Pertussis and the Swedish Childhood Vaccination Program

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Swedish childhood vaccinations (1)
- Smallpox 1816-1976
- Diphtheria 1947-
- Tuberculosis 1953-75
  - 1975- risk groups
  - 1953-86 PPD-neg teenagers
- Tetanus 1953-
- Pertussis 1953-79 (whole cell)
  - 1996- (acellular)

Swedish childhood vaccinations (2)
- Polio (IPV) 1957-64 campaigns
  - 1965-
- Rubella 1974-82 girls
  - 1982-
- Measles 1971-1982
- Mumps 1982-
- Hib 1992-
- Hepatitis B 1996- risk groups

Swedish childhood program
- Few doses
- Space 6 mo before third dose = booster dose
- Late 4th dose
- Two MMR-doses since 1982
- High vaccination coverage
- 17 y hiatus without general pertussis vaccination

Different types of pertussis vaccine
- Whole-cell vaccines (DTPw)
- Acellular vaccines (DTPa)
  - one or more purified components from Bordetella pertussis
- Combination vaccines - administered in combination with diphtheria-tetanus (trivalent) or with these and other vaccines

Pertussis in Sweden 1911-2005; Incidence per 100,000

- Incidence per 100,000
- GP reports
- Laboratory reports
- DTPw
- DTPa
General vaccination program

- **Aim**
  - Containment
  - Elimination
  - Eradication

- **Method**
  - Direct protection against disease/infection
  - Indirect protection (reduced transmission)

**NOTE!**
Diseases are different, so are also the vaccines

General vaccination or not?

**HEALTH TECHNOLOGY ASSESSMENT**

- Epidemiology (“Do we have a problem?”)
- Technology (“Is vaccination a method to solve the problem?”)
- Attitudes (“Do we want this solution?”)
- Organisation (“Can we handle vaccination?”)
- Economy (“Can we afford it?”)

(State Serum Institute, Denmark)

General vaccination or not?

1. Would general vaccination significantly improve public health?
2. If yes, is the vaccine safe (enough) for the individual?
3. If yes, are there disadvantages on the population level?
4. If no, what is the balance between cost and benefit?

(National Public Health Institute, Finland)

Decision elements...

**EPIEMIOLOGY**

**VACCINE**

**IMPLEMENTATION**
- organisation, attitudes

**ECONOMY**

Choice of strategies

- **General or targeted vaccination?**
  - children, also other age groups?
  - medical risk groups, contacts around cases?

- **For each strategy – evaluation of**
  - primary series with/without booster
  - timing of boosters (if needed)
  - the role of maternal antibodies

- **For each vaccine – evaluation of**
  - one strategy
  - combination of strategies

General vaccination of infants against pertussis

*(Wirsing von König, ESPID 2005)*

**What can we achieve?**
- Reduced incidence (reduced morbidity)
- in pre-school children
- of typical disease
- Reduced transmission

**What can we not achieve?**
- Protection of newborns and young infants
- Eradication of disease
- Eradication of bacteria
- Long-term protection

Can herd immunity be achieved?

No herd immunity?
Herd immunity

- Immunity at population level
- Immunity of the individual requires an immunogenic vaccine + a valid schedule
- Population immunity = sum of individual immunity + effect of reduced transmission of disease

Herd immunity hence depends on
- the vaccine and the timing and number of doses
- the vaccination coverage
- but also on the attack rate of disease
- contagiousness
- intensity of contact
- duration of infectious period

Herd immunity against pertussis?

- Proportion of immunes (p) should exceed 1 - 1/R₀
  - If R₀ = 15 (measles, pertussis), p should exceed 93%.

Assumption: Proportion of immunes (p) = proportion vaccinees x individual protective efficacy

If so, what coverage is needed?

- Efficacy of measles vaccine is probably ≈ 93%,
- but acellular pertussis vaccines???

What is wrong?

- Wrong assumption?
- Waning immunity??
  - Measles vaccine does induce a longterm immunity, but Pa vaccines do not
  - Milder disease in vaccinees
    ⇒ reduced contagiousness during a shorter period
- Or what????

What is the duration of protection - when are boosters needed?

Nicole Guiso, ESPID 2003:

- Immunity after disease
  - 12-15 y (in endemic countries)
- Immunity after vaccination with DTPw
  - 6-8 y after vaccination (primary vaccination and a booster during second year of life)
- Immunity after vaccination with DTPa
  - probably at least 4-6 y, follow-up ongoing
  - not yet known if there are differences between vaccines

The pertussis surveillance project in Sweden - clinical & epidemiological part

Results

The overall incidence of culture-confirmed pertussis dropped from 121-150/100 000 in 1994-1995 to 11-16/100 000 in 2001-2005. The highest incidence still occur in infants below 5 months of age
- who either are unvaccinated or
- have received only one dose of DTPa-IPV-Hib
Most hospitalisations occur in infants who are unvaccinated.

Waning protection indicated by:

- A fairly stable age-specific incidence in vaccinees for about 5 years after the third dose, without a later booster dose, with increasing age-specific incidences from age 6 years
- The highest age specific incidences in vaccinated cohorts among 8-9-year-olds born 1996, the first DTPa cohort.
Priorities and strategies
(vaccination program)

"We must define priorities" (Wirsing von König, ESPID 2005)
- Infants
- Pre-school children
- Adolescents
- Adults
- Risk groups, ex medical attendees, families with infants

Possible strategies
- Direct protection - against disease/infection
- Indirect protection - reduced transmission
- Additional strategies

Example, focusing on infants...

INDIVIDUAL PROTECTION
- Vaccination during pregnancy?
- Vaccination of newborns?
- Earlier start of vaccination?

INDIRECT PROTECTION
- General vaccination of infants
- Booster to preschool/school children
- Booster to adolescents/adults?
- Cocoon strategy?

ADDITIONAL STRATEGIES
- Antibiotics
- Contact tracing

Key requirements for a successful immunization program

- Surveillance strategy
  - monitoring the outcome (impact on age-specific disease incidence & age-specific immunity in the population)
  - monitoring the process (vaccine uptake, vaccine safety monitoring)
- A framework
  - for making and implementing policy decisions in the light of surveillance information
  - including a policy making committee

Parts of post-implementation surveillance strategy

1. Disease surveillance
2. Seroepidemiology
3. Vaccination coverage
4. Surveillance of adverse events

1. Objectives of disease surveillance

Vaccine preventable diseases

- Pre-implementation
  - estimate burden
  - decide strategy
- Post implementation
  - monitor effectiveness / efficacy
  - predict impact
- Nearing elimination
  - identify pockets of susceptibles
  - modify strategy accordingly

1. Disease surveillance

**methodological issues**

- Direct/indirect approaches
  - "before and after-studies"
  - cohort or case-control studies
- Ascertainment of cases
- vaccination history
- Effectiveness
  - denominator
- Epidemiology of pathogen?
  - colonization/serotype

"Source of data and case definition must change with incidence of disease/stage of programme."

Between 1990 and 1999, pertussis increased in all age groups in the US
Trend was strongest among adolescents and adults

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**Pertussis in Sweden 1986-2005; Culture or PCR-confirmed cases per month**

**The pertussis surveillance project in Sweden - clinical & epidemiological part**

**Aims**
- To document the effect of aplerular pertussis vaccines, introduced at 3, 5 and 12 months of age in 1996, on the pertussis incidence in Sweden
- To collect background data for timing of later booster dose(s)

**Method**
- Analyses of annual national data from 1986 to 2005: reports on age specific incidence of culture/PCR-confirmed Bordetella pertussis
- Enhanced surveillance from Oct 1997 to Sept 2005 (except Gothenburg area until 2003) of culture/PCR-confirmed cases in children born from 1996: clinical follow-up by telephone interviews with ascertainment vaccination status and documentation of clinical outcome
- Primary case definition: Detection of B. pertussis by culture or PCR in a clinical sample, regardless of symptoms

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**Pertussis surveillance Sweden, Clinical epidemiology, 8 y report**

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**The pertussis surveillance project in Sweden - clinical & epidemiological part**

Background, cont.

Pertussis became endemic during the 17-year hiatus without pertussis vaccination. From 1996, the 3 dose coverage rapidly reached 98-99%, since introduction of Pa in 1996 only meant switching from DT to DTPa. Many children born –95 received catch-up vaccination and many infants born 93-94 were vaccinated in Stockholm Trial 2.

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**Pertussis, ex 2**

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**Pertussis, ex 3**

Annual adjusted notification rate, Australia, 1917–2000

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**Pertussis, ex 1**

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**Pertussis in Sweden 1986-2005; Culture or PCR-confirmed cases per month**

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**Pertussis surveillance Sweden, Clinical epidemiology, 8 y report**
Pertussis in vaccinated vs non-vaccinated country
(Nicole Guiso, ESPID 2003)

Low vaccine coverage
- High morbidity and mortality in infants and pre-school children
- Unknown epidemiology in adults
- Regular asymptomatic contacts throughout life

High vaccine coverage
- Low morbidity and mortality in infants and pre-school children
- Increase in adolescents and adults
- Few asymptomatic contacts throughout life

Age-specific incidence of pertussis 1992-2005

Typical pertussis
- Used to be a well-known childhood disease
  - Endemic with peaks every 3-5 years
  - Affects mainly pre-school children, tiresome for children and parents
  - Sometimes serious in infancy

WHO meeting on case definition of pertussis; Geneva, 10-11 January 1991
- Culture- or PCR-confirmed pertussis with twenty-one days or more of spasmodic cough

Atypical pertussis
- Not a very well-known disease
  - Reduction in circulation but still endemic with small peaks every 3-5 years
  - Affects mainly older children and adults
  - May be life-threatening in infancy

WHO and EU clinical case definitions for surveillance from 2003 (revision ongoing)
- Cough illness lasting >2 weeks with paroxysms, inspiratory whoop or post-tussive vomiting
- Clinical picture compatible with pertussis (EU)
  - or a case diagnosed as pertussis by a physician (WHO)

Culture or PCR-confirmed pertussis in infants before and after 1996

Before and after introduction of DTPa at 3, 5 and 12 months

1. Importance of case definition

- Differences in efficacy estimates depend on:
  - type of study (RCT, CCT, cohort, household study...)
  - case definition; duration of cough, paroxysmal etc.
  - (WHO-definition, CDC-def, all suspected pertussis)
  - laboratory verification or not
  - background incidence
  - duration of follow-up (normally 2-3 y)
  - other factors in the study design
  
  Fine. Dev Biol Stand 1997;89:123-33

- Are national/international incidences comparable over time and between regions/countries?
  - Ex USA: Only cough >2 v is reported to CDC...

2. Objectives of seroepidemiology/immunosurveillance

- Monitor age-specific immunity before and after introduction of general vaccination
- Evaluate success of immunization programme (particularly useful when incidence ↓)
- Identify groups with low immunity

**NOTE**
- Presence/absence of antibodies often but not always indicator of individual protection/lack of immunity
- There is often but not always a good correlation between antibody levels and protection (exception: e.g. pertussis)
- A distinction between naturally induced and vaccine induced antibodies is in most cases impossible

Procurement of DTPa vaccines in Sweden

- Infanrix® (3v)
- Di-Te-Kik®
- Infanrix® (3v)/Pentavac® (5v)
- Infanrix® (3v)/Infanrix-Polio+Hib® (5v)
- Infanrix-Polio+Hib® (5v)
- Infanrix® (3v)/Infanrix-Polio+Hib® (5v)
- Pentavac®

- 2001
- 2002
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014

- County

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25

- 2001
- 2002
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- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014

Provision of DTPa vaccines in Sweden
2. Seroepidemiology - antibody dynamics

- Reduced circulation of pathogen
  - boosting opportunities ↓
  - waning of both natural and vaccine induced immunity
  - antibody levels ↓
- Lower levels of vaccine induced antibodies
  - persistence of maternal antibodies ↓

Decay of antibodies against PT..
Experiences from Trial I + booster studies in the DTPa5 group of Trial I and Trial II (Hallander et al)

1 – <9 months: \( Y = 65.057 \times e^{-0.2396D} \)
9 – months: \( Y = 79.771 \times D - 1.0525 \)

Predicted duration 65 mths; 50% >= 1 EU/ml

B and T cell responses, what a vaccinologist should know...

- Primary B cell response
  - Early antibody production (days)
  - Proliferation-differentiation of plasmacells (10days-6w)
  - isotype switch, avidity maturation + memory B cells

Process depending on vaccine (antigen nature & dose) but also on genetics (B/T-repertoire) + state of activation of the innate immunity

Antibody titer reflect the number of short-lived plasmablasts (peak+rapid decline) and of long-lived plasmacytes (slower decline)

- Secondary B cell response
  - Memory B cells rapidly differentiate into ASC
  - rapid (day 4-7) and strong increase in IgG, different avidity profile (higher avidity)

Affinity maturation takes pt weeks.
B and T cell responses, what a vaccinologist should know.

(ADVAC, Prof. Claire-Anne Siegrist, Geneva)

- Primary T cell response
  - Dendritic cells essential, activate naïve T-cells
  - Also maturation of T-cell response (progressive differentiation of effector CD8 cells into memory cells) takes time
  - Differentiation depending on antigen nature & dose, route of exposure, costimulators, genetic factors...

- Secondary T cell response
  - Memory T cells persist long time and are capable of antigen independent renewal
  - Rapid recall responses to antigen with effector functions and proliferation (antigen-driven)

Prime-boost concept
- Higher possible frequency to maintain memory T cell qualities after different vaccination regimens

2. A range of laboratory methods...

- ELISAs, neutralisation tests etc
  - Varying sensitivity & specificity with antigen and test method. Functional tests more important at low antibody concentrations

- NOTICE! Different needs in seroprevalence and vaccine studies!
  - Seroprevalence methods need high accuracy in the low range of antibodies, whereas the high range of antibodies is of more interest in post-vaccination studies

3. Vaccination coverage

- "Administrative methods"
  - Number of doses distributed

- Studies of health service delivery records
  - "Random samples", house-hold surveys
  - Periodic reviews of health records

NOTE
Varying denominators...
- Number of births/year
- Number of infants that survive first year of life
- Number of children within a specific age range
- Number of children attending child health care

The pertussis surveillance project:
Timing of the 3.5-12 month doses

Timing of vaccination in relation to recommended ages
- 3 months (90 days)
- 5 months (150 days)
- 12 months (365 days)

Mean ages at vaccination (days)

<table>
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<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
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<tr>
<td>Trial 1994</td>
<td>100</td>
<td>174</td>
<td>386</td>
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<td>n = 72690</td>
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<td>Surveillance</td>
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<td>176</td>
<td>383</td>
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<tr>
<td>Project 1996-2005 (vaccine data for 1572 children)</td>
<td></td>
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</tbody>
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The Swedish method

- Child health care
  - Annual reports in January
  - Children with 2 y birthday during the previous calendar year (= age 24-35 months)
  - n = number of children registered (in comparison with population statistics)

- School health care
  - Annual reports at end of 6th grade
  - Children ~12 y
  - n = number of children in school (in comparison with population statistics)

3. Vaccination coverage

Pertussis notifications and vaccine uptake, UK, 1940 - 2004

- Pertussis, ex 4

- Pertussis surveillance project 1996-2005 (vaccine data for 1572 children)
3. Towards improved vaccination coverage reporting

- SVEVAC – information system for vaccinations

4. Adverse event (AE)

- Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

ICH 1996: Good Clinical Practice: Consolidated guideline.

4. Passive vs. active surveillance

- **Passive reporting**
  - Reporting of events suspected by clinicians to be vaccine reactions

- **Active surveillance**
  - Requires a procedure for identifying all clinically significant events which occur within defined post-vaccination periods


4. Bradford Hill’s criteria for causation

- **Strength of association**
  - Frequency with which the factor is found in the disease
  - Frequency with which it occurs in the absence of the disease

- **Consistency**
  - Has it been repeatedly observed by different persons, in different places, circumstances and times?

- **Specificity**
  - Association of a particular exposure with a particular disease

- **Temporality**
  - Cause must precede effect

- **Ancestry**
  - Similar evidence with another drug


4. Towards improved vaccine safety surveillance

- **Passive surveillance**
  - to give alarm signals
  - to generate hypotheses

- **Active surveillance (e.g. record linkage)**
  - to investigate the hypothesised association
  - to estimate vaccine attributable risk

- **Standard case definitions**

NOTE: A signal does not prove causality!

Special characteristics of vaccines as pharmaceutical products

- Administered to a healthy subjects, often infants
- Adverse reactions may occur to individuals who would not have encountered the disease, if left unvaccinated
- Extremely high standards necessary for safety and efficacy of vaccines

Benefits need to outweigh the risks overwhelmingly!