Advances in Experimental Medicine and Biology 764

Nigel Curtis
Adam Finn
Andrew J. Pollard *Editors*

Hot Topics in Infection and Immunity in Children IX

Springer

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Volume 764

For further volumes:
http://www.springer.com/series/5584

Nigel Curtis · Adam Finn
Andrew J. Pollard
Editors

Hot Topics in Infection and Immunity in Children IX

Springer

Editors
Nigel Curtis
Professor of Paediatric Infectious Diseases
The University of Melbourne;
Infectious Diseases Unit
The Royal Children's Hospital
Melbourne;
Infectious Diseases & Microbiology Research Group
Murdoch Children's Research Institute
Parkville, Australia
nigel.curtis@rch.org.au

Adam Finn
David Baum Professor of Paediatrics
University of Bristol
Bristol, UK
adam.finn@bristol.ac.uk

Andrew J. Pollard
Professor of Paediatric Infection & Immunity
Director, Oxford Vaccine Group
University of Oxford
Oxford, UK
andrew.pollard@paediatrics.ox.ac.uk

ISSN 0065-2598
ISBN 978-1-4614-4725-2 ISBN 978-1-4614-4726-9 (eBook)
DOI 10.1007/978-1-4614-4726-9
Springer New York Dordrecht Heidelberg London

Preface

The ninth 'Infection and Immunity in Children' (IIC) course was held in July 2011 at St Catherine's College, Oxford, UK. This book, the ninth in the series, comprises chapters based on presentations made at that course. The series provides succinct and readable updates on virtually every topic of relevance to Paediatric Infectious Diseases (PID).

The tenth edition is currently in preparation following the 2012 course, which once again had a programme delivered by renowned top-class speakers. The programme for the eleventh course, planned for 26–28th June 2013, is being finalised as this book goes to press.

PID has emerged as a powerful discipline for the improvement of child health in Europe and worldwide over the last quarter of a century. The European Society for Paediatric Infectious Diseases (ESPID) now holds the largest annual conference in PID in the world and sponsors a wide range of educational activities for trainees and specialists. Among them is the Oxford IIC course, which, with other ESPID-sponsored activities, is an integral part of the two-year Oxford Diploma in PID. This course began in 2008 and continues to enrol trainees from all over Europe, being the first recognised academic qualification of any kind in PID outside North America.

The future of PID promises to be eventful, challenging and fascinating, as new infections emerge, old infections evolve and new diagnostic techniques, treatments and vaccines become available. There is much that is new to learn about and we hope this book will provide a further useful contribution to the materials available to trainees and practitioners in our important and rapidly developing field.

Melbourne, Australia — Nigel Curtis
Bristol, UK — Adam Finn
Oxford, UK — Andrew J. Pollard

Acknowledgments

We thank all the speakers from the 2011 'Infection and Immunity in Children' (IIC) course who gave their time both to attending the meeting and to contributing presentations, discussion and chapters for this book. We also thank their co-authors, many of whom are trainees who have also attended the course on one or more occasions.

Since its early days, the course has been organised by Sue Sheaf. Its continuing and growing success is in large part due to her efforts, which include all the necessary liaison with the faculty, the handling of applications and bursaries for all the delegates, working with the college with respect to all practical arrangements for the course, the audiovisual team, the social programme and, of course, cajoling us, the organisers, into doing our part, to name but a few. Without Sue, the Oxford IIC course would not be what it is and we cannot thank her enough.

Another difficult task is the administration of the production of successive editions of this book. As anyone who has ever been involved in putting together a publication of this kind will know, this is a major undertaking requiring a skilled and dedicated team of professionals. Pamela Morison is that team. Careful copyediting and correction of the materials provided by the authors, editors and publishers is essential to ensuring a high-quality final product and Pam is the person who does this work. She also has to persuade all these parties to deliver the materials in a timely fashion, which Pam does with the right mix of persuasiveness and insistence. For Pam's good-natured approach, diplomatic skills and all her hard work we thank her and gratefully share with her the credit for this book's production.

We thank the European Society for Paediatric Infectious Diseases (ESPID) for consistent support and financial assistance for this and previous courses and also for providing bursaries, which have paid the costs of many young ESPID members' attendance. We also acknowledge the recognition given to the course by the UK Royal College of Paediatrics and Child Health (RCPCH).

Finally, we are grateful to the staff of St Catherine's College, Oxford, UK where the course was held and to several pharmaceutical industry sponsors who generously offered unrestricted educational grants towards the budget for the meeting.

Contents

1 **Innovation for the 'Bottom 100 Million': Eliminating Neglected Tropical Diseases in the Americas** 1
Peter J. Hotez, Eric Dumonteil, Michael J. Heffernan and Maria E. Bottazzi

2 **Non-typhoidal Salmonella in Children: Microbiology, Epidemiology and Treatment** 13
Gabrielle M. Haeusler and Nigel Curtis

3 **Invasive Fungal Infections in Patients with Chronic Granulomatous Disease** 27
Stefanie Henriet, Paul E. Verweij, Steven M. Holland and Adilia Warris

4 ***Clostridium difficile* in Children: A Review of Existing and Recently Uncovered Evidence** 57
Oliver Morris, Marc Tebruegge, Ann Pallett, Steve M. Green, Andrew D. Pearson, Andrew Tuck, Stuart C. Clarke, Paul Roderick and Saul N. Faust

5 **Diarrhea Among Children in Developing Countries** 73
James P. Nataro

6 **Building Confidence in Vaccines** 81
Jennifer C. Smith, Mary Appleton and Noni E. MacDonald

7 **Chronic Recurrent Multifocal Osteomyelitis** 99
Marion R. Roderick and Athimalaipet V. Ramanan

8 **Recognition and Treatment of Chlamydial Infections from Birth to Adolescence** 109
Toni Darville

9 **Treatment of Resistant Bacterial Infections in Children: Thinking Inside and Outside the Box** 123
Gilat Livni and Shai Ashkenazi

10 An Encephalitis Primer 133
Dominic Kelly

11 The Evidence Behind Prophylaxis and Treatment of Wound Infection After Surgery 141
Mona A. Al-Dabbagh and Simon Dobson

12 Infectious Risks Associated with Biologics 151
David Isaacs

13 Cat Scratch Disease and Other *Bartonella* Infections 159
Kenneth M. Zangwill

14 When to Think of Immunodeficiency? 167
Andrew Cant and Alexandra Battersby

15 Mycetoma Caused by *Madurella mycetomatis:* A Completely Neglected Medico-social Dilemma 179
Alex van Belkum, Ahmed Fahal and Wendy W. J. van de Sande

16 Elucidation and Clinical Role of Emerging Viral Respiratory Tract Infections in Children 191
Inge Ahout, Gerben Ferwerda and Ronald de Groot

17 Urinary Tract Infections in Children: Microbial Virulence Versus Host Susceptibility 205
Catharina Svanborg

18 Preventing Urinary Tract Infections in Early Childhood 211
Gabrielle J. Williams, Jonathan C. Craig and Jonathan R. Carapetis

19 How to Get and Get Rid of Gonorrhea 219
Jennifer C. Smith, Tim Mailman and Noni E. MacDonald

20 Management of Severe Malaria: Results from Recent Trials 241
Peter Olupot-Olupot and Kathryn Maitland

Index 251

Contributors

Inge Ahout Department of Pediatrics, Radboud University Medical Centre, Nijmegen, The Netherlands
e-mail: I.Ahout@cukz.umcn.nl

Mona A. Al-Dabbagh Division of Infectious and Immunological Diseases, Department of Pediatrics, BC Children's Hospital, Vancouver, Canada; King Abdulaziz Medical City, Jeddah, Saudi Arabia
e-mail: dabbaghM@ngha.med.sa

Mary E. Appleton Pediatric Infectious Diseases, Dalhousie University, Canadian Center for Vaccinology, IWK Health Center, Halifax, Canada
e-mail: mary.appleton@iwk.nshealth.ca

Shai Ashkenazi Professor of Pediatrics, Sackler Faculty of Medicine, Schneider Children's Medical Center, Petach Tikva, Israel
e-mail: ashai@post.tau.ac.il

Maria E. Bottazzi Sabin Vaccine Institute and Texas Children's Center for Vaccine Development, Departments of Pediatrics and Molecular Virology & Microbiology, National School of Tropical Medicine, Baylor College of Medicine, Houston, USA
e-mail: Bottazzi@bcm.edu

Andrew Cant Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK
e-mail: andrew.cant@nuth.nhs.uk

Jonathan R. Carapetis Telethon Institute for Child Health Research, University of Western Australia, Perth, Australia.
e-mail: jcarapetis@ichr.uwa.edu.au

Stuart C. Clarke Academic Unit of Clinical & Experimental Sciences, Faculty of Medicine, University of Southampton and Health Protection Agency, Southampton, UK
e-mail: S.C.Clarke@soton.ac.uk

Jonathan C. Craig School of Public Health, University of Sydney, Centre for Kidney Research, Children's Hospital at Westmead, Sydney, Australia
e-mail: Jonathan.craig@sydney.edu.au

Nigel Curtis Department of Paediatrics, The University of Melbourne; Infectious Diseases Unit, The Royal Children's Hospital Melbourne; Infectious Diseases & Microbiology Research Group, Murdoch Children's Research Institute, Parkville, Australia
e-mail: nigel.curtis@rch.org.au

Toni Darville Division of Pediatric Infectious Diseases, College of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
e-mail: darvilletonil@chp.edu

Simon Dobson Division of Infectious and Immunological Diseases, Department of Pediatrics, BC Children's Hospital, Vancouver, Canada
e-mail: sdobson@cw.bc.ca

Eric Dumonteil Laboratorio de Parasitologia, Centro de Investigaciones Regionales "Dr Hideyo Noguchi", Universidad Autonoma de Yucatan, Merida, Yucatan, Mexico
e-mail: edumonte@tulane.edu

Ahmed Fahal University of Khartoum, Mycetoma Research Centre, Khartoum, Sudan
e-mail: ahfahal@hotmail.com

Saul N. Faust Academic Unit of Clinical & Experimental Sciences, Faculty of Medicine, University of Southampton, University Hospital Southampton NHS Foundation Trust, NIHR Wellcome Trust Clinical Research Facility, Southampton, UK
e-mail: s.faust@soton.ac.uk

Gerben Ferwerda Department of Pediatrics, Radboud University Medical Centre, Nijmegen, The Netherlands
e-mail: J.Ferwerda@cukz.umcn.nl

Adam Finn Paediatrics, University of Bristol, Bristol Royal Hospital for Children, Bristol, UK.
e-mail: adam.finn@bristol.ac.uk

Steve M. Green Health Protection Agency, Southampton, UK
e-mail: S.Green@soton.ac.uk

Ronald de Groot Department of Pediatrics, Radboud University Medical Centre, Nijmegen, The Netherlands
e-mail: R.deGroot@cukz.umcn.nl

Gabrielle M. Haeusler Infectious Diseases Unit, The Royal Children's Hospital Melbourne, Parkville, Australia
e-mail: gabrielle.haeusler@rch.org.au

Michael J. Heffernan Sabin Vaccine Institute and Texas Children's Center for Vaccine Development, Departments of Pediatrics and Molecular Virology & Microbiology, National School of Tropical Medicine, Baylor College of Medicine, Houston, USA
e-mail: mjheffer@bcm.edu

Stefanie Henriet Department of Pediatric Infectious Diseases and Immunology, Nijmegen Institute for Infection, Inflammation and Immunity, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
e-mail: S.Henriet@cukz.umcn.nl

Steven M. Holland Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, USA
e-mail: SHOLLAND@niaid.nih.gov

Peter J. Hotez Sabin Vaccine Institute and Texas Children's Center for Vaccine Development, Departments of Pediatrics and Molecular Virology & Microbiology, National School of Tropical Medicine, Baylor College of Medicine, Houston, USA
e-mail: hotez@bcm.edu

David Isaacs Department of Infectious Disease and Microbiology, Children's Hospital at Westmead, Westmead, Australia
e-mail: davidi@chw.edu.au

Dominic Kelly Children's Hospital, Oxford, UK
e-mail: dominic.kelly@paediatrics.ox.ac.uk

Gilat Livni Sackler Faculty of Medicine, Department of Pediatrics A, Schneider Children's Medical Center of Israel, Petach Tikva, Israel
e-mail: gilat@orange.net.il

Noni E. MacDonald Pediatric Infectious Diseases, Dalhousie University, Canadian Center for Vaccinology, IWK Health Center, Halifax, Canada
e-mail: noni.macdonald@dal.ca

Tim Mailman Dalhousie University, IWK Health Center, Halifax, Canada
e-mail: tim.mailman@iwk.nshealth.ca

Kathryn Maitland KEMRI-Wellcome Trust Programme, Kilifi, Kenya; Department of Paediatrics, Imperial College, London, UK
e-mail: kathryn.maitland@gmail.com

Oliver Morris Academic Unit of Clinical & Experimental Sciences, Faculty of Medicine, University of Southampton, University Hospital Southampton NHS Foundation Trust, NIHR Wellcome Trust Clinical Research Facility, Southampton, UK
e-mail: omorris@doctors.org.uk

James P. Nataro Department of Pediatrics, University of Virginia School of Medicine, University of Virginia Children's Hospital, Charlottesville, USA
e-mail: JPN2R@hscmail.mcc.virginia.edu

Peter Olupot-Olupot Mbale Regional Referral Hospital, Mbale, Uganda

Ann Pallett University Hospital Southampton NHS Foundation Trust, Southampton, UK
e-mail: Ann.Pallett@uhs.nhs.uk

Andrew D. Pearson Department of Advanced Computational Biology, University of Maryland, USA
e-mail: drandrewpearson@googlemail.com

Andrew J. Pollard Oxford Vaccine Group, University of Oxford; Children's Hospital, Oxford, UK
e-mail: andrew.pollard@paediatrics.ox.ac.uk

Athimalaipet V. Ramanan Bristol Royal Hospital for Children, Bristol; Royal National Hospital for Rheumatic Diseases, Bath, UK
e-mail: Athimalaipet.Ramanan@UHBristol.nhs.uk

Marion R. Roderick Bristol Royal Hospital for Children, Bristol, UK
e-mail: rodericks1000@hotmail.com

Paul Roderick Academic Unit of Primary Care and Population Sciences, Faculty of Medicine, University of Southampton, UK
e-mail: pjr@soton.ac.uk

Jennifer C. Smith Pediatric Infectious Diseases, Dalhousie University, Canadian Center for Vaccinology, IWK Health Center, Halifax, Canada
e-mail: jaurora777@yahoo.ca

Catharina Svanborg Department of Microbiology, Immunology and Glycobiology, Institute of Laboratory Medicine, Lund University, Lund, Sweden
e-mail: Catharina.Svanborg@med.lu.se

Marc Tebruegge Academic Unit of Clinical & Experimental Sciences, Faculty of Medicine, University of Southampton, University Hospital Southampton NHS Foundation Trust, Southampton, UK
e-mail: M.Tebruegge@soton.ac.uk

Andrew Tuck Academic Unit of Clinical & Experimental Sciences, Faculty of Medicine, University of Southampton and Health Protection Agency, Southampton, UK
e-mail: A.C.Tuck@soton.ac.uk

Alex van Belkum bioMérieux, Microbiology Unit, La Balme-Les-Grottes, France
e-mail: alex.vanbelkum@biomerieux.com

Wendy W. J. van de Sande Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands
e-mail: w.vandesande@erasmusmc.nl

Paul E. Verweij Department of Medical Microbiology, Nijmegen Institute for Infection, Inflammation and Immunity, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
e-mail: P.Verweij@mmb.umcn.nl

Adilia Warris Department of Pediatric Infectious Diseases and Immunology, Nijmegen Institute for Infection, Inflammation and Immunity, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
e-mail: A.Warris@cukz.umcn.nl

Gabrielle J. Williams School of Public Health, University of Sydney, Centre for Kidney Research, Children's Hospital at Westmead, Sydney, Australia
e-mail: gabrielle.williams1@health.nsw.gov.au

Kenneth M. Zangwill Pediatric Infectious Diseases, David Geffen School of Medicine at UCLA, Harbor-UCLA Medical Center, Los Angeles, USA
e-mail: kzangwill@uclacvr.labiomed.org

Speakers at the ninth ‘Infection and Immunity in Children’ (IIC) course held in July 2011 at St Catherine’s College, Oxford, UK

1 Innovation for the 'Bottom 100 Million': Eliminating Neglected Tropical Diseases in the Americas

Peter J. Hotez, Eric Dumonteil, Michael J. Heffernan and Maria E. Bottazzi

Abstract

An estimated 100 million people in the Latin American and Caribbean (LAC) region live on less than US$2 per day, while another 46 million people in the US live below that nation's poverty line. Almost all of the 'bottom 100 million' people suffer from at least one neglected tropical disease (NTD), including one-half of the poorest people in the region infected with hookworms, 10 % with Chagas disease, and up to 1–2 % with dengue, schistosomiasis, and/or leishmaniasis. In the US, NTDs such as Chagas disease, cysticercosis, toxocariasis, and trichomoniasis are also common among poor populations. These NTDs trap the poorest people in the region in poverty, because of their impact on maternal and child health, and occupational productivity. Through mass drug administration (MDA), several NTDs are on the verge of elimination in the Americas, including lymphatic filariasis, onchocerciasis, trachoma, and possibly leprosy. In addition, schistosomiasis may soon be eliminated in the Caribbean. However, for other NTDs including hookworm infection, Chagas disease, dengue, schistosomiasis, and leishmaniasis, a new generation of 'anti-poverty vaccines' will be required. Several vaccines for dengue are under development by multinational pharmaceutical companies, whereas others are being pursued through non-profit product development partnerships (PDPs), in collaboration with developing country manufacturers in Brazil and Mexico. The Sabin Vaccine Institute PDP is developing a primarily preventive bivalent recombinant human hookworm vaccine,

P. J. Hotez (✉) · M. J. Heffernan · M. E. Bottazzi
Sabin Vaccine Institute and Texas Children's Center for Vaccine Development, Departments of Pediatrics and Molecular Virology & Microbiology, National School of Tropical Medicine, Baylor College of Medicine, Houston, USA
e-mail: hotez@bcm.edu

M. J. Heffernan
e-mail: mjheffer@bcm.edu

M. E. Bottazzi
e-mail: Bottazzi@bcm.edu

E. Dumonteil
Laboratorio de Parasitologia, Centro de Investigaciones Regionales "Dr Hideyo Noguchi", Universidad Autonoma de Yucatan, Merida, Yucatan, Mexico
e-mail: edumonte@tulane.edu

N. Curtis et al. (eds.), *Hot Topics in Infection and Immunity in Children IX,*
Advances in Experimental Medicine and Biology 764, DOI 10.1007/978-1-4614-4726-9_1,

Table 1.1 Poverty in the Americas. (Data from [1, 4])

	Region	
	Latin America & Caribbean	United States
Population in 2010	578 million	306 million
Living on less than $1 per day in 2005	8.2 %	
Estimated number of people living on less than $1 per day	48 million	
Living on less than $2 per day in 2005	17.1 %	
Estimated number of people living on less than $2 per day	99 million	
Living below the poverty line in 2010		15.1 %
Number of people living below the poverty line		46 million

Table 1.2 Countries in the Americas with the lowest Human Development Indices. (Data from [3])

Country	2008 HDI rank	Comparator countries with similar HDI rank
Haiti	148	Sudan, Kenya
Guatemala	121	South Africa, Gabon
Nicaragua	120	South Africa, Gabon
Honduras	117	Mongolia, Kyrgyzstan
Bolivia	111	Egypt, Indonesia
Guyana	110	Egypt, Indonesia
El Salvador	101	Algeria, Cape Verde, Vietnam
Paraguay	98	Sri Lanka, Iran

which is about to enter phase 1 clinical testing in Brazil, as well as a new therapeutic Chagas disease vaccine in collaboration with several Mexican institutions. The Chagas disease vaccine would be administered to seropositive patients to delay or prevent the onset of Chagasic cardiomyopathy (secondary prevention). Together, MDA and the development of new anti-poverty vaccines afford an opportunity to implement effective control and elimination strategies for the major NTDs in the Americas.

1.1 Introduction: Poverty in the Americas

Today, almost one-fifth of the 578 million people who live in the Latin American and Caribbean (LAC) region live in severe poverty. As shown in Table 1.1, an estimated 50 and 100 million people live on less than US$1.25 per day (the World Bank poverty level) and US$2 per day, respectively [1]. These populations represent the LAC region's bottom 100 million. Poverty has an uneven distribution in the LAC region, such that the bottom 100 million cluster in defined geographical areas of Mexico and Central America, South America, and in areas with large indigenous populations. For example, almost one-half of rural households in Mexico are considered poor, most of them in southern Mexico; one-half of the population of Central America also lives in poverty [2]. Four of the eight LAC countries with the lowest human development indices (HDIs) are found in Central America, including Guatemala, Nicaragua, Honduras, and El Salvador (Table 1.2) [3], where poverty disproportionately affects indigenous populations [2]. Among South American populations, there are an estimated 20 million poor in Brazil, particularly in the northeastern part of the country, and especially among women and children [2]. Some of the poorest people in LAC live in indigenous communities and mountainous areas of Bolivia, Peru, and Ecuador and in the Chaco of Bolivia and Paraguay [2, 3]. More than one-third of impoverished LAC populations live in the Andean region [2]. The Caribbean countries of Haiti and Guyana also stand out for their low HDIs [3]. Overall, the HDIs of the poorest countries in the LAC region are similar to many poor African and Asian countries (Table 1.2).

Poverty in the Americas is not restricted to the LAC region [4–6]. With the recent recession in the US the percentage of people living below the poverty line has increased to its highest level in more than 50 years [4]. It was recently determined that the US poverty rate has increased to 15 %, with 46 million people living below the poverty line [4]. Poverty in the US also has an uneven distribution, with the highest rates along the Gulf Coast and in South Texas [5, 6]. Poverty

Table 1.3 The neglected tropical diseases of the Latin American and Caribbean (LAC) region. (Modified from [9])

Disease	Estimated DALYs in LAC (million)	Estimated number of cases (million)	Estimated bottom 100 million affected (%)	Countries most affected
Hookworm	0.1–1.9	50	50	Brazil, Paraguay, Guatemala, Colombia
Ascariasis	0.1–1.1	84	84	Brazil, Mexico, Guatemala, Argentina
Trichuriasis	0.3–1.1	100	100	Brazil, Mexico, Colombia, Guatemala
Chagas disease	0.7	8–9	10	Bolivia, Mexico, Colombia, Central America
Dengue	0.1	>0.6	1	Brazil, Caribbean
Leishmaniasis	<0.1	0.1	1	Brazil, Colombia, Peru, Nicaragua, Bolivia
Schistosomiasis	<0.1	1.8	2	Brazil, Venezuela, Suriname, Saint Lucia
Lymphatic FIlariasis	<0.1	0.7	1	Haiti, Brazil, Dominican Republic, Guyana
Trachoma	<0.1	1.1	1	Brazil, Guatemala
Leprosy	<0.1	<0.1[a]	<1	Brazil
Onchocerciasis	<0.1	<0.1	<1	Guatemala, Mexico, Ecuador, Venezuela, Brazil, Colombia
Human rabies from dogs	<0.1	<100[b]	<1	Haiti, Bolivia
Cysticercosis	ND	0.4	<1	ND
Toxoplasmosis	ND	ND	ND	Brazil

ND not determined
[a] New cases
[b] Cases

also occurs in the Canadian and the Alaskan Arctic among Inuit and related populations [7].

1.2 Neglected Tropical Diseases in the Americas

Among the LAC region's bottom 100 million, approximately one-half lack adequate food [8]. Equally tragic are the results of our previous analysis showing that almost all the bottom 100 million suffers from one or more neglected tropical disease [9]. Globally, the neglected tropical diseases or 'NTDs' comprise 17 major chronic parasitic and related infections [10–12]. Importantly, they not only adversely affect the health of infected individuals, but also trap people in poverty, because of their long-term impact on child growth and cognitive development, pregnancy outcome, and occupational productivity [11, 13]. Shown in Table 1.3 is a ranking of the leading NTDs in the LAC region by disease burden, measured in disability-adjusted life years. The leaders are hookworm and other soil-transmitted helminths, Chagas disease (American trypanosomiasis), and dengue, followed by leishmaniasis, schistosomiasis, lymphatic filariasis, trachoma, leprosy, onchocerciasis, and cysticercosis [9]. Almost all of the bottom 100 million are infected with one or more soil-transmitted helminths, including trichuriasis, ascariasis, and hookworm. Approximately 10 % are affected by Chagas disease and 1 % by dengue fever. Precise prevalence data for toxoplasmosis in the LAC region is lacking, however it is believed to be common, especially in Brazil [14]. With the exception of Chagas disease and possibly trachoma, most of the NTDs were introduced into the Americas through the Atlantic slave trade [15], and these conditions still disproportionately affect African-American and indigenous populations [9].

Table 1.3 also shows the disproportionate representation of the most common NTDs in low HDI countries, for example, hookworm in Paraguay and Guatemala, and Chagas disease in Bolivia and in several Central American countries

Table 1.4 Major neglected infections of poverty in the US. (Modified from [5])

Disease	Estimated number of cases (million)	Major populations affected
Toxocariasis	1–3	African American
Trichomoniasis	0.9	African American
Chagas disease	Up to 1	Hispanic American
Dengue	0.1–0.2	Hispanic American
Cysticercosis	0.04–0.16	Hispanic American

[9]. Dengue and dengue haemorrhagic fever (DHF) have become more prevlent throughout the LAC region [16]. Brazil has the largest number of NTDs of any country in the LAC region [9, 17], mostly among impoverished populations in the northeastern part of the country. However, the severe poverty in northeastern Brazil does not affect its HDI sufficiently to rank that country in the bottom tier.

The economic downturn in the US has increased media attention to the plight of the Northern American poor, and with it, increased recognition of a hidden underbelly of neglected infections of poverty [5, 6]. Some NTDs found in the LAC region are also found in South Texas and the Gulf Coast, including Chagas disease, cysticercosis, and dengue (Table 1.4) [5, 6]. Of particular concern is evidence suggesting autochthonous transmission of Chagas disease and dengue in these regions. High prevalence rates of toxocariasis and trichomoniasis also occur among people living in poverty in the US and presumably throughout the Americas [5, 6].

1.3 Adverse Effects on Maternal and Child Health, Poverty, and Conflict

Overall, there are three major adverse health and socioeconomic consequences of high prevalence NTDs in the Americas, related to their impact on (1) maternal and child health, (2) poverty, and (3) conflict (Box 1).

Box 1 Effects of the High Burden NTDs on Maternal and Child Health, Poverty, and Conflict in the LAC Region

Maternal Child Health

- Hookworm is associated with anemia in children and pregnancy leading to intellectual and cognitive deficits, low neonatal birth weight, and increased maternal morbidity.
- Chagas disease in pregnancy increases the risk of miscarriage and preterm birth and is associated with vertical transmission in 1 in 20 seropositive mothers resulting in neonatal infection and death.
- Dengue and DHF disproportionately affect children and in pregnancy are linked with elevated rates of preterm birth, cesarean delivery, and vertical transmission.

Poverty

- Hookworm is associated with 40 % reduction in future wage earning.
- Chagas disease results in economic losses exceeding US$ 1 billion annually with lifetime costs per patient averaging almost US$ 12,000.
- High dengue economic costs remain under investigation.

Conflict

- Destabilizing effects on agricultural productivity, land use, food security, economic growth.
- Links with guerilla movements and narcotrafficking.

1.3.1 Maternal and Child Health

It is not commonly appreciated that the highest burden NTDs in the LAC region, including hookworm and the other soil-transmitted hel-

minths, Chagas disease, and dengue exert special adverse consequences for the health of children and women.

Hookworms cause chronic intestinal blood loss leading to iron deficiency anemia and protein malnutrition. Hookworm anemia is more pronounced in women and children because of their unique iron metabolisms [18]. Throughout the LAC region *Necator americanus* is the predominant species causing hookworm disease and anemia [9, 18]. In children this infection is associated with deficiencies in physical growth and cognitive development, while in pregnancy it is linked to increased maternal morbidity and poor neonatal outcomes [18]. Two recent systematic reviews confirm the association between hookworm infection and anemia in children and pregnant women [19, 20]. Specifically, in the LAC region *N. americanus* infection was recently linked to anemia in young children in rural Minas Gerais State, Brazil [21], and with low neonatal birth weight among pregnant women in Peru [22].

Chagas disease has also emerged as an important maternal and child health problem, with mother-to-child transmission increasingly recognized as an important route of infection [23]. Pregnancy has been shown to enhance *T. cruzi* parasitemia [24], with vertical transmission and congenital infection (characterized by hepatosplenomegaly, hydrops, and neonatal death) occurring in an estimated 1 in 20 seropositive mothers [23, 25]. In North America alone there are an estimated 40,000 pregnant women with Chagas disease, and several thousand newborns are likely to be infected with *T. cruzi* annually [26]. The numbers throughout Latin America would therefore be expected to be several-fold higher. Aside from congenital infection, Chagas disease during pregnancy increases the risk of miscarriage, preterm birth, and neonatal infection, which may cause infant death or severe sequelae [25].

Dengue and DHF disproportionately affect children in much of the developing world, including during outbreaks in the LAC region [27, 28]. Additionally, a recent systematic review confirms the harmful effects of dengue during pregnancy, including elevated rates of preterm birth, Cesarean delivery, and vertical transmission [29].

1.3.2 Poverty and Conflict

The mechanisms by which the NTDs actually promote or cause poverty have been reviewed previously. These mechanisms include specific effects on maternal and child health, in addition to the health of workers in the tropics, and agricultural productivity [11, 13]. A retrospective analysis of hookworm in the American South revealed that chronic hookworm infection in childhood reduce future wage earning by 40 % [30], postulated to be due to its harmful effects on child cognitive development. Similarly, Chagas disease is associated with US$1.2 billion in economic losses annually, because of its impact on maternal and child health and occupational productivity, as well as the very high costs of treatment, with a lifetime cost averaging almost US$12,000 per patient [31]. Economic losses from dengue in India were recently estimated to be US$27.4 million during a 2006 epidemic [32], however a recent systematic review concluded that the economic literature on dengue is "sparse" and results are conflicting because of the use of inconsistent assumptions [33]. NTDs also promote conflict and warfare through destabilizing effects on agricultural productivity, abandonment of arable lands, food insecurity and decrements in educational attainment and wage earning [34]. In the LAC region an association has been noted between guerilla movements and the trafficking of narcotics with Chagas disease and leishmaniasis [35].

1.4 Eliminating NTDs in the Americas

Several high-prevalence NTDs, including lymphatic filariasis, onchocerciasis, and trachoma are being eliminated as public health problems in the LAC region [9]. The term elimination refers to reduction in the incidence of a specific infection to zero or below a threshold that can no longer sustain transmission. Such elimination efforts rely heavily on mass MDA, often with drugs donated by the pharmaceutical industry, including ivermectin for onchocerciasis; diethyl-

Table 1.5 Latin American and Caribbean countries that have successfully eliminated their neglected tropical diseases as a public health problem. (Modified from [38])

Disease	Countries
Chagas disease	Brazil, Chile, Uruguay
Schistosomiasis	Dominican Republic, Guadeloupe, Martinique, Puerto Rico
Lymphatic Filariasis	Costa Rica, Suriname, Trinidad and Tobago
Trachoma	Mexico
Leprosy	All except Brazil
Onchocerciasis	Elimination pending in the six affected countries

carbamazine and albendazole for lymphatic filariasis; and azithromycin for trachoma [36]. Through MDA along with other control measures including integrated vector management, lymphatic filariasis has been eliminated from Costa Rica, Suriname, Trinidad, and Tobago (Table 1.5), with expectations that this disease might also be eliminated from the few remaining endemic countries, including Brazil, Haiti, Dominican Republic, and Guyana by 2020.

Similarly through the Onchocerciasis Elimination Programme of the Americas (OEPA) it should be possible to eliminate onchocerciasis in the six remaining endemic countries, Guatemala, Mexico, Venezuela, Ecuador, Colombia, and Brazil, where approximately 0.52 million people are at risk for infection, while trachoma remains only in Brazil, Guatemala, and in five municipalities of neighboring Chiapas state in Mexico [37–39]. Today, such elimination efforts are being coordinated by the Pan American Health Organization in association with the Interamerican Development Bank and a Global Network for NTDs based at the Sabin Vaccine Institute. It has been estimated that US$128 million will be required to eliminate these three infections in the LAC region by the year 2020 [39], and a special "LAC fund" has been established in order to receive public and private donations for this purpose.

Through MDA with praziquantel, schistosomiasis remains endemic in only four LAC countries, including Brazil, St. Lucia, Suriname, and Venezuela, having been previously eliminated from Martinique, Guadeloupe, Puerto Rico and the Dominican Republic, with an expectation that this disease might be eliminated from the Caribbean in the coming years [37, 38]. Because of multi-drug therapy with dapsone, clofazimine, and rifampin, fewer than 34,000 registered cases of leprosy remain in the Americas, with all but about 4,000 cases being in Brazil [40]. Canine rabies has also been largely eliminated. The majority of the cases of canine rabies transmitted to humans occur in poor neighborhoods in Haiti and Bolivia [37].

The highest prevalence NTDs, including hookworm and the other soil-transmitted helminths, Chagas disease, dengue, and leishmaniasis, in addition to schistosomiasis in Brazil, will not be eliminated solely by relying on existing technologies, even though some progress has been achieved with MDA with albendazole/mebendazole and praziquantel (for soil-transmitted helminths and schistosomiasis, respectively) and integrated vector management for Chagas disease, dengue, and leishmaniasis [38]. In the case of hookworm, high rates of mebendazole drug failure and post-treatment reinfection have been reported, and although repeated MDA targeting children may have an impact on reducing the transmission of ascariasis and trichuriasis, it is not expected to have an impact on hookworm infection because of hookworm's unique transmission dynamics among adults [41]. Similarly, integrated vector management has so far been successful for eliminating Chagas disease only in the southern Cone of South America (Brazil, Chile, Uruguay), whereas elsewhere insecticide resistance, reinvasion and recolonization of reduviid vectors after spraying have thwarted control efforts [42]. Therefore, a recent "audacious" call to eliminate all of the 17 NTDs as defined by the WHO will require a new generation of technologies, especially the development of NTD vaccines [38].

1.5 New 'Anti-Poverty Vaccines' will be Required

Vaccines to combat the NTD vaccines are also known as the 'anti-poverty vaccines' because of their potential impact on economic development in addition to improving health [13, 43].

Table 1.6 Vaccines under development for Latin America's neglected tropical diseases. (Modified from [43])

Disease	Type of vaccine under development	Stage of development	Organization leading vaccine development efforts	Industrial partners
Chagas disease	Human therapeutic vaccine	Preclinical	Sabin Vaccine Institute PDP (Chagas Vaccine Initiative)	Birmex and CINVESTAV
Cysticercosis	Veterinary vaccine	Animal trials	Universidad Nacional Autonoma de Mexico	Pending
Dengue	Human preventive vaccine	Phase 1 and 2	GSK, Merck & Co., Sanofi-Pasteur, Instituto Butanan	GSK, Merck & Co., Sanofi-Pasteur, Instituto Butanan
Foodborne trematode infections	Veterinary vaccine	Animal trials	FIOCRUZ (Oswaldo Cruz Foundation)	Ouro Fino
Hookworm infection	Human preventive vaccine	Phase 1	Sabin Vaccine Institute PDP (Human Hookworm Vaccine Initiative)	FIOCRUZ-Bio-manguinhos; Aeras, Fraunhofer CMB
Leishmaniasis	Human preventive, therapeutic, and veterinary	Phase 1 and 2 and animal trials	Infectious Diseases Research Institute (IDRI)	Instituto Butantan
Schistosomiasis	Human preventive vaccine	cGMP manufacture*	Sabin Vaccine Institute PDP (Schistosomiasis Vaccine Initiative), FIOCRUZ	Aeras, Instituto Butantan, Ouro Fino

* *cGMP* current good manufacturing practices

Table 1.6 lists the major anti-poverty vaccines under development in the Americas, which include new human vaccines against *Trypanosoma cruzi*, dengue virus, hookworm, leishmania species, and schistosoma species, in addition to veterinary vaccines against *Taenia solium* and *Fasciola hepatica* (a food-borne trematode) to prevent transmission to humans [43]. Of these vaccines, only the dengue vaccine is being developed and produced by the multinational vaccine manufacturers, including three vaccines being developed independently by Merck & Co., GlaxoSmithKline, and Sanofi-Pasteur [43, 44]. The other anti-poverty vaccines are largely being developed by non-profit product development partnerships (PDPs) in association with developing country manufacturers [43]. One reason why dengue vaccine development receives investment from multinational pharmaceutical companies is the large potential commercial market for such a product, given that dengue affects people living in wealthier urban centers, whereas the other anti-poverty vaccines target almost exclusively the bottom 100 million in the LAC region, and their counterparts in Africa and Asia [43]. There is some overlap, however, as a Brazilian company Ouro Fino Animal Health is developing a *Fasciola hepatica* vaccine for livestock (http://www.veterinaryproducts1.com/supplier/ouro-fino-animal-health.html), which could prevent transmission to humans, while the developing country manufacturer, Instituto Butantan is also developing its own dengue vaccine (http://www.butantan.gov.br/home).

Today, efforts to develop and test anti-poverty vaccines targeted for human disease in the Americas are being led by PDPs, in collaboration with Latin American developing country manufacturers [43]. Most of these manufacturers, in turn, are owned and operated by scientific enterprises directly supported by federal and state governments in Latin America, including FIOCRUZ Bio-Manguinhos (through support of the Brazilian Ministry of Health), Instituto Butantan (State of Sao Paulo, Brazil), Birmex (Laboratorios de Biologicos y Reactivos de Mexico, Mexican Ministry of Health), and Cuba's Instituto Finlay [43]. Some examples of PDP-manufacture collaborations are shown in Table 1.6 and include the non-profit Infectious Disease Research Institute (Seattle, Washington), which is working with Instituto Butantan for leishmaniasis vaccine development, while the Sabin Vaccine Institute PDP (Houston, Texas and Washington, DC) is working with FIOCRUZ, (together with the US-based Aeras and Fraunhofer Center for

Molecular Biolotechnology) to develop a human hookworm vaccine, and with CINVESTAV (Centro de Investigacion y de Estudios Avanzados del Instituto Politecnico Nacional (Center for Research and Advanced Studies)) and Birmex for a Chagas disease vaccine. Each of these vaccines is either at the stage of pilot manufacture under cGMP (current good manufacturing practices) or in early clinical development [43].

1.6 Hookworm and Chagas Disease Vaccines

Progress in the development of a vaccine against hookworm was reviewed recently [45]. In brief, the human hookworm vaccine is a bivalent vaccine comprised of two recombinant antigens, which are parasitic enzymes involved in blood feeding [45]. The vaccine targets the adult stages of *N. americanus*, the most common hookworm worldwide and almost the exclusive hookworm in the LAC region. One of the antigens is a recombinant *N. americanus* glutathione S-transferase (*Na*-GST-1) expressed in yeast, an enzyme required by the parasite for heme binding and heme detoxification. The other is a recombinant *N. americanus* aspartic protease (*Na*-APR-1) expressed in plants, an enzyme required for hemoglobin degradation. Both recombinant antigens induce high levels of IgG antibody and have demonstrated protective immunity in laboratory animals, with reduced host worm burden and/or blood loss [45]. The recombinant proteins have completed pilot cGMP manufacture, and *Na*-GST-1 has entered phase 1 clinical testing. Ultimately both antigens would be formulated on alum and possibly combined with a second adjuvant such as a synthetic lipid A [45]. The target product profile of the human hookworm vaccine relies on its use to prevent moderate and heavy *N. americanus* infections in children under the age of 10 years [45]. The vaccine may be incorporated into the Expanded Program on Immunization (EPI) in order to be co-administered with measles and other childhood vaccines to infants (children under the age of one), or it may be co-administered with a single dose of anthelmintic drug in older children already infected with hookworm. The desired efficacy of the human hookworm vaccine is at least 80 % against moderate and heavy hookworm infections for at least 5 years after immunization [45]. The cost-effectiveness of such a vaccine was recently confirmed under a number of different scenarios [46].

Progress on the development of a vaccine for Chagas disease has also been reviewed recently [47]. Unlike the human hookworm vaccine, which is a primarily preventive vaccine, the Chagas vaccine is being proposed as a therapeutic vaccine for the treatment of individuals who have been infected with *T. cruzi* and have seroconverted. In such individuals, who have so-called "indeterminate" status (with no clinical, electrocardiographical or radiological evidence of disease), approximately 20–30 % subsequently develop Chagasic cardiomyopathy [48]. There is an urgent need for new therapeutic approaches for these patients, especially in order to eradicate *T. cruzi* parasites in the myocardium that are responsible for progression to cardiomyopathy and heart failure. A recent meta-analysis of the two currently available drugs benznidazole and nifurtimox concluded that their efficacy in late chronic infection is doubtful and does not result in seroreversion [49, 50], although a larger randomized placebo-controlled study is in progress [51]. Moreover, prolonged treatment courses lasting 2–3 months are required and result in serious side effects in up to one-half of the patients, with 10–20 % discontinuing therapy as a result [52, 53]. The drugs are also contraindicated in pregnancy and are extremely expensive to purchase and administer [54].

The target groups for this therapeutic vaccine are adults, particularly pregnant women to improve birth outcomes and prevent congenital infection, and children over the age of two, in Chagas disease-endemic areas. The vaccine is under development by the Sabin Vaccine Institute PDP and the Texas Children's Center for Vaccine Development in collaboration with the US National Institutes of Health and three Mexican institutions, the Autonomous University of Yucatan (UADY), CINVESTAV, and Birmex (Mexico's public sector vaccine manufacturer).

The bivalent vaccine is comprised of two *T. cruzi* recombinant proteins formulated on alum. One of the antigens is a unique *T. cruzi* 24 kDa antigen (Tc24) and the other belongs to a family of *T. cruzi* surface transialidases (TSA-1). Proof of concept for the protective effect of these antigens is based on experimental immunizations in *T. cruzi*-infected laboratory animals, together with identifiable mechanisms of protective immunity [47, 55–58]. In acutely and chronically-infected mice the combined antigens produced significantly reduced parasitemia and myocardial inflammation compared to controls [58]. Because protection requires the stimulation of $CD8^+$ T cells and production of interferon gamma [58], the vaccine incorporates a second adjuvant comprised of a synthetic lipid A. The requirement for this second adjuvant will be determined pending preclinical studies and early clinical trials.

Ascertaining the feasibility of expression of Tc24 and TSA-1 as soluble recombinant proteins for the purpose of process development, scale-up and current Good Manufacturing Practices (cGMP) manufacture is currently in progress. It is expected that during process development and scale-up, studies to evaluate protein attributes and stability will be established. In addition, formulation studies with alum and other adjuvants will be performed. Ultimately, the ability of these formulations to protect mice from acute and chronic *T. cruzi* infections will be confirmed.

It is anticipated that successfully eliciting Th1 immune responses will be a key to human therapeutic vaccination against Chagas disease [47, 55–58]. Th1-type immune responses are characterized by the generation of $CD8^+$ T cells, which can target intracellular pathogens [55–58]. While several purified recombinant protein vaccines are in clinical development, they are limited by poor immunogenicity and inadequate stimulation of Th1 immunity [59, 60]. Particulate-based systems can increase the delivery of antigens to antigen-presenting dendritic cells, while simultaneously maintaining antigen integrity [60]. Equally important, particulate systems can co-deliver immunopotentiating agents and activate $CD8^+$ cells. Using this strategy, the two recombinant *T. cruzi* antigens under development will be encapsulated in nanoparticles that will also contain an adjuvant molecule such as the TLR3 agonist poly(I:C). It has been previously shown that ovalbumin formulated in this manner elicits antigen-specific $CD8^+$ T cell responses *in vitro* that greatly exceed those produced either by the antigen alone or antigen encapsulated without the TLR3 agonist [61]. We will therefore attempt to simultaneously develop the Chagas disease vaccine as a nanoparticle vaccine using these technologies, and evaluate it in an experimental therapeutic mouse model for *T. cruzi* infection. An alternate delivery system under consideration is a viscous polysaccharide solution, which forms an extracellular antigen depot at the injection site [62]. Still another option is to examine viral vectors and heterologous prime-boost approaches. This approach has been successful for other systems requiring induction of Th1-type immunity [63–65].

1.7 Concluding Statement

While estimates indicate that less than US$200 million will be required to eliminate lymphatic filariasis, onchocerciasis, and trachoma from the Americas, there are still the added costs of continuing control efforts with MDA for other NTDs (with costs possibly exceeding US$300 million) [37], in addition to the costs of integrated vector management and the estimated US$1.2 billion required annually for Chagas disease alone, presumably much of which is treatment costs [66] In addition to jumping the scientific hurdles, the challenge of vaccine development includes demonstration of cost effectiveness, and this has now been shown for both human hookworm and Chagas disease vaccines [46, 66]. These two vaccines, in addition to vaccines to prevent leishmaniasis, schistosomiasis, and dengue, represent urgently needed control measures for a full scale elimination effort for all of the major NTDs in the Americas. Such activities in the Western Hemisphere are part of a larger "audacious goal" for

elimination of all of the 17 NTDs as the most common infections of the world's poor and legacies of neglect, ignorance, and slavery [38]. Thus, an opportunity is now in hand for the major PDPs, research institutes and developing country manufacturers in the LAC region, together with the major development banks and PAHO to draft an elimination strategy for the NTDs in the Americas.

Acknowledgements The development of the human hookworm vaccine is supported by grants to the Sabin Vaccine Institute from the Bill & Melinda Gates Foundation, the Dutch Ministry of Foreign Affairs, and the Brazilian Ministry of Health. The feasibility studies for the development of the Chagas disease vaccine is supported by funds from the Carlos Slim Health Institute (Instituto Carlos Slim de la Salud) and the SouthWest Electronic Energy Medical Research Institute.

References

1. http://data.worldbank.org/topic/poverty. Accessed 3 Sept 2011
2. http://www.ruralpovertyportal.org/web/guest/region/home/tags/americas. Accessed 3 Sept 2011
3. http://www.eoearth.org/article/Human_Development_Index_for_Latin_America_Caribbean_Nations. Accessed 3 Sept 2011
4. http://www.census.gov/newsroom/releases/archives/income_wealth/cb11-157.html. Accessed 13 Sept 2011
5. Hotez PJ (2008) Neglected infections of poverty in the United States of America. PLoS Negl Trop Dis 2:e256
6. Hotez PJ (2011) America's most distressed areas and their neglected infections: the United States Gulf Coast and the District of Columbia. PLoS Negl Trop Dis 5:e843
7. Hotez PJ (2010) Neglected infections of poverty among the indigenous peoples of the Arctic. PLoS Negl Trop Dis 4:e606
8. http://www.worldhunger.org/articles/Learn/world%20hunger%20facts%202002.htm. Accessed 3 Sept 2011
9. Hotez PJ, Bottazzi ME, Franco-Paredes C, Ault S, Periago MR (2008) The neglected tropical diseases of Latin America and the Caribbean: a review of disease burden and distribution and a roadmap for control and elimination. PLoS Negl Trop Dis 2:e300
10. Hotez PJ, Fenwick A, Kumaresan J, Molyneux DH, Ehrlich Sachs S, Sachs JD, Savioli L (2007) Control of neglected tropical diseases. N Engl J Med 357:1018–1027
11. Hotez PJ, Fenwick A, Savioli L, Molyneux DH (2009) Rescuing the bottom billion through control of neglected tropical diseases. Lancet 373:157–155
12. World Health Organization (2010) Working to overcome the global impact of neglected tropical diseases. First WHO report on neglected tropical diseases. Geneva. http://www.who.int/neglected_diseases/2010report/en/index.html. p 172
13. Hotez PJ, Ferris M (2006) The anti-poverty vaccines. Vaccine 24:5787–5799
14. Furtado JM, Smith JR, Belfort R, Gattey D, Winthrop KL (2011) Toxoplasmosis: a global threat. J Global Infect Dis 3:281–284
15. Lammie PJ, Lindo JF, Secor WE, Vasquez J, Ault SK et al (2007) Eliminating lymphatic filariasis, onchocerciasis and schistosomiasis from the Americas: breaking a historical legacy of slavery. PLoS Negl Trop Dis 1:e71
16. Tapia-Conyer R, Mendez-Galvan JF, Gallardo-Rincon H (2009) The growing burden of dengue in Latin America. J Clin Virol 46(Suppl 2):S3–6
17. Hotez PJ (2008) The giant anteater in the room: Brazil's neglected tropical diseases problem. PLoS Negl Trop Dis 2:e177
18. Hotez PJ, Brooker S, Bethony JM, Bottazzi ME, Loukas A, Xiao SH (2004) Hookworm infection. N Engl J Med 351:799–807
19. Smith JL, Brooker S (2010) Impact of hookworm infection and deworming on anemia in non-pregnant populations: a systematic review. Trop Med Int Health 15:776–795
20. Brooker S, Hotez PJ, Bundy DAP (2008) Hookworm-related anaemia among pregnant women: a systematic review. PLoS Negl Trop Dis 2:e291
21. Brooker S, Jardim-Botelho A, Quinnell RJ, Geiger SM, Caldas IR, Fleming F, Hotez PJ, Correa-Oliveira R, Rodrigues LC, Bethony JM (2007) Age-related changes in hookworm infection, anaemia and iron deficiency in an area of high Necator americanus hookworm transmission in south-eastern Brazil. Trans R Soc Trop Med Hyg 101:146–154
22. Larocque R, Casapia M, Gotuzzo E, MacLean JD, Soto JC et al (2006) A double-blind randomized controlled trial of antenatal mebendazole to educe low birthweight in a hookworm-endemic area of Peru. Trop Med Int Health 11:1485–1495
23. Theiler RN, Rasmussen SA, Treadwell TA, Jamieson DJ (2008) Emerging and zoonotic infections in women. Infect Dis Clin North Am 22:755–772
24. Siriano L da R, Luguetti AO, Avelar JB, Marra NL, de Castro AM (2011) Chagas disease: increased parasitemia during pregnancy detected by hemoculture. Am J Trop Med Hyg 84:569–574
25. Perez-Lopez FR, Chedraui P (2010) Chagas disease in pregnancy: a non-endemic problem in a globalized world. Arch Gynecol Obstet 282:595–599
26. Buekens P, Almendares O, Carlier Y, Dumonteil E, Eberhard M, Gamboa-Leon R, James M, Padilla N, Wesson D, Xiong X (2008) Mother-to-child transmission of Chagas disease in North America:

why don't we do more? Matern Child Health J 12:283–286
27. Giraldo D, Sant'anna C, Perisse AR, March MD, Souza AP, Mendes A, Bonfim M, Hofer CB (2011) Characteristics of children hospitalized with dengue fever in an outbreak in Rio de Janeiro, Brazil. Trans R Soc Trop Med Hyg 105(10):601–603 (Epub 2011 Aug 19)
28. Rodriguez-Barraquer I, Cordeiro MT, Braga C, de Souza WV, Marques ET, Cummings DA (2011) From re-emergence to hyperendemicity: the natural history of the dengue epidemic in Brazil. PLoS Negl Trop Dis 5:e935
29. Pouliot SH, Xiong X, Harville E, Paz-Soldan V, Tomashek KM, Breart G, Buekens P (2010) Maternal dengue and pregnancy outcomes: a systematic review. Obstet Gynecol Surg 65:107–118
30. Bleakley H (2007) Disease and development: evidence from hookworm eradication in the American South. Q J Econ 122:73–117
31. Lee BY, Bacon KM, Connor DL, Willig AM, Bailey RR (2010) The potential economic value of a Trypanosoma cruzi (Chagas disease) vaccine in Latin America. PLoS Negl Trop Dis 4(12):e916
32. Garg P, Nagpal J, Khairnar P, Seneviratne SL (2008) Economic burden of dengue infections in India. Trans R Soc Trop Med Hyg 102:570–577
33. Beatty ME, Beutels P, Meltzer MI, Shepard DS, Hombach J, Hutubessy R, Dessis D, Coudeveille L, Dervaux B, Wichmann O, Margolis HS, Kuritsky JN (2011) Health economics of dengue: a systematic literature review and expert panel's assessment. Am J Trop Med 84:473–488
34. Hotez PJ, Thompson TG (2009) Waging peace through neglected tropical disease control: a US foreign policy for the bottom billion. PLoS Negl Trop Dis 3:e346
35. Beyrer C, Villar JC, Suwanvanichkij V, Singh S, Baral SD et al (2007) Neglected diseases, civil conflicts, and the right to health. Lancet 370:619–627
36. Hotez PJ (2009) Mass drug administration and the integrated control of the world's high prevalence neglected tropical diseases. Clin Pharamcol Therap 85:659–664
37. Schneider MC, Aguilera XP, Barbosa da Silva Jr J, Ault SK, Najera P, Martinez J, Requejo R, Nicholls RS, Yadon Z, Silva JC, Leanes LF, Periago MR (2011) Elimination of neglected diseases in Latin America and the Caribbean: a mapping of selected diseases. PLoS Negl Trop Dis 5:e964
38. Hotez P (2011) Enlarging the "audacious goal": elimination of the world's high prevalence neglected tropical diseases. Vaccine (in press)
39. Bitran R, Martorell B, Escobar L, Munoz R, Glassman A (2009) Controlling and eliminating neglected diseases in Latin America and the Caribbean. Health Aff (Millwood) 28:1707–1719
40. World Health Organization (2011) Leprosy update, 2011. World Epidemiol Rec 36:389–400
41. Hotez PJ, Bethony J, Bottazzi ME, Brooker S, Diemert D, Loukas A (2006) New technologies for the control of human hookworm infection. Trends Parasitol 22:327–331
42. Reithinger R, Tarleton R, Urbina JA, Kitron U, Gurtler RE (2009) Eliminating Chagas disease: challenges and a roadmap. BMJ 338:b1283
43. Hotez P (2011) A handful of 'anti-poverty' vaccines exist for neglected diseases, but the world's poorest billion people need more. Health Aff 30:1080–1087
44. Coller BA, Clements DE (2011) Dengue vaccines: progress and challenges. Curr Opin Immunol 23:391–398
45. Hotez PJ, Bethony JM, Diemert DJ, Pearson M, Loukas A (2010) Developing vaccines to combat hookworminfection and intestinal schistosomiasis. Nat Rev Microbiol 8:814–826
46. Lee BY, Bacon KM, Bailey R, Wiringa AE, Smith KJ (2011) The potential economic value of a hookworm vaccine. Vaccine 29:1201–1210
47. Quijano-Hernandez I, Dumonteil E (2011) Advances and challenges towards a vaccine against Chagas disease. Hum Vaccin (in press)
48. Rassi Jr A, Rassi A, Marin-Neto JA (2010) Chagas disease. Lancet 375:1388–1402
49. Perez-Molina JA, Perez-Ayala A, Moreno S, Fernandez-Gonzalez MC, Zamora J, Lopez-Velez R (2009) Use of benznidazole to treat chronic Chagas' disease: a systematic review with a meta-analysis. J Antimicrob Chemother 64:1139–1147
50. Sarli Issa V, Alcides Bocchi E (2010) Antitrypanosomal agents: treatment or threat? Lancet 376:768–769
51. Marin-Neto JA, Rassi A Jr, Morillo CA et al on behalf of BENEFIT Investigators (2008). Rationale and design of a randomized placebo-controlled trial assessing the effects of etiologic treatment in Chagas cardiomyopathy: the BENznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT). Am Heart J 156:37–43
52. Pinazo M-J, Munoz J, Posada E, Lopez-Chejade P, Gallego M, Ayala E, del Cacho E, Soy D, Gascon J (2010) Tolerance of benznidazole in treatment of Chagas' disease in Adults. Antmicrob Agents Chemother 54:4896–4899
53. Viotti R, Vigliano C, Lococo B, Alvarez MG, Petti M, Bertocchi G, Armenti A (2009) Side effects of benznidazole as treatment in chronic Chagas disease: fears and realities. Expert Rev AntiInfect Therap 7:157–163
54. Castillo-Riqueime M, Guhl F, Turriago B, Pinto N, Rosas F, Florez Moartinez M, Fox-Rushby J, Davies C, Campbell-Lendrum D (2008) The costs of preventing and treating Chagas disease in Colombia. PLoS Negl Trop Dis 2(11):e336
55. Dumonteil E, Escobedo-Ortegon J, Reyes-Rodriguez N, Arjona-Torres A, Ramirez-Sierra J (2004) Immunotherapy of Trypanosoma cruzi infection with DNA vaccines in mice. Infect Immun 72(1):46–53
56. Zapata-Estrella H, Hummel-Newell C, Sanchez-Burgos G, Escobedo-Ortegon J, Ramirez-Sierra MJ, Arjona-Torres A, Dumonteil E (2006) Control of

Trypanosoma cruzi infection and changes in T-cell populations induced by a therapeutic DNA vaccine in mice. Immunol Lett 103:186–191
57. Sanchez-Burgos G, Mezquite-Vega RG, Escobedo-Ortegon J et al (2007) Comparative evaluation of therapeutic DNA vaccines against Trypanosoma cruzi in mice. FEMS Immunol Med Microbiol 50:333–341
58. Limon-Flores AY, Cervera-Cetina R, Tzec-Arjona JL et al (2010) Effect of a combination DNA vaccine for the prevention and therapy of Trypanosoma cruzi infection in mice: role of $CD4^+$ and $CD8^+$ cells. Vaccine 28(46):7414–7419
59. O'Hagan DT, De Gregorio E (2009) The path to a successful vaccine adjuvant—'the long and winding road'. Drug Discov Today 14:541–551
60. Oyewumi MO, Kumar A, Cui Z (2010) Nano-microparticles as immune adjuvants: correlating particle sizes adn the resultant immune responses. Expert Rev Vaccines 9:1095–1107
61. Heffernan MJ, Kasturi SP, Yang SC, Pulendran B, Murthy N (2009) The stimulation of CD8+ T cells by dendritic cells pulsed with polyketal microparticles containing ion-paired protein antigen and poly(inosinic acid)-poly(cytidylic acid). Biomaterials 30:910–918
62. Heffernan MJ, Zaharoff DA, Fallon JK, Schlom J, Greiner JW (2011) In vivo efficacy of a chitosan/IL-12 adjuvant system for protein-based vaccines. Biomaterials 32:926–932
63. Roller CS, Reyes-Sandoval A, Cottingham MG, Ewer K, Hill AVS (2011) Viral vectors as vaccine platform: deployment in sight. Curr Opin Immunol 23:377–382
64. Cavenaugh JS, Awi D, Mendy M, Hill AVS, Whittle H, McConkey S (2011) Partially randomized, non-blinded trial of DNA and MVA therapeutic vaccines based on hepatitis B virus surface protein for chronic HBV infection. PLoS One 6:e14626
65. Hill AVS, Reyes-Sandoval A, O'Hara G, Ewer K, Lawrie Al, Goodman A, Nicosia A, Folgori A, Colloca S, Coretese R, Gilbert SC, Draper SJ (2010) Prime-boost vectored malaria vaccines. Hum Vaccin 6:78–83
66. Lee BY, Bacon KM, Connor DL, Willig AM, Bailey RR (2010) The potential economic value of a Trypanosoma cruzi (Chagas disease) vaccine in Latin America. PLoS Negl Trop Dis 4(12):e916

Non-typhoidal Salmonella in Children: Microbiology, Epidemiology and Treatment

2

Gabrielle M. Haeusler and Nigel Curtis

Abstract

Non-typhoidal *Salmonellae* (NTS) are an important cause of infectious diarrhoea world-wide. In the absence of immune deficiency, gastroenteritis caused by NTS is usually mild, self limiting and rarely requires intervention. NTS are also an important cause of invasive disease, particularly in developing countries, likely secondary to the high prevalence of co-existing malnutrition, malaria and HIV infection. This review provides an overview of the microbiology, epidemiology and pathogenesis of NTS, and compares recommendations for the treatment of NTS gastroenteritis in children.

2.1 Introduction

Non-typhoidal *Salmonellae* (NTS) are an important cause of infectious diarrhoea world-wide. In the absence of immune deficiency, gastroenteritis caused by NTS is usually mild, self limiting and rarely requires intervention. NTS are also an important cause of invasive disease, particularly in developing countries, likely secondary to the high prevalence of co-existing malnutrition, malaria and HIV infection. Antibiotic treatment of NTS gastroenteritis has been the subject of a meta-analysis, but questions regarding exactly which patients should be treated and the optimal regimen remain unanswered. This review provides an overview of the microbiology, epidemiology and pathogenesis of NTS, and compares recommendations for the treatment of NTS gastroenteritis in children.

N. Curtis (✉)
Department of Paediatrics, The University of Melbourne; Infectious Diseases Unit, The Royal Children's Hospital Melbourne; Infectious Diseases & Microbiology Research Group, Murdoch Children's Research Institute, Parkville, Australia
e-mail: nigel.curtis@rch.org.au

G. M. Haeusler
Infectious Diseases Unit, The Royal Children's Hospital Melbourne, Parkville, Australia
e-mail: gabrielle.haeusler@rch.org.au

2.2 Classification and Microbiology

The genus *Salmonella* belongs to the family of Enterobacteraciae. *Salmonella* are separated into two species, *Salmonella enterica* and *Salmonella bongori* (previously classified as subsp. V.), with the former being further classified into six subspecies (I, *S. enterica* subsp. *enterica*; II,

N. Curtis et al. (eds.), *Hot Topics in Infection and Immunity in Children IX,*
Advances in Experimental Medicine and Biology 764, DOI 10.1007/978-1-4614-4726-9_2,