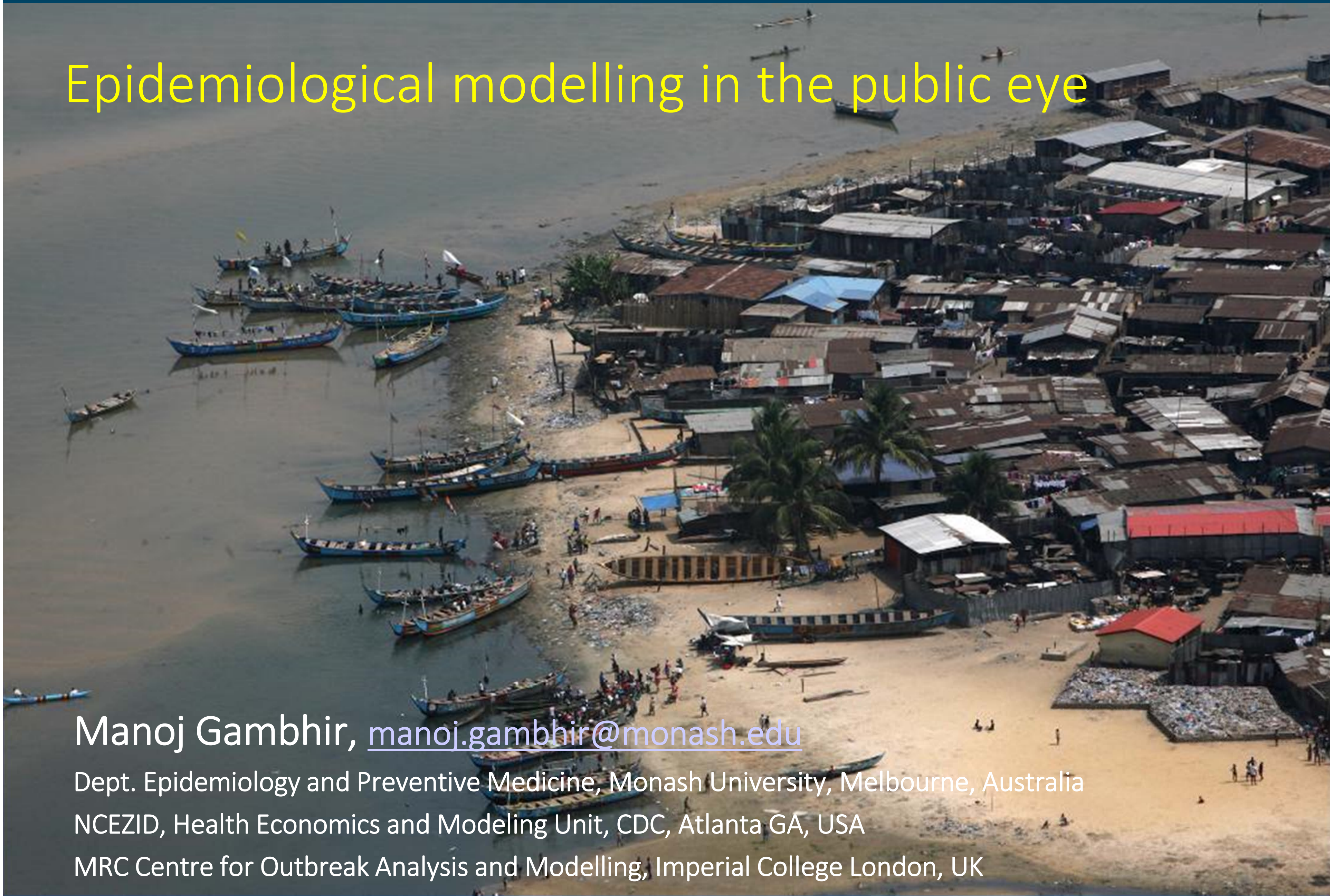

Epidemiological modelling in the public eye

Manoj Gambhir, manoj.gambhir@monash.edu

Dept. Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

NCEZID, Health Economics and Modeling Unit, CDC, Atlanta GA, USA

MRC Centre for Outbreak Analysis and Modelling, Imperial College London, UK

- Modelling at CDC
  - ✓ Pertussis
  - ✓ Ebola

Modelling at CDC


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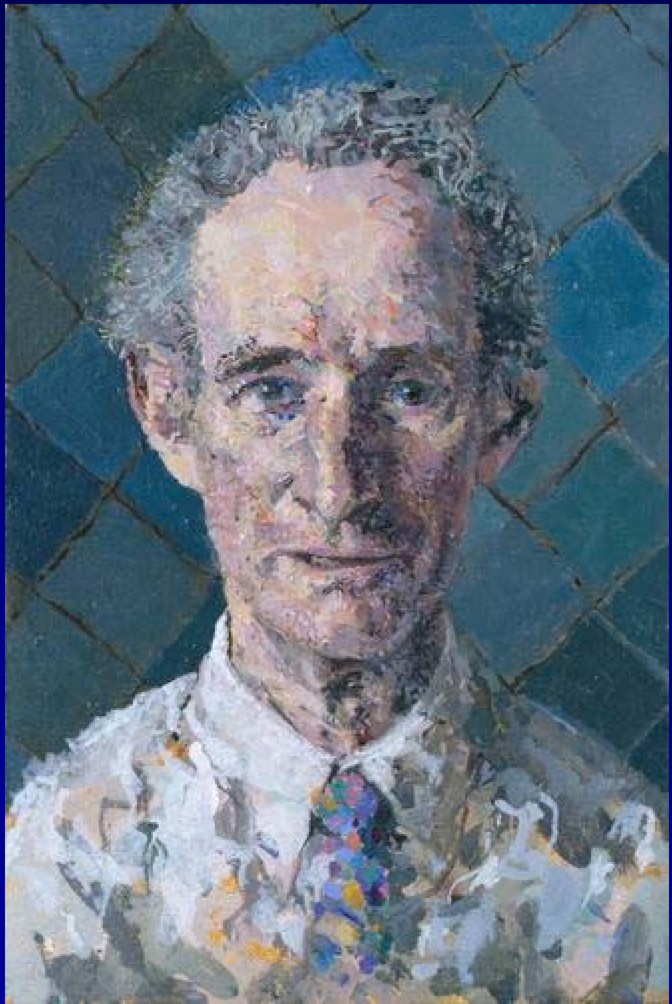
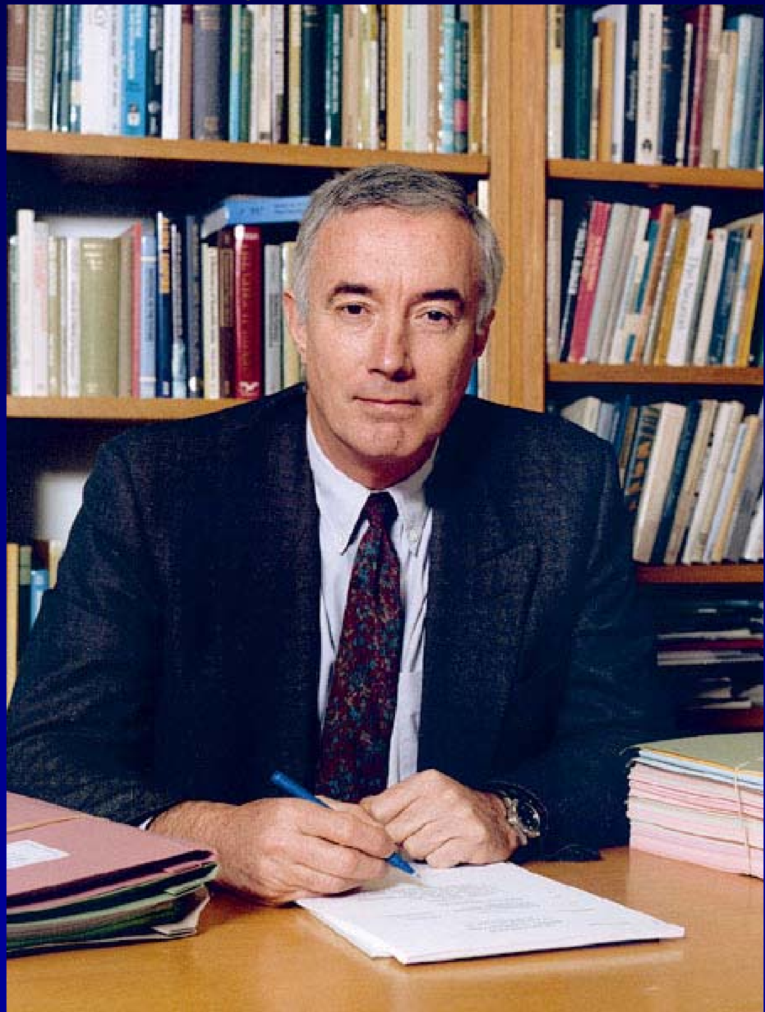
Lord Robert May & Sir Roy Anderson





Nature Vol. 280 2 Au

review

Populatio

Roy M. Anders
Zoology Department and C
Robert M. May
Biology Department, Prince

If the host populat assumed), a wider part of a two-part experiments, and u second part of the indirectly transmitt

ANY contemporary ecol devoted to predator–prey embraces field and labor mathematical models, an prey and predator popula action.

In natural communitie evidence suggests that p viruses, bacteria, protoz likely to play a part analog of predators or resource l plant and animal populati Park's[1] experiments in w drastically reduced the p *Tribolium casteneum*, and outcome of its competiti studies of the way the e *tenuabilis* influences the insect *Hydrometra myra* importance of infectious lations of wild mammals such factor in bird popula sheep in North America infection by the lungwor which then predispose t monia[8,9] On a grand scal

Reprinted from Nature, Vol. 333, No. 6173, pp. 514-519, 9 June 1988

Epidemiological pa transn

Roy M. And
* Parasite Epidemiolo
† Biology Department

Epidemiological d accumulating, but

IT is now seven yea syndrome) was first the etiological age type 1), was discov the National Instit throughout the wo cases reported bet and 133 countries r ation in February 1 concerning both in likely demographic extensively in the h tries and why hete developing countri

The potential fo consequently AIDS magnitude of the b that group[5–8]. R_0 es produced, on aver stages of the epide tible. As such, it de infected individual duration of their re partners acquired p category), times the βcD. Setting aside meant by 'average' sufficient to assign components. In thi such assignments, i tainties that are em we believe can tent

Incubation and

Most epidemiologi uniform level of inf incubation period onset of AIDS[5–9]. I tion intervals main cases and cohort st seroconversion is k fusion associated c bation periods in p activity, or indeed recent analysis[12] of diagnosis of AIDS incubation periods older than 12 yr (ba tion intervals wher after infection, $p(\tau) = \exp(-a\tau^c)$ and a and c are constants). In

THE RO SOCIET

Epider

Roy M. And
Steve
[1]*Department o*
[2]*21 Sassoo*

This paper aetiological meters and formulation with the on make simpl tive in the c be so with further und defined bio presented i

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Ebola Virus Disease in West Africa — The First 9 Months of the Epidemic and Forward Projections

WHO Ebola Response Team*

ABSTRACT

BACKGROUND

On March 23, 2014, the World Health Organization (WHO) was notified of an out break of Ebola virus disease (EVD) in Guinea. On August 8, the WHO declared th epidemic to be a "public health emergency of international concern."

METHODS

By September 14, 2014, a total of 4507 probable and confirmed cases, includin 2296 deaths from EVD (Zaire species) had been reported from five countries i West Africa — Guinea, Liberia, Nigeria, Senegal, and Sierra Leone. We analyzed detailed subset of data on 3343 confirmed and 667 probable Ebola cases collecte in Guinea, Liberia, Nigeria, and Sierra Leone as of September 14.

The re-emergence of the viral aetiological agent of SARS in China at the end of 2003 (Paterson 2004), following the epidemic earlier in the year affecting many countries, rang alarm bells in the WHO and elsewhere. Thankfully,

devastation earlier in 2003. A clear priority is further surveillance of animals in settings where the human virus spread extensively so as to better understand the origins of the epidemic in humans and the role of animal reservoirs.

Male homosexual	0.60	35	48

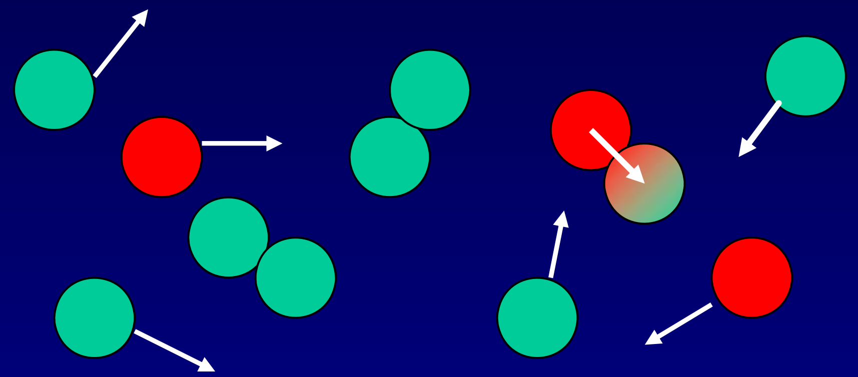
Host population

The simple SIR epidemic model

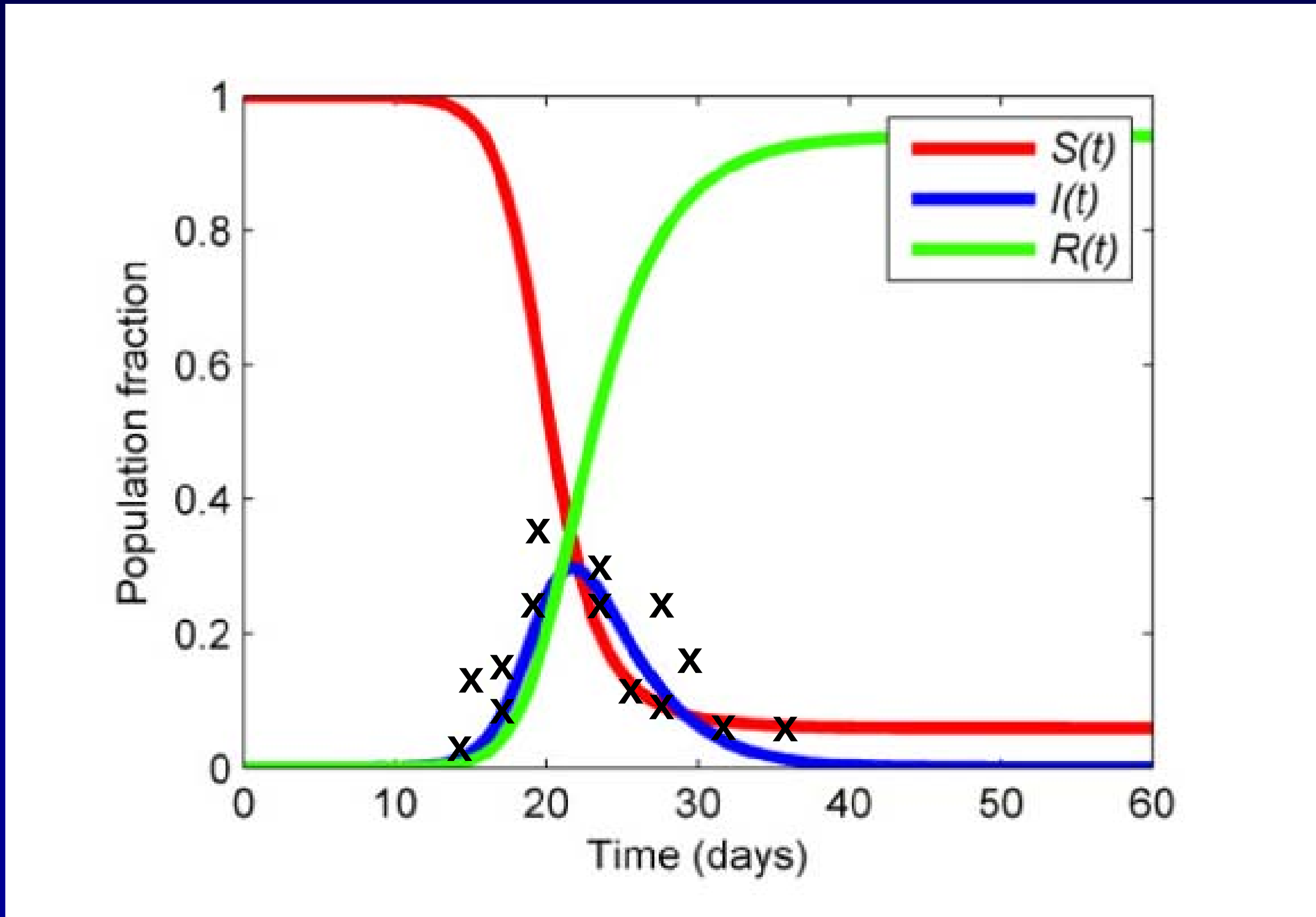
S	I	R
Susceptible	*Infected*	*Recovered*

The simple SIR epidemic model

$$S \xrightarrow{\lambda} I$$



As infecteds increase, *rate* increases



S(t)
I(t)
R(t)
Population fraction
Time (days)
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60

2009: H1N1 influenza pandemic

Projects throughout CDC

Pertussis Explaining the recent upsurge in cases in 7-10 yos and rise in overall cases

Ebola 2014-2015 West African epidemic

Projects throughout CDC

Pertussis Explaining the recent upsurge in cases in 7-10 yos and rise in overall cases

Ebola 2014-2015 West African epidemic

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POLITICS EDUCATION BAY AREA CHICAGO

Whooping C
Epidemic

By JESSE McKINLEY
Published: June 23, 2010

SAN FRANCISCO
health authorities
state on Wednesda
background — to g

The announcemen
reports of pertussis
often is mistaken f
told, 910 cases hav
under investigation
largest in the state

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Whooping-cough booster may soon be added The CDC advisory panel, however, rejected adding chicken pox, a setback for vaccine-maker Merck.
July 1, 2005

Chemical In Child Vaccines Stirs Debate
July 8, 1999

Web Site Makes Case For Vaccines Children's Hospital Of Phila. Aims To Ease Fears About The Growing Number Of Shots Required.
October 16, 2000

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Cases of whooping cough in United States highest since 1959

December 12, 2012 | By Don Sapatkin, Inquirer Staff Writer

With pertussis at its highest level nationally in a half-century, the Philadelphia region has been weathering a spike that in some places is more than triple the previous record set two years ago.

"We're sort of way off the scale this year," said Stephen Ostroff, Pennsylvania's acting physician general. "It really started picking up in the summer, and once kids got back to school, the [pertussis] was already there."

Cases of pertussis, also known as whooping cough, often decline in late fall into early winter. In Philadelphia, which recorded 50 cases for August - more typical of an entire year - infections plummeted last month. But there has been no major decrease statewide, Ostroff said.

Story continues below.

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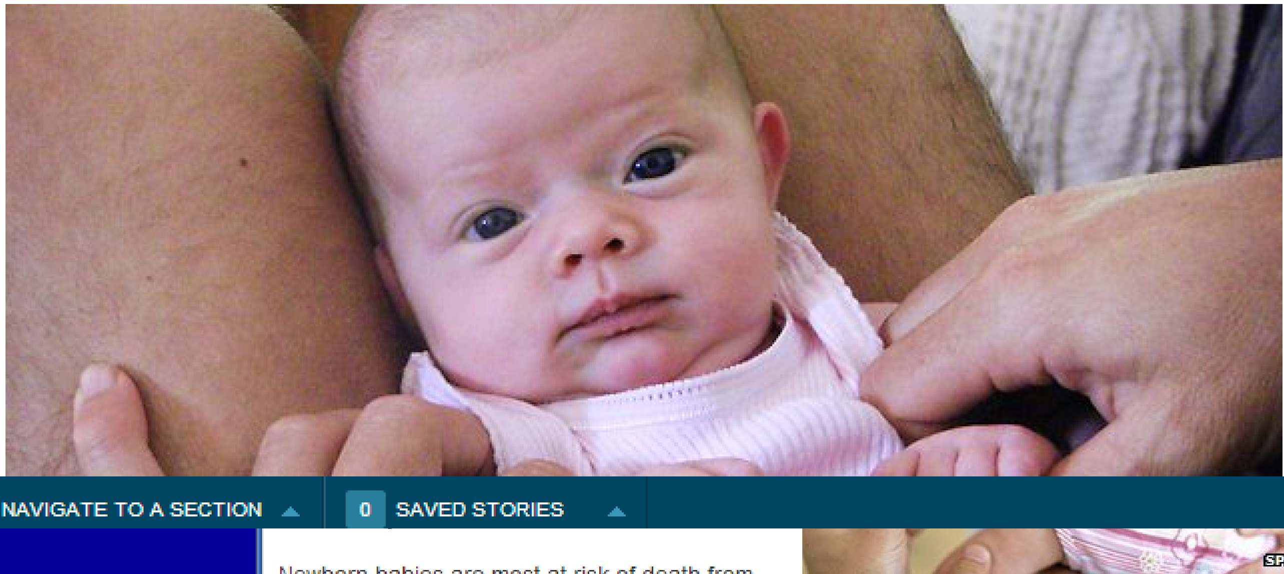
How worried should we be about the whooping cough epidemic?

MARY-ROSE MACCOLL The Australian April 28, 2012 12:00AM



NAVIGATE TO A SECTION   0 SAVED STORIES

Newborn babies are most at risk of death from the disease.

Babies are offered a whooping cough vaccine at two, three and four months of age

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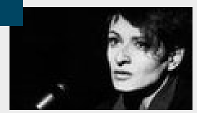
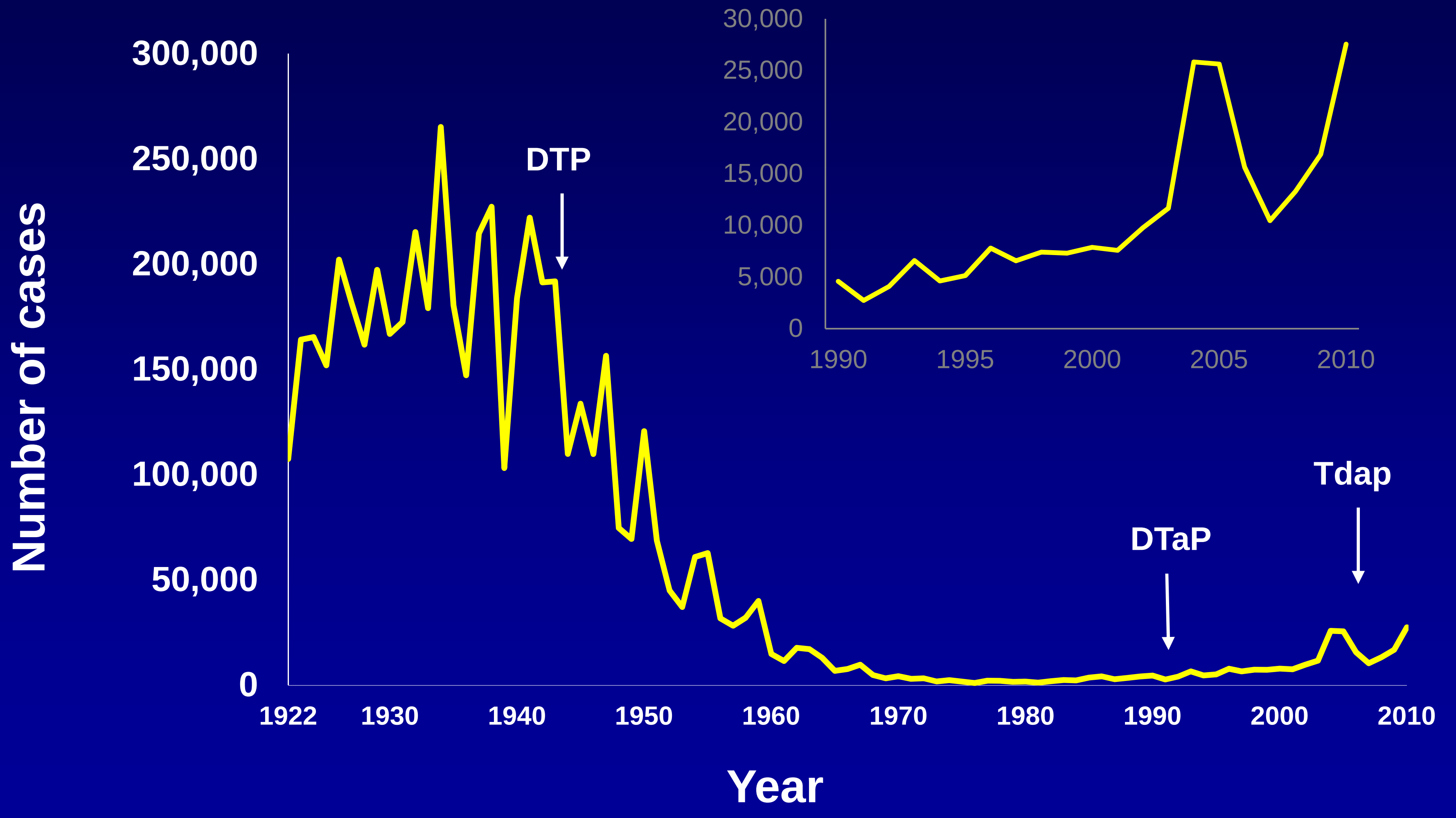


In harmony

Did this woman change history with one song?

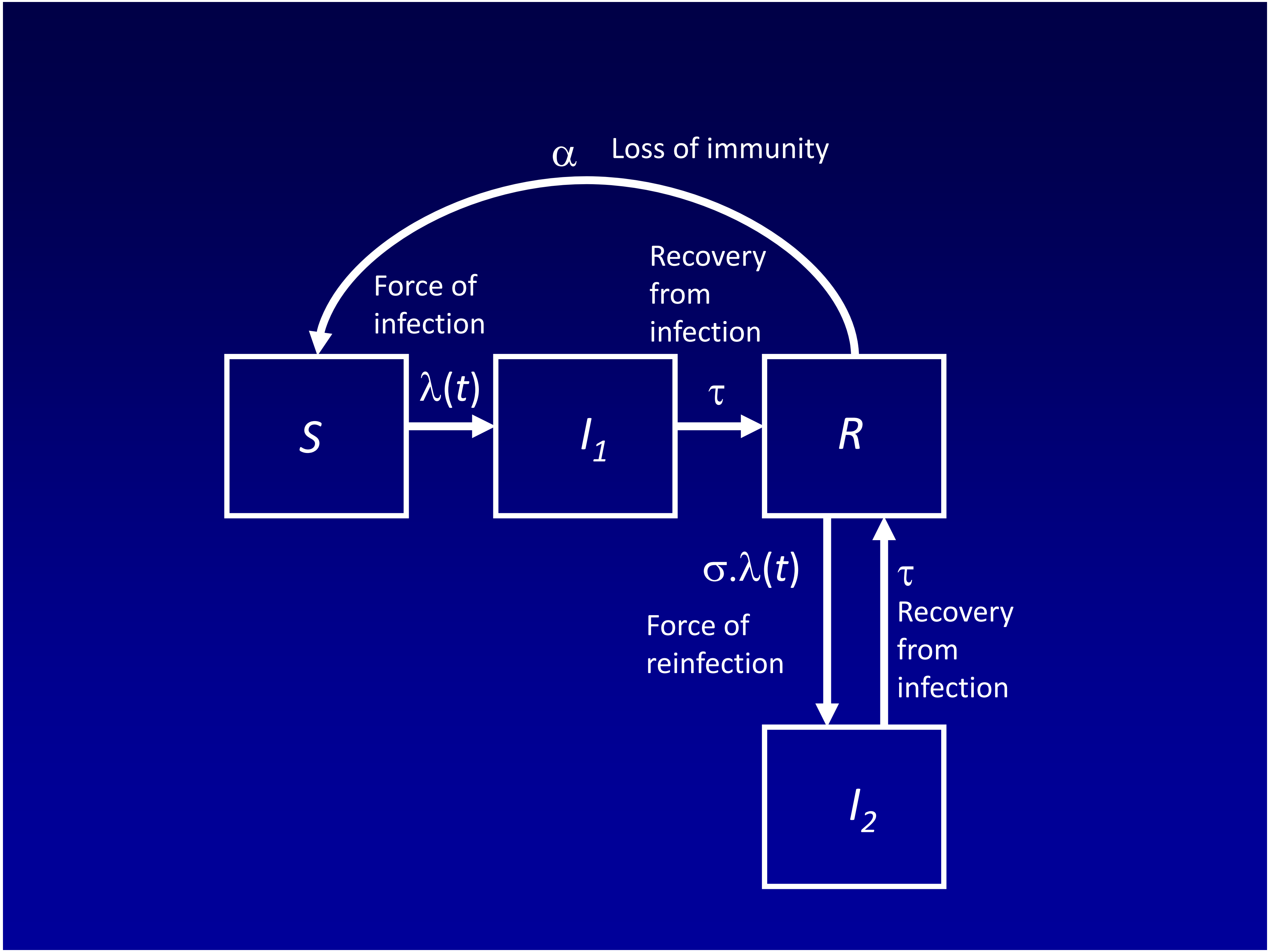
Reported pertussis cases – 1922-2010



SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service

Questions from leadership

Is the effectiveness and duration of protection of the new vaccine different to the old?



α Loss of immunity
Force of infection
Recovery from infection
S
λ(t)
I1
τ
R
σ.λ(t)
Force of reinfection
τ
Recovery from infection
I2

Table 1. Descriptions of the nested models that were fitted to the NNDSS incidence data.

Model	Description	DIC
1	Protection duration of whole cell vaccine same as natural infection; acellular vaccine same as whole-cell	-9720
2	Protection duration of whole cell vaccine same as natural infection; different efficacy for acellular vaccine	-9570
3	Protection duration of whole cell vaccine same as natural infection; different protection duration for acellular vaccine;	-9250
4	Protection duration of whole cell vaccine different from natural infection; acellular vaccine same as whole-cell	-9800
5	Protection duration of whole cell vaccine same as natural infection; protection duration and efficacy different for acellular vaccine	-8422
6	Whole cell vaccine protection duration different from natural infection; different efficacy for acellular vaccine	-9183
7	Whole cell vaccine protection duration different from natural infection; different protection duration for acellular vaccine	-9230
8	Whole cell vaccine protection duration different from natural infection; protection duration and efficacy different for acellular vaccine	-8417

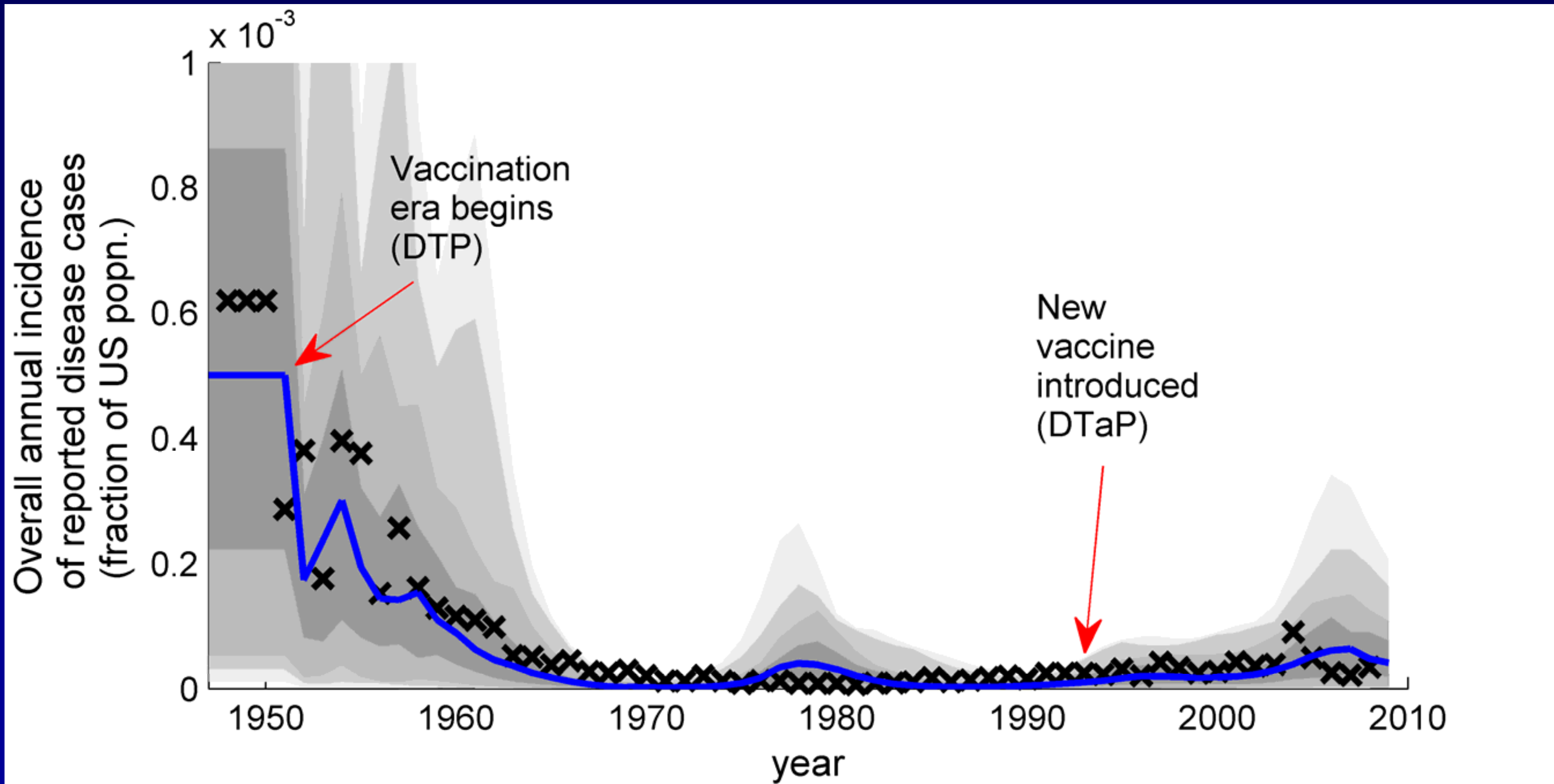
The mean posterior values of the Deviance Information Criterion (DIC) of the models are given in the rightmost column.

doi:10.1371/journal.pcbi.1004138.t001

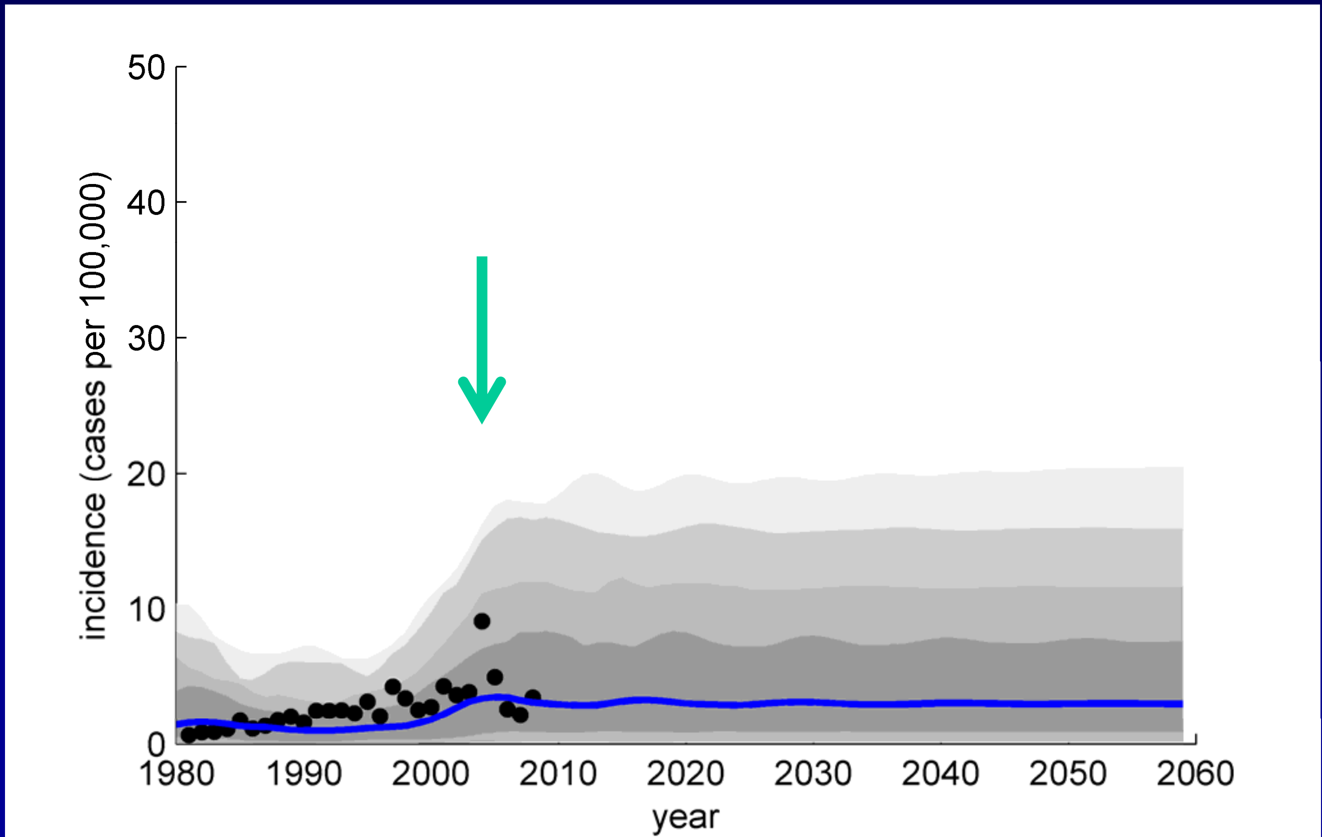
Gambhir M, Clark TA, Cauchemez S, Tartof SY, Swerdlow DL, et al. (2015) A Change in Vaccine Efficacy and Duration of Protection Explains Recent Rises in Pertussis Incidence in the United States. PLoS Comput Biol 11(4): e1004138. doi:10.1371/journal.pcbi.1004138
http://journals.plos.org/ploscompbiol/article?id=info:doi/10.1371/journal.pcbi.1004138

PLOS | COMPUTATIONAL BIOLOGY

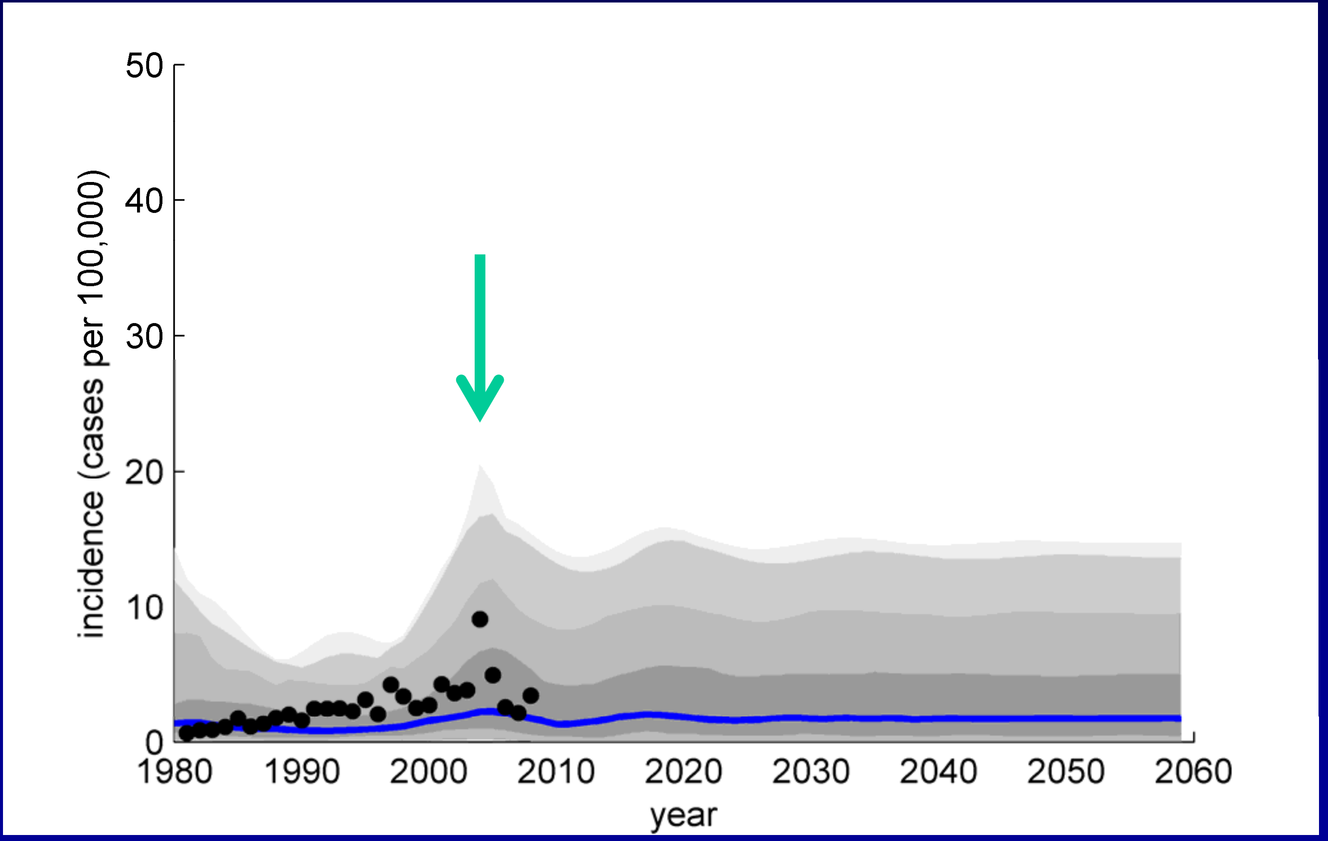
Total incidence since vaccination began: model vs. data



Projecting forward in time



*VE*coverage=10%*



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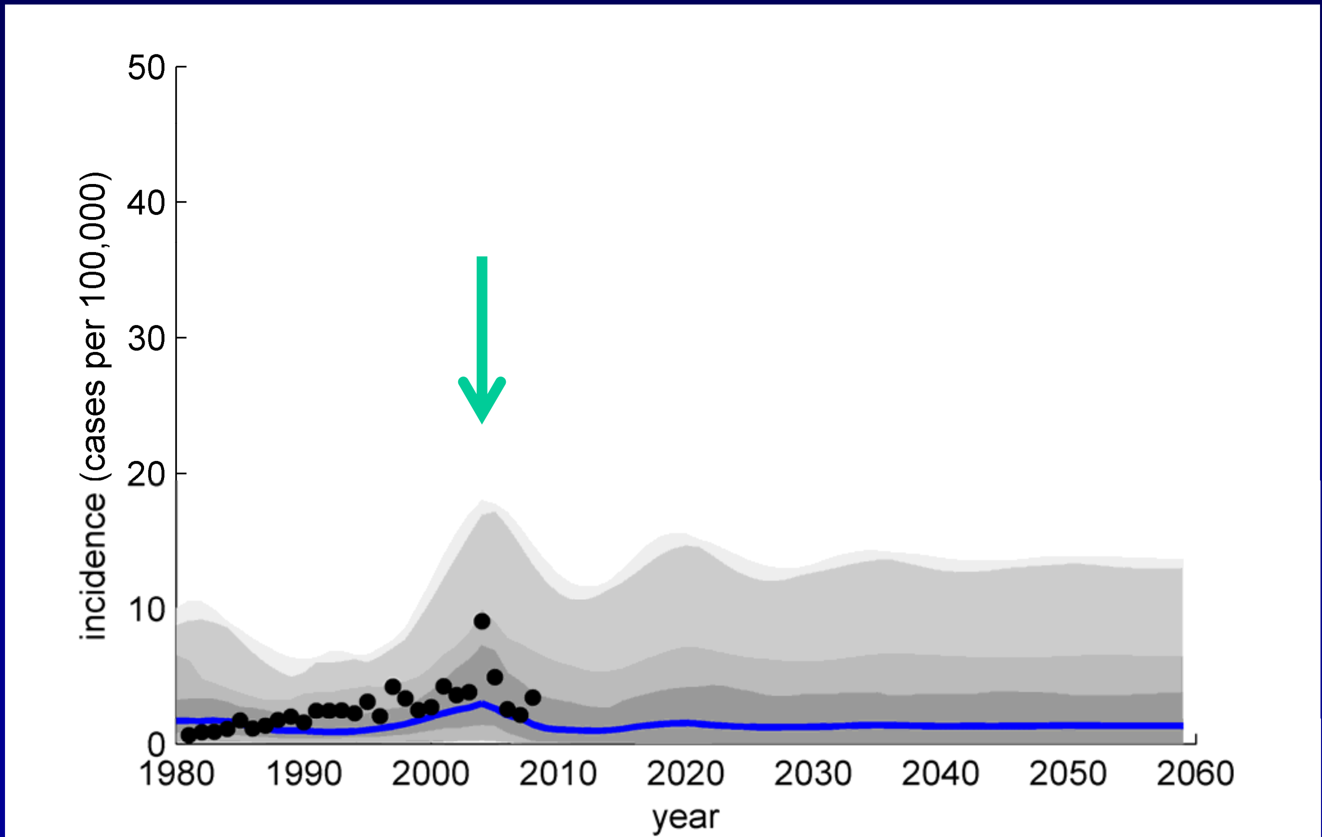
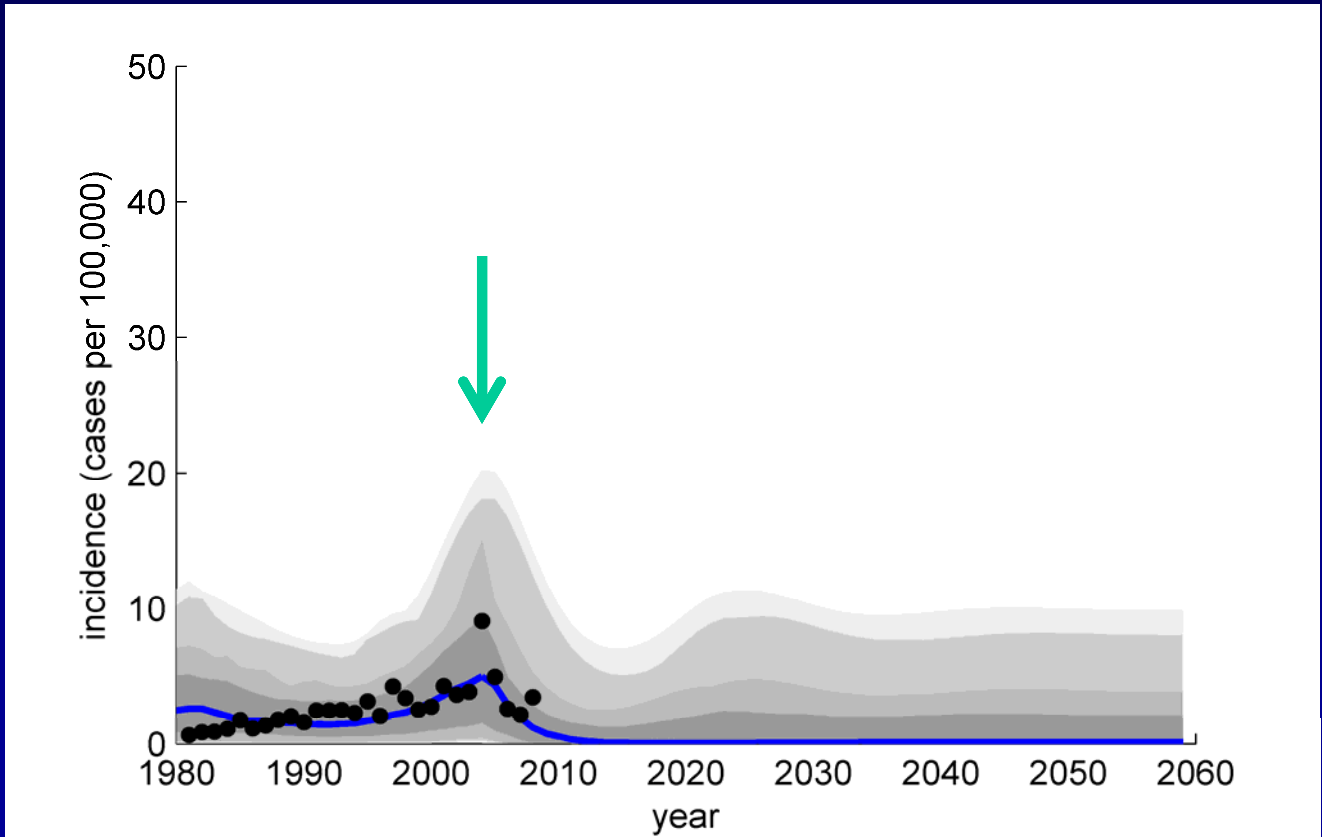


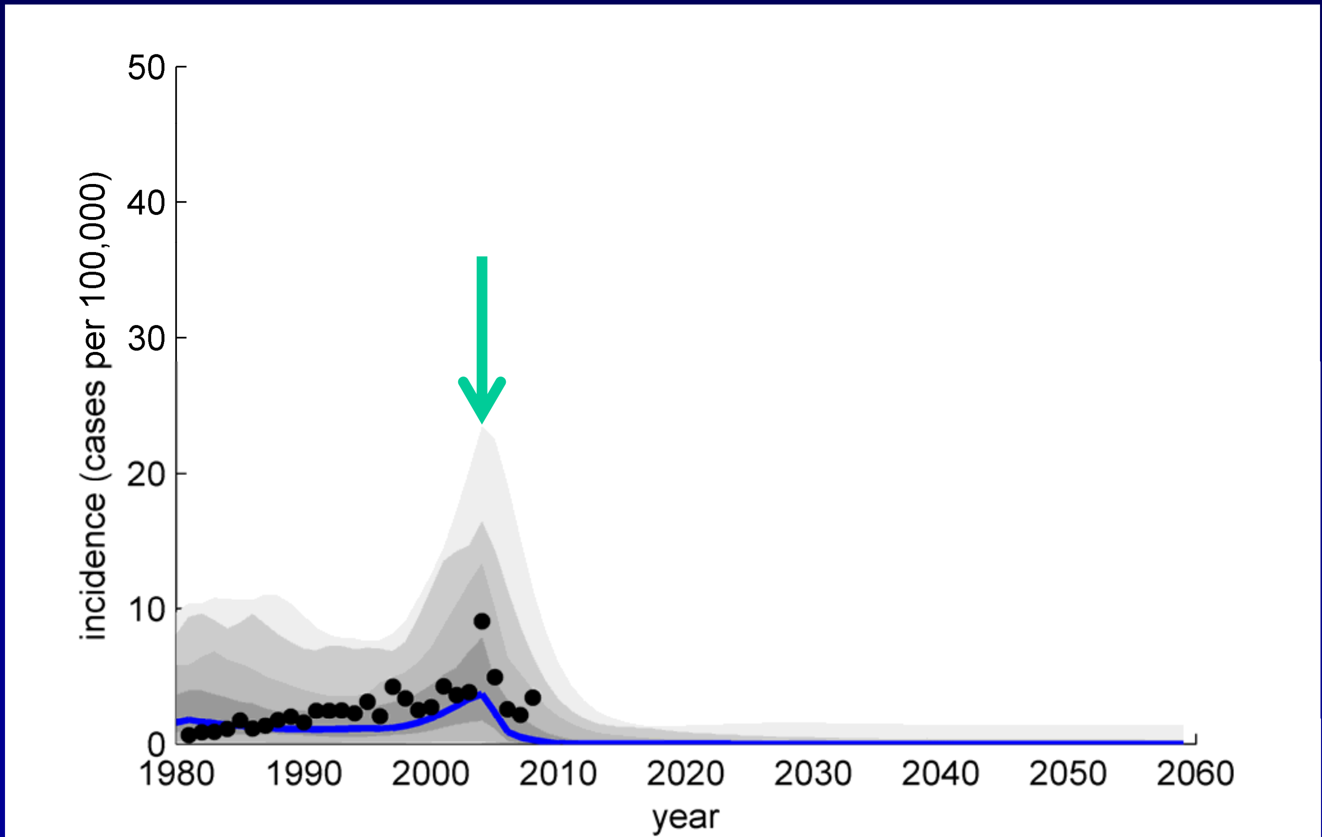
incidence (cases per 100,000)
50
40
30
20
10
0
1980
1990
2000
2010
2020
2030
2040
2050
2060
year

70%



incidence (cases per 100,000)
50
40
30
20
10
0
1980
1990
2000
2010
2020
2030
2040
2050
2060
year

90%



50
40
30
20
10
0
incidence (cases per 100,000)
1980
1990
2000
2010
2020
2030
2040
2050
2060
year

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RESEARCH ARTICLE

A Change in Vaccine Efficacy and Duration of Protection Explains Recent Rises in Pertussis Incidence in the United States

Manoj Gambhir[1,2,3]*, Thomas A. Clark[4], Simon Cauchemez[5,6], Sara Y. Tartof[7], David L. Swerdlow[2,8], Neil M. Ferguson[5]

1 Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia, **2** Modeling Unit, National Center for Immunization and Respiratory Diseases (NCIRD), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America, **3** IHRC, Inc., Atlanta, Georgia, United States of America, **4** Meningitis and Vaccine Preventable Diseases Branch, Division of Bacterial Diseases, NCIRD, CDC, Atlanta, Georgia, United States of America, **5** Medical Research Council Centre for Outbreak Analysis and Modelling, Imperial College London, London, United Kingdom, **6** Mathematical Modelling of Infectious Diseases Unit, Institut Pasteur, Paris, France, **7** Kaiser Permanente Southern California, Kaiser Permanente Research, Department of Research & Evaluation, Pasadena, California, United States of America, **8** Office of Science and Integrative Programs, NCIRD, CDC, Atlanta, Georgia, United States of America

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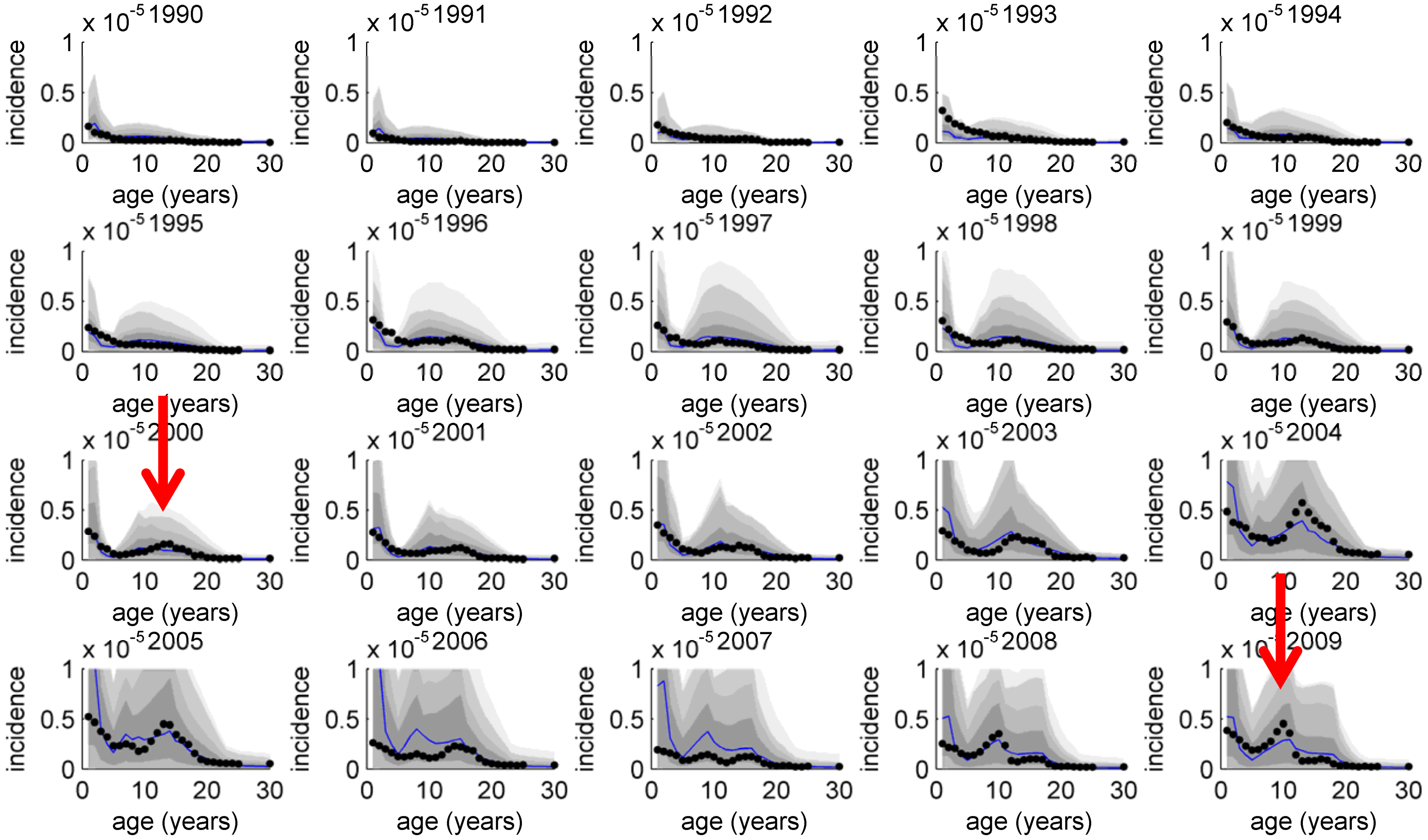

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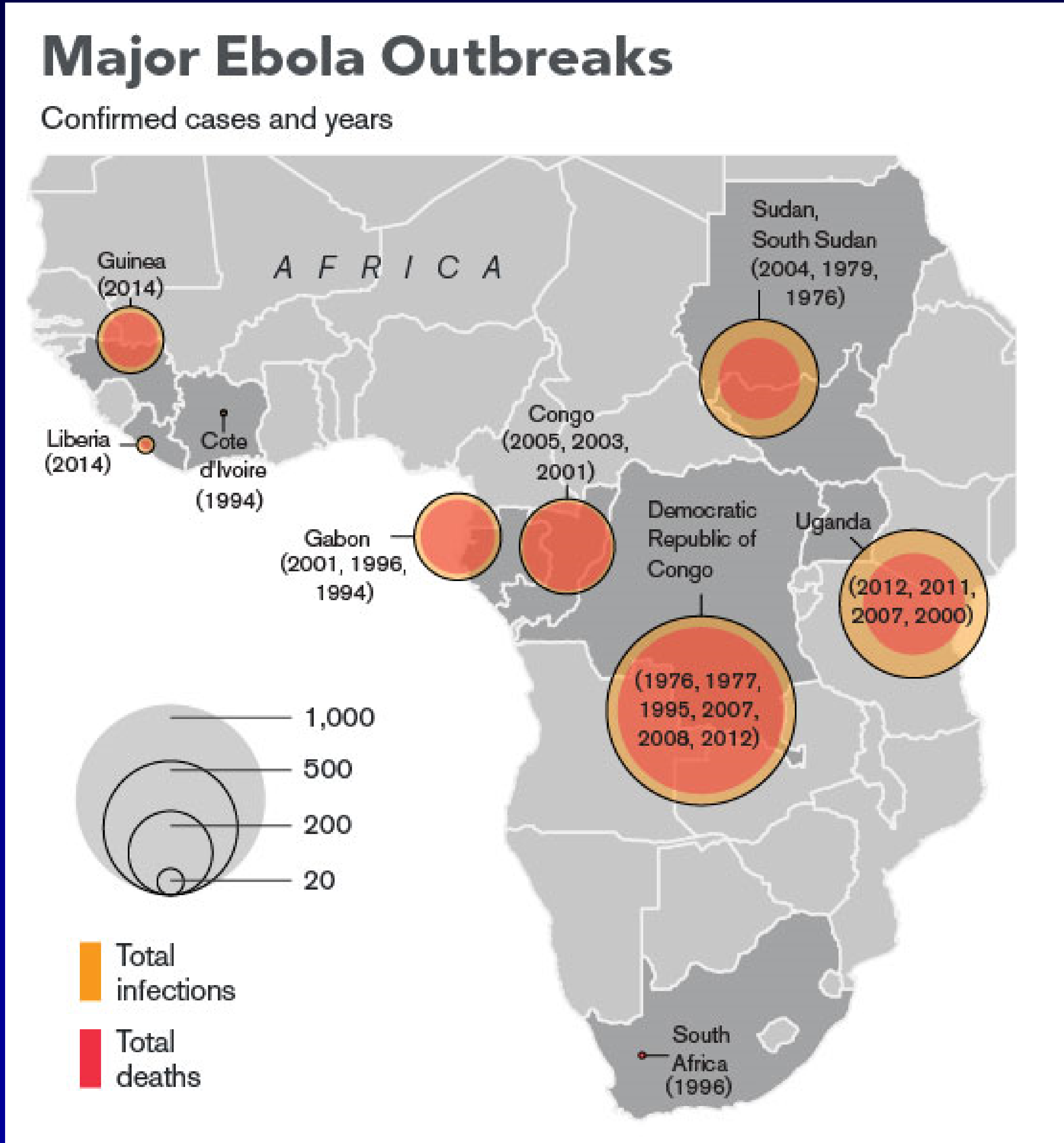
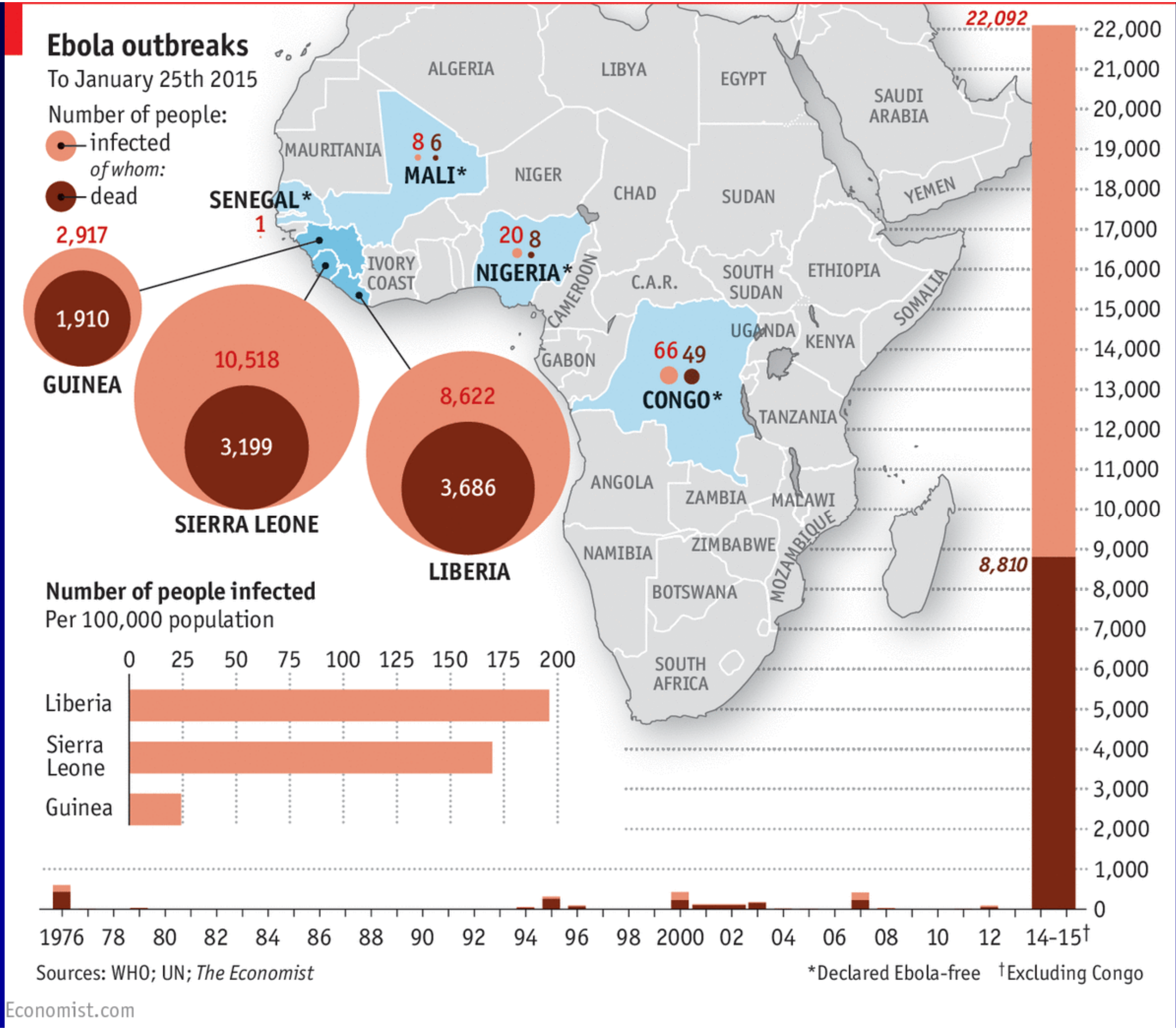
Projects throughout CDC

Pertussis Explaining the recent upsurge in cases in 7-10 yos and rise in overall cases

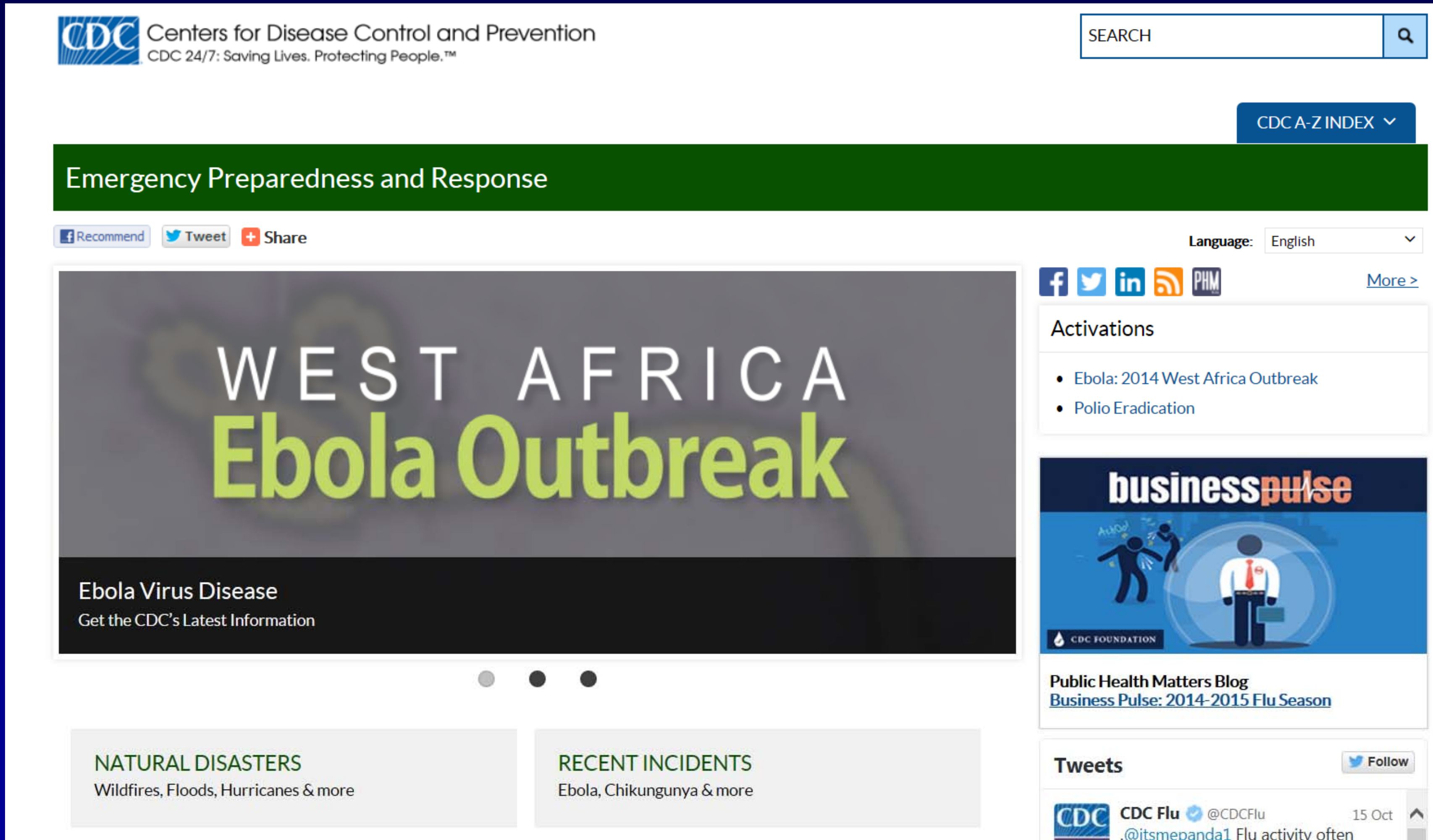
Ebola 2014-2015 West African epidemic

Ebola


Major Ebola Outbreaks
Confirmed cases and years
A F R I C A
Guinea (2014)
Liberia (2014)
Cote d'Ivoire (1994)
Gabon (2001, 1996, 1994)
Congo (2005, 2003, 2001)
Sudan, South Sudan (2004, 1979, 1976)
Democratic Republic of Congo
(1976, 1977, 1995, 2007, 2008, 2012)
Uganda
(2012, 2011, 2007, 2000)
South Africa (1996)
1,000
500
200
20
Total infections
Total deaths



Ebola outbreaks
To January 25th 2015
Number of people:
infected
of whom:
dead
ALGERIA
LIBYA
EGYPT
SAUDI ARABIA
MAURITANIA
8 6
MALI*
NIGER
CHAD
SUDAN
YEMEN
SENEGAL*
1
2,917
1,910
GUINEA
20 8
NIGERIA*
IVORY COAST
CAMEROON
C.A.R.
SOUTH SUDAN
ETHIOPIA
SOMALIA
UGANDA
KENYA
GABON
66 49
CONGO*
TANZANIA
10,518
3,199
SIERRA LEONE
8,622
3,686
LIBERIA
ANGOLA
ZAMBIA
MALAWI
MOZAMBIQUE
NAMIBIA
ZIMBABWE
BOTSWANA
SOUTH AFRICA
Number of people infected
Per 100,000 population
0 25 50 75 100 125 150 175 200
Liberia
Sierra Leone
Guinea
22,092
8,810
22,000 21,000 20,000 19,000 18,000 17,000 16,000 15,000 14,000 13,000 12,000 11,000 10,000 9,000 8,000 7,000 6,000 5,000 4,000 3,000 2,000 1,000 0
1976 78 80 82 84 86 88 90 92 94 96 98 2000 02 04 06 08 10 12 14-15†
Sources: WHO; UN; The Economist
*Declared Ebola-free †Excluding Congo
Economist.com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Ebola, Chikungunya & more
Tweets
Follow
CDC Flu @CDCFlu 15 Oct
.@itsmepanda1 Flu activity often

CDC Emergency Response Activation Levels

Level 1

The highest level of response reserved for critical emergencies. CDC assigns the largest number of staff possible to work 24/7 on the response. To date, there have been three Level 1 responses: Ebola outbreak (2014), H1N1 influenza outbreak (2009) and Hurricane Katrina (2005).

Level 2

The CDC experts in the particular disease lead the response with a large number of other staff from the program area. A large number of staff from CDC's Emergency Operations Center may assist with the response.

Level 3

The CDC experts in the particular disease lead the response with some of their own staff. Some staff from CDC's Emergency Operations Center may assist in the response. CDC decides when a different level of response is needed.

CDC Emergency Response
When public health emergencies occur, CDC's Emergency Operations Center (EOC) manages the response. The EOC has three levels of response.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CS250674

CDC Emergency Response Activation Levels

Level 1

The highest level of response reserved for critical emergencies. CDC assigns the largest number of staff possible to work 24/7 on the response. To date, there have been three Level 1 responses: Ebola outbreak (2014), H1N1 influenza outbreak (2009) and Hurricane Katrina (2005).

Level 2

CDC leaders integral to the Ebola response, including epidemiologists, laboratorians, logistics, and more, assemble in agency’s command center to discuss next steps in directing the response at CDC Emergency Operations Center in Atlanta, August 8. Spencer Lowell for TIME magazine

Questions from leadership

How many cases might there be?

When will the epidemic end?

What will it take to end the epidemic?

Epidemiol. Infect. (2007), **135**, 610–621.
doi:10.1017/S0950268806007217 Printed in the United Kingdom

Understanding the dynamics of Ebola epidemics

J. LEGRAND*, R. F. GRAIS, P. Y. BOELLE, A. J. VALLERON AND A. FLAHAULT

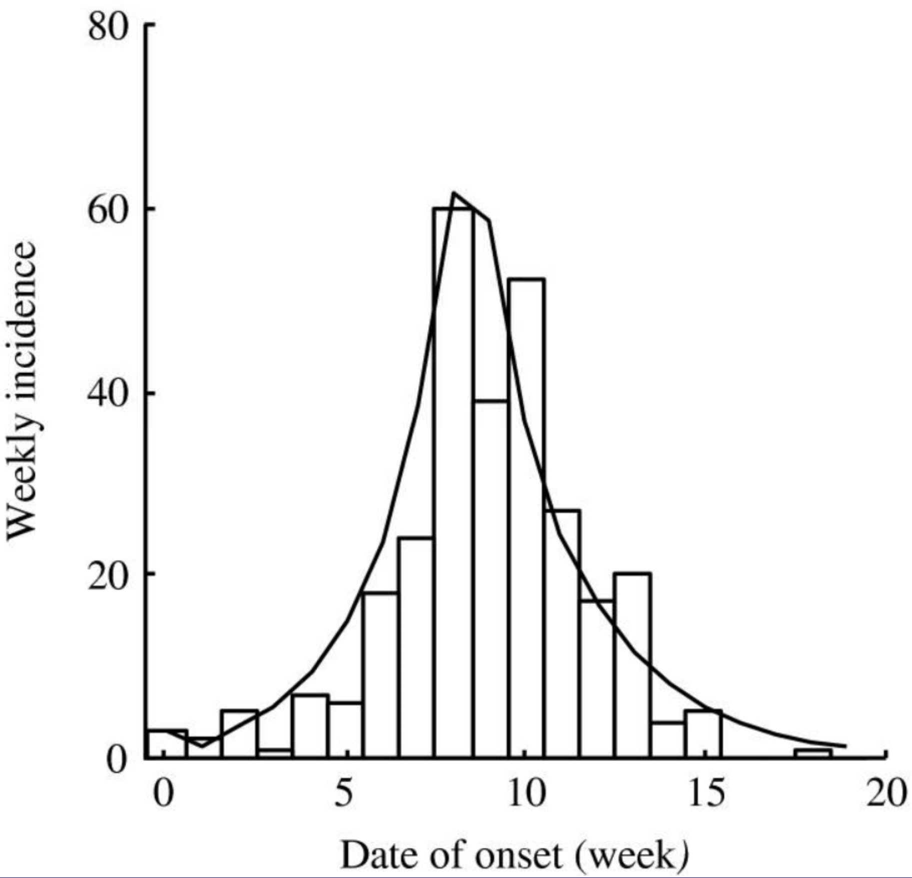
INSERM, UMR-S 707, Paris, France, and Université Pierre et Marie Curie-Paris 6, UMR-S 707, Paris, France

(*Accepted 14 July 2006; first published online 26 September 2006*)

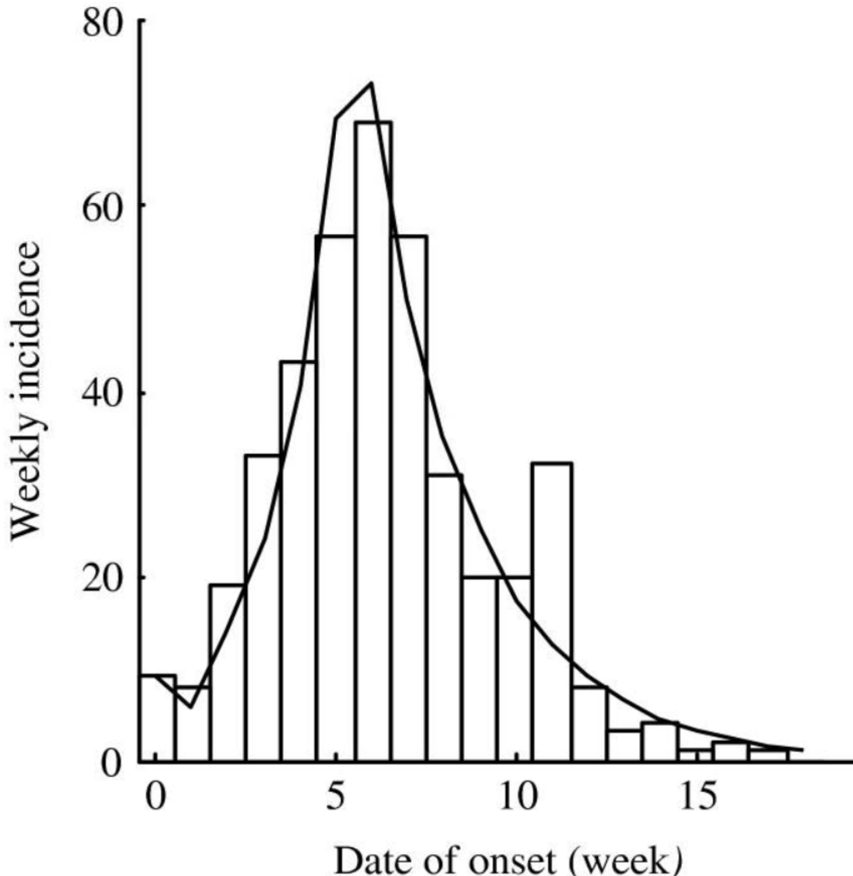
SUMMARY

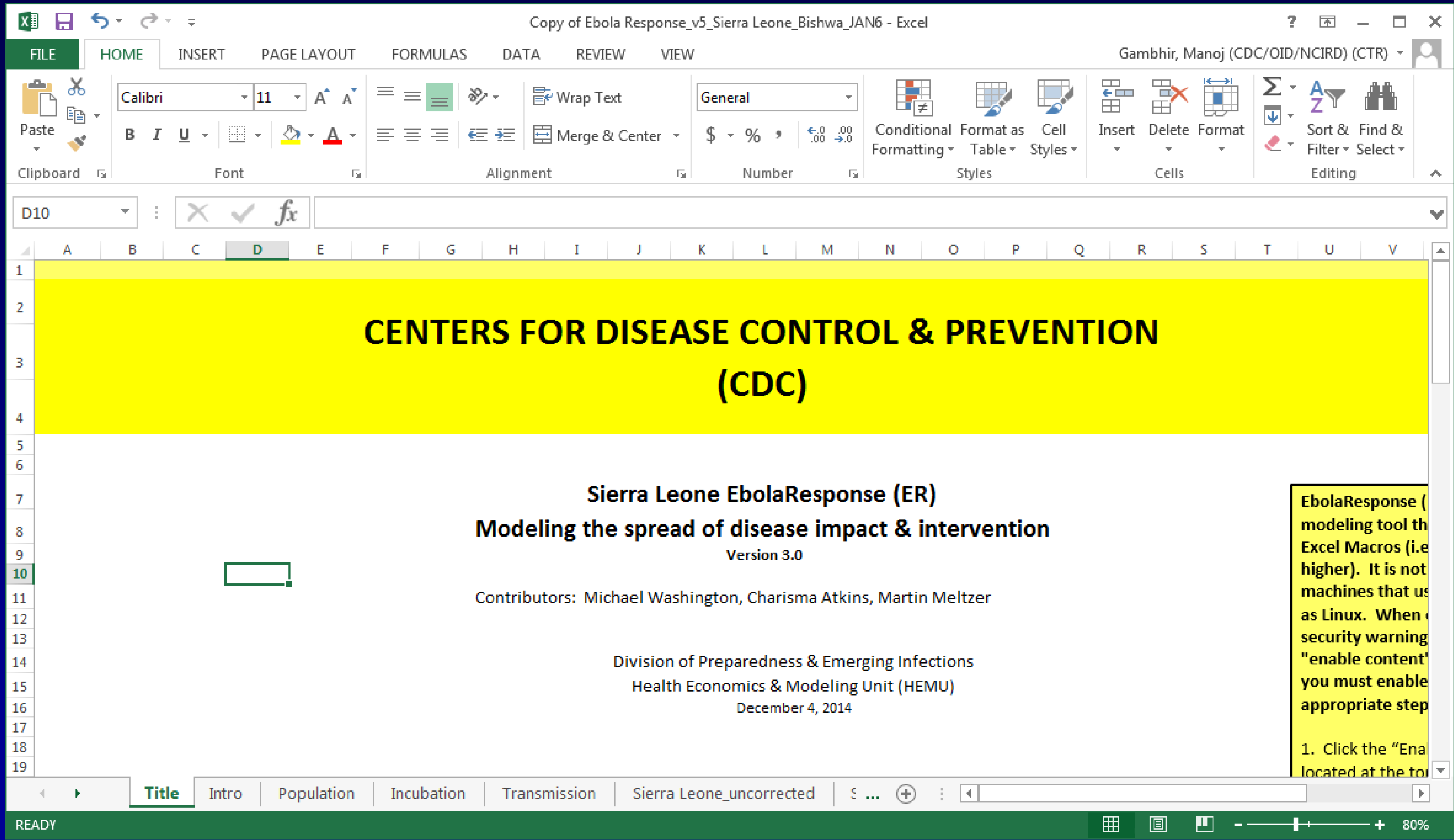
Ebola is a highly lethal virus, which has caused at least 14 confirmed outbreaks in Africa between 1976 and 2006. Using data from two epidemics [in Democratic Republic of Congo (DRC) in 1995 and in Uganda in 2000], we built a mathematical model for the spread of Ebola haemorrhagic fever epidemics taking into account transmission in different epidemiological settings. We estimated the basic reproduction number (R_0) to be 2·7 (95% CI 1·9–2·8) for the 1995 epidemic in DRC, and 2·7 (95% CI 2·5–4·1) for the 2000 epidemic in Uganda. For each epidemic, we quantified transmission in different settings (illness in the community, hospitalization, and traditional burial) and simulated various epidemic scenarios to explore the impact of control interventions on a potential epidemic. A key parameter was the rapid institution of control

DRC (1995)



Uganda (2000)

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Paste
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Merge & Center
Alignment
General
Number
Conditional Formatting
Format as Table
Cell Styles
Styles
Insert
Delete
Format
Cells
Sort & Filter
Find & Select
Editing
D10
CENTERS FOR DISEASE CONTROL & PREVENTION
(CDC)
Sierra Leone EbolaResponse (ER)
Modeling the spread of disease impact & intervention
Version 3.0
Contributors: Michael Washington, Charisma Atkins, Martin Meltzer
Division of Preparedness & Emerging Infections
Health Economics & Modeling Unit (HEMU)
December 4, 2014
EbolaResponse (
modeling tool th
Excel Macros (i.e
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machines that us
as Linux. When
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Incubation
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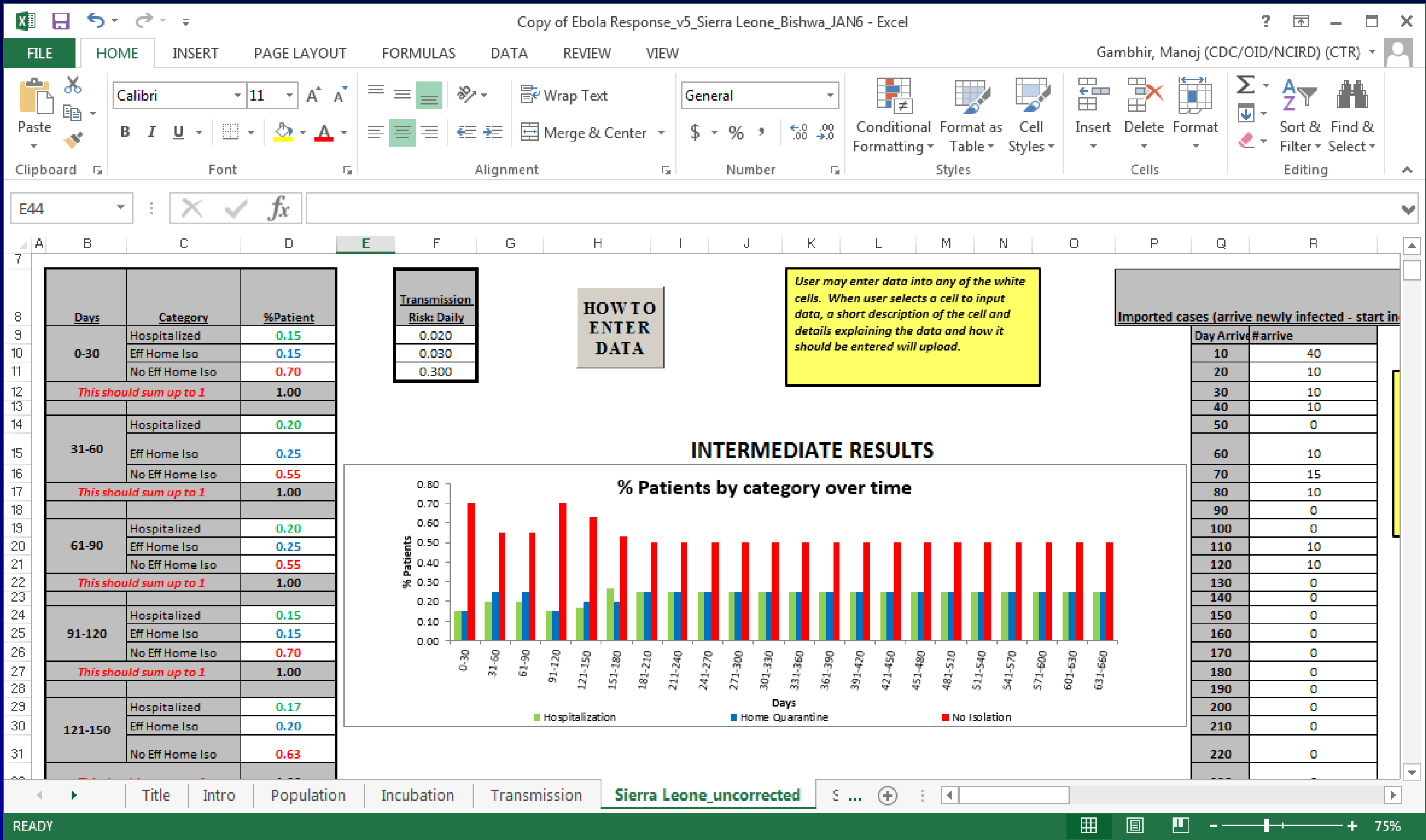
Copy of Ebola Response_v5_Sierra Leone_Bishwa_JAN6 - Excel
Gambhir, Manoj (CDC/OID/NCIRD) (CTR)
Days
Category
%Patient
0-30
Hospitalized 0.15
Eff Home Iso 0.15
No Eff Home Iso 0.70
This should sum up to 1 1.00
31-60
Hospitalized 0.20
Eff Home Iso 0.25
No Eff Home Iso 0.55
This should sum up to 1 1.00
61-90
Hospitalized 0.20
Eff Home Iso 0.25
No Eff Home Iso 0.55
This should sum up to 1 1.00
91-120
Hospitalized 0.15
Eff Home Iso 0.15
No Eff Home Iso 0.70
This should sum up to 1 1.00
121-150
Hospitalized 0.17
Eff Home Iso 0.20
No Eff Home Iso 0.63
Transmission Risk: Daily
0.020
0.030
0.300
HOW TO ENTER DATA
User may enter data into any of the white cells. When user selects a cell to input data, a short description of the cell and details explaining the data and how it should be entered will upload.
INTERMEDIATE RESULTS
% Patients by category over time
% Patients
Days
Hospitalization
Home Quarantine
No Isolation
Imported cases (arrive newly infected - start in
Day Arrive
arrive
10 40
20 10
30 10
40 10
50 0
60 10
70 15
80 10
90 0
100 0
110 10
120 10
130 0
140 0
150 0
160 0
170 0
180 0
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200 0
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220 0
Title
Intro
Population
Incubation
Transmission
Sierra Leone_uncorrected
READY
75%

Centers for Disease Control and Prevention

MMWR

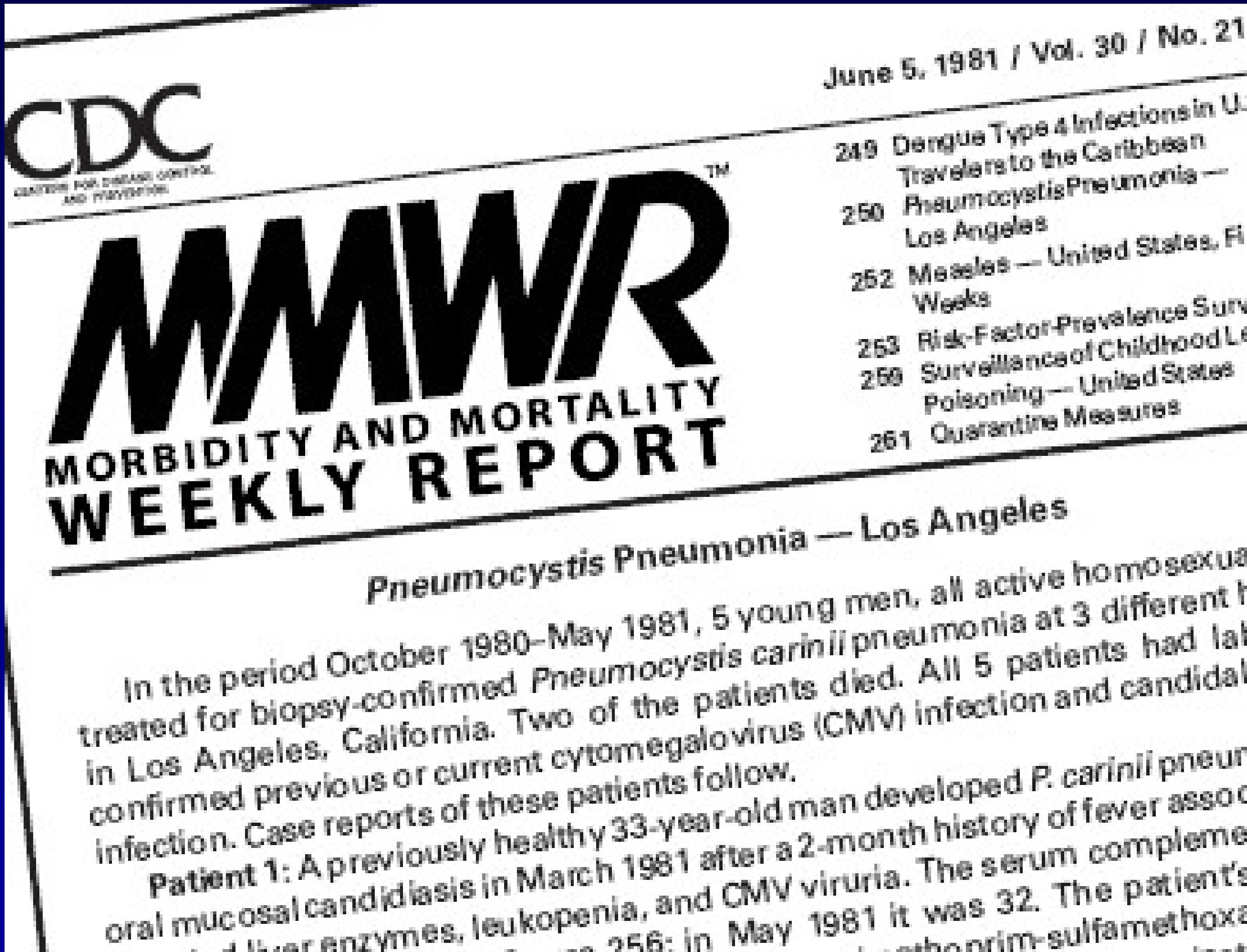
Morbidity and Mortality Weekly Report

Supplement / Vol. 63 / No. 3

September 26, 2014

Estimating the Future Number of Cases in the Ebola Epidemic — Liberia and Sierra Leone, 2014–2015

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention



June 5, 1981 / Vol. 30 / No. 21

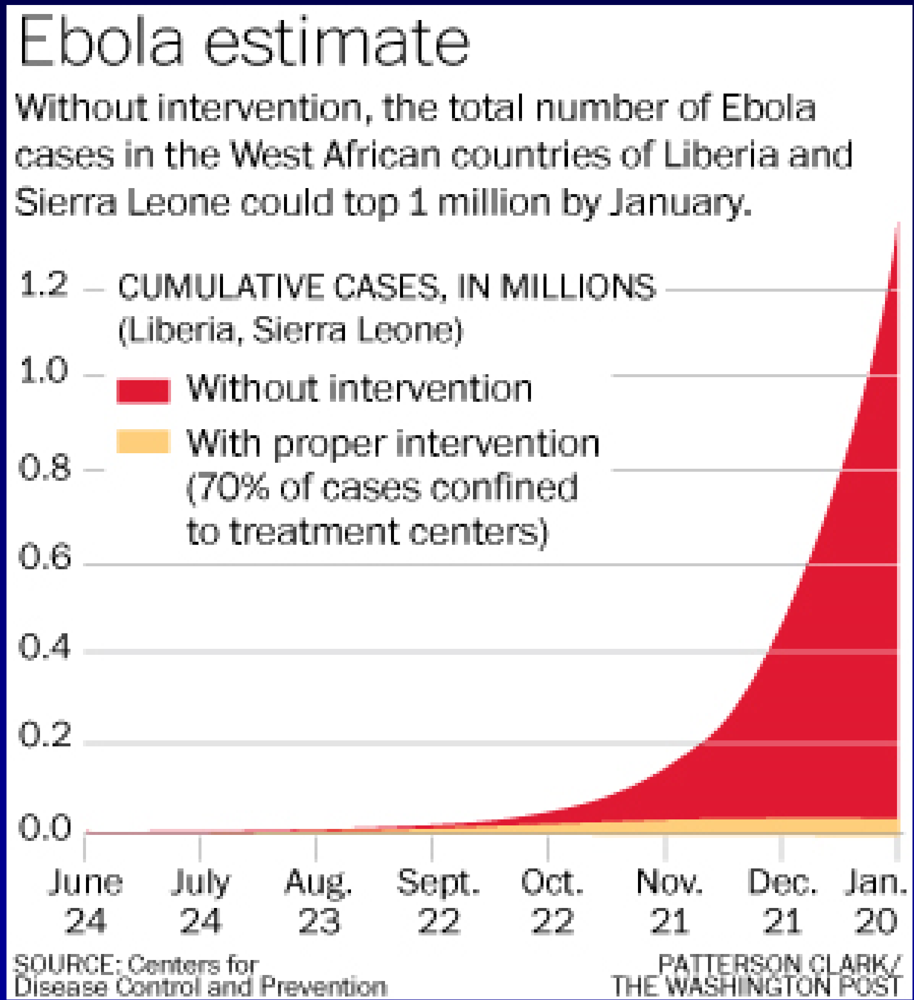
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

MMWR™
MORBIDITY AND MORTALITY WEEKLY REPORT

Pneumocystis Pneumonia — Los Angeles

In the period October 1980–May 1981, 5 young men, all active homosexua
treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different h
in Los Angeles, California. Two of the patients died. All 5 patients had lab
confirmed previous or current cytomegalovirus (CMV) infection and candidal
infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneum
oral mucosal candidiasis in March 1981 after a 2-month history of fever assoc
liver enzymes, leukopenia, and CMV viruria. The serum compleme
256; in May 1981 it was 32. The patient's
trimethoprim-sulfamethoxa


Ebola estimate
Without intervention, the total number of Ebola cases in the West African countries of Liberia and Sierra Leone could top 1 million by January.
CUMULATIVE CASES, IN MILLIONS
(Liberia, Sierra Leone)
Without intervention
With proper intervention
(70% of cases confined
to treatment centers)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
June 24
July 24
Aug. 23
Sept. 22
Oct. 22
Nov. 21
Dec. 21
Jan. 20
SOURCE: Centers for Disease Control and Prevention
PATTERSON CLARK/ THE WASHINGTON POST

Ebola Cases Could Reach 1.4 Million Within Four Months, C.D.C. Estimates

DANIEL BEREHULAK FOR THE NEW YORK TIMES

A Red Cross team removed the body of a woman believed to have died of Ebola in Monrovia, Liberia, last week. Officials urge caution in handling victims' bodies.

Worst-Case Scenario Can Still Be Avoided

By DENISE GRADY

Yet another set of ominous projections about the Ebola epidemic in West Africa was released Tuesday, in a report from the Centers for Disease Control and Prevention that gave worst- and best-case estimates for Liberia and Sierra Leone based on computer modeling.

In the worst-case scenario, the two countries could have a total of 21,000 cases of Ebola by Sept. 30 and 1.4 million cases by Jan. 20 if the disease keeps spreading without effective methods to contain it. These figures take into account the fact that many cases go undetected, and estimate that there are actually 2.5 times as many as reported.

In the best-case model, the epidemic in both countries would be "almost ended" by Jan. 20, the report said. Success would require conducting safe funerals at which no one touches the bodies, and treating 70 percent of patients in settings that reduce the risk of transmission. The report said the proportion of patients now in such settings was about 18 percent in Liberia and 40 percent in Sierra Leone.

The caseload projections are based on data from August, but Dr. Thomas R. Frieden, the C.D.C. director, said the situation appeared to have improved since then because more aid had begun to reach the region.

"My gut feeling is, the actions we're taking now are going to make that worst-case scenario not come to pass," Dr. Frieden said in a telephone interview. "But it's important to understand that it could happen."

Outside experts said the modeling figures were in line with estimates by others in the field.

"It's a nice job," said Ira Longini, a professor of biostatistics at the University of Florida who has also done computer modeling of

low compared with those generated by other models. He said that if some of the latest data from the World Health Organization is plugged into the C.D.C. model, "the very large numbers of estimated cases are, unfortunately, even larger."

The current official case count is 5,843, including 2,803 deaths, according to the W.H.O.

from the C.D.C., but the W.H.O. report also noted that many cases were unreported and said that without effective help, the three most affected countries would soon be reporting thousands of cases and deaths per week. It said its projections were similar to those from the C.D.C.

The W.H.O. report also raised, for the first time, the possibility

when those hospitals would be ready, or who would staff them.

Dr. Frieden said the Defense Department had already delivered parts of a 25-bed unit that would soon be set up to treat health workers who become infected, a safety measure he said was important to help encourage health professionals to volunteer. He said that more aid groups

He added, "If even the medium case comes to pass, with, say, 700,000 cases by January, the epidemic will quickly overwhelm the capabilities that the U.S. plans to send."

The W.H.O. reported that a new center had just opened in Monrovia, the Liberian capital, with 120 beds for treatment and 30 for triage. Patients were al-

"Where are they going to go?" he said.

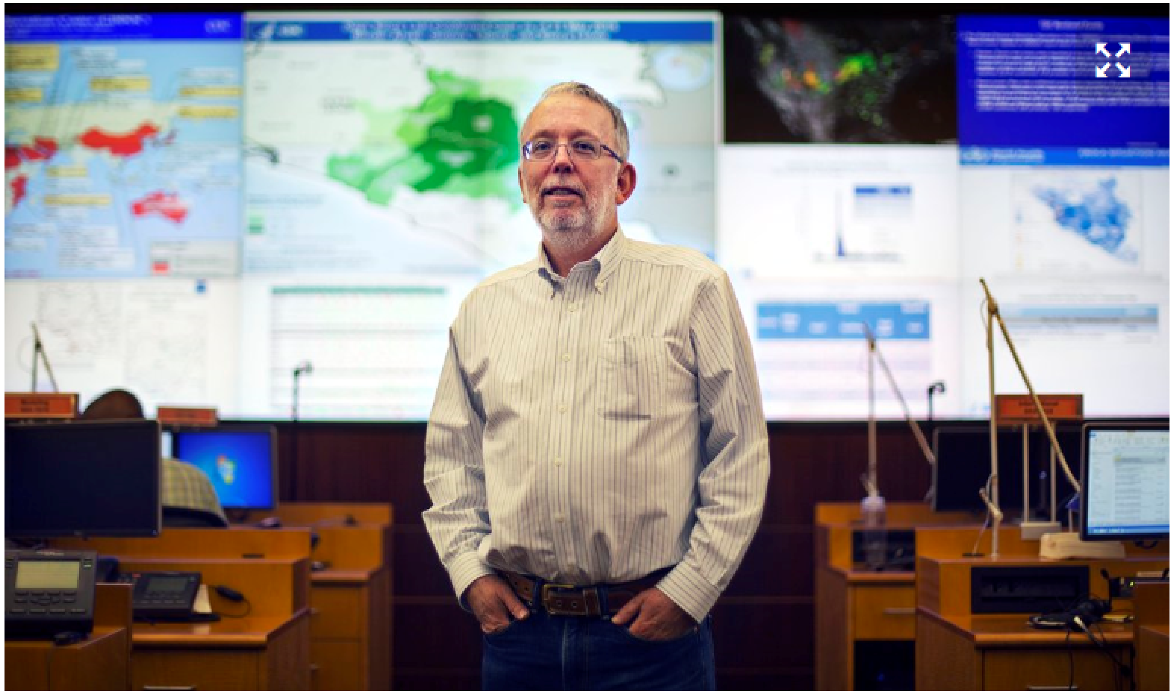
Though providing home-care kits may seem like a pragmatic approach, some public health authorities said they were no substitute for beds in isolation or containment wards.

But Dr. Frieden said that home care had been used to help stamp out smallpox in Africa in the 1960s. The caregivers were often

Health | Nation | Nation & World

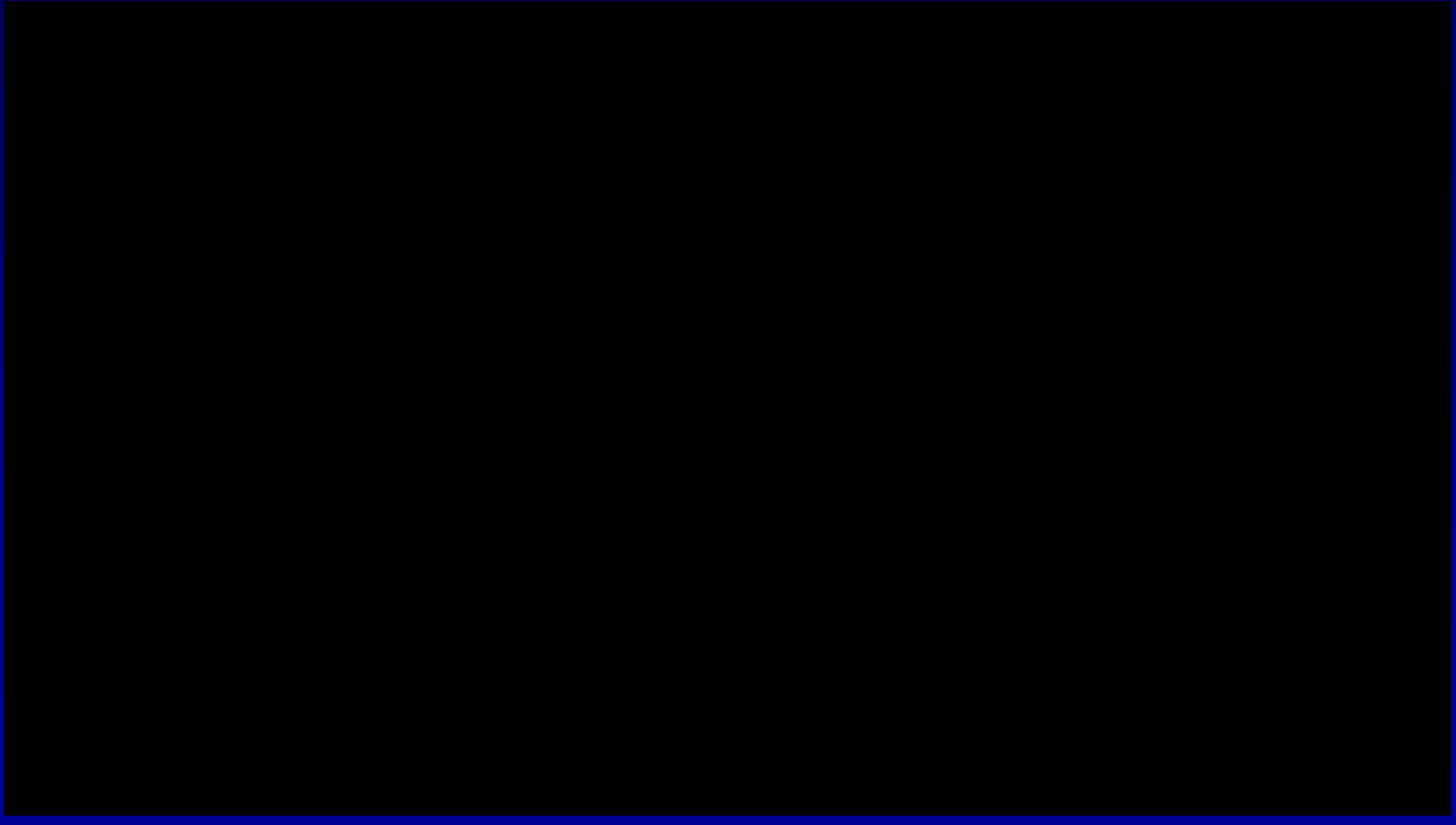
CDC's overblown estimate of Ebola outbreak draws criticism

Originally published August 1, 2015 at 2:24 pm | *Updated August 1, 2015 at 5:51 pm*



Martin Meltzer, standing in the Emergency Operations Center at the Centers for Disease Control and Prevention in Atlanta, is a disease modeler for the agency. (David Goldman/AP)

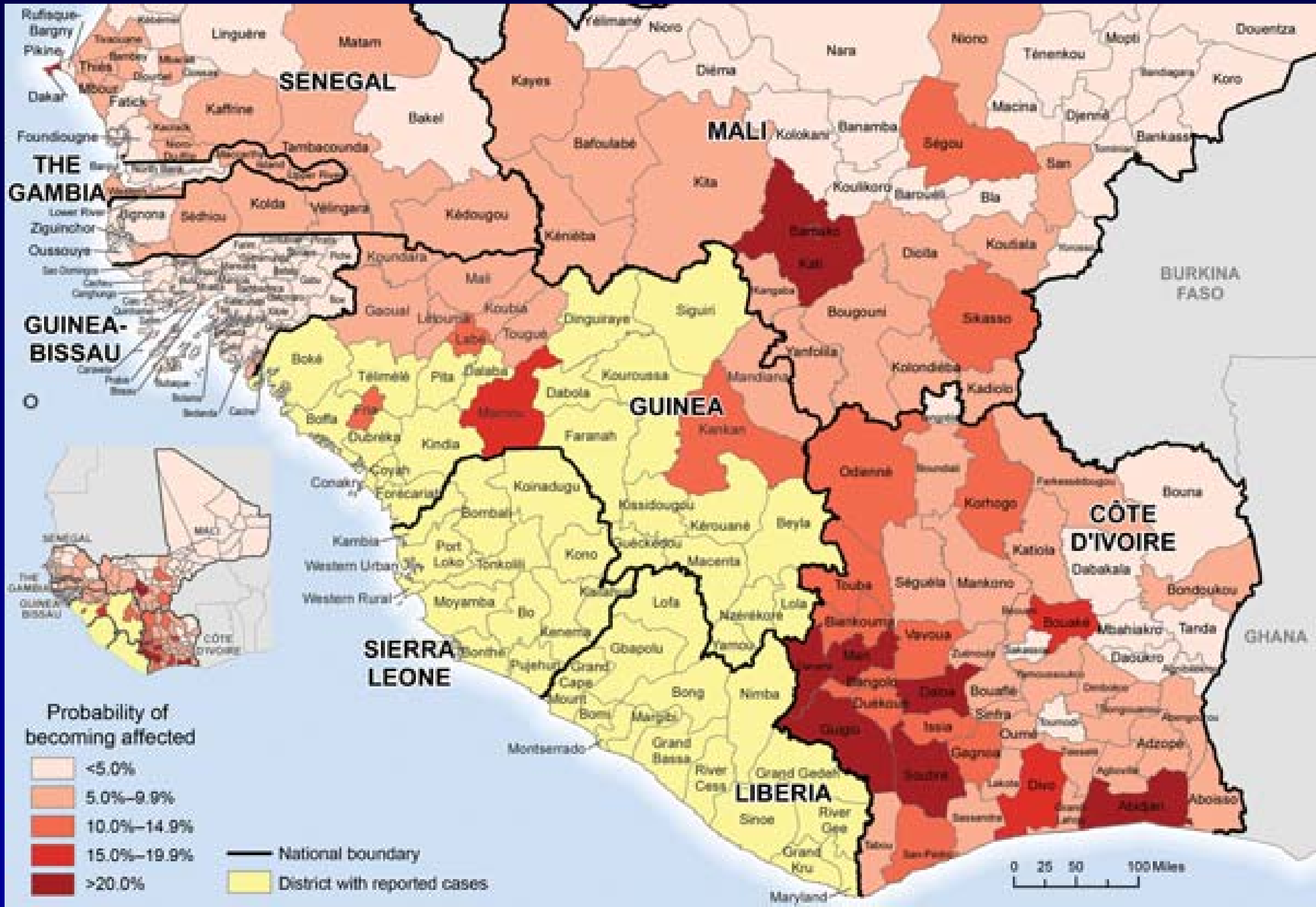
Disease modelers use math to try to provide a more precise picture of a certain situation or to predict how the situation will change, and have become critical in the world of infectious diseases. But the accuracy — or inaccuracy — of such models is increasingly a talking point.



Questions from leadership

Where should ETUs be constructed next?

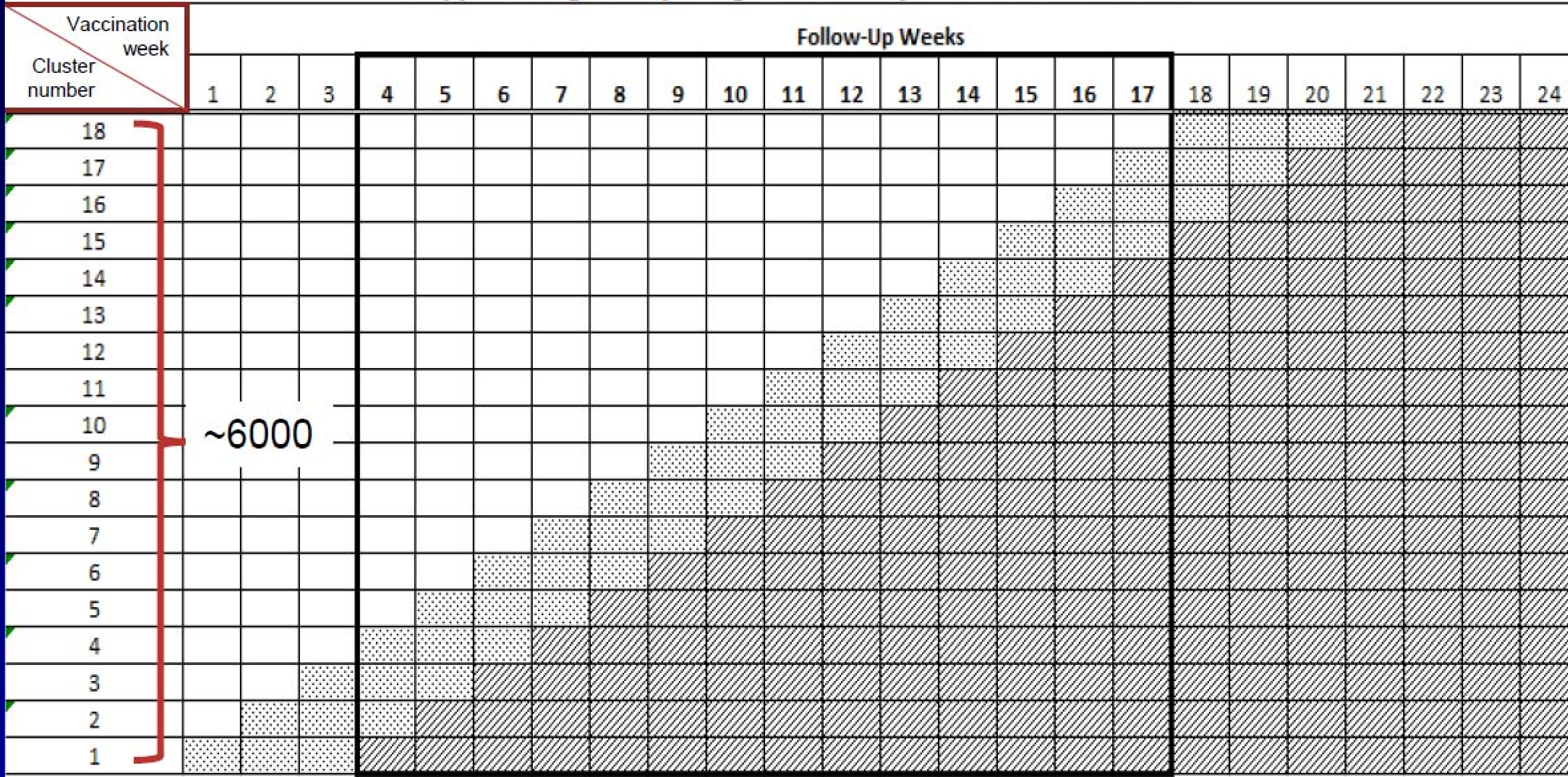
Which neighboring countries are at the highest risk?


SENEGAL
MALI
THE GAMBIA
GUINEA-BISSAU
GUINEA
SIERRA LEONE
LIBERIA
CÔTE D'IVOIRE
BURKINA FASO
GHANA
Probability of becoming affected
<5.0%
5.0%–9.9%
10.0%–14.9%
15.0%–19.9%
>20.0%
National boundary
District with reported cases
0 25 50 100 Miles

Questions from leadership

What's a viable vaccine trial design during the outbreak?

Stepped wedge study design - 18 week phase-in of vaccination



type of person-time		proportions
unvaccinated		0.50
vaccinated, seroconverting		n/a
vaccinated, seroconvered		0.50

Bolded square highlights follow-up time usable for efficacy analyses, excluding 21 day sero-conversion time. Usable follow-up weeks contain both unvaccinated and vaccinated cohort time.

Example Vaccination Groups: (1) facility HCW such as doctors, nurses, phlebotomists (2) facility support such as cooking and food delivery, housekeeping, sanitation (3) ambulance teams (4) burial teams. Each of 3 shifts is a treated as a different Vaccination Group. Vaccination Groups and shifts are distributed evenly across Vaccination Weeks, with a vaccination weeks assigned at random.

Specific questions

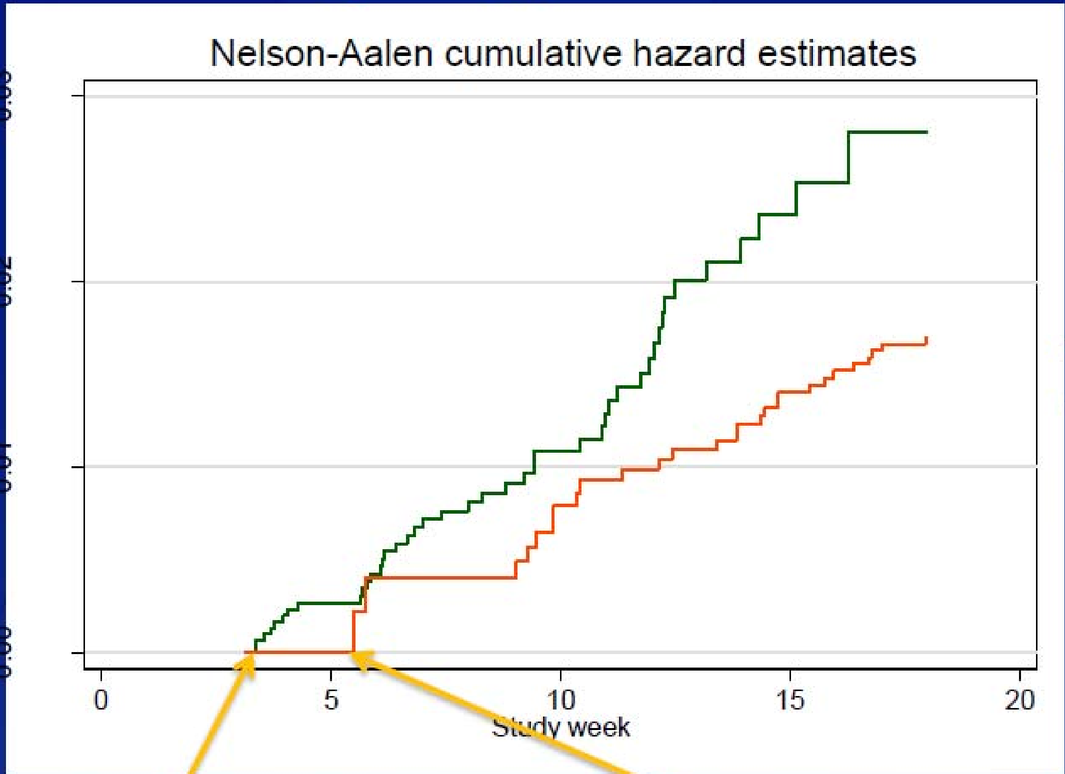
Will an e.g. Cox Proportional Hazards approach be able to account for:

-Declining background disease risk

-Clustering of disease risk

-Healthy vaccinee effect

Example simulation (single model run):



Unvaccinated: 43 cases
0.81 cases/person-month

Vaccinated: 27 cases
0.51 cases/person-month

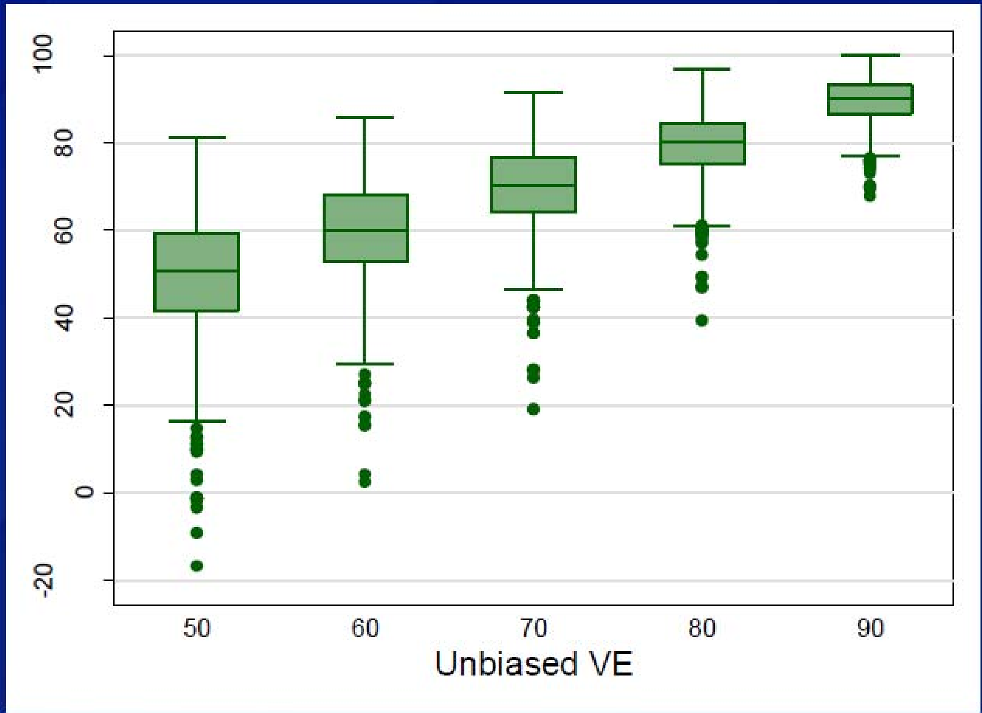
No cases included until first vaccinee reaches end of seroconversion period

Longer lag to accrue vaccinated cases

Hazard ratio:
0.55 (0.32 – 0.96)
Vaccine Efficacy:
45% (4% -68%)

No bias: Predicted VE

1000 runs at each VE input (range 50% to 90%)



Statistical power and validity of Ebola vaccine trials in Sierra Leone: a simulation study of trial design and analysis

Steven E Bellan, Juliet R C Pulliam, Carl A B Pearson, David Champredon, Spencer J Fox, Laura Skrip, Alison P Galvani, Manoj Gambhir, Ben A Lopman, Travis C Porco, Lauren Ancel Meyers, Jonathan Dushoff

Summary

Background Safe and effective vaccines could help to end the ongoing Ebola virus disease epidemic in parts of west Africa, and mitigate future outbreaks of the virus. We assess the statistical validity and power of randomised controlled trial (RCT) and stepped-wedge cluster trial (SWCT) designs in Sierra Leone, where the incidence of Ebola virus disease is spatiotemporally heterogeneous, and is decreasing rapidly.

Methods We projected district-level Ebola virus disease incidence for the next 6 months, using a stochastic model fitted to data from Sierra Leone. We then simulated RCT and SWCT designs in trial populations comprising geographically distinct clusters at high risk, taking into account realistic logistical constraints, and both individual-level and cluster-level variations in risk. We assessed false-positive rates and power for parametric and non-parametric analyses of simulated trial data, across a range of vaccine efficacies and trial start dates.

Findings For an SWCT, regional variation in Ebola virus disease incidence trends produced increased false-positive rates (up to 0·15 at α=0·05) under standard statistical models, but not when analysed by a permutation test, whereas analyses of RCTs remained statistically valid under all models. With the assumption of a 6-month trial starting on Feb 18, 2015, we estimate the power to detect a 90% effective vaccine to be between 49% and 89% for an RCT, and between 6% and 26% for an SWCT, depending on the Ebola virus disease incidence within the trial population. We estimate that a 1-month delay in trial initiation will reduce the power of the RCT by 20% and that of the SWCT by 49%.

Interpretation Spatiotemporal variation in infection risk undermines the statistical power of the SWCT. This variation also undercuts the SWCT's expected ethical advantages over the RCT, because an RCT, but not an SWCT, can prioritise vaccination of high-risk clusters.

Lancet Infect Dis 2015

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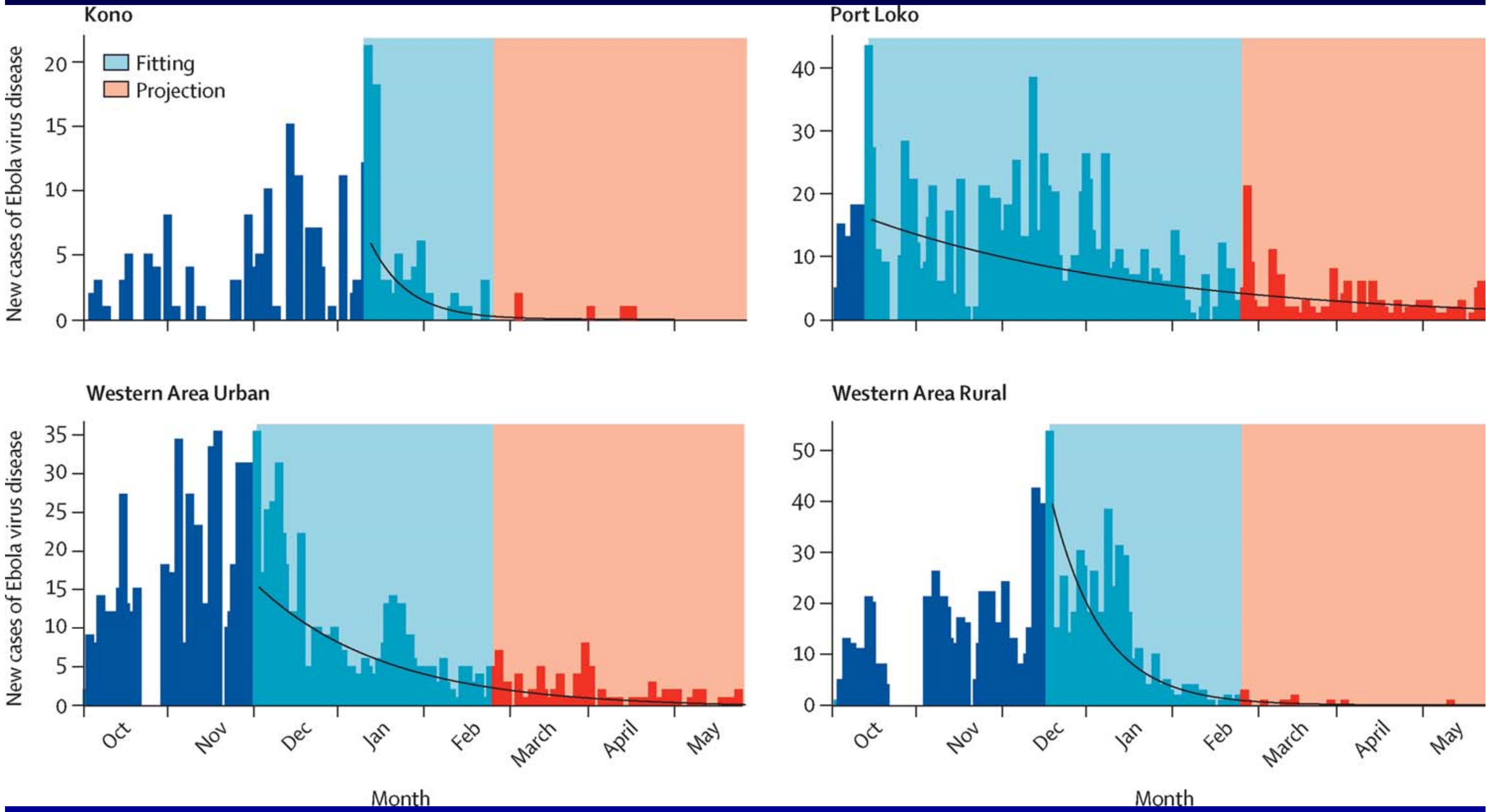
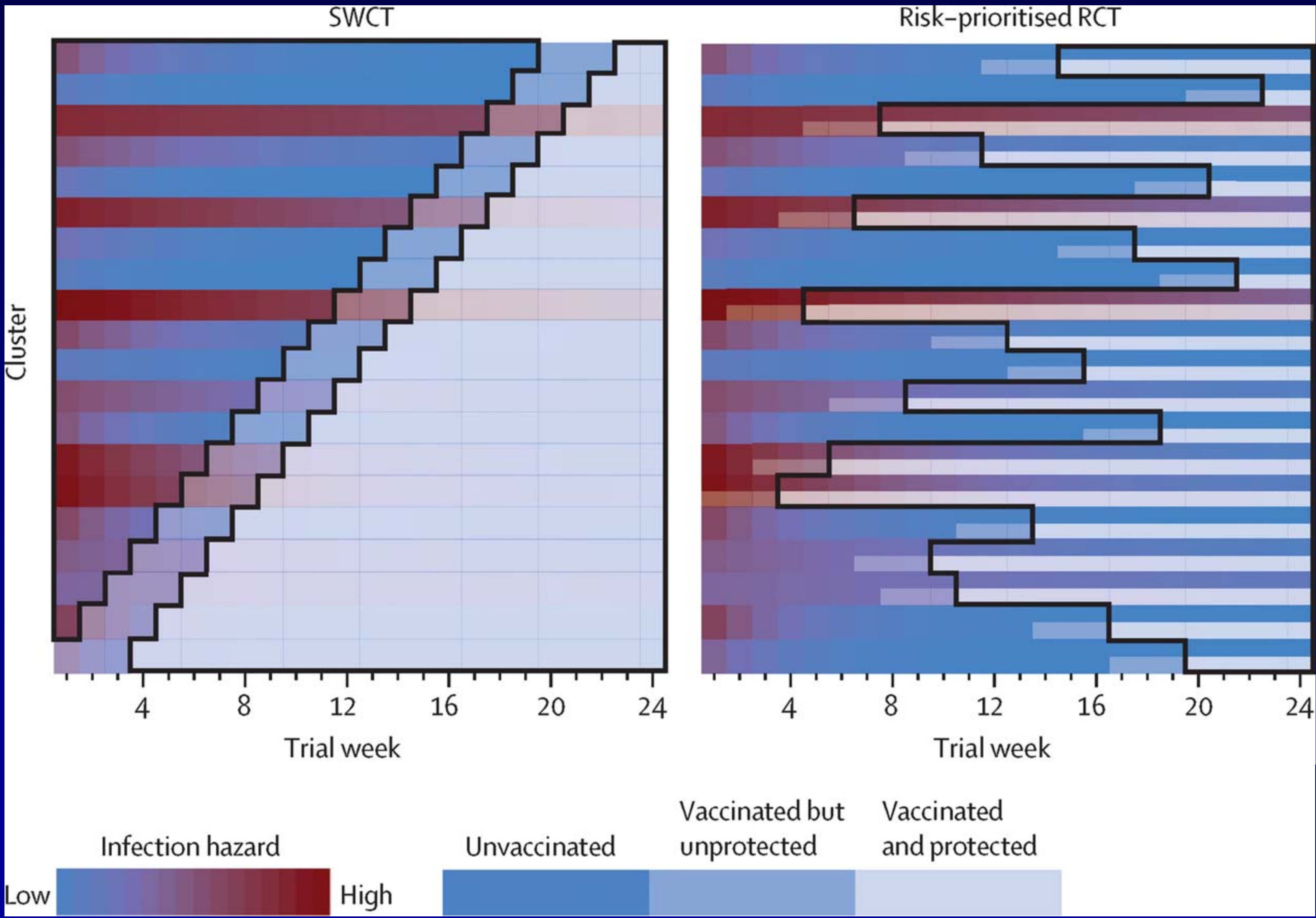
See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(15)70159-3

Center for Computational Biology and Bioinformatics (S E Bellan PhD) **and Department of Integrative Biology** (S J Fox BS, Prof L A Meyers PhD), **The University of Texas at Austin, Austin, TX, USA; Department of Biology** (J R C Pulliam PhD) **and Emerging Pathogens Institute** (J R C Pulliam, C A B Pearson PhD), **University of Florida, Gainesville, FL, USA; School of Computational Science and Engineering** (D Champredon MSc) **and Department of Biology** (J Dushoff PhD), **McMaster University, Hamilton, ON**


Kono
Fitting
Projection
Port Loko
Western Area Urban
Western Area Rural
New cases of Ebola virus disease
Oct
Nov
Dec
Jan
Feb
March
April
May
Month



SWCT
Risk–prioritised RCT
Cluster
4
8
12
16
20
24
Trial week
Infection hazard
Low
High
Unvaccinated
Vaccinated but unprotected
Vaccinated and protected

The work of other groups

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ebola Virus Disease in West Africa — The First 9 Months of the Epidemic and Forward Projections

WHO Ebola Response Team*

ABSTRACT

BACKGROUND

On March 23, 2014, the World Health Organization (WHO) was notified of an outbreak of Ebola virus disease (EVD) in Guinea. On August 8, the WHO declared the epidemic to be a “public health emergency of international concern.”

METHODS

By September 14, 2014, a total of 4507 probable and confirmed cases, including 2296 deaths from EVD (Zaire species) had been reported from five countries in West Africa — Guinea, Liberia, Nigeria, Senegal, and Sierra Leone. We analyzed a detailed subset of data on 3343 confirmed and 667 probable Ebola cases collected in Guinea, Liberia, Nigeria, and Sierra Leone as of September 14.

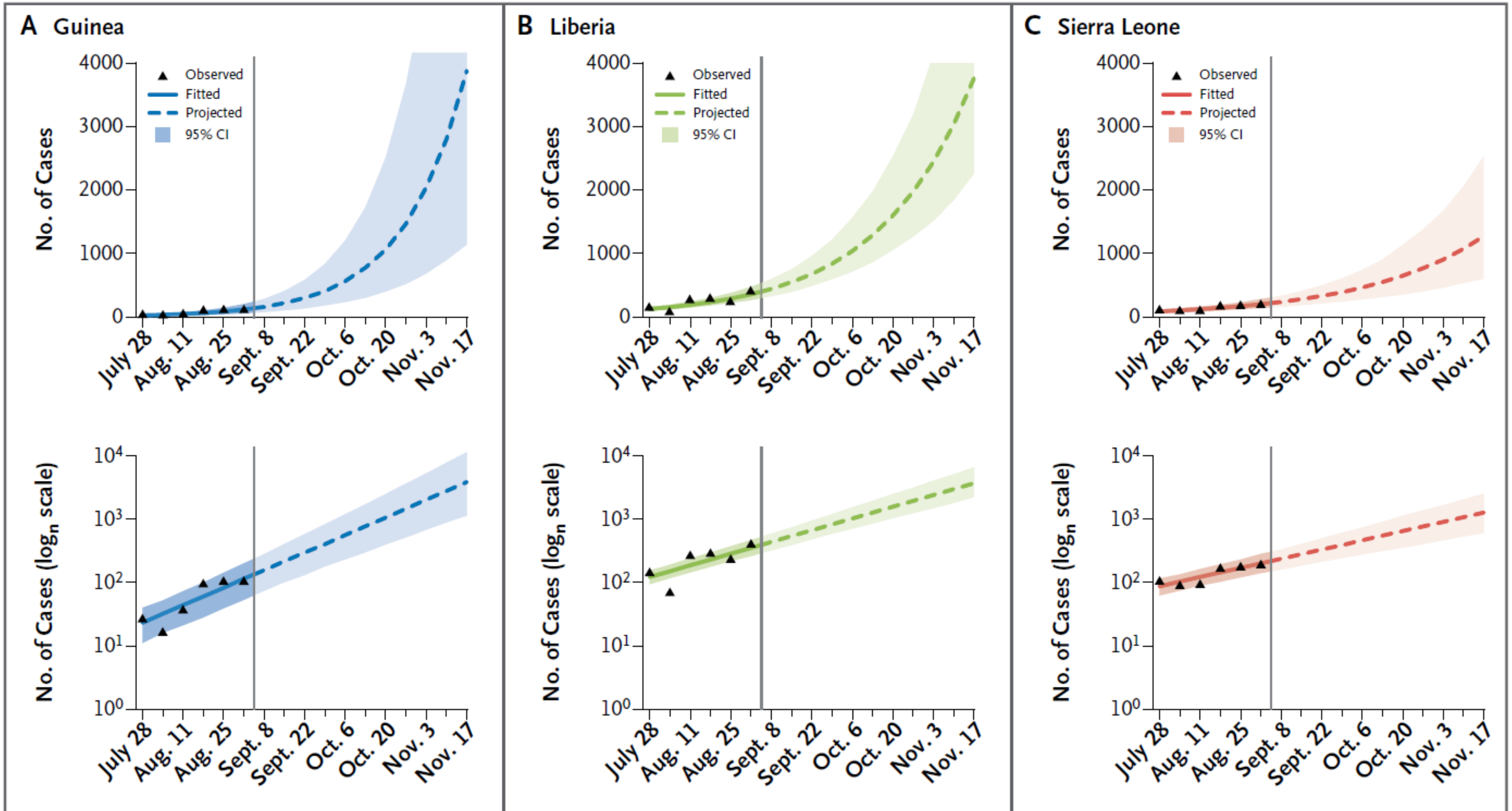


Figure 4. Observed and Projected Case Incidence.

Observed and projected weekly case incidence in Guinea (Panel A), Liberia (Panel B), and Sierra Leone (Panel C) are shown on linear (upper panels) and logarithmic (lower panels) scales

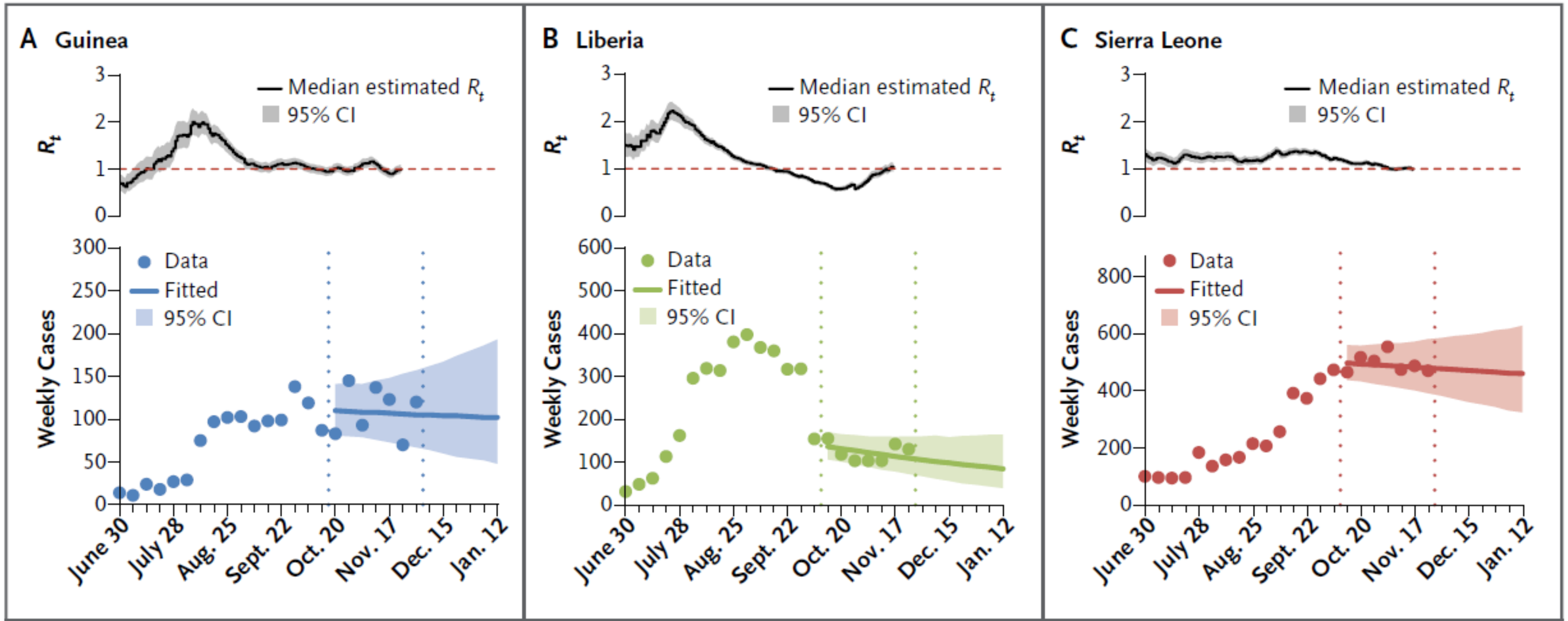


Figure 1. Case Reproduction Numbers and Weekly Incidence in Guinea, Liberia, and Sierra Leone.

Shown are the estimated case reproduction number (R_t) over time (upper panels) and the observed and projected weekly incidence (lower panels) of confirmed and probable cases of Ebola virus disease (EVD), according to the date of symptom onset, from the week beginning June 30, 2014, until the week beginning January 12, 2015, on the basis of data reported through December 7 for Guinea and November 30 for Liberia and Sierra Leone. The projections shown in the lower panels were generated from R_t estimates derived from data on case incidence (daily situation reports) for the 7 weeks through December 7 for Guinea and November 30 for Liberia and Sierra Leone (the time period delineated by the vertical dotted lines).

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Assessing the International Spreading Risk Associated with the 2014 West African Ebola Outbreak

SEPTEMBER 2, 2014 · RESEARCH

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REVISIONS

This article is either a revised version or has previous revisions

Edition 1 - September 2, 2014

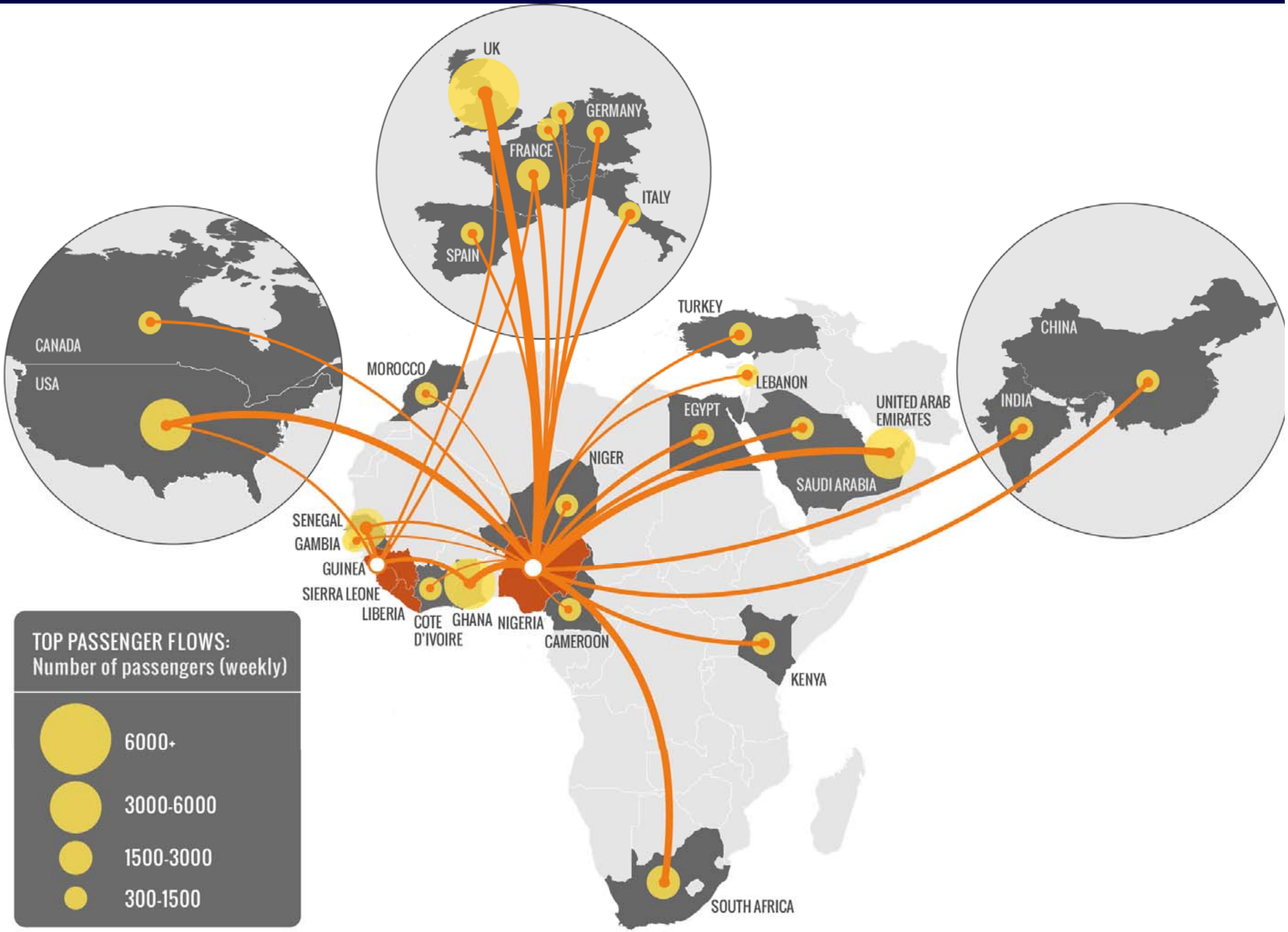
AUTHORS

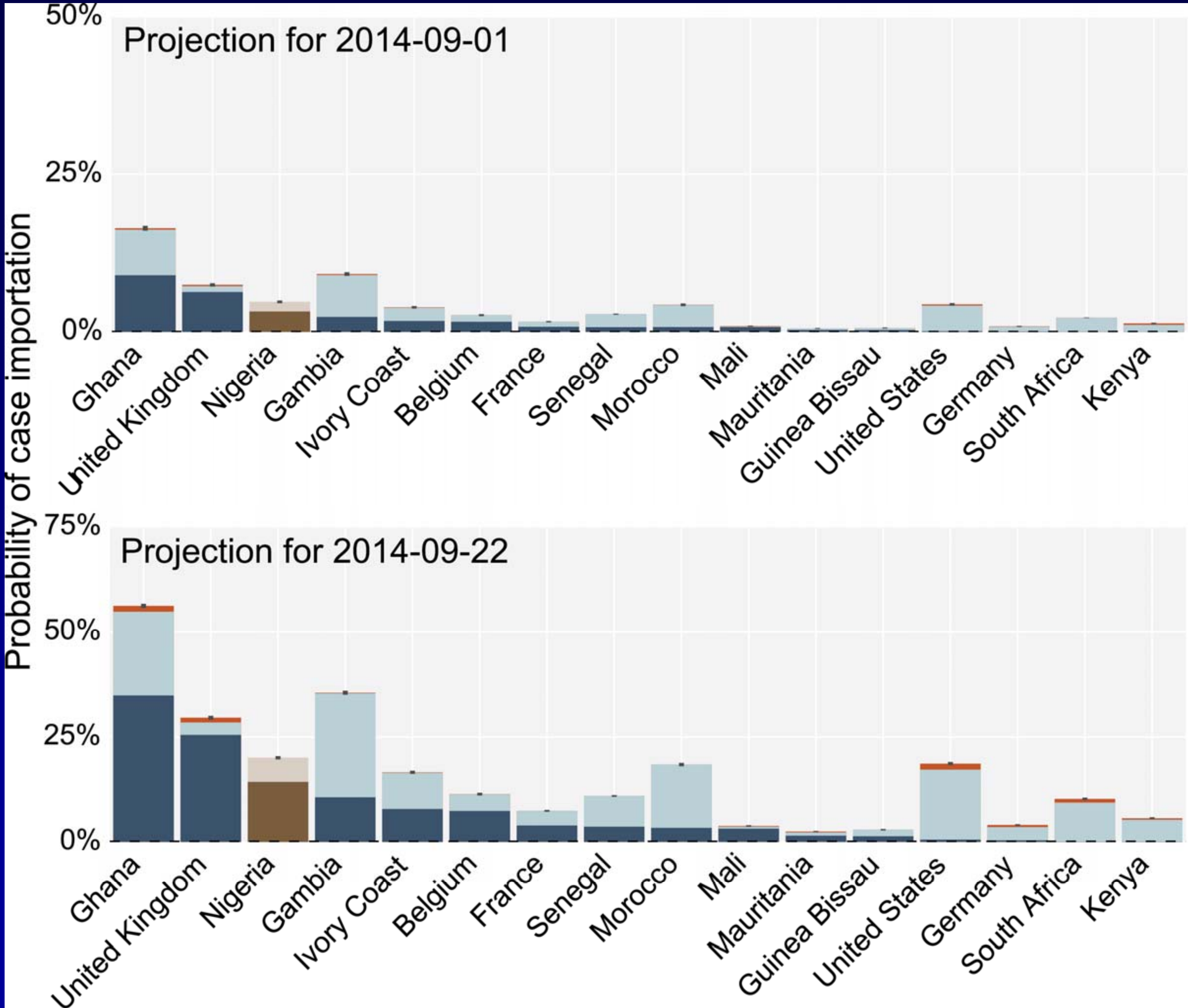
Marcelo F. C. Gomes Ana Pastore y Piontti Luca Rossi Dennis Chao Ira Longini M. Elizabeth Halloran
Alessandro Vespignani

ABSTRACT

Background: The 2014 West African Ebola Outbreak is so far the largest and deadliest recorded in history. The affected countries, Sierra Leone, Guinea, Liberia, and Nigeria, have been struggling to contain and to mitigate the outbreak. The ongoing rise in confirmed and suspected cases, 2615 as of 20 August 2014, is considered to increase the risk of international dissemination, especially because the epidemic is now affecting cities with major commercial airports.

Method: We use the Global Epidemic and Mobility Model to generate stochastic, individual based simulation


UK
GERMANY
FRANCE
ITALY
SPAIN
CANADA
USA
MOROCCO
TURKEY
LEBANON
EGYPT
UNITED ARAB EMIRATES
SAUDI ARABIA
CHINA
INDIA
NIGER
SENEGAL
GAMBIA
GUINEA
SIERRA LEONE
LIBERIA
COTE D'IVOIRE
GHANA
NIGERIA
CAMEROON
KENYA
SOUTH AFRICA
TOP PASSENGER FLOWS:
Number of passengers (weekly)
6000+
3000-6000
1500-3000
300-1500



Probability of case importation
Projection for 2014-09-01
50%
25%
0%
Ghana
United Kingdom
Nigeria
Gambia
Ivory Coast
Belgium
France
Senegal
Morocco
Mali
Mauritania
Guinea Bissau
United States
Germany
South Africa
Kenya
Projection for 2014-09-22
75%
50%
25%
0%
Ghana
United Kingdom
Nigeria
Gambia
Ivory Coast
Belgium
France
Senegal
Morocco
Mali
Mauritania
Guinea Bissau
United States
Germany
South Africa
Kenya

Lessons

Modelling’s major contribution comes very early (when sit. awareness is poor)

Embed within a public health agency

Academic publication often isn’t useful during an emergency (but is afterward)

Thank you for your time!

Special thanks to:

David Swerdlow
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Martin Meltzer
Rebekah Borse
Isaac Fung
Neil Ferguson
Simon Cauchemez
Christl Donnelly
Tom Clark
Ben Lopman
Amy Pinsent

+ many others

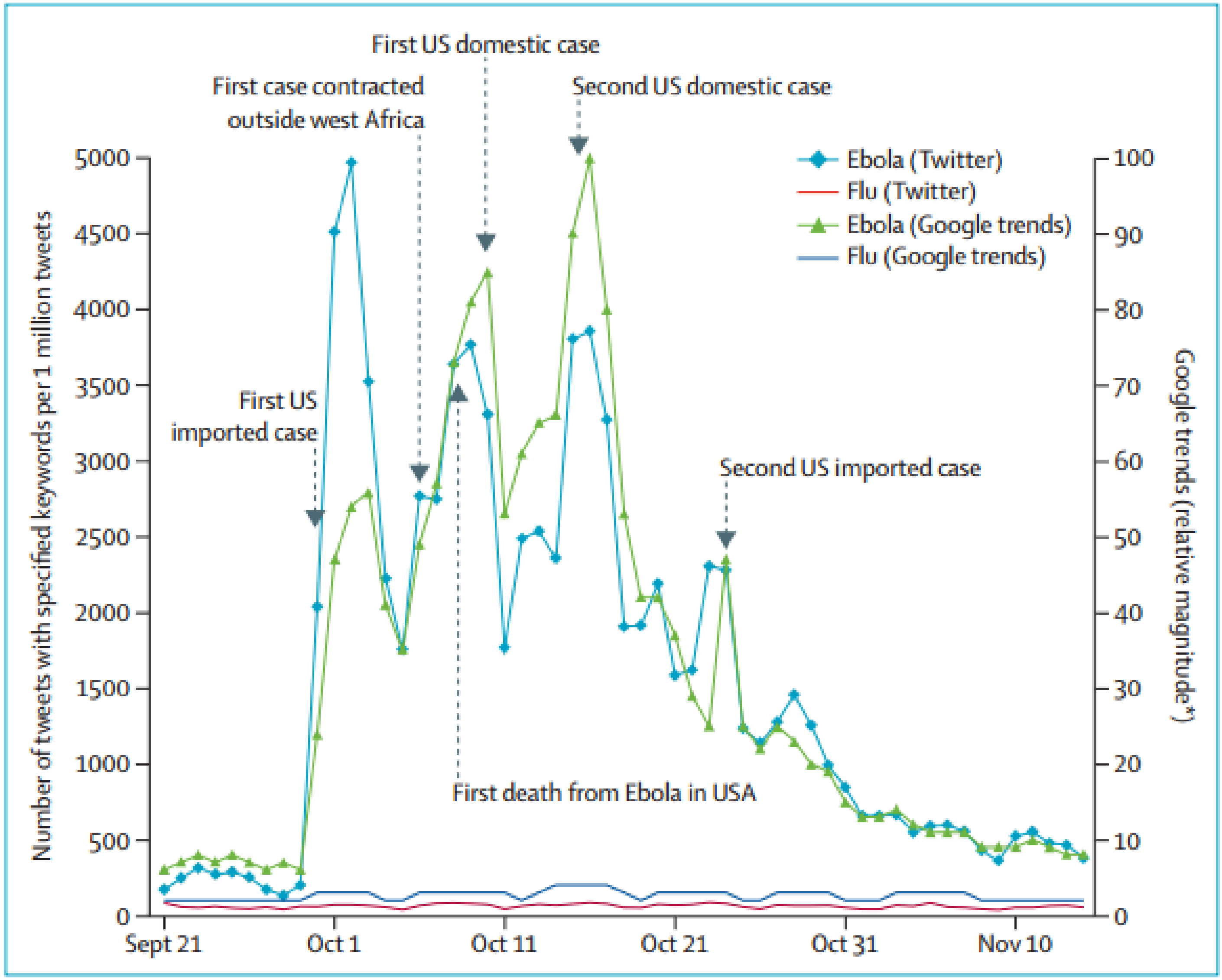
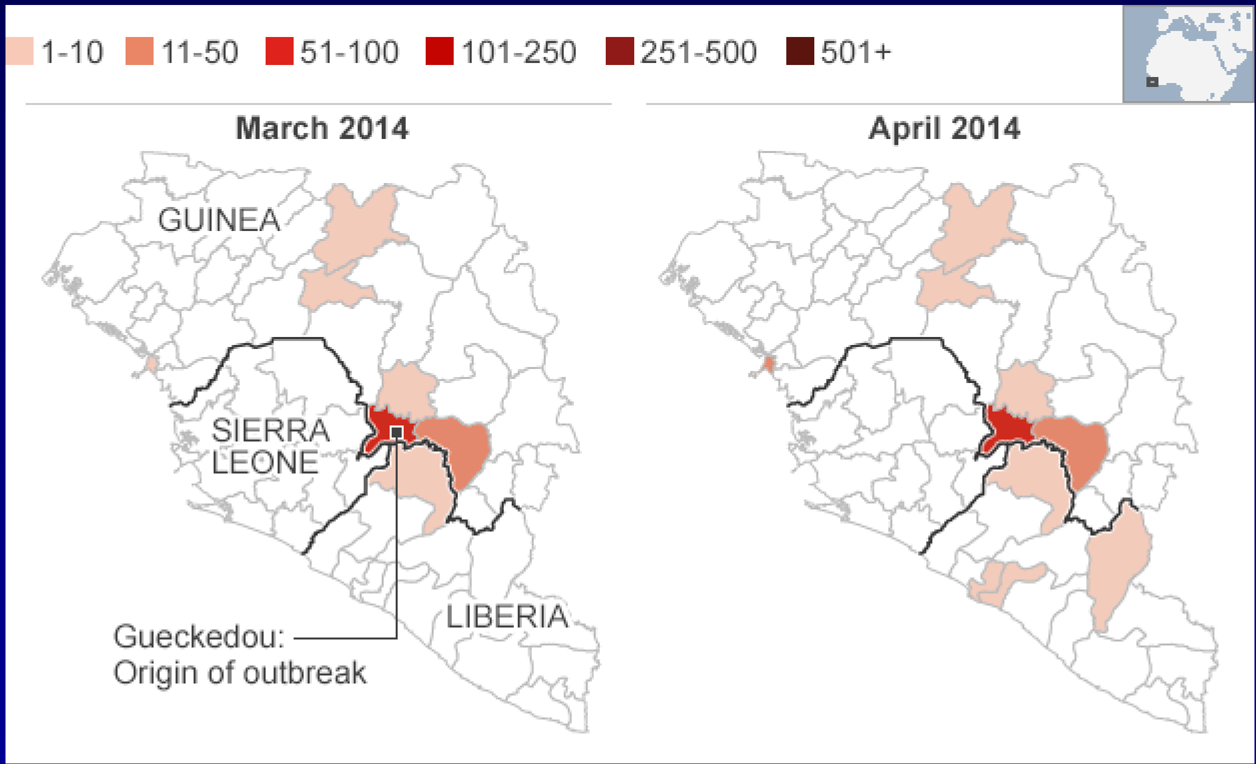
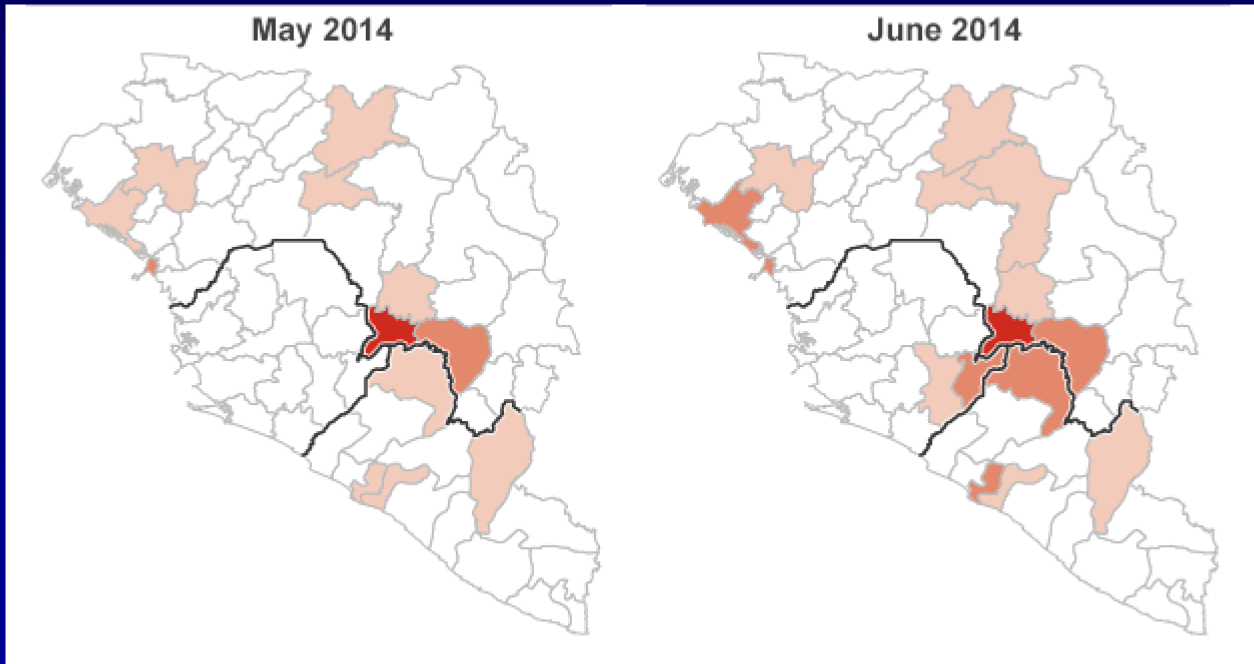
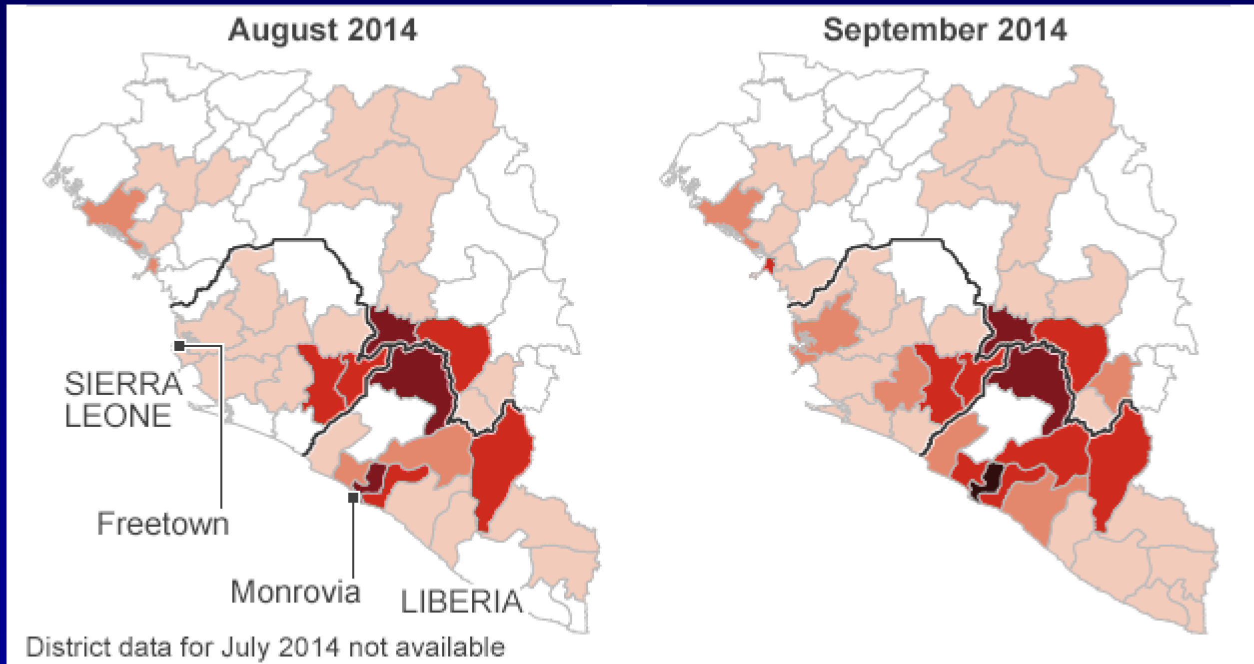


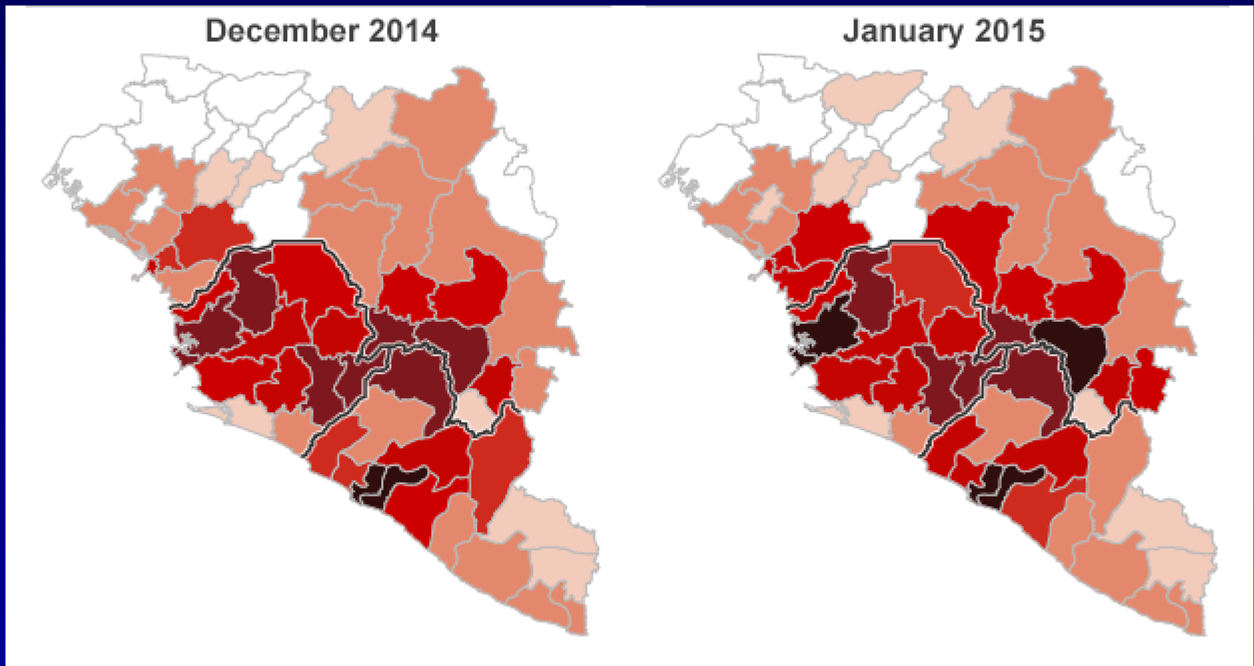
Figure: **Temporal trends on Twitter and Google about Ebola and influenza (flu) before, during, and after Ebola cases in the USA, September to November, 2014**

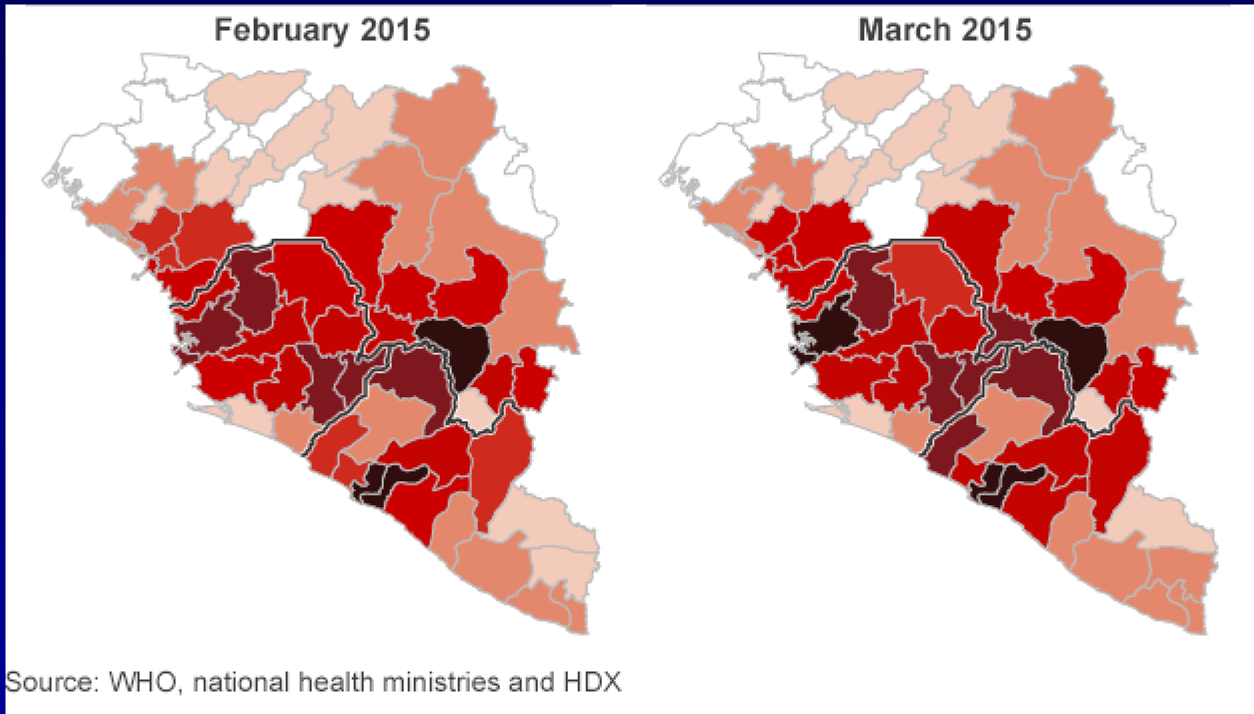
*Numbers are relative to the highest number of searches done on Google (for Ebola on Oct 16).

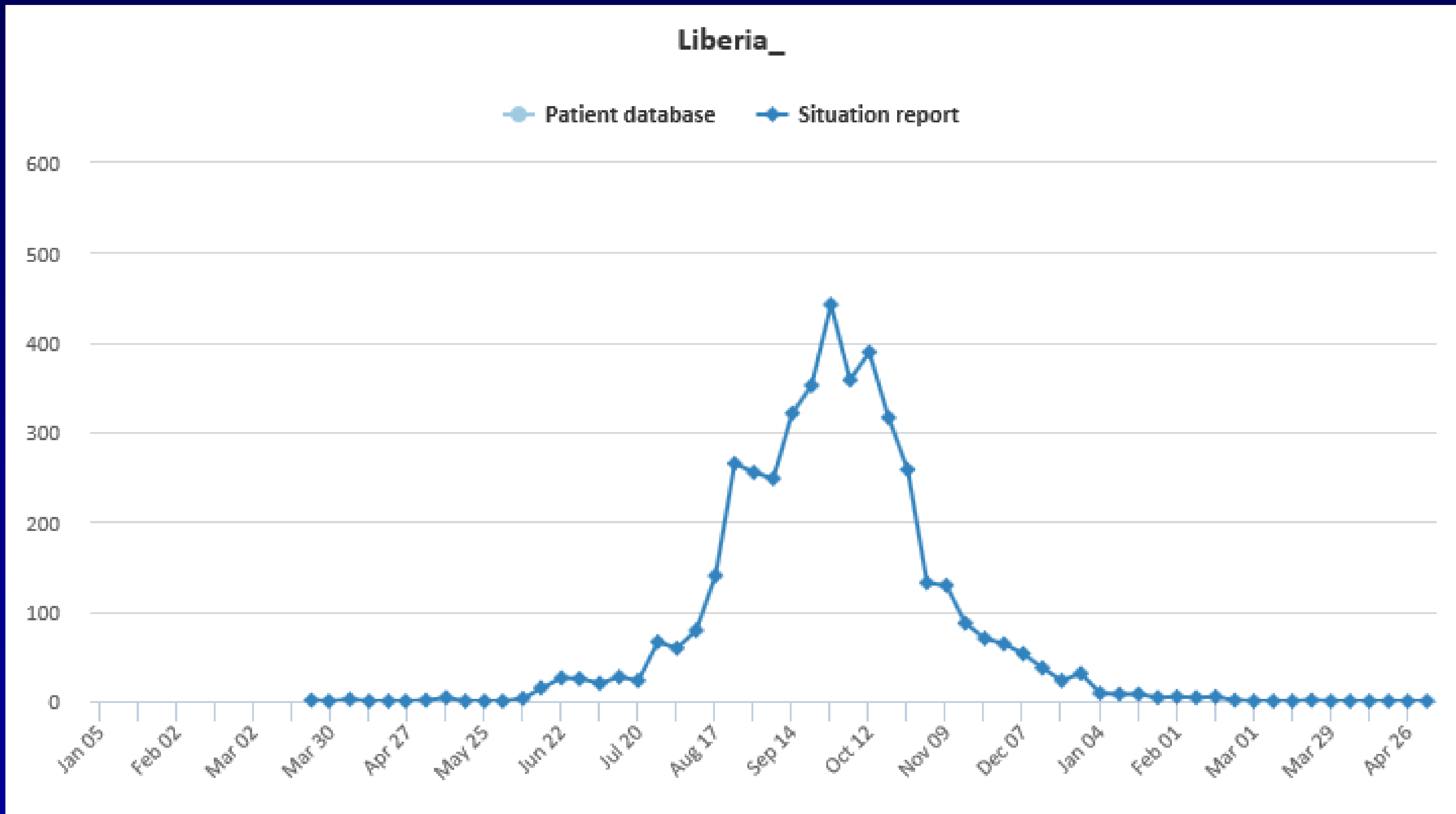

1-10
11-50
51-100
101-250
251-500
501+
March 2014
April 2014
GUINEA
SIERRA LEONE
LIBERIA
Gueckedou:
Origin of outbreak


May 2014
June 2014

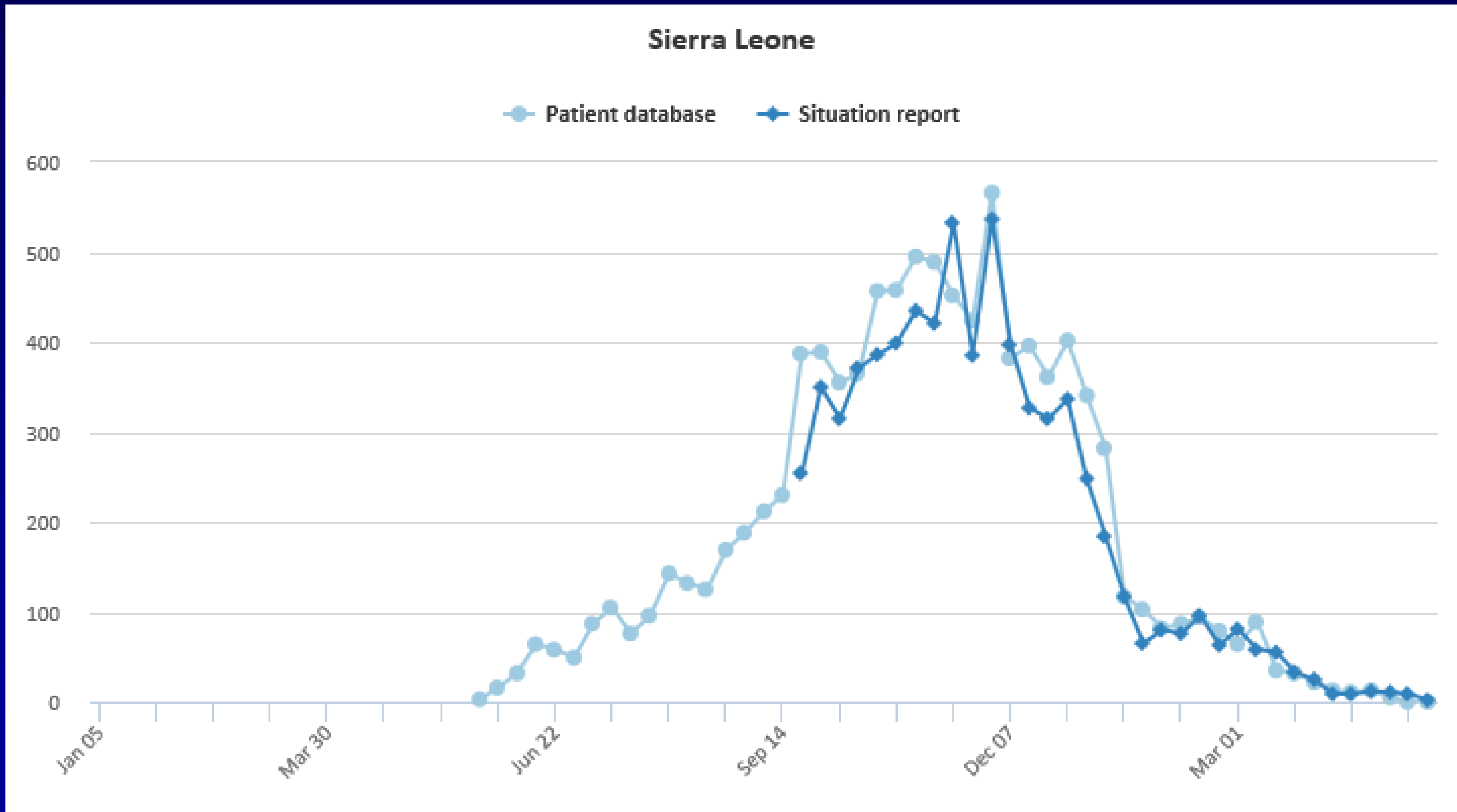

August 2014
September 2014
SIERRA
LEONE
Freetown
Monrovia
LIBERIA
District data for July 2014 not available


December 2014
January 2015

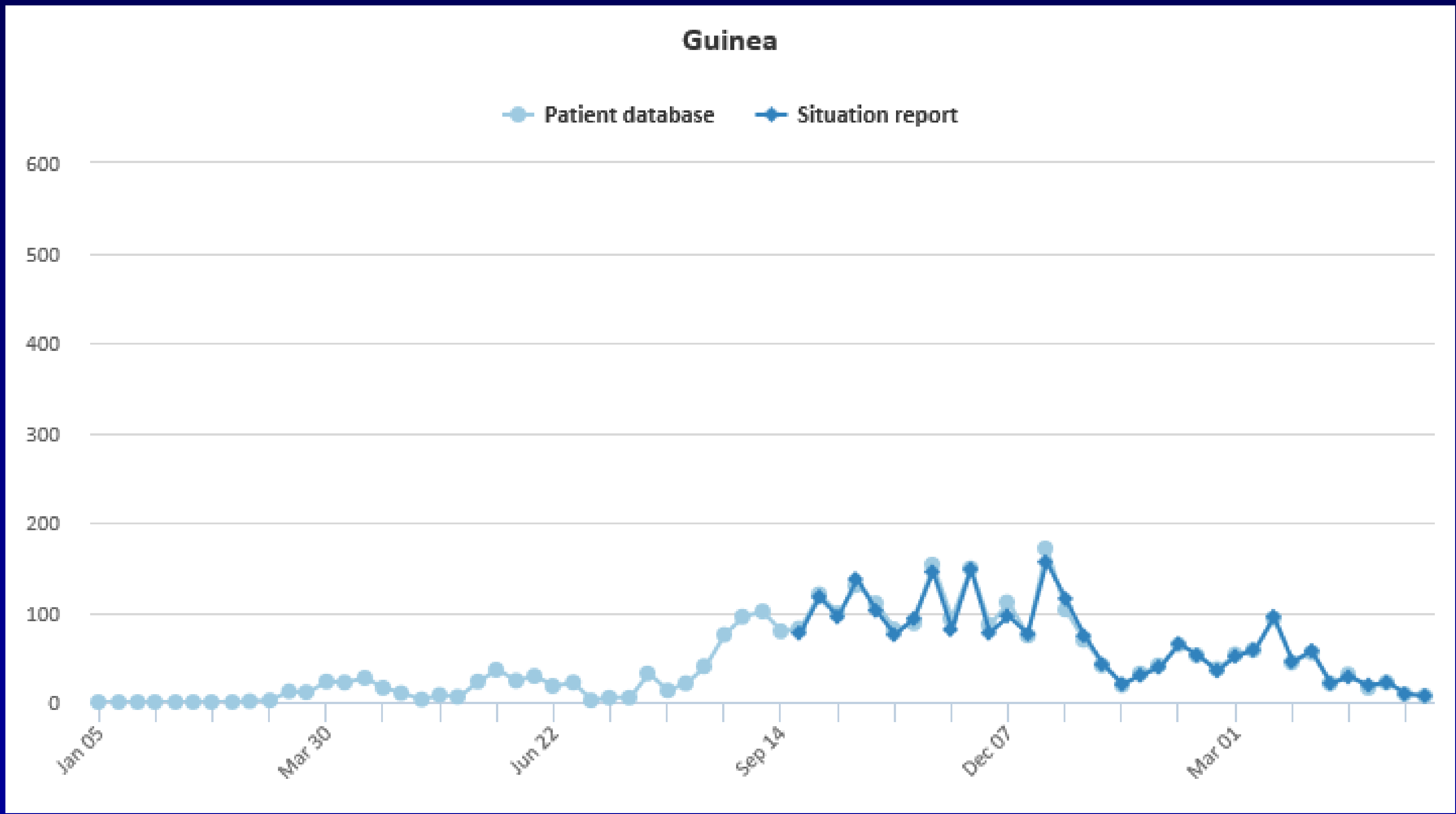

February 2015
March 2015
Source: WHO, national health ministries and HDX



Liberia_
Patient database
Situation report
600
500
400
300
200
100
0
Jan 05
Feb 02
Mar 02
Mar 30
Apr 27
May 25
Jun 22
Jul 20
Aug 17
Sep 14
Oct 12
Nov 09
Dec 07
Jan 04
Feb 01
Mar 01
Mar 29
Apr 26



Sierra Leone
Patient database
Situation report
600
500
400
300
200
100
0
Jan 05
Mar 30
Jun 22
Sep 14
Dec 07
Mar 01


Guinea
Patient database
Situation report
600
500
400
300
200
100
0
Jan 05
Mar 30
Jun 22
Sep 14
Dec 07
Mar 01

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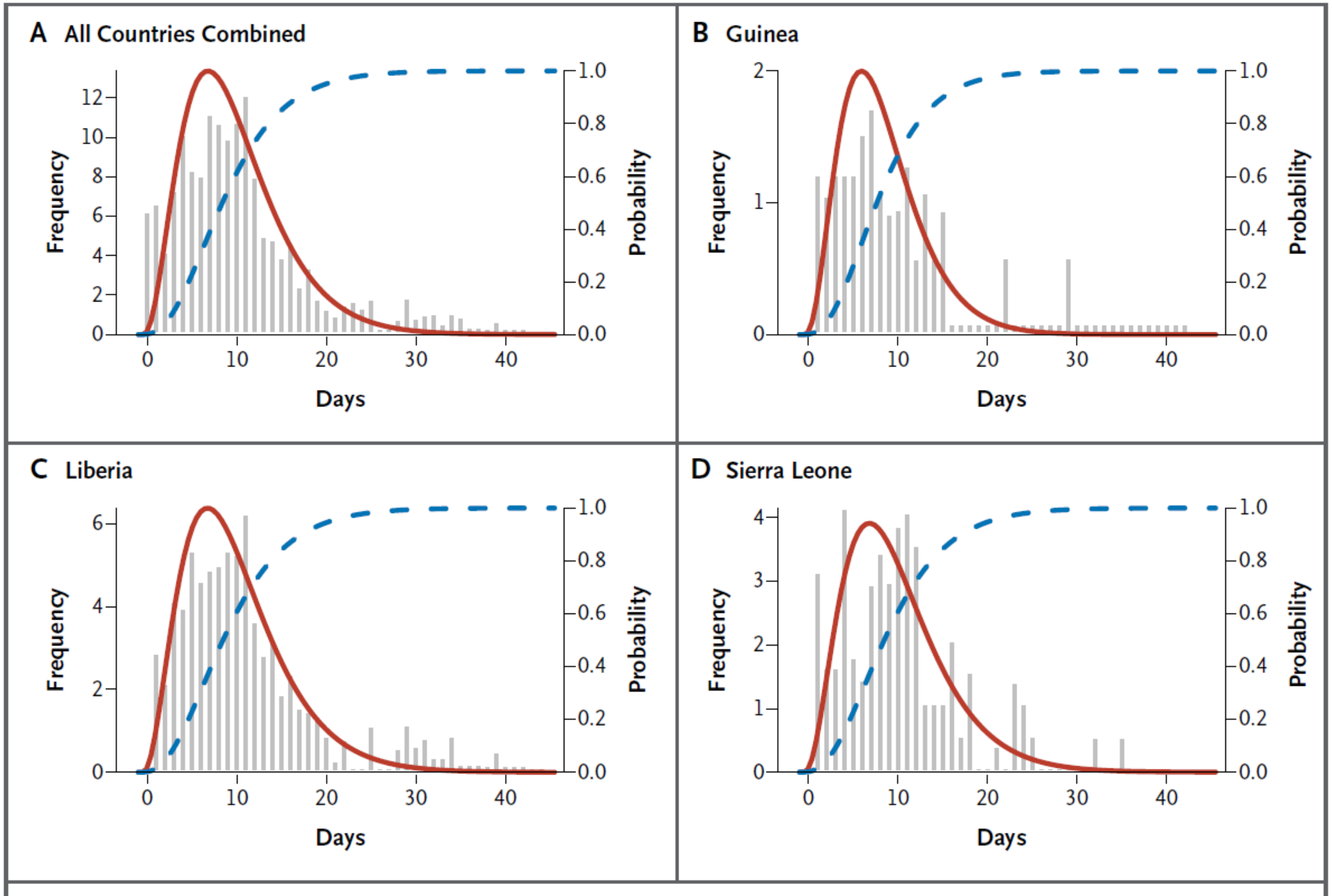

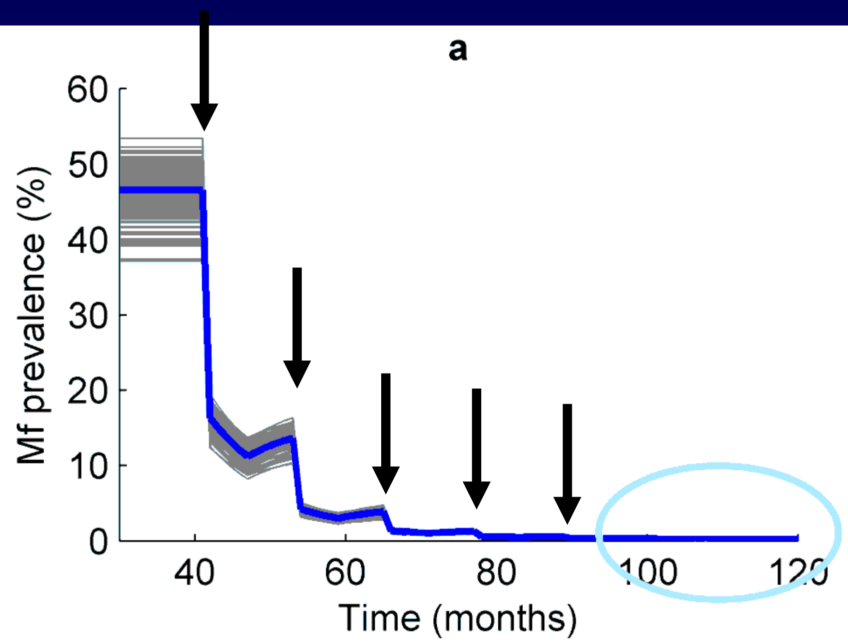

a
Mf prevalence (%)
60
50
40
30
20
10
0
40
60
80
100
120
Time (months)

Table 2. Parameter estimates for the best-fitting model, Model 8 (models outlined in Table 1).

Parameter description	Value
Vaccine efficacies & waning	
Whole-cell	
Vaccine efficacy of 1st 3 doses/4th/5th dose	90% [87%, 94%]
Rate of loss of whole-cell vaccine immunity	$3x10^{-5}yr^{-1}$ [$2x10^{-6}$, $2x10^{-4}$] i.e. essentially lifelong
Acellular	
Vaccine efficacy of 1st 3 doses/4th/5th dose	80% [78%,82%]
Rate of loss of acellular vaccine immunity	$0.018yr^{-1}$ [0.015, 0.020] i.e. average of approx. 50 yrs protection
Tdap	
Vaccine efficacy	As acellular
Epidemiological Parameters	
Basic reproduction number, R_0	11.0 [9.9, 11.5]
Rate of loss of natural immunity	$3x10^{-5}yr^{-1}$ [$2x10^{-6}$, $2x10^{-4}$] i.e. essentially lifelong (as for whole-cell)
Relative susceptibility of individuals to subsequent infection (with reference to naïve individuals)	32% [29%, 35%]
Relative infectiousness of individuals with subsequent infection (with reference to primary-infected individuals)	17% [14%, 23%]
Year of reporting rate change	None
Mean reporting rate prior to change	6.0% [0.1%, 22%]
Mean reporting rate after change	n/a

doi:10.1371/journal.pcbi.1004138.t002

Gambhir M, Clark TA, Cauchemez S, Tartof SY, Swerdlow DL, et al. (2015) A Change in Vaccine Efficacy and Duration of Protection Explains Recent Rises in Pertussis Incidence in the United States. PLoS Comput Biol 11(4): e1004138. doi:10.1371/journal.pcbi.1004138
http://journals.plos.org/ploscompbiol/article?id=info:doi/10.1371/journal.pcbi.1004138

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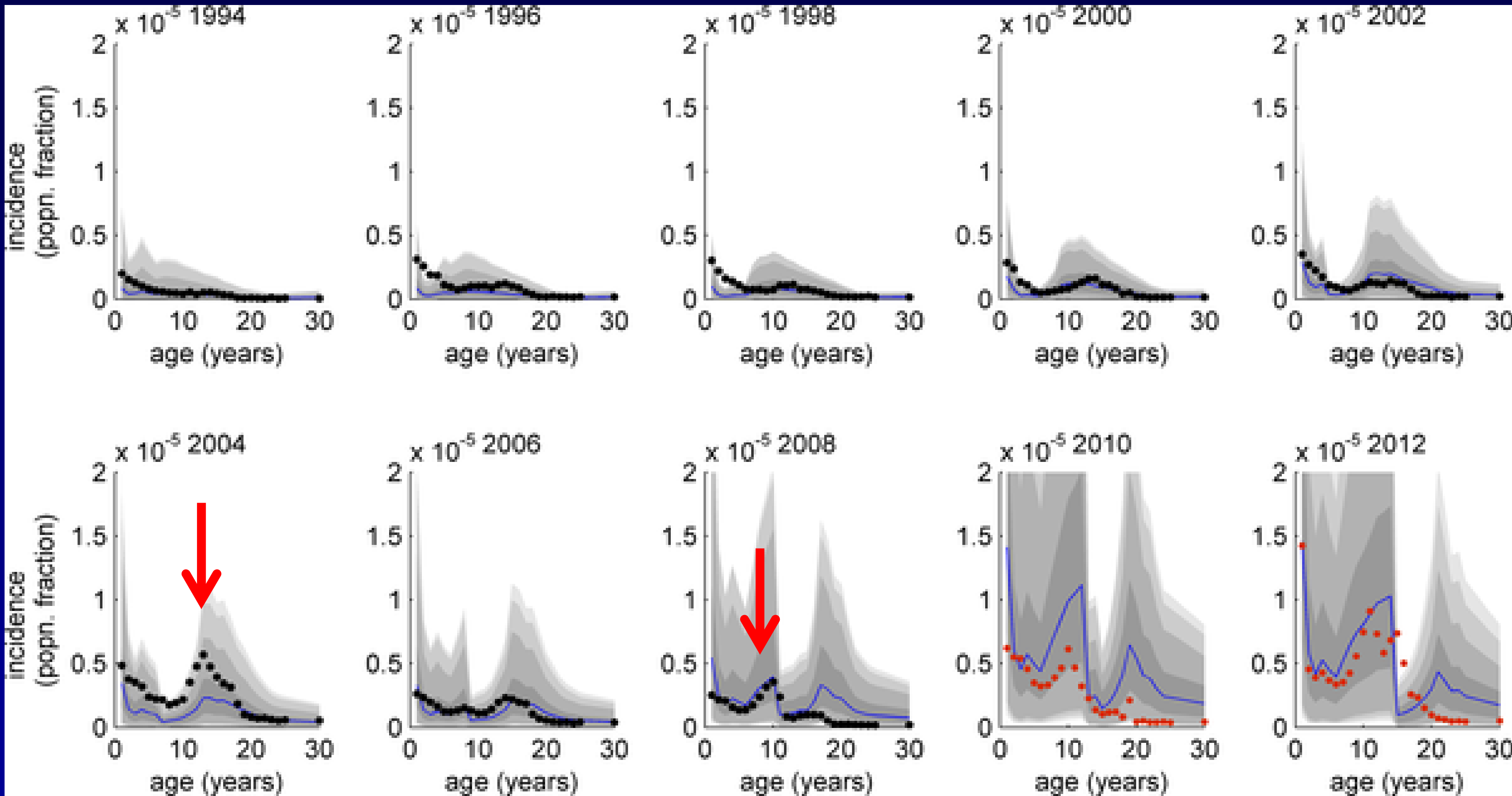
Fig 3. Cross-sectional incidence of disease over age of population.



Gambhir M, Clark TA, Cauchemez S, Tartof SY, Swerdlow DL, et al. (2015) A Change in Vaccine Efficacy and Duration of Protection Explains Recent Rises in Pertussis Incidence in the United States. PLoS Comput Biol 11(4): e1004138. doi:10.1371/journal.pcbi.1004138

http://journals.plos.org/ploscompbiol/article?id=info:doi/10.1371/journal.pcbi.1004138

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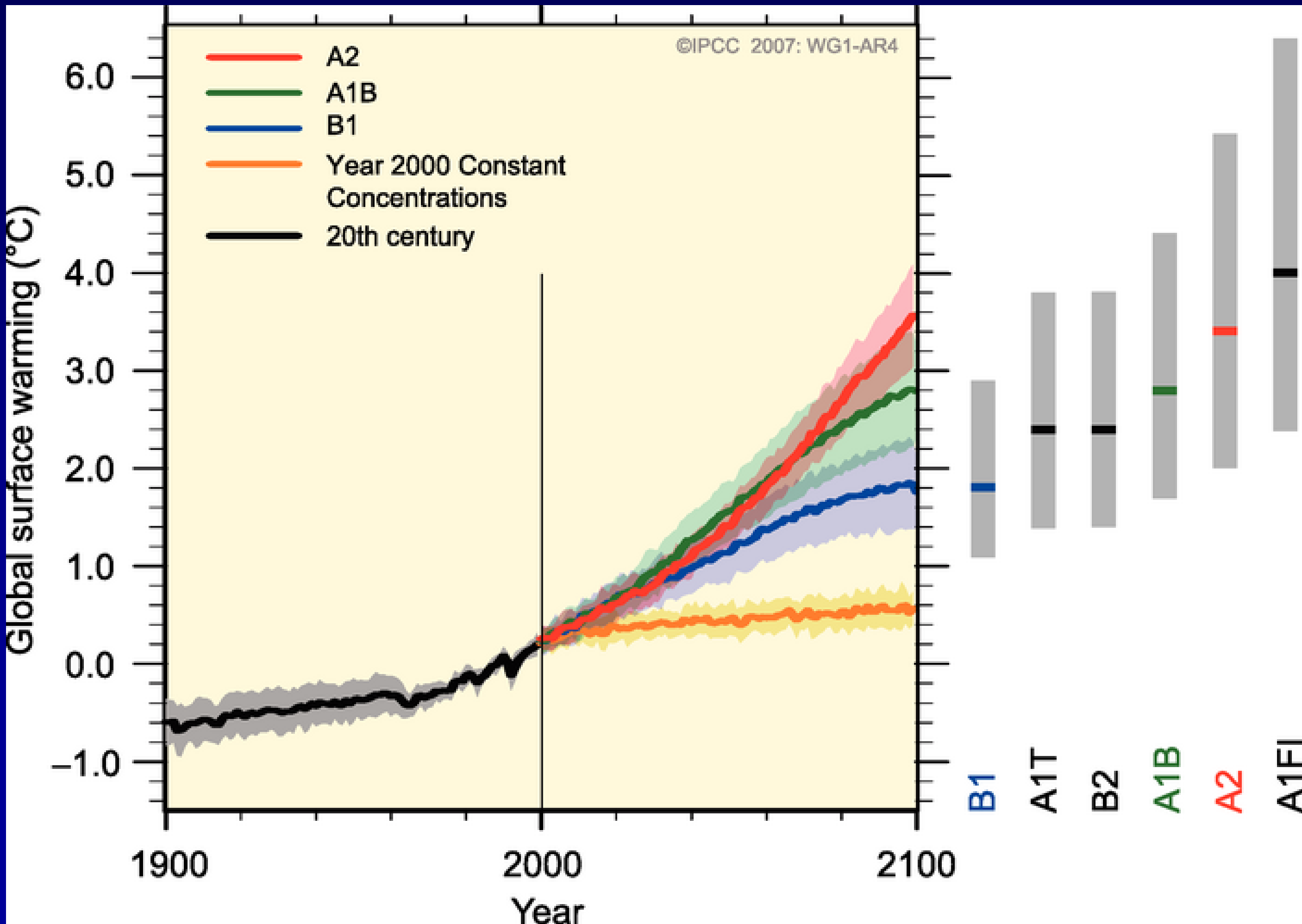
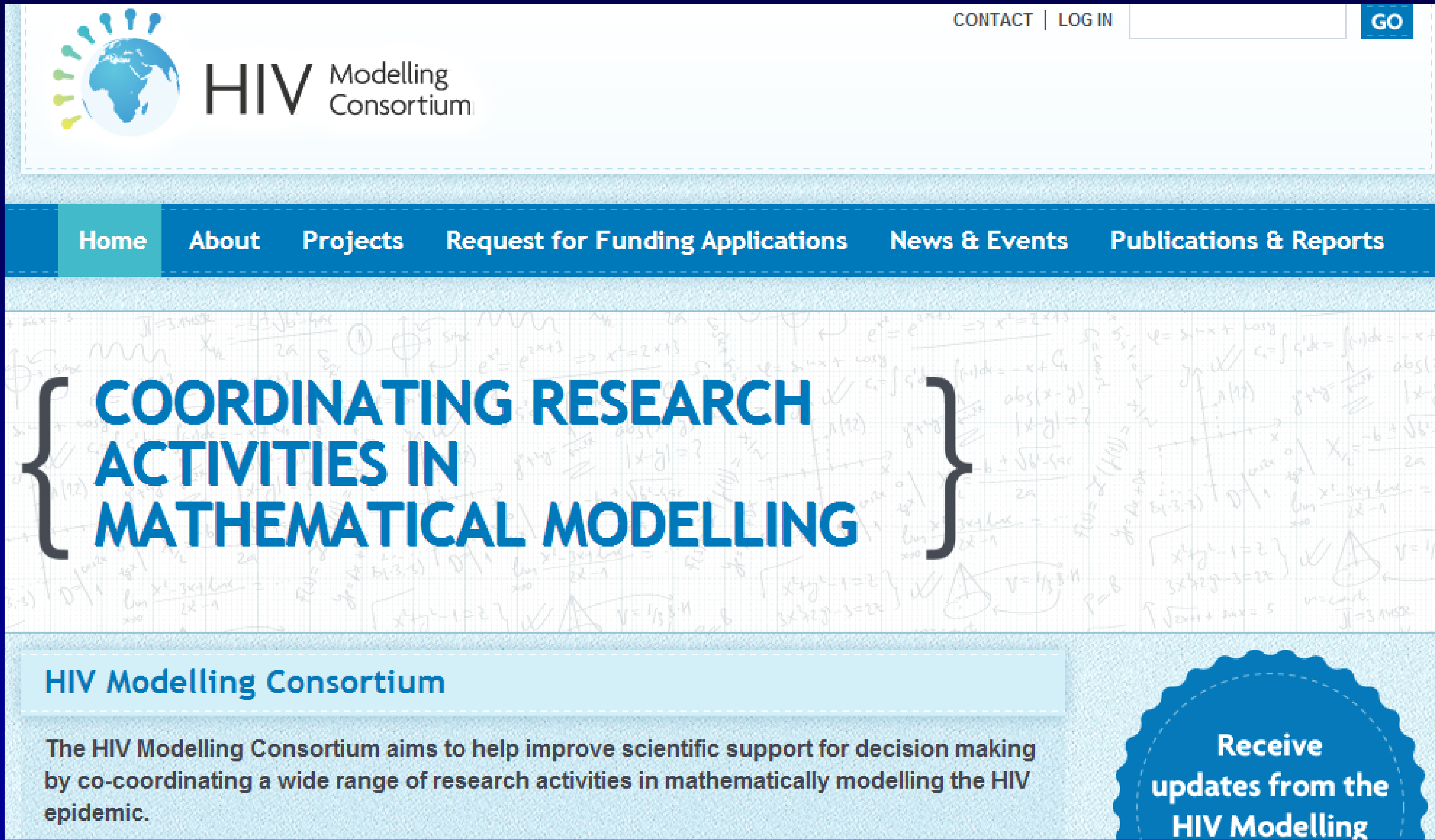
NTD Modelling Consortium

Multi-model ensembles

IPCC report (AR4)

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PLoS MEDICINE

HIV Treatment as Prevention: Systematic Comparison of Mathematical Models of the Potential Impact of Antiretroviral Ther

Jeffrey W. Eaton[1]*, Leigh F. Johns
Anna Bershteyn[6], David E. Bloom[3]
Salal Humair[3,11], Daniel J. Klein[6], E
Edward A. Wenger[6], Brian G. Willi

1 Department of Infectious Disease Epidemiology, Imperial
Cape Town, Cape Town, South Africa, 3 Harvard School of
University of KwaZulu-Natal, Mtubatuba, South Africa, 5 D
Laboratory, Bellevue, Washington, United States of Ameri
8 Medical Research Council Centre for Outbreak Analysis a
9 Erasmus University, Rotterdam, Netherlands, 10 Depar
11 School of Science and Engineering, Lahore University
13 Futures Institute, Glastonbury, Connecticut, United Sta

Abstract

Background: Many mathematical mode
on new HIV infections. Comparing resu
slightly different questions and have re
mathematical models simulating the sa
about the epidemiological impact of ex

Methods and Findings: Twelve indep
scenarios in South Africa and reported a
threshold for treatment eligibility, access
individuals start treatment on average 1
3 y, the models projected that HIV incid
counterfactual scenario in which there
incidence. The impact of optimistic interv
substantial uncertainty about the theore
next four decades. The number of pe

Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models

Jeffrey W Eaton [illegible] Cambiano, Leonid Chindelevitch, Anne Cori, Jan A C Hontelez, Salal Humair, Cliff C Kerr, Daniel J Klein, Sharmistha Mishra, Kate M Mitchell, Brooke E Nichols, Peter Vickerman, Roel Bakker, Till Bärnighausen, Anna Bershteyn, David E Bloom, Marie-Claude Boily, Stewart T Chang, Ted Cohen, Peter J Dodd, Christophe Fraser, Chaitra Gopalappa, Jens Lundgren, Natasha K Martin, Evelinn Mikkelsen, Elisa Mountain, Quang D Pham, Michael Pickles, Andrew Phillips, Lucy Platt, Carel Pretorius, Holly J Prudden, Joshua A Salomon, David A M C van de Vijver, Sake J de Vlas, Bradley G Wagner, Richard G White, David P Wilson, Lei Zhang, John Blandford, Gesine Meyer-Rath, Michelle Remme, Paul Revill, Nalinee Sangrujee, Fern Terris-Prestholt, Meg Doherty, Nathan Shaffer, Philippa J Easterbrook, Gottfried Hirnschall, Timothy B Hallett

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Summary

Background New WHO guidelines recommend initiation of antiretroviral therapy for HIV-positive adults with CD4 counts of 500 cells per μL or less, a higher threshold than was previously recommended. Country decision makers have to decide whether to further expand eligibility for antiretroviral therapy accordingly. We aimed to assess the potential health benefits, costs, and cost-effectiveness of various eligibility criteria for adult antiretroviral therapy and expanded treatment coverage.

Methods We used several independent mathematical models in four settings—South Africa (generalised epidemic, moderate antiretroviral therapy coverage), Zambia (generalised epidemic, high antiretroviral therapy coverage), India (concentrated epidemic, moderate antiretroviral therapy coverage), and Vietnam (concentrated epidemic, low antiretroviral therapy coverage)—to assess the potential health benefits, costs, and cost-effectiveness of various eligibility criteria for adult antiretroviral therapy under scenarios of existing and expanded treatment coverage, with results projected over 20 years. Analyses assessed the extension of eligibility to include individuals with CD4 counts of 500 cells per μL or less, or all HIV-positive adults, compared with the previous (2010) recommendation of initiation with CD4 counts of 350 cells per μL or less. We assessed costs from a health-system perspective, and calculated the incremental cost (in US$) per disability-adjusted life-year (DALY) averted to compare competing strategies. Strategies were regarded very cost effective if the cost per DALY averted was less than the country's 2012 per-head gross domestic product (GDP; South Africa: $8040; Zambia: $1425; India: $1489; Vietnam: $1407) and cost effective if the cost per DALY averted was less than three times the per-head GDP.

Findings In South Africa, the cost per DALY averted of extending eligibility for antiretroviral therapy to adult patients with CD4 counts of 500 cells per μL or less ranged from $237 to $1691 per DALY averted compared with 2010 guidelines. In Zambia, expansion of eligibility to adults with a CD4 count threshold of 500 cells per μL ranged from improving health outcomes while reducing costs (ie, dominating the previous guidelines) to $749 per DALY averted. In both countries results were similar for expansion of eligibility to all HIV-positive adults, and when substantially expanded treatment coverage was assumed. Expansion of treatment coverage in the general population was also cost effective. In

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See Online for an audio interview with Tim Hallett

*Contributed equally

MRC Centre for Outbreak Analysis and Modelling (A Cori PhD, Prof C Fraser PhD), Department of Infectious Disease Epidemiology (J W Eaton PhD, S Mishra MD, M-C Boily PhD, E Mountain MSc, M Pickles PhD, Prof T B Hallett PhD), Imperial College London, London, UK; Center for Health Decision Science (N A Menzies MPH, Prof J A Salomon PhD), Department of Global Health and Population


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- **9 diseases** incl: schistosomiasis, lymphatic filariasis, trachoma, soil transmitted helminths

2 questions from BMGF

Are we on target for the 2020 goals with current strategies?

If not, what other strategies will be required, and where?

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Gambhir and Pinsent *Parasites & Vectors* (2015) 8:530
DOI 10.1186/s13071-015-1133-6

Parasites & Vectors

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Manoj Gambhir

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Citation: Liu F, Po
B, West SK, et al. (
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Abstract

Background: T
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Methods: In thi
impact of treatm
possibility of inc
endemic setting

Pinsent *et al. BMC Medicine* (2016) 14:71
DOI 10.1186/s12916-016-0614-6

BMC Medicine

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Enhanced antibiotic distribution strategies and the potential impact of facial cleanliness and environmental improvements for the sustained control of trachoma: a modelling study

Amy Pinsent[1*], Matthew J. Burton[2] and Manoj Gambhir[1]

Abstract

Background: Despite some success in controlling trachoma with repeated mass drug administration (MDA), some hyperendemic regions are not responding as fast as anticipated. Available data suggests that individuals with higher bacterial infection loads are less likely to resolve infection following a single dose of treatment, and thus remain a source of re-emergent infection following treatment. We assessed the potential impact of a new double-dose