To valuable to waste: the role of individual patient / participant / animal data meta-analyses
data is the new oil

we need to find it, extract it, refine it, distribute it and monetize it.

David Buckingham
Where are we now

- Doctors make life or death decisions on extremely limited information
- Only 30-40% of diagnosis and treatment decisions is evidence based

- Researchers and scientists draw broad conclusions from
  - small datasets,
  - a tiny slice of the population
  - over a short period of time
Wearables & IBM Watson

“It’s far more important to know what person the disease has than what disease the person has.”

Hippocrates, 400 B.C
Animal studies
The challenges.....

- Heterogeneity of data
- Inconsistency or incompleteness
- Privacy (iCloud, insurance etc.)
- Ecosystem
- Translation
- Validity
- .....?
→ What can we learn from Individual Patient / Participant / Animal Data meta-analyses
What is an IPD meta-analysis?

- Involves the central collection, checking and analysis of individual participant data
**Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement**

<table>
<thead>
<tr>
<th>Reporting guideline provided for? (i.e. exactly what the authors state in the paper)</th>
<th>Reporting systematic reviews and meta-analyses of individual participant data (IPD).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>English</td>
</tr>
</tbody>
</table>
Number individual participant data (IPD) meta-analyses published to August 2015 and proportion of IPD provided.
Why IPD?

Overall result from single typical trial

Searching for many subgroups
How to solve this problem?

- Clinical **AND** methodological knowledge warranted to solve this

- Individual Patient Data (IPD) meta-analyses
  → Unique opportunity to identify subgroups that benefit more or less from an intervention
Why IPD meta-analysis?

- Major improvement in subgroup analysis
  - Greater power
  - All measured subgroups available
  - Recoding into identical subgroups might be possible

- But also:
  - Time to event analyses
  - Other multivariate analyses
Comparison of treatment effect across two groups of patients when individual participant data (IPD) or aggregate data (AD) are used.
Benefits of IPDMA

• Improved quality
• Improved outcome data
• Improved analysis quality
• Improved trial identification, interpretation and dissemination via collaborative approach

• Collaboration can lead directly to new trials and studies

• Results may lead to better guidelines

• Improve methods for RCTs, IPD and other meta-analyses
  • Use IPD as resource for research into bias, analysis methods, e.g. how to impute missings, combine randomised and non-randomised studies
An example: antibiotics for AOM
Evidence: Cochrane review

**Review:** Antibiotics for acute otitis media in children  
**Comparison:** 01 Antibiotic versus Placebo  
**Outcome:** 01 Pain

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI</th>
<th>Weight (%)</th>
<th>Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Pain at 24 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Burke 1991</td>
<td>53/112</td>
<td>50/117</td>
<td>-</td>
<td>34.4</td>
<td>0.98 [0.58, 1.64]</td>
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<tr>
<td>Thalin 1985</td>
<td>58/159</td>
<td>58/158</td>
<td>-</td>
<td>44.2</td>
<td>0.99 [0.63, 1.60]</td>
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<tr>
<td>vanBuchem 1981a</td>
<td>13/47</td>
<td>11/40</td>
<td>-</td>
<td>10.5</td>
<td>1.01 [0.30, 2.57]</td>
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<tr>
<td>vanBuchem 1981b</td>
<td>17/48</td>
<td>10/36</td>
<td>-</td>
<td>10.9</td>
<td>1.41 [0.56, 3.55]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>306</td>
<td>351</td>
<td></td>
<td>100.0</td>
<td>1.03 [0.70, 1.39]</td>
</tr>
</tbody>
</table>

Total events: 141 (Treatment), 135 (Control)  
Test for heterogeneity chi-square=0.92 df=3 p=0.91 I²=0.0%  
Test for overall effect z=0.17 p=0.9

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI</th>
<th>Weight (%)</th>
<th>Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 Pain at 2-7 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Appelman 1991</td>
<td>11/67</td>
<td>10/54</td>
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<tr>
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<td>29/114</td>
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<td>0.85 [0.34, 1.22]</td>
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<tr>
<td>Danoisaux 2000</td>
<td>69/117</td>
<td>89/123</td>
<td>-</td>
<td>19.8</td>
<td>0.55 [0.32, 0.94]</td>
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<tr>
<td>Halsted 1988</td>
<td>17/62</td>
<td>7/27</td>
<td>-</td>
<td>5.5</td>
<td>1.08 [0.30, 2.97]</td>
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<tr>
<td>Kaleida 1991</td>
<td>19/488</td>
<td>38/402</td>
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<td>19.7</td>
<td>0.50 [0.29, 0.85]</td>
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<tr>
<td>Mygind 1981</td>
<td>15/72</td>
<td>29/77</td>
<td>-</td>
<td>11.4</td>
<td>0.46 [0.22, 0.90]</td>
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<tr>
<td>Thalin 1985</td>
<td>15/158</td>
<td>25/158</td>
<td>-</td>
<td>12.8</td>
<td>0.57 [0.29, 1.10]</td>
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<tr>
<td>vanBuchem 1981a</td>
<td>6/46</td>
<td>10/38</td>
<td>-</td>
<td>4.8</td>
<td>0.43 [0.14, 1.27]</td>
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<tr>
<td>vanBuchem 1981b</td>
<td>10/48</td>
<td>11/35</td>
<td>-</td>
<td>5.7</td>
<td>0.57 [0.21, 1.56]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1189</td>
<td>1118</td>
<td></td>
<td>100.0</td>
<td>0.57 [0.45, 0.73]</td>
</tr>
</tbody>
</table>

Total events: 182 (Treatment), 248 (Control)  
Test for heterogeneity chi-square=3.42 df=8 p=0.91 I²=0.0%  
Test for overall effect z=4.81 p=0.00001

**NNT=17**
Method

- Systematic literature search for randomised trials on effectiveness antibiotics
- Ask investigators for raw data
- Recode and analyse individual data
- Identify children which benefit more or less from treatment with antibiotics
Results

- Identified RCTs (n=19)
  - 9 RCTs excluded
  - 10 eligible RCTs
    - 4 RCTs excluded
      - 6 RCTs included in the IPD meta-analysis
## Results: effects antibiotics

<table>
<thead>
<tr>
<th></th>
<th>RD</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 years + bilateral AOM</td>
<td>25%</td>
<td>4</td>
</tr>
<tr>
<td>&lt; 2 years + unilateral AOM</td>
<td>5%</td>
<td>20</td>
</tr>
<tr>
<td>≥ 2 years + bilateral AOM</td>
<td>12%</td>
<td>9</td>
</tr>
<tr>
<td>≥ 2 years + unilateral AOM</td>
<td>4%</td>
<td>25</td>
</tr>
</tbody>
</table>
Results: Children with pain/fever

< 2 years with bilateral AOM

≥ 2 years with unilateral AOM
## Results: pain and/or fever

<table>
<thead>
<tr>
<th>Otorrhea</th>
<th>RD</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>36%</td>
<td>3</td>
</tr>
<tr>
<td>no</td>
<td>14%</td>
<td>8</td>
</tr>
</tbody>
</table>
Children with pain and/or fever

AOM with otitis media
AOM without otitis media
Guidelines

• Dutch, NHG guideline:

Medicamentevaste behandeling

* Adviseer in alle gevallen pijnstilling; paracetamol is eerste keuze (zie tabel voor doseringen).
* Instrueer de verzorgers van het kind contact op te nemen als het kind zieker wordt of niet verbetert.
* Antimicrobiële behandeling is geindiceerd:
  – bij een ernstig zie kind of als het kind zieker wordt;
  – bij risicofactoren voor complicaties;
* Overweeg antimicrobiële behandeling bij kinderen:
  – <2 jaar met een duabelzijdige OMA;
  – die al bij de eerste presentatie tijdens een OMA episode otorroe hebben;
  – bij wie na drie dagen geen verbetering is opgetreden.
* Eerste keuze is amoxicilline gedurende 1 week; geef bij contra-indicaties voor amoxicilline azitromycine gedurende 3 dagen of cotrimoxazol gedurende 5-7 dagen (zie tabel voor doseringen).
* Instrueer de verzorgers van het kind contact op te nemen als het kind binnen 48 uur na het starten van het middel niet verbetert.

• Guidelines in other countries:
  • Revised according to our findings in the UK, Sweden, USA, France, Denmark and Norway
Conclusions

• Individual participant data (IPD) meta-analyses are resource demanding, time consuming, and methodologically challenging, but when conducted well, provide more detailed and potentially more reliable results.

• We have to ensure that procedures to access IPD do not become over-burdensome, over-costly, and prohibitive.