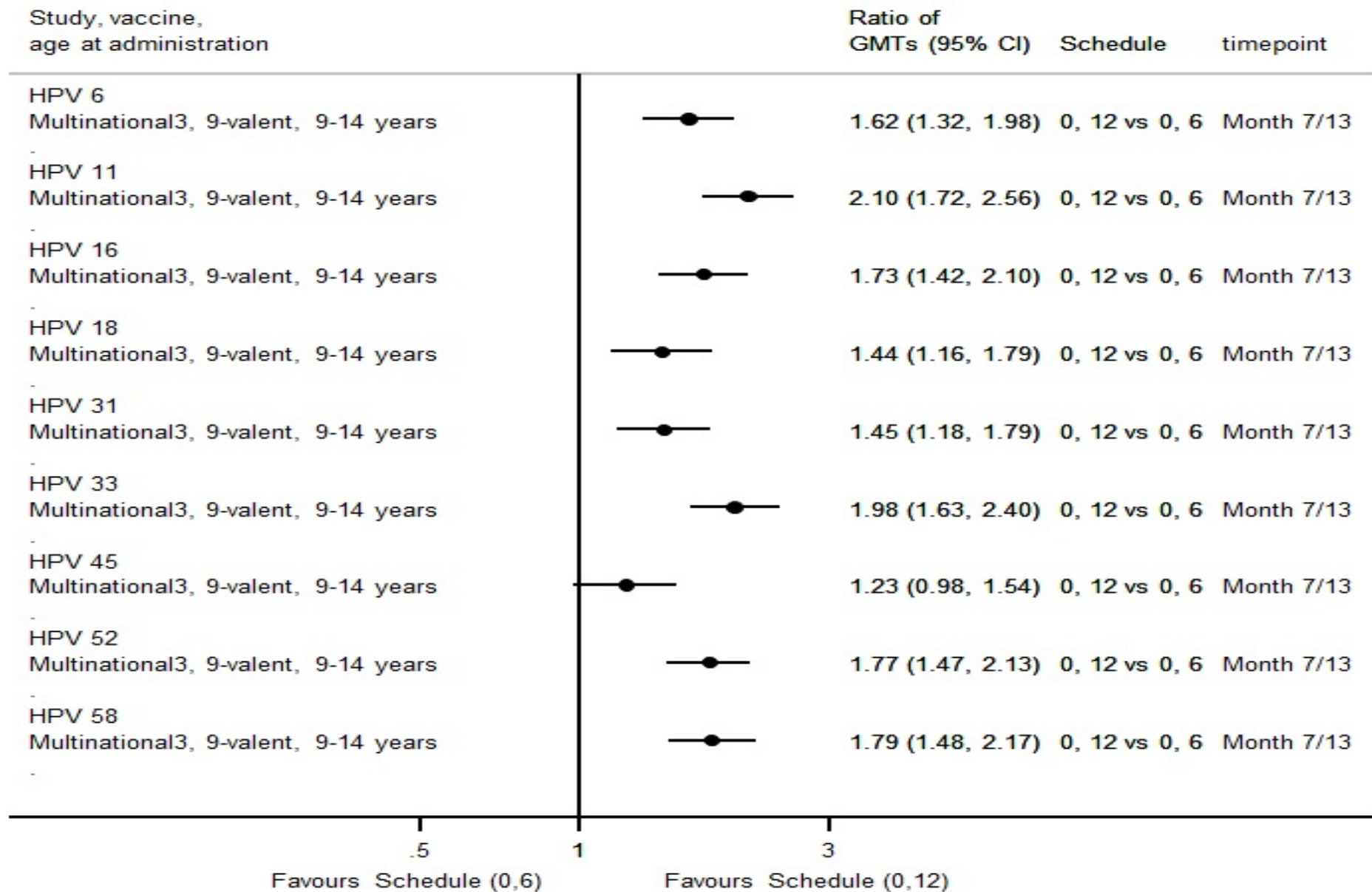
0,2 month 0,6 month

Two doses vs two doses comparing interval bivalent vaccine; 6 months vs 12 months

Outcome	Forest plot	Certainty of the evidence (GRADE)
Ratio of GMTs follow up: 7 months	<p>Study, Ratio of GMTs (95% CI) Schedule timepoint</p> <hr/> <p>HPV 16</p> <p>Multinational2, 2-valent 1.22 (1.10, 1.34) 0, 12 vs 0, 6 Month 13</p> <p>Multinational2, 2-valent 1.43 (1.26, 1.62) 0, 12 vs 0, 6 Month 36</p> <p>HPV 18</p> <p>Multinational2, 2-valent 1.12 (1.01, 1.25) 0, 12 vs 0, 6 Month 13</p> <p>Multinational2, 2-valent 1.29 (1.15, 1.44) 0, 12 vs 0, 6 Month 36</p> <p>.5 1 2</p> <p>Favours schedule (0,6) Favours schedule (0,12)</p>	⊕⊕⊕⊕ HIGH

0,6 month 0,12 month

Two doses vs two doses comparing interval **nonavalent** vaccine; 6 months vs 12 months



0,6 month 0,12 month

Summary:

Two doses vs two doses comparing interval, in females aged 9 to 14 years

- Bivalent vaccine
 - 6 month > 2 months
 - 12 month > 6 months
- Nonavalent vaccine
 - 12 month > 6 months
- Greater intervals?

Outline

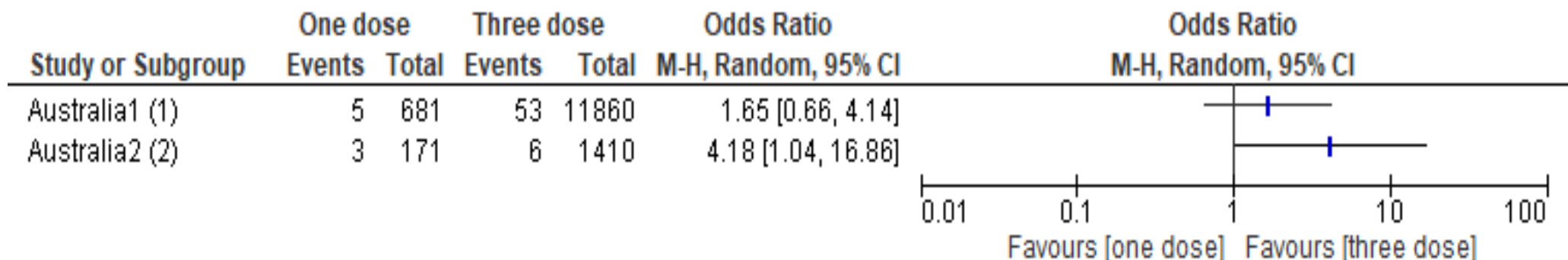
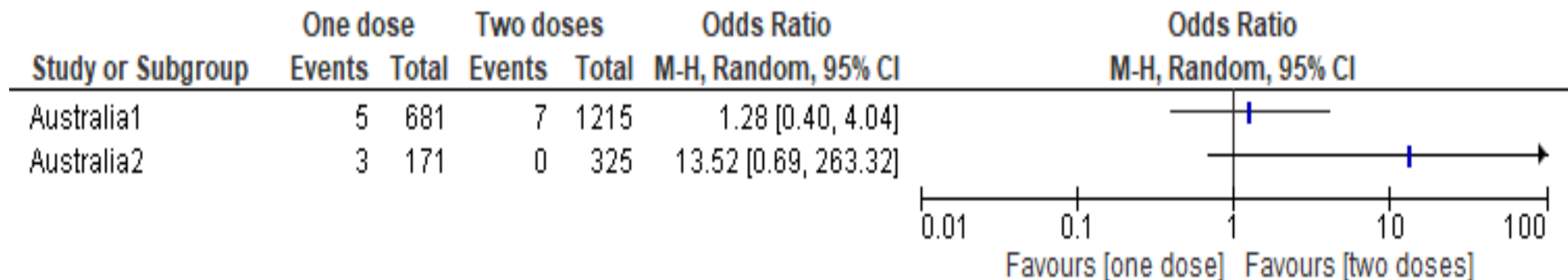
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- **Efficacy of one dose of HPV vaccine**
- Efficacy and immunogenicity in males with HIV and men who have sex with men (MSM)

One dose of HPV vaccine

- 18 observational studies
- No RCTs
 - at least two ongoing studies

One dose versus 2 or 3 doses

Any high grade histological abnormalities, < 16 years

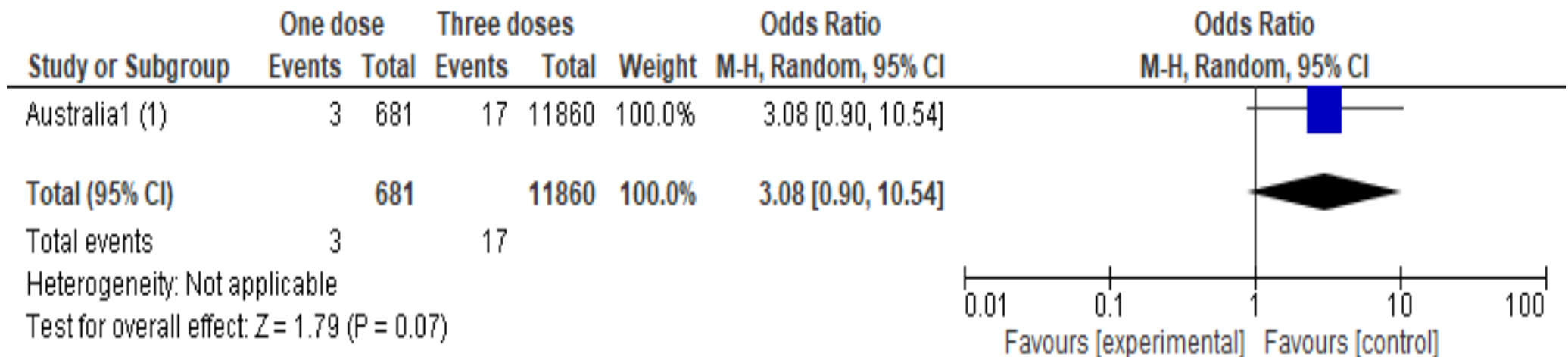


Footnotes

(1) < 16 years

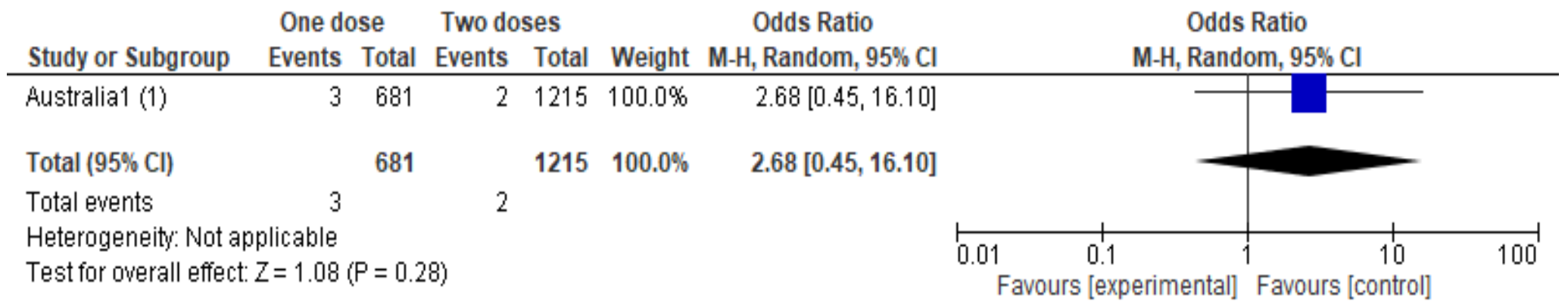
(2) 11-14 years

One dose versus 2 or 3 doses CIN3



Footnotes

(1) 4-valent vaccine; < 16 years

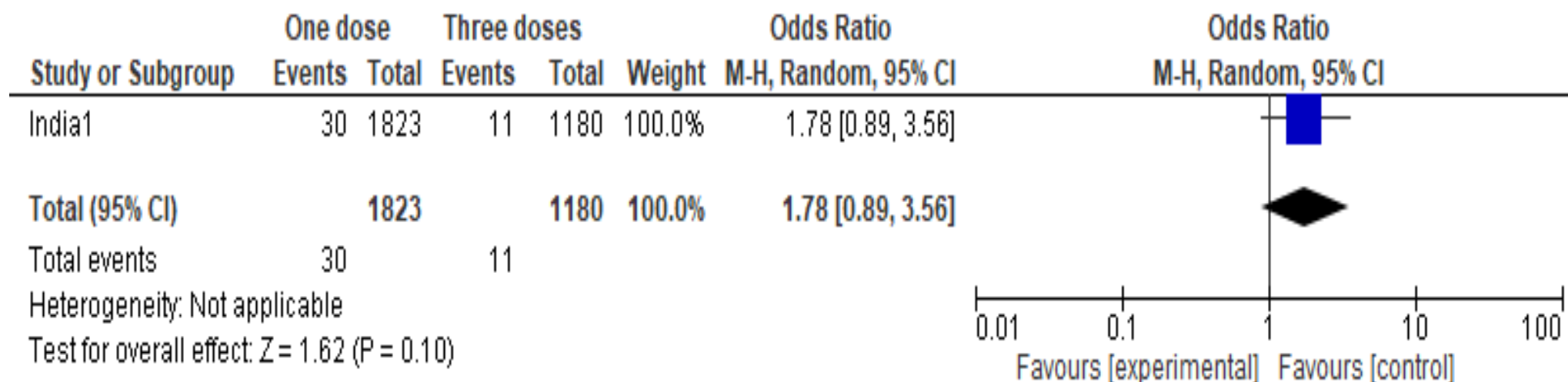
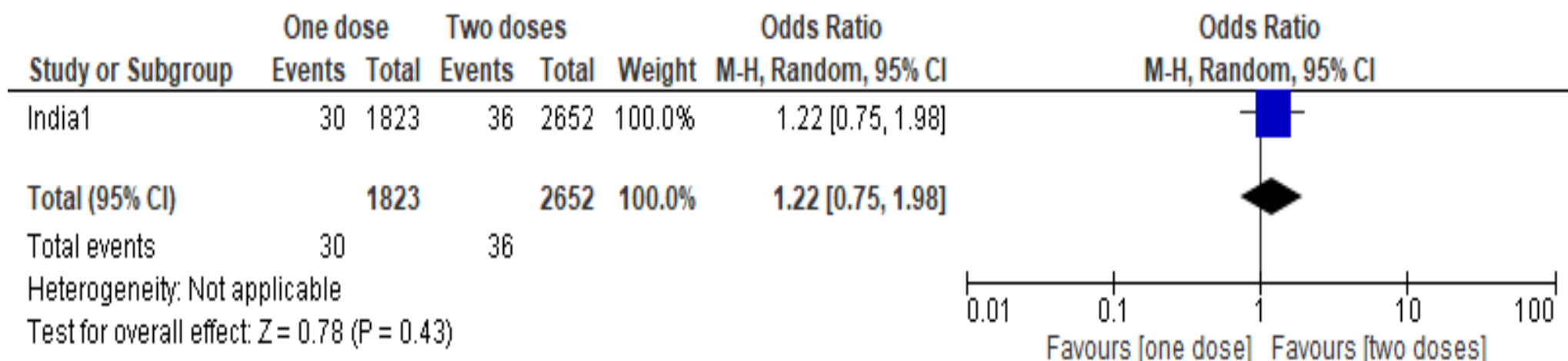


Footnotes

(1) 4-valent vaccine; < 16 years

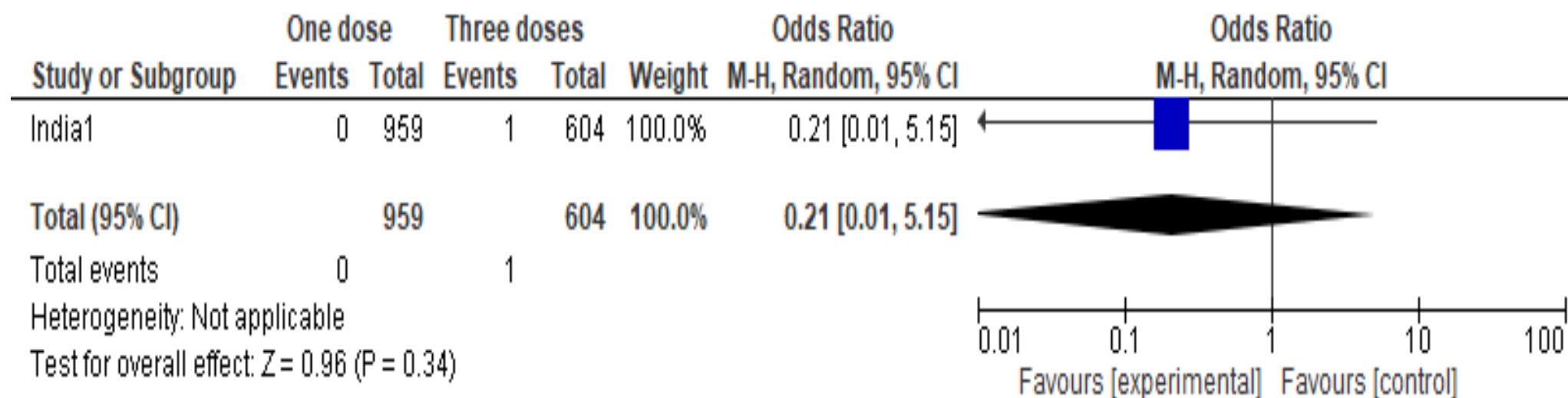
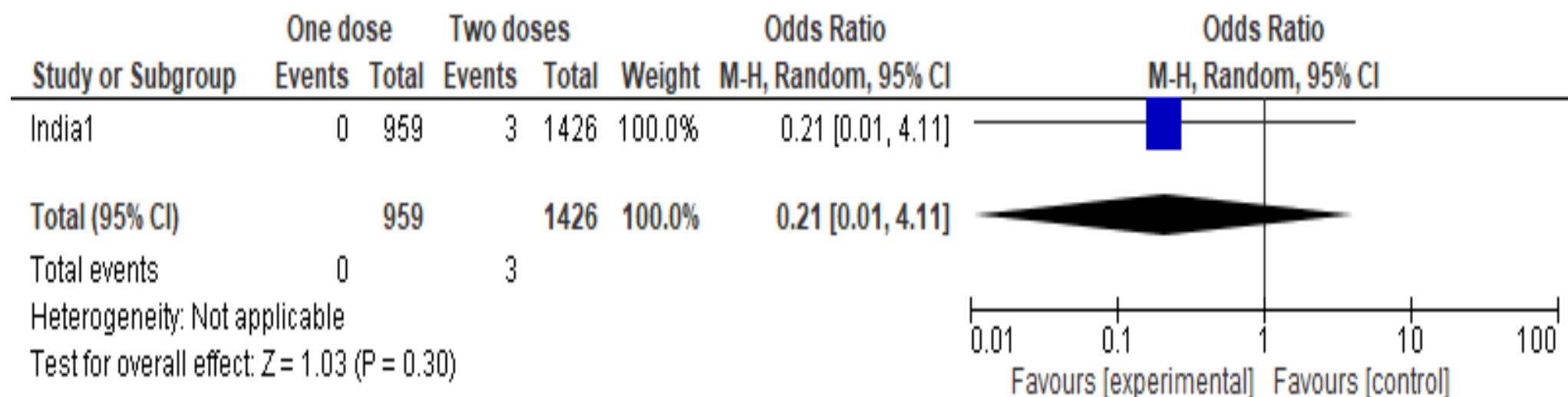
One dose versus 2 or 3 doses

Cumulative incidence HPV 16/18



One dose versus 2 or 3 doses

Persistent infection HPV 16/18



HPV 1-dose key findings

- Insufficient evidence so far for SAGE to recommend a 1 dose schedule (compared with 2 doses)
- Promising data from observational studies but methodological limitations

Outline

- Comparison of two doses vs three doses HPV vaccine
- Efficacy and immunogenicity in females with HIV
- Comparison of interval between doses (two dose schedule)
- Efficacy of one dose of HPV vaccine
- **Efficacy and immunogenicity in boys, men with HIV and men who have sex with men (MSM)**

Males - Key findings

- Boys and girls (9-15 years) receiving HPV vaccine appear to have similar GMTs after 7 months
- Quadrivalent vaccine probably reduces external genital lesions in 16-26 year old men compared to control
- In MSM, quadrivalent vaccine probably reduces anal intraepithelial neoplasia (AIN grade 1, 2, 3; any HPV type) at 2.9 years compared with control
- Only low to very low certainty evidence on efficacy of quadrivalent vaccine on people with HIV

Summary

- Burden data show importance of focus in Asia and Africa for elimination goals
- Incidence data provide potential numerical targets for elimination
- Immunogenicity and VE data review supports current 2 dose recommendation in girls
- Longer gap between doses is more immunogenic (i.e. at least 12 months)
- HIV+ review supports current policy
- One dose programmes promising with accumulating data but further RCT data needed for a recommendation