Safety and Immunogenicity of Tetanus-Diphtheria-Acellular Pertussis Vaccine (Tdap) During Pregnancy

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for the Canadian Tdap
Pregnancy Investigator Group

Disclosures

- **Research Funding**
  - Government
    - CIHR
    - Public Health Agency of Canada
  - Institution
    - IWK Health Centre
  - Industry
    - GlaxoSmithKline
    - Sanofi Pasteur
    - Pfizer
    - Merck
    - PREVENT

- **Consultant/Advisory Board/Committee**
  - Government
    - NACI Influenza Working Group
    - CDC Pertussis Working Group
    - NS, PEI, and NB Depts of Health
  - NGO
    - PATH
    - Gates Foundation
  - Industry
    - PREVENT
    - ImmunoVaccine
    - GlaxoSmithKline
    - Sanofi Pasteur
    - VBI
    - Folia

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Background

- Due to shifting epidemiology, pertussis incidence continues to increase in infants < 6 months of age who are too young to be vaccinated.
- Most deaths from pertussis occur in infants who have not begun their primary immunization series.
- Active immunization, even with a birth dose, would still result in a window of susceptibility.

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Background

- Maternal immunization provides the opportunity to provide passive protection to the high risk newborn until protection through active immunization can be achieved.
- Studies in the UK have demonstrated that maternal immunization is an effective strategy.
- We undertook a RCT to assess the safety and immunogenicity of Tdap during pregnancy and the effect of passive antibody on the active immune response of the newborn infant.

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Purpose of the study

- To determine if immunization in the late third trimester of pregnancy is safe, and provides passive antibody to the infant sufficient to protect the infant in the critical neonatal period, without suppressing the infant's immune response to active immunization

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Methods

- Study Design
  - Double-blind randomized clinical trial using Tdap and Td vaccine (Sanofi Pasteur). Participants randomized in a 1:1 ratio
- Study Subjects
  - Healthy women 18-45 years of age in late third trimester of pregnancy (≥ 34-<35 weeks)
    - Safety pause after the first 50 women/infants with interim analysis by Data Monitoring and Safety Board

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Methods –Assessment: Women

- Vaccine associated adverse events for 7 days post immunization
- Medically significant and serious adverse events for duration of study
- Serum IgG against pertussis antigens (PT, FHA, PRN, FIM), diphtheria and tetanus toxoids
  - pre-vaccination, postpartum, 2, 4, 6, 7 and 12 months
- Serum IgA against pertussis antigens
  - pre-vaccination, postpartum, 7 and 12 months
- Breast milk IgA against pertussis antigens
  - Post partum, 2, 4, 6, 7 months of age

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Methods –Assessment: Infants

- Serum IgG against pertussis antigens (PT, FHA, PRN, FIM), Hib, diphtheria and tetanus before and following DTaP-IPV-Hib (Sanofi Pasteur)
  - Cord blood, 2, 4, 6, 7, 12, 13 months
- Serum IgA against pertussis antigens
  - Cord blood, 2, 7, 12, 13 months
- Growth measurements (head circumference, length, weight)
  - birth, 2, 4, 6, 7, 12, 13, 18 months
- Bayley-III® developmental screening
  - 18 months

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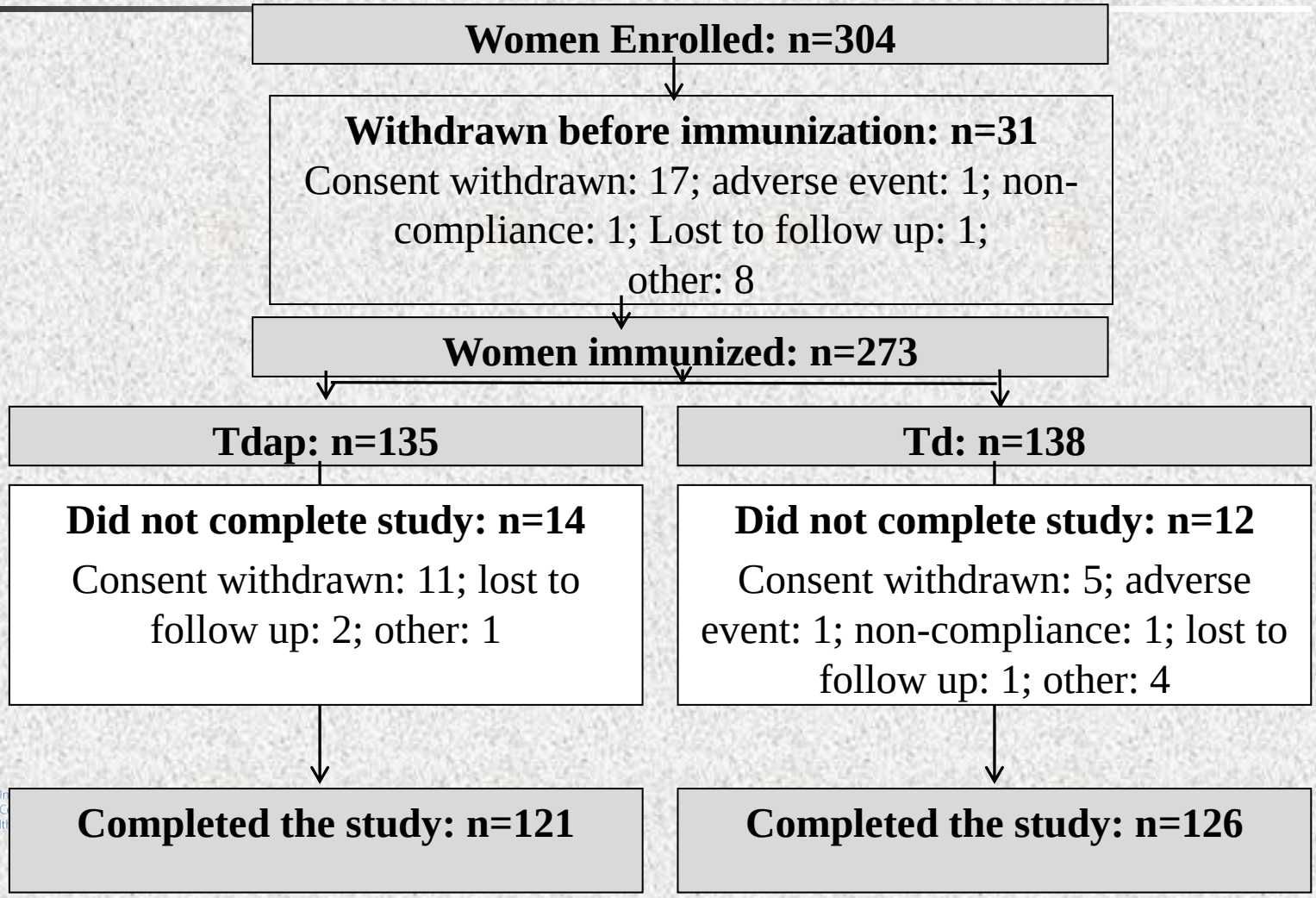
Participant Flow: Women



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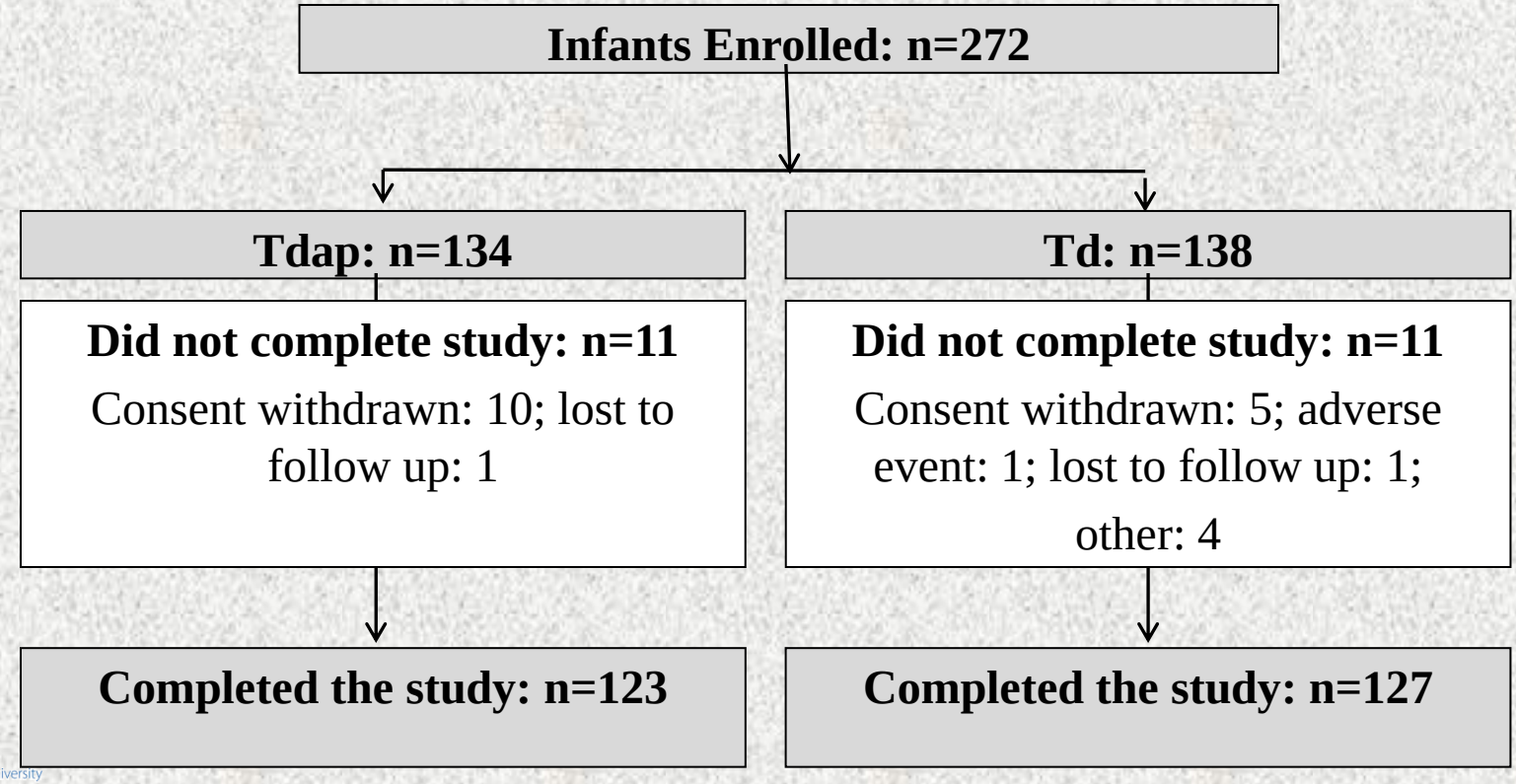
Participant Flow: Infants



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Results: Demographics: Women

- Mean age 31.2 years (range 20-45 years)
  - Td 31.43 years (20-44 years)
  - Tdap 30.96 years (20-45)
- Ethnicity
  - Td 86.96% Caucasian
  - Tdap 79.26% Caucasian
- Gravida/Parity
  - Td G 2.21 (1-10), P 0.64 (0-5)
  - Tdap G 2.04 (1-7), P 0.47 (0-3)

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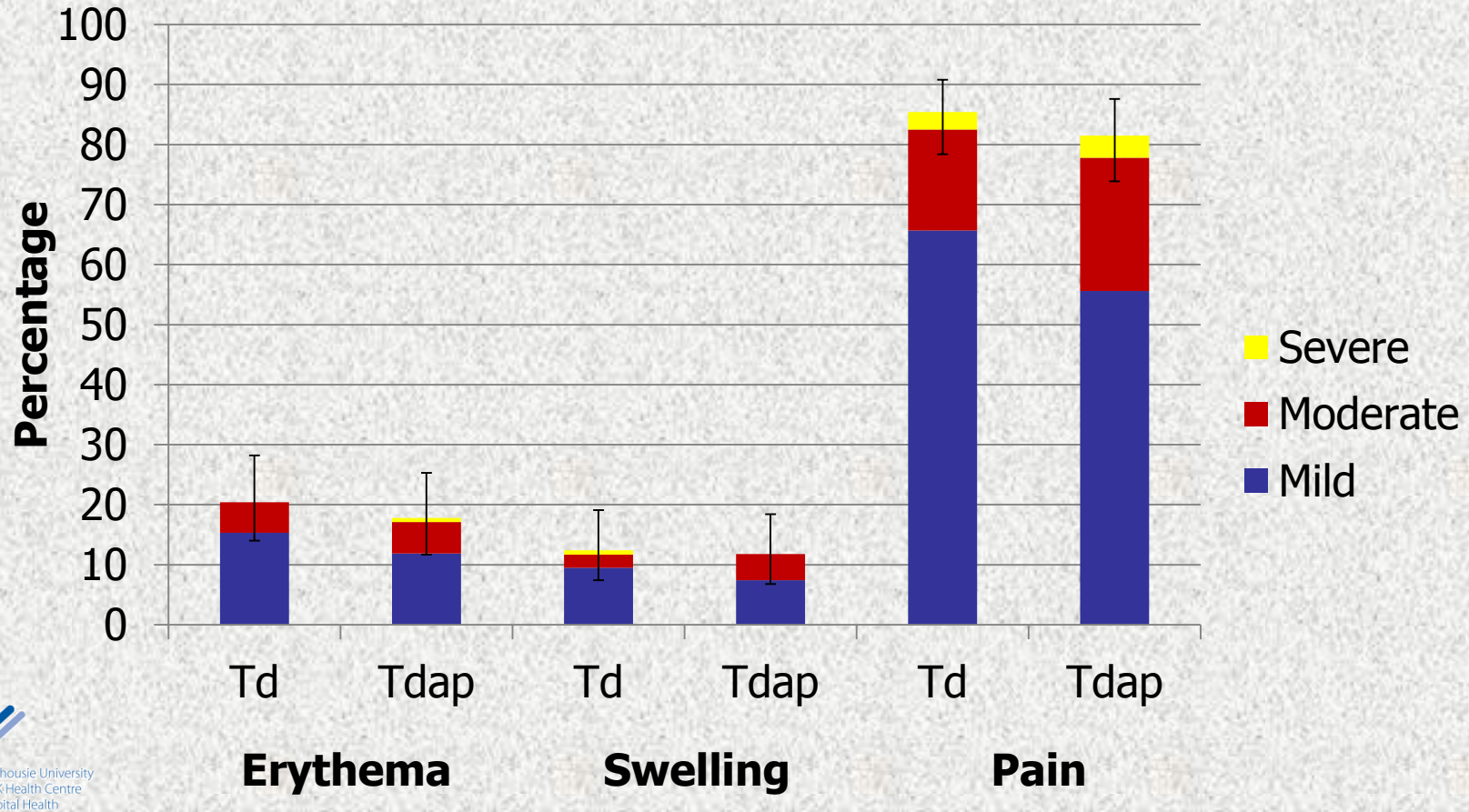
Injection Site Adverse Events: Women



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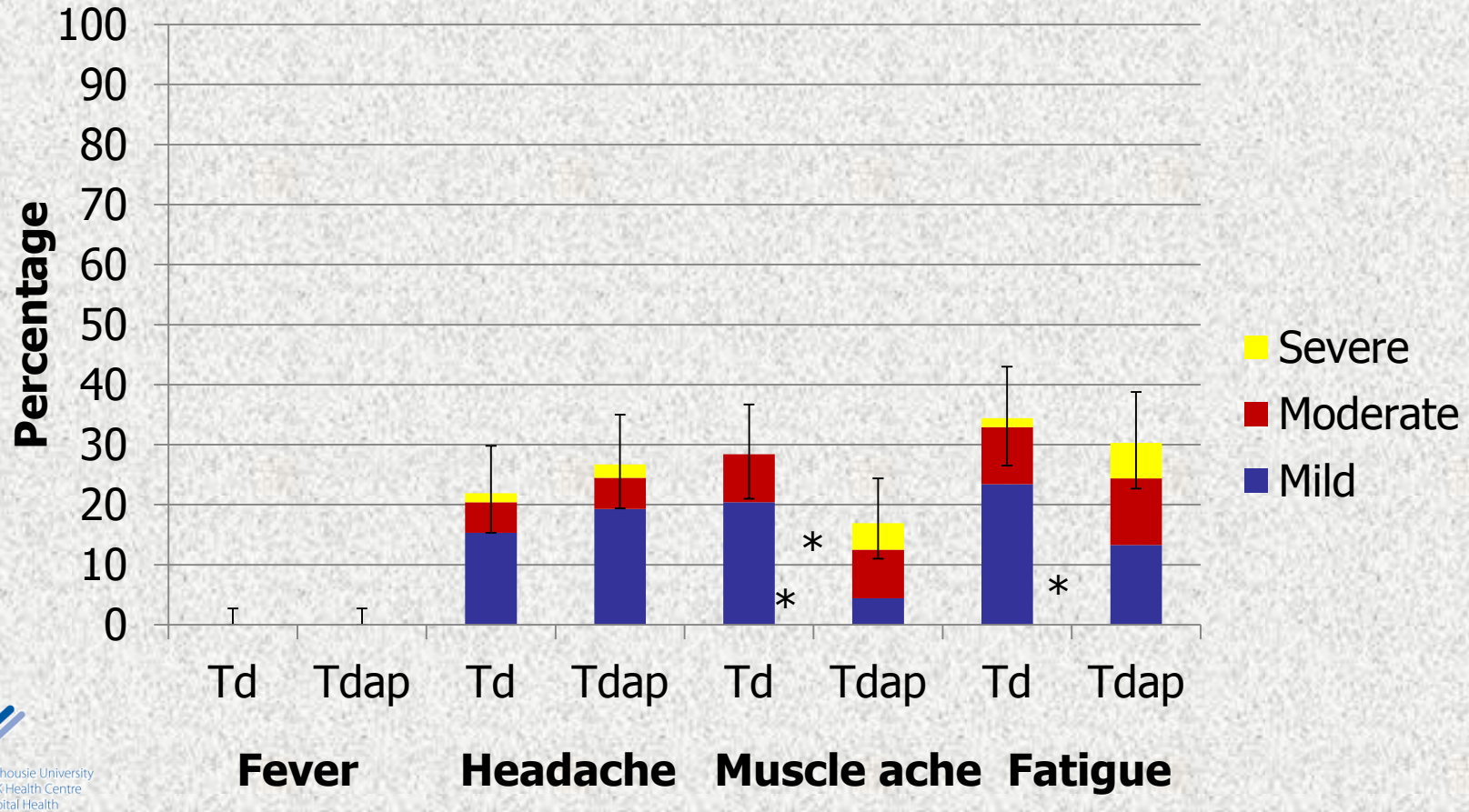
Systemic Adverse Events: Women



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* $p<0.05$

Serious Adverse Events

- 10 (7.4%) women in the Tdap group reported 11 SAEs compared to 10 (7.2%) women reporting 14 SAEs in the Td group.
- 15 (11.2%) infants in the Tdap group reported 20 SAEs compared to 22 (15.9%) infants reporting 28 SAEs in the Td group.

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Serious Adverse Events: Women

Category	Adverse Event	Td	Tdap	Vaccine Related
Cardiac	Congestive heart failure	1		No
Gastrointestinal	Crohn's disease	1		No
Infections	Gastroenteritis		2	No
	UTI	1	1	No
	Perineal infection	1		No
Psychiatric	Adjustment disorder	1		No
Renal	Nephrolithiasis	1		No
Reproductive	Decreased lactation	1	1	No
Respiratory	Pulmonary embolism		1	No
Vascular	Hypertension	1		No

Pregnancy Adverse Events

Adverse Event	Td	Tdap	Vaccine Related
Gestational hypertension		2	1 possibly, 1 no
HELLP Syndrome	1*		Possibly*
Post-partum hemorrhage	1	1	No
Pre-eclampsia	2*	1	1 possibly*, 2 no
Premature delivery	1*	2	1 possibly*, 2 no
Retained placenta	1		No
Meconium aspiration		2	No
Neonatal asphyxia/hypoxia	2		No

* 1 Td recipient with HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, pre-eclampsia, and premature delivery considered by investigator to be possible related to vaccination

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Serious Adverse Events: Infants

Category	Adverse Event	Td	Tdap	Vaccine Related
Congenital heart	Pulmonary stenosis		1	No
	Septal defect	2		No
Gastrointestinal	GERD		1	No
	Intussusception	1		No
General	Fever/other general	4		No
Hepatic	Hyperbilirubinemia/jaundice		6	No
Infections	RSV/bronchiolitis	4	1	No
	Sepsis/meningitis	3	1	No
	Otitis media	1	1	No
	Respiratory tract/pneumonia	3	1	No
	HSV		1	No
	UTI		2	No
	Periorbital cellulitis	1		No
CNS	Lethargy, decreased response, facial palsy, sleep disturbance	5	2	No
Nutrition	Failure to thrive/poor wt gain	1	1	No

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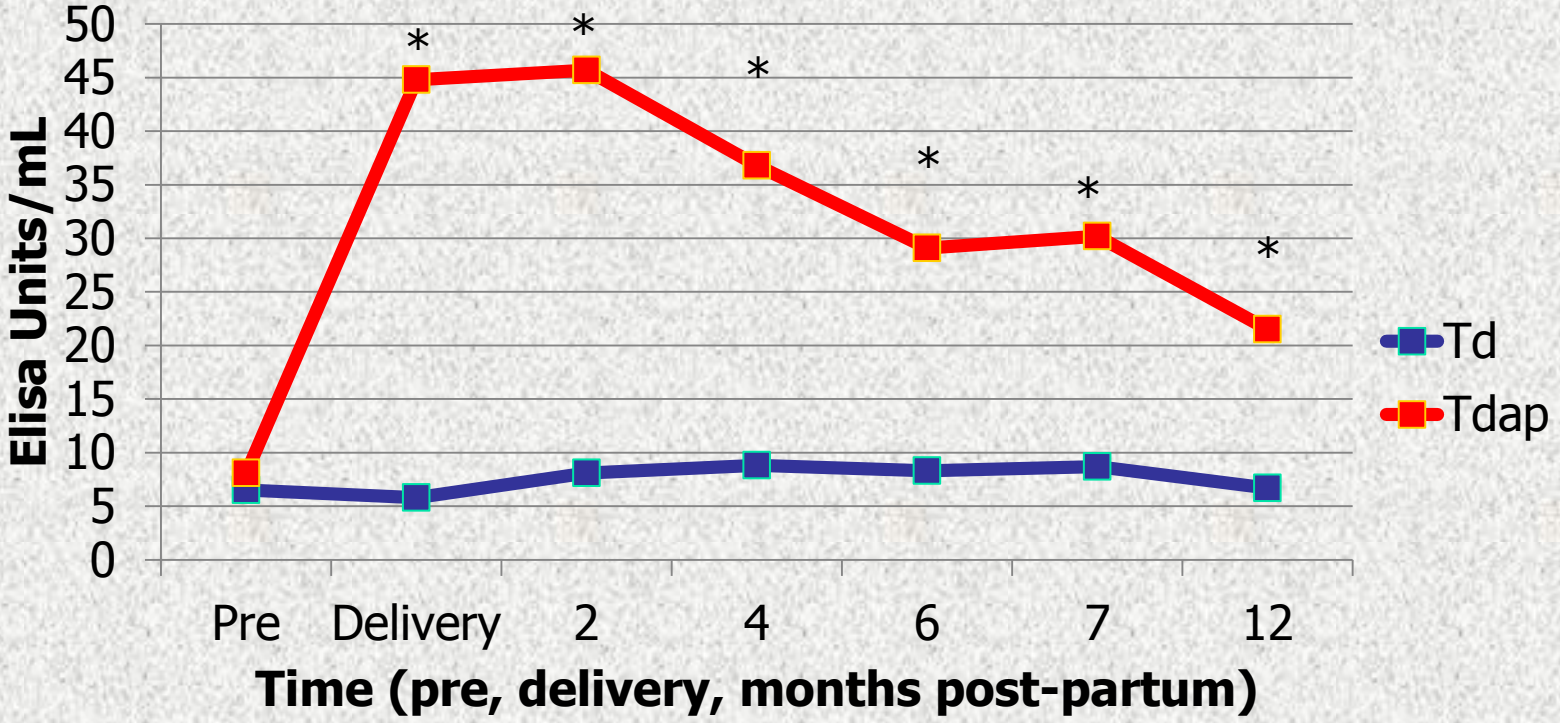
Antibody response in women: PT



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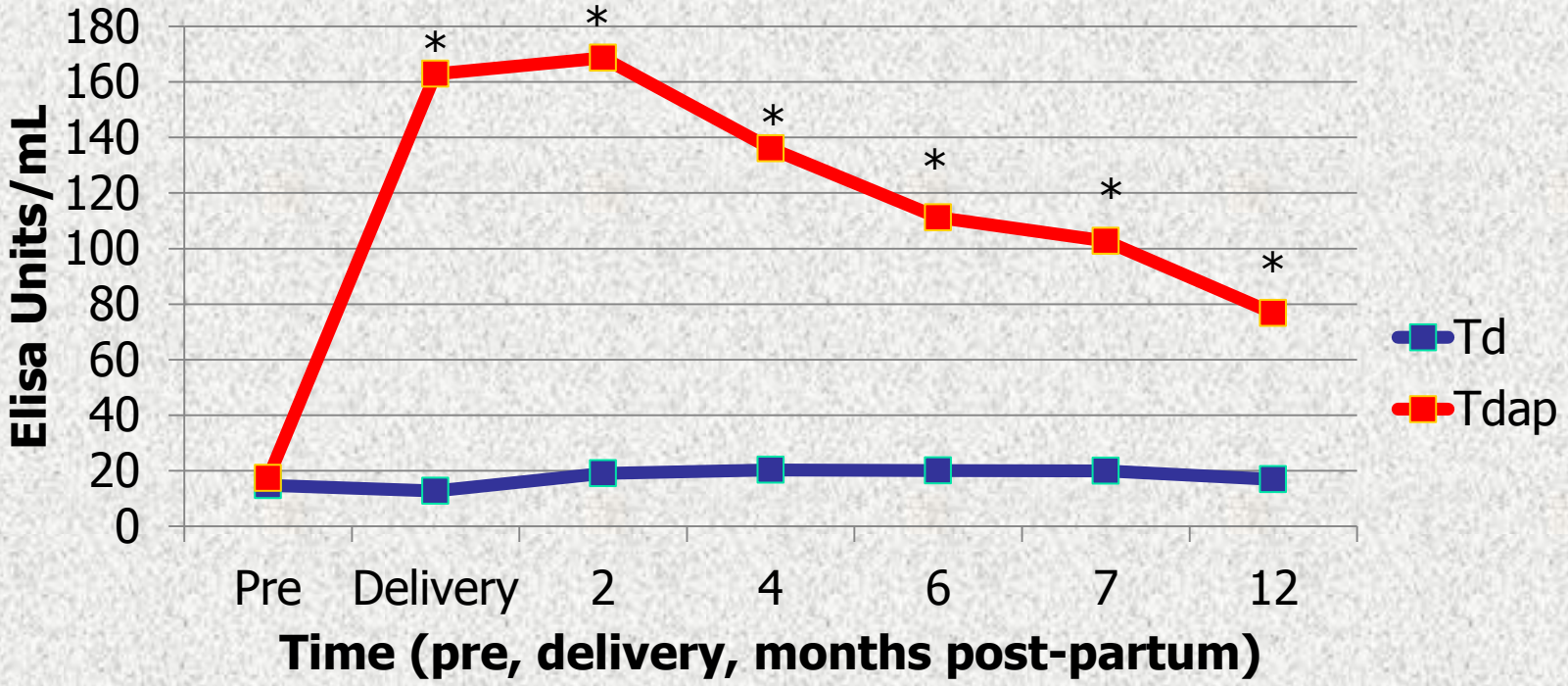
* $p<0.05$

Antibody response in women: FHA



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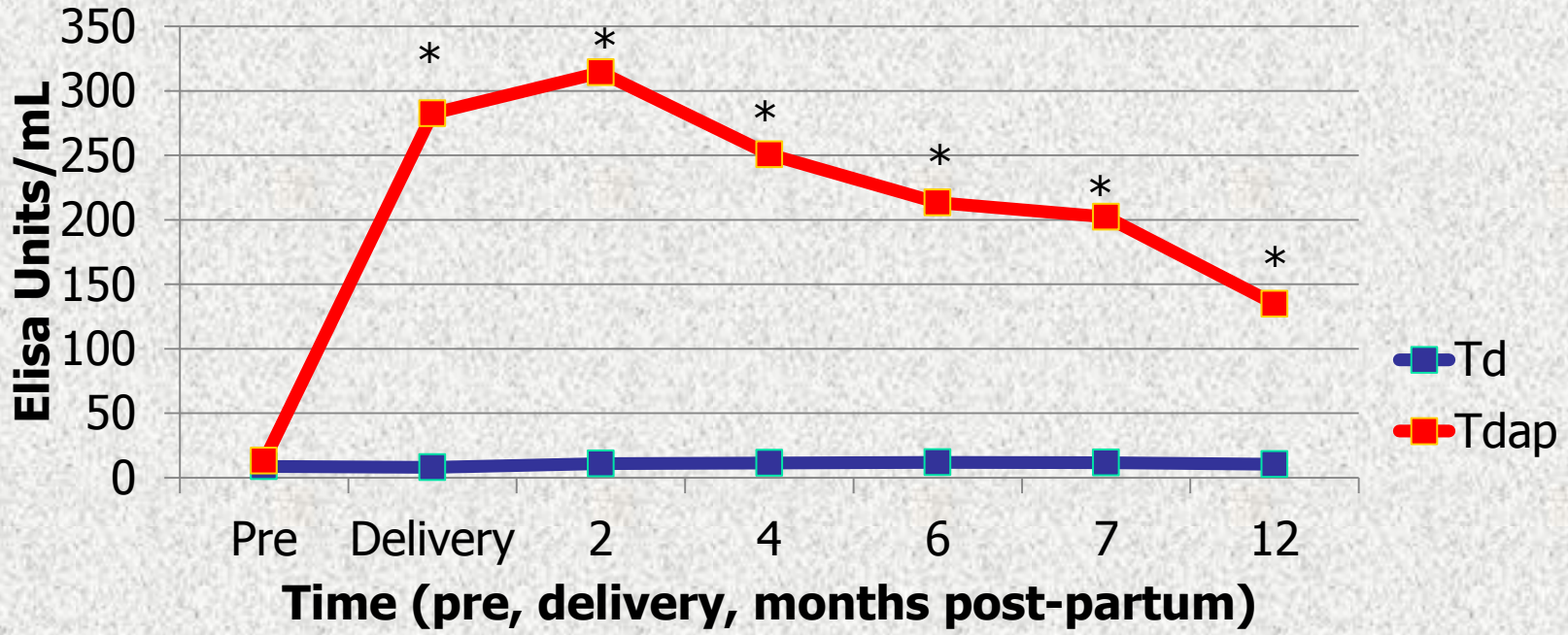
Antibody response in women: PRN



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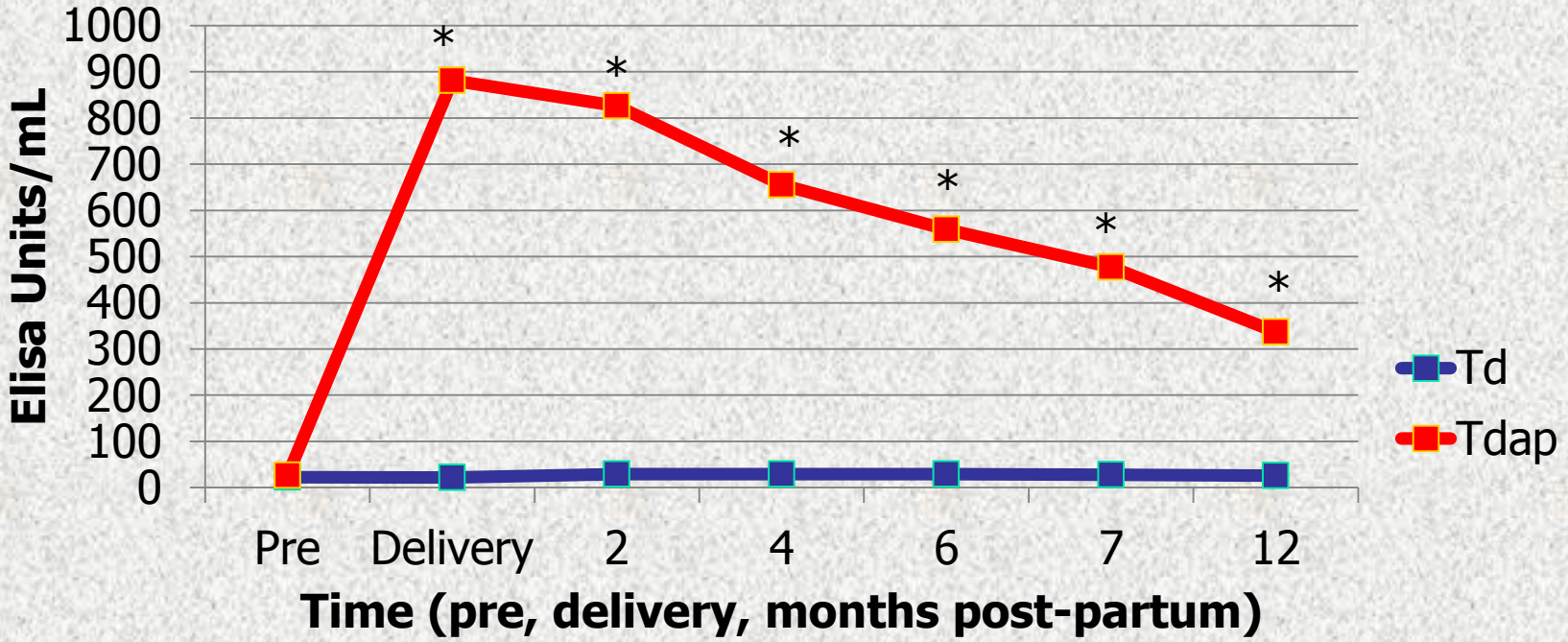
* $p<0.05$

Antibody response in women: FIM



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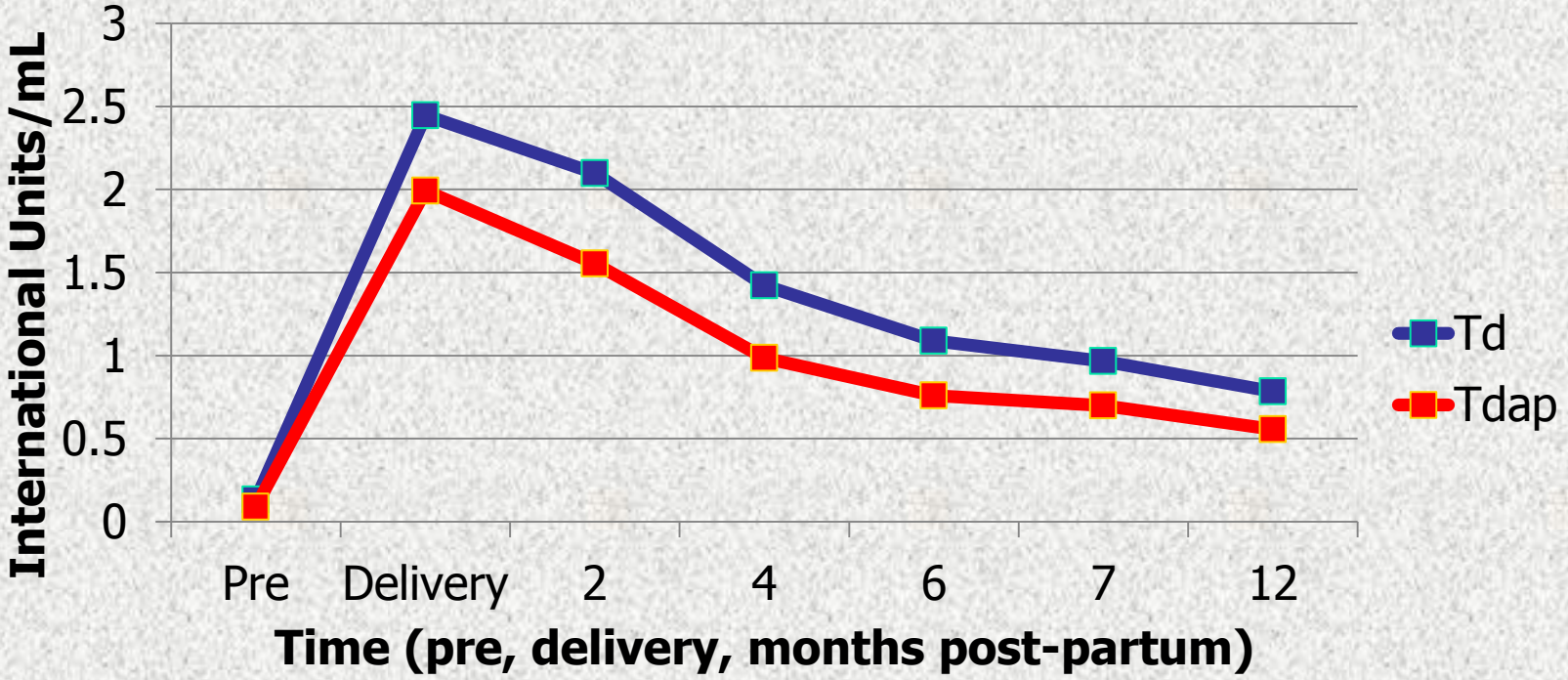
* p<0.05

Antibody response in women: Diphtheria



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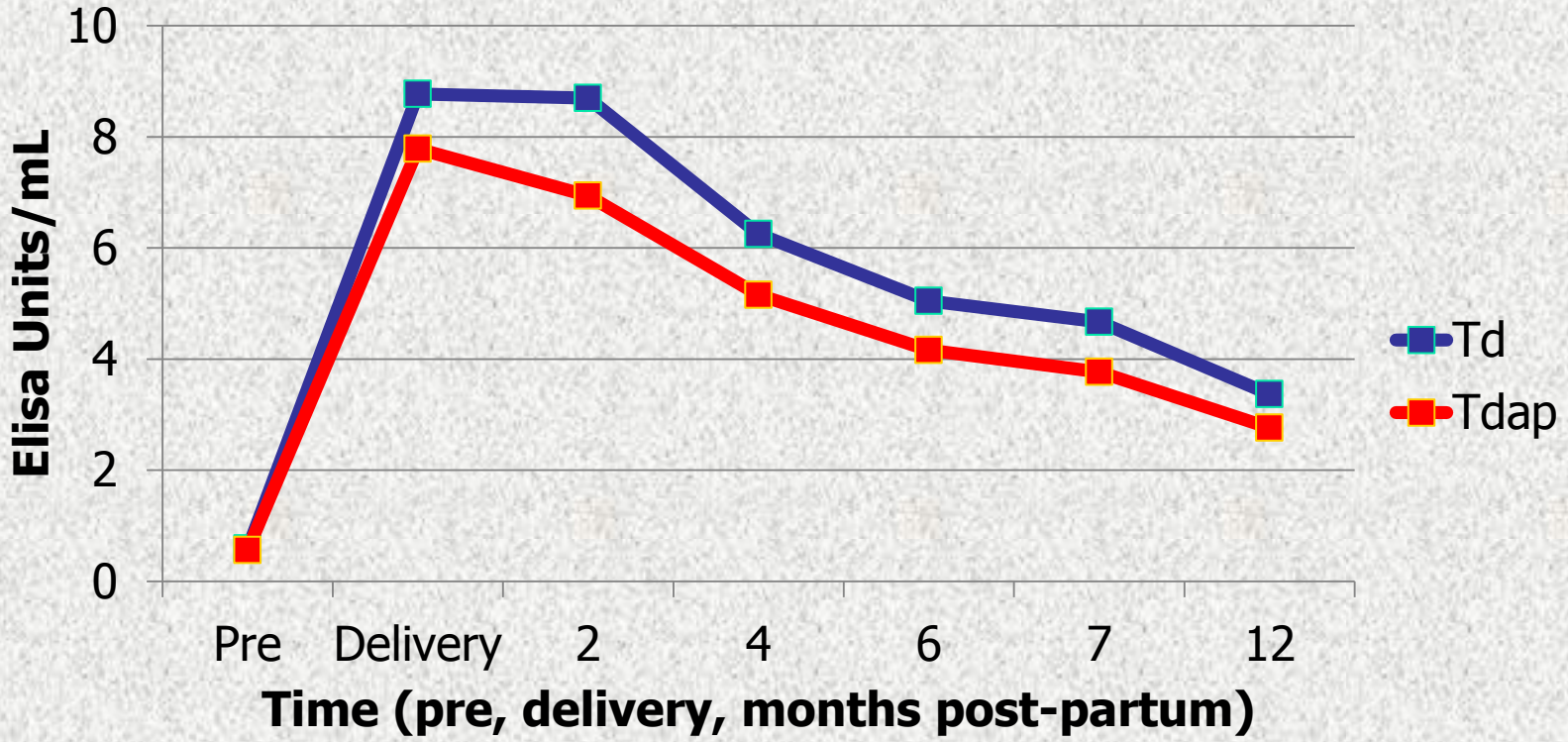
Antibody response in women: Tetanus



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Maternal to Fetal Antibody Transfer (for Tdap)

Antigen	Fetal: Maternal Ratio at Delivery (95% CI)
PT	1.19 (1.11, 1.29)
FHA	1.13 (1.07, 1.20)
PRN	1.04 (0.97, 1.12)
FIM	1.18 (1.08, 1.30)
Dip	1.15 (1.04, 1.27)
Tet	1.18 (1.10, 1.26)
PRP	0.36 (0.32, 0.42)

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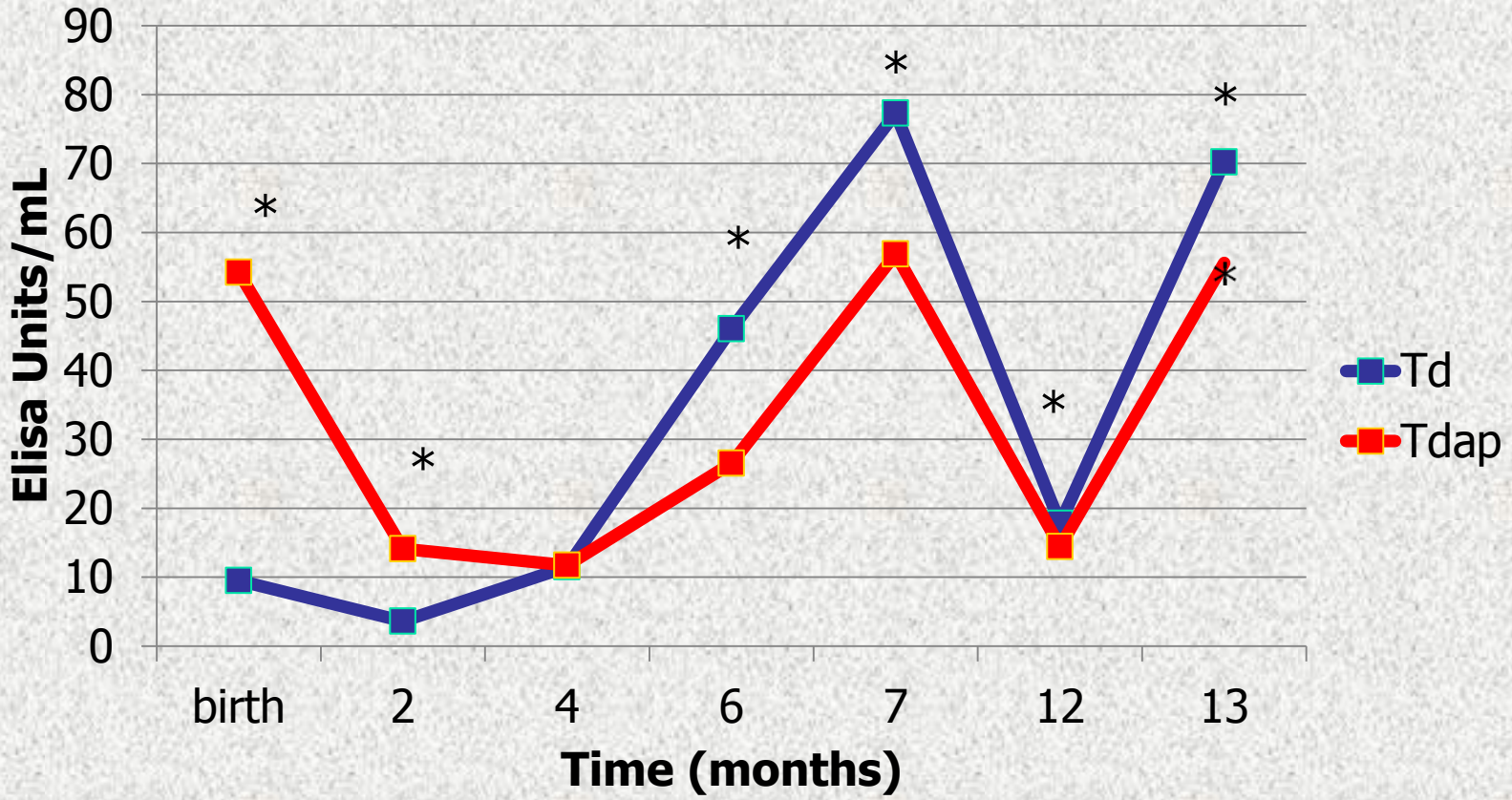
Antibody response in infants: PT



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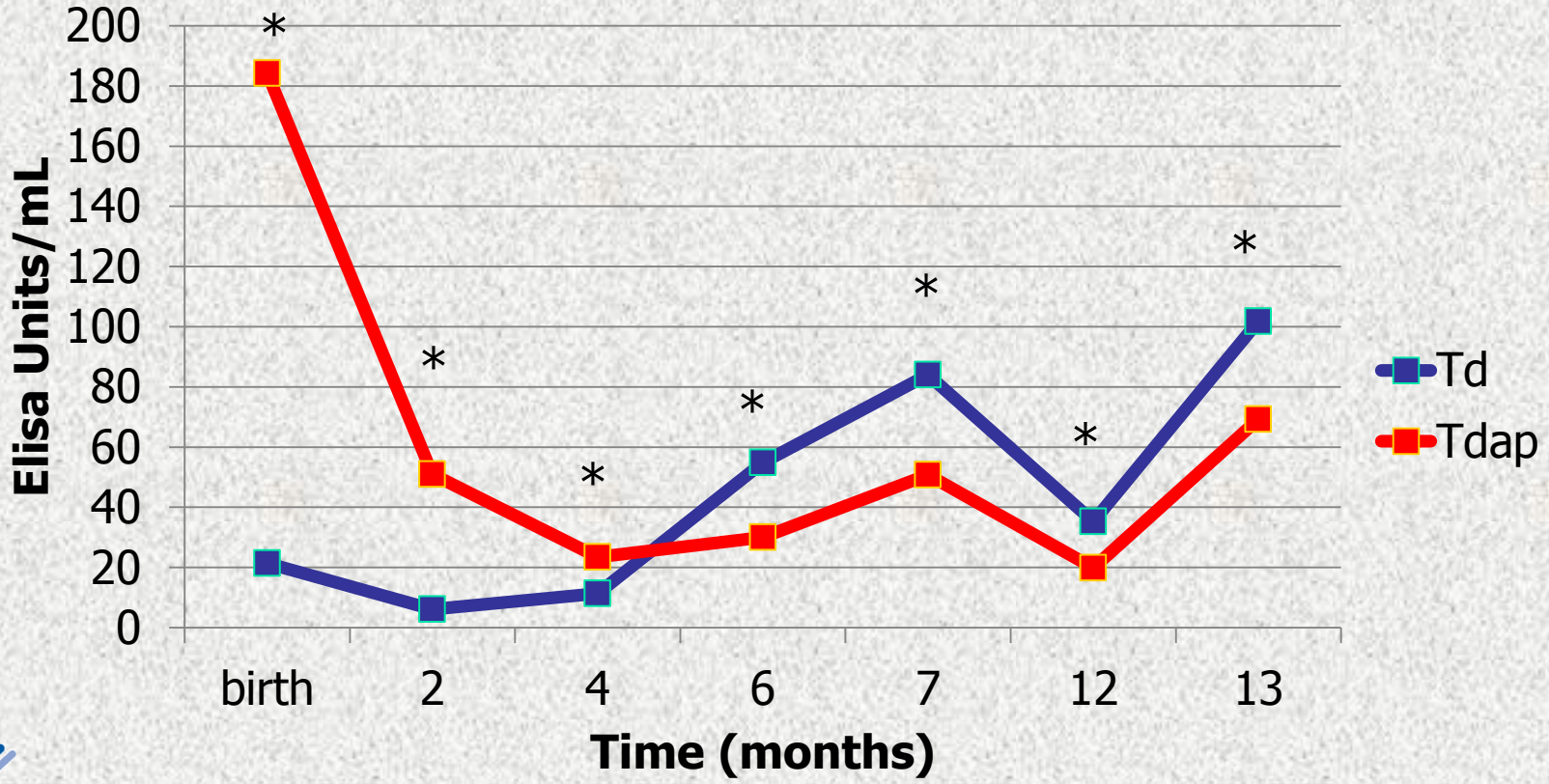
* p<0.05

Antibody response in infants: FHA



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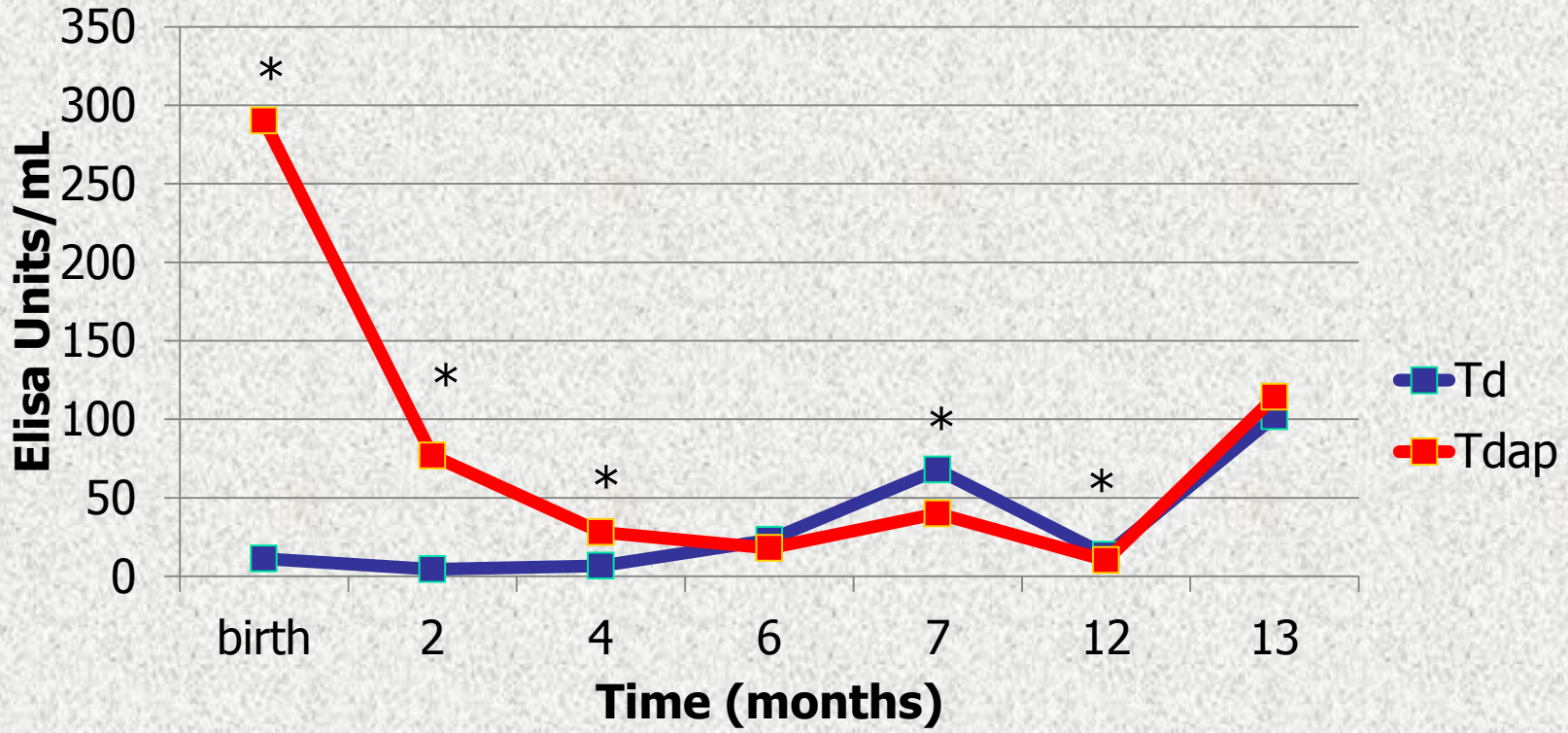
* $p<0.05$

Antibody response in infants: PRN



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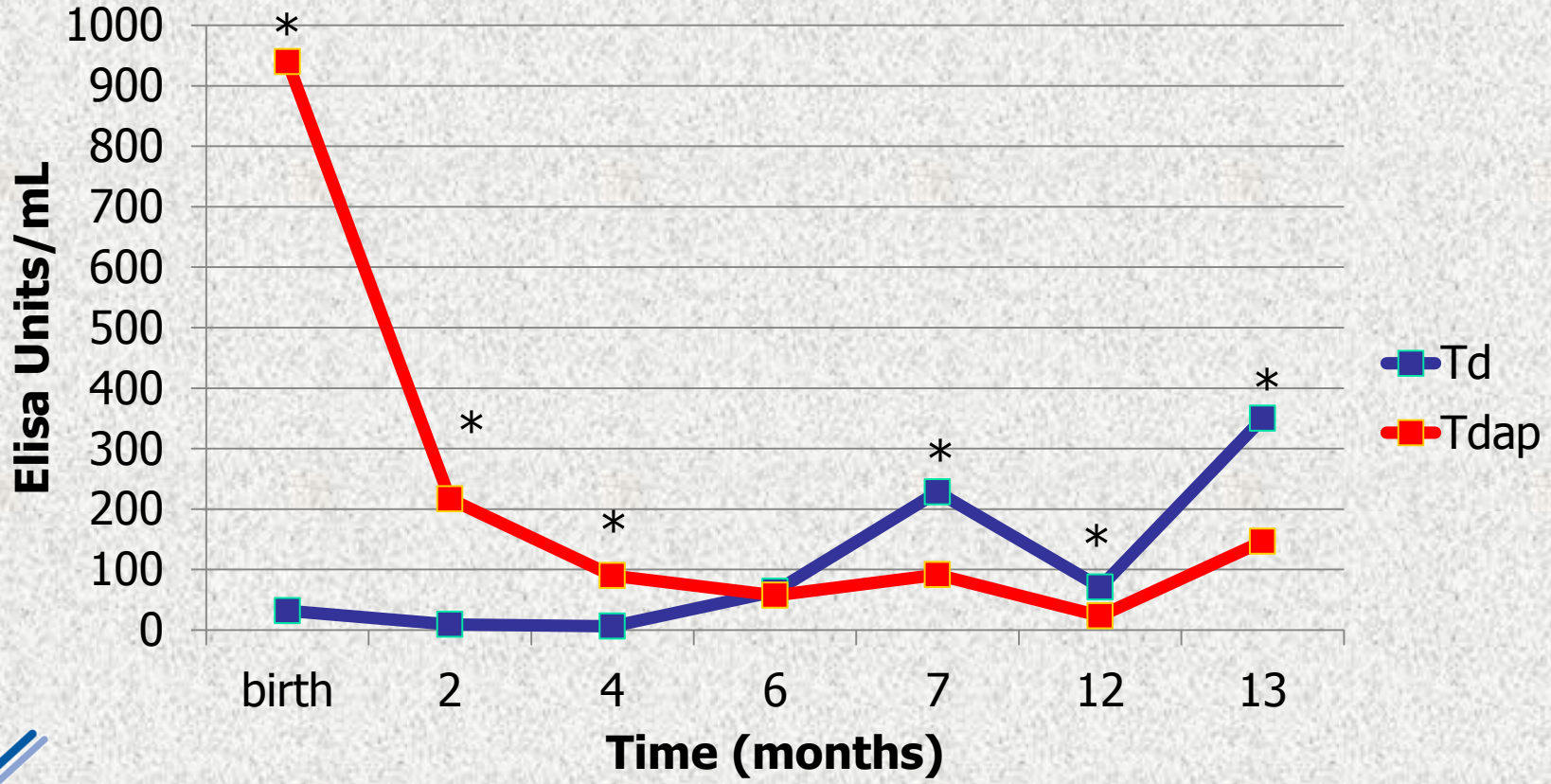
Antibody response in infants: FIM



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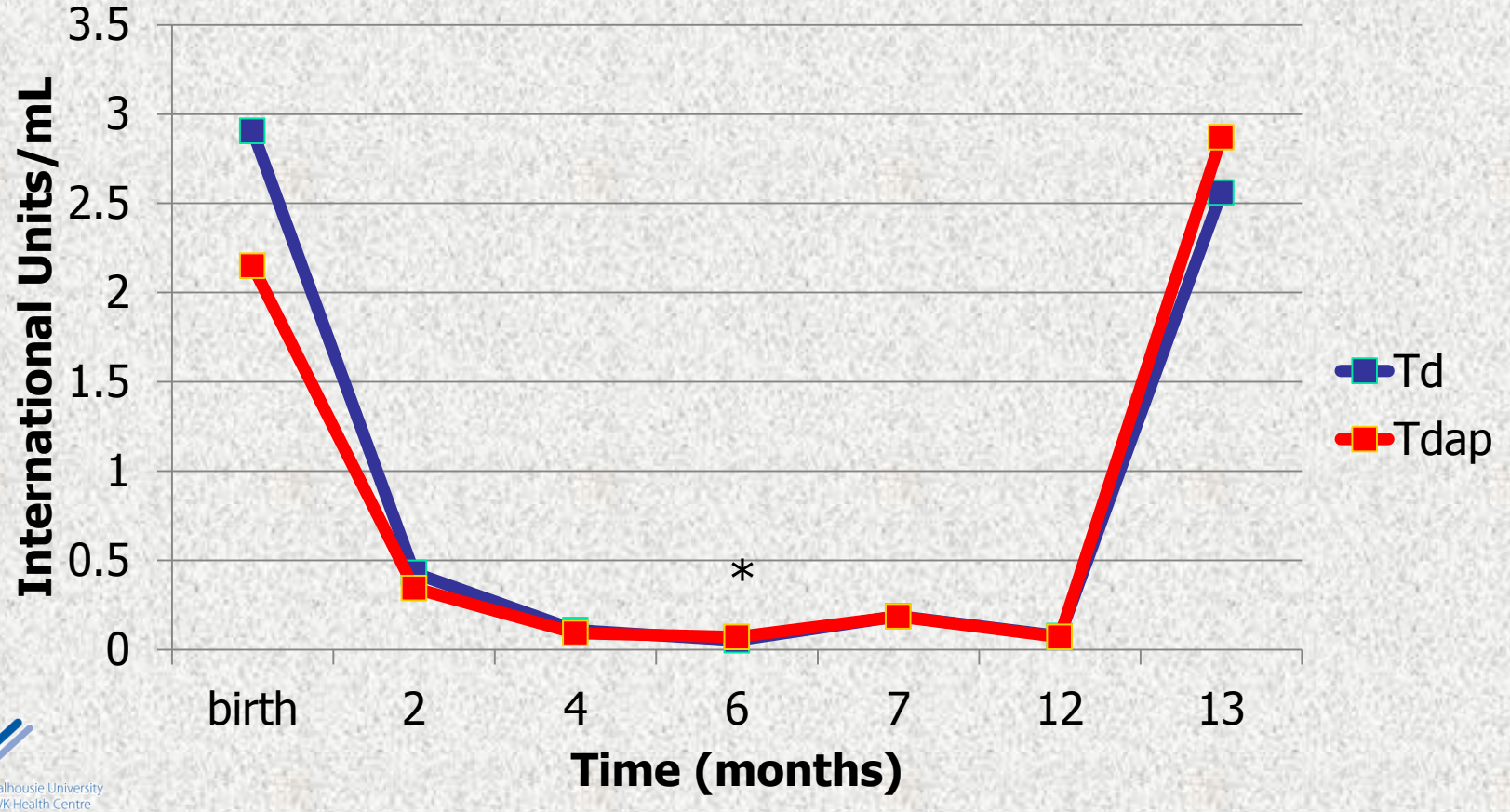
Antibody response in infants: Diphtheria



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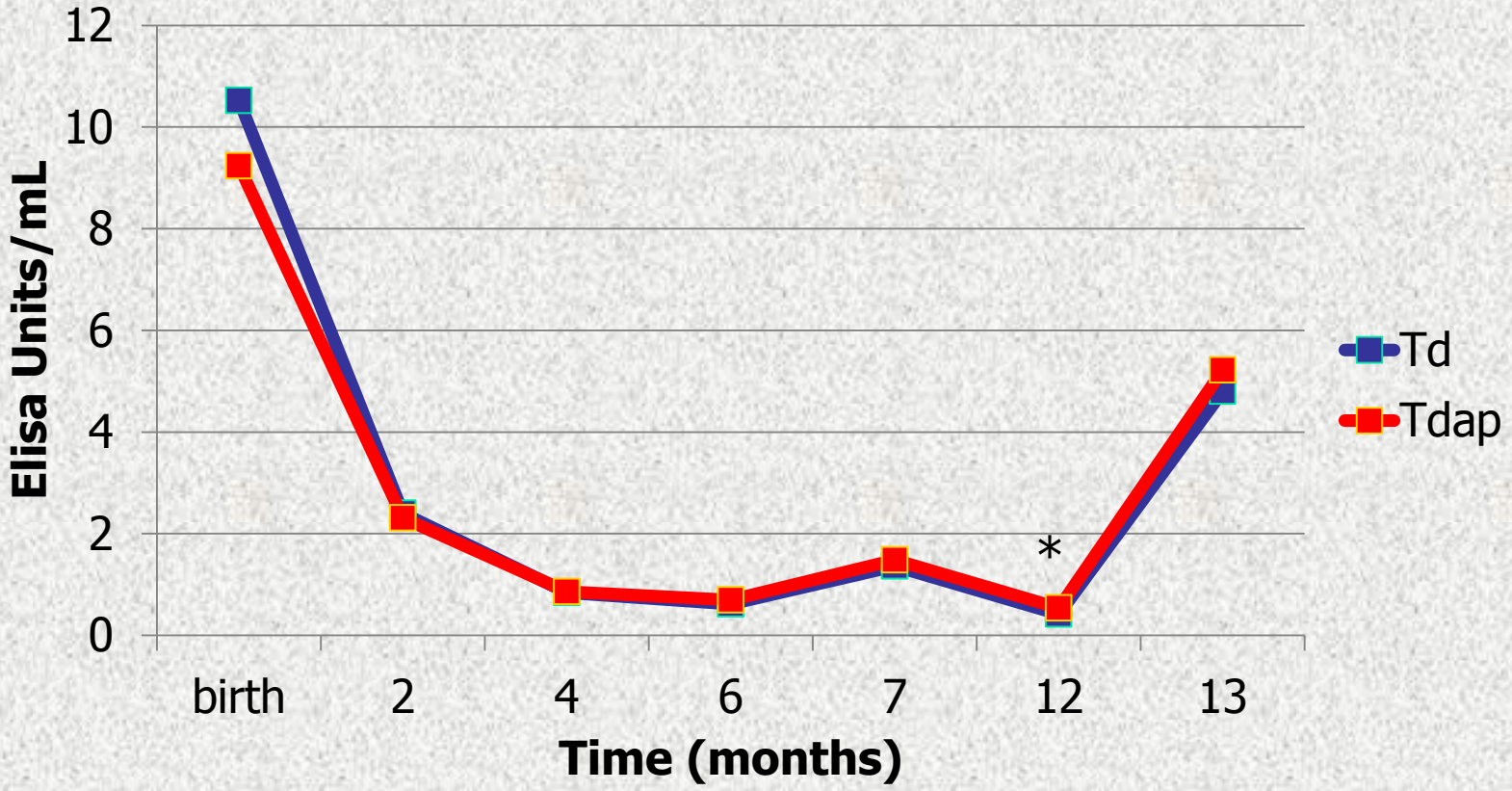
Antibody response in infants: Tetanus



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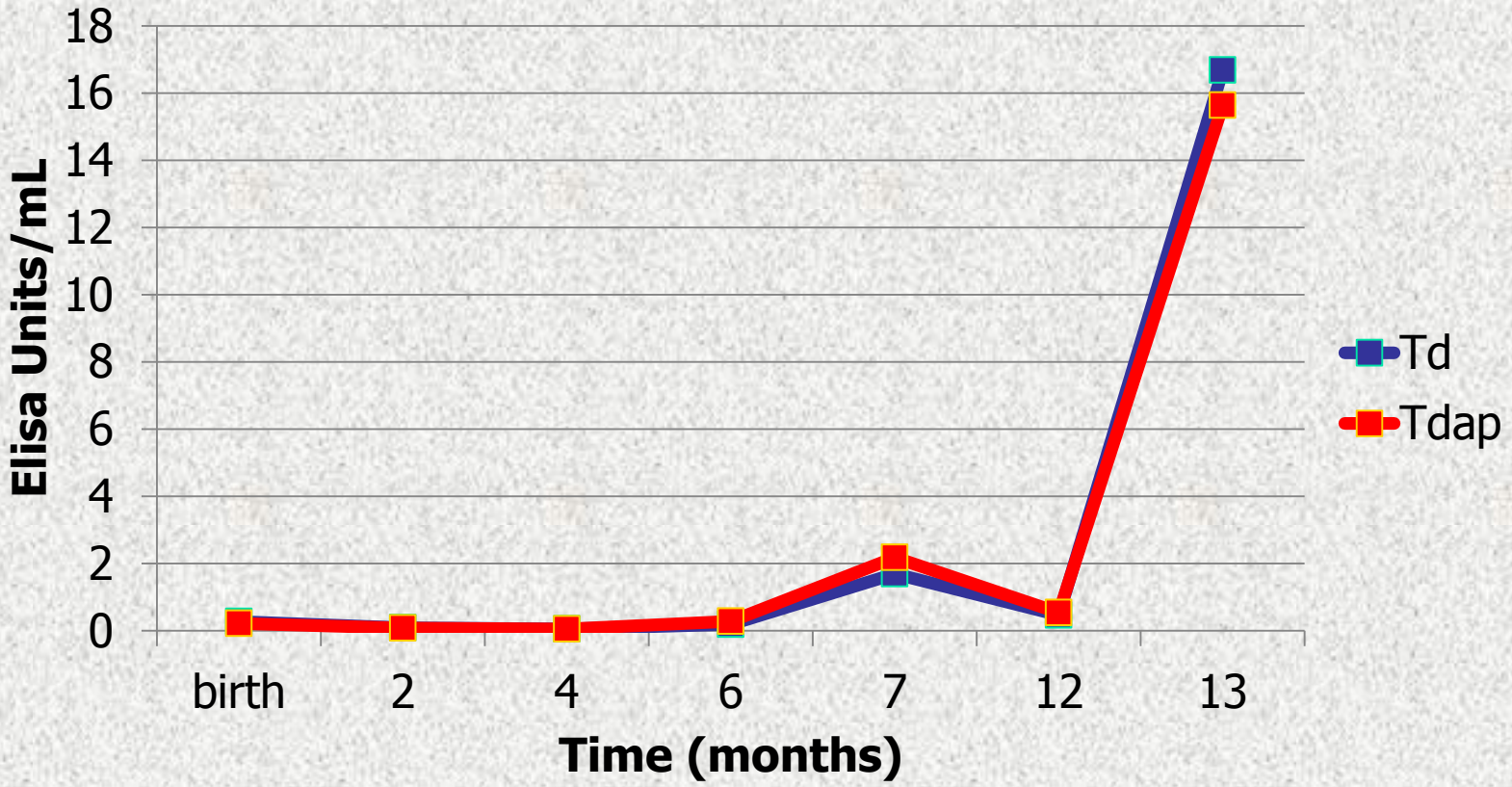
* $p<0.05$

Antibody response in infants: PRP



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Summary

- Tdap or Td during pregnancy is not associated with significant adverse maternal, fetal, or infant outcomes.
- Antibodies against all antigens were transferred to the fetus with fetal:maternal antibodies ratios >1.0
- Antibodies against pertussis antigens were significantly higher at birth in infants of mothers immunized with Tdap compared to Td; higher levels persisted at 2 months (PT) or 4 months (FHA, PRN, FIM).
- Antibody levels were significantly lower for all 4 pertussis antigens at 7 months of age and before the 12 month booster; levels remained lower post booster for PT, FHA, and FIM.

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Conclusions

- Immunization with Tdap in the 3rd trimester is well tolerated by pregnant women and achieves high antibody levels against all pertussis antigens, and diphtheria and tetanus toxoids.
- High levels of antibodies are transferred to the infant and remain higher for 2-4 months than in infants of mothers immunized with Td.

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Conclusions

- In general, antibody levels after the primary series and booster are lower in infants of mothers immunized with Tdap than Td.
- In view of the effectiveness of maternal immunization in preventing deaths from pertussis in newborns, ongoing monitoring is needed to assess the effect of the diminished response to active immunization on disease later in infancy.

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Questions and Discussion

Acknowledgements

- Funding for the study provided by Sanofi Pasteur
- Nurses, research assistants, laboratory personnel
- Women and infants who participated in the study.

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