传染病防控生物信息学和数据整合

SIMON RAYNER（徐翊)

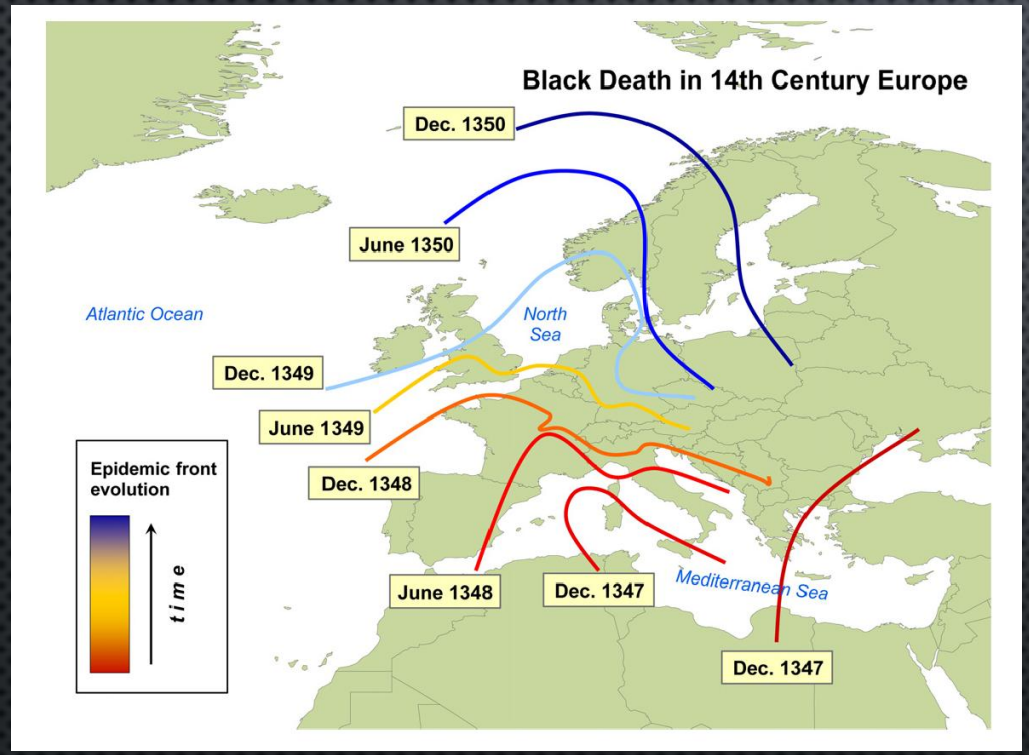
WHAT DO I WANT TO TALK ABOUT TODAY?

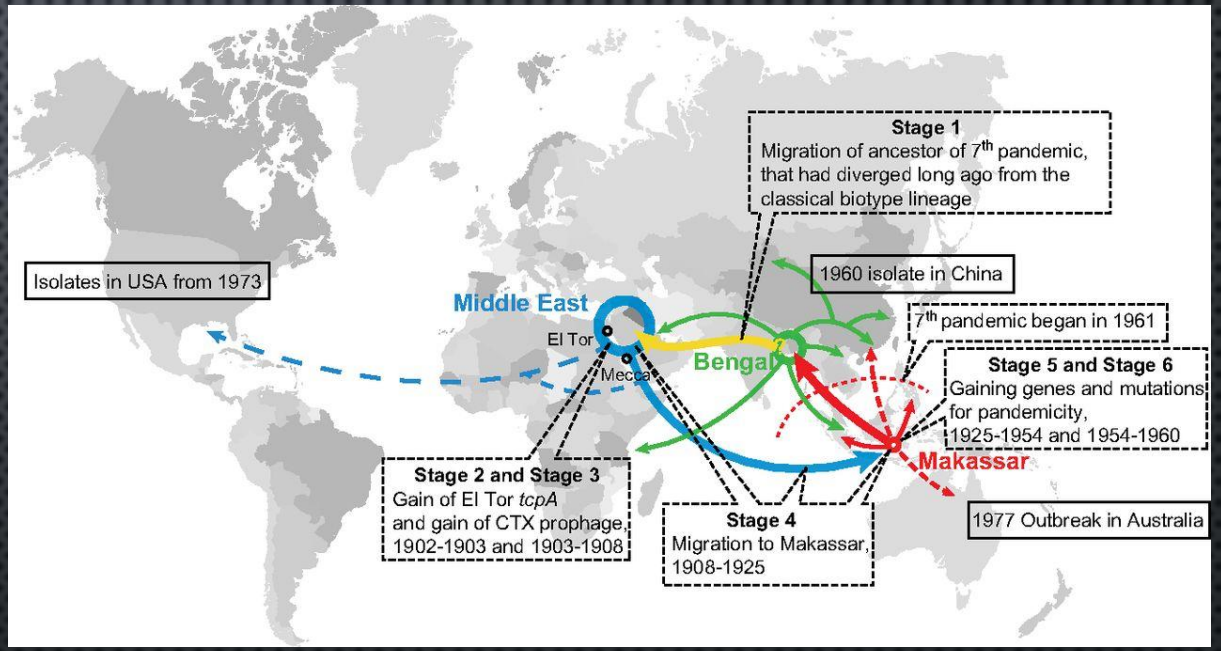
I only have 25 minutes

Provide a general overview of what we can do with computational biology (Not too many details)
(用25分钟给大家简单介绍一下利用计算生物学我们可以做些什么)

DISEASE TRANSMISSION (疾病传播)

The rate of dispersion has been increasing over the centuries (传播速率逐年增长)





1st Plague pandemic 14th century
(14世纪的瘟疫大流行)

Réalité complexe et modèles en épidémiologie
Comptes Rendus Biologies 330, (4) 2007, 364-374
https://doi.org/10.1016/j.crvi.2007.02.014

7th cholera pandemic 20th century
(20世纪的霍乱大流行)

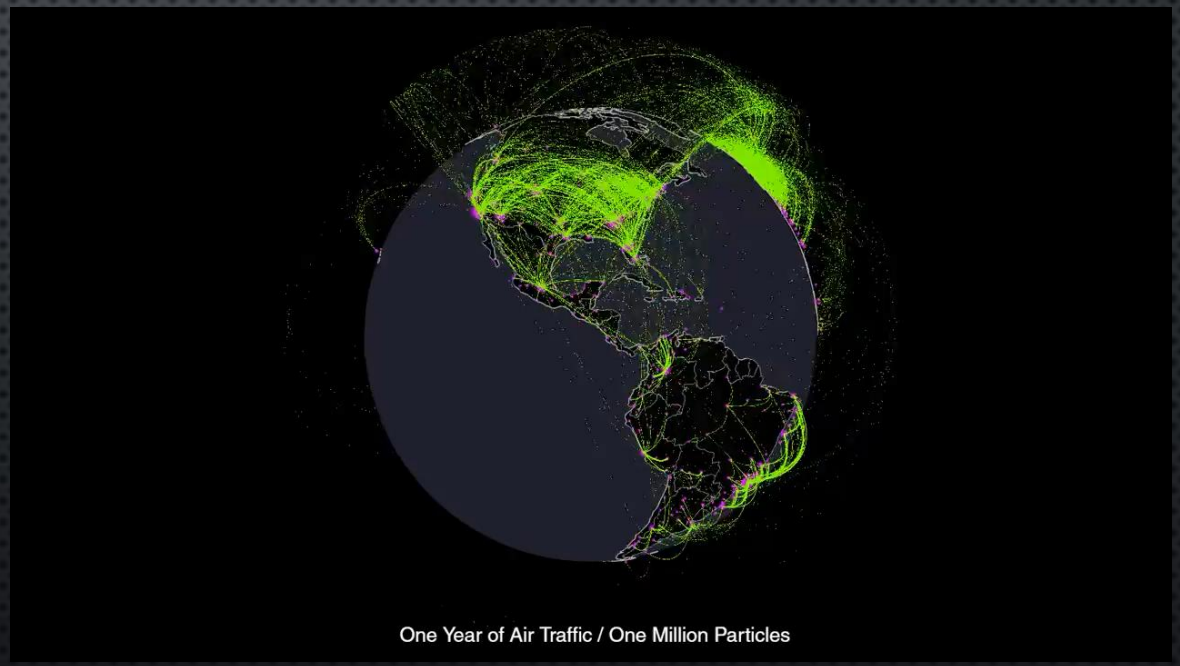
Origins of the current seventh cholera pandemic
PNAS November 29, 2016 113 (48) E7730-E7739
https://doi.org/10.1073/pnas.1608732113

THE NEW WORLD ORDER

We are entering a new phase in infectious disease outbreaks (传染病暴发新纪元)

- World is more highly connected than ever before (全球化进程加速)
- travel / global trade / migration (旅游/国际贸易/移民)

GLOBAL GOODS TRADE



AIR TRAVEL 2010 (ONE POINT = 2000 PASSENGERS

Technological advances have made globalization possible (技术革新推动全球化)

The internet (这不是广告)

- it's much easier to book a trip, (旅游预定一步到位)
- find accommodation, (找房有携程去哪儿途牛帮你)
- buy something in another country (海外购物不是梦)

Smartphones (一部智能手机)

- Don't need to speak the language, (普通话走遍天下)
- don't need maps, (全球地图手中握)

How does globalization impact disease transmission? (全球化如何影响疾病传播?)

- increased frequency and range of travel (旅游频次增长和范围扩大)
- human incursion into new areas (开发新的人类活动区域)
- change in diet (饮食改变)
- social upheaval (社会变动)
- climate change (气候变化)

Consequences

- More pathogen introductions (病原体多元化)
- Emergence of new pathogens (新发传染病)
- Introduction of known pathogens to naïve populations (易感人群受感染)
- Entrenchment of pathogens rather than die out (防御而非消灭)

How can we use computational approaches to investigate infectious disease outbreaks?
如何利用计算和模拟的方法调查传染性疾病的暴发?

What is the timeline of a typical outbreak? (少量病例—较多病例—传染病大暴发)

SMALL NUMBER OF PATIENTS REPORTING GENERAL CLINICAL SYMPTOMS → INCREASING NUMBER OF PATIENTS REPORTING SAME SYMPTOMS → DEVIATION FROM EXPECTING SEASONAL VARIATION OR SEVERITY?

Compare SARS to Ebola

- Ebola, very distinct and serious symptoms (埃博拉病毒感染症状严重)
- SARS, not so obvious (相比较，SARS感染症状不那么明显)

Early stage intervention is important in both cases (早期干预的重要性)

Integrated clinical and computational investigation can provide valuable insight (临床和计算数据的整合具有重要价值)

But how can we combine clinical and computational?

For example:

CLINICAL
Perform tests to detect antigens to a set of common pathogens
(ELISA/PCR)
(临床检测包括ELISA/PCR等)

COMPUTATIONAL
Sequencing of pathogen isolate
Phylogenetic analysis
(计算生物学利用分离株序列进行系统进化分析)

Need to decide what sort of questions we want to ask

- Can we identify the virus? (能否鉴别病毒)
- Where did the outbreak originate? (病毒溯源)
- When did the outbreak originate? (暴发的时间)
- How is the virus transmitting? (传播方式)
- single or multiple introduction(s)? (单个或多个起源)

RNA VIRUSES

Most of the important outbreaks are from RNA viruses

In general (but not always)

RNA viruses cause acute infections, DNA viruses tend to establish persistent viruses (RNA病毒引起急性感染，DNA病毒建立慢性感染)

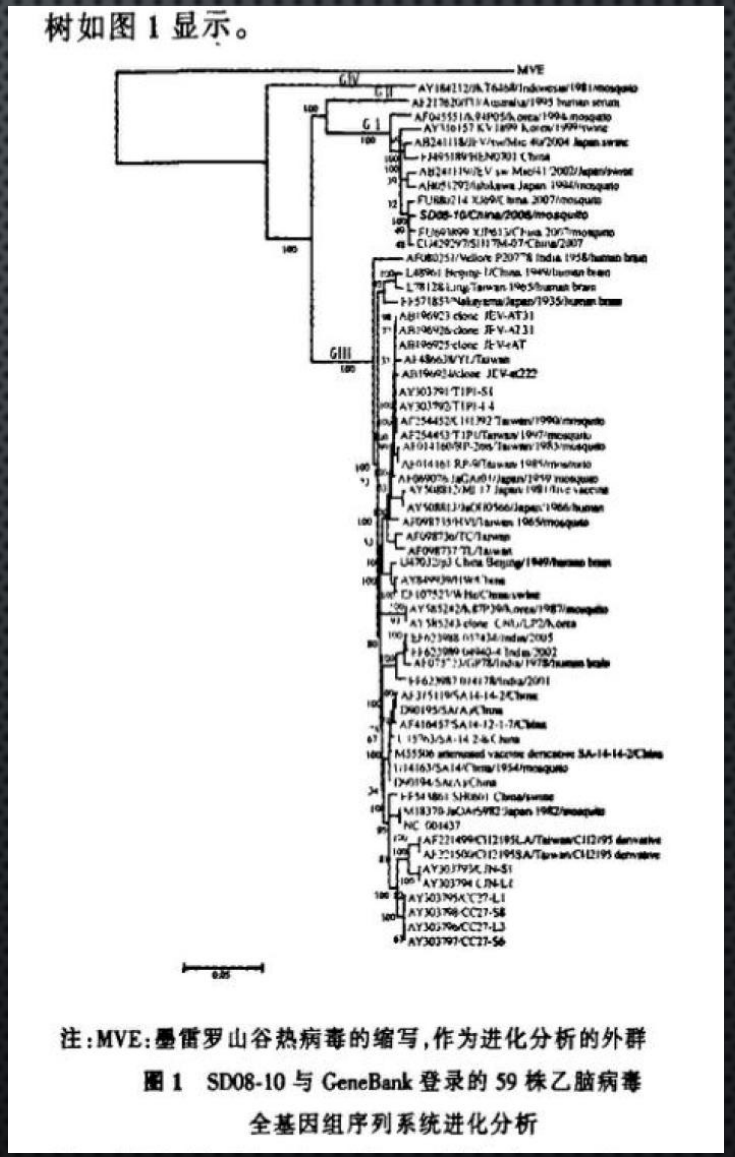
ZIKA INFLUENZA HEPATITIS C

HIV DENGUE EBOLA

RABIES SARS EV71 JEV

PHYLOGENETICS

A typical way of analyzing the sequence from an isolate
(构建系统进化树——分离株序列的常规分析方法)



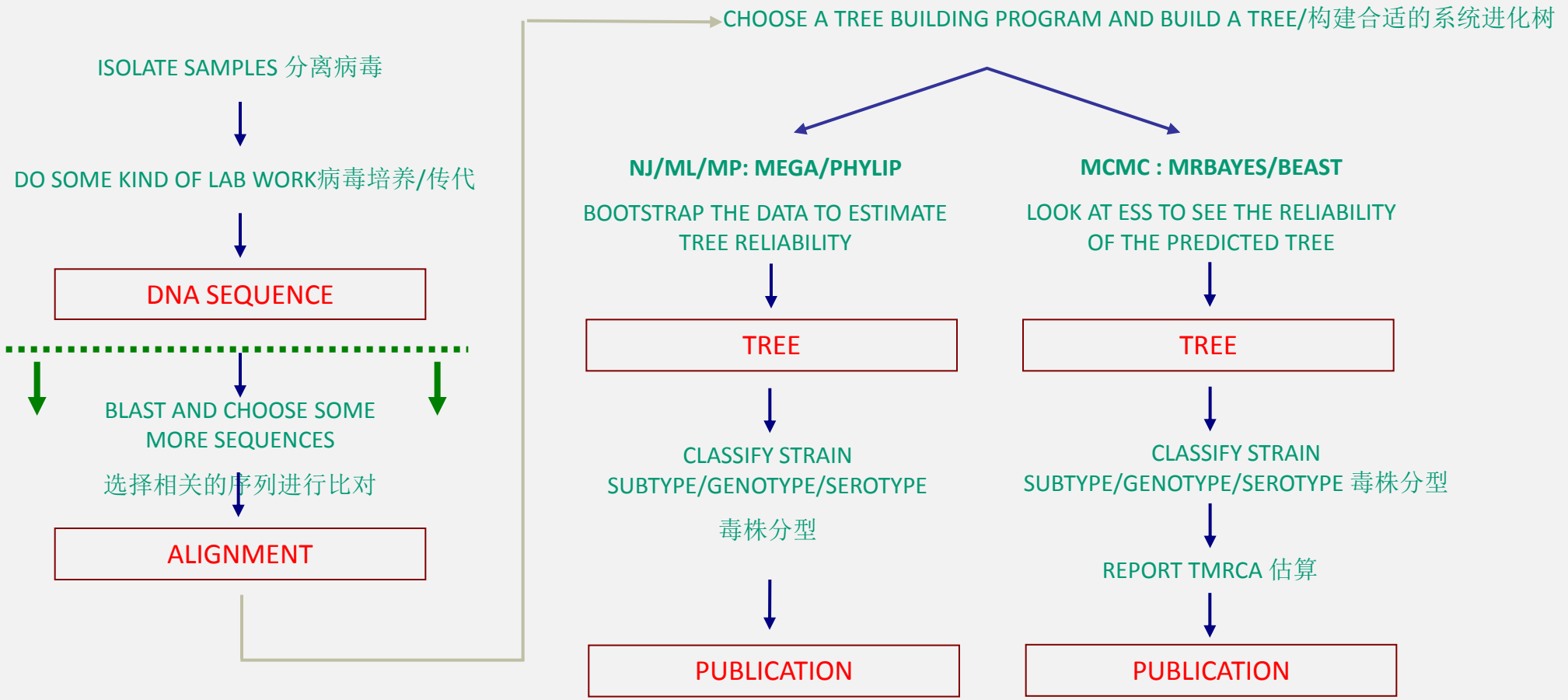
注:MVE:墨留罗山谷热病毒的缩写,作为进化分析的外群

图 1　SD08-10 与 GeneBank 登录的 59 株乙脑病毒全基因组序列系统进化分析

SEQUENCE → ALIGNMENT → TREE

A TYPICAL WAY OF ANALYZING A VIRUS ISOLATE USING BIOINFORMATICS

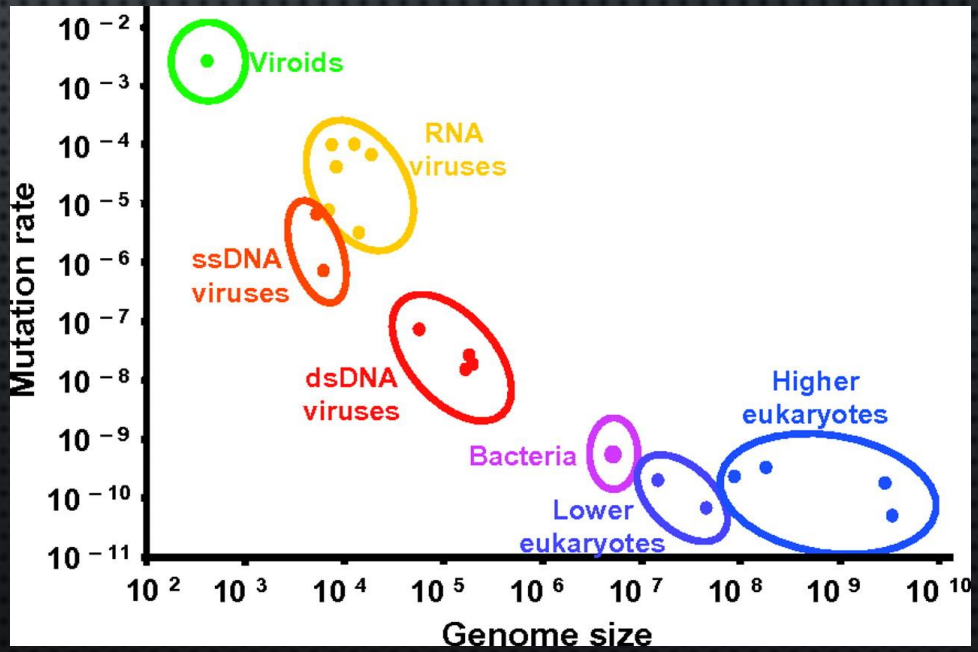
SELECT SURFACE PROTEINS AS THESE ARE UNDER "CONSTANT" EVOLUTIONARY PRESSURE FROM HOST IMMUNE SYSTEM(选择表面结构蛋白进行序列分析)
ALWAYS SEEK THE LONGEST POSSIBLE GENE SEQUENCES (更长的序列，更丰富的进化信息)



Simplistic, but it can reveal valuable insight into transmission processes (建树为病原的传播过程提供有价值的信息)

RNA viruses have high mutation and replication rates and can accumulate genetic variation on the same scale as virus transmission
(RNA病毒的高突变率使病毒基因组随传播过程积累更多的遗传变异)

Can investigate epidemiological dynamics and emergence over a short time scale
(可在较短的时间尺度上研究流行病的发生和发展).



Integrating the data can tell us a lot more. examples (数据整合能挖掘更多信息)

One good thing is that the technology that helped achieve globalization is also helping us investigate its impact

(促进全球化的同时亦推动全球化影响相关的研究)

improved computing power, new algorithms (e.g. TMRCA phylogeography), better experimental technology (e.g. NGS)

(提高计算能力，优化算法模型，运用高通量技术).

We also have the ability to collect other related data, such as environment, demographics (收集环境和人口学数据)

The Most Recent Common Ancestor (TMRCA) (最近共同祖先).

If we have sample isolates of known date, and sampling across a long enough time period, we can estimate the date of the most recent individua from which the samples originate (在较广的时间范围内采集已知年代的病原样本，我们可以利用这些样本的基因序列估算它们的最近共同祖先的起源时间)

Estimating the TMRCA for swine H1N1 outbreak for each segment helped to predict the order of re-assortment events that produced the highly infectious strain that lead to the epidemic (通过估算H1N1每个基因片段的TMRCA来推测高致病性流感病毒的重配顺序和流行暴发过程)

nature Vol 459|25 June 2009|doi:10.1038/nature08182

LETTERS

Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic

Gavin J. D. Smith[1], Dhanasekaran Vijaykrishna[1], Justin Bahl[1], Samantha J. Lycett[2], Michael Worobey[3], Oliver G. Pybus[4], Siu Kit Ma[1], Chung Lam Cheung[1], Jayna Raghwani[2], Samir Bhatt[4], J. S. Malik Peiris[1], Yi Guan[1] & Andrew Rambaut[2]

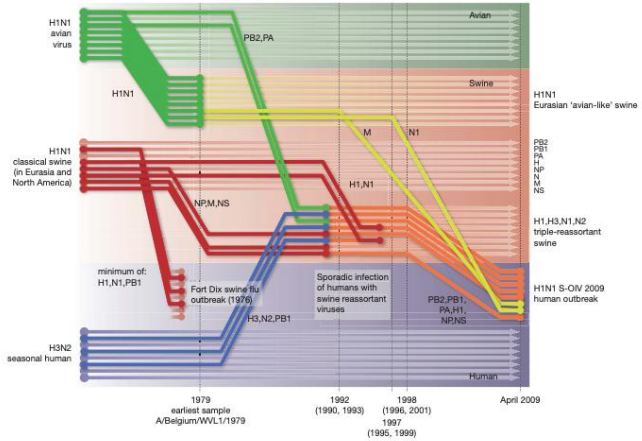


Figure 1 | Reconstruction of the sequence of reassortment events leading up to the emergence of S-OIV. Shaded boxes represent host species; avian (green), swine (red) and human (grey). Coloured lines represent interspecies-transmission pathways of influenza genes. The eight genomic segments are represented as parallel lines in descending order of size. Dates marked with dashed vertical lines on 'elbows' indicate the mean time of divergence of the S-OIV genes from corresponding virus lineages. Reassortment events not involved with the emergence of human disease are omitted. Fort Dix refers to the last major outbreak of S-OIV in humans. The first triple-reassortant swine viruses were detected in 1998, but to improve clarity the origin of this lineage is placed earlier.

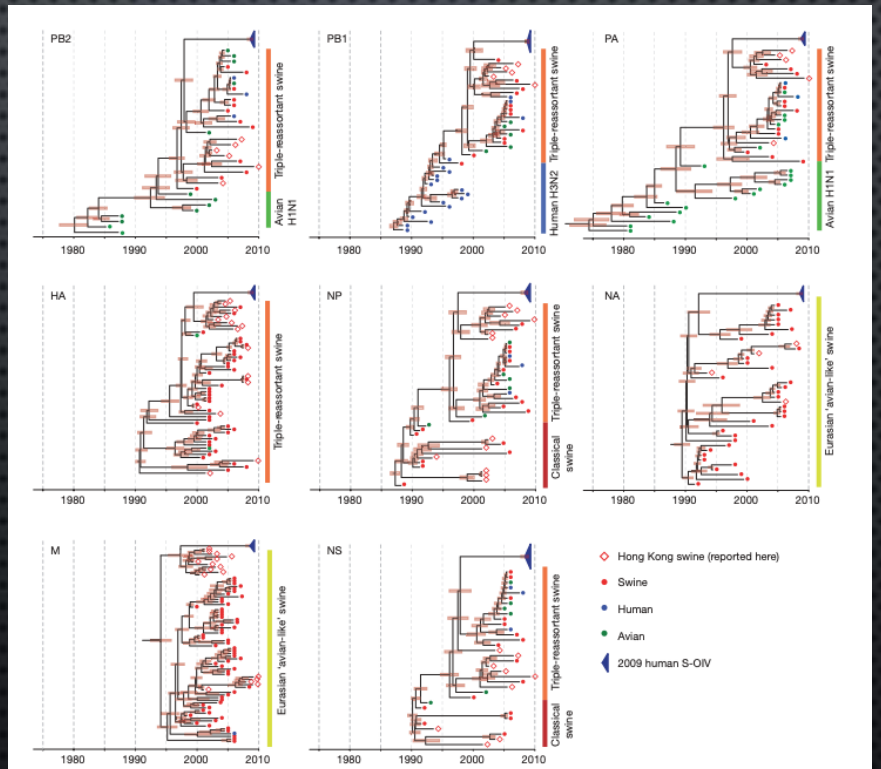
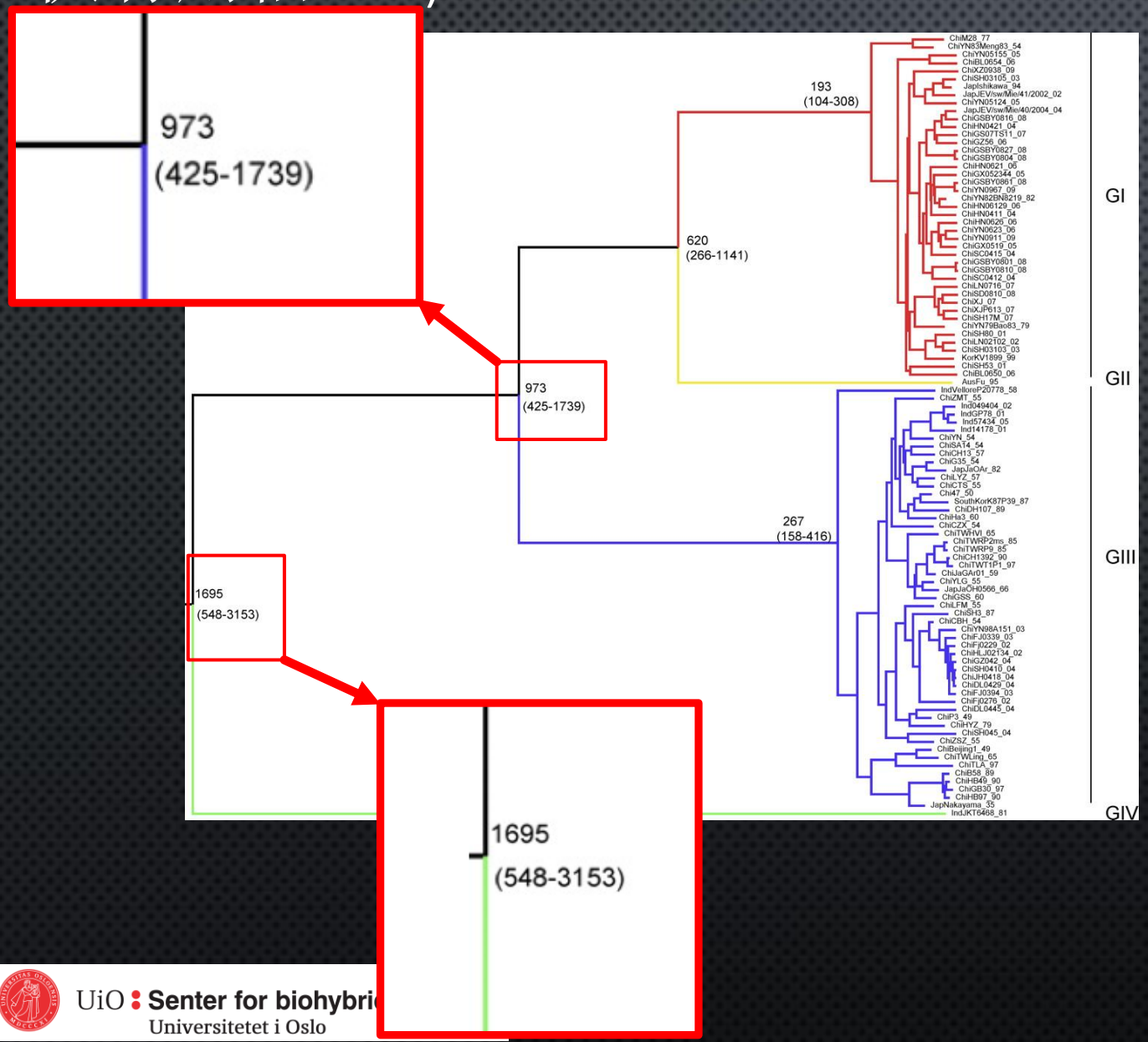


Figure 2 | Genetic relationships and timing of S-OIV for each genomic segment. Symbols represent sampled viruses on a timescale of when they were sampled and coloured by host species (pigs, red; humans, blue; birds, green). Internal nodes are reconstructed common ancestors with 95% credible intervals on their date given by the red bars. The S-OIV outbreak strains are represented by a blue triangle, with the apex representing the common ancestor of these.

In March and early April 2009, a new swine-origin influenza A (H1N1) virus (S-OIV) emerged in Mexico and the United States[1]. During the first few weeks of surveillance, the virus spread worldwide to 30 countries (as of May 11) by human-to-human transmission, causing the World Health Organization to raise its pandemic alert to level 5 of 6. This virus has the potential to develop into the first influenza pandemic of the twenty-first century. Here we use evolutionary analysis to estimate the time-scale of the origins and the early development of the S-OIV epidemic. We show that it was derived from several viruses circulating in swine, and that the initial transmission to humans occurred several months before recognition of the outbreak. A phylogenetic estimate of the gaps in genetic surveillance indicates a long period of unsampled ancestry before the S-OIV outbreak, suggesting that the reassortment of swine lineages may have occurred years before emergence in humans, and that the multiple genetic ancestry of S-OIV is not indicative of an artificial origin. Furthermore, the unsampled history of the epidemic means that the nature and location of the genetically closest swine viruses reveal little about the immediate origin of the epidemic, despite the fact that we included a panel of closely related and previously unpublished swine influenza isolates. Our results highlight the need for systematic surveillance of influenza in swine, and provide evidence that the mixing of new genetic elements in swine can result in the emergence of viruses with pandemic potential in humans[2].

What about an example where TMRCA isn't so helpful? (TMRCA无法提供有用信息?)



JOURNAL OF VIROLOGY, Oct. 2011, p. 9847–9853 Vol. 85, No. 1
0022-538X/11/$12.00 doi:10.1128/JVI.00825-11

Emergence of Genotype I of Japanese Encephalitis Virus as the Dominant Genotype in Asia▽

Xiao-Ling Pan,[1]† Hong Liu,[1]† Huan-Yu Wang,[1] Shi-Hong Fu,[1] Hai-Zhou Liu,[2] Hai-Lin Zhang,[3] Ming-Hua Li,[1] Xiao-Yan Gao,[1] Jing-Lin Wang,[1] Xiao-Hong Sun,[1] Xin-Jun Lu,[1] You-Gang Zhai,[1] Wei-Shan Meng,[1] Ying He,[1] Huan-Qin Wang,[1] Na Han,[2] Bo Wei,[2] Yong-Gan Wu,[2] Yun Feng,[3] Du-Juan Yang,[3] Li-Hua Wang,[1] Qin Tang,[1] Guoliang Xia,[1] Ichiro Kurane,[4] Simon Rayner,[2]* and Guo-Dong Liang[1]*

1. The date range of isolated samples is negligible compared to the estimated TMRCA (采集样品的时间范围太小)
2. The TMRCA doesn't tell us anything useful anyway (TMRCA的置信区间太大无法提供有用信息)

Xiao-Ling Pan et al. J. Virol. 2011; doi:10.1128/JVI.00825-11

OPEN ACCESS Freely available online PLoS PATHOGENS

Phylodynamics and Human-Mediated Dispersal of a Zoonotic Virus

Chiraz Talbi[1], Philippe Lemey[2], Marc A. Suchard[3], Elbia Abdelatif[4], Mehdi Elharrak[5], Nourlil Jalal[6], Abdellah Faouzi[6], Juan E. Echevarría[7], Sonia Vazquez Morón[7], Andrew Rambaut[8,9], Nicholas Campiz[10], Andrew J. Tatem[10,11], Edward C. Holmes[9,12], Hervé Bourhy[1]*

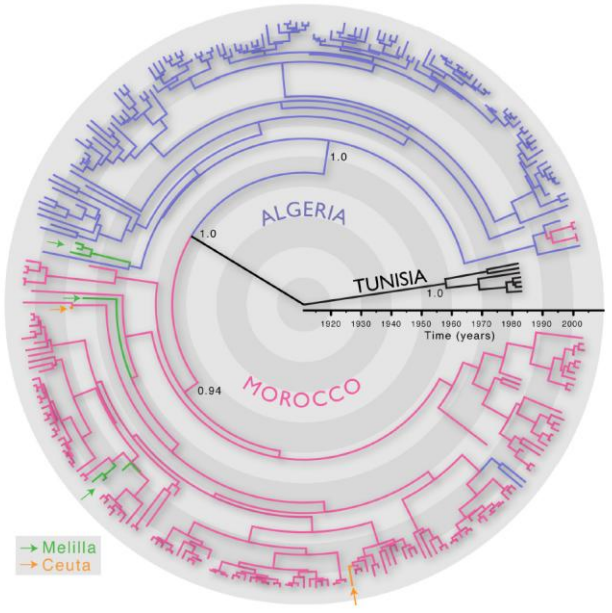


Figure 1. MCC tree of 287 sequences of the Africa 1 clade, estimated from the N, P and G-L genes and intergenic regions of dog RABV, and showing the spatial structure of the viral lineages. Branches are colored according to the locations of viral sampling. Branch lengths are estimated in time units (years) as indicated by the time bar. Posterior clade probability values (>0.9) are shown for key nodes. Although Melilla and Ceuta are considered Spanish locations they are in fact Moroccan enclaves. As such they do not represent virus dispersal across the strait of Gibraltar.
doi:10.1371/journal.ppat.1001166.g001

Use phylogenetics and spatial modelling to understand how rabies is spreading in North Africa (通过系统发育学和空间模型研究狂犬病毒在北非的传播)

- Roads are important (公路的重要性)
- Administrative borders restrict spread (行政边界限制传播)

Advanced model (先进的模型)

Not really new findings (并非新的发现)

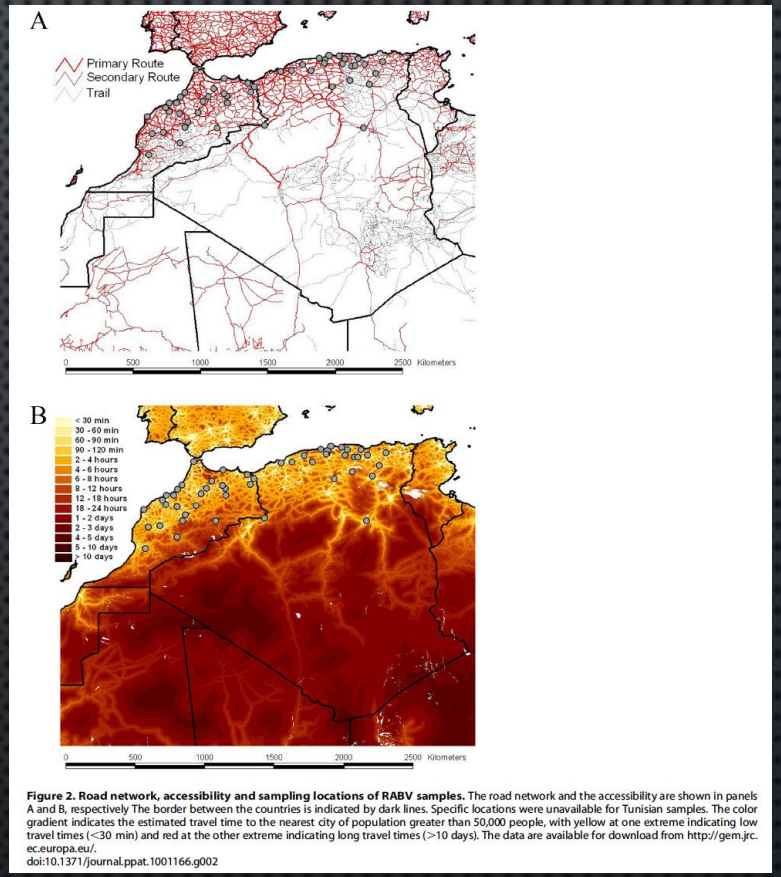


Figure 2. Road network, accessibility and sampling locations of RABV samples. The road network and the accessibility are shown in panels A and B, respectively The border between the countries is indicated by dark lines. Specific locations were unavailable for Tunisian samples. The color gradient indicates the estimated travel time to the nearest city of population greater than 50,000 people, with yellow at one extreme indicating low travel times (<30 min) and red at the other extreme indicating long travel times (>10 days). The data are available for download from http://gem.jrc.ec.europa.eu/.
doi:10.1371/journal.ppat.1001166.g002

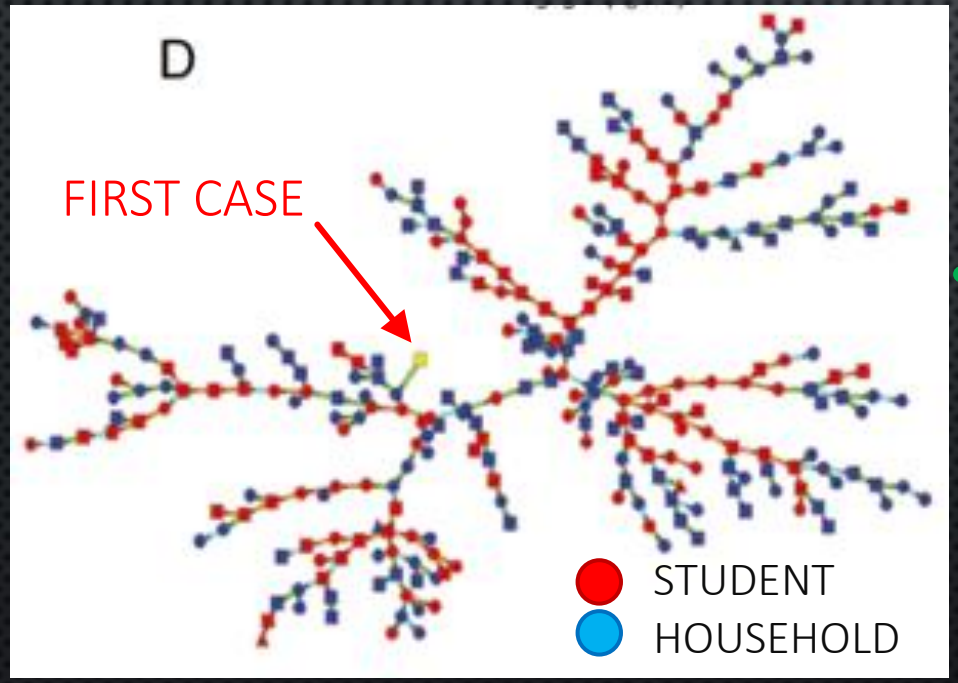
PNAS

Role of social networks in shaping disease transmission during a community outbreak of 2009 H1N1 pandemic influenza

Simon Cauchemez[a,1], Achuyt Bhattarai[b], Tiffany L. Marchbanks[c], Ryan P. Fagan[b], Stephen Ostroff[c], Neil M. Ferguson[a], David Swerdlow[b], and the Pennsylvania H1N1 working group[b,c,2]

[a]Medical Research Council Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, School of Public Health, Imperial College London, London W2 1PG, United Kingdom; [b]Centers for Disease Control and Prevention, Atlanta, GA 30333; and [c]Pennsylvania Department of Health, Harrisburg, PA 17120-0701

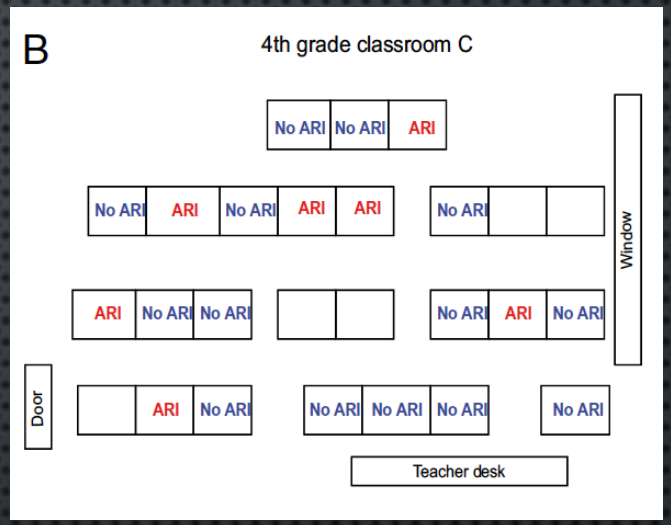
RECONSTRUCTED TRANSMISSION TREE (重建传播树)



STUDENTS SPREAD INFECTION AMONGST THEMSELVES

INFECTION DIES OUT AT HOME (学生之间传播，但家庭是传播的终点)

INFECTION DOESN'T SPREAD BY SEATING LOCATION (传播与学生座位分布无关)



IT SPREADS AMONG FRIENDS (在亲密的同学之间传播)

INTEGRATING DATA TYPES TELLS US MORE ABOUT INFECTION PATHS (不同类型数据的整合揭露更全面的传播过程)

PNAS February 15, 2011 108 (7) 2825–2830
www.pnas.org/cgi/doi/10.1073/pnas.1008895108

Integrated data sources are more useful
(不同来源数据的有效整合非常有意义)

However, there is one problem….

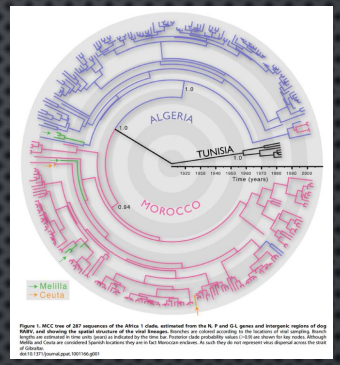
OPEN ACCESS Freely available online

PLoS PATHOGENS

Phylodynamics and Human-Mediated Dispersal of a Zoonotic Virus

Chiraz Talbi[1], Philippe Lemey[2], Marc A. Suchard[3], Elbia Abdelatif[4], Mehdi Elharrak[5], Nourlil Jalal[6], Abdellah Faouzi[6], Juan E. Echevarría[7], Sonia Vazquez Morón[7], Andrew Rambaut[8,9], Nicholas Campiz[10], Andrew J. Tatem[10,11], Edward C. Holmes[9,12], Hervé Bourhy[1]*

1 Institut Pasteur, Unit Lyssavirus Dynamics and Host Adaptation, Paris, France,
2 Rega Institute,Katholieke Universiteit Leuven, Leuven, Belgium,
3 Departments of Biomathematics and Human Genetics, David Geffen School of Medicine, UCLA, Los Angeles, California, USA Department of Biostatistics, UCLA, Los Angeles, California, USA,
4 Institut Pasteur d'Algerie, Laboratoire de la Rage, Recherche et Diagnostic, Alger, Algerie,
5 Biopharma Laboratoire, Rabbat, Maroc,
6 Institut Pasteur du Maroc, Laboratoire de Virologie Me´dicale, Casablanca, Maroc,
7 Instituto de Salud Carlos III, Servicio de Microbiologı´a Diagno´ stica, Madrid, Spain,
8 Institute of Evolutionary Biology, University of Edinburgh, Ashworth Laboratories, Edinburgh, United Kingdom,
9 Fogarty International Center, National Institutes of Health, Bethesda, Maryland, United States of America,
10 Department of Geography, University of Florida, Gainesville, Florida, United States of America,
11 Emerging Pathogens Institute, University of Florida, Gainesville, Florida, United States of America,
12 Center for Infectious Disease Dynamics, Department of Biology, The Pennsylvania State University, Pennsylvania, USA



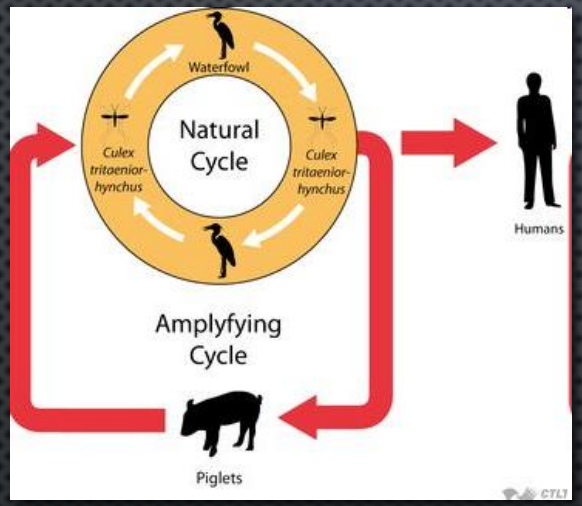
13 DIFFERENT GROUPS

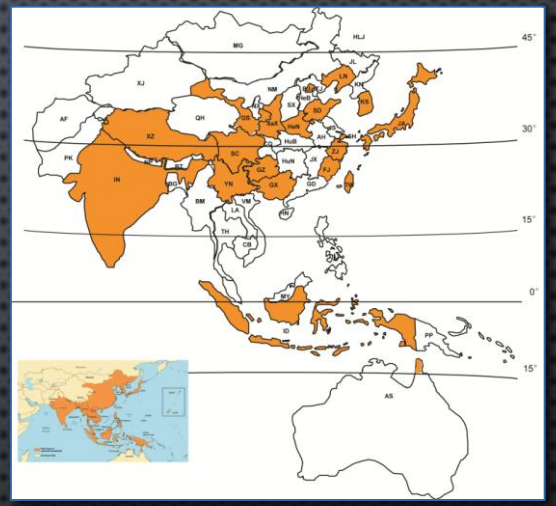
This analysis was not a trivial task, it required many different types of expertise (问题在于这样规模的调查研究涉及很多不同类型的学科交叉)

How can we use these approaches in everyday work? (在我们日常的工作中可行性如何?)

JAPANESE ENCEPHALITIS VIRUS
(乙型脑炎病毒)

JAPANESE ENCEPHALITIS VIRUS - BACKGROUND





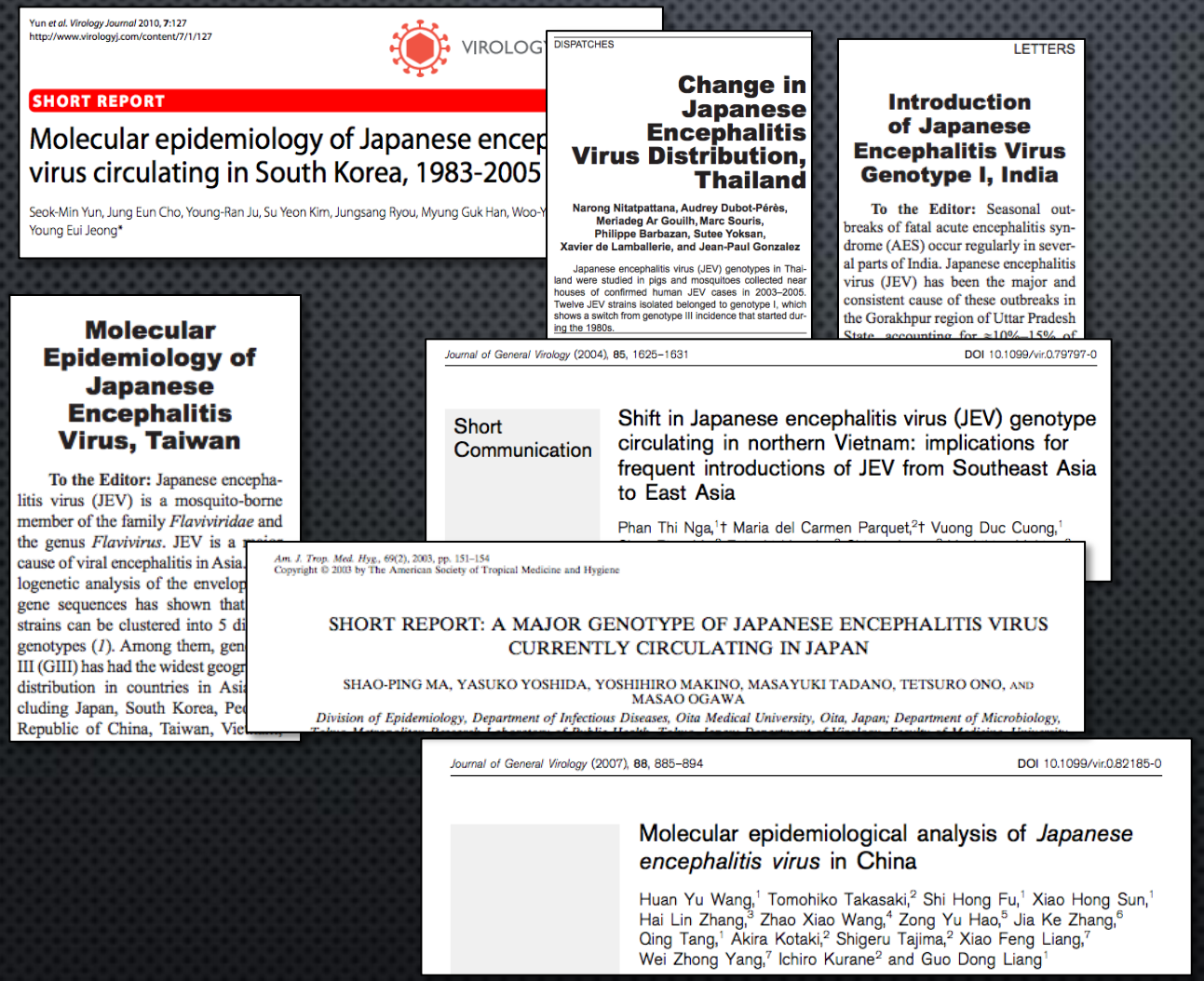
mosquito-borne zoonotic pathogen (蚊虫传播的动物传染病病毒)

major cause of viral encephalitis: 35,000–175,000 infections/10,000–15,000 deaths annually.

50% of survivors suffer from lingering neurological effects (最主要的病毒性脑炎病毒: 50%的存活者有神经系统方面的后遗症)

phylogenetic studies based on the envelope protein indicate there are five genotypes (基于E蛋白序列的系统发育分析显示JEV有5个基因型)

REGIONAL SITUATION FOR JEV



Yun et al. Virology Journal 2010, 7:127
http://www.virologyj.com/content/7/1/127

SHORT REPORT

Molecular epidemiology of Japanese encep
virus circulating in South Korea, 1983-2005

Seok-Min Yun, Jung Eun Cho, Young-Ran Ju, Su Yeon Kim, Jungsang Ryou, Myung Guk Han, Woo-Y
Young Eui Jeong*

DISPATCHES

Change in Japanese Encephalitis Virus Distribution, Thailand

Narong Nitatpattana, Audrey Dubot-Pérès, Meriadeg Ar Gouilh, Marc Souris, Philippe Barbazan, Sutee Yoksan, Xavier de Lamballerie, and Jean-Paul Gonzalez

Japanese encephalitis virus (JEV) genotypes in Thailand were studied in pigs and mosquitoes collected near houses of confirmed human JEV cases in 2003–2005. Twelve JEV strains isolated belonged to genotype I, which shows a switch from genotype III incidence that started during the 1980s.

LETTERS

Introduction of Japanese Encephalitis Virus Genotype I, India

To the Editor: Seasonal outbreaks of fatal acute encephalitis syndrome (AES) occur regularly in several parts of India. Japanese encephalitis virus (JEV) has been the major and consistent cause of these outbreaks in the Gorakhpur region of Uttar Pradesh

Molecular Epidemiology of Japanese Encephalitis Virus, Taiwan

To the Editor: Japanese encephalitis virus (JEV) is a mosquito-borne member of the family *Flaviviridae* and the genus *Flavivirus*. JEV is a
cause of viral encephalitis in Asia.
logenetic analysis of the envelop
gene sequences has shown that
strains can be clustered into 5 di
genotypes (*1*). Among them, gen
III (GIII) has had the widest geogr
distribution in countries in Asi
cluding Japan, South Korea, Pe
Republic of China, Taiwan, Vie

Journal of General Virology (2004), 85, 1625–1631 DOI 10.1099/vir.0.79797-0

Short Communication

Shift in Japanese encephalitis virus (JEV) genotype circulating in northern Vietnam: implications for frequent introductions of JEV from Southeast Asia to East Asia

Phan Thi Nga,[1]† Maria del Carmen Parquet,[2]† Vuong Duc Cuong,[1]

Am. J. Trop. Med. Hyg., 69(2), 2003, pp. 151–154
Copyright © 2003 by The American Society of Tropical Medicine and Hygiene

SHORT REPORT: A MAJOR GENOTYPE OF JAPANESE ENCEPHALITIS VIRUS CURRENTLY CIRCULATING IN JAPAN

SHAO-PING MA, YASUKO YOSHIDA, YOSHIHIRO MAKINO, MASAYUKI TADANO, TETSURO ONO, AND MASAO OGAWA

Division of Epidemiology, Department of Infectious Diseases, Oita Medical University, Oita, Japan; Department of Microbiology,

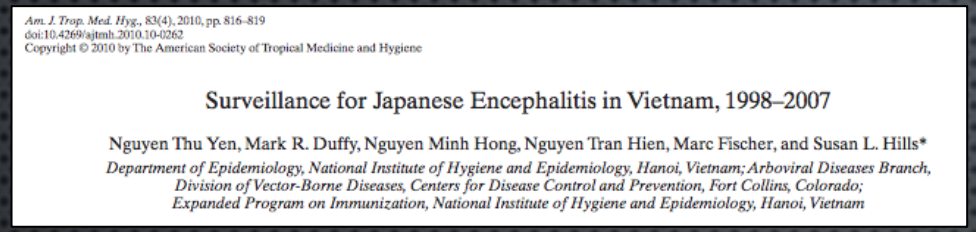
Journal of General Virology (2007), 88, 885–894 DOI 10.1099/vir.0.82185-0

Molecular epidemiological analysis of *Japanese encephalitis virus* in China

Huan Yu Wang,[1] Tomohiko Takasaki,[2] Shi Hong Fu,[1] Xiao Hong Sun,[1] Hai Lin Zhang,[3] Zhao Xiao Wang,[4] Zong Yu Hao,[5] Jia Ke Zhang,[6] Qing Tang,[1] Akira Kotaki,[2] Shigeru Tajima,[2] Xiao Feng Liang,[7] Wei Zhong Yang,[7] Ichiro Kurane[2] and Guo Dong Liang[1]

Many reports on JEV in different countries (许多不同的国家和地区报道了JEV的感染情况)

UNTIL THE EARLY 1990s G-III WAS DOMINANT → G-I BEGAN TO EMERGE (以90年代为分界点，由GIII占主导变为GI占主导)



Am. J. Trop. Med. Hyg., 83(4), 2010, pp. 816–819
doi:10.4269/ajtmh.2010.10-0262

Surveillance for Japanese Encephalitis in Vietnam, 1998–2007

Nguyen Thu Yen, Mark R. Duffy, Nguyen Minh Hong, Nguyen Tran Hien, Marc Fischer, and Susan L. Hills*

Department of Epidemiology, National Institute of Hygiene and Epidemiology, Hanoi, Vietnam; Arboviral Diseases Branch, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado; Expanded Program on Immunization, National Institute of Hygiene and Epidemiology, Hanoi, Vietnam

DISPATCHES

Change in Japanese Encephalitis Virus Distribution, Thailand

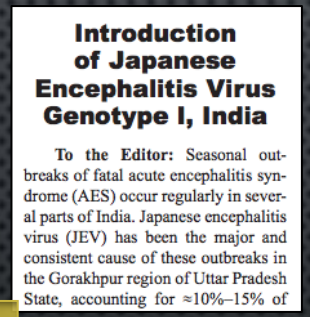
Narong Nitatpattana, Audrey Dubot-Pérès, Meriadeg Ar Gouilh, Marc Souris, Philippe Barbazan, Sutee Yoksan, Xavier de Lamballerie, and Jean-Paul Gonzalez

Japanese encephalitis virus (JEV) genotypes in Thailand were studied in pigs and mosquitoes collected near houses of confirmed human JEV cases in 2003–2005. Twelve JEV strains isolated belonged to genotype I, which shows a switch from genotype III incidence that started during the 1980s.

Japanese Encephalitis Virus Genotype Replacement, Taiwan, 2009–2010

Yi-Ying Chen,[1] Yi-Chin Fan,[1] Wu-Chun Tu,[1] Rey-Yi Chang, Chen-Chang Shih, In-Houng Lu, Maw-Shien Chien, Wei-Cheng Lee, Ter-Hsin Chen, Gwong-Jen Chang, and Shyan-Song Chiou

Genotype I of Japanese encephalitis virus first appeared in Taiwan in 2008. Phylogenetic analysis of 37 viruses from pig farms in 2009–2010 classified these viruses into 2 unique subclusters of genotype I viruses and suggested multiple introductions and swift replacement of genotype III by genotype I virus in Taiwan.



Introduction of Japanese Encephalitis Virus Genotype I, India

To the Editor: Seasonal outbreaks of fatal acute encephalitis syndrome (AES) occur regularly in several parts of India. Japanese encephalitis virus (JEV) has been the major and consistent cause of these outbreaks in the Gorakhpur region of Uttar Pradesh State, accounting for ≈10%–15% of

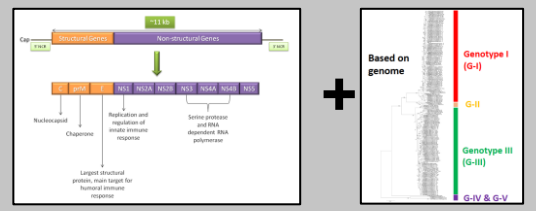
- Japan before 1991 GIII, after 1995 GI
- Korea after 1993 GI
- Thailand after 2000 GI
- Viet Nam after 2001 GI
- India before 2008 GIII dominant,
  after 2009 GIII & GI co-circulation
- China 2001 ~ 2005(71%) GIII &GI co-circulation

These reports are a local level
Can we learn more from learning more by investigating the data as a whole? (如何将所有的JEV本地感染报道整合起来分析该病毒全球的流行情况?)

These reports inform us on the local (national) scale, but tell us nothing about what is driving this displacement (不同国家和地区的JEV流行情况无法解答主导基因型为何会改变这一问题)

COLLECTIVELY THE JEV SEQUENCE DATA IS EXPANSIVE

SO, WHAT HAPPENS IF WE PUT EVERYTHING TOGETHER?
(把所有数据整合起来会得到什么结果?)



GET ALL JEV SAMPLES FROM GENBANK REGARDLESS OF GENOMIC REGION AND CLASSIFY BY GENOTYPE

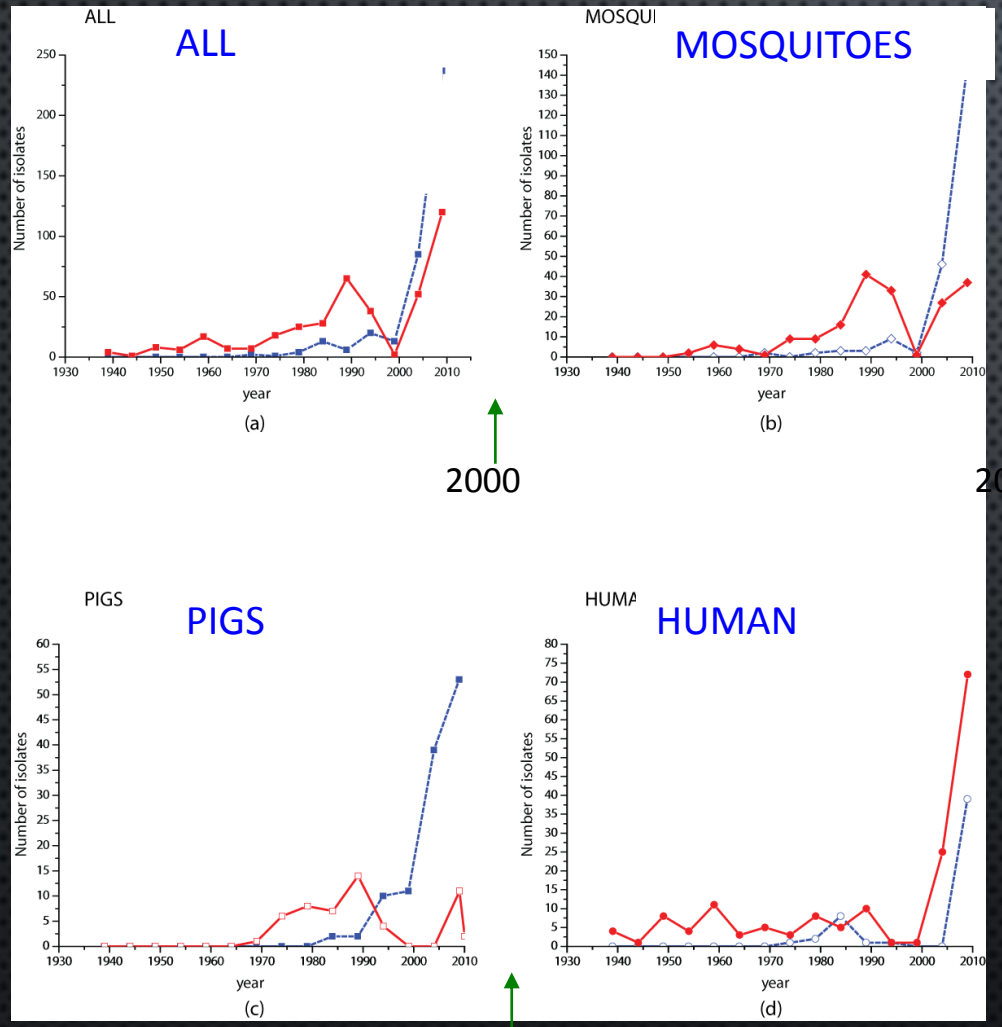
~900 ISOLATES

Host	Genotype GIII	Genotype GI
Mosquito	197	278
pig	54	120
Human	175	54
Horse	4	1
Bat	6	0
midge	2	1
bird	1	0
total	439	454

STRANGE!
(值得思考!)

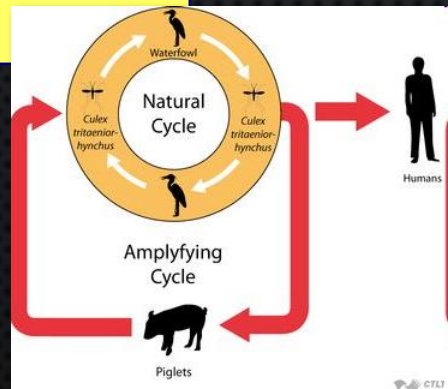
INVESTIGATE DISTRIBUTION BY HOST, DATE AND LOCATION. (按宿主，采样时间和地点分别调查JEV的分布情况)

HOST CASES HAVE DIFFERENT PROFILES



THE CHANGE IN THE RATIO OF GI:GIII ISOLATES FROM PIG AND MOSQUITO IS CONSISTENT WITH THE GRADUAL EMERGENCE OF G-I (猪和蚊子体内GIII到GI主导地位的变化与整体变化一致)

HOWEVER,
THE MAJORITY OF HUMAN ISOLATES ARE STILL G-III (然而人类群体中JEV依然是GIII占主导)



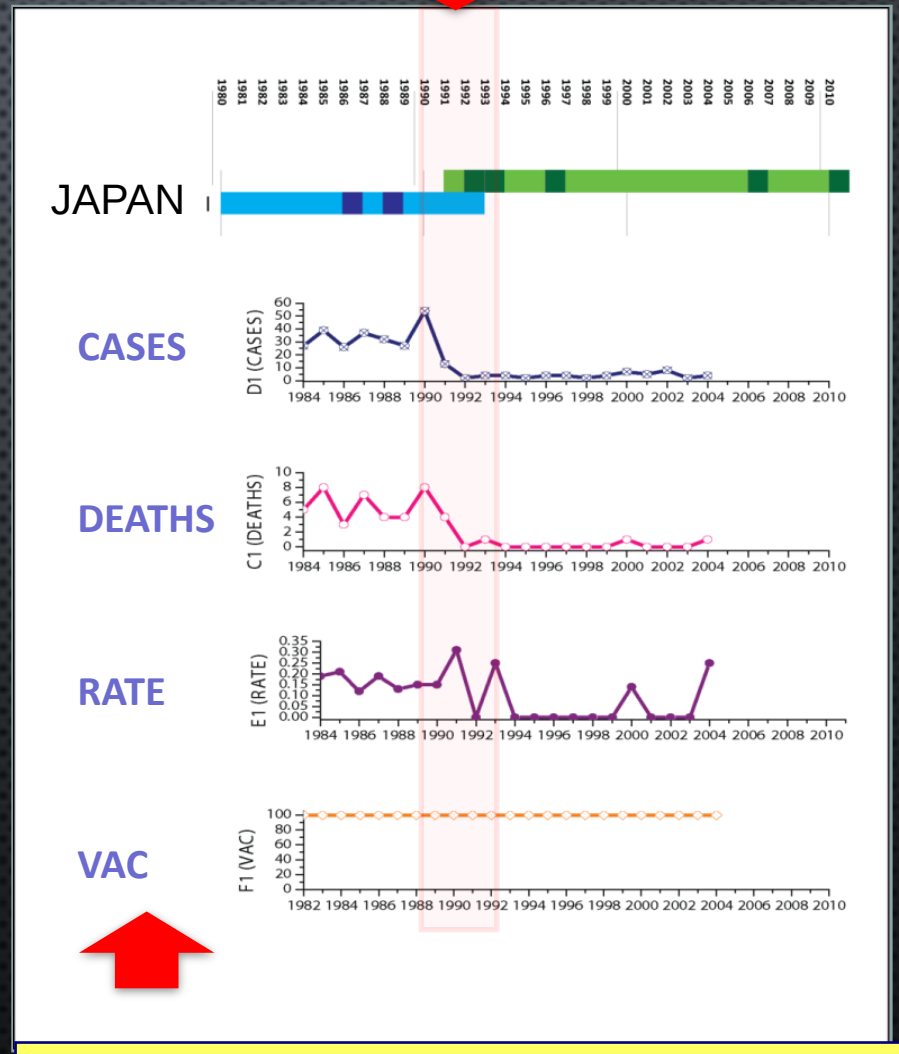
ADD IN VACCINATION DATA

MINE LITERATURE TO FIND PAPERS WITH SURVEILLANCE DATA (CASES, DEATHS, VACCINATION) (JEV防控数据的挖掘)

INVESTIGATE RELATIONSHIP OF THESE VARIABLES WITH GENOTYPE SHIFT
(流行病防控因素与基因型替换的关系)

- G-III ISOLATE FOUND
- G-III ISOLATE NOT FOUND
- G-III ISOLATE FOUND
- G-III ISOLATE NOT FOUND

GENOTYPE SHIFT COINCIDES WITH DROP IN CASES
(基因型替换与防控措施相关)



100% VACCINATION OVER THE COURSE OF STUDY
(研究区间的疫苗覆盖率100%)

GI IS MORE EFFICIENT AT INFECTING MOSQUITOES (GI在蚊子体内的感染效率更高，可能提高GI的传播效率)

THE TRADE-OFF IS IT IS LESS EFFECTIVE AT INFECTING HUMANS
(GI在人体内的感染效率较低，这可能是GI在进化过程中的权衡机制导致)

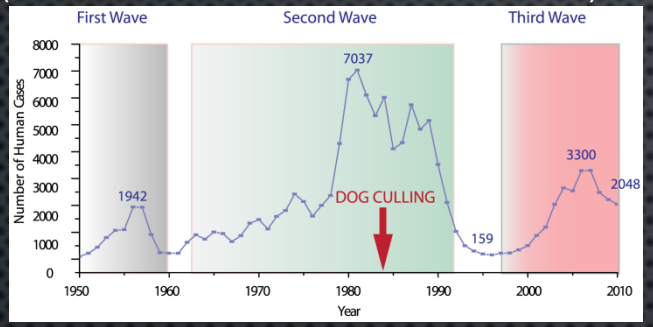
HUMANS ARE A DEAD END HOST
(人类是JEV的终宿主)

COMBINING DATA IS MORE INFORMATIVE
(数据整合可以提供更多有效信息)

RABIES IN CHINA – USE A SIMILAR APPROACH BY INTEGRATING DATA (中国狂犬病研究——利用数据整合)

3 major epidemics since 1949

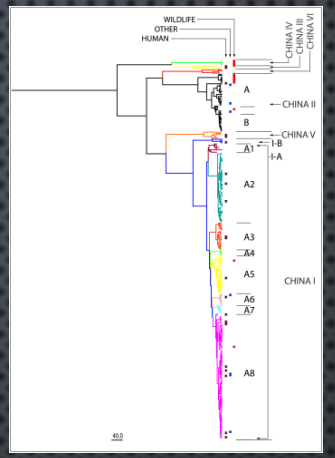
(自1949年以来3个主要的大流行)



MOST RECENT OUTBREAK BEGAN IN THE 1990S (最近的暴发始于90年代)

CONSOLIDATE DATA FROM DIFFERENT SOURCES (整合不同来源的数据)

INVESTIGATE VARIATION OF LINEAGES OVER TIME (分析谱系随时间的变异情况)

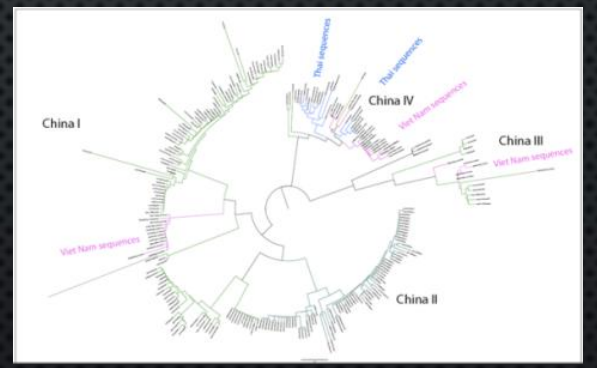


6 main lineages I – VI (6个主要的进化谱系)

China I is displacing China II (China I 取代China II)

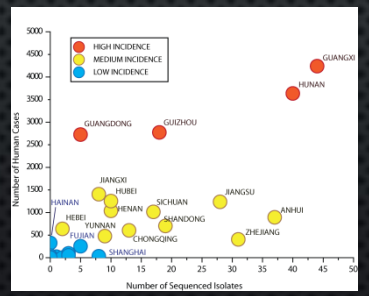
Observation of strain replacement

China III to VI is from wildlife spillover (China III到VI四支来源于野生动物)



National borders halt spread to neighboring countries

(国界阻止病毒扩散至邻国)



Summary of Surveillance Program

- Efficient use of resources? (病毒监控体系—资源的有效利用?)

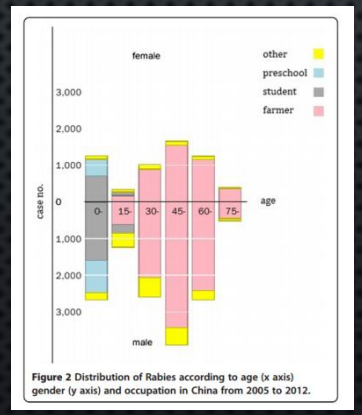


Figure 2 Distribution of Rabies according to age (x axis) gender (y axis) and occupation in China from 2005 to 2012.

Investigation of social factors and vaccination

(社会因素和疫苗保护情况)

GUIDE NATIONAL POLICY

(为病毒防控的相关政策建立提供指导意见)

UiO : Senter for biohybridteknologi
Universitetet i Oslo

Disease reporting

NECESSARY FOR SHARING IMPORTANT INFORMATION

病例报道

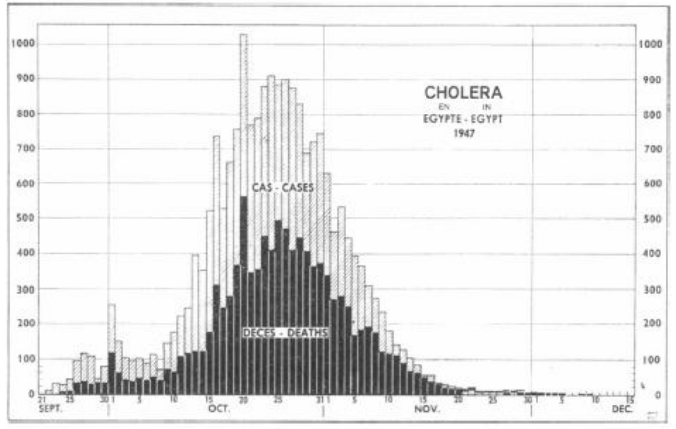
传染病方面重要信息共享的渠道

HOW THEY USED TO DO IT (1947) (70年前我们怎么做)

CHOLERA EPIDEMIC IN EGYPT (1947)

A Preliminary Report

Sir ALY TEWFIK SHOUSHA, Pasha, M.D.
Under-Secretary of State, Ministry of Public Health, Cairo, Egypt



The details of the epidemic, expressed in daily cases and deaths, are diagrammatically represented in the chart, while Table I shows the total number of cholera cases and deaths as distributed in the provinces and governorates. The weekly distribution is given in Table II.

On the next day, two more cases of vomiting and diarrhœa were seen at Fakus. Their condition was rather severe, so they were advised to enter the general hospital for treatment.

On the next day, Sunday, the medical officer of health of El Korein was rather perplexed about the reporting of ten deaths during that day. On Sunday evening, he saw a case of vomiting and diarrhœa. Next morning he saw another case, and deaths began to be reported from seven till noon.

He at once communicated with his senior medical officer of health, who in turn reported to the Director of the Epidemic Section of the Ministry of Public Health. That was about 4 p.m. on 22 September 1947. The last-mentioned officer consulted the Director-General of the Department of Preventive Medicine, and it was agreed that three senior members of the medical staff of the Epidemic Section should at once proceed to El Korein for investigation, as the

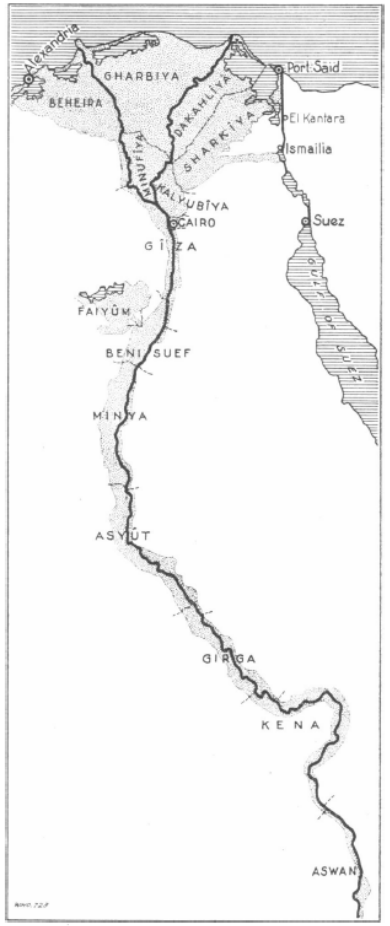


Table I

TOTAL NUMBERS OF CHOLERA CASES AND DEATHS AND ISOLATION HOSPITALS

Province or governorate	Population (1947 Census)	Cholera cases	Cholera deaths	Isolation hospitals
Cairo	2,100,486	126	32	4
Alexandria	928,237	183	78	3
Frontiers	216,872	5	3	—
Port Said	178,432	37	4	1
Suez	108,250	31	5	1
Ismailia	132,810	234	149	2
Damietta	124,104	302	156	2
Deheira	1,242,478	1,470	764	17
Gharbîya	2,316,619	4,599	1,958	39
Minufiya	1,168,777	1,816	644	22
Dakahliya	1,366,085	4,939	2,955	27
Sharqîya	1,290,890	4,089	2,141	12
Kalyubîya	687,169	1,099	385	7
Gîza	822,424	260	70	3
Faiyûm	671,885	512	296	6
Beni Suef	613,365	676	389	7
Minya	1,061,417	10	8	—
Asyût	1,379,875	35	13	3
Girga	1,288,425	131	70	5
Kena	1,106,296	250	157	5
Aswan	285,551	—	—	—
Total	19,090,447	20,804	10,277	166

Cholera Epidemic in Egypt (1947). Bulletin of the World Health Organization 1948. 1 (2), 353 – 381

HOW WE DO IT NOW (2019) (70年后我们依然这么做)

RESEARCH

Recurrent Cholera Outbreaks, Democratic Republic of the Congo, 2008–2017

Brecht Ingelbeen,[1] David Hendrickx,[1] Berthe Miwanda, Marianne A.B. van der Sande, Mathias Mossoko, Hilde Vochten, Bram Riems, Jean-Paul Nyakio, Veerle Vanlerberghe, Octavie Lunguya, Jan Jacobs, Marleen Boelaert, Benoît Ilunga Kebela, Didier Bompangue, Jean-Jacques Muyembe

Table 1. Suspected cases reported and number of samples collected, tested, and confirmed, countrywide, during cholera outbreaks, Democratic Republic of the Congo, 2008–2017

Location	Period	No. suspected cases			No. samples collected (% positive)			Serotype		
		Age <5 y	Age ≥5 y	Total	Age <5 y	Age ≥5 y	Total	Inaba	Ogawa	Hikojima
DRC	Jan 2008–Nov 2017	66,008	204,483	270,852	2,028 (34)	7,482 (30)	9,510 (31)	2,612	274	7
Reported outbreaks* in hot spot provinces										
North Kivu, South Kivu, Tanganyika	Aug–Nov 2009	1,935	9,641	11,652	20 (50)	189 (33)	209 (35)	11	63	0
North Kivu, South Kivu, Tanganyika	Aug–Nov 2017	6,653	14,709	21,362	5 (20)	41 (27)	46 (26)	5	7	0
Haut Katanga	Jan–Mar 2008	1,278	4,712	5,990	3 (67)	16 (50)	19 (53)	7	0	0
Haut Katanga	Jan–Apr 2013	1,935	6,504	8,441	1 (100)	11 (55)	12 (58)	4	3	0
Haut Lomami	Jan–Dec 2014	1,285	3,359	4,644	0	0	0	0	0	0
Ituri	Jan–Sep 2012	828	3,868	4,696	0	0	0	0	0	0
Reported outbreaks* in non–hot spot provinces										
Congo River	Jan 2011–Dec 2012	2,809	11,878	14,686	89 (30)	578 (26)	667 (27)	179	0	0
Congo River	Sep 2015–2017	4,991	20,330	25,422	123 (7)	633 (19)	756 (17)	118	10	0
Kwilu, Kwango, Kasai, Lomami, Sankuru	Jul–Nov 2017	374	2,123	2,497	0	10 (20)	10 (20)	1	1	0

*Defined as >1 laboratory-confirmed cholera cases with evidence of local transmission and an increase in the number of suspected cases for >3 consecutive weeks, or weekly incidence >1,000 cases for >3 consecutive weeks for provinces reporting cases all year round, or increasing number of suspect cases for >3 consecutive weeks if no cholera samples were submitted to the national reference laboratory for testing.

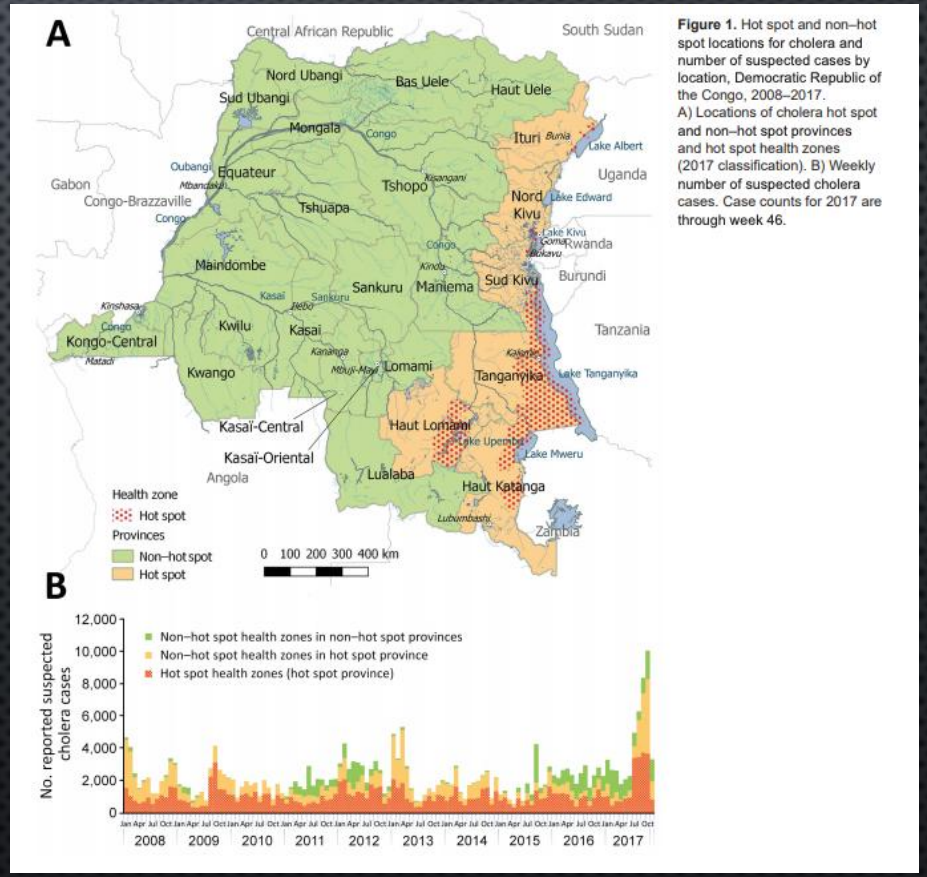


Figure 1. Hot spot and non–hot spot locations for cholera and number of suspected cases by location, Democratic Republic of the Congo, 2008–2017. A) Locations of cholera hot spot and non–hot spot provinces and hot spot health zones (2017 classification). B) Weekly number of suspected cholera cases. Case counts for 2017 are through week 46.

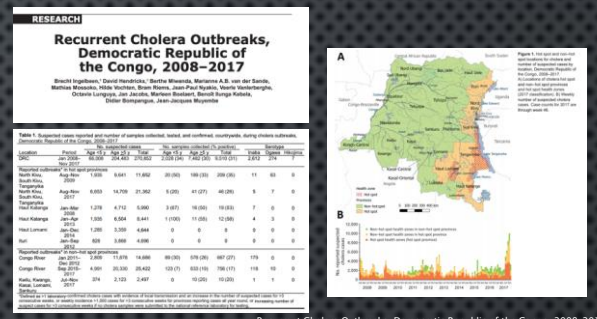
Recurrent Cholera Outbreaks, Democratic Republic of the Congo, 2008–2017
25 (5) 2019
https://doi.org/10.3201/eid2505.181141

ANOTHER PROBLEM…

Journal title	Average duration			Review reports (1st review rnd.)			
(click to go to journal page)	1st rev. rnd	Tot. handling	Im. rejection	Number	Quality	Overall rating	Outcome
Emerging Infectious Diseases	43.6 weeks	43.6 weeks	n/a	2	4 (very good)	0 (very bad)	Rejected
	Motivation: Exceptionally slow review process, with no communication from the journal. Even when we requested updates they just gave non-specific responses. The slowness of review is not acceptable, especially as the manuscript was time sensitive in regards to its material.						

43,6 weeks to review (然而漫长的审稿时间)

How do we share information in a timely way? (我们该如何及时地分享信息呢?)


RESEARCH

Recurrent Cholera Outbreaks, Democratic Republic of the Congo, 2008–2017

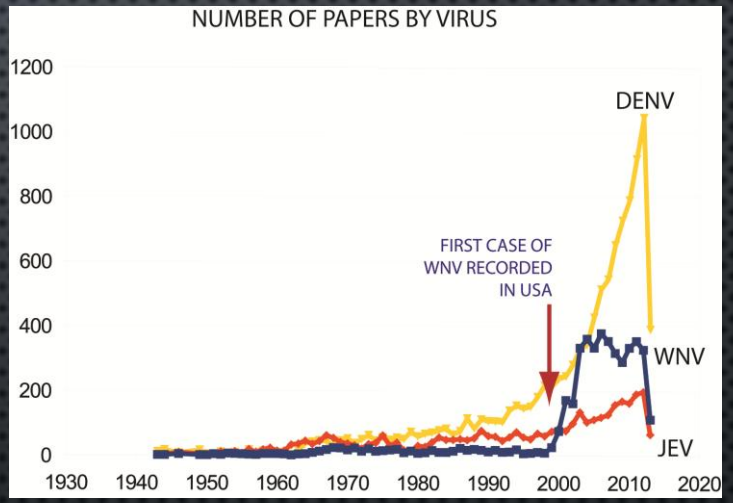
Recurrent Cholera Outbreaks, Democratic Republic of the Congo, 2008–2017
25 (5) 2019
https://doi.org/10.3201/eid2505.181141

https://www.biorxiv.org/

AND ANOTHER PROBLEM

Collect all publications on Dengue, West Nile Virus (WNV) and JEV and look at journal and associated Impact Factor（例如黄病毒家族中，仅少数病毒如DENV和WNV等，受高影响因子的杂志青睐)

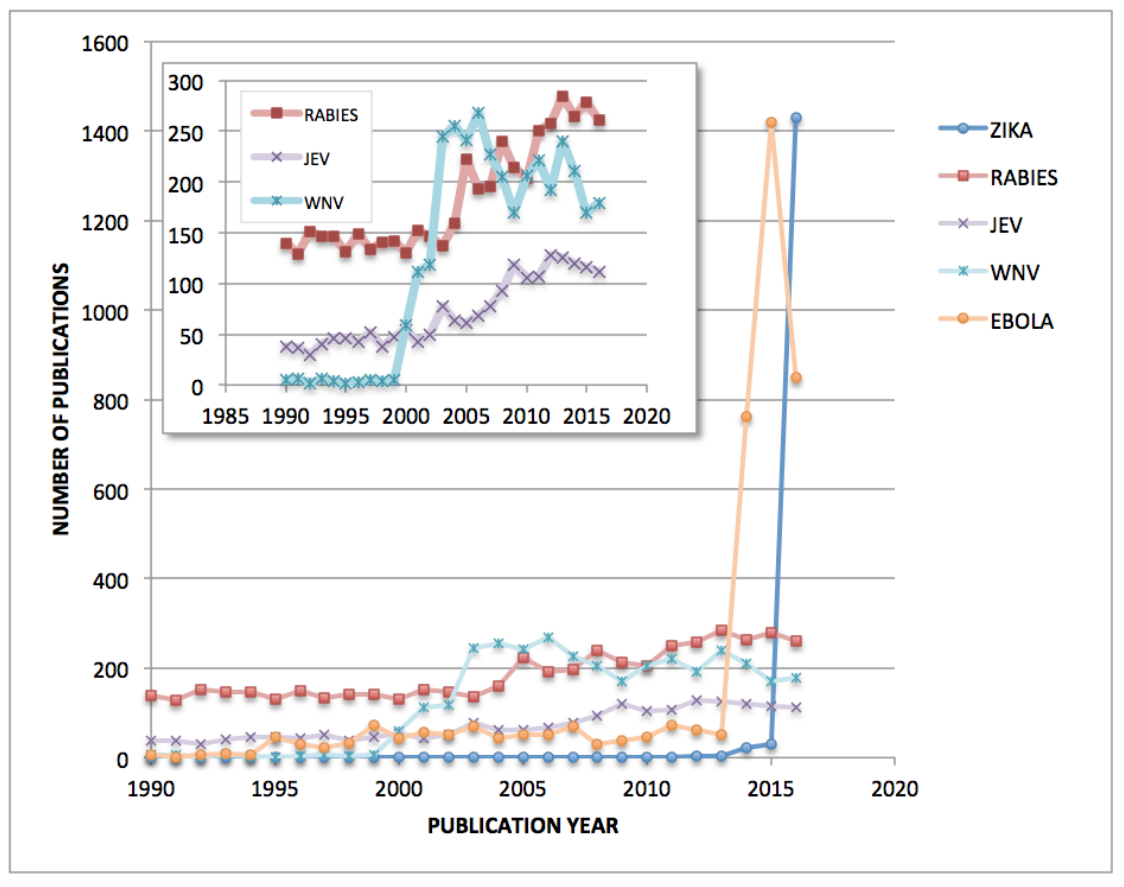
		DENV	JEV	WNV
Estimated no of deaths / year		12000		12000	200
Publications by Journal	**IF**			
Virology Journal	2.3	55	28	20
Virology	3.2	167	52	99
Journal of General Virology	3.3	142	59	56
Plos One	4	116	16	42
Journal of Clinical Virology	4	70	10	13
Journal of Virology	5.4	232	65	131
MBE	5.5	5	0	2
PNAS	9.9	40	0	18
Plos Pathogens	10	28	1	18
Nature Structural Biology	12.7	5	0	1
BMJ	14.1	30	2	12
Nature journals	25	105	8	61
Science	31	19	1	17
NEJM	35.0	9	2	11
Nature	36	26	0	13



journals with higher impact factors (IF > 10) are significantly more likely to publish work on Dengue and WNV. JEV is more likely to be published in lower impact factor journals (IF < 10).
(chi-squared test, $p = 2.13 \times 10^{-12}$) (DENV和WNV研究发表文章的影响因子远大于JEV)

If we consider annual fatality rates and number of published papers for each virus
(JEV 0.15 papers/death, DENV 0.6 papers/death, WNV 19.5 papers/death).

WHAT ABOUT OTHER DISEASES?
(新发和烈性病毒研究的受关注程度远高于其他病毒研究)



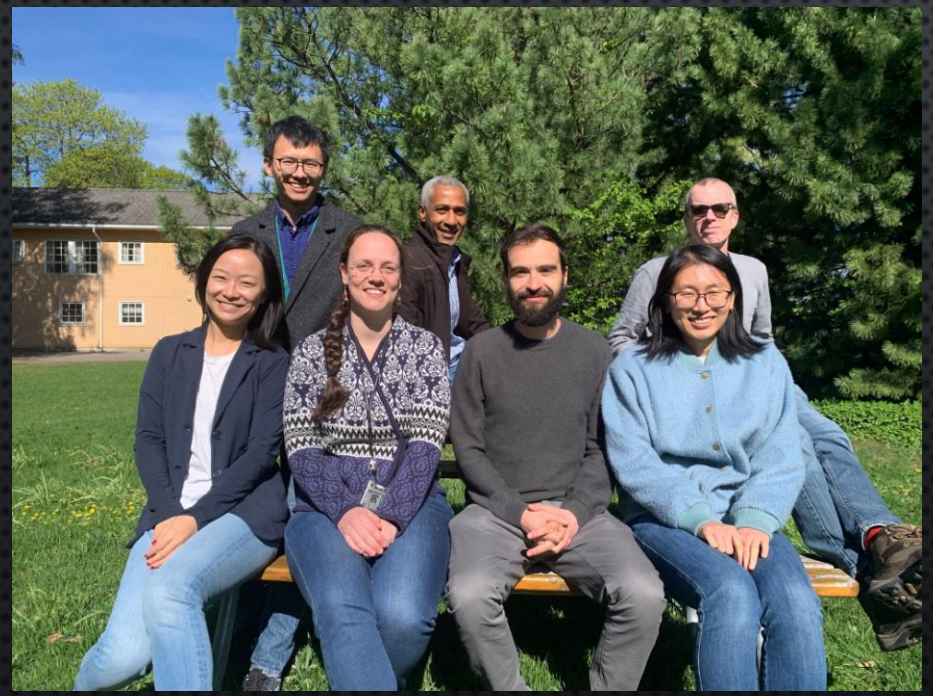
OPEN ACCESS Freely available online
PLoS PATHOGENS

Phylodynamics and Human-Mediated Dispersal of a Zoonotic Virus

Chiraz Talbi[1], Philippe Lemey[2], Marc A. Suchard[3], Elbia Abdelatif[4], Mehdi Elharrak[5], Nourlil Jalal[6], Abdellah Faouzi[6], Juan E. Echevarría[7], Sonia Vazquez Morón[7], Andrew Rambaut[8,9], Nicholas Campiz[10], Andrew J. Tatem[10,11], Edward C. Holmes[9,12], Hervé Bourhy[1]*

CONCLUSIONS

- Computational Biology/Methodology can be valuable tools for investigating and preventing epidemics (计算生物学是研究和预防流行病暴发的重要手段)
- Asking the right question is important (提出对的问题)
- Using the right tools is important (使用正确的研究手段)
- Collaboration is important. Brings together the necessary expertise (跨学科合作十分重要)



Thank you/Tusen Takk / 谢谢!

Scan me

Ping a.no

UiO : Senter for biohybridteknologi
Universitetet i Oslo