Surveillance
Part 2

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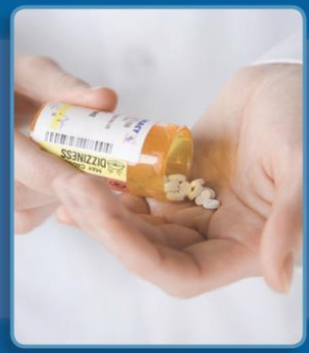
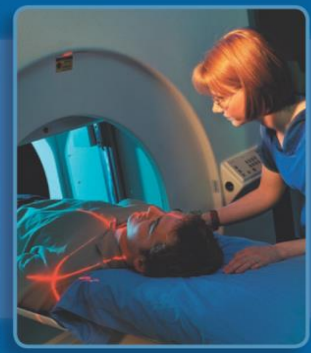
Periodic Population-based Surveys

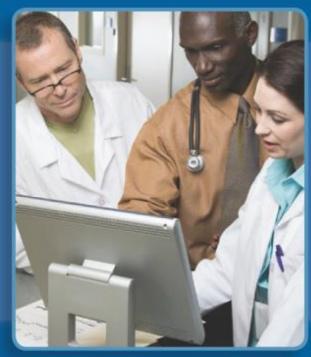
- Used for surveillance if surveys are repeated on a regular basis
- Careful attention to the methodology
- They are more costly and are usually conducted on an annual basis

Sentinel Surveillance

- May be active or passive
- Usually active, and based on selected institutions or individuals that provide regular, complete reports on diseases, interventions or adverse events
- It also provides additional data on cases.







The Sentinel Initiative

National Strategy for Monitoring Medical Product Safety

May 2008

Department of Health and Human Services
U.S. Food and Drug Administration
Office of Critical Path Programs
www.fda.gov/oc/initiatives/criticalpath/

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Cover photos: top left Centers for Disease Control and Prevention (CDC); subsequent photos Getty Images

FDA Sentinel Initiative

- Uses electronic record linkage and medical records for safety evaluation
- Mandated by FDA Amendments Act of 2007 to establish a post market risk identification and analysis system to link and analyze safety data from multiple sources
- The July 1, 2012 goal was to include 100 million patient records in the system with ability to carry out active surveillance for detection of safety risk associated with medical product usage.

Mini-Sentinel

- Congress mandated FDA develop a safety surveillance system based on electronic health data
- Mini-Sentinel is a five year pilot program. Its goals:
  - Develop capacity to use existing automated healthcare data
  - Develop and evaluate scientific methods
  - Evaluate safety issues
  - Assess barriers and challenges
- 2013 marked Mini-Sentinel's fourth year

Mini-Sentinel

http://www.minisentinel.org/

Search

Home | About Us | Assessments | Methods | Data | Communications | Related Links

Welcome to Mini-Sentinel

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to create an active surveillance system - the Sentinel System - to monitor the safety of FDA-regulated medical products. Mini-Sentinel uses pre-existing electronic healthcare data from multiple sources. Collaborating Institutions provide access to data as well as scientific and organizational expertise.

Mini-Sentinel is part of the FDA's Sentinel Initiative, which is exploring a variety of approaches for improving the Agency's ability to quickly identify and assess safety issues.

NEW POSTINGS

- Data Quality Review and Characterization Programs v3.0.1
- Report: Intussusception Risk After Rotavirus Vaccination in U.S. Infants
- Publication: Validity of diagnostic codes to identify cases of severe acute liver injury in the U.S. Food and Drug Administration's Mini-Sentinel Distributed Database
- Distributed Query Tool – DataMart Administrator Manual v3.2
- Distributed Query Tool – Investigator

Syndromic Surveillance

"An investigational approach where health department staff, assisted by automated data acquisition and generation of statistical alerts, monitor disease indicators in real-time or near real-time to detect outbreaks of disease earlier than would otherwise be possible with traditional public health methods"

CDC MMWR 2004;53(No.RR-5)

Syndromic Surveillance

- Active or passive system that uses case definitions based entirely on clinical features without clinical or laboratory diagnosis
- For example, collecting the number of cases of diarrhea rather than cases of cholera, or "rash illness" rather than measles).
- Inexpensive and faster than systems that require laboratory confirmation, often used as first system in developing countries

Other Surveillance Data Sources

- Data collected for other purposes can be used as a source of surveillance data
- Large health care utilization database
- Electronic medical record systems
- Patient registries established for other purposes
- Longitudinal, observational cohort studies
- Post-Approval Phase IV and other RCTs

Surveillance Study Methods

Surveillance Study Methods

- The public health surveillance purpose and the way data is captured and recorded will determine the types of study methods that will be required including:
  - Study Design
  - Data Analysis
  - Dissemination
  - Linking with public health action
  - Program Evaluation

Surveillance Study Methods

- The public health surveillance purpose and the way data is captured and recorded will also determine the types of analyses that should be performed. Analyses such as:
  - Descriptive statistics
  - Data mining
  - Modeling
- The type of analysis will also depend on the purpose – exploratory, descriptive or inferential.

Statistical Methods

- Design and analysis of observational studies (including propensity score and marginal structural models expertise)
- Meta-analyses
- Data mining and signal detection
- Survey methodology
- Time series analysis
- Graphical and computational methods
- Analyses of registry and health care databases

CDC Surveillance Resource Center

Interactive Database Systems

Web query systems that provide up-to-date data

Methods

Guidance on conducting and evaluating surveillance systems, and data standardization

Legal, Ethical, Policy Issues

Regulation guidance for collecting and sharing data

Tools & Templates

Adaptable forms and templates, survey questionnaires, slide sets, software, and toolkits

http://www.cdc.gov/surveillancepractice/index.html

Geospatial and Time Trends

- Graphical representations in terms of place an time are useful methods for detecting alerts and signals
- Spot higher than usual event rates over time
- If hot spots are geographically close, focus on common cause
- For post-marketing drug surveillance, potentially contamination might be linked to a local source

FluView

National and Regional Level Outpatient Illness and Viral Surveillance

Season: 2012-13 | weeks: 40 50 1 10 20 29

National | HHS Regions | Census Divisions

Choose components to view

Map | Line Chart | Pie Chart | Column Chart

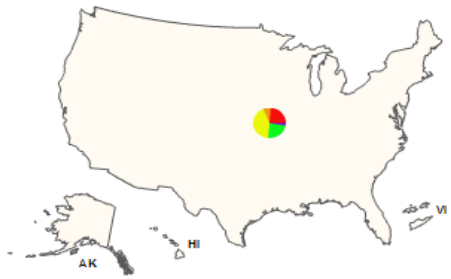
Download Data | Help

Map

Influenza Positive Tests Reported to CDC and ILI Activity, National Summary, 2012-13 Season, week ending Jul 20, 2013

Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet

Download Image



Piechart Legend
(Piechart includes data from most recent 3 weeks of season)

- A (H1) - **0**
- A (Unable to Subtype) - **0**
- A (H3) - **45**
- 2009 H1N1 - **14**
- A (Subtyping not Performed) - **79**
- B - **45**
- H3N2v - **5**
- No Data

Map Legend

- ILI Elevated
- ILI Normal
- No Data

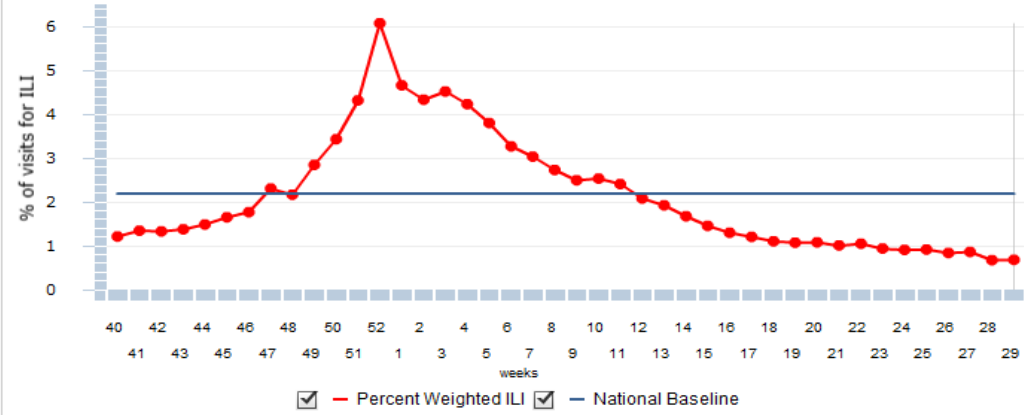
3 weeks ending July 20, 2013

Line Chart ILINet

Percentage of visits for ILI, National Summary, 2012-13 Season through Jul 20, 2013

Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet

Download Image | Download Data



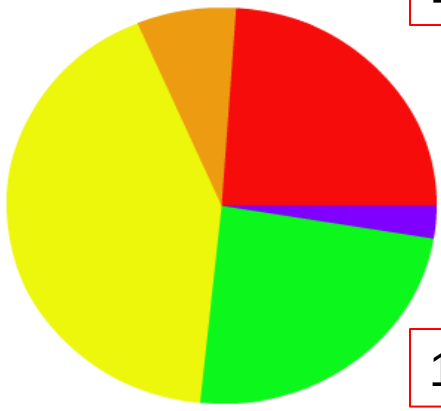
Pie Chart WHO/NREVSS

Influenza Positive Tests Reported to CDC, National Summary, 2012-13 Season, weeks ending Jun 30, 2013 - Jul 20, 2013

Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet

Download Image

188 total cases



Number of Influenza Positive Tests

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- 2009 H1N1 - **14**
- A (Subtyping not Performed) - **79**
- B - **45**
- H3N2v - **5**
- No Data

14 2009 H1N1 cases

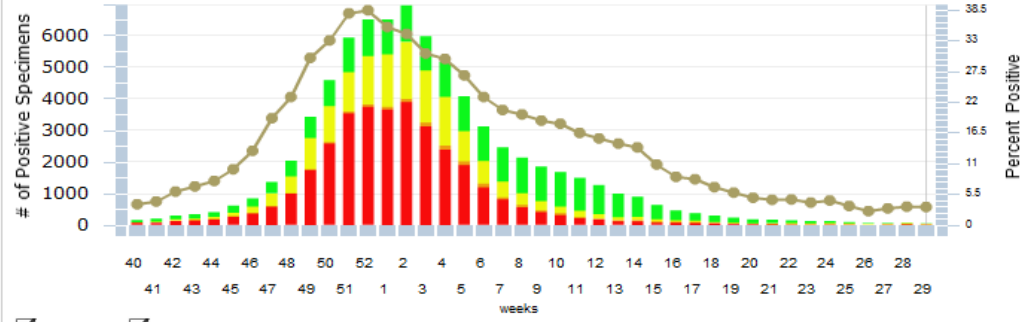
Stacked Column Chart WHO/NREVSS

Influenza Positive Tests Reported to CDC, National Summary, 2012-13 Season through Jul 20, 2013

Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet

Download Image | Download Data

Click and drag to create rectangle to zoom

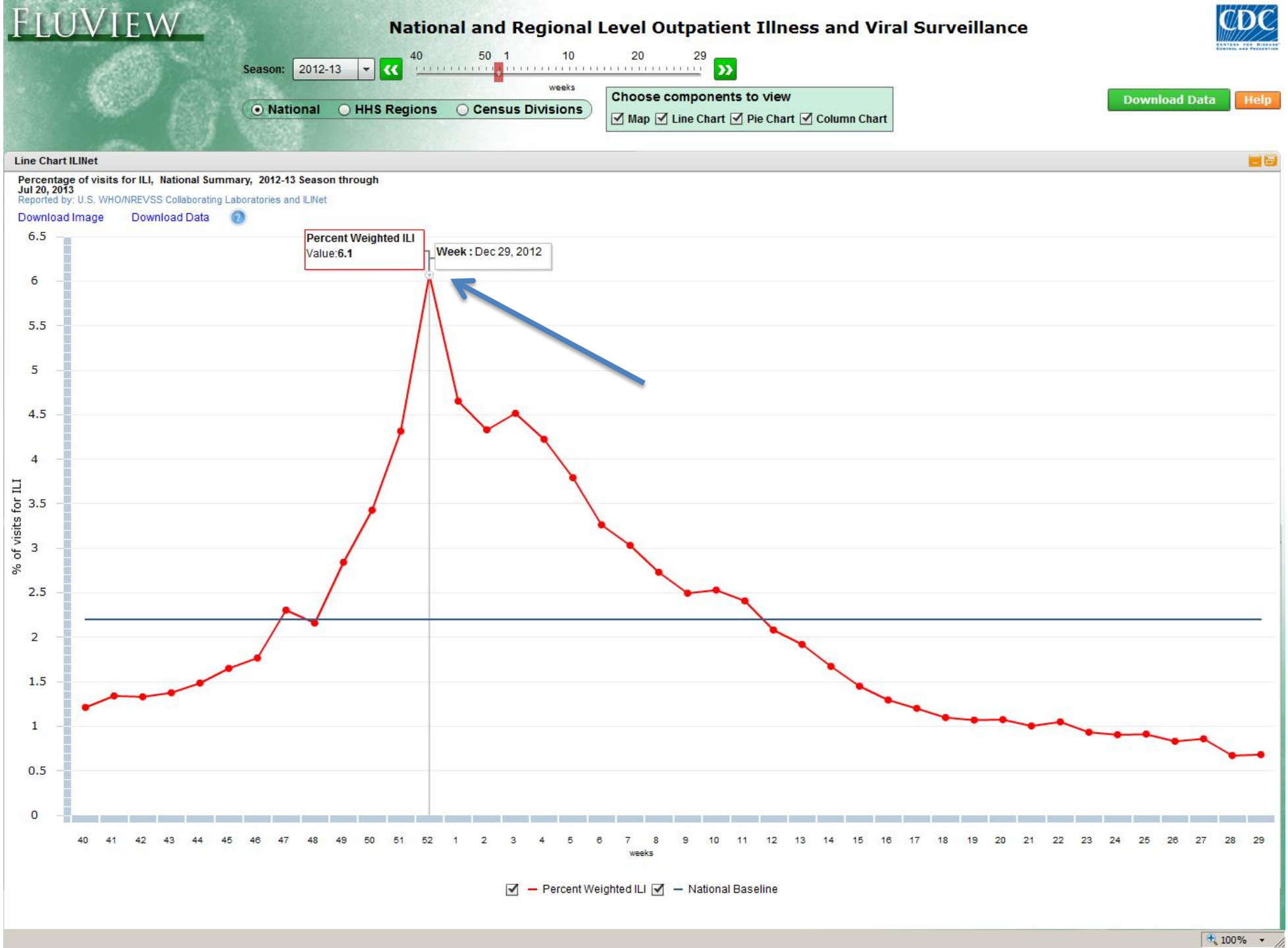


Check All | Percent Positive

A (H1) | A (H3) | A (Subtyping not Performed) | H3N2v

A (Unable to Subtype) | 2009 H1N1 | B

125%


FLUVIEW
National and Regional Level Outpatient Illness and Viral Surveillance
CDC
Season: 2012-13
40 50 1 10 20 29
weeks
National
HHS Regions
Census Divisions
Choose components to view
Map
Line Chart
Pie Chart
Column Chart
Download Data
Help
Line Chart ILINet
Percentage of visits for ILI, National Summary, 2012-13 Season through Jul 20, 2013
Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet
Download Image
Download Data
Percent Weighted ILI
Value:6.1
Week : Dec 29, 2012
% of visits for ILI
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
40 41 42 43 44 45 46 47 48 49 50 51 52 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
weeks
Percent Weighted ILI
National Baseline
100%

FluView

National and Regional Level Outpatient Illness and Viral Surveillance

Season: 2012-13 | weeks: 40 50 1 10 20 29

National | HHS Regions | Census Divisions

Choose components to view: Map | Line Chart | Pie Chart | Column Chart

Download Data | Help

Map

Influenza Positive Tests Reported to CDC and ILI Activity, National Summary, 2012-13 Season, week ending Dec 29, 2012
Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet

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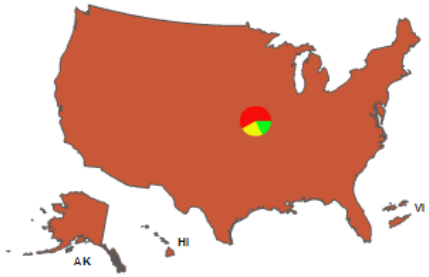


Piechart Legend
(Piechart includes data from most recent 3 weeks of season)
- A (H1) - **0**
- A (Unable to Subtype) - **0**
- A (H3) - **9849**
- 2009 H1N1 - **181**
- A (Subtyping not Performed) - **3924**
- B - **3081**
- H3N2v - **0**
- No Data

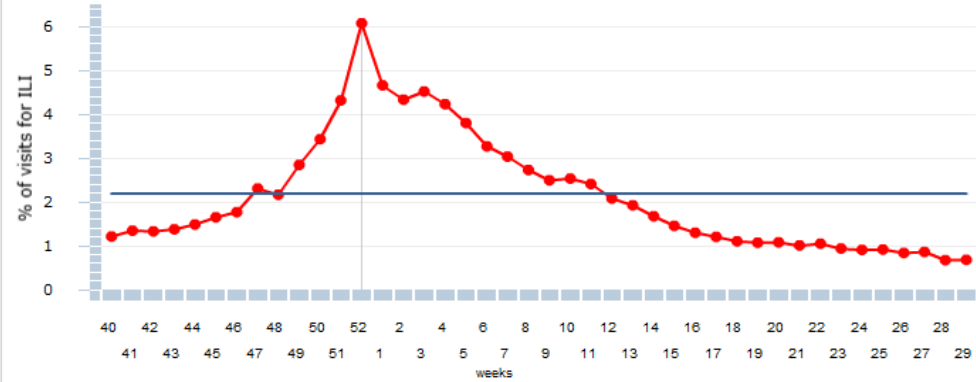
Map Legend
- ILI Elevated
- ILI Normal
- No Data

3 weeks ending Dec 29, 2012

Line Chart ILINet

Percentage of visits for ILI, National Summary, 2012-13 Season through Jul 20, 2013
Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet

Download Image | Download Data

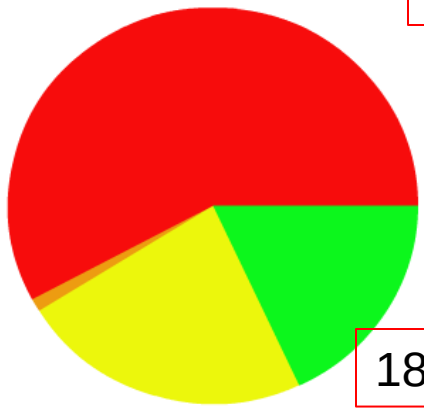


Pie Chart WHO/NREVSS

Influenza Positive Tests Reported to CDC, National Summary, 2012-13 Season, weeks ending Dec 09, 2012 - Dec 29, 2012
Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet

Download Image

17,035 total cases



Number of Influenza Positive Tests
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- 2009 H1N1 - **181**
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- B - **3081**
- H3N2v - **0**
- No Data

181 2009 H1N1 cases

Stacked Column Chart WHO/NREVSS

Influenza Positive Tests Reported to CDC, National Summary, 2012-13 Season through Jul 20, 2013
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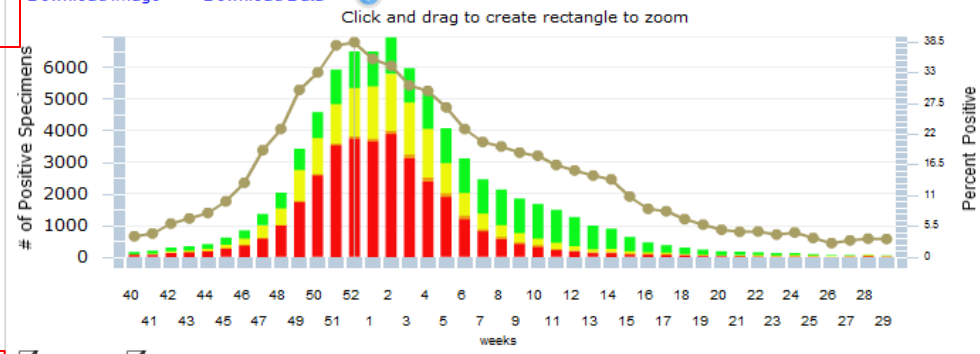
Download Image | Download Data



100%

FluView

National and Regional Level Outpatient Illness and Viral Surveillance

Season: 2012-13 | 40 50 1 10 20 29 (weeks)

National | HHS Regions | Census Divisions | Region: Region 1

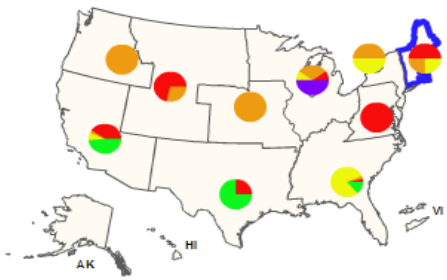
Choose components to view
Map | Line Chart | Pie Chart | Column Chart

Download Data | Help

Map

Influenza Positive Tests Reported to CDC and ILI Activity, by HHS Region, 2012-13 Season, week ending Jul 20, 2013
Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet

Download Image | Hide National Comparison Chart



National

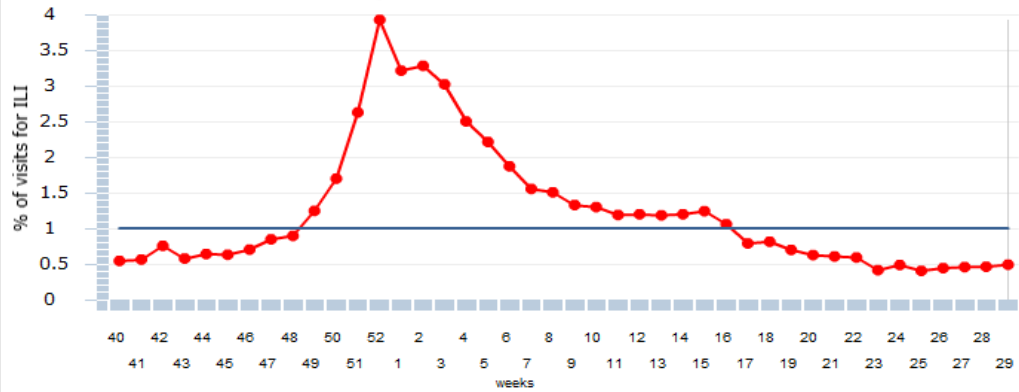
Piechart Legend
(Piechart includes data from most recent 3 weeks of season)
- A (H1) - **0**
- A (Unable to Subtype) - **0**
- A (H3) - **2**
- 2009 H1N1 - **1**
- A (Subtyping not Performed) - **1**
- B - **0**
- H3N2v - **0**
- No Data

Map Legend
- ILI Elevated
- ILI Normal
- No Data

Line Chart ILINet

Percentage of visits for ILI, HHS Region 1, 2012-13 Season through Jul 20, 2013
Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet

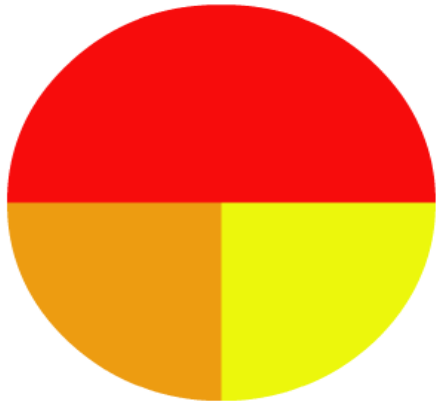
Download Image | Download Data



Pie Chart WHO//NREVSS

Influenza Positive Tests Reported to CDC, HHS Region 1, 2012-13 Season, weeks ending Jun 30, 2013 - Jul 20, 2013
Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet

Download Image



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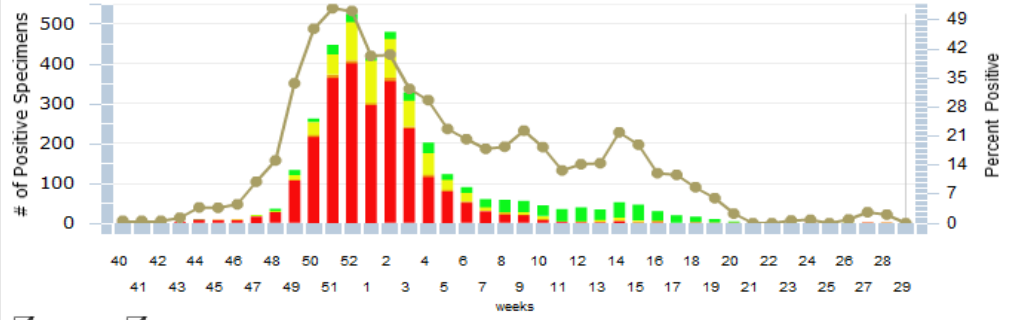
- H3N2v - **0**
- No Data

Stacked Column Chart WHO//NREVSS

Influenza Positive Tests Reported to CDC, HHS Region 1, 2012-13 Season through Jul 20, 2013
Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet

Download Image | Download Data

Click and drag to create rectangle to zoom



Check All | Percent Positive

A (H1) | A (H3) | A (Subtyping not Performed) | H3N2v
A (Unable to Subtype) | 2009 H1N1 | B

125%

Office of Surveillance, Epidemiology, and Laboratory Services

Behavioral Risk Factor Surveillance System

2011: Have you ever been told by a doctor that you have diabetes?

Responses: **Yes** Yes, pregnancy-related No No, pre-diabetes or borderline diabetes

Display: Nationwide

- [x] **States**
- [x] **MMSAs**

Percent
- <= 8.6
- 8.7 to 9.7
- 9.8 to 10.5
- 10.6 to 11.2
- >= 11.3
- No Data

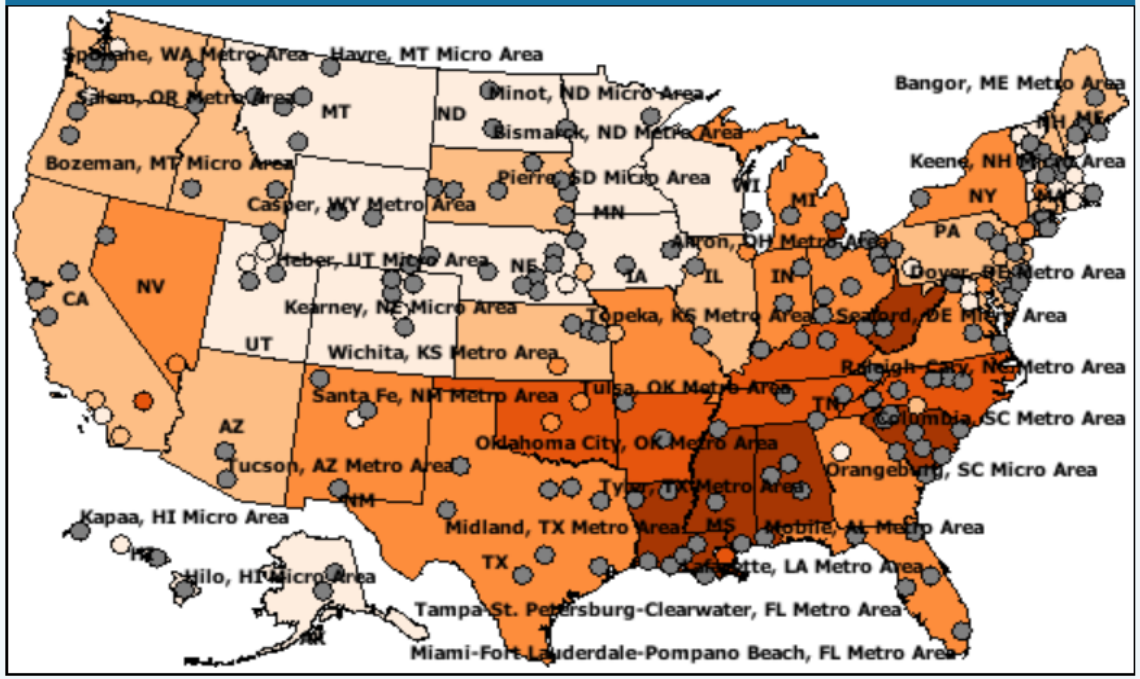
Data Classification: Natural Breaks

Change Data Classification

Download GIS Data

Show:
- [ ] Outlying Territories
- [x] State Labels
- [x] MMSA Labels

2011 Percentage of respondents reporting Yes



info

zoom in

zoom out

pan

Reset Map

Print/Save Map

Pharmacovigilance

"The pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines."

Source: The Importance of Pharmacovigilance, WHO 2002

Drug Withdrawals Since 2000

Troglitazone (Rezulin)	2000	Withdrawn because of risk of hepatotoxicity; superseded by pioglitazone and rosiglitazone
Alosetron (Lotronex)	2000	Withdrawn because of risk of fatal complications of constipation; reintroduced 2002 on a restricted basis
Cisapride (Propulsid)	2000s	Withdrawn in many countries because of risk of cardiac arrhythmias
Amineptine (Survector)	2000	Withdrawn because of hepatotoxicity, dermatological side effects, and abuse potential.
Phenylpropanolamine (Propagest, Dexatrim)	2000	Withdrawn because of risk of stroke in women under 50 years of age when taken at high doses (75mg twice daily) for weight loss.
Trovafloxacin (Trovan)	2001	Withdrawn because of risk of liver failure
Cerivastatin (Baycol, Lipobay)	2001	Withdrawn because of risk of rhabdomyolysis
Rapacuronium (Raplon)	2001	Withdrawn in many countries because of risk of fatal bronchospasm
Rofecoxib (Vioxx)	2004	Withdrawn because of risk of myocardial infarction
Co-proxamol (Distalgesic)	2004	Withdrawn in the UK due to overdose dangers.
mixed amphetamine salts (Adderall XR)	2005	Withdrawn in Canada because of risk of stroke. See Health Canada press release. The ban was later lifted because the death rate among those taking Adderall XR was determined to be no greater than those not taking Adderall.
hydromorphone extended-release (Palladone)	2005	Withdrawn because of a high risk of accidental overdose when administered with alcohol
Thioridazine (Melleril)	2005	Withdrawn from U.K. market because of cardiotoxicity
Pemoline (Cylert)	2005	Withdrawn from U.S. market because of hepatotoxicity

Drug Withdrawals Since 2000

Pemoline (Cylert)	2005	Withdrawn from U.S. market because of hepatotoxicity
Natalizumab (Tysabri)	2005-2006	Voluntarily withdrawn from U.S. market because of risk of Progressive multifocal leukoencephalopathy (PML). Returned to market July, 2006.
Ximelagatran (Exanta)	2006	Withdrawn because of risk of hepatotoxicity (liver damage).
Pergolide (Permax)	2007	Voluntarily withdrawn in the U.S. because of the risk of heart valve damage. Still available elsewhere.
Tegaserod (Zelnorm)	2007	Withdrawn because of imbalance of cardiovascular ischemic events, including heart attack and stroke. Was available through a restricted access program until April 2008.
Aprotinin (Trasylol)	2007	Withdrawn because of increased risk of complications or death; permanently withdrawn in 2008 except for research use
Inhaled insulin (Exubera)	2007	Withdrawn in the UK due to poor sales caused by national restrictions on prescribing, doubts over long term safety and too high a cost
Lumiracoxib (Prexige)	2007-2008	Progressively withdrawn around the world because of serious side effects, mainly liver damage
Rimonabant (Acomplia)	2008	Withdrawn around the world because of risk of severe depression and suicide
Efalizumab (Raptiva)	2009	Withdrawn because of increased risk of progressive multifocal leukoencephalopathy; to be completely withdrawn from market by June 2009
Sibutramine (Reductil)	2010	Withdrawn in Europe, Australasia, and the U.S. because of increased cardiovascular risk
Gemtuzumab ozogamicin (Mylotarg)	2010	Withdrawn in the U.S. due to increased risks of veno-occlusive disease and based on results of a clinical trial in which it showed no benefit in acute myeloid leukemia (AML)
Rosiglitazone (Avandia)	2010	Withdrawn in Europe because of increased risk of heart attacks and death. This drug continues to be available in the U.S.

Data Mining Methods

- Computational process of discovering patterns in large data bases
- Combines computational and statistical methods
- Primary method of signal detection in the FDA Adverse Events Reporting Systems (FAERS)
- Useful for large, passive surveillance systems

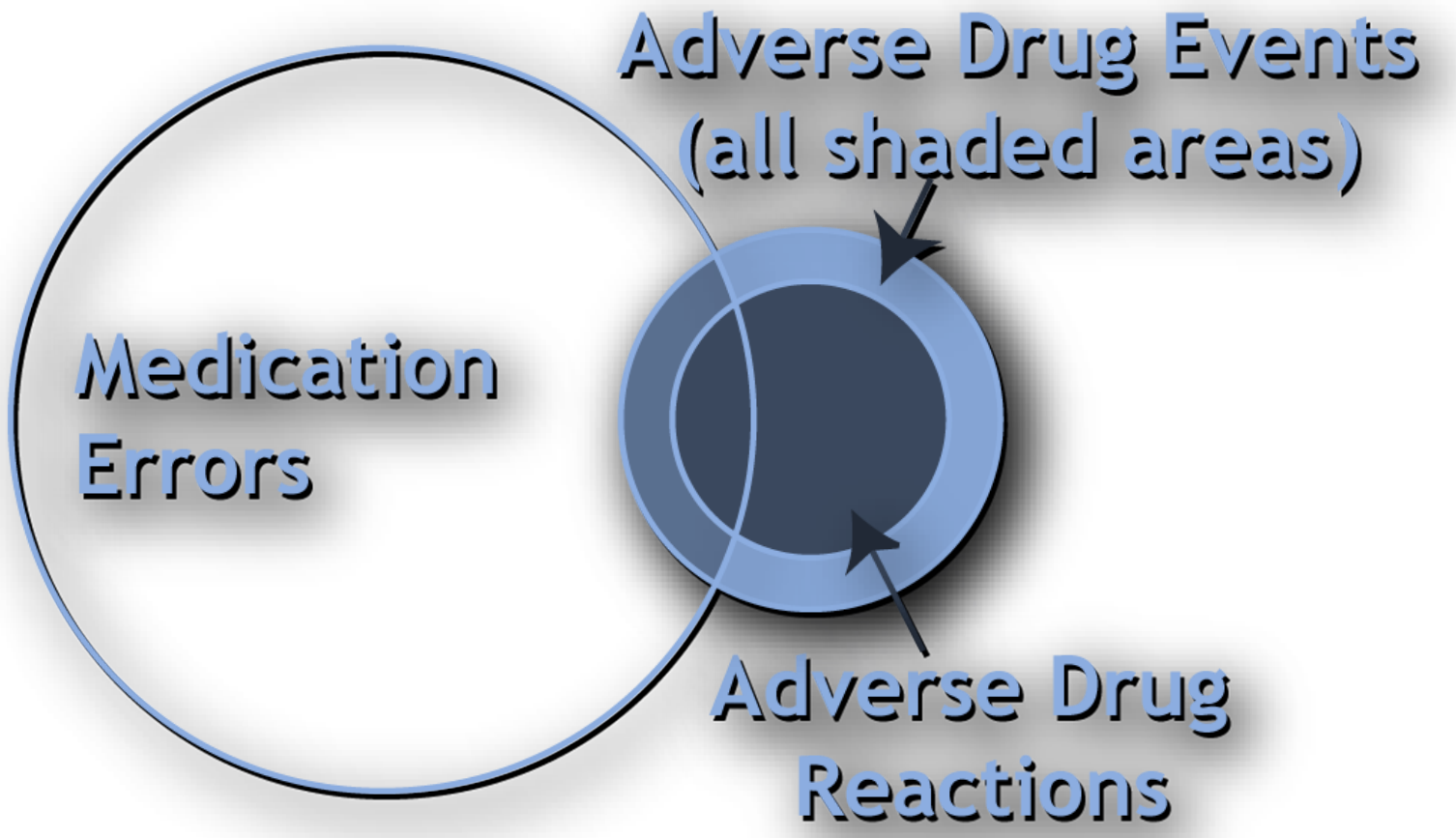
Short Definitions

Adverse Drug Event – Harm caused by the drug or the use of a drug

Adverse Drug Reaction – Harm directly caused by the drug at normal doses

Medication Error – Inappropriate use of a drug that may or may not result in harm

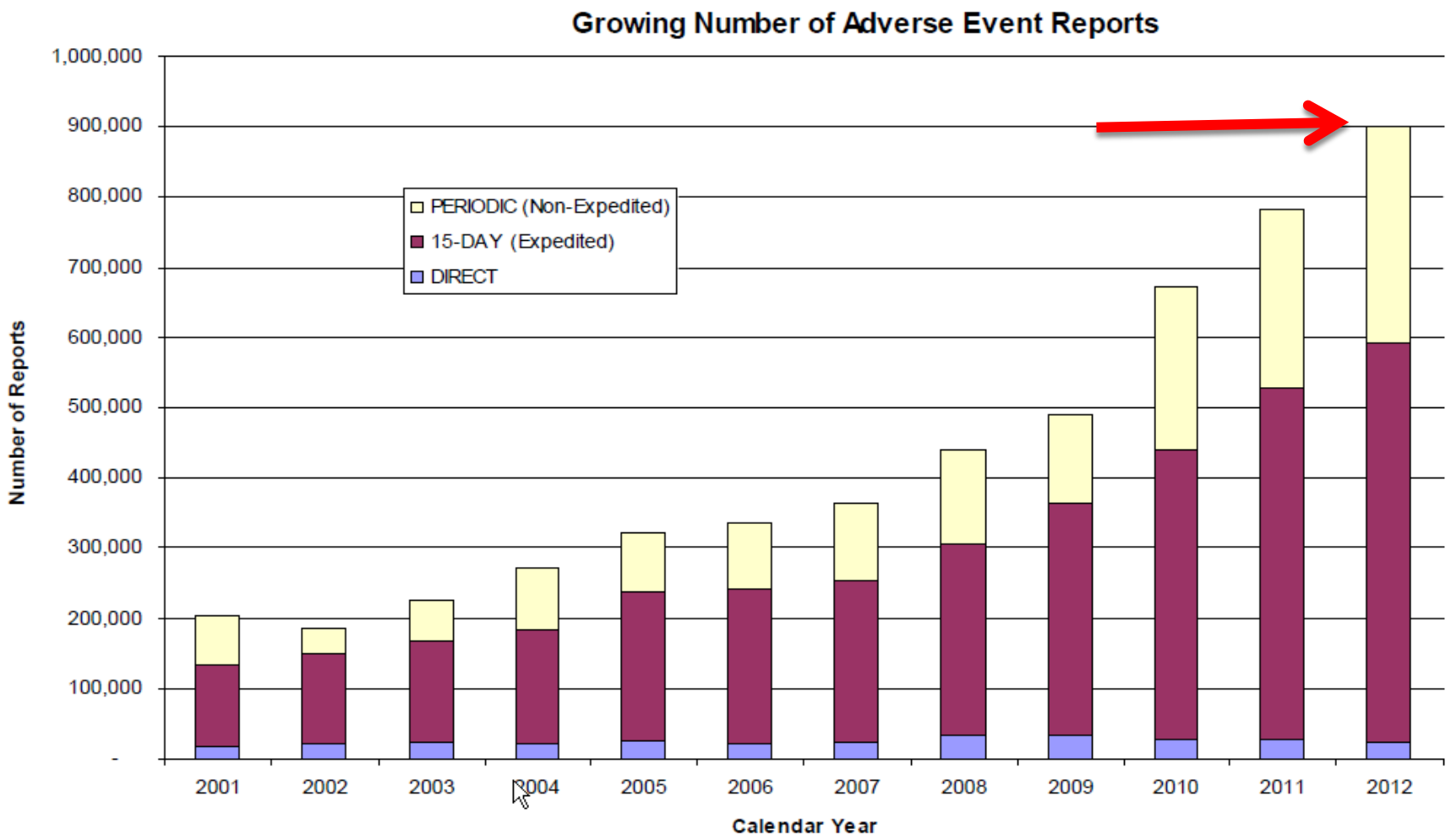
Spontaneous Reports of ADRs



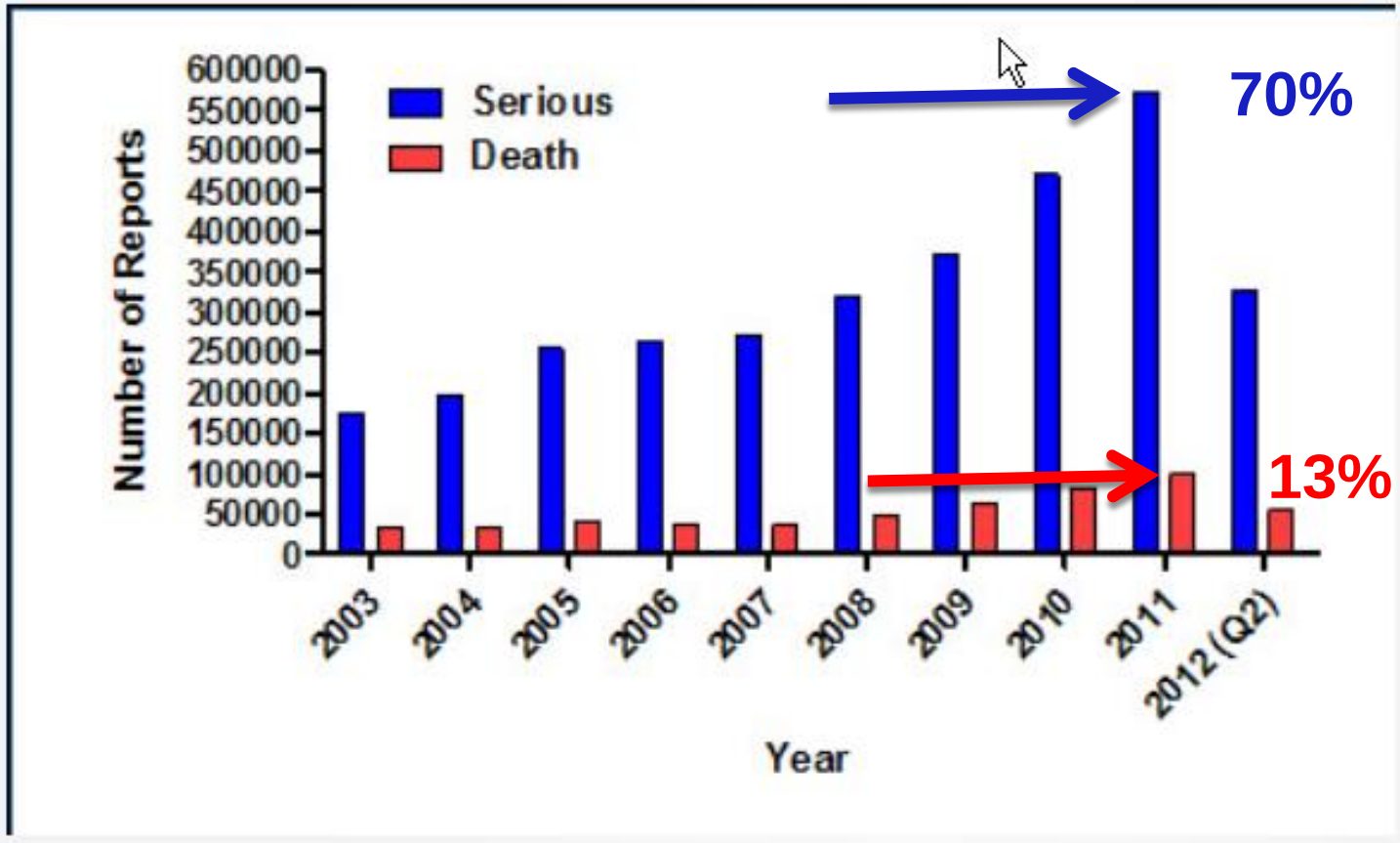
Spontaneous Reports and FAERS

- FDA Adverse Events Reporting System
- Computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- > 7 million reports since 1969
- Nearly 1 million new reports in 2012

Adverse Events in FAERS by Year



Patient Outcomes in FAERS by Year



This figure illustrates the patient outcome(s) for reports in FAERS since the year 2003 until the end of the second quarter of 2012. Serious outcomes include death, hospitalization, life-threatening, disability, congenital anomaly and/or other serious outcome.

Statistical Associations - Signals

- Proportional reporting ratio (PRR)
- Reporting OR (ROR)
- Yule's Q (YULE)
- $\chi 2$ test (CHI)
- Bayesian confidence propagation neural networks (BCPNN)
- Empirical Bayes Gamma Poisson Shrinker (EBGPS)
- Tree-based Scan Statistic (TBSS)

Sentinel Surveillance Assessments

- Exposures to medical products
- Occurrences of particular diagnoses and medical procedures
- Health outcomes among individuals exposed to medical products
- Impact of FDA's regulatory actions and interventions

Sentinel Statistical Methods

- Signal refinement – what else explains an association?
- Estimating causal risk differences – how to control for multiple confounders in the concurrent control design with a single time exposure
- Case-based approaches -- case-crossover, case-time control, self-controlled case series, and Bayesian hierarchical extensions across outcomes
- Signal evaluation - applying high-dimensional propensity score adjustment to medical product safety surveillance systems

Summary

- Public health surveillance enables public health leaders to make evidence-based decisions.
- Surveillance systems provide integrated functions including monitoring, detection, response and evaluation.
- Public health surveillance systems should be implemented whenever there is a critical need to monitor disease incidence, the consequences of health care interventions or treatments such as drugs, devices, biologics and vaccines.

Summary

- Post-marketing surveillance of regulated medical products can be used to
  - detect medical errors
  - manufacturing defects
  - contamination
  - counterfeit products
  - rare or new adverse reactions, and
  - to identify new subgroups prone to adverse reactions

Summary

- Passive reporting systems of spontaneous reports of adverse reactions to medical products will continue to play an increasingly critical role in post-marketing surveillance especially as web-based applications, information technology and computational algorithms become increasingly more sophisticated.
- In addition, new initiatives based upon linked electronic medical records, such a the FDA's Sentinel and Mini Sentinel program, will provide the newest frontier and promise in the science of surveillance.