

出國報告（出國類別：其他會議）

赴美國芝加哥參加第九屆流感防治
大會（**OPTIONS IX for THE
CONTROL OF INFLUENZA**）

服務機關：衛生福利部疾病管制署

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派赴國家：美國

出國期間：105 年 8 月 24 日至 8 月 28 日

報告日期：105 年 9 月 30 日

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壹、背景說明與開會目的

流感防治大會（Options for the Control of Influenza）為流感領域中最重要的國際會議，每三至四年始召開一次，專門討論A型流感預防，控制和治療，包括季節性流感和流感大流行的準備。今年的流感防治年會在美國的芝加哥舉行，本次會議研討的範圍包括臨床科學、病毒學與發病機制、公共衛生、醫療保健政策及流感大流行的整備規劃。參與此次會議的專家學者們包括了病毒學家，傳染病，肺/重症護理專家和其他臨床醫生，科學家，公共衛生和流行病學研究人員和專家，醫療保健政策制定者和政府及非政府機構的工作人員。

會議目的為參與流感預防、控制和治療，包括季節性和流行病學之規劃等等，交換國家最先進的科學信息，促進國際和多學科的全方面合作研究，從基礎科學、病毒學到流行病學和感染控制，以及流感疫苗、抗病毒藥物的效果與開發，並提供政府機構，學術界和非政府機構研究單位等代表之間互相交流與討論的機會。

貳、行程表

日期	工作日誌	地點	行程內容
105/8/23	啟程	台北→舊金山→芝加哥	路程
105/8/23	抵達	芝加哥	抵達
105/8/24-8/28	會議	芝加哥喜來登酒店	參與會議
105/8/29-8/30	返程	芝加哥→舊金山→台北	路程

參、會議過程

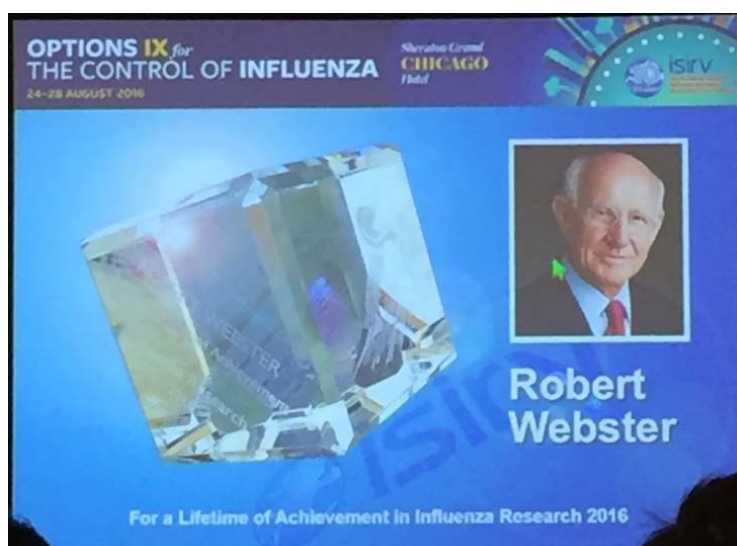
本次會議行程從8月24日下午5點開始到8月28日下午3點，每天早上為全體性的共同會議，安排3-4位專家學者進行專題演講，其他時段依病毒學與致病機轉、臨床科學、公共衛生3個主題分類在同時段安排各研究單位發表15分鐘的口頭報告，這次會議共有829篇海報分別安排在4天展示。

會議開始主席先頒發兩位傑出奉獻獎，第一位是杰弗裡·席爾德博士，他是

一位病毒學、公共健康、流感、疫苗和生物控制的研究學家。他曾擔世界衛生組織（WHO）國家流感醫學研究中心主任，他參與了流感病毒的抗原性分析、世衛組織全球流感監測網路的科學活動和流感疫苗組成在國際建議的協調發展。



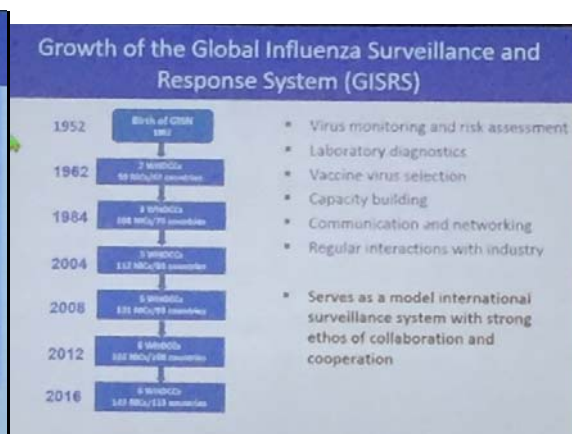
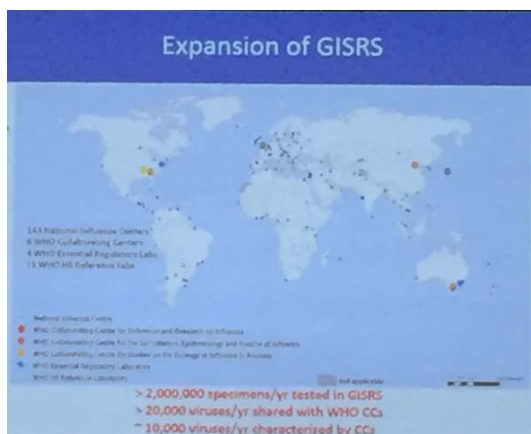
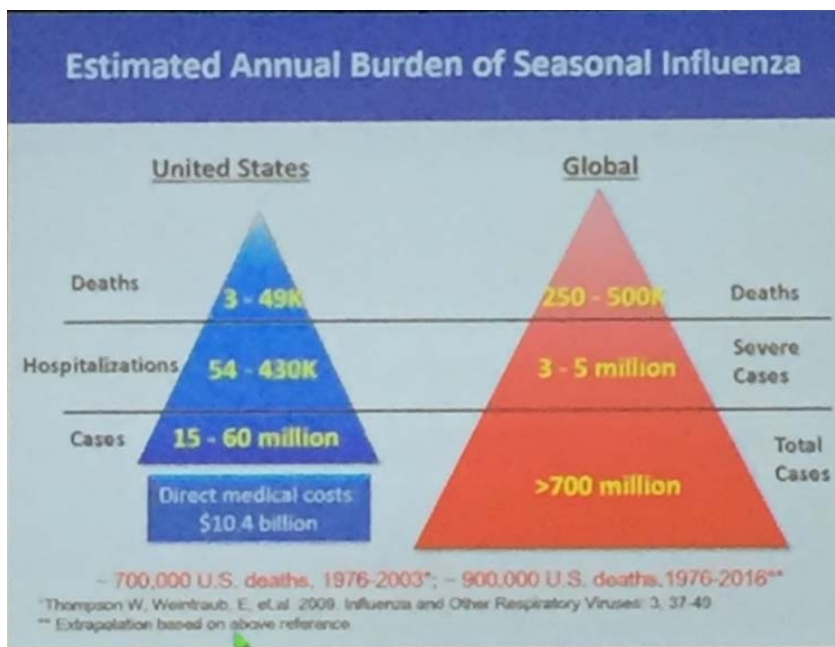
第二位是羅伯特·韋伯斯教授，他是一位禽流感的權威，他發現了禽流感病毒和人類流感病毒之間的關聯性，不同物種身上的流感病毒會進行重組，產生的大流行病毒。



接下來由南西考克斯博士發表開場演說，他表示每年季節性流感造成全球的負擔，直接的醫療費用有10.4億，新型流感仍有潛在的大流行風險，因為全球是越來越擁擠、人口越來越密集，人與人之間的交流往來越來越頻繁，使流感大流

行容易快速地蔓延，並導致更多人死亡，因此流感檢測、預測和預防是我們最大的挑戰。在個人及公共衛生觀點上，包括RT-PCR、快速檢測和診斷，擴展WHO的全球流感監測系統全球流感監測及應變系統（Global Influenza Surveillance and Response System，簡稱GISRS），建立GISRS能力，改善和加強流感大流行防範框架（PIP）與共享潛在人類大流行的流感病毒，和提高發展中國家疫苗和其它流行病相關的問題。

流感大流行是可以引起嚴重的社會，經濟和政治壓力，往往不可預知的。需要一個整體的方法，以確保當下一次大流行的發生，世界上所有的國家團結合作，能夠迅速而有效的應對，以降低發病率和死亡率。



H5N1疫情事件導致流感大流行防範框架（PIP）的建立，許多年前低收入和中等收入國家提供資訊和病毒樣本予WHO全球流感計畫（GIP），中高收入國家的製藥公司得到免費的流感病毒樣本，並進行疫苗研發與取得專利，從中獲得利潤，而低收入和中等收入國家卻無法購買疫苗，印尼在2006-2007年拒絕與WHO共享H5N1流感分離菌株樣品，以直接抗議在分享病毒樣品及疫苗研發技術方面的不公平，主張國際法原則的主權，在聯合國生物多樣性公約（CBD）規則中呼籲國家擁有保護生物和遺傳資源的主權。印尼的行動驚動了全球衛生界，由於印尼已經被禽流感重創，所以在追蹤流感病毒（H5N1）的合作是非常重要的，如果無法取得印尼的流感病毒株，全球監測將遭到破壞。在2005年的國際衛生條例是具有法律約束力的國際法，並沒有要求生物樣品的共享，因此WHO花了4年及數百萬美元來談判，努力設法在公共衛生和創新以及知識產權之間的關係方面發揮戰略性和核心作用，將病毒共用和利益分享建立在平等的基礎上。印尼目前已經成為正在發展或已經具有國內疫苗生產能力的幾個中低收入國家之一，其他幾個獲得WHO技術轉化項目支持的國家包括巴西、中國、埃及、印度、哈薩克斯坦、墨西哥、南韓、羅馬尼亞、塞爾維亞、南非、泰國和越南。

流感大流行防範框架（PIP）之建立是全球公共衛生的一個里程碑，匯集各成員國大流行性流感的防範和應對作法。它的主要目標包括：改善和加強與人類潛在的大流行、透過GISRS共享流感病毒;和提高發展中國家疫苗和其它大流行相關資源。要求醫藥行業支付GISRS每年營運成本的一半（280萬美元/年）；70%的捐款分配給中低收入國家，用於改善大流行和季節性流感，預留30%作為大流行期間購買疫苗等，並承諾疫苗和抗病毒藥物的10%用於在發展中國家使用的義務。

由於病毒不分國界，因此這種觀察監測是國際性的，為預防流感病毒造成人類健康的威脅，每年全球流感疫苗須隨時更新，以預防全球流感病毒的大流行。自1952年起，WHO啟用全球流感監測網絡（Global Influenza Surveillance Network，簡稱GISN），監測全球流感病毒演化，發現數種新型流感病毒造成全球大流行。1973年WHO正式將GISN應用於選擇流感疫苗株，1998年開始WHO分別於2月與9月召開兩次技術諮詢會議（疫苗組成會議），分別對北半球與南半球季節性流感

疫苗選株提出建議 (Vaccine Consulting Meeting, 簡稱VCM), 並於2011年將GISN更名為GISRS。過去幾年, WHO積極強化GISRS平台, 期能有效應用於流感疫苗株製備, 其過程如下:

1. 因應流感病毒的基因快速演化與變異, 結合WHO合作中心 (Collaboration Center, 簡稱CC) 與國家流感中心 (National Influenza Center, 簡稱NIC) 有效地監控全球流感病例數的分布;
2. 提高實驗室檢驗流感病毒技術, 有效辨認流感病毒的基因型別與抗原變異, 訂定實驗室的標準流程;
3. 採用新的、快速的資料分析方法, 處理全世界各個實驗室間的流感病毒數據的差異性, 可以有效縮短流感疫苗株選株的時間。

目前全球有113個組織會員國家143個國家流感中心和6個世衛組織合作中心、4個管制實驗室、13個H5參考實驗室。每年對病毒做出建議。

以下與本組業務相關內容摘要分述如下:

一、 **Pandemic planning**: 主講者為Wenqing Zhang, MD

1918年西班牙流感大流行曾經造成全世界約5億人感染, 5千萬到1億人死亡 (當時世界人口約17億人), 傳播範圍達到太平洋群島及北極地區; 其全球平均致死率約為2.5%-5%, 在1947年4月3日召開第三屆流感的臨時委員會時, 來自荷蘭Dr. C. van den Berg代表建議成立流感顧問委員會。WHO於1948年7月8日成立世界流感中心, 1952年9月WHO啟用全球流感監測網絡 (GISN) 也就是全球流感監測和應對系統 (GISRS) 的前身。1969年世界衛生大會通過國際衛生條例, 2011年第64屆世界衛生大會決議通過採用大流行性流感防範 (PIP) 框架。其目標是改進大流行性流感的防範和應對, 並加強預防大流行性流感, 為此應改善和加強WHO GISRS, 目的是落實公正、透明、公平和有效的系統, 以便平等地共享H5N1病毒及其它可能引起人類間大流行的流感病毒; 和獲得疫苗並共享其它利益, 例如標準材料轉讓協議 (SMTA2), 另外WHO也規畫指導文件如大流行性流感風險管理 (PIRM) 框架, 強調所有風險管理的方法 (如突發

公共衛生事件風險管理)，加強整個政府和社會的風險管理，WHO 進行溝通和全球風險評估，結合新的發展例如 PIP 框架。

在 2009 年 H1N1 流感大流行時迅速啟動 GISRS 系統，所有後續反應的觸發：

- (0 天) 4 月 25 日提供基因序列的診斷
- (3 天) 4 月 28 日提供診斷建議
- (7 天) 5 月 2 日提出第一個 RTAPcR 套件
- (31 天) 5 月 26 日大流行性疫苗病毒建議
- (32 天) 5 月 27 日第一個可用的候選疫苗重組病毒

流感大流行是不可預知的，但卻能引起嚴重的社會、經濟和政治壓力，預先的規劃和準備是幫助減輕流感流行或傳染病影響的重要關鍵。WHO 提供指導性文件，包括流感疫情調查指導、流感大流行監測、流感大流行風險評估工具

(TIPRA) 及協調國內和國際對流感大流行的防備，並支持各國建立制定國家大流行準備計畫和模擬演習能力。

WHO 流感公共衛生研究議程 (Public Health Research Agenda for Influenza) 是圍繞五個重點進行：(1) 減少流感大流行出現的風險 (2) 限制人畜共通傳染病大流行及季節性流感的蔓延 (3) 最大限度減少人畜共通傳染病大流行及季節性流感疫情的影響 (4) 更好的治療 (5) 促進公共衛生工具開發與應用。

現今各國交流頻繁，衛生安全是全球性問題。來自傳染病，化學和放射事件的威脅，可能會波及多個國家。因此 196 個國家同意共同努力，以防止和應對公共衛生危機。該協議被稱為國際衛生條例 (IHR)，並和 WHO 發揮協調作用。透過國際衛生條例，WHO 協調公共衛生風險國家，並與合作夥伴密切合作，以幫助各國建立檢測，報告和應對公共衛生事件的能力。

目前流感疫苗的限制

1. 無法有效對抗抗原 drift 及 shift：抗原的結合位點 (HA 或 NA) 具有高度變異性，單一位點的變異就會嚴重影響疫苗效益。
2. 對其他亞型別的病毒交叉保護效果有限
3. 免疫力不持久，尤其在老人及小孩
4. 需要分離病毒

5. 大宗疫苗仍需仰賴雞蛋
6. 禽流感疫苗需要添加佐劑
7. 疫苗效益不佳

流感疫苗（GAP）的全球行動計畫是通過三個主要途徑，以減少流感疫苗在世界各國季節性流行和大流行性流感目前的全球性短缺的綜合戰略：

1. 增加季節性疫苗的使用：鼓勵各國增加季節性流感疫苗的使用。可減少季節性流感感染造成的疾病負擔，有助於國家應對流行病的準備，並能激勵產業發展製造疫苗。
2. 增加疫苗生產能力：集中於增加對大流行性流感疫苗的產能沒有預期中的季節性流感疫苗的需求量相應增加。季節性流感疫苗生產能力已經從2006年每年不到500萬劑增加至2010年每年接近十億劑。14個發展中國家已獲得資助建立國內流感疫苗製造能力：巴西，中國，埃及，印度，印尼，伊朗，哈薩克斯坦，墨西哥，韓國，羅馬尼亞，塞爾維亞，南非，泰國和越南。這些廠商中，五個目前擁有的市場（印度，印尼，羅馬尼亞，韓國和泰國共和國）對持牌疫苗，其餘都處於後期開發階段。財政支持已經被美國，日本的政府，亞洲開發銀行，加拿大政府和英國政府健康與人類服務部提供。
3. 研發：鼓勵產業進行疫苗研究和開發，利用新技術開發更有效力的疫苗（例如：是更安全的，對老人嬰幼兒免疫抑制患者具有高度保護效果，價格便宜容易進行大規模生產，為單次劑量、耐高溫等）。

流感大流行無法預知發生的時間，一旦發生又會很快地散播，因此更完善的準備及規劃，可拯救更多的生命，這是全球共同承擔的責任。建立可靠、有意義的動物、人和環境健康部門的國際合作非常必要，有助於迅速的察覺潛在的傳染病流行，快速啟動公共健康預防和控制指導及干預。

二、 Effectiveness of Antivirals：主講者為 Jonathan Nguyen-Van-Tam, DM

流感在臨床表現較不易察覺，常與其他呼吸道病毒感染無法區分，基層醫療

並不重視呼吸道病毒感染檢查。了解 ITT (流感確認) 與 ITTI (實驗室檢查確診流感) 之間的差異, 可以幫助我們了解神經胺酶抑制劑 (NAIs) 的具體效果。

Clinical presentation

- Clinically influenza is often indistinguishable from other ARI of virus aetiology
- No emphasis on testing for RVI in primary care; ITT analysis is relevant from PH perspective – program effectiveness
- ITT (influenza confirmed) = ITTI is preferred to understand efficacy
- *Examining differences between ITT and ITTI can help understand specific mode of action of NAIs

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NAIs 在許多的研究中都顯示可以減少疾病持續時間及降低併發症、住院、死亡率, 在 Treanor et al. JAMA 2000 年研究結果顯示, 在 18~65 歲感染流感的成人, 給予 Oseltamivir 每日 2 次 75 毫克比安慰劑組縮短疾病持續時間 32 小時, 在 Whitley et al. PIDJ 2001 研究顯示, 在感染流感的兒童可縮短疾病持續時間 36 小時。

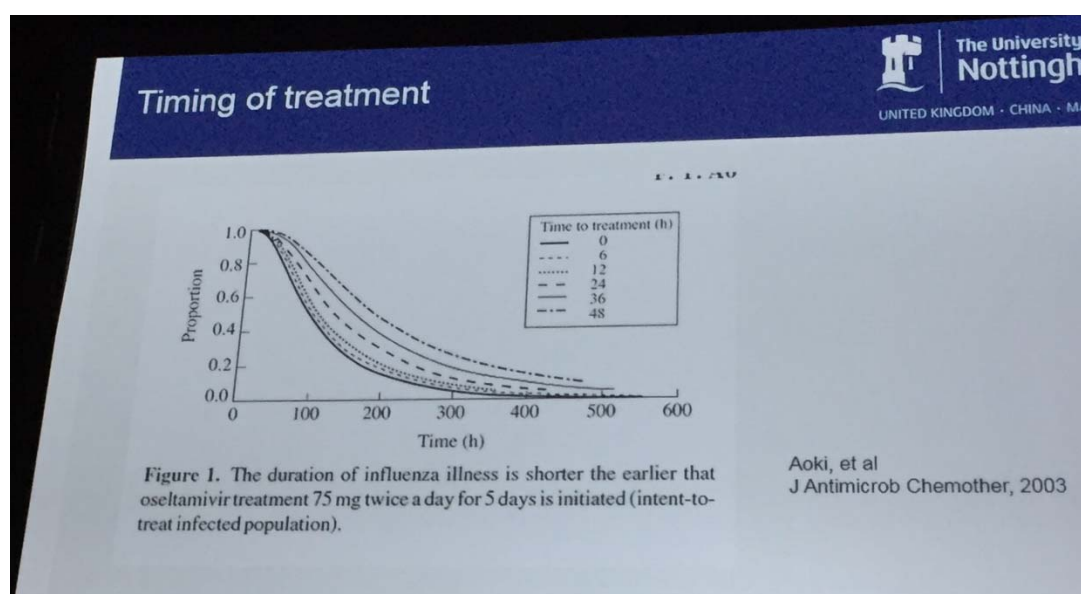
Illness duration

- Figure: Treanor et al. JAMA 2000
- 32h reduction in illness duration
- Whitley et al. PIDJ 2001
- Broadly similar data in children (36 hours)

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Participants with missing values were censored. One patient (not shown, oseltamivir, 75-mg group) had a censored value of 20.3 days. $P < .001$ for placebo vs oseltamivir, 75 mg twice daily; $P = .006$ for placebo vs oseltamivir, 150 mg, twice daily.

Cochrane 統合分析 2014 年羅氏公司的研究數據，為了描述 NAIs 對於流感在各年齡族群中潛在的效益與危害，回顧所有包含已發表與未發表的隨機安慰劑對照試驗與法規評論的臨床研究報告，主要結果：在所有年齡組中，oseltamivir 對於成人的治療到初次症狀緩解所需時間減少了 16.8 小時，這代表到初次症狀緩解所需時間由 7 天減少至 6.3 天。對於有氣喘的兒童沒有影響，相反的，對健康的兒童則減少 29 小時。Zanamivir 在成人的治療上到初次症狀緩解所需時間減少了 0.60 天，等於將症狀的平均持續期由 6.6 天減少至 6.0 天，對於兒童的影響則不顯著。Oseltamivir 對成人住院治療沒有顯著的影響，在兒童或預防也沒有顯著的影響，沒有 zanamivir 的住院治療資料記錄。另外 Oseltamivir 顯著地減少了自覺性、經檢查發現以及未確診的肺炎（1%）。顯著藥物相關的不良反應包括噁心及嘔吐。



Oseltamivir 與 zanamivir 在縮短成人流感症狀緩解所需時間上有一定的影響，但在氣喘兒童上則無。使用任一種藥品做為預防，可以減低罹患症狀性流感的風險。由於缺乏診斷定義，包含 oseltamivir 或 zanamivir 的治療試驗無法解決流感併發症（例如肺炎）是否減少的问题。Oseltamivir 的使用，增加成人出現不良效應，例如噁心、嘔吐、精神影響及腎臟相關事件與兒童出現嘔吐的風險。是否使

用兩種 NIs 來預防或治療流感的決定時，需考量效益與危害之間的平衡。

多布森 2015 年統合分析，以隨機，雙盲，安慰劑控制試驗，在成人給予 Oseltamivir 75 mg 每天 2 次，九項試驗共 4328 例，結果與 Cochrane 研究分析結果是一致的，在 ITTI 中可縮短症狀持續時間約 1 天的時間（25.2 小時），亦可減少下呼吸道需要抗生素治療的併發症，但增加的噁心和嘔吐的發生。ITT 中所有症狀緩解縮短 17.8 小時。

流感抗病毒藥劑的有效性 Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) 研究聯盟，以個別病人數據 individual patient data (IPD) 統計分析 A (H1N1) pdm09 病毒感染住院病人與 NAI 治療和 X 光確診流感相關肺炎 influenza-related pneumonia (IRP) 之間的關聯，包括入住重症加護病房 (ICU)，使用呼吸器，急性呼吸窘迫症候群 (ARDS) 和 IRP 患者的死亡率。成果衡量指標包括 1) 死亡率 2) 流感相關性肺炎 3) 住院 (社區數據) 4) 住院時間。研究對象來自 38 個國家和 6 個 WHO 區域共 80 個研究組，收集 29,234 人住院治療(與已知的死亡狀態和 NAI 數據)、9,327 X 光影像資料(和 NAI 數據)、3,376 社區治療和住院情況資料 (不包括對入院當天治療的患者)。附加分析依年齡分組 (成人，兒童)、孕婦、重症加護病房 (ICU) 及實驗室 A (H1N1) 確診的病例。

結果：所有年齡組實驗室確認個案與小於 16 歲兒童可降低死亡率，16 歲以上加護病房住院病患 2 天內使用 NAI 可降率死亡率，越早使用 NAI 存活率越高。對於降低住院的發生有顯著的效果。

Outcome: Mortality

Exposure: NAI treatment at anytime vs No NAI treatment

Population Subgroups	Crude OR (95% CI)	Adjusted ¹ OR (95% CI)
Lab confirmed cases (all ages)	0.94 (0.81 - 1.09)	0.82 (0.70 - 0.95)
Lab confirmed and clinical diagnoses (all ages)	0.92 (0.81 - 1.05)	0.81 (0.70 - 0.93)
Adults (16 years and above)	0.82 (0.70 - 0.95)	0.75 (0.64 - 0.87)
Children (<16 years)	1.02 (0.73 - 1.42)	0.82 (0.58 - 1.17)
Pregnant (13 - 54 years)	0.47 (0.24 - 0.90)	0.46 (0.23 - 0.89)
ICU patients (adults ≥16 years)	0.74 (0.57 - 0.95)	0.72 (0.56 - 0.94)

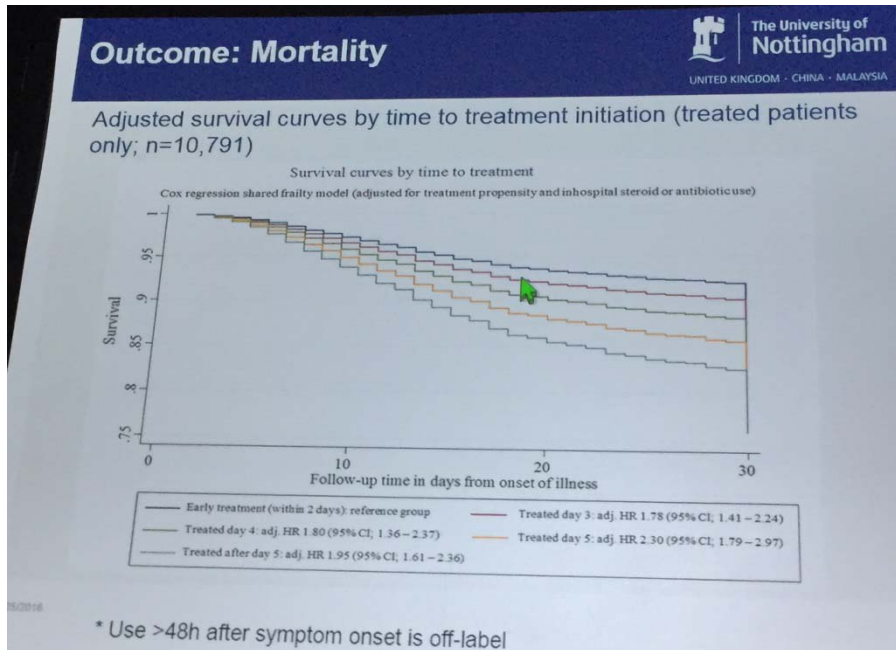
¹Adjusted for propensity score quintile, steroid use in hospital, antibiotic treatment in hospital
Statistically significant results in bold

Does later* treatment with NAIs offer benefits?

Exposure: Later NAI (>2 days)* vs. no treatment

Population Subgroups	Crude OR (95% CI)	Adjusted ¹ OR (95% CI)
Lab confirmed cases (all ages)	1.25 (0.98 - 1.59)	1.17 (0.92 - 1.51)
Lab and clinically confirmed (all ages)	1.27 (1.00 - 1.61)	1.20 (0.93 - 1.54)
Adults (16 years and above)	1.01 (0.77 - 1.32)	1.01 (0.76 - 1.33)
Children	1.34 (0.78 - 2.31)	1.29 (0.75 - 2.21)
Pregnant (13 - 54 years)	0.72 (0.26 - 2.01)	0.70 (0.24 - 2.06)
ICU patients (adults ≥16 years)	0.61 (0.43 to 0.86)	0.65 (0.46 to 0.93)

¹Adjusted for propensity score quintile, steroid use in hospital, antibiotic treatment in hospital
* Use >48h after symptom onset is off-label



綜合以上的研究結果顯示，NAI 治療可降低 2009-2010 年流行期間的住院患者死亡率。確認早期治療的重要性，以及早期使用 NAI 可降低症狀持續時間及降低死亡率，即使是在症狀開始 2 天以後使用，或是在重症病患仍有降低死亡率的好處。研究結果贊成在 2009-2010 年流感大流行期間儲備 NAI 和住院患者使用 NAIs 的決策。

三、 **Pandemic and Pre-pandemic Vaccines, Where Are We Now?** 主講者為 **Rick A. Bright, PhD**

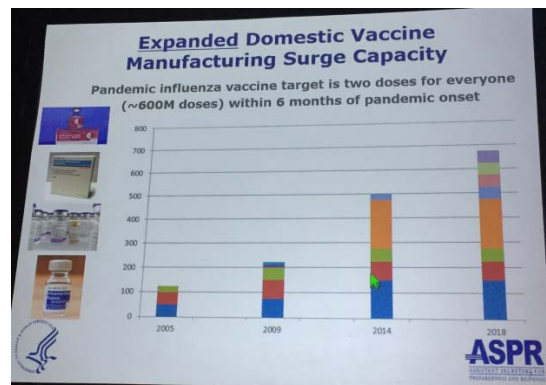
在 2005 年之前反應能力不足以應對流感大流行的威脅，因為沒有儲備大流行前疫苗或抗病毒藥物、國內產能有限、全球疫苗供應嚴重不足，有限的開發管道、候選 H5N1 疫苗免疫抗原性差、美國所有核准的季節性流感疫苗是根據雞蛋（20 世紀 40-50 年代的技術）無 cell-based 或基因重組疫苗、沒有大流行性流感疫苗與 ASPR 佐劑。

美國生物醫學高級研究與發展管理局（Biomedical Advanced Research and Development Authority，簡稱 BARDA）是美國衛生和人類服務部（HHS）下屬的一個部門，主要是以綜合系統的方法，為應對公共衛生醫療緊急事件的必需疫

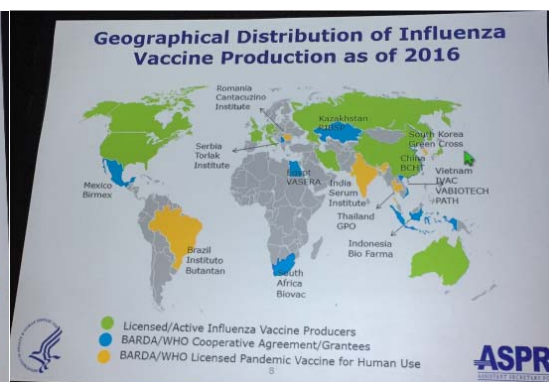
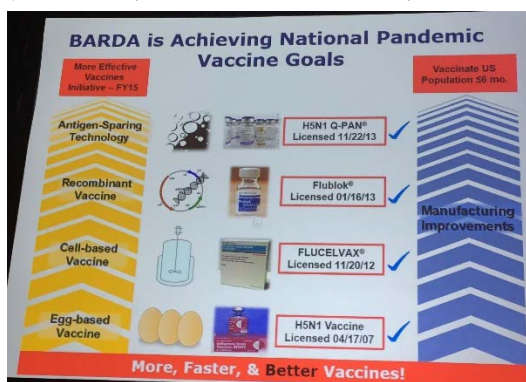
苗、藥物、療法和診斷工具的發展與採購提供支持，與美國 CDC、美國食品和藥物管理局（FDA）和美國國立衛生研究院（NIH）為合作夥伴關係。

BARDA 的流感大流行策略：

1. 發展成本低廉的口罩，以及可再使用的口罩與呼吸器，以因應大流行時的大量使用。
2. 在開發中國家，也有大流行疫苗 5 億劑疫苗的生產量能。
3. 儲備疫苗。
4. 在美國，在大流行公布的 6 個月內可以供應 6 億劑疫苗，且發展廣效、免疫效果更長的疫苗。
5. 發展快速診斷技術。



BARDA 已經完成國家流感大流行疫苗的目標，包括更有效的疫苗、抗原放大技術、重組疫苗、細胞培養疫苗、雞胚胎蛋疫苗。擴大了國內疫苗製造的量能，從 2005 年約 1 億劑到 2018 年超過 6 億劑。



2016 年流感疫苗生產的地理分布

在儲備大流行前疫苗：

(一) 完成部分：

1. 已儲備了高危險族群需要的 H5N1 及 H7N9 病毒株
2. FDA 已許可了 pre-EUA
3. 建立穩定性及使用性的監測與評估計畫
4. 能因應 2009H1N1 大流行及 2013 年 H7N9 爆發流行

(二) 主要的挑戰：

1. 抗原及佐劑已經儲存超過 10 年
2. 儲存的抗原穩定性有變異
3. 長期儲存的抗原與佐劑，使用效益資料非常有限

(三) Path Forward（未來要做的事）

1. 持續監測對人類有高度威脅的流感病毒株，並儲備之
2. 對於使用長期儲備的疫苗與佐劑應有明確的規定，並且應更新目前儲備策略

在國內疫苗生產量能：

(一) 已完成部分：

1. 已提高雞胚胎但疫苗產能（Sanofi）
2. Holly Springs, NC facility（Seqirus）
3. Pearl River, NY facility（PSC）
4. 確保每年雞蛋的供應
5. 國內佐劑生產
6. 能因應突發大量需求
7. 已完成網絡建立

(二) 主要的挑戰：

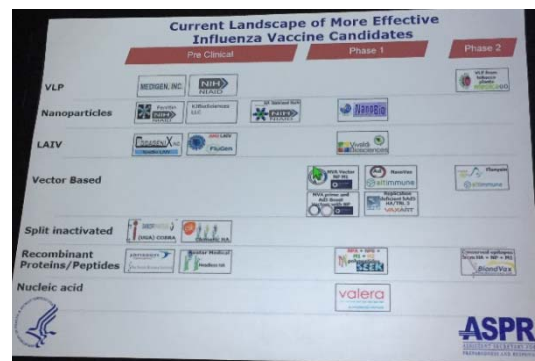
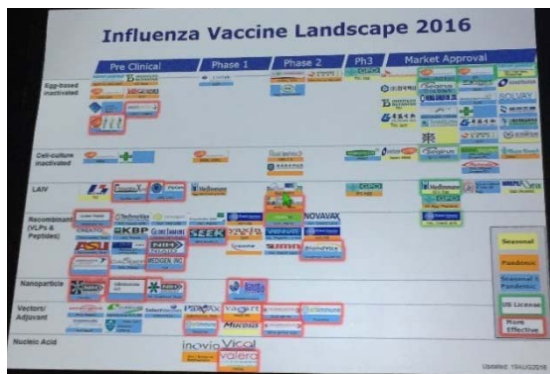
1. 需要維持快速因應的設施與能力
2. 重組及細胞培養疫苗在市場上遇到阻力

(三) Path forward（未來要做的事）

1. 確保 United Scientific Group (USG) 有最好的結果
2. 利用科技平台強化疫苗產能

更有效的疫苗，需結合更好的疫苗設計、佐劑及疫苗投予方式，疫苗、藥物的發展非常昂貴、高風險且耗時，目前流感疫苗的限制：

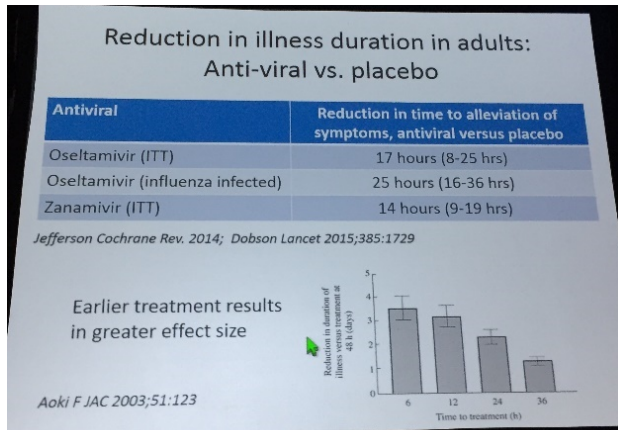
1. 無法有效對抗抗原 drift 及 shift：抗原的結合位點（HA 或 NA）具有高度變異性，單一位點的變異就會嚴重影響疫苗效益。
2. 對其他亞型別的病毒交叉保護效果有限。
3. 免疫力不夠持久，尤其在老人及小孩。
4. 需要分離病毒。
5. 大宗疫苗仍需仰賴雞蛋。
6. 禽流感疫苗需要添加佐劑。
7. 疫苗效益不佳。



目前季節性流感疫苗及大流行候選疫苗研發情況，BARDA 能夠迅速，有效地應對突發新興的威脅，以盡量減少其影響，並及時恢復能力，未來應繼續監測對人類高度威脅之流感毒株，並快速生產與儲備，更新儲備策略，對於長期儲備的疫苗和佐劑能更明確界定使用途徑，在臨床研究中持續評估儲備疫苗的安全性和免疫原性，積極與美國政府合作，以解決醫療對策和公共健康及國內製藥和生物技術部門的存在需求。

四、Early Use of Antiviral Drugs：主講者為 Allison McGeer, MD

流感是呼吸系統疾病，肺炎診斷是困難的，許多研究中都顯示早期給予抗病毒藥劑的好處。國際多中心在 1999-2000 年流感季節的研究中顯示在成人流感病人早期給予抗病毒藥劑可以增強治療效果，減少一半的病程，恢復較快，可加速臨床症狀減輕的時間，減少併發症的風險，但會增加噁心和嘔吐的發生。



Adverse events oseltamivir vs placebo RCTs - prophylaxis

Event	% occurrence in Placebo arm	Risk ratio [95% CI] OS vs. Placebo
Headache (on treatment)	2.4-39%	1.2 (1.05, 1.33)
Nausea (on treatment)	1.1-7.1%	2.0 (1.2, 3.2)*
Neurologic body system (on treatment)	4.1-43%	1.2 (1.0, 1.4)
GI body system (on treatment)	11-17%	1.4 (1.2, 1.6)*
Renal body system (on-treatment)	0-0.7%	3.2 (0.96, 11) P=.06
Reproductive body system (off treatment)	0.2-1.6%	0.49 (0.24, 1.0)
Psychiatric body system (on and off treatment)	0.4-1.6%	1.8 (1.1, 3.1)

81 adverse event comparisons: 8 specific symptoms, 19 body system categories, each on-treatment, off-treatment and combined

Jefferson Cochrane Rev. 2014

在有氣喘的孩童症狀減輕的時間則不明顯。克流感平均可以縮短症狀 29 小時，對於有氣喘的兒童縮短 5 小時；瑞樂沙縮短症狀 26 小時。

RCTs of antivirals, children

	Reduction in time to alleviation of symptoms, antiviral versus placebo
Oseltamivir	29 hours (12-47 hours)
All children	29 hours (12-47 hours)
Children with asthma	5 hours (-41-11 hours)
Zanamivir	26 hours (-4-56 hours)

	Risk ratio, 95% CI
Oseltamivir	
Otitis media	0.80 (0.62, 1.02)
Zanamivir	-

Dawood AVRes 2016 (N=683; seasonal): Terminated due to low accrual; no significant antiviral effect identified

Jefferson Cochrane Rev. 2014

2010 年法國的研究中發現在 H3N2 為主病毒感染流感的成人中，使用克流

感加上瑞樂沙（聯合治療組）的治療效果，並沒有比單獨使用克流感治療有效，也不比單獨使用瑞樂沙顯著有效，但是在聯合治療組噁心及嘔吐的副作用比單獨使用組較容易發生。在 2013 年的研究中發現，給予流感重症住院病人克流感劑量雙倍劑量的治療效果並沒有優於標準劑量。在 2015 年孟加拉的研究顯示，在城市環境中流感確診者使用克流感治療可以減少家庭二次感染機率，因此在擁擠的環境中給予抗病毒藥劑治療可以減少家庭流感病毒的傳播。

在加拿大多倫多研究顯示，住院病人中早期給予抗病毒藥劑與降低死亡率有顯著的相關性，年齡越大與察爾森合併症評分越高者會影響增加住院天數。

Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data

	Crude analysis		Adjusted* analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Laboratory confirmed or clinically diagnosed, all ages, n=29 234	0.92 (0.81-1.05)	0.21	0.81 (0.70-0.93)	0.0024
Laboratory confirmed cases, all ages, n=25 001	0.94 (0.81-1.09)	0.42	0.82 (0.70-0.95)	0.0104
Adults (≥16 years), n=19 816	0.82 (0.70-0.95)	0.0071	0.75 (0.64-0.87)	0.0002
Children (<16 years), n=9218	1.02 (0.73-1.42)	0.90	0.82 (0.58-1.17)	0.28
Pregnant women, n=2166	0.47 (0.24-0.90)	0.0228	0.46 (0.23-0.89)	0.0215
Critical care patients				
Adults (≥16 years), n=5103	0.74 (0.57-0.95)	0.0187	0.72 (0.56-0.94)	0.0155
Children (<16 years), n=1725	0.84 (0.52-1.37)	0.49	0.70 (0.42-1.16)	0.17

OR=odds ratio. *Adjusted for treatment propensity (by quintile), corticosteroid use, and antibiotic use.

Table 2: Neuraminidase inhibitor treatment (at any time) versus none

Muthuri SG et al., Lancet Resp Med 2014;5:395

Antiviral Therapy and Outcomes of Influenza Requiring Hospitalization in Ontario, Canada

Allison McGeer,^{1,2} Karen A. Green,¹ Agron Plevneshi,¹ Athynay Shigayeva,¹ Nilofar Siddiqi,¹ Janet Raboud,^{1,2} and Donald E. Low,^{1,2} for the Toronto Invasive Bacterial Diseases Network¹
¹Toronto Medical Laboratories and Mount Sinai Hospital, ²University of Toronto, and ³University Health Network, Toronto, Canada

Table 4. Multivariable analysis of the impact of antiviral therapy on mortality associated with laboratory-confirmed influenza requiring hospitalization, Toronto Invasive Bacterial Diseases Network surveillance, 2005-2006.

Variable	OR (95% CI)	P
Oseltamivir therapy	0.21 (0.06-0.80)	.02
Intensive care unit admission	10.5 (3.9-27)	<.001
Charlson comorbidity score (per point)	1.3 (1.0-1.8)	.03
Time from onset of symptoms to emergency department presentation (per 24-h period)	0.51 (0.31-0.87)	.01

Clin Infect Dis 2007;45:1568

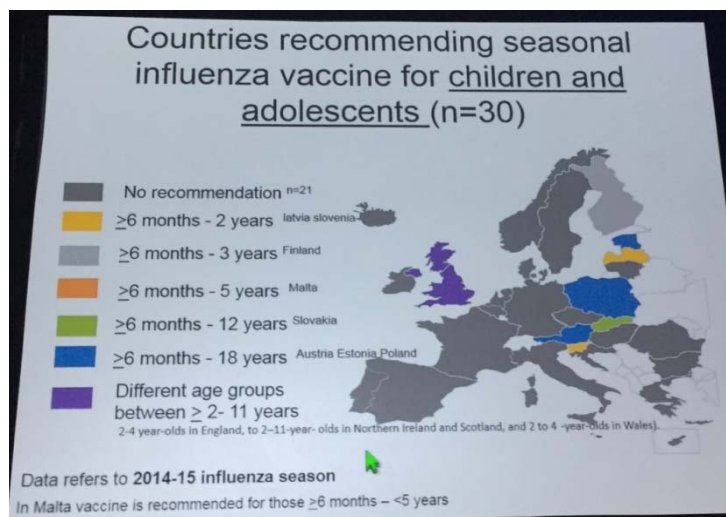
英國醫學科學研究院在 2015 年的建議：1.不用將藥物使用於非重症的流感病患，2.住院再使用，尤其是建議孕婦要使用，3.治療應盡量在 48 小時內使用，4.如果流感疫情的是更致命的或顯示並發症和死亡的發生率更高，那麼擴大使用抗病毒藥劑的使用人數是合理的。

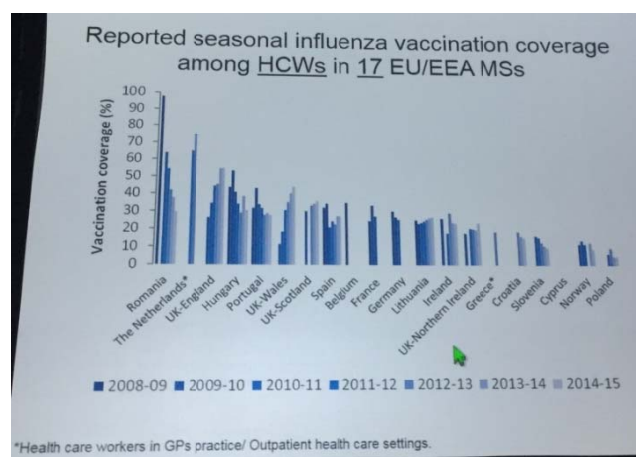
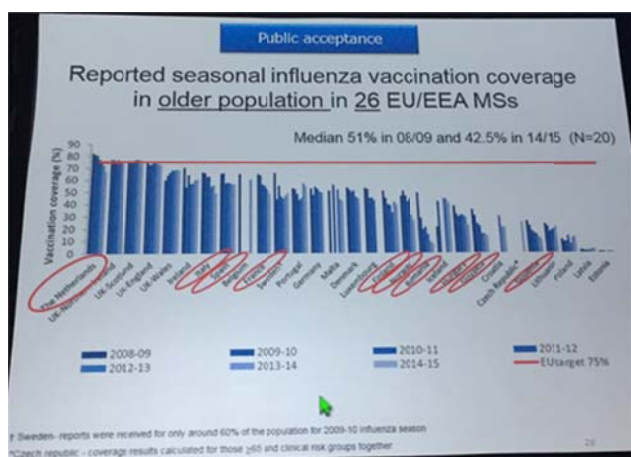
未來面臨的挑戰包括（1）對於神經胺酸酶抑制劑在流感重症患者的有效性不明確，實證資料仍不足，（2）目前僅為 50%患者能在發病 48 小時內就醫，（3）門診快速診斷（快篩）不易取得，且太貴，（4）為下一個大流行儲備藥物到底是不是必須的，仍然是一個難解的政策決定。我們可以做些什麼？研發新的抗病毒藥物、研發新的診斷方法可快速確診流感個案，更深入了解流感住院患者使用抗病毒藥物效果，持續進行觀察性研究，重新評估，以做為下一次大流行的依據。

五、Improving Vaccine Uptake in Target Groups：由 Darina O’Flanagan, MB 主講

歐洲理事會（EC）於 2009 年的建議，於 2014-2015 年時，應該要達到 75% 的疫苗接種率的族群包括，1.老年群體 2.慢性病患 3.提升醫護人員（醫護人員）疫苗接種率。WHO 於 2012 年建議，優先接種對象包括，1.孕婦 2.兒童（<5 歲） 3.老年群體 4.慢性病患 5.醫護人員。

30 個歐洲國家對於年長族群接種流感疫苗建議的調查，在老年人口疫苗接種率在大多數國家都落後（除荷蘭和英國），建議 50 歲以上接種，有 2 個國家；建議 55 歲以上接種，有 2 個國家；建議 59 歲以上接種，有 1 個國家；建議 60 歲以上接種，有 6 個國家；建議 65 歲以上接種，有 19 個國家。調查 2008 年至 2015 年各流感季慢性病患的定義，主要包括呼吸（肺）疾病、心血管疾病、腎臟病、免疫抑制病患、代謝異常、HIV/AIDS、腎臟病、病態肥胖及長期使用 Aspirin 治療的兒童。自 2010 年起，有越來越多國家將病態肥胖列入。30 個歐洲國家對於兒童和青少年接種流感疫苗建議的調查仍有 21 個國家未建議。孕婦自 2008 年起，有越來越多國家建議孕婦應該接種流感疫苗，且從建議第 2-3 孕程接種轉向全孕程都可接種。歐洲國家大部分國家都建議醫事人員應該接種流感疫苗。歐盟老人流感疫苗接種率目標 75%，20 個國家中，只有 4 個國家達到。2008-2009 年平均接種率約 51%，但 2014-2015 年下滑至 42.5%。學齡前幼兒接種率（40-60%）比台灣（32%）高，5-11 歲約 70-80%，與台灣（70%）相當。慢性病患接種率 30-80%。醫事人員接種率，羅馬尼亞及荷蘭較高，其餘國家都偏低。





在 2013 年愛爾蘭居民 (≥ 18 歲) 全國性調查，以電腦抽出 1,770 名受訪者，進行電話訪問，調查高風險族群及醫護人員流感疫苗及肺炎鏈球菌低接種率的因素，了解一般醫師在疫苗接種建議上的角色，不願意接種疫苗的主要原因為不認為自己有風險，若醫師建議或接種疫苗是免費的，則高風險族群更願意去接種疫苗。

在歐洲國家老人流感疫苗接種率，已經持續 7 個流感季沒有提升，甚至下滑，無法達到歐盟 2014-2015 的 75% 標準；在醫事人員及慢性病患，只有半數國家偵測醫事人員接種率，有 1/3 國家偵測慢性病患接種率，接種率屬中、低狀況，且連續 7 年都沒有增加趨勢；在孕婦只有 1/3 國家偵測，僅英國接種率中等，其他國家都很低；在兒童的接種率上僅英國中等，其他國家都還很低。另外醫護人員的接種率太低是一個重要的問題，如果連疫苗的提供者都不相信疫苗，則如何對病患做出接種建議？因此各國應該強化與執行各類族群的接種率監測，且應建立各類對象接種率的比較，建立疫苗成本效益分析的科學實證，將更好的疫苗提供給每個人。

沒有風險，就沒有安全。關鍵是在於教育民眾使其了解，有利的措施（包括疫苗）都存在一定的風險，但是必須確定利要大於弊。因此溝通的重點包括：

1. 建立有效溝通平台，可進行雙向溝通，透過網路傳布健康訊息。
2. 確認關鍵人物（如醫護人員）能活躍的出現於媒體或公眾注意的地方。
3. 尋找網紅，作為相關宣導大使。

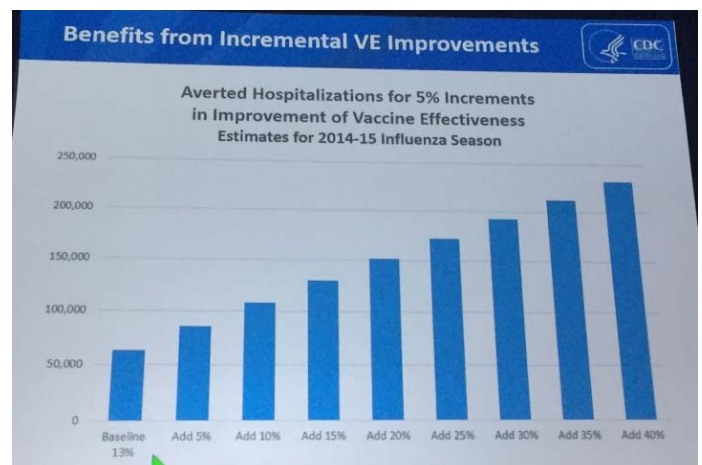
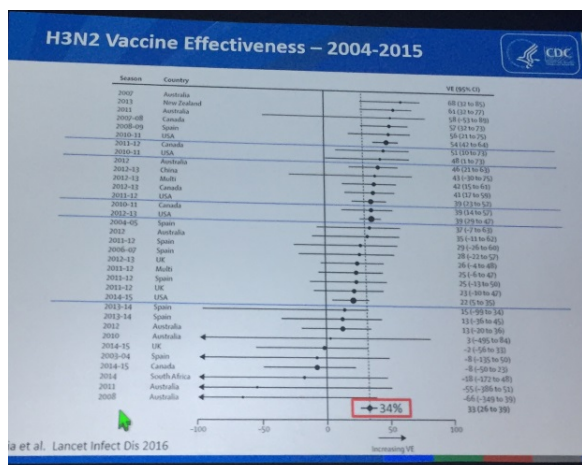
4. 快速澄清錯誤訊息。
5. 舉成功案例並分享之。

另外也需要搭配提升接種可近性措施，包括：

1. 擴大合約點。
2. 主動訪視未給予回應的高危險族群。

六、Improving on Influenza Vaccines: Managing the Challenges of Vaccine Mismatch

疫苗株與環境流行是否吻合，將影響疫苗的效益，然而，即使疫苗株不吻合，疫苗仍然能帶給接種者一些保護力。



2004 起至 2015 年，H3N2 疫苗株的效益，平均 34%，隨時間以及地點都不一樣。隨著疫苗效益的增加，可以相對的減少住院數，如疫苗效益增加 10%，減少的住院數可從 5 萬增加到 10 萬。

WHO 對於增強流感疫苗效益的建議包括：1) 2014-2015 年改善疫苗選株，2) 2015 年在香港開會得到的建議為：強化病毒監測、改善候選疫苗株的建立、強調後來異軍突起的病毒株、確定病毒演化分析的角色、發展更廣效、長效的疫苗，3) 強調法規。流感病毒不斷變化的性質需要持續的全球監測和頻繁改變流感疫苗。自 1952 年以來，世衛組織全球流感監測和應對系統 (GISRS) 一直在

監測流感病毒的演變，並已用於檢測，風險評估和應對可能引起大流行的流感病毒出現的全球性平台。自 1973 年以來，WHO 建議流感疫苗病毒正式列入 GISRS 監控。自 1998 年以來，每年兩次分別於二月和九月對北半球和南半球的流感季節提出建議。

新的疫苗改善合作-SIVI：

1. 季節性流感疫苗改善 (SIVI) 倡議：由 BARDA、FDA、NIH 及 CDC 共同合作，向美國衛生國務卿負責，季節型流感疫苗的改善也是大流行準備的一部分。
2. 五年計畫：(1) Virus Characterization and CVV (候選疫苗病毒) 發展 (2) 試劑準備 Reagent Preparation (3) 生產 Production (4) 配送與接種 Distribution and Vaccination。

提高疫苗病毒的選擇需要改進的領域：

- (一)病毒監測與病毒篩選：增加送檢的樣本數量、即時性和代表性；加強國家流感監測能力和能量及建立合作協議；如何提高效率精簡收集病毒株方式。擴大 GISRS 從 2015 年 7 月至 2016 年 8 月從 38 個國家增加到 81 個國家，成長 50%，有阿富汗，阿爾巴尼亞，亞美尼亞，保加利亞，格魯吉亞，黎巴嫩，黑山，摩洛哥和菲律賓等國家加入。
- (二)病毒鑑定：提升病毒進化預測能力，結合疾病預防控制中心、世界衛生組織和合作者共同開發的模型，全基因組的下一代測序數據。
- (三)候選疫苗病毒 (CVV)：努力提高產蛋菌株的可用性，利用血凝素抑制試驗 (HI 試驗) 及抗原檢測鑑定，以確定疫苗產生免疫反應是否足夠。
- (四)疫苗效價分析：進行效力測定試劑的開發，並支持新效價測定的開發和許可程序。
- (五)溝通和協調：增加世衛組織合作中心、ERLS 之間溝通，與疫苗生產商，相關的實驗室和監管機構合作，以促進疫苗的生產和許可程序，支持新的監測和疫苗技術的研究。
- (六)分配與接種：建立疫苗使用監測，提高疫苗接種率。
- (七)新疫苗：開發保護性更廣泛、效果更持久的疫苗。

肆、心得與建議

透過本次會議能更深入瞭解流感大流行歷史演變過程，從過去的每一次大流行的經驗中，分析流感病毒的演變不足的地方，由於對未來發生的流感大流行制定應對防範計畫較為困難，部分原因在於下次大流行的明確的症狀、流行病學特徵、病毒學特性和疾病傳播模式等許多重要特徵均是未知數。在這種情況下，制定公共衛生計畫和評估所需的資源時，需要用有關流感流行病學的假設來幫助作出決策，根據以往疫情經驗和發生的情況所作的推測，將有助於推動應對大流行的各項準備工作，並用來確定可能有效的防治措施，讓整備工作更完整。

另外在會議中對於 WHO 在季節性流感及流感大流行的病毒監測、預防、抗病毒藥劑治療及疫苗開發等的運作方式以及建議，做了很詳細的說明，也強調國際合作及公平互惠的重要性，如何將流感準備從檢測、評估、應答轉移到更上游：從源頭預防傳染病的發生，從而更好地保護動物和人類健康，保護環境，是未來要朝向的目標。在流感疫苗接種政策部分，雖然世界衛生組織已呼籲多年，在歐洲國家仍有部分族群流感疫苗接種率仍不理想，如老人、慢性病患、醫護人員等接種率皆未達歐盟 75% 的建議目標，另外也提到醫護人員未接種疫苗會間接影響民眾接種意願，臨床醫師也扮演重要的角色，因此在推動接種政策上應強化與執行各類族群的接種率監測，用同樣的方法進行年度人口調查以建立各類對象接種率的比較，增加接種可近性如擴大合約點、主動訪視未接種的高危險族群，建立有效溝通平台，並進行雙向溝通，隨時澄清錯誤訊息，確認關鍵人物作為宣導大使等。

本次會議課程除全體性的共同會議，安排 3-4 位專家學者進行專題演講外，另依病毒學與致病機轉、臨床科學、公共衛生等 3 個主題分類，在同時段安排專題演講或研究發表口頭報告等，內容相當豐富且多元化，建議在經費許可的情況下，未來可增派人員持續參加此會議，建議由與流感及流感大流行病毒研究、監測、防治及整備等領域相關之同仁皆能一同參與，可於同時段分別參與不同主題會議，以取得更多元的資訊，拓展視野。

附錄1、會議照片



報到



會議會場



海報展示區

Direct and Indirect Benefits of Pediatric Influenza Immunization on US Hospitalizations

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Introduction

Between 2006–2011, the US Advisory Committee of Immunization Practices (ACIP) gradually broadened its recommendations for annual influenza vaccination to include healthy children from 6–23 mo, 24–59 months, 5 to 18 years, and eventually everyone over the age of 6 months.

We analyzed the population-level effects of this policy on influenza-related hospitalizations.

Results

Fig 1: Trends in pediatric (<5 yrs) influenza vaccine uptake across US states

Fig 2: Age-stratified hospitalization time series and disease burden model for Wisconsin

Age group	Flu	Respiratory	Cardio-respiratory
0-5 yrs	-0.42**	-0.47**	-0.52**
6-17 yrs	-0.28**	-0.34**	-0.40**
18-49 yrs	-0.12**	-0.16**	-0.20**
50-64 yrs	-0.07**	-0.09**	-0.11**
65-79 yrs	-0.04**	-0.05**	-0.06**
80-94 yrs	-0.02**	-0.03**	-0.04**
≥ 95 yrs	-0.01**	-0.01**	-0.02**

***P<0.0001, **P<0.001, *P<0.05

Fig 4: Transmission-model predictions of direct and indirect reductions in flu burden

Conclusions

- Pediatric vaccine coverage increased from ~0% to ~52% between 1999–2012 in the US and remained stable among seniors
- Important vaccine heterogeneity between states
- Solid statistical evidence of direct vaccine effects in children ≤ 19 yrs
 - consistent across disease outcomes
 - analysis stratified by season weaker
- Weak statistical evidence of indirect effects
- Ecological trends studies prone to biases; influenza burden difficult to measure
- Mathematical models indicate modest herd immunity benefits expected at current vaccination levels
- Indirect benefits may clarify with increasing vaccine uptake

Methods

- Age-specific vaccination rates based on the National Immunization Survey (NIS) and Behavioral Risk Factor Surveillance System (BRFSS).
- Weekly hospitalizations for pneumonia and influenza and respiratory and circulatory causes from the State Inpatient Databases of the Agency for Health Care Research & Quality, 1999–2012.
- Influenza burden models with influenza and RSV proxies and splines for time & seasonal trends.
- Vaccine benefits evaluated by modeling seasonal influenza-associated hospitalization rates as a function of vaccine coverage and dominant influenza subtype

Acknowledgments

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Authors declare no conflicts of interest related to this study.

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MULTINATIONAL INFLUENZA SEASONAL MORTALITY STUDY (MISMS)
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Influenza incidence and associated cost among young program : implications for Thailand's influenza vaccination

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Background

- Since 2009, through the national vaccine program the Government of Thailand has funded the seasonal influenza vaccine for 11 million high-risk persons including:
 - Persons aged ≥ 65 years
 - Persons with chronic underlying medical conditions
 - Pregnant women after the first trimester
 - Children aged 6-35 months
- Each year, approximately 3.1 million doses of trivalent inactivated influenza vaccine (TIV) are purchased and administered free of charge, on the first come-first served basis, to a fraction of the 11 million high-risk population.
- However, healthy children 6-35 months been considered a lower priority than other groups, from provincial health care providers' perspective.
- One reason could be from lacking of information on disease burden in this group.
- Therefore, we prospectively followed a cohort of children 6-35 months to evaluate and compare the rate of influenza infection and cost of illness between healthy children and children with underlying medical conditions.

Methods

- We enrolled healthy and high-risk (any of the following: prematurity, congenital heart defects, chronic lung disease, neuromuscular disease) children aged 0-35 months, matched on age and time of enrollment.
- At Queen Sirikit National Institute of Child Health (QSNICH) in Bangkok, Thailand, caregivers were called weekly for 2 years to identify episodes of acute respiratory illness (ARI); ≥ 2 of the following: fever, cough, sore throat or rhinorrhea.
- Children with ARI were tested for influenza by RT-PCR.
- Illnesses were categorized as severe or mild depending on whether they required hospitalization or not.
- We collected direct and indirect costs associated with the illness, including costs subsidized by the healthcare system.
- Population-averaged Poisson models are used to compare incidence by risk group, adjusting for influenza vaccination and recent history of influenza like illness in the household.
- Differences in cost, adjusted by distance from residence to the QSNICH, were analyzed by quantile regression.

Results

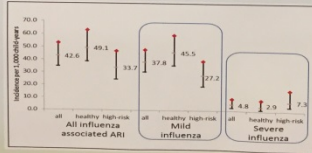
Between August 2011 and September 2015, 490 high-risk and 659 healthy children were enrolled (Table 1)

Table 1 Diseases in the high risk children

High risk conditions	No.	%
1 disease	313	63.9
► Prematurity	183	58.5
► Heart diseases	50	16.0
► Respiratory diseases	29	9.3
► Neurologic diseases and developmental delay	28	8.9
► Others (hemoglobinopathy, metabolic, kidney, liver diseases, HIV)	23	7.3
2 diseases	103	21.0
3 diseases or more	74	15.1
Total	490	100

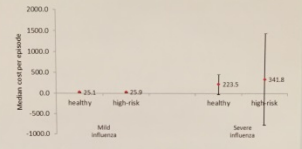
- There were 3,108 ARI episodes with 164 PCR-confirmed influenza over 1,980 child-years.
- The adjusted incidence are 42.6 per 1000 child-years; 49.1 among healthy vs. 33.7 among high-risk children; $p=0.04$.
- Incidence of mild influenza-associated ARI was significantly higher among the healthy children (45.5 per 1000 child-years) than the high-risk children (27.2 per 1000 child-years; $p\leq 0.01$).
- The incidence of severe influenza-associated ARI was lower among healthy (2.9 per 1000 child-years) than high-risk children (7.3 per 1000 child-years, $p=0.15$) but the difference was not statistically significant

Figure 1 Influenza incidence per 1,000 child-years compared between healthy and high-risk children



- The median cost per influenza episode for mild illness was \$25.1 among healthy children and \$25.9 among high-risk children and it did not differ significantly ($p=0.89$).
- The median cost for severe illness was \$223.5 among healthy children and \$341.8 among high-risk children ($p=0.70$).

Figure 2 Influenza cost/episode compared between healthy and high-risk children



Conclusion

- Although high-risk children had a higher, non-significant incidence of severe ARI associated with influenza, healthy children had a statistically significant higher incidence of mild influenza-associated ARI.
- The costs for influenza-associated ARI were similar between healthy children and high-risk children, supporting inclusion of healthy children 6-35 months among target groups for influenza vaccination.

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Knowledge, Attitudes and Practices Related to Seasonal Influenza Vaccine Among Pregnant Women in Vietnam, 2015

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Population: 94 million (July 2015)

Birth rate: 15.96 births/1,000 population (2015)

2015 births: 1,500,240

Good knowledge: defined as ≥ 14 of 21 knowledge questions correct

Positive attitude: defined as ≥ 24 of 36 attitude questions correct

Good practice: defined as having received influenza vaccine during this pregnancy.

Factors associated with vaccination were examined by using logistic regression models.

Introduction

Pregnant women are at higher risk of severe influenza, but influenza vaccination in Vietnam is self-pay and less than 5% of Vietnamese pregnant women receive influenza vaccine. To understand barriers and how to increase influenza vaccine use among pregnant women, we administered a knowledge, attitudes and practices (KAP) survey to this target group.

Methods

During October 2014 - August 2015, we conducted a survey from a convenience sample of pregnant women attending antenatal clinics at four hospitals located in the city with the highest influenza vaccine use in each of the four regions of Vietnam. Trained interviewers conducted face-to-face interviews. The questionnaire was similar to validated ones used in other countries. We defined good knowledge, positive attitude and good practice (see box below left)

Results

- 1,254 pregnant women were enrolled, among whom 807 (64%) demonstrated good knowledge; 1,128 (90%) had a positive attitude, but only 93 (7%) reported influenza vaccination during this pregnancy.
- Most (58%) women agreed influenza vaccine is safe during pregnancy and only 12% disagreed; 71% agreed vaccination effectively prevents influenza for their unborn child and 82% for themselves and less than 1% disagreed with either.
- Only 191 (15%) of 1,254 pregnant women received a health care provider (HCP) recommendation for influenza vaccination.
- A HCP recommendation was significantly associated with vaccination (OR: 72; 95% CI: 37-139).

Conclusions

- The majority of pregnant women at hospital antenatal clinics in Vietnam have good knowledge and attitude towards influenza vaccination during pregnancy.
- Most pregnant women trust the advice of their physicians and believe influenza vaccination during pregnancy is safe and effective for both mother and fetus, but only a minority of women had their physicians recommend influenza vaccination.
- A minority of health care providers recommended influenza vaccination to pregnant women suggesting health care providers may be a barrier to influenza vaccination in pregnant women in Vietnam.

Recommendation

- Should provide more effective education on influenza vaccination during pregnancy routinely to health care providers and to pregnant women during antenatal visits.

Results

- Multivariable analysis indicated that the immunization rate was significantly associated with higher education (OR: 1.6; 95% CI: 1.2-2.3) and good knowledge (OR: 1.9; 95% CI: 1.1-3.0). Immunization rate was not associated with parity, age or hospital.

Results

- If their physician were to recommend getting influenza vaccine during pregnancy, 87% of pregnant women said they would.
- However, if their relatives recommended it, only 39% of pregnant women said they would.

Category	Yes (%)	No (%)
Heard about influenza vaccine	54%	46%
Received HCP recommendation for influenza vaccination	20%	80%
Vaccinated this pregnancy	43%	57%

82 of 93 vaccinated pregnant women received a recommendation for influenza vaccination from a HCP

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The Options IX for the Control of Influenza, Chicago, 24 - 28 August 2016

Do adults with influenza-like illness have the same healthcare seeking behavior in the summer and winter influenza epidemics?

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Background
 Influenza is one of most contagious respiratory infection diseases, and associated with high morbidity and mortality. Influenza epidemics occur predominantly during winter months in temperate regions. However, in the tropics and subtropics, seasonal influenza virus transmission continues around the year. No studies have investigated differences between annual winter and summer epidemics in subtropical regions, in terms of healthcare seeking behavior of seeking medical consultation and self-medication amongst adults with influenza-like illness (ILI).

Methods
 Two rounds household telephone surveys were conducted during July-August 2014 and March-April 2015, one month after summer and winter influenza peaks in the subtropical city Hong Kong. Households were contacted by random digital dialing of landline telephone numbers but the participants might be different between two surveys. Healthcare seeking behaviors of seeking medical care and self-medication by over-the-counter drugs due to ILI were using the next birthday method from each household. ILI over who was selected by using the next birthday method from one adult aged 18 years or over, was defined as at least two of the symptoms of fever (>37.8°C), cough, sore throat, headache, or myalgia. The probabilities of seeking medical care (private and/or public emergency department, clinics for western medicine, Traditional Chinese Medicine therapy or hospitalization) and self-medication related to self-reported ILI were compared between the winter and summer epidemics by Chi-square tests. Logistic regression models were used to explore demographic factors, symptoms and chronic conditions associated with medical care seeking behaviors and self-medication, respectively.

Results
 Among 516 and 539 adult respondents in the summer and winter surveys, 22.6% and 38.0% reported ILI symptoms, and 40.5% and 46.6% of them sought medical care, respectively. There was no significant difference in healthcare seeking behavior between the summer and winter epidemics, except a higher proportion of self-medication in winter. Women, adults with diabetes and the symptoms of cough, shortness of breath, runny nose were more likely to seek medical consultations for ILI symptoms. Those older than 60 years were less likely to take self-medication, whereas regular smokers and those with the symptom of sore throat were more likely to do so.

Conclusions
 Healthcare seeking behavior of the general public was not significantly different between these two epidemics. However, influenza was associated with increased healthcare utilization in winter, both winter and summer epidemics in Hong Kong. Our findings highlight the need for increasing influenza surveillance sites in sentinel private clinics, which could provide more reliable and real-time surveillance information.

The cost-effectiveness of quadrivalent seasonal influenza vaccines in England
 Dom Thornton¹, Edwin van Leeuwen¹, Mary Ramsay¹, Richard Pebody¹ and Marc Baguelin^{1,2}
¹ Public Health England, ² London School of Hygiene and Tropical Medicine

INTRODUCTION
 Influenza is a major infectious disease in England. Quadrivalent A and B strains are recommended for most adult influenza vaccine. Children, young adults and the elderly are also recommended to receive influenza vaccine. The current influenza vaccine programme in England is based on a quadrivalent inactivated influenza vaccine (QIV) containing two A and two B strains. The current programme is based on a quadrivalent inactivated influenza vaccine (QIV) containing two A and two B strains. The current programme is based on a quadrivalent inactivated influenza vaccine (QIV) containing two A and two B strains.

METHODS
 We used the RIVM-ModEpiSim in package 'Epi' to simulate four different vaccination strategies: Programme 1: QIV for high-risk, QIV for low-risk; Programme 2: QIV for high-risk, QIV for low-risk; Programme 3: QIV for high-risk, QIV for low-risk; Programme 4: QIV for high-risk, QIV for low-risk.

RESULTS
 The estimated burden of influenza in England is high in the winter season. The current programme is based on a quadrivalent inactivated influenza vaccine (QIV) containing two A and two B strains. The current programme is based on a quadrivalent inactivated influenza vaccine (QIV) containing two A and two B strains.

DISCUSSION
 Our model demonstrates that the introduction of the QIV to the current programme is an effective method of reducing the burden of influenza in England. The current programme is based on a quadrivalent inactivated influenza vaccine (QIV) containing two A and two B strains.

Dropnet precautions are adequate for protection of healthcare workers managing mechanically ventilated patients with severe influenza
 RK Virk^{1,2,3}, S Balasingam^{1,2}, DA Wang^{1,2}, SQ Howe^{1,2}, OM Sessions^{1,2}, J Phua^{1,2,3}, E Koay^{1,2,3}, PA Tambyah^{1,2,3}
¹ National University of Singapore, ² Lee Kong Chian School of Medicine, ³ National University Health System, Singapore

Background and Objectives:
 Influenza is one of the most important public health threats worldwide. The disease is highly contagious and is characterised by seasonal epidemics and pandemics upon introduction of new subtypes of the virus. Despite the enormous burden of the disease, there are surprisingly few data on the transmission of influenza virus to healthcare workers (HCWs) in the intensive care unit (ICU) setting where the most critically ill patients are cared for. In the present study, we report on the transmission of influenza in patients admitted to ICU to the HCWs using droplet precautions.

Methods
 Six ICU patients (two on ECMO; two continuously mechanically ventilated; one intermittently ventilated and one not ventilated) were identified with laboratory-confirmed influenza infection by polymerase chain reaction (PCR) of a routine clinical sample. All attending HCWs (including physicians, nurses, allied health personnel and cleaners) were invited to take part in the study. HCWs who gave informed consent provided the following samples between the first day (day 0) the ICU patient was confirmed with influenza until day 10 unless the patient was discharged earlier: Day 0, 1, 2, 5 and 10 nasal swabs for virus detection by PCR; Day 0, 1, 2 and 5 hand swabs for virus detection by PCR.

Results
 100 HCWs attending to 6 ventilated patients in ICU were recruited. Serology: 1: Haemagglutination inhibition data

Subjects	Median (IQR) HI titre/50 µl
Nurses	20 (10 - 40)
Non Nurses	30 (10 - 80)

Two HCWs were found to have seroconverted against H2N2 virus, which was not the same influenza subtype as the index ICU patient (pandemic H1N1 2009). This suggests that they might have had mild influenza infection but did not contract it from the ICU as there was no other influenza admission concurrently at that time.


Conclusions
 Environmental swabbing was also performed on sites in the room housing the ICU patient on days 0, 1 and 2. These sites included the bedside table, the inside door knob, the stethoscope, call bell, bedrail and three suctioned catheters.

Novel Influenza Infection and Pregnancy: Development of a Research Network for Pandemic Studies

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BACKGROUND

- An influenza pandemic requires a rapid and integrated approach to urgently address important public health questions.
- Pregnant women, because of anatomic, hormonal, immunologic, and cardiovascular changes, are at high risk for complications of seasonal and pandemic influenza, including severe illness and death.¹⁻⁴
- Hospitalization rates among pregnant women with confirmed 2009 pandemic influenza A H1N1 (A/1918) pdm09 infection were four times those of the general population.^{5,6}
- A/1918 pdm09 infection resulted in greater morbidity and mortality among pregnant women than non-pregnant women of reproductive age.^{1,3,6}
- Compared to non-pregnant women, pregnant women were also at increased risk of influenza-associated death during previous influenza pandemics.^{7,8}




METHODS

- CDC, in cooperation with ARI Associates, set out to develop a research infrastructure to enable rapid initiation of epidemiologic studies during an influenza pandemic.
- As part of a larger research platform, a key component was to establish a network of United States sites to conduct observational studies and optimize data collection on pregnant women during an influenza pandemic.
- The objective of the pregnancy domain of the research platform was to address 4 main objectives in pregnant and postpartum women:
 - To evaluate the effectiveness of pandemic vaccine in reducing illness and severity.
 - To evaluate the use and effectiveness of treatment with antivirals to reduce adverse clinical outcomes.
 - To describe clinical and epidemiologic characteristics of pandemic influenza.
 - To estimate the incidence of pandemic influenza illness and severe influenza-associated outcomes.



RESULTS

- During September 2014-September 2015, 7 large academic medical centers were selected as sites:
 - Baylor College of Medicine
 - Columbia University Medical Center
 - Kaiser Permanente Northern California
 - Kaiser Permanente Northwest
 - Magee-Women's Research Institute/University of Pittsburgh Medical Center
 - University of Alabama at Birmingham
 - University of Utah Health Sciences Center and Intermountain Medical Center




★ Pandemic Pregnancy Network Sites

- A protocol was developed with 2 main studies:
 - A study of medically-attended acute respiratory illness (MAARI) resulting in ambulatory care visits or hospitalizations during pregnancy and up to 8 weeks postpartum.
 - Women with acute respiratory illness (ARI)
 - Collection of respiratory specimens
 - A prospective, longitudinal cohort study of ~1000 pregnant women at 6 study sites, including data collection through 8 weeks postpartum.
 - Women <28 weeks gestation followed by active medical record surveillance with twice weekly text messaging e-mails
 - Nasal swab self-collection with ARI

CONCLUSIONS

This unique pre-positioned research network is poised to address important epidemiologic questions in pregnant and postpartum women during the next influenza pandemic.

- By having protocols and study materials approved and ready for use, we will optimize our ability to perform timely public health research.
- Data from these studies will be crucial to inform risk assessment and develop guidelines for prevention and treatment of novel influenza.



National Center for Immunization and Respiratory Diseases
Influenza Division



Influenza in pregnant women during 3 seasons, between 2013-2016 in Portugal

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Portuguese Influenza Reference Laboratory, Infectious Diseases Department, National Institute of Health Dr. Ricardo Jorge, LISBON, PORTUGAL

Background

Since the 2009 pandemic, pregnant women (PW) had been assumed as a high risk group for increased morbidity and mortality linked to influenza infection. From 2013 to 2016, the Portuguese Influenza Surveillance Programme integrates an obstetric unit network that reports influenza-like illness (ILI) cases and collects nasopharyngeal samples for influenza surveillance and diagnosis. The aim of this study was to characterize cases of influenza infection in pregnant women during 2013-2016 in Portugal.

Materials and Methods

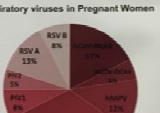
Between 2013 and 2016, ILI cases in PW were compared with ILI in non-pregnant women (NPW), aged between 15 and 44 years. In study period were reported 634 ILI cases (220 ILI in 2013/14, 152 in 2014/15 and 262 in 2015/16) of whom 140 in PW. Influenza and other respiratory viruses diagnosis were performed by multiplex RT-PCR. Data regarding symptoms, hospitalization, vaccination and antiviral treatment were recorded.

Results

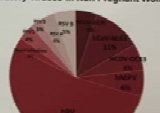
- Confirmed influenza cases in pregnant women (PW) and non-pregnant women aged 15-44 (NPW) between 2013 and 2016 seasons

Seasons	Influenza	A/H1N1pdm09		A/H3		B/Victoria		B/Yamagata	
		n/Total	%	%	%	%	%	%	%
2013/14	PW	30/52	57.7	80.0	20.0	0	0	0	0
	NPW	107/168	63.1	61.4	38.6	0	0	0	0
2014/15	PW	14/26	53.8	0	7.1	0	92.9	0	0
	NPW	80/126	63.5	5.0	31.3	0	63.8	0	0
2015/16	PW	32/71	45.1	96.9	3.1	0	0	0	0
	NPW	81/291	42.4	96.3	1.2	1.2	1.2	1.2	1.2

Respiratory viruses in Pregnant Women



Respiratory viruses in Non Pregnant Women



Conclusions

- PW must still be considered a high risk group for influenza and other respiratory viruses infection.
- This study highlights that influenza A/H1N1pdm09 and B/Yamagata presented a higher frequency of infection in PW compared to NPW that might be associated with increased risk for complications.
- Reinforcement of vaccination campaigns will be a challenge in influenza prevention, nevertheless, influenza vaccination is free and highly recommended in Portugal for PW risk group.

Antiviral effects of black raspberry (*Rubus coreanus*) seed and gallic acid

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¹Department of Biotechnology and Bioinformatics, Korea University, ²Department of Food and Nutrition, Chulung Women's University

ABSTRACT

Influenza is a serious public health concern worldwide as it causes significant morbidity and mortality. The advantages of drug-resistant virus strains require new approaches for the treatment of influenza. In this study, *Rubus coreanus* seed (RCSF) that is left over from the production of wine or juice was found to show antiviral activities against influenza type A and B viruses. Using thin-layer adsorption assay, viral replication was almost completely inhibited by simultaneous treatment with the RCSF extract of more than 1.0 μg/ml against RCSF1. One of the polyphenols derived from RCSF1, gallic acid (GA), identified by liquid chromatography-tandem mass spectrometry, showed inhibitory effects against both influenza type A and B viruses, albeit at relatively high concentrations. RCSF1 was found to hemagglutinate influenza viruses, which hemagglutination significantly inhibited virus particles. However, GA was found to only disrupt the viral particles by using transmission electron microscopy. In BALB/c mice infected with influenza virus, oral administration of RCSF1 significantly improved the survival rate and reduced the viral loads in the lungs. Our results demonstrate that RCSF1 and GA have potent and broad antiviral activity against influenza A and B type viruses and are promising sources of agents that target influenza.

Keywords: influenza virus, *Rubus coreanus*, black raspberry seed, antiviral activity, gallic acid

MATERIALS AND METHODS

RESULTS

CONCLUSION

RCSF1 was found to hemagglutinate virus, inhibited hemagglutination significantly and disrupted viral particles, whereas gallic acid, one of the polyphenols derived from RCSF1, also found to only disrupt the viral particles by using transmission electron microscopy.

RCSF1 and gallic acid show potent and broad antiviral activity against influenza A and B type viruses and are promising sources of agents that target viral particles.

The authors have no competing interests.

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The Epidemiological Characteristics of the Largest Epidemic of Avian Influenza Viruses in Taiwan, 2015

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ABSTRACT

The unexpected largest epidemic of avian influenza (AI) in history occurred in 2015 with the highest attack rate in pigs and economic loss in Taiwan. Both temporal and spatial characteristics of this epidemic were analyzed by host species. Phylogenetic and viral sequence analyses of all the early 10 Taiwan H5N2 clade 2.3.4.4 HPAIVs covering the three subtypes were analyzed. The causing agents included the three subtypes (H5N2, H5N1 and H5N3) of the 1997 clade 2.3.4.4 highly pathogenic AI viruses (HPAIVs) and one Taiwan endemic chicken H5N2 (Mexican-like) and one co-circulating avian influenza virus (AIV). However, co-circulation of mixed subtypes, with H5N2 clade 2.3.4.4 HPAIVs accompanied by the H5N1, H5N3 subtypes or old H5N2 viruses in the [A/Anhui/K229/2013 (H5N1)/H5N3] and [A/Taiwan/15/2015 (H5N2)] HPAIVs. Phylogenetic and sequence analyses of early 10 Taiwan H5N2 clade 2.3.4.4 HPAIVs revealed that the HPAIVs were more distant to southern Taiwan, very different from the wild birds flying route in the autumn, implying domestic spread of these viruses might occur after the impact of Japan as well as Taiwan influenza viruses isolated from poultry farmers with influenza-like illness is necessary to maintain the emergence of novel AIVs capable to infect humans.

INTRODUCTION

A virus of avian influenza (AI) in history occurred in 2015 with the highest attack rate in pigs and economic loss in Taiwan. Both temporal and spatial characteristics of this epidemic were analyzed by host species. Phylogenetic and viral sequence analyses of all the early 10 Taiwan H5N2 clade 2.3.4.4 HPAIVs covering the three subtypes were analyzed. The causing agents included the three subtypes (H5N2, H5N1 and H5N3) of the 1997 clade 2.3.4.4 highly pathogenic AI viruses (HPAIVs) and one Taiwan endemic chicken H5N2 (Mexican-like) and one co-circulating avian influenza virus (AIV). However, co-circulation of mixed subtypes, with H5N2 clade 2.3.4.4 HPAIVs accompanied by the H5N1, H5N3 subtypes or old H5N2 viruses in the [A/Anhui/K229/2013 (H5N1)/H5N3] and [A/Taiwan/15/2015 (H5N2)] HPAIVs. Phylogenetic and sequence analyses of early 10 Taiwan H5N2 clade 2.3.4.4 HPAIVs revealed that the HPAIVs were more distant to southern Taiwan, very different from the wild birds flying route in the autumn, implying domestic spread of these viruses might occur after the impact of Japan as well as Taiwan influenza viruses isolated from poultry farmers with influenza-like illness is necessary to maintain the emergence of novel AIVs capable to infect humans.

MATERIALS AND METHODS

A. Surveillance of Avian Influenza in Taiwan

B. Epidemiological Data Analysis

C. Viral Sequence and Phylogenetic Data Analysis

RESULTS

A. Serological Surveillance Data

B. Temporal Characteristics of the 2015 AI Epidemic in Taiwan

C. Spatial Characteristics of the 2015 AI Epidemic in Taiwan

D. Temporal relationship between global epidemiology of H5N2 clade 2.3.4.4 HPAIVs and Taiwan's H5N2 subtypes

DISCUSSION

This 2015 AI epidemic involved the highest numbers of outbreaks, largest areas, most diverse avian species, and multiple co-circulating subtypes of HPAIVs in Taiwan's history, thus being the greatest economic loss and human contact on public health. Temporal relationship of the subtypes of the H5N2 clade 2.3.4.4 viruses in Korea, Japan, and Taiwan in 2014 and those in Korea, Japan and Taiwan in January of 2015 clearly predicted the wild bird flyways, illustrating the urgent need for international collaboration on wild bird surveillance.

Options IX for the Control of Influenza, 24 – 28 August 2016, Chicago, USA

Effectiveness of seasonal influenza vaccine IIV3 in reducing influenza like illness and influenza related health seeking behavior among children in Suzhou, China, 2014-2015

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INTRODUCTION

In 2014-2015 influenza season, many children over 6 months to 6 years of age received the northern hemisphere trivalent inactivated influenza vaccine (IIV3) in Suzhou city. To estimate of vaccine effectiveness (VE) in reducing influenza like illness and influenza related health seeking behavior among children. We actively followed a cohort of children who with or without received influenza vaccine in this season.

METHODS

Study sites

This study was conducted in Suzhou, a developed city in eastern China. There were 10 communities from 4 counties in Suzhou being selected as the sites for our observational study (Figure 1).

Study subjects' enrollment and follow up

Children aged ≥6 months were enrolled from 15 kindergartens of 10 communities in the 4 districts or counties. Children <36 months who were too young to attend kindergartens were enrolled in vaccination clinics (Figure 2).

RESULTS

Table 1. Population profile of the study subjects

No. of enrollment	Vaccinated group		Control group		Total	P _{χ²}	
	N	%	N	%			
6-35	483	29.5	481	29.3	964	29.4	
Age (months) 36-48	457	27.9	496	30.3	953	29.1	
49-72	699	42.6	662	40.4	1361	41.5	
73-96	884	53.9	874	53.4	1758	53.6	
Gender	755	46.1	764	46.6	1519	46.4	
Female	111	6.8	100	6.2	211	6.5	
Male	1514	93.2	1509	93.8	3023	93.5	
Pre-maturity	Yes	18	1.1	27	1.7	45	1.4
Chronic disease	No	1519	98.9	1570	98.3	3189	98.6
Received IIV3 in 2014-2015	Yes	85	5.2	72	4.4	157	4.8
Medicine purchase	Yes	1554	94.8	1567	95.6	3121	95.2
Feeling way during outbreak	Artificial	259	16.1	204	12.6	463	14.4
Mixed	301	18.7	347	21.5	648	20.1	

Table 2. VE for IIV3 in reducing ILI, ILI and influenza related health seeking behaviors

ILI	Vaccinated group		Control group		VE (%)	95%CI
	No. of cases	Incidence rate (per 100 persons-months)	No. of cases	Incidence rate (per 100 persons-months)		
ILI	378	4.8	370	4.5	-8.9	-24.5, 8.8
Purchase of medicine by self	703	12.5	659	11	-12.7	-22.5, -3.7
Hospitalization	623	13.1	736	16.1	14.0	7.2, 20.4
Lab-confirmed influenza*	13	9.3	7	8.1	-19.6	-199.4, 52.3

Table 3. Median cost of health seeking behaviors due to ILI (USD\$)

Medicine purchase	Vaccinated group		Control group		Z _{test}	P
	No. of cases	Median cost	No. of cases	Median cost		
Medicine purchase	703	4.9 (3.3-8.1)	659	5.2 (3.3-8.1)	7.1	0.007
Clinical visit	623	32.5 (16.4-68.8)	736	26.8 (15.9-48.8)	5.2	0.023
Hospitalization	55	159.3 (8.0-227.6)	42	227.6 (97.4-606.5)	6.0	0.014

CONCLUSION

No significant preventive effect of IIV3 was found against lab-confirmed influenza and ILI from November 2014-August 2015, but IIV3 significantly reduced respiratory infection related clinical visits.

Vaccinated children cost less than controls when they had ILI-related health seeking behaviors, indicating a less severe illness.

It is important to estimate VE in future years with larger numbers of influenza-confirmed ILI cases and when there is a better match between the predominant circulating influenza strain and the vaccine strains.

附錄2、議程

Wednesday, 24 August 2016

- 5:00 pm - 5:15 pm Welcome from the ISIRV President
- 5:15 pm - 5:30 pm Welcome from Options Organizing Chair
- 5:30 pm - 6:30 pm Keynote Address
- 6:30 pm - 8:00 pm Welcome Reception in the Exhibit Hall

Thursday, 25 August 2016

- 8:30 am - 10:30 am Morning Plenary Session – [Public Health Focus](#)
- 10:30 am - 11:00 am Coffee Break in the Exhibit Hall
- 11:00 am - 12:30 pm Concurrent Oral Abstract Sessions
- 12:30 pm - 2:00 pm Sponsored Lunch Symposium
- 2:00 pm - 4:00 pm Concurrent Featured Symposia
- 4:00 pm - 4:30 pm Coffee Break in the Exhibit Hall
- 4:30 pm - 6:00 pm Concurrent Oral Abstract Sessions
- 6:00 pm - 7:30 pm Poster Session I with Presenters in Attendance

Friday, 26 August 2016

- 8:00 am - 10:00 am Morning Plenary Session – [Virology & Pathogenesis Focus](#)
- 10:00 am - 10:45 am ISIRV General Meeting
- 10:45 am - 11:15 am Coffee Break in the Exhibit Hall
- 11:15 am - 12:30 pm Concurrent Oral Abstract Sessions
- 12:30 pm - 2:00 pm Sponsored Lunch Symposium
- 2:00 pm - 4:00 pm Concurrent Featured Symposia
- 4:00 pm - 4:30 pm Coffee Break in the Exhibit Hall
- 4:30 pm - 6:00 pm Concurrent Oral Abstract Sessions
- 6:00 pm - 7:30 pm Poster Session II with Presenters in Attendance

Saturday, 27 August 2016

- 8:30 am – 10:30 am Morning Plenary Session – [Clinical Science Focus](#)
- 10:30 am - 11:00 am Coffee Break in the Exhibit Hall
- 11:00 am - 12:30 pm Concurrent Oral Abstract Sessions
- 12:30 pm - 2:00 pm Break
- 2:00 pm - 4:00 pm Concurrent Featured Symposia
- 3:30 pm – 4:00 pm Population Impact of a Pediatric Vaccination Policy
- 4:00 pm - 4:30 pm Coffee Break in the Exhibit Hall

4:30 pm - 6:00 pm Oral Abstract Session - [Virology & Pathogenesis Focus](#)

4:30 pm - 6:00 pm Public Health/Clinical Science **Pregnancy** Symposium

6:00 pm - 7:30 pm Poster Session III with Presenters in Attendance

8:30 pm - 11:30 pm Mystic Blue Boat Cruise - Offsite Event

Sunday, 28 August 2016

8:30 am - 10:30 am Concurrent Featured Symposia

Public Health Featured Symposia: Practical Issues in the Control of Influenza

10:30 am - 11:00 am Coffee Break

11:00 am - 12:30 pm Concurrent Oral Abstract Sessions

12:30 pm - 1:00 pm Break

1:00 pm - 3:00 pm Closing Plenary Session