Childhood Influenza in China

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http://www.who.int/influenza/en/

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Influenza

Pandemic Influenza: an Evolving Challenge

2018 marks the 100th anniversary of one of the largest public health crises in modern history, the 1918 influenza pandemic known colloquially as "Spanish flu." The intensity and speed with which it struck were almost unimaginable – infecting one-third of the earth's population, which at the time was about 500 million people. By the time it subsided in 1920, tens of millions people are thought to have died.

Although influenza has been with humankind for millenia, the global spread and impact is in many respects a function accelerated in modern times. Urbanization, mass migration, global transport and trade accelerate the spread of pandemics.

Read the story

New Contributed Photographs Collection / Otis Historical Archives / National Museum of Health and Medicine

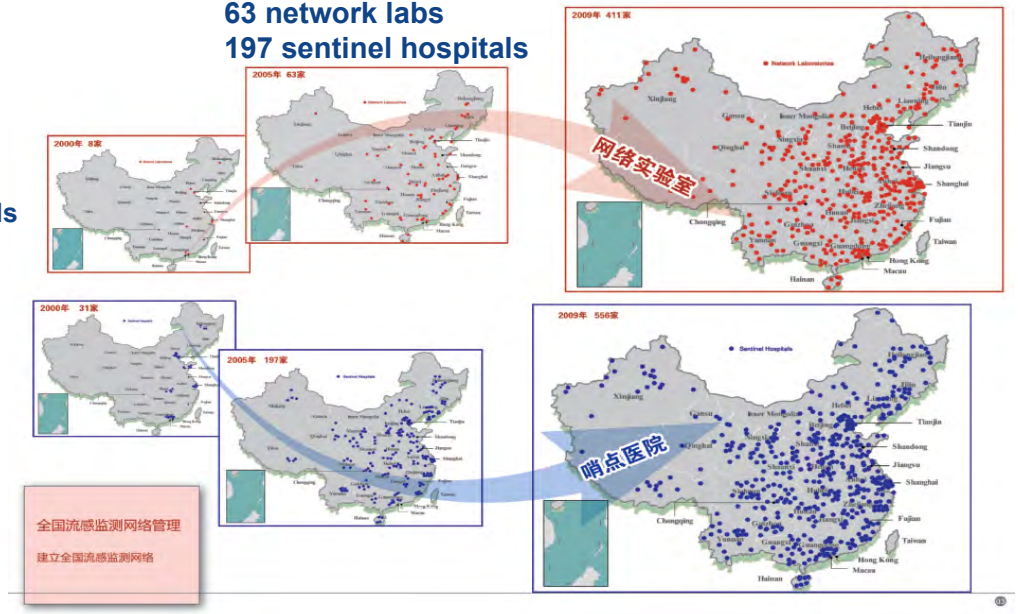
ILI & Flu monitoring system in China

中华人民共和国国家卫生健康委员会
National Health Commission of the People's Republic of China

In 2009
411 network labs
556 sentinel hospitals

In 2005
63 network labs
197 sentinel hospitals

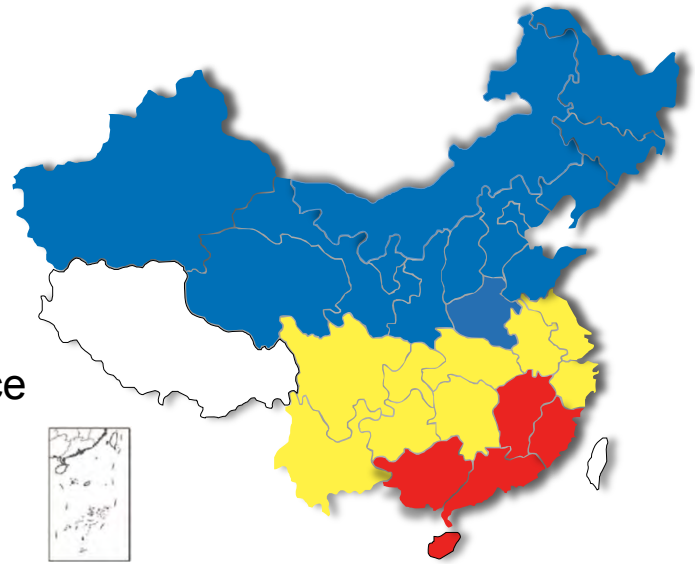
In 2000
8 network labs
31 sentinel hospitals



Influenza seasonal characteristics by virus type and geography in China.

FLU A **a diversity of seasonal patterns**

- Northern provinces (latitudes ＞33°N) experience winter epidemics.
- Souther provinces (latitude ＜27°N) experience peak activity in spring.
- Provinces at intermediate latitudes experience semi-annual epidemic cycles.



FLU B **experience winter epidemics in most of regions in China**

Yu H, et al (2013). PLoS Med 10(11): e1001552.

Children - high risk groups of influenza higher mortality in developing countries

World Health Organization http://www.who.int/mediacentre/factsheets/fs211/en/

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Influenza (Seasonal)

Fact sheet
November 2016

WHO

- The annual incidence of influenza in the world: adult 5% -10%, children 20-30%[1]. every year 3 million -5 million cases, 250,000 -500,000 deaths.
- Yearly influenza epidemics can seriously affect all populations, but the highest risk of complications occur among pregnant women, children aged 6–59 months, the elderly, individuals with specific chronic medical conditions such as HIV/AIDS, asthma, and chronic heart or lung diseases, and health-care workers.
- The effects of seasonal influenza epidemics in developing countries are not fully known, but research estimates indicate that 99% of deaths in children under 5 years of age with influenza related lower respiratory tract infections are found in developing countries

[1]WHO Weekly Epidemiological Record. No.33， 2005， pp. 279-287

Children - high risk groups of influenza higher mortality in developing countries

- Viral aetiologies like respiratory syncytial virus (RSV) and influenza virus are associated with the majority of episodes of ALRI in children and the elderly

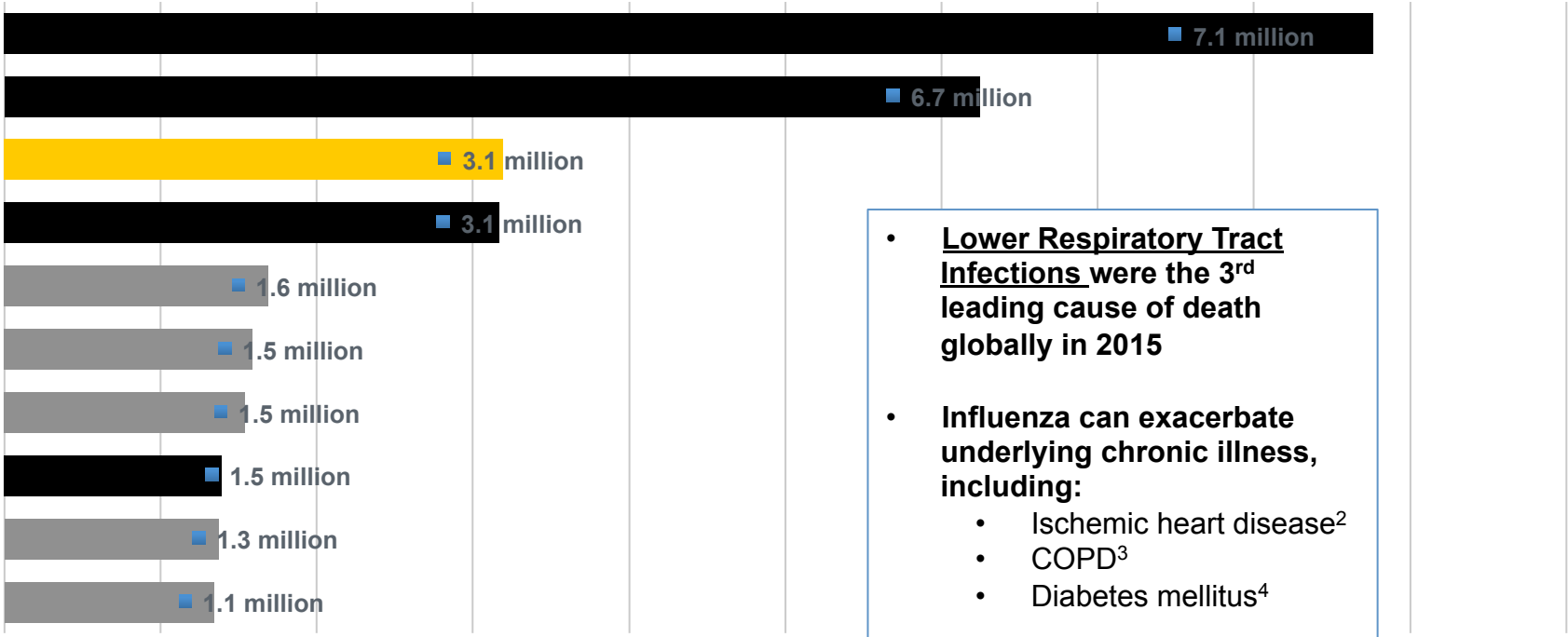
Graham, Editors. 2001, Aspen Publishers, Inc.:Gaithersburg, Maryland. p. 439-476.rs.

- Recent research showed, for 92 countries, that among children younger than 5 years, 9243–105 690 influenza-associated respiratory deaths occur annually.

A Danielle Iuliano. The Lancet. 2018,391(10127):1285-1300

Global burden of disease

The 10 leading causes of death in the world 2015[1]



- **<u>Lower Respiratory Tract Infections</u> were the 3rd leading cause of death globally in 2015**
- **Influenza can exacerbate underlying chronic illness, including:**
  - Ischemic heart disease[2]
  - COPD[3]
  - Diabetes mellitus[4]
- **In deaths attributed to these conditions, influenza is an underappreciated**

1. WHO Media Center Fact Sheet No.310 (http://www.who.int/mediacentre/fac

2. CDC https://www.cdc.gov/flu/heartdisease/

Incidence and mortality in the US 2017-2018influenza season

发病与住院（北美）

- 流感检出阳性高峰期与往年相近
- 流感相关住院率106.6/10万，高于2012-2017流感季（31~64/10万）
- 2岁以下占33%、5-9岁占25%的ICU住院

死亡

- 美国该流感季流感相关儿童死亡180例，高于既往（2012-2013最高171例）
- 37%的死亡与B 型病毒相关
- 中国儿童流感相关死亡不清楚

WHO.Review of the 2017-2018influenza season in the north hemisphere. http://www.who.int/wer

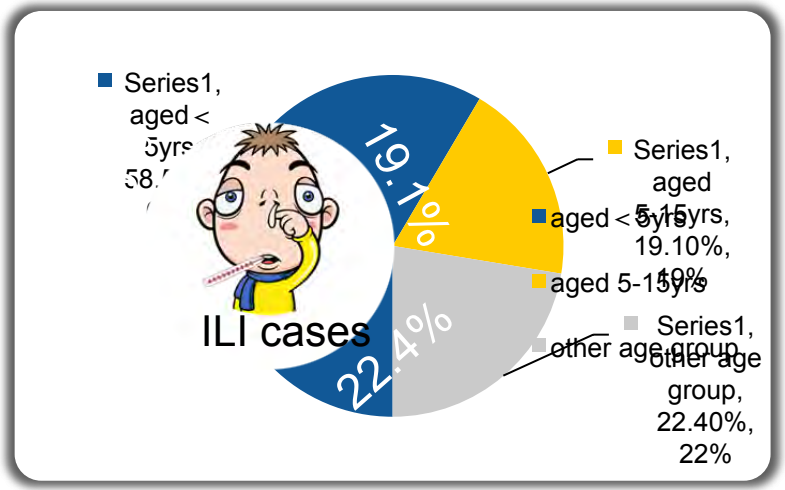
Significant effect on children's population in China

It's estimated that,every year

10%-15% children need be treated to hospital due to influenza [1]

II

22-33 million affected per year [2]



Epidemiological characteristics of ILI [1]
(40,894 ILI cases were detected in 2008,China)

[1] Ru-ning Guo, et al. PLoS One. 2012,7(7):e41403.
[2] the date of the 6th China Population Census(2010) showed the population of children is222million.

Global Burden of Influenza in Pediatric Respiratory Hospitalizations

Table 3. Pooled estimates of global pediatric influenza-associated hospitalizations per year, by age group, development status, and WHO region, among studies using PCR diagnostic testing.

Characteristic	*N* (Number of Countries)	Pooled Percent Positive (95% CI)	Hospitalized ALRI Episodes (Thousands)*	Global Influenza-Associated Hospitalizations (Thousands) **	Influenza-Associated Hospitalizations per 100,000 Children
Age group					
<6 mo	15 (14)	4.8 (3.3–6.9)	—	—	—
<1 y	26 (21)	6.1 (5.1–7.4)	6,136 (5,168–7,287)	374 (264–539)	284 (200–409)
<2 y	23 (18)	7.1 (6.1–8.4)	—	—	—
<5 y	48 (35)	7.4 (6.2–8.8)	11,751 (9,837–12,054)	870 (610–1,237)	135 (95–193)
5–17 y	27 (22)	16.4 (13.6–19.8)	—	—	—
<18 y	42 (32)	9.5 (8.1–11.0)	—	—	—
Age <5 y by development status					
Industrialized	7 (4)	5.9 (4.6–7.5)	551 (408–745)	33 (19–56)	48 (28–81)
Developing	41 (31)	7.7 (6.4–9.3)	11,200 (9,429–13,309)	862 (603–1,238)	150 (105–216)
Age <5 y by WHO region					
Africa	16 (13)	8.2 (6.4–10.6)	3,084 (1,985–4,791)	253 (127–508)	174 (87–349)
Americas	7 (5)	4.6 (2.8–7.4)	1,333 (920–1,934)	61 (26–143)	79 (33–185)
Eastern Mediterranean	1 (1)	7.4 (NA)	889 (628–1,258)	66 (46–93)†	95 (67–135)†
Europe	5 (4)	7.1 (1.5–32.7)	402 (252–642)	29 (4–210)	53 (7–387)
Southeast Asia	7 (4)	8.5 (6.7–10.8)	3,274 (2,008–5,341)	278 (135–577)	157 (76–326)
Western Pacific	12 (8)	8.5 (6.8–10.6)	2,143 (1,660–2,764)	182 (113–293)	153 (95–246)

The influenza-associated hospitalization rate in developing countries was 3-fold that in industrialized countries

Lafond KE, et al. Global Role and Burden of Influenza in Pediatric Respiratory Hospitalizations, 1982–2012: A Systematic Analysis. PLoS Med 2016.

Economic burden of affected children in China

Costs per episode for influenza patients and associated risk factors in China, 2013 (US$)[a]

Characteristic		Direct cost		Indirect costs	Total cost	Multiple linear regression (95 % Confidence interval)[b]
		Medical cost	Non-medical cost			
outpatients	Age group (years)	$p = 0.062$	$p < 0.001$	$p = 0.006$	$p = 0.003$	
	< 5 ($n = 122$)	85 (84)	36 (53)	75 (75)	196 (152)	Reference
	5–14 ($n = 232$)	63 (68)	28 (43)	61 (61)	153 (121)	−52 (−89,−22)[f]
inpatients	Age group (years)	$p < 0.001$	$p = 0.046$	$p = 0.018$	$p < 0.001$	
	< 5 ($n = 144$)	980 (775)	315 (336)	213 (178)	1508 (1021)	Reference
	5–14 ($n = 79$)	1031 (2014)	229 (197)	157 (150)	1417 (2112)	−52 (−402,566)

The economic burden of influenza-associated outpatient and inpatient children in China is substantial, particularly for **children aged < 5 years**

Yang et al. Infectious Diseases of Poverty (2015) 4:44

北京儿童医院
BEIJING CHILDREN'S HOSPITAL

Comparative analysis of acute respiratory infection virus pathogens in outpatient and inpatient children 2010-2012

Objective

- 2010年3月－2012年2月北京儿童医院门诊及住院的临床诊断为ARI的患儿共2066例

✓门诊病例1050例：男孩644例，女孩406例，平均年龄3.48岁（3.48±2.79岁）

✓住院病例1016例：男孩635例，女孩381例，平均年龄3.82岁（3.82±3.89岁）

Method

- 标本采集：
  - ✓ 门诊患儿在就诊当日采集咽拭子1份
  - ✓ 住院患儿在住院当日/次日采集咽拭子或鼻咽吸取物1份
- 核酸提取：
  - ✓ 门诊病例标本：QIAamp® MinElute® Virus Spin Kit
  - ✓ 住院病例标本：自动核酸提取仪NucliSens easyMAGTM
- 呼吸道病毒核酸检测：

  (RT)-PCR检测：RSV，HRV，PIV， IFV，ADV，EV，HCOV，HMPV，HBOV

Results

- 病毒检出情况：
  - ✓门诊病例：阳性检出率为53.9%(566/1050)

    住院病例：阳性检出率为69.7%(708/1016)

    住院病例病毒总阳性检率明显高于门诊病例

    (χ^2 ＝54.394，P=0.000)
  - ✓门诊病例：IFV、ADV、PIV

    住院病例：RSV、HRV、PIV

Table 1 Detection of various viruses in children with acute respiratory infections in outpatient and inpatient hospitals in different age groups(%)

病毒种类	门诊病例					住院病例				
	<1岁 (N=169)	1~<3岁 (N=350)	3~<6岁 (N=354)	≥6岁 (N=177)	合计 （N=1050）	<1岁 (N=348)	1~<3岁 (N=218)	3~<6岁 (N=147)	≥6岁 (N=303)	合计 （N=1016）
RSV	7 (4.1)	33 (9.4)	23 (6.5)	3 (1.7)	66 (6.3)	196 (56.3)	82 (37.6)	20 (13.6)	24 (7.9)	322 (31.7)
HRV	8 (4.7)	21 (6.0)	23 (6.5)	11 (6.2)	63 (6.0)	105 (30.1)	68 (31.2)	29 (19.7)	34 (11.2)	236 (23.2)
PIV	13 (7.7)	55 (15.7)	31 (8.8)	7 (4.0)	106 (10.1)	82 (23.6)	56 (25.7)	18 (12.2)	18 (6.3)	175 (17.2)
ADV	4 (2.4)	31 (8.9)	43 (12.1)	36 (20.3)	114 (10.9)	39 (11.2)	40 (18.3)	12 (8.1)	15 (4.9)	106 (10.4)
IFV	14 (8.3)	34 (9.7)	46 (13.0)	22 (12.4)	116 (11.0)	15 (4.3)	15 (6.9)	7 (4.8)	22 (7.3)	59 (5.8)
HMPV	3 (1.8)	15 (4.3)	20 (5.6)	2 (1.1)	40 (3.8)	17 (4.9)	12 (5.5)	7 (4.8)	8 (2.6)	44 (4.3)
HCOV	4 (2.4)	14 (4.0)	14 (4.0)	0 (0)	32 (3.0)	13 (3.7)	8 (3.7)	2 (1.4)	3 (1.0)	26 (2.6)
HBOV	0 (0)	7 (2.0)	2 (0.6)	0 (0)	9 (0.9)	40 (11.5)	58 (26.6)	9 (6.1)	14 (4.6)	121 (11.9)
EV	5 (3.0)	22 (6.3)	58 (16.4)	8 (4.5)	93 (8.9)	14 (4.0)	4 (1.8)	5 (3.4)	5 (1.7)	28 (2.8)
总计	52 (30.8)	203 (58.0)	229 (64.7)	80 (46.3)	566(53.9)	313 (89.9)	196 (89.9)	84 (57.1)	115 (38.0)	708 (69.7)

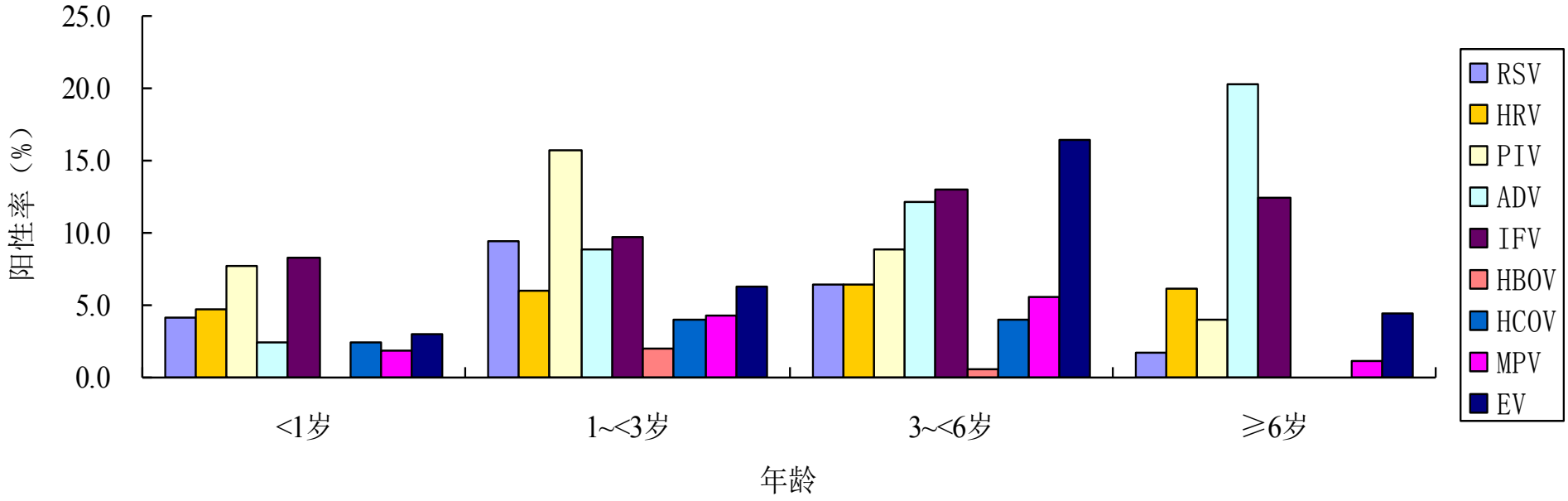


Figure 1. Detection of various viruses in different age groups in outpatient children

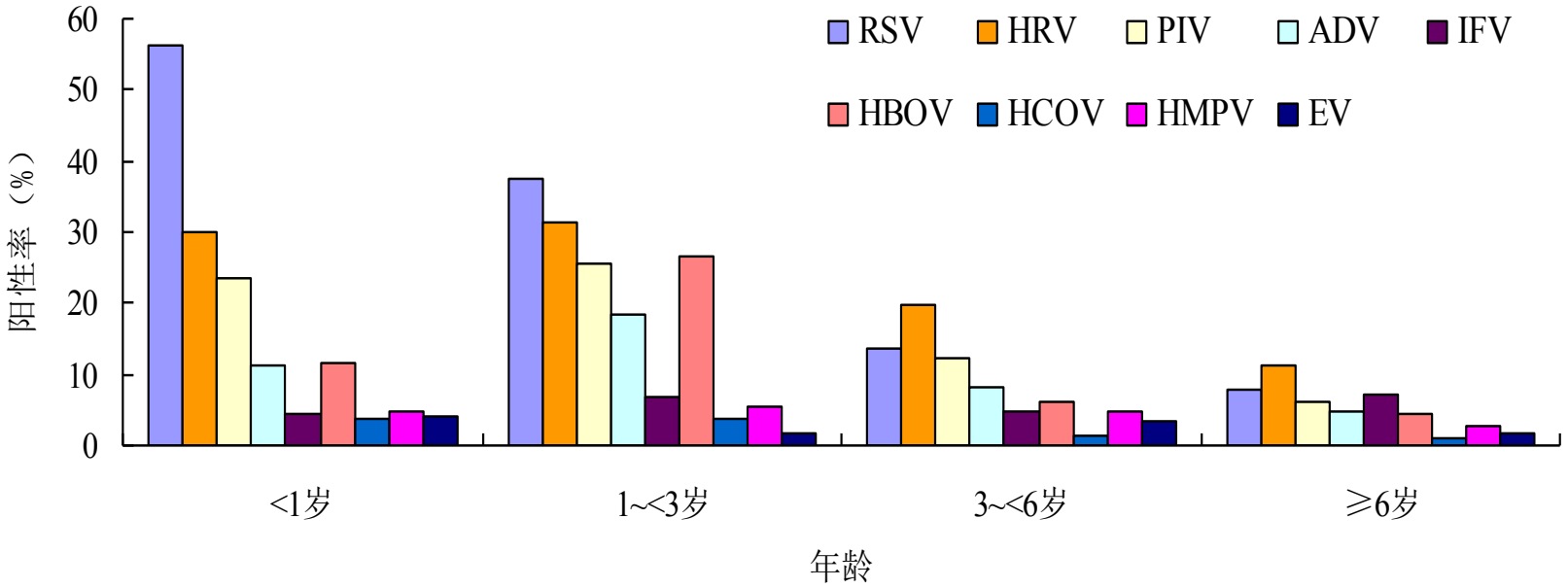


Figure 2. Detection of viruses in different age groups of inpatient children

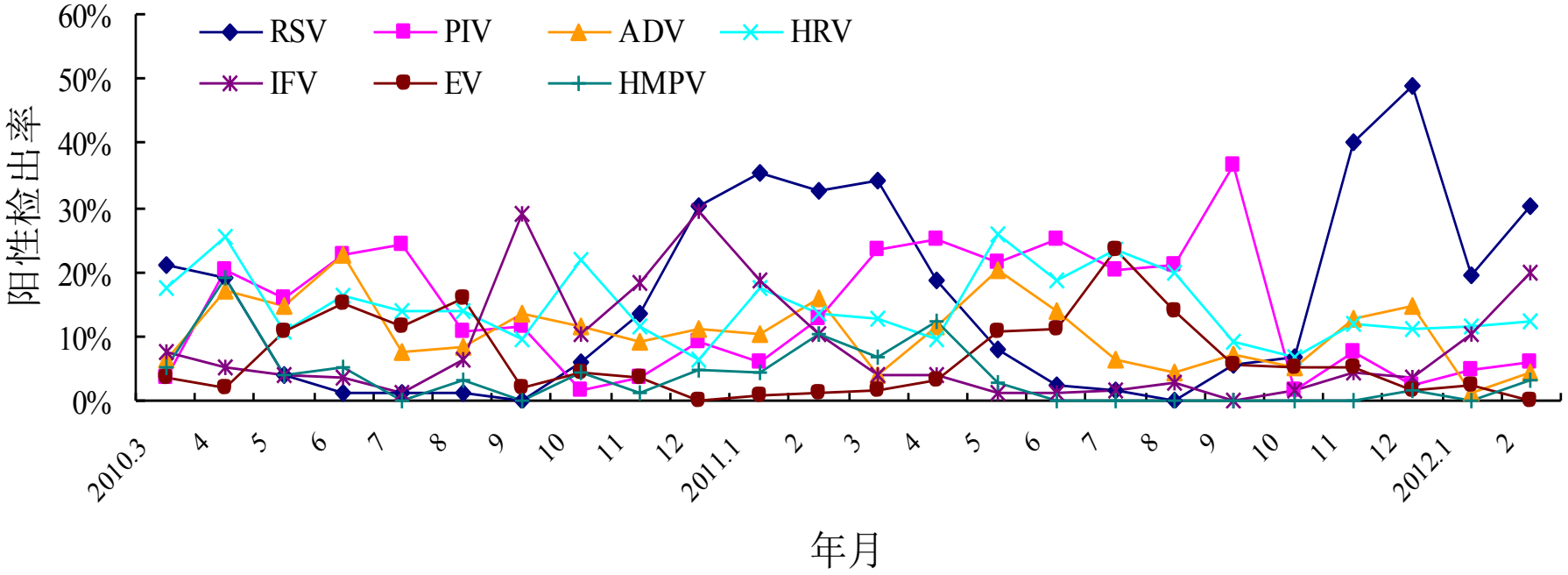


图1 各种病毒感染的季节分布

Clinical manifestations of childhood influenza

一般健康儿童感染流感可能表现为轻型流感，多突然起病，表现为流感样症状，主要症状为发热，体温可达39-40℃，畏寒，多伴流涕，鼻塞，咳嗽，咽痛，头痛，肌痛等，少部分出现腹泻和呕吐等消化道症状。

婴幼儿流感的临床症状往往不典型，可出现高热惊厥。新生儿流感少见，但易合并肺炎，常有败血症表现，如嗜睡、拒奶、呼吸暂停等。在小儿，流感病毒引起的喉炎、气管炎、支气管炎、毛细支气管炎、肺炎及胃肠道症状较成人常见。

Clinical manifestations of childhood influenza

重症患儿病情发展迅速，多在5-7d出现肺炎，体温经常持续39℃以上，呼吸困难，伴顽固性低氧血症，可快速进展为急性呼吸窘迫综合征（ARDS）、脓毒症、感染性休克、心力衰竭、心脏停搏、肾衰竭，甚至多器官功能障碍。其首要死亡原因是呼吸系统并发症。合并细菌感染增加流感死亡率。

1 year and 4 months boy, developed cough and fever, and developed dyspnea and expiration 1 day after onset, and died fourth days after admission

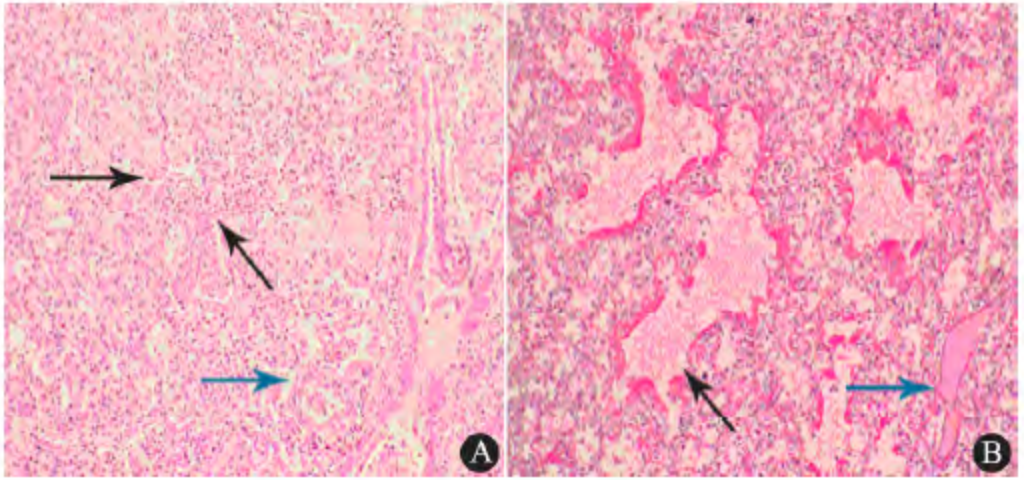


图3　患儿肺组织病理学检查结果

Fig 3　Pathological findings of lung in the patient

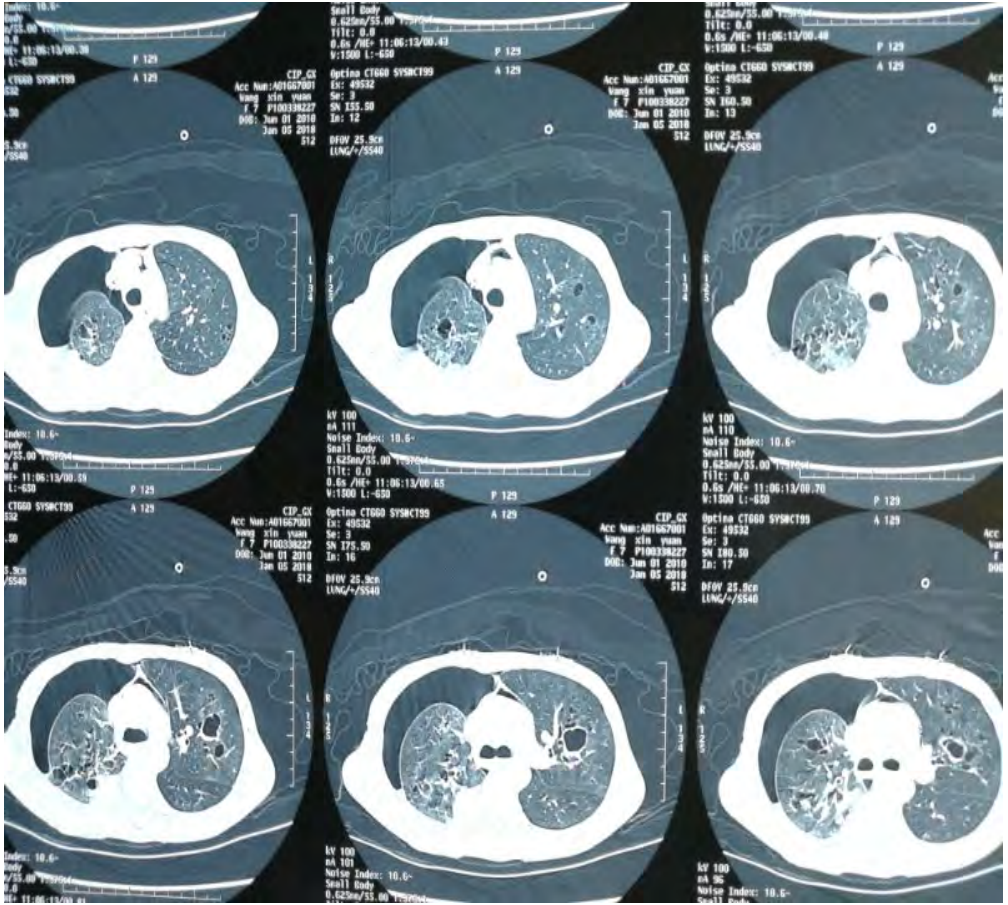
Notes　A: lung consolidation, slurry , neutrophils and monocytes in alveolar space (black arrows), most of the alveolar septa retained (blue arrows), damaged district (HE staining, × 400); B: hyaline membrane: homogenous red edged membranoid substance distributed around the alveolar duct and surface of alveoli (black arrows) , alveoli collapsed (blue arrows) (PAS staining, ×400)

Necrotizing Tracheobronchitis in Influ A H1N1 child

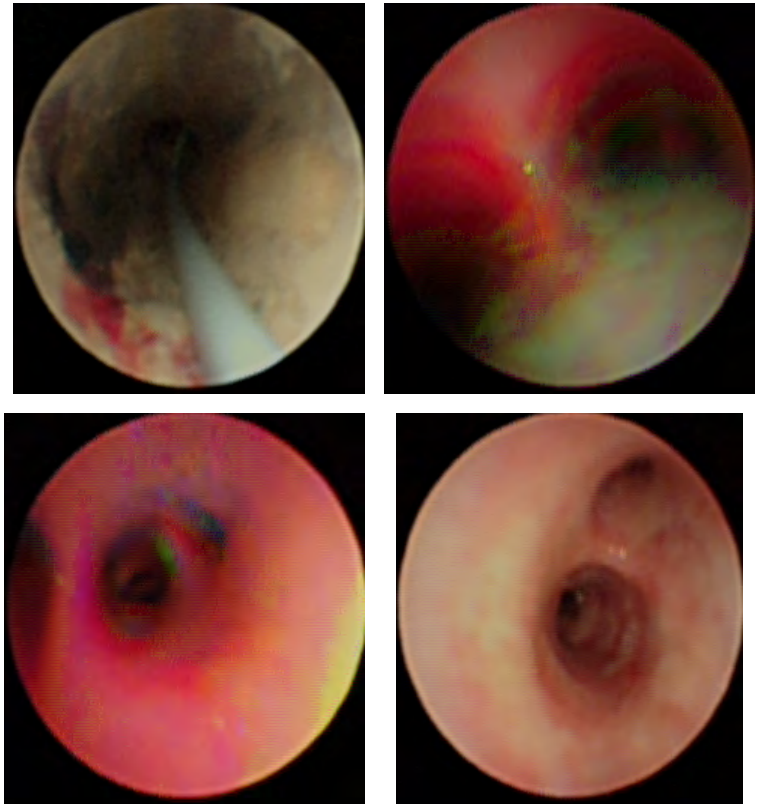
- 7 years old, girl
- Chief complication "fever, cough for 5 days, hoarseness for 2 days" .
- The maximum body temperature is 40℃, with chills, cough with sputum.
- WBC 5.4 *10 ^ 9 / L, N 53.1%, L 38%, HGB 122 g / L, PLT 192 *10 ^ 9 / L, CRP 15mg / L .
- Chest X-ray revealed the inner lung shadow in the right lung.

From Cao Ling, Capital Institute of Pediatrics

lmission）



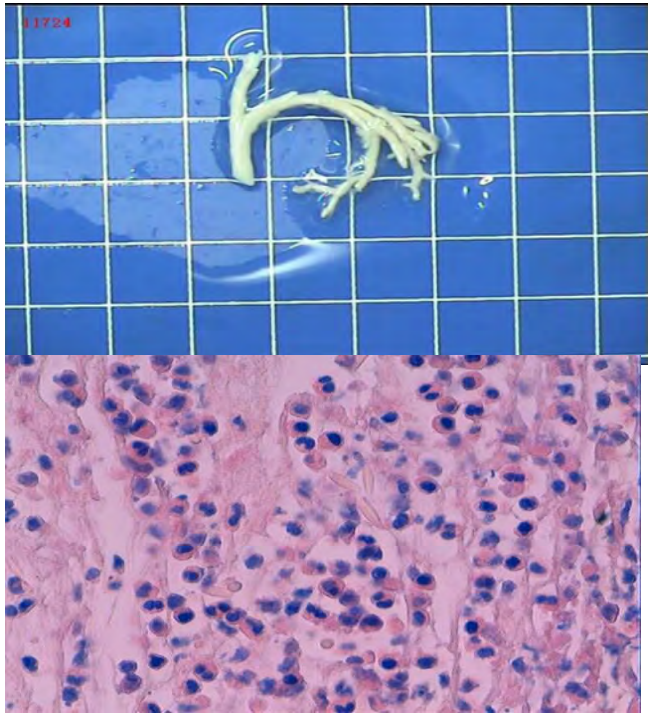
2018-01-05（16th day on admission）

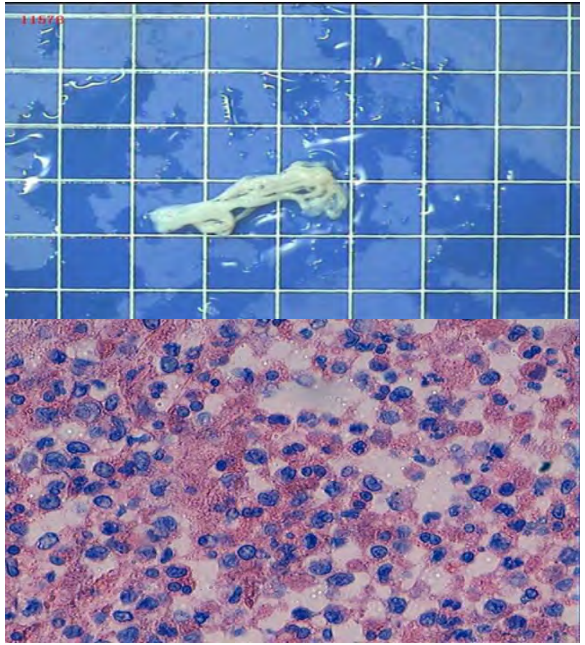


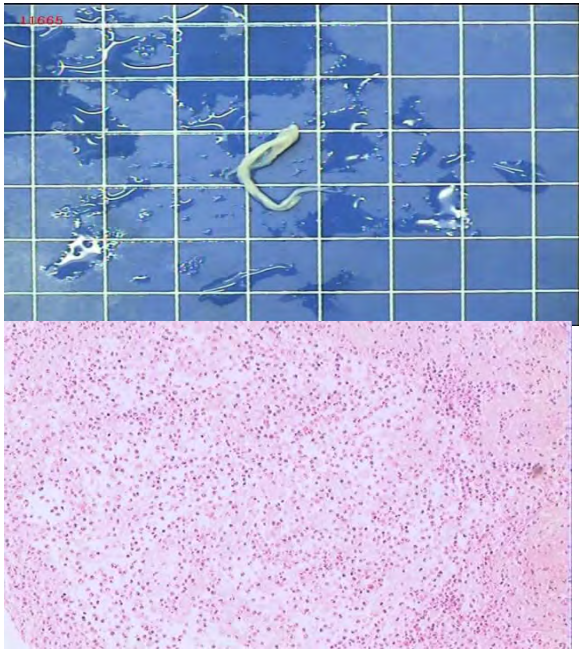
2018-01-08（19th day on admission）

Microscopic diagnosis:
tracheal bronchitis (necrotizing, suppurative)
Mucus congestion and poor ventilation in the right upper lobe, right lower lobe and left lower lobe.
Influenza associated with pseudomembranous tracheobronchitis

Influenza associated plastic bronchitis







Multicenter Clinical study of inpatient children with influenza A(H1N1) in 2009

- 纳入标准：2009年9月1日至2010年2月28日在全国17个单位住院的患儿，年龄在16岁以内
- 均经咽拭子、鼻咽或气管抽取物实时荧光定量PCR（real-time RT-PCR）检测证实为2009甲型H1N1流感病毒感染。
- 实验室检查结果以入院时或第一次为准，按各医院正常参考值，统计增高或降低。

General information

- 810例住院患儿中，男508例，女302例；
- 年龄从1个月至16岁，中位年龄为43个月，5岁以下550例，占67.9%，2岁以下204例，占25.2%；
- 从起病到入院时间（病程）平均5.5 d；平均住院日为9.9 d

Clinical manifestations

临床表现	例数（%）	临床表现	例数（%）
发热	780（96.3）	喘息	219（27.0）
流涕	294（36.3）	呼吸困难	163（20.1）
鼻塞	192（23.7）	呕吐	130（16.0）
咽痛	147（18.1）	腹泻	66（8.1）
头痛	57（7.0）	腹痛	46（5.7）
肌痛	29（3.6）	脱水	6（0.7）
胸痛	13（1.6）	嗜睡（24 h 以上）	64（7.9）
咳嗽	759（93.7）	烦躁（24 h 以上）	79（9.8）
咯痰	347（42.8）	惊厥	32（4.0）
咯血	8（1.0）	昏迷	11（1.4）

发热和咳嗽占90%以上；卡他症状占1/3

喘息和呼吸困难占20%～30%，--儿童特点

消化系统症状占15%；--2009H1N1特点

神经系统症状接近10%，--我国特点

Basic diseases

- **伴有基础疾病148例（18. 5%）**
- 主要：哮喘53例，肾病综合征19例，白血病14例，先心病12例，癫痫12例，
- 其余：过敏性紫癜5例、实体肿瘤4例（淋巴瘤2例、肾母细胞瘤1例、神经母细胞瘤1例）、高热惊厥4例、川崎病3例、地中海贫血3例、缺铁性贫血3例、再生障碍性贫血2例、血小板减少性紫癜2例、手足口病2例、肺结核2例、系统性红斑狼疮、肺透明膜病、间质性肺炎、肾炎、still‘s病、脑瘫、乙型肝炎、溶血性贫血各1例。

Laboratory examinations

实验室检查结果	例数（%）	实验室检查结果	例数（%）
外周血白细胞计数增高	194（24.0）	丙氨酸转氨酶增高	106（13.1）
外周血白细胞计数降低	183（22.6）	天冬氨酸转氨酶增高	257（31.7）
中性粒细胞比率增高	236（29.1）	乳酸脱氢酶增高	346（42.7）
中性粒细胞比率降低	259（32.0）	肌酸激酶增高	174（21.5）
淋巴细胞比率降低	240（29.6）	肌酸激酶同工酶增高	148（18.3）
血红蛋白降低	135（16.7）	肌钙蛋白增高	22（2.7）
血小板降低	80（9.9）	肌酐或尿素增高	27（3.4）
CRP 增高	306（37.8）	心电图异常	87（10.9）
血沉（ESR）增高	114（14.1）		

血常规异常、CRP增高，肝功能异常及心肌酶增高比较常见

Co-infections

- 627例进行了细菌和真菌培养，100例（**15.9%**）阳性，分别为肺炎链球菌34例，真菌12例，溶血链球菌11例，鲍曼不动菌10例，肺炎克雷伯9例，铜绿假单胞菌8例，金黄色葡萄球菌6例，卡他莫拉菌3例，表皮葡萄球菌2例，人葡萄球菌、黄杆菌、奈瑟菌、肠球菌和大肠杆菌各1例。
- 730例进行了肺炎支原体和呼吸道病毒检测，肺炎支原体阳性123例（**16.8%**），呼吸道合胞病毒阳性19例，季节性流感A阳性20例，腺病毒、副流感病毒阳性各2例，EB病毒和CMV阳性各1例。

Complications

- 呼吸系统：586例（72.3%）出现肺炎，其中46例（7.8%）合并胸腔积液，30例（5.1%）合并气胸、纵膈气肿或皮下气肿（除外气管插管机械通气过程中发生者），54例（9.2%）合并ARDS，110例（18.8%）合并呼吸衰竭
- **神经系统：49例(6.0%)，32例脑病，17例脑炎**
- 其他：30例（3.7%）合并心肌炎；7例（0.9%)合并肌炎。

Treatment

- **665例（82.1%）**使用奥司他韦抗病毒治疗，48 h内使用者164例，占20.2%
- **282例（34.8%）**使用甲泼尼龙、地塞米松等肾上腺糖皮质激素治疗—**效果不明确**
- **205例（25.3%）**使用IVIG治疗—**效果不明确**
- **100%** 患儿在住院前或住院时使用抗生素治疗，主要为β内酰胺类抗生素
- **281例（34.7%）**需要吸氧，使用无创持续正压通气治疗者24例
- **159例（19.6%）**需入住ICU
- **88（10.9%）**例接受气管插管和机械通气

Sequelae

- **788例（97.3%）**治愈或好转出院；3例因有严重基础疾病放弃治疗（其中2例同时伴有脑炎/脑病）
- **19例（占住院病例2.3%）**死亡，占危重症病例的10.4%
- **死亡原因：**8例主要死于脑炎/脑病；10例主要死于严重肺炎、ARDS和呼吸衰竭，其中5例同时伴有脑炎/脑病；1例主要死于继发性真菌性脑膜炎
- **流感相关性脑炎/脑病：高的发生率和死亡率与国外的报道明显不同，应该引起国内儿科医生的高度关注**

Results and Conclusion -- High Risk Factors in Critical Cases

因素	危重症（183）	非危重症（627）	OR 值(95%*CI*)	*P* 值
年龄：				
中位年龄	44（月）	42（月）		
5 岁及以上	63（34.4%）	197（31.4%）	1.07（0.75～1.51）	0.12
性别： 男性	123（67.2%）	385（61.4%）	1.29（0.91～1.83）	0.15
WBC 计数增高	**73（39.9%）**	**121（19.3%）**	**2.78(1.94～3.96)**	**<0.01**
WBC 计数降低	45（24.6%）	138（22.0%）	1.16（0.79～1.70）	0.46
中性粒细胞比率增高	**96（52.5%）**	**140（22.3%）**	**3.84（2.72～5.41）**	**<0.01**
中性粒细胞比率降低	45（24.6%）	214（34.1%）	0.63（0.43～0.92）	<0.05
淋巴细胞比率增高	39（21.3%）	115（18.3%）	1.21（0.80～1.81）	0.37
淋巴细胞比率降低	**96（52.5%）**	**144（23.0%）**	**3.70（2.62～5.24）**	**<0.01**
CRP 增高	**106（57.9%）**	**200（31.9%）**	**2.94（2.10～4.12）**	**<0.01**
基础疾病	**46（25.1%）**	**102（16.3%）**	**1.73（1.16～2.57）**	**<0.01**
48 h 内使用奥司他韦	46（25.1%）	118（18.8%）	1.45（0.98～2.14）	0.06

② Clinical guidelines of childhood influenza in China

Releated clinical guidelines on influenza in China

- Guidelines for diagnosis and treatment of influenza(2011)
- Guidelines for epidemic response to ILI outbreaks(2012)
- Management of Community-Acquired Pneumonia in Children (2013 Revised Edition)
- Diagnosis and treatment protocol for human infections with avian influenza A(H7N9)(2014)
- Expert concensus document on clinical management of infected cases with Highly Pathogenic Avian Influenza_H5N1 (draft)
- Technical Guidelines for the Application of Seasonal Influenza Vaccine in China (2014-2015)
- Chinese expert concensus document on treatment and prevention of influenza with antiviral drugs(2016)
- Collection of Technical Documents for Chinese National Influenza Center（2017）
- Influenza diagnose and treatment programme (2018)

Expert Concensus Document on Diagnosis andTreatment of Influenza in Children(2015)


·1296·

·标准·方案·指南·

儿童流感诊断与治疗专家共识(2015年版)

etiology

epidemiology

diagnose

complication

treatment

prevention

1st expert concensus docement on children influenza in China

For further regulating the diagnosis and treatment of influenza in children, Chinese Pediatric Pulmonoogy Society, CMA had organized the Chinese experts to publish ***Expert Concensus Document on Diagnosis and Treatment of Influenza in Children(2015)*** on the base of prior clinical guidelines and new references reported.

This document is suitable for pediatric use to enhance the diagnosis and treatment of influenza in children and reduce the damage for children and society due to influenza in China

Kunling Shen, et al. Chin J Appl Clin Pediatr. 2015,30(17):1296-1303.

③ Treatment of childhood influenza in China

Influenza Antiviral Medications in China

Chin Tradit Pat Med

连花清瘟胶囊

蒲地蓝口服液

双黄连口服液

柴银类制剂

喜炎平注射液

鱼腥草注射液

.....

Chemicals

Oseltamivir

Zanamivir

Peramivir

adamantines

Abidol

Ribavirin

.....

Recommended[1,2]

Oral Oseltamivir

CFDA: children aged ≥1yrs

MSA：all aged children

Inhaled Zanamivir

Children aged ≥7yrs

Peramivir (iv.)

Critically ill patients

[1] Kunling Shen, et al. Chin J Appl Clin Pediatr. 2015,30(17):1296-1303.

[2] Chen Wang, Kunling Shen. Natl Med J China.2016,96(2):85-90.

New Influenza Antiviral medications in China

Osetamivir Phosphate Granules

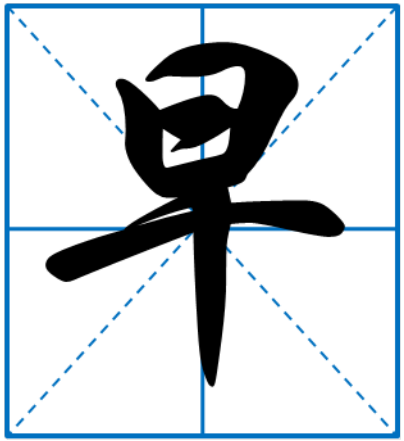
- Global exclusive formulation
- Developed for children
- Marketed in 2008 in China
- Produced by HEC Pharma

New Influenza Antiviral medications in China

The sum. of New influenza antiviral medications approved by CFDA & candidates in China(2010-2015)

Name	Approval time
Peramivir & Sodium Chloride Injection	2013-04-05
Influenza pills	2010
Furong Anti-influenza Tablets/Granules/Capsules	2014/2014/2013
Julan Liugan Tablets/Granules/Capsules	2015/2010/2015
M090(New target candidate) Guangzhou Institutes of Biomedicine & Health , CAS	developing (Inhibit both M2 and IL mediation)

Treatment Principles of Influenza in Children

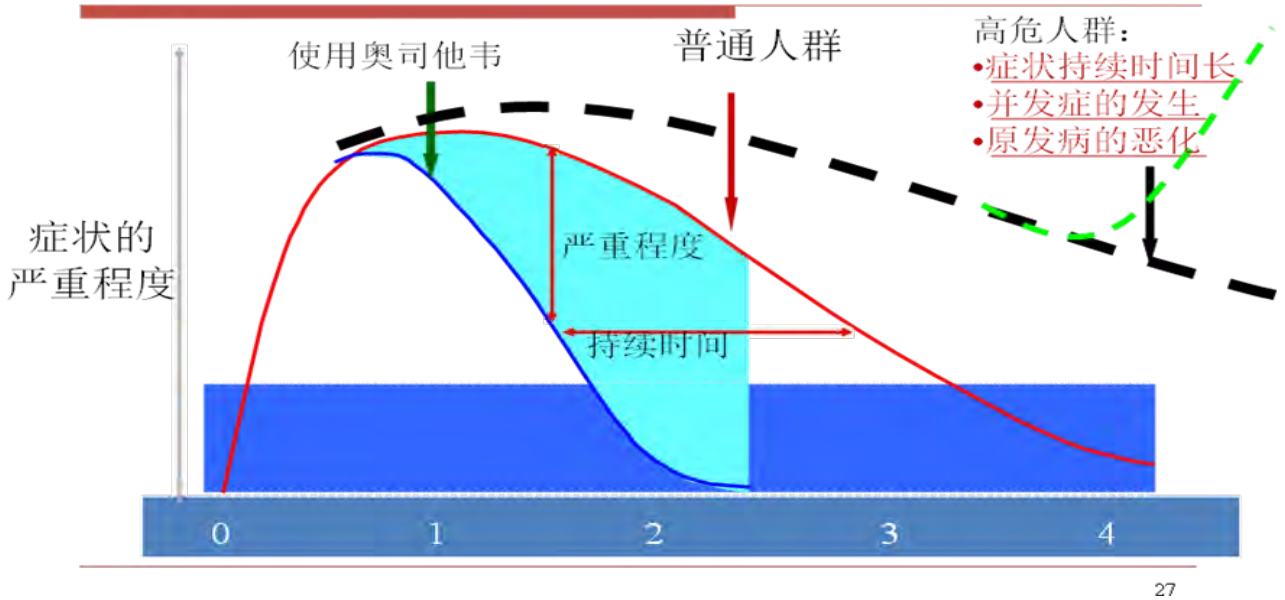


Evaluate the status, criticality, onset timing and local epidemic situation , and then determine the treatment plan. The antiviral treatment should be start within 48h of symptoms onset , avoid abusing antibiotics[1]

Reduce the risk for death and complications from influenza
Shorten the duration of fever and illness symptoms
Reduce the hospitalization rates and economic burden
Save the public medical resources

[1] Kunling Shen, et al. Chin J Appl Clin Pediatr. 2015,30(17):1296-1303.

A schematic diagram of the natural process of childhood influenza and the treatment of oseltamivir



- 使用磷酸奥司他韦，治疗流感病毒引起的感冒，能有效缩短发热时间、缩短病程、减少并发症、减少抗生素的使用；
- 在患者出现临床症状36小时或48小时内尽早开始磷酸奥司他韦治疗

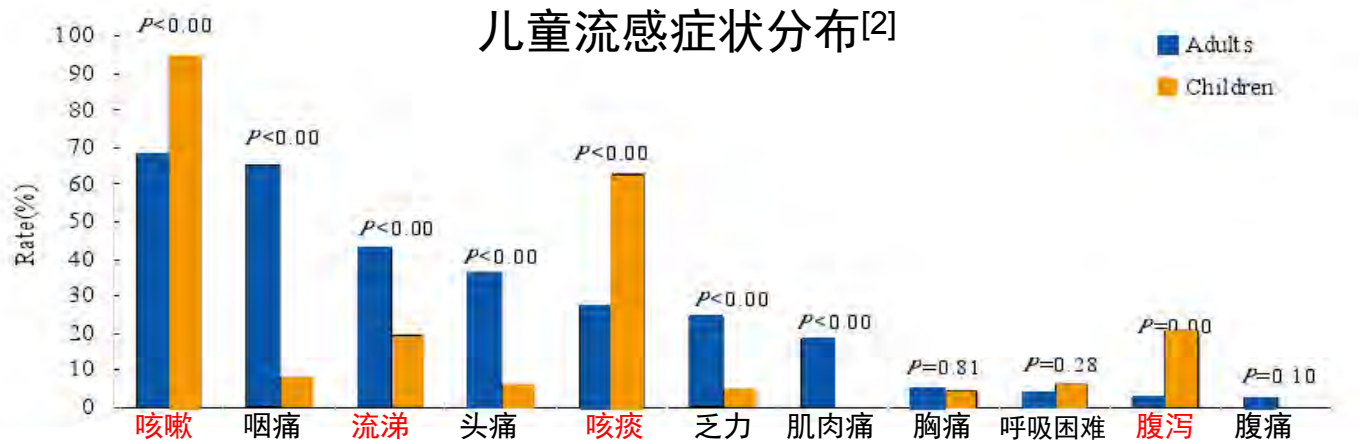
48

Diagnostic criteria

1

流感样症状

发热（腋下体温≥38℃），伴咳嗽或咽痛之一，缺乏实验室确定判断为某种疾病的依据。



[1] 卫生部，流感样病例暴发疫情处置指南（2012年版）
[2] 魏茂提.我国部分地区呼吸系统病毒性病原体检测研究。2011：13-44.

Usage of anti-influenza drugs

适应人群	治疗量(5天)	预防量（10天）
奥司他韦		
≥12个月		
≤15Kg	30mg/次，bid	30mg/次，qd
＞15~23Kg	45mg/次，bid	45mg/次，qd
＞23~40Kg	60mg/次，bid	60mg/次，qd
＞40Kg	75mg/次，bid	75mg/次，qd
9~11个月	3.5mg/(Kg·次)，bid	3.5mg /(Kg·次)，qd
0~8个月	3.0mg/(Kg·次)，bid	3-8月龄 3.0mg/(Kg·次)，qd 0-3月龄需经临床评估
扎那米韦		
≥7岁治疗 ≥5岁预防	10mg，bid	10mg，bid

Recommended dose and course of treatment for anti-influenza virus in children

药物	范围	用药途径	适用范围（FDA）	剂量及疗程（治疗：5d/预防：10d）	耐药	主要副作用
金刚烷胺类（M2I）	甲型	口服	≥1yr	● 目前我国和全球监测资料表明几乎100%及季节性甲性流感病毒（H1N1、H3N2）对烷胺类药物耐药。 ● 不良反应主要见于神经系统，有神经质、焦虑、注意力不集中和轻度头痛等。 ● 不建议单独应用金刚烷胺和金刚乙胺治疗及预防甲型流感病毒感染！		
金刚乙胺（M2I）	甲型	口服	≥1yr			
奥司他韦(NAI)	甲型&乙型	口服	治疗≥14d 预防≥3个月	儿童（颗粒剂） 治疗：最佳给药时间为48h以内，症状出现96h后给药也有疗效，儿童使用奥司他韦是安全的。 ● 早产儿使用剂量低于足月儿 ● 胎岭小于38周，剂量为1.0mg/kg•次，bid ● 胎龄38~40周婴儿，1.50mg/kg•次，bid ● 胎龄40周以上3mg/kg•次，bid 预防：3mg/kg•次，qd	• 我国季节性甲型流感病毒（H3N2）、2009年甲型H1N1流感病毒敏感。 • 国外研究报道有1.2%的H1N1流感毒株对其耐药。	主要是胃肠道症状
扎那米韦(NAI)	甲型&乙型	吸入	≥7yr	10mg(分两次吸入，bid，间隔12h)	很少	不建议用于重症或有并发症的患者

Use security

Safety of use of oseltamivir phosphate worldwide

	2007	2008	2009	2010	2011
0~16岁	696310	1107679	3245291	443371	1075599
17岁以上	884598	2338946	4186960	650537	1594029
年龄不确定	134	59	204	678	896
处方总量	1581042	344685	7432455	1094585	2670524

FDA：截至2011年16岁以下儿童使用5941250张处方，结论是安全的。

FDA关于 1～12岁儿童患者临床安全性试验：

- 1032例1～12岁的患者，其中698名无基础病患儿和334名有哮喘病史的6～12岁患儿
- 患儿中发生率大于1%的不良事件最高的是呕吐，其他比较常见的不良事件是腹痛、耳痛和结膜炎。这些不良事件一般只出现一次，继续服药也可缓解，大多数情况下不会导致停止治疗。不良事件和药物无直接相关性。
- 磷酸奥司他韦组儿童恢复正常的健康和活动的时间较安慰剂组提前约2天。

④ Prevention of childhood influenza in China

Global authoritative recommendations-WHO/ CDC

World Health Organization

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

CDC 中国疾病预防控制中心
CHINESE CENTER FOR DISEASE CONTROL AND PREVENTION

世界卫生组织（WHO）

美国疾病预防控制中心（美国CDC）

中国疾病预防控制中心（中国CDC）一致推荐：

接种流感疫苗是预防流感的最有效手段[1-4]

CDC > MMWR

Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2018–19 Influenza Season

Recommendations and Reports / August 24, 2018 / 67(3):1–20

1. WHO. 流感（季节性）. 实况报道. 2016年11月. http://www.who.int/mediacentre/factsheets/fs211/zh/
2. https://www.cdc.gov/flu/protect/keyfacts.htm
3.https://www.cdc.gov/mmwr/volumes/67/rr/rr6703a1.htm?s_cid=rr6703a1_w
4. 冯录召, 等. 中华流行病学杂志. 2014;35(12):1295-1319.

Vaccination status of the United States influenza season 2017-2018

National Early-Season Flu Vaccination Coverage, United States,

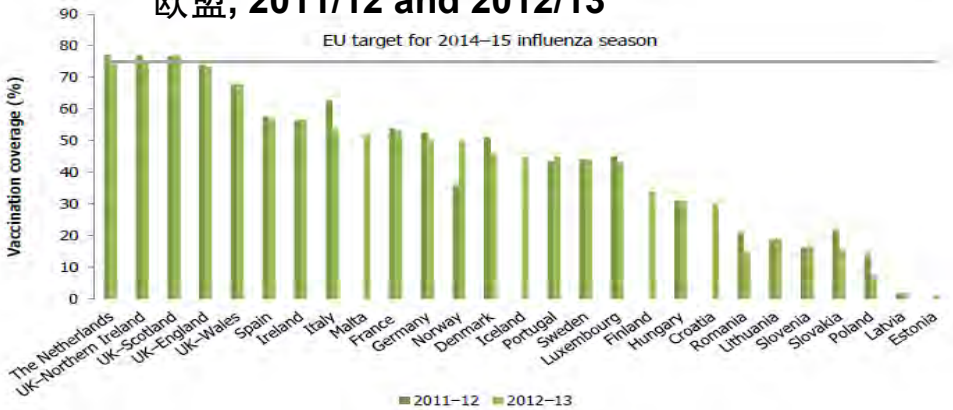
Key Findings

- Only approximately two of every five children and adults in the United States had received an influenza (flu) vaccination by early November 2017:
  - 38.6% of all persons 6 months and older
  - 38.8% of children 6 months through 17 years
  - 38.5% of adults 18 years and older

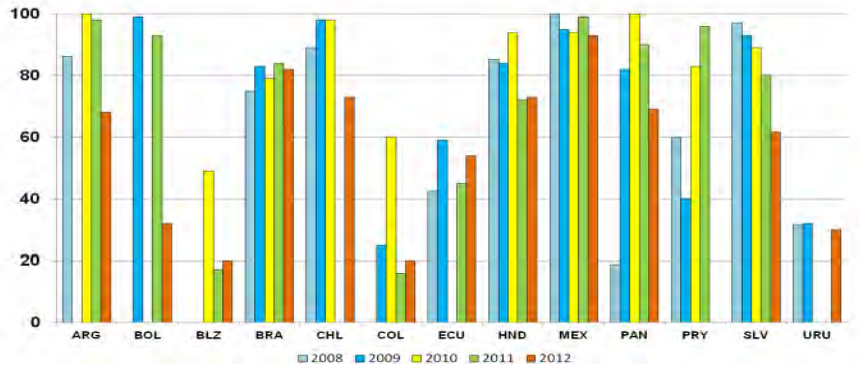
https://www.cdc.gov/flu/fluvaxview/nifs-estimates-nov2017.htm

Influenza vaccination rates in different nations

欧盟, 2011/12 and 2012/13



拉丁美洲. 2008-2012



巴西2016年人群	流感疫苗覆盖率（%）
儿童（6个月-5岁）	66.47
医务工作者	86.50
孕妇	56.63
产妇（产后< 45天）	79.37
老年人	72.92
原住民	38.80
总体（包括其他人群）	70.51

中国, 5 城市居民

- 北京山东湖南河南四川: 2009/10 8.5%；2010/11 9.5%；2011/12 4.3%
- 远低于发达国家以及部分发展中国家

Pan American Health Organization (2014); ECDC;

http://ecdc.europa.eu/en/press/news/_layouts/forms/News_DispForm.aspx?List=8db7286c-fe2d-476c-9133-18ff4cb1b568&ID=1154 ;

1. 孕妇
2. 6 月龄以下婴儿的家庭成员和看护人员
3. 6~23月龄的婴幼儿
4. 2~5岁儿童
5. 60岁及以上老年人
6. 特定慢性病患者
7. 医务人员

Influenza Vaccines in China

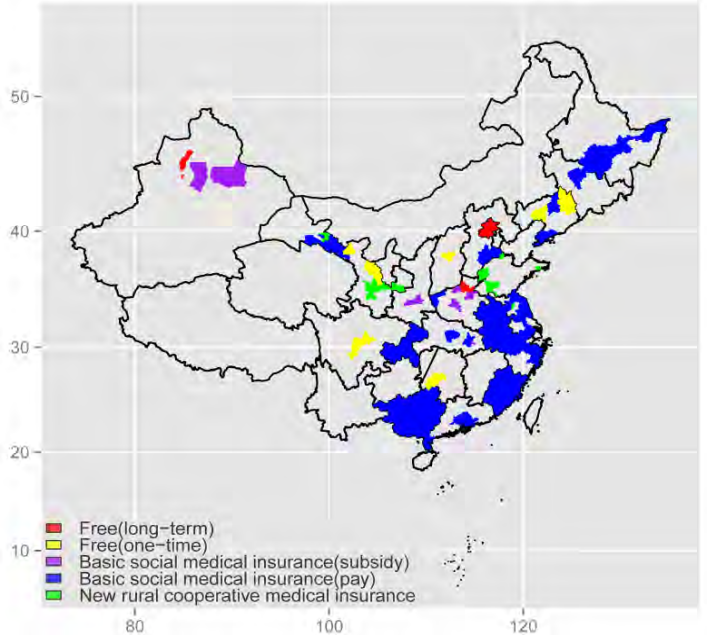
Vaccine Dose for Children	● TIV, suitable for children aged ⩾6months ● 0.25ml type/each HA7.5ug, suitable for infant aged 6~35 months ● 0.5ml type/each HA15ug,suitable for children aged ⩾36months
Vaccine priority children	● **The household and caregivers of Infants aged ＜6 months**. ● **Infants aged 6-23months**：the high risk of severely ill case，and high hospitalization burden , should be priority for vaccination. ● **Children aged 2~5 years**：higher disease burden, lower than the group aged ⩽2years. ● **Children with some chronic medical conditions** , eg, chronic respiratory disease.

Technical Guidelines for the Application of Seasonal Influenza Vaccine in China (2014-2015)

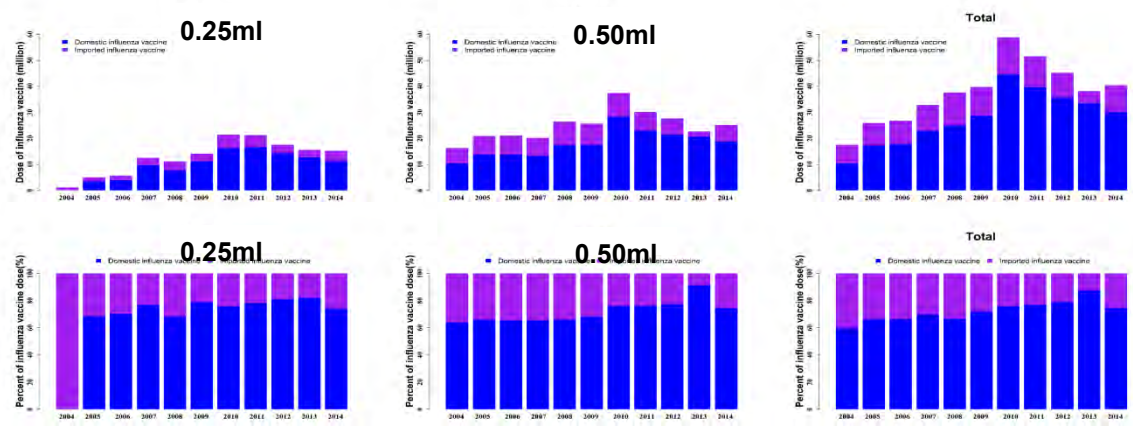
Influenza Vaccines in China

Special policy of influenza vaccination in the some regions of China

- **Regions of Long term for free**: Beijing, Karamay , Xinxiang
- **Regions of one time for free** : Shanghai（EXPO time）, Liaoning（Flood area）
- **Basic medical Insurance , New rural cooperation medical insurance**



Influenza Vaccines in China



- During 2004-2010，the supply of influenza vaccines rised from 17.5 million doses (13.6 dose/ 1000 person) to 58.8 million doses (44.1 dose/1000 person,235%).In 2013,reduced to the level in 2008,and then rised slightly in 2014.
- The vaccine coverage rate in person aged ≥6months is only 1.3-3.6% in China.
- The rate of domestic vaccines rised from 60% in 2004 to 87% in 2013.

Technical Guidelines for the Application of Seasonal Influenza Vaccine in China (2014-2015)

In Beijing, school-based vaccinations reduced a substantial number of influenza

- The author developed a dynamic transmission model to assess the impact of influenza vaccination in school children， by uing existing surveillance and immunization data,aged 5-14 years for the 2013/14, 2014/15, and 2015/16 seasons.
- The corresponding prevented fractions to all children aged 5-14 years were 76.3%, 38.5%, and 43.9%.

Yi Zhang. Influenza Other Respi Viruses. 2018;1–8.

Influenza Chemoprophylaxis in China

Antiviral medications

Oseltamivir：

For the recommended，
take the medicine within 48h exposed continuously till the last exposed 7-10d.
If not taken the medicine within 48h,also be recommended to administration

RECOMMENDED PERSON

1. For children at high risk of complications from influenza for whom influenza vaccine is contraindicated, or who are immunocompromised and may not respond to vaccine.

2. For children at high risk during the 2 weeks after influenza immunization

3. For family members or HCP who are close exposure to the unimmunized children at high risk, or unimmunized children who are younger than 24 months.

4. For control of influenza outbreaks for unimmunized staff and children in a closed institutional setting with children (eg, kindergarten)

5. For postexposure prophylaxis to the family members and close contacts of an infected person.

6. When circulating strains of influenza virus in the community are not matched with seasonal influenza vaccine strains

[1] Kunling Shen, et al. Chin J Appl Clin Pediatr. 2015,30(17):1296-1303.

Conclusions

1. There is great affected children's population in China, involving 22-33 million children per year.
2. Children is susceptible to influenza, and the high-risk group of critical cases. Some severe complications could be found in children with influenza A.
3. The diease burden of influenza effected children in China is substantial， particularly for **children aged ＜5 years.**
4. At present China has established Comprehensive ILI& Flu etiology monitoring system , that can detect and report the influenza variation in time.
5. The seasonal influenza vaccine coverage rate in China is low.
We need improve it in future.

Thanks for your attention