

Improving standards for vaccine quality assurance

Ian Feavers, Head of Bacteriology



The Global Vaccines Landscape: Opportunities



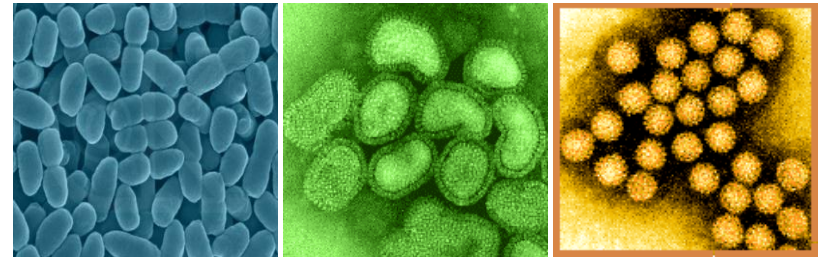
- Exciting times
- New players, new approaches
- Expanding manufacturing base
 - Increased access to existing vaccines
 - New vaccines for regionally important diseases
 - Tailored formulations (different serotypes)
 - New targets (e.g. Hep E, EV71, Vi-conjugates etc)
 - Potentially lower costs
 - Economic as well as health gain for producer countries



The Global Vaccines Landscape: Challenges and Risks



- Vaccines are often technically difficult, complex and expensive to manufacture
 - Pathogenic starting materials
 - Adventitious agent risks
 - Multiple components
 - Complex supply chains
- Customers are extremely demanding, unforgiving and have long memories



The Global Vaccines Landscape: Challenges and Risks



- Administered mostly to young children - the most sensitive population possible
 - Extremely low tolerance of risk
- Vaccines are victims of their own success
 - Diseases they prevent disappear, resulting in complacency, altered apparent risk/benefit ratio
- Public confidence is fragile
- Vaccine issues are not seen as product-specific
- Absolutely crucial for everyone in the business that vaccine quality standards are maintained at a high level

Effective standardisation more important than ever

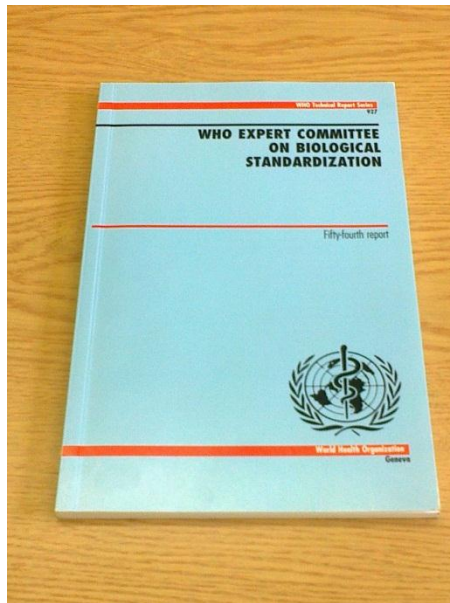
- Ensuring continued supply of safe and effective vaccines
 - Accurate and consistent dosing (potency)
 - Consistency of manufacturing quality
 - Assuring safety
- Laying the groundwork for development of new vaccines
- Promoting worldwide access through supporting market competition
- Promoting economic growth

“Standards contribute at least as much as patents to economic growth”

“The macroeconomic benefits of standardisation exceed the benefits to companies alone”

Swann, The Economics of Standardisation, Report for the UK Department of Business Innovation and Skills, 2010.

Written Standards and Reference Materials



- Evidence based
- Written: Scientific basis for setting recommendations and specifications
- Measurement:
 - a) Standardization of assays – initial steps
 - b) Further development and refinement of QC tests and assays for evaluation of vaccines – evolving concept

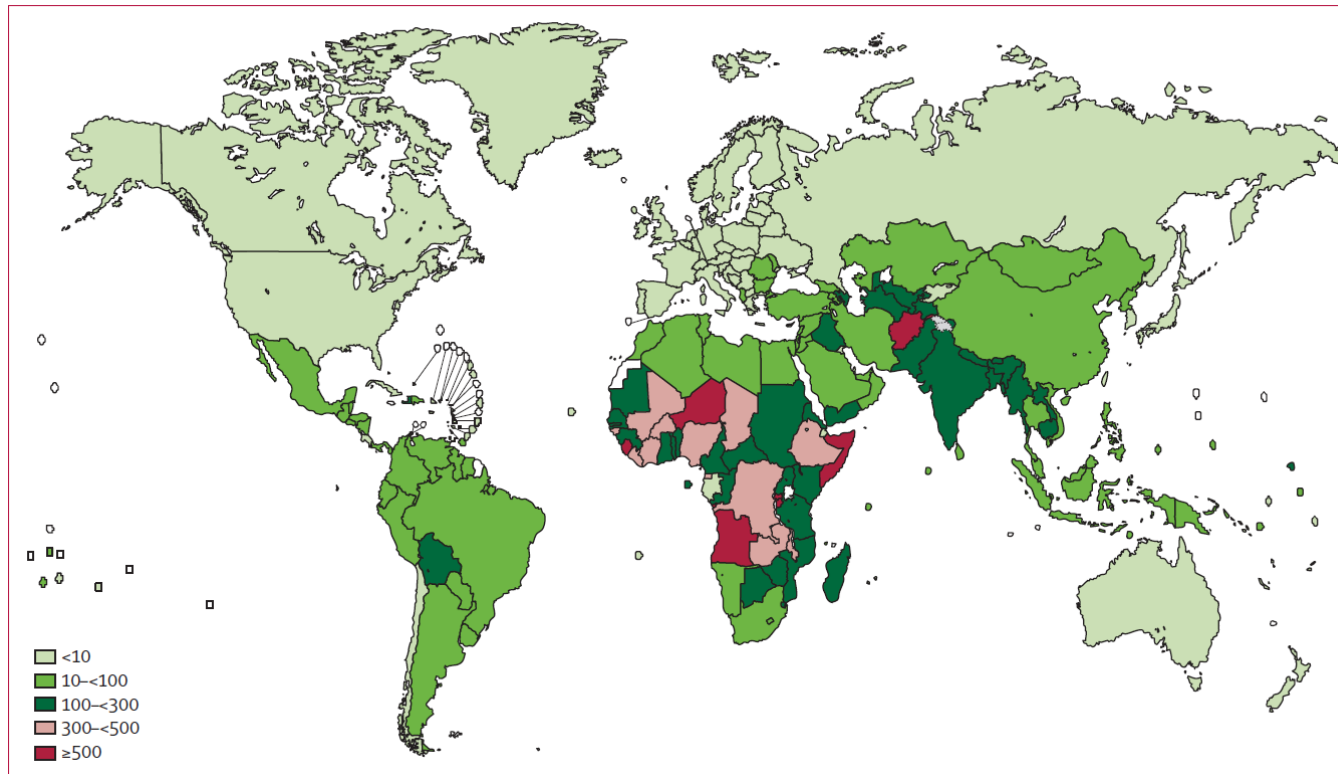


Pneumococcal Disease



- *Streptococcus pneumoniae* is a leading cause of bacterial pneumonia, meningitis, and sepsis in children
- Estimates of child deaths caused by *S. pneumoniae* range from 0.7-1.0 million every year worldwide
- Over 90 serotypes of pneumococcus, most disease caused by a limited number of serotypes
- Regional differences in serotype distribution
- Ten- and 13-valent polysaccharide conjugate vaccines widely used in Europe, the US and Australia
- Two international vaccine manufacturers unlikely to meet global demand

Pneumococcal Disease



Pneumococcal deaths per 100 000 children younger than 5 years

Serological criteria for evaluation and licensure

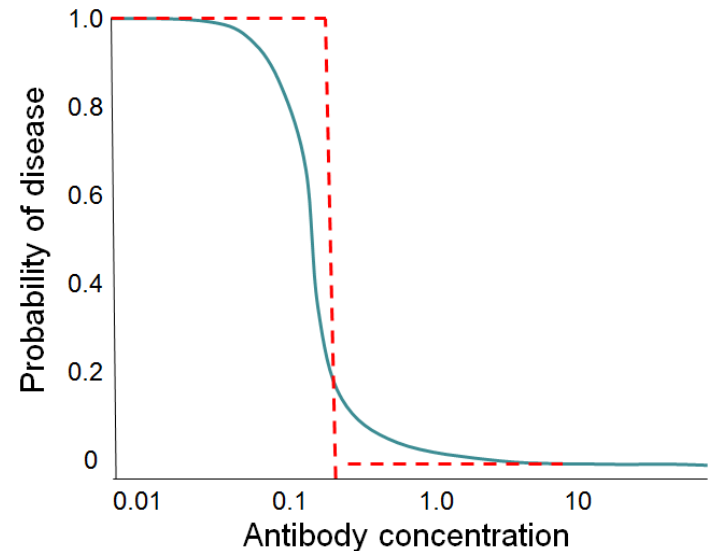


- Increasingly difficult to conduct efficacy trials
 - Prevnar™ and Synflorix™ widely adopted in routine programmes in regions with the infrastructure to conduct large efficacy trials
- Serological criteria essential for the evaluation of new formulations and new serotypes
- WHO recommendations based on efficacy data from three trials
 - North California Kaiser Permanente
 - American Indian (Navajo)
 - South African

Simplifying assumptions and caveats



- Protection is related to IgG (ELISA)
- Protection relates to the post primary dose
- The relationship between risk of disease and antibody concentration can be expressed as a step function
- Protective levels are similar across all serotypes
- Protective levels are similar across trials and populations
- Correlate at a population level
 - does not relate to individual level protection or risk of disease



Vaccine Efficacy



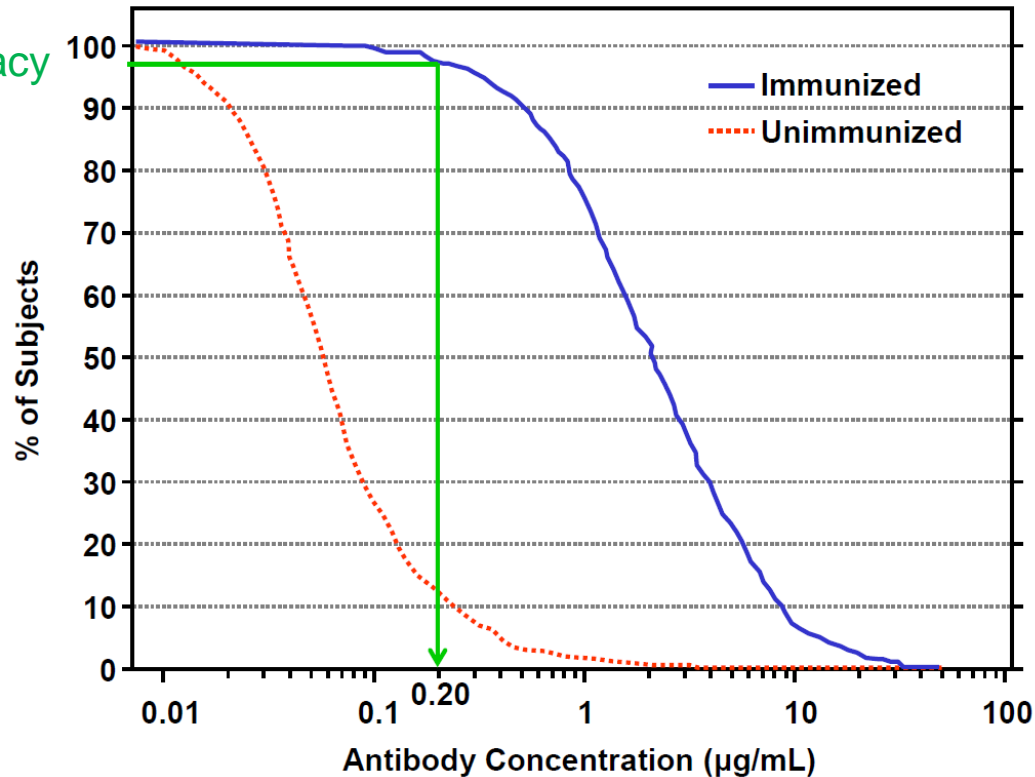
$$VE = 1 - \frac{\text{Probability of disease in Vaccinated}}{\text{Probability of disease in Unvaccinated}}$$

$$\therefore VE = 1 - \frac{\% \text{ Vaccinated subjects } [Ab] < Ab_{\text{protective}}}{\% \text{ Unvaccinated with } [Ab] < Ab_{\text{protective}}}$$

Reverse Cumulative Distributions of Post-Dose 3 ELISA Antibody Concentrations in NCKP Population: 7 Serotype Aggregates

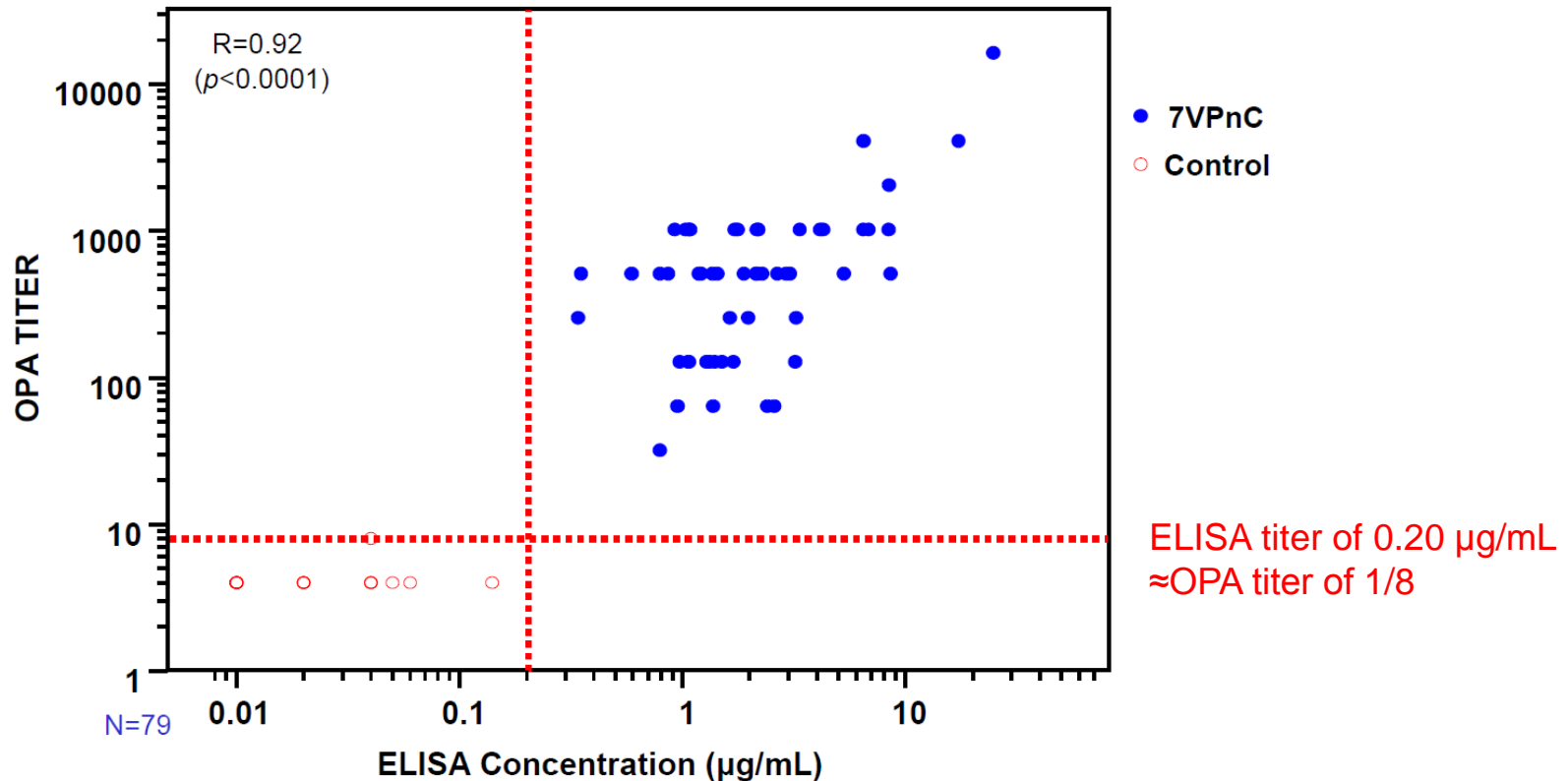


Vaccine efficacy
97.4%



Predicted VE with 0.2µg/mL is 97.3%

Post-Dose 3 Opsonophagocytic Antibody Response

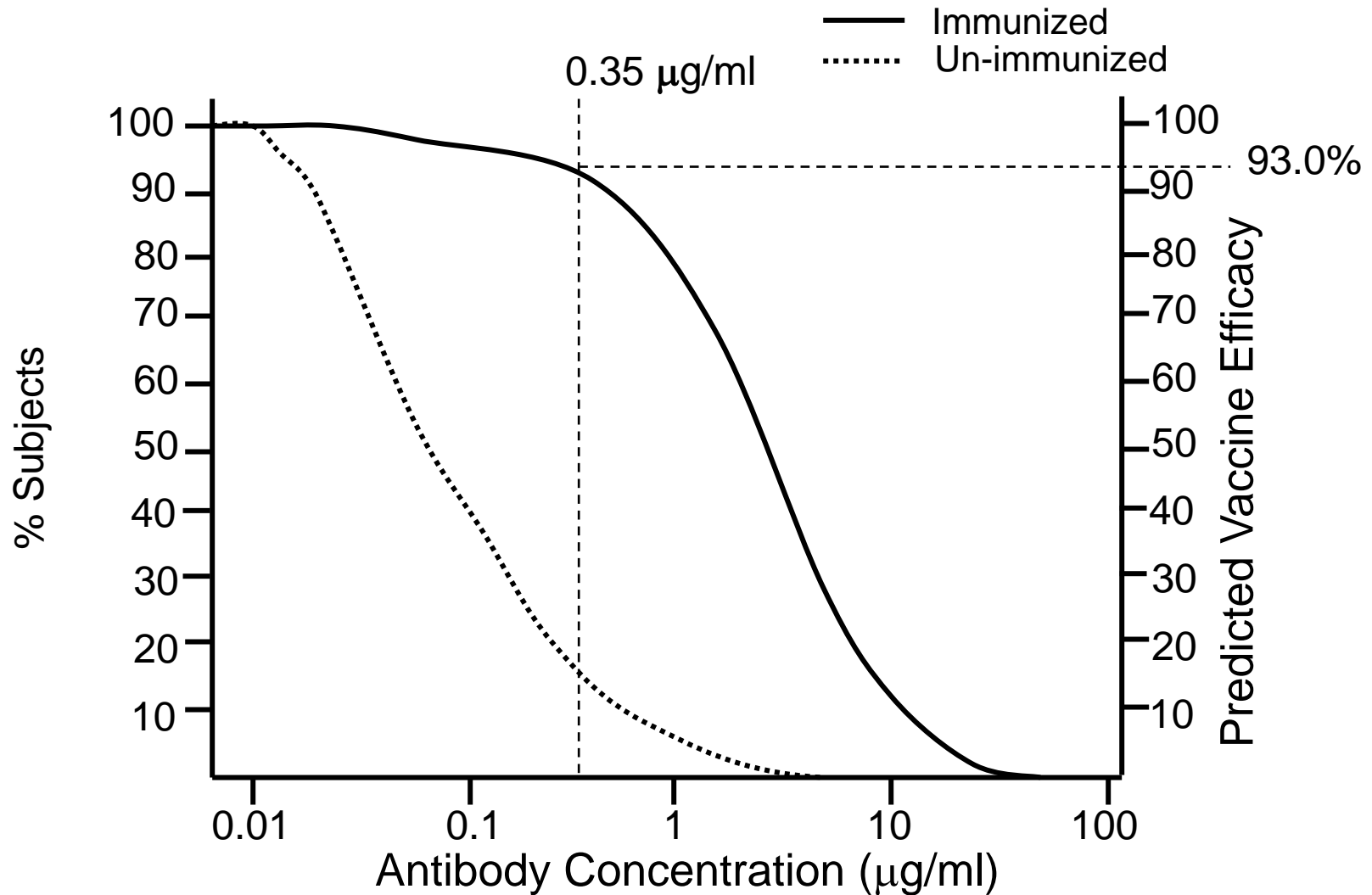


Efficacy against invasive disease caused by 7 vaccine serotypes



	No. of Cases		Vaccine Efficacy	Protective Level ($\mu\text{g/mL}$)
	Controls	Vaccinated		
Kaiser Permanente	39	1	97.4% (84.8, 99.9)	0.18 (0.03,0.67)
American Indian	8	2	76.8% (-9.4, 95.1)	1.00 (0.25,>50)
South Africa (7 shared types in HIV –ve children)	10	1	90.0% (29.7, 99.8)	0.68 (0.03,6.00)
Pooled	57	4	93.0% (81.0, 98.2)	0.35 (0.09,0.89)

Reverse cumulative distribution of pooled antibody concentrations



Primary end point



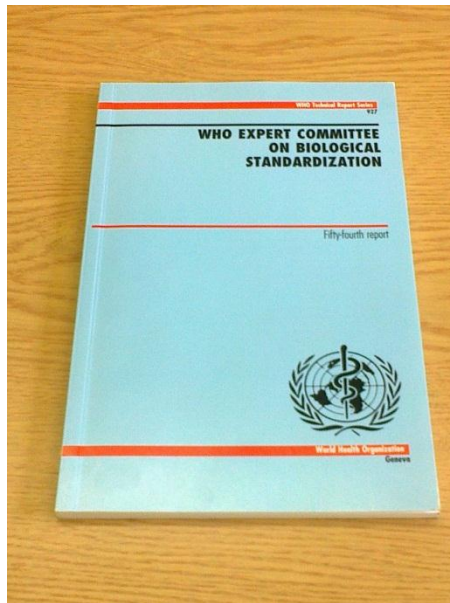
- IgG concentration measured by ELISA collected 4 weeks after 3rd dose of vaccine
- Single reference concentration of 0.35 $\mu\text{g/ml}$ for all serotypes
- This does not necessarily predict protection in an individual
- Based on ELISA without pre-adsorption with 22F
- Head-to-head comparison with licensed product preferred method of evaluation
- Non-inferiority not an absolute requirement
- Failure to meet non-inferiority criteria for one or more existing serotypes decided on a case-by-case basis
- New serotypes evaluated for non-inferiority to the aggregate response to serotypes in the licensed product

- Functional antibodies
 - Opsonophagocytic assay
- Immunological Memory
 - Boosting with plain polysaccharide
 - Antibody avidity

WHO Reference Laboratories

1. The Institute of Child Health, London, UK
2. The Bacterial Respiratory Pathogen Reference Laboratory, The University of Birmingham, Alabama, USA.

Written Standards and Reference Materials



- Written recommendations for pneumococcal conjugated vaccines were adopted by ECBS in 2003 and subsequently revised in 2009
http://www.who.int/biologicals/vaccines/Pneumo_final_23APRIL_2010.pdf
- Measurement:
 - reference serum 89-SF (CBER)
 - replacement and first IS reference serum 007sp (NIBSC & CBER)
 - QC serum panel (NIBSC)



1st International Standard Human Pneumococcal Serum



CLINICAL AND VACCINE IMMUNOLOGY, Oct. 2011, p. 1728–1736
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Establishment of a New Human Pneumococcal Standard Reference Serum, 007sp[∇]

D. Goldblatt,^{1*} B. D. Plikaytis,² M. Akkoyunlu,³ J. Antonello,⁹ L. Ashton,¹ M. Blake,³ R. Burton,⁴
R. Care,⁷ N. Durant,⁶ I. Feavers,⁷ P. Fernsten,⁵ F. Fievet,⁶ P. Giardina,⁵ K. Jansen,⁵ L. Katz,¹¹
L. Kierstead,⁸ L. Lee,³ J. Lin,⁴ J. Maisonneuve,¹⁰ M. H. Nahm,⁴ J. Raab,⁸ S. Romero-Steiner,²
C. Rose,² D. Schmidt,² J. Stapleton,¹² and G. M. Carlone²

- The human pneumococcal reference serum 89SF was set up in early 1990s
- Weight-based units assigned to antibodies to 11 PnPS serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F) by ELISA and human standard reference serum, USNRP IS 1644.
- Used as the reference in the evaluation of the 7-valent pneumococcal conjugate vaccine
- By 2005 it was estimated only 2-5 years supply remained
 - Risk that link with the clinical efficacy would be lost
- Replacement should be suitable for the standardisation of both ELISA and opsonophagocytosis assay (OPA)
- 89SF never established as a WHO standard

1st International Standard Human Pneumococcal Serum



- Clinical protocol run between July 2007 and July 2008 at the University of Iowa (PI: Jack Stapleton MD)
 - 275 volunteers immunised with Pneumovax II (23-valent PS vaccine)
 - Volunteers were bled 4 and 8 weeks post immunisation
 - 32 bags (16 donors) set aside to be filled as QC sera
 - Sera shown to be free from HAV, HBV, HCV, HIV and Parvovirus
- Filling and lyophilisation
 - Serum filled at 6ml per vial
 - Lyophilised under contract
 - 15,333 vials were filled with a CV of fill of <1%
 - Moisture 0.7%
 - Bioburden below level of detection

1st International Standard Human Pneumococcal Serum

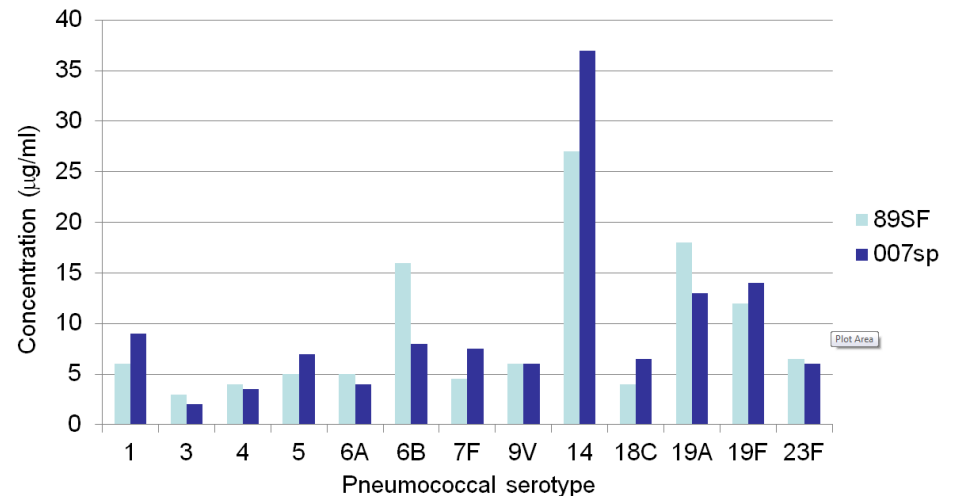


- Antibody concentrations in 007sp established relative to 89SF using the WHO reference ELISA
- Excellent agreement for panel of 12 WHO calibration sera
- Project to assign opsonophagocytic units nearing completion

TABLE 1. Assigned IgG antibody concentrations for 007sp

Pneumococcal capsular serotype	IgG ELISA concn (µg/ml)	95% CI		<i>n</i> ^a
		Lower	Upper	
1	8.50	7.88	9.16	200
3	1.45	1.36	1.55	200
4	3.33	2.95	3.77	200
5	7.51	7.04	8.02	210
6A	3.93	3.74	4.14	200
6B	9.05	7.59	10.80	225
7F	8.30	8.14	8.46	200
9V	6.44	6.06	6.84	200
14	37.99	34.86	41.39	220
18C	7.30	6.80	7.84	205
19A	13.87	11.51	16.73	205
19F	14.61	12.68	16.82	200
23F	5.95	5.21	6.81	215

^a *n* represents the number of repeat runs performed in five laboratories.



Replacement of TYS by NIBSC

- TYS: the 'old' WHO IS for Vi PS (equine antibody)
 - Established in 1935 by Dr Felix now exhausted
- Material selected as replacements for TYS:
 - Human anti-Vi PS IgG
- Use:
 - Benchmark for immuno-diagnostic assays to analyse anti-Vi IgG levels in sera from clinical trials
 - Confirm identity of Vi PS in plain and conjugate vaccines
- Endorsed by WHO/ECBS in 2009

NIBSC 10/126

Human anti-Vi PS IgG



- Appr 1350 mls were donated
 - ✓ Nine samples from volunteers of a PhII trial of a Vi-TT conjugate, now licensed in India
 - ✓ From an endemic area
 - ✓ Likely to contain anti-TT abs
 - ✓ Absence of blood-borne viruses Ag/Ab
 - ✓ Fill met WHO criteria
 - ✓ 1680 ampoules in stock
- Purpose:
 - ✓ Benchmark for immuno-diagnostic assays for Typhoid
 - ✓ Identity of Vi – component in vaccines

Collaborative study

- 10 participants from China, India, Italy, Korea, Vietnam, UK & US.
 - Vaccine manufacturers, NRAs and research institutes
- 2 Sample packs - 3 coded samples and the NIH standard.
- Samples from each pack tested twice on different days.
- All raw results submitted to NIBSC for analysis by October
 - Assess linearity and parallelism of 10/126
 - Assign Unitage to 10/126
- Submit report to WHO Expert Committee On Biological Standardization in 2014.

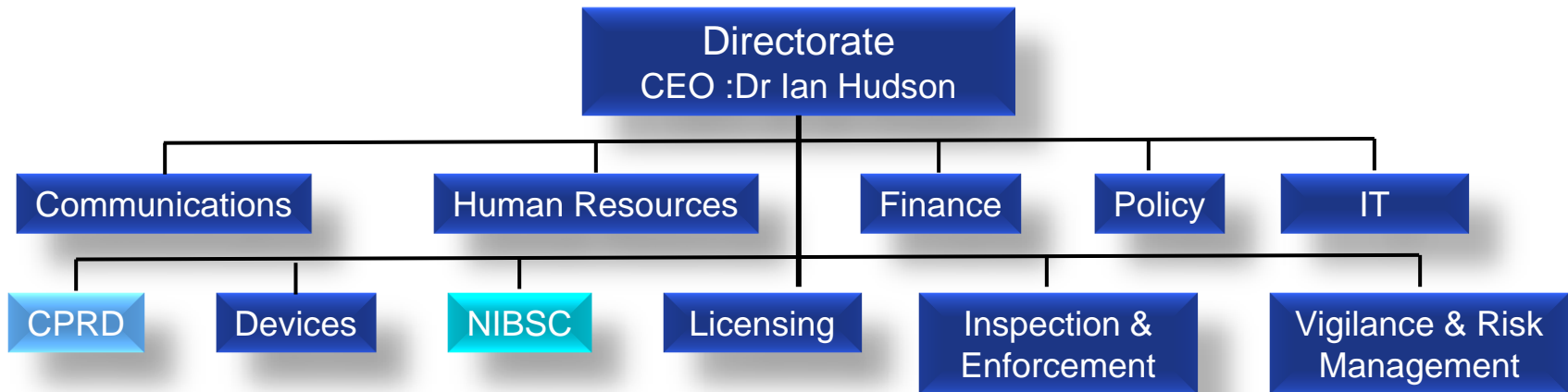
Study aims

- To analyse the anti-Vi IgG content of both reference materials by ELISA.
- To determine a correlation between both materials and assign a unitage for the candidate IS 10/126.
- To assess the suitability of the candidate standard 10/126 as an international standard for human anti-Vi PS antibody
- Submit final report to ECBS (WHO Expert Committee On Biological Standardization) for approval in October 2014.
- To assess the reactivity both preparations in various immunoassays currently in use.

MHRA Divisional Structure



- NIBSC joined the MHRA in April 2013
 - UK National Regulatory Authority
 - Leading Regulator in European Community
 - Wealth of experience in licensing vaccines and other biologicals
 - Source of formal (EU licensing) and informal regulatory advice



- Strengthened capability and breadth of expertise in vaccines

What we can offer DCVMN

- Standards and reference materials
- Medicines testing expertise
- Advice on vaccine development, licensing, pharmacovigilance (MHRA)
- Training
 - Assay development/use of global standards/lot release
- Specialist expertise/research capability/materials
 - Supporting innovation

