Vaccine policy and safety surveillance in England and Wales

Professor Elizabeth Miller

Health Protection Agency, UK
The European landscape

• Common regulatory agency for certain pharmaceuticals across the European Union – European Medicines Agency (EMA)

• But -
  Ÿ National regulatory authorities (NRAs) still have approval powers for certain products

• For disease surveillance there is the European Centre of Disease Prevention and Control (ECDC)

• But -
  Ÿ Each country decides it own vaccination schedule
  Ÿ Great variation in vaccines used, number of doses and age
  Ÿ No uniformity in disease or adverse event surveillance methods
Establishment of an EU/EEA network for validation and association studies

- Since 2008, ECDC funds a consortium of researchers in 10 EU/EEA MS
- VAESCO - Vaccine Adverse Event Surveillance and Communication
- Project was accelerated due to use of new pandemic vaccines

Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe


Collaborators (25)
A collaborative approach to investigating the risk of thrombocytopenic purpura after measles–mumps–rubella vaccination in England and Denmark

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- Common protocol studies
  - Feasible
  - Cumbersome even for most experienced statisticians
  - Requires manual data elaboration at local sites
• Set up in 1948
• Largest organisation in Europe
• Centrally funded from taxes
• Free healthcare at point of use for all
• Unique NHS number
Primary and secondary NHS care in the UK

Primary care (General Practice)
- Patients are registered with only one GP at a time (records transfer if change of GP)
- GP acts as gatekeeper and initial point of NHS access
- Comprises over 90% of all NHS contacts
- All GPs now have electronic records

Secondary care (Hospitals)
- Access via referral from GP (elective and acute admissions)
- Or presenting via Emergency Room
Organisation of national vaccination programme in UK (England, Wales, Scotland and Northern Ireland)

- Same schedule in each devolved administration
- Vaccines purchased for UK by a national tender
- Delivered free to every vaccinator (GP) who is paid for giving the vaccine
- Policy recommendations made to health minister by independent expert committee (Joint Committee on Vaccination and Immunisation)
- To be recommended a vaccination programme must be cost effective (around $30,000 to $45,000 per QALY gained)
Supporting the National Immunisation Programme: the role of the HPA

- Recommendations to ministers
- JCVI
  - Presentation of surveillance data
  - Investigation of policy options
  - Immunisation Dept, HPA
    - Clinical Trials
    - Vaccine Coverage
    - Disease surveillance
    - Serological surveillance
  - Mathematical modelling and economic analyses
  - Monitoring safety & efficacy
## UK Paediatric Immunisation schedule
(around 90% coverage for most vaccines)

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Age at vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2mths</td>
</tr>
<tr>
<td>Diphtheria (D), tetanus (T), 5-component acellular pertussis (aP), Hib conjugate, Inactivated polio vaccine (IPV)</td>
<td>X</td>
</tr>
<tr>
<td>Meningococcal C conjugate (MCC)</td>
<td></td>
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<tr>
<td>Pneumococcal conjugate (PCV13)</td>
<td>X</td>
</tr>
<tr>
<td>Combined Hib/ MenC vaccine</td>
<td></td>
</tr>
<tr>
<td>Measles, Mumps, Rubella vaccine</td>
<td></td>
</tr>
<tr>
<td>DTaP5 /IPV or dTaP 3 /IPV</td>
<td></td>
</tr>
<tr>
<td>Measles, Mumps, Rubella vaccine</td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria and polio (Td/IPV)</td>
<td></td>
</tr>
<tr>
<td>HPV (girls only)</td>
<td></td>
</tr>
</tbody>
</table>
Routine systems for vaccine safety surveillance

Yellow Card system
- Run by the UK licensing authority (Medicines and Healthcare Products Regulatory Agency: MHRA)
- Passive reporting system, vaccines included with other drugs
- Health professionals and patients can report
- Signal generation and identification of possible risk factors for AEs

Risk Management plans as a requirement for licensure
- The manufacturer must undertake post-licensure pharmacovigilance or special studies to address potential risks as appropriate
Data Sources used in vaccine safety surveillance at the HPA

General Practice Research Database (GPRD)
- Covers about 5% of UK population
- Individual level primary care consultations, hospital referrals, prescriptions and vaccinations
- Validation possible by free text and contacting GP

Hospital Episode Statistics database (HES)
- Covers all admissions in England
- ICD 10 coded diagnoses
- Validation by case note review
- With appropriate approvals, NHS number can be used to contact GP for vaccination history

National child health databases
- Covers all children in England and Wales
- Separate databases around the country with different formats
- Date of immunisation and vaccine type recorded
- Some batch information available
- Records can be linked to HES admissions via NHS number with appropriate national and local approvals
Pathway for investigation of vaccine AE

- Event identification
  - Yellow Cards
  - Clinical trials
  - Ecological associations
  - Case series’ reports
  - Studies in other countries
  - Biological plausibility

- Initial rapid assessment
  - Individual case assessment
  - Ecological study using Hospital Episode data
  - Observed vs Expected (e.g. for Yellow cards)

- Epidemiological Studies
  - Self Controlled Case Series (SCCS)
  - Case-coverage
  - Cohort
  - Case Control
Self Controlled Cases-Series (SCCS) Design


Only requires unbiased sample of cases and a pre defined risk period

For each individual each day and event in the study period will fall inside or outside the risk period.

Cases act as their own controls so individual level confounding not a problem

Measure of association is incidence in risk period relative to incidence in background period

WEB SITE: http://statistics.open.ac.uk/sccs

Has papers, examples and macros to run the method in GLIM, Stata, SAS, Genstat and R.
From Miller et al 2001

Admissions by weeks from MMR to ITP

- MMR vaccination
- Frequency
- Weeks before MMR Vaccine
- Weeks after MMR Vaccine
Relative incidence (RI) estimate and attributable risk per dose

• RI for ITP within 6 weeks of MMR = 3.27  95% CI (1.49 - 7.16)
• Cases in risk period 13
• Cases attributable to vaccine = 9
• Estimated doses of vaccine given to population from which the cases arose: 290000
• Risk per dose due to MMR = 1 in 32,300
Additional approaches

- Routinely available HES /GPRD data sets may not be suitable for investigation of all adverse event signals

- MMR and autism required scrutiny of child disability databases, visits to special schools etc and collaboration with community paediatricians

- Current pandemic vaccine and narcolepsy study requires collaboration with clinicians at sleep centres

- Follow up with GP for vaccination history of cases
HPA Studies performed or in progress (last 17 years)

- MMR and aseptic meningitis (Farrington 1995 – risk 1 in 16000 Urabe, Miller 2007- No risk from new mumps strain)
- MMR and ITP (Miller 2001 – risk 1 in 32000 doses, Stowe 2007 2nd dose - no effect, Andrews 2012 with Denmark - risk 1 in 50,000)
- MMR and aseptic meningitis (Farrington 1995 – risk 1 in 16000 Urabe, Miller 2007- No risk from Priorix )
- MMR and bacterial infections (Miller 2003 – no effect, Stowe 2009 – no effect - also looking at viral infections)
- MMR and gait disturbance (Miller 2004 – no effect)
- MMR and serious neurological disease (Ward 2007, risk 1 in 365,000)
- OPV and intussusception (Andrews 2001 – no effect)
- DTP (thimerosal containing) and developmental problems (Andrews 2004– no effect)
- DTaP (5 in 1) verses DTwP for rare and common outcomes (Andrews 2010 – confirmed lower reactogenicity of  DTaP
- MCC and purpura (Andrews 2007– no effect)
- MCC and convulsions (Andrews 2007 – no effect)
- MCC and relapse of nephrotic syndrome (Taylor 2007 - no effect)
- Influenza vaccine and Bell’s Palsy (Stowe 2006 – no effect)
- Influenza vaccine and Guillain-Barré syndrome (Stowe 2009 – no effect of vaccine but increased risk following influenza like illness)
- H1N1 pandemic influenza vaccine and Guillain-Barré syndrome (Andrews 2011, no effect)
- Influenza vaccines and convulsions (Stowe 2011, no effect for trivalent, possible effect on day 0 for H1N1 pandemic vaccine)
- H1N1 pandemic influenza vaccine and Narcolepsy (Ongoing)
Relative incidence for various conditions in defined post vaccination risk periods studied by HPA from 1995-2012
The rest of the HPA team

- Nick Andrews – statistician
- Julia Stowe – research fellow (manages datasets, obtains approvals, writes protocols, conducts data linkage, does case note reviews)

*With special thanks to:*

- Prof Paddy Farrington who developed the SCCS method
- Pauline Kaye (Waigh) who developed the HES/Child Health record linkage methods