

# Group A streptococcal vaccines: challenges and progress

Florian Schödel

Philimmune LLC

# Thanks to:

- Jonathan Carapetis, Telethon Institute for Child Health Res., West Perth, AU
- James Dale, Univ. Memphis TN
- John Fraser, Univ. Auckland, NZ
- Michael Good, Queensland Inst. Med. Res., NZ

# Group A streptococcal diseases

- Superficial infection
  - Pharyngitis
  - Pyoderma
- Invasive diseases
  - Septicaemia
  - Pneumonia, osteomyelitis...
  - Necrotising fasciitis
- Toxin mediated diseases
  - Scarlet fever
  - Streptococcal toxic shock syndrome
- Post-streptococcal autoimmune sequelae
  - Acute rheumatic fever / rheumatic heart disease
  - Post-streptococcal glomerulonephritis



## Summary of estimated global burden of GAS diseases

Disease	Number of existing cases	Number of new cases each year	Number of deaths each year
Rheumatic heart disease	15.6 million	282,000*	233,000 <sup>†</sup>
History of acute rheumatic fever without carditis, requiring secondary prophylaxis	1.88 million	188,000*	
RHD-related infective endocarditis		34,000	8,000
RHD-related stroke	640,000	144,000	108,000
Acute post-streptococcal glomerulonephritis	§	472,000	5,000
Invasive group A streptococcal diseases		663,000	163,000
<b>Total severe cases</b>	<b>18.1 million</b>	<b>1.78 million</b>	<b>517,000</b>
Pyoderma	111 million		
Pharyngitis		616 million	

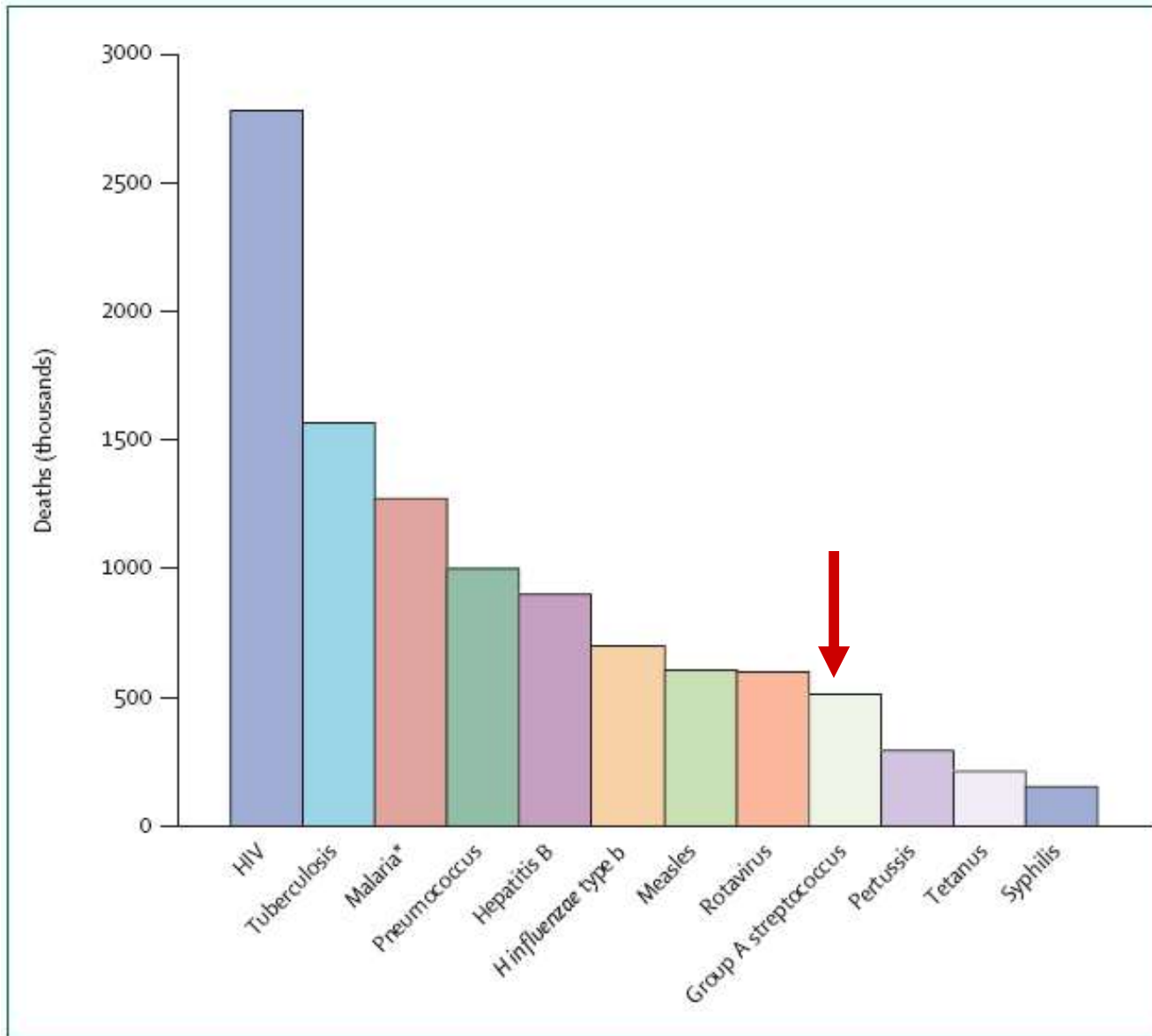
# GBD 2010 estimates\*

	<b>1990</b>	<b>2005</b>	<b>2010</b>
Prevalence	29,172,383	33,468,203	34,232,795
YLL	13,267,810	9,670,605	8,720,292
YLD	1,150,422	1,365,502	1,429,575
DALY	14,418,232	11,036,107	10,149,867
Deaths	462,579	363,864	345,110

Compared to previous 2005 publication:  
15.6 million cases  
233,000 deaths

NOTE: Modelling still needs work – 2010 estimates should be updated during 2014, but are unlikely to fall

# Estimated global mortality from individual pathogens, 2002



Lancet Infect Dis  
2005;5:685-94

# Challenges

- Attributable burden of disease – more information available, but gaps remain
- Safety perceptions due to one historical study – largely resolved, CFR changed – more clinical safety data will accrue with development of new candidates
- Serotype diversity – see below
- Commercial interest? Strep throat viable commercial target?

# GAS Vaccine Candidate Antigens with *in vivo* Evidence of Protection

Antigen	Location	Function
Type-specific M peptides	Cell surface	Opsonic epitopes
C-repeat M peptides	Cell surface	Opsonic epitopes
M-related proteins (Mrp)	Cell surface	Opsonic epitopes
C5a peptidase (SCPA)	Secreted	Cleaves C5a
Pili (T antigen)	Cell surface	Adhesion
Serine protease (ScpC)	Secreted	Cleaves IL-8 and other chemokines
Serine esterase (Sse)	Secreted	Tissue invasion
Cysteine protease (SpeB)	Secreted	Proteolysis of bact. and host proteins
Group carbohydrate	Cell surface	Opsonic epitopes
Serum opacity factor (Sof)	Cell surface Secreted	Opsonic epitopes/Fn binding
FBP54	Cell surface	Adhesin/Fn binding
Sfb1	Cell surface	Adhesin/Fn binding
GAS 40	Cell surface	Unknown/opsonic epitopes
Nine common antigens		Unknown

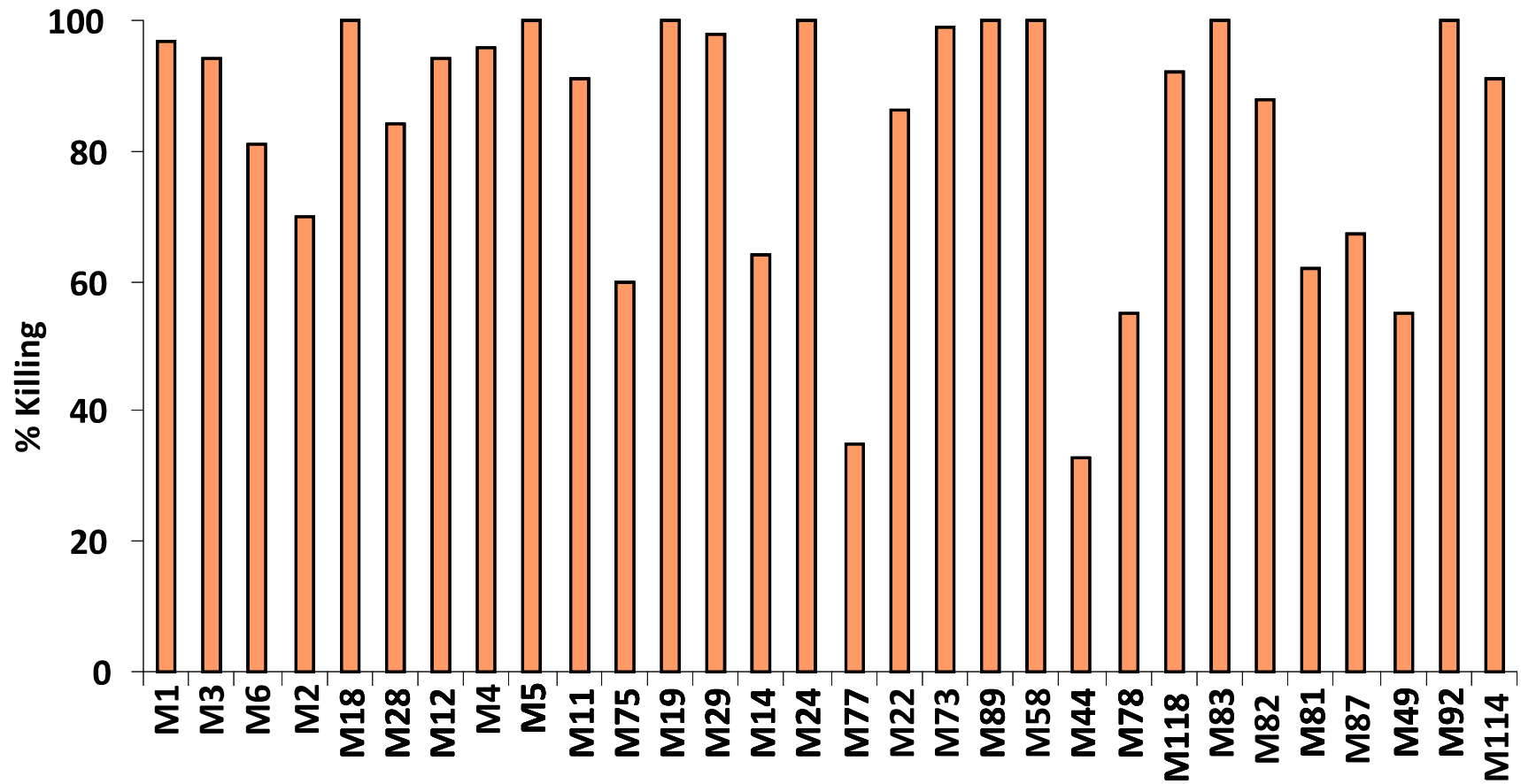


# Two clinically most advanced vaccine candidates

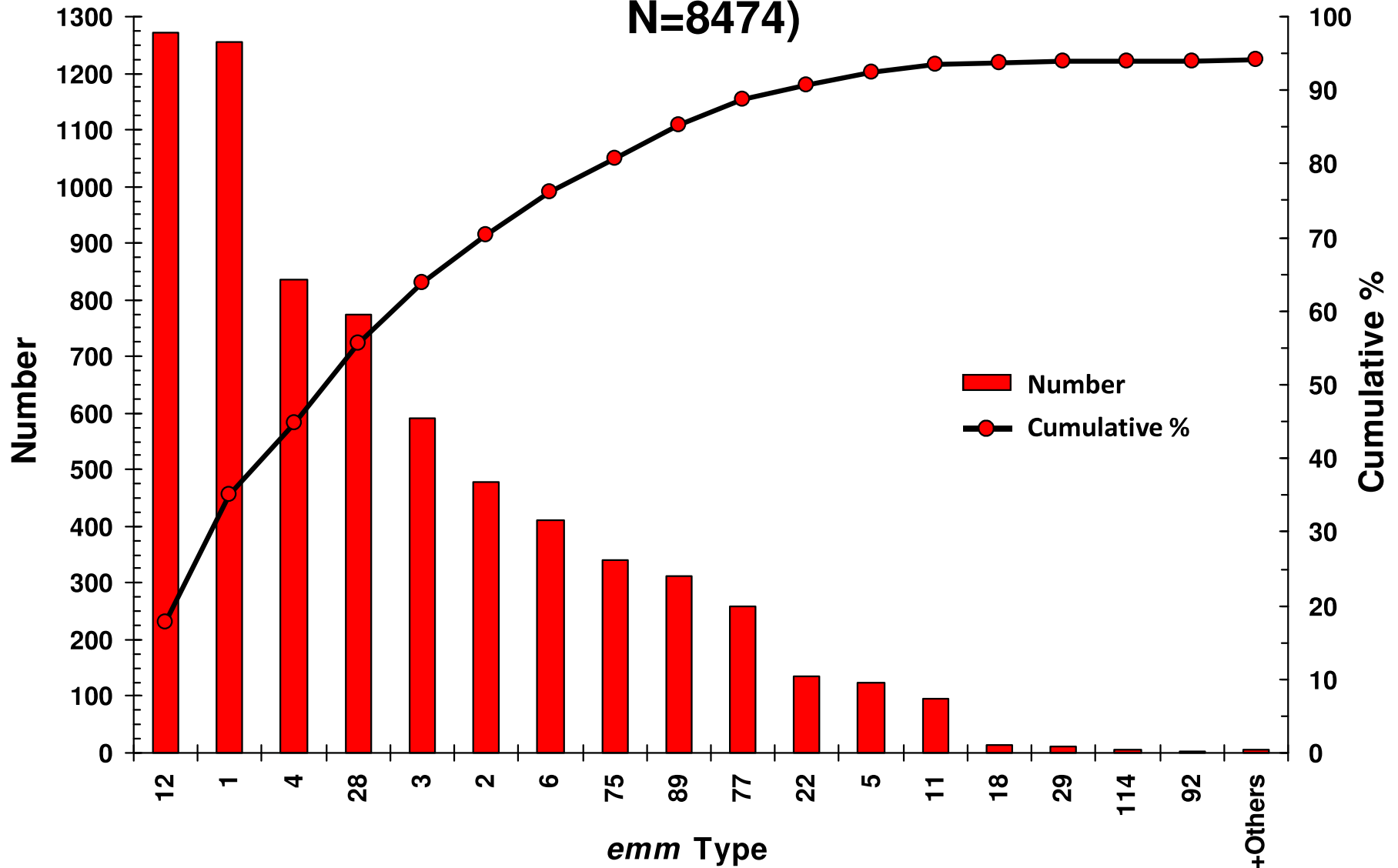
- Recombinant multivalent M protein fusion peptides
- 30 valent
- Short conserved M protein peptide conjugate J8



# Bactericidal Antibodies Evoked by 30-Valent Vaccine

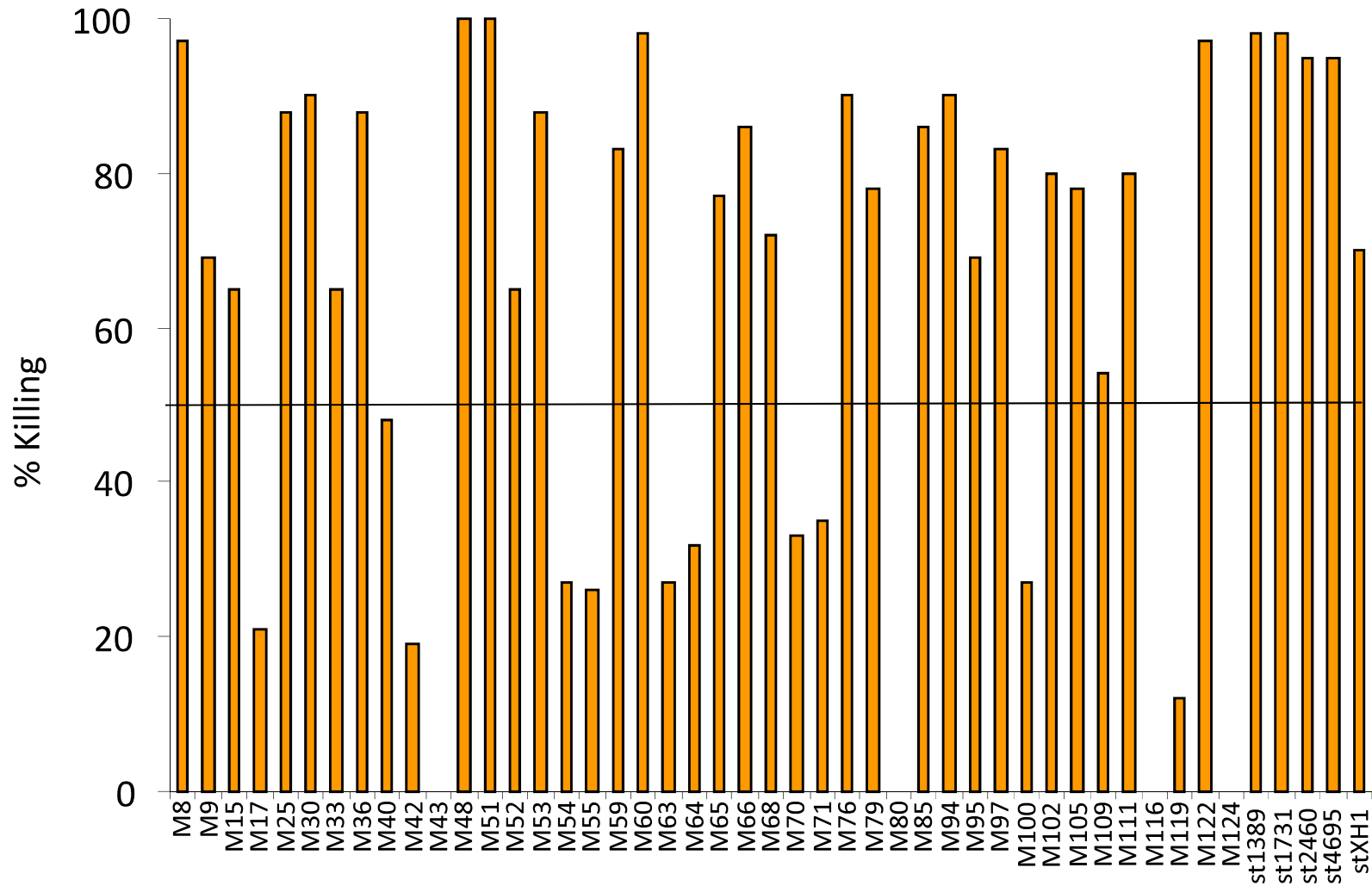


# U.S. and Canadian GAS Pharyngitis *emm* Types Included in 30-Valent Vaccine (U.S. and Canada, Study Years 1-7, 2000-07, N=8474)

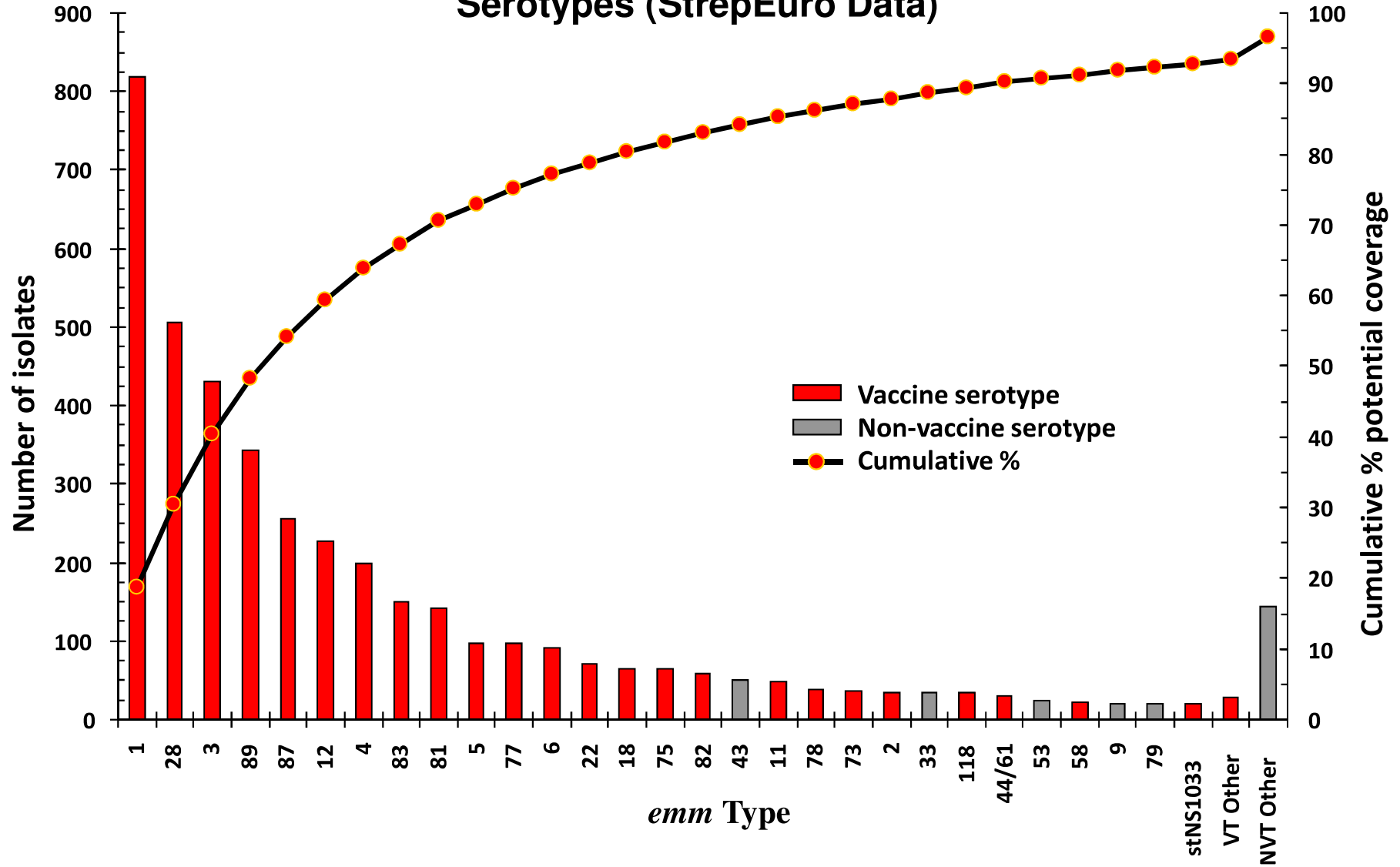


+5 *emm* types with <4 isolates each

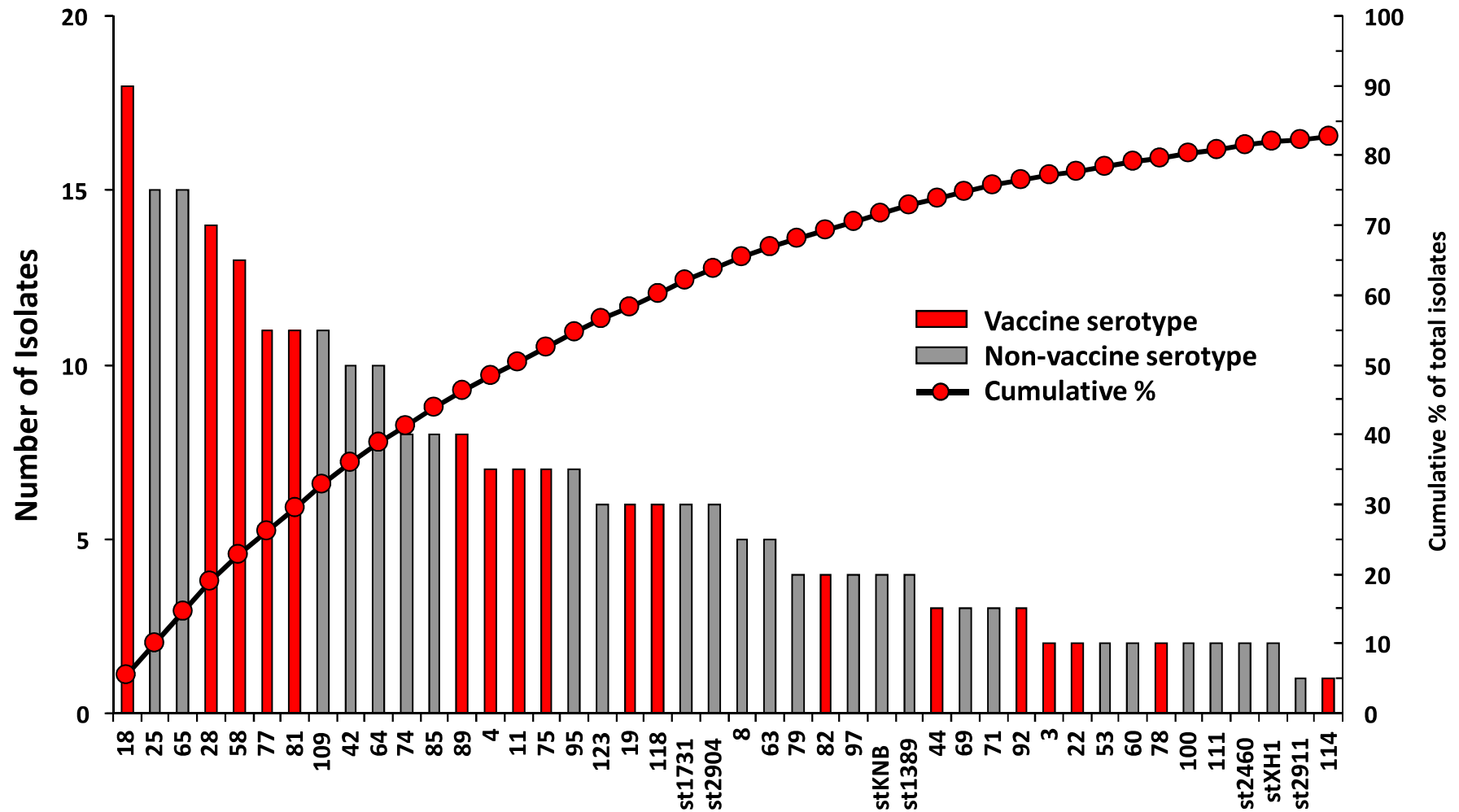
# Bactericidal Antibodies Evoked by 30-Valent Vaccine against Non-Vaccine Serotypes of GAS



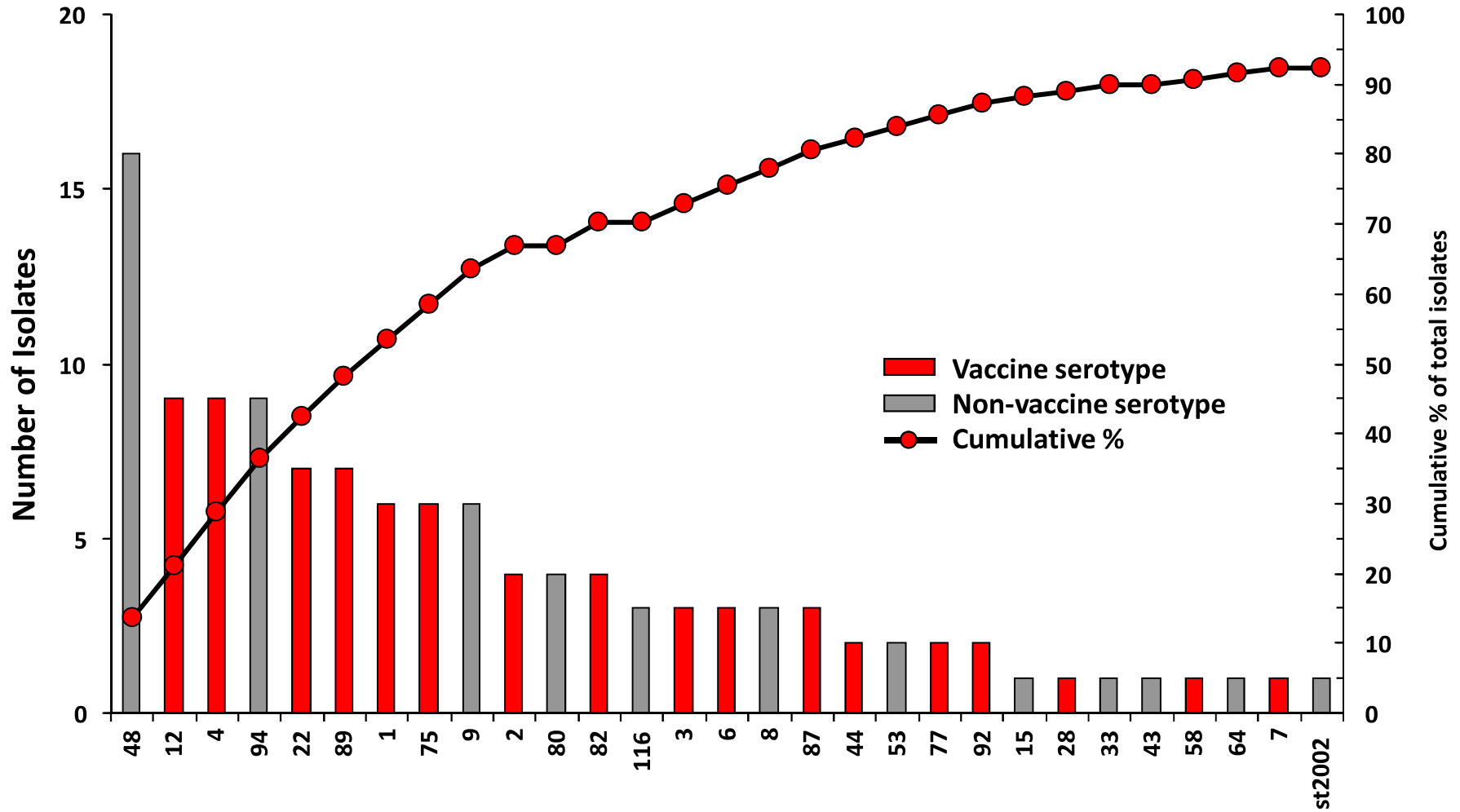
# Potential Coverage of 30-valent Vaccine against Invasive GAS in Europe Based on Bactericidal Activity Observed against Vaccine and Non-vaccine Serotypes (StrepEuro Data)



# Potential Coverage of 30-valent Vaccine in Bamako, Mali Based on Bactericidal Activity Observed against Vaccine and Non-vaccine Serotypes



# Bactericidal Activity of 30-Valent Vaccine Antisera against Cape Town Pharyngitis *emm* Types, N=118 (Vaccine and Non-vaccine Serotypes)





## **Summary of Bactericidal Antibodies Evoked in Rabbits by the 30-valent Vaccine Against Vaccine and Non- Vaccine Serotypes**

- Total emm-types tested: 83
- Vaccine types + non-vaccine types >50% killing: 73 (88%)
- Bactericidal killing of >50% observed with 43/53 (81%) non-vaccine serotypes
- Of the 43 serotypes that displayed >50% killing, average bactericidal activity was 80%

# Potential Coverage of 30-Valent Vaccine Based on Vaccine Types and Cross-Opsonized Non-vaccine Types

	% Total isolates (cases)	
	VT only	VT + NVT (cross-opsonized)
Pharyngitis-NA	98	98
Invasive Disease-US	90	93
Invasive Disease-Europe	78	97
Pharyngitis-Bamako	40	<b><u>84</u></b>
Pharyngitis-Cape Town	59	<b><u>90</u></b>

# Future of the 30-Valent Vaccine

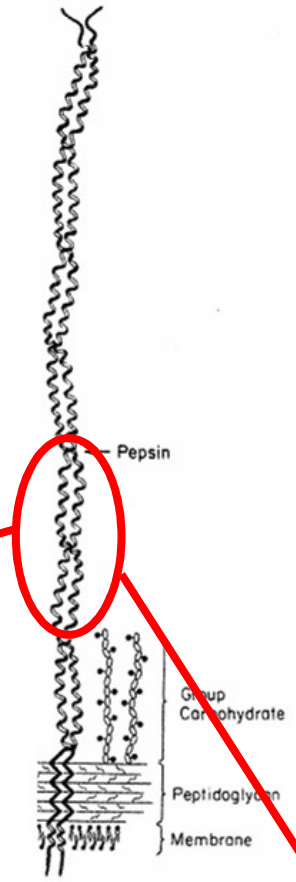
- Basic pre-clinical work completed
- Comprehensive assessment of cross-opsonic antibodies with GAS isolates from developing countries is ongoing
- Vaxent has entered into a license agreement/collaboration with the Pan-Provincial Vaccine Enterprise Inc. (PREVENT) of Canada
- PREVENT and Vaxent will jointly develop the 30-valent vaccine
- GMP manufacturing is underway
- Next steps include pre-clinical toxicology studies and a phase 1 clinical trial in Halifax (Scott Halperin, PI)

# Summary and Conclusions

- Recombinant multivalent M protein-based vaccines have been well-tolerated and highly immunogenic in early phase clinical trials
- A new 30-valent vaccine in pre-clinical development evokes bactericidal antibodies against all 30 vaccine serotypes of GAS and is free of tissue cross-reactive epitopes
- Immunity against GAS may not be as “type-specific” as once thought; the 30-valent vaccine antisera cross-opsionized 81% of the non-vaccine serotypes tested to date
- M protein-based vaccines may provide coverage sufficient for developed and developing countries (more data are required)

# The J8 vaccine

- Animal data encouraging
- Adult vaccine phase I trials underway in 2013 – single dose safe and immunogenic in 6 volunteers



p145	LRRDLASREAKKQVEKAL		
p146		AKKQVEKALEEANSKLAALE	
p147		EANSKLAALEKLNKELEESK	
p148			KLNKELEESKKLTEKEKAEEL
p149			KLTEKEKAEELQAKLEAEAKA
p150			QAKLEAEAKALKEQLAKQAE
p151			LKEQLAKQAEELAKLRAGKA
p152			ELAKLRAGKASDSQTPDTKP
p153			SDSQTPDTKPGNKAVPGKGQ
p154			GNKAVPGKGQAPQAGTKPNQ.....

J8

Courtesy Professor Michael Good, QIMR



National

Next Article: [Refugee deal 'concerning'](#)

## Funding for rheumatic fever vaccine

1:38 PM Saturday Feb 9, 2013

☆ Save

18

7

0

0

0

New Zealand and Australia will pump \$3 million into finding a potential vaccine for rheumatic fever.

Prime Minister John Key and Australian counterpart Julia Gillard announced the transtasman initiative in Queenstown today during their annual talks.

The two governments will contribute equal shares of \$3m in funding over the next two years to identify a potential vaccine for the disease, which can lead to long-term heart damage known as rheumatic heart disease.

In New Zealand, rheumatic heart disease kills about 150 people per year, while hospitalisation for both rheumatic fever and rheumatic heart disease costs about \$12m.

In Australia, the prevalence of rheumatic fever was 25 times higher among indigenous people than other Australians.

Mr Key said rheumatic fever was a significant issue for Maori, Pacific, Australian Aboriginal, and Torres Strait Islander communities.

He said an effective vaccine would be "a major step forward for the health of these communities in both countries and across the Pacific".

Ms Gillard said: "This joint Australian and New Zealand Government investment will fund the evaluation of three potential vaccine candidates currently under development to identify one that could then proceed to clinical trials."

### Related Tags

- Health
- Politics



Be part of the news. Send pics, video and tips to nzherald.

Send »



Holiday Accommodation

Where

Find

### National headlines

- Attack on kitten 'absolutely disgusting'
- Dental therapist fined and censured
- Up-skirt video teacher avoids jail
- Witness felt helpless as vehicle sank
- Kiwi released in Northland
- Guilty verdicts over Pike River disaster [VIDEO](#)
- Law change allows dream to be fulfilled [VIDEO](#)
- Parole hearing for drink-driving killer
- Diver almost drowns on Hertz mission
- Baby hospitalised with critical injuries

[More National headlines »](#)

*a little piece of home*



*Movie night*

**WATCH NOW** »

A STAR ALLIANCE MEMBER

# CANVAS (Coalition to Accelerate New Vaccines Against Streptococcus)

- aka the Trans-Tasman GAS vaccine initiative

- NZD 3 million first tranche in 2013-4 budgets of NZ and Aust
- To evaluate up to three vaccines for proof of principle (broadly cross-reacting functional antibodies)
- ? Subsequent tranche of \$30-40 million
- Awaiting response from NHMRC and NZ HRC

# Summary

- Clear need for a GAS / RF vaccine
- A century of research, but recent progress
- A commercially viable vaccine to prevent strep throat might be first step
- Test and make available for high disease burden areas
- Concerted efforts needed to overcome real and perceived obstacles
  - Potential for Trans-Tasman Initiative