# Tectonic shifts in the health information economy: Case studies in mining existing data for public health

John Brownstein, PhD

**Children's Hospital Boston, Harvard Medical School** 













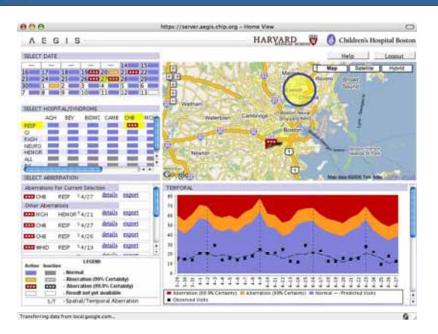


## How to measure population health?



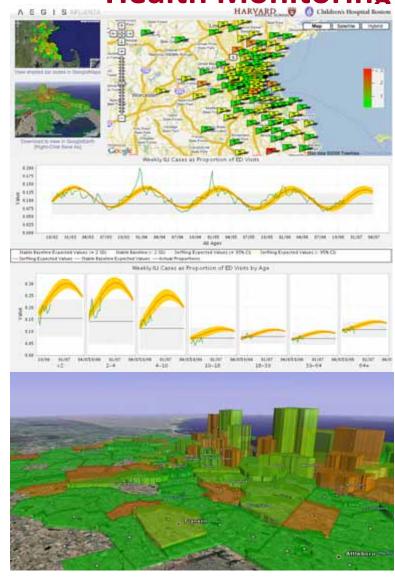
# Standard Approaches: RCT and Observational Studies

- Small sample sizes
- Detection of rare events is often impossible
- Rare diseases not usually considered
- Often cost prohibitive
- Difficulty in repurposing data
- Not geared to vulnerable populations
- Data not available in real-time or near real-time

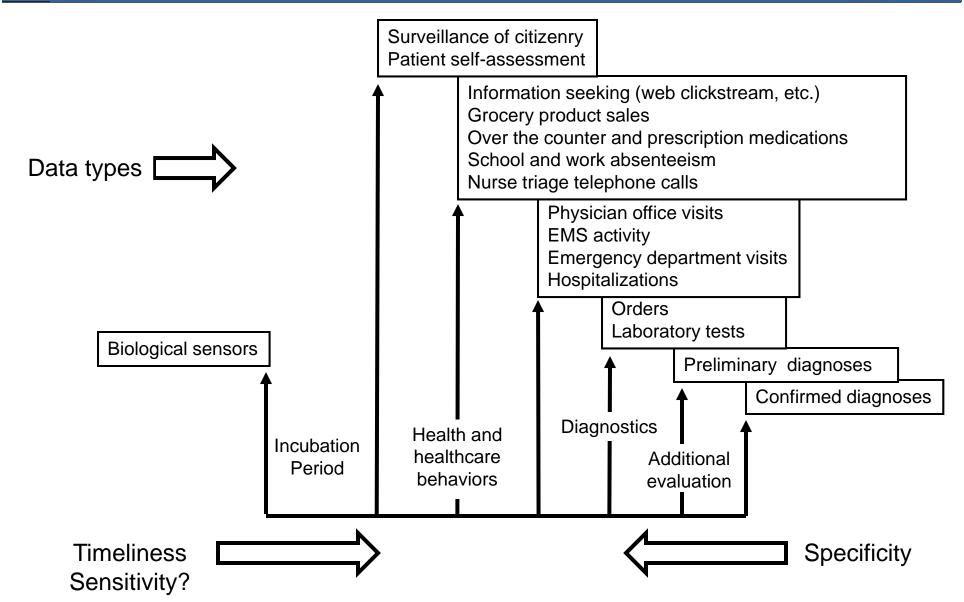




## Real-time Population Health Monitoring









### Non-traditional Health care data sources

- Emergency department chief complaints
- International Classification of Disease (ICD) codes
- Text-based notes
- Laboratory data
- Radiological reports
- Physician reports



### Non traditional non-healthcare data sources

- Retail sales data
- 911 operators
- Call triage centers
- School absenteeism
- Animal surveillance
- Internet-based reports
- Patient self-assessment

### How to measure population health?

Non-traditional healthcare data



### **Case study: Challenge of Drug Safety**

- Premarketing maximize likelihood that approved drugs are safe and effective
- Issues: many small, short term RCT means missing occurrence of rare but serious adverse drug events, drug interactions, late events, pregnancy, different effects in subgroups
- Challenge of early detection relies on US postmarketing system



## **Goals of pharmacovigilance**

- Early and reliable detection of problem drugs
- Characterization of magnitude of impact

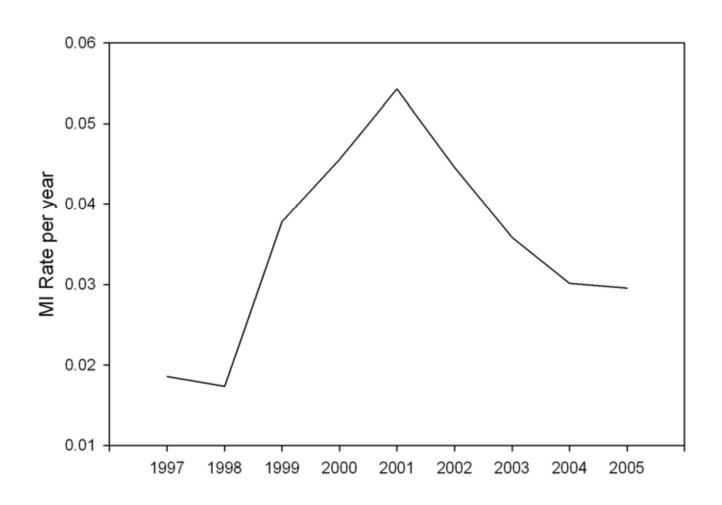


### Pharmacovigilance and EMR

- Accumulating evidence suggests critical insights can be realized from monitoring large clinical databases
- Analytical epi studies of large exposed patients clearly outweigh current federal system for collected information
- Need for automated real-time denominator based methods that is capable of capturing rare events
- Existing electronic medical record databases means that exposure and outcome data can be linked without much extra cost or invasion of privacy

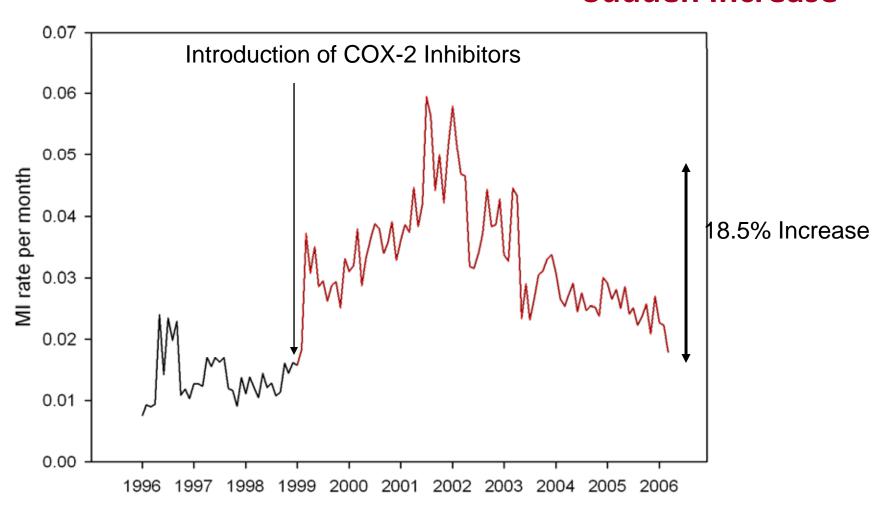


# Yearly trends in MI Partners Healthcare (1997-2005)



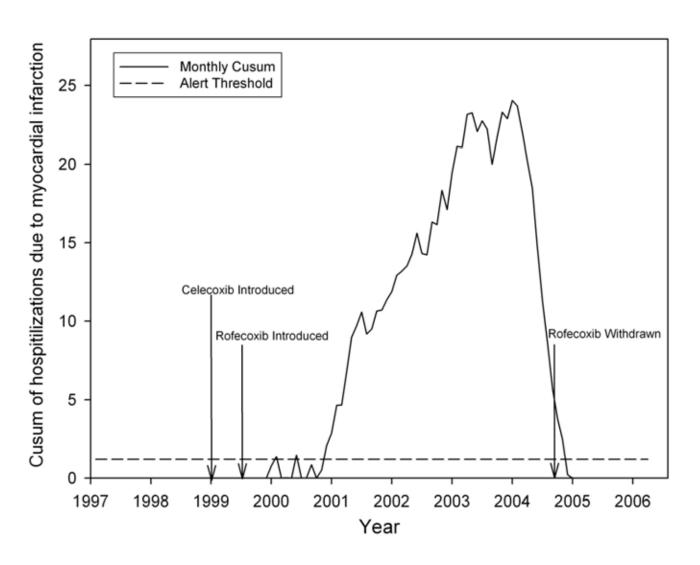


# Monthly trends in Myocardial Infarction: Sudden Increase





### **Signal Detection**

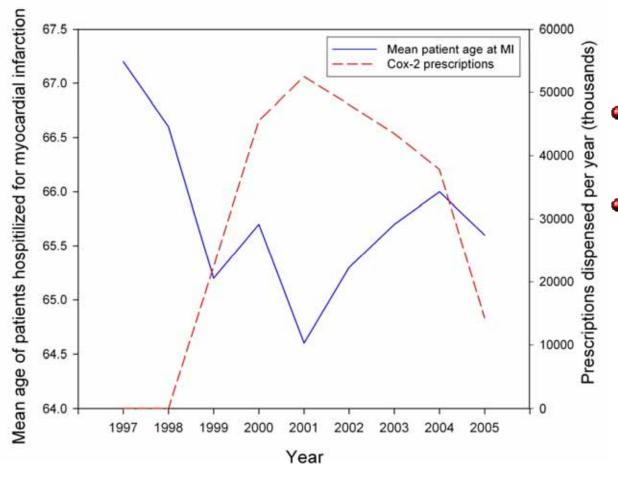


### First signal:

- 1 year after Celecoxib
- 8 months after Rofecoxib



### **Effect on patient age**



- Negative association between mean age at MI and prescription volume
- Spearman correlation0.67, P<0.05</li>



# Partners i2b2 Pharmacovigilance Initiative Methodology Goals

- To develop model that enables retrospective identification of events in defined patient cohort
- Identify a method for identifying patients receiving their care and prescriptions at Partners (to identify event if occurs)
- Provides framework for identifying patients in prospective manner for real-time analysis

# **US Population with Diabetes**

Total population*	Total U.S. population 301,736	With diagnosed diabetes		With undiagnosed diabetes		Total with diabetes*	
		17,486	5.8%	6,640	2.2%	24,126	8.0%
Race/ethnicity							
Non-Hispanic white	199,091	11,403	5.7%	4,520	2.3%	15,923	8.0%
Non-Hispanic black	37,002	2,775	7.5%	699	1.9%	3,474	9.4%
Non-Hispanic other	20,101	1,076	5.4%	317	1.6%	1,393	6.9%
Hispanic	45,541	2,231	4.9%	1,104	2.4%	3,335	7.3%
Sex							
Male	148,744	8,543	5.7%	3,113	2.1%	11,656	7.8%
Female	152,992	8,943	5.8%	3,528	2.3%	12,471	8.2%
Age (years)							
<18	73,878	157	0.2%	35	0.1%	192	0.3%
18–34	70,373	96 <del>4</del>	1.4%	669	1.0%	1,633	2.3%
35-44	43,356	1,686	3.9%	1,174	2.7%	2,860	6.6%
45-54	43,838	3,443	7.9%	1,327	3.0%	4,770	10.9%
55–59	18,235	2,307	12.7%	756	4.1%	3,063	16.8%
60-64	14,323	2,261	15.8%	775	5.4%	3,036	21.2%
65-69	10,690	1,879	17.6%	850	8.0%	2,729	25.5%
≥70	27,042	4,788	17.7%	1,055	3.9%	5,843	21.6%
Insurance							
Private	169,886	7,057	4.2%	3,018	1.8%	10,075	5.9%
Government	91,794	8,997	9.8%	2,891	3.1%	11,888	13.0%
Uninsured	40,055	1,432	3.6%	731	1.8%	2,163	5.4%

Source: Combined information from the 2004–2006 NHIS, 2004 NNHS, 1999–2004 NHANES, and the U.S. Census Bureau population estimates for 2007. \*Numbers do not necessarily sum to totals because of rounding.

ADA: Economic Costs of Diabetes in the U.S. in 2007. Diabetes Care. 31:596, 2008



### FDA Approved Medications for Type 2 Diabetes - 2008

Medication*	Route of Administration	Year of Introduction or FDA Approval	as a Reduction in the Glycated Hemoglobin Concentration  percentage points	
Insulin	Parenteral	1921	≥2.5	
Inhaled insulin	Pulmonary	2006	1.5	
Sulfonylureas	Oral	1946	1.5	
Biguanides	Oral	1957		
Metformin†	Oral	1995	1.5	
Alpha-glycosidase inhibitors	Oral	1995	0.5-0.8	
Thiazolidinediones	Oral		0.8-1.0	
Troglitazone;:	Oral	1997		
Rosiglitazone	Oral	1999		
Pioglitazone	Oral	1999		
Glinides	Oral	1997	1.0–1.5	
GLP analogues	Parenteral	2005	0.6	
Amylin analogues	Parenteral	2005	0.6	
DPP-IV inhibitors	Oral	2006	0.5-0.9	

<sup>\*</sup> GLP denotes glucagon-like peptide, and DPP-IV dipeptidyl peptidase IV.

<sup>†</sup> Metformin has been available in other countries since 1957 but was approved in the United States in 1995.

<sup>‡</sup>Troglitazone was approved in 1997 but was withdrawn from the market in 2000 because of hepatotoxicity.





Division of Cechnology

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#### Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

#### ABSTRACT

#### **BACKGROUND**

Rosiglinas one is widely used to treat patients with type 2 diabetes mellious, but its from the General Circle, Cleveland, Adelfect on cardiovas onlar morbidity and mortality has not been determined.

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#### Markings

We conducted searches of the published literature, the Web tits of the Food and "F Drug Administration, and a clinical-trials register maintained by the date mann-

From the Cleveland Clinic, Cleveland, Address seprint requests to Dr. Ninse at the Department of Codiovascular Medicine, Cleveland Clinic, 9500 Bud & Ave., Cleveland, OH 44185, or at nits ensigned.

Their analysis and notice that the secretary is an

In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

#### e substitutions

Rosigling one was associated with a significant increase in the fish of myocardial infarction and with an increase in the fish of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time to event analysis. Despise these limitations, parkents and providers thould consider the potential for serious adverse cardiovascular effects of treatment with rosigling one for type 2 diabates.





# Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
/	no. of events/t	(2010-01)		
Myocardial infarction	5 5.0	(,0)		
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88-2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74-3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80-2.21)	0.27
Overall			1.43 (1.03-1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17-4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52-2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17-3.86)	0.78
Overall			1.64 (0.98-2.74)	0.06



### **EMR Pharmacoepi Study**

- Inclusion criteria: Patient is on a diabetes medication
- Analyzing patients Outpatient Encounter or Inpatient Encounter over 6 month intervals
- Characterize patients
  - Age, Gender, Prior cardiovascular disease, use of hypertensive Meds, use of hyperlipidemic Meds, Outpatient insulin, Charlson score, Creatinine, Hba1c, Race, insurance
- For each 6 month period
  - > Patient must have inpatient/outpatient visit
  - Determine whether prescribed:
    - Rosiglitazone, Metformin, Sulfonylurea, Pioglitazone
- Follow patients longitudinally
  - > Earliest time period that pt meets cohort definition
  - Analyze patient observation periods until: Death, Myocardial Infarction (IC9-410.x), End of Study or gap in care



### **Drug Exposure: Preliminary Results**

- Total T2D patient- 6 month periods between 1/1/2000 12/31/2006:
  - 159,604 periods (from 34,278 patients)
- Total patient-6 month periods on Rosiglitazone:
  - 8,707 periods (4,274 patients)
  - > 2,888 mono-therapy (1,909 patients)
  - > 1,936 with metformin alone
  - > 1,709 with sulfonylurea alone
  - > 2,174 with all three
- Total patient-6 month periods on Metformin
  - > 48,713 periods (18,162 patients)
  - 28,630 mono-therapy (12,774 patients)
- Total patient-6 month periods on Sulfonylurea:
  - 40,694 periods (17,157 patients)
  - 20,838 mono-therapy (11,435 patients)

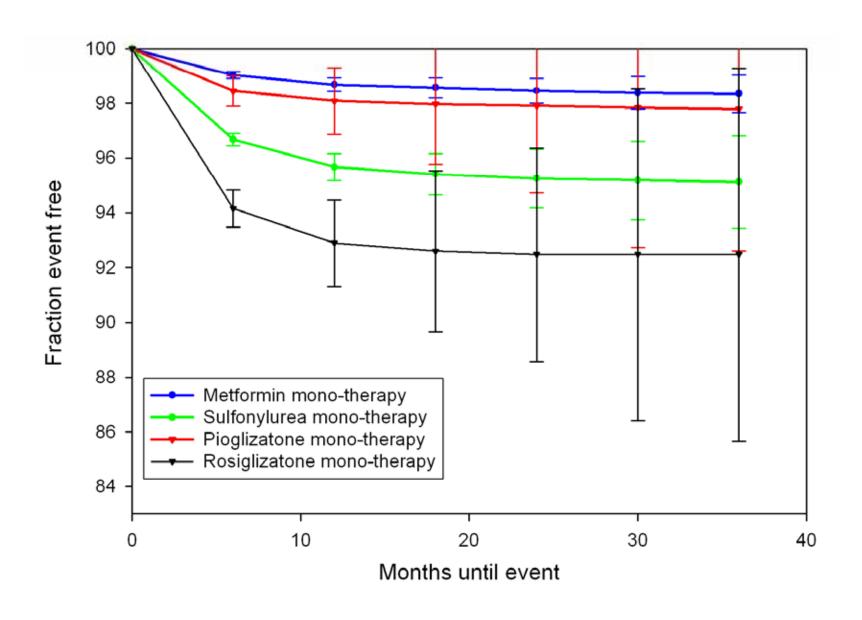


### Pharmacovigilance Rosiglitazone Study Event Identification in relation to Drug Exposure

- Total events
  - > 5,108 MI events (64 per 1000 patient-years)
- Total events associated with Rosiglitazone:
  - > 477 MI events (110 per 1000 patient-years)
  - > 203 MI events on mono-therapy (141 per 1000 patient-years)
- Total events associated with Metformin
  - > 1,544 MI events (63.4 per 1000 patients-years)
  - > 721 MI events on mono-therapy (50 per 1000 patients-years)
- Total events associated with Sulfonylurea:
  - 2,405 MI (118 per 1000 patients-years)
  - > 1512 MI events on mono-therapy (145 per 1000 patient-years)



### Time to event





# Diabetes Mellitus Avandia Study Modeling Strategy

- Fit generalized linear models (GLM)
- Poisson distribution
- Exposure time as offset
- Accounts for overdispersion
- Model:
  - Univariate
  - > Full Coverage Model (Only variables with data on each individual)
  - Comprehensive Model (All 11 variables)



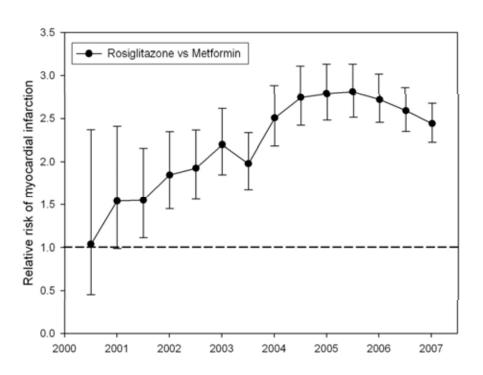
### **Model Results**

- Rosiglitazone vs Metformin:
  - Crude RR: 3.0 (95% CI 2.7-3.3)
  - Comprehensive Adjusted RR: 2.5 (95% CI 2.2-3.0)
- Rosiglitazone vs Sulfonylurea:
  - → Crude RR: 1.0 (95% CI 0.9-1.2)
  - Comprehensive Adjusted RR: 1.2 (95% CI 1.0-1.5)
- Rosiglitazone vs Pio:
  - → Crude RR: 1.5 (95% CI 1.2-1.9)
  - Comprehensive Adjusted RR: 1.6 (95% CI 1.2-2.3)

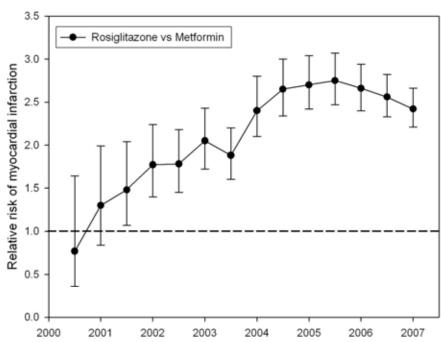


### **Prospective Surveillance**

#### **Initial Model**



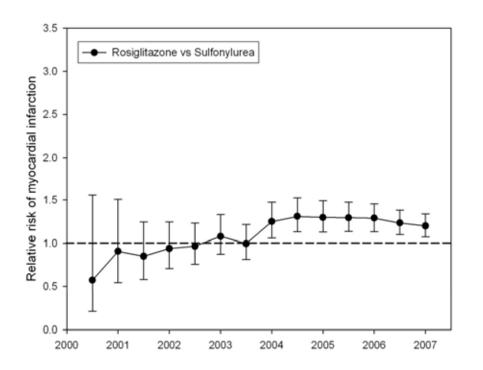
### Full Coverage Model



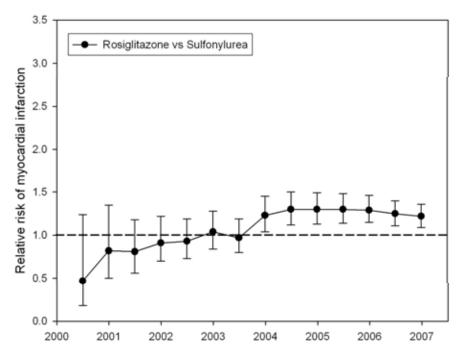


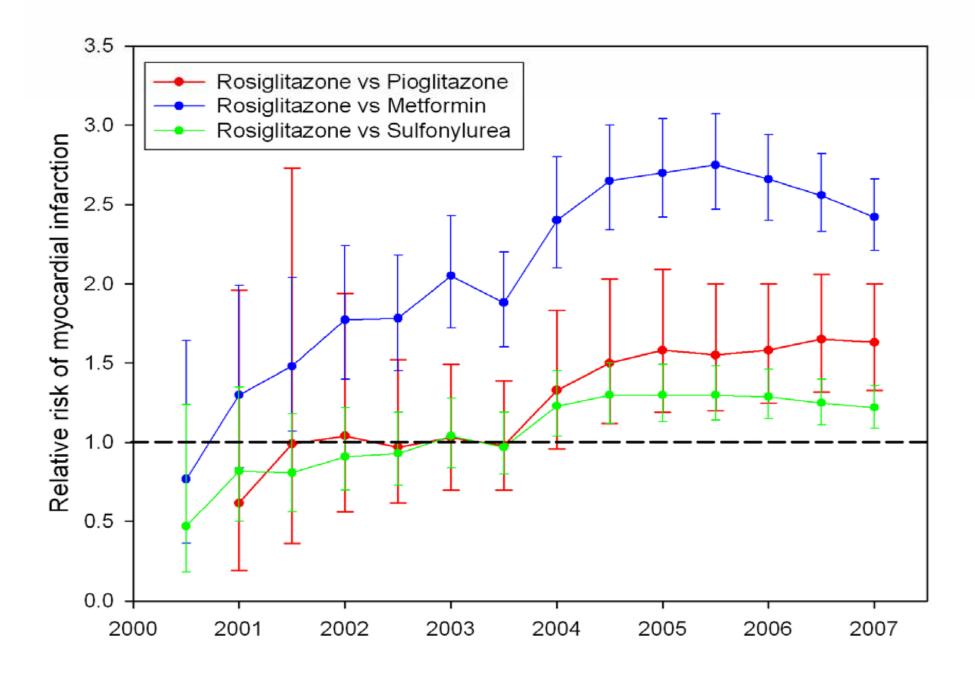
### **Prospective Surveillance**

### **Initial Model**



### Full Coverage Model



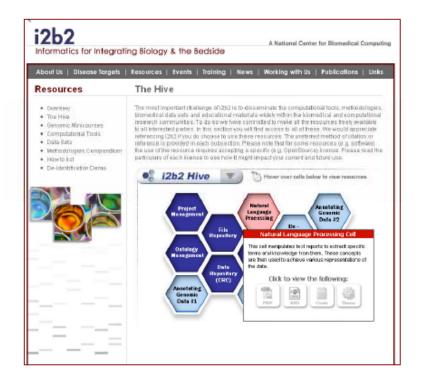


### **Study findings**

- Despite model assumptions, identified potential CV risk of rosiglitazone based on real-word population
- $\bullet$  Confounding by indication  $\rightarrow$  pio results provide confidence
- Risk is consistent with other studies
  - ➤ RR against Sulfonylurea of 1.2 → same as NEJM meta-analysis, but higher than others
  - $\triangleright$  RR against Metformin of 2.5  $\rightarrow$  higher than other studies
  - Trend is similar to McAffee et al with increased risk when comparing to metformin but results in that study were not significant
  - ➤ RR against Pio of 1.6 → consistent with recent Gerritis paper (showed 22% reduction in AMI for PIO)
- EMRs as an innovative approach to rapid safety signal detection

### **Ongoing Research Challenges**

- Much electronic information is in free text
- Medical record data are not complete
- Data quality
- Relationship to RCT data
- Patient Privacy





# **Next Steps**

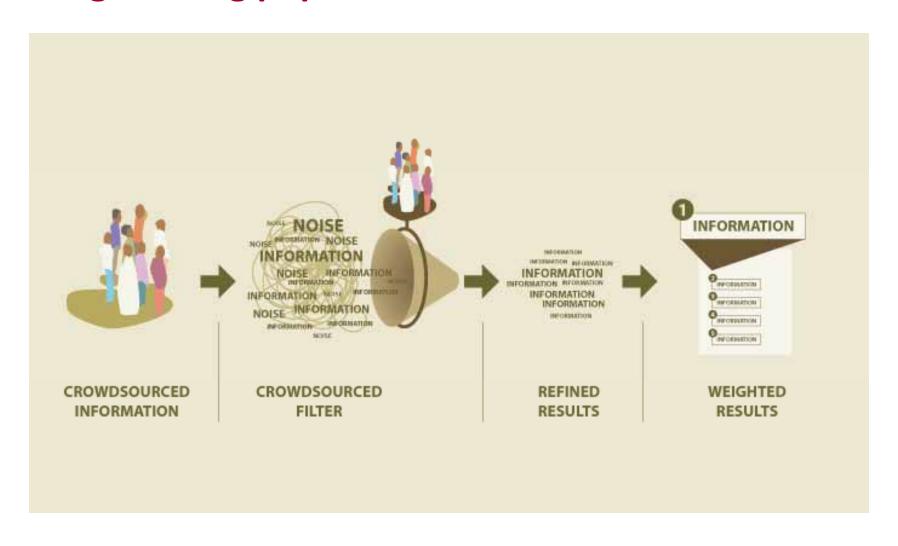
- NLP approaches to augment drug exposure identification
- Experiment with other drug-event associations
- Relevance networks to look at all comparisons and identify unknown associations
- Implementing methodology and visualization prospective monitoring

### How to measure population health?

Non-traditional non-healthcare data



## gathering population data outside healthcare





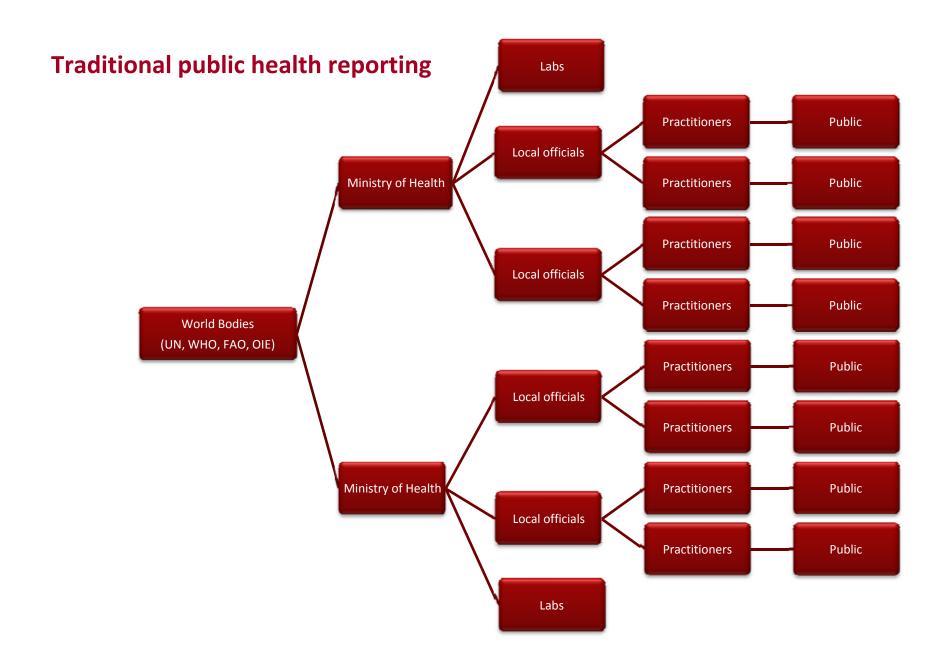
### Case Study: Emerging threat of infectious diseases

- Breakdown of public health measures
- Drug and pesticide resistance
- Unsuccessful vaccine development
- Environmental change
- Human demographics and behavior
- International travel and commerce (ie: wildlife)



### **Public Health Surveillance**

- Need for evidence-based decisions for implementation and targeting of control activities
- Challenge outside the scope and budget of traditional surveillance systems









#### Influenza A (H1N1) Reports







#### Influenza A (H1N1) Virus, 2009 — Online Monitoring

John S. Brownstein, Ph.D., Clark C. Freifeld, B.S., and Lawrence C. Madoff, M.D.

Portada Edición impresa Especiales Multimedia Servicios Escríbanos

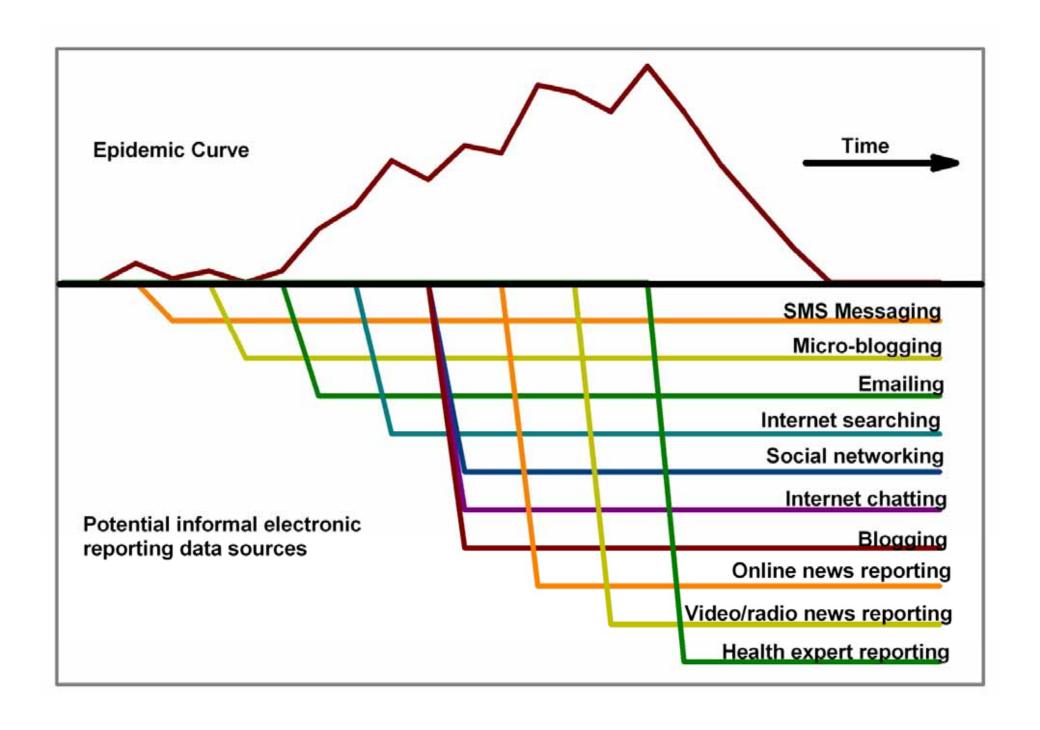
Usted está aquí: Portada ightarrow 2009 ightarrow 04 ightarrow 01 ightarrow Veracruz: reporta agente municipal extraño brote epidémico que ha cobrado dos vidas

Veracruz: reporta agente municipal extraño brote epidémico que ha cobrado dos vidas

Enviar esta página a alguien
Imprimir esta página

La funcionaria de La Gloria informó que el raro padecimiento ha afectado a 60 por ciento de sus tres mil habitantes con infecciones respiratorias.

















### **HealthMap Article Processing**



#### **Acquisition**

>20,000 sites Every hour; 24/7

#### **Extraction**

1800 disease patterns 5000 location patterns

#### Categorization

6 million phrases 91% accuracy

### **Aggregation**

Text Matching Similarity Score

# Usage







- 1,000-150,000 unique visitors/day
- >1,000,000 since launch in 9/06
- Top visitors:
  - CDC.gov
  - WHO.int
  - DHS.gov
  - National, state, local public health depts
  - NGOs
  - National Conventions





### **Public Health Resource**









July 8, 2008 in Health | 0 comments | Post a comment

#### World Wide Wellness: Online Database Keeps Tabs on Emerging Health Threats

A new tool tracks diseases, contaminants and other threats as they occur worldwide By Adam Hadhazy



News travels fast—especially online—and a group of scientists intends to put this to good use by monitoring and trying to stop infectious diseases in their tracks.

TEXT SIZE: = +

Researchers at Children's Hospital Boston and Harvard Medical School have launched a datamining project called HealthMap. This automated system scours news services and online discussion forums, pooling information about emerging health threats worldwide.

By doing so, HealthMap provides a glimpse of potential disease outbreaks in local pockets, often before government and other health agencies such as the World Health Organization and the U.S. Centers for Disease Control and Prevention (CDC) realize they are threats.

"We hope that HealthMap will be able to identify outbreaks before traditional organizations become aware of them," says John Brownstein, co-founder of HealthMap and an assistant professor at the

### **Tool for general population**

Researchers Track Disease With Google News, Google.org Money

By Alexis Madrigal July 07, 2008 | 7:00:03 PM Categories: Disease, Pandemic, Web/Tech





#### Hot Spots

Select: all, none Ginfo
Salmonella (224)
Not 'vs Classified (149)
Okvian Influenza (110)
Oberia (49)
Ocholera (45)
Opoisoning (40)

O Tuberculosis (33)

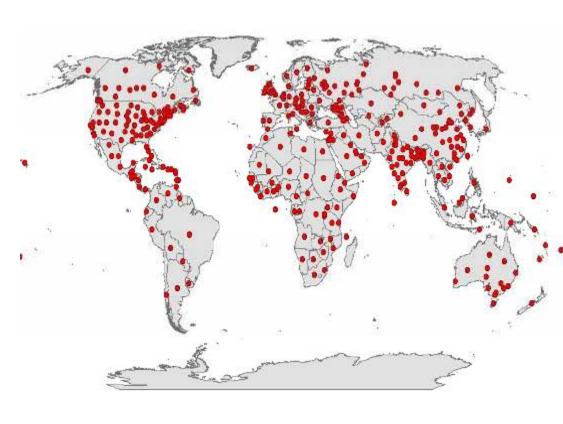
#### Before Traveling, You May Want a Checkup

Tuesday, March 20, 2007; Page HE02

Salmonellaoutbreaks

What's New Now you can satisfy your morbid curiosity and discover what diseases are plaguing your favorite vacation spot before hopping the next flight. Instead of stumbling through a host of blogs and news sites, visit <a href="http://www.healthmap.org">http://www.healthmap.org</a>, created by Boston epidemiologist Clark Freifeld and research software developer John Brownstein to track disease outbreaks around the world.

# **HealthMap Stats**



- > 200 alerts per day
- >200,000 alerts so far
- Alerts in 201 countries & territories
- 175 disease categories
- Five languages English,
   French, Spanish, Russian,
   Chinese, Portuguese, Arabic

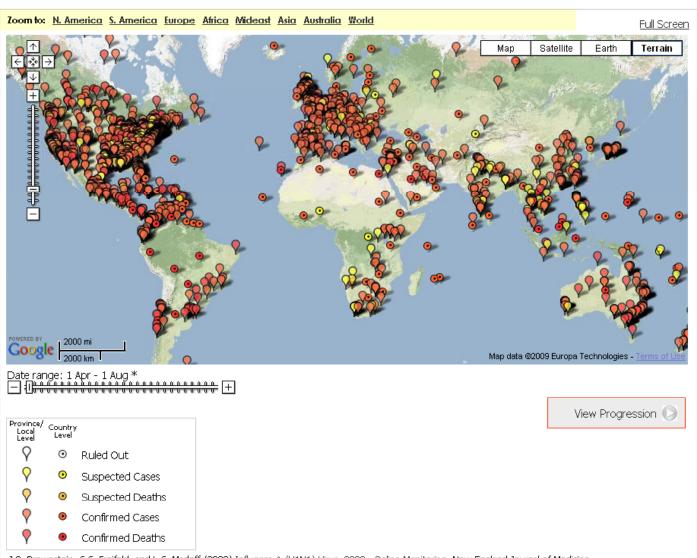




#### Influenza A (H1N1) Reports





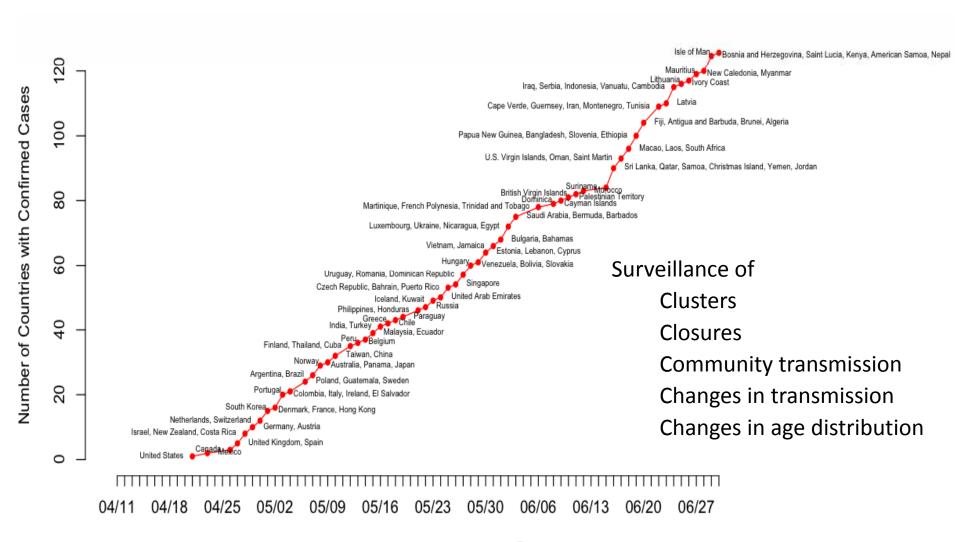


J.S. Brownstein, C.C. Freifeld, and L.C. Madoff (2009) Influenza A (H1N1) Virus, 2009 - Online Monitoring, New England Journal of Medicine

Official data is obtained from CDC and WHO daily Influenza A (H1N1) updates. Informal data sources are a subset of reports from the <u>HealthMap</u> database. The case numbers shown are cumulative counts, HealthMap is a public website bringing together disparate data sources to achieve a unified view of the current global state

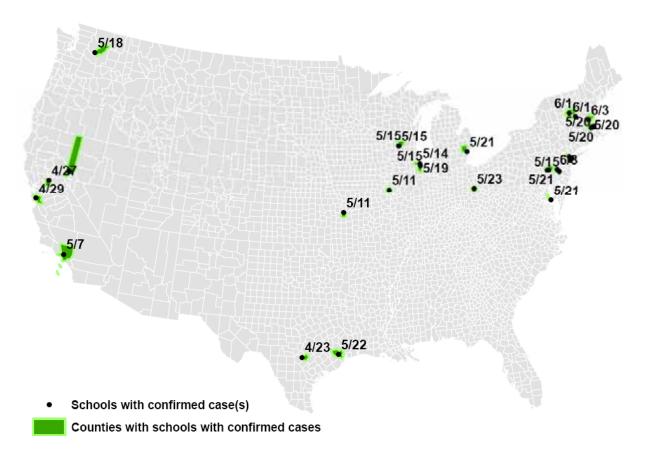


# **Global Spread of H1N1**





### **School closures**



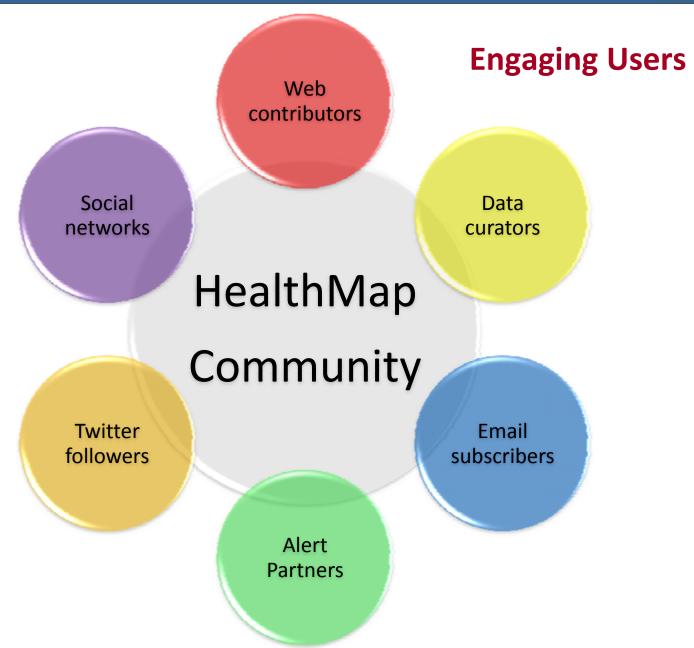
- 37 schools with at least one confirmed case in 25 counties in 14 states
- 32 public schools, 5 private;
- 13 schools in urban districts; 16 schools in suburban districts; 6 schools in smaller towns; 2 schools in rural areas

37 schools with cases compared with the other 10,035 schools in the 25 counties containing the outbreak schools

→ Increased risk in urban more affluent areas (increased travel history, healthcare access, reporting bias...)

# Moving from passive to active surveillance: Participatory Epidemiology







# **HealthMap and Participatory Epidemiology**





# **Community Input: Digital Disease Detectives**



# Iceland reports its first death from swine flu, cases have spiked on island in recent weeks

By THE ASSOCIATED PRESS (CP) - 1 day ago

REYKJAVIK, Iceland — Icelandic health officials reported their country's first swine flu death Monday amid a spike in cases on the North Atlantic island.

The victim, an 18-year-old disabled woman, died after falling ill about 11 days ago, Iceland's Directorate of Health said in a statement. The woman had a pre-existing lung condition which contributed to her death, according to Dr. Olafur Baldursson, the director of medicine at Reykjavik's Landspitali University Hospital, where she died.

"The girl had been multiply disabled for a long period of time and suffered from a chronic pulmonary disease," Baldursson told journalists Monday.

Iceland, a county of about 300,000 people, has so far seen a total of 479 laboratory-confirmed cases of the virus - many of them occurring in the past two weeks. Until recently the virus was largely confined to the capital, but swine flu has now spread across the country, resulting in "a huge drop" in school attendance in some rural areas, according to the health directorate.

The directorate added that the virus was adding considerably to the work of the small nation's health care service.

Swine flu, first identified in April, is a global epidemic. The World Health Organization says there have been nearly 400,000 laboratory confirmed cases and over 4,700 deaths linked to the illness. But many countries have stopped counting individual cases and the organization says the true totals are likely to be much higher.

THE CANADIAN PRESS

#### Map



Outbreak missing from the map? Help us by adding it:

http://URL-of-Disease-Outbreak-Report

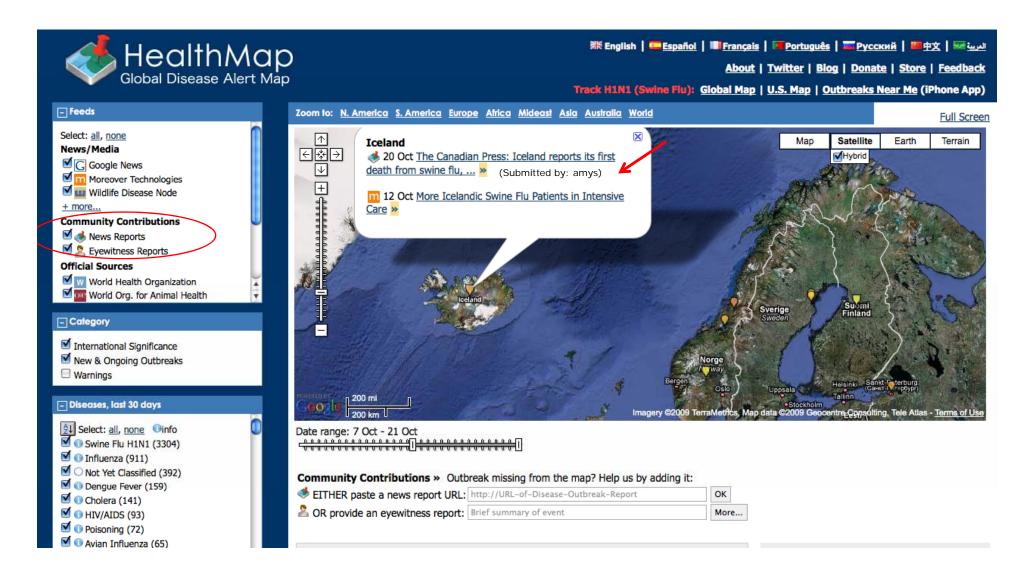
Username or Email

OΚ





# **HealthMap Community Feed**





## **Community input: Digital Disease Detectives**



#### Outbreak missing from the map? Help us by adding it:

http://URL-of-Disease-Outbreak-Report

Username or Email

ОΚ

and encountered fruit bats, which can carry the Marburg virus. The Ugandan government closed the cave after a tourist from the Netherlands died from Marburg in July.

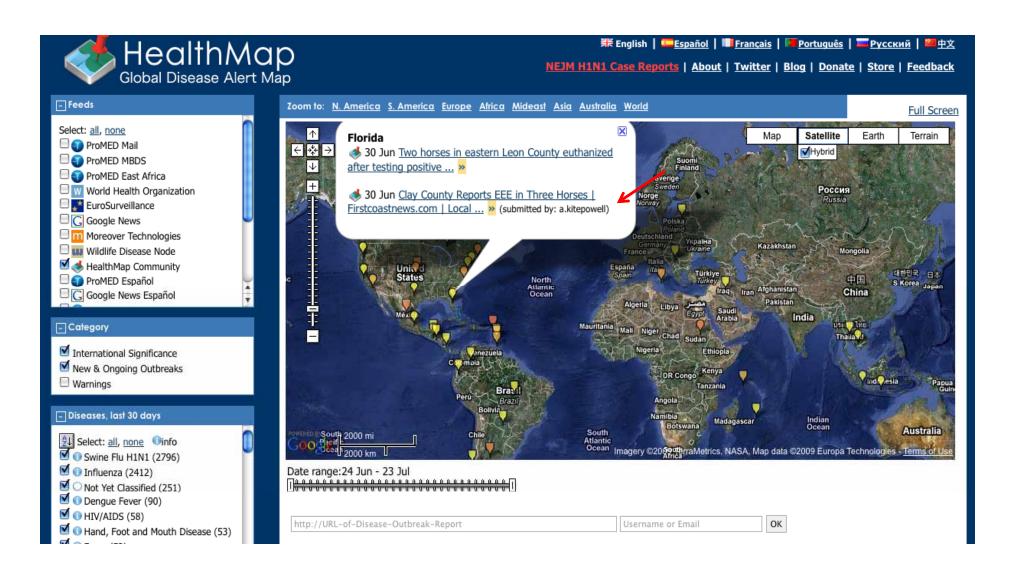
The patient was treated at Lutheran Medical Center in January 2008 and sought follow-up care in July, after learning of the tourist's death. The patient recovered and his or her identity wasn't disclosed.

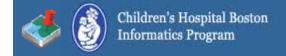
Pierre Rollin, acting chief of the <u>Special Pathogens Branch</u> of the CDC, said specialized tests of the initial sample taken in January 2008 confirmed the illness in the Colorado patient in December.





# **HealthMap Community Feed**





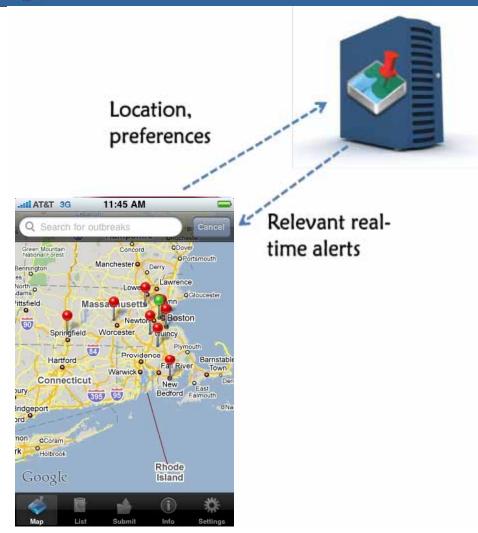




Wednesday, Sep. 09, 2009

### Is a Swine Flu Outbreak Coming? Ask Your iPhone

By Bryan Walsh























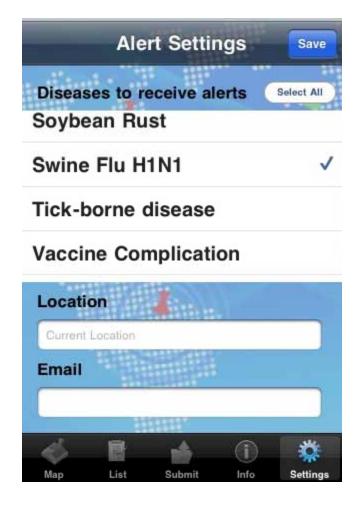




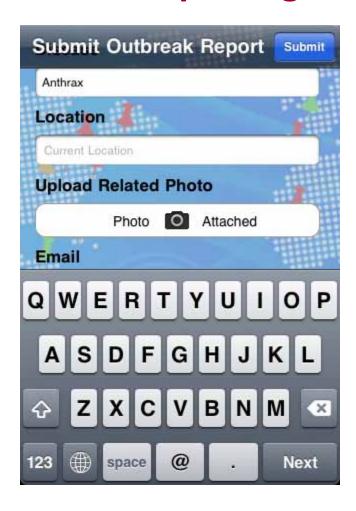




# **Geo-alerting**



# **Geo-reporting**





### 80k downloads in first week





### crowd-sourced surveillance

- Closures "Outbreak of laboratory-confirmed H1N1 in schools in the provinces of Lucca and Pisa, Tuscany, Central Italy" "Canterbury elementary school closed until 10/23 due to 30% percent of students out with flu."
- Clinical "10 year old boy confirmed test positive. Innitial onset came on fast with extreeme headache, fatigue, and low/med grade fever. He bagan tamiflu same day. Is asthmatic. So far is recovering well."
- Clusters "First my 5 year old son got it then my 18 month old daughter got it. Now my wife and I both have it."



### **Part II: Conclusions**

- Value in the fusion and visualization of distributed electronic resources
- Complements traditional healthcare data sources by providing customized real-time intelligence for the broad scope of international public health activities
- Importance of multi-lingual, collaborative approach that minimizes information overload and engages users



# **Key questions**

- What are the regulatory obstacles impacting your work?
- What are the resource needs required to replicate your work at other institutions?
- What are the priority short term "translational" questions in your fields that would represent the most rapid payoff on investment?



# **Regulatory Obstacles**

#### Non-traditional healthcare data

- IRB
- Data security
- Anonymization of data (especially when considering rate events)
- Data standards
- Adoption of EMRs is low (only 33% of physician offices use)
- Lack of universal patient identifier
- Data often silo'ed by clinical specialty, lab service, etc.

#### Non-traditional non-healthcare data

Much of the non-traditional data falls outside regulatory structures

### **Resources Needed**

#### Non-traditional healthcare data

- NLP approaches (eg: augment drug exposure identification)
- Database storage capacity
- IT infrastructure
- Signal processing technology
- Implementing methodology and visualization
- Prospective monitoring (human analysts)
- Validation efforts
- Common data "clearinghouses" allow parties to publish data while retaining control
  - Patient locator/identifier/anonymization services
  - Patient consent
  - Billing code resolution
  - Drug metadata

### **Resources Needed**

#### Non-traditional non-healthcare data

- Validation efforts
- Population representativeness
- Extrapolation of results
- Appropriate denominators
- Historical baseline
- Self-report biases
- Sampling frame
- Signal to noise
- Validity of empirical surveillance data for epidemiologic studies
- Value to make regulatory decisions



# **Priority short term question**

- Mining EMRs for discovery (safety, benefit, drug interactions)
- Mining search usage data for discovery (safety and benefit and drug interactions)
- Use of social networking for clinical trials recruiting, safety and discovery
- Mobile devices and EMR, to reach underserved populations US & worldwide
- Beyond drug safety: could we have discovered virus CFS association from EMR data?



### **Public Health 2.0 and EMRs**





# **Social Networking and EMRs**

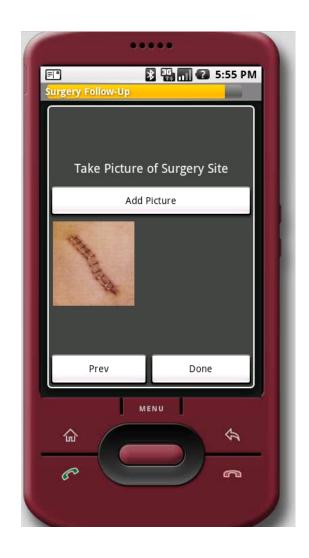


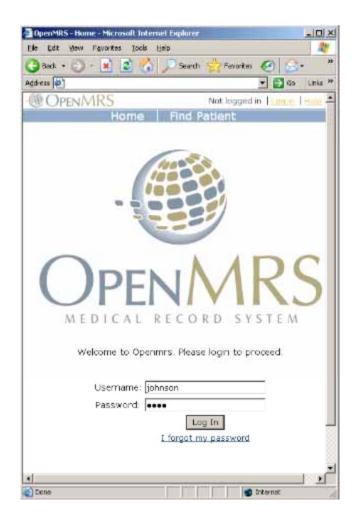


Real time group and individual measurement of outcomes, treatment side effects, adverse events



### **Mobile Devices and EMRs**







#### **HealthMap Team**

- John Brownstein, PhD
- Clark Freifeld
- Mikaela Keller, PhD
- Susan Aman
- Amy Sonricker, MPH
- Emily Chan, MSc

#### **Children's Hospital Informatics Program**

- Ken Mandl, MD MPH
- Ben Reis, PhD
- Isaac Kohane, MD PhD

#### **Partners**

- Susanne Churchill, PhD
- Shawn Murphy, MD PhD

#### **Collaborators**

- Larry Madoff (MA-DPH/ProMED)
- Marjorie Pollack (ProMED)
- Tim Brewer (ProMED)

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