INFECTIOUS DISEASES AFFECTING AFRICA

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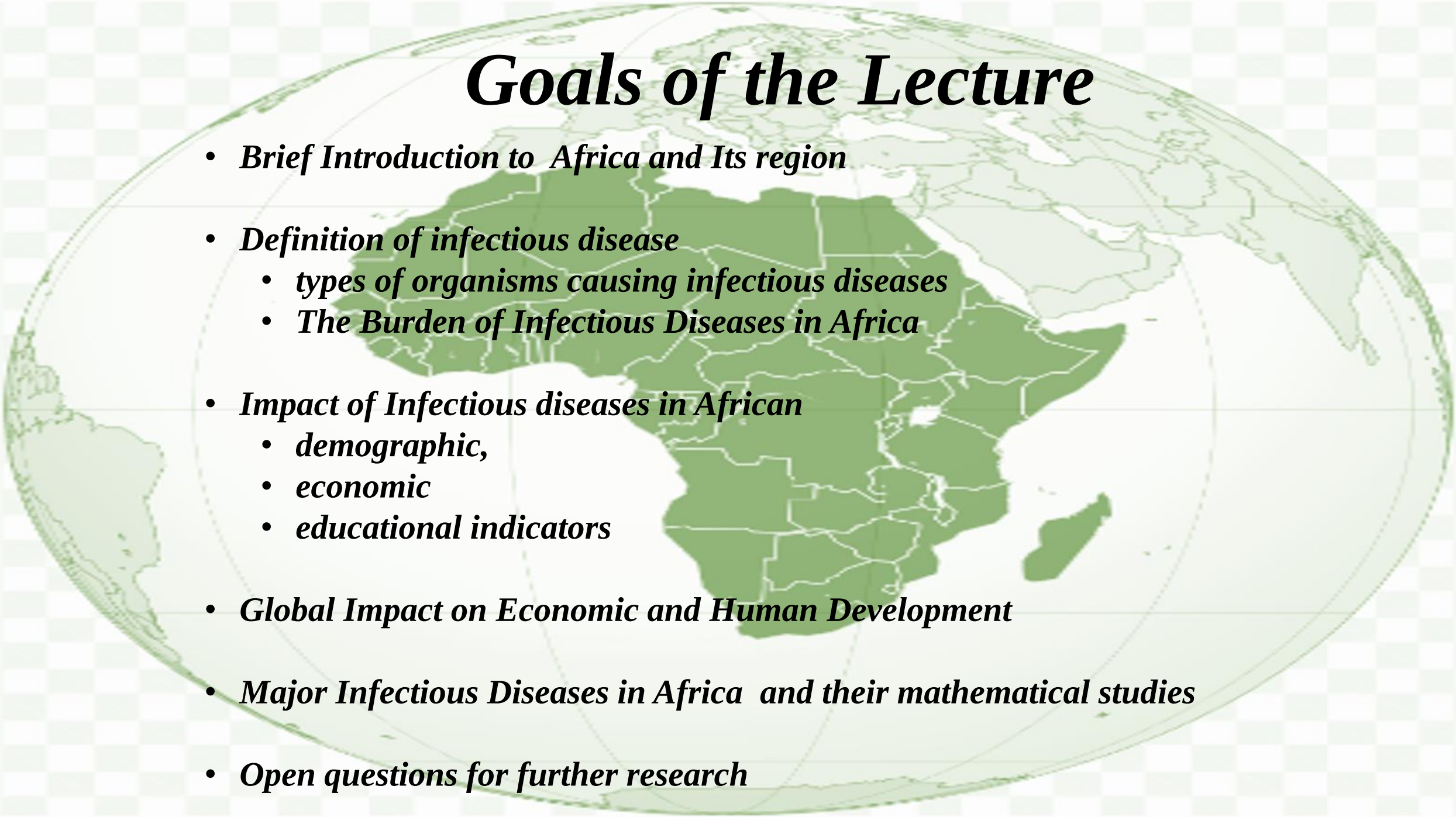
Goals of the Lecture



- *Brief Introduction to Africa and Its region*
- *Definition of infectious disease*
  - *types of organisms causing infectious diseases*
  - *The Burden of Infectious Diseases in Africa*
- *Impact of Infectious diseases in African*
  - *demographic,*
  - *economic*
  - *educational indicators*
- *Global Impact on Economic and Human Development*
- *Major Infectious Diseases in Africa and their mathematical studies*
- *Open questions for further research*

Africa and its region

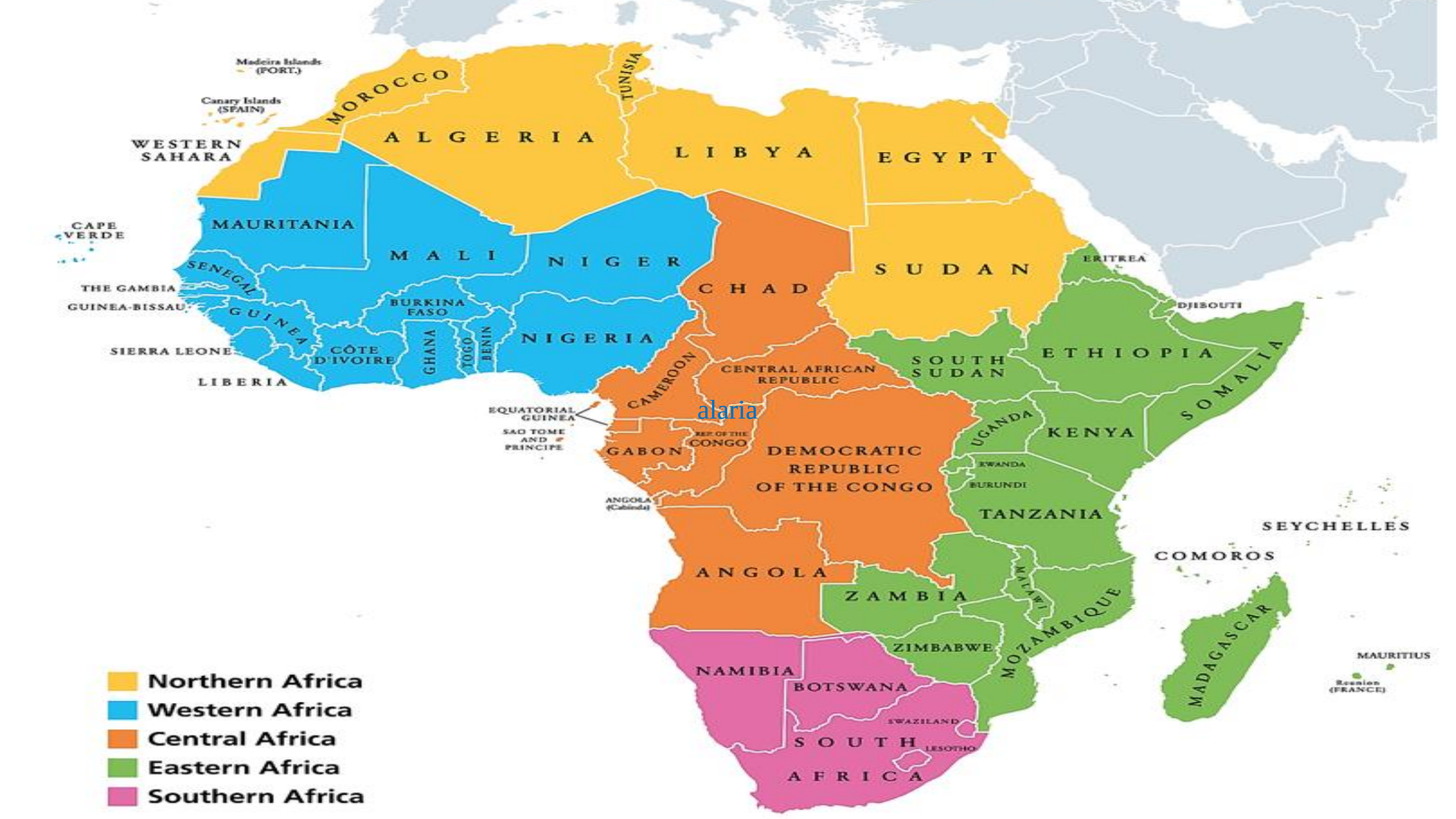
- Africa is the second largest continent in the world and comprises of about 54 independent countries[1].

- There are five(5) regions of Africa:

    i. Northern Africa (with 5 countries)
    ii. West Africa (with 16 countries)
    iii. East Africa (with 18 countries and the most populated)
    iv. Middle Africa (with 9 countries)
    v. Southern Africa (with 6 countries and the least populated)

- An estimated 1.369 billion people live in Africa which represent about 12% of the world population [2].

- Nigeria is the most populous country in Africa, while the Seychelles is the least populous.


Madeira Islands (PORT.)
Canary Islands (SPAIN)
MOROCCO
TUNISIA
WESTERN SAHARA
ALGERIA
LIBYA
EGYPT
CAPE VERDE
MAURITANIA
MALI
NIGER
CHAD
SUDAN
ERITREA
SENEGAL
THE GAMBIA
GUINEA-BISSAU
GUINEA
BURKINA FASO
DJIBOUTI
SIERRA LEONE
CÔTE D'IVOIRE
GHANA
TOGO
BENIN
NIGERIA
ETHIOPIA
LIBERIA
CAMEROON
CENTRAL AFRICAN REPUBLIC
SOUTH SUDAN
SOMALIA
EQUATORIAL GUINEA
SAO TOME AND PRINCIPE
GABON
REP. OF THE CONGO
DEMOCRATIC REPUBLIC OF THE CONGO
UGANDA
KENYA
RWANDA
BURUNDI
TANZANIA
ANGOLA (Cabinda)
SEYCHELLES
COMOROS
ANGOLA
ZAMBIA
MALAWI
MOZAMBIQUE
ZIMBABWE
MADAGASCAR
MAURITIUS
Reunion (FRANCE)
NAMIBIA
BOTSWANA
SWAZILAND
SOUTH AFRICA
LESOTHO
Northern Africa
Western Africa
Central Africa
Eastern Africa
Southern Africa
alaria

What are Infectious diseases?

- Infectious diseases, also known as communicable diseases, are diseases caused by pathogens that get into the human bodies [3]. It can be emerging or reemerging infectious diseases.

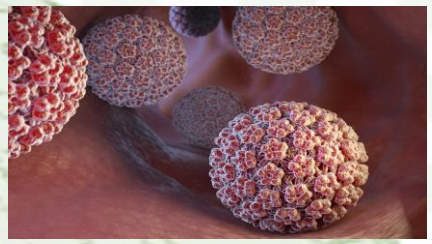
- Emerging infectious diseases are unknown diseases with previously outbreaks or known diseases that are rapidly increasing in incidence or geographic range in the last two decades or with uncontrollable persistence of diseases [4].
  - Such as HIV infections, SARS, Lyme disease, Escherichia coli O157:H7 (E. coli), hantavirus, dengue fever, West Nile virus, and the Zika virus.

- Reemerging diseases are diseases that reappear after they have been on a significant decline. They include malaria, tuberculosis, cholera, pertussis, influenza, pneumococcal disease, and gonorrhea [5].

- Emerging infectious diseases in Africa include HIV/AIDS, Ebola, Lassa, and COVID-19.

- Re-emerging infectious diseases in Africa include West Nile Virus, MPox, Tuberculosis and Drug-resistant malaria.

Pathogens of the infectious diseases

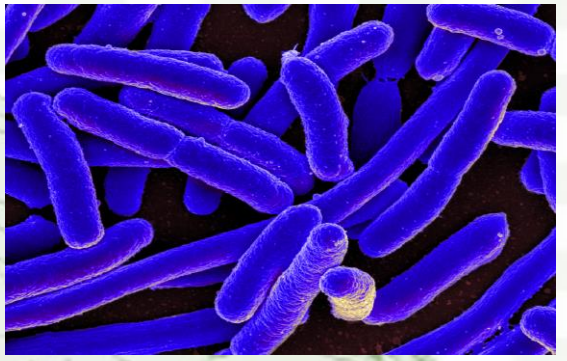


- There are five(5) pathogens causing infectious diseases: namely
  i. Viruses ii. Bacteria iii. Fungi iv. Parasites v. Prions

- **Viruses are small germs (pathogens) that can infect host and make them sick. Host can be humans, plants, animals, bacteria and fungi [6].**

- Influenza viruses (avian flu ("bird flu") and swine flu (H1N1)
- Human herpesviruses (chickenpox, shingles, Epstein-Barr and cytomegalovirus)
- Coronavirus (SARS-CoV-2, that causes COVID-19)
- Human papillomaviruses (HPV can lead to cancers such as cervical cancer)
- Enteroviruses (polio, hand, foot and mouth disease.)
- Orthopoxviruses (Mpox, smallpox)
- Hepatitis viruses (Hepatitis A, B and C)
- Flaviviruses (Zika, West Nile, dengue fever, yellow fever)
- Retroviruses (HIV and human T-lymphotropic virus 1 (HTLV-1))
- Oncoviruses (viruses-cause cancer such as HIV, HPV, Epstein-Barr, Hepatitis B & C)
- Satellite viruses (can't reproduce without "helper" viruses and are found in plants)
- Bacteriophages called "phages," (specifically infect bacteria)

Bacteria

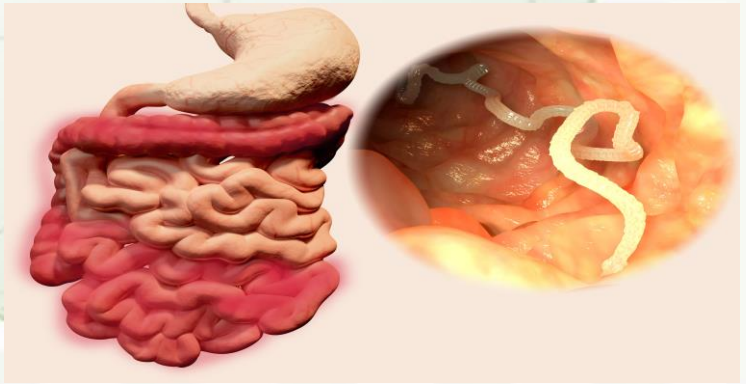


- Bacteria are living things with only a single cell that can reproduce quickly.
- Common bacterial diseases include

Sepsis, Pneumonia, Urinary tract infections (UTI), Meningitis, Wound infections, Tuberculosis, Diarrhoea, Dysentery, Malaria, Typhoid, Cholera, Influenza, Tuberculosis, Measles, Legionnaire's Disease, Anthrax, Dysentery[7]

Parasites

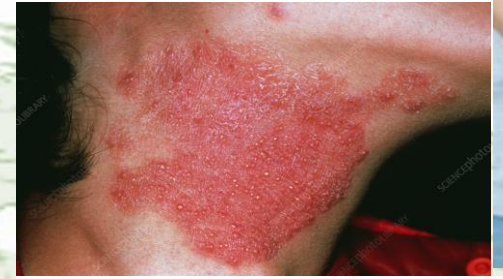
- Parasites are organisms that live in, on or with another organism (host) where they feed, grow or multiply in a way that harms their host.
  - They need their host for their survival. For this reason, they rarely kill their host, but they often carry diseases that can be life-threatening.



Major Parasite diseases in Africa

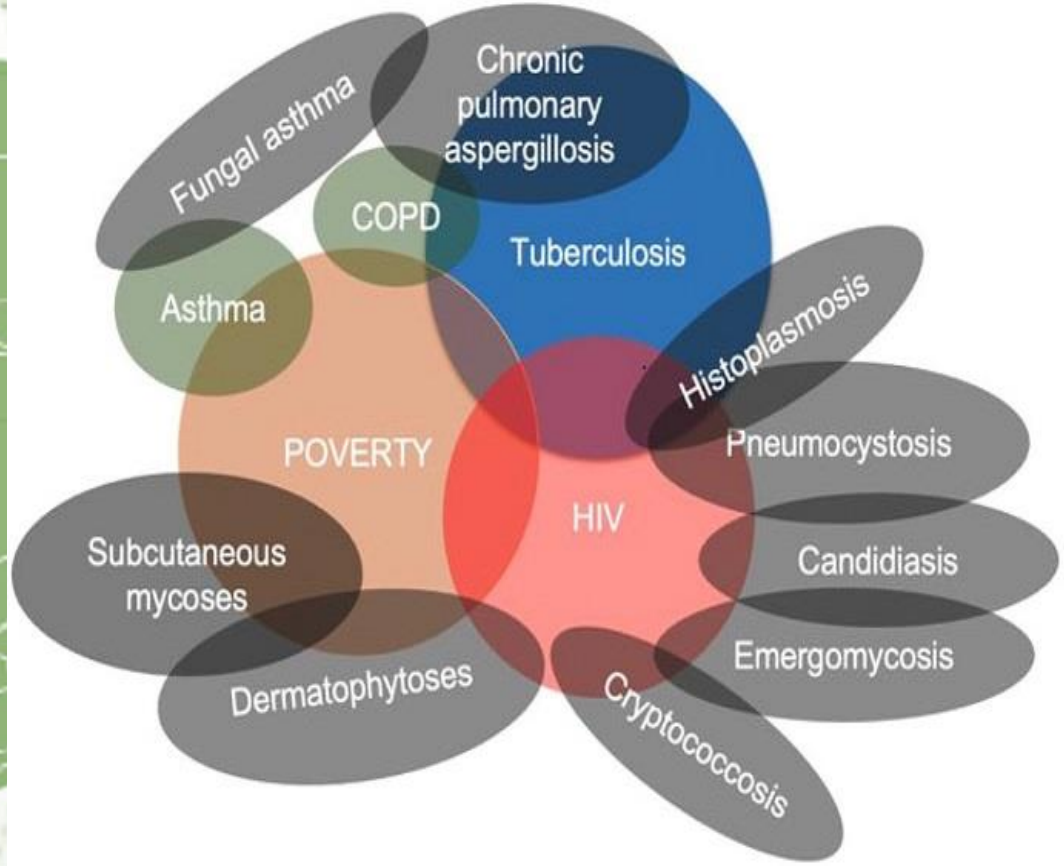
Giardiasis, Leishmaniasis, Lymphatic Filariasis, Malaria, Hookworm Onchocerciasis, Schistosomiasis, Trypanosomiasis, Guinea-Worm.

Fungi



- Fungi are living things that are classified separately from plants or animals. They move around by spreading out or sending spores (reproductive parts) into the air or environment. [8]

- Fungal infections are most common on our skin or nails, but cause infections in your mouth, throat, lungs, urinary tract and many other parts of your body.
  - Mainly driven by heavy affliction of poverty, tuberculosis (TB) and human immunodeficiency virus (HIV) and contribute largely to the burden of diseases in Africa.



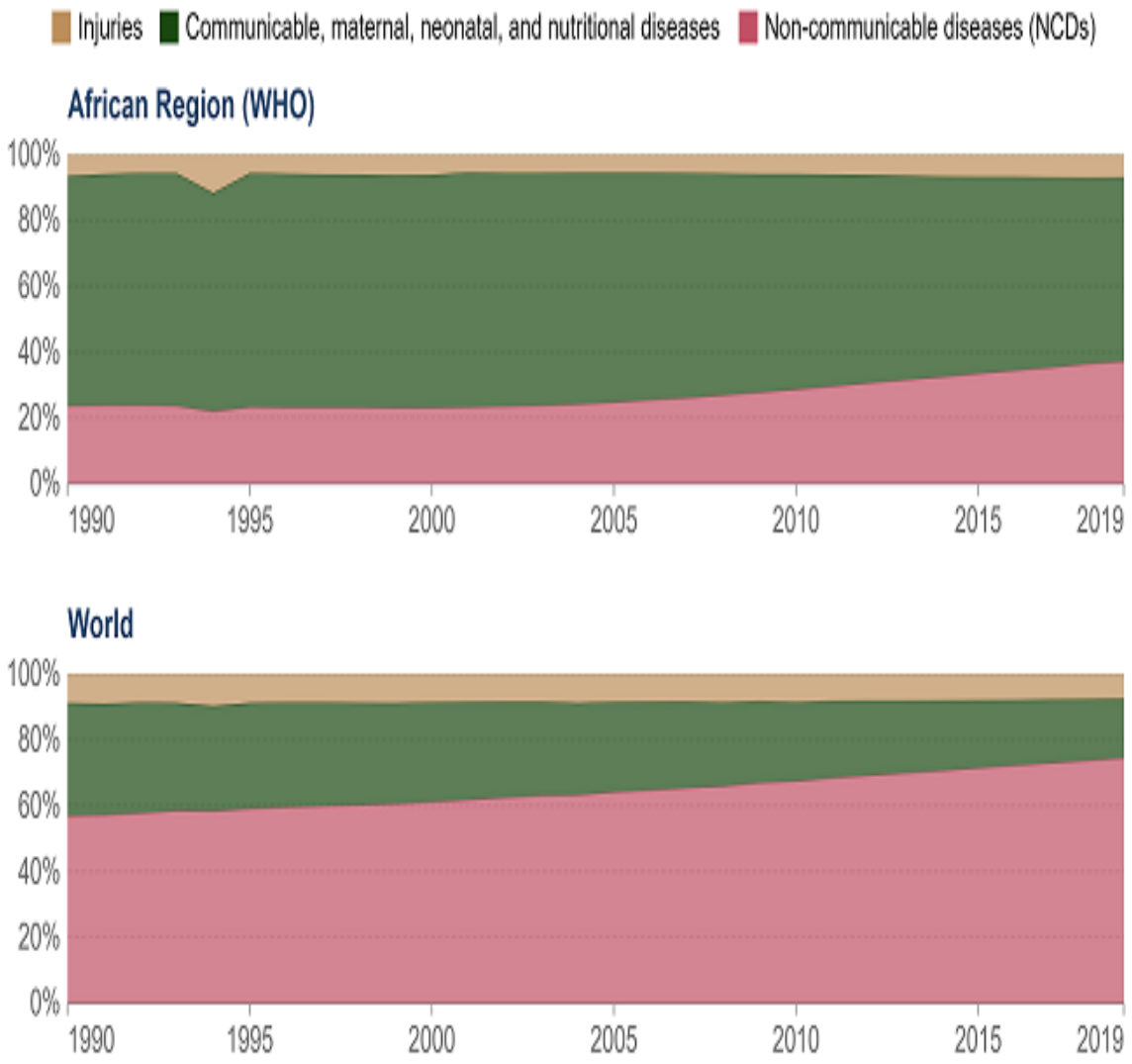
Prions

- A prion is a type of protein that can trigger normal proteins in the brain to fold abnormally.
- Affect both humans and animals and are sometimes spread to humans by infected meat products.
- The most common form of prion disease that affects humans is Creutzfeldt-Jakob disease (CJD)[9].

The Burden of Infectious Diseases in Africa

- Infectious diseases remain the leading cause of death across Africa and continue to kill millions of persons yearly.
- In Africa, about 4.1 million deaths were caused by infectious diseases in 2019 alone[10]
  - Poverty and Poor healthcare among the contribution
    - In 2001, one person spent on average $36 on healthcare in Africa [12]
    - 32% of the population is undernourished due to poverty; five of the six worst countries for mortality of children under 5 years are in Africa [11]
    - 70% of its population survives on less than $2 a day[2],

Causes of Death



Source: IHME, Global Burden of Disease (2019)

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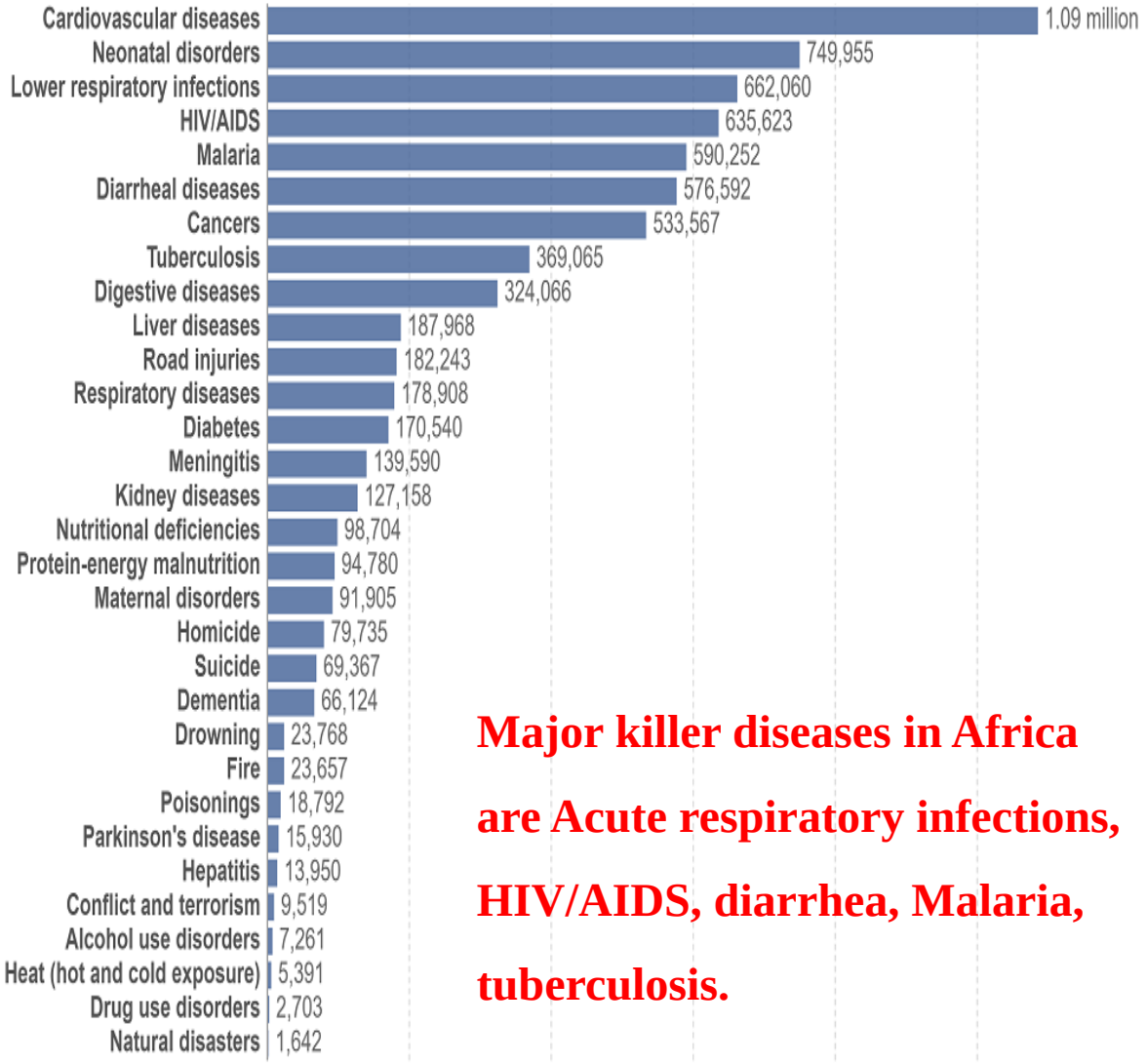
Cause of death in Africa



Major killer diseases in Africa are Acute respiratory infections, HIV/AIDS, diarrhea, Malaria, tuberculosis.

Source: IHME, Global Burden of Disease (2019)

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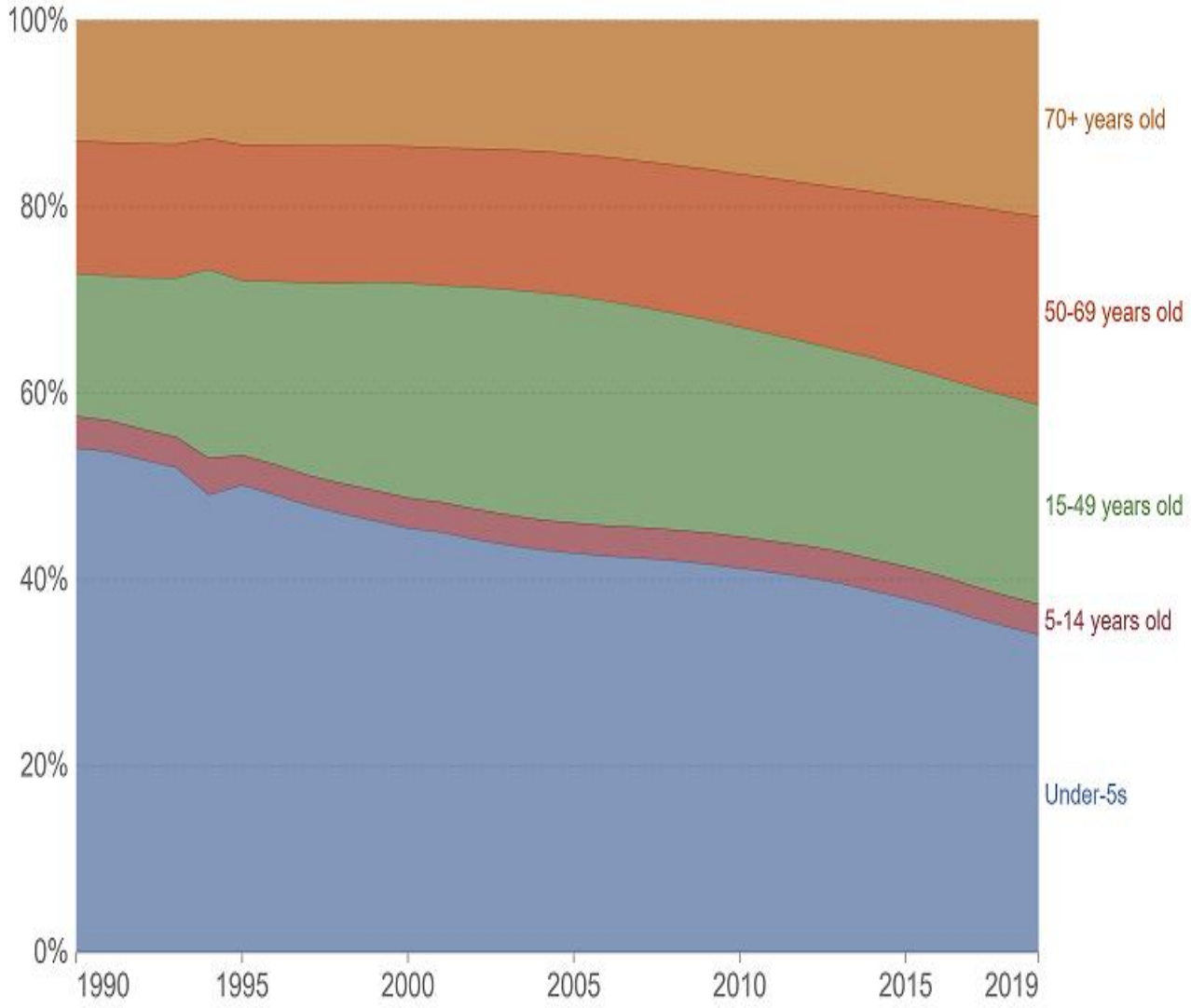
Deaths by age in Africa



Source: IHME, Global Burden of Disease (2019)

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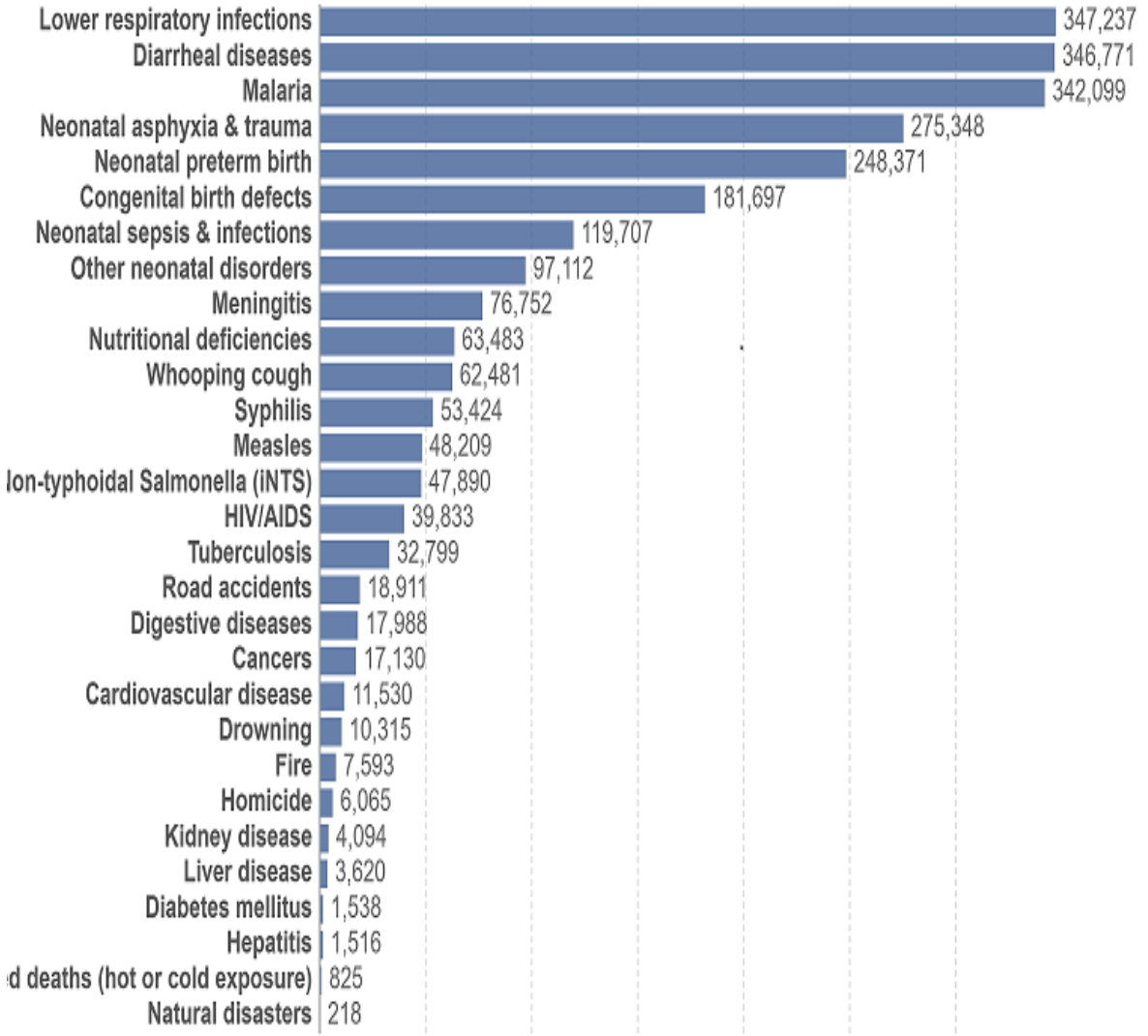
Under 5 age cause of death (Africa)



/E, Global Burden of Disease (2019)

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Neglected tropical diseases

- **Neglected tropical diseases (NTDs)** are a diverse group of 20 conditions that are mainly prevalent in tropical areas, where they affect more than 1 billion people who live in impoverished communities[13].

- **‘neglected’** as they mostly affect the poorest populations living in rural areas, urban slums and conflict zones and almost absent from the global health agenda.
  - Most NTDs are vector-borne (animal reservoirs) and are associated with complex life cycles.
  - Responsible for impaired childhood growth, mental retardation, blindness, amputation and diverse disability conditions

List of NTDs

Buruli Ulcer, Chagas Disease, Dengue, Chikungunya, Dracunculiasis, Echinococcosis, Foodborne Trematodiases, African Sleeping Sickness, Leishmaniasis, Leprosy, Lymphatic Filariasis, Mycetoma, Onchocerciasis, Rabies, Scabies, Schistosomiasis, Soil-Transmitted Helminths, Snakebite Envenoming, Taeniasis and Cysticercosis, Trachoma [13].

Impact of Infectious Diseases in Africa Development

- **Impact on Health and demographic Indicators: :** affects mortality rates, life expectancy, and sex and age distributions [12].
  - It averagely reduces life expectancy of 38 African countries to 47 years life expectancy
  - Causes more deaths especially infant mortality
  - Lost of numerous health care work force and mobilization of more than half of all hospital beds due to AIDS and other infectious diseases
- **Impact on economic Indicators:** affecting business, investment, industry and agricultural sustainability [12].
  - HIV/AIDS kills and disables adults in their best productive lives, and cost between 11.7 and 35.1% of the GNP in Africa
  - Malaria costs Africa more than US$12 billion a year, slowing its economic growth by 1.3% annually
  - Over 3 million livestock die annually due to Sleeping sickness causing loss of US$4.5 billion in agriculture

Impact of Infectious Diseases in Africa Development

- **Impact on Education**
  - Infectious disease pressure causes thousands of primary school children to drop put of school.
  - It affect the cognitive ability of children, the capacity of teachers, the upbringing of families and the efficiency of staff and managers.
  - Malaria affects the education capacity of African countries as it affected mostly under 5 African children while diarrhea highly affect school attendance [12].

Global Impact on Economic and Human Development

- Malaria account for 10% of Africa’s disease burden which supposed to be 32% lower without malaria
- In Africa countries, 34 countries belong to the lower-income group, 12 are lower middle-income countries, only 8 countries are classified as higher-middle-income and no African country has reached the high-income level.
- For human development (HD), no African countries belong to “High HD”, most of African countries are in the “Low HD” while the remaining occupy “Medium HD” group.
- In 15 years (1990–2006), HIV/AIDS made African countries to lost tens of places in the human development ranking [12].

Infectious Diseases in Africa

The discussion will based on the following

- Pathogens: viral, bacterial, fungal, and parasitic and their disease burdens in Africa region.
- The mode of transmission, prevention, and treatment of the diseases.
  - Viral diseases such as Ebola virus disease and Lassa fever
  - Bacteria diseases such as tuberculosis and cholera
  - Fungal infection; cryptococcosis
  - Parasitic diseases such as schistosomiasis, onchocerciasis and malaria.

Note. HIV/AIDS is not discussed in this lecture because it is global not particular to Africa.

Major infectious diseases affecting Africa

Disease name	Disease genre	Disease burden (estimated cases/death)*
Amebiasis	Parasitic disease	70,000 deaths
Cholera	Bacterial disease	3-5 million/100,000-120,000 deaths
Dengue	Viral disease	390 million/indetermination
Ebola	Viral disease	15,000 deaths
Giardiasis	Parasitic disease	Indetermination
Guinea-Worm	Parasitic disease	Indetermination
Hepatitis	Viral disease	Hepatitis A: 1.4 million cases Hepatitis B: 240 million cases/780,000 deaths Hepatitis C: 130-150 million cases/350,000 to 500,000 deaths Hepatitis E: 20 million cases/56,600 deaths
HIV/AIDS	Viral disease	35 million cases/1.5 million deaths
Hookworm	Parasitic disease	Indetermination
Leishmaniasis	Parasitic disease	1.3 million cases/20,000 to 30,000 deaths
Lymphatic Filariasis	Parasitic disease	120 million cases
Malaria	Parasitic disease	198 million cases/584,000 deaths (2013)
Onchocerciasis	Parasitic disease	Indetermination
Polio	Viral disease	416 cases (2013)
Schistosomiasis	Parasitic disease	20,000 to 200,000 deaths
Syphilis	Viral disease	Indetermination
Trypanosomiasis	Parasitic disease	6314 cases (2013)
Tuberculosis	Bacterial disease	9 million cases/1.5 million (2013)
Typhoid	Bacterial disease	22 million cases/216,500 deaths (2011)
Yellow Fever	Viral disease	200,000 cases/30,000 deaths

*The data are cited from WHO website accessed May 23rd, 2017.

Note: These diseases account for nearly 80% of the total infectious disease burden and claim more than 6million people per year

80% of the global burden account to malaria and schistosomiasis.

Tuberculosis

- Tuberculosis (TB) is a deadly infectious disease that has been in endless war with man since ancient time and the organism, Mycobacterium sp was discovered by Robert Koch in 1882 [14].
- TB has killed humans for thousands of years and still infects 10 million people annually [15, 16].

TB Organism:

Mycobacterium tuberculosis (Mtb) and Mycobacterium africanum (Maf) together named as human-adapted Mycobacterium tuberculosis complex (hMTBC).

Maf is restricted to West Africa region only with 50% of TB cases implicated to it [14, 17].

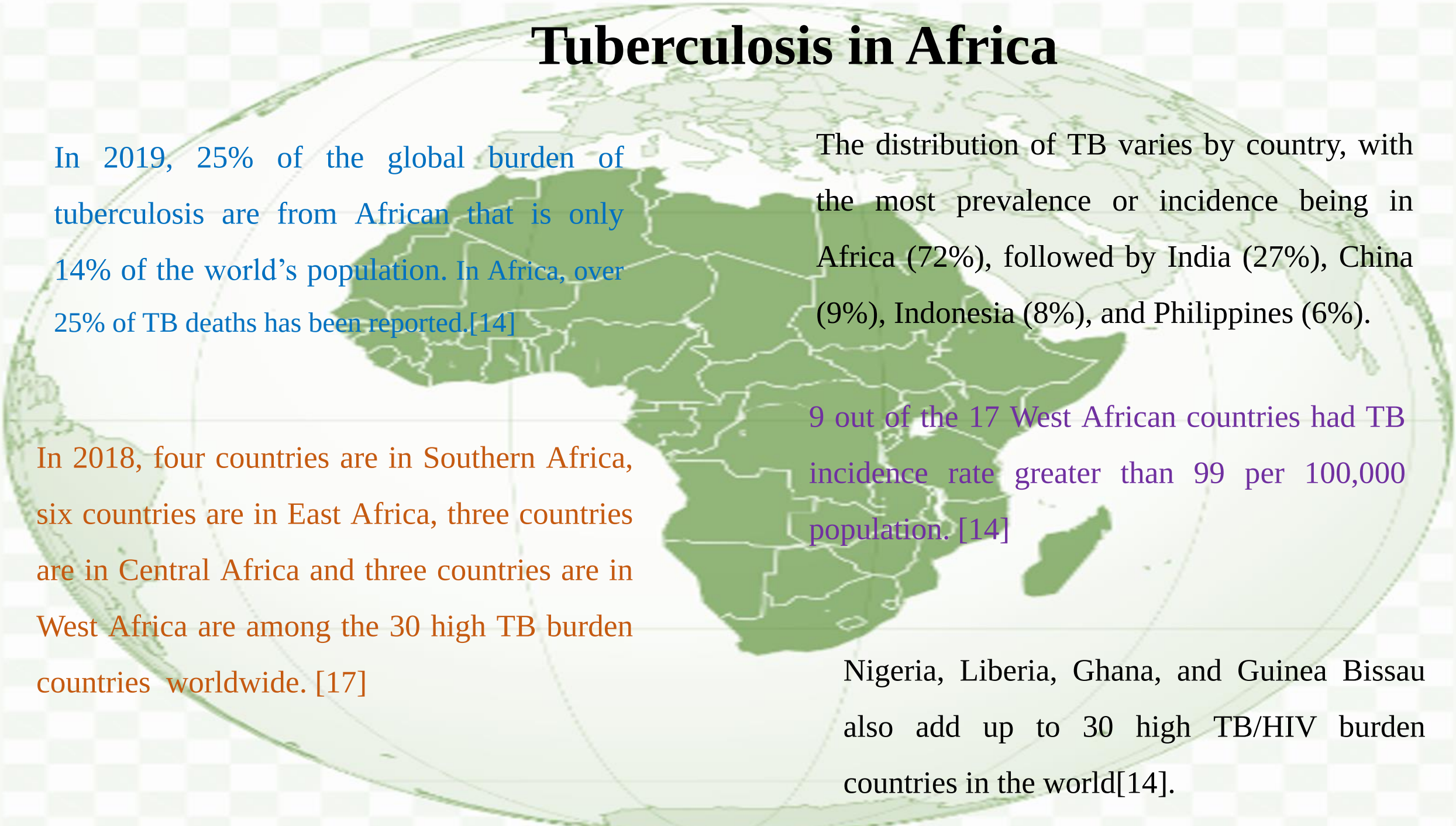
Major risk factors for TB

human immunodeficiency virus (HIV), older age, lower socioeconomic status such as homelessness, overcrowding, poor nutrition and prolonged close contact with patient with tuberculosis [17].

Main route for the transmission of TB

Via inhalation aerosolized droplets from someone with sputum positive tuberculosis into the lungs [18].

Tuberculosis in Africa



In 2019, 25% of the global burden of tuberculosis are from African that is only 14% of the world's population. In Africa, over 25% of TB deaths has been reported.[14]

The distribution of TB varies by country, with the most prevalence or incidence being in Africa (72%), followed by India (27%), China (9%), Indonesia (8%), and Philippines (6%).

9 out of the 17 West African countries had TB incidence rate greater than 99 per 100,000 population. [14]

In 2018, four countries are in Southern Africa, six countries are in East Africa, three countries are in Central Africa and three countries are in West Africa are among the 30 high TB burden countries worldwide. [17]

Nigeria, Liberia, Ghana, and Guinea Bissau also add up to 30 high TB/HIV burden countries in the world[14].

Tuberculosis Interventions

Controls

- Vaccination with bacille Calmette-Guérin (BCG),
- Early case detection using both clinical and laboratory tools
- Appropriate treatment with antibiotics.
- Recently, Gene Xpert as the main rapid diagnostic tool for TB in Sub-Saharan [17].

Challenges in controlling TB

TB remains prevalent because of HIV co-infection, severe stigmatization, delay in case detection, poor adherence to multidrug regimens and emergence resistant strains of hMTBC to antibiotics [14, 17, 18, 19].

WHO initiated the "End Tb Strategy" in 2014

To reduce the number of TB deaths and TB incidence by 90% and 80% respectively by 2030 and 95% and 90% respectively by 2035[14].

So far, there has been a slow pace of success which fell very short of the target [14].

Mathematical Models of TB

- Mathematical models have an important role in the planning of TB control programs in Africa.
- Modelling is a useful tool to understand the dynamics of an epidemic that would help to prevent spreading.
- Mathematical models contribute to prediction of future epidemic and its control.

First mathematical model for TB transmission dynamics

Waaler [21] in 1962 developed a linear system of difference equations model for TB given by

$$E_{t+1} = E_t + aI_t + eE_t - d_2E_t - gE_t$$

$$I_{t+1} = I_t - eE_t - d_3E_t + gE_t$$

The equations for latent-TB (E) and infectious-TB (I) classes were assumed to be uncoupled from the equation for the susceptible class.

a = Incidence rate; e = the per-capita progression rate from E to I; g = per capita treatment rate (treated individuals will become members of latent-TB class again.);
d_2 = per-capita death rate of E class; a
d_3 = per capita death rate of I class

Limitation

This linear model did not model the mechanics of TB transmission.

Mathematical Models of TB

- Brogger developed an improved model [22] of Waaler's by introducing

  i. heterogeneity (age), ii. Combined linear and nonlinear infection rates, $\beta S\left(1 - Z + Z\frac{I}{N}\right)$.

  Z = an adjusting parameter to differentiate between normal infection, superinfection, and direct leaps (within a very short period, an uninfected individual becomes a lesion case or an active-TB case).

  Z = 1 gives nonlinear term, $\frac{\beta SI}{N}$, and, Z = 0 gives a linear term βS (infection rate $\propto$ No. of susceptible)

  - The prevalence , $\frac{I}{N}$, is for adjusting all flow rates.
  - Aim to compare different control strategies inclusive finding and treating more cases, the utilization of vaccination, and mass roentgenograph.

Limitation

It is a difference model.

Mathematical Models of TB

- First nonlinear system of Ordinary Differential Equation for TB by ReVelle [23, 24]
  - i. Infection rate depends linearly on the prevalence using the probabilistic approach (homogeneous mixing)
  - ii. The total population governed by the Malthus model
  - Aim: to apply to developing nations.
  - Further developed an optimization model that was use to select control strategies at a minimal cost.

Limitation of ReVelle model
ignored population structure.

Many dynamical models have been studied for TB in developing nations.

- Chaves and Song [25] discussed different TB models

i. Slow and fast routes SEI model: Infection rate is divide into E class (slow route) and I class (fast route)

ii. Variable latent period model: arbitrary distribution for the latency period not exponential latent period

iii. Multiple strains model: drug-sensitive and drug-resistant types

iv. Multiple strains and variable latent period: only consider the age of the infection with drug sensitive strain

The modified SIR model

- Based on modifying basic non-demographics SIR model proposed by Kermack and McKendrick, the basic SIR model including the death and the birth rates for TB is given by [26] as

$$\frac{dS(t)}{dt} = bN - \frac{\beta S(t)I(t)}{N} - \mu S(t)$$

$$\frac{dI(t)}{dt} = \frac{\beta S(t)I(t)}{N} - (\mu + \gamma)I(t)$$

$$\frac{dR(t)}{dt} = \gamma I(t) - \mu R(t)$$

with subject to

$$S(0) \geq 0, I(0) \geq 0, R(0) \geq 0.$$

$$\mathrm{N}(t) = S(t) + \mathrm{I}(t) + \mathrm{R}(t)$$

- β = transmission rate, γ = recovery rate
- μ = death rate, b = birth rate .
- Here, it is assumed that $\mu = b$ so we have a close population, .
- β and γ are within the range is (0,1).
- Basic reproduction number, $R_0 = \frac{\beta}{\gamma+\mu}$.
- $R_0 < 1$, TB eradicate in the community
- R_0>1, TB remains in the community.

Limitation

- This model does not take into account age, vaccination or waning immunity.

SEIR model for TB disease

- It is an extension of SIR which include an exposed individuals[26]

$$\frac{dS(t)}{dt} = bN - \frac{\beta S(t)I(t)}{N} - \mu S(t)$$

$$\frac{dE(t)}{dt} = \frac{\beta S(t)I(t)}{N} - (\mu + \epsilon)E(t)$$

$$\frac{dI(t)}{dt} = \epsilon E(t) - (\mu + \gamma)I(t)$$

$$\frac{dR(t)}{dt} = \gamma I(t) - \mu R(t)$$

with subject to

$$S(0) \geq 0, E(0) \geq 0, I(0) \geq 0, R(0) \geq 0.$$

$$\mathrm{N}(t) = S(t) + \mathrm{E}(t) + \mathrm{I}(t) + \mathrm{R}(t)$$

- $E(t)$ = Individuals who are infected but not showing symptoms of the disease,
- ϵ = the rate at which the exposed individuals become infective;
- Here, it is assumed that $\mu = b$
- $\frac{1}{\epsilon}$ = mean latent period.
- Basic reproduction number, $R_0 = \frac{\beta\epsilon}{(\gamma+\mu)(\epsilon+\mu)}$

Limitation

- This model does not take into account age, vaccination or waning immunity.

BSEIR model for TB disease

- It is an extension of SEIR which include vaccination of new born babies[26].

$$\frac{dB(t)}{dt} = \Lambda p - kB(t)$$

$$\frac{dS(t)}{dt} = kB(t) + \Lambda(1-p) - \frac{\beta S(t)I(t)}{N} - \mu S(t)$$

$$\frac{dE(t)}{dt} = \frac{\beta S(t)I(t)}{N} - (\mu + \epsilon)E(t)$$

$$\frac{dI(t)}{dt} = \epsilon E(t) - (\mu + \gamma)I(t)$$

$$\frac{dR(t)}{dt} = \gamma I(t) - \mu R(t)$$

with subject to

$$B(t) \geq 0, S(0) \geq 0, E(0) \geq 0, I(0) \geq 0, R(0) \geq 0.$$

$$\mathrm{N}(t) = B(t) + S(t) + \mathrm{E}(t) + \mathrm{I}(t) + \mathrm{R}(t)$$

- $\mathrm{B}(t)$ =BCG vaccinated,
- $p \in (0,1)$ = the fraction of the newborns vaccinated successfully;
- Λ = recruitment rate
- the vaccination prevents for only 10 to 15 years
- natural death rate for B(t) is neglect since natural death of children is 1%.
- Since μ and Λ do not have taken equally, N(t) changes with respect to time.

Limitation

- This model does not take into account age, vaccination or waning immunity.

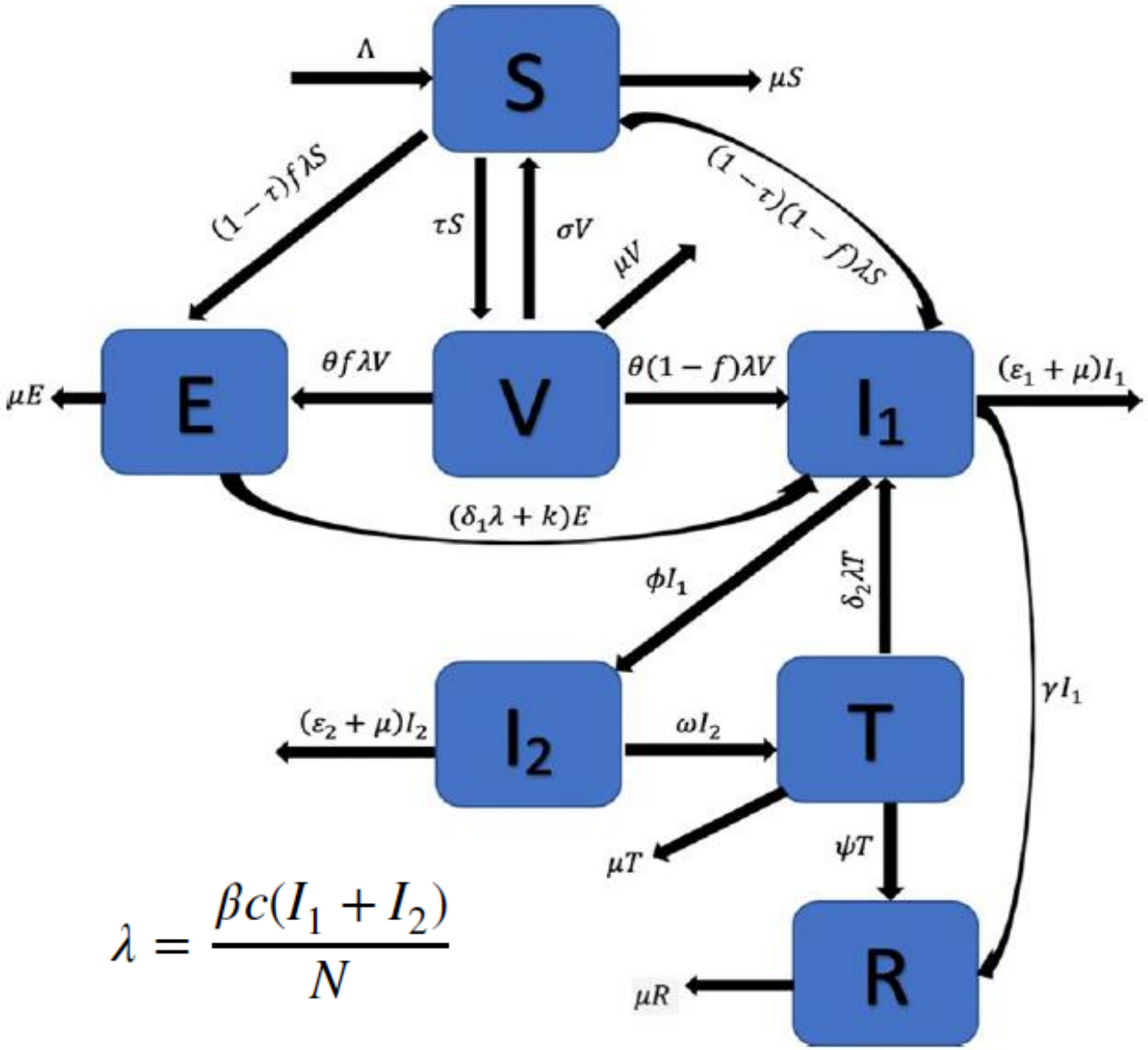
Some Mathematical models for TB transmission dynamics

- Chavez and Feng [27] focused on four models to understand the disease transmission dynamics of TB.
- Röst and Wu [28] proposed a new SEIR model in which the infectivity depends on age.
- Dontwi et al. [29] described the spreading of TB in Amansie West District Ghana by using the standard SEIR model.
- Yali Yang et al. [30] evaluated the cost of control strategies by using an SEIR model.
- Side et al. [31] proposed a SIR and an SEIR models for TB and analysed these models.
- Zhang et al. [32] set up a new mathematical model for TB in China using the data from January 2005 to December 2012.

TB model with vaccination and diagnosis

$$
\begin{aligned}
S' &= \Lambda + \sigma V - [(1-\tau)\lambda + \tau + \mu]S \\
V' &= \tau S - (\theta\lambda + \sigma + \mu)V \\
E' &= (1-\tau)f\lambda S + \theta f\lambda V - (\delta_1\lambda + k + \mu)E \\
I_1' &= (1-\tau)(1-f)\lambda S + \theta(1-f)\lambda V \\
&\quad + (\delta_1\lambda + k)E - (\gamma + \phi + \varepsilon_1 + \mu)I_1 + \delta_2\lambda T \\
I_2' &= \phi I_1 - (\omega + \varepsilon_2 + \mu)I_2 \\
T' &= \omega I_2 - (\delta_2\lambda + \psi + \mu)T \\
R' &= \gamma I_1 + \psi T - \mu R
\end{aligned}
$$

$$N(t) = S(t) + V(t) + E(t) + I_1(t) + I_2(t) + T(t) + R(t)$$



$$\lambda = \frac{\beta c(I_1 + I_2)}{N}$$

E = latently infected humans,
I_1 = undiagnosed infectious human,
I_2 = diagnosed infectious human. [33]

Some Vaccination models for TB transmission dynamics

- Liu et al. [34] proposed a combination of constant vaccination and pulse vaccination.
- Egbetade and Ibrahim [35] incorporate treatment, migration and vaccination.
- Rangkuti et al. [36] explained the spread of TB using VSEIR, V for vaccination
- Egonmwan et al. [37] incorporates vaccination of newborn children and older susceptible individuals into their model.

Some Optimal control models with Cost-effectiveness analysis for TB

- Athithan and Ghosh [38] considered an optimal control model with the case detection of TB infections as control
- Abouelkheir et al. [39] proposed a drug-resistant TB optimal control model.
- Kereyu and Demie [40] incorporated distancing, case finding, and treatment as control efforts.
- [41] studied Optimal control model with time-dependent nonpharmaceutical and latent case-finding controls with pay-off term reflecting the goal set by WHO.

Further research possibility on TB

- It is good to consider treatment relapse due to antibiotic resistance.
- Booster dose of TB vaccination in the age structure model
- Effect of aerosol and contaminated environmental transmissions of TB in Africa, even though the contaminated environment has been considered in China [44].

Malaria

Malaria is a vector borne parasitic disease caused by the *plasmodium species* and transmitted to humans by female anopheles mosquito during blood meal.

Malaria was once common in half of the world populations before it later became eliminated in many regions except the tropics.

Plasmodium specie for malaria: Plasmodium falciparum.

Causes: lethal infections and responsible for ~80% of all malaria cases and ~90% of deaths [42].

The sporozoites disappears into the liver in the body within few minutes to hours when they invade the liver and multiply in number and reproduce.

Symptoms

fever, chills, pain.

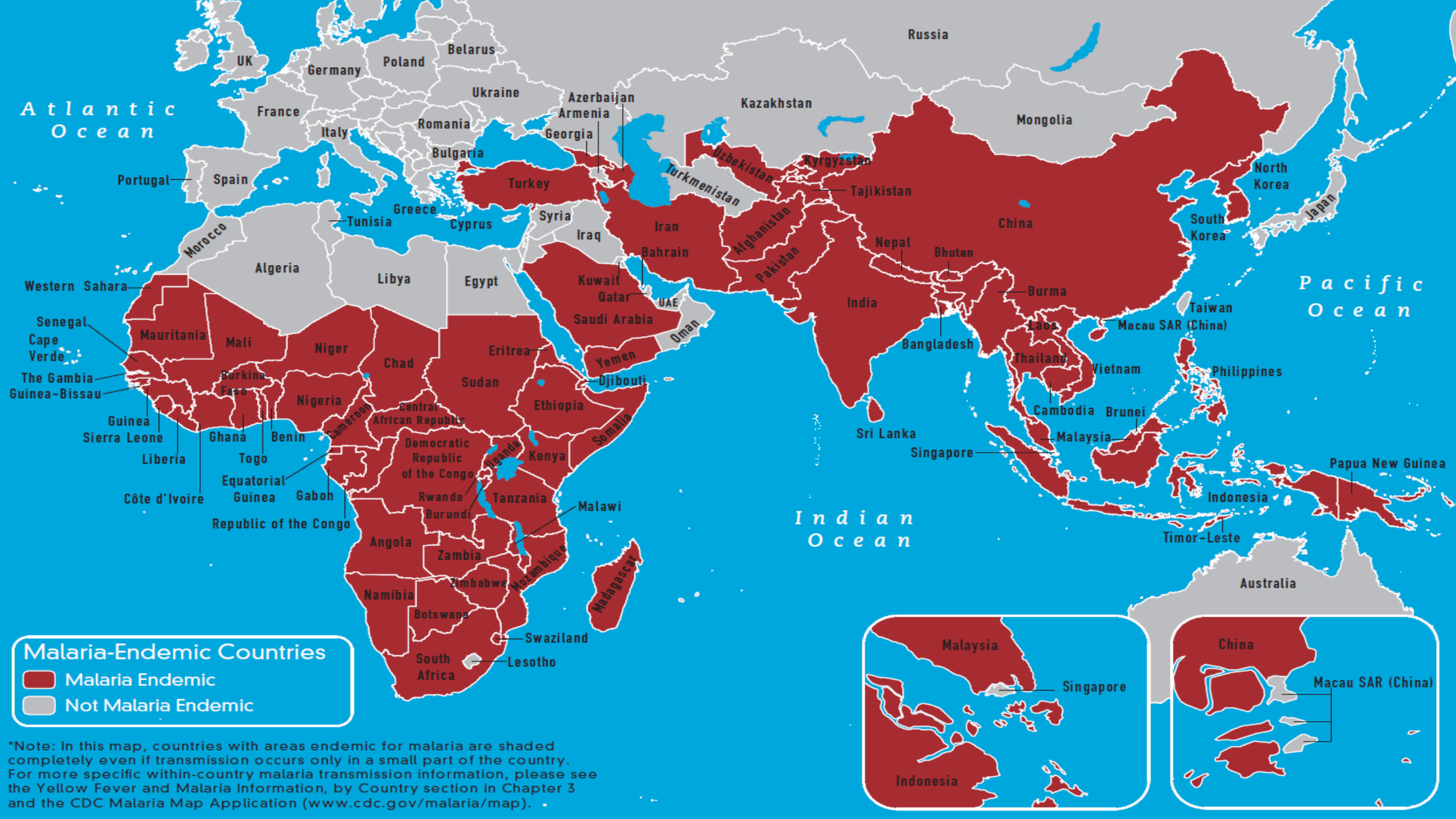
Progress to shock, convulsion, coma and death.

Global burden of Malaria

- From 2000 to 2015, death toll for malaria fell by about 40% from 896,000 in 2000 to 562,000 in 2015.
- There has been stagnation since then. The 2019 COVID pandemic disrupted effort and caused increase in mortality in 2020.
- Malaria killed 558, 000 persons in 2019 alone.

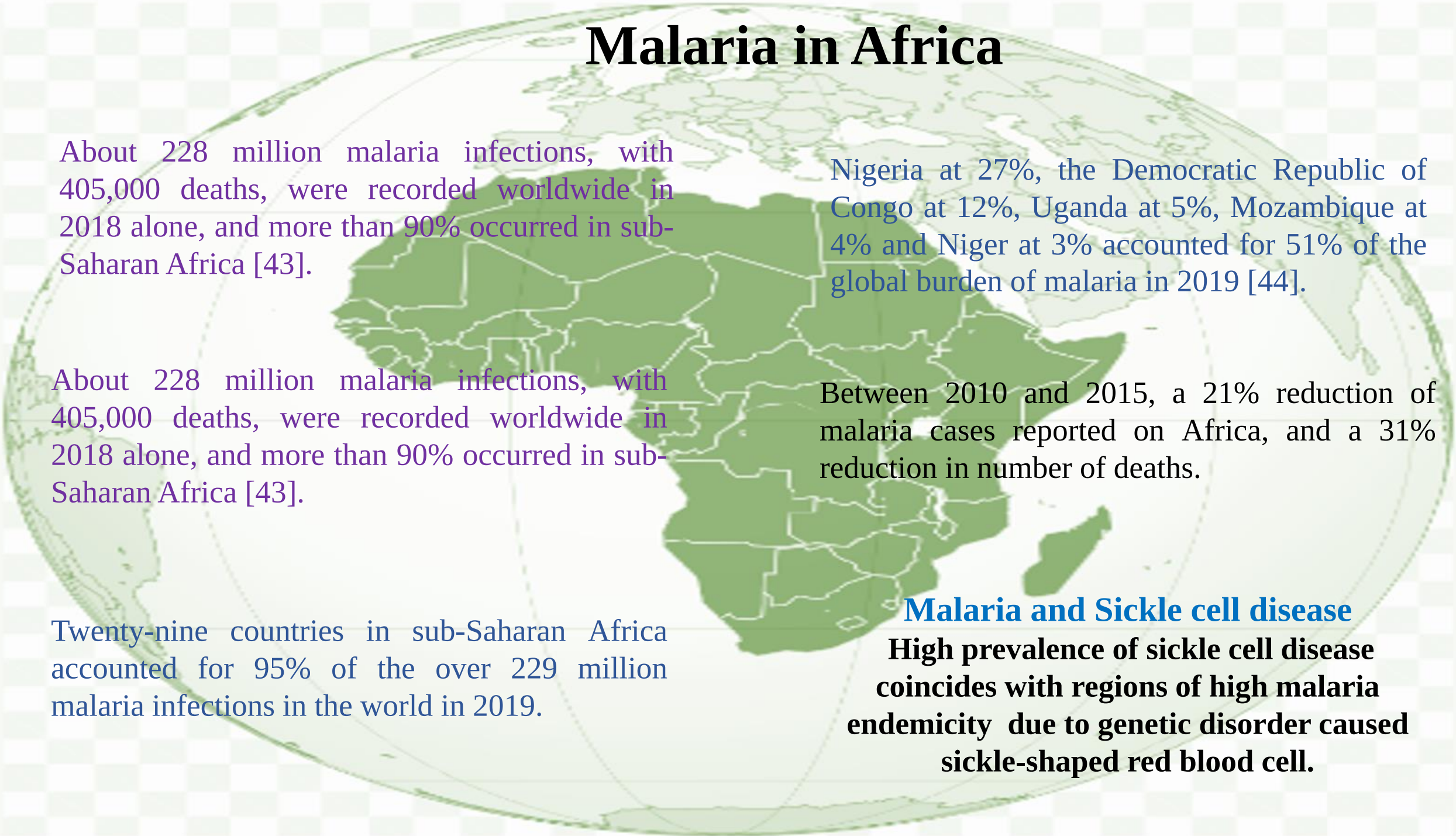
Mortality in children

- It is the leading cause of mortality among children.
- Under five children accounted for about 55% of the death burden due to malaria in 2019.



*Note: In this map, countries with areas endemic for malaria are shaded completely even if transmission occurs only in a small part of the country. For more specific within-country malaria transmission information, please see the Yellow Fever and Malaria Information, by Country section in Chapter 3 and the CDC Malaria Map Application (www.cdc.gov/malaria/map).

Malaria in Africa



About 228 million malaria infections, with 405,000 deaths, were recorded worldwide in 2018 alone, and more than 90% occurred in sub-Saharan Africa [43].

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Twenty-nine countries in sub-Saharan Africa accounted for 95% of the over 229 million malaria infections in the world in 2019.

Nigeria at 27%, the Democratic Republic of Congo at 12%, Uganda at 5%, Mozambique at 4% and Niger at 3% accounted for 51% of the global burden of malaria in 2019 [44].

Between 2010 and 2015, a 21% reduction of malaria cases reported on Africa, and a 31% reduction in number of deaths.

Malaria and Sickle cell disease

High prevalence of sickle cell disease coincides with regions of high malaria endemicity due to genetic disorder caused sickle-shaped red blood cell.

Malaria Interventions

Public health measures

- widespread use of insecticides
- drainage of swamplands for agriculture purposes
- socioeconomic development: effective treatment assessable and improved housing
- Insecticide treated bed nets
- indoor residual spraying

Malaria eradication Focus

- drug and insecticide resistance,
- funding for malaria control (Most important),
- vaccine against malaria
- socioeconomic prosperity.
- the quality of antigen based rapid diagnostic malaria test kits.
- Malnutrition

Intervention to prioritized

- A new malaria vaccine, RTS'R is undergoing stage three clinical trials in some countries mostly in Sub-Saharan Africa.[1]
- It has shown a modest 39% efficacy.
- It has also shown promise with a prediction that in fully immunized children it can avert 484 deaths per 100,000 [42].

Early Mathematical Models of Malaria

First malaria model: Ross model

- Sir Ronald Ross demonstrated the life-cycle of the malaria parasite in mosquito in 1890's [45].
- He later developed a simple model, SIS SI model, now known as the classical "Ross model" [46] in 1911,
- showed that reduction of mosquito numbers "below a certain figure" (Transmission threshold) was sufficient to counter malaria - a concept far ahead of his time.

Macdonald Model

George Macdonald [47] in the 1950s modified Ross model by including latency in the mosquito due to malaria parasite development that implicated the adult female mosquito survivorship.

Result: provided a rationale for massive WHO malaria campaign on use of the insecticide dichlorodiphenyltrichloroethane (DDT) that killed mosquitoes.

Anderson and May Model

Introduce Latency of infection in humans in Macdonald's model [48]

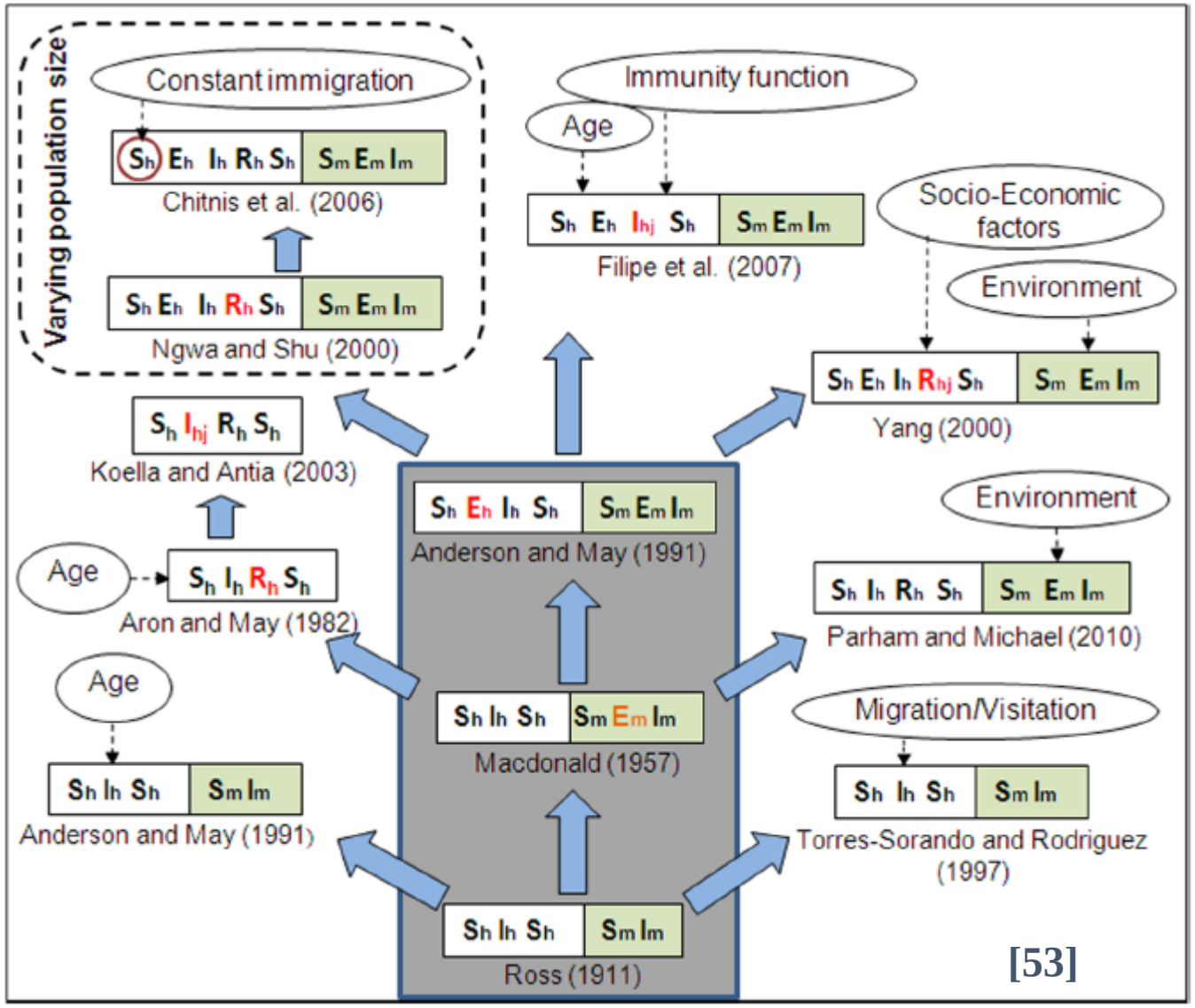
SEIR Extension and Modification of Ross, Macdonald and Anderson and May Models

- effect of age structure of prevalence [48],
- migration and visitation of people [49].
- human immunity, parasite diversity, and resistance[50, 51, 52].

Major advantage of these early models

Provide a suitable control strategy through the Transmission threshold criterion, termed as basic reproductive number, R_0, based on the reproductive capacity of the parasite [53].

SIS, SI, SEIR Extension and Modification of Ross, Macdonald and Anderson and May Models



[53]

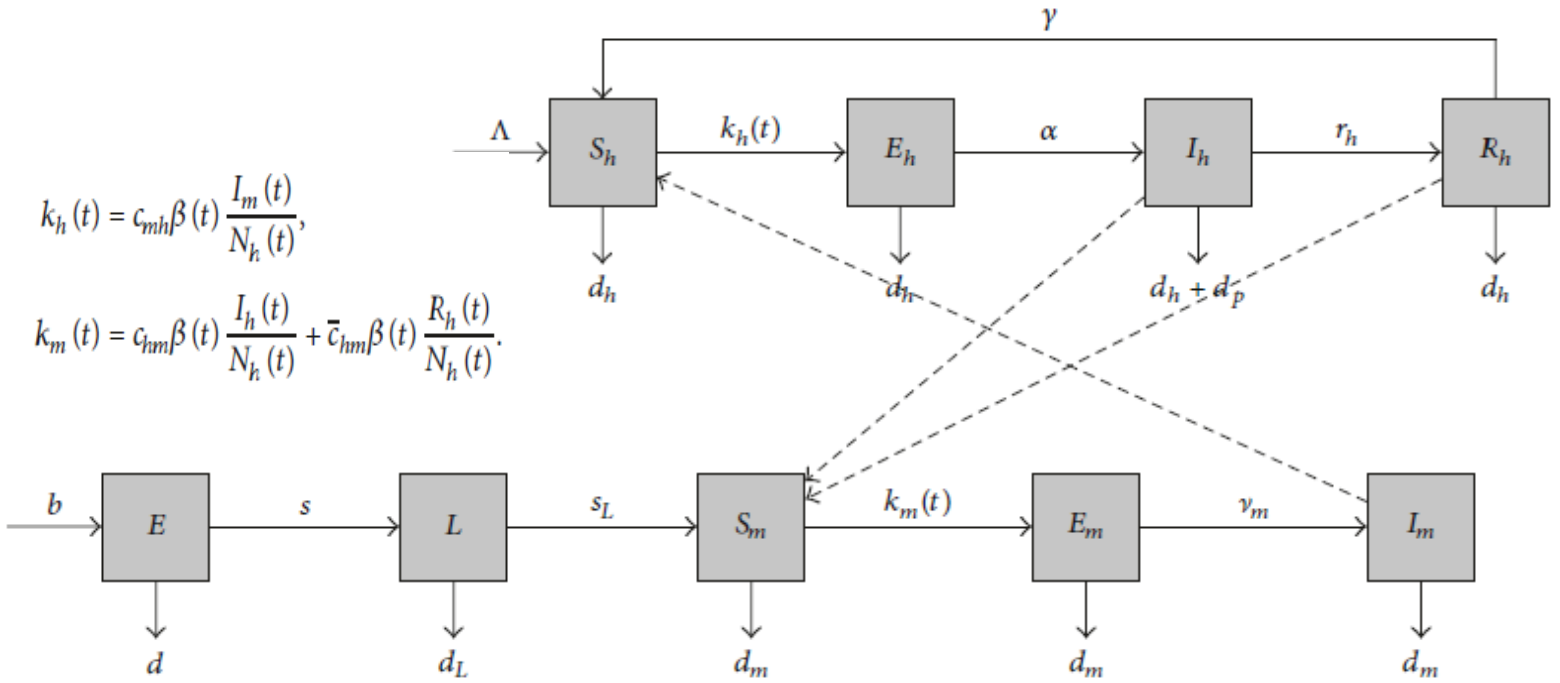
Evolution and grouping of different types of SEIR malaria models.

Subscripts 'h' and 'm' stands for human and mosquito. Double folded boxes are for both human & mosquito population, and single fold boxes are only for human. First time addition of a new compartment is shown in red. The subscript 'j' (= 1, 2, 3) indicates further subdivision of the corresponding compartment. Three models inside the big grey box are considered as the Basic malaria models in this paper. Dotted arrows show the incorporation of complex factors in different models or specific compartment (red circle). Total population size is constant for all models, except the ones inside the dashed box.

Complex Mathematical models for Malaria Disease

- **Age (age and gender in humans [54, 55]) and Immunity (Immune class [56, 57])**
- **Host-pathogen variability and resistant strain models**
  - Variable antigenic response, immune selection, pathogen strain structure [58]
  - Inclusion of evolution of drug resistance [59]
  - resistant-strain models based on evolution of drug resistance through host immunity [60],
  - drug resistance due to environmental, pharmacological and genetic factors [61].
- **Environmental factors**
  - temperature, humidity, rainfall and wind patterns [62,63].
  - periodic or noisy form of the force of infection [64].
  - environmental fluctuations [65]
  - Social and economic factors: malaria and poverty are intimately related
    - fertility, population growth, premature mortality, misdiagnosis: Mostly case studies
  - Migration and visitation [49]
  - Linking the within-host and between-host dynamics of malaria [66, 67]
  - Stochastic models
    - individual variability in individual based models [68,67],
    - probabilistic variation in different variables and parameters of transmission [67,69].
    - spatial contact structure and temporal forcing [70,71].

Age-structured malaria model with seasonality



$$k_h(t) = c_{mh}\beta(t)\frac{I_m(t)}{N_h(t)},$$

$$k_m(t) = c_{hm}\beta(t)\frac{I_h(t)}{N_h(t)} + \bar{c}_{hm}\beta(t)\frac{R_h(t)}{N_h(t)}.$$

$$N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t),$$

$$A(t) = S_m(t) + E_m(t) + I_m(t).$$

Parameter	Description
Λ	Constant recruitment rate for humans
d_h	Human death rate
α	Transmission rate of humans from E_h to I_h
d_p	Disease-induced death rate for humans
r_h	Recovery rate of humans
γ	Per capita rate of loss of immunity for humans
s_L	Transfer rate from L to adult
d_m	Death rate for adult vectors
ν_m	Transmission rate of mosquitoes from E_m to I_m
c_{mh}	Probability of transmission of infection from I_m to S_h
c_{hm}	Probability of transmission of infection from I_h to S_m
$\bar{c}_{hm}$	Probability of transmission of infection from R_h to S_m
K_E	Available breeder sites occupied by eggs
K_L	Available breeder sites occupied by larvae
s	Transfer rate from E to L
b	Eggs laying rate
d	Death rate of eggs
d_L	Larvae death rate

Assumptions

- All vector population measures refer to densities of female mosquitoes,
- The mosquitoes bite only humans,
- There is no vertical transmission of malaria,
- All the new recruits are susceptible.

Age-structured malaria model with seasonality

$$\frac{dE}{dt}(t) = b\left(1 - \frac{E(t)}{K_E}\right)A(t) - (s+d)E(t),$$

$$\frac{dL}{dt}(t) = s\left(1 - \frac{L(t)}{K_L}\right)E(t) - (s_L + d_L)L(t),$$

$$\frac{dS_h}{dt}(t) = \Lambda + \gamma R_h(t) - (d_h + k_h(t))S_h(t),$$

$$\frac{dE_h}{dt}(t) = k_h(t)S_h(t) - (d_h + \alpha)E_h(t),$$

$$\frac{dI_h}{dt}(t) = \alpha E_h(t) - (d_h + d_p + r_h)I_h(t),$$

$$\frac{dR_h}{dt}(t) = r_h I_h(t) - (d_h + \gamma)R_h(t),$$

$$\frac{dS_m}{dt}(t) = s_L L(t) - (d_m + k_m(t))S_m(t),$$

$$\frac{dE_m}{dt}(t) = k_m(t)S_m(t) - (\nu_m + d_m)E_m(t),$$

$$\frac{dI_m}{dt}(t) = \nu_m E_m(t) - d_m I_m(t).$$

Limitations

- The effect of climate change on the life cycle of mosquitoes.
- The larva and pupa class were not distinguished.
- The degree of vulnerability of human populations.

Despite much work on this disease, malaria still has high infection cases in Africa. According to [72], immature mosquitoes have impact on the malaria dynamic. Therefore, it is crucial to study further the life cycle of the anopheles and the climate change effect. Also, vaccination and how many proportions of the population are vaccinated is essential to further research.

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