Introduction to infectious diseases

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with thanks to Ottar Bjornstad for sharing some slides…

Research Projects

Students are expected to undertake research projects linked to topics covered in the ASI. Students may work individually or in small groups (up to 4), and collaboration between students from Africa and the US is highly encouraged. Projects will be conducted under the oversight of the faculty mentors whose committments students obtained as prerequisite for acceptance to ASI, with further input from one or more of the ASI lecturers. During allotted time periods and un-scheduled time during the ASI, students will have opportunities to discuss project work with ASI lecturers.

On **Friday, June 22**, students will be expected to submit a brief description of their project plans, comprising at minimum a paragraph describing the study system, research questions, and methods that will be applied. More developed reports, including preliminary results, will be welcomed!

Six months following the ASI, students will be expected to submit technical reports describing the successful execution of the project, to be published in a joint publication on the DIMACS website or as DIMACS Technical Reports. If resources are available, students may be brought together in regional meetings to present their work and interact further with ASI faculty.

Outline

Microparasites and macroparasites

Immunity and evolution

Clinical course of disease

Epidemiological terms and data

Population-level patterns

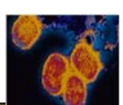
Impacts of infectious diseases in Africa and worldwide

Microparasites

- Small size
- **Multiplication within host**
- **Multiple infections (usually) don't matter**
- Short generation time → rapid evolution
- No specialized infective stages
- Often lead to crisis in host… immunity or death
- Infections can be transient or chronic
- **Dynamic unit: host infection/immune status (Susceptible-Infectious-Recovered)**

Viruses

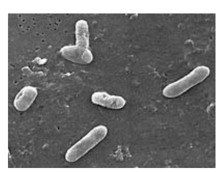
- Microscopic particles that infect cells of living organisms.
- Can replicate only by infecting a host cell and "high-jacking" its machinery.
- Co-evolved viruses interact with many host systems, and often try to block specific or general immune functions.
- Carry genetic information as DNA or RNA. Genomes range from 3 kb-1.2 Mb)
- Evolve very fast due to short generation times and error-prone replication.



Small pox

Ebola virus

Influenza



Bordetella pertussis

Bacillus anthracis

Staphylococcus aureus

Bacteria

- Unicellular organisms, usually a few micrometers long.
- Most bacteria live in environment (or inside other organisms) and do not cause disease.
- Estimated that human body has 10 times as many bacteria as human cells!
- A small minority of bacterial species are pathogens and cause disease.
- Evolve fast compared to eukaryotes, but slowly compared to viruses.
- Genome size from 160 kb to 12.2 Mb

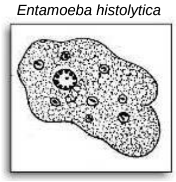
Fungi

Entomophagous fungi

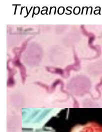
Tinea pedis

Protozoa

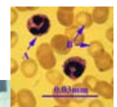
Entamoeba histolytica



Trypanosoma

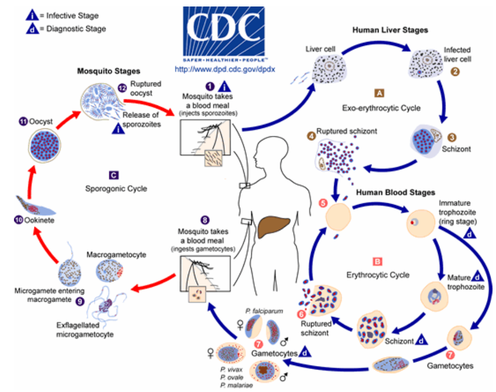


Plasmodium

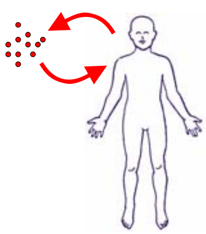


Leishmania

Life cycle of *Plasmodium* (malaria)

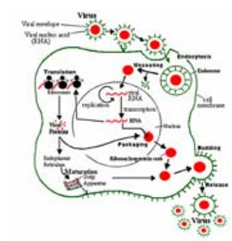


Life cycle of a respiratory virus



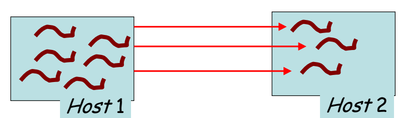
The real action for a viral life cycle takes place inside the host cell.

e.g. Life cycle of Influenza A



Macroparasites

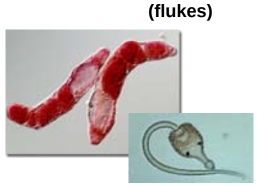
- Large body size
- **No multiplication within host**
- **Multiple infections matter**
- Long generation time & chronic infections
- Specialized infective stages and complex life cycles
  - Usually cannot complete life cycle within host
- Host morbidity depends on burden
- Infections are usually chronic
- **Dynamic unit: host parasite burden**



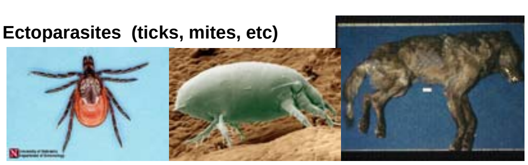
Macroparasites

Nematodes (roundworms)

Trematodes (flukes)



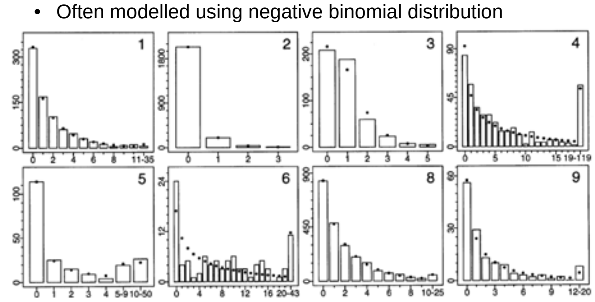
Ectoparasites (ticks, mites, etc)



Macroparasites

Parasite burden is aggregated within particular hosts

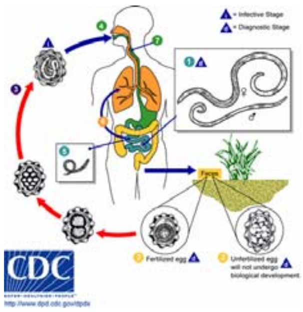
- Often modelled using negative binomial distribution

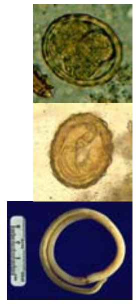


Direct life cycle

Ascariasis

Ascaris lumbricoides (hookworm)

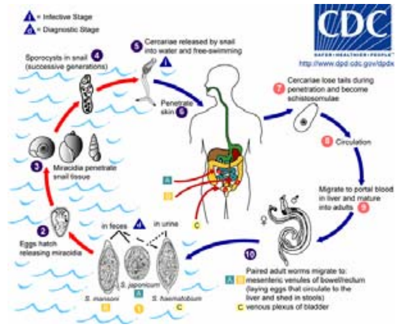


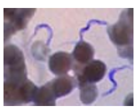


Indirect life cycle

Schistosomiasis

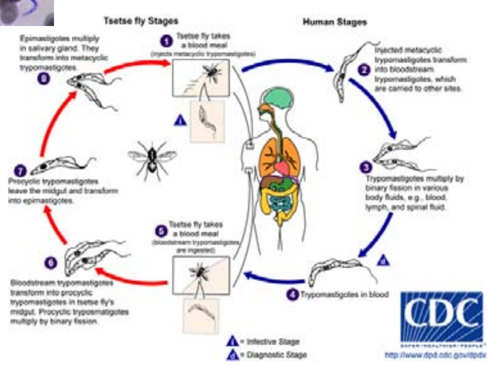
Schistosoma mansoni





Vectored life cycle

Trypanosoma brucei   Sleeping sickness



Immunity

1) A state in which a host is not susceptible to infection or disease, or

2) the mechanisms by which this is achieved. Immunity is achieved by an individual through one of three routes:

Innate immunity genetically inherited, not specific to particular parasites

Acquired or adaptive immunity conferred after contact with a disease (specific to that parasite)

Artificial immunity after a successful vaccination.

Just like there is a huge diversity of infectious pathogens and parasites, **there is a huge diversity of immune pathways** involved in adaptive and innate immunity**.**

Hugely over-simplified picture of immune mechanisms

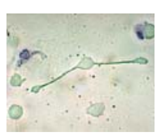
Example: response to bacterial infection

<u>Innate immunity</u> begins immediately

(i) Macrophages in lungs recognize molecules in the bacterial wall as foreign ('antigens'),

(ii) Macrophages produce signals that attract neutrophils,

(iii) Neutrophils kill bacteria.



<u>Adaptive immunity</u> begins after several days

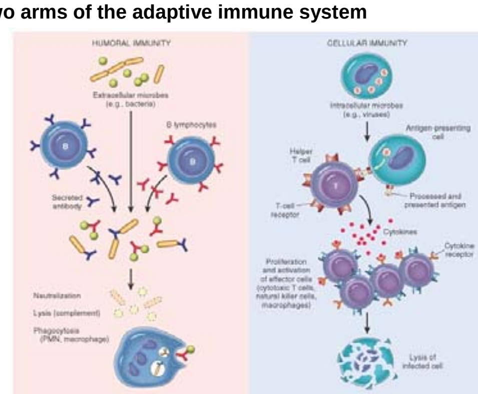
(i) Antigens stimulate antigen-specific B cells,

(ii) Stimulated B cells multiply to produce (a) rapidly antibody-producing B cells (plasma cells) and (b) long-lived memory cells

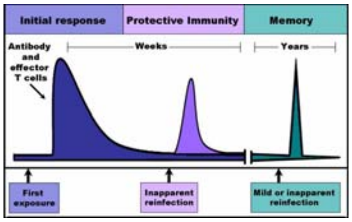
(iii) Antibodies bind to antigens

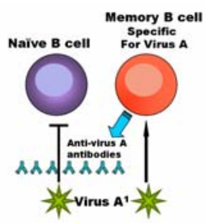
(iv) Cytotoxic T cells recognize bound antibodies and kill bacteria

Two arms of the adaptive immune system



Immune memory





http://en.wikipedia.org/wiki/Image:Immune_response.jpg

Pathogen evolution

Microparasites have short generation times and evolve rapidly in response to selective pressures.

Because pathogen evolution is much faster than host evolution, on short to medium timescales (say <100 years) we usually just think about pathogen evolution.

Three classes of pathogen evolution are important:

1. **Drug resistance**

   e.g. chloroquine-resistant malaria

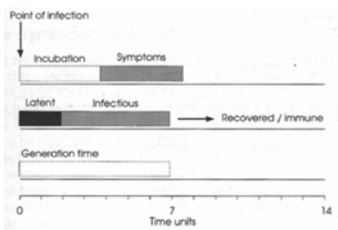
2. **Immune escape**

   e.g. influenza strains

3. **Adaptation to new hosts**

   e.g. SARS: bats (?) → civets → humans

Processes within a host: clinical course



Incubation period: time from infection to appearance of symptoms

Latent period: time from infection to beginning of transmission

- called pre-patent period for macroparasites

Infectious period: time during which individual can transmit disease

- may not be the same as symptomatic period!!

Generation time (or **serial interval**): time from infection of one host to infection of a secondary case caused by that host.

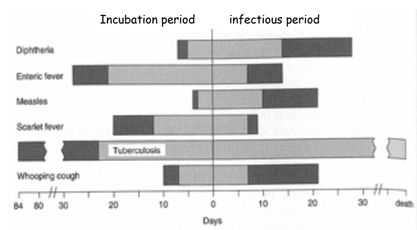
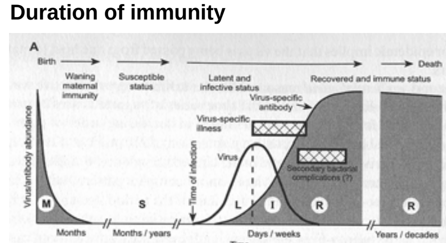


Figure 3.1. Incubation periods and periods of communicability for each of the six diseases. Bars are divided to show lower (light stipple) and upper (dark stipple) estimates of the duration of each period.

Table 3.1 Incubation, latent and infectious periods (in days) for a variety of viral and bacterial infections. Data from Fenner and White (1970), Christie (1974), and Benenson (1975)

Infectious disease	Incubation period	Latent period	Infectious period
Measles	8–13	6–9	6–7
Mumps	12–26	12–18	4–8
Whooping cough (pertussis)	6–10	21–23	7–10
Rubella	14–21	7–14	11–12
Diphtheria	2–5	14–21	2–5
Chicken pox	13–17	8–12	10–11
Hepatitis B	30–80	13–17	19–22
Poliomyelitis	7–12	1–3	14–20
Influenza	1–3	1–3	2–3
Smallpox	10–15	8–11	2–3
Scarlet fever	2–3	1–2	14–21

Duration of immunity



Host immunity following exposure to a pathogen can last:

lifelong (e.g. measles)

a few years (e.g. influenza)

not at all (e.g. gonorrhea)

Immunity can also be partial – i.e. not full protection from subsequent infection or disease.

Transmission

Transmission is the central process in infectious disease dynamics (it puts the 'infectious' in infectious disease).

Pay attention to biology and sociology underlying transmission!

Important questions

How does the mode of transmission affect the host contact structure relevant to disease spread?

Are there important heterogeneities among hosts that will impact transmission?

How does it affect disease control measures?

Modes of transmission

Direct (droplet, aerosol, fomite)
e.g. influenza, measles, SARS

Sexual transmission
e.g. HIV, gonorrhea, HSV-2, chlamydia

Vector-borne (mosquitoes, tse-tse flies, sandflies, ticks, fleas)
e.g. malaria, trypanosomiasis, leishmaniasis

Free-living infectious stages and environmental reservoirs
e.g. helminths, anthrax

Waterborne, foodborne, fecal-oral
e.g. cholera, polio, Salmonella

Infectious disease epidemiology

Incidence: number of new infections per unit time.

Prevalence: proportion of population that is infected at a particular time.

Attack rate: proportion of susceptible individuals in a given setting that become infected.

Force of infection: Per capita rate of infection per unit time.

Seroprevalence: Proportion of population carrying antibodies indicating past exposure to pathogen.

Note on epidemiological jargon:

Epidemiologists often use "rate" differently from mathematicians. It's not always a number per unit time. Often instead it's a number per 100,000 individuals.

Population-level patterns

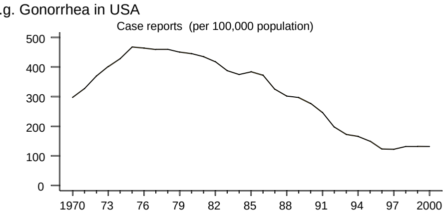
1) **Endemic infections**

Endemic A term to describe levels of infection which do not exhibit wide fluctuations through time in a defined place.

For microparasites, the term is used (slightly differently) to indicate an infection that can **persist locally** without need for reintroduced from outside host communities.

Stable endemicity is where the incidence of infection or disease shows no secular trend for increase or decrease.

e.g. Gonorrhea in USA

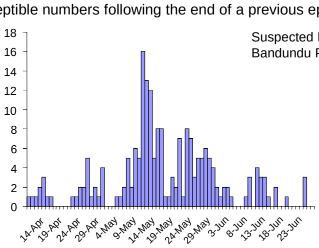


Population-level patterns

2) Simple epidemics

Epidemic A rapid increase in the levels of an infection. Typical of the microparasitic infections (with long lasting immunity and short generation times), an epidemic usually begins with an exponential rise in the number of cases and a subsequent decline as susceptible numbers are exhausted.

Epidemics may arise from the introduction of a novel pathogen (or strain) to a previously unexposed (naive) population or as a result of the regrowth of susceptible numbers following the end of a previous epidemic.



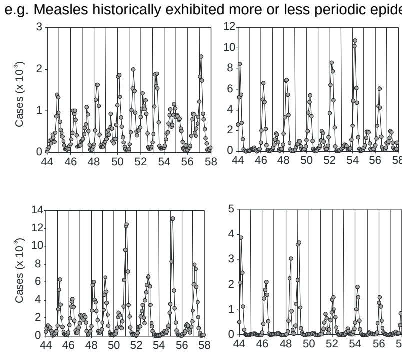
Suspected Ebola Deaths
Bandundu Province, Zaire - Apr-Jun 1995

"Epidemic curve"

Population-level patterns

3) Recurrent epidemics

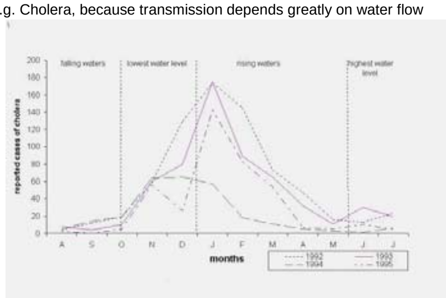
e.g. Measles historically exhibited more or less periodic epidemics



Population-level patterns

4) Seasonal endemism

e.g. Cholera, because transmission depends greatly on water flow



Rreported cases of cholera in the Brazilian Central Amazon region. This region is characterized by seasonal flooding of the Negro and Amazon Rivers, driven mainly by snow melt in the Andean headwaters of the Amazon River

Impacts of infectious disease

Infectious disease is estimated to account for >50% of all deaths in sub-Saharan Africa.

Percentage of total deaths

1	HIV/AIDS	19.0
2	Malaria	10.1
3	Lower respiratory infections	10.0
4	Diarrheal diseases	6.6
5	Perinatal conditions	5.3
6	Measles	4.1
7	Cerebrovascular disease	3.3
8	Ischemic heart disease	3.2
9	Tuberculosis	2.9
10	Road traffic accidents	1.8

http://www.dcp2.org/pubs/GBD/3/Table/3.10

Microparasites & Humans - history

- 1914 - Influenza A killed 20 million people
- Plague reduced European populations by 25% (and up to 70%) in 13th century:
- Rubella - 30,000 still births in USA during the 1960s

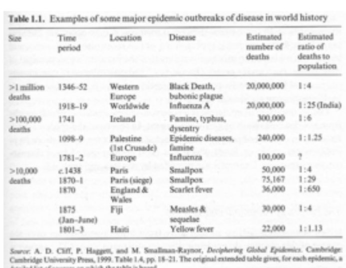


Table 1.1. Examples of some major epidemic outbreaks of disease in world history

Size	Time period	Location	Disease	Estimated number of deaths	Estimated ratio of deaths to population
>1 million deaths	1346–52	Western Europe	Black Death, bubonic plague	20,000,000	1:4
	1918–19	Worldwide	Influenza A	20,000,000	1:25 (India)
>100,000 deaths	1741	Ireland	Famine, typhus, dysentry	300,000	1:6
	1098–9	Palestine (1st Crusade)	Epidemic diseases, famine	240,000	1:1.25
	1781–2	Europe	Influenza	100,000	?
>10,000 deaths	c.1438	Paris	Smallpox	50,000	1:4
	1870–1	Paris (siege)	Smallpox	75,167	1:29
	1870	England & Wales	Scarlet fever	36,000	1:650
	1875 (Jan–June)	Fiji	Measles & sequelae	30,000	1:4
	1801–3	Haiti	Yellow fever	22,000	1:1.13

Source: A. D. Cliff, P. Haggett, and M. Smallman-Raynor, *Deciphering Global Epidemics*. Cambridge: Cambridge University Press, 1999. Table 1.4, pp. 18–21. The original extended table gives, for each epidemic, a detailed list of sources on which the table is based.

HIV/AIDS

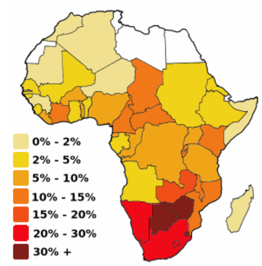
Estimated 39 million people (33-46 million) living with HIV/AIDS in 2005

Estimates for sub-Saharan Africa (2005):

25.8 million people living with HIV/AIDS

3.2 million people newly infected with HIV

2.4 million people died of AIDS

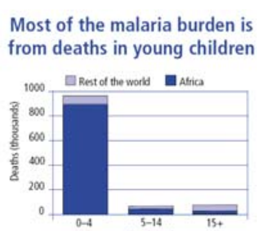


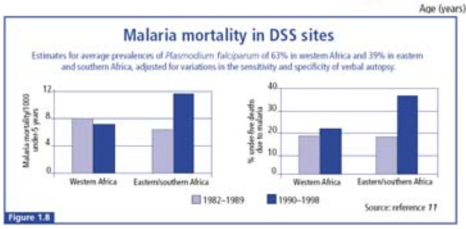
HIV prevalence

Malaria

More than 300 million clinical cases per year.

Estimated 1 million deaths per year, >90% in sub-Saharan Africa and focused in children.





Tuberculosis

Major opportunistic infection for people living with HIV/AIDS in sub-Saharan Africa.

2.4 million cases and 540,000 TB deaths annually in sub-Saharan Africa.

INFECTIOUS DISEASE:

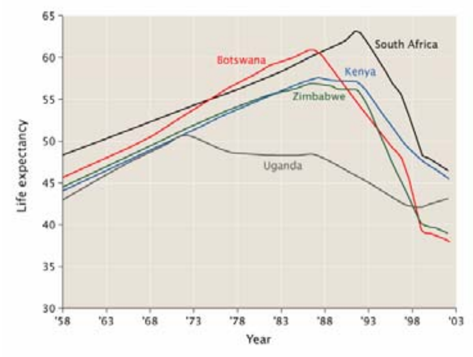
Extensively Drug-Resistant TB Gets Foothold in South Africa

Jon Cohen

An outbreak of what's called "extensively drug-resist ... , Sou
Africa, appears to be nearly twice as large as origin ... fficial
held in Johannesburg last week to discuss what we

XDR-TB patient causes furore

US officials are concerned that a man infected with an extensively drug-resistant form of tuberculosis (XDR-TB) may have transmitted the disease to fellow passengers on two international flights he took.



http://en.wikipedia.org/wiki/HIV/AIDS_in_Africa

13 major neglected diseases of Africa

Protozoan infections

African trypanosomiasis (Sleeping sickness), Kala-azar (Visceral leishmaniasis), Chagas Disease

Helminth Infections

Soil Transmitted Helminth Infections, Ascaris, Trichuris, Hookworm infection, Schistosomiasis, Lymphatic Filariasis (Elephantiasis), Onchocerciasis (River Blindness), Drancunculiasis (Guinea Worm)

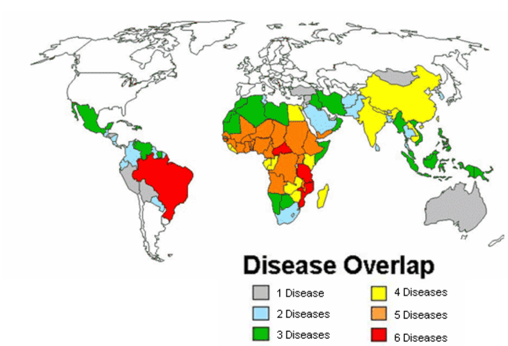
Bacterial infections

Trachoma, Leprosy, Buruli Ulcer

http://gnntdc.sabin.org/index.html

Neglected diseases

Estimated 534,000 deaths per year

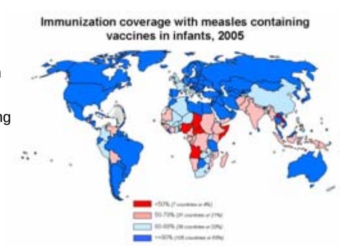


Childhood diseases

Measles

Effective vaccine exists, but approximately 410,000 children die every year.

Death rate of 1-5% in developing countries, or 10-30% in malnourished children.



Mortality and morbidity in the US

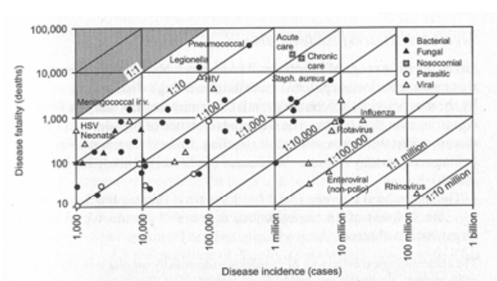
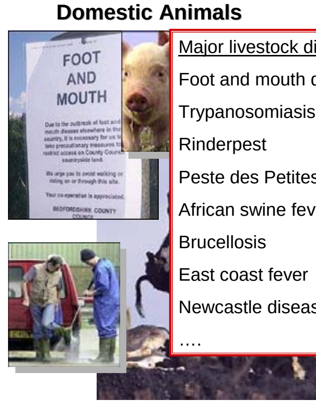


Fig. 1.4. Annual mortality and morbidity from major infectious and parasitic diseases in the United States in the mid 1980s. Note that both disease fatality and disease incidence are plotted on logarithmic scales. The diagonal lines represent the fatality/case ratio.

Source: drawn from data in Bennett, *et al.* 1987, *op. cit.* [note 23], Table 1, pp. 104–7.

Microparasites & Domestic Animals



Major livestock diseases in Africa

- Foot and mouth disease
- Trypanosomiasis
- Rinderpest
- Peste des Petites Ruminantes
- African swine fever
- Brucellosis
- East coast fever
- Newcastle disease
- ….

Microparasites & Wildlife

Bovine tuberculosis in Kruger National Park
- buffalo, lions, kudu, etc

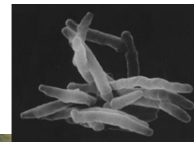
Rinderpest in African ungulates

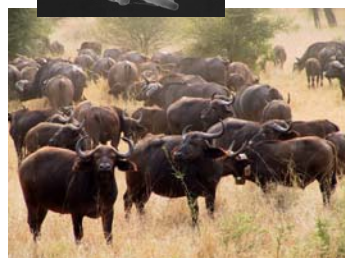
Canine distemper in Serengeti lions

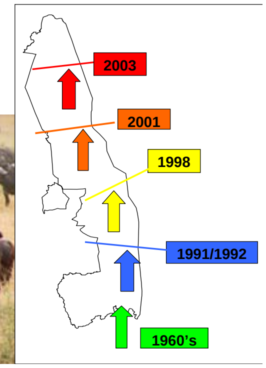
Rabies in Ethiopian wolves

Anthrax in Etosha ungulates

Bovine tuberculosis in African buffalo







Rinderpest in Africa

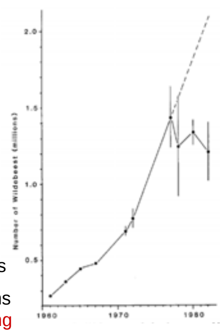
Massive epidemic in 1890s devastated wild ungulates.

→80-90% mortality of buffalo, eland, wildebeest, giraffe, antelopes

1950s: vaccination of cattle began.

→ Population increase for ungulates

Rinderpest held ungulate populations to ~20% of their disease-free carrying capacity.



Sinclair et al, 1985

Cassava mosaic disease

Plant disease caused by Cassava mosaic geminivirus, vectored by whiteflies.

Crop losses as high as 40% in important staple food of east, central and west Africa.