Research Seminars in Medicine
Introduction to Pharmacoepidemiology I

Vera Ehrenstein, MPH, DSc
Department of Clinical Epidemiology
Aarhus University Hospital
Aarhus, Denmark
10 December 2014
Some definitions of **SEMINAR**

- an advanced or graduate course often featuring **informality and discussion**
- a meeting for **giving and discussing information**

http://www.merriam-webster.com/dictionary/seminar
Phases of drug development

• Preclinical: Chemical/animal testing
• **Phase I studies:**
  – N=20-80 healthy volunteers
  – Safety, metabolism
• **Phase II studies:**
  – N=100s patients
  – Efficacy, short-term safety
  – May or may not have control (placebo) group
• **Phase III studies (preauthorization):**
  – 1000s patients, main indication
  – Randomized controlled trials (RCT)
  – Dose, efficacy: CAN IT WORK?
Phases of drug development

• Phase IV (postauthorization):
  – all patients, indications
  – RCT/non-interventional studies
  – Long-term safety, rare adverse events
  – Effectiveness: DOES IT WORK?
Why not stop after clinical trials?

• Too short to detect long-term side effects
• Too small to detect rare side effects
• Conducted in selected populations
• Few outcomes assessed
• Not all indications assessed
• Drug interactions are unknown
• Clinical epidemiology: Study of the outcome of illness
• Pharmacoepidemiology: study of the outcome of intervention

Basic question
• Do the benefits of an treatment outweigh its risks?
Pharmacoepidemiology: scope

Application of epidemiologic reasoning, methods, and knowledge to the study of the uses and effects (beneficial and adverse) of drugs (and biologics), vaccines, and devices in human populations.

Types of study by aim

• Uses: drug utilization – descriptive studies
  – Demographics
  – Comorbidities
  – Contraindications
  – Off-label use
Drug utilization

Use of prescribed drugs among primiparous women: an 11-year population-based study in Denmark

Anne-Mette Bay Bjørn¹
Mette Nørgaard¹
Heidi Holmager Hundborg¹
Ellen Aagaard Nohr²
Vera Ehrenstein¹

Purpose: To describe patterns of prescribed drug use over time among primiparous women in Denmark.

Methods: Through the Danish Medical Birth Registry, we identified all primiparous women giving live birth or stillbirth at ≥ 22 gestational weeks in northern Denmark, from 1999 to 2009. From the Aarhus University Prescription Database we obtained information on the women’s prescriptions for reimbursed drugs filled from 30 days before conception until delivery.
Figure 1: Prevalence of prescribed drug use according to age among primiparous women. Northern Denmark 1999–2009.
Types of study by aim

• **Uses**: drug utilization – descriptive studies
  – Demographics
  – Comorbidities
  – Contraindications
  – Off-label use

• **Effects** (intended and not) – analytic studies
  – Additional indications (postmarketing RCT)
  – Effectiveness for main indication (in real clinical practice)
  – Safety: adverse effect monitoring/pharmacovigilance
  – Comparative effectiveness (active comparators)

Immediate postmarketing period
Patient population over time

"… early users of newly marketed medications may be highly differential with respect to the benefits and adverse effects of alternative treatment."

‘The Catch 22’ of risk-benefit assessment

• Need to prescribe a drug in real-life settings to get reliable data on benefit-risk profile
• Reluctance to prescribe the drug without reliable data on benefit/risk profile
Sources of safety ‘signals’

• Spontaneous reporting
• Case reports (thalidomide)
• Pharmacoepidemiologic studies
• Safety surveillance, monitoring using electronic health data (EHR)
  – pharmacovigilance
Nordic National Health Registers

Medical Birth Registers
- 1967
- 1973
- 1987

Patient Registers
- 1967
- 1977
- 1987
- 2009

Prescribed Drug Registers
- 1994
- 1994/5
- 2003
- 2004
- 2005

Cancer Registers
- 1943
- 1953
- 1955
- 1960

Cause of Death Registers
- 1943
- 1951
- 1961
- 1969
- 1971

Courtesy of Associate Professor Helle Kieler
Advantages of Nordic data

- Total population coverage
- Prospective and routine data collection
- Universal health care
- Individual-level linkage

At least one component is absent in:
- Medicare/Insurance/Veterans Admin (US)
- General Practice Databases (UK, NL)
- Regional claims databases (Canada)
The Nordic prescription databases as a resource for pharmacoepidemiological research—a literature review

B Wettermark\textsuperscript{1,2*}, H Zoëga\textsuperscript{3,4}, K Furu\textsuperscript{5,6}, M Korhonen\textsuperscript{7}, J Hallas\textsuperscript{8}, M Nørgaard\textsuperscript{9}, AB Almærsdottir\textsuperscript{8,10}, M Andersen\textsuperscript{1,2,8}, K Andersson Sundell\textsuperscript{11}, U Bergman\textsuperscript{1,2}, A Helin-Salmivaara\textsuperscript{12}, M Hoffmann\textsuperscript{13}, H Kieler\textsuperscript{1}, JE Martikainen\textsuperscript{14}, M Mortensen\textsuperscript{9}, M Peitzold\textsuperscript{15}, H Wallach-Kildemoes\textsuperscript{16}, C Wallin\textsuperscript{1} and HT Sørensen\textsuperscript{9†}
Figure 2. Number of pharmacoepidemiological studies ($n = 108$) based on the Nordic prescription databases published in 2005–2010, by selected patient populations and study type. The remaining studies ($n = 407$) included either the entire population in the country/region or all patients exposed to a certain drug group or diagnosed with a specified disease during a given period.
Total studies 515
More than 1 country 4 (!)
Non-Nordic databases: Why?

- Collaboration/requirement for funding
- Not all variables measured
- Homogeneous population (ethnicity)
- Not enough data!
Europe - UK

• CPRD – Clinical Practice Research Datalink (formerly General Practice Research Database)
• THIN – The Health Information Network
The Clinical Practice Research Datalink (CPRD)

• Since 1987
• Ca. 600 GP-practices in England
  • Approx. 6% of UK population
• 11 mio ‘research standard’ patients/67 mio person-years
• Build-in permanent data checks
• Available by license ($$) www.cprd.com
CPRD – type of data

- Administrative: birth date, practice membership dates, deaths
- Clinical: diagnoses, including those from specialists and hospital stays
- Medications: issued prescriptions – with prescribed dose
- Laboratory data
- Lifestyle: BMI, smoking, alcohol use
Europe - NL

- IPCI – The Integrated Primary Care Information Database
- PHARMO Record Linkage System
- IADB – pharmacy dispensing database
- MONDRIAAN project
The IPCI database

- Participating general practitioners (voluntary)
- Since 1994/ 1.5 mio patients (also historical)
- Diagnoses, labs, referrals
- Indications for prescriptions
- Managed by Erasmus University (access)

http://www.ipci.nl
EU databases: strengths

• Rich clinical data, including anthropometrics

• Primary and secondary-care diagnoses are often available

• Laboratory data

• Lifestyle data (smoking, alcohol use)

• For medications: indication and prescribed dose
EU databases: limitations

- GP databases subject to follow-up loss (practice changes)
- No lifelong follow-up
- Linkage not straightforward
- No linkage to non-medical data
US data sources for PE

• Health maintenance organizations (HMO)
• Medicare and Medicaid
• Veterans Administration (VA)
Health Maintenance Organizations (HMO)

- Insurance-company ‘managed care’ health care plan
- Primary care provided = gatekeeper
- Closed network of healthcare providers
HMORN Sites

www.hmoresearchnetwork.org

[Map of the United States showing various health care sites and their locations, including Kaiser Permanente sites, HealthPartners, and others.]
Type of Data

- Administrative
  - Birth date, sex, enrollment dates
- Claims (billing e-records of medical encounters)
  - Pharmacy dispensing (NDC)
  - Diagnoses from hospitalizations/ambulatory visits (ICD)
- Electronic medical records (EMR)
  - Detailed clinical data (procedures, labs, radiology, referrals, BMI, health behaviors)

NDC=national drug codes, ICD=international classification of diseases
### Table 12.2 Demographic characteristics of HMO Research Network member health plans (primary model / % EMR data)

<table>
<thead>
<tr>
<th>Health plan</th>
<th>GHS</th>
<th>GHC</th>
<th>HPHC</th>
<th>HPRF</th>
<th>HFHS</th>
<th>KPCO</th>
<th>KPG</th>
<th>KPH</th>
<th>KPNC</th>
<th>KPNW</th>
<th>KPSC</th>
<th>LCF</th>
<th>MHS</th>
<th>MCRF</th>
<th>MPCI</th>
<th>S&amp;W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary model</td>
<td>Mixed</td>
<td>HMO</td>
<td>Mixed</td>
<td>Mixed</td>
<td>HMO</td>
<td>Mixed</td>
<td>HMO</td>
<td>HMO</td>
<td>HMO</td>
<td>HMO</td>
<td>HMO</td>
<td>Mixed</td>
<td>Mixed</td>
<td>HMO</td>
<td>Mixed</td>
<td>HMO</td>
</tr>
<tr>
<td>Total enrolled, x1000</td>
<td>229</td>
<td>617</td>
<td>762</td>
<td>687</td>
<td>208</td>
<td>451</td>
<td>271</td>
<td>216</td>
<td>3,130</td>
<td>471</td>
<td>3,324</td>
<td>194</td>
<td>1,800</td>
<td>160</td>
<td>220</td>
<td>203</td>
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<tr>
<td>% with EMR data</td>
<td>36</td>
<td>69</td>
<td>35</td>
<td>83</td>
<td>TBD</td>
<td>83</td>
<td>100</td>
<td>98.5</td>
<td>TBD</td>
<td>98</td>
<td>TBD</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>60</td>
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<td></td>
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</tr>
<tr>
<td>% ≤17 years</td>
<td>19</td>
<td>20</td>
<td>24</td>
<td>35</td>
<td>18</td>
<td>22</td>
<td>24</td>
<td>22</td>
<td>22</td>
<td>23</td>
<td>25</td>
<td>39</td>
<td>41</td>
<td>24</td>
<td>19</td>
<td>30</td>
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<tr>
<td>% 18–44 years</td>
<td>29</td>
<td>33</td>
<td>39</td>
<td>28</td>
<td>29</td>
<td>34</td>
<td>39</td>
<td>35</td>
<td>34</td>
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<td>22</td>
<td>33</td>
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<td>22</td>
<td>33</td>
</tr>
<tr>
<td>% 45–64 years</td>
<td>28</td>
<td>33</td>
<td>33</td>
<td>30</td>
<td>35</td>
<td>30</td>
<td>31</td>
<td>30</td>
<td>29</td>
<td>31</td>
<td>28</td>
<td>20</td>
<td>19</td>
<td>26</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>% 65+</td>
<td>24</td>
<td>13</td>
<td>4</td>
<td>4</td>
<td>18</td>
<td>14</td>
<td>7</td>
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<td>13</td>
<td>11</td>
<td>15</td>
<td>5</td>
<td>17</td>
<td>19</td>
<td>9</td>
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</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Female</td>
<td>52</td>
<td>53</td>
<td>52</td>
<td>52</td>
<td>55</td>
<td>53</td>
<td>53</td>
<td>50</td>
<td>52</td>
<td>52</td>
<td>52</td>
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<td>53</td>
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<tr>
<td>Race*</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>% White</td>
<td>96</td>
<td>82</td>
<td>75</td>
<td>81</td>
<td>54</td>
<td>74</td>
<td>63</td>
<td>25</td>
<td>51</td>
<td>84</td>
<td>38</td>
<td>55</td>
<td>95</td>
<td>97</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>% African American</td>
<td>&lt;1</td>
<td>3</td>
<td>16</td>
<td>9</td>
<td>33</td>
<td>5</td>
<td>33</td>
<td>&lt;1</td>
<td>8</td>
<td>3</td>
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<td>1</td>
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<td>8</td>
</tr>
<tr>
<td>% Asian American</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>&lt;1</td>
<td>63</td>
<td>17</td>
<td>5</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>&lt;1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>% American Indian</td>
<td>&lt;1</td>
<td>1</td>
<td>&lt;1</td>
<td>1</td>
<td>&lt;1</td>
<td>1</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>2</td>
<td>0</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>% Hispanic</td>
<td>1.4</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>15</td>
<td>&lt;1</td>
<td>3</td>
<td>19</td>
<td>6</td>
<td>41</td>
<td>38</td>
<td>0</td>
<td>&lt;1</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>% Other</td>
<td>&lt;1</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>17</td>
<td>5</td>
<td>1</td>
<td>&lt;1</td>
<td>0</td>
<td>5</td>
<td>&lt;1</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

*May be >100% if multiple responses allowed at collection, “other” may include persons reporting multiple races.
See Table 12.1 for definitions of abbreviations.
HMOs: strengths

• Large and diverse samples
• Broad population coverage
• Ability to re-contact members
• Rich clinical data
• Standard data layouts facilitate multicenter-research
HMOs: limitations

- Uninsured are not represented (unemployed, selection bias)
- Gaps in coverage (employment-based)
- Outsourced and out-of-pocket services not represented
- Completeness may vary
US Government claims

- Medicaid – est. 1965, a payer plan
- Medicare – est. 1965, a payer plan
- Department of Veterans Affairs (VA) Health Care System – est. 1930, a payer/provider plan
Medicaid

- Largest US-government funded health coverage (ca. 60 mio)
- Eligibility: low-income pregnant women, poor families with children, chronically disabled, low-income
- State-administered
  - Low-income definitions/benefits offered vary by state
Medicare

- Funded 100% by the US federal gov’t
- Eligibility: age 65+, some disabilities, end-stage-renal disease, amyotrophic lateral sclerosis
- Parts A, B, C, D cover different types of care
- Most require co-payment or deductible
Veterans Affairs (VA)

- A large integrated health care system (medicine, surgery, rehab, medications)
- A provider of health services, funded by US gov’t
- Eligibility: US military veterans, >90% men
Table 14.1 Demographic characteristics of the Medicaid, Medicare, and Veterans Health Administration populations\textsuperscript{54-59}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medicaid (2008)\textsuperscript{\textdagger}</th>
<th>Medicare (2009)</th>
<th>Veterans Health Administration (2009)\textsuperscript{\textdagger\textdagger}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>% US*</td>
<td>Number</td>
</tr>
<tr>
<td>Total Enrollment</td>
<td>58 238 773</td>
<td>19.1</td>
<td>46 520 716</td>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31 512 082</td>
<td>54.1</td>
<td>25 742 676</td>
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<tr>
<td>Male</td>
<td>21 824 014</td>
<td>37.5</td>
<td>20 778 040</td>
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<tr>
<td>Unknown</td>
<td>4 902 677</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>2 006 749</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>9 670 904</td>
<td>16.6</td>
<td>20 778 040</td>
</tr>
<tr>
<td>6-12</td>
<td>9 516 371</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td>13-14</td>
<td>2 334 030</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>15-18</td>
<td>4 837 569</td>
<td>8.3</td>
<td>&lt;19</td>
</tr>
<tr>
<td>19-20</td>
<td>1 956 043</td>
<td>3.4</td>
<td>19-34</td>
</tr>
<tr>
<td>21-44</td>
<td>12 637 182</td>
<td>21.7</td>
<td>35-54</td>
</tr>
<tr>
<td>45-64</td>
<td>5 639 547</td>
<td>9.7</td>
<td>55-64</td>
</tr>
<tr>
<td>65-74</td>
<td>2 011 317</td>
<td>3.5</td>
<td>65-74</td>
</tr>
<tr>
<td>75-84</td>
<td>1 631 909</td>
<td>2.8</td>
<td>75-84</td>
</tr>
<tr>
<td>85+</td>
<td>1 103 551</td>
<td>1.9</td>
<td>85+</td>
</tr>
<tr>
<td>Age group missing</td>
<td>4 894 411</td>
<td>8.4</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Combining databases: examples

- FDA Mini-Sentinel Program (USA)
- EU-ADR – Exploring and Understanding adverse drug reactions (Europe)
- OMOP – Observational Medical Outcome Partnership (USA)
- …Many more!
Principles of combining data

• Harmonization of protocol/code  
  – exposure, outcome, covariates
• Harmonization of data management – common data model (CDM)
• Data sharing via a common platform

The U.S. Food and Drug Administration’s Mini-Sentinel program: status and direction

Richard Platt¹, Ryan M. Carnahan², Jeffrey S. Brown¹, Elizabeth Chrischilles², Lesley H. Curtis³, Sean Hennessy⁴, Jennifer C. Nelson⁵, Judith A. Racoosin⁶, Melissa Robb⁶, Sebastian Schneeweiss⁷, Sengwee Toh¹ and Mark G. Weiner⁸

Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR Project

Preciosa M. Coloma¹, Martijn J. Schuemie¹, Gianluca Trifirò¹, Rosa Gini², Ron Herings³, Julia Hippisley-Cox⁴, Giampiero Mazzaglia⁵, Carlo Giaquinto⁶, Giovanni Corrao⁷, Lars Pedersen⁸, Johan van der Lei¹ and Miriam Sturkenboom¹,⁹ on behalf of the EU-ADR consortium
The FDA Sentinel Initiative

- **2007 - FDA Amendments Act (FDAAA),** mandating FDA to establish an active surveillance system for monitoring drugs, using electronic health records (EHR).

- **Goal:** a streamlined infrastructure to harness the data in existing automated HER to actively monitor the safety of medical products continuously and in real-time.

http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm149340.htm
Mini-Sentinel

- Pilot project of the Sentinel Initiative

Focus on

- **Assessments** - Medical product exposures, health outcomes, and links between them
- **Methods** - for identifying, validating, and linking medical product exposures and health outcomes
- **Data** - Mini-Sentinel Distributed Dataset and tools used to access the data

http://mini-sentinel.org/
The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction

![Diagram of Signal Generation, Signal Refinement, Signal Evaluation]

<table>
<thead>
<tr>
<th>Aim = Identify excess risk</th>
<th>All (suspected and unanticipated) adverse events (AEs), all products</th>
<th>Specific product: AE pairs of prior concern</th>
<th>A highly suspected product: AE pair</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approach</strong></td>
<td>Consider many AEs or Product: AE pairs (100's, 1000's)</td>
<td>Prospective repeated (sequential) monitoring of accumulating data, or one-time expedited analysis of product: AE pairs (typically 5-10)</td>
<td>One-time, in-depth and rigorous investigation of a single pair</td>
</tr>
</tbody>
</table>

Pharmacoepidemiology and Drug Safety
pages 1-8, 19 JAN 2012 DOI: 10.1002/pds.2343
Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR Project
Common database model (CDM).

Customizable!!!
### Table 3

Unified Medical Language System concepts projection into the four terminologies for five events of interest

<table>
<thead>
<tr>
<th>Event</th>
<th>UMLS concept unique identifier</th>
<th>Preferred term</th>
<th>ICD9-CM</th>
<th>ICD10</th>
<th>RCD</th>
<th>ICPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>C0155626</td>
<td>Acute myocardial infarction</td>
<td>410.x</td>
<td>I21.x</td>
<td>G30z, XE0U0h</td>
<td>K75, K75002</td>
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<tr>
<td></td>
<td>C0428953</td>
<td>ECG: myocardial infarction</td>
<td>323., 3232.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C0232320</td>
<td>ECG: antero-septal infarct</td>
<td>323.5</td>
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<tr>
<td></td>
<td>C0428956</td>
<td>ECG: posterior/inferior infarct</td>
<td>323.5</td>
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</tr>
<tr>
<td></td>
<td>C0428955</td>
<td>ECG: subendocardial infarct</td>
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Combining multiple healthcare databases for postmarketing drug and vaccine safety surveillance: why and how?

G. Trifiro¹,², P. M. Coloma¹, P. R. Rijnbeek¹, S. Romio¹,³, B. Mosseveld¹, D. Weibel¹, J. Bonhoeffer⁴,⁵, M. Schuemie¹,⁶,⁷, J. van der Lei¹ & M. Sturkenboom¹

From the ¹Department of Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands; ²Department of Clinical and Experimental Medicine, University of Messina, Messina; ³Department of Clinical and Preventive Medicine, Università Milano-Bicocca, Milan, Italy; ⁴Brighton Collaboration Foundation; ⁵University Children’s Hospital Basel, University of Basel, Basel, Switzerland; ⁶Janssen Research and Development LLC, Titusville, NJ, USA; and ⁷Observational Medical Outcomes Partnership, Foundation for the National Institutes of Health, Bethesda, MD, USA
Combining multiple healthcare databases for postmarketing drug and vaccine safety surveillance: why and how?
Advantages of multidatabase-monitoring with CDM

- **Numbers**: rare/weak/null associations
- **Diversity**: populations/exposures/data type
- **Speed**: (rofecoxib & MI)
- **Standardization**: Same protocol/data/analyst
- **Efficiency**: avoiding work duplication
- **Control**: data custodian retains data
- **Privacy**: patient protection issues addressed
Take-home message

• Most of the knowledge about benefits and risks of treatments comes from non-experimental studies
• This type of research nearly exclusively relies on data from routine databases.
• One database (country) is often insufficient
• Methodological developments follow the trend of multi-database research (Big Data)
• ”The future ain’t what it used to be”

Yogi Berra as quoted by J Gagne, *Epidemiology* 2013