Global epidemiology of pertussis

C H Wirsing von König
DEVELOPMENT OF A PERTUSSIS COMPONENT VACCINE IN JAPAN

Y. Sato a b, M. Kimura a b, H. Fukumi a b

Abstract

Antibodies against two physicochemically purified haemagglutinins (HAs) of Bordetella pertussis (filamentous HA and leucocytosis-promoting-factor HA) protect laboratory animals from pertussis. A vaccine containing these two HAs was prepared and tested in trials involving about 5000 children. Culture supernatant of Bordetella pertussis, phase I, was treated with ammonium sulphate, and a crude extract of the HAs was extracted from the precipitate by the use of concentrated sodium chloride. This crude extract was fractionated by sucrose density gradient centrifugation to obtain an HA preparation practically free of endotoxin. The HA preparation was treated with formalin to destroy its ability to induce leucocytosis and to cause histamine sensitisation. Aluminium hydroxide was added to the preparation as an adjuvant. The component vaccine is not only potent as judged by the mouse test but is also less than one-tenth as toxic as whole-cell vaccine as judged by leucocytosis promotion, histamine sensitisation, and endotoxicity tests. Field trials showed that component vaccine was as effective as and produced less side-effects than did conventional whole-cell vaccine. The vaccine has been used for mass immunisation in Japan since the autumn of 1981.
Where is Krefeld?
Global epidemiology: WHO data for the WP region

### Global and regional immunization profile

#### Western Pacific Region

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<td>Total population</td>
<td>1789883</td>
<td>1779286</td>
<td>1768379</td>
<td>1757902</td>
<td>1747115</td>
<td>1735122</td>
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<td>Live births</td>
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<td>23775</td>
<td>23724</td>
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<td>Surviving infants</td>
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<td>Pop. less than 5 years</td>
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<td>1172553</td>
<td>1180205</td>
<td>1180541</td>
<td>1175117</td>
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<td>Pop. less than 15 years</td>
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<td>3741490</td>
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<td>426594</td>
<td>448907</td>
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<td>Female 15-49 years</td>
<td>4772113</td>
<td>4783247</td>
<td>474007</td>
<td>471756</td>
<td>468958</td>
<td>446952</td>
<td>390839</td>
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#### Number of reported cases

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<td>Diphtheria</td>
<td>153</td>
<td>120</td>
<td>99</td>
<td>88</td>
<td>75</td>
<td>61</td>
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<tr>
<td>Hib meningitis</td>
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<td></td>
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<tr>
<td>Measles</td>
<td>49460</td>
<td>46730</td>
<td>47748</td>
<td>112294</td>
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<td>Mumps</td>
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<td>402993</td>
<td>142556</td>
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<td>Pertussis</td>
<td>47477</td>
<td>40560</td>
<td>25245</td>
<td>4984</td>
<td>9164</td>
<td>32328</td>
<td>35953</td>
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<td>Polio</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5963</td>
<td>11420</td>
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<tr>
<td>Rubella</td>
<td>45966</td>
<td>73077</td>
<td>128847</td>
<td>85104</td>
<td>42912</td>
<td>5745</td>
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<td>Rubella (CRS)</td>
<td>0</td>
<td>11</td>
<td>3</td>
<td>174</td>
<td>0</td>
<td>3</td>
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<td>Tetanus (neonatal)</td>
<td>1280</td>
<td>1782</td>
<td>2004</td>
<td>2248</td>
<td>2854</td>
<td>4127</td>
<td>628</td>
<td>1572</td>
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<td>Tetanus (total)</td>
<td>1536</td>
<td>1592</td>
<td>1328</td>
<td>3970</td>
<td>2330</td>
<td>2020</td>
<td>3414</td>
<td>8343</td>
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<td>Yellow fever</td>
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<td>0</td>
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#### Percentage of target population vaccinated, by antigen

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<td>97</td>
<td>96</td>
<td>93</td>
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<td>86</td>
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<tr>
<td>DTP1</td>
<td>97</td>
<td>97</td>
<td>96</td>
<td>97</td>
<td>96</td>
<td>86</td>
<td>90</td>
<td>75</td>
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<tr>
<td>DTP3</td>
<td>96</td>
<td>97</td>
<td>95</td>
<td>95</td>
<td>92</td>
<td>85</td>
<td>90</td>
<td>85</td>
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<td>HepB3</td>
<td>91</td>
<td>92</td>
<td>92</td>
<td>89</td>
<td>85</td>
<td>40</td>
<td>0</td>
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<td>Hib3</td>
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<td>0</td>
<td>0</td>
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<td>MCV</td>
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<td>95</td>
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<td>92</td>
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<td>5</td>
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<td>Pneumococcal</td>
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<td>76</td>
<td>71</td>
<td>71</td>
<td>73</td>
<td>67</td>
<td>42</td>
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<td>96</td>
<td>97</td>
<td>96</td>
<td>93</td>
<td>86</td>
<td>94</td>
<td>5</td>
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<td>TT2plus</td>
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<td>61</td>
<td>63</td>
<td>58</td>
<td>63</td>
<td>67</td>
<td>37</td>
<td>7</td>
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</tbody>
</table>

Labor: Medizin Kre

MVZ
Global epidemiology: worldwide estimates

- 1999 burden of disease:
  - Number of cases worldwide: 48.5 millions
  - Deaths worldwide: 295,000

- Crowcroft NS, Stein C, Duclos P, Birmingham M.
  - How best to estimate the global burden of pertussis?
Where do the data come from?

• Statutory notification
  - Passive / active
• Sentinel surveillance
  - Passive / active
• Hospital discharge data
• Death statistics
Example: ECDC and AUS surveillance data


<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence / Coverage</th>
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<tr>
<td>Germany</td>
<td>6-20</td>
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<tr>
<td>Greece</td>
<td>&lt;0.1</td>
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<tr>
<td>Netherlands</td>
<td>14-44</td>
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<tr>
<td>Norway</td>
<td>68</td>
</tr>
<tr>
<td>Portugal</td>
<td>0.5</td>
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<tr>
<td>UK</td>
<td>1.7</td>
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<tr>
<td>Australia</td>
<td>172</td>
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Why the differences?

- Bacteria with changing virulence
- Different basic epidemiological parameters
- Data acquisition
- Public awareness
- Case definition
- Laboratory confirmation
- Vaccination history
- Vaccine coverage / Vaccine type(s)
Epidemiology of pertussis: Basics

Â *Bordetella pertussis*

ï Have the bacteria become more or less virulent?

ï Does this influence the epidemiology and vaccine effectiveness?
Epidemiology of pertussis: Basics

Å *Bordetella pertussis*

- Have the bacteria become more virulent?
  - The genome changes over time


- *Bordetella pertussis* strains circulating in Europe in 1999 to 2004 as determined by pulsed-field gel electrophoresis.

Epidemiology of pertussis: Basics

Â *Bordetella pertussis*

ï Have the bacteria become more virulent?
Â maybe yes

ï Marieke J Bart, Marjolein van Gent, Han GJ van der Heide, Jos Boekhorst, Peter Hermans, Julian Parkhill, and Frits R Mooi:

ï Comparative genomics of prevaccination and modern *Bordetella pertussis* strains

Epidemiology of pertussis: Basics

**Å Bordetella pertussis**

- Have the bacteria become more virulent? 
  - Maybe no

- Bouchez V, Brun D, Cantinelli T, Dore G, Njamkepo E, Guiso N.
  - First report and detailed characterization of B. pertussis isolates not expressing Pertussis Toxin or Pertactin
Epidemiology of pertussis: Basics

**Bordetella pertussis**

- Have the bacteria become more or less virulent?
- The bacteria change/adapt over time
- Does this influence the epidemiology and vaccine effectiveness?
- Until now: probably not
Epidemiology of pertussis: Basics

Minimal infectious dose:

- ~140 CFU
  - MacDonald H, MacDonald E
  - Experimental pertussis
  - J. Infect. Dis. 1933; 53:328
Epidemiology of pertussis: Basics

- Basic reproduction number: \((R_o)\)
- Usual assumption for a susceptible population:
  \(R_o \sim 12-17\)

- i.e.: Black AJ, McKane AJ.
- Stochasticity in staged models of epidemics: quantifying the dynamics of whooping cough.
Epidemiology of pertussis: Basics

Â Basic reproduction number: \( R_0 \)
Â EU countries based on mixing matrices
Â \( R_0 \sim 5-6 \)

ï Kretzschmar M, Teunis PF, Pebody RG.
ï Incidence and reproduction numbers of pertussis: estimates from serological and social contact data in five European countries.
Clinical Case Definitions of Pertussis

Clinical case definitions have been developed by the WHO and the CDC and the ECDC, but

- These are not universally applied so inter-country comparisons and global evaluations are difficult
- Many adolescent/adult cases may not comply with the WHO definition, which was designed for use in vaccine efficacy trials

WHO recommended case definition

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**Clinical case definition**
- A case diagnosed as pertussis by a physician
- or
  - A person with a cough lasting at least two weeks with at least one of the following symptoms:
    - Paroxysms (i.e. fits) of coughing
    - Inspiratory whooping
    - Post-tussive vomiting (i.e. vomiting immediately after coughing) without other apparent cause

**Criteria for laboratory confirmation**
- Isolation of *Bordetella pertussis* or
- Detection of genomic sequences by means of the polymerase chain reaction (PCR) or
- Positive paired serology

**Case classification**
- Clinically confirmed: A case that meets the clinical case definition but is not laboratory-confirmed
- Laboratory confirmed: A case that meets the clinical case definition and is laboratory-confirmed
Pertussis: Clinical Case Definitions

Å Sensitivity of clinical case definitions in an outbreak situation (culture positive cases):

- Any cough: 98%
- Cough >14 days: 84%
- Paroxysmal cough >7 days: 54%

Case Definition of Pertussis for Surveillance Purposes

Paroxysmal cough

- 0-6 mo
- 7 mo-9 y
- ≥ 10 y

- Paroxysmal cough PLUS
  - Whoop OR
  - Apnea OR
  - Post-tussive emesis OR
  - Cyanosis OR
  - Seizure

- Non-productive, paroxysmal cough of >2 weeks duration without fever PLUS
  - Whoop OR
  - Apnea OR
  - Post-tussive emesis OR
  - Worsening of symptoms at night

- Paroxysmal cough without fever PLUS
  - Whoop OR
  - Apnea OR
  - Post-tussive emesis
Diagnosis of *B.pertussis* infections: When do patients seek medical attention?

Å Median days of coughing before visit:

- Schoolchildren, aged 7-12 years:
  Å 7.8 days (PCR positives)
- Adolescents, aged 12-18 years:
  Å 12.5 days (PCR positives)
- Adults, aged 18-81 years:
  Å 17.3 days (PCR positives)

Riffelmann et al., in preparation
Clinical symptoms and laboratory tests
(Courtesy Dr. Nicole Guiso, Institut Pasteur, Paris)

<table>
<thead>
<tr>
<th>Incubation (days)</th>
<th>DNA detectable</th>
<th>Antibodies detectable</th>
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<tbody>
<tr>
<td>7 to 10d</td>
<td>catarrhal</td>
<td>convalescent</td>
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<tr>
<td>1 to 2 weeks</td>
<td>paroxysmal</td>
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<tr>
<td>3 to 6 weeks</td>
<td>atypical cough</td>
<td></td>
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<tr>
<td></td>
<td>rhinorrhea</td>
<td></td>
</tr>
<tr>
<td>1 to 12 weeks</td>
<td>cyanosis</td>
<td></td>
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<tr>
<td></td>
<td>lymphocytosis</td>
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<tr>
<td></td>
<td>vomiting whoops</td>
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Surveillance of *B. pertussis* Infections: What Do You Want to Know?

- All infections?
- Symptomatic infections?
- Infections with medical resource use?
- Severe infections?
- Infections in infants?
- Infections in other specific groups?
- Changes in vaccine effectiveness?
GPI Recommendations for Pertussis Surveillance

Å Pertussis is most threatening in infants, so the aim should primarily be to prevent disease in infants

Å In countries with no or very limited programs, pertussis surveillance should start with infants and young children

Å Interventions can be measured by reduction of disease in infants and children
Methods for Surveillance

- Sentinel studies
  - Easier to manage than countrywide diagnosis programs
  - Often most cost-effective solution
- A well-trained local reference lab is critical
- Recording infants hospitalized for pertussis is easiest and most important way to monitor pertussis disease
- Pertussis surveillance data can be generated by using the infrastructure already in place to monitor other diseases
Which Surveillance System to Detect Pertussis?

Many effective surveillance systems worldwide including:

- Switzerland (SENTINELLA) with 200 sentinel offices (mainly GPs). Suspected cases are confirmed by free PCR. Underreporting, as PCR is only used on clinically suspected cases.

- France (Renacoq) with 43 hospitals. Confirmation predominantly by culture and PCR.

- Sweden: Most complete system. Has followed cohorts from birth.
Which Surveillance System to Detect Pertussis?

Many effective surveillance systems worldwide including:

- Canada (IMPACT) - Active monitoring system, covers 90% of tertiary care pediatric beds, 50% of the Canadian pediatric population, covering ages 0–16 years

- The Netherlands - Serological diagnostic database (RIVM), and a GP sentinel surveillance. Large serosurveys carried out in 1995-6 and 2006-7

- Massachusetts, USA - Recognized as the best system in the USA. Uses specific single-serum PT ELISA
Which Surveillance System to Detect Pertussis?

Å The best (ideal) surveillance system is probably following total birth cohorts, as Sweden has done

   i Not necessary to do this everywhere, as results are likely to be similar worldwide where vaccination programs are in place

Å The best surveillance system depends on what questions need to be answered. Different countries may want to know different things

Å Order of importance is: Infant > childhood > adults. What you investigate depends on where you are on the continuum
The Effect of PCR on Pertussis Epidemiology
Example: Minnesota

Source: Minnesota Dept of Health
Effect of Serology on Pertussis Epidemiology
Example: Massachusetts; cut-off: ~200 IU/ml

MA population of total US 2%
MA notified cases of total US 23%
Adolescents (1998), cases per 100,000 per year
   Notified cases (CDC) 4
   Massachusetts 71
Adults, (2003), cases per 100,000 per year
   Notified cases (CDC) 0.8
   Massachusetts 11

Use of Population-Based Seroepidemiology: European Sero-epidemiology Network (ESEN)

Population: 20–65 years old, sampled in EU countries
% of cohort with IgG anti-PT ≥ 125 EU/ml:

- The Netherlands: 1.4%
- Finland: 1.5%
- Germany (former GDR): 1.7%
- France: 2.3%
- Germany (former FRG): 3.0%
- UK: 5.0%
- Italy: 6.5%

Culture / PCR positive cases from paediatricians in the Krefeld region

![PCR chart]

Labor:Medizin Krefeld
MVZ

5th International Vaccinology Workshop
% of blood donors with presumptive recent contact to pertussis
cut-off: IgG-anti-PT >100 IU/ml
Application of seroepidemiology

Tracking trends of presumptive recent pertussis infection (cut-off: 62.5 IU/ml)

- Proportion of 5-9 year old decreased
- Proportion of 35-49 year old increased

Quinn HE, McIntyre PB, Backhouse JL, Brotherton J, Gilbert GL

The utility of seroepidemiology for tracking trends in pertussis infection

Application of seroepidemiology

- Estimating recent contact to pertussis:
- Cut-off 40 IU/ml
  - Ages 6-8 years: 9.1%
  - Ages 12-20 years: 14.6%

- Wang CQ, Zhu QR.
- Seroprevalence of Bordetella pertussis antibody in children and adolescents in China.
Application of seroepidemiology

- Cut-offs used for estimating a presumptive recent contact to pertussis:

  - MA (diagnosis, surveillance): ~200 IU/ml
  - EU (surveillance): 125 IU/ml
  - D (surveillance): 100 IU/ml
  - AUS (surveillance): 62.5 IU/ml
  - CHN (surveillance): 40 IU/ml
Mortality data

Â WHO estimates: 295,000 deaths a year

Â Case-fatality ratio in infants (WHO):
   ï up to 4.0%

Â Case fatality ratio in the EUVacNet data:
   ï 0.0 ï 2.1%

Â West Africa (Senegal) before vaccination
   ï 2.8%
Surveillance of Pertussis: What is needed?

Å Education, both of clinicians and the general public, is central to improving control of pertussis
Å An updated clinical definition of pertussis is required
   í Current CDC and WHO definitions are focused on detecting childhood cases
Å Correct sampling of nasopharyngeal samples for PCR is important
Å In-house and commercial ELISA tests should quantify IgG anti-PT
Epidemiology of pertussis: Summary I

Â *Bordetella pertussis* continues to circulate worldwide
Â Pertussis remains the least well controlled vaccine-preventable disease
Â The awareness of pertussis being a disease of all ages is lacking in many countries
Â Newborns and young infants bear the brunt of morbidity and mortality
Epidemiology of pertussis: Summary II

- Changes in the bacterial genome are observed
- Infection and immunization only confer protection for some time
- Standardized diagnostic procedures (PCR and IgG-anti-PT serology) are available
- Various surveillance systems with different goals are instituted in most countries
- Data from different epidemiological surveillance systems are difficult to be compared head-to-head
- Time series of data from unaltered systems in one jurisdiction can deliver information about trends in incidence and age distribution