The World Health Organization lists 17 Tropical Diseases as a priority.

**Protozoa**
- Chagas disease
- Trypanosomiasis
- Leishmaniasis

**Virus**
- Rabies
- Dengue

**Helminth**
- Cysticercosis/Taeniasis
- Dracunculiasis (guinea worm disease)
- Echinoioccosis
- Trematodiasis
- Lymphatic filariasis
- Onchoceriasis (River-blindness)
- Schistosomiasis
- Soil-transmitted helminthiasis

**Bacteria**
- Buruli ulcer
- Leprosy
- Trachoma
- Yaws

There are 100’s of Tropical Diseases. Why these 17?
They used the following criteria:

1. Diseases associated with poverty which are concentrated in the tropics (those living less than $1-2/day)

2. Usually do not kill but have huge impact on the individual’s quality of life (large disease burden)

3. Large economic impact

4. Limited ability of local health care system to respond

How are these factors quantified?
How much of a health problem are neglected diseases? Is there a way to quantify the burden of an individual disease?

In early 1990s, a study by the World Bank, WHO, and the Harvard School of Public Health launched an initiative to devise a metric to quantify disease burden.

Three objectives:

1. Facilitate inclusion of non-fatal diseases on global health policies (previous focus on mortality of rates of children under 5)
2. Decouple health policy decisions from influence of advocacy groups
3. To quantify disease burden that could also be used for to measure the cost effectiveness of interventions
DALY --- disability adjusted life year is a metric used to estimate the total disease burden on a population

DALYs estimate the number of “healthy” life years lost due to disease or disability by incorporating non-fatal as well as fatal conditions.

YLD- years of life lived with a disability
YLL- years life lost due to premature death

DALY = YLD + YLL

Premise that the best approach for measuring disease burden is to use units of time as a measure (or more precisely, time of healthy years of life lost)

http://www.who.int/healthinfo/nationalburdenofdiseasemanual.pdf
Neglected disease burden much higher than many diseases of the west

Infection rates and global disease burden:

<table>
<thead>
<tr>
<th>Disease</th>
<th>DALYs</th>
<th>Infected globally</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hookworm infection</td>
<td>22.1 million</td>
<td>576 million</td>
</tr>
<tr>
<td>2 Ascaris</td>
<td>10.5 million</td>
<td>807 million</td>
</tr>
<tr>
<td>3 Trichuris</td>
<td>6.4 million</td>
<td>604 million</td>
</tr>
<tr>
<td>4 Lymphatic filariasis</td>
<td>5.8 million</td>
<td>120 million</td>
</tr>
<tr>
<td>5 Schistosomiasis</td>
<td>4.5 million</td>
<td>207 million</td>
</tr>
<tr>
<td>6 Trachoma</td>
<td>2.3 million</td>
<td>84 million</td>
</tr>
<tr>
<td>7 Onchocerciasis</td>
<td>0.5 million</td>
<td>37 million</td>
</tr>
<tr>
<td>8 Snakebites</td>
<td>???????</td>
<td>4.5 million (2.7 million seriously injured)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125,000 deaths</td>
</tr>
<tr>
<td>Total</td>
<td>52.1 million</td>
<td>&gt;1 billion</td>
</tr>
</tbody>
</table>

Breast Cancer               | 12.1 million|
Prostate Cancer             | 3.8 million |
Stroke                      | 39.4 million|
Why DALYs are important?

Investments in health for poor and middle-income countries began growing in the 1990s, then exploded after the turn of the century:

AIDS, Tuberculosis and Malaria and GAVI, the Vaccine Alliance.

The funds were spent buying and distributing drugs, vaccines, and bed nets; fighting malnutrition; and shoring up flagging health systems.

Were the funds distributed appropriately?
Skewed funding: Diseases that cause the highest burden in poor countries often receive little international aid.

In 2010, HIV/AIDS received the biggest chunk; little aid went to noncommunicable diseases like diabetes, whose burden is large and growing.

Cardiovascular (Heart attack Stroke), Diabetes, Cancer, Respiratory Diseases

Measured in DALYs

Source: Institute for Health Metrics and Evaluation
Mismatch between international aid and disease burden

“Expected International Aid” based on a country’s disease burden (DALY) and gross domestic product
Does this aid actually help combat these diseases?

For example:

Since 2002, more than $10 billion devoted to malaria control.

1. Bed nets treated with insecticides
2. Hundreds of millions of doses of a powerful combination therapy,
3. Widespread indoor spraying of homes with insecticide
4. Education programs

The World Health Organization estimates that between 2000 and 2012, malaria cases have dropped by 25% worldwide and deaths have been cut by 42%

So it appears the money was well spent ?????
But in April, researchers at the widely respected Center for Global Development (CGD) in Washington, D.C., triggered a fierce debate among malaria experts when they wrote in a blog post that:

“They couldn't find a single study with convincing data that showed how a large-scale intervention directly led to lower numbers of cases or deaths.”

That is, one must answer the question “What would have happened if these interventions were not in place”

“We know from a bunch of small-scale studies that bed nets can protect you from mosquitoes biting you. That's not what we're interested in evaluating. In the real world, nets aren't always used, for instance because they're uncomfortable on hot nights or people think there are few mosquitoes around.”
This debate has created a new field of study in the global Health community called **Impact Evaluation**

“It's becoming increasingly difficult for the development assistance world to take credit for changes that might have occurred without their interventions—and to ignore the possibility that the money might have spared more people from disease if spent elsewhere.

“Agencies have come to realize that impact evaluation is the only way you can meaningfully talk about results. They want to be able to go back to their funders or boards and say, ‘We've lifted 18 million out of poverty.’”

Howard White, International Initiative for Impact Evaluation (3ie)
Masters degree program in impact evaluation for international development

School of International Development

With 98% of our students satisfied with their course, and 97% satisfied with the teaching they receive - we are ranked 5th for Geography & Environmental Studies

Guardian University Guide 2015

- **Duration**: 1 years
- **Attendance**: Full Time
- **School of Study**: International Development
- **Course Organiser**: Dr. Maren Duvendack
- **Award**: Degree of Master of Science
Bottom line:

Make sure that the little that is spent on Neglected Tropical Diseases is used efficiently.
Just over two years ago, the Center for Disease Control (CDC) stated:

“Ebola could infect 1.4 million people by January 2015” (Sept 23, 2014)

AND The New England Journal of Medicine wrote

The notion that Ebola could become endemic in West Africa — spreading routinely, rather than in sporadic outbreaks — is "a prospect that has never before been contemplated"
Previous outbreaks in rural communities. Recent outbreak in densely populated urban areas.
Major Ebola pandemic averted, but flare-ups still occur

Countries with Former Widespread Transmission and Current, Established Control Measures

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Cases (Suspected, Probable, and Confirmed)</th>
<th>Laboratory-Confirmed Cases</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea²</td>
<td>3814</td>
<td>3358</td>
<td>2544</td>
</tr>
<tr>
<td>Sierra Leone³</td>
<td>14124</td>
<td>8706</td>
<td>3956</td>
</tr>
<tr>
<td>Liberia⁴</td>
<td>10678</td>
<td>3163</td>
<td>4810</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>28616</strong></td>
<td><strong>15227</strong></td>
<td><strong>11310</strong></td>
</tr>
</tbody>
</table>

GUINEA & LIBERIA
MARCH 2016
- 13 cases
- >1200 contacts
- Sexual transmission suspected
- CDC staff supported emergency response coordination at 5 command centers and 50 health care facilities, deployment of rapid tests, and vaccination of 1750 people at-risk

Then

Now
The Lancet study was done in 11,841 residents of Guinea last year. Among the 5,837 people who got the vaccine, none came down with Ebola 10 or more days later. There were 23 Ebola cases among the thousands of others not immediately vaccinated.

Ring Vaccination Method
Now that the outbreak is largely contained, what are the next steps:

1. What are the lessons learned that should be applied to the next outbreak?
2. What are the long term consequences to the affected communities?
3. What are the best methods for treatment and containment?
4. What are we learning about the mechanisms of transmission?
5. How might the cultural and ethics issues be handled in future outbreaks?
Ebola key facts

Ebola virus disease (EVD), formerly known as Ebola haemorrhagic fever, is a severe, often fatal illness in humans.

EVD outbreaks have a case fatality rate of up to 90%.

In previous outbreaks EVD outbreaks occur primarily in remote villages in Central and West Africa near tropical rainforests.

Current outbreaks occurring in heavily populated cities

The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission.

Fruit bats of the Pteropodidae family are considered to be the natural host of the Ebola virus.

Severely ill patients require intensive supportive care.

Vaccines are still being developed.
Ebola virus is the causative agent of Ebola hemorrhagic fever (EHF), a disease affecting humans and other primates.

The incubation period for EHF is 2-21 days and typical early symptoms include fever, chills, malaise, and muscle pain, followed by the onset of symptoms indicative of multi-organ stress and subsequent failure.

The disease is highly contagious, spreading through direct contact with infected body fluids or skin/mucus membrane contact.

Treatment requires specialized facilities and highly trained health care professionals.
The Ebola outbreak in West Africa is the most explosive in history.

The type of Ebola causing the outbreak — called Zaire — is the deadliest strain. Until this year, it had been seen only in Central Africa, about 2,500 miles away.

Many signs point to bats as the main source of Ebola. Scientists have found Ebola antibodies in bat species that are widespread throughout Africa. The virus infects and replicates inside bats, but it doesn't kill the animals. So bats can easily spread Ebola.

Ebola virus traveled 2,500 miles from rural central Africa to urban regions in West Africa
Ebola genome: Linear single-stranded negative-sense RNA 19kb in length (1/160,000 of the human genome)

It encodes only 7 structural proteins
Glycoprotein- spikes projecting into host derived membranes

Nucleocapsid - RNA/protein complex at center of virus
RNA helically encompasses: NP nucleoprotein, VP35, VP30 and L protein (polymerase)

Matrix proteins- VP40 an VP24 located between the envelope and nucleocapsid
Ebola is a negative-stranded RNA virus (Filovirus: Ebola, Marburg)

Baltimore classification (first defined in 1971) is a classification system that places viruses into one of seven groups depending on a combination of their nucleic acid (DNA/RNA) strandedness (single-stranded or double-stranded), sense and method of replication.
The viral life cycle begins with host cell entry through a poorly understood mechanism.

Once inside the viral RNA-dependent RNA polymerase (L) binds the 19 kb genome as a complex with other factors and transcribes the negative strand genome into a positive strand mRNA to be translated by the host cell's machinery.

Once the concentration of nucleocapsid viral proteins reach a sufficient level, the RNA polymerase switches modes to genome replication, producing full-length positive strand genomes to be transcribed into negative orientation.

These genomes self assemble with other virus proteins and bud from the host cell, sheathed in host cell membrane, thus completing the cycle.
Ebola uses an RNA dependent RNA polymerase to produce mRNA and replicate its genome.

mRNA (+ strand)

Genomic RNA (- strand)
Ebola generates a positive-strand RNA for transcription and replication.
Ebola targets the dendritic cells of the immune system?

Once the virus enters the body, it targets dendritic cells, which normally display signals of an infection on their surfaces to activate T lymphocytes—the white blood cells that could destroy other infected cells before the virus replicates further. With defective dendritic cells failing to give the right signal, the T cells don’t respond to infection.
Initial Symptoms: Influenza-like fatigue, fever, headaches, joint- muscle- abdominal pain, vomiting diarrhea.

Diagnosis difficult because early symptoms similar to other tropical diseases malaria and dengue.

50% of the patients bleed from lesions in mucous membrane, GI tract, nose gums vagina and internal organs.

Death rate 70-90% with 1 to 2 weeks after first symptoms.
Trouble in the bloodstream
When immune cells known as macrophages are attacked by Ebola, they release proteins that cause coagulation in the bloodstream, blocking blood flow to organs such as the liver, brain and kidneys.

Red blood cells break apart when moving through small vessels filled with clots. The spleen becomes overwhelmed with broken blood vessels.

As cells in the liver are destroyed, the blood loses its normal ability to clot, exacerbating any internal or external hemorrhaging.
Death occurs within weeks

People who die from the disease usually develop severe symptoms early on and die between days 6 and 16, succumbing to extreme low blood pressure, multi-organ failure and the shock of severe infection. The death rate can be as high as 90 percent.
Bats are likely the disease reservoirs of Ebola

**Ebolavirus Ecology**

**Enzootic Cycle**
New evidence strongly implicates bats as the reservoir hosts for ebolaviruses, though the means of local enzootic maintenance and transmission of the virus within bat populations remain unknown.

**Ebolaviruses:**
- Ebola virus (formerly Zaire virus)
- Sudan virus
- Tai Forest virus
- Bundibugyo virus
- Reston virus (non-human)

**Epizootic Cycle**
Epizootics caused by ebolaviruses appear sporadically, producing high mortality among non-human primates and duikers and may precede human outbreaks. Epidemics caused by ebolaviruses produce acute disease among humans, with the exception of Reston virus which does not produce detectable disease in humans. Little is known about how the virus first passes to humans, triggering waves of human-to-human transmission, and an epidemic.

Human-to-human transmission is a predominant feature of epidemics.

Following initial human infection through contact with an infected bat or other wild animal, human-to-human transmission often occurs.
Bat-filled tree in a Guinean village may have been ground zero for the Ebola outbreak

The first person to become infected was a toddler that lived in a house near the tree. His family died of Ebola soon after.
Identifying the reservoir species is key to combating many diseases

1. Natural host of an infectious disease pathogen
2. These hosts often do not get the disease carried by the pathogen or there are only minor effects
3. Often a third organism is involved in pathogen transmission from the reservoir to the target species (known as the Vector species)
4. Identification of natural reservoirs critical in combating the disease
Why identifying reservoir populations is important

In Zimbabwe, officials wanted to know whether vaccinated dogs would result in Rabies elimination

Maintenance reservoir community
Success of elimination of Guinea worm due to the fact that there is not a non-human reservoir species

Strategy was to break cycle of infection using nylon water filters
What if wilderbeasts were a reservoir population for Guinea Worm?

Would the filtration strategy been as successful?
Over the past few years, dogs have become infected with Guinea worm. This threatens to thwart complete eradication of the disease.
Although many emerging diseases of human, domestic animal, and wildlife populations are assumed to be maintained in reservoir hosts these reservoirs are rarely identified.

Below are attempts to combat human viral infections based on assumed reservoir populations

1. Approximately 1 million pigs were slaughtered in Malaysia in 1999 to control the Nipah virus

2. Several million chickens were slaughtered in Hong Kong in 1998 and 2001 to prevent a projected pandemic of *Influenza A virus*

3. Several million cows were slaughtered in Britain to curtail the epidemic of bovine spongiform encephalopathy and its possible transmission to humans

We don’t know if these were effective because we do have enough knowledge about the reservoir populations of these viruses

For Rhodesian sleeping sickness, isolation of *T. brucei rhodesiense* from a single bushbuck in the 1950s led to the assumption that wildlife was the principal reservoir for human disease and resulted in widespread culling of wildlife for disease control.
Fruit bats as reservoirs of Ebola virus

Bat species eaten by people in central Africa show evidence of symptomless Ebola infection.

The first recorded human outbreak of Ebola virus was in 1976, but the wild reservoir of this virus is still unknown. Tests for Ebola were performed in more than a thousand small vertebrates that were collected during Ebola outbreaks in humans and great apes between 2001 and 2003 in Gabon and the Republic of the Congo. Evidence of asymptomatic infection is found by Ebola virus in three species of fruit bat, indicating that these animals may be acting as a reservoir for this deadly virus.
Is the fruit bat an essential member of natural Ebola reservoir? Are there other reservoir species?

Yes  No

Course of Action
Ebola disrupts gorillas in a very unique way with entire populations quickly moving from an affected region and dissolving.

Once gorillas become aware of an Ebola threat they began to purposely isolate themselves, no longer immigrating with neighboring populations and only rarely breeding.

The virus quickly runs out of hosts, disappearing from shrinking populations entirely in the course of a few months.
Rabies is major cause of death in many countries

Rabies occurs in more than 150 countries and territories.

More than 55,000 people die of rabies every year mostly in Asia and Africa.

40% of people who are bitten by rabid animals are children under 15 years of age.

Wound cleansing and immunization within a few hours after contact with a suspect rabid animal can prevent the onset of rabies.

Every year, more than 15 million people worldwide receive a post-exposure vaccination to prevent the disease—this is estimated to prevent hundreds of thousands of rabies deaths annually.
This study estimates that globally canine rabies causes approximately

3.7 million DALYs (95% CIs: 1.6-10.4 million) disability-adjusted life years

8.6 billion USD economic losses annually (95% CIs: 2.9-21.5 billion)

59,000 human deaths (95% Confidence Intervals: 25-159,000)

For comparison

DALYs due to War and Disaster (2013) 6.1 million (95% CI: 3.5–11.1)
- Exposure to forces of nature 1.3 million (95% CI: 0.8–2.5)
- Collective violence and legal intervention 4.8 million (95% CI: 2.6–8.7)
40% of those infected with rabies are children.

Rabies is the 7th most severe global infectious disease with respect to Years of Life Lost (YLL).

Rabies is a neglected disease of poor and vulnerable populations whose deaths are rarely reported. It is estimated only 3% of rabies cases are reported.

It occurs mainly in remote rural communities where measures to prevent dog to human transmission have not been implemented.
Rabies is a zoonotic disease (a disease that is transmitted to humans from animals) that is caused by a virus.

The disease affects domestic and wild animals, and is spread to people through close contact with infectious material, usually saliva, via bites or scratches.

More than 95% of human rabies deaths occur in Asia and Africa. Once symptoms of the disease develop, rabies is nearly always fatal.
History of Rabies

2300 BC  Dog owners in the Babylonian city of Eshnunna are fined heavily for deaths caused by their dogs biting people.

400 BC  Aristotle writes that “dogs suffer from madness. This causes them to become irritable and all animals they bite become diseased.” By now, the Greeks have two special rabies gods; one to prevent rabies, (Arisaeus, son of Apollo) and a one to heal rabies, (Artemis).

1271  First large rabies outbreak reported. 30 people die after rabid wolves invade a German village.

1804  Zinke, a German scientist demonstrates rabies is passed through saliva.

1883  Pasteur and Roux create a rabies vaccine from the spinal cord of an infected animal and tests it on dogs.

1885  Joseph Meister is mauled by a rabid dog and brought to Pasteur. Pasteur gives him the rabies vaccine immediately, despite the risks to his own career as he is not a doctor, but a chemist. The treatment was successful, and Pasteur was hailed as a hero.
Effector B cells secrete antibodies, which can act over long distances to help eliminate extracellular pathogens and their toxins.

Effector cytotoxic T cells kill infected target cells also by means of proteins that they either secrete or display on their surface.

After the body eliminates the disease, some microbe-fighting B cells are converted into memory cells. Memory B cells can quickly divide into plasma cells and make more antibody if needed.

Weakened viruses activate the adaptive immune system leaving the individual with a supply of memory B cells for protection against the virulent viral strain.

Vaccines activate the adaptive immune system
Two clinical forms of Rabies

Furious or classical (80% of infections)
Numb--non-classical or paralytic (20% of infections)

Furious symptoms: Hydrophobia- fear of water/drinking, larynx spasms, animals extreme aggression and randomly attack objects animals humans. Simultaneous shedding of rabies virus in the saliva

Numb symptoms: Weak and paralyzed
Survival after onset of symptoms less than a week

Primary treatment:
One dose with rabies immunogloblin and five doses immunization with inactivated rabies virus vaccines immediately after exposure

Difficult to achieve in developing countries

CDC warning: Wake up with a bat in your room – you need to get vaccinated
RABIES VIDEO

https://www.youtube.com/watch?v=oxYpWlEgkSA
Jeanna Giese returns to see Willoughby at Children’s Hospital of Wisconsin in Milwaukee after he successfully treated her for rabies.
The Milwaukee protocol is controversial

It has been performed over 26 times since its inception in 2004 but has only saved one life. Overwhelming failure has lead health official to label the protocol a red herring.

Critical Appraisal of the Milwaukee Protocol for Rabies: This Failed Approach Should Be Abandoned.

Therapies suggested in the Milwaukee protocol include therapeutic coma, ketamine infusion...... None of these therapies can be substantiated in rabies or other forms of acute viral encephalitis. Serious concerns over the current protocol recommendations are warranted. The recommendations made by the Milwaukee protocol warrant serious reconsideration before any future use of this failed protocol.
In Latin America, Vampire Bats are a major reservoir of the Rabies virus

Dog to Human transmission eliminated, but Bat to Human still continue

Introduction of Cattle a problem- easy target for bats (stationary, same place every night)
Human also provided roosting sites: Buildings, bridges, wells

Bats as a reservoir species: only 10% of bats die from rabies the other 90% are carriers
Bats highly social providing a means of efficient bat to bat transmission (grooming, blood meal sharing)

Human victims- sleeping outdoors or building in which bats gain access (also low cattle areas)
Measures to reduce vampire bat population have been ineffective

1. Dynamite, Cynanide gas- these had obvious downside of killing many species and dispersing vampire bat populations

2. Poison - anticoagulants- capture and coat bat with Warfinins spiked vaseline. Or coat cattle or roosts with the vaseline.

These techniques have been used for over 40 years. Over that time the vampire bat populations has increased
Rabies, like Ebola, is a negative-stranded RNA virus

(Filovirus: Ebola, Marburg)
Rabies virus is neurotropic virus and 12kb negative strand RNA genome of 12kb encoding five proteins

RNA encapsulated into a nucleoprotein
The incredible journey of the Rabies virus

The virus enters muscle tissue near the bite

Enters neighboring neuron

Travels through the peripheral nervous system to the central nervous system (2 weeks to 6 years)

Once in the brain it undergoes extensive replication

Replicated virus migrates to salivary glands

Rabies virus in brain impairs serotonin transmission resulting in aggressive outbursts

THIS IS ACCOMPLISHED WITH A VERY SMALL 12KB GENOME CONTAINING ONLY 5 GENES!!!
Rabies hijacks the transport machinery of the cell
Rabies travels to brain by associating with a Dynein microtubule motor protein

Movement of Rabies through neurons imaged live with Fluorescent labeled viral particles

Rabies P protein binds Minus-end Motor Dynein
Don’t do this !!!
WOUND MANAGEMENT

- Cleansing-with soap and water (minimum 10min) punctured wound irrigated with catheters
- Chemical treatment-virucidal agents- 70% alcohol, povidine iodine, tincture iodine, etc
- Local administration of rabies antiserum
- Suturing - done after 24-48hrs with antiserum locally
- Antibiotics
- Immunization against tetanus
- Wound not to be dressed or bandaged
Stay after class- you are slated for a presentation Thursday Jan 26th

Shona Allen
Chandra Lucas
Doan Brandon
Taimor Mohammad
Van Lau
Jethro Marasigan
Kindness Nwakudu
Quincy Okobi
Manon Pilaud
Sarah Raisedana
Benafsha Sahibzadah
Armit Takhar

"Relax. I just had a cappuccino."
Dengue fever

Key facts
- Dengue is a mosquito-borne viral infection.
- The infection causes flu-like illness, and occasionally develops into a potentially lethal complication called severe dengue.
- The global incidence of dengue has grown dramatically in recent decades.
- About half of the world's population is now at risk.
- Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas.
- Severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries.
- There is no specific treatment for dengue/severe dengue, but early detection and access to proper medical care lowers fatality rates below 1%.
- Dengue prevention and control solely depends on effective vector control measures.

<table>
<thead>
<tr>
<th>Disease</th>
<th>DALYs</th>
<th>Papers (Pubmed)</th>
<th>Papers (Pubmed)/100 DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>0.83 Million</td>
<td>14,780</td>
<td>1.8</td>
</tr>
<tr>
<td>Rabies</td>
<td>1.46 Million</td>
<td>13,467</td>
<td>0.9</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0.92 Million</td>
<td>280,352</td>
<td>31</td>
</tr>
</tbody>
</table>

Aedes aegypti is the mosquito vector of the Dengue virus (via mosquito saliva)

Bites during daylight
**Dengue**

The US centers for Disease Control and Prevention has billed dengue as the most important mosquito-borne disease affecting humans - ahead of malaria and encephalitis - with an estimated 2.5 billion at risk worldwide.

Yet this disease is largely ignored by the biomedical research community:

<table>
<thead>
<tr>
<th>Disease</th>
<th>DALYs</th>
<th>Papers (Pubmed)</th>
<th>Papers (Pubmed)/100 DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>0.83 Million</td>
<td>14,780</td>
<td>1.8</td>
</tr>
<tr>
<td>Rabies</td>
<td>1.46 Million</td>
<td>13,467</td>
<td>0.9</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0.92 Million</td>
<td>280,352</td>
<td>31</td>
</tr>
</tbody>
</table>
Dengue is a positive-stranded RNA virus (Flavivirus) 10-11kb genome- 7 genes

Other viruses in this family include: West Nile, Yellow fever, Encephalitis)

Shaped like a golf-ball with dimples where the proteins meet
Unusual as most viruses contain spikes to interact with host cell

Adenovirus- common cold
Dengue fever is a severe flu-like illness which presents as a ‘fever-arthralgia-rash’ syndrome, sometimes with mild internal/external bleeding. It is unpleasant but not life-threatening.

The severe form of Dengue infection known as Dengue Haemorrhagic Fever (arose in 1950s) causes severe internal/external bleeding, serious dysfunction of organs such as the liver or brain, and - most seriously - circulatory failure.

Such 'dengue shock syndrome' tends to affect children in Asia but all ages in the Americas. It can kill within hours of the onset of symptoms.
Local and imported cases of Dengue in the past three months: 1289
Planning a trip to Hawaii?

Risk Areas for Potential Dengue Infection
Hawaii—2015–2016

As of January 6, 2016

Total number of confirmed cases 207

Onset Date

- Cases no longer infectious to mosquitoes
- Cases likely still infectious to mosquitoes
- Illness that began during this time may not yet be reported to/confirmed by HDOH

(HDOH preliminary data - subject to change pending new information)

Risk levels for potential dengue infection: • High Risk  • Moderate Risk  • Some Risk
The transmission cycle of the Dengue virus in West Africa

**Host:** Human

**Vector:** Mosquito

**Reservoir Species:** Primate

---

The transmission cycle of the Dengue virus in Hawaii

**Host:** Human

**Vector:** Mosquito
The existence of an abundant reservoir population for specific diseases makes eradication difficult.

<table>
<thead>
<tr>
<th>Disease (virus)</th>
<th>Known reservoir hosts</th>
<th>Other susceptible hosts</th>
<th>Transmission host to humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avian influenza (H5N1, H7N9, H7N7, H9N2, H3N2 and others)</td>
<td>Waterfowl and wild birds</td>
<td>Bats, cats, dogs, ferrets, pigs, poultry (chickens, ducks and turkeys) and marine mammals</td>
<td>Chickens</td>
</tr>
<tr>
<td>'Swine flu' strains (H1N1 and H3N2)</td>
<td>Pigs</td>
<td>Ferrets, foxes, cats, dogs, poultry (chickens, ducks and turkeys) and marine mammals</td>
<td>Pigs</td>
</tr>
<tr>
<td>SARS (SARS coronavirus)</td>
<td>Bats</td>
<td>Civet cats</td>
<td>Civet cats</td>
</tr>
<tr>
<td>Dengue fever (dengue virus)</td>
<td>Primates</td>
<td>Unknown</td>
<td>Mosquitoes</td>
</tr>
<tr>
<td>Hendra (Hendra virus)</td>
<td>Bats</td>
<td>Horses and ferrets</td>
<td>Horses</td>
</tr>
<tr>
<td>Rabies (rabies virus and other lyssaviruses)</td>
<td>Bats</td>
<td>Cats, cattle, coyotes, dogs, foxes, horses, mongooses, primates, raccoons, sheep, skunks and wolves</td>
<td>Bats and dogs</td>
</tr>
<tr>
<td>Ebola viral haemorrhagic fever (Ebola virus)</td>
<td>Bats</td>
<td>Primates</td>
<td>Primates and bats</td>
</tr>
</tbody>
</table>
Failure of Milwaukee protocol

Rabies movement through neuron mechanism

Rabies as a molecular tool


Diabolical effects of rabies encephalitis.

Vampire Bat Rabies: Ecology, Epidemiology and Control
Nicholas Johnson,1,* Nidia Aréchiga-Ceballos,2 and Alvaro Aguilar-Setien3
After five or more days, patients often develop signature signs of an Ebola infection:

- Bumpy red rash on the face, neck, torso and arms; skin can flake off
- Severe diarrhea, nausea and vomiting
- Chest pain, shortness of breath, headache, confusion, bloodshot eyes, hiccups or seizures
- Spontaneous bruising, skin hemorrhages
- Bleeding from the eyes, ears, nose, mouth, mucus membranes and rectum.
- Spontaneous miscarriage
Exposure

Ebola virus particles occupy an infected person’s blood and other bodily fluids, which can enter another person through the eyes, mucous membranes, scratches on the skin or from a hypodermic needle — not from from the air or from insects.

The bodies of people who have died of the disease are highly infectious. Without protective equipment, shaking hands with an Ebola patient or being within three feet of a patient for long periods of time is less risky, but not advisable.

In small West African villages, the close personal attention given to sick or dead family members can easily spread the disease.
Early symptoms

Usually, a little over a week after exposure to the Ebola virus, people begin having symptoms: fever, chills, muscle pain, sore throat, weakness and general discomfort. In its early stages, Ebola can resemble malaria, typhoid fever or bacterial respiratory infections.

Staging the attack

The virus attacks immune cells in the bloodstream, which carry the infection to the liver, spleen and lymph nodes. Ebola blocks the release of interferon, a protein made by immune cells to fight viruses. Infected immune cells migrate out of the spleen and lymph nodes, through the bloodstream or lymph ducts to other tissues and organs.
Multi-system collapse

Ebola damages many kinds of tissue in the body, either by the virus infecting cells or by the body’s extreme inflammatory response.

A breakdown of the adrenal glands leads to dangerously low blood pressure and a decreased ability to produce steroid hormones.

The body’s connective tissues are attacked, as are the cells that line body cavities and surfaces.

Liver failure and kidney failure often occur.

Fluid accumulates in the brain. Convulsions can cause patients to spread infectious blood and other bodily fluids.
A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins.

The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.
What is Passive Immunotherapy?

- Antibodies donated from another individual who contracted a disease which would help the recipient’s macrophages to attack diseased cells or foreign tissue.
- Injection of donor plasma would carry antibodies that help the immune system recognize the antigens on foreign bodies, cells infected by viruses, disease.

Ebola, like many viruses, works in part by inhibiting interferon—a type of molecule that cells use to hinder further viral reproduction. In a new study, researchers found that one of Ebola’s proteins, called VP24, blocks transport of interferon.