Cohort and registries link: The Danish experience

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Agenda

• Unique opportunities for postlicensure vaccine research in Denmark

• Some examples of the kind of studies that can be undertaken
Post-licensure epidemiology

Pre-licensure
- Development
- Preclinical testing
- Phase I-III trials
- Efficacy
- Safety

Post-licensure
- General use
- Ad-hoc epidemiological studies
- Uptake
- Effectiveness
- Safety
Post-licensure epidemiology

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When an Entire Country Is a Cohort

Denmark has gathered more data on its citizens than any other country. Now scientists are pushing to make this vast array of statistics even more useful.

For years, any woman who got an abortion had to accept more than the loss of her fetus: For some unknown reason, she also faced an elevated risk for breast cancer. At least that was what several small case-control studies had suggested before Mads Melbye, an epidemiologist at the Statens Serum Institute in Copenhagen, undertook the largest effort ever to explore the link. He and his colleagues obtained records on 400,000 women in Denmark’s national Abortion Register, then checked how many of the same women were listed in the Danish Cancer Register. Their foray into the two databases led to a surprising result: As they reported in *The New England Journal of Medicine* in 1997, there appears to be no connection between abortion and breast cancer.

Their success underscores the value of a trove of data the Danish government has accumulated on its citizenry, which today totals about 5 million people. Other Scandinavian countries have created powerful database systems, but Denmark has earned a preeminent reputation for possessing the most complete and interwoven collection of statistics touching on almost every aspect of life. The Danish government has compiled nearly 200 databases, some begun in the 1930s, on everything from medical records to sociodemographic data on jobs and salaries. What makes the databases a plum research tool is the fact that they can all be linked by a 10-digit personal identification number, called the CPR, that follows each Dane from cradle to grave. According to Melbye, “our registers allow for instant, large cohort studies that are impossible in most countries.”

But Melbye and other scientists think they can extract even more from this data gold mine. They argue that not enough money is being spent on maintaining and expanding existing databases, and they say that red tape is hampering studies that require correlation of health and demographic data. The problem is that, while they have unfettered access to more than 80 medical databases maintained by the Danish hospitals, their database of 70,000 people in Denmark is still by its promises docetri for askew data

Statistics to release data concerns. “The evidence that inf individuals do not live longer,” says Mats Rytter Bech, is that there is no such thing as a healthy lifestyle. Sc Kaar Tappe who twins are born more than 90 of older, Christen genes about a man longevity by the unmat or the Danish Tw

The health care system and the smaller studi

Unique possibilities for for epidemiological research in Denmark
The Danish registries are unique

- an investment worth billions of Danish kroner
- Follow the individual from birth to grave
- follow diseases through generations (gene/environment)
- millions of individuals
- results are robust

CRS-number

Birth characteristics
Diseases
Prescribed medication
Vaccinations
Childcare facilities
School performance
Family, place of living
Education, employment
Biological specimens
Childhood vaccination registry

Family doctor ➔ Bill with details

National Health Insurance, National Board of Health

All registrations + Information from other registries

National Childhood Vaccination Register 1990-2009 (the only in the world?)
Type, dose, date, crs-number

Payment to MD
Childhood Vaccination programme in Denmark

**Danish childhood vaccination program**

- Voluntary
- Free of charge

- Statens Serum Institut mandated by law to supply the vaccines to the childhood programme – all children vaccines from same manufacturer

**Vaccines today**

- DTaP-IPV / Hib, 3,5, and 12 m
- MMR, 15 m and 4 yrs. (12 yrs.)
- DTaP-IPV booster, 5 yrs.
- HPV 1,2, and 3, 12 yrs.

**Major changes in 1990s**

- Introduction of Hib, 1993
- Whole cell P -> Acell. P, 1997
- OPV -> IPV, 2003
Short examples of postlicensure studies

Effectiveness
Herd immunity
Booster strategy considerations
Safety
Childhood Vaccination Registry
Hospital Discharge Registry
Psychiatric Registry
Birth Registry
CPR Registry – Demography
Statistics Denmark – Socio-economic

Exposure
Outcome
CRS-Number
Lab results

Potential confounders
**Materials**

- CRS registry
- Vaccination registry
- Hospital registries, etc.

½ mil. + children

birth vac outcome
dead, emigration, end of follow-up, whichever first

**Methods**

- Survival analysis
- Poisson regression

Incidence rate ratios
Impact of Hib vaccination

- PRP-T Vaccine introduced May 1993
- Cohort: all children liveborn June 1987-December 1998
- 758,988 children followed from birth or 1 January, 1991, whichever occurred last
- 2,664,040 person-years of follow-up
- Meningitis (Hib, non-Hib) from National Hospital Discharge Registry
- 141 Hib meningitis cases (94 before, 47 after vaccination introduced)
- Risk/confounding factors: BW, gestational age, birth complications, birth order, season, gender
- Survival times aggregated and analysed using log-linear poisson regression, producing estimates of RR of Hib meningitis
Hib continued

- Effectiveness (1, 2, 3 doses) of vaccine was calculated comparing vaccinated children with unvacc (period before induction)
  \[ \text{VE} = 1 - \text{RR} \]  (adj. for age)

- Indirect protection: calculated relative to the period before the introduction and adj. for age
Adherence to programme
## Hib Vaccine Effectiveness

<table>
<thead>
<tr>
<th>Hib vaccination</th>
<th># cases</th>
<th>Person years</th>
<th>Vaccine effectiveness against Hib meningitis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>one dose</td>
<td>2</td>
<td>499,296</td>
<td><strong>97.7</strong> (90.8-99.5)</td>
</tr>
<tr>
<td>two doses</td>
<td>2</td>
<td>549,149</td>
<td><strong>98.9</strong> (95.7-99.7)</td>
</tr>
<tr>
<td>three doses</td>
<td>1</td>
<td>770,250</td>
<td><strong>99.3</strong> (94.9-99.9)</td>
</tr>
</tbody>
</table>

Adjusted for age and compared to not-vaccinated (Jan. 1991-May 1993)
Relative risk of Hib meningitis in unvaccinated children after introduction of Hib vaccination
Hib final

- Vaccine failure:
  
  Hib meningitis >2 weeks after 3 doses of vaccine: 1 case in 295,803 series
  
  = 0.00034%

- Could Hib meningitis been classified as non-Hib meningitis?
  
  Comparing children w/3 doses versus not-vaccinated: RR= 1.43 (0.90-2.27)
The Danish situation:

Whole cell vaccine 1961-1996:
5 and 9 weeks and 10 month schedule

Acellular toxoid vaccine since 1997:
3,5 and 12 months schedule
Effectiveness of a pertussis toxoid vaccine

Cohort study of 541,525 children during 1994 - 2001
- 1262 cases of pertussis

Outcome measures:
- Vaccine effectiveness
- Incidence rates before and after introduction

Results

<table>
<thead>
<tr>
<th></th>
<th>VE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 d.</td>
<td>37%</td>
</tr>
<tr>
<td>2 ds.</td>
<td>72%</td>
</tr>
<tr>
<td>3 ds.</td>
<td>93%</td>
</tr>
</tbody>
</table>

*Born 1997-2001
# of pertussis cases and proportion of unvaccinated

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of cases</th>
<th>Proportion unvaccinated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>113</td>
<td>31</td>
</tr>
<tr>
<td>1996</td>
<td>114</td>
<td>26</td>
</tr>
<tr>
<td>1997</td>
<td>173</td>
<td>49</td>
</tr>
<tr>
<td>1998</td>
<td>101</td>
<td>61</td>
</tr>
<tr>
<td>1999</td>
<td>116</td>
<td>71</td>
</tr>
<tr>
<td>2000</td>
<td>99</td>
<td>61</td>
</tr>
<tr>
<td>2001</td>
<td>103</td>
<td>73</td>
</tr>
</tbody>
</table>
Impact of pre-school booster vaccination on pertussis in 0-1 year-old children

- Cohort of all children born in Denmark, 1977-2001
- Place of residence to identify household members and their vaccination history
- Rate ratios of pertussis hospitalisations according to number, age, and vac status of household members
- Estimated the preventable proportion of hospitalisations among 0-1 year-old-children according to age at booster (4-6 years), booster uptake, and efficacy of the booster against transmission
RR for pertussis hospitalisation before 2 years of age and living with one other child

<table>
<thead>
<tr>
<th>Age of other child (years)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>(66)</td>
</tr>
<tr>
<td>2</td>
<td>(151)</td>
</tr>
<tr>
<td>3</td>
<td>(222)</td>
</tr>
<tr>
<td>4</td>
<td>(184)</td>
</tr>
<tr>
<td>5</td>
<td>(113)</td>
</tr>
<tr>
<td>6</td>
<td>(90)</td>
</tr>
<tr>
<td>7</td>
<td>(59)</td>
</tr>
<tr>
<td>8</td>
<td>(37)</td>
</tr>
<tr>
<td>9</td>
<td>(16)</td>
</tr>
<tr>
<td>10-13</td>
<td>(34)</td>
</tr>
<tr>
<td>14-17</td>
<td>(25)</td>
</tr>
</tbody>
</table>

(Referent: Living with no other children)
RR for pertussis hospitalisation before 2 years of age and living with one other child

Booster vaccination

Preventable proportion of hospitalisations: 7%-33%

Most realistic scenario: 18%
# RR for pertussis hospitalisation in children born 1990-2001

<table>
<thead>
<tr>
<th>Living with one other child fully vaccinated (age)</th>
<th>Rate Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living without other children</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>0-1 year</td>
<td>0.94</td>
<td>0.53-1.69</td>
</tr>
<tr>
<td>2 years</td>
<td>1.57</td>
<td>1.16-2.14</td>
</tr>
<tr>
<td>3 years</td>
<td>2.13</td>
<td>1.60-2.83</td>
</tr>
<tr>
<td>4 years</td>
<td>2.02</td>
<td>1.38-2.94</td>
</tr>
<tr>
<td>5 years</td>
<td>2.84</td>
<td>1.79-4.51</td>
</tr>
<tr>
<td>6-8 years</td>
<td>2.99</td>
<td>1.81-4.92</td>
</tr>
<tr>
<td>9-11 years</td>
<td>1.45</td>
<td>0.20-10.39</td>
</tr>
</tbody>
</table>
Effectiveness of pertussis vaccines in preterm children

• Previous (small) studies evaluating immunogenicity in preterm and full-term children demonstrated similar responses.

• Pertussis specific antibody titers in preterm often found to be lower than in full-term children.
Effectiveness of pertussis vaccination according to gestational age

<table>
<thead>
<tr>
<th>Number of doses</th>
<th>Acellular pertussis vaccine</th>
<th>p value for homogeneity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20–36 weeks</td>
<td>37–41 weeks</td>
</tr>
<tr>
<td></td>
<td>VE¹</td>
<td>95% CI</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>0%</td>
<td>Referent</td>
</tr>
<tr>
<td>1. dose</td>
<td>45%</td>
<td>(12%–65%)</td>
</tr>
<tr>
<td>2. dose</td>
<td>77%</td>
<td>(57%–88%)</td>
</tr>
<tr>
<td>3. dose</td>
<td>90%</td>
<td>(69%–97%)</td>
</tr>
</tbody>
</table>
Safety studies
Examples of registry-based vaccine studies from our group

MMR vaccination and autism (NEJM 2002)
Thimerosal in vaccines and autism (JAMA 2003)
BCG (TB vaccine) and allergy (JAMA 2003)
Polio vaccination (SV40) and cancer (JNCI 2003)
MMR vaccination and epilepsy (JAMA 2004)
Vaccination and type-1 diabetes (NEJM 2004)
Non-specific effects of childhood vaccines (JAMA 2005)
Pertussis pre-school booster vaccination (Vaccine 2006)
MMR vaccination and risk of allergy (AJE 2008)
Effectiveness of two pertussis vaccines in preterm Danish children (Vaccine 2009)
New resources

• Building a system (person-identifiable) to register all persons receiving the H1N1 vaccine in Denmark

• By 2011, we will have a nation-wide register of all vaccinations given in Denmark (person-identifiable)
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