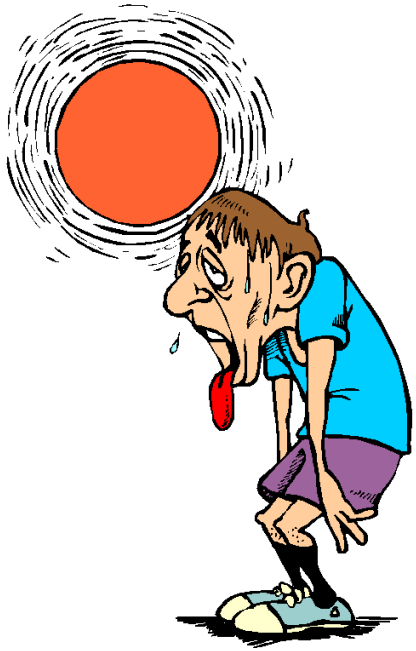


What's Hot in Adult ID?

AMMI Canada-CACMID Annual Conference
Quebec City, 2013

Gerald Evans, MD FRCPC
Chair, Division of Infectious Disease
Professor of Medicine
Queen's University

AMMI Canada
CONFLICT OF INTEREST DISCLOSURE SLIDE

In the past 2 years I have been an employee of:	**QUEEN'S UNIVERSITY**
In the past 2 years I have been a consultant of:	**ONTARIO MOHLTC**
In the past 2 years I have held investments in the following pharmaceutical organizations, medical devices companies or communications firms:	**NONE**
In the past 2 years I have been a member of a Scientific advisory board of:	**MERCK**
In the past 2 years I have been a speaker for:	**NONE**
In the past 2 years I have received research support (grants) from:	**MERCK, ASTELLAS, BIOCRYST**
In the past 2 years I have received honoraria from:	**NONE**
I agree to disclose approved and non-approved indications for medications in this presentation:	**NO**
I agree to use generic names of medications in this presentation:	**YES**

There are no relationships to disclose ☐

Stuff I thought was “Hot”

- Sepsis
  - Of Mice and Men
- Drug safety
  - Fungal infections
  - Old drugs that kill
- Emerging infections
  - Novel coronavirus
  - H7N9
  - CRE
- New cures
  - The cure for CDI
  - A cure for HIV?
- Designer Vaccines

Sepsis: Of Mice and Men

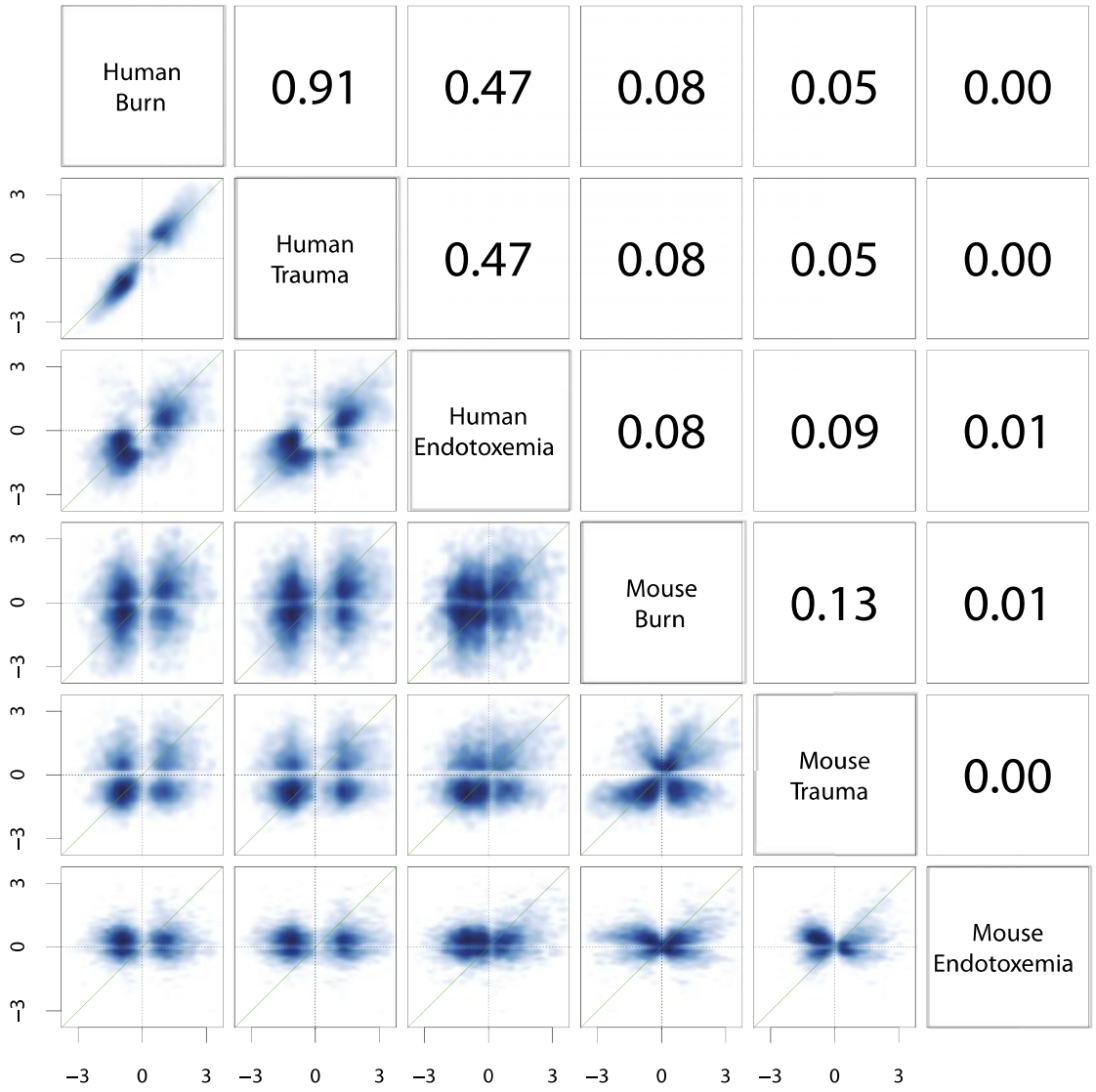
- Murine models have been extensively used to identify and test drug candidates for sepsis in subsequent human trials
- Very few of these human trials have shown success
  - To date, there have been nearly 150 clinical trials testing candidate agents intended to block the inflammatory response in critically ill patients and <u>every one of these trials failed</u>

Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok[a,1], H. Shaw Warren[b,1], Alex G. Cuenca[c,1], Michael N. Mindrinos[a], Henry V. Baker[c], Weihong Xu[a], Daniel R. Richards[d], Grace P. McDonald-Smith[e], Hong Gao[a], Laura Hennessy[f], Celeste C. Finnerty[g], Cecilia M. López[c], Shari Honari[f], Ernest E. Moore[h], Joseph P. Minei[i], Joseph Cuschieri[j], Paul E. Bankey[k], Jeffrey L. Johnson[h], Jason Sperry[l], Avery B. Nathens[m], Timothy R. Billiar[l], Michael A. West[n], Marc G. Jeschke[o], Matthew B. Klein[j], Richard L. Gamelli[p], Nicole S. Gibran[j], Bernard H. Brownstein[q], Carol Miller-Graziano[k], Steve E. Calvano[r], Philip H. Mason[e], J. Perren Cobb[s], Laurence G. Rahme[t], Stephen F. Lowry[r,2], Ronald V. Maier[j], Lyle L. Moldawer[c], David N. Herndon[g], Ronald W. Davis[a,3], Wenzhong Xiao[a,t,3], Ronald G. Tompkins[t,3], and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program[4]

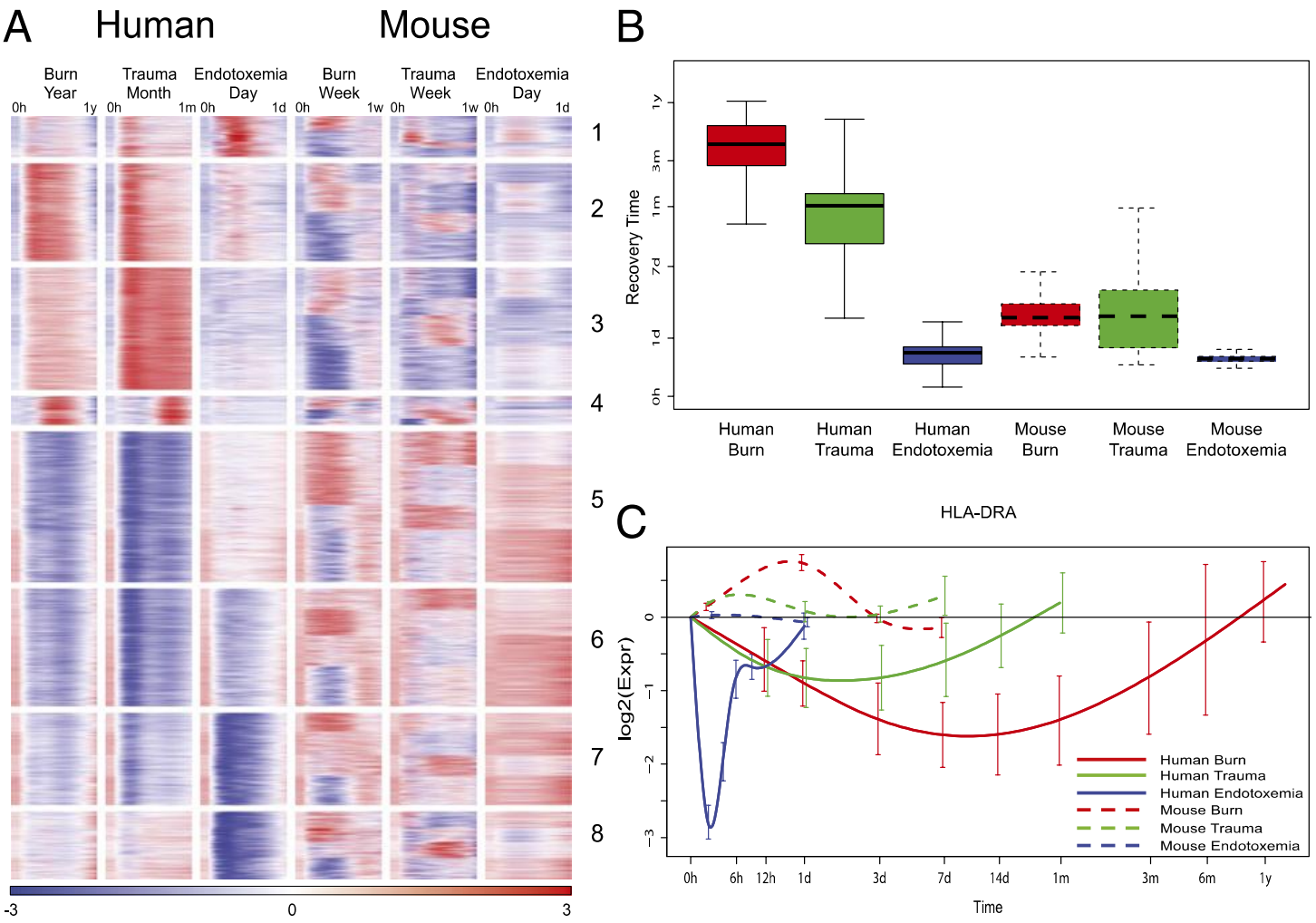
www.pnas.org/cgi/doi/10.1073/pnas.1222878110

- The Inflammation and Host Response to Injury, Large Scale Collaborative Research Program
  - Multiple studies on the genomic responses to systemic inflammation in patients and human volunteers as well as murine models
- Systematic comparison of the genomic response between human inflammatory diseases and murine models
  - Gene expression
  - Temporal gene response
  - Major signaling pathway activation and regulation



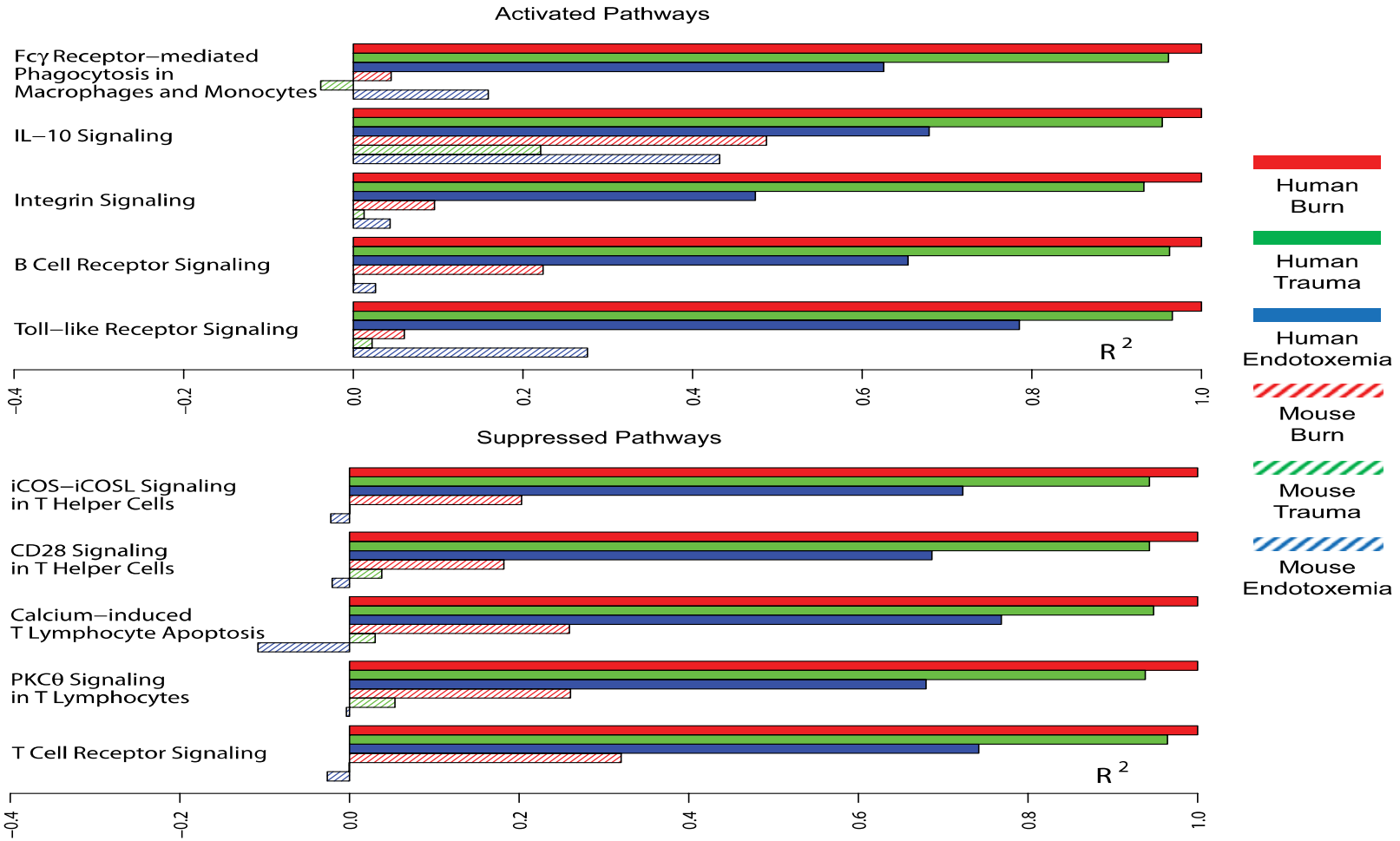
Correlation of gene changes among human and mouse burn, trauma or endotoxemia. Human burn and trauma are highly correlated (R^2=0.91), but mouse burn and trauma are poorly correlated (R^2=0.13)

Seok et al at www.pnas.org/cgi/doi/10.1073/pnas.1222878110



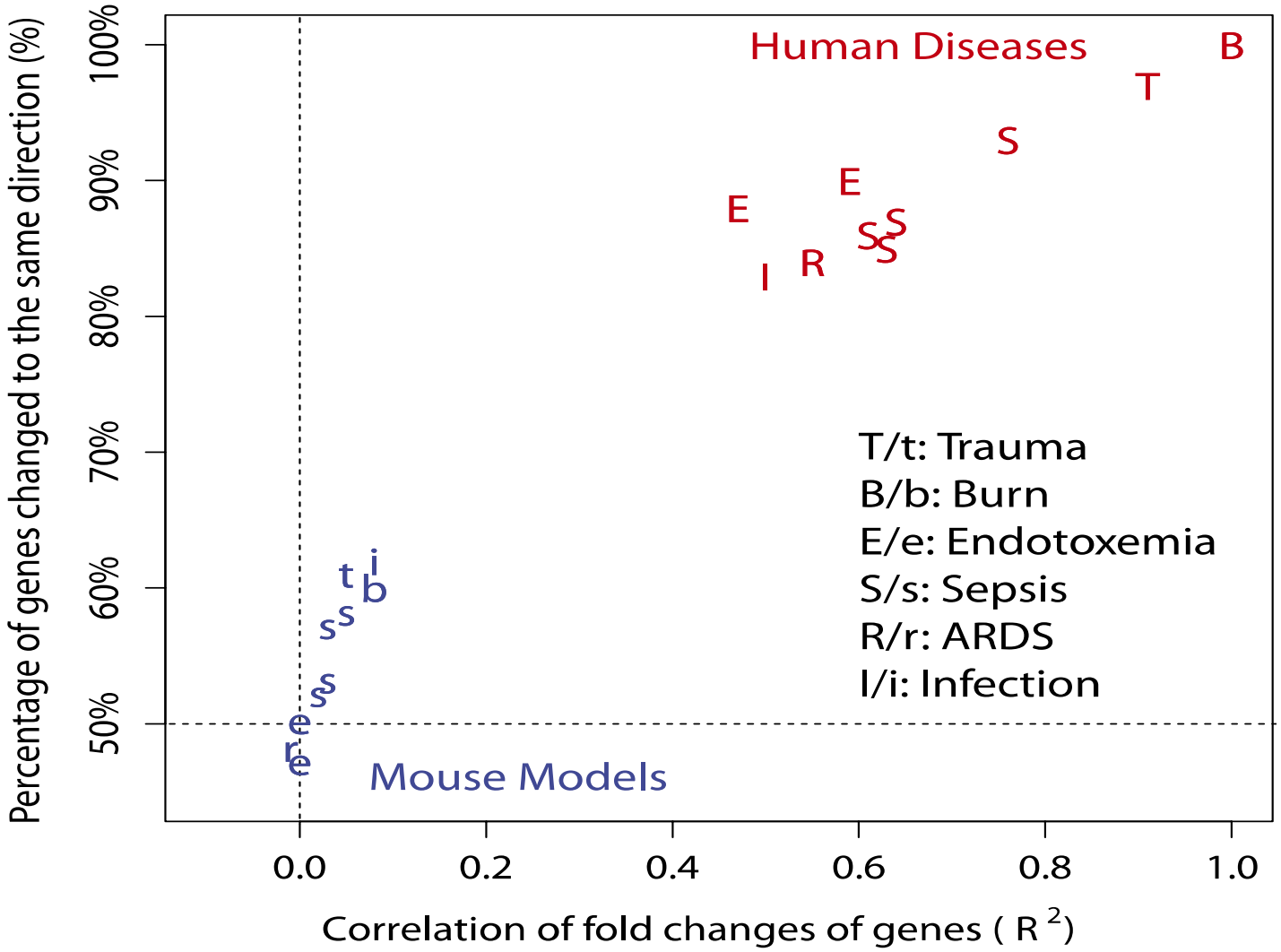
Comparison of time-course gene changes for human and mouse burns, trauma and endotoxemia.

Seok et al at www.pnas.org/cgi/doi/10.1073/pnas.1222878110



Pathway comparisons between human and mouse burns, trauma or endotoxemia

Seok et al at www.pnas.org/cgi/doi/10.1073/pnas.1222878110

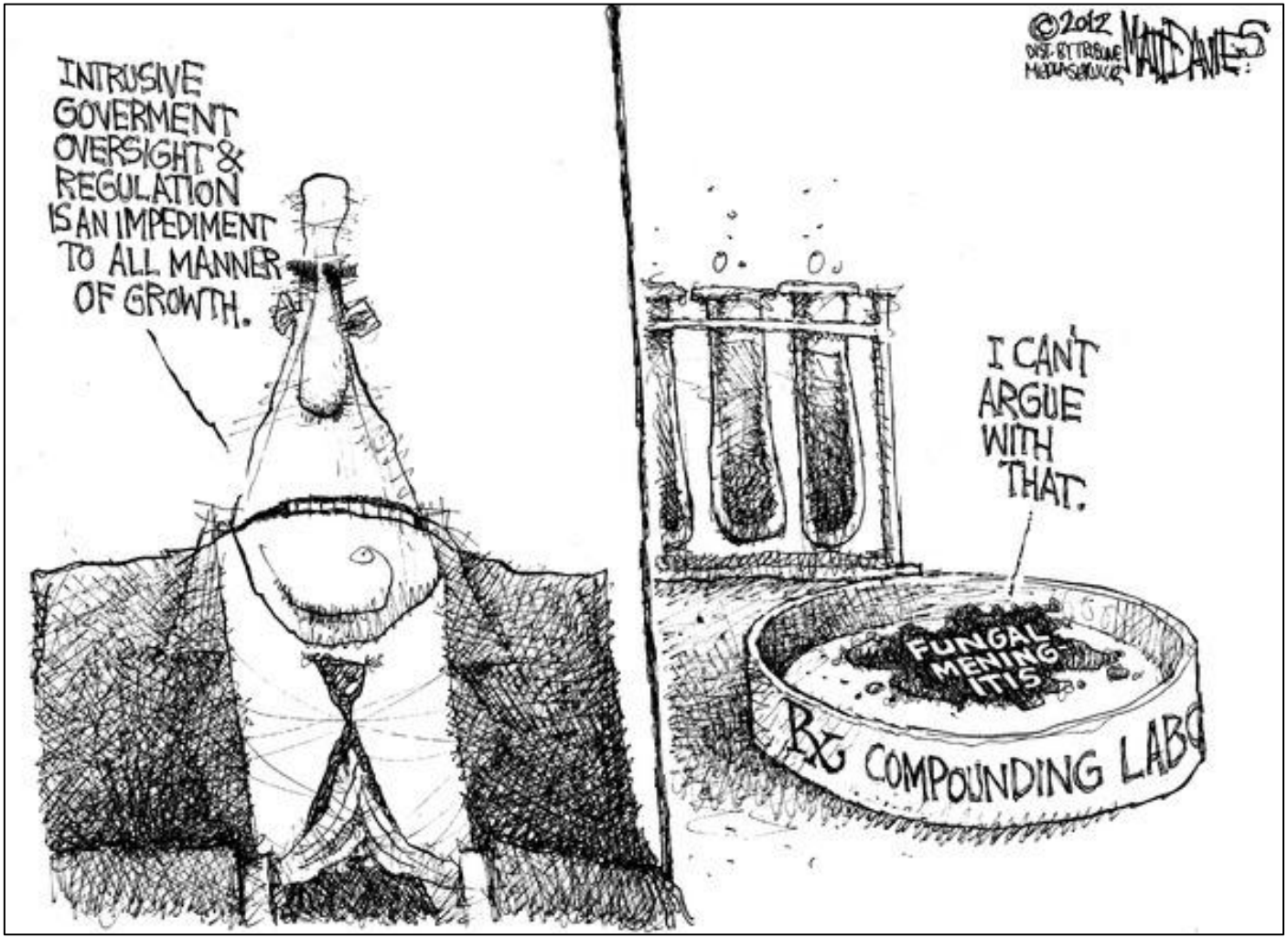


Comparison of genomic responses to severe acute inflammation from different etiologies in human and murine models

Seok et al at www.pnas.org/cgi/doi/10.1073/pnas.1222878110

What this tells us

- Models are models and sometimes the model is wrong
  - Mouse models may be useful in some areas of medicine but not in inflammation
- Sepsis research needs a new model
- Why didn't anyone figure this out before?
  - We need more model busting like this to be done with animal models of human disease
  - Likely billions of wasted dollars


©2012
MATT DAVIES
INTRUSIVE GOVERMENT OVERSIGHT & REGULATION IS AN IMPEDIMENT TO ALL MANNER OF GROWTH.
I CAN'T ARGUE WITH THAT.
FUNGAL MENINGITIS
RX COMPOUNDING LABS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fungal Infections Associated with Contaminated Methylprednisolone Injections — Preliminary Report

Rachel M. Smith, M.D., M.P.H., Melissa K. Schaefer, M.D., Marion A. Kainer, M.B., B.S., M.P.H., Matthew Wise, Ph.D., Jennie Finks, D.V.M., M.V.P.H., Joan Duwve, M.D., M.P.H., Elizabeth Fontaine, M.S.P.H., Alvina Chu, M.H.S., Barbara Carothers, L.P.N., Amy Reilly, R.N., Jay Fiedler, M.S., Andrew D. Wiese, M.P.H., Christine Feaster, R.M., Lex Gibson, B.S., Stephanie Griese, M.D., Anne Purfield, Ph.D., Angela A. Cleveland, M.P.H., Kaitlin Benedict, M.P.H., Julie R. Harris, Ph.D., M.P.H., Mary E. Brandt, Ph.D., Dianna Blau, D.V.M., Ph.D., John Jernigan, M.D., J. Todd Weber, M.D., and Benjamin J. Park, M.D., for the Multistate Fungal Infection Outbreak Response Team

Table 2. National Attack Rates for All Infections and National and State-Specific Attack Rates for Meningitis and Spinal and Paraspinal Infections, as of December 10, 2012.

Description	No. of Cases	Persons Potentially Exposed*	No. of Cases/100 Persons Potentially Exposed (95% CI)†
National attack rate, all infections	590	13,534	4.4 (4.0–4.7)
National attack rate, meningitis and spinal and paraspinal infections‡	569	12,069	4.7 (4.3–5.1)

Source: RM Smith et al N Engl J Med 2012 DOI: 10.1056/NEJMoa1213978

The Story

- First case (*Aspergillus* meningitis) reported in Tennessee on Sept. 18, 2012
- 37 deaths in 590 cases reported to date
- All cases tied to preservative-free methylprednisolone vials produced by a single pharmacy, New England Compounding Center in Framingham, MA

Source: RM Smith et al N Engl J Med 2012 DOI: 10.1056/NEJMoa1213978

US Fungal Infections Outbreak

- Total cases = 590
  - Preliminary report on 386 cases
- Presentations
  - Meningitis (78%)
  - Spinal & paraspinal infections (17%)
  - Peripheral joint infections (5%)
- Most common fungi isolated
  - *Exserohilum rostratum* n=100
  - *Aspergillus fumigatus* n=1
  - *Cladosporium* sp. and others N=10

Source: RM Smith et al N Engl J Med 2012 DOI: 10.1056/NEJMoa1213978

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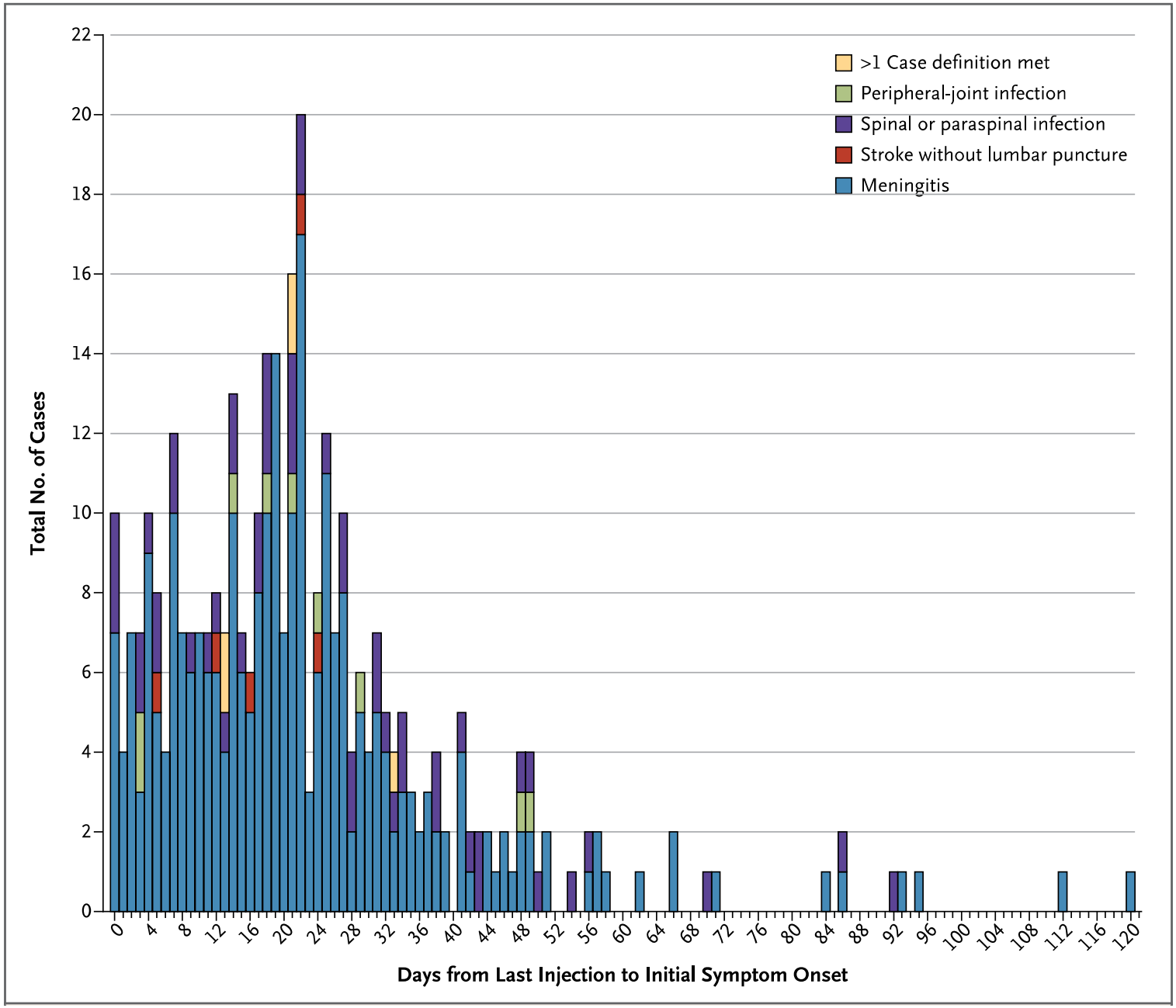
Source: RM Smith et al N Engl J Med 2012 DOI: 10.1056/NEJMoa1213978

Patient Demographics

Table 1. Characteristics of Patients with Fungal Infections Associated with Contaminated Lots of Methylprednisolone Acetate.*

Characteristic	All Cases† (N = 386)	Meningitis Only (N = 300)	Spinal and Paraspinal Infections Only (N = 65)	Peripheral-Joint Infections Only‡ (N = 10)
Demographic and clinical data				
Female sex — no. (%)	233 (60)	184 (61)	37 (57)	6 (60)
Age — yr				
Median	64	64	65	51
Range	16–92	16–92	32–87	43–84
Interquartile range	51–74	51–74	53–73	46–59
Immunosuppressed — no. (%)	35 (9)	25 (8)	6 (9)	2 (20)
Incubation period — days§				
Median	20	19	22	21
Range	0–120	0–120	0–92	3–49
Interquartile range	11–29	10–27	13–38	14–29
Incubation period in patients who received only 1 injection — days¶				
Median	22	22	25	21
Range	0–120	0–120	0–70	3–29
Interquartile range	12–32	12–32	11–41	11–27

Source: RM Smith et al N Engl J Med 2012 DOI: 10.1056/NEJMoa1213978



Source: RM Smith et al N Engl J Med 2012 DOI: 10.1056/NEJMoa1213978

Table 1. Characteristics of Patients with Fungal Infections Associated with Contaminated Lots of Methylprednisolone Acetate.*

Characteristic	All Cases† (N = 386)	Meningitis Only (N = 300)	Spinal and Paraspinal Infections Only (N = 65)	Peripheral-Joint Infections Only‡ (N = 10)
Initial symptoms — no./total no. (%)				
Headache	292/382 (76)	251/297 (85)	33/64 (52)	3/10 (30)
Back pain	144/382 (38)	94/297 (32)	44/64 (69)	1/10 (10)
Neck pain or stiffness	138/382 (36)	117/297 (39)	16/64 (25)	2/10 (20)
Fever	107/382 (28)	95/297 (32)	7/64 (11)	2/10 (20)
Photophobia	75/382 (20)	66/297 (22)	8/64 (12)	0
Joint pain	33/382 (9)	4/297 (1)	15/64 (23)	10/10 (100)
Exposure data				
Lot exposure known — no./total no. (%)	285/386 (74)	221/300 (74)	51/65 (78)	4/10 (40)
Exposed to lot 05212012@68	41/285 (14)	37/221 (17)	2/51 (4)	0
Exposed to lot 06292012@26	237/285 (83)	177/221 (80)	49/51 (96)	4/4 (100)
Exposed to lot 08102012@51	49/285 (17)	44/221 (20)	3/51 (6)	0
Exposed to only one lot	243/285 (85)	184/221 (83)	48/51 (94)	4/4 (100)
05212012@68	17/243 (7)	16/184 (9)	0	0
06292012@26	201/243 (83)	146/184 (79)	46/48 (96)	4/4 (100)
08102012@51	25/243 (10)	22/184 (12)	2/48 (4)	0
Procedures involving methylprednisolone acetate during the outbreak period — no./patient				
Median	1	1	1	2
Range	1–6	1–4	1–6	1–4
Type of injection known — no./total no. (%)	325/386 (84)	255/300 (85)	50/65 (77)	9/10 (90)
Epidural or paraspinal injection	313/325 (96)	252/255 (99)	50/50 (100)	0
Peripheral-joint or other injection	8/325 (2)	0	0	8/9 (89)
Both	4/325 (1)	3/255 (1)	0	1/9 (11)

Source: RM Smith et al N Engl J Med 2012 DOI: 10.1056/NEJMoa1213978

Outcomes & Lab Data

Characteristic	All Cases† (N=386)	Meningitis Only (N=300)	Spinal and Paraspinal Infections Only (N=65)	Peripheral-Joint Infections Only‡ (N=10)
Treatment and Outcome				
Antifungal treatment documented — no./total no. (%)	311/386 (81)	236/300 (79)	61/65 (94)	8/10 (80)
Voriconazole monotherapy	180/311 (58)	121/236 (51)	47/61 (77)	8/8 (100)
Amphotericin monotherapy	1/311 (<1)	1/236 (<1)	0	0
Voriconazole and amphotericin	130/311 (42)	114/236 (48)	14/61 (23)	0
Development of stroke — no./total no. (%)	33/386 (9)	28/300 (9)	0	0
Ischemic	23/33 (70)	18/28 (64)	0	0
Hemorrhagic	5/33 (15)	5/28 (18)	0	0
Both	4/33 (12)	4/28 (14)	0	0
Unknown	1/33 (3)	1/28 (4)	0	0
Evidence of fungus — no.	111	97	8	1
Documented by PCR only	76	67	5	1
Documented by culture only	13	12	1	0
Documented by histopathological assessment only	0	0	0	0
Documented by >1 technique	22	18	2	0
Exserohilum species	100	86	8	1

Source: RM Smith et al N Engl J Med 2012 DOI: 10.1056/NEJMoa1213978

What this tells us

- Healthcare-acquired infections present in surprising ways
- Drug regulation is an important part of drug safety
- Fungus and steroids are a bad mix
- Thank god for the border!
- There’s a lot of fungus amongst us

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Azithromycin and the Risk of Cardiovascular Death

Wayne A. Ray, Ph.D., Katherine T. Murray, M.D., Kathi Hall, B.S., Patrick G. Arbogast, Ph.D., and C. Michael Stein, M.B., Ch.B.

- A retrospective cohort study of mortality among patients in the Tennessee Medicaid program
  - 347,795 prescriptions for azithromycin, 1,391,180 matched control periods with no study antibiotic treatment
  - 1,348,672 prescriptions for amoxicillin, 264,626 prescriptions for ciprofloxacin, and 193,906 prescriptions for levofloxacin

Source: WA Ray et al N Engl J Med 2012;366:1881-90

Table 1. Demographic and Clinical Characteristics of Patients at the Time That the Prescriptions for the Study Antibiotics Were Filled and at the Beginning of the Control Period for Persons Who Received No Antibiotic Treatment.*

Characteristic	No Antibiotic	Amoxicillin†	Ciprofloxacin	Levofloxacin	Azithromycin
Prescriptions (no.)	1,391,180	1,348,672	264,626	193,906	347,795
Mean age (yr)	48.6	47.7	50.5	51.5	48.6
Female sex (%)	77.5	73.3	75.5	73.5	77.5
Current or past use of medications (%)					
Angiotensin-converting–enzyme inhibitor	28.1	24.0	28.4	32.8	28.1
Beta-blocker	21.6	17.3	20.9	24.8	21.5
Calcium-channel blocker	20.2	19.9	22.8	24.3	20.2
Digoxin	2.5	3.5	3.8	3.6	2.5
Loop diuretic	17.3	15.1	20.1	23.8	17.2
Other diuretic	25.9	22.4	26.3	28.9	25.9
Statin	28.1	17.9	25.2	34.5	28.0
Insulin	6.5	6.9	10.2	10.2	6.5
Oral hypoglycemic agent	16.5	13.1	18.9	21.9	16.5
Beta-agonist	40.5	28.1	28.6	43.5	40.3
Glucocorticoid	3.3	2.8	3.8	4.8	3.3
Coexisting conditions (%)					
Heart failure	4.3	3.9	5.3	6.8	4.3
Chronic obstructive pulmonary disease	5.5	4.6	5.1	6.8	5.4
Complications of diabetes‡	7.4	6.5	11.3	11.7	7.5
Incontinence of urine or feces	2.9	2.1	4.6	4.3	2.9
Use of wheelchair or walker	2.3	1.6	3.2	3.8	2.3
Hospitalization for cardiovascular condition (%)	7.2	6.0	8.5	9.5	7.2
Hospitalization for other condition (%)	15.7	14.8	19.1	20.4	15.8
Visit to emergency department in the past 30 days (%)	13.9	11.3	15.6	18.0	13.9
Use of any antibiotic in the past 30 days (%)	27.9	28.4	38.6	40.3	27.0§
Mean summary score for risk of cardiovascular disease¶	9.2	9.5	10.3	10.6	9.3

Source: WA Ray et al N Engl J Med 2012;366:1881-90

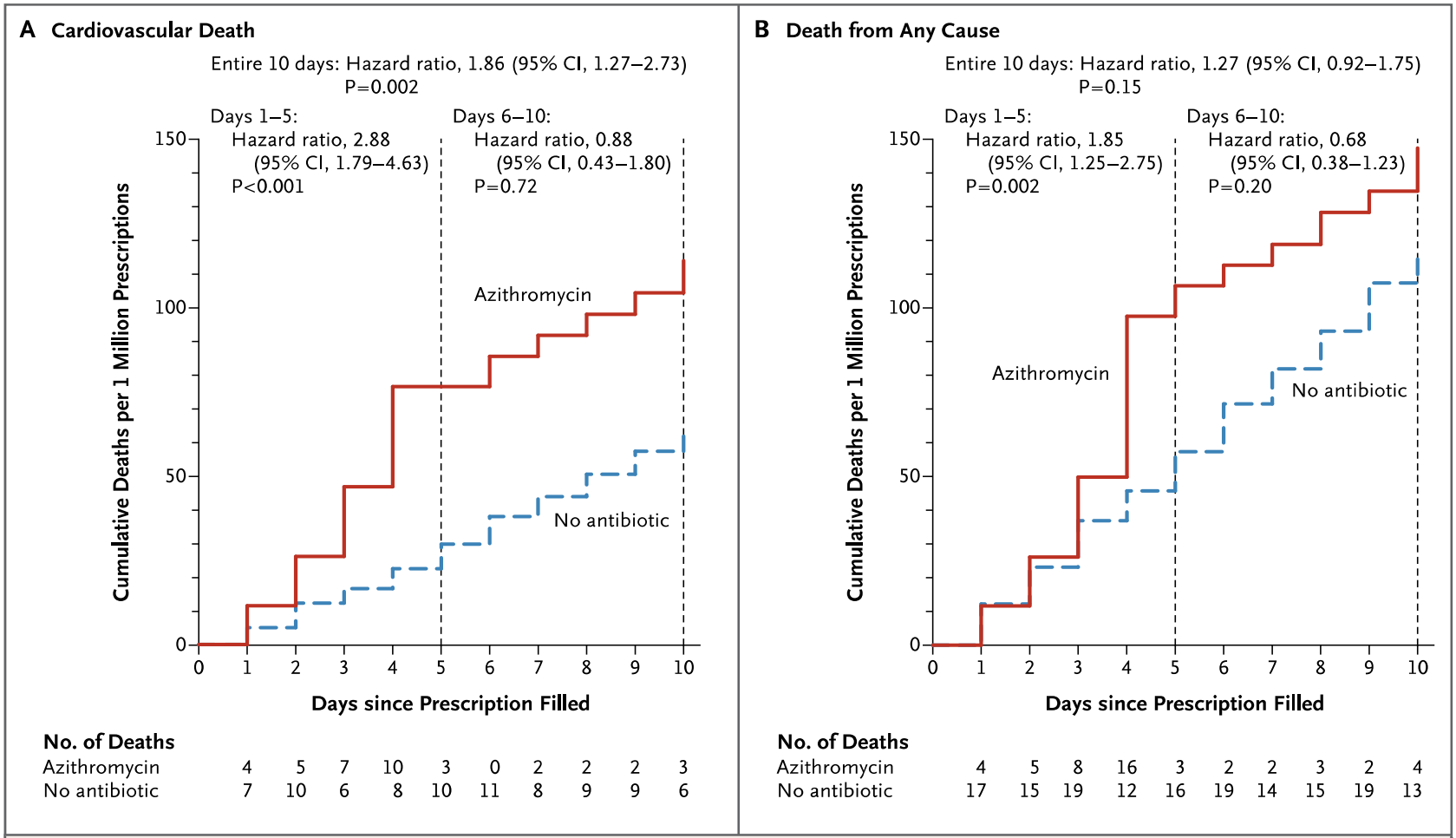


Figure 1. Cumulative Incidence of Cardiovascular Death and Death from Any Cause among Patients Who Took Azithromycin and Persons Who Did Not Take Study Antibiotics during a 10-Day Period.

The 10-day period began with the date on which the prescription was filled for patients who took azithromycin, with a matched period for persons who did not take study antibiotics (the reference group). The cumulative incidence in the reference group was not adjusted; the cumulative incidence in the group of patients who took azithromycin was adjusted for demographic factors and propensity score by multiplying the unadjusted incidence by the ratio of the adjusted to the unadjusted hazard ratio for the 10-day period.

Source: WA Ray et al N Engl J Med 2012;366:1881-90

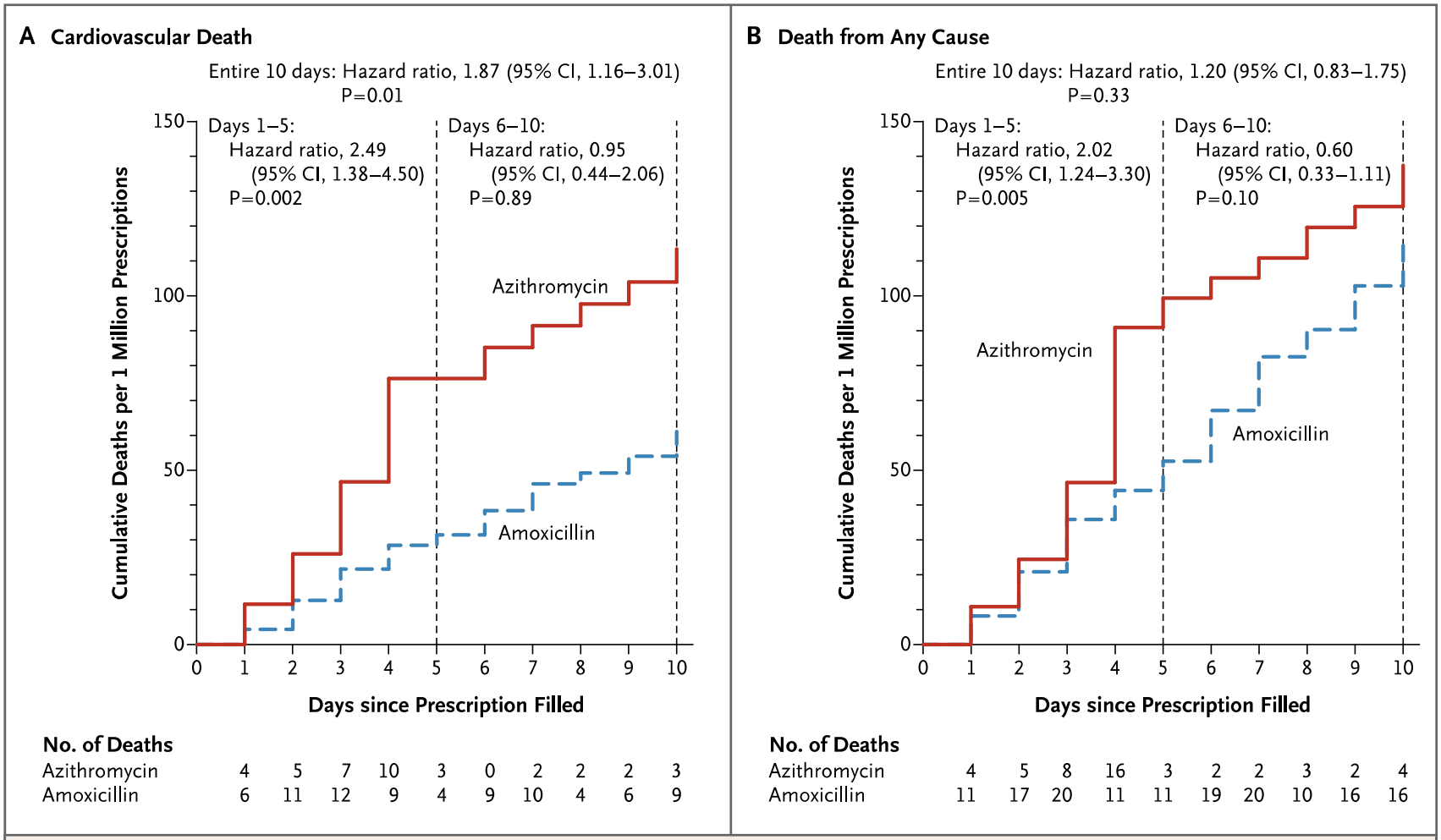


Figure 2. Cumulative Incidence of Cardiovascular Death and Death from Any Cause for Patients Who Took Azithromycin or Amoxicillin during a 10-Day Period.

The 10-day period began with the date on which the prescription was filled. The cumulative incidence for patients who took amoxicillin (the reference group) was not adjusted; the cumulative incidence for patients who took azithromycin was adjusted for demographic factors and propensity score by multiplying the unadjusted incidence by the ratio of adjusted to unadjusted hazard ratios for the 10-day period.

Source: WA Ray et al N Engl J Med 2012;366:1881-90

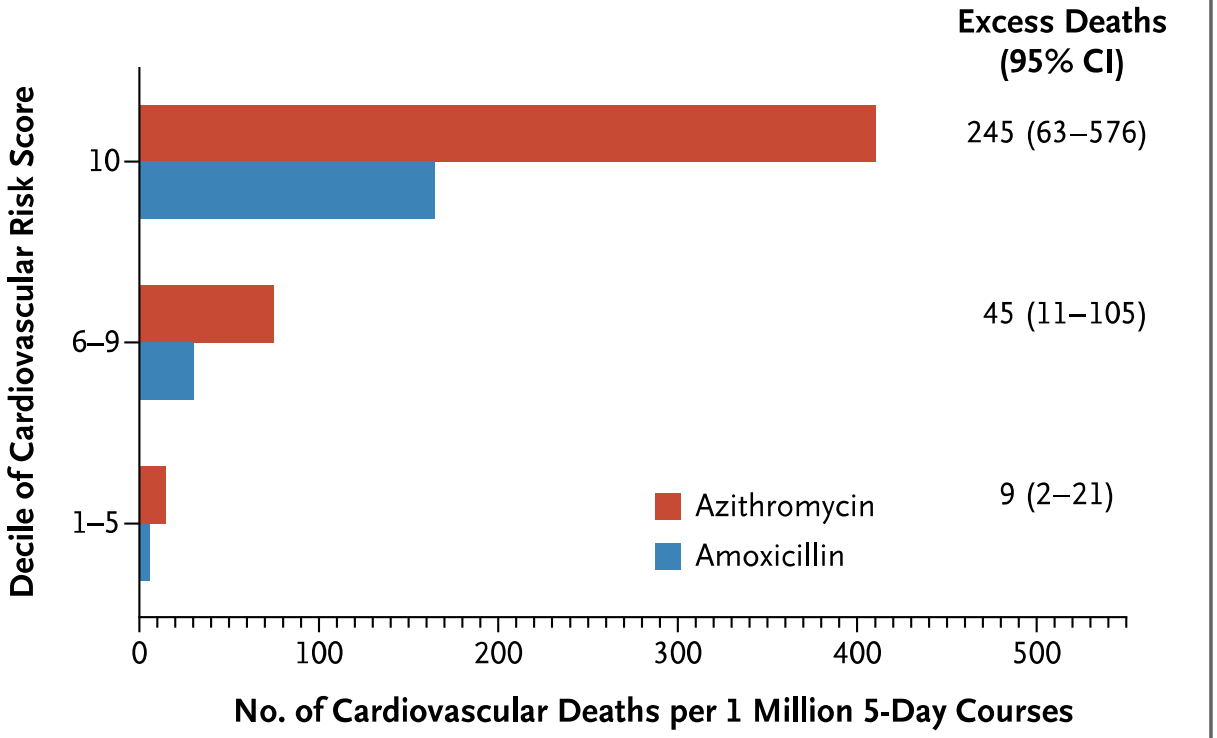


Figure 3. Excess Risk of Cardiovascular Death with Azithromycin as Compared with Amoxicillin, According to Decile of Cardiovascular Risk Score.

The analysis of excess risk was adjusted for demographic factors and propensity score, which included the recorded antibiotic indication. The excess risk of cardiovascular death with azithromycin (i.e., the difference in the cumulative incidence of cardiovascular death with azithromycin and with amoxicillin) is shown, with the 95% confidence interval (CI), according to the risk-score decile. The characteristics of the patients who took azithromycin, according to decile of risk score for cardiovascular disease, are shown in Table 12 in the Supplementary Appendix.

Source: WA Ray et al N Engl J Med 2012;366:1881-90

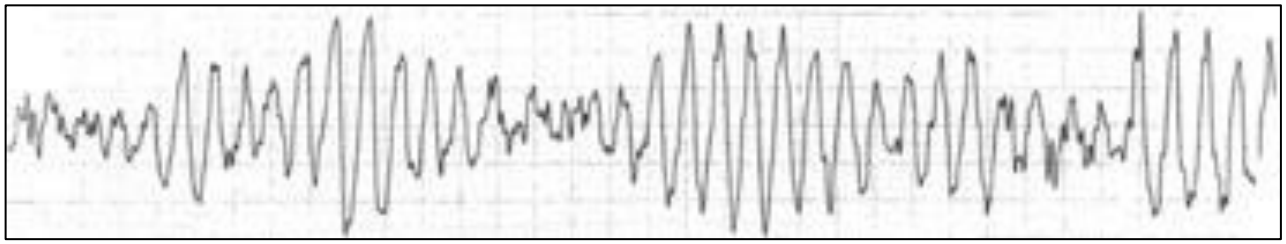
Study Conclusions

- During 5 days of azithromycin therapy, there was a small absolute increase in cardiovascular deaths
  - Compared with amoxicillin, there were 47 additional cardiovascular deaths per 1 million courses of azithromycin therapy
  - For patients in the highest decile of baseline risk of cardiovascular disease, there were 245 additional cardiovascular deaths per 1 million courses

Source: WA Ray et al N Engl J Med 2012;366:1881-90

What this tells us

- Old drugs can still be unsafe drugs
- Population-based therapeutic studies are useful to detect safety signals
- Antibiotic use can be a killer



Emerging Infections

Who is this?

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

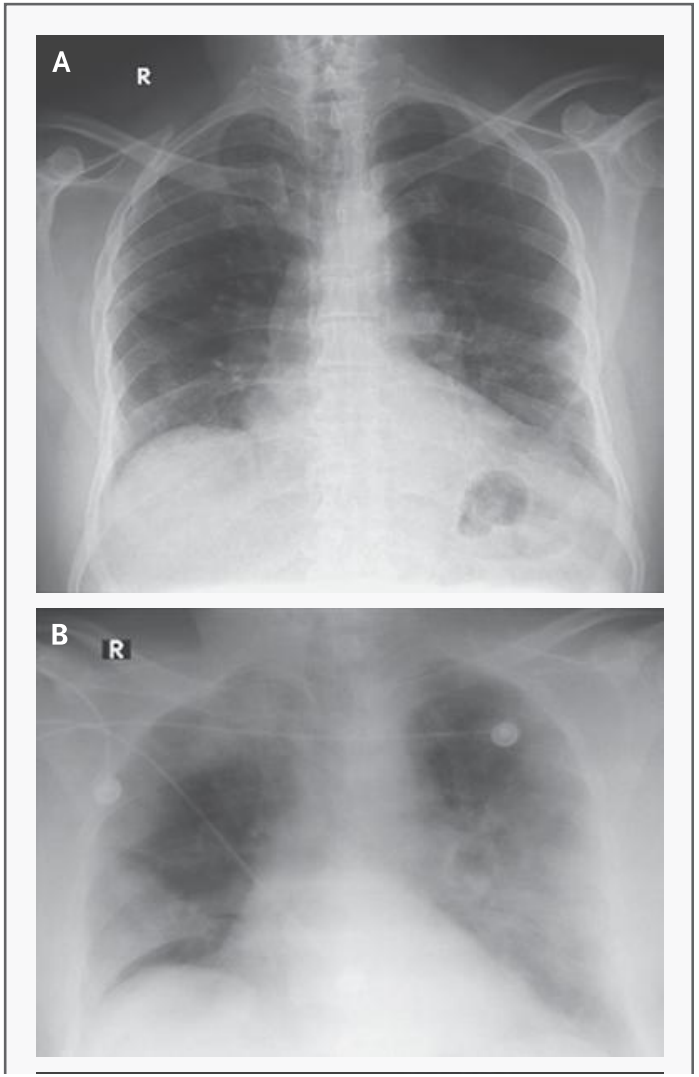
Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia

Ali Moh Zaki, M.D., Ph.D., Sander van Boheemen, M.Sc., Theo M. Bestebroer, B.Sc., Albert D.M.E. Osterhaus, D.V.M., Ph.D., and Ron A.M. Fouchier, Ph.D.

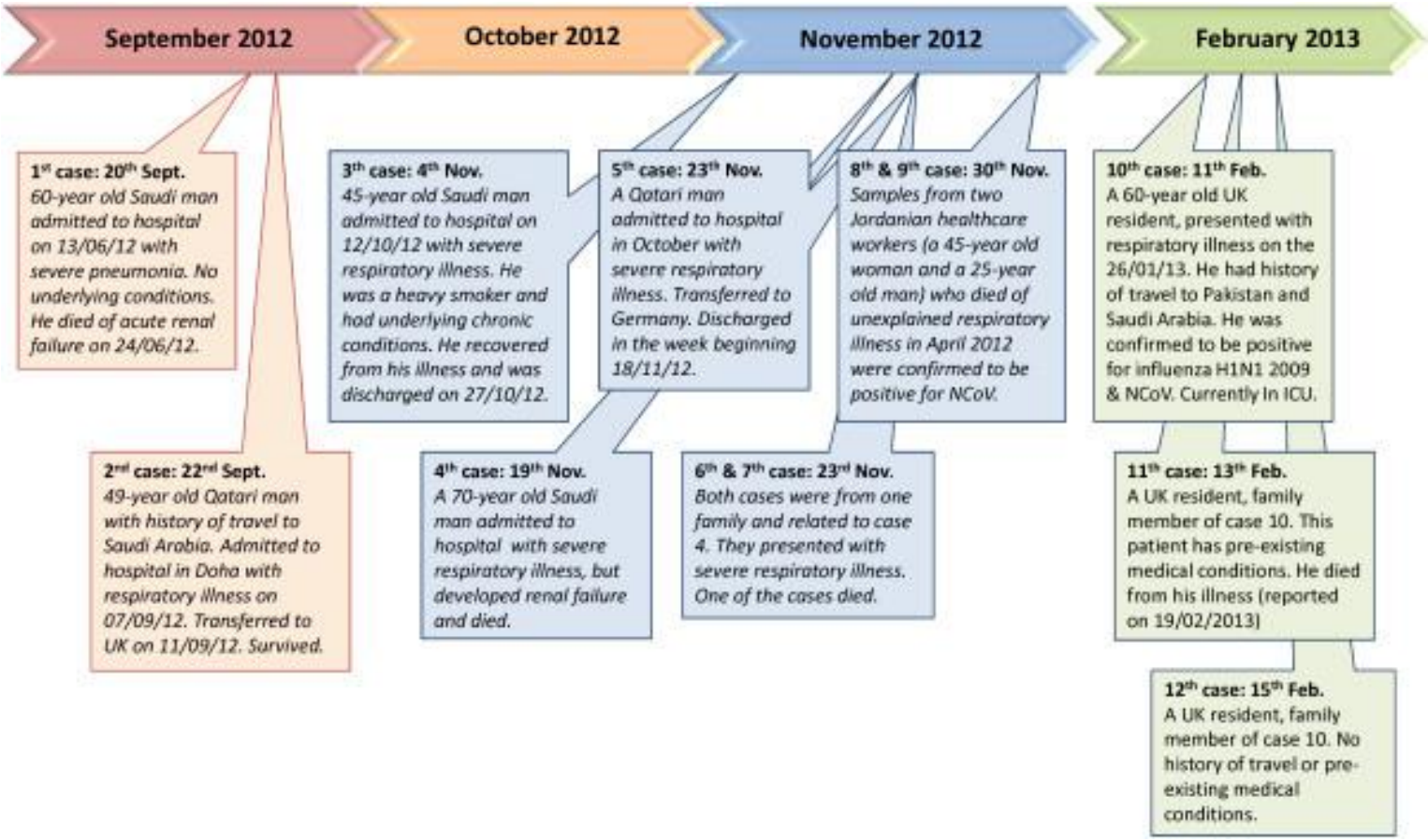
AM Zaki et al N Engl J Med 2012;367:1814-20

Index Patient

- 60 year old Saudi male
- Seen in June 2012 with 7-day history of fever & cough
- Patient died 11 days after admission with respiratory and renal failure



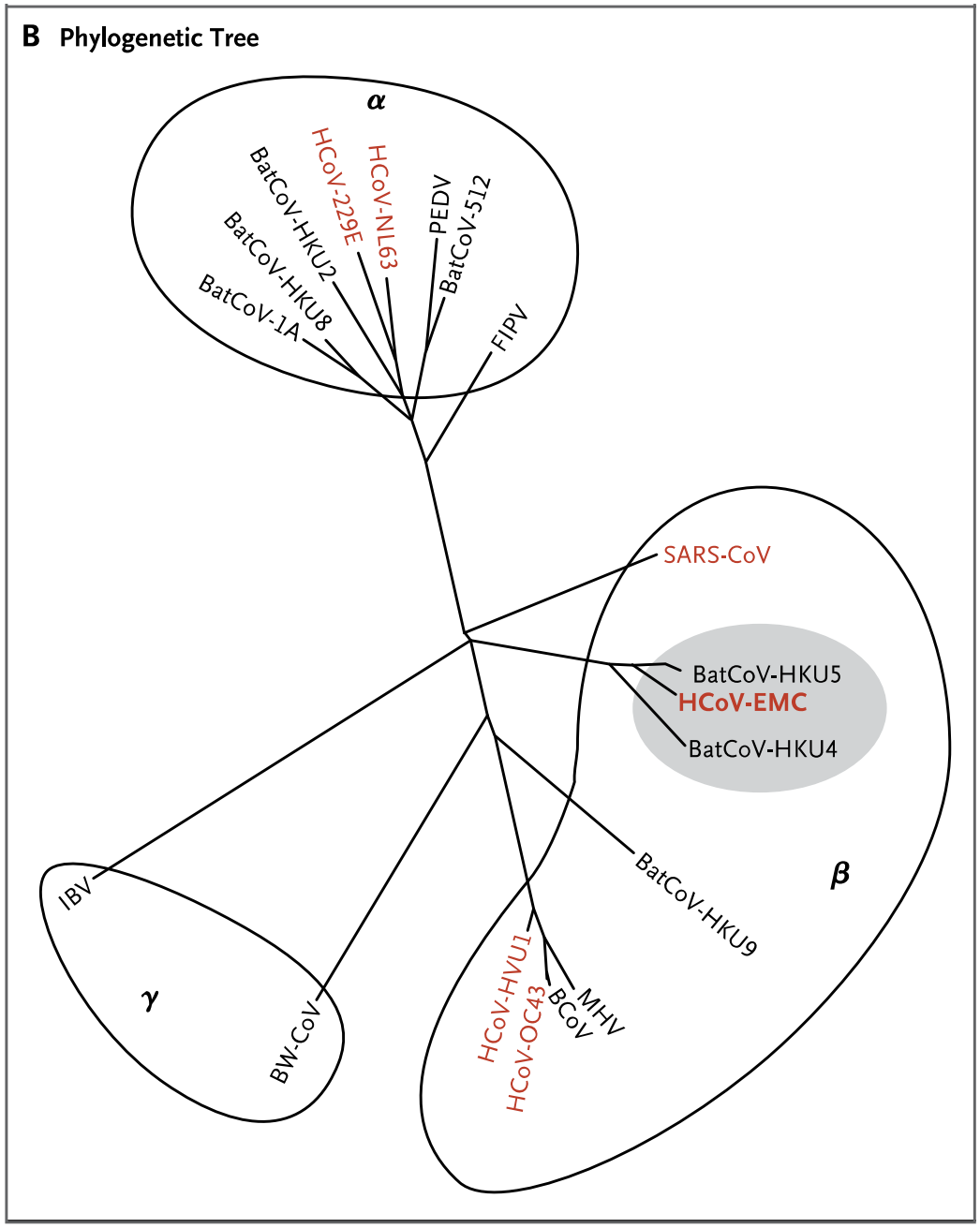
AM Zaki et al N Engl J Med 2012;367:1814-20


September 2012
October 2012
November 2012
February 2013
1st case: 20th Sept.
60-year old Saudi man admitted to hospital on 13/06/12 with severe pneumonia. No underlying conditions. He died of acute renal failure on 24/06/12.
2nd case: 22nd Sept.
49-year old Qatari man with history of travel to Saudi Arabia. Admitted to hospital in Doha with respiratory illness on 07/09/12. Transferred to UK on 11/09/12. Survived.
3th case: 4th Nov.
45-year old Saudi man admitted to hospital on 12/10/12 with severe respiratory illness. He was a heavy smoker and had underlying chronic conditions. He recovered from his illness and was discharged on 27/10/12.
4th case: 19th Nov.
A 70-year old Saudi man admitted to hospital with severe respiratory illness, but developed renal failure and died.
5th case: 23th Nov.
A Qatari man admitted to hospital in October with severe respiratory illness. Transferred to Germany. Discharged in the week beginning 18/11/12.
6th & 7th case: 23rd Nov.
Both cases were from one family and related to case 4. They presented with severe respiratory illness. One of the cases died.
8th & 9th case: 30th Nov.
Samples from two Jordanian healthcare workers (a 45-year old woman and a 25-year old man) who died of unexplained respiratory illness in April 2012 were confirmed to be positive for NCoV.
10th case: 11th Feb.
A 60-year old UK resident, presented with respiratory illness on the 26/01/13. He had history of travel to Pakistan and Saudi Arabia. He was confirmed to be positive for influenza H1N1 2009 & NCoV. Currently In ICU.
11th case: 13th Feb.
A UK resident, family member of case 10. This patient has pre-existing medical conditions. He died from his illness (reported on 19/02/2013)
12th case: 15th Feb.
A UK resident, family member of case 10. No history of travel or pre-existing medical conditions.

Novel Coronavirus - HCoV

- In September 2012, a novel coronavirus was isolated from the index patient
  - The clinical presentation was reminiscent of the outbreak caused by the SARS-coronavirus (SARS-CoV)
  - Sequence analysis of the new virus revealed that it was a member of the same genus as SARS-CoV
- By March 26, 2013, 17 laboratory- confirmed cases had been reported with 11 deaths
  - The first 9 cases were in individuals resident in the Middle East
  - 3 recent cases were in family members resident in the UK
  - Most recent case is UAE resident treated in Germany

Source: WHO at http://www.who.int/csr/don/2013_03_26/en/index.html



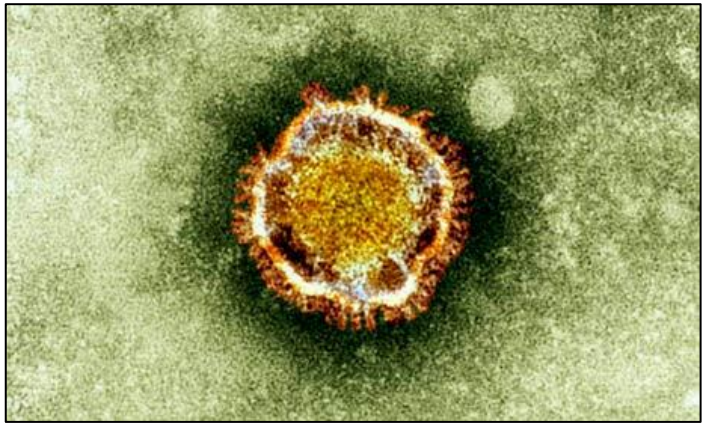
AM Zaki et al N Engl J Med 2012;367:1814-20

OBSERVATION

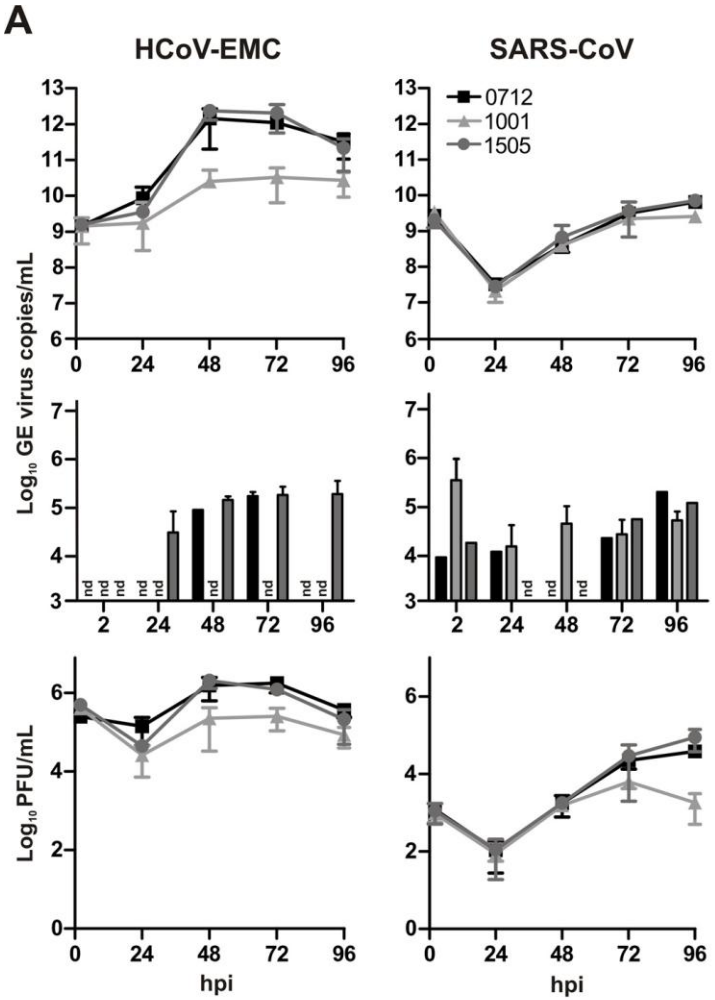
Efficient Replication of the Novel Human Betacoronavirus EMC on Primary Human Epithelium Highlights Its Zoonotic Potential

Eveline Kindler,[a] Hulda R. Jónsdóttir,[a] Doreen Muth,[b] Ole J. Hamming,[c] Rune Hartmann,[c] Regulo Rodriguez,[d] Robert Geffers,[e] Ron A. M. Fouchier,[f] Christian Drosten,[b] Marcel A. Müller,[b] Ronald Dijkman,[a] Volker Thiel[a,g]

Institute of Immunobiology, Kantonal Hospital, St. Gallen, Switzerland[a]; Institute of Virology, University of Bonn Medical Center, Bonn, Germany[b]; Department of Molecular Biology and Genetics, Centre for Structural Biology, University of Aarhus, Aarhus, Denmark[c]; Institute of Pathology, Kantonal Hospital, St. Gallen, Switzerland[d]; Genome Analytics Group, Helmholtz Center for Infection Research, Braunschweig, Germany[e]; Viroscience Lab, Erasmus Medical Center, Rotterdam, The Netherlands[f]; Vetsuisse Faculty, University of Zürich, Zürich, Switzerland[g]



Effective replication of HCoV in bronchial epithelial cells



Updated WHO Surveillance Criteria for NCoV as of March 18, 2013

1. A person with an ARI and indications of pulmonary parenchymal disease (e.g. pneumonia or ARDS), based on clinical or radiological evidence of consolidation, who requires admission to hospital

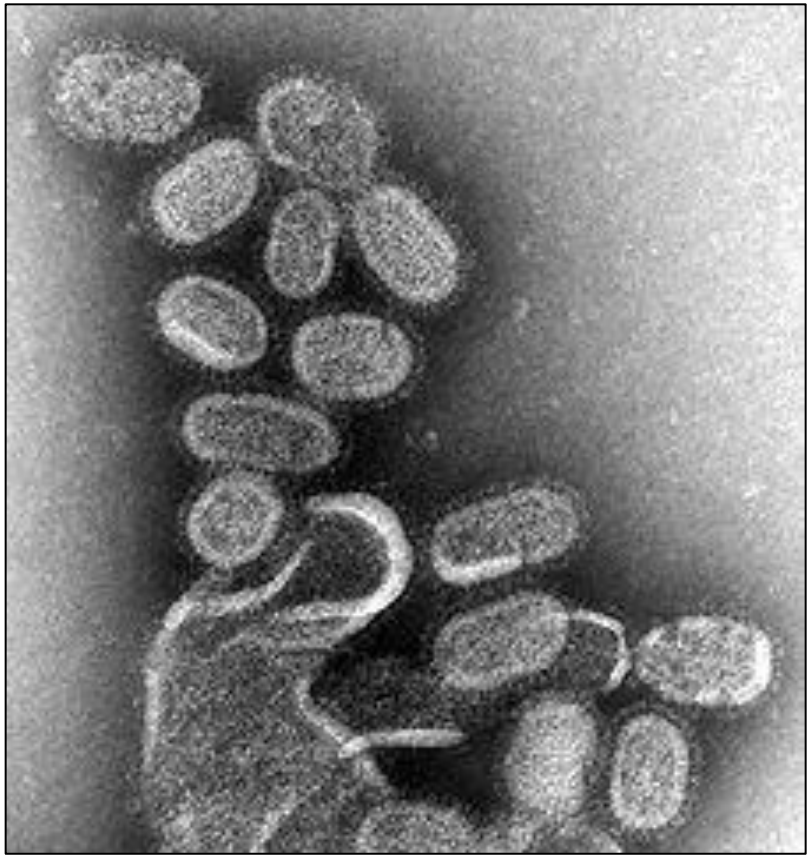
AND any of the following:

- The disease occurs as part of a cluster that occurs within a 10-day period , without regard to place of residence or history of travel, unless another aetiology has been identified.
- The disease occurs in HCW who has been working in an environment where patients with severe acute respiratory infections are being cared for, particularly patients requiring intensive care, without regard to place of residence or history of travel, unless another aetiology has been identified.
- Develops an unexpectedly severe clinical course despite appropriate treatment, without regard to place of residence or history of travel, even if another aetiology has been identified, if that alternate aetiology does not fully explain the presentation or clinical course of the patient.

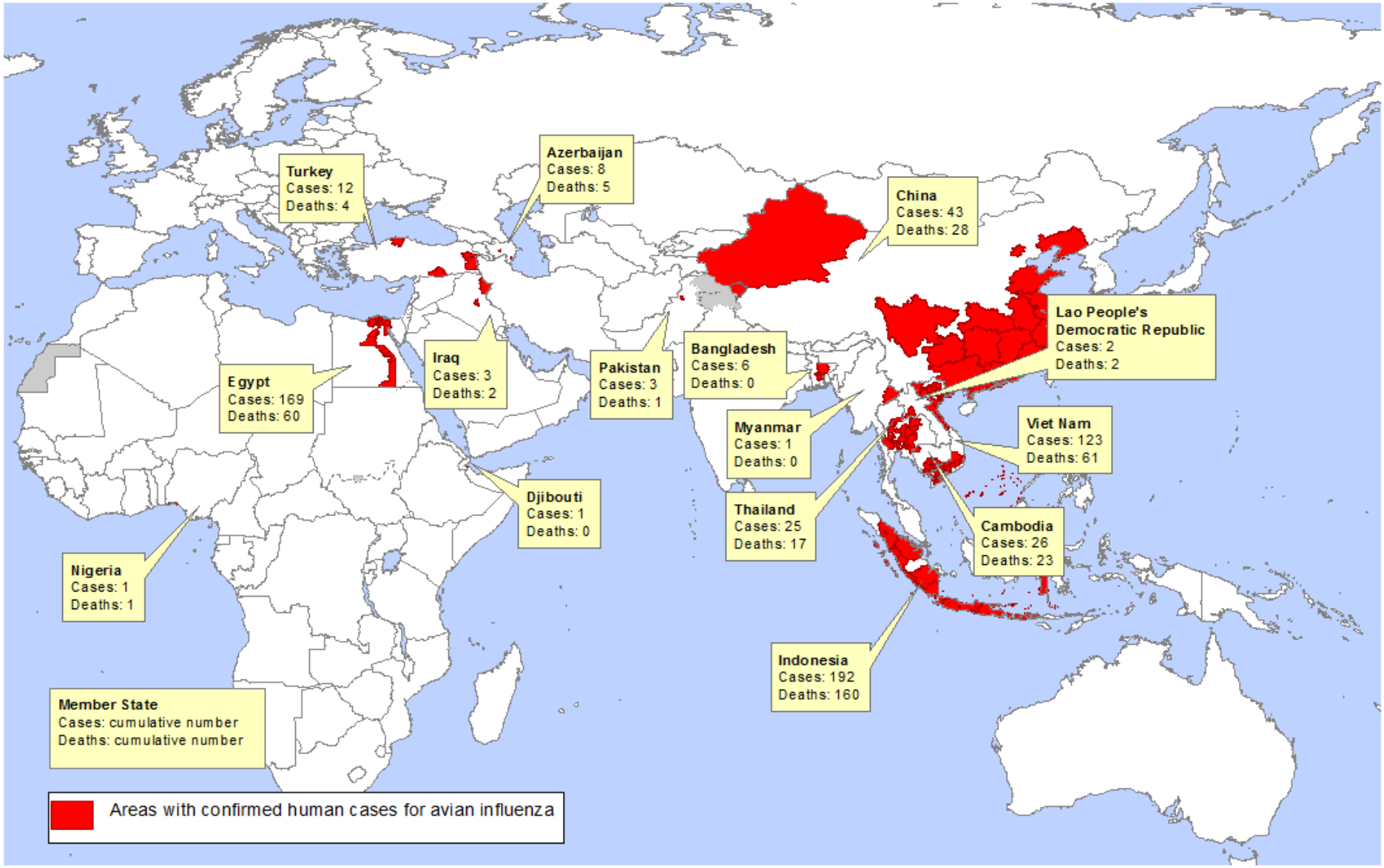
Updated WHO Surveillance Criteria NCoV

2. A person with an acute respiratory illness of any degree of severity who, within 10 days before onset of illness, had close contact with a confirmed or probable case of novel coronavirus infection, while the case was ill
3. For countries where the novel coronavirus has already been detected, the minimum standard for surveillance should be testing of patients with severe respiratory disease requiring mechanical ventilation

It’s back…



Areas with confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2013*



*All dates refer to onset of illness
Data as of 01 February 2013
Source: WHO/HIP

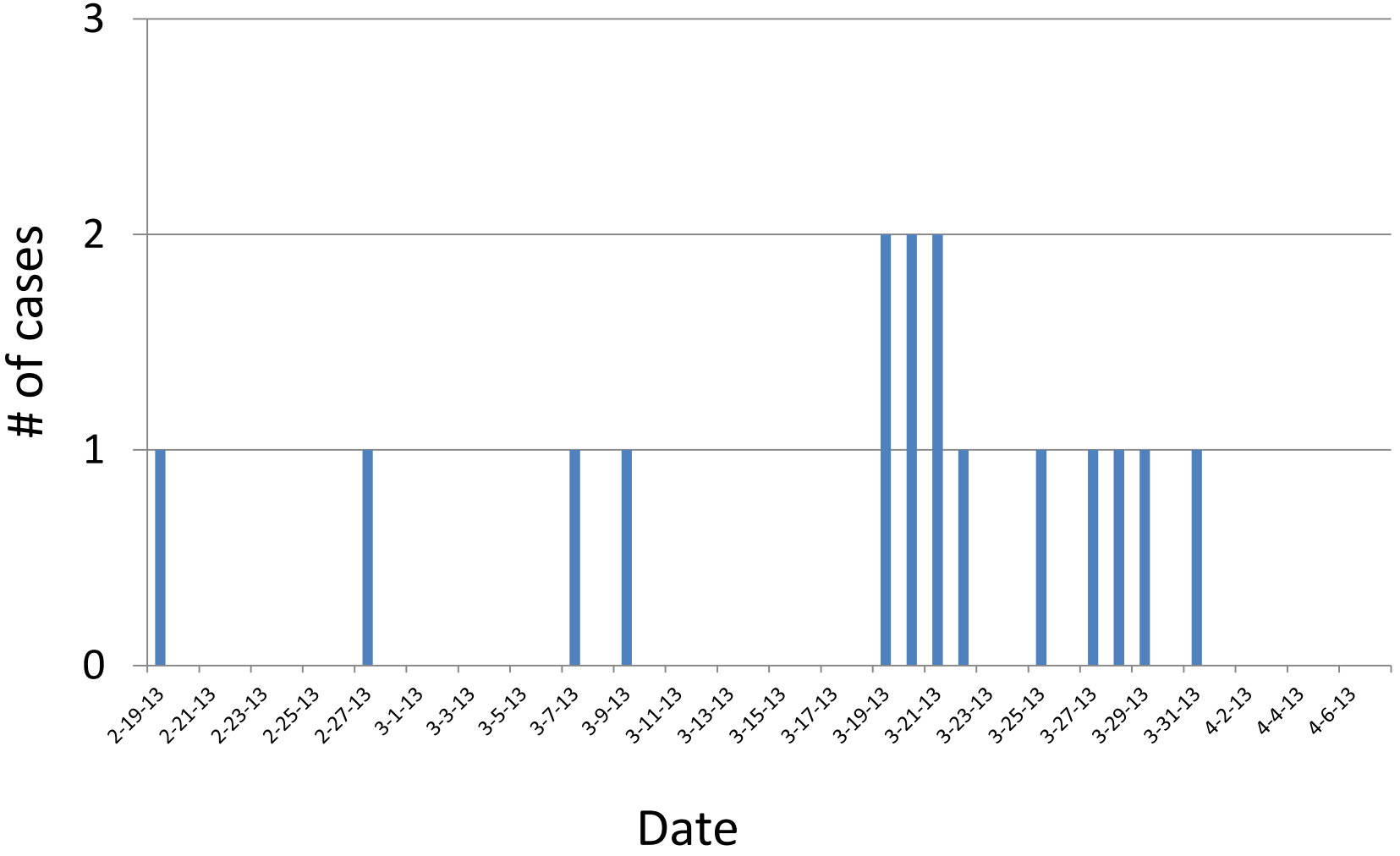
Influenza H7N9

- On March 31, 2013 health authorities in China notified WHO of 3 lab-confirmed cases of avian influenza A (H7N9) virus infection causing severe respiratory illness
- NML has access to the H7N9 whole genome sequence through the Global Initiative on Sharing Avian Influenza Data
- Whole genome analysis
  - Does not contain HPAI sequence
  - Appears to confer optimal temperature growth for mammalian species
- CDC progressing with early work on vaccine candidates

H7N9 Epidemiology

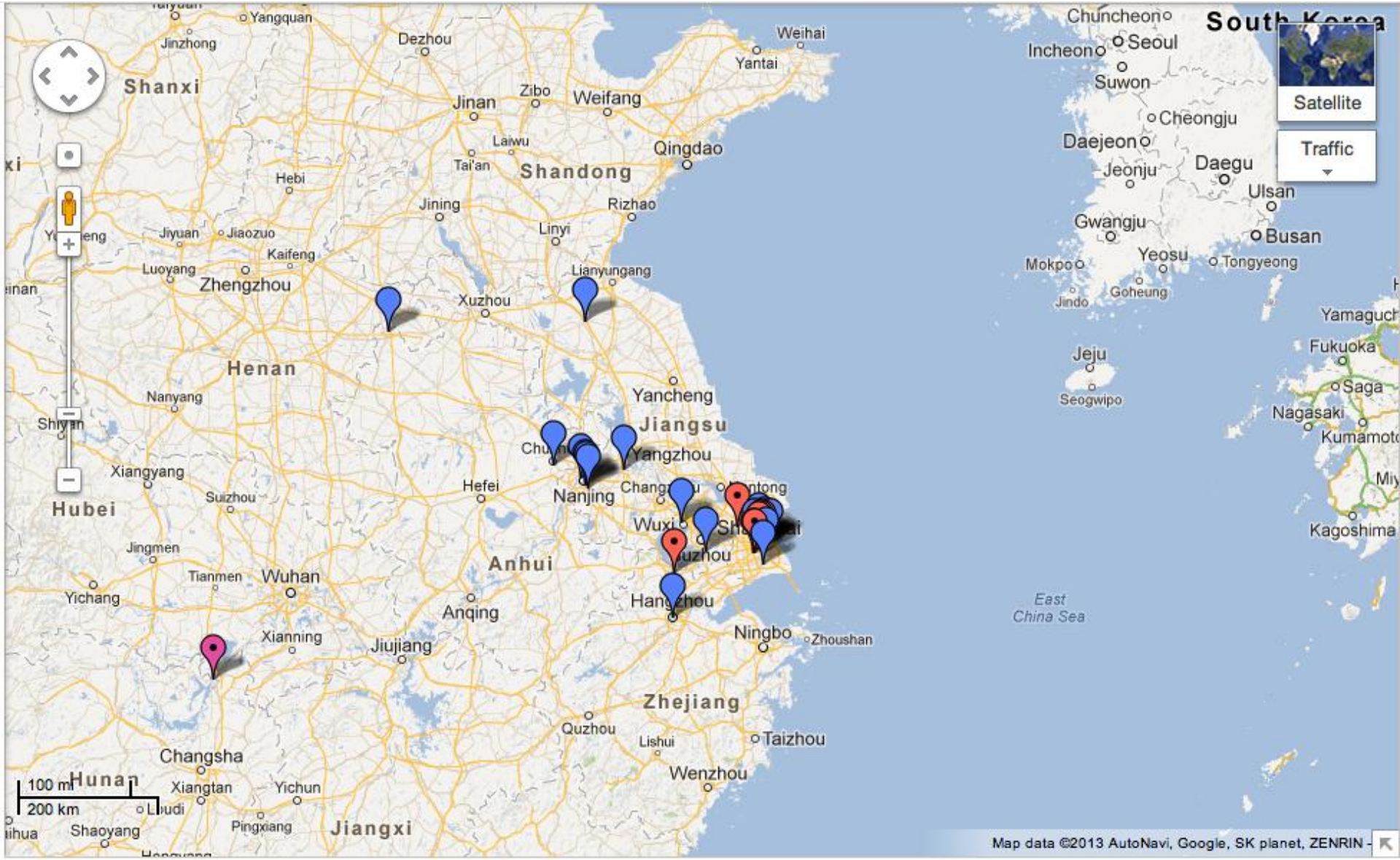
- Early in the disease, patients experience high fever and cough, which then progresses to pneumonia and severe acute respiratory distress
- The pandemic risk, route of transmission, incubation period and reservoir are unknown at this
- A wide range of zoonotic investigations are underway in China, including Poultry and Swine.
- At this time human-to-human transmission has not been established, and China is monitoring contacts of cases closely for signs and symptoms of illness

H7N9 as of April 5, 2013



H7N9 Map as of April 3, 2013

H7N9 Map as of April 8, 2013



H7N9 as of April 5, 2013

Location	Sex	Age	Onset	Hospitalization	Death	Report date
Shanghai	M	87	13-02-19	13-02-24	13-03-04	13-03-31
Shanghai	M	27	13-02-27	13-03-03	13-03-10	13-03-31
Chuzhou, Anhui Prov	F	35	13-03-09	13-03-19		13-03-31
Nanjing, Jiangsu Prov	F	45	13-03-19	13-03-27		13-04-03
Shuyang, Jiangsu Prov	F	48	13-03-19	13-03-30		13-04-03
Suzhou, Jiangsu Prov	M	83	13-03-20	13-03-29		13-04-03
Wuxi, Jiangsu Prov	F	32	13-03-21	13-03-28		13-04-03
Taicang, Zhejiang Prov	M	38	13-03-07	13-03-18	13-03-27	13-04-04
Hangzhou, Zhejiang Prov	M	67	13-03-25	13-04-02		13-04-04
Zhejiang Prov	M	64	13-03-29	13-03-31	13-04-04	13-04-04
Shanghai	M	48	13-03-28	13-04-03	13-04-03	13-04-04
Shanghai	F	67				13-04-04
Shanghai	F	52			13-04-03	13-04-04
Shanghai	M	4				13-04-04
Nanjing, Jiangsu Prov	F	61	13-03-20	13-04-02		13-04-05
Nanjing, Jiangsu Prov	M	79	13-03-21	13-03-31		13-04-05

Case count: 16
Deaths: 6

Draft Guidance for IPAC of Severe Respiratory Illness

Infection Prevention and Control Measures Including Type of Precautions and Personal Protective Equipment	
Routine Practices	For all patients, at all times, in all health care settings.
Contact and Droplet Precautions	Includes gloves and a gown as per point of care risk assessment. Unrecognized contamination of the patient care environment may warrant use of gloves and gowns for all patients with nCoV. A mask and face/eye protection should be worn when the health care workers will be working within two metres of the patient.
Airborne Precautions	For performing aerosol-generating medical procedures*. A respirator and face/eye protection is recommended for all health care workers present in a room where an aerosol-generating medical procedure is being performed on a patient.

What this tells us

- Another SARS is just around the corner
- We need to study potential zoonotic sources more closely
  - More interaction with our veterinary colleagues
- Surveillance and communication must be encouraged for early detection of new infectious diseases

CRE: What we thought VRE would be

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 62
March 5, 2013

Vital Signs: Carbapenem-Resistant Enterobacteriaceae

CRE in 2012

- Carbapenem-resistant Enterobacteriaceae (CRE) have become highly resistant to most or all antibiotics
- In the US, the incidence of CRE has increased from about 1% to 4% during the past decade
  - CRE bloodstream infections are associated with mortality rates approaching 50%.
- CRE has now spread throughout the United States
  - About 4% of acute-care hospitals and 18% of long-term acute-care hospitals reported at least one CRE to the NHSN in the first 6 months of 2012
  - Nearly all patients with CRE were currently or recently treated in a health- care setting

TABLE 1. Number and percentage of facilities reporting carbapenem-resistant* Enterobacteriaceae† from a catheter-associated urinary tract infection (CAUTI) or a central-line–associated bloodstream infection (CLABSI), by selected characteristics — United States, National Healthcare Safety Network, January–June 2012

Characteristic	No. of facilities with carbapenem-resistant Enterobacteriaceae from CAUTI or CLABSI	Total no. of facilities performing CAUTI or CLABSI surveillance (N = 3,918)	(%)§¶
Facility type			
All acute-care hospitals	181	3,918	(4.6)
Short-stay acute-care hospital	145	3,716	(3.9)
Long-term acute-care hospital	36	202	(17.8)
Hospital size (no. of beds)			
<100	48	1,609	(3.0)
100–299	46	1,480	(3.1)
300–499	41	541	(7.6)
≥500	45	258	(17.4)
Medical school affiliation			
Yes	102	1,079	(9.5)
No	53	2,839	(1.9)
U.S. Census region**			
Northeast	63	658	(9.6)
Midwest	30	927	(3.2)
South	50	1,503	(3.3)
West	29	804	(3.6)
Other††	9	26	(34.6)

CRE in US: 2001-2011

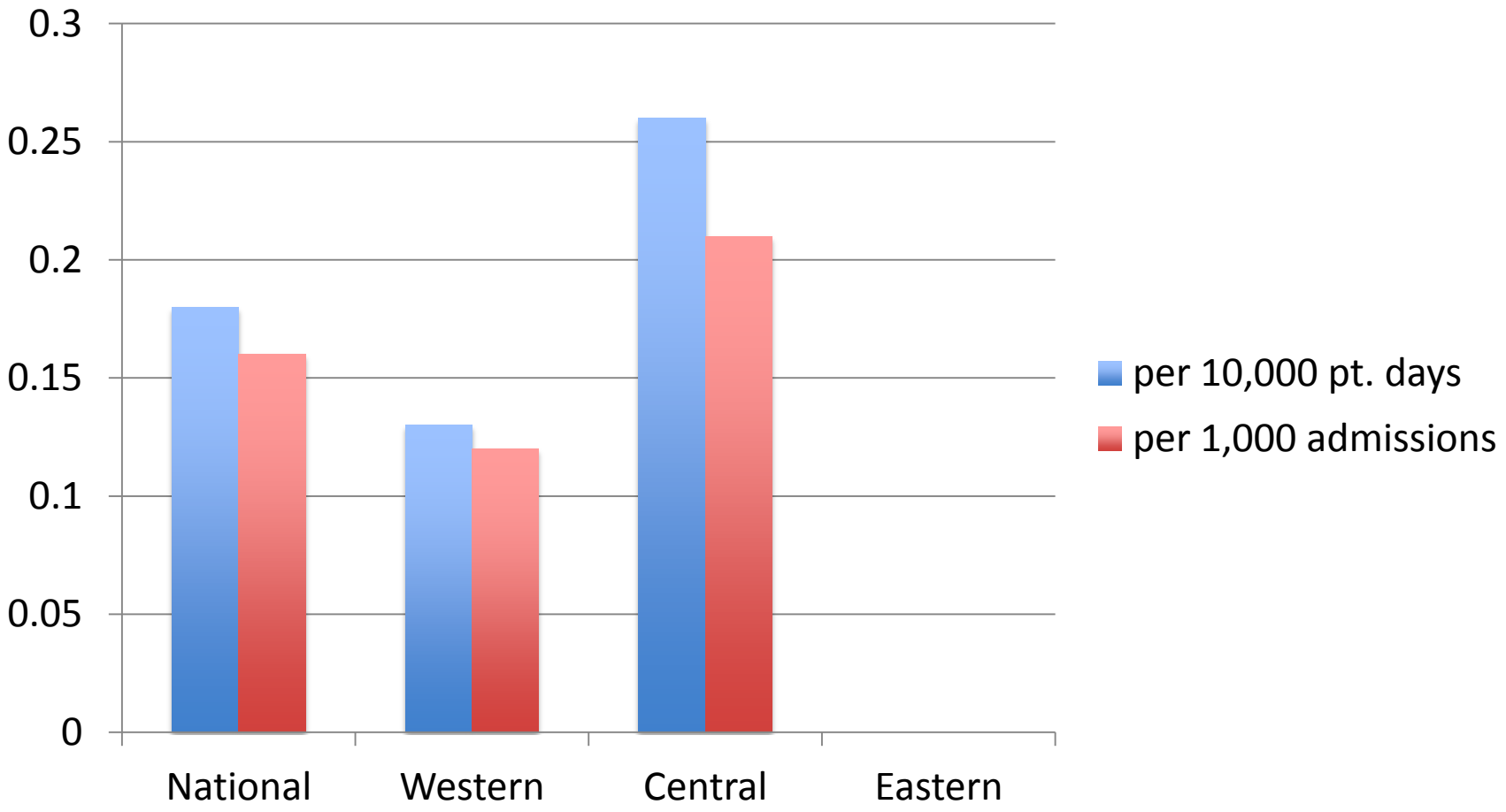
TABLE 2. Number of Enterobacteriaceae isolates, percentage reported to be tested against carbapenems, and percentage reported as carbapenem-resistant,* by data source, year, and type of organism — United States, National Nosocomial Infections Surveillance system (NNIS), National Healthcare Safety Network (NHSN), and the Surveillance Network–USA (TSN)†

	NNIS (2001)			NHSN (2011)		
Type of organism	**No. of isolates**	**Reported as tested against ≥1 carbapenem No. (%)**	**Reported as carbapenem-resistant* No. (%)**	**No. of isolates**	**Reported as tested against ≥1 carbapenem No. (%)**	**Reported as carbapenem-resistant* No. (%)**
Klebsiella pneumoniae and *oxytoca*	654	253 (38.7)	4 (1.6)	1,902	1,312 (69.0)	136 (10.4)
Escherichia coli	1,424	421 (29.6)	4 (1.0)	3,626	2,348 (64.8)	24 (1.0)
Enterobacter aerogenes and *cloacae*	553	288 (52.1)	4 (1.4)	1,045	728 (69.7)	26 (3.6)
Total	**2,631**	**962(36.6)**	**12 (1.2)**	**6,573**	**4,388 (66.8)**	**186 (4.2)**

TABLE 3. Number and percentage of episodes of positive cultures for carbapenem-resistant* *Enterobacteriaceae*† (N = 72) from three communities,§ by selected characteristics — United States, Emerging Infections Program, August–December 2011

Characteristic	No.	(%)
Patient characteristics		
Female sex	36	(50)
White race	32	(45)
Median age (range) (yrs)	60	(8–91)
<18	2	(3)
≥65	30	(42)
Type of health-care exposure¶		
Hospitalization	34	(72)
Presence of urinary catheter within the past 2 days	22	(47)
Long-term care facility	17	(36)
Surgery	12	(26)
Presence of other indwelling device within the past 2 days	11	(23)
Presence of central line within the past 2 days	9	(19)
None	6	(4)
Dialysis	3	(13)
Outcome		
Hospitalized	59	(82)
Intensive-care unit within 7 days of positive culture	16	(22)
Died	3	(4)

CRE in Canada: CNISP Data 2010-11



Source: Mounchili A et al Carbapenem-Resistant Gram-Negative Enterobacteriaceae and Acinetobacter baumannii in Canadian Acute Care Hospitals(CNISP) 2010-2011 Submitted to JAC

CRE in Canada: CNISP Data 2010-11

Table 1. Carbapenem-Resistant Gram-negative bacteria, CNISP 2010-2011

Pathogens	NON-Carbapenemase producers (n= 78)	Carbapenemase Producers (n= 78)						Overall
		KPC[1]	NDM-1[2]	VIM[3]	GES[4]	OXA-23[5]	Subtotal	
Enterobacter spp.	**43 (35%)**	4 (3%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	**5 (4%)**	**48 (34%)**
Klebsiella pneumoniae	**8 (6%)**	21 (17%)	8 (7%)	1 (1%)[6]	0 (0%)	0 (0%)	**29 (23%)**[7]	**37 (30%)**
Escherichia coli	**11 (9%)**	1 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	**2 (2%)**	**13 (11%)**
Serratia marcescens	**2 (2%)**	7 (6%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	**8 (7%)**	**10 (8%)**
Morganelli morganii	**8 (6%)**	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	**1 (1%)**	**9 (7%)**
Citrobacter freundii	**4 (3%)**	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**	**4 (3%)**
Providencia rettgeri	**1 (1%)**	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**	**1 (1%)**
Cedecea spp.	**1 (1%)**	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**	**1 (1%)**
Acinetobacter baumannii	**0 (0%)**	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	**1 (1%)**	**1 (1%)**
Overall	**78 (63%)**	**33 (27%)**	**9 (7%)**	**2 (2%)**	**2 (2%)**	**1 (1%)**	**46 (37%)**	**124 (100%)**

[1] KPC = *Klebsiella pneumoniae* carbapenemase
[2] NDM-1 = New Delhi metallo-beta-lactamase 1
[3] VIM = Verona integronencoded metallo-beta-lactamase
[4] GES = Guiana Extended Spectrum beta-lactamase
[5] OXA-23 = Oxacillinase-23
[6] KPC was isolated from the same specimen; consequently, this isolate was counted twice (under KPC & VIM).
[7] The subtotal amount to 29 because one *K. pneumoniae* isolate from which both KPC & VIM were isolated were counted as one.

Source: Mounchili A et al Carbapenem-Resistant Gram-Negative Enterobacteriaceae and Acinetobacter baumannii in Canadian Acute Care Hospitals(CNISP) 2010-2011 Submitted to JAC

CRE: IPAC Implications

- Preventing spread is important
  - Active case detection
  - Contact precautions for colonized or infected patients
  - Cohorting of patients and staff
  - Encouraging appropriate antibiotic use in all settings
  - Communication about infections when patients transfer

What this tells us

- CRE is going to be what we thought VRE was going to be
- We need IPAC precautions now to slow the advance of CRE into the hospital environment
- We need investment into new antimicrobials effective against CRE

Cures?

Fake Stool: The Next Step

Petrof *et al. Microbiome* 2013, **1**:3
http://www.microbiomejournal.com/content/1/1/3

Microbiome

METHODOLOGY Open Access

Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut

Elaine O Petrof[1*†], Gregory B Gloor[2†], Stephen J Vanner[1], Scott J Weese[3], David Carter[4], Michelle C Daigneault[5], Eric M Brown[5], Kathleen Schroeter[5] and Emma Allen-Vercoe[5]

Study Design

- Proof of principle study
- Two patients with recalcitrant CDI
  - Failed at least 3 courses of metronidazole and/or oral vancomycin
  - Infected with hypervirulent *C. difficile* ribotype 078
- Stool substitute
  - Pure culture of 33 bacterial isolates purified from intestinal bacterial cultures from a single healthy donor
  - Infused throughout the right and mid-colon via colonoscopy
- Each patient reverted to their normal bowel pattern within 2 to 3 days and remained symptom-free at 6 months

Table 1 Composition of stool substitute (RePOOPulate)

Closest species match, inferred by alignment of 16S rRNA sequence to GreenGenes database[a]	% identity to closest match	Relative abundance (by biomass) in RePOOPulate formulation
Acidaminococcus intestinalis	100	+++
Bacteroides ovatus	99.52	+
Bifidobacterium adolescentis (two different strains)	99.79	++
	99.79	++
Bifidobacterium longum (two different strains)	99.86	+++
	99.16	+++
Blautia producta	96.43	+
Clostridium cocleatum	91.92	+
Collinsella aerofaciens	98.73	+
Dorea longicatena (two different strains)	99.62	+
	99.60	+
Escherichia coli	99.80	+
Eubacterium desmolans	94.90	+
Eubacterium eligens	98.15	+++++
Eubacterium limosum	97.05	+
Eubacterium rectale (four different strains)	99.59	+++++
	99.60	+++++
	99.19	+++++
	99.53	+++++
Eubacterium ventriosum	100	++
Faecalibacterium prausnitzii	99.17	+++++
Lachnospira pectinoshiza	95.22	+
Lactobacillus casei/paracasei	99.47	+
Lactobacillus casei	99.74	+
Parabacteroides distasonis	99.45	++
Raoultella sp.	99.40	+
Roseburia faecalis	99.65	++
Roseburia intestinalis	100	++
Ruminococcus torques (two different strains)	99.15	+++
	99.29	+++
Ruminococcus obeum (two different strains)	94.89	+
	94.69	+
Streptococcus mitis[b]	99.79	+

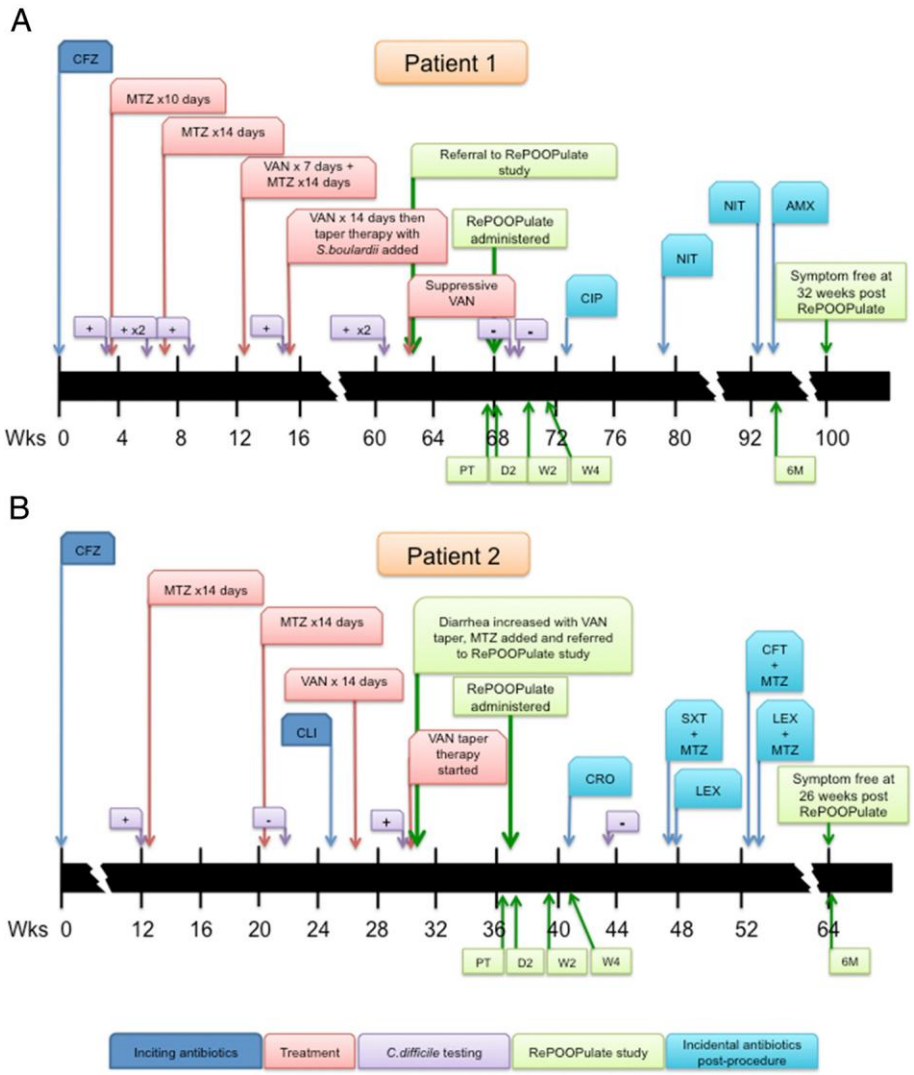


Figure 1 Clinical timeline of events for Patients 1 and 2. Sequence of events for the first two patients enrolled in the study. **(A)** Patient 1 had *Clostridium difficile* initially occurring after a pre-operative course of cefazolin for elective total knee arthroplasty. **(B)** Patient 2 had *C. difficile* initially occurring after a course of cefazolin for cellulitis. Both patients had multiple courses of antibiotic treatment for the *C. difficile* infection with both vancomycin and metronidazole prior to enrollment, as indicated. In addition, Patient 1 received the probiotic *Saccharomyces boulardii*. Prior to treatment with the stool substitute preparation RePOOPulate (RP), stool collection on each patient was carried out at 2 days pre treatment (PT), day 2 post treatment (D2), week 2 post treatment (W2), week 4 post treatment (W4), and 6 months post treatment (6 M). Toxin assays for *C. difficile* were also performed (purple boxes), with results as shown. Incidental antibiotic use post treatment is indicated. AMX, amoxicillin; CFZ, cefazolin; CIP, ciprofloxacin; CLI, clindamycin; CRO, ceftriaxone; LEX, cephalexin; MTZ, metronidazole; NIT, nitrofurantoin; SXT, trimethoprim-sulfamethoxazole; VAN, vancomycin.

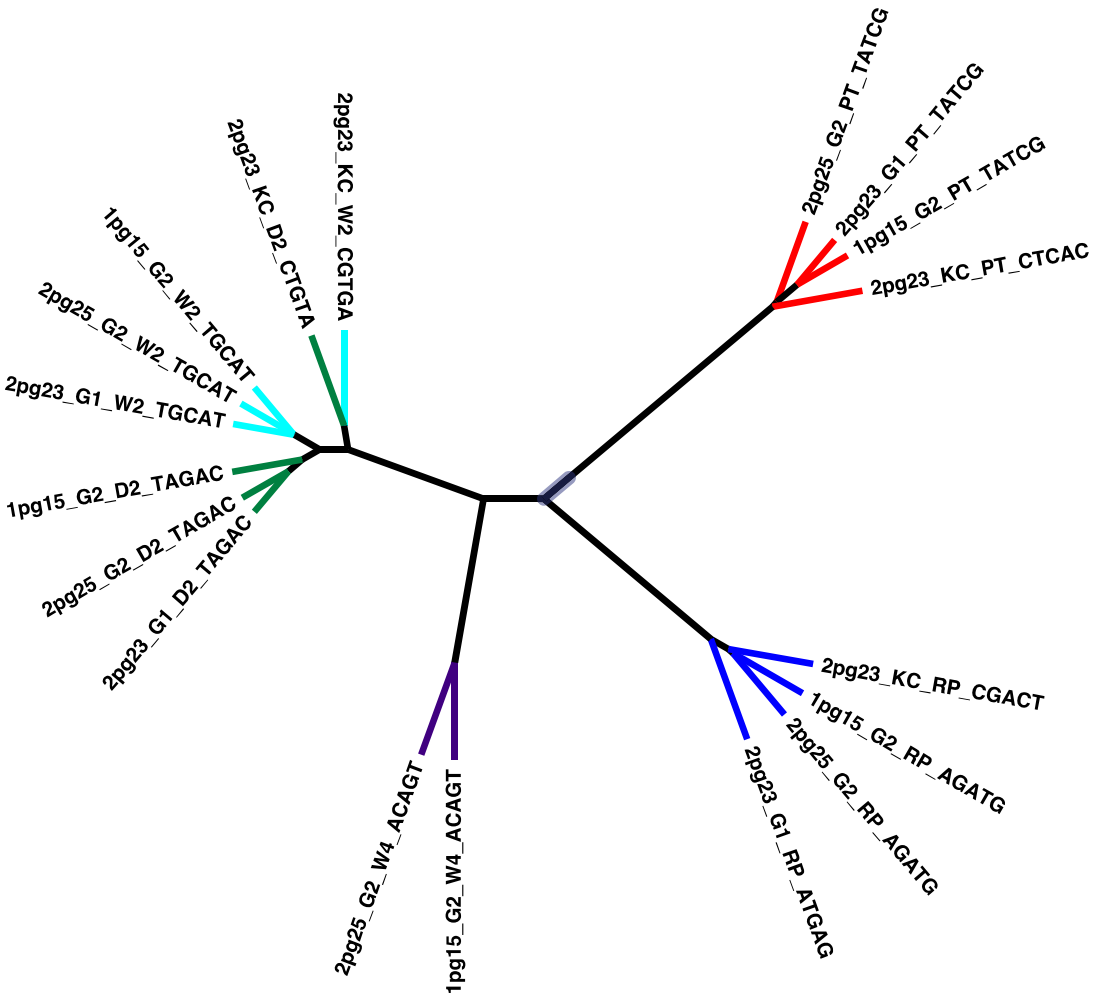


Figure 2 Distance tree of weighted UniFrac distances between samples for Patient 1 amplified and sequenced independently. Distance tree calculated by the unweighted pair group method with arithmetic mean. Branch tips are colored by sample: red, pre-treatment; blue, RePOOPulate formulation. Post-treatment samples are colored green (D2), cyan (W2), and purple (W4). Tip label fields are separated by an underscore character and the fields are: Ion Torrent run ID, person and time of amplification, sample identifier, barcode sequence.

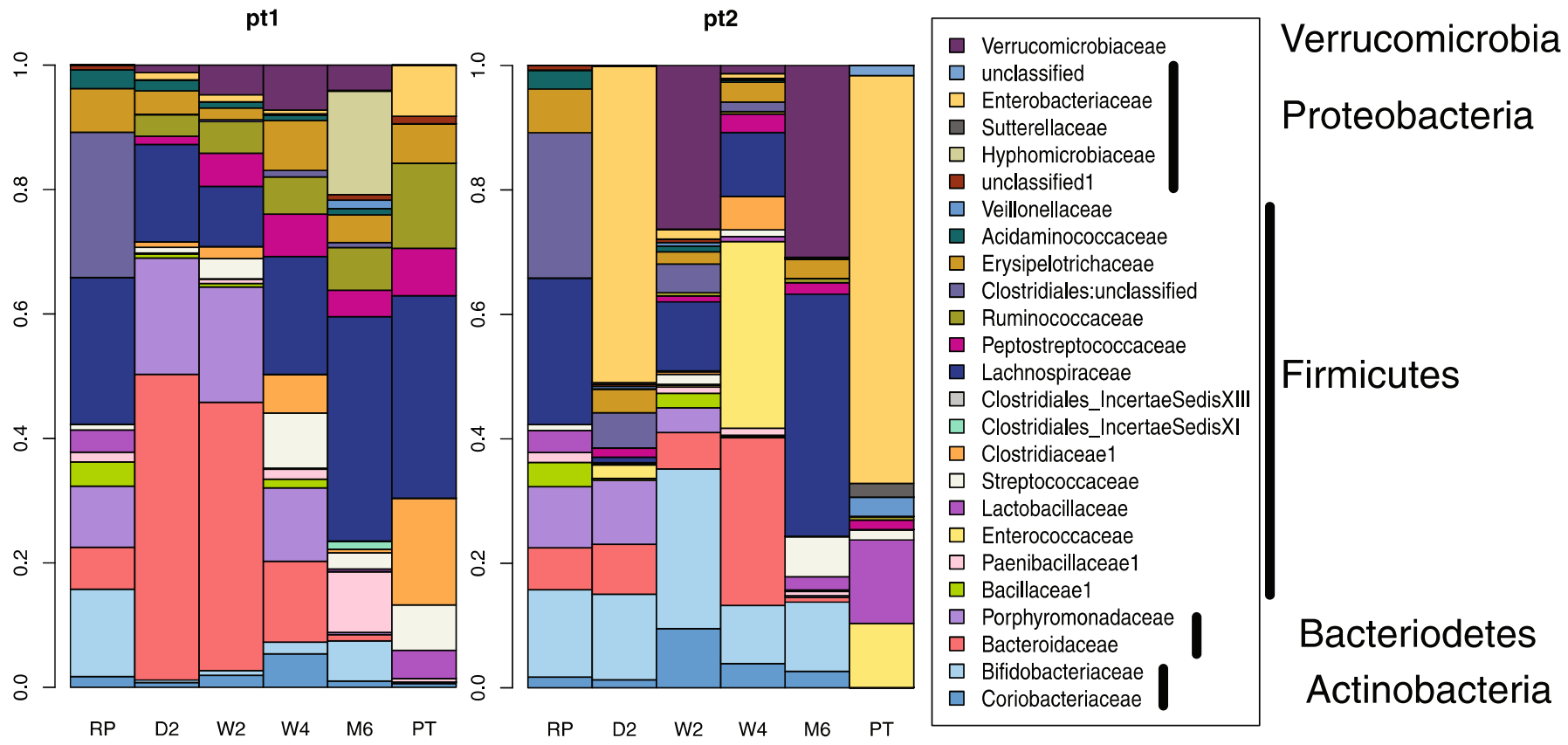


Figure 4 Barplot of abundance at the family level. Operational taxonomic units (OTUs) that comprised more than 0.5% of the OTUs in any sample were grouped into the appropriate family and plotted. These plots show how the actual composition of each sample changes over time. Note that the two patients had very different initial microbiota compositions. The compositional differences were maintained at all time points, suggesting that environmental or genetic factors were important in shaping community structure.

What this tells us

- Despite the complexity of the human fecal microbiome, effective artificial stool for treating CDI is possible
- Artificial stool could make stool “transplant” more palatable
- Artificial microbiome therapy may be possible for other diseases e.g. bacterial vaginosis, chronic sinusitis,

The Beginning of the End?

OPEN ACCESS Freely available online

PLOS | PATHOGENS

Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

Asier Sáez-Cirión[1]*, Charline Bacchus[2], Laurent Hocqueloux[3], Véronique Avettand-Fenoel[4,5], Isabelle Girault[6], Camille Lecuroux[6], Valerie Potard[7,8], Pierre Versmisse[1], Adeline Melard[4], Thierry Prazuck[3], Benjamin Descours[2], Julien Guergnon[2], Jean-Paul Viard[5,9], Faroudy Boufassa[10], Olivier Lambotte[6,11], Cécile Goujard[10,11], Laurence Meyer[10,12], Dominique Costagliola[7,8,13], Alain Venet[6], Gianfranco Pancino[1], Brigitte Autran[2], Christine Rouzioux[4,5]*, the ANRS VISCONTI Study Group[¶]

Sáez-Cirión et al PLOS Pathogens 2013; 9: 1-12

PTC Study Population

- 14 HIV-1-infected pts. with durable viral control following the interruption of effective ART that was initiated during 1° HIV infection (PHI)
  - 12/14 had symptomatic PHI
- The median ART duration = 36.5 months
- Viral control persisted for a median of 89 months following the discontinuation of ART
  - 8/14 had VL below the detection limit in all available samples after treatment interruption
  - 6/14 had occasional increases in VL

Sáez-Cirión et al PLOS Pathogens 2013; 9: 1-12

Table 1. Characteristics of PTC included in the study.

Code	Sex[1]	Year of diagnostic	PHI[2]	Fiebig	ART initiation	ART combination[3]	Time on cART (months)	Time since interruption (months)
OR1	M	1996	Sympt	V	2 NRTI		81	82
OR2	F	2001	Sympt	V	3 NRTI+PI→3 NRTI		24	101
OR3	F	1996	Sympt	I	2 NRTI→2 NRTI+PI		92	107
OR8	M	1998	Sympt	III	2 NRTI+PI→3 NRTI		60	72
KPV	M	2001	Sympt	V	NNRTI+2 NRTI→3NRTI		13	104
GXR	F	1998	Sympt	III	2 NRTI+PI		86	48
CXK	M	1999	Asympt	V	2 NRTI+PI		39	75
MWP	M	1999	Sympt	V	2 NRTI+PI		12	115
JOGA	F	2002	Sympt	IV	2 NRTI+PI[7]		17	72
OCP	M	2002	Sympt	V	2 NRTI+PI→3 NRTI		31	59
LY1	M	2001	Sympt	III	2 NRTI+PI→3 NRTI		23	101
LY2	M	2000	Asymp	V	3 NRTI		56	84
MO1	M	1999	Sympt	V	2 NRTI+PI→2 NRTI+NNRTI		48	93
SL2	M	1998	Sympt	V	3 NRTI+PI→3NRTI		34	113
MEDIAN		1999		V			36.5	89

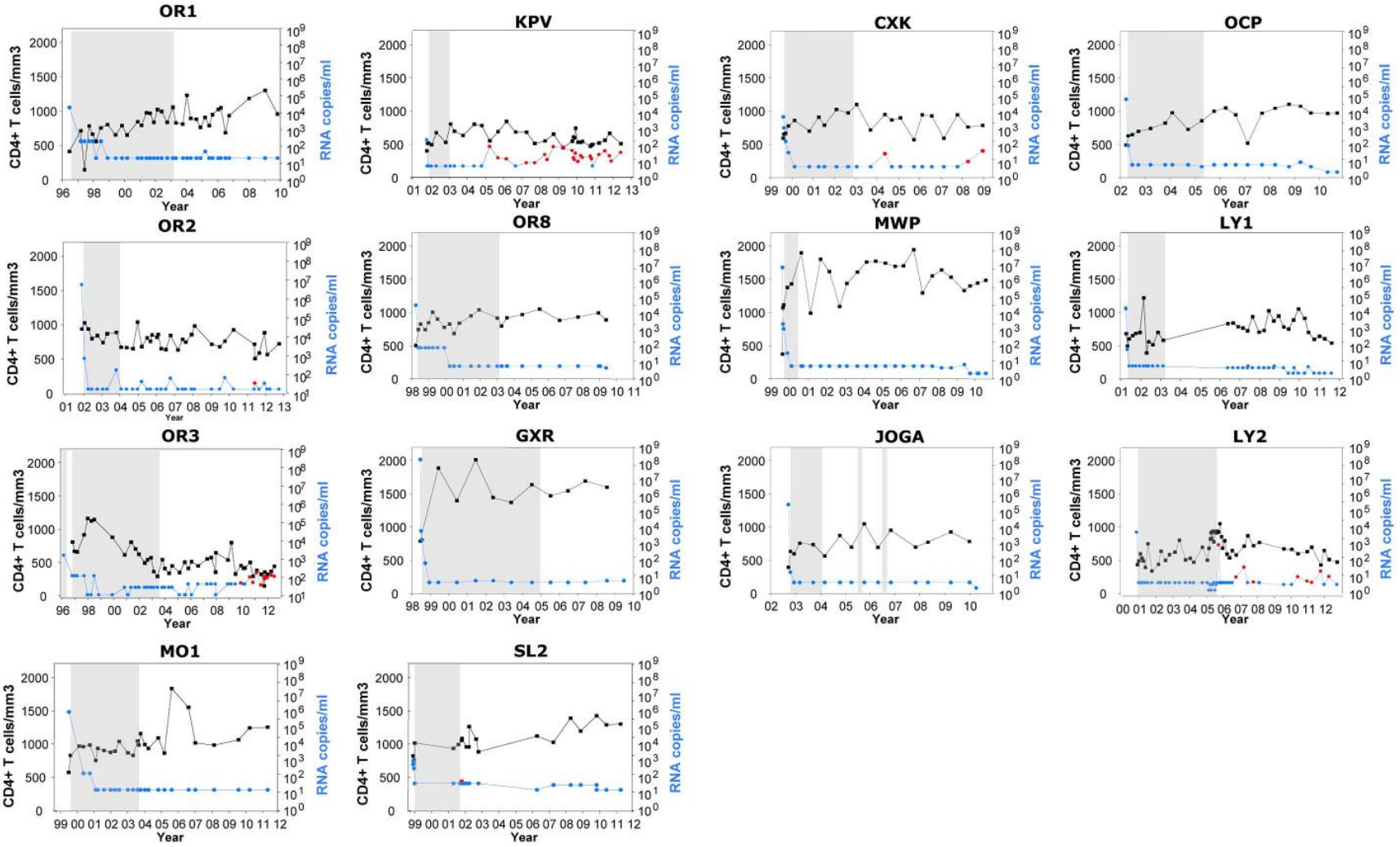


Figure 1. Long-term control of viremia and stable CD4+ T cell counts in fourteen patients after interruption of antiretroviral treatment initiated in primary HIV-1 infection. CD4+ T cell counts (in black) and plasma HIV-1 RNA viral loads (in blue) during the follow-up after PHI diagnosis in the 14 PTCs included in the study. The detectable viral loads after treatment interruption are indicated in red. The gray areas represent the periods during which the patients received cART.
doi:10.1371/journal.ppat.1003211.g001

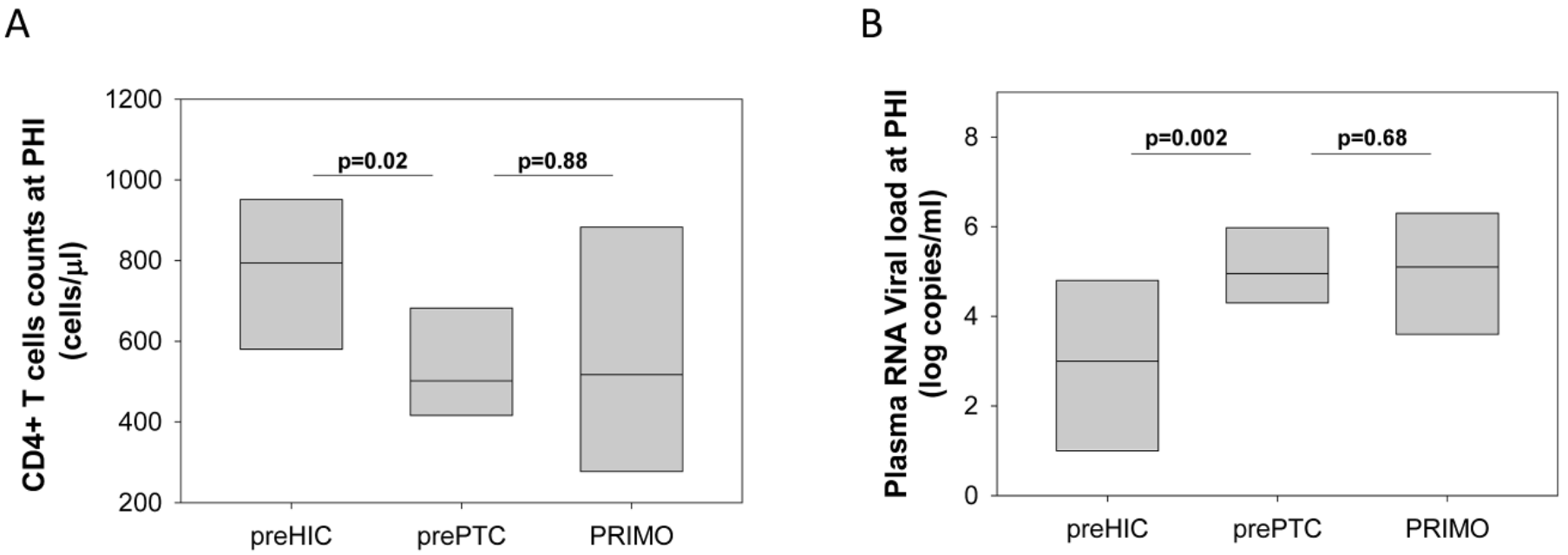
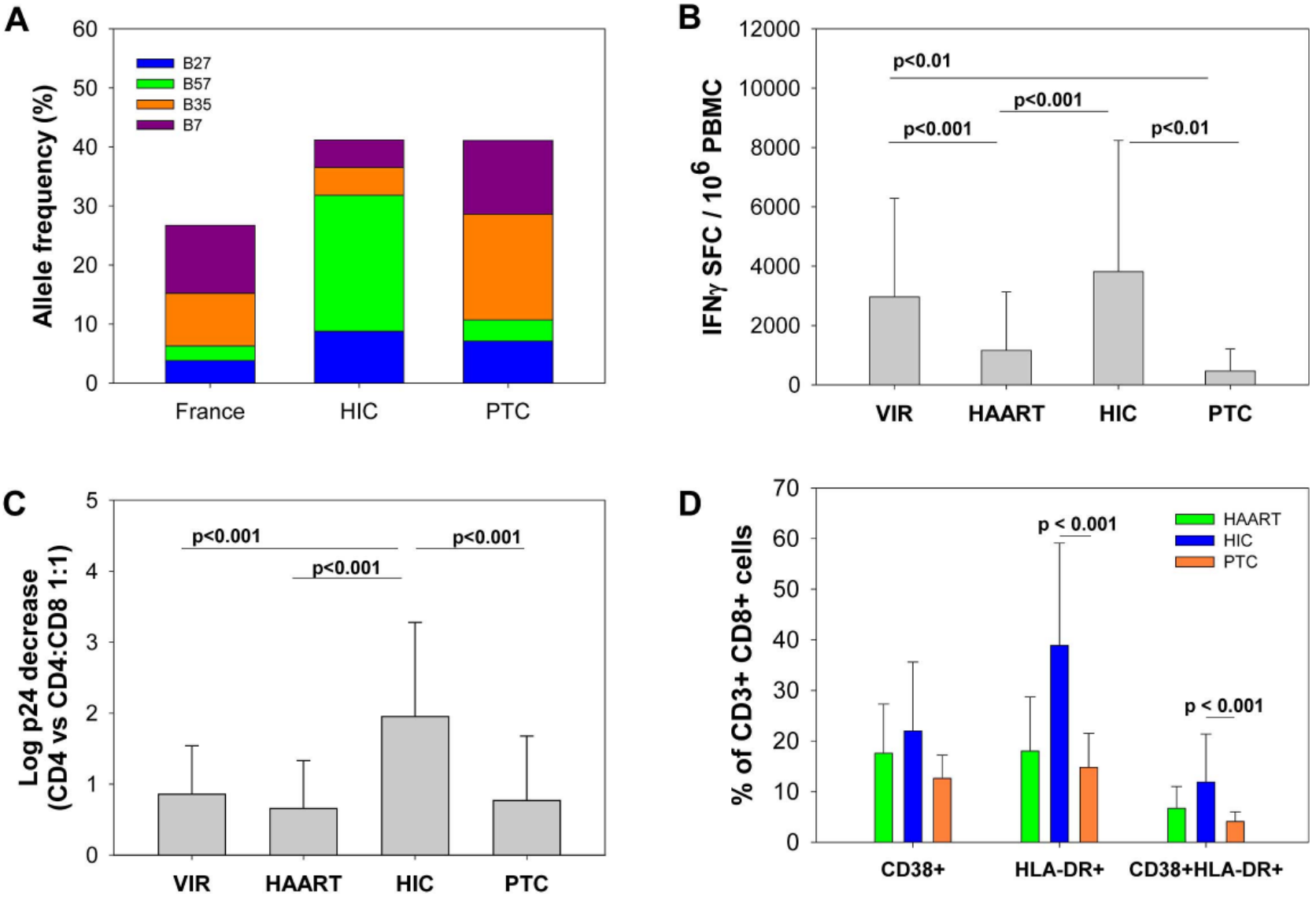
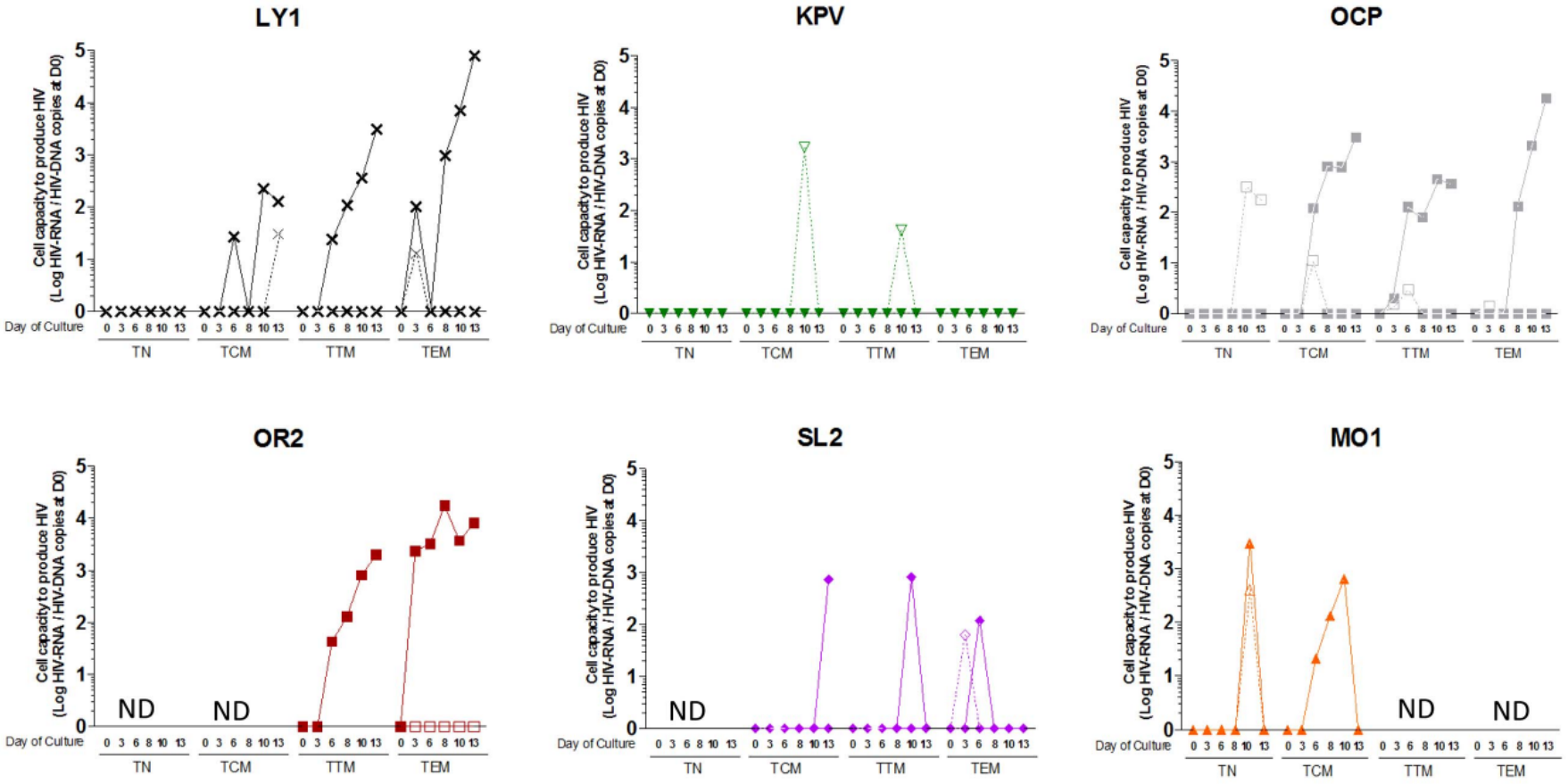


Figure 2. Patients to become post-treatment controllers have higher viral loads and lower CD4+ T cell counts than HIV controllers during primary HIV infection. CD4+ T cell counts (**A**) and plasma viral load (**B**) during the primary infection for the patients enrolled in the ANRS PRIMO cohort who later exhibited spontaneous control of infection (preHIC; n = 8) [16], for the PTCs included in our study (n = 14) and for the patients in the ANRS PRIMO cohort who did not control infection (n = 1,245). The median and the 10^{th} and 90^{th} percentiles are shown for each group.
doi:10.1371/journal.ppat.1003211.g002



Sáez-Cirión et al PLOS Pathogens 2013; 9: 1-12

Post-Treatment HIV-1 Controllers



Sáez-Cirión et al PLOS Pathogens 2013; 9: 1-12

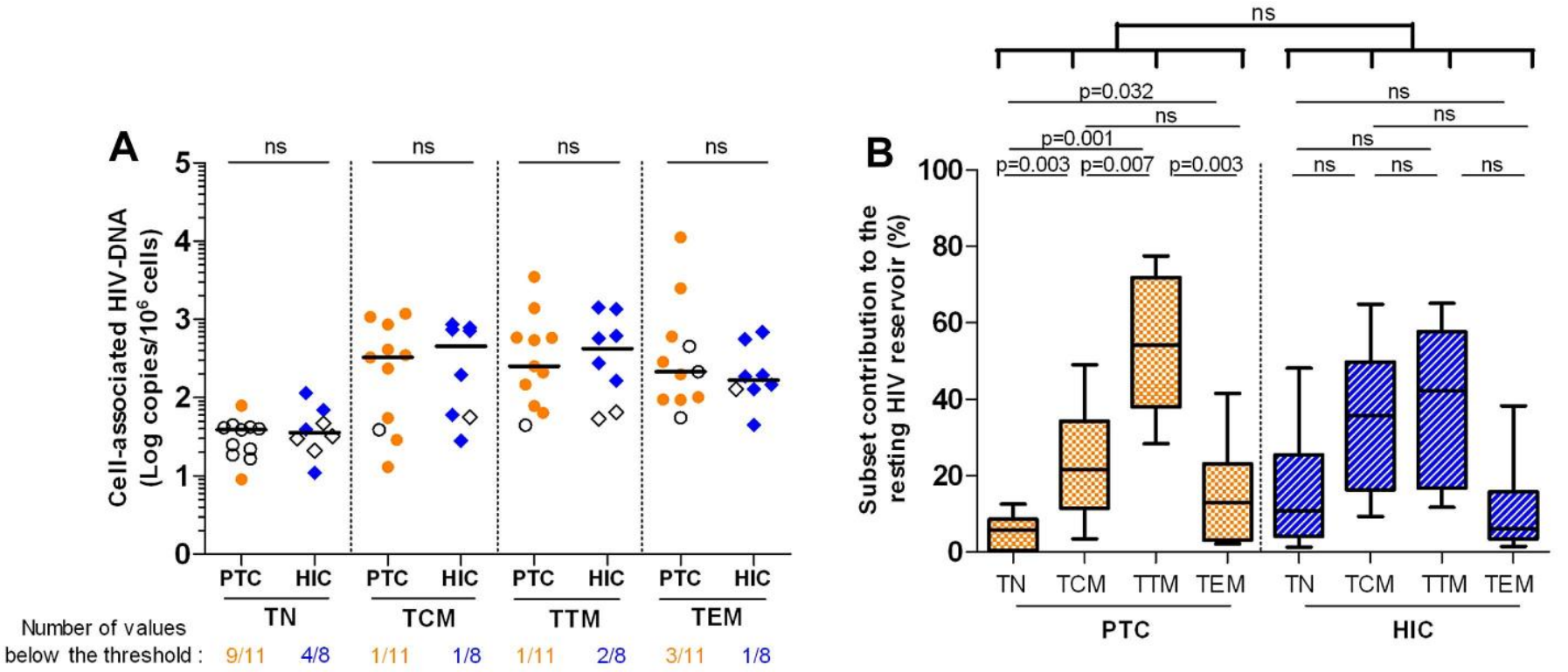


Figure 6. Weak contribution of long-lived resting CD4+ T cells to the HIV reservoir in the post-treatment controllers. A. HIV infection levels in the resting TN, TCM, TTM and TEM cells of 11 PTCs and 8 HICs. The results are expressed as the log10 HIV DNA copy numbers per million cells, and the medians are represented. The open symbols are values below the threshold of detection. 'ns' are non significant p values. **B.** CD4+ T cell subsets contribution to the resting HIV reservoir, considering both infection levels and frequency. The results are expressed as the median percentage of the resting CD4 HIV reservoir, with interquartile range [25%–75%] and minimum and maximum values. Statistical analyses were applied between all subsets from a single group as well as between each subset from the two groups.
doi:10.1371/journal.ppat.1003211.g006

What this tells us

- A functional cure for HIV infection is possible
- An argument for early ART in PHI
- Better understanding of the early and late dynamics of the HIV reservoir in the human host

Designing Better Vaccines: The Future of Vaccine Development

OPEN ACCESS Freely available online

PLOS | PATHOGENS

Rational Engineering of Recombinant Picornavirus Capsids to Produce Safe, Protective Vaccine Antigen

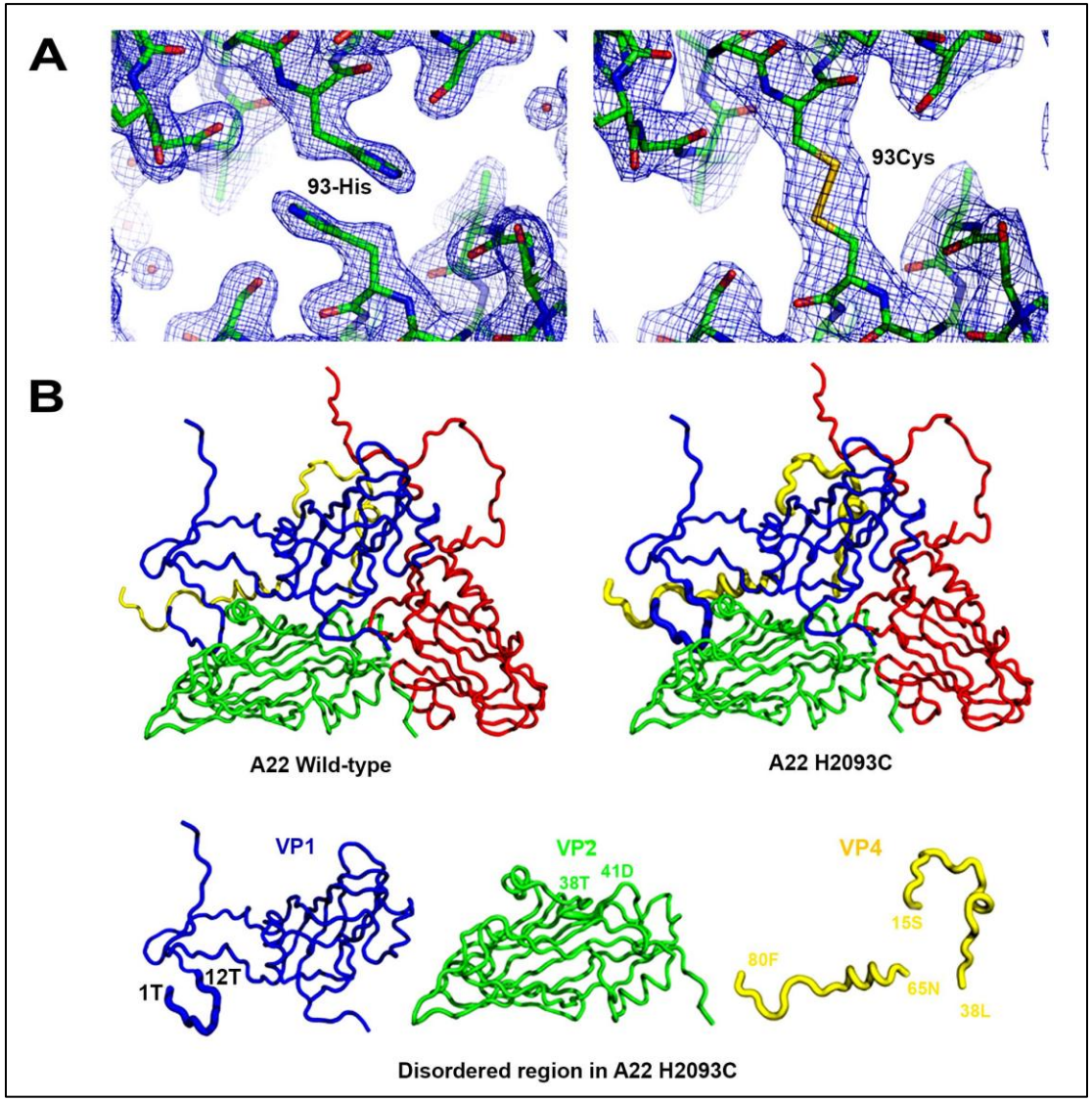
Claudine Porta[1,2☯], Abhay Kotecha[2☯], Alison Burman[1], Terry Jackson[1], Jingshan Ren[2], Silvia Loureiro[3], Ian M. Jones[3], Elizabeth E. Fry[2]*, David I. Stuart[2,4]*, Bryan Charleston[1]*

1 The Pirbright Insitute, Pirbright, Woking, United Kingdom, **2** Division of Structural Biology, The Henry Wellcome Building for Genomic Medicine, Headington, University of Oxford, Oxford, United Kingdom, **3** Animal and Microbial Sciences, University of Reading, Whiteknights, Reading, United Kingdom, **4** Diamond Light Source, Harwell Science and Innovation Campus, Didcot, United Kingdom

FMDV Vaccine

- FMDV is a picornavirus that causes foot-and-mouth disease of animals
- Safe and effective FMDV vaccines can be made from recombinant virus-like particles (VLP) that lack the viral genome
- Synthesis of stable forms of such particles on a large scale has proved difficult due to 2 key problems
  - A protease required for the proper processing of the polyprotein precursor is toxic for host cells
  - Empty VLPs tend to be physically unstable in comparison to virus particles containing nucleic acid

X-ray Crystallography of VLP Capsid



Engineered FMDV Vaccine Efficacy

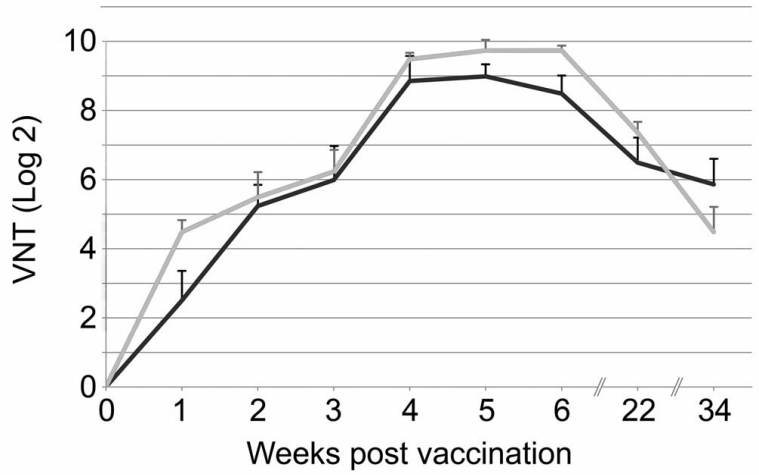
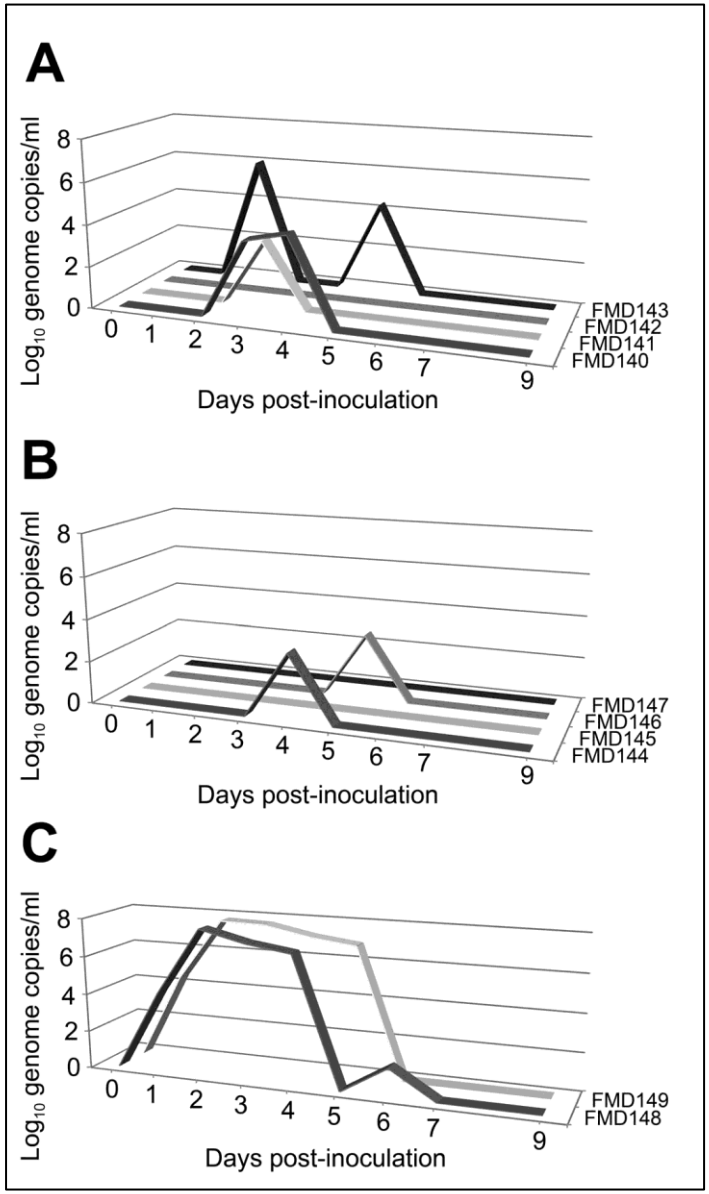


Figure 4. Virus neutralising antibody titres pre-challenge. The group mean virus neutralising antibody titres (Log2) for animals inoculated with A22-wt (black line) or A22-H2093C (grey line) are shown from week 0 to week 34. All animals were vaccinated on week 0 and week 3. Blood samples were taken at weekly intervals until week 6 and then on week 22 and finally on week 34 when challenge with live virus was carried out. Error bars represent the standard error of the mean.
doi:10.1371/journal.ppat.1003255.g004



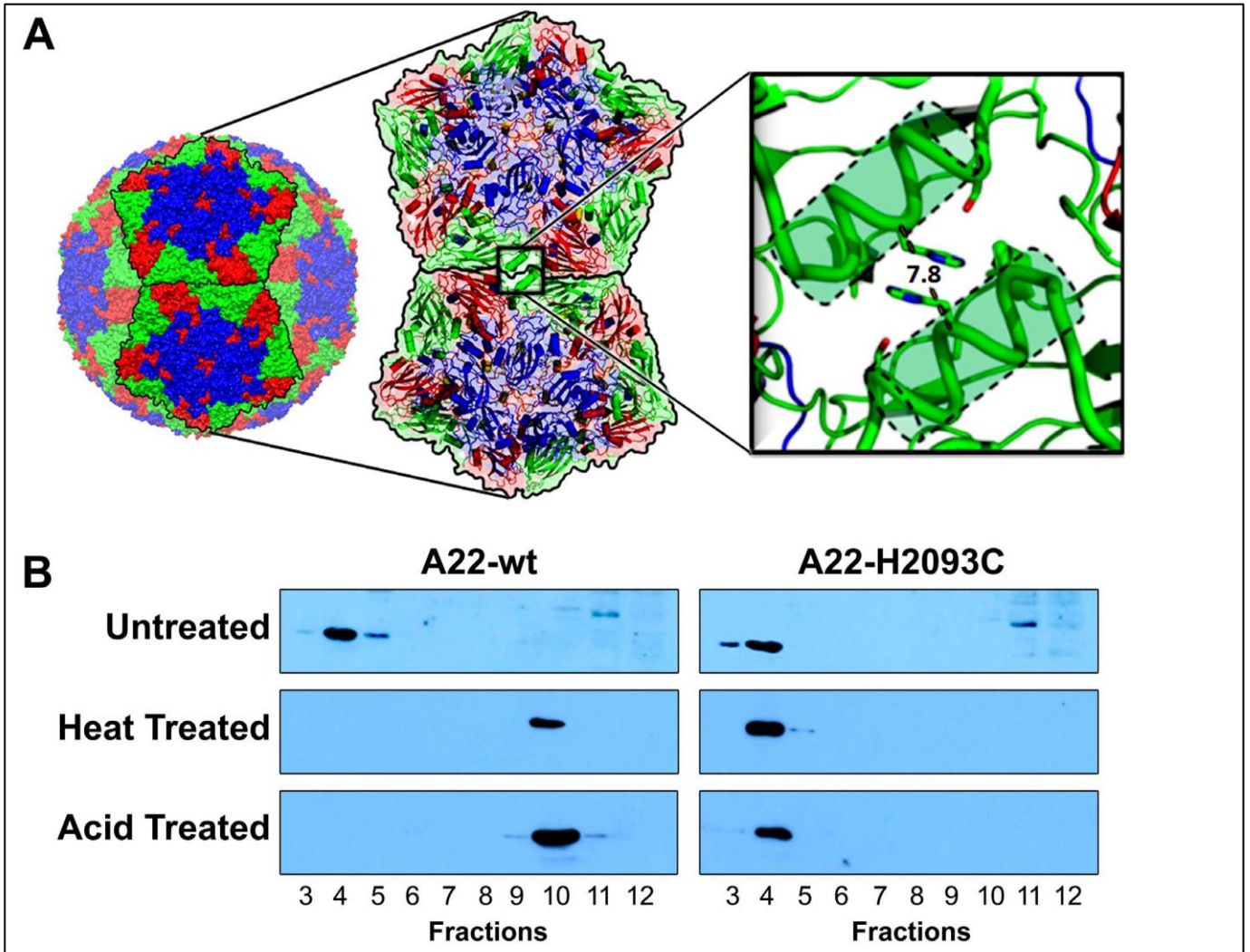


Figure 1. Rational design to produce stable empty capsids of FMDV A22. (a) The crystal structure of FMDV serotype A22 [2] was analysed as described in Materials and Methods. This led to the prediction and modelling of a potential disulphide bond between pentamers by mutation to cysteine of VP2 histidine residue 93, located on the α-helix at the two-fold symmetry axis. (b) Western blot analyses of A22-wt and A22-H2093C empty capsids, expressed from recombinant vaccinia viruses and sedimented through 15–45% sucrose gradients. Each gradient was fractionated from the bottom. FMDV capsid proteins were detected using an anti-FMDV strain A22 polyclonal antibody raised in guinea pigs. Crude extracts were left untreated, heated to 56°C for 2 h or acidified to pH 5.2 for 15 min. Following both heat and acid treatments A22-H2093C capsids remained intact and migrated to fraction 4, as before treatment, whereas A22-wt capsids fractured, remaining near the top of the gradient in fraction 10.
doi:10.1371/journal.ppat.1003255.g001

What this tells us

- Better vaccines through rational engineering are coming
- This should improve vaccine effectiveness, safety and stability
- Collaboration between multi-disciplinary teams with vaccinologists, structural biologists, etc. can lead to important steps forward

Stuff I thought was “Hot”

- Sepsis
  - Of Mice and Men
- Drug safety
  - Fungal infections
  - Old drugs that kill
- Emerging infections
  - Novel coronavirus
  - H7N9
  - CRE
- New cures
  - The cure for CDI
  - A cure for HIV?
- Designer Vaccines

Resolutions for 2013

Popular New Year's resolutions	Resolutions that are more likely to succeed
• Get rich	• Catch a unicorn
• Marry George Clooney	• Make some alien friends
• Go to the gym more	• Kill a dragon
• Study harder	• Touch the sun