

# Recommendation and Policy of Influenza Vaccination in China

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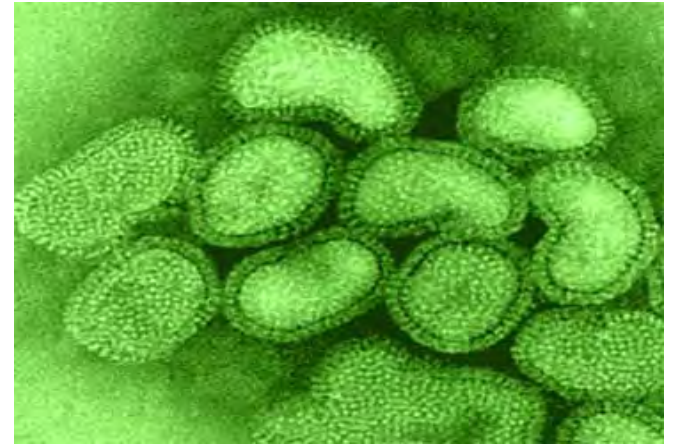
Influenza Vaccine Working Group, China's NIAC

2018-Sep-9, Beijing



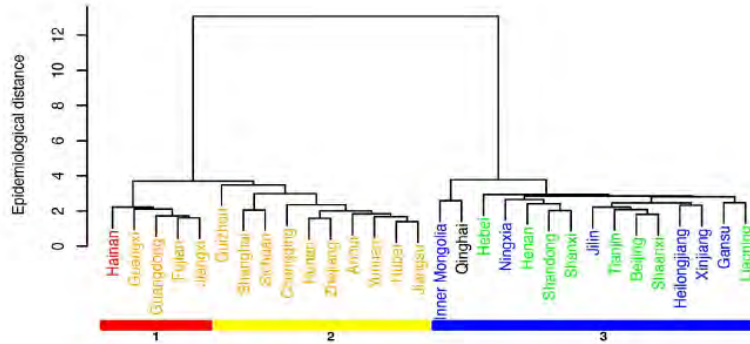
# Seasonal Influenza

- Health and economic burden
- Influenza vaccine supply and demanding
- Target vaccinated population
- Evidence-based vaccine recommendation
- Policy advocacy

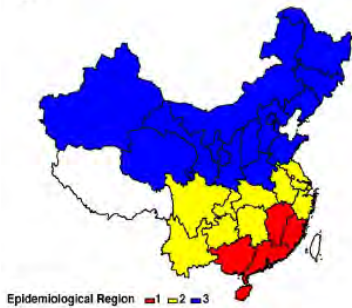


# Marked differences: Seasonality of A and B

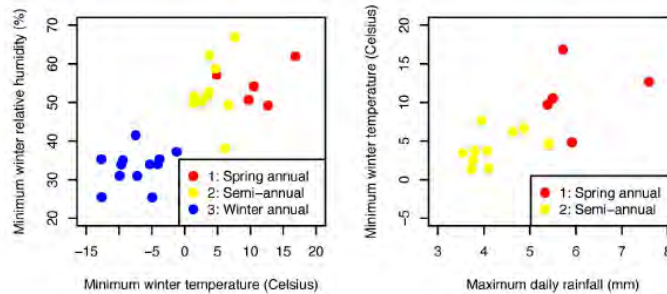
A



B



C



- Annual periodicity of A increased with latitude
  - Nor China (>33°N): in January–February
  - Southernmost regions (<27°N): April–June
  - Intermediate latitudes (27°N-33°N): semi-annual (January–February and June–August)
- B predominated in colder months throughout most of China.

- Regional-specific vaccination strategies.
- Minimum temperature, hours of sunshine, and maximum rainfall.

# Influenza-associated mortality

Table 4. Comparison of estimates of annual influenza-associated excess mortality in China and other selected locations, by age and cause of death as coded<sup>a</sup> or recorded

Study area	Model	Study period	Proportion of influenza seasons by:		Excess deaths (per 100 000 people)					
			A(H3N2)	B	All ages			Age ≥ 65 years		
					P&I	R&C	AC	P&I	R&C	AC
Australia <sup>15</sup>	Poisson	1997–2004	NA	NA	NA	NA	NA	15.2	80.4	101.2
China (Guangzhou) <sup>21</sup>	Poisson	2004–2006	2/3	0/3	1.0	9.9	10.6	NA	104.1	111.3
China (northern cities) <sup>b</sup>	Negative binomial	2003–2008	2.5/6	1/6	0.4	12.4	18.0	3.1	106.0	150.8
China (northern cities) <sup>b</sup>	Serfling	2003–2008	2.5/6	1/6	0.4	13.4	17.0	2.6	108.1	131.3
China (southern cities) <sup>b</sup>	Negative binomial	2003–2008	2.5/6	1/6	0.5	8.8	11.3	3.6	64.3	75.4
China (Hong Kong SAR) <sup>19</sup>	Poisson	1996–1999	4/4	0/4	4.1	12.4	16.4	39.3	102.0	136.1
Italy <sup>11,12</sup>	Serfling	1970–2001	21/31	5/31	1.9–2.2	NA	11.6–18.6	12.7–14.2	NA	71.2–115.7
Mexico <sup>16</sup>	Serfling	2000–2008	6/9	1/9	1.5	12.7	15.7	10.4 <sup>c</sup>	115.6 <sup>c</sup>	147.4 <sup>c</sup>
Singapore <sup>22</sup>	Negative binomial	1996–2003	8/8	0/8	2.9	11.9	14.8	46.9	155.4	167.8
United States <sup>4</sup>	Poisson	1990–1999	6/9	2/9	3.1	13.8	19.6	22.1	98.3	132.5
United States <sup>3</sup>	Poisson	1976–2002	14/27	9/27	NA	9.9	NA	NA	72.4	NA
United States <sup>5</sup>	Poisson	1976–2007	17/31	9/31	2.4	9.0	NA	17.0	66.1	NA
United States <sup>10</sup>	Serfling	1980–2001	12/21	6/21	2.9	NA	15.0	22.0	NA	100.0

- Excess R&C mortality: 12.4 and 8.8/100,000 in northern and southern
- Most (86%) occurred among people aged ≥ 65 years
- Higher in B-dominant seasons than H3N2 or H1N1 predominated



# Influenza-associated mortality

- 128 Disease surveillance point (DSP) mortality sites, influenza-associated respiratory excess deaths

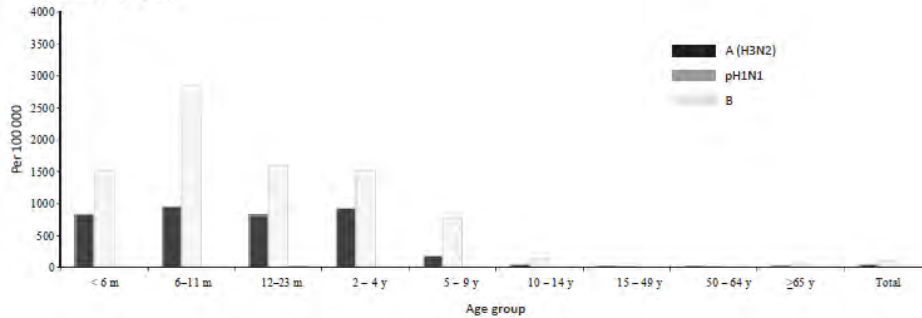
		Excess deaths	
Death cause		Rates for all-age (95% CI)	No. for all-age (95% CI)
A(H1N1)pdm in 2009–2010	R&C	9.4 (4.6–18.6)	126 242 (61 002–248 383)
	Respiratory	2.4 (1.1–5.4)	32 501 (14 052–72 033)
	All-cause	13.8 (6.3–28.1)	184 453 (84 785–375 433)
Seasonal epidemics*	R&C	11.1 (5.0–32.2)	148 694 (66 966–430 665)
	Respiratory	5.0 (2.4–12.6)	66 382 (32 022–168 536)
	All-cause	15.1 (6.3–48.9)	202 357 (84 465–653 765)
B epidemic in 2007–2008	R&C	14.4 (8.7–21.6)	192 210 (116 644–288 725)
	Respiratory	5.7 (3.7–8.2)	76 787 (49 173–109 744)
	All-cause	18.8 (11.0–30.3)	251 919 (147 781–405 597)

\*Average of five interpandemic seasons 2004–2005 through 2008–2009.

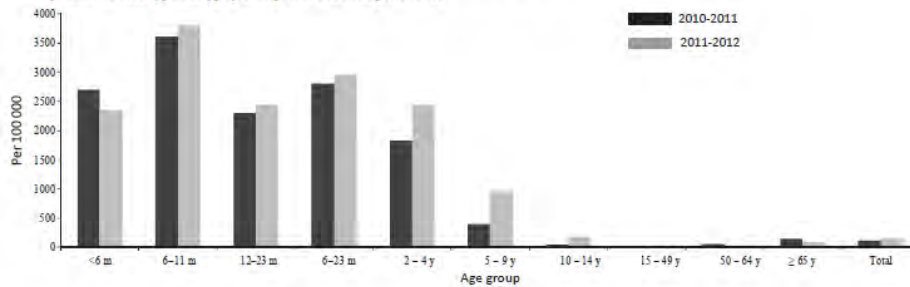


# Substantial hospitalization burden

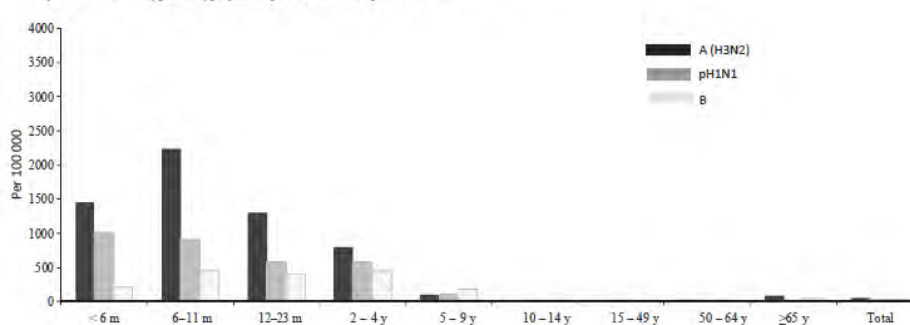
Panel A. Estimated hospitalization rates attributable to influenza by age group



Panel B. Estimated hospitalization rates attributable to influenza by age group and by influenza viruses' type/subtype from April 5, 2010 to April 3, 2011



Panel C. Estimated hospitalization rates attributable to influenza by age group and by influenza viruses' type/subtype from April 3, 2011 to April 8, 2012



- 13% of SARI cases confirmed influenza, 69% aged <5 yrs
- Estimated 115 and 142 SARI hospitalizations per 100,000 during 2010–11 and 2011–12
- Highest rate among children aged 6–11 months

# Influenza-associated ILI burden by province

- Overall influenza was associated with 2.5 (95% CI: 1.5, 3.6) ILI consultations per 1,000 persons each year
- Highest influenza-associated ILI burden was observed in Shanghai, Beijing, Tianjin and Zhejiang province

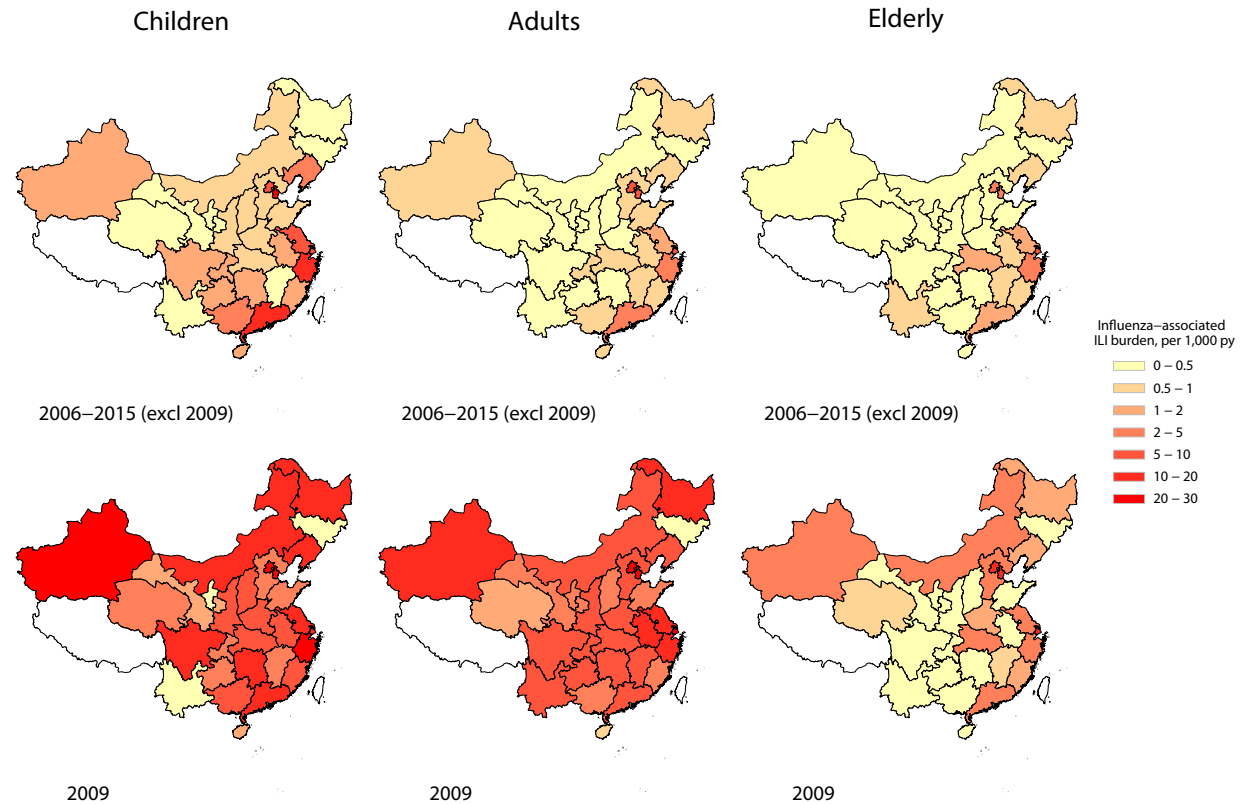


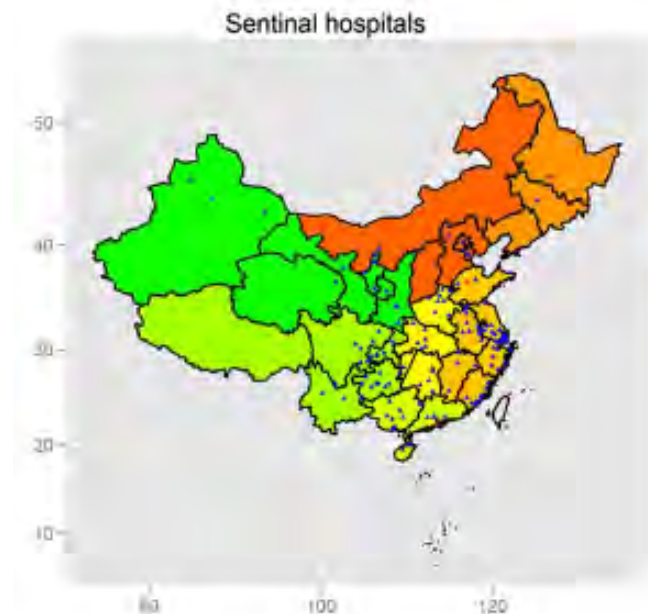
Figure. Average influenza-associated ILI burden in 30 provinces in China, 2006-2015.

- In 2009, there were 7.5 (95% CI: 5.9, 9.3) people consulted due to influenza virus per 1,000 persons, with a higher rate in 2009 across all provinces compared to other years

# Economic burden of influenza-associated outpatients visits and hospitalizations

	N	Direct medical costs	Direct non-medical costs	Indirect costs	Total costs
Influenza outpatients	529	70 (69)	26 (44)	59 (59)	155 (122)
Influenza inpatients	254	1038 (1315)	277 (288)	197 (169)	1511 (1465)

- Higher costs: Patients <5 and ≥60 yrs, and those with underlying medical conditions

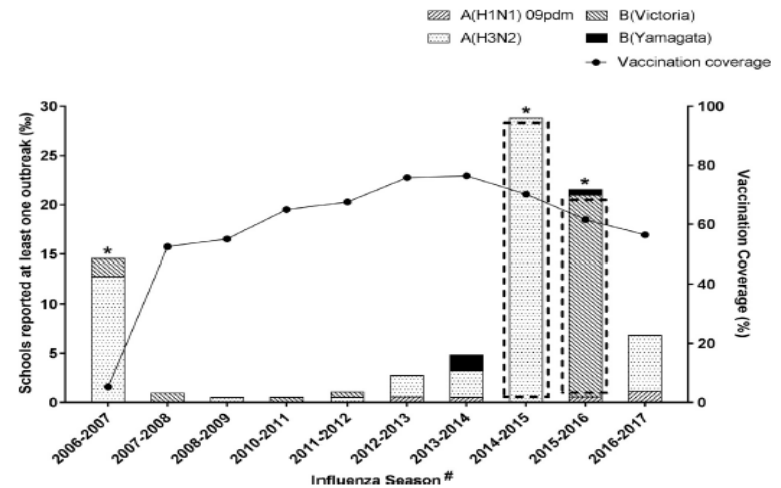


Yang J, et al. *Infect Dis Poverty*, 2015.



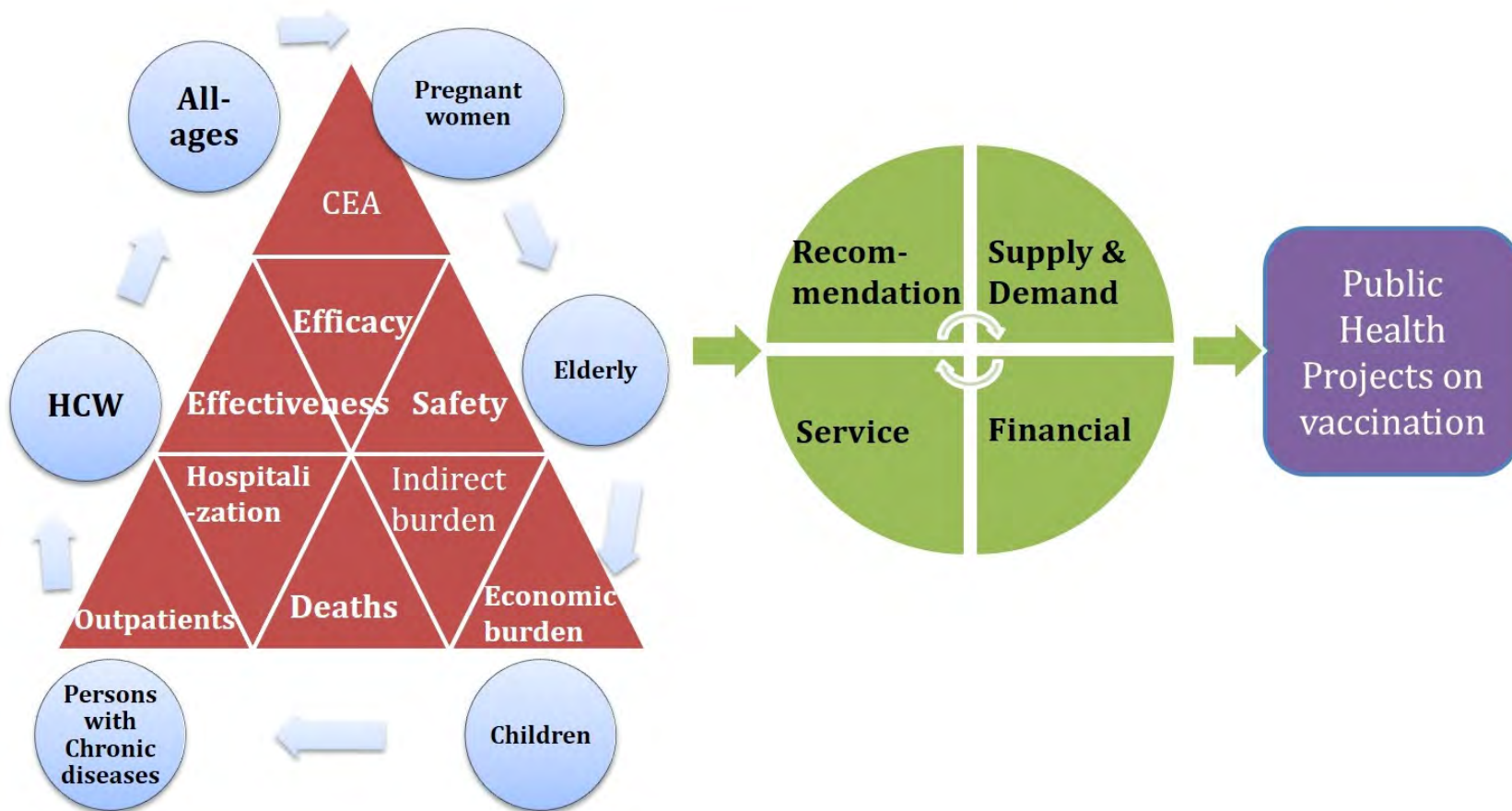
# Influenza Vaccine Effectiveness in Beijing

- 2012-13, all age: 52% (12-74)
- 2013-14, elderly: 32% (-48-69)
- 2014-2015, all age: -18% (-49-6)
- 2014-15, school children: 38% (12-57)
- 2006-2017, school outbreaks, significant decrease



Yang P et al. Vaccine. 2014; Zhang L et al. Hum Vaccin Immunother. 2018 ; Ma C et al. Hum Vaccin Immunother. 2017; Zhang L et al. Pediatr Infect Dis J. 2017 ; Pan Y et al. Vaccine. 2017

# Evidence-based decision-making



# Evidence-based recommendation for individual

- Pregnant women
- Family members and caregivers of infants <6 months of age
- Infants and children aged 6–23 months
- Children aged 2–5 y
- Elderly 60 y of age
- Persons with specific chronic underlying diseases
- Healthcare workers



# Influenza vaccines supply in 2018-19

- Quadrivalent Inactivated influenza vaccines (IIV4)
  - Hualan biological product co., LTD, 15 ug, for >36 months
- Trivalent Inactivated influenza vaccines (IIV3)
  - Changchun institute of biological products co., LTD
  - Hualan biological product co., LTD
  - Shenzhen Sanofi Pasteur biological products co., LTD
  - Dalian Aleph biological pharmaceutical co., LTD
  - ...

# Phase 3 RCT of QIV (15ug) in China

## 15 $\mu$ g四价流感病毒裂解疫苗III期临床研究设计简表

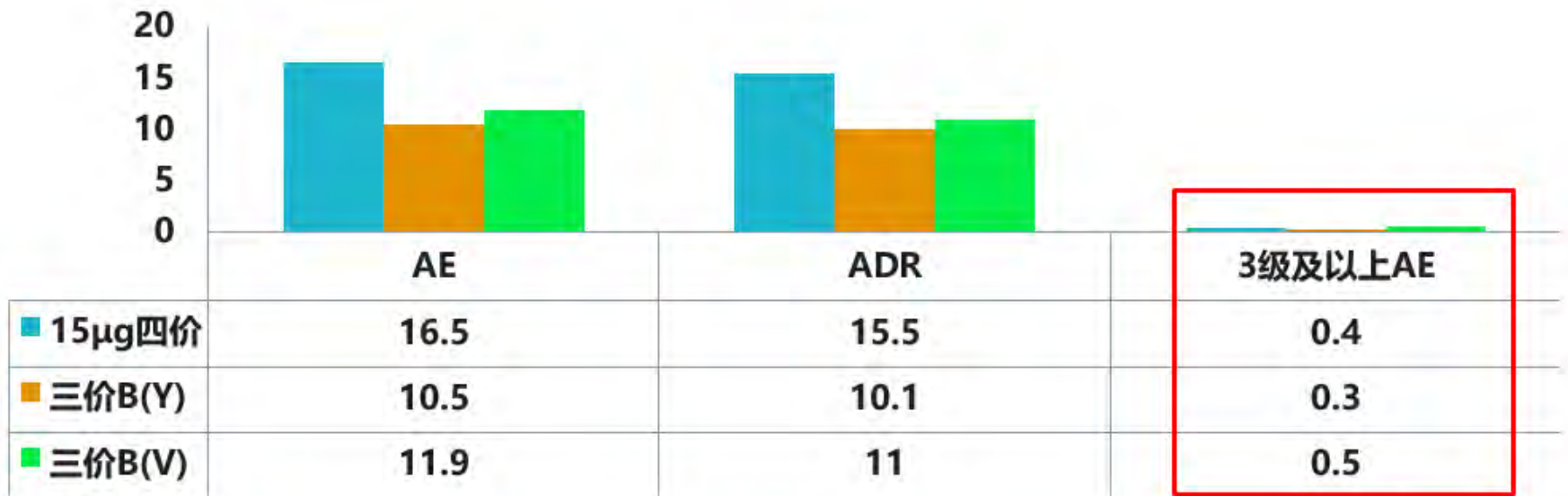
年龄组	入组人数			接种程序	安全性观察	抗体检测
	三价 (By)	三价 (Bv)	15 $\mu$ g四价			
> 60岁	375人	375人	375人	全程1针	0-180天	0、28天
18-60岁	200人	200人	200人	全程1针	0-180天	0、28天
9-17岁	200人	200人	200人	全程1针	0-180天	0、28天
3-8岁	200人	200人	200人	0、21天, 全程2针	0-201天	0、21、49天

**试验主要目的：**评价15 $\mu$ g/剂四价流感疫苗在3岁及以上健康人群中按全程一针免疫程序接种后的安全性和免疫原性，为疫苗注册提供临床依据。





# Safety of QIV licensed in China



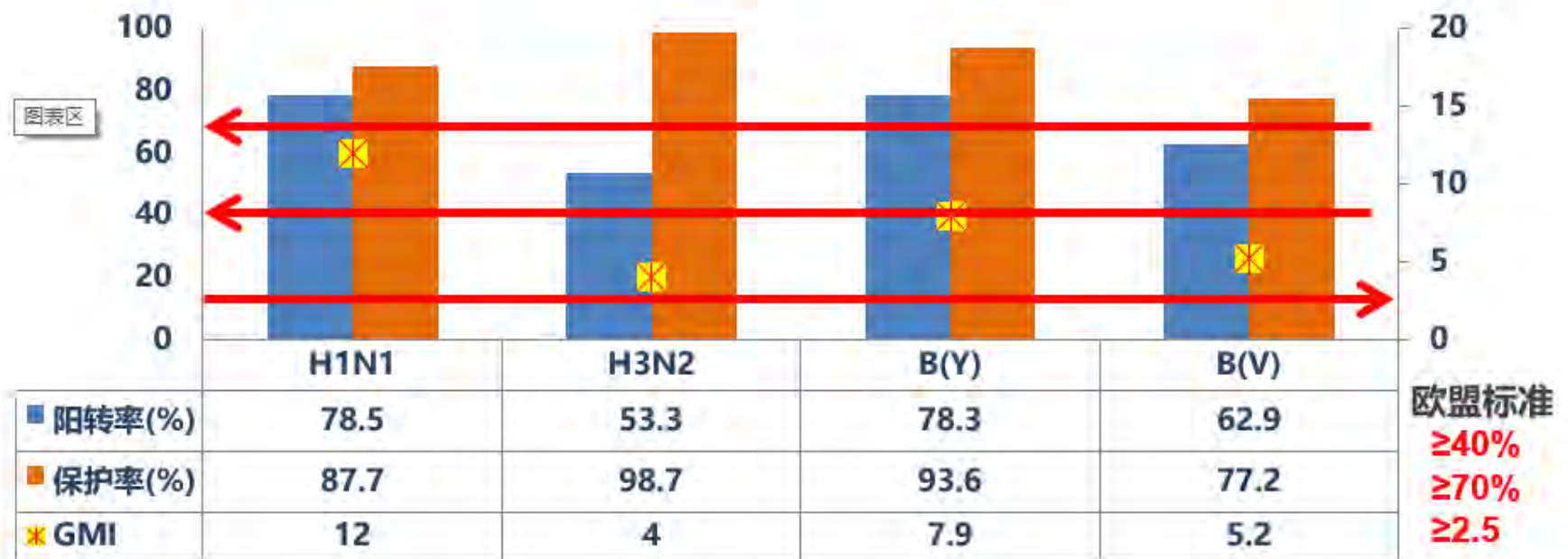
- **试验结果显示：**四价流感疫苗在3岁及以上人群中单针接种后，总体不良事件及ADR发生率及与疫苗接种相关的不良反应发生率略高于两个三价对照疫苗组，不良症状反应多为**发热、疼痛、红肿等**。四价流感和三价对照流感疫苗均具有可接受的安全性。

AE: Adverse Events Following Immunization

ADR: Adverse Drug Reaction

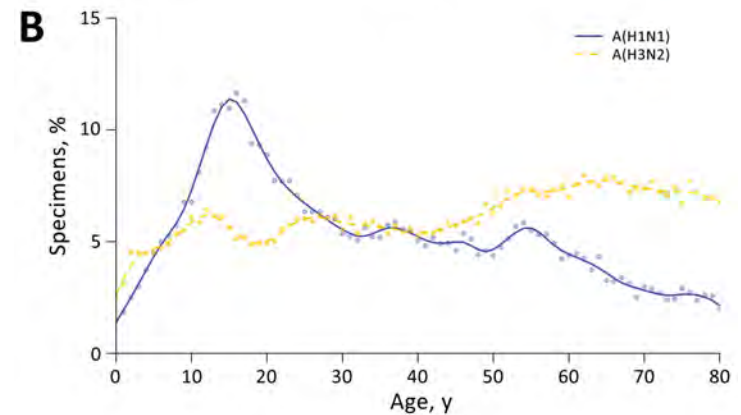
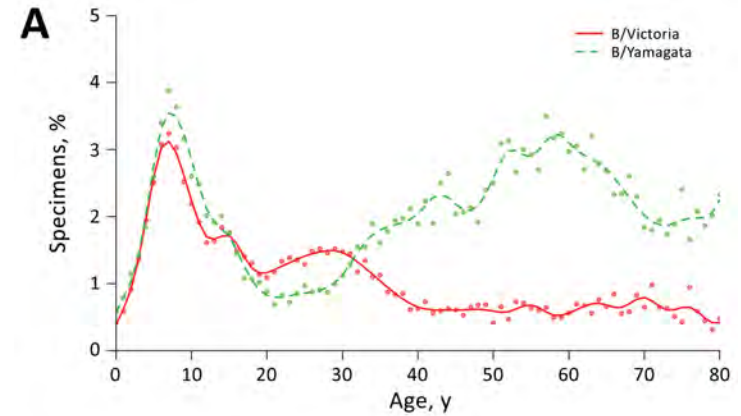
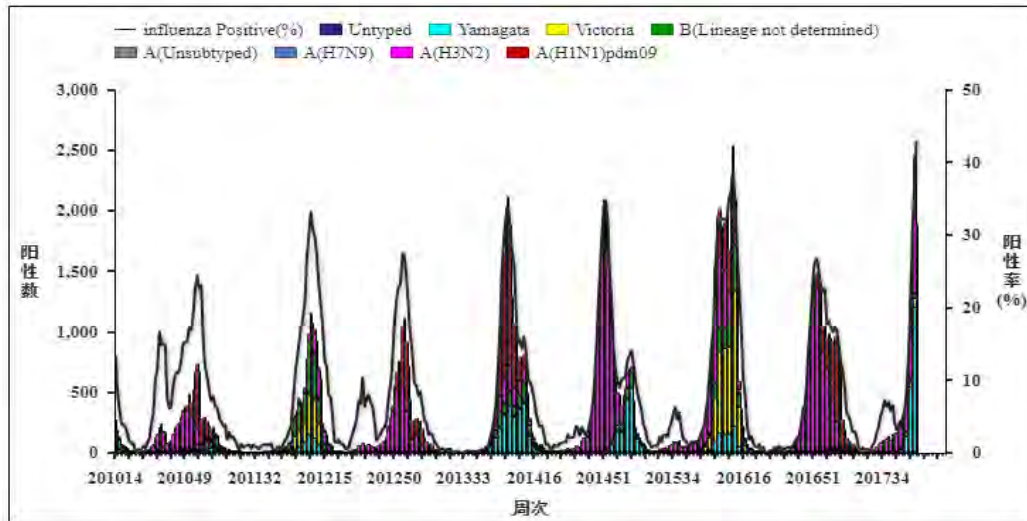
SAE: Severe adverse events

# Immunogenicity of QIV licensed in China



➤ 试验疫苗四个亚型流感病毒HI抗体阳转率、保护率、免后/免前抗体GMT增长倍数均达到了欧盟评价标准，具有良好的免疫原性。

# Influenza B in China



# Priority populations

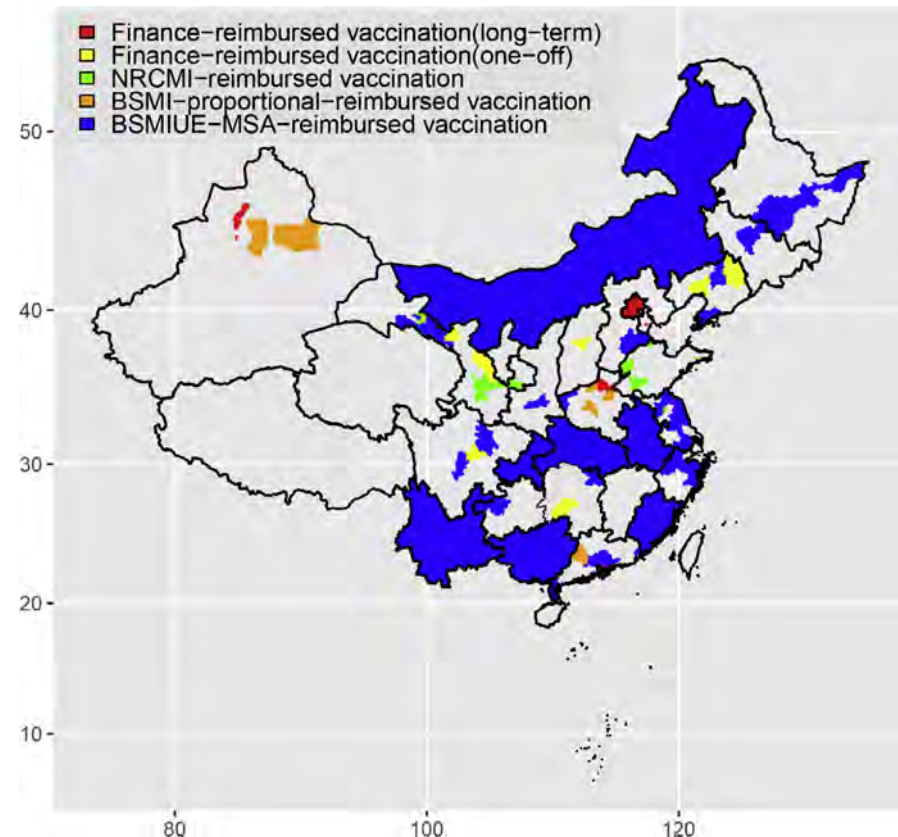
Region	No. of priority population (thousand)					
	6–59 months	Elderly	Persons aged 5–59 years with chronic illness	Pregnant	Health workers	Total
<b>Total</b>	<b>71,710</b>	<b>193,300</b>	<b>129,061</b>	<b>22,210</b>	<b>9780</b>	<b>426,061</b>

6–59 months	Elderly	Budget (million, US\$)				Total	Percent of total budget in Government Health Expenditure (%) <sup>a</sup>	Percent of total budget in Gross Domestic/Regional Product per capita (%) <sup>a</sup>
		Persons aged 5–59 years with chronic illness	Pregnant	Health workers				
187 (178–195)	309 (297–322)	210 (202–218)	36 (34–37)	16 (14–16)	757 (726–789)	4.777 (4.579–4.975)	0.080 (0.077–0.083)	



# Category II vaccine, and diverse regional reimbursement policies

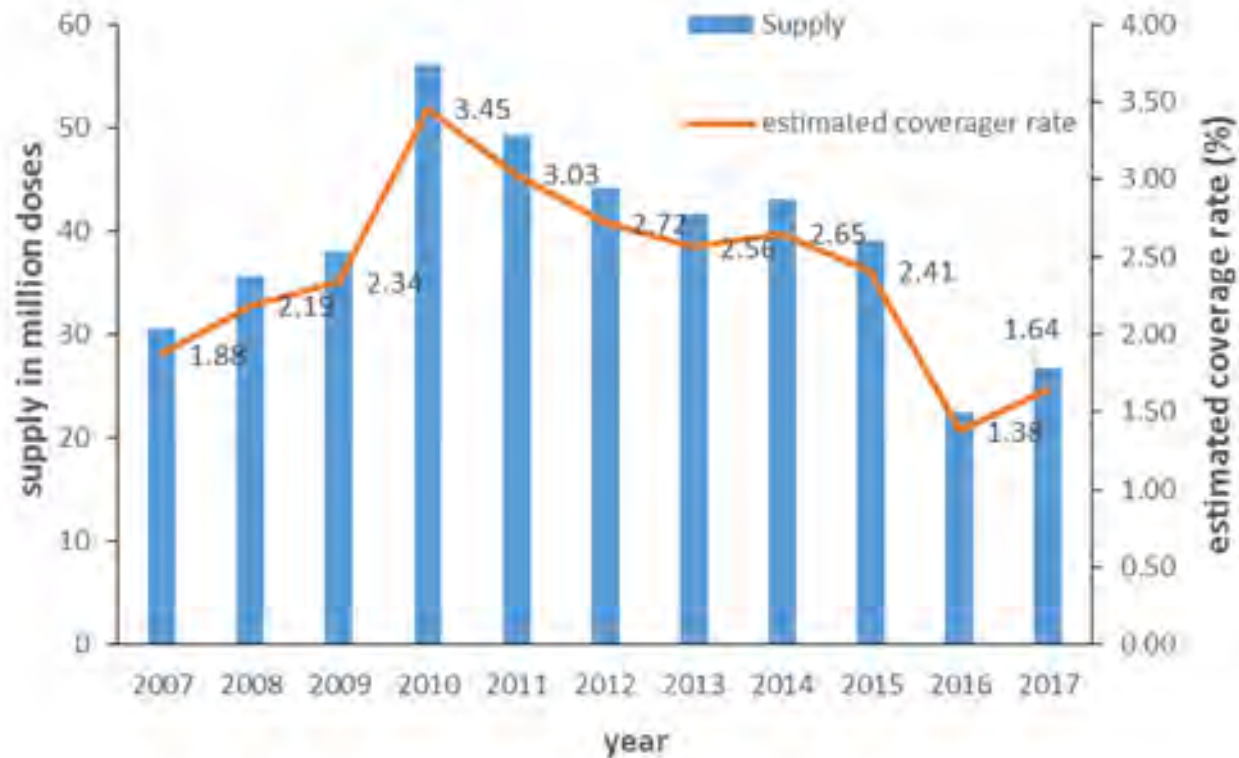
- Till 2016, regular reimbursement policies for influenza vaccination are available in 61 mutually exclusive regions, comprising 8 provinces, 45 prefectures, and 8 counties
  - Local Government Financial Department
  - Basic Social Medical Insurance





# Low Influenza Vaccine Coverage in China

- The average national vaccination coverage was just 1.3–3.5% between 2004 and 2017



Data source: CFDA



# Vaccination coverage among all high risk groups in China remains low

Population 重点人群	China 中国	United States 美国 (14/15) <sup>1</sup>
Pregnant women 孕妇	0 (12/13) <sup>2</sup>	50.3%
Young children 儿童	26% (6m-5y; 11/12) <sup>3</sup>	70.4% (6-59m)
Older adults 老年人	4.3% ( $\geq 60y$ ; 11/12) <sup>4</sup>	66.7% ( $\geq 65y$ )
Healthcare workers 医务人员	4.8% (13/14) <sup>5</sup>	77.3%

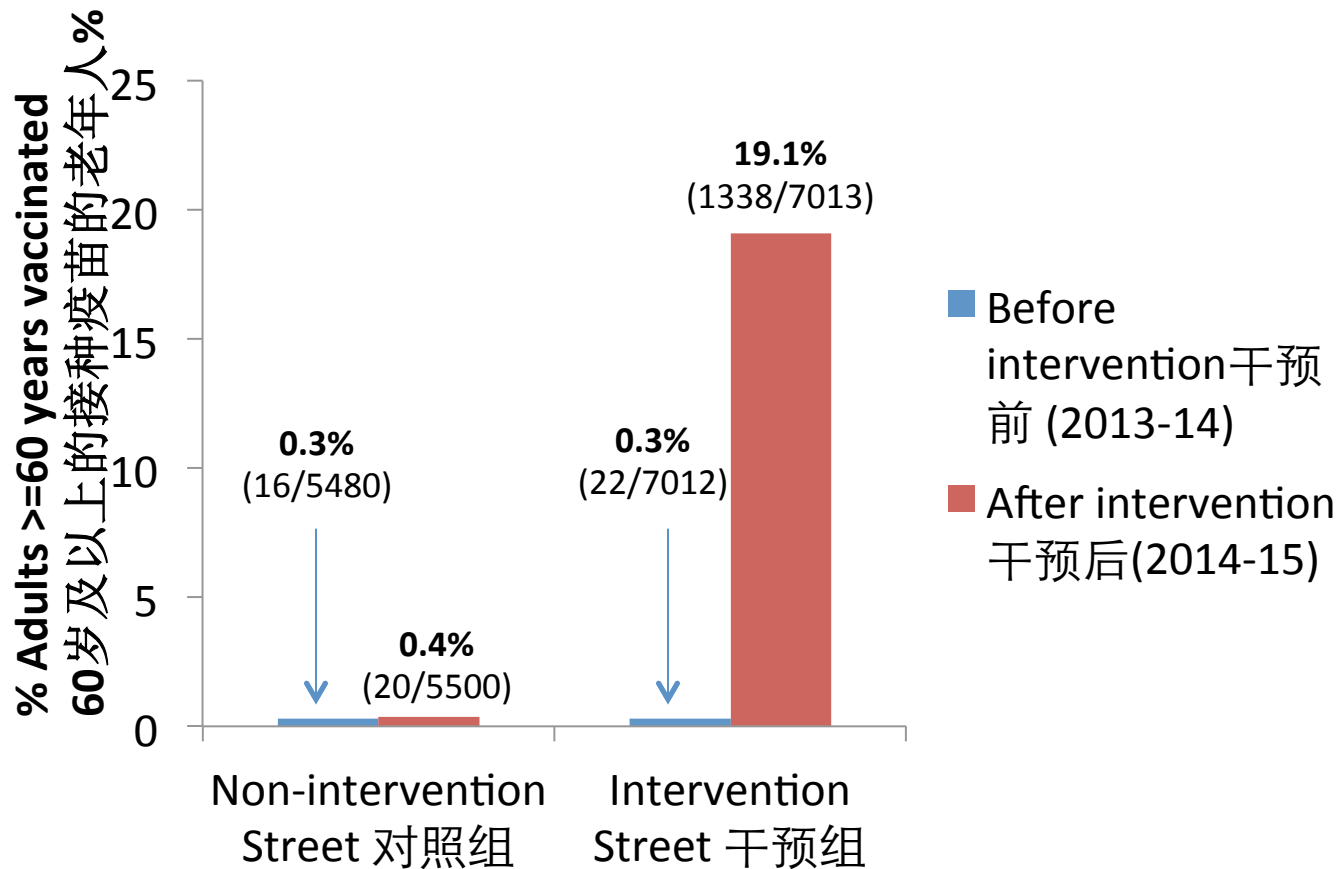
Data sources:

1. <http://www.cdc.gov/mmwr/index2015.html>
2. KAP study Suzhou (n=1700)
3. Bu L, Hao X, Li S, et al. (2015). Chinese Journal of Public Health 31(6).
4. Zhou L, Su Q, Xu Z, et al. (2013). PLoS ONE 8(9): e73724.
5. KAP study Qingdao (n=1670)

# Older adults on intervention street had higher seasonal influenza vaccination coverage

## post-intervention, Ningbo, 2013-2015

### 宁波干预组的老年人在干预后接种率提高, 2013-2015



# Policies to Improve Influenza Vaccination

Barriers	Detail measures to improve influenza vaccine coverage
<b>Category 2 vaccine</b>	<ul style="list-style-type: none"> <li>• Reimbursed fully or partially by the local Government Financial Department, or BSMI(Basic Social Medical Insurance</li> <li>• Implemented a policy of free mandatory vaccination by hospital for HCWs against influenza</li> <li>• Jointly with education department, focus on uptake of influenza vaccines among preschool children and students</li> </ul>
<b>Accessibility to vaccination services</b>	<ul style="list-style-type: none"> <li>• Establish adult vaccination clinics, provide accessible and convenient vaccination</li> <li>• Promote the approval ,introduction and research on new influenza vaccine</li> </ul>
<b>Less awareness</b>	<ul style="list-style-type: none"> <li>• Take a variety of ways and means to vigorously carry out health education and raise the awareness of the public and HCWS on influenza vaccine.</li> </ul>
<b>Low recommendations of HCWs</b>	<ul style="list-style-type: none"> <li>• Strengthen the training of HCWs</li> <li>• Advocate HCWs to recommend influenza vaccine vaccination to high-risk groups by health prescriptions and basic public health service assessment</li> </ul>
<b>Pregnancy women</b>	<ul style="list-style-type: none"> <li>• Revise the conflict between the Chinese Pharmacopoeia and the WHO influenza vaccine position paper, which is the term “pregnancy women are taboo for influenza vaccination”</li> </ul>

# Acknowledgements

- China CDC: Dr. FENG Zijian, LI Zhongjie, Lance Rodewald
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