

出國報告（出國類別：研究）

第十二屆亞太地區疫苗學進階課程
The 12th International Advanced Course on
Vaccinology in Asia-Pacific Regions

服務機關：疾病管制局
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派赴國家：韓國(首爾)
出國期間：2012/5/14-19
報告日期：2012/7/30

出國提要表：

日期	工作 日誌	地 點	行 程 內 容
101/5/13 (日)	啟程 接駁	台北→首爾	路程 (搭乘陸上交通赴首爾大學)
101/5/14 (一)	課程	首爾	參與課程
101/5/15 (二)	課程	首爾	參與課程
101/5/16 (三)	課程	首爾	參與課程
101/5/17 (四)	課程	首爾	參與課程
101/5/18 (五)	課程	首爾	參與課程
101/5/19 (六)	課程/返程 抵達	首爾→台北	參與課程及路程及抵達(由韓國返台北)

摘要：

本次課程為期 6 天共設計 30 堂與疫苗學相關課程，授課方式以演講及小組討論 2 方式進行經驗分享交流，上課內容包括有疫苗沿革、全球疫苗使用與面臨的問題、疫苗研發與發展、疫苗上市前臨床試驗效益安全性評估注意事項、接著到疫苗上市後及計畫執行後評估、技術轉移、疫苗導入評估內容及疫苗政策推動溝通、夥伴關係建立及當前各國面臨問題及未來疫苗趨勢等，課程安排依疫苗發展時序介紹，加深對疫苗發展的瞭解及當前面臨問題的認識，其中透過小組討論演練的安排更增進學員間瞭解各國家現況及對課程內容加深印象。

建議積極參加國際免疫合作計畫或與非政府組織接觸，將建立國際夥伴關係亦有助於疫苗資源的獲取。本課程偏重理論及原則性內容，較缺乏實務內容及困境對應政策因應，可做為培養疫苗基本知識繼續參加的良好課程，但對於疫苗實務結合建議參加 GAVI 進階課程。

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壹、目的：

期望藉由本研習課程瞭解疫苗研發、試驗、評估、推展及生產標準，與疫苗學最新發展、接種政策制訂、成本效益評估方法等知能，並與國際交流瞭解並汲取亞太地區國家疫苗政策與執行經驗，以作為提升流感疫苗接種計畫推動效益參考。

貳、過程

一、與會行程、人員及地點：

(一) 人員：第 4 組李佳琳。

(二) 行程與地點

日期	5/13(週日)	5/14(週一)~5/19 (週六)	5/19(週六)
地點	台北→首爾	首爾 IVI	首爾→台北
工作記要	啓程及抵達，報到	課程	返程及抵達

主辦單位(International Vaccine institute,IVI) 為世界衛生組織下設立之國際組織，於 1997 年由聯合國成立，總部位於韓國首爾，曾在非洲、亞洲及拉丁美洲 28 個國家從事疫苗研究合作，致力於針對發展中國家發展新疫苗及疫苗接種計畫推行，協助這些國家提升疫苗涵蓋率及新疫苗使用及效益評估等，以協助改善影響該些國家當前面臨重要健康議題。

本次課程為該組織舉辦本課程的第 12 屆。學員來自歐、美、非、亞太地區等國家，以亞太地區國家為主，約 100 位學員。學員背景為政府或私人機構與疫苗發展相關之醫師、研究人員或公衛官員等。上課的老師們來自 IVI、研究機構、藥廠、公益或國際組織等。主辦單位為精進課程內容符合學員需要，除於申請時請學員提出課程需求外，並於請學員提供各課程進行課後評量，做為改善依據。



叁、內容

本次研習共計30堂相關課程，依每日議程順序排列，並與本次研習學習目標且新訊息等之重要主題，進行重點摘錄。本次課程資料亦可進入<http://www.ivi.int/course/index.asp>網站擷取。

一、第一天(Day 1)

DAY 1: Monday, May 14, 2012

0900 0920 **Welcome address Christian Loucq**

Introduction to vaccinology and use of vaccines in context of global health

Chairperson: Christian Loucq

0920 0940 Course Introduction Course Coordinator

0940 1020 Vaccine sciences: An overview with historical perspectives Francis E. Andre TAB 1

1020 1040 Coffee break

1040 1120 The role of vaccines in supporting country millennium development goals, 2015

Anne-Isabelle Degryse-Blateau TAB 2

1120 1200 Epidemiological principles for infectious diseases Paul Kilgore TAB 3

1220 1400 Lunch

Translational research of vaccine development and discovery

Chairperson: Francis E. Andre

1400 1440 Methods for multi-disciplinary translational vaccine development and introduction

Thomas F. Wierzba TAB 4

1440 1520 Clinical development of an oral cholera vaccine at NICED Dipika Sur TAB 5

1520 1540 Coffee break

Immunology in vaccinology

Chairperson: Richard Mahoney

1540 1620 Basic aspects of immunology Hiroshi Kiyono TAB 6

1620 1700 Status of Korean vaccine industry & MBRI's strategy Yeup Yoon TAB 7

1700 1710 Summary and Adjourn Course faculty

D1 課綱：

今天課程可分為 3 個部分，第 1 部份針對疫苗發展歷史及全球疫苗使用狀況做概略式的介紹，第 2 部分就感染症流行病學及 IVI 協助疫苗發展、轉移及接種的推展原則介紹，第 3 部分就疫苗之免疫學基本原理及南韓疫苗工業介紹，以下就當日第 1 部分及第 3 部分重要概念及新知內容，摘重點課程如下：

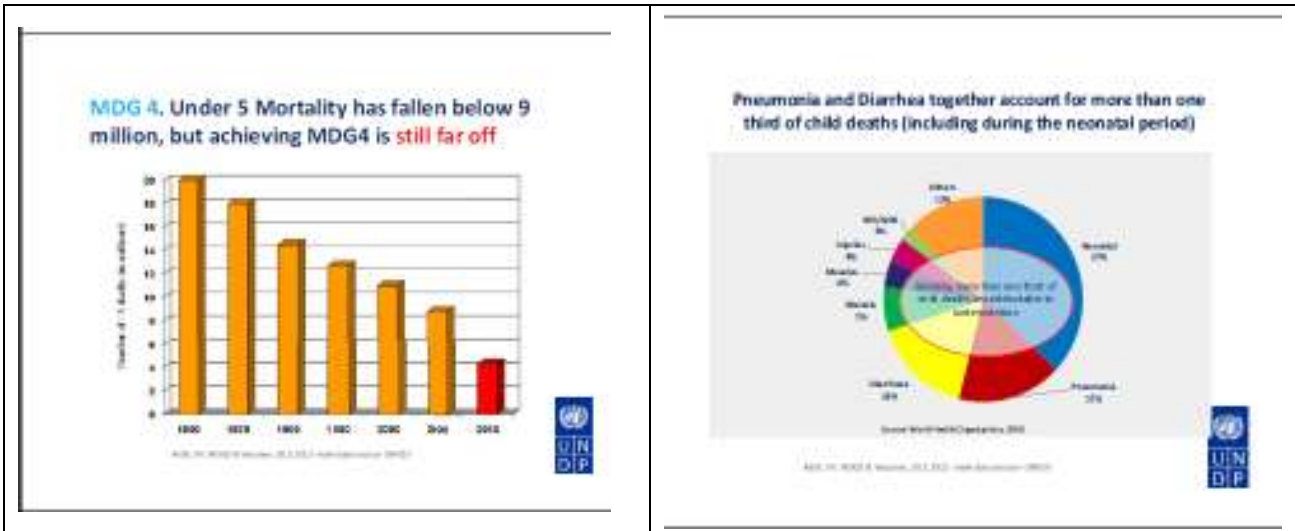
課程 2：疫苗在「千禧年發展目標」所扮演的角色

內容：

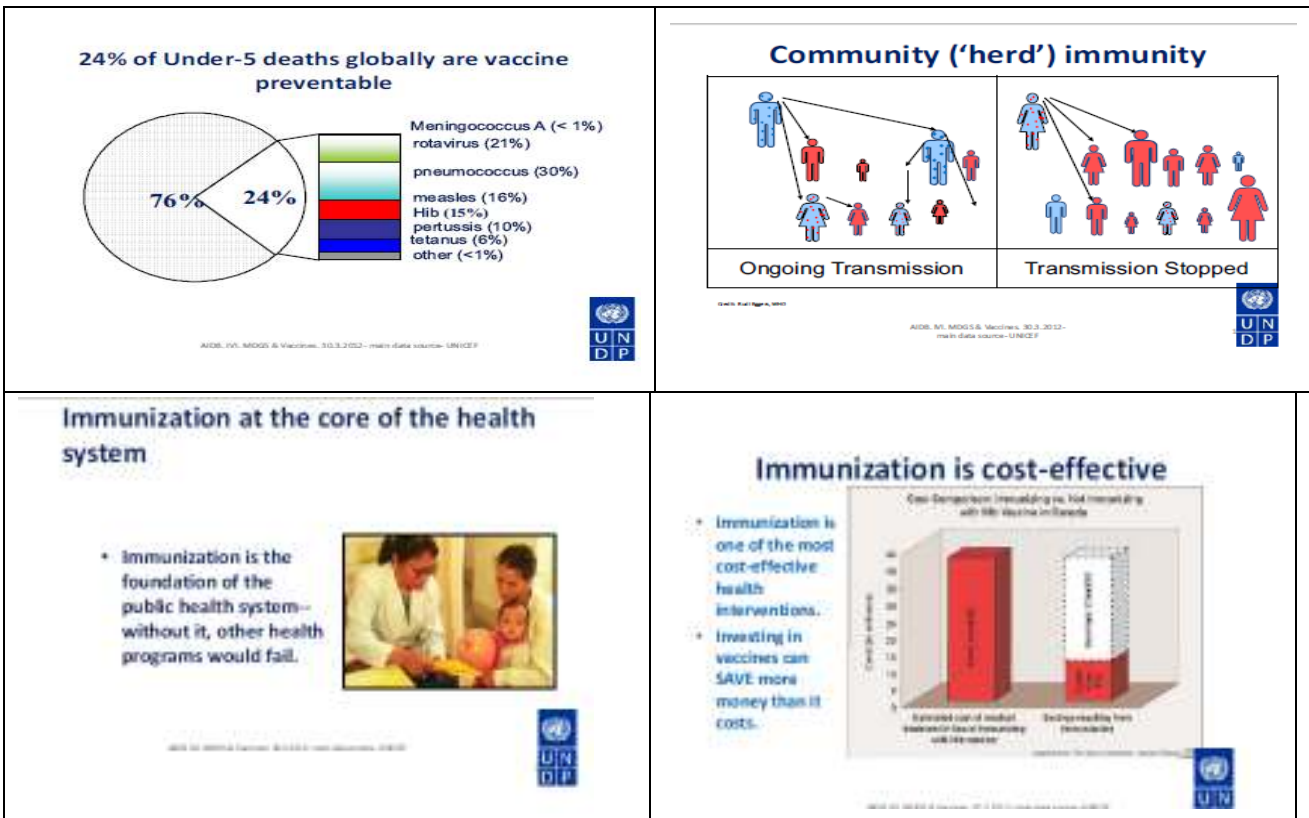
- (一) 千禧年發展目標 (Millennium Development Goals; MDGs)，係聯合國與全世界所有國家及主要發展機構共同展現的藍圖，這是一幅由這些國家和機構全力以赴來滿足全世界最窮人的需求，最近一次聯合國千禧年發展目標首腦會議於 2010 年 9 月 22 日落幕，會中各國承諾將藉助會議成果文件中確定的行動、政策和戰略，盡一切努力於

2015 年實現千禧年發展目標，包括消滅貧窮與飢餓、普及初級教育、促進兩性平等、降低兒童死亡、改善產婦健康、打擊愛滋病毒/愛滋病、環境永續發展及全球伙伴關係等 8 項重要目標。其中第四個目標-降低兒童死亡與疫苗接種有關。

(二) 目前每年全球兒童死亡數約 810 萬人，惟距離 2015 年 500 萬以下目標，尚差 2/3 的距離，而引起兒童死亡因素以肺炎及腹瀉為主要因素，約佔 1/3。



(三) 兒童死亡率的降低一半以上原因來自於預防接種的效益，全球每年因預防接種拯救了將近 300 萬的兒童，引起 5 歲以下孩童的死亡原因中，有 24% 可藉由疫苗接種來避免如麻疹、肺炎、百日咳等，而且接種率高時還可以阻斷病毒及細菌的傳播，因此完整接種的情況下社區中每個人將更安全。

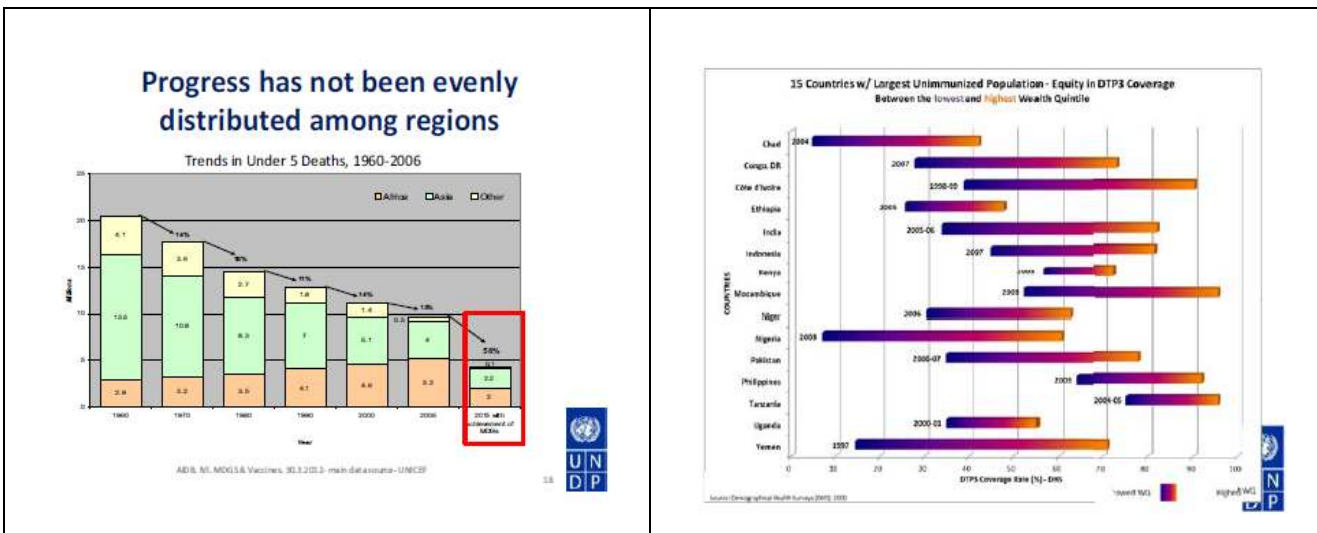


(四) 預防接種是最具經濟效益的健康介入方式，可用疫苗越多可拯救的生命就越多，目前傳統 EPI 涵蓋疫苗種類最多，然而諸如黃熱病、流感、Hib 等疫苗尚未被充分利用，其

他如瘧疾、結核病及 HIV 等疫苗則是未來可使用的疫苗。

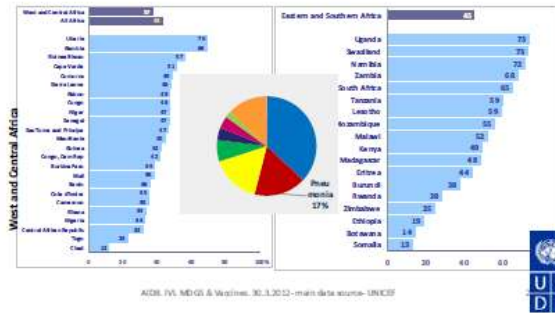


(五) 1960 年至 2006 年間 5 歲以下兒童死亡率下降趨勢在全球各區進展進度不一，於亞洲及其他地區有明顯下降，但在非洲地區不降反增加，其問題在於貧富差距影響接種率高低、在缺乏醫療地區肺炎成為致死的疾病、缺乏新疫苗導入使用諸如 B 肝及 Hib 以及疫苗採購及財務上面臨持續性的問題。



Pneumonia: a killer for lack of treatment

Care seeking for pneumonia (% of children under five with suspected pneumonia being taken to an appropriate care provider)



New Vaccines

- Introduction of Pneumococcal Conjugate Vaccine and Rotavirus Vaccine
- Proven potential for mortality reduction
- Catalyst for Integration with other interventions
- Potential for strengthening routine immunisation

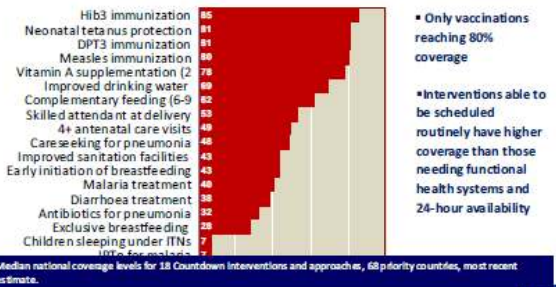


New vaccines are slow to reach the children who need them most



- Children in developing countries lack access to newer vaccines that protect against hepatitis B and *Haemophilus influenzae* type b (Hib).
- Children in the industrialized world routinely receive that protection.

Immunization can reach the unreached



(六) 光有疫苗是不足夠的，疫苗接種必須透過健全的衛生體系提供連貫一致性的執行，因此推行前首先應依照當地流行病學狀況確認優先順序及其限制，再藉由適當的計畫，推行、監測與調整。另外還需配合其他千年發展目標如消滅貧窮與飢餓、改善產婦健康、打擊 HIV/AIDS、環境持續性的達成才能有效較低兒童的死亡率。

Vaccines alone are not enough...

Role of health systems – consistent Delivery

- many interventions cannot be delivered episodically (campaigns)
- systems based approach becomes essential.
- Appropriate planning and delivery
 - First step is to identify critical set of interventions according to local epidemiology
 - Define constraints to delivery
- Implement, monitor and adjust.

Reducing child mortality requires the achievement of all health-related MDGs



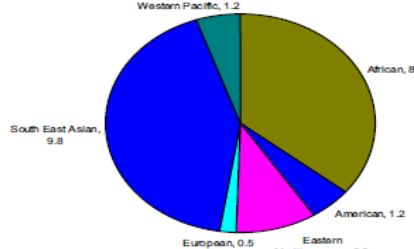

- poverty and hunger (MDG 1)
- improving maternal health and empowering women (MDG 5)
- combating HIV and AIDS, malaria and other major diseases (MDG 6)
- improving water and sanitation (MDG 7)

MDG 7: DRINKING WATER (2006 status)

World overall **ON TRACK** for MDG target



(七) 水和衛生是另外重要問題，用水和肥皂洗手，是降低兒童肺炎（下降 23%）和痢疾（下降 42-47%）有效的方式，因此改善衛生是最具經濟效益的介入。

<p>Hygiene: Hand washing with soap.....</p> <ul style="list-style-type: none"> • can reduce diarrhoea rates by 42-47% • can reduce Acute Respiratory Infections by up to 23% • by mothers and birth attendants can reduce neonatal mortality rates by 44% <p>Cost-effectiveness of hygiene promotion as a <i>health intervention</i>: US \$ 3.35/ Disability Adjusted Life Year</p>  <p>Global Handwashing Day October 15</p> <p><small>AIDS, HIV, MDOG & Vaccines, 30.3.2012-main data source- UNICEF</small></p> 	<p>23.2 million infants not immunized (DTP3) 2009</p>  <table border="1"> <caption>DTP3 Coverage by Region (2009)</caption> <thead> <tr> <th>Region</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Western Pacific</td> <td>1.2</td> </tr> <tr> <td>African</td> <td>8.3</td> </tr> <tr> <td>American</td> <td>1.2</td> </tr> <tr> <td>Eastern Mediterranean</td> <td>2.2</td> </tr> <tr> <td>European</td> <td>0.5</td> </tr> <tr> <td>South East Asian</td> <td>9.8</td> </tr> </tbody> </table> <p><small>Source: WHO/UNICEF coverage estimates 1990-2009, July 2010 Date of data: 13 July 2010</small></p> <p><small>AIDS, HIV, MDOG & Vaccines, 30.3.2012-main data source- UNICEF</small></p> 	Region	Percentage	Western Pacific	1.2	African	8.3	American	1.2	Eastern Mediterranean	2.2	European	0.5	South East Asian	9.8
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(八) 目前要加速採取的行動包括：專注於影響兒童致死的問題、放大基本維持生命的介入措施、生命週期期間提供服務及照顧、擴大以社區為基礎的照顧方法、提高女童和婦女的教育、加強衛生系統、顯著增加衛生系統投資（國內外）、加強夥伴關係（私人，民間組織，專業協會，研究機構）。

<p>Actions for acceleration</p> <ul style="list-style-type: none"> • Focus on the main killers of children • Scale up essential life-saving interventions • Services and care through the life cycle • Expand community-based approaches • Increase girl and women's education • Strengthen health systems • Significantly increase the investments (both national and external) in health systems • Strengthen partnerships (private, CSO, professional associations, research institutions) <p><small>AIDS, HIV, MDOG & Vaccines, 30.3.2012-main data source- UNICEF</small></p> 	<p>Decade of Vaccines</p>  <p>DAVOS 29 January 2010 Bill and Melinda Gates Pledge \$10 Billion in Call for Decade of Vaccines to support research, production and delivery of life-saving vaccines to children in developing countries</p> <p>World Health Assembly May 2010 "...Vaccines are one of the best life-saving buys on offer, preventing an estimated 2 to 3 million deaths each year. WHO and UNICEF, in close collaboration with the Gates Foundation, countries, and partners, are initiating a process to define the ambitions and scope of this Decade of Vaccines."</p> <p><small>AIDS, HIV, MDOG & Vaccines, 30.3.2012-main data source- UNICEF</small></p> 
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(九) 疫苗的未來 10 年，2010 年 1 月 29 日比爾和梅林達·蓋茨承諾 100 億美元在十年的疫苗研究上，並提供給發展中國家兒童使用，而世界衛生組織於 2010 年 5 月也宣布疫苗是對於挽救生命最好的方法，每年可預防 2-3 百萬人的死亡，世衛組織和兒童基金會與蓋茨基金會密切合作，國家和合作夥伴，將啟動下個疫苗十年的範圍。

心得小結：

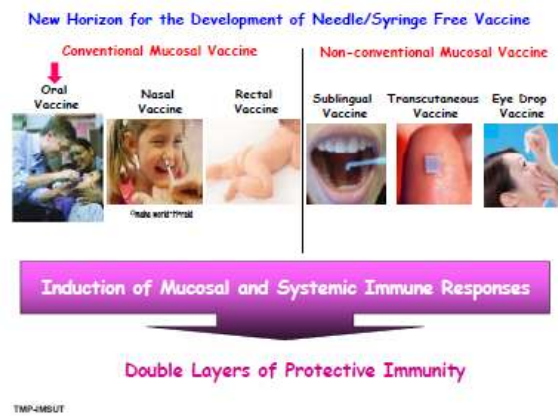
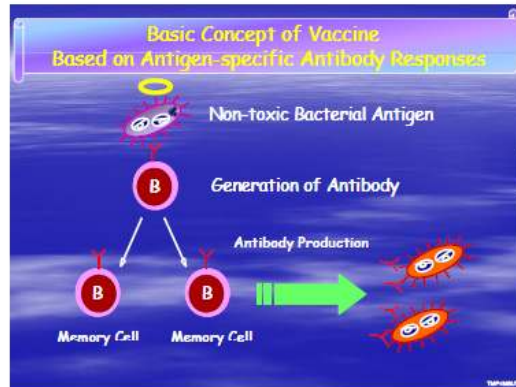
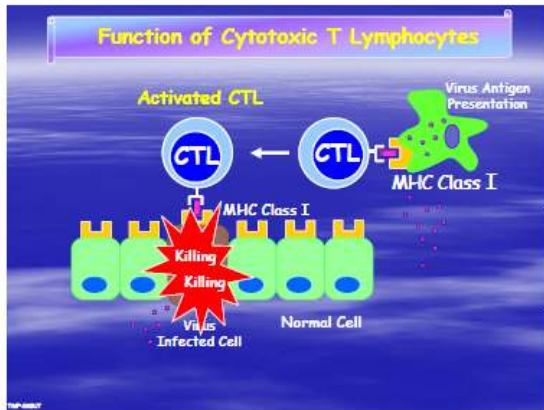
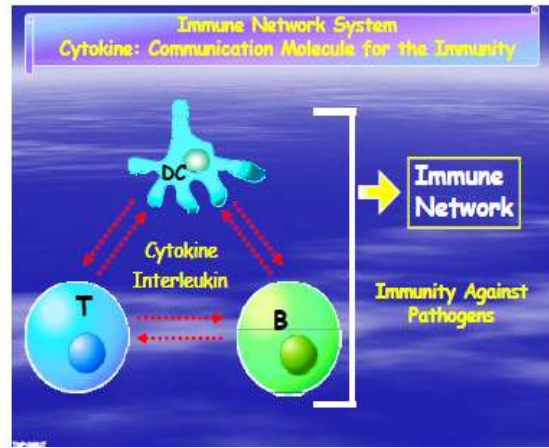
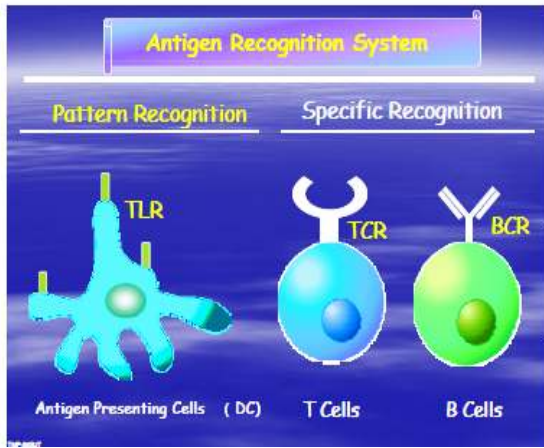
我國每千新生嬰兒 5 歲以下死亡率由 1960 年的千分之 50.1 降為 2005 年千分之 7 人，與美國、加拿大、韓國相當，但高於日本與新加坡，而該年齡層兒童的主要死因，以事故傷害、先天性畸形、惡性腫瘤、敗血症及肺炎等，其中如肺炎及敗血症等感染症部分，都值得未來瞭解分析原因，如歸屬疫苗可預防疾病所引起，則應透過現有新疫苗導入制度推展於我國兒童使用，以維兒童健康並為全球千年目標貢獻部份成果。

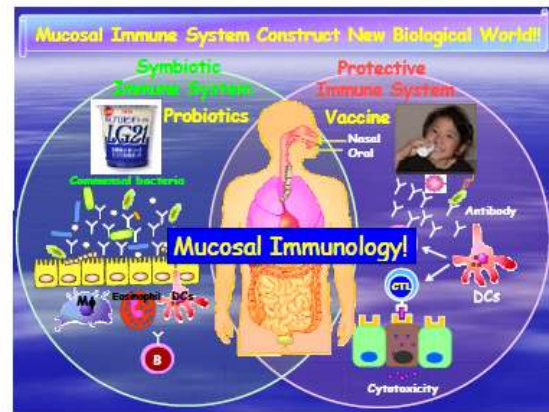
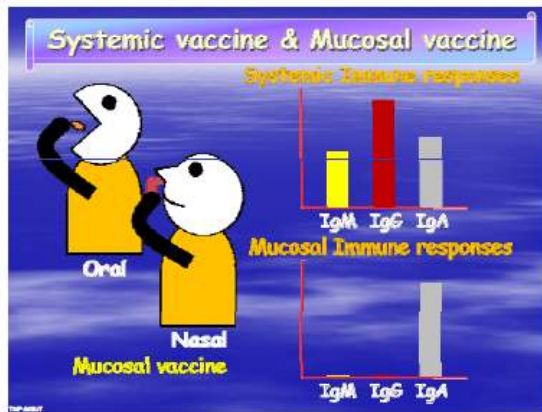
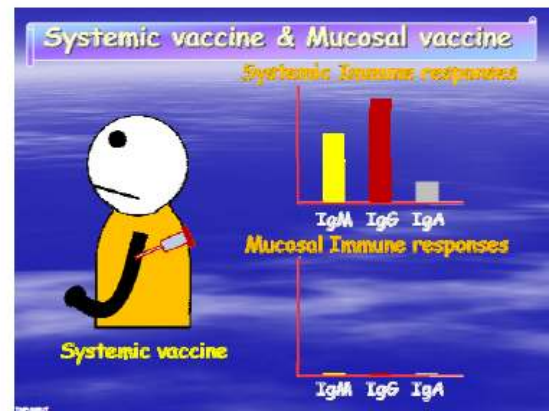
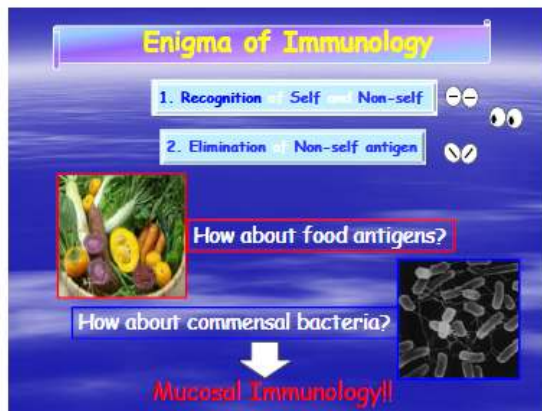
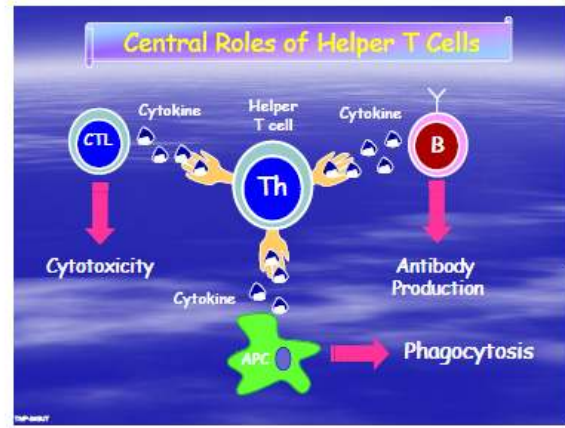
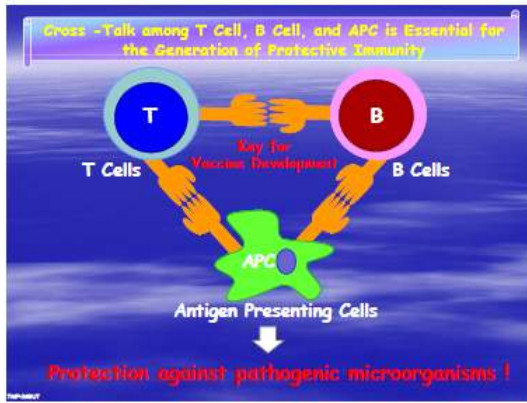
另我國相當幸運已走過醫學公共衛生落後及物資貧乏需接受外援抵抗傳染病的過去，國內應強調得來不易的疫苗計畫推行及接種成果及讓民眾珍惜接種疫苗機會，另於國際間強調夥伴關係的同時，適時將我國從無到有的公共衛生及防疫體系建立等等經驗實質分享，或援助發展中及落後國家，將有助於成為國際間一份子。

課程 6：疫苗的基礎免疫原理

內容：

- (一) 本課程介紹疫苗的免疫形成機轉，釐清 Innate、adoptive immunity 及 Mucosal immunity 的差異。
- (二) 早在 1796 年英國醫生 **Edward Jenne** 發明牛痘天花疫苗後開啓免疫學的歷史，後來德國醫生 **Emil von Behring** 發現打了毒素所產生的抗毒素血清，可中和毒素，應用這樣的免疫反應可預防白喉及百日咳，也就是疫苗的概念。
- (三) 免疫系統牽涉到許多種類細胞的活化且要能互相合作的小組工作，Innate v.s. adoptive immunity，差異在於 Innate immunity 是人體天然防禦屏障，並無免疫記憶能力，而 adoptive immunity 具有專一性確認外來或內在源，具有免疫記憶能力，免疫學的流程是由 Innate immunity 到 adoptive immunity 再產生特異性抗體及 CTL 反應。
- (四) Antigen recognition 系統包括有典型的及特異性的可確認抗原的細胞，先由典型確認抗原細胞 (DC) 確認，分別活化具專一性的 CTL 產生毒殺細胞及 T cell 與 B cell 產生抗體及後續記憶免疫。
- (五) 利用 Mucosal immunology 製造疫苗可達到預防疾病的效果，因該類疫苗的 systemic immune responses 與 Systemic vaccine 相差不多，加上 Mucosal vaccine 接種的方便性及易保存性，不但可解決不敢注射問題，以提升接種率，亦可解決冷鏈維持的困難，有助於維持疫苗校價，因此是值得發展及研究。





課程 7：南韓疫苗工業發展與政策

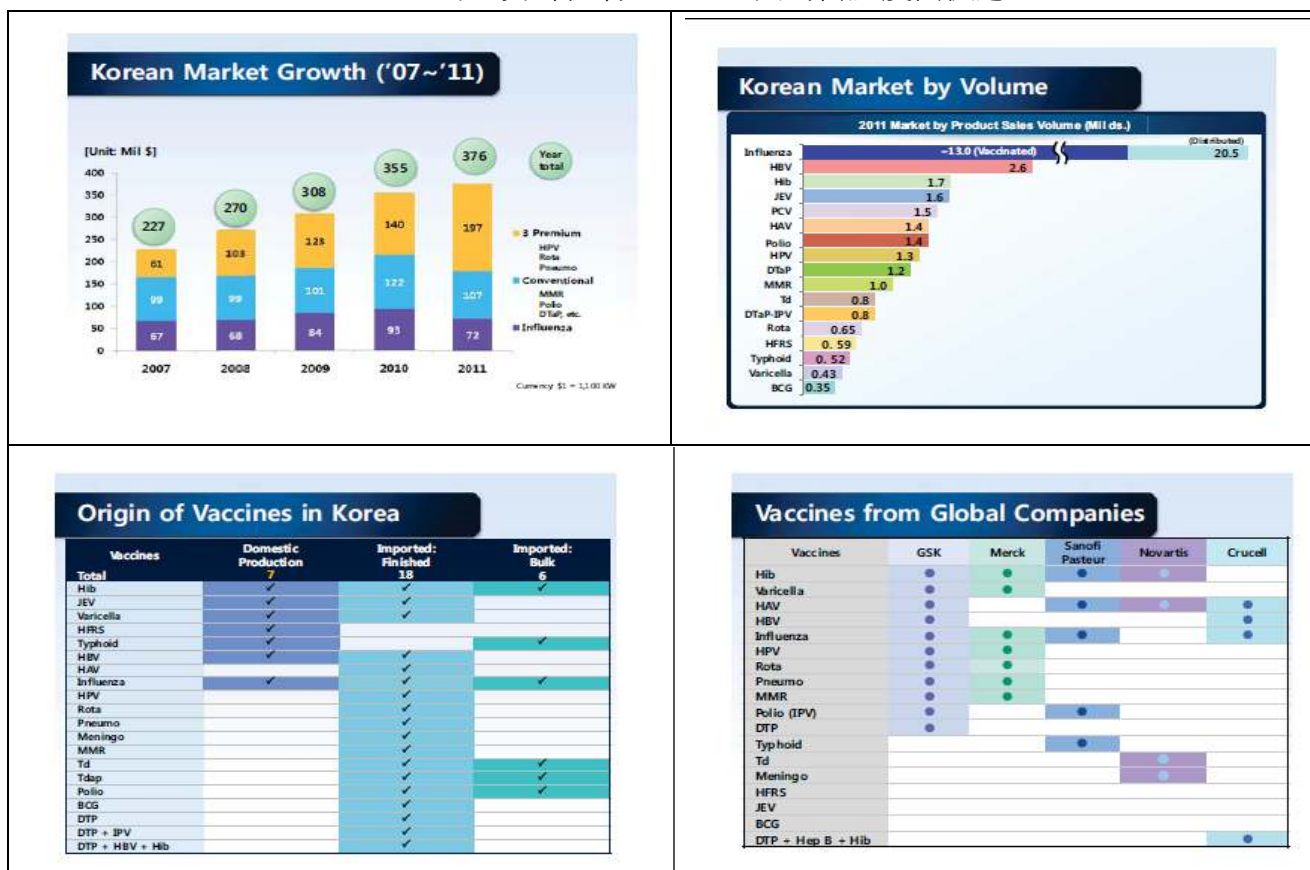
內容：

(一) 南韓疫苗市場現況：

1. 疫苗銷售額由 2007 年 2.27 億美元逐年成長至 2011 年的 3.76 億美元，成長率約 4 成，主要來自於 HPV、Rota、Pneumo 及流感等疫苗的貢獻，以疫苗類別來看，流感及傳統疫苗銷售額呈下降趨勢，而高價疫苗如 HPV、輪狀病毒及肺炎疫苗之銷售額則呈逐年上升趨勢。
2. 2011 年各類疫苗銷售量情形，以流感疫苗最多約 2,050 萬劑（實際接種約 1,300 萬劑）、其次分別為 HBV (260 萬劑)、Hib(170 萬劑)、PCV(150 萬)、HAV (140 萬劑)、polio(140 萬劑)、HPV (130 萬劑)、DTaP(120 萬劑)、MMR (100 萬劑)、Td(80 萬劑)、DTap-IPV(80

萬劑)、Rota(65 萬劑)、HFRS (59 萬劑)、Typhoid (52 萬劑)、Varicella(43 萬劑)、BCG (35 萬劑)

- 3.目前供應來源包括國產疫苗 (Green Cross Corp 等 8 家廠商)、國際性國外疫苗 (GSK、Sanofi Pasteur、Novartis、Merck、Crucell)、日本 (Biken、kaketsuken) 及中國 (Chengdu、Changchun)。
- 4.國內廠商可產製流感等 7 種疫苗,由國外進口 18 項疫苗成品及 6 種疫苗原液 (bulk), 流感疫苗來源以國產、外商產品及原液三種形式並存,進口商包括 GSK、Sanofi Pasteur、Merck、Crucell), 另外僅有 HFRS 全由自產疫苗供應。



- (二) 南韓疫苗擴展市場發展方向,以增加成人疫苗 (HPV、HAV、Td、Tdap、PPV) 市場、導入高價疫苗 (Rota、PCV) 及將 NPI 疫苗由 8 項擴增至 10 項 (增加 DTap+IPV 及 Tdap) 三方向進行。
- (三) 該國疫苗工業於 2009 年 H1N1 新型流感大流行前,政府提供研發治療性疫苗的經費,而國內廠採被動式配合發展,因此疫苗多仰賴國外進口;H1N1 新型流感大流行之後,政府增加提供基礎疫苗研發及疫苗接種經費,國內廠商積極投入發展,因此國產疫苗供應快速增加。

Korean Market Trend

◆ Growing Adult Vaccines Market

- e.g. HPV, HAV, Td, Tdap, PPV (Pneumo polysaccharide)

◆ Introduction of Expensive Pediatric Vaccines

- e.g. Rota, PCV (Pneumo conjugate)

◆ Expansion of National Immunization Program (NIP) Vaccines (8 → 10)

- MMR, Polio, HBV, DTaP, JEV, Td, BCG, Varicella
- DTaP + IPV, Tdap (new in 2012)

Dynamic Industrial Changes

Before the H1N1 Pandemic

- Passive Vaccine Development
- Dependent on Import
- Governmental Support: Focused on R&D of Therapeutic Vaccines

After the H1N1 Pandemic

- Domestic Companies Actively Involved in Development
- Rapid Increase of Manufacturing Facilities for Local Production (e.g. Il-Yang, LGLS, SK Chemicals etc.)
- Governmental Support: Enhanced on R&D of Basic Vaccines and Vaccination

Vaccine Development Activities by Local Companies

LG Life Science

- Euvax B: HBV M
- Eu-Hib: Meningitis M
- Eutravac: D,T,aP + HBV NDA
- Euforavac: D,T,wP + HBV NDA
- LBVF0101: D,T,wP + HBV + Hib Ph III
- Pentavalent: Liquid Formulation PC
- Polio: IPV R

Boryung

- JEV: Cell Culture Ph III
- Td: Adult Td Ph I
- Polio: IPV R
- DTaP R
- DTaP + IPV R

SK Chemicals

- Influenza: Cell Culture PC
- Pneumococcus PC

Others

- Il-yang
Influenza: Egg based PC
- Chong Kun Dang
HPV PC
- Kolon Life Science
HPV PC

Summary of Korean Market

- Status**
 - Total of \$367 Mil in 2011
 - Mainly by HPV, Rota, Pneumo and Influenza
 - Dominated by global companies
- After the H1N1 Pandemic**
 - Active R&D by local companies
 - Enhanced governmental supports on R&D of basic vaccines
- Promising Target Country**
 - Good regulatory structure
 - Excellent academic infrastructure
 - High standard of healthcare system

(四) 韓國政府在鼓勵疫苗產業發展上給予的支持包括，增加接種地點、增加 NIP 接種項目、減少 NIP 疫苗接種時民眾負擔等增加疫苗使用並設置疫苗接種資訊系統監測疫苗使用狀況，未來還需再加強法規結構、學術機構合作及強化衛生體系能力。

Enhanced Governmental Supports

Enhanced Supports on Pediatric Immunization

- Increased No. of vaccination sites under governmental support
 - 253 → 6,975
- Increased No. of vaccines in National Immunization Program
 - DTaP-IPV & Tdap now included
 - 8 → 10
- Reduced NIP vaccination cost payable by each person
 - 15,000KW → 5,000KW
- New electronic birth registration system to manage the immunization schedules



(五) 韓國於 2009 新型流感大流行間完成 Hwasun 疫苗廠區建置，並當年 9 月成功製造韓國第一個國產雞胚胎蛋培養之裂解型流感疫苗 (GCFLU) 及 pandemic H1N1 疫苗 (GreenFLU)，

1. 季節流感疫苗(GCFLU)於 2011 年估計產量約達 1,000 萬劑，並於 2011 年 4 月通過 WHO 的確效 (PQ) 並於全球 34 國家完成註冊登記。
2. Pandemic H1N1 疫苗 (GreenFLU) 僅限於韓國使用，分為含佐劑及不含佐劑 2 種類型疫苗，各類型疫苗產量各約 1,250 萬劑，佐劑成分為 MF59，並於 2010 年 5 月通過 WHO 的確效 (PQ)。

History of Vaccine Developments

1983	World's third HBV (Hepavax® B)	
1988	World's first vaccine against the epidemic hemorrhagic fever renal syndrome (Hantavax®)	
1993	World's second vaccine against the Chicken Pox (Suduvax®)	
2009	Hwasun plant completed KFDA approval for seasonal influenza vaccine (GCFLU®) & Pandemic H1N1 vaccine (GreenFLU®)	
2010	WHO PQ for H1N1 vaccine (GreenFLU®)	
2011	WHO PQ for seasonal influenza vaccine (GCFLU®)	

Hwasun Plant

Location	Hwasun, Korea	
Land size	100,000 m ²	
Building area	12,300 m ²	
Floor space	23,200 m ²	
Construction	2006 : Ground breaking 2008 : Completion of construction & validation 2009 : Approval of pandemic & seasonal influenza vaccine	

Seasonal Flu Vaccine "GC FLU®"

Split, inactivated Seasonal Influenza Vaccine

Indication	Seasonal influenza	
Launch	September, 2009	
Characteristics	1) Egg based trivalent influenza vaccine 2) 0.25mL & 0.5mL pre-filled syringe 3) First seasonal flu vaccine in Korea	
Market Status	✓ GCC: 11 million doses (2011) ✓ Global: 450 million doses (2011)	

H1N1 Vaccine "Green FLU® S"

Split, inactivated Pandemic Influenza Vaccine

Indication	Pandemic H1N1 influenza	
Launch	October, 2009	
Characteristics	1) Egg based monovalent influenza vaccine 2) 0.5mL single dose prefilled syringe 3) Only H1N1 vaccine in Korea 4) 12.5 million doses	

WHO PQ (May 10, 2010)

WHO prequalified vaccines

Fluoride search for prequalified vaccines with product details

For a complete list of WHO prequalified vaccines click on the 'GO' button without selecting options for vaccine type, manufacturer or country of manufacture.

To select a subset of vaccines, click on the '▼' next to vaccine type, manufacturer (implies country of manufacture) in each category, one or more selections can be made by clicking the box next to the '▼'.

MG1109 (AI)


Whole virion, inactivated Pre-pandemic vaccine

Indication	Avian Influenza
Status	Ph III
Launching Plan	Q1 2015
Characteristics	<ol style="list-style-type: none"> 1) Egg based monovalent H5N1 vaccine 2) Alum gel adjuvant 3) Efficacy was confirmed in 346 healthy subjects 4) Supported by KCDC

(六) 目前著重研發疫苗包括：

- 1.大流行疫苗 (MG1109)：該疫苗為雞胚胎蛋培養，全病毒顆粒型不活化疫苗，含有 Alum gel 成份佐劑，韓國目前以 H5N1 單株疫苗研發處於 Phase III，預計於 2015 年第一季上市，由 KCDC 支持。
- 2.炭疽疫苗 (GC1109)：該疫苗為重新組合抗原 (83KDa) 疫苗，含有 Alum gel 成份佐劑，目前處於 Phase II，預計於 2014 年第 4 季上市，由 KCDC 支持。
- 3.細胞培養型流感疫苗 (CCIV)：該疫苗以細胞培養方式，製造大流行及季節性流感疫苗，目前處於臨床試驗前期，將使用 MDCK 懸浮液培養，預計於 2016 年上市，由 KTEPIK 支持。
- 4.其他如 Td、DTaP、Varicella、BCG 等疫苗亦研發中，約於 2014-2018 陸續上市。

<div style="background-color: #0056b3; color: white; padding: 5px; text-align: center;">GC1109 (Anthrax)</div> <p style="text-align: center; color: #0056b3;"><i>Recombinant Protective Antigen, Anthrax Vaccine</i></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="background-color: #0056b3; color: white;">Indication</td> <td>Anthrax</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Status</td> <td>Ph II (n=115)</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Launching Plan</td> <td>Q4 2014</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Characteristics</td> <td> <ol style="list-style-type: none"> 1) Target vaccine antigen - Protective antigen (83kDa) 2) Alum gel adjuvant 3) Ph I. Safety confirmed in 20 healthy subjects 4) Supported by KCDC </td> </tr> </table>	Indication	Anthrax	Status	Ph II (n=115)	Launching Plan	Q4 2014	Characteristics	<ol style="list-style-type: none"> 1) Target vaccine antigen - Protective antigen (83kDa) 2) Alum gel adjuvant 3) Ph I. Safety confirmed in 20 healthy subjects 4) Supported by KCDC 	<div style="background-color: #0056b3; color: white; padding: 5px; text-align: center;">GC1107 (Td)</div> <p style="text-align: center; color: #0056b3;"><i>Adsorbed Diphtheria-Tetanus combined Toxoid</i></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="background-color: #0056b3; color: white;">Indication</td> <td>Tetanus and Diphtheria</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Status</td> <td>Ph II/III (n=170)</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Launching Plan</td> <td>2014</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Characteristics</td> <td> <ol style="list-style-type: none"> 1) High purity 2) Alum gel adjuvant 3) Well tolerated and significant boost of anti-tetanus and anti-diphtheria antibodies observed in 40 healthy subjects </td> </tr> </table>	Indication	Tetanus and Diphtheria	Status	Ph II/III (n=170)	Launching Plan	2014	Characteristics	<ol style="list-style-type: none"> 1) High purity 2) Alum gel adjuvant 3) Well tolerated and significant boost of anti-tetanus and anti-diphtheria antibodies observed in 40 healthy subjects
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<div style="background-color: #0056b3; color: white; padding: 5px; text-align: center;">GC1108 (DTaP)</div> <p style="text-align: center; color: #0056b3;"><i>Diphtheria-Tetanus-acellular Pertussis Combined Vaccine</i></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="background-color: #0056b3; color: white;">Indication</td> <td>Tetanus, Diphtheria and Pertussis</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Status</td> <td>Preclinical</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Launching Plan</td> <td>2018</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Characteristics</td> <td> <ol style="list-style-type: none"> 1) High Quality - acellular pertussis antigens: 3 components (PT, FHA, and Pertactin) 1) Alum gel adjuvant </td> </tr> </table>	Indication	Tetanus, Diphtheria and Pertussis	Status	Preclinical	Launching Plan	2018	Characteristics	<ol style="list-style-type: none"> 1) High Quality - acellular pertussis antigens: 3 components (PT, FHA, and Pertactin) 1) Alum gel adjuvant 	<div style="background-color: #0056b3; color: white; padding: 5px; text-align: center;">MG1111 (Suduvax® II)</div> <p style="text-align: center; color: #0056b3;"><i>Live attenuated Varicella Vaccine</i></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="background-color: #0056b3; color: white;">Indication</td> <td>Varicella</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Status</td> <td>Preclinical</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Launching Plan</td> <td>2016</td> </tr> <tr> <td style="background-color: #0056b3; color: white;">Characteristics</td> <td> <ol style="list-style-type: none"> 1) Advanced version of Suduvax® 2) GCC's own vaccine strain: MAV/06 strain - > \$10 million export thru PAHO - Safety and Efficacy confirmed 3) Supported by Ministry of Health, Welfare and Family Affairs </td> </tr> </table>	Indication	Varicella	Status	Preclinical	Launching Plan	2016	Characteristics	<ol style="list-style-type: none"> 1) Advanced version of Suduvax® 2) GCC's own vaccine strain: MAV/06 strain - > \$10 million export thru PAHO - Safety and Efficacy confirmed 3) Supported by Ministry of Health, Welfare and Family Affairs
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<p>GC1121 (BCG) <i>Whole bacteria, Live Attenuated BCG vaccine</i></p> <table border="1"> <tr> <td>Indication</td> <td>Tuberculosis</td> </tr> <tr> <td>Status</td> <td>Research</td> </tr> <tr> <td>Launching Plan</td> <td>2017</td> </tr> <tr> <td>Characteristics</td> <td> 1) Establishment of BCG-Korea strain from BCG Pasteur 1173P2 2) Collaboration with Korean Institute of Tuberculosis and KCDC 3) Supported by Ministry of Health, Welfare and Family Affairs </td> </tr> </table>	Indication	Tuberculosis	Status	Research	Launching Plan	2017	Characteristics	1) Establishment of BCG-Korea strain from BCG Pasteur 1173P2 2) Collaboration with Korean Institute of Tuberculosis and KCDC 3) Supported by Ministry of Health, Welfare and Family Affairs	<p>GC1117 (CCIV) <i>Cell Culture based, Split, inactivated Influenza vaccine</i></p> <table border="1"> <tr> <td>Indication</td> <td>Pandemic/Seasonal Influenza</td> </tr> <tr> <td>Status</td> <td>Preclinical</td> </tr> <tr> <td>Launching Plan</td> <td>2016</td> </tr> <tr> <td>Characteristics</td> <td> 1) MDCK Suspension Culture 2) Supported by Trans-governmental Enterprise for Pandemic Influenza in Korea (TEPIK) </td> </tr> </table> 	Indication	Pandemic/Seasonal Influenza	Status	Preclinical	Launching Plan	2016	Characteristics	1) MDCK Suspension Culture 2) Supported by Trans-governmental Enterprise for Pandemic Influenza in Korea (TEPIK)
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(七) 在未來推展疫苗政策上，政府將以協助取得季節性、大流行及細胞培養之流感疫苗、DTaP 及痘病毒類疫苗之經銷權及對 HPV、Rota、HAV、Dengue 及 EV71 疫苗的發展。
心得小結：

韓國政府在 2009 年 H1N1 新型流感大流行疫情期間，積極投注大量經費與資源，快速提升國內疫苗廠自產疫苗能力並達自給自足，過程中政府部門 KFDA 及 KCDC 的支持扮演重要角色，並為永續經營國內疫苗產業，因應未來大流行準備及於全球疫苗工業占一席之地，政府積極協助擴充國內市場並借助 IVI 於 WHO 角色功能，向外爭取韓產疫苗銷售至國外的經銷權，因此無論於防疫上或經濟發展上，均有相當大的助益。

反觀我國人口、幅員及疫苗產業資源有限，加上國際地位不明狀況，因此於國內市場狹小又於取得國外經銷權將面臨很大困難，以韓國為例，人口約 5,000 萬人為我國 2 倍大，尚需擴展海外市場才足以維持疫苗產業永續發展，我國更應對於這方面加強與努力；然國內疫苗產業現況無法興盛，而又有大流行疫苗儲備及取得重要疫苗的防疫需求，建議可收集鄰近國家疫苗產業發展進度及尋求建立伙伴關係，以尋求穩定疫苗供貨來源。

二、第二天(Day 2)

DAY 2: Tuesday, May 15, 2012

Discovery and development of vaccines: new approaches

Chairperson: Francis E. Andre

0930 1010 Challenges and methods for vaccine antigen and adjuvant discovery Margaret A. Liu
 TAB 8

1010 1050 New approaches of vaccinology Rodney Carbis TAB 9

1050 1110 Coffee break

Vaccine trials and evaluating vaccine effectiveness

1110 1150 Phase I, II, and III clinical trial methods for vaccine evaluation Karin Hardt TAB 10

1150 1230 Analytical considerations of evaluation in vaccine studies Yoon Hong Choi TAB 11

1230 1400 Lunch

Overview of clinical research and regulatory issues

Chairperson: Karin Hardt

1400 1440 From pre-clinical research to vaccine development: Example in malaria Christian Loucq TAB 12

1440 1520 Regulatory aspects in vaccine trials and studies Julie B. Milstien TAB 13

1520 1540 Coffee break

Chairperson: Paul E. Kilgore

Evaluation of vaccine impact and mass immunization compaigns

Chairperson: Lulu C. Bravo

1540 1620 Post-licensure evaluation of vaccine impact Imran Khan TAB 14

1620 1700 From research to implementation: JE vaccine introduction in Nepal Yashovadan Pradhan TAB 15

1700 1710 Summary and Adjourn Course faculty

1730 1930 **Welcome dinner**

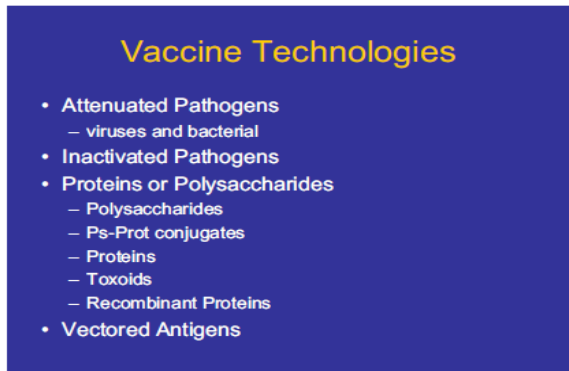
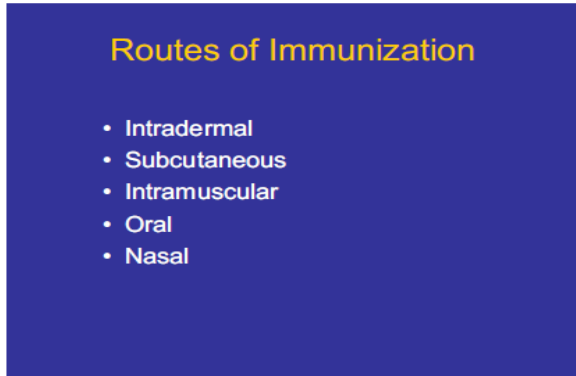
D2 課綱：

今天課程可分為 4 部分，第 1 部份針對目前疫苗發展困境與最新發展趨勢進行介紹，第 2 部分疫苗研發實驗及效益評估方法介紹，第 3 部分臨床試驗及法規介紹，第四部分大型疫苗接種之疫苗影響評估，就當日摘重點課程如下：

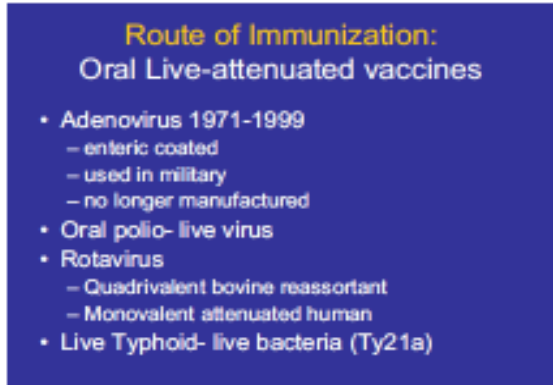
課程 8：製作新疫苗的挑戰：抗原及佐劑的發明與運送系統

內容：

- (一) 疫苗抗原製作技術包括活性減毒病原、不活化病原、蛋白質與多醣體及傳染媒介抗原，接種疫苗抗原可經由皮內、皮下、肌肉、口腔及鼻腔等途徑，其中口服疫苗為現在及未來發展趨勢。

 <p>Vaccine Technologies</p> <ul style="list-style-type: none">• Attenuated Pathogens<ul style="list-style-type: none">– viruses and bacterial• Inactivated Pathogens• Proteins or Polysaccharides<ul style="list-style-type: none">– Polysaccharides– Ps-Prot conjugates– Proteins– Toxoids– Recombinant Proteins• Vectedored Antigens	 <p>Routes of Immunization</p> <ul style="list-style-type: none">• Intradermal• Subcutaneous• Intramuscular• Oral• Nasal
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- (二) 目前發展出口服活性減毒疫苗產品，包括口服小兒麻痺疫苗 (oral polio)、輪狀病毒疫苗及傷寒疫苗 (Live Typhoid-live bacteria)，另外於 1971-1999 年曾使用於軍隊的腸溶性腺病毒疫苗已不再生產。

 <p>Route of Immunization: Oral Live-attenuated vaccines</p> <ul style="list-style-type: none">• Adenovirus 1971-1999<ul style="list-style-type: none">– enteric coated– used in military– no longer manufactured• Oral polio- live virus• Rotavirus<ul style="list-style-type: none">– Quadrivalent bovine reassortant– Monovalent attenuated human• Live Typhoid- live bacteria (Ty21a)	
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- (三) 活性減毒疫苗包括天花等 13 種疫苗，其面臨的常見問題如潛在性致病性、難以區分是


否疫苗引起的疾病、自然感染可能不會誘發免疫或最佳的免疫反應及降低原有抗體的效。

<p>Type of Vaccines: Live Attenuated</p> <ul style="list-style-type: none"> • Smallpox • Rabies • BCG • Yellow Fever • Polio (oral) • Measles • Mumps • Rubella • Adenovirus • Varicella • Rotavirus (Rotarix) <ul style="list-style-type: none"> • Other attenuation technologies <ul style="list-style-type: none"> – Rotaviruses <ul style="list-style-type: none"> + human bovine reassortant – Cold-adapted flu <ul style="list-style-type: none"> + CAIV 	<p>Issues for Live Attenuated Virus Vaccines</p> <ul style="list-style-type: none"> • Potential reversion to virulence <ul style="list-style-type: none"> – Polio – Concern for HIV • Problematic to distinguish subsequent infection from vaccination <ul style="list-style-type: none"> – TB/BCG • Natural infection may not induce immunity or optimal immune responses <ul style="list-style-type: none"> – HIV • Decreased efficacy due to pre-existing Ab <ul style="list-style-type: none"> – Influenza • Decoy antigens on the virus <ul style="list-style-type: none"> – HIV
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(四) 不活化全細胞型抗原疫苗包含傷寒等 10 種疫苗，而蛋白質型疫苗包含 B 型肝炎疫苗等 3 種疫苗，利用類毒素或部分病毒製作成疫苗

<p>Type of Vaccines: Killed Whole Pathogen</p> <ul style="list-style-type: none"> • Typhoid Vi polysaccharide <ul style="list-style-type: none"> – Deep s.c. or i.m. • Cholera • Plague • Pertussis • Influenza • Rickettsia • Polio • Rabies (cell culture) • TBE • Hepatitis A 	<p>Type of Vaccines: Proteins</p> <ul style="list-style-type: none"> • Hepatitis B <ul style="list-style-type: none"> – plasma derived – Recombinant (Yeast and mammalian cell) • Acellular pertussis • Lyme <ul style="list-style-type: none"> – Recombinant (E. Coli) • HPV- Human Papilloma Virus <ul style="list-style-type: none"> – Recombinant (Yeast)
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(五) 多醣體疫苗是利用細菌莢膜蛋白製作成疫苗，現在有的結合型多醣體蛋白疫苗包括有肺炎鏈球菌、腦膜炎雙球菌及嗜血桿菌等疫苗。

<p>Type of Vaccines Polysaccharide</p> <ul style="list-style-type: none"> • Bacterial capsular Ps <ul style="list-style-type: none"> – Pneumococcus – Meningococcus – <i>H. influenzae</i> PRP – Typhoid (Vi)  <p>Source: MeningitisUK.org</p>	<p>Type of Vaccines: Polysaccharide-Protein Conjugates</p> <ul style="list-style-type: none"> • Pneumococcus • Meningococcus • <i>H. influenzae</i> PRP
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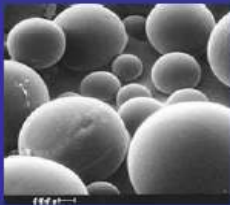
(六) 佐劑是一種與抗原混合或搭配接種的一種物質。它的機轉可儲存抗原、穩定抗原結構、增加抗原進入免疫細胞、活化免疫細胞及誘導 MHC I 類或 II 反應，進而產生免疫反應發生。

Adjuvants: Mechanisms

- Depot of antigen
 - Emulsions, microspheres
- Stabilize antigen conformation
 - Non-ionic co-polymers
- Increase delivery of Ag to immune cells
 - Particles
- Activate immune cells
 - Cytokines, TLR agonists
- Induction of MHC Class I or II responses

(七)佐劑種類包含有無機(氫氧化鋁、磷酸鋁)、MF-59(水包油型微流性乳化); rCholera Toxin B subunit (CTB)、MPL 單磷酸鹽脂質(如 AS02、AS04)，其中無機物質為最常見的佐劑，MF-59 效果則與明礬差不多，AS04 為 MPL + alum 成分使抗體的反應強，持續時間比用明礬較長，AS06 為 MPL+QS21 為油水乳劑目前用於瘧疾疫苗尚於臨床試驗中。

Microparticles



Adjuvants

- Inorganic: e.g. alum (aluminum hydroxide and aluminum phosphate)
 - Most common human adjuvant
 - Th2 biasing
- MF-59
 - (oil-in-water Micro-Fluidized emulsion); oil: squalene; 2 surfactants
 - Th2 biasing but less so than alum
 - In influenza vaccine

Adjuvants

- rCholera Toxin B subunit in Dukoral oral inactivated cholera vaccine
 - CTB also provides cross-protective immunity against ETEC
- New IVI (VaBiotech, Shanta) killed whole cell cholera vx does not have CTB

Adjuvants

- MPL- Monophosphoryl Lipid A
 - MPL from LPS; differs from native lipid A of LPS
 - Component of Melacine (cancer vaccine)
 - Component of GSK Adjuvant Systems:
 - AS04 (MPL + alum)
 - Adjuvant for HPV vaccine
 - Ab response stronger, longer duration than with alum
 - AS02 (MPL + QS21 oil-in-water emulsions)
 - Adjuvant for malaria vaccine in clinical trials
- Experimental
 - Virosomes spherical vesicles with integrated envelope proteins derived from influenza virus, predominantly hemagglutinin
 - QS-21 (*Quilaja saponaria*) Th1 and Th2; Ab and CTL
 - CpG: TLR 9 agonist

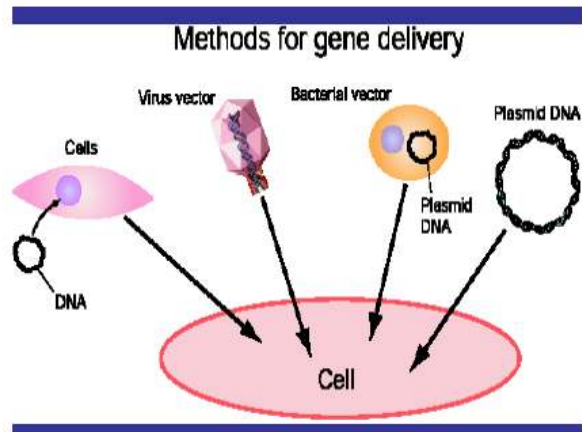
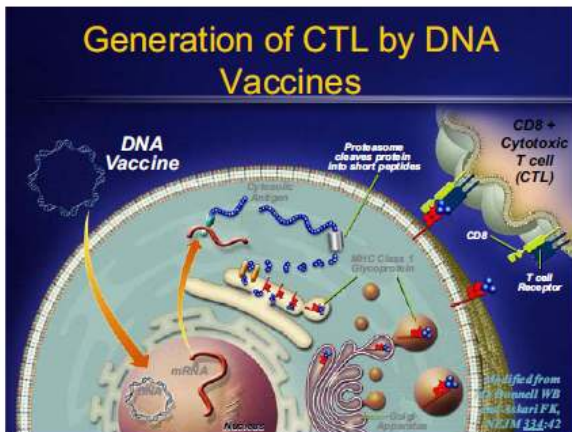
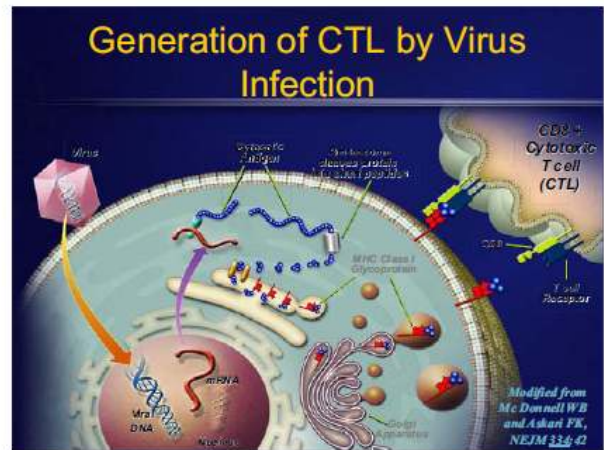
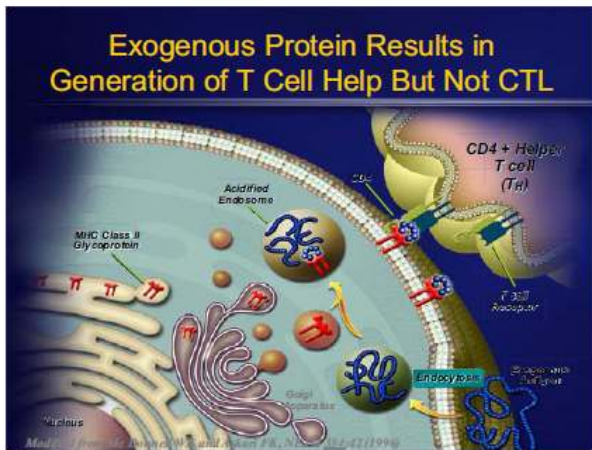
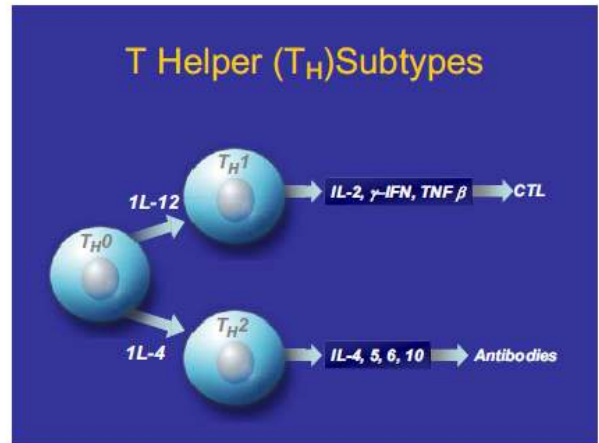
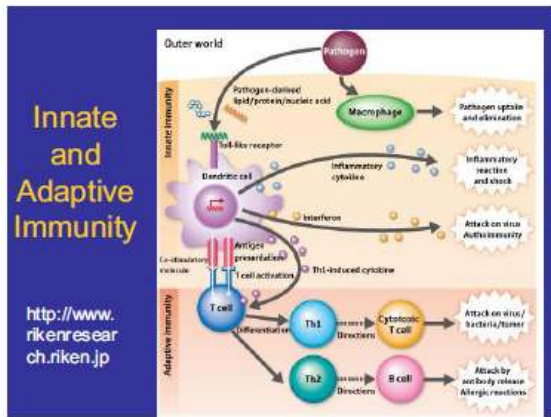
(八)傳統之減毒或死毒法製造的疫苗，因無法有效刺激專一性的殺手 T (cytotoxic T cells) 活化，因此於效果有限，而基因型疫苗有具有類似活病毒型疫苗，其抗原呈現方式的不同，可使病毒進入體細胞後，才由細胞大量製造病毒蛋白。這種內生性蛋白 (endogenous proteins)，經由第一型組織抗原(MHC class I)呈現後，可以活化殺手 T 細胞。另外被轉殖破壞死亡的細胞，將釋放病毒抗原經細胞吞噬而引發抗體反應，因此基因型疫苗有下列優點將成為疫苗發展趨勢。

1. 可用於全球疾病的優勢；
2. 刺激先天免疫及後天免疫活性；
3. 刺激抗體產生、及 CTL、Th(Th1)活化，有助提升免疫效果；
4. 抗體可經由宿主做轉譯後修飾；

5.細胞膜上抗體活化 B-cell 使免疫系統更成熟。

(九) 目前領有許可證之 DNA 疫苗或 DNA plasmid 產品都以動物用疫苗。

(十) 目前進行臨床試驗之人用 DNA 疫苗包括有大流行流感疫苗等可用於預防傳染性疾病或治療用之疫苗共 7 項。



<p>Type of Vaccines: Gene-Based</p> <ul style="list-style-type: none"> • Viral vectors <ul style="list-style-type: none"> – Proven technology: Vaccinia Rabies vaccine – Vector issues: potency, safety • Bacterial vectors <ul style="list-style-type: none"> – Experimental – Possible oral administration • DNA vaccines <ul style="list-style-type: none"> – Experimental, still not potent enough – Advantages of generic technology for global diseases 	<p>Types of Vaccines: Gene-Based</p> <ul style="list-style-type: none"> • Prime-boost strategies <ul style="list-style-type: none"> – DNA followed by viral vector or protein <ul style="list-style-type: none"> • Experimental 																				
<p>DNA Vaccines</p> <ul style="list-style-type: none"> • Potential advantages for global diseases <ul style="list-style-type: none"> – Generic technology (manufacturing) – Stability – No anti-vector immunity • Stimulates innate and adaptive immunity • Stimulates Ab, CTL, Th, including Th1 • Antigens have host post-translational modifications • Can generate membrane-bound antigens 	<p>Examples of DNA vaccines (single entity) in clinical trials</p> <ul style="list-style-type: none"> • Pandemic influenza • Ebola • West Nile • SARS • Hepatitis B • Bovine viral diarrhea virus • Non-infectious diseases <ul style="list-style-type: none"> – Multiple Sclerosis – Melanoma – Prostate Cancer 																				
<p>Licensed DNA Vaccines: Veterinary</p> <p>2005: 2 DNA vaccines licensed Horses: Equine encephalitis vaccine Salmon: Infectious Haematopoietic Necrosis Virus vaccine 2010 Dog melanoma vaccine approved</p>	<p>Licensed DNA Plasmid Products</p> <table border="1"> <thead> <tr> <th>Indication</th> <th>Species</th> <th>Year</th> <th>Immune Response</th> </tr> </thead> <tbody> <tr> <td>West Nile virus</td> <td>Horses</td> <td>2005</td> <td>Neutralizing Ab</td> </tr> <tr> <td>Infectious Haematopoietic Necrosis virus</td> <td>Fish</td> <td>2005</td> <td>Innate + Adaptive</td> </tr> <tr> <td>Melanoma</td> <td>Dogs</td> <td>2010</td> <td>Adaptive</td> </tr> <tr> <td>Increase litter survival + size</td> <td>Pigs</td> <td>2008</td> <td>N/A</td> </tr> </tbody> </table>	Indication	Species	Year	Immune Response	West Nile virus	Horses	2005	Neutralizing Ab	Infectious Haematopoietic Necrosis virus	Fish	2005	Innate + Adaptive	Melanoma	Dogs	2010	Adaptive	Increase litter survival + size	Pigs	2008	N/A
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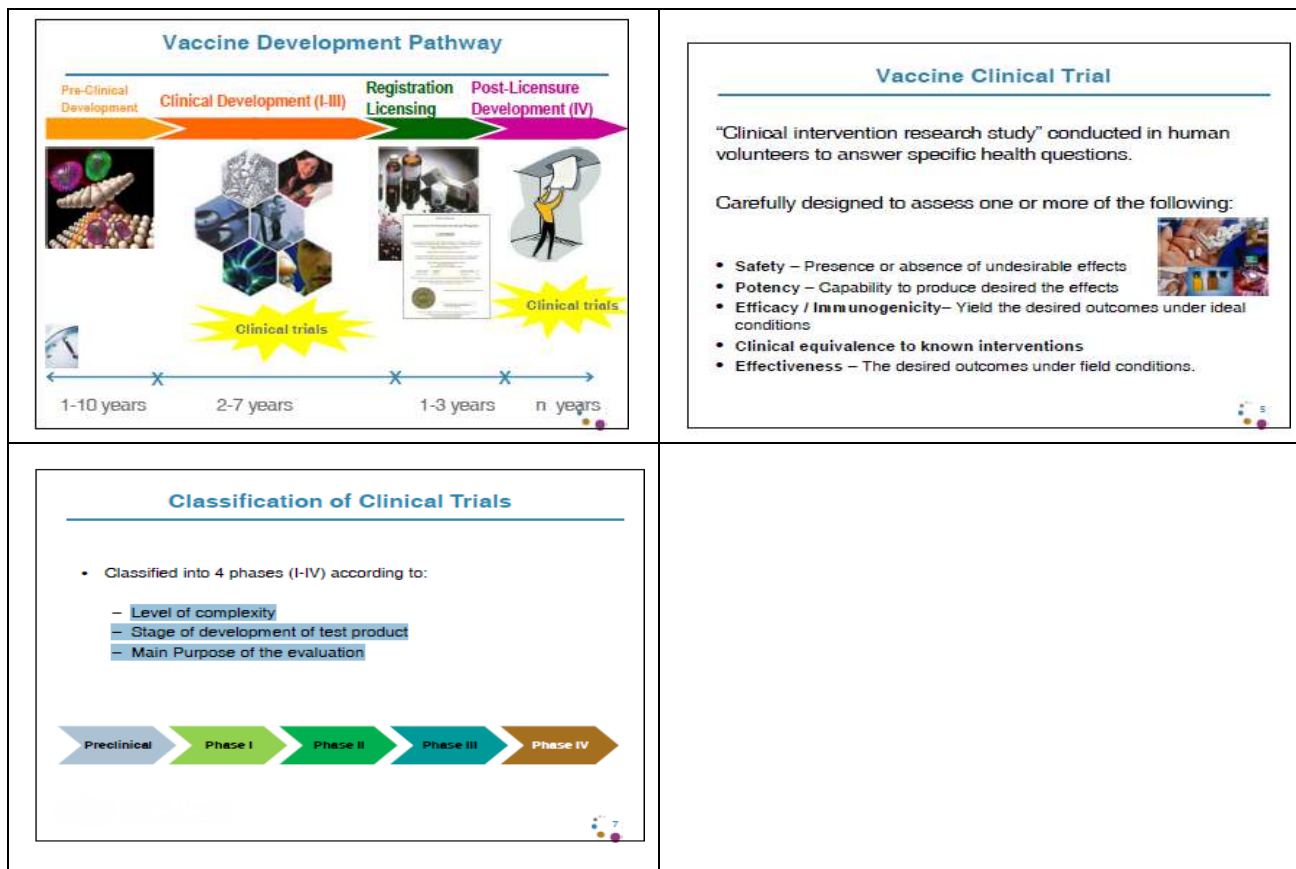
心得小結：

傳統技術製造之疫苗現行常面臨的問題於免疫效價、維持時間、抗原製造困難、每年施打或接種不便及儲存困難，因而造成推行計畫困難接種率不佳，或因效果不好因而無法有效控制疫情以及政策制訂上的困難，於本課程呈現的 DNA 疫苗似乎讓上述問題找到一些解決的蜀光，然人用 DNA 疫苗均尚在臨床實驗階段中，至技術成熟還需配合其他生醫科技持續發展下，未來可望可突破現有技術並有助於疫情的控制。然新技術製造疫苗於售價相對可能較高，因此除瞭解疫苗發展動態外，我國應隨時檢視疫苗政策推展架構及財務狀況，以利提早調整與爭取預算，以利於疫苗發展上市後能快速接軌，使民眾接種到最具效益的疫苗。

課程 10：第一至三期臨床試驗評估方法

內容：

1. 本課程介紹新疫苗上市前所需經過流程及各期臨床試驗評估內容差異。
2. 新疫苗的發展從研發到上市約需 20 年時間，上市後仍須持續評估與研究，臨床試驗類別許多種，其中疫苗臨床試驗是一種臨床介入性質的研究，透過自願受試者參與研究回答特殊健康問題，過程必要要注意安全、校力、效益免疫效價等。並依照複雜程度、產品發展階段及評估目的等將臨床試驗分為 4 期。




3. 第一期(Phase 1 study)：為新研發疫苗第一次注射於人體，約需 20 個健康受試者，以評估疫苗安全性、耐受性以及免疫反應。
4. 第二期(Phase 2 study)：為新疫苗觀念及可行的的證明，約需 50-200 健康人，以選擇及調整新疫苗做終成分及劑量，及決定最佳的接種時程、途徑，同時再次確認安全性。
5. 三期(Phase 3 study)，為確認保護效力及免疫反應與保護效力的關連性，約需 100-10,000 健康人，做大規模的安全性確認並與其他上市疫苗共同接種。此階段試驗為註冊及取得許可證做準備，因此要有大量受試者、狀況必須模擬成與未來使用相似，要用對照隨機雙盲研究法，估計最終產品成分，因此在這一期可說是，必須以接近實際狀況的田野環境，利用大量受試者去評估疫苗於長期或短期的效益及安全性。
6. 四期(Phase 4 study)：為上市後的試驗如市場後監測及特殊人群的適應症等。

Phase I Clinical Trial Phase I "1st Time in Human"

- FTIH



Phase I: First administration in man
~ 20 usually adults - Healthy



- Evaluate overall safety in humans
- Might evaluate tolerability of increasing doses of vaccine (dose escalation)
- Determine safety of one, two or more successive vaccinations
- Evaluate immune response (ie Seroconversion rate)

Phase II Clinical Trial Phase II

Proof of Concept / Feasibility
~ 50 - 200 healthy subjects

- Select and justify final dose and formulation
- Determine the most efficient vaccination schedule (primary vaccination course)
- Determine most efficient route of vaccination
- Confirm the safety profile
- Proof of Concept (POC)

Phase III Clinical Trial Phase III

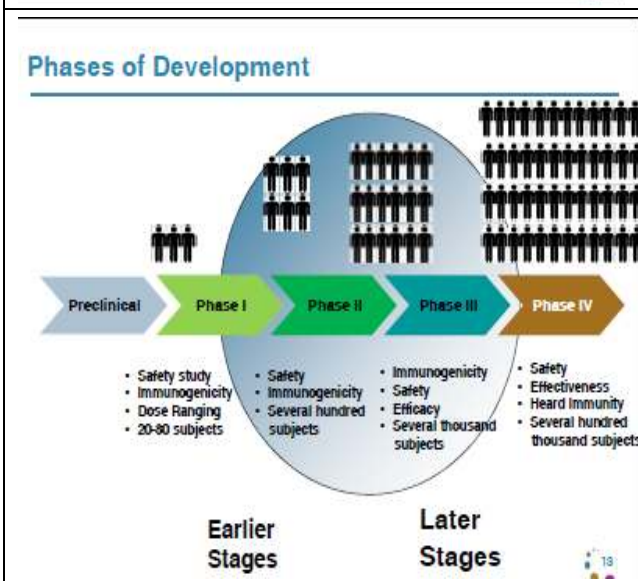
- Protective Efficacy / Safety
- 100 to > 10000 healthy subjects

- Protective efficacy** : demonstrate that vaccine prevents infection / disease
- Immune correlate of protection**
- Manufacturing process evaluation** :
 - Immunological bridge from lots used in Phase II (-III) trials to final commercial scale lots
 - Show consistency of 3 successive lots produced at industrial scale
- Safety** : Large safety database requested by Health Authorities
- Co-administration** with licensed vaccines



Phase IV Clinical Trial Phase IV

- Trials performed post-licensure
- Commercial lots
- Examples**:
 - Post Marketing Surveillance (often a condition of licensure)
 - New schedule
 - Long term persistence
 - Timing of booster dose(s)
 - New indication in special population

7. 進行臨床試驗有一定的程序要進行，過程中對於調查者或其他人的責任及程序上遵從性都應確認或受監測。

<p>Vaccine Clinical Trial Protocol</p> <ul style="list-style-type: none"> I. Background information & the rationale for the trial II. Methods and procedures including product, dosage, administration, subject, expected effect and parameters to measure. III. Ethics and Human Subject Protection IV. Quality assurance Measures <ul style="list-style-type: none"> Documentation Methods Standard Operating Procedures Monitoring procedures V. Data Analysis plan <ul style="list-style-type: none"> Statistical plan Interpretation of results Release of results <p style="text-align: right;"><i>Also usually the "contract" with investigator</i></p>	<p style="text-align: center;">I. Background Information</p> <hr/> <p>Purpose of clinical trial must be clearly defined and should include:</p> <p>Rationale for vaccine trial, information on safety and immunogenicity in preclinical trials, benefits over current tools, potential public health impact</p> <p>Statement of the <u>overall aim</u> of the study</p> <p>Clearly stated <u>specific objectives</u> (measurable)</p>
<p style="text-align: center;">II. Methods and Procedures</p> <hr/> <ul style="list-style-type: none"> ✓ Study Design ✓ Subjects, inclusion & exclusion criteria ✓ Randomization method and blinding ✓ Sample size calculation ✓ Product Specifics ✓ Procedures: Physical examination, vaccination schedule, samples to be taken, records.. ✓ Tools & methods of data collection ✓ Interpretation of results ✓ Conditions for early termination <p style="text-align: center;">Investigator's responsibilities Responsibilities of others Compliance monitoring</p>	<p style="text-align: center;">III. Ethics & Human Subjects Protection</p> <hr/> <p>Principles of research Ethics</p> <ol style="list-style-type: none"> 1. Research must protect the health and lives of humans, including communities. 2. Must protect dignity and privacy of humans. 3. Must protect the environment and animals. 4. Must conform to acceptable principles of the field, whether scientific or sociological.
<p style="text-align: center;">IV. Quality Assurance measures</p> <hr/> <p>Set of Documentation Methods and Standard Operating Procedures, including monitoring procedures, that allow for</p> <p style="text-align: center;">-> conducting, performing, monitoring, auditing, recording, analyzing, and reporting clinical trials</p> <p>Provides assurance that data and reported results are credible and accurate and that the rights and confidentiality of subjects are protected</p>	

課程 11：疫苗效益評估研究之分析考量

內容：








- (一) 本課程主要介紹疫苗效益評估的方法及其應考慮的事項，本局進行效益評估方法較以著重以觀察性研究(observational studies)方法進行，本次課程另介紹利用數學模式 (Mathematical model) 分析經濟效益評估，運用該模式可進行計畫前、中、後之效益評估，將有助於作為預算爭取及計畫成果之科學佐證資料，以下就課程重點說明如下：
- (二) 首先是疫苗效益 (VE) 部分：要釐清 Vaccine efficacy 與 Vaccine effectiveness 這兩個疫苗評估常用的名詞的不同及使用方式：
1. Vaccine efficacy 就是在理想較接近「臨床試驗」的研究設計下，獲得施打疫苗受試者個

人的直接保護效果，過程必須掌握黃金標準及隨機與雙盲設計原則，研究時要注意成本、樣本大小、代表性、道德問題，及不同的易感性，疫苗研發準備上市前，多參考 vaccine efficacy 的研究結果，結果運用要注意樣本的解釋。

2. Vaccine effectiveness 被歸類於「觀察性研究」所得之疫苗效益，研究方法包括 cohort study、household contact study、case control study 和 screening method (又稱 case population)，因為受試者是在接近自然的狀況下接種疫苗並進行評估，理想上 Vaccine effectiveness 比較能真實反應疫苗施打後真實的效益，疫苗上市後，多參考的是 vaccine effectiveness 的研究結果，結果運用要注意各種誤差(bias)。

- (1) 較少使用的 Screening methods 適合與監測資料一起使用，如人口中的接種率已知下，將個案接種率與人口接種率做比較，分析時要注意下列幾點：接種率必須涉及相同人口、不可以當作干擾因子調整，除非人口的接種率當作變相分層、logistic 回歸分析時要將接種率因子去掉、接種率必須準確。
- (2) Screening method 的計算公式是先得知族群的疫苗涵蓋率(vaccine coverage)與罹患該疫苗可預防疾病的個案族群之疫苗涵蓋率，就可推估 VE 之計算值，為較快速簡單的方法。

<p>Analytical considerations of evaluation in vaccine studies</p>  <ul style="list-style-type: none"> • Vaccine effectiveness (VE) • Mathematical model • Economic evaluation 	
<p>Vaccine effectiveness</p>  <ul style="list-style-type: none"> • Definitions • Study designs for estimating VE • Potential pitfalls in estimating VE • How to interpret VE estimates 	<p>Vaccine effects</p>  <ul style="list-style-type: none"> • Efficacy: <ul style="list-style-type: none"> • Direct protection to a vaccinated individual as estimated from clinical trials • Effectiveness: <ul style="list-style-type: none"> • Direct protection measured in a partly vaccinated population • Impact: <ul style="list-style-type: none"> • Population level effect of a vaccination campaign. • Herd immunity: <ul style="list-style-type: none"> • Indirect effect of vaccination due to reduced disease transmission.

<p>Mathematical definition of vaccine efficacy</p> <p>Percentage reduction in the chance when vaccinated individuals compared to unvaccinated.</p> <p>Let ARU = disease attack rate in unvaccinated and ARV = disease attack rate in vaccinated.</p> <p>Then, $VE(\%) = \frac{(ARU - ARV)}{ARU} \times 100 \text{ or } VE = 1 - RR$ where $RR = \frac{ARV}{ARU}$ (usually <1).</p> <p>Attack rate (AR) = $\frac{\text{No of cases}}{\text{No of persons at risk}}$</p> 	<p>Estimating Efficacy - clinical trials</p>  <ul style="list-style-type: none"> • Gold standard • evaluate optimal clinical protection of vaccine in target population (phase 3b trial) • compare new vaccine to either placebo or control vaccine • Randomised, double-blind design • only difference between individuals is vaccine status • control for confounding and bias in study design • can randomise individuals or sometimes communities <p>Issues</p> <ul style="list-style-type: none"> • cost, sample size, representation, ethical issues, differential susceptibility
<p>Estimating vaccine effectiveness observational studies</p>  <ul style="list-style-type: none"> • Cohort study • Household contact study • Case control study • Screening method (case population) 	<p>Cohort study</p>  <ul style="list-style-type: none"> • Retrospective as part of outbreak investigation or using database such as General Practice data • Define discrete population at risk (cohort) e.g. school • Obtain vaccination status • Compare risk of disease in vaccinated and unvaccinated groups • If vaccination status changes during the study period then use the person time approach <p>* Not good for rare diseases as unlikely to have sufficient power or expensive.</p>
<p>Household Contact study</p>  <ul style="list-style-type: none"> • Useful to ensure that vaccinated and unvaccinated have an equal opportunity for exposure. • Each household with a primary case is a mini-cohort; • Index and primary cases within each household identified - Identify primary cases - List all household contacts and identify as secondary, tertiary cases etc. - With the secondary cases calculate attack rates in vaccinated and unvaccinated individuals. Repeat this within the tertiary cases etc. - Sum across households to get overall ARs and hence estimate of VE <p>* Need detailed data on timing of onsets. Households with more cases maybe more likely to be identified.</p>	<p>Case Control study</p>  <p>Cases of illness & controls should be representative of the population from which cases arose</p> <p>Get vaccine history from both groups</p> $VE = 100 \times (1 - OR)$ <p>* Selection of controls may be difficult → Bias</p> $OR = \frac{\text{odds of vaccinated in cases}}{\text{odds of vaccinated in controls}}$
<p>Screening method</p>  <p>For use with surveillance data – population vaccine coverage known Compare coverage in cases with population</p> $VE = 1 - \frac{PCV \times (1 - PPV)}{(1 - PCV) \times PPV}$ <p>where PCV = proportion of cases vaccinated, PPV = proportion population vaccinated</p> <ul style="list-style-type: none"> • Coverage must relate to the same population as cases (so stratify by age etc) • Cannot adjust for confounding variable unless population coverage stratified by that variable • Analyse by logistic regression with an 'offset' for coverage <p>* Coverage data must be accurate – uncertainty not allowed for in 95% CIs</p>	

(3) 在觀察性研究方法評估 VE 要注意事項為下：

- 個案定義：不同觀察點會有不同的 VE
- 個案確認方式:個案定義的敏感性(sensitivity)及特異性(specificity)將影響研究結果，如果無接種者的敏感性高時所估計的 VE 會高於真的 VE。對於多劑型疫苗評估，如果為評估疫苗完整接種的效益時，則要排部分接種個案。
- 疫苗接種史確認：要避免接種狀態錯誤分類的問題，對於個案及非個案的疫苗接種史都應測底的確認。
- 干擾因子：感染及接種狀況會受年齡及社經地位因子影響，因此分析時控制年齡干擾因子是非常重要的，可運用分層及多變相回歸方式進行分析。

<p>Methodological Issues</p> <ul style="list-style-type: none"> • case definition • case ascertainment • vaccine history • confounding 	<p>Methodological issues: case definition (1)</p> <p>Different endpoints may have different true VE:</p> <ul style="list-style-type: none"> • clinical disease • hospitalised case (severe) • carrier state
<p>Methodological issues: case definition (2)</p> <p>Specificity and sensitivity of the case-definition</p> <p>Specificity: case definition based only on clinical criteria may result in false-positive diagnoses</p> <ul style="list-style-type: none"> → ARV increases relatively more than ARU → artificial reduction in VE <p>Sensitivity: case definition with low sensitivity usually only lowers precision (except test-negative case control design)</p> <p>Differential sensitivity: If more sensitive in the unvaccinated then VE estimate will be higher than true VE.</p>	<p>Methodological issues: - multiple doses</p> <ul style="list-style-type: none"> • May need >1 dose of vaccine for full protection • Partial vaccination may afford some protection <ul style="list-style-type: none"> - If classify partially vaccinated as unvaccinated → decrease ARU - If classify partially vaccinated as vaccinated → increase ARV <p>if require effectiveness of full course of vaccination → exclude partially vaccinated cases</p>
<p>Methodological issues: - confounding</p> <ol style="list-style-type: none"> Both exposure to infection and vaccination coverage may vary by age, location, socio-economic factors --> confounding. Controlling for age is important as disease incidence and vaccine coverage are often both age-dependent. Potential solutions: <ul style="list-style-type: none"> • stratified analysis • multivariable regression analysis – logistic regression 	<p>Methodological issues: vaccine history ascertainment</p> <ul style="list-style-type: none"> • Avoid misclassification of vaccination status <ul style="list-style-type: none"> - bias VE to be lower than true VE e.g. due to recall bias • Equal effort to confirm vaccination status amongst cases and non-cases <ul style="list-style-type: none"> - vaccination histories should be documented using GP, clinic or computer records <ul style="list-style-type: none"> - Parental recall → overestimate vaccine coverage - Written records → underestimate vaccine coverage - individuals with missing vaccination records should be excluded from the analysis

(四) 高價疫苗越來越多之情況下，推行計畫前必須先有經濟效益評估結果做為基礎，評估前要有疾病治療費用、生活品質人年 (QALY)、疫苗費用及長期疾病發生率趨勢等資料，如果疫苗的保護期限是終身及沒有間接作用時，則可利用 VE 做長期效益估計，

否則，需利用數理模式預測疫苗的影響（包含間接作用）以及免疫力衰退情形。

(五) 最後結論，疫苗效益可於許可證核准前（隨機對照試驗）及後（觀察性的數據）執行，各種方法會受不同偏差影響下產生不同程度的錯誤，VE 並不適合估計群體中多個案的疫苗影響，因此利用動態的數學模式估計長期的成本效益將是較為適當的工具。

<p>What information do you need for this C/E?</p> <ul style="list-style-type: none"> • Treatment costs • Quality-Adjusted Life Years (QALY) • Vaccine costs • Long-term change in disease incidence <p>Is VE enough for producing such long-term estimates?</p> <p>Yes/No.</p> <ul style="list-style-type: none"> • Yes, if the duration of the vaccine protection is life-long and no indirect effects. • Otherwise, mathematical models are required to predict the impact of the vaccine including indirect effects as well as the waning. 	<p>Summary</p> <ul style="list-style-type: none"> <input type="checkbox"/> Vaccine effectiveness can be estimated before (RCTs) and after (observational data) the vaccine licensure. <input type="checkbox"/> These methods could be vulnerable to different biases. <input type="checkbox"/> Vaccine effectiveness not suitable for estimating its impact in the population in many cases. <input type="checkbox"/> Dynamical transmission models would provide an appropriate tool for such estimation and long-term estimates for its cost-effectiveness analysis.
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課程 14：疫苗上市後的影響評估（第四期臨床試驗）

內容：

1. 本課程介紹疫苗上市後評估項目及評估的方法，也就是所稱第四期臨床試驗，監測重點為上市後的安全性及保護力的監測。

<pre> graph TD A[Phase I: Safe and Immunogenic in Healthy Adults?] -- Yes --> B[Phase II: Safe and Immunogenic in the Target Population?] A -- No --> A1[] B -- Yes --> C[Phase III: Safe and Protective in the Target Population?] B -- No --> B1[] C -- Yes --> D[Phase IV: Subtly Safe and Protective in Practice?] C -- No --> E[Translational Research] E --> F[Introduce into Public Health Practice] F --> D D -- Yes --> D1[] D -- No --> D2[] </pre>	<p>Generalizability of Vaccine efficacy results from Phase III trials</p> <ul style="list-style-type: none"> • Spectrum of recipients in practice is different <ul style="list-style-type: none"> – Pneumococcal polysaccharide vaccine results in gold miners of South Africa could not be replicated in high risk groups for disease • Vaccine storage and administration may be less than optimal <ul style="list-style-type: none"> – Cold chain – Health staff training <ul style="list-style-type: none"> • Measles and Polio • Concomitant administration of other drugs/diet <ul style="list-style-type: none"> – Breast milk interference with live oral rotavirus vaccine • Herd protection <ul style="list-style-type: none"> – Hib conjugate vaccine • Targeted outcome of vaccine may be different from more practical effects in real life situation
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2. 以 IVI 的疫苗影響評估研究為例，該評估研究目的，即為評估疫苗導入後是否能帶來令人滿意的效果，如疾病負擔降低或節省醫療費用，評估方法包括有：疫苗接種率調查、特定監測及全人口之接種後不良反應及疾病負擔評估監測、疫苗效益研究（觀察性研究）。

<h3>Methods to Assess Vaccine Impact</h3> <ul style="list-style-type: none"> • Vaccine coverage surveys • Surveillance Data <ul style="list-style-type: none"> – Adverse Events Following Immunization – Disease burden estimates • Population Based Surveys <ul style="list-style-type: none"> – Adverse Events Following Immunization – Disease burden estimates • Vaccine effectiveness studies <ul style="list-style-type: none"> – Observational evaluation <ul style="list-style-type: none"> • Cohort studies • Nested case control studies – Experimental evaluation <ul style="list-style-type: none"> • Cluster Randomized trials <p><small>INTERNATIONAL VACCINE NETWORK</small></p>	<h3>Vaccination Coverage Assessment</h3> <ul style="list-style-type: none"> • A system that collects data about the structure, process and outcomes of the immunization program • A system that collects national, state and selected geographic estimates of vaccination coverage levels among target population • Critical in assessment of programmatic aspect of immunization <ul style="list-style-type: none"> – Identify risk groups – Racial and ethnic disparities – Clustering of vaccination coverage – Comparison of effect of new vaccine introduction on existing vaccines <p><small>INTERNATIONAL VACCINE NETWORK</small></p>
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- 課程中特別提到，為什麼一定要有疫苗上市後監測，主要是因為疫苗上市前雖然經過 3 期臨床試驗，但樣本還是有限（如不良反應發生率如為 1/1000，約需 5 萬個受試者，才能達到統計上顯著差異），因此藉由上市後監測可以發現”罕見的不良反應”。
- 因此，疫苗上市後安全性監測重點，是要去確認罕見的事件，因此經由主動及被動的雙重監測系統是有必要的，而且能增強受種者的信心及穩定度，但是有些不良反應並非真的由疫苗所引起，因此使用這些資料時必須很謹慎，而監測資料僅能做為問題存在的初步線索，確立問題則需透過其他額外的研究。

<h3>Post-licensure vaccine safety surveillance</h3> <ul style="list-style-type: none"> • Post-licensure surveillance and evaluation of adverse events following immunization <ul style="list-style-type: none"> – Passive surveillance: e.g., Vaccine Adverse Event Reporting System (co-managed by FDA and CDC) – Active surveillance: e.g., Phase IV studies conducted by manufacturers, government agencies • Why do we need post-marketing surveillance? <ul style="list-style-type: none"> – Rare adverse events may not be detected in pre-licensure studies – Why? Because even very large clinical trials have limitations. For example, to detect a doubling in an adverse event that occurs at a rate of 1/1000 would require a sample size of 50,000 (two-arm, power=80%, alpha=5%) <p><small>INTERNATIONAL VACCINE NETWORK</small></p>	<h3>Important points on vaccine safety surveillance</h3> <ul style="list-style-type: none"> • Clinical trials are designed to rule out major (common) safety issues • Post-licensure safety surveillance is important to identify rare events • A combination of passive and active routine post-licensure safety surveillance is essential to maintain the wellbeing and confidence of the vaccine recipients • BUT many adverse events that follow vaccination are not caused by the vaccine! <ul style="list-style-type: none"> – Safety surveillance data should be interpreted with caution – Safety surveillance data can provide the first clue that a problem exists – Additional studies can then be conducted to answer the questions, as was done in response to the reported cases of intussusception following administration of RotaShield® vaccine <p><small>INTERNATIONAL VACCINE NETWORK</small></p>
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- 綜合以上投影片，疫苗是降低疾病負擔重要的工具，但是接種疫苗不是完全沒有風險的，因此用適當的方法監測疫苗上市後的罕見不良反應是有必要的，而且評估疫苗上市後效益有助於政策訂定，收集到的相關資料都應拿出來分析及宣導。

第三天

DAY 3: Wednesday, May 16, 2012

Ethical consideration in vaccine studies

Chairperson: Thomas F. Wierzba

0930 1010 Ethical principles and the design and conduct of vaccine research: An overview Greg Smith TAB 16

1010 1050 Specific issues in developing countries for ethical perspectives Juntra Karbwang Laothavorn TAB 17

1050 1110 Coffee break

Surveillance and risk communication of vaccine-preventable diseases

Chairperson: Dukhyoung Lee

1110 1150 Surveillance studies of vaccine-preventable diseases Tony Nelson TAB 18

1150 1230 Vaccine safety evaluations and risk communication Patrick Zuber TAB 19

1230 1400 Lunch

Communication strategy for vaccines and vaccination

Chairperson: Margaret A. Liu

1400 1440 Socio-behavioral methods for the development and evaluation of social mobilization and communication in

vaccine trials and feasibility studies

Alfred Pach TAB 20

1440 1520 Messages to the public and to the healthcare professionals Lulu C. Bravo TAB 21

1520 1530 **Group Photo**

1540 **Seoul sightseeing**

D3 課綱：

今天課程可分為 3 部分，第 1 部份介紹疫苗研究時應考慮的倫理議題，第 2 部分為疫苗可預防疾病之疾病監測及風險溝通的注意事項，第 3 部分為疫苗及疫苗接種的溝通策略，就當日摘重點課程如下：

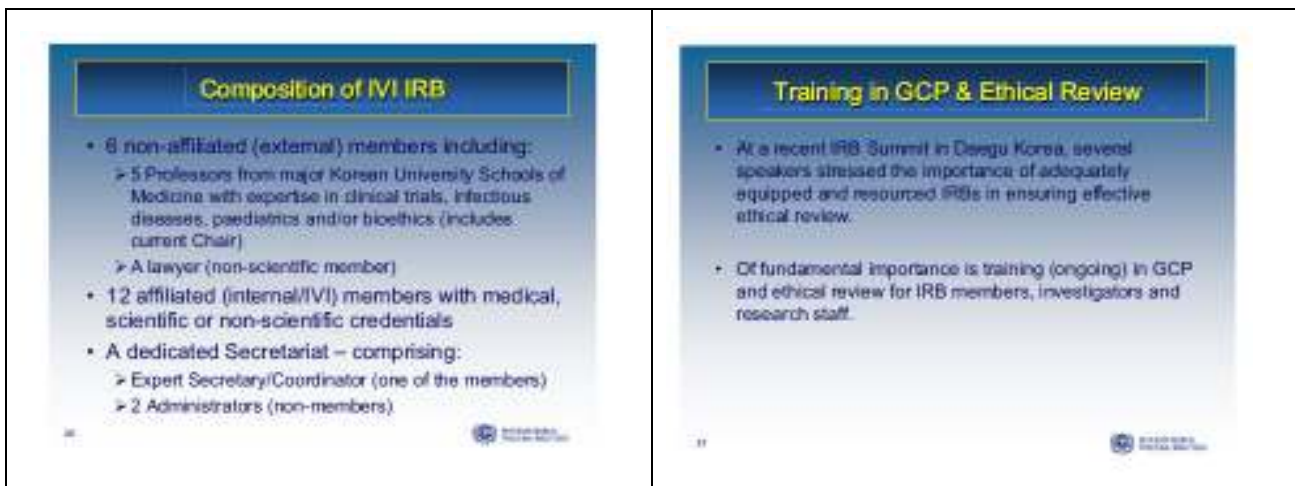
課程 16：疫苗研究之倫理原則及其設計與執行

內容：

1. 所謂倫理是哲學的一支，用來解決道德上的問題，倫理與疫苗間有顯著的關係，因為疫苗與一般藥品不同，其主要於疾病的預防，因此當疫苗反映在倫理上，就會有明顯的後果。
2. 最著名的非法臨床試驗審判為 1946 年德國紐倫堡審判，23 位醫生中 20 人被控參與人體實驗，其中 7 人處死刑，有鑑於此，世界醫學協會（WMA）發展出“赫爾辛基宣言”（Declaration of Helsinki）的道德聲明，涉及人類受試者的醫學研究原則，包括研究和識別的人力物力數據。雖然“宣言”主要針對醫生，WMA 鼓勵其他參加醫學研究涉及人類受試者也採取這些原則。
3. 1993 年國際醫學科學組織理事會（CIOMS）創立國際人體生物性研究之倫理指引，於 2002 年由原來 15 條原則更新為 21 條指引，主要為受試者的告知、安全維護、退出、調整及受治療權利等詳細內容如下：

4. 1979 年美國全國委員會撰寫 1 本 Belmont report，內容對於保護在生物醫學的人類受試者的原理與原則，並據以做後續 1991 年以後的法規得修訂。
5. 總和紐倫堡法典、赫爾辛基宣言、和醫學組織理事會所提供指引，在貝爾蒙報告在人體實驗對象研究的基本道德原則概述，最重要原則為自主權（尊重人權）、有益的與正義公平的。
6. 國際協調會議（ICH-International Conference on Harmonisation）所定優良臨床規範（GCP-good clinical practice），是一種用於涉及人類參與的試驗科目的國際性倫理和科學的設計、執行、記錄和報告量化標準。
7. 所有的研究都必須有機構審查委員會（IRB）或倫理委員會（EC）的批准後才能執行，以確保能保護及幫助受試者以及保護調查者及其機構。IRB 的功能及組織成員詳細內容如投影片。
8. 結論，現在的倫理原則與原理依據過去經驗已修正，但倫理的準則是需要不斷的評估與修改，儘管疫苗研究複雜性越來越高，但研究人員應繼續有義務遵守道德，即使在最困難的條件下指引，另外更不能低估 IRB 的重要性、GCP 的培訓和倫理的檢討。GCP 的培訓網站為 <https://www.citiprogram.org/>。

 <p>Declaration of Helsinki</p> <ul style="list-style-type: none"> • The World Medical Association (WMA) developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. • Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to also adopt these principles. 	 <p>CIOMS – Guidelines</p> <ol style="list-style-type: none"> 1. Ethical justification and scientific validity of biomedical research involving human subjects 4. Individual informed consent 7. Involvement to participate in research 8. Benefits and risks of study participation 9. Special limitations on risk when research involves individuals who are not capable of giving informed consent 10. Research in populations and communities with limited resources 12. Equitable distribution of burdens and benefits in the selection of groups of subjects in research 13. Research involving vulnerable persons 18. Safeguarding confidentiality 19. Right of injured subjects to treatment and compensation
 <p>Role of Institutional Review Boards</p> <ul style="list-style-type: none"> • All studies must have Institutional Review Board (IRB) or Ethics Committee (EC) approval prior to initiation of a research protocol in order to: <ul style="list-style-type: none"> > To assure the protection of human subjects in research projects > To facilitate human subject research > To protect the investigators and the institution 	 <p>What does an IRB look for?</p> <p>Includes (<i>inter alia</i>):</p> <ul style="list-style-type: none"> • The proposed research design is scientifically sound & will not unnecessarily expose subjects to risk. • Risks to subjects are reasonable in relation to anticipated benefits (if any) to subjects. • Subject selection is equitable. • Additional safeguards required for subjects likely to be vulnerable to coercion or undue influence. • Informed consent is obtained from research subjects or their legally authorized representative(s). • Subject safety is maximized. • Subject privacy & confidentiality are maximized.



課程 19：疫苗安全性評估及危機溝通

內容：

1. 由於疫苗是接種到健康人體上，因此一般民眾對於疫苗引起不良反應的容忍度很低，安全性標準期望也比一般藥品為高，因此國家監管單位嚴格把守疫苗品質是非常重要的。
2. 接種後不良事件（**Adverse event observed following immunization**，**AEFI**）與疫苗不良反應（**Adverse vaccine reaction**）是不同的，引起 **AEFI** 很多可能非疫苗所引起，而疫苗不良反應則是因疫苗相關事件引起或促使發生的。
3. 一旦發生不良反應個案時，要保持與病患及家屬有良好的關係，並提供充分的資訊以避免誤解。
4. 潛在性會引起疫苗不良反應的成分包括有抗原、增進疫苗反應物質及減少污染物質等，目前的技術不可能沒有不良反應，重要的事盡量使不良事件最小化，並確保疫苗可安全使用。
5. 另外，如何有效快速發現疫苗危機訊息非常重要，國家內要有疫苗安全監測及調查系統外，建立與國家之間互相支持能力也很重要，藉由 **IHR** 管道通報疫苗不良反應監視訊號，經過全球疫苗安全委員會（**GACVS**）討論分析結果，經由網際網路增進疫苗安全訊息於全球傳遞。
6. 世界衛生組織為達成主動性的監測全球疫苗安全策略，設立三個重要目標分別為由先協助低收入國家建立基本疫苗安全活動，接著為加強研發新疫苗國家之監測能力，最後則達成全球疫苗安全監測架構。
7. 綜上小結，在基礎確保疫苗安全方式，政府應包括要致力於藥物安全監測資源及管理原則，我國在藥物安全監測資源方面，較缺乏清楚的危機溝通政策，而在管理原則上面，對於疫苗安全訊息亦無分享給其他國家機制，為來需逐步建立相關機制。

Some vaccine components can potentially lead to adverse reaction



National systems for vaccine safety



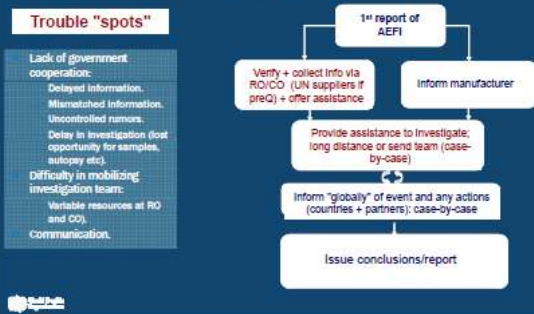
National AEFI surveillance systems WHO action to strengthen capacity of National Regulatory systems



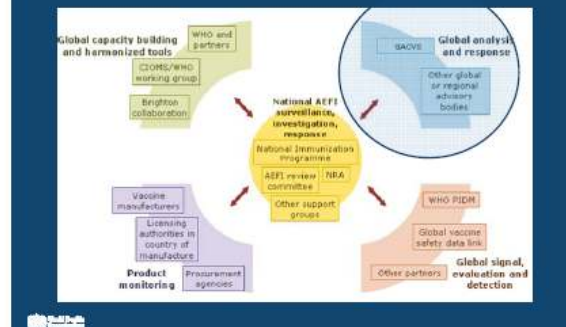
Investigative capacity for crisis management

- Quality of investigations challenging:**
 - Particularly for non-programmed events.
 - Often conducted by non-experienced staff higher up in hierarchy (competing interests).
 - Requires intensive external support, particularly for new and/or pre-qualified vaccines.
- Significant delays:**
 - Start and preliminary closure of investigations delayed.
 - Risk of speculation and mistrust into immunization programmes.
- Scarcity of captured evidence:**
 - Investigation failing to capture relevant information, limited capacity to exclude other likely coincidental aetiologies.

Global Vaccine Safety Crisis Management



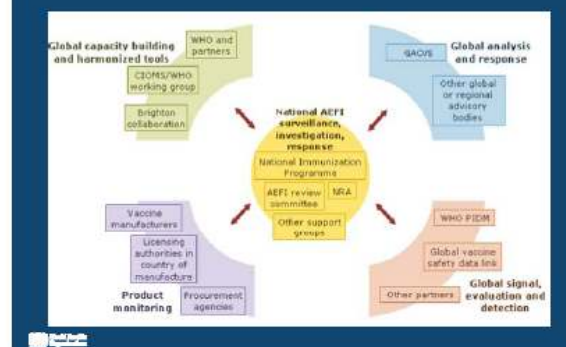
Inter-country support Analysis and response

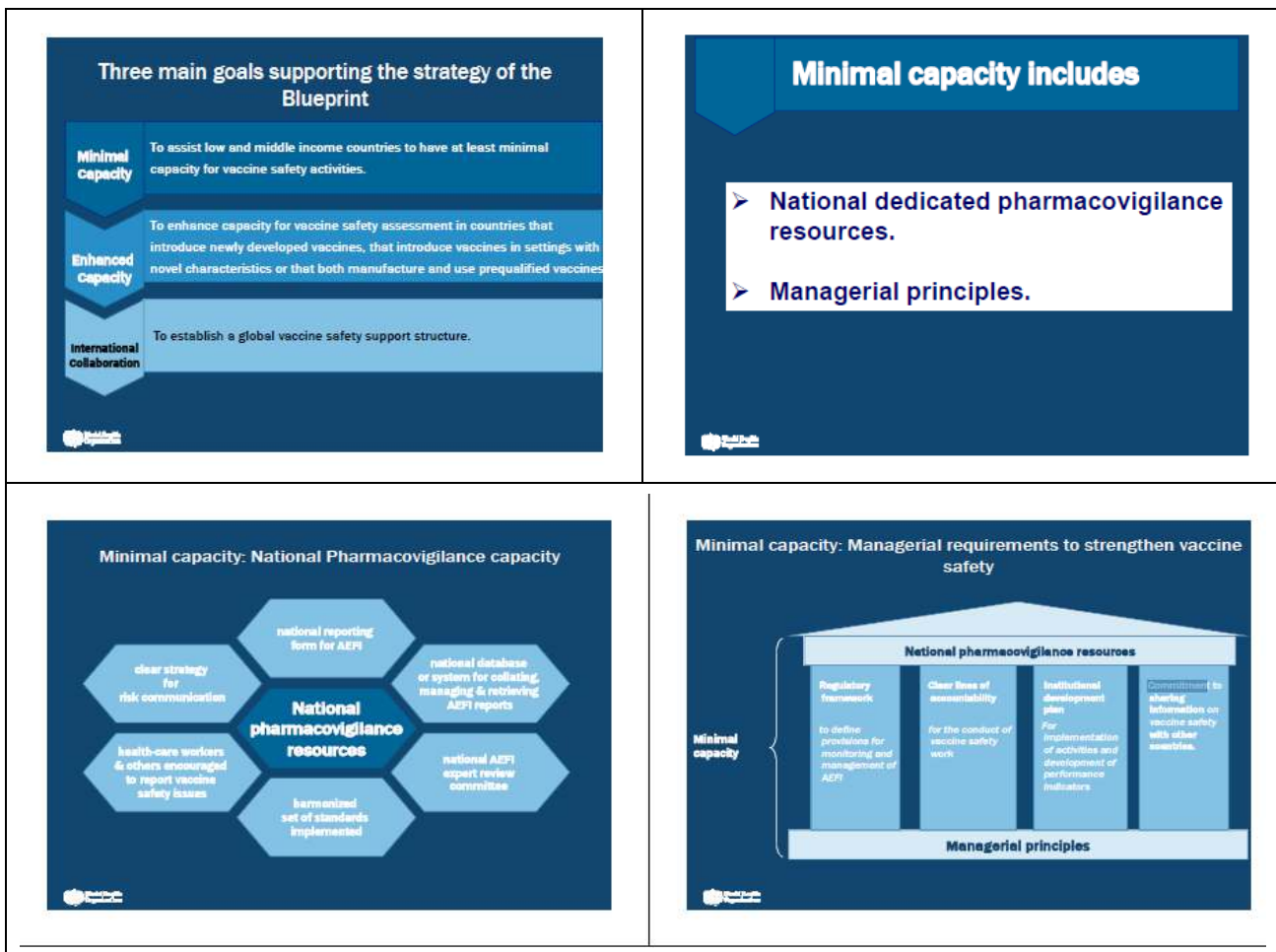


Global advisory committee on vaccine safety (GACVS)

- Established June 1999.**
- Mandate:**
 - Enable WHO to respond promptly, efficiently, and with scientific rigor to vaccine safety issues.
- Composition:**
 - 12 to 15 members.
 - Specialized in epidemiology, statistics, clinical medicine, pharmacology/toxicology, infectious diseases, immunology and drug regulation.
 - Active or retired from governmental agencies, public health institutes, drug regulation agencies, medical research institutes and universities.

Global Vaccine Safety Initiative





課程 21：大眾及醫護人員得訊息傳遞方式

內容：

本課程的講者為於菲律賓當地推動疫苗接種公益團體中非常活躍的人物，經由講者分享推動疫苗活動經驗，講者認為提升接種率最好透過訓練、衛生教育、宣導及研究等方式併同進行，較能爭取大眾共識，進而提升接種率。並鼓勵從事疫苗接種人員踴躍參與社會中疫苗推動活動及事務。

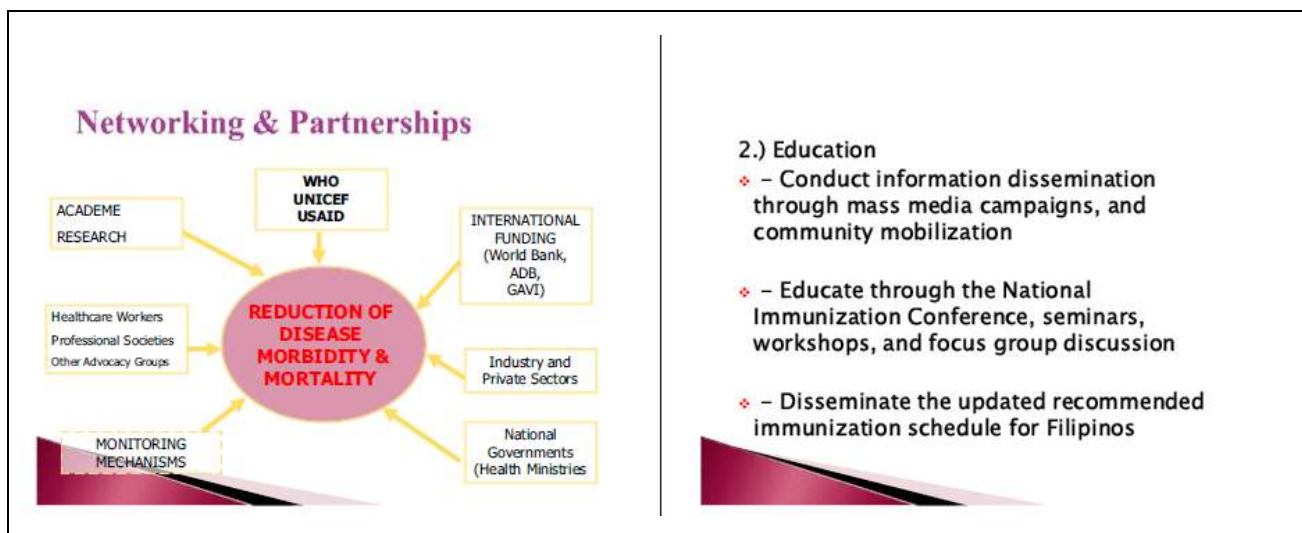
Challenges to Increasing Immunization Coverage

- ▶ 1. Lack of Awareness of the Value of vaccine/vaccination
- ▶ 2. Lack of surveillance and local or regional epidemiological studies
- ▶ 3. Competing interests and major health problems
- ▶ 4. Lack of champions
- ▶ 5. Lack of political will

STRATEGIES

1.) Partnership and networking

- ❖ – Collaborate with national and local government, health care organization, NGOs, foundations, and private volunteer groups involved in similar programs
- ❖ – Partner with international organizations with similar objectives through international conferences, advisory group meetings, and policy development
- ❖ – Implement vaccine outreach program and services



第四天

DAY 4: Thursday, May 17, 2012

Accelerating vaccine introduction

0930 1010 Evidence-based decision-making processes for vaccine introduction William Schluter TAB 22

1010 1050 Models of accelerating the development and introduction: HPV vaccines Cecilia Ladines-Llave TAB 23

1050 1110 Coffe break

Partnerships for global vaccine introduction

1110 1150 Global investment cases for new vaccine introduction Brian Maskery TAB 24

1150 1230 Vaccine access: Strategies for success Richard Mahoney TAB 25

1230 1400 Lunch

Case study 1 - from vaccine licensure to routine use in immunization programs

1400 1415 Case study and group exercises 1: From vaccine licensure to introduction TAB 26

1415 1520 Group work for case study Facilitators

1520 1540 Coffee break

1540 1630 Presentation and discussion of case study Group Discussants

1630 1640 Summary and preview Course faculty

D4 課綱

今天課程可分為 3 部分，第 1 部份介紹加速新疫苗導入方法及注意事項，第 2 部分全球推展新疫苗導入合作關係，第 3 部分以實例進行小組討論演練前幾日課程內容，就當日摘重點課程如下：

課程 22：疫苗決策所需的科學證據

內容：

本課程介紹於在做疫苗計畫決策時，要參考各面向科學證據，包括有國內疾病負擔、疫苗效益、疫苗安全性、疫苗的負擔能力（計畫可持續性）、推行計畫的能力（包括冷鏈）以及疫苗生產或供應能力等，我國於疫苗計畫決策上相較於東南亞國家是相對成熟，決策時亦已考量或收集相關講師所建議的資料，上課資料補充如下。

<h3>South East Asia Regional Criteria to Assess Prior to Introducing New or Underutilized Vaccines*</h3> <ul style="list-style-type: none"> □ Disease burden (incidence/prevalence, absolute number, morbidity/mortality, pandemic/epidemic potential); □ Efficacy of the vaccine; □ Safety of the vaccine; □ Affordability of the vaccine (programmatic sustainability); □ Programme capacity (including cold chain); □ Availability of domestic or regional vaccine production capacity; <p><small>*Report of the South-East Asia Regional Vaccine Prioritization Workshop, Bangkok, 2008</small></p>	<h3>Critical Factors for Decision-making in New Vaccine Introduction</h3>
<h3>Summary of Recommendations</h3> <ul style="list-style-type: none"> □ All programs <ul style="list-style-type: none"> □ Hepatitis B □ Hib □ Rubella □ Pneumococcal □ Rotavirus □ Programs to consider <ul style="list-style-type: none"> □ Cholera □ Hepatitis A □ HPV □ Influenza □ JE □ Meningococcal □ Mumps □ Rabies □ Tickborne encephalitis □ Typhoid 	<h3>Summary</h3> <ul style="list-style-type: none"> □ Understanding country-specific disease burden is the first step in evidence-based decision making for routine immunization; □ In addition to EPI antigens, disease burden from hepatitis B, Hib, rubella, pneumococcal, and rotavirus appears to be high and widespread that all countries should consider introduction of vaccines; □ Introduction of other new and underutilized vaccines should be based on disease burden studies and Government priorities;

課程 24：全球投資新導入的疫苗-以口服霍亂疫苗為例

內容：

本課程以 IVI 組織以口服霍亂疫苗導入個案為例，說明全球導入新疫苗評估方式，課程中說明導入疫苗前必須先瞭解霍亂在全球的負擔狀況？服用霍亂疫苗目標為何？哪些國家可能採用霍亂疫苗及什麼時候？疫苗供應可符合預計的需求？接種疫苗後可拯救多少生命？疾病對經濟影響為何？計劃的成本多少？財源方案和問題為何？這幾個面向都需要考慮，IVI 推行口服霍亂疫苗（OCVs）結果，可提供做為全球引進口服霍亂疫苗控制霍亂的證據，評估結果顯示霍亂在南亞及非洲的疾病負擔比較高的，使用新疫苗控制成本較低且無需緩衝期，因此引進 OCVs，將是非常符合成本效益，尤其是針對兒童的計劃，穩定可預見的 OCVs 需求，將成為持續推動疫苗能力和向捐助者證明霍亂疫苗接種的價值，並可確保足夠的疫苗供應。

Why a global investment case?

- To provide a global evidence base for investing in cholera vaccination as part of a larger strategy that includes improvements to water and sanitation
 - What is the global burden of cholera?
 - How to target cholera vaccination?
 - Which countries are more likely to adopt cholera vaccines and when?
 - Can supply capacity meet projected demand?
 - How many cases averted and lives saved with the vaccine?
 - What impact does disease have on the economy?
 - How much will the program cost?
 - What are financing options and issues?

Investment case components

Investment case components

Conclusions

- The global investment case provides evidence supporting the feasible introduction of OCVs for control of endemic cholera
 - Burden of disease is high in South Asia and Africa
 - New vaccines are lower in cost and do not require buffer
 - The introduction of OCVs would be very cost-effective, especially programs targeting children
- A relatively modest-sized stockpile would be inexpensive, but would still be large enough to be of value
- A stockpile could also be a 'gateway' to sustainable cholera vaccine introduction
 - Steady predictable demand would motivate investment in vaccine capacity and demonstrate the value of cholera vaccination to donors, helping to ensure adequate vaccine supply

課程 25：導入新疫苗獲准策略

內容：

本課程說明新疫苗政策導入通常在疫苗上市後許多年之後，爲了加速新疫苗政策導入，需要提早在疫苗研發時期同時，就對各面項問題進行評估與接近的活動，課程中所評估或先行活動的提面向包含有疫苗發展進度掌握、法規面、製造廠能力、國家政策考量、財物面及採購程序以及分配與接種率等問題。

另課程中說明到影響國家衛生政策革新的決定因素，包括有政府和私部門支持研發程度、高（國際）標準產品開發能製造力、國內市場的擴增、國際出口市場包括銷售國際組織的創造、適當的系統管理知識產權及建立適當規範安全性和有效性法規等，這些都會影響新疫苗政策導入是否會成功的關鍵問題，當前超過 30% 發展中國家推展新疫苗政策面臨延遲 10 年問題，因此需透過疫苗還在研發階段就要開始接近活動、協調可用性、經濟負擔能力，以爲預測及預防這些延遲問題。

The determinants of health innovation

- **R&D:** Support in the public and private sectors
- **Manufacture:** Develop ability to make products to high (international) standards
- **Domestic markets:** Create markets including government health distribution
- **Export markets:** Enter international trade including sales to international organizations such as UNICEF
- **IP:** Create appropriate systems to manage IP
- **Regulation:** Create appropriate systems to achieve safety and efficacy

Time Lag

Cumulative percentage of countries beginning to implement each intervention, by income group. Years following first licensure.

	5 years		10 years		15 years	
	Low income	Lower-middle income	Low income	Lower-middle income	Low income	Lower-middle income
Hepatitis B	0%	0%	3%	24%	10%	41%
Hemophilic (Hemolytic type B (HB))	0%	0%	3%	0%	15%	26%
Enterovirus	0%	15%	—	—	—	—
Parasitocidal	0%	0%	5%	13%	—	—
Average Vaccines	0%	5%	4%	12%	—	—

Source: Alan Brooks, 2011

Vaccine Development and Introduction The Old View



Vaccine Development and Introduction The New View



Access Activities

Development (Pre-Clinical and Clinical)	Regulatory	Manufacturing	Introduction	Marketing and Procurement	Distribution / Uptake
<ul style="list-style-type: none"> Identify public and private partners with market complexity Integrate product objectives into R&D decisions (e.g., trial site selection) Stakeholder needs and market context Review of choice studies ICI and MVI studies Develop business models Identify GATE to meet regulatory needs 	<ul style="list-style-type: none"> Define regulatory strategy Refine regulatory requirements Integrate regulatory management plan 	<ul style="list-style-type: none"> Inform agreements with manufacturing partners Ensure manufacturing capacity is in place and QP for process Develop product presentation 	<ul style="list-style-type: none"> Ensure timely regulatory decisions Ensure implementation of studies and dissemination projects Support issuance of approvals (e.g., WHO) Address global health and country decision-making Support dissemination of country decision-making tools Define pathways for policy decisions Capacity building 	<ul style="list-style-type: none"> Develop financing options Allocate to work financing for procurement and patient use Optimize critical estimates of production and delivery costs 	<ul style="list-style-type: none"> Identify suppliers Regulate pricing
<ul style="list-style-type: none"> Regulate product naturally Assess health burden and R&D pre-qual Application Establish pharmacovigilance plan and monitor data 	<ul style="list-style-type: none"> Assess manufacturing partners Regulatory custom and quality agreements 	<ul style="list-style-type: none"> Support country decision-making Contribute to global policy decisions Design and execute plans Provide R&E data Develop new product messages Develop new treatment guidelines 	<ul style="list-style-type: none"> Identify source Determine costs for introduction and delivery Financing opportunities 	<ul style="list-style-type: none"> Identify distribution channels Monitor supplier performance and stock-outs Train health care providers Develop marketing campaigns Conduct ongoing monitoring 	

Source: GHI analysis, "Ensuring that Developing Countries have Access to New Healthcare Products: The Role of Product Development Partnerships" (Thompson, A Study of R&D Access Activities and Timelines), Prop et al.

Summary

- The introduction of new vaccines still takes a long time after initial regulatory approval
- Efforts to speed up introduction need to start early in the development process and build progressively
- Access is a complex field of detailed activities that can speed up introduction
- The DVI is seeking to address this complex field and help insure the rapid uptake of dengue vaccines

小組討論：

今天下午是小組討論時間，所有成員分為 6 個小組，每組分別對肺炎鏈球菌、霍亂、登革熱及傷寒 4 種疾病議題，運用前幾日上課原理針對該疾病議題，如何發展所需疫苗到推展疫苗政策進行實務演練，最後推派代表分享小組總結。

本人參與小組被分配討論議題傷寒，為利情境設定，小組學員們選定以巴基斯坦進行情境演練，從討論中必須合作回答出傷寒的基本資料為何、如何確認疾病負擔、如何進行疫苗臨床評估、疫苗由誰供應及經費如何分擔、國家疫苗諮詢會決定政策需要哪些資訊、最後依據

上述資料特性，討論出針對此疾病所需的疫苗產品等議題答案，經由本次討論過程對上課內容重新溫故知新一番外，又能瞭解到傷寒在巴基斯坦是很大的健康問題，尤其沒有適用於 2 歲以下小孩的疫苗，目前非常需要世界衛生組織協助發展及提供結合型疫苗施打，另外該國非常缺乏疫苗執行經費，需藉由各國捐贈經費才足以推動疫苗接種的執行困境。由於本組學員們也大多來自國內也面臨傷寒疾病威脅的國家，因此意見交換上易有共鳴。

第五天(Day 5)

DAY 5: Friday, May 18, 2012

Pediatric immunization and beyond

Chairperson: Thomas F. Wierzba

0930 1010 Vaccination schedule: History, rationales and limitations Carine Dochez TAB 27

1010 1050 Cost sharing for National Immunization Program (NIP) in Korea Dukhyoung Lee TAB 28

1050 1110 Coffee break

Adult immunization for pneumococcal vaccines

Chairperson: Francis E. Andre

1110 1150 Polysaccharide versus conjugate vaccines Joe Schmitt TAB 29

1150 1230 Pneumococcal conjugate vaccines: Clinical programs and implications Shilpa Patil TAB 30

1230 1400 Lunch

Case study 2 - from sustained vaccine use to disease reduction

Moderator: Paul Kilgore with colleagues

1400 1415 Case study and group exercises 2: From sustained vaccine use to disease reduction TAB 31

1415 1520 Group work for case study analysis Facilitators

1520 1540 Coffee break

1540 1630 Presentation and discussion of case study Group discussants

1630 1640 Summary and preview

D5 課綱

今天課程可分為 3 部分，第 1 部份介紹幼兒預防接種的現在與未來，第 2 部分介紹肺炎疫苗運用於成人預防接種現況，第 3 部分以實例進行小組討論演如何持續推動疫苗接種來降低疾病發生，就當日摘重點課程如下：

課程 27：疫苗接種時程：歷史、原理及限制

內容：

本課程主要介紹在安排疫苗接種時程的原理與注意事項，由於每個國家的流行病學、衛生基礎設施及資源的差異極大，因此很難建立一個適用所有國家的免疫計劃，各國僅能參考 WHO 的建議時程表，再依照該國疫情狀況調整安排屬於自己的接種時程表，接種時間表不是一成不變的，要視相關科學資料調整，免疫學是一個不斷發展的科學，因此要善用搭配新疫苗可以降低成本和精簡整合與其他疫苗，以下重要投影片摘要如下：

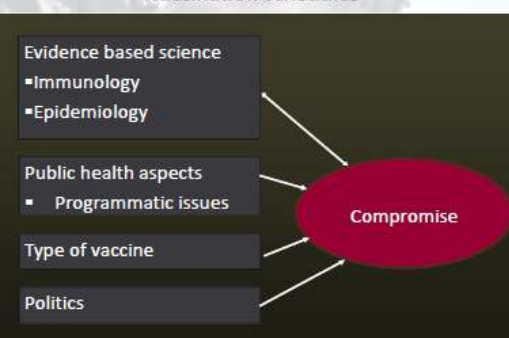
WHO recommendations



- DTC, polio, diphtheria, tetanus, pertussis and measles vaccines (part of WHO's 8th issue 2010)
- Vaccination against hepatitis B (recommended by WHO since the early 1990s, all infants 1997, 2000 - 2000 - 2000 High, combined with DTP (trivalent, pertussis))
- Vaccination against Hib disease (4/2000, combined with DTP (mainly as pertussis))
- Vaccination against TT, meningococci ... in risk areas
- RV, pneumococci, HPV ... (GIVS strategic area 2)

GIVS

Vaccination schedules



Evidence based science

- Immunology
- Epidemiology

Public health aspects

- Programmatic issues

Type of vaccine

Politics

Compromise

Vaccination schedules

Age of vaccination depends on:

- Risk of disease
- Risk of complication
- Maturity of the immune system
- Potential interference by passive maternal antibodies

→ Vaccines are usually recommended for the youngest age group at risk for experiencing the disease for whom efficacy and safety have been demonstrated.

Plotkin, Chanash & Offit. Vaccines, 5th edition

Global Immunisation Vision and Strategy (GIVS)



Four strategic areas

1. Protecting more people → Expand immunisation beyond infancy to older age groups
2. Introducing new vaccines and technologies
3. Integration with other interventions in health system context
4. Global interdependence

By 2010: 90% coverage nationally and 80% in all districts; 90% reduction of global mortality due to measles (compared to 2000)

By 2015: 2/3 reduction of global childhood mortality and morbidity due to VPDs (compared to 2000)

Global Immunisation Vision and Strategy (GIVS)

Four strategic areas

1. Protecting more people → Expand immunisation beyond infancy to older age groups
2. Introducing new vaccines and technologies
3. Integration with other interventions in health system context
4. Global interdependence



Rationale for adolescent vaccination

- To counter a specific risk in older age
 - Primary series: Vaccines specifically targeted for adolescents
 - Vaccines to prevent STIs (e.g. HPV)
- Waning of immunological response:
 - Booster doses for some vaccines routinely given during infancy and early childhood because immunity wanes over time
 - Additional doses can increase the duration of protection through later adolescence and adulthood
 - E.g. Tetanus

Mackroth et al. Vaccine 2010; 28: 1138-1147

Rationale for adolescent vaccination

- Missed or incomplete vaccination, and the vaccine-preventable disease still is a threat in adolescence and beyond
 - Many infants and young children do not receive all vaccines recommended for early childhood on schedule
 - Catch-up vaccination (e.g. HepB)
- Which vaccination in each category is highly different for each country (very few in low-income countries)

Mackroth et al. Vaccine 2010; 28: 1138-1147

Channels for reaching adolescents

- School based facilities
- Routine visits in primary care
- Campaigns
- School attendance required by law and is very high, especially in primary school = easy catchment
- Reaching out-of-school children (often deprived, disadvantaged groups at greater health risk)
- Consent (parental, adolescent)

Summary of WHO position papers Adolescent vaccination

	Adolescents
HPV	3 doses for girls
Rubella	1 dose (adolescent girl or women of child bearing age if not previously vaccinated)
DTP	Booster Td
Hepatitis B	3 doses if not previously vaccinated

Advantages of combination vaccines

- For immunisation system
 - Cost reduction
 - Eliminate separate vials, packaging, labeling
 - Eliminate cold chain storage expansion
 - Eliminate additional needles and syringes
 - Simplified logistics and delivery infrastructure
 - Delivery, central storage, and administration
 - Simplified vaccine handling and inoculation
 - Better coverage with fewer inoculations
 - Simplified record keeping and surveillance
 - Increase compliance and increased acceptance
- For community
 - Less injections, therefore **better acceptability**
 - Fewer clinic visits, therefore **more convenient**
 - Less side effects, therefore **more compliance**

課程 28：韓國於全國免疫力計畫（NIP）成本分攤方式

內容：

本課程介紹韓國的 NIP 成本分攤的方式及面臨困境及挑戰，本課程由韓國 CDC 局長主講，說明該國 NIP 自 1954 年開始推行，於 2002 年總統選舉時，將降低 NIP 成本障礙列為選舉宣言，為達成這個目標，該國於 2002-2009 年建立 NIP 資訊登錄系統，並從 2005 年起利用系統資料，逐年分析 NIP 在各城市之成本效益，於 2006 年完成 NIP 法律授權及成本分攤的法律，後於 2008 年逐漸擴大 NIP 計畫規模。

2009 年開始推行 NIP 補助金額計畫，每一種 NIP 疫苗約只要 7,000 韓元(約台幣 269 元)，2010 年該國國家健康與福利委員會希望增加 NIP 補助經費，每一種 NIP 疫苗只要花費 5,000 韓元（在 2011 年預算草案規劃接種費約額外增加 33.8 億韓元預算），但本草案在 2010 年底的預算委員會並未獲通過，後於 2011 年 2 月韓國爆發牛隻口蹄疫投注 100 億後仍防疫失敗，相關團體才反思用於小孩的防疫竟不如家畜類，於 2011 年 7 月兒科醫生的理事會決定積極投入疫苗費用補貼方案等努力下，2012 年該國宣布 12 歲以下幼兒（1999 年 1 月 1 日以後出生者）NIP 計畫中每劑疫苗費用由原來 1.5 萬韓元（約 625 元台幣）降為 5,000 韓元（約 200 元台幣）。為鼓勵孩子接種，該國衛生單位接種資料與出生登錄系統連線可透過簡訊通知父母接種日期，父母也可線上查詢孩子接種狀況。

NIP timeline 2

- 1980 - MMR introduced
- 1983 - measles, polio as NIP; smallpox discontinued, typhoid fever turned SIA*
- 1985 - HB vaccine (domestic product) introduced as SIA
- 1990 - cholera vaccination discontinued
- 1995 - Japanese encephalitis vaccine got market-based price; HB vaccine as NIP
- 1997 - 2nd dose MMR recommended; 2000 - MR catch-up
- 2002 - mumps, rubella as NIP
- 2004 - OPV replaced by IPV
- 2005 - chickenpox vaccination as NIP
- 2010 - Japanese encephalitis (1985 as SIA) vaccine as NIP

* Supplementary immunization activity

NIP cost sharing timeline 1

- 2002 - the plan for lowering cost barrier to NIP ("the plan") was included in major manifestos for the Presidential election
- 2002~2009 - NIP registry information system
- 2005 June~ 2011 - NIP cost and fee analysis
- 2005 July – pilot project 1 for the plan at Gunpo city and Daegu metropolitan city
 - public health center proportion 61% -> 10%, overall vaccination rate 102% increase compared with 2004

NIP cost sharing timeline 2

- 2006 - pilot project 2 by enhancing public health center capacity at Gangneong city, Yangsan city and Yeongi gun
- Evaluation of the two pilot projects
project 1 revealed better (AHP* result 0.559 to 0.441)
- 2006~2007 - advisory committees for the plan
- project evaluation, fee settling, education and training
- 2006 Sep - the law revised in support of delegation and cost sharing of NIP
- 2008 - gradual expansion of the plan was adopted by the Lee Myung-bak Government

* analytic hierarchy process

NIP cost sharing timeline 3

- 2009 - NIP vaccine cost subsidy program – in average 7,000 won for each NIP vaccine (user pays inoculation fee of 15,000 won)
- 2010 - Health and welfare Committee of National Assembly added the money for the plan (additional 33.8 billion won for central government with inoculation fee of 5,000 won) in 2011 budget draft
- 2010 year end - Executive subcommittee of Special Committee for Budget failed to deal with the budget item for the plan

Challenges

- 2005 June - an MP raised a crucial con to the plan at the 3rd session of Special committee for Budget
"despite vaccinations can be done enough by nationwide public health centers, the plan significantly reduces the portion of public health center and expands it to private hospitals and clinics.
I see the details of the budget plan – 33.3 billion won for public health center whereas 97 billion won to private in 2006; 11.3B vs 154B in 2007; 17.6B vs 187.2B in 2008...
I urge the Minister to make sure to look into with caution.
If it goes as it is several problems will turn out. Look into closely and carefully."

(Kim BH, MP of Hannara Party to Minister Kim Geun-tae)

Opportunities

- 2011 Feb - foot and mouth disease outbreak and late decision of vaccination for all the cattle at the cost of 100 billion won after several phases of failed containment
"Our kids are treated not better than cow and pig" (Dr Bae GR, Director of Immunization Management)
- Hannara Party once again promised to let the plan go
- 2011 July - Pediatrician Practitioner's Council decided to actively join the vaccine cost subsidy program
- 2011 Aug – within term resignation of Seoul City Mayor and supplementary election expected in October
- Memory of repercussion when executive subcommittee of Special Committee for Budget failed to deal with the budget item for the plan in 2010 Dec

Summary of 2012 plan

The government announced Monday that it will cover most of the cost of 10 vaccinations for children. Inoculation fees will be set at 5,000 won(\$4.20) a shot, down from the previous average of 15,000 won, according to the Ministry of Health and Welfare. The 10 vaccinations are BCG, DTaP, IPV, MMR, DTaP-IPV, Td, Tdap, Japanese encephalitis, hepatitis B and chickenpox. The reduced price will be applied to children under 12 year born after January 1, 1999. The shots will be available at 6,975 medical institutions nationwide including public health centers.

(cont'd)

Summary of 2012 plan

The government decided to add DTaP-IPV and Tdap to its subsidy list for their effectiveness in prevention of multiple illnesses. "Such 'combo vaccines' will reduce the number of inoculation sessions," said Lee Dukhyoung an official of the Korea Centers for Disease Control and Prevention. In order to encourage all children to be inoculated, the health authorities have linked their computer network to the birth-registry system to inform the parents of vaccination dates through SMS. Parents will also be able to check their children's vaccination status online.

titled "Seoul reduces cost of child vaccinations"
The Korea Herald, 3 January by Bae Ji-sook

課程 29：多醣體型疫苗與結合型疫苗之比較

內容：

本課程說明防治細菌型疾病接種疫苗之重要性及現行研發之多醣體型疫苗與結合型疫苗差異性，由於多醣體型疫苗與結合型疫苗作用機轉不同，選擇上亦要所瞭解。

流行性感嗜血桿菌(Hib)、流行性腦膜炎雙球菌及肺炎鏈球菌這三種病原體特性相似且流行病學、產生疾病均類似，多醣體型疫苗因無法激發 T-cell 及 B-Cell 反應，因此對於 2-5 歲幼兒的免疫力及保護力有其限制，而結合性疫苗免疫反應雖好，但結合方式不同，會對於抗體反應、T-cell 免疫性、長期保護力、流行改變、接種劑次及成人適應症上等的表現都會有所

不同。

Microbial exposures & diseases throughout life

Prenatal	Neonatal	< 5 years	5-18	Adult	Elderly
Rubella-virus CMV ZDV	HSV HPV HIV HBV	RSV Influenza PPV RV RV	Measles-virus Mumps-virus Rubella-Virus HPV	HSV HPV HIV	Influenza RSV HAV
Lactaria	GBS Enterobacteria C.diff	C. difficile H. influenzae B H. meningitidis S. pneumoniae Salmonella S. pertussis	Mycoplasma S. pertussis	S. pertussis	S. pneumoniae M. tuberculosis S. pertussis
Toxoplasma			Plasmodium		

Encapsulated bacteria: Disease spectrum in children

Disease	H. influenzae b	N. meningitidis ABCWY(X)	S. pneumoniae
Colonization	++	++	+++
Acute otitis media	+	(+)	+++
Sinusitis	+	(+)	+++
Pneumonia	+	(+)	+++
Invasive disease	+++	+++	+++
Meningitis	+++	+++	+++
Arthritis	++	(+)	+
Others, e.g.	Epiglottitis Facial cellulitis	Cardiac involvement	Primary peritonitis

Immune response to polysaccharide vaccines in Adults

Polysaccharide vaccines

- Poor immunogenicity and efficacy in children
- Limited immunogenicity in adults/elderly
 - Limited prevention of invasive disease (IPD)
 - No prevention of pneumonia
 - Waning immunity with age / comorbidities
 - Limited duration of protection (2-5 years)

Immune response to conjugates vaccine

Polysaccharides versus conjugates

Property	Polysaccharide	Conjugate
Effective in infants	No	Yes
Immune memory	No	Yes
Prolonged protection	No	Yes
Booster effect	No	Yes
Hyporesponsiveness	Yes	No
Reduction of carriage	No	Yes
Herd effect	No	Yes

小組討論：

今天下午是小組討論時間，延續昨日小組討論方式及分組議題，今日本小組以越南做為情境模擬，討論傷寒疫苗如取得許可後要如何持續推動疫苗接種，從學員們的分享與討論發現，各國推行疫苗計畫所要面臨的問題大同小異，諸如民眾的觀念、物流冷鏈系統、地域特性、疫苗供應能力、政治意願及經濟負擔，但各國面臨各項問題困難度不一，諸如東南亞國家民眾相對好溝通，但是往往政治問題會干擾疫苗經費獲得及計畫推行，另外政府財政不佳時，往往接種政策無法持續支持，其向國際申請捐贈疫苗或財源對於延續疫苗計畫顯得更為重要。

DAY 6: Saturday, May 19, 2012

Special lecture and closing

Chairperson: Christian Loucq

0930 1030 Keynote closing speech: The changing face of the vaccine research and development

Francis E. Andre TAB 32

1030 1050 Coffee break

1050 1150 Closing ceremony Christian Loucq

1150 Lunch

課綱：今日為訓練課程最後一日，課程由主持人之一 Dr. Francis E. Ander 總結目前疫苗研發、發展及使用上所要面臨的挑戰做說明，並鼓勵大家持續為疫苗推動努力。

目前在發展中國家面臨重要三大重要問題，分別是疫苗使用權缺乏、不能平等接種所需的疫苗及投資於發展中國家重要疾病的疫苗資源過少。全球疫苗免疫聯盟(GAVI)和其基金解決當前問題提供全球 75 個最貧窮國家資助計畫以降低這些差距，其他全球為免疫力共同努力的組織除了該基金會主要捐贈者比爾蓋茲基金會外、諸如 WHO、世界銀行、兒童基金會等都為全球免疫力努力中。

全球 98%醫療花費屬於治療性藥物或處置，小於 2%花費用於疫苗，顯示全球投資疫苗預防疾病比例仍過低，要如何說服疫苗是省成本值得投資介入方式，是值得大家努力推動的，在經濟學層面分析疫苗接種的價值，可從降低治療的需求、疾病發生、死亡率、發生率、生產力損失及住院率等層面進行，傳統上在這些計算直接與間接醫療費用、避免疾病的發生、避免死亡及避免/增加殘疾調整生命年 (DALYs 和 QALYs) 的分析，多帶有許多不確定性，因此決策需考量道德、社會重要目標及疫苗非私有財等角度進行決策，且多侷限有多少錢投資多少健康介入行為，因此貧窮國家越不可能獲得健康投資。

新思維應要倡導與評估疫苗接種效益時，應考量健康可提升人口素質以創造財富的角度探討，以東南亞奇蹟-人口紅利帶來生產總值的增加為例，因此分析效益時可從認知發展和教育程度、勞動生產率、儲蓄、外商直接投資、控制人口出生率及避免感染及其效益等面項加以分析疫苗效益，例如 GAVI 計算其計畫回收報酬率，是以扣後成本與收入增加的比較，該組織估計免疫計畫 2005 年回收報酬率約 12%，到 2020 年將增加到 18%。

隨著生技產業新技術發展，疫苗新技術發展可適用於許多疾病的預防，採行疫苗接種作為預防保健介入措施日益顯得重要，而疫苗推動需建立在臨床醫生、衛生主管部門、立法者、製造商和民眾之間維持公眾信任之上。因此未達到全體健康需要公部門、私部門及伙伴關係組織一起合作努力。

The Three Gaps

- **ACCESS**
 - 30 million newborns un-immunized per year
 - stagnant or falling coverage in some regions
- **EQUITY**
 - many children in developing countries miss important newer vaccines (hep B, Hib) and/or receive unsafe injections
- **INVESTMENT**
 - too little investment in vaccines which primarily impact developing countries

The GAVI Alliance and Fund

- Major source of funding for 75 poorest countries
- Critical role of Gates Foundation: committed \$ 1.5 Billion to establish GAVI Fund
- Coverage up significantly in many countries
- Most countries introduced Hepatitis B vaccine some Hib and YF
- Injection safety
- Developing country manufacturers now making DTP-HB and DTP-HB Hib and AD syringes

The Global Immunization Landscape



Global spending on medicines

98% on therapeutic drugs, 2% on vaccines !

Economic evaluation of vaccination

- **The traditional view**
 - ✓ Direct & indirect costs
 - ✓ Averted illnesses
 - ✓ Averted deaths
 - ✓ DALYs & QALYS averted/gained
 - ✓ Avoided medical & indirect costs

Is an intervention cost effective? Traditional view

- Perspectives
 - healthcare provider (direct medical costs)
 - society (non-medical direct costs + indirect costs)
- Cost / DALY averted (WHO)
 - <GNI: HIGHLY cost effective
 - 1–3 x GNI: cost effective
 - >3 x GNI: NOT cost effective
- Some uncertainties in Cost Effectiveness Analysis require sensitivity analyses (best/worse-case scenario)

From income to health: the traditional view



- Better nutrition
- Better access to clean water
- Better sanitation
- More access to better health care
- Better psycho-social resources

Magnitude of the effect of health on wealth



- A 10-yr gain in life expectancy \cong 1% increase in GDP growth per year (typically 40% higher GDP)
- One third of "East-Asian miracle" (~ extra 2% GDP growth/yr) due to "demographic dividend"

Bloom DE et al. World Economics 2005; 4(3): 15–39

From health to income: the full story



- Increased productivity
- Positive impact on education
- Increased foreign direct investment
- Demographic dividend
 - parents realise fewer births needed
 - fewer children are easier to nurture and educate
 - larger workforce as children mature

Bloom DE et al. World Economics 2005; 6(3): 15-39

Comprehensive economic evaluation of vaccination

The traditional view

- ✓ Direct and indirect costs
- ✓ Averted illnesses
- ✓ Averted deaths
- ✓ DALYs + QALYS averted/gained

The new view

- ✓ Cognitive development and educational attainment
- ✓ Labour productivity
- ✓ Savings
- ✓ Foreign direct investment
- ✓ Fertility control – demographic dividend
- ✓ Averted downstream infections and their benefits

Effect of childhood vaccination on cognitive development

- Cebu Longitudinal Health and Nutrition Survey
- 1975 children aged 10 years (born 1983/84)
- Immunisation and test score data
- Analysis controlled for confounders (e.g. socio-economic status)
- Immunised children had significantly higher scores in IQ and language (5% level) and maths (10% level)

Bloom DE et al. World Economics 2005; 6(3): 15-39

Rate of return for GAVI Alliance programme

- GAVI Alliance expanded programme (HiB, Hep B, yellow fever) – US\$13 billion over 15 years for low-income nations
- Use GAVI Alliance estimates of averted child deaths and life table to translate averted deaths into increased probability of adult survival
- Use estimates in economics literature to translate increased probability of adult survival (a proxy measure for morbidity declines) into growth of wages and income per capita
- Compare discounted costs and income gains by computing rate of return to the GAVI programme

Bloom DE et al. World Economics 2005; 6(3): 15-39

The GAVI bottom line...

The rate of return to investment in the GAVI immunisation programme is *conservatively* estimated at **12%** in 2005, rising to **18%** in 2020

Bloom DE et al. World Economics 2005; 6(3): 15-39

Some examples of therapeutic vaccines against...

- Drug abuse
e.g. specific antibodies that bind nicotine → activity in brain ↓ → addiction ↓
- Arthritis, psoriasis
e.g. anti-TNF- α antibodies
- Hypertension
e.g. Renin-angiotensin-aldosterone-system
- Allergies e.g. hay fever
- Obesity e.g. ghrelin, regulator of appetite

Choosing Health

- UK, National Health Service (NHS)
 - A White Paper entitled 'Choosing Health' calls for a major shift in the nation's healthcare approach, moving away from sickness towards a Wellness platform.

Therapy → Prevention

Hall C. Healthier population 'could save NHS billions'. www.health.telegraph.co.uk, 3 Jan 2004.

Public
Private
Partnership

is essential to
achieve the goal of
Health for All



肆、心得：

本次為本人首次參加國際為期 6 天訓練課程，該課程相當充實與完整，從疫苗沿革、全球疫苗使用與面臨的問題、疫苗研發與發展、疫苗上市前臨床試驗效益安全性評估注意事項、接著到疫苗上市後及計畫執行後評估、技術轉移、疫苗導入評估內容及疫苗政策推動溝通、夥伴關係建立及當前各國面臨問題及未來疫苗趨勢等等。

本次課程為主辦單位 IVI 第 12 屆的訓練課程，大會相當熟練課程安排及時間掌握，課程

進行流暢且所邀請的講師講述內容符合主題，由於學員以東南亞非英語系國家居多，考量學員語言問題，盡量放慢或解釋容易瞭解，在這個課程中，重新複習疫苗學基本原理及效益評估方法，並了解亞洲發展中國家當前面臨疫苗可預防疾病之疾病負擔狀況及疫苗缺乏困境，以及疫苗導入評估考量面向及疫苗成本效益評估作為疫苗導入前應先進行評估的概念，有利於強化未來疫苗政策分析上邏輯思維及應注意事項，課程最令我收穫最多的是瞭解到整體性疫苗研發的進度與未來研發趨勢，對於疫苗新的製造技術充滿期許，隨著技術提升，對於現行面臨每年接種或接種效益不佳問題等阻礙接種率提升、疫苗安全性、疫苗儲存之冷鏈系統問題，且也許隨著疫苗技術提升或變更，將有指日可待解決的一天，但新技術製造疫苗帶來效益，相對的其價格亦較高，顯示面對高價疫苗時代日漸的來臨，為永續經營國家免疫力計畫，我國對於評估新疫苗導入時程應提前規劃爭取疫苗推動財源，或於財源爭取困難下變更經費分攤比例，是值得深思且需及早規劃的問題。

全球經濟蕭條，各國紛紛面臨政府財源緊縮問題，為避免預防性健康介入-疫苗接種常被犧牲或被延遲推行，在導入每項疫苗政策現行分析與收集疾病負擔、疫苗效益、疫苗安全的資料已不足，成本效益評估資料成為必備且重要有力說服爭取預算的工具，而計畫導入推行後也應進行實際的成本效益評估，以瞭解疫苗效益為何？然評估效益方式很多，各種方法都需留意方法學上的限制以避免錯誤解釋問題，未來以國家整體競爭力角度進行疫苗接種回收報酬力評估的新觀點，也將是運用為成本效益評估可參考的方向。

另對韓國疫苗工業突飛猛進的進步及有長遠持續經營發展的策略感到印象深刻，該國長遠發展策略有助於疫苗工業興起外，另有助於疫病大流行時的因應，反思我國在缺乏長遠疫苗工業經營環境下，如何獲得即時或穩定的疫苗供貨來源，更是應提早準備與規劃。

最後，這次課程吸取課堂知識外，更拓展國際視野認識國際間非官方國際組織如 IVI、GAVI，對於發展中國家於在傳染病的控制所投入的協助與長久經營，課程所提為達成 Health for all 是需要所有部門合作，我國在疫苗控制傳染病經驗相較東南亞國家是相當成熟，尚待積極參加國際免疫合作計畫，以建立國際夥伴關係。

伍、建議：

1. 成本效益評估為疫苗政策及導入新疫苗前必須具備的基礎資料，建議我國建立一套疫苗成本效益評估機制，將有助於疫苗經費之爭取。
2. 課程內容美中不足之處為偏重理論及原則性內容，較缺乏實務內容及困境因應政策，小組討論議題亦偏重亞洲發展中國家及非洲等國家當前所面臨嚴重疾病，因此與我國實務問題較難做結合，因此，本課程值得對未來承辦疫苗業務人員基礎訓練或為拓展人員國際視野及瞭解參亞太地區疫苗事務繼續參加的良好課程，但對於與疫苗實務結合之研討則建議參加 GAVI 等進階課程。