Numbers of people affected by various NTDs

*Each of the following diseases affects*

>100 mill: Soil-transmitted intestinal diseases (Ascaris, Trichura and hookworms); Schistosomiasis; Scabies

>10 mill: Dengue; foodborne trematodes (Clonorchis, Fasciola, Opisthorchis, Paragonimimus); Lymphatic filaria; Onchocerca

>1-10 mill: Chagas disease; Leishmaniasis; Trachoma; Cysticercosis; Cystic echinococcosis

*Many thousands*: Leprosy; Rabies; Human African trypanosomiasis
Status of vaccines against NTDs

Existing (+); existing but poor (+/-); advanced stage (AS); early stage (ES)

• **Viral**: Dengue (AS), Chikungunya (ES); Rabies (+)
• **Bacterial**: Buruli ulcer (+/-); Leprosy (+/-); Trachoma (ES); Yaws (ES)
• **Fungal**: Mycetoma (ES), Chromoblastomycosis/deep mycoses (ES)
• **Parasitic** (protozoan): Chagas disease (AS); Human African
trypanosomiasis (ES); Leishmaniais (AS)
• **Parasitic** (metazoan): Dracunculiasis (ES); Echinococcosis (ES);
Foodborne trematodiasis (ES); Lymphatic filariasis (AS);
Onchocerciasis (ES); Schistosomiasis (AS); Soil-transmitted
helminthiases (AS); Taeniasis/Cysticercosis (ES)
• **Parasitic** (ectoparasites): Scabies and other ectoparasites (ES)
• **Non-infectious diseases**: Snakebite envenoming (ES)
Which NTD-vaccines should be prioritised?

• Vaccines against any serious illness spinning out of current control?
  (Dengue/other arboviruses, Leishmaniasis, Chagas disease, trichuriasis, hookworm disease, foodborn trematodiasis, cystic echinococcosis)

• Those potentially preventing the heaviest current disease burden?
  (Major intestinal infections (Ascaris, Trichiuris, Hookworm); Dengue fever; Foodborne trematodes (Clonorchis, Fasciola, Opisthorchis, Paragonimus)

• Promising vaccines already in advanced stages of development?
  (Dengue, Hookworm, Schistosomiasis)
Status following implementation of current control measures (i.e. with or without existing vaccines)

- **Heading towards elimination**: Dracunculiasis; Human African trypanosomiasis; Lymphatic filariasis; Trachoma; Yaws
- **Significant gains**: Rabies; Leprosy; Onchocerciasis; Ascariasis; Schistosomiasis; Cysticercosis
- **Minimal gains**: Trichuriasis; Hookworm disease; Foodborne trematodiasis (Clonorchis, Fasciola, Opisthorchis, Paragonimus); Cystic echinococcosis
- **Loosing the battle**: Dengue and other arbovirus infections; Leishmaniasis; Chagas disease
Possible CEPI support for development of vaccine against NTDs

My personal priority list

• **High priority:** Human echinococcosis; Human cysticercosis; Schistosomiasis; Lymphatic filariasis; Onchocerciasis; Leishmaniasis; African trypanosomiasis; Chagas disease

• **Medium priority:** Soil-transmitted helminthiases; Foodborne trematodes; Trachoma; Dengue fever

• **Low priority:** Snakebite envenoming; Ectoparasites (scabies); Yaws; Buruli ulcer; Leprosy; Rabies; Chikungunya
Status of vaccines against individual NTDs
Status of vaccines against dengue fever

• **Background:** Flavi-viral, vector borne disease; endemic in > 100 countries. Each year, about 400 mill infected, 100 mill diseased. Four related, but structurally flexible serotypes induce type-specific immunity. Immune enhancement may cause serious haemorrhagic fever.

• **Vaccine:** Since 2015-16, a live, tetravalent vaccine («Dengvaxia») is authorized for age group 9-45 in several high-burden areas. Protective efficacy 50-60% against infection. Safety acceptable, but interference with other flaviviruses such as Zikavirus may occur.

• Dengue is a promising target for international vaccine manufacturers and several vaccine candidates are now in clinical trials

• **Suggested priority for CEPI support:** Medium
Status of vaccines against chikungunya virus

• **Background:** Chikungunya is a viral disease transmitted by infected mosquitoes. It causes fever and severe, often debilitating joint pain, but is rarely fatal. May be mistaken for dengue or zika (same vector). Chikungunya outbreaks have been identified in over 60 countries in Asia, Africa, Europe and the Americas. Infection results in immunity. No specific treatment.

• **Vaccines:** So far, there is no vaccine against chikungunya.

• More than 20 candidate vaccines for are under development; some are in phase I/II trials. Vaccine candidates being evaluated include chimeric, attenuated or inactivated viruses, subunit preparations, and virus-like particles (VLPs) as well as plasmid DNA.

• **Suggested priority for CEPI support:** Low
Status of vaccines against rabies

• **Background:** Several 100,000s are exposed to rabievirus annually, mainly through dog bites. Rabies occurs in >100 countries, causing about 55,000 deaths/year. *Children in Africa & Asia are most affected (95%). All clinical infections are fatal.*

• **Vaccines:** For many years, excellent, low-cost cell-culture based vaccines are globally widely available. Also, human (or horse) anti-rabies immunoglobulin is widely available.

• **Suggested priority for CEPI support:** Low
Status of vaccines against leprosy

**Background:** Leprosy is a chronic mycobacterial disease mainly of peripheral nerves, skin, mucosa and eyes, and resulting in permanent disability. Global prevalence is ~200 000; but high annual transmission rates in some regions mainly in India result in a similar number of newly infected cases.

- Multidrug treatment (MDT: dapsone, rifampicin and clofazimine) offers safe, effective and easily administered cure. For protection of contacts, one single dose of rifampicin is 60% effective. Leprosy prevalence is relatively low and declining.
- **Vaccines:** BCG vaccination offers 50% protection of *M. leprae* contacts, and BCG plus one dose of rifampicin results in 80% protection. A promising Indian vaccine based on *M. indicus pranii* is undergoing clinical trials

- **Suggested priority for CEPI support:** Low
Status of vaccines against trachoma

• **Background:** Some types (biovars) of *Clamydia trachomatis* cause chronic conjunctivitis/irreversible blindness. Prevalent in >40 countries. Enormous economic burden. In 2016, 85 mill received antibiotics and 200 000 surgical treatment for trachoma. Trachoma may be controlled without access to specific trachoma vaccine. WHO target: elimination of trachoma as a PH problem by 2020.

• **Vaccines:** There is currently no vaccine against trachoma.

• A few vaccine candidates mainly aiming at clamydial STD are now in clinical trials. One is based on the clamydial antigen BD584 which seems to protect against all common species of *Chlamydia trachomatis*, including biovars causing trachoma.

• **Suggested priority for CEPI support:** Medium
Status of vaccines against Buruli ulcer

• **Background:** Disfiguring skin necrosis caused by *Mycobacterium ulcerans* occur in 33 countries of Africa, Latin America and Western Pacific. Some 2000 new cases reported annually, mostly in children. Curable if detected in early stages. Probably declining incidence.

• **Vaccine:** No vaccine available

• Pathogenesis poorly understood. Some antigens of *M. bovis* bacille Calmette-Guérin (BCG) and especially of *M. marinum* cross-react with *M. ulcerans*. Experiments in mice show that recombinant BCG expressing MU-antigens such as MU-Ag85A and EsxH could represent an effective vaccine strategy.

• **Suggested priority for CEPI support:** Low
Status of vaccines against yaws

• **Background:** Yaws is a chronic bacterial infection of the skin, bone and cartilage mainly of children the poorest communities of tropical Africa, Asia, Latin America and the Pacific. Caused by Treponema pallidum subsp. pertenue. Penicillin and azithromycin highly effective. Small outbreaks of yaws still occur, but globally declining incidence. WHO aims at eradication by 2020 based on single dose of oral azithromycin.

• **Vaccine:** No vaccine available. (Also development of vaccines against syphilis, a related but far more important disease, has failed so far)

• **Suggested priority for CEPI support:** Low
Status of vaccines against Chagas disease

• **Background:** Chagas disease (American trypanosomiasis) is caused by the mainly vector-borne and intracellular protozoan Trypanosoma cruzi. Wild-life reservoir. ~8 million people infected worldwide, mostly (99%) in Latin America; 25 million people risk acquiring the disease. Each year >10 000 people die from chronic cardiac or intestinal manifestations of the disease. Conventional drug treatment risky and efficient only in early stages.

• **Vaccines:** No vaccine available.

• Many vaccine candidates in progress, i.a. DNA coding for the TcG2 and TcG4 proteins of T. cruzi. A novel approach is the engineered trivalent immunogen Traspain, a chimeric antigen tailored to present a multivalent display of domains from key parasitic molecules. Traspain is adjuvanted with STING (stimulator of interferon genes) and shows protection against infection and tissue damage in animal models.

• **Suggested priority for CEPI support:** High
Status of vaccines against African trypanosomiasis

• **Background:** African trypanosomiasis (African sleeping sickness) is caused by the tsetse-fly transmitted, protozoan haemoflaggelate Trypanosoma brucei. Most common (97%) is *T. brucei gambiense* (chronic disease, human reservoir); *T. brucei rhodesiense* (3%) (acute disease, animal reservoir including cattle). In total ~20 000 cases/year. Population at risk: 65 mill. Vast economic losses are due to livestock infections.

• The parasite progresses through different life cycle stages in its two hosts, altering its pattern of gene expression in the process. The unique and highly complex biology of trypanosomes, e.g. endless variability of parasitic surface coating (genetic rearrangements) and mechanisms of immune suppression (including suppression of immunological memory) allows the parasite to escape from - or resist - mammalian immunity.

• **Vaccines:** Currently, no vaccines against trypanosomiasis are available.

• Vaccine development against trypanosomiasis represents an extreme challenge. A number of candidate vaccines (including veterinary vaccines) are in early stages of development.

• **Suggested priority for CEPI support:** High
Status of vaccines against leishmaniasis

• **Background:** Leishmania is a zoonotic protozoan parasitic transmitted by different sandfly species. Affects 12 mill mainly poor people in 98 tropical/subtropical countries. 20 leishmanial species. 3 main forms of the leishmaniasis: visceral, cutaneous, and mucocutaneous. About 0.7-1 mill new cases and 0.2-0.3 mill deaths each year. Advanced cases may be difficult to treat, medicines often expensive, and/or unavailable. Vector control/reduction of reservoir animals essential.

• **Vaccines:** No antileishmania vaccine available

• Inoculation of live parasites (leishmanization) protects against cutaneous forms, but is hazardous. Numerous efforts based on selected antigens have failed. Promising strategies used in mouse models include the use of genetically attenuated *Leishmania infantum* against visceral leishmaniasis and recombinant live *Leishmania tarentolae* secreting the sand fly salivary antigen for protection against *Leishmania major* infection.

• **Suggested priority for CEPI support:** High
Status of vaccines against Onchocerca volvulus

• **Background:** Onchocerciasis (river blindness) occurs in 31 countries, 17 mill have dermal microfilaria (99% in Africa), 120 mill at risk. Nematode larvae transmitted by blackflies. Chemoprophylaxis (ivermectin) in endemic regions requires 1-2 doses annually for 10-15 years. Ivermectin are excluded from children under 5 yrs. Drug resistance may develop and ivermectin can cause serious adverse events in loa loa infected patients. For final disease control, combined chemo- and immunoprophylaxis is required.

• **Vaccines:** No vaccine available.

• Experimental vaccine candidates combining different parasitic antigen and adjuvants such as Ov-103 and Ov-RAL-2, with the adjuvants alum, Advax 2 and MF59 induce protective immunity in mice. The Onchocerciasis Vaccines for Africa Initiative (TOVA) plans to take at least one vaccine candidate to Phase 1 trials by 2017 and Phase 2 trials by 2020.

• **Suggested priority for CEPI support:** High
Status of vaccines against lymphatic filariasis

• **Background:** The disease is caused by the thread-like nematode worms (filariae) *Wuchereria bancrofti, Brugia malayi* and *Brugia timori*) which lodge in the lymphatics. Microfilaria circulating in the blood are transmitted to new hosts by mosquito vectors. Clinical manifestations are lymphoedema of the limbs, genitals and recurrent acute febrile attacks. An estimated 120 million people infected, mainly in Africa and east and south Asia. Elimination is based on annual mass administration of albendazole and ivermectin (or diethylcarbamazine). For final disease control, combined chemo- and immunoprophylaxis is required.

• **Vaccines:** No filariasis vaccine available.

• Experimental vaccine candidates including a multivalent fusion protein vaccine (rBmHAT) confer >95% protection against the challenge infection with *Brugia malayi* infective larvae (L3) in mouse and gerbil models and in rhesus macaques. Similar results were obtained in mice using a multivalent DNA based vaccine comprising BmALT-2 and BmHSP antigens of filariasis.

• **Suggested priority for CEPI support:** High
Status of vaccines against schistosomiasis («Bilharzia»)

• **Background:** 5 species of Schistosoma, most important: *S. mansoni* & *S. japonicum* (intestinal) and *S. haematobium* (urogenital). Complex life cycle includes different hosts and stages. >700 million people live in endemic areas. Control measures mainly based on antihelminth drugs. In 2015, 200 million persons in 50 tropical and sub-tropical countries required preventive praziquantel treatment, and >60 million were treated for manifest disease.

• **Vaccines:** No vaccines available against schistosomiasis

• Numerous vaccine candidates in progress using new technologies to identify exposed, essential molecules in the live parasite. >100 vaccine antigens are identified, about 25 have shown some level of protection in mouse models, but only 3 molecules, *S. mansoni* fatty acid binding protein (*Sm14*), *S. mansoni* tetraspanin (*Sm-TSP-2*) and *S. haematobium* glutathione S-transferase (*Sh28GST*), have entered human clinical trials. Smp80 (calpain) is undergoing testing in non-human primates.

• **Suggested priority for CEPI support:** High
Status of vaccines against *T. solium* taeniasis (human cysticercosis)

- **Background:** Humans infected with *T. solium* tapeworms pass faecal tapeworm eggs which are infective for pigs and humans. Ingested eggs develop to larvae (cysticerci) in organs such as muscles, skin, eyes and central nervous system. Neurocysticercosis may affect 2.56–8.30 million, but reliable data on prevalence and geographical distribution of *T. solium* taeniasis/cysticercosis in people and pigs is still scarce.

- Control measures based on human- and pig-targeted mass drug administration seem the most efficacious current approach.

- **Vaccines:** No vaccine against *T. solium*/human cysticercosis available.

- In pigs, *T. solium* recombinant vaccines (TSOL18 and SP3VAC) induces near complete protection against the larval infection. TSOL18 in combination with cysticidal oxfendazole treatment resulted in complete protection from *T. solium* taeniasis. Thus, currently a veterinary vaccine seems the best candidate to reduce human cysticercosis.

- **Suggested priority for CEPI support:** High
Status of vaccines against human echinococcosis

• **Background:** The larval stage of the tapeworm Echinococcus may cause **cystic** echinococcosis: (hydatidosis, *E. granulosus*, domestic animals, global, 95% of cases) and **alveolar** echinococcosis: (*E. multilocularis*, dogs/foxes, Northern hemisphere, 0.3-0.5 million cases). Humans infected through ingestion of parasite eggs in (food, water, soil), or contact with animal hosts. The parasite has evolved sophisticated strategies to escape host immune responses.

• **Echinococcosis affects >1 million people (~20 000 deaths/year.)** Prevalence in humans may locally reach 5-10%, in animals 20-95%. Complicated treatment, high societal costs. Prevention includes deworming (praziquantel, dogs/sheep/foxes), food inspection (hydatidosis), slaughterhouse/personal hygiene, and recently, vaccination of lambs.

• **Vaccines:** No human vaccine available.

• **Potential antigens for human echinococcal vaccines include rBCG-EgG1Y162 and *E. granulosus* glutathione S-transferase (EgGST), both inducing promising protection in mice.

• A recombinant (EG95) vaccine successfully prevents *E. granulosus* in sheep.

• **Suggested priority for CEPI support:** High
Status of vaccines against foodborne trematode infections

**Background:** Foodborne trematode infections are zoonotic infections caused by flatworms or “flukes”. Acquired through ingestion larval stages of the parasite (raw fish, crustaceans, plants). Transmission cycles differ, but all involve intermediate hosts (molluscs, fishes or crustaceans).

Most important are: *Clonorchis* spp. (intestines); *Opisthorchis* spp. (intestines); *Fasciola* spp. (liver); and *Paragonimus* spp. (lungs). These parasites infect some 40 million people, most cases in east/south-east Asia, and in central/south America. Control measures include preventive chemotherapy, food safety practices and education.

**Vaccines:** No human vaccine against foodborne trematodes

Recent trematode candidate vaccines include a recombinant protein and DNA vaccines targeting cathepsin proteases against *Fasciola*; recombinant tegumental antigen CsTP22.3 against *Clonorchis*; and an *O. viverrini*-crude somatic antigen preparation CSAg against *Opisthorchis*.

**Suggested priority for CEPI support:** Medium
Status of vaccines against soil-transmitted helminthiases

• **Background:** Worldwide, soil-transmitted helminth infections affect about 1.5 billion people. Most important are the roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*) and hookworms (*Necator americanus* and *Ancylostoma duodenale*). Where human faeces contaminate the soil or water in deprived communities, infection is acquired by accidental ingestion of faecal eggs (*Ascaris, Trichuris*), or larval penetration of naked skin (hookworms). Control measures include periodical deworming (mebendazole/albendazole), health education, and improved sanitation.

• The global target is to eliminate morbidity due to soil-transmitted helminthiases in children by 2020. This will be obtained by regularly treating at least 75% of the children in endemic areas (an estimated 873 million).

• **Vaccines:** No human vaccines

• The Sabin Vaccine Institute is currently developing a pan-anthelmintic vaccine that simultaneously targets ascariasis, trichuriasis and hookworm infection. This institute also develops a human hookworm vaccine based on *Na*-APR-1 and *Na*-GST-1 antigens. This vaccine is under development and in clinical trials in Africa and the Americas.

• **Suggested priority for CEPI support:** Medium
Status of vaccines against ectoparasitoses: Example scabies

• **Background**: Scabies is a parasitic infection of the skin caused by a mite, *Sarcoptes scabiei*. The mites burrow under the skin to live and lay eggs which causes intense itching, especially at night. Despite availability of effective treatment, over 300 million people in the world are infected. Numerical simulations indicate that treatment alone could control scabies, although vaccination plus treatment would be the best approach. Transmission studies show an initial increase in *S. scabiei* numbers subsequent to primary infestation with a gradual reduction as host immunity develops. Further knowledge concerning the immunomodulatory effects of parasite evasion mechanisms is essential for rational vaccine design.

• **Vaccines**: Currently, there are no scabies vaccines

• Few candidate vaccines. An experimental DNA vaccine based on *S. scabiei* genes encoding paramyosin (PAR) induced a mixed Th1/Th2 response in mice.

• **Suggested priority for CEPI support**: Low
Status of vaccines against snakebite envenoming

• **Background:** The number of venomous snakebites that occur each year may be as high as five million. They result in about 2.5 million poisonings and 20,000 to 125,000 deaths. Snake bites occur most commonly in rural areas of Africa, Asia and Latin America. Venomous bites can cause paralysis, bleeding disorders, kidney failure and tissue destruction. Snake-specific antivenom is the only effective treatment, but often unaffordable or unavailable. Recent studies show that generation of venom-specific toxin antibodies by DNA immunization offers a more rational for treatment of envenoming than conventional antivenom.

• **Vaccines:** No vaccines available

• **Suggested priority for CEPI support:** Low