Cross-Protection Efficacy GARDASIL®

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Vaccines & Infectious Disease

Merck & Co., Inc.

Presentation Outline

- Contribution of HPV Types to Cervical Disease
- Approach to Cross-Protection Evaluation
- Results
- Clinical Benefit of Cross-Protection

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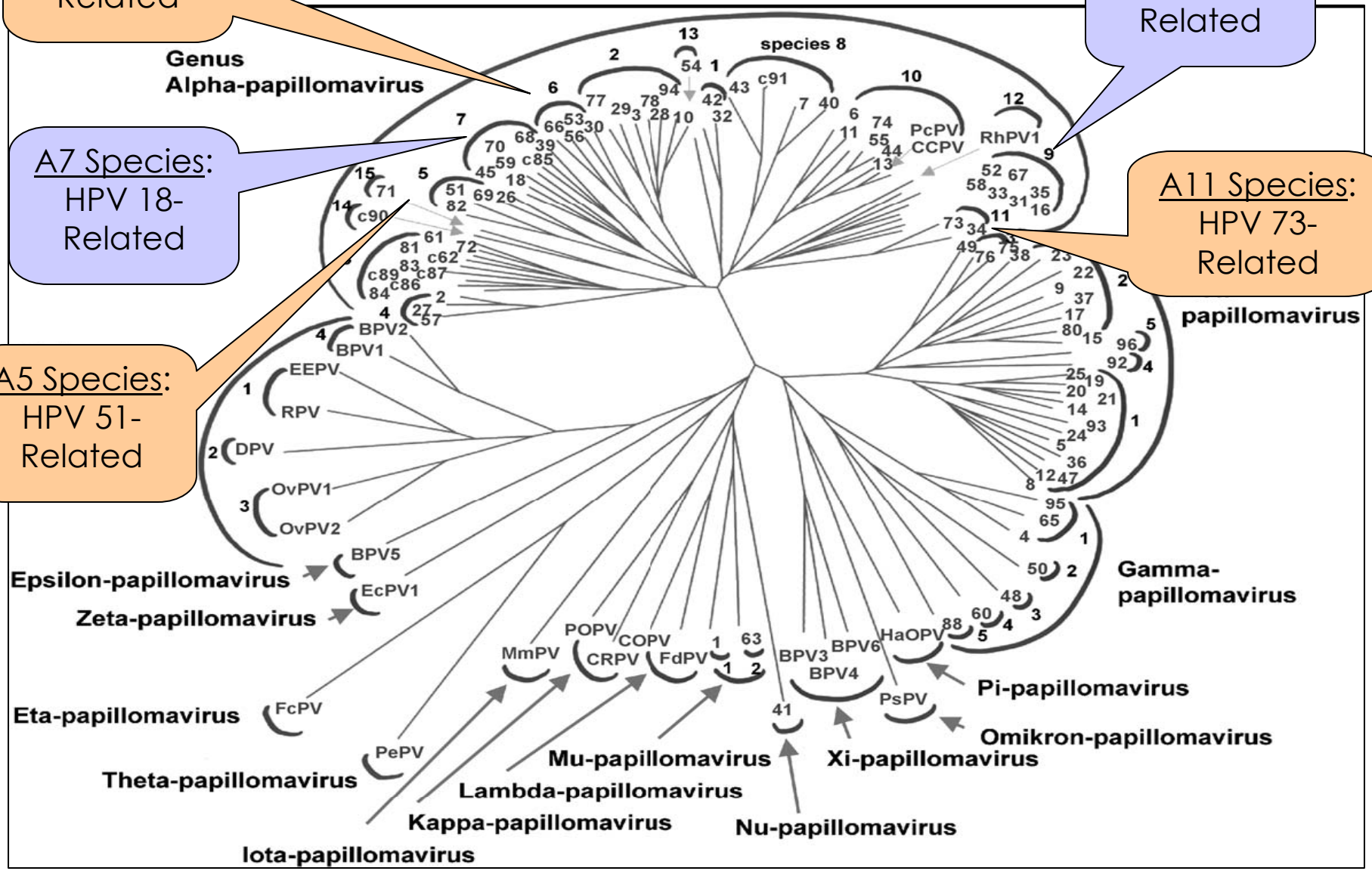
Cancer-Causing HPV Species
HPV Phylogenetic Tree



Contribution of HPV Types to Cervical Cancer

Species/HPV Type	Contribution
Species A9	**70.6%**
HPV 16	**58.7%**
HPV 31	3.8%
HPV 33	2.3%
HPV 35	1.4%
HPV 52	2.2%
HPV 58	2.2%
Species A7	**18.7%**
HPV 18	**12.2%**
HPV 39	0.5%
HPV 45	4.7%
HPV 59	1.2%
HPV 68	0.1%
Species A5/A6/A11	**2.5%**
Type X (unidentified) or Infection with >3 Types	**8.2%**

To calculate HPV type contribution in cases of infection with ≥2 HPV types, a hierarchy based on the pathogenicity of types was used (HPV 16>18>31/45>33/52/58>all others).

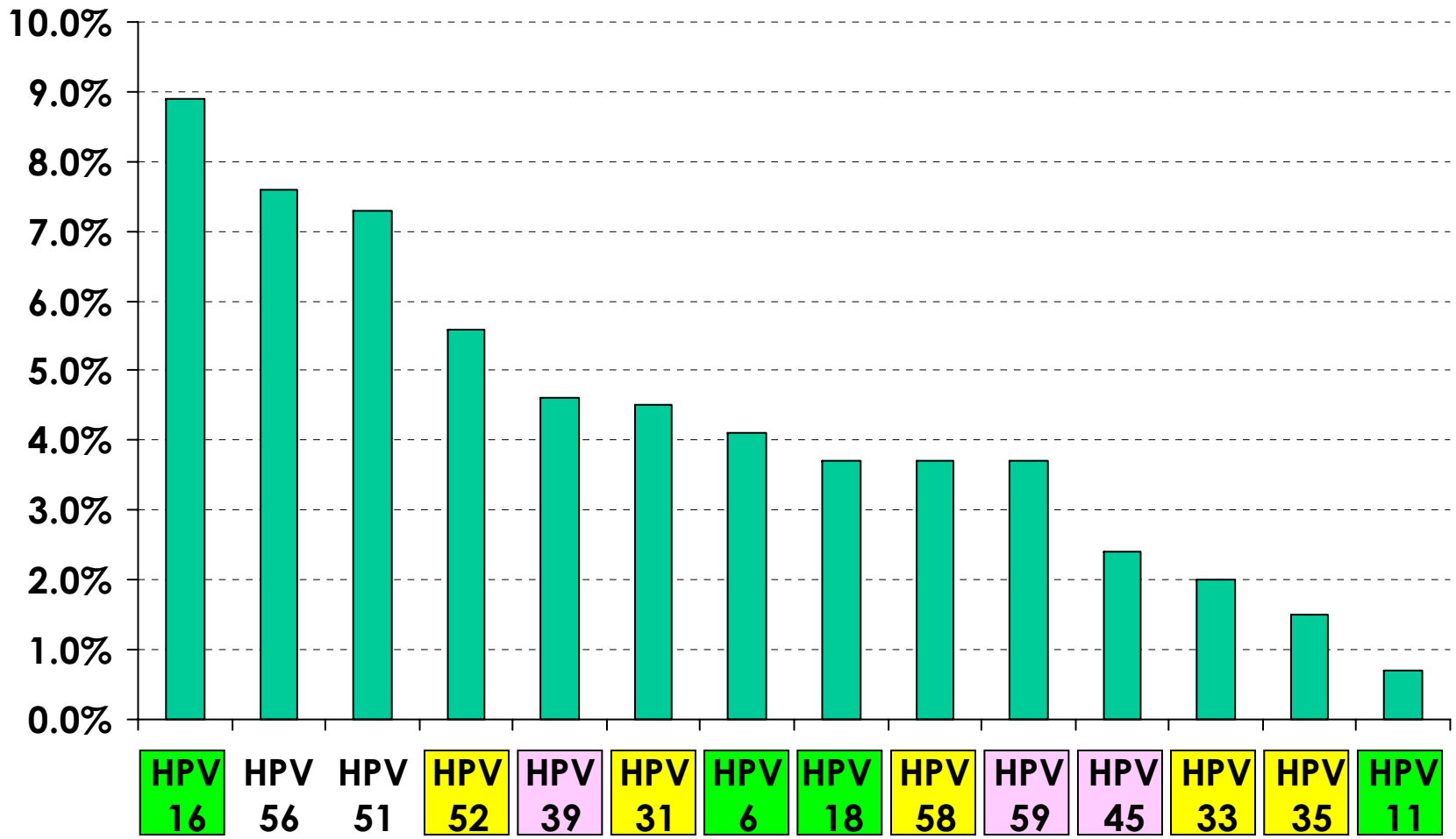
Adapted from Munoz et al. *NEJM* 2003

Natural History Findings from FUTURE I/FUTURE II

Phase III Studies of GARDASIL™ in 16- to 26-Year-Old Women

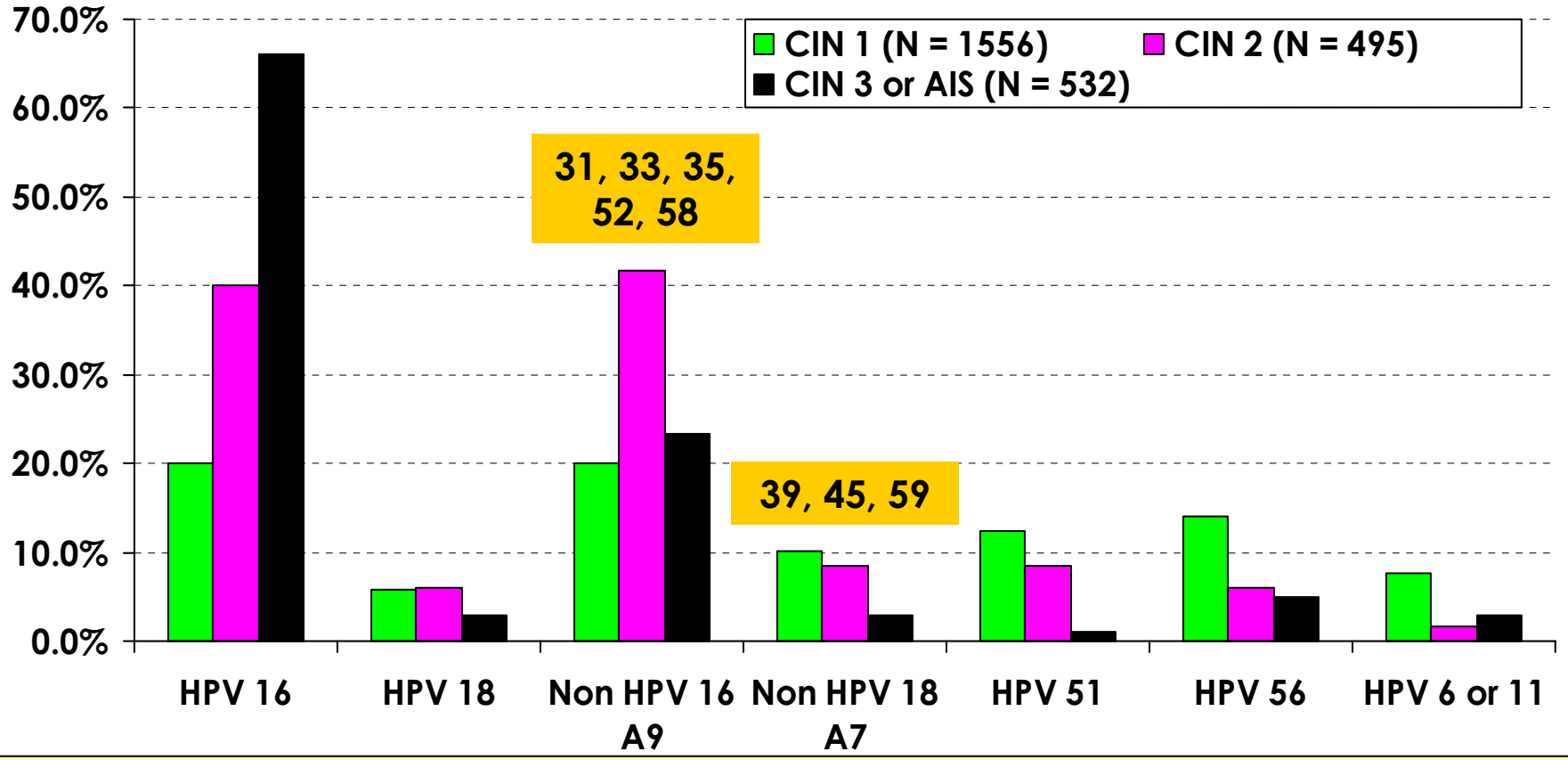
FUTURE I/II: HPV PCR Status at Day 1

At Day 1, 32.8% of Subjects Were Positive to ≥1 HPV Type



Species A9 (HPV 16-Related): Common in CIN 2/3

Contribution of HPV Species to Incident Cases in CIN 16-26 Year-Old Placebo Subjects in the Generally HPV-Naïve Population† of FUTURE I/II



For non-vaccine types, only cases in which vaccine types were NOT detected are included

† Women who, at Day 1, were negative to 14 common HPV types and had a negative Pap test

Conclusion: Natural History Studies

- Contribution of HPV types varies with lesion type
- Cervical cancer
  - Co-infection is uncommon
  - HPV 16/18 responsible for 70 to 75%
  - HPV 31, 33, 45, 52, 58 responsible for an additional ~15%
- High grade lesions
  - Co-infection is common
  - HPV 16 and HPV 16-related types predominate
  - HPV 18 also important
  - HPV 18-related types less important
- Low grade lesions
  - Co-infection is common
  - HPV 16 most common, but many others contribute

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Cross-Protection Evaluation of GARDASIL™ Choice of HPV Types

HPV Type	Proportion in Cervical Cancer	Species	Coat Protein Homology
HPV 16	**58.7%**	**A9**	**Prototype**
HPV 18	**12.2%**	**A7**	**Prototype**
HPV 45	**4.7%**	**A7**	**88%**
HPV 31	**3.8%**	**A9**	**83%**
HPV 33	**2.3%**	**A9**	**81%**
HPV 52	**2.2%**	**A9**	**80%**
HPV 58	**2.2%**	**A9**	**80%**
HPV 35	1.4%	A9	81%
HPV 59	1.2%	A7	78%
HPV 51	0.7%	A5	--
HPV 56	0.6%	A6	--
HPV 39	0.5%	A7	77%
HPV 26, 53, 66, 68, 82	0.9%	Various	--

To calculate HPV type contribution in the setting of infection with ≥2 HPV types, a hierarchy based on the pathogenicity of HPV types was used (HPV 16>18>31/45>33/52/58>all others).

Adapted from Munoz et al. *NEJM* 2003

WHO Opinion Regarding Cross-Protective Efficacy Standards

Expert Committee on Biologic Standardization

- Cross-neutralization studies cannot be used to predict efficacy against non-vaccine types
- Efficacy data are needed to demonstrate cross-protection
  - Incidences of lesions (such as CIN of any grade, CIN2/3 or AIS) due to the types in question; and/or
  - Viral persistence (Persistent Infection ≥12 months)

http://www.who.int/biologicals/publications/trs/areas/vaccines/human_papillomavirus/en/index.html

Cross-Protection Evaluation: GARDASIL™

- **Infection Cross-Protection (Substudy of FUTURE I, N= 3571)**
  - Persistent HPV 31/33/45/52/58 infection or related disease
  - Testing for 16, 18, 35, 59 also conducted
- **Disease Cross-Protection (FUTURE I/II, N= 17,599)**
  - HPV 31/45-related CIN (any grade) or AIS
  - HPV 31/33/45/52/58-related CIN (any grade) or AIS
  - Testing for HPV 6, 11, 16, 18, 35, 51, 56, 59 also conducted
- **Up to 4 years of follow-up**

Relevant Population for Evaluation

- **Generally HPV-Naïve – At Day 1:**
  - Negative Pap
  - Negative to 14 HPV types
- **Methodological advantage:**
  - Each women starts at the same status (no mixed prevalent/incident infections)
  - All lesions after Day 1
- **Clinical relevance:**
  - Approximates primary cohorts for vaccination

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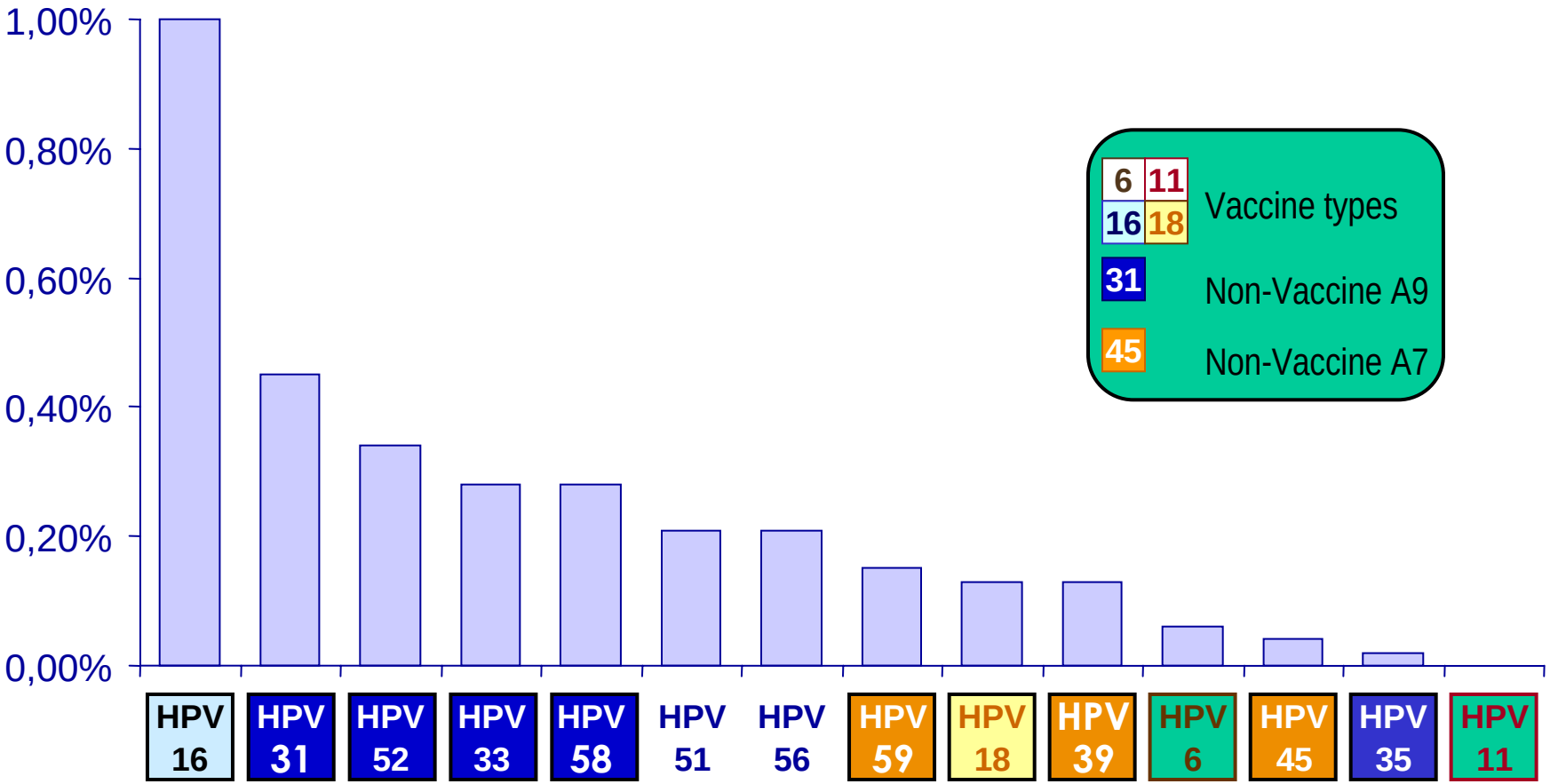
In FUTURE I/II, Most New CIN 2/3 or AIS Cases Were Caused by Species A9

Cumulative Incidence of CIN 2/3 or AIS Among Placebo Subjects in the Generally HPV-Naïve Population of FUTURE I/II



GARDASIL™: Cross-Protection Against CIN 2/3 + AIS

Primary Type Clusters in the Generally HPV-naïve Population

Causal HPV Type	GARDASIL™	Placebo	Efficacy	95% CI
HPV 31/45	8	21	62%	10,85
HPV 31/33/45/52/58	27	48	43%	7,66

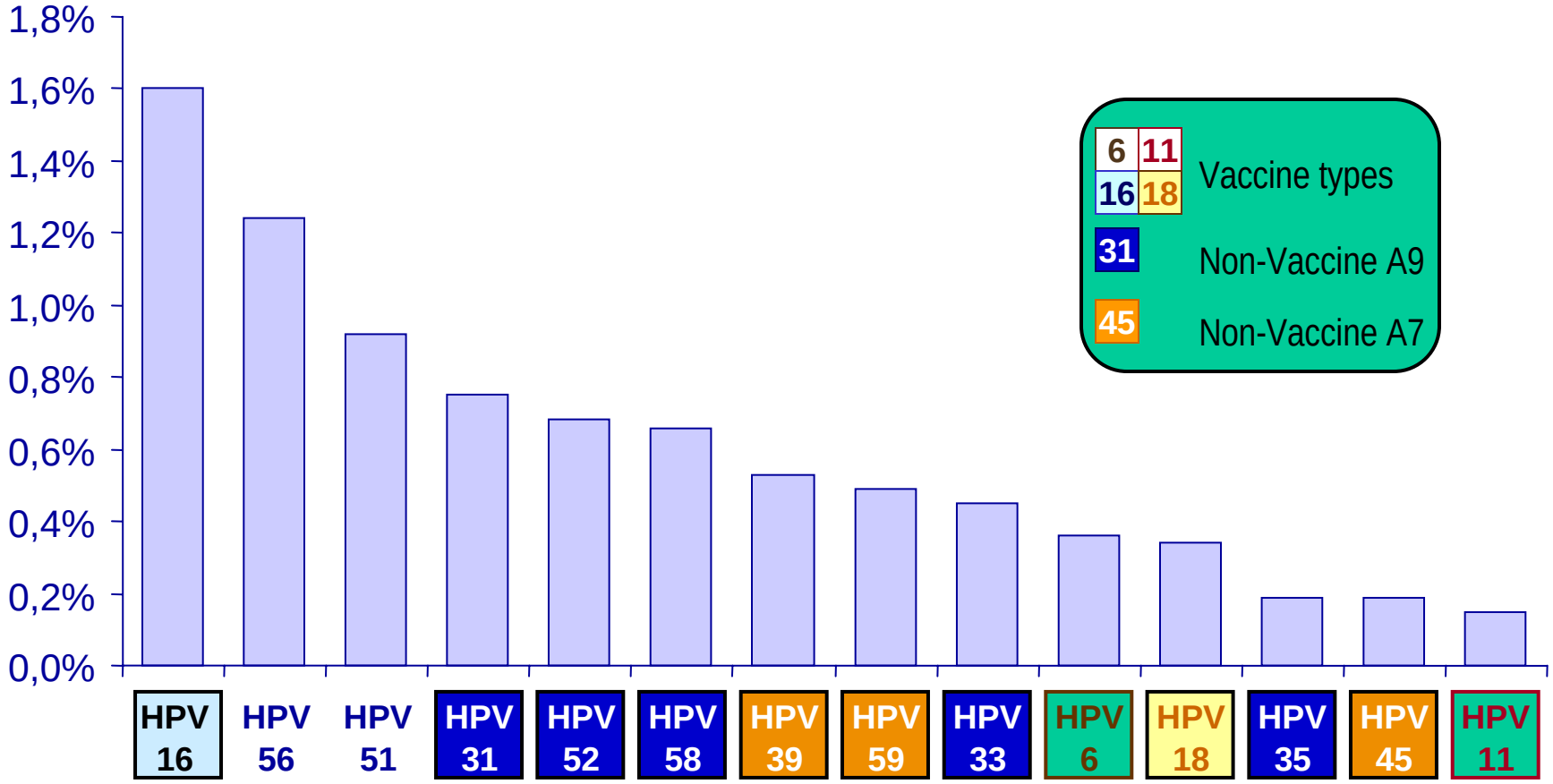
GARDASIL™: Cross-Protection Against CIN 2/3 + AIS

By Species and Overall in the Generally HPV-naïve Population

Causal HPV Type	GARDASIL™	Placebo	Efficacy	95% CI
10 Non-vaccine Oncogenic Types HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	**38**	**62**	**38%**	**6, 60**
A9 Species HPV 31, 33, 35, 52, 58	**26**	**48**	**45%**	**10, 68**
A7 Species HPV 39, 45, 59	**8**	**15**	**46%**	**-35, 80**

In FUTURE I/II, New CIN Lesions Were Caused by Many HPV Types

Cumulative Incidence of CIN (Any Grade) or AIS Among Placebo Subjects in the Generally HPV-Naïve Population of FUTURE I/II



GARDASIL™: Cross-Protection Against CIN (Any Grade) + AIS

Primary Type Clusters in the Generally HPV-naïve Population

Causal HPV Type	GARDASIL™	Placebo	Efficacy	95% CI
HPV 31/45	23	42	45%	6, 68
HPV 31/33/45/52/58	66	99	33%	8, 52

GARDASIL(TM): Cross-Protection Against CIN (Any Grade) + AIS

By Species and Overall in the Generally HPV-naïve Population

Causal HPV Type	GARDASIL™	Placebo	Efficacy	95% CI
10 Non-vaccine Oncogenic Types HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	**135**	**185**	**27%**	**8, 42**
A9 Species HPV 31, 33, 35, 52, 58	**64**	**97**	**34%**	**8, 52**
A7 Species HPV 39, 45, 59	**36**	**54**	**33%**	**-4, 57**

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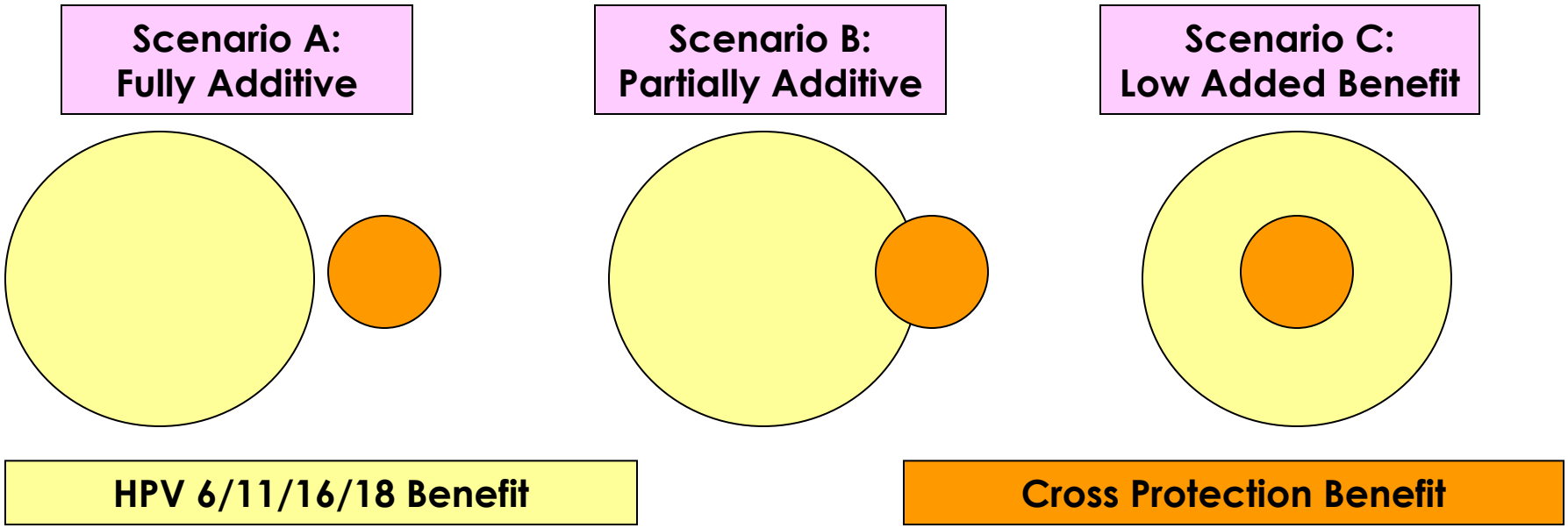
Additional Public Health Impact of Cross-Protection is Complex

- In setting of infection with >1 type, added benefit may differ from value in isolation
  - Coinfection is common
  - Risk for HPV infection is dependent on sexual behavior
- Theoretical cross-protection benefit - fewer women with events and/or fewer events in individual women



Analysis of Benefit: Generally HPV-Naïve Population

Placebo Group	Vaccine Group	Cases Prevented

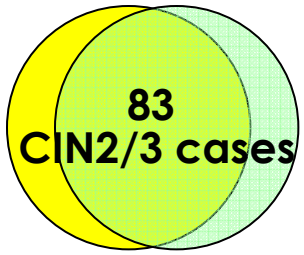
Efficacy against 16/18 only:
Counting does not consider if there is also HPV 31/33/45/52/58 in the lesion

51 CIN2/3 cases — Minus — 0 CIN2/3 cases — Equals — 51 CIN2/3 cases

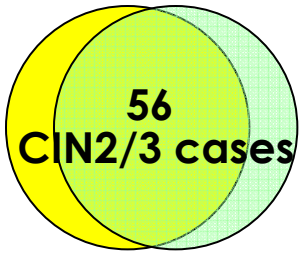
Efficacy against 31/33/45/52/58 only:
Counting does not consider if there is also HPV 16/18 in the lesion

48 CIN2/3 cases — Minus — 27 CIN2/3 cases — Equals — 21 CIN2/3 cases

Efficacy against 16/18/31/33/45/52/58:
In placebo group, 16 cases included ≥2 types: HPV 16 or 18 + HPV 31, 33, 45, 52, or 58
None of the cases in the vaccine group has such overlap (zero cases of HPV 16/18)



Minus — 27 CIN2/3 cases — Equals —



Net Benefit = 5 Add'l Cases Prevented

Efficacy of GARDASIL™

Clinical Benefit of GARDASIL™ has 3 components

- Major component – HPV 16/18 prevention : ~100% efficacy
  - Cervical, vulvar, vaginal cancer (via precursors)
  - CIN 1/2/3 + AIS; VIN; VaIN
- Major component – HPV 6/11 prevention: ~100% efficacy
  - Genital Warts
  - CIN
- Important added benefit - Cross-Protection: ~38% efficacy
  - Against 10 additional oncogenic strains that account for ~20% of worldwide cervical cancers
  - CIN 2/3, CIN reduction observed in HPV-naïve girls/women