Global Health: Non-Infectious Disease

1. Explain the concept of epidemiological transition
2. Describe the current burden of non-infectious diseases and their disparities worldwide
3. Identify the commonest non-infectious causes of world mortality and some of the causes underlying their high incidence

Epidemiology and Epidemiological Transition

- Clinical medicine is concerned with cases of disease and the disease burden for the individual patient
- Epidemiology is concerned with disease rates and the burden of disease in populations

What is epidemiology?
“The study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control health problems”. This considers:

- Distribution of disease:
  e.g. global patterns
- Cause/determinants of disease:
  e.g. risk factors
- Prevention and health promotion

Epidemiological Transition
“The shift from infectious and deficiency diseases to chronic non-communicable diseases as the result of socio-demographic changes among the poorer countries”

- Complex and dynamic: the health and disease patterns of a society evolve in diverse ways as a result of demographic, socioeconomic, technological, cultural, environmental and biological changes
- Several stages of transition may overlap in the same country. For example, the decline in infectious diseases may be slow/stagnant in some sectors of the population while non-communicable diseases may be increasingly rapidly in another sector of the same population
- During the epidemiologic transition, a long-term shift occurs in mortality and disease patterns whereby pandemics of infection are replaced by degenerative and man-made diseases

Cardiovascular Disease Epidemiology

Lecture Notes

Epidemiological Trends:

- **Time** - measured in rate per population over time period (e.g. years, decades, days etc)
  - HD has highest rate increase since ~1940s
  - Between 1930 and 1950, Canada saw mortality rate almost double
  - USA saw highest mortality rate from CHD in approx 1970s
- **Person** - race, gender, sex- AGE adjusted to remove effect of ageing population
  - Incidence of CHD related deaths in men greater than women
- **Place** - rate according to place (at a particular time) e.g. country
  - Prevalence rate in California and Hawaii greater than Japan, but many Japanese moved to Hawaii and California
Risk Factors:

- **Raised Blood pressure**
  - 62% of all strokes and 49% of all HD attributable to raised BP
- **Tobacco**
  - Smoking curtails life by 10 years, but prevalence of smoking has decreased, i.e. though smoking ban etc
- **High cholesterol**
- **Obesity**
- **Underweight and Unsafe sex**
  - These are mainly applicable in developing countries

**Hypertension**

“Essential hypertension is a type of disease not hitherto recognised in medicine in which the defect is quantitative not qualitative. It is difficult for doctors to understand because it is a departure from the ordinary process of binary thought to which they are brought up. Medicine in its present state can count up to two but not beyond”

- The higher the BP, the higher the risk of death
- “Normotension”: the highest BP in the range of blood pressures not treated with drugs
- Lifestyle factors- especially diet- are key in explaining differences between populations in the rise in BP with age and the consequent prevalence of high BP at older ages
- Increased smoking → increased BP → increased cholesterol → approx 20 fold difference in risk of CVD

**Serum Cholesterol**

- good predictive marker
- Well–measured, so that a single measure characterises the population reasonably well
- Longitudinal studies show prognostic validity
- However poor ability to discriminate between cases and non-cases of heart disease

**Study Guide Notes**

- CD (mainly CHD and stroke) accounted for some 14.3 million deaths worldwide (in 1990), 28.3% of all deaths- 9.1 mil in developing world, 5.2 mil in developed world
- Coronary heart disease and stroke respectively rank first and second among cause-specific mortality worldwide.
- by 2020, an estimated more than doubling of mortality from both CHD and stroke in developing countries, comprising an estimated 69% and 76% respectively of all deaths from these causes worldwide.
- wide global discrepancies in incidence and mortality from coronary heart disease, having low rates in Japan and high rates in the UK and other western countries, and in the formerly socialist economies of Europe.
- At all ages, mortality rates are higher in men than women.
- Trends in mortality have been declining in many countries in recent years (after a large rise in coronary heart disease mortality up to the 1960s and 1970s), though there has been a recent rise in the formerly socialist economies of Europe. These epidemiological patterns indicate that environmental rather than genetic factors underlie much of the variation in cardiovascular disease risk worldwide.
- Three risk factors related to diet and lifestyle are particularly important: high blood pressure, tobacco smoking and serum cholesterol levels.
- The burden of disease attributable to these risk factors is high in the developing as well as the developed countries.
- Worldwide trends in overweight and obesity will increase the burden of Non-communicable disease including metabolic disorders and diabetes.
Cancer Epidemiology

Lecture Notes

Overview

Environmental factors, i.e. smoking can be why men have a higher incidence of cancer
Affects the whole world
Estimated age-standardised incidence rates per 100,000 allows larger comparisons to be made between incidence in different populations
Different cancers have different incidence and distribution around the world
2nd cause of death worldwide
Use of pap smears, cigarette smoking reduction (through ban etc), HPV vaccine → reduced number of cancer diagnosis
1 in 2 for men, 1 in 3 for women – probabilities of cancer

Data

- It is informative to look at rates (incidence or mortality) or risks (prevalence) to get insight in the absolute number of cases
- Incidence = number of new cases
- Prevalence = number of cases at a particular time
- Mortality = number of deaths

Changes in disease rates

Changes in mortality and incidence over time reflect changes in:
- Exposures
- Diagnosis
- Screening
- Treatment (mortality only)

Mortality Rates

- Mortality has fallen for most cancers, in particular stomach cancer (-35%), and cervical cancer (-29%), but this is not true for female lung cancer
- ~1 in 4 of all cancer deaths is due to smoking
- Smoking is associated with increased risk for at least 15 types of cancers
- Smoking causes 90% of lung cancer deaths and 80% in women
- Smoking cessation decreases life risk for lung cancer, i.e. stopping at age 30 decreases your risk of lung cancer mortality by ~10%

Avoidable causes of cancer

- Tobacco
- Alcohol
- Reproductive and sexual behaviour
- Occupation
- Pollution
- Medicines
- Geophysical factors
- Infection
- Diet
- Unknown?
Arsenic

Long-term exposure to arsenic via drinking-water causes cancer of the skin, lungs, urinary bladder, and kidney, as well as other skin changes such as pigmentation changes and thickening (hyperkeratosis).

Arsenic associated cancer epidemic in Bangladesh and West Bengal: prevention- removal of arsenic from the wells, thus eliminating population exposure is the most effective way to eliminate this cancer epidemic

Viruses, Bacteria and Parasites

Infections cause about 4% in the UK but 18% of all cancers worldwide. The most important are:

- Helicobacter pylori (a chronic gastric bacterial infection)- causes stomach cancer
- Human papillomaviruses (HPV)- causes cervical cancer. There has been a reduction in British cervical cancer mortality due to screening.
- Hepatitis B and C- cause liver cancer

Cervical Cancer Vaccination

- Highly effective against HPV 16 and 18, but there are other types so will not prevent all cervical cancers remains to be established
- Potential greatest in developing countries, but costs preclude their widespread use
- Long-term effect of vaccination on mortality

Study Guide Notes

- Cancer is a major public health problem throughout the world, causing more than a quarter of all deaths in many countries.
- Accounted for about 12.5% of the deaths worldwide in 2002, when 11 million people were diagnosed with cancer.
- By 2020, there could be as many as 15 million new cases per year.
- Cancer burden is shifting to less developed countries, in which 60% of these cases are likely to occur.
- vary in incidence between different populations and every type of cancer is rare in some part of the world. Lung, breast and colorectal cancer are currently the most commonly diagnosed cancers, whereas lung cancer, stomach cancer and liver cancer are the most common causes of cancer death.
- rates in migrants tend to converge towards local cancer rates over time, pointing to a role for modifiable risk factors; At least a third of all cancers are likely to be preventable.
- Age-specific cancer incidence and mortality rates have fallen for some cancer sites, while other cancers have become more common, reflecting changes in relevant 11 exposures, diagnosis, treatment, and screening.
- can take 20 years to appear
- current cancer rates are affected by changes that took place in the past.
- Rates of smoking-related cancers in women, for example, will continue to increase; as will the number of cases attributable to asbestos exposure.
- Smoking and overweight will become more important contributors to cancer rates than infections in less developed countries.
Global Health: Infectious diseases

1. Describe the current burden of infectious diseases and their disparities worldwide
2. Identify the six commonest infectious causes of world mortality and some of the causes underlying their high incidence
3. Define and distinguish incidence, prevalence and mortality
4. Understand the drivers of an AIDS epidemic, success and challenges of the response

Human evolution

- Homosapiens relatively young - <100,000 yrs
- Generation time approx 25 yrs
- In comparison with generation of virus within a virus of mins/ hours
- Therefore pathogens evolving on an infinitely faster timescale
- Most diverse part of human genome - HLA: this tells us that infectious diseases are the most selective evolution pressure
- In trying to combat these generation time difference, we have developed the pharmaceutical industry. However between discovery and use of drugs in the pharmaceutical industry approx 15 yrs, perhaps vaccines are 10 yrs. Therefore despite modern medicine, pathogens have evolutionary advantage
- Instantaneous dealing with all infectious agents - non-specific immune response which targets all pathogens.

Scientific methods in epidemiology

- **Immunological and disease surveillance** - empirical base for analysis and interpretation, serum analysis can show complete infection history, one drop of saliva can show this for viruses
- **Mathematical and statistical methods** - analysis of infectious disease transmission and control
- **Clinical epidemiological studies** - typical course of infection - incubation period etc
- **Household and community based studies**
- **New methods in epidemiology** - phylogenetics, bioengineering, web-based surveillance e.g. google hits of specific diseases can be compared to classical surveillance, can show instance of specific infections etc

The changing world

- **Population growth** continues, although more linearly. This is important for infection: greater population density, greater transmission per unit time. Each transmission event is a chance for evolution, therefore greater population size leads to a greater rate of evolution

- **Feeding/Water**: growing population requires more food etc. The proportion of undernourished people decreased from the 1960s, but is now increasing, particularly climatically stressed regions. Increasingly as a species, we are living as large aggregates, e.g. Honk Kong. This leads to increased proximity of livestock to humans, which increases. approx 95% of our pathogens come from intimate relationships from livestock

- **Increasing travel and travel methods**: allows for wider transmission of infectious diseases around the world, i.e. domestic to global transmission. HIV strains can be used to identify where people are from
- **Global spread**: global connective patterns- highly connected therefore with a highly transmittable respiratory infection can be expected to transmit globally over a very short time, e.g. H1N1

### Recent Events

- **West Nile Virus**
  - First reported in US in 1999
  - Caused more than 19,000 cases of human illness including >750 deaths by mid 2009
  - Bird→mosquito→human

- **Bovine Spongiform Encephalopathy**
  - Spread from cow to cow via meat and bone meal protein in feed
  - The aetiological agent has been transmitted to humans causing vCJD, apparently via consumption of contaminated beef or beef products
  - Not RNA or DNA, therefore how does it replicate?

- **Anthrax**
  - bio weapons
  - 2001- 22 diagnosed
  - 11 contratced cutaneous form and all survived
  - Among 11 who became ill via inhalation, 5 died
  - Virtually all cases due to Bacillus anthacis

- **H5N1 - WHO May 2008**
  - Case mortality rate- 62%
  - 383 cases in humans
  - 241 deaths
  - Poor transmission in humans

- **SARS**
  - China 2003
  - “solved itself” – virus was ill suited to human transmission, so in essence was easy to control

- **Malaria**
  - vaccine in trial at the moment
  - Difficult as genetic landscape is constantly changing; sex, mutation (poor proof-reading mechanism), variable gene expression (when immune system recognises antigens, it switches genes and expresses different antigens on surface)
  - In phylogenetic analysis, we see we acquired malaria from gorillas- zoonotic transmission

- **HIV**
  - At end of 2009, 36-40 million worldwide estimated to be infected with HIV-1
  - Dealing antigenically with a totally “moving target” - mutations occurring daily
  - Stratified by risk group@ sex workers, men with GUD, pregnant women
  - 4 classes of drugs currently- but everything depends on patient adhering to drug
  - If drugs not taken properly, drug resistance emerges- evolution of strong resistance to the most effective HIV drugs.
  - Compulsive obsessive- take drugs at the right time every day 10%
  - Completely chaotic- constantly taking drugs at incorrect times or forgetting
  - Evolution- zoonotic- from chimpanzees: feeding un-cooked meat with blood entering from abrasions in mouth
As our population size is growing, and we are so closely related, this type of emergence of disease will become more common.

**Neglected Tropical Diseases**
- Worms lead to stunted growth and decreased school performance in children
- <$0.50 for packages intervention- delivery costs for donated drugs
- Post-treatment, child returns to normal height/weight ratio
- >500 mil infected

**Vaccination and herd immunity**

- 1968: introduction of mass immunisation programme
- Still new introductions of new vaccines, e.g. HPV vaccines
- Potential for prevention of different cancers which look to viruses for origins
- Critical community size: min population size at which measles fadeouts (proportion of weeks with no cases) become rare- maintain endemically these infections, i.e. only a sufficient amount of population must be immunised in order to leave a small enough population that the infection cannot survive. Although with common viruses these CCS tend to be large. This size can be worked out using maths.

**Basic principles in Infectious Disease epidemiology**

The magnitude of $P_c$, the fraction of each birth cohort that must be immunised to block transmission is given by the following simple expression:

$$P_c = \frac{L-A}{L-b}/\varepsilon$$

The parameter $b$ is the average age at first vaccination

$L$ is life expectancy (related to the net birth rate)

$A$ is the average age at infection prior to mass immunisation.

Vaccine efficacy $= \varepsilon$, ranging from 0-1.

- Age-specific serology: used to calculate the average age at infection, the average duration of maternal antibody protection and the degree of herd immunity
- Breast feeding: temporary protection for child from all pathogens mother has encountered (but maternal antibodies only have a half life of about 6 months)
- If child is immunised before 6 months, vaccine is less effective in presence of maternal antibodies
- **Vaccine Efficacy:**
  - Measles: 90-95%
  - Mumps: 72-88%
  - Rubella: 95-98%

**Whole genome sequencing**

- TB – 4,411,529 base pairs
- Can look at critical genes for antigens, pathogens etc
- Becomes complicated when 3 genomes are imposed upon each other, people responds very differently to rhinovirus (which is also hugely genetically variable)- outcome of clinical infection?
Influenza- H1N1

- Different viral types:
  - Abundant- e.g. rhinovirus
  - Evolutionary- e.g. HIV
- Very poor systems internationally for data capture, for both influenza-like symptoms, and viral diagnosis
- Surveillance for new emergence of infection- program in Toronto that relies on media to capture information about unusual mortalities etc

Mistakes made:
- When the virus emerged in Mexico- three genome- human, chicken, pigs, case fatality was very high so was classified as severe pathogenic influenza group
- Not like seasonal influenza; this is more reliant on herd immunity. Due to the latency period of influenza, most infectiousness occurs by the time symptoms occur.
- Serology H1N1 household studies- within the typical age group (6-15), many asymptomatic therefore can be seen as not a serious epidemic

Policy Objectives: Pandemic Flu Contingency Plan
- Minimize morbidity and mortality – with fixed or variable budget.
- Buy as much time as possible to wait for vaccine development.
- Minimize duration of the epidemic and impact on economy.
- Minimize peak prevalence below a defined level to avoid collapse of health care systems.

Typical pattern of an infective virus
- Susceptible
- Latency
- Infectivity
- Recovery

AIDS: History and Progression

The history
- 1959
  - Patient: David Carr, 25 yrs old
  - Occupation: Naval sailor
  - Symptoms: Tired, night sweats, breathlessness, loss of weight
  - Progression: Died after 20 weeks. Autopsy showed PCP (pneumocystis carinii pneumonia), CMV (cytomegalovirus)
  - Never seen before in adults
- 1980
  - 33 yr old man
  - PCP
  - Died few months later
  - “no prior history that should predispose him to PCP”
- 1981
  - Dr had seen 5 men with similar illness
  - All in their 30s, white, homosexual
  - GRID – gay related immune deficiency
  - CDC: immune disease surveillance
  - Initial hypothesis:
    - Environmental factor: drugs, poppers
    - Infectious disease: new virus, strange combination of existing agents
USA Epidemic Growth
- June 1981- 5 cases PCP
- July 1981- 26 cases of Kaposi sarcoma (very unusual)
- Dec 1981- 180 cases
- March 1982- 285 cases
- Jan 1983 >1000 cases
- 1993 – 79000 cases
- Now 1.3 million people living with HIV

Development of Understanding
- Hypothesis of drug use was supported by the parallel of IDU (injection drug use)
- Heterosexual incidence → 1985 discovery of HIV virus
- Babies are presenting

NOW
- HIV seen as a global disease
- Transmission through sexual contact or blood
- 90% of disease in developing countries
- Research: epidemiology (distribution- dictates where funding goes), natural history (length of infection before death etc), treatment
- Need to start looking for antibody test to find who if infected
- USA: paid donation of blood, which lead to increase in spread of disease
- Over 7400 new HIV infections a day in 2007
  - 96% low/middle income countries
  - 1000 in children < 15 yrs old
  - 6300 adults >15 yrs old, 50% women, 45% young women (15-24)
- Global estimates
  - 33 mil people living with HIV
  - 2.7 mil new infections in 2009
  - 2 mill death to AIDS in 2009
  - Therefore can be seen as a stable infection

Prevalence
- The frequency of a particular disease in a population at a point in time
- = No of cases/ no of people in population
- Measures burden of disease in a population
- Useful for planning, eg planning the no of children that will be brought up without mothers due to death from aids
- Can be used to compare burden of chronic disease between populations
- Global interest financially, socially etc- whether it is increasing or decreasing
- Adult prevalence rates go between 1-5% of the population in the US in 1985- focused on “high-risk” core groups, whereas in Africa- significantly higher prevalence- which increased much greater by 2005 (up to 34%) even though very little of “high-risk” core group eg drug users
- In China, people are still getting paid to donate blood, therefore still increased risk of a much higher prevalence
- In Russia- needle sharing for vaccination programs, injection drug use etc
- In terms of numbers- prevalence shows the proportion infected in a given population
Incidence

- The number of new infections within a population over time i.e. is the epidemic growing?
- 2.7 mill in 2007- estimated no of adults and children newly infected
- Cumulative incidence (risk) = new cases of disease in a given time period/no of disease free people at start of period
- Must use a sample that is truly representative of entire population, ie using random sampling, and then extrapolate

Relationships of prevalence and incidence

- Incidence- new cases into the bucket
- Prevalence- how much already in the bucket
- Related to incidence and duration of infection
- Increase incidence, increase prevalence- relies on the disease lasting

HIV

- No of new cases not changing rapidly
- Increased survival
- Increased detection- leading to observed increase in prevalence

Mortality

- No of deaths from a disease in a population over a given time = deaths from disease in a given time period/population at start of the period
- Estimated aids related deaths in 2005 = 2.8 million- 2 mil in Africa

Since the beginning

- More than 65 mil people infected
- 25 mil died from HIV related causes
- 2.7 mil new infections/yr (40% 15-24)
- 15 mil children orphaned by AIDS
- 40 mil currently living with HIV, more than 95% who live in developing countries

UN General Assembly

- 2006 high level meeting on AIDS
- Stated AIDS was an “unprecedented human catastrophe”
- Recognised as a global emergency

Development and Response

- First cases of AIDS 1981
- identified virus 1985
- first test 1986 first treatment AZT -1987
- Found that treating mothers could protect babies from transmission- in the 1990s
- 1995-95- triple antiviral therapy, only in developing countries
- 2005- 3 by 5 initiative, goal of 3 mil people in developing world to have access to therapy
Antiretroviral Therapy (ART)

- Increasing prevalence by reducing mortality
- Can help with “slim”
- New infections: treatment = 5:2
- In USA, mortality= 1.4% per year
- Mortality in Sub Saharan Africa = 8.2 % per year
- Defining need- aids or aids defining diagnosis- CD4 count of 200 – WHO definition
- Actually people should be receiving treatment earlier, at approx 350 CD4 count
- Most recent research pushes towards immediate treatment

IAS 2010 Treatment 2.0

- Recognize and use HIV treatment as a tool for preventing new infections
- Develop better combination antiretroviral medications and cheaper diagnostics tools
- Find ways to lower other HIV-related costs
- Expand the availability of HIV testing and build stronger links between HIV testing and care
- Encourage and support community leadership in expanding and improving local HIV responses.

Funding

- Projected costs of delivering and maintaining UNIVERSAL ART ACCESS with a CD4 count <200= $42 billion now, $54 by 2015
- Treatment prevents future infections through transmission, which could save money in the future

Universal test and treat

- No intervention—stabilizes incidence
- ART CD4 <350 cells per microlitre—reduce incidence
- Universal treating for all people – theoretically eradicate the disease

Mother to child transmission

- Prenatal treatment – prevent transmission
- Post natal treatment- breastfeeding- prevents treatment
- But then what happens if they want more children etc?
- Transmission risk between sexual partners when on treatment- as prevalence increases, the chance if having an infected partner increased. If viral load is less than 400, they don’t transmit. This does not matter with respect to gender receiving treatment

Global access to treatment

- 45% pregnant women have access to treatment to protect baby
- Less than 40% of people know their HIV status
- 2008- 42% in people needing therapy had access
- 6.7 million people need ART 2.9 mil are on ART
- Global total number of people on ART 4.7  million

Study Guide Notes

Burden of infectious disease:

More than 90% of deaths from infectious diseases are caused by a handful of diseases: lower respiratory infections, HIV/AIDS, diarrhoeal diseases, tuberculosis, malaria and measles. Most notably, infectious diseases are the leading cause of death in sub-Saharan Africa (see chart).
Leading Causes of Death Due to Infectious Diseases, 2002
- Lower respiratory infections 3.9 million
- HIV/AIDS 2.8 million
- Diarrhoeal diseases 1.8 million
- Tuberculosis 1.6 million
- Malaria 1.2 million
- Measles 0.6 million


AIDS epidemic - successes and challenges of the response:
- One of the great success stories in the fight against AIDS, is the very broad access to antiretroviral therapy (ART) for HIV that has been achieved in poor countries.
- HIV treatment is prolonging millions of lives but, unfortunately, we cannot treat our way out of this epidemic. For every person put on HIV treatment today, five are newly infected with HIV.
- There have also been declines in HIV prevalence in pregnant women in recent years.
- There are a number of effective HIV prevention methods available today, including safer sex, safer injection practices, condom use, and male circumcision. There are, however, also social obstacles attached to each of these. And we have seen that, even when these interventions are fully funded and supported by states and social institutions, they have only been able to drive HIV infection rates down to a certain level.
- In order to further reduce HIV incidence we need new biomedical tools -- the most important of these will be an effective HIV vaccine.

Key measures of disease in the population

- **Case**
  - Epidemiology is based on the ability to quantify the occurrence of disease in populations. This requires a clear definition of what is meant by a case. This could be a person who has the disease, health disorder, or suffers the event of interest.
  - The epidemiological definition of a case is not necessarily the same as the clinical definition.

- **Prevalence**
  - *Prevalence* is the frequency of a disease in a population at a point in time; hence it is often called *point prevalence*.

  **Point prevalence** = Number of cases in a defined population at one point in time / Number of persons in a defined population at the same point in time

  - Prevalence is a proportion. It is the only measure of disease occurrence that can be obtained from cross sectional studies. It measures the burden of disease in a population. Prevalence measures status (a condition: a subject affected by a specific disease).

- **Incidence**

  Incidence quantifies the number of new cases of a disease within a specified time interval. Incidence measures events (a change from a healthy state to a diseased state).

  **Incidence** = Number of new cases of disease in a given time period / Number of disease-free persons at the beginning of that time period
This measure of incidence can be interpreted as the probability, or risk, that an individual will develop the disease during a specific time period.

**Incidence** measures new cases while **prevalence** measures all, cases new and old. The prevalence is dependent upon the number of new cases (incidence), and the time that they remain cases (duration of disease). Individuals only leave the “pool” of prevalent cases when they recover or die.

**Example: HIV infection**
- In the UK, the numbers of new cases of HIV being diagnosed each year (incidence) is rising.
- The numbers of deaths from AIDS has declined, due to improved treatment with Highly Active Anti-Retroviral Therapy (HAART).
- Therefore the duration of disease is increasing.
- The consequence is a steep increase in the prevalence of HIV (the number of people living with HIV).

The importance of evidence in the practice of medicine

**EP 3 - Dr Paul Aylin (d.paylin@imperial.ac.uk)**

1. Recognise the role of evidence based practice in clinical medicine
2. List and define possible explanations for observed associations (chance, bias, confounding, and causation) and cite examples of each
3. Be able to describe the hierarchy of evidence in study design
4. List the Bradford-Hill criteria for establishing causation and apply these to specific examples
5. Be able to apply epidemiological skills to clinical decision making

**Evidence Based Medicine (EBM)**

- The concept of evidence based medicine has been evolving over the past 30 years, although the ideas may have been used earlier. For example, George Washington passed away as a result of blood-letting. Judgements over whether or not blood-letting was beneficial were then discussed (This is an early comparison of EBM). The first concept of a clinical trial was performed considering different treatments for scurvy, e.g. sufuric acid, salt water etc.
- Methods to critically appraise clinical information (trials, EP studies etc) and classify it according to the strength of evidence were first presented in a Canadian Medical Association Journal series on how to critically appraise literature in the early 1980s.
- Concepts emerging from the literature on “critical appraisal” promoted what has become known as evidence based medicine (EBM), suggesting that clinicians should use critical appraised information in clinical practice for optimal care of their patients.

**Sackett Definition:** the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients
Criticism

- Generates controversy that has questioned the value in clinical practice
- Some practicing doctors regard it as an academic exercise
- Not always translated well for General Practice
- The body of evidence is so vast it is impossible for any clinician to have the time to critically appraise even one article per week let alone the number that would need to be appraised to answer questions (estimated at 3.5 per clinical session) arising in a busy practice.
- Governments, healthcare commissioners and providers have used the jargon of EBM to justify decisions, directives or incentives that are seen by clinicians as inappropriate.

Hierarchy of Studies

- Systematic reviews and meta-analysis
- Randomised controlled trials
- Cohort studies
- Case-control studies
- Ecological studies
- Descriptive/cross-sectional studies
- Case report-series studies

Resources: Cochrane library, BMJ publication of EBM

Why EBM Matters to clinicians

- Revalidation- of fitness to practice- tests how up-to-date on knowledge
- Patient care
- Medical knowledge
- Practice-based learning and improvement
- Interpersonal and communication skills
- Professionalism

Use of EBM

- **Clinical findings**- interpretations of findings
- **Aetiology**- causes of disease
- **Clinical manifestations of disease**- how often and when
- **Differential diagnosis**- and selecting which are most likely
- **Diagnostic tests**
- **Prognosis**- likely clinical course of events after diagnosis
- **Therapy**- select most effective treatments
- **Prevention**- identifying and modifying risk factors, and how to diagnose disease early by screening

*Note: does NOT replace clinical decision making but is only a tool is deciding best treatment and therapies are best for your patients. However we still do not know that much about current treatments.*

Homeopathy - NHS spends about £4 mil/yr treating 54,000 patients in 4 homeopathic hospitals

Variation in surgical procedures

- Hysterectomy
- Tonsillectomy
Dilation and curettage/hysteroscopy
Myringotomy
Lower back surgery

Where does epidemiology fit?

EP evidence underpins clinical medicine in terms of aetiology etc, and effectiveness of treatment. It is “the study of the distribution of health related states or events and the determinants of health related states or events in specified populations, and the application of this study to control of health problems- to promote, protect and restore health”

Example 1: Sudden Infant Deaths

Theories to explain

- Sudden arrest of breathing
- Infection
- Suffocation
- Inhalation of vomit
- Enlargement of the thymus
  Status Thymo-lymphaticus: compresses the trachea and hinder respiration
  1930s irradiation of the thymus gland in infancy recomm ended. A more careful statistical investigation, this theory was described as an example of medical mythology.
- Sleeping position- 1970s saw a trend of sleeping babies on their front

Definition: the sudden death of any infant or young child which is unexpected by history, and in which a thorough post mortem examination fails to demonstrate an adequate cause of death

Recent risk factors

- Toxic gas in mattresses
- Sleeping position (9x)
- Smoking (9x)
- Temperature/overwrapping
- Bottle-feeding
- Infection
- Infanticide

Case Control studies were carried out in order to investigate causes of SID, including considering sleeping position etc. Following the evidence released, a campaign was set up called “Reduce the risk of Cot Death”, and the DOH set up “Back to Sleep”

The cause is still not known, although the no of deaths has decrease from 1,326 in 1989 to 305 in 2007

Association and Causation

- Association refers to the statistical dependence between two variables, that is the degree to which the rate of disease in persons with a specific exposure is either higher or lower than the rate of disease without that exposure
- A link, relationship or correlation
Evaluating a statistical association

- **Chance**: make inference/estimations about the strength of an association from samples rather than whole populations
  - Sample size
  - Power calculations
  - Probability (P) values and statistical significance (p=1/20)
  - The role of chance can be assessed by appropriate statistical significance tests or a confidence interval (range of values in which true value lies)

- **Bias**: a systematic error leading to an incorrect estimate. It is a consequence of a defect in the study design, which is very hard to remove,
  - Selection bias - systematic difference between the characteristics of the people selected and those that were not. To get around this, use random selection or use the entire population
  - Measurement bias - occurs when measurements or classifications of disease or exposure are inaccurate
  - Observer

- **Confounding**: mixing of effects between exposure, the disease and a third factor.
  - Account for confounding using matching, randomisation, stratification and multivariate analysis
  - E.g. smoking, social class

- **Causal effect**: judgement of a cause-effect relationship based on a chain of logic that addresses two main areas
  - Observed association between an exposure and a disease is valid
  - Totality of evidence taken from a number of sources supports a judgement of causality
  - Must eliminate chance, bias and confounding before considering causal effect

**Bradford-Hill 1965 Factors to consider**

- **Strength of the association**
  - Measured by the magnitude of the relative risk
  - A strong association is more likely to be causal, e.g. smoking- 20x lung cancer increase
  - A weak association is more likely to be the result of confounding or bias, but does not rule out causal connection, e.g. passive smoking and lung cancer

- **Consistency with other investigations**
  - If similar results have been found in different populations using different study designs then the association is more likely to be casual since it is unlikely that all studies were subject to the same type of errors
  - A lack of consistency does not exclude a causal association since different exposure levels and other conditions may reduce the impact of the causal factor in certain studies

- **Specificity**
  - If a particular exposure increases the risk of a certain disease but not the risk of other diseases then this is strong evidence in favour of a cause-effect relationship e.g. Mesothelioma- cancer of lining around lungs-associated to asbestos exposure
  - One-to-one relationships between exposure and disease are rare and lack of specificity should not be used to refute a causal relationship; for example cigarette smoking causes many diseases

- **Temporal relationship**
  - Essential criterion
  - For a putative (alleged) risk factor to be the cause of a disease it has to precede the disease outcome
This is generally easier to establish from cohort studies but rather difficult to establish from cross-sectional or case-control studies when measurements of the possible cause and the effect are made at the same time.

- It does not follow that a reverse time order is evidence against the hypothesis.

**Dose-response relationship**
- Further evidence of a causal relationship is provided if increasing levels of exposure lead to increasing risks of disease.
- Some casual associations only show a single jump/threshold rather than a monotonic trend.
- E.g. give up smoking - risk of lung cancer decreases.

**Plausibility**
- The association is more likely to be casual if consistent with other knowledge (e.g. animal experiments, biological mechanisms etc).
- This should not be taken too seriously, because lack of plausibility may simply reflect lack of scientific knowledge, e.g. theories before the microscope.

**Coherence**
- Implies that a cause and effect interpretation does not conflict with what is known of the natural history.
- Absence of coherent information as distinguished from the presence of conflicting information should not be taken as evidence against causal association.

**Experimental evidence**
- From humans or animals.
- Evidence from human experiments is seldom available and animal research relates to different species and different levels of exposure.

**Analogy**
- Source of more elaborate hypotheses about the association in question.
- Absence of such analogies only reflects lack of imagination or experience, not falsity of the hypothesis.

**Descriptive studies and routine data**

**Example of what happens if you don’t practice EBM - Wakefield and MMR vaccine**

1. Be able to distinguish each type of study design by its core defining features
2. To understand the major sources of routine data on health and illness in the UK
3. To be able to describe the strengths and weaknesses of routine health data
4. To understand standardised mortality ratios and provide examples of their use in comparing health in populations

**Clinical Studies**

**Hierarchy**
- Systematic reviews and meta-analysis (highest)
- Randomised controlled trials
- Cohort studies
• Case-control studies
• Ecological studies
• Descriptive/cross-sectional studies
• Case report/series (lowest)

Descriptive vs. Analytical Studies

➢ Descriptive
  - DISTRIBUTION of disease: what population or sub-groups are at risk, what geographical locations, frequency over time

➢ Analytical
  - DETERMINANTS of disease: test hypotheses with ultimate goal of judging whether exposure causes or prevents disease

Descriptive Studies

In epidemiology, descriptive studies examine the distribution of disease across various factors including population or sub-groups, geographical location and time period. They describe the distribution of factors or disease in relation to:

- Person (e.g. age, sex, race, marital status, occupation, lifestyle)
- Place (e.g. variation between and within countries)
- Time (variation over time and season)

These use:

➢ CROSS-SECTIONAL SURVEY INFORMATION
  - Useful for health care providers to allocate resources efficiently and plan effective prevention, i.e. allocation of funding in the NHS
  - Provide clues leading to hypotheses which can be tested in analytical studies
  - Describe status of individuals with respect to absence or presence of both exposure and disease assessed at the same point in time
  - cannot easily distinguish whether exposure preceded disease

EXAMPLES of Cross-Sectional Survey Information

1. Health Survey for England
   - Series of annual surveys about England’s health
   - First proposed in 1990 to improve information of morbidity by the new Central Health Monitoring Unit within the Department of Health
   - From 1994 onwards, the survey was carried out by the Joint Survey Unit of the National Centre of Social Research and the Department of Epidemiology and Public Health at UCL

   **AIMS:**
   - to provide annual data about the nation's health
   - to estimate the proportion of the population with specific health conditions
   - to estimate the prevalence of risk factors associated with those conditions
   - to assess the frequency with which combinations of risk factors occur
   - to examine differences between population sub-groups
   - to monitor targets in the health strategy
   - (from 1995) to measure the height of children at different ages, replacing the national study of health and growth.

   **CORE QUESTIONS:**
   - questions on general health and psycho-social indicators
   - smoking
   - alcohol
   - demographic and socio-economic indicators
questions about use of health services and prescribed medicines - focus may vary each year to suit the modular content of the survey
 measurements of height, weight and blood pressure

2. 2001 Census
3. General Household Survey

Other Descriptive Studies:

- Place
  - Geography
  - Hospital
  - Unit
  - *E.g. MORTALITY from open procedures in children aged under one year for 11 centres; data derived from Hospital Episode Statistics (HES)*

- Time trends
  - Standardised death rates over time
  - Infections
  - *E.g. MORTALITY RATE for and number of open operations on children aged under one year from April 1991 to April 2002 in 11 English centres using HES*

- ROUTINE DATA
  “Data that are routinely collected and recorded in an ongoing systematic way, often for administrative or statutory purpose and without any specific research question in mind at the time of collection”

TYPES:

- **Health outcome data** e.g.
  - Mortality/Births
  - Cancer registrations
  - Notification of infectious diseases
  - Terminations of pregnancy
  - Congenital anomalies
  - Hospital admissions
  - Community systems
  - GP data
  - Prescription data
  - Road Traffic Accidents

- **Exposures and health determinant data** e.g.
  - Smoking
  - air pollution
  - crime statistics
  - housing conditions

- **Disease prevention data** e.g.
  - screening uptake
  - immunisation uptake

- **Demographic data** e.g.
  - census population counts
  - Mid-year population estimates inc projections
  - Electoral register

- **Geographical data** e.g.
  - health authority and PCT boundaries
  - location of GP practices

- **Health service provision data**, e.g.
  - bed/staff counts
Advantages and Disadvantages of Routine Data

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Relatively cheap</td>
<td>• May not answer the question wanted (no information or not enough detail)</td>
</tr>
<tr>
<td>• Already collected and available for analysis</td>
<td>• Incomplete ascertainment (not every case captured)</td>
</tr>
<tr>
<td>• Standardised collection procedures</td>
<td>• Variable quality of data (e.g. variable diagnosis fields)</td>
</tr>
<tr>
<td>• Relatively comprehensive and representative – population coverage, large numbers</td>
<td>• Validity may be variable (i.e. do they measure what you think they measure?)</td>
</tr>
<tr>
<td>• Wide range of recorded items</td>
<td>• Disease labelling may vary over time or by area</td>
</tr>
<tr>
<td>• Available for past years so comparisons can be made</td>
<td>• Coding changes may create increases or decreases in rates, e.g. ICD9 to ICD10</td>
</tr>
<tr>
<td>• Experience in use and interpretation of data</td>
<td>• Need careful interpretation</td>
</tr>
</tbody>
</table>

EXAMPLES:

Population Census
- Began in 1801. Every 10 years
- Population estimates
- Health question
- Other health indicators
- Unemployment
- Ethnicity
- Age
- Overcrowding

Vital Registration: Information Collected in E&W

<table>
<thead>
<tr>
<th>Births</th>
<th>Deaths</th>
<th>Marriages</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Date of birth</td>
<td>- Date of death</td>
<td>- Date of marriage</td>
</tr>
<tr>
<td>- Place of birth</td>
<td>- Place of death</td>
<td>- Place of marriage</td>
</tr>
<tr>
<td>- Name of child</td>
<td>- Name of deceased</td>
<td>- Names if bride &amp; groom</td>
</tr>
<tr>
<td>- Sex of child</td>
<td>- Sex of deceased</td>
<td>- Occupations of bride &amp; groom</td>
</tr>
<tr>
<td>- Names of child’s parents</td>
<td>- Age of deceased at death</td>
<td>- Previous marital status of bride &amp; groom</td>
</tr>
<tr>
<td>- Occupation of parents</td>
<td>- Cause of death</td>
<td>- Ages of bride &amp; groom</td>
</tr>
<tr>
<td>- Description of informant</td>
<td>- (up to three causes)</td>
<td>- Names of parents of bride &amp; groom</td>
</tr>
<tr>
<td></td>
<td>- Description of informant</td>
<td>- Occupation of fathers of bride &amp; groom</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Form of ceremony</td>
</tr>
</tbody>
</table>

Mortality data as a measure of Health
- Death certificates
- Local registrars of births and deaths
- ONS for coding and processing
- Produced as routinely published tables; General DH1, By area DH5, By cause DH2 etc
• Public Health Mortality Files
• Data extracts

**Standardised Mortality Ratio (SMR)**
• Ratio adjusted for age (often also sex)
• Represents the ratio of the number of observed deaths (or cases of disease) \( O \) in a particular population to the number that would be expected \( E \), if that population had the same mortality or morbidity experience as a standard population, corrected for differences in age structure \( \text{SMR} = \frac{O}{E} \)

**Birth data as a measure of Health**
• Birth certificates
• Local registrar of births and deaths
• ONS for coding and processing
• Produced as routinely published tables; FM1
• Fertility calculated using populations estimates

**Cancer Registrations**
• Voluntary notification to local cancer registry; Can be electronic or paper notification
• Also from death certificates
• Useful for both incidence and survival information
• Increasingly being linked with hospital admissions

**Infectious Disease Notifications**
• Reported by doctors
• Incidence of disease
• Includes food poisoning, meningitis, tuberculosis and plague

**GP data (consultations ± prescribing)**
• Individual practice computer systems
• Morbidity surveys in General Practice (most recent MSGP4 in 1991/2)
• Quality and Outcomes Framework Information
• Continuous collection of data e.g. GPRD, DIN, Meditel, QRESEARCH
• Weekly Returns Service (spotter practices)

**Quality and Outcomes Framework (QOF)**
• component of the new General Medical Services contract for GPs from April 2004
• QOF rewards practices for the provision of quality care, and helps to fund further improvements in the delivery of clinical care
• Collected in a national database system: Quality Management Analysis System

➢ The clinical domain
   MANY indicators in key areas: coronary heart disease, left ventricular disease, stroke or transient ischaemic attack, hypertension, diabetes, chronic obstructive pulmonary disease, epilepsy, hypothyroidism, cancer, mental health, and asthma – more each year

**EXAMPLES OF CHD INDICATORS**
- CHD 1. The practice can produce a register of patients with coronary heart disease
- CHD 2. The percentage of patients with newly diagnosed angina
- CHD 3. The percentage of patients with CHD, whose notes record smoking status in the past 15 months, except those who have never smoked where smoking status need be recorded only once
- CHD 4. The percentage of patients with coronary heart disease who smoke, whose notes contain a record that smoking cessation advice has been offered within the last 15 months
- CHD 5. The percentage of patients with coronary heart disease whose notes have a record of blood pressure in the previous 15 months
- CHD 6. The percentage of patients with coronary heart disease, in whom the last blood pressure reading (measured in the last 15 months) is 150/90 or less

- The organisational domain
  56 indicators in 5 areas: records and information about patients, patient communication, education and training, practice management and medicine management.

- The patient experience domain
  Four indicators in two areas: patient surveys and consultation length.

- The additional services domain
  Ten indicators in four areas: cervical screening, child health surveillance, maternity services, and contraceptive services.

Royal College of General Practitioners- Sentinel Practices
- Data are collected routinely from a network of approximately 100 practices
- Tabular summary provided of the number of patients seen each week categorised by gender, age group and disease or disease group.
- The data are processed to provide incidence and prevalence rates of diseases

Prescribing analysis and cost tabulation (PACT)
- Prescribing Analyses and Costs
- No clinical information
- It counts scripts not patients
- No information on duration of prescription
- 5% of prescriptions are not redeemed

Factors affecting hospital statistics
Study Design: Cohort and case-control

EP 5 - Dr Petra Wark (p.wark@imperial.ac.uk)

1. To distinguish and describe the design of case control and cohort studies by their core defining features
2. To describe where cohort and case control studies fit in the hierarchy of epidemiological studies
3. To list the strengths and weaknesses of cohort studies and case control studies
4. To be able to interpret odd ratios and rate ratios
5. To be able to calculate crude odds ratios and rate ratios from a two-by-two table
6. To be able to evaluate the appropriateness of case control and cohort designs for particular research questions

Case-control studies

- Case-control studies are commonly used in epidemiology as observational analytical studies
- They have a retrospective design, whereby cases are defined and their exposure compared with controls
- Controls are selected to represent a source population of cases
- Exposure determined post-diagnosis
- Odds ratio is measure of relative risk

PROCEDURE:
E.g. Is there an association between frequent use of mobile phones and risk of brain cancer?

1. **From source population, select cases (sufferers), and controls**
   e.g. Cases: brain tumours, controls: from population without cancer
2. **Subdivide cases and controls into whether or not the subject has been exposed. Obtain information on past exposures and other factors**
   e.g. Examine mobile phone use to classify people factors into exposure categories
3. **Compare proportions of people exposed in cases and controls, and calculate an odds ratio for cases/controls exposure**
   e.g. Compare proportion of frequent mobile phone users in cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Controls</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

(a+c) (b+d)

Odds ratio (OR)= (ad)/(cd)

Selection of Cases

*After having established a clear definition and strict diagnostic criteria of the disease, selections are made from:*
- Disease registries (e.g. for cancer)
- Records of physicians (e.g. GPs)
- Hospital admission or discharge records
- Pathology department log books
- Screening units (e.g. for breast cancer)

Selection of Controls

- Selection of an appropriate comparison group is the most difficult and critical issue in the design of case-control studies
• Controls are subjects free of the disease (or outcome of interest) during the same period of time in which the cases were identified.
  - They should come from the population of individuals who would have been identified and included as cases had they also developed the disease.
  - They should be representative of that population

Sources of Controls
• General population
• Random digit dialing
• Neighborhood
• Friends/relatives
• Hospital or clinic-based

Measurements of Exposure
- self-reported (leads to recall bias)
- Interviews
- Questionnaires
- More objective measures:
  • Hospital records, employer registries
  • Blood, urine tests, etc

Interpretation of odds ratios

<table>
<thead>
<tr>
<th></th>
<th>OR&lt;1</th>
<th>OR=1</th>
<th>OR&gt;1</th>
</tr>
</thead>
<tbody>
<tr>
<td>In terms of odds</td>
<td>Odds of exposure for cases &lt; odds of exposure for controls</td>
<td>Odds of exposure for cases = odds of exposure for controls</td>
<td>Odds of exposure for cases &gt; odds of exposure for controls</td>
</tr>
<tr>
<td>In terms of disease risk</td>
<td>The exposure is associated with a decreased risk of the disease</td>
<td>The exposure is not associated with the disease</td>
<td>The exposure is associated with an increased risk of the disease</td>
</tr>
</tbody>
</table>

Strengths and Weaknesses of Case Control Studies

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Good for rare disease</td>
<td>- Selection bias during selection of controls</td>
</tr>
<tr>
<td>- Quick</td>
<td>- Recall bias during investigations of exposures</td>
</tr>
<tr>
<td>- Cost efficient</td>
<td>- Uncertainty of exposure-disease time (temporal) relationship</td>
</tr>
<tr>
<td>- Can investigate many exposures simultaneously</td>
<td></td>
</tr>
<tr>
<td>- Good at examining diseases with long latency periods</td>
<td>- Poor for rare exposures</td>
</tr>
<tr>
<td></td>
<td>- Cannot calculate incidence rates directly</td>
</tr>
</tbody>
</table>

Cohort Studies

What is a cohort?
A “cohort” is a group of people who have something in common. They can represent the disease-free population from which cases with the disease eventually arise

- Observational analytical epidemiological studies
- A group of people (cohort) followed over time
- Prospective or retrospective design
- A prospective cohort study ascertains disease during follow-up, whereas a retrospective cohort study looks at events that already happened
- Exposures measured prior to disease (prospective)
- Retrospective cohort studies use previously recorded information on exposures
• Can directly measure incidence of disease in exposed and non-exposed people, which can be used to calculate rate ratios or risk ratios

PROCEDURE:
1. Select Individuals without the disease of interest into exposed and unexposed groups
   e.g. exposed: women who received fertility drugs, unexposed: women who didn’t receive the fertility drugs
2. Follow the cohorts over time and determine how many people got disease over a certain time
   e.g. examine how many ovarian cancers occurred in both groups separately, and ideally when
3. Compare the risks of disease in the different cohorts
   e.g. compare risk of disease for women who received the fertility drugs with risk for women who didn’t

Retrospective Cohorts
• Use data from registries (such as from occupational registries, medical records of patients treated in the past) to collect data on past exposure
• Link data to a disease/mortality registry and record the outcome

Calculating the Risk Ratio
→

Completeness of cohort
• When enumerating a cohort, the investigator should attempt initially to identify as many subjects as possible without invoking any restrictions.
• If the study population does not include all the subjects eligible according to the identification criteria, it is possible that the people overlooked or omitted would differ with regard to exposure characteristics and/or vital status.

Follow-up
• Once information on exposure has been obtained for each member of the cohort, the occurrence of the disease(s) of interest, vital status and causes of death have to be ascertained.
• Each person has to be followed up, and the disease endpoint, cause of death or his being alive assessed.
  - Failure to ascertain disease incidence or vital status for any appreciable segment of a study group may lead to erroneous or misleading conclusions
  - People lost to follow-up may be atypical, either because of vital status or of previous exposure, or factors (such as age) associated either with exposure or outcome

Interpretation of Relative Risks

<table>
<thead>
<tr>
<th>RR&lt;1</th>
<th>RR=1</th>
<th>RR&gt;1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interpretation</td>
<td>Interpretation</td>
<td>Interpretation</td>
</tr>
<tr>
<td>Risk of disease among exposed &lt; risk of disease among the exposed</td>
<td>Risk of disease among exposed = risk of disease among unexposed</td>
<td>Risk of disease among the exposed &gt; risk of disease among the unexposed</td>
</tr>
<tr>
<td>In terms of exposure</td>
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<td>In terms of exposure</td>
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<td>The exposure is associated with a decreased risk of disease</td>
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Strengths and Weaknesses of Cohort Studies

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Able to look at multiple outcomes</td>
<td>- Inefficient for studying rare diseases</td>
</tr>
<tr>
<td>- Able to follow through the natural history of disease</td>
<td>- Expensive and time consuming (if prospective)</td>
</tr>
<tr>
<td>- Good design to look at risks related to rare exposures</td>
<td>- Loss to follow-up may introduce bias</td>
</tr>
<tr>
<td>- Incidence can be calculated</td>
<td>- Healthy worker effect may cause bias in occupational cohorts</td>
</tr>
<tr>
<td>- Can minimise bias in estimating exposure if prospective</td>
<td></td>
</tr>
</tbody>
</table>

Note: Confounding (mixing of effects between exposure, the disease and a third factor) may occur in both case-control and cohort studies

Study Design: clinical trials
EP 6 - Helen Ward (h.ward@imperial.ac.uk)

1. To understand the unique significance of, and key components in, the clinical trial design
2. To appreciate the potential biases and limitations in clinical trials
3. To be able to interpret the findings presented from clinical trials
4. To be able to evaluate the appropriateness of the clinical trial design for particular research questions

Lecture Notes

Importance of good trials- DES diethylstilboestrol

- synthetic oestrogen compound
- 1949- suggested prevents miscarriage
- Evidence- case reports of successful use
- Late 1950s- 15% of pregnant women given DES
- 1958- randomised controlled trial:
  - no effect on miscarriage
  - use of DES gradually declined
- 1971- mini-epidemic of vaginal cancer in adolescent girls in Boston, distinctive “clear cell” adenocarcinoma. Very few cases before this
- 1971- case control study; 8 cases, 32 controls. 7/8 cases received DES.
- clear cell adenocarcinoma of vagina and cervix, in daughters of women who took DES

DES adverse effects
- Infertility
- tubal pregnancy
- Miscarriage
- premature delivery
- men exposed to DES before birth have genital abnormalities
- DES mothers are at increased risk for breast cancer

Summary:
- DES introduced on poor evidence of effectiveness
- Case studies with no control group
- Previous animal experiments ignored
- Widespread use despite no effect
- Led to long term effects not immediately apparent
- Case control study confirmed the link
- Cohort study would take too long

Note: Randomised controlled trials are second in the hierarchy of studies. They are usually only carries out on things that are likely to be beneficial, e.g. drugs

What is a clinical trial?

- *A planned experiment in humans designed to measure the effectiveness of an intervention, e.g. a new drug, a surgical procedure, a vaccine, complementary therapy*
- Different from other epidemiological designs
- Most epidemiological studies (surveys, cross sectional, cohort, case control, ecological) are observational
- Trials are experimental

Features of a clinical trial

<table>
<thead>
<tr>
<th>Essential</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Control group- may be given a placebo, or the current best available treatment</td>
<td>• Participant is blind to assignment</td>
</tr>
<tr>
<td>• Prospective- cannot do a trial in retrospect, as give treatment and look at outcome</td>
<td>• Researcher is blind to assignment</td>
</tr>
<tr>
<td>• Participants randomised to intervention or control</td>
<td>• This is known as (double) blinding</td>
</tr>
<tr>
<td></td>
<td>• AIM: RANDOMISED CONTROL DOUBLE-BLIND CLINICAL TRIAL</td>
</tr>
<tr>
<td></td>
<td>• However this cannot always happen, e.g. surgery trials</td>
</tr>
</tbody>
</table>

Trial Design

Defined population - have condition or are eligible

Examples

**Dr James Lind - 1747**
- First evidence of a trial
- Ship’s surgeon
- 12 sailors with scurvy
- 6 pairs- ended after 6 days
Streptomycin trial, 1948
- Patients with pulmonary TB
  - 55 streptomycin, 52 bed rest alone
- Results after 6 months
  - Mortality 7.3% (4) compared to 35.7% (15)
  - Absolute reduction in mortality = 35.7 – 7.3 = 28.4%
  - Relative risk reduction = 28.4/35.7 = 79.6%
  - Number needed to treat (to save one life) = 3.5
- But
  - Lot of side effects
  - Rapid resistance
  - Improvement not sustained

Essential Features (detail)

- **Controls**
  - are eligible for the intervention but receive
  - Placebo (inactive substance eg sugar pill, water injection)
  - standard clinical practice - otherwise unethical
  - The control group is those study participants who do not receive the intervention under assessment.
  - A control group must be included otherwise you cannot be sure why the outcome happened; it may be due to the new treatment or it may have happened anyway.
- **Randomisation**
  - Eligible people (i.e. have the condition you are interested in) are recruited
  - Researcher randomly allocates them to receive the intervention or control
  - To remove bias in treatment allocation
  - Otherwise the investigator may choose different patients for each group.
  - BGC vaccine for TB in children
    - deaths from TB were five times higher in the control group than the vaccinated children
    - doctors offered new vaccine to children with “cooperative” parents
    - These parents were more educated, health conscious
    - Their children had lower mortality from TB regardless of the vaccination
- **Blinding**
  - Single blind: The patient does not know whether they are getting the new treatment or not
  - Double blind: neither the patient nor the doctor knows which treatment they are getting
  - To prevent measurement bias
  - People who are getting a new treatment (or treatment compared with no treatment) often report improvement in subjective symptoms because they are enthusiastic and hopeful (PLACEBO EFFECT)
  - Similarly if a doctor knows that a patient is on the new or active drug they may look for more improvements.
More examples

**RCT of penicillin for sore throat**

- Penicillin V does not reduce the duration of symptoms or the use of analgesics
- Penicillin V does not affect school attendance
- Penicillin V does not reduce recurrences of sore throat
- These findings are irrespective the presence of group A streptococci
- Penicillin V may reduce streptococcal sequelae
- (quinsy, scarlet fever, impetigo)
- But these can be treated once diagnosed

Conclusion: Nearly all children with a sore throat in Western communities can be treated safely without penicillin

**Salk Polio vaccine, 1954**
- RCT
- Hundreds of thousands of children
- Salk vaccine
- Control
- Results: Vaccinated rate per 100,000 = 16, control rate per 100,000=57
- The relative risk of polio in the unvaccinated group was 57/16 = 3.6
- The reduction is risk with the vaccine is
- \((\text{Risk in unvaccinated} - \text{risk in vaccinated})/ \text{risk in unvaccinated} * 100\)
- \((57-16)/57 * 100 = 72\)
- i.e. the trial showed a 72% reduction in risk of polio

**Ethics and Consent**
- Regulation aims to protect patients
- All clinical trials have to be
  - Registered
  - reviewed by an independent scientific committee
  - approved by a Research Ethics Committee
  - adhere to government and international guidelines.
- Independent data monitoring committee
- researchers check progress during the trial
- they unblind the results to see if there is any major difference in outcome
- If there is a large difference they have the power to stop the trial.
• All participants in a trial must provide informed consent, and be free to withdraw at any time without affecting their care

More Examples

TGN1412 trial
• Phase 1 trial, Northwick Park
• 6 men left seriously ill
• Report stated
  • “The novel drug, caused multiple organ failure in the six men who were injected with it at Northwick Park Hospital, London, UK.
  • the serious adverse reactions were the result of an “unpredicted biological action of the drug in humans”
  • this led to even more regulation

Phases of clinical trials for drug development

- **Phase I**
  - test the safety of a new treatment (after all animal trials)
  - small number of people, usually healthy volunteers

- **Phase II**
  - test to see whether the treatment is effective, at least in the short term
  - Continue to look at safety
  - a few hundred people usually with the condition

- **Phase III**
  - compare the new treatment with the current or placebo
  - look at how well the new treatment works
  - Continue to monitor side effects
  - Several thousand patients

- **Phase IV**
  - After drug has been marketed
  - Measure effect in various populations, rare side effects

Evaluating and Reporting

**Efficacy**: the true biological effect of a treatment

**Effectiveness**: effect of a treatment when actually used in practice

Purpose of RCT

• That new treatment is better than the best already available
• That new treatment is not **worse** than those already available- i.e. if the new treatment is cheaper

Analysing RCT

- Is it a high quality trial?
  - Randomisation
  - Completeness of follow-up
Clinical and statistical significance
- Negative as well as positive outcomes

**Does it apply to my practice?**
- Patients adequately described
- Intervention adequately described

**Potential endpoints**
- Death from any cause
- Death from the target condition
- Complete response / disease-free survival
- Partial response
- Clinical response / time to progression

**More examples**

**Jupiter trial: Rosuvastatin**
- 18000 people with high C-reactive protein
- Aim to see if reduced risk of cardiovascular events
- Trial stopped after two years follow-up
  - highly significant difference
  - hazard ratio 0.56 (95% CI 0.46 to 0.69; P<0.00001)
- HR of 0.56 = 44% reduction in risk
- CER; control event rate (251 events) = 1.36 per 100 person yrs
- EER; experimental event rate (142) = 0.77 per 100 person yrs
- Relative Risk Reduction = \( \frac{\text{CER}}{\text{EER}} \) = 1.36 – 0.77 = 44%
  - \( \frac{\text{CER}}{\text{EER}} \) = 1.36
- Absolute Risk Reduction = 0.59 per 100 person years
- NNT* = 1/ARR = 169
- This means you need 169 person years of treatment to prevent on vascular event

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**Screening**

EP 7 - Helen Ward (h.ward@imperial.ac.uk)

1. To understand basic principles and practice of screening
2. Define validity for screening tests, and calculate sensitivity, specificity and predictive value
3. Define criteria for screening programmes

“**Screening is the practice of investigating apparently healthy individuals with the object of detecting unrecognised disease or its precursors in order that measures can be taken to prevent or delay the development of disease or improve prognosis**”

Public Health: considers population health, and aims to improve and promote the health of the nation

**Why screen?**
- Early diagnosis of disease where early intervention improves prognosis
- Identification of high risk individuals where intervention improves prognosis
• Identification of those posing a risk to others
• People would prefer not to get ill
• Widespread belief that early detection is better
• Screening programmes should do more good than harm. Screening can do harm, e.g. use of x-rays, amniocentesis, invasive testing, false positives

Examples

Chlamydia Screening
• Most common STI
• Incidence: >100,000 new cases a year
• Prevalence: 10% young people
• Long term sequelae
  - PID, infertility, ectopic pregnancy
• asymptomatic

Opportunistic Screening
• Young adults attending a healthcare setting for some other reason and offered
• Uptake
• Positivity rates > 10%, 13% in men
• Management- requires a lot of campaigning

What is a screening test?
• Identifies those most likely to have the condition
• Excludes those least likely to have it

How to screen
• Start off with a population, some will have the disease in question, most will not.
• Remember in real situation some of original population will refuse screening.
• Divides into high and low risk but not diagnostic, so some people high risk will not have disease and some people low risk will have disease.
• undergo diagnostic tests
• Put results into two by two table

Validity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test +ve</td>
<td>A</td>
<td>B (false –ve)</td>
</tr>
<tr>
<td>Test -ve</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>A+C</td>
<td>B+D</td>
</tr>
</tbody>
</table>

Based on a “gold standard” definition or test

- **Sensitivity**
  - ability to pick up true positives
  - Sensitivity = a/(a+c)

- **Specificity**
  - ability to exclude true negatives
- Specificity = \( \frac{d}{b+d} \)

- **predictive value**
  - proportion of test result that are correct
  - Positive predictive value = \( \frac{a}{a+b} \)
  - Negative predictive value = \( \frac{d}{c+d} \)

- **Prevalence** = \( \frac{(a+c)}{(a+b+c+d)} \)

The predictive value of a test depends on its sensitivity and specificity, as well as the prevalence of the disease in the population.

**Challenges for screening**

- Generally screening low prevalence populations
- Therefore need a very high specificity
- This often means a lower sensitivity, i.e. what is the cut off for saying a test is positive or negative

**More examples**

**Screening for Hypertension**

- Blood pressure varies within an individual
- A single measurement may be difficult to interpret
- Compare blood pressure readings taken in a doctor’s surgery
- The “gold standard” is hypertension diagnosed by multiple readings over time

**Approaches to screening**

<table>
<thead>
<tr>
<th>Mass</th>
<th>Opportunistic</th>
<th>Targeted</th>
<th>Systematic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applies to whole population (usually defined by age or gender)</td>
<td>The population is approached when they make contact for another reason</td>
<td>Select sub-groups thought to be at increased risk</td>
<td>The population is called for screening using a register</td>
</tr>
</tbody>
</table>

**Examples**

- **Mass systematic**
  - Breast cancer
  - Cervical cancer
  - PKU
- **Mass opportunistic**
  - Chlamydia
  - Cholesterol
- **Targeted systematic**
  - Haemoglobinopathies
  - TB contacts
- **Targeted opportunistic**
  - HIV in GUM clinics
  - TB in immigrants

**Current Major UK screening programs**

- **Cancer**
  - Cervical cancer
  - Breast cancer
  - Colorectal cancer
  - NOT prostate cancer
- **CVD**
  - Hypertension
  - Cholesterol
  - Abdominal aortic aneurysm
- **Infections**
  - TB
  - HIV
  - Chlamydia
  - Syphilis

**Criteria for Screening**

- **Disease**
  - Important health problem
  - Well recognized pre-clinical stage
  - Natural history understood
  - Detectable by screening
  - Long latent period
- **Diagnostic test**
  - Valid
  - Simple and cheap
  - Safe and acceptable
  - reliable
- **Diagnosis and treatment**
  - Facilities are adequate
  - Effective, acceptable and safe treatment available
  - Cost effective and sustainable

**Cervical Cancer**

- 2400 new cases cervical cancer per annum
- Early diagnosis, effective treatment
- Women aged 25 – 64
  - Syrly 25- 49,
  - 3 yearly 50 – 65
- Liquid based cytology
- 80% coverage
- £150million per year
- Effective:
  - Incidence fell 42% 1988 – 1997
  - Saves 4500 lives per year

**Breast Cancer**
- Accounts for 6% of all female deaths in UK
- One in 9 women will develop breast cancer at some time in their life.
- Estimated risk according to age group:
  - < 25, 1 in 15,000
  - < 50, 1 in 50
  - < 60, 1 in 23
- 80% cases in post-menopausal women

**Classification**
- **In situ carcinoma**
  - Ductal
  - Lobular
- **Invasive carcinoma** - penetration into surrounding tissue
- **TNM classification**
  - T: tumour size (0-4)
  - N: palpable nodes (0-3)
  - M: metastasis (0-1)
- **Benign micro-calcification**

**NHS UK screening programme**
- Aims to detect early breast cancer (1988)
- Single/double view Mammography
- Women aged 50-64 (but now also up to 70)
- 3 year intervals
- 1.5M women screened each year

**Mammography**
- Diagnosis of cancer in those with negative mammography
  - Clinical breast examination
  - Cytology or histology
- Monitor Effect of screening programme
  - Monitor routine data after introduction of screening programme – problems of interpretation
  - Perform a randomized trial of screening vs. standard care
- **HIP randomized trial**
  - 67% accepted invitation for two view mammography and clinical examination
  - Followed up with yearly mammography and clinical examination
  - Controls received routine medical care
  - 10 years after entry, treatment group's mortality due to breast cancer was about 30% below the control group's
  - Largest effect in women > 50 years
  - Cases in treatment group were less severe
Note: use of mammography reduces risk of death from breast cancer, but can lead to a false positive and unnecessary treatment.

**Systematic review and meta-analysis of breast cancer screening**
- Comparing incidence before and after screening introduced in 5 countries
- “Over-diagnosis” estimated at 52%, 1 in 3 cases
- USA diagnosed incidence increased from 1 in 12 to 1 in 8 (since 1980)

**Colorectal Cancer**
- Incidence 35,000 per year UK
- Rising 1% per year in men
- Mortality 16,000 per year
- 2nd most common cancer death
- 5 year survival ~50%

**Risk factors**
- Age > 50
- Previous polyp
- IBD (Crohns/UC)
- Red meat, fat and low vegs
- Obestiry
- No exercise
- Smoking and alcohol
- Familial adenomatous polyposis

**Screening**
- From April 2006
- Faecal occult bloods
- Cheap test
- Need follow-up facilities

**Abdominal Aortic Aneurysm (AAA)**
- Definition: an increase in aortic diameter by greater than 50%/ aortic diameter of >3cm
- More prevalent in elderly men (male to female ratio 4:1)
- Important health problem
  - 6000 deaths per year
  - 2% male deaths above the age of 55 years
  - Prevalence 1% to 13% men
- Risk factors
  - Hypertension, peripheral vascular disease, family history
- 75% are asymptomatic
- Mortality of emergency operation > 50%
- Mortality of elective surgery < 5%
Screening

- Ultrasound
- Men > 65 years - target hypertensives?
- Single scan at 65 years - reduces death from ruptured AAA by 70% in screened population
- Could reduce aneurysm mortality 42%

Evaluation of Screening Programmes

- **Feasibility**
  - Feasibility will depend on how easy it is to organise the population to attend for screening, whether the screening test is acceptable, whether facilities and resources exist to carry not the necessary diagnostic tests following screening.

- **Effectiveness**
  - Effectiveness is evaluated by measuring the extent to which implementing a screening programme affects the subsequent outcomes. This is difficult to measure because of a number of biases that affect most of the study designs used:
  - Selection bias - those who attend for screening are different
  - Lead-time bias - early diagnosis results in increase in time from diagnosis to death even if natural history of disease is unaltered by intervention.
  - Length bias - Periodic screening is more likely to identify less aggressive cancers – cases identified likely to have better prognosis than who present with symptoms.

- **Cost**
  - The cost of screening programmes is important. Resources for health care are limited and there are many competing demands for available money, health care professionals and facilities.
  - The relative cost-effectiveness of a screening programme compared with other forms of health care should therefore be considered. Costs relate not just to the implementation of the screening programme but also to the further diagnostic tests and the subsequent cost of treatment.
  - On the other hand, in the absence of screening, costs will be incurred by the treatment of patients in more advances stages of disease.

- **Ethics**
  - Risks of the test
  - Risks of subsequent diagnostic tests
  - Risks of subsequent treatment
  - False positive result causes unnecessary anxiety
  - False negative result will give false reassurance

Prostate Cancer

- **Morbidity**
  - most common cancer in men in the UK (almost 25% of all new male cancer diagnoses)
  - Incidence 111.2 cases per 100,000 men (32,000 new cases a year in the UK)

- **Mortality**
  - most common cause of cancer-related deaths in men
  - 13% of all male cancer deaths, 10,000 men die from the disease each year
  - Most tumours are slow growing
  - Five year survival rate 71%
  - Difficult to distinguish those tumours that will progress rapidly
• More men die with than of prostate cancer

**Screening Tests**

- **Prostate Specific Antigen (PSA)**
  - Not specific to cancer
  - Positive predictive value around 30%
  - Negative predictive value very high

- **Digital rectal examination**
  - Non-specific
  - Not always acceptable

**Treatment**

- **Radiotherapy:**
  - 25 – 60% become impotent
  - 10% get diarrhoea or bowel problems
  - 5% get bladder problems (incontinence)

- **Surgery:**
  - 20% incontinence
  - 20-80% impotence
  - 0.5% mortality

- **Active monitoring**
  - Aim to avoid side effects
  - But cancer may spread
  - Difficult to cope with

**Current Thinking**

- **Screening** for breast and prostate cancer has
  - increased the number of cancers detected
  - Increased expense and morbidity from detection and treatment of cancers that pose minimal risk

- **To improve screening, recommend research**
  - to identify markers that discriminate minimal-risk from high-risk disease;
  - identify less aggressive interventions for minimal-risk disease
  - develop effective prevention, screening, and treatment strategies for high-risk disease

**Study Guide Notes**

**Purpose of screening**

- Screening is carried out where the detection of disease at an early stage leads to improved *prognosis*
- If earlier detection does not offer any hope of improved outcome then screening is generally not indicated. For example, earlier detection of breast cancer allows treatment (surgery, radiotherapy and chemotherapy) that can reduce mortality (leading to increased survival).
- Screening may also be used for *risk factors*, i.e. to identify people at increased risk of developing disease where interventions will reduce that risk (for example screening for high blood cholesterol levels or high blood pressure, and then offering lifestyle advice and/or drug therapy to reduce the risk of cardiovascular disease).
- Screening may also be used to identify people with *infectious disease* where treatment or other control measures will improve the outcome for the individual (e.g. Chlamydia screening), or prevent ongoing transmission to others (e.g. screening food handlers for salmonella, health workers for hepatitis B).
Limitations

• screening may, inadvertently, do more harm than good. This could include false alarms, inducing anxiety, and the treatment of early disease which would not otherwise have become a problem.
• When considering population screening programmes the benefits and harms must be carefully assessed, and the benefits should always outweigh the harms.
• For example, one study of breast cancer screening showed that for every 50,000 screens carried out, 2820 women would be found to have “abnormal” results requiring further investigation. Only 129 of these turned out to be invasive cancer. While mortality in the population was reduced, there are also considerable costs associated with the identification of women with “abnormal results” who face further investigation and considerable anxiety.

Screening tests

• The validity of any test is its ability to distinguish between subjects with the condition and those without.
• To assess the validity of a screening test the true disease status of the individuals must be known, usually through a definitive test which is referred to as the gold standard.
• Validity is described in terms of sensitivity and specificity of the test. An additional test parameter is the predictive value.

Approaches to screening

• Screening can either involve the whole population (mass), or selected groups who are anticipated to have an increased prevalence of the condition (targeted)
• In either of these there may be a systematic programme where people are called for screening (e.g. cervical cancer, breast cancer) or an opportunistic programme when a person presents to the doctor for some other reason and they are offered a test (e.g. Chlamydia screening in young people, blood pressure screening in older people).

Major screening programmes in the UK

➢ Antenatal screening: syphilis, HIV, hepatitis B, rubella, chromosome abnormalities, foetal growth etc. Some of these are offered to all pregnant women, others are based on risk assessments.
➢ Neonatal and childhood: Newborn babies are screened for phenylketonuria, hypothyroidism, haemoglobinopathies and sickle cell disease (in some geographical areas where these conditions are more common). Babies are also checked for congenital hip dislocation. Routine checks in later childhood screen for problems with hearing and development.
➢ Cancers There are systematic programmes for breast cancer and cervical cancer in women. A screening programme for bowel cancer has started 2006) for all men and women aged 60 – 69. There is no systematic screening programme for prostate cancer at the moment, although this is under review.
➢ Infections A new national opportunistic screening programme for chlamydia in young people (under 25) is currently being rolled out across the country. People attending sexual health services are offered screening for HIV. Hepatitis B screening is mandatory for health care workers.
➢ Cardiovascular disease Targeted and opportunistic screening is carried out for blood pressure, high cholesterol, diabetes in primary care.

Criteria for Screening (based on WHO criteria)

• Disease important health problem
• well recognized pre-clinical stage
• natural history understood
• long period between first signs and overt disease
• Diagnostic test valid (sensitive and specific)
• simple and cheap
• safe and acceptable
• Reliable
• Diagnosis and treatment facilities are adequate
• effective, acceptable and safe treatment available
• cost effective
• Sustainable

Systematic reviews and meta-analysis
EP 8 - Dr Teresa Norat (t.norat@imperial.ac.uk)

1. To understand the need for conducting systematic reviews and meta-analyses.
2. To appreciate the potential biases and limitations of systematic reviews and meta-analyses.
3. To be able to interpret the findings presented in published systematic reviews and meta-analyses.
4. To be able to critically appraise published systematic reviews and meta-analysis.

Why undertake a systematic review?

• Single studies are often unable to conclusively answer a research question.
  o Poor study design or small numbers - low power - false negative results
  o Study will often look only at a subset of the potential study population (the very old, most severely ill), making the results difficult to generalise.
• Because of the high volume of data that need to be considered by practitioners and researchers, it has become impossible for the individual to critically evaluate and state current knowledge in many areas
• In order to provide more generalisable conclusions, researchers can conduct a systematic review of the primary studies on a particular research questions
• A systematic review is used to “put together” all different single studies, with different designs. (C=cross sectional, DB=double-blind, P=parallel, NR= not reported, O=open, SB= single blind). When considering multiple studies, you have to consider how the studies vary.

Systematic review: ‘A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review.’

Advantages
• Transparent process because of the explicit methods in identifying and rejecting studies
• Meta-analysis, if appropriate, will enhance the precision of estimates of treatment effects
• Systematic reviews may demonstrate the lack of adequate evidence and thus identify areas where further studies are needed
• Explicit methods limit bias in identifying and rejecting studies.
• Conclusions are more reliable and accurate because of methods used.
• Results of different studies can be formally compared to establish generalisability of findings and consistency of results.
• Inconsistencies in results across studies can be identified and new hypotheses generated about particular subgroups.
• Quantitative systematic reviews (meta-analyses) increase the precision of the overall result.
• Recommendations from reviews based on balanced inferences from the collated research.
• need systematic reviews to efficiently integrate existing information
• provide data for rational decision making

What is involved in a systematic review?

Stage I
Planning the review - Need to clearly define the research question to be addressed. This question is usually framed around the definition of study participants, intervention (exposure), outcomes and study designs on interest.

Stage II
Identification of research - requires clearly defined search criteria and a thorough search of all published medical literature (including exhaustive searches of reference lists, conference proceedings and contact with researchers in the field to identify unpublished studies)

Selection of studies: eligibility/inclusion criteria should be defined and based on:
- study design
- year of study
- publication language
- sample-size/precision
- specific exposure/intervention
- specific outcome
- completeness of information

Study Quality Assessment: may be assessed according to recognized or user-defined criteria e.g. Cochrane handbook, should assess selection/measurement/attrition bias in study design. Should preferably be assessed before study results known, and should ideally be assessed independently by more than one assessor.

Stage III
Reporting and dissemination: study details need to be abstracted from each eligible study along with the effect estimate. These details need to be tabulated in a meaningful way, including details of the populations, interventions, outcomes and study design. This will often also include a summary of findings. The last step consists in estimating an overall effect by combining the data, if meta-analysis is deemed appropriate.

CASE STUDY OF SYSTEMATIC REVIEW ON POWERPOINT

Reviewing a systematic review

1. Was a clear, unambiguous and predefined question addressed?
   In terms of populations, interventions/exposures, outcomes and study designs?
2. Was a comprehensive search for relevant literature carried out?
   Grey literature; time frame; appropriate inclusion/exclusions; languages; duplicate & independent assessment of literature?
3. Was methodological quality of each study assessed appropriately?
   Quality used as inclusion criteria? Quality measures appropriate? Studies weighted according to quality?
   Heterogeneity due to quality?
4. Was heterogeneity explored?
   Heterogeneity due to populations, interventions/exposures, outcomes and study designs?
5. How credible is the evidence?

Meta-Analysis
**Definition:** ‘the use of statistical techniques in a systematic review to integrate the results of included studies’. The studies themselves are the primary units of analysis; there is no access to raw data from each study.

**Advantages**
- Meta-analysis techniques combine the published estimates of effect from each study to generate a pooled overall risk estimate.
- Can include more subjects than any single constituent study, and produce a more reliable and precise estimate of effect.
- Can explore differences (heterogeneity) between published studies.
- Can identify whether publication bias is occurring.

**Disadvantage**
- If the studies are too heterogeneous, it may be inappropriate, even misleading to statistically pool the results from separate studies.

**What is involved?**
- Effect estimates are abstracted (or calculated) from the selected studies.
- These individual study effect estimates are pooled to produce a weighted average effect across all studies.
- Studies are weighted according to a measure of its importance.
  - Most weight to informative studies (often large studies with precise effect estimates).
  - Least weight to less informative studies (smaller with imprecise effect estimates).

**Statistical models used**
- **Fixed Effects Model**
  - Assumes there is a single ‘true’ underlying effect.
  - Used when the effect of the exposure/intervention is the same in all studies.
- **Random Effects Model**
  - Assumes there is a distribution of effects due to between study variation and random variation.
  - Used when the effect of the exposure/intervention is heterogeneous.

**Presenting the Results**

**Forest plot**
- the most common way of presenting the results from a meta-analysis.
- A Forest plot is a graphical representation of the results from each study included in a meta-analysis, together with the combined meta-analysis result.
- Each study is represented by a box and line— the size of the box corresponds to the weight given to that individual study; the horizontal lines correspond to the 95% confidence intervals.
- The overall estimate from the meta-analysis is usually shown at the bottom, as a diamond. The centre of the diamond and dashed line corresponds to the summary effect estimate; the width of the diamond represents the confidence interval around this estimate.

**Publication Bias**
• Refers to the greater likelihood of research with statistically significant results to be published in the peer-reviewed literature in comparison to those with null or non-significant results.

• Failure to include all relevant data in a meta-analysis may mean the effect of an intervention/exposure is over (or under) estimated.

• Publication bias is caused when only a subset of the relevant data is available.

• Publication bias in meta-analyses can be explored using Funnel plots.

• Funnel plots show whether there is a link between study size (or precision) and the effect estimate.

Funnel Plots

• A funnel plot which is symmetric about the mean effect and shaped like an upside down funnel indicates no publication bias.

• A plot with the lower right or left hand corner of the plot missing indicates that publication bias is present.

Heterogeneity

• Studies that are trying to answer the same question may still differ with respect to:
  - Populations
  - Interventions
  - Outcomes
  - Study design.

• Even when these factors are homogenous, heterogeneity may still exist because of:
  - Clinical differences
  - Methodological differences
  - Unknown study characteristics

Assessing heterogeneity

➢ Sensitivity analysis
  - One study is excluded at a time and impact of its removal is evaluated on the summary.
  - Analyse different subgroups e.g. males vs. females, and see whether results differ.

➢ Galbraith (radial) plots
  - Facilitate the examination of heterogeneity, including detection of OUTLIERS.

Dealing with heterogeneity

• If none exists, a FIXED EFFECTS MODEL can be used to pool the effect estimates.

• If some exists, this can be allowed for by using a RANDOM EFFECTS MODEL.

• If too much exists, it might not be appropriate to pool the studies.

• If specific sub-groups of studies display heterogeneity, these can be pooled separated in sub-analysis.
**NB: Limitations in conducting systematic reviews** - If the methodological quality of studies is inadequate then the findings of reviews of this material may also be compromised. Publication bias can distort findings because studies with statistically significant results are more likely to get published.

**CASE STUDY ON POWERPOINT**

Reviewing a meta-analysis

1. **How sensitive were the results to the way the review was carried out?**
   To inclusion/exclusion criteria; fixed versus random effects; sub group analyses?
2. **Was heterogeneity explored?**
   Galbraith plots; sub group analyses with respect to sub groups of populations, interventions/exposures, outcomes, study designs, study quality.
3. **Was publication bias an issue?**
   Evidence for ‘missing’ studies? What impact might this have had on the pooled estimate?
4. **Was it appropriate to pool the studies?**
   Were studies sufficiently homogeneous for to be pooled?
5. **Was the appropriate model used to pool effect estimates?**
   Fixed versus random effects model.
6. **Did different sub groups of studies give similar results?**
   Were results consistent across sub-groups? How generalisable are the findings, are there new hypotheses that should be explored?

**The Cochrane Collaboration**

- Produces and disseminates systematic reviews of healthcare interventions
- Major product is the COCHRANE DATABASE OF SYSTEMATIC REVIEWS- published quarterly
- Deals mainly with clinical controlled trials of healthcare interventions

**Summary**

- Single studies rarely provide a conclusive, universal answer to a question.
- Systematic reviews can provide an invaluable overview of evidence on a particular topic.
- Meta-analyses can provide:
  - A single, more precise, estimate of intervention/exposure effect.
  - A greater understanding of similarities/differences among studies.
  - An assessment of likely publication bias.
- Inconsistencies in results across studies can be identified and new hypotheses generated about particular subgroups.
- Systematic reviews/meta-analyses can provide a evidence-base for clinical decisions.
Familiarity with - core concepts of public health and health promotion

1. Definitions
2. Wider determinants of health
3. Levels of Prevention
4. High Risk vs. Population approach
5. Conceptual framework for designing Public Health and Health Promotion interventions
6. Examples of evidence based programmes
7. Public Health programmes in the UK

Health

Definition of Health - “a resource for everyday life, not the objective of living. Health is a positive concept emphasising social and personal resources, as well as physical capacities”

Definition of Public Health - “the science and art of preventing disease, prolonging life and promoting health through organised efforts of society”

Indicators of Health

- Life expectancy at birth - number of years someone is expected to live from birth; often by region. This has changed due to improvements in medical care infrastructure. Within the same region, life expectancy is dependent on socioeconomic status.
- Deprivation and mortality - deprivation is often classified by where a person lives and their living conditions.
- Employment/occupation - manual vs. Professional employment affects the number of occupational hazards, as well as mental health (through the security of regular payments etc)
- Deprivation and behaviour - e.g. smoking and drinking
- Age & Gender - may relate to behaviour, e.g. sexual behaviour, risk behaviour
- Education - level of education relates to behaviour, e.g. smoking prevalence

Causes of mortality and disease risk factors

- Underweight
- Overweight
- Smoking
- Alcohol consumption
- Hypertension
- Sexual behaviour, i.e. unsafe sex
- Iron deficiency
- Cholesterol
- Low intake of fruit and vegetables
- Physical inactivity

The Wider Determinants of Health

These influence the causes/risk factors for disease and mortality:

- General socioeconomic, cultural and economic conditions
- Living and working conditions
- Social and community influences
- Individual lifestyle factors
- Age, sex and hereditary factors

**Health Promotion**

“the process of enabling people to increase control over the determinants of health, and to improve their health”

- Recognition people cannot do this individually- action toward social, economic and environmental factors so as to alleviate their impact on public and individual health
- Focuses on health rather than disease
- Strengthens skills and capabilities of individuals
- Approach takes into account:
  - The broad definition of health
  - The scope of prevention
  - Limitation of health services
  - Role of individuals, groups and governments

**What does it involve?**

- **Clinical intervention**
  - Biomedical
  - Prevention; screening, immunisation
- **Health education**
  - Traditional, e.g. education about smoking etc
- **Health public policy**
  - Legal, fiscal and social measures
  - Makes individual healthy choices easier
  - E.g. seatbelt legislation, smoking ban
- **Community development**
  - Individuals/groups setting their own agenda

**The Ottawa Charter**

Identifies 3 strategies for health promotion:

- **ADVOCACY** for health to create the essential conditions for health as indicated
- **ENABLING** all people to achieve their full health potential
- **MEDIATING** between the different interests in society in pursuit of health

These strategies are supported by 5 priority action areas:

- Build healthy public policy
- Create supportive environments for health
- Strengthen community action for health
- Develop personal skills
- Reorient health services

**The Jakarta Declaration**

Building on the Ottawa Charter; identifies five priorities:

- Promote social responsibility for health
- Increase investments for health development
- Expand partnerships for health promotion
- Increase community capacity and empower the individual
- Secure an infrastructure for health promotion

The Tannahill Model

A simple and practical framework which advocates 3 health promotion approaches:

1. **Health Education** - influences knowledge
2. **Health protection** - legislative, fiscal and social measures
3. **Prevention** - medical interventions to reduce risk

**Health education**

- To prevent ill-health and promote good health
- Emphasis on the individual
- Needs to be sensitive to cultural, economic and social circumstances
- Comprises of giving information, clarification of attitudes and values, and development of decision making skills

- **Biomedical**
  - Freedom from illness
  - Assumes medical intervention can prevent and cure
  - Medical profession responsible for health - therefore need to educate, promote and cure disease

- **Behavioural**
  - Assumes the benefits of a healthy lifestyles
  - Uses techniques which influence knowledge – attitudes - behaviour

- **Educational**
  - Information giving
  - Learning skills as well as knowledge

- **Client-centred**
  - Help individuals to identify their own priorities on which they wish to take action

**Health Protection**

**What?**

- Fiscal measures
- Regulation
- Legislation

**How?**

- Advocacy to ensure that health dimension is considered in all of government and commercial policy
- Making it possible for people to make health choices
- Commercial impact by regulating markets for safety, taxation, and creating infrastructure

**Prevention**

There are four levels of prevention:

- **Primordial**
  - Prevention of factors promoting the emergence of lifestyles, behaviours, exposure patterns which contribute to increased risk of disease
Primary
- Actions to prevent the onset of disease
- Limit exposure to risk factors
- Includes health promotion and specific protection e.g. vaccines

Secondary
- To halt progression once the illness is already started; early diagnosis and treatment

Tertiary
- Rehabilitation to minimise residual disability and complications

Approaches

High Risk
- Identifying those in special need (target rescue operation), e.g. screening among SCA patients
- Controlling exposure or providing protection against effect of exposure

STRENGTHS
- Effective (high motivation of individual and physician)
- Efficient (cost-effective use of resources)
- Appropriate to individual
- Easy to evaluate

WEAKNESSES
- Palliative and temporary (misses a large amount of disease)
- Risk prediction not accurate
- Limited potential - misses out on info about relatives and friends
- Hard to change individual behaviours

Prevention Paradox: If risk is low and prevalence of risk is high: large burden of disease; If risk is high and prevalence of risk is low: small burden of disease. A large number of people at a small risk may generate more cases of the disease than a small number of people who are at higher risk.

The prevention paradox is such – A preventive measure which brings much benefit to the population often offers little to each participating individual.

Population
- Recognition that the occurrence of common diseases and exposures reflects the behaviour and circumstances of society
- Idea that small changes lead to a bigger influence

STRENGTH
- Equitable (attributable risk may be high where risk is low if a lot of people are exposed to that low risk)
- Radical
- Large potential for population
- Behaviourally appropriate

WEAKNESSES
- Small advantage to individual
- Poor motivation of subject
- Poor motivation of physician
- Benefit: risk ratio worrisome
- Expensive
- Risk of over-treatment
- Medicalisation
Where can health promotion operate?
- Internationally
- Nationally
- Locally
- Individually

Impact of health promotion
- The population
- The community
- The individual

Examples of Health Promotion projects
- **Stanford 5 city project**
  - Largest research effort
  - Testing the hypothesis: community health education programs can decrease cardiovascular risk, morbidity, and mortality in larger communities
  - The study developed many educational programs that were effective and innovative; overall the intervention appeared to produce declines in blood pressure and smoking, but not cholesterol or obesity.
- **Malnourished children’s programme, Jamaica**
- **The sonagachi HIV/AIDS InternationL project (SHIP)**
  - W. H. O. model STD/HIV prevention program for sex workers based in Kolkata, India
  - Components of the program include:
    - peer education
    - condom social marketing
    - reproductive health care
    - community organizing
    - worker's/human rights activism
    - micro-credit
    - education and training programs
    - self-regulatory anti-trafficking initiatives
  - Resulted in low rates of HIV infection and STIs in Sonagachi relative to the rest of the country.
- **Using national health accounts in Mexico**

Current Public Health Initiatives
- **The Wanless Report**
  - Wanless 1 and 2
  - The disease burden
  - “fully engaged scenario”
  - Focus on prevention and the wider determinants of health
  - Cost-effectiveness of actions to improve health and reduce inequalities

Choosing Priorities
- Smoking
- Alcohol
- Obesity
- Sexual Health
- Teenage Pregnancy
- Mental Health
• Choosing a better diet and activity

➢ **Smoking Cessation**
  - Example of role of doctors working with individuals
  - NICE guidelines
  - Legislation
  - Taxation
  - Media campaigns
  - School activities, healthy workplaces
  - One-to-one support
  - Clinics
  - Prescription of nicotine replacement therapy NRT and bupropion (Zyban)
  - Referral to specialist services

➢ **Alcohol Harm Reduction Strategy**
  - National alcohol strategy
  - A review of NHS alcohol spending
  - More help for people who want to drink less
  - Sharpened criminal justice for drunken behaviour and underage sales
  - Trusted guidance for parents and young people
  - Public information campaigns to promote a new ‘sensible drinking’ culture
  - Public consultation on alcohol pricing and promotion
  - Local alcohol strategies

➢ **Tackling Obesity- Change for Life**
  - UK 4th most obese country in developing world
  - 23% of adults in 2005
  - Raising Healthy Kids- Change 4 life: 8 ways to change for life

➢ **Sexual Health – National Chlamydia Screening Programme**
  - GUM clinics
  - Was established in 2003 with the objective of controlling chlamydia through the early detection and treatment of asymptomatic infection, thus preventing the development of sequelae and reducing onward disease transmission.

➢ **Tackling Teenage Pregnancy**
  - SURE START: government programme- aims to achieve better outcomes for children and parents
  - Increases availability of childcare
  - Improving health and emotional development of young children
  - Supporting parents as parents and in employment

➢ **Vaccination programmes**
  - UK NHS immunisation
  - Immunisation represents the other kind of preventive approach, which leaves intact the underlying causes of incidence and seeks instead to interpose some new, supposedly protective intervention (eg, immunization, drugs, jogging). Here the onus is on the activists to produce adequate evidence of safety.

**Social Marketing**

• Its primary aim is to achieve a particular ‘social good’ (rather than commercial benefit), with clearly defined behavioral goals
• It is a systematic process phased to address short, medium and long-term issues
• It uses a range of marketing techniques and approaches – “marketing mix”
• Adaptable approach, increasingly being used to achieve and sustain behaviour goals on a range of social issues. In health-related social marketing, the ‘social good’ can be articulated in terms of achieving specific, achievable and manageable behaviour goals, relevant to improving health and reducing health inequalities.
• Although other research has shown that social advertising can be effective in changing ‘discrete’ behaviours (such as getting a child vaccinated), more complex lifestyle changes may require a combination of education and economic, environmental and organisational influences.

The Customer Triangle

• **Customer or consumer orientation** - A strong ‘customer’ orientation with importance attached to understanding where the customer is starting from, their knowledge, attitudes and beliefs, along with the social context in which they live and work. Developing insight into “who is the customer, what does he believe, how does he behave?”
• **Behaviour and behavioural goals** - Clear focus on understanding existing behaviour and key influences upon it, alongside developing clear behavioural goals. These can be divided into actionable and measurable steps or stages, phased over time.
• **'Intervention mix' and 'marketing mix'** - Using a mix of different interventions or methods to achieve a particular behavioural goal. When used at the strategic level this is commonly referred to as the 'intervention mix', and when used operationally it is described as the 'marketing mix'.
• **Audience segmentation** - Clarity of audience focus using audience segmentation to target effectively.
• **‘Exchange’** - Use of the ‘exchange’ concept – understanding what is being expected of people, and the real cost to them.
• **‘Competition’** - Use of the ‘competition’ concept. This means understanding factors that impact on people and that compete for their attention and time.
• Social Marketing involves a “total planning process” which includes – scoped, develop, implement, evaluate and follow-up

Commission on Social Determinants of Health

• Improve the conditions of daily life – the circumstances in which people are born, grow, live, work, and age
• Tackle the inequitable distribution of power, money, and resources – the structural drivers of those conditions of daily life – globally, nationally, and locally
• Measure the problem, evaluate action, expand the knowledge base, develop a workforce that is trained in the social determinants of health, and raise public awareness about the social determinants of health

The Marmot Review

6 policy Objectives

• Give every child the best start in life
• Enable all children young people and adults to maximise their capabilities and have control over their lives
• Create fair employment and good work for all
• Ensure a healthy standard of living for all
• Create and develop healthy and sustainable places and communities
• Strengthen the role and impact of ill health prevention
Introduction to critical appraisal

EP 10 – Dr Claire Robertson (c.robertson@imperial.ac.uk)

Critical appraisal: the process of systematically examining research evidence to assess its validity, results and relevance before using it to inform a decision

- Makes sense of research evidence, and put new knowledge into practice
- Core part of clinical practice
- Improves communication with patients - patients increasingly ask whether they should have a new treatment and if it will increase their survival or not
- Also important for medical students

Three phases involved:

1. Finding Research Evidence
2. Appraising research evidence
3. Presenting critical appraising findings to lectures and peers

Finding Research Evidence

(MEDICINE DATABASES, GUIDES AND FURTHER HELP FROM IMPERIAL WEBSITE)

Use a systematic method to find your references:
- Defining the topic
- Write a clear question
- Consider key words
- Refine your search to generate a manageable set of results, or broaden your search terms if you want to identify more articles
- P- patients/problem of interest
- I- intervention of interest
- C- control/alternative
- O- outcome of interest

➢ Identify sources of information
- Electronic search engines, e.g. Medline, PubMed
- Acknowledged experts
- Practitioners
- Theses, conference papers etc
- NB: remember that while the internet contains a great deal of factually correct and useful information, it also contains a great deal of unsubstantiated and incorrect information. As a general rule therefore, it is preferable to avoid using internet-based information, unless obtained from published sources, academic/government institutions or charities.

➢ Keeping records
- RefWorks, Endnote- useful electronic system
- Accurate bibliographical details
- Search histories
- Critique details
- Key information

Literature search

Key points:
- What search engine? Year?
- Define your topic – use to guide search terms
- Be systematic in your search methodology – start with the big question, then narrow it step by step to make sure you don’t exclude papers too quickly and lose important information
- Use a variety of different information sources, and ensure all contain trusted information
- Keep good notes/bibliography
- Identify key points and scope of each article, and examine why findings sometimes contradictory, positives and negatives

Appraising research evidence

Used to organize your review and can be generic or specifically focused

General appraisal checklists

- The question: what is the question the researchers are trying to answer? Is there a hypothesis? Is the question relevant? Is the research original (size more substantial, methods more rigorous, do the results add to meta-analysis, is the population studied in any different way, important clinical issue?)
- Design: what is the design (how high in the hierarchy of studies- see earlier lecture, is the study design appropriate)
- Population: sample size (has a power calculation been conducted, are results generalizable), how were the subjects recruited (is there any bias? Better to do random sample), inclusion criteria (essentially
defines the population to which the results can be extrapolated), exclusion criteria (refine the population and remove avoidable sources of bias), were the subjects studies in “real life” circumstances?

- **Methods**: what specific intervention was being considered and was it compared with control? What outcome (does it relate to mortality/morbidity rates) and how was it measured? Duration of follow-up
- **Analysis**: statistical tests, chance and confounding consideration
- **Confounders**
- **Bias**: in measurement/selection (techniques used, appropriate?), systematic bias in RCT by randomly allocating participants, use appropriate statistical methodologies to adjust for differences in populations in case-control and cohort studies, completeness of follow up- ignoring drop outs leading to bias? Blind vs double-blind
- **Ethics**: informed consent, is there known research with a reason for discontinuation of study?
- **Interpretation**: correct? Causal inference made (think Bradford-Hill)

**Specific appraisal checklists**

- For comprehensive lists of reporting guidelines, including:
  - Experimental studies
    - RCT – CONSORT
    - Infection control/interventional studies – ORION
  - Observational studies
    - STROBE
    - Genetic association studies – STREGA
    - Anecdotes of suspected drug reactions – PHARMA
    - Tumour marker prognostic studies – REMARK
    - Internet e-surveys – CHERRIES
  - Diagnostic accuracy studies – STARD
- Reliability + agreement studies – GRRAS
- Systematic reviews – PRISMA/ MOOSE
- Qualitative research – COREQ/RATS
- Quality improvement studies – SQUIRE
- Other reporting guidelines:
  - Clinical guidelines – COGS
  - Evaluation studies in health informatics – STARE-HI

**Presenting critical appraisal findings**

If you are reviewing a number of papers in one area, it is often worth doing this within a series of tables. This will be of great use if you wish to conclude giving a “balance of evidence” overview; by considering the number of papers you have found (i.e. number of rows), you can quickly refer to the number of studies which identified a direct, inverse and no association – use this to rationalize why your expected relationship may not have been evidenced.

**Critically summarising a paper**

- **Why did they do it?**
- **What did they do?**
  - Was the design appropriate?
  - Is the study original?
  - Who is the study about?
Was the study design sensible?

What did they find?
- Is bias controlled for?
- Is the study blinded (if appropriate)?
- Were the appropriate statistics applied?

What did they conclude?

Approaching your literature review

- Find models
- Problem formulation - which topic is under consideration and what are the constituent issues?
- Literature search - using key words etc, use complete and comprehensive reviews
- Evaluation of findings
- Analysis and interpretation of literature
- Critical and evaluate account
- Summarise, synthesise and analyse
- Describe and analyse the existing evidence base
- Detail what gaps you've found
- Reveal similarities and differences, consistencies and inconsistencies and controversies

NB: Things to avoid

- Describe what someone else as done
- Annotated reference list

The ideal design for different outcomes

- Therapeutic method: e.g. efficacy, alternative methods etc  – randomised controlled trials
- Diagnosis method: e.g. efficacy, reliability etc - cross-sectional study
- Screening: e.g. value of tests which enable pre-symptomatic diagnosis - cross-sectional study
- Prognosis: longitudinal cohort study
- Causation: e.g. environmental, lifestyle factors etc and their impact on health- cohort, case control or case reports
International Health I: Poverty, Health and Development

1. Describe the extent of health and income inequalities worldwide
2. Describe poverty and child mortality rates in different parts of the world
3. Describe the relationship between GDP per capita and child mortality rates across developed and developing countries
4. Understand some the key factors that might explain why some countries with similar incomes achieve variant child health outcomes

Income Distribution

World income distribution

- Daily income is measured in dollars
- It varies from below $1 to above $100 per day. These figures are adjusted for inflation and the differences in living costs in different countries
- World population 6.1 billion
- Income is unevenly distributed
- The distribution is closely clustered around $1 per day- Millennium Development Goal- reduce by half the proportion of people living on <$1 per day (starting in 1990- aims to make 20% by 2015)
- There is a secondary smaller peak at around $40 per day
- The richest 20% of the world hold 74% of world income
- There has been an exponential increase in the number of people living below the poverty line
- The projections indicate the reduction of poverty goal should be met by 2015

Regional income distribution

- Africa: 66% below poverty line- 630 mil population
- OECD: 0% below poverty line- 1,130 mil population
- Latin America: 8% below poverty line, 520 mil population
- East europe: 2% below poverty line, 410 mil
- East asia: 20% below poverty line, 1,880 mil
- South asia; 23%, 1,430 mil
- Most of poverty reduction is occurring in Asia, and there is an Africanisation of poverty occurring

Reasons for income distribution

- Reduction in poverty in Asia, increase in sub-Saharan Africa
- Industrialisation- employment in labour intensive industries (more labour than technology- more technology than labour = capital intensive industries)
- AIDS
- Little aid invested in sub-Saharan Africa
- International factors: debt burden
- Good economic policies in Asia
Regional Differences in Health and Income

- Average income is measured as GDP per capita
- Child survival (%); usually expressed as a fraction of deaths under 5 per 1000 life births
- Regions of increasing GDP per capita appear to have a higher child survival rate
- The child survival % reflects the health of the population
- Sub-Saharan Africa: 82% child survival
- OECD: 99.4% child survival
- The child survival % has improved around the world
- In sub-Saharan Africa, the child survival rate is almost the same, although it is poorer than 25 years ago
- Within sub-Saharan Africa, the range of child survival % has many deviations from the trend line. Some countries, e.g. Mauritius appear to be converting their wealth more efficiently into population health
- In many oil-dependent countries, wealth tends to be clustered within certain sites, but this is not always reflected in the population health
- Within all regions, there are many deviations from an obvious trend as different countries have vastly different child survival %
- There are huge deficits of women in certain populations (50-60 million in the world)
- Relative robustness of health under dictatorship
- There are also many deviations from the trend that increased wealth leads to increased child survival, e.g. US had 4x higher GDP per capita than Malaysia, but Malaysia has a higher child survival

There are intermediating factors which allow different countries to convert wealth into health more efficiently

- Political structure
- Vaccination programmes
- Infectious diseases, e.g. diarrhoeal diseases, meningitis, HIV
- Social determinants of health, e.g. sanitation, water supply
- Nutrition, i.e. food supplementation
- Education of women; women can then get better jobs which leads to a higher household income, as well as education of their children. Women’s literacy rate is more influential as women’s independently earned income tends to be used more directly for improvement of child health

Development Directions in China

- Health decisions are made by governments, not health professionals
- After 1980, average income grew rapidly, but health improved much less, i.e. stagnation in child health
- The same policy which unleashed economic growth in fact destroyed the health system
- By allowing people to keep more of their income, collapsed the revenue of the commune
International Health II: Globalisation and Health Worker Migration

EP 12 - Mr Mike Rowson (m.rowson@ich.ucl.ac.uk)

1. Outline the reasons for health worker migration for poorer to richer countries
2. Assess how feasible it is to prevent health worker migration in the context of globalised labour markets of health professionals
3. Evaluate some of the proposed solutions for problems exacerbated by health worker migration

Reasons for migration

- Wages
- Quality of healthcare
- Equality
- Work opportunity
- Opportunity to improve skill
- Poor management of healthcare system

Challenge of globalisation

- Step-change in migration from low-income to rich countries particularly of nurses
- Migration widens health inequalities
- Also blurs the boundaries between rich and poor nations
- Policy resolutions are difficult, because there are only predominantly biomedical solutions- global health is actually economic, social, political, cultural and biomedical problem

Global health workforce

- Total health workforce of around 60 million
- Over 75% of the worlds doctors live in cities

Critical shortage

- Less than 2.5 healthcare providers per 1000 population
- Below this rate - 57 counties
- There is an estimated 2.4mil extra doctors, nurses and midwives needed globally to meet this coverage rates; 4.3 mil if we estimate for all providers

E.g. of Inequality indicators

- Need: high mortality
- Staffing: low number of health workers per 1000 population
- Outputs: low number of births with skilled attendant, low immunisations

The labour market

What factors are driving health workers to migrate and try to integrate with the labour market (looking for jobs) in other countries?

- Levels of international inequality
- Attributes of different health systems – ability to upgrade qualifications, reduce workload, improved health service, possibility of promotion
- Government policies
- Current living circumstances – possibility of a safer environment, improved living conditions
- The benefits and costs of the migration, both financial and non-financial
- The worker’s ability to “observe” wages in other countries
- Technological change
- Social networks

In the UK there is an extremely high dependency on healthcare workers from abroad. What is pulling workers to the UK?
- NHS spending spree - requires more employment
- Relaxing of Britain’s immigration
- Price of intercontinental travel decrease
- Cost of international phonecalls decrease
- Private recruitment
- Internet - searching for jobs is easy
- Changing population demographic- aging population

The government can influence these, but cannot fully control these intermediate factors.

**Does migration matter?**

**Costs:**
- Possibility of worse health outcomes due to reduced quality of healthcare?
- Creates extra pressure on current workers in the health systems
- Also creates further pressure for migration as increases competition of labour market

**Benefits:**
- Circular migration may mean new skills are introduced into the system
- With increasing density of healthcare works, maternal and child survival increase
- However puts pressure on government to respond to wage/health system reform demands, as well as do more efficient substitution of skills

**Reducing health worker migration**
- Ethical recruitment – limit recruitment from other countries, banning active recruitment unless government-government agreement
- Creating incentives to stay – address the factors causing people to leave e.g. low pay, ensure sufficient international aid is invested in health systems
- Responding to “perverse subsidy” (financial transfer from poor to rich) – compensation
- Deepen international partnerships
Demonstrate an understanding of global health issues with regards to waterborne infectious diseases

The scale of the problem

- >1 billion people live on <£1/1.50 per day
- These people also tend to suffer from neglected tropical diseases, which:
  - Impair intellectual + physical development in children
  - Cause adverse pregnancy outcomes
  - Reduce productive capacity/worker productivity
- I.e. poverty promotes disease, and vice versa

Neglected Tropical Diseases (NTDs)

- NTD are often chronic, disfiguring, stigmatizing + disabling
- NTDs do not include malaria, HIV or TB, but consist of:
  - Viral infections – dengue fever, rabies
  - Protozoan infections – leishmaniasis, human African, trypanosomiasis, chagas disease
  - Bacterial infections – leprosy, buruli ulcer, trachoma, endemic treponematoses
  - Helminth infections – schistosomiasis, ascariasis, hookworm infection, trichuriasis, lymphatic filariasis, onchocerciasis, dracunculiasis, cysticercosis, echinococcosis
  - Fungal infections – mycetoma, paracoccidiomycosis
  - Ectoparasitic infections – scabies, myiasis, tungiasis
- E.g. to remember: leprosy, schistosomiasis, blinding trachoma, river-blindness, guinea worm, helminthiasis, leishmaniasis, lymphatic filariasis, trypanosomiasis

Viral NTDs

Dengue fever

- 4 serotypes
- Vector – aegypti mosquitoes
- Occurs in tropical and sub-tropical areas
- Prevalence increased
- Symptoms after 3-14 days after bite
- Febrile
- Haemorrhagic fever lethal complication
- No treatment
**Bacterial NTDs**

<table>
<thead>
<tr>
<th>Buruli ulcer</th>
<th>Leprosy</th>
<th>Trachoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Chronic necrotizing skin disease caused by mycobacterium ulcerans</td>
<td>- Chronic disease caused by mycobacterium leprae – replication rate slow, long incubation period</td>
<td>- Leading cause of preventable blindness</td>
</tr>
<tr>
<td>- Early detection essential to prevent disabilities</td>
<td>- 99% natural immunity</td>
<td>- Eyelashes turn in and scratch cornea → irreversible blindness</td>
</tr>
<tr>
<td>- Untreated, causes massive destruction of skin</td>
<td>- Multi-drug therapy available</td>
<td>- “SAFE” strategy:</td>
</tr>
<tr>
<td>- May require limb amputations</td>
<td></td>
<td>S- surgery to correct eyelids and lashes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A- antibiotics to treat infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F- face washing to prevent transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E- environmental improvement to reduce flies</td>
</tr>
</tbody>
</table>

**Protozoal NTDs**

<table>
<thead>
<tr>
<th>Human African Trypanosomiasis (HAT) “sleeping sickness”</th>
<th>Chagas disease (American trypanosomiasis)</th>
<th>Leishmaniasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Transmitted by the tsetse fly – limited distribution</td>
<td>- Transmitted by triatamine bug</td>
<td>- Transmitted by the sandfly</td>
</tr>
<tr>
<td>- Trypanosoma brucei gambiense – (90% of cases) west and central Africa; chronic infection which may only present with symptoms at advanced stage following CNS damage</td>
<td>- Trypanosome cruzi – region of the Americas, 10 mil affected, causes acute infection lasting 2 months followed by chronic phase of different clinical forms</td>
<td>- 12 mil currently infected</td>
</tr>
<tr>
<td>- Trypanosome brucei rhodesiense –eastern and southern Africa; causes acute infection which develops rapidly and usually is fatal</td>
<td></td>
<td>- Dermal (cutaneous) leishmaniasis – nasty suppurring would which self-heal, diffuse form produces chronic lesions</td>
</tr>
</tbody>
</table>

**Helminth NTDs**

<table>
<thead>
<tr>
<th>Schistosomiasis</th>
<th>Onchocerciasis (river blindness)</th>
<th>Podoconiosis (non LF elephantiasis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Blood-borne fluke of schistosoma spp.</td>
<td>- Black fly vector</td>
<td>- Non-infectious, caused by absorption of silica particles from the soil → lymphatics fibrose and obstruct</td>
</tr>
<tr>
<td>- Freshwater snail intermediate host</td>
<td>- 37 mil infected</td>
<td>- Femoral nodes enlarge</td>
</tr>
<tr>
<td>- 5 species causing 2 forms of disease: intestinal and urogenital</td>
<td>- &gt;99% African</td>
<td>- Swells in stages: watery bag, rubbery, wooden</td>
</tr>
<tr>
<td>- 207 mil infected</td>
<td>- Causes blindness and severe skin disease</td>
<td></td>
</tr>
<tr>
<td>- Sequelae – haematuria, hepatosplenomegaly</td>
<td>- OCP (control programme) – vector control using insecticides, Ivermectin treatment relieved 40 mil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- APOC (African programme for control) – includes remaining endemic countries, treatment and vector elimination</td>
<td></td>
</tr>
</tbody>
</table>

- Morbidity management – regular cleaning with soap and water
- Hydrocoelectomy – costs $50
- 120 mil affected, 1.3 bil at risk
- 81 endemic countries
- Infection by filarial nematodes
- 40 mil people live with symptoms
- Morbidity management – regular cleaning with soap and water
- Hydrocoelectomy – costs $50
Soil-transmitted helminths:
- ascariasis (1.2 bil)
- trichuriasis (795 mil)
- hookworm (740 mil)

Guinea worm
- Only in Africa
- Contaminated drinking water
- Targeted for eradication by WHO

The NTD iceberg

Burden of disease
- 56.6 million people
- Highlighted at target in millennium development goals, however it also contributes to the other goals
- Child growth and development reduced
- Affects poor and marginalised low-income countries
- Discrimination of sufferers is both a cause and consequence of NTDs
- Health intervention and research/development only recently improved

Clinical Interventions

Management with existing tools
- Involves integrated management by local health capacities
- Specialised services not required as no individual diagnosis is required
- Safe, single dose, free or cheap drugs are given

Preventative chemotherapy
- Existing field-applicable tool – involves regular “preventative” treatment resulting in sustained control/elimination
- Simple, cheap diagnosis
- Large scale treatment of the groups/communities in need
- Used for treatment of ascariasis, trichuriasis, hookwork, schistosomiasis, lymphatic filariasis, trachoma, onchocerciasis (in decreasing use order)

Mass Drug Administration (MDA)
- WHO recommended strategy to implement MDA in areas where prevalence rates are above certain thresholds
- Diagnosis and treatment is impossible because of diagnostic costs, but the drugs are safe and effective
School based treatments

- Teachers easy to train
- Wide distribution of schools
- Highest burden of disease in children
- Allows treatment before presentation of symptoms
- Usually high attendance, although misses students who are absent

Pharmaceutical donations

- Merck & Co Inc – Mectizan for onchocerciasis + filariasis
- GlaxoSmithKline – albendazole for filariasis + de-worming tablets for children
- Johnson & Johnson – mebendazole for intestinal worms
- Pfizer – azithromycin for trachoma
- Novartis – MDT for leprosy
- EISAI
- MedPharm + E. Merck – praziquantel

Schistosomiasis control initiative

- Treatment focussed – for schistosomiasis + STH
- Started at imperial college
- Focussed on 6 sub-saharan countries
- Expanded to include all preventative chemotherapy NTDs
- >40 mil treatments
- Have led to reduction in schistosomiasis in Burkina Faso, Uganda

Rapid impact package

- Used for the big 7 NTDs
- Costs $0.50 per person per year
- Includes drugs + delivery + equipment + health education materials + training of personell + monitoring and evaluation
- Package of 4 drugs (NEED TO LEARN)
  - Albendazole/Mebendazole
  - Praziquantel
  - Ivermectin/DEC
  - Azithromycin
- There is new political momentum for the use of RIP:
  - EU-US Summit June 2008
  - G8-Hokkaido Summit July 2008
  - UK-DFID September 2008