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JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

Epidemiology and Control of Malaria

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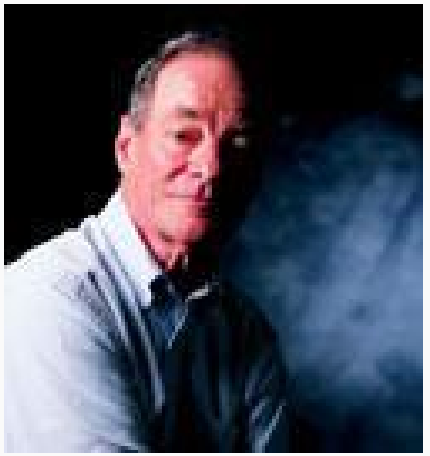

- Fellow of the American College of Physicians and of the American College of Epidemiology
- Expertise in the design and implementation of quality assurance management methods for developing countries; the development of burden of disease measures and their use in health planning and health sector reform; and epidemiological methods for field trials in developing countries
- Extensive work in the establishment of public health programs and in building capacity in public health education in developing countries

Lecture Outline

- Reading
  - Epidemiology and control of Malaria, Chapter 22. In Nelson, Williams, and Graham (Eds.), IDE. Aspen 01.
  - Morrow, R. H., and Moss, W. J. Chapter 26. In Nelson, Williams, and Graham (Eds.), IDE, 2cd. Jones and Bartlett 07.
- Web sites
  - Multilateral Initiative on Malaria, mim.su.se; Roll Back Malaria, rbm.who.int/partnership; CDC/USAID; WHO
- All malaria
  - Africa
  - Everywhere else
- Generic malaria cycle and potential reproductive increase
- Malaria species that infect humans
- Mosquito vectors
  - Behavioral characteristics
  - EIR and VC
- Levels of endemicity
- Public health importance

Lecture Outline

- Pathogenesis in humans
  - Human defense systems
  - Genetic
  - Immune responses
- Clinical patterns
- Malaria in pregnancy
- Epidemiological patterns
- Control strategies: components
  - Vector control
  - Diagnosis
  - Treatment
  - Vaccines
- Control strategies for Africa
- Future directions

Epidemiology and Control of Malaria: Learning Objectives

- Explain why malaria is so much more important in Africa than anywhere else
- Diagram the generic malaria cycle and note potential reproductive increases at each stage of development
- Name the main malaria species that infect humans and outline the distinctive characteristics of each
- Sketch out the main features of the life cycle of a mosquito vector and describe the major behavioral characteristics that influence success as a malaria vector
- Define the entomological inoculation rate (EIR) and vectorial capacity (VC)
- Define the four levels of malaria endemicity and explain the public health consequences of each
- Rate the public health importance of malaria as compared to other diseases

Epidemiology and Control of Malaria: Learning Objectives

- Outline the pathogenesis of *P. falciparum* disease in humans
- Describe the major human defense systems against malaria, including innate, genetic, and acquired immune responses
- Categorize the main clinical patterns of severe malaria disease
- List the important consequences of falciparum malaria in pregnancy
- Compare the epidemiological patterns of *P. falciparum* disease according to intensity of transmission
- Review the main features (including advantages and limitations) of strategies to control *P. falciparum* disease through vector control, through case finding and treatment, and through immunization
- Discuss likely directions for future research toward malaria control

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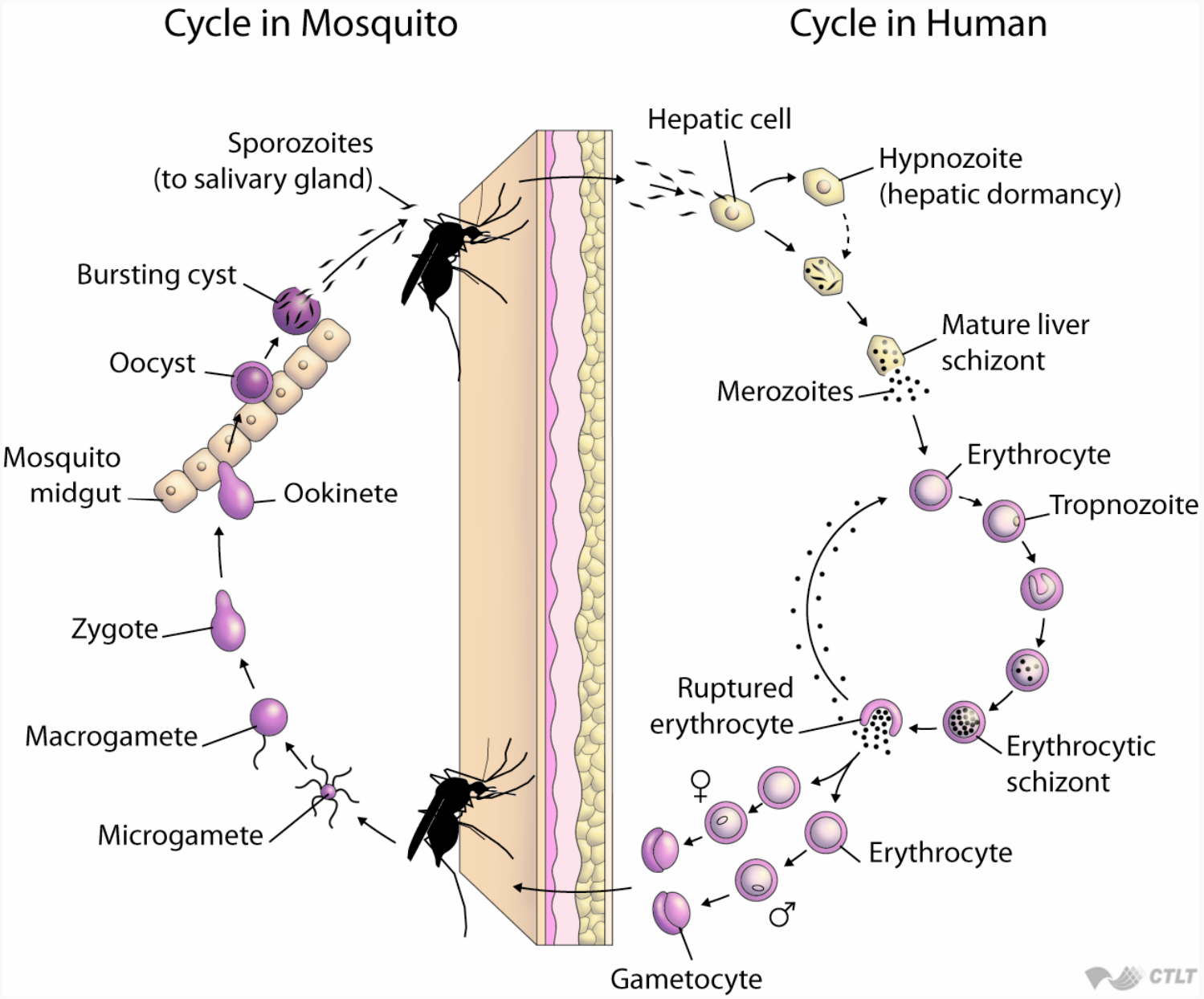
Section A

Malaria: The Parasite, the Vector, and Measures of Transmission

Life Cycle of the Malaria Parasite



Quantitative Aspects of the Cycle

- A single *P. falciparum* merozoite → 10 billion new merozoites
- One pair of gametocytes → 10,000 sporozoites
- One blood meal → dozens of gametocytes → potential for millions of sporozoites per bite
- But, in fact, most bites fewer than 25
  - Five percent more than 100
- Actual infant infection rate—about 20% of sporozoite rate
  - But wide variation—place and season and technique
- Relation to severity of disease

Malaria Parasites of Humans

Species	Intra-RBC schizont period	Type of RBC	Relapse (hypnozyte)	Global distribution
P. vivax	48 hours	Reticulocytes	Yes	Everywhere except sub-Saharan Africa
P. ovale	48 hours	Reticulocytes	Yes	Africa
P. malariae	72 hours	Older RBCs	No	Everywhere
P. falciparum	48 hours	All	No	Tropical regions

Anophelines and Their Life Cycle

- Anopheles genus: hundreds of species, but only 50–60 can transmit malaria
  - *A. stephensi* breeds in tin cans and confined spaces
  - *A. gambiae* prefers small open sunlit pools
- Four stages
  - Egg → larva → pupa → adult
  - 7- to 20-day cycle (depends on species and environment)

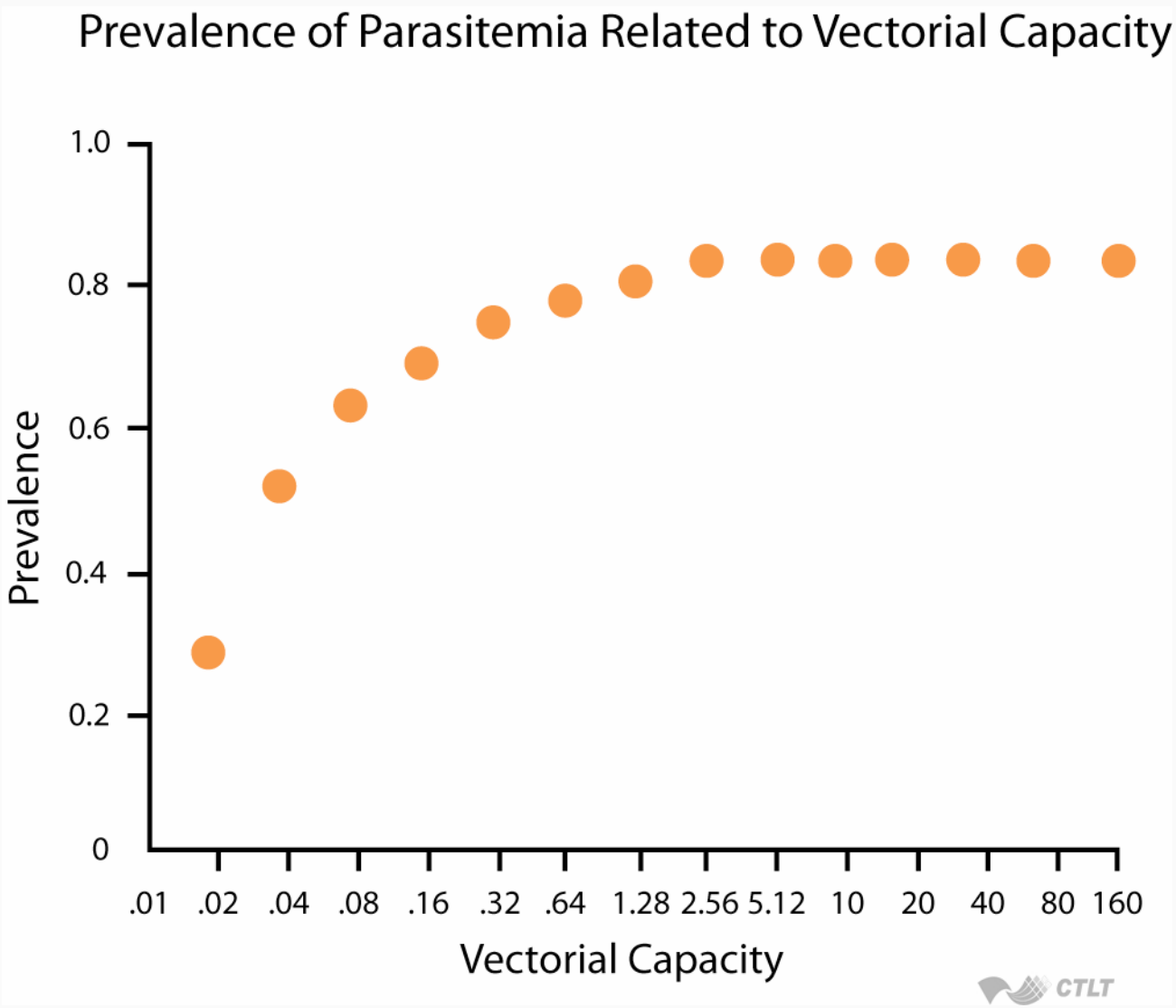
Anophelines and Their Life Cycle

- The female
  - Emergence → mates (once and for all—stores sperm)
  - Blood meal → lays eggs in batch of several dozens
  - 3 to 12 batches in lifetime → total of 200 to 1,000 eggs
  - Each batch requires a blood meal, a rest, and then favored water site for laying
  - Blood meals every 48 hours
- Behavior
  - Host feeding preferences
  - Biting and resting habits
    - Indoor vs. outdoor
    - Time of night—or day
  - Favored water habitat for egg laying
- Sporogonic (extrinsic) cycle of malaria in vector
  - 7 to 10 days → then infectious with each blood meal thereafter

Basic Indices of Malaria Transmission

- Entomologic inoculation rate (EIR) = human landing rate x sporozoite rate
- Vectorial capacity (VC) = ma^2p^n / -logp
  - m = density of vectors
  - a = proportion of blood meals from humans
  - p = daily survival probability
  - n = extrinsic incubation period
  - p^n = fraction of vectors that survive extrinsic cycle
  - 1 / -logp = remaining expectation of life

Prevalence of Parasitemia Related to Vectorial Capacity



Geographical Areas Classified by Intensity of Transmission

- Geographical areas classified by intensity of transmission (based upon percent of children, age 2–9, with enlarged spleens and malaria parasitemia)

1. **Holo-endemic:** intense transmission with continuing high EIRs where everyone is infected with malaria parasites all the time. In older children and adults, parasites difficult to detect because of high levels of immunity, but sufficient search will generally reveal the presence of parasites. *Criteria:* Spleen and parasite rates of over 75%.
2. **Hyper-endemic:** regular, often seasonal transmission to all, but immunity in some does not confer continuing protection at all times. *Criteria:* Spleen and parasite rates from 50–75%.
3. **Meso-endemic:** transmission fairly regularly but at much lower levels. Danger is occasional epidemics involving those with little immunity resulting in fairly high mortality. *Criteria:* Spleen and parasite rates from 10–50%.
4. **Hypo-endemic:** limited malaria transmission and population with little or no immunity. Danger is severe malaria epidemics involving all age groups. *Criteria:* Spleen and parasite rates less than 10%.

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Section B

Human Responses to Malaria Infection and Its Public Health Significance

Human Defense Systems Against Malaria

- Innate
  - Reticuloendothelial system
- Genetic polymorphisms
- Acquired responses
  - Humoral
  - Cellular
  - Cytokine cascades

Human Genetic Polymorphism in Response to Malaria

- Hemoglobin
  - ß globin chain
    - Hemoglobin S (sickle trait and disease)
    - C and E
  - ß and α globin chains
    - ß and α thalasemias (Mediterranean anemia)
- Red blood cell enzyme mutations
  - G-6-PD deficiency
- Red blood cell cytoskeletal abnormalities
  - Ovalocytosis
- Red blood cell membrane mutation
  - Duffy blood group factor

Malaria and Sickle-Cell Trait

- Sickle-cell trait
  - Hemoglobin AS (sickle cell trait) in tropical Africa ranges 16–30% in adults
    - 28% AS
    - 72% AA
  - Hardy-Weinburg Law ($a^2 + 2as + s^2 = 1$)
    - Assume that all born with SS die before adulthood
    - Then gene allele frequency in adult population
      - 14% s
      - 86% a
  - Selection coefficient for AA genotype
    - 0.14 / (1 – 0.14) = 0.1628
  - Ratio of AS genotype to AA genotype individuals in adulthood
    - 1 / (1 – 0.1628) = 1.194
  - Equivalent to a 20% (19.4%) excess death rate of AA before adulthood

Malaria and Sickle-Cell Trait

- Sickle-cell trait (continued)
  - Age-specific rise in sickle-trait rate in West Africa
    - 23.60% AS in newborns
    - 28.96% AS in adults
  - Equivalent to a 24% case fatality rate in AA due to malaria
    - Those with AA = 76.40% of newborn, but only 71.04% of adults
    - If no deaths in AS, then 0.2896 = (236) / (236 + AA)
    - AA = 579 instead of 764 at birth, thus (764 – 579) / 764 = 24.3% deaths among those born with AA—which would be due to malaria since no other cause differentially affects AA as compared to AS

Malaria and Public Health Importance

- Public health significance of a disease = incidence and consequent disability and death
  - In low-transmission areas this is a useful formulation
  - In high-transmission holo-endemic Africa, however, everyone is infected all the time and neither incidence nor prevalence has much meaning
- Every year for 50 years WHO reported “1 to 2 million children died from malaria”
  - Recently “refined”—from 800,000 to 3 million
- In most child deaths in Africa, malaria is a contributing factor even though death may be attributed to other causes
- In Ghana, malaria—the leading cause of loss of healthy life years (HeaLYs or DALYs)—accounts for nearly 10% of total loss

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Section C

Clinical and Epidemiological Aspects of Severe Malaria

Clinical and Epidemiological Aspects of Severe Malaria (1)

- Severe disease vs. non-severe disease in high-transmission areas
  - The first cut
- Severe in under-fives in holo-endemic areas
  - Major syndromes
    - Severe anemia
    - Neurological diseases, including cerebral malaria
    - Respiratory distress
  - Contributing factors
    - Hypoglycemia
    - Metabolic acidosis
  - Rapid progression to death, 18 to 72 hours

Prevalence of WHO Criteria for Severe Malaria in Kilifi

- Prevalence of WHO criteria for severe malaria in 1,844 consecutive malaria admissions in Kilifi, Kenya

Defining criteria	No. of children evaluated	Prevalence (%)	Mortality (%)
Un-arousable coma	1,844	10.0	16.8
Severe malaria anemia	1,816	17.6	4.7
Respiratory distress	1,833	13.7	13.9
Hypoglycemia	698	13.2	21.7
Circulatory collapse	1,844	0.4	71.4
Repeated convulsions	1,842	18.3	6.8
Acidosis	110	63.6	21.4
Impaired consciousness	1,844	8.2	6.0
Jaundice	1,806	4.7	11.9
Prostrated	1,571	12.2	5.2
Hyperpyrexia	1,842	0.6	1.6
Hyperparasitemia	110	8.9	4.3

Clinical and Epidemiological Aspects of Severe Malaria (2)

- Epidemiological features of severe malaria
  - Severe malaria vs. non-severe
    - As intensity of transmission increases
      - Proportion of asymptomatic malaria shifts to younger ages
      - Proportion of severe disease shifts to younger ages
  - In a given area, the pattern of severe malaria varies with age
    - Severe anemia predominates in the youngest ages, 15–24 months
    - Coma is more common in the older ages, 36–48 months
  - Between areas with differing intensity of transmission
    - Age distribution of severe malaria shifts downward with increased intensity
    - Relative proportion of severe anemia to coma increases with increased intensity
  - For a given annual EIR, areas with a relative constancy of transmission have a higher proportion of severe anemia in those who have severe disease, whereas areas with intense seasonal transmission have a higher proportion with coma

Malaria in Pregnancy

1. Effects of pregnancy on the immune system
    i. Placenta
    ii. Parity
2. Special risks to the mother from malaria
    i. Severe anemia
    ii. Death
3. Special risks to the fetus
    i. Prematurity
    ii. Low birth weight
    iii. Still birth
    iv. Issue of first trimester effect
4. Special risks to the infant after live birth
5. Prevention treatment
    i. Antenatal therapeutic anti-malarials every month
    ii. Insecticide-treated nets (ITNs)

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Section D

Control of Malaria: Vectors, Drugs, and Vaccines

Drugs and Their Uses

- Treatment and prophylaxis
  - Quinine, quinidine
  - Chloroquine, amodiaquine, and relatives
  - Pyrimethamine and combinations
  - Proquanil and chlorproguanil
  - Mefloquine
  - Halofantrine
  - Artemisinin and derivatives (qinghaosu)
  - Antibiotics—tetracycline, clindamycin, rifampicin
- “Causal” prophylaxis
  - Primaquine
- Combination chemotherapy, e.g., artemisinin plus X
  - Now essential despite increase in adverse reactions and cost

Vaccines and Their Uses

- Directed against
  - Sporozoites (plus)
  - Asexual forms (Patarroyo)
  - Gametocytes (plus) “transmission-blocking”

Control Strategies for Malaria in Africa: A Holistic Approach

- What can be done now
  - General infrastructure/improved management and coverage
  - Community and household empowerment
  - Role of vector control with an EIR < 100
    - Environmental improvements to reduce breeding
    - Residual insecticide household (role for DDT)
    - Bed-nets impregnated
    - Personal protection
  - Role of vector control with an EIR > 100
    - Bed-nets impregnated
    - Personal protection
  - Household use of anti-malarials for under-fives by mothers
  - Intermittent preventive therapy
    - For pregnant women
    - For under-fives
  - Monitoring for anti-malarial resistance everywhere
  - Improved immunization coverage, especially in remote areas in anticipation of effective vaccines

Control Strategies for Malaria in Africa: A Holistic Approach

- New tools
  - Vaccine development, especially asexual phase, but perhaps sporozoite with new developments
  - Drug development and acceleration of those in the pipeline
  - Understanding of the molecular biology of the parasite
  - Understanding of the sporogonic cycle to aid in re-engineering of the anopheline
  - Improved entomological field methods for better understanding of micro-epidemiological variation
  - Understanding mechanism of drug resistance and factors that contribute to its spread
  - Better diagnostic tests that rapidly and inexpensively indicate drug resistance