

# Maternal Influenza Vaccination An Update from Africa

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# Influenza infection during pregnancy

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- » Pregnant women have **higher morbidity** from influenza compared with non-pregnant women.
- » Evidence from seasonal epidemics, previous pandemics and the A/H1N1pdm09 demonstrates that pregnant women (and their offspring) are at increased risk of **influenza related complications**.
  - > USA: A/H1N1pdm09 infected pregnant women had 6-fold higher mortality rate than non-pregnant women.
  - > South Africa: pregnancy or puerperium was a risk factor among A/H1N1pdm09 deaths. 25/91 deaths (28%) in pregnant women.

Neuzil et al., Am J Epidemiol 1998.

Van Kerkhove et al., PLoS Med 2011; Archer et al., Euro Surv 2009; Louie et al., N Engl J Med 2010.

# Effects of influenza infection during pregnancy

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## » Increased risk of fetal loss<sup>1</sup>:

- > Norway: risk of fetal death increased among women with a clinical diagnosis of A/H1N1pdm09 (AHR 1.91; 95% CI: 1.1 to 3.4)

## » Increased risk of pre-term births<sup>2</sup>:

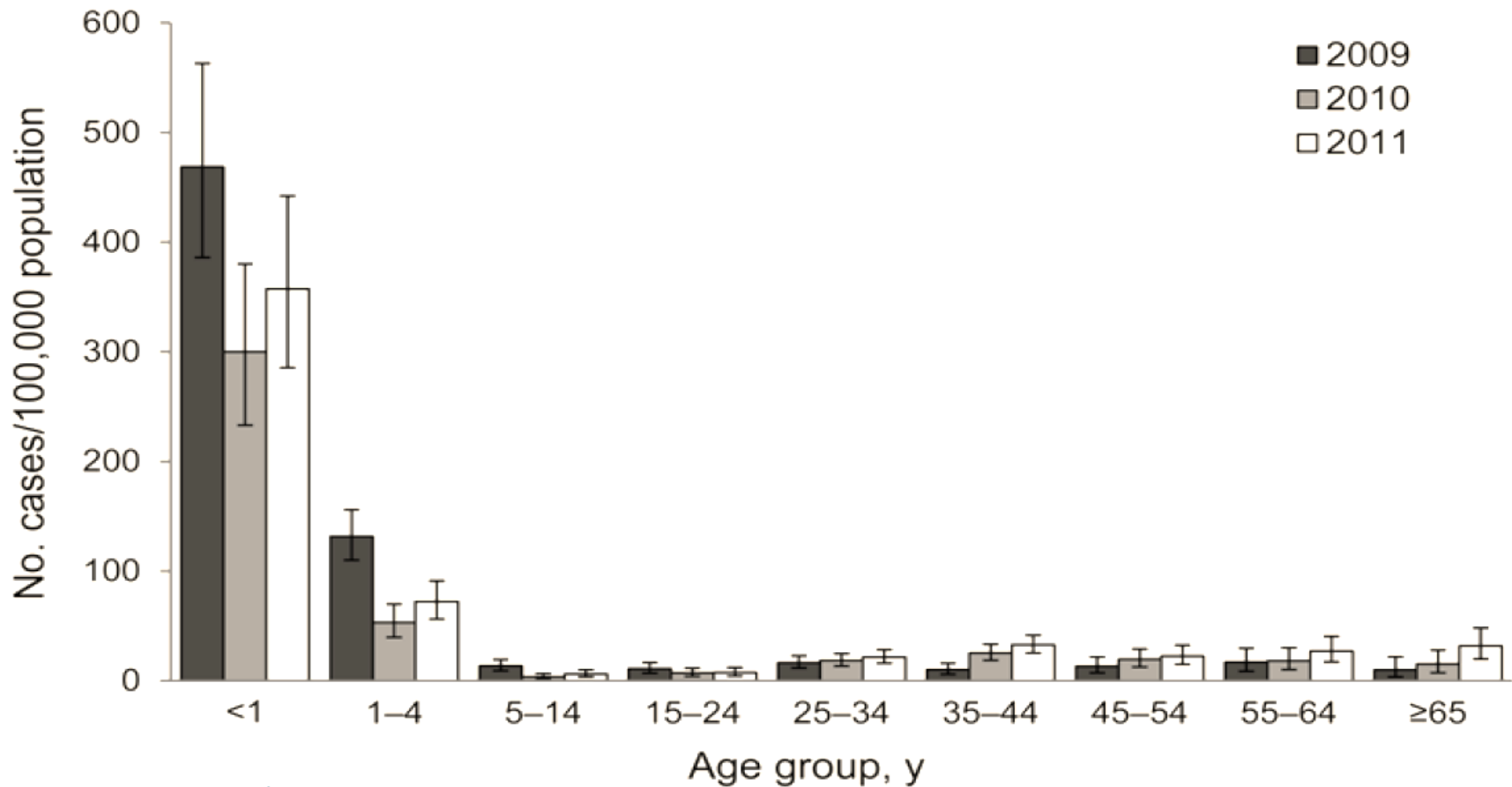
- > UK: newborns of A/H1N1pdm09-infected women were more likely to be born prematurely than were infants of comparison women (aOR 4.0; 95% CI: 2.7 to 5.9)
- > USA: women who delivered while hospitalized with A/H1N1pdm09 63.6% delivered pre-term infants vs. to 12.3% of all USA births

## » Low-birth weight<sup>3</sup>:

- > Nova Scotia: 1990-2002 infants born to women hospitalized for ARI were more likely to be SGA (RR 1.66) and with LBW ( $p < 0.009$ )
- > USA: infants of mothers hospitalized with A/H1N1pdm09 born after discharge, 25% were SGA (compared to 10% of all US births)

<sup>1</sup>Haberg et al., N Engl J Med 2013; <sup>2</sup>Pierce et al., BMJ 2011; MMWR 2011; <sup>3</sup>Dodds et al., CMAJ 2007; MMWR 2011

# Incidence of confirmed influenza associated hospitalization in Soweto, South Africa



Cohen et al., Emerg Infect Dis 2013.

# Influenza infection in HIV-infected individuals

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- » HIV infection is associated with **prolonged duration** and **increased severity** of influenza illness<sup>1</sup>.
- » In South Africa<sup>2</sup>:
  - 91 deaths during A/H1N1pdm09 - 32 HIV status was known  
17 (53%) HIV-infected
- » Women who are pregnant and HIV infected lie at the intersection of 2 high-risk conditions that, in combination, may pose particular vulnerability to influenza infection.

<sup>1</sup>Couch et al., Clin Infect Dis 1999; Safrin et al., Chest 1990; Radwan et al., Clin Infect Dis, 2000; Liu et al., Rev Med Virol 2013; Neuzil et al., JAMA 1999; Kunisaki et al., Lancet Infect Dis 2009

<sup>2</sup>Archer et al., Euro Surveill 2009; Moodley et al., SAMJ 2011

# MatFlu study South Africa

## Methods

- » Double-blind, randomized, placebo-controlled trials in Soweto in 2011 and 2012.
- » Study participants: confirmed HIV-uninfected/infected pregnant women (20-36 weeks of gestational age).
- » Study products: WHO IIV3 recommended for Southern Hemisphere for the 2011 and 2012 (H1N1 A/California, H3N2 A/Victoria and B/Brisbane) and saline solution as placebo.



- » Participants followed up weekly until 24 weeks post-partum/of age for acute respiratory illness or hospitalization for acute cardio-pulmonary illness.
- » At the time of illness episodes, respiratory specimens collected for influenza virus testing by real-time PCR.
- » Nested immunogenicity cohort.

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# Baseline demographics of HIV-uninfected women

Efficacy cohort	IIV3 N=1062	Placebo N=1054
Mean age (SD); years	26.4 (5.3)	25.9 (5.3)
Median BMI (IQR)	28.0 (24.6, 32.1)	27.4 (24.1, 31.6)
Mean Gestational Age (SD); weeks	26.7 (4.4)	26.9 (4.4)
Median gravidity (IQR)	2.0 (0.0, 3.0)	2.0 (0.0, 3.0)
Median parity (IQR)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)
Immunogenicity cohort	N=188	N=188
Mean age (SD); years	26.0 (5.3)	25.6 (5.3)
Median BMI (IQR)	28.3 (25.2, 33.3)	27.5 (24.1, 31.2)
Mean Gestational Age (SD); weeks	26.7 (4.3)	26.8 (4.4)
Median gravidity (IQR)	2.0 (1.0, 2.0)	2.0 (1.0, 3.0)
Median parity (IQR)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)
Mean days after vacc of 1 month post-vacc visit (SD)	29.4 (2.1)	29.5 (2.1)
Mean days after vacc of delivery visit (SD)	84.4 (33.0)	92.1 (37.3)
Mean days after vacc of 24 weeks post-partum visit (SD)	243.9 (38.1)	248.9 (39.3)

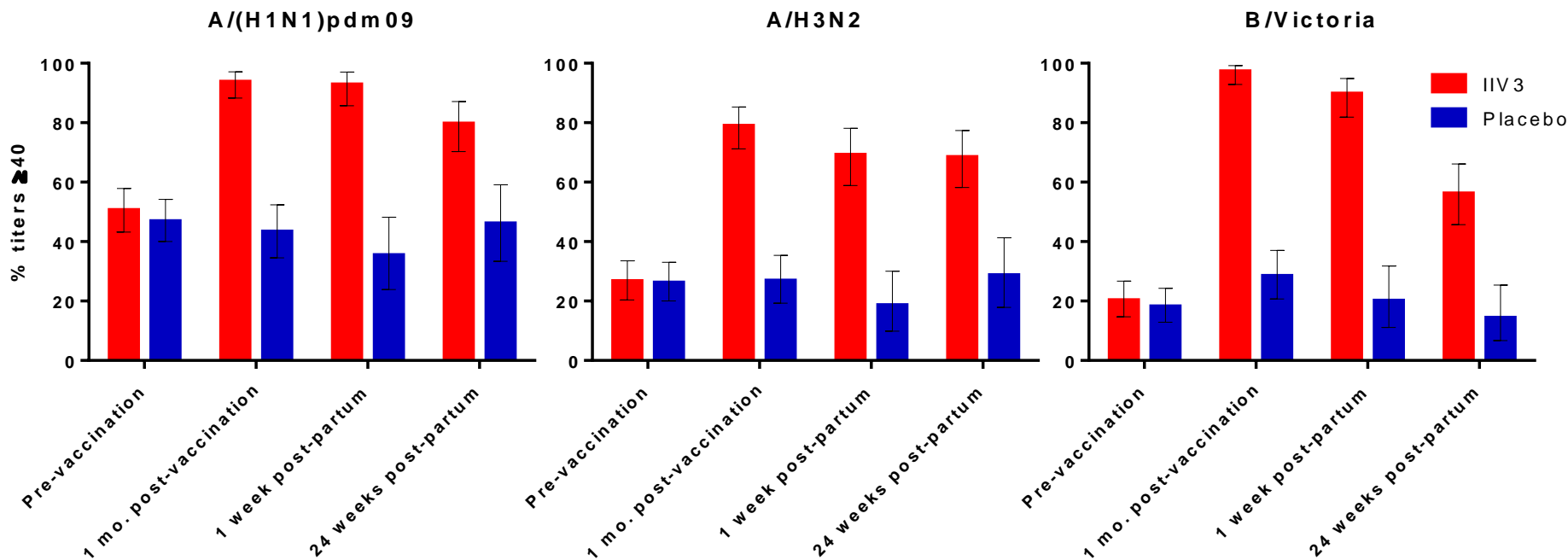
# Demographic and clinical characteristics of HIV-infected women

Maternal characteristics	IIV3 N=100	Placebo N=94
Mean age (SD); years	27.2* (4.9)	29.2* (5.1)
Mean Gestational Age (SD); weeks	27.6 (3.9)	26.9 (3.7)
Mean BMI (SD)	29.2 (5.0)	28.3 (5.7)
Median gravidity (IQR)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
Median parity (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Median CD4+ T-lymphocyte count at enrolment; cells per microliter (IQR)	410.0 (284.0, 572.0)	379.0 (245.0, 550.0)
Median HIV-1 viral load at enrolment; copies per milliliter (IQR)	1679.0 (118.5, 15906.5)	399.0 (39.0, 9990.0)
Number on HAART (%)	22* (22.0)	38* (40.4)
Number on PMTCT specific ART (%)	54* (54.0)	32* (34.0)
Number on HAART at delivery (%)	33 (33.0)	44 (46.8)
Number on PMTCT specific ART at delivery (%)	52* (52.0)	35* (37.2)



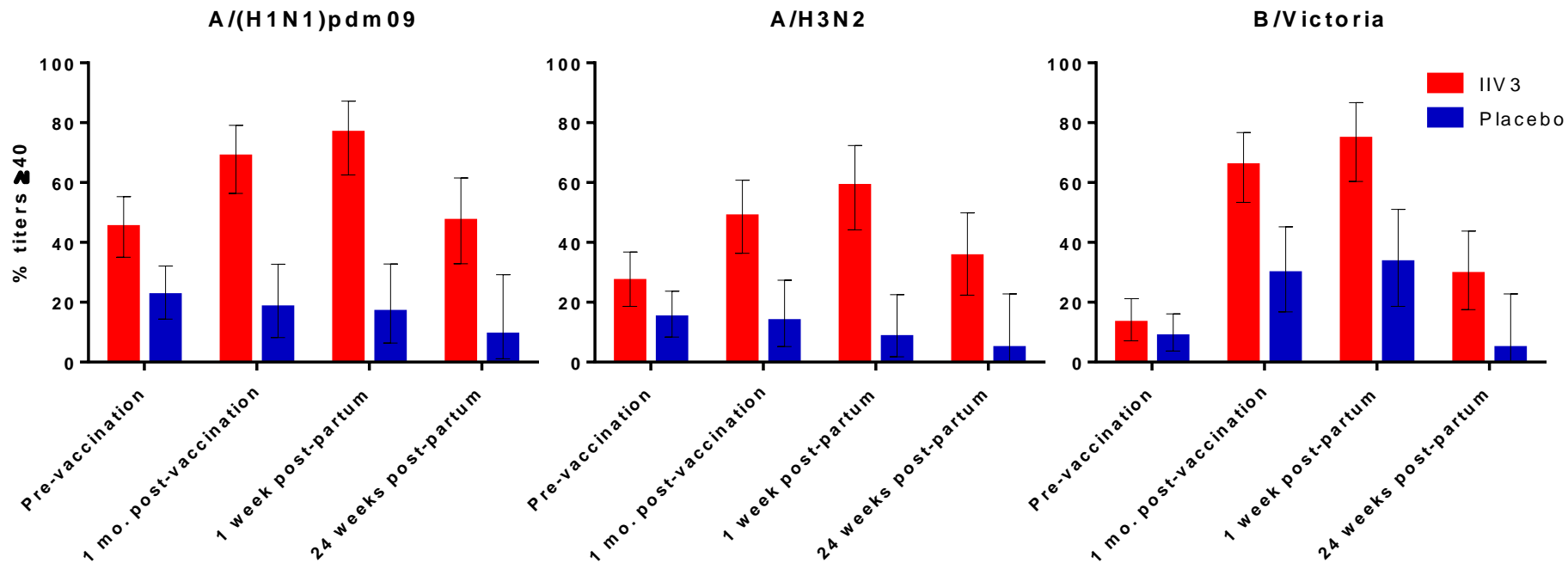


# Immunogenicity in HIV-uninfected pregnant women - Seroprotection levels



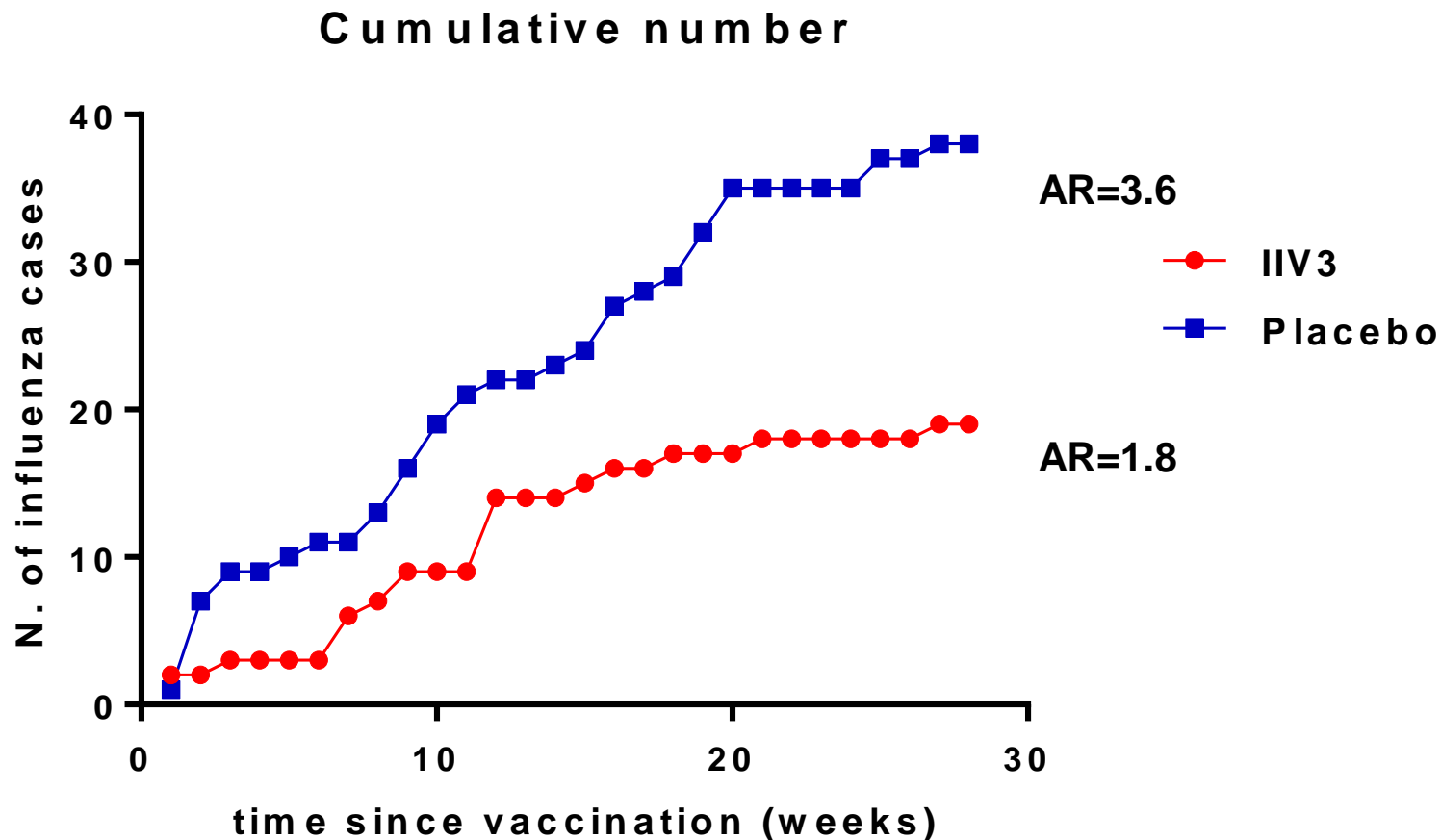
	A/(H1N1)			A/H3N2			B/Victoria		
	IIV3 N=142	Placebo N=148	p-value	IIV3 N=142	Placebo N=148	p-value	IIV3 N=142	Placebo N=148	p-value
<b>Seroconversion %; (95%CI)</b>	72.5 (64.4, 79.7)	8.1 (4.3, 13.7)	<0.001	64.8 (56.3, 72.6)	2.7 (0.7, 6.8)	<0.001	92.3 (86.6, 96.1)	2.0 (0.4, 5.8)	<0.001

# Immunogenicity in HIV-infected pregnant women - Seroprotection levels



	A/(H1N1)			A/H3N2			B/Victoria		
	IIV3 N=70	Placebo N=55	p-value	IIV3 N=70	Placebo N=55	p-value	IIV3 N=70	Placebo N=55	p-value
<b>Seroconversion %; (95%CI)</b>	42.9 (31.1, 55.3)	5.5 (1.1, 15.1)	<0.001	35.7 (24.6, 48.1)	3.6 (0.4, 12.5)	<0.001	40.0 (28.5, 52.4)	16.4 (7.8, 28.8)	0.004

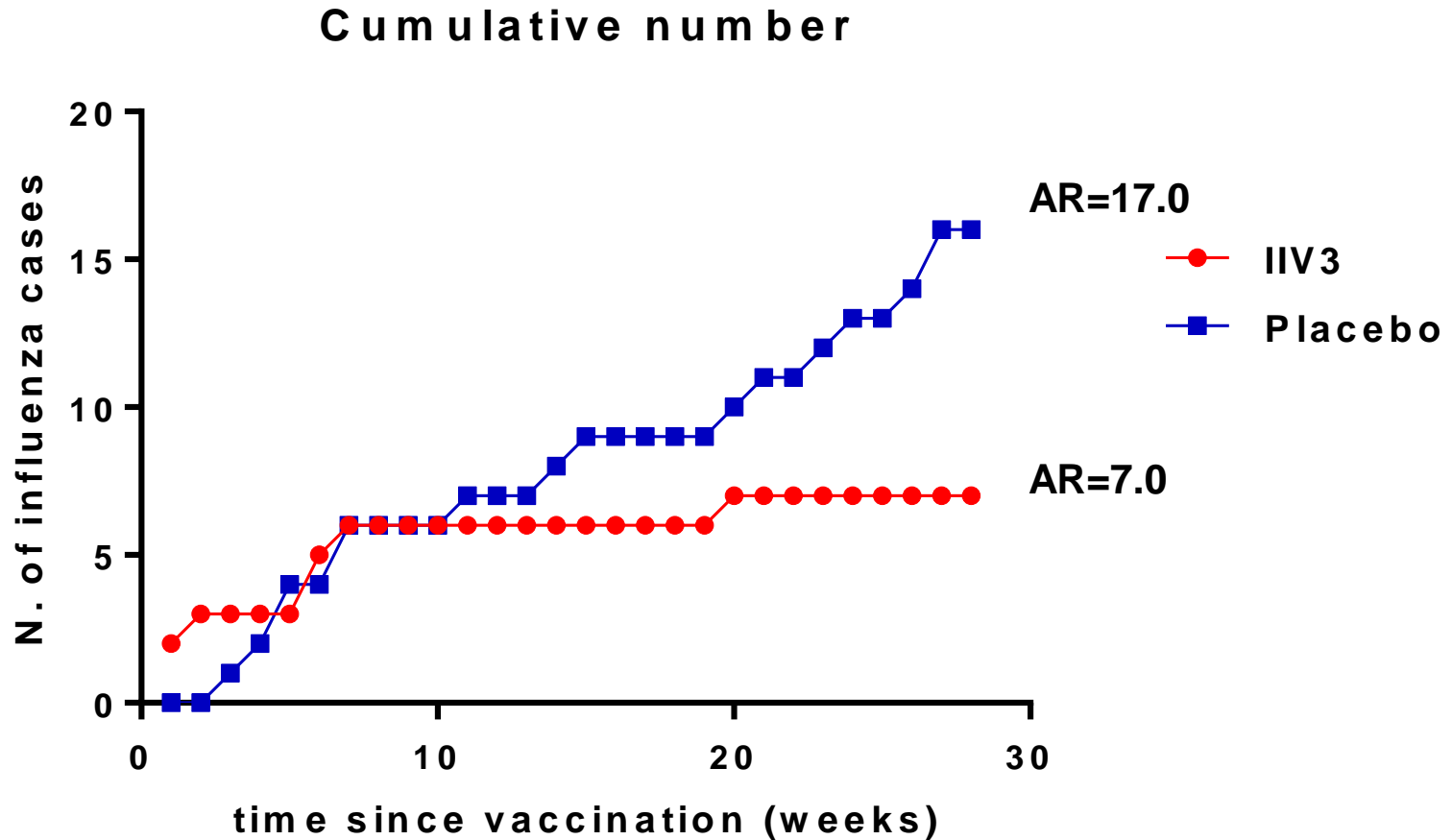
# IIV3 efficacy in HIV-uninfected pregnant women in preventing PCR confirmed influenza until 24 wks post-partum



**VE (ITT): 50.4% (95%CI: 14.5; 71.2)**

**VE (PP): 54.4% (95%CI: 19.5; 74.2)**

# IIV3 efficacy in HIV-infected pregnant women in preventing PCR confirmed influenza until 24 wks post-partum



**aVE (ITT): 57.7% (95%CI: 0.2; 82.1)**

**aVE (PP): 70.6% (95%CI: 23.0; 88.8)**

# Fetal and newborn outcomes

## HIV-uninfected cohort

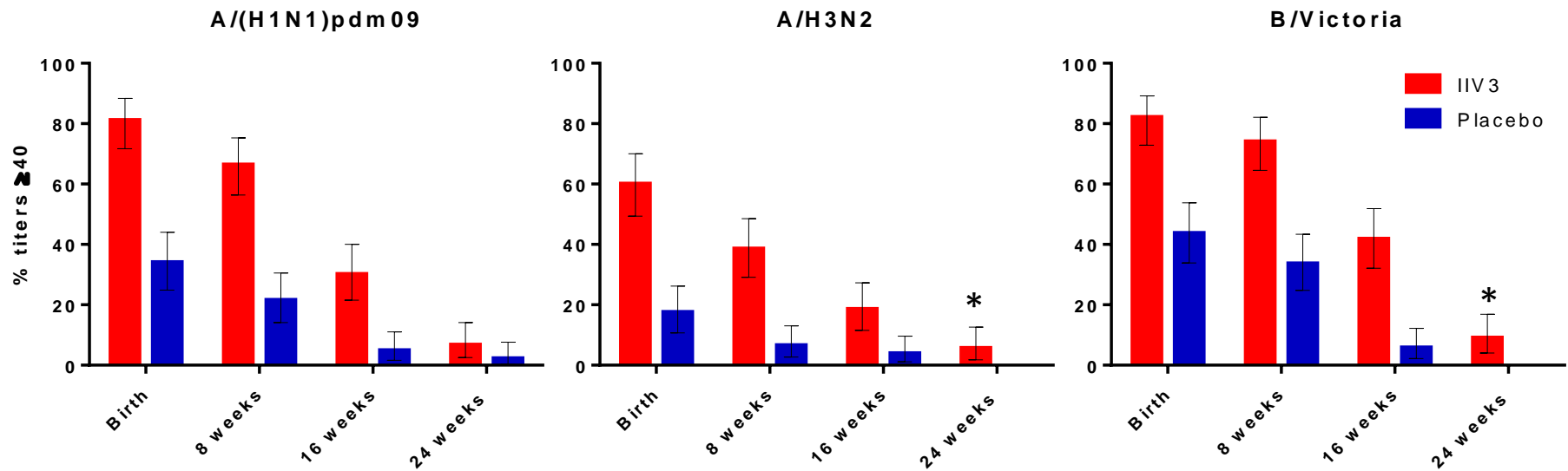
Number of fetal outcomes known	IIV3 N=1043	Placebo N=1037
Miscarriages (<28 weeks GA),n (%)	3 (0.3)	5 (0.5)
Stillbirths (≥28 weeks GA), n (%)	15 (1.4)	9 (0.9)
Live born viable, n (%)	1025 (98.3)	1023 (98.7)
Preterm birth <37 <sup>0/7</sup> , n (%)	108 (10.5)	96 (9.4)
Median birth weight (range); kg	3.1 (0.5, 4.6)	3.1 (0.4, 4.8)
Low birth weight (<2500gr), n (%)	132 (12.9)	122 (12.0)
Admission post-delivery (%)	71 (6.9)	71 (6.9)

# Fetal and newborn outcomes

## HIV-infected cohort

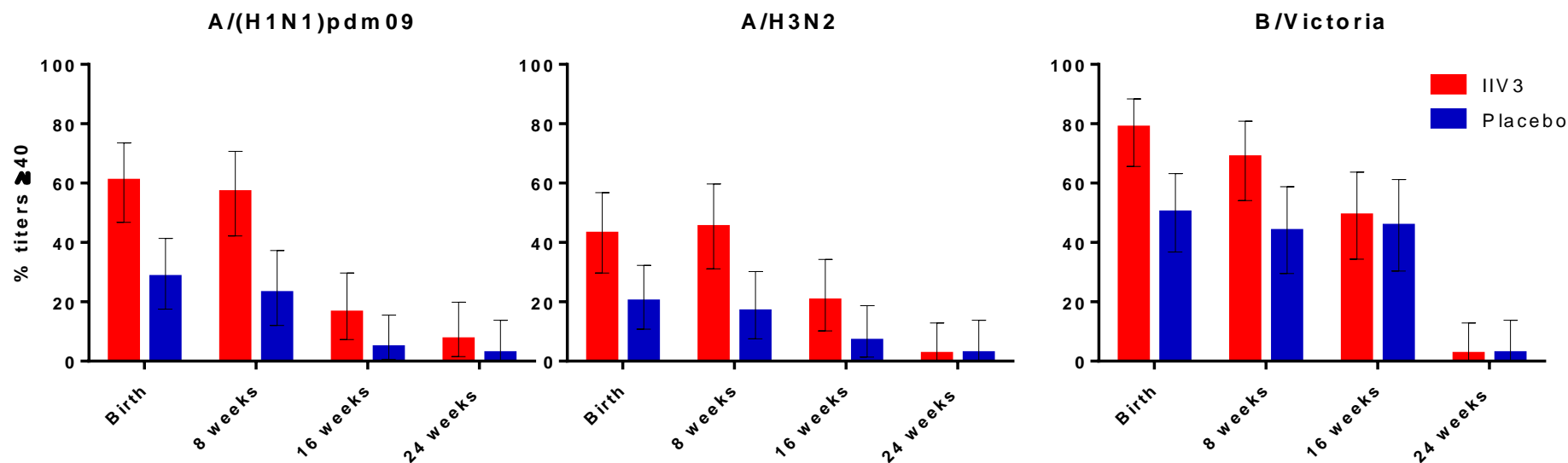
Number of fetal outcomes known	IIV3 N=100	Placebo N=94
Live born viable, n (%)	100 (100.0)	88 (100.0)
Preterm birth <37 <sup>0/7</sup> , n (%)	13 (13.0)	13 (14.8)
Median birth weight (range); kg	2.9 (0.8, 4.3)	3.0 (1.9, 4.0)
Low birth weight (<2500gr), n (%)	14 (14.0)	15 (17.2)
Normal vaginal deliveries, n (%)	58 (58.0)	53 (60.2)
Admission post-delivery (%)	6 (6.0)	3 (3.4)

# Immunogenicity in HIV-unexposed Infants-seroprotection levels



	A/(H1N1)			A/H3N2			B/Victoria		
	IIV3 N=95	Placebo N=103	p-value	IIV3 N=95	Placebo N=103	p-value	IIV3 N=95	Placebo N=103	p-value
Newborn to maternal HAI ratio; (95%CI)	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)	0.78	0.7 (0.6, 0.9)	0.7 (0.6, 0.8)	0.49	0.8 (0.7, 0.9)	1.0 (0.9, 1.2)	0.04

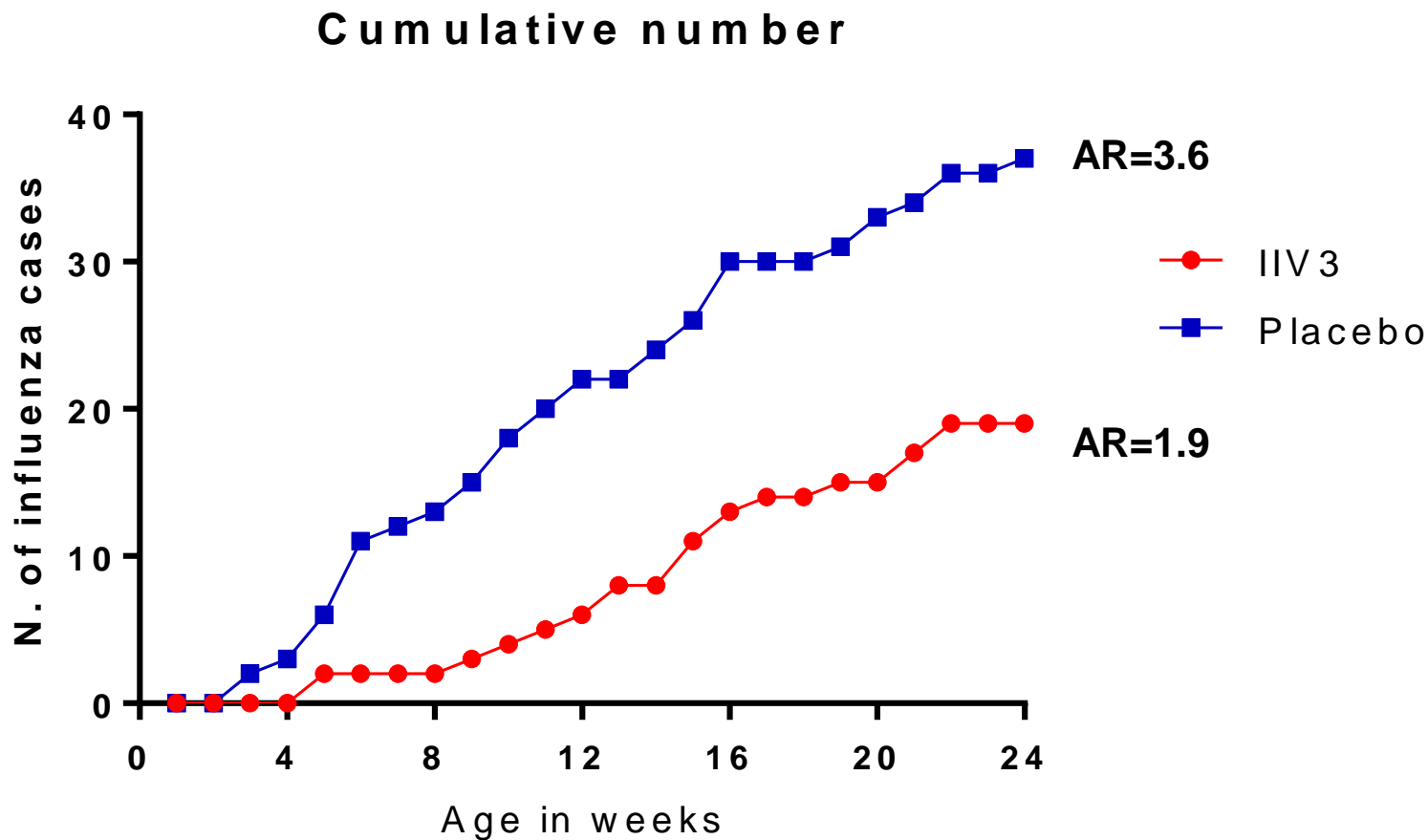
# Immunogenicity in HIV-exposed Infants- seroprotection levels



	A/(H1N1)			A/H3N2			B/Victoria		
	IIV3 N=56	Placebo N=60	p-value	IIV3 N=56	Placebo N=60	p-value	IIV3 N=56	Placebo N=60	p-value
Newborn to maternal HAI ratio; (95%CI)	0.7 (0.5, 0.8)	0.9 (0.7, 1.2)	0.05	0.9 (0.8, 1.1)	1.4 (1.1, 1.7)	0.01	1.0 (0.8, 1.2)	1.2 (1.0, 1.6)	0.11

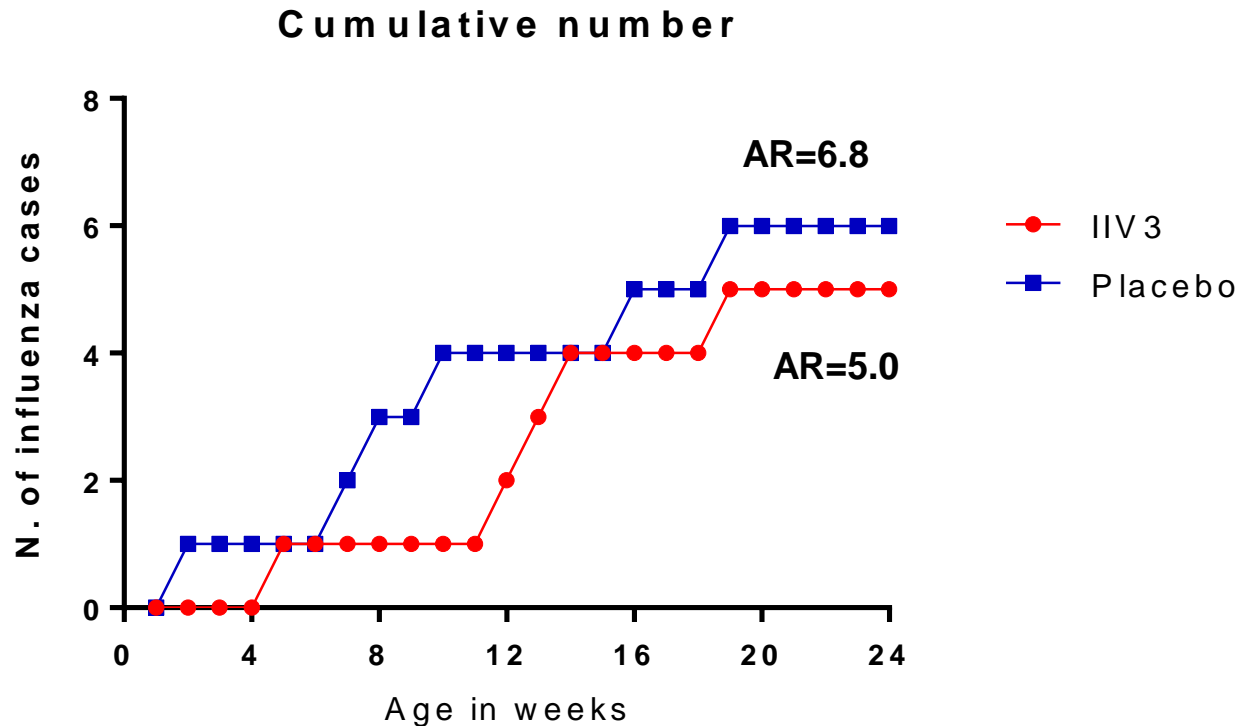


# IIV3 efficacy in HIV-uninfected pregnant women in preventing PCR confirmed influenza in their infants until 24 wks of age



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

# IIV3 efficacy in HIV-infected pregnant women in preventing PCR confirmed influenza in their infants until 24 wks of age



VE (ITT): 26.7% (95%CI: -132.0; 76.8)

VE (PP): 42.3% (95%CI: -96.9; 83.1)

**50% of mothers of infants with confirmed influenza illness also had confirmed influenza at the same time**



# Conclusion: HIV-uninfected Cohort

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- » IIV3 vaccination of HIV-uninfected pregnant women induced good humoral immune responses.
- » IIV3 partially efficacious (PP: 54%) in preventing PCR-confirmed influenza illness in pregnant HIV-uninfected women up until 24 weeks post-partum.
- » IIV3 partially efficacious (PP: 46%) in preventing PCR-confirmed influenza illness in infants of HIV-uninfected women up until 24 weeks of age.

# Conclusion: HIV-infected Cohort

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- » IIV3 less immunogenic in HIV-infected compared to HIV-uninfected women.
- » Higher attack rate of PCR-CI in HIV-infected (17%) than HIV-uninfected (3.6%) placebo recipients.
- » IIV3 efficacious (PP: 70%) in preventing PCR-confirmed influenza illness in pregnant HIV-infected women up until 24 weeks post-partum.
- » High prevalence of concurrent influenza illness in mothers of HIV-exposed infants with PCR-CI.
- » Efficacy in protecting HIV-exposed infants to be established, however, similar point-estimate compared to HIV-unexposed infants.

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