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The selection of pneumococcal serotypes for a developing-world vaccine: A meta-regression analysis of immunogenicity

I have no actual or potential conflict of interest in relation to this program.

{**Or** disclose any real or apparent conflict(s) of interest that may have a direct bearing on the subject matter of the program.}

G7 asks GAVI and World Bank to Improve Immunization

Advanced Market Commitments

- Two-tier pricing
- AMC Pneumo pilot launched in Rome February 2007
- $1.5 billion pledged by Italy, United Kingdom, Canada, Norway, Russia, and the Gates Foundation

Target Product Profile

- Vaccine formulations for developing countries
- Disease burden, vaccine efficacy data
- GAVI's PneumoADIP, WHO, PATH, others

PneumoADIP

- Johns Hopkins Bloomberg School of Public Health
- Alliance with WHO, funded by GAVI
- Activities
  - Surveillance and Research
  - Communications and Advocacy
  - Vaccine Access and Implementation

PATH

Program for Appropriate Technology in Health

Founded in 1977

PATH's Vaccine Portfolio

- Malaria Vaccine Initiative
- Meningococcal Group A conjugate vaccine
- New rotavirus vaccines
- New influenza vaccines
- Vaccines against ETEC and *Shigella*
- **New pneumococcal vaccines**

Pneumococcal Vaccine Project

- Goal: Accelerate development of safe, effective, and affordable vaccines against *S. pneumoniae* in order to reduce childhood acute lower respiratory infections and mortality in Africa and other low-income regions
- Resources: ~US$84 million (2 grants)
- Time frame: 2004 to 2011

Pneumococcal Vaccine Project Objectives

1. Advance protein vaccine candidates.
2. Support development of low-cost conjugate vaccines.
3. Genome analysis to define vaccine targets.
4. Validate immune mechanism of protection against carriage.
5. Pursue other strategies arising from a review of technologies.
6. Engage the pneumococcal research community to advance the field of pneumococcal vaccine development.

TPP Serotype Selection

At least 60% coverage based on prevalence

Problem:

What is the prevalence worldwide and in GAVI eligible countries?

- Report from GAVI PneumoADIP
- Recent report from China
  - Includes serogroup sub-typing not previously done
- No recent data from India

Selection of most prevalent serotypes is geography dependent.

Diag Micro inf Dis 61: 256 (2008)		GAVI PneuADIP (2007)		PneuADIP Worldwide (2007)		PneuADIP		Consensus	
China		GAVI		World		India		?	
	%		%		%		%		
19F	42.1	1	13.8	14	27	1			
19A	11.7	14	13.8	6B	11.3	2			
6B	7.3	5	13.8	1	7.7	45			
14	7.8	6A	5.7	19F	7.7	14			
23F	5.8	19F	5.6	23F	6.8	5			
15	4.4	23F	5.6	6A	5.4	12A			
5	0.7	19A	4.6	18C	5.1	16			
11	0.9	6B	4.1	5	4.8	7F			
		2	3.1	19A	4.1				
		4	2.1	9V	3.9				
		9V	1.8	4	3.6				
		18C	1.7	7F	1.8				
		7F	1.4	3	1.5				

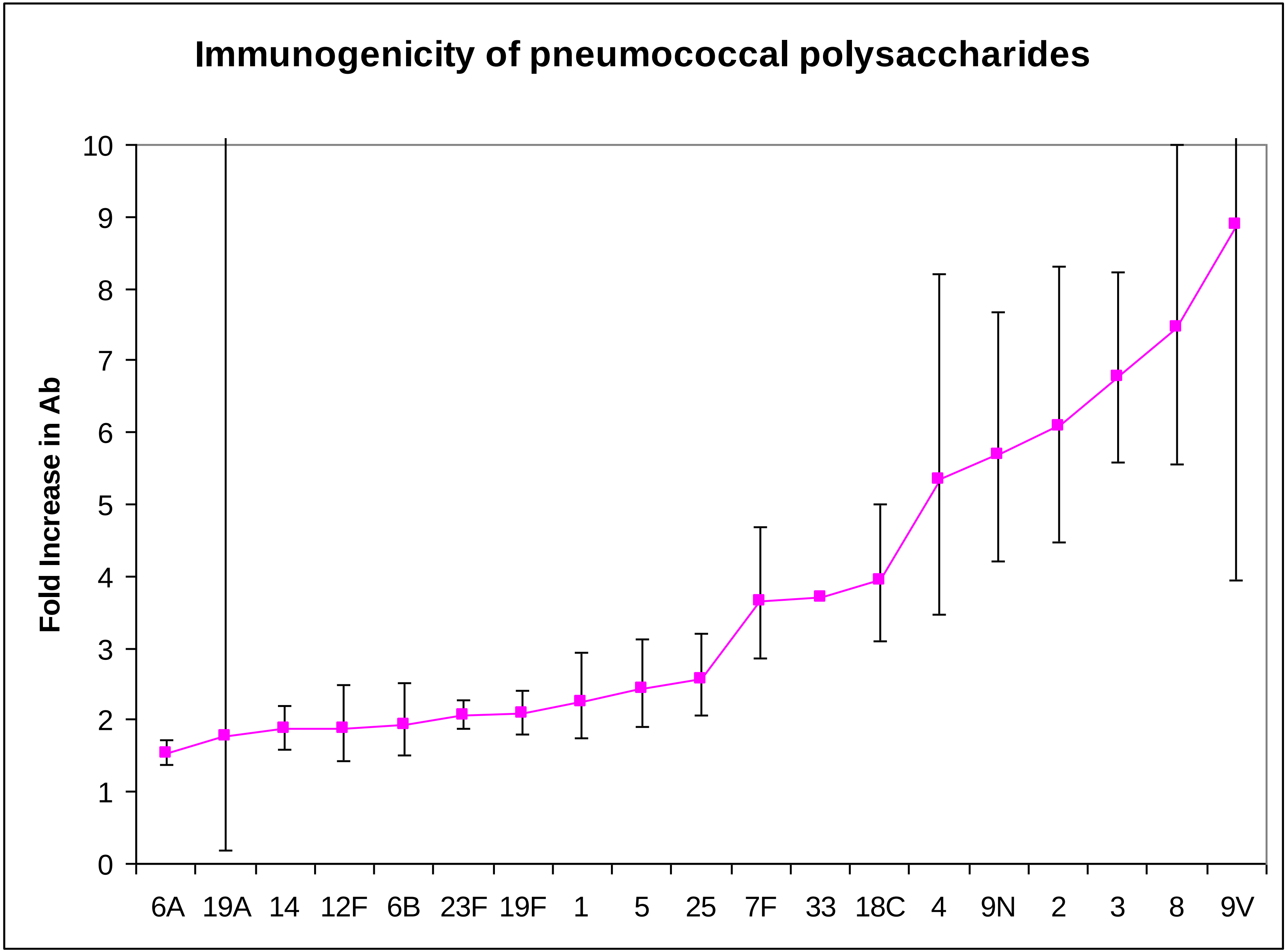
An Alternate Way to Select Serotypes: Polysaccharide Immunogenicity

- Rationale:
  - Mechanism of protection against pneumococcus is opsonophagocytosis (Serotype Ab + C’)
  - More immunogenic serotypes will induce Serotype Ab response after colonization

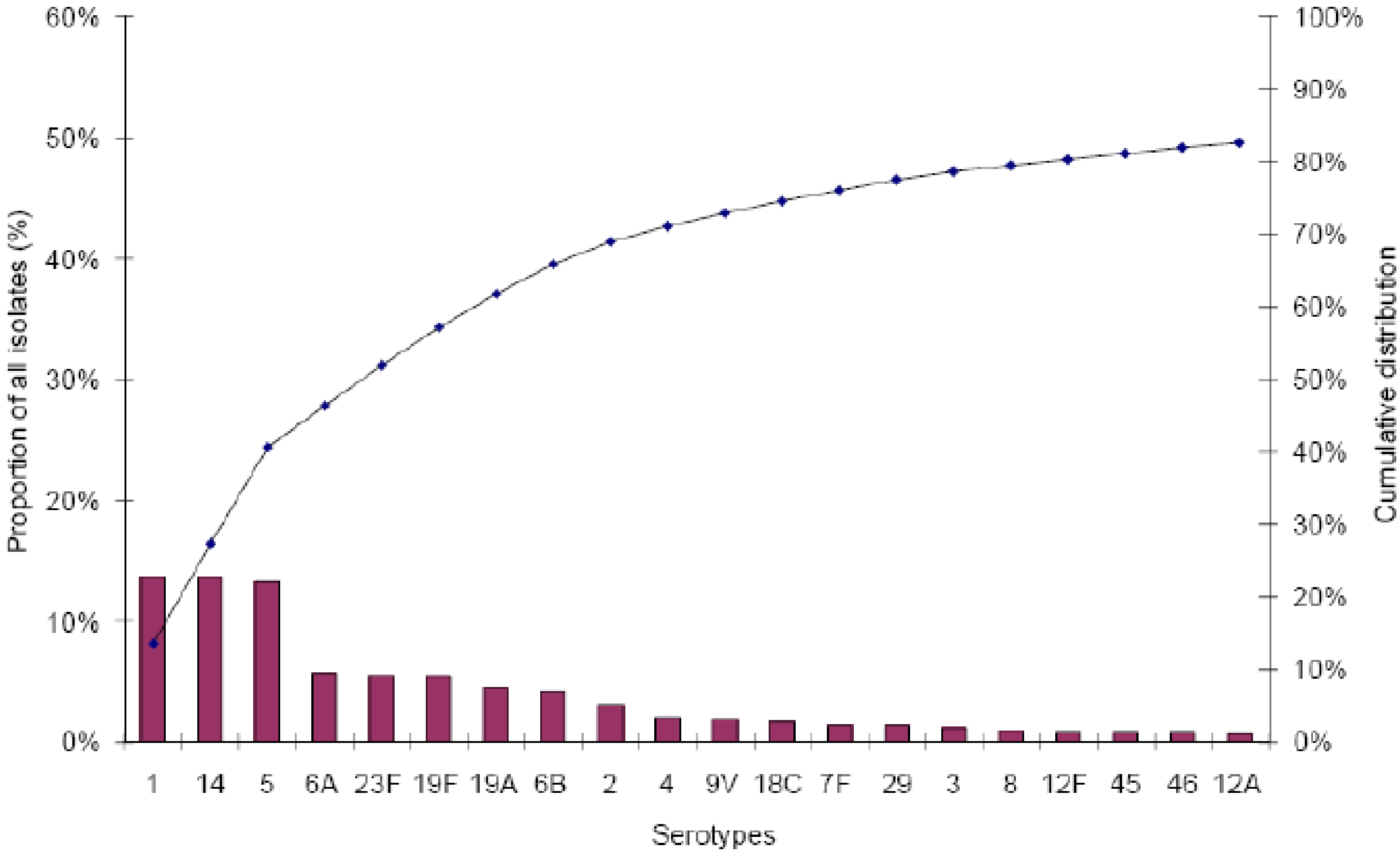
- Conclusion:
  - Select least immunogenic serotypes

28 Studies Identified, 15 have statistical analysis

Study	County	Error calculations	Trial Type	Vaccine	Serotypes tested	Age at immunisation (years)	Route of ad-ministration	Serological method	Number of subjects per group
Balmer 2007	UK	Quart.	Obs.	23V	1, 3, 5, 7F, 19A	0.5	i.m.	FACS	27
Barrett 1984	USA	SEM	Obs.	8V	3, 6A, 18C, 19F, 23F	0.33, 0.79, 1.3	s.c.	ELISA	10 - 22
Blum 2000	Israel	95% CI	RCT	23V	4, 6B, 9V, 14, 18C, 19F, 23F	2.5	i.m.	ELISA	84
Borgono 1978	Chile		RO	12V	1, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, 23D	0.33, 0.75, 1.54	s.c.	RIA	7 - 26
Cowan 1978	USA	SD	OC	8V	1, 3, 6A, 7F, 14, 18C, 19F, 23F	0.17, 0.25, 0.42, 0.62, 1.33	s.c.	Indirect haemagglutinin	9 - 16
Douglas 1983	Australia		CRT	14V	1, 2, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, 23F, 25	0.71, 1.21, 1.71, 2.45, 3.46, 4.25		RIA	6 - 36
Karma 1980	Finland		CRT	14V	3, 6A, 14, 19F, 23F	0.5, 1, 2, 3, 4, 5	i.m.	RIA	19 - 49
Koskela 1981	Finland		Obs.	14V	3, 6A, 14, 18C, 19F, 23F	1, 4.5	i.m.	RIA/ELISA	7 - 22
Koskela 1986	Finland		CRT	14V	3, 6A, 7F, 8, 12F, 14, 18C, 19F, 23F	0.625	i.m.	RIA/ELISA	33
Lawrence 1983	USA		OC	14V	1, 3, 6A, 7F, 8 9N, 12F, 14, 18C, 19F, 23F	2, 3, 4, 5	i.m.	RIA	2 - 10
Leach 2008	Australia	95% CI	OC	23V	1, 3, 5, 7F, 12F, 18C, 19A,	1.5	i.m.	ELISA	29
Leinonen 1986	Finland	95% CI	Obs.	14V	3, 6A, 8, 18C, 19F, 23F	0.5, 1.5, 2.5, 3.5, 4.5	i.m.	RIA	40
Lottenbach 1999	USA	95% CI	RCT	23V	6B, 14, 18C, 19F, 23F	0.92		ELISA	10
Makela 1981	Finland		Obs.	14V	3, 6A, 19F, 23F	0.5	i.m.	RIA	31
O’Brien 1996	USA	SD	RCT	23V	6B, 23F	1.96	i.m.	ELISA	15
Obaro 1997	Gambia	95% CI	RCT	23V	6B, 14, 18C, 19F, 23F	2.65	i.m.	ELISA	27

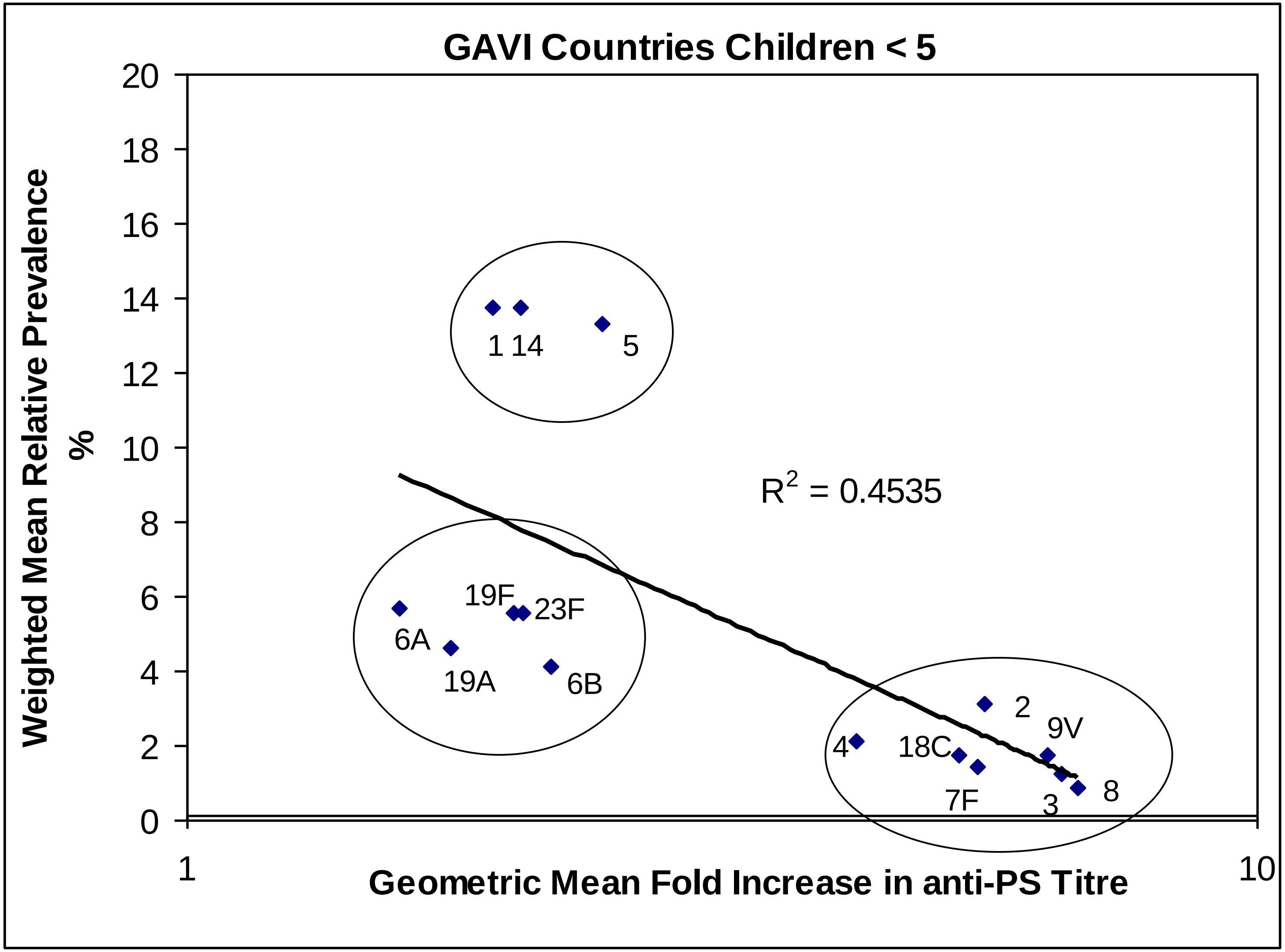

Immunogenicity of pneumococcal polysaccharides
Fold Increase in Ab
0
1
2
3
4
5
6
7
8
9
10
6A
19A
14
12F
6B
23F
19F
1
5
25
7F
33
18C
4
9N
2
3
8
9V

Proportionate and cumulative serotype distribution of isolates from GAVI Countries (invasive disease, children < 5, 1980 to 2007)



PnemoADIP

Immunogenicity of pneumococcal polysaccharides is inversely correlated with relative prevalence of serotypes in GAVI Countries



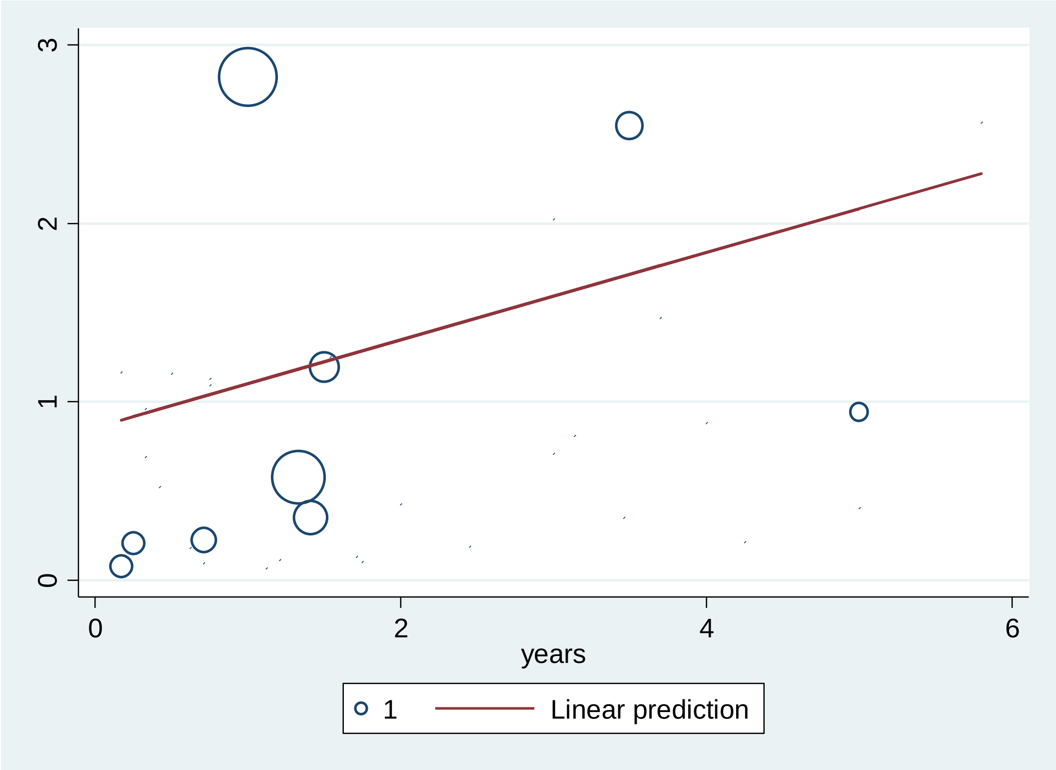
Conclusions

- Correlation gives 3 clusters
- 45% suggest additional virulence factor(s)
  - antibiotic resistance
  - genetic factors
- A vaccine selected on immunogencity is the *same* as selected based on prevalence in GAVI countries, but does not justify 4, 9V or 18C
- 1, 5, 6B, 14, 19A, 19F, 23F

Is there a better way to compare data across different serotypes?

- Meta-regression
  - Developed over the last 10-15 years
  - Study level aggregates as co-variates explain heterogeneity
  - Variance of data is used for weighting
  - Different mathematical models
    - Fixed effect
    - Random effects
  - Variance estimated using N (subject per arm)

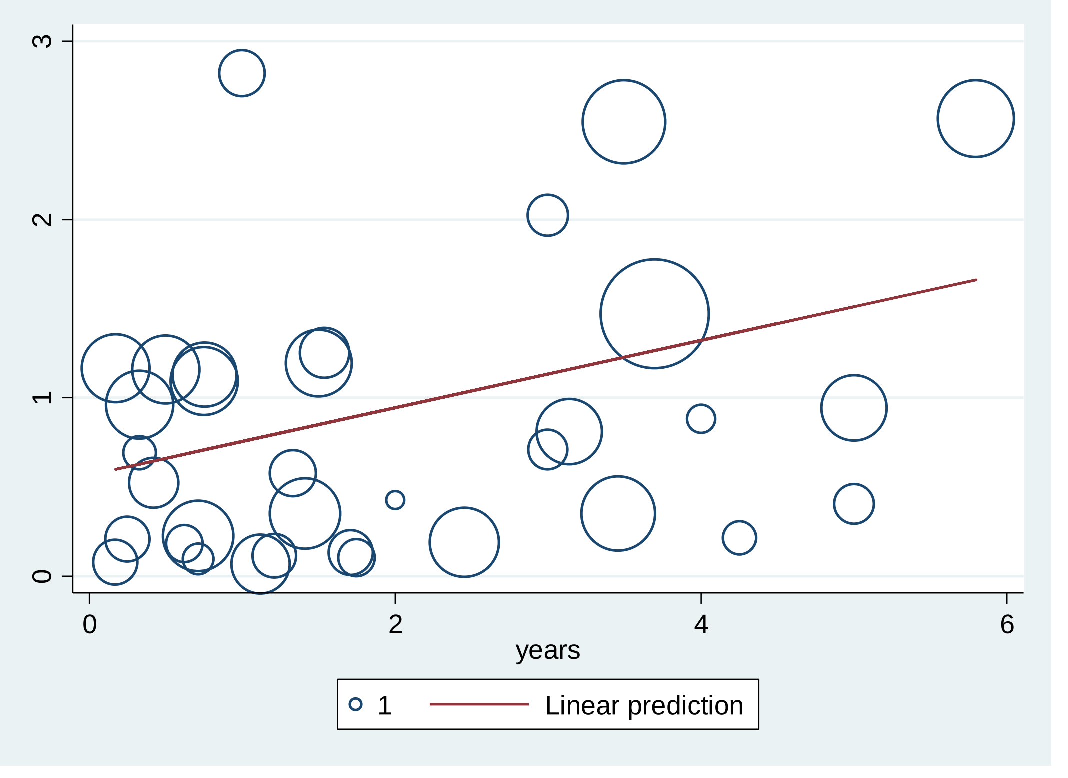
Serotype 1 log fold increase vs age



p=0.58

Only a few publications report the variance

Serotype 1 log fold increase vs age



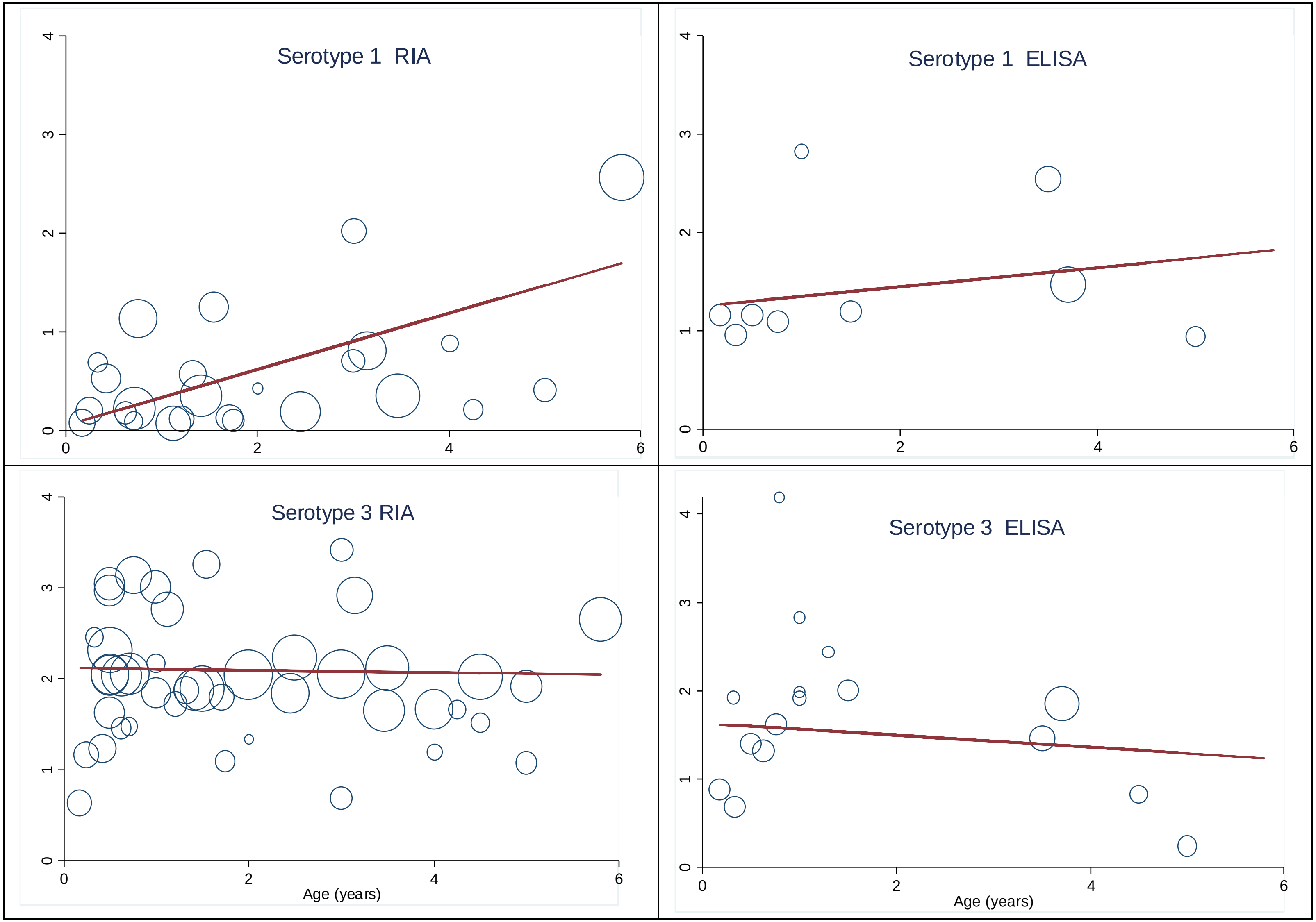
p=0.03

Estimate proportional variance by 30/n

Results of meta-regression of data from 28 studies

- No differences between RIA and ELISA data, except serotypes 1 and 3; thus data can be combined.
- No consistent differences for other study treatments: dosage, route, location, time of sample, number of serotypes in vaccine
- Immunogenicity correlated with age in 4 serotypes, and a trend in 4 more.
- Appears to be 2 distinct effects, T-independent response, and another regulation

Differences in RIA and ELISA data can be explained by selection bias



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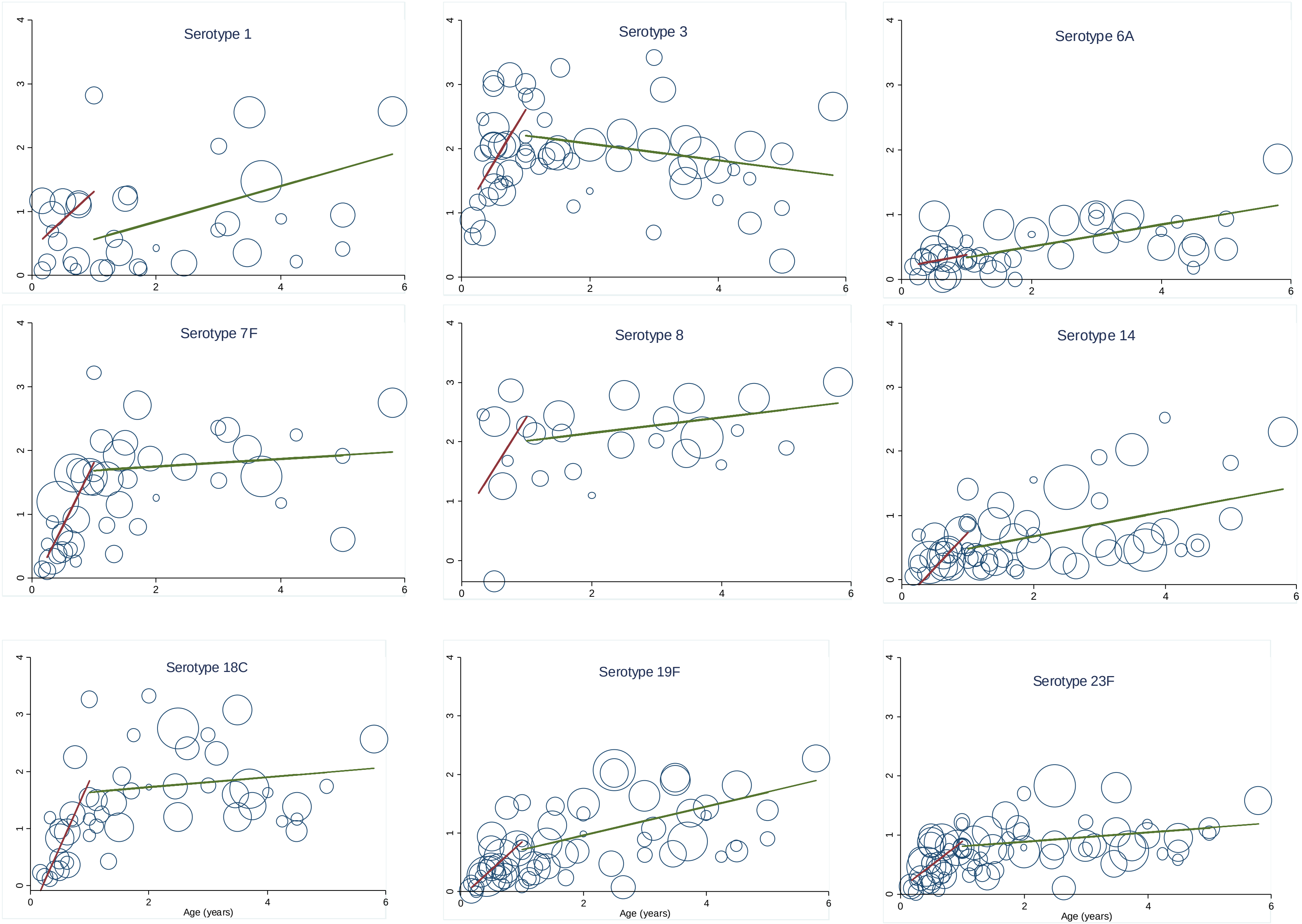
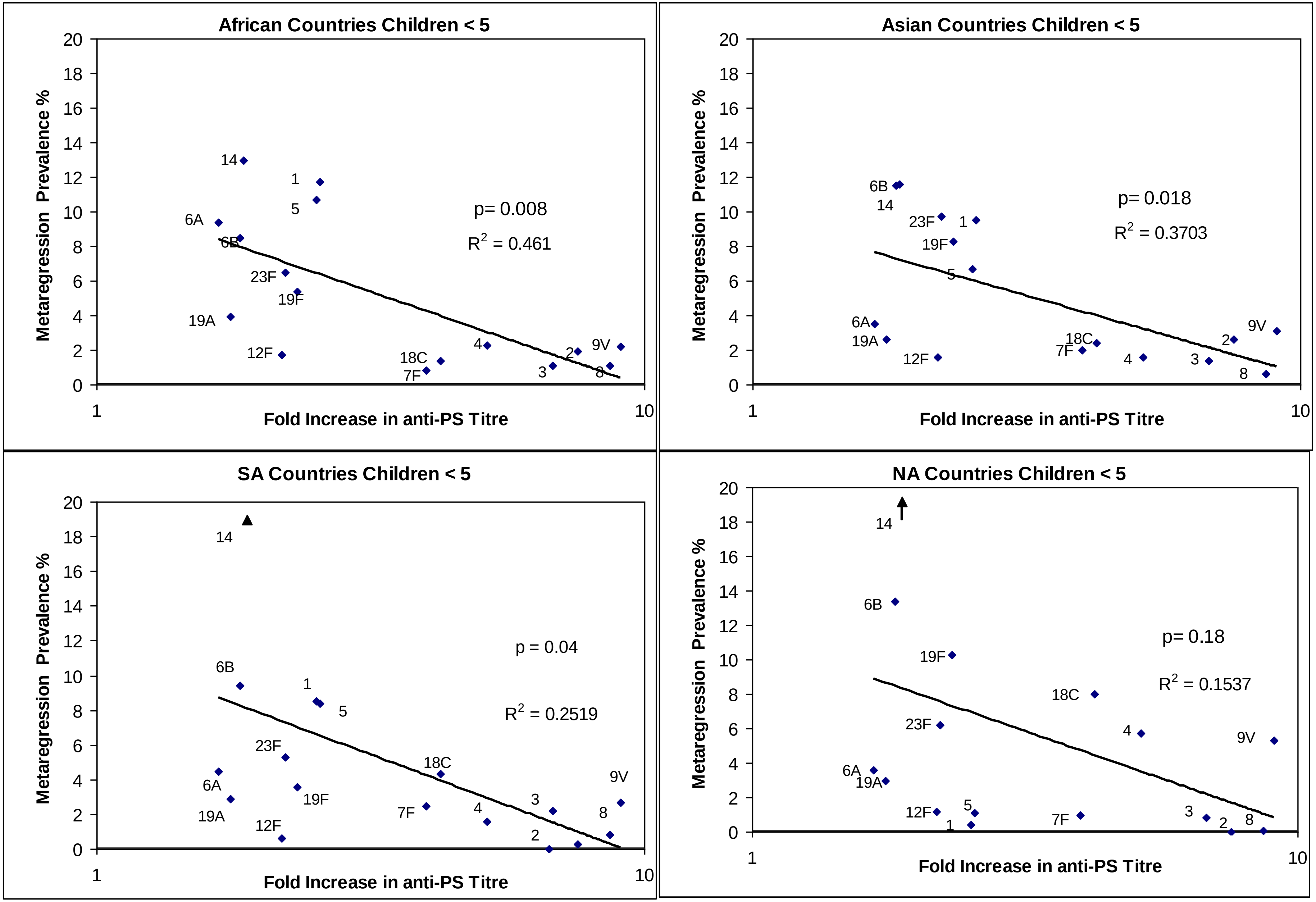
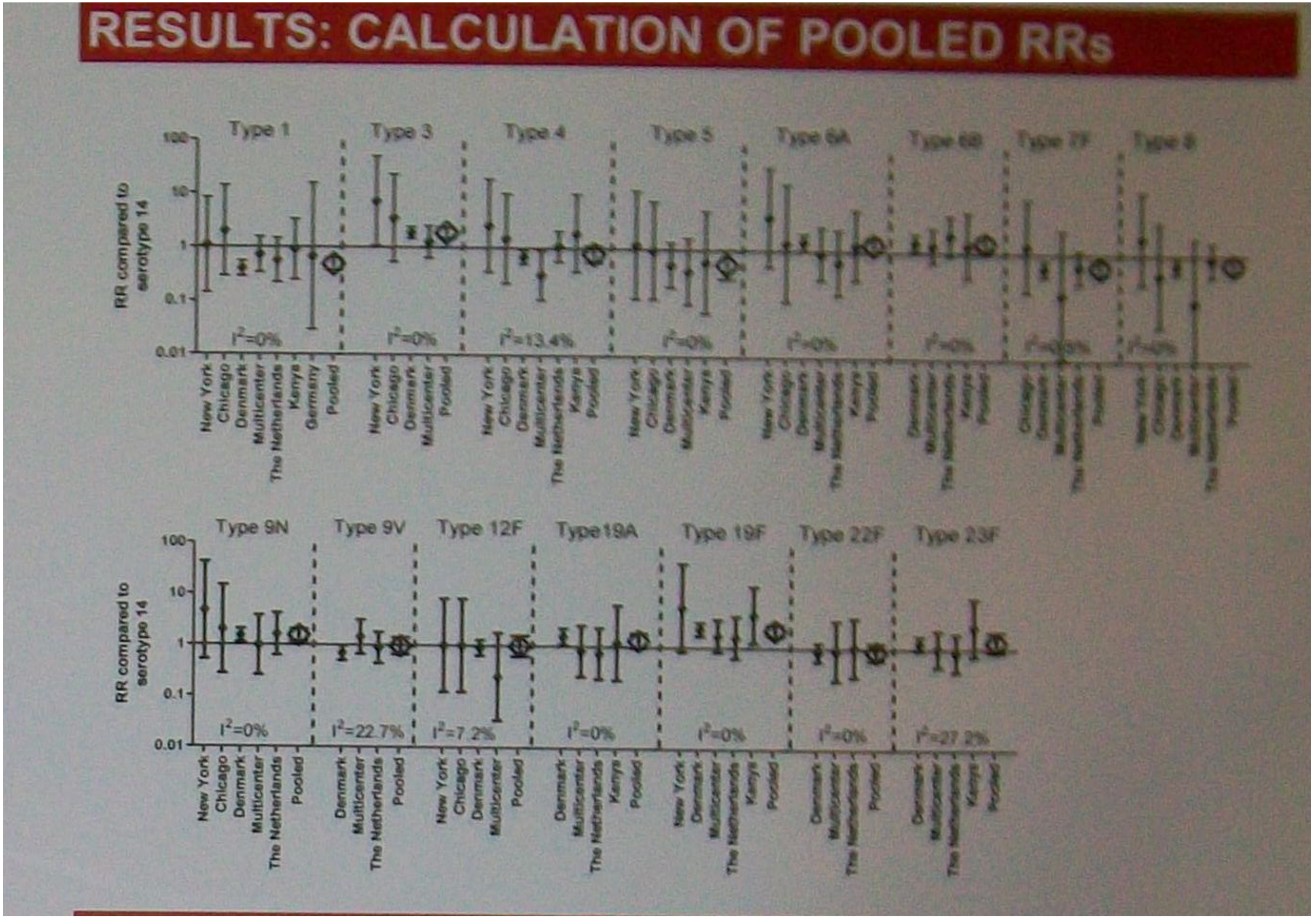
Immunogenicity vs age for 9 serotypes. Metagression lines at < or >1 year



IPD Prevalence vs immunogenicity in different regions



Similar approach at Harvard School of Public Health



Conclusions

- Meta-regresion supports the preliminary conclusions that prevalence is 15 to 46% correlated to polysaccharide immunogenicity
- Correlation differs by region. Clusters not evident in some regions
- Another virulence factor, possibly antibiotic resistance, accounts for excess prevalence of some serotypes
- Meta-regression confirms the selection of serotypes 1, 5, 6B, 14, 19A, 19F, 23F for a vaccine.