PERISCOPE: road towards effective control of pertussis

*The PERISCOPE Consortium**

The resurgence and changing epidemiology of pertussis in high-income countries, the high infant mortality caused by pertussis in low-income countries, and the increasing morbidity in all age groups worldwide call for a concerted effort to both improve the current vaccines and develop new vaccines and vaccination strategies against pertussis. In this Personal View, we identify several key obstacles on the path to developing a durable solution for global control of pertussis. To systematically address these obstacles, the PERtussIS Correlates Of Protection Europe (PERISCOPE) Consortium was established in March, 2016. The objectives of this consortium are to increase scientific understanding of immunity to pertussis in humans induced by vaccines and infections, to identify biomarkers of protective immunity, and to generate technologies and infrastructure for the future development of improved pertussis vaccines. By working towards the accelerated licensure and implementation of novel, well tolerated, and effective pertussis vaccines, we hope to strengthen and stimulate further collaboration and transparency between the key stakeholders, including the public, the scientific community, public health institutes, regulatory authorities, and vaccine manufacturers.

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*Members listed at the end of the paper

Correspondence to:
Dr Dimitri A Diavatopoulos, Radboud University Medical Center, Radboud Institute for Molecular Life Sciences, Department of Laboratory Medicine, 6525 GA Nijmegen, Netherlands
dimitri.diavatopoulos@radboudumc.nl

Introduction

Whole-cell pertussis (wP) vaccines have been a cornerstone of national immunisation programmes since the 1940s. Nowadays, most low-income and middle-income countries continue to use wP vaccines, whereas in high-income and many middle-income countries the acellular pertussis (aP) vaccines, with a more favourable reactogenicity profile, have nearly completely replaced the wP vaccines since the 1990s. Unfortunately, despite nearly 70 years of universal childhood vaccination, pertussis has proven difficult to control. The disease is an important cause of infant mortality in low-income countries,[1] and is associated with considerable morbidity in all age groups worldwide. Although combined diphtheria-tetanus-pertussis (DTaP) vaccine coverage has improved greatly in many low-income countries after the Expanded Programme on Immunisation began in 1974, large numbers of individuals still do not have access to vaccination,[2] leaving vulnerable infants at risk of developing severe pertussis.

Pertussis incidence has also been steadily rising in the last two decades in several countries with high vaccination coverage.[1,3,4] The pattern of disease resurgence is particularly obvious in school-aged children, adolescents, and adults and is therefore thought to be related to waning of immunity with age.[5–9] Disease incidence is also increasing in infants too young to be protected by vaccination.[10,11] Although the effectiveness of the current pertussis vaccines in infants is well established, there is a need to investigate the underlying causes of disease resurgence in other at-risk populations, in particular concerning the differences between aP vaccines and wP vaccines in generating long-term protection. Defining immunological signatures linked to durable protection against pertussis disease, and identifying immunological correlates of protection against infection and transmission, will be important to inform and expedite the design, development, and regulatory approval of new vaccines.

What is the cause of the resurgence of pertussis?

The epidemiology of pertussis is not fully understood and many factors have likely contributed to the resurgence. Increased disease awareness and improved diagnostic tools such as PCR have increased the number of reported pertussis cases,[12] allowing identification of cases that previously remained undetected by traditional culture-based methods. Unfortunately, comparisons between countries are complicated by differences in surveillance systems, vaccination programmes, vaccine composition, and the use of molecular diagnostics in health-care systems. Epidemiological data have yielded evidence of more persistent protection after primary vaccination with wP vaccines than with aP vaccines,[7,8] suggesting that waning immunity contributes to the resurgence of pertussis in some countries with widespread use of aP vaccination. Currently available data, although often incomplete and mostly based on clinical observations without laboratory confirmation, show no evidence that pertussis poses a major health problem in low-income and middle-income countries that still use wPs,[13–15] and the current WHO recommendation is for these countries to continue using wPs.[16]

Mathematical modelling of pertussis incidence and attack rates in the UK and the USA suggests that asymptomatic transmission in vaccinated populations may also contribute to resurgence.[17,18] The presence of high anti-pertussis toxin (PT) IgG has been used to indicate recent exposure in individuals vaccinated at least 1 year ago. In a large cross-sectional, population-based serosurveillance study in the Netherlands, a significant increase in high anti-PT IgG was found in individuals older than 9 years, increasing from 4·0% in 1995–96 to 9·3% in 2006–07,[19] supporting the hypothesis that there is significant circulation of pertussis, much of which goes undetected. Pertussis resurgence is not universal and the incidence of pertussis already increased in some countries before the switch to aP vaccines.[3,20] The resurgence of pertussis also implicates genetic changes in the bacterium that causes pertussis, *Bordetella pertussis*. Although there are still no studies demonstrating a direct causal relationship between newly emerging *B pertussis* lineages (eg, PtxP3 lineage) and vaccine effectiveness, the current hypothesis is that adaptation to

Panel: Definition of terms*

Bordetella pertussis
Gram-negative pathogenic coccobacillus of the genus *Bordetella*

Transmission
The successful transfer of *B pertussis* between individuals or by experimental inoculation—ie, demonstration of the presence of *B pertussis* in the nasopharynx (or lower airways) by PCR with primers specific for *B pertussis* at a given timepoint in the exposed individual. Transmission of *B pertussis* might lead to colonisation within a reasonable period of exposure (<4 weeks).

Colonisation
Demonstration of the presence of viable *B pertussis* in the nasopharynx (or lower airways—eg, on autopsy) by culture (replicating bacteria) at a given timepoint. Colonisation might lead to infection.

Carriage
Demonstration of colonisation at least at two different timepoints in the absence of infection, with a maximum interval of 4 weeks. The period of carriage is defined by the first and last demonstration of *B pertussis* colonisation.

Infection
The presence of *B pertussis* in the nasopharynx (or lower airways on autopsy) as demonstrated by culture or PCR with primers specific for *B pertussis* or serological criteria as defined by EU reference laboratories,[28] which causes damage and induces an immune response in the host. If the damage induced by *B pertussis* infection is significant, this will lead to a disease state (pertussis). Otherwise the infection might remain asymptomatic.

Pertussis (disease)
Pertussis (or whooping cough) is a disease defined by cough with or without paroxysms, whooping, or vomiting with convincing evidence of causation by *B pertussis* infection rather than any other explanation.

Correlate(s) of protection
A measurable profile of immune response(s) in an individual who resolved proven *B pertussis* infection or disease, or who was immunised against pertussis, which correlates with a specified state of protection when subsequently exposed to *B pertussis*. Ideally, the profile is measured before exposure, or after pertussis, or after the last dose of immunisation.

Immune profile
A measurable immunological indicator or a combination of measurable indicators that define the potential for protection against *B pertussis* colonisation, carriage, or infection in an individual who does not currently have clinically apparent pertussis or is colonised by *B pertussis*. Indicators may include specific cells, molecules, genes, or gene products, including antibodies, cytokines, and metabolites. Indicators may be transiently measurable, such as gene transcription shortly after vaccination, or may be measurable over a longer duration of time, like serum antibodies.

Correlate of protection against transmission
Immune profile that correlates with prevention of *B pertussis* transmission when exposed to *B pertussis*.

Correlate of protection against colonisation and carriage
Immune profile that correlates with prevention of *B pertussis* colonisation when exposed to *B pertussis*. If colonisation cannot be prevented but on further testing within a short period of time (few days) *B pertussis* colonisation is not detected anymore, at least carriage was prevented.

Correlate of protection against infection
Immune profile that correlates with prevention of *B pertussis* infection when exposed to *B pertussis*.

Correlate of protection against pertussis (disease)
Immune profile that correlates with prevention of pertussis or reduction of severity of pertussis when exposed to *B pertussis*.

*Result of consensus finding among PERISCOPE investigators based on relevant publications.[25-30]

vaccine-mediated selective pressure has resulted in strains with increased fitness.[21,22] A development in the last decade is the emergence of *B pertussis* strains that no longer express one or more of the vaccine antigens. Pertactin-deficient strains in particular have been described to expand in several countries using aP vaccines, with prevalence reaching nearly 100% in some parts of the USA.[23,24]

Which obstacles need to be overcome?

Vaccination continues to play a pivotal part in preventing pertussis-related morbidity and mortality. Nonetheless, the indications of differences between aP and wP vaccines in their ability to induce persistent immunity in humans, and baboon studies showing that neither wP nor aP vaccines were able to prevent colonisation and transmission of *B pertussis*, have made clear that there are substantial gaps in the understanding of pertussis immunity. To find a systematic and durable solution to control pertussis, several obstacles need to be overcome. We have included a glossary of definitions for various aspects related to clinical endpoints and correlates of protection (panel), which may facilitate future discussions.

Following the large investment in the development of aP vaccines in the 1980s and 1990s, aP vaccines appeared to be effective and research and development expenditure was consequently reduced. Although precise numbers on local and global investments are difficult to obtain, the

number of yearly publications on pertussis noticeably dropped after the first DTaP licensure in 1996 and the subsequent implementation into childhood immunisation programmes (figure 1). An unwanted consequence of discontinuous funding was fragmentation of pertussis research, with no clear integration of the epidemiological, microbiological, immunological, and clinical aspects. Targeted funding is thus required to ensure integrated research efforts involving all the above areas can be undertaken. Additionally, advances in the field of vaccine research, particularly in immunology and systems biology, now offer new opportunities that will help to better understand the mechanism(s) of protective immunity against *B pertussis*.

Pertussis vaccines were licensed using clinical endpoints of protection against severe disease, according to a specific case definition, as demonstrated from large, complex, and expensive field trials conducted in the 1990s,[31] with different *B pertussis* populations compared to now. Although durable protection against disease is an essential aspect of all pertussis vaccines, new insights gained from findings from animal studies have raised the possibility of differences between individual vaccines with regards to their effect on other aspects of infection. For instance, studies in the baboon challenge model showed that although aP and wP vaccines prevent disease equally well, wP vaccines were more protective than aP vaccines against asymptomatic colonisation of the airways and concomitant transmission to a naive animal.[32] Therefore, developing methods to evaluate protection against asymptomatic infection and prevention of transmission in humans will be useful to gain a complete picture of the effectiveness of new vaccines against asymptomatic infection and controlling disease on a population basis.

A major hurdle for the development and licensure of new pertussis vaccines is the scarcity of established immunological correlates of protection in humans. Most aP vaccine efficacy studies reported immunogenicity data based on specific antibody concentrations in blood quantified by ELISA. Results from clinical studies show that high levels of anti-PT serum antibodies, and to a lesser extent pertactin and fimbriae, correlate with protection against typical pertussis.[30–32] This finding is supported by observations from antenatal immunisation studies that demonstrate the efficacy of aP vaccine-induced antibodies in preventing death and severe morbidity from pertussis in neonates.[33,34] Although pertussis-antibody ELISA is the only immunoassay approved by regulatory authorities and used in licensing of pertussis vaccines, there are doubts about its predictive value for long-term effectiveness. There are many potential immunological parameters that could contribute to protection and are potential correlates of protection. For instance, assessment of functional antibody activity might give a more relevant picture of the immunological responses induced by various pertussis

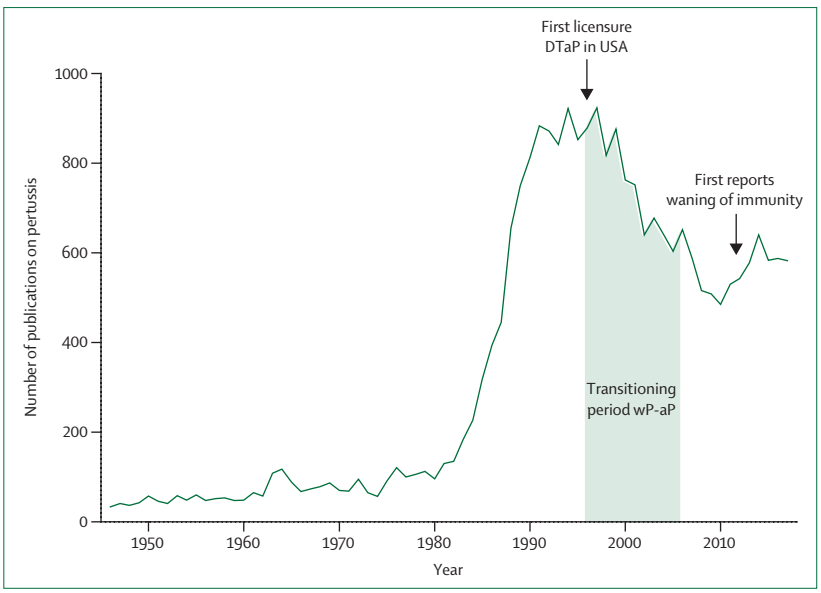

Figure 1: **Number of publications with pertussis in the title or abstract in 1945–2017**
DTaP=diphtheria-tetanus-pertussis. wP=whole-cell pertussis. aP=acellular pertussis.

vaccines, as reflected by reported differences in opsonising bactericidal antibodies[35] and bacterial adherence inhibiting antibodies[36] between wP and aP vaccines. Similarly, a study by Ross[37] identified key differences in memory T cells in mice, showing that cellular immunity is induced with a T-helper cell (Th)2 and Th17 bias by aP vaccines and a Th1 or Th17 bias by wP vaccines.[29,37] Although studies in children by van der Lee and coworkers[40] demonstrated a similar polarisation regarding Th1 and Th2 responses,[38–40] the role of Th17 responses in humans has not yet been fully characterised.[41] Standardised methods to assess functional antibodies or pertussis-specific cell-mediated immunity are not yet available. Although both aP and wP vaccines are effective in preventing pertussis in infants,[31,42] epidemiological studies have suggested that aP-induced protection wanes more rapidly than wP-induced protection.[7,8] Neither vaccination nor natural infection induces lifelong protection.[43,44] Efforts to prolong protection by administering additional booster aP vaccine doses to children and adolescents have unfortunately not been as successful as expected.[5,6] Primary vaccination with wP or aP vaccines generates differences in the quality, quantity, longevity, and so-called boostability of immunological memory.[45] This early imprinting of immunological memory by primary vaccination affects the subsequent response to booster vaccination.[40,46,47] By understanding the underlying mechanisms of memory imprinting, it might be possible to confer durable protection.

A key priority of pertussis control is to protect vulnerable neonates and young infants against severe pertussis from birth until they have been vaccinated. This is particularly important given the widespread circulation of *B pertussis*

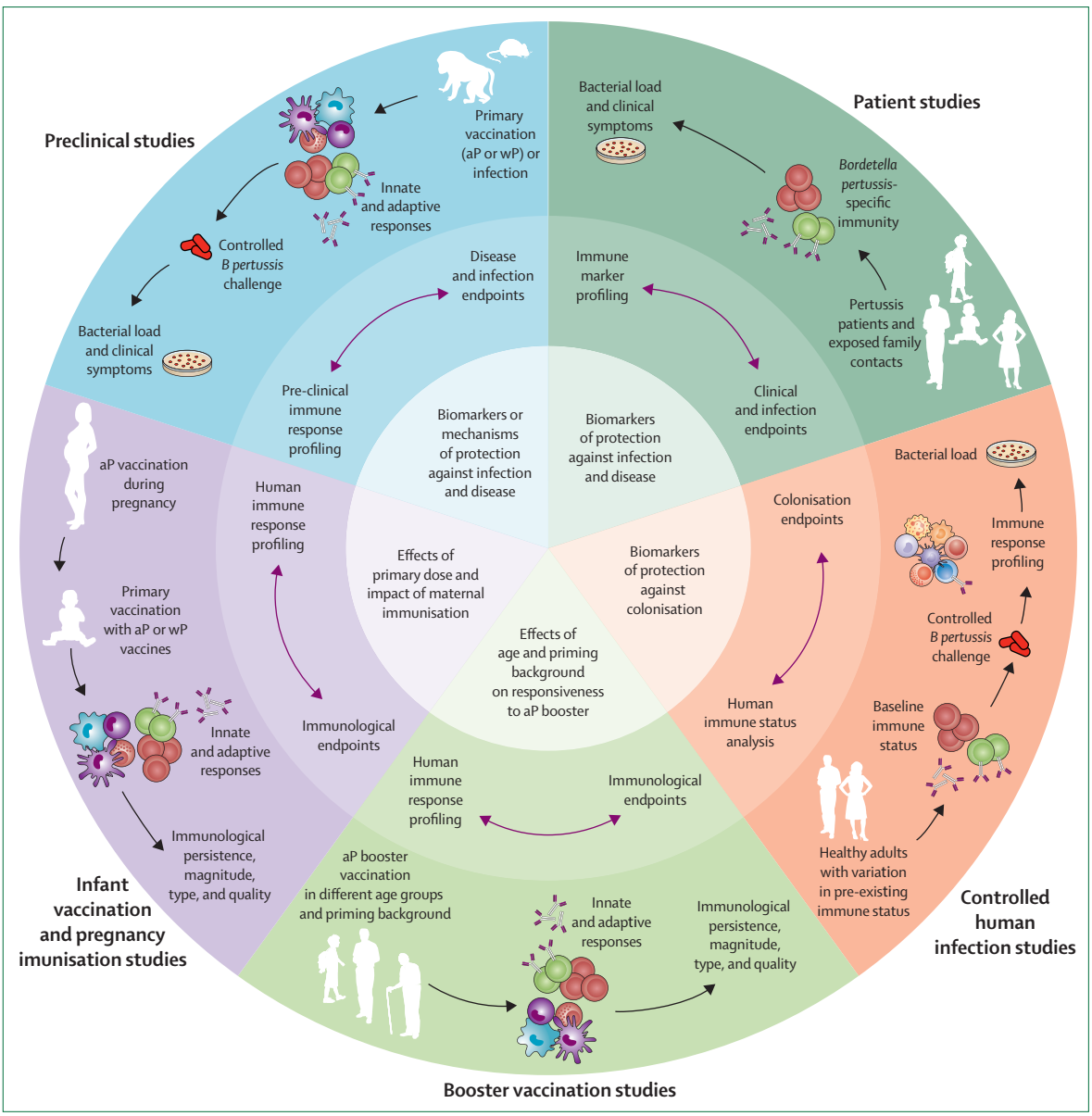

Figure 2: **Overview of the clinical and preclinical studies in PERtussIS Correlates Of Protection Europe (PERISCOPE)**
The outer circle shows the general study design of the various (pre)clinical studies and the measurements and endpoints in PERISCOPE. The middle circle shows the comparative analyses that can be made between the immunological measurements and the endpoints for each study. The inner circle shows the biological insights and biomarkers that each study is expected to deliver. aP=acellular pertussis. wP=whole-cell pertussis.

among parents and older siblings.[19] Hypothetically, this goal can be achieved by either giving pertussis vaccines to neonates or to pregnant women, which capitalises on passive protection through transplacental transfer of maternal antibodies. Although aP vaccination studies in neonates showed that vaccination immediately after birth is safe and immunogenic, immunological interference against non-pertussis vaccine components was observed following subsequent immunisation at later timepoints.[48–52] Consequently, aP vaccination of neonates has effectively been abandoned. Because of its success in the UK,[33,34] the USA,[53] and several other countries, antenatal pertussis vaccination is increasingly being implemented in high-income and middle-income countries. Although the immediate benefits of such programmes are evident, several questions remain to be answered concerning the potential effect of maternal antibodies on the infant's response to primary immunisation with wP or aP vaccines, or to other vaccines received in the first year of life.

The PERISCOPE project

The resurgence and changing epidemiology of pertussis call for a concerted effort to improve pertussis vaccines,

or develop new vaccines and vaccination strategies against pertussis. To systematically address these issues, the PERtussIS Correlates Of Protection Europe (PERISCOPE) Consortium was established as a public–private partnership, funded by the Innovative Medicines Initiative and the Bill & Melinda Gates Foundation.

The ultimate objective of PERISCOPE is to create a solid scientific basis for facilitating and accelerating the development of improved pertussis vaccines or vaccination strategies. PERISCOPE will approach this objective from multiple angles (figure 2) through a series of preclinical and clinical studies. These studies will exploit existing knowledge on pertussis biology and immunity,[37,54,55] and build on solid experience of the partners with clinical and preclinical trials.[40,45,46,56] Together, these studies will help to gain a thorough scientific understanding of the underlying mechanisms and biomarkers of protective immunity to *B pertussis* in humans, investigate differences between wP and aP vaccines in relation to immunological function and persistence, investigate the effect of antenatal immunisation on infant responses to primary pertussis vaccination, and strengthen technological means of testing novel vaccine candidates in animal and human models of disease and asymptomatic infection.

Randomised multicentre clinical studies comparing aP versus wP vaccination will be done in infants in both Europe and Africa to identify differences in immunological memory. To understand the effect of antenatal vaccination, these trials will include a group with infants born to mothers who received a booster dose of aP vaccine during pregnancy. Furthermore, vaccination trials will be undertaken in different age groups to study the effect of primary vaccination on innate and adaptive responses to an aP-booster vaccine.[40,45,46,56] Data from these studies will serve as a reference for future studies with novel formulations.

Another objective is to establish a safe and reproducible model of controlled *B pertussis* infection in humans. For ethical reasons these studies are done in adults, most of whom will have been vaccinated against pertussis during infancy, which will influence their response to infection. This model can be used to address several key questions and offers a means to identify and eventually validate correlates of protection against asymptomatic infection. For instance, immune profiles can be compared between culture-positive and culture-negative individuals to help to identify immune factors involved in protection. Challenging humans with *B pertussis* will also provide important insights into the human pathobiology of infection and the immune response to infection. Once this model has been established, future studies outside the scope of PERISCOPE can use it to evaluate novel vaccine formulations with *B pertussis* colonisation as an endpoint. In addition to the controlled human challenge studies, we intend to establish and use immunological research in a cohort of naturally infected pertussis patients and their family members or contacts. This approach will allow for analysis of potential correlates of protection in the context of natural exposure.

For more on the **PERISCOPE project** see http://www.periscope-project.eu

Increased capacity for preclinical evaluation is needed to support the screening of novel vaccines, particularly in the baboon model that was established at the US Food and Drug Administration by the Merkel group.[57–59] The baboon model is the only animal model to date that allows for evaluation of *B pertussis* infection, disease,[57] and transmission.[32,58] One of our objectives is therefore to make this model accessible by expanding its use in Europe. By harmonising study designs across baboon and human studies, it will be possible to compare immune response profiles and link these to long-term protection against both *B pertussis* transmission and disease. The selective use of mouse models, including knockout mice,[37,55] will be essential to complement studies in humans and baboons, and to decipher the mechanisms of protective immunity and the biological role of putative biomarkers.

A crucial step forward is to develop several standardised immunological assays to characterise the range of immune responses to pertussis in humans and to identify biomarkers and potential correlates of protection that could help to expedite the development process of novel vaccines. We anticipate that antibody assays that measure functional activity of vaccine-induced antibodies will more likely yield biomarkers and correlates of protection than antibody assays that solely measure antigen binding capacity. We will focus on antibody-mediated inhibition of bacterial attachment to respiratory epithelial cells (early colonisation), bactericidal activity (early to late infection), opsonophagocytosis and killing (early to late infection), and neutralisation of PT (disease).

Although cellular immunity likely plays an important part in protection against *B pertussis*, T-cell responses against *B pertussis* have not been extensively studied in humans, largely because of the absence of well established and fully standardised assays to analyse *B pertussis*-specific T cells in a clinical trial setting. It is therefore imperative to develop a standardised pertussis T-cell assay, which will allow for a thorough investigation of T-cell responses against *B pertussis* and enable cross-study comparisons. Although memory B cells have been extensively studied in humans,[40,46,56] to establish a standardised assay to quantify *B pertussis* antigen-specific plasma and memory B cells is also important.

To minimise the risk that putative correlates of protection are solely directed against a single strain or antigen, a representative panel of *B pertussis* strains will be used for testing in relevant immunoassays.

With use of systems biology approaches,[60,61] discrete immune signatures might be uncovered that provide important clues on how immunological memory is (re)programmed following aP and wP vaccination, and how this differs from infection-induced immunity. An important deliverable of PERISCOPE is the establishment

of a TranSmart database that will facilitate an integrated data analysis. This database will allow us to analyse patterns of the early immune response and link these to adaptive immune responses or clinical endpoints.

Studies will be done to investigate the development and maintenance of B-cell and T-cell immunological memory following vaccination and infection. A comprehensive investigation of how the antigen-specific B-cell response develops over time can provide important insights towards the role of antibodies in protection. This will also provide an opportunity to analyse the B-cell receptor repertoire and combine it with functional antibody readouts, an approach that has proven to be incredibly useful for influenza vaccine research.[62] A similar analysis of T-cell immunity is warranted, because a better understanding of the functional plasticity of *B pertussis*-specific T cells could help to guide the design and use of novel pertussis booster vaccines.

PERISCOPE is a human-centric project with a strong focus on the identification of putative immunological correlates of protection. There are several areas of interest that PERISCOPE will not be able to address, even though they might bring important insights. These include genetic changes in *B pertussis*, potential new vaccine formulations, novel vaccine antigens, and vaccination beyond one pregnancy.

Through PERISCOPE we aim to promote scientific innovation and rebuild the ecosystem and technical infrastructure that is needed to evaluate novel pertussis vaccines. Ultimately, the potential modification of current vaccine formulations, immunisation schedules, and research and development of novel vaccine formulations will be affected by the availability of reliable preclinical and clinical models, and a robust immunological toolbox to be deployed in clinical studies. Overall, the PERISCOPE Consortium aims to increase the ability of academic researchers, biotechnology organisations, and pharmaceutical organisations worldwide to evaluate and select pertussis vaccines, and also to find the most promising ones for further clinical development.

Conclusion

The epidemiology of pertussis has changed substantially since the introduction of the universal pertussis childhood vaccination programmes. Although several research groups are now actively developing novel pertussis vaccines, major technical and scientific hurdles remain that need to be overcome to enable this effort. In this Personal View, the PERISCOPE Consortium outlines essential steps that might help to expedite the development of novel pertussis vaccines and to reduce the risks of late-stage vaccine candidate failure. We acknowledge the huge collaborative effort required and hope that working together with partners in all parts of the world along this initial roadmap will strengthen and stimulate further collaboration and transparency between the key stakeholders and increase the chance of achieving the ultimate goal of bringing pertussis under control.

Contributors

DAD, PLH, and RdG developed the concept and drafted the manuscript. DAD conceptualised and produced the figures. UH conceptualised the panel. All authors have been involved in the design of the PERISCOPE project and have critically reviewed and edited the manuscript.

The PERISCOPE Consortium

Dimitri A Diavatopoulos, Kingston H G Mills, Kent E Kester, Beate Kampmann, Marcela Silerova, Ulrich Heininger, Jacques J M van Dongen, Robbert G van der Most, Martijn A Huijnen, Emilio Siena, Nathalie Mielcarek, Martina M Ochs, Philippe Denoël, Guy Berbers, Annemarie M Buisman, Marien I de Jonge, Craig Fenwick, Andrew Gorringe, Qiushui He, Dominic Kelly, Roger Le Grand, Camille Locht, Françoise Mascart, Jussi Mertsola, Alberto Orfao, Giuseppe Pantaleo, Andrew J Pollard, Andrew Preston, Robert Read, Peter Sebo, Cecile van Els, Branislav Vecerek, Patricia Londoño-Hayes, and Ronald de Groot. Radboud University Medical Center, Radboud Institute for Molecular Life Sciences, Laboratory of Medical Immunology, Section Pediatric Infectious Diseases, Nijmegen, Netherlands (D A Diavatopoulos PhD, M I de Jonge PhD, Prof R de Groot MD); Radboud Center for Infectious Diseases, Radboudumc, Nijmegen, Netherlands (D A Diavatopoulos, M I de Jonge, Prof R de Groot); School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland (Prof K H G Mills PhD); Sanofi Pasteur, Discovery Drive, Swiftwater, PN, USA (K E Kester MD); MRC Unit The Gambia, Atlantic Road, Fajara, The Gambia, West Africa (Prof B Kampmann MD); The Vaccine Centre, London School of Hygiene and Tropical Medicine, London, UK (B Kampmann); GlaxoSmithKline, Rixensart, Belgium (M Silerova PhD, R G van der Most PhD, P Denoël PhD); University of Basel Children's Hospital, Infectious Diseases and Vaccinology, Basel, Switzerland (Prof U Heininger MD); Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, Netherlands (Prof J J M van Dongen MD); Centre for molecular and Biomolecular Informatics, Radboud Institute for Molecular Life Sciences, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands (Prof M A Huijnen PhD); GlaxoSmithKline, Siena, Italy (E Siena PhD); Centre for Infection and Immunity of Lille, University of Lille, U1019, UMR 8204, Lille, France (N Mielcarek, Prof C Locht PhD); Le Centre National de la Recherche Scientifique, UMR 8204, Lille, France (N Mielcarek, Prof C Locht); INSERM U1019, Lille, France (N Mielcarek, Prof C Locht); CHU Lille, Lille, France (N Mielcarek, Prof C Locht); Institut Pasteur de Lille, Lille, France (N Mielcarek, Prof C Locht); Sanofi Pasteur, Marcy L'Etoile, France (M M Ochs PhD, P Londoño-Hayes PhD); Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands (G Berbers PhD, A M Buismann PhD, C van Els PhD); Division of Immunology and Allergy, Lausanne University Hospital, Lausanne, Switzerland (C Fenwick PhD, Prof G Pantaleo MD); Public Health England, Porton Down, Salisbury, UK (Prof A Gorringe PhD); Department of Medical Microbiology and Immunology, University of Turku, Turku, Finland (Prof Q He MD, Prof J Mertsola MD); Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, UK (D Kelly MD, Prof A J Pollard MD); CEA, INSERM U1184, Immunology of Viral Infections and Autoimmune Diseases, Université Paris, Paris, France (R Le Grand PhD); Laboratory of Vaccinology and Mucosal Immunity, Université Libre de Bruxelles, Brussels, Belgium (Prof F Mascart MD); Department of Medicine and Cytometry Service, University of Salamanca, Salamanca, Spain (Prof A Orfao MD); Milner Centre for Evolution and Department of Biology and Biochemistry, University of Bath, Bath, UK (A Preston PhD); NIHR Southampton Biomedical Research Centre, University of Southampton, University Hospital Southampton NHS Foundation Trust, Southampton, UK (Prof R Read MD); and Laboratory of Molecular Biology of Bacterial Pathogens (Prof P Sebo PhD), Laboratory of Post-transcriptional Control of Gene Expression (B Vecerek PhD), Institute of Microbiology of the ASCR, Czech Academy of Sciences, Prague, Czech Republic.

Declaration of interests

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