新发突发传染性病毒的传播机制与防控策略

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中国科学院微生物研究所
2019-11-21

科普著作《流感病毒——躲也躲不过的敌人》：高福院士带你探究流感病毒的前世今生

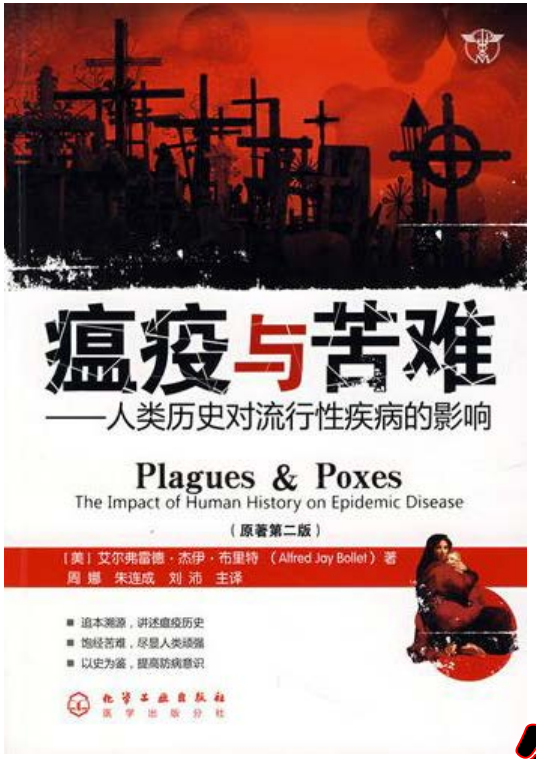
预售10天

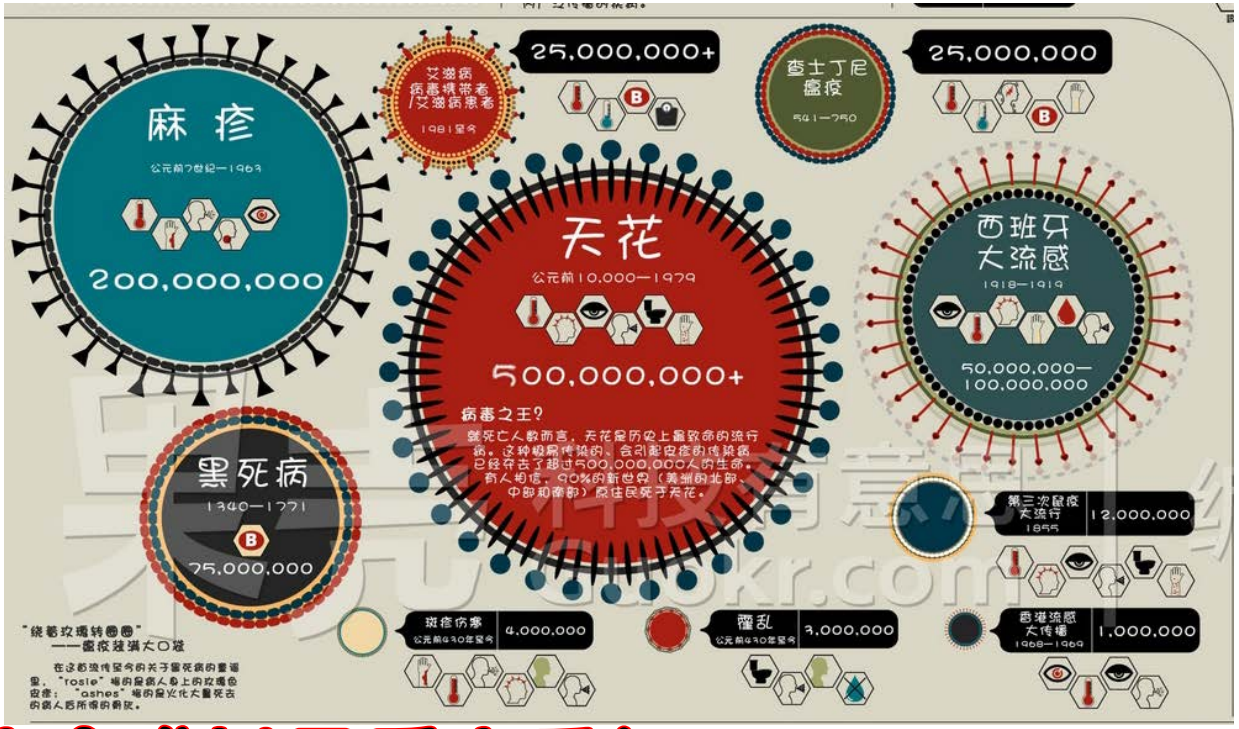
10000册售罄！

首印当月即重印！

中国科学技术出版社
科学普及出版社

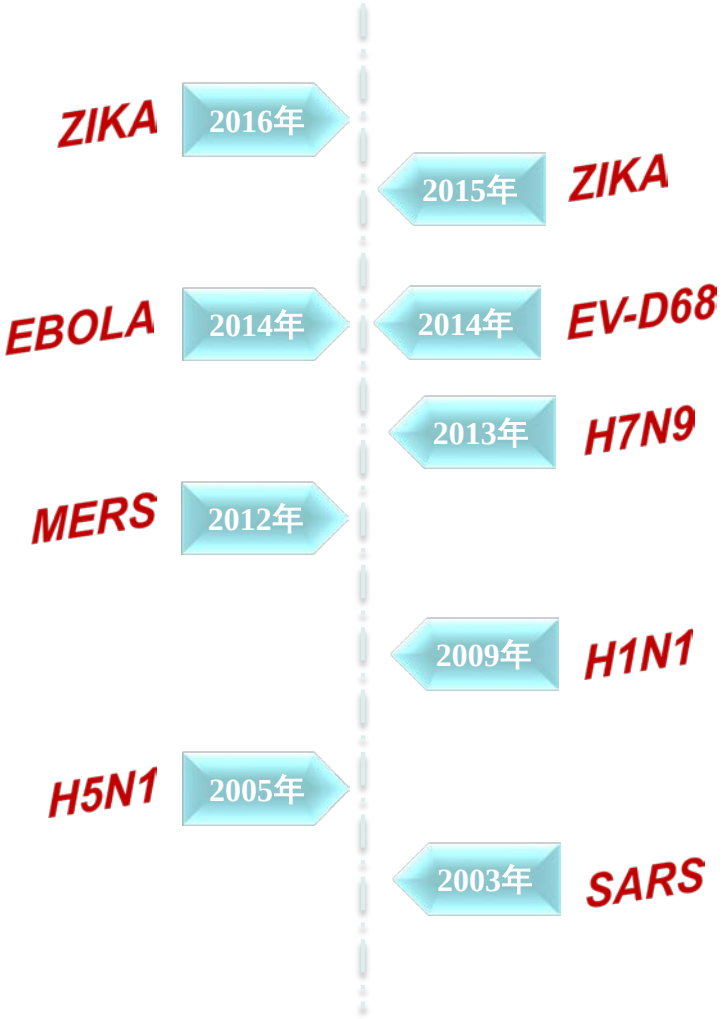
传染病与人类历史

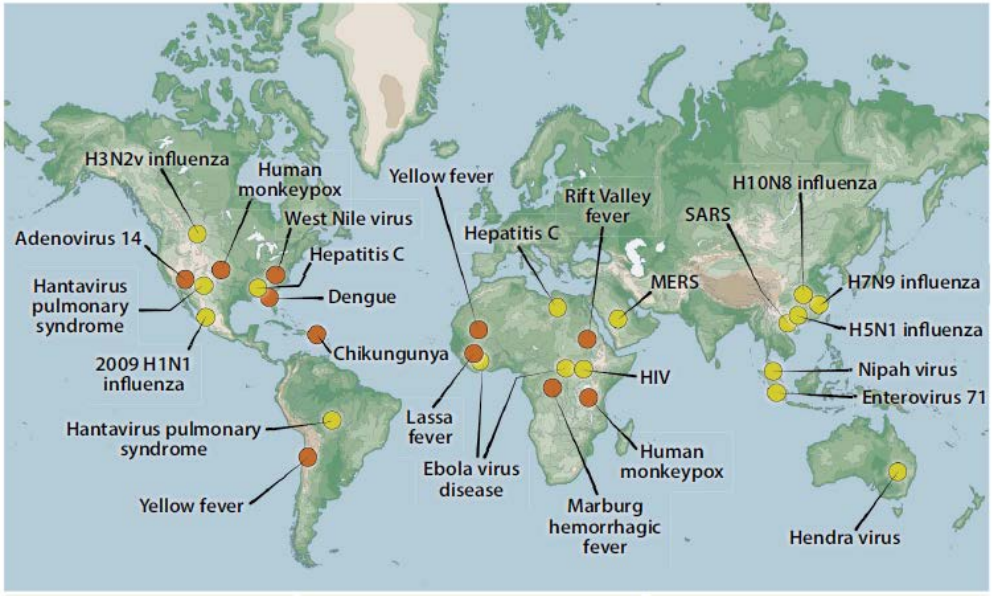




生命难以承受之重！

新发突发传染病现状





Marston, HD et al. *Science Translational Medicine*. 2014; 6(253): 1-6

新发突发传染病呈现出

愈演愈烈、愈发愈快的趋势。

疾病来源

为什么会有这么多的病毒伴随着我们?

……—非典型性肺炎病毒—禽流感病毒—中东呼吸综合征病毒—埃博拉病毒—寨卡病毒—……

疾病来源

新发突发传染病

?天灾

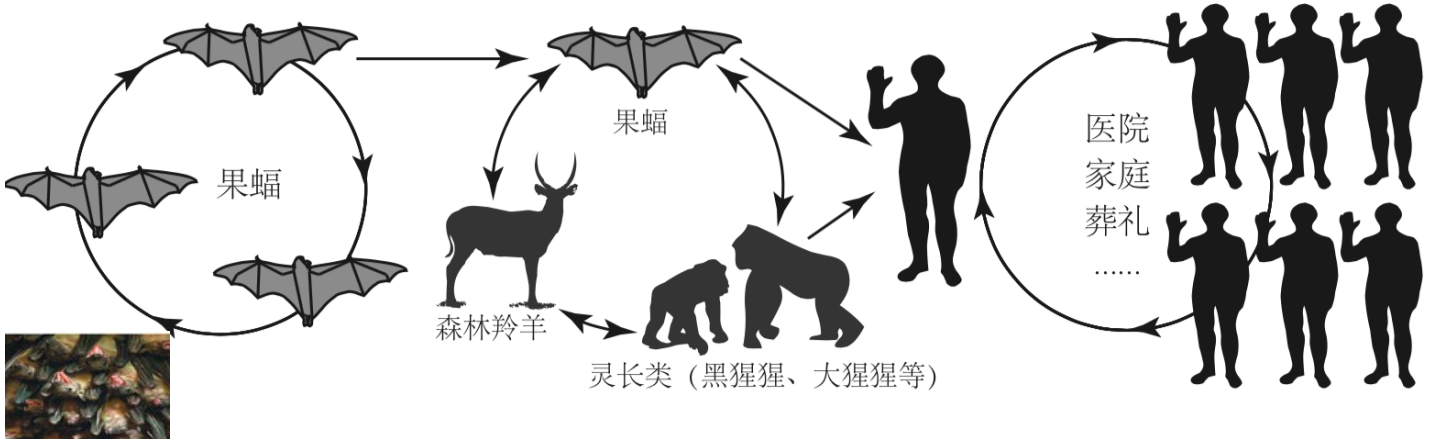
? 人祸+天灾

?人祸

疾病来源

埃博拉病毒生态链

蝙蝠 → 其它哺乳动物 → 人

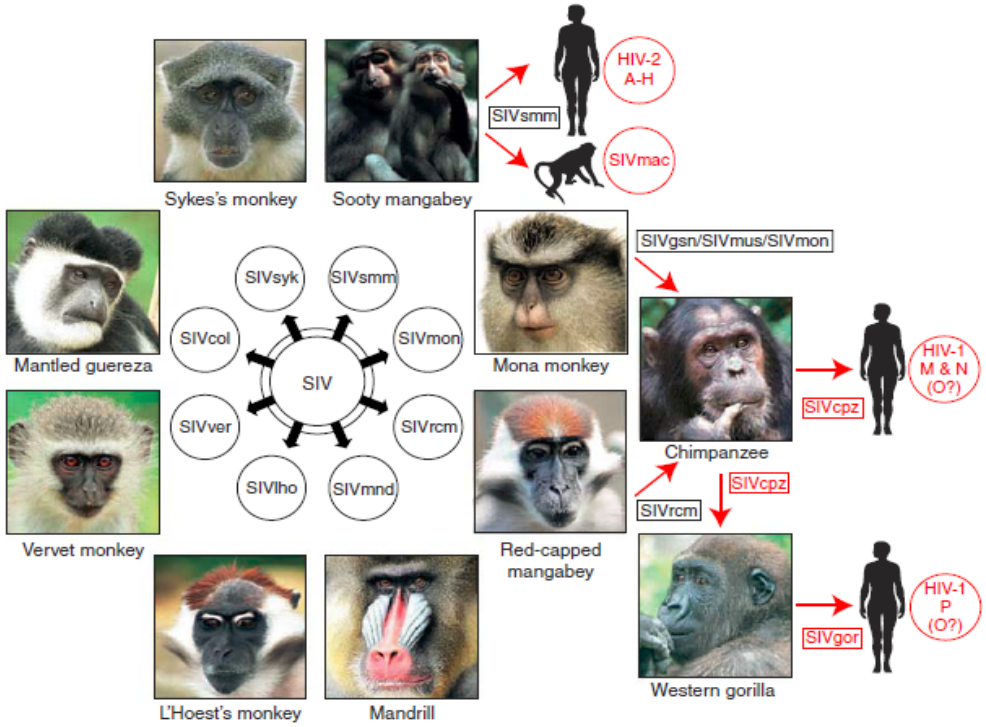


天然宿主/储存库　　中间宿主　　人　　人际传播

疾病来源

人免疫缺陷病毒（HIV）

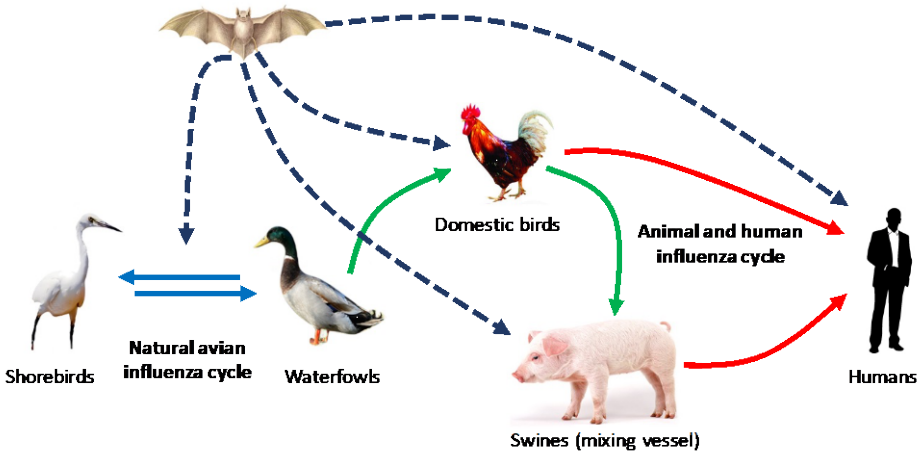
生态链与起源

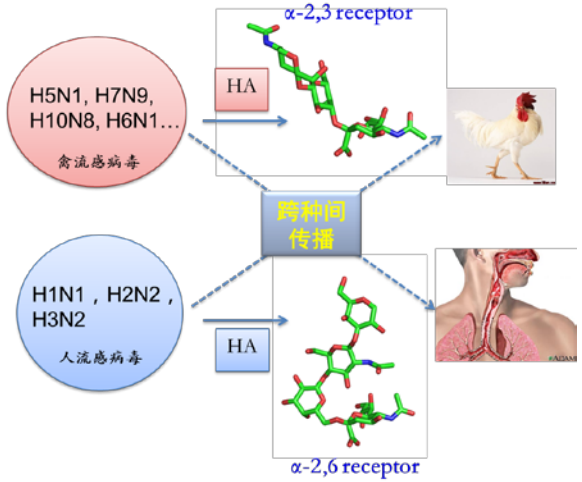


Sharp, P.M. et al. 2011, CSH Perspectives

疾病来源

流感病毒生态系统





Shi and Gao et al., 2014, Nature Reviews Microbiology

- 流感病毒在自然界中主要在野生鸟类中循环，但是家禽和家畜可以作为中间宿主将流感病毒传给人类
- 病毒受体结合特性的转变是病毒实现跨种传播的决定因素之一

疾病来源

气候和生态变化

受威胁的绝不止是北极熊和企鹅

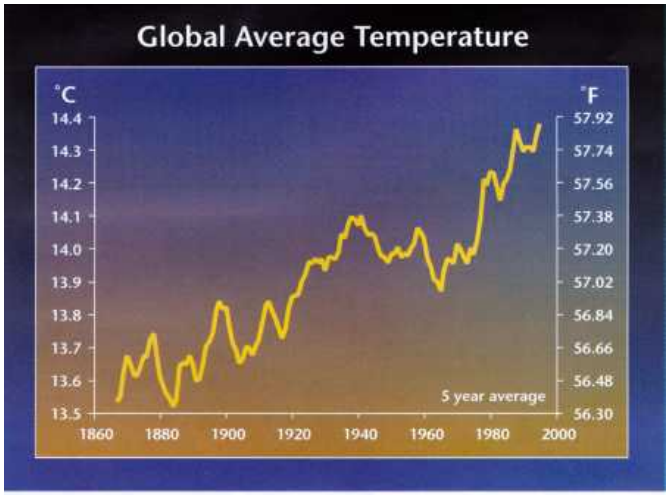
疾病来源

全球人口流动加速传染病的传播

传染病

疾病来源

人类行为的改变



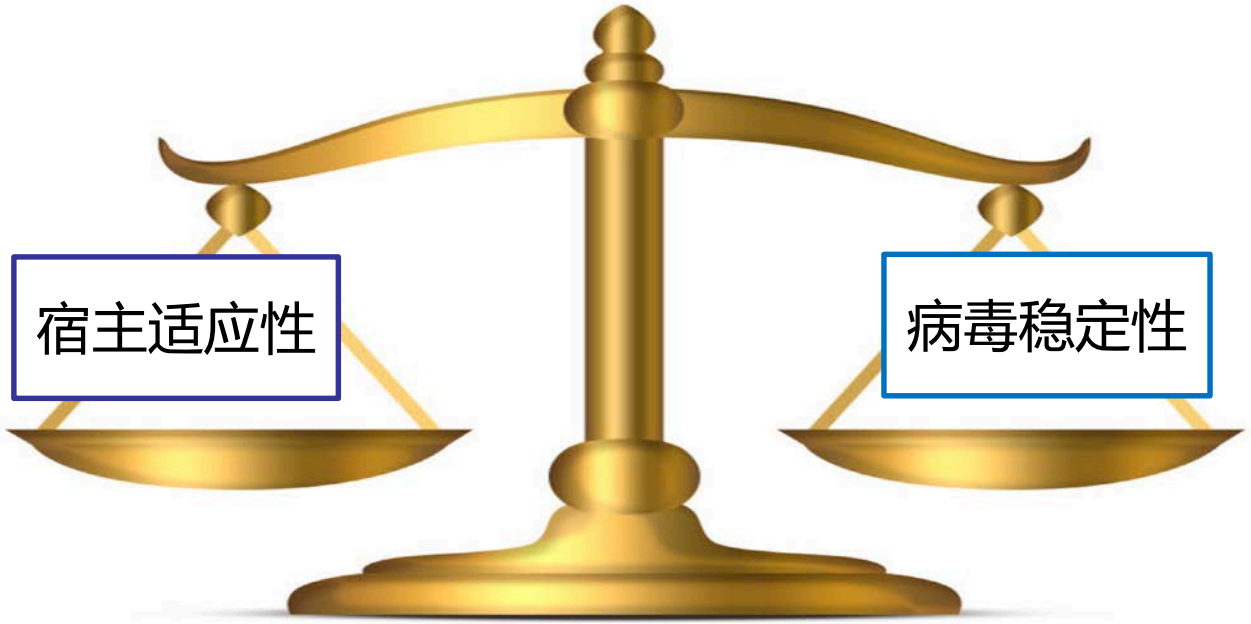
- 二氧化碳含量急剧增加
- 全球变暖对我们健康的影响

防控手段

下一个挑战人类的病毒是什么？

- DRC　埃博拉
- 巴西　黄热病
- 印度　尼　帕
- …… ……

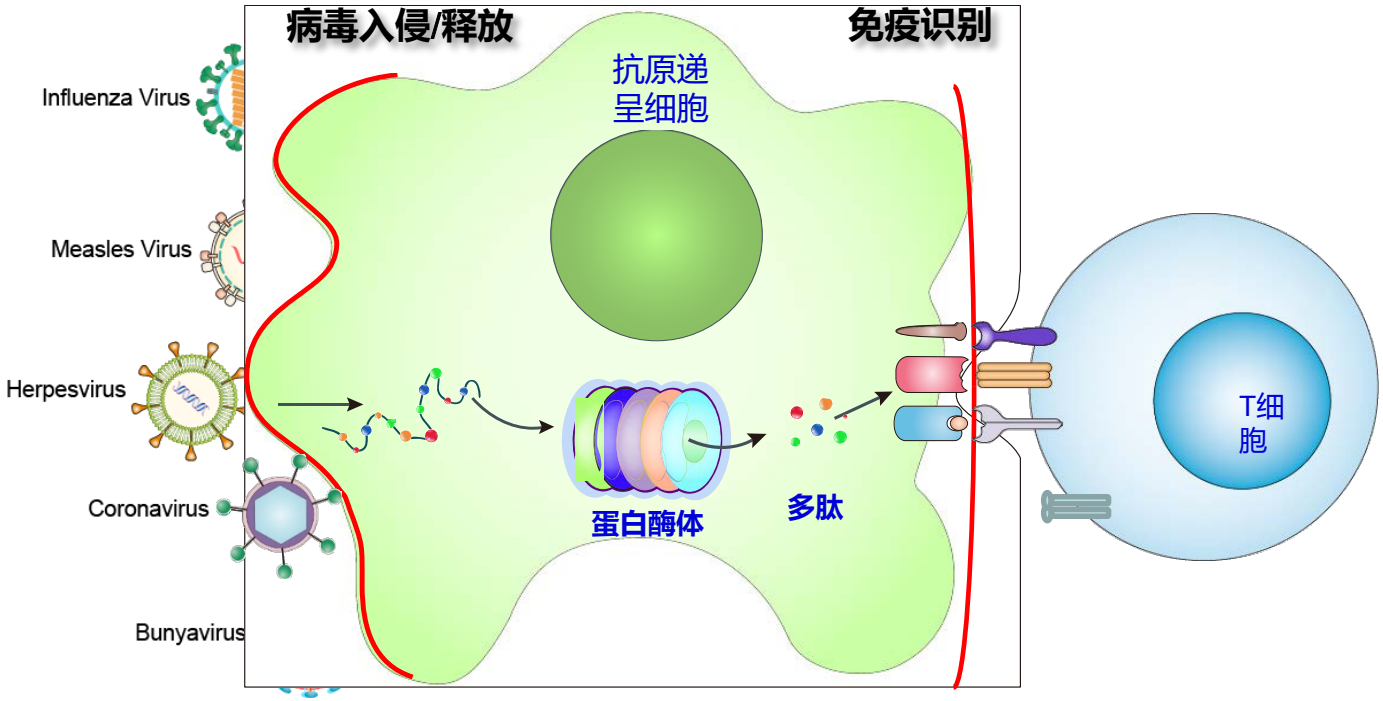
防控手段



宿主适应性：通过提高病毒突变频率，实现宿主适应

病毒稳定性：在宿主中维持一定的突变频率，实现病毒的稳定传代

George’s “surface” work



George’s “surface” work

1. 发现宿主细胞表面介导病毒侵入细胞的受体
2. 病毒囊膜蛋白前体在宿主细胞内的酶切加工

Attacks by Emerging Infectious Diseases

Leading Edge
Commentary

Cell

From "A"IV to "Z"IKV: Attacks from Emerging and Re-emerging Pathogens

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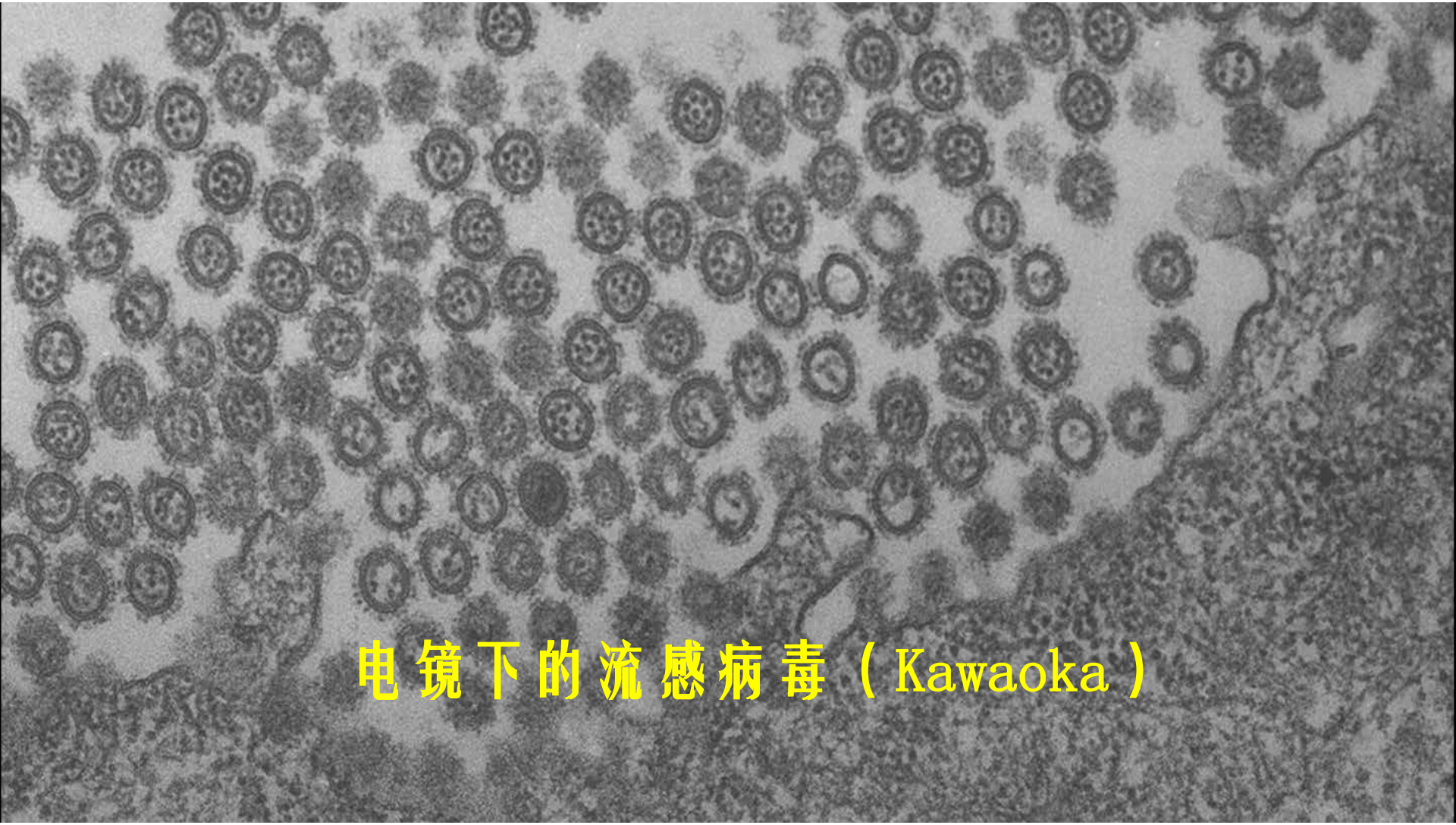
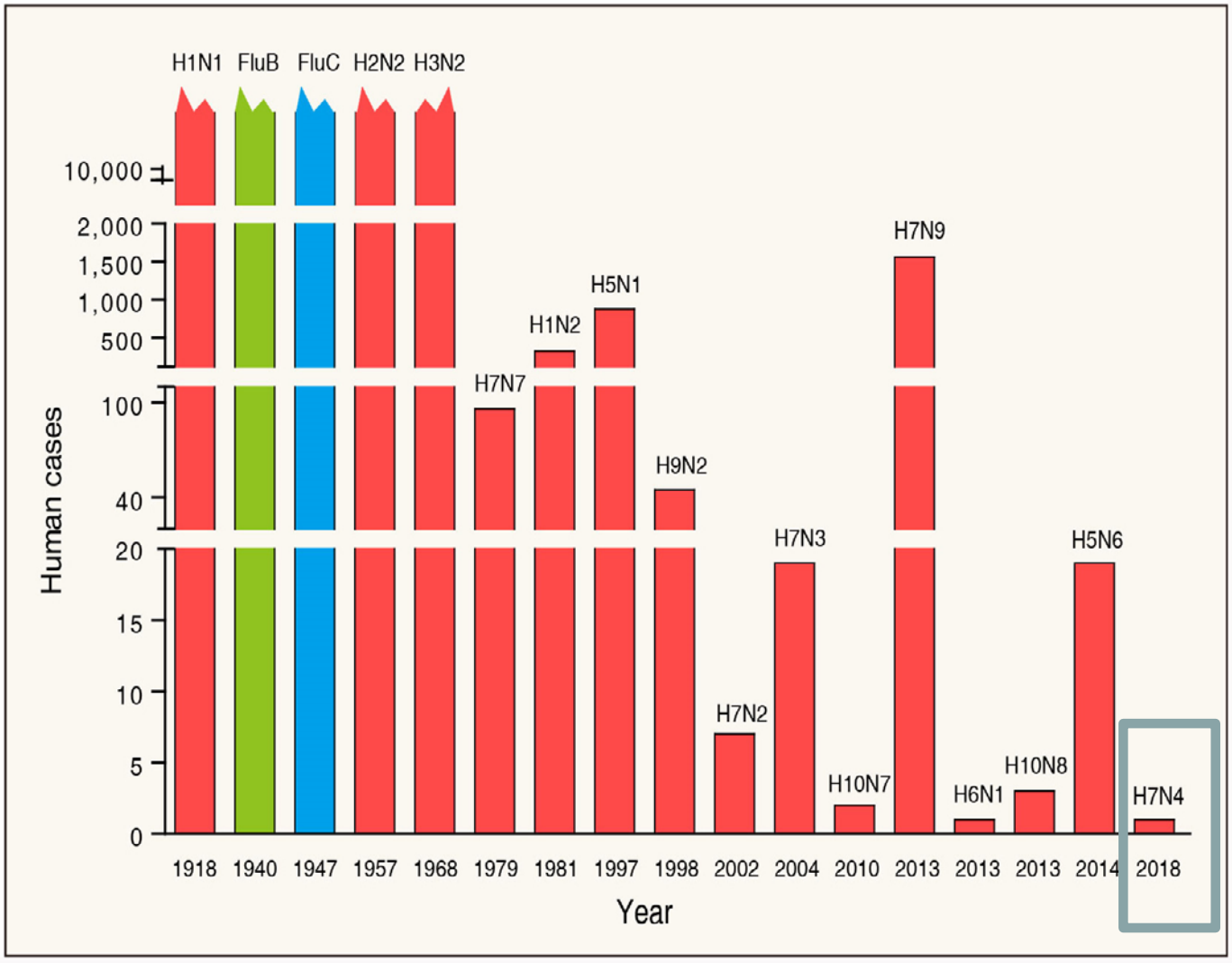
[1]Chinese Center for Disease Control and Prevention (China CDC), China
[2]CAS Key Laboratory of Pathogenic Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences (CAS), China
*Correspondence: gaof@im.ac.cn
https://doi.org/10.1016/j.cell.2018.02.025

100 years after the infamous "Spanish flu" pandemic, the 2017–2018 flu season has been severe, with numerous infections worldwide. In between, there have been continuous, relentless attacks from (re-)emerging viruses. To fully understand viral pathogenesis and develop effective medical countermeasures, we must strengthen current surveillance and basic research efforts.

Gao et al, Cell, 2018

流感	項目	普通感冒
流感病毒	致病原	腺病毒、呼吸道融合病毒等
全身性	影響範圍	呼吸道局部症狀
突發性	發病速度	突發／逐漸性
喉嚨痛、倦怠、肌肉痠痛	臨床症狀	喉嚨痛、鼻塞、噴嚏
高燒３－４天	發燒	發燒１－３天
嚴重、無法上課／工作	病情	較輕微
約１－２週	病程	約２－５天
肺炎、心肌炎	併發症	少見（中耳炎或其他）
高傳染性	傳染性	傳染性不一
接種疫苗	預防	注意衛生


电镜下的流感病毒（Kawaoka）

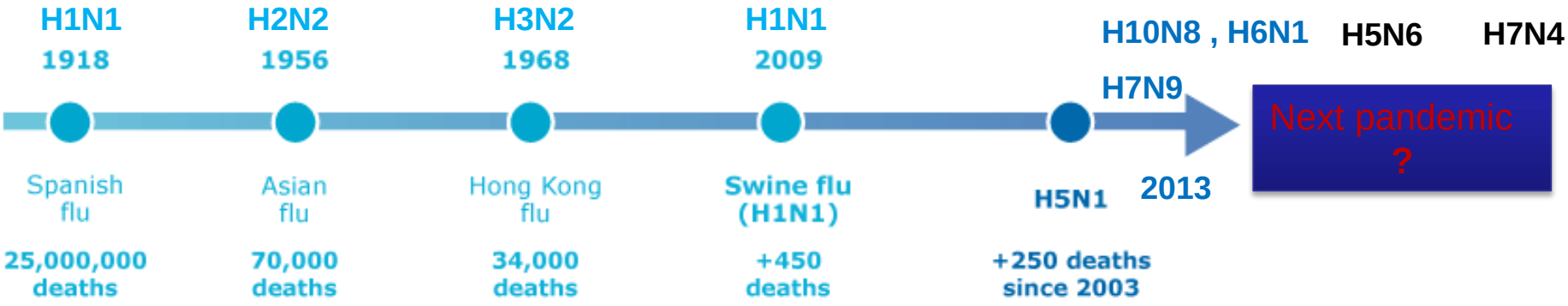


Gao et al, Cell, 2018

历史上的流感

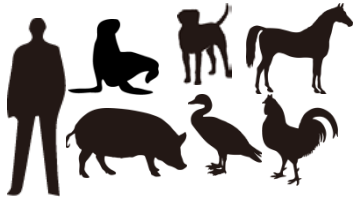
1918 pandemic H1N1 virus

Human-infecting avian H7N9 virus

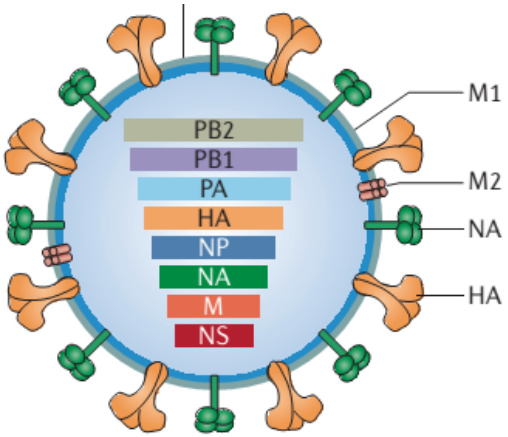


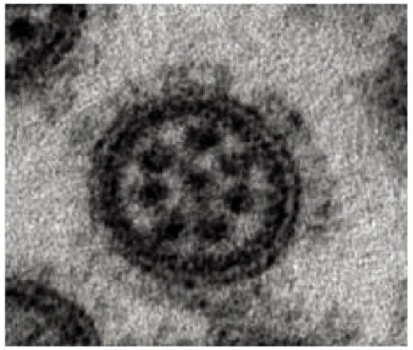
流感病毒的分类

Influenza A virus

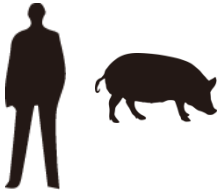


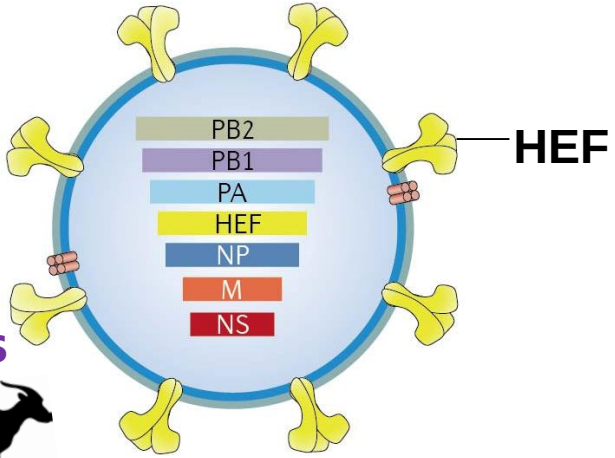
Influenza B virus





Influenza C virus





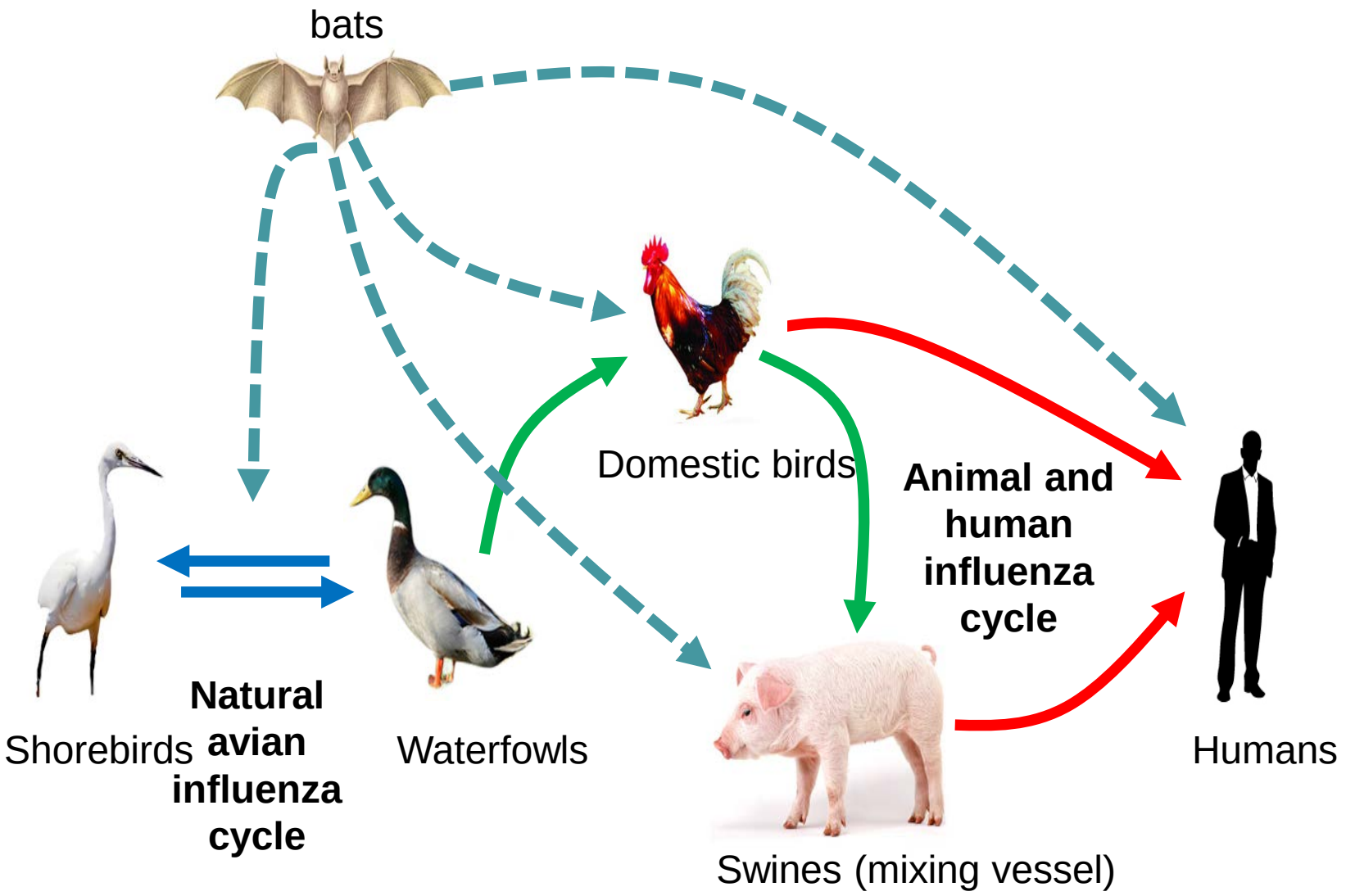
Influenza D virus

Family: *Orthomyxoviridae*

Enveloped, segmented, single-stranded, negative-sense RNA virus

Diameter: 80~120nM

禽流感病毒的跨种传播生态圈



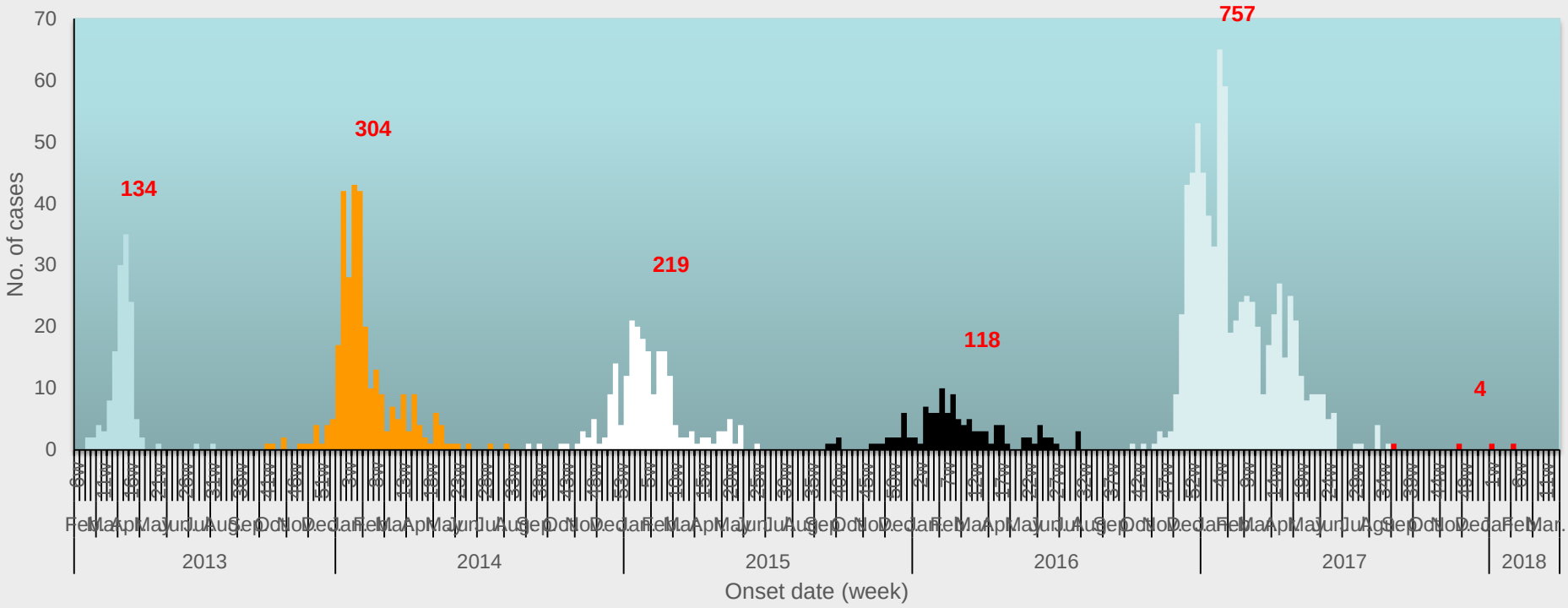
我国人感染H7N9病毒统计

[As of 31 March. 2018]

- ***1536 cases***
- ***27 provinces***
- ***611 deaths***

The 6th wave

- ***Only 4 cases***
- ***4 provinces***



H7N9: 4 years path

From low pathogenic to highly pathogenic AIV

Hemagglutinin 4 AA insertion for efficient cleavage: R(G)KRT(I)

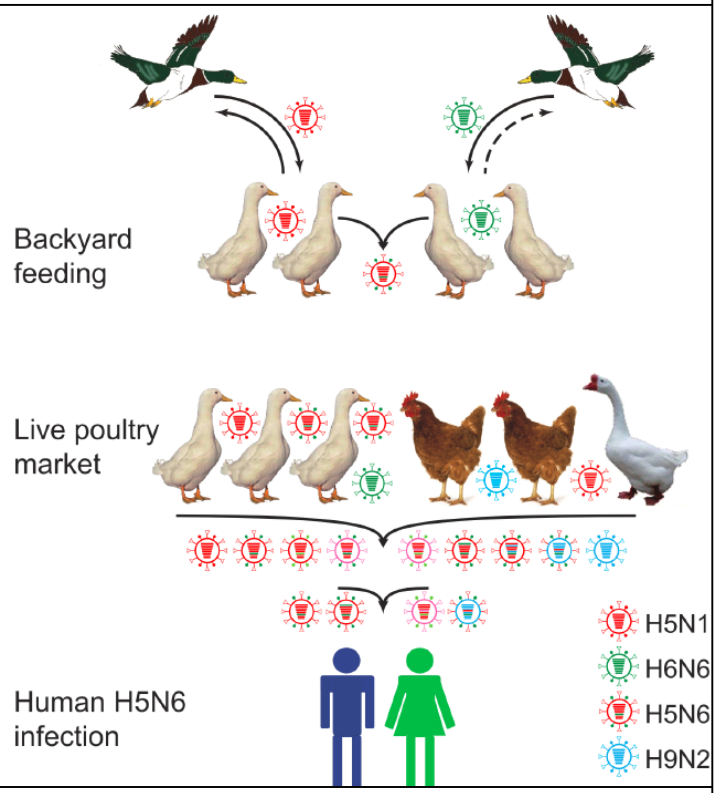
PKRKRTARGL

PKGKRIARGL

PKGKRTARGL

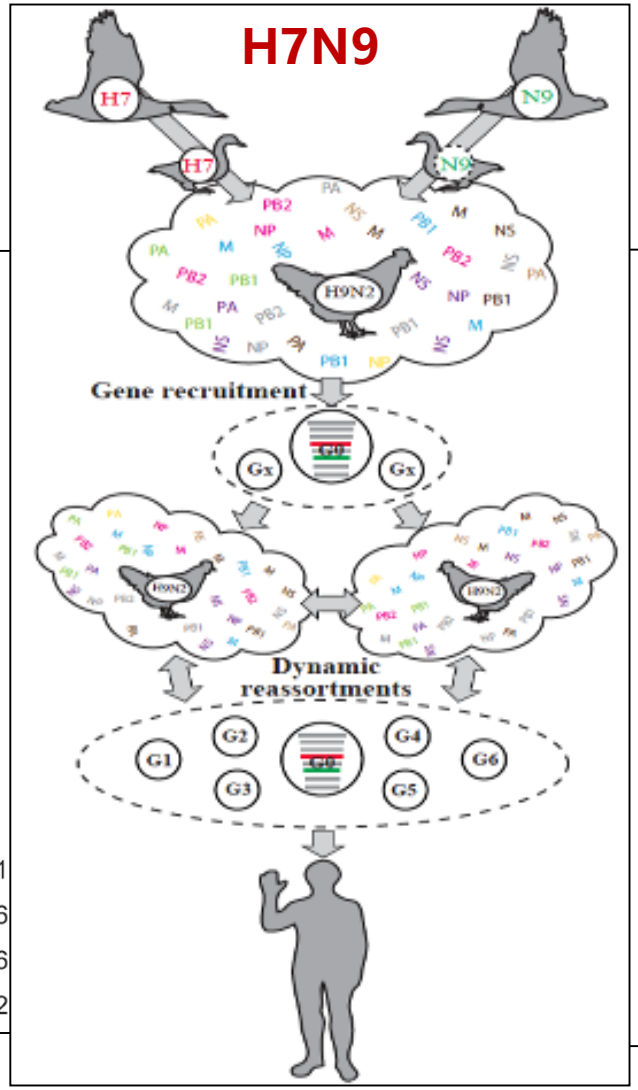
野鸟对新型禽流感病毒的起源进化和流行传播发挥重要作用

H5N6



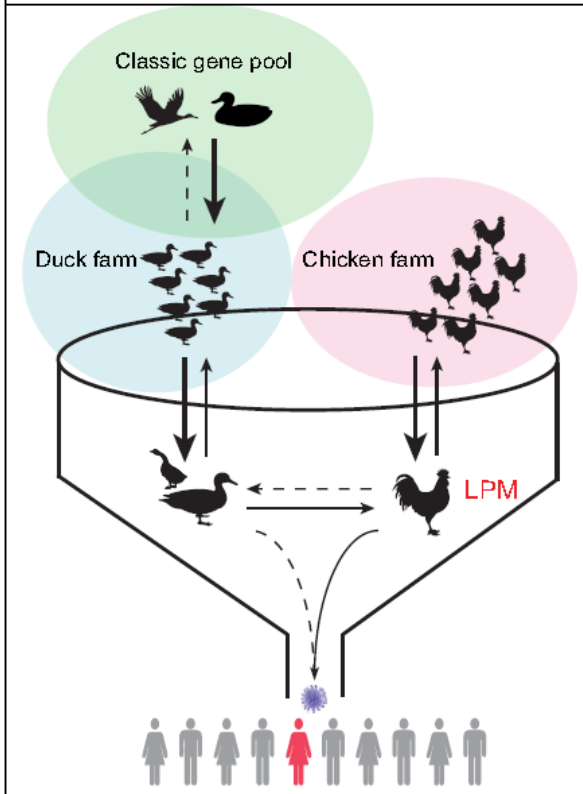
Cell host microbe. 2016 Dec 14;20(6):810-821.

H7N9



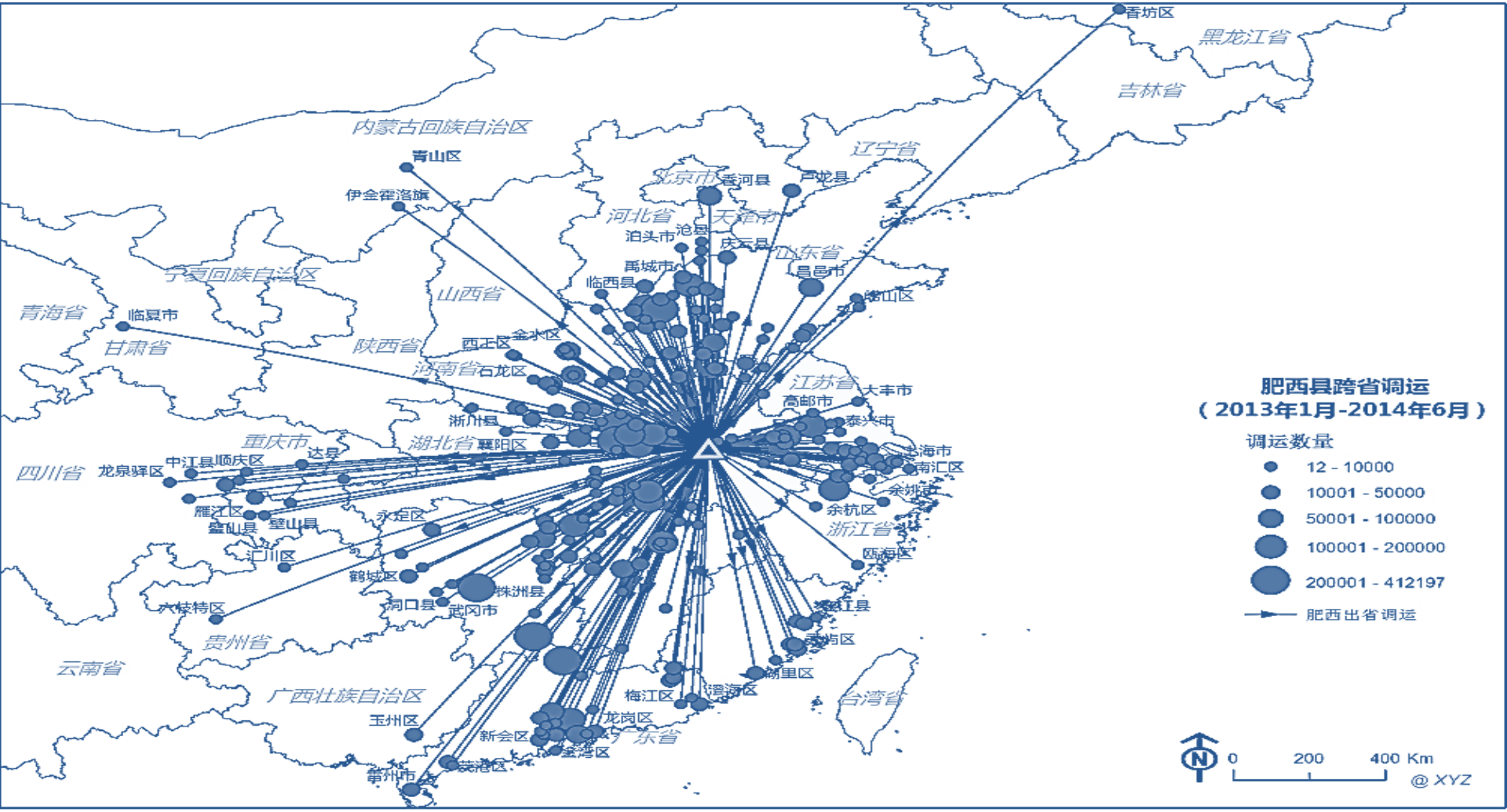
Cui L. et al. Nat Commun. 2014;5:3142.

H10N8



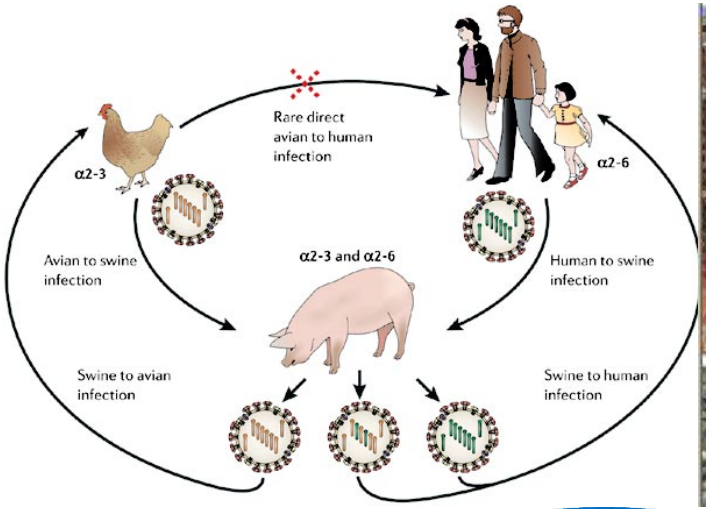
Ma C. et al, J Virol. 2015, 89(7):3534-41

活禽交易运输与H7N9病毒的流行传播

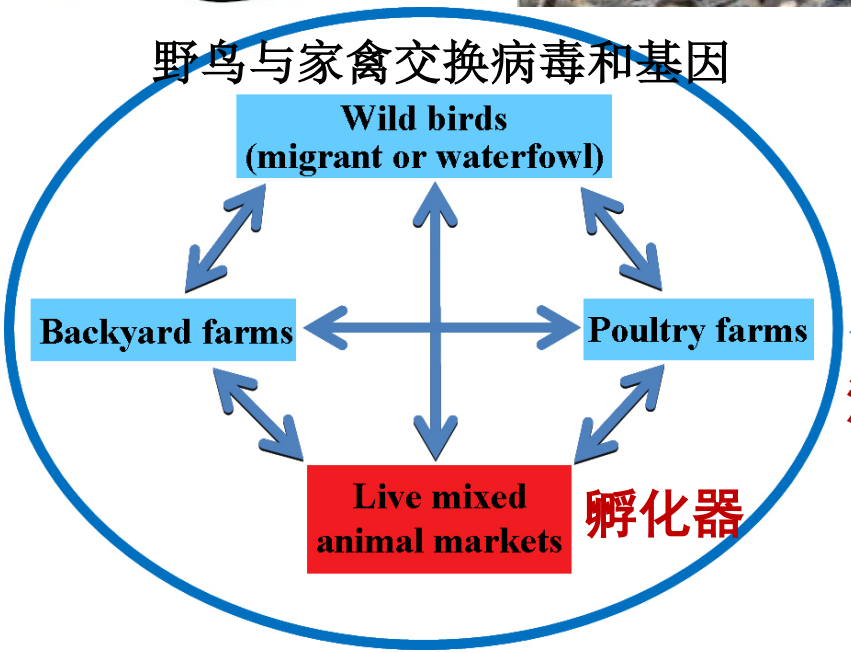


*养殖场活禽调运示意图 (CCDC)

活禽市场对新型禽流感病毒的进化和传播具有重要贡献



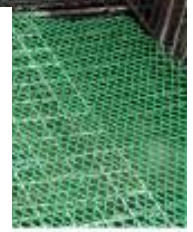
野鸟与家禽交换病毒和基因

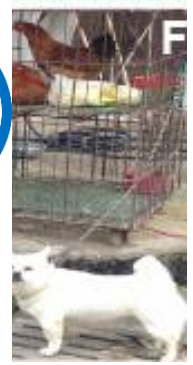


Live animal/
poultry trading

流行传播途径

Other regions
(province or country)

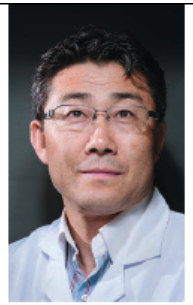




J Virol. 2015, 89(17):8671-6

LPMs act as an “incubator” for the novel AIVs.

呼吁：中国、东南亚等国停止活禽交易



George F. Gao is director of the CAS Key Laboratory of Pathogenic Microbiology and Immunology at the Institute for Microbiology of the Chinese Academy of Sciences, Beijing; vice president of the Beijing Institutes of Life Science, Beijing; president of the Chinese Society for Virology, Beijing; and deputy director general of the Chinese Center for Disease Control and Prevention, Beijing. E-mail: gaof@im.ac.cn

EDITORIAL

Influenza and the Live Poultry Trade

LIVE POULTRY TRADE AT LOCAL MARKETS HAS LONG BEEN A PART OF CHINA'S NATIONAL IDENTITY. From small villages to big cities, the gathering and selling of different birds in this vibrant atmosphere is at the heart of the country's cuisine culture. Unfortunately, the backdrop to this tradition has changed. Last year, the H7N9 virus, a new strain of influenza A, jumped from birds to humans, causing 144 cases of human infection and 47 deaths in China. Now a second wave of this flu is coursing through the country, with 258 confirmed cases and 99 deaths as of 8 April 2014. Scientific evidence points to a connection between the conditions at these live markets and the spread of flu, suggesting that until other means are found to prevent the transmission of or effectively treat the illness, China must shut down live poultry markets to prevent further spread of the virus and a possible global pandemic.

Early in 2013, the Chinese Center for Disease Control and Prevention and several prominent Chinese research groups quickly identified H7N9 as the causative agent of the emerging flu. The source of the virus was immediately traced to live poultry markets. With a call for an immediate shutdown of these markets in major cities, including Hangzhou and Shanghai (where the first H7N9 human infection cases were found), the government quickly controlled the spread of the virus. But the government deemed long-term closure to be economically unviable, and the markets reopened soon after the summer. At the beginning of the new flu season in October, the virus bounced back in the eastern Yangtze River delta region. This year, it has spread to the Canton region (Guangdong province) in China, which is alarming because live poultry markets are commonplace there.

Approximately 87% of the people infected with H7N9 had close contact with live poultry or exposure to a contaminated environment such as the poultry markets, where the virus can spread quickly through birds. Poultry transportation between provinces is probably playing an important role in its spread across China. Although it is generally believed that H7N9 has not developed human-to-human

Science, 2014-04-18

我们所见的只是冰山之一角

16H X 9N =144

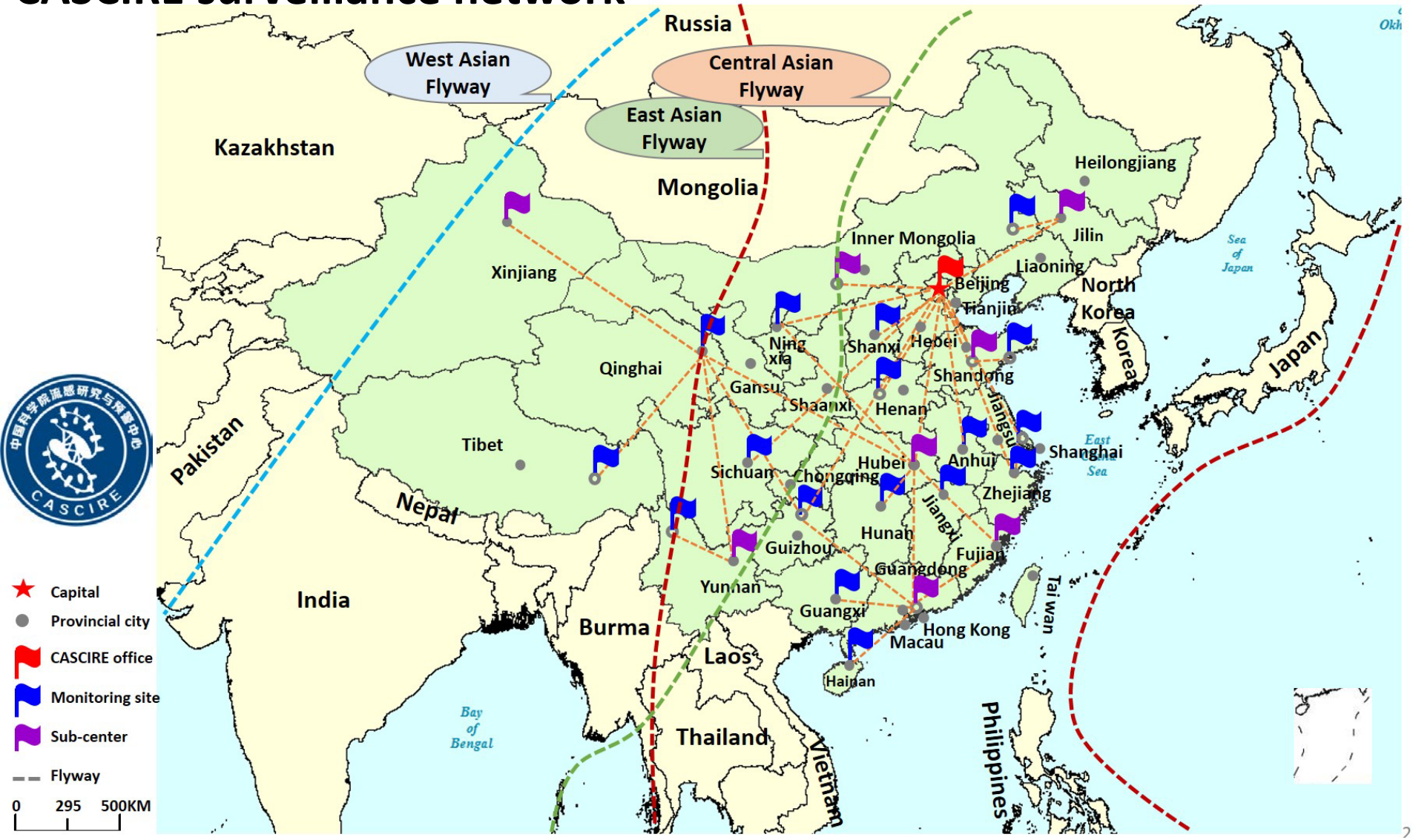
+2

中国科学院流感研究与预警中心

病原监测预警、遗传变异、跨种传播和致病机制、药物和疫苗设计

中国科学院流感研究与预警中心--病原监测网络

CASCIRE surveillance network

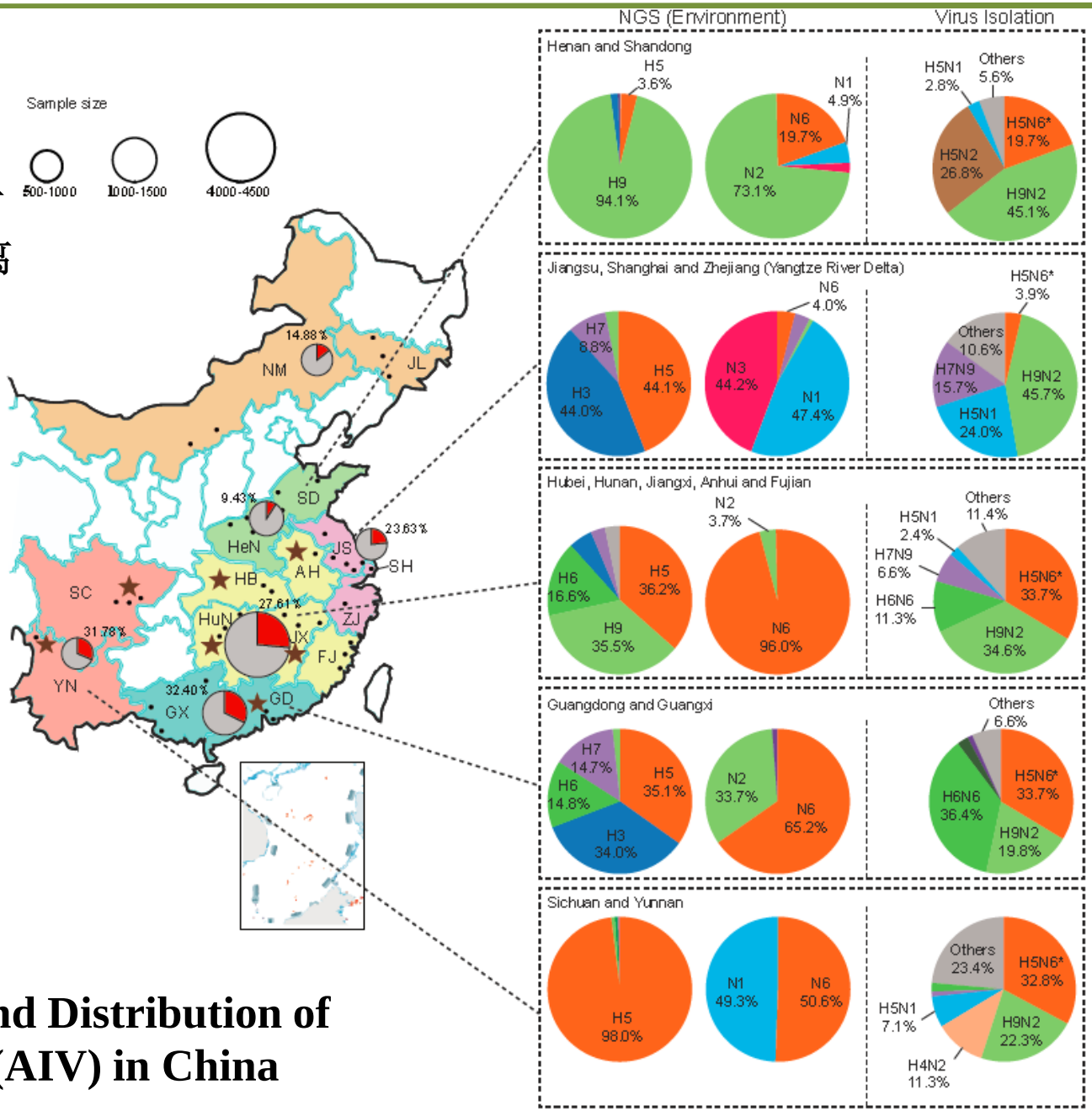


新型禽流感病毒的流行预警

H5N6优势流行

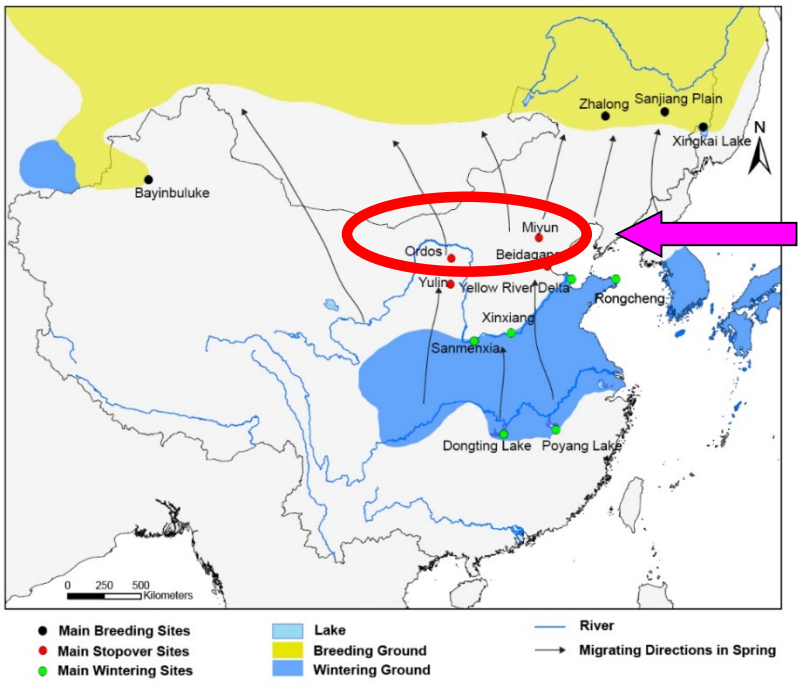
- 范围：16个省份-39个城市
- 研究方法：NGS、病毒分离
- 结果：

(1)北方地区主要以H9N2为主;
(2)长三角地区以南H5N6比重增大，成为优势流行毒株之一;
(3)长三角、华中、华南地区也有一定比例H7N9存在。
(4)H5N8占总分离测序病毒的0.53%。



Map of Sampling Sites and Distribution of Avian Influenza Viruses (AIV) in China

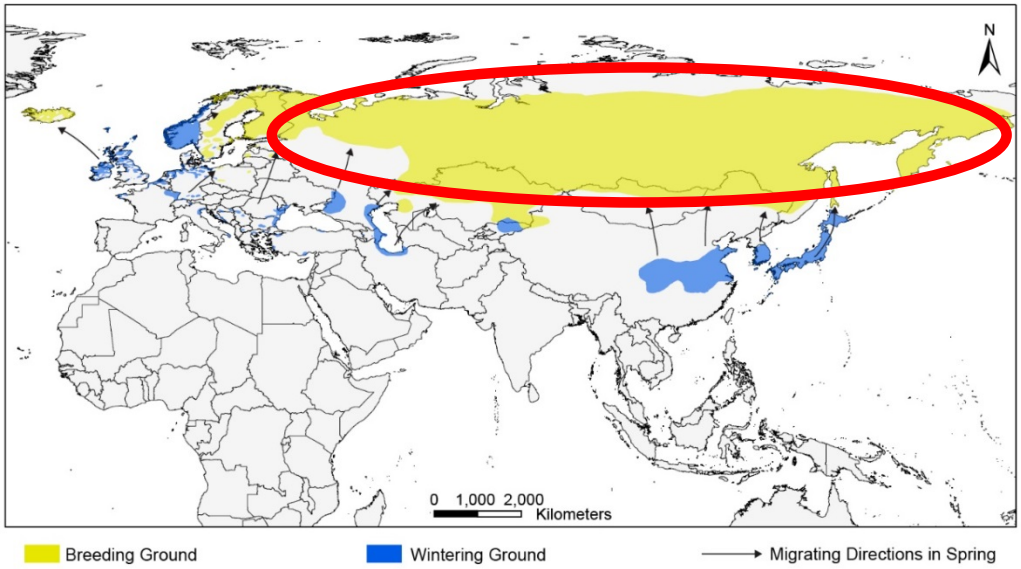
新型禽流感病毒的流行预警



预警！！

高危险区域

SMX-like Clade 2.3.2.1c H5N1病毒潜在传播路径。



高危险区域

Sci Rep. 2015,5:12986.

新型禽流感病毒的流行预警

SMX-like Clade 2.3.2.1c H5N1

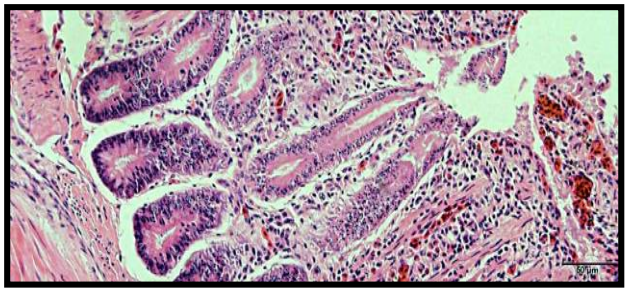


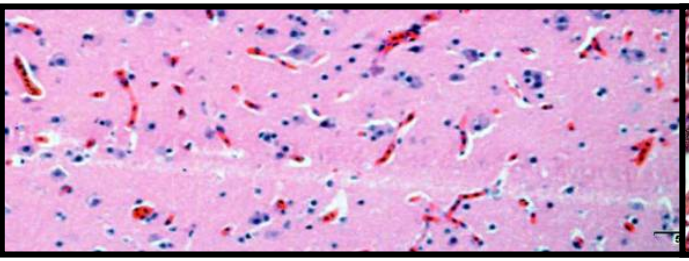
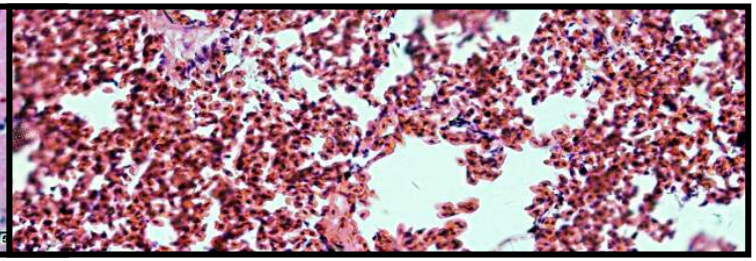

2015年1月三门峡黄河库区

Sci Rep. 2015,5:12986

预警：首次成功案例





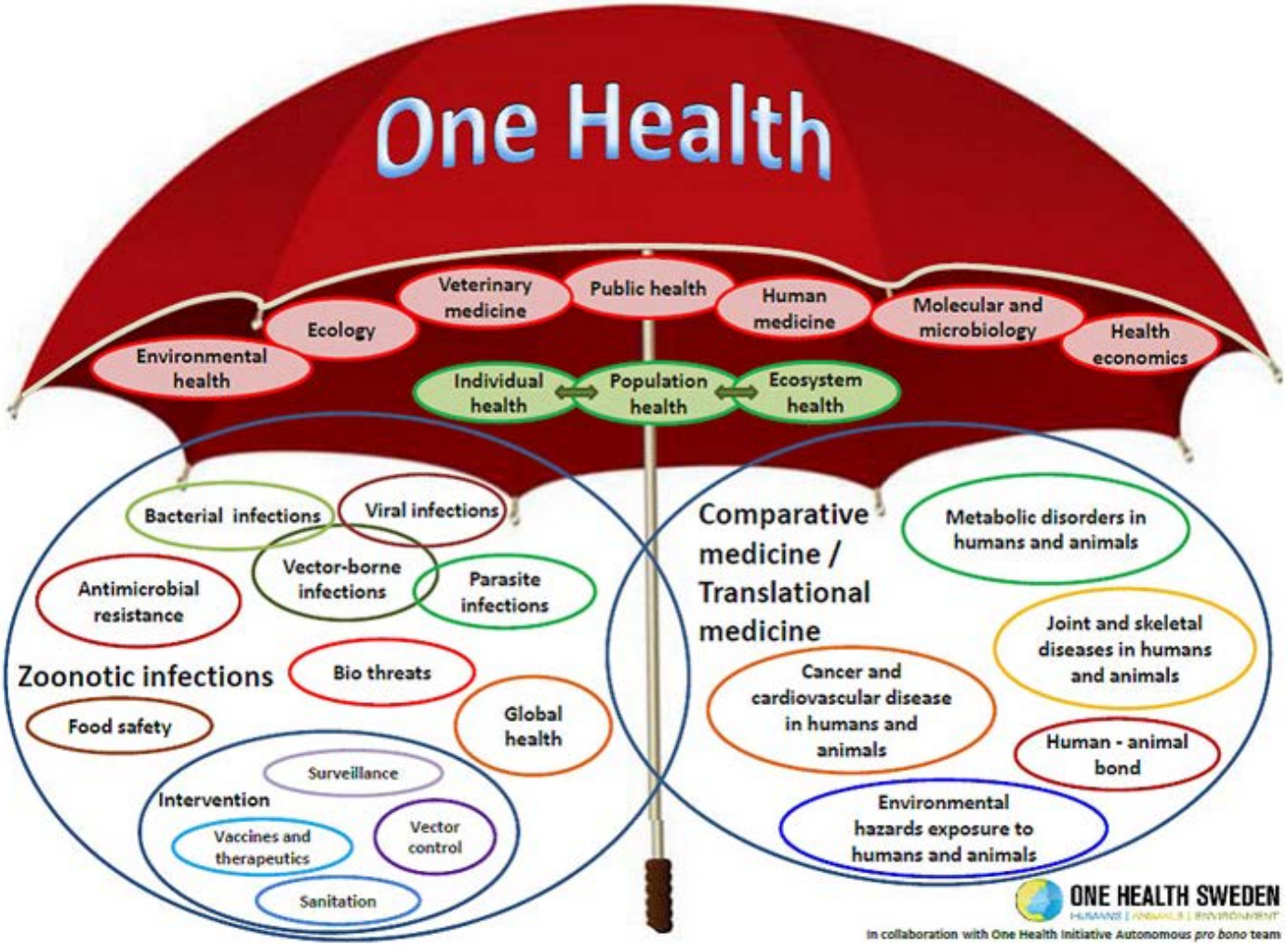




2015年5月内蒙古

Virologica Sinica. 2016

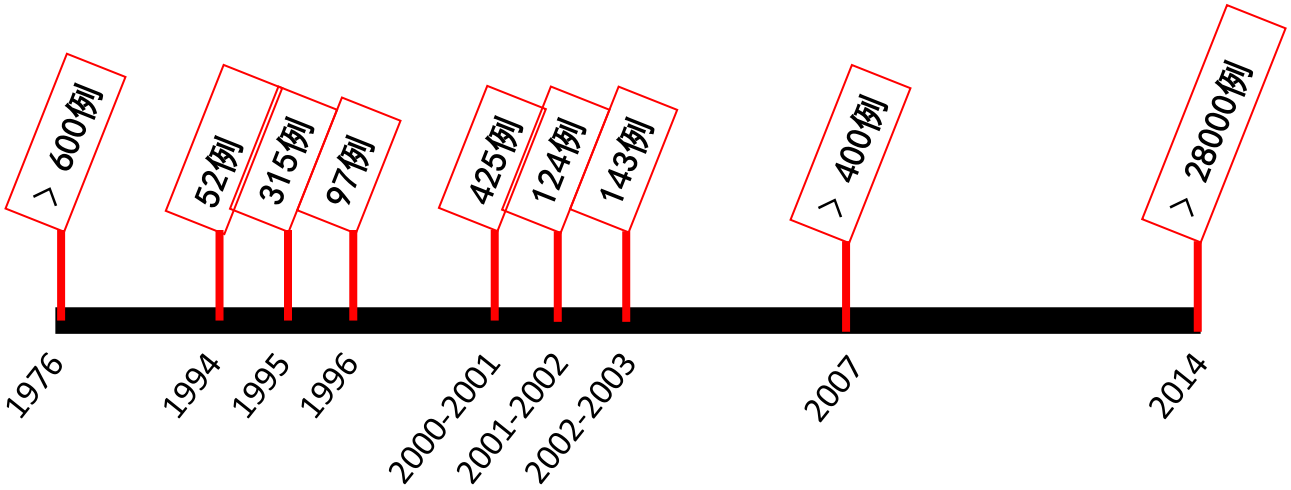
中国科学院流感研究与预警中心--病原监测网络

野生动物、家畜、人

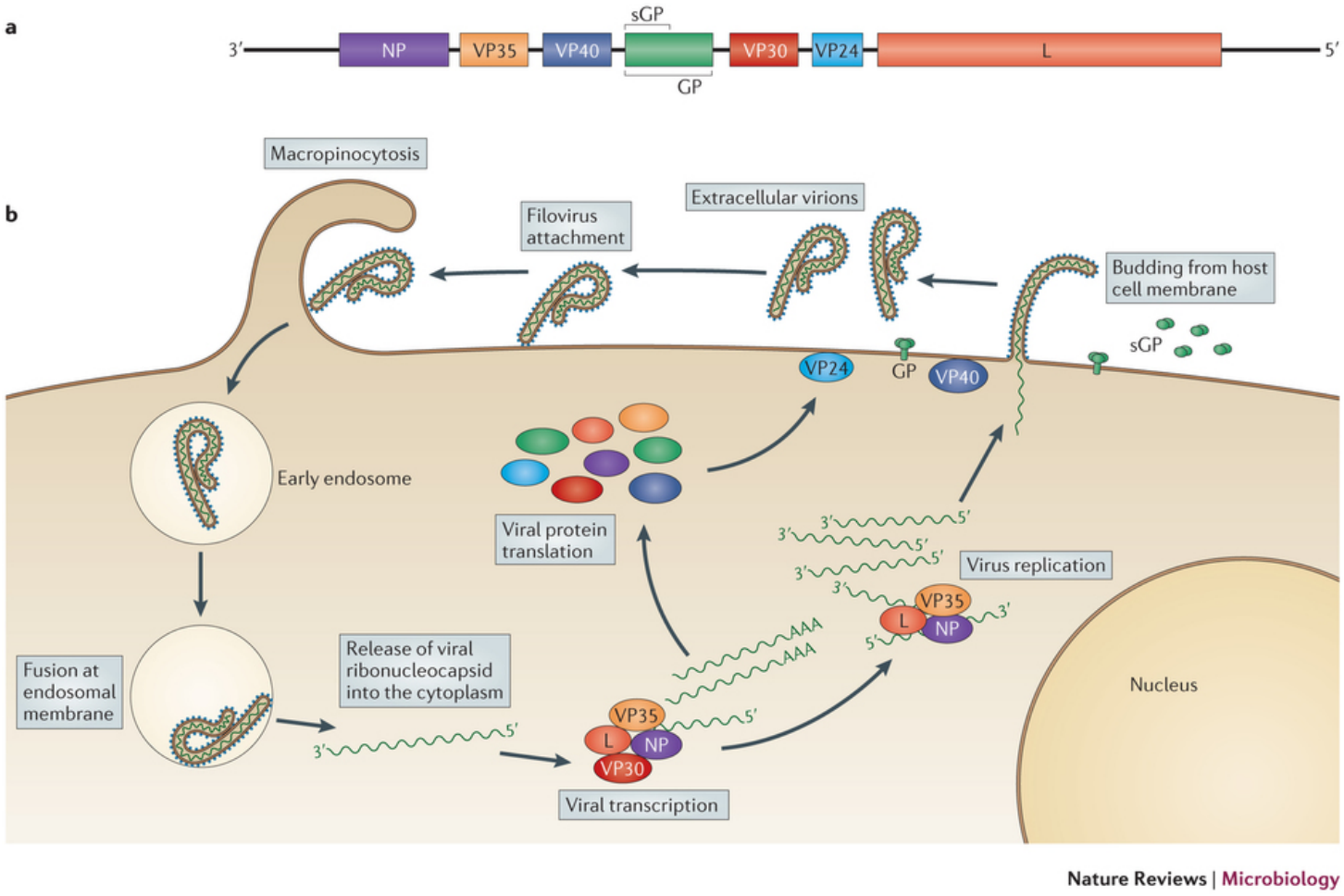


流感病毒雕塑——中国科学院奥运园区

埃博拉疫情暴发历史



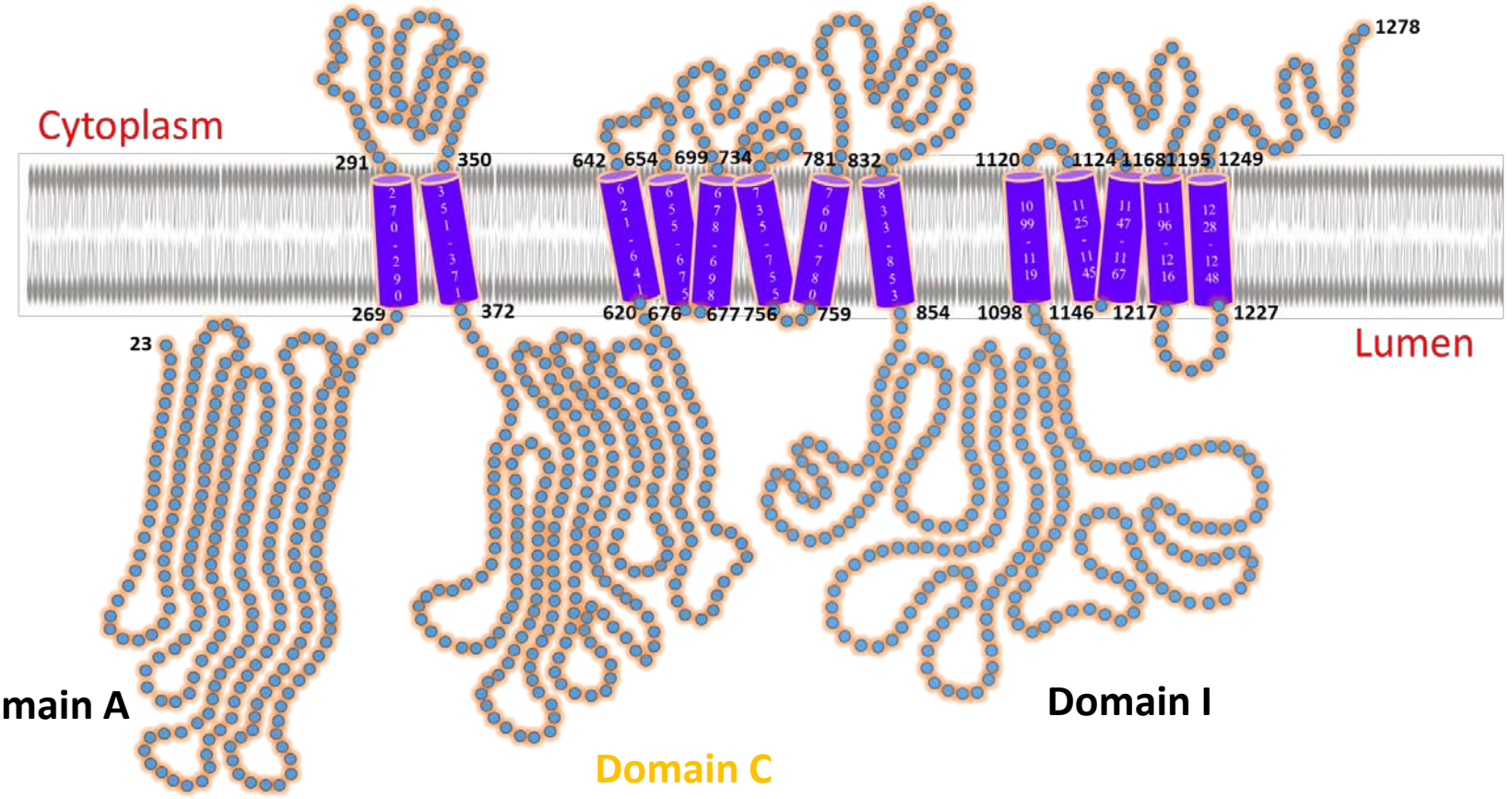
- 1976年首次报道
- 近10次大规模暴发（感染人数规模超过50人）
- 极高的病死率
- 2014年的西非疫情是有史以来规模最大的，已造成28000多例感染病例和11000多例死亡病例（截至2015.9）

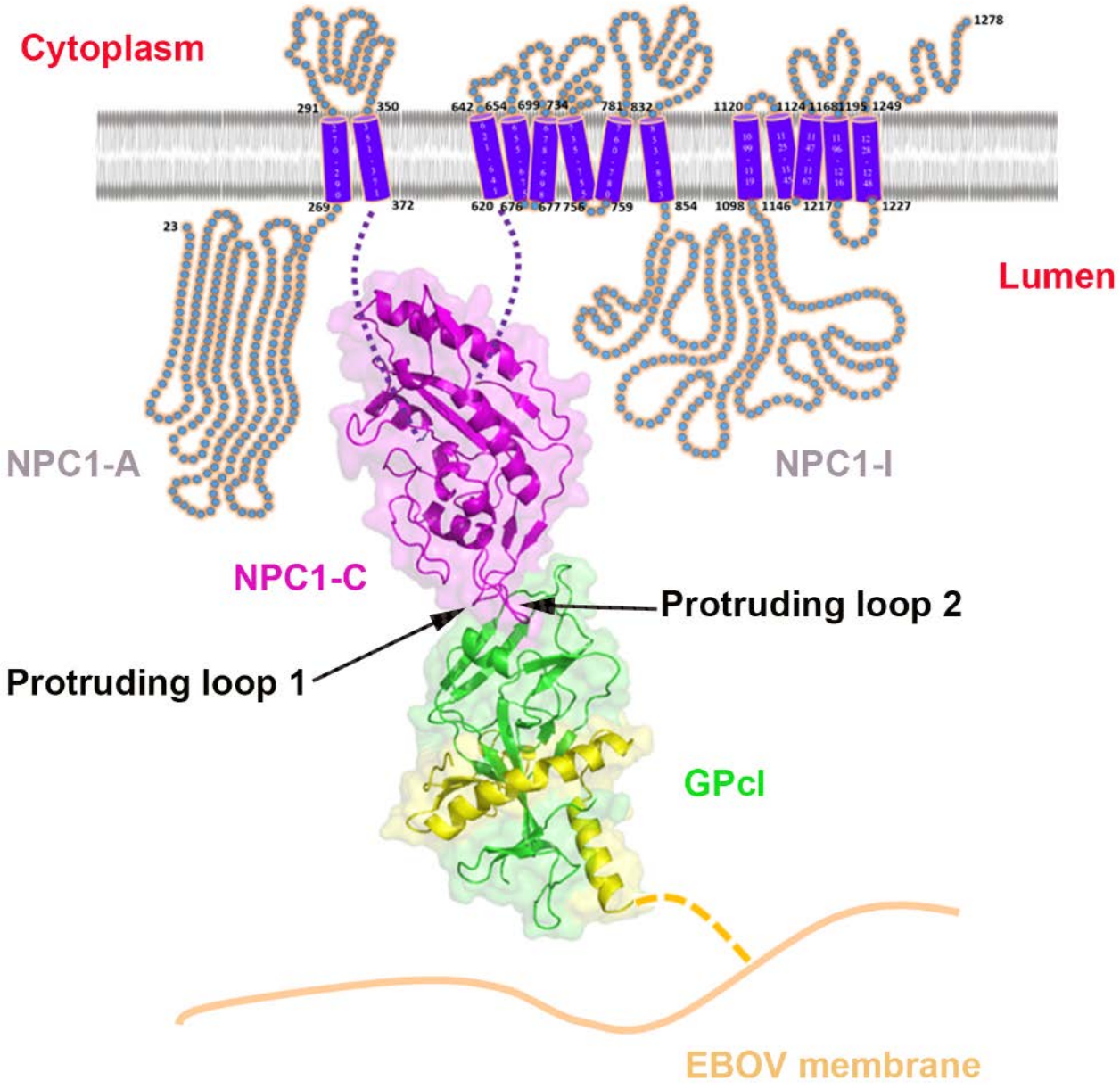


第一步：埃博拉病毒吸附在宿主细胞表面：
Tim家族，如何介导病毒粘附？
其它蛋白？受体？

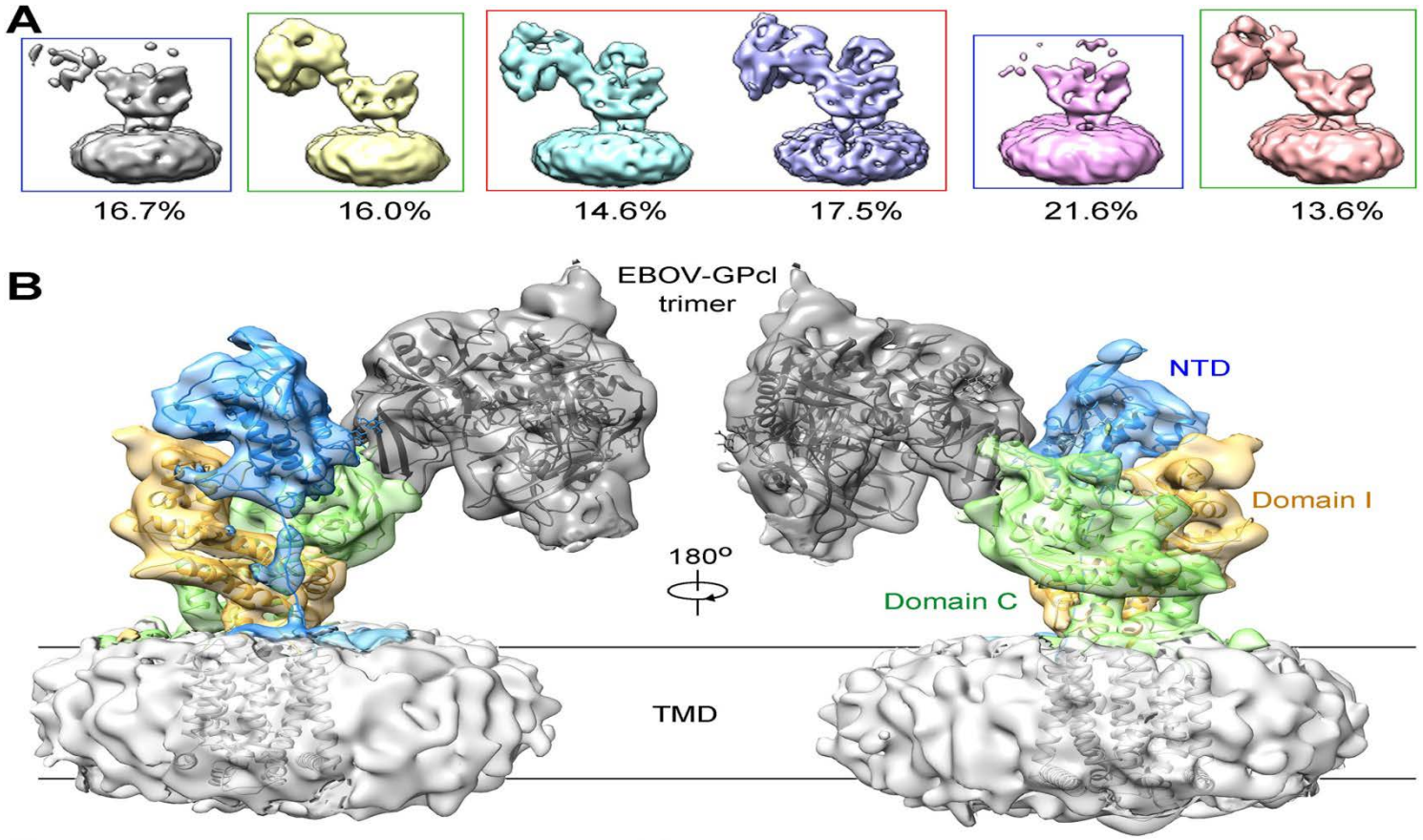
第二步：埃博拉病毒在内吞小体中发生膜融合：
NPC1，TPC，膜内受体？
如何与病毒表面GP蛋白相互作用？

激活态GP蛋白结合NPC1分子的腔内结构域 C (NPC1-C)

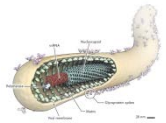



Cytoplasm
Lumen
1278
291
350
642
654
699
734
781
832
1120
1124
1168
1195
1249
269
372
620
676
677
756
759
854
1098
1146
1217
1227
23
NPC1-A
NPC1-I
NPC1-C
Protruding loop 2
Protruding loop 1
GPcl
EBOV membrane

Cryo-EM architecture of the complex between EBOV-GPcl and NPC1



The 5th fusion triggering mode



埃博拉病毒

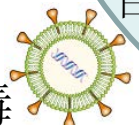
流感病毒

登革病毒

艾滋病毒

Type I：结合受体或辅助受体，单个蛋白介导膜融合

疱疹病毒



Type II：结合受体，多个蛋白介导膜融合

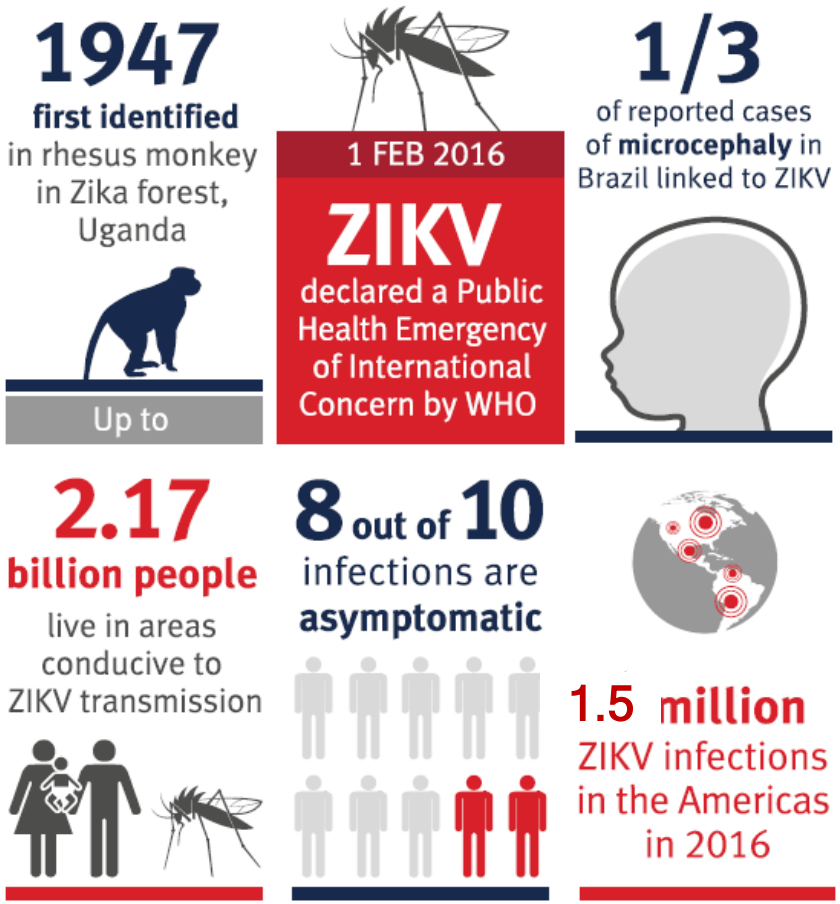
Type III：结合细胞膜表面受体后，内吞到内体中，低pH值环境里，单个蛋白介导膜融合

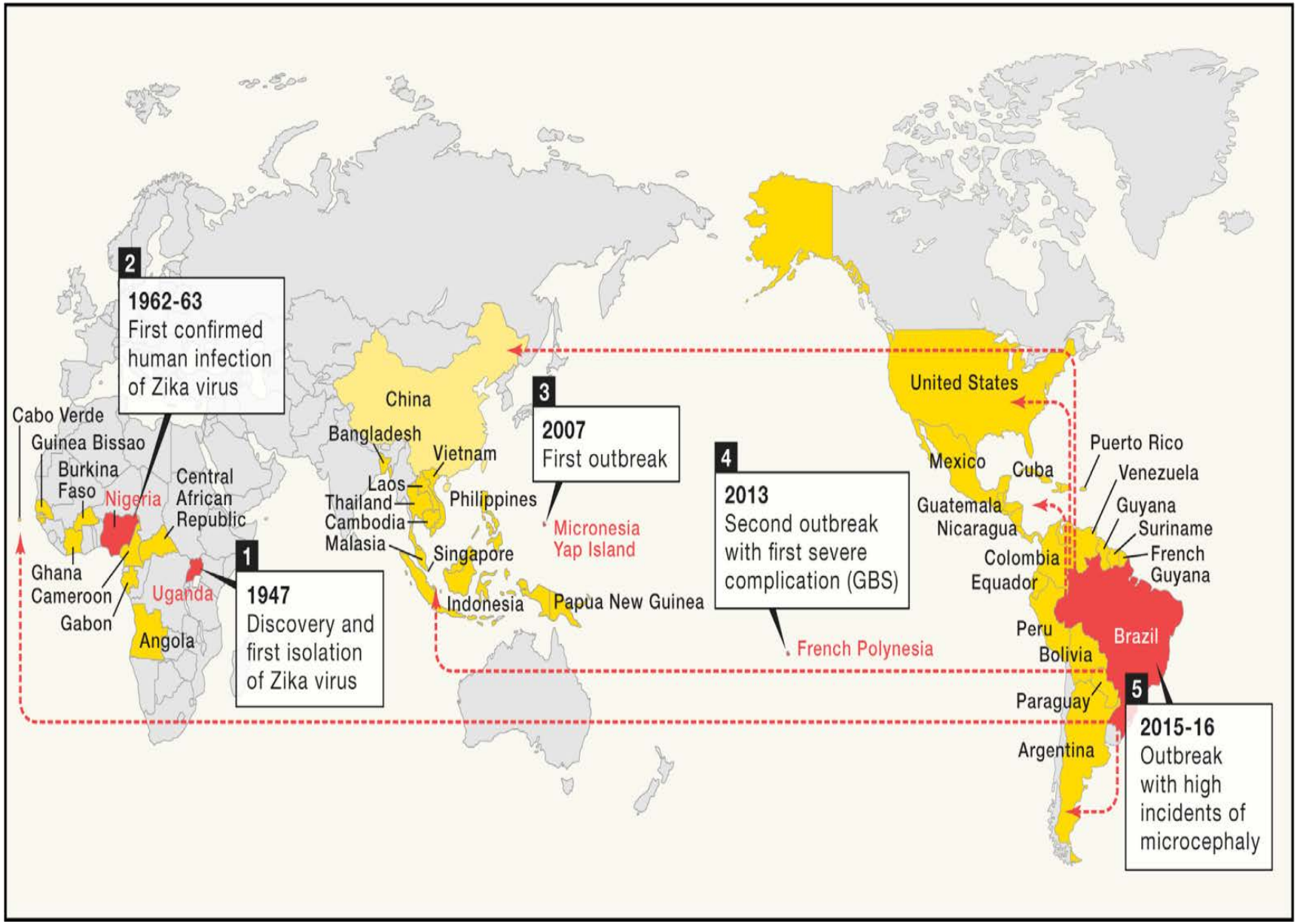
Type IV：内吞到内体里，低pH值环境里，不结合受体，单个蛋白介导膜融合

Type V：结合内体受体后，低pH值环境里，单个蛋白介导膜融合

寨卡病毒 Zika virus （ZIKV）

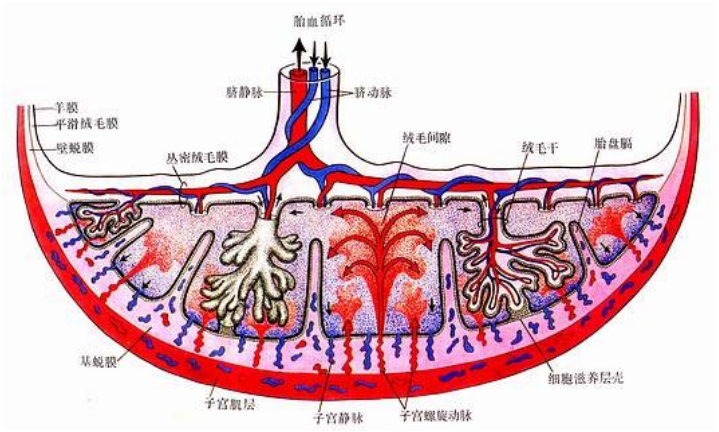
- 单股正链RNA病毒，是一种虫媒病毒，主要通过伊蚊传播。
- 引起发热、头痛、皮疹、关节炎、结膜炎等。孕妇感染会引起新生儿小头症。



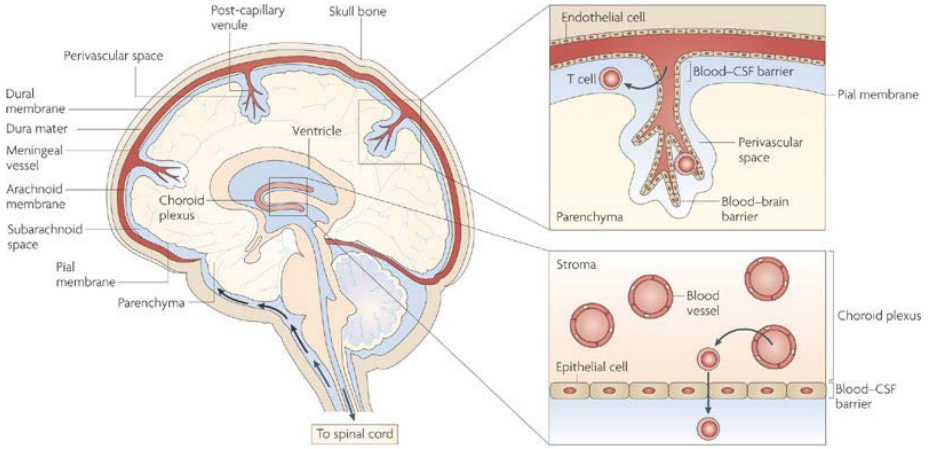


Gao, Cell, 2018

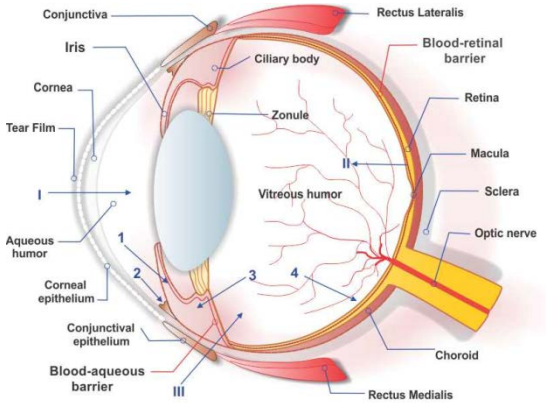
寨卡病毒突破了人体四大免疫屏障



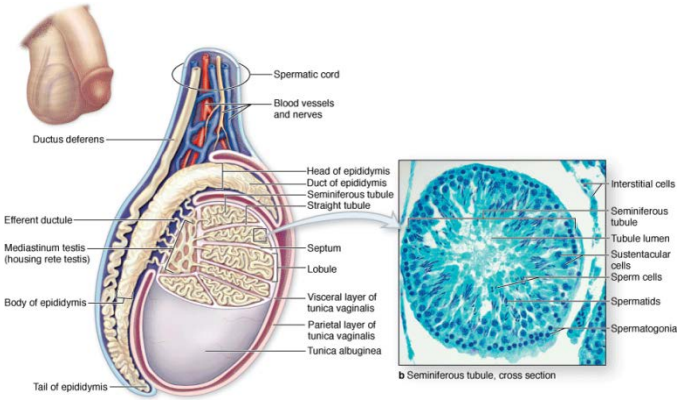
血-胎屏障



血-脑屏障



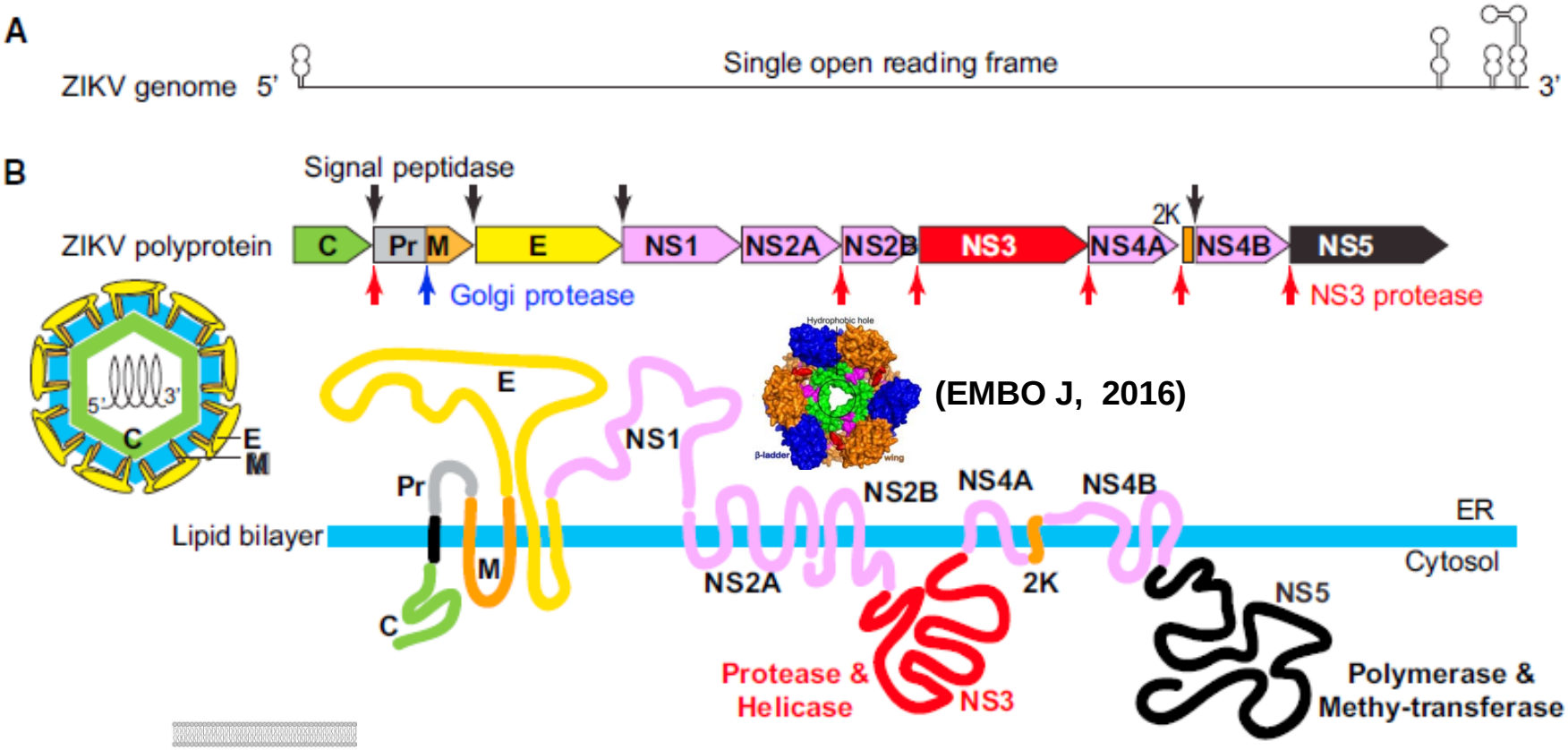
血-眼屏障

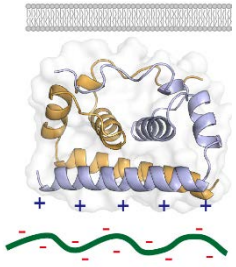


血-睾屏障

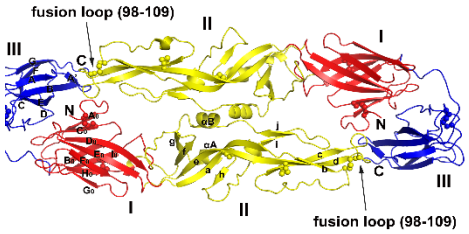
(Cell, 2017)

寨卡病毒基因组和蛋白组成

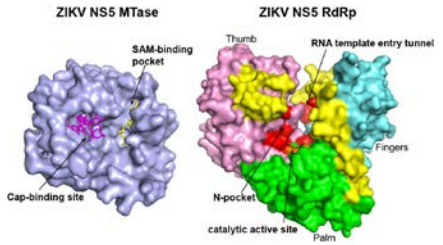




(JMB, 2018)

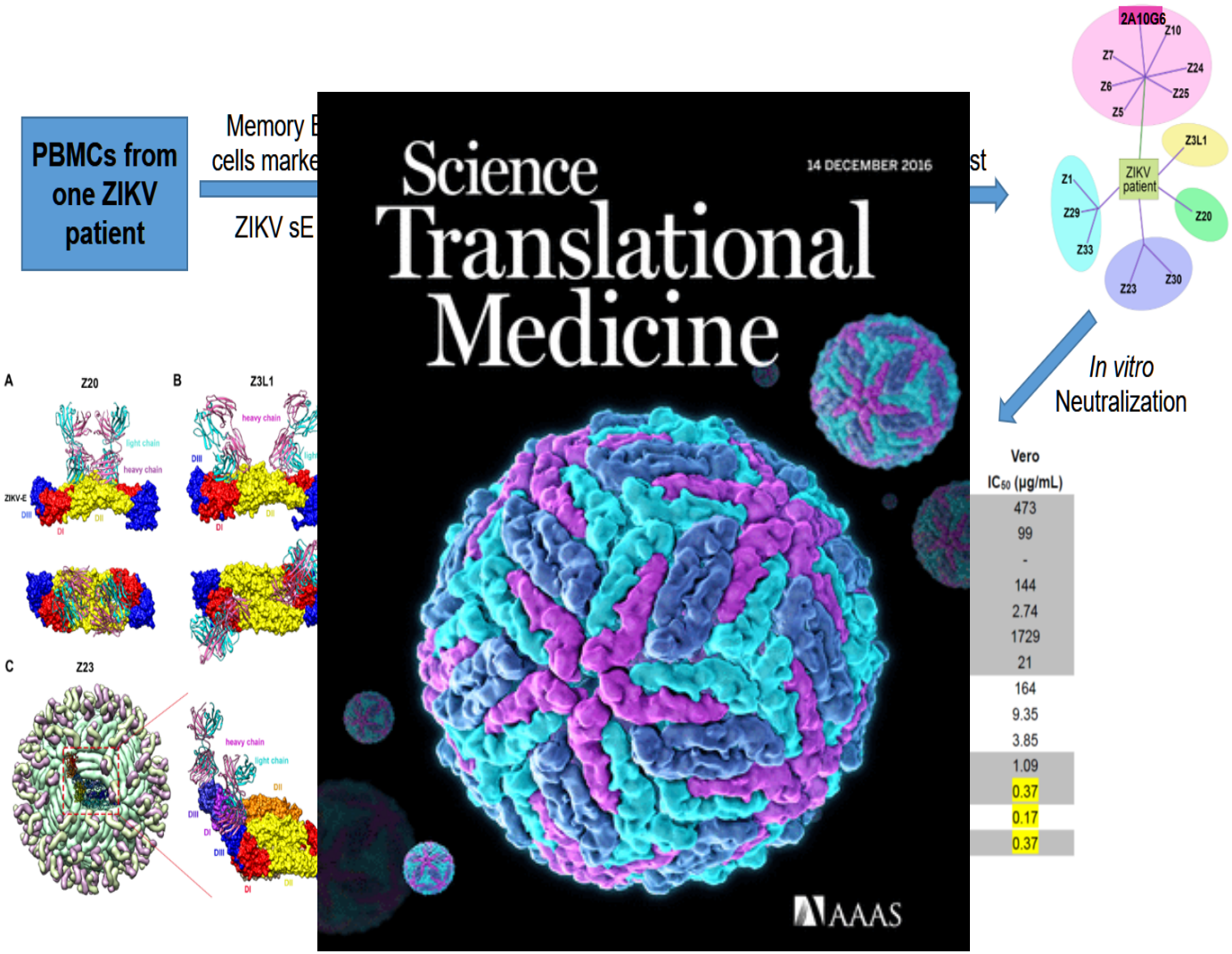


(Cell Host Microbe, 2016)



(EMBO J, 2017)

寨卡患者中分离人源中和抗体



Vero IC_{50} (μg/mL)
473
99
-
144
2.74
1729
21
164
9.35
3.85
1.09
0.37
0.17
0.37

基孔肯雅病毒（Chikungunya virus, CHIKV）

关节炎和水肿

斑丘疹和手掌红斑

面部及外耳红疹

急性期

（70-95%）

毒血症 1-7天

1-21天

高热（90-95%）、多关节痛（> 80%）及全身疼痛、肌痛、发疹等症状（36-64%）

急性后期

（60-80%）

22-90天

晨僵(持续> 30分钟)，软组织水肿、腕管综合征、肌痛、头痛虚弱、睡眠质量变化和神经心理问题

慢性期

（50%→5%）

90天之后

关节症状可持续数年，通常伴有疲劳、头痛或抑郁情绪，严重影响人们的生活质量

(C.M. Okeoma, 2016; Tanabe et al., 2018)

全球病毒组计划

Science

INFECTIOUS DISEASES

The Global Virome Project

Expanded viral discovery can improve mitigation

By **Dennis Carroll, Peter Daszak, Nathan D. Wolfe, George F. Gao, Carlos M. Morel, Subhash Morzaria, Ariel Pablos-Méndez, Oyewale Tomori, Jonna A. K. Mazet**

全球目前共发现**111 个病毒科**

在这111个病毒科中，全球病毒组计划将靶向其中已有感染人报道的**25**个病毒科病毒

在这25个病毒科中，预计有**167万**种未知病毒存在于哺乳动物和鸟类这些宿主占病毒暴发风险的99%

在这167万种病毒中，预计有**63.1万-82.7万**种病毒有可能感染人

中国国家病毒组计划(CNVP)

GVP Global Leads: George F. Gao, Dennis Carroll, Peter Daszak

2016年9月12日，国际病毒组计划联合主席Peter Dazak教授和美国USAID全球健康安全与发展部门主任Dennis Carroll教授到访中国科学院微生物研究所，与国内十几位领域专家进行了深入沟通。希望中国在GVP项目中做出引领，并成为其他国家开展病毒组计划的范本。同时还议定与2017年2月在北京召开“中国国家病毒组计划(CNVP)推进会”，深入研讨中国国家病毒组计划和全球病毒组计划的进展事宜。

GVP旨在通过全球科学家10年的新型合作模式，监测发现地球上绝大多数、对人类具有潜在危害的未知病毒，以实现针对某种可能暴发病毒的提前防控。

CNVP拟开展研究内容：

1）野生动物中病毒本地调查研究

2）重要家畜禽中病毒多样性研究

3）环境中病毒多样性研究

4）动物基因组内逆转录病毒研究

5）未知病毒检测、分离等方法学研究

6）针对未知病毒的测序技术研究

7）病毒组数据分析技术研究

8）数据库与信息平台建设

感染病防控策略总结

- 持续监测
- 主动出击
- 防控关口前移
- 重视基础研究
- 加强应用研究

疾病防控

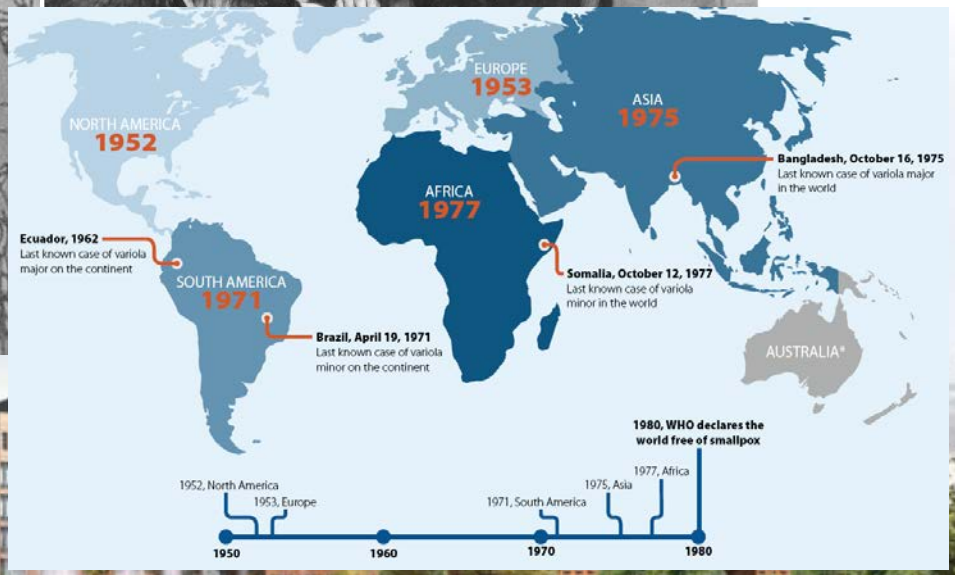
疫苗、免疫学与传染病防控

人类历史第一个疫苗-牛痘疫苗
爱德华-詹纳——免疫学之父

中国古代“人痘”防天花的经验医学

天花

1980年WHO宣布通过疫苗接种人类消灭天花



疾病防控

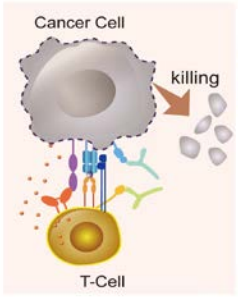
免疫学发展与疾病防治

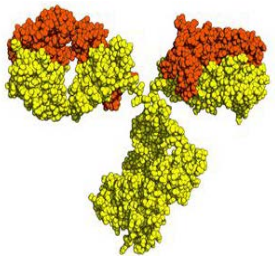
□近30年来现代免疫学理论和技术研究突飞猛进，在传染病疫苗开发、肿瘤治疗等领域不断取得突破。

中国埃博拉疫苗（rAd5-EBOV）

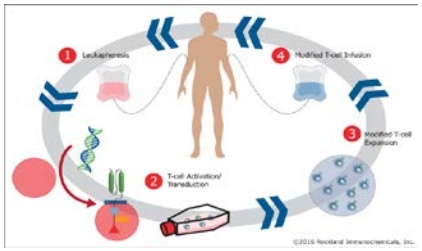
肿瘤免疫治疗

- 免疫检查点抗体治疗





- CAR-T细胞治疗



免疫治疗使肿瘤治愈从“不可能”到“可能”

2012年Emily成为第一个接收CAR-T治疗的ALL患者

2015年Jimmy Carter晚期黑色素瘤因使用PD-1抗体药消失

挑战与机遇

- 多种传染病的流行暴发威胁依然存在；
- 突发事件等重要公共卫生问题时有发生；
- 食品安全、环境污染、营养 - 环境 - 职业相关健康问题日臻突出；
- 慢性非传染性疾病压力不断增加。

挑战

- 国家、社会、民众对疾病预防控制工作要求的提高
- 国家经济发展和投入的增加
- 基础科学研究的进展
- 全国疾控系统的完善和建立

机遇

安全卫生的生活环境是防控传染病的第一道防线

Thank you!