出國報告（出國類別：國際會議）

第 3 屆全球結核病疫苗高峰會

服務機關：衛生署疾病管制局
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報告日期：2013/4/22

摘要

第一屆全球結核病疫苗高峰會在 2001 年初舉行，隨著越來越多的臨床前期疫苗的發明以及疫苗進如臨床試驗，第二屆(2010 年) 和第三屆 (2013 年)，高峰會相繼舉行。此次的主題爲 progress collaborating sustainability，在南非的開普敦舉行。世界衛生組織的 2050 年目標，是 TB elimination，所以疫苗的重要性，不言可喻。此次開會原本就訂在可以得之新疫苗 MVA85A 臨床試驗 2b 結果的此時，與會的專家學者，討論的主題是怎麼從發展了 13 年但證實無效的疫苗效益試驗中，得到經驗，再出發，將在報告中針對此議題及幾個較有希望的疫苗 candidates 進行介紹。

台灣今天透過參加大會，可以了解現在全球在發展新疫苗，遇到的瓶頸問題、預計要解決挑戰的方向，預計提供給研究單位和防治單位參考；除了開會，此行就近拜訪 West cape province TB control department，了解南非結核病管理的現況，並透過大會安排，前往臨床試驗基地。

只有有效的疫苗，全球才有可能達到世界衛生組織的 2050 年目標: elimination of TB；考量到台灣現況，建議有三: 1.南非的 TB control 資源雖不足但並非沒有資源，台灣若有心從事這方面的外交突破，可以從省的層級，由 TB 資訊系統切入，來進行協助。2.由於台灣的結核病發生率不論哪個族群都不夠高，如果打算發展結核病疫苗，台灣較適合進行臨床前及臨床一期試驗，但熟練地執行安全且適當的動物模式是必須要有的基本功夫。3.發展疫苗需要大量的資金，全球主要的資源來自於 EDCTP (歐盟), DGIS (荷蘭), UK-DFID (英國), Bill & Melinda Gates Foundation, NIH (美國)，研究單位必須有能力跟其他頂尖學術單位競爭。

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壹、目的

透過參加大會，可以了解現在全球在發展新疫苗，遇到的瓶頸問題、預計要解決挑戰的方向，預計提供給研究單位和防治單位參考。

貳、過程

行程

日期	工作日誌	地　　點	行　程　內　容
3/23-24	去程	台北→香港→約翰尼斯堡→	路程
3/25-27	開會	開普敦	開會
3/28	拜訪 SATVI 試驗基地	開普敦	參訪
3/29-30	回程	開普敦→約翰尼斯堡→香港→台北	路程

大會議程

	行程及會議內容	重點報告	Special Events
2013/3/23-24	出發及抵達南非開普敦		
2013/3/25	Registration, opening, & plenary sessions	結核流行病學及疫苗學	Opening
2013/3/26	Plenary & breakout sessions /poster discussion and oral presentation	疫苗臨床試驗及臨床前期發展中疫苗	Satellite session: The MVA85A Phase IIb Trial: Results and Implications for the Field
2013/3/27	Workshops /plenary & breakout sessions /poster discussion and oral presentation	5 workshops: 討論如何推動 2012 年世界結核病日發表在 Tuberculosis 上的 TB Vaccines: A Strategic Blueprint for the Next Decade Closing ceremony	Satellite session: Human and Animal TB: Exploring the Links and Opportunities for Vaccine Development
2013/3/28	Site visits	SATVI site visit	
2013/3/29-30	離開南非開普敦-> 抵達台灣		

MON **25 MAR**

7h00 **3rd Floor**	Registration Opens
9h00 – 12h15 **Lecture Theatre 1**	**SPECIAL OPENING SESSION – PART I** **Innovation in Addressing the Global TB Epidemic** Co-chairs: Willem Hanekom, South African Tuberculosis Vaccine Initiative (SATVI), South Africa | Tom Evans, Aeras , USA *Featuring:* The Honourable Aaron Motsoaledi, Minister of Health, South Africa Yvonne Chaka Chaka, South Africa Anthony S. Fauci, Director, NIAID/NIH, USA (by videoaddress) Máire Geoghegan-Quinn, European Commissioner for Research, Innovation and Science, Ireland (by videoaddress) **SPECIAL OPENING SESSION – PART II** **Perspectives on the Need for New TB Vaccines and Progress in TB Vaccine Development** Co-chairs: Jelle Thole, TuBerculosis Vaccine Initiative, Netherlands | Hassan Mahomed, Western Cape Department of Health / Stellenbosch University, South Africa | Ann Ginsberg, Aeras, USA **Perspectives on the Need for New TB Vaccines- Community perspective** Linda Sibeko, SATVI Community Advisory Board, South Africa **Cost-effectiveness of future TB vaccines in low- and middle-income countries** Gwen Knight, London School of Hygiene and Tropical Medicine, UK **Vaccination and the prospects for TB elimination** Chris Dye, World Health Organization, Switzerland **OPENING PLENARY** **Collaboration and cooperation: The Stop TB Partnership Working Group on New Vaccines** Michel Gréco, Working Group on New Vaccines, France **Opening plenary address: The past and future of TB vaccine development: Forward with clinical trials or more basic research?** Stefan Kaufmann, Max Planck Institute for Infection Biology, Germany
12h15 – 13h30 **3rd Floor**	**Lunch** (Poster & Exhibit Area)
13h30 – 14h30 **Lecture Theatre 1**	**PLENARY SESSION I : Creativity in Research & Discovery, Part I** Chair: David Lewinsohn,Oregon Health & Science University, USA **Mechanisms of Protection in the Lung**
13h35 – 13h50	**Factors contributing to the susceptibility of the lung to tuberculosis** Andrea Cooper, Trudeau Institute, USA
13h50 – 14h05	**Mucosal Immunization: relevance to protection against tuberculosis?** Per Brandtzaeg, University of Oslo, Norway
14h05 – 14h30	**Questions and discussion**
14h30 – 15h30 **Lecture Theatre 1**	**PLENARY SESSION II : Creativity in Research & Discovery, Part II** Chair: Chris Wilson, Bill & Melinda Gates Foundation, USA **Translational Research and Models that Mimic Human Disease** **Viewpoints:**
14h30 – 14h45	**Modelling of transmission of infection** Edward Nardell, Harvard School of Public Health/Partners in Health, USA
14h45 – 14h55	**Blocking naturally acquired infection** Glyn Hewinson, Veterinary Laboratory Agencies, UK
14h55 – 15h05	**Animal models of clinically latent infection** Joanne Flynn, University of Pittsburgh, USA
15h05 – 15h15	**Human mycobacterial challenge models** Helen McShane, University of Oxford, UK
15h15 – 15h30	**Questions and discussion**
15h30 – 16h00	**Coffee/Tea Break**
16h00 – 17h15 **Lecture Theatre 1**	**PLENARY SESSION III : Correlates of Immunity and Biomarkers for TB Vaccines** Chair: Warwick Britton, Centenary Institute of Cancer Medicine and Cell Biology, Australia
16h05 – 16h20	**Correlates of risk of TB disease in adolescents** Willem Hanekom, SATVI, South Africa
16h20 – 16h35	**Evaluating vaccine effects on TB infection rates among adolescent populations** Steven Self, Fred Hutchinson Cancer Research Center, USA
16h35 – 16h55	**Systems analysis of TB vaccines and TB disease risk** Dan Zak, Seattle Biomedical Research Institute, USA
16h55 – 17h15	**Questions and Discussion**
17h15 – 18h30 3rd Floor	**Opening Reception and Poster Viewing** (Poster & Exhibit Area)
18h30 – 21h30 *Buses depart from Kramer building at 18h30*	**Forum Dinner, Moyo Restaurant, Stellenbosch** *Sponsored by* Aeras, Bill & Melinda Gates Foundation, Emergent BioSolutions, European & Developing Countries Clinical Trials Partnership (EDCTP), South African Tuberculosis Vaccine Initiative (SATVI), and the TuBerculosis Vaccine Initiative (TBVI)

TUE **26 MAR**

7h00 **3rd Floor**	Registration Opens
9h00 – 12h15 **Lecture Theatre 1**	**PLENARY SESSION IV : Preventive Vaccines in Advanced Clinical Trials** Co-chairs: Gavin Churchyard, Aurum Institute for Health Research, South Africa | Peggy Johnston, Bill & Melinda Gates Foundation, USA
8h35 – 9h05	**Boosting BCG with MVA85A – clinical trials and efficacy data** Helen McShane, University of Oxford, UK
9h05 – 9h25	**AERAS-402/Crucell Ad35** Macaya Douoguih, Crucell, The Netherlands
9h25 – 9h45	**Progress of the M72/AS01E tuberculosis vaccine candidate into Phase IIB efficacy trial** Dereck Tait, Aeras, South Africa
9h45 – 10h05	**Prospects for novel tuberculosis protein-based subunit vaccines** Else Marie Agger, Statens Serum Institute, Denmark
10h05 – 10h25	**Latest development of VPM1002: a new prime vaccine on the horizon** Leander Grode, Vakzine Projekt Management, Germany
10h25 – 10h45	**Questions and discussion**
10h45 – 11h15	**Coffee/Tea Break**
11h15 – 12h45 **Lecture Theatre 2**	**BREAKOUT SESSION I : Biomarkers** Chair: Stefan Kaufmann, Max Planck Institute for Infection Biology, Germany
11:15 – 11:32	**Biomarkers of the early response to Mtb infections as indicators of vaccine efficacy** Gilla Kaplan, Public Health Research Institute Center, University of Medicine and Dentistry of New Jersey, USA
11:32 – 11:44	**TB biomarker discovery** Tom Ottenhoff, Leiden University Medical Centre, The Netherlands
11:44 – 11:56	**Progression from M.tuberculosis infection to TB disease is marked by an increased interferon response and perturbation of blood leukocyte subsets** Adam Penn-Nicholson, SATVI, South Africa
11:56 – 12:08	**Evaluation of a human BCG challenge model as a method of assessing anti-mycobacterial immunity induced by BCG and a candidate TB vaccine, MVA85A, alone and in combination** Stephanie Harris, University of Oxford, UK
12:08 – 12:20	**T-Cell biomarkers in TB disease and latent infection** Alexandre Harari, Centre Hospitalier Universitaire Vaudois (CHUV), University of Lausanne, Switzerland
12:20 – 12:32	**Identification of biomarkers for Mycobacterium tuberculosis infection and disease in BCG-vaccinated young children in southern India** Ruth Stavrum, The Gade Institute, University of Bergen, Norway
12h32 – 12h45	**Discussion**
11h15 – 12h45 **Lecture Theatre 1**	**BREAKOUT SESSION II : Vaccines in Early Clinical Development** Chair: Souleymane MBoup, Laboratoire de Bacteriologie-Virologie, Centre Hospitalier Universitaire Aristide Le Dantec, Senegal
11h15 – 11h30	**ID93** Steve Reed, Infectious Disease Research Institute (IDRI), USA
11h30 – 11h45	**MTBVAC, from the lab to the clinical trials** Carlos Martin, University of Zaragoza, Spain
11h45 – 12h00	**Potent T cell immunogenicity of a novel human type 5 adenovirus-based tuberculosis vaccine in humans despite pre-existing anti-adenovirus 5 immunity** Fiona Smaill, Mc Master University, Canada
12h00 – 12h15	**A phase I double-blind, randomized, placebo-controlled to evaluate the safety and immunogenicity of BCG and AERAS-404 administered as a prime-boost regimen to HIV-negative, TB-negative, BCG-naïve adults** Giuseppe Pantaleo, Lausanne University Hospital, Switzerland
12h15 – 12h30	**Heparin-binding haemagglutinin as a vaccine candidate against tuberculosis** Camille Locht, Institute Pasteur Lille, France
12h30 – 12h45	**Discussion**
11h15 – 12h45 **Lecture Theatre 3**	**BREAKOUT SESSION III : New Emerging Vaccines, Part I** Chair: Tom Evans, Aeras, USA
11h15 – 11h30	**Interference with mycobacterial Zmp1-mediated subversion of the host's immune response provides a rationale for improvement of BCG** Peter Sander, University of Zürich, Switzerland
11h30 – 11h45	**Evaluation of a lipid sub-unit tuberculosis vaccine using the Guinea pig model** Martine Gilleron, Centre National de la Recherche Scientifiq (CNRS), France
11h45 – 12h00	**Immunogenicity of aerosol and intradermal MVA85A in the lungs and peripheral blood of healthy BCG-vaccinated UK adults** Iman Satti, University of Oxford, UK
12h00 – 12h15	**Methods in the development of stable, unmarked recombinant BCG vaccine strains** Charles Bourne, Aeras, USA
12h15 – 12h30	**Development of a dual TB/HIV vaccine using optimised strains of BCG** Shivan Chetty, University of Cape Town, South Africa
12h30 – 12h45	**Safety signal associated with recombinant BCG vaccination: immunologic clue or chance occurrence?** Daniel Hoft, St. Louis University, USA

12h45 – 14h30 **3rd Floor**	**Lunch and poster viewing** (Poster & Exhibit Area)
14h35 – 16h00 **Lecture Theatre 1**	**PLENARY SESSION V : Pathways to Global Introduction of New TB Vaccines** Chair: Angeline Nanni, Aeras, USA
14:35 – 14:55	**Global policy for public health use of new vaccines** Helen Rees, WHO Strategic Advisory Group of Experts (SAGE), South Africa
14:55 – 15:15	**Perspectives from endemic countries** Gregory Hussey, National Advisory Group on Immunization, South Africa
15:15 – 15:35	**Issues and experiences in adolescent and adult vaccination campaigns** Marc LaForce, Serum Institute, USA
15:35 – 16:00	**Questions and discussion**
16h00 – 16h30	**Coffee/Tea Break**
16h30 – 18h00 **Lecture Theatre 2**	**BREAKOUT SESSION IV : Design of Clinical Trials and Epidemiology** Chair: Mark Cotton, Stellenbosch University, South Africa
16h30 – 16h45	**Determine TB prevalence and incidence, select trial sites and choose target populations for TB vaccines** Suzanne Verver, KNCV Tuberculosis Foundation, The Netherlands
16h45 – 17h00	**Design of TB vaccine efficacy trials for different study populations** Mark Hatherill, SATVI, South Africa
17h00 – 17h15	**Remarkable durability of Ag85a specific CD4 T cell memory responses up to 6 years after MVA85A vaccination** Thomas Scriba, SATVI, South Africa
17h15 – 17h30	**The influence of sociodemographic characteristics on retention of an infant cohort in western Kenya in preparation for future TB vaccine trials** Patience Oduor, KEMRI/CDC, Kenya
17h30 – 17h45	**TB exposed or infected infants as a target population for efficacy trials of new vaccines** Angelique Kany Kany Luabeya, SATVI, South Africa
17h45 – 18h00	**Questions and discussion**
16h30 – 18h00 **Lecture Theatre 3**	**BREAKOUT SESSION V : Regulatory Issues for New TB Vaccines** Chair: Mike Brennan, Aeras, USA
16h30 – 16h40	**Time to regulatory and ethical approval of TB vaccine trials in South Africa** Hennie Geldenhuys, SATVI, South Africa
16h40 – 16h45	**Historical approvals of clinical trial applications and protocol amendments from four African national regulatory authorities** Jan Chappell, Aeras, USA
16h45 – 18h00	**Roundtable discussion with regulatory authorities** Helen Rees, SAGE, South Africa Helen Ndagije, National Drug Authority, Uganda Portia Nkambule, Medicines Control Council, South Africa Mair Powell, European Medicines Agency (EMA), UK Jim Southern, Developing Countries Vaccine Regulators Network (DCVRN), South Africa Paul Tanui, NEPAD Agency, South Africa
16h30 – 18h00 **Lecture Theatre 1**	**BREAKOUT SESSION VI : New Emerging Vaccines, Part II** Chair: Christine Sizemore, NIAID/NIH, USA
16h30 – 16h45	**Vaccines to induce bactericidal immunity against Mycobacterium tuberculosis** Bill Jacobs, Albert Einstein College of Medicine, USA
16h45 – 17h00	**M. tuberculosis attenuated mutants as novel vaccine candidates** Olivier Neyrolles, CNRS, France
17h00 – 17h15	**Intranasal immunization with recombinant human parainfluenza type 2 virus-Ag85B showed protective effects against Mycobacterium tuberculosis infection** Yasuhiro Yasutomi, National Institute of Biomedical Innovation, Japan
17h15 – 17h30	**Lipoproteins determine the antigenicity of a new protective membrane vesicle-based vaccine against Mycobacterium tuberculosis** Rafael Prados-Rosales, Albert Einstein College of Medicine, USA
17h30 – 17h45	**Dose-dependent immune responses of the novel tuberculosis vaccine, AERAS-402, to mycobacteria-specific CD4+ and CD8+ T cells in healthy infants previously vaccinated with BCG** Benjamin Kagina, SATVI, University of Cape Town, South Africa
17h45 – 18h00	**An unbiased genome-wide Mycobacterium tuberculosis gene-expression approach to discover new antigens for human T cells that are expressed during pulmonary infection** Tom Ottenhoff, Leiden University Medical Center, The Netherlands
18h00 – 19h30	**Poster Viewing Area Open**
18h15 – 21h00 **Lecture Theatre 1**	**SATELLITE SESSION : The MVA85A Phase IIb Trial: Results and Implications for the Field** **Hors d'oeuvres and refreshments will be served starting at 18:15. Panel discussion to begin at 19h00.** *Hosted by* Aeras, Emergent BioSolutions, University of Oxford, South African Tuberculosis Vaccine Initiative and the Wellcome Trust

WED **27 MAR**

7h00 **3rd Floor**	Registration Opens
7h30 – 9h00	**MORNING WORKSHOPS : Continuing to Advance the Blueprint**
Lecture Theatre 3	**SESSION I: Creativity in research and discovery** Chair: Uli Fruth, WHO, Switzerland Rapporteur: David Lewinsohn, Oregon Health and Science University, USA
Classroom 2A	**SESSION II: Correlates of immunity and biomarkers for TB vaccines** Chair: Gerhard Walzl, Stellenbosch University, South Africa Rapporteur: Camille Locht, Institute Pasteur Lille, France
Classroom 2B	**SESSION III: Harmonization and cooperation of clinical trials** Chair: Lew Barker, Aeras, USA Rapporteur: Michele Tameris, South African Tuberculosis Vaccine Initiative, South Africa
Classroom 4A	**SESSION IV: Rational selection of TB vaccine candidates** Chair: Barry Walker, Aeras, USA Rapporteur: Jelle Thole, TBVI, The Netherlands
Classroom 4B	**SESSION IV: The critical need for advocacy, communications and resource mobilisation** Chair: Robert Nakibumba, Africa for Health Research Initiative, Stop TB Partnership Working Group on New Vaccines, Uganda Rapporteur: Mandy Slutsker, ACTION Global Health Advocacy Partnership, USA
9h00 – 10h00 **Lecture Theatre 1**	**Report Back from Morning Workshops** Chair: Ann Ginsberg, Aeras, USA Workshop rapporteurs
10h00 – 11h00 **Lecture Theatre 1**	**PLENARY SESSION VI : Building Support Through Advocacy and Communications** Chair: Jennifer Woolley, Aeras, USA **Roundtable discussion on the role of advocacy and communications in supporting and advancing TB vaccine R&D at all levels, from the community to the global level** Kaitlin Christenson, Global Health Technologies Coalition, USA Gavin Churchyard, Aurum Institute for Health Research, South Africa Nick Herbert, Member of Parliament, UK Kari Stoever, Aeras, USA Wim Vandevelde, Global TB Community Advisory Board, South Africa
11h00 – 11h30	**Coffee/Tea Break**
11h30 – 13h00 **Lecture Theatre 1**	**BREAKOUT SESSION VII : Preclinical Animal Models and Therapeutic Vaccines** Chair: Frank Verreck, BPRC, The Netherlands
11h30 – 11h45	**Therapeutic immunization against Mycobacterium tuberculosis is an effective adjunct to antibiotic treatment** Rhea Coler, IDRI, USA
11h45 – 12h00	**Early clinical measures reminiscent of human TB predict survival in NHP models in support of quantitative pre-clinical vaccine evaluation** Frank Verreck, BPRC, The Netherlands
12h00 – 12h15	**HPA global role in pre-clinical evaluation of novel vaccines** Simon Clark, Health Protection Agency, UK
12h15 – 12h30	**Pre-clinical screening of TB vaccines in the era of clinical efficacy testing** Ann Williams, Health Protection Agency, UK
12h30 – 12h45	**Chest imaging and lung function tests for the assessment of safety of an investigational TB vaccine in patients treated for pulmonary tuberculosis** Richard van Zyl-Smit, University of Cape Town, South Africa
12h45 – 13h00	**Enhanced immune responses against ESAT- 6 might induce hypersensitivity in Mycobacterium tuberculosis infected mice treated with ESAT-6/Ag85a chimeric plasmid DNA** Zhongming Li, Shanghai H&G Biotechnology Company, China

11h30 – 13h00 **Lecture Theatre 2**	**BREAKOUT SESSION VIII : Late Breaker** Chair: Juhani Eskola, Finnish National Institute for Health and Welfare, Finland	
11h30 – 11h45	**Enzymes of the sulphate assimilation pathway induced during intracellular growth are novel protective antigens of Mycobacterium tuberculosis** Warwick Britton, Centenary Institute, University of Australia, Australia	
11h45 – 12h00	**Characterization of novel multi-antigenic vaccine candidates with pan-HLA coverage against M. tuberculosis** Lior Carmon, Vaxil BioTherapeutics Ltd, Israel	
12h00 – 12h15	**Improved BCG mediated protection in necrosis-prone C3Heb/FeJ inbred mice following infection with W-Beijing strains of Mycobacterium tuberculosis** Diane Orway, Colorado State University, USA	
12h15 – 12h30	**Polyantigenic DAR-901: an inactivated whole cell vaccine for the prevention of tuberculosis** Ford von Reyn, Geisel School of Medicine at Dartmouth, USA	
12h30 – 12h45	**Phase II randomised controlled trial to evaluate safety and immunogenicity of MVA85A and selective, delayed BCG vaccination in infants of HIV infected mothers** Mark Hatherill, SATVI, South Africa	
12h45 – 13h00	**In-situ hsp-complex vaccines from BCG as TB vaccine candidates** Camilo Colaco, ImmunoBiology Ltd, UK	
11h30 – 13h00 **Lecture Theatre 3**	**BREAKOUT SESSION IX : Operational Issues Involved in Planning and Implementing Clinical Trials** Chair: Videlis Nduba, KEMRI/CDC Research and Public Heath Collaboration, Kenya	
11h30 – 11h45	**Assessing volunteer understanding in clinical research: lessons learned from implementation of a mixed method assessment of understanding tool (AOU) tool in HIV vaccine clinical trials** Judie Mbogua, IAVI, Kenya	
11h45 – 12h00	**Collection of PBMCs (peripheral blood mononuclear cells) in an infant TB vaccine trial: Challenges and lessons** Grace Kaguthi, KEMRI/CDC, Kenya	
12h00 – 12h15	**Retention, recruitment and enrolment into a South African TB vaccine trial** Trevor Beattie, Aurum Institute, South Africa	
12h15 – 12h30	**An early morning sputum sample is necessary for the diagnosis of pulmonary tuberculosis, even with more sensitive techniques: A prospective cohort study among adolescent TB-suspects in Uganda** Willy Ssengooba, Makerere University College of Health, Uganda	
12h30 – 12h45	**Willingness to participate in trials of and acceptability of new tuberculosis vaccines among HIV -infected adults with high CD4 counts** Tendesayi Kufa, Aurum Institute, South Africa	
12h45 – 13h00	**Questions and Discussion**	
11h30 – 12h45 **Classroom 2A**	**BREAKOUT SESSION X : Advocacy and Resource Mobilisation for TB Vaccines: Strategies and Tactics** Co-chairs: Lucy Ghati, NEPHAK / Stop TB Partnership Working Group on New Vaccines, Kenya | Erna Balk, TBVI, The Netherlands	
11h30 – 11h45	**Advocacy towards increased EU funding for TB vaccines research** Fanny Voitzwinkler, Global Health Advocates, France	
11h45 – 12h00	**Working in coalitions to advance an R&D agenda** Kaitlin Christenson, Global Health Technologies Coalition, USA	
12h00 – 12h15	**Utilising vaccine support networks to build community engagement for vaccine trials** Evelyn Kibuchi, Kenya AIDS NGO Consortium (KANCO), Kenya	
12h15 – 12h30	**Utilising data and modelling for evidence-based advocacy** Angeline Nanni, Aeras, USA	
12h30 – 12h45	**Researchers as advocates** David Lewinsohn, Oregon Health and Science University, USA]	
12h45 – 13h00	**Questions and Discussion**	
13h00 – 14h15 **3rd Floor**	**Lunch** (Poster & Exhibit Area)	**SATELLITE SESSION: Human and Animal TB: Exploring the Links and Opportunities for Vaccine Development** *Hosted by* Aeras and Glyn Hewinsohn of the of the Animal Health and Veterinary Laboratories Agency (AHVLA)

贊助單位芳名錄

14h15 – 15h45 **Lecture Theatre 1**	**PLENARY SESSION VII : Sustaining the Global TB Vaccine Portfolio** Co-chairs: Line Matthiessen, European Commission, Belgium | Kari Stoever, Aeras, USA
14:20 – 14:30	**Overview of financing gap and approaches to resource mobilisation** Kari Stoever, Aeras, USA
14:30 – 15:30	**Perspectives on sustaining the pipeline** **Innovative financing mechanisms** Thomas Barrett, European Investment Bank, Belgium **Towards EDCTP-II** Charles Mgone , EDCTP, The Netherlands **Multinational corporations** Didier Lapierre, GSK Biologicals, Belgium **China's contributions to TB vaccine R&D** Jueren Lou, China National Biotec Group (CNBG), China
15:30 – 15:45	**Questions and discussion**
15h45 – 16h30 **Lecture Theatre 1**	**CLOSING SESSION** Chairs: Hassan Mahomed, Western Cape Department of Health / Stellenbosch University, South Africa | Jelle Thole, TBVI, The Netherlands | Ann Ginsberg, Aeras, USA **CLOSING PLENARY ADDRESS** Mario Raviglione, WHO, Switzerland **TB Elimination: Where we are and what are the needs**

此次參訪相關位置

結核病疫苗背景介紹

目前世上最廣泛使用且唯一用來對抗結核病的疫苗—卡介苗（Bacille Calmette-Guerin；BCG）爲 1908 年，由法國的 Calmette 及 Guerin 兩位醫師，將有毒的牛型結核桿菌(*M. bovis*）經多次的人工繼代培養而減毒馴化的活性疫苗。卡介苗已被證實可以預防幼兒發生結核性腦膜炎，但根據臨床試驗的結果顯示，傳統卡介苗對成年人的保護性差異相當大，其效價可自 0% 至 80%不等，Murray 等人推測一個具有 50%保護效果(protective efficacy)新疫苗的研發與施打，到 2030 年前可以防止九百萬人死於結核病。而近期發生廣泛抗藥性結核菌(Extensively drug resistant tuberculosis, XDR-TB)的出現無異使結核病防治上更加困難，由此可見新疫苗研發的迫切性。

大會性質

世界衛生組織的 2050 年目標，是 TB elimination，所以疫苗的重要性，不言可喻。全球結核病疫苗高峰會歷史上一共開了三次，第一次是 2001 年，只有 10 幾位專家參加；隨著越來越多的臨床前期疫苗的發明以及疫苗進如臨床試驗，第二屆(2010 年, Tallinn, Estonia)就有將近 200 人參加，並在那一次開會後，由 Stop TB working group on new vaccines (目前 chair 是 Michael Greco，此次剛好跟他參加了同一個 workshop)，WHO，AERAS，Bill & Melinda Gates Foundation, TBVI，美國 NIH 和 NIAID 及其他組織的支持，於 2012 年 324 世界結核病日，將 TB 疫苗發展的藍圖，發表在期刊 Tuberculosis 上，對未來 10 年發展疫苗最重要的五個關鍵 (***Five keys to progress)*** 提出想法:

- Creativity in research and discovery.
- Correlates of immunity and biomarkers for TB vaccines.
- Clinical trials: harmonization & cooperation.
- Rational selection of TB vaccine candidates.

- The critical need for advocacy, community acceptance and funding.

第三屆，也就是此次會議選在南非的 Cape town (開普敦)舉行，有其特別意義。在 2010 年開始進入 phase 2b 收案之新疫苗 MVA85A 臨床試驗，已經預知可以在 2012 年底有 2-year-follow-up 的結果。而這個人類史上第一個 phase 2b 新結核病疫苗的臨床試驗就是在開普敦城外 100 公里的農業小鎮 Worcester 執行的，故此次會議還有 optional site visit，讓我們有機會到 site 去一探究竟。在今年初，Michele TamerisHassan，Mark Hatherill，Hassan Mahomed 以及 Helen Mcshane 共同發表於 Lancet 的文章，已經告訴我們，雖然在動物實驗和臨床試驗 phase 2a 的結果都一致的樂觀，但是在這個將近 3000 位多個嬰兒加入的隨機雙盲臨床試驗，對於 primary end point，兒童結核病的發病，沒有效果。此次的主題爲 progress collaborating sustainability，而與會的專家學者，就是要討論「如何從發展了 13 年但證實無效的疫苗效益試驗中，得到經驗，再出發」。

開會內容 snapshots

第一天議程包括全球結核病的流行狀況，推論 2050 年如要根除結核病，疫苗的發展與潛伏性感染的控制與治療，配合目前的結核病防治策略將有希望達成。緊接的是討論有關結核菌如何引起人體抵抗，包括在肺部的先天與後天免疫反應，並藉由不同動物模式了解致病機制。第二天議程,上午聚焦於各式預防性 TB vaccine 的臨床試驗，包括 MVA85A，M72，H1，H56，以及 rBCG vaccine (VPM1002)。下午討論各式 biomarker 的運用與新研發的 TB vaccine 之證實研究，其他同時進行之會議包括新佐劑運用於結核病疫苗，clinical trial 設計以及相關法規的討論。第三天議程以 workshops 分五個子題同時進行包括: 創新研發、找尋免疫力與 biomarker 與疫苗的關聯性、clinical trial 之共同合作與資訊共享、如何決定新疫苗進入下一階段測試的依據，以及強化資源的運用與資訊溝通。下午則探討如何國際合作以及世界主要國家對於新疫苗之研發包含歐盟、美國、南非、與中國的研究概況，最後由 WHO Stop TB department 的 Director， Mario Raviglion 總結要根除結核病。目前的處境以及還需要強化的事項，以期待 2050 年結核病的根除。

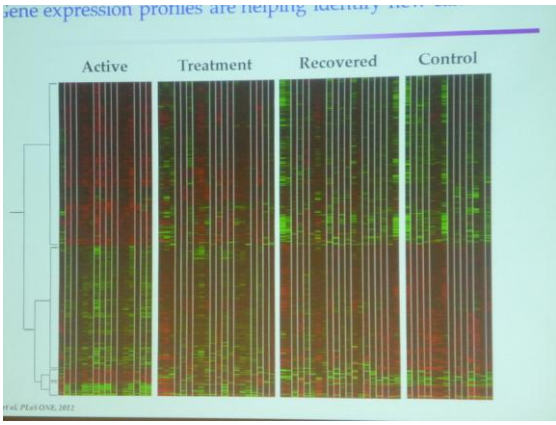
從臨床前期試驗到大型嬰兒臨床試驗

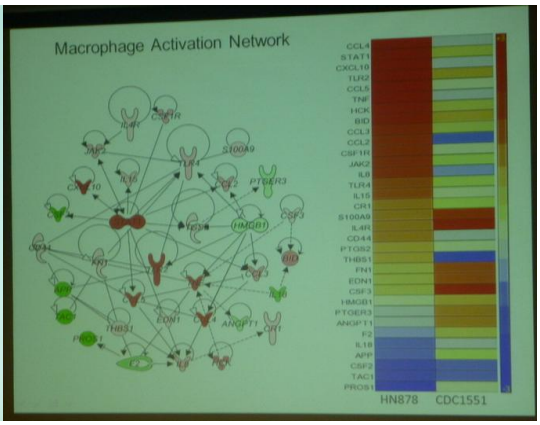
本次會議中以英國發明 MVA 85A vaccine 的 phase 2 b clinical trial 最爲大家關注，因爲它是第一個 new TB vaccine 於嬰兒測試保護效率。MVA85A 是以改造過的牛痘病毒 (vaccinia virus Ankara; MAV) 表現結核分枝桿菌的 Ag85A 抗原。Helen McShan 就 MVA85A 臨床試驗從臨床前動物試驗的資料，一直到臨床 phase 1, phase 2a 的成果，再次說明，並針對相關收集的生物標記及未來展望進行闡述。雖然結果並不如其先前動物試驗結果，但也讓科學家學到需要更多對此疾病的研究: 包括對結核菌與及人體之間的互動，例如不同時期細菌的特性與基因表現，以及在感染部位人體的先天與後天免疫反應如何，如此方能找出對抗細菌的方法。爲了測試疫苗的效果，又衍生出如何發展合適的動物模式來測試疫

苗，且能用於預測是否能夠有效預測人體試驗的結果；此外，如何尋找 biomarker 運用於病人感染 TB 病況的監控，其他包括如何在有限的資源下如何結合政府與民間力量吸引更多優秀人才從事結核病相關研究。

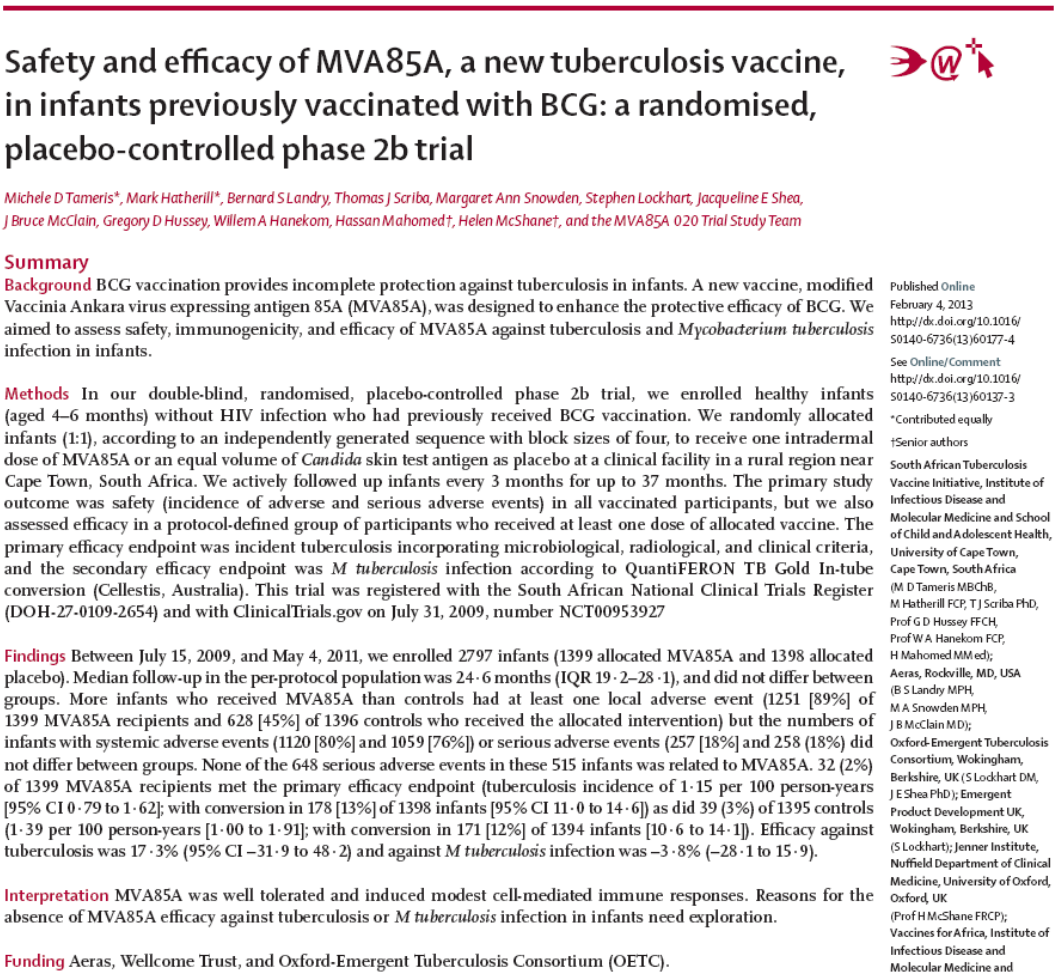
幾位執行 non-human primate (NHP) 的動物試驗專家，已針對此次的失敗，設計新的動物試驗，繼續針對人類對動物與人類在結核病上防禦機制及疾病表現的相同點及不同點，進行了解，以避免重蹈動物試驗都成功但一進到人類就不成功的窘境。會場中有其他學者也對支持這些臨床試驗的 AERAS 進行提問，這些試驗所得到得臨床檢體，其實是大家想要進一步發展新的疫苗成功的關鍵，但這些檢體僅掌握在少數研究者的手中，對於未來的發展恐怕很難有突破性的發展。AERAS 將這個議題拋出，Helen McShan 也沒有正面的回應，但是提到嬰幼兒的檢體 (包括 PBMC)其實很少量，可能很難分享給其他研究者。

學者發現，透過 RNA transcriptomes 的 protein genomic 進行 quantitative PCR (qPCR)，從發病者到接受治療到復原期，qPCR 表現皆與控制組(未發病未被感染者)截然不同。此次臨床試驗之前有大規模進行南非開普敦青少年的結核感染盛行率調查，其中追蹤到發病的個案，早在發病前兩年，transcriptomes 的 protein 就已經跟沒有發病的其他受試者不同了。如果我們能夠多了解從 recent infection 到 latency 到 active disease 之間，每個 stage 的生物標記若都能一一找出並確認與疾病自然病程的關係，則未來新疫苗的發展將會有足以預測 phase 2b 結果的 surrogate markers，如此離疫苗發展成功的距離又能跨進一大步!





MVA 85A vaccine 的 phase 2 b clinical trial 試驗結果其實是已經發表在 Lancet 上:



Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris*, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team

Summary

Background BCG vaccination provides incomplete protection against tuberculosis in infants. A new vaccine, modified Vaccinia Ankara virus expressing antigen 85A (MVA85A), was designed to enhance the protective efficacy of BCG. We aimed to assess safety, immunogenicity, and efficacy of MVA85A against tuberculosis and *Mycobacterium tuberculosis* infection in infants.

Methods In our double-blind, randomised, placebo-controlled phase 2b trial, we enrolled healthy infants (aged 4–6 months) without HIV infection who had previously received BCG vaccination. We randomly allocated infants (1:1), according to an independently generated sequence with block sizes of four, to receive one intradermal dose of MVA85A or an equal volume of *Candida* skin test antigen as placebo at a clinical facility in a rural region near Cape Town, South Africa. We actively followed up infants every 3 months for up to 37 months. The primary study outcome was safety (incidence of adverse and serious adverse events) in all vaccinated participants, but we also assessed efficacy in a protocol-defined group of participants who received at least one dose of allocated vaccine. The primary efficacy endpoint was incident tuberculosis incorporating microbiological, radiological, and clinical criteria, and the secondary efficacy endpoint was *M tuberculosis* infection according to QuantiFERON TB Gold In-tube conversion (Cellestis, Australia). This trial was registered with the South African National Clinical Trials Register (DOH-27-0109-2654) and with ClinicalTrials.gov on July 31, 2009, number NCT00953927

Findings Between July 15, 2009, and May 4, 2011, we enrolled 2797 infants (1399 allocated MVA85A and 1398 allocated placebo). Median follow-up in the per-protocol population was 24·6 months (IQR 19·2–28·1), and did not differ between groups. More infants who received MVA85A than controls had at least one local adverse event (1251 [89%] of 1399 MVA85A recipients and 628 [45%] of 1396 controls who received the allocated intervention) but the numbers of infants with systemic adverse events (1120 [80%] and 1059 [76%]) or serious adverse events (257 [18%] and 258 (18%) did not differ between groups. None of the 648 serious adverse events in these 515 infants was related to MVA85A. 32 (2%) of 1399 MVA85A recipients met the primary efficacy endpoint (tuberculosis incidence of 1·15 per 100 person-years [95% CI 0·79 to 1·62]; with conversion in 178 [13%] of 1398 infants [95% CI 11·0 to 14·6]) as did 39 (3%) of 1395 controls (1·39 per 100 person-years [1·00 to 1·91]; with conversion in 171 [12%] of 1394 infants [10·6 to 14·1]). Efficacy against tuberculosis was 17·3% (95% CI –31·9 to 48·2) and against *M tuberculosis* infection was –3·8% (–28·1 to 15·9).

Interpretation MVA85A was well tolerated and induced modest cell-mediated immune responses. Reasons for the absence of MVA85A efficacy against tuberculosis or *M tuberculosis* infection in infants need exploration.

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本次會議中，針對 MVA85A 臨床試驗的部分，Michele Tameris 代表團隊報告 phase 2b 收案的規模，整理如下:

實際收案且留在 trial 中的病人有 2397 位，case verification ward(CVW)住院次數達 1000 多次，雖然有 600+次被分類爲 SAE 但是跟疫苗無關，總共有 120 套痰或者胃抽取液確認培養出結核分枝桿菌。

020 By The Numbers	
4 754	Subjects Screened
2 797	Subjects Randomized
2 597	Normal Completers
200	Early Terminators
3.3	# Years between FPFV and LPLV
32 059	Subject Visits
735	Average # days each subject was on study
1 193	CVW Admissions
648	Serious Adverse Events
831	TB Treatment/Prophylaxis Medications
14 691	Total Blood Draws (Safety, Immunology, Quantiferon)
2 342	Sputum Samples collected in the CVWard
61	Sputum Samples pos. for TB in CV Ward
2 342	Gastric Washings collected in the CVWard
59	GW Samples pos. for TB in CV Ward

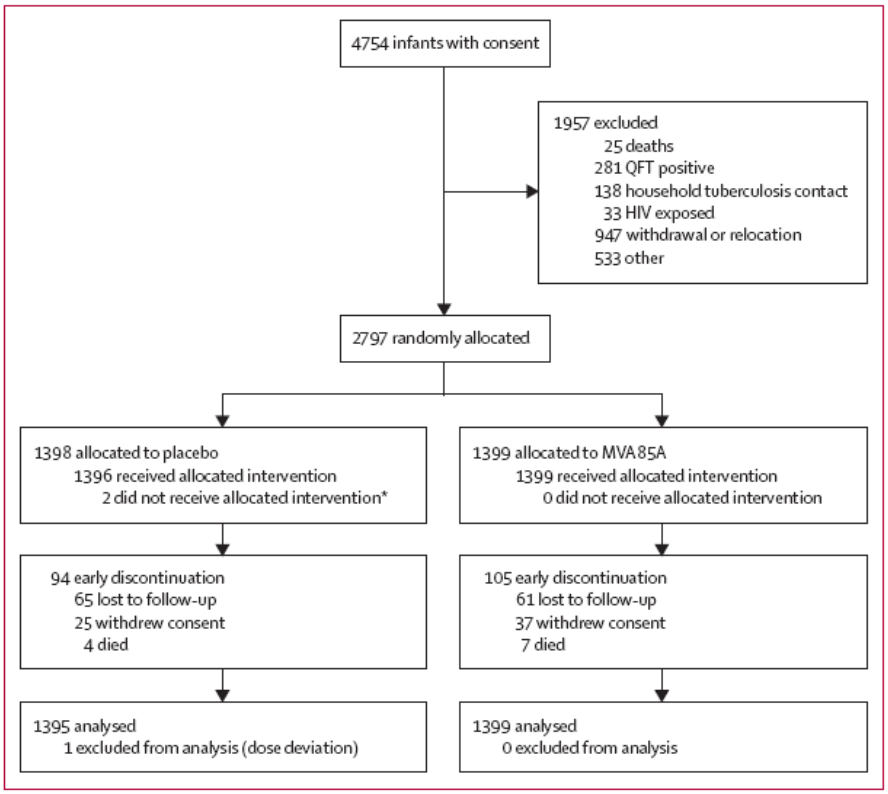


Figure 1: **Trial profile**
*One infant developed gastroenteritis that precluded inclusion and one infant became ineligible after a randomisation error. QFT=QuantiFERON-TB Gold In-tube.

兩個隨機分派的組別，病人沒有 demographics 上的差異:

	Placebo (n=1395)	MVA85A (n=1399)	Overall (n=2794)
Age, days	145·7 (13·5)	146·6 (14·3)	146·2 (13·9)
Sex, male	714 (51%)	708 (51%)	1422 (51%)
Ethnic group			
Black	267 (19%)	287 (21%)	554 (20%)
Mixed race	1126 (81%)	1107 (79%)	2233 (80%)
Asian	1 (<1%)	3 (<1%)	4 (<1%)
White	1 (<1%)	2 (<1%)	3 (<1%)
Weight			
Infants assessed	1389 (>99%)	1394 (>99%)	2783 (>99%)
Mean, kg	6·47 (0·98)	6·45 (0·99)	6·46 (0·98)
Full-term birth (≥38 weeks)	983 (70%)	1031 (74%)	2014 (72%)

Data are mean (SD) or n (%).

Table 1: **Demographics and baseline characteristics of the per-protocol population**

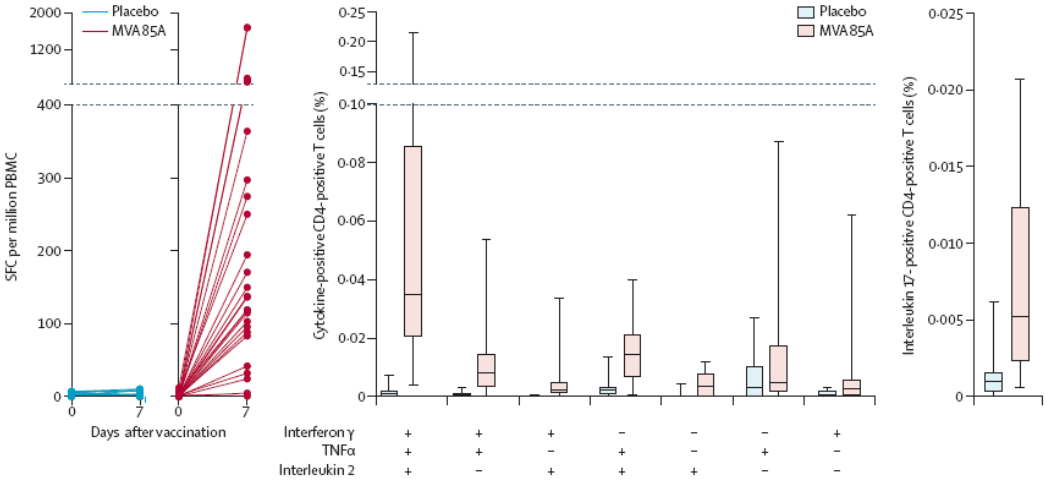


Figure 2: **Vaccine immunogenicity**
(A) Frequencies of Ag85A-specific T cells measured by interferon-γ enzyme-linked immunosorbent spot assay in infants in study group 2 (27 infants in the MVA85A group and 27 infants in the placebo group) before administration of placebo or MVA85A (day 0) and 7 days after vaccination. (B) Frequencies of cytokine-expressing Ag85A-specific Th1 (CD4-positive T cells expressing IFN-γ, TNFα, or interleukin 2) and (C) frequencies of Ag85A-specific Th17 (CD4-positive T cells expressing interleukin 17) cells, measured by whole blood intracellular cytokine staining 28 days after administration of placebo or MVA85A to infants in study group four (17 infants in the MVA85A group and 19 infants in the placebo group). SFC=spot-forming cells. PBMC=peripheral blood mononuclear cell.

試驗結果大失所望，primary end-point 也就是 culture proved TB case incidence 兩組沒有顯著差異，secondary end-point 包括臨床診斷的 TB，新增感染率都沒有顯著的差異。

	Placebo (n=1395)	MVA85A (n=1399)	Vaccine efficacy
Endpoint 1 (primary efficacy endpoint)	39 (3%)	32 (2%)	17·3% (−31·9 to 48·2)
Endpoint 2 (exploratory efficacy endpoint)	52 (4%)	55 (4%)	−6·9% (−56·1 to 26·9)
Endpoint 3 (exploratory efficacy endpoint)	177 (13%)	196 (14%)	−12·1% (−37·4 to 8·5)

Data are n (%) or % (95% CI). Participants with more than one diagnosis were analysed in each level of diagnosis attained. Vaccine efficacy and corresponding 95% CI was estimated with the Cox regression model (1 − estimated hazard ratio).

Table 2: **Primary and secondary efficacy endpoints**

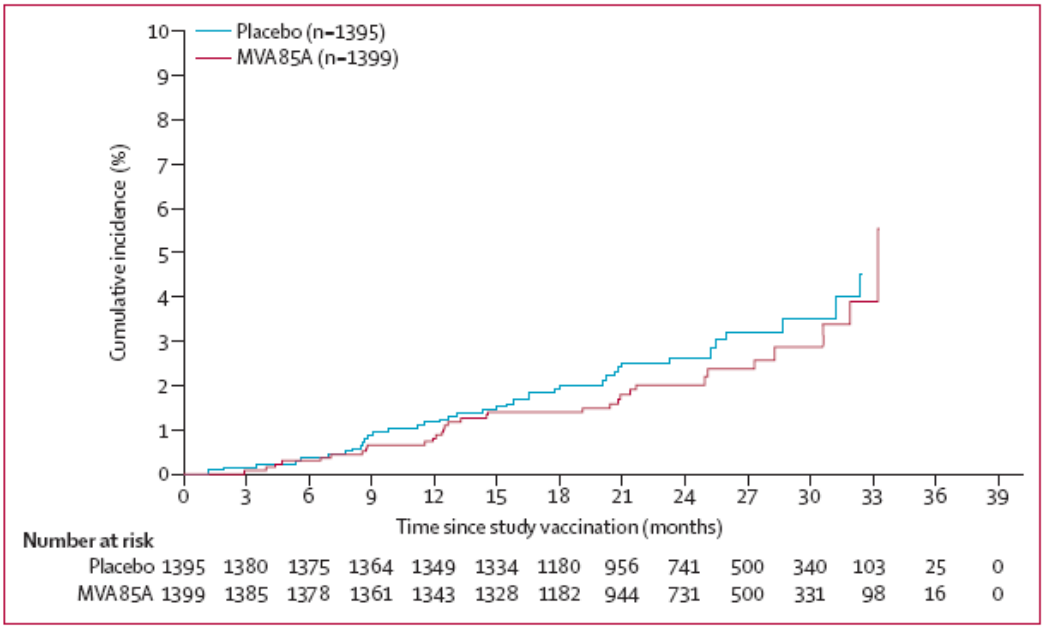
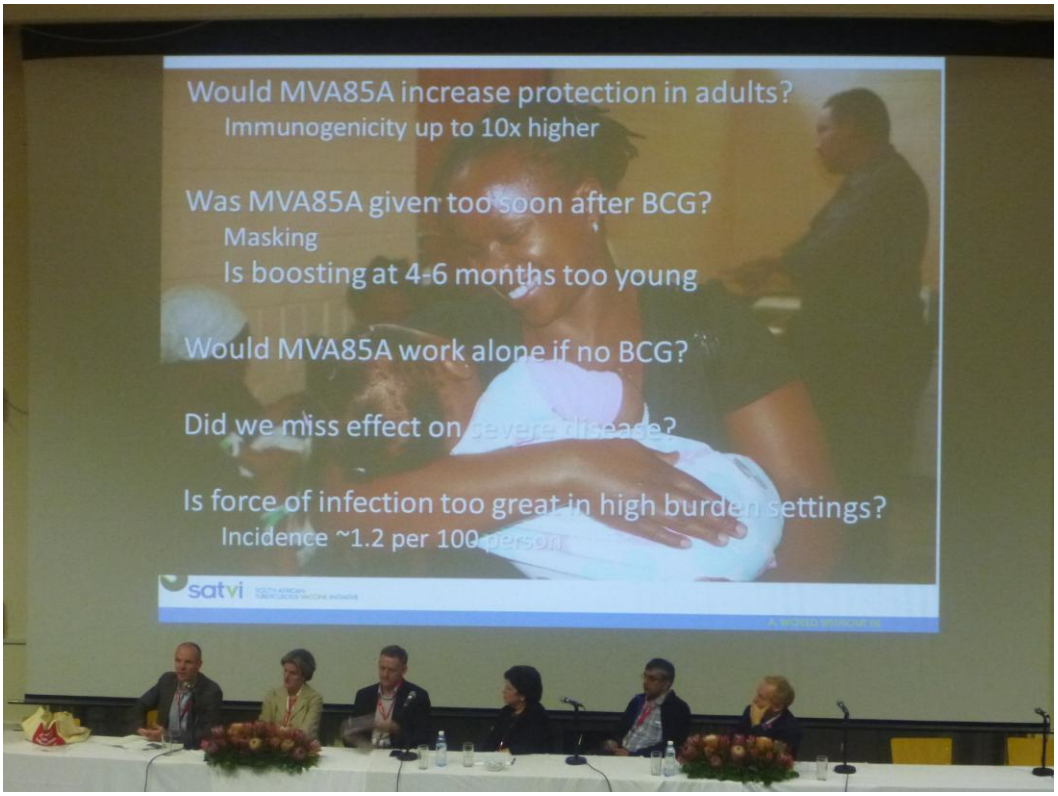


Figure 3: **Cumulative incidence of diagnosis of tuberculosis endpoint 1**



檢討起來有幾個未來可以思考再精進的方向:

1. MVA85A 在 phase 1 人類(成人) 的 immunogenicity 和動物(實驗)的免疫結果是相對比嬰兒接種後的免疫結果，高出 10 倍以上，所以會不會同樣的試驗，在成人會有不同的結果。
2. 在 4-6 個月大的時候，進行 MVA85A 接種，原本是希望在發生自然感染之前，趕緊 booster，但如果這時免疫不夠強，會不會追加得太早 (其他疫苗的臨床試驗，甚至可以分成不同年齡進行追加並追蹤免疫力的產生狀況，但 TB 並沒有這麼做)?
3. 因爲 BCG 有保護嬰幼兒不受 TB 死亡的危害，故在設計 trial 時，每個受試者都是接受過 BCG 接種的，如果沒有 BCG 接種在前面，會不會不一樣? 又由於 BCG 本身在不同的受試者身上帶來的效果是沒有辦法確認的，會不會發病的個案其實是 BCG 就已經無效的個案?
4. 在動物試驗時可以依照犧牲動物之後驗出檢體中的菌量，得以評估疫苗的效果，但在人類試驗沒有辦法，以至於對於疾病嚴重度的效果，可能有但無法評估。
5. 在動物試驗時可知，當氣態給予的菌量過高，其實不論有沒有打過 BCG 的動物全部都會死亡；如果我們做試驗的區域，特定的受試者所遭遇到的感染劑量，像動物碰到的劑量一樣高，或者說累計的劑量很大(因爲每 100 人年會有 1.2 個個案產生)，那是不是也無法看出疫苗的保護力?

其他重要的新結核病疫苗的研發與臨床試驗結果

1. **Recombinant BCG vaccine: VPM1002** (recombinant *M. bovis* BCG Δ ureC::Hly+:: Hyg+,genetic background "Danish, subtype Prague")

是利用表現李斯特菌溶菌素 (listeriolysin)，藉以改變吞噬小體 (phagosome) 通透性，促使抗原可由吞噬小體(phagosome)釋放，並經由 HLA class Ⅰ 分子呈現抗原，激發 $CD8^+$ T 細胞的活化，此重組疫苗目前已在南非進入第二期的臨床試驗 (Phase IIa)。

2. 病毒載體疫苗

a.MVA85A 是以改造過的牛痘病毒 (vaccinia virus Ankara; MVA) 表現結核分枝桿菌的 Ag85A 抗原，此疫苗施打於曾注射過卡介苗的老鼠、天竺鼠、牛等動物身上，可誘發更佳的保護效果，且這個疫苗已完成第二期臨床實驗 (phase IIb) 並且失敗。

b.以腺病毒 (adenovirus)爲載體，如 Aeras-402 是利用一種在複製上有缺陷的腺病毒 (adenovirus serotype 35) 做爲載體，藉其表現結核分枝桿菌的抗原包括 Ag85A、Ag85B 和 TB 10. 疫苗目前即將進入第二期臨床試驗 (phase IIb)。

3.次單位疫苗 (subunit vaccine): 次單位疫苗主要是由蛋白質佐以免疫性佐劑 (immunological adjuvant)所組成，此類疫苗的優點爲較少引起有害的反應，且因其使用的抗原成分通常爲已知分子，容易再次製造，但因疫苗的主成分是由蛋白質所組成，所以缺點爲蛋白質純化的過程所費不貲，且有可能需要二次追加注射以增進免疫效果：

a. M72 是由葛蘭素史克藥廠 (Glaxo-SmithKline Biologicals, GSK) 藉由純化結核分枝桿菌 (*M. tuberculosis* 39 and 32) 一個 72 kDa 的蛋白 (Rv1196 and Rv0125) 配合佐劑 AS01 (Liposome-based, surface-active saponin QS21 and TLR-4

ligand) 和 AS02 (oil-in-water emulsion, surface-active saponin QS21 and TLR-4 ligand) 所研發出來的疫苗。此疫苗在 phase I 的階段已證實可誘發抗原專一性的 $CD4^+$ T 細胞免疫反應，並即將進入第二期臨床試驗 (phase IIb)。

b. Hybrid-I 則是由丹麥血清研究所 (Statens Serum Institute, SSI) 藉由純化結核分枝桿菌的兩個分泌性抗原 ESAT-6 和 Ag85B，配合奧地利生技公司 Intercell 所研發的佐劑 IC-31 (cationic antimicrobial peptide (KLKL5KLK polypeptide) and TLR-9 ligand) 或丹麥血清研究所自行開發的佐劑 CAF01 (Liposome-based, lipoid MINCLE ligand25) 所研發而成的疫苗。

c. HyVac 4/AERAS-404 是由 Ag85B 和 TB 10.4 佐以佐劑 IC-31 所研發而成的疫苗。

與當地省級的 TB control 部門見面以及參訪 SATVI 臨床試驗基地

Pro. Hassan Mahomed 去年底，已經從 UCT (University of Cape town) 轉到位在 Cape town 市區的 West Cape Department of Health 上班，投身於公共衛生。所以他介紹 TB Prevention and Management 的 Alvera Swartz 讓我們有機會了解南非 TB control 的狀況。南非分成數個省，其中 West Cape 算是經濟較佳的一個省，白人多爲英國，荷蘭的後裔之外，黑人爲主要的人口。整個 West Cape 有 5 百萬人口，旗下 30 個 districts，有將近 600 個鎮，雖然每個鎮都有類似衛生所的 public primary clinics，但是差異很大，根據我們實地到 SATVI 臨床試驗基地所在地 Worcester 的衛生所進行訪視，沒有 X 光設備、實驗室、當然也不提供住院服務。

病人發現有兩個方式，一爲因症就醫，一爲透過病人的接觸者，發現病人。

登記病人是用個案報告卡，再傳到 sub-district 的層級，由這個層級將資料輸入 web-based 系統，省的層級每季被國家中央要求個案登記資料，而 district 則每月稽催 sub-district 將資料鍵入。根據 Alvera 的估計，未通報的約有 4 成，因爲私人醫療可以不進行通報，也沒有什麼辦法強制通報。這個比例我詢問 Hassan，Mark Hatherill 以及 Michele Tameris 這些在 UCT 服務的流病專家，得到的答案不謀而合。 這跟 WHO 聲稱的 detection rate 超過 70%，實在是有不小的差距。病人因症就醫，使用 AFS 兩套進行診斷，並進行 HIV 檢驗 (超過 50%的病人是 HIV positive)。X 光不是常規，如果病人是小孩或者是 HIV 病人，才會轉到 district 醫院去照 CXR 以及痰培養；接觸者檢查則主要是症狀篩檢，成人如果有症狀就留 AFS，有症狀的小朋友則轉介 CXR，沒症狀的小孩和 HIV positive 接觸者則做 TST 後 (很驚訝地發現有執行 TST)，再依照 TST 結果來給 IPT。在加強期，衛生所要求民眾每日到點都治，一週五日，雖然所主任回答如果病人無法來衛生所，他們也會派 out-reach workers 去送藥，不過從民眾大多來到點就知道，outreach 的資源不足，而一個衛生所的涵蓋範圍約爲可以走路到達的距離，所以應該勉強可以都治前兩個月，但後面的持續期我想就很困難達成。

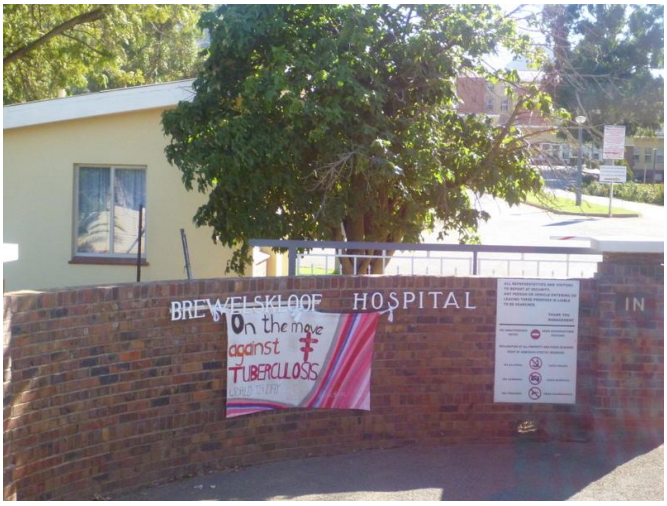
爲了要推動 Xpert (一種 WHO 在第三世界國家大量推行的快速 RMP 抗藥性篩檢)，下個月會開始有訓練，以 50%以上是 HIV positive 且 MDRTB 抗藥又相對盛行，確實是值得推動 Xpert 的地方。去年 MDRTB 新案有 2000 名，因爲有 web-base 系統登記，所以新案得以掌握，但實際盛行率不清楚，因爲病人一旦失

聯，因爲 TB 通報不是靠 ID 來登記的，無法串聯系統了解病人的預後；過去 MDRTB 一律住院由醫院收治，由醫院進行通報到 web-based 的系統進行登記，直到病人培養陰性再轉出去；但是由於病人增加快速，醫院已經住不下這些 MDRTB 病人，故依照 WHO 建議，進行 decentralized 的策略，讓病人回到社區治療。所以病人回到社區，不是每個鎮都有足夠的醫療系統可以面對，一旦有問題，必須到 district 醫院去診治。然而即使有五六間過去有能力可以收治 MDRTB 的指定醫院的隔離病房，預計只要負責收治 XDRTB 病人，但因爲 Linazolid 太貴，在南非不是公立醫療保險的免費藥物 (來不及問其他第五類的藥物是否有同樣的問題)，所幸 aminoglycosides 的供貨算平順。結論是，收治並不等於治療，XDRTB 病人留在醫院，主要的目的是不要擺在社區傳播，但依然會有院內感染控制的問題。因爲接觸者沒有紀錄 ID，故無法有效地利用系統，完成 MDRTB/XDRTB 接觸者檢查提早診斷 MDRTB/XDRTB 的功用。

南非除了上述系統性問題，還有它特有的區域性問題，礦工，監獄及非法移民。擁有豐富天然原物料的南非，和 Zambia 一樣，都有相當大的跨國採礦業，這些採礦公司通常沒有太注重採礦工人的工作環境，當然薪水也非常低，在先天環境不佳，後天條件又欠缺的情況下，礦工的 TB 發生率一向都是高的不得了，同時伴隨著慢性矽肺病。開會期間，SABC (South Africa BBC)電視台的一個辯論節目，題目叫”Did Mining benefit Africa?” ，可見採礦公司在非洲被視爲是國家財富的來源，但同時底層的民眾並未因此而改善生活，仍然生活在沒有自來水沒

有家戶馬桶的窘境之中，而礦工們的健康問題，也完全不是超低的薪水可以涵蓋或者保障的。監獄一向是 TB control 非常挑戰的區域，南非國父，Nelson Mandela，被關在 Cape town 3 公里外的 Robbon Island 監獄 27 年間，就結核病發作過，到現在都飽受慢性肺病之苦，就在開會結束的週四，電視台播出現任總統 Jacob 宣布 Mandela 四個月內三度住院的消息，內容是 Mandela 已經 94 歲但因爲慢性肺病又遇到新的感染，故再度入院，但希望民眾勿驚慌。而今年的世界結核病日活動，衛生部長也跟法務部長一起到監獄內一日遊，宣示監獄內處理結核病的決心。南非算是比較富裕的非洲國家，又是金磚五國之一，雖然貧富差距甚大，仍然是其他國家嚮往移民的地方。還面臨其他非洲國家的非法移民，困難登記及無從管理起的問題。

SATVI 臨床試驗的團隊成員



SATVI 臨床試驗基地就在結核病醫院的院區內

試驗基地要招募受試者的幅員非常廣大，約 600KM^2 範圍，故需要大量的車輛接

送受試者及其家屬

執行收案及接種疫苗觀察副作用的試驗基地 **(Trial house)**

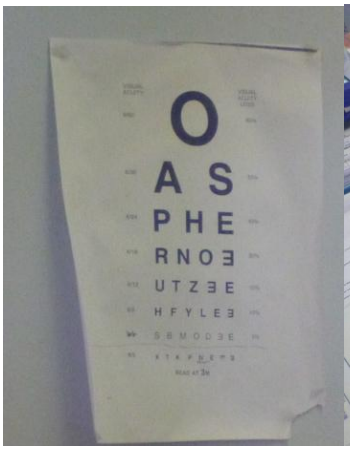
藥局 (cold chain)

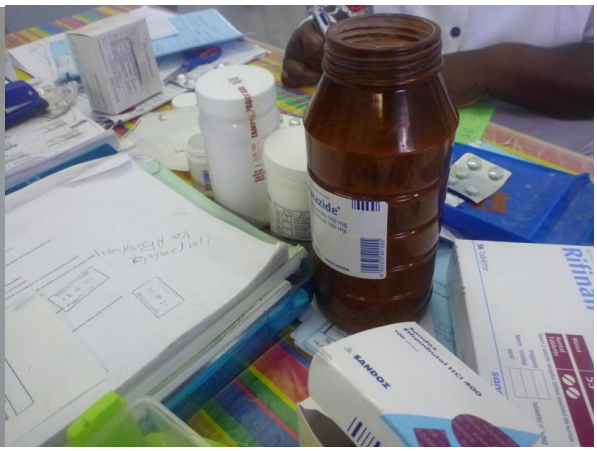
Case verification ward (CVW)

試驗基地另一角 (Trial house)

Out-reach worker Gloria，當天也擔任嚮導，右邊則是 Mark，是 clinical trial 的 PI。

Trial site 的衛生所，該國 NGO 表示，這已經堪稱示範中心，窗明几淨以外，自然通風良好，病人雖多 (6000 人/月)但不擁擠，每天有一名醫師和九名護理師協助診療，從 TB/HIV, DM/HTN 慢性病，產前檢查全都得照顧。





TB clinic 以前兩個月到點 DOT 爲主，Rifinah、EMB、PZA 都用原廠的藥。






收案的其中一個小部落叫 Mandela square，是一個沒有自來水、電力供應的小部落。滿地垃圾外，因爲缺水，塵土飛揚，幾戶人家共用一個流動廁所，但因爲氣候乾燥，整體衛生狀況不感覺特別糟糕。學齡前的兒童在自家門口嬉鬧，遇到我們這群訪客，倒也大方，張大眼睛觀察我們，團員把手上被分配到的小點心，全找出來分給孩子們。孩子們天真地說謝謝，一路上還有年輕人認出車子是從 SATVI 開出來的，比比手肘，看看有沒有要招募新的受試者，畢竟收案後每一次抽血，就會有 150 ZAR (相當於 600 元台幣)，相當有吸引力，而且可以獲得較佳的健康資訊。Gloria 說，在這邊收案不算困難，較常見遇到的收案瓶頸，就是媽媽或女性個案已經同意收案，但是回家後又不願意，因爲爸爸或丈夫、男朋友反對。

叁、心得及建議

結核病是一個蔓延全世界且至今尚無法有效撲滅的重大傳染病，而根據菌株分型及流行病學報告得知，北京株未來恐成爲造成台灣結核病感染及流行的最主要菌株，而現行卡介苗的保護性效果，尚無法全面的預防結核病感染，因此一個具有優良保護效果的替代性疫苗，對結核病的防治是當前急迫需要的。一個新疫苗的產生極爲耗時費資，除了要以動物實驗確定其具有良好的免疫能力，以期通過前臨床試驗外，還須審慎評估其用於人身上的安全性及是否有良好的保護效果。經過冗長的臨床試驗階段後，疫苗製造還必須以良好的製程來生產 (good manufacturing practices, GMP)，以確保疫苗的品質。隨著全世界科學家共同的努力及對結核分枝桿菌致病機制的了解，期待能在不久的未來能產生出一個替代性的疫苗，並能有效控制結核病的感染與傳播。只有有效的疫苗，全球才有可能達到世界衛生組織的 2050 年目標: elimination of TB。所以，站在結核病控制的立場，發展疫苗是全球結核病控制必要的策略及手段，當然不可因爲一時的失敗而放棄。

建議如下:

1. 南非的 TB control 資源雖不足但並非沒有資源，台灣若有心從事這方面的外交突破，可以從省的層級，由 TB 資訊系統切入，來進行協助。
2. 由於台灣的結核病發生率不論哪個族群都不夠高，如果打算發展結核病疫苗，台灣較適合進行臨床前及臨床一期試驗，但熟練地執行安全且適當的動物模式是必須要有的基本功夫。
3. 發展疫苗需要大量的資金，全球主要的資源來自於 EDCTP (歐盟), DGIS (荷蘭), UK-DFID (英國), Bill & Melinda Gates Foundation, NIH (美國)，研究單位必須有能力跟其他頂尖學術單位競爭。