Immune response and correlates of protection against *Shigella*

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Shigellosis

- Common all over the world and hyperendemic in developing countries.

- *Shigella spp*. was one of the four major pathogens significantly associated with moderate-to-severe diarrhea in children aged <60 months in the recent GEMS study.

- Children with the disease have an increased risk for persistent diarrhoea, nutritional faltering, and death.

Kotloff et al. Lancet 2013; von Seidlein L. et. al. PLOS Med. 2006

Genus *Shigella*

- *S. sonnei* is the leading *Shigella* species in industrialized countries
- *S. flexneri (*mostly serotypes 2a and 6*)* prevails in developing countries
- *S. boydii* and *S. dysenteriae* are responsible for around10-15% of cases of shigellosis
- *S. sonnei* emerges globally with improvement in sanitation and socio-economic level of countries, regions and populations (Ex. Vietnam, China, Bangladesh)

Livio S. et al. Clin. Infect. Dis. 2014; Ud-Din A et. al PLos One 2013 ; Vingh H et al. BMC Infect. Dis. 2009 ; Qiu S. et al. Clinical Infectious Diseases 2015

Shigellosis in Israel

- **Highly endemic**
- **Mean incidence rate of 80-100 culture-proven cases per 100,000 per year**
- **About 10-20 times higher than the incidence rate in the US**
- **Children aged 1-4 and soldiers serving under field conditions – at highest risk**

Cohen D et al. 2001; 2014

Natural *Shigella* Infection

- Induces around 70% serotype specific protection
- Length of protection not clear (~2 years)
- Solid protection is probably attained after consecutive exposures to *Shigella* antigens
- Potential correlates of protection, important for vaccine development and evaluation, are incompletely defined.

DuPont HL et al.1972; Ferrecio C et al. 1991; Lerman Y. at al. 1994; Cohen et al. 1991 and 2014; Thomas M. et al. 1972.

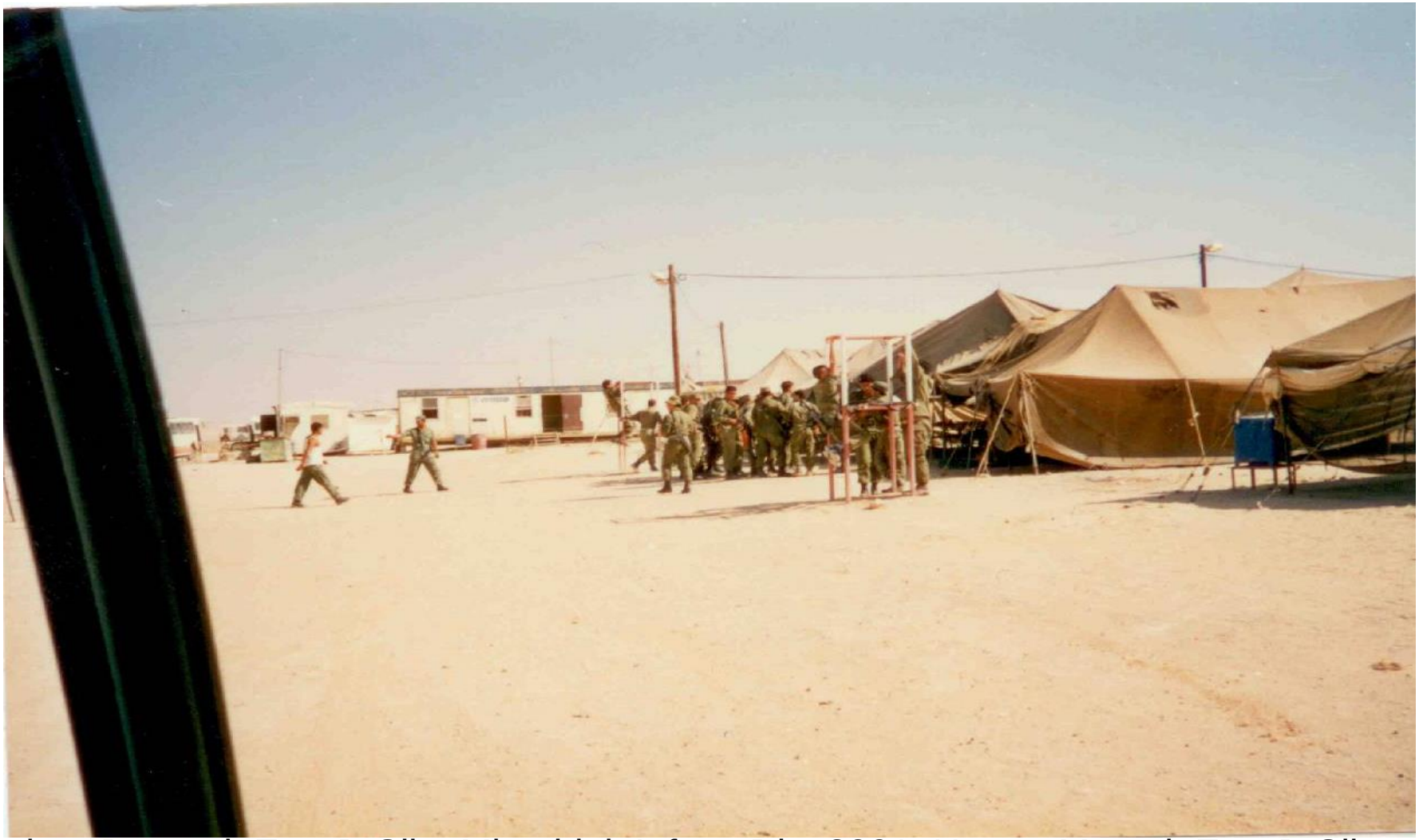
Criteria for potential correlates of protection against *Shigella*

- Significantly elicited by *Shigella* natural infection.
- Associated with a reduced risk of disease under natural conditions of exposure or in human challenge studies .
- Associated with protection induced by a candidate vaccine in efficacy studies.
- Have functional capabilities.

Components of the immune response to Shigella LPS following natural infection

- Serum antibodies (IgG, IgA, IgM)
- Secretory antibodies (sIgA)
- Urinary antibodies (sIgA)
- Antibody Secreting Cells
- B memory cells
- T cell response (cytokines)

Soldiers in field units, high incidence of shigellosis in 1980s and 1990s; S. sonnei and S. flexneri equally distributed together responsible for 90% of the cases of disease,



Cohen D. et al. Eur. J. Clin. Microbiol. Infect. Dis, 2001; Huerta M et al. Eur. J. Clin. Microbiol. Infect. Dis 2005

Serum IgG anti-LPS antibodies

*** Case-control studies (outbreaks).**

*** Prospective studies.**

Serum anti-*Shigella* LPS antibodies

Non-IgM fraction detected by passive HA after treatment of sera with 2-ME

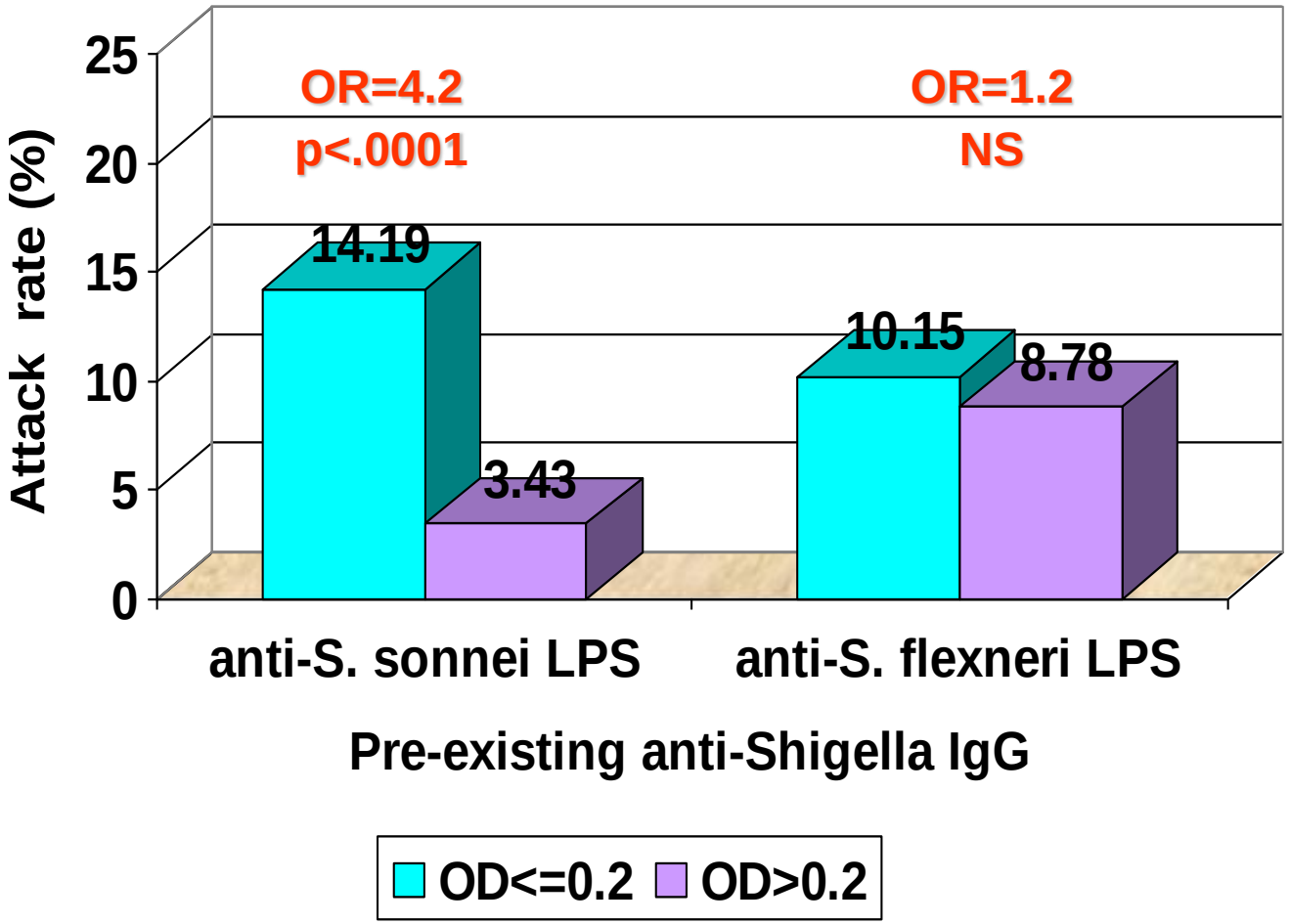
or

IgG fraction detected by ELISA.

Strongly associated with protection against disease caused by the homologous strain of *Shigella*.

Cohen D et al. JID 1988; Cohen D et al. JCM 1990

Pre-existing anti-LPS antibodies & *S. sonnei* Shigellosis.



Cohen D & al., J.Infect. Dis. 1988: Cohen D & al. J. Clin. Microbiol. 1990

Shigella Conjugate Vaccines

Detoxified O-specific polysaccharide covalently bound to a protein:

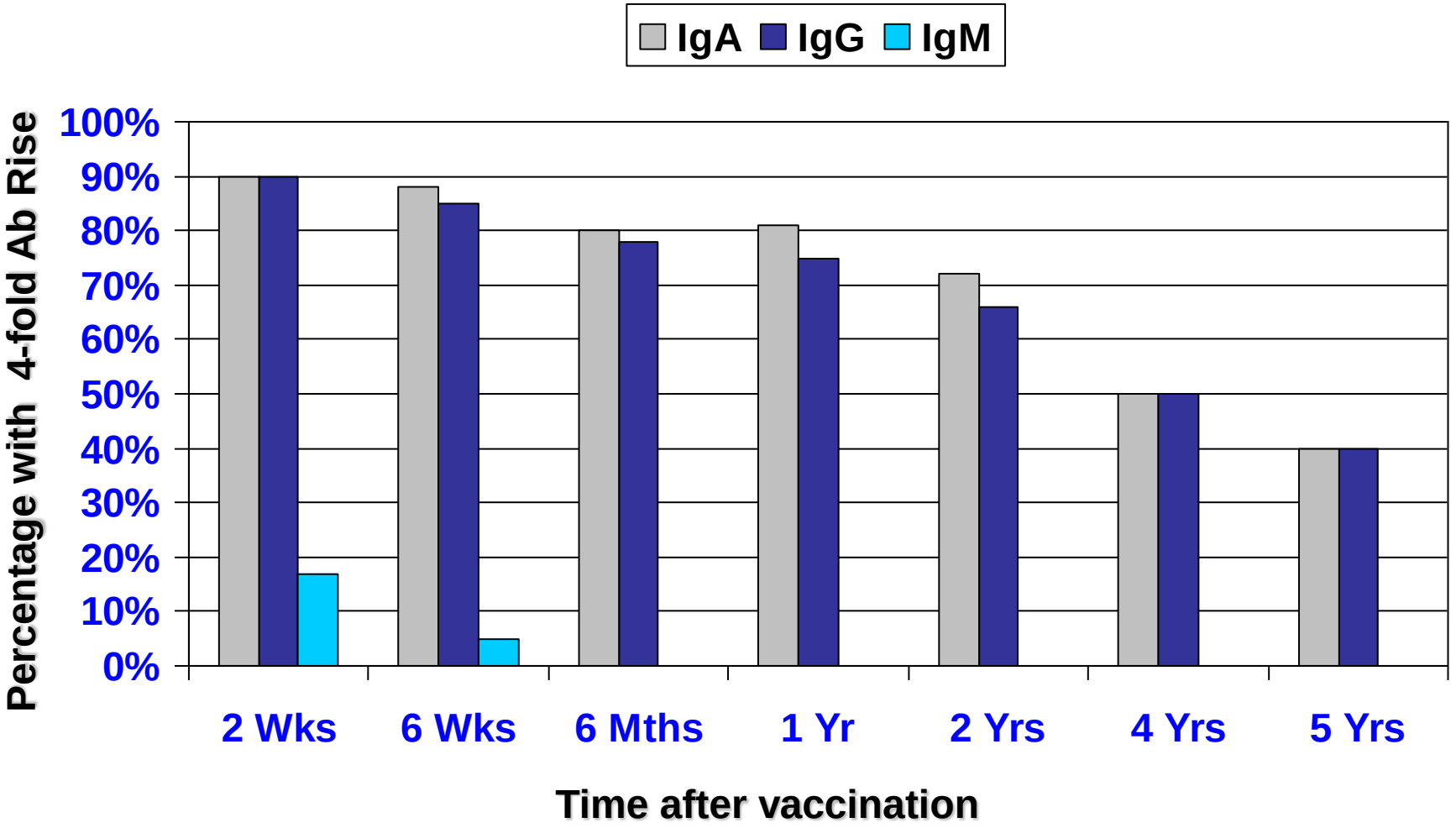
***S.flexneri* 2a – rEPA.**

***S.sonnei* – rEPA.**

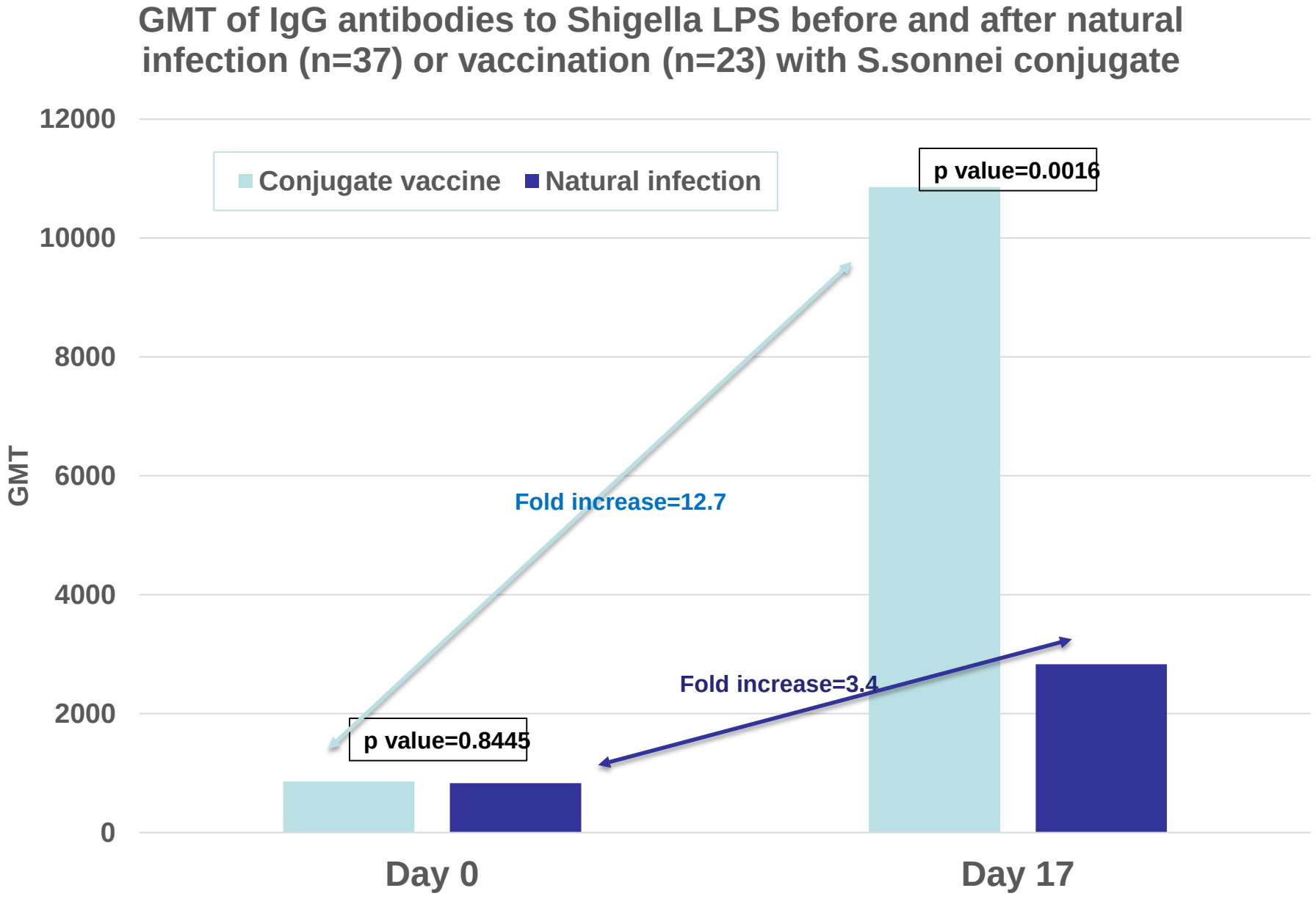
With the capability to elicit high serum LPS antibodies when injected IM

Robbins JB, Chu C, Schneerson R. Clin. Infect. Dis 1992

Antibody response to *S. sonnei* LPS after immunization with the *S.sonnei conjugate*



Cohen & al., Infect. Imm. 1996


GMT of IgG antibodies to Shigella LPS before and after natural infection (n=37) or vaccination (n=23) with S.sonnei conjugate
12000
10000
8000
6000
4000
2000
0
GMT
Conjugate vaccine
Natural infection
p value=0.0016
Fold increase=12.7
Fold increase=3.4
p value=0.8445
Day 0
Day 17

Antibody-Secreting Cell Response (ASC) – IgA (*Shigella sonnei & flexneri* Conjugate Vaccines)

	No./Total (Percent) with Significant ASC Response*		**Arithmetic Mean of Positive Results**	
	Ss-LPS	**Sf-LPS**	**Ss-LPS**	**Sf-LPS**
S.Sonnei vaccinees	**18/23 (78%)**	**0/8 (0%)**	**3311.4**	**-**
S.Flexneri vaccinees	**0/6 (0%)**	**13/19 (68%)**	**-**	**693.9**

* ASC result >=18 spots/Mcells: based on the mean (3.33) + 2SD (2x6.97) found in non-vaccinees

THE LANCET

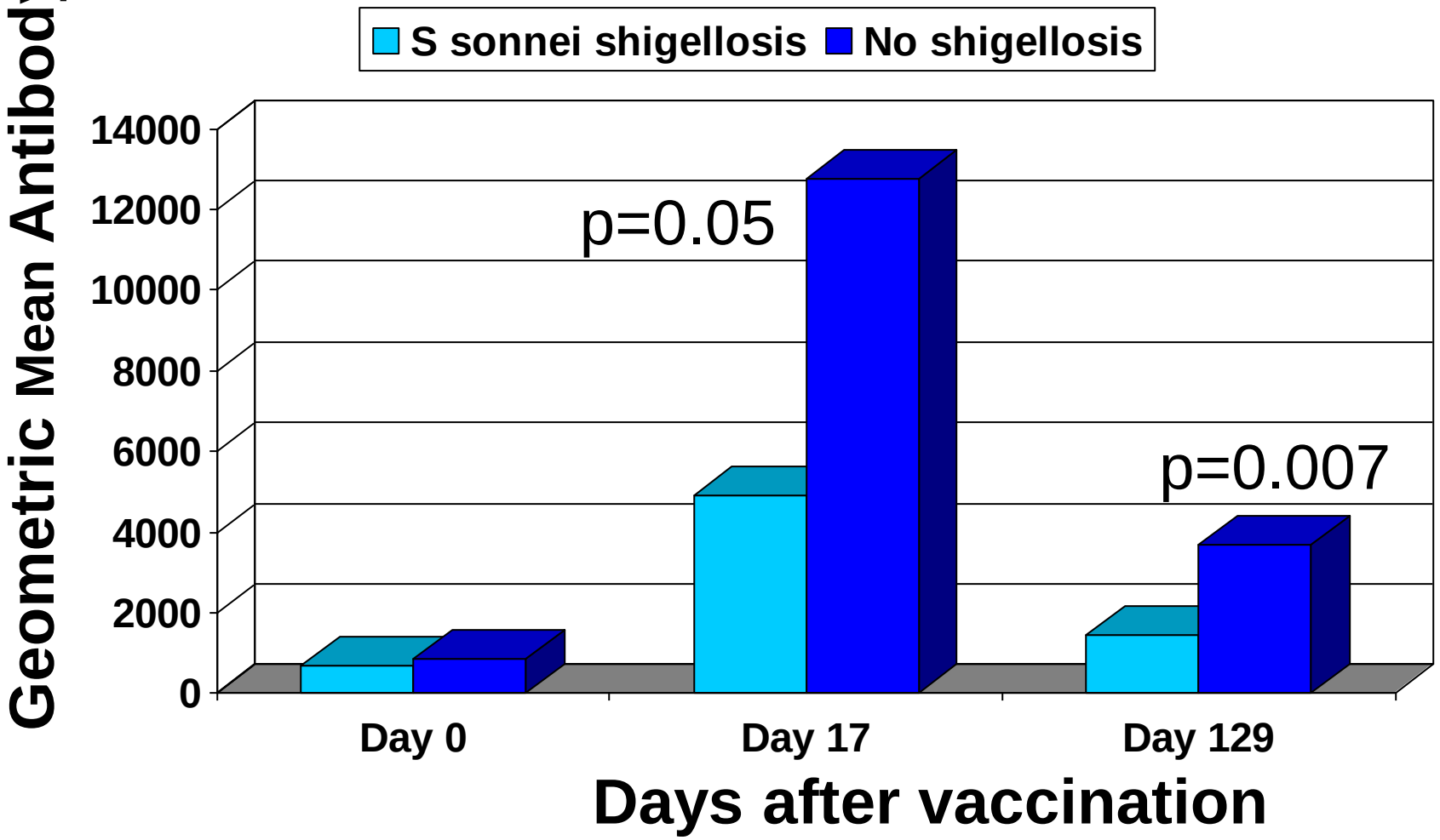
Double-blind vaccine-controlled randomised efficacy trial of an investigational *Shigella sonnei* conjugate vaccine in young adults

Dani Cohen, Shai Ashkenazi, Manfred S Green, Michael Gdalevich, Guy Robin, Raphael Slepon, Miri Yavzori, Nadav Orr, Colin Block, Isaac Ashkenazi, Joshua Shemer, David N Taylor, Thomas L Hale, Jerald C Sadoff, Danka Pavliakova, Rachel Schneerson, John B Robbins

74% protective efficacy in young adults

Lancet 1997; 349:155-159

GMT of IgG antibodies to S *sonnei* LPS among recipients of S *sonnei*-rEPA in group D*



* An outbreak of *S. sonnei* shigellosis occurred immediately after vaccination

Vaccine 28 (2010) 2231–2235

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Age-related efficacy of *Shigella* O-specific polysaccharide conjugates in 1–4-year-old Israeli children

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Efficacy of 2 doses of Shigella sonnei conjugate vaccine among Israeli children by age

Age	Vaccine administered				Efficacy	(95% CI)	P
	S. sonnei		*S. flexneri* 2a				
	N	Cases	*N*	Cases			
a. *Shigella sonnei*							
1–2 years	516	18	476	16	3.8%	(101.1, 46.5)	0.91
>2–3 years	497	8	481	12	35.5%	(−56.4, 73.4)	0.33
>3–4 years	371	3	358	10	71.1%	(−4.43, 92.0)	0.04
All ages	1384	29	1315	38	27.5%	(−16.9, 54.0)	0.18
b. *Shigella flexneri* 2a							
1–2 years	516	3	476	3	−8.4%	(−434.5, 78.0)	0.99
>2–3 years	497	4	481	3	22.5%	(−244.4, 82.6)	0.99
>3–4 years	371	1	358	1	−3.6%	(−1550, 93.5)	0.99
All ages	1384	8	1315	7	7.9%	(−153.2, 66.5)	0.87

Passwell JH et al. 2010

Age-related IgG anti-LPS levels 2-3 weeks after second vaccine dose of Shigella conjugates

		G.M IgG anti-LPS (EU)		
Vaccine	Age (years)	N	S.sonnei Ag	S.flexneri 2a
S.sonnei	1-2	38	1.4	3.43
	>2-3	44	3.71	7.53
	>3-4	29	6.38	9.51
S.flexneri 2a	1-2	43	0.25	18.98
	>2-3	53	0.42	26.96
	>3-4	30	0.76	43.86

Passwell JH et al. 2010

Clinical Immunology (2013) 148, 35–43

available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

Shigella antigen-specific B memory cells are associated with decreased disease severity in subjects challenged with wild-type *Shigella flexneri* 2a

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Shigella-specific IgA B memory cells and serum IgG LPS antibodies might play a protective role in humans

Conclusions

- Serum IgG antibodies to *Shigella* LPS emerge as a correlate of protection with mechanistic capabilities.

- We continue to evaluate the possible added value of other immune parameters following exposure to natural infection and candidate vaccines.

- Highly immunogenic vaccines are needed to immunize better than natural infection especially in pediatric populations.

S. flexneri 2a –PS tetanus toxoid synthetic glycoconjugate made at Institut Pasteur (projected phase 1 in adults in Israel, 2016)

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