The Interface of Non-communicable and Infectious Diseases:

Influenza, Pneumonia and Vaccination

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Outline

- Global demographic and social changes
- Obesity and Smoking
- Rise of non-communicable disease: COPD & DM
- Community acquired pneumonia (CAP) and NCDs
- Influenza infection and pneumonia
- Is influenza vaccine a pneumonia vaccine?

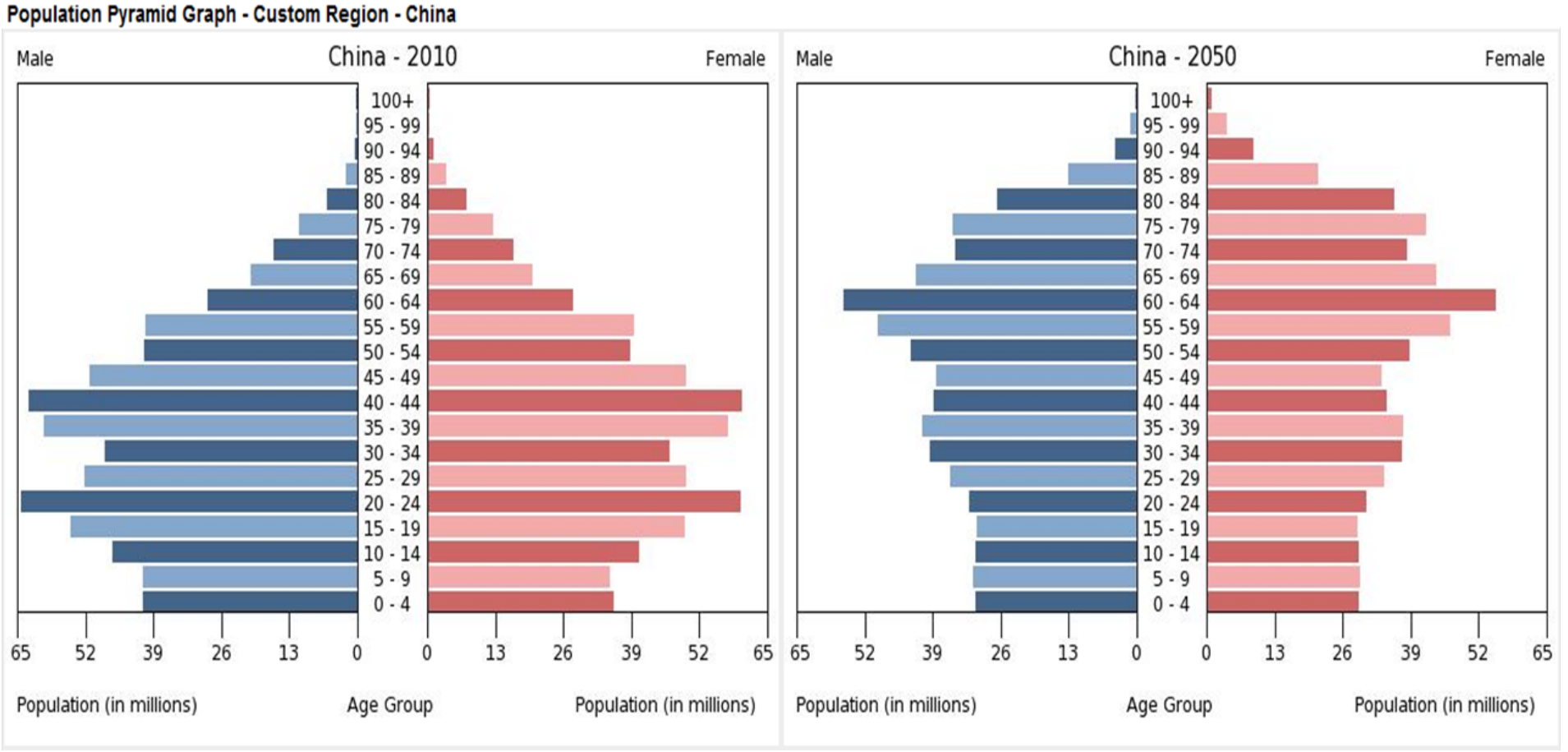
Demographic and Economic Transitions are Reshaping Global Public Health Priorities

- Aging population
- Urbanization

These powerful forces are contributing to..

- Sedentary lifestyles and dietary changes
- Exposure to airborne pollution
- Increased use of alcohol
- Stress and crowding
- Persistently high rates of tobacco use

Demographic Shift in China: 2010-2050



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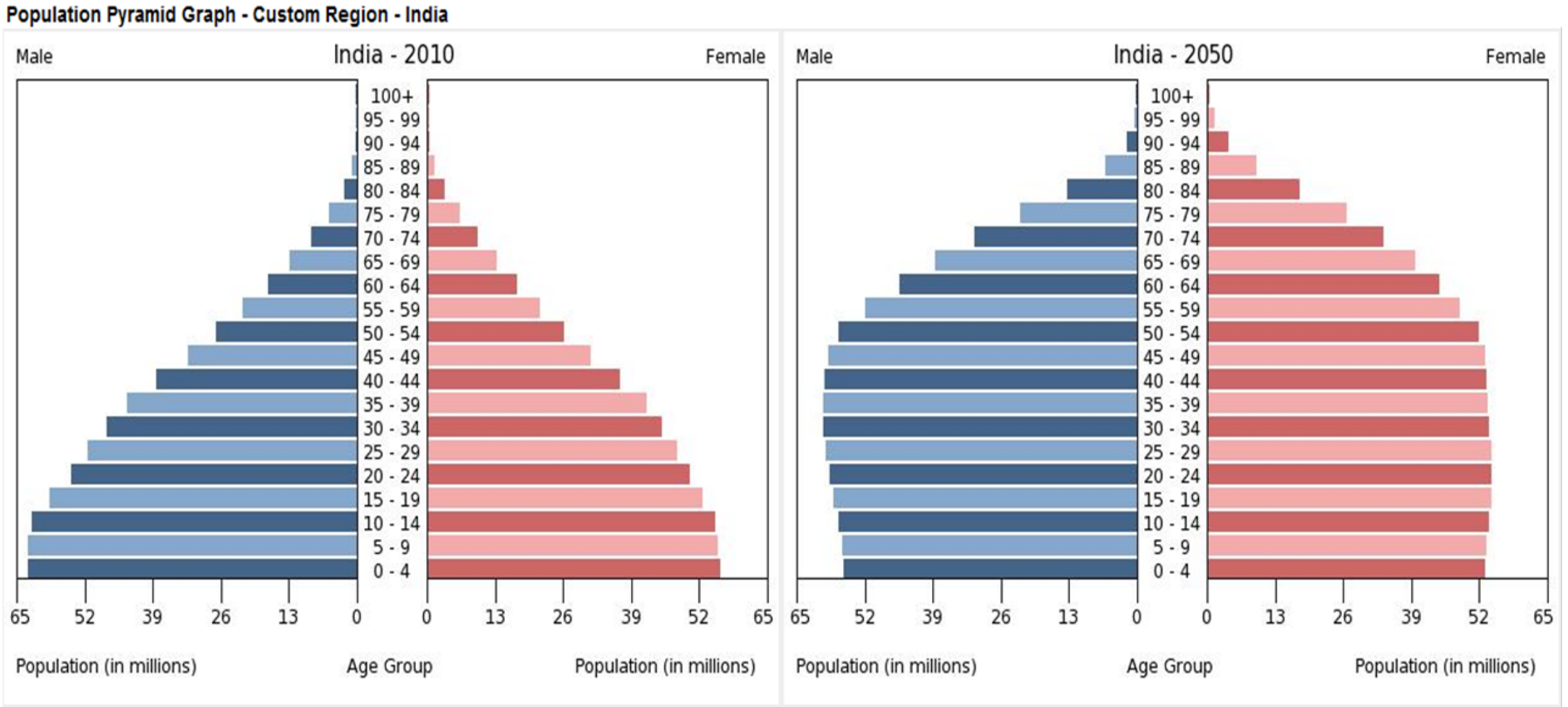
Demographic Shift in India: 2010-2050



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http://www.fdbetancor.com/2012/06/04/the-american-century/

Urbanization is Changing the Face of the Planet

- The urban population has grown from 746 million in 1950 to 3.9 billion in 2014

- By 2030, 9% of the world's population will be living in just 41 megacities
- Asia accounts for over half of the world's 29 megacities and is home to 53 per cent of the world's urban population
- Between 2014 and 2050, India is projected to add 404 million urban dwellers. China will add 292 million

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http://www.economist.com/node/21642053

http://esa.un.org/unpd/wup/Highlights/WUP2014-Highlights.pdf

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The Global Burden of Obesity

- Overweight and obese individuals increased from 857 million in 1980, to **2.1 billion in 2013**
- Countries with greatest rates: #1 USA, #2 China, #3 India
- In the Middle East and Micronesia, the prevalence of obesity exceeds 50% in both men and women
- Prevalence is greater in urban areas and generally women are more affected than men
- No country has reported significant **decreases** in obesity for the past three decades

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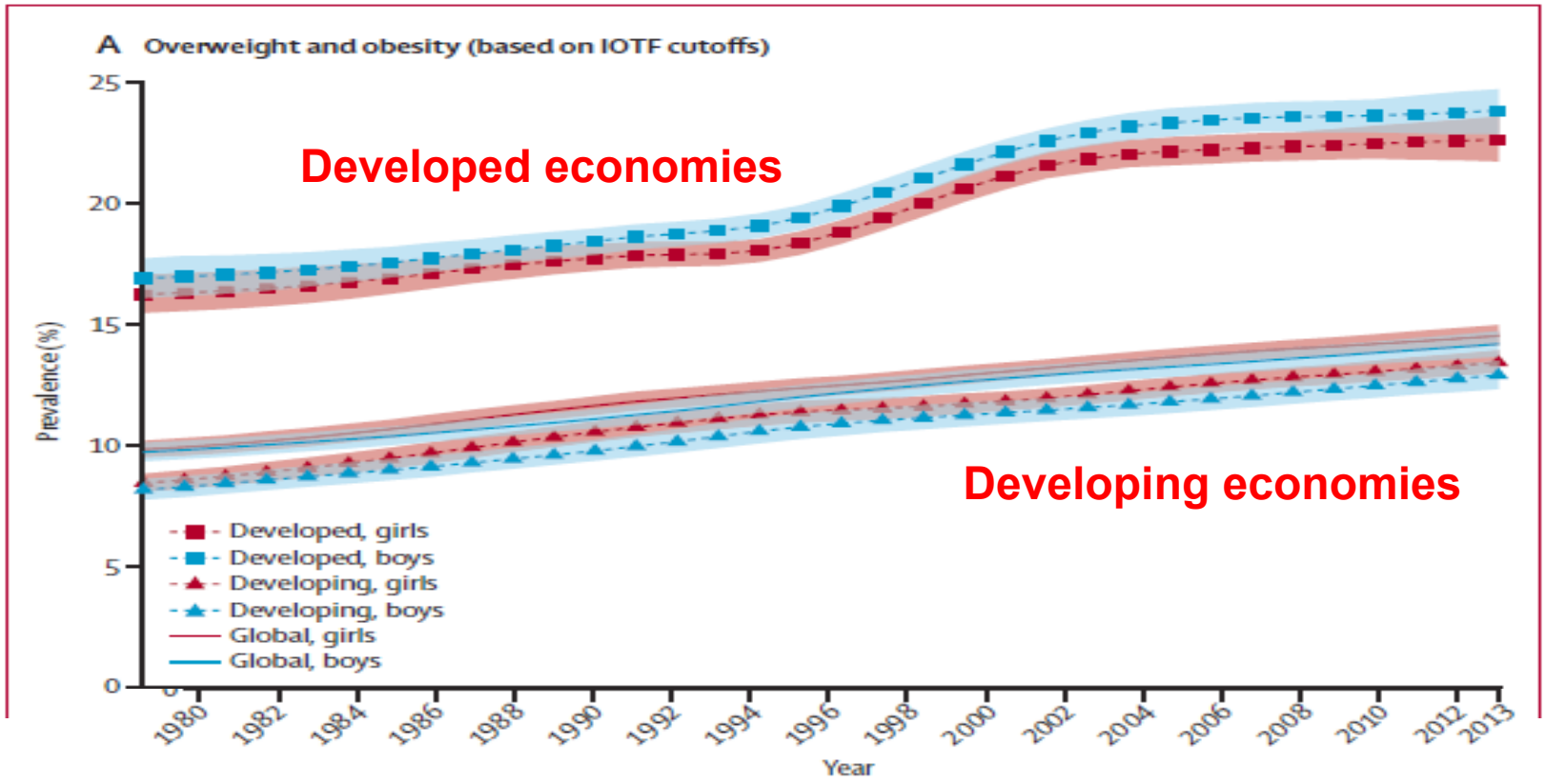
Ng, M et al. Global, regional, and national prevalence of overweight and obesity in children and adults. *Lancet* 2014; 384: 766–81

Obesity: Costly and increasing

- **In 2010, obesity was estimated to cause 3 to 4 million deaths and 3.9 per cent of years of life lost globally**



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Huge Numbers of Aging Cigarette Smokers

- 25% of the Chinese population smoke (>300 million)
- 18% of the Indian population smoke (>225 million)
- 34% of the Indonesian population smoke (>57 million)
- 22% of Japanese population smoke (>30 million)

- **There will be an estimated 1.1 billion tobacco smokers in 2025**

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1. www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index1.html
2. Lancet. 2015 Mar 14;385(9972):966-76..Global trends and projections for tobacco use, 1990-2025: an analysis of smoking indicators from the WHO Comprehensive Information Systems for Tobacco Control.

The Perfect Storm?

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- Global demographic and social changes
- Obesity and Smoking
- **Rise of non-communicable disease: COPD & DM**
- Community acquired pneumonia (CAP) and NCDs
- Influenza infection and pneumonia
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Chronic Obstructive Pulmonary Disease

- COPD includes emphysema, asthma & chronic bronchitis and is the 3rd leading cause of death worldwide[1]
- Approximately 80 percent of COPD deaths are caused by smoking[2]
- Smokers are nearly 13 times as likely to die from COPD as those who have never smoked[2]
- Other risk factors include exposure to air pollution, secondhand smoke and occupational dusts and chemicals[3]
- The risk of developing COPD among continuous smokers is at least 25%[4]

1. http://www.who.int/mediacentre/factsheets/fs310/en/
2. U.S.DHHS.. The Health Consequences of Smoking—50 Years of Progress: Surgeon General, 2014.
3. Global Strategy for the Diagnosis, Management, and Prevention of COPD, Updated 2011.
4. Lokke, A. Et al. Developing COPD--25 years follow-up study . Ugeskr Laeger. 2006 Dec 11;168(50):4422-4.

Type II Diabetes

- **Obesity is a primary risk factor for Type II Diabetes (>90% of all DM)[1]**
- **Complications include renal failure, cardiovascular disease, blindness, neuropathy, skin conditions, and Alzheimer's disease[1]**
- **About 80% of the world's diabetics live in LMICs**
- **Prevalence is increasing; currently 14% in urban areas and 8% in rural areas[2]**
- **India currently has more than 65 million Type II Diabetics[2]**
- **By 2030, there will be about 79.4 million type II diabetics in India[3]**

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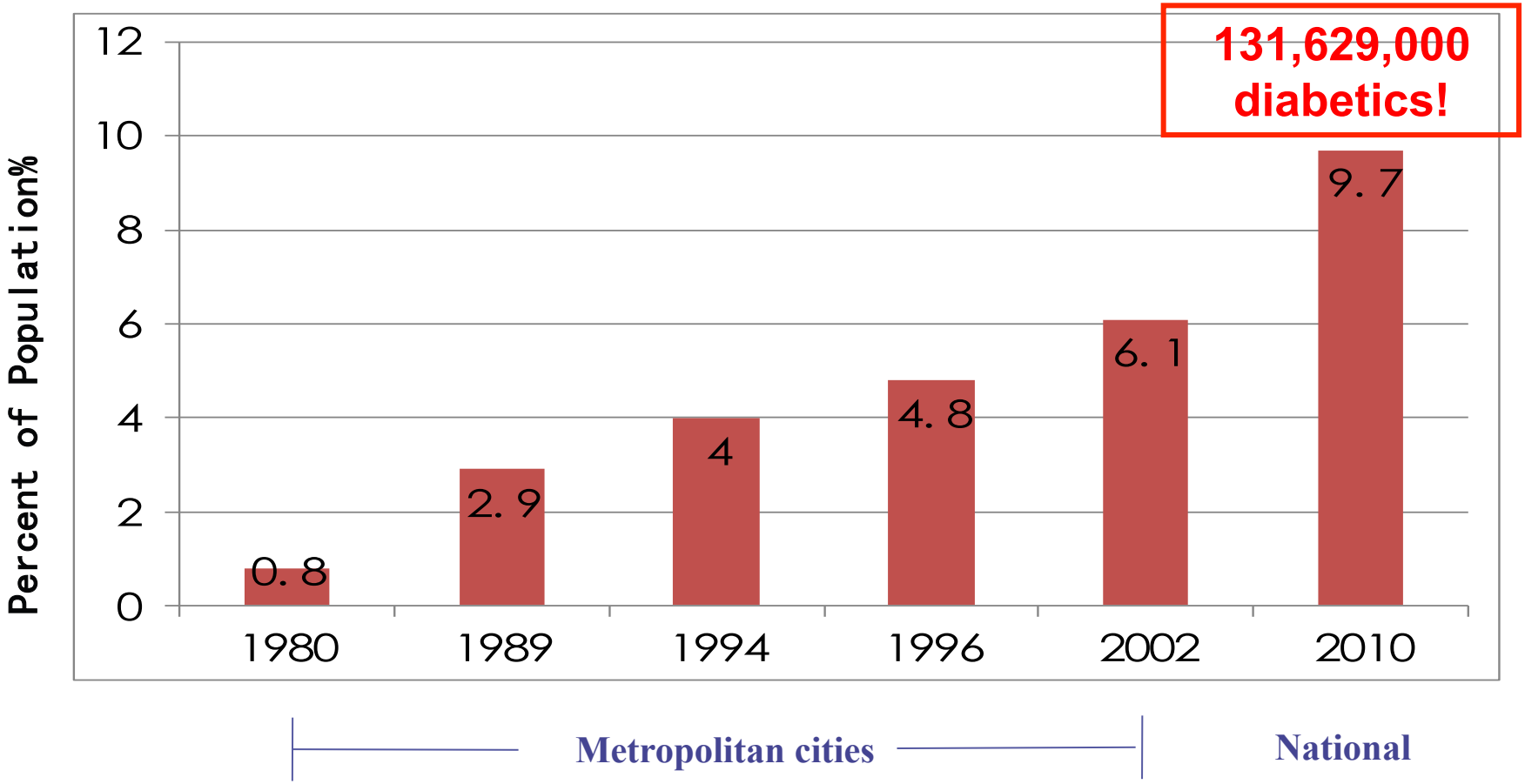
1. http://www.mayoclinic.org/diseases-conditions/diabetes/basics/risk-factors/con-20033091
2. Shrivastava U. Need for Ethnic-Specific Guidelines for Prevention and Management of Type 2 Diabetes in South Asians. Diabetes Technol Ther. 2015 Mar 31.
3. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. AMJ 2014, 7, 1,45-48

Explosive Rise in Type II Diabetes in China: 1980 to 2010



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1. Diabetes survey among adults in metropolitan cities: 1980-1996, National Nutrition and Health Survey in 2002, PRC Chronic Disease and Behavioral Risk Factors Survey in 2010
2. Yang, W. et al. "Prevalence of diabetes among men and women in China." NEJM 362.12 (2010): 1090-1101.
3. Xu, Yu, et al. "Prevalence and control of diabetes in Chinese adults." JAMA 310.9 (2013): 948-959.

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Community Acquired Pneumonia in Adults

- **Community-acquired pneumonia (CAP) is an important global cause of disease in older adults with high rates of hospitalizations and mortality[1]**
- **Lower respiratory tract infections are the 4th most common cause of death globally, and the 2nd most frequent reason for years of life lost**
- **Major risk factors include:**
  - **Increasing age**
  - **Smoking, alcoholism**
  - **Immunosuppressive conditions including diabetes**
  - **COPD, cardiovascular disease, liver or renal disease**

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1. Torres A, Peetermans WE, Viegi G, et al. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax. 2013;68:1057–1065.

The interface between NCD and pneumonia

- Pneumonia is more frequent and/or more difficult to treat in persons with COPD, obesity, diabetes
- Chronic inflammation leads to hyper-reactive, chronically up-regulated immune responses that, paradoxically, have poor microbial killing efficiency
- Mechanical issues such as reduced lung volumes, altered ventilation patterns, sleep apnea and poor gas exchange increase risk
- Metabolic dysregulation broadly affects both the innate and adaptive immune systems, negatively impacting humoral and cell mediated immunity

- **In one review, 71% of 955 adult CAP patients from 8 Asia Pacific countries had at least one non-communicable disease[2]**

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1. S. P. Fisher-Hoch et al. Obesity, diabetes and pneumonia. Tropical Medicine and International Health . Vol 18 no 12 pp 1510–1519 December. 2013
2. J.H. Song et al. International Journal of Antimicrobial Agents 31 (2008) 107–114

Severity and cost of CAP increases in the presence of NCDs

- **Objective:** Assess the disease burden of pneumonia according to age and presence of underlying diseases in patients admitted with CAP
- **Methods:** Retrospective, observational study of 693 Korean patients with CAP (≥ 50 years) from 11 hospitals. Disease burden defined as total per-capita medical fee, severity, hospital length of stay (LOS), and mortality
- **Results:**
  - **Subjects with underlying disease had a 3X higher severity scores, were older , and had a 2X higher mortality than those without an NCD**
  - **Total per-capita medical costs were nearly doubled, and hospital LOS was longer (mean, 8.38 days vs. 6.42 days; $p < 0.01$) in patients with NCDs**

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Lee, JY et al. Disease burden of pneumonia in Korean adults aged over 50 years stratified by age and underlying diseases. Korean J Intern Med 2014;29:764-773

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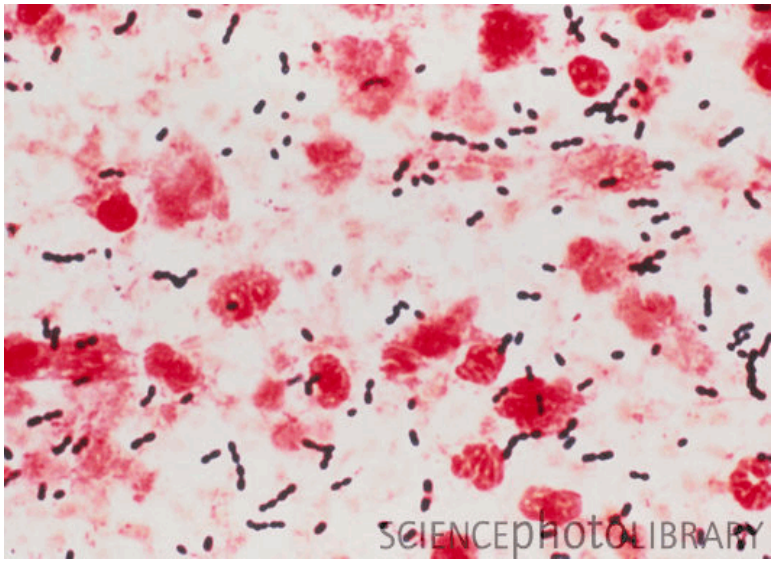
Influenza and bacterial pneumonia – constant companions

- Influenza is often complicated by bacterial infections-especially *Streptococcus pneumoniae and Staphylococcus aureus.*



- The annual incidence of pneumococcal disease closely correlates with the influenza season. Antibiotic resistance (MRSA) greatly increases the health risks[2,3]

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1. van der Sluijs *et al*. Bacterial pneumonia with influenza *Critical Care* 2010, **14**:219
2. Khater F, Moorman JP: Complications of influenza. *South Med J* 2003,96:740-743.

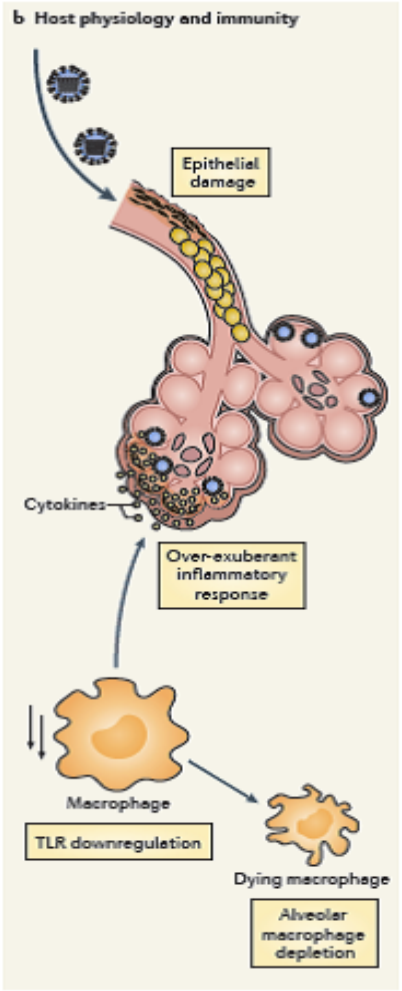
Pathophysiology & Clinical Aspects

- Characterized by complex interactions between pathogens and host factors; decreased mucociliary clearance of bacteria, macrophage dysfunction, and delays in return to homeostasis[1]

- A cascade of increased bacterial growth, immune-mediated pathology, and increased morbidity and mortality

- Radiologic features consistent with influenza often overlap with those of bacterial pneumonia[2]

- Sequential infections are difficult to diagnose if the influenza infection has resolved by the time the patient presents with secondary bacterial pneumonia



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1. McCullers. The co-pathogenesis of influenza viruses with bacteria in the lung. Nat Rev Microbiol. 2014 Apr;12(4):252-62.
2. Kumar, A etal. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA* 2009, 302:1872-1879.

Influenza, Bacteria, Pneumonia Sequence

1) Primary influenza pneumonia typically develops between days 2-5 of infection

2) Influenza-associated bacterial pneumonia (co-infection) is often more severe and can be present in up to 1/3 of severe influenza infections requiring ICU admission

3) Post-influenza bacterial pneumonia follows influenza by 7-14 days and occurs after viral clearance from the respiratory tract

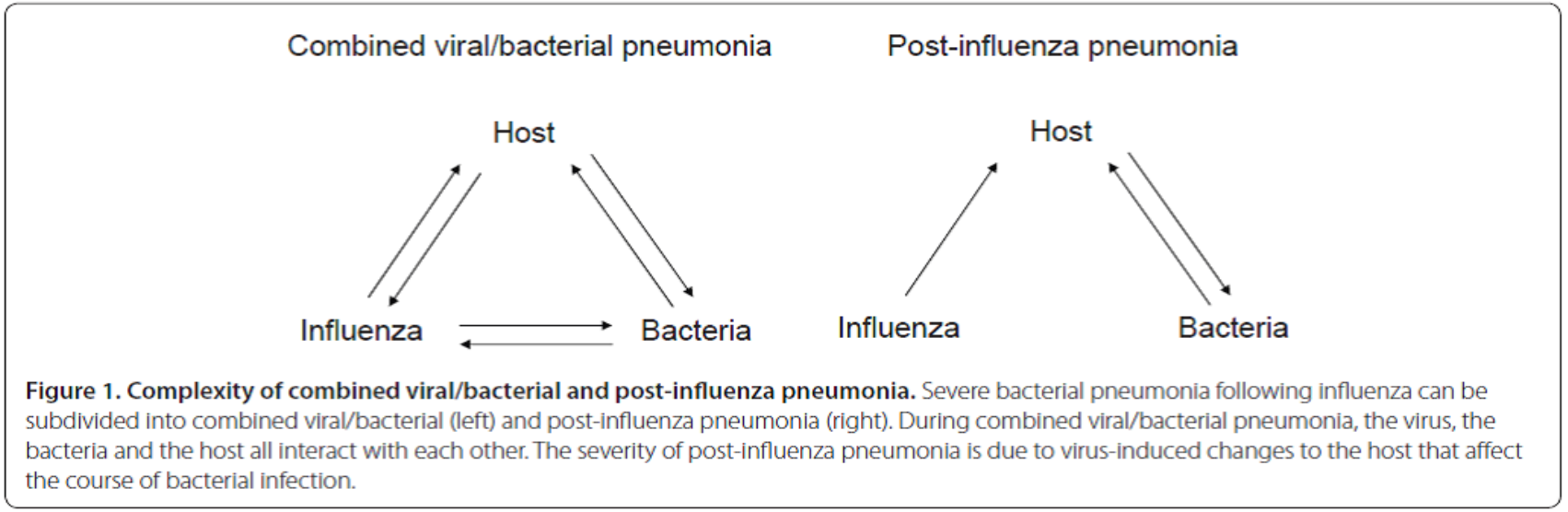

Figure 1. Complexity of combined viral/bacterial and post-influenza pneumonia. Severe bacterial pneumonia following influenza can be subdivided into combined viral/bacterial (left) and post-influenza pneumonia (right). During combined viral/bacterial pneumonia, the virus, the bacteria and the host all interact with each other. The severity of post-influenza pneumonia is due to virus-induced changes to the host that affect the course of bacterial infection.

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Campigotto, A. Influenza-associated bacterial Pneumonia. Expert Rev. Anti Infect. Ther. 13(1), 55–68 (2015)

Influenza Virus Pneumonia Meta-Analysis

- **Background**: Respiratory viral infections are increasingly recognized as important contributors to community acquired pneumonia. Conventional diagnostic methods have underestimated the burden.

- **Methods:** Meta-Analysis of studies of CAP etiology using **PCR** methods

- **Results:** 23 studies with 6,404 adult subjects globally
  - **Respiratory viruses contributed between 8.6 and 56.2% of all CAP**
  - **12% of all CAP is the result of mixed viral / bacterial infection**
  - **Influenza incidence in CAP was 8.9% (95% CI; 7.1-10.6%)**
  - **Influenza virus infections were the number one viral cause of CAP**

- **Conclusion: Influenza is the most important cause of viral CAP in adults. Influenza vaccination may reduce the burden of CAP.**

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Wu, X. et al. Incidence of Respiratory Viral Infections in Adult Patients with Community-Acquired Pneumonia: Respiration 2015;89:343–352

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Inactivated Influenza Vaccines for Prevention of Community-Acquired Pneumonia

Background: Up to 4 million cases, 600,000 hospitalizations and 45,000 deaths occur each year in the USA.

Methods: Probability and stochastic (decision tree) models were used to predict the benefits of influenza vaccination to reduce CAP using **conservative** assumptions

- **VE against influenza estimated at 54.5%**
- **Vaccination rate of 38.2%**
- **Rate of influenza without vaccination 5.3%**
- **Rate of CXR-confirmed CAP after influenza infection 4.1%**
- **Relative risk of CAP given influenza in the elderly 1.6**

Results: Influenza is associated with 15% of all Community Acquired Pneumonia
Stochastic model influenza vaccine effectiveness against CAP was 7%

Conclusion: Model likely underestimates the impact of vaccination. **Because CAP is so common, even modest efficacy would prevent up to 288,000 cases per year**

Ferdinands, JM. Influenza Vaccine for Prevention of Pneumonia. Epidemiology • Volume 24, Number 4, July 2013

Are there additive effects from receiving both influenza and pneumococcal vaccines?

- Yes, possibly. But polysaccharide vaccines have not demonstrated convincing efficacy against nonbacteremic pneumonia in controlled trials[1]
- In high risk groups such as COPD, some studies report an additive benefit

Additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbation in patients with chronic lung disease

Akitsugu Furumoto[a], Yasushi Ohkusa[e], Meng Chen[a], Kenji Kawakami[b], Hironori Masaki[c],

The additive benefits of influenza and pneumococcal vaccinations during influenza seasons among elderly persons with chronic lung disease

Kristin L. Nichol*

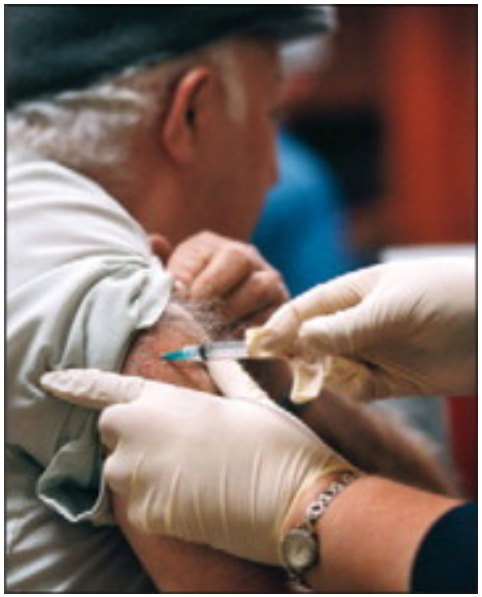
- Pneumococcal conjugated vaccines may have greater impact?

1.Moberly, SA. et al. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD000422.

Korean Study of Influenza & Pneumococcal Vaccines to Prevent Pneumonia

- **Methods:** Multicenter, prospective cohort study of Korean patients visiting emergency rooms with influenza-like illness in 2013-14

- **Results:** Among 2,217 patients with vaccination records, 31.9% (707) had received influenza vaccine and 9.7% (216) received PPV23 vaccine
  - The adjusted (age, BMI, smoking, NCDs) effectiveness of influenza vaccine for preventing pneumonia was 64.0% and 35.0% for hospitalization
  - PPV23 vaccination did not reduce pneumonia or hospitalization



- **Conclusion:** Rather than PPV23 vaccination, influenza vaccination may reduce pneumonia development and hospitalization

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Song JY, et al. 2015. Prospective cohort study on the effectiveness of influenza and pneumococcal vaccines in preventing pneumonia development and hospitalization. Clin Vaccine Immunol 22:229 –234.

Summary

- Massive demographic shifts are changing global public health priorities
- Hundreds of millions of middle-aged people are developing COPD and DM, making them more vulnerable to serious complications from influenza
- Influenza is a common cause of viral pneumonia and secondary bacterial pneumonia
- Studies to estimate influenza vaccine effectiveness to prevent pneumonia hospital admissions in patients with chronic disease are needed
- Conservative models suggest that influenza vaccination could prevent at least 7% of all community acquired pneumonia
- Expanded use of influenza vaccine could substantially reduce the burden of CAP in adults with underlying chronic diseases

Thank you

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