

Clinical experience with use of whole cell vaccines in the neonatal period

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NCIRS

National Centre for Immunisation Research & Surveillance

Neonatal use of whole cell vaccines

1. History

- pertussis vaccines
- epidemiology
- the age controversy

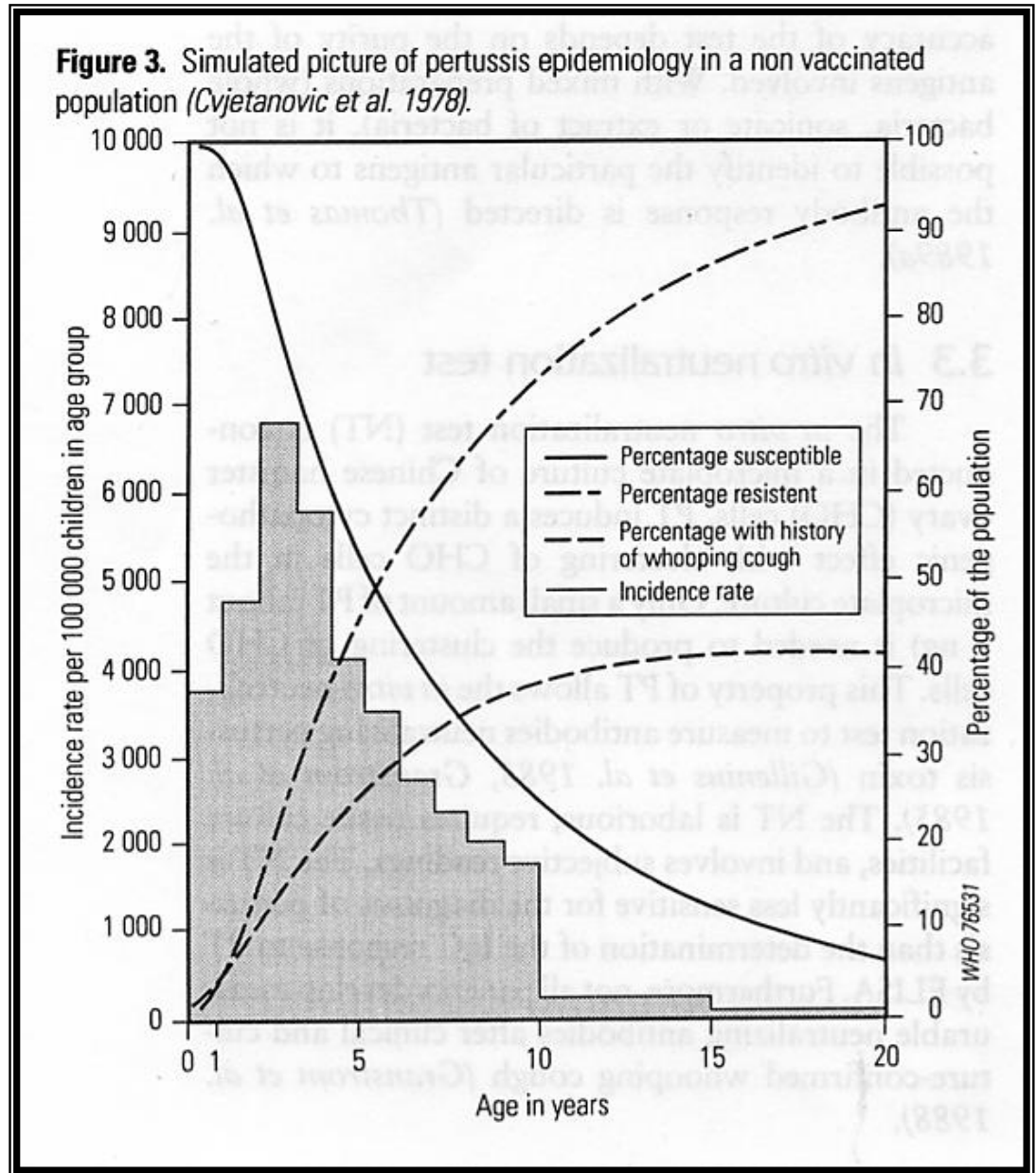
2. Clinical Trials

- immunogenicity
- protection against pertussis

3. Conclusions

Pertussis in the pre-vaccine era¹

¹ Cvjetanovic et al Bull WHO 1978
Pertussis in a non-vaccinated population



Page 327 “ In very young children (under a year old) the disease is always a cause of anxiety.... If there should be much broncho-pneumonia, naturally the danger will be great; so also if convulsions are severe.....”

Page 328 “ There is no apparent reason why we may not some day find a specific for the catarrhal stage of pertussis.....some indeed think they have already found such in a *vaccine*, prepared with Bordet-Genou Bacillus of Pertussis....”

THE DISEASES OF CHILDREN

BY THE LATE
SIR JAMES FREDERIC GOODHART
BART., M.D., LL.D.ABERD., F.R.C.P.

TWELFTH EDITION

EDITED BY
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WITH 68 ILLUSTRATIONS



LONDON
J. & A. CHURCHILL
7, GREAT MARLBOROUGH STREET

1925

Factors affecting immunogenicity of whole-cell vaccines¹

Vaccine

- potency
- antigen
- adjuvant

Infant

- age
- doses
- dose spacing
- maternal antibody
- time to testing

Assay

- sensitivity
- variability

¹Halsey and Galaska., *Bull WHO* 1985; 63:115

Sauer, L.W., 'The age factor in active immunisation against whooping cough', *AMJ Pathol*, 1941;17:719-23.

Cases

- N = 1434 children < 3 months
- 1cc *H. pertussis* vaccine x 6 weeks
- 1933-40
- 1940 mailed questionnaire
 - 76% response rate

Controls

- N = 1000 births
- 1940 mailed questionnaire
 - 464 (47%) response rate

256 no vaccine
208 vaccine @ 7 months

Sauer, L.W., 'The age factor in active immunisation against whooping cough', *AMJ Pathol*, 1941;17:719-23.

Results:

	Total	Pertussis	AR/100
No vaccine	256	38	14.8
< 3 months	1110	91	8.2
> 7 months	208	3	1.44

Conclusions:

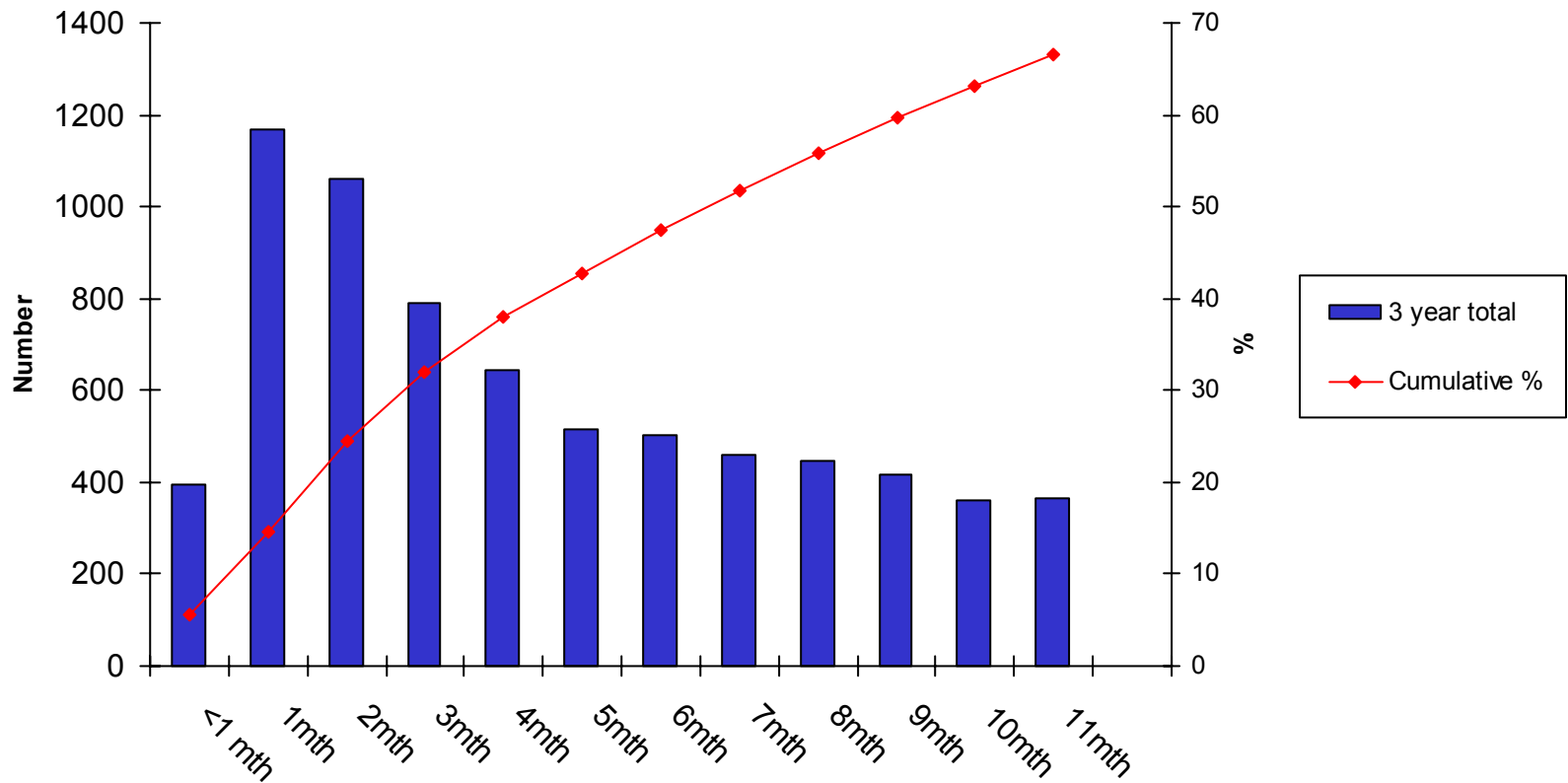
- pertussis risk ↑ ↑ in < 3 months group
- give vaccine @ > 7 months

Studies of DTPw initiated from birth to 4 weeks of age 1945 - 1953

Author	Year	P	N	Age at first dose
Sako (US)	1945	P	1007	4-8 weeks
		DPT	1294	
Waddell (US)	1946	P	50/43	1 week
Adams (US)	1949	P	21/19	1 week
Di Sant Agnese (US)	1949	DPT	125	1 week
	1950		{ 108 47	
Lippsett (US)	1953	P	22	4 weeks

continued

Deaths from pertussis age US 1938-40 ¹

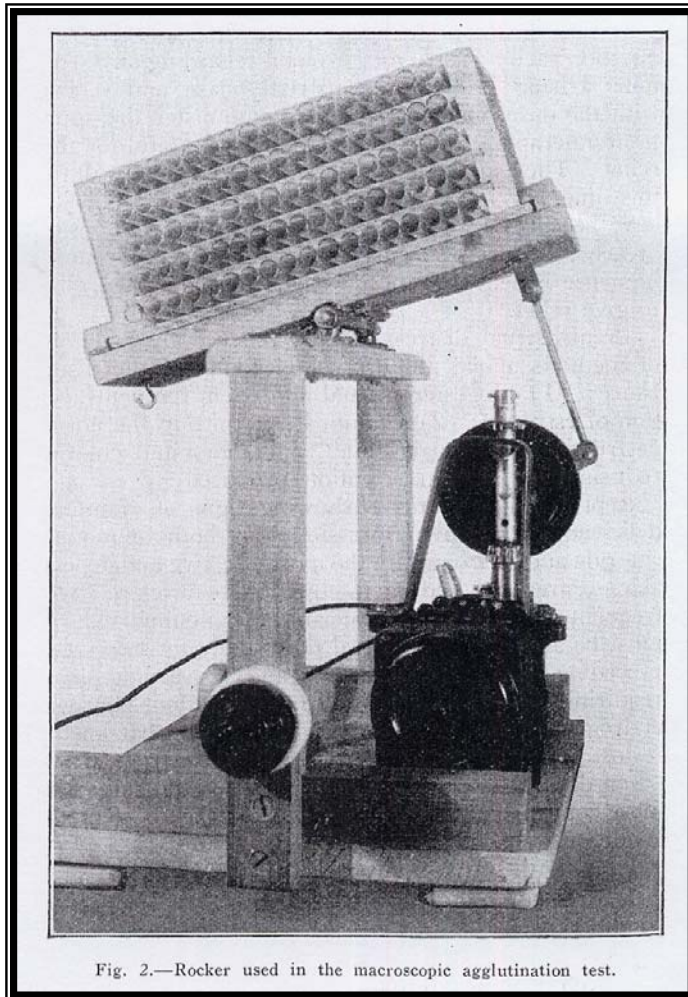


1. Sako et al JAMA 1945; 127: 379

Sako,W. et al. Early immunization against pertussis with alum precipitated vaccine. *JAMA* 1945;127:379-384

- N = 3793 infants 2-12 weeks
- New Orleans - well baby clinics
- 3 doses @ 1-2 months
2-3 months
3-4 months

Sako,W. et al. Early immunization against pertussis with alum precipitated vaccine. *JAMA* 1945;127:379-384



Agglutination tests N = 500

	All pos (%)	Strong pos (%)
1 month	60	40
2 months	69	38
3 months	74	42
6 months	76	43
12 months	70	37
24 months	63	25

Sako,W. et al. Early immunization against pertussis with alum precipitated vaccine. *JAMA* 1945;127:379-384

	Pertussis (death)		No pertussis
Immunised	27	(0)	114
Not immunised	118	(12)	17

VE = 96.6%

Immunised cases strong (+) = 1/27
 negative = 16/27 (59%)

**Sako W. Studies on pertussis immunization.
J Pediatr 1947; 30: 29-40.**

Vaccine N = 8690

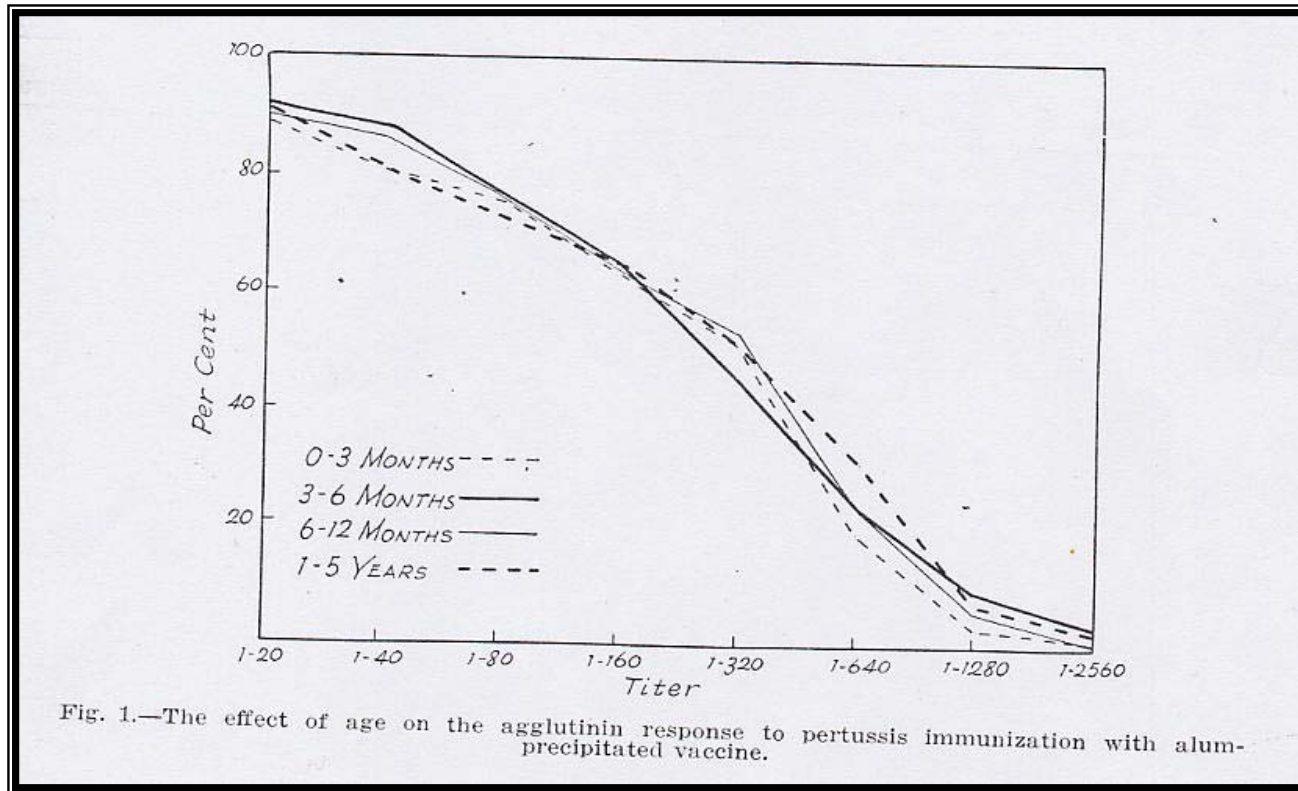
x 3 doses alum precipitated

Age

2 weeks to 5 years

N = 5028 < 3 months

Sako W. Studies on pertussis immunization. *J Pediatr* 1947;30:29-40.



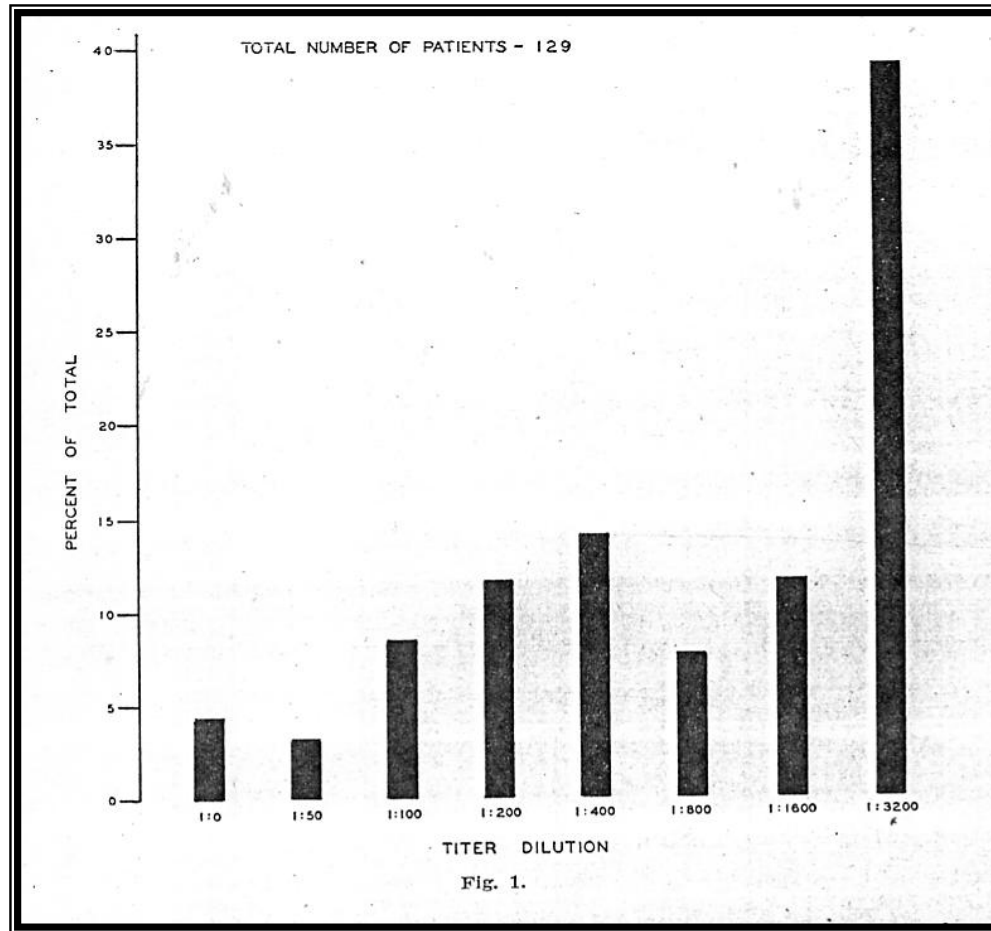
Waddell & L'Engle, *J Pediatrics*, 1946;29:487-492

Site: Charlottesville VA

	First dose = 1 week N = 129	First dose = 8 weeks N = 38
< 1:400	30%	13%
≥ 1 :400	70%	87%

“Local and systemic reactions.....were negligible at this early age.....much less frequent than at 7 months....”

**Waddell WW Jr, L'Engle CS Jr. Immune response to early administration of pertussis vaccine.
J Pediatrics 1946;29:487-492.**



Adams, J.M. Kimball, A.C. Adams, F.H. Early immunization against pertussis. *American Journal of Diseases of Children* 1947;74:10-18.

Group II x 3 weekly by first month - N = 21

Group III x 3 monthly by 4 months N = 19

	No rise	“Good” titres
Group II	6/21 (29%)	5/21 (24%)
Group III	5/19 (26%)	

Du Pan RM. The vaccination of the newborn infant against pertussis. *J Pediatrics* 1958;53:180-186.

3 groups

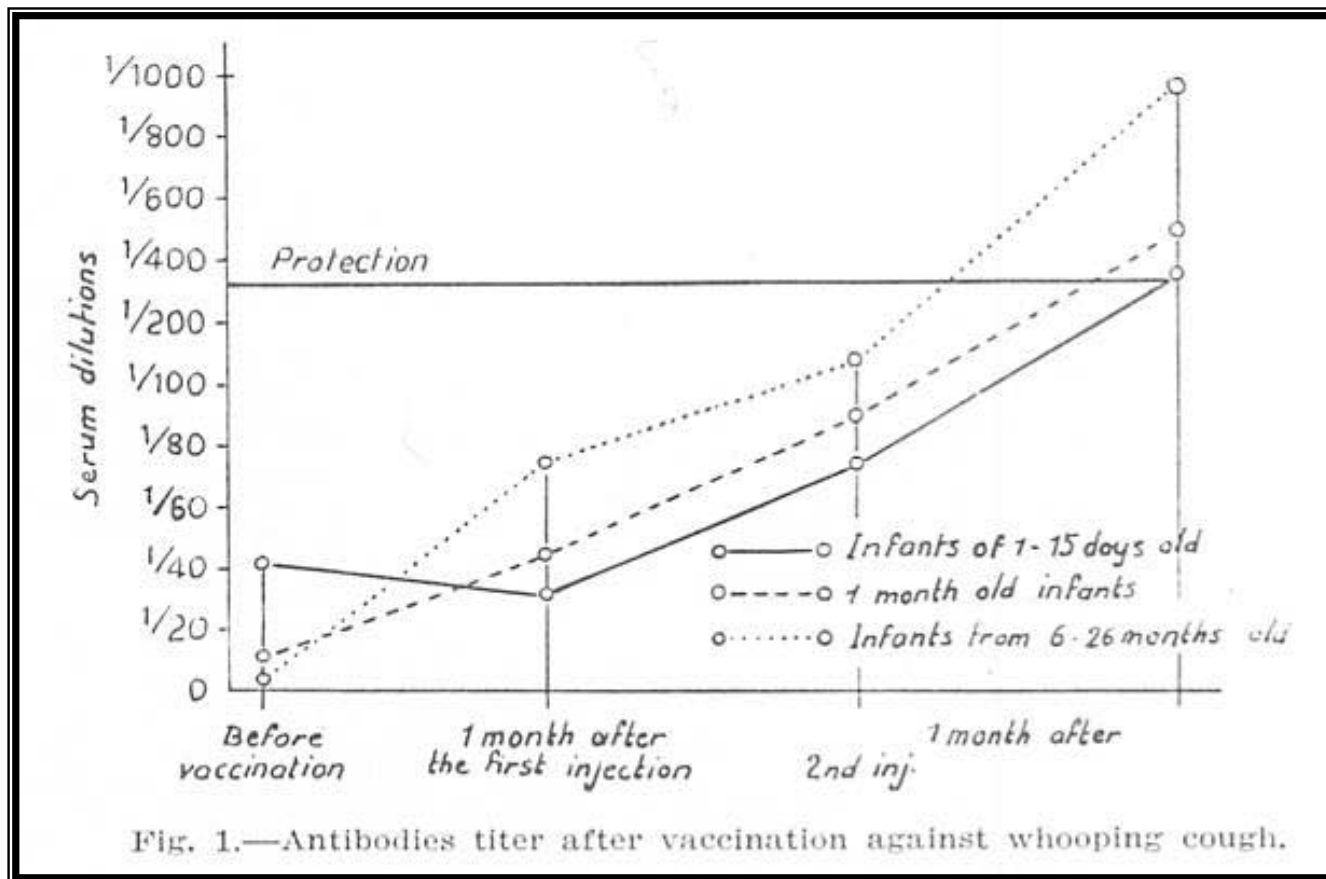
1. 1 - 15 days
2. 1 month
3. 6 - 26 months

Alum Precipitated DTP (Cutter)

1 month intervals

N not stated

Du Pan RM. The vaccination of the newborn infant against pertussis. *J Pediatrics* 1958;53:180-186.



Di Sant'Agnesse PA. Combined immunization against diphtheria, tetanus and pertussis in newborn infants. I. Production of antibodies in early infancy. *Pediatrics* 1949;3:20-33.

DTP

- 1 week, 5 weeks, 9 weeks - group X
- > 3 months, 1 month intervals - group B
- % with titre < 1:406

Time post series

- | | | |
|----------------|-----|----|
| • 1 month | 46* | 14 |
| • 4-6 months | 67* | 18 |
| • post booster | 37* | 8 |

* = $P < 0.05$

Di Sant' Agnese PA. Combined immunization against diphtheria, tetanus and pertussis in newborn infants.

III. Relationship of age to antibody production.

Pediatrics 1949;3:333-344.

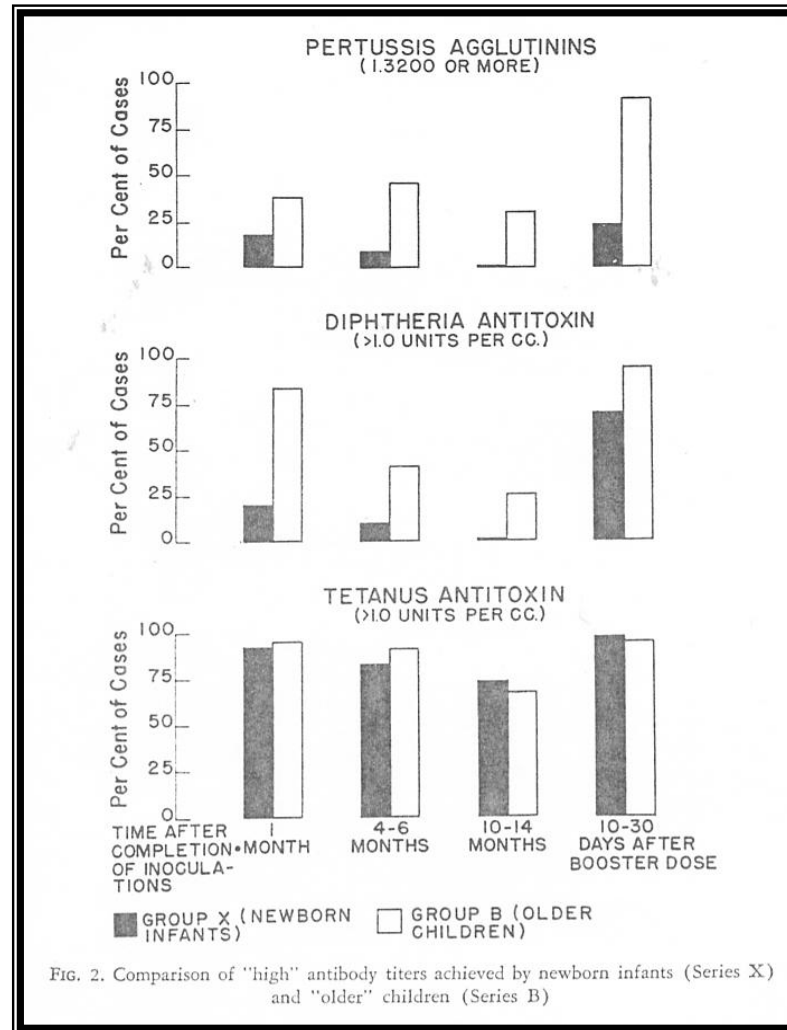
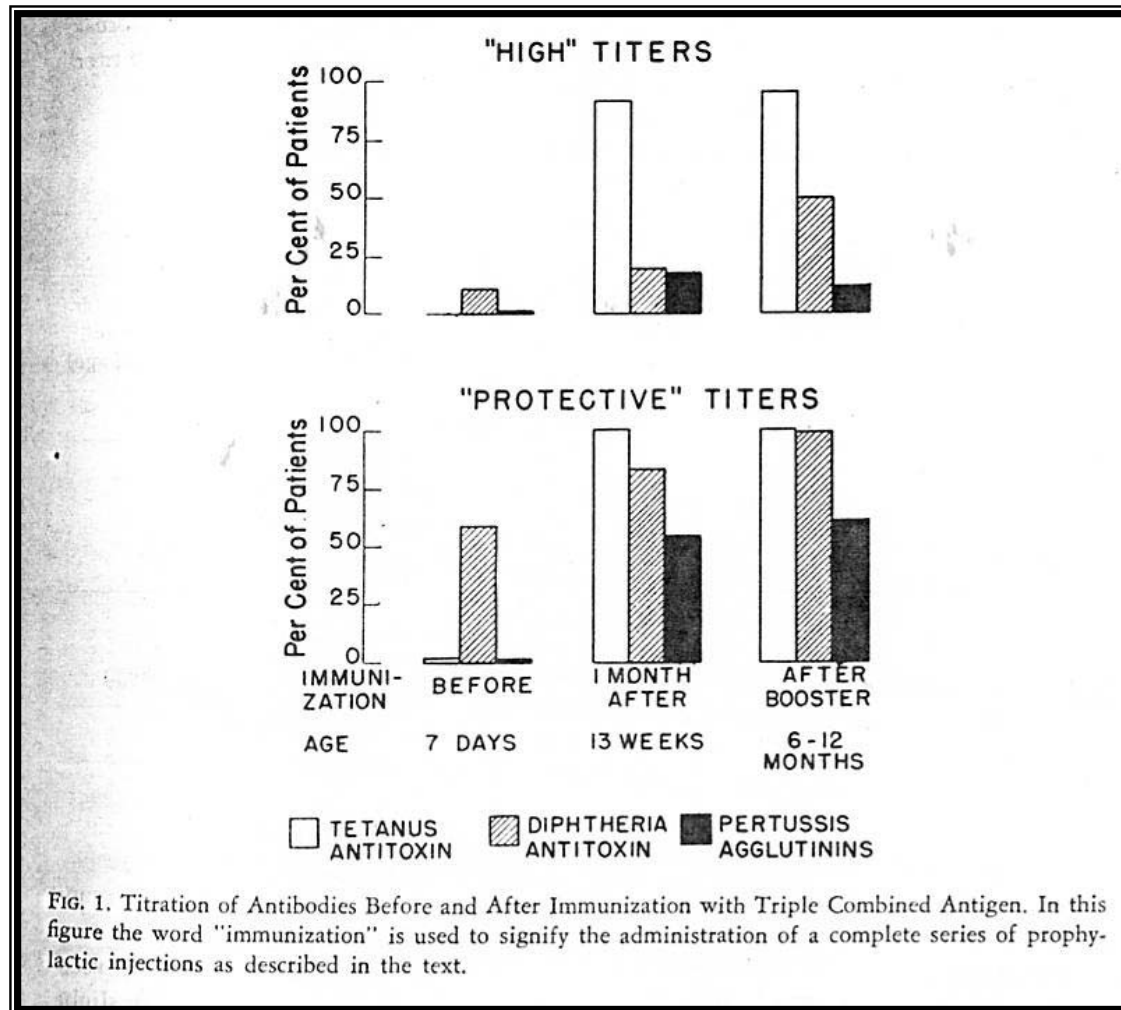


FIG. 2. Comparison of "high" antibody titers achieved by newborn infants (Series X) and "older" children (Series B)

Di Sant'Agnes PA. Combined immunization against diphtheria, tetanus and pertussis in newborn infants.

I. Production of antibodies in early infancy.

Pediatrics 1949;3:20-33.



Adams, J.M. Kimball, A.C. Adams, F.H. Early immunization against pertussis. *American Journal of Diseases of Children* 1947;74:10-18.

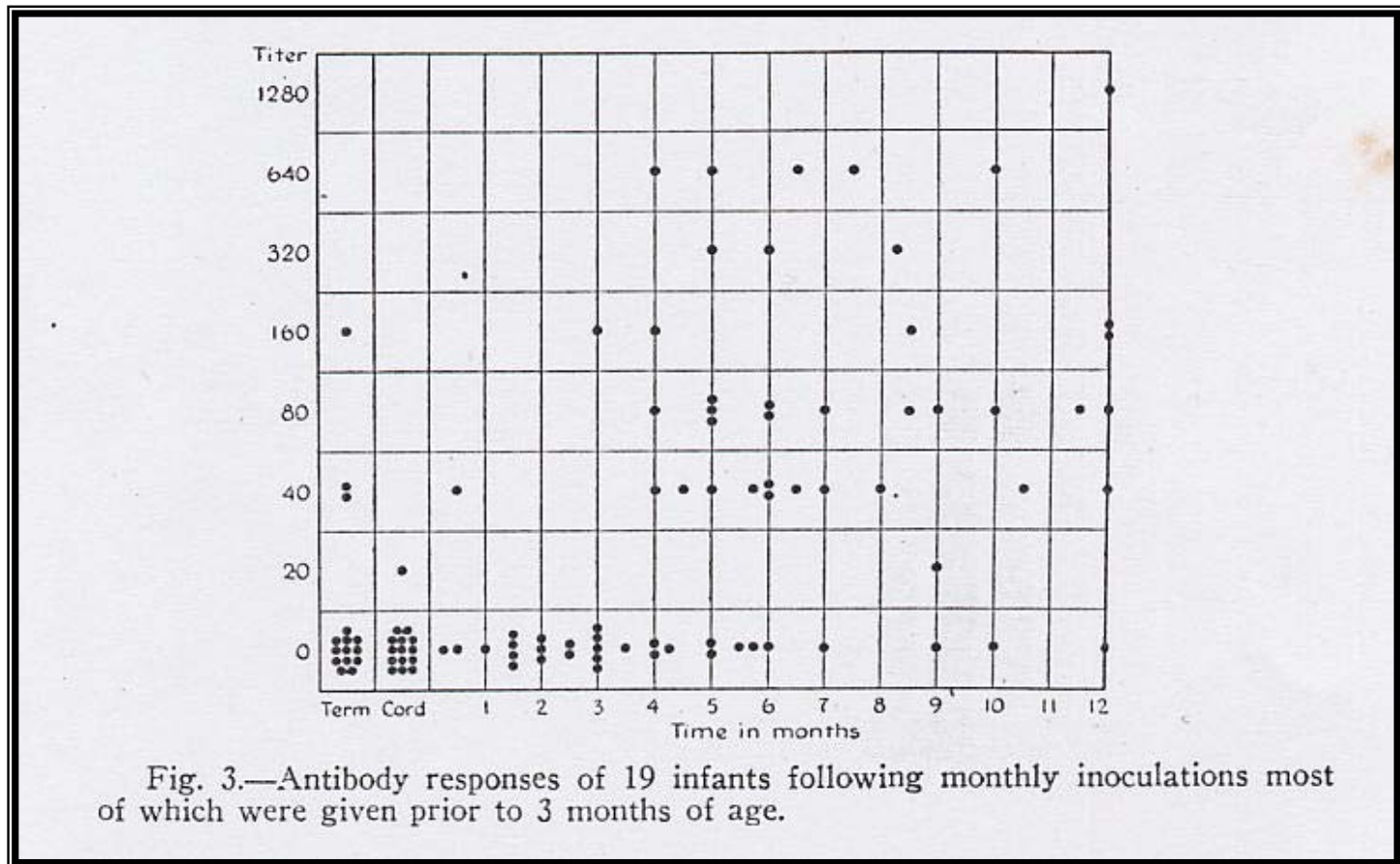
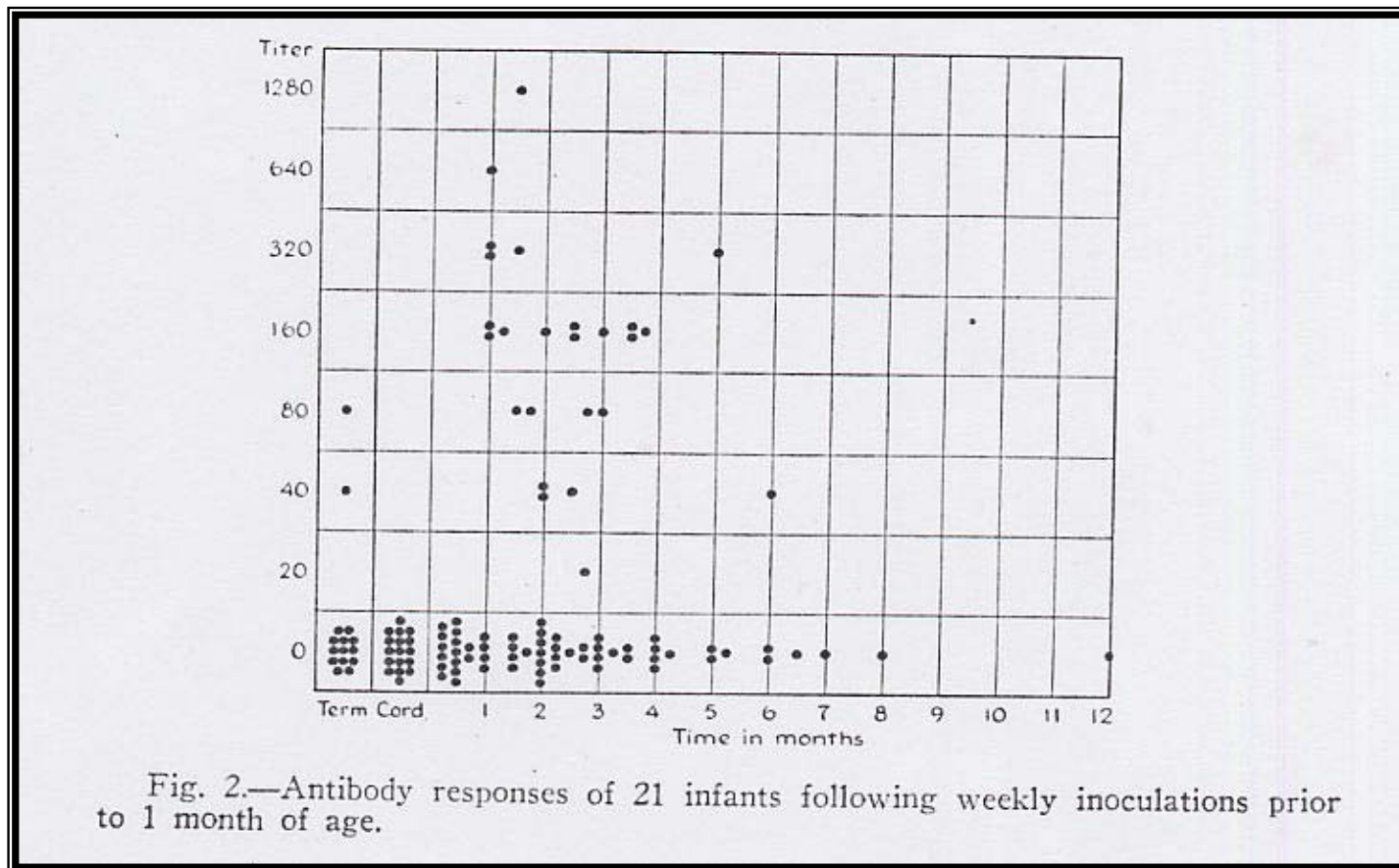


Fig. 3.—Antibody responses of 19 infants following monthly inoculations most of which were given prior to 3 months of age.

Adams, J.M. Kimball, A.C. Adams, F.H. Early immunization against pertussis. *American Journal of Diseases of Children* 1947;74:10-18.



Studies of DTPw initiated from birth to 4 weeks of age 1959 - 1984

Author	Year	P	N	Age at first dose
Provenzano (US)	1959	DPT	7	4 weeks
Gaisford (UK)	1960	DPT	31	1 week
Butter (UK)	1962	P	121	1 week
Barrett (US)	1963	DPT	49	1-2 days
Provenzano (US)	1965	DPT	8	1 day
Abayomi (Nigeria)	1973	DPT	217	< 2 days
Barraff (US)	1984	DPT	10/13	3-5 days

Total

2900 (599)

Gaisford W, Feldman GV, Perkins FT. Current immunization problems. *J Pediatrics* 1960;56: 319-330.

- N = 31 infants
- cord blood
- 1 week, 5 weeks, 9 weeks - DTP 1ml
- blood 6 weeks after 9 week DTP = 15 weeks

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IMMUNIZATION AND ANTIBODY RESPONSE IN THE NEWBORN INFANT

I. Pertussis Inoculation within Twenty-four Hours of Birth

R. WILLIAM PROVENZANO, M.D., † LESLIE H. WETTERLOW, B.S.,‡ AND CHARLES L. SULLIVAN, M.D.§

CAMBRIDGE AND BRIGHTON, MASSACHUSETTS

**Provenzano RW, Wetterlow LH, Sullivan CL.
Immunization and antibody response in the newborn
infant. I. Pertussis inoculation within twenty-four
hours of birth. *N Engl J Med* 1965;273:959-965.**

Pertussis-containing vaccine 6 -< 2 hours after birth

- Group 1 P+P+P @ 3 week intervals
 then 2xDTP @4 week intervals
- Group 2 3xDTP @1 day, 1 month, 2 months
- Boosters with DTP @ 12 and 24 months

Outcome: pertussis agglutinins

**Provenzano RW, Wetterlow LH, Sullivan CL.
Immunization and antibody response in the newborn
infant. I. Pertussis inoculation within twenty-four
hours of birth. *N Engl J Med* 1965;273:959-965.**

1. Maternal antibody N = 5 Group 1

N = 3 Group 2

- 5/5 with data available responded to booster DTP
- little response to P

2. No maternal antibody N = 11 Group 1

N = 5 Group 2

- post DTP 2 4 (25%) no agglutinins
- post booster 1 10/10 antibody

Butler NR, Wilson BDR, Benson PF, et al. Response of infants to pertussis vaccine at one week and to poliomyelitis, diphtheria, and tetanus vaccine at six months. *Lancet* 1962;2:112-115

Vaccine

Schedule	1, 6, 12 weeks
Pertussis	@ 1 week - plain or adsorbed
DTP - IPV	@ 6 and 12 weeks
Serum	12 weeks post 10 pre and post booster

Controls

matched by age, sex and street
followed for 2 years
Pertussis determined by cough history

Butler NR, Wilson BDR, Benson PF, et al. Response of infants to pertussis vaccine at one week and to poliomyelitis, diphtheria, and tetanus vaccine at six months. *Lancet* 1962; 2: 112-115

N=943 both arms	Vaccine (AR)	Control (AR)
Any illness	347 (37%)	353 (37%)
Measles	75 (8%)	61 (6%)
Cough (not paroxysmal)	160 (17%)	186 (20%)
Pertussis	102 (1.5)	34 (5.1)

Butler NR, Wilson BDR, Benson PF, et al. Response of infants to pertussis vaccine at one week and to poliomyelitis, diphtheria, and tetanus vaccine at six months. *Lancet* 1962;2:112-115

Agglutinins vs disease

- Plain vaccine lower response post primary (69% vs 90%, GMT 28 vx 131)
- AR for plain vaccine = adsorbed
- Fewer household contacts pertussis in plain group

Baraff LJ, Leake RD, Burstyn DG, et al. Immunologic response to early and routine DTP immunization in infants. *Pediatrics* 1984;73:37-42.

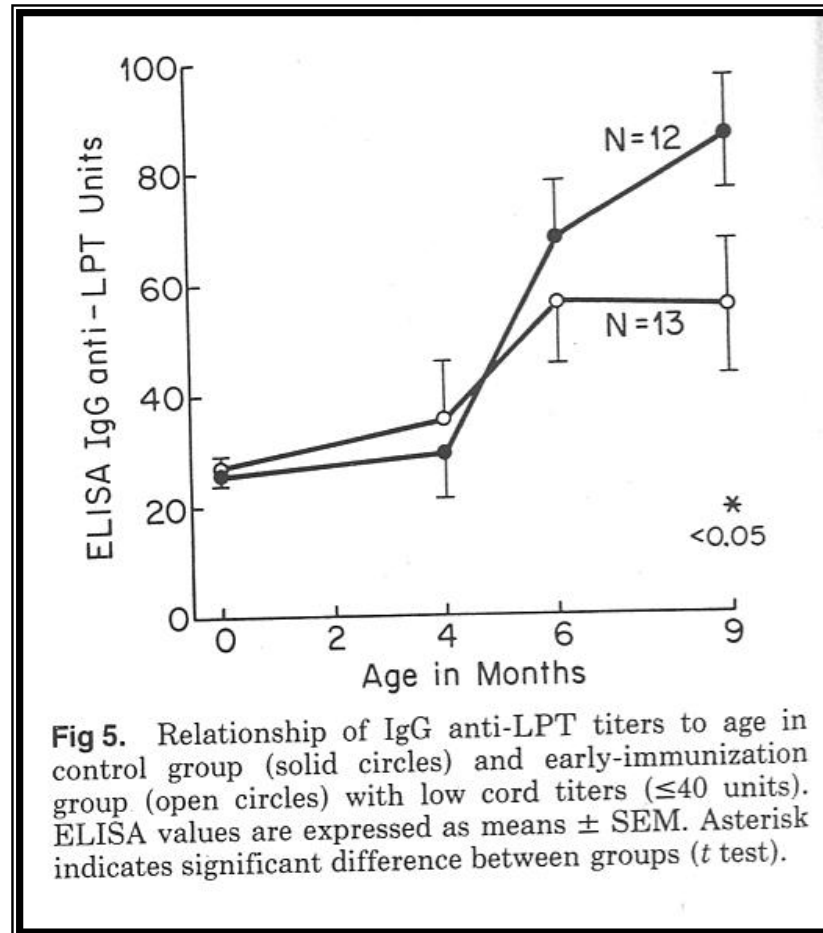
1979 N=91

1. Randomised to healthy newborns before nursery discharge (mean 4 days) + 2,4,6
2. Outcomes PT, FHA (ELISA) agglutinins (microagglutination)
3. Serum cord, 4,6,9 months

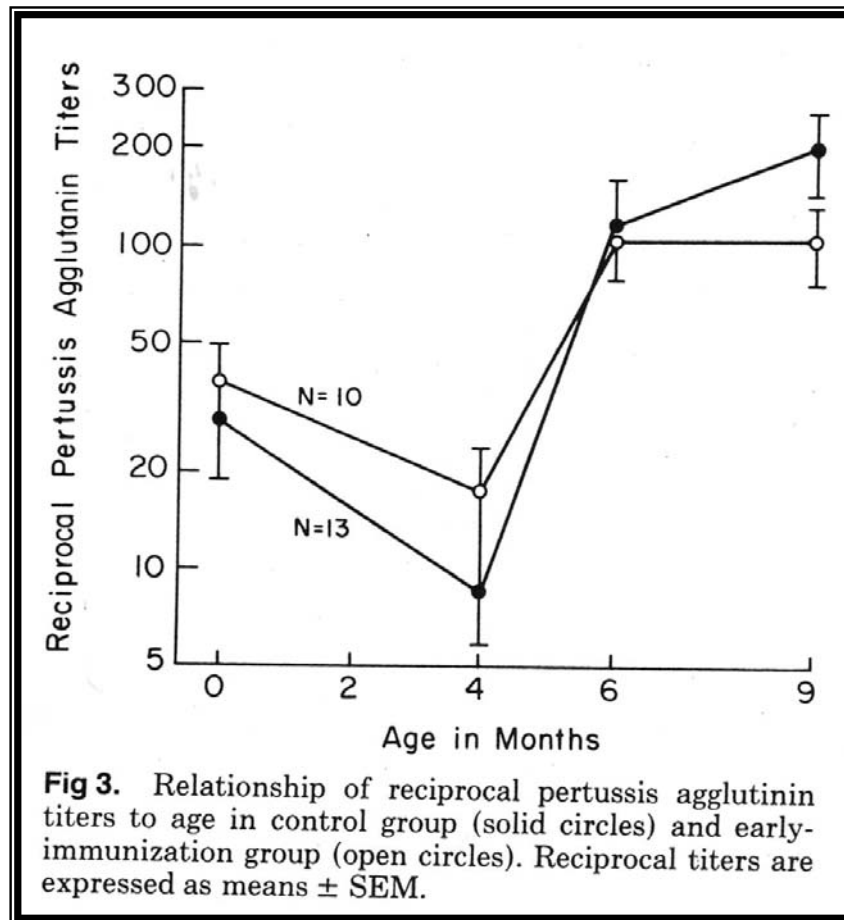
All visits N = 42 (46%)

All bloods N = 30 (33%)

Baraff LJ, Leake RD, Burstyn DG, et al. Immunologic response to early and routine DTP immunization in infants. *Pediatrics* 1984;73:37-42.



Baraff LJ, Leake RD, Burstyn DG, et al. Immunologic response to early and routine DTP immunization in infants. *Pediatrics* 1984;73:37-42.

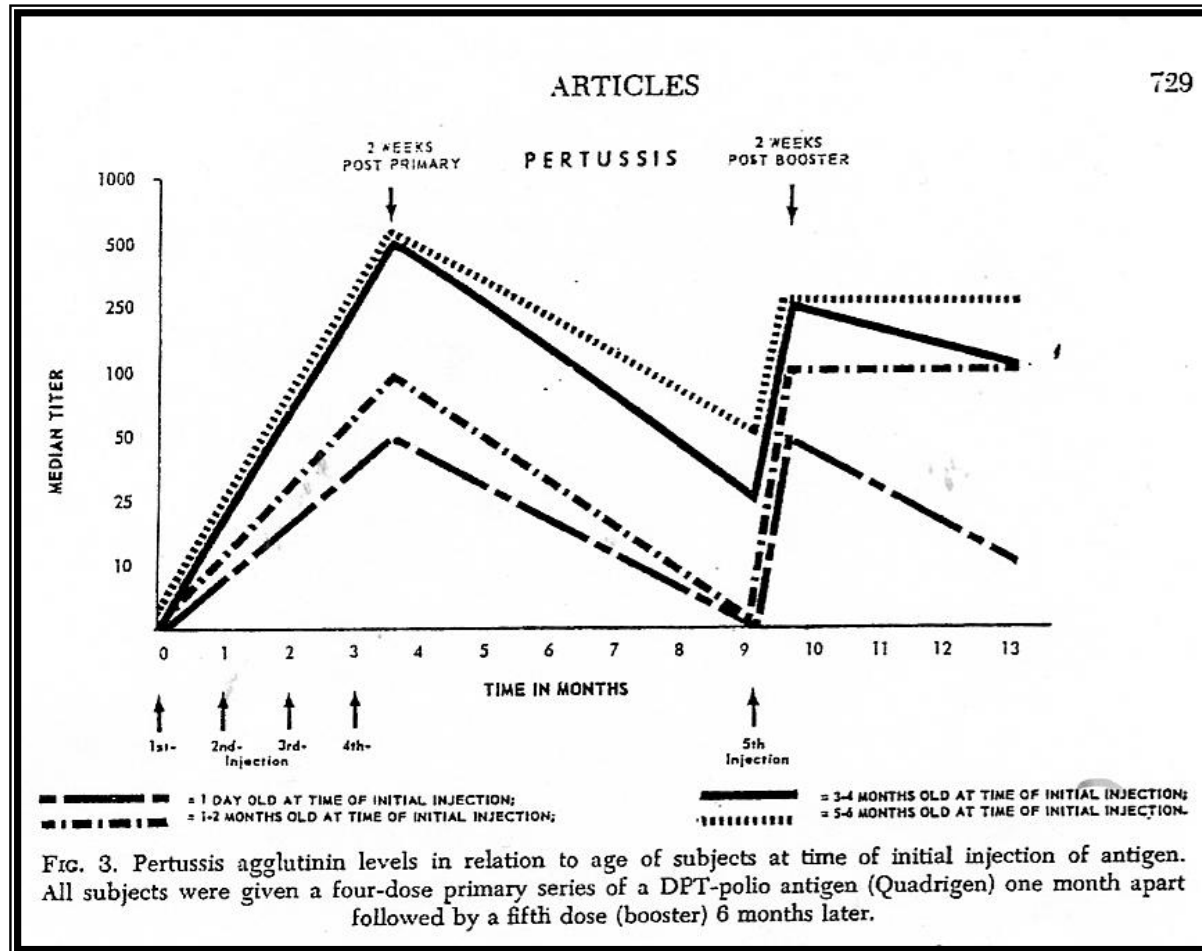


Abayomi I, Woodland M, Morley D. Whooping cough vaccine at birth. *J Trop Pediatr Environ Child Health*. 1973;19:3-4.

- Village of Imea, Nigeria
- Even dates DTP < 48hrs after birth
- Odd dates 1mo, 2mo, 3mo
- Early Group 4/217 (1.8%) pertussis
- One month group 7/210 (3.3%)

“It is hoped that as a result of this study workers in a larger population may consider undertaking wider studies.....”

Barrett CD Jr, McLean IW Jr, Molner JG, et al. Multiple antigen immunization of infants against poliomyelitis, diphtheria, pertussis, and tetanus. *Pediatrics* 1962;30:720-736.



Conclusions

1. Comparisons are difficult

- differing vaccines
- serology imperfect but.....
- early Pw does prevent pertussis

2. Outstanding issues

- optimum schedule
- protection against pertussis in industrialised and non-industrialised settings