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)

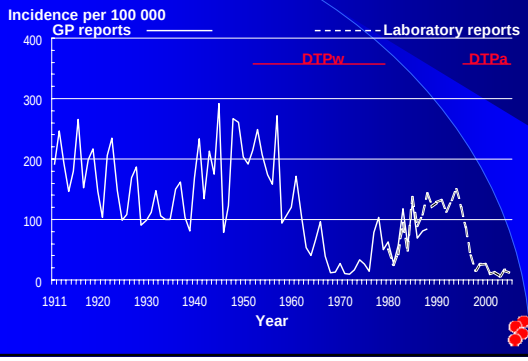
Swedish childhood vaccinations *(2)*

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

Swedish childhood program

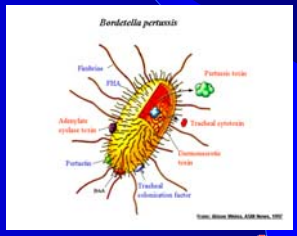
- Few doses
- Space 6 mo before third dose = booster dose
- Late 4th dose
- Two MMR-doses since 1982
- High vaccination coverage
- 17 y hiatus without general pertussis vaccination

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



Different types of pertussis vaccine

- Whole-cell vaccines (DTPw)
- Acellular vaccines (DTPa)
  - one or more purified components from *Bordetella pertussis*
- Combinaton vaccines
  - administered in combination with diptheria-tetanus (trivalent) or with these and other vaccines



General vaccination program

- *Aim*

  Containment
  ⇩
  Elimination
  ⇩
  Eradication

NOTE! Diseases are different, so are also the vaccines

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

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?”)

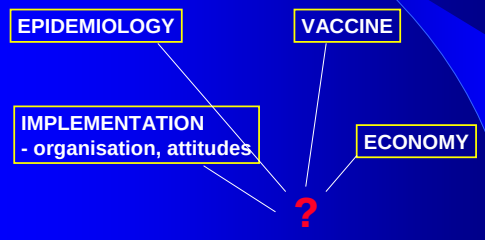
(State Serum Institute, Denmark)

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…



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

Can herd immunity be achieved?

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

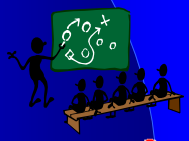
} No herd immunity?

Herd immunity

- Immunity at population level
- Immunity of the individual requires an immunogenic vaccin + 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 vaccinaton coverage*

but also on the attack rate of disease
- *contagiousness*
- *intensity of contact*
- *duration of infectious period*



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Herd immunity against pertussis?

- Proportion of immunes (p) should exceed $1 - 1/R_0$
  If R_0 = 15 (measles, pertussis), p should exceed 93%.
- Assumption: Proportion of immunes (p) = proportion vaccineees x individual protective efficacy
- If so, what coverage is needed?

  Efficacy 100% - coverage >93/100 = >93%
  95% >93/95 = >97,9%
  93% >93/93 = >100%
- *Efficacy of measles vaccine is probably ≈93%, but acellular pertussis vaccines???*

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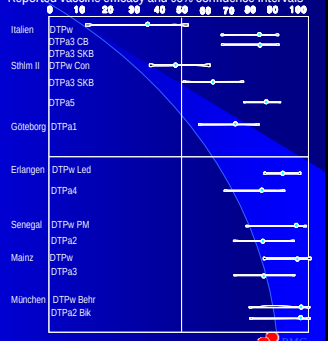
Efficacy trials of acellular pertussis vaccine, *reference list*

Publication	*First author*	*Study*
Lancet 1988;1:955-60	No authors listed	JNIH6-JNIH7, RCT
Am J Dis Child 1992;146:167-72	Storsaeter	JNIH6-JNIH7, household study
N Engl J Med 1995;333:1045-50	Trollfors	Gothenburg, RCT
J Pediatr 1997;130:532-6	Trollfors	Gothenburg household study
N Engl J Med 1996;334:341-8	Greco	Italy, RCT
N Engl J Med 1996;534:349-55	Gustafsson	Stockholm I, RCT
Vaccine 1998;16:1907-16	Storsaeter	Stockholm I, household study
JAMA 1996;275:37-41	Schmitt	Mainz, cohort study
Lancet 1997;350:1569-77	Olin	Stockholm II, RCT
Vaccine 1997;15:1606-12	Simondon	Senegal, RCT
Pediatr Infect Dis J 1997;16:1038-44	Liese	München, CCT
Pediatrics 1998;101:1-11	Stehr	Erlangen, RCT
Pediatrics 1998;102:546-53	Heininger	Erlangen, household study

Reported vaccine efficacy and 95% confidence intervals[1]



[1] *Wassilak S, Fine P. Dev Biol Stand 1997;89:187-93*

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What is wrong?

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

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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 lifte)
- Immunity after vaccination with DTPa
  - probably at least 4-6 y, follow-up ongoing
  - not yet known if there are differences between vaccines

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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 incidence in vaccinated cohorts among 8-9-year-olds born 1996, the first DTPa cohort.**

Pertussis surveillance Sweden, Clinical epidemiology, 8 y report

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, familys with infants

Possible strategies

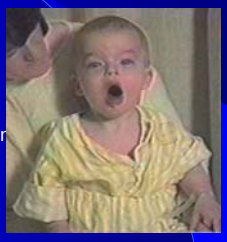
- *Direct protection - against disease/infection*
- *Indirect protection - reduced transmission*
- *Additional strategies*

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

Bloom BR & Lambert PH, eds, The VaccineBook, Academic Press 2003

Parts of post-implementation surveillance strategy

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

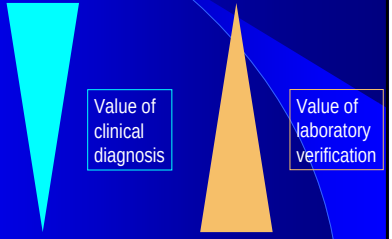
1. Objectives of disease surveillance
Vaccine preventable diseases

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

Observation system and methods may vary with time…

1. Objectives of disease surveillance
Vaccine preventable diseases

- Pre-implementation
- Post-implementation
- Nearing elimination



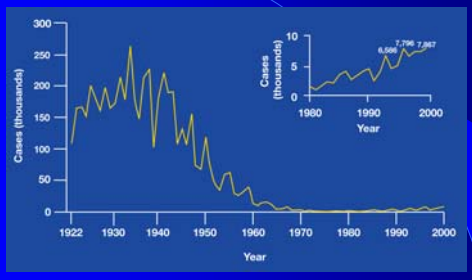
1. Disease surveillance

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”

Pertussis, *ex 2*

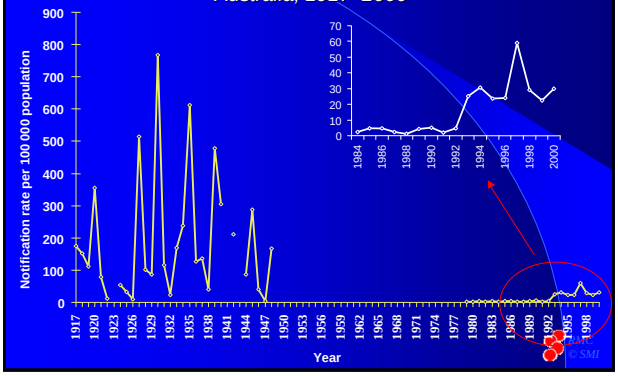


- Between 1980 and 1989, pertussis increased in all age groups in the US[1]
- Trend was strongest among adolescents and adults

[1]CDC, 2002

Pertussis, *ex 3*

Annual adjusted notification rate, Australia, 1917–2000

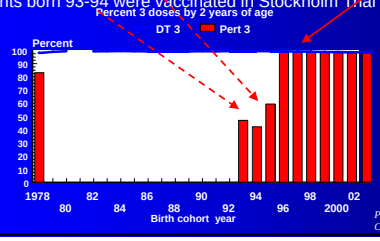


The pertussis surveillance project in Sweden - clinical & epidemiological part

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.



Pertussis surveillance Sweden, Clinical epidemiology, 8 y report

The pertussis surveillance project in Sweden - clinical & epidemiological part *from October 1997 to September 2005*

Aims

- To document the effect of acellular 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)

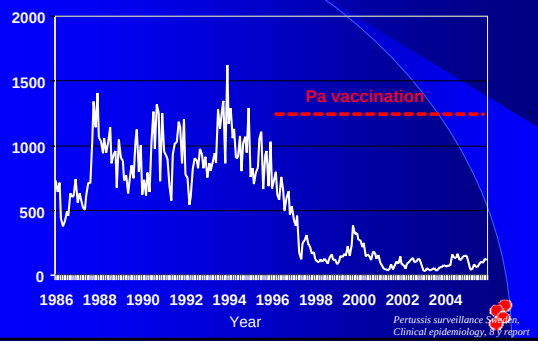
Method

- 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

Pertussis surveillance Sweden, Clinical epidemiology, 8 y report

Pertussis in Sweden 1986-2005;

Culture or PCR-confirmed cases per month



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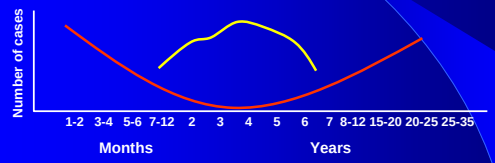
Pertussis in vaccinated vs non vaccinated country
(Nicole Guiso, ESPID 2003)

Nicole Guiso
ESPID 030409
Taormina, Sicily

Low vaccine coverage

- *High mobidity and mortality in ~~infants~~ pre-school children
- *Incidence > 200/100,000
- *Unknown epidemiology in adults
- *Regular asymptomatic contacts throughout life



High vaccine coverage

- *Low morbidity and mortality in ~~infants~~ pre-school children
- *Incidence <10/100,000
- *Increase in adolescents and adults
- *Few asymptomatic contacts throughout life

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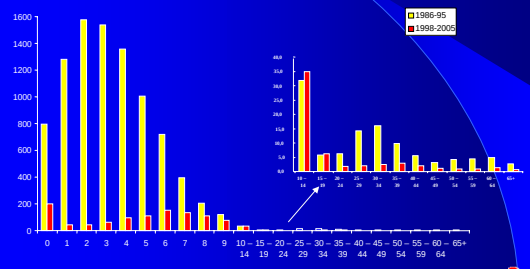
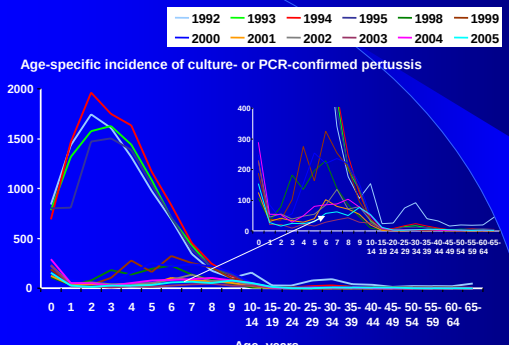
Mean age-specific incidence of pertussis during the years 1992-95 and 1998-2005
(before and after introduction of DTPa in 1996)



Pertussis surveillance Sweden, Clinical epidemiology, 8 y report

Age-specific incidence of pertussis 1992-2005



Pertussis surveillance Sweden, Clinical epidemiology, 8 y report

Typical pertussis

Used to be a well-known childhood disease

- Endemic with peaks every 3-5 y
- 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

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Atypical pertussis*

Not a very well-known disease

- Reduction in circulation but still endemic with small peaks every 3/5 y
- 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)

*von König et al. Pertussis in adults and infants. Lancet Inf Dis 2002;2:744-50

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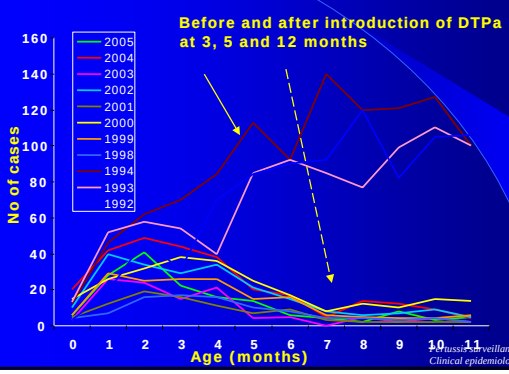
Culture or PCR-confirmed pertussis in infants before and after 1996



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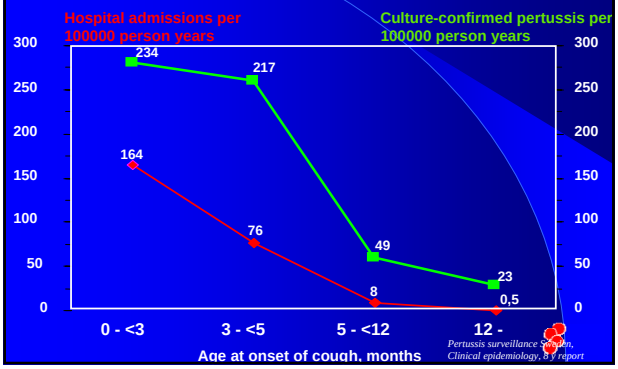
Enhanced surveillance Oct 1997- Sept 2005, Incidence and hospital admissions

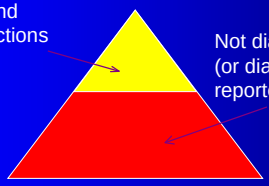


Pertussis surveillance Sweden, Clinical epidemiology, 8:1 report

Reported pertussis - tip of the iceberg?

Diagnosed and reported infections

Not diagnosed (or diagnosed but not reported) infections



Different case definitions in different countries!

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1. Importance of case definition

- Differences in efficacy estimates depend on
  - type of study (RCT, CCT, cohort, household study...)
  - case defintion; 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...

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1. *Problems with estimating vaccine efficacy from clinical surveillance data*

- *If case definition is non-specific*
  - efficacy estimates will be falsely low
- *If vaccine protects better against severe disease*
  - using a more specific case definition will increase efficacy
- *If diagnosis is biased by vaccine status*
  - better reporting/confirmation in unvaccinated gives higher efficacy
- *If unvaccinated groups are more exposed*
  - efficacy will be over-estimated
- *If prior infection has occurred in unvaccinated group*
  - efficacy will decline with age

Standard case definitions needed

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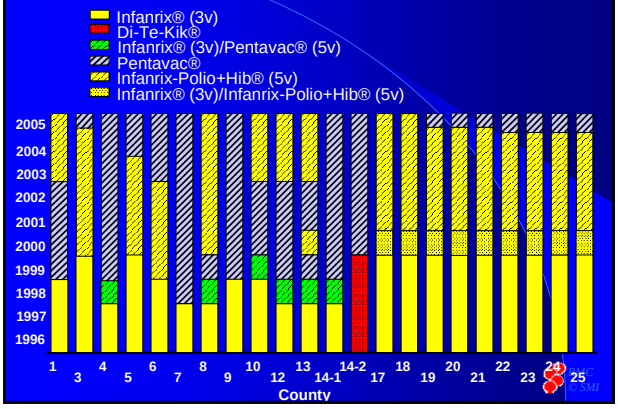
Procurement of DTPa vaccines in Sweden



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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/abscence 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

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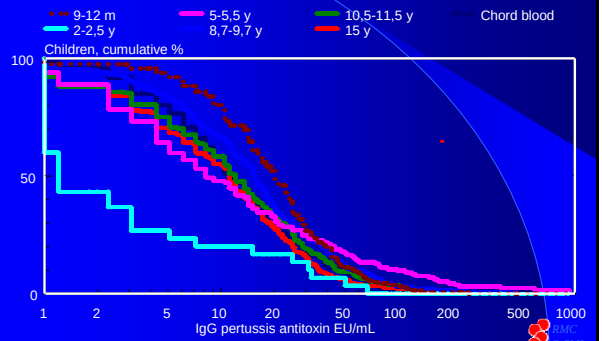
2. Seroepidemiology - antibody dynamics

- *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 ↓

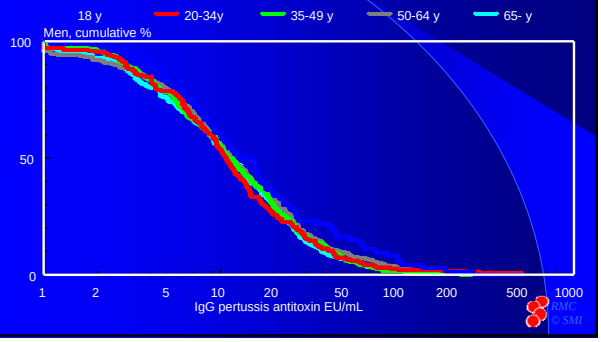
Anti-PT antibodies in children

Serosurvey 1997



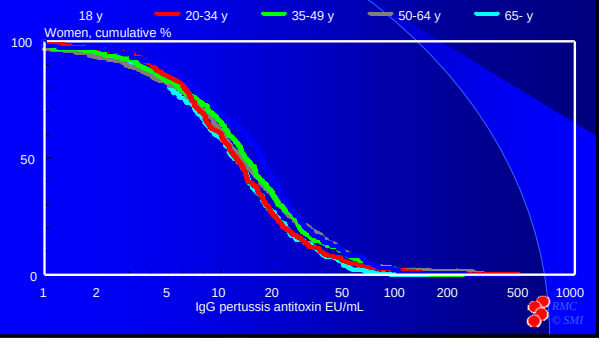
Anti-PT antibodies in men

Serosurvey 1997



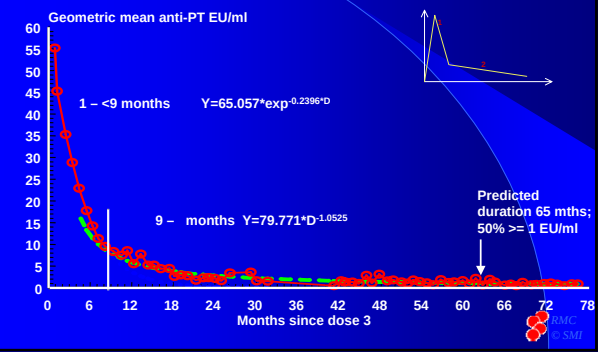
Anti-PT antibodies in women

Serosurvey 1997



Decay of antibodies against PT..

Experiences from Trial I + booster studies in the DTPa5 group of Trial I and Trial II (Hallander et al)



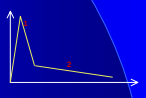
B and T cell responses, what a vaccinologist should know..

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

- ✓ Primary B cell response
  - Early antibody production (days)
  - Proliferation-differentiation of plasmacells (10days-6wk)
  - ⇒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 titers reflect the number of short-lived plasmablasts (peak+rapid decline)[1] and of long-lived plasmacytes (slower decline)[2]



- ✓ 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 ≥4 months

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. Weeks rather than months?**
- 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
- **Studies needed comparing memory T cell qualities after different vaccination regimens**

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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 needs high accuracy in the low range of antibodies, whereas the high range of antibodies is more of interest in post-vaccination studies

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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

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3. Vaccination coverage
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)

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The pertussis surveillance project[1]
Timing of the 3-5-12 month doses

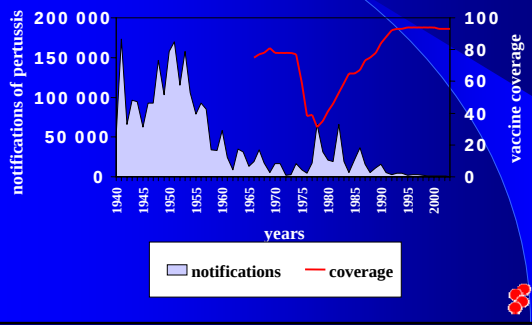
Timing of vaccination in relation to recommended ages
- 3 months (90 days)
- 5 months (150 days)
- 12 months (365 days)

Mean ages at vaccination (days)	Dose 1	Dose 2	Dose 3
Trial 2 1994 (n = 72 698 infants included in the 3-5-12 mo group)	100	174	386
Surveillance project 1996-2005 (vaccination data for 1572 children)	98	176	383

[1]19961001-20050930, 1572 episoder

Pertussis surveillance Sweden, Clinical epidemiology, 8 y report

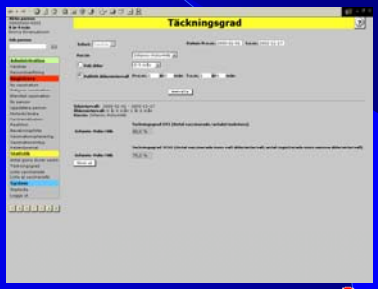
Pertussis, *ex 4*
Pertussis notifications and vaccine uptake, UK, 1940 - 2004



RMC © SMI

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

Miller et al. Dev Biol Stand 1998; 95: 235-43

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
- *Coherence*
  - with generally known facts of the natural history and biology of the disease
- *Analogy*
  - similar evidence with another drug

Bradford-Hill A. The Environment and Disease: Association or Causation? Proc Royal Soc Med 1966; 58:295

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!