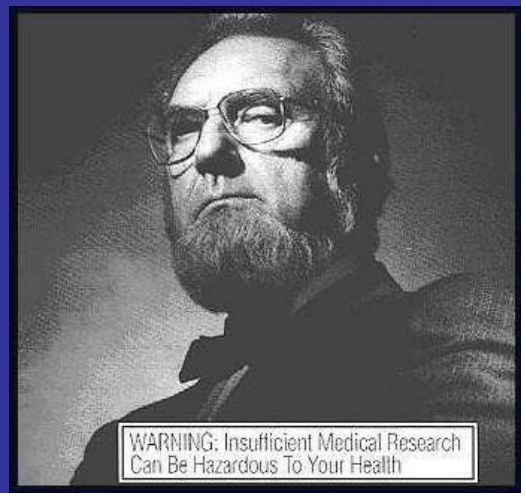
BIOE 301

Lecture Twenty-Three



Future of Bioengineering in World Health

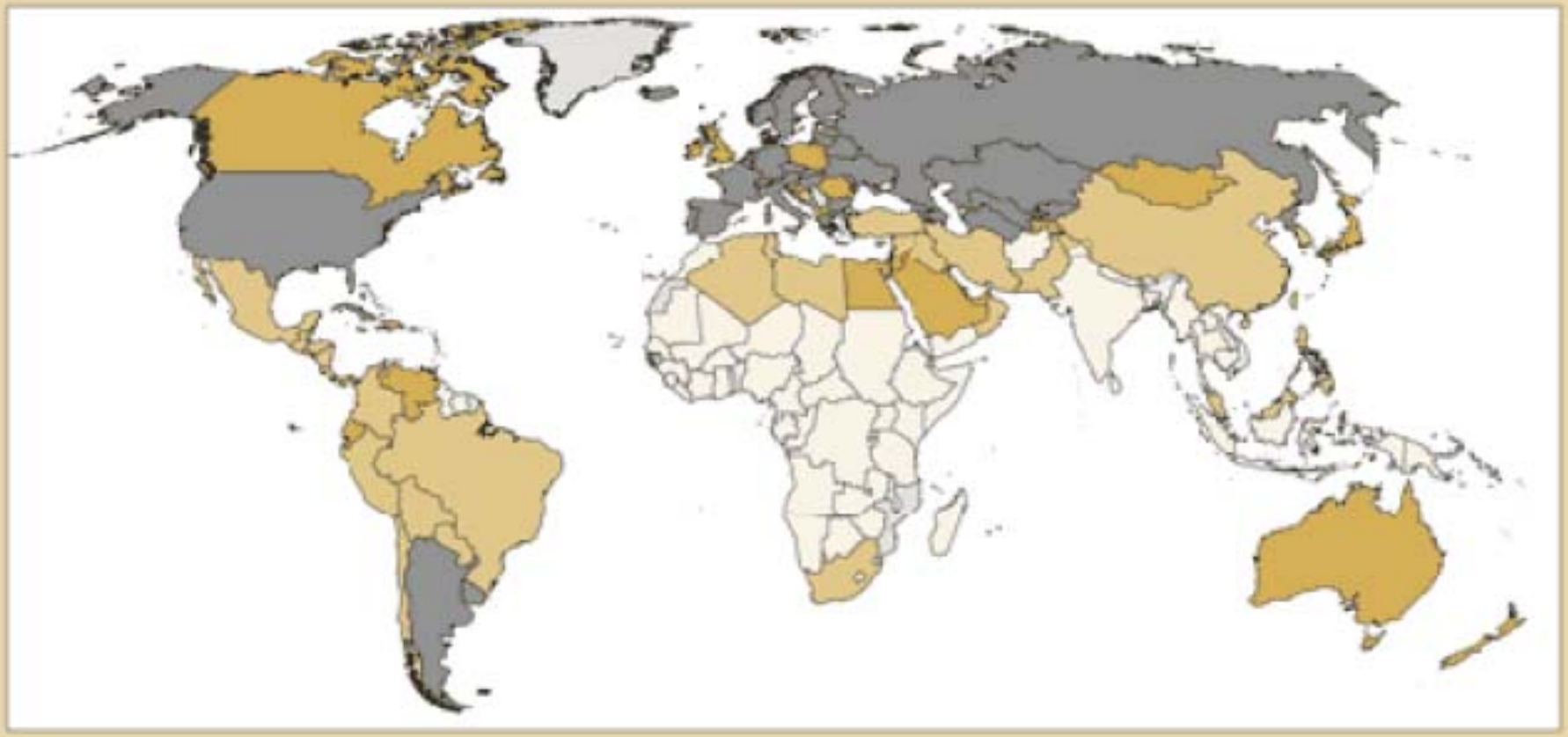
MULTIDISCIPLINARY!!!!!!!!

Map 6

Physicians per 1,000 people

Most recent available year

Source: World Bank 2004d.



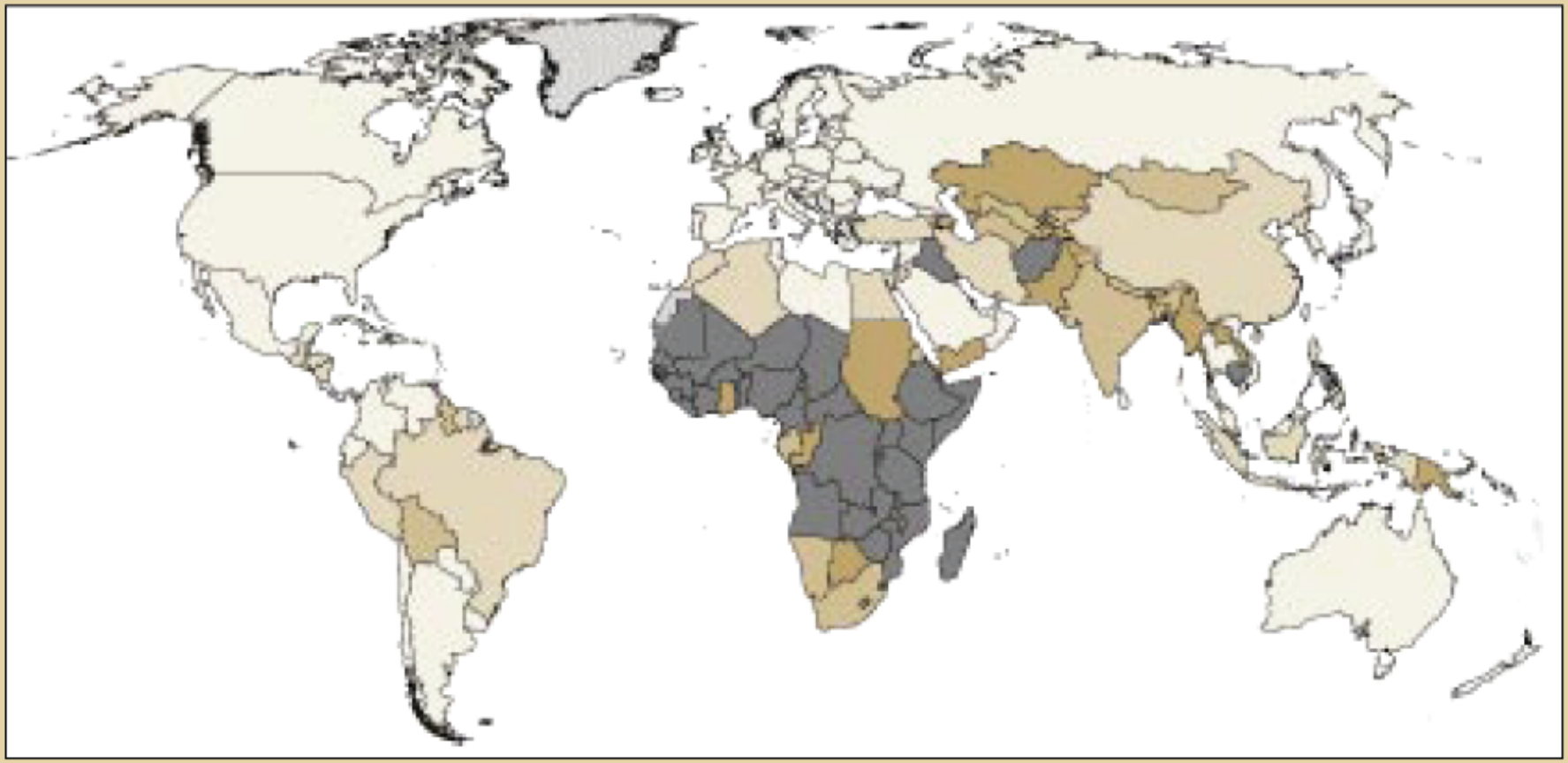
http://www.unmillenniumproject.org/reports/index.htm

Map 1

Child mortality rate, 2002

Under-five mortality rate (per 1,000 live births)

Source: World Bank 2004d.



☐ Less than 30 ☐ 30–60 ☐ 60–90 ☐ 90–120 ☐ More than 120 ☐ No data

http://www.unmillenniumproject.org/reports/index.htm

Map 7

Antiretroviral drug coverage

Share of HIV-infected individuals in need of treatment who have access to antiretroviral drugs (%), 2003

Source: USAID and others 2004.

http://www.unmillenniumproject.org/reports/index.htm

Millenium Development Project

- Task Force on Hunger
  Halving hunger: it can be done
- Task Force on Education and Gender Equality
  Toward universal primary education: investments, incentives, and institutions
- Task Force on Education and Gender Equality
  Taking action: achieving gender equality and empowering women
- **Task Force on Child Health and Maternal Health**
  Who's got the power? Transforming health systems for women and children
- **Task Force on HIV/AIDS, Malaria, TB, and Access to Essential Medicines, Working Group on HIV/AIDS**
  Combating AIDS in the developing world
- **Task Force on HIV/AIDS, Malaria, TB, and Access to Essential Medicines, Working Group on Malaria**
  Coming to grips with malaria in the new millennium
- **Task Force on HIV/AIDS, Malaria, TB, and Access to Essential Medicines, Working Group on TB**
  Investing in strategies to reverse the global incidence of TB
- **Task Force on HIV/AIDS, Malaria, TB, and Access to Essential Medicines, Working Group on Access to Essential Medicines**
  Prescription for healthy development: increasing access to medicines
- Task Force on Environmental Sustainability
  Environment and human well-being: a practical strategy
- Task Force on Water and Sanitation
  Health, dignity, and development: what will it take?
- Task Force on Improving the Lives of Slum Dwellers
  A home in the city
- Task Force on Trade
  Trade for development
- **Task Force on Science, Technology, and Innovation**
  Innovation: applying knowledge in development

http://www.unmillenniumproject.org/reports/index.htm

Investment and Policy Clusters

- ***Health systems: ensuring universal access to essential services***
  - Best provided through an integrated district health system centered on primary care and first-level referral hospitals
  - Practical investments and policies for a functioning health system include
    - training and retaining competent, motivated health workers
    - strengthening management systems
    - providing adequate supplies of essential drugs
    - building clinics and laboratory facilities
- ***Science, technology, and innovation: building national capacities***
  - Creating science advisory bodies to the national government
  - Expanding science and engineering faculties in universities and polytechnics
  - Strengthening development and entrepreneurial focus in science and technology curricula
  - Promoting business opportunities in science and technology
  - Promoting infrastructure development as a technology learning process

http://www.unmillenniumproject.org/reports/index.htm

What Role is Bioengineering Playing?

- Biotechnology has emerged as one of the methods to address health and other challenges in developing world
  - Molecular diagnostics
  - Recombinant vaccines
  - Vaccine and drug delivery
  - Bioremediation
  - Bioinformatics
  - Nutritionally enriched genetically modified crops

Lancet 2005; 365: 1105-07.

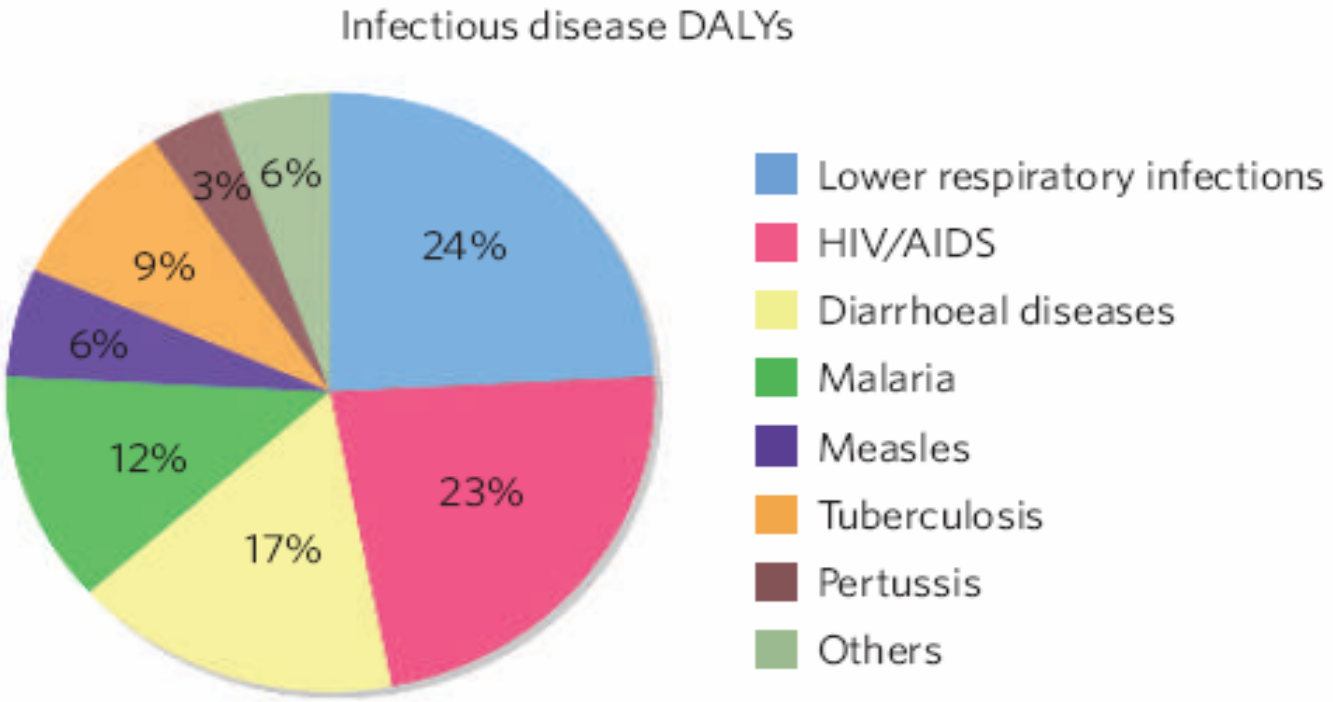


Figure 1 | Disability-adjusted life years (DALYs) for infectious and parasitic diseases. To properly reflect the full impact of a disease, disease burdens can be measured in DALYs by adding the years of life lost by a person's premature death to the time lived with a disability. Infectious and parasitic diseases accounted for almost 30% of all DALYs and 15 million deaths each year worldwide. Shown are the infectious and parasitic diseases responsible for the DALYs in 2005 (figures from the US Centers for Disease Control and Prevention).

Nature 7101 (442), 27 July 2006 p 329-484

Need for Innovative Diagnostic Platforms for these Diseases

- Initial funding by Bill and Melinda Gates Foundation
- 4 common central laboratory techniques
  - Blood chemistry
  - Immunoassays
  - Nucleic-acid amplification
  - Flow cytometry
- However, central laboratory model not applicable to the developing world!

Nature 7101 (442), 27 July 2006 p 329-484

Benefits of POC Diagnostics

- Access to diagnostic tools previously unavailable
- Faster and more accurate
- Better epidemiological data for disease modeling
- Define economics of a healthcare system
- Better utilization of minimally trained personnel
- Better use of existing therapeutics

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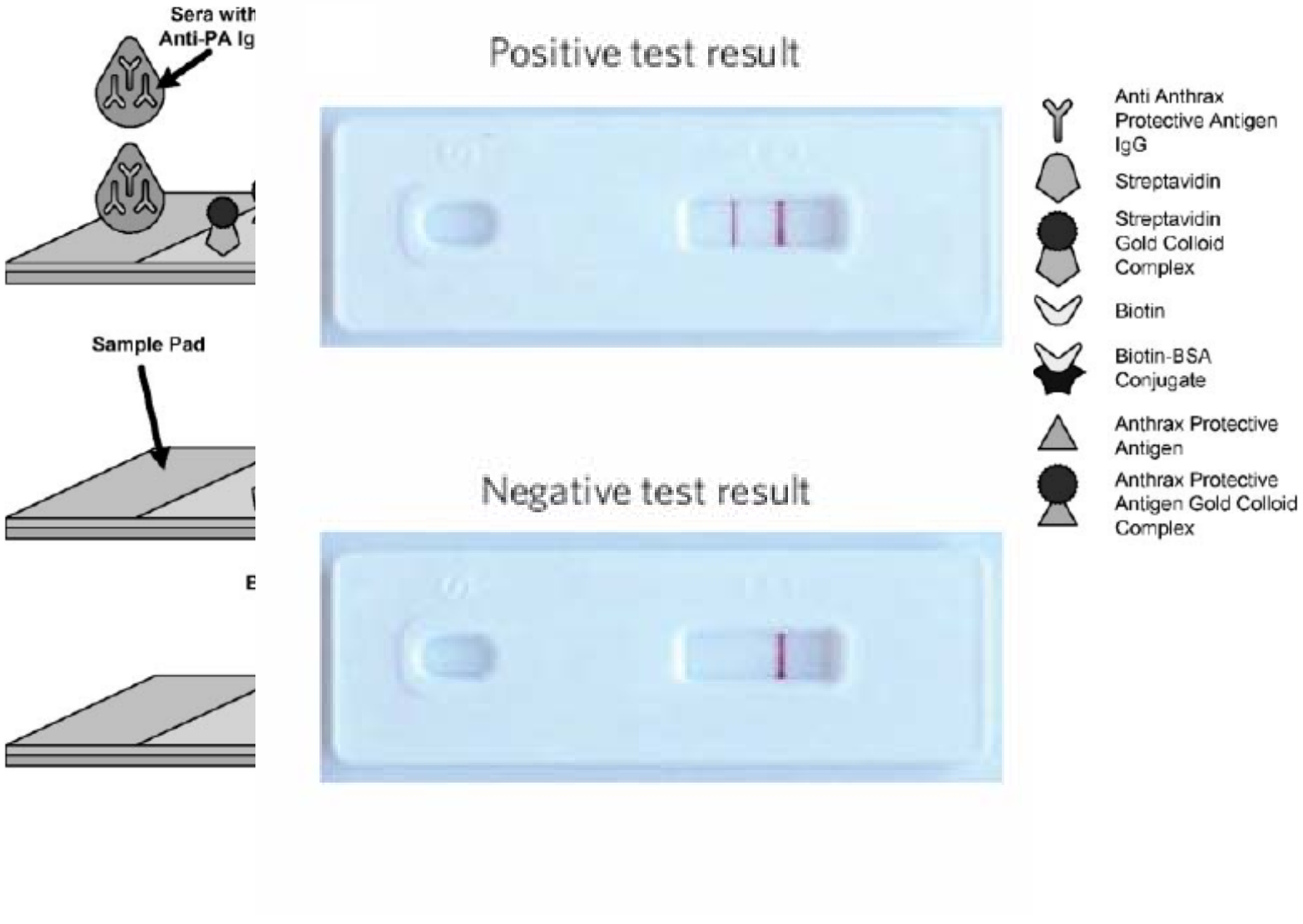
Lateral Flow or Immunochromatographic Strip



Clin. Vaccine Immunol. Biagini et al. 13 (5): 541

Some ICS Available Tests

- Diphtheria
- STI's
  - Gonorrhea
  - Syphilis
  - Chancroid
  - Chlamydia
- Vitamin A deficiency
- *P. Falciparum* malaria
- HIV
- Hepatitis B
- Pregnancy
- Fecal leukocytes
- Proteinuria

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Microfluidic Diagnostics

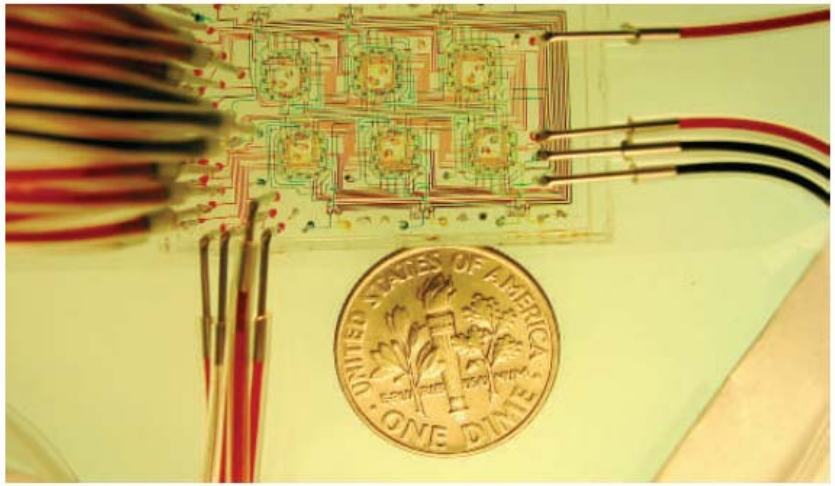

Figure 1 | A microfluidic chemostat. Microfluidic devices — here, a microfluidic chemostat used to study the growth of microbial populations — now routinely incorporate intricate plumbing. This device includes a high density of pneumatic valves. The colours are dyes introduced to trace the channels. (Image reproduced, with permission, from ref. 65.)

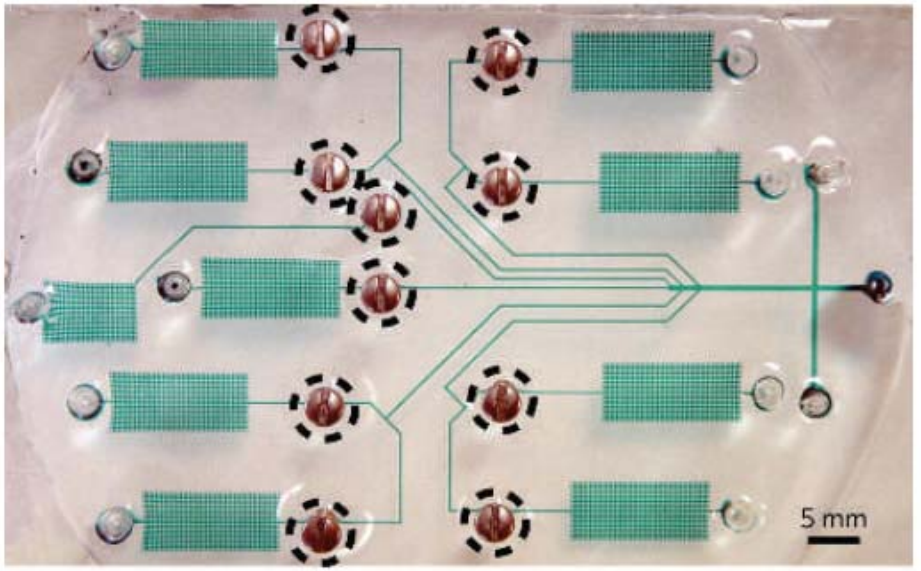

Figure 5 | A simple, inexpensive microfluidic diagnostic device. Components of microfluidic devices can be designed to be inexpensive and easy to operate. This device[7] performs sandwich immunoassays — tests that are used widely in medicine and biological research. The screws in this system (marked with dashed circles) act as simple, manually operated valves. Green-dyed water marks the channels. Low-cost, portable, easy-to-operate microfluidic devices such as this one may find applications in resource-poor environments. (Image adapted, with permission, from ref. 7.)

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Discuss the article you read, *Application of Microchip Assay System for the Measurement of C-reactive Protein in Human Saliva*, Lab Chip. 2005, 5, 261-269.

- What is the biggest advantage of this platform for the developing world?
- What was the most convincing piece of data presented for the ETC platform?

DALYs Saved with New Diagnostics

Table 1 | Potential impact of improved access to diagnostics

Infectious disease area	Clinical decision points	Potential DALYs or lives saved per year
ALRI	Identification of children aged <5 years with bacterial ALRI among those presenting with ARI for antibiotic treatment or in severe cases for hospitalization	A new diagnostic test for bacterial ALRI with at least 95% sensitivity and 85% specificity accompanied by greater treatment access and minimal laboratory infrastructure requirements could save ≥405,000 adjusted lives. A new diagnostic for severe ALRI would also bring significant benefit provided access to effective hospital care is increased globally.
HIV/AIDS	Identification of HIV infection in infants aged <12 months	A test with 90% sensitivity, 90% specificity and minimal laboratory infrastructure requirements could save ~ 180,000 DALYs if 5% of the targeted population has access to ART, and ~2.5 million DALYs could be saved if 100% of the population has access to ART.
Diarrhoeal diseases	The detection of *G. lamblia, C. parvum* and enteroaggregative *E. coli* to reduce diarrhoea-related stunting in children	A test with 90% sensitivity, 90% specificity and minimal laboratory infrastructure requirements for each of the pathogens *G. lamblia, C. parvum* and enteroaggregative *E. coli* could reduce the prevalence of stunting by 12.5% and save 2.8 million DALYs. This result assumes that the cost of treatment is US$6 and the positive externalities associated with treatment are equal to 0.25 DALYs.
Malaria	Diagnosis in febrile children aged <5 years in sub-Saharan Africa	A test with 95% sensitivity, 95% specificity and minimal laboratory infrastructure requirements could save ~1.8 million adjusted lives and prevent 396 million unnecessary treatments per year. A new test with no infrastructure requirements and 90% sensitivity and specificity would save ~2.2 million adjusted lives and prevent ~447 million unnecessary treatments per year.
TB	Diagnosis of active infections in symptomatic individuals, with or without concomitant HIV infection	A rapid diagnostic requiring no laboratory infrastructure, with at least 85% sensitivity for smear-positive and smear-negative cases, and 97% specificity, could save ~400,000 lives annually.
Sexually transmitted infections	Syphilis screening of antenatal women	A new diagnostic test that is at least 86% sensitive, 72% specific, requires minimal laboratory infrastructure and has either a 100% rate of return for test results or a 100% treatment rate could save ≥138,000 adjusted lives and avert >148,000 stillbirths. A similar test requiring no laboratory infrastructure could save >201,000 adjusted lives and avert 215,000 stillbirths.
Sexually transmitted infections	Gonorrhoea and chlamydia screening and diagnosis in female CSWs	A new diagnostic with 85% sensitivity and 90% specificity for both gonorrhoea and chlamydia that requires minimal laboratory infrastructure could save ~3 million DALYs, avert >12 million incident gonorrhoea and chlamydia infections, and prevent >161,000 HIV infections among female CSWs in sub-Saharan Africa, China and southeast Asia. A test that requires no laboratory infrastructure could save ~4 million DALYs, avert >16.5 million incident gonorrhoea and chlamydia infections, and prevent >212,000 HIV infections.

AIDS, acquired immunodeficiency syndrome; ALRI, acute lower respiratory infection; ARI, acute respiratory infection; ART, anti-retroviral therapy; *C. parvum, Cryptosporidium parvum*; CSWs, commercial sex workers; DALYs, disability-adjusted life years; *E. coli, Escherichia coli; G. lamblia, Giardia lamblia*; HIV, human immunodeficiency virus; TB, tuberculosis.

Nature S1, 23 November 2006

Requirements of New Diagnostic Techniques

Table 3 | User requirements for infectious disease tests at sites with minimal and no laboratory infrastructure

Clinical decisions	Infrastructure level*	Possible sample types	Biomarker possibilities	Sensitivity/specificity	Time requirement
Diagnosis of bacterial ALRI in children, to initiate antibiotic therapy	No laboratory infrastructure	Blood (finger prick), urine, saliva, breath	Bacterial antigens, host factors (for example, possibly TREM-1), possibly volatile organics in breath	>95%/85%	<1 h
Diagnosis of severe ALRI requiring hospitalization	No laboratory infrastructure	None (for example, pulse oximetry), blood (finger prick), urine, breath	SaO_2, blood chemistry (for example, pH, CO_2); metabolites from breath	>85%/>90%; at least 50% of the population must have access to hospital care	
Detection of HIV infection in infants aged <12 months	Minimal infrastructure	Blood (heel stick, fresh or dried on filter paper), saliva	HIV RNA, HIV antigens (for example, p24), host factors	>90%/>90%	<1 h†
Diarrhoeal symptoms and detection of *G. lamblia*, *C. parvum*, and enteroaggregative *E. coli*	Minimal infrastructure	Faeces, vapours	Organism antigens, host factors, adhesion assays (*E. coli*), volatile organics	>90%/>90%	<1 h
Diagnosis of malaria in febrile children aged <5 years in sub-Saharan Africa	Minimal infrastructure	Blood (finger prick) urine, saliva	Parasite antigens (for example, HRP2); new antigens	95%/95% minimum down to at least 500 parasites per ml	<5 min
	No laboratory infrastructure	Blood (finger prick), urine, saliva	Parasite antigens (for example, HRP2); new antigens	90%/90% minimum down to at least 500 parasites per ml	< 5 min
Case detection of active TB in symptomatic HIV positive and negative individuals	Minimal infrastructure (for example, TB clinic)	Sputum (adults), blood (venipuncture), urine	Nucleic acids; bacterial antigens (many examples, but not well studied); metabolites in breath	85%/97% for smear negative/positive	<1 h
	No laboratory infrastructure	Sputum (adults), blood (finger prick), urine	Nucleic acids; bacterial antigens	>85%/97% for smear negative/positive	<1 h
Syphilis screening in antenatal women	Minimal infrastructure	Blood (finger prick), saliva, urine	Cardiolipin in RPR (currently used); marker that correlates with transmission to infant would be ideal	86%/72% (RPR)	<1 h
	No laboratory infrastructure	Blood (finger prick), saliva, urine		Same or better than RPR	<1 h
Chlamydia and gonorrhoea diagnosis in female CSWs	Minimal infrastructure	Urine or vaginal swab	Bacterial antigens (for example, MOMP for *C. trachomatis*; ribosomal protein for *N. gonorrhoeae*); nucleic acids	85%/90%	<1 h
	No laboratory infrastructure				
	No laboratory infrastructure	Blood (finger prick), urine, breath			<1 h

*Data from Table 2. †In some of the papers in this series, <2 h is proposed. Here, we recommend the more aggressive goal of <1 h as a stronger safeguard against patients leaving the site of testing prior to a treatment decision. ALRI, acute lower respiratory infection; CO_2, carbon dioxide; CSWs, commercial sex workers; *C. parvum, Cryptosporidium parvum; C. trachomatis, Chlamydia trachomatis; E. coli, Escherichia coli; G. lamblia, Giardia lamblia*; HIV, human immunodeficiency virus; HRP2, histidine-rich protein 2; MOMP, major outer membrane protein; *N. gonorrhoae, Neisseria gonorrhoae*; RPR, rapid plasma reagin; SaO_2, oxygen saturation; TB, tuberculosis; TREM-1, triggering receptor expressed on myeloid cells-1.

Nature S1, 23 November 2006

Lastly, but Certainly not Least…

- Don’t forget the larger issues
  - Social
  - Economic
  - Political
  - Ethical

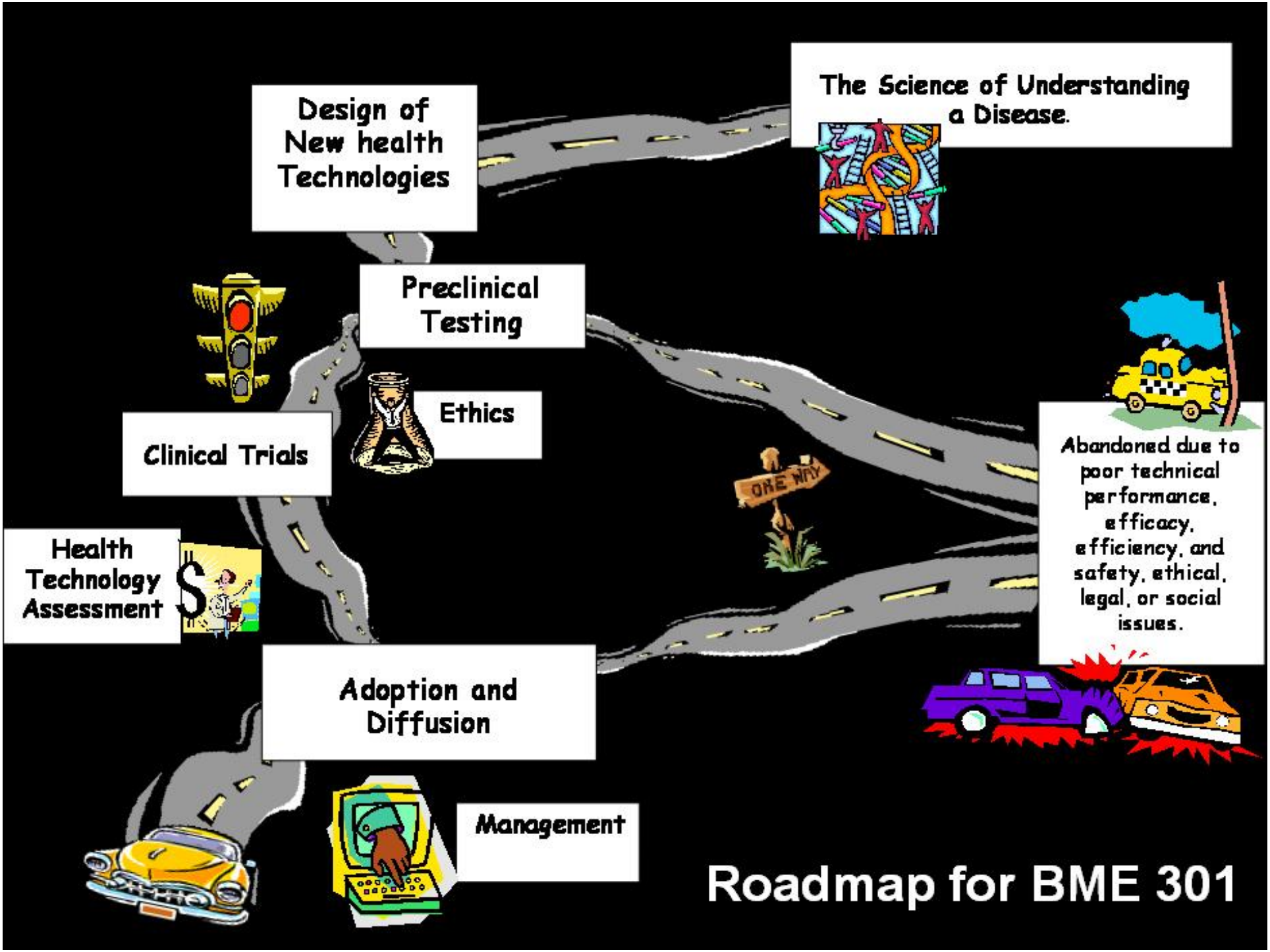
For More Detailed Discussion

- 

  http://www.unmillenniumproject.org/reports/index.htm

- *Nature* 7101 (442), 27 July 2006 p 329-484

- *Nature* S1, 23 November 2006


Design of New health Technologies
The Science of Understanding a Disease.
Preclinical Testing
Ethics
Clinical Trials
ONE WAY
Health Technology Assessment
Abandoned due to poor technical performance, efficacy, efficiency, and safety, ethical, legal, or social issues.
Adoption and Diffusion
Management
Roadmap for BME 301

Exam Review

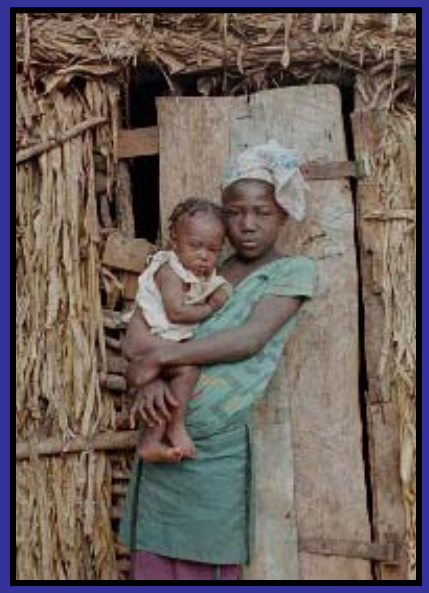
For the Developing world, order the following problems from the greatest to least cause of mortality in the age range 0-4 yrs.

- Malaria
- Perinatal conditions
- Diarrheal diseases
- Lower respiratory infections

Leading causes of mortality: ages 0-4

- Developing world
  1. Perinatal conditions
  2. Lower respiratory infections
  3. Diarrheal diseases
  4. Malaria
- Developed world
  1. Perinatal conditions
  2. Congenital anomalies
  3. Lower respiratory infections
  4. Unintentional injuries

What are the major health problems worldwide?



Back in January, you heard the story of a young woman from rural Haiti who died from AIDS-related opportunistic infections.

She was at-risk for dying from AIDS long before she met the man who gave her the virus. In other words, she was a victim of "structural violence."

Define structural violence, and list its components.

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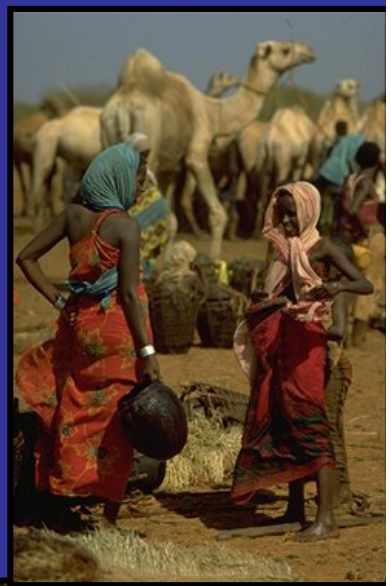
Structural Violence

- Non-physical violence imposed by the powerful upon the weak, which *structures* the victim's living situation such that his/her choices in life are limited.
  - Poverty
  - Gender
  - Education
  - Racism
  - And many others...



Lecture 5 & 6 Review

- In which health system does the market have the least influence? Welfare
- Which health system is most associated with low income developing nations?

  None- health systems reflect cultural, political & economic values
- Developed vs developing world: which has the highest % out of pocket expenses?

  Developing world→ leads to poverty!

Lecture 5 & 6 Review

- Name 4 reasons for increasing health care costs in the US:
    1. Aging population
    2. Increased technology use
    3. Prescription drug costs
    4. Administrative burden
- In what ways does technology actually DECREASE health care costs:
    1. Increased outpatient procedures
    2. Longer productive life spans
- Which of the following did NOT contribute to the Oregon plan:
    a. Increased use of managed care plans
    b. Increased tax revenues
    c. Individual mandate to obtain health insurance
    d. Community value decisions

c. Associated with the Massachusetts plan

List the steps in the engineering design method in the proper order.

- Evaluate solutions
- Communicate results
- Develop solutions
- Identify a need
- Define the problem (goals, constraints)
- Gather information

Engineering Design Method

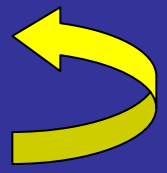
- Fashioning a product made for a practical goal in the presence of constraints
- Six design steps:
  1. Identify a need

SPECS →

  2. Define the problem (goals, constraints)
  3. Gather information
  4. Develop solutions

FMEA →

  5. Evaluate solutions
  6. Communicate results
     - Papers, patents, marketing



Refine Design

Review: Pathogens and the Immune System

- How does the innate immune system defend against bacteria on a rusty nail?
- How does the adaptive immune system defend against the flu virus?

Bacteria vs. Innate immune system

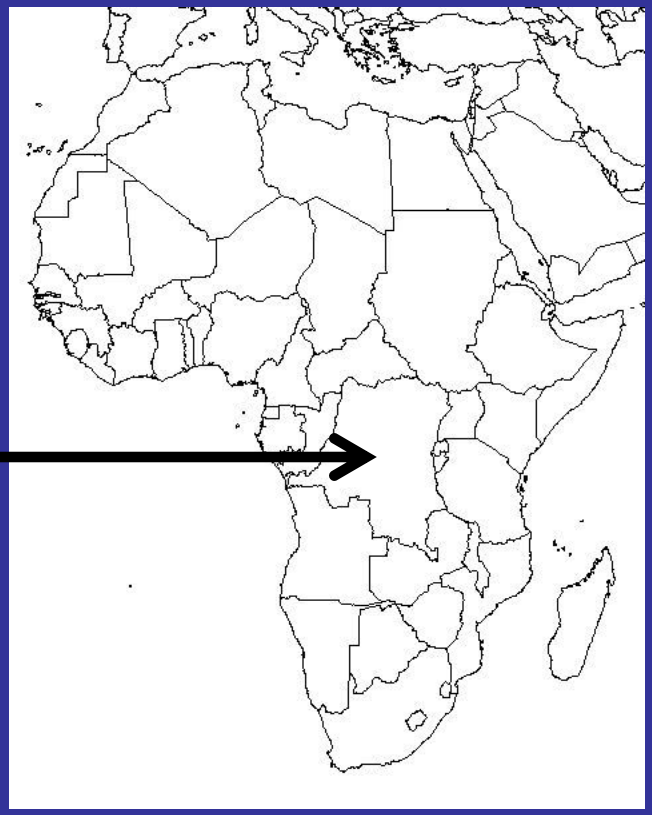
- Produces general response when pathogens pass physical barriers
- Macrophages and other professional phagocytes
  - Kill invaders
  - Signal other immune cells
  - Present antigen to adaptive immune system
- Complement proteins
  - Attach to and tag pathogens for destruction
  - Recruit more immune cells

Flu virus vs. Adaptive immune system

- Antibody-mediated
  - Antigen forms bridge between pathogen and killer cells and phagocytes
- Cell-mediated
  - Upon first exposure and infection, body builds up “memory” of immune cells
  - Memory B and T cells recognize pathogen, rapidly clone
    - T cells – helper or killer
    - B cells – produce more antibodies

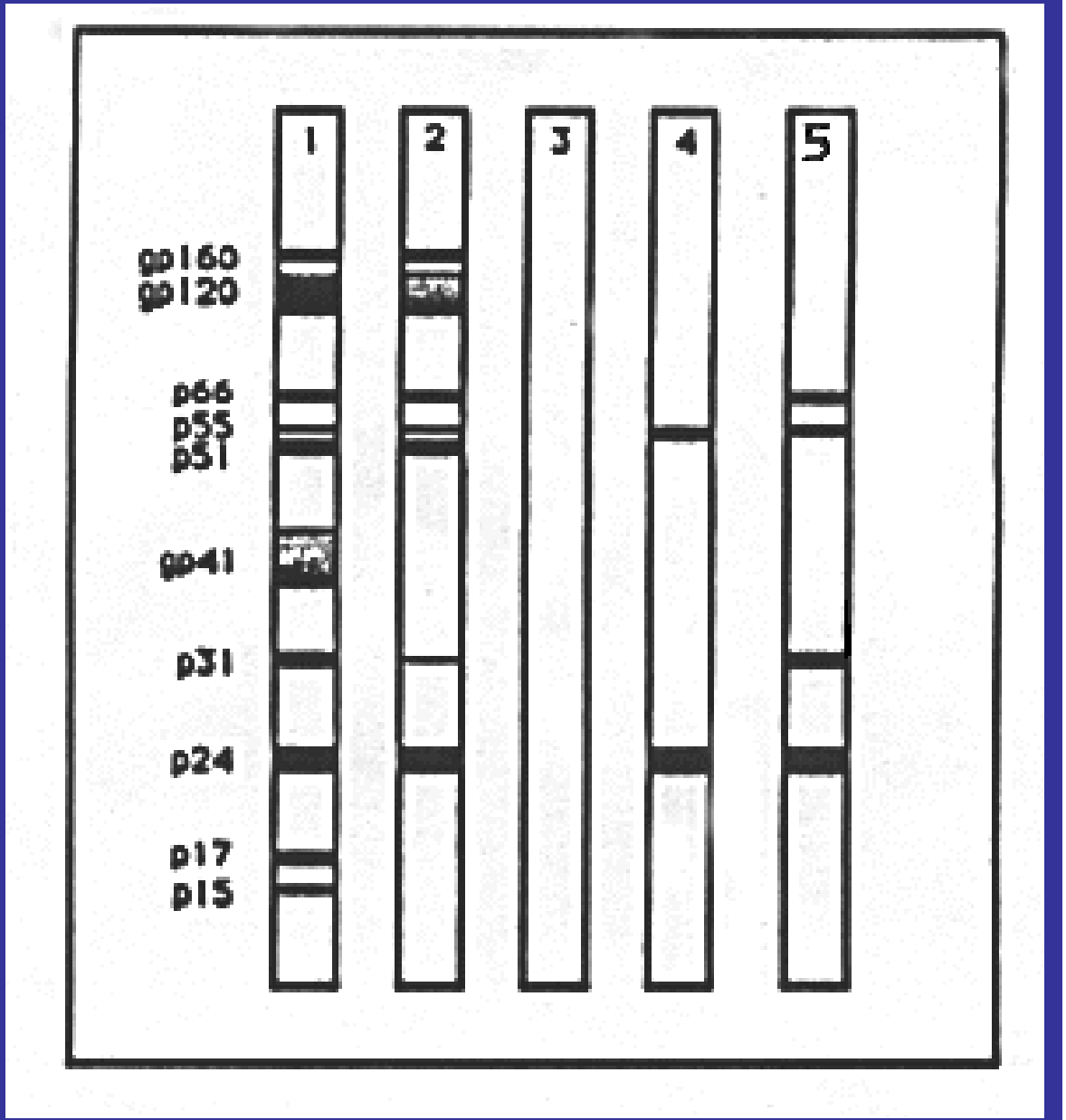
What is this centrally located sub-Saharan country in Africa where 1 million people are living with HIV?

DEMOCRATIC REPUBLIC OF CONGO



You are seeing the results of five Western blots. Person 1 has HIV. Person 3 does not. Does person 5 have HIV?

Person 2 does, but we cannot say for Person 4 and 5. P24 is positive, But p17 and gp120 are negative.



What are the two major challenges for biomarker based cancer screening?

- Cost of the test
- Lack of instrumentation
- Improper validation due to small clinical trials
- Variability among Patient's
- Lack of complete understanding of pathophysiology
- Late stage biomarkers dominate

Answer

- Lack of complete understanding of pathophysiology limits the discovery of early biomarkers, and with our models and tools we are very biased towards late stages of the disease
- The other factors such as cost, patient's variability are also important factors but not the most significant ones

Arrange the following physiological changes in cancer development, starting with the earliest changes to late stage of the disease

- Blood vessels
- Increase in size of nuclei
- Mutation/ Mutations
- Chromosomal changes
- Metastasis
- Overexpression of growth receptors

Answer

- Mutations
- Growth factor overexpression
- Chromosomal Alterations
- Increase in size of nuclei
- Blood Vessel- Angiogenesis
- Metastasis

Question

The inner layer of heart muscle is known as the
A) Endocardium
B) Epicardium
C) Myocardium

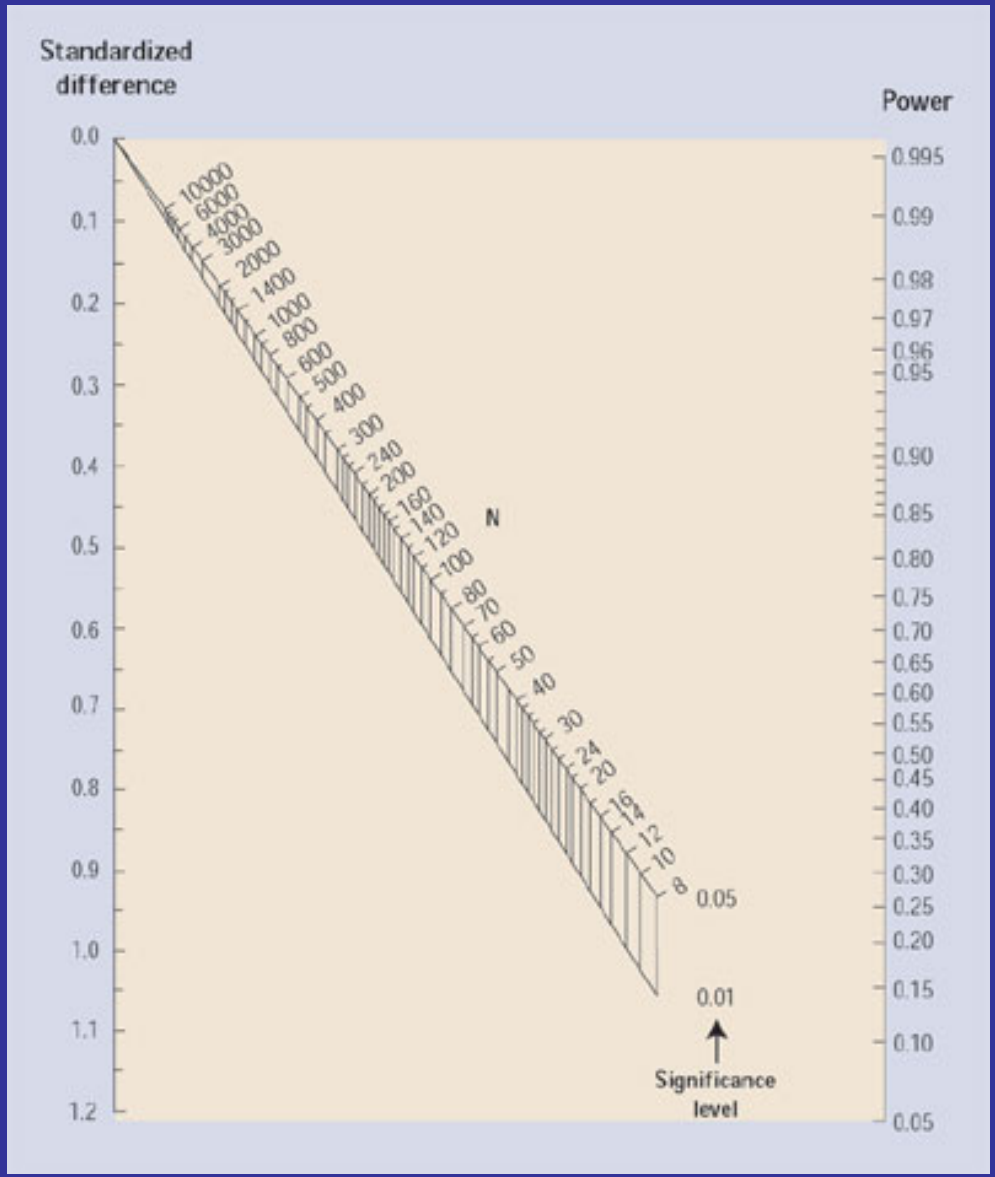
Answer

The inner layer of heart muscle is known as the A) Endocardium

In the heart, the endocardium is the innermost layer of tissue that lines the chambers of the heart. Its cells, embryologically and biologically, are similar to the endothelial cells that line blood vessels. The endocardium overlies the much more voluminous myocardium, the muscular tissue responsible for the contraction of the heart. The outer layer of the heart is termed epicardium and the heart is surrounded by a small amount of fluid enclosed by a fibrous sac called the pericardium.

Drug Eluting Stent – Sample Size

- Treatment group:
  - Receive stent
- Control group:
  - Get angioplasty
- Primary Outcome:
  - 1 year restenosis rate
- Expected Outcomes:
  - Stent: 10%
  - Angioplasty: 45%
- Error rates:
  - p = .05
  - Beta = 0.2
  - Standardized difference = 0.784



Drug Eluting Stent – Sample Size

Expected Outcomes:

- Stent: 10%
- Angioplasty: 45%
- Standardized difference = 0.784

Error rates:

- p = .05
- Beta = 0.2

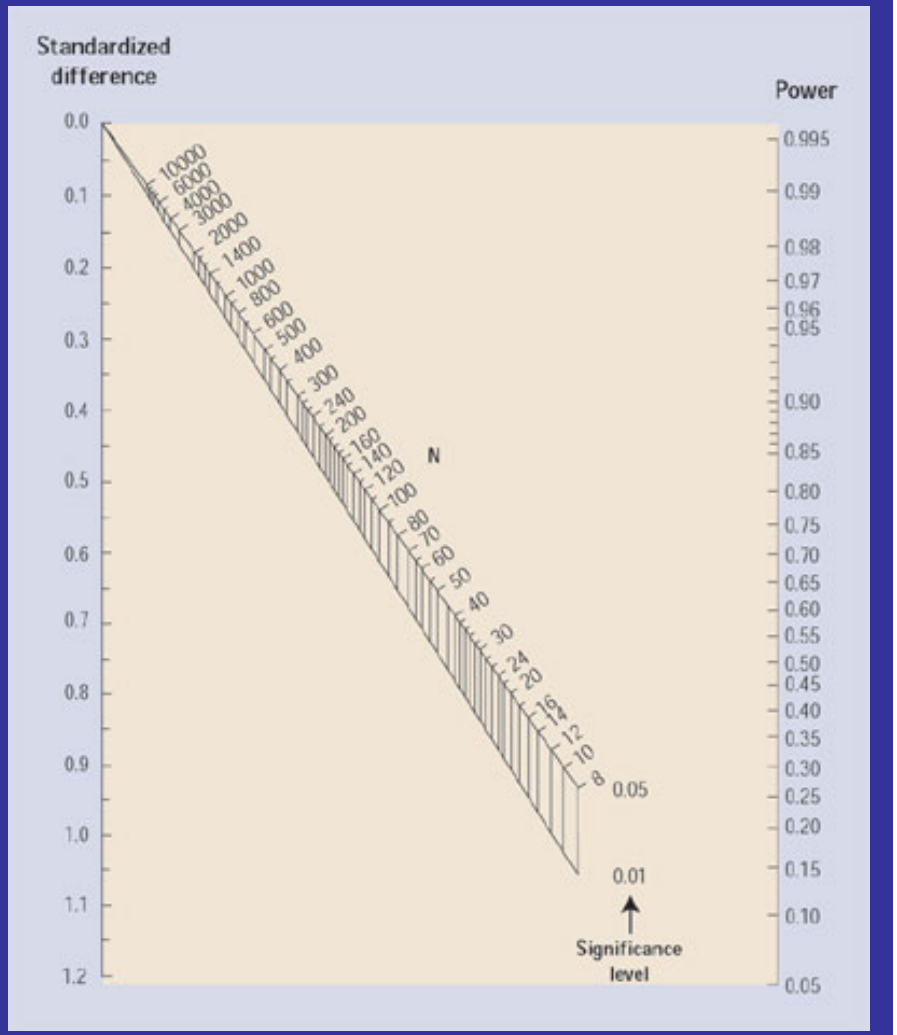
Question: what is the sample size and patients in each arm?

a. Sample size 55 patients; 55 in each arm.

b. Sample size 23 patients; 23 in each arm.

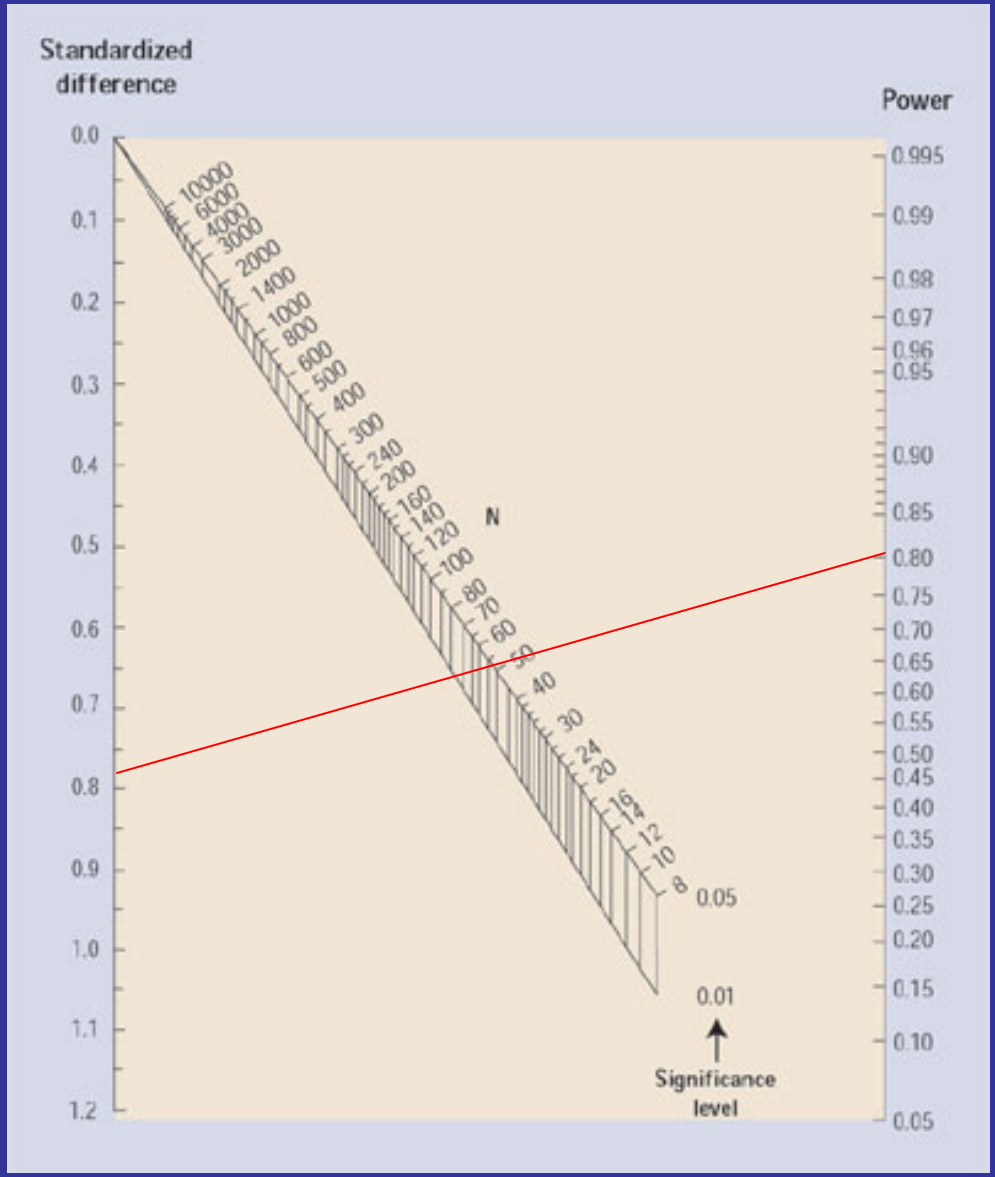
c. Sample size 55 patients; 23 in each arm.

d. Sample size 23 patients; 55 in each arm.



Drug Eluting Stent – Sample Size

- Connect Standardized difference 0.784 and power 0.8
- Sample size is roughly 55 patients
- So 23 patients in each arm/group



- Medical device classes were established by the device amendments to the FD&C Act. Which class of medical device does the following describe?
  - Not life sustaining, but must meet performance standards
  - Examples include blood pressure monitors, guide wires
  - Includes 60% of devices

A. Class I
B. Class II
C. Class III
D. Class IV

Class II