IMPROVING GLOBAL HEALTH BY PREVENTING PNEUMOCOCCAL DISEASE

Report from the All-Party Parliamentary Group on Pneumococcal Disease Prevention in the Developing World

All-Party Parliamentary Group on Pneumococcal Disease Prevention in the Developing World

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APPG Mission Statement

The All-Party Parliamentary Group (APPG) on Pneumococcal Disease Prevention in the Developing World was formed on 23rd January 2007 in response to the urgent need to improve child survival and tackle the devastating impact of pneumococcal disease in the developing world.

The parliamentarians that constitute the APPG will work to raise awareness among their colleagues nationally, across Europe and around the world about pneumococcal disease, its prevention through vaccination, and international efforts to ensure sustainable financing.

Pneumonia is the leading infectious cause of child mortality worldwide, causing an estimated 1.9 million (or 19%) of the estimated 10 million child deaths each year. Pneumococcal disease is the leading cause of child pneumonia deaths, as well as the second leading cause of childhood meningitis deaths. It kills more than 1.6 million people including between 700,000 and 1 million children under five each year. Pneumococcal disease is a growing and increasingly urgent global problem. HIV infected children are 20 to 40 times more likely to get pneumococcal disease.

Many of these deaths could be averted with the use of a simple vaccine. Without a concerted effort on behalf of the global community, pneumococcal disease will continue to claim the lives of hundreds of thousands of children each year.

Investing in vaccines would contribute to achieving the United Nations' Millennium Development Goal of reducing child deaths by two-thirds between 1990 and 2015. The hope is that healthy children will, in turn, benefit from education and contribute to improved and more robust economic growth in developing countries.

The APPG aims to achieve its goals by working closely with civil society, academia, international organisations and industry.

For more information on the APPG and the for the full evidence transcript, please visit: www.appg-preventpneumo.org.uk

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FOREWORD

Pneumococcal disease kills over 1.6 million people each year. The vast majority of its victims come from the world's poorest countries and half of them are children under the age of five. It is extraordinary, in view of these facts, that pneumococcus remains a relatively unknown disease and does not have a higher place on the agenda of the international community.

Since it was established in 2007, the All Party Parliamentary Group on Pneumococcal Disease Prevention in the Developing World has done a huge amount of work to build awareness and understanding of this forgotten killer. I congratulate the group for all its work and for having come together to research and produce this report.

This government is determined to address the scourge of pneumococcal disease. We are working in partnership with the governments of Italy, Canada, Russia and Norway and the Bill and Melinda Gates Foundation to contribute $1.5 billion, collectively, to the pilot Advance Market Commitment (AMC). This highly innovative project has the potential to save millions of lives over the next twenty years by accelerating the availability of new pneumococcal vaccines in developing countries across the world. If this pilot is successful, the AMC approach could be used to incentivise the development of vaccines and treatments for other global diseases.

I look forward to reviewing, together with our international partners, the conclusions and recommendations of your report.

The Rt Hon Douglas Alexander MP,
Secretary of State for International Development

LIST OF ABBREVIATIONS

AMC
Advance Market Commitment

APPG
All Party Parliamentary Group on Pneumococcal Disease Prevention in the Developing World

DFID
Department for International Development

EPI
Expanded Programme on Immunisation

GAVI Alliance
Formerly Global Alliance for Vaccines Initiative

The Global Fund
The Global Fund to Fight AIDS, Tuberculosis and Malaria

GNI
Gross National Income

GSK
GlaxoSmithKline

HIV/AIDS
Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome

Hib
Haemophilus influenzae type b

IFFIm
International Finance Facility for Immunisation

IPD
Invasive Pneumococcal Disease

M&E
Monitoring and Evaluation

MDG
Millennium Development Goals

META
Medicines Transparency Alliance

MRF
Meningitis Research Foundation

MSF
Médecins Sans Frontières

NGOs
Non-Governmental Organisations

PACE
Pneumococcal Awareness Council of Experts

PEPFAR
The United States President's Emergency Plan for Relief

PCV
Pneumococcal Conjugate Vaccines

PPV
Pneumococcal Polysaccharide Vaccines

R&D
Research and Development

TB
Tuberculosis

TPP
Target Product Profile

UNICEF
United Nations Children's Fund

WHO
World Health Organisation

EXECUTIVE SUMMARY

This report summarises the results of the All-Party Parliamentary Group for Pneumococcal Disease Prevention in the Developing World (APPG) inquiry into pneumococcal disease in the developing world. It represents an exhaustive 6-month inquiry into the global disease burden of pneumococcal disease and pneumonia, the interventions available to prevent and treat it and an innovative pilot mechanism to accelerate its prevention called the Advance Market Commitment (AMC) for pneumococcal vaccines. As part of this review, the APPG invited internationally recognised experts in fields relating to pneumococcal disease and pneumonia, health and immunisation financing, paediatrics, immunology, global health and international development to submit written evidence to the Group.

The APPG received written submissions from 37 individuals and organisations and also heard oral evidence from 16 leading international specialists. Evidence came from across the globe including developing nations such as Mali, Kenya, the Philippines, The Gambia, India, Pakistan, Bangladesh; middle-income nations such as Lebanon; and the developed world including the UK and the USA. Evidence was submitted by national governments, pharmaceutical companies, multi-laterals, NGOs and funding organisations. We are very encouraged that there has been such an impressive level of global interest and we hope that this report can increase the level of public knowledge and discourse surrounding pneumococcal disease, which has been so severely lacking. This impressive response indicates the breadth of global interest in the disease and strengthens the report.

In expanding such discourse, we hope to supplement the efforts of other organisations, such as the WHO, UNICEF, the Sabin Institute, Pneumococcal Awareness Council of Experts (PACE), The GAVI Alliance and PneumoADIP. These organisations work tirelessly to raise awareness among the media, public, politicians and NGOs of the human, clinical and economic tolls exerted by a disease that causes the deaths of up to one million children under five each year.[1]

Perhaps, the most consistent point made by witnesses who gave evidence to the APPG, is that while pneumococcal disease affects millions of children and families every year, not enough has been done historically to defeat it. This is a preventable tragedy – vaccines do exist but are not being used widely enough.[2]

Globally, 10 million young children die every year: one every three seconds. In response to this tragedy, when the UN approved the eight Millennium Development Goals (MDGs) in 2000, one of them, MDG4 set the challenging target of a two-thirds reduction in mortality among children aged under five by 2015. Treating and preventing infectious disease is central to meeting this goal: more than five million children under five years of age die from infections annually. [3] [4]

Evidence was submitted by national governments pharmaceutical companies, multi-laterals, NGOs and funding organisations.

1 Prof David Goldblatt, University College London (UCL), written evidence, page 392

2 UNICEF/WHO, *Pneumonia: The forgotten killer of children,* New York, UNICEF, 2006, page 27

3 United Nations Department of Public Information, *The Millennium Development Goals and The United Nations Role,* October 2002

4 Initiative for Vaccine Research, World Health Organization, January 2005, *State of the art of vaccine research and development,* January 2005, page ix

S. pneumoniae is the number one vaccine-preventable killer in the world.

Vaccination is perhaps the most efficient and cost effective way of reducing morbidity and mortality from infectious diseases. 'Pneumococcal conjugate vaccines' (PCVs), for example, confer immunity against *Streptococcus pneumoniae* (*S. pneumoniae*) in young children and can indirectly protect non-immunised members of the community (including the elderly and non-vaccinated children) by reducing transmission of the bacterium.[5] *S. pneumoniae* is the number one vaccine-preventable killer in the world[6] and thus PCVs have enormous potential to prevent the tragedy of pneumococcal disease. More than 98% of deaths attributable to pneumococcal disease occur in developing countries.[7] In 2005, the WHO estimates that pneumococcal disease caused approximately 1.6 million deaths, between 700,000 and 1 million of which were children under five years of age.[8]

S. pneumoniae causes several serious diseases including pneumonia, septicaemia and meningitis. Apart from the acute signs and symptoms, pneumococcal disease can cause permanent disability or death. While pneumococcal disease is a significant cause of morbidity and mortality worldwide, some groups bear a disproportionate share of the burden, such as the very young, the elderly,[9] the economically disadvantaged[10] and those with HIV/AIDS.[11] The pneumococcal vaccine offers the global community the opportunity to prevent this devastating disease.

The pilot pneumococcal AMC includes the partnership of and commitments from GAVI, developing countries, donors and vaccine manufacturers.[12] According to GAVI:

Advance Market Commitments (AMCs) are a new approach to public health funding designed to stimulate the development and manufacture of vaccines for developing countries. Donors commit money to guarantee the price of vaccines once they have been developed, thus creating the potential for a viable future market. Decisions about which diseases to target, criteria for effectiveness, price and long-term availability are made in advance by an independent advisory group. The donor commitments provide vaccine makers with the incentive they need to invest the considerable sums required to conduct research, train staff and build manufacturing facilities.[13]

At the same time, the AMC mechanism aims to assure developing countries of safe, effective vaccines with predicable financing and pricing.

If the pilot pneumococcal AMC proves successful, future AMCs could fund interventions against other endemic diseases[14] and, possibly, fund developments in other areas important to global health and development such as environmental issues.[15] For this to happen, it is vital that the governance structures and processes are fit for purpose and that stakeholders reach consensus on specific, measurable outcomes.

We congratulate the UK Government for taking a lead on this important initiative and we welcome the commitment to reduce health inequalities that Britain's investment in the AMC represents. We also congratulate

5 Ray GT, Whitney CG, Fireman BH et al., Cost-effectiveness of pneumococcal conjugate vaccine: evidence from the first 5 years of use in the United States incorporating herd effects, *The Pediatric infectious disease journal* J 2006;25:494-501

6 World Health Organization, *Global Immunization Data*, January 2008, page 2

7 Dr Thomas Cherian, WHO, written evidence, page 204

8 Dr J Lob-Levyt, GAVI, written evidence, page 193

9 Bernatoniene J and Finn A, Advances in pneumococcal vaccines: advantages for infants and children, *Drugs* 2005;65:229-55

10 UNICEF/WHO, *op cit.*, page 18

11 Nuorti JP, Butler JC, Gelling L et al., Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California, *Annals of Internal Medicine* 2000;132:182-90

12 Philippe Le Houérou, the World Bank, written evidence, page 182

13 About AMCs, http://www.vaccineamc.org/about.html, last accessed October 7, 2008

14 Philippe Le Houérou, the World Bank written evidence, page 182

15 Joint Statements from Canada, Italy, Norway, Russian and the Bill and Melinda Gates Foundation, written evidence, page 189

GAVI, PneumoADIP and other stakeholders for their success in translating the political will into specific strategies and tactics that will accelerate delivery of life-saving interventions to the most impoverished countries and vulnerable populations worldwide. Our grateful thanks go to all those who submitted written evidence and supplied background papers and information; also to the individuals and organisations who gave oral evidence in two evidence sessions at Westminster in April and June 2008. We are especially grateful to those who travelled from developing countries around the world to attend the evidence sessions.

We found that the consensus of initial impressions is that the AMC should accelerate the availability of affordable, effective pneumococcal vaccines to the world's poorest countries in a sustainable manner. Indeed, we could not envisage a more appropriate or practical system capable of providing an adequate supply of affordable vaccine.

In conclusion, the APPG finds convincing evidence that pneumococcal disease is a serious, preventable cause of death and disability in need of urgent action. The Group consistently heard the message that this disease is under-recognised and that until recently, few dedicated efforts had been made to tackle it. This is partly due to the fact that severe pneumococcal disease is now a rarity in the developed world and it came as a shock to the APPG that the pneumococcus, virtually conquered in the UK, causes such enormous, inexcusable, preventable morbidity and mortality worldwide. We fully support the opinion of our technical expert witnesses that the existing and near-term vaccines, together with strengthening of health systems, should be a major focus of prevention efforts. Evidence presented to the Group also indicates that success will require sustained political will, continued funding for research, strengthening of surveillance systems in developing countries and international coordination of efforts.

In 2005, the WHO estimates that pneumococcal disease caused approximately 1.6 million deaths, between 700,000 and 1 million of which were children under five years of age.

Vaccination is perhaps the most efficient and cost effective method of reducing morbidity and mortality from treatable infectious diseases.

1 INTRODUCTION

1.1 Vaccines and the developing world

One child dies every three seconds, which equates to 10 million children globally each year. For this reason the 2000 Millennium Summit agreed that reducing childhood mortality represents an urgent economic, political and humanitarian priority for health services and governments worldwide. Millennium Development Goal 4 (MDG4) sets the challenging target of reducing mortality by two-thirds among children under five years of age by 2015. Infectious diseases are responsible for millions of deaths worldwide and claim the lives of more than five million children under five each year, making their prevention key to meeting MDG4.[16] [17]

Vaccination is perhaps the most efficient and cost effective method of reducing morbidity and mortality from treatable infectious diseases. The WHO Initiative for Vaccine Research remarked, "With the exception of water sanitation, no other modality – not even antibiotics – has had such a major effect on mortality reduction and population growth".[18] Other authorities concur. Letvin et al commented, "Vaccination is perhaps the most powerful of all medical interventions".[19]

The growing number of effective, well-tolerated vaccines means that many diseases previous generations feared are now near medical curiosities across the developed world. In the USA, vaccines reduced deaths from diphtheria, mumps, pertussis (whooping cough) and tetanus by at least 99%.[20] During the past 25 years, vaccination has eliminated smallpox worldwide, polio from the western hemisphere and virtually eliminated *Haemophilus influenzae* as a cause of life-threatening disease in North America and Europe.[21]

Vaccination programmes are vitally important to developing countries' health systems. When Kenya included *H influenzae type b* (Hib) vaccine as part of the country's routine immunisation programme, within three years, the incidence of Hib among children younger than five years of age fell 88% compared to baseline levels before the vaccine's introduction.[22] Such a reduction in disease numbers would lead to a reduction in hospital admissions (thereby alleviating some pressure on developing health systems) which significantly hinder the implementation of comprehensive immunisation programmes in many developing countries and improved health care in general. Limited healthcare budgets, cold chain requirements and adequate health staffing are also of significant concern.

It is common for there to be a lag of up to 15 years between a vaccine's availability in the developed world and its widespread availability in developing countries[23] and this is unacceptable. There is a need for "innovative instruments" to eliminate the time lag between development and availability of vaccines. According to a joint statement from Canada, Italy, Norway, Russia and the Bill and Melinda Gates Foundation, (who along with the United Kingdom make up the AMC donors) these

16 United Nations Department of Public Information, *The Millennium Development Goals and The United Nations Role,* October 2002

17 Initiative for Vaccine Research World Health Organization, *State of the art of vaccine research and development* January 2005, page ix

18 *ibid.,* page ix

19 Letvin NL, Bloom BR, Hoffman SL, Prospects for vaccines to protect against AIDS, tuberculosis, and malaria, *JAMA* 2001;285: 606-11

20 Roush SW, Murphy TV, Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States, *JAMA* 2007;298:2155-63

21 Letvin NL, Bloom BR, Hoffman SL, op. cit., pages 606-11

22 Cowgill KD, Ndiritu M, Nyiro J et al., Effectiveness of *Haemophilus influenzae type b* Conjugate vaccine introduction into routine childhood immunization, *JAMA,* 2006;296:671-8

23 Parliamentary Under-Secretary of State for International Development (PUSS DFID), Gillian Merron MP, written evidence, page 381

innovative instruments "can help bridge the gap between available resources and development goals set by the international community, most notably the Millennium Development Goals".[24] Against this background, the report considers the issues surrounding new and existing methods to fight pneumococcal disease (pneumococcus) in the developing world.

The death toll from preventable and treatable infectious diseases worldwide, such as pneumococcal disease – which is the number one vaccine preventable killer of children worldwide,[25] illustrates the urgent need for new vaccines and improved implementation and access to developing country immunisation programmes. The scarcity of vaccines against diseases under-addressed by developing countries, such as pneumococcal disease, partly reflects the traditional lack of investment in research and development of interventions for diseases affecting poor countries. Strikingly, only 10% of the billions of dollars invested in biomedical research worldwide funds research into diseases affecting 90% of the world's population.[26] Clearly, this inequitable distribution needs to be corrected.

It is common for there to be a lag of up to 15 years between a vaccine's availability in the developed world and its widespread availability in developing countries and this is unacceptable.

1.2 Pneumococcal disease: a serious, preventable and largely unknown disease

Reducing mortality from pneumococcal disease is essential if the international community is to meet the MDGs, in particular MDG4. The WHO estimates that pneumococcal disease causes approximately 1.6 million deaths each year and about half of these are children aged less than five years old.[27] The WHO's official position is that pneumococcal vaccines should be prioritised to be part of each national immunisation programme, particularly in countries with a high child mortality.[28]

Despite the considerable social, clinical and economic burdens, the WHO and UNICEF describe pneumonia as the "forgotten killer of children".[29] Professor Adam Finn, an academic paediatrician at Bristol University and director of the South West Medicines for Children Local Research Network, commented that while pneumonia and other diseases caused by *S. pneumoniae* are "highly prevalent", much of the morbidity and mortality "goes relatively unnoticed".[30]

1.3 Rationale for the inquiry

In February 2008, we announced an inquiry into the prevention of pneumococcal disease in the developing world. Our inquiry focused on the lack of awareness surrounding pneumococcal disease and the potential impact of the pilot pneumococcal AMC as an international demand-led funding mechanism. The AMC aims to speed up the development and introduction of pneumococcal vaccines into the developing world. We hope to raise awareness among the international community, national governments, the media, public, politicians and

24 Joint Statements from Canada, Italy, Norway, Russian and the Bill and Melinda Gates Foundation, written evidence, page 185

25 World Health Organisation, *Global Immunization Data*, January 2008, page 2

26 Matthews KR and Ho V, The grand impact of the Gates Foundation, *EMBO Reports,* 2008;9:409-12

27 Dr Orin Levine, PneumoADIP, written evidence, page 386

28 WHO Weekly epidemiological record 2007, No 12, pages 93-104

29 UNICEF/WHO, *op.cit*., page 29

30 Prof Adam Finn, University of Bristol, written evidence, page 214

Despite the considerable social, clinical and economic burdens, the WHO and UNICEF describe pneumonia as the "forgotten killer of children".

NGOs of the human, clinical and economic tolls exerted by this often overlooked, but largely preventable killer of children.

If the pilot pneumococcal AMC proves successful, the process could offer a model to tackle other preventable endemic diseases, by encouraging the development and production of appropriate vaccines or other interventions.[31] The AMC has the potential to foster solutions, not just in the areas of pneumococcal disease, but health in general. The mechanism could also help speed progress in other development areas, such as environmental issues.[32] Therefore, it is critical that the AMC's foundations are secure, that the governance structures and processes are fit for purpose and that the key stakeholders reach consensus on specific outcomes.

The UK is contributing US$485 million of the US$1.5 billion committed to the pilot pneumococcal AMC.[33] While we heartily welcome the commitment to reducing health inequalities that this investment represents, Parliament has a responsibility to ensure taxpayers' money is being invested in the most effective and efficient way to maximise health and developmental outcomes. It is therefore necessary to scrutinise the progress to date.

31 Philippe Le Houérou, World Bank, written evidence, page 182

32 Joint Statements from Canada, Italy, Norway, Russian and the Bill and Melinda Gates Foundation, written evidence, page 189

33 PUSS DFID, Gillian Merron MP, written evidence, page 382

2 PNEUMOCOCCAL DISEASE IN THE DEVELOPING WORLD

2.1 Diseases associated with pneumococcal disease

2.1.1 Pneumococcal pneumonia

S. pneumoniae is the most common cause of pneumonia worldwide[34] causing approximately 36% of all childhood pneumonias.[35] *S. pneumoniae* can cause potentially life-threatening lung infections including severe pneumonia, which hinders the movement of oxygen into the bloodstream, potentially resulting in death from respiratory failure.[36] Patients who survive pneumococcal pneumonia may recover completely, but are at much greater risk of contracting further illnesses. Because there are several distinct strains (or serotypes) of *S. pneumoniae*, recovery from a previous infection does not guarantee protection against future episodes.[37] Antibiotic therapy improves the outcome, but some patients die, even with antibiotics and hospital care. Where treatment is delayed or unavailable, the risk of death is higher.

2.1.2 Invasive pneumococcal disease: meningitis and septicaemia

S. pneumoniae can also infect the bloodstream after entering the body (bacteraemia, septicaemia).[38] The blood can transport *S. pneumoniae* to numerous organs, most notably to the membranes surrounding the brain, where it causes life-threatening meningitis.[39]

Invasive pneumococcal infections often prove rapidly fatal, even where good medical treatment is readily available. In developed countries, up to 20% of people who contract pneumococcal meningitis die,[40] however, in the developing world mortality is closer to 50%, even among hospitalised patients.[41] In one study from The Gambia, 48% of children who contracted pneumococcal meningitis and reached hospital did not survive.[42]

Patients who do survive invasive pneumococcal infections are commonly left with severe long-term handicap and disabilities. Pneumococcal meningitis, for example, can cause deafness, multiple neurological handicaps, learning difficulties, low IQ and dependency on others, even when health professionals diagnose the invasive infection rapidly and treat appropriately.[43] [44] [45] In addition, pneumococcal septicaemia and meningitis may cause problems with co-ordination, concentration, memory and attention, as well as psychological and behavioural effects that undermine education, work and social relationships.[46] In a study from The Gambia, 36% of children who survived pneumococcal meningitis were left with serious neurological problems and 29% showed less severe long-term effects.[47] Data from the Dhaka Shishu Hospital, Bangladesh, suggests that pneumococcal disease is responsible for 35% of all meningitis cases seen there and that 55% of the children who have contracted meningitis are permanently disabled.[48]

34 Chris Head, MRF, written evidence, page 228

35 Prof Fred Were, Kenyan Paediatric Association, written evidence, page 296

36 UNICEF/WHO, *op.cit.*, page 8

37 Prof Adam Finn, Bristol University, written evidence, page 216

38 *ibid.*, written evidence, page 215

39 *ibid.*, written evidence, page 215

40 Chris Head, MRF, written evidence, page 229

41 World Health Organization, Pneumococcal vaccines, *The Weekly Epidemiological Record* 2003; 14:110-9

42 Goetghebuer T, West TE, Wermenbol V et al., Outcome of meningitis caused by *Streptococcus pneumoniae and Haemophilus influenzae* type b in children in The Gambia, *Trop Med Int Health* 2000; 5:207-13

43 Prof Adam Finn, Bristol University, written evidence, page 216

44 Bedford H, de Louvois J, Halket S et al., Meningitis in infancy in England and Wales: follow up at age 5 years, *BMJ* 2001;323:533-6

45 Hoogman M, van de Beek D, Weisfelt M et al., Cognitive outcome in adults after bacterial meningitis, *J Neurol Neurosurg Psychiatry 2007*; 78:1092-6

46 Chris Head, MRF, written evidence, page 230

47 Goetghebuer T, West TE, Wermenbol V et al., *op. cit.*, pages 207-13

48 PneumoADIP, *Leading Experts Unite to Understand the Burden of Pneumococcal Disease* http://pneumoadip.org/documents/releases/2005_01_18-bangladesh.pdf last accessed 8 October, 2008

2.1.3 Pneumococcal otitis media

Otitis media (infection of the middle ear) is the most common manifestation of pneumococcal disease.[49] Children who develop pneumococcal otitis media normally recover completely but some develop chronic serious otitis media (fluid in the middle ear) which can impair hearing at the age when speech is developing,[50] potentially compromising educational attainment and linguistic skills. In the worst cases, pneumococcal otitis media can lead to deafness.[51]

2.2 The burden of pneumococcal disease

2.2.1 The epidemiological situation

Compared with other diseases affecting the developing world, determining the incidence of pneumococcal disease is relatively difficult.[52] This is due to a number of factors including the difficulty of stringent laboratory testing and sample collection and the unavailability of quality surveillance data in developing countries. There is no simple method to obtain the samples for such testing without potentially harming patients,[53] and testing the most commonly available specimens still may miss up to 90% of cases. This lack of epidemiological evidence has likely contributed to a gross under-appreciation of the economic, clinical and human burdens imposed by pneumococcal disease and hindered public health planning and decision-making in developing countries.

2.2.2 A common killer

According to the WHO, at least one child dies of pneumococcal disease every minute, making it the leading cause of childhood pneumonia deaths in the developing world[54] and the number one vaccine-preventable cause of death in children worldwide.[55] In absolute numbers, developing countries with large populations, such as India, Bangladesh and Indonesia, report the largest numbers of deaths from pneumococcal disease.[56]

- 10 countries in Asia and sub-Saharan Africa account for over 60% of pneumococcal disease deaths worldwide[57]
- In Bangladesh, a "very conservative" estimate suggests that 50,000 children die annually from pneumococcus[58]
- Among Indian children, pneumonia causes a quarter of all deaths. That is, 410,000 children under five die of pneumonia each year and of these, between 123,000 and 164,000 are estimated to die from pneumococcal pneumonia[59]
- The Aga Khan University estimated that in the Pakistani Province of Sindh, pneumococcal meningitis occurs at a rate of 11 per 100,000. Low detection rates and cases managed in hospitals not included in this study contribute to what is likely a six-fold underestimate. The actual rate could be as many as 66 cases of pneumococcal meningitis

49 Dagan R, The potential of pneumococcal conjugate vaccines to reduce antibiotic resistance, *Adv Exp Med Biol,* 2004;549:211-9

50 Prof Adam Finn, Bristol University, written evidence, page 216

51 *ibid.*, page 215

52 Madhi SA, Kuwanda L, Cutland C et al., The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and -uninfected children, *Clin Infect Dis* 2005;40:1511-8

53 *ibid.*, pages 1511-8

54 World Health Organization, Vaccinating African children against pneumococcal disease saves lives, 25 March 2005, http://www.who.int/mediacentre/news/statements/2005/s03/en/index.html, last accessed 7 October 2008

55 World Health Organization, *Global Immunization Data 2008*, January 2008

56 Dr Thomas Cherian, WHO, first oral evidence session, page 8, lines 11-20

57 Dr Thomas Cherian, WHO, written evidence, page 204

58 Prof Samir Saha, Bangladesh Institute of Child Health (ICH), 5 June 2008, second oral evidence session, page 156, line 10

59 Dr Suresh Jadhav, Serum Institute of India, written evidence, page 349

per 100,000 infants.[60] In the UK in 2005, only 94 infants in total were confirmed to have contracted pneumococcal meningitis[61]

- Countries in Sub-Saharan Africa have the highest mortality rates from pneumococcal disease.[62] Pneumonia causes 21% of deaths of children under five in these countries[63]

In oral evidence, we heard that the annual incidence of pneumococcal disease in The Gambia and South Africa is 224 and 345 per 100,000 of the population respectively.[64] In Kenya, it is estimated that 250,000 children (of the approximately six million population) will contract a pneumococcal disease related illness.[65] These figures compare to only 731 children in England and Wales contracting pneumococcal disease in 2005 in total.[66]

2.2.3 Risk factors for pneumococcal disease

Several risk factors contribute to the disproportionately heavy burden that pneumococcal disease imposes on the developing world. Other diseases prevalent in developing countries can exacerbate the risk of infection with *S. pneumoniae*, such as:

- Children with HIV/AIDS are up to 40 times more likely to contract pneumococcal disease.[67] In one study, a new pneumococcal vaccine protected 83% of children from *S. pneumoniae* infection and protected 65% of those children who were infected with HIV.[68] Given the higher risk to HIV positive children, this level of protection is significant
- Sickle cell disease (a genetic condition that affects red blood cells and is most common among people of African descent)[69]
- Immune deficiencies due to genetic factors or medical treatment for cancer or other illnesses[70]
- Diseases or injuries that undermine the spleen's function[71]

High-risk individuals should therefore be prioritised in any pneumococcal vaccine programme.[72]

Educational, environmental and cultural factors also conspire to increase the risk of pneumococcal disease among people living in developing countries:

- Parents may not recognise the symptoms of pneumonia in children or appreciate the importance of seeking immediate medical help.[73] The same is also true for invasive pneumococcal disease (IPD). The Meningitis Research Foundation (MRF) stated in their evidence that Health professionals and the public associate a non-blanching rash and the sudden onset of illness with a diagnosis of meningitis. IPD typically displays a slower onset and the non-blanching rash seen in meningococcal infection is generally absent in pneumococcal infection. This makes early detection and treatment more difficult[74]
- Overcrowding is commonly known to increase the likelihood of exposure to and transmission of *S. pneumoniae*[75 76]

60 Rehan Hafiz, Ministry of Health, Pakistan, written evidence, page 342

61 UK Health Protection Agency, http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733815884?p=1203409671918, last accessed 7 October 2008

62 Dr Thomas Cherian, WHO, 24 April 2008, first oral evidence session, page 8, lines 17-20

63 Dr Suresh Jadhav, Serum Institute of India, written evidence, page 347

64 Prof Tumani Corrah, MRC The Gambia, 5 June 2008 second oral evidence session, page 121, lines 22-24

65 Prof Fred Were, Kenya Paeditaric Association (KPA), 5 June 2008, second oral evidence session, page 122, lines 12-15

66 UK Health Protection Agency, http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733751944?p=1203409671918, last accessed 7 October 2008

67 Dr Orin Levine, PneumoADIP, written evidence, page 385

68 Klugman KP, Madhi SA, Huebner RE et al., A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection, *N Engl J Med* 2003;349:1341-8

69 Dr Thomas Cherian, WHO, 24 April 2008, first oral evidence session, page 9, lines 2-5

70 Prof Adam Finn, Bristol University, written evidence, page 216

71 *ibid.*, page 216

72 *ibid.*, page 216

73 UNICEF/WHO, *op.cit.*, page 18

74 Chris Head, MRF, written evidence, page 228

...children suffering from malnutrition are significantly more likely to develop acute respiratory infections such as pneumonia.

- Malnutrition is one of the key underlying risk factors associated with infant mortality in the developing world[77] and children suffering from malnutrition are significantly more likely to develop acute respiratory infections such as pneumonia[78]
- Poor indoor air quality increases the risk of developing pneumococcal pneumonia. In the rural areas of many developing countries, children breathe in high concentrations of smoke as they are carried on their mother's back whilst she cooks by burning timber in an open stove[79]

2.2.4 Economic impact of pneumococcal disease

As well as the devastating health impact on individuals, the disease also exerts significant economic pressure on families, developing governments and struggling health systems, further contributing to the cycle of poverty.

In their oral evidence, Professor Fred Were of the Kenyan Paediatric Association and Professor Tumani Corrah of the Medical Research Council in The Gambia discussed the serious economic impact of pneumococcal disease on individual families. This includes the costs of lost work hours, hospital and treatment, ambulance or transportation and, in the worst cases, funeral costs.[80] All these issues represent a significant economic drain on families, communities and developing world governments.

The lack of adequate healthcare staff in the developing world means the primary caregiver, usually the mother or the grandmother, has to leave the rest of her family and stay with a sick child in hospital.[81] Furthermore, the disability associated with pneumococcal disease in childhood reduces a child's future economic potential, placing further stress on families by absenting one of the major wage earners for an indeterminate amount of time. The social contours of families and communities are thus disturbed along with their financial stability.

The following examples illustrate the economic impact that pneumococcal disease can have on the developing world.

- In Kenya, pneumococcal disease accounts for one in three hospital admissions among children[82]
- According to a study published in 2007, treating pneumococcal meningitis costs up to US$5,435 per child in Brazil, Chile and Uruguay. The cost of treating a child with pneumococcal pneumonia ranged from US$372 in Brazil to US$3,483 in Chile. The cost of treating a child with acute otitis media ranged from US$20 in Brazil to US$217 in Chile.[83] The Gross National Income (GNI) per capita for Brazil and Chile is US$4,710 and US$6,810[84] respectively, therefore the cost of treating pneumococcal disease is significant

Caring for children left disabled by pneumococcal disease leads to further economic concerns. Developing countries generally do not have the infrastructure or societal organisation to offer adequate care to the

75 Prof Adam Finn, Bristol University, written evidence, page 214

76 Dr Thomas Cherian, WHO, written evidence, page 204

77 Dr Thomas Cherian, WHO, 24 April 2008, first oral evidence session, page 31, lines 18-25

78 Dr Suresh Jadhav, Serum Institute of India, written evidence, page 352

79 *ibid*., page 352

80 Prof Fred Were and Prof Tumani Corrah, 5 June 2008, second oral evidence session, page 144, lines 12-25 and page 145, lines 1-18

81 Prof Tumani Corrah, MRC The Gambia, 5 June 2008, second oral evidence session, page 122, lines 1-4

82 Prof Fred Were, KPA, 5 June 2008, second oral evidence session, page 125, lines 7-8

83 Constenla D Evaluating the costs of pneumococcal disease in selected Latin American countries, *Rev Panam Salud Publica*, 2007;22:268-78

84 World Bank, http://web.worldbank.org/, last accessed 7 October 2008

disabled,[85] so the burden is placed on families who often struggle to cope.[86] In Bangladesh, for example, few schools specialise in the care of disabled children and therefore many mothers of disabled children are unable to work, imposing a considerable strain on family finances.

2.3 Vaccines to prevent pneumococcal disease

2.3.1 An overview of pneumococcal vaccines

Pharmaceutical companies first launched vaccines to prevent pneumococcal disease in adults more than 20 years ago. Studies showed that these 'pneumococcal polysaccharide vaccines' (PPVs) showed little or no effectiveness in young children and in other groups, including the elderly, showed only modest, short-lasting benefits.[87]

In 2000, a 7-valent 'pneumococcal conjugate vaccine' (PCVs), which confers immunity against seven common strains of *S. pneumoniae* in young children, was approved in the US and made part of routine childhood immunisation. Vaccinating children has indirectly protected non-immunised members of the community, including the elderly and non-vaccinated children by reducing the transmission of *S pneumonia*[88] This effect is called herd immunity. One study has found that a 7-valent pneumococcal vaccine prevented more than twice as many IPD cases in 2003 through indirect effects on pneumococcal transmission (i.e., herd immunity) than through its direct effect of protecting vaccinated children.[89]

PCVs are extremely stable and can potentially stay at room temperature for long periods,[90] although countries applying to GAVI must be able to show adequate cold chain capacity and other health systems requirements to be approved for vaccine funding.[91]

S. pneumoniae has 91 serotypes (or strains)[92] and the first generation PCV protects against the seven serotypes most common in North America (seven valent). However, the distribution of serotypes responsible for pneumococcal disease differs across the world. In most developing countries, the seven serotypes in the available vaccine account for approximately 50 to 60% of all infections. Furthermore, it has been stated that the price of the seven-valent vaccine was too high for developing countries to afford introduction into their immunisation programmes.[93]

Between 20 and 25 *S. pneumoniae* serotypes are responsible for the vast majority of cases of pneumococcal disease worldwide.[94] Vaccine biochemistry is quite complex and manufacturers must re-engineer their processes to produce different multi-valent vaccines.[95] Two new formulations, which target a larger number of important pneumococcal serotypes worldwide, are in late stages of development.[96]

85 Prof Fred Were, KPA, 5 June 2008, second oral evidence session, page 142, lines 7-8

86 Prof Samir Saha, ICH, 5 June 2008, second oral evidence session, page 159, lines 1-13

87 Bernatoniene J and Finn A, *op.cit*., pages 229-55

88 Ray GT, Whitney CG, Fireman BH et al., *op.cit*., pages 494-501

89 Reingold A, Hadler J, Farley MM, et al., Direct and Indirect Effects of Routine Vaccination of Children With 7-Valent Pneumococcal Conjugate Vaccine on Incidence of Invasive Pneumococcal Disease—United States, pages 1998-2003

90 Dr Thomas Cherian, WHO, 24 April 2008, first oral evidence session, page 54, lines 12-14

91 The GAVI Alliance, Guidelines on Country Proposals For Support to: Immunisation Services, Injection Safety and New and Underused Vaccines, July 2007

92 Dr Kate Taylor, GSK, written evidence, page 241

93 Dr Jean-Marie Okwo-Bele, WHO, written evidence, page 199

94 Prof Adam Finn, Bristol University 24 April 2008, first oral evidence session, page 25 lines 4-7

95 Dr Kate Taylor, GSK, written evidence, page 241

96 *ibid*., page 241

2.3.2 Disease biological diversity

The biological diversity of *S. pneumoniae* means that, hypothetically at least, routine use of the vaccine can shift the prominence of serotypes responsible for pneumococcal disease in a given population. In other words, the traditionally less dominant serotypes could become more prevalent due to the success of PCVs in suppressing the originally most common serotypes.[97]

The pattern of serotypes responsible for pneumococcal disease may also change naturally over time or under vaccination programmes. In the USA, between one and three serotypes seem to be causing more cases of pneumococcal disease since the vaccine's implementation.[98] However, disentangling the natural drift in serotypes from the effect of the vaccine can prove problematical.[99] Serotype 19A is one strain that has become more widespread in the USA following the vaccine's introduction but remains an uncommon cause of severe childhood disease compared to pre-vaccine introduction levels. At the same time, Serotype 19A also became more prevalent in Israel, which does not use the vaccine.[100] On-going surveillance for pneumococcal disease is clearly important to this process because it helps us monitor the overall effects of the vaccine programme.

The Gambia has implemented a surveillance system in one part of the country to determine whether the introduction of the vaccine influences the serotypes not covered by a vaccine, as well as to monitor the overall impact of the vaccine on disease.[101] Kenya also plans to introduce a surveillance system.[102] The three sites in the Philippines that perform pneumococcal surveillance showed that between 1989 and 1999 the seven serotypes covered by the vaccine accounted for 49% of cases. In the last five years, these accounted for 67% of cases as one of the serotypes suddenly predominated.[103] These data demonstrate that surveillance systems in developing countries can offer clinically and epidemiologically valuable information and that supporting surveillance is important.

2.3.3 The effectiveness of pneumococcal vaccines

Gains from immunisation increase as the incidence of disease increases. However, these gains are compromised when there is a decrease in the availability of diagnostic and treatment services for children who do become ill.[104] That said, large controlled trials, including studies from South Africa[105] and The Gambia,[106] indicate that PCV significantly reduces the morbidity and mortality associated with pneumococcal disease.

The South African study assessed the effect of a 9-valent PCV given to 19,922 children (aged six to 14 weeks) while 19,914 received a placebo. Among children without HIV infection, the PCV reduced by 83% the incidence of a first episode of invasive pneumococcal disease due to the nine serotypes included. The vaccine's efficacy was 65% among HIV-infected children. Among fully vaccinated, HIV-negative children, the incidence of first episode pneumonia confirmed on x-ray fell by 25%.

97 Prof Adam Finn, Bristol University, first oral evidence session, page 27, lines 6-12

98 *ibid.*, page 27, lines 6-9

99 *ibid.*, page 27, lines 9-20

100 *ibid.*, page 27, lines 11-15

101 Prof Tumani Corrah, MRC The Gambia, 5 June 2008, second oral evidence session, page 128 lines 2-10

102 Prof Fred Were, KPA, 5 June 2008, second oral evidence session, page 128, lines 24-25

103 Prof Lulu Bravo, University of Philippines, 5 June 2008 second oral evidence session, page 164, lines 8-12

104 Ray GT, Whitney CG, Fireman BH et al., *op.cit.*, pages 494-501

105 Klugman KP, Madhi SA, Huebner RE et al., *op.cit.*, pages 1341-8

106 Cutts FT, Zaman SM, Enwere G et al., Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial, *Lancet* 2005;365:1139-46

A study from eastern Gambia vaccinated 8,718 children (aged between six and 51 weeks) with a 9-valent PCV and 8,719 with a placebo. The vaccine reduced by 37% the number of first episodes of pneumonia confirmed by x-ray in immunised children. The vaccine also reduced by 77% invasive pneumococcal disease caused by serotypes covered by the vaccine. The rate of invasive pneumococcal disease due to all serotypes halved. All-cause mortality declined by 16% and admissions to hospital from all causes fell by 15%.[107] These compelling results provide a platform for the future of PCVs and suggest that vaccination will markedly reduce the number of children who require care for and die from acute pneumococcal infections.

2.3.4 How many deaths could pneumococcal vaccination prevent?

UNICEF noted that pneumonia causes more than two million of the 10 million annual deaths in children less than five years of age.[108] In the 72 countries eligible for support from GAVI, 3.79 million children aged between three and 29 months die annually.[109] Pneumococcal vaccination could prevent more than 7 million deaths by 2030 globally[110] and save the lives of 139,000 in India, Pakistan, Ethiopia, Tanzania and Nigeria each year.[111] In Kenya, alone, pneumococcal vaccination could prevent an estimated 20,000 to 25,000 deaths annually.[112]

In developed countries, routine immunisation with PCVs dramatically reduced the incidence of pneumococcal disease within two to three years.[113] The same is expected to occur in developing countries.[114] This rapid impact should allow donors to assess the clinical effectiveness of the pneumococcal AMC within a reasonably short period of time.

2.3.5 Prevention in conjunction with treatment

Previously, the developing world has focused on treating pneumococcal disease and pneumonia rather than preventing it. We believe that while treatment is and should continue to be an important facet to the management of this disease, prevention is the key to minimising the disease burden.

Doctors frequently prescribe antibiotics for syndromes attributed to pneumococcal disease. In the UK and other developed countries antibiotics are available only on prescription. However, in some parts of the developing world certain antibiotics can be bought 'over the counter' from pharmacists.[115] Such untargeted and inappropriate use and wide availability can encourage antibiotic resistance, potentially making the drugs ineffective.[116] The rapid emergence of antibiotic resistance is adding to the burden of pneumococcal disease by significantly contributing to the numbers of treatment failures and deaths from this disease.[117] [118] [119] [120]

However, in recent studies of a 9-valent PCV, the incidence of invasive pneumococcal disease caused by strains resistant to penicillin fell by 67%. The incidence of disease caused by strains resistant to another widely used antibiotic combination (trimethoprim plus sulfamethoxazole) declined by 56%.[121]

107 Cutts FT, Zaman SM, Enwere G et al., *op.cit*., pages 1139-46

108 Dr Peter Salama, UNICEF, written evidence, page 210

109 Dr Suresh Jadhav, Serum Institute of India, written evidence, page 348

110 Joint Donor Statement, An Advance Market Commitment for Pneumococcal Vaccines, July 10, 2008, available at http://www.vaccineamc.org/july2008_pop.html, last accessed 9 October 2008

111 Dr Suresh Jadhav, Serum Institute of India, written evidence, page 348

112 Prof Fred Were, KPA, 5 June 2008, second oral evidence session, page 123, lines 10-11

113 Reingold A, Hadler J, Farley et al., *op.cit*., pages 1998-2003

114 Dr Jean-Marie Okwo-Bele, WHO, written evidence, page 200

115 Prof, David Goldblatt, University College London (UCL), 5 June 2008, second oral session, page 131, lines 17-20

116 Dagan R, *op.cit*., pages 211-9

117 Prof Samir Saha, ICH, 5 June 2008, second oral evidence session, page 165, lines 9-20

118 Klugman KP, Bacteriological evidence of antibiotic failure in pneumococcal lower respiratory infections, *European Respiratory Journal Supplement*, 2002; 36:3s-8s.

119 Dagan R. Clinical significance of resistant organisms in otitis media, *Pediatric Infectious Diseases Journal*, 2000;19(4):378

120 Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis, *Pediatric Infectious Diseases Journal*, 1993; 12:389-94.

121 Klugman KP, Madhi SA, Huebner RE et al., *op.cit*., pages 1341-8

Health systems in the developing world are severely over-stretched by the numbers of patients suffering from pneumococcal disease and pneumonia.

Health systems in the developing world are severely over-stretched by the numbers of patients suffering from pneumococcal disease and pneumonia.[122] If fewer patients presented with the disease, health systems could focus the saved resources on other diseases, which would improve patient care and the functioning of health systems overall. In the Dhaka Shishu hospital, it is common for mothers with sick children to be turned away because there are no beds and these children often die as the mother moves them to another hospital.[123]

Treatment programmes will still be necessary, for instance, a patient may be infected by a serotype not covered by a multi-valent vaccine. However, we feel that it is better to be proactive than reactive and prevention of the disease is our primary focus.

122 Prof Lulu Bravo, University of the Philippines, 5 June 2008, second oral evidence session, page 155, lines 12-24

123 Prof Samir Saha, ICH, 5 June 2008, second oral evidence session, page 160, lines 5-18

3 PREVENTING PNEUMOCOCCAL DISEASE IN THE DEVELOPING WORLD

3.1 Why has pneumococcal disease not been a focus previously?

The APPG was initially formed as a reaction to the disturbingly high level of child deaths in the developing world. The Group set itself the task of increasing awareness of the burden of pneumococcal disease in the developing world. An overwhelming amount of evidence detailed low awareness of this disease and its impact on families and communities, not just among the public, but also among developed and developing world politicians, stakeholders and decision makers, who until recently, did not regard pneumococcal disease as a major killer or as a vaccine-preventable disease despite being the number one vaccine preventable killer of children under five[124].

The APPG was initially formed as a reaction to the disturbingly high level of child deaths in the developing world.

...evidence detailed low awareness of this disease and its impact on families and communities.

The lack of a standard message around pneumococcal disease and the brief, inconsistent media attention focused on developing countries has contributed to this under-awareness.[125]

The focus on other disease areas has also been a significant contributor. It is unarguable that AIDS, tuberculosis and malaria are enormous global health problems that deserve substantial resources. However, the focus on these diseases led, almost, to the omission of other diseases in discussions on reducing mortality and morbidity from infectious disease.[126]

There has been an absence of technical consensus around pneumococcal disease and vaccines as there has been no agreement on the most effective and efficient method to accelerate the introduction of a vaccine into immunisation schedules. Previously, there was no credible demand for vaccines from developing countries and limited donor commitment to funding. The lack of communication between donors, countries and industry as well as an unpredictable supply of vaccine fuelled uncertainty.[127]

Developing world heath systems contribute to the under-appreciation of pneumococcal disease as a public health priority. Surveillance for pneumococcal disease in most parts of the world has historically been under-funded and of limited usefulness. Even when meningitis and pneumonia surveillance existed, data was not standardised between countries. As a result, while most clinicians expected that pneumococcal disease imposed a heavy global disease burden, there was no robust data to support this.[128] However, the recent development of simple diagnostic criteria for pneumonia should aid diagnosis[129] and should be disseminated widely.

Thanks to the work of the WHO, the GAVI Alliance and PneumoADIP, politicians, public health officials and donors in developing countries, are beginning to recognise pneumococcal disease as a major health problem. Clinicians now recognise that timely diagnosis and treatment with inexpensive antibiotics can cure many cases of pneumococcal disease,

124 World Health Organization, *Global Immunization Data 2008*, January 2008, page 2

125 Dr Orin Levine, PneumoADIP, written evidence, page 386

126 *ibid.*, page 386

127 *ibid.*, page 386

128 *ibid.*, page 386

129 UNICEF/WHO, *op.cit.*, page 22

...inexpensive antibiotics can cure many cases of pneumococcal disease, while immunisation with PCV raises the prospect of primary prevention.

while immunisation with PCV raises the prospect of primary prevention.[130] This reflects a growing awareness of the disease burden, the promising results of clinical trials and successful vaccination programmes in the UK, USA, Australia and elsewhere.[131] [132] [133] [134]

3.2 The importance of health systems

Tackling any infectious disease requires a multifaceted approach that encompasses education to tackle risk factors and ensure timely presentation, prevention and treatment. For example, immunisation is only as effective as the delivery system. The AMC does not directly strengthen health systems, but GAVI eligibility criteria require participating countries to demonstrate an adequate level of capacity to introduce vaccines. Authorities in The Gambia suggested that the availability of the pneumococcus vaccine would strengthen their Expanded Programme on Immunisation (EPI) system.[135] This would potentially enhance the delivery of existing as well as innovative vaccines. The AMC works within existing systems facilitated and supported by GAVI. Therefore, the AMC will not increase the economic burden on developing country health systems and, if successful, should indirectly free resources.[136] Pneumococcal vaccination programmes should work in concert with other interventions including encouraging breast-feeding; micronutrient supplementation to increase nutritional status of children; and improving ambient air quality.[137] [138]

130 Prof Adam Finn, Bristol University, written evidence, page 218

131 Dr Orin Levine, PneumoADIP, written evidence, page 386

132 Klugman KP, Madhi SA, Huebner RE et al., *op.cit.*, pages 1341-8

133 Cutts FT, Zaman SM, Enwere G et *op.cit.*, pages 1139-46

134 Black S, Shinefield H, Fireman B et al., Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children Northern California Kaiser Permanente Vaccine Study Center Group, *Pediatr Infect Dis J*, 2000;19:187-95

135 Prof Tumani Corrah, MRC The Gambia, 5 June 2008, second oral evidence session, page 124, lines 22-24

136 Joint Statements from Canada, Italy, Norway, Russian and the Bill and Melinda Gates Foundation, written evidence, page 189

137 Dr Peter Salama, UNICEF, written evidence, page 212

138 Dr Orin Levine, PneumoADIP, written evidence, page 388

4 THE AMC AS AN INNOVATIVE FINANCING MECHANISM FOR IMPROVING HEALTH

4.1 Existing funding mechanisms focusing on developing world diseases

The plight of children and adults in the developing world encouraged NGOs and governments to develop a range of international funding mechanisms to improve the health of developing nations. The following outlines the different funding mechanisms currently in existence:

Funding mechanism	Description
International Finance Facility for Immunisation (IFFIm)	IFFIm uses a bond to frontload money to fund immunisation that donor countries pay back over 20 years with interest. The IFFIm has six governmental donors and aims for bond issue of US$4 billion. Currently, the UK is the largest contributor.
The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund)	The Global Fund directs increased resources to fight these three diseases in areas of greatest need. It is a partnership between governments, civil society, the private sector and affected communities. The Fund currently supports 127 countries, including 55 nations that are not GAVI eligible.[139]
UNITAID	UNITAID is an international drug purchase facility established by the governments of France, Brazil, Chile, Norway and the UK that seeks to produce a sustained strategic market intervention to drive price reduction and increases in supply. UNITAID focuses its interventions primarily on preventing and treating HIV/AIDS, malaria and tuberculosis and targets countries with a GNI per capita under US$3,595. Partners with targeted programmes can argue for the inclusion of other countries.[140]
The United States President's Emergency Plan for Relief (PEPFAR)	PEPFAR authorises US$48 billion to focus on HIV/AIDS, tuberculosis and malaria.[141] The programme targets 115 countries, 15 of which are referred to as "focus countries".[142]
Medicines Transparency Alliance (MeTA)	MeTA, set up by the UK's DFID, works "through national and international partners… to support national efforts to enhance transparency and build capacity in medicines policy, procurement and supply chain management". MeTA should strengthen transparency and accountability as well as improve access to information about medicine quality, availability and pricing.[143]

Pneumococcal vaccination programmes should work in concert with other interventions.

GAVI works with the WHO and UNICEF to develop the political structures, financing and technical innovation needed to accelerate the introduction of new vaccines.

139 Dr Thomas Cherian, WHO, written evidence, page 206

140 *ibid.*, page 206

141 Reauthorizing PEPFAR, http://www.pepfar.gov/documents/organization/107750.pdf, last accessed 7 October 2008

142 Dr Thomas Cherian, WHO, written evidence, page 206

143 Medicines Transparency Alliance, http://www.dfidhealthrc.org/MeTA/index.html, last accessed 7 October 2008

The measles vaccine was included in immunisation programmes in developing countries almost 20 years after its introduction into developed countries.

GAVI provides funding for health systems strengthening, vaccines and immunisation in countries with the lowest GNI per capita. According to the current eligibility criteria, 72 countries are currently eligible to receive financial assistance from GAVI, should they request it. Only Timor-Leste has not yet requested support.[144] GAVI also disburses funds obtained through mechanisms such as the International Finance Facility for Immunisation (IFFIm) and the pneumococcal AMC.[145] GAVI works with the WHO and UNICEF to develop the political structures, financing and technical innovation needed to accelerate the introduction of new vaccines.[146]

Each of these funding mechanisms and initiatives addresses different objectives and specific components of the global health challenge. As the AMC is demand-led, the mechanism may provide a more significant incentive than approaches aiming to 'push demand'.[147] Based on the written and oral evidence, we agree with Dr Jerald Sadoff, (President & Chief Executive Officer Aeras Global TB Vaccine Foundation) that a broad, diverse and comprehensive choice of funding mechanisms will help to engage as many stakeholders as possible.[148]

4.2 The need for innovative funding mechanisms for vaccines

Children in wealthier nations receive innovative vaccines earlier than children in poorer nations. This discrepancy contributes to marked differences in survival and other measures of health between the developed and developing world.[149] There are also discrepancies within countries due to differences in income.[150] Market forces appear to be a main cause of the delay in vaccine introduction into developing countries.

4.2.1 Factors driving vaccine costs

In general, vaccines are introduced into developing countries between 10 and 15 years after their launch in high-income markets.[151] The measles vaccine was included in immunisation programmes in developing countries almost 20 years after its introduction into developed countries.[152]

The vaccine's manufacturers accept that this time lag is unacceptable: Jim Connolly, Executive Vice President and General Manager, Wyeth Vaccines commented that if GAVI meets its timelines for introduction of Prevenar, Wyeth's 7-valent pneumococcal vaccine (in some markets known as Prevnar), which is not funded through the AMC, "we should witness the first dose in child in late 2008/early 2009 (eight years following the introduction of Prevenar in the U.S.)… This represents an improvement over the traditional delay between introduction of new vaccines in developed and developing countries. That having been said, a delay of 8-9 years is too long considering the life-saving potential of pneumococcal vaccine."[153]

Pharmaceutical companies often introduce vaccines in low-income countries only after a patent expires.[154] The expiration of intellectual property protection allows generic manufacturers, often supported by

144 Country data for GAVI-supported countries http://www.gavialliance.org/performance/country_results/index.php, last accessed 7 October 2008

145 Dr Thomas Cherian, WHO, written evidence, page 206

146 Dr Nina Schwalbe, GAVI Alliance, 24 April 2008, first oral evidence session, page 40, lines 4-10

147 Dr Jerald Sadoff, Aeras, written evidence, page 372

148 *ibid*., page 372

149 Prof Adam Finn, Bristol University, written evidence, page 216

150 Prof Lulu Bravo, University of the Philippines, 5 June 2008, second oral evidence session, page 161, lines 10-14

151 Dr Ruth Levine, Center for Global Development (CGD), written evidence, page 367

152 Dr Thomas Cherian, WHO, written evidence, page 205

153 Jim Connolly, Wyeth, written evidence, page 258

154 Dr Ruth Levine, CGD, written evidence, page, 367

donors, to offer the vaccine at relatively low prices. Additionally, costs typically fall over time because of the development of innovations in the production process.[155]

Modern vaccines, such as multi-valent PCVs, are more complex to develop and more expensive to manufacture than older vaccines, such as those used to eradicate smallpox.[156] Developing new manufacturing capacity, even when modifying existing facilities, can cost $200-300 million.[157] Both generic and branded pharmaceutical companies charge a high initial price for newly developed vaccines to recoup their investment, before they can seek to make a profit.

At western market prices, a single dose of a new vaccine can cost up to a thousand times more than a dose of one of the now common childhood vaccines like tetanus or measles.[158] Some companies, such as GlaxoSmithKline Biologicals, claim to vary pricing depending on a country's ability to pay, although the volumes of vaccines purchased and the agreements' duration also influence the price. In 2007, GSK produced 1.1 billion doses of vaccines, 80% of which went to the developing world.[159] GSK claim that GAVI countries pay 10-20% of the price that richer countries pay, which sustains Research & Development (R&D).[160] A third of GSK's candidate vaccines target diseases of the developing world including vaccines for malaria, HIV and TB.[161]

Wyeth entered arrangements with middle-income countries (e.g. Mexico and Uruguay) to include their proprietary pneumococcal vaccine, Prevenar, in national immunisation programmes. In their oral evidence, Wyeth stated that they were enacting tiered pricing to facilitate access to Prevenar and their 13-valent conjugate pneumococcal vaccine, which is in late stage clinical testing.[162] The APPG would like to commend efforts on behalf of all parties to assure tiered pricing of vaccines for low-income countries.

The APPG would like to commend efforts on behalf of all parties to assure tiered pricing of vaccines for low-income countries.

4.2.2 Cost, supply and demand

We heard suggestions that the price of a vaccine depends more on competition – the maximum that any particular market can sustain –than on the R&D investment cost arguments made by the pharmaceutical companies. According to this model, the price of existing vaccines will decline markedly once direct competitors or improved (e.g. greater valency) vaccines reach the market.[163]

The relatively high cost of many modern vaccines exacerbates the problems developing countries face when they want to purchase vaccines and in some cases is the major barrier. Uncertain demand for vaccines from developing countries means that many companies are reluctant to invest in developing better vaccines and increasing supply capacity, which has also helped keep prices high. The relatively high prices, in turn, suppress demand from developing countries.[164]

155 Dr Ruth Levine, CGD, written evidence, page 367

156 Prof Adam Finn, Bristol University, written evidence, page 217

157 Dr Kate Taylor, GSK, 5 June 2008, second oral evidence session, page 107, lines 22-25

158 Prof Adam Finn, Bristol University, written evidence, page 217

159 Dr Kate Taylor, GSK, 5 June 2008, second oral evidence session, page 91, lines 16-17

160 *ibid*., page 90, lines 16-17

161 *ibid*., page 90 lines 22-25 and page 91, lines 1-3

162 John Furey, Wyeth, 5 June 2008, second oral evidence session, page 93, lines 9-15

163 Prof David Goldblatt, ICH, 5 June 2008, second oral evidence session, page 140, lines 22-25 and page 141, lines 1-4

164 Dr Thomas Cherian, WHO, written evidence, page 205

...politicians and public health officials in many developing countries are unaware of the burden of illness imposed by diseases such as Hib, *S. pneumoniae* and rotavirus.

It is important to stress that developing countries want access to life saving vaccines. Prof Samir Saha, Professor of Microbiology at Bangladesh Institute of Child Health and a Senior Consultant in Microbiology at the Dhaka Shishu Hospital commented that parents understand the value of vaccines, but "The only constraint is they cannot pay for these vaccines".[165] From the perspective of the developed world, it is easy to underestimate the impact of an extra few cents or dollars on the price of a vaccine for resource poor nations.[166]

It was evident throughout discussions with witnesses that politicians and public health officials in many developing countries are unaware of the burden of illness imposed by diseases such as Hib, *S. pneumoniae* and rotavirus. Developing countries rarely have the resources to perform diagnostic tests, contributing to an ignorance of disease burden and weak demand. This has meant that many developing countries, failing to recognise what impact the vaccine might have, did not initially introduce it even when highly subsidised. International agencies and donor countries should build awareness among national decision-makers about pneumococcal disease and the potential for prevention by implementing immunisation programmes using PCV.[167]

Against this background, initiatives that promote the development of vaccines for specific diseases affecting the developing world (particularly exclusive strains) will help create and maintain demand.[168]

4.3 The Advance Market Commitment

4.3.1 An introduction to the AMC

The AMC provides an innovative demand-led approach that should spur market forces to accelerate the implementation of health improvement strategies in developing countries that might otherwise take years, even decades, to occur.[169] According to PneumoADIP, the AMC offers "an innovative way to protect the lives of the world's poorest children by making vaccines available in developing countries more quickly". The AMC is based on guaranteeing "the purchase of vaccines once they are developed, as long as they meet stringent, pre-agreed criteria about effectiveness, cost and availability. It is a collaborative effort among developing countries, donor nations, and vaccine manufacturers",[170] that targets long-term affordable prices of vaccines. The pneumococcal AMC specifically aims to speed the availability of multi-valent pneumococcal vaccines, but the AMC mechanism itself could be used for a number of different purposes.

Critically, the pneumococcal AMC applies only to vaccines that meet the needs of developing countries (e.g. optimal valency formulations, ease of delivery and cost). At present, low awareness leads to low demand,[171] but the combination of cost, serotype and formulation should maximise the number of lives potentially saved and therefore ensure demand.[172]

165 Prof Samir Saha, ICH, 5 June 2008, second oral evidence session, page 172, lines 22-23

166 Prof David Goldblatt, UCL, 5 June 2008, second oral evidence session, page 147, lines 18-19

167 Dr Thomas Cherian, WHO, written evidence, page 205

168 *ibid*., page 205

169 Prof Adam Finn, Bristol University, written evidence, page 218

170 PneumoADIP Vaccine Financing, http://pneu.pneumoadip.org/intro-financing.cfm, last accessed 7 October 2008

171 Dr Orin Levine, PneumoADIP, written evidence, page 386

172 Dr Jean-Marie Okwo-Bele, WHO, written evidence, page 199

By establishing the developing world as a viable market, the AMC will encourage research into vaccines to prevent other diseases endemic in poor countries. Furthermore, the AMC could establish an 'economic ripple' that spreads into other parts of the economy. By reducing the cost of the vaccine and lowering expenditure on treating the consequences of the disease, developing countries will have more resources to invest in meeting other healthcare priorities, such as tackling and preventing disease or developing infrastructure.

Professor Donald Light, Professor of Comparative Health Care Policy at the University of Medicine & Dentistry of New Jersey, USA, provided evidence that regarded the AMC model as abandoning the initiative's original aim. He argued that the final AMC model represents a purchase mechanism rather than one designed to create demand. In his evidence, he claims that the AMC will lead to increased profits for pharmaceutical companies and a decrease in the number of children that could benefit from the vaccine.[173]

We believe the terms of reference for any initiative should evolve in light of experience, expediency and political reality. The consensus view of the majority of stakeholders we heard from is that the pilot AMC should include vaccine purchase as well as development. We believe that the pilot AMC is an evolution of the concept and does not abandon the original intention of stimulating the early availability of vaccines. Indeed, we expect future AMCs to address and assess early stage products and that the experience gained from the pilot AMC for pneumococcal vaccines will provide valuable lessons to improve the mechanism. While the terms of reference need adequate discussion and clear definition and may need to evolve further, we should not lose sight of the primary aim: to improve the health and save the lives of children in developing countries.

Enhanced frontloading and the setting of a hard tail price cap as outlined by the AMC Expert Group Report[174] and provisionally agreed to by the AMC Donor Group,[175] potentially satisfies the concerns surrounding pricing.

4.3.2 Pneumococcal vaccines: a logical choice for the pilot AMC

The AMC commissioned expert, independent advice on the specification for the pneumococcal vaccine as well as the economic and financial terms for purchasing the PCV. In February 2006, an independent committee was convened to decide which disease area would be the target for the pilot AMC. The committee was composed of 60% developing country members and chaired by Dr. Ntaba, the former Minister of Health from Malawi.[176] The AMC also drew on the advice and expertise of several relevant multilateral organisations, including the WHO, UNICEF, GAVI, PneumoADIP and the World Bank. These discussions facilitated informed decisions on the structure of the mechanism and allowed the donors to make financial commitments. The legal framework agreed between the stakeholders codifies these commitments and structures.[177]

> ...the AMC offers "an innovative way to protect the lives of the world's poorest children by making vaccines available in developing countries more quickly..."

173 Prof Donald Light, University of Medicine & Dentistry of New Jersey, written evidence, page 400-401

174 The AMC Economic Expert Group Final Report, *Advance Market Commitment for Pneumococcal Vaccines*, April 1st 2008

175 Response of the AMC Donor Committee to the Interim Report of the Economic Expert Group, April, 2008

176 Dr J Lob-Levyt, GAVI, written evidence, page 192

177 Joint Statements from Canada, Italy, Norway, Russian and the Bill and Melinda Gates Foundation, written evidence, page 187

Based on historical experience, in the absence of an AMC or other financial effort, no pneumococcal vaccines will reach the world's poorest countries before about 2023.

Pneumococcal disease was seen as a logical choice for the pilot to assess several areas encompassed by the AMC:

- Pneumococcal vaccines fit within existing immunisation delivery systems and PCVs offer proven ability to reduce childhood mortality in communities with the greatest burden of disease[178] [179]
- There is a large global market for pneumococcal vaccines in the developing world and experts believe there will be a demand.[180] The pilot pneumococcal AMC can leverage existing industry investments in research and development for high and middle-income markets. The pilot AMC will pay only for the incremental investment needed to supply the best possible pneumococcal vaccine in developing countries. "The pneumococcal AMC will mean that children in the developing world will be able to receive lifesaving pneumococcal vaccines faster," Dr Orin Levine, Executive Director, PneumoADIP told the APPG. "Based on historical experience, in the absence of an AMC or other financial effort, no pneumococcal vaccines will reach the world's poorest countries before about 2023"[181]
- The pneumococcal AMC integrates readily into a package of activities that build awareness in developing countries about disease burden and that strengthen the ability of their health systems to introduce new vaccines[182]
- As the vaccines become available, the pneumococcal AMC offers an opportunity to make a rapid difference to health and economic well-being in some of the most impoverished nations
- In most countries, the seven serotypes covered by Prevenar accounts for just up to 50 -60% of cases of pneumococcal disease.[183] Research should develop vaccines suitable for the developing world

To date, the AMC partners have consulted with a range of stakeholders including developing countries, experts, civil society organisations and industry.[183] We hope that this report will add to this discussion.

4.3.3 Governance of the pneumococcal AMC

A core principle of the AMC is that the developing countries themselves make the final decision on whether they want a vaccine, making it a demand-led initiative. As such, the AMC provides vaccine manufacturers with the market certainty needed to make investment decisions.[185] Several mechanisms ensure the appropriate use of public funds and donor grants committed to the AMC, which should in turn help with the acceptance of future AMCs.

The WHO led an expert group with in-depth knowledge of pneumococcal disease that created a predefined 'Target Product Profile' for vaccines to be covered by the pilot AMC. According to GAVI, "the TPP will take into consideration available delivery systems in terms of immunisation schedule (number of doses and timing of vaccination), route of administration, temperature sensitivity of the product, presentation and

178 Klugman KP, Madhi SA, Huebner RE, et al., *op.cit*., pages 1341-8

179 Cutts FT, Zaman SM, Enwere G et al., *op.cit*., pages 1139-46 E1139-46

180 Prof Tumani Corrah, MRC The Gambia, 5 June, second oral evidence session, page 138, line 10

181 PneumoADIP, written evidence, page 347

182 Dr Ruth Levine, CGD, written evidence, page 368

183 Dr Kate Taylor, GSK, written evidence, page 241

184 Joint Statements from Canada, Italy, Norway, Russian and the Bill and Melinda Gates Foundation, written evidence, page 187

185 *ibid*., page 189

absence of interference with other essential health interventions in the target population."[186]

The TPP ensures that AMC funds only purchase vaccines that are effective and suitable for use in developing countries. An independent assessment committee of experts approves each vaccine. Neither donors, manufacturers nor other stakeholders can influence the approval of a specific vaccine.[187] The mechanism ensures that the AMC only funds vaccines that meet developing countries needs and countries must apply for the vaccine through GAVI.[188]

The TPP ensures that AMC funds only purchase vaccines that are effective and suitable for use in developing countries.

In accordance with GAVI's procedures and guidelines, countries requesting the vaccine will make a small, per-dose, co-payment. This payment signals the country's commitment, in this case, to a childhood pneumococcal vaccination programme. The AMC also draws on the expertise of UNICEF and the World Bank as procurement agency and administrator of funds, respectively. GAVI instigated an extensive and transparent consultation process to communicate this plan to developing countries, civil society organisations and the vaccine industry.

A robust monitoring and evaluation framework will measure the AMC's short-term impact and track the value received for funds over the longer term.[189] Donors are not involved in the day-to-day implementation of the pneumococcal AMC, but during and after the implementation phase, they will be able to evaluate whether these procedures work as envisaged, deliver on agreed financial commitments and monitor and evaluate progress.[190]

4.3.4 Criteria for success

The overall criteria for the pneumococcal AMC's success are reduced child mortality and morbidity and the proportion of the population vaccinated.[191] [192] Donors agreed on a Monitoring and Evaluation (M&E) framework encompassing the achievement and timing of two key criteria:

- The development of pneumococcal vaccines targeted for and demanded by developing countries
- The long-term supply of suitable and affordable vaccines that meet the needs of developing countries

The M&E framework established a baseline and requires ongoing monitoring, initial process evaluation and a full final evaluation.[193]

In his evidence, Philippe Le Houérou, from the World Bank, stressed the importance of assessing whether the pneumococcal AMC achieved predictable and sustainable pricing and tested its effectiveness as a demand-led mechanism. The World Bank also commented that an appropriate reporting structure that assesses the use of good governance practices, appropriate fiduciary management and the capacity to track and measure results is important to show that public funds are used for

186 AMC Structure, http://www.vaccineamc.org/mechanism.html, last accessed 7 October 2008

187 Joint Statements from Canada, Italy, Norway, Russian and the Bill and Melinda Gates Foundation, written evidence, page 187

188 Dr Thomas Cherian, WHO, written evidence, page 206

189 Joint Statements from Canada, Italy, Norway, Russian and the Bill and Melinda Gates Foundation, written evidence, page 188

190 *ibid*., page 189

191 *Ibid*., page 186

192 PUSS DFID, Gillian Merron MP, written evidence, page 382

193 Joint Statements from Canada, Italy, Norway, Russian and the Bill and Melinda Gates Foundation, written evidence, page 186

The pneumococcal AMC is currently moving from the planning to implementation phase.

the intended purpose.[194] We suggest that interim reports from the AMC specifically address these important issues.

4.3.5 Initial impressions of AMC

The pneumococcal AMC is currently moving from the planning to implementation phase. The need to implement appropriate governance meant that the design phase lasted longer than originally envisaged.[195] However, stakeholders' initial impressions are broadly positive.

Members of AMC donor countries and organisations who gave testimony commented that the demand-led mechanism leaves beneficiary countries in the driving seat. Synergies between donors' commitments and market forces that the AMC creates by establishing appropriate incentives make the process highly efficient. The donors agreed that progress to date is "fully consistent" with the project's objectives and has been transparent, well coordinated and inclusive with respect to both the beneficiaries and other stakeholders. The input from independent technical experts ensures the process is conducive to flexible evolutionary thinking about the AMC concept, while paying due attention to governance and evaluation.[196] The World Bank also praised the AMC pneumococcal pilot for "its openness and extensive consultations".[197]

Médecins Sans Frontières (MSF) considers the AMC pneumococcal pilot "to be an interesting proposal to secure greater access to vaccines in the developing world and as such has actively participated in the redesign process with GAVI Alliance". However, MSF regards the pilot project as an experiment and has stated "Questions about the place of the AMC – which may well be deemed an unsuccessful or inappropriate alternative financing model in the future - vis-à-vis other financing mechanisms are therefore premature."[198] PACE, MSF and GAVI believe that no alternative to the AMC could currently provide an adequate supply of vaccine at an affordable price.

UNICEF commented that it "is highly supportive of any additional funding and mechanism that can help address children's right to health" and that "the principles of the AMC – to encourage the development and supply capacity of suitable vaccines for children in developing countries – are beyond objection".[199] UNICEF noted that the pneumococcal AMC pilot "provides additional funding for children's vaccines and explores an innovative approach to address the market failures to meet the needs of the developing world."[200] GAVI regards the AMC as a "critical new tool" to accelerate the availability of pneumococcal vaccines to the world's poorest countries in "a sustainable manner".[201]

194 Philippe Le Houérou, World Bank, written evidence, page 181

195 Joint Statements from Canada, Italy, Norway, Russian and the Bill and Melinda Gates Foundation, written evidence, page 188

196 *ibid*., page 184

197 Philippe Le Houérou, World Bank, written evidence, page 180

198 Joint Save the Children and Médecins Sans Frontières, written evidence, page 221

199 Dr Peter Salama, UNICEF, written evidence, page 210

200 *ibid*., page 211

201 Dr Julian Lob-Levyt, GAVI, written evidence, page 192

5 CONCLUSION

5.1 Conclusion

It is clear from the evidence provided throughout the inquiry, that pneumococcal disease is a major global health problem. It is also obvious that action has been slow as pneumococcal disease has been under-recognised by national leaders in donor and developing countries.[202] Consequently, few initiatives have been aimed at controlling pneumococcal disease. Technical experts confirmed that expanded use of pneumococcal vaccines, together with strengthening of health systems and continued research into new vaccines and treatments could be expected to effectively and rapidly improve health and reduce costs in the developing world.

It is clear from the evidence provided throughout the inquiry, that pneumococcal disease is a major global health problem.

However, based on the evidence presented, the Group sees significant signs of progress as the AMC has moved pneumococcal disease up the political agenda. We could not envisage a more appropriate or practical system to provide an adequate supply of vaccine at an affordable price. Our initial impressions are that this 'demand-led' mechanism should accelerate the availability of effective pneumococcal vaccines to the world's poorest countries in a sustainable manner.[203] The experience gained by implementing and evaluating the pneumococcal AMC should offer insights that are potentially applicable to other vaccines and other problems.

We congratulate the leadership displayed by AMC donor nations and organisations – Canada, Italy, Norway, Russia, the UK and the Bill and Melinda Gates Foundation – for committing funding to this potentially life-saving mechanism. We further congratulate the WHO, UNICEF, GAVI, PneumoADIP and other stakeholders for their unprecedented efforts in raising awareness of pneumococcal disease. This change in attitude reflects the growing awareness of the disease burden, clinical trial results and successful experience with routine vaccination programmes in other countries.[204] [205] [206] [207] The AMC represents one manifestation of this welcome change in awareness of pneumococcal disease and the value of pneumococcal vaccines.

However, the success of the pilot pneumococcal AMC will require ongoing cooperation within the international community and the maintenance of financial and political support from the main funding partners. We conclude that the pilot pneumococcal AMC and other non-AMC initiatives that potentially follow could help to markedly reduce the disability, morbidity and mortality associated with this under-recognised killer and help to reduce child mortality in accordance with MDG4.

It is vital that the global community continues to expand research and improve health systems to ensure the promise of the AMC will live up to expectations. For the millions of children who could potentially benefit from this life-saving vaccine, it is imperative that the AMC process is closely monitored; scientific research surrounding pneumococcal disease and pneumonia remains a priority and developing health systems are continually improved.

202 Dr Thomas Cherian, WHO, written evidence, page 208

203 Dr Julian Lob-Levyt, GAVI, written evidence, page 192

204 Dr Orin Levine, PneumoADIP, written evidence, page 386

205 Klugman KP, Madhi SA, Huebner RE et al., *op.cit.*, pages 1341-8

206 Cutts FT, Zaman SM, Enwere G et al., *op.cit.*, pages 1139-46

207 Black S, Shinefield H, Fireman B et al., *op.cit.*, pages 187-95

The World Bank... praised the AMC pneumococcal pilot for "its openness and extensive consultations".

5.2 Recommendations

It is important to recognise that new pneumococcal vaccines are not a universal remedy to the problems associated with pneumococcal disease and pneumonia, but they do have the potential to substantially reduce the devastating effect the disease can have on individuals and their families in the developing world. To ensure the success of the AMC process, it is essential that donor nations and organisations continue to drive research on the burden of pneumococcal disease and pneumonia in the developing world.

Recomendation 1

Recognised international health funding mechanisms such as the Global Fund and IFFIm fund immunisations and the management of diseases such as malaria, tuberculosis and HIV/AIDS. As a result, UK Government statements, policies and strategies specifically recognise and focus on these diseases, as the UK Government is a major driver and financial contributor to both mechanisms. The AMC funds prevention of pneumococcal disease, including pneumonia, through a similarly recognised mechanism.

We recommend that the UK Government give equal prominence and standing to pneumococcal disease and pneumonia in its statements, policies and strategies as with malaria, tuberculosis and HIV/AIDS. We also recommend that world governments give equal prominence and standing to pneumonia and pneumococcal disease as they ascribe to other conditions.

Recomendation 2

The lack of a standard message around pneumococcal disease, technical factors and poor surveillance, have exacerbated the pervasive under-appreciation of pneumococcal disease as a public health priority.

We recommend that the governments of developing countries increase their commitments, where possible, to prevent and treat pneumonia and meningitis, the two most common manifestations of serious pneumococcal disease.

Recomendation 3

We believe that ongoing monitoring and evaluation is essential to secure public trust in the use of the large sums of public funding committed to the pneumococcal AMC. Public scrutiny of spend, transparency of management and robust evidence-based statistics are essential to maintain this trust.

We recommend that the Department for International Development (DFID) and the AMC partners publish regular updates on the progress of the pneumococcal AMC programme. We recommend that the UK Government and all AMC donors continue to monitor and evaluate the pilot AMC and work to assure that future AMCs benefit from the lessons learned.

Recomendation 4

We believe that continued research into pneumococcal disease and vaccination is vital for improved epidemiology, more accurate diagnosis and monitoring of changes in serotype. Current PCVs are not effective against all serotypes of pneumococcal disease, particularly some strains that are common in adults and the elderly, (*S. pneumoniae* kills about 800,000 adults annually).[208] In addition to this, herd immunity should ensure that adult mortality declines following the introduction of vaccination in children. AMC donors should engage with pharmaceutical companies to discuss developing vaccines effective against a larger variety of *S. pneumoniae* serotypes.

We recommend that AMC donors and other international governments consider supporting further research initiatives to discover and develop novel vaccines for the developing world and for adults who are also affected by pneumococcal disease.

Recomendation 5

AMC donor nations and organisations, as well as other key stakeholders should encourage other governments to contribute to supporting and backing further efforts to strengthen health systems including the areas of education, prevention, treatment and management of pneumococcal disease and pneumonia and other diseases that affect the developing world.

We recommend that the UK Government and other organisations, such as GAVI, support ongoing international efforts to strengthen health systems in the developing world, including through the International Health Partnership.

Recomendation 6

Educational, environmental and cultural factors increase the risk of pneumococcal disease. For example, parents may not recognise the symptoms in their children and might not appreciate the importance of seeking medical help.[209] Overcrowding, poor domestic air quality and malnutrition also increase the likelihood of exposure, transmission and the development of the disease.[210] The MRF stated in their written evidence that "…it is particularly important to engage with the public. Effective communication about disease burden and the importance of vaccination plays a vital role."[211]

We recommend that governments and agencies take this opportunity to educate people on the signs, symptoms and risk factors for pneumococcal disease.

We congratulate the leadership displayed by AMC donor nations and organisations…

208 Dr Orin Levine, PneumoADIP, written evidence, page 389

209 UNICEF/WHO, *op.cit.*, page 16

210 Nuorti JP, Butler JC, Gelling L et al., *op.cit.*, pages 182-90

211 Chris Head, MRF, written evidence, page 236

Perhaps, the most consistent point made by witnesses who gave evidence to the APPG, is that while pneumococcal disease affects millions of children and families every year, not enough has been done historically to defeat it.

6 GLOSSARY

Advance market commitment (AMC)
An advance market commitment provides a way of accelerating the discovery and manufacture of vaccines. It is based on the concept of guaranteeing the purchase of vaccines once they are developed, providing that they meet stringent, pre-agreed criteria on effectiveness, cost, and availability, and that developing countries demand them. The aim is to stimulate investment in research, development, and the establishment of manufacturing facilities, while giving governments in developing countries control over which vaccines they need. By guaranteeing an affordable long-term price, often referred to as the tail price, the AMC supports sustained use of the vaccine.

Burden of disease
The magnitude of a health problem in an area, measured by mortality (deaths), morbidity (persons affected by disease or illness), and other indicators such as permanent disability.

Cold chain
The system used for keeping and distributing vaccines in good condition. This consists of a series of storage and transport links, all of which are designed to keep the vaccine at the correct temperature until it reaches the user.

Combination (or combined) vaccines
Vaccines administered simultaneously as one preparation to protect against multiple infectious diseases or to prevent morbidity caused by multiple serotypes of the same pathogen.

Conjugate vaccine
A conjugate vaccine contains an antigen (the immunity producin molecule) bound to a carrier protein (which will allow the antigen access to areas of a cell where the carrier protein may go).

Expanded Program on Immunisation (EPI)
Launched by WHO in 1974 as a global infrastructure to enable health systems in countries to deliver a series of basic vaccines to infants, this program is the foundation for routine immunisation services throughout the developing world. Many countries still refer to their national immunisation systems as 'EPI'.

Gambia PCV Trial
A vaccine efficacy study in The Gambia of the 9-valent pneumococcal conjugate vaccine (PCV) in which it was demonstrated that multi-valent pneumococcal conjugate vaccines are safe and effective (even for HIV-positive children, as demonstrated by a trial of the same vaccine in South Africa) and that the vaccine has the potential to make a major health impact, especially in rural settings where access to treatment is limited.

GAVI Alliance (GAVI)
The GAVI Alliance – formerly the Global Alliance for Vaccines and Immunisation – is a public- private partnership focused on saving children's lives and protecting people's health by increasing access to immunisation in poor countries.

GAVI-eligible country
Countries with less than US$1000 per capita Gross National Income (GNI) can receive GAVI support. There are currently 72 GAVI-eligible countries throughout the world that are designated as eligible for GAVI support based on World Bank economic classification.

Haemophilus influenzae type b (Hib)
A bacterium that can cause a range of illnesses including meningitis, bacteraemia, ear, sinus and joint infections and pneumonia.

Herd immunity
Herd immunity occurs when a large enough portion of a population (usually 90%) is vaccinated against a microbe (such as S. pneumoniae) such that transmission of disease to others is reduced. Unvaccinated people coming in contact with those who have received the vaccine therefore have a lower chance of becoming infected by that microbe.

Gross national income (GNI)
Gross national income is the total value produced within a country (i.e., its gross domestic product) together with its income received from other countries (such as interests and dividends), less similar payments made to other countries.

Live attenuated virus vaccines
Live attenuated virus vaccines mimic natural exposure while being unable to cause disease, but do ideally induce immunologic memory and lifelong immunity. These vaccines generally require only one or two immunizations, since the immune responses they induce are very durable.

Millennium Development Goals (MDGs)
Adopted in 2000 by representatives from 189 countries, the Millennium Development Goals are time-limited commitments made by governments throughout the world to reduce poverty and promote human development. There are eight interrelated goals, each with a number of key measurable targets to be met by 2015.

Meningitis
Swelling of the meninges, (the protective membrane surrounding the brain and spinal cord during infection) is called meningitis, which can lead to paralysis, permanent neurological deficits and death. Both viruses and bacteria can cause meningitis and rates of bacterial meningitis – the more severe form – vary with seasonal changes in some areas of Africa, a phenomenon referred to as epidemic meningitis. Pneumococcus is one of the most important causes of both epidemic and non-epidemic meningitis around the world.

Treating and preventing infectious disease is central to meeting this goal: more than five million children under five years of age die from infections annually.

PneumoADIP
PneumoADIP was created by GAVI in 2003 and is based at the John Hopkins Bloomberg School of Public Health. Its aim is to expedite the development of pneumococcal vaccines and accelerate their introduction in developing countries.

Pneumococcal polysaccharide vaccine (PPV)
An inactivated bacterial vaccine that protects against infection with Streptococcus pneumoniae.

Pneumonia
A condition in which the alveoli (the tiny air-containing sacs of the lungs) become inflamed and fill with fluid, making breathing and adequate oxygen intake difficult. Although several agents such as viruses, fungi and other bacteria can cause pneumonia, Streptococcus pneumoniae is the leading cause of severe pneumonia in children in developing countries.

Prevenar / Prevnar
Prevenar (also spelled Prevnar in some markets) is the brand name of a 7-valent pneumococcal conjugate vaccine used to prevent Streptococcus pneumoniae (pneumococcus) infections such as pneumonia, meningitis and septicaemia in infants and young children. Prevenar, manufactured by Wyeth, has been used in the US since 2000 and is also part of the routine immunisations in other developed countries. The vaccine includes antigens from the following 7 serotypes of pneumococcus: 4, 6B, 9V, 14, 18C, 19F and 23F.

Pull mechanisms
Pull mechanisms provide a market incentive for increased commitment to vaccine and drug research and development. An incentive for industry's investment into product development is created by money only being paid out once a product has been developed. Should a manufacturer be unsuccessful, no funds are paid out. The AMC for pneumococcal vaccine is an example of a pull mechanism.

Push mechanisms
A push mechanism uses direct funding to accelerate the development of a vaccine (e.g. direct funding of research in laboratories or universities). Push and pull funding are complementary sources of investment. Push mechanisms are intended to reduce the risks and costs of R&D investment, paying before a product is available.

Sepsis
Also known as septicaemia, sepsis is an infection of the blood that may be caused by a number of bacteria, including Streptococcus pneumoniae.

Serotypes
A sub-classification of a virus or bacterium. The serotype is determined by the cell-surface proteins (antigens) of the virus or bacterium.

Serotype replacement
Serotype replacement is part of a natural process whereby infections caused by certain strains of a disease (sometimes known as replacement disease) can occur with slightly elevated frequency once other strains have been suppressed by a vaccine or other intervention (e.g. antibiotics).

Surveillance
Consistent monitoring over time of the incidence or prevalence of a particular disease in a specified population. By establishing the presence of severe disease, surveillance can demonstrate the potential for disease prevention and facilitates the setting of health priorities.

Vaccine
A vaccine is a preparation of killed or inactivated infectious agents or subunits of the agent's components that is used to stimulate immunity. Once immunity is established, upon exposure to an infectious agent such as a virus or bacterium, the body can more quickly and efficiently recognise and neutralise the threat.

Valency/Valent
Valency indicates the number of distinct types or groups protected against in a given vaccine formulation.