Lec.1 # Public Health **Dr. Shaymaa A. Majed**

Health

Health is a dynamic state of complete physical, mental, spiritual and social well- being and not merely the absence of disease or infirmity.

The determinant of health

There are many influences on individual and population health. It is generally accepted that the determinant of health include the physical environment, social environment, individual behaviour, genetic inheritance, and health care.

- Physical environment

Physical environment includes both the natural (weather, soil, water, animal life, and other such attributes), and built environment (the structures that people have created for housing, commerce, transportation, and so forth). Health threat may arise from both the natural and built environment. Common health threats related to the natural environment include weather- related disasters such as tornados, hurricanes, and earthquakes, as well as exposure to infectious disease agents that are endemic in region such as *plasmodium falciparum,* the microbe that causes malaria and is endemic in Africa.

Health threats related to the built environment include exposure to toxins and unsafe conditions, particularly in occupational and residential settings where people spend most of their time. Many occupation expose workers to disease causing substances, farm workers are injured from farm machinery and falls that result in sprains, strains, fractures, and abrasions. There are well documented health threats to office workers from indoor air pollution including passive exposure to tobacco smoke, nitrogen dioxide from gas fuelled cooking stoves, formaldehyde exposure, and other health problems encountered in sealed office buildings. In residential settings, exposure to pollutants from nearby industrial facilities, toxic waste sites, or a high volume of traffic presents hazards for many (heavy impact on low-income and minority communities).

- Social environment

The social environment is defined by the major organizing concepts of human life, social network, family, and occupation. Individual's lives are ruled by religious, political, economic, and organizational rules that reflect the cultural standards, values, and beliefs of their particular social context. These rules affect how individuals live and behave; their relationships with others; and what resources and opportunities individuals have to influence their lives. They shape the relationship between individuals and the natural environment and how the built environment is conceived and developed. Important aspects of the social environment are the status, resources, and power that individual's socioeconomic status (a combination of education, occupation, and income/wealth) and an individual's race and/ or ethnicity.

Public Health 101 Series

Introduction to Epidemiology

Shaymaa A. Majed

Course Topics

Introduction to Epidemiology

1. A Public Health Approach
2. What Is Epidemiology?
3. Key Concepts and Terms
4. Calculating Rates
5. Approach and Methodology
6. Data Sources and Study Design
7. Investigating an Outbreak

Learning Objectives

After this session, you will be able to

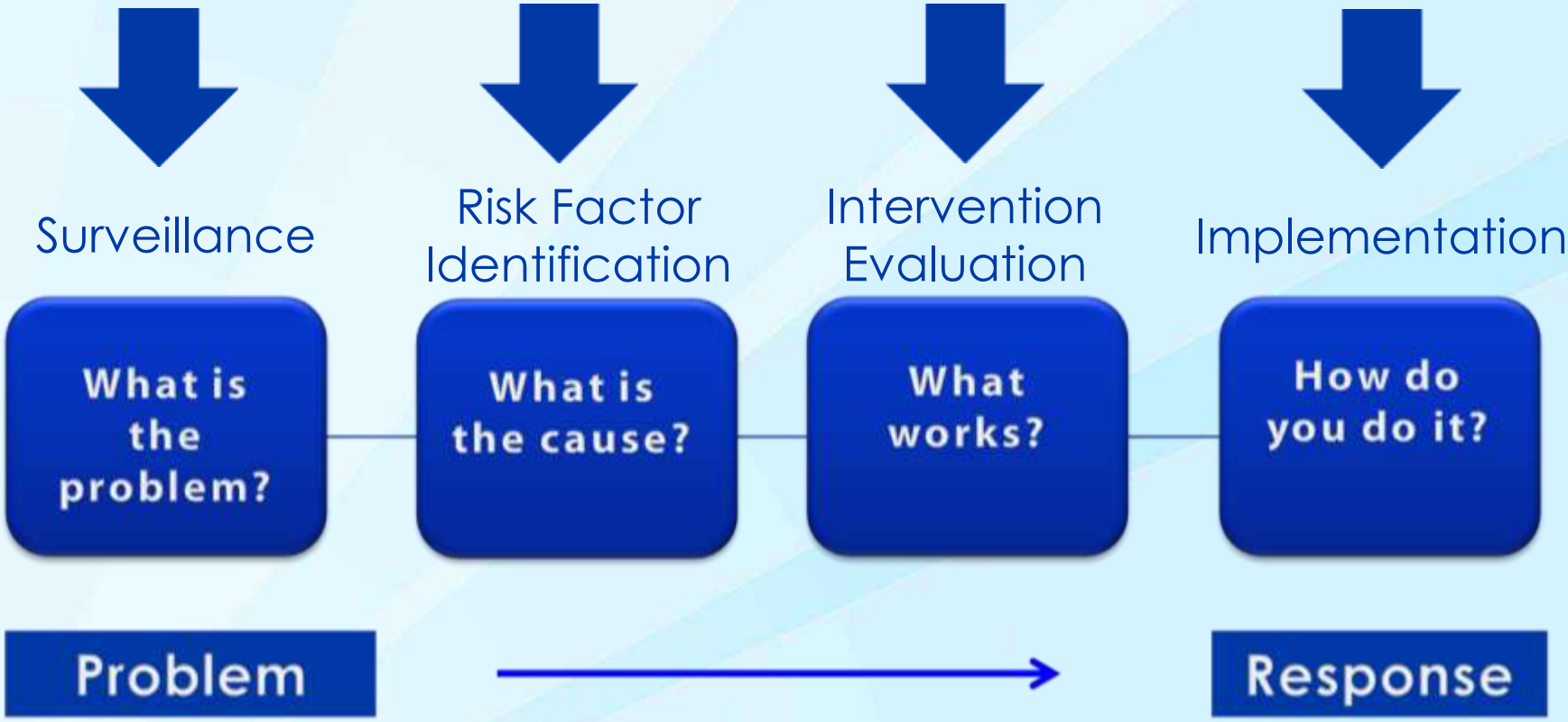
- define epidemiology
- describe basic terminology and concepts of epidemiology
- identify types of data sources
- identify basic methods of data collection and interpretation
- describe a public health problem in terms of time, place, and person
- identify the key components of a descriptive epidemiology outbreak investigation

Topic 1
A Public Health Approach

Public health problems are diverse and can include infectious diseases, chronic diseases, emergencies, injuries, environmental health problems, as well as other health threats.

Regardless of the topic, we take the same approach to a public health problem by following four general steps

A Public Health Approach



Public Health Core Sciences

- **To implement the public health approach, practitioners use and apply scientific methods. These methods come from a series of core sciences that provide the foundation.**
- **These sciences include Public Health Surveillance, which we use to monitor a public health situation.**

- **Epidemiology enables us to determine where diseases originate, how or why they move through populations, and how we can prevent them.**

- **Public Health Laboratories support public health by performing tests to confirm disease diagnoses. Laboratories also support public health by conducting research and training.**
- **As we continue to move from the use of paper documents to electronic health records, Public Health Informatics continues to increase in importance. Informatics deals with the methods for collecting, compiling, and presenting health information. It enables us to use electronic data effectively when addressing a public health situation.**

- **Prevention Effectiveness is closely linked to public health policy. Prevention effectiveness studies provide important economic information for decision makers to help them choose the best option available.**
- **these five core sciences can help us protect and promote the public's health by giving public health practitioners the answers they need. Public health is better able to respond to the situation by using contributions from each of these sciences. One science alone cannot answer the questions and provide a solution**

Topic 2
What Is Epidemiology?

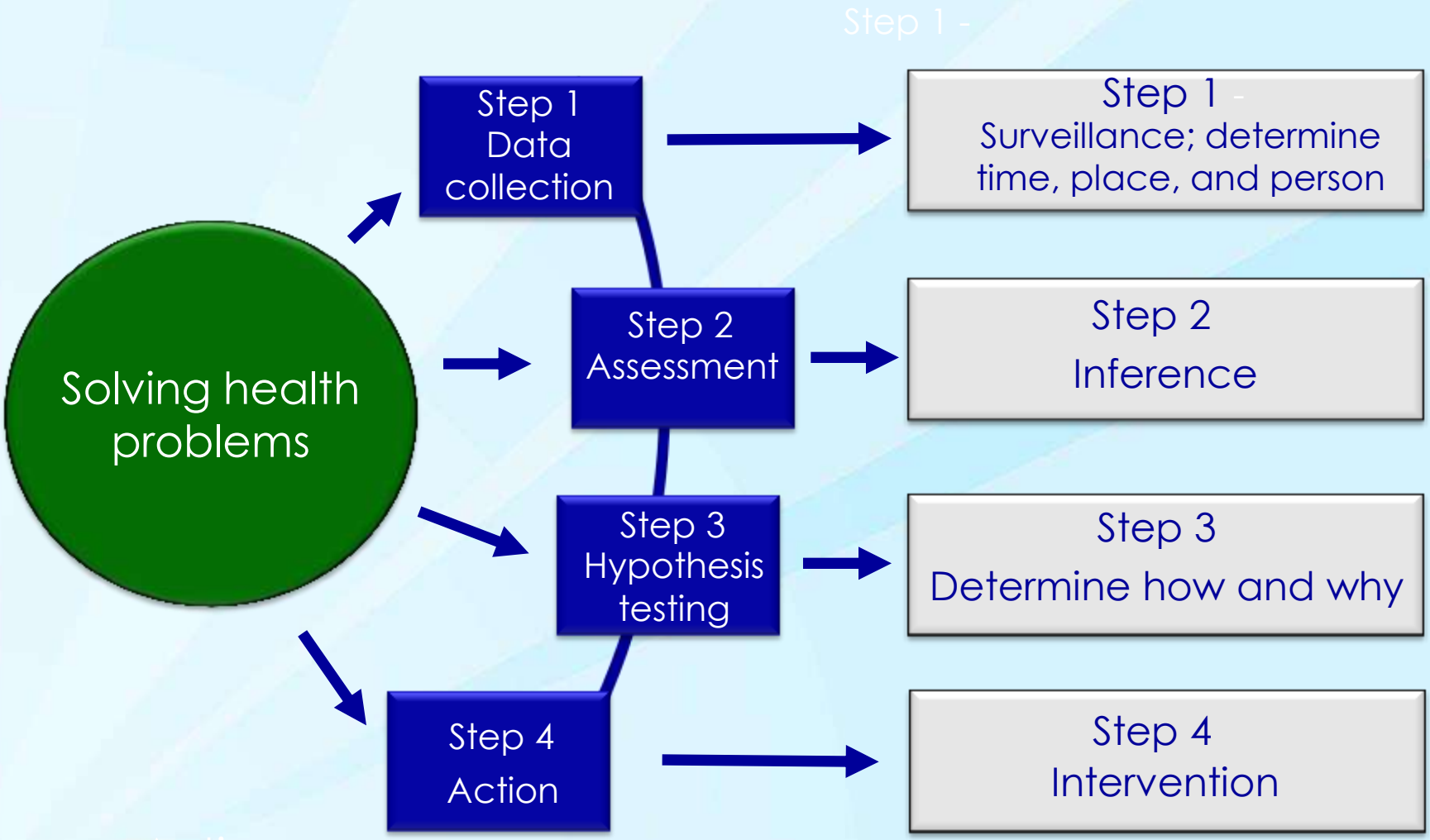
Epidemiology — Defined

Study of the distribution and determinants of health-related states among specified populations and the application of that study to the control of health problems

Epidemiology Purposes in Public Health Practice

- Discover the agent, host, and environmental factors that affect health
- Determine the relative importance of causes of illness, disability, and death
- Identify those segments of the population that have the greatest risk from specific causes of ill health
- Evaluate the effectiveness of health programs and services in improving population health

Solving Health Problems



- First, data are collected about health problems occurring among the population through public health surveillance. The data collected include information about when the problem occurred, as well as where and who were affected (that is, time, place, and person). This is known as descriptive epidemiology, and it will be covered in greater detail later in the course.

- Next, the epidemiologist establishes inferences on the basis of the collected data and draws initial conclusions on the basis of those data. From there, he or she uses the information to generate hypotheses about what might be causing the health problem

- Then, the how and why of a condition is determined by conducting tests or studies to determine if the hypothesis is accurate. This determination of how and why is known as analytic epidemiology, which will also be covered later in this course.

- Finally, the epidemiologist takes action. In public health, that action is known as an intervention. We take action to intervene to prevent the condition from spreading further or to promote healthy behaviors. The epidemiologist recommends or implements some form of action at the population level (for example, a community intervention.)

Knowledge Check

All of the following illustrate the purpose of epidemiology in public health, except

A. identifying populations who are at risk for certain diseases.

B. assessing the effectiveness of interventions.

✓ C. providing treatment for patients in clinical settings.

D. determining the importance of causes of illness

Knowledge Check

Epidemiologists use a model for studying infectious disease and its spread that involves the microbe that causes the disease, the organism that harbors the disease, and the external factors that cause or allow disease transmission. This is also known as

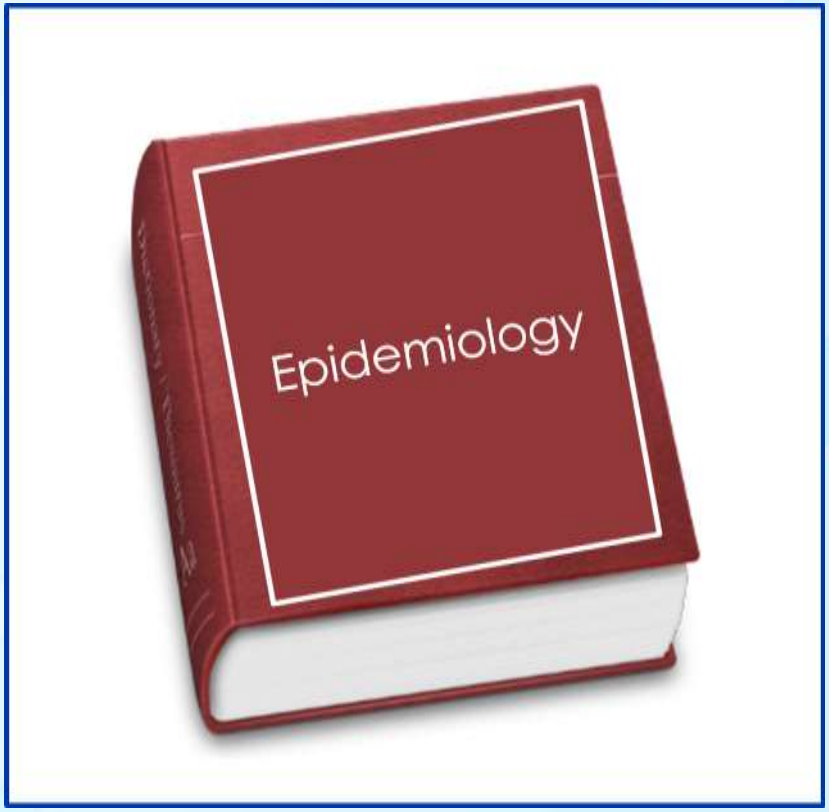
A. host, vector, and transmission.

B. transmission, host, and environment.

✓ C. host, agent, and environment.

D. organism, transmission, and environment.

Topic 3
Epidemiology Key Terms



Epidemiology Key Terms

epidemic or outbreak: disease occurrence among a population that is in excess of what is expected in a given time and place.

cluster: group of cases in a specific time and place that might be more than expected.

endemic: disease or condition present among a population at all times.

pandemic: a disease or condition that spreads across regions.

rate: number of cases occurring during a specific period; always dependent on the size of the population during that period.

Knowledge Check

Match each term with the correct example.

A. endemic	B. pandemic	C. epidemic

A. endemic 1. Malaria is present in Africa at all times because of the presence of infected mosquitoes. Malaria is _____ in Africa.

C. epidemic 2. The Ebola virus in parts of Africa is in excess of what is expected for this region. This virus is a/an _____.

B. pandemic 3. HIV/AIDS is one of the worst global diseases in history. It is a/an _____.

Knowledge Check

Choose the correct answer.

A. distribution B. cluster C. determinant

In March 1981, an outbreak of measles occurred among employees at Factory X in Fort Worth, Texas.

This group of cases in this specific time and place can be described as a cluster.

Topic 4
Calculating Rates

Comparing Population Characteristics

Rates help us compare health problems among different populations that include two or more groups who differ by a selected characteristic

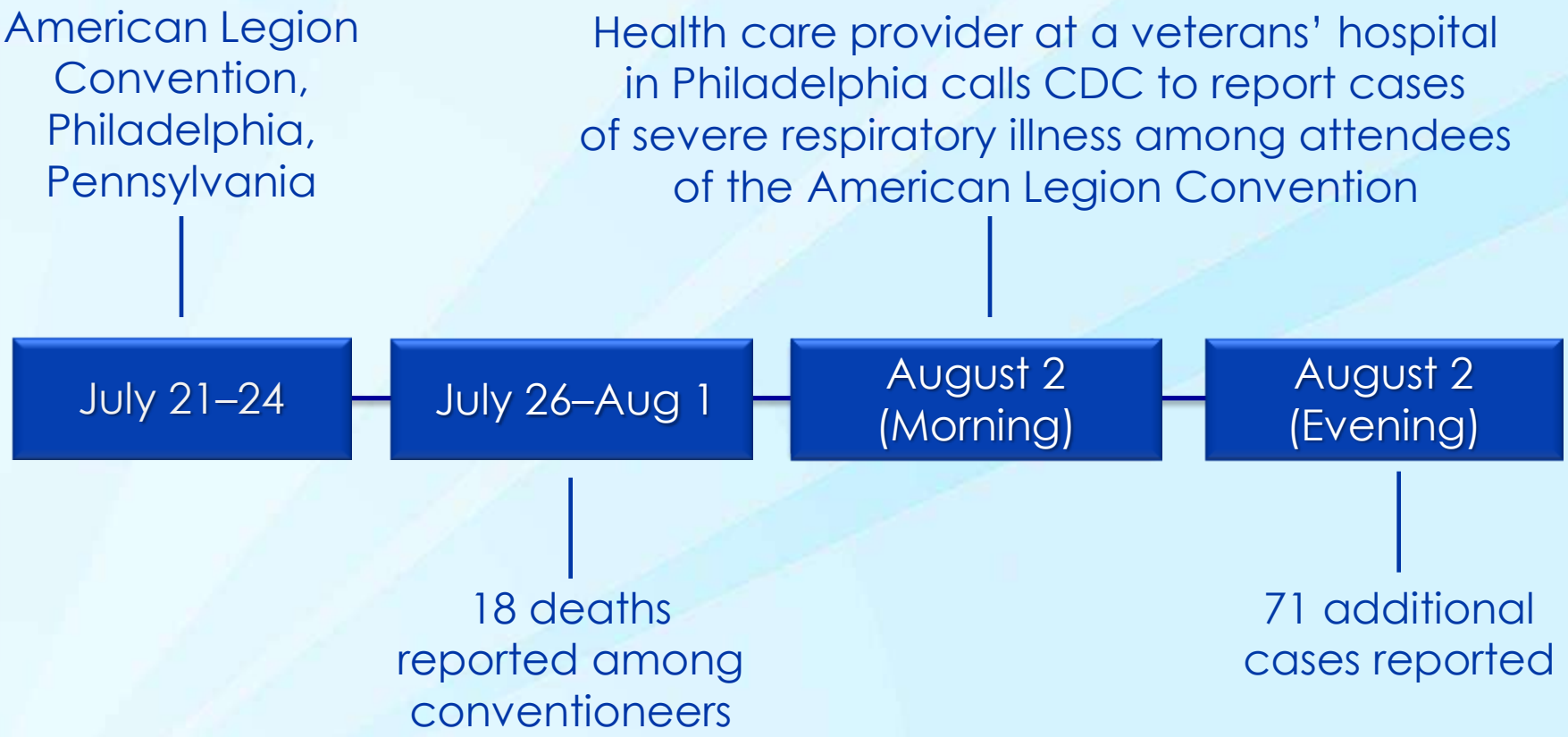
Rate Formula

To calculate a rate, we first need to determine the frequency of disease, which includes

- the number of cases of the illness or condition
- the size of the population at risk
- the period during which we are calculating the rate

$$\text{Rate (\%)} = \frac{\text{number of cases}}{\text{population at risk}} \times 100$$

Scenario: Unexplained Pneumonia



- Members of the American Legion gathered for the annual American Legion Convention held July 21 through 24, 1976, in Philadelphia.
- Soon after the convention began, a substantial number of attendees were admitted to hospital emergency departments or were examined in doctors' offices with acute onset of fever, chills, headache, malaise, dry cough, and muscle pain.
- More troublesome is that during July 26 to August 1, a total of 18 conventioneers died, reportedly from pneumonia
- On the morning of August 2, a nurse at a veterans' hospital in Philadelphia called CDC to report cases of severe respiratory illness among convention attendees.
- Subsequent conversations that day with public health officials uncovered an additional 71 cases among persons who had attended the convention.
- The goal was to find out why these conventioneers were becoming ill and, in some cases, dying

Legionnaires' Disease, by Age Group

Hotel A Residents

➡ Time: July 21–24, 1976

	Frequency	Unit size	
Age (yrs)	Sick	Total	Percentage
≥39	3	44	6.8
40–49	9	160	5.6
50–59	27	320	8.4
60–69	12	108	11.1
≥70	11	54	20.4
Unknown	0	2	0

- These cases of unexplained pneumonia were investigated and subsequently given the name Legionnaires' disease because of the association with attendance at the American Legion Convention during July 1976.
- The chart depicts how CDC investigators focused on a particular hotel as the possible source of the outbreak because that was a common factor among all of the ill men. The investigators wanted to find out if any trends existed by age group among hotel guests who became ill. Here you can see the three elements that constituted the epidemiologic rates.
- We can calculate the rate at which each age group became ill after staying at or attending a meeting at Hotel A during the convention by using a basic formula.

Legionnaires' Disease Rate

Hotel A Residents

Time: July 21–24, 1976

	Frequency	Unit	Rate
Age (yrs)	**Sick**	**Total**	**Percentage**
≥39	3	44	6.8
40–49	9	160	5.6
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60–69	12	108	11.1
≥70	11	54	20.4
Unknown	0	2	0

Knowledge Check

On Day 1 of a technology conference in San Diego, 15 presenters who were setting up for their sessions in Annex X became ill with flu-like symptoms. During the course of the conference, 20 participants who attended sessions in Annex X also became ill with the same symptoms.

To begin calculating the rate of this outbreak, investigators should first determine

A. the size of the conference population.

✓ B. the number of cases of illness.

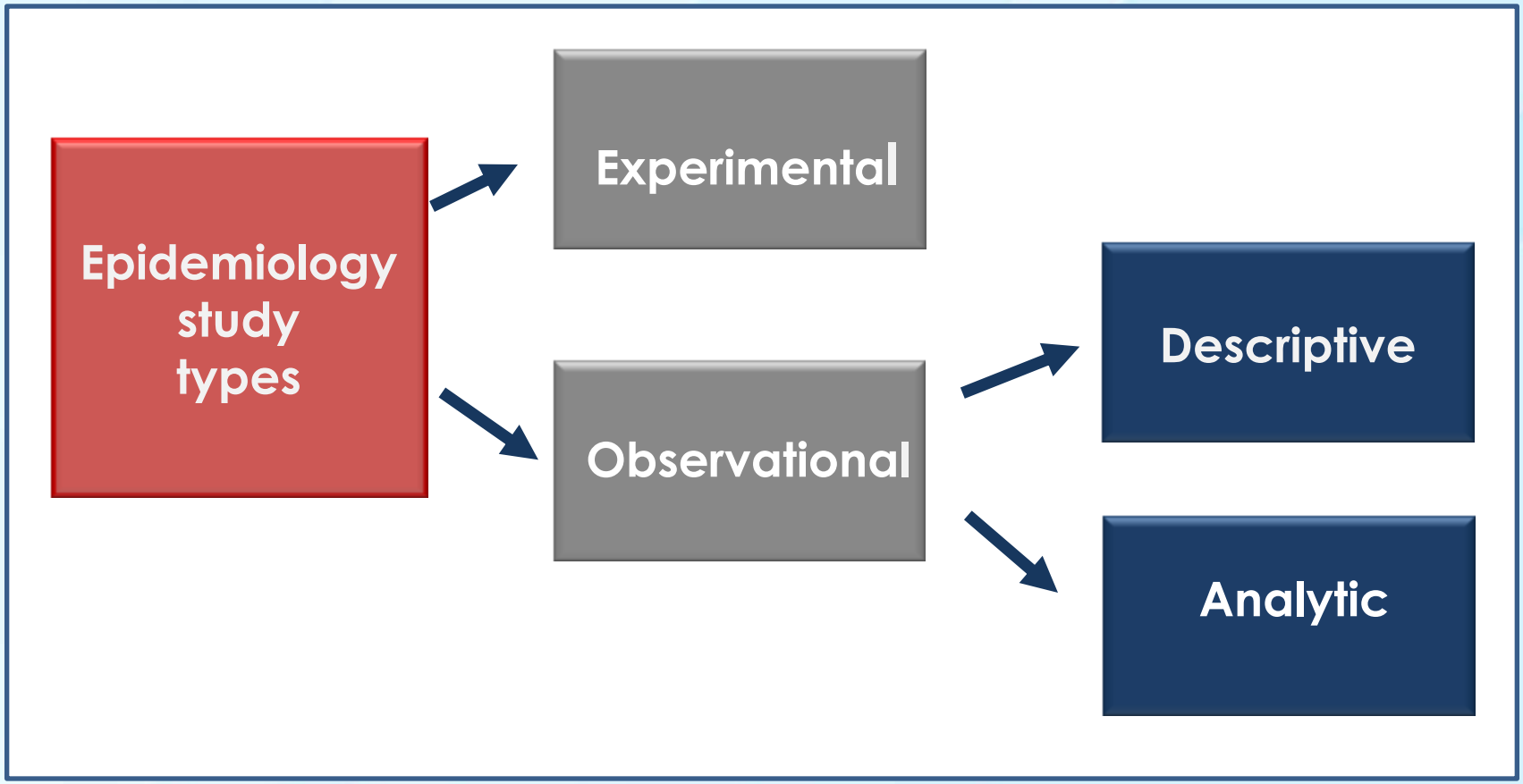
C. the number of days the conference was held.

D. the location of the conference.

Topic 5

Epidemiology Approach and Methods

Epidemiology Study Types



- In an experimental study, the investigators can control certain factors within the study from the beginning. An example of this type is a vaccine efficacy trial that might be conducted by the National Institutes of Health. In such a trial, the investigators randomly control who receives the test vaccine and who does not among a limited group of participants; they then observe the outcome to determine if it should to be used more widely
- In an observational study, the epidemiologist does not control the circumstances. These studies can be further subdivided into descriptive and analytic.
- Descriptive epidemiology is the more basic of these categories and is fundamental to what epidemiologists do. In a descriptive study, the epidemiologist collects information that characterizes and summarizes the health event or problem.

- In the analytic study, the epidemiologist relies on comparisons between different groups to determine the role of different causative conditions or risk factors.

Descriptive and Analytic Epidemiology

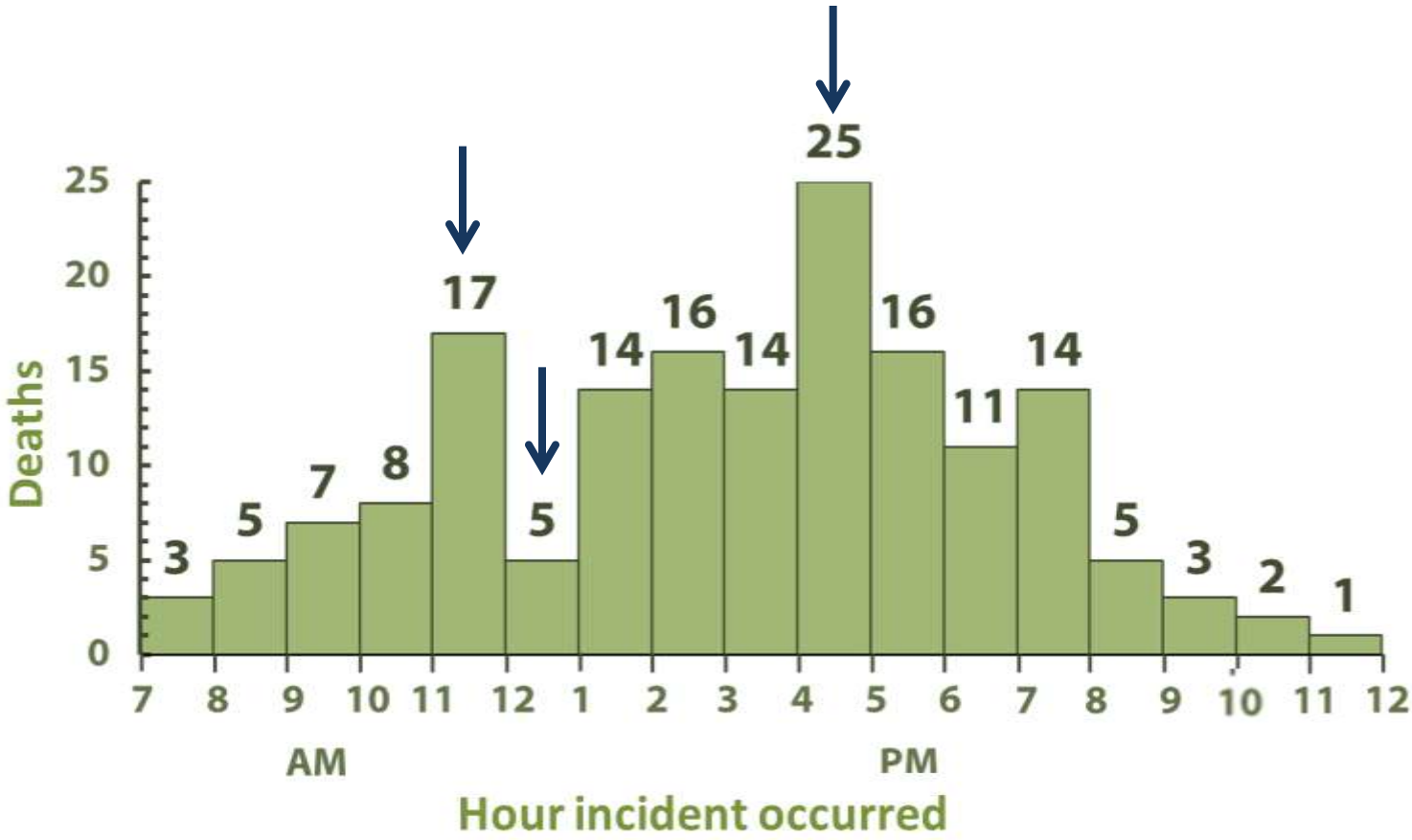
Descriptive epidemiology	Analytic epidemiology
When was the population affected?	How was the population affected?
Where was the population affected?	Why was the population affected?
Who was affected?	

Fatalities Associated with Farm Tractors

In 1982, the number of farm tractor-associated deaths was described in terms of time, place, and person by using records from an existing surveillance system

- In 1982, an epidemiologist in the Georgia Department of Public Health became interested in the number of deaths associated with farm tractors. He determined he could examine this problem by using readily available data — death certificate records that were included in an existing surveillance system. He obtained the death certificate records for all deaths that had occurred in Georgia during 1971 through 1981 that were associated with farm tractor incidents.
- After collecting the data, he used the information to describe the problem in terms of time, place, and person and then generated a hypothesis for further study.

Fatalities Associated with Farm Tractors



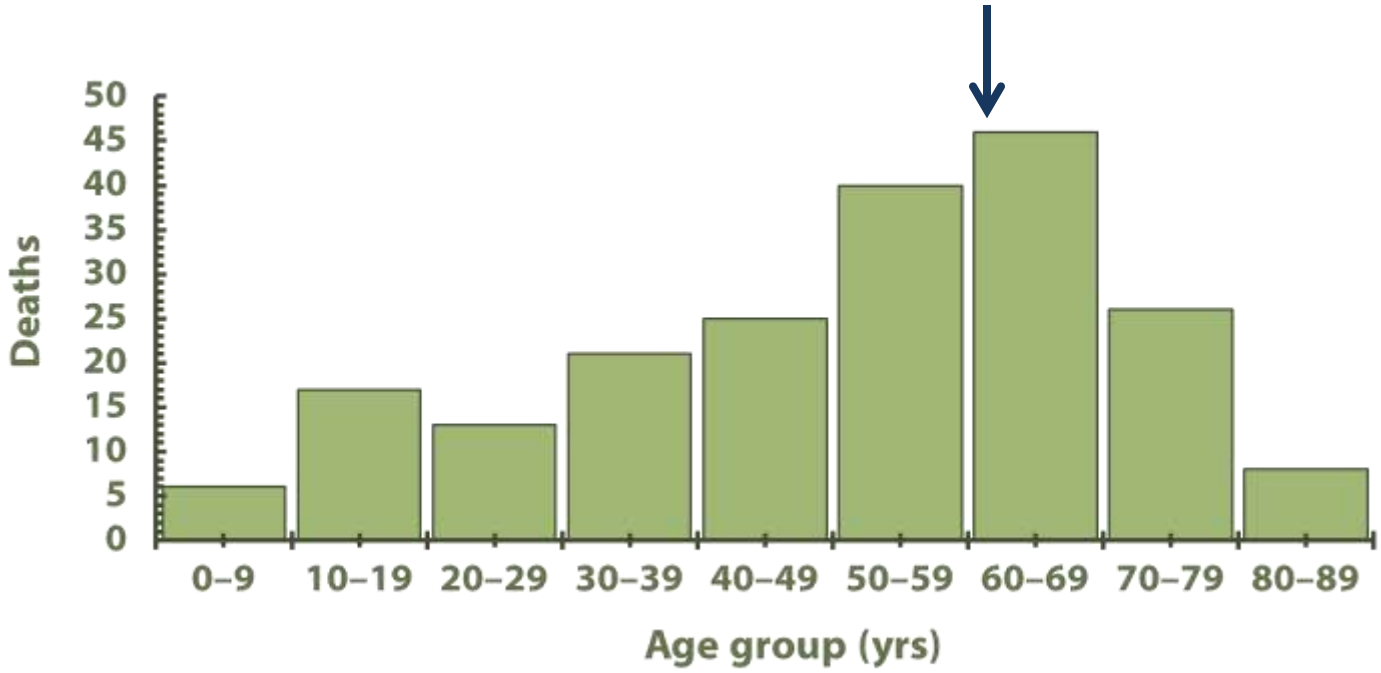
- This graph describes the when for 166 of the farm tractor-associated deaths. We can examine the data by looking at the time of day when the deaths occurred.

- What inferences can we make from this graph?

  Peaks in deaths occurred just before lunch and during late afternoon.

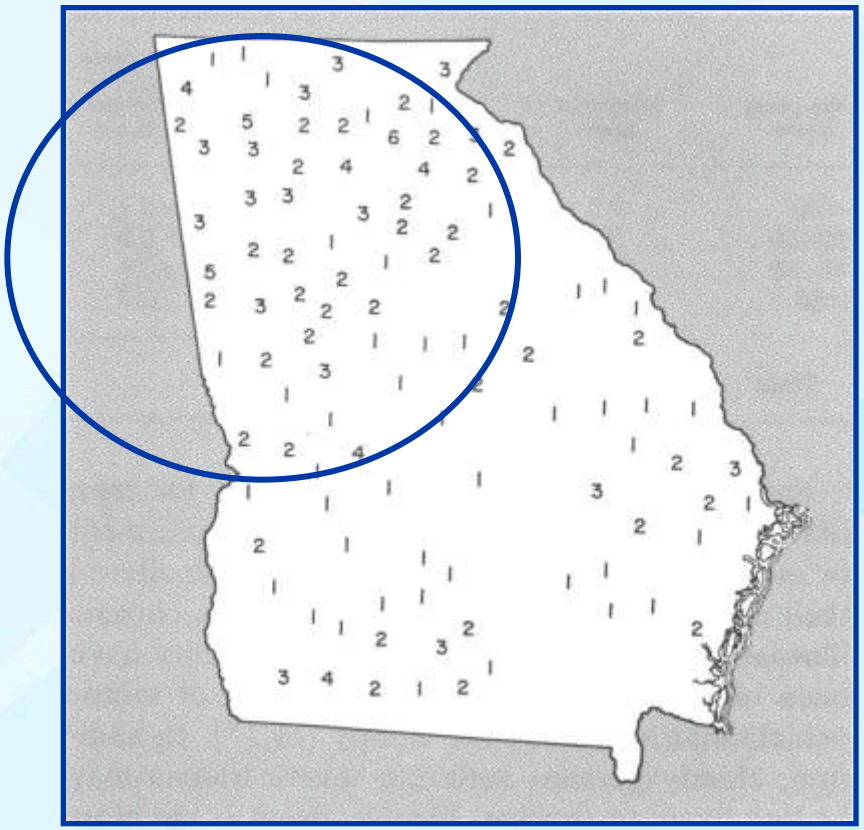
We can infer that deaths occur when farmers are probably most fatigued right before lunch, which might lead to the increase in deaths in late morning. More deaths occur in late afternoon when children are home from school. Conversely, fewer deaths occur while the farmers are probably eating their lunch.

Fatalities Associated with Farm Tractors



An increase in the number of deaths occurred among older persons, which again, is part of the descriptive analysis.

Fatalities Associated with Farm Tractors



Most of the deaths occurred in the northern areas of Georgia, which has a more mountainous terrain. Fewer deaths occurred in south-central Georgia, which is characterized by much flatter farmlands.

Knowledge Check

Choose the correct answer from the following choices:

A. Qualitative B. Experimental C. Observational

C. Observational

An epidemiologist is doing a study on the sleep patterns of college students but does not provide any intervention. What type of study is this?

Knowledge Check

Match each term to the correct example below.

A. Descriptive B. Analytic

B. Analytic 1. A study of heart disease comparing a group who eats healthy foods and exercises regularly with one who does not in an effort to test association

A. Descriptive 2. A study to describe the eating habits of adolescents aged 13–18 years in Community X

Topic 6

Epidemiology Data Sources and Study Design

Data Sources and Collection Methods

Source	Method	Example
Individual persons	• Questionnaire • Survey	• Foodborne illness outbreak • Health data on U.S. residents
Environment	• Samples from the environment (river water, soil) • Sensors for environmental changes	• Collection of water — check for chemical
Health care providers	• Notifications to health department if cases of certain diseases are observed	• Report cases of meningitis to health department
Nonhealth–related sources (financial, legal)	• Sales records • Court records	• Cigarette sales • Intoxicated driver arrests

Conducting Studies

Studies are conducted in an attempt to discover associations between an exposure or risk factor and a health outcome

Cross-Sectional Study

Patient studied based on being part of a group.

Ex. Newyorkers

women

Tall people

Cross-Sectional Study

- Frequency of disease and risk factors identified
  - how many have lung cancer
  - how many smoke
- Patient not followed for month/years
- The main outcome of this study is prevalence
  - -50% of New Yorker smoke
  - -25% of New Yorkers have lung
- May have more than one group
  - -50% of men have lung cancer and 25% of women have lung cancer
- Group not followed over time

Cross-Sectional Study

Example 1: New Yorkers were surveyed to determine whether they smoke and whether they have a morning coffee the study found a smoking prevalence of 50% among responders 25 percent reported morning coffee

- what type of study?
- what can be determined?

Cross-Sectional Study

Example 2: using a national u.s. database rates of lung cancer were determined among New Yorkers Texans and Californians lung cancer prevalence was 25% in New York 30% in Texas and 20% in California

- the researchers concluded that living in Texas is associated with higher rates of cancer so some key points here because there are different groups this might confuse you and make you think that this is some type of case control or cohort study but it's not note that there is a lack of a time frame

Cross-Sectional Study

Example 3: researchers discover a gene that they believe leads to development of diabetes a sample of 1000 patients is randomly selected all patients are screened for the gene presence or absence of diabetes is determined from a patient questionnaire it is determined that the gene is strongly associated with diabetes

- key points here note the lack of a time frame they're not following patients for years so this makes it very likely it's a cross-sectional study note that the patients are not selected by disease or exposure which is the way they're selected for cohort and case-control studies

Cohort Study

- compare a group with exposure to a group without and it's very important that you remember that this is the way patients are identified they are identified by exposure so for example if we wanted to whether smoking causes lung cancer we would identify patients based on whether they smoke or not. by monitoring them over time whether exposure changes the likelihood of disease

Cohort Study

- most cohort studies are what's called prospective it means they identify patients with without the exposure and monitor them going forward in time sometimes they're done
- retrospectively so you can look back in time and see whether or not they had disease

Cohort Study

- the main outcome measure of a cohort

study is a relative risk which is defined by the risk ratio represents how much exposure increases the risk of disease

- an example of the results you might get from a cohort study you might find that 50% of smokers get lung cancer within five years 10% of non-smokers get lung cancer within 5 years this would give you a risk ratio of 50 divided by 10 or 5 and this means that smokers are 5 times more likely to get lung cancer than non-smokers

Cohort Study

- Example: a group of 100 New Yorkers who smoke were identified based on a screening questionnaire at a local hospital these patients were compared to another group that reported no smoking both groups received follow-up surveys asking about development of lung cancer annually for the next three years the prevalence of lung cancer was 25 percent among smokers and 5 percent among non-smokers.
- what type of study ? it's a prospective cohort study

Case-Control Study

Subjects identified as having a disease or condition are compared with subjects without the same disease or condition

Case-Control Study

- the opposite of a cohort study instead of identifying exposure and looking for disease in this case we're looking for disease first and then exposure
- an example of a case control study might be people with lung cancer and your cases have to have a mixture of exposed and unexposed you can't just identify smokers with lung cancer you've got to have some smokers and some non-smokers and then you've got to go and find a control group and the control group also has to contain a mixture of smokers and non-smokers exposed or unexposed patients once you've

Case-Control Study

- Example: a group of 100 New Yorkers with lung cancer were identified based on a screening questionnaire at a local hospital these patients were compared to another group that reported no lung cancer both groups were questioned about smoking status within the past 10 years the prevalence of smoking was 25 percent among lung cancer patients and 5 percent among non lung cancer patients

Knowledge Check

Which of the following are examples of a health-related source of data collection?

A. Intoxicated driver arrests.

✓ B. Electronic health records.

✓ C. Measurement of toxins in a river.

D. Medical board action against a physician.

Knowledge Check

Match each study with correct definition.

_____ 2. A study of women aged 50–60 years in a community located close to a nuclear power facility.

_____ 3. Subjects who have received nutritional counseling and who have exercised twice a week are compared with subjects who have not.

QUESTIONS?

DEMOGRAPHY

Demography is defined as "the study of populations, especially with reference to size and density, fertility, mortality, growth, age distribution, migration, and vital statistics and the integration of all these with social and economic conditions" Vital statistics include births, deaths, population by age, sex, by location of residence, marital status, socioeconomic status, and migration. Birth data are derived from mandatory reporting of births and mortality data from compulsory death certificates. Other sources of data are population registries including marriage, divorce, adoption, immigration as well as economic and labor force statistics compiled by governmental agencies, census data, and data from special household surveys. These form the basic data sets for demographers. Demography measures trends over time of indices such as birth and death rates, rural-urban residential patterns, marriage and divorce rates and migrations, as well as social and economic conditions. Since public health deals with disease as it occurs in the population, the definition of populations and their characteristics is fundamental.

A census is an enumeration of the population recording the identity of all persons in every residence at a specified time. The census provides important information on all members of the household, including age, date of birth, sex, occupation, national origin, marital status, income, relation to head of the household, literacy, education levels, and health status (e.g., permanent handicapping conditions). Other information on the home and its facilities include type of building, number of rooms, electricity, major home appliances (e.g., stove, refrigerator), toilet and bathroom facilities (e.g., bathtub, shower), car ownership and home heating (stove or central), food purchases, and spending on clothing, entertainment, and other consumption items. Usually census surveys are carried out to determine trends in important economic or demographic data such as family incomes, nutrition, employment, and other social indicators. Accuracy of such a complex and costly process cannot be 100%, but great care is taken to assure maximum response

and standardization in interview methods and processing to assure precision. Despite its limitations, the census is accepted as the basis of statistical definition of a population.

A demographic transition occurs when there is a substantive change in the age distribution of a population. Population growth is mainly affected by birth and death rates, although other factors such as migration, war, political chaos, famine, or natural disasters may affect population distribution. Changing population patterns also accompany economic development, a process known as demographic transition. This is often characterized by the following stages:

1. Traditional: high and balanced birth and death rates;

2. Transitional: falling death rates and sustained birth rates;

3. Low stationary: low and balanced birth and death rates;

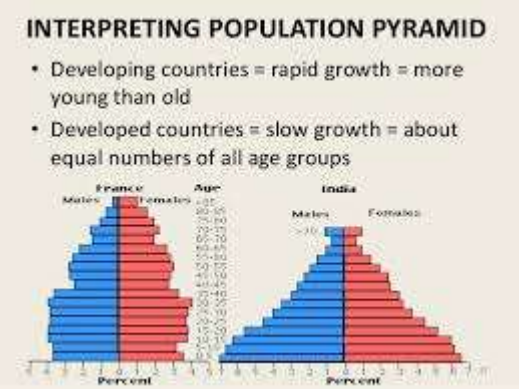
4. Graying of the population: increased proportion of elderly as a result of decreasing birth and death rates, and increasing life expectancy;

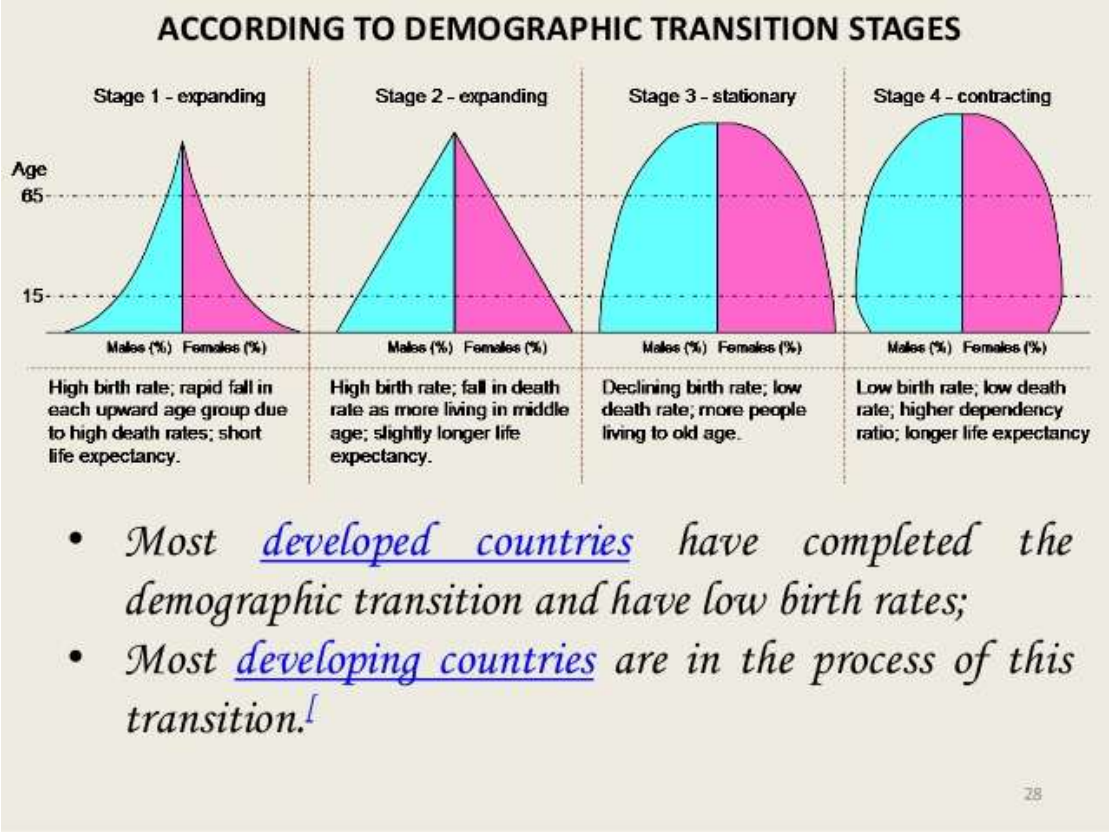
5. Regression: migration or increasing death rates among young adults due to trauma, AIDS, early cardiovascular disease or war resulting in steady or declining longevity (demographic regression).

Population Pyramid

A population pyramid provides a graphic demonstration of the age and sex at a point in time. A country or region with a wide population base has a high birth rate and a large percentage of its population under age 15, usually accompanied by limited resources and is a formula for continued poverty. A population pyramid with a narrow base (i.e., few young people) and a growing elderly population will have a smaller work force to provide for the "dependent age" population (i.e., both the young and the old). With a smaller working age population to support these costs, adverse economic consequences may prejudice costly pension and health services. Other factors may also affect the population pyramid, for example, the loss of a large number of people during wartime. This loss affects a particular age-sex group as well as

fertility patterns both during and after the war, for example, a post-war "baby boom."





Population trends

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Three major factors determine the population dynamics of a population:

- Births (fertility)
- Deaths (mortality)
- Migration

If some groups within a population grow or decline faster than others, the composition of the whole is altered. These three factors determine the most basic characteristics of a population, as well as its demographic future.

- Birth add to the population, while deaths subtract from population. Migration can either add or subtract from population.
- Therefore, the growth of nations population is determined by number of births minus the number of deaths plus the net migration rate

- $Pt = P0 + B - D \pm M$, where

Pt= population at the time in the future

P0= the base population

B= births between time 0 and t

D= deaths between time 0 and t

M= net migration

Pt, and P0 which can be obtained through census

D and B which can get through vital registration.

Fertility

- **The number of births that occur to an individual or in a population**
- In 1998, fertility rates of national populations ranged from an average of 1.2 children per woman in Italy, Latvia , Spain, and several other European countries to 7.4 children per woman in the West African country of Niger.
- In US average was 2.0
- For the world it is 2.9

Fecundity

The physiological ability of individuals or couples to have children.

- Some are infecund due to disease or genetic dysfunction.
- Mothers could be infecund when they breastfeed.

Factors accounting for fertility fecundity gaps

There are usually gaps between fertility and fecundity. What are the factors that may account for the gaps:

Cultural, economic, and health factors interfere with the process of human reproduction.

- **Cultural values** e.g. (Does the society value large or small families?)

Fertility Proximate determinants

- In US. and most developed countries ***contraceptive use and abortion*** are the most important proximate determinants. The rate of contraceptive use in US, Brazil, Australia, and few East and South East Asia have contraceptive use rates of >= 75%.
- **Spain** recorded **the lowest fertility rate** in a nation 1.15 births per woman of rep age. Basically due to 72% using contraceptives. **Russia** achieved low fertility rates due to having easier access to **abortion.**

Proximate determinants

- When contraceptive and abortion prevalence rates are low, the postpartum infecundity and marriage determinants are more important.
- African countries:

  women marry early and bring more children, but they breast feed for 2-3 years, thus prolonging the period of infecundity following childbirth.

Fertility Measurement

Birth Rate

- **The birth rate (also called the crude birth rate)**
- **It is the most easily obtained and most common reported Definition:** It gives the average annual number of births during a year per 1,000 persons in the population at midyear;

The birth rate is usually the dominant factor in determining the rate of population growth. It depends on both the level of fertility and the age structure of .the population

Fertility Measurement

Crude Birth Rate

- *There were 24 births per 1,000 population in Kuwait in 1994 :*

Number of births (38,868) divided by the Total population (1,620,086) x K (1,000)= 24.0

- In Jordan it is 26.79 est. 2011.

- Around the world, birth rates vary widely.

- In Western Sahara's, a very high birth rate 47 per 1,000 in 1996, while
- Italy's it is very low, 9 per 1,000, also in 1996,

Fertility Measurement
General Fertility Rate

- **The general fertility rate GFR, (also called the fertility rate) ,is the number of live births per 1,000 women ages 15-49 in a given year.**
- The GFR is a somewhat more refined measure than the birth rate because it relates births to the age-sex group at risk of giving birth (usually defined as women ages 15-49).

General Fertility Rate

- The GFR sums up, in a single number, the fertility of all women at a given point in time.
- Yemen's general fertility rate in the early 1990s was 238 live births per 1,000 women ages 15-49— (34 yrs) one of the highest in the world. (TFR =7)

The Czech Republic's, it was very low at a rate of 34 per 1,000 women aged 15-49 in 1996. (TFR = 1)

Mortality

- **Death Rate: Definition:** It is the average annual number of deaths during a year per 1,000 population at midyear; also known as **crude death rate.** The death rate, while only a rough indicator of the mortality situation in a country, accurately indicates the current mortality impact on population . growth

- The dramatic reduction in death rates over the last two centuries can be explained by changes in the social and economic determinants of health and to lesser extent by public health intervention.
- Death rates for infants are higher than death rates for older children. One explanation is that infants are less resistant to disease.

Crude Death Rate

- In the early 1990s, the death rate in Turkey was 6.6 per 1,000 population.

  Number of deaths (405,000)/ Total population (61,644,000) x K (1,000) = 6.6

- In the early 1990s, Guinea's death rate was 20 per 1,000 population, while Singapore's was 5 per 1,000.

- **In Jordan 2.69 deaths/1,000 population (July 2011 est.)**

Infant Mortality Rate

- **Definition:** This entry gives the number of deaths of infants under one year old in a given year per 1,000 live births in the same year; included is the total death rate, and deaths by sex, *male* and *female*. This rate is often used as an indicator of the level of health in a country.

Migration

- Migration could be immigration or emigration. Immigration refers to people moving in and emigration refers to people moving out. Young people between the ages of 20 and 30 are the most mobile. Compared to the people in a population who do not migrate, migrants have a higher levels of education. The donor area loses the investment in those individuals. The recipient area get a young, motivated, and educated citizen and has to pay nothing for that persons development.

Maternal Mortality Ratio

- The maternal mortality ratio is the number of women who die as a result of complications of pregnancy or childbearing in a given year per 100,000 live births in that year.
- Deaths due to complications of spontaneous or induced abortions are included.
- **a maternal death** is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.

Life Expectancy

- Life expectancy is an estimate of the *average* number of additional years a person could expect to live if the age-specific death rates for a given year prevailed for the rest of his or her life.
- Life expectancy is a hypothetical measure because it is based on current death rates and actual death rates change over the course of a person's lifetime.
- Each person's life expectancy changes as he or she grows older and as mortality trends change.

Population Composition

Age and Sex Composition

- Age and sex are the most basic characteristics of a population.
- Every population has a different age and sex composition— **the number and proportion of males and females in each age group—**
- This structure can have considerable impact on the population's social and economic situation, both present and future.

Population Composition
Age and Sex Composition

- Populations could be relatively young / developing countries, About 40 % less than 15 years e.g. Africa.. Jordan . Less than 4% are older groups.
- Relatively old populations (aging), developed countries, more than 10% over 65 years e.g. Europe/ Less than 25% of pop less than 15 years.

Age and Sex Composition

- Young and old populations have markedly different age compositions; as a consequence, they also have different proportions of the population in the labor force or in school, as well as different medical needs, consumer preferences, and even crime patterns.

NON COMMUNICABLE DISEASE

NCD IS A MEDICAL CONDITION OR DISEASE

- which is not infectious
- with long duration
- relatively slow in progress

- which a person is unaware of the disease unless or otherwise examined
- a silent killer of people

MAJOR NCDS

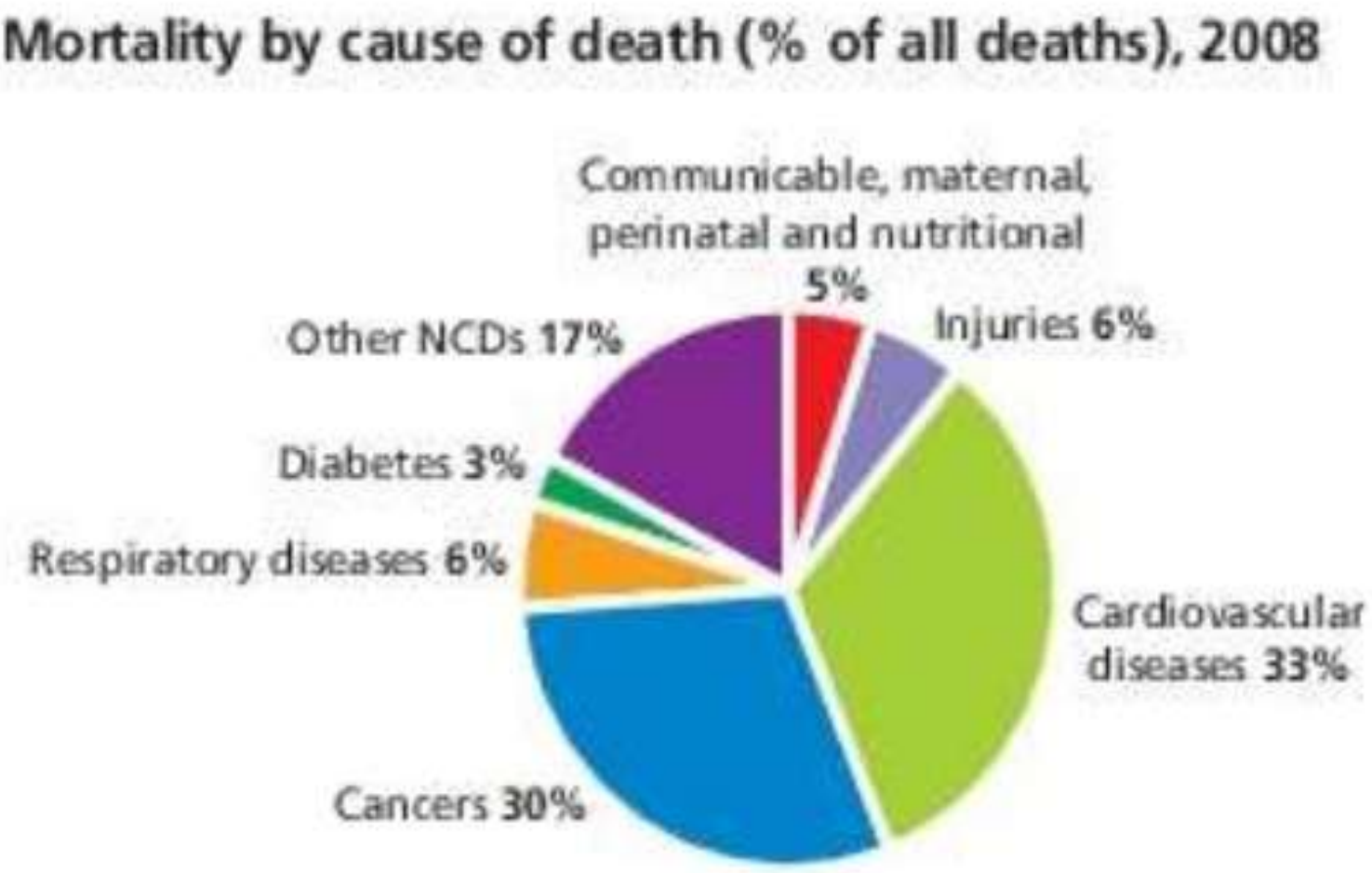
- Cardiovascular diseases- (heart attacks and strokes)
- Cancer
- Diabetes

- Chronic respiratory diseases – (asthma)

WHY … IMPORTANT TO KNOW ABOUT NCDS ??

- The number one cause of death in the world. (more than 36 million people)
  - Cardiovascular diseases- 48%
  - Cancer- 21%
  - Diabetes- 3%
  - Chronic respiratory diseases - 12%
- More than 9 million deaths are premature (under 60 years of age) and could be prevented

STATUS OF NCDS IN CANADA



http://www.commonwealthofnations.org/wp-content/uploads/2013/08/mcd-canada_CHP13.jpg

CHARACTERISTICS OF NCDS :

- Not caused by an acute infection
- Have common risk factors
- Cause long-term harm
- Need a long-term (or even life-long) treatment
- Cause both men and women equally
- Sometimes, cause disability

CAUSES FOR NCDS (RISK FACTORS)

- Unhealthy diet
- Tobacco usage
- Physical inactivity
- Stress factors
- Overweighed (obese)
- Genetics
- Harmful use of alcohol
- Environmental factors

IF YOU ...

- Have a person in your family ever had one of the NCDs
- Have High blood pressure
- Have High cholesterol level
- Are obese (over weight)
- Are exposed to air pollution
- Have raised blood glucose level
- Are exposed to Environmental factors

- **YOU ARE AT RISK !!!!!!!!!**

CLASSIFICATION OF RISK FACTORS

- **Background risk factors**- age, sex, level of education and genetic composition

  -cannot be changed

- **Behavioral risk factors**- tobacco and alcohol use, unhealthy diet and physical inactivity

  -can be modified

- **Intermediate risk factors**- elevated blood lipids, diabetes, high blood pressure and overweight/obesity

  -can be controlled

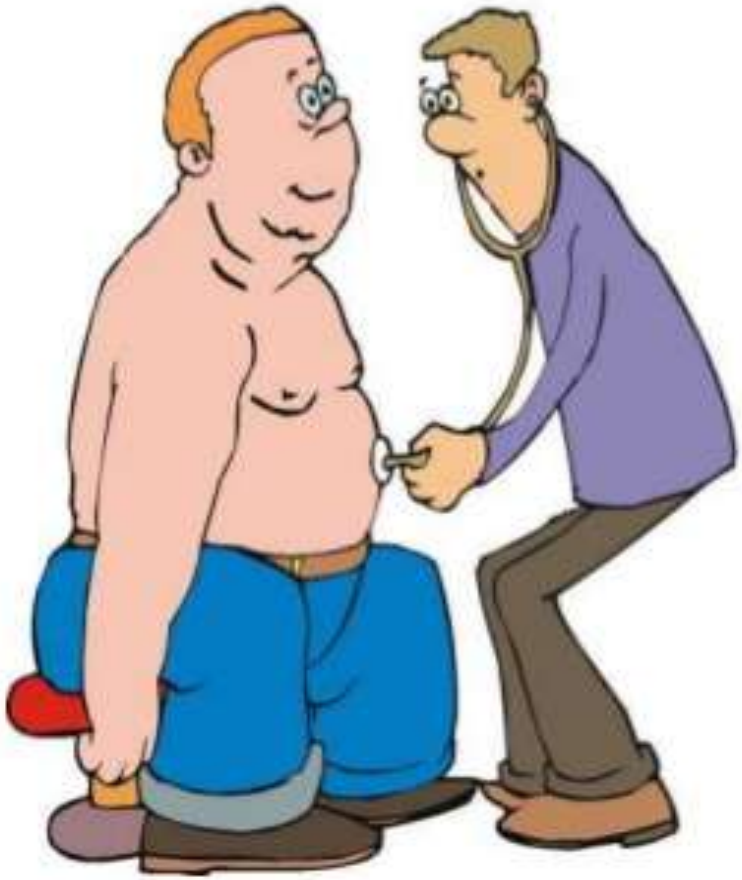
IF... MAJOR RISK FACTORS ARE CONTROLLED

- Around three-quarters of heart diseases,
- Stroke
- Type 2 diabetes
- 40% of cancer

would be prevented

HOW TO MINIMIZE THE RISK ?

- Healthy diet
- Regular exercise
- Change the environment
- Modify the habits
- Regular medical check-ups



CONCLUSION

- The NCDs may not be able to cure completely

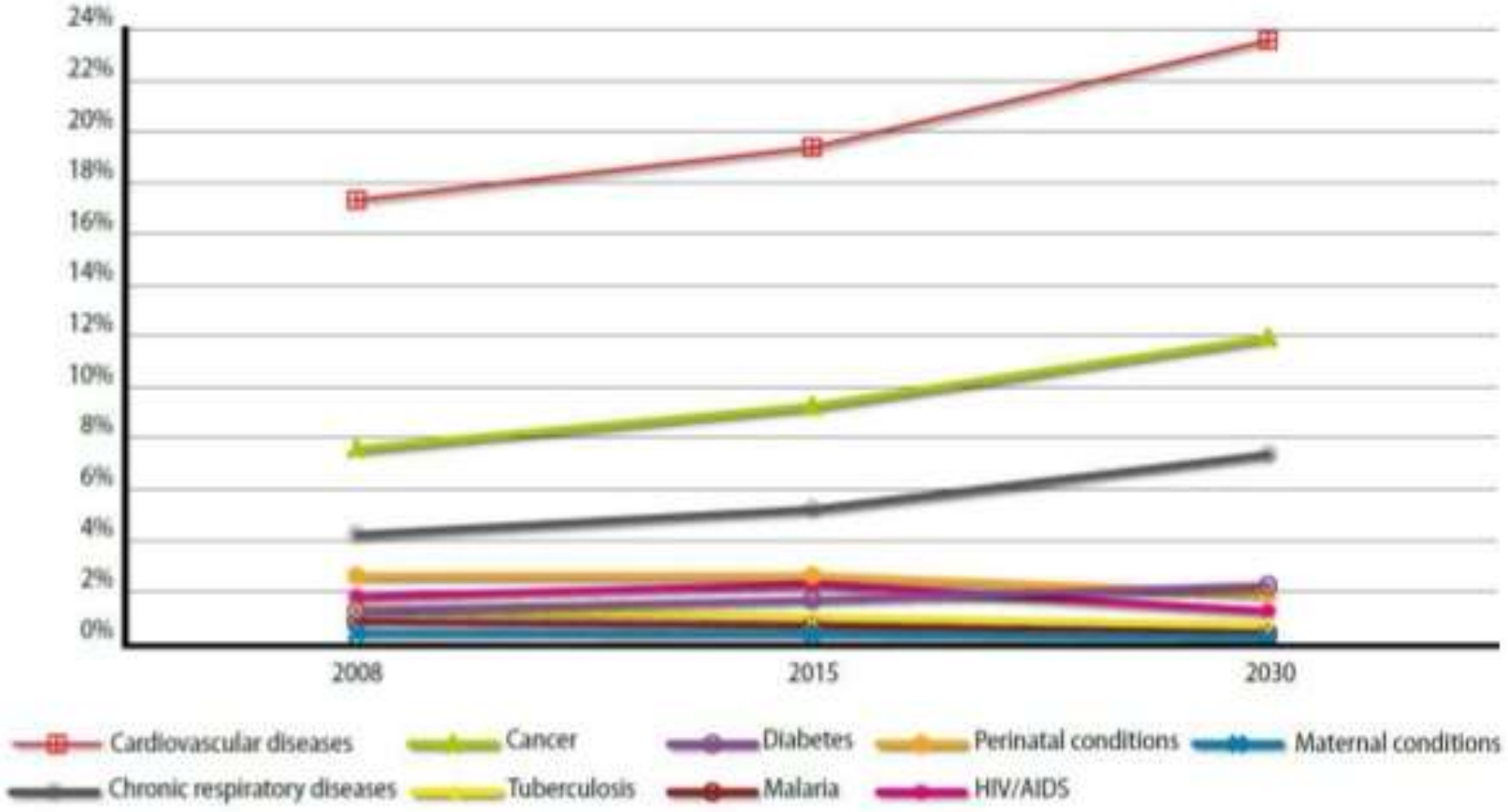
BUT

- Can be **controlled**

AND

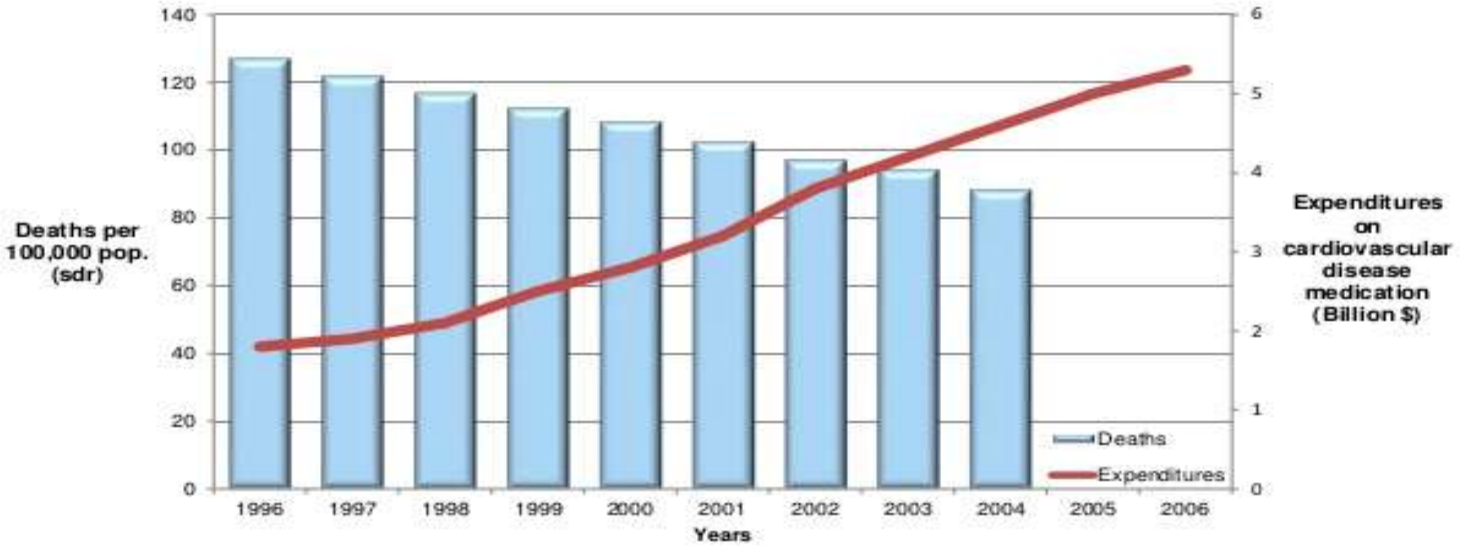
- **are preventable** through effective interventions that tackle risk factors

Figure [101] **Graph showing the projected mortality trends from 2008 to 2030 for NCDs, CVDs and communicable diseases (*5*).**



Treating NCDs is costly.

Canada's declining deaths from heart disease due in part to an increase in treatment.



Source: Centre for Chronic Disease Prevention and Control, Public Health Agency of Canada, using data from OECD HEALTH DATA 2010; and CMAJ, July 7, 2009 - 1881 (1-2).

Intervention for prevention works...

For every **$1 invested** in labelling on cigarette packages there is a **saving of $52** for the Canadian economy including **$8** for Government[1]

For Worksite Health Promotion, the Atlantic Health and Wellness Institute found that **returns per dollar** ranged from **$1.64** to **$3.98** based on employee risk factors after 3 months of intervention[2]

Sources: [1]Health Canada, 2011.
[2]Spencer & Associates, 2002.

COMMUNICABLE DISEASES

What is a communicable disease

- Can be transmitted from
- Also called, infectious, transmittable
- Spread by infectious agent (pathogens)
  - bacteria, viruses, parasites

Non-communicable diseases

- Not causes by infectious agents
- Not transmissable from person to person
  - They may be inheritable genetically
- Examples
  - Hypertension, diabetes, heart disease

Historical Pandemics

- The Black Death (plague): started in 14th century, killed 75 million people
- Cholera: killed tens of millions during the 19th century, remains a public health concern
- Influenza
- Measles
- Smallpox
- Malaria
- AIDS

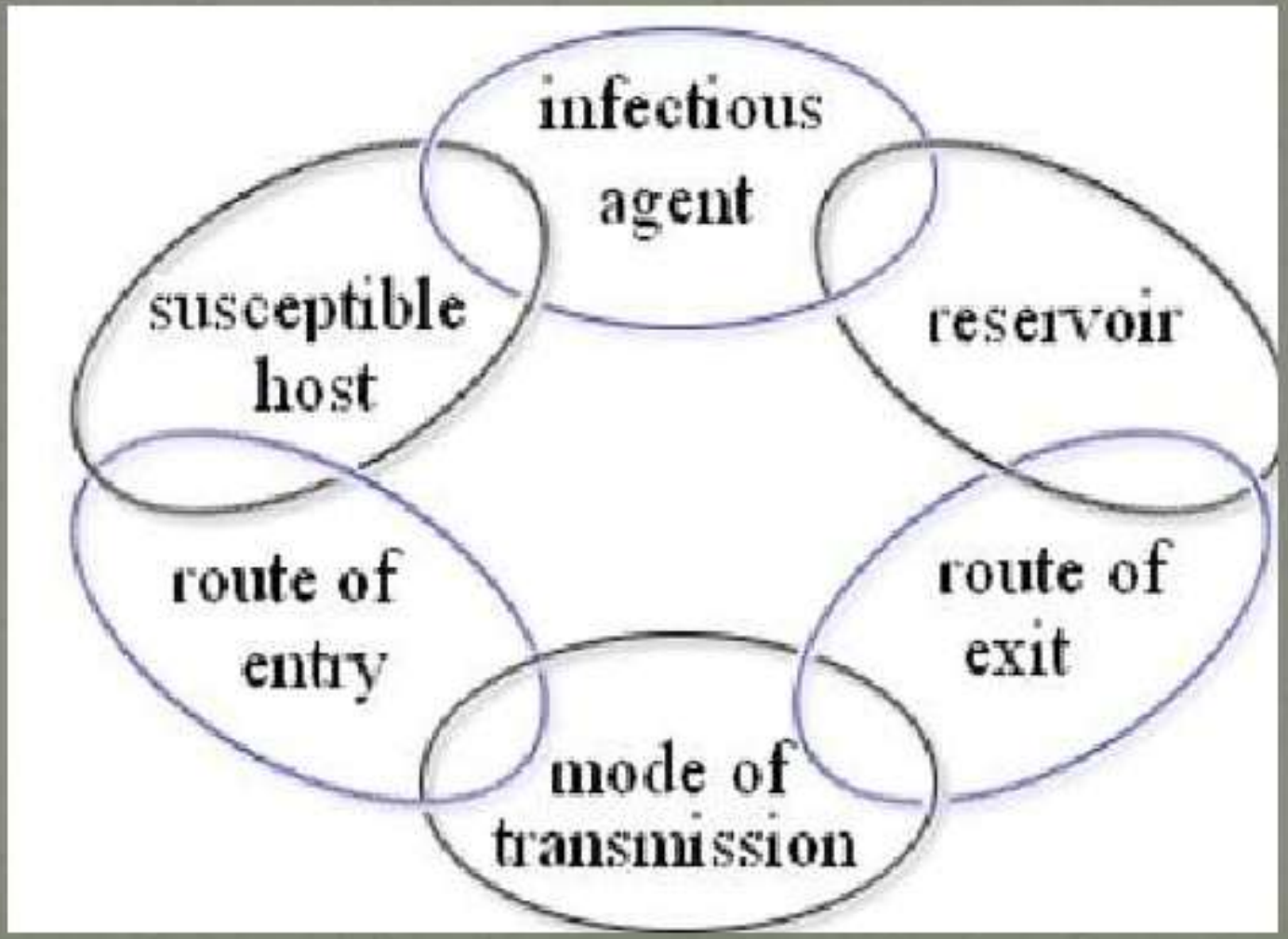
Clinical classification of communicable dz

- Diarrheal diseases
  - Symptoms: diarrhea, abdominal pain
  - Ex: cholera
- Respiratory diseases
  - Symptoms: shortness of breath, cough
  - Ex: pneumonia
- Febrile illness
  - Symptom: fever
  - Ex: Malaria

Epidemiological classification of communicable dz

- Waterborne: contaminated water
  - Ex: cholera
- Foodborne: contaminated food
  - Ex: salmonella
- Airborne: transmitted through air
  - Ex: TB
- Vector-borne: vectors like mosquitos or rats
  - Ex: malaria

Factors in disease transmission



Modes of transmission:

the route by which infectious agent is transmitted

Direct

- Physial contact
- Sexual contact
- Biting
- Direct projection of droplets
- Across placenta

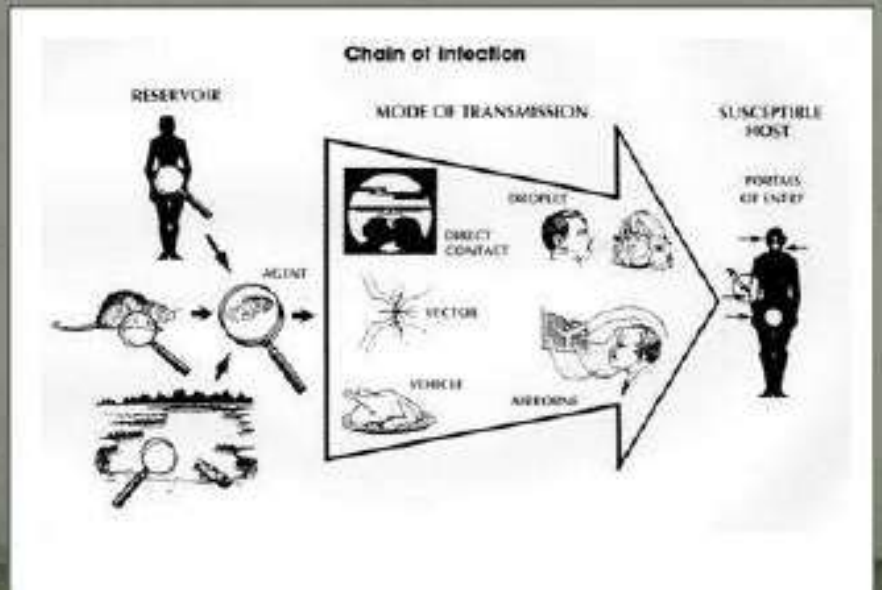
Indirect

- Air bourne
- Vector-borne
- Vehicle-borne

Reservoirs of infections agents:

where pathogens normally stay before infecting humans

- Human/animal reservoirs = infected host
  - Examples
    - Animals: dogs / rabies vrus
    - Improperly handled food: raw fish/ **Opisthorchis viverrini**
    - **Enviornmental reservoirs**



Route of Entry:

the site through which the pathogen enters the host

- Respiratory tract: breathed in through lungs
  - Ex: Mycobacterium Tuberculosis

- Gastrointestinal tract: enter through the mouth
  - Ex: diarrheal diseases
- Skin: breaks in skin integrity
  - Ex: malaria parasite after mosquito bite

Susceptible host and Risk factors

- Not every exposure results in disease
- Susceptible hosts develop the disease after exposure
- Factors that increase susceptibility: Risk factors
  - Poor or no immunity
  - Lack of vaccination
  - Poor nutrition
  - Coexistent disease

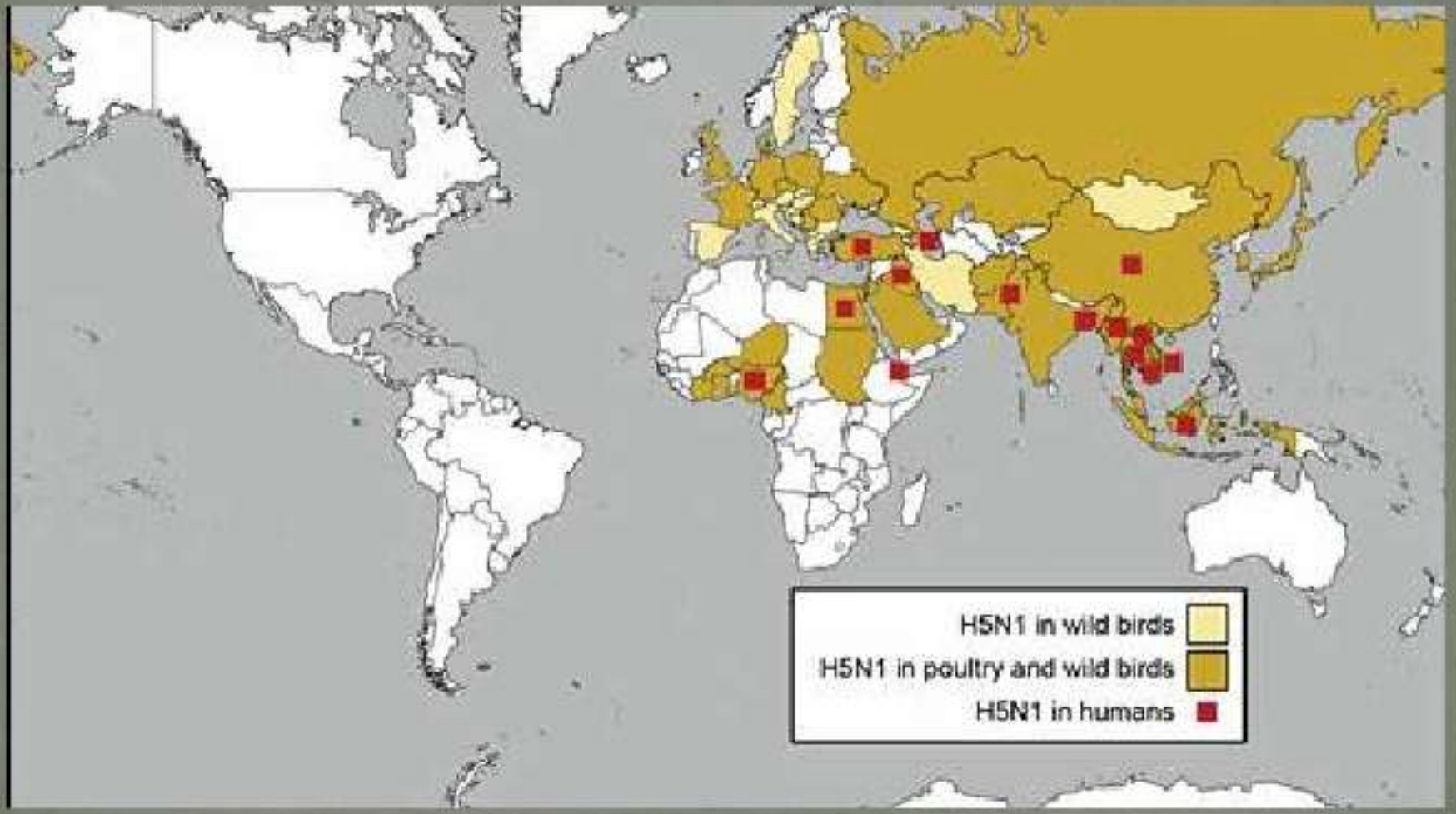
Influenza

- Viral infection
  - Affects mammals and birds
- Common symptoms
  - Chills, fever, body pain, soar throat, weakness
- Transmitted through air
  - Cough or sneeze
  - Also direct contact with bird dropping/secretions
  - Can be killed by sunlight, detergent, disinfectant

Influenza

- Global seasonal epidemics
  - 250,000-500,000 deaths annually
- Major influenza pandemics in 20th century
  - H5N1 (2009): avian flu (Asia)
  - Influenza A H1N1 (2009): swine/avian flu (N. America)
- Vaccination available for specific strains
  - Not widely available
  - Usually in developed countries
  - Usually to high risk populations

H5N1 pandemic 2009



Severe Acute Respiratory Syndrome
SARS

- Viral respiratory disease in humans
- Hong Kong, 2009 epidemic
- 8422 cases, 900 deaths
  - 10% fatality
  - Spread to 37 countries in a few weeks
- Did not reach pandemic proportions

Tuberculosis

- Most deadly infectious disease
  - Soon will be overtaken by AIDS
- Caused by bacteria, *Mycobacterium tuberculosis*
- Spread through the air from infected cough/sneeze
- Classic symptoms:
  - Chronic cough, blood tinged sputum, fever, night sweats, weight loss
- One third of global population infected with TB bacteria
  - 1 new infection every second

HIV/AIDS

- Globally : 33 million people living with HIV
  - 0.8% of adult population
  - 2.6 million newly infected in 2009
  - Most new infecting in developing countries
  - New cases decreased 16% from 2001-2009
  - Women account for 51% of people living with HIV
- SEAR: 3.5 million people living with HIV
  - India, Indonesia, Myanmar, Nepal, Thailand

Malaria (mainly *P. falciparum*)

- Impact:
  - > 2 billion people at risk
  - +/- 300 million cases/yr
  - +/- 2 million deaths/yr., mainly African kids
- Biology:
  - Vector-borne (Anopheles mosquito)
  - Gradually acquired, incomplete immunity

Malaria: Control

- Bednets, especially when insecticide-treated
- Early diagnosis & treatment requires access to functioning lab, effective drugs
- Domiciliary spraying
- Control of larval breeding
  - Environmental, chemical, biological
- Chemoprophylaxis of selected groups
- Vaccine: not yet

- Multiple organisms
  - Rotavirus and other viruses, various types of *E. coli*, Salmonella, Shigella, Campylobacter, giardia, cr yptosporidia, ? helminths etc.
- Different types/patterns of diarrhea:
  - acute watery, dysentery, chronic
- Main mechanism of death, esp. in acute watery dd
  - Dehydration
- Risks:
  - unsafe drinking water, poor sanitation, unavailable washing water, malnutrition, not breast feeding, probably HIV, traditional treatment practices, and misuse of medication

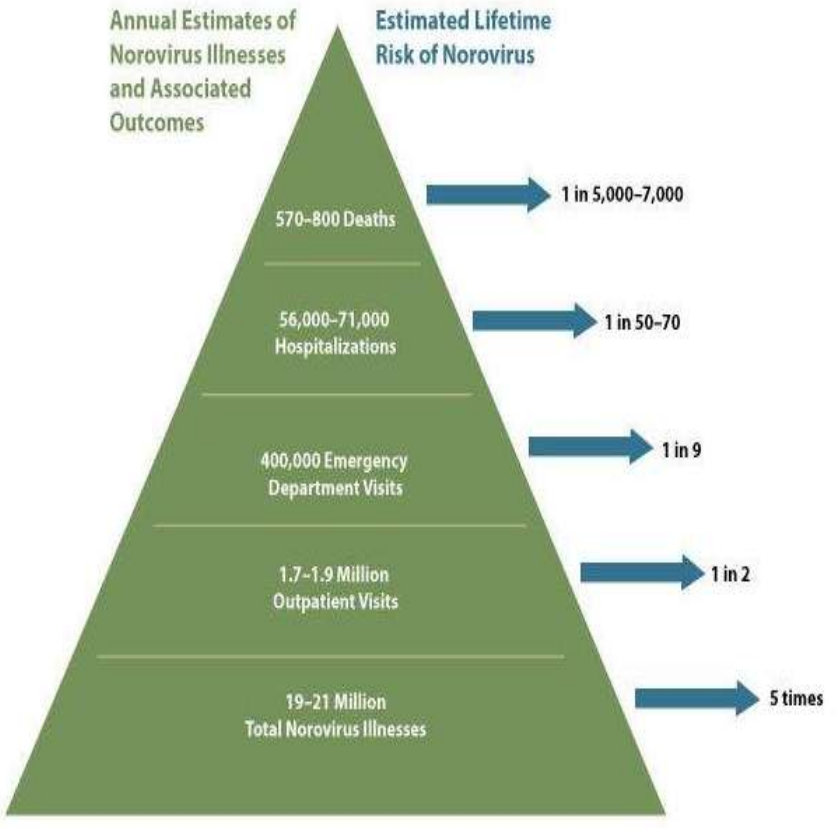
Diarrhea: Prevention & Management

- Prevention:
  - Better drinking water, better sanitation, more washing water, food safety, hygiene, breast feeding & food safety, immunization
  - ??rotavirus vaccine
- Management
  - Oral rehydration with appropriate fluid (cereal-based ORS probably better)
  - Continued breast (or other feeding if weaned)
  - Avoid dangerous traditional practices (withholding oral intake, purges etc.)
  - Train health workers that ORS, not medicines, is the treatment (except for dysentery).

NOROVIRUS

NOROVIRUS

- Norovirus is very contagious.
- Is the most common cause of acute gastroenteritis in the US.
  - Causes 19-21 million illnesses
  - Contributes to 56,000-71,000 hospitalizations
  - 570-800 deaths
- Can spread quickly in closed places, such as daycare centers, nursing homes, schools and cruise ships.
- Causes acute but self-limited diarrhea, often with vomiting, abdominal cramping, fever and fatigue.
  - Most individuals recover from acute symptoms with 2-3 days, but can be more severe in vulnerable populations.



NOROVIRUS

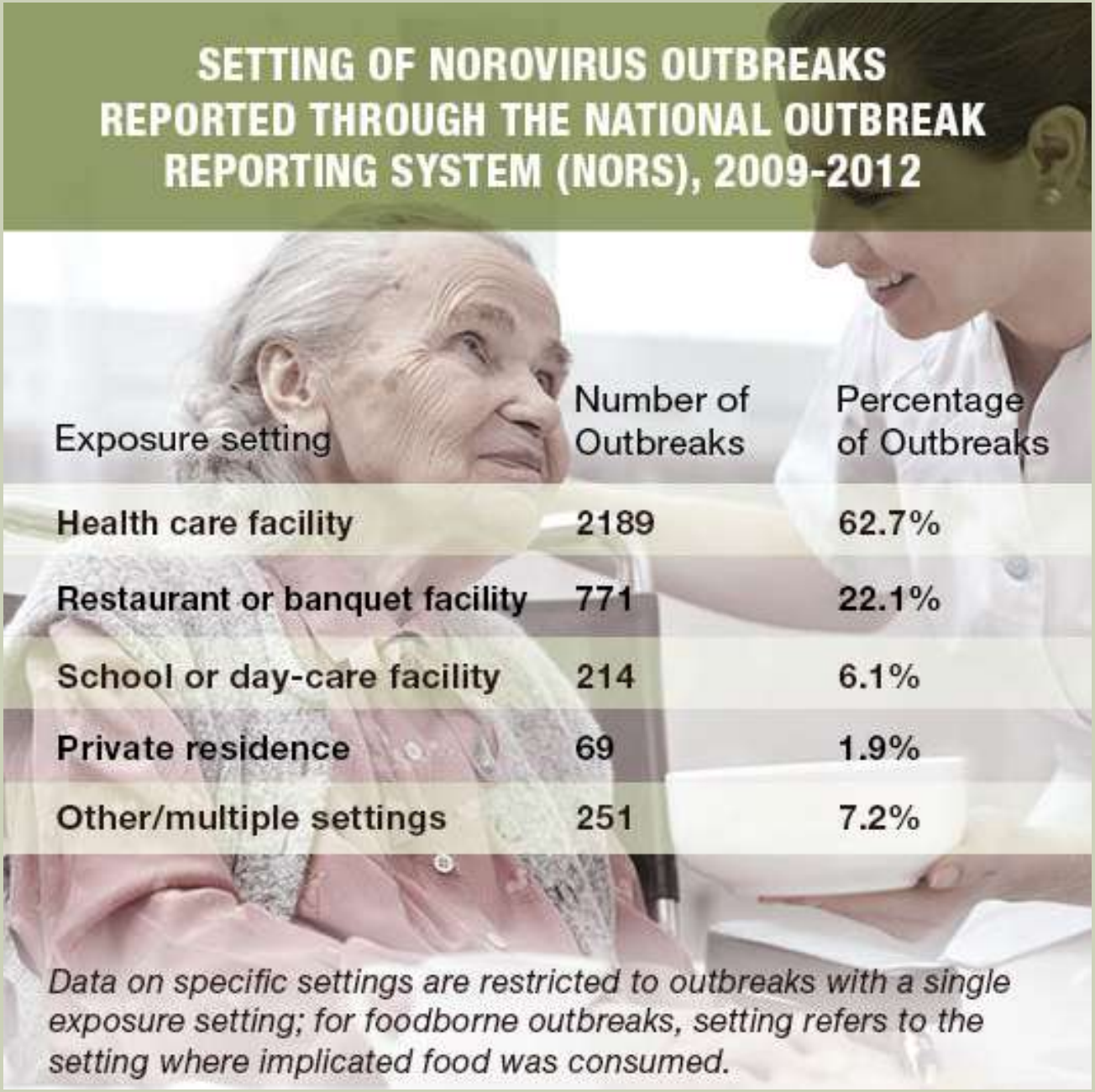
- Norovirus was first identified as the cause of a gastroenteritis outbreak in Norwalk, Ohio, in 1968
- Noroviruses are a group of nonenveloped, single-stranded RNA viruses classified into the genus *Norovirus* (previously referred to as Norwalk-like viruses or small round-structured viruses) of the family *Caliciviridae*.
- Noroviruses can be divided into at least five genogroups, designated GI--GV, based on amino acid identity in the major structural protein. The strains that infect humans are found in GI, GII, and GIV, whereas the strains infecting cows and mice are found in GIII and GV, respectively

NOROVIRUS OUTBREAKS

- Periodic increases in norovirus outbreaks tend to occur in association with the emergence of new strains that evade population immunity. These emergent strains rapidly replace existing strains predominating in circulation and can sometimes cause seasons with unusually high norovirus activity

NOROVIRUS IN HEALTHCARE FACILITIES

- Norovirus is a recognized cause of gastroenteritis outbreaks in healthcare facilities.
- Healthcare facilities are the most commonly reported settings of norovirus gastroenteritis outbreaks in the US.
- Outbreaks of gastroenteritis in healthcare settings pose a risk to patients, healthcare personnel, and to the efficient provision of healthcare services.



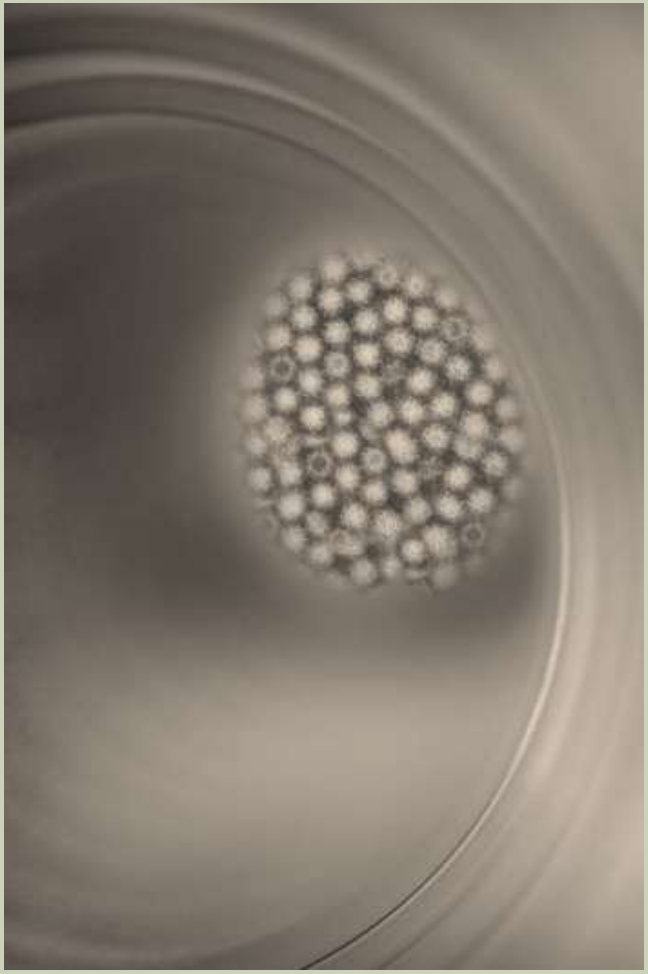
SETTING OF NOROVIRUS OUTBREAKS REPORTED THROUGH THE NATIONAL OUTBREAK REPORTING SYSTEM (NORS), 2009-2012

Exposure setting	Number of Outbreaks	Percentage of Outbreaks
Health care facility	2189	62.7%
Restaurant or banquet facility	771	22.1%
School or day-care facility	214	6.1%
Private residence	69	1.9%
Other/multiple settings	251	7.2%

Data on specific settings are restricted to outbreaks with a single exposure setting; for foodborne outbreaks, setting refers to the setting where implicated food was consumed.

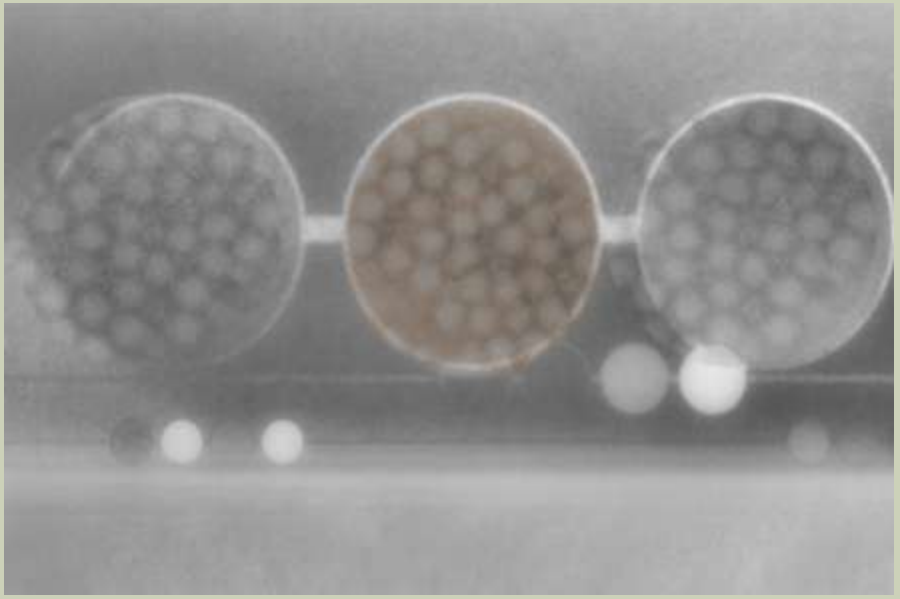
CLINICAL DISEASE

- Infectious dose: 18-1000 viral particles
- Incubation period: 12-48 hours
- Acute-onset vomiting and/or diarrhea
  - Watery, non-bloody stools
  - Abdominal cramps, nausea, low-grade fever
  - 30% infections asymptomatic
- Most recover after 12-72 hours
  - Up to 10% seek medical attention; some require hospitalization and fluid therapy
  - More severe illness and death possible in elderly and those with other illnesses



VIRAL SHEDDING

- Primarily in stool, but can also be present in vomitus
- Shedding peaks 4 days after exposure
- In some individuals, shedding may occur for at least 2-3 weeks
- May occur after resolution of symptoms



TRANSMISSION OF DISEASE

- Person to person
  - Direct fecal-oral
  - Ingestion of aerosolized vomitus
  - Indirect via fomites or contaminated environment
- Food
  - Contamination by infected food handlers
- Recreational and Drinking Water
  - Well contamination from septic tank
  - Chlorination system breakdown
- **In healthcare, the most likely and common modes of transmission are through direct contact with infected persons or contaminated equipment**

IMMUNITY TO NOROVIRUS

- Short-term immunity after infection
- There is little cross protective immunity (against different genotypes)
- No long-term immunity
  - Protection believed to last less than one year, and in some studies, protection may only last a few months
- Genetic susceptibility
  - A portion of the population may be genetically resistant to norovirus infection
  - Currently no commercially available test to identify those who might carry genes conferring resistance to norovirus infection

LABORATORY CONFIRMATION OF NOROVIRUS

- Reverse transcription polymerase chain reaction (RT-PCR) confirmation is the preferred diagnostic for norovirus
  - Differentiate genogroup I and genogroup II norovirus
- Rapid commercial assays have recently been cleared by FDA for preliminary identification of norovirus when testing multiple specimens during outbreaks
  - Poor sensitivity (50%)
  - Samples that test negative should be confirmed by second technique

WHAT SHOULD STAFF DO IF THEY SUSPECT NOROVIRUS?

- Key Infection Control Activities
  - Rapid identification and isolation of suspected cases of norovirus gastroenteritis
  - Communicating the presence of suspected cases to Infection Preventionists
  - Promoting increased adherence to hand hygiene, particularly the use of soap and water after contact with symptomatic patients
  - Enhanced environmental cleaning and disinfection
- Promptly initiate investigations
  - Collection of clinical and epidemiological information
  - Obtain clinical samples

INFECTION CONTROL: PATIENT ISOLATION OR COHORTING

- In healthcare settings where risk of transmission is high, use of isolation precautions is often the most effective means of interrupting transmission

- CONTACT PRECAUTIONS – single occupancy room with a dedicated bathroom, strict adherence to hand hygiene, wear gloves and gown upon room entry
  - Use Contact Precautions for a minimum of 48 hours after the resolution of symptoms
  - Symptomatic patients may be cohorted together
  - Exclude ill staff members and food handlers in healthcare facilities for a minimum of 48 hours following resolution of their symptoms
  - Exclude non-essential personnel and visitors

INFECTION CONTROL: HAND HYGIENE

- Wash hands with soap and water after contact with symptomatic patients
- Alcohol-based hand sanitizers
  - Currently available products appear to be relatively ineffective against norovirus
  - Consider using FDA-compliant alcohol-based hand sanitizers for other indications (e.g., before contact with norovirus patient)

INFECTION CONTROL:
ENVIRONMENTAL CLEANING AND DISINFECTION

- The use of chemical cleaning and disinfecting agents are key in interrupting norovirus spread from contaminated environmental surfaces
- Increase the frequency of cleaning and disinfection of patient care areas and frequently touched surfaces
  - e.g., increase ward/unit level cleaning to twice daily, with frequently touched surfaces cleaned and disinfected three times daily
- It is critical to follow manufacturer instructions for methods of application, amount, dilution and contact time.

INFECTION CONTROL: OTHER CONSIDERATIONS

- To reduce transmission, and depending on the magnitude of the outbreak, cohort staff to care for patients who are
  - Asymptomatic unexposed
  - Asymptomatic, potentially exposed
  - Symptomatic
- Remove shared food items for staff or patients for the duration of the outbreak
- Group activities for patients may need to be suspended; minimize patient movements within a patient care area to help control transmission

SURVEILLANCE FOR NOROVIRUS CASES

- Units can use a “line list” to track symptomatic staff and patients
- During an outbreak, collect key information to assist with controlling the outbreak and to inform outbreak details
- Suggested line list elements
  - Case (staff/patient) identifier
  - Case location
  - Symptoms
  - Outcome/Date of Resolution
  - Diagnostics submitted

REPORTING OUTBREAKS

- Internal Communication
  - Report gastroenteritis outbreaks (e.g., 2 or more suspected or confirmed cases among staff or patients) to infection control units
  - Outbreaks should also be reported to clinical management
  - Important to include communications, laboratory, environmental services, admitting, occupational health departments

Zika Virus

- Background: virology
- Epidemiology
- Research
- Public Health recommendations
- Future: vaccines
- Where to get more information

What is Zika?

Zika is a virus primarily transmitted by certain types of mosquitoes

In pregnant women, Zika infection is linked to microcephaly – a birth defect in which a baby's head is smaller than expected

There is no vaccine or treatment for the Zika virus

Where is Zika Found?

The virus has been known about since 1947, but was not present in the US

Previously outbreaks occurred in Africa, Southeast Asia, and the Pacific Islands

Recently, it has been spreading throughout Latin America and the Caribbean and outbreaks are occurring in many countries

How is Zika Spread?

Mosquitos:

- *Aedes* family of mosquitos
- Known as “tiger” mosquitoes
- Different from West Nile mosquitos
- *Aedes* mosquitos bite during the day and at night
- Need small amounts of water to reproduce (amount of water in a bottle cap)

Zika Virus Symptoms

- Asymptomatic infections are common, only one in four people infected with ZIKV are believed to develop symptoms.

- The disease symptoms are usually mild and last for 2 to 7 days.

- Signs and symptoms suggestive of Zika virus infection may include a combination of the following:

- Maculo-papular rash (90%)
- itching or pruritus
- fever (65%)
- headache (45%)
- arthralgia or arthritis (65%)
- myalgia (48%)
- lower back pain
- retro-orbital pain (39%)
- oedema (19%)
- vomiting (10%).

From a pregnant woman:

If a woman is pregnant and becomes infected with Zika through a mosquito bite or sexual transmission, her fetus is at risk for Zika

How is Zika Spread?

Sexual contact:

If a man with Zika virus (even if he doesn't show symptoms) engages, he can transmit the virus to his partner

Through travel:

If someone travels to an area with Zika transmission and gets Zika, then returns and gets bitten by a mosquito, that

Baltimore for example has the mosquitoes that transmit Zika

Baltimore's urban landscape makes an ideal breeding ground

Lots of travel, especially in summer months

How do I know if I have Zika?

Only 1 of 5 people will even show symptoms

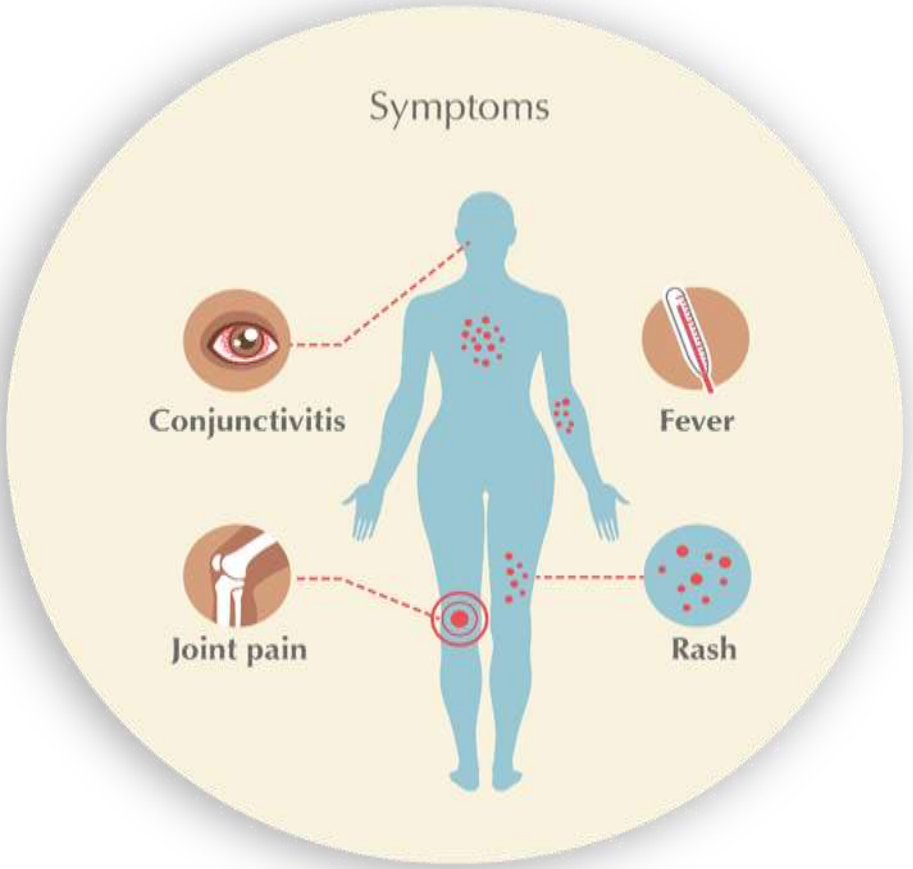
Symptoms include:

mild fever

rash

joint aches

red eyes



How do I treat Zika?

There is no vaccine for Zika

There are no medications to treat Zika

Prevention is the best way to protect yourself

Mosquito season starts at the beginning of May- be prepared!

How do I prevent mosquito bites?

Reduce breeding grounds! Eliminate standing water!

Empty or turn over anything that has collected water such as buckets, planters, toys, pools*, birdbaths, flowerpots, or trash containers

Properly dispose of unwanted objects like old tires, broken toys, etc.

Cover trash cans or other items or containers that can collect water

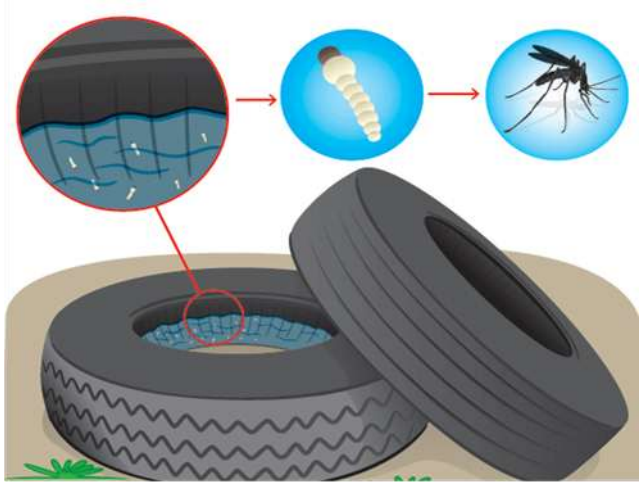
Check inside and outside your home

*chlorinated pools are ok

How do I prevent mosquito bites?

Pick up trash and litter in your neighborhood— the amount of water in a bottle cap is enough for mosquitoes to lay eggs

Join a community cleanup to target problem areas where trash may be accumulating



How do I prevent mosquito bites?

Keep mosquitoes out of your home

Keep screens on your windows and doors and repair any holes

Use air conditioning

when possible

How do I prevent mosquito bites?

Wear light weight, long sleeved shirts and pants

Treat clothing with permethrin spray

Permethrin is an insecticide that kills mosquitoes

Do not use permethrin on skin

Follow instructions on package

How do I prevent mosquito bites?

Use safe and effective repellents- Always follow product instructions

Do not spray repellent on skin under clothing- spray the clothing

If using sunscreen, put sunscreen on first, then insect repellent

How do I protect my family from mosquitos?

For babies and children:

Cover stroller and baby carrier with mosquito netting when outside

Do not use products containing oil of lemon, eucalyptus or para-menthanediol on children younger than 3 years old

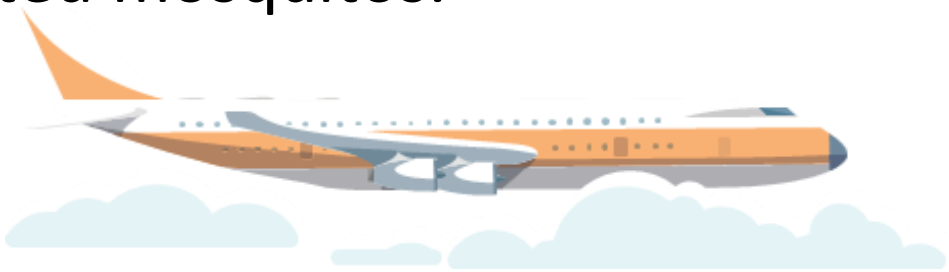
Do not use insect repellents on babies younger than 2 months old

What should I do if I travel to an area with Zika?

Strictly follow steps to prevent mosquito bites to protect yourself and your family

Even if you do not feel sick, take steps to prevent mosquito bites for 3 weeks after you return

This will help prevent the spread of Zika to uninfected mosquitos.



Women who are planning pregnancy

After a woman leaves an area with active Zika virus transmission, it is recommended that she should avoid becoming pregnant for 8 weeks

- Should also consider partner's status..

What should pregnant do ?

Delay travel to areas with Zika transmission. If you travel, talk to your doctor before your trip

If you want to get pregnant, talk to your doctor before you travel

Take extra precautions to avoid mosquito bites

What do I do if I get bitten?

If you get bitten and start showing Zika symptoms (fever, rash, joint pain, red eyes) call your health care provider

Your health care provider will determine whether or not you should receive Zika testing

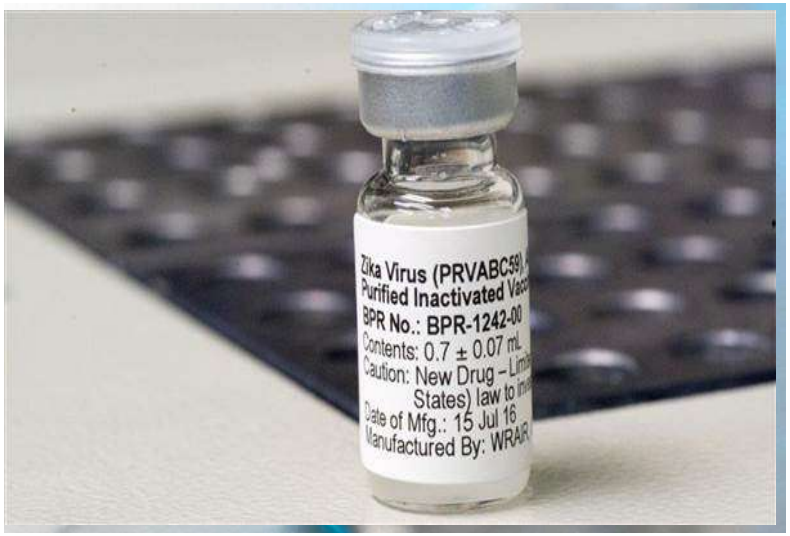
What is the Health Department doing?

Surveillance to determine where Aedes mosquitoes are present

Responding to standing water reports to eliminate standing water

If you see standing water in your neighborhood, eliminate if possible.

Vaccines



- US National Institute for Allergy and Infectious Disease has already created vaccine platforms for other flaviviruses that can be used as a starting point for a Zika vaccine.
- Several vaccine approaches:
  - A DNA-based vaccine that uses a strategy similar to a flavivirus vaccine for West Nile Virus (already tested in phase 1 trials)
  - A live-attenuated Zika vaccine building on a similar vaccine approach for dengue virus.

Congratulations!
This is the last lecture

WHAT'S FLU TO YOU? STOMACH "FLU" VERSUS INFLUENZA

Dr. Shaymaa A. Majed

“I HAD THE FLU…”

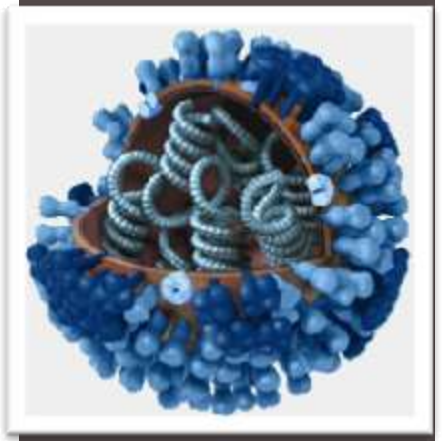

Pepto-Bismol
BISMUTH SUBSALICYLATE
UPSET STOMACH RELIEVER/ANTIDIARRHEAL
CHERRY
16 FL OZ (1 PT) (473 mL)

“I HAD THE FLU…”

INFLUENZA = "FLU"

INFLUENZA ≠ STOMACH "FLU"

INFLUENZA



Influenza pandemics—frequency

- Occur about every 30 years, or about three times each century
- New strain of flu not recognized by the immune systems of the population
- Rapidly spread worldwide

www.globalchicago.org

The Spanish Flu Pandemic of 1918

Killed more people than any other disease in history

Caused more deaths than WWI, WWII, the Korean War, and the Vietnam War combined

Unusually high attack rates among young and otherwise healthy adults (soldiers)

Doughboys - 1918
Info.detnews.com

INFLUENZA

- A common seasonal respiratory disease associated with high levels of morbidity and mortality each winter.

- Common symptoms:
  - Fever
  - Cough
  - Sore throat
  - Headache
  - Body aches
  - Chills

- Less common: vomiting (mostly in children)

CLINICAL DISEASE

- Abrupt onset of respiratory disease typically lasting 3-7 days, with related malaise and cough lasting up to two weeks.
- Common complications include: pneumonia, bronchitis, sinus and ear infections and exacerbation of existing respiratory issues.
- High risk groups: children, the elderly, pregnant woman and immunocompromised individuals.
- Incubation period: 2 days.

TRANSMISSION

- Infected persons can spread influenza about one day prior to symptom onset, and 5 to 7 days after symptom development. Children may be able to spread the virus for longer than 7 days.

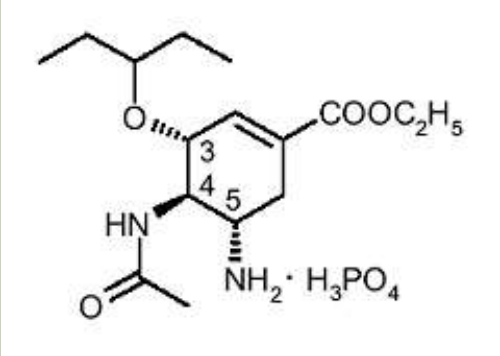
- Influenza is mainly transmitted via respiratory secretions in droplet form. Contact within contaminated surfaces is a secondary source of transmission.

- General prevention efforts include:
  - **Vaccination**
  - Hand washing
  - Disinfection of surfaces
  - Not touching face with unwashed hands
  - Staying home when ill and avoiding others who are ill

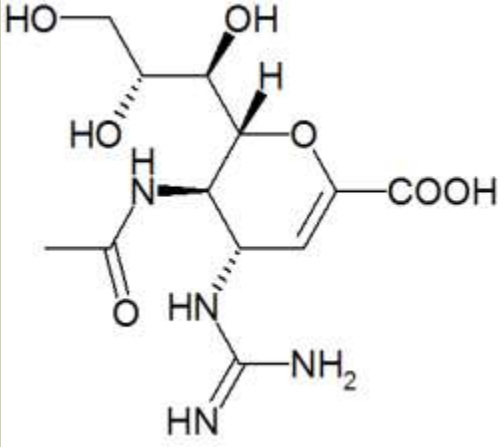
LABORATORY CONFIRMATION

- Positive influenza lab tests are
  - PCR
  - Respiratory Viral Panel (RVP)

INFLUENZA ANTIVIRALS



Oseltamivir (Tamiflu)



Zanamivir (Relenza)

Treatment with influenza antivirals is recommended in a hospital setting for all confirmed and suspected cases of influenza when the patient is in a high-risk category. **The recommendation is to NOT WAIT for a positive test to begin antiviral treatment.**

INFLUENZA ANTIVIRALS

In facilities with residents, treatment or prophylaxis with influenza antivirals are recommended for:

- All confirmed and suspected cases of influenza when the patient is in a high risk category (treatment dose).
- All resident contacts of confirmed and suspected cases of influenza when the contact is in a high-risk category (prophylactic dose):
  - Roommates
  - partners
  - Residents on the same floor/wing/etc.
- ***NEW!*** All long term care staff contacts of confirmed and suspected cases during H3N2 seasons when the vaccine is poorly matched to the circulating strain (like 2014-15, prophylactic dose).

INFECTION PREVENTION: VACCINATION

Yearly seasonal influenza vaccination is recommended for patients, residents, family members and health care workers.

- Different kinds of seasonal influenza vaccines are available.
- No current recommendations for particular vaccine types over others.

INFECTION CONTROL: ACTIVE SURVEILLANCE

- Daily active surveillance of residents, staff and visitors for a health care facility should be initiated during outbreaks.
- Active surveillance should continue for one week after the most recent case is identified.
- Active surveillance provides situational awareness and can guide other infection control measures.

INFECTION CONTROL

- Placing ill patients/residents in a private room. OR place residents suspected of having influenza together.
- Masking of staff and visitors when entering the room of patient/resident (dispose of mask upon exit).
- Masking of the patient/resident during transport.

- Duration: 7 days after onset OR 24 hours after the resolution of fever and respiratory symptoms (or longer).

INFECTION CONTROL: EMPLOYEE/VISITOR SCREENING

Screen employees and visitors for respiratory illness:

- Employees:
  - Track employee health
  - Have ill employees stay home
- Visitors:
  - Discourage ill visitors from entering facility
  - Require masking of visitor
  - Restrict all visitors or young visitors during active outbreaks (facility discretion)
  - Post signs!

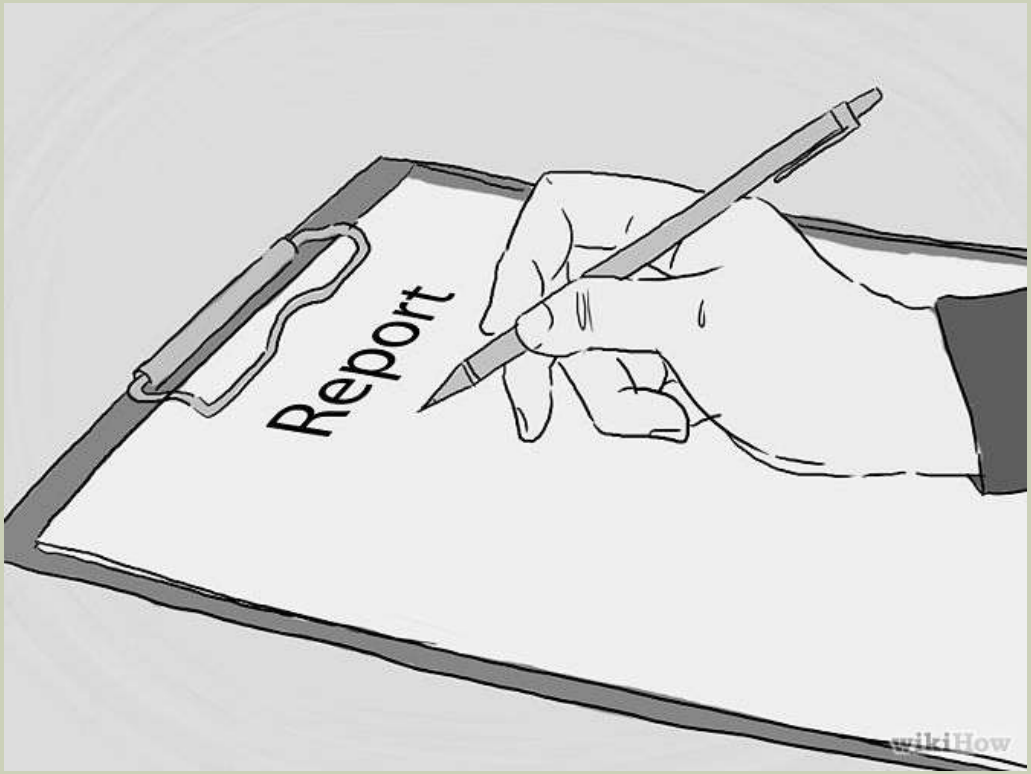
INFECTION CONTROL: CLEANING AND DISINFECTION

- Proper cleaning in infection are important to controlling influenza and other respiratory viruses that can live on surfaces for several hours.

- Routine cleaning is typically sufficient:
  - Clean and disinfect surfaces and objects that are touched often
  - Use cleaning/disinfecting products approved for effectiveness against influenza A viruses (alternative: solution of one tablespoon of bleach to 4 cups water)
  - For visibly dirty surfaces, clean with a general cleaner, rinse with water.
  - Consider disinfecting wipes for often used electronic items, such as phones and computers

REPORTING

Influenza “outbreaks” in health care institutional settings are reportable.



- **Overview of the Immune System.**

The immune system is the body's defense against infectious organisms and other invaders. Through a series of steps called the immune response, the immune system attacks organisms and substances that invade body systems and cause disease. The immune system in mammals can be broken down into 2 major subsystems, the innate and the adaptive.

Human Cells Recognize Conserved Features of Pathogens.

Microorganisms do occasionally breach the epithelial barricades. It is then up to the innate and adaptive immune systems to recognize and destroy them, without harming the host. Consequently, the immune systems must be able to distinguish self from non-self. The innate immune system relies on the recognition of particular types of molecules that are common to many pathogens but are absent in the host. These pathogen-associated molecules (called *pathogen-associated* or

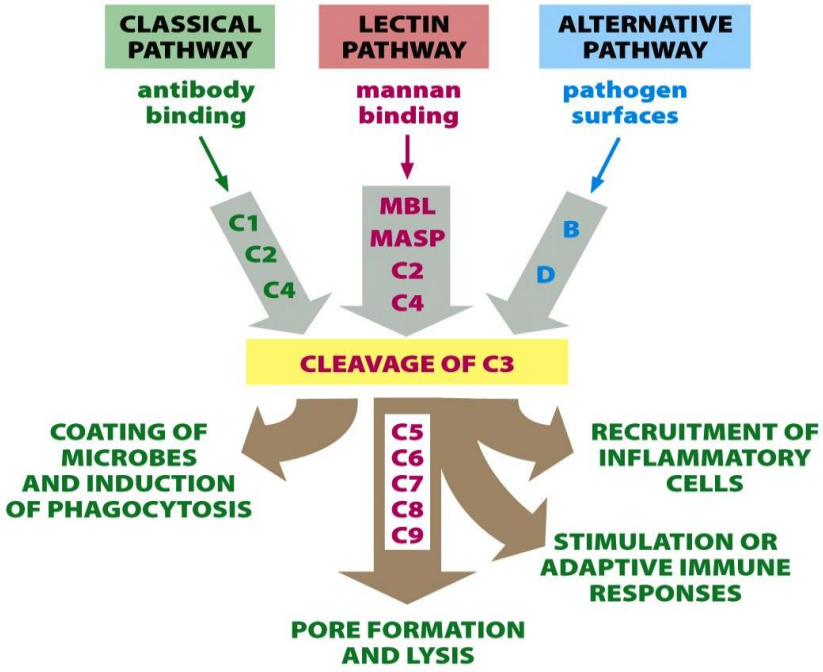
microbe-associated immunostimulants) trigger two types of innate immune responses—*inflammatory responses* and phagocytosis by professional phagocytes (neutrophils and macrophages), and by *dendritic cells*, which activate T cells of the adaptive immune system. Both the inflammatory and phagocytic responses can occur quickly, even if the host has never been previously exposed to a particular pathogen. The **microbe-associated immunostimulants** are of various types. Most are not exclusive to pathogens, but are found in many bacteria. Bacterial translation initiation differs from eukaryotic translation initiation in that *formylated methionine*, rather than regular methionine, is generally used as the first amino acid. Therefore, any peptide containing formylmethionine at the N-terminus must be of bacterial origin. Formylmethionine-containing peptides act as very potent chemo-attractants for neutrophils, which migrate quickly to the source of such peptides and engulf the bacteria producing them. In addition, molecules that do not occur in multicellular hosts compose the outer surface of many microorganisms, and these molecules also act as immunostimulants. They include the peptidoglycan cell wall and flagella of bacteria, as well as lipopolysaccharide (LPS) on Gram-negative bacteria. They also include molecules in the cell walls of fungi, including mannan, glucan, and chitin. Many eukaryotic parasites also contain

unique membrane components that act as immunostimulants, including glycosylphosphatidylinositol in *Plasmodium.*
The various classes of microbe-associated immunostimulants often occur in repeating patterns and are therefore often called *pathogen-associated molecular patterns (PAMPs).* Several types of dedicated receptors in the host, collectively called **pattern recognition receptors**, recognize these patterns. These receptors include soluble receptors in the blood (components of the *complement system*, which we discuss later) and membrane-bound receptors on or in host cells (including members of the *Toll-like receptor family*. The cell-associated receptors have two functions: they initiate the phagocytosis of the pathogen, and they activate a program of gene expression in the host cell responsible for innate immune responses. Some of the complement components also aid in phagocytosis and, in some cases, the direct killing of the pathogen.

Complement Activation Targets Pathogens for Phagocytosis or Lysis

The **complement system** consists of about 30 interacting soluble proteins that are made mainly by the liver and circulate in the blood and extracellular fluid. Most are inactive until an infection activates them. They were originally identified by their ability to amplify and "complement" the action of antibodies, but some complement components are also pattern recognition receptors that microbe-associated immunostimulants activate directly. There are three distinct pathways of complement activation—the *classical pathway*, the *lectin pathway*, and the *alternative pathway*. The early components of all three pathways act locally to activate C3, which is the pivotal component of complement. Individuals with a C3 deficiency are subject to repeated bacterial infections. The early components are proenzymes, which are activated sequentially by proteolytic cleavage. The cleavage of each pro-enzyme in the series activates the next component to generate a serine protease, which cleaves the next proenzyme in the series, and so on.
Many of these cleavages liberate a biologically active small peptide fragment that can attract phagocytic cells such as neutrophils, and a membrane-binding larger fragment. The binding of the large fragment to a cell membrane, usually the surface of a pathogen, helps to carry out the next reaction in the sequence.
The larger fragment of C3, called C3b, binds covalently to the surface of the pathogen, where it recruits fragments of cleaved C2 and C3 to form a

proteolytic complex (C4b, C2b, C3b) that catalyzes the subsequent steps in the complement cascade. Specific receptors on phagocytic cells that enhance the ability of these cells to phagocytose the pathogen also recognize C3b. In addition, receptors on B cells recognize C3b, which is the reason that C3b-coated pathogens are especially efficient at stimulating B cells to make antibodies. The smaller fragment of C3 (called C3a), as well as fragments of C4 and C5, act independently as diffusible signals to promote an inflammatory response by recruiting phagocytes and lymphocytes to the site of infection. IgG or IgM antibody molecules bound to the surface of a microbe activate the **classical pathway**. **Mannan-binding lectin**, the protein that initiates the second pathway of complement activation, is a serum protein that forms clusters of six carbohydrate-binding heads around a central collagen-like stalk. This assembly binds specifically to mannose and fructose residues in bacterial cell walls that have the correct spacing and orientation to match up perfectly with the six carbohydrate-binding sites, providing a good example of a pattern recognition receptor. These initial binding events in the classical and lectin pathways cause the recruitment and activation of the early complement components. Molecules on the surface of pathogens often activate the **alternative pathway**; activation of the classical or lectin pathways also activates the alternative pathway, forming a positive feedback loop that amplifies the effects of the classical or lectin pathway. Membrane-immobilized C3b, produced by any of the three pathways, triggers a further cascade of reactions that leads to the assembly of the late complement components to form *membrane attack complexes*. These Complexes assemble in the pathogen membrane near the site of C3 activation and have a characteristic appearance in negatively stained electron micrographs, where they are seen to form aqueous pores through the membrane. For this reason, and because they perturb the structure of the bilayer in their vicinity, they make the membrane leaky and can, in some cases, cause the microbial cell to lyse.



Phagocytic Cells Seek, Engulf, and Destroy Pathogens

Macrophages and neutrophils display a variety of cell-surface receptors that enable them to recognize and engulf pathogens. These include pattern recognition receptors such as TLRs, receptors for antibodies produced by the adaptive immune system, and receptors for the C3b component of complement. Binding to any of these receptors induces actin polymerization at the site of pathogen attachment, causing the phagocyte's plasma membrane to surround the pathogen and engulf it in a large membrane-enclosed phagosome phagocytosis by a macrophage or neutrophil generally leads to the ingested pathogen's death. Unsurprisingly, some pathogens use specific mechanisms to avoid phagocytosis by macrophages or neutrophils. One strategy is to secrete a thick, slimy layer of polysaccharides, called a *capsule*, which blocks access of complement components to the bacterial surface and also makes it physically difficult for the phagocytic cell to bind to and engulf the bacterium.

Another strategy, used by *Yersinia pestis* (the causative bacterium of plague), for example, is to deliver a toxin into the macrophage via a type III secretory system that disrupts the assembly of the actin cytoskeleton and thereby prevents phagocytosis. Exposure to both microbe-associated immunostimulants and chemical signals produced by the immune response to the pathogen enhances the phagocytic and killing power of the phagocytes. This exposure is said to "activate" the phagocyte, putting it in a state of high alert, in which not only is it more effective at phagocytosing and killing pathogens, but it also releases cytokines to

attract more white blood cells to the site of infection. Specialized lysosomal derivatives fuse with the phagosomes, delivering enzymes such as lysozyme and acid hydrolases that can degrade the pathogen's cell wall and proteins. While macrophages generally survive this killing frenzy and live to kill again, neutrophils usually do not. Dead and dying neutrophils are a major component of the pus that forms in acutely infected wounds

Activated Macrophages Contribute to the Inflammatory Response at Sites of Infection

When a pathogen invades a tissue, it almost always elicits an **inflammatory response**. Changes in local blood vessels cause a response characterized by pain, redness, heat, and swelling at the site of infection (physicians have recognized these four signs of inflammation, the blood vessels dilate and become permeable to fluid and proteins, leading to local swelling and an accumulation of blood proteins that aid in defence, including components of the complement cascade. At the same time, the endothelial cells lining the local blood vessels are stimulated to express cell adhesion proteins that facilitate the attachment and extravasion of white blood cells, initially neutrophils, followed later by lymphocytes and monocytes (the blood-borne precursors of macrophages).

Various signalling molecules mediate the inflammatory response at the site of an infection. Activation of TLRs results in the production of both lipid signalling molecules, such as prostaglandins, and protein (or peptide) signalling molecules, such as cytokines, all of which contribute to the inflammatory response, as do the complement fragments released during complement activation. Some of the cytokines produced by activated macrophages are chemoattractants (called *chemokines*). Some of these attract neutrophils, which are the first cells recruited in large numbers to the site of a new infection. Other cytokines trigger *fever*, a rise in body temperature. On balance, fever helps fight infection, since most bacterial and viral pathogens proliferate better at lower temperatures, whereas adaptive immune responses are more potent at higher temperatures. Still other pro-inflammatory signalling molecules stimulate endothelial cells to express proteins that trigger blood clotting in local small vessels.

By occluding the vessels and cutting off blood flow, this response can help prevent the pathogen from entering the bloodstream and spreading the infection to other parts of the body. The same inflammatory responses that help control local infections, however, can have disastrous consequences when they occur in response to a disseminated infection in the bloodstream, a condition called *sepsis*. The systemic release of pro-

inflammatory signalling molecules into the blood causes dilation of blood vessels, and loss of plasma volume, which, together, cause a large fall in blood pressure, or *shock*; in addition, there is widespread blood clotting. The end result, known as *septic shock*, is often fatal. In appropriate local inflammatory responses can also contribute to chronic diseases, such as *asthma* and arthritis.

Virus-Infected Cells Take Drastic Measures to Prevent Viral Replication

The microbe-associated immunostimulants on the surface of bacteria and parasites that are so important in eliciting innate immune responses against these pathogens are generally not present on the surface of viruses. The only general way that a host cell can recognize the presence of a virus is to detect unusual elements of the viral genome, such as the double-stranded RNA (dsRNA) that is an intermediate in the life cycle of many viruses which can be recognized by the Toll-like receptor (TLR9). Mammalian cells are particularly adept at recognizing the presence of dsRNA, and they can mobilize a program of intracellular responses to eliminate it. The program occurs in two steps. First, the cell degrades the dsRNA into small fragments (about 21–25 nucleotide pairs in length), using the enzyme *Dicer*. These double-stranded fragments bind to any single-stranded RNA (ssRNA) in the host cell that has the same sequence as either strand of the dsRNA fragment, leading to the destruction of the ssRNA. Second, the dsRNA induces the host cell to produce and secrete two cytokines—**interferon**-a (**IFN**a) and **interferon**-b (**IFN**b).The interferons activate a latent ribonuclease, which non-specifically degrades ssRNA. They also indirectly activate a protein kinase that phosphorylates and inactivates the protein synthesis initiation factor eIF-2, thereby shutting down most protein synthesis in the embattled host cell. Apparently, by destroying most of its RNA and transiently halting most of its protein synthesis, the host cell inhibits viral replication without killing itself. If these measures fail, the cell takes the even more extreme step of killing itself by apoptosis to prevent the virus from replicating, often with the help of a killer lymphocyte. Not surprisingly, many viruses have acquired mechanisms to defeat or avoid these intracellular defense processes. Influenza virus encodes a protein that blocks the recognition of dsRNA by Dicer. Many viruses, including most of those that are able to cause disease in healthy hosts, use various mechanisms to block the activation of the interferon pathway. Some viruses also inhibit host cell apoptosis, which can have the side-effect of promoting the development of cancer.

Natural Killer Cells Induce Virus-Infected Cells to Kill Themselves

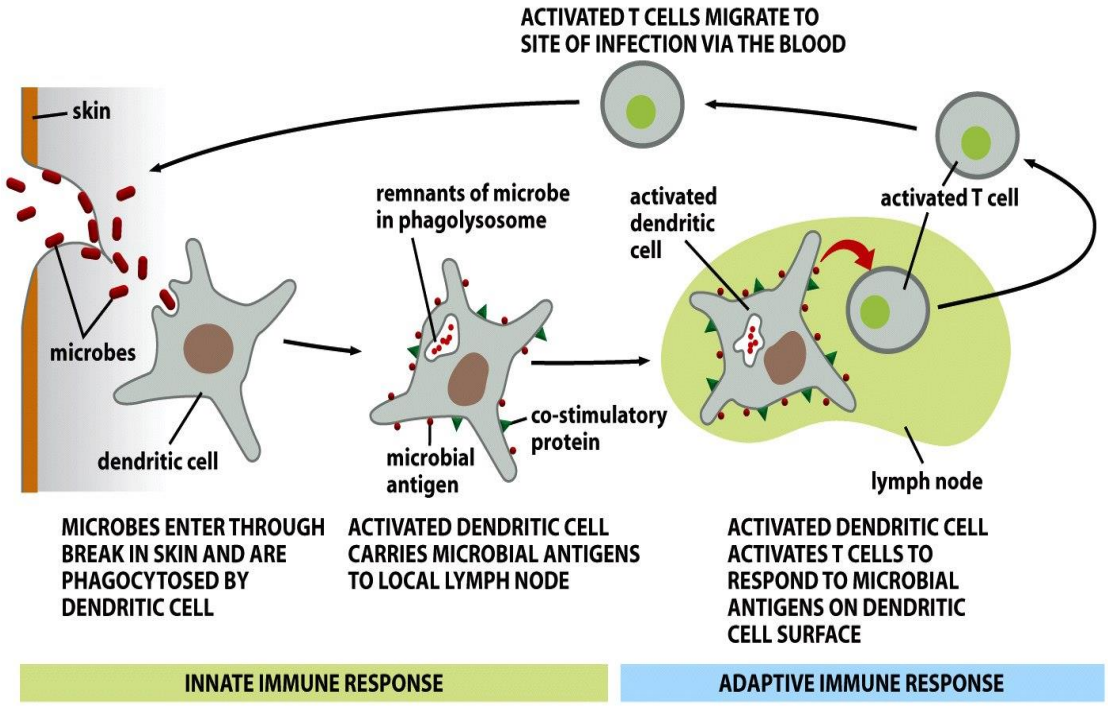
Interferons have other, less direct ways of blocking viral replication. One of these is to enhance the activity of **natural killer cells** (**NK cells**), which are part of the innate immune system. Like cytotoxic T cells of the adaptive immune system, NK cells destroy virus-infected cells by inducing the infected cells to kill themselves by undergoing apoptosis. The ways in which cytotoxic T cells and NK cells distinguish virus-infected cells from uninfected cells, however, is different. Both cytotoxic T cells and NK cells recognize the same special class of cell surface proteins to detect virus-infected host cells, The proteins are called **class I MHC proteins**. Cytotoxic T cells recognize peptide fragments of viral proteins bound to these MHC proteins on the surface of virus infected cells. By contrast, NK cells monitor the level of class I MHC proteins on the surface of all host cells: high levels inhibit the killing activity of NK cells, so that NK cells selectively kill host cells expressing low levels, which are mainly virus-infected cells and some cancer cells.

The reason that class I MHC protein levels are often low on virus-infected cells is that many viruses have developed mechanisms to inhibit the expression of these proteins on the surface of the cells they infect, to avoid detection by cytotoxic T lymphocytes. Adenovirus and HIV, for example, encode proteins that block class I MHC gene transcription. Both NK cells and cytotoxic T lymphocytes kill infected target cells by inducing them to undergo apoptosis before the virus has had a chance to replicate.

Dendritic Cells Provide the Link between the Innate and Adaptive Immune Systems

Dendritic cells are crucially important cells of the innate immune system that are widely distributed in the tissues and organs of vertebrates. They display a large variety of pattern recognition receptors that enable the cells to recognize and phagocytose invading pathogens and to become activated in the process. The dendritic cells cleave the proteins of the pathogens into peptide fragments, which then bind to MHC proteins that carry the fragments to the cell surface. The activated dendritic cells now carry the pathogen-derived peptides, as complexes with MHC proteins, to a nearby lymphoid organ such as a lymph node, where they activate T cells of the adaptive immune system to join in the battle against the specific invader. In addition to the complexes of MHC proteins and microbial peptides displayed on their cell surface, activated dendritic cells

also display special, cell-surface co-stimulatory proteins that help activate the T cells. The activated dendritic cells also secrete a variety of cytokines that influence the type of response that the T cells make, ensuring that it is appropriate to fight the particular pathogen. In these ways, dendritic cells serve as crucial links between the innate immune system, which provides a rapid first line of defence against invading pathogens, and the adaptive immune system, which provides slower but more powerful and highly specific ways of attacking an invader.



Summary

Physical barriers preventing infection, cell-intrinsic responses to infection, and innate immune responses provide early lines of defence against invading pathogens. All multicellular organisms possess these defences. In vertebrates, innate immune responses can also recruit specific and more powerful adaptive immune responses. Innate immune responses rely on the body's ability to recognize conserved features of microbial molecules that are not made by the host. These microbe-associated immunostimulants include many types of molecules on microbial surfaces, as well as the double-stranded RNA of some viruses. Many of these microbial molecules are recognized by pattern recognition receptors, including the toll-like receptors (TLRs) found in both plants and animals. In vertebrates, microbial surface molecules also activate complement, a group of blood proteins that are activated in sequence to target the microbe for phagocytosis by macrophages and neutrophils, to disrupt the membrane of the microbe, and to produce an inflammatory response. The phagocytes use a combination of degradative enzymes, antimicrobial peptides, and reactive oxygen species to kill the invading microorganism; in addition, they secrete signal molecules that trigger an inflammatory response. Cells infected with viruses produce interferons, which induce a series of cell responses, inhibit viral replication, and activate the killing activities of natural killer cells. Dendritic cells of the innate immune system ingest microbes at sites of infection and carry them and their products to local lymph nodes, where they activate T cells of the adaptive immune system to make specific responses against the microbes.

Lecture 3 Dr. Shaymaa A. Abbas

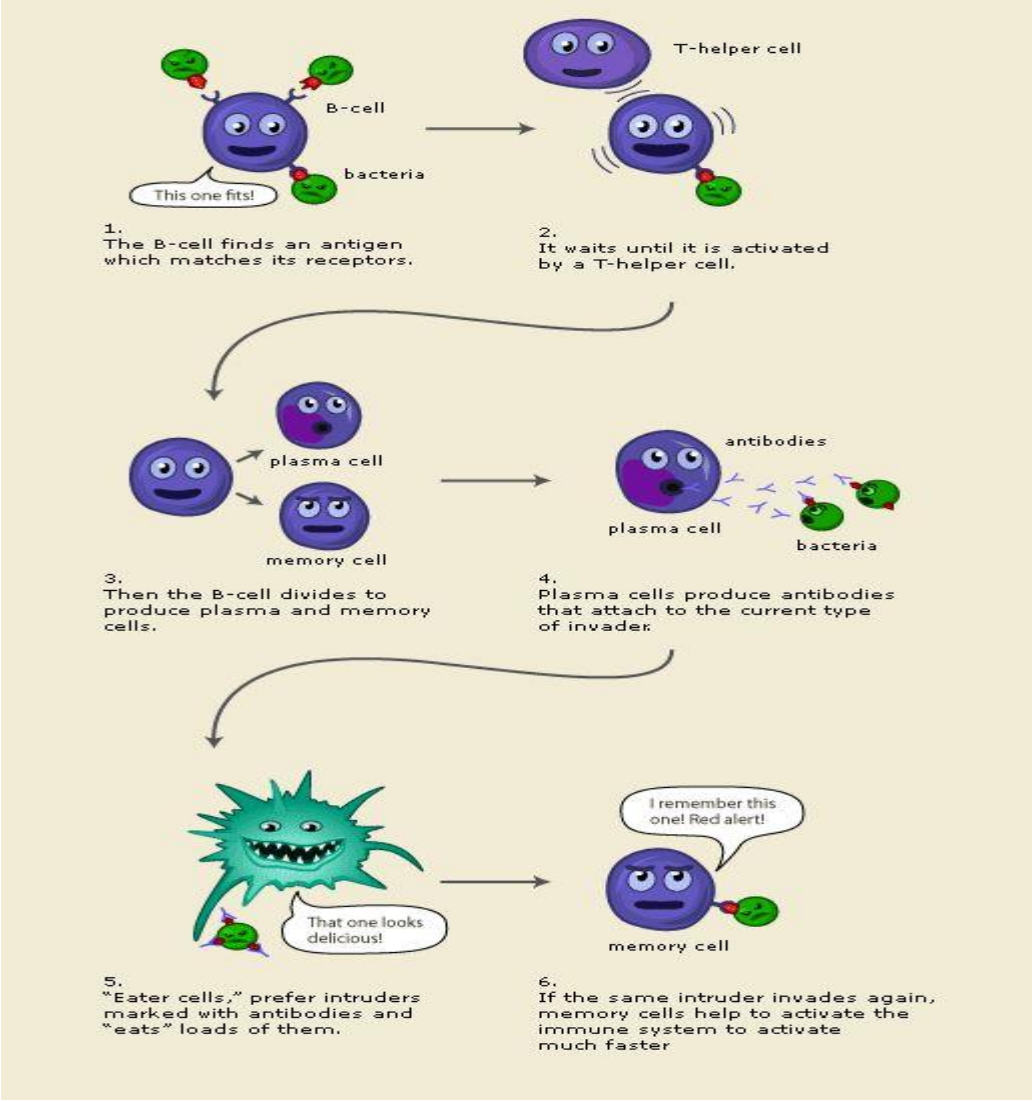
The Adaptive Immune System

Our **adaptive immune system** saves us from certain death by infection. An infant born with a severely defective adaptive immune system will soon die unless extraordinary measures are taken to isolate it from a host of infectious agents, including bacteria, viruses, fungi, and parasites. All multicellular organisms need to defend themselves against infection by such potentially harmful invaders, collectively called **pathogens**. Invertebrates use relatively simple defence strategies that rely chiefly on protective barriers, toxic molecules, and phagocytic cells that ingest and destroy invading microorganisms *(microbes)* and larger parasites (such as worms). Vertebrates, too, depend on such **innate immune responses** as a first line of defence (discussed in lec.1), but they can also mount much more sophisticated defences, called **adaptive immune responses**. In vertebrates, the innate responses call the adaptive immune responses into play, and both work together to eliminate the pathogens. Any substance capable of eliciting an adaptive immune response is referred to as an **antigen** (*anti*body *gen*erator).

Whereas the innate immune responses are general defence reactions, the adaptive responses are highly specific to the particular pathogen that induced them, and they provide long-lasting protection. A person who recovers from measles, for example, is protected for life against measles by the adaptive immune system, although not against other common viruses, such as those that cause mumps or chickenpox.

Adaptive immune responses eliminate or destroy invading pathogens and any toxic molecules they produce. Because these responses are destructive, it is important that they are directed only against foreign molecules and not against molecules of the host itself. The adaptive immune system uses multiple mechanisms to avoid damaging responses against self-molecules. Occasionally, however, these mechanisms fail, and the system turns against the host, causing *autoimmune diseases*, which can be fatal.

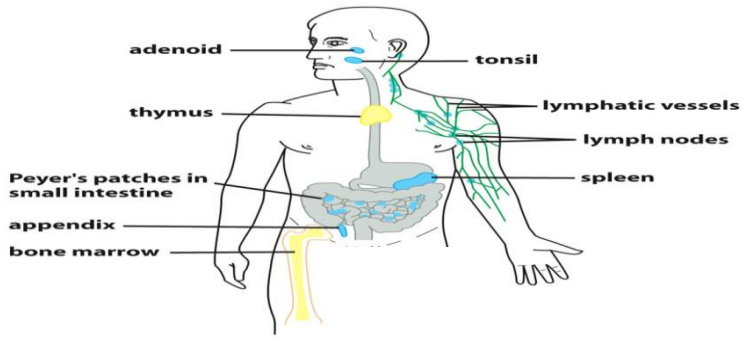
Adaptive immune responses are carried out by white blood cells called **lymphocytes**. There are two broad classes of such responses—*antibody responses* and *T-cell-mediated immune responses*—and different classes of lymphocytes, called B cells and T cells, respectively, carry them out. In **antibody responses**, B cells are activated to secrete antibodies, which are proteins called *immunoglobulin*. The antibodies circulate in the bloodstream and permeate the other body fluids, where they bind specifically to the foreign antigen that stimulated their production. Binding of antibody inactivates viruses and microbial toxins (such as tetanus toxin or diphtheria toxin) by blocking their ability to bind to receptors on host cells. Antibody binding also marks invading pathogens for destruction, mainly by making it easier for phagocytic cells of the innate immune system to ingest them.



In **T-cell-mediated immune responses**, the second class of adaptive immune responses, activated T cells react directly against a foreign antigen that is presented to them on the surface of a host cell, which is therefore referred to as an *antigen-presenting cell*. Remarkably, T cells can detect microbes hiding inside host cells and either kill the infected cells or help the infected cells or other cells to eliminate the microbes. The T cell, for example, might kill a virus infected host cell that has viral antigens on its surface, thereby eliminating the infected cell before the virus has had a chance to replicate. In other cases, the T cell produces signal molecules that either activates macrophages to destroy the microbes that they have phagocytosed or help activate B cells to make antibodies against the microbes.

LYMPHOCYTES AND THE CELLULAR BASIS OF ADAPTIVE IMMUNITY

Lymphocytes are responsible for the astonishing specificity of adaptive immune responses. They occur in large numbers in the blood and lymph (the colourless fluid in the lymphatic vessels that connect the lymph nodes in the body to each other and to the bloodstream). They are also concentrated in **lymphoid organs**, such as the thymus, lymph nodes (also called lymph glands), spleen, and appendix. Lymphocytes develop in the thymus and bone marrow (yellow), which are therefore called central (or primary) lymphoid organs. The newly formed lymphocytes migrate from these primary organs to peripheral (or secondary) lymphoid organs, where they can react with foreign antigen. Only some of the peripheral lymphoid organs (blue) and lymphatic vessels (green) are shown; many lymphocytes, for example, are found in the skin and respiratory tract, the lymphatic vessels ultimately empty into the bloodstream (not shown).



The Innate and Adaptive Immune Systems Work Together

Lymphocytes usually respond to foreign antigens only if the **innate immune system** is first activated. As discussed in lec.1, the rapid innate immune responses to an infection depend largely on **pattern recognition receptors** made by cells of the innate immune system. These receptors recognize microbe-associated molecules that are not present in the host organism, called *microbe-associated immunostimulants.* Because they often occur in repeating patterns, they are also called *pathogen-associated molecular patterns (PAMPs).*PAMPs include repeated patterns of molecular structure in microbial nucleic acids, lipids, polysaccharides, and proteins. Some of the pattern recognition receptors are present on the surface of professional phagocytic cells (phagocytes) such as macrophages and neutrophils, where they mediate the uptake of pathogens, which are then delivered to lysosomes for destruction. Others are secreted and bind to the surface of pathogens, marking them for destruction by either phagocytes or a system of blood proteins collectively called the *complement system* (discussed in lec.1). Still others, including the *Toll-like receptors (TLRs)*, activate intracellular signalling pathways that lead to the secretion of extracellular signal molecules that promote inflammation and help activate adaptive immune responses.

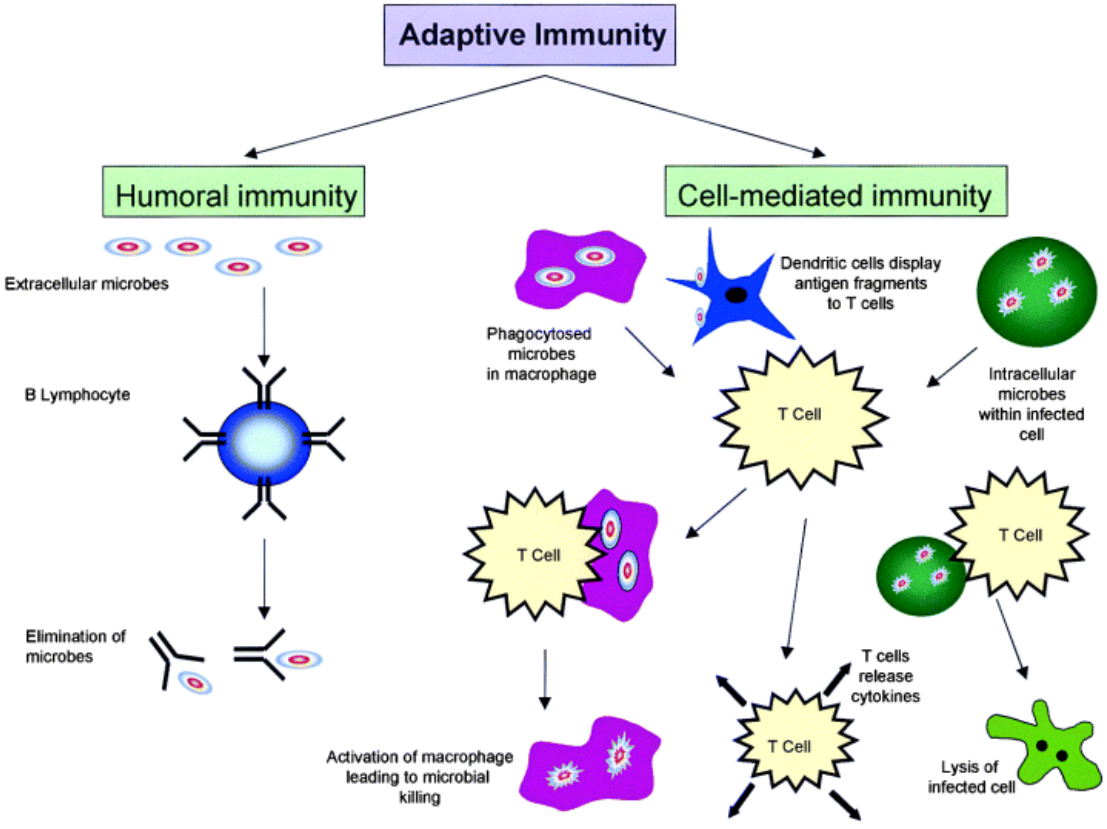
The cells of the vertebrate innate immune system that respond to PAMPs and activate adaptive immune responses most efficiently are **dendritic cells**. Present in most tissues, dendritic cells express high levels of TLRs and other pattern recognition receptors, and they function by presenting microbial antigens to T cells in peripheral lymphoid organs. In most cases, they recognize and phagocytose invading microbes or their products or fragments of infected cells at a site of infection and then migrate with their prey to a nearby lymph node; in other cases, they pick up microbes or their products directly in a peripheral lymphoid organ such as the spleen. In either case, the microbial PAMPs activate the dendritic cells so that they, in turn, can directly activate the T cells in peripheral lymphoid organs to respond to the microbial antigens displayed on the dendritic cell surface. Once activated, some of the T cells then migrate to the site of infection, where they help destroy the microbes. Other activated T cells remain in the lymphoid organ, where they help keep the dendritic cells active, help activate other T cells, and help activate B cells to make antibodies against the microbial antigens.

Thus, innate immune responses are activated mainly at sites of infection (or injury), whereas adaptive immune responses are activated mainly in peripheral lymphoid organs such as lymph nodes and spleen. Both types of responses work together to eliminate invading pathogens and foreign macromolecules. As part of the adaptive immune response, some lymphocytes proliferate and differentiate into memory cells, which are able to respond faster and more efficiently the next time the same pathogen invades.

T CELLS AND MHC PROTEINS

There are three main functionally distinct classes of T cells. **Cytotoxic T cells** kill infected cells directly by inducing them to undergo apoptosis. **Helper T cells** help activate B cells to make antibody responses, cytotoxic T cells to kill their target cells, dendritic cells to stimulate T cell responses, and macrophages to destroy microorganisms that either invaded the macrophage or were ingested by it. Finally, **regulatory T** cells suppress the activity of effector T cells and dendritic cells and are crucial for self tolerance. All T cells express cell-surface, antibody like receptors (TCRs), which are encoded by genes that are assembled from multiple gene segments during T cell development in the thymus. TCRs recognize fragments of foreign proteins that are displayed on the surface of host cells in association with MHC proteins. T cells are activated in peripheral lymphoid organs by antigen-presenting cells, which express peptide–MHC complexes, co-stimulatory proteins, and various cell–cell adhesion molecules on their cell surface. The most potent of these antigen-presenting cells are dendritic cells, which are specialized for antigen presentation and are required for the activation of naïve T cells. Class I and class II MHC proteins have crucial roles in presenting foreign protein antigens to T cells: class I MHC proteins present antigens to cytotoxic T cells, while classII MHC proteins present antigens to helper and regulatory T cells. Whereas class I proteins are expressed on almost all vertebrate cells, class II proteins are normally restricted to those cell types that interact with helper T cells, such as dendritic cells, macrophages, and B lymphocytes. Both classes of MHC proteins have a single peptide-binding groove, which binds small peptide fragments derived from proteins. Each MHC protein can bind a large set of peptides, which are constantly being produced intracellularly by normal protein

degradation processes. However, class I MHC proteins mainly bind fragments produced in the cytosol, while class II MHC proteins mainly bind fragments produced in endocytic compartments. After they have formed inside the target cell, the peptide–MHC complexes are transported to the cell surface. Complexes that contain a peptide derived from a foreign protein are recognized by TCRs, which interact with both the peptide and the walls of the peptide-binding groove of the MHC protein. T cells also express CD4 or CD8 co-receptors, which simultaneously recognize non-polymorphic regions of MHC proteins on the antigen-presenting cell or target cell: helper cells and regulatory cells express CD4, which recognizes class II MHC proteins, while cytotoxic T cells express CD8, which recognizes class I MHC proteins. These processes help to ensure that only T cells with potentially useful receptors survive and mature, while all of the others die by apoptosis. First, T cells that can respond to peptides complexed with self MHC proteins are positively selected; subsequently, the T cells in this group that can react strongly with self peptides complexed with self MHC proteins are eliminated. Helper and cytotoxic T cells that leave the thymus with receptors that could react with self antigens are eliminated, functionally inactivated, or actively suppressed when they recognize self antigens on non-activated dendritic cells.



Lecture 4 Dr. Shaymaa A. Abbas

Antibody characteristic features:

Antibodies (Ab) are Y- shaped protein structures produced by cells of the B- lymphocyte lineage, composed of two large heavy chains and two smaller light chains, stabilized with disulphide bonds. Each chain is composed of variable (V) and constant (C) domains based on variability in the amino acid sequence. The light chain is composed of one constant (C_L) and one variable region (V_L). In contrast heavy chain is composed of one variable (V_H) domain and several constant domains (C_H1, C_H2, C_H3, etc) based on the class of the antibody. The main functional domains are the relatively constant Fc region, which interacts with cellular Fc receptors and complement and the Fab region, which contains the antigen binding site (**Fig**.1). The smallest part that maintains the antigen binding affinity is the variable fragment (Fv), which in recombinant form is commonly stabilized with a 15-amino acid peptide linker. The variable domain of both heavy and light chains is composed of hypervariable loops, known as complementarity determining regions (CDRs) that determine the antibody specificity to bind antigen. There are five different classes of antibodies: IgG, IgM, IgA, IgD, IgE classified according to the differences in the amino acid sequences in the constant region of their heavy chains. The IgG antibodies have heavy chains named γ-chains; IgM have μ-chains; IgA have α-chains; IgE have ε-chains; and IgD have δ-chains. Based on small differences in the constant region of the heavy chain, antibody classes are further divided into subclasses, for instance subclasses of IgGs are IgG1, IgG2, IgG3 and IgG4 in humans. There are also two light chain types, κ and λ, which will be of the same type in any particular antibody molecule.

As mentioned above, the development of hybridoma techniques, that involve immunizing mice with a target antigen and then fusing mouse lymphocytes with myeloma cell line cells, is used to generate murine monoclonal antibodies. However, as human anti- mouse antibody (HAMA) responses develop in patients treated with murine antibodies, chimeric monoclonal antibodies were generated using genetic engineering technology, where the mouse variable region (V) of both heavy and light chains are combined with the constant region (C) of the heavy and the light chains from human antibodies. Although these

chimeric monoclonal antibodies exhibited reduced immunogenicity, however, the HAMA responses developed in patients were still considerable. In the next leap forward, humanized monoclonal antibodies were generated from grafting of only the complementary determining regions (CDRs) of a mouse antibody onto human variable regions. With the advent of phage display technology, this was taken further toward generation of fully human antibodies by which genes encoding for the Fab or Fv fragments of human antibodies are expressed in bacteriophage, and subsequently selected and expressed in *E.coli*. In addition to phage display, fully human antibodies are also generated after immunizing transgenic mouse strains that express human variable domains. The transgenic mice have impaired endogenous murine Ig machinery; therefore only human antibodies are expressed (**Fig**.2). The immunogenic potential is significantly reduced with both humanized and fully human antibodies that have similar properties to human endogenous IgGs.

Monoclonal antibodies and polyclonal antibodies are the two varieties of antibodies, which are used in therapeutics as well as in research applications. Both monoclonal and polyclonal antibodies interact with the same antigen. The main difference between monoclonal and polyclonal antibodies is that monoclonal antibodies are produced by the same clone of plasma B cells, and they bind to a unique epitope whereas polyclonal antibodies are produced by different clones of plasma B cells, and they bind to the different epitopes in the same antigen.

In general, naked antibody molecules are rarely potent cytotoxic agents, therefore they can be linked to cytotoxic drugs, toxins, or radionuclides to enhance their anti-cancer activity. The optimal characteristics for efficacious and safe antibody-based therapy are high affinity to the target antigen, internalization following binding, non-immunogenicity and limited normal tissue expression of the target antigen. Moreover, the isotype of the mAb is another key point to consider in Ab-based therapy design as it will affect whether the targeted therapy has the potential to kill cells via antibody-dependent cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) in addition to the killing induced by cytotoxic agents or toxin.

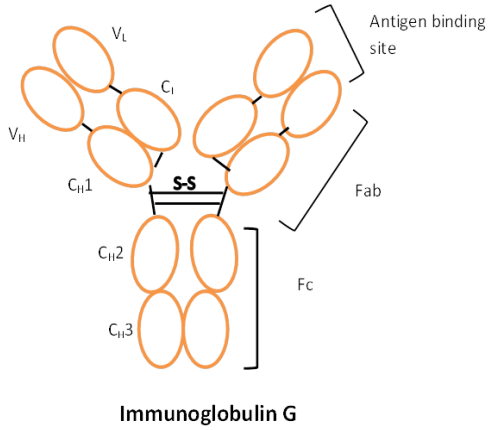


Figure.1: Antibody structure:
Fc and Fab fragments of an antibody molecule (immunoglobulin G).

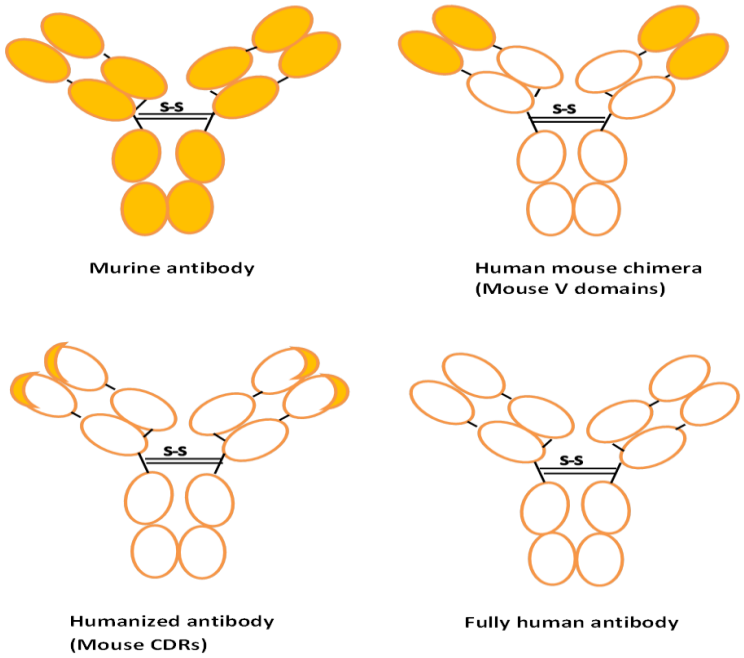
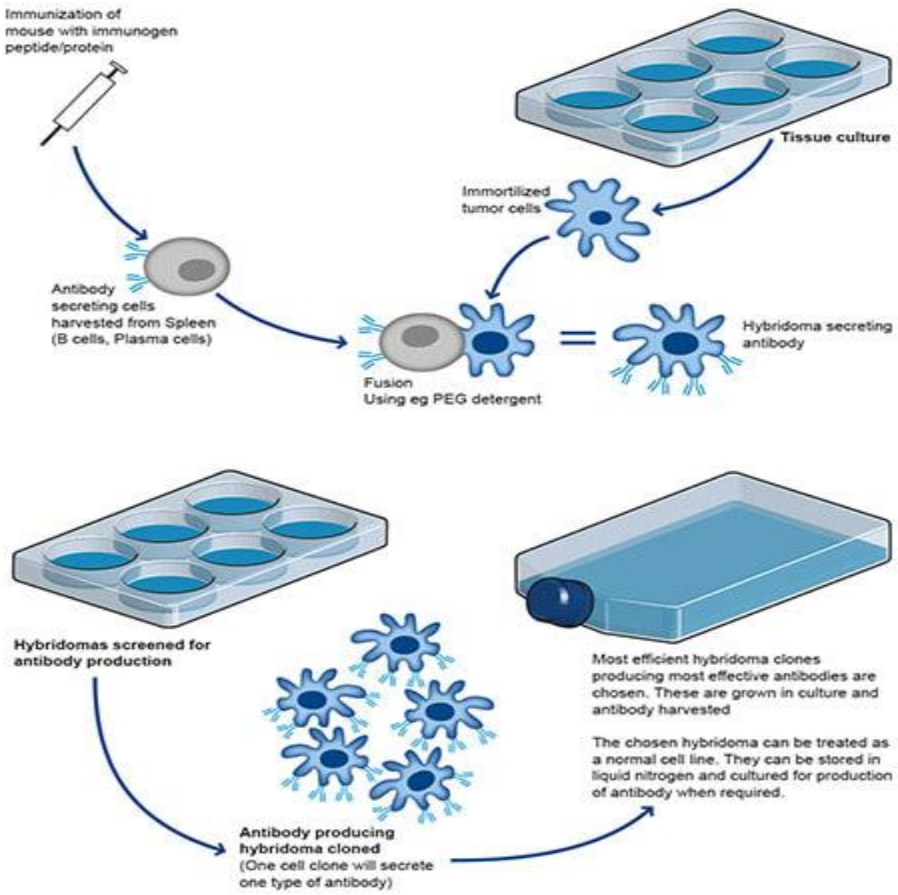


Figure.1: Types of monoclonal antibodies generated:
Murine antibody (entirely of murine origin), chimeric antibody (murine variable region combined with human constant region), humanized antibody (human antibodies with murine CDR region grafted onto the human variable region), fully human antibody (entirely of human origin).

Antibody production


Immunization of mouse with immunogen peptide/protein
Tissue culture
Immortilized tumor cells
Antibody secreting cells harvested from Spleen (B cells, Plasma cells)
Fusion
Using eg PEG detergent
Hybridoma secreting antibody
Hybridomas screened for antibody production
Most efficient hybridoma clones producing most effective antibodies are chosen. These are grown in culture and antibody harvested
The chosen hybridoma can be treated as a normal cell line. They can be stored in liquid nitrogen and cultured for production of antibody when required.
Antibody producing hybridoma cloned
(One cell clone will secrete one type of antibody)

Lecture 5 Dr. Shaymaa A. Abbas

HYPERSENSITIVITY REACTIONS

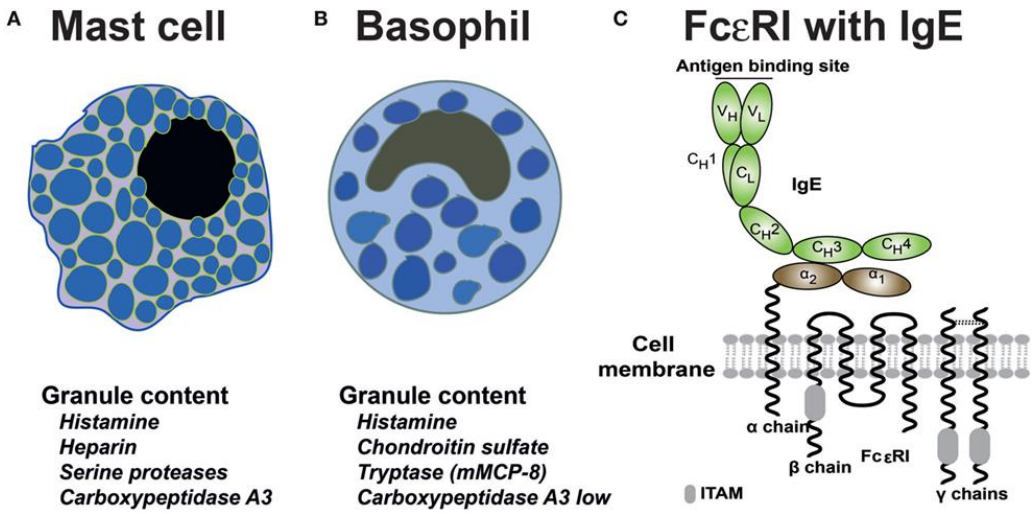
Hypersensitivity refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system. Hypersensitivity reactions require a pre-sensitized (immune) state of the host. Hypersensitivity reactions can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved and time taken for the reaction. Frequently, a particular clinical condition (disease) may involve more than one type of reaction.

TYPE I HYPERSENSITIVITY

Type I hypersensitivity is also known as immediate or anaphylactic hypersensitivity. The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis). The reaction may cause a range of symptoms from minor inconvenience to death. The reaction usually takes 15 - 30 minutes from the time of exposure to the antigen, although sometimes it may have a delayed onset (10 - 12 hours).

Immediate hypersensitivity is mediated by IgE. The primary cellular component in this hypersensitivity is the mast cell or basophil. The reaction is amplified and/or modified by platelets, neutrophils and eosinophils. A biopsy of the reaction site demonstrates mainly mast cells and eosinophils.

The mechanism of reaction involves preferential production of IgE, in response to certain antigens (often called allergens). The precise mechanism as to why some individuals are more prone to type-I hypersensitivity is not clear. However, it has been shown that such individuals preferentially produce more of TH cells that secrete IL-4, IL-5 and IL-13 which in turn favor IgE class switch. IgE has very high affinity for its receptor on mast cells and basophils.



The allergen that induce the production of specific IgE Ab in human they could be:

- Plant pollens, mold spores
- House dust, house dust mites
- Animal hair, feather
- Food (milk, egg, fish, peanut, chocolate)
- Insect venom
- Drugs and chemical

Diagnostic tests for immediate hypersensitivity include skin (prick and intradermal) tests, IgE antibodies are measured against the suspected allergens by enzyme immunoassay (ELISA).

Therapeutic measures:

- Avoidance of the responsible allergen (environmental control). It is easily accomplished with food allergen, but may be difficult with inhaled allergen.
- Hypo sensitization involves injecting the patient overtime with gradually increasing doses of the responsible allergen. This stimulates the production of IgG blocking Ab which react with offending allergen and prevent its combining with IgE Ab on the mast cell.
- Symptomatic treatment is achieved with anti-histamines which block histamine receptors. Late onset allergic symptoms, particularly bronchoconstriction is treated with (Singulair,

Accolate) Symptomatic, although short term, relief from bronchoconstriction is provided by bronchodilators (inhalar) such as (Terbutaline, Albuterol). Thophylline is also used to relieve bronchopulmonary symptoms.

TYPE II HYPERSENSITIVITY

Type II hypersensitivity is also known as cytotoxic hypersensitivity and may affect a variety of organs and tissues. The antigens are normally endogenous, although exogenous chemicals which can attach to cell membranes can also lead to type II hypersensitivity. The reaction time is minutes to hours. Type II hypersensitivity is primarily mediated by antibodies of the IgM or IgG classes and complement. Phagocytes and NK cells may also play a role.

Pathogenesis mechanism:

The combination of IgG or IgM with Ag (epitopes) on cell surface or tissue may lead to one of the following destructive process:

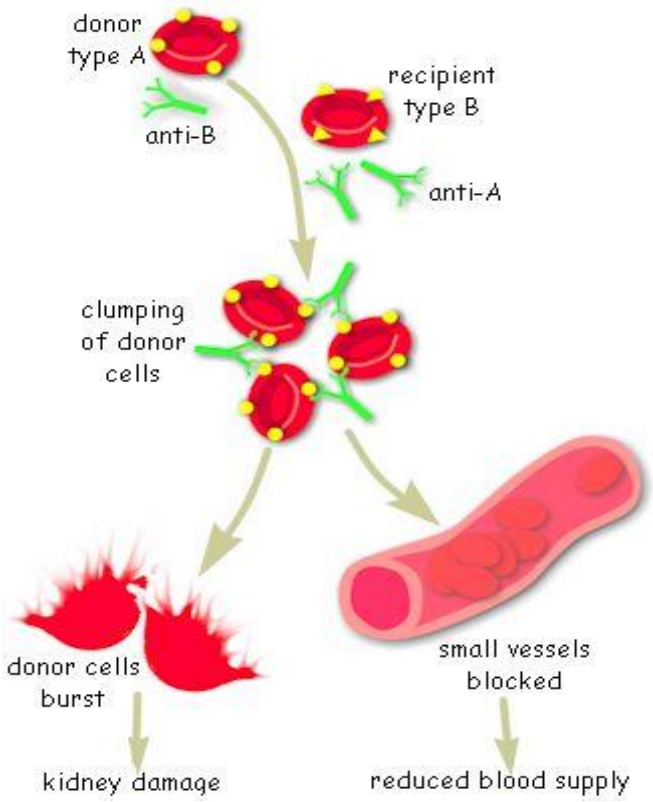
- Lysis or inactivation of the target cell by activation of the complement system.
- Phagocytosis of the target cells with or without complement (either directly through antibody FC receptor present on phagocyte or by immune adherence where C_{3b} have receptors on phagocytic cells.
- Lysis or inactivation of target cells by antibody dependent cytotoxicity (ADCC) through the action of NK cells.

  Clinical examples of Type II responses include:

  - Certain autoimmune diseases where Ab's produced vs membrane Ag's
    - Grave's Disease – Ab's produced vs thyroid hormone receptor
    - Myasthenia Gravis – Ab's produced vs acetylcholine recpetors
    - Autoimmune hemolytic anemia – Ab's produced vs RBC membrane Ag's
  - Hemolytic Disease of the Newborn

- Hyperacute graft rejection
  - Blood Transfusion reactions
  - Graft rejection

Transfusion reactions



Produced by mismatched blood types

- Destroys foreign RBC by complement-mediated lysis triggered by IgG
- Produces fever, intravascular clots, lower back pain, Hgb in urine

Hemolytic Disease of the Newborn

- Occurs via maternal IgG Ab's crossing the placenta
- In severe cases causes **erythroblastosis fetalis**
  - Most commonly develops in Rh- mother with Rh+ fetus

    - Exposure to Rh+ fetal RBC's stimualtes prod of memory/plasma
    - Activation of memory cells in subsequent pregnancy stimulate IgG Ab's which can cross the placenta
    - mild-severe hemolytic anemia ensues along with bilirubin which affects the brain/CNS
- Treatment centers on anti-Rh antibodies (Rhogam)
- Mothers can be tested for anti-Rh antibodies to check for a rise in titre
- Isolated fetal RBC's can be checked for anti-Rh IgG w/ Coombs test

Drug-induced hemolytic anemia

- Drugs such as aspirin and antibiotics can bind to the surfaces of RBC's
- Such complexes can trigger Ab-mediated cell lysis by complement activation

TYPE III HYPERSENSITIVITY

Type III hypersensitivity is also known as immune complex hypersensitivity. The reaction may be general (*e.g.*, serum sickness) or may involve individual organs including skin (*e.g.*, systemic lupus erythematosus, Arthus reaction), kidneys (*e.g.*, lupus nephritis), lungs (*e.g.*, aspergillosis), blood vessels (*e.g.*, polyarteritis), joints (*e.g.*, rheumatoid arthritis) or other organs. This reaction may be the pathogenic mechanism of diseases caused by many microorganisms.

The reaction may take 3 - 10 hours after exposure to the antigen (as in Arthus reaction). It is mediated by soluble immune complexes. They are mostly of the IgG class, although IgM may also be involved. The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (non-organ specific autoimmunity: *e.g.*, systemic lupus erythematosus, SLE). The body may be exposed to an

excess of Ags in a number of circumstances. The union of such Ags with subsequently formed Abs (IgG or IgM) form soluble complexes at fixed sites within the body, where they may give rise to acute inflammatory reaction. When complement is activated, the anaphylatoxin c_{3a} , c_{5a} will cause the release of mast cell mediators resulting in increased vascular permeability.

These chemotactic factors, and those released by mast cells will lead to an influx of polymorphnueclear cells (neutrophils). This in turn result in the extracellular release of polymorph granules contents particularly when the complex is deposited on a basement membrane and can not be phagocytosed (because it is very small), the proteolytic enzymes of the granules released from the neutrophils will damage local tissues and intensify the inflammatory response. So pathogenic mechanism involves interplay of Ag, Ab, complement and neutrophils.

Therapeutic measures:

- Reduction of inflammation by asprin,antihistamine, corticosteroids.
- Suppression of immune response by corticosteroids and cytotoxic immune suppression drugs (methotrexate)
- Removal of offending complexes by plasmapheresis.

TYPE IV HYPERSENSITIVITY

Type IV hypersensitivity is also known as cell mediated or delayed type hypersensitivity. The classical example of this hypersensitivity is tuberculin (Montoux) reaction, which peaks 48 hours after the injection of antigen (PPD or old tuberculin). The lesion is characterized by induration and erythema.

Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, *etc.*) and granulomas due to infections and foreign antigens. Another form of delayed hypersensitivity is contact dermatitis (poison ivy), chemicals, heavy metals, *etc.*) in which the lesions are more popular. Type IV hypersensitivity can be classified into three categories depending on the time of onset and clinical and histological presentation

Mechanisms of damage in delayed hypersensitivity include T lymphocytes and monocytes and/or macrophages. Cytotoxic T cells (Tc) cause direct damage whereas helper T (TH1) cells secrete cytokines which activate cytotoxic T cells and recruit and activate monocytes and macrophages, which cause the bulk of the damage. The delayed hypersensitivity lesions mainly contain monocytes and a few T cells.

Major lymphokines involved in delayed hypersensitivity reaction include monocyte chemotactic factor, interleukin-2, interferon-gamma, TNF alpha/beta, *etc.*

Therapeutic measures:

- Avoidance of allergens
- Reduction of inflammation with asprin and other non-steroidal anti-inflammatory agents.
- Immune suppression drugs

Characteristics	Type-I (anaphylactic)	Type-II (cytotoxic)	Type-III (immune complex)	Type-IV (delayed type)
Antibody	IgE	IgG, IgM	IgG, IgM	None
Antigen	Exogenous	Cell surface	Soluble	Tissues and organs
Response time	15-30 minutes	Minutes-hours	3-8 hours	48-72 hours
Appearance	Weal and flare	Lysis and necrosis	Erythema and edema, necrosis	Erythema and induration
Histology	Basophils and eosinophil	Antibody and complement	Complement and neutrophils	Monocytes and lymphocytes
Transferred with	Antibody	Antibody	Antibody	T-cells
Examples	Allergic asthma, hay fever	Erythroblastosis fetalis Goodpasture's nephritis	SLE, farmer's lung disease	Tuberculin test, poison ivy, granuloma

Lecture 6 Dr. Shaymaa A. Abbas

TUMOR IMMUNOLOGY

Immunosurveillance: A hypothetical physiological role for the immune system to detect and eliminate malignant clones of cells as they arise.

Tumor antigens: Classification of tumor antigens based on their patterns of expression. Tumor specific antigens (TSAs): antigens that are expressed on tumor cells but not on normal cells; some of these are unique to individual tumors. Tumor associated antigens (TAAs): antigens that are also expressed on normal cells; in most cases, normal cellular constituents whose expression is aberrant or dysregulated in tumors.

• Classification of tumor antigens based on molecular nature of antigen.

Products of Mutated Oncogenes and Tumor Suppressor Genes, whose products are required for malignant transformation or for maintenance of the malignant phenotype.

Products of Other Mutated Genes. Tumor antigens may be produced by mutated genes whose products are not related to the transformed phenotype, and may have no known function.

Aberrantly Expressed Normal Cellular Proteins. Tumor antigens may be normal cellular proteins that are over-expressed or aberrantly expressed in tumor cells (e.g. Testes antigen family of tumor antigens)

Tumor Antigens Encoded by Genomes of Oncogenic Viruses. The products of oncogenic viruses function as tumor antigens and elicit specific T cell responses that may serve to eradicate the tumors. (e.g. proteins encoded by: □ Epstein-Barr virus (EBV), which is associated with B cell lymphomas and nasopharyngeal carcinoma □ Human papilloma virus (HPV), which is associated with cervical carcinomas. The adaptive immune system can prevent the growth of DNA virus induced tumors. A competent immune system may play a role in surveillance against virus-induced tumors because of its ability to recognize and kill virus-infected cells.

Oncofoetal antigens : These are the proteins that are highly expressed in cancer cells as well as in foetus undergoing development but are absent in the adult cell. The two most thoroughly characterized oncofetal antigens are carcinoembryonic antigen (CEA, CD66) made by many carcimomas, and alpha-fetoprotein (AFP), made by liver and germ cell tumors. □

Tissue specific differentiation antigens**:** Tumors express molecules that are normally present on the cells of origin. These antigens are called differentiation antigens because they are specific for particular lineages or differentiation stages of various cell types. Their importance is as potential targets for immunotherapy, and for

identifying the tissue of origin of tumors. Examples include CD10, and CD20 on B cell tumors, prostate specific antigen on prostatic carcinomas.

Altered Glycolipid and Glycoprotein Antigens. Most human and experimental tumors express higher than normal levels of and/or abnormal forms of surface glycoproteins or glycolipids, which may be diagnostic markers and targets for therapy. These altered molecules include gangliosides, blood group antigens, and mucins. This class of tumor associated antigens is a target for cancer therapy with specific antibodies. Altered glycolipid tumor antigens include CA-125 and CA-19-9, expressed on ovarian carcinomas, and MUC-1, expressed on breast carcinomas.

Immune response to tumors

Tumor Immune response mostly occurs in two forms either by innate immune response or by adaptive immune response.

-Innate immune response to tumors

Natural killer cells (NK cells)

Around 15% of mammalian blood lymphocytes are composed of NK cells. NK cells can be activated by interferons from virus infected cells or by IL-12 from activated macrophages. NK cells are large, granular, and non-phagocytic cells that are derived from bone marrow. NK cells can kill certain tumor cell lines and are quite effective in eliminating the cells that has low class I MHC expression.

Macrophages

Macrophages can prevent the spread of cancer based on their activation state. Activated macrophages can kill transformed cells more efficiently than the normal cell. Macrophages treat the tumor cells like an infectious organism and produces cytokine tumor necrosis factor (TNF) to kill the tumor.

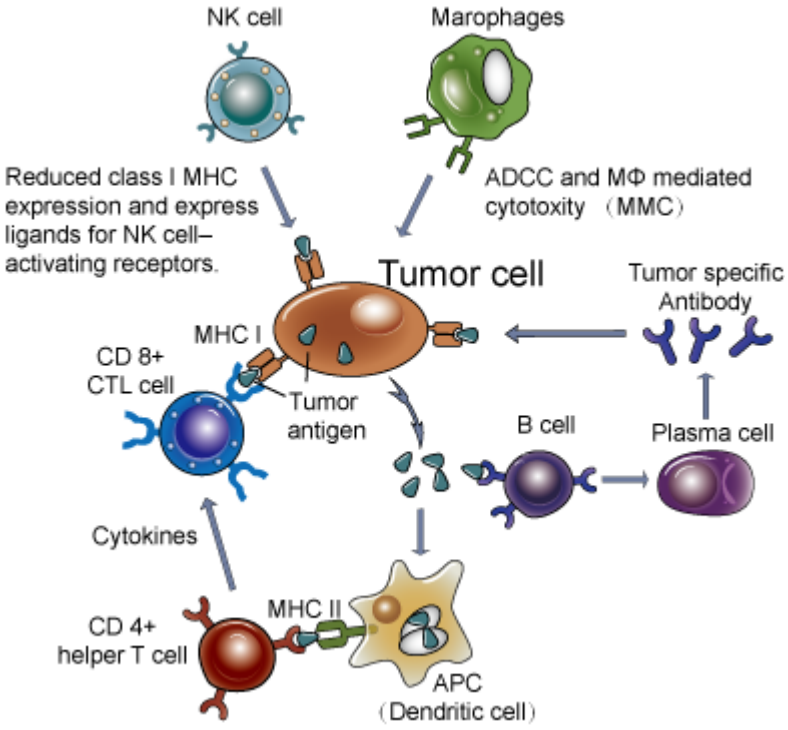
-Adaptive immune response to tumors

T-lymphocytes

The basis of adaptive tumor immunity is to destroy tumor cells by CD8+ CTLs. Functioning of CD8+ cell requires cross presentation of the tumor antigen by the dendritic cells.

Antibodies

These are known to kill tumors either by stimulating antibody-dependent cell mediated cytotoxicity or by the activation of complement system. Even though there is some immune response by antibodies in which NK cells mediate the destruction of tumor cells but antibody response towards tumors is not quite effective in most of the tumor cases.



Evasion of immune responses by tumors:

• Class I MHC expression may be down-regulated on tumor cells so that they cannot be recognized by CTLs.

• Tumors lose expression of antigens that elicit immune responses.

• Tumors may fail to induce strong CTL responses because of lack of costimulators, class II MHC molecules

• The products of tumor cells may suppress anti-tumor immune responses.

Immunotherapy for tumors:

Immunotherapy for tumors is aimed at augmenting the weak host immune response to the tumors (active immunity), or at administering tumor-specific antibodies or T cells, a form of passive immunity.

Therapy with Anti-Tumor Antibodies

A monoclonal antibody specific for the oncogene Her-2/Neu, which is expressed at high levels in some tumors, has shown success in breast cancer patients, and is now approved for clinical use. • Tumor-specific antibodies may be coupled to toxic molecules, radioisotopes, and anti-tumor drugs, to promote delivery of these cytotoxic agents specifically to the tumor (immunotoxins)