



**WHO-IFPMA ROUND TABLE**  
**WHO/Industry Drug Development**  
**Working Group**



**Working paper on priority infectious diseases requiring additional R&D**

**July 2001**

**Summary**

The WHO-IFPMA Working Group on medicines R&D has undertaken a detailed investigation of the levels of public and private R&D that is underway in the principal infectious diseases affecting the world today. These include the infectious diseases that are a particular burden for developing countries.

Whilst it is always possible to do more, the Working Group's view was that for many infectious diseases, such as HIV/AIDS and sexually transmitted diseases, there is currently a substantial level of R&D activity underway. By contrast, major diseases which present scientifically tractable targets but have had insufficient product R&D are **malaria** and **tuberculosis**. Recent initiatives to address these priority diseases include major Public-Private Partnerships in the Medicines for Malaria Venture (MMV) and Global Alliance for TB Drug Development (GATB). Assuming these initiatives are supported and sustained, they should be in a position to contribute in a major way in future to addressing the R&D shortfall in these diseases.

The Working Group has undertaken further disease analysis which revealed a second tier of diseases requiring additional drug R&D. These are (in alphabetical order) African trypanosomiasis, Chagas disease, leishmaniasis, lymphatic filariasis, onchocerciasis and schistosomiasis. It is the view of the Working Group that whilst each of these diseases represent significant scientific challenges with no guarantee of success, nevertheless if appropriate incentives were in place there is the prospect of new medicines being produced. These diseases are not strictly equal in need or similar in their profile. Existing products for **African trypanosomiasis**, **Chagas disease** and **leishmaniasis** (all caused by kinetoplastid protozoa) are mostly parenteral in use, need multiple administrations, have serious side effects and are increasingly becoming compromised by acquired resistance. A single additional Public-Private Partnership (PPP) for 'such diseases, modelled on MMV or GATB, may be an appropriate way forwards. As a grouping these diseases also have the advantage that the causative organisms are phylogenetically closely related and this may mean that chemical series or even individual new drugs will be effective across all three of them.

By contrast, there are good products available for schistosomiasis and lymphatic filariasis and onchocerciasis, plus research underway through WHO/ TDR. Furthermore, the trends in these diseases appear to be stable or falling in response to

## FINAL

control programmes. As a consequence and without suggesting that these diseases do not merit additional R&D attention, it is not the recommendation of the Working Group to establish a separate PPP for these diseases at this time. It is also felt that attempting to include them with the kinetoplastida PPP would represent an unhelpful loss of focus.

While the acute respiratory diseases, in particular those caused by the pneumococci, and the diarrhoeal diseases remain major causes of morbidity and mortality, the tools to prevent and or treat both groups are at hand. In the case of the former, only the epidemiology of the pneumococcus in the developing world remains as a barrier to the development of conjugated vaccines for children. In the case of diarrhoeal diseases, access to clean water and the appropriate use of sanitary measures would have the greatest effect.

These conclusions have been reached by the Working Group based on data and expertise within WHO and the research based pharmaceutical industry, and we would like to express our particular thanks to the many contributors to the work. The next stage will be a broader sharing and discussion of the work undertaken to date.

### **Introduction**

Infectious diseases represent one of the greatest medical challenges –possibly the single greatest challenge – to mankind in the 21<sup>st</sup> century. The burden of infectious diseases falls particularly if not exclusively on the less developed countries; addressing the resulting challenges requires new global initiatives.

The problems posed by these diseases are complex with an underlying basis in poverty. Socio-economic conditions can have enormous impact on the burden of infectious diseases on a given population; this is amply illustrated by the history of the decline of tuberculosis with the rise in standard of living even before the advent of drugs active against the tubercle bacillus. Similarly, the practice of sanitary disposal of human waste and access to clean drinking water afford enormous health benefits to human health. Simple methods of controlling or constraining vectors of human diseases such as insecticide-impregnated bed nets preclude the need to treat many potential victims of malaria. But there remain many infectious diseases for which there are ongoing needs for specific drug therapy, some because there is little hope for better living conditions in the near future.

Every infectious disease is unique. For some, products exist and are accessible. For many, products exist but there are problems with access, affordability or acquired drug resistance. In some diseases product R&D is underway but has yet to deliver. In other diseases, limited product R&D is underway because the scientific basis for rational study is insufficient. In other diseases limited product R&D is underway not because of scientific barriers but because industry doubts that returns would cover the cost of the investment and support ongoing R&D.

The research-based pharmaceutical industry invested an estimated \$43.3 billion in R&D in 2000, and the smaller biotechnology companies an estimated further \$11.2 billion.<sup>1,2</sup> The net result is a wealth of new medicines, including many for major infectious diseases such as HIV/AIDS. However, the emphasis of R&D tends to be

towards diseases when returns are more likely to cover the costs and pay for ongoing R&D. This means in practice the diseases prevalent in the developed countries, with proportionately less spent on new drugs and vaccines for those (infectious) diseases that primarily affect developing countries.

Whilst acknowledging its central importance today, this paper does not address the key question of ‘access’ to currently available medicines. The objective of the present work is to identify definitively those infectious diseases which are most in need of new medicines or vaccines, and to give some sense of the priority areas for *additional* R&D. In many cases the ideal solution would be for a vaccine, but where a vaccine seems unlikely in the short or medium term because of the scientific challenges involved, then new medicines may well be appropriate.

## **Methodology**

The approach employed by the Working Group has been first to establish a working list of infectious diseases and review disease burden as a pointer to priorities. The criteria used for assessing disease impact included, in addition to disability adjusted life years (DALYs): mortality, societal costs, likelihood of treatment and forward trends. The next stage was to review existing interventions on the basis of availability and any limitations of medicines. The proper place of vaccines and of non-medical interventions was also considered. Current levels of industry activity for each disease were assessed; whilst it is impossible to define what is ‘enough,’ a qualitative judgement was reached on the basis of the amount of competitive R&D known to be underway. A judgement on the need for additional medicines R&D was therefore made both on the basis of the current or likely future availability of medicines and of other treatment approaches. Altogether a combination of 17 assessment criteria have been used by the Working Group, as detailed in Table 1.

Base data are presented in Table 2, and those diseases for which, in the view of the Working Group, specific additional R&D is justified are presented in Table 3. The following pages present some summary observations about the diseases to give a flavour of the analysis. Wide consultation within WHO and the industry has been undertaken to date to substantiate the tables and conclusions. Numbers for DALYS and for deaths used in this section as well as in the Tables have been taken directly from The World Health Report 2000.

## **Diseases analysed**

The Working Group’s analysis was restricted to infectious diseases since it is these that represent the greatest area of concern, but this should not be taken to mean that chronic disorders are of no importance in developing countries.

In addition to the ‘traditional’ infectious diseases, the Working Group noted but did not specifically address certain other types of infection, such as those forms of cancer now known to be associated with viral etiologies (other than hepatitis B and C), human papilloma virus (a cause of cervical cancer), or the Epstein-Barr virus (a contributing cause of Burkitt’s lymphoma).

## Priorities determined by DALYs

The starting point for prioritisation was disease burden as expressed in DALYs.<sup>4</sup> These numbers are estimates at best, derived from data available to epidemiologists at WHO. They are however appropriate and sufficiently reliable for the purpose of the present work in identifying priorities for additional R&D efforts. The Working Group recognises that this is only one way of approaching the analysis, and alternatives, such as providing greater weight to morbidity/mortality in the early years of life, might be equally appropriate. The problem of double disease counting was also noted: but again the analysis undertaken is not sensitive to this issue.

## Results

Global infectious diseases can be simplistically but helpfully banded into four categories, according to the size of their impact estimated in DALYs.

### 1. Band 1: DALYs > 70 millions

Acute respiratory infections (96.7), Diarrhoeal diseases (72.1), HIV/AIDS (89.8)

### 2. Band 2: DALYs 20-69 millions

Malaria (45.0), Tuberculosis (33.3), Measles (29.8)

### 3. Band 3: DALYs 10-19 millions

Sexually-transmitted infections (19.7), Pertussis (10.9), Tetanus (12.0)

### 4. Band 4: DALYs < 10 millions

Lymphatic filariasis and onchocerciasis (6.0), Meningitis (9.8), GI nematode infestations (2.7), Hepatitis (2.8), Leishmaniasis (2), Schistosomiasis (1.9), Trachoma (1.2) and other diseases.

## Band 1 diseases

*Acute respiratory diseases.* A range of interventions is currently available, including vaccines for *S. pneumoniae* and *H. influenzae* and medicines for non-specific acute respiratory diseases. Problems with currently available technology are access (healthcare infrastructures and affordability) to both vaccines and treatment and the development of acquired resistance due to injudicious use of available antibiotics. New medicines are particularly needed for pneumococcal disease, in which case resistance to commonly used antibiotics is becoming widespread, for influenza and for respiratory syncytial virus (RSV) infections where treatment is expensive and requires specialized complicated equipment. In the case of RSV there is probably insufficient R&D underway for both treatment and prevention. In addition, it is now recognised that simple interventions such as the use of high potency vitamin A can have major impact on infant mortality from this disease. Targeted research in this area might yield significantly greater impact than the development of new specific medicines or vaccines for those at greatest risk.

*Diarrhoeal diseases.* Non-specific interventions such as oral rehydration are particularly important in the case of diarrhoeal diseases, and form the mainstay of treatment to prevent fatalities, especially in infant diarrhoea, and in cholera at any age. However the WHO have also identified the need for antihypersecretory drugs as

## FINAL

adjunctive therapy with oral rehydration. A range of interventions is currently available, including vaccines against *Vibrio cholerae*. The general role of antimicrobials is questionable, and inappropriate use surely contributes to bacterial resistance. However there are specific situations, such in acute cholera, where antibiotics may be lifesaving. Judicious use, and further development of specifically targeted antibiotics against infections such as *Shigella* would be a considerable benefit.

*HIV/AIDS*. The importance of this infection and the ravages it inflicts on humankind cannot be over-emphasised. However, as will be seen from the final prioritisation table the research underway in the private and academic spheres does not indicate the need for *additional* private-public partnerships for research into new therapies, except perhaps in the area of prophylactic vaccines for developing-country clades of the virus.

### **Band 2 diseases**

*Malaria* persists as a major health problem for several reasons: vector control in some areas has become more difficult either because of the political and environmental pressures to stop using insecticides which may be toxic to humans; slow progress in the discovery of an effective vaccine; and the ability of the causative organisms to develop resistance to existing therapies.

*Tuberculosis* control and treatment is plagued by the rampant spread of HIV/AIDS; to a small degree development of resistance to therapy has also occurred in some areas. While BCG is used successfully in some countries, a broadly effective, well accepted vaccine is not available.

*Measles* has been eliminated as an indigenous disease only in Finland and in the USA; prevention is crucial as there is no effective therapy. In developing countries, effective vaccination programmes are limited by the absence of an effective heat stable vaccine (one which requires neither freezer nor refrigerator temperatures). There is therefore research need to identify such a vaccine to support the global effort on measles vaccination.

### **Band 3**

*Sexually transmitted infections*, other than scabies and pubic lice, may generally be prevented by the use of male condoms. While drug treatment may be considered adequate by some standards, access is a problem and in addition, the proportion of gonococci which are resistant to more than one antibiotic is on the rise world-wide. Gonococcal vaccines have been in the research area for decades, but a safe and effective vaccine is not around the corner.

*Pertussis* is a highly morbid disease in many children and fatal in some; recently there has been an upsurge of recognition of this disease in adults, but since there is no very useful treatment in either, the more extensive use of either whole-cell vaccines or the newer acellular versions is needed. If the trend in adult cases continues, it may be necessary to recommend boosters for adults. Adequate studies of the full range of

## FINAL

newer vaccines is virtually impossible and the utility and success of these products will be tested in the real world. Access to the vaccines is absolutely critical.

*Tetanus* invariably decreases when the toxoid vaccines are used; they are essential because the disease itself does not confer immunity, and the treatment even in tertiary care centres is disappointing. The principal problem in the management of tetanus is ensuring the adequate penetration of EPI programmes into the high risk areas as a preventive measure.

### Band 4

*Meningitis*, while not at the top of this band, falls into a different category to most of the others as its epidemiology in many parts of the less-developed world is not known in sufficient detail. For most of the viral forms (other than for mumps, measles and varicella) there are no vaccines nor are there adequate drug treatments. However, from the published literature it appears that the distribution of the various aetiologies is not dissimilar to that seen in the more developed countries. Thus access to adequate treatment in a medical facility is key to a reasonable rate of survival. Better yet would be full access to the available preventative measures in the form of haemophilus conjugate vaccines, pneumococcal conjugate vaccines, and meningococcal vaccines. These are insufficiently available now, and should be used prior to the arrival of even more effective vaccines. The one aetiology where the distribution appears to differ is meningococcal meningitis - in developed countries the A strains predominate whereas in the south, the C strain is much more common. A vaccine is available, but not deployed. There is no vaccine for the B strain.

The major filariases include *lymphatic filariasis* (LF) and *onchocerciasis* and there has been substantial progress in both control and treatment of these. For LF there have been extensive efforts to reduce the prevalence and incidence of the disease by reducing the number of circulating microfilariae using one or more of the several **microfilaricides** available; combinations have proven to be remarkably effective, even if they are not **macrofilaricides**. The latter class of drug would take less time to bring about control of the disease. In the case of onchocerciasis, ivermectin when properly used may be effective not only in relieving symptomatic disease, but in blocking transmission by reducing the microfilariae counts in the skin. For both LF and onchocerciasis experts would still prefer to have an effective **macrofilaricide**.

*Gastrointestinal nematode* infestations are almost ubiquitous in distribution in warmer temperate climates and in the tropics. The combined effects including blood loss, malnutrition and retarded physical and mental growth are difficult to assess accurately, but excepting those parasites with a life cycle within the human host, infestations can generally be controlled by sanitary measures. Drug treatment should not be considered a modality superior to proper disposal of human waste and access to clean water – medicines constitute a stop-gap measure, not a final answer.

*Hepatitis A, B, and C* represent a very broad spectrum of seriousness of disease, especially with respect to immediate outcome and long term effects. The vaccines for A and B are very effective and broadly available although not universally affordable. A vaccine against C is not yet available; nor is it clear when it will be. Treatment of hepatitis A is symptomatic. Treatment available for hepatitis B and C in the form of

## FINAL

interferon alpha and lamivudine is complex and there are again issues of affordability. In addition, these treatments are not entirely effective and in consequence new modalities are needed. Furthermore, inexpensive diagnostic tools are needed so that the need for drug treatment can be met.

*Trachoma* treatment and control have been a priority at WHO and recent interest exhibited by way of donation of effective treatments are encouraging; furthermore, sanitary measures in the form of hand washing appear to have had an impact on the transmission of trachoma. A vaccine is not on the horizon.

*Schistosomiasis* treatment has been dramatically improved since the advent of chemotherapy using praziquantel; resistance to both oxamniquine and praziquantel probably cannot be prevented. Mollusciciding has been effective, but new ecological niches have been created in many areas where water projects for irrigation or power generation have been introduced. There is clearly a need for R&D aimed at a replacement for praziquantel.

*Leishmaniasis* is broadly prevalent in the south, but the visceral form, *Kala-azar* (K-A) is concentrated in four countries- Brazil, Sudan, Bangladesh, and India. Control of all forms with pyrethroid-impregnated bed nets has improved. Treatment of K-A with antimonials is now limited by acquired drug resistance. Treatment with liposomal formulations of amphotericin B is simple and safe but affordability issues restrict broad access; the possibility of the use of a new compound, miltefosine, an orally active agent, brings new hope for those suffering this debilitating disease. Controlled studies for cutaneous and mucocutaneous forms are lacking.

*African trypanosomiasis*, while one of the least prevalent of the diseases here reviewed, has increased in prevalence and incidence in the past ten years or so. While tsetse traps are effecting in helping control the disease, the treatments for the most part are inadequate or inaccessible. Eflornithine, a relatively new drug, while an improvement over previous therapies, has had a limited impact thus far because of supply problems, now hopefully solved.

*Chagas' disease* is coming under control in the southern cone of South America thanks to effective vector control; however, safe and highly effective therapy for existing chronic cases of the disease is still lacking.

### **Summary of conclusions**

In the category of major diseases which present scientifically tractable targets but have insufficient product R&D, are malaria and tuberculosis. WHO's establishment of its Roll Back Malaria programme and its Stop TB initiative are indications of the size and challenge of these diseases. Further disease prioritisation based on available evidence revealed a second tier of neglected diseases, after malaria and TB. This list is (alphabetically) African trypanosomiasis, Chagas disease, leishmaniasis, lymphatic filariasis and onchocerciasis and schistosomiasis. It is the view of the Working Group that whilst all of these diseases represent significant scientific challenges with no guarantee of success, nevertheless if appropriate incentives were in place there is the prospect of new medicines or vaccines being produced. It is however a sobering

## FINAL

observation that this list is very similar to that identified more than two decades ago, in a major US National Academy of Sciences conference<sup>3</sup>.

These diseases are not strictly equal in need or similar in their profile. Existing products for **African trypanosomiasis, Chagas disease and leishmaniasis** (caused by kinetoplastid protozoa) are mostly parenteral in use, need multiple administrations, have serious side effects and are increasingly becoming compromised by acquired resistance. A single additional Public-Private Partnership (PPP) for them, modelled on MMV or GATB, may be an appropriate way forwards. As a grouping they also have the advantage that the causative organisms are phylogenetically closely related and this may mean that a single chemical series or even individual new drugs will be effective across all three diseases.

By contrast, there are good products available for schistosomiasis and lymphatic filariasis and onchocerciasis, plus research underway through WHO/TDR. Further, the trends in these diseases appears to be stable or falling in response to control programmes. As a consequence, without suggesting that these diseases do not merit additional R&D attention, it is not the recommendation of the Working Group to establish a separate PPP for these diseases at this time. It is also felt that attempting to include them with the Kinetoplastida PPP would represent an unhelpful loss of focus.

In addition to these 'tropical' diseases, a number of specific pathogens are of concern and may require additional R&D attention. These are respiratory syncytial virus (RSV), *Shigella*, *Salmonella*, *Giardia* and *Entamoeba*.

## References

1. Centre for Medicines Research International Report: Activities of the International Pharmaceutical Industry in 1999: Pharmaceutical Investment and Output. M.S. Ogg et al, CMR00-137R, 2000.
2. Ernst & Young. European Life Sciences 99. Sixth Annual Report: Communicating Value. 1999. Biotechnology R&D projected from this survey of 395 European and US biotechnology using the average increase in R&D expenditure over the preceding three years.
3. Pharmaceuticals for Developing Countries. Conference Proceedings. Institute of Medicine, National Academy of Sciences, Washington D.C., 1979.
4. The World Health Report 2000, WHO, Geneva, 2001.

**Table 1. Explanation and key to Tables 2 and 3.**

The 17 criteria used in the analysis are described below. Tables 2 and 3 are split into three parts:

Part 1: Disease burden and future trends (criteria 1-6)

Part 2: Existing interventions (criteria 7-10)

Part 3: Medicines R&D needs and priorities (criteria 11-17)

<b>Column (Criterion)</b>	<b>Entry</b>
1	Diseases listed as per World Health Report 2000 and sub-divided where applicable into major pathogens (e.g. <i>Streptococcus pneumoniae</i> ) or constituent diseases (e.g. syphilis)
2	Disability adjusted life years in millions (from World Health Report 2000)
3	Mortality p.a. in millions (from World Health Report 2000)
4	Costs to society = impact that disease in individual has on society (i.e. indirect costs)
5	Target population (i.e. number of cases) and proportion of those actually receiving treatment per annum. (Numbers/best estimate for most recent year of data available)
6	Trends over next 20 years for entries in columns 2-4
7	Non-drug interventions; e.g. vaccine, pesticide, bed-nets, etc.
8	Effective available drugs
9	Treatment of infected cases prevents secondary cases?
10	Limitations of existing drugs e.g. acquired resistance, serious adverse events, unavailability of oral dosage form, dosage regimens that do not favour good compliance
11	Desirable non-drug interventions (e.g. vaccine) and feasibility.
12	New drugs needed
13	New drug R&D <i>technically</i> feasible (i.e. doable)
14	Industry levels of engagement at current time;
15	Public sector support needed to engage industry in new R&D;
16	Priorities for new drug R&D
17	Priorities for new drug R&D that need public sector support Comments/Footnotes

**Glossary for Acronyms and Abbreviations Used in the Tables**

APOC	African Program for Onchocerciasis Control
ARI	acute respiratory infection
BCG	Bacille Calumette-Guerrain ( vaccine against TB)
DEC	diethylcarbamazine (drug to treat onchocerciasis)
DOTS	directly observed therapy (for tuberculosis)
ETEC	enterotoxigenic <i>E.coli</i>
GATB	Global Alliance against TB
Hep B S ag	hepatitis B surface antigen
LF	lymphatic filariasis
MMV	Medicines for Malaria Venture
OCP	Onchocerciasis Control Program
ORF, ORS	oral rehydration formula, solution
PPP	Public-Private Partnership
rX	treatment/prescription
SAE	serious adverse experience
SP	sulphadoxine/pyrimethamine
STI	sexually transmitted infection
TDR	Tropical Disease Research (at WHO)

**Table 2 Infectious diseases reviewed. Part 1. Disease burden and future trends (criteria 1-6)**

1. DISEASE	2. DALYs (Millions)	3. Mortality per annum (millions)	4. Costs to society	5. No. clinical cases per annum: number likely to be accessible for treatment per annum (p.a). m = million	6. Trends over next 20 yr
<b>ACUTE RESPIRATORY INFECTIONS</b> <i>Streptococcus pyogenes</i> <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> other bacteria ( <i>Legionella</i> , <i>Mycoplasma</i> , <i>Chlamydia</i> ,)	96.7	3.96			
<i>Influenza</i>			High		Stable (?)
RSV Other viruses					
<b>DIARRHOEAL DISEASES</b> Non Specific Etiologies	72.1	2.213		Very high for Oral Rehydration Sol'n. (ORF)	
<i>Shigella</i>					Stable to Falling
<i>Vibrio cholerae</i>				50-100% dependent on site of outbreak	Stable to Falling
<i>Salmonella</i> (incl. <i>typhi</i> )					Stable to Falling

FINAL

<i>Campylobacter</i>				Especially traveler's	Rising
<i>E. coli (ETEC etc)</i>				Endemic, but also traveler's	Stable
Rotavirus				Major cause in infants < 1 yr.	Stable to Rising
other viruses					
<i>Giardia lamblia</i>				Difficult to assess. Chronic form is endemic	Stable
Amoebic dysentery				Difficult to assess. Chronic form is endemic	Stable
<b>HIV/AIDS</b>	89.8	2.673			
<b>MALARIA</b>	45	1.09	Ranges from High to Low, depending on parasite species and local transmission rates: in Africa estimated to be >\$1.8 billion per annum	300 m clinical cases per annum, about 100m treatments (total chloroquine suggests more than 100m). Epidemics difficult to manage with high death rate.	Rising, especially in epidemic-prone areas, frontier areas of development and social disruption
<b>MEASLES</b>	29.8	0.875			Falling
<b>TUBERCULOSIS</b>	33.3	1.669	High	8 m / 6 m	Falling to Rising - depends on meeting control targets
<b>SEXUALLY-TRANSMITTED INFECTIONS</b> Syphilis Gonorrhoea Chlamydia Chancroid Herpes	19.7	0.0178			

FINAL

<b>PERTUSSIS</b>	10.9	0.295	Medium		Falling
<b>TETANUS</b>	12	0.377	Medium		Falling
<b>MENINGITIS</b>	9.8	0.171			
<i>S. pneumoniae</i> (see ARI)			Unknown		Unknown
<i>H. influenzae</i> (see ARI)			Unknown		Falling. with vaccine use
<i>Neisseria meningitidis</i>	3.7	0.063: 1997 WHO estimates 37% of bacterial meningitis mortality due to meningococcal disease	Unknown		Falling. with vaccine use
Neonatal meningitis			Unknown		Falling. with PCN prophylaxis
<b>LYMPHATIC FILARIASIS &amp; ONCHOCERCIASIS</b>	4.9 1.08	0 0	Lymphatic filariasis (LF): Medium  Onchocerciasis: High  Social impact of both : High	LF: 80 m infections, increasingly being treated: control programs starting. Onchocerciasis: 30 m infections, control program underway (OCP/APOC) and Lat. Amer.	Lymphatic Filariasis - Falling  Onchocerciasis - Falling  Rate of fall dependent on control program impact
<b>GI NEMATODE</b>	2.65	0.016	Medium	> 1 billion infections per annum	Stable

FINAL

<b>INFESTATIONS</b>					
<b>HEPATITIS</b> A B C	2.79	0.124	Low High High		Unknown Falling Unknown
<b>LEISHMANIASIS</b>	1.98	0.057	Visceral: High  Mucocutaneous: High  Cutaneous: Medium to Low	Visceral: 0.5 m new cases p.a., 90% in Bangladesh, Brazil, India & Sudan mostly accessible Mucocutaneous: ? Cutaneous: ?	Visceral : Stable generally but epidemics occur  Mucocutaneous: Stable  Cutaneous: Stable
<b>SCHISTOSOMIASIS</b>	1.93	0.014	Medium	200 m infections	Stable: local intense control programs may have impact: Falling
<b>TRACHOMA</b>	1.2	0			
<b>AFRICAN TRYPANOSOMIASIS</b> <i>(T.b.rhodesiense and gambiense)</i>	2.05	0.066	Low, except in epidemic situations, where it can be High	About 250,000 cases pa in non-epidemic years / about 25,000 treatments	Stable
<b>CHAGAS DISEASE</b>	0.676	0.021	High due to chronic cardiac and GI infections.	12-25 m chronic infections, mostly not treated (no effective treatment)	Falling in Southern Cone where vector control in operation; otherwise Stable

FINAL

<b>DENGUE</b>	0.465	0.013	High	1998 reported 1.2 m; estimate c. 50m, >90% accessible	Rising
<b>JAPANESE ENCEPHALITIS</b>	1.05	0.006	Medium	Estim. 30,000, >75% accessible	Stable to Falling
<b>LEPROSY</b>	0.476	0.003			
<b>POLIO</b>	1.725	0.002			
<b>DIPHThERIA</b>	0.151	0.004			

**Table 2. Infectious diseases reviewed. Part 2: Existing interventions (criteria 7-10)**

<b>DISEASE</b>	<b>7. Non-drug interventions available</b>	<b>8. Currently used drugs</b>	<b>9. Impact of successful treatment on spread of infection</b>	<b>10. Limitations of existing drugs (assuming access achieved)</b>
<b>ACUTE RESPIRATORY INFECTIONS</b>				
<i>S. pyogenes</i>	No	Yes, beta lactams, macrolides, quinolones	Yes	Acquired Resistance; virulence factors and host immunity both important
<i>S. pneumoniae</i>	Yes, vaccine; 7 valent conjugate vaccine - pediatric; 23 valent - Adults partially effective	Yes, beta lactams, macrolides, quinolones	No	Acquired Resistance; Affordability; access to new drugs an issue
<i>H. influenzae</i>	Yes, (HiB conjugate vaccine) partially effective	Yes, beta lactams, macrolides, quinolones	No	Acquired Resistance; Affordability; access to new drugs an issue
other bacteria ( <i>Legionella</i> , <i>Mycoplasma</i> , <i>Chlamydia</i> ), Influenza	No	Yes, macrolides, tetracyclines	No	
RSV	Yes; killed vaccine for adults partially effective	Yes, neuraminidase inhibitors	No	Acquired Resistance; Affordability; Partially effective
other viruses	No (vaccine in development)	Yes, Monoclonal antibodies, ribavirin	No	Affordability; not oral; Partially effective
	No	No	Not Applicable	Not Applicable
<b>DIARRHOEAL DISEASES</b>				

FINAL

Non Specific Etiologies	Yes, Oral Rehydration	Yes, but antibiotics not recommended	No	ORS is standard therapy
<i>Shigella</i>	No	Yes	Yes?	Acquired Resistance
<i>Vibrio cholerae</i>	Yes, vaccine	Yes	Yes	Acquired Resistance
<i>Salmonella</i> (incl. <i>typhi</i> )	Yes, ( <i>S. typhi</i> ), No (others)	Yes	Yes asymptomatic carriers after rX	Acquired Resistance
<i>Campylobacter</i>	No	Yes	Yes	Acquired Resistance
<i>E. coli</i>	No (ETEC vaccines in development)	Yes	Not Applicable	Not Applicable
Rotavirus	No (vaccines in development)	No	Not Applicable	Not Applicable
Other viruses	No	No	Not Applicable	Not Applicable
Giardia	Yes, Sanitation/Water improvement	Metronidazole, Tinidazole	Generally not in developing countries	Limited range and increasing resistance
Amoebic dysentery	Yes, Sanitation/Water improvement	Metronidazole, Tinidazole	Generally not in developing countries	Very limited range and increasing resistance
<b>HIV/AIDS</b>	Condoms	Yes	No – Treatment may not preclude ongoing infectivity	Acquired Resistance, Affordability, Poor compliance, SAE; Partially effective
<b>MALARIA</b>	Insect repellants/ pesticides/bed nets/ environmental management	Chloroquine & amodiaquine, Sulphadoxine / pyrimethamine (SP), Quinine, Halofantrine, Mefloquine, Atovaquone/ proguanil (Malarone), Artemether/Lumefantrine, (Co-artem), Primaquine (vivax only).	No, Most drugs available suppress infection in blood but not gametocytes, therefore no effect on transmission	Chloroquine: acquired Resistance; not all stages SP: Acquired Resistance; not all stages Quinine: acquired Resistance; compliance, Halofantrine: SAE; not all stages, Mefloquine: R; Affordability; not all stages, Aes, Malarone: Affordability; not all stages, Co-artem: Affordability; not all stages, Primaquine: SAE; poor comp

FINAL

<b>MEASLES</b>	Yes, vaccine	No	Not Applicable	NA
<b>TUBERCULOSIS</b>	No, (exc. BCG)	Yes, (DOTS)	Yes	Acquired Resistance; Poor compl (duration and complexity) unless DOTS is used
<b>SEXUALLY-TRANSMITTED INFECTIONS</b>	Condoms for all			
Syphilis	No	Yes, beta lactams	Yes	Acquired Resistance  Acquired Resistance; problem for immunocompromised; see note 6 Acquired Resistance
Gonorrhoea	No	Yes, beta lactams	Yes	
Chlamydia	No	Yes, macrolides, tetracyclines	Yes	
Herpes	No	Yes, nucleosides	Yes, Partially effective	
Chancroid	No	Yes	Yes	
<b>PERTUSSIS</b>	Yes, vaccine	Yes	Yes	Poor response
<b>TETANUS</b>	Yes, vaccine	Yes	No	Expensive
<b>MENINGITIS</b>				
<i>Strep. pneumoniae</i> (see ARI)	Yes, (Vaccine ? Effective)	Yes, beta lactams	?	Acquired Resistance (do not always prevent sequelae)
<i>Haem. influenzae</i> (see ARI)	Yes	Yes, beta lactams	Yes	Acquired Resistance (do not always prevent sequelae)
<i>Neisseria meningitidis</i>	Yes, (vaccines for A, A+C, A+C+Y+W135)	Yes, beta lactams	No (but prophylaxis - Yes)	Not oral; R (<10%); some say oral may be effective
Neonatal meningitis	No	Yes	Yes (MD compliance needed)	Acquired Resistance for coliforms

FINAL

<p><b>LYMPHATIC FILARIASIS &amp; ONCHOCERCIASIS</b></p>	<p>LF: vector control  Oncho, vector control</p>	<p>LF: diethylcarbamazine, Ivermectin, Albendazole, Albendazole combinations Oncho: ivermectin</p>	<p>Yes  Yes</p>	<p>Not all stages. DEC plus albendazole may kill adult worms in LF. . Moxidectin might kill adult filariae</p>
<p><b>GI NEMATODE INFESTATIONS</b></p>	<p>Improve water, sanitation and education</p>	<p>Mebendazole, Albendazole, Levamisole, Pyrantel, (Ivermectin- Strongyloides)</p>	<p>Yes, probably only benzimidazoles</p>	<p>?Emerging resistance within 20 y. Spectrum of all single drugs limited Trichuris is a special problem Do not forget tapeworms and flukes</p>
<p><b>HEPATITIS</b> A B  C</p>	<p>Yes, vaccine Yes, vaccine  No</p>	<p>No Interferon, Lamivudine  Interferon, ribavirin</p>	<p>Not Applicable No  No</p>	<p>Acquired Resistance, Serious Adverse Events, not oral, poor compliance; Partial efficacy, Affordability Affordability, SAE, not oral, poor compliance.</p>
<p><b>LEISHMANIASIS</b></p>	<p>Vector contact avoidance</p>	<p>Sodium stibogluconate, meglumine antimonate, amphotericin B, pentamidine</p>	<p>Yes; effective treatment will stop transmission locally. Current problem is compliance</p>	<p>Antimonials: acquired Resistance All: SAE; not oral; poor compliance</p>
<p><b>SCHISTOSOMIASIS</b></p>	<p>Molluscicides</p>	<p>Praziquantel; oxaamniquine</p>	<p>Yes</p>	<p>Praziquantel: acquired Resistance</p>

FINAL

				(anecdotal) Oxamniquine: Acquired Resistance (not all species)
<b>TRACHOMA</b>	No	Yes	No	
<b>AFRICAN TRYPANOSOMIASIS</b> <i>(T.b.rhodesiense and gambiense)</i>	Tsetse traps	Early: suramin, pentamidine, Late: melarsaprol, eflornithine  Need effective drug for T.b.rh.	Yes	Suramin, pentamidine: acquired Resistance; Serious AdverseEvents; not all stages  Melarsoprol: Serious Adverse Events; not oral Eflornithine: not oral; not all species: expensive
<b>CHAGAS DISEASE</b>	Insecticides: intensive house spraying and surveillance	Nifurtimox, Benznidazole (acute & early chronic only)	Yes	Not all stages
<b>DENGUE</b>	Some (vector control) but not very effective	No	Not Applicable	Not Applicable
<b>JAPANESE ENCEPHALITIS</b>	Yes - vaccine	No	Not Applicable	Not Applicable
<b>LEPROSY</b>	No	Yes	Yes	Acquired Resistance; Poor compliance
<b>POLIO</b>	Yes - vaccine	No	Not Applicable	
<b>DIPHThERIA</b>	Yes - vaccine	Yes	Yes	Acquired Resistance

FINAL

**Table 2. Infectious diseases reviewed. Part 3: Medicines R&D needs and priorities (criteria 11-17)**

<b>DISEASE</b>	<b>11. Non-drug interventions preferable / R&amp;D feasible</b>	<b>12. New drugs needed</b>	<b>13. New drug R&amp;D feasible</b>	<b>14. Industry engaged in R&amp;D</b>	<b>15. Public sector support needed in drug R&amp;D</b>	<b>16. Priorities for new drug R&amp;D</b>	<b>17. Priorities needing public sector support</b>
<b>ACUTE RESPIRATORY INFECTIONS</b>							
<i>S. pyogenes</i>		Yes	High	High to Medium	No		
<i>Strep. pneumoniae</i>	Vaccine/Feasibility High	Yes	High	High	No		
<i>H. influenzae (H.i.)</i>	PS & PS Conjugate Vacc. available; Non-type H.i: Feasibility - Moderate to Low	Yes	High	High to Low	No		
other bacteria ( <i>Legionella, Mycoplasma, Chlamydia</i> )		Yes	Medium to High	High to Medium	No		
Influenza	Vaccine Feasibility - Moderate	Yes	High	High	No		
RSV	Feasibility - Moderate to Low	Yes	Low to Medium	Low to Medium	No		
other viruses	Vaccine- Feasibility Low	Yes	Low	Low to Medium	No		
<b>DIARRHOEAL DISEASES</b>							
Non Specific Interventions	Better use of ORS	Yes – antisecretory agents	Medium	Low	Yes		

FINAL

<i>Shigella</i>	Vaccine Feasibility Moderate to Low	Yes for resist	Medium	Low	No		
<i>Vibrio cholerae</i>	Vaccine for prophylaxis Feasibility High	Yes	Low	Low	No		
<i>Salmonella</i> (incl. <i>typhi</i> )	Yes especially <i>S. typhi</i>	Yes for resist	Medium	Low	No		
<i>Campylobacter</i>	No	Yes	Medium	Low	No		
<i>E. coli</i>	ETEC vaccine Feasibility- High	Yes for resistance	High	Medium	No		
Rotavirus	Vaccine Feasibility- High	Not Applicable	Not Applicable	Not Applicable	Not Applicable		
other viruses		No					
<i>Giardia lamblia</i>	No	Yes- current rX limited and unsatisfactory	Low	Low	?		
Amoebic dysentery	No	Yes- current rX limited and unsatisfactory	Low	Low	?		
<b>HIV/AIDS</b>	Vaccine Feasibility- Moderate to Low	Yes	Yes	High	No		
<b>MALARIA</b>	Vaccine regarded as most cost effective control measure / severe scientific and technical obstacles still to be overcome; Feasibility- Low	Yes	High	Low (pre- MMV). Some activity in Res. Pharma. Some Research, little Development	Yes (would encourage involvement in both R&D)	Yes new chemicals not related to current drugs	

FINAL

<b>MEASLES</b>	Vaccine available through Expanded Program for Immunization. Major problem distribution	Yes - vaccine for immunocomp.; Heat-stable vaccine desirable	Low	No?	?		
<b>TUBERCULOSIS</b>	Vaccine Feasibility Low to Moderate	Yes	High, but long development time (WHO – TDR)	Low	Yes	Sterilizing agents with Long half life	
<b>SEXUALLY-TRANSMITTED INFECTIONS</b>							
Syphilis	No	No	Low	Low	No		
Gonorrhoea	No	Yes	High	High	No		
Chlamydia	Yes if feasible	Yes	High	High	No		
Herpes	Yes if feasible; Vaccine Feasibility- Moderate to Low	Yes	High	Medium - Some activity in big Pharma, Vaccine in development	No		
Chancroid		Yes					
<b>PERTUSSIS</b>	Yes (improved vaccine)	No		No			
<b>TETANUS</b>	Yes	No		No			
<b>MENINGITIS</b>						Identification of new molecular targets	
<i>Strep. pneumoniae</i> (see ARI)	Yes, multivalent vaccine	Yes	High	High	No		
<i>H. influenzae</i> (see ARI)	Yes	Yes	High	High	No		

FINAL

<i>Neisseria meningitidis</i>	Yes (multivalent vaccine)	Yes (oral vaccine?)	High	High	No		
Neonatal meningitis	Yes Grp. B Strep. Vaccine Feasibility Moderate to Low	Yes	Medium	Medium	No		
<b>LYMPHATIC FILARIASIS &amp; ONCHOCERCIASIS</b>	Elimination (in the Americas and in Africa) of both diseases believed possible with current drugs	Yes; macrofilaricide would speed elimination; need new for other filariae; Resistance may be a problem.	High- single drug may not target both conditions. Do not forget Loa loa, Mansonella, etc.	No to Low	Yes	Identification of new molecular targets	
<b>GI NEMATODE INFESTATIONS</b>	Improved public health measures; Feasibility - Moderate	Yes as resistance will occur	Yes, ivermectin, milbemycins, nitazoxanide	Low to No	No (WHO); Yes (Industry)	new targets, not tubulin	
<b>HEPATITIS</b>							
A	Vaccine already as prophylaxis	No self limiting		No			
B	Vaccine already as prophylaxis	Yes for late disease and carriage of Hep B S Ag; also as combinations	Medium	Medium	Yes		

FINAL

		with Lamivudine					
C	Vaccine- Feasibility Low	Yes	Low	High	No		
<b>LEISHMANIASIS</b>	Vaccines would be cost-effective / first generation killed whole organism. Candidate vaccines in clinic; Feasibility Moderate	Yes	High, miltefosine, sitamaquine; paramomycin (for visceral Leish.) (WHO/TDR);	Low (except in partnership with TDR). However, 1 drug in Devel. with Pharmaceutical Co.	Yes	oral, potent <28 days Rx	
<b>SCHISTOSOMIASIS</b>	Vaccines would be cost-effective / first generation recombinant protein candidate vaccines in clinic but progress slow; Feasibility Low	Yes. Probability of Praziquantel resistance high in medium term. (WHO)	High (WHO/TDR)	No	Yes Essential	New molecular targets	
<b>TRACHOMA</b>	No	No		No			
<b>AFRICAN TRYPANOSOMIASIS</b> ( <i>T.b.rhodesiense and gambiense</i> )	Vaccines unlikely (antigenic variation); Vector control could be improved; Feasibility Low.	Yes esp. T.b.rh (WHO/TDR)	High (WHO/TDR)	No Market very small	Yes. Essential	Non toxic for both; prefer oral drug	

FINAL

<b>CHAGAS DISEASE</b>	Autoimmune disease so vaccines dangerous. Success with vector control in Southern cone; ? Ability to be replicated in North	Yes, for chronic infections. ? Also for acute if Southern Cone Program is successful.	High for chronic. (WHO/TDR)	Low to No	Yes. Market large but difficult to focus on targets.		
<b>DENGUE</b>	Vaccine (multivalent). Feasibility High	Yes but unlikely to be effective	Not Applicable	Not Applicable			
<b>JAPANESE ENCEPHALITIS</b>	Improved (live) vaccine. Feasibility High	No					
<b>LEPROSY</b>	Should be eliminated with current tools	No unless resistance occurs	Not Applicable	Not Applicable	Not Applicable		
<b>POLIO</b>	Vaccine - Yes	No					
<b>DIPHThERIA</b>	Vaccine - Yes	No					

**Table 3. Priority infectious diseases for which additional R&D is required. Part 1. Disease burden and future trends (criteria 1-6)**

<b>1. DISEASE</b>	<b>2. DALYs (Millions)</b>	<b>3. Mortality per annum (Millions)</b>	<b>4. Costs to society</b>	<b>5. No. clinical cases per annum (p.a.): number likely to be accessible per annum. m = million</b>	<b>6. Trends over next 20 years</b>
<b>MALARIA</b>	45	1.09	Ranges from High to Low, depending on parasite species and local transmission rates: in Africa estimated to be >\$1.8 p.a.	300 m clinical cases p.a., about 100m treatments (total chloroquine suggests more than 100m). Epidemics difficult to manage with high death rate.	Rising, especially in epidemic-prone areas, frontier areas of development and social disruption
<b>TUBERCULOSIS</b>	33.3	1.669	High	8 m / 6 m	Falling to Rising - depends on meeting control targets
<b>LYMPHATIC FILARIASIS &amp; ONCHOCERCIASIS</b>	4.9 1.08	0 0	Lymphatic filariasis (LF): Medium  Onchocerciasis: High  Social impact of both: High	LF: 80 m infections, increasingly being treated: control programs starting.  Onchocerciasis: 30 m infections, control program underway (OCP/APOC) and Lat. Amer.	Lymphatic Filariasis: Falling  Onchocerciasis: Falling  Rate of fall dependant on control program impact
<b>LEISHMANIASIS</b>	1.98	0.057	Visceral: High  Mucocutaneous: High Cutaneous: Medium to Low	Visceral: 0.5 m new cases pa, 90% in Bangladesh, Brazil, India & Sudan mostly accessible Mucocutaneous: ? Cutaneous: ?	Visceral : Stable generally but epidemics occur Mucocutaneous: Stable Cutaneous: Stable
<b>SCHISTOSOMIASIS</b>	1.93	0.014	Medium	200 m infections	Stable: local intense control programs may have impact; Result would be Falling

FINAL

<b>AFRICAN TRYPANOSOMIA- SIS</b> ( <i>T.b.rhodesiense</i> <i>and gambiense</i> )	2.05	0.066	Low, except in epidemic situations, where it can be High	about 250,000 cases pa in non-epidemic years / 25,000 treatments	Stable
<b>CHAGAS' DISEASE</b>	0.676	0.021	High due to chronic cardiac and gastrointestinal infections.	12-25 m chronic infections, mostly not treated (no effective treatment)	Falling in Southern Cone where vector control in operation; otherwise Stable

**Table 3. Priority infectious diseases for which additional R&D is required. Part 2: Existing interventions (criteria 7-10)**

<b>DISEASE</b>	<b>7. Non-drug interventions available</b>	<b>8. Currently used drugs</b>	<b>9. Impact of successful treatment on spread of infection</b>	<b>10. Limitations of existing drugs (assuming access achieved)</b>
<b>MALARIA</b>	Insect repellants/ pesticides/ bed nets/ environmental management	Chloroquine & amodiaquine, Sulphadoxine / pyrimethamine (SP), Quinine, Halofantrine, Mefloquine, Atovaquone/ proguanil (Malarone), Artemether/Lumefantrine (Co-artem), Primaquine (vivax only).	No: Most drugs available suppress infection in blood but not gametocytes, therefore no effect on transmission	Chloroquine: Acquired Resistance; not all stages. SP: Acquired Resistance; not all stages. Quinine: acquired Resistance; compliance. Halofantrine: SAE; not all stages. Mefloquine: R; Affordability; not all stages, Aes. Malarone: Affordability; not all stages. Co-artem: Affordability; not all stages, Primaquine: SAE; poor compliance.
<b>TUBERCULOSIS</b>	BCG; control of HIV critical	Yes DOTS)	Yes	Acquired Resistance; Poor compliance (duration and complexity) unless DOTS used
<b>LYMPHATIC FILARIASIS &amp; ONCHOCERCIASIS</b>	LF: vector control  Onchocerciasis: vector control	LF: diethylcarbamazine, Ivermectin, Albendazole, Albendazole combinations Oncho: Ivermectin	Yes  Yes	Not all stages. DEC and albendazole may kill adult worms in LF.  Moxidectin may also kill adult filariae.
<b>LEISHMANIASIS</b>	Vector contact avoidance	Sodium stibogluconate; meglumine antimonate; amphotericin B; pentamidine	Yes, Effective treatment will stop transmission locally. Current problem is compliance	Antimonials: Acquired Resistance All: SAE; not oral; poor compliance

FINAL

<b>SCHISTOSOMIASIS</b>	Molluscicides	Praziquantel; oxamniquine	Yes	Praziquantel: Acquired Resistance (anecdotal)  Oxamniquine: Acquired Resistance (not all species)
<b>AFRICAN TRYPANOSOMIASIS</b> <i>(T.b.rhodesiense and gambiense)</i>	Tsetse traps	Early: suramin; pentamidine Late: melarsoprol; eflornithine  need effective drug for T.b.rhodesiense.	Yes	Suramin, pentamidine: Acquired Resistance SAE's; neither active against all stages  Melarsoprol: Serious Adverse Events; not oral Eflornithine: not oral; not all species: expensive
<b>CHAGAS DISEASE</b>	Insecticides: intensive house spraying and surveillance	Nifurtimox, Benznidazole (acute & early chronic only)	Yes	Not all stages

**Table 3. Priority infectious diseases for which additional R&D is required. Part 3. Medicines R&D needs and priorities (criteria 11-17)**

<b>DISEASE</b>	<b>11. Non-drug interventions preferable / R&amp;D feasible</b>	<b>12. New drugs needed</b>	<b>13. New drug R&amp;D feasible</b>	<b>14. Industry engaged in R&amp;D</b>	<b>15. Public sector support needed in drug R&amp;D</b>	<b>16. Priorities for new drug R&amp;D</b>	<b>17. Priorities needing public sector support</b>
<b>MALARIA</b>	Vaccine thought most cost effective control / severe scientific and technical obstacles still to be overcome; Feasibility-Low	Yes	High	Low (pre-MMV). Some research activity in Research Pharm. Industry. Little Development	Yes; (would encourage involvement in both R&D)	Yes; new chemical class needed.	
<b>TUBERCULOSIS</b>	Vaccine Feasibility: Low to Moderate	Yes	High, but long development time (WHO/TDR)	Low	Yes	Sterilizing agents Long half life	
<b>LYMPHATIC FILARIASIS &amp; ONCHOCERCIASIS</b>	Elimination (in the Americas and in Africa) of both diseases believed possible with current drugs.	Yes; macrofilaricide would speed elimination; need new drug for other filariae. Resistance may be a problem.	High, NB: single drug may not target both LF and Oncho. Need to consider Loa, Mansonella, and other species.	Low	Yes	Identification of new molecular targets.	

FINAL

<b>LEISH-MANIASIS</b>	Vaccines would be cost-effective; first generation - killed whole organism. Candidate vaccines in clinic / Moderate Feasibility.	Yes	High: miltefosine, sitamaquine; paramomycin (for visceral Leish.) (WHO): Industry less optimistic	Low (except in partnership with TDR). One drug in development with pharmaceut. co.	Yes	Oral, potent, <28 days Rx
<b>SCHISTOSO-MIASIS</b>	Vaccines would be cost-effective / first generation recombinant protein candidate vaccines in clinic but progress slow. Feasibility Low	Yes. Probability of Praziquantel resistance high in medium term. (WHO)	High (WHO) Industry less optimistic	None	Yes (essential)	New molecular targets
<b>AFRICAN TRYPANOSO-MIASIS</b> ( <i>T.b.rhodesiense</i> and <i>gambiense</i> )	Vaccines unlikely (antigenic variation); Vector control could be improved; Feasibility Low.	Yes esp. T.b.rhodesiense (WHO)	High (WHO) Industry less optimistic	None: Market very small	Yes (essential)	Non toxic for both; prefer oral drug
<b>CHAGAS' DISEASE</b>	Autoimmune disease so vaccines may be dangerous. Success with vector control in Southern cone; ? Ability for replication in the North	Yes; for chronic infections. ? Also for acute if Southern Cone Programs successful.	High for chronic. Probability Low for acute (WHO).	Low to None	Yes. Market large but difficult to focus on targets.	