Prediction of vaccination safety and pharmacovigilance

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The First WHO Integrated Meeting on development and clinical trials of Influenza vaccines that induce broadly protective and long-lasting immune responses

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Vaccines: Challenges for pharmacovigilance

- As with any new pharmaceutical product, safety specification of a new vaccine is limited at licensure
  - Trials limited in size, duration, risk groups etc
- Vaccine trials for novel vaccines generally identify events >1/1,000
  - Enough to establish reactogenicity
  - Isolated serious events – cannot assess causality
- With annual strain changes even fewer patients are exposed before widespread use
- Marketing authorisation holders have specific legal responsibilities to monitor the safety and balance of risks and benefits for their products
- Need robust systems in place to monitor safety in real-life and identify new hazards and risk factors
  - Responsibility of the regulator as a public health body
Spontaneous reporting

- UK Yellow Card Scheme
  www.mhra.gov.uk/yellowcard

- Pros and Cons
  - Real-time, rapid, permanent
  - Accessible, anyone can report
  - Can detect very rare risks
  - Under-reporting, subject to biases
  - Cannot confirm causality

- Can encourage reporting
  - Dedicated portal for H1N1 reporting
  - Specifically asked for brand, batch, immunisation history, & time to onset
  - 3,310 YCs during campaign for Pandemrix & Celvapan (1000 in first month)
  - 10 cases of GBS
Power of box A

- We need A, B, C, D to evaluate and quantify risk
- Parents/media only see ‘A’
  - Healthy before vaccine – difficult to believe coincidence
- The ‘A’neecdote can be more persuasive than the statistics
- C & D often limited with mass vaccination (prospective)
  - But, we can utilise our data sources to give the context
- Enhanced pharmacovigilance plans need to be in place from day one

<table>
<thead>
<tr>
<th>Event</th>
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<tbody>
<tr>
<td>Vaccine</td>
<td>A</td>
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<tr>
<td>No vaccine</td>
<td>C</td>
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Key elements of vaccine pharmacovigilance

- Building on the strengths of Yellow Cards & routine signal detection methods
  - ‘Real-time’, proactive signal detection
  - population-wide (rare risks), accessible to all

- Addressing the limitations of Yellow Cards
  - under/(over)-reporting, limited context (e.g. exposure)

- Avoiding misuse/misinterpretation of Yellow Cards
  - active, transparent communications (A & C – events and context)

  Enhanced, proactive, real-time surveillance

- Specific to vaccination campaign
  - continually taking into account previous experience
Putting spontaneous data in context

- **CPRD** – The Clinical Practice Research Datalink
  - 5 million ‘acceptable’ active patients in over 600 GP practices
  - Patient and practice demographics, clinical records, prescriptions
  - External record linkage to other NHS datasets

- Determine background rates of ‘expected’ adverse events (e.g. autoimmune and neuroinflammatory conditions) per 100,000 persons vaccinated

- Obtain near real-time estimates of vaccine exposure from Department of Health

- Combine these data for real-time ‘observed vs. expected’
  - Sequential method that adjusts for multiple testing preferable for real-time monitoring
  - Weekly ‘observed / expected’ ratios converted to log likelihood ratios and compared to a critical threshold
  - Critical threshold, if reached, indicates observed > expected
  - Identify signals in real-time, OR have confidence that reporting is within the norm
Statistical approaches to surveillance

- Observed vs. expected analyses are a very flexible method
  - Can be applied to any exposure with good denominator data
  - Any event can be included and analysis updated as new data is available

- Strengths
  - Uses existing, real-time/available data sources
  - Cheap, rapid, adaptable
  - Can identify rare risks
  - Allows anecdotal reports to be placed in context
  - Rapid, responsive (e.g. febrile seizures with seasonal flu vaccine in 2010)
  - Sensitivity analyses can account for levels of under-reporting

- Limitations
  - Delayed reporting
  - Requires prior hypothesis
  - Cannot confirm causality

Quick, evidence based risk assessment whilst we wait formal observational studies
Pandemrix & Guillain-Barré syndrome

Snapshot O/E analysis:

- Expected number = 8.19 (4.2 million, 6 weeks)
- Observed number = 10
- Rate ratio = 1.23 [0.59-2.26]

- O/E served purpose of generating a signal whilst allowing communication of the context - i.e. no suggestion of a 1976-like risk

- Large epidemiological studies have since confirmed the lack of a significant association with GBS e.g. Andrews et al. (Vaccine, 2011)
The future: Building on O/E with the enhanced use of CPRD and other data

- CPRD is extending to include more practices and more linkages
- Therefore, it is becoming increasing valuable for rapid and robust vaccine pharmacovigilance
  - Can be used to examine C & D – the rates of events in those not vaccinated
  - Observed vs. expected methodologies can be extended
  - Possibly using historical controls
  - Could also be used for obtaining rapid data on uptake
- But spontaneous reports and CPRD are not our only data sources…
  - Other medical databases
  - Medical and scientific literature
  - Clinical trials and studies
  - Non-UK data and other regulatory authorities

Risk assessment carried out on the totality of data
The future of vaccine pharmacovigilance in the UK

- Passive surveillance identifies signal - CPRD analysis confirms/quantifies risk
- National Institute of Biological Standards and Control (NIBSC) research confirms root cause, and develops new assays to reduce/eliminate future risk
- CPRD active surveillance to confirm effectiveness of assay/risk minimisation measures

A holistic, proactive approach

The lab
- Plausibility
- Root cause
- Assays

Routine PV processes

The health record
- Safety
- Effectiveness
- Patterns of use
- Impact of action

Well communicated to all stakeholders