

# It Takes a Program To Vaccinate Safely and Effectively

DCVMN Training Workshop: Vaccine Safety and  
Pharmacovigilance Strategies

**Developing Countries Vaccine Manufacturers Network**

Beijing, P.R. China

May 8, 2017

Lance Rodewald, MD

**WHO China Office, EPI Team  
WPRO, World Health Organization**

**MEASLES**



**RUBELLA**



**POLIO**



**VARICELLA**



**MENINGOCOCCEMIA**



**HAEMOPHILUS  
INFLUENZAE  
TYPE B**



**MUMPS**



**DIPHThERIA**

# Vaccines Can Be Great Tools for Public Health

## 疫苗能够成为公共卫生的伟大工具

- Vaccine developers see a burden of disease worthy of prevention
- Vaccines are licensed on the basis of effectiveness, safety, and production consistency
- But, should a vaccine be used?
  - Benefits > risks and costs?
- And if so, **how** should the vaccine be used?
  - The answer to this question should come from the program
- 疫苗研发者看到了值得去预防的疾病的负担
- 疫苗在基于有效性、安全性和产品一致性后予以注册
- 但是，是不是疫苗就该使用呢？
  - 收益>风险和花费
- 如果收益>风险和花费，那又该怎么用？
  - 这个问题的答案应该从免疫规划这里来找

# Goals Are Constrained by Biology

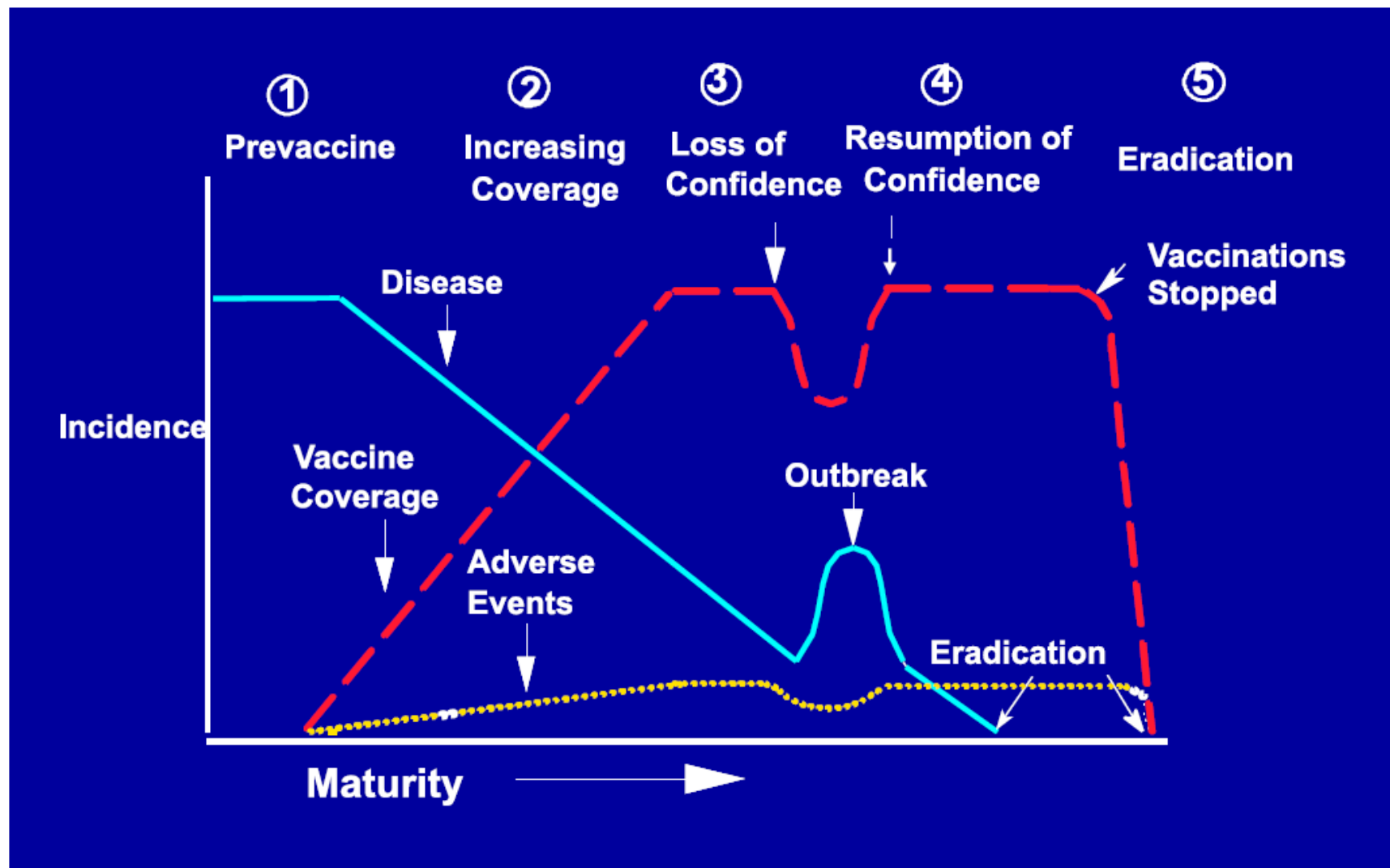
## 目标会受到生物学的限制

- Goals
    - Individual protection
    - Control
    - Elimination
    - Eradication
  - Constraints
    - Age-based vaccine efficacy
    - Duration of protection
    - Post-exposure prophylaxis?
    - Pathogen stability
    - Non-human reservoir?
    - Population characteristics
- 目标
    - 个人保护
    - 控制
    - 消除
    - 消灭
  - 限制
    - 基于年龄的疫苗效力
    - 保护时限
    - 暴露后预防
    - 病原稳定性
    - 非人类宿主
    - 人群特征

# Strategy Transforms Goals Into Recommendations

## 免疫策略把目标转化为建议

- Recommendations
  - Biologically achievable
  - Programmatically feasible
  - Based on evidence
    - Surveillance
    - Epidemiology
    - Vaccinology
- This sounds good, but it is only the start
- 建议
  - 生物学上是可成功的
  - 操作上是可行的
  - 基于证据
    - 监测
    - 流行病学
    - 疫苗学
- 听起来不错，但这只是开始



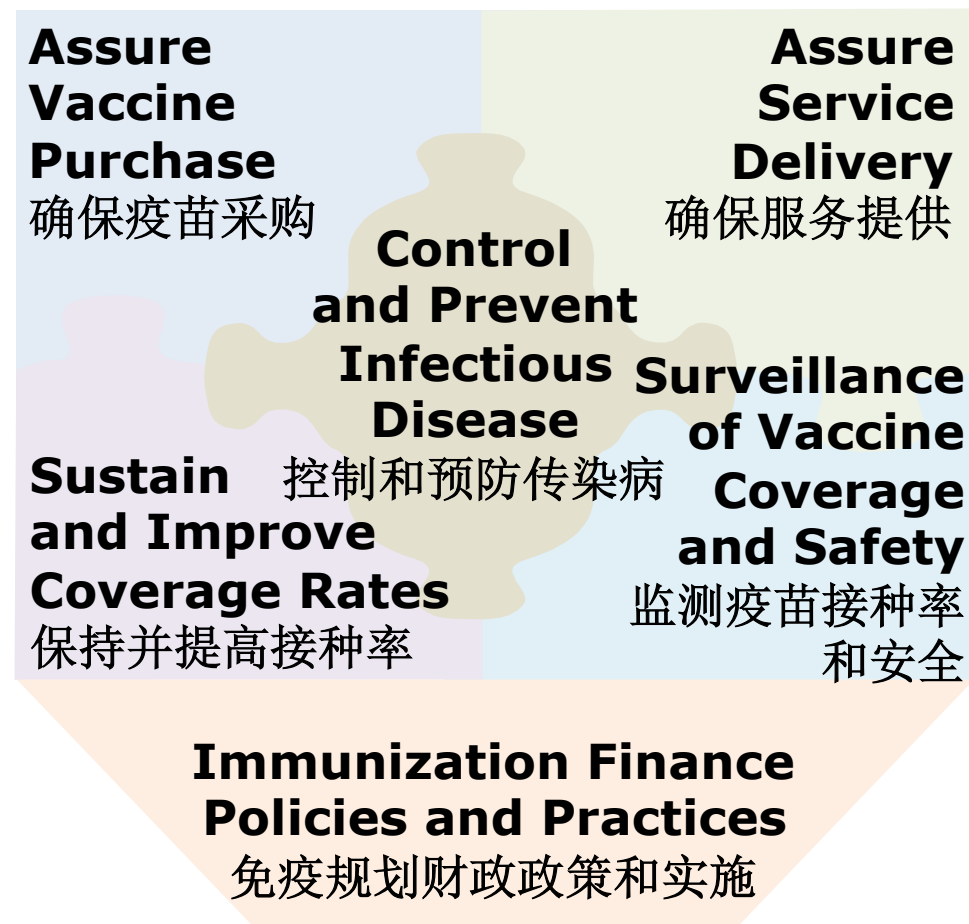
**FIGURE 2**

Evolution of a vaccine program. Reproduced with permission. Chen RT, Orenstein WA. Epidemiologic methods in immunization programs. *Epidemiol Rev.* 1996;18(2):102. Copyright © 1996 by the Oxford University Press.



# Six Roles of Immunization Programs

## 免疫规划的六个功能



# Critically Important Immunization Monitoring and Evaluation

## 至关重要的预防接种监测和评估

- Disease surveillance: outbreak and case analyses
  - Vaccine safety:
  - Vaccine effectiveness:
  - Vaccine supply:
  - Parent perceptions:
  - Provider practices:
  - Coverage: clinic, school, population
  - **Adds up to monitoring program policy and performance so that policy can be adjusted as needed to achieve goals**
- 疾病监测：暴发和病例分析
  - 疫苗安全性
  - 疫苗有效性
  - 疫苗供应
  - 父母认知
  - 接种人员实践
  - 接种率：诊所、学校、人群
  - 监测免疫规划政策和实施情况，以便政策可以根据需要进行调整，并最终实现目标



## MAJOR ARTICLE

# Evaluation of the Impact of Hepatitis B Vaccination among Children Born during 1992–2005 in China

Xiaofeng Liang,<sup>1,a</sup> Shengli Bi,<sup>2,a</sup> Weizhong Yang,<sup>1,a</sup> Longde Wang,<sup>3,a</sup> Gang Cui,<sup>3</sup> Fuqiang Cui,<sup>1</sup> Yong Zhang,<sup>2</sup> Jianhua Liu,<sup>1</sup> Xiaohong Gong,<sup>1</sup> Yuansheng Chen,<sup>1</sup> Fuzhen Wang,<sup>1</sup> Hui Zheng,<sup>1</sup> Feng Wang,<sup>2</sup> Jing Guo,<sup>1</sup> Zhiyuan Jia,<sup>2</sup> Jingchen Ma,<sup>5</sup> Huaqing Wang,<sup>1</sup> Huiming Luo,<sup>1</sup> Li Li,<sup>1</sup> Shuigao Jin,<sup>1</sup> Stephen C. Hadler,<sup>4</sup> and Yu Wang<sup>1</sup>

<sup>1</sup>Chinese Center for Disease Control and Prevention, <sup>2</sup>Institution of Virology Disease Control, Chinese Center for Disease Control and Prevention, <sup>3</sup>Ministry of Health, and <sup>4</sup>World Health Organization, Beijing, and <sup>5</sup>Hebei Provincial Center for Disease Control and Prevention, Shijiazhuang, China

## EXPERT REVIEWS

# Control of hepatitis B in China: prevention and treatment

*Expert Rev. Anti Infect. Ther.* 9(1), 21–25 (2011)

Yu Wang<sup>1</sup> and Jidong Jia<sup>1</sup>

<sup>1</sup>Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China  
<sup>\*</sup>Author for correspondence: jia\_jd@ccmu.edu.cn

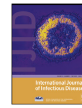
A high rate of chronic HBV infection in China is mainly the result of perinatal or early childhood transmission. Therefore, universal vaccination against HBV in infants has been very successful in the control of chronic HBV infection, with the prevalence of hepatitis B surface antigen decreasing from nearly 10% to approximately 7% in the general population. Adoption of Good Clinical Practice and proper conduction of well-designed clinical trials on conventional and pegylated interferons and nucleos(t)ide analogs have generated important clinical data. The publication and promotion of the evidence-based national guidelines have greatly improved the

International Journal of Infectious Diseases 16 (2012) e82–e88



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International Journal of Infectious Diseases

journal homepage: [www.elsevier.com/locate/ijid](http://www.elsevier.com/locate/ijid)



Review

Impact of the implementation of a vaccination strategy on hepatitis B virus infections in China over a 20-year period

Zhuanbo Luo, Lanjuan Li, Bing Ruan<sup>\*</sup>

National Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qing-Chun Road, Hangzhou 310003, People's Republic of China

Hu et al. *BMC Infectious Diseases* 2012, **12**:221  
<http://www.biomedcentral.com/1471-2334/12/221>



## RESEARCH ARTICLE

Open Access

Gaps in the prevention of perinatal transmission of hepatitis B virus between recommendations and routine practices in a highly endemic region: a provincial population-based study in China

Yali Hu<sup>1,4†</sup>, Shu Zhang<sup>1†</sup>, Chao Luo<sup>1</sup>, Qilan Liu<sup>2</sup> and Yi-Hua Zhou<sup>3,4\*</sup>

Timely birth dose and infant vaccination

# HEPATITIS B STRATEGY

REVIEW

*Human Vaccines & Immunotherapeutics* 11:6, 1534–1539; June 2015; © 2015 Taylor & Francis Group, LLC

# Strategy vaccination against Hepatitis B in China

Xueyan Liao and Zhenglun Liang

National Institutes for Food and Drug Control No.2, Tiantan Xili, Beijing, China

# Hepatitis B Transmission from Mother to Newborn (1)

## 乙肝的母婴传播（1）

- Women with chronic HBV infection have active HBV virus in their blood and body fluids
- During pregnancy, the developing fetus is protected from infection by the placenta
- However, during childbirth, the baby becomes covered with the mother's blood and body fluids
- This exposes the baby to active and infectious hepatitis B virus
- 慢性乙肝感染的女性，其血液和体液中有活动的乙肝病毒
- 怀孕期间，成长中的胎儿由胎盘保护其免受感染
- 但是，在生产过程中，婴儿会被母亲的血液和体液所覆盖
- 这导致婴儿暴露于活动性和感染性的乙肝病毒

# Hepatitis B Transmission from Mother to Newborn (2)

## 乙肝的母婴传播（2）

- The active HBV virus will usually infect the newborn baby if nothing is done
- If a newborn baby is infected, he or she will almost certainly develop chronic, lifelong hepatitis B infection
- Babies that are infected during childbirth usually will not show signs of illness – they will appear healthy, often for decades
- People with chronic HBV infection can then transmit HBV virus to others
- 如果什么措施也不采取，活动性乙肝病毒通常会感染新生儿
- 如果新生儿被感染，他/她将几乎必然发展为慢性和终生感染乙肝的状态
- 生产过程感染乙肝病毒的婴儿一般将不会出现疾病症状，他们会表现为健康，并持续数十年。
- 慢性乙肝感染人群可以把病毒传给别人

# HBV Vaccination Strategy

## 乙肝疫苗接种策略

- Timely HBV vaccine can cause the baby's immune system to resist HBV infection by inactivating the virus
- But, HBV vaccination has to happen quickly, before the HBV infection occurs –within 24 hours of birth
- Therefore, vaccination of babies born to mothers with chronic HBV infection is a medical emergency
- Two more HBV vaccine doses must also be given during infancy for full protection
- 及时接种乙肝疫苗，能够通过灭活的病毒使婴儿的免疫系统抵御乙肝病毒的感染。
- 但是，乙肝疫苗的接种必须很快完成。乙肝病毒感染发生之前—出生后24小时之内。
- 因此，对慢性乙肝母亲生育儿童接种疫苗应属紧急的医疗处置措施。
- 婴儿期内，必须接种2剂次以上的乙肝疫苗来实现全程保护。

# Prevention of Chronic Hepatitis B Infection

## 控制慢性乙肝感染

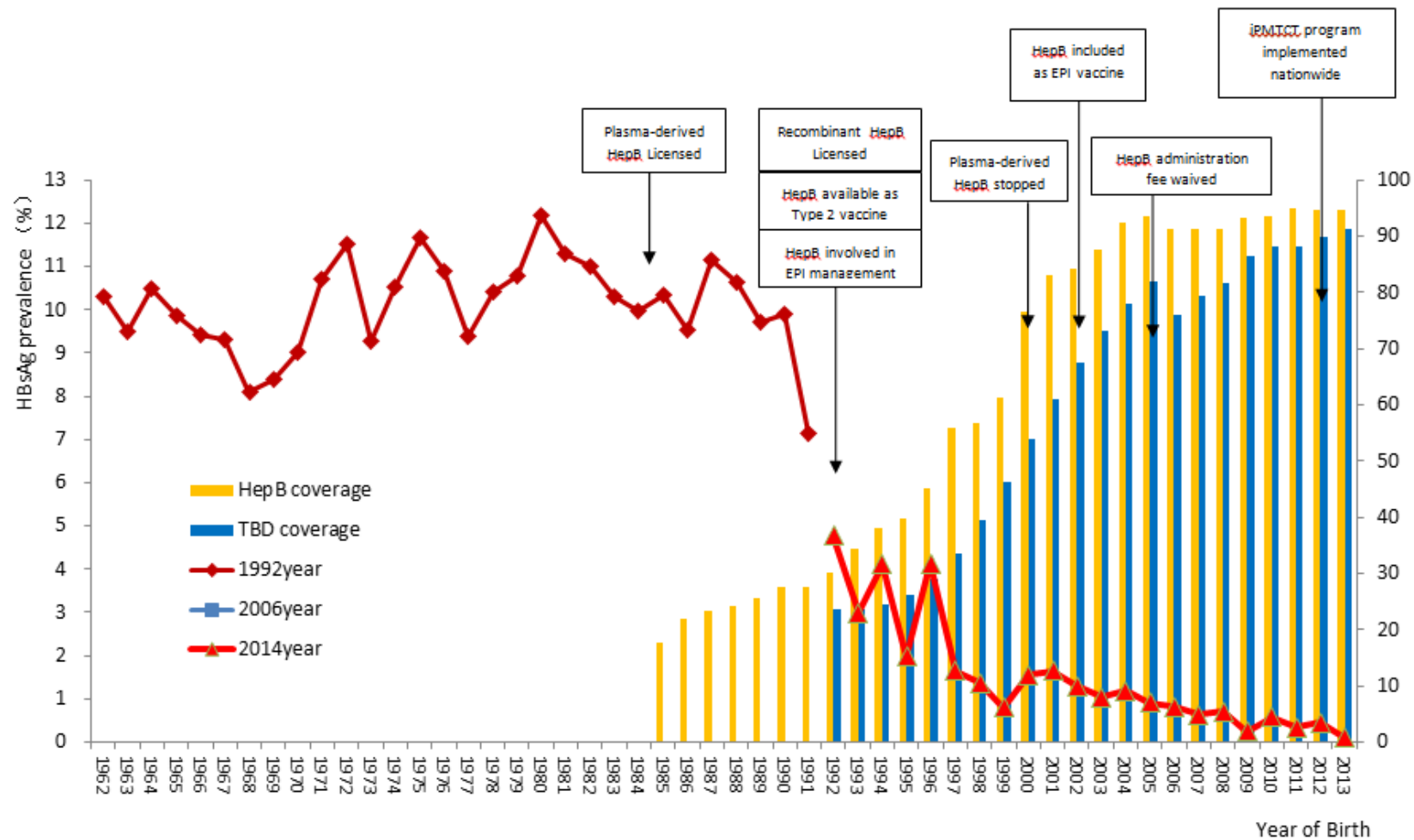
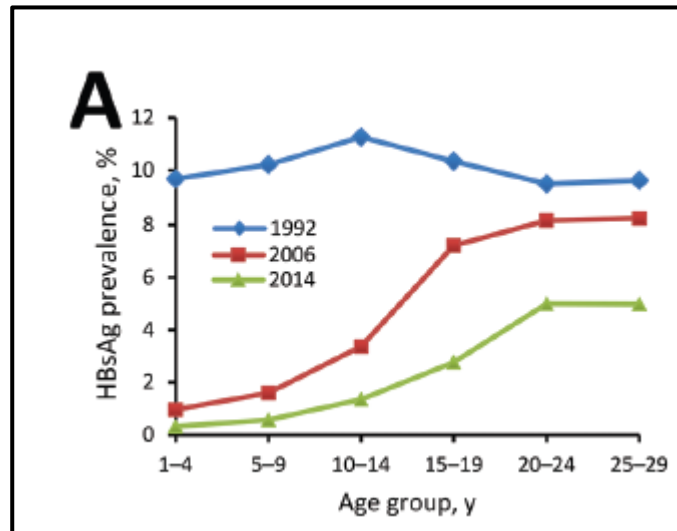


Figure modified from: Cui FQ, et al. Prevention of Chronic Hepatitis B after 3 Decades of Escalating Vaccination Policy, China. *Emerging Infectious Diseases*, 2017;23(5):765-772.

# Prevention of Chronic Hepatitis B after 3 Decades of Escalating Vaccination Policy, China

Fuqiang Cui,<sup>1</sup> Lipin Shen,<sup>1</sup> Li Li,<sup>1</sup> Huaqing Wang,<sup>1</sup> Fuzhen Wang,<sup>1</sup> Shengli Bi,  
Jianhua Liu, Guomin Zhang, Feng Wang, Hui Zheng, Xiaojin Sun, Ning Miao,  
Zundong Yin, Zijian Feng, Xiaofeng Liang, Yu Wang



## Discussion

Compared with the prevaccine era, chronic HBV infection in China has been reduced by 90% (from 10.5% to 0.8%) among children <15 years of age and by 97% (from 9.9% to 0.3%) among children <5 years of age. Disparities by region and urban/rural status that existed among young children in 1992 and 2006 were largely eliminated by 2014. Lower HBsAg prevalence among young children in 2014 (1.0%) compared with 2006 (0.3%) shows increasing effectiveness of the program.

HBsAg prevalence among 1–29-year-olds declined 46% during 1992–2006 (from 10.1% to 5.5%) and 52% during 2006–2014 (from 5.5% to 2.6%). As a result of China's program, an estimated 120 million HBV infections and 28 million chronic infections were averted.







**IJE**

*International Journal of Epidemiology*, 2016, 441–449  
doi: 10.1093/ije/dyv349  
Original article



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Health Policies and Interventions

## Loss of confidence in vaccines following media reports of infant deaths after hepatitis B vaccination in China

Wenzhou Yu,<sup>1†</sup> Dawei Liu,<sup>1†</sup> Jingshan Zheng,<sup>1†</sup> Yanmin Liu,<sup>1†</sup> Zhijie An,<sup>1†</sup> Lance Rodewald,<sup>2†</sup> Guomin Zhang,<sup>1</sup> Qiru Su,<sup>1</sup> Keli Li,<sup>1</sup> Disha Xu,<sup>1</sup> Fuzhen Wang,<sup>1</sup> Ping Yuan,<sup>1</sup> Wei Xia,<sup>2</sup> Guijun Ning,<sup>1</sup> Hui Zheng,<sup>1</sup> Yaozhu Chu,<sup>1</sup> Jian Cui,<sup>1</sup> Mengjuan Duan,<sup>1</sup> Lixin Hao,<sup>1</sup> Yuqing Zhou,<sup>1</sup> Zhenhua Wu,<sup>1</sup> Xuan Zhang,<sup>1</sup> Fuqiang Cui,<sup>1</sup> Li Li<sup>1</sup> and Huaqing Wang<sup>1\*</sup>

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EXCLUSIVES: CDC admits lies Gravity water filters lab test results Top 10 Ebola preps to do NOW Nature's antivirals revealed CDC






### Hepatitis B vaccine kills eight babies in China; drug manufacturer says 'coincidence'


Friday, March 07, 2014 by: Ethan A. Huff, staff writer  
Tags: vaccines, baby deaths, hepatitis B

## Commentary: Assessing the impact of temporally associated adverse events on neonatal hepatitis B vaccination

Eric Wiesen<sup>1</sup> and Xi Li<sup>2</sup>

<sup>1</sup>Global Immunization Division, Centers for Disease Control and Prevention. E-mail: ejw2@cdc.gov and <sup>2</sup>Consultant. E-mail: xi.cira.li@gmail.com

*International Journal of Epidemiology*, 2016, 449–450  
doi: 10.1093/ije/dyv080



Coincidental deaths following HBV vaccination

# 2013-2014 HEPATITIS B EVENT

# 2013-2014 乙肝疫苗事件

# What Happened? (1)

## 发生什么？（1）

- Hunan Economic News reported that 2 infants died after receiving Biokangtai HBV vaccine
- CFDA and NHFPC sent experts to investigate
- 19 DEC - Media reported 2 more deaths following BKT HepB vaccine
- 17 deaths and 1 case of allergic shock following BKT HepB reported
- 21 DEC – CFDA suspends all BKT vaccine
- 湖南经济新闻报道了2例婴儿接种康泰公司的乙肝疫苗后死亡
- 食药总局和卫生计生委派出专家开展调查
- 12月19日，媒体报道了另外2例接种康泰乙肝疫苗死亡的病例
- 报道了17例死亡和1例过敏性休克病例是由于接种了康泰乙肝疫苗
- 12月21日，食药总局叫停了所有康泰疫苗

# What Happened? (2)

## 发生什么（2）

- CFDA and NHFPC conducted joint investigations
  - Clinical and epidemiological
  - Vaccine tests
  - Manufacturing practices and facility
- WHO invited to participate in inspections and review data
- 3 JAN – Announcement of preliminary investigation results
  - Deaths were coincidental
  - WHO supported results
- 食药总局和卫计委开展联合调查
  - 临床和流行病学调查
  - 疫苗检测
  - 生产过程和设施调查
- 世卫组织被邀请参与检查和核实数据
- 1月3日，公布了初步的调查结果
  - 死亡病例是耦合
  - 世卫支持调查结果

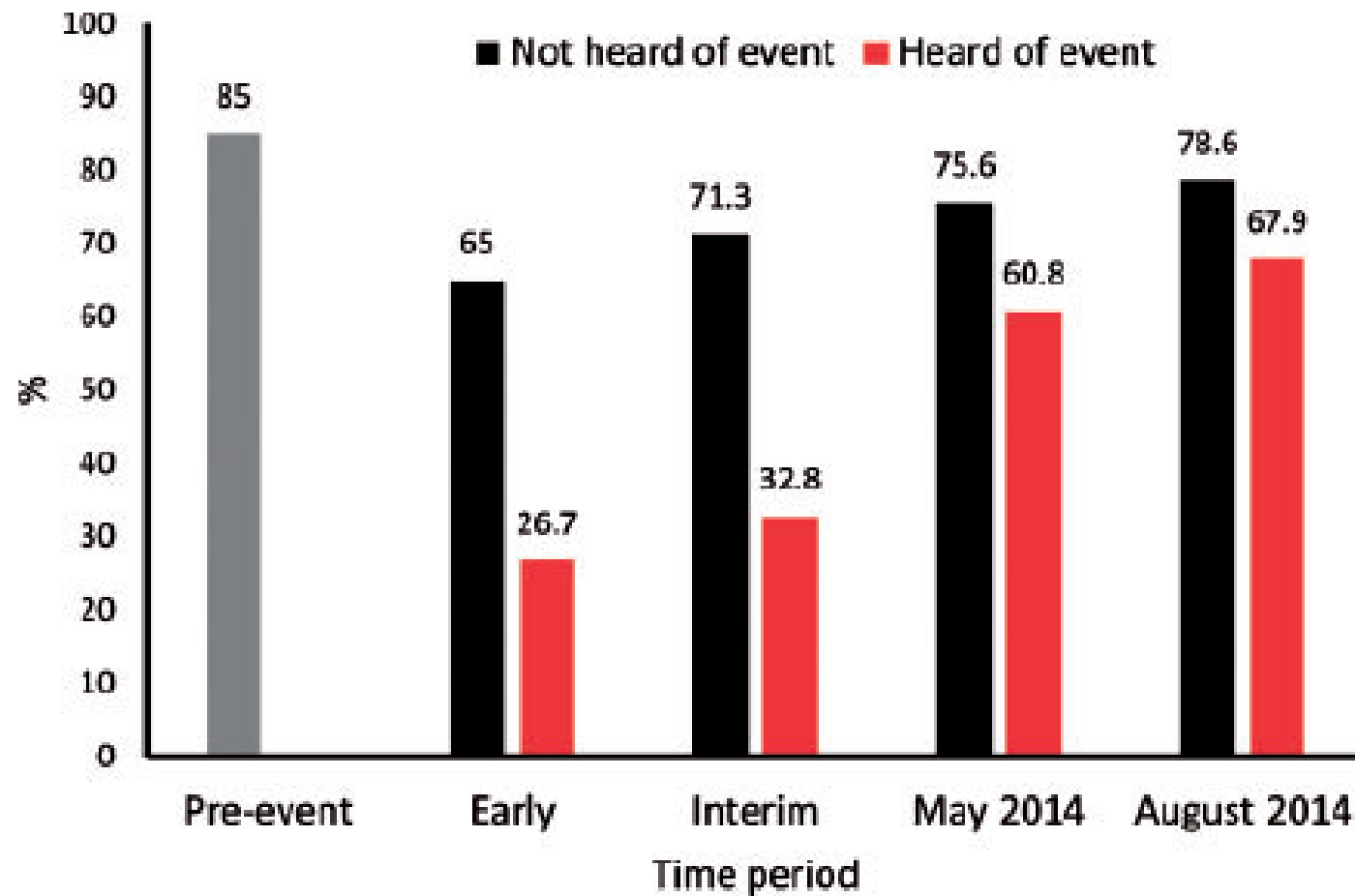
# What Happened? (3)

## 发生什么 (3)

- 17 JAN – CFDA and NHFPC announce final results of investigation
  - Vaccine within quality specifications
  - Manufacturing within specifications
  - None of the deaths were caused by BKG HepB
  - Allergic shock in 1 infant may have been due to HepB or vitamin K
- 1月17日，食药总局和卫计委宣布最终调查结果
  - 疫苗质量符合标准
  - 生产符合标准
  - 死亡与疫苗无关
  - 1例过敏性休克可能与乙肝疫苗或者维生素K有关
- Market authorization of BKT vaccines restored by CFDA
- 康泰疫苗被允许重新上市

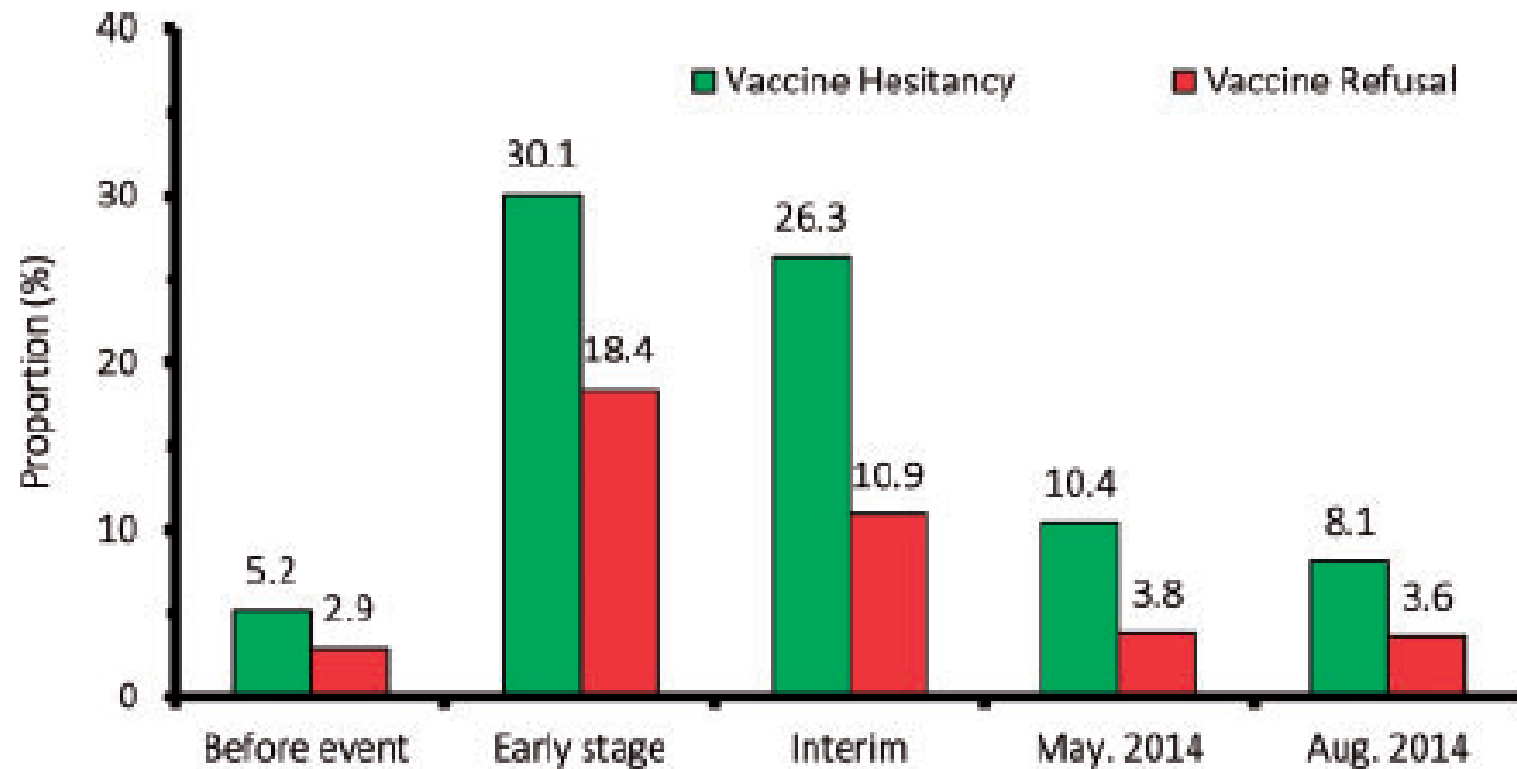
**Table 2.** Final classification of the 18 cases reported during the hepatitis B vaccine event in China

Case	Gender	Age	No. doses of HepB	Interval vaccination-death	Diagnosis	Causal categorization	Reported before or after the suspension
1	M	1 month	2	11 h	Severe pneumonia	Coincidental event	Before
2	M	1 month	2		Anaphylaxis	Vaccine product-related reaction	Before
3	M	1 month	2	24 h	Haemorrhagic pneumonia	Coincidental event	Before
4	M	1 month	2	48 h	Severe, acute bronchopneumonia	Coincidental event	Before
5	M	8 months	3	19 h	Infant muggy syndrome	Coincidental event	Before
6	M	1 month	1	16 h	Asphyxia	Coincidental event	After
7	M	0 day	1	1 hour	Neonatal haemorrhagic pneumonia / asphyxia	Coincidental event	After
8	M	1 day	1	52 h	Amniotic fluid aspiration pneumonia	Coincidental event	After
9	M	2 months	2	25 days	Asphyxia	Coincidental event	After
10	M	5 days	1	7 days	Renal failure	Coincidental event	After
11	M	6 months	3	5 days	Severe infant diarrhoea and dehydration	Coincidental event	After
12	F	1 days	1	73 h	Neonatal necrotizing enterocolitis with digestive tract perforation	Coincidental event	After
13	M	10 days	1	8 days	Meconium aspiration pneumonia	Coincidental event	After
14	M	1 day	1	20 h	Severe pneumonia with respiratory failure	Coincidental event	After
15	M	1 month	2	6 days	Infant muggy syndrome	Coincidental event	After
16	F	15 days	1	15 days	Congenital heart disease	Coincidental event	After
17	M	3 days	1	2 days	Neonatal asphyxia	Coincidental event	After
18	M	1 month	2	2 days	Sudden infant death syndrome	Coincidental event	After

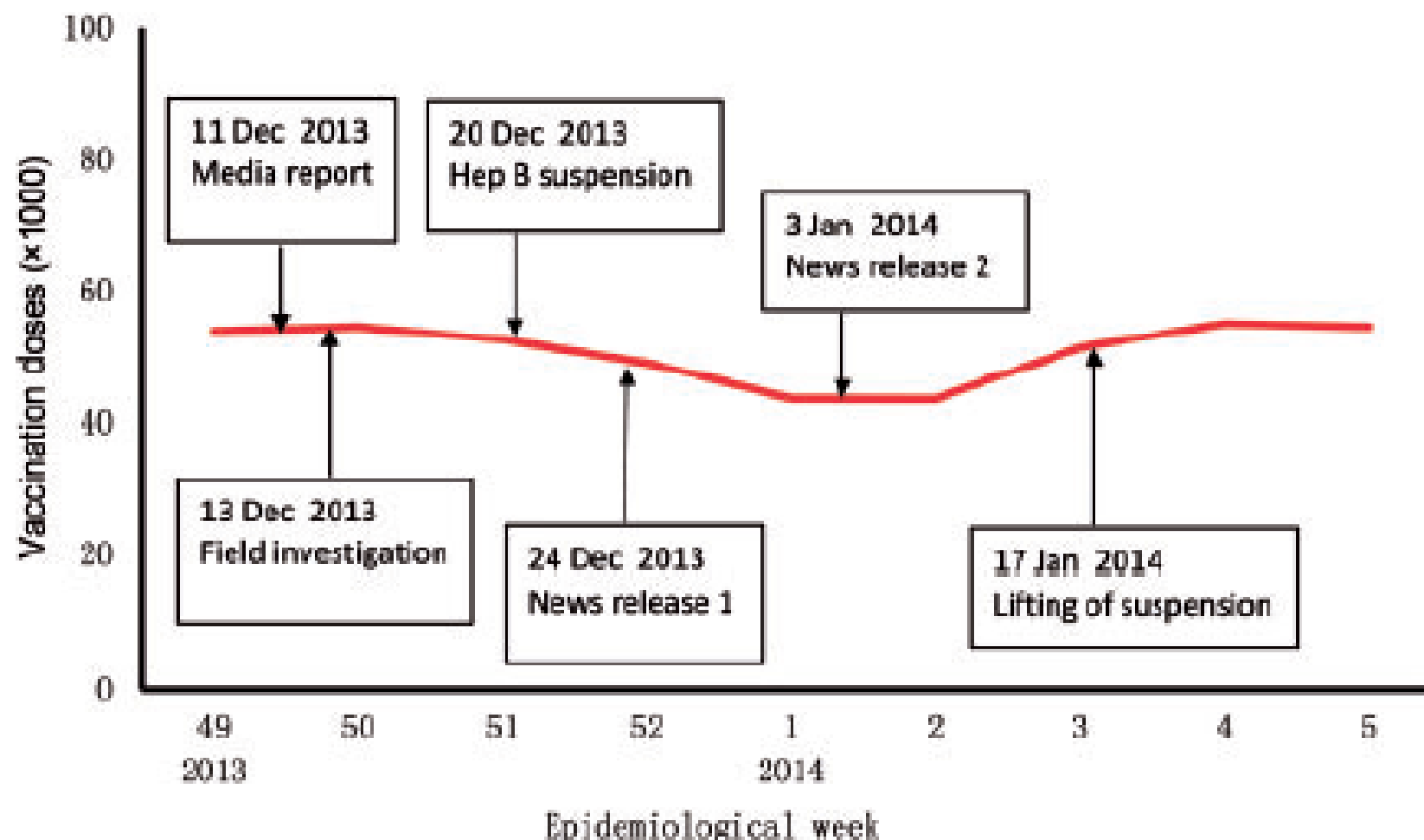


**Figure 1** Perception of safety of domestic vaccines among guardians before and after the hepatitis B vaccine event (Percentage of respondents answering 'very safe' or 'safe' to the question of 'At the moment, do you think domestically produced hepatitis B vaccine is safe?').

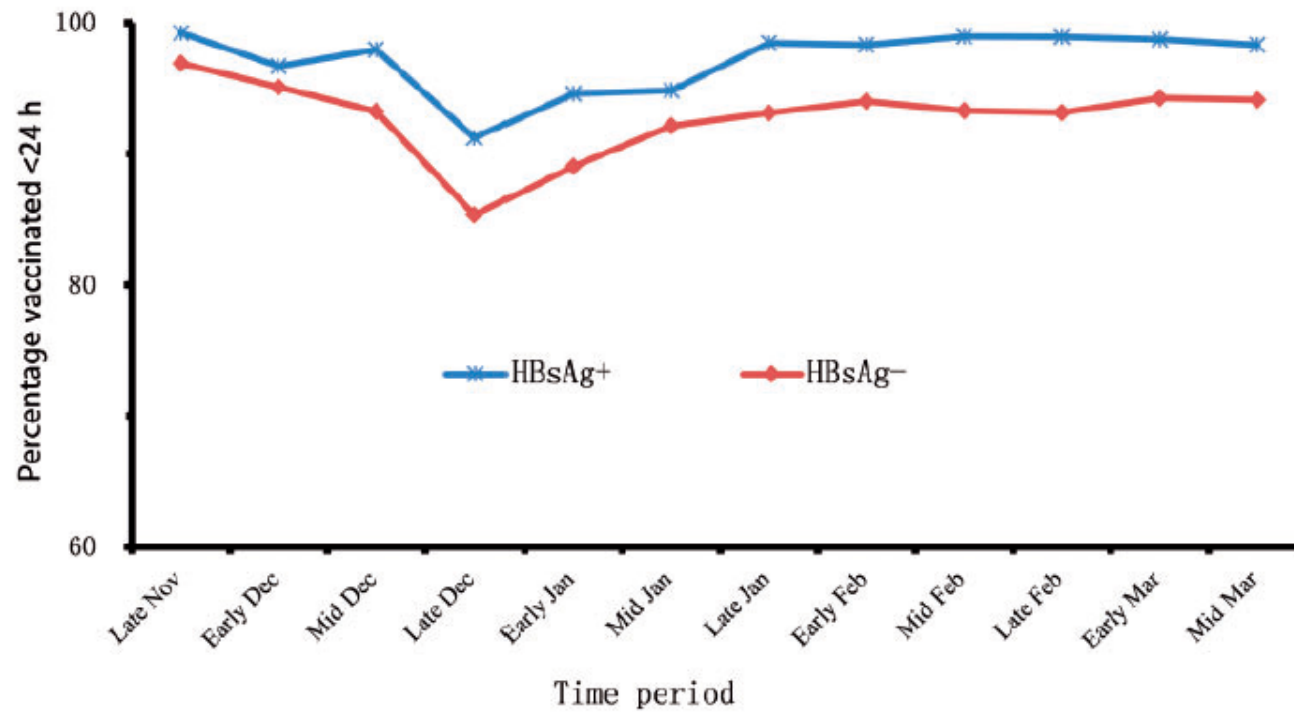




**Figure 2** Percentage of vaccine hesitancy and refusal among guardians before and after the hepatitis B vaccine event (Hesitant: guardians answering 'hesitant' to the question of 'Is this event likely to influence your decision to have your child receive his or her next vaccination?'; Refuse: guardians answering 'no' to the question of 'Will you have your child vaccinated at the next vaccination visit?').



**Figure 3** Trend curve of the weekly vaccination doses for the three doses of hepatitis B vaccination in 10 provinces/municipalities.



**Figure 4** Hepatitis B vaccination rates of newborn infants within 24 h of birth in 100 hospitals of eight provinces before and after the event by maternal HBsAg status (Birth dose vaccination and HBsAg positivity are based on hospital medical record review).

# What Contributed to Success?

## 有什么好的经验

- Supplying alternative HepB when BKT HepB was suspended
- Launching immediate investigation
- Inviting WHO participation
- Holding periodic media briefings
- Monitoring confidence and vaccine use
- 当康泰乙肝疫苗叫停时，供应另一厂家的疫苗
- 立即开展调查
- 邀请WHO参与
- 定期对媒体通报
- 监测公众信心和疫苗使用量

# What Was Learned?

## 有什么教训

- Coincidental AEFI are difficult to explain convincingly
- Suspension of a vaccine resulted in immediate loss of confidence in the vaccine
- Monitoring media and parental concerns should continue
- A comprehensive communication strategy is important to maintain confidence in vaccines
- 耦合的AEFI很难解释
- 叫停疫苗会导致对疫苗的信心立即下降
- 监测媒体和家长的关注点应该继续下去
- 综合性的宣传沟通策略对保持疫苗信心是很重要的

# Coincidental versus Causal AEFI

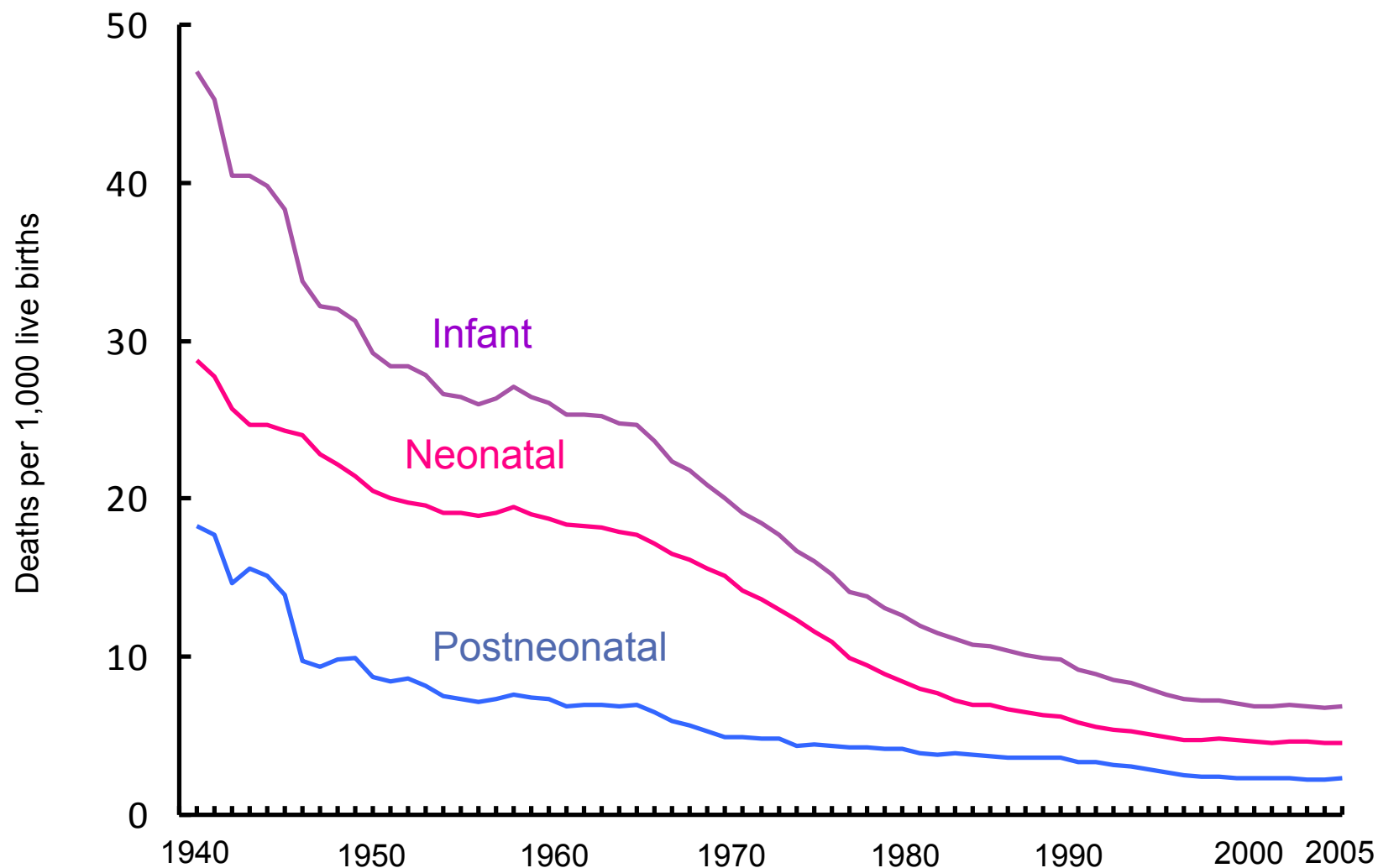
## 偶合症Vs 疫苗不良反应

- AEFI → Adverse Event Following Immunization, such as death following vaccination
  - Coincidental (vaccine not-caused)
    - Infant death happened after vaccination
    - Infant death would have happened even if there was no vaccination
  - Causal (vaccine-caused)
    - Infant death happened after vaccination
    - Infant death would not have happened without the vaccination
- AEFI → 疫苗接种后不良事件，诸如接种后死亡
  - 偶合症（非疫苗引起）
    - 婴儿接种疫苗后发生的死亡
    - 婴儿即使不接种疫苗也会发生的死亡
  - AEFI（疫苗引起的）
    - 婴儿接种疫苗后发生的死亡
    - 婴儿不接种疫苗就不会发生死亡



Figure 6. Infant, neonatal, and postneonatal mortality rates:  
United States, 1940-2005

图6. 婴儿期、新生儿期、后新生儿期死亡率：美国（1940-2005）





NOTE: Rates are infant (under 1 year), neonatal (under 28 days), and postneonatal (28 days-11 months) deaths per 1,000 live births in specified group. Source: U.S. CDC

# How Do Coincidental Deaths Happen?

## 偶合死亡是怎么发生的？

- Unfortunately, about 1 percent of infants die in the first year of life
- Causes of death include prematurity, congenital heart disease, pneumonia, Sudden Infant Death Syndrome, etc.
- An infant can appear healthy before becoming ill and dying, and almost all healthy-appearing infants will be vaccinated
- This is a set-up for a death coincidental to vaccination
- 不幸的是，大约有1%的婴儿会在1岁以内死亡
- 死亡原因包括：早产、先天性心脏病、肺炎、婴儿猝死综合征等等
- 婴儿出现疾病或死亡前常表现为健康状态，此时会被接种疫苗。
- 这就是疫苗接种所致偶合的机制


**VACCINE SAFETY BASICS**  
e-learning course



Case study A

Case study B

Case study C

Glossary

MODULE 3: Adverse events following immunization

Module 1

Module 2

Module 3

Module 4

Module 5

Module 6

General Assessment

COINCIDENTAL EVENTS

CONTENT

*Expected coincidental deaths following DTP vaccination in selected countries<sup>26</sup>*

Country	Infant Mortality Rate per 1000 live births (IMR)	Number of births per year (N)	Number of infant death during year in		
			Month after immunization	Week after immunization	Day after immunization
			= (IMR×N/12)×nv×ppv	= (IMR×N/52)×nv×ppv	= (IMR×N/365)×nv×ppv
Australia	5	267,000	300	69	10
Cambodia	69	361,000	5,605	1,293	185
China	18	18,134,000	73,443	16,948	2,421
Japan	3	1,034,000	698	161	23
Laos	48	170,000	1,836	424	61
New Zealand	5	58,000	65	15	2
Philippines	26	2,236,000	13,081	3,019	431

*Note: Assumes uniform distribution of deaths and that children who are near death will still be immunized.*

nv = number of immunization doses: assumed here to be three dose schedule; 3.

ppv= proportion of population vaccinated: assumed here to be 90% for each dose; 0.9.

<http://vaccine-safety-training.org/coincidental-events.html>

# Hepatitis B Vaccine and Infant and Neonatal Deaths

## 乙肝疫苗和婴儿/新生儿死亡

- Among children, death rates are highest among the youngest
- In the first year of life, the first month of life has the highest death rate
- In the first month of life, the first day of life has the highest death rate of all days
- Because hepatitis B vaccine must be given on the first day of life, coincidental deaths will occur following HBV vaccine
- 儿童期，年龄越小死亡率越大
- 1岁以内，1月龄内的死亡率是最高的
- 1月龄内，第一天的死亡率是最高的
- 因为乙肝疫苗必须在第一天接种，接种后偶合死亡是一定会发生的

# Population Methods for Causality Determination

## 因果判定的人群研究方法

- Individual deaths following vaccination require investigation to determine cause of death
- Population studies are used to determine whether a vaccine does cause death, and if so, how frequently
- Population studies compare death rates of children to did and who did not get vaccinated
- Population studies have shown that if routinely used vaccines cause death, it is at such a low level that it is difficult to even detect
- 接种后死亡的个案，需要通过调查来判定死亡原因
- 人群研究常用来确定某疫苗是否会引起死亡。如果是，引起的死亡率是多少。
- 人群研究是比较儿童死亡率在接种疫苗和不接种疫苗两个人群中的不同
- 人群研究显示如果常规接种的疫苗能引起死亡，那也只会保持在较低，甚至难以察觉到的水平。

## Population Studies of Infant Deaths Following HBV Vaccination

### 乙肝疫苗接种后婴儿死亡的人群研究

- \* Studied over 350,000 live births and reviewed all deaths in first 29 days of life (neonatal period)
  - 1,363 neonatal deaths reviewed
  - There were 72 vaccinated deaths
  - Found no deaths caused by HBV vaccine
- \*\* Reviewed all neonatal AEFI
  - 1,771 adverse events
  - 18 deaths following HBV vaccine
  - Various causes of death; no link to vaccine was seen
- \*研究了35万个活产儿并对每一例29天内死亡的病例作了回顾
  - 共回顾了1363例死亡
  - 72例发生在接种后
  - 没有一例是乙肝疫苗引起的
- \*\*回顾了所有新生儿AEFI
  - 1771个不良事件
  - 接种后出现18例死亡
  - 死亡原因多样，但没有和疫苗相关的死亡

\* Eriksen et al, Pediatric Infect Dis J 2004;23:656

\*\* Niu et al, Arch Ped Adolesc Med 1999;153:1279

RESEARCH ARTICLE

Open Access

Gaps in the prevention of perinatal transmission of hepatitis B virus between recommendations and routine practices in a highly endemic region: a provincial population-based study in China

Yali Hu<sup>1,4†</sup>, Shu Zhang<sup>1†</sup>, Chao Luo<sup>1</sup>, Qilan Liu<sup>2</sup> and Yi-Hua Zhou<sup>3,4\*</sup>

RESEARCH PAPER

Human Vaccines & Immunotherapeutics 12:1, 70–76; January 2016; © 2016 Taylor & Francis Group, LLC

## Hepatitis B-related knowledge and vaccination in association with discrimination against Hepatitis B in rural China

Lijie Yu<sup>1</sup>, Jian Wang<sup>1,\*</sup>, Dawei Zhu<sup>2</sup>, Anli Leng<sup>1</sup>, and Knut R Wangen<sup>3</sup>

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<sup>2</sup>Center for Health Policy and Management; Institute of Medical Information & Library; Chinese Academy of Medical Sciences; Peking Union Medical College; Beijing, China;

<sup>3</sup>Department of Health Management and Health Economics; University of Oslo; Oslo, Norway

CDC

**MMWR**

Morbidity and Mortality Weekly Report

Recommendations and Reports December 23, 2005 / Vol. 54 / No. RR-16

**A Comprehensive Immunization Strategy  
to Eliminate Transmission of Hepatitis B Virus Infection  
in the United States**

Recommendations of the Advisory Committee  
on Immunization Practices (ACIP)

Part 1: Immunization of Infants, Children, and Adolescents

 ISEA

*International Journal of Epidemiology*, 2016, 44:1–449  
doi: 10.1093/ije/dyv349  
Original article



Health Policies and Interventions

## Loss of confidence in vaccines following media reports of infant deaths after hepatitis B vaccination in China

Wenzhou Yu,<sup>1†</sup> Dawei Liu,<sup>1†</sup> Jingshan Zheng,<sup>1†</sup> Yanmin Liu,<sup>1†</sup> Zhijie An,<sup>1†</sup> Lance Rodewald,<sup>2†</sup> Guomin Zhang,<sup>1</sup> Qiru Su,<sup>1</sup> Keli Li,<sup>1</sup> Disha Xu,<sup>1</sup> Fuzhen Wang,<sup>1</sup> Ping Yuan,<sup>1</sup> Wei Xia,<sup>2</sup> Guijun Ning,<sup>1</sup> Hui Zheng,<sup>1</sup> Yaozhu Chu,<sup>1</sup> Jian Cui,<sup>1</sup> Mengjuan Duan,<sup>1</sup> Lixin Hao,<sup>1</sup> Yuqing Zhou,<sup>1</sup> Zhenhua Wu,<sup>1</sup> Xuan Zhang,<sup>1</sup> Fuqiang Cui,<sup>1</sup> Li Li<sup>1</sup> and Huaqing Wang<sup>1\*</sup>

<sup>1</sup>National Immunization Program, Chinese Center for Disease Control and Prevention, Beijing, China and <sup>2</sup>World Health Organization Office in China, Beijing, China

Many challenges to overcome in China and globally

# GETTING TO ZERO TRANSMISSION

# 通往零传播

# Implications of the 2014 HBV Serosurvey

## 2014年乙肝血清学调查的含义

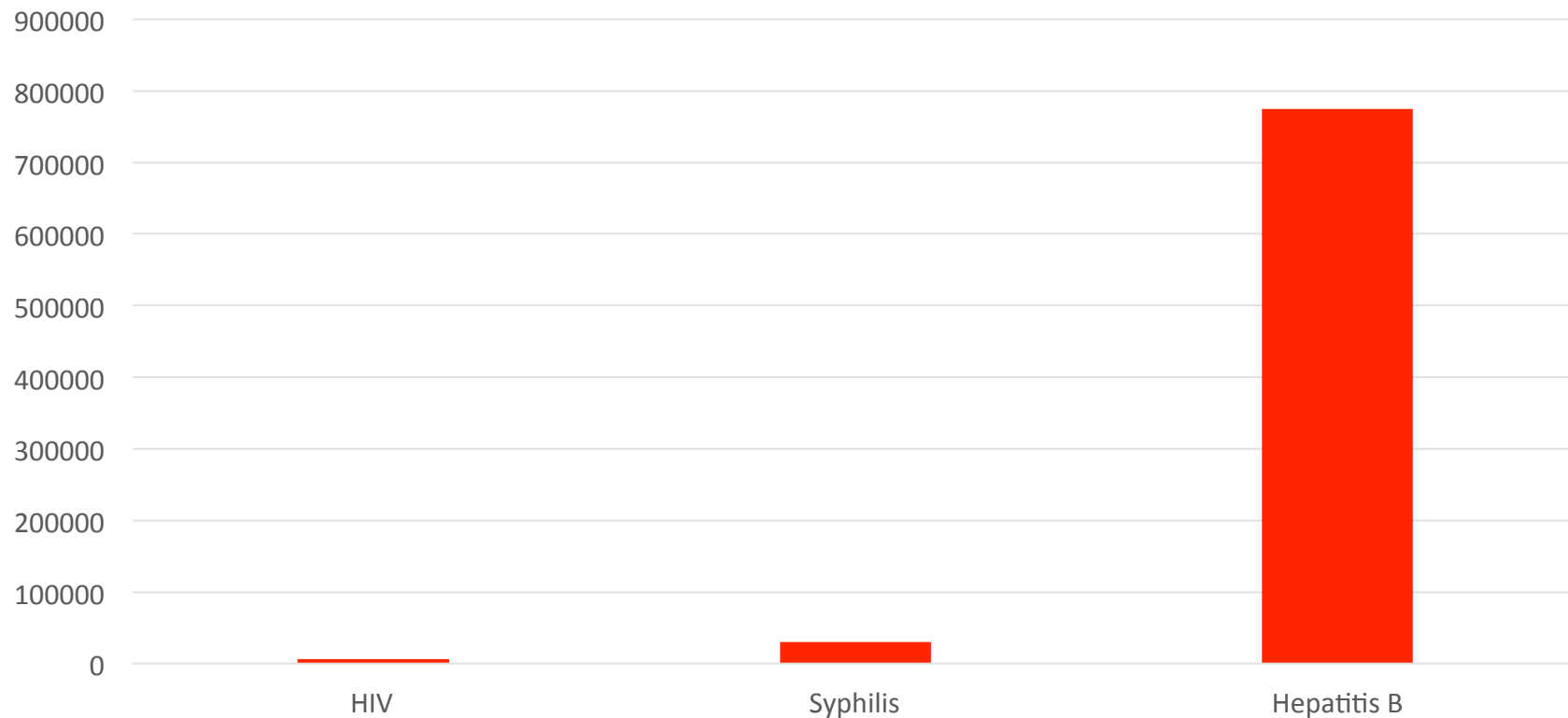
- Annual burden of prevention is large - ~ 750,000 HBsAg+ births
- Prevention must continue for decades
- 0.32% HBsAg prevalence means about 50,000 newborns infected each year
- New infections must be identified to improve prevention
- 疾病预防的任务依然很重—75万新生儿是由表面抗原阳性母亲生产
- 还需要数十年的持续努力
- 0.32%的乙肝表面抗原携带率意味着每年有5万个新生儿被感染
- 必须了解这些新感染者的原因来提升预防措施



# Integrated PMTCT for HIV, Syphilis, and Hepatitis B

## PMTCT项目: 艾滋病、梅毒和乙肝

Births to Screen-Positive Women in China, 2013  
> 12.5 million women screened in 41% of counties in China

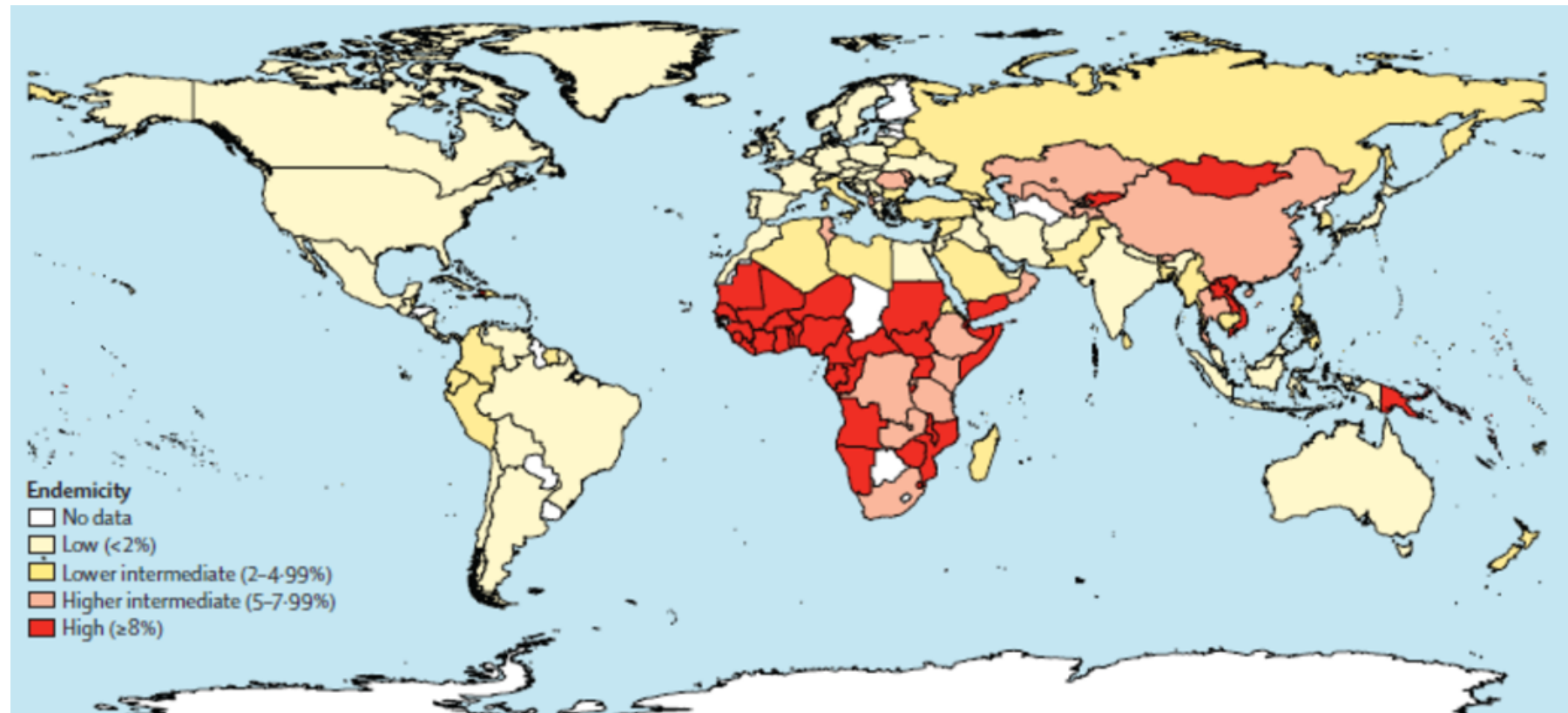


# Post-Vaccination Serological Testing of HBV-Exposed Infants

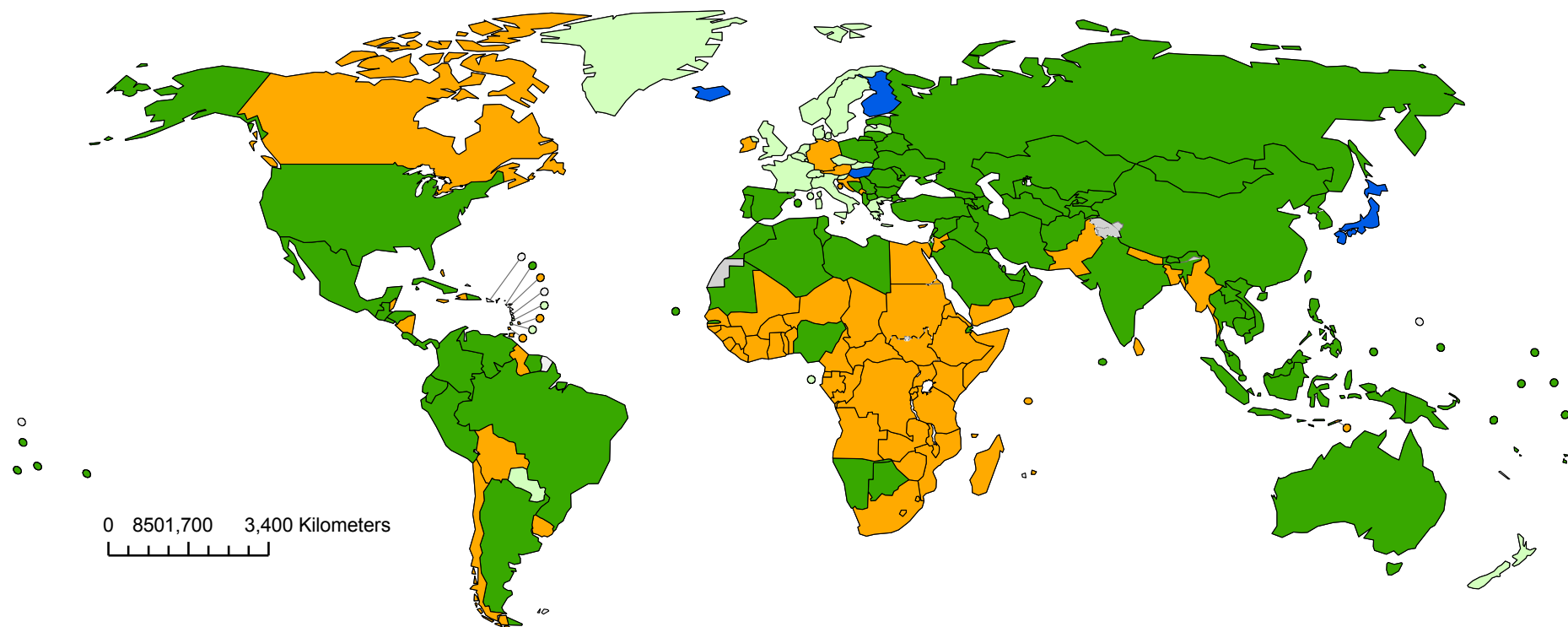
## 乙肝病毒暴露婴儿在预防接种后的血清学检测

- For child, determines
  - Protected for life
  - Infected, needs care
  - Susceptible, revaccinate
- For program, determines if breakthrough infections are
  - Program failure
  - Strategy failure
- PVST is not included in China's iPMTCT package of care
  - Feasible to implement?
  - Cost effectiveness?
  - Acceptable to parents?
- 对儿童，判定
  - 终生获得保护
  - 感染，需要治疗
  - 易感，重新接种
- 对预防接种，判定是否阻断了感染
  - 接种失败
  - 策略失败
- 预防接种后成功率检测没有包含在母婴阻断传播项目中
  - 执行的可行性
  - 成本效益
  - 家长接受程度

# 2010 Estimated Global HBsAg Endemicity



# Countries with Hepatitis B Birth dose (HepB-BD) vaccine in the national immunization programme



<span style="color: green;">■</span> HepB-BD introduced to date	(97 countries or 49%)
<span style="color: lightgreen;">■</span> HepB-BD only for infants born to HBsAG-positive mothers	(22 countries or 11%)
<span style="color: orange;">■</span> HepB in schedule but no HepB-BD	(71 countries or 37%)
<span style="color: blue;">■</span> HepB given only for risk groups or adolescents	(4 countries or 2%)
<span style="color: grey;">■</span> Not available	
<span style="color: grey;">■</span> Not applicable	

Data source: WHO/IVB Database as at 05 September 2016  
and ECDC published data at  
<http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx>  
194 WHO Member States  
Map production Immunization Vaccines and Biologicals (IVB),  
World Health Organization  
Date of slide: 05 September 2016

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2016. All rights reserved.



**Table 1: Summary of WHO Position Papers - Recommendations for Routine Immunization**

Antigen		Children (see Table 2 for details)	Adolescents	Adults	Considerations (see footnotes for details)
<b>Recommendations for all</b>					
BCG <sup>1</sup>		1 dose			Exceptions HIV
Hepatitis B <sup>2</sup>		3-4-doses (see footnote for schedule options)	3 doses (for high-risk groups if not previously immunized) (see footnote)		Birth dose Premature and low birth weight Co-administration and combination vaccine Definition high-risk
Polio <sup>3</sup>		3 doses, with DTP			OPV birth dose Transmission and importation risk criteria Type of vaccine
DTP <sup>4</sup>		3 doses	Booster (Td) (see footnote)	Booster (Td) in early adulthood or pregnancy	Delayed/interrupted schedule Combination vaccine
<i>Haemophilus influenzae</i> type b <sup>5</sup>		3 doses, with DTP			Single dose if 12-24 months of age Delayed/interrupted schedule Co-administration and combination vaccine
Pneumococcal (Conjugate) <sup>6</sup>	Option 1	3 doses, with DTP			Vaccine options Initiate before 6 months of age Co-administration HIV+ and preterm neonates booster
	Option 2	2 doses before 6 months of age, plus booster dose at 9-15 months of age			
Rotavirus <sup>7</sup>		Rotarix: 2 doses with DTP RotaTeq: 3 doses with DTP			Vaccine options
Measles <sup>8</sup>		2 doses			Combination vaccine; HIV early vaccination; Pregnancy
Rubella <sup>9</sup>		1 dose (see footnote)	1 dose (adolescent girls and/or child bearing aged women if not previously vaccinated; see footnote)		Achieve and sustain 80% coverage Combination vaccine and Co-administration Pregnancy
HPV <sup>10</sup>			3 doses (girls)		Vaccination of males for prevention of cervical cancer is not recommended at this time

## WHO推荐的免疫接种程序

[http://www.who.int/immunization/policy/Immunization\\_routine\\_table1.pdf](http://www.who.int/immunization/policy/Immunization_routine_table1.pdf)

# Vaccines Not In the Program

## 没有纳入常规免疫的疫苗

- Licensed, domestic-made
    - Hib
    - Varicella
    - Rotavirus
    - Influenza
  - Licenced, imported
    - Human papillomavirus
    - Pneumococcal conjugate
  - Not licensed
    - Domestic, large combination vaccines
- 已注册，国产
    - Hib
    - 水痘
    - 轮状病毒
    - 流感
  - 已注册，进口
    - 人乳头瘤病毒疫苗
    - 肺炎结合疫苗
  - 未注册
    - 国产的多种联合疫苗

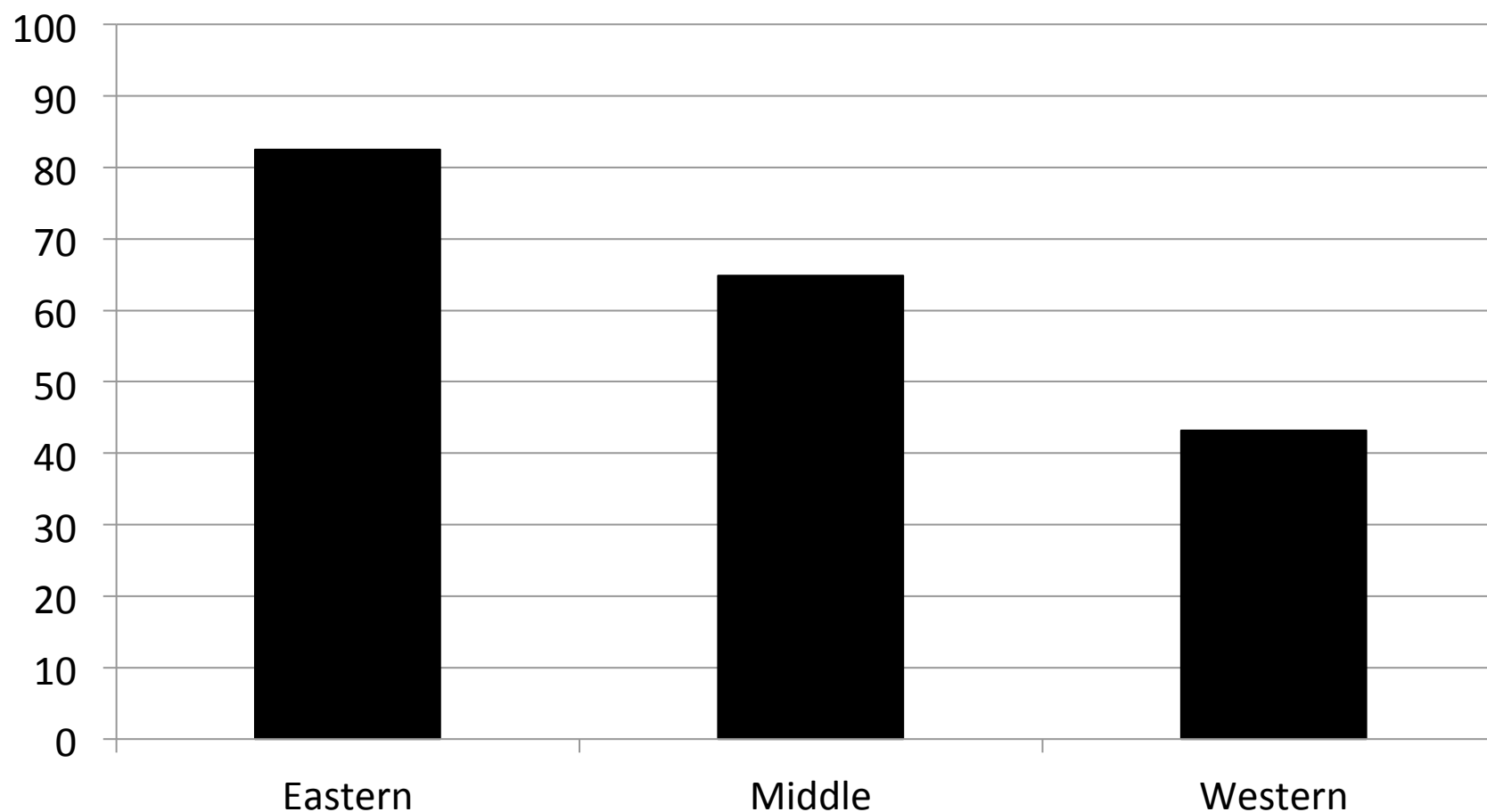
# MCV2 Coverage by Province; County-Level Survey, 2013

## 2013年2剂次含麻疹成分疫苗调查接种率



# Immunization Status of Type 2 Vaccines by Region, China 2011

## 2011年中国不同地区2类疫苗接种情况

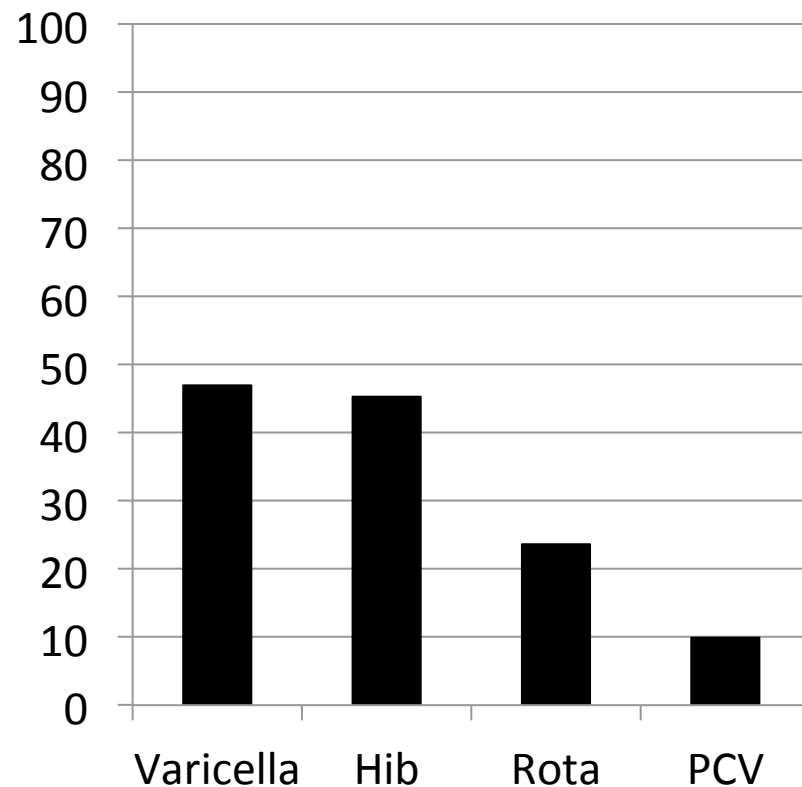




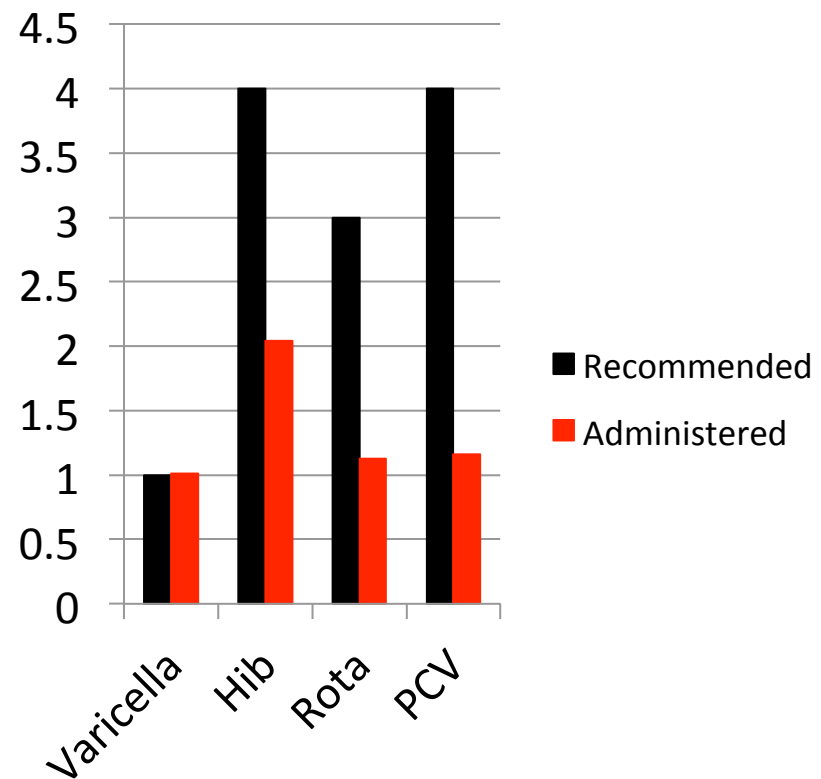
# Type 2 Vaccines: Percentage of Children with at Least 1 Dose; China, 2011

## 2类疫苗：接种至少1剂的儿童比例

% Children With at Least 1 Dose



Doses per vaccinated child



South China Morning Post 南華早報

CHINA

SUN Oct 13, 2013 Updated: 5:06am

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China wins WHO backing for encephalitis vaccine

Drug to fight deadly Japanese encephalitis that has been used by China since 1988 has been cleared for United Nations agencies to use

Stephen Chen

binglin.chen@scmp.com

Thursday, 10 Oct

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In a first, China has had a vaccine pre-qualified for worldwide use by the World Health Organisation, a move that could help fight a deadly fever threatening millions of people, many of them children in developing countries.

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Approved by WHO for lifesaving use across Asia

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UN health agency approves new encephalitis vaccine to protect children in developing countries

Margaret Chan, Director-General of the World Health Organization (WHO). Photo: PAHO/WHO

9 October 2013 – The United Nations health agency has approved a new vaccine against Japanese encephalitis (JE), stressing that access to the vaccine will help save the lives of children in developing countries.

9

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# China approves new polio vaccine, shows innovative muscle

SHANGHAI Thu Jan 15, 2015 8:26am GMT

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(Reuters) - China has approved a new polio vaccine, the first of its kind to be produced in the country, a month after local authorities gave the green light for a home-grown Ebola vaccine amid Beijing's push to become a world leader in producing innovative drugs.

The development drew praise from the World Health Organization (WHO) on Thursday who said the vaccine, which will be given to Chinese children as part of routine disease prevention, would help the global fight against the polio virus.

China's private and state-run medical laboratories have been growing in sophistication, helping reduce reliance on imported medicines and competing with global rivals.

"This new vaccine is a critically important weapon in the fight against polio as the world nears the eradication of this dreaded disease," Bernhard Schwartländer, WHO representative in China, said in a statement.

Friday Jan 16, 2015 Beijing 4°C~7°C

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## Domestic vaccine for polio licensed

2015-01-16 08:46 China Daily Web Editor: Si Huan [comment](#) [0](#)

A medical worker gives a polio vaccine to a child in Hami prefecture in Northwest China's Xinjiang Uygur autonomous region. Cai Zengle / for China Daily

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## World's first inactivated Sabin polio vaccine approved by China FDA

January 15, 2015 | By [EJ Lane](#)

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China's FDA has awarded marketing approval of the world's first Sabin strain inactivated polio vaccine, marking a milestone as well for the Institute of Medical Biology of the Academy of Medical Sciences.

The institute independently developed the strain but tapped the assistance of the World Health Organization (WHO), the U.S. Centers for Disease Control and Prevention (CDC), Japan's National Institute of Infectious Diseases (NIID), the European Medicines Agency (EMA) and the U.K. in the review process, CFDA said.

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## China approves new vaccine against poliomyelitis

Source:Xinhua Published: 2015-1-16 9:23:00

China's drug watchdog has licensed a new vaccine against the poliomyelitis, the **Ministry of Science and Technology** announced Thursday.

The vaccine (S-IPV) is manufactured by the Institute of Medical Biology of the Chinese Academy of Medical Sciences, located in Kunming, southwest China's Yunnan province.

It was welcomed by the World Health Organization (WHO). "The new vaccine will be an important weapon in the fight against polio as the world nears the eradication of the deadly disease," said Dr. Bernhard Schwartlander, WHO Representative in China.

2015, 90, 185–200

No. 18



World Health  
Organization

Organisation mondiale de la Santé

## Weekly epidemiological record Relevé épidémiologique hebdomadaire

1ST MAY 2015, 90th YEAR / 1<sup>er</sup> MAI 2015, 90<sup>e</sup> ANNÉE

No. 18, 2015, 90, 185–200

<http://www.who.int/wer>

### Contents

185 Hepatitis E vaccine:  
WHO position paper, May 2015

### Hepatitis E vaccine: WHO position paper, May 2015

### Note de synthèse: position de l'OMS à propos du vaccin contre l'hépatite E, mai 2015

*Special groups and outbreak situations:* There may be special situations such as outbreaks where the risk of hepatitis E or of its complications or mortality is particularly high. The current WHO position concerning routine programmes should not preclude the use of the vaccine in these specific situations. In particular, the use of the vaccine to mitigate or prevent outbreaks of hepatitis E should be considered as well as the use of the vaccine to mitigate consequences in high risk groups such as pregnant women.

## Making Hepatitis E a Vaccine-Preventable Disease

Eyasu Teshale, M.D., and John W. Ward, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

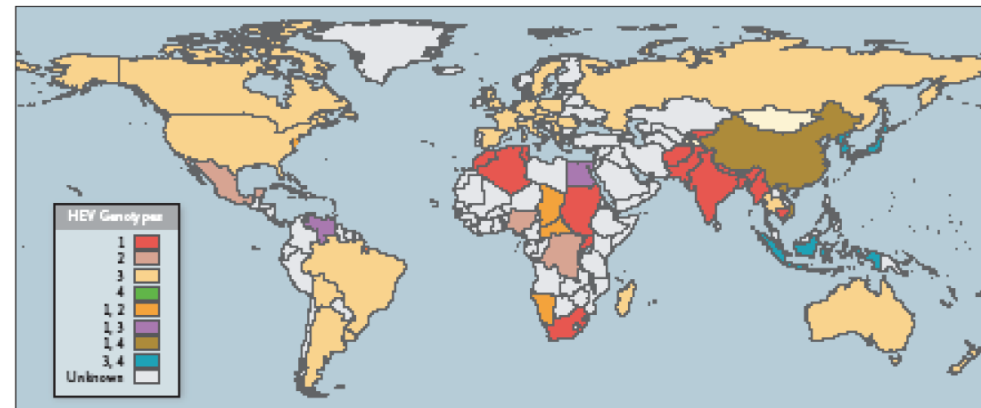
### ORIGINAL ARTICLE

## Long-Term Efficacy of a Hepatitis E Vaccine

Jun Zhang, M.Sc., Xue-Feng Zhang, M.Sc., Shou-Jie Huang, M.Sc., Ting Wu, Ph.D., Yue-Mei Hu, M.Sc., Zhong-Ze Wang, B.Sc., Hua Wang, M.D., Han-Min Jiang, B.Sc., Yi-Jun Wang, M.Sc., Qiang Yan, M.Sc., Meng Guo, B.Sc., Xiao-Hui Liu, B.Sc., Jing-Xin Li, M.Sc., Chang-Lin Yang, B.Sc., Quan Tang, B.Sc., Ren-Jie Jiang, M.Sc., Hui-Rong Pan, Ph.D., Yi-Min Li, M.D., J. Wai-Kuo Shih, Ph.D., Mun-Hon Ng, Ph.D., Feng-Cai Zhu, M.Sc., and Ning-Shao Xia

### PERSPECTIVE

### MAKING HEPATITIS E A VACCINE-PREVENTABLE DISEASE



Geographic Distribution of HEV Genotypes in Locally Acquired HEV Infection.

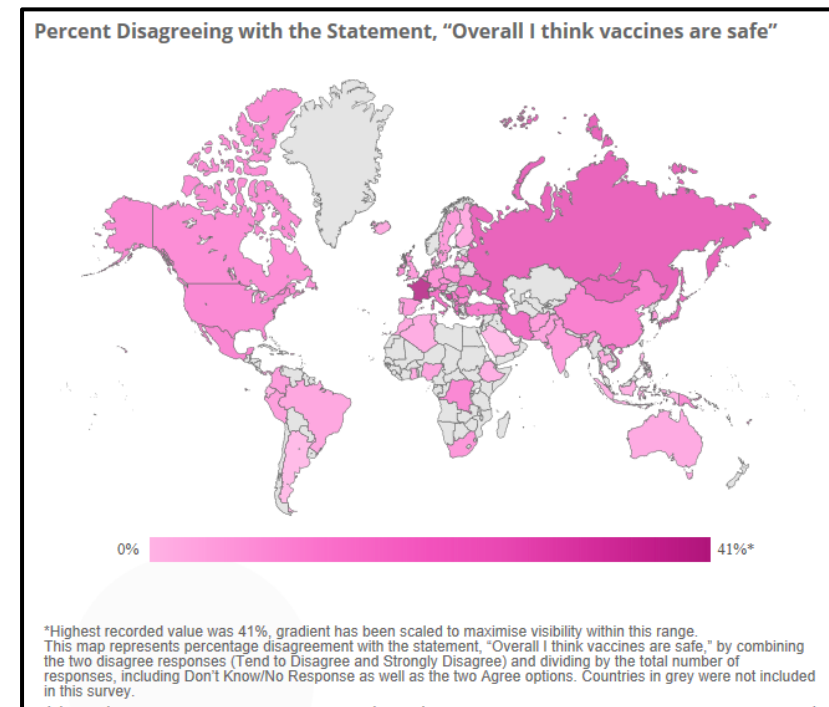
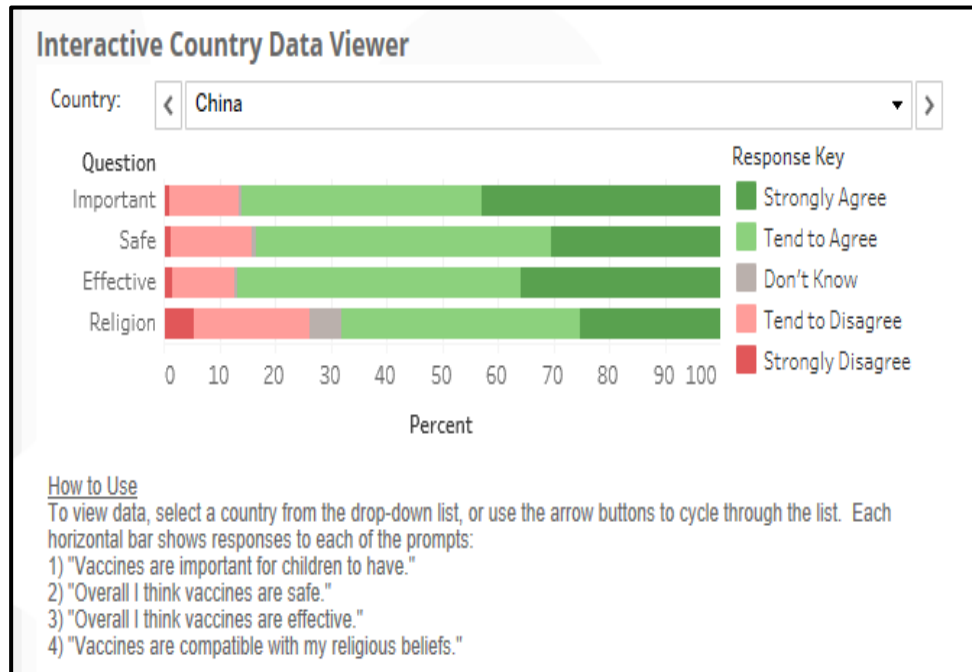
The map shows the predominant locally acquired human genotype in each country. Data are from the Division of Viral Hepatitis, Centers for Disease Control and Prevention.

Weekly Epidemiological Record 2015;18:185

New England Journal of Medicine 2015;372:899-901 and 914-922

# Raising and Sustaining Confidence in Vaccines

## 不断增加和维持对疫苗的信心





# A Chain of Scientific Support

## 科学性支持的链条

- Clinicians support parents to keep their children healthy
- Immunization programs support clinicians to keep their vaccinations effective
- Surveillance for disease, coverage, parent concerns, and safety support immunization programs
- Leadership, management, and finances support the whole enterprise
- 临床医生支持儿童家长保持其儿童的健康
- 免疫规划支持临床医生保持其疫苗接种的有效性
- 针对疾病、接种率、家长关注和安全性开展监测来支持免疫规划
- 领导团队、管理、财政支持整个事业

# Conclusions

- If a vaccine is worth using, it is worth using properly
- Expert and evidence-based guidance and monitoring are necessary to accomplish immunization goals
- Detection and response to safety signals helps keep the immunization program safe and effective
- As the epidemiology changes, vaccination strategy may also need to change
- New vaccines pose an exciting challenge to develop strategies to maximize the benefits of the vaccine



**THANK YOU!**  
**谢谢大家!**