NAME_____

PANDEMIC COMPARISON

	BACTERIAL	VIRAL
WHAT MICROBE CAUSES DISEASE		
COMMON HUMAN SYMPTOMS	FEVER, COUGH, SNEEZING	FEVER, COUGH, SNEEZING
BLOOD WORK /CULTURE		
MEDICAL TREATMENTS		
EFFICACY OF MEDICAL TREATMENTS		
COMMON METHODS OF TRANSMISSION		
COMMON SUGGESTIONS TO PREVENT TRANSMISSION		
HOW LONG CAN IT LIVE ON SURFACES		
HOW CAN IT BE KILLED ON SURFACES		
TYPICAL R0(RNAUGHT)		
PREVIOUS EPIDEMICS/PANDEMICS		

PANDEMIC INFORMATION

BENEDUCCI

General Concepts

Manifestations of Infection

The clinical presentation of an infectious disease reflects the interaction between the host and the microorganism. This interaction is affected by the host immune status and microbial virulence factors. Signs and symptoms vary according to the site and severity of infection. Diagnosis requires a composite of information, including history, physical examination, radiographic findings, and laboratory data.

Microbial Causes of Infection

Infections may be caused by bacteria, viruses, fungi, and parasites. The pathogen may be exogenous (acquired from environmental or animal sources or from other persons) or endogenous (from the normal flora).

Specimen Selection, Collection, and Processing

Specimens are selected on the basis of signs and symptoms, should be representative of the disease process, and should be collected before administration of antimicrobial agents. The specimen amount and the rapidity of transport to the laboratory influence the test results.

Microbiologic Examination

Direct Examination and Techniques: Direct examination of specimens reveals gross pathology. Microscopy may identify microorganisms. Immunofluorescence, immuno-peroxidase staining, and other immunoassays may detect specific microbial antigens. Genetic probes identify genus- or species-specific DNA or RNA sequences.

Culture: Isolation of infectious agents frequently requires specialized media. Nonselective (noninhibitory) media permit the growth of many microorganisms. Selective media contain inhibitory substances that permit the isolation of specific types of microorganisms.

Microbial Identification: Colony and cellular morphology may permit preliminary identification. Growth characteristics under various conditions, utilization of carbohydrates and other substrates, enzymatic activity, immunoassays, and genetic probes are also used.

Serodiagnosis: A high or rising titer of specific IgG antibodies or the presence of specific IgM antibodies may suggest or confirm a diagnosis.

Antimicrobial Susceptibility: Microorganisms, particularly bacteria, are tested in vitro to determine whether they are susceptible to antimicrobial agents.

Introduction

Some infectious diseases are distinctive enough to be identified clinically. Most pathogens, however, can cause a wide spectrum of clinical syndromes in humans. Conversely, a single clinical syndrome may result from infection with any one of many pathogens. Influenza virus infection, for example, causes a wide variety of respiratory syndromes that cannot be distinguished clinically from those caused by streptococci, mycoplasmas, or more than 100 other viruses.

Most often, therefore, it is necessary to use microbiologic laboratory methods to identify a specific etiologic agent. Diagnostic medical microbiology is the discipline that identifies etiologic agents of disease. The job of the clinical microbiology laboratory is to test specimens from patients for microorganisms that are, or may be, a cause of the illness and to provide information (when appropriate) about the in vitro activity of antimicrobial drugs against the microorganisms identified (Fig. 10-1).

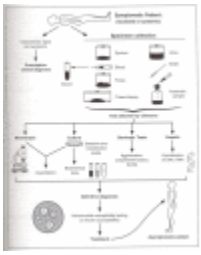

Figure 10-1

Laboratory procedures used in confirming a clinical diagnosis of infectious disease with a bacterial etiology.

The staff of a clinical microbiology laboratory should be qualified to advise the physician as well as process specimens. The physician should supply salient information about the patient, such as age and sex, tentative diagnosis or details of the clinical syndrome, date of onset, significant exposures, prior antibiotic therapy, immunologic status, and underlying conditions. The clinical microbiologist participates in decisions regarding the microbiologic diagnostic studies to be performed, the type and timing of specimens to be collected, and the conditions for their transportation and storage. Above all, the clinical microbiology laboratory, whenever appropriate, should provide an interpretation of laboratory results.

Manifestations of Infection

The manifestations of an infection depend on many factors, including the site of acquisition or entry of the microorganism; organ or system tropisms of the microorganism; microbial virulence; the age, sex, and immunologic status of the patient; underlying diseases or conditions; and the presence of implanted prosthetic devices or materials. The signs and symptoms of infection may be localized, or they may be systemic, with fever, chills, and hypotension. In some instances the manifestations of an infection are sufficiently characteristic to suggest the diagnosis; however, they are often nonspecific.

Microbial Causes of Infection

Infections may be caused by bacteria (including mycobacteria, chlamydiae, mycoplasmas, and rickettsiae), viruses, fungi, or parasites. Infection may be endogenous or exogenous. In endogenous infections, the microorganism (usually a bacterium) is a component of the patientapos;s indigenous flora. Endogenous infections can occur when the microorganism is aspirated from the upper to the lower respiratory tract or when it penetrates the skin or mucosal barrier as a result of trauma or surgery. In contrast, in exogenous infections, the microorganism is acquired from the environment (e.g., from soil or water) or from another person or an animal. Although it is important to establish the cause of an infection, the differential diagnosis is based on a careful history, physical examination, and appropriate radiographic and laboratory studies, including the selection of appropriate specimens for microbiologic examination. Results of the history, physical examination, and radiographic and laboratory studies allow the physician to request tests for the microorganisms most likely to be the cause of the infection.

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Specimen Selection, Collection and Processing

Specimens selected for microbiologic examination should reflect the disease process and be collected in sufficient quantity to allow complete microbiologic examination. The number of microorganisms per milliliter of a body fluid or per gram of tissue is highly variable, ranging from less than 1 to 10^8 or 10^{10} colony-forming units (CFU). Swabs, although popular for specimen collection, frequently yield too small a specimen for accurate microbiologic examination and should be used only to collect material from the skin and mucous membranes.

Because skin and mucous membranes have a large and diverse indigenous flora, every effort must be made to minimize specimen contamination during collection. Contamination may be avoided by various means. The skin can be disinfected before aspirating or incising a lesion. Alternatively, the contaminated area may be bypassed altogether. Examples of such approaches are transtracheal puncture with aspiration of lower respiratory secretions or suprapubic bladder puncture with aspiration of urine. It is often impossible to collect an uncontaminated specimen,

and decontamination procedures, cultures on selective media, or quantitative cultures must be used (see above).

Specimens collected by invasive techniques, particularly those obtained intraoperatively, require special attention. Enough tissue must be obtained for both histopathologic and microbiologic examination. Histopathologic examination is used to distinguish neoplastic from inflammatory lesions and acute from chronic inflammations. The type of inflammation present can guide the type of microbiologic examination performed. If, for example, a caseous granuloma is observed histopathologically, microbiologic examination should include cultures for mycobacteria and fungi. The surgeon should obtain several samples for examination from a single large lesion or from each of several smaller lesions. If an abscess is found, the surgeon should collect several milliliters of pus, as well as a portion of the wall of the abscess, for microbiologic examination. Swabs should be kept out of the operating room.

If possible, specimens should be collected before the administration of antibiotics. Above all, close communication between the clinician and the microbiologist is essential to ensure that appropriate specimens are selected and collected and that they are appropriately examined.

Microbiologic Examination

Direct Examination

Direct examination of specimens frequently provides the most rapid indication of microbial infection. A variety of microscopic, immunologic, and hybridization techniques have been developed for rapid diagnosis (Table 10-1).

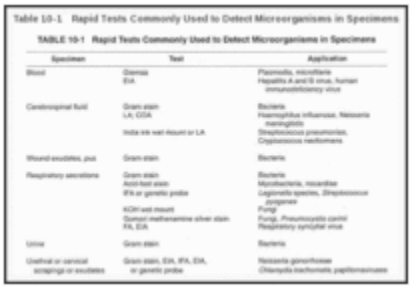

Table 10-1 Rapid Tests Commonly Used to Detect Microorganisms in Specimens

TABLE 10-1 Rapid Tests Commonly Used to Detect Microorganisms in Specimens

Specimen	Test	Application
Blood	Dramaa EIA	Plasmodia, microfilaria Hepatitis A and B virus, human immunodeficiency virus
Cerebrospinal fluid	Gram stain LA, COA India ink wet mount or LA	Bacteria Haemophilus influenzae, Neisseria meningitidis Streptococcus pneumoniae, Cryptococcus neoformans
Wound exudates, pus	Gram stain	Bacteria
Respiratory secretions	Gram stain Acid-fast stain IFA or genetic probe KOH wet mount Gomori methenamine silver stain FA, EIA	Bacteria Mycobacteria, nocardiae Legionella species, Streptococcus pyogenes Fungi Fungi, Pneumocystis carinii Respiratory syncytial virus
Urine	Gram stain	Bacteria
Urethral or cervical scrapings or exudates	Gram stain, EIA, IFA, EIA, or genetic probe	Neisseria gonorrhoeae Chlamydia trachomatis, papillomaviruses

Table 10-1

Rapid Tests Commonly Used to Detect Microorganisms in Specimens.

Sensitivity and Specificity

The sensitivity of a technique usually depends on the number of microorganisms in the specimen. Its specificity depends on how morphologically unique a specific microorganism appears microscopically or how specific the antibody or genetic probe is for that genus or species. For example, the sensitivity of Cram stains is such that the observation of two bacteria

per oil immersion field (X 1,000) of a Gram-stained smear of uncentrifuged urine is equivalent to the presence of $\geq 10^5$ CFU/ml of urine. The sensitivity of the Gram-stained smear for detecting Gram-negative coccobacilli in cerebrospinal fluid from children with *Haemophilus influenzae* meningitis is approximately 75 percent because in some patients the number of colony-forming units per milliliter of cerebrospinal fluid is less than 10^4. At least 10^4 CFU of tubercle bacilli per milliliter of sputum must be present to be detected by an acid-fast smear of decontaminated and concentrated sputum.

An increase in the sensitivity of a test is often accompanied by a decrease in specificity. For example, examination of a Gram-stained smear of sputum from a patient with pneumococcal pneumonia is highly sensitive but also highly nonspecific if the criterion for defining a positive test is the presence of any Gram-positive cocci. If, however, a positive test is defined as the presence of a preponderance of Gram-positive, lancet-shaped diplococci, the test becomes highly specific but has a sensitivity of only about 50 percent. Similar problems related to the number of microorganisms present affect the sensitivity of immunoassays and genetic probes for bacteria, chlamydiae, fungi and viruses. In some instances, the sensitivity of direct examination tests can be improved by collecting a better specimen. For example, the sensitivity of fluorescent antibody stain for *Chlamydia trachomatis* is higher when endocervical cells are obtained with a cytobrush than with a swab. The sensitivity may also be affected by the stage of the disease at which the specimen is collected. For example, the detection of herpes simplex virus by immunofluorescence, immunoassay, or culture is highest when specimens from lesions in the vesicular stage of infection are examined. Finally, sensitivity may be improved through the use of an enrichment or enhancement step in which microbial or genetic replication occurs to the point at which a detection method can be applied.

Techniques

For microscopic examination it is sufficient to have a compound binocular microscope equipped with low-power (1OX), high-power (40X), and oil immersion (1OOX) achromatic objectives, 10X wide-field oculars, a mechanical stage, a substage condenser, and a good light source. For examination of wet-mount preparations, a darkfield condenser or condenser and objectives for phase contrast increases image contrast. An exciter barrier filter, darkfield condenser, and ultraviolet light source are required for fluorescence microscopy.

For immunologic detection of microbial antigens, latex particle agglutination, coagglutination, and enzyme-linked immunosorbent assay (ELISA) are the most frequently used techniques in the clinical laboratory. Antibody to a specific antigen is bound to latex particles or to a heat-killed and treated protein A-rich strain of *Staphylococcus aureus* to produce agglutination (Fig. 10-2). There are several approaches to ELISA; the one most frequently used for the detection of microbial antigens uses an antigen-specific antibody that is fixed to a solid phase, which may be a latex or metal bead or the inside surface of a well in a plastic tray. Antigen present in the

specimen binds to the antibody as inFig. 10-2. The test is then completed by adding a second antigen-specific antibody bound to an enzyme that can react with a substrate to produce a colored product. The initial antigen antibody complex forms in a manner similar to that shown inFigure 10-2. When the enzyme-conjugated antibody is added, it binds to previously unbound antigenic sites, and the antigen is, in effect, sandwiched between the solid phase and the enzyme-conjugated antibody. The reaction is completed by adding the enzyme substrate.

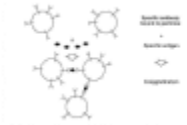

Figure 10-2

Agglutination test in which inert particles (latex beads or heat-killed *S aureus*Cowan 1 strain with protein A) are coated with antibody to any of a variety of antigens and then (more...)

Genetic probes are based on the detection of unique nucleotide sequences with the DNA or RNA of a microorganism. Once such a unique nucleotide sequence, which may represent a portion of a virulence gene or of chromosomal DNA, is found, it is isolated and inserted into a cloning vector (plasmid), which is then transformed into Escherichia coli to produce multiple copies of the probe. The sequence is then reisolated from plasmids and labeled with an isotope or substrate for diagnostic use. Hybridization of the sequence with a complementary sequence of DNA or RNA follows cleavage of the double-stranded DNA of the microorganism in the specimen.

The use of molecular technology in the diagnoses of infectious diseases has been further enhanced by the introduction of gene amplication techniques, such as the polymerase chain reaction (PCR) in which DNA polymerase is able to copy a strand of DNA by elongating complementary strands of DNA that have been initiated from a pair of closely spaced oligonucleotide primers. This approach has had major applications in the detection of infections due to microorganisms that are difficult to culture (e.g. the human immunodeficiency virus) or that have not as yet been successfully cultured (e.g. the Whipple's disease bacillus).

Culture

In many instances, the cause of an infection is confirmed by isolating and culturing microorganism either in artificial media or in a living host. Bacteria (including mycobacteria and mycoplasmas) and fungi are cultured in either liquid (broth) or on solid (agar) artificial media. Liquid media provide greater sensitivity for the isolation of small numbers of microorganisms; however, identification of mixed cultures growing in liquid media requires subculture onto solid media so that isolated colonies can be processed separately for identification. Growth in liquid media also cannot ordinarily be quantitated. Solid media, although somewhat less sensitive than

liquid media, provide isolated colonies that can be quantified if necessary and identified. Some genera and species can be recognized on the basis of their colony morphologies.

In some instances one can take advantage of differential carbohydrate fermentation capabilities of microorganisms by incorporating one or more carbohydrates in the medium along with a suitable pH indicator. Such media are called differential media (e.g., eosin methylene blue or MacConkey agar) and are commonly used to isolate enteric bacilli. Different genera of the Enterobacteriaceae can then be presumptively identified by the color as well as the morphology of colonies.

Culture media can also be made selective by incorporating compounds such as antimicrobial agents that inhibit the indigenous flora while permitting growth of specific microorganisms resistant to these inhibitors. One such example is Thayer-Martin medium, which is used to isolate *Neisseria gonorrhoeae*. This medium contains vancomycin to inhibit Gram-positive bacteria, colistin to inhibit most Gram-negative bacilli, trimethoprim-sulfamethoxazole to inhibit *Proteus* species and other species that are not inhibited by colistin and anisomycin to inhibit fungi. The pathogenic *Neisseria* species, *N gonorrhoeae* and *N meningitidis*, are ordinarily resistant to the concentrations of these antimicrobial agents in the medium.

The number of bacteria in specimens may be used to define the presence of infection. For example, there may be small numbers ($\leq 10^3$ CFU/ml) of bacteria in clean-catch, midstream urine specimens from normal, healthy women; with a few exceptions, these represent bacteria that are indigenous to the urethra and periurethral region. Infection of the bladder (cystitis) or kidney (pyelone-phritis) is usually accompanied by bacteriuria of about $\geq 10^4$ CFU/ml. For this reason, quantitative cultures (Fig. 10-3) of urine must always be performed. For most other specimens a semiquantitative streak method (Fig. 10-3) over the agar surface is sufficient. For quantitative cultures, a specific volume of specimen is spread over the agar surface and the number of colonies per milliliter is estimated. For semiquantitative cultures, an unquantitated amount of specimen is applied to the agar and diluted by being streaked out from the inoculation site with a sterile bacteriologic loop (Fig. 10-3). The amount of growth on the agar is then reported semiquantitatively as many, moderate, or few (or 3+, 2+, or 1+), depending on how far out from the inoculum site colonies appear. An organism that grows in all streaked areas would be reported as 3+.

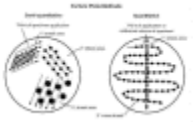

Figure 10-3

Quantitative versus semiquantitative culture, revealing the number of bacteria in specimens.

Chlamydiae and viruses are cultured in cell culture systems, but virus isolation occasionally requires inoculation into animals, such as suckling mice, rabbits, guinea pigs, hamsters, or primates. Rickettsiae may be isolated with some difficulty and at some hazard to laboratory workers in animals or embryonated eggs. For this reason, rickettsial infection is usually diagnosed serologically. Some viruses, such as the hepatitis viruses, cannot be isolated in cell culture systems, so that diagnosis of hepatitis virus infection is based on the detection of hepatitis virus antigens or antibodies.

Cultures are generally incubated at 35 to 37°C in an atmosphere consisting of air, air supplemented with carbon dioxide (3 to 10 percent), reduced oxygen (microaerophilic conditions), or no oxygen (anaerobic conditions), depending upon requirements of the microorganism. Since clinical specimens from bacterial infections often contain aerobic, facultative anaerobic, and anaerobic bacteria, such specimens are usually inoculated into a variety of general purpose, differential, and selective media, which are then incubated under aerobic and anaerobic conditions (Fig. 10-4).

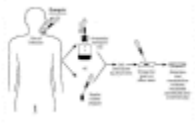

Figure 10-4

General procedure for collecting and processing specimens for aerobic and/or anaerobic bacterial culture.

The duration of incubation of cultures also varies with the growth characteristics of the microorganism. Most aerobic and anaerobic bacteria will grow overnight, whereas some mycobacteria require as many as 6 to 8 weeks.

Microbial Identification

Microbial growth in cultures is demonstrated by the appearance of turbidity, gas formation, or discrete colonies in broth; colonies on agar; cytopathic effects or inclusions in cell cultures; or detection of genus- or species-specific antigens or nucleotide sequences in the specimen, culture medium, or cell culture system.

Identification of bacteria (including mycobacteria) is based on growth characteristics (such as the time required for growth to appear or the atmosphere in which growth occurs), colony and microscopic morphology, and biochemical, physiologic, and, in some instances, antigenic or nucleotide sequence characteristics. The selection and number of tests for bacterial identification depend upon the category of bacteria present (aerobic versus anaerobic, Gram-positive versus Gram-negative, cocci versus bacilli) and the expertise of the microbiologist examining the culture. Gram-positive cocci that grow in air with or without added CO_2 may be identified by a

relatively small number of tests (seeCh.12). The identification of most Gram-negative bacilli is far more complex and often requires panels of 20 tests for determining biochemical and physiologic characteristics. The identification of filamentous fungi is based almost entirely on growth characteristics and colony and microscopic morphology. Identification of viruses is usually based on characteristic cytopathic effects in different cell cultures or on the detection of virus- or species-specific antigens or nucleotide sequences.

Interpretation of Culture Results

Some microorganisms, such as *Shigella dysenteriae, Mycobacterium tuberculosis, Coccidioides immitis,* and influenza virus, are always considered clinically significant. Others that ordinarily are harmless components of the indigenous flora of the skin and mucous membranes or that are common in the environment may or may not be clinically significant, depending on the specimen source from which they are isolated. For example, coagulase-negative staphylococci are normal inhabitants of the skin, gastrointestinal tract, vagina, urethra, and the upper respiratory tract (i.e., of the nares, oral cavity, and pharynx). Therefore, their isolation from superficial ulcers, wounds, and sputum cannot usually be interpreted as clinically significant. They do, however, commonly cause infections associated with intravascular devices and implanted prosthetic materials. However, because intravascular devices penetrate the skin and since cultures of an implanted prosthetic device can be made only after incision, the role of coagulase-negative staphylococci in causing infection can usually be surmised only when the microorganism is isolated in large numbers from the surface of an intravascular device, from each of several sites surrounding an implanted prosthetic device, or, in the case of prosthetic valve endocarditis, from several separately collected blood samples. Another example, *Aspergillus fumigatus,* is widely distributed in nature, the hospital environment, and upper respiratory tract of healthy people but may cause fatal pulmonary infections in leukemia patients or in those who have undergone bone marrow transplantation. The isolation of *A fumigatus* from respiratory secretions is a nonspecific finding, and a definitive diagnosis of invasive aspergillosis requires histologic evidence of tissue invasion.

Physicians must also consider that the composition of microbial species on the skin and mucous membranes may be altered by disease, administration of antibiotics, endotracheal or gastric intubation, and the hospital environment. For example, potentially pathogenic bacteria can often be cultured from the pharynx of seriously ill, debilitated patients in the intensive care unit, but may not cause infection.

Serodiagnosis

Infection may be diagnosed by an antibody response to the infecting microorganism. This approach is especially useful when the suspected microbial agent either cannot be isolated in culture by any known method or can be isolated in culture only with great difficulty. The

diagnosis of hepatitis virus and Epstein-Barr virus infections can be made only serologically, since neither can be isolated in any known cell culture system. Although human immunodeficiency virus type 1 (HIV-1) can be isolated in cell cultures, the technique is demanding and requires special containment facilities. HIV-1 infection is usually diagnosed by detection of antibodies to the virus.

The disadvantage of serology as a diagnostic tool is that there is usually a lag between the onset of infection and the development of antibodies to the infecting microorganism. Although IgM antibodies may appear relatively rapidly, it is usually necessary to obtain acute- and convalescent-phase serum samples to look for a rising titer of IgG antibodies to the suspected pathogen. In some instances the presence of a high antibody titer when the patient is initially seen is diagnostic; often, however, the high titer may reflect a past infection, and the current infection may have an entirely different cause. Another limitation on the use of serology as a diagnostic tool is that immunosuppressed patients may be unable to mount an antibody response.

Antimicrobial Susceptibility

The responsibility of the microbiology laboratory includes not only microbial detection and isolation but also the determination of microbial susceptibility to antimicrobial agents. Many bacteria, in particular, have unpredictable susceptibilities to antimicrobial agents, and their susceptibilities can be measured in vitro to help guide the selection of the most appropriate antimicrobial agent.

Antimicrobial susceptibility tests are performed by either disk diffusion or a dilution method. In the former, a standardized suspension of a particular microorganism is inoculated onto an agar surface to which paper disks containing various antimicrobial agents are applied. Following overnight incubation, any zone diameters of inhibition about the disks are measured and the results are reported as indicating susceptibility or resistance of the microorganism to each antimicrobial agent tested. An alternative method is to dilute on a $\log_2$ scale each antimicrobial agent in broth to provide a range of concentrations and to inoculate each tube or, if a microplate is used, each well containing the antimicrobial agent in broth with a standardized suspension of the microorganism to be tested. The lowest concentration of antimicrobial agent that inhibits the growth of the microorganism is the minimal inhibitory concentration (MIC). The MIC and the zone diameter of inhibition are inversely correlated (Fig. 10-5). In other words, the more susceptible the microorganism is to the antimicrobial agent, the lower the MIC and the larger the zone of inhibition. Conversely, the more resistant the microorganism, the higher the MIC and the smaller the zone of inhibition.

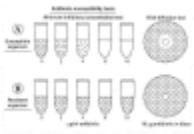

Figure 10-5

Two methods for performing antibiotic susceptibility tests. (A) Disk diffusion method. (B) Minimum inhibitory concentration (MIC) method. In the example shown, two different microorganisms are tested by (more...)

The term susceptible means that the microorganism is inhibited by a concentration of antimicrobial agent that can be attained in blood with the normally recommended dose of the antimicrobial agent and implies that an infection caused by this microorganism may be appropriately treated with the antimicrobial agent. The term resistant indicates that the microorganism is resistant to concentrations of the antimicrobial agent that can be attained with normal doses and implies that an infection caused by this microorganism could not be successfully treated with this antimicrobial agent.

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Physical and Chemical Control of Microorganisms

I. In most medical settings, the control of microorganisms is of paramount concern. **Decontamination** refers to the destruction or removal of microorganisms from instruments, materials, body surfaces, etc. Many agents and procedures have been developed to accomplish this end. It is imperative that you, as a medical professional, understand the modes of action, level of activity and other factors which influence the effectiveness of these procedures and agents.

A. Generally, decontamination involves **physical** and/or **chemical** agents. Physical agents include high temperature, radiation, filtration or cavitating sound waves. A myriad of chemical decontamination agents exists. For the most part, they are substances that react with and thus alter some important molecular component of the cell.

B. Microorganisms are not uniformly affected by physical and chemical decontamination. Susceptibility to the effects of physical and chemical agents depends upon the type of microorganism and at what stage in the microorganism's lifecycle they are exposed to the agent. When choosing and applying a method of decontaminating materials, it is important that you understand what type of organism is being targeted and the relative resistance of that organism.

1. The target with the **highest resistance** is the bacterial endospores. Endospores are ubiquitous in the environment. Many bacteria found in the soil are capable of forming these structures. Introduced into deep wounds or during surgical procedures, these spores can cause severe problems. Thus surgical equipment and other materials used in invasive procedures need to be decontaminated in such a way as to destroy these agents.

2. Targets with the **moderate resistance** include protist cysts, sexual fungal spores, nonenveloped viruses (many enteric viruses including those responsible for polio, Hepatitis A and Hepatitis E), Mycobacterium *tuberculosis*, *Staphylococcus aureus* and members of the genus *Pseudomonas*.

3. Targets with the **least resistance** include vegetative cells of most microbes, enveloped viruses (including those viruses responsible for AIDS and Hepatitis B), and asexual fungal spores.

C. There are several terms that have precise meanings. When these terms are used in a product description or as part of procedural instructions it is important that you are aware of these precise meanings.

1. **Sterilization** refers to any process that destroys or removes all infectious organisms including endospores and viruses.

2. **Disinfection** refers to any physical process or application of any chemical that will kill the growing (**vegetative**) microbial cells. These processes need not kill or inactivate endospores. A **disinfectant** is a chemical capable of killing microbial cells. It should be understood that if a chemical is referred to as a disinfectant, it is to be used on inanimate objects and **not** to be used on body surfaces.

3. **Sanitize** refers to any mechanical process (scrubbing, rinsing, etc.) that reduces the microbial load on a surface. **Sanitizers** are chemical agents that assist in this task. These are usually soaps or detergents.

4. **Microbicidal agents** are chemicals that will kill or destroy microorganisms. Among the microbicidal agents are those that target specific microorganisms including:

a. **fungicidal agents** which are designed to kill fungi;
b. **bactericidal agents** which are designed to kill bacteria;
c. **sporicidal agents** which are designed to destroy endospores;
d. **viricidal agents** which are designed to destroy viruses.

5. **Microbiostasis** refers to the inhibition of growth of microorganisms. This does not mean that the organisms are killed simply that they are unable to grow. Refrigeration and many antimicrobial drugs exert a microbistatic effect.

a. **Bacteriostatic agents** are chemicals that inhibit the growth of bacteria.
b. **Fungistatic agents** are chemicals that inhibit growth of fungi.

5. **Disinfection** refers to any physical process or application of any chemical that will kill the growing (**vegetative**) microbial cells. These processes need not kill or inactivate endospores. A **disinfectant** is a chemical capable of killing microbial cells. It should be understood that if a chemical is referred to as a disinfectant, it is to be used on inanimate objects and **not** to be used on body surfaces.

6. **Antisepsis** refers to those practices that keep microorganism from entering the sterile tissues. The application of these practices is referred to as **aseptic technique**. Antiseptics are those chemicals that can be applied to tissue surfaces to kill or inhibit the growth of microorganisms.

II. There are several factors that will influence the effectiveness of antimicrobial agents. When attempting to sterilize, disinfect or sanitize a surface and in the application of aseptic technique, these factors must be taken into consideration.

A. **Time of exposure** The amount of time that the microorganisms are exposed to any agent (physical or chemical) will greatly affect how many microorganism are destroyed. Short exposures often kill the most susceptible organism and thus select for the more robust organisms. This can be counter productive in that the robust organism will then come to dominate the population of microorganisms and will often rapidly replace the organisms killed by the brief exposure.

B. **Microbial load** The number of microorganisms must be also considered. Highly contaminated substances will require more protracted exposure to eliminate all living contaminates.

C. **Type organism or organisms** As mentioned earlier, different organisms display differing susceptibilities to antimicrobial agents. If elimination of vegetative cells is the aim, less stringent measures can be taken. If, on the other hand, endospores must be eliminated more rigorous measures will be required.

D. **Temperature, pH and osmolarity** Many antimicrobial agents lose their effectiveness under certain environmental conditions and become more effective under others. Generally speaking, higher temperatures lead to increased rates of antimicrobial affect. No such broad statement can be made for the relative effectiveness of agents under differing conditions of pH and osmolarity. For some agents, decreases in pH make them more effective while other agents become inactive as the pH drops. It becomes important that the affect which pH and osmolarity exert on the efficacy of an antimicrobial agent be understood and taken into account when using that agent.

E. **Concentration or intensity of agent** Usually for an agent to be effective it must be present at or above a certain concentration or intensity.

F. **Milieu** This term refers to other substances (proteins, solvents, etc.) that are present in the environment that you are trying to disinfect. These other substances may interfere with the action of the chemical or physical agent you intend to use to kill the bacteria. This is especially true of proteins. High levels of protein will interfere with the action of many chemical agents and will reduce the effectiveness of some physical agents.

III. Many chemical agents are available that are said to be effective at reducing of eliminating bacteria from the environment or from body surfaces. **Disinfectants** are

chemical compounds that are designed to kill bacteria and are to be used **only** on inanimate objects. **Antiseptics** are compounds designed to kill or inhibit the growth of bacteria on external body surfaces or certain mucus membranes. In clinical settings these agents, when used properly, are an important part of aseptic technique. But overuse of these products, especially outside of clinical settings, carries several risks. First, the inappropriate reduction of nonpathogenic normal flora on external body surfaces and mucus membranes can lead to infection by pathogenic organisms. (i.e. Some yeast infections can be traced to the inappropriate use of antiseptic douche.) Secondly, genes for resistance to antimicrobial drugs have been shown to be found on the same plasmids as genes for resistance to certain antiseptics and disinfectants. Thus, inappropriate use of antiseptics and disinfectants selects for those organisms that carry these plasmids. As a consequence of this overuse of antiseptics and disinfectants, the level of drug resistance increases in those bacterial populations that are found in the environment and on the body. It is important that you are aware of the appropriate usage of antiseptics and disinfectants. It is equally important that you are not pulled in by the current media driven hyperbole regarding the need to kill every bacterium that is found on the body or in the environment.

IV. The actual manner in which a physical or chemical agent affects bacteria is referred to as its **mode of action**. Generally speaking, if the mode of action of a chemical or physical agent interferes with a process or destroys a structure that is common to both the target microorganisms and our cells, high levels of side effects can be expected. For many drugs, the mode of action entails interference with a process that is unique to the target microorganism, thus minimizing the impact the agent has on our cells.

A. The cell wall is a common target of antimicrobial action. Most bacteria and all fungi have cell walls while our cells lack them. Thus agents that interfere with the synthesis of or specifically destroy the cell wall can be used at high concentration with little chance of affecting our cells.

1. As we will see later, many antimicrobial drugs exert their effect by interfering with the processes that lead to the synthesis of the cell wall.
2. In the case of the gram-negative cell wall, destruction of the outer membrane by solvents and detergents can be easily accomplished.
3. Many bodily secretions contain the enzyme **lysozyme**. This enzyme digests the peptidoglycan of the gram-positive cell wall.

B. Many disinfectants damage the cell membrane. This can be accomplished by disrupting the phospholipid bilayer or altering the transmembrane proteins. Remember, the membrane is a structure shared by both our cells and the cells of microorganisms, most agents with this mode of action can not be used internally or on mucus membranes as they will harm our cells also.

1. Organic solvents and strong **surfactants** both act by dissolving the phospholipid bilayer. This destroys the barrier that usually limits movement of ions and other chemicals into or out of the cell.
2. Agents that alter transmembrane proteins destroy the ability of a cell to selectively import or export substances and, in the bacterial cell, can lead to the inactivation of cytochromes and ATP synthase. Inactivation of these proteins destroys the ability of the cell to generate ATP.

C. As previously discussed, microorganisms contain many different types of large biochemicals including proteins, DNA, RNA, and lipids. Agents that will damage or inhibit the synthesis of these biological polymers will have an adverse effect on the microorganism.

1. Damage to a cell's DNA will inhibit that cell from properly reproducing and stop the use of the DNA as a guide to make RNA. This, in turn, will keep the cell from making proteins that were coded for by the damaged DNA. It appears that all living organisms have the ability to repair DNA. This repair mechanism involves enzymes that will remove the damaged DNA and replace it with functioning DNA. This process is very error prone and thus results in high levels of mutations in the DNA. It also takes time to carry out the repair process, so rapidly growing cells that divide before they have the time to fix the damaged DNA are more adversely effected than slow growing cells.

a. Bombardment of cells with **radiation** will lead to DNA damage.
b. Certain drugs bind to the enzymes needed to make DNA or RNA and interfere with the functioning of these enzymes.
c. **Nucleotide analogs** are chemicals that have considerable similarities to the nucleotides used in the synthesis of DNA. Often the enzymes that make DNA cannot distinguish between a real nucleotide and a nucleotide analog. When the analog is added to a growing DNA strand during replication, the synthesis of the DNA strand immediately stops. This keeps cells from copying their DNA completely. Cells that receive only partial copies of the DNA are usually not viable and immediately die.

2. It should be clear at this point the central role played by proteins in metabolic process. Without the action of those proteins known as enzymes, life could not continue. Thus by blocking the synthesis of proteins or inactivation of existing enzymes an organism can be killed. Many antimicrobials work solely or in part by altering the tertiary structure (shape) of a protein or by blocking the active site of an enzyme.

a. The osmolarity of a solution and hydrophilic attraction between amino acids in the protein and water help determine the tertiary structure of a protein. Under normal conditions the proper shape is taken on. But altering the osmolarity or adding substances to the environment which alter hydrophilic bonds, will lead to the protein losing it proper shape.

b. Proteins assume their proper shape and are stable in that configuration only at a very limited temperature range. Outside of that range (either hotter or colder) the protein will take on a different shape and its functionality will be decreased or eliminated. Alteration of the shape of protein through chemical or physical means is referred to as **denaturing**.

c. Reactive chemicals will often covalently bind to proteins. This changes the shape of a protein in ways that leave it unable to function properly.

d. Many antimicrobial drugs bind to the ribosome or active site of RNA polymerase. By blocking the action of these two enzymes protein synthesis can be effectively shut down.

V. Chemical agents do not have equal levels of disinfection. Certain agents are very effective and will inactive even endospores. These agents are said to have a **high level of activity**. Agents with an **intermediate level of activity**will kill vegetative cells of the most resistant organism (TB, naked viruses), sexual fungal spores. Agents with a **low level of activity** kill vegetative cells of less resistant organisms and enveloped viruses.

A. **Halogens** react with proteins in such a way that secondary and tertiary structure is altered. Most halogens exert an intermediate level of activity. Examples of halogen based agents are bleach, chlorine and bromine gas (water purification for drinking and swimming pools), iodine and iodophores (Betadine, providone).

B. **Phenolic agents** disrupt membranes and alter secondary and tertiary structure of proteins. Most of these agents exhibit intermediate to low level of

activity. Examples of common phenolic compounds include Hibiclens, creosote (a wood preservative) and amphyl.

C. **Alcohols** At 50-95% concentration are effective in disrupting membranes and alter protein tertiary structure. At 95-100% concentrations alcohols mainly serve to dehydrate cells. Alcohols exhibit an intermediate level of activity.

D. **Hydrogen peroxide** produces reactive hydroxyl radicals that oxidize proteins and other organic molecules. This chemical alteration leads to changes in the tertiary structure of proteins, which leads to reduced function by these proteins. Hydrogen peroxide exhibits a high level of activity.

E. **Detergents** mainly disrupt membranes but also will alter the tertiary structure of some proteins. Most detergents exhibit a low level of activity.

F. **Ethylene oxide** is the gas used to sterilize instruments that can not be autoclaved (referred to as **gas sterilization**). It chemically alters proteins, DNA and RNA. It exhibits a high level of activity.

VI. Sterilization, sanitization or simply affecting microbiostasis of inanimate substances can be accomplished through several physical means.

A. Heat is widely used to sterilize and sanitize objects and solutions. The goal (whether you hope to render the substances sterile or simply reduce the bacterial load) and the possible target organisms must be considered. Most vegetative cells are easily destroyed by heat while endospores are much more resistant.

1. The thermal energy of heat has a greater effect in the form of moist heat. This involves exposing the solutions or items to be sterilized to boiling or steam. Boiling occurs at the 100° C and the steam produced by boiling is usually at that temperature. Though this temperature is effective against vegetative cells, it is not very effective against endospores. By allowing the boiling to occur in a pressurized chamber, the boiling point and the steam produced by this boiling is hotter. One of the most common types of medical sterilizers is the **autoclave**. The autoclave usually is pressurized so that the boiling point is pushed to 121° C by raising the pressure to 15 pounds per square inch.

2. Many solutions do not hold up well to the high heats and pressures of the autoclave. Gentler means of decontamination are needed. These means usually do not produce sterile solutions but reduce the bacterial count so that the solutions spoil more slowly. These methods utilize lower temperatures and target the vegetative cells.

a. Tradition pasteurization methods (known as **batch pasteurization**) involve heating the solution to 63° -65° C for 30min. These methods kill most of the vegetative cells and decrease the rate of spoilage.
b. **Flash pasteurization** involves heating the solutions to 71.6° C for 15 seconds. These have similar effects as batch pasteurization.
c. Ultrahigh temperature (or **ultrapasteurization**) involves superheating the solution to 134° C for 1-2 seconds. This usually produces a sterile or nearly sterile solution.

3. To have the same decontaminating effect as moist heat, dry heat temperatures must be much higher. Commonly in laboratories, flaming of instruments (placing them in a flame and heating them to very high temperatures) is a common means for rapidly decontaminating an instrument. On a larger scale, hospitals **incinerate** (burn) contaminated wastes to kill any and all microorganisms contaminating these wastes.

B. Sanatizing surfaces often involves the use of surfactants. In this setting the surfactant is designed to loosen the bacteria from the surface by binding to the charged materials on the surface of the microorganism. These charged proteins and polysaccharides help the microorganism attach to surfaces. The surfactant binds to these charges and thus interferes with the ability of the microorganism to attach to the surface. The microorganism can then be simply wiped away.
C. In the home and in the medical setting, control of microbial growth is affected by keeping materials cold (freezing or refrigerating). It should be noted that this does not kill the microorganisms, cold simply stops or slows the rate of growth of the microbes. **Desiccation** involves removal of water from the material that you wish to preserve. Desiccation stops the activity of the enzymes of the microbes contaminating these materials which, in turn, stops growth. When the materials are rehydrated, the microbes often continue their growth.
D. Several types of radiation are commonly used to kill contaminating organisms.
1. **Ionizing radiation** penetrates organic matter very easily and when it strikes a molecule it will often cause the molecule to breakdown into highly reactive ions. If the radiation hits a DNA strand it will cause alteration of breakage of the strand. Other molecules in the vicinity of the DNA that are hit by the radiation can give rise to highly reactive ions. These ions then react with DNA, leading to breaks in the "backbone" of the DNA strand. In either case the DNA is damaged. The most commonly used form of ionizing radiation is **gamma radiation.** It is used to sterilize drugs and medical supplies that are sensitive to heat. Increasingly, gamma radiation is being used to treat foods. Recently, poultry and beef producers received approval

from the FDA to allow gamma irradiation of these meats to reduce the chances of transmission of several common pathogens.

2. **Ultraviolet radiation (UV light)** reacts with the pyrimidine bases of DNA (thymine and cytosine). When UV radiation hits DNA it imparts the pyrimidine bases with substantial amounts of energy. This energy allows the pyrimidines to form inappropriate covalent bonds with adjacent pyrimidine bases. This covalent linkage between the pyrimidine bases is known as a **pyrimidine dimer**. These dimers interfere with the ability of the effected pyrimidines to complementary base pair. This destroys the ability of the damaged DNA to carry out transcription or replication. Repair of this damage can occur but this process is error prone and thus introduces mutations into the repaired DNA.

E. For many solutions the most effective means of decontamination is to force the solution through a filter. **Filtration** is especially useful in sterilizing extremely sensitive drugs that would be adversely effected by any of the aforementioned means of decontamination. The size of the openings in the filter (**pore size)** will determine which pathogens are removed from the solution. Extremely small pores are necessary to remove viral pathogens

DISINFECTANTS

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Tuberculosis, food poisoning, cholera, pneumonia, strep throat and meningitis: these are just a few of the unsavory diseases caused by bacteria. Hygiene—keeping both home and body clean—is one of the best ways to curb the spread of bacterial infections, but lately consumers are getting the message that washing with regular soap is insufficient. Antibacterial products have never been so popular. Body soaps, household cleaners, sponges, even mattresses and lip glosses are now packing bacteria-killing ingredients, and scientists question what place, if any, these chemicals have in the daily routines of healthy people.

Traditionally, people washed bacteria from their bodies and homes using soap and hot water, alcohol, chlorine bleach or hydrogen peroxide. These substances act nonspecifically, meaning they wipe out almost every type of microbe in sight—fungi, bacteria and some viruses—rather than singling out a particular variety.

Soap works by loosening and lifting dirt, oil and microbes from surfaces so they can be easily rinsed away with water, whereas general cleaners such as alcohol inflict sweeping damage to cells by demolishing key structures, then evaporate. "They do their job and are quickly dissipated into the environment," explains microbiologist Stuart Levy of Tufts University School of Medicine.

Unlike these traditional cleaners, antibacterial products leave surface residues, creating conditions that may foster the development of resistant bacteria, Levy notes. For example, after spraying and wiping an antibacterial cleaner over a kitchen counter, active chemicals linger behind and continue to kill bacteria, but not necessarily all of them.

When a bacterial population is placed under a stressor—such as an antibacterial chemical—a small subpopulation armed with special defense mechanisms can develop. These lineages survive and reproduce as their weaker relatives perish. "What doesn't kill you makes you stronger" is the governing maxim here, as antibacterial chemicals select for bacteria that endure their presence.

As bacteria develop a tolerance for these compounds there is potential for also developing a tolerance for certain antibiotics. This phenomenon, called cross-resistance, has already been demonstrated in several laboratory studies using triclosan, one of the most common chemicals found in antibacterial hand cleaners, dishwashing liquids and other wash products. "Triclosan has a specific inhibitory target in bacteria similar to some antibiotics," says epidemiologist Allison Aiello at the University of Michigan School of Public Health.

When bacteria are exposed to triclosan for long periods of time, genetic mutations can arise. Some of these mutations endow the bacteria with resistance to isoniazid, an antibiotic used for treating tuberculosis, whereas other microbes can supercharge their efflux pumps—protein machines in the cell membrane that can spit out several types of antibiotics, Aiello explains. These effects have been demonstrated only in the laboratory, not in households and other real world environments, but Aiello believes that the few household studies may not have been long enough. "It's very possible that the emergence of resistant species takes quite some time to occur…; the potential is there," she says.

Apart from the potential emergence of drug-resistant bacteria in communities, scientists have other concerns about antibacterial compounds. Both triclosan and its close chemical relative triclocarban (also widely used as an antibacterial), are present in 60 percent of America's streams and rivers, says environmental scientist Rolf Halden, co-founder of the Center for Water and Health at Johns Hopkins Bloomberg School of Public Health. Both chemicals are efficiently removed from wastewater in treatment plants but end up getting sequestered in the municipal sludge, which is used as fertilizer for crops, thereby opening a potential pathway for contamination of the food we eat, Halden explains. "We have to realize that the concentrations in agricultural soil are very high," and this, "along with the presence of pathogens from sewage, could be a recipe for breeding antimicrobial resistance" in the environment, he says.

Triclosan has also been found in human breast milk, although not in concentrations considered dangerous to babies, as well as in human blood plasma. There is no evidence showing that current concentrations of triclosan in the human body are harmful, but recent studies suggest that it acts as an endocrine disrupter in bullfrogs and rats.

Further, an expert panel convened by the Food and Drug Administration determined that there is insufficient evidence for a benefit from consumer products containing antibacterial additives over similar ones not containing them.

"What is this stuff doing in households when we have soaps?" asks molecular biologist John Gustafson of New Mexico State University in Las Cruces. These substances really belong in hospitals and clinics, not in the homes of healthy people, Gustafson says.

Of course, antibacterial products do have their place. Millions of Americans suffer from weakened immune systems, including pregnant women and people with immunodeficiency diseases, points out Eugene Cole, an infectious disease specialist at Brigham Young University. For these people, targeted use of antibacterial products, such as triclosan, may be appropriate in the home, he says.

In general, however, good, long-term hygiene means using regular soaps rather than new, antibacterial ones, experts say. "The main way to keep from getting sick," Gustafson says, "is to wash your hands three times a day and don't touch mucous membranes."

HOUSEHOLD CLEANING

In the ongoing battle between you and household germs, you may think germs have the advantage. Unlike you, they can be just about everywhere at once. And when it comes down to hand-to-hand combat, you may be too rushed or tired or just have better things to do. They don't.

Yet keeping household germs at bay helps keep colds, flu, and other infectious illnesses from spreading. This on-the-go cleaning guide can help you get the upper hand with germs by focusing your efforts on the places where they lurk the most.

Where the Germs Are

As a rule of thumb, any area of your home with high traffic and surfaces that get touched a lot is a germ bank.

Not all germs are harmful. But where there are germ strongholds, the conditions are favorable for disease-causing viruses or bacteria to lurk.

One study found the kitchen sink had more bacteria than the toilet or garbage can. The only bathroom hotspot in the study's top 10 was the toothbrush holder. Why? Toothbrush holders are often near the toilet, and flushing the toilet sends a fine spray of mist that can contaminates them. They also tend to be neglected because people focus on cleaning the toilet and more obvious germ hotspots.

Getting Started: What You Need to Kill Germs

Cleaning with soap and hot water removes dirt and grime and gets rid of some germs. Cleaning alone is usually enough for many surfaces. But you may want to disinfect areas where there are a lot of germs.

A cleaner-disinfectant can be good for germ speed cleaning because it combines these two steps. You can use it for most kitchen countertops and bathroom surfaces.

Areas with sticky spills and dirt you can see should be cleaned with soap and water and then disinfected. You can make an inexpensive and effective disinfectant by mixing no more than 1 cup of bleach in 1 gallon of water. Never mix bleach with ammonia or vinegar.

Apply it and leave on for three to five minutes, then rinse and let air dry to save time. Or dry with a clean towel.

Always wear gloves and open some windows when you use products with bleach.

White vinegar or hydrogen peroxide are other effective homemade cleaners. Never mix hydrogen peroxide and vinegar together, however. And if you use hydrogen peroxide, test it first on an unseen surface to make sure it doesn't discolor or fade it.

Daily Speed Cleaning for Germs

You can take down some serious germ strongholds in a half-hour or less a day. If you don't have children or pets, it's even faster because you get to skip the last three steps. Start in the kitchen:

- Clean and disinfect countertops, sink faucet and handles, refrigerator handles, and cutting boards. Check the manufacturer's directions for specialty countertops.
- Clean with dishcloths that you can throw in the washer with hot water. Replace towels and dishcloths daily.
- Clean spills on the kitchen floor to keep them from attracting more dirt and bacteria.
- Empty bathroom wastebaskets and those with dirty diapers, and take out the garbage. Spritz the containers with sanitizing spray.
- Clean and sanitize the bathroom sink faucet and handles.
- Put pet dishes in the dishwasher.
- If you have a child in diapers, clean and disinfect the changing table.
- If your child uses pacifiers, put them on the top shelf of the dishwasher if they are dishwasher safe. Otherwise, wash it and any toys your child mouths with soap and hot water. Check toy cleaning labels first.

Everyday Preventive Actions That Can Help Fight Germs, Like Flu

CDC recommends a three-step approach to fighting the flu.

CDC recommends a three-step approach to fighting influenza (flu). The first and most important step is to get a flu vaccination each year. But if you get the flu, there are prescription antiviral drugs that can treat your illness. Early treatment is especially important for the elderly, the very young, people with certain chronic health conditions, and pregnant women. Finally, everyday preventive actions may slow the spread of germs that cause respiratory (nose, throat, and lungs) illnesses, like flu. This flyer contains information about everyday preventive actions.

How does the flu spread?

Flu viruses are thought to spread mainly from person to person through the coughing, sneezing, or talking of someone with the flu. Flu viruses also may spread when people touch something with flu virus on it and then touch their mouth, eyes, or nose. Many other viruses spread these ways too.

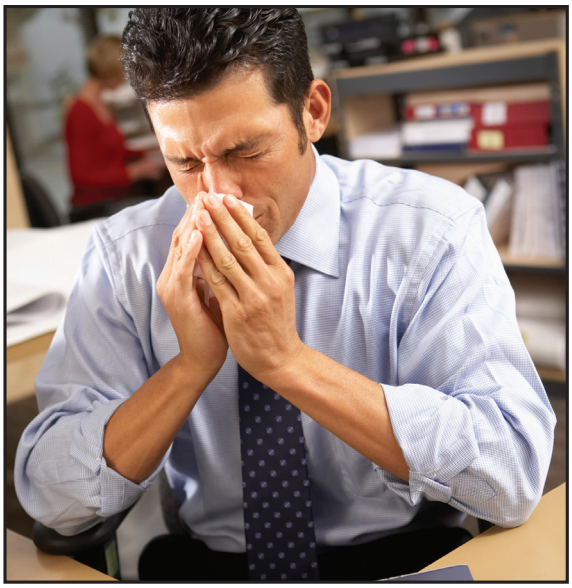
People infected with flu may be able to infect others beginning 1 day **before** symptoms develop and up to 5-7 days **after** becoming sick. That means you may be able to spread the flu to someone else before you know you are sick as well as while you are sick. Young children, those who are severely ill, and those who have severely weakened immune systems may be able to infect others for longer than 5-7 days.

What are everyday preventive actions?

Everyday preventive actions are steps that people can take to help slow the spread of germs that cause respiratory illness, like flu. These include the following personal and community actions:

- Cover your nose and mouth with a tissue when you cough or sneeze. This will block the spread of droplets from your mouth or nose that could contain germs.
- Wash your hands often with soap and water. If soap and water are not available, use an alcohol-based hand rub.
- Avoid touching your eyes, nose, and mouth. Germs spread this way.
- Try to avoid close contact with sick people.
- If you or your child gets sick with a respiratory illness, like flu, limit contact with others as much as possible to help prevent spreading illness. Stay home (or keep your child home) for at least 24 hours after fever is gone except to seek medical care or for other necessities. Fever should be gone without the use of a fever-reducing medicine.
- If an outbreak of flu or another illness occurs, follow public health advice. This may include information about how to increase distance between people and other measures.

What additional steps can I take at work to help stop the spread of germs that can cause respiratory illness, like flu?



- Find out about your employer's plans if an outbreak of flu or another illness occurs and whether flu vaccinations are offered on-site.
- Routinely clean frequently touched objects and surfaces, including doorknobs, keyboards, and phones, to help remove germs.
- Make sure your workplace has an adequate supply of tissues, soap, paper towels, alcohol-based hand rubs, and disposable wipes.
- Train others on how to do your job so they can cover for you in case you or a family member gets sick and you have to stay home.
- If you begin to feel sick while at work, go home as soon as possible.

What additional preventive actions can I take to protect my child from germs that can cause respiratory illness, like flu?

- Find out about plans your child's school, child care program, or college has if an outbreak of flu or another illness occurs and whether flu vaccinations are offered on-site.
- Make sure your child's school, child care program, or college routinely cleans frequently touched objects and surfaces, and that they have a good supply of tissues, soap, paper towels, alcohol-based hand rubs, and disposable wipes on-site.
- Ask how sick students and staff are separated from others and who will care for them until they can go home.

Everyday preventive actions can help slow the spread of germs that can cause many different illnesses and may offer some protection against the flu.

For more information, visit www.cdc.gov , or www.flu.gov, or call 1-800-CDC-INFO.

Pandemic Influenza:
The Critical Issues and North Carolina's Preparedness Plan

Jeffrey P. Engel, MD

A Brief Primer

Influenza pandemics have been recorded throughout human history, on average occurring three times in a century, with ten in the last 300 years. Influenza pandemics are simultaneous worldwide epidemics and occur when a new influenza virus evolves that infects humans, is spread efficiently from person-to-person, and because of no prior immunity causes severe disease and death. Between pandemics, called the inter-pandemic period, the milder seasonal influenza (also known as the "flu") exists in the wintertime months in populations living outside of the tropical zones, whereas in the tropics, influenza is a year-around disease. Seasonal viruses are adapted pandemic strains that have weakened mainly due to developed immunity in the human population.

Influenza is characterized by the abrupt onset of fever, chills, muscle pain, and joint pain, followed within hours by respiratory symptoms including cough and congestion. It is a disease primarily of the upper respiratory tract, which in uncomplicated cases resolves in about a week. Complications include bronchitis, pneumonia (both primary viral and secondary bacterial), heart inflammation (myocarditis), and brain inflammation (encephalitis); death can result from any of these complications. In a typical season in the United States, 36,000 people die of influenza, deaths occurring chiefly among infants and the elderly.

The type A influenza virus is unique among viruses because it allows for genetic recombination to occur by the exchange of any or all of its eight gene segments of two different influenza virus strains. Additionally, the influenza virus can mutate and gradually adapt to new environments. Such recombination and adaptation in type A influenza viruses are the cause of pandemics.

Type A virus subtypes are named by the viral surface proteins, hemagglutinin (HA) and neuraminidase (NA), which elicit an immune response, and thus, comprise major components of the influenza vaccine. In nature, 16 HA and 9 NA proteins exist; however, the human pandemic and seasonal viruses have contained only the subtypes, H1, 2, or 3 and N1, 2, or 3.

The Animal-Human Interface: Zoonotic Influenza

Only type A influenza virus is capable of infecting a broad host range, primarily water fowl and shore birds. Wild water fowl usually harbor type A influenza in their digestive tract and have no symptoms. Spread to other susceptible hosts, usually related species like domestic poultry, happens directly with species intermingling or indirectly via contact with contaminated surface water because type A influenza virus can survive in fresh water for days to weeks.

Type A influenza virus is a type of infectious disease that is transmittable under natural conditions from vertebrate animals to

"The impact of a pandemic or any disaster is proportional to how prepared individuals and society are. Preparedness is a shared responsibility that requires local, state, and federal public health systems to form a robust response network."

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humans, also called "zoonosis." Zoonoses are usually sporadic; however, they are also the origins of epidemics and pandemics. If a human is exposed to an infectious agent from another animal, an infection results if the person is susceptible. Disease may range from asymptomatic to severe, resulting in immunity and recovery or death. An epidemic or pandemic erupts when the disease microorganism adapts via genetic mutation to the new human host and becomes capable of human-to-human transmission. Notorious examples of recent zoonotic-origin pandemics include the human immunodeficiency virus (HIV), the cause of AIDS (from chimpanzees in West Africa),[1] and the severe acute respiratory syndrome (SARS)-coronovirus (from bats in Southeast Asia).[2]

Type A influenza viruses are often the source of sporadic zoonotic infections, most often from avian, or bird, viruses. Humans are exposed to avian influenza viruses in developing countries across Eurasia and Africa due to animal husbandry practices that involve close contact with diseased or dead domestic fowl, especially ducks and chickens. In developed countries, zoonotic influenza infections have occurred in commercial poultry workers managing infected flocks.

Not all zoonotic influenza cases are of avian origin. In 1976, several soldiers at Fort Dix, New Jersey developed infections, some fatal, from a type A swine influenza virus. It is unknown how these individuals were exposed to a swine virus; however, this cluster led some scientists and policy makers to the false conclusion that this was the harbinger of the next pandemic. It was from this event that the infamous "Swine Flu" vaccination program emanated.

Contemporary methods in the study of human viruses provide information about influenza viruses dating back to 1889. The four pandemics between 1889 and 1968 were of avian origin, and they differed only in the number of avian influenza genes present in the pandemic strain (Table 1).

Table 1.
Hypothesized Evolution of Pandemic Influenza A Viruses[3]

Pandemic	Subtype	Avian Genes
1889	H2N2	?
1918 "Spanish"	H1N1	8
1957 "Asian"	H2N2	3 (PB1,* HA, NA)
1968 "Hong Kong"	H3N2	2 (PB1, HA)

* PB1 is a viral gene encoding a replication enzyme

H5N1: The Next Pandemic?

In the last 50 years, the science of influenza has made many great strides. In addition to the molecular study of the virus, worldwide human and animal surveillance and the study of population health have greatly expanded. The World Health Organization (WHO) has devoted huge resources to influenza monitoring and study. WHO coordinates the global influenza laboratory surveillance network that characterizes circulating human seasonal virus strains. This information is used to determine the annual human vaccine.

Through this global network, human disease due to avian influenza strain H5N1 was first reported in Hong Kong in 1997. Because this was an avian strain capable of causing severe infections in humans (six of 18 cases reported were fatal), WHO increased the pandemic alert level to Phase 3 (Table 2). Virtually all Hong Kong chickens were slaughtered in an attempt to eradicate the virus. This appeared to have been successful because no further clusters of H5N1 in people or domestic poultry were reported for several years. However, beginning in December of 2003, outbreaks in poultry and humans were reported in Vietnam and Thailand, and through 2006 human reports have increased across Eurasia and Africa with an alarming 60% case-fatality rate (Figure 1).

Table 2.
WHO Pandemic Phases

Period	Phase	Event
Interpandemic	1	No new subtype in humans
	2	No new subtype in humans, animal subtype poses risk
Pandemic alert	3	Human infections with new subtype, no human-to-human spread
	4	Small clusters of limited human-to-human spread
	5	Larger human clusters, but spread still localized
Pandemic	6	Increased and sustained transmission in the general population

H5N1 is currently widespread in wild and domestic birds in Eurasia and Africa with sporadic and often fatal cases in humans. It has notched up the WHO pandemic alert system to Phase 3 since 1997 and satisfies all but one important property of a pandemic-causing influenza virus (Figure 2). Will H5N1 mutate and become capable of efficient human-to-human transmission?

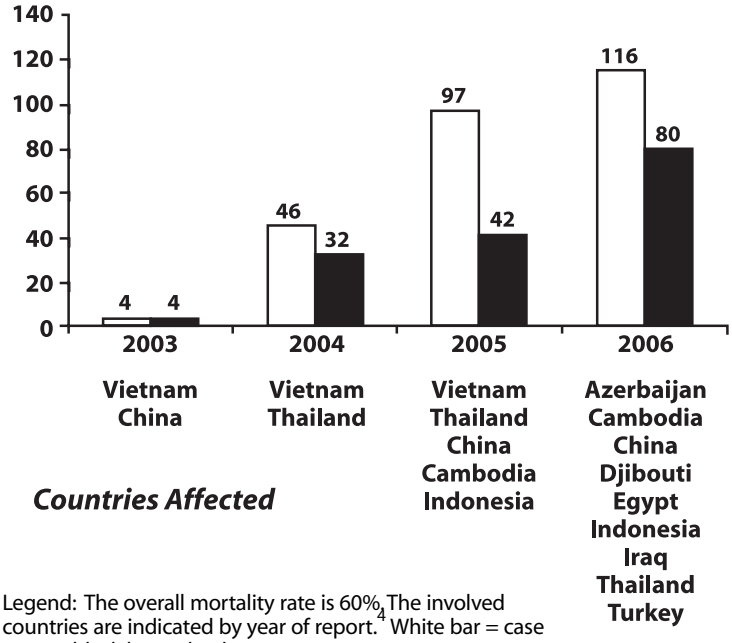
The Present Threat: When, Not If

If we know that pandemics are of avian origin and that they occur cyclically, on average three times in a century, then the question is when will the next avian influenza virus emerge that will cause the next pandemic? Certainly, H5N1 is the leading candidate. In regards to preparation, several subquestions can be generated that assist planning for the next pandemic:

- When will the virus arrive and spread?
- How much time from its source to arrival in the United States or North Carolina?
- What will the principal age and other risk groups be?
- How many will be affected?
- What will be the morbidity?
- What will be the mortality?

In terms of transmission dynamics or spread, nothing is more concerning to an epidemiologist than a community respiratory

Figure 1.
Epidemiological Curve of Reported H5N1 Human Cases by Reporting Country, 2003-2006."



Legend: The overall mortality rate is 60%.[4] The involved countries are indicated by year of report. White bar = case counts, black bar = deaths.

virus. Transmitted through respiratory droplets from a cough or a sneeze, or direct contact from a person's hands, these viruses can literally spread like wildfire through a susceptible population. The basic reproductive number, R_0, pronounced "R-zero" or "R-naught," is the expected number of people a contagious person could infect during the infectious period.[6] An R_0 greater than 1 ($R_0 > 1$) results in a self-sustaining outbreak until there are no more exposed susceptible people. In prevaccination days, a community respiratory virus like mumps with a short incubation period and an $R_0 = 6$ would literally burn through a school-age population.

Influenza virus with an incubation period of 1-5 days and $R_0 = 3$ moves quickly through a community as well. With seasonal influenza, however, R_0 is proportionately reduced by population immunity. For example, if half of the population is immune (from natural infection or vaccination) in a given season, $R_0 = 1.5$.[6] In a pandemic, however, potentially everyone is susceptible and, at least in the beginning, there will be no vaccine, thus the wildfire analogy.

Worse Case Scenario: A Syndemic

It behooves planners to assume the worst, and for pandemic influenza, that would be a 1918 "Spanish flu"-like pandemic. Worldwide, the second epidemic wave (there were three waves) of the Spanish flu, caused by an H1N1 subtype, swept across the globe with amazing speed and destruction. In its wake, 50 million people died; in the United States the death toll was 500,000 during the later summer and fall of 1918. Equally disturbing were the high attack and mortality rates that occurred in previously well people in the second and third decade of life, quite unusual for influenza that usually kills the very young and very old.

Historical accounts of young adult victims of the Spanish flu revealed a rapid death due to respiratory failure. People were well one day and dead the next, with facial cyanosis (blue discoloration from lack of oxygen) and a rapid breathing pattern occurring in the hours before death (a condition we now call the acute respiratory distress syndrome or ARDS). Examination of diseased lung tissue showed air sac damage from viral pneumonia. The body's response to the pneumonia caused leaks in the air sacs, drowning the victims (non-cardiogenic pulmonary edema).

In preparing for the next pandemic, it would be helpful to understand why the Spanish flu was so catastrophic. Certainly one reason was the virus itself. The second wave virus has been reconstructed from 1918 victims' lung tissue (both from exhumed remains frozen in the Alaskan tundra and lung tissue preserved from an autopsy sample).[7] The reconstructed 1918 virus was found to be highly lethal in the mouse model following intranasal infection. Genetic sequencing revealed it to be a zoonotic type A influenza virus strain whose entire genetic makeup was from a mutated bird strain. This truly novel virus adapted to the new human host acquiring the capability, through evolution, to spread efficiently from person-to-person.

However, in understanding the calamity of 1918, a separate analysis of the social milieu is required, specifically exploring the agents of human activity existing at the time. Historian and author John M. Barry carefully chronicles the global situation in 1918, particularly as the United States prepared for World War I.[8] Barry's meticulous research of influenza death records and outbreaks associated with massive troop deployments, staging, and overcrowding is compelling. Epidemics in Boston and Philadelphia were traced to ill troops arriving from overseas and

Figure 2.
Checklist of Pandemic Properties of Avian Influenza Type A/H5N1[5]

- ☑ Widespread prevalence in migratory birds; broad host range
- ☑ Continued outbreaks among domestic poultry
- ☑ Mammalian infection (cats, pigs, etc.) lethal
- ☑ Virus is evolving
- ☑ Sporadic human cases
  - – Most in young and healthy
  - – Case-fatality 60%
  - – Rare person-to-person transmission
- ☐ Sustained and rapid person-to-person transmission

an overcrowded patriotic street parade, respectively. Many more examples are cited and all are consistent with massive human crowding and/or movement in the presence of a virulent respiratory virus. In epidemiologic terms, in some settings (barracks, troop ships, etc.), a virus reproductive number (R_0) of 5 or higher was common. Thus, the sociologic and biologic conditions in 1918 formed the perfect storm, a syndemic.

A syndemic is defined as "two or more afflictions, interacting synergistically, contributing to excess burden of disease in a population."[9] The term was first used by anthropologist Merrill Singer describing the HIV epidemic among the urban poor in the United States: the SAVA syndemic, for substance abuse, violence and AIDS.[10] He described a new virulent infectious virus, HIV also of zoonotic origins,[1] which spread efficiently by needle sharing intravenous drug abuse and unprotected sexual behavior that wrecked havoc among the poor, particularly in urban minority communities in the United States.

For 21st century pandemic influenza planning, then, I argue that to prevent a 1918-like scenario, we must do syndemic planning. Taking examples from recent natural disasters, such as the 1995 Chicago heat wave that killed 700 elderly people in a week,[11] the 2005 tsunami in Indonesia, Hurricane Katrina in New Orleans, or the SAVA syndemic, the common lesson learned is that the natural disaster impact, whether in a developing nation or the United States, is greatly multiplied by crowding and poverty. In 1918, the global population was 1.8 billion; today it is 6.5 billion, 2.7 billion (42%) living in moderate to extreme poverty as measured by income less than $2/day.[12]

The syndemic model predicts that the next influenza pandemic will be catastrophic in countries such as India and China where 36% of the world population lives, many in poverty and in crowded urban areas. Although these sociologic conditions exist in some areas in the United States and North Carolina, more worrisome in developed countries are the equally vulnerable including those without health insurance or who are underinsured; those who lack the capacity to access information due to illiteracy, low English-speaking skills, and other forms of social isolation; and finally, select special populations such as the homeless, institutionalized, and the underserved mentally ill.

If a 1918-like influenza virus causes the next pandemic, how our nation and state mitigate the impact will depend on pandemic and syndemic prevention. To accomplish this, at the national, state, and local level, public health is leading the planning efforts for the health care sector, government, and society.

Summary of North Carolina's Pandemic Influenza Preparedness Efforts

The fundamental objective of pandemic influenza planning is to save lives. To be successful, all corners of society must plan, including individuals and families, business and industry, schools and universities, and state and local government. These overarching plans, referred to as pandemic implementation strategies, are underway or complete in many sectors, but beyond the scope of this review. Here, I will highlight the critical components of *North Carolina's Public Health Pandemic Influenza Plan*.[13]

Quenching

In public health, prevention is the key, thus a critical strategy is the early detection of initial outbreaks and rapid containment of the disease where it emerges, a process known as quenching.[14] Through global and national collaboration with the WHO and the Centers for Disease Control and Prevention (CDC), once an influenza pandemic is declared somewhere in the world, the North Carolina Division of Public Health (DPH) will enhance frontline detection and response and rapid laboratory diagnosis. The early cases in North Carolina will likely be among travelers to regions where person-to-person transmission is ongoing.

In WHO pandemic phases 4, 5, and early 6, international travel advisories will be issued by federal authorities. DPH will notify health care providers of the situation and explain how to suspect and manage patients who may be manifesting pandemic influenza symptoms. Suspect patients shall be reported immediately to local or state public health agencies (North Carolina General Statute 130A-135), isolated (NCGS 130A-145),[15] and treated with antiviral medication pending laboratory confirmation. The North Carolina State Laboratory for Public Health will activate three regional labs in Charlotte, Asheville, and Greenville, as well as the core facility in Raleigh, to rapidly (within hours) process clinical specimens (nasopharyngeal swabs) for detection of the pandemic strain. These labs will not attempt to cultivate pandemic viruses because of the biosafety hazard; cultural confirmation will be done solely by the CDC in Atlanta, Georgia.

The goal of quenching is for public health and other response agencies to aggressively keep the $R_0 < 1$. Once a suspected patient has been reported to public health agencies, active surveillance will begin to identify close contacts (eg, airplane passengers, household and workplace contacts). If an index case is presumptively confirmed by the labs, symptomatic contacts will be isolated and referred for medical evaluation and asymptomatic contacts will be quarantined for 10 days (or the maximum incubation period) from the time of last contact to a case. Based on what is known about the contagiousness and virulence of the pandemic virus, quarantined people may be offered antiviral prophylaxis at no cost from a federal or state stockpile. Antiviral prophylaxis of exposed contacts in quarantine may be the single most effective strategy in preventing a full-blown pandemic, an $R_0 > 1$.

Isolation and quarantine are restrictions of movement and/or action of the sick (isolation) and the well but exposed (quarantine). An effective quenching plan requires rapid active surveillance and diagnosis, treatment or post-exposure prophylaxis with antivirals, and enforcement of isolation and quarantine. During the 2003 SARS response in North Carolina confirmation of a single case led to the isolation of three persons and the quarantine of 30 others. All affected people complied with local public health authorities, law enforcement was not necessary, and the spread was contained.

WHO Phase 6: Widespread Pandemic in North Carolina

Planning assumptions identify a point in time when quenching fails or is no longer feasible. This may happen if there are multiple simultaneous outbreaks across the state, a local jurisdiction's capacity to quench is overwhelmed and there are no state or federal assets available to assist, or supplies of antiviral medications are depleted leaving enough only to treat the sickest. To decrease illness and death, the strategy at such a point will be to slow the spread and buy time until an influenza pandemic vaccine is available. To accomplish this, countermeasures known as nonpharmaceutical and pharmaceutical interventions will be used.

Nonpharmaceutical Interventions

The nonpharmaceutical intervention for preventing or slowing a pandemic is the physical separation of people. This is accomplished in fundamentally two ways: personal protective equipment for those who must be close to the sick (health care workers, first responders) and social distancing and hygiene. The worst-case scenario is that 50% or more of those who become ill will seek medical care. The number of hospitalizations and deaths will depend on the virulence of the pandemic virus and Table 3 projects these numbers based upon the experiences of the moderate and severe pandemics of 1957 and 1918. Depending on severity, health care medical surge plans must scale accordingly, the largest challenge being the maintenance of adequate staffing. To provide for the safety of those on the frontline, occupational health protection through infection control is a critical planning component. In hospitals, respiratory droplet and airborne precautions that are part of everyday activity will be essential during a pandemic. For routine patient care, properly donned and doffed eye protection and a plain surgical mask are adequate along with hand washing with soap and water before and after patient contact. For higher risk contact where infectious aerosols are more likely to be generated (eg, airway suctioning, resuscitation, bronchoscopy), a fit-tested N-95 respirator is required. In the community, there is no evidence that personal protective equipment, such as the donning of masks by well people, will prevent transmission of influenza. Hence, stockpiling masks or respirators outside of the health care setting is not recommended and is not part of the *NC Pandemic Influenza Plan*.

Table 3.
Impact of an Influenza Pandemic in North Carolina*

Characteristic	Moderate (1957-like)	Severe (1918-like)
Illness	3,000,000	3,000,000
Outpatients	1,600,000	1,600,000
Hospitalized	35,000	300,000
Deaths	8,000	65,000

* Numbers based on NC population = 9,000,000; 35% attack rate (CDC FluAid 2.0)

The broader community containment strategy will rely on social distancing interventions. In WHO Phase 6 for a moderate to severe pandemic, at some threshold a state of emergency will be declared where so-called mass quarantine will be utilized. Mass gatherings including entertainment venues like sporting events and theaters will be canceled or closed, religious services will be discouraged or prohibited, nonessential workers will be told to remain at home, and schools and universities will be closed. In 1918, the city of St. Louis implemented these measures and succeeded in reducing influenza-related mortality. Indeed, government may not need to impose these measures because individuals are likely to self-quarantine if the pandemic is bad enough.

The societal disruptions will be immense, but can be lessened by cross-sector preparation. Continuity of operations planning is the core of the national implementation strategy and is essential for critical industries such as utilities, businesses, educational institutions, and government.

Pharmaceutical Interventions

Pharmaceutical interventions refer to the specific countermeasures for prevention and treatment of influenza A infections: antiviral medications and vaccines. The planning assumption for antivirals is that they will be effective in the treatment and prevention of pandemic influenza. Although clinical trials will be difficult to conduct against the current H5N1 threat, there is accumulating evidence that these drugs will have broad-spectrum activity against pandemic influenza.[16] The current federal government guideline calls for the stockpiling of enough antiviral medications to treat 25% of the population, roughly two million five-day courses for North Carolina. The stockpiling challenges lie in accumulating an adequate supply to meet the need, establishing rationing criteria until the supply is adequate, and extending the shelf-life beyond five years.

Assuming the antiviral medications are found to be life-saving and the supply is inadequate at the time of the pandemic, then difficult rationing decisions will have to be made. To ensure fairness and equity and to assist frontline providers, the *NC Pandemic Influenza Plan* aligns with the federal tier groups to receive antiviral treatment in the event of suspected influenza illness only.[17] The top five tier priority groups to receive treatment are hospitalized patients, health care workers and emergency medical technicians, high-risk outpatients including the immunocompromised and pregnant women, public health responders (eg, vaccinators, vaccine and antiviral manufacturers, government decision makers) including public safety (police, fire, and corrections), and increased risk outpatients (children 12-23 months, adults aged 65 years and above, and people with chronic medical conditions). To reiterate, this rationing scheme is for treatment only, it is assumed during a widespread WHO phase 6 event, there will not be enough medication for prevention.

The second pharmaceutical intervention is a pandemic vaccine, which can abort the pandemic once available for the

entire population. The planning assumption, however, is that it will probably take a year or more to scale up production to immunize everyone. Further, because the population will be naïve to the pandemic virus, a booster shot will be required one month after the priming dose. Thus, once again, rationing of the first supplies of the pandemic vaccine is a planning component aligning with federal tier groups.[17] In Tier 1, there are four subtiers who will get the vaccine first:

1) Vaccine and antiviral manufacturers, essential medical and public health workers;
2) High-risk persons (> 65 years old, medical co-morbidities)
3) Pregnant women, household contacts of severely immuno-compromised, household contacts of children < 6 months old;
4) Public health emergency response workers, key government leaders.

Syndemic Prevention: Preparedness and Communication

Ultimately, how North Carolina responds to a severe influenza pandemic will depend upon countermeasures applied equitably to all who reside in the state. Since human beings are the vector and reservoir of the disease, neglecting or limiting resources to any sector of society (outside of established rationing protocols) does not make any epidemiologic sense. In addition, it is unrealistic to believe that society can mitigate the syndemic conditions of crowding, poverty, and the needs of special populations in advance of a rapidly moving pandemic wave. How do we approach this daunting challenge?

The impact of a pandemic or any disaster is proportional to how prepared individuals and society are. Preparedness is a shared responsibility that requires local, state, and federal public health systems to form a robust response network. Implementation strategies must build international and domestic, animal and human health, and public and private sector partnerships. Health, security, and economic protection are at stake, and all these risks should be managed cooperatively.

Syndemic prevention will rely on our ability to reach those outside of traditional networks, and to accomplish this, clear communication channels must be established to the public using trusted messengers. Health disparities during a disaster are preventable if people are prepared with accurate and timely information. How well public health is able to coordinate consistent messages, encourage people to take action steps to prepare now, and provide updates when new information becomes available will determine how we weather the perfect storm. **NCMJ**

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School Guide

How to Clean and Disinfect Schools to Help Slow the Spread of Flu

Cleaning and disinfecting are part of a broad approach to preventing infectious diseases in schools. To help slow the spread of influenza (flu), the first line of defense is getting vaccinated. Other measures include covering coughs and sneezes, washing hands, and keeping sick people away from others. Below are tips on how to slow the spread of flu specifically through cleaning and disinfecting.

1. Know the difference between cleaning, disinfecting, and sanitizing.

Cleaning removes germs, dirt, and impurities from surfaces or objects. Cleaning works by using soap (or detergent) and water to physically remove germs from surfaces. This process does not necessarily kill germs, but by removing them, it lowers their numbers and the risk of spreading infection.

Disinfecting kills germs on surfaces or objects. Disinfecting works by using chemicals to kill germs on surfaces or objects. This process does not necessarily clean dirty surfaces or remove germs, but by killing germs on a surface after cleaning, it can further lower the risk of spreading infection.

Sanitizing lowers the number of germs on surfaces or objects to a safe level, as judged by public health standards or requirements. This process **works by either cleaning or disinfecting** surfaces or objects to lower the risk of spreading infection.

2. Clean and disinfect surfaces and objects that are touched often.

Follow your school's standard procedures for routine cleaning and disinfecting. Typically, this means daily sanitizing surfaces and objects that are touched often, such as desks, countertops, doorknobs, computer keyboards, hands-on learning items, faucet handles, phones, and toys. Some schools may also require daily disinfecting these items. Standard procedures often call for disinfecting specific areas of the school, like bathrooms.

Immediately clean surfaces and objects that are visibly soiled. If surfaces or objects are soiled with body fluids or blood, use gloves and other standard precautions to avoid coming into contact with the fluid. Remove the spill, and then clean and disinfect the surface.

3. Simply do routine cleaning and disinfecting.

It's important to match your cleaning and disinfecting activities to the types of germs you want to remove or kill. Most studies have shown that the flu virus can live and potentially infect a person for only 2 to 8 hours after being deposited on a surface. Therefore, it is not necessary to close schools to clean or disinfect every surface in the building to slow the spread of flu. Also, if students and staff are dismissed because the school cannot function normally (e.g., high absenteeism during a flu outbreak), it is not necessary to do extra cleaning and disinfecting.

Flu viruses are relatively fragile, so standard cleaning and disinfecting practices are sufficient to remove or kill them. Special cleaning and disinfecting processes, including wiping down walls and ceilings, frequently using room air deodorizers, and fumigating, are not necessary or recommended. These processes can irritate eyes, noses, throats, and skin; aggravate asthma; and cause other serious side effects.

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Centers for Disease Control and Prevention

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4. Clean and disinfect correctly.

Always follow label directions on cleaning products and disinfectants. Wash surfaces with a general household cleaner to remove germs. Rinse with water, and follow with an EPA-registered disinfectant to kill germs. Read the label to make sure it states that EPA has approved the product for effectiveness against influenza A virus.

If an EPA-registered disinfectant is not available, use a fresh chlorine bleach solution. To make and use the solution:

- Add 1 tablespoon of bleach to 1 quart (4 cups) of water. For a larger supply of disinfectant, add ¼ cup of bleach to 1 gallon (16 cups) of water.
- Apply the solution to the surface with a cloth.
- Let it stand for 3 to 5 minutes.
- Rinse the surface with clean water.

If a surface is not visibly dirty, you can clean it with an EPA-registered product that both cleans (removes germs) and disinfects (kills germs) instead. Be sure to read the label directions carefully, as there may be a separate procedure for using the product as a cleaner or as a disinfectant. Disinfection usually requires the product to remain on the surface for a certain period of time.

Use disinfecting wipes on electronic items that are touched often, such as phones and computers. Pay close attention to the directions for using disinfecting wipes. It may be necessary to use more than one wipe to keep the surface wet for the stated length of contact time. Make sure that the electronics can withstand the use of liquids for cleaning and disinfecting.

Routinely wash eating utensils in a dishwasher or by hand with soap and water. Wash and dry bed sheets, towels, and other linens as you normally do with household laundry soap, according to the fabric labels. Eating utensils, dishes, and linens used by sick persons do not need to be cleaned separately, but they should not be shared unless they've been washed thoroughly. Wash your hands with soap and water after handling soiled dishes and laundry items.

5. Use products safely.

Pay close attention to hazard warnings and directions on product labels. Cleaning products and disinfectants often call for the use of gloves or eye protection. For example, gloves should always be worn to protect your hands when working with bleach solutions.

Do not mix cleaners and disinfectants unless the labels indicate it is safe to do so. Combining certain products (such as chlorine bleach and ammonia cleaners) can result in serious injury or death.

Ensure that custodial staff, teachers, and others who use cleaners and disinfectants read and understand all instruction labels and understand safe and appropriate use. This might require that instructional materials and training be provided in other languages.

6. Handle waste properly.

Follow your school's standard procedures for handling waste, which may include wearing gloves. Place no-touch waste baskets where they are easy to use. Throw disposable items used to clean surfaces and items in the trash immediately after use. Avoid touching used tissues and other waste when emptying waste baskets. Wash your hands with soap and water after emptying waste baskets and touching used tissues and similar waste.

www.cdc.gov/flu/school

1-800-CDC-INFO

Guidance on
Preparing Workplaces for an Influenza Pandemic

OSHA 3327-05R 2009

www.osha.gov

Occupational Safety and Health Act of 1970

"To assure safe and healthful working conditions for working men and women; by authorizing enforcement of the standards developed under the Act; by assisting and encouraging the States in their efforts to assure safe and healthful working conditions; by providing for research, information, education, and training in the field of occupational safety and health."

This publication provides a general overview of a particular standards-related topic. This publication does not alter or determine compliance responsibilities which are set forth in OSHA standards, and the *Occupational Safety and Health Act*. Moreover, because interpretations and enforcement policy may change over time, for additional guidance on OSHA compliance requirements, the reader should consult current administrative interpretations and decisions by the Occupational Safety and Health Review Commission and the courts.

This information will be made available to sensory impaired individuals upon request. Voice phone: (202) 693-1999; teletypewriter (TTY) number: 1-877-889-5627.

Guidance on
Preparing Workplaces for an Influenza Pandemic

U.S. Department of Labor

Occupational Safety and Health Administration

OSHA 3327-05R
2009

Contents

Introduction

A pandemic is a global disease outbreak. An influenza pandemic occurs when a new influenza virus emerges for which there is little or no immunity in the human population, begins to cause serious illness and then spreads easily person-to-person worldwide. A worldwide influenza pandemic could have a major effect on the global economy, including travel, trade, tourism, food, consumption and eventually, investment and financial markets. Planning for pandemic influenza by business and industry is essential to minimize a pandemic's impact. Companies that provide critical infrastructure services, such as power and telecommunications, also have a special responsibility to plan for continued operation in a crisis and should plan accordingly. As with any catastrophe, having a contingency plan is essential.

This guidance is advisory in nature and informational in content. It is not a standard or a regulation, and it neither creates new legal obligations nor alters existing obligations created by OSHA standards or the *Occupational Safety and Health Act* (OSH Act). Pursuant to the OSH Act, employers must comply with hazard-specific safety and health standards as issued and enforced either by OSHA or by an OSHA-approved State Plan. In addition, Section 5(a)(1) of the OSH Act, the General Duty Clause, requires employers to provide their employees with a workplace free from recognized hazards likely to cause death or serious physical harm. Employers can be cited for violating the General Duty Clause if there is a recognized hazard and they do not take reasonable steps to prevent or abate the hazard. However, failure to implement any recommendations in this guidance is not, in itself, a violation of the General Duty Clause. Citations can only be based on standards, regulations, or the General Duty Clause.

In the event of an influenza pandemic, employers will play a key role in protecting employees' health and safety as well as in limiting the impact on the economy and society. Employers will likely experience employee absences, changes in patterns of commerce and interrupted supply and delivery schedules. Proper planning will allow employers in the public and private sectors to better protect their employees and lessen the impact of a pandemic on society and the economy. As stated in the President's *National Strategy for Pandemic Influenza*, all stakeholders must plan and be prepared.

The Occupational Safety and Health Administration (OSHA) developed this pandemic influenza planning guidance based upon traditional infection control and industrial hygiene practices. It is important to note that there is currently no pandemic; thus, this guidance is intended for planning purposes and is not specific to a particular viral strain. Additional guidance may be needed as an actual pandemic unfolds and more is known about the characteristics of the virulence of the virus, disease transmissibility, clinical manifestation, drug susceptibility, and risks to different age groups and subpopulations. Employers and employees should use this planning guidance to help identify risk levels in workplace settings and appropriate control measures that include good hygiene, cough etiquette, social distancing, the use of personal protective equipment, and staying home from work when ill. Up-to-date information and guidance is available to the public through the www.pandemicflu.gov website.

The Difference Between Seasonal, Pandemic Influenza and Avian Influenza

Seasonal influenza refers to the periodic outbreaks of respiratory illness in the fall and winter in the United States. Outbreaks are typically limited; most people have some immunity to the circulating strain of the virus. A vaccine is prepared in advance of the seasonal influenza; it is designed to match the influenza viruses most likely to be circulating in the community. Employees living abroad and international business travelers should note that other geographic areas (for example, the Southern Hemisphere) have different influenza seasons which may require different vaccines.

Pandemic influenza refers to a worldwide outbreak of influenza among people when a new strain of the virus emerges that has the ability to infect humans and to spread from person to person. During the early phases of an influenza pandemic, people might not have any natural immunity to the new strain; so the disease would spread rapidly among the population. A vaccine to protect people against illness from a pandemic influenza virus may not be widely available until many months after an influenza pandemic begins. It is important to emphasize that there currently is no influenza pandemic. However, pandemics have occurred throughout history and many scientists believe that it is only a matter of time before another one occurs. Pandemics can vary in severity from something that seems simply like a bad flu season to an especially severe influenza pandemic that could lead to high levels of illness, death, social disruption and economic loss. It is impossible to predict when the next pandemic will occur or whether it will be mild or severe.

Avian influenza (AI) – also known as the bird flu – is caused by virus that infects wild birds and domestic poultry. Some forms of the avian influenza are worse than others. Avian influenza viruses are generally divided into two groups: low pathogenic

avian influenza and highly pathogenic avian influenza. Low pathogenic avian influenza naturally occurs in wild birds and can spread to domestic birds. In most cases, it causes no signs of infection or only minor symptoms in birds. In general, these low path strains of the virus pose little threat to human health. Low pathogenic avian influenza virus H5 and H7 strains have the potential to mutate into highly pathogenic avian influenza and are, therefore, closely monitored. Highly pathogenic avian influenza spreads rapidly and has a high death rate in birds. Highly pathogenic avian influenza of the H5N1 strain is rapidly spreading in birds in some parts of the world.

Highly pathogenic H5N1 is one of the few avian influenza viruses to have crossed the species barrier to infect humans and it is the most deadly of those that have crossed the barrier. Most cases of H5N1 influenza infection in humans have resulted from contact with infected poultry or surfaces contaminated with secretions/excretions from infected birds.

As of February 2007, the spread of H5N1 virus from person to person has been limited to rare, sporadic cases. Nonetheless, because all influenza viruses have the ability to change, scientists are concerned that H5N1 virus one day could be able to sustain human to human transmission. Because these viruses do not commonly infect humans, there is little or no immune protection against them in the human population. If H5N1 virus were to gain the capacity to sustain transmission from person to person, a pandemic could begin.

An update on what is currently known about avian flu can be found at www.pandemicflu.gov.

How a Severe Pandemic Influenza Could Affect Workplaces

Unlike natural disasters or terrorist events, an influenza pandemic will be widespread, affecting multiple areas of the United States and other countries at the same time. A pandemic will also be an extended event, with multiple waves of outbreaks in the same geographic area; each outbreak could last from 6 to 8 weeks. Waves of outbreaks may occur over a year or more. Your workplace will likely experience:

- **Absenteeism** - A pandemic could affect as many as 40 percent of the workforce during periods of peak influenza illness. Employees could be absent because they are sick, must care for sick family members or for children if schools or day care centers are closed, are afraid to come to work, or the employer might not be notified that the employee has died.
- **Change in patterns of commerce** - During a pandemic, consumer demand for items related to infection control is likely to increase dramatically, while consumer interest in other goods may decline. Consumers may also change the ways in which they shop as a result of the pandemic. Consumers may try to shop at off-peak hours to reduce contact with other people, show increased interest in home delivery services, or prefer other options, such as drive-through service, to reduce person-to-person contact.
- **Interrupted supply/delivery** - Shipments of items from those geographic areas severely affected by the pandemic may be delayed or cancelled.

Who Should Plan for a Pandemic

To reduce the impact of a pandemic on your operations, employees, customers and the general public, it is important for all businesses and organizations to begin continuity planning for a pandemic now. Lack of continuity planning can result in a cascade of failures as employers attempt to address challenges of a pandemic with insufficient resources and employees who might not be adequately trained in the jobs they will be asked to perform. Proper planning will allow employers to better protect their employees and prepare for changing patterns of commerce and potential disruptions in supplies or services. Important tools for pandemic planning for employers are located at www.pandemicflu.gov.

The U.S. government has placed a special emphasis on supporting pandemic influenza planning for public and private sector businesses deemed to be critical industries and key resources (CI/KR). Critical infrastructure are the thirteen sectors that provide the production of essential goods and services, interconnectedness and operability, public safety, and security that contribute to a strong national defense and thriving economy. Key resources are facilities, sites, and groups of organized people whose destruction could cause large-scale injury, death, or destruction of property and/or profoundly damage our national prestige and confidence. With 85 percent of the nation's critical infrastructure in the hands of the private sector, the business community plays a vital role in ensuring national pandemic preparedness and response. Additional guidance for CI/KR business is available at: www.pandemicflu.gov/plan/pdf/CIKRpandemicInfluenzaGuide.pdf.

Critical Infrastructure and Key Resources

Key Resources

- Government Facilities
- Dams
- Commercial Facilities
- Nuclear Power Plants

Critical Infrastructure

- Food and Agriculture
- Public Health and Healthcare
- Banking and Finance
- Chemical and Hazardous Materials
- Defense Industrial Base
- Water
- Energy
- Emergency Services
- Information Technology
- Telecommunications
- Postal and Shipping
- Transportation
- National Monuments and Icons

How Influenza Can Spread Between People

Influenza is thought to be primarily spread through large droplets (droplet transmission) that directly contact the nose, mouth or eyes. These droplets are produced when infected people cough, sneeze or talk, sending the relatively large infectious droplets and very small sprays (aerosols) into the nearby air and into contact with other people. Large droplets can only travel a limited range; therefore, people should limit close contact (within 6 feet) with others when possible. To a lesser degree, human influenza is spread by touching objects contaminated with influenza viruses and then transferring the infected material from the hands to the nose, mouth or eyes. Influenza may also be spread by very small infectious particles (aerosols) traveling in the air. The contribution of each route of exposure to influenza transmission is uncertain at this time and may vary based upon the characteristics of the influenza strain.

Fotosearch/Blend Images

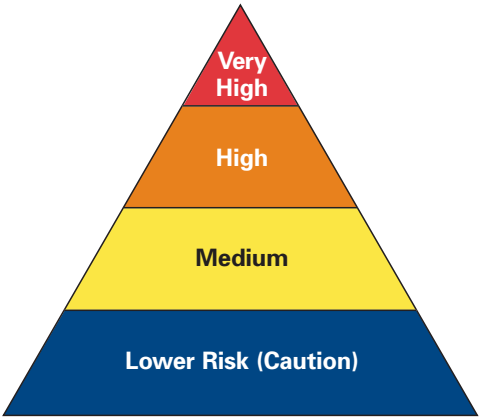
Classifying Employee Exposure to Pandemic Influenza at Work

Employee risks of occupational exposure to influenza during a pandemic may vary from very high to high, medium, or lower (caution) risk. The level of risk depends in part on whether or not jobs require close proximity to people potentially infected with the pandemic influenza virus, or whether they are required to have either repeated or extended contact with known or suspected sources of pandemic influenza virus such as coworkers, the general public, outpatients, school children or other such individuals or groups.

- *Very high exposure risk* occupations are those with high potential exposure to high concentrations of known or suspected sources of pandemic influenza during specific medical or laboratory procedures.
- *High exposure risk* occupations are those with high potential for exposure to known or suspected sources of pandemic influenza virus.
- *Medium exposure risk* occupations include jobs that require frequent, close contact (within 6 feet) exposures to other people

(continued on page 12)

Occupational Risk Pyramid for Pandemic Influenza



Very High Exposure Risk:

- Healthcare employees (for example, doctors, nurses, dentists) performing aerosol-generating procedures on known or suspected pandemic patients (for example, cough induction procedures, bronchoscopies, some dental procedures, or invasive specimen collection).
- Healthcare or laboratory personnel collecting or handling specimens from known or suspected pandemic patients (for example, manipulating cultures from known or suspected pandemic influenza patients).

High Exposure Risk:

- Healthcare delivery and support staff exposed to known or suspected pandemic patients (for example, doctors, nurses, and other hospital staff that must enter patients' rooms).
- Medical transport of known or suspected pandemic patients in enclosed vehicles (for example, emergency medical technicians).
- Performing autopsies on known or suspected pandemic patients (for example, morgue and mortuary employees).

Medium Exposure Risk:

- Employees with high-frequency contact with the general population (such as schools, high population density work environments, and some high volume retail).

Lower Exposure Risk (Caution):

- Employees who have minimal occupational contact with the general public and other coworkers (for example, office employees).

such as coworkers, the general public, outpatients, school children, or other such individuals or groups.

- *Lower exposure risk (caution)* occupations are those that do not require contact with people known to be infected with the pandemic virus, nor frequent close contact (within 6 feet) with the public. Even at lower risk levels, however, employers should be cautious and develop preparedness plans to minimize employee infections.

Employers of critical infrastructure and key resource employees (such as law enforcement, emergency response, or public utility employees) may consider upgrading protective measures for these employees beyond what would be suggested by their exposure risk due to the necessity of such services for the functioning of society as well as the potential difficulties in replacing them during a pandemic (for example, due to extensive training or licensing requirements).

To help employers determine appropriate work practices and precautions, OSHA has divided workplaces and work operations into four risk zones, according to the likelihood of employees' occupational exposure to pandemic influenza. We show these zones in the shape of a pyramid to represent how the risk will likely be distributed (see page 11). The vast majority of American workplaces are likely to be in the medium exposure risk or lower exposure risk (caution) groups.

How to Maintain Operations During a Pandemic

As an employer, you have an important role in protecting employee health and safety, and limiting the impact of an influenza pandemic. It is important to work with community planners to integrate your pandemic plan into local and state planning, particularly if your operations are part of the nation's critical infrastructure or key resources. Integration with local community planners will allow

you to access resources and information promptly to maintain operations and keep your employees safe.

Develop a Disaster Plan

Develop a disaster plan that includes pandemic preparedness (See www.pandemicflu.gov/plan/businesschecklist.html) and review it and conduct drills regularly.

- Be aware of and review federal, state and local health department pandemic influenza plans. Incorporate appropriate actions from these plans into workplace disaster plans.
- Prepare and plan for operations with a reduced workforce.
- Work with your suppliers to ensure that you can continue to operate and provide services.
- Develop a sick leave policy that does not penalize sick employees, thereby encouraging employees who have influenza-related symptoms (e.g., fever, headache, cough, sore throat, runny or stuffy nose, muscle aches, or upset stomach) to stay home so that they do not infect other employees. Recognize that employees with ill family members may need to stay home to care for them.
- Identify possible exposure and health risks to your employees. Are employees potentially in contact with people with influenza such as in a hospital or clinic? Are your employees expected to have a lot of contact with the general public?
- Minimize exposure to fellow employees or the public. For example, will more of your employees work from home? This may require enhancement of technology and communications equipment.
- Identify business-essential positions and people required to sustain business-necessary functions and operations. Prepare to cross-train or develop ways to function in the absence of these positions. It is recommended that employers train three or more employees to be able to sustain business-necessary functions and operations, and communicate the expectation for available employees to perform these functions if needed during a pandemic.

- Plan for downsizing services but also anticipate any scenario which may require a surge in your services.
- Recognize that, in the course of normal daily life, all employees will have non-occupational risk factors at home and in community settings that should be reduced to the extent possible. Some employees will also have individual risk factors that should be considered by employers as they plan how the organization will respond to a potential pandemic (e.g., immuno-compromised individuals and pregnant women).
- Stockpile items such as soap, tissue, hand sanitizer, cleaning supplies and recommended personal protective equipment. When stockpiling items, be aware of each product's shelf life and storage conditions (e.g., avoid areas that are damp or have temperature extremes) and incorporate product rotation (e.g., consume oldest supplies first) into your stockpile management program.

Make sure that your disaster plan protects and supports your employees, customers and the general public. Be aware of your employees' concerns about pay, leave, safety and health. Informed employees who feel safe at work are less likely to be absent.

- Develop policies and practices that distance employees from each other, customers and the general public. Consider practices to minimize face-to-face contact between employees such as e-mail, websites and teleconferences. Policies and practices that allow employees to work from home or to stagger their work shifts may be important as absenteeism rises.
- Organize and identify a central team of people or focal point to serve as a communication source so that your employees and customers can have accurate information during the crisis.
- Work with your employees and their union(s) to address leave, pay, transportation, travel, childcare, absence and other human resource issues.
- Provide your employees and customers in your workplace with easy access to infection control supplies, such as soap, hand sanitizers, personal protective equipment (such as gloves or surgical masks), tissues, and office cleaning supplies.

- Provide training, education and informational material about business-essential job functions and employee health and safety, including proper hygiene practices and the use of any personal protective equipment to be used in the workplace. Be sure that informational material is available in a usable format for individuals with sensory disabilities and/or limited English proficiency. Encourage employees to take care of their health by eating right, getting plenty of rest and getting a seasonal flu vaccination.
- Work with your insurance companies, and state and local health agencies to provide information to employees and customers about medical care in the event of a pandemic.
- Assist employees in managing additional stressors related to the pandemic. These are likely to include distress related to personal or family illness, life disruption, grief related to loss of family, friends or coworkers, loss of routine support systems, and similar challenges. Assuring timely and accurate communication will also be important throughout the duration of the pandemic in decreasing fear or worry. Employers should provide opportunities for support, counseling, and mental health assessment and referral should these be necessary. If present, Employee Assistance Programs can offer training and provide resources and other guidance on mental health and resiliency before and during a pandemic.

Protect Employees and Customers

Educate and train employees in proper hand hygiene, cough etiquette and social distancing techniques. Understand and develop work practice and engineering controls that could provide additional protection to your employees and customers, such as: drive-through service windows, clear plastic sneeze barriers, ventilation, and the proper selection, use and disposal of personal protective equipment.

These are not comprehensive recommendations. The most important part of pandemic planning is to work with your employees, local and state agencies and other employers to develop cooperative pandemic plans to maintain your operations

and keep your employees and the public safe. Share what you know, be open to ideas from your employees, then identify and share effective health practices with other employers in your community and with your local chamber of commerce.

How Organizations Can Protect Their Employees

For most employers, protecting their employees will depend on emphasizing proper hygiene (disinfecting hands and surfaces) and practicing social distancing (see page 26 for more information). Social distancing means reducing the frequency, proximity, and duration of contact between people (both employees and customers) to reduce the chances of spreading pandemic influenza from person-to-person. All employers should implement good hygiene and infection control practices.

Occupational safety and health professionals use a framework called the "hierarchy of controls" to select ways of dealing with workplace hazards. The hierarchy of controls prioritizes intervention strategies based on the premise that the best way to control a hazard is to systematically remove it from the workplace, rather than relying on employees to reduce their exposure. In the setting of a pandemic, this hierarchy should be used in concert with current public health recommendations. The types of measures that may be used to protect yourself, your employees, and your customers (listed from most effective to least effective) are: engineering controls, administrative controls, work practices, and personal protective equipment (PPE). Most employers will use a combination of control methods. There are advantages and disadvantages to each type of control measure when considering the ease of implementation, effectiveness, and cost. For example, hygiene and social distancing can be implemented relatively easily and with little expense, but this control method requires employees to modify and maintain their behavior, which may be difficult to sustain. On the other hand, installing clear plastic barriers or a drive-through window will be more expensive and take a longer

time to implement, although in the long run may be more effective at preventing transmission during a pandemic. Employers must evaluate their particular workplace to develop a plan for protecting their employees that may combine both immediate actions as well as longer term solutions.

Here is a description of each type of control:

Work Practice and Engineering Controls - Historically, infection control professionals have relied on personal protective equipment (for example, surgical masks and gloves) to serve as a physical barrier in order to prevent the transmission of an infectious disease from one person to another. This reflects the fact that close interactions with infectious patients is an unavoidable part of many healthcare occupations. The principles of industrial hygiene demonstrate that work practice controls and engineering controls can also serve as barriers to transmission and are less reliant on employee behavior to provide protection. Work practice controls are procedures for safe and proper work that are used to reduce the duration, frequency or intensity of exposure to a hazard. When defining safe work practice controls, it is a good idea to ask your employees for their suggestions, since they have firsthand experience with the tasks. These controls should be understood and followed by managers, supervisors and employees. When work practice controls are insufficient to protect employees, some employers may also need engineering controls.

Engineering controls involve making changes to the work environment to reduce work-related hazards. These types of controls are preferred over all others because they make permanent changes that reduce exposure to hazards and do not rely on employee or customer behavior. By reducing a hazard in the workplace, engineering controls can be the most cost-effective solutions for employers to implement.

During a pandemic, engineering controls may be effective in reducing exposure to some sources of pandemic influenza and not others. For example, installing sneeze guards between customers and employees would provide a barrier to transmission. The use of barrier protections, such as sneeze guards, is common practice for both infection control and industrial hygiene. However, while the

installation of sneeze guards may reduce or prevent transmission between customers and employees, transmission may still occur between coworkers. Therefore, administrative controls and public health measures should be implemented along with engineering controls.

Examples of work practice controls include:

- Providing resources and a work environment that promotes personal hygiene. For example, provide tissues, no-touch trash cans, hand soap, hand sanitizer, disinfectants and disposable towels for employees to clean their work surfaces.

Additional photos: CDC/Kimberly Smith

- Encouraging employees to obtain a seasonal influenza vaccine (this helps to prevent illness from seasonal influenza strains that may continue to circulate).
- Providing employees with up-to-date education and training on influenza risk factors, protective behaviors, and instruction on proper behaviors (for example, cough ettiquette and care of personal protective equipment).

CDC/Jim Gathany

- Developing policies to minimize contacts between employees and between employees and clients or customers.

More information about protecting yourself, your coworkers and employees, and your family can be found at www.pandemicflu.gov.

Examples of engineering controls include:

- Installing physical barriers, such as clear plastic sneeze guards.
- Installing a drive-through window for customer service.
- In some limited healthcare settings, for aerosol generating procedures, specialized negative pressure ventilation may be indicated.

This photo shows a clear plastic barrier between employees and customers that can reduce occupational exposure to the general public.

Administrative Controls - Administrative controls include controlling employees' exposure by scheduling their work tasks in ways that minimize their exposure levels. Examples of administrative controls include:

- Developing policies that encourage ill employees to stay at home without fear of any reprisals.
- The discontinuation of unessential travel to locations with high illness transmission rates.
- Consider practices to minimize face-to-face contact between employees such as e-mail, websites and teleconferences. Where possible, encourage flexible work arrangements such as telecommuting or flexible work hours to reduce the number of your employees who must be at work at one time or in one specific location.
- Consider home delivery of goods and services to reduce the number of clients or customers who must visit your workplace.
- Developing emergency communications plans. Maintain a forum for answering employees' concerns. Develop Internet-based communications if feasible.

Personal Protective Equipment (PPE) - While administrative and engineering controls and proper work practices are considered to be more effective in minimizing exposure to the influenza virus, the use of PPE may also be indicated during certain exposures. If used correctly, PPE can help prevent some exposures; however, they

should not take the place of other prevention interventions, such as engineering controls, cough etiquette, and hand hygiene (see www.cdc.gov/flu/protect/stopgerms.htm). Examples of personal protective equipment are gloves, goggles, face shields, surgical masks, and respirators (for example, N95). It is important that personal protective equipment be:

- Selected based upon the hazard to the employee;
- Properly fitted and some must be periodically refitted (e.g., respirators);
- Conscientiously and properly worn;
- Regularly maintained and replaced, as necessary;
- Properly removed and disposed of to avoid contamination of self, others or the environment.

Employers are obligated to provide their employees with protective gear needed to keep them safe while performing their jobs. The types of PPE recommended for pandemic influenza will be based on the risk of contracting influenza while working and the availability of PPE. Check the www.pandemicflu.gov website for the latest guidance.

The Difference Between a Facemask and a Respirator

It is important that employers and employees understand the significant differences between these types of personal protective equipment. The decision on whether or not to require employees to use either surgical/procedure masks or respirators must be based upon a hazard analysis of the employees' specific work environment and the differing protective properties of each type of personal protective equipment. The use of surgical masks or respirators is one component of infection control practices that may reduce transmission between infected and non-infected persons.

It should be noted that there is limited information on the use of surgical masks for the control of a pandemic in settings where there is no identified source of infection. There is no information on

respirator use in such scenarios since modern respirators did not exist during the last pandemic. However, respirators are now routinely used to protect employees against occupational hazards, including biological hazards such as tuberculosis, anthrax, and hantavirus. The effectiveness of surgical masks and respirators has been inferred on the basis of the mode of influenza transmission, particle size, and professional judgment.

To offer protection, both surgical masks and respirators must be worn correctly and consistently throughout the time they are being used. If used properly, surgical masks and respirators both have a role in preventing different types of exposures. During an influenza pandemic, surgical masks and respirators should be used in conjunction with interventions that are known to prevent the spread of infection, such as respiratory etiquette, hand hygiene, and avoidance of large gatherings.

Surgical Masks - Surgical masks are used as a physical barrier to protect employees from hazards such as splashes of large droplets of blood or body fluids. Surgical masks also prevent contamination by trapping large particles of body fluids that may contain bacteria or viruses when they are expelled by the wearer, thus protecting other people against infection from the person wearing the surgical mask.

Surgical/procedure masks are used for several different purposes, including the following:

- Placed on sick people to limit the spread of infectious respiratory secretions to others.
- Worn by healthcare providers to prevent accidental contamination of patients' wounds by the organisms normally present in mucus and saliva.
- Worn by employees to protect themselves from splashes or sprays of blood or body fluids; they may also have the effect of keeping contaminated fingers/hands away from the mouth and nose.

Surgical masks are not designed or certified to prevent the inhalation of small airborne contaminants. These small airborne contaminants are too little to see with the naked eye but may still be capable of causing infection. Surgical/procedure masks are not

designed to seal tightly against the user's face. During inhalation, much of the potentially contaminated air passes through gaps between the face and the surgical mask, thus avoiding being pulled through the material of the mask and losing any filtration that it may provide. Their ability to filter small particles varies significantly based upon the type of material used to make the surgical mask, and so they cannot be relied upon to protect employees against airborne infectious agents. Only surgical masks that are cleared by the U.S. Food and Drug Administration and legally marketed in the United States have been tested for their ability to resist blood and body fluids.

Respirators - Respirators are designed to reduce an employee's exposure to airborne contaminants. Respirators are designed to fit the face and to provide a tight seal between the respirator's edge and the face. A proper seal between the user's face and the respirator forces inhaled air to be pulled through the respirator's filter material and not through gaps between the face and respirator. Respirators must be used in the context of a comprehensive respiratory protection program, (see OSHA standard 29 CFR 1910.134, or www.osha.gov/SLTC/respiratoryprotection/index.html). It is important to medically evaluate employees to assure that they can perform work tasks while wearing a respirator. Medical evaluation can be as simple as a questionnaire (found in Appendix C of OSHA's Respiratory Protection standard, 29 CFR 1910.134). Employers who have never before needed to consider a respiratory protection plan should note that it can take time to choose a respirator to provide to employees and to arrange for a qualified trainer and provide training, fit testing, and medical evaluation for their employees. If employers wait until an influenza pandemic actually arrives, they may be unable to provide an adequate respiratory protection program in a timely manner.

Types of Respirators

Respirators can be air supplying (e.g., the self-contained breathing apparatus worn by firefighters) or air purifying (e.g., a gas mask that filters hazards from the air). Most employees affected by pandemic influenza who are deemed to need a respirator to minimize the likelihood of exposure to the pandemic influenza virus

in the workplace will use some type of air purifying respirator. They are also known as "particulate respirators" because they protect by filtering particles out of the air as you breathe. These respirators protect only against particles—not gases or vapors. Since airborne biological agents such as bacteria or viruses are particles, they can be filtered by particulate respirators.

Air purifying respirators can be divided into several types:

- *Filtering facepiece respirators*, where the entire respirator facepiece is comprised of filter material. This type of respirator is also commonly referred to as an "N95" respirator. It is discarded when it becomes unsuitable for further use due to excessive breathing resistance (e.g., particulate clogging the filter), unacceptable contamination/soiling, or physical damage.
  - *Surgical respirators* are a type of respiratory protection that offers the combined protective properties of both a filtering facepiece respirator and a surgical mask. Surgical N95 respirators are certified by NIOSH as respirators and also cleared by FDA as medical devices which have been designed and tested and shown to be equivalent to surgical masks in certain performance characteristics (resistance to blood penetration, biocompatibility) which are not examined by NIOSH during its certification of N95 respirators.
- *Reusable or elastomeric respirators*, where the facepiece can be cleaned, repaired and reused, but the filter cartridges are discarded and replaced when they become unsuitable for further use. These respirators come in half-mask (covering the mouth and nose) and full-mask (covering mouth, nose, and eyes) types. These respirators can be used with a variety of different cartridges to protect against different hazards. These respirators can also be used with canisters or cartridges that will filter out gases and vapors.
- *Powered air purifying respirators*, (PAPRs) where a battery-powered blower pulls contaminated air through filters, then moves the filtered air to the wearer's facepiece. PAPRs are significantly more expensive than other air purifying respirators but they provide higher levels of protection and may also increase the comfort for some users by reducing the physiologic burden

associated with negative pressure respirators and providing a constant flow of air on the face. These respirators can also be used with canisters or cartridges that will filter out gases and vapors. It should also be noted that there are hooded PAPRs that do not require employees to be fit tested in order to use them.

All respirators used in the workplace are required to be tested and certified by the National Institute for Occupational Safety and Health (NIOSH). NIOSH-certified respirators are marked with the manufacturer's name, the part number, the protection provided by the filter (e.g., N95), and "NIOSH." This information is printed on the facepiece, exhalation valve cover, or head straps. If a respirator does not have these markings it has not been certified by NIOSH. Those respirators that are surgical N95 respirators are also cleared by the FDA and, therefore, are appropriate for circumstances in which protection from airborne and body fluid contaminants is needed.

When choosing between disposable and reusable respirators, employers should consider their work environment, the nature of pandemics, and the potential for supply chain disruptions. Each pandemic influenza outbreak could last from 6 to 8 weeks and waves of outbreaks may occur over a year or more. While disposable respirators may be more convenient and cheaper on a per unit basis, a reusable respirator may be more economical on a long-term basis and reduce the impact of disruption in supply chains or shortages of respirators.

Classifying Particulate Respirators and Particulate Filters

An N95 respirator is one of nine types of particulate respirators. Respirator filters that remove at least 95 percent of airborne particles during "worst case" testing using the "most-penetrating" size of particle are given a 95 rating. Those that filter out at least 99 percent of the particles under the same conditions receive a 99 rating, and those that filter at least 99.97 percent (essentially 100 percent) receive a 100 rating.

In addition, filters in this family are given a designation of N, R, or P to convey their ability to function in the presence of oils that are found in some work environments.

"N" if they are Not resistant to oil. (e.g., N95, N99, N100)

"R" if they are somewhat Resistant to oil. (e.g., R95, R99, R100)

"P" if they are strongly resistant (i.e., oil Proof). (e.g., P95, P99, P100)

This rating is important in work settings where oils may be present because some industrial oils can degrade the filter performance to the point that it does not filter adequately. Thus, the three filter efficiencies combined with the three oil designations lead to nine types of particulate respirator filter materials. It should be noted that any of the various types of filters listed here would be acceptable for protection against pandemic influenza in workplaces that do not contain oils, particularly if the N95 filter type was unavailable due to shortages.

Replacing Disposable Respirators

Disposable respirators are designed to be used once and are then to be properly disposed of. Once worn in the presence of an infectious patient, the respirator should be considered potentially contaminated with infectious material, and touching the outside of the device should be avoided to prevent self-inoculation (touching the contaminated respirator and then touching one's eyes, nose, or mouth). It should be noted that a once-worn respirator will also be contaminated on its inner surface by the microorganisms present in the exhaled air and oral secretions of the wearer.

If a sufficient supply of respirators is not available during a pandemic, employers and employees may consider reuse as long as the device has not been obviously soiled or damaged (e.g., creased or torn), and it retains its ability to function properly. This practice is not acceptable under normal circumstances and should only be considered under the most dire of conditions. Data on decontamination and/or reuse of respirators for infectious diseases are not available. Reuse may increase the potential for contamination; however, this risk must be balanced against the need to provide respiratory protection. When preparing for a pandemic, employers who anticipate providing respiratory protection to employees for the duration of the pandemic should consider using reusable or elastomeric respirators that are designed to be cleaned, repaired and reused.

Dust or Comfort Masks

Employers and employees should be aware that there are "dust" or "comfort" masks sold at home improvement stores that look very similar to respirators. Some dust masks may even be made by a manufacturer that also produces NIOSH-certified respirators. Unless a mask has been tested and certified by NIOSH, employers do not know if the device will filter very small airborne particles. The occupational use of respirators, including those purchased at home improvement or convenience stores, are still covered by OSHA's Respiratory Protection standard.

Note: Some respirators have an exhalation valve to make it easier for the wearer to breathe. While these respirators provide the same level of particle filtration protection to the wearer, they should not be used by healthcare providers who are concerned about contaminating a sterile field, or provided to known or suspected pandemic patients as a means of limiting the spread of their body fluids to others.

Note: Additional respirator and surgical mask guidance for healthcare workers has been developed and is available at www.pandemicflu.gov/plan/healthcare/maskguidancehc.html. This document, "Interim Guidance on Planning for the Use of Surgical Masks and Respirators in Health Care Settings during an Influenza Pandemic," provides details on the differences between a surgical mask and a respirator, the state of science regarding influenza transmission, and the rationale for determining the appropriate protective device.

Steps Every Employer Can Take to Reduce the Risk of Exposure to Pandemic Influenza in Their Workplace

The best strategy to reduce the risk of becoming infected with influenza during a pandemic is to avoid crowded settings and other situations that increase the risk of exposure to someone who may be infected. If it is absolutely necessary to be in a crowded setting,

the time spent in a crowd should be as short as possible. Some basic hygiene (see www.cdc.gov/flu/protect/stopgerms.htm) and social distancing precautions that can be implemented in every workplace include the following:

- Encourage sick employees to stay at home.
- Encourage your employees to wash their hands frequently with soap and water or with hand sanitizer if there is no soap or water available. Also, encourage your employees to avoid touching their noses, mouths, and eyes.
- Encourage your employees to cover their coughs and sneezes with a tissue, or to cough and sneeze into their upper sleeves if tissues are not available. All employees should wash their hands or use a hand sanitizer after they cough, sneeze or blow their noses.

EyeWire, Inc.

- Employees should avoid close contact with their coworkers and customers (maintain a separation of at least 6 feet). They should avoid shaking hands and always wash their hands after contact with others. Even if employees wear gloves, they should wash their hands upon removal of the gloves in case their hand(s) became contaminated during the removal process.
- Provide customers and the public with tissues and trash receptacles, and with a place to wash or disinfect their hands.
- Keep work surfaces, telephones, computer equipment and other frequently touched surfaces and office equipment clean. Be sure that any cleaner used is safe and will not harm your employees or your office equipment. Use only disinfectants registered by the U.S. Environmental Protection Agency (EPA), and follow all directions and safety precautions indicated on the label.
- Discourage your employees from using other employees' phones, desks, offices or other work tools and equipment.
- Minimize situations where groups of people are crowded together, such as in a meeting. Use e-mail, phones and text messages to communicate with each other. When meetings are

necessary, avoid close contact by keeping a separation of at least 6 feet, where possible, and assure that there is proper ventilation in the meeting room.

- Reducing or eliminating unnecessary social interactions can be very effective in controlling the spread of infectious diseases. Reconsider all situations that permit or require employees, customers, and visitors (including family members) to enter the workplace. Workplaces which permit family visitors on site should consider restricting/eliminating that option during an influenza pandemic. Work sites with on-site day care should consider in advance whether these facilities will remain open or will be closed, and the impact of such decisions on employees and the business.
- Promote healthy lifestyles, including good nutrition, exercise, and smoking cessation. A person's overall health impacts their body's immune system and can affect their ability to fight off, or recover from, an infectious disease.

Workplaces Classified at Lower Exposure Risk (Caution) for Pandemic Influenza: What to Do to Protect Employees

If your workplace does not require employees to have frequent contact with the general public, basic personal hygiene practices and social distancing can help protect employees at work. Follow the general hygiene and social distancing practices previously recommended for all workplaces (see page 26). Also, try the following:

- Communicate to employees what options may be available to them for working from home.
- Communicate the office leave policies, policies for getting paid, transportation issues, and day care concerns.
- Make sure that your employees know where supplies for hand hygiene are located.

- Monitor public health communications about pandemic flu recommendations and ensure that your employees also have access to that information.
- Work with your employees to designate a person(s), website, bulletin board or other means of communicating important pandemic flu information.

More information about protecting employees and their families can be found at: www.pandemicflu.gov.

Workplaces Classified at Medium Exposure Risk for Pandemic Influenza: What to Do to Protect Employees

Medium risk workplaces require frequent close contact between employees or with the general public (such as high-volume retail stores). If this contact cannot be avoided, there are practices to reduce the risk of infection. In addition to the basic work practices that every workplace should adopt (see page 26), medium risk occupations require employers to address enhanced safety and health precautions. Below are some of the issues that employers should address when developing plans for workplace safety and health during a pandemic.

Work Practice and Engineering Controls

- Instruct employees to avoid close contact (within 6 feet) with other employees and the general public. This can be accomplished by simply increasing the distance between the employee and the general public in order to avoid contact with large droplets from people talking, coughing or sneezing.
- Some organizations can expand internet, phone-based, drive-through window, or home delivery customer service strategies to minimize face-to-face contact. Work with your employees to identify new ways to do business that can also help to keep employees and customers safe and healthy.

- Communicate the availability of medical screening or other employee health resources (e.g., on-site nurse or employee wellness program to check for flu-like symptoms before employees enter the workplace).
- Employers also should consider installing physical barriers, such as clear plastic sneeze guards, to protect employees where possible (such as cashier stations).

Administrative Controls

- Work with your employees so that they understand the office leave policies, policies for getting paid, transportation issues, and day care concerns.
- Make sure that employees know where supplies for hand and surface hygiene are located.
- Work with your employees to designate a person(s), website, bulletin board or other means of communicating important pandemic flu information.
- Use signs to keep customers informed about symptoms of the flu, and ask sick customers to minimize contact with your employees until they are well.
- Your workplace may consider limiting access to customers and the general public, or ensuring that they can only enter certain areas of your workplace.

Personal Protective Equipment (PPE)

Employees who have high-frequency, close contact with the general population that cannot be eliminated using administrative or engineering controls, and where contact with symptomatic ill persons is not expected should use personal protective equipment to prevent sprays of potentially infected liquid droplets (from talking, coughing, or sneezing) from contacting their nose or mouth. A surgical mask will provide such barrier protection. Use of a respirator may be considered if there is an expectation of close contact with persons who have symptomatic influenza infection or if employers choose to provide protection against a risk of airborne transmission. It should be noted that wearing a respirator may be

physically burdensome to employees, particularly when the use of PPE is not common practice for the work task. In the event of a shortage of surgical masks, a reusable face shield that can be decontaminated may be an acceptable method of protecting against droplet transmission of an infectious disease but will not protect against airborne transmission, to the extent that disease may spread in that manner.

Eye protection generally is not recommended to prevent influenza infection although there are limited examples where strains of influenza have caused eye infection (conjunctivitis). At the time of a pandemic, health officials will assess whether risk of conjunctival infection or transmission exists for the specific pandemic viral strain.

Employees should wash hands frequently with soap or sanitizing solutions to prevent hands from transferring potentially infectious material from surfaces to their mouths or noses. While employers and employees may choose to wear gloves, the exposure of concern is touching the mouth and nose with a contaminated hand and not exposure to the virus through non-intact skin (for example, cuts or scrapes). While the use of gloves may make employees more aware of potential hand contamination, there is no difference between intentional or unintentional touching of the mouth, nose or eyes with either a contaminated glove or a contaminated hand. If an employee does wear gloves, they should always wash their hands with soap or sanitizing solution immediately after removal to ensure that they did not contaminate their hand(s) while removing them.

When selecting PPE, employers should consider factors such as function, fit, ability to be decontaminated, disposal, and cost. Sometimes, when a piece of PPE will have to be used repeatedly for a long period of time, a more expensive and durable piece of PPE may be less expensive in the long run than a disposable piece of PPE. For example, in the event of a pandemic, there may be shortages of surgical masks. A reusable face shield that can be decontaminated may become the preferred method of protecting against droplet transmission in some workplaces. It should be noted that barrier protection, such as a surgical mask or face shield, will protect against droplet transmission of an infectious disease

but will not protect against airborne transmission, to the extent that the disease may be spread in that manner. Each employer should select the combination of PPE that protects employees in their particular workplace. It should also be noted that wearing PPE may be physically burdensome to employees, particularly when the use of PPE is not common practice for the work task.

Educate and train employees about the protective clothing and equipment appropriate to their current duties and the duties which they may be asked to assume when others are absent. Employees may need to be fit tested and trained in the proper use and care of a respirator. Also, it is important to train employees to put on (don) and take off (doff) PPE in the proper order to avoid inadvertent self-contamination (www.osha.gov/SLTC/respiratoryprotection/index.html). During a pandemic, recommendations for PPE use in particular occupations may change, depending on geographic proximity to active cases, updated risk assessments for particular employees, and information on PPE effectiveness in preventing the spread of influenza.

Workplaces Classified at Very High or High Exposure Risk for Pandemic Influenza: What to Do to Protect Employees

If your workplace requires your employees to have contact with people that are known or suspected to be infected with the pandemic virus, there are many practices that can be used to reduce the risk of infection and to protect your employees. Additional guidance for very high and high exposure risk workplaces, such as healthcare facilities, can be found at: www.pandemicflu.gov and www.osha.gov.

Very high and high exposure risk occupations require employers to address enhanced safety and health precautions in addition to the basic work practices that every workplace should adopt (see page 26). Employers should also be aware that working in a high

risk occupation can be stressful to both employees and their families. Employees in high risk occupations may have heightened concern about their own safety and possible implications for their family. Such workplaces may experience greater employee absenteeism than other lower risk workplaces. Talk to your employees about resources that can help them in the event of a pandemic crisis. Keeping the workplace safe is everyone's priority. More information about protecting employees and their families can be found at: www.pandemicflu.gov.

Work Practice and Engineering Controls

Employers should ensure that employees have adequate training and supplies to practice proper hygiene. Emergency responders and other essential personnel who may be exposed while working away from fixed facilities should be provided with hand sanitizers that do not require water so that they can decontaminate themselves in the field. Employers should work with employees to identify ways to modify work practices to promote social distancing and prevent close contact (within 6 feet), where possible. Employers should also consider offering enhanced medical monitoring of employees in very high and high risk work environments.

In certain limited circumstances ventilation is recommended for high and very high risk work environments. While proper ventilation can reduce the risk of transmission for healthcare workers in the same room as infectious patients, it cannot be relied upon as the sole protective measure. Thus, a combination of engineering controls and personal protective equipment will be needed.

- When possible, healthcare facilities equipped with isolation rooms should use them when performing aerosol generating procedures for patients with known or suspected pandemic influenza.
- Laboratory facilities that handle specimens for known or suspected pandemic patients will also require special precautions associated with a Bio-Safety Level 3 facility. Some recommendations can be found at: www.cdc.gov/flu/h2n2bs13.htm.

Employers should also consider installing physical barriers, such as clear plastic sneeze guards, to protect employees where possible (for example, reception or intake areas). The use of barrier protections,

such as sneeze guards, is common practice for both infection control and industrial hygiene.

Administrative Controls (Isolation Precautions)

If working in a healthcare facility, follow existing guidelines and facility standards of practice for identifying and isolating infected individuals and for protecting employees. See the U.S. Department of Health and Human Services' pandemic influenza plan for health-care facilities at: www.hhs.gov/pandemicflu/plan/sup4.html.

Personal Protective Equipment (PPE)

Those who work closely with (either in contact with or within 6 feet) people known or suspected to be infected with pandemic influenza virus should wear:

- Respiratory protection for protection against small droplets from talking, coughing or sneezing and also from small airborne particles of infectious material.
  - N95 or higher rated filter for most situations.
  - Supplied air respirator (SAR) or powered air purifying respirator (PAPR) for certain high risk medical or dental procedures likely to generate bioaerosols.
  - Use a surgical respirator when both respiratory protection and resistance to blood and body fluids is necessary.
- Face shields may also be worn on top of a respirator to prevent bulk contamination of the respirator. Certain respirator designs with forward protrusions (duckbill style) may be difficult to properly wear under a face shield. Ensure that the face shield does not prevent airflow through the respirator.
- Medical/surgical gowns or other disposable/decontaminable protective clothing.
- Gloves to reduce transfer of infectious material from one patient to another.
- Eye protection if splashes are anticipated.

The appropriate form of respirator will depend on the type of exposure and on the transmission pattern of the particular strain of

influenza. See the National Institute for Occupational Safety and Health (NIOSH) Respirator Selection Logic at: www.cdc.gov/niosh/docs/2005-100.

Educate and train employees about the protective clothing and equipment appropriate to their current duties and the duties which they may be asked to assume when others are absent. Education and training material should be easy to understand and available in the appropriate language and literacy level for all employees. Employees need to be fit tested and trained in the proper use and care of a respirator. It is also important to train employees to put on (don) and take off (doff) PPE in the proper order to avoid inadvertent self-contamination (www.osha.gov/SLTC/respiratoryprotection/index.html). Employees who dispose of PPE and other infectious waste must also be trained and provided with appropriate PPE.

During a pandemic, recommendations for PPE use in particular occupations may change depending on geographic location, updated risk assessments for particular employees, and information on PPE effectiveness in preventing the spread of influenza. Additional respirator and surgical mask guidance for healthcare workers has been developed and is available at www.pandemicflu.gov/plan/healthcare/maskguidancehc.html. This document, *Interim Guidance on Planning for the Use of Surgical Masks and Respirators in Health Care Settings during an Influenza Pandemic*, provides details on the differences between a surgical mask and a respirator, the state of science regarding influenza transmission, and the rationale for determining the appropriate protective device.

What Employees Living Abroad or Who Travel Internationally for Work Should Know

Employees living abroad and international business travelers should note that other geographic areas have different influenza seasons and will likely be affected by a pandemic at different times than the United States. The U.S. Department of State emphasizes that, in the event of a pandemic, its ability to assist Americans traveling and

residing abroad may be severely limited by restrictions on local and international movement imposed for public health reasons, either by foreign governments and/or the United States. Furthermore, American citizens should take note that the Department of State cannot provide Americans traveling or living abroad with medications or supplies even in the event of a pandemic.

In addition, the Department of State has asked its embassies and consulates to consider preparedness measures that take into consideration the fact that travel into or out of a country may not be possible, safe, or medically advisable during a pandemic. Guidance on how private citizens can prepare to shelter in place, including stocking food, water, and medical supplies, is available at the www.pandemicflu.gov website. Embassy stocks cannot be made available to private American citizens abroad, therefore, employers and employees are encouraged to prepare appropriately. It is also likely that governments will respond to a pandemic by imposing public health measures that restrict domestic and international movement, further limiting the U.S. government's ability to assist Americans in these countries. As it is possible that these measures may be implemented very quickly, it is important that employers and employees plan appropriately.

More information on pandemic influenza planning for employees living and traveling abroad can be found at:

www.pandemicflu.gov/travel/index.html

www.cdc.gov/travel

www.state.gov/travelandbusiness

For More Information

Federal, state and local government agencies are your best source of information should an influenza pandemic take place. It is important to stay informed about the latest developments and recommendations since specific guidance may change based upon the characteristics of the eventual pandemic influenza strain, (for example, severity of disease, importance of various modes of transmission).

Below are several recommended websites that you can rely on for the most current and accurate information:

www.pandemicflu.gov
(Managed by the U.S. Department of Health and Human Services; offers one-stop access, including toll-free phone numbers, to U.S. government avian and pandemic flu information.)

www.osha.gov
(Occupational Safety and Health Administration website)

www.cdc.gov/niosh
(National Institute for Occupational Safety and Health website)

www.cdc.gov
(Centers for Disease Control and Prevention website)

www.fda.gov/cdrh/ppe/fluoutbreaks.html
(U.S. Food and Drug Administration website)

OSHA Assistance

OSHA can provide extensive help through a variety of programs, including technical assistance about effective safety and health programs, state plans, workplace consultations, and training and education.

Safety and Health Program Management Guidelines

Effective management of worker safety and health protection is a decisive factor in reducing the extent and severity of work-related injuries and illnesses and their related costs. In fact, an effective safety and health management system forms the basis of good worker protection, can save time and money, increase productivity and reduce employee injuries, illnesses and related workers' compensation costs.

To assist employers and workers in developing effective safety and health management system, OSHA published recommended *Safety and Health Program Management Guidelines* (54 *Federal Register* (16): 3904-3916, January 26, 1989). These voluntary guidelines can be applied to all places of employment covered by OSHA.

The guidelines identify four general elements critical to the development of a successful safety and health management system:

- Management leadership and worker involvement,
- Worksite analysis,
- Hazard prevention and control, and
- Safety and health training.

The guidelines recommend specific actions, under each of these general elements, to achieve an effective safety and health system. The *Federal Register* notice is available online at www.osha.gov.

State Programs

The Occupational Safety and Health Act of 1970 (OSH Act) encourages states to develop and operate their own job safety and health plans. OSHA approves and monitors these plans. Twenty-four states, Puerto Rico and the Virgin Islands currently

operate approved state plans: 22 cover both private and public (state and local government) employment; Connecticut, New Jersey, New York and the Virgin Islands cover the public sector only. States and territories with their own OSHA-approved occupational safety and health plans must adopt standards identical to, or at least as effective as, the Federal OSHA standards.

Consultation Services

Consultation assistance is available on request to employers who want help in establishing and maintaining a safe and healthful workplace. Largely funded by OSHA, the service is provided at no cost to the employer. Primarily developed for smaller employers with more hazardous operations, the consultation service is delivered by state governments employing professional safety and health consultants. Comprehensive assistance includes an appraisal of all mechanical systems, work practices, and occupational safety and health hazards of the workplace and all aspects of the employer's present job safety and health program. In addition, the service offers assistance to employers in developing and implementing an effective safety and health program. No penalties are proposed or citations issued for hazards identified by the consultant. OSHA provides consultation assistance to the employer with the assurance that his or her name and firm and any information about the workplace will not be routinely reported to OSHA enforcement staff. For more information concerning consultation assistance, see OSHA's website at www.osha.gov.

Strategic Partnership Program

OSHA's Strategic Partnership Program helps encourage, assist and recognize the efforts of partners to eliminate serious workplace hazards and achieve a high level of worker safety and health. Most strategic partnerships seek to have a broad impact by building cooperative relationships with groups of employers and workers. These partnerships are voluntary relationships between OSHA, employers, worker representatives, and others (e.g., trade unions, trade and professional associations, universities, and other government agencies).

For more information on this and other agency programs, contact your nearest OSHA office, or visit OSHA's website at www.osha.gov.

OSHA Training and Education

OSHA area offices offer a variety of information services, such as technical advice, publications, audiovisual aids and speakers for special engagements. OSHA's Training Institute in Arlington Heights, IL, provides basic and advanced courses in safety and health for Federal and state compliance officers, state consultants, Federal agency personnel, and private sector employers, workers and their representatives.

The OSHA Training Institute also has established OSHA Training Institute Education Centers to address the increased demand for its courses from the private sector and from other federal agencies. These centers are colleges, universities, and nonprofit organizations that have been selected after a competition for participation in the program.

OSHA also provides funds to nonprofit organizations, through grants, to conduct workplace training and education in subjects where OSHA believes there is a lack of workplace training. Grants are awarded annually.

For more information on grants, training and education, contact the OSHA Training Institute, Directorate of Training and Education, 2020 South Arlington Heights Road, Arlington Heights, IL 60005, (847) 297-4810, or see Training on OSHA's website at www.osha.gov. For further information on any OSHA program, contact your nearest OSHA regional office listed at the end of this publication.

Information Available Electronically

OSHA has a variety of materials and tools available on its website at www.osha.gov. These include electronic tools, such as Safety and Health Topics, eTools, Expert Advisors; regulations, directives and publications; videos and other information for employers and workers. OSHA's software programs and eTools walk you through challenging safety and health issues and common problems to find the best solutions for your workplace.

OSHA Publications

OSHA has an extensive publications program. For a listing of free items, visit OSHA's website at www.osha.gov or contact the OSHA Publications Office, U.S. Department of Labor, 200 Constitution

Avenue, NW, N-3101, Washington, DC 20210; telephone (202) 693-1888 or fax to (202) 693-2498.

Contacting OSHA

To report an emergency, file a complaint, or seek OSHA advice, assistance, or products, call (800) 321-OSHA or contact your nearest OSHA Regional or Area office listed at the end of this publication. The teletypewriter (TTY) number is (877) 889-5627.

Written correspondence can be mailed to the nearest OSHA Regional or Area Office listed at the end of this publication or to OSHA's national office at: U.S. Department of Labor, Occupational Safety and Health Administration, 200 Constitution Avenue, N.W., Washington, DC 20210.

By visiting OSHA's website at www.osha.gov, you can also:

- File a complaint online,
- Submit general inquiries about workplace safety and health electronically, and
- Find more information about OSHA and occupational safety and health.

(OOC 5/2009)

OSHA Regional Offices

Region I
(CT,* ME, MA, NH, RI, VT*)
JFK Federal Building, Room E340
Boston, MA 02203
(617) 565-9860

Region II
(NJ,* NY,* PR,* VI*)
201 Varick Street, Room 670
New York, NY 10014
(212) 337-2378

Region III
(DE, DC, MD,* PA, VA,* WV)
The Curtis Center
170 S. Independence Mall West
Suite 740 West
Philadelphia, PA 19106-3309
(215) 861-4900

Region IV
(AL, FL, GA, KY,* MS, NC,* SC,* TN*)
61 Forsyth Street, SW, Room 6T50
Atlanta, GA 30303
(404) 562-2300

Region V
(IL, IN,* MI,* MN,* OH, WI)
230 South Dearborn Street
Room 3244
Chicago, IL 60604
(312) 353-2220

Region VI
(AR, LA, NM,* OK, TX)
525 Griffin Street, Room 602
Dallas, TX 75202
(972) 850-4145

Region VII
(IA,* KS, MO, NE)
Two Pershing Square
2300 Main Street, Suite 1010
Kansas City, MO 64108-2416
(816) 283-8745

Region VIII
(CO, MT, NO, SO, UT,* WY*)
1999 Broadway, Suite 1690
PO Box 46550
Denver, CO 80202-5716
(720) 264-6550

Region IX
(AZ,* CA,* HI,* NV,* and American Samoa,
Guam and the Northern Mariana Islands)
90 7th Street, Suite 18-100
San Francisco, CA 94103
(415) 625-2547

Region X
(AK,* ID, OR,* WA*)
1111 Third Avenue, Suite 715
Seattle, WA 98101-3212
(206) 553-5930

* These states and territories operate their own OSHA-approved job safety and health programs and cover state and local government employees as well as private sector employees. The Connecticut, New Jersey, New York and Virgin Islands plans cover public employees only. States with approved programs must have standards that are identical to, or at least as effective as, the Federal OSHA standards.

Note: To get contact information for OSHA Area Offices, OSHA-approved State Plans and OSHA Consultation Projects, please visit us online at www.osha.gov or call us at 1-800-321-0SHA.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U.S. Department of Labor

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Business Pandemic Influenza Planning Checklist

In the event of pandemic influenza, businesses will play a key role in protecting employees' health and safety as well as limiting the negative impact to the economy and society. Planning for pandemic influenza is critical. To assist you in your efforts, the Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) have developed the following checklist for large businesses. It identifies important, specific activities large businesses can do now to prepare, many of which will also help you in other emergencies. Further information can be found at **www.pandemicflu.gov** and **www.cdc.gov/business**.

1.1 Plan for the impact of a pandemic on your business:

Completed	In Progress	Not Started	
☐	☐	☐	Identify a pandemic coordinator and/or team with defined roles and responsibilities for preparedness and response planning. The planning process should include input from labor representatives.
☐	☐	☐	Identify essential employees and other critical inputs (e.g. raw materials, suppliers, sub-contractor services/ products, and logistics) required to maintain business operations by location and function during a pandemic.
☐	☐	☐	Train and prepare ancillary workforce (e.g. contractors, employees in other job titles/descriptions, retirees).
☐	☐	☐	Develop and plan for scenarios likely to result in an increase or decrease in demand for your products and/or services during a pandemic (e.g. effect of restriction on mass gatherings, need for hygiene supplies).
☐	☐	☐	Determine potential impact of a pandemic on company business financials using multiple possible scenarios that affect different product lines and/or production sites.
☐	☐	☐	Determine potential impact of a pandemic on business-related domestic and international travel (e.g. quarantines, border closures).
☐	☐	☐	Find up-to-date, reliable pandemic information from community public health, emergency management, and other sources and make sustainable links.
☐	☐	☐	Establish an emergency communications plan and revise periodically. This plan includes identification of key contacts (with back-ups), chain of communications (including suppliers and customers), and processes for tracking and communicating business and employee status.
☐	☐	☐	Implement an exercise/drill to test your plan, and revise periodically.

1.2 Plan for the impact of a pandemic on your employees and customers:

Completed	In Progress	Not Started	
☐	☐	☐	Forecast and allow for employee absences during a pandemic due to factors such as personal illness, family member illness, community containment measures and quarantines, school and/or business closures, and public transportation closures.
☐	☐	☐	Implement guidelines to modify the frequency and type of face-to-face contact (e.g. hand-shaking, seating in meetings, office layout, shared workstations) among employees and between employees and customers (refer to CDC recommendations).
☐	☐	☐	Encourage and track annual influenza vaccination for employees.
☐	☐	☐	Evaluate employee access to and availability of healthcare services during a pandemic, and improve services as needed.
☐	☐	☐	Evaluate employee access to and availability of mental health and social services during a pandemic, including corporate, community, and faith-based resources, and improve services as needed.
☐	☐	☐	Identify employees and key customers with special needs, and incorporate the requirements of such persons into your preparedness plan.

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1.3 Establish policies to be implemented during a pandemic:

Completed	In Progress	Not Started	
☐	☐	☐	Establish policies for employee compensation and sick-leave absences unique to a pandemic (e.g. non-punitive, liberal leave), including policies on when a previously ill person is no longer infectious and can return to work after illness.
☐	☐	☐	Establish policies for flexible worksite (e.g. telecommuting) and flexible work hours (e.g. staggered shifts).
☐	☐	☐	Establish policies for preventing influenza spread at the worksite (e.g. promoting respiratory hygiene/ cough etiquette, and prompt exclusion of people with influenza symptoms).
☐	☐	☐	Establish policies for employees who have been exposed to pandemic influenza, are suspected to be ill, or become ill at the worksite (e.g. infection control response, immediate mandatory sick leave).
☐	☐	☐	Establish policies for restricting travel to affected geographic areas (consider both domestic and international sites), evacuating employees working in or near an affected area when an outbreak begins, and guidance for employees returning from affected areas (refer to CDC travel recommendations).
☐	☐	☐	Set up authorities, triggers, and procedures for activating and terminating the company's response plan, altering business operations (e.g. shutting down operations in affected areas), and transferring business knowledge to key employees.

1.4 Allocate resources to protect your employees and customers during a pandemic:

Completed	In Progress	Not Started	
☐	☐	☐	Provide sufficient and accessible infection control supplies (e.g.hand-hygiene products, tissues and receptacles for their disposal) in all business locations.
☐	☐	☐	Enhance communications and information technology infrastructures as needed to support employee telecommuting and remote customer access.
☐	☐	☐	Ensure availability of medical consultation and advice for emergency response.

1.5 Communicate to and educate your employees:

Completed	In Progress	Not Started	
☐	☐	☐	Develop and disseminate programs and materials covering pandemic fundamentals (e.g. signs and symptoms of influenza, modes of transmission), personal and family protection and response strategies (e.g. hand hygiene, coughing/sneezing etiquette, contingency plans).
☐	☐	☐	Anticipate employee fear and anxiety, rumors and misinformation and plan communications accordingly.
☐	☐	☐	Ensure that communications are culturally and linguistically appropriate.
☐	☐	☐	Disseminate information to employees about your pandemic preparedness and response plan.
☐	☐	☐	Provide information for the at-home care of ill employees and family members.
☐	☐	☐	Develop platforms (e.g. hotlines, dedicated websites) for communicating pandemic status and actions to employees, vendors, suppliers, and customers inside and outside the worksite in a consistent and timely way, including redundancies in the emergency contact system.
☐	☐	☐	Identify community sources for timely and accurate pandemic information (domestic and international) and resources for obtaining counter-measures (e.g. vaccines and antivirals).

1.6 Coordinate with external organizations and help your community:

Completed	In Progress	Not Started	
☐	☐	☐	Collaborate with insurers, health plans, and major local healthcare facilities to share your pandemic plans and understand their capabilities and plans.
☐	☐	☐	Collaborate with federal, state, and local public health agencies and/or emergency responders to participate in their planning processes, share your pandemic plans, and understand their capabilities and plans.
☐	☐	☐	Communicate with local and/or state public health agencies and/or emergency responders about the assets and/or services your business could contribute to the community.
☐	☐	☐	Share best practices with other businesses in your communities, chambers of commerce, and associations to improve community response efforts.

Epidemiologic Concepts for the Prevention and Control of Infectious Diseases

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Abstract

We will review the epidemiologic concepts for the prevention and control of infectious diseases. Public health and medical professionals are familiar with common interventions to prevent or control infectious diseases. However, the underlying epidemiologic concepts that drive and guide these interventions are less familiar. Although we focus on acute infectious diseases, these concepts are broadly applicable to communicable diseases, including chronic or neoplastic diseases caused by exogenous transmissible agents such as human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV and HCV), human papilloma virus (HPV), and prions.

Keywords: Infectious diseases, Communicable diseases, Transmission dynamics, Infectious disease epidemiology

Learning objectives

After completing this review readers will be able to describe…

- The transmission of microbial agents from an infectious source to a susceptible human host;
- The natural history of infection and infectiousness;
- How humans and microbes interact with each other and their environment to produce infectious disease epidemics;
- The haracteristics of infectives that increase transmission;
- The characteristics of susceptibles that increase transmission;
- Six control strategies for interrupting transmission; and
- Control measures based on the six control strategies.

1. Introduction

We will review the epidemiologic concepts for the prevention and control of infectious diseases. Public health and medical professionals are familiar with the interventions to prevent or control infectious diseases (Table 1). However, the underlying epidemiologic concepts that drive and guide these interventions are less familiar. Although we focus on acute infectious diseases, these concepts are broadly applicable to communicable diseases, including chronic or neoplastic diseases caused by exogenous transmissible agents such as human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV and HCV), human papilloma virus (HPV), and prions.

A better understanding of the core epidemiologic concepts will (1) help researchers prioritize and conduct studies to identify and optimize prevention and control interventions; (2) help clinicians understand their role and how it directly and indirectly contributes to containment efforts; (3) help field investigators use a systematic and comprehensive approach to hypotheses generation and testing when conducting outbreak investigations; (4) help responders design, implement, and evaluate interventions to control and prevent acute microbial threats as well as endemic infectious diseases; and (5) help planners design, test, and evaluate infectious disease emergency operations response plans.

Table 1: Common interventions to prevent and control infectious diseases

Control measures
Alter risk factors
Prophylactic immunization
Post-exposure management
Diagnosis and treatment
Infection control practices
Case finding and isolation
Contact tracing and quarantine
Environmental control measures
Identify and control infectious sources

Our primary focus is on infectious disease transmission mechanisms, transmission dynamics, and transmission containment. The design, implementation, and evaluation of strategies to control infectious diseases can be improved by using a systematic, integrated epidemiologic approach, especially for acute or novel microbial threats that require special public health actions (e.g., severe acute respiratory syndrome [SARS], human pandemic influenza, or bioterrorism). Furthermore, we stress the value and importance of understanding the epidemiologic control points that drive infectious disease transmission dynamics.

1.1. Epidemiologic concepts

Epidemiology is "[t]he study of the distribution and determinants of health related states and events in populations, and the application of this study to control health problems" [1].

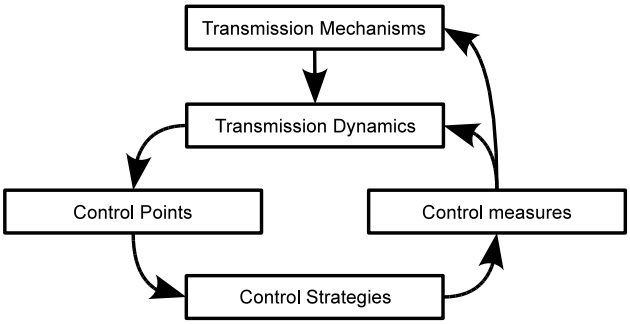

Figure 1: The relationship between infectious disease transmission mechanisms, transmission dynamics, and transmission containment (control points, control measures, and evaluation

By health-related states or events, we mean the occurrence or condition of infection, disease, injury, disability, or death. Epidemiologic studies are designed to answer well-defined investigative questions while minimizing threats to making valid inferences (chance, bias, and confounding). Most medical and public health professionals are familiar with the epidemiologic approach to public health action. Infectious diseases differ in important ways from non-infectious diseases because of the mechanisms by which microbial agents are transmitted and the population dynamics of transmission and disease occurrence. To improve our conceptual understanding, we use a systematic, comprehensive, and integrated approach (Figure 1). Specifically, we cover the following:

1. Transmission mechanisms
   (a) Chain model of infectious diseases
   (b) Natural history of infection and infectiousness
   (c) Convergence model of human-microbe interaction
2. Transmission dynamics
   (a) Reproductive number
   (b) Infection rate among susceptibles
   (c) Generation time
3. Transmission containment
   (a) Control points
   (b) Control strategies
   (c) Control measures

First, we review infectious disease transmission mechanisms. How are infections transmitted and why? Second, we review infectious disease transmission dynamics. At the population level, what mechanisms explain the transmission of microbial agents and the appearance of infectious cases? How do infectious cases interact with susceptible hosts? Third, we review transmission containment. From our study of transmission dynamics, we identify transmission control points for preventing and controlling infectious diseases. We will use these control points to guide the development of appropriate control measures. This process helps us to evaluate the success or failure of our control measures.

2. Transmission mechanisms

2.1. Chain model of infectious diseases

The Chain Model of infectious diseases contains the key components that must be "linked" in order for an infection to occur. (Figure 2). First, there is a *susceptible host*. Second, there is a *microbial agent* capable of adhering, entering, infecting, and causing disease in the susceptible host. In its natural settings, the microbial agent multiplies and survives in a *reservoir*. The *source* is where the microbial agent is when it is transmitted to the susceptible host. The reservoir can also be a source of infection. The *portal of exit* is how the agent exits the source. The *mode of transmission* is the mechanism by which the agent is transmitted from the source to the host (e.g., contact, droplet, airborne, etc.). And the *portal of entry* is how the agent enters the susceptible host (e.g., respiratory tract, gastrointestinal tract, genitourinary tract, skin). For example, enterohemorrhagic *Escherichia coli* (EHEC), most commonly *E. coli* O157:H7, elaborate Shiga toxins that can result in severe human disease, including hemorrhagic colitis and hemolytic uremic syndrome [2]. Cattle are the major reservoir for EHEC; up to 5% can be asymptomatic excetors of the organism. The source of infection for humans can be ingestion of contaminated foods or water, but also can be direct contact with colonized cattle or their environment. The most commonly recognized mode of transmission is human ingestion of contaminated ground beef.

Susceptible host. Human host susceptibility is a relative attribute and depends on the condition of host defenses. Host defenses consist of innate immunity and acquired immunity. *Innate immunity* consists of nonspecific mechanisms that do not require prior exposure to foreign agents in order to resist or fight invasion of the host by these foreign agents. The first lines of defense are intact skin and mucous membranes, and any breach in these provide a portal of entry. Nonspecific inflammation and phagocytosis[1] provide a second line of innate defense. The other type of host defense is *acquired immunity*, which can be active or passive. Acquired *active* immunity is comprised of

[1] Inflammatory cells (macrophages and granulocytes) fight infection by engulfing microbes.

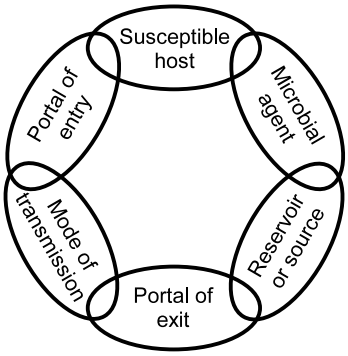

Figure 2: The chain model of infectious diseases

host antibody or cellular immune defense mechanisms that target specific foreign agents based on prior exposure to this or antigenically similar agents. Vaccination is a form of active immunization. Acquired *passive* immunity is when a host receives preformed antibodies that were made in other hosts. Receipt of immune globulin is a form of passive immunization.

Microbial agent. Microbial agents or their toxins can cause human disease. We focus on transmissible agents that are microbes, microbe-like, or their toxins. Microbes are complex, reproducing microorganisms such as viruses, bacteria, parasites, and fungi. Prions are transmissible, self-propagating proteins that can cause disease (usually neurodegenerative diseases called spongiform encephalopathies). With respect to terminology, we refer generically to microbes (or microbial agents), a specific agent (e.g., *Clostridium botulinum*), or a microbial toxin (e.g. botulinum toxin). Although we are focusing on the transmission of microbial agents, diseases can also be caused by transmission of non-microbial agents such as chemical toxicants.

Microbial reproduction can occur outside or inside the host. For example, staphylococcal food poisoning occurs when *S. aureus* grows in food substrate and elaborates enterotoxin. Ingestion of preformed enteroxin in food results in clinical symptoms (nausea, vomiting, watery diarrhea) 1 to 6 hours after ingestion [3]. *S. aureus* can also grow inside a host causing a local abcess or causing systemic shock from the elaboration of the toxic shock syndrome toxin. Host injury can occur directly from the invading microbe, from a inflammatory host immune response, or from organ hypoperfusion (septic shock).

Infection and transmission are two sides of the same coin: infection is from the perspective of a susceptible host and transmission is from the perspective of an infectious source. *Infection* is acquisition of a microbe by a host [4] (see Figure 3). *Infectivity* is the probability of infection given exposure to a microbial agent. *Transmission* is the transfer (infection) of a microbe from an infectious source to a host. Transmission can occur within species (intra-species), between species (inter-species), or between the environment and a species. *Transmissibility* is the probability of microbe transfer to a host given contact (exposure). This is also called the *transmission probability*.

Infection can result in several possible states: elimination, commensalism, colonization, persistence, or disease. Microbe *elimination* from the host occurs from physical factors, host flora interference, immune response, or medical therapy. *Commensalism* occurs when a microbe is acquired early in life and becomes part of the normal microbial flora. Commensals do not cause host damage unless there is impaired immunity or altered microbial flora. Infection can result in *colonization*[2] where a microbe is recovered from a non-sterile site at which host damage is not clinically apparent. Colonization is transient and results in either microbe elimination, persistance, or host disease. Infection can result in microbial *persistence* when the microbe is not eliminated from the host and may or may not continue

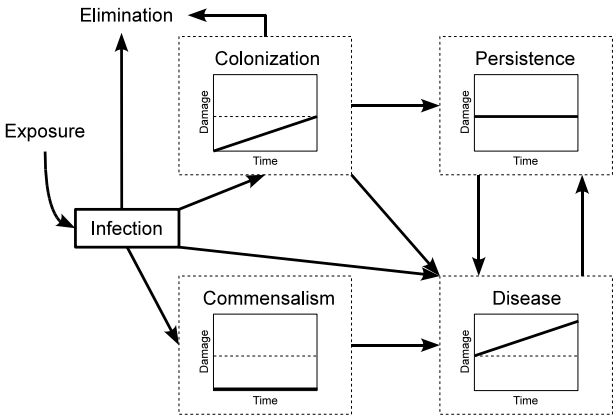

Figure 3: Damage-response framework of microbial pathogenesis: Infection (microbial acquisition by a host) leads to elimination, commensalism, colonization, persistence, or disease. The solid line represents host damage from host-microbe interaction. The dashed line represents the threshold at which the level or quality of host damage leads to persistence or disease. Source: Adapted from [4]

to cause host damage. Chronic hepatitis C infection and latent tuberculosis infection are both examples of persistence.

Disease is a state of infection where the host-microbe interaction results in sufficent host damage to be detectable by diagnostic tests, or to cause clinical symptoms or signs [5]. Disease can occur quickly after infection or can develop from commensalism, colonization, or persistence states. The term *pathogenicity* describes the probability of developing disease given infection. The term *virulence* describes the probability of severe disease, complication, or death given disease. For example, *Neisseria meningitidis* colonizes the human oronasapharynx resulting in a host immune response and eventual elimination. However, pathogenic strains are more likely to invade the bloodstream, causing meningococcemia, and the most virulent strains cause severe meningococcal disease (meningitis or septic shock) and death.

Reservoir. Reservoirs for microbes can be either human, animal, or environmental. Generally, the reservoir contains nutritional substrate to support microbial growth. Bacteria that sporulate are an exception; for example, *Bacillus* and *Clostridium* species can survive extreme conditions as spores, and only germinate into a vegetative form when conditions are favorable. To control an infectious disease, we must know the primary reservoir(s). For some infectious diseases, human are the only reservoir: polio, hepatitis A (B and C), measles, mumps, rubella, varicella, smallpox (before eradication[3]), and malaria. In large part, smallpox was eradicated from the human species because humans were the only reservoir—this is a necessary, but not sufficient, condition for successful eradication [6]. Other necessary conditions for eradication include that the microbial agent is not part of the normal human flora, and that effective prevention measures exist (e.g., vaccination).

[2] Colonization is synonymous with a "carrier" state.

[3] Eradication is defined as the extinction of the causative agent in man as well as in nature, leading to the cessation of all control measure including vaccination [6].

Table 2: Chain Model of Infectious Diseases—Reservoirs

1. Human
   (a) Symptomatic illness
   (b) Carriers
   (c) Asymptomatic (no illness during infection)
   (d) Incubatory (pre-illness)
   (e) Convalescent (post-illness recovery)
   (f) Chronic (persistent infection)
2. Animal (zoonoses)
3. Environment

In contrast, the eradication of human infectious diseases is very unlikely when animals are the primary reservoir for the microbial agent. Examples of human infectious diseases for which animals are the primary reservoir include West Nile virus disease (West Nile virus in migratory birds via mosquito vectors), Lyme disease (*Borrelia burdorferi* in rodents via tick vectors), enterohemorrhagic colitis (bloody diarrhea) and hemolytic-uremic syndrome (*E. coli* O157:H7 in cattle via ingestion), and cryptosporidiosis (*Cryptosporidium parvum* in calves). Human infectious diseases acquired from animals are called zoonoses or zoonotic infections. Several of the potential bioterrorism agents naturally cause zoonotic infections including *Yersinia pestis* (plague), *Bacillus anthracis* (anthrax), *Francisella tularensis* (tularemia), and *Brucella species* (brucellosis). In general, these microbes are well adapted to their animal reservoir, growing inside their hosts, and being efficiently transmitted between animal hosts. When a zoonotic disease occurs in humans, the agent is often not adapted to the human host and sustained human-to-human transmission may not occur. We see this phenomenom with West Nile virus infection, bat and dog-variant rabies, and avian influenza virus—all of which cause human disease, but are then not transmitted efficiently from human to human.

Examples of human infectious diseases for which the environment is the reservoir for the agent include botulism (neurotoxin from *Clostridium botulinum* in soil), tetanus (neurotoxin from *Clostridium tetani* in soil), legionellosis (*Legionella species* in water), Mycobacterium avium complex infections (*Mycobacterium avium complex* in soil and water), coccidioidomycosis (*Coccidioides immitis* in soil and dust), blastomycosis (*Blastomyces dermatitidis* in soil and dust), and aspergillosis (*Aspergillus* fungal species are ubiquitous in the environment). Environmental microbes that are ubiquitous are unavoidable. Many of these microbes are nonpathogenic in the face of a competent host immune system. However, in a severely immunocompromised host, these microbes can be deadly (e.g., *Pneumocystis jirovecii*[4] pneumonia in AIDS patients).

[4]Previously termed *P. carinii* [7]

Source. The source is where the infectious agent survives or reproduces prior to transmission to a host. The source of infection is a primary focus in any investigation of an infectious disease outbreak. However, because the reservoir can serve as the source of infection, understanding microbe reservoirs is necessary to conduct a thorough investigation. Therefore, any reservoir is a potential source (human, animal, environment). A non-reservoir source can be almost anything; the only requirement is that the microbe must survive in or on the source until it is transmitted to the host. In an outbreak investigation, if the known reservoirs or the usual sources are not implicated as the source of the outbreak, then analytic studies may be necessary to identify an unsuspected or new source and redirect the investigation. Only hypotheses that are considered by investigators can be tested in an analytic study. Therefore, if an analytic study does identify a potential source, investigators may need to re-think their current hypotheses or consider new hypotheses (see Case Study 1).

Case Study 1 Postoperative Serratia marcescens wound infections traced to an out-of-hospital source [8]

"From 25 August to 28 September 1994, 7 cardiovascular surgery (CVS) patients at a California hospital acquired postoperative *Serratia marcescens* infections, and 1 died. To identify the outbreak source, a cohort study was done of all 55 adults who underwent CVS at the hospital during the outbreak. Specimens from the hospital environment and from hands of selected staff were cultured. *S. marcescens* isolates were compared using restriction-endonuclease analysis and pulsed-field gel electrophoresis. Several risk factors for *S. marcescens* infection were identified, but hospital and hand cultures were negative. In October, a patient exposed to scrub nurse A (who wore artificial fingernails) and to another nurse—but not to other identified risk factors—became infected with the outbreak strain. Subsequent cultures from nurse A's home identified the strain in a jar of exfoliant cream. Removal of the cream ended the outbreak. *S. marcescens* does not normally colonize human skin, but artificial nails may have facilitated transmission via nurse A's hands."

Portal of exit. When a portal of exit exists, it determines how the infectious agent exits the source/reservoir. The portal of exit for an infectious human or animal is most commonly the respiratory, gastrointestinal or genitourinary tract, or a wound or ulcerative lesion on the skin or mucous membrane. Bloodborne pathogens exit the source through bleeding, phlebotomy, or sometimes genital secretions (e.g., HBV, HIV). When possible, portals of exit should be covered; for example, covering one's mouth and nose when coughing or sneezing, or bandage dressing an oozing skin wound. During the SARS outbreaks, while the respiratory tract was quickly identified as a portal of exit, it was not appreciated that the gastrointestinal tract harbored a large viral load until a single SARS case with diarrhea produced a large outbreak [9].

Table 3: Chain Model of Infectious Diseases—Mode of Transmission

1. Contact
   (a) Direct contact (e.g., touching, kissing, having sex)
   (b) Indirect contact (e.g., intermediate object, fomites)
2. Respiratory droplets (large particles: secrections, cough, sneeze)
3. Airborne (small particles: droplet nuclei, dust)
4. Vehicle-borne (e.g., ingestion, instrumentation, infusion/injection)
5. Vector-borne (e.g., mechanical, biologic)
6. Vertical transmission (e.g., in utero, at birth, breast milk)

Mode of tranmission. The mode of transmission is the mechanism by which the microbial agent gets from the source to the susceptible host (Table 3). Microbes can be transmitted from the source to the host by contact, respiratory droplet, airborne, vehicle-borne, or vector-borne routes.

Contact transmission occurs from direct physical contact with a source (e.g., touching, kissing, having sex), indirect contact with a contaminated intermediate object (e.g., environmental surfaces, fomites), or vertical transmission from mother to child before, during, or after birth. The vehicle-borne category includes ingestion of contaminated food or water, instrumentation (e.g., urinary catheter), injection (including injection drug use), and infusion (e.g., intravenous catheter). Vector-borne transmission can be biologic (vector feeding on the host) or mechanical (contaminated fly appendage contaminating a food item).

Droplet transmission occurs via large droplets ($>$ 10 microns) and secretions generated from the respiratory tract during coughing, sneezing, or talking. These droplets can directly enter the eyes, nose, or mouth, or indirectly by self inoculation by contaminated hands. Large respiratory droplets settle to the ground and environmental surfaces; however, smaller droplets (6–10 microns) may be suspended briefly (for several minutes), and inhaled into the proximal respiratory tract of the host [10].

Airborne transmission occurs when microbes are suspended in air on droplet nuclei ($<$ 5 microns) or dust, and can be transmitted over long distances and time intervals. Suspended droplet nuclei can be inhaled deep into the lungs. Airborne transmission can be obligate, preferential, or opportunistic [11]. *Obligate airborne* transmission occurs with microbes (e.g., *Mycobacterium tuberculosis*) that, under natural conditions, can only infect a host when aerosols are inhaled deep into the lung. *Preferential airborne* transmission occurs with microbes (e.g., measles virus) that predominantly infect a host by deposition of droplet nuclei in distal airways, but can also infect via other modes such as droplet transmission. *Opportunistic airborne* transmission occurs when a microbe infects a host predominantly by non-airborne modes but, under the right host or environmental conditions, can also infect via aerosolization. Opportunistic airborne transmission explained some of the "super spreading" events observed with the SARS outbreaks [12, 13].

Some microbes can be transmitted via multiple modes. Shigellosis, an extremely infectious bacterial gastroenteritis of humans, is an example. *Shigella* is generally described as being transmitted via the "fecal-oral" route. However, this description is insufficient to design control measures because it only summarizes the portals of exit and entry. More specifically, the modes of transmission include direct contact (person-to-person physical contact, including sexual), indirect contact (contaminated fomites), and vehicle-borne (ingestion of contaminated food or water). Therefore, understanding *all* the modes of transmission is necessary to implement preventive measures, to conduct an outbreak investigation, and to implement control measures during an outbreak.

Portal of entry. The portal of entry is where the infectious agent enters the host. Possible portals of entry include the following:

- Mucous membrane surfaces
  - Nose, mouth, oropharynx
  - Gastrointestinal tract
  - Genitourinary tract
  - Respiratory tract
  - Anorectum
- Cutaneous (or percutaneous)[5]

Practical application. Understanding the chain model of infectious diseases is essential for implementing common sense infection control and worker safety measures. For example, agents transmitted primarily by large repiratory droplets and secretions include influenza virus, *Neisseria meningitidis* (meningococcal disease), *Yersinia pestis* (pneumonic plague), and *Variola virus* (smallpox).[6] Large respiratory droplets fall out of the air, settling close to the source (usually within 3 feet). Therefore, common sense transmission control measures for these communicable agents include: having the infectious case cover the portal of exit ("respiratory hygiene" and "cough etiquette"); having the susceptible host use barrier methods to cover portals of entry (face mask, goggles); having the infectious case and susceptible host disinfect their hands ("hand hygiene"); and having the susceptible host increase their awareness of touching their face, mouth, nose and eyes with their hands ("hand awareness"). Hand awareness may reduce self inoculation from hands that have had contact with infectious patients or contaminated environmental surfaces.

Respiratory airborne agents transmitted by droplet nuclei include measles and varicella viruses, and *Mycobacterium tuberculosis*. Droplet nuclei remain suspended in the air for longer periods of time and can travel over distances. Reducing the risk of airborne transmission requires diluting and/or filtering air. Air can be diluted by increasing ventilation (opening the

[5] Skin or skin penetration

[6] Historically, small proportion of patients aerosolized the virus.

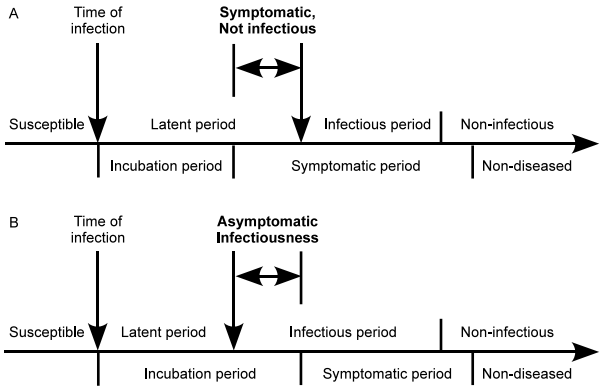

Figure 4: The Natural History of Infection and Infectiousness: A: When the latent period is longer than the incubation period, an infected person develops symptoms before becoming infectious. B: when the latent period is shorter than the incubation period, the infected person becomes infectious before developing symptoms (asymptomatic infectiousness).

windows), and it can be filtered by wearing a personal respirator. The common N-95 respirator is a snug-fitting face mask that filters air by the negative pressure generated by normal inspiration. To work properly, these respirators must be fitted and tested with the intended user. A higher level of protective, but much more expensive, alternative is wearing a powered air-purifying respirator (PAPR) hood. Preventing the spread of droplet nuclei to distant areas in a given facility can be achieved by implementing engineering controls that might include a negative pressure room for the infectious patient and assuring that any potentially recirculated air undergoes high efficiency particulate air (HEPA) filtration. Hospital and community infection control practices are derived from these basic concepts. We now understand the conceptual basis for contact, droplet, and airborne precautions in infection control practices [14].

2.2. *Natural history of infection and infectiousness*

To effectively interrupt transmission we also need to understand the natural history of infection, infectiousness, and disease and how they relate to each other. While clinicians focus on curing diseases and relieving symptoms, in public health we focus on understanding the dynamics of infection and infectiousness in order to prevent transmission (Figure 4). From the time a susceptible person is infected until he or she develops symptoms is called the *incubation period*. Clinicians are familiar with the incubation period because it helps them narrow their differential diagnosis when the causative agent is unknown. From the time a susceptible person becomes infected until he or she becomes infectious is called the *latent period*. The latent period is followed by the infectious period. The infectious period ends because the patient has cleared the infection or has died. When the latent period is longer than the incubation period, an infected person develops symptoms before becoming infectious. However, when the latent period is shorter than the incubation period, the infected person becomes infectious before developing symptoms (asymptomatic infectiousness).

Asymptomatic infectiousness. Asymptomatic infectiousness is the important driver of several infectious diseases with a large public health impact. For example, HIV infection is transmitted by direct person to person contact via blood or genital fluids. In the absence of any treatment, HIV-infected persons are infectious for a median of 10 years before developing symptoms of AIDS [15]. Hence, HIV-infected persons are potentially infecting many people (by sex or sharing injection drug use paraphenelia) for years before knowing they are infected. Likewise, many hepatitis C virus (HCV) infected persons can be infectious decades before developing symptoms that lead to a diagnosis of chronic HCV infection [16]. Persons with hepatitis A, measles, and influenza infection are infectious about 1 week, 3–4 days, and 1–2 days before developing symptoms, respectively [17]. Identifying exposed contacts can be more difficult when the exposure occurred before the infectious source developed symptoms, especially if the exposure occurred years before.

In contrast, with smallpox (when it existed), the latent period was longer than the incubation period, therefore patients developed symptoms (e.g., high fevers, muscle aches) before becoming infectious. In fact, patients with smallpox were most infectious after the rash onset. This made detection and isolation of cases and contact tracing and vaccination an effective disease control strategy. Likewise, patients infected with the human SARS coronavirus were infectious after developing respiratory symptoms and were progressively more infectious as their disease worsened. Hence, most secondary infections occurred among health care workers and close household contacts caring for very ill persons. This also helped to explain why transmission of SARS in the community was not sustained [18].

2.3. *Convergence model of microbe-human interaction*

In March, 2003, the "Convergence model of human-microbe interaction" was published by the Institute of Medicine (IOM), Committee on Emerging Microbial Threats to Health in the 21st Century [19]:

> The convergence of any number of factors can create an environment in which infectious diseases can emerge and become rooted in society. A model was developed to illustrate how the convergence of factors in four domains impacts the human-microbe interaction and results in infectious disease (Figure 5). . . . The emergence and spread of microbial threats are driven by a complex set of factors, the convergence of which can lead to consequences of disease much greater than any single factor might suggest. Genetic and biological factors allow microbes to adapt and change, and can make humans more or less susceptible to infections. Changes in the physical environment can impact on the ecology of vectors and animal reservoirs, the transmissibility of microbes, and the activities of humans that expose them to certain threats. Human behavior, both individual and collective, is perhaps the

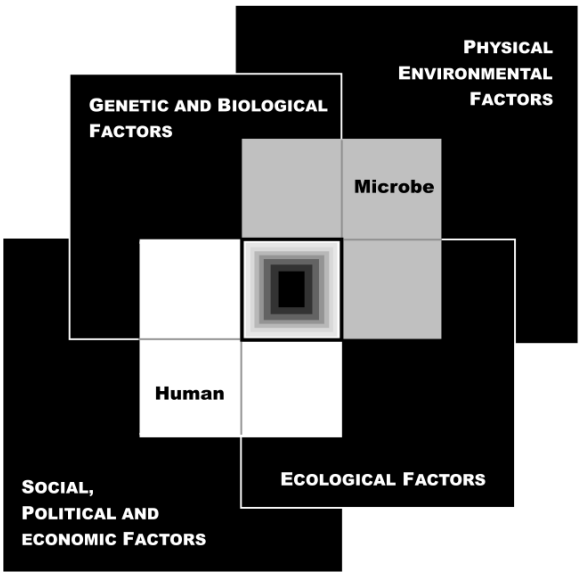

Figure 5: Convergence model of human-microbe interaction. At the center of the model is a box representing the convergence of factors leading to the emergence of an infectious disease. The interior of the box is a gradient flowing from white to black; the white outer edges represent what is known about the factors in emergence, and the black center represents the unknown. Interlocking with the center box are the two focal players in a microbial threat to health—the human and the microbe. The microbe-host interaction is influenced by the interlocking four domains of the determinants of the emergence of infection [19].

> most complex factor in the emergence of disease. Emergence is especially complicated by social, political, and economic factors—including the development of megacities, the disruption of global ecosystems, the expansion of international travel and commerce, and poverty—which ensure that infectious diseases will continue to plague us. Today we also face the threats of intentionally introduced biological agents.

Epidemiologists can think of this model as an updated version of the agent-host-environment model of infectious disease causation, also referred to as the "epidemiologic triad" [20]. However, the Convergence model provides important detail. More specifically, the IOM Committee considered the following individual factors as major contributors to the emergence and re-emergence of microbial threats to health:

- Microbial adaptation and change;
- Human susceptibility to infection;
- Climate and weather;
- Changing ecosystems;
- Economic development and land use;
- Human demographics and behavior;
- Technology and industry;
- International travel and commerce;
- Breakdown of public health measures;
- Poverty and social inequality;
- War and famine;
- Lack of political will; and

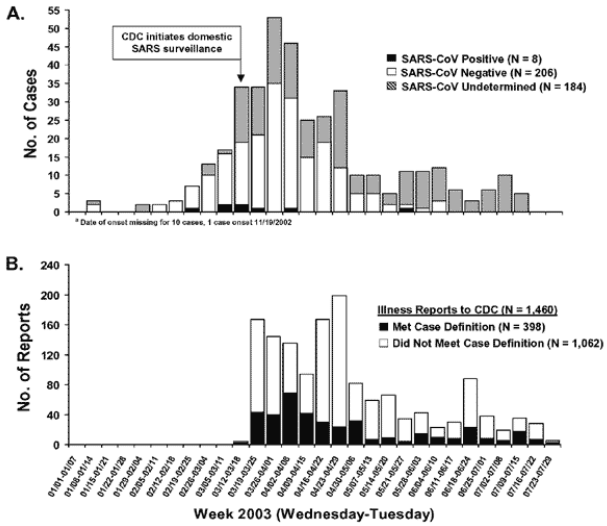

Figure 6: Probable cases of severe acute respiratory syndrome, by reported source of infection—Singapore, February 25–April 30, 2003. Source: CDC [22]

- Intent to harm.

Through this integrated approach, we are reminded that causes can be complex, interrelated, and interdependent. The success or failure of our infectious disease prevention and control programs may depend on these factors, and how they interact. The current epidemic of highly pathogenic H5N1 avian influenza and the imminent threat of human pandemic influenza highlight the Convergence model [19, 21].

3. Transmission dynamics

Transmission dynamics is the population-level view of transmission of microbial agents with the occurrence of infectious disease cases. We cover the reproductive number, the infection rate among susceptibles, and the generation time.

3.1. The reproductive number

To understand the reproductive number it helps to adopt the perspective of a microbial agent that has infected and produced an infectious human case. In order for a communicable microbial agent to survive among humans, it must produce (directly or indirectly), on average, at least one other infectious human case. This is the only way microbes can survive in a host population. The reproductive number is the average number of secondary infectious cases produced by cases during their infectious periods. If $R < 1$, the number of new cases will decline and eventually go to zero. If $R \approx 1$, the production of new cases will assume a steady state. If $R > 1$, the number of new cases will increase (growing epidemic). The SARS outbreak in Singapore, 2003, illustrates this general process (Figure 6).

Under different host population conditions, the reproductive number gives us different insights. We will consider the reproductive number under two primary scenarios: when an infection is introduced into a population (at time $t = 0$) and as

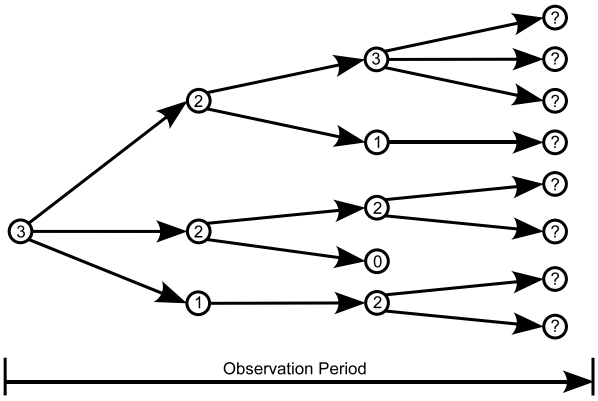

Figure 7: The reproductive number is the average number of secondary cases produced by infectious cases during their infectious periods. Each circle represents an infectious case, and the circle contains the number of secondary cases he or she produced. For example, the first case (at the far left) produced 3 secondary infectious cases, and so forth. Therefore, to calculate the average reproductive number, calculate the arithmetic average of the number of secondary cases: $(3+2+2+1+3+1+2+0+2)/9 = 1.8$.

an epidemic evolves ($t > 0$). Two key factors affect how an epidemic (and R) evolves: the fraction of the population that is susceptible, and the presence and level of control measures. Under different scenarios, we will cover the basic reproductive number (R_0), the effective reproductive number (R), and the control reproductive number (R_C). Figure 7 illustrates how the reproductive number is calculated.

3.1.1. Basic reproductive number (R_0)

If an infectious case were introduced into a population ($t = 0$), we would like to know the inherent potential for this case to cause an epidemic. To do this, we pose the following question: If a single infectious case[7] was introduced into a completely susceptible population with no control measures, how many secondary infectious cases would be produced, on average? This is called the basic reproductive number (R_0).[8] The basic reproductive number allows us to compare different microbial agents for their potential to cause epidemics in a population. More importantly, understanding the components that determine R_0 is necessary to designing and implementing control strategies.

$$R_0 = dcp \tag{1}$$

In Equation 1 (from the perspective of an infectious case), d is the duration of infectiousness, c is the contact rate with susceptible hosts, and p is the transmission probability—the probability of infecting a susceptible host when contact occurs. By "source," we are usually thinking of an infectious human case; however, it could be an infectious mosquito or a contaminated blood product used for transfusion. For each microbial agent and infectious disease, "contact" and "transmission" need

[7] Also called "infective."

[8] R_0 is pronounced "R naught" or "R zero"

Table 4: Estimated per-act risk (Transmission probability) for acquisition of HIV, by exposure route to an infected source. Source: CDC [25]

Exposure route	Risk per 10,000 exposures
Blood transfusion	9,000
Needle-sharing injection-drug use	67
Receptive anal intercourse	50
Percutaneous needle stick	30
Receptive penile-vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive penile-vaginal intercourse	5
Receptive oral intercourse on penis	1
Insertive oral intercourse with penis	0.5

to be defined carefully. Contact is an exposure episode. For example, for an HIV-infected man, contact might be defined as unprotected, insertive intercourse with another person. For a microbial agent, we generally define transmission to mean sufficient transfer of the agent to lead to an infection (pathological persistence in host, subclinical injury to host, or evidence of a host immune response). For example, transmission of hepatitis C virus can result in HCV infection (pathological persistence in blood), subclinical injury (liver inflammation with or without scarring), or presence of anti-HCV antibodies (evidence of a host immune response). Therefore, the operational definition of transmission probability will vary depending on the microbial agent and the outcomes under consideration.

Understanding the transmission probability can be less intuitive. Consider sexual transmission of HIV infection. Before the era of anti-retroviral therapy, the median time from infection to the development of AIDS was 10 years [23]. Therefore, the median duration of infectiousness was well over 10 years because even patients with advanced HIV disease could remain sexually active. The contact rate of HIV-infected patients with potentially susceptible hosts was measured through confidential surveys [24]. The transmission probability—the per act risk of an HIV-infected patient transmitting HIV to a susceptible sexual partner—has been studied extensively and the results are summarized in Table 4. In general, the per sexual act HIV transmission risk is very low. For example, the average risk of a woman contracting HIV infection from an infected man after having a single episode of unprotected penile-vaginal intercourse would be 10 in 10,000 (1 in 1,000). Therefore, R_0 for HIV transmission would be determined primarily from the duration of infectiousness and the contact rate.

Another familiar example of transmission probability is the secondary attack "rate" (really a risk) among susceptible household contacts who are exposed to an infectious index case. Secondary attack risks are usually estimated for infections that can be transmitted through household contact, such as tuberculosis, measles, chickenpox, influenza, and viral gastroenteritis.

In spite of the importance of R_0, it is difficult to measure empirically. This is because the necessary conditions—an index infectious case being introduced into a completely suscepti-

ble population without control measures—rarely occurs except when a novel microbial agent is introduced and spreads before it has been identified. For example, when HIV infection was introduced into San Francisco's gay male community in the late 1970s and early 1980s, these conditions were met. Similarly, the uncontrolled transmission of HCV among injections drug users before the availability of anti-HCV antibody testing is another of these rare occurrences in which R_0 can be measured. Another situation in which the necessary conditions for measuring R_0 were met occurred when the human SARS-coronavirus was introduced into several countries (China, Canada, Singapore, Taiwan, Viet Nam, etc.) causing outbreaks before the agent of SARS was identified.

3.1.2. Effective reproductive number (R)

The R_0 represents the inherent potential for an agent to cause an epidemic after the introduction of an infectous case into a population. However, the actual or effective reproductive number (R) after the introduction of an infectious cases into a population (still without control measures) would be a function of the basic reproductive number (R_0) and the fraction of the population (x) that is susceptible upon the introduction ($t = 0$) of the infectious case (Equation 2). If $x = 1$ (completely susceptible population), then $R = R_0$.

$$R = R_0 x \tag{2}$$

3.1.3. Control reproductive number (R_C)

From Equation 2, it is apparent that we could prevent an epidemic ($R < 1$) by sufficiently reducing x by some control measure. In this case, the effective reproductive number in the presence of control measures is called the control reproductive number (R_C) [26]. If the fraction susceptible, x, gets small enough, eventually R_C becomes less than 1. Therefore, decreasing the fraction of susceptibles is a proven strategy to get $R_C < 1$: we usually achieve this by vaccination.

The effect of vaccination:. If vaccination is our control measure, then $x = 1 - hf$, where f is the fraction of the population that has been vaccinated (*vaccine coverage*), and h is the fraction of those vaccinated that have complete protection (*vaccine efficacy*[9]). For a well-studied, vaccine-preventable disease, the basic reproductive number and vaccine efficacy are known. Armed with these data, and using simple algebra, we can estimate what fraction of the population would need to be vaccinated to bring $R_C < 1$. In other words, $R_C = R_0(1 - hf) < 1$ becomes

$$f > \frac{1 - (1/R_0)}{h}, \tag{3}$$

where f is the minimum vaccine coverage necessary to get $R_C < 1$.

For example, R_0 was between 3 and 5 for smallpox. The smallpox vaccine had a pre-exposure vaccine efficacy of about 98%. Therefore, if smallpox were re-introduced into the human population and spread naturally, then we would need to vaccinate at least 68% of the population if $R_0 \approx 3$, and at least 82% of the population if $R_0 \approx 5$, to get $R_C < 1$.

Table 5: Basic reproductive number for selected vaccine-preventable diseases

Disease	R_0
Measles	12–18
Pertussis	12–17
Diphtheria	6–7
Smallpox	5–7
Polio	5–7
Rubella	5–7
Mumps	4–7
HIV/AIDS	2–5
SARS	2–5
Influenza A (1918 H1N1)	2–3

Displayed in Table 5 are various R_0 values and vaccine coverage thresholds (f) for selected vaccine-preventable diseases [28]. This information is useful in several ways. First, we can use R_0 to compare the communicability of these infectious diseases. Notice that the R_0 for smallpox is much smaller than the R_0 for, say, measles. The differences in R_0 are primarily explained by the transmission mechanisms (p. 2). Smallpox was primarily transmitted by large respiratory droplets, and patients were not infectious until they developed a rash (that is, there was little to no asymptomatic infectiousness). In contrast, measles is spread by the airborne mode, and an infected person is infectious before the onset of the rash. As a result, measles is much more infectious than smallpox. Second, notice that an effective control measure (in this case, vaccination) does not need to be applied to the whole susceptible population to be successful; it only needs to be implemented sufficiently to make $R_C < 1$, although in public health practice we strive to protect as many people as is feasible and affordable.

Figure 9 displays a real-world example of these concepts—both R_0 and R_C [29]. On February 23, 2003, SARS was introduced into Toronto, Canada, and followed by two epidemic curves representing hospital outbreaks. In March, the early part of the first curve 1 rises rapidly and its slope approximates R_0: the average number of secondary cases when an index case was introduced into a completely susceptible population and without control measures. Once the outbreak was recognized and control measures were implemented, the epidemic curve peaked and returned to baseline approximately mid-to-late April. However, lulled by the disappearance of cases, infection control practices were relaxed and SARS was re-introduced in early May. Infection control measures were immediately re-instituted and we can see the subsequent "blunting of the curve" in late May. In this second curve, the initial slope was less steep and it approximates R_C. Therefore, in this completely susceptible population, the initial slope in the first curve measures R_0, the average number of secondary cases in the absence of control measures, and the initial slope in the second curve measures R_C, the average number of secondary cases in the presence of

[9] This is a simplification but serves our purposes. For a complete discussion, see Halloran [27].

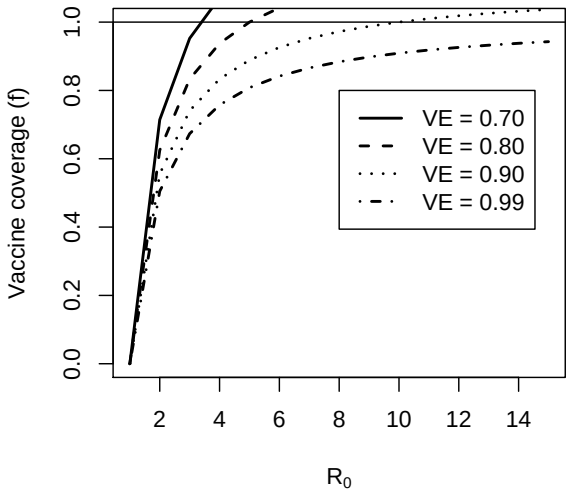

Figure 8: The vaccine coverage (f) required to get the control reproductive number ($R_C < 1$) given the basic reproductive number (R_0) and vaccine effectiveness (h). For a high effective vaccine or low R_0, only a proportion of the population needs to gets vaccinated to get $R_C < 1$. This is a general property of interventions: they need to reach a sufficient proportion of the population to get $R_C < 1$

control measures.

3.1.4. Reproductive number changes with time ($t > 0$)

So far, we have considered the reproductive number upon the introduction of an infectious case into a population. However, as an epidemic evolves over time ($t > 0$), the average number of secondary cases changes. As a function of time (t), the effective reproductive number is denoted by $R(t)$, and the control reproductive number is denoted by $R_C(t)$.

For illustration, we simulated a smallpox outbreak where an infectious case of smallpox was introduced into a closed population of 10,000 susceptible people under four different scenarios (Figure 10). Curve A1 is the epidemic curve of prevalent smallpox cases in the absence of control measures. Curve B1 is the corresponding curve for the effective reproductive number,

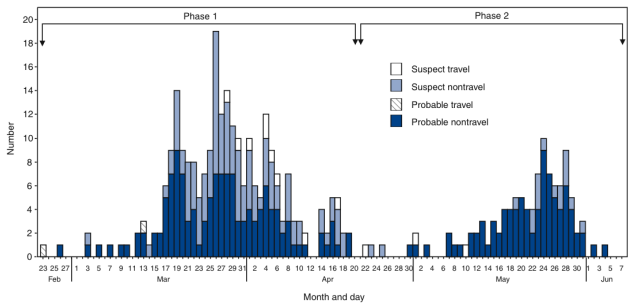

Figure 9: Number of reported cases of severe acute respiratory syndrome ($N = 361$), by classification and date of illness onset—Ontario, February 23–June 7, 2003. Source: CDC [29]

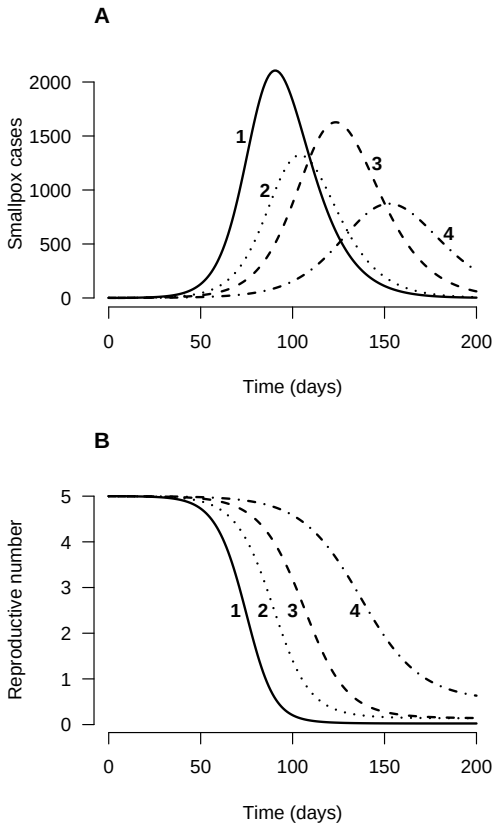

Figure 10: Simulated smallpox outbreak after introducing a single infectious case into a susceptible population of 10,000. Incubation period was 12 days, duration of infectiousness was 10 days, and $R_0 = 5$. Top curve (A) displays the prevalent cases, and bottom curve (B) displays the effective reproductive numbers. Curves A1 and B1 are without control measures. Curves A2 and B2 display the effect of vaccinating 70% of susceptibles. Curves A3 and B3 display the effect of case isolation, reducing the effective duration of infectiousness from 10 days to 7 days. Curves A4 and B4 display the effect of both control measures. Curves B2, B3, and B4 display the control reproductive number (R_C).

calculated from $R(t) = R_0 x(t)$. R_0 drives the initial exponential increase in Curve A1. Even in the absence of control measures, the epidemic curve peaks and the number of prevalent cases declines. In a closed population, this happens because the supply of susceptible hosts is depleted (and $x(t)$ decreases). This also happens with infections, such as influenza, that move rapidly through open communities. Notice that the effective reproductive number changes with time (Curve B1). The effective reproductive number is a dynamic number and, in this case, eventually drops below 1, and the epidemic burns out. Even in the absence of control measures, the natural transmission dynamics of an epidemic may lead to extinction of the disease ($R(t) < 1$); particularly in a closed (or approximately closed) population.

In Figure 10, Curves A2, A3, and A4 are the epidemic smallpox curves in the presence of control interventions. Curves B2, B3, and B4 are the corresponding $R_C(t)$s. Notice that the effect of control measures is to shift and blunt the epidemic curve. Our goal in communicable disease control is to blunt the epidemic curve (representing occurrence of fewer cases) *and* get $R_C(t) < 1$ so that the epidemic burns out. The effects of early control measures on an outbreak curve can also be seen in Figure 9.

As an epidemic spreads, susceptibles are infected and become infectious (known as "infectives"). Eventually, infectives are "removed" from the infectious state; they

- become noninfectious and immune;
- become noninfectious and not immune (susceptible again); or
- die.

For a closed population (no migration in or out) where infectives either die or become noninfectious with immunity, the number of susceptibles declines even in the absence of control measures. For an epidemic that moves rapidly through the population, the number of susceptibles also declines, even if the population is open. When the number of susceptibles declines, even in the absence of control measures, the average number of secondary cases produced by infectious cases also declines with time. In other words, the effective reproductive number ($R(t)$) actually changes over time:

- If $R(t)$ persists above 1, the epidemic continues to grow.
- If $R(t)$ persists around 1, the infection becomes endemic.
- If $R(t)$ persists below 1, the infection becomes extinct.

In summary, when an infectious case is introduced into a population ($t = 0$), the basic reproductive number (R_0) represents the inherent epidemic potential when the population is completely susceptible and there are no control measures. When a fraction x of the population is susceptible, the effective reproductive number (R) represents the actual epidemic potential where $R = R_0 x$. In the presence of control measures, R becomes R_C. If $R > 1$ at $t = 0$, an epidemic occurs; however, both $R(t)$ and $R_C(t)$ will change as the epidemic evolves over time ($t > 0$). The difference between $R(t)$ and $R_C(t)$ represents the impact of control measures. We see this in Figure 10. Consequently, using this approach, a logical goal of control measures is to (1) delay the outbreak peak, (2) decrease the magnitude of the outbreak peak, and (3) reduce the total number of infectious disease cases [30].

3.2. Infection rate among susceptibles

Understanding the components of the reproductive number focused our attention on key transmission control points, including duration of infectiousness, contact rate, transmission probability, and fraction of the population that is susceptible. However, to complete the picture we must consider the transmission process from the perspective of a susceptible host.

In epidemiology, the infection rate among susceptibles is the number of new infections divided by the person-time at risk. However, it's more instructive to consider the components of infection (Equation 4) with the following questions: First, what is the contact rate (c) with a potentially infectious source? Second, what is the probability that the potential source is infectious ($P(t)$)? And third, what is the transmission probability (p) given contact with an infectious source?

$$I(t) = cpP(t) \tag{4}$$

This perspective introduces an important new parameter to consider—the probability the potential source is infectious, $P(t)$. The contact rate is driven by behavior, the probability a potential source is an infectious case is driven by the prevalence of infectious cases, and the transmission probability is driven by biology and behavior.

3.2.1. Contact rate

The infection rate among susceptibles, $I(t)$, is a common and important epidemiologic measure of occurrence. Understanding the underlying components not only gives insights into the population level processes, but also helps us to develop and refine research questions, and to incorporate new research findings. Consider, for example, sexual contact rates among men who have sex with men (MSM). HIV researchers have hypothesized that selection of sexual partners (sexual mixing) in the MSM community is not random. In fact, sexual mixing is heterogeneous, with selection being influenced by age and HIV serological status. Older men (who are more likely to be infected) tend to select younger men (who are less likely to be infected). Known HIV-positive men tend to select known HIV-positive partners, and known HIV-negative men tend to select known HIV-negative partners. This has been called "serological sorting." At a population level, for a given contact rate, age sorting can result in more new infections, and serological sorting can result in fewer new infections. We can appreciate that these new research findings must act through the contact rate parameter.

3.2.2. Probability a source is infectious

A first approximation of $P(t)$ is the prevalence of infectious cases circulating in the target community. For example, in San Francisco in the mid-1980s, an MSM who randomly selected a

sexual partner from the MSM community had an approximate 50% chance of selecting an HIV-infected sexual partner [31]. That is, P was approximately 0.5. These components (contact rate (c), transmission probability (p), and prevalence (P)) act together to cause an increase or decrease in the infection rate, $I(t)$. Knowing individual parameters is not sufficient to predict infection rates. For example, if the contact rate was very high (e.g., high rates of unprotected anal intercourse), but the prevalence of HIV-infection was zero, the infection rate would still be zero. HIV transmission prevention efforts have focused on affecting the contact rate and the transmission probability.

Blood banks prevent the transmission of bloodborne pathogens, such as HIV, HBV, and HCV, by donor deferral and screening blood to reduce the prevalence of contaminated blood units, P. The transmission probability (p)—the risk of infection after receiving a contaminated unit—is close to 1, and not amenable to post-exposure interventions to reduce the risk. Reducing the contact rate (i.e., blood transfusions) has limited effectiveness because, for many patients, blood transfusions are medically indicated and life-saving. Hence, an effective prevention strategy targets lowering the prevalence of contaminated units. The prevalence largely determines the per blood unit risk, and this risk has continued to decline as better methods for blood screening are developed and implemented [32].

3.2.3. Transmission probability

The transmission probability (p) is the risk of infection given contact to an infectious case. The transmission probability is determined by

- Susceptibility of the uninfected host;
- Infectiousness of the source; and
- Interruption of transmission (by physical, chemical, engineering, or environmental methods).

For an HIV-uninfected person, an ulcerative sexually transmitted disease increases their susceptibility to HIV infection. For an HIV-infected person, anti-viral therapy may reduce their infectiousness by reducing the blood and seminal/vaginal fluid viral load. Finally, condoms can interrupt HIV transmission.

3.3. Generation time

Generation (or serial time) is the average time between the onset of symptoms in a given infectious individual and the onset of symptoms in individuals that person has infected. Communicable diseases with shorter generation times require more rapid detection and implementation of control measures. For example, the generation time of influenza cases is about 3 days [33]. During human pandemic influenza, this leaves little time to effectively identify, contact, and quarantine exposed persons. In contrast, the generation time of hepatitis A cases is measured in weeks, leaving more time to identify exposed persons and administer post-exposure immune globulin.

Table 6: Transmission control points and control strategies

Control points	Control strategies
Contact rate (c)	1. Reduce contact rate
Probability potential source is infectious (P)	2. Reduce probability potential source is infectious
Duration of infectiousness (d)	See #3
Transmission probability (p)	3. Reduce infectiousness
	4. Interrupt transmission
	5. Reduce susceptibility
Fraction susceptible in population (x)	6. Reduce fraction susceptible

4. Transmission containment

Designing and implementing transmission containment interventions involves three steps:

1. Identify control points;
2. Derive control strategies; and
3. Design and implementing control measures.

4.1. Control points

From Equations 1 (p. 8), 2 (p. 9), and 4 (p. 11), we have identified five transmission control points. All infectious diseases act through these control points. Therefore, the success or failure of our disease control interventions is ultimately explained by their impact on these five control points:

1. Contact rate (c);
2. Probability potential source is infectious (P);
3. Duration of infectiousness (d);
4. Transmission probability (p); and
5. Fraction of population that is susceptible (x)

4.2. Control strategies

Now we can develop a comprehensive prevention and control strategy that always makes sense. Using this approach, we derive six control strategies (Table 6). These six strategies map back onto the five control points. Here are the six essential contral strategies in more detail:

1. Reduce contact between susceptibles and potential infectives
2. Reduce probability potential sources are infectious
3. Reduce biological susceptibility of susceptibles
4. Reduce biological infectiousness of infectives
5. Interrupt transmission between infectious source and susceptible host

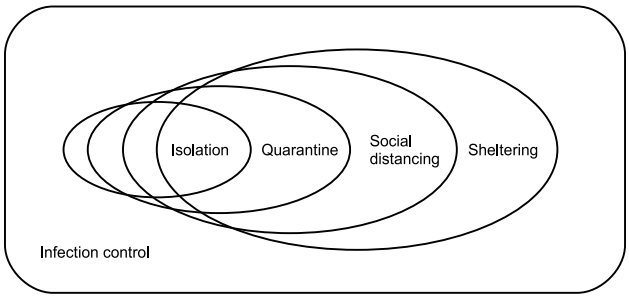

Figure 11: Summary of community mitigation measures. Isolation measures are applied to infectious cases. Quarantine measures are applied to exposed persons who may be in their incubation period yet infectious (i.e., past their latent period). Sheltering measures apply to persons or communities who have not been exposed. Social distancing measures apply to persons who are mixing or potentially mixing and whose exposure and infectious status may be unknown. All these measures require different levels of competence in infection control practices. Source: Adapted from [35].

6. Reduce fraction susceptible

It is important to consider the six strategies together. Failure to do so can result in unintended adverse effects. For example, suppose we introduce an HIV vaccine with a low efficacy. Although this will decrease the fraction of susceptibles, if the vaccination provides vaccinees with a false sense of protection and they increase their high risk behavior (i.e., increase the contact rate), then we may actually worsen the epidemic with this intervention [34].

4.3. Control measures

To design infectious disease control measures, we select control measures based on these six strategies (Table 7). Using these control strategies assures that our control measures are comprehensive and make epidemiologic sense. For example, consider the public health and medical response measures for human pandemic influenza (Table 8). Our epidemiologic concepts provide the rationale for these measures, and they provide guidance in the development of specific containment activities. To develop infection control guidelines, we apply concepts from the Chain Model of Infectious Diseases (reservoir, mode of transmission, etc.). Community mitigation measures are designed to reduce the contact rate between potential infectives and susceptibles (Figure 11 and Table 9) at home, school, workplace, and community [30]. Notice that some of these measures can act at multiple levels: finding cases ("case finding") provides data for surveillance, results in case isolation, and can lead to treatment. In turn, case isolation reduces the contact rate, and treatment reduces the magnitude and the duration of infectiousness. Finally, these concepts help us evalute the success or failure of our control measures.

5. Summary

In this review, we covered the epidemiologic concepts for preventing and controlling infectious diseases. We described transmission mechanisms, transmission dynamics, and transmission containment. Under transmission mechanisms, we reviewed the Chain Model of Infectious Diseases, the Natural History of Infection and Infectiousness, and the Convergence Model of Human-Microbe Interaction. Under transmission dynamics, we reviewed the reproductive number, the infection rate among suseceptibles, and the generation time. And under transmission containment, we reviewed control points, control strategies, and control measures.

Understanding of these core concepts helps us prioritize and conduct studies to identify and optimize prevention and control interventions. Clinicians can be informed about their role and how it directly and indirectly contributes to overall containment efforts. Field investigators can be guided to conduct an outbreak investigations using a systematic and comprehensive approach to hypothesis generation and testing. Communicable disease controllers can improve their design, implementation, and evaluation of interventions to control and prevent acute microbial threats as well as endemic infectious diseases. Finally, public health planners can improve the design, testing, and evaluation of their infectious disease emergency operations response plans.

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Table 7: Transmission control strategies and control measures

1. Reduce contact between susceptibles and potential infectives
   (a) Behavior change (host and/or source)
   (b) Case isolation
   (c) Case finding for intervention (e.g., isolation)
   (d) Contact tracing for intervention (e.g., quarantine)
   (e) Quarantine of exposed (individual, community, geographic boundary [Cordon sanitaire])
   (f) Sheltering (e.g., isolation of nonexposed)
   (g) Reduction in the number of infectious sources
   (h) Social distancing (school closures, travel restrictions)
2. Reduce probability potential sources are infectious
   (a) Case finding for intervention (isolation, treatment, etc.)
   (b) Identification and control of infectious sources
   (c) Vaccination
3. Reduce biological susceptibility of susceptibles
   (a) Vaccination (Pre- and post-exposure)
   (b) Immune globulin (Pre- and post-exposure)
   (c) Antimicrobial drug (Pre- and post-exposure)
   (d) Treatment of co-factor (e.g., ulcerative STD)
4. Reduce biological infectiousness of infectives
   (a) Treatment of cases
   (b) Vaccination (Pre- and post-exposure)
5. Interrupt transmission between infectious source and susceptible host, given contact
   (a) Physical and chemical methods (e.g., barriers: masks, goggles, condoms; respirators; hand sanitizers, etc.)
   (b) Engineering controls (e.g., HEPA filters, negative pressure rooms)
   (c) Environmental controls (e.g., disinfection)
6. Increase herd immunity (population-level effects)
   (a) Vaccination, consider the following:
      i. Naturally-acquired immunity
      ii. Fraction vaccinated (vaccine coverage)
      iii. Vaccine efficacy (fraction fully protected)

Table 8: Public health and medical response to pandemic influenza

1. Surveillance and epidemiology
2. Laboratory diagnostics
3. Transmission containment
   (a) Community mitigation measures
      i. Isolation of cases (infectious)
      ii. Quarantine of exposed (potentially infectious)
      iii. Social distancing measures
         A. School closures or suspension of classes
         B. Cancellation of large public gatherings, events, etc.
         C. Travel restrictions (to and from affected areas)
      iv. Sheltering (isolation of non-exposed)
   (b) Vaccine distribution and use
   (c) Antiviral drug distribution and use
4. Environmental and occupational health services
5. Infection control and clinical guidelines
6. Health care services, including mental health, and surge capacity
7. Health communications (media, public, clinicians, health care facilities)

Table 9: Community mitigation strategies for pandemic influenza

Home interventions

- Voluntary isolation of ill at home (adults and children); combine with use of antiviral treatment as available and indicated;
- Voluntary quarantine of household members in homes with ill persons (adults and children); consider combining with antiviral prophylaxis if effective, feasible, and quantities sufficient.

School interventions (child social distancing)

- Dismissal of students from schools and school based activities, and closure of child care programs;
- Reduce out-of-school social contacts and community mixing.

Workplace/Community interventions (adult social distancing)

- Decrease number of social contacts (e.g., encourage teleconferences, alternatives to face-to-face meetings);
- Increase distance between persons (e.g., reduce density in public transit, workplace);
- Modify, postpone, or cancel selected public gatherings to promote social distance (e.g., postpone indoor stadium events, theatre performances);
- Modify workplace schedules and practices (e.g., telework, staggered shifts).

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Diagnosis of viral and bacterial diseases

D.P. KNOWLES, Jr. and J.R. GORHAM *

Summary: The potential contributions of techniques, such as restriction enzyme analysis, nucleic acid detection, the polymerase chain reaction and competitive inhibitive tests, are only beginning to be defined. The extraordinary promise of these procedures has yet to be fully realized.

However, before these techniques are accepted and widely used, they should be shown to have sensitivity and specificity comparable to those of current tests. Finally, they should be safe, easy to conduct and automated to facilitate the study of large numbers of specimens.

KEYWORDS: Biotechnology - Competitive ELISA - DNA probes - ELISA - Monoclonal antibodies - Nucleic acid hybridization - Polymerase chain reaction (PCR) - Restriction enzyme analysis (REA).

Field veterinarians, laboratory diagnosticians and disease control officials will be confronted by new methods of diagnosis. Professionals dealing with infectious diseases will have to become familiar with these techniques. The primary purpose of this review is to point out new research focusing on diagnosis by restriction enzyme analysis (REA) and nucleic acid probes. The polymerase chain reaction (PCR) and production of antigens for diagnostic tests will also be discussed. Monoclonal antibodies and ELISA are widely employed in infectious disease diagnosis. Consequently, their use is more appropriately discussed under specific disease agents in other publications. However, currently a major use of monoclonal antibodies is in competitive inhibition diagnostic tests. These tests will be briefly discussed.

The use of restriction enzyme analysis, nucleic acid probes is relegated to specialized laboratories principally involved in basic research or developing diagnostic tests. Within the next few years, the use of these new techniques for routine diagnosis may no longer be cumbersome and time consuming. The polymerase chain reaction for the *in vitro* amplification of DNA is already being used in a variety of diagnostic applications and has greatly improved the sensitivity of some diagnostic tests.

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DIAGNOSIS BY RESTRICTION ENZYME ANALYSIS (REA)

The commonly employed serological tests to identify viruses are usually not sufficiently sensitive to distinguish closely-related isolates of a virus serotype or a virus mutant. Restriction enzyme analysis (nucleic acid fingerprinting) can detect differences in the genomes of the same virus serotypes (18, 40). If it is desired to map the genome of a DNA virus, the DNA is extracted and clipped into fragments at specific nucleotide sequences. The resultant DNA fragments are then separated in agarose gel by electrophoresis and visualized with ethidium bromide. The fragments are then radiolabeled with complementary DNA (cDNA) tags with phosphorus 32 to determine the difference or similarities in the genomes.

An example for the possible use of REA in epidemiological studies is given in Fig. 1. In this instance it might be employed to determine the differences/similarities in the genomes of three virus isolates. In this way the involvement of a particular isolate and the tracing of an isolate epidemiologically related within a country or between countries should be possible. Tables I and II document the use of REA [the material for these tables was derived from the MEDLINE Database System which is part of MEDLARS (Medical Literature Analysis and Retrieval System), a service of the National Library of Medicine of the United States].

TABLE I

Diagnosis of viral diseases by restriction endonuclease analysis (REA)

Disease	Significant findings	Reference
Aujeszky's disease (Pseudorabies)	The DNAs of 560 field isolates of Aujeszky's disease virus were analyzed by REA to determine the origin of the virus, mode of introduction, variability of the genomes and stability of the marker.	53
Aujeszky's disease	See references.	9, 34, 35, 36, 70, 75, 77, 100
Bovine herpesviruses	5 of 6 sheep isolates and 3 of 4 goat isolates yielded unique restriction patterns that differ from each other by one or more bands. Sheep isolate DNA patterns were different from goat isolate patterns and all restriction endonuclease analysis patterns were similar to the patterns for BHV-1/IBRV, but different from that of BHV-1/IPVV or BHV-6.	104
Bovine herpesvirus-1 (IBR)	Vaccine strains were probably the source of infection in 2 of 6 isolates collected from the field.	103
Bovine herpesvirus-1 (IBR)	Mammary gland isolates had restriction fragment profiles comparable to infectious pustular vulvo-vaginitis and not IBR.	44
Bovine herpesvirus-1 (IBR)	REA in diagnostic and epidemiological studies of bovine herpesvirus-1 is limited to analysis between types and subtypes, and is not applicable for the examination of isolates from within a BHV-1 subtype.	105

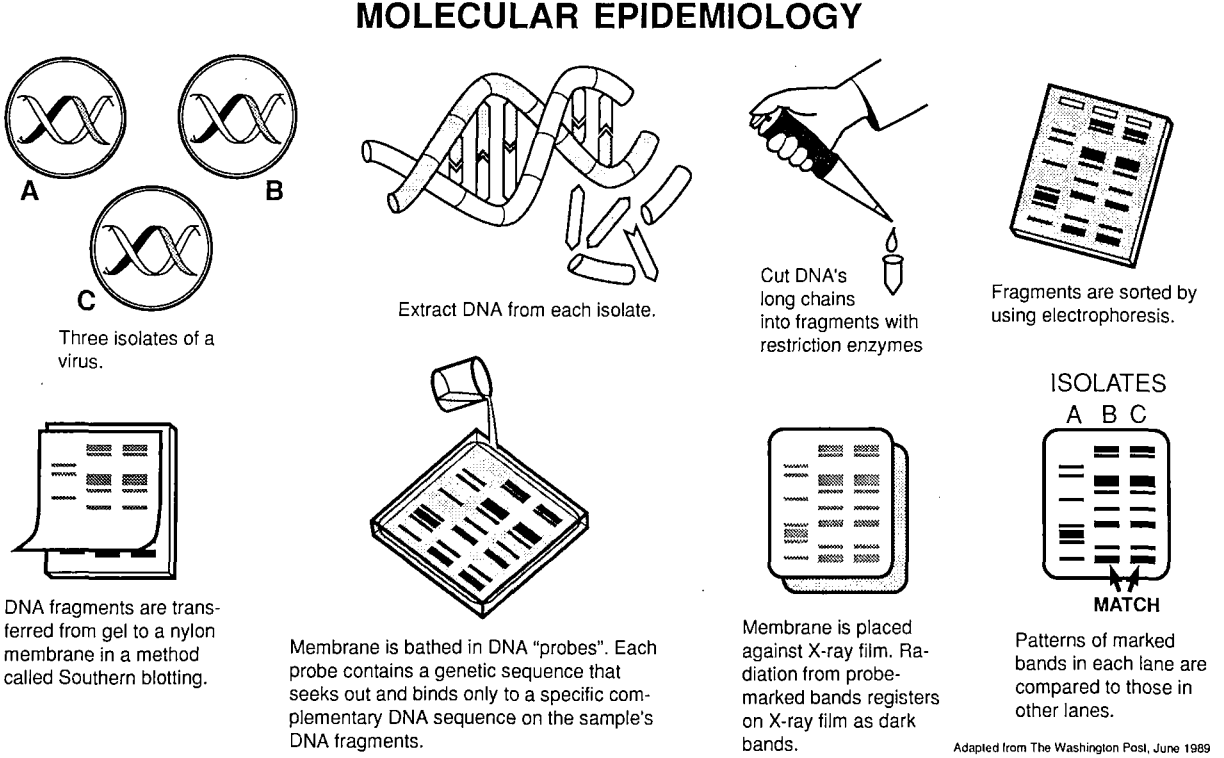

FIG. 1

The restriction endonuclease analysis (DNA fingerprinting) procedure

TABLE II

Diagnosis of bacterial and other diseases by restriction endonuclease analysis (REA)

Micro-organism	Significant findings	Reference
Leptospira	The reference strain *hardjo-prajitno*, used in diagnostic tests and vaccines, differed in REA fragments allowing strain differentiation from North American *hardjo-bovis* strains.	97
Leptospira and other pathogens	The classification of *Leptospira interrogans* into serogroups and serovars by REA is described. REA has also been used on *Campylobacter*, *Brucella*, *Chlamydia* and *Mycobacterium*.	98
Mycobacterium bovis	REA is a useful method for inter- and intraspecific classification of the tuberculosis complex.	19
Mycobacterium paratuberculosis	*M. paratuberculosis* isolates are genetically very similar.	106
Pasteurella multocida	Isolates of *P. multocida* were characterized (fingerprinted) phenotypically and genotypically to differentiate strains of fowl cholera.	88
Corynebacterium pseudotuberculosis	Examination of isolates from sheep, goats, horses and cattle by REA was carried out.	89
Yersinia enterocolitica	Detection of an endonuclease of the gene might result in more rapid determination of the prominently pathogenic serotype of *Y. enterocolitica*.	68

Except for the use of REA in epidemiological studies, the potential diagnostic value of REA is not clear. A question confronting veterinary diagnosticians in the future will be: what level of detected differences between viruses or bacteria is significant? REA can detect single base pair substitutions in DNA based on the loss or acquisition of a restriction endonuclease site. However, if the loss or acquisition of restriction endonuclease site(s) is not represented by differences of the compared viruses or bacteria to cause disease, it may be concluded that the difference detected by REA is not significant. Where REA may prove extremely valuable is in the detection of a pathogenic strain of virus or bacteria when pathogenic and non-pathogenic strains cannot be differentiated serologically. This would of course depend on the difference in pathogenicity being represented by different REA patterns.

DIAGNOSIS BY DNA PROBES

The use of DNA hybridization procedures provides a powerful tool in the diagnosis of bacterial and virus diseases through the use of highly conserved DNA sequences. DNA probes exhibit remarkable specificity (6, 16, 65).

A simplistic illustration of the use of a probe is shown in Fig. 2. To make a probe, DNA is heated or treated chemically until the two strands separate. Each strand will recognize and bind to a strand of DNA that has complementary nucleotide bases. To put it another way, a DNA probe will "search" the tissues of an animal or an insect for the complementary nucleotide (sequence) of a pathogen. To determine whether binding (hybridization) has occurred, the single strand of the probe DNA is usually labeled with radioactive ^{32}P.

Denatured DNA is freed from clinical specimens (blood, saliva, urine, exudates) and applied to nitrocellulose filters (dot-blot procedure). If the DNA sequence of the probe and the target DNA of the clinical specimen are complementary they will hybridize. Next, the filter is checked for the presence of the label of the probe. The specimen is positive for the pathogen if the label is detected. If the specimen is negative, the labeled probe will not bind to the sample and will be washed away in the procedure. Although the "hot" radioactive probes are very sensitive, they have some disadvantages. The ^{32}P isotope has a half-life of only a couple of weeks and is a radiation hazard.

To facilitate commercial use of DNA probes, radioactive tags will have to be replaced with sensitive, long shelf-life non-radiolabeled tags. Presently, most laboratories involved in making probes are utilizing the tenacious attraction of biotin and avidin from egg white. In this instance, the DNA probe is labeled with biotin and is detected by streptavidin, which is linked to horseradish peroxidase or alkaline phosphate which yield conspicuous color in the presence of their substrates and can be assayed. Also, the streptavidin can be conjugated with a fluorescent dye. Biotin-labeled probes have a long shelf-life, and the assay time can be reduced to a couple of hours, whereas the radiolabeling procedure usually requires an overnight radiograph. Some investigators using biotinylated probes have encountered sensitivity problems. A new technique which shows promise is the use of DNA probes labeled with the cholesterol digoxigenin and detected with an antibody-alkaline phosphatase conjugate and either a colorimetric or chemiluminescent substrate (5).

There are increasing numbers of research reports, but currently there are no DNA or RNA probes commercially available for use in veterinary diagnostic laboratories. Research papers in which DNA probes were employed are given in Tables III, IV and V.

POLYMERASE CHAIN REACTION

Polymerase chain reaction (PCR) procedure exploits natural DNA replication, mass producing *in vitro* a desired sequence of DNA. PCR can amplify two copies of a small region of 100 to 400 base pairs into millions of copies. The steps in the PCR process are outlined in three publications (28, 83, 84).

Briefly, amplification of DNA by the PCR is accomplished via a succession of incubation steps at different temperatures. The target DNA is heat denatured; specific primers are then annealed at low temperature and extended with Taq DNA polymerase at an intermediate temperature utilizing the target DNA as a template (84). These steps, referred to as cycles, are repeated 20 to 40 times, yielding amplification of target

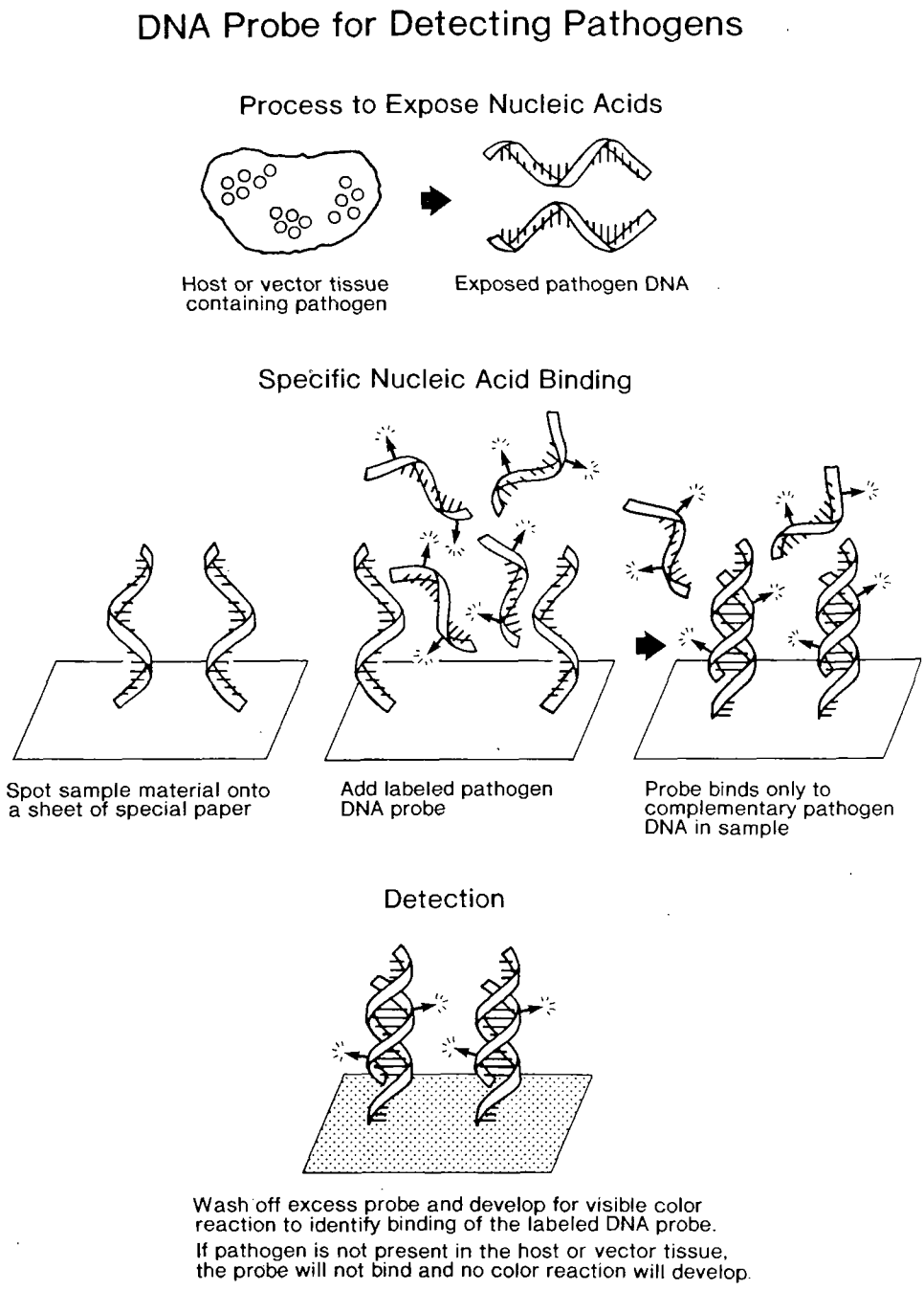

FIG. 2

An illustration showing the use of a DNA probe

TABLE III

Diagnosis of virus diseases by nucleic acid probes

Disease	Significant findings	Reference
African swine fever	A ^{32}P-DNA probe detected African swine fever virus in field samples.	15
Aujeszky's disease (Pseudorabies)	A practical *in situ* hybridization was developed for rapid diagnosis of pseudorabies virus in pigs. The method utilizes routine formalin fixed and paraffin-embedded tissue sections.	8
Aujeszky's disease (Pseudorabies)	The DNA hybridization procedure using ^{32}P probes may be useful for studying the latency of Aujeszky's disease (PRV).	61
Aujeszky's disease (Pseudorabies)	Infection was detected in nasal and tonsilar cells, lymphocytes in organ specimens by filter hybridization. The results agree with those obtained by virus isolation and conventional nucleic acid hybridization. The sensitivity and specificity of both isotope-labeled and biotinylated probes were compared.	7
Aujeszky's disease (Pseudorabies)	An *in situ* hybridization method was developed for rapid diagnosis in pigs. The method uses routine formalin-fixed and paraffin-embedded tissue sections, non-radioactive biotin-labeling and simple hybridization procedures.	8
Aujeszky's disease (Pseudorabies)	DNA probes were developed for use in dot hybridization to detect the presence of pseudodorabies virus in tissues.	52
Aujeszky's disease (Pseudorabies)	A DNA-hybridization dot-blot technique was developed to detect Aujeszky's virus DNA in porcine tissues.	62
Aujeszky's disease (Pseudorabies)	A DNA hybridization technique was developed to detect the presence of pseudorabies virus DNA. The results indicated that this procedure may be useful for studying the latency of pseudorabies viral infection.	61
Aujeszky's disease (Pseudorabies)	Two DNA probes were used in a dot hybridization to detect pseudorabies virus in infected tissues. There was a strong correlation between results obtained by dot hybridization and conventional methods of viral isolation from the same tissue specimens.	52
Aujeszky's disease (Pseudorabies)	Latent viral DNA sequences were detected in the tri-geminal ganglia of swine which had recovered from pseudorabies.	39

TABLE III (contd.)

Disease	Significant findings	Reference
Aujeszky's disease (Pseudorabies)	A DNA-hybridization dot-blot technique was developed to test for the presence of pseudorabies virus DNA in porcine tissues. Viral DNA was present in high concentrations in the spleen and liver with seronegative pigs that contain no detectable infective virus.	25
African swine fever	African swine fever virus was detected by DNA hybridization.	15
Bluetongue	Four different cloned probes derived from 3 genome segments were defined by different hybridization recognition capabilities. The diagnostic and genetic relationship studies on bluetongue virus (BTV) using various genetic probes were discussed.	92
Bluetongue	A biotin-labeled probe derived from a DNA copy of segment 3 RNA of bluetongue virus of serotype 17 was described.	82
Bluetongue	A dot hybridization technique was suitable for detecting and identifying bluetongue virus in cell culture.	91
Bluetongue	RNA probes labeled with 35S CTP were used to identify viral nucleic acid in bluetongue virus cell culture isolates. Specific hybridization signals were obtained in as few as 3 hours in assays.	20
Bluetongue	Dot-blot and Northern blot hybridization methods to determine the relatedness of serotypes 2, 10, 11, 13 and 17 were compared. Northern blot hybridization was more consistent than the dot-blot method.	101
Bluetongue	Comparative hybridizations show that variation occurs within the RNA genome of bluetongue virus.	38
Bovine herpesvirus-1 (IBR)	Argentine isolates of bovine herpesvirus-1 were detected by dot-blot nucleic acid hybridization using ^{32}P nick-translated plasmatic probes.	4
Bovine herpesvirus-1 (IBR)	Biotin-labeled DNA probes for IBR/IPV virus (BHV-1) were used to detect nucleic acid in infected cell cultures and clinical specimens by *in situ* hybridization.	26
Bovine herpesvirus-1 (IBR)	BHV-1 DNA was detected in nasal swabs and exudate from experimentally infected cattle by blot hybridization.	25
Bovine herpesvirus-1 (IBR)	As little as 10 pg of BHV-1 DNA was detected by dot-blot hybridization with ^{32}P labeled DNA in bovine semen.	72

TABLE III (contd.)

Disease	Significant findings	Reference
Bovine immunodeficiency-like virus (BIV)	Biologically active clones of BIV were developed to determine the prevalence of BIV in cattle populations.	12
Equine herpesvirus type-1 (EHV-1)	Aborted fetuses were analyzed for the presence of virus DNA by means of Southern blot and dot-blot hybridization. The specificity of the methods was confirmed although the sensitivity was inferior to classical techniques such as virus isolation.	69
Bovine adenovirus	A DNA probe was capable of detecting infection of cell cultures and in nasal swabs and faeces.	66
Bovine enteric coronavirus	Virus was detected earlier by electron microscopy but the best agreement was between dot-blot hybridization and virus isolation.	87
Bovine enteric coronavirus	See reference.	102
Bovine leukosis	DNA hybridization using ^{32}P-labeled plasmids detected infection in cattle negative to the immunodiffusion test as well as cattle positive to immunodiffusion test.	79
Bovine virus diarrhoea	A DNA probe was hybridized with all cytopathic and non-cytopathic strains tested 100 times more sensitive than infectivity assays for detection of the virus. Hybridization did not occur with nucleic acids from bovine coronavirus, bluetongue virus, bovine adenovirus or uninfected cell cultures.	13
Bovine enteric coronavirus	A ^{32}P DNA probe detected as little as 25 pg of RNA from the parental virus but did not detect RNA from the nonparental virus even when amounts up to 10 ng per dot were used. The specificity reflects the antigenic diversity between these two coronaviruses.	87
Canine distemper virus	DNA probes and single-stranded RNA probes were used to detect genome and messenger RNA of distemper virus in organs from dogs.	67
Canine parvovirus	See reference.	24
Foot and mouth disease virus (FMDV)	Biotinylated complementary DNA and RNA probes detected foot and mouth disease infection in cell culture. The technique could prove useful in diagnosis of animals and in the detection of foot and mouth disease virus in biologics submitted for importation.	64

TABLE III (contd.)

Disease	Significant findings	Reference
Foot and mouth disease virus	Under optimal hybridization conditions, the minimal level of detection for FMDV-RNA was one picogram.	60
Foot and mouth disease virus	Infectivity in dot-blot hybridization techniques were compared for detection of FMDV in oesophageal-pharyngeal fluids from experimentally infected cows. The virus was not recovered from some samples at 180 and 560 days post infection although specific viral RNA was detected by dot-blot hybridization. These results emphasize the usefulness of molecular hybridization techniques for FMDV carrier detection.	81
Porcine parvovirus (PPV)	The probe was evaluated by dot hybridization for PPV in infected cell cultures. The probe was specific for PPV-infected cells and 100 times more sensitive than the standard haemagglutination test.	49
Porcine parvovirus	A DNA probe was capable of detecting one haemagglutinating unit in cell cultures and also detecting the virus in suspensions of internal organs from mummified fetuses of experimentally infected sows.	48
Rabies	Rabies virus RNA was detected in paraffin tissues using *in situ* hybridization. *In situ* hybridization has potential application as a diagnostic test for rabies and in studies for rabies pathogenesis.	43
Rinderpest and peste des petits ruminants	cDNA probes can be used to distinguish rinderpest and peste des petits ruminants.	23
Rotavirus	See reference.	76
Seal morbillivirus	DNA probes were used to examine spleen tissues from seals. A new morbillivirus (not canine distemper) was associated with seal deaths.	56
Avian infectious bronchitis virus (IBV)	A hybridization test for the identification of virus isolates of avian infectious bronchitis virus was developed for use when serum neutralization tests were inadequate.	14
Marek's disease	A dot-blot DNA hybridization test detected Marek's disease virus in feather tips of infected chickens.	22
Channel catfish virus	A nucleic acid probe for channel catfish virus prepared by recombinant techniques consisted of a specific viral DNA fragment. Viral DNA was detected in some tissues of infected fish.	107

TABLE IV

Diagnosis of bacterial and other diseases by nucleic acid probes

Micro-organism	Significant findings	Reference
Corynebacterium kutscheri	The method described is more rapid and more specific than conventional immunological and culture procedures used to detect *C. kutscheri*.	85
Escherichia coli	The method of hybridization permits the simultaneous examination of a large number of samples, but its application as a routine method would require the cloning of genes of all toxins.	57
Escherichia coli	A non-radiological dot-blot hybridization test developed for enterotoxigenic *E. coli* was a more suitable approach in the field than the hybridization assay based on ^{32}P labeled DNA probes.	10
Escherichia coli	Biotinylated oligonucleotide probes were hybridized to detect the ST1a toxin gene.	46
Escherichia coli	Blot hybridization was a reliable replacement for the ligated porcine gut loop assay to detect stable toxin-B producing *E. coli*.	55
Escherichia coli	DNA probes were used to detect *E. coli* enterotoxins by the blot technique.	50
Escherichia coli	Commercial kits containing alkaline phosphatase-labeled oligonucleotide probes for *E. coli* heat-stable enterotoxins and heat-labile enterotoxin were compared with bioassays and radio-labeled recombinant probes to identify enterotoxigenic *E. coli*. There was very good agreement among the 3 methods.	63
Escherichia coli	Probes were prepared to determine prevalence of K99 adhesion factor and enterotoxins in *E. coli* isolates collected from cases of enteric and systemic disease.	58
Mycobacterium paratuberculosis	A DNA probe that detects *M. paratuberculosis* in faecal material of infected animals was developed. The probe detected as few as 105 organisms when hybridized under stringent conditions. The probe did not differentiate members of the *Mycobacterium avium*-M intracellular-*M. paratuberculosis* complex.	41
Leptospira interrogans serovar *hardjo* genotype *hardjo-bovis*	The probe is specific for this genotype and does not hybridize to genomic DNA of any other leptospire pathogen commonly found in North America.	51

TABLE IV (contd.)

Micro-organism	Significant findings	Reference
Leptospira interrogans serovar *hardjo* type *hardjo-bovis*	Leptospires were detected in 60 of 75 urine samples from challenge-exposed cows by nucleic acid hybridization in 24 samples by a fluorescent antibody test, and in 13 samples by bacteriological culture.	11
Leptospira interrogans	*In situ* DNA hybridization using biotin-labeled leptospiral DNA was performed on blood, urine and liver smears for identifying *L. interrogans*. The procedure can be completed in only 4 hours. No cross hybridization was observed with other bacteria.	95
Leptospira, *Haemophilus* and *Campylobacter*	*In situ* DNA hybridization using biotin-labeled bacterial DNA was performed on clinical specimens to investigate its application as a technique as a rapid detection of pathogenic micro-organisms.	96
Leptospira interrogans serovar *hardjo*	Biotin labeled or ^{32}P labeled probes in dot-blot or *in situ* hybridization showed high sensitivity and cross hybridization.	29
Leptospires	DNA hybridization detected leptospiral organisms in homogenized kidneys from experimentally infected pigs and in homogenates of pig kidneys collected at abattoirs.	59
Leptospira interrogans serovar *hardjo* type *hardjo-bovis*	A diagnostic probe distinguished *hardjo-bovis* from other pathogenic leptospires common in domestic animals in North America. Using this probe it was possible to identify infected cattle shedding *hardjo-bovis* in their urine.	108
Leptospira	Nucleic acid probes were developed for *L. interrogans* and *L. pomona* and *L. kennewicki*.	98
Listeria monocytogenes	A fragment of the beta-haemolysin gene from *Listeria monocytogenes* was used to screen different bacterial strains by DNA colony hybridization.	21
Mycoplasma	A DNA probe was prepared for screening purposes.	47
Mycoplasma hyopneumoniae	A cloned fragment of *M. hyopneumoniae* DNA produced a probe capable of approximately 10 pg of the mycoplasma DNA.	93
Mycoplasma gallisepticum	The specificity and sensitivity of this probe were demonstrated by dot-blot and Southern hybridizations.	86

TABLE IV (contd.)

Micro-organism	Significant findings	Reference
Mycoplasma gallisepticum	A biotinylated DNA probe detected *M. gallisepticum* within 24 hours. It reacted strongly with homologous and weakly with other mycoplasmas.	33
Mycoplasma gallisepticum	A DNA probe from the vaccine F strain (K810) and the reference S6-strain of *M. gallisepticum* were cloned in *E. coli*.	45
Mycoplasma gallisepticum and *Mycoplasma synoviae*	DNA probes specific for *Mycoplasma gallisepticum* and *M. synoviae* were hybridized with the DNA of a wide spectrum of strains within each homologous species but did not react with heterologous species or with DNA from any other avian mycoplasma or bacteria tested. The use of DNA probes for the early detection of *M. gallisepticum* infection can replace culture techniques and less effective serological methods.	42
Mycobacterium avium Complex	DNA probes hold promise for the future identification of *Mycobacterium* species in the clinical laboratory. Improvement in the shelflife and use of nonradioactive labels would greatly expand the usefulness of these probes.	80
Mycoplasma hyorhinis	A DNA probe for *Mycoplasma hyorhinis* demonstrated specific Southern hybridization and dot hybridization when tested against a group of different *Mycoplasma* spp.	94
Salmonella	Salmonella species in meat products have been identified by DNA probes.	31
Salmonella newport	A probe was developed to trace *Salmonella newport* in an epidemic.	90
Haemophilus ducreyi	Three probes consistently detected *H. ducreyi* in pure and mixed cultures. The use of these probes will facilitate the laboratory diagnosis of the genital pathogen.	73
Campylobacter	DNA probes that are specific for *Campylobacter* were developed.	78
Campylobacter	See reference.	17
Salmonella	DNA hybridization assays for the detection of salmonellae in foods were described.	78

TABLE V

Diagnosis of chlamydial and rickettsial diseases by nucleic acid probes

Micro-organism	Significant findings	Reference
Avian chlamydiae	DNA-spot hybridization cell culture and direct immunofluorescence staining were compared for the detection of avian *Chlamydia psittaci* strains in cell culture and routine samples submitted for diagnosis. All three tests performed similarly.	99
Anaplasma marginale	A nucleic acid probe was at least 4,000 times more sensitive than light microscopy. Hybridization of the probe with blood from anaplasmosis carrier cattle showed that parasitaemia was highly variable. Results suggest that at any given time individuals within a group of cattle may differ in their ability to transmit disease.	27
Anaplasma marginale	A DNA probe was species specific and detected *A. marginale* DNA derived from bovine lymphocytes and *Dermacentor* ticks either as nymphs or adults.	37
Anaplasma marginale	See reference	2

DNA sequences. The key to geometric amplification of target DNA sequences by the PCR is selection of paired primers which, when extended, will create additional reciprocal primer annealing sites for primer extension in subsequent cycles.

PCR is fast becoming a powerful tool in detecting infections in host tissues and vectors. Even when a small number of host cells are infected, PCR can target and amplify a gene sequence that has become integrated into the DNA of infected host cells.

The polymerase chain reaction may prove to be very useful in the diagnosis of chronic-persistent infections such as those caused by retroviruses (bovine leukemia virus, caprine arthritis-encephalitis virus, etc.) and tickborne hemoparasitic diseases (equine and bovine babesiosis, etc.). These diseases present serious problems in terms of diagnosis and prevention since infected animals often do not demonstrate clinical signs until there is advanced disease, and infected animals appear to be a constant potential source for transmission. While serological tests are usually accurate for identification of animals exposed to an organism, they do not provide information on the status of the particular organism within the individual animal. It was recently reported that the DNA of the human immunodeficiency virus (HIV) had been identified via PCR in patients which were serologically negative to HIV (74). Should a similar situation be found in veterinary medicine; that is animals which are seronegative for an organism yet harbor its DNA, PCR could prove very useful in identifying such animals (Table VI). This could be especially important in eradication programs.

TABLE VI

The use of the polymerase chain reaction (PCR)

Disease	Significant findings	Reference
Feline herpesvirus (rhinotracheitis)	PCR increased the specificity of probes.	71
Leptospires	Urine samples were investigated using PCR assay, culture isolation, dot- and quick-blot hybridization, and serological tests. This comparative study suggests that amplification by PCR may be a valuable method for the detection of leptospires in cattle urine.	30

PRODUCTION OF ANTIGENS BY RECOMBINANT DNA TECHNOLOGY

A problem which is encountered using current diagnostic tests is that the test antigens must be continuously produced from cell culture or harvested from an infected animal. These antigen preparations:

1) are expensive

2) often have a short shelf-life

3) need to be standardized with each new batch, and

4) potentially contain additional antigens which may be recognized by animals immunized with vaccines prepared from cell culture systems and may yield false positive tests. Production of antigens for diagnostic tests by molecularly cloning potentially overcomes these problems.

A general procedure for the preparation of an antigen by recombinant DNA technology is as follows. An antigen of potential diagnostic significance is identified by studying the antibody response of the host to the proteins of the organism in question. For example, immunodominance may be defined as those organism proteins against which there is the highest antibody titer. Following identification of proteins of potential diagnostic significance, specific reagents such as monoclonal antibodies or monospecific-polyvalent sera may be generated for use in screening recombinant libraries for the protein(s) of interest. Recombinant libraries may be produced from the genomic DNA of the organism or by cDNA synthesis using messenger RNA (mRNA) from the organism as a template. Preparation of genomic DNA for cloning is accomplished by random shearing followed by linker addition or partial digestion with a restriction endonuclease. In either case, the DNA is molecularly cloned into a prokaryotic or eukaryotic expression system, and the library screened for expression of the desired protein. An example for cloning a foreign gene into *Escherichia coli* for expression of a recombinant antigen is shown in Fig. 3. The use and applications of recombinant antigens in diagnostic assays have recently been discussed (32).

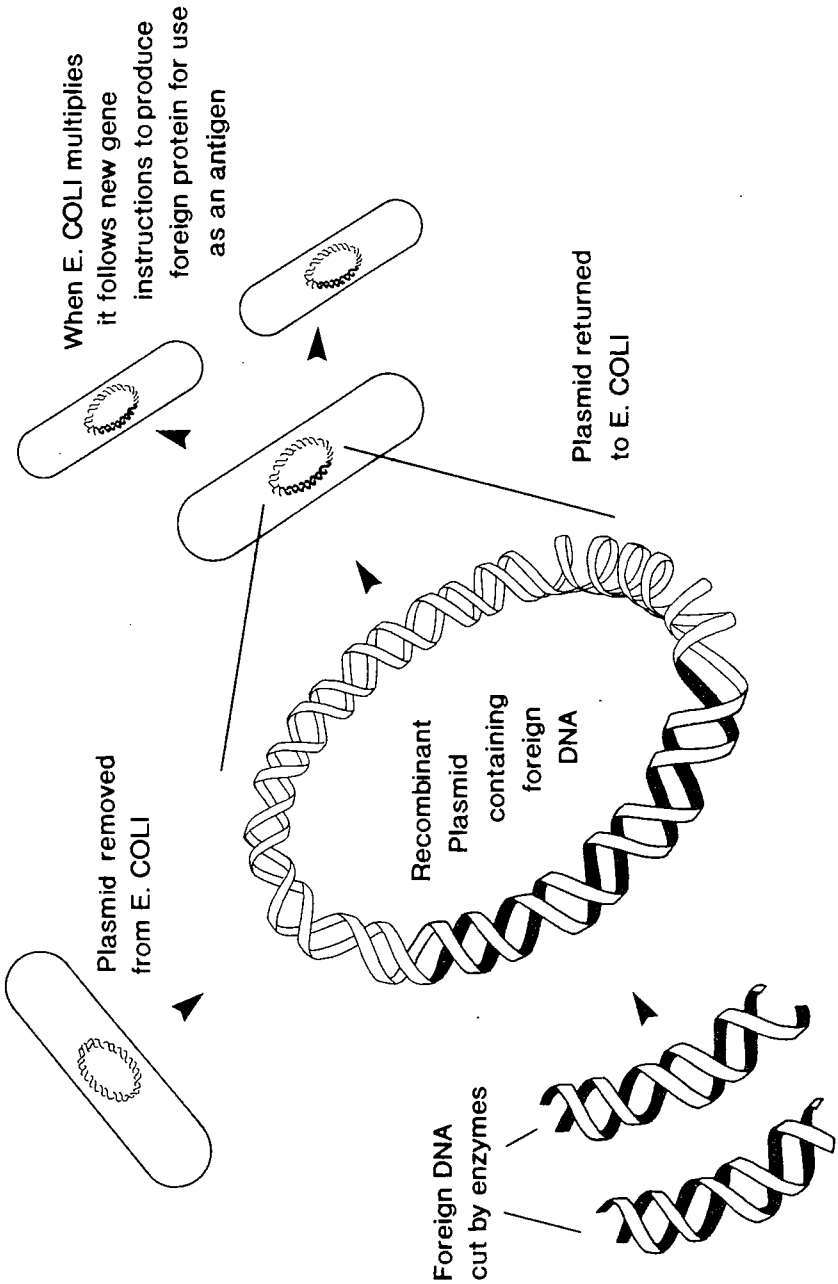

FIG. 3

The recombinant DNA procedure used to produce protein antigens

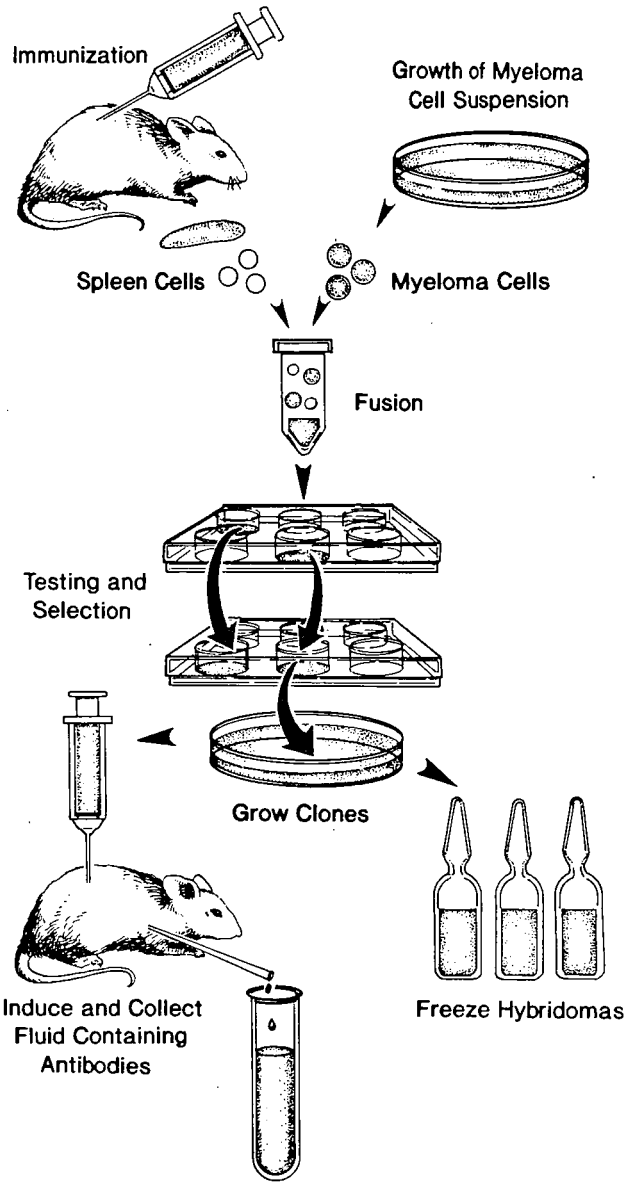

FIG. 4

The preparation of monoclonal antibodies

MONOCLONAL ANTIBODIES (MAbs) FOR THE DIAGNOSIS OF DISEASE IN COMPETITIVE INHIBITION TESTS

Because of their specificity, MAbs have been widely used in the diagnosis of viral and bacterial diseases. Their preparation is given in Fig. 4. It is not the purpose of this paper to review the numerous applications in which monoclonal antibodies have been successfully employed. There have been exhaustive reviews of monoclonal antibody technology as related to animal viruses and bacteria and the reader should consult the literature on specific diseases.

However, the use of monoclonal antibodies in competitive enzyme-linked immunosorbent assays (ELISA), also referred to as a blocking ELISA, has recently come to the forefront as a method to detect the presence of anti-organism antibody. Since introduced by Anderson (3), the use of monoclonal antibodies in a competitive ELISA is becoming widely used (1, 54). A prominent advantage of the competitive ELISA is that the specificity is in the monoclonal and not the antigen preparation. This feature allows the use of crude antigen preparations. Briefly, the strategy is to incubate an antigen preparation from the organism in question with dilutions of test serum. A monoclonal antibody specific for the organism is then added and allowed to compete with the test serum for binding to the antigen preparation. Detection of monoclonal antibody binding may be accomplished by a number of different enzymes (alkaline phosphatase, etc.) which are conjugated to a second antibody. A positive serum inhibits the binding of the monoclonal antibody to the antigen preparation, and results in a titratable decrease in substrate cleavage by the enzyme conjugated to the second antibody.

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DIAGNOSTIC DES MALADIES VIRALES ET BACTÉRIENNES. – D.P. Knowles, Jr. et J.R. Gorham.

Résumé : *Les applications potentielles des techniques comme l'analyse par enzymes de restriction, la détection d'acides nucléiques, la technique d'amplification enzymatique (PCR) et les tests de compétition/inhibition en sont seulement à leur début. Les avantages extraordinaires que l'on peut espérer tirer de ces procédés restent encore à réaliser pleinement.*

Cependant, pour que ces techniques soient acceptées et largement utilisées, il convient de démontrer qu'elles possèdent une sensibilité et une spécificité comparables aux tests d'usage courant. De plus, elles doivent avoir fait la preuve de leur innocuité, être d'application simple et automatisées afin de faciliter l'étude d'un grand nombre de prélèvements.

MOTS-CLÉS : Analyse par enzyme de restriction - Anticorps monoclonaux - Biotechnologie - ELISA - Hybridation d'acides nucléiques - Sondes d'ADN - Technique d'amplification enzymatique (PCR) - Test de compétition ELISA.

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DIAGNÓSTICO DE ENFERMEDADES VIRALES Y BACTERIANAS. – D.P. Knowles, Jr. y J.R. Gorham.

Resumen: Las potenciales aplicaciones de las técnicas como el análisis por enzimas de restricción, la detección de ácidos nucleicos, la técnica de amplificación enzimática (PCR) y las pruebas de competencia/inhibición sólo están empezando. Las extraordinarias promesas de dichos procedimientos aún están por realizarse completamente.

Sin embargo, para que estas técnicas sean aceptadas y utilizadas ampliamente, hay que demostrar que poseen una sensibilidad y especifidad comparables con las de pruebas de uso corriente. Además, deben ser inocuas, de aplicación simple y automatizadas con objeto de facilitar el estudio de gran número de muestras.

PALABRAS CLAVE: Análisis por enzimas de restricción - Anticuerpos monoclonales - Biotecnología - ELISA - Hibridación de ácidos nucleicos - Prueba de competencia ELISA - Sondas de ADN - Técnica de amplificación enzimática (PCR).

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