2. Randomized serum specimens

At eight time points (three-month intervals) a subset of 100 individuals who received each vaccine (DTaP, DTP and DT) was randomly selected (day of second dose; day of third dose; one month after third dose; three, six and nine months after third dose; day of fourth dose; one, three and six months after fourth dose). Randomization had been performed before start of enrolment.

Goal: to construct antibody kinetic curves for each vaccination group so that serological diagnosis of pertussis infection can be made by a single serum at the time of an illness in a study subject.

3. Results pending

Further ancillary studies
- Household contact sub-study: Integrated in the study protocol; results pending
- Serologic correlate of protection: Calculations will be based on seven months and 19 months-serology specimens and/or randomized serum specimens before illness and the respective kinetic curves.
- Efficacy using secondary case definitions: Results pending

ACKNOWLEDGEMENT

We acknowledge the contributions of the Pertussis Vaccine Study Group which comprises study physicians in 227 private practices who enrolled and followed all study subjects. We also appreciate the help of the Lederle-Praxis and Quintiles Ltd. staff and the Study Advisory Board. In addition we would like to thank our laboratory technicians, Mrs. Carmen Lorenz and Regina Pollak and the study secretaries Mrs. Ingeborg Boatey, Gerlind Baierlacher and Monika Reissinger for their assistance.
Vaccination schedule: Vaccines were given at two, four and six months of age together with BCG (2 mo) and IPV (two, four and six months). No booster dose of pertussis vaccine, nor of any other vaccine.

Dates of study:
- Start of enrolment: May 2, 1990
- End of enrolment: July 7, 1994
- Last case considered: December 31, 1994

Case definition:
- Clinical syndrome: 21 days or more of any cough
- Confirmation criteria: culture or serology or epidemiological link within 28 days with a culture-confirmed case
- For relative efficacy (primary objective): culture or serology or contact with a culture-positive case
- For absolute efficacy (secondary objective): culture or serology or child-positive PCR plus culture-confirmed contact.

Case detection and investigation:
- Surveillance method: active surveillance by weekly home visits of each compound (residential unit) of the study area by field worker with subsequent weekly epidemiological and clinical follow-up of every coughing case by a physician. Proximity investigation of other compounds by field physicians during investigation.
- NOTE: Population under surveillance was not restricted to vaccinated children, but considered all children under 15 years old.
- Trigger symptom for investigation: eight days or more of any cough.

Case ascertainment:
- Clinical syndrome: Clinical history and weekly examination by a physician until the end of the cough;
- Confirmation criteria:
- Culture: naso-pharyngeal aspirate collected through suction catheter in both nostrils. Second aspirate collected one week after the first one if cough continuing;
- Serology:
- Specimen collection: Specimen 1 and Specimen 2 capillary blood samples (600 ul): Specimen 1 taken at first visit and Specimen 2 six-to-eight weeks after onset of cough.
- Criteria: ELISA PT ≥ two-fold rise in IgG
  Elisa FHA ≥ two-fold rise in IgG
  Specimen 2 titre had to be ≥ 4 Minimum Level of Detection (MLD)
  IgG PT: MLD = 2; IgG FHA: MLD = 2.5
- Standardization: local reference serum titred versus FDA serum
- Other lab testing: PCR for Bordetella pertussis for all study children (if cough ≥ eight days).

Efficacy:

Primary objective: Relative efficacy
Frequency measure of disease: Incidence density
Start of follow-up for VE analysis: 28 days after dose three
Mean duration of follow-up: 22 months
Number included in efficacy analysis: 3619
by arm
<table>
<thead>
<tr>
<th></th>
<th>DTaP</th>
<th>DTwP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1847</td>
<td>1772</td>
<td></td>
</tr>
</tbody>
</table>

Observed incidence (cases/100 child-years)
by severity
<table>
<thead>
<tr>
<th></th>
<th>DTaP</th>
<th>DTwP</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 21 days any cough</td>
<td>6.20</td>
<td>3.90</td>
</tr>
<tr>
<td>≥ 21 days any cough</td>
<td>2.91</td>
<td>0.92</td>
</tr>
<tr>
<td>and at least one day paroxysmal cough</td>
<td>1.28</td>
<td>0.51</td>
</tr>
<tr>
<td>≥ 21 days of paroxysmal cough and whoops</td>
<td>0.59</td>
<td>0.22</td>
</tr>
</tbody>
</table>

RR (AC/WC) 95% CI
0.92 3.18 (2.10-4.81)
0.51 2.54 (1.43-4.51)
0.22 2.69 (1.13-6.39)

Secondary objective: Absolute efficacy
Frequency measure of disease secondary attack rates (household case contact study)
Note: For inclusion, case confirmation by epidemiologic linkage required positive PCR validation of the case child.
Start of follow-up for VE analysis: 28 days after dose three for three-dose recipients, eight months for 0 dose children.
Number included in absolute efficacy analysis:
by group
<table>
<thead>
<tr>
<th></th>
<th>DTaP</th>
<th>DTwP</th>
</tr>
</thead>
<tbody>
<tr>
<td>108*</td>
<td>159</td>
<td></td>
</tr>
</tbody>
</table>

* Data differ from those actually presented at the Symposium due to the application of the requirement for permanent residency in the area, as for vaccinated children.

Observed attack rate per group
<table>
<thead>
<tr>
<th></th>
<th>DTaP</th>
<th>DTwP</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 21 days any cough</td>
<td>0.53</td>
<td>0.34</td>
</tr>
<tr>
<td>≥ 21 days of paroxysmal cough</td>
<td>0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>and whoops</td>
<td>0.04</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Absolute vaccine efficacy per group
<table>
<thead>
<tr>
<th></th>
<th>DTaP</th>
<th>DTwP</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (95% CI)</td>
<td>53 (23-71)</td>
<td>74 (55-85)</td>
</tr>
<tr>
<td>21 days and cough</td>
<td>85 (66-93)</td>
<td>96 (80-99)</td>
</tr>
</tbody>
</table>

Safety:
Surveillance: severe adverse reactions observed by field workers during two weekly visits following vaccination; each possible adverse event investigated at home by field physicians.
Number included in safety analysis: n=4821
by dose
<table>
<thead>
<tr>
<th></th>
<th>DTaP</th>
<th>DTwP</th>
</tr>
</thead>
<tbody>
<tr>
<td>6661</td>
<td>6595</td>
<td></td>
</tr>
</tbody>
</table>

* Data differ from those actually presented at the Symposium due to the application of the requirement for permanent residency in the area, as for vaccinated children.
Efficacy of a Three-Component Acellular Pertussis Vaccine (DTaP) in Early Childhood after Household Exposure to «Typical» (WHO-Defined) Pertussis

H.-J. Schmitt
Kinderklinik der Johannes Gutenberg-Universität, Mainz, Germany

Study design: Prospective, blinded household contact study.

Ethical review: Approved by the various local committees responsible. (Ethikkommissionen der Landesärztekammern)

Population: Infants in six areas in (former) West Germany with a high incidence of pertussis.

- Inclusion criteria for vaccination protocol (APV39)
  - written informed consent of legal guardians
  - good clinical condition
  - age 12-16 weeks
  - no active, chronic disease
  - no immunosuppression

- Exclusion criteria for vaccination protocol
  - currently active disease
  - previous D, T or P vaccination
  - severe adverse event following any previous dose of study vaccine

- Inclusion criteria for household contact study (APV50)
  - index case with WHO-defined (typical) pertussis in household
  - household contact of this index case had to be in the 6-47 month age bracket
  - at least four weeks after administration of last (third) DTaP-dose to contact
  - written informed consent of legal guardians

- Exclusion criteria for household contact study
  - booster dose (fourth dose DTaP) given
  - exclusion of co-primary and tertiary cases (primary analysis)

- Number of children vaccinated with DTaP
  22,505

- Number of evaluable secondary contacts
  for all case definitions of pertussis: 412;
  after exclusion of co-primary and tertiary cases analysing WHO-defined pertussis: 360

Sites: 123 paediatricians in six study areas of (former) West Germany

Vaccines: three-component (PT, FHA, pertactin) DTaP (SmithKline Beecham Biologicals, Rixensart); DT (Behringwerke, Marburg); DTwP (Behringwerke, Marburg)

Immunogenicity:

Sample size: D'TaP; n=57; D'TwP; n=39
Collection schedule: pre, post2 and one month post-dose three
GMT (% responders) by arm and antigen
responder = Specimen 2 ≥ 24 times Specimen 1

<table>
<thead>
<tr>
<th>ELISA IU IgG FHA</th>
<th>CHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP</td>
<td></td>
</tr>
<tr>
<td>38.0 (95)</td>
<td>46.7 (94.7)</td>
</tr>
<tr>
<td>DTwP</td>
<td></td>
</tr>
<tr>
<td>22.1 (92.9)</td>
<td>88.1 (92.7)</td>
</tr>
</tbody>
</table>

Further ancillary studies:

- Household transmission: analysis in progress;
- Duration of protection: analysis in progress;
- Serologic correlate of protection: not performed;
- One and two doses vaccine efficacy: analysis in progress.

Events within 48 hours:
- Rectal temperature > 40°C 0 0
- High-pitched or persistent crying (≥ three hours) 0 8
- HHE/collapse 0 0
- Generalized cyanosis 0 0
- Seizure 2 2
- Startle reactions 9 22
Pertussis Vaccine Trials

Editors: F. Brown, D. Greco, P. Mastrantonio, S. Salmaso, S. Wassilak
This book contains the proceedings of the International Symposium on Pertussis Vaccine Trials, held in Rome in October 1995. The meeting was organized following the almost simultaneous release of the results of five clinical trials and two other clinical studies of acellular pertussis vaccines. These large, multi-centre studies, conducted independently and over several years, explored the efficacy, safety, and immunogenicity of several acellular pertussis vaccines, comparing them with whole-cell vaccine and/or placebo. In addition, the book covers other major topics concerning the use of acellular and whole-cell pertussis vaccines, including basic biological and epidemiological questions, various considerations in interpreting the studies' results, regulatory issues, and worldwide perspectives on the expanded use of acellular vaccines.

Bringing together the world's leading experts in this field of research and summarizing all the major aspects of pertussis prevention and control, this book is a vital reference for paediatricians, public health officials, microbiologists, immunologists, epidemiologists and all biomedical scientists who produce or regulate the use of vaccines.
Developments in Biological Standardization

Vol. 89

This series Dev Biol Stand begins with Vol. 23 and is the continuation of both "PROGRESS in Immunobiological Standardization, Vols 1-5" and "SYMPOSIA SERIES in Immunobiological Standardization, Vols 1-22".

Series Editor
Fred Brown
Plum Island Animal Disease Center
Greenport NY, USA

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Pertussis Vaccine Trials

Istituto Superiore di Sanità, Rome, Italy
October 30-November 1, 1995

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International Association of Biological Standardization (IABS)

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Developments in Biological Standardization

Organizations of the Symposium

Session I: Pertussis: Confronting the Problem
Chairpersons: G. Vicari and J. La Montagne

Session II: Trial Synopses
Chairpersons: G. Curnin and P.H. Lambert

Session III: Vaccine Safety Overview
Chairpersons: H.H. Bogaerts and P. Begue
Rapporteur: B.M. Assael

Session IV: Vaccine Efficacy
Chairpersons: P. Olin and J.D. Cherry
Rapporteur: S.G.F. Wassilak and P.E.M. Fine

Session V: Serological Assays and Confirmation
Chairpersons: S. Plotkin and C. Manclark
Rapporteur: E. Griffiths

Session VI (part 1): Microbiology and Immune Response
Chairpersons: C.A. Hellman and H. Hallander
Rapporteur: D.L. Burns

Session VI (part 2): Microbiology and Immune Response
Chairpersons: R. Rappuoli and K. Edwards
Rapporteur: B. Meade

Session VII: Future Strategies
Chairpersons: S. Ditmann and L. Barreto
Rapporteur: D.L. Burns

Roundtable Discussion on Regulatory and Standardization Issues
Roundtable Discussion on the Application of Trial Results to Public Health
Roundtable Discussion on Future Research

Summary and Conclusions
Rapporteur: W.A. Orenstein
Istituto Superiore di Sanità, Rome, Italy

September 1992

Proceedings of the First International Symposium on Pertussis Vaccine Trials

Introduction

As Director of the Istituto Superiore di Sanità, it is my privilege to welcome you to the International Symposium on Pertussis Vaccine Trials. The Minister of Health for Italy, Professor Elio Guzzanti, who unfortunately could not be with us this morning, has asked me to convey his best wishes for a highly successful meeting.

As we all know, vaccines represent one of the great medical achievements of the past 100 years. However, progressing from basic scientific research to providing the public with safe and effective products requires considerable time and effort; this has been termed by my co-chairperson Dr. La Montagne as "the vaccine continuum." In many parts of the world, indirect markers of efficacy, such as immunogenicity, have been sufficient for authorizing the mass use of vaccines. However, efficacy results from controlled studies and a very low incidence of side-effects which are increasingly being considered as fundamental prerequisites for the mass licensing of vaccines. Documented efficacy has been particularly needed for bacterial vaccines, such as pertussis, which lack such clear serological correlates. Large-scale safety and efficacy are difficult to determine for some vaccines, unless a collaborative effort is made, such as joint ventures involving research institutions, governmental organizations responsible for public health, and industry. In fact, these are the people present at this meeting.

It is my strong belief that these three days in Rome will represent a fundamental chapter in the history of pertussis vaccines. We are extremely fortunate that seven trials and other studies for evaluating efficacy have been concluded this year. This has provided us with an excellent opportunity for meeting and discussing in depth the large body of knowledge obtained. Given that the results of nearly all these studies have already been made public, this will somewhat alleviate the pressure of presenting results for the first time and perhaps encourage us to speak even more freely. Specifically, the results of the studies reveal that the trials have confirmed their main hypotheses: that is, new acellular vaccines overall are at least as efficacious as the whole-cell vaccines, and are much safer.

The programme for this Symposium does have some limitations: not all relevant issues will be given as much time as they perhaps deserve or some may not be covered at all. Nonetheless, I am sure that you will all take full advantage of the three days dedicated to an issue that elsewhere is limited to short seminars or round tables. The most important characteristic of the Symposium will be the open and frank discussion among scientists dedicated to vaccination, and we encourage all participants to take an active part in the discussion.

I understand that the session chairpersons have been assigned quite a difficult task, and we are grateful to them for having accepted this challenge. The session rapporteurs have also been provided with a rather heavy workload. Though the participants of the Symposium are represented by technical persons working in this field, many others who are not present will be interested in the pertussis vaccines and many would like to know what has been discussed. Thus the proceedings will be fundamental: I am grateful to the Symposium faculty for having accepted to put in writing their presentation and discussion and to the Editor of "Developments in Biological Standardization" for having provided us with the opportunity to publish a special volume.

This Symposium is the result of a co-ordinated co-sponsorship. I would like to thank the organizations involved for their faith in the Istituto Superiore di Sanità in organizing this complicated endeavour and for the generous financial support that has made the symposium possible. I also express my gratitude to the many individuals who contributed to the organization of this Symposium, especially the Organizing Committee and the staff of the Istituto Superiore di Sanità. Finally, I would like to thank all participants in general for their dedication to this endeavour. I wish you the greatest success.

Professor G. Vicari
Director, ISS
Preface from the Organizing Committee

The field of pertussis vaccine research witnessed, within a year, the conclusion of unprecedented family of efficacy studies. Seven clinical trials and other studies of vaccine efficacy have been conducted since 1990; these ended in 1994-95; an eighth remains underway while the results of its safety evaluation have been made available. For this reason, the Istituto Superiore di Sanità hosted the investigators of these eight studies at the International Symposium on Pertussis Vaccine Trials in Rome on October 30 - November 1, 1995. Over 450 persons attended, including scientists in academia, government and industry interested in the outcome of the studies.

Three of these studies were conducted in Germany and three in Sweden; one each was conducted in Italy and Senegal. All were directed by European investigators. For the Symposium, we have designated the various studies by the country or city of the principal investigator; comparison among the various studies is limited, but some interpretations can be made.

The introductory session of the Symposium reviewed the background for pertussis vaccination policies and research approaches. Session II consisted of a concise presentation of each clinical study by the principal investigator, having prepared trial synopses in advance for Symposium participants; we present here those concise synopses. Session III reviewed the data on vaccine safety accumulated in the eight studies. Session IV examined in detail the determinants and results of the efficacy estimates from the seven studies. Sessions V and VI reviewed the laboratory issues related to pertussis diagnosis in the studies and the immune responses to pertussis vaccines. For Sessions III to VI, some of the speakers have chosen to submit extended abstracts to summarize their presentations. Session VII comprised a series of round tables on the regulatory, public health and research aspects of the use of acellular pertussis vaccines; some of these viewpoints have been detailed by the presenter in these proceedings.

Much of the detailed information obtained from each of the various studies was shared in advance with the speakers to help in the preparation of their presentations. We are extremely grateful for the rich exchange of information which occurred before the meeting, the excellent presentations, the full discussion during the sessions and the camaraderie we felt while hosting this event. Chairpersons were responsible for directing each session, including adding unscheduled speakers, and facilitating discussion. The Symposium was structured to allow a great deal of discussion and the Rapporteurs have done an excellent job in summarizing these discussions. We wish to thank all the Chairmen and Rapporteurs for their assistance. Dr. Geoffrey Schild helped coordinate the scientific and organizing committees.

We wish to thank all the sponsoring agencies and manufacturers and the other members of the Scientific and Organizing Committees. We thank the staff of the Infectious Disease Unit at the Istituto Superiore di Sanità – in particular, Eva Appelgreen, Mark Kanife, Antonella Lattanzi and Christine Locascio – and the staff of the Development of Biological Standardization for their invaluable assistance.

Donato Greco
Steven Wassilak
Adverse Reactions of a Pertussis Toxoid Vaccine in a Double-Blind Placebo-Controlled Trial.
J. Taranger, B. Trollfors, N. Knutsson

Minor Adverse Events in a Comparative Efficacy Trial in Germany in Infants Receiving Either the Lederle/Takeda Acellular Pertussis Component DTP (DTaP) Vaccine, the Lederle Whole-Cell Component DTP (DTP) or DT Vaccine
S. Schmitt-Grohé, K. Siehr, J.D. Cherry, U. Heininger, M.A. Ueberall, S. Lausswey, T. Eckhardt and the Pertussis Vaccine Study Group

Rapporteur's Summary
B.M. Assael

Session IV

Vaccine Efficacy
Chairpersons: P. Olin and J.D. Cherry
Rapporteurs: S.G.F. Wassilak, P. Fine

Implications of Different Study Designs for the Evaluation of Acellular Pertussis Vaccines
P.E.M. Fine

Case Definitions

Preparation and Composition of Acellular Pertussis Vaccines. Consideration of Potential Effects on Vaccine Efficacy
E.L. Hewlett

Absolute Efficacy of Acellular Pertussis Vaccines in Household Settings
J. Storaes, L. Gustafsson

Estimation of Pertussis Vaccine Efficacy in the Presence of Covariates in Three Randomized Trials
W.C. Blackwelder, M.J. VanRaden, M.A. Deloria

Absolute and Relative Efficacy of Whole-Cell Vaccines
H.S. Jafari

The Effectiveness of Whole-Cell Pertussis Vaccines
S.A. Plotkin

Factors Influencing the Analysis of Secondary Prevention of Pertussis

The Role of Bordetella pertussis Infections in Adults in the Epidemiology of Pertussis
J.D. Cherry

Rapporteurs' Summary
S.G.F. Wassilak, P. Fine

Session V

Serological Assays and Confirmation
Chairpersons: S. Plotkin and C. Mainclark
Rapporteur: E. Griffiths

A Comparison of Enzyme Immuno-Assays Used to Measure Serum Antibodies to Components of Bordetella pertussis
F. Lynn, G.F. Reed, B.D. Meade

Diagnostic Pertussis Serology in the Recent Clinical Efficacy Studies of Acellular Vaccines
H.O. Hallander

Serological Responses to Infection with B. pertussis
A. Giammanco, S. Tozzi, M. Genovese, G. Mangiaracina, G. Giammanco, A. Chiarini

Differences by Antigen in Seroconversion: Sensitivity, Specificity and Bias in the Serological Confirmation of Pertussis
S.G.F. Wassilak, A. Anemona, M. Giuliano, A. Giammanco

Rapporteur's Summary
E. Griffiths

Session VI, Part 1

Microbiology and Immune Response
Chairpersons: C.A. Heilman and H. Hallander
Rapporteur: D.L. Burns

Isolation, Identification and Characterization of Bordetella pertussis
N. Guiso

Bordetella pertussis Serotype of Clinical Isolates in Sweden During 1970-1995 and Influence of Vaccine Efficacy Studies
M. Tiru, P. Askold, M. Granström, H. Hallander

Diagnostic Polymerase Chain Reaction
E. Reizenstein

Bordetella parapertussis Infections
P. Mastrantonio, M. Giuliano, P. Stefanelli, G. De Marchi, G. Tabarini, M. Quarto, A. Moiraghi

Rapporteur's Summary
D.L. Burns

Session VI, Part 2

Microbiology and Immune Response
Chairpersons: R. Rappuoli and K. Edwards
Rapporteur: B. Meade

Comparison of Serological Results in the NIAID Multicenter Acellular Pertussis Trial with Recent Efficacy Trials
K.M. Edwards, M.D. Decker

Antibody Kinetics and Long-Term Seroprevalence in the Italian Clinical Trial of Acellular Pertussis Vaccines

Factors Influencing Antibody Responses to Acellular Pertussis Vaccines
B. Trollfors

Methods for Estimating Serological Correlates of Protection
G.R. Siber

Bordetella pertussis-Specific Th1/Th2 Cells Generated Following Respiratory Infection or Immunization with an Acellular Vaccine: Comparison of the T Cell Cytokine Profiles in Infants and Mice
M. Ryan, L. Gotheors, J. Storaes, K.H.G. Mills
Cell-Mediated Immunity after Pertussis Vaccination and after Natural Infection

307

F. Zepp, M. Knuff, P. Habermehl, H.J. Schmitt, C. Meyer, R. Clemens, M. Slaoui

Acellular Vaccines Induce Cell-Mediated Immunity to Bordetella pertussis Antigens in Infants

315

C.M. Ausiello, P. Urbani, A. La Sala, R. Lande, A. Piscitelli, A. Cassone

Examination of Similarities between Diphtheria and Pertussis and their Toxoids Provide Insight into Vaccine-Induced Protection to Bordetella pertussis

321

R. Schneerson, J.B. Robbins, J. Taranger, T. Lagerard, B. Trollfors

Japanese Experience with 60 Million Doses of Acellular Pertussis Vaccines

327

H. Sato

Epidemiology of Pertussis and Use of Acellular Pertussis Vaccines in Japan

331

H. Kuno-Sakai, M. Kimura

Rapporteur’s Summary

333

B. Meade

Session VII

Future Strategies

Chairpersons: S. Dittmann and L. Barreto
Rapporteur: D. Burns

Roundtable Discussion on Regulatory and Standardization Issues

339

Regulatory Issues Concerning Pertussis Vaccines

341

M. Tira

A Consideration of Control Requirements for Acellular Pertussis Vaccines

343

M.J. Corbel, D.K.L. Xing

Regulatory and Standardization Issues

349

R. Winsnes

Rapporteur’s Summary

351

D.L. Burns

Roundtable Discussion on the Application of Trial Results to Public Health

353

Public Health Application of Acellular Pertussis Vaccines

355

S.C. Hadler, W.A. Orenstein

Acellular Pertussis Vaccines: The Next Step

363

S.A. Halperin

Public Health Implications: United Kingdom

367

E. Miller

Rapporteur’s Summary

369

D.L. Burns

Roundtable Discussion on Future Research

371

Safety of Acellular Pertussis Vaccine: Follow-up Studies

373

R.T. Chen

Issues Regarding Future Research on Pertussis Vaccines

377

D.L. Burns

Are Serological Responses to Acellular Pertussis Antigens Sufficient Criteria to Ensure that New Combination Vaccines are Effective for Prevention of Disease?

379

D.M. Granoff, R. Rappuoli

Rapporteur’s Summary

381

D.L. Burns

Some Thoughts for Future Pertussis Research in Europe

M. Pletschette

Rapporteur’s Summary

D.L. Burns

Summary and Conclusions

Rapporteur’s Summary of the Symposium

W.A. Orenstein