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.
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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
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.
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
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 and 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.
3 weeks ending July 20, 2013

188 total cases

14 2009 H1N1 cases
3 weeks ending Dec 29, 2012

17,035 total cases

181 2009 H1N1 cases
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
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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troglitazone (Rezulin)</td>
<td>2000</td>
<td>Withdrawn because of risk of hepatotoxicity; superseded by pioglitazone and rosiglitazone</td>
</tr>
<tr>
<td>Alosetron (Lotronex)</td>
<td>2000</td>
<td>Withdrawn because of risk of fatal complications of constipation; reintroduced 2002 on a restricted basis</td>
</tr>
<tr>
<td>Cisapride (Propulsid)</td>
<td>2000s</td>
<td>Withdrawn in many countries because of risk of cardiac arrhythmias</td>
</tr>
<tr>
<td>Aminoptine (Survortor)</td>
<td>2000</td>
<td>Withdrawn because of hepatotoxicity, dermatological side effects, and abuse potential.</td>
</tr>
<tr>
<td>Phenylpropanolamine (Propagent, Dexatrim)</td>
<td>2000</td>
<td>Withdrawn because of risk of stroke in women under 50 years of age when taken at high doses (75mg twice daily) for weight loss.</td>
</tr>
<tr>
<td>Trovafloxacin (Trovan)</td>
<td>2001</td>
<td>Withdrawn because of risk of liver failure</td>
</tr>
<tr>
<td>Cerivastatin (Baycol, Lipobay)</td>
<td>2001</td>
<td>Withdrawn because of risk of rhabdomyolysis</td>
</tr>
<tr>
<td>Rapacuronium (Raplon)</td>
<td>2001</td>
<td>Withdrawn in many countries because of risk of fatal bronchospasm</td>
</tr>
<tr>
<td>Rofecoxib (Vioxx)</td>
<td>2004</td>
<td>Withdrawn because of risk of myocardial infarction</td>
</tr>
<tr>
<td>Co-proxamol (Distalgesic)</td>
<td>2004</td>
<td>Withdrawn in the UK due to overdose dangers.</td>
</tr>
<tr>
<td>mixed amphetamine salts (Adderall XR)</td>
<td>2005</td>
<td>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.</td>
</tr>
<tr>
<td>Hydromorphone extended-release (Palladone)</td>
<td>2005</td>
<td>Withdrawn because of a high risk of accidental overdose when administered with alcohol</td>
</tr>
<tr>
<td>Thiordazine (Molineil)</td>
<td>2005</td>
<td>Withdrawn from U.K. market because of cardiotoxicity</td>
</tr>
<tr>
<td>Pemoline (Cylert)</td>
<td>2005</td>
<td>Withdrawn from U.S. market because of hepatotoxicity</td>
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<td>2005</td>
<td>Withdrawn from U.S. market because of hepatotoxicity</td>
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<tr>
<td>Xarelto (Exanta)</td>
<td>2006</td>
<td>Withdrawn because of risk of hepatotoxicity (liver damage)</td>
</tr>
<tr>
<td>Periactin (Permax)</td>
<td>2007</td>
<td>Voluntarily withdrawn in the U.S. because of the risk of heart valve damage. Still available elsewhere.</td>
</tr>
<tr>
<td>Tegaserod (Zelnorm)</td>
<td>2007</td>
<td>Withdrawn because of imbalance of cardiovascular ischemic events, including heart attack and stroke. Was available through a restricted access program until April 2008.</td>
</tr>
<tr>
<td>Aprotinin (Trasylol)</td>
<td>2007</td>
<td>Withdrawn because of increased risk of complications or death; permanently withdrawn in 2008 except for research use</td>
</tr>
<tr>
<td>Inhaled insulin (Exubera)</td>
<td>2007</td>
<td>Withdrawn in the UK due to poor sales caused by national restrictions on prescribing, doubts over long term safety and too high a cost</td>
</tr>
<tr>
<td>Lumiracoxib (Prexige)</td>
<td>2007-2008</td>
<td>Progressively withdrawn around the world because of serious side effects, mainly liver damage</td>
</tr>
<tr>
<td>Rimonabant (Acomplia)</td>
<td>2008</td>
<td>Withdrawn around the world because of risk of severe depression and suicide</td>
</tr>
<tr>
<td>Efalizumab (Raptiva)</td>
<td>2009</td>
<td>Withdrawn because of increased risk of progressive multifocal leukoencephalopathy, to be completely withdrawn from market by June 2009</td>
</tr>
<tr>
<td>Sibutramine (Reductil)</td>
<td>2010</td>
<td>Withdrawn in Europe, Australasia, and the U.S. because of increased cardiovascular risk</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin (Mylotarg)</td>
<td>2010</td>
<td>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)</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>2010</td>
<td>Withdrawn in Europe because of increased risk of heart attacks and death. This drug continues to be available in the U.S.</td>
</tr>
</tbody>
</table>
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

Medication Errors

Adverse Drug Events (all shaded areas)

Adverse Drug Reactions
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:

Growing Number of Adverse Event Reports:

- PERIODIC (Non-Expedited)
- 15-DAY (Expedited)
- DIRECT
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
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.
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
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 as the FDA’s Sentinel and Mini Sentinel program, will provide the newest frontier and promise in the science of surveillance.