Safeguarding public health

Risk Management for Vaccines

Dr Philip Bryan

Reinforcing patient safety in Europe

14-15 June 2011

Zagreb, Croatia

Vaccine Risk Management – Regulatory vs Public Health function

- Regulatory tools defined in legislation
- New Pharmacovigilance Legislation will strengthen the role of Risk Management Plans (RMPs)
- Regulators and industry need to ensure vaccine RMPs are fit for purpose
  - Legislation and RMPs are a focus of separate sessions
- This session focuses on strategic and scientific principles to strengthen vaccine risk management from public health perspective

Content

- Immunisation programmes and infrastructure
- Vaccine programme safety and effectiveness
- Vaccine quality and adverse events
- Systems to identify new risks (‘signal detection’)
- Approaches to evaluating safety ‘signals’
- Planning for mass immunisation
    - E.g. Pandemic (‘swine flu’) vaccine

Why treat vaccines any different to drugs in Risk Management Planning?

- Vaccines (mostly) given to the healthy
    - Lower tolerance of risks
- Perception of benefits can be low
    - Serious disease rare, herd immunity
- Given to large % of the population
    - Often mass immunisation campaigns
    - +++ event reports
    - Lack of comparable control groups

And……

- ‘Generic’ vaccines do not exist
    - Biological variability
- Risk/Benefit balance is dynamic
    - Temporal and geographic (e.g. oral polio)
- Vaccine scares can have massive impact
    - Not only on target population but on wider population – resurgence of disease

- **ALL aspects of pharmacovigilance require special considerations for vaccines**

The Benefits of Vaccination

- After provision of clean water, vaccination is the most effective global public health intervention

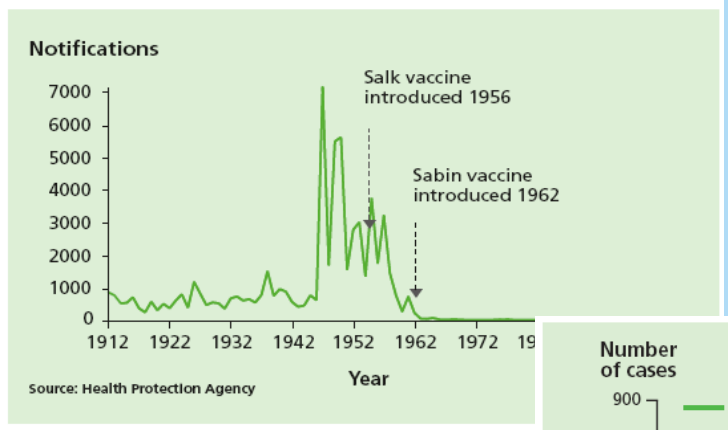
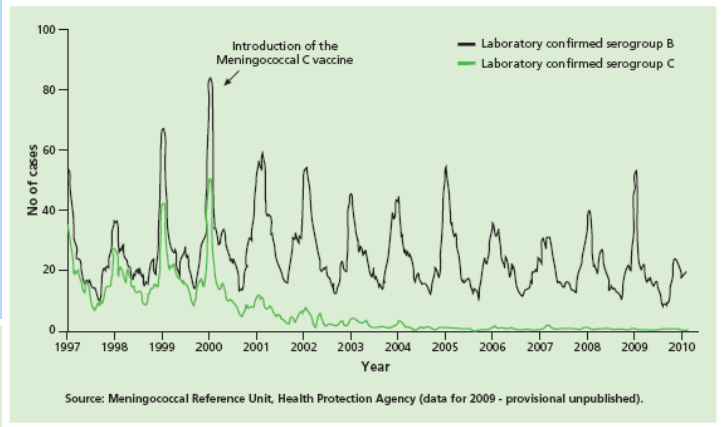
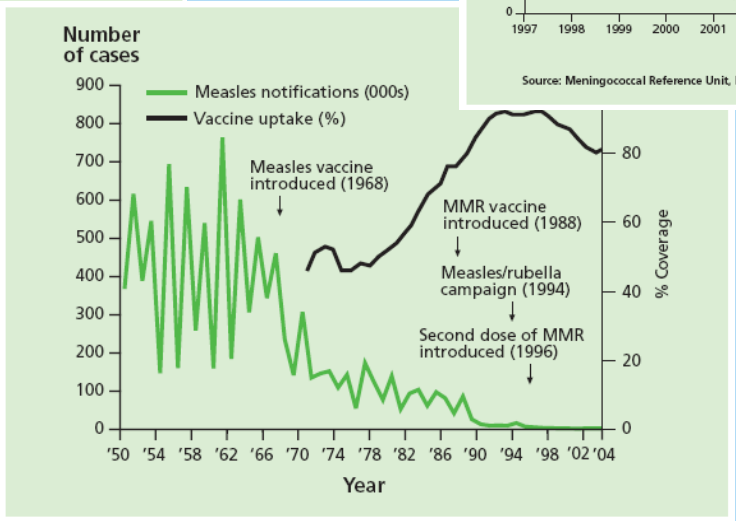


Figure 26.1 Polio notifications in England and Wales (1912-





Source – 'Green Book'

Not forgetting smallpox eradication……

Unfounded vaccine scares

- Pertussis vaccine and encephalopathy (1970s)
  - Resurgence in pertussis in UK
- MMR (and thiomersal) and autism (1990s-)
  - Measles outbreaks, general vaccine confidence
- Hepatitis B vaccines and multiple sclerosis (1990s)
  - Adolescent programme in France stopped
- Polio vaccines and contamination (contraceptives, HIV…)
  - Hindered the global eradication campaign (Africa)

MHRA

daughters vaccinated, others are adamant that it has triggered alarming side-effects . . .

HOW SAFE IS THE CERVICAL CANCER JAB?

by Rachel Porter

began. It was the summer holidays when she first noticed that Carly, her eldest daughter, was seriously out of sorts.

'Anyone who knew Carly before will tell you what a chatterbox she was. She had so much energy she

Teenage girls sue over cancer jab

EXCLUSIVE

By **Lucy Johnston** HEALTH EDITOR

A GROUP of British teenagers has launched the first legal action against the makers of a controversial cervical cancer jab.

reaction. These people are innocent, but may become seriously disabled as a result of the jab. I want to see justice for them."

So far there have been more than 1,300 reported reactions to the jab in

of saving lives."

'I would ban this vaccine'

Cervical cancer vaccine quarantined after death of girl (14)

MARK HENNESSY and **EITHNE DONNELLAN**

BRITISH HEALTH authorities

vaccine. Just one of those was regarding Cervarix. The other seven involved Gardasil, manufactured by Merck & Co.

at a school in Liverpool, and became paralysed from the waist down. She has spent almost all of the time since in hospital.

JAB 'AS DEADLY AS THE CANCER'

Cervical drug

Cancer jab has left me unable to walk

EXCLUSIVE

By **Lucy Johnston** HEALTH EDITOR

A CHILD specialist has linked the controversial cer-

The Challenges

- Rapidly identifying and evaluating potential risks
- Providing targeted and tailored information
  - Explaining the science and nature of data
  - Communicating benefits and safety
- Promoting confidence in safety surveillance systems, and thereby the vaccine programme

Immunisation Programmes

- Effective Risk Management planning for vaccines requires an understanding of:
    - the (national) immunisation programme
    - the (national) regulatory, policy and clinical framework
    - the infrastructure for delivery of the programme
    - the various stakeholders and their needs
- These aspects are broadly consistent between countries
- However, immunisation schedules can differ widely
    - **Safety profile (and R/B) of individual vaccines may differ as a consequence**

Vaccine programme stakeholders

- Public health authority (including Govt)
- Disease surveillance networks
- Regulatory authority
- Batch release authority (OMCL)
- Healthcare professionals and healthcare delivery systems
- The public and the media
- Pharmaceutical industry

Immunisation Schedules

- Schedules are invariably dynamic

  - novel vaccines and combinations
  - new vaccine brands, antigens, timing
  - disease prevalence
  - risk vs benefit (e.g. live vs inactivated polio vaccine)
  - vaccine availability and supply

    - **All could impact on safety**

    - **Need for <u>constant, proactive</u> horizon-scanning**

      - **anticipate changes**
      - **have risk management plans in place in advance**

Product safety vs Programme safety

- All vaccines carry intrinsic, product-specific risks

  - Vaccine antigens or excipients/adjuvants
  - Host factors
  - Biological variation/quality defects

- Need effective systems to identify, evaluate and communicate such risks

  - includes rapidly distinguishing possible cause from likely coincidence

- However, risk management must also focus on the safety of the vaccine programme

Programme-related events

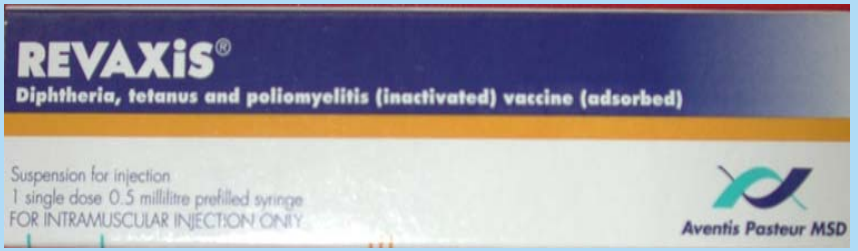
- Sepsis due to contaminated needles/vials
- Cold chain breakdown
- Poor injection technique
- Faints/panic attacks due to fear of needle
- User error

  - All avoidable with good training and infrastructure

- Complexity of schedules means that <u>mistakes do happen</u>
- Need to monitor and minimise errors

Programme related event – example

- Packaging
  - Similar brands and packaging in same programme
  - Admin error reports, potential for safety/efficacy issue
  - Need to horizon scan such issues in plans



Vaccine efficacy and effectiveness

- Efficacy evaluated in pre-licensure trials
  - Protective efficacy, i.e. protection against the disease
    - Not always feasible or necessary
  - Immunogenicity
    - Correlates of protection
      - Antibodies, T cells, other surrogate endpoints
      - E.g. pre-cancerous lesions for HPV vaccines
- Effectiveness
  - 'Real-life' use as part of a programme
  - Effect of concomitant vaccines and disease burden
  - Requires national coverage and disease surveillance data

Vaccine failures

- Few, if any, vaccines are 100% effective
- Vaccine failure is also a safety issue since target diseases are serious
  - Primary failure – poor/none response to initial course (e.g. 5-10% failure of first dose measles)
  - Secondary failure – protection wanes over time (need for boosters)
- Generally defined as confirmed infection due to vaccine antigen/serotype, following full primary course, ≥ 7 days after last priming/booster dose

Effectiveness of the programme

- Need systems to monitor effectiveness (including vaccination failures)
- Often part of national disease surveillance programme
    - requires close links between regulators and public health bodies/disease surveillance networks
- New EU pharmacovigilance legislation - opportunity for effectiveness evaluation to be core requirement in RMP
    - will strengthen post-authorisation R/B assessment
    - Industry may not have routine access to the data required for this
    - Regulators/public health bodies will need to facilitate

Vaccine quality

- Manufacturing changes, associated biological variation and quality defects inherent risk with vaccines
- Risk Management Systems must monitor and assess potential clinical consequences
- Requires close links between regulators and official medicines control laboratories (OMCLs)
- Batch identification and traceability critical

Vaccine safety pre-licensure

- EMA Note for guidance on the clinical evaluation of vaccines (CHMP/VWP/164653/2005)
- Defined list of solicited local (e.g. injection site ADRs) and systemic events (e.g. fever, headache, nausea)
    - **‘reactogenicity’**
- As a minimum, trials powered to assess reactogenicity at a frequency >1,1000
- Unsolicited serious events (SAEs) – cannot assess causality
- RMP must have plans to evaluate any SAEs of concerns

Vaccine safety post-licensure

- **Key steps in pharmacovigilance**

  - Data collection
  - Signal detection
  - Risk assessment
  - Risk-benefit evaluation/Expert advice
  - Action (regulatory/other)
  - Communication

- Broad principles and methods no different to medicines

  - However, well co-ordinated immunisation programmes provide opportunities for **tailored, proactive risk management**

Data collection

- Passive surveillance

  - E.g. UK Yellow Card Scheme
    - All vaccines and medicines


YellowCard

SUSPECTED ADVERSE DRUG REACTIONS

PATIENT DETAILS

SUSPECTED DRUG(S)

SUSPECTED REACTION(S)

OTHER DRUGS

REPORTER DETAILS

CLINICIAN

- Pros and Cons
  - Real-time, rapid, permanent
  - Can detect very rare risks
  - Under-reporting, subject biases
  - Formal studies required to confirm and quantify a risk

BUT, very often the only data available and judgements have to be made on passive data alone

Signal detection - Enhanced passive surveillance (1)

- Address limitations and focus on strengths of passive data

  - Power to identify very rare events
  - Reduce under-reporting (stimulate/encourage reporting, involve patients/parents, improve access to reporting)
  - Make it real-time (e.g. web-based)

- Obtain near real-time estimates of vaccine exposure

  - E.g. local/national public health authorities
  - Stratify by age/risk group

Signal detection - Enhanced passive surveillance (2)

- Utilise population-based incidence data (e.g. GPRD)
  - Derive age/gender-stratified data on incidence of medical 'events of interest' from historical cohorts

- Combine these 3 data sources to:

  - Optimise value of passive data in signal detection

  - Help to rapidly communicate such data in the context of 'expected' background events

➡ 'Observed vs expected'

‘Observed vs expected’

- ‘Real-time’ surveillance
  - Establish the ‘expected’ per N doses
  - Compare reporting rate to expected incidence
  - Adjust for multiple, daily statistical testing (e.g. Maximised Sequential Probability Ratio Test (MaxSPRT)
  - Adjust for variable under-reporting
- Case definitions
  - Validated and standardised
  - Allow comparisons across countries and pooling
  - E.g. Brighton Collaboration

Risk Assessment

- In a few instances, can have confidence in causal association based on individual reports/clusters:
    - Injection site events
    - Immediate hypersensitivity
    - Isolation of vaccine virus (live) in body tissues
    - Event very similar to natural infection (live vaccines – need to exclude wild virus)
    - Cluster of onset times (if reporting bias excluded)
- But, majority of new events/signals will have unknown/ill-defined aetiology or occur naturally in population
    - **For most new signals of serious risks, formal studies required to assess causal association**

Study approaches

- Issue for **routine** vaccines is high exposure
    - lack of an appropriate (if any) control group
    - reasons for non-vaccination (or vaccination) associated with outcome – e.g. socio-economic status, health status when vaccine was due
- E.g. DTP vaccine and SIDS
    - Most case control/cohort studies show protective effect - 'healthy vaccinee'
- CC/cohort method still applicable for routine vaccines with suitable controls and adjustment

- **But, case-only methods offer alternative approach**

Case only approaches

- Self-controlled case series, Case-crossover, Risk-interval analysis
  - Rapid and relatively inexpensive
  - Need only cases - cases act as their own controls
    - Most individual-level confounders automatically adjusted
  - Identify a series of ‘control’ periods before/after ‘risk window’
- Issues:
  - Need to define a plausible risk period
    - Not always easy to define – can be unknown
    - Short (e.g. febrile seizure) or long (e.g. MS, autism)
  - Precise onset of illness required
    - Easy for e.g. GBS, facial palsy
    - Difficult with insidious onset – e.g. MS, CFS

Other approaches

- Active surveillance
  - Limited utility for rare, serious risks
- Ecological studies
  - Groups rather than individuals
  - Rapid, inexpensive
  - Associations at an individual level not necessarily replicated at group level
- Phased geographical vaccine introduction
  - E.g. cluster randomised trial
  - Often not feasible on public health/ethical grounds

Planning and implementing a new vaccine risk management strategy

- Understand full safety specification (from RMP)
  - Identify key risks and/or gaps
- Understand when and how programme will be implemented
  - Target Group
  - Immunisation schedule
  - Number in cohort – number of doses
  - Who will administer – primary care? schools?
- Anticipate and plan for the issues likely to arise
  - Look at the vaccine
  - Look at similar vaccines
  - Look at prior experience in similar populations

Pandemic ‘swine flu’ H1N1v vaccine

- Planning in place for several years (bird flu?)

- Novel vaccines (monovalent, adjuvanted)
  - ‘mock-up’ licence process
  - pre-licensure safety database very limited

- Planned for reasonable worst case scenario

  - Mass immunisation campaign
  - Pressures on healthcare system and resource
  - Impact on national infrastructure (e.g. post)
  - Business continuity

April/May 2009……

… ….July 2009……..


The Mail ON SUNDAY

£10 OFF Your shopping at TESCO

COUPONS INSIDE – AND THEY'RE VALID ALL WEEK

Money off CDs, DVDs, clothes, jewellery, household, electricals and much, much more!

SEE PAGE 37

SWINE FLU JAB LINK TO KILLER NERVE DISEASE

EXCLUSIVE: Leaked letter reveals concern of neurologists over 25 deaths in America

WORLD EXCLUSIVE My diary of my best friend

'Dangers' of the fast-track swine flu vaccine

By DAILY MAIL REPORTER
Last updated at 2:58 AM on 28th July 2009

European Medicines Agency strategy

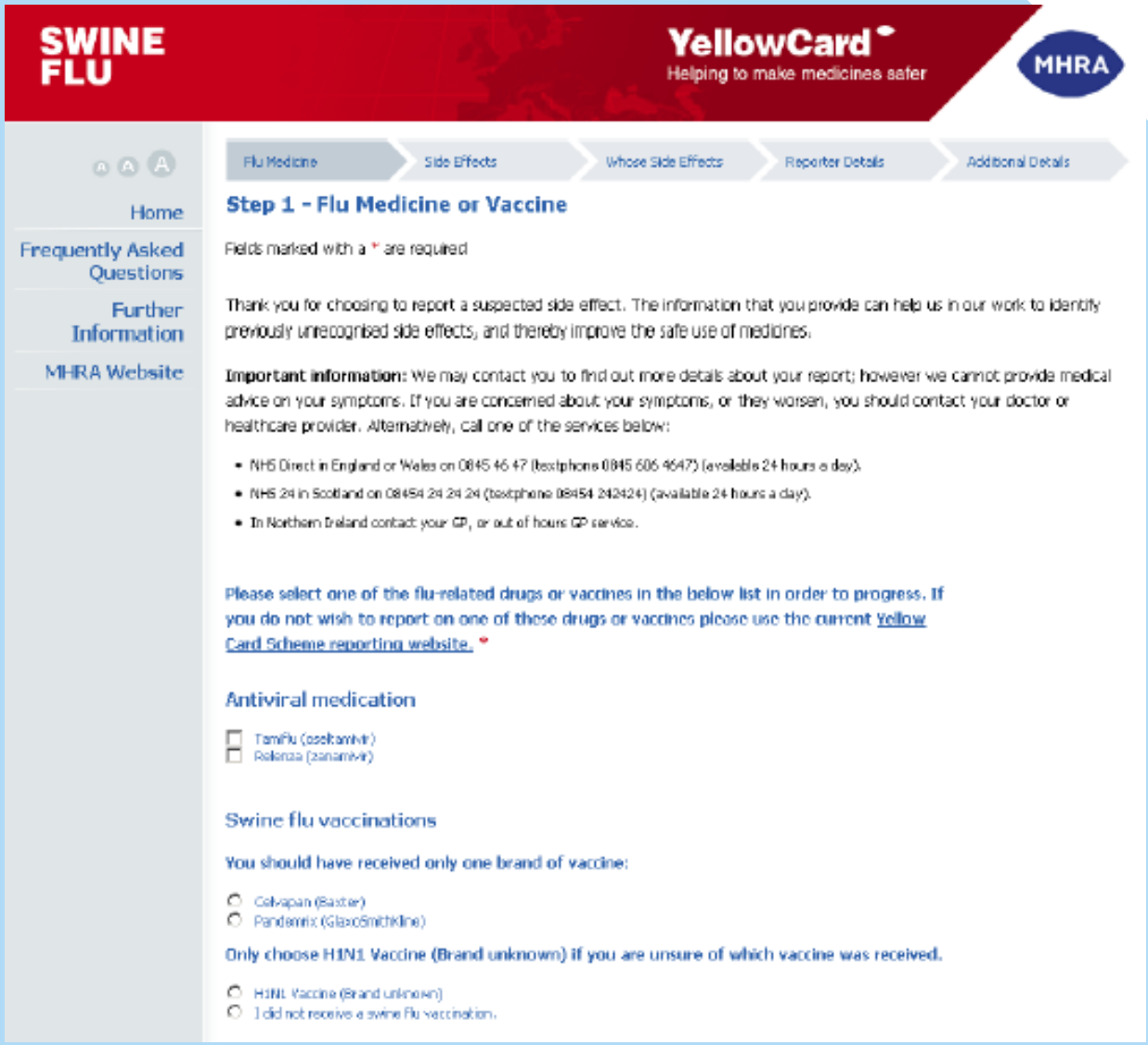
- EMA Crisis Management Plan implemented

  - core RMPs (simplified PSURs, PASS study etc)
  - EMA co-ordinated EU pharmacovigilance activities
  - Weekly safety updates (ADRs, exposure, EV analysis)
  - Pandemic Rapid Response Expert Group (PREG)
  - ECDC liaison

- Encouraged use of ‘observed vs expected’ in signal detection and analysis

UK Enhanced passive surveillance

- Optimise passive reporting
- On-line
- Fully automated
  - Large volume of ADRs
  - resilient to business continuity pressures
- Daily analysis

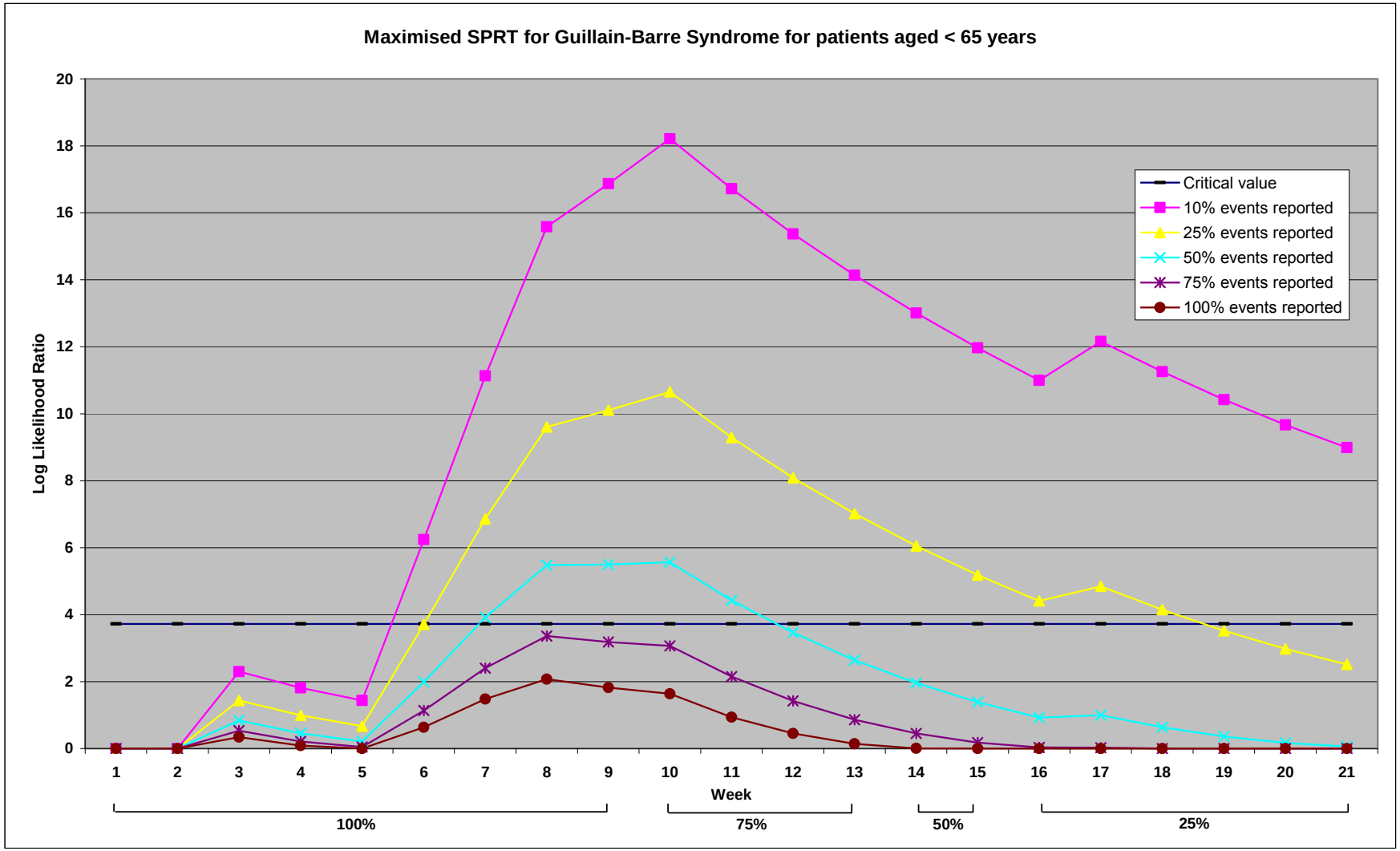


UK observed vs expected

Background conditions per 4 million doses* for ‘adverse events of interest in defined population groups (e.g. adolescents immunised in school)

	Incidence rate / 100,000 / year	***‘Expected’ within 42 days****
Bell’s palsy	27.18	132.87
Encephalitis	1.55	7.57
Guillain-Barré Syndrome	0.92	4.49
Chronic Fatigue Syndrome	47.44	231.92
Coeliac disease	17.58	85.94
Glomerulonephritis	6.71	32.80
Haemolytic anaemia	0.63	3.08
Multiple Sclerosis	1.84	9.00
Myasthenia Gravis	0.22	1.08
Myelitis	1.08	5.28
Systemic lupus erythromatosus	5.20	25.42

UK observed vs expected – Guillain Barre Syndrome



Communication – Public Assessments

- Weekly, proactive and transparent
- Assist interpretation of passive data
- Give public a balanced overview of safety
- Minimise mis-use of data by media
  - Get in first, Create our own headlines

UK Suspected Adverse Reaction Analysis

Swine Flu (H1N1) Vaccines – Celvapan and Pandemrix

4 February 2010

This report provides an overview of all UK reports of suspected adverse reactions to the new swine flu (H1N1) vaccines (Celvapan and Pandemrix) received by MHRA between Monday 15th October 2009 and Tuesday 19th January 2010 (inclusive)[1]. These reports have been voluntarily submitted to MHRA

4. **The total number of reports and the nature of suspected adverse reactions reported so far are as expected at this stage in the immunisation campaign.** The most frequently reported suspected adverse reactions continue to be injection site reactions (e.g. pain, swelling,

6. Three cases of still birth have been reported in the UK to date. It is estimated that more than 258,000 pregnant women across Europe[4] have now been vaccinated with H1N1 vaccines (including at least 132,000 women in England). The number of cases of adverse pregnancy outcomes reported to date does not exceed what would be expected based on normal background rates in the absence of vaccination. **There is no evidence of any risks to pregnancy.**

of vaccinees. This includes an adjustment for likely under-reporting of cases. The total number of suspected cases of GBS reported in the UK (and Europe) following vaccination does not exceed the number of cases that would be expected in the normal background population (i.e. in the absence of vaccination) suggesting that these cases were probably coincidental events.

CONCLUSIONS

- Need to continually horizon-scan for changes in immunisation programme and anticipate likely issues based on past experience
    - Proactive and tailored vaccine risk management strategies should be planned well in advance
- Need to optimise data collection and make best use of all available data sources
- Communications should be balanced, taking account of the variety of stakeholders in vaccine safety
- Risk Management Plans will become an increasingly important regulatory tool to evaluate balance of risks and benefits in a real-life setting

Guidelines and further reading

- European Medicines Agency Vaccine PhV guideline
  - Sep 2008 – Doc. Ref. EMEA/CHMP/PhVWP/503449/2007
- WHO Global Advisory Committee on Vaccine Safety (GACVS) - www.who.int/vaccine_safety/en/
- Brighton Collaboration -www.brightoncollaboration.org
  - Global initiative to standardise collection of vaccine ADR data
  - Wide range of case definitions established
- US CDC Vaccine Safety - www.cdc.gov/vaccinesafety

- **Literature**

- Special Methodological Consideration Issues in Pharmacoepidemiology Studies of Vaccine Safety – Robert.T.Chen – *Pharmacoepidemiology*, Third Edition, 2000
- Control without separate controls: evaluation of vaccine safety using case-only methods – Farrington, CP *Vaccine* 2004: 22; 2064-2070
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- Comparison of epidemiologic methods for active surveillance of vaccine safety. McClure DL, et al *Vaccine.* 2008 Jun 19;26(26):3341-5