

1:30 pm–2:30 pm SESSION III: Human Health Perspective: State of the Art

Moderators: A/Prof Yee Sin LEO - Singapore & Dr. Patrick Brennan - USA

Clinical and Epidemiological Descriptions of Human H5N1 Infection in Indonesia
Dr. Triono Soendoro - Indonesia

Pathogenesis of Human H5N1 Disease
Dr. JSM Peiris - Hong Kong

Pandemic Influenza: Antiviral treatment and Infection Control
Dr. Frederick G. Hayden – World Health Organization

2:30 pm–3:30 pm SESSION IV: Surveillance Activities

Moderators: Dr. Linda Lambert - USA & Dr. Remigio Olveda - Philippines

A Surveillance System for Early Detection of Highly Pathogenic H5N1 Avian Influenza in Migratory Birds in the United States and U.S.-Associated Pacific Islands
Dr. Christopher J. Brand - USA

Avian Influenza in Turkiye
Dr. Fethiye Coven - Turkiye

H5N1 Surveillance at the Human/Animal Interface
Dr. Michael L. Perdue – World Health Organization

3:30 pm–3:45 pm Coffee/Tea Break

3:45 pm – 5:00 pm SESSION V: Research and Development Activities

Moderators: Dr. Masato Tashiro - Japan & Dr. Bing ZENG - China

Development of H5N1 Influenza Vaccines in Japan
Dr. Masato Tashiro - Japan

Evaluation of Different Approaches for the Development of Vaccines Against Avian Influenza Viruses
Dr. Robert L. Atmar - USA

Generation and Update of Laboratory Diagnosis Systems for H5N1 Highly Pathogenic Avian Influenza
Dr. Takato Odagiri - Japan

Passive Immunoprophylaxis and Therapy with Humanized Monoclonal Antibody Specific for Influenza A H5 Hemagglutinin in Mice
Dr. Brendon J. Hanson - Singapore

Saturday, November 18th

Venue: Level 2 - Waterfront Ballroom

8:00 am–9:30 am Scientific Program and Closing Remarks

Moderator: A/Prof. REN Ee Chee - Singapore

Pandemic Preparedness and Response to Animal and Human Influenza in Indonesia

Dr. I Nyoman Kandun - Indonesia

Mitigation Strategies for Pandemic Influenza in the United States

Dr. Catherine A. Macken - USA

Possibility of Early Containment of Potential Influenza Pandemic

Dr. Hitoshi Oshitani - Japan

Closing Remarks and Meeting Summary – Drs. Sasazuki and Haase

9:30 am–10:00 am Coffee/Tea Break

PARTICIPANT WORKSHOPS – Breakout Rooms (all in Level 2): To be announced

Workshop #1 - Animal Influenza Surveillance

Workshop #2 - H5N1 Immunoassays

Workshop #3 - Influenza Sequencing, Bioinformatics, and Reagents

Workshop #4 - Seroepidemiology Protocol Development

Workshop #5 - Funding Opportunities/Grantsmanship

-Participants will choose one morning workshop and one afternoon workshop

-Each workshop will be repeated two times—once in the morning, once in the afternoon

10:00 am–12:30 pm Morning Workshops

12:30 pm–1:30 pm Buffet Lunch

1:30 pm–4:00 pm Afternoon Workshops

4:00 pm–5:00 pm Networking Session (Workshop participants and facilitators)
Light Refreshments Served

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第 1 1 回汎太平洋新興再興感染症国際会議 報告書

(The 11th International Conference on Emerging Infectious Diseases in the Pacific Rim)

開催日 : 平成 18 年 11 月 16 日 (木) ~18 日 (土)

開催場所 : Grand Copthorne Water Front Hotel

日米急性呼吸器感染症専門部会長
鈴木宏 (新潟大学大学院医歯学総合研究科)

本会議は鳥インフルエンザのパンデミックの脅威への取り組みとの副題による会議として行われた。参加者は、日本、米国、シンガポール、ベトナム、中国、インドネシア、タイ、ラオス、マレーシア、インド、モンゴール、トルコ等から総勢 149 名であった。なお、この会議後に米国側の主催による 5 つの部門に分かれてのワークショップが開かれた。

第 1 日目の会議概要

本会議に先立ってシンガポールの Biopolis からの 5 名の講演により、本組織の紹介を兼ねて、種々の活動が紹介された。

Guest Scientific speakers による講演で、本会議が始まった。Sugamura (日本) が炎症性腸疾患の OX40 シグナルとの関連について、次に Krause (米国) がインフルエンザ・パンデミックの歴史的考察について、自分の関わりも含め講演した。特にスペイン風邪からの教訓として、患者の回復期血清投与による死亡減少は、今後のパンデミック時のモノクローナル抗体も含む免疫療法への重要な情報となる可能性を指摘した。

第 2 日目の会議概要

Session I: Agricultural perspective

本会議の主題である鳥インフルエンザについて獣医学側からの視点として Overview and history of avian influenza を二人の講演が行われ、全体像の認識を確認した。

Webster (米国) により過去 250 年間にこれまで 10 回のインフルエンザ世界大流行 (パンデミック) があり、それと関連する動物 (特に鳥) インフルエンザの研究の歴史、現在の高病原性鳥インフルエンザ A/H5N1 の流行、世界的なウイルス系統の流れの概説があった。特に、パンデミックになる発生が水鳥からであり、自然宿主であることが確認された事や、Kida や Shortridge 等の研究から東南アジアがトリの市場を発端とするパンデミック発生を把握する疫学センターになることを論じた。

Kida (日本) はインフルエンザウイルスのエコロジーとして、カモでの抗原性維持機構を解析し、新型インフルエンザ発生機序として、豚が鳥と人とのインフルエンザを媒介する中間宿主的役割を果たしている可能性を解説した。パンデミック発生ウイルスとして H5N1 以外も視野に入れらるべきとの警鐘を鳴らし、将来のパンデミックに備えた多種類のタイプを網羅したバンクを確立した事を報告した。青海省を起源とする A/H5N1 (CladeII) がアフリカ、中東にまで短時間で広がったこと、日本での家禽での H5N2 発生状況について解説し、ユーラシア大陸・アラスカでの鳥インフルエンザサーベイランスの現状と重要性を強調し、今回の話題を独占した「サーベイランス、サーベイランス、サーベイランス」の言葉を残した。

Views from the field: specific topic for each country として、3カ国における状況が報告された。最初に香港から Guan は中国における H5N1 について論じ、特に青海湖の役割を解説し、ここで発生したウイルスが7ヶ月でシベリア、アフリカ、欧州へと伝播した事実を示した。中国南部の市場でのサーベイランスから H5N1 は家禽全般に浸淫している事が示され、現在の A/H5N1 は遺伝子型がベトナム・タイ系(Clade I)、青海省系(Clade II)、雲南亜種系(Clade II)、インドネシア系統 (Clade II) に分別され、2005 年より福建省で新しい系統のウイルスが出現し、2006 年には中国南部の検出株の 90%を占める主流株となり、今後世界的に広がっていく可能性を述べた。

Dung (ベトナム) はベトナムにおけるワクチン接種による H5N1 の制御の経験を報告した。2002 年にガチョウでの H5N1 の発生が起点となり鳥とヒトでの流行が発生し、対策とし4千万羽の鳥を殺傷処分した、それに加え、各戸を回って小規模農家にもワクチン接種を行い、2005 年には 33 省、7800 万羽の鶏に二回のワクチン接種と、接種後の血清学検査により 74%の鳥が防御に有効な抗体価を示し、鳥の発生報告はベトナム全土で激減したことを報告した。しかし、ワクチン接種の効果判断や中止する最適な目安がない問題も提起された。

Poovorawan (タイ) はタイで明らかになった猫、犬科への H5N1 の感染とその伝播経路を示し、対策として、タミフルを予防投与されてもこの伝播が見られ、有効性が見られなかったことが報告された。しかし、これらの動物からヒトへの感染は見られないが、モニターする必要性は高い事が指摘された。

Session II: The Animal-Human Interface

これまで大きな流行を示してきたカンボジア、ベトナムにおけるヒトと動物の感染伝播の関連性について報告された。

Vong (カンボジア) がカンボジアでの A/H5N1 調査 (60%以上の家禽の感染と 100%が死亡した場合に施行) として発生周囲の動物及び接触した人を検討し、人の患者は感染鳥の 400メートル以内に発生し、患者発生があった村民の抗体陽転者はいなかったとした。しかし、重傷例の把握だけで全体像は不明なままであり、広範囲な血清疫学の必要性も指摘された。

Katz (米国) は A/H5N1 の血清抗体価の測定方法と問題点として、中和法 (Microneutralization test) が現在最も信頼性があり、血球凝集素抑制試験(Hemagglutinin Inhibition Assay)には馬血球が適しているとした。1997 年の香港での流行で無症候性抗体陽性者が見られたが、2003 年以降のタイ、韓国、カンボジアでの A/H5N1 ウイルスは強毒化しており無症候性陽性者が少なかったが、鳥と接触する仕事の人々における鳥インフルエンザウイルス感染のリスク、頻度を早急に研究すべきとした。

Nguyen (ベトナム) はベトナムの食、住文化と H5N1 流行との関連を論じた。多くの患者は農民であり、発症している家禽との接触、発生地域の住民、家禽の生の血液摂取、患者との接触などが見られ、これらのリスク因子の解析を基にした戦略が重要であることが指摘された。

Session III: Human Health Perspective; State of the Art

鳥インフルエンザの人感染に関する病態・病因と治療に関してのセッションで、Soendoro (インドネシア) がインドネシアにおけるヒトにおける臨床的、疫学的状況を示した。2005 年 7 月から 2006 年 10 月までの間 69 人の A/H5N1 の感染があり、約 40%が小児で 90%以上

が咳と呼吸困難、主要な検査所見として白血球減少と血小板減少が見られ、75.4%と高い致命率を示した。分離されたウイルスは全て Clade II-subclade I に属し、鳥由来で 73%がアマンタジン耐性であった。

Peiris (香港) はヒトの A/H5N1 感染した際の病態生理とし、急速に進行するウイルス性肺炎は免疫の過剰反応による ARDS が本態であり、TH1, TH2, TNF α などのサイトカインがウイルス感染により誘導され生じるとした。現在流行のウイルスはまだヒト-ヒト感染が容易に起こっていないが、今後伝播しやすいように変異し、パンデミックになる脅威は高まっている事も指摘した。

Hayden (WHO) は抗ウイルス剤によるパンデミックへの対策を論じ、有効な抗ウイルス剤の現状と今後期待できる新薬について発表し、現在経口投与の薬剤(ザナミビル)が静注や筋注が可能となり、重症患者への投与が容易になること、その他数種類の作用機序の異なる新薬が臨床治験に入っていることを述べた。有効とされるノイラミニダーゼ阻害剤による H5N1 の治療において、投与量と期間はまだ不確実であり耐性株発生があるなど、東南アジアにおける臨床試行ネット網確立が急務であるとした。

Session IV: Surveillance Activities

鳥、人でのインフルエンザ・サーベイランス活動について、3人の講演が行われた。

Brand (米国) は米国と関連諸国における野鳥における A/H5N1 を含めた高病原性インフルエンザ・サーベイランスの重要性を強調し、北米、太平洋各国の渡りルートを含めた状況として、2006年に北米を中心とした調査では A/H5 や A/H7 は検出されなかったとした。

Coven (トルコ) は 2005年に起こったトルコにおける鳥インフルエンザを報告し、ウイルス学的には青海省由来のウイルスと思われ、最終的には 250万羽の鳥を殺傷処分し、流行を押しやることに成功し、これまで家禽、野鳥を含めた全国的サーベイランスを継続中であるが、2006年は A/H5 陽性例はなかったとした。

Perdue (WHO) は生きた動物を扱う市場の H5N1 流行への大きな役割が明確となり、ヒトと動物との関連性を検討するサーベイランスするサイトとして重要であることを繰り返し強調し、WHO を通じた各国の取り組み、特に感染リスクの高いライブ・マーケットの取り締まりが重要であることを述べた。

Session V: Research and Development Activities

パンデミック対策としてワクチン、診断法、治療法に関して4人の講演が行われた。

Tashiro (日本) は日本における H5N1 ワクチン製造の現状を示した。現在 Clade I 用のワクチンが臨床治験フェーズ 2 と 3 にあり、アルミニウム・アジュバント使用により、5 μ g/unit で HAI 法では 43%が、NT 法では 70%に 40 倍以上の抗体価上昇を認め反応は良好であり、15 μ g/unit の方が抗体価上昇は高い。しかし、実際には 5 μ g/unit の二回接種を選択し、パンデミックのための備蓄として A/H5N1 ワクチン 4 百万ドーズを来春までに準備し、現在 clade2 との交差反応の有無を検討しているとした。

Atmar (米国) でも H5N1 ワクチン製造の現状を示し、Clade I 株によるスプリットワクチンでは 90 μ g/unit でも抗体価上昇が不良で、現在小児や、ブースター効果も含め追跡中であるとした。

Odagiri (日本) は H5N1 の実験室診断法について触れ、ウイルスの変異があり、最適な診

断法を選択することは重要であり、HA 遺伝子をターゲットとした新しい PCR プライマーの開発、SyBr Green を用いた Real Time PCR、Loop-LAMP 法を用いた検出法を検討し、より感度、特異度を上げる方法を開発しているとした。

Hanson (シンガポール) は有効なワクチン、抗ウイルス剤に改善の余地がある現在、他の方法を検討する必要がある、その一つとして、H5N1 への HA 蛋白に対する中和抗体活性を持つモノクローナル抗体の予防、治療への応用が考えられ、A/H5 暴露後 3 日目までの投与でも有効である可能性が動物モデルで示されたと報告した。

Session VI: Scientific Program

パンデミック戦略と関連した 3 つの講演が行われた。

Kandun (インドネシア) により A/H5N1 に対するインドネシアの現状と政府の取り組みについて報告され、各省庁間の協力体制が弱いこと、貧困のため鳥を有償で (一羽=1.25 ドル) 買い取らないと殺傷処分が進まないこと、入院費を政府負担としたこと、一部の地域では迷信のため予防投与が難しかったこと、鳥のコントロールのためにワクチンが導入され、最後に制圧には国際機関の協力が重要であることを強調した。

Macken (米国) は米国におけるパンデミック流行時の伝播状況の数学モデルにより対策の影響を検討し、感染率 (Reproductive Rate-R0) が 1.7 程度であれば、十分な量の抗インフルエンザ使用が罹患数を減少させ、ワクチン接種はたとえ抗原性が完全に一致していても小児に重点的に接種すれば患者数を減らすことができるが、R0 が高い場合は旅行制限、学校閉鎖、抗インフルエンザ剤投与、ワクチン接種とさまざまな対策を組み合わせねば患者数は減らないことが予想されるとした。

Oshitani (日本) は、WHO の取り組みを述べ、抗ウイルス剤の広範囲な使用、ヒトの移動、社会活動の制限等の多様な方面の対処法があり、報告の遅れがその後の対策を遅らせ患者数を増加させるため、各地域で鳥インフルエンザ発生をすばやく発見し、対策をたてることが重要であるとした。

ポスター発表 8 題が会場で展示され、参加者からの議論が行われた。

Sasazuki と Haase より閉会の辞があり、会が専門家の知見を深め成功裏のうちに終了したことが宣言された。

Participant Workshops

本会議終了後、参加者の自由参加により、米国側の主催する 5 つのワークショップ瓦解際された。

Workshop #1 - Animal Influenza Surveillance

Workshop #2 - H5N1 Immunoassays

Workshop #3 - Influenza Sequencing, Bioinformatics, and Reagents

Workshop #4 - Seroepidemiology Protocol Development

Workshop #5 - Funding opportunities? grantsmanship

Agenda

US/Japan Cooperative Medical Science Meeting
11th Acute Respiratory Infections (ARI) Subcommittee
January 21- 23, 2007, Hotel Hankyu Expo Park, Osaka

January 21 (Sun)

15:00-18:00 Acute Respiratory Infection Subcommittee Meeting

January 22 (Mon)

Workshop 1. Drug-resistance of ARI pathogens

8:30-8:40 Opening Remarks

Dr. H Suzuki (Niigata University/Japan)

Dr. L Lambert (NIH/US)

8:40-10:40 Session 1. Current situation in US and Japan

Moderators: Dr. L Bakaletz & Dr. Y Arakawa

1. Dr. Kei Kasahara (Nara Medical School): Clonal dissemination of macrolide-resistant and penicillin-susceptible serotype 3 and penicillin-resistant Taiwan 19F-14 and 23F-15 *Streptococcus pneumoniae* isolates in Japan.
2. Dr. Kazuhiro Tateda (Toho University): Recent trends of antibiotic resistance of bacteria in respiratory tract infections: is Japan a Hot-Spot?
3. Dr. Kazunori Tomono (Osaka University): Update of the Japanese Guideline for Community-Acquired Pneumonia.
4. Dr. Williams Shafer (Emory University): Drug efflux pumps: contributions to bacterial resistance to antimicrobials and pathogenicity.

10:30-11:00 Coffee Break

11:00-12:30 Session 2. Current situation of Pediatric and ENT area in Japan

Moderators: Dr. J Weiser & Dr. K Tateda

5. Dr. Satoshi Iwata (Tokyo Medical Center): Drug-resistance in pediatric infectious diseases
6. Dr. Naruhiko Ishiwada (Chiba University): Acute respiratory tract infections caused by drug resistant bacteria in Japanese pediatric patients.

7. Dr. Muneki Hotomi (Wakayama Medical University): High prevalence of antimicrobial resistant pathogens in pediatric acute otitis media in Japan-How to suppress antibiotic resistance?

12:30-13:30 Lunch

13:30-15:30 Session 3. Current situation in Asian countries

Moderators: Dr. D Stephen & Dr. K Tomono

8. Mrs. Surang Dejsirilert (Thai NIH): Drug-resistance of ARI pathogens in Thailand,

9. Dr. Kamruddin Ahmed (Oita University): Drug-resistance of ARI pathogens in Turkey.

10. Dr. Hiroshi Watanabe (Kurume University): Prevalence of *Haemophilus influenzae* with resistant gene isolated from young children with acute lower respiratory tract infections in Nha Trang, Vietnam.

11. Dr. Reiko Saito (Niigata University): H3N1 amantadine resistance in Japan.

15:30-16:00 Coffee Break

Workshop 2 ARI and Pneumococcal vaccine

Moderators: Dr. M Apicella & Dr. H Watanabe

16:00-18:00

1. Dr. Kazuyoshi Kawakami (Tohoku University): Innate immune lymphocyte-mediated host defense to pneumococcal infection: an implication for pneumococcal vaccine.

2. Dr. David Stephan (US): Drug resistance of pneumococcal strains after introduction of pneumococcal conjugate vaccine.

3. Dr. Kazunori Oishi (Osaka University): Pneumococcal conjugate vaccine improves the reduced or impaired serum opsonic activity of HIV-infected adults.

4. Dr. Akitsugu Furumoto (Nagasaki University): Additive effects of pneumococcal polysaccharide vaccine in combination with influenza vaccine on acute exacerbation in patients with chronic lung diseases.

Reception 19:00~