

# Influenza vaccines

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# The problem

# HIV-infected individuals at higher risk from influenza

## Relative Risk of Influenza-Related Excess Death Rates in Adults with AIDS, Compared with Reference Population Groups and Periods in South Africa (1998–2005) and the USA

Mortality Outcome	South African Adults Aged 25–54 Years With AIDS			US Adults Aged 25–54 Years With AIDS			
	vs South African General Population Aged ≥65 Years	vs US Adults Aged 25–54 Years With AIDS in Pre-HAART Era	Pre-HAART vs HAART Era	vs General Population Aged 25–54 Years in Pre-HAART Era	vs General Population Aged ≥65 Years in Pre-HAART Era	vs General Population Aged 25–54 Years in HAART Era	vs General Population Aged ≥65 Years in HAART Era
Influenza-related excess all-cause death rate, RR (95% CI) <sup>a</sup>	2.2 (1.0–5.1)	1.3 (0.3–5.3)	5.6 (1.3–24)	150 (49–460)	4.1 (1.4–13)	44 (16–121)	0.8 (0.2–3.3)
Influenza-related excess P&I death rate, RR (95% CI) <sup>a</sup>	3.8 (2.2–6.6)	1.2 (0.4–3.5)	2.6 (0.9–7.1)	208 (74–583)	2.5 (0.9–7.2)	73 (47–113)	0.9 (0.5–1.7)

All estimates given for South Africa are considered to predate the highly active antiretroviral therapy era in this country.

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; P&I, pneumonia and influenza; RR, relative risk.

<sup>a</sup> Determined with negative binomial regression.

Cohen, C., et al., Influenza-related mortality among adults aged 25–54 years with AIDS in South Africa and the United States of America. Clin Infect Dis, 2012. 55(7): p. 996–1003.



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Post-HAART, influenza-related mortality in adults with AIDS dropped 3–6-fold but remained elevated compared with the general population

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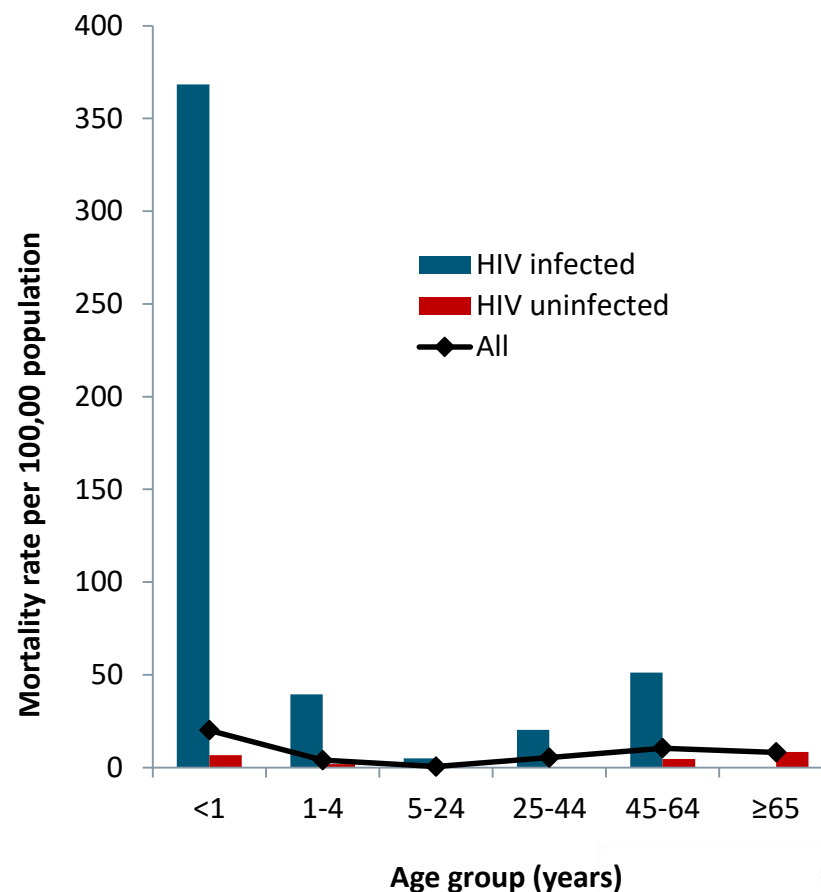
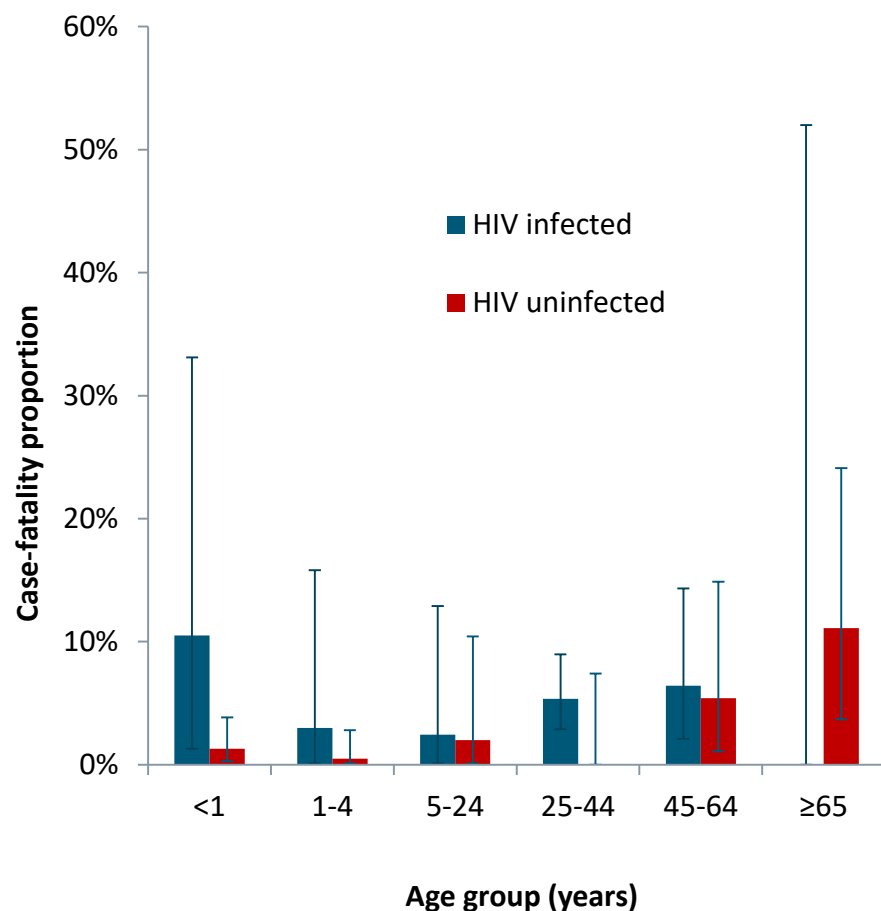
In South Africa and the USA adults with AIDS experienced an elevated risk of influenza-associated death, 150–200-fold higher than that in the general population of the same age and 2–4-fold higher than that in adults aged ≥65 years

Cohen, C., et al., Influenza-related mortality among adults aged 25–54 years with AIDS in South Africa and the United States of America. Clin Infect Dis, 2012. 55(7): p. 996–1003.



# Influenza infection in HIV-infected individuals

Case-fatality proportions and mortality rates by age group and HIV status amongst patients hospitalized with influenza-associated SARI, 2009-2013



# Influenza Vaccines

# Groups recommended for influenza vaccination

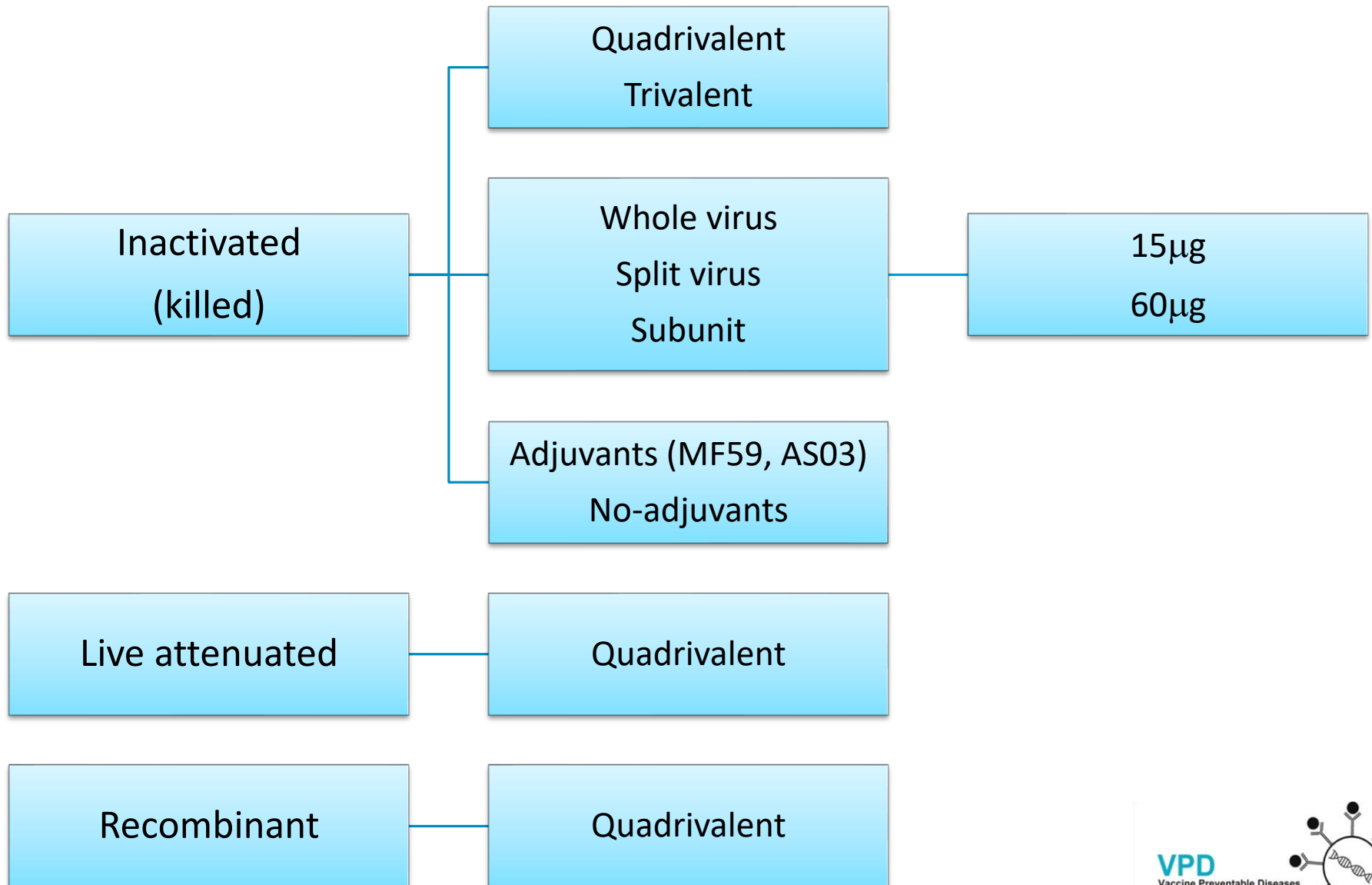
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The recommendation for groups to be prioritised are reviewed annually. The following are among the groups that were prioritised for the publicly-funded influenza vaccination campaign in 2017:

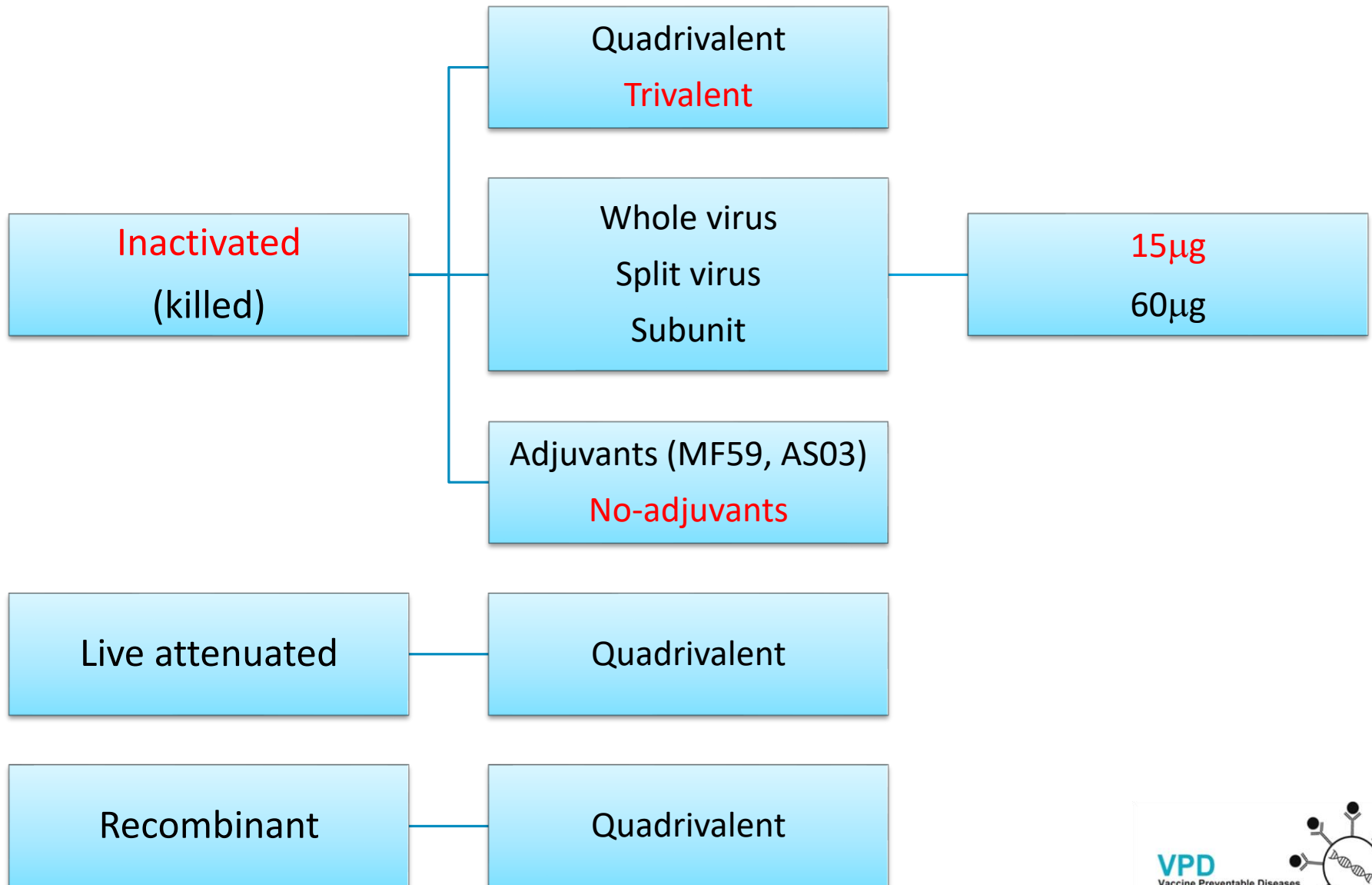
- Pregnant women at all stages of pregnancy, including the post-partum period
- HIV-infected individuals
- Individuals ( $\geq 6$  months old) who are at high risk of influenza and its complications due to underlying medical conditions and who are receiving regular medical care for conditions such as chronic pulmonary (including tuberculosis) and cardiac diseases, chronic renal diseases, diabetes mellitus and similar metabolic disorders, individuals who are immuno-suppressed
- Persons aged  $>65$  years



# Types of seasonal influenza vaccine



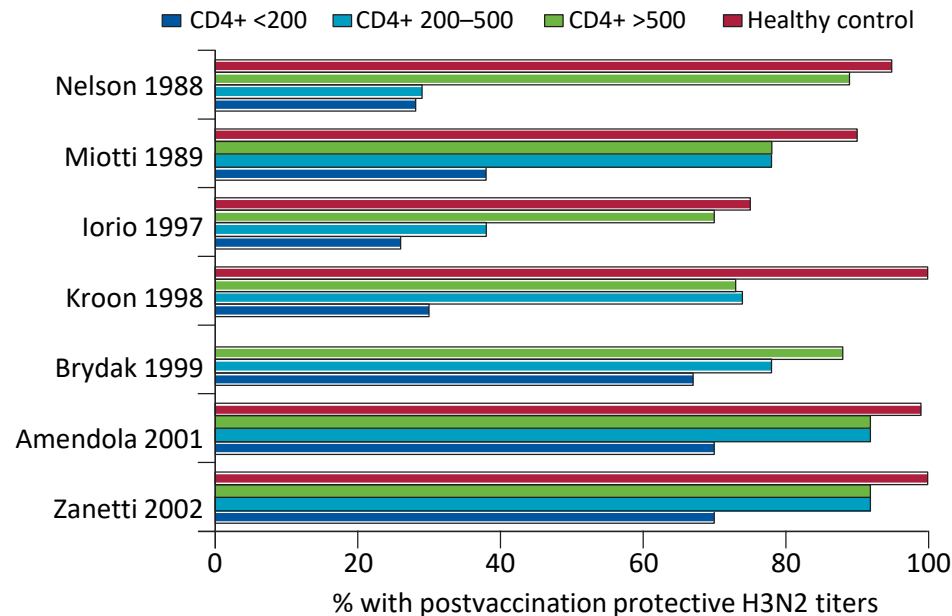
# Types of seasonal influenza vaccine



# Influenza Vaccination of HIV-infected Subjects

# Predictors of influenza vaccine immune response in HIV-infected patients

## ➤ CD4 cell counts >200/ $\mu$ L



From: Kunisaki et al. Lancet Infect Dis, 2009, 9: 493-504

## ➤ HIV viral load

(Evison et al. CID, 2009; 48: 1402-12)

(Yamanaka et al. J Acquir Immune Defic Syndr, 2005; 39: 167-73)

## ➤ Young age and shorter duration of HIV infection

(Crum-Cianflone et al. CID, 2011; 52: 138-146)

# Immunogenicity of TIV in HIV-infected Adults

## South Africa 2008

Table 4. Seroconversion Rates Measured by Hemagglutinin Inhibition Assay (HAI) to Influenza Virus Strains in Antiretroviral (ART) Naive and ART-Stable HIV-Infected Adults Randomized to Trivalent Inactivated Influenza (TIV) Vaccine or Placebo

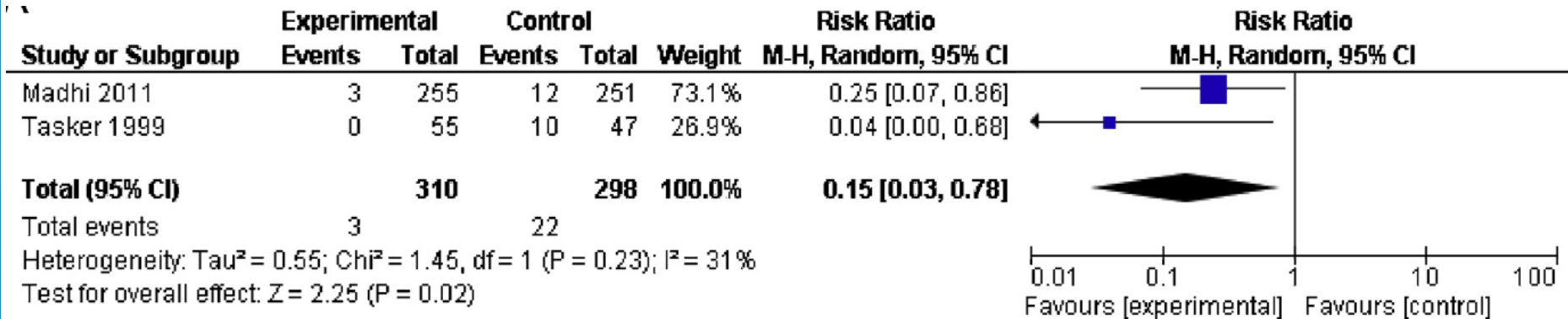
Immunogenicity measure	ART naïve			Stable-ART			Overall		
	TIV N = 49	Placebo N = 44	P value	TIV N = 48	Placebo N = 47	P value	TIV N = 97	Placebo N = 91	P value
H1N1 HAI assay									
Seroconversion (%) <sup>a</sup>	17 (34.7) <sup>d</sup>	0 (0)	<.0001	34 (70.8) <sup>d</sup>	2 (4.3)	<.0001	51 (52.6)	2 (2.2)	<.0001
H3N2 HAI assay									
Seroconversion (%)	25 (51.0) <sup>d</sup>	0 (0)	<.0001	34 (70.8) <sup>d</sup>	2 (4.3)	<.0001	59 (60.8)	2 (2.2)	<.0001
Influenza B HAI assay									
Seroconversion	22 (44.9) <sup>d</sup>	1 (2.3)	<.0001	30 (62.5) <sup>d</sup>	3 (6.4)	<.0001	52 (53.6)	4 (4.4)	<.0001

Seroconversion defined as: HAI titers of  $\geq 1:40$  if baseline titers were  $\leq 1:10$ ; or a  $>4$ -fold increase in those with baseline titers  $> 1:10$



# Meta-analysis of Efficacy of Influenza Vaccine in HIV-infected Adults

## Laboratory-confirmed influenza

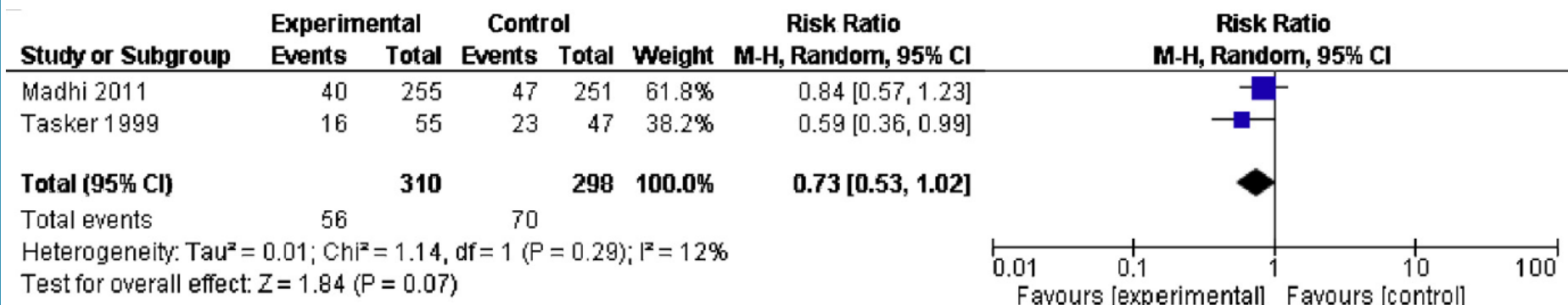


In adults, TIV prevented laboratory-confirmed influenza with a pooled efficacy of 85%

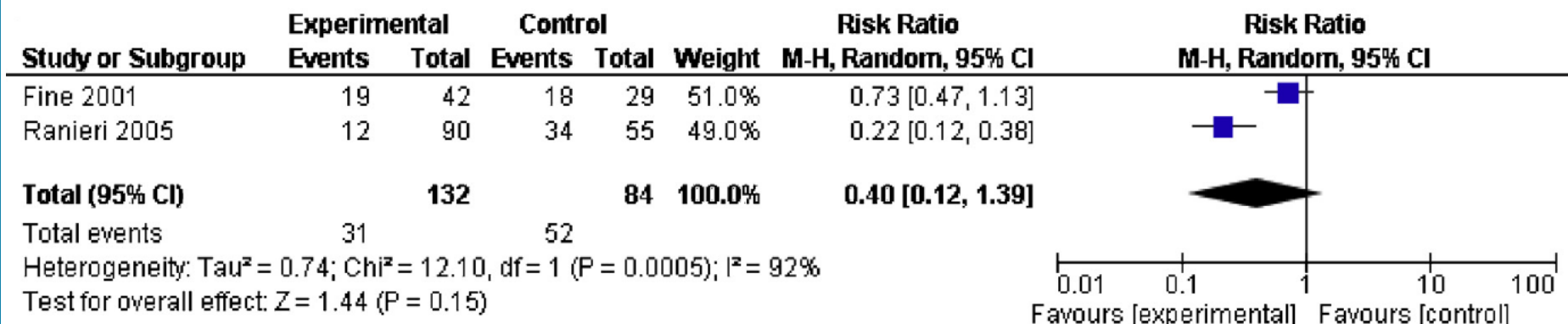
One cohort study showed an effectiveness of 71% (95%CI: 44, 85) for prevention of laboratory-confirmed influenza

# Meta-analysis of Effectiveness of Influenza Vaccine in HIV-infected Adults

## Any respiratory illness



## Influenza-like illness



Pooled effectiveness against influenza-like illness was 60% (95%CI: -39, 88) 2 cohort studies.

No significant effects of vaccination on risk of all cause hospitalization and all-cause pneumonia.

# Efficacy and immunogenicity of TIV in HIV-infected children, 2009

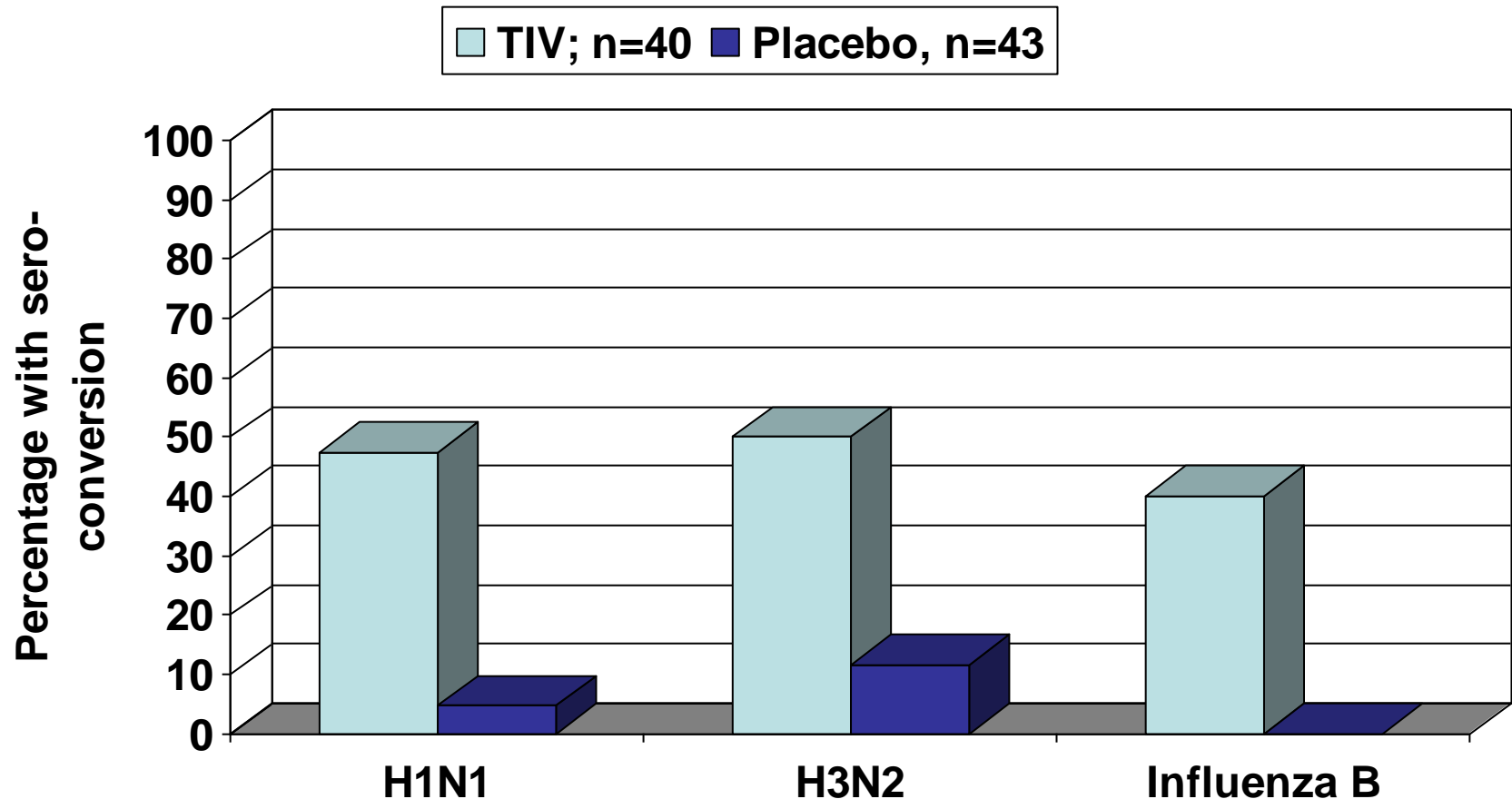
- Children received 2 doses of TIV or placebo 1 month apart (0.5ml/dose if  $\geq 36$  months or 0.25ml if younger)
- TIV 2009 southern hemisphere formulation (vaccination: Feb-May 2009)
- Immunogenicity measures 1-month after 2<sup>nd</sup> dose
- Surveillance for ILI
- Laboratory testing for Influenza

## Baseline demographic and clinical information for the study cohort

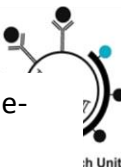
	TIV N=206	Placebo N=204
Total follow up time (weeks)	2579.1	2576.7
Median Age (range) months	23.1 (6.0-59.9)	24.0 (6.0-59.8)
6-<36 months % (n)	79.1% (163)	72.6% (148)
Female : Male	1.5:1	1.1:1
Median weight (range)	10.9 (5.4 – 23.9)	10.9 (5.8 – 19.5)
Breastfed % (n)	16.5% (34)	20.1% (41)
Proportion on ARV % (n)	92.2% (190)	91.7% (187)
Median CD4+ count (IQR)	1770.0 (464-4390)	1648.0 (491-4615)
Median CD4+ % (range)	33.5 (16.3 – 59.7)	33.4 (15.2- 54.0)



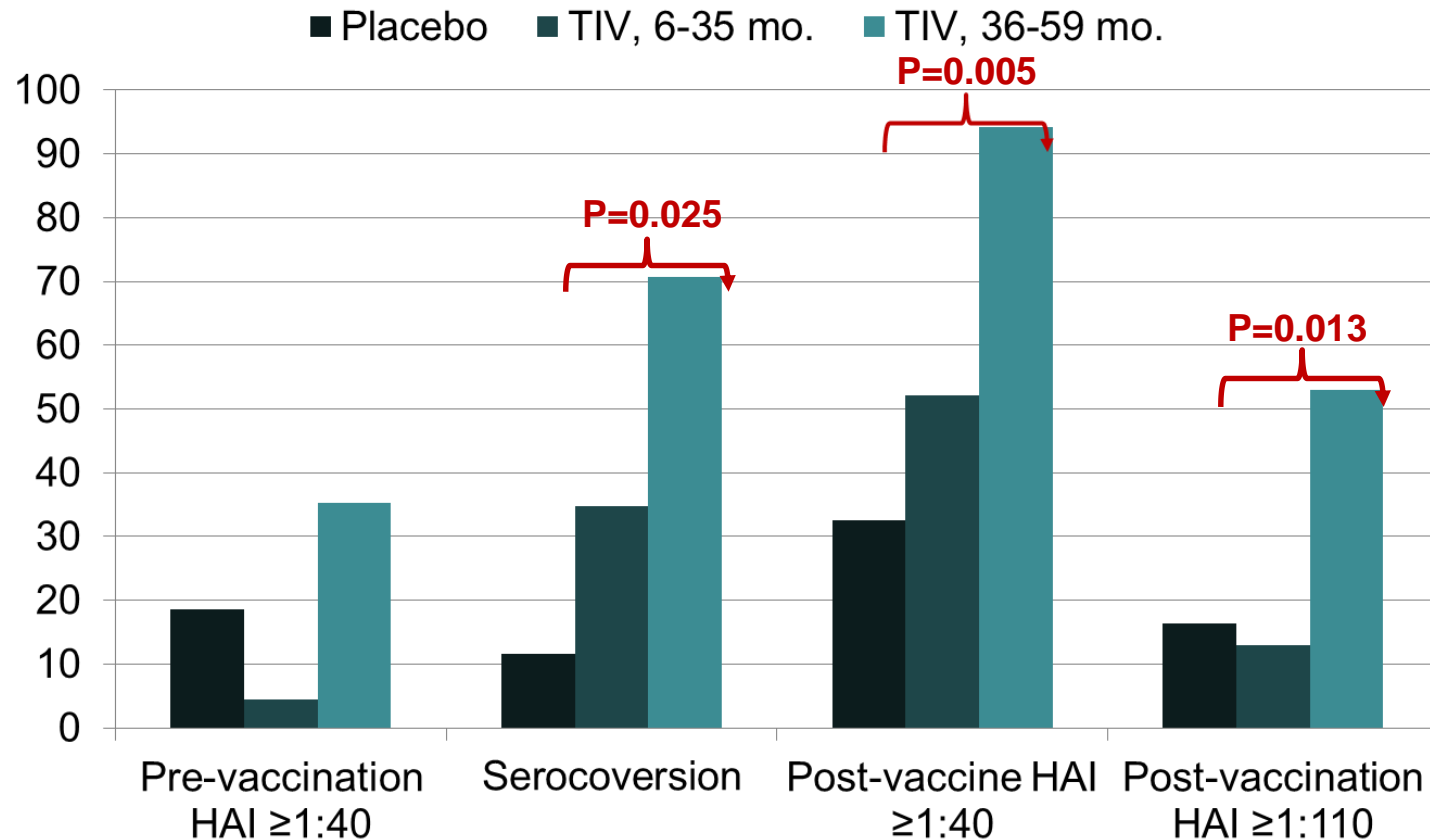
# Seroconversion rate to vaccine strains in HIV-infected vaccine and placebo recipients



Adapted from: Madhi, S.A., et al., Efficacy and immunogenicity of influenza vaccine in HIV-infected children: a randomized, double-blind, placebo controlled trial. AIDS, 2013. 27(3): p. 369-79.

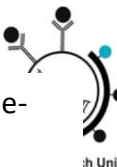


# H3N2 HAI Responses pre-vaccination and 1-month post 2<sup>nd</sup> dose TIV in HIV-infected children



Poor immunogenicity against the dominant wild-type circulating strain, particularly in the younger age-group

Adapted from: Madhi, S.A., et al., Efficacy and immunogenicity of influenza vaccine in HIV-infected children: a randomized, double-blind, placebo controlled trial. AIDS, 2013. 27(3): p. 369-79.



# Efficacy of TIV Against Seasonal Influenza in HIV-infected Children South Africa, 2009

Measure	Intent to treat			Vaccine efficacy (95% C.I.)
	Total N= 410	TIV N= 206	Placebo N=204	
Seasonal influenza follow-up period in child-weeks <sup>a</sup>	5502.1	2752.3	2749.8	
Illness visits; n (incidence) <sup>b</sup>	144 (2.6)	66 (2.4)	78 (2.8)	Not calculated
ILI episodes; n (incidence) <sup>b</sup>	74 (1.3)	29 (1.1)	45 (1.6)	
1 <sup>st</sup> episodes of ILI; n(incidence) <sup>b</sup>	55 (1.0)	24 (0.9)	31 (1.1)	22.6 (−36.2, 56.6)
All confirmed influenza illness; n (incidence) <sup>b</sup>	40 (0.7)	19 (0.7)	21 (0.8)	Not calculated
1 <sup>st</sup> episode confirmed influenza illness; n (incidence) <sup>b</sup>	38 (0.7)	17(0.6)	21 (0.8)	19.1 (−61.0, 59.9)
1 <sup>st</sup> episode confirmed H3N2 illness; n (incidence) <sup>b</sup>	35 (0.6)	16 (0.6)	19 (0.7)	15.9 (−72.8, 59.5)

<sup>a</sup>Total follow-up time during circulation of seasonal influenza virus.

<sup>b</sup>Incidence per 100 child-weeks.

# Influenza vaccination of pregnant women

# Increased risk of influenza–associated mortality among pregnant women in South Africa

Estimated annual influenza–associated mortality among pregnant and non-pregnant women of childbearing by HIV status and RR for mortality associated with pregnancy 1999–2009

Cause of Death	Estimated Mean Annual Seasonal Influenza—Associated Deaths (1999–2009)				Crude Relative Risk (Pregnant vs Nonpregnant) (95% CI)	Age-Standardized Relative Risk (Pregnant vs Nonpregnant) (95% CI)
	Pregnant		Nonpregnant			
	No. (95% CI)	Rate <sup>b</sup> (95% CI)	No. (95% CI)	Rate <sup>b</sup> (95% CI)		
All-cause						
HIV <sup>−</sup>	14 (8–20)	1.5 (.9–2.1)	90 (57–123)	0.9 (.6–1.2)	1.6 (1.2–2.0)	2.4 (2.1–2.7)
HIV <sup>+</sup>	109 (62–156)	74.9 (42.7–107.1)	824 (519–1129)	41.2 (26.0–56.4)	1.8 (1.3–2.3)	2.9 (2.1–3.7)
Total	123 (70–176)	12.6 (7.2–18.0)	914 (576–1252)	7.3 (4.6–10.0)	1.7 (1.2–2.2) <sup>c</sup>	2.8 (1.7–3.9) <sup>c</sup>
All-respiratory						
HIV <sup>−</sup>	7 (3–11)	0.9 (.4–1.4)	45 (25–65)	0.5 (.3–.7)	1.8 (1.3–2.3)	2.3 (1.8–2.8)
HIV <sup>+</sup>	60 (27–93)	41.3 (18.6–64.0)	410 (226–595)	20.5 (11.3–29.7)	2.0 (1.4–2.6)	2.9 (1.9–3.9)
Total	67 (30–104)	6.8 (3.1–10.5)	455 (250–660)	3.8 (2.1–5.5)	1.9 (1.2–2.6) <sup>c</sup>	2.8 (1.6–4.0) <sup>c</sup>
All-circulatory						
HIV <sup>−</sup>	3 (1–5)	0.4 (.2–.6)	16 (8–14)	0.2 (.1–.3)	2.1 (1.2–3.0)	3.9 (2.9–5.2)
HIV <sup>+</sup>	28 (12–44)	19.3 (8.1–30.5)	142 (67–217)	7.4 (3.5–11.3)	2.6 (1.6–3.6)	4.1 (3.6–4.5)
Total	31 (13–49)	3.1 (1.3–4.9)	158 (74–242)	1.3 (.6–2.0)	2.4 (1.5–3.3) <sup>c</sup>	4.0 (3.7–4.4) <sup>c</sup>
Pneumonia and influenza						
HIV <sup>−</sup>	6 (3–9)	0.8 (.4–1.2)	35 (20–50)	0.4 (.2–.6)	1.9 (1.1–2.7)	2.7 (1.9–3.5)
HIV <sup>+</sup>	53 (25–81)	36.8 (17.3–56.3)	320 (182–458)	16.9 (9.6–24.2)	2.2 (1.3–3.1)	3.1 (2.2–4.0)
Total	59 (28–90)	6.1 (2.9–9.3)	355 (202–508)	2.9 (1.7–4.1)	2.1 (1.3–2.9) <sup>c</sup>	2.9 (1.8–4.0) <sup>c</sup>

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

<sup>a</sup> Estimated from model 1 (overall deaths) and model 2 (deaths by HIV status).

<sup>b</sup> Crude death rates per 100 000 person-years.

<sup>c</sup> Relative risk adjusted for HIV status.

Tempia S. et al., Mortality Associated With Seasonal and Pandemic Influenza Among Pregnant and Nonpregnant Women of Childbearing Age in a High-HIV-Prevalence Setting-South Africa, 1999–2009. Clin Infect Dis, 2015. 61(7): p. 1063–70



# Epidemiology of acute LRTI among infants in South Africa 2010–2013

## Incidence Rates and Incidence Rate Ratios by HIV Infection and Exposure Status for Infants Aged <6 Months Hospitalized With LRTI in Soweto

8% were HIV infected, 34% were HEU and 58% were HUU

Case	Unadjusted No. of Cases	Incidence Rates per 100 000 Population			Incidence Rate Ratio	
		HUU (95% CI)	HEU (95% CI)	HIV-Infected (95% CI)	HEU/HUU (95% CI)	HIV-Infected/HUU (95% CI)
All LRTI	1410	10 313 (9858–10 784)	14 097 (13 252–14 982)	39 622 (34 179–45 692)	1.4 (1.3–1.5) <sup>a</sup>	3.8 (3.3–4.5) <sup>a</sup>
RSV-associated LRTI	469	3507 (3244–3787)	5003 (4505–5541)	6709 (4589–9471)	1.4 (1.3–1.6) <sup>a</sup>	1.9 (1.3–2.7) <sup>a</sup>
Rhinovirus-associated LRTI	426	3074 (2827–3357)	4581 (4105–5097)	10 063 (7420–13 342)	1.5 (1.3–1.7) <sup>a</sup>	3.3 (2.4–4.4) <sup>a</sup>
Adenovirus-associated LRTI	165	1253 (1097–1424)	1563 (1291–1877)	4612 (2890–6983)	1.2 (1.0–1.6) <sup>a</sup>	3.7 (2.3–5.7) <sup>a</sup>
Enterovirus-associated LRTI	102	680 (567–809)	1196 (959–1474)	2935 (1605–4924)	1.8 (1.3–2.3) <sup>a</sup>	4.3 (2.3–7.5) <sup>a</sup>
hMPV-associated LRTI	78	573 (470–692)	816 (622–1050)	1887 (863–3582)	1.4 (1.1–2.0) <sup>a</sup>	3.3 (1.5–6.5) <sup>a</sup>
Influenza-associated LRTI	56	434 (344–539)	503 (354–693)	1677 (724–3304)	1.2 (0.8–1.8)	3.9 (1.6–8.0) <sup>a</sup>
PIV1-associated LRTI	23	139 (91–204)	354 (231–518)	0	2.5 (1.4–4.6) <sup>a</sup>	0
PIV2-associated LRTI	12	107 (65–165)	95 (38–196)	0	0.9 (0.3–2)	0
PIV3-associated LRTI	72	557 (455–675)	693 (516–912)	1258 (4616–2738)	1.2 (0.9–1.8)	2.3 (0.8–5.1)
<i>Pneumococcus</i> -associated LRTI <sup>b</sup>	16	139 (90–204)	109 (47–214)	629 (130–1838)	0.8 (0.3–1.8)	4.5 (0.9–14.7)

Cohen, C., et al. Epidemiology of Acute Lower Respiratory Tract Infection in HIV-Exposed Uninfected Infants. *Pediatrics*. 2016 Apr;137(4).

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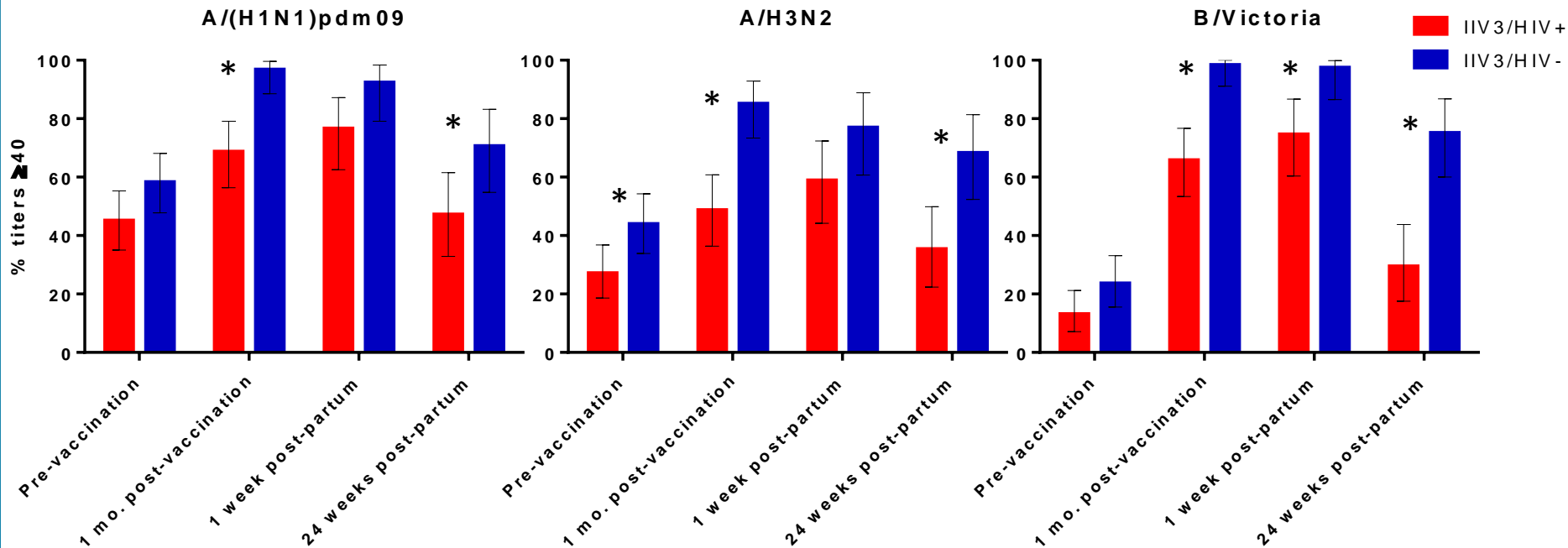
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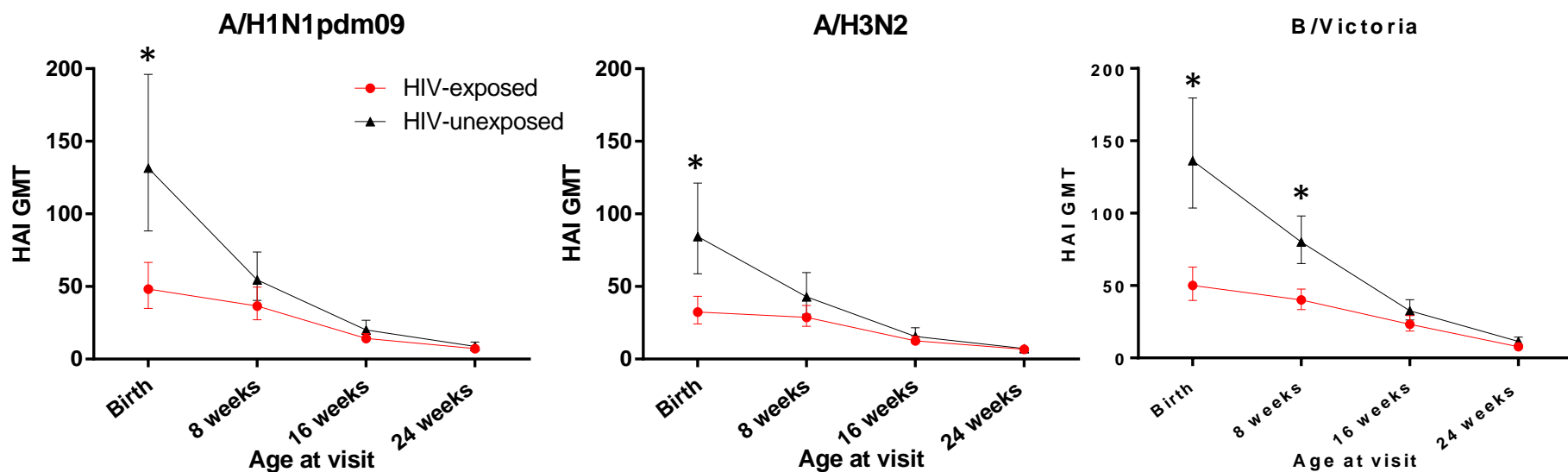
# Immunogenicity in HIV-infected vs. HIV-uninfected women



	A/H1N1			A/H3N2			B/Victoria		
	HIV-	HIV+	p-value	HIV-	HIV+	p-value	HIV-	HIV+	p-value
Seroconversion, %; (95%CI)	70.0	42.9	0.001	63.3	35.7	0.002	91.7	40.0	<0.001

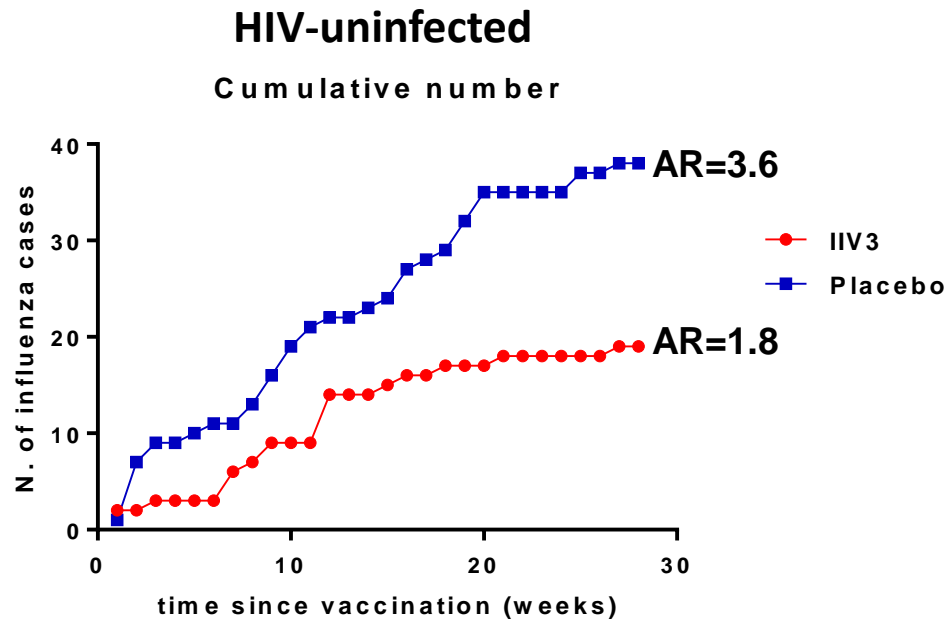


# Transplacental antibody transfer and antibody persistence in HIV-exposed and HIV-unexposed infants

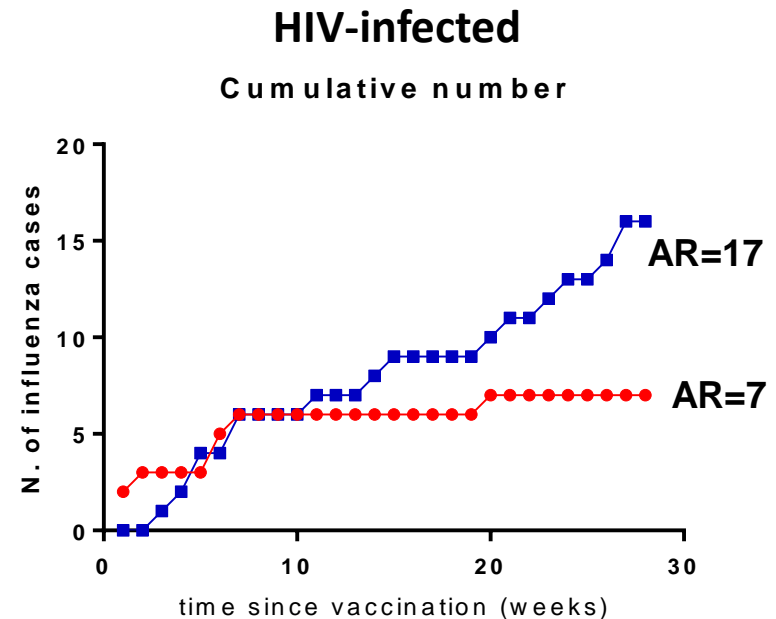


	A/H1N1			A/H3N2			B/Victoria		
	HIV- N=39	HIV+ N=56	p-value	HIV- N=39	HIV+ N=56	p-value	HIV- N=39	HIV+ N=56	p-value
Newborn to maternal HAI ratio; (95%CI)	0.9 (0.7, 1.1)	0.7 (0.5, 0.8)	0.046	0.8 (0.6, 1.1)	0.9 (0.8, 1.1)	0.50	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	0.99

# IIV3 efficacy pregnant women in preventing PCR confirmed influenza until 24 weeks post-partum



**VE (ITT): 50.4% (95%CI: 14.5; 71.2)**  
**VE (PP): 54.4% (95%CI: 19.5; 74.2)**

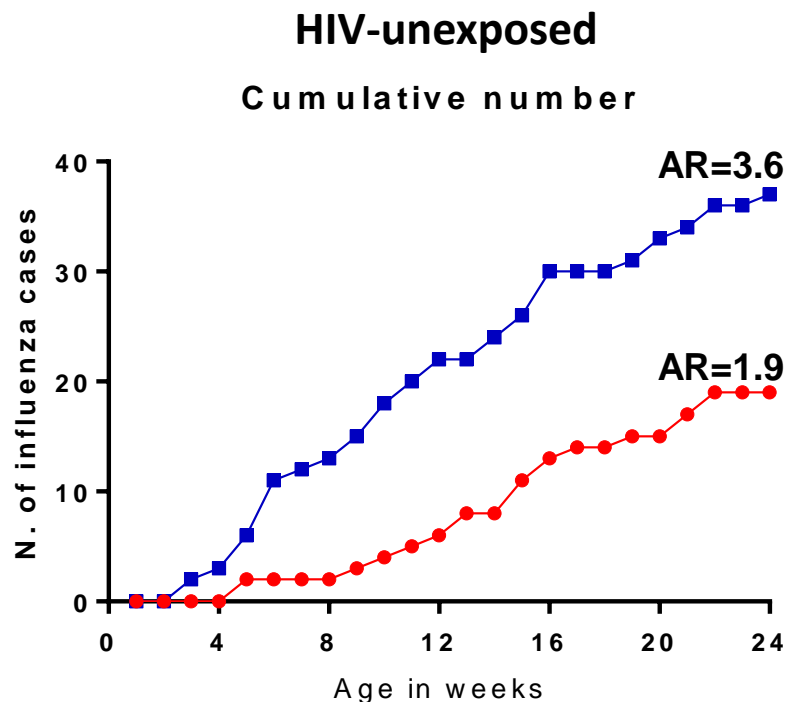


**aVE (ITT): 57.7% (95%CI: 0.2; 82.1)**  
**aVE (PP): 70.6% (95%CI: 23.0; 88.8)**

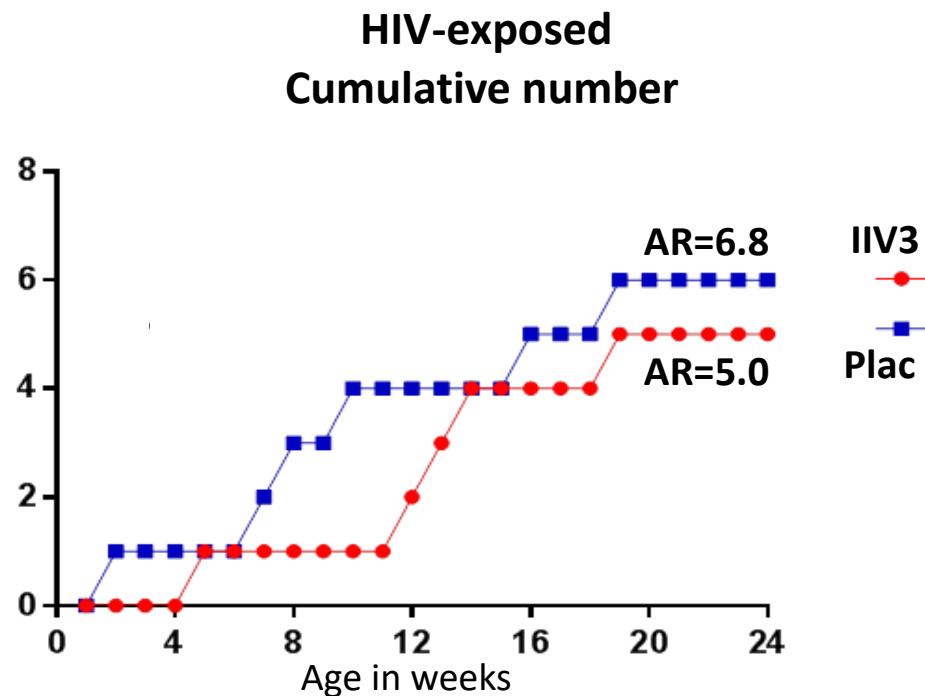
IIV3, inactivated influenza vaccine; VE, vaccine-efficacy

Adapted from: Madhi, S.A. N Engl J Med, 2014. 371(10): p. 918-31.

# IIV3 efficacy against influenza illness in infants up until 24 weeks of age



VE (ITT): 48.8% (95%CI: 11.5; 70.3)  
VE (PP): 45.6% (95%CI: 2.4; 69.7)

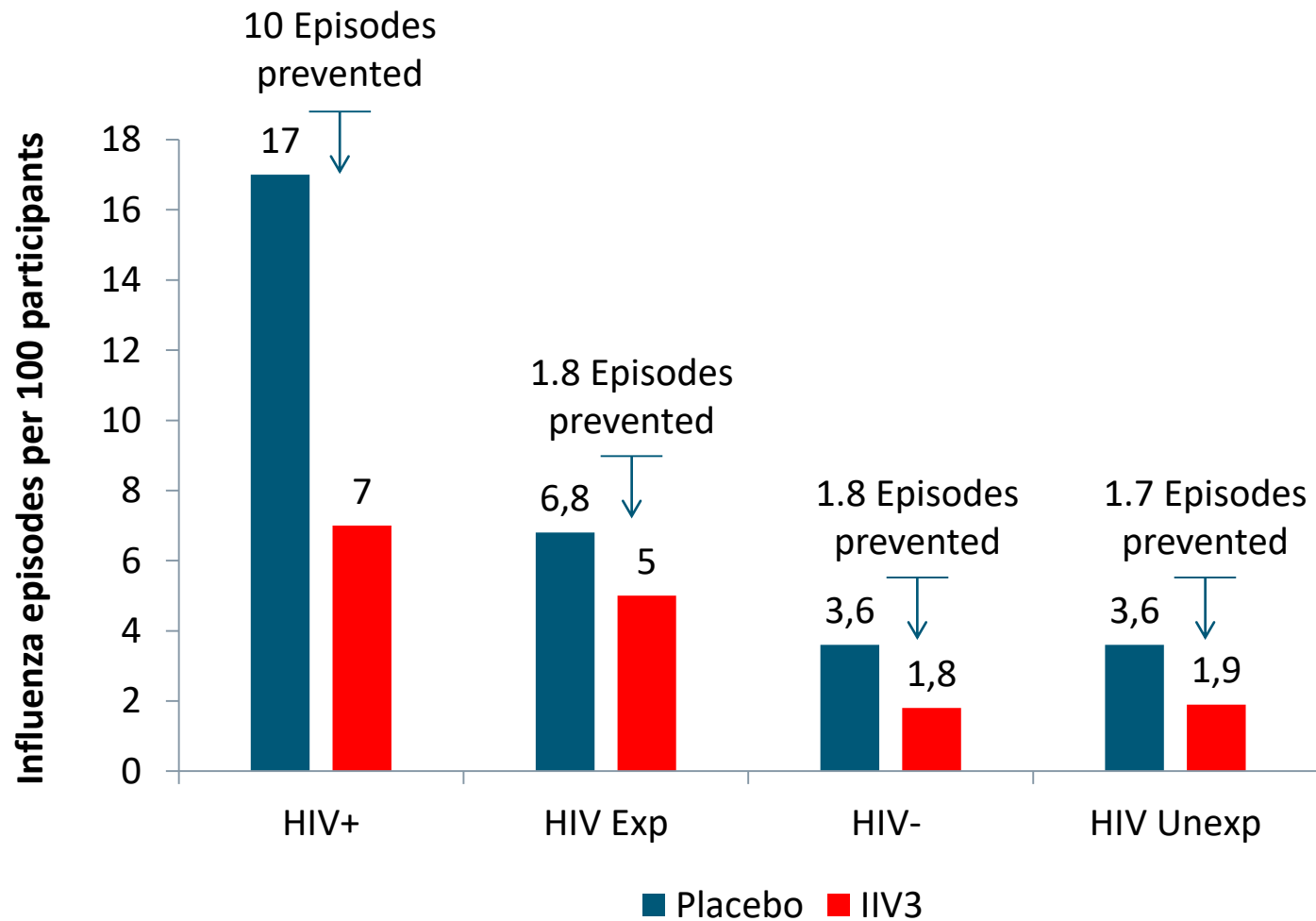


VE (ITT): 26.7% (95%CI: -132.0; 76.8)  
VE (PP): 42.3% (95%CI: -96.9; 83.1)

IIV3, inactivated influenza vaccine; VE, vaccine-efficacy

Adapted from: Madhi, S.A. N Engl J Med, 2014. 371(10): p. 918-31.

# IIV3 efficacy and influenza episodes prevented per 100 persons



**Efficacy 57.7%**

(0.2, 82.1)

**26.7%**

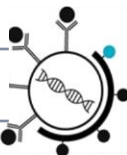
(-132.0, 76.8)

**50.4%**

(14.5, 71.2)

**48.8%**

(11.6, 70.4)



# New Vaccination Strategies

# New Vaccination Strategies

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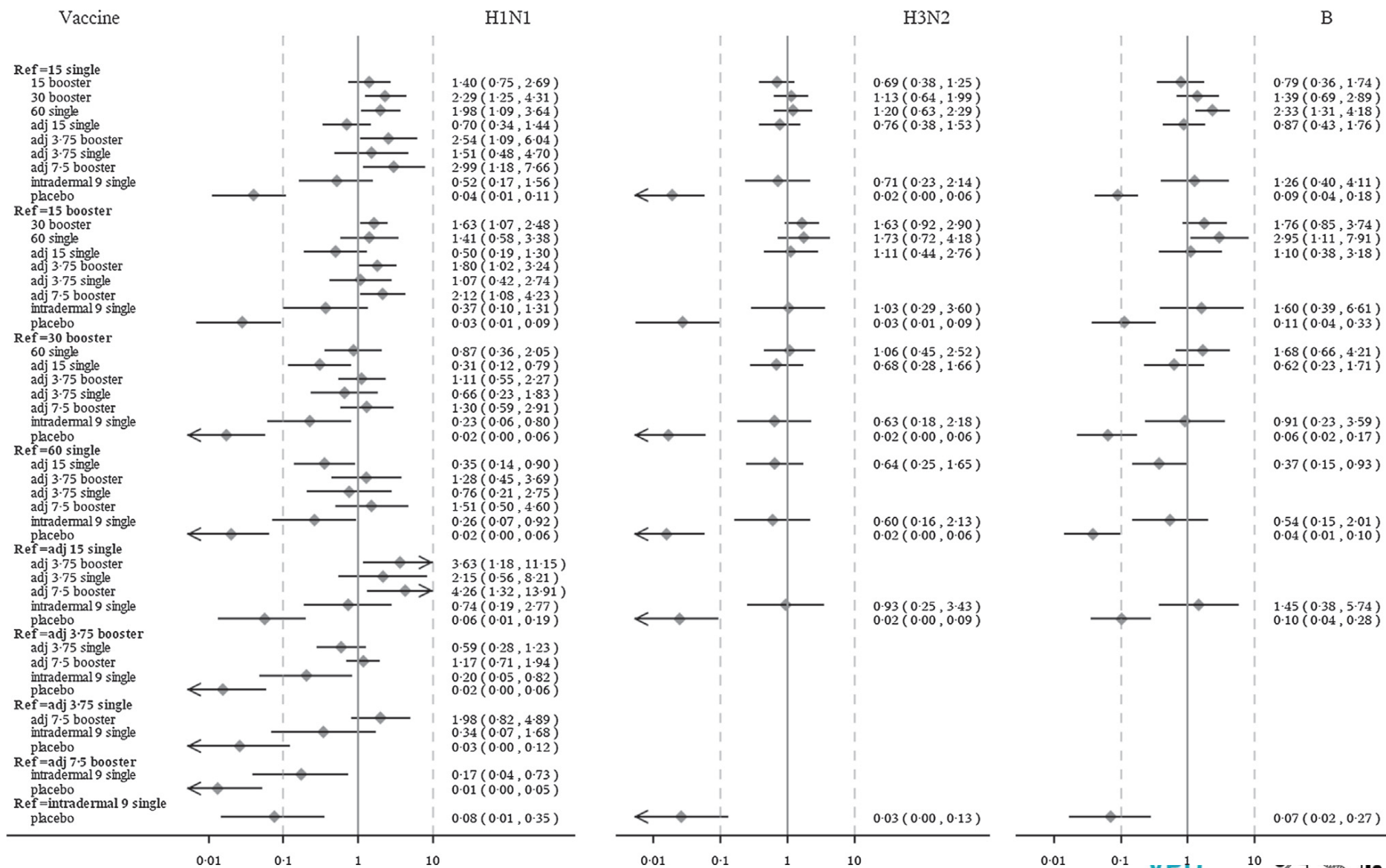
- » New strategies have been evaluated to increase the immune response in HIV-infected individuals:
- » increase the concentration of antigen,
- » multiple dose vaccination,
- » use of vaccine adjuvant,
- » different routes of vaccine delivery  
transcutaneous immunization.

# New Vaccination Strategies

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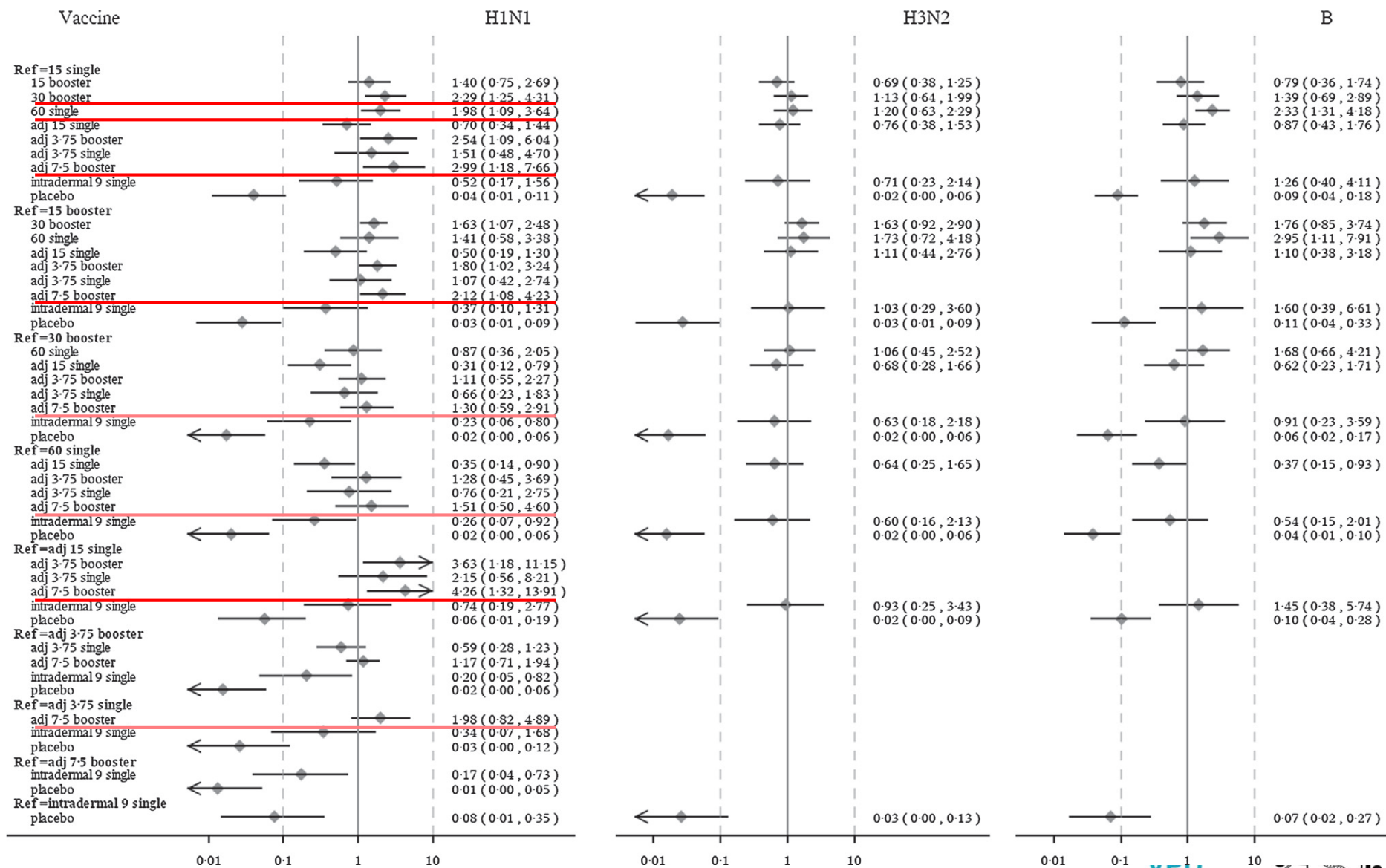
- » **15 Single**
  - » 15 Booster
  - » 30 Booster
  - » 60 Single
  - » 15 Single intradermal
- 
- » Adjuvant 15 Single
  - » Adjuvant 3.75 Single or Booster
  - » Adjuvant 7.5 Booster

# Meta-analysis of vaccination strategies on seroconversion

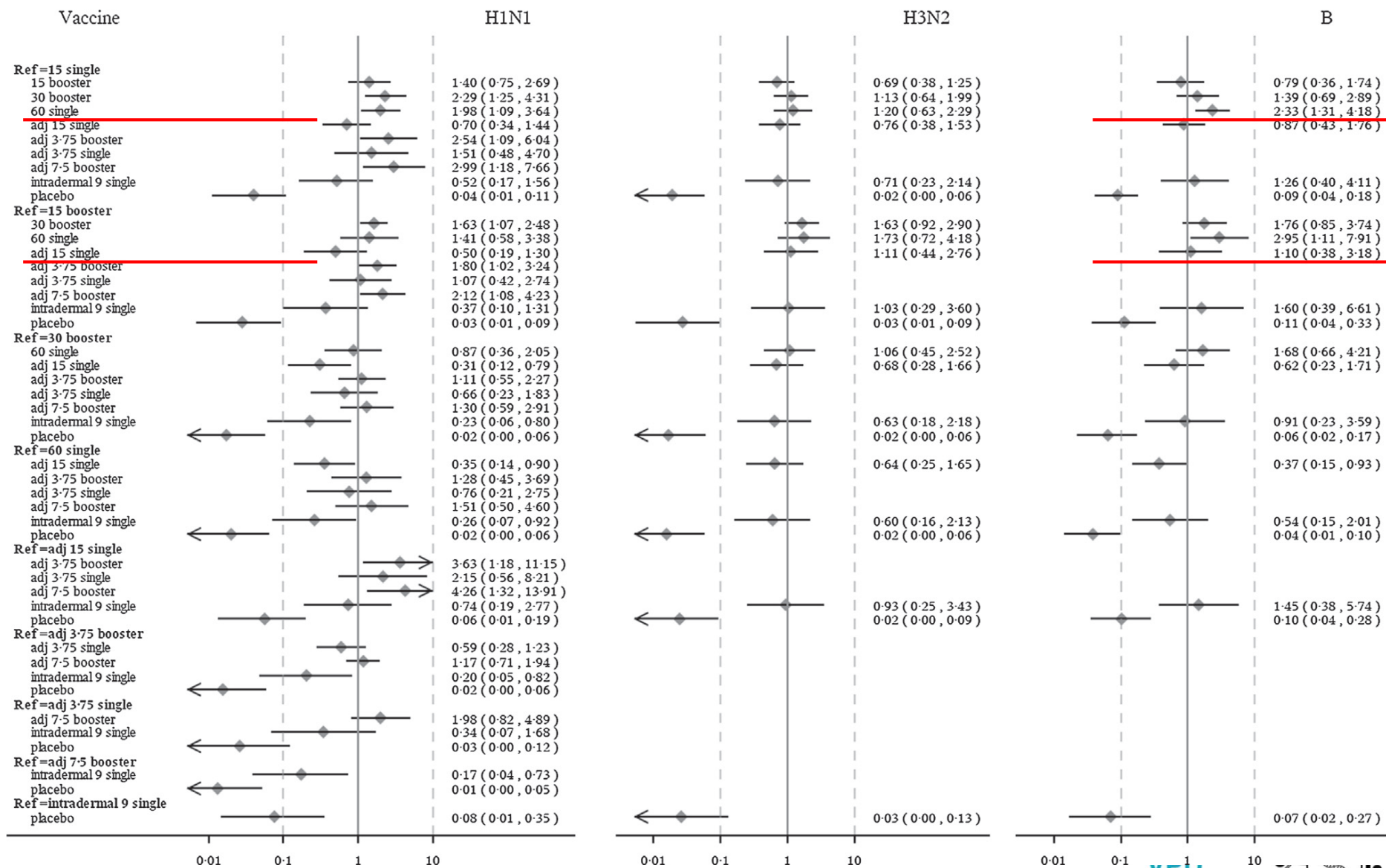




# Meta-analysis of vaccination strategies on seroconversion



# Meta-analysis of vaccination strategies on seroconversion



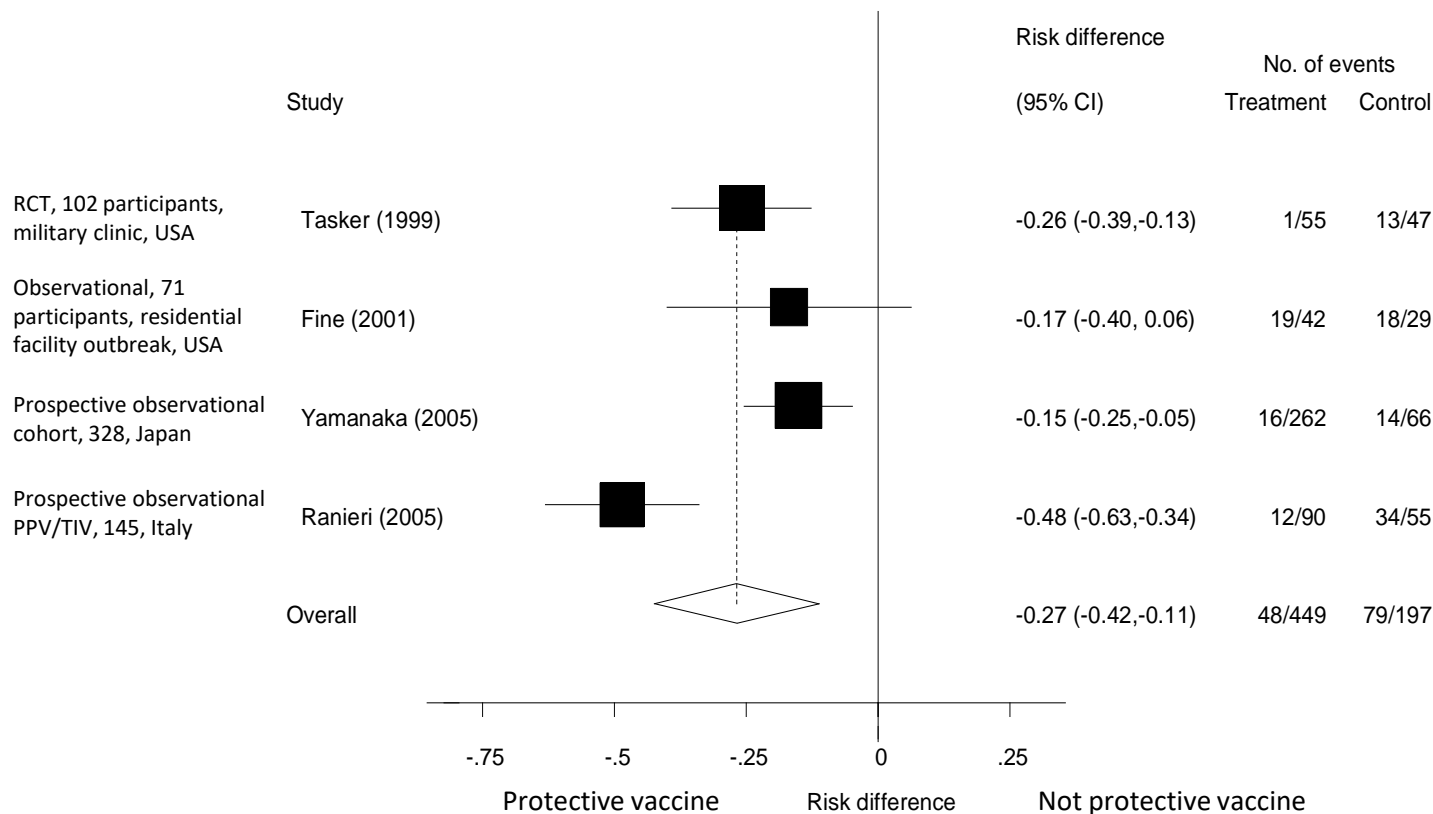
# Conclusions

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- » High influenza burden in the HIV-infected population.
- » Influenza vaccines induce a T cell-dependent response (humoral immunity). The depletion of T-helper cells during HIV infection leading to inadequate T-cell signalling can cause vaccination failure.
- » Influenza vaccines are less immunogenic in HIV-infected compared to HIV-uninfected individuals.
- » Influenza vaccines are efficacious in preventing confirmed influenza illness in HIV-infected adults.
- » HIV infection is also associated with deficiencies in cell-mediated immunity.
- » Influenza vaccination is safe HIV-infected individuals.

# THANK YOU

# Meta-analysis of Effectiveness of Influenza Vaccine in HIV-infected Adults (N=646)



Heterogeneity chi-squared = 14.23 (d.f. = 3), p = 0.003, I<sup>2</sup> = 76.8%  
 Test of RD=0: z = 2.28, p = 0.004

From: Atashili J et al. BMC Infect Dis, 2006, 6 (138): 1-6