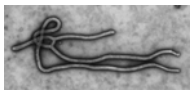
BIOE 301

Lecture Ten

Summary

- How do vaccines work?
  - Stimulate immunity without causing disease
- How are vaccines made?
  - Non-infectious vaccines
  - Live, attenuated bacterial or viral vaccines
  - Carrier Vaccines
  - DNA Vaccines
- How are vaccines tested?
  - Lab/Animal testing
  - Phase I-III human testing
  - Post-licensure surveillance
- Impact of vaccines

Vaccine Trials in the News... Ebola



- 2003 pre-clinical trials
- 2010
  - New species of Ebola - Bundibugyo - emerged in 2007
  - Experimental vaccines being developed against other lethal Ebola species
    - found to totally protected against it
    - did not stimulate antibodies against the new species
    - protection depended entirely on **cellular immunity**

"The dogma is that viruses require an antibody response to prevent the virus from entering the cell," Sullivan says. "This is truly the first time that cell-mediated immunity alone has been shown to be protective against virus infection."

Vaccine Trials in the News... Ebola

- Study Design
  - 8 macaques – 4 vaccinated / 4 unvaccinated
  - All inoculated with lethal doses of Ebola
  - Vaccinated animals survived, Unvaccinated animals died
- Vaccine
  - pieces of the Zaire & Sudan viruses' protein-sugar coat (glycoprotein) inserted into a type of common cold virus
  - The cold virus carries the Ebola glycoprotein into cells of the vaccine recipients
  - 4 "priming" shots, followed a year later with a booster

"There's no way to do trials of Ebola vaccines in humans. Unlike, say, a vaccine for HIV, there's no identifiable group of people at risk for Ebola..."

Vaccine Trials in the News... HIV

- 2009: 3rd largest AIDS vaccine trial to date
  - Cost the US government $105 M
  - Largest done in humans: >16,000 participants
- Controversy:
  - Combination of 2 vaccines that each failed when tested for use individually
  - 2004 editorial in Science signed by 22 top AIDS researchers:
    - Suggested trial was a waste of $$

NPR: AIDS Vaccine Prevents Some HIV Infections

HIV Vaccine

- Vaccines Tested:
  - Sanofi-Aventis Alvac-HIV
    - Carrier vaccine
    - Canarypox virus with 3 AIDS virus genes grafted onto it
    - Stimulate cell mediated immunity
  - Genentech Aidsvax
    - Non-infectious sub-unit vaccine
    - Contains two recombinant gp120 proteins found on surface of different strains of HIV virus
    - Stimulate anti-body mediated immunity

HIV Vaccine

- Study Design
  - Followed 16,402 Thai volunteers
  - Men & women, ages 18-30
  - Recruited from general population
  - Half got six doses of combination of two different vaccines
  - Half got placebo
  - Followed for 3 years

HIV Vaccine

- Ethics:
  - All were offered condoms
  - Taught how to avoid infection
  - Promised lifelong ARVs if infected

HIV Vaccine

- Results:
  - Placebo group: 74 infected
  - Vaccinated group: 51 infected
- Vaccine Effectiveness
  - Effect size: 23 people of >16,000
  - From ~0.9% to ~0.6% incidence
  - A 31% decrease
- 1st time any protective effect observed

HIV Vaccine

- Conclusions:
  - Studies to be done to understand why worked
    - What is unique about those it worked in?
    - Through what mechanism did it work?!
    - Why those vaccinated who become HIV+ didn't develop any protective effect?
  - Those who became infected have as much virus in blood whether they got vaccine or placebo
    - Suggests vaccine does not produce neutralizing Abs

Dangers of Vaccine Trials

- Most researchers feel first HIV vaccines will not be more than 40-50% effective
  - Will vaccinated individuals engage in higher risk behaviors?
  - Vaccine could cause as much harm as it prevents
  - http://www.npr.org/templates/story/story.php?storyId=113177004
- Future vaccines cannot be tested against placebo, would be unethical

In-Class Activity

- Town Hall Meeting
  - A Ugandan community has been asked to participate in a clinical trial of an HIV vaccine
  - 10 volunteers to role play, 3 Ugandan council members & 7 experts both for & against
  - Remaining students represent the community making the decision to participate or not
  - One by one volunteers explain their stance
  - Audience may ask questions at any time
  - Does the community choose to participate?

Ethics of Clinical Research

- Humans have not always treated each other humanely in the name of science
- Ethics of Clinical Research
  - Famous Case Studies
  - Codes governing ethical conduct of research:
    - Nuremberg Code
    - Belmont Report
  - Case Studies Revisited
  - Functions of the IRB
- Applications to current controversies

Case I:Tuskegee Syphilis Study

- Goal:
  - Examine natural history of untreated syphilis
- Subjects:
  - 400 black men with syphilis
    - Half to receive standard Rx
    - Half to be left untreated
  - 200 normal controls

Case I:Tuskegee Syphilis Study

- Experiment:
  - 1932:
    - Standard Rx: injection of compounds containing heavy metals
    - Treatment reduced mortality but heavy metals thought to cause syphilis complications
    - Treatment withheld from infected men
  - 1942:
    - Death rate 2X higher in treatment group
  - 1940s:
    - Penicillin available
    - Men not informed of this
  - Study continued until 1972 when first publicized

Case I:Tuskegee Syphilis Study

- Consent Process:
  - No informed consent
  - Men misinformed that some study procedures (spinal taps) were free 'extra treatment'

Case II: Willowbrook Studies

- Goal:
  - Understand natural history of infectious hepatitis
- Subjects:
  - Children at Willowbrook State School
  - An institution for 'mentally defective persons'
- Experiment:
  - Carried out from 1963-1966
  - Subjects deliberately infected with hepatitis
    - Fed extracts of stool from infected persons
    - Injected with purified virus
  - Vast majority of children admitted acquired hepatitis

Case II: Willowbrook Studies

- Consent Process
  - Parents gave consent
  - Due to crowding, Willowbrook was at times closed to new patients
  - Hepatitis project had its own space
  - In some cases, only way to gain admission was to participate in the study

Case III: Jewish Chronic Disease Hospital Study

- Goal: Study rejection of cancer cells
  - Healthy patients reject cancer cell implants quickly
  - Cancer patients reject cancer cell implants much more slowly
  - Is this due to decreased immunity because of presence of cancer or is it manifestation of debility?
- Subjects:
  - Patients hospitalized with various chronic debilitating diseases
- Experiment:
  - Took place in 1963
  - Patients injected with live liver cancer cells

Case III: Jewish Chronic Disease Hospital Study

- Consent Process:
  - Negotiated orally, but not documented
  - Patients not told that cancer cells would be injected because this might scare them unnecessarily
  - Investigators justified this because they were reasonably certain the cancer cells would be rejected

Case IV: San Antonio Contraceptive Study

- Goal:
  - Which side effects of OCP are due to drug?
  - Which are by-products of every-day life?
- Subjects:
  - 76 Impoverished Mexican-American women with previous multiple pregnancies
  - Patients had come to a public clinic seeking contraceptive assistance.

Case IV: San Antonio Contraceptive Study

- Experiment:
  - Took place in the 1970s
  - Randomized, double-blind, placebo controlled trial
  - Cross-over design
  - All women were instructed to use vaginal cream as contraceptive during the study
  - 11 women became pregnant during study, 10 while using placebo
- Consent Process:
  - None of the women were told study involved placebo

Nuremberg Code: 1949

- Voluntary consent of the human subject is absolutely essential
- Experiment should yield fruitful results for good of society, obtainable in no other way
- Experiments should avoid all unnecessary mental and physical suffering
- No experiment should be performed if it is believed that death or disabling injury may occur

Belmont Report: 1979

- From Dept. of Health, Education & Welfare
- Statement of:
  - Basic ethical principles and guidelines to resolve ethical problems associated with conduct of research with human subjects
- Three basic ethical principles:
  - Respect for persons
  - Beneficence
  - Justice

Belmont Report: What is research?

- Clinical Practice:
  - Interventions designed solely to enhance well-being of an individual patient that have a reasonable expectation of success
- Research:
  - An activity to test a hypothesis
  - Permit conclusions to be drawn
  - Contribute to generalizable knowledge
  - Usually described in formal protocol that sets forth an objective and procedures to reach that objective

Respect for Persons

- All individuals should be treated as autonomous agents
- Demands that subjects enter into research:
  - Voluntarily
  - With enough information to make a decision
- Persons with diminished autonomy are entitled to special protection
  - Prisoners
  - Children

Beneficence

- Make efforts to secure patients' well-being
  - Do No Harm
  - Maximize possible benefits
  - Minimize possible harms
- One should not injure one person regardless of benefits that may come to others

Justice

- Who should receive benefits of research and who should bear its burdens?
- Some ways to distribute burdens & benefits:
  - To each person an equal share
  - To each person according to individual need
  - To each person according to individual effort
- 19th Century:
  - Poor ward patients were research subjects
  - Wealthy private patients received benefits of research
- Selection of research subjects must be scrutinized:
  - Are some classes are being selected because of easy availability, compromised position or manipulability.

Application of Belmont Report

- Informed Consent
- Assessment of Risks and Benefits
- Selection of Subjects

Informed Consent

- Information:
  - Research procedure, purpose of study, risks and anticipated benefits, alternative procedures, statement offering subject opportunity to withdraw at any time
- Comprehension:
  - Must present information in a way subject can understand
  - Must not be disorganized, too rapid, above subject's educational level
- Voluntariness:
  - Consent must be given voluntarily
  - Persons in positions of authority cannot urge course of action

Assessment of Risks & Benefits

- Research must be justified based on favorable risk/benefit assessment
  - Risk:
    - Possibility that harm may occur
      - Brutal or inhumane treatment of subjects is never morally justified
      - Risks should be reduced to those necessary to achieve research objective
  - Benefit:
    - Positive value related to health or welfare

Selection of Subjects

- Individual Justice:
  - Researchers must select subjects fairly
  - Must not select only potentially beneficial research to some subjects in their favor
  - Must not select only "undesirable" persons for risky research.
- Social Justice:
  - Distinctions be drawn between classes that ought and ought not to participate in research based on ability of that class to bear burdens
  - Adults before children

Case I:Tuskegee Syphilis Study

- Respect for persons
- Beneficence
- Justice

- 1997:
  - President Clinton formally apologizes to subjects of the study
  - http://www.npr.org/programs/morning/features/2002/jul/tuskegee/

Case II: Willowbrook Studies

- Respect for persons
- Beneficence
- Justice

Case III: Jewish Chronic Disease Hospital Study

- Respect for persons
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Case IV: San Antonio Contraceptive Study

- Respect for persons
- Beneficence
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Role of IRB

- Work with investigators to be sure that the rights of subjects are protected
- Educate research community and public about ethical conduct of research
- Resource centers for information about Federal guidelines
- Not a police force

Real Controversies

- Egg Donation
  - http://www.eggdonor.com
  - http://www.npr.org/templates/story/story.php?storyId=5035034
- Life Threatening Situations
  - http://www.npr.org/templates/story/story.php?storyId=1045001
- Terminally Ill Patients