Challenges to Rotavirus Vaccine Introduction: Risk management strategies

The UK position

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Deciding UK vaccination policy

Case made to ministers for funding for new/revised programme

JCVI advises Department of Health

National independent expert advisory policy group (Joint Committee on Vaccination and Immunisation)

Economic analysis of policy options

Epidemiology/burden of disease/UK trials/postlicensure effectiveness & safety

Licensed indications
Potential risks associated with introduction of rotavirus vaccines

Unanticipated serious adverse event

Virological risks

– Reassortment with wild type rotavirus produces pathogenic variant
– Emergence of new strains with loss of efficacy of vaccine

Causes intussusception

– Too rare to detect risk in prelicensure trials
– Used in different age groups to those in the trials
– Occurs in selected subgroups not included in trials

Loss of confidence in vaccine due to publicity given to IS cases occurring by chance
The Government was last night accused of a cover-up over the safety of a meningitis vaccine after 11 teenagers died after being given the jab.

**A fatal cover-up?**

**Life, death and the meningitis vaccine**

**FEW THINGS ARE more emotionally charged than the decisions parents must make in the care of their children. With mass vaccination programmes, those decisions are made by millions of parents.**

**The British government is being accused of withholding vital information from parents about the risks and benefits of the meningitis vaccine.**

**The Department of Health believes that reactions to the new meningitis C vaccine could have killed 11 schoolchildren, but has denied any cover-up.**

The Department of Health believes that reactions to the new meningitis C vaccine could have killed 11 schoolchildren, but has denied any cover-up. This is a copy of a cover-up. This will not stand up to close scrutiny.

**The vaccine has been rushed to market without enough research into its long-term effects.**

**Teenager's death raises fears over meningitis jabs**

**By CAROL MORGAN**

**Meningitis jab is safe, health officials insist**

**By Sandra Leslie**

**New vaccine has saved 100 lives**

**Wonder drug launched in a blaze of publicity**

**Youngsters struck down as vaccine is rushed in**

Eleven die after new vaccine
Rotavirus vaccine and intussusception – what is the question?

Are the new rotavirus vaccines safer than RotaShield® when in routine use?

- Odds ratio in case-control study for IS in the 3-14 day period was 21.7 (95% CI 9.6 to 48.9)

Are the new rotavirus vaccines as safe in routine use as in the pre-licensure studies?

- Upper 95% CI of RR estimate of IS within 30 days from pre-licensure placebo-controlled trials is around 2.5 (GSK product)

What is the lowest attributable risk of IS that would be acceptable?

- RotaShield® risk was around 1 per 5000 -10,000 doses
- Would 1 per 25,000 or 100,000 doses be acceptable?*

Is there any IS signal with the new rotavirus vaccine from routine surveillance data sources?

Sansom et al Am J Epidem 2001 suggest risk of 1 in 2000 acceptable to parents (if vaccine cheap enough)!
Methods for post-marketing vaccine safety evaluation in the UK

• Passive reports to the licensing authority (Yellow Cards)

• Enhanced reporting of vaccine-associated cases from clinicians (e.g. British Paediatric Surveillance Unit)

• Ecological study

• Analytic epidemiological study (e.g. case-control or self controlled case-series method)
Passive surveillance based on Yellow Card reports

Doctors, nurses, pharmacists, patients (parents) can report any suspected reaction to a pediatric vaccine

Variable quality of information on diagnosis, interval after vaccination, outcome and concomitant vaccines

Can be used for signal generation by comparing

– Adverse event reporting patterns for other vaccines

– Observed VS expected rates for specific AEs
Data needed for calculation of IS cases within X days of vaccination expected by chance.
Limitations of reliance on passive adverse event reports

Relative reporting rates for different vaccines influenced by vaccine-specific risk perception (eg MMR and autism)

Observed Vs expected comparisons require assumptions about completeness of passive reports (only 50% of SIDS expected by chance within 48 hours of Men C were reported on Yellow Cards) and stability of background risk over time
Advantages of Yellow Card system

Utilises existing routine AE surveillance system

Can generate signals for hitherto unexpected AEs

Observed Vs expected analyses likely to detect substantial vaccine-attributable risk

Observed vaccine-associated cases could be augmented by stimulated clinician reporting eg via pediatricians

– what is the risk period with a 2/3/4 month schedule?

– Pediatrician reporting only yielded a risk estimate for aseptic meningitis of 1/250,000 for Urabe vaccine Vs true risk of 1/10,000
Potential for ecological study?

IS admissions to hospitals in England by monthly age group and year (April- March) in children aged 2-5 months
Number of additional IS cases in children aged 2-5 months for different attributable risks in 14 day post vaccination period after each dose at 2/3/4 months with 90% coverage: 
total background cases = 120 (41 in risk period)

<table>
<thead>
<tr>
<th>Attributable risk per course</th>
<th>No. of additional attributable cases</th>
<th>Relative incidence in 0-14 day period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 1000</td>
<td>540</td>
<td>14.0</td>
</tr>
<tr>
<td>1 in 3300</td>
<td>162</td>
<td>5.0</td>
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<tr>
<td>1 in 10,000</td>
<td>54</td>
<td>2.3</td>
</tr>
<tr>
<td>1 in 20,000</td>
<td>27</td>
<td>1.65</td>
</tr>
<tr>
<td>1 in 100,000</td>
<td>5.4</td>
<td>1.13</td>
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</tbody>
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Feasibility of an analytic epidemiological study to detect increased risk in 0-14 day post-vaccination period

Requires method for unbiased ascertainment of a large sample of IS cases and their vaccination histories

Study duration/size critically dependent on size of risk to be excluded/detected

<table>
<thead>
<tr>
<th>No. Cases &lt;1yr</th>
<th>Detectable RR (80% power, 5% sig)</th>
</tr>
</thead>
<tbody>
<tr>
<td>74*</td>
<td>2.3</td>
</tr>
<tr>
<td>162</td>
<td>1.75</td>
</tr>
<tr>
<td>325</td>
<td>1.51</td>
</tr>
<tr>
<td>650</td>
<td>1.38</td>
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</tbody>
</table>

*all IS hospital cases in Thames region (where record linkage in place) from one year’s birth cohort of approx 150,000. If followed up for one year, an attributable risk of around 1 per 10,000 doses could be excluded; to exclude an AR of 1 per 20,000 would require 4 years data (approx 5yr study).
Conclusions

Clear objectives needed for any post-marketing surveillance of vaccine-associated IS

What is ideal needs to be tempered with what is feasible

Problems for analytic study
– to detect rapidly a rare risk (<1 in 10,000)
– post-vaccination risk period of 30 days with a 2/3/4 month schedule leaves little non-risk background period if using self controlled case series analysis method
– likely high coverage (>90%) raises problems for a case-control study

Proposal:
– risk management strategy based on routine data sources which would probably generate a signal if risk around 1 in 10,000 doses via ecological and/or Yellow cards

– Only proceed to analytic study using record linkage if signal from routine data sources
ACKNOWLEDGMENTS

Nick Andrews, Statistics Unit

Julia Stowe, Immunisation Department