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OVERVIEW OF SAFETY DATA OF INITIAL CLINICAL TRIALS

Pier Luigi Lopalco

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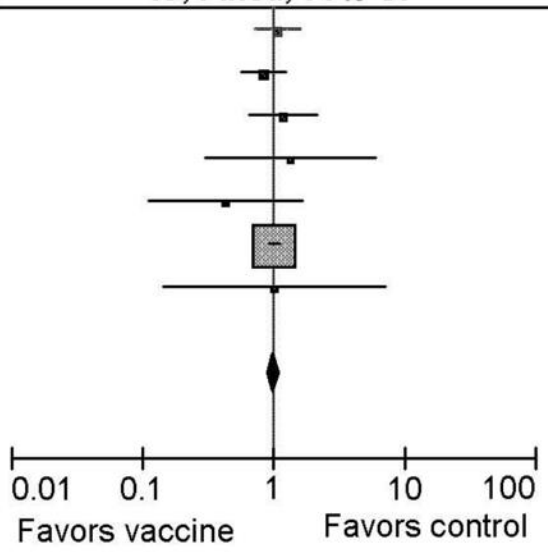
Phase II and III RCTs
Serious Adverse Events

Study	Vaccine Subjects	Vaccine Total	Control Subjects	Control Total	Risk Ratio IV, Fixed, 95% CI
FUTURE I	48	2673	45	2672	1.07 [0.71, 1.60]
FUTURE II	45	6019	54	6031	0.83 [0.56, 1.24]
Harper et al	22	531	19	538	1.17 [0.64, 2.14]
Koutsky & Mao et al	4	1194	3	1198	1.34 [0.30, 5.96]
Munoz et al	3	1908	7	1902	0.43 [0.11, 1.65]
PATRICIA	701	9319	699	9325	1.00 [0.91, 1.11]
Villa et al	2	272	2	274	1.01 [0.14, 7.10]
Total (95% CI)	825	**21916**	829	**21940**	**1.00 [0.91, 1.09]**

Heterogeneity: Chi² = 2.84, df = 6 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)



Lu B, Kumar A, Castellsagué X, Giuliano AR. Efficacy and Safety of Prophylactic Vaccines against Cervical HPV Infection and Diseases among Women: A Systematic Review & Meta-Analysis. *BMC Infectious Diseases*. 2011;11:13. doi:10.1186/1471-2334-11-13.

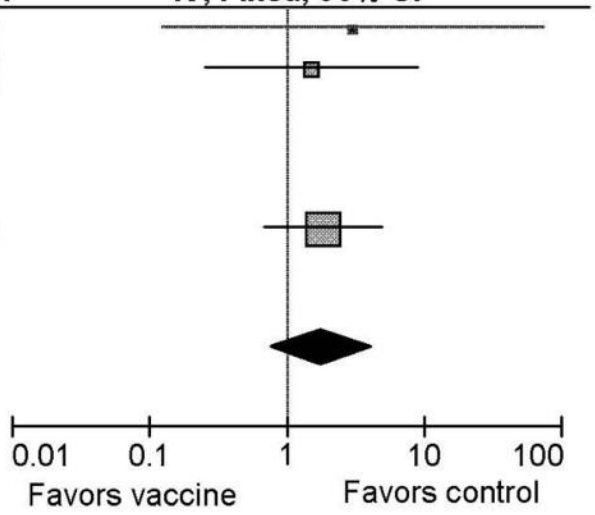
Lu et al. safety review

- **Pain at injection** site was the most frequently reported AE ranging from 83.0 - 93.4% in vaccine groups and 75.4 - 87.2% in control groups.
- **Headache and fatigue** were the most common vaccine-related systemic AEs observed in approximately 50 – 60% of all participants
- **Serious AE reported** included abnormal pregnancy outcomes, blood and lymphatic system disorder, hepatobiliary disorder, immune system disorder, cardiac and vascular disorder, gastrointestinal disorder, musculoskeletal and connective tissue disorder, nervous system disorder, psychiatric disorder, renal and urinary disorder, reproductive system and breast disorder, respiratory, thoracic and mediastinal disorder, skin and subcutaneous tissue disorder, neoplasm, infection and infestation, injury, poisoning and procedural complications
- The pooled **RR 1.00 (95% CI: 0.91-1.09)** suggesting a statistically insignificant difference in the risk of serious AEs between vaccine and control groups

Phase II and III RCTs
Injection Related SAEs

Study	Vaccine Subjects	Vaccine Total	Control Subjects	Control Total	Risk Ratio IV, Fixed, 95% CI
FUTURE I	1	2673	0	2672	3.00 [0.12, 73.58]
FUTURE II	3	6019	2	6031	1.50 [0.25, 8.99]
Harper et al	0	531	0	538	Not estimable
Koutsky & Mao et al	0	1194	0	1198	Not estimable
Munoz et al	0	1908	0	1902	Not estimable
PATRICIA	11	9319	6	9325	1.83 [0.68, 4.96]
Villa et al	0	272	0	274	Not estimable
Total (95% CI)	15	**21916**	8	**21940**	**1.82 [0.79, 4.20]**

Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.16)



Lu B, Kumar A, Castellsagué X, Giuliano AR. Efficacy and Safety of Prophylactic Vaccines against Cervical HPV Infection and Diseases among Women: A Systematic Review & Meta-Analysis. *BMC Infectious Diseases*. 2011;11:13. doi:10.1186/1471-2334-11-13.

Phase II and III RCTs
Injection Related SAEs

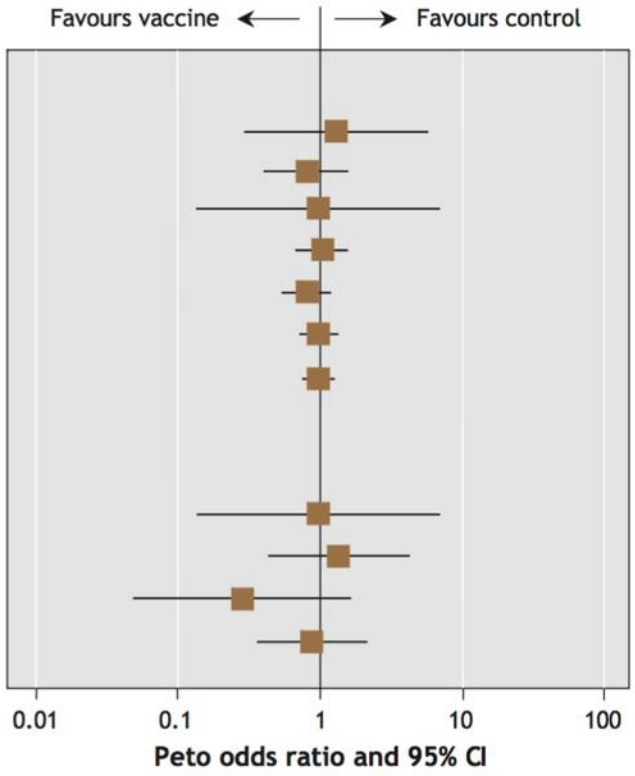
- Injection related SAEs included bronchospasm, gastroenteritis, headache, hypertension, injection-site pain, decrease in joint movement at injection site, hypersensitivity to injection, chills, headache and fever.
- Four of the seven trials reported zero injection-related SAEs.
- Among those reporting vaccine-related serious AEs, the event rate ranged from 0-0.1%. Overall there was no statistically significant difference in the risk for vaccine-related serious AEs between vaccine and control groups (**RR, 1.82; 95% CI: 0.79-4.20**)

Lu B, Kumar A, Castellsagué X, Giuliano AR. Efficacy and Safety of Prophylactic Vaccines against Cervical HPV Infection and Diseases among Women: A Systematic Review & Meta-Analysis. *BMC Infectious Diseases*. 2011;11:13. doi:10.1186/1471-2334-11-13.

Other reviews on pre-licensure safety data on bHPV and qHPV

- Rambout L et al. CMAJ, 2007

Study	Peto odds ratio (95% confidence interval)	No. of events / No. of participants: Vaccine	Control
≥ 1 serious adverse events			
Koutsky et al[20]	1.36 (0.31-5.98)	4/1130	3/1150
Harper et al[19]	0.83 (0.42-1.64)	16/373	19/371
Villa et al[24]	1.01 (0.14-7.19)	2/272	2/274
FUTURE I[17]	1.07 (0.71-1.61)	48/2673	45/2672
FUTURE II[16]	0.83 (0.56-1.24)	45/6019	54/6031
PATRICIA[22]	1.02 (0.88-1.20)	330/9319	323/9325
Overall	*1.00 (0.87-1.14)*	$I^2 = 0$	
Death			
Harper et al[19]	Not estimable	0/373	0/371
FUTURE I[17]	1.00 (0.14-7.10)	2/2673	2/2672
FUTURE II[16]	1.40 (0.45-4.34)	7/6019	5/6031
PATRICIA[22]	0.30 (0.05-1.74)	1/9319	4/9325
Overall	*0.91 (0.39-2.14)*	$I^2 = 0$	



Other reviews on pre-licensure safety data on bHPV and qHPV

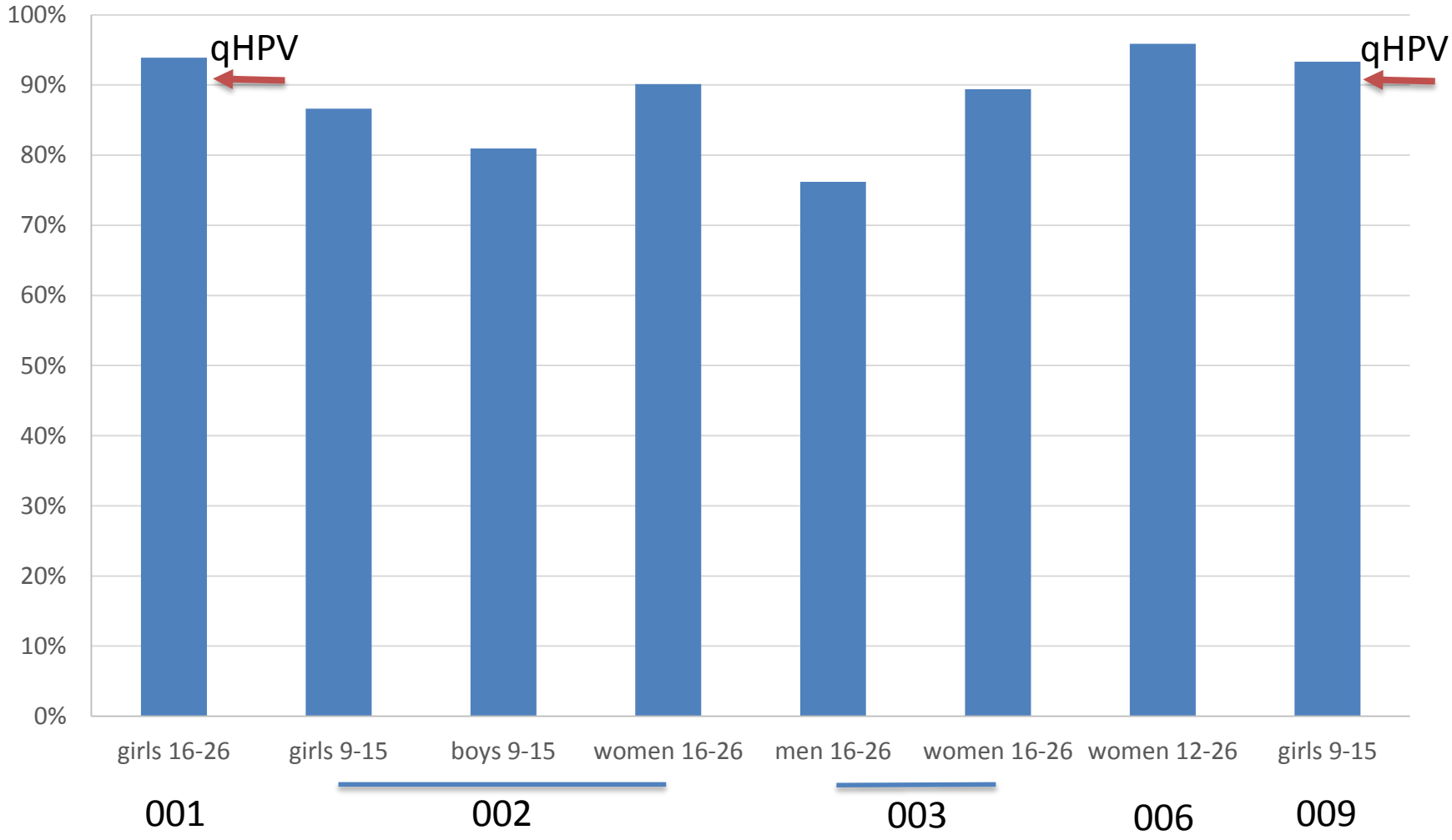
- Agorastos T et al. Vaccine, 2009
  - Women participating in the trials (**n > 60,000**)
  - Among recipients of the quadrivalent (4vHPV) vaccines, systemic AEFI within 15 days of vaccination, observed at a frequency of at least 1.0% and greater than placebo, included **fever, nausea, and dizziness**. Local reactions at the injection site (**pain, redness, and swelling**) were significantly more frequent in vaccine than placebo recipients. There were **very few serious vaccine related adverse events** (<0.1%) and they were no more frequent than in those receiving placebo.
  - A **similar AEFI profile was apparent for the bivalent** (2vHPV) vaccine, with significantly more local reactions in vaccinees than placebo recipients, and higher rates of some systemic AEFIs (within 7 days) including fatigue, headache and myalgia

9vHPV vaccine safety

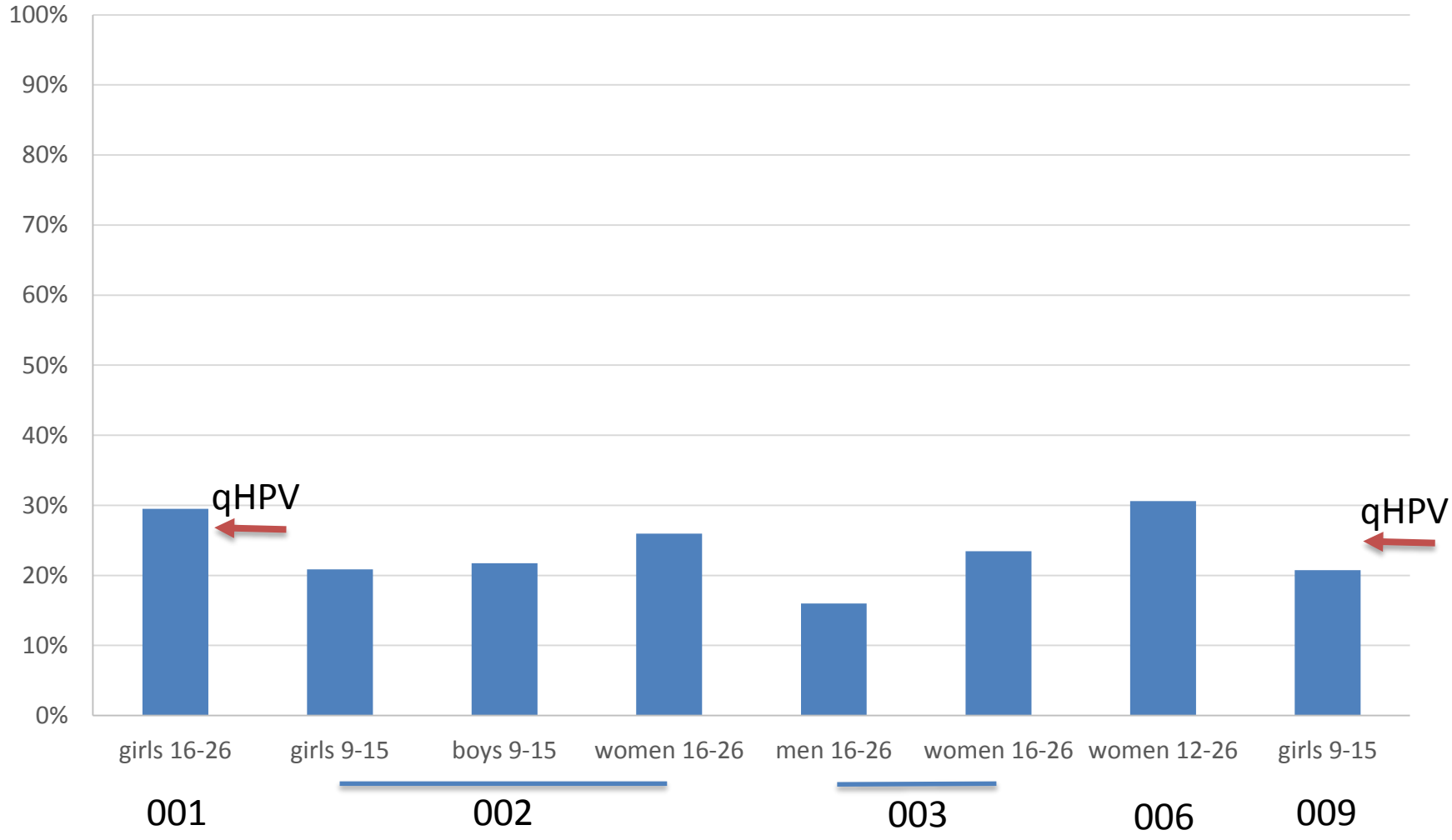
girls 9-15= 2,222; women 16-26=9,220; boys 9-15= 662; men 16-26= 1,394

Study	Design	Populations included in safety assessment
001	Efficacy and immunogenicity in women 16-26 yro	7,071 9vHPV 7,078 qHPV
002	Immunogenicity in women 16-26 yro and boys/girls 9-15 yro	1,923 girls 9-15 yro 662 boys 9-15 yro 466 women 16-26 yro
003	Immunogenicity and safety in men and women 16-26 yro	1,394 men 16-26 yro 1,075 women 16-26 yro
006	Immunogenicity and safety in women 16-26 yro previously vaccinated with qHPV	608 9vHPV 305 saline placebo
009	Immunogenicity and safety in girls 9-15 yro	299 9vHPV 300 qHPV

One or more AE



Vaccine-related systemic AE



Vaccine-related SAEs

N= 13,498

- 1 boy 9-15 yro
  - asthma, hospitalised and fully recovered

- 2 women 16-26 yro
  - severe headache and fever, hospitalised and fully recovered, study 002;
  - purulent tonsillitis, hospitalised and fully recovered, study 006

9vHPV vaccine safety - coadministration

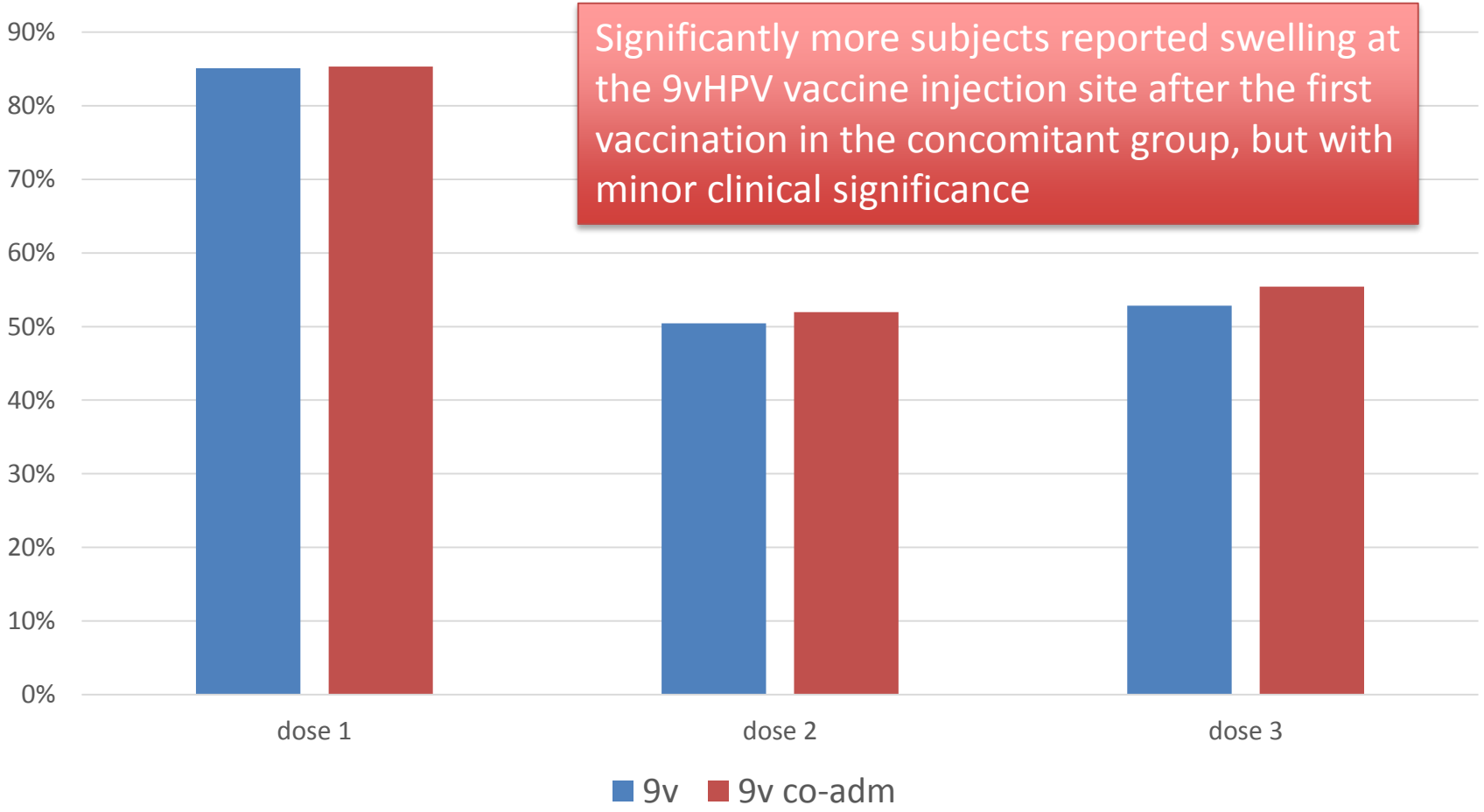
boys and girls 11-15 yro= 1,147 concomitant vs 1,148 non-concomitant group

Study	Design	Populations included in safety assessment
007	Coadministration with Repevax® in 11-15 yro	*526 boys and girls 11-15 yro concomitant group* *528 boys and girls 11-15 yro non-concomitant group*
007	Coadministration with Menactra™ and Adacel™ in 11-15 yro	*621 boys and girls 11-15 yro concomitant group* *620 boys and girls 11-15 yro non-concomitant group*

One or more AE

coadministration with Menactra™ and Adacel™

boys and girls 11-15= 621 concomitant vs 620 non-concomitant group

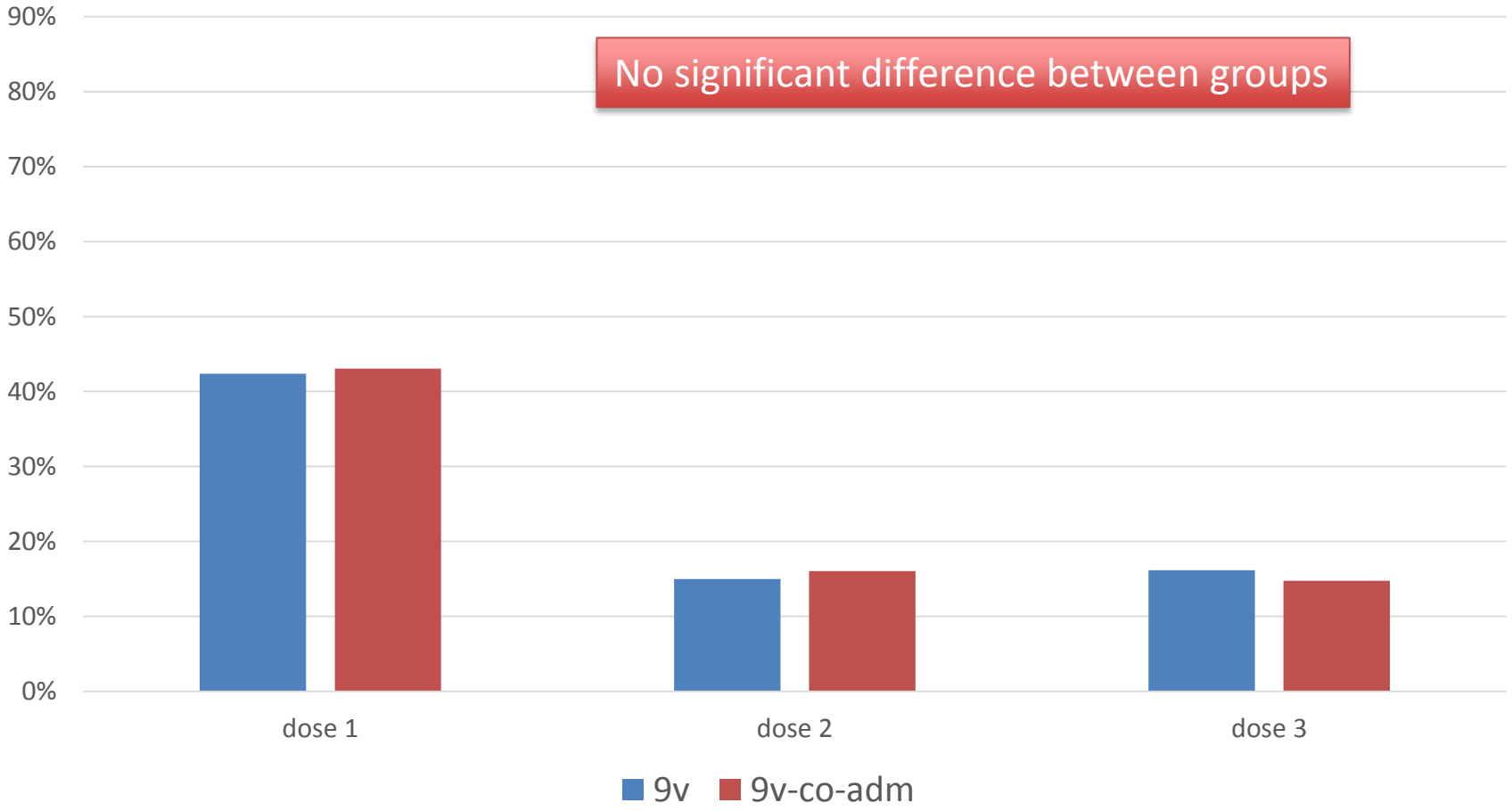


Significantly more subjects reported swelling at the 9vHPV vaccine injection site after the first vaccination in the concomitant group, but with minor clinical significance

Vaccine-related systemic AE

coadministration with Menactra™ and Adacel™

boys and girls 11-15= 621 concomitant vs 620 non-concomitant group



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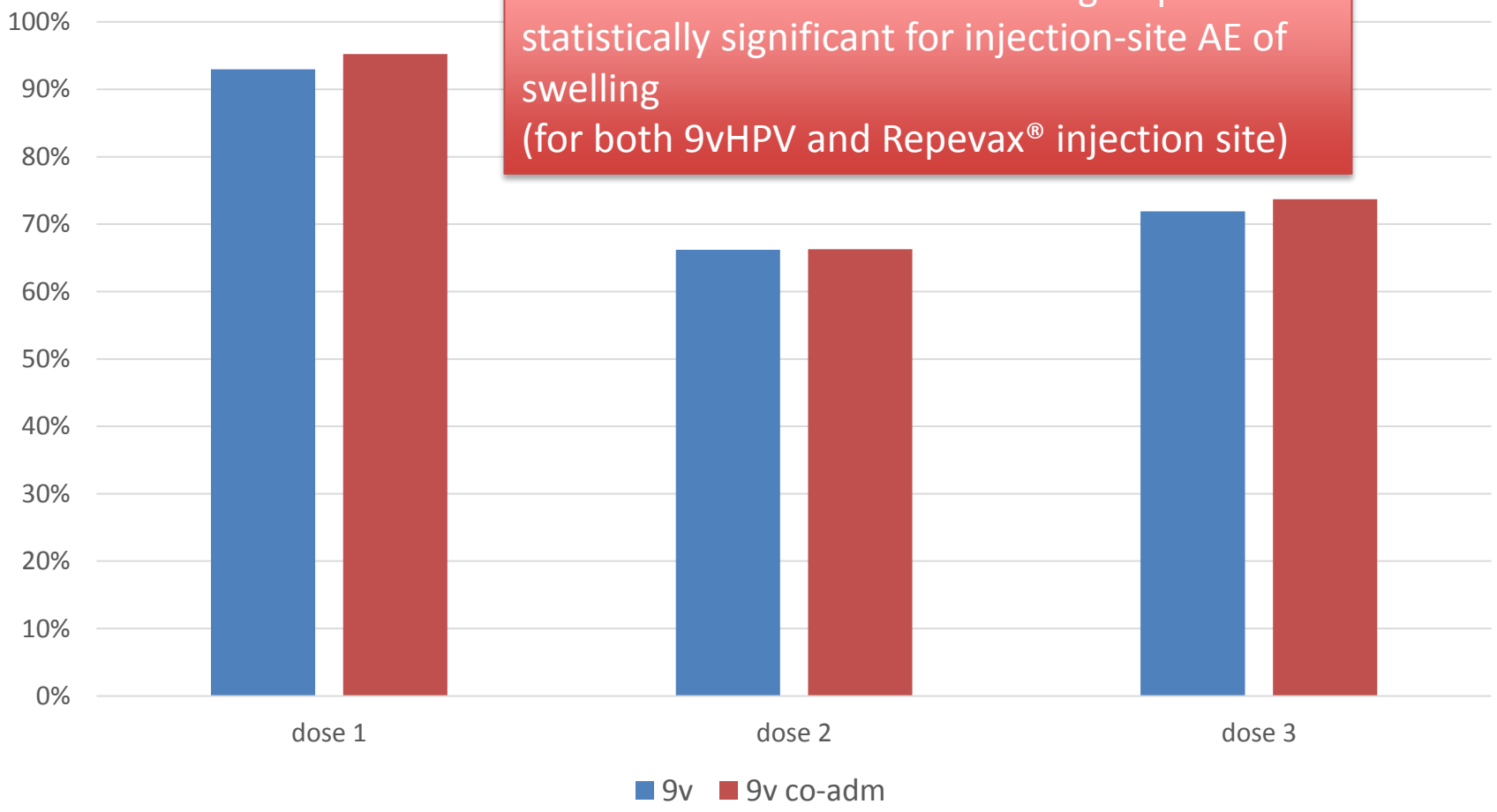
One or more AE

coadministration with REPEVAX®

boys and girls 11-15= 526 concomitant vs 528 non-concomitant group

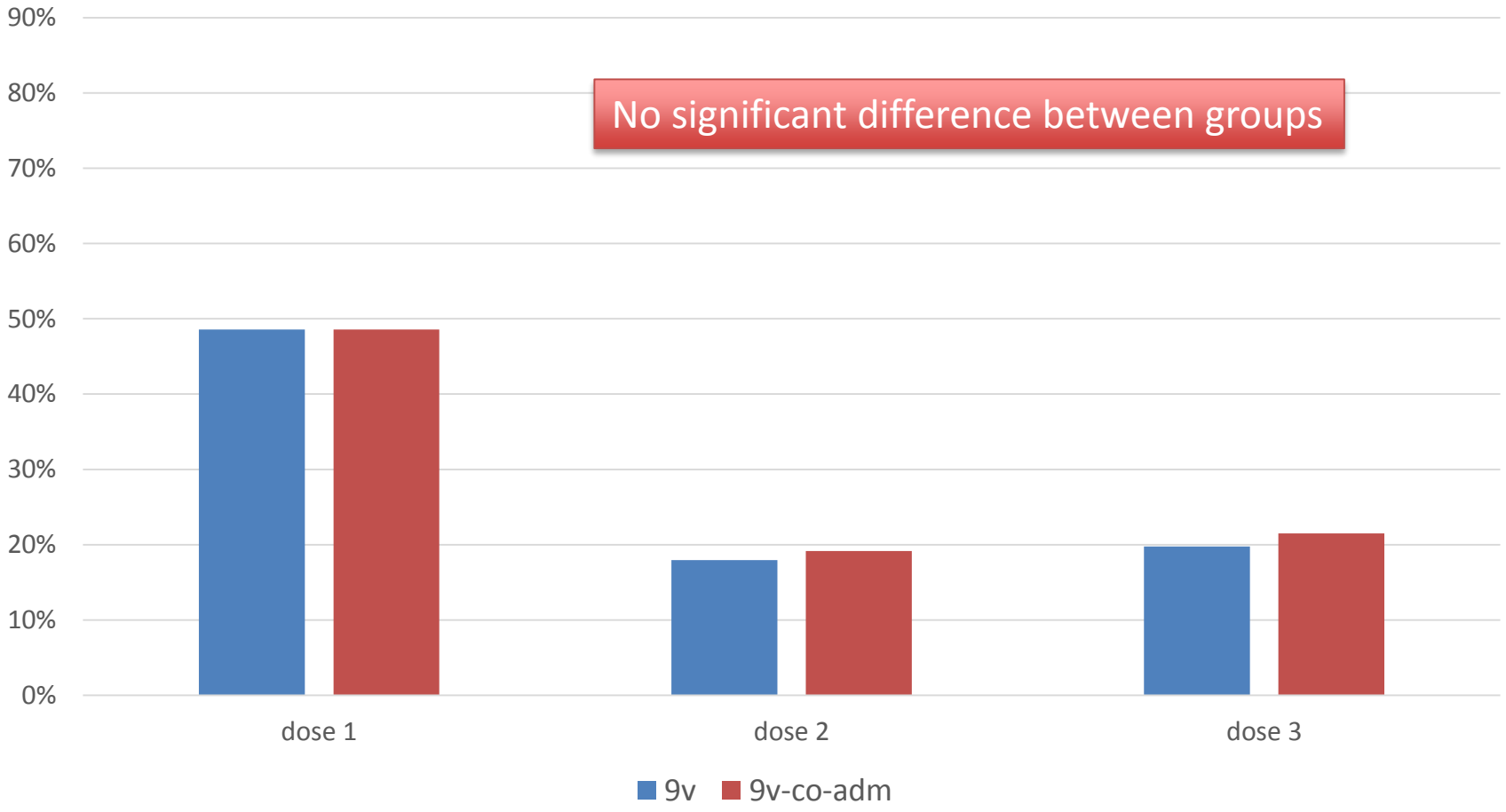
The risk difference between the groups was statistically significant for injection-site AE of swelling
(for both 9vHPV and Repevax® injection site)



Vaccine-related systemic AE

coadministration with REPEVAX®

boys and girls 11-15= 526 concomitant vs 528 non-concomitant group



ASIA:

how to make your own home-made syndrome using very poor evidence

ASIA case diagnostic criteria

Major Criteria:

- Exposure to an external stimuli (Infection, vaccine, silicone, adjuvant) prior to clinical manifestations.
- The appearance of 'typical' clinical manifestations:
  - Myalgia, Myositis or muscle weakness
  - Arthralgia and/or arthritis
  - Chronic fatigue, un-refreshing sleep or sleep disturbances
  - Neurological manifestations (especially associated with demyelination)
  - Cognitive impairment, memory loss
  - Pyrexia, dry mouth
- Removal of inciting agent induces improvement
- Typical biopsy of involved organs

Minor Criteria:

- The appearance of autoantibodies or antibodies directed at the suspected adjuvant
- Other clinical manifestations (i.e. irritable bowel syn.)
- Specific HLA (i.e. HLA DRB1, HLA DQB1)
- Evolvement of an autoimmune disease (i.e. MS, SSc)

For the diagnosis of ASIA, at least two major or one major and two minor criteria must be met

Shoenfeld Y, Agmon-Levin N. 'ASIA' - autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun. 2011;36(1):4-8.

Published review*

- "The quadrivalent HPV (virus types 6, 11, 16 and 19) recombinant vaccine has been mainly associated not only to SLE but also to RA, mixed connective tissue disease, Sjogren's syndrome, dermatomyositis and SSc" [Slade BA et al. JAMA, 2009]
- Slade BA et al. JAMA, 2009: "There were 51 reports of autoimmune disorders to the VAERS system, including 26 reports of autoimmune disorder (not otherwise specified), 1 report of scleroderma, 1 report of dermatomyositis, 18 reports of systemic lupus erythematosus, 13 reports of rheumatoid arthritis, 1 report of Sjögren syndrome, and 4 reports of mixed connective tissue disease."

* Vera-Lastra O, Medina G, Cruz-Dominguez M del P, Jara LJ, Shoenfeld Y. Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome): clinical and immunological spectrum. Expert Rev Clin Immunol. 2013;9(4):361-73.

Adding to the list…

- **Chronic fatigue syndrome** and **fibromyalgia** following immunization with the hepatitis B vaccine: another angle of the 'autoimmune (auto-inflammatory) syndrome induced by adjuvants' (ASIA).
- Hepatitis B vaccination and **undifferentiated connective tissue disease**: another brick in the wall of the autoimmune/inflammatory syndrome induced by adjuvants (Asia).
- Human papilloma virus vaccine and **primary ovarian failure**: another facet of the autoimmune/inflammatory syndrome induced by adjuvants.
- **Postural Orthostatic Tachycardia With Chronic Fatigue** After HPV Vaccination as Part of the "Autoimmune/Auto-inflammatory Syndrome Induced by Adjuvants": Case Report and Literature Review.
- Adjuvants and **lymphoma** risk as part of the ASIA spectrum.
- The **sick building syndrome** as a part of 'ASIA' (autoimmune/auto-inflammatory syndrome induced by adjuvants).
- …

CoI

- “Yehuda Shoenfeld has acted as a consultant for the no-fault U.S. National Vaccine Injury Compensation Program. L.T. has served as an expert witness in cases involving adverse reactions following qHPV vaccine administration.”
- He is also on the Scientific Advisory Board for the Children's Medical Safety Research Institute

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Conclusions

- Both bHPV and qHPV provided an excellent safety profile during pre-marketing evaluation:
  - pain at injection site (local) and headache and fatigue (systemic) were the most frequent common AEs
  - No significant difference between vaccine and control group for SAEs
- Pre-marketing studies on 9vHPV confirm the same safety profile than qHPV
- Literature review revealed the presence of numerous papers on HPV vaccination and ASIA syndrome, having a very limited level of evidence (case-series only, no causal relationship whatsoever)

Thank you for your attention

pierluigi.lopalco@unipi.it