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Objective

● To conduct cost-effectiveness analysis of infectious disease interventions and assist in prioritization of limited public health resources.

● New River Valley, Virginia, USA
  ○ Infectious disease outbreaks
    ■ Pertussis
    ■ Tuberculosis
    ■ Fungal meningitis
Pertussis

2011 outbreak
Pertussis

- **Bacteria**
  - bordetella pertussis

- **Symptoms**
  - whooping cough
  - fever

- **Transmission**
  - air-borne
Pertussis infection timeline

- **Bacterial Infection**: Incubation Period (7-10 days)
- **Symptoms Appear**: Catarrhal Stage (1-2 wks)
- **No longer infective**: Paroxysmal Stage (1-6 wks, up to 10 wks)
- **Convalescent Stage**: (weeks to months)

- **Latent Period**: (Same as Incubation Period)
- **Infectious Period**: (First 21 days of illness: Onset of symptoms and Catarrhal Stage)
Vaccine

- DTaP vaccine
  - Diptheria
  - Tetanus
  - Pertussis
### Vaccines

#### Pre-Vaccine Era Estimated Annual Morbidity in the U.S.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pre-Vaccine</th>
<th>Decrease</th>
<th>Recent Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>21,053</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>H. Influenza</td>
<td>20,000</td>
<td>99%</td>
<td>243</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>117,333</td>
<td>91%</td>
<td>11,049</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>66,232</td>
<td>83%</td>
<td>11,249</td>
</tr>
<tr>
<td>Measles</td>
<td>930,217</td>
<td>99%</td>
<td>61</td>
</tr>
<tr>
<td>Mumps</td>
<td>162,344</td>
<td>99%</td>
<td>182</td>
</tr>
<tr>
<td>Pertussis</td>
<td>200,752</td>
<td>93%</td>
<td>13,506</td>
</tr>
<tr>
<td>Pneumococcal Disease</td>
<td>16,369</td>
<td>74%</td>
<td>4,167</td>
</tr>
<tr>
<td>Polio</td>
<td>16,316</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,748</td>
<td>99%</td>
<td>4</td>
</tr>
<tr>
<td>Congenital Rubella</td>
<td>152</td>
<td>99%</td>
<td>1</td>
</tr>
<tr>
<td>Smallpox</td>
<td>29,005</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>Tetanus</td>
<td>580</td>
<td>98%</td>
<td>14</td>
</tr>
<tr>
<td>Varicella</td>
<td>4,085,129</td>
<td>89%</td>
<td>449,343</td>
</tr>
</tbody>
</table>
Basic reproduction rate - $R_o$

- $R_o$
  - Average number of secondary cases caused by the primary case in a susceptible population

- Epidemic
  - $R_o > 1$

- Endemic
  - $R_o = 1$

- Elimination
  - $R_o < 1$

- Eradication
  - $R_o = 0$

Effective reproductive rate

$R \sim R_o \times (1 - \text{interventions impact})$
$R$ and vaccination

- Elimination
  - $R < 1$

  \[ f = \text{fraction of population that are vaccinated} \]
  \[ (1 - f) = \text{fraction of susceptible population} \]

- For herd immunity
  - minimum fraction/threshold ($f_h$) of population to be vaccinated
    - $R = R_0 (1 - f_h) < 1$
    - $f_h > 1 - (1 / R_0)$

- Pertussis
  - Herd immunity $\sim (92-94)\%$
DTaP vaccine

Change in DTP (Diphtheria, Tetanus and Pertussis) Vaccination Coverage, 2006–2011 (children ages 19–35 months)

Herd Immunity Threshold (immunization coverage needed to prevent disease transmission)
- Diphtheria (85%)
- Pertussis (whooping cough) (92–94%)
- Tetanus (no threshold; not transmitted from person to person)

State met threshold for both diphtheria and pertussis in 2006 (gray)

State did not meet top-level herd immunity in 2011 (red)

State met top-level herd immunity in 2011 (blue)

Many states were below the safe diphtheria level in 2011; 49 were below the safe pertussis level.
Pertussis Incidence - Virginia

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Cases</th>
<th>Rate per 100,000</th>
<th>Number of Outbreaks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>128</td>
<td>1.65</td>
<td>6</td>
</tr>
<tr>
<td>2008</td>
<td>198</td>
<td>2.55</td>
<td>9</td>
</tr>
<tr>
<td>2009</td>
<td>222</td>
<td>2.82</td>
<td>10</td>
</tr>
<tr>
<td>2010</td>
<td>384</td>
<td>4.87</td>
<td>10</td>
</tr>
<tr>
<td>2011</td>
<td>399</td>
<td>5.06</td>
<td>13</td>
</tr>
</tbody>
</table>
Pertussis outbreak (2011)
New River Valley

- 72 cases

- Prime impact
  - private school
    - vaccination rate ~ 0%
New River Health District Intervention

- Vaccination & health education campaigns

- Vaccine clinics
  - school
  - community
Economic evaluation

ICER - Incremental Cost-Effectiveness Ratio

ICER = \( \frac{\text{Cost}_{\text{new intervention}} - \text{Cost}_{\text{control}}}{\text{Effectiveness}_{\text{new intervention}} - \text{Effectiveness}_{\text{control}}} \)
Data sources (cost)

- New River Health District
  - employee hours
  - number of vaccines
  - clinical hours

- US Census Data
  - average salary of various positions

- CDC
  - vaccine price list archive
    - cost of vaccines
## Intervention cost

### Health Department Costs

<table>
<thead>
<tr>
<th>Position</th>
<th># of</th>
<th>Hours</th>
<th>Hourly Salary + Benefits</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epi</td>
<td>1</td>
<td>200</td>
<td>43.39</td>
<td>8678</td>
</tr>
<tr>
<td>Nurse Epi</td>
<td>1</td>
<td>16</td>
<td>35.97</td>
<td>575.52</td>
</tr>
<tr>
<td>Planner</td>
<td>1</td>
<td>24</td>
<td>48.71</td>
<td>1169.04</td>
</tr>
<tr>
<td>Director</td>
<td>1</td>
<td>45</td>
<td>95.7</td>
<td>4306.5</td>
</tr>
<tr>
<td>Clerical</td>
<td>1</td>
<td>26</td>
<td>31.07</td>
<td>807.82</td>
</tr>
<tr>
<td>Nurse Manager SR.</td>
<td>1</td>
<td>10</td>
<td>47.6</td>
<td>476</td>
</tr>
<tr>
<td>Public Health Nurse</td>
<td>1</td>
<td>12</td>
<td>39.38</td>
<td>472.56</td>
</tr>
<tr>
<td>Public Health Nurse Senior</td>
<td>1</td>
<td>16</td>
<td>41.34</td>
<td>661.44</td>
</tr>
<tr>
<td><strong>Total State Personell Cost</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>17146.88</strong></td>
</tr>
</tbody>
</table>

### Clinical Costs

<table>
<thead>
<tr>
<th>Position</th>
<th># of</th>
<th>Hours</th>
<th>Hourly Salary + Benefits</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>6</td>
<td>122</td>
<td>81</td>
<td>9882</td>
</tr>
<tr>
<td>Physicians Assistant</td>
<td>1</td>
<td>24</td>
<td>41.54</td>
<td>996.96</td>
</tr>
<tr>
<td>Nurse practitioner</td>
<td>3</td>
<td>74</td>
<td>43.97</td>
<td>3253.78</td>
</tr>
<tr>
<td>Nurse</td>
<td>9</td>
<td>208</td>
<td>31.1</td>
<td>6468.80</td>
</tr>
<tr>
<td>Nursing Assistant</td>
<td>1</td>
<td>26</td>
<td>11.54</td>
<td>300.04</td>
</tr>
<tr>
<td>Medical Assistant</td>
<td>2</td>
<td>52</td>
<td>13.87</td>
<td>721.24</td>
</tr>
<tr>
<td>Clerk</td>
<td>9</td>
<td>198</td>
<td>13</td>
<td>2574</td>
</tr>
<tr>
<td>LPN</td>
<td>1</td>
<td>26</td>
<td>19.42</td>
<td>504.92</td>
</tr>
<tr>
<td><strong>Total Physician cost</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>24701.74</strong></td>
</tr>
</tbody>
</table>

### Vaccine Costs

<table>
<thead>
<tr>
<th>Position</th>
<th># of Vaccines</th>
<th>Individual Vaccine Cost</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>School Clinic</td>
<td>47</td>
<td>26.26</td>
<td>1234.22</td>
</tr>
<tr>
<td>Public Clinic</td>
<td>40</td>
<td>26.26</td>
<td>1050.4</td>
</tr>
<tr>
<td><strong>Total Vaccine Clinic Cost</strong></td>
<td></td>
<td></td>
<td><strong>2284.62</strong></td>
</tr>
</tbody>
</table>

### Summary

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total State Personell</td>
<td><strong>17146.88</strong></td>
</tr>
<tr>
<td>Total Medical Cost</td>
<td><strong>24701.74</strong></td>
</tr>
<tr>
<td>Total Vaccine Clinic</td>
<td><strong>2284.62</strong></td>
</tr>
<tr>
<td>Total Overall Cost</td>
<td><strong>44133.24</strong></td>
</tr>
</tbody>
</table>
DALY, YLL, YLD

- **DALY**
  - *Disability Adjusted Life Year*

- **YLL**
  - *Years of Life Lost due to premature death*

- **YLD (Years Lived with Disability)**
  - *Years of Life Lost due to Disability*
    - population: (prevalence) * (disability weight)
    - individual: (years with disability) * (disability weight)

- **DALY = YLL + YLD**

One DALY equals one lost year of healthy life.
Daly = YLD + YLL

Daly
Disability Adjusted Life Years is a measure of overall disease burden, expressed as the cumulative number of years lost due to ill-health, disability or early death.

YLD = Years Lived with Disability

YLL = Years of Life Lost

Healthy life
Disease or Disability
Expected life years

Early death
**DALY = YLL + YLD**

DALY: Disability Adjusted Life Years
YLL: Years of Life Lost due to premature death
YLD: Years of Life Lost due to Disability
**DALY = YLL + YLD**

LE = Average Life Expectancy = 78.7
MR = Mortality rate of pertussis worldwide = .001
I = Number of Confirmed Cases = 72
DW = Pertussis Disability Weight = .137

### Calculation of YLL

<table>
<thead>
<tr>
<th></th>
<th>Average Age</th>
<th># of Confirmed Pertussis Cases</th>
<th>YL = # cases*(LE-Avg. Age)</th>
<th>YLL = [YL(Adults)*MR] + [YL(Children)*MR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>36.33</td>
<td>29</td>
<td>1228.73</td>
<td>4.28</td>
</tr>
<tr>
<td>Children</td>
<td>7.69</td>
<td>43</td>
<td>3053.43</td>
<td></td>
</tr>
</tbody>
</table>

### Calculation of YLD

<table>
<thead>
<tr>
<th></th>
<th>Duration of illness (years)[L]</th>
<th>YLD = I<em>DW</em>L</th>
<th>YLD\text{Averted} = YLD\text{Possible} - YLD\text{Actual}</th>
</tr>
</thead>
<tbody>
<tr>
<td>YLD\text{Actual}</td>
<td>.125</td>
<td>1.23</td>
<td>1.63</td>
</tr>
<tr>
<td>YLD\text{Possible}</td>
<td>.29</td>
<td>2.86</td>
<td></td>
</tr>
</tbody>
</table>
\[
ICER = \frac{\text{Cost}_{\text{new intervention}} - \text{Cost}_{\text{control}}}{\text{Effectiveness}_{\text{new intervention}} - \text{Effectiveness}_{\text{control}}}
\]

**Incremental Cost-Effectiveness Ratio**

\[
\text{DALY} = \text{YLL} + \text{YLD} \\
= 4.28 + 1.63 \\
= 5.91 \text{ DALYs}
\]

Cost of Intervention = $44,133.24  \\
Cost of no Intervention = $0

\[
ICER = \frac{\$44,133.24}{5.91 \text{ DALYs}}
\]

**ICER** = $7,468 / DALY averted
Tuberculosis

2011 outbreak
Tuberculosis

- Bacteria
  - Mycobacterium tuberculosis

- Symptoms
  - Respiratory problems

- Transmission
  - Air-borne

- Latent TB infection
  - \( \frac{1}{3} \) global
    - Asymptomatic
    - Non-infectious

- Active TB disease
  - Symptomatic
  - Infectious
Natural history of TB infection

- **Exposure**
- **Infection**
  - **Dendritic Cell** (innate response)
  - **T Cell** (adaptive response)
- **Initial immune control of bacteria**
- **Granuloma**
- **Elimination of bacteria**
- **Lifelong containment**
- **Reactivation**
- **Active TB**
- **Onward transmission**
- **Latent TB**
- **Active TB**
Figure 3. Transmission of Tuberculosis and Progression from Latent Infection to Reactivated Disease.

Among persons who are seronegative for the human immunodeficiency virus (HIV), approximately 30 percent of heavily exposed persons will become infected. In 5 percent of persons with latent infection, active disease will develop within two years, and in an additional 5 percent, progression to active disease will occur later. The rate of progression to active disease is dramatically increased among persons who are coinfected with HIV.

- P Small 2001
Tuberculosis outbreak (2011)
New River Valley

- New River Valley jail
  - 1 case
    - 41 year old
    - 6 month history of TB symptoms
    - HIV+
  - admitted to hospital
    - TB and HIV drug treatment
    - isolation
New River Valley Regional Jail

- Inmate population
  - week day
    - 880
  - weekend
    - 930-940

- New inmates
  - ~ (50-60) / week

- Employees
  - ~ 200
LTBI treatment - 3HP

- 3 month treatment
  - once a week
    - isoniazid
    - rifapentine

- DOT
  - directly observed therapy
LTBI treatment

- 35 inmates
  - PPT+
  - chest x-ray -
  - HIV -

- 28 inmates
  - 3HP treatment
  - 17 completed

- 21 staff
  - PPT+
  - chest x-ray -
  - HIV -

- 10 staff
  - 3HP treatment
SEIS (Susceptibles-Exposed-Infectious-Susceptibles) tuberculosis

\[ \lambda = \text{Force of infection} \]
\[ \lambda \cdot S \]
SEIS

\[
\begin{align*}
\frac{dS}{dt} &= -\beta SI + \gamma I \\
\frac{dE}{dt} &= +\beta SI - \delta E \\
\frac{dI}{dt} &= +\delta E - \gamma I
\end{align*}
\]
**SEIS epidemiological model**
(Susceptibles-Exposed-Infectious-Susceptibles)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda$</td>
<td>Uninfected entry rate</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Transmission rate</td>
</tr>
<tr>
<td>$R_1$</td>
<td>Exit rate</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>1/(treatment period)</td>
</tr>
<tr>
<td>$\lambda_{E_S}$</td>
<td>Short latent entry rate</td>
</tr>
<tr>
<td>$\lambda_{E_L}$</td>
<td>Long latent entry rate</td>
</tr>
<tr>
<td>$\lambda_L$</td>
<td>Life time latent entry rate</td>
</tr>
<tr>
<td>$R_2$</td>
<td>1/(time period until hospitalization)</td>
</tr>
<tr>
<td>$p$</td>
<td>Fraction of population that may develop active disease</td>
</tr>
<tr>
<td>$f_s$</td>
<td>1/(short latent period)</td>
</tr>
<tr>
<td>$f_L$</td>
<td>1/(long latent period)</td>
</tr>
</tbody>
</table>

**Differential equations**

\[
\begin{align*}
\frac{dS}{dt} &= \lambda - \beta SI - R_1 S + \gamma I \\
\frac{dE_S}{dt} &= \lambda_{E_S} + \left(\frac{p}{2}\right) \beta SI - f_s E_S - R_1 E_S \\
\frac{dE_L}{dt} &= \lambda_{E_L} + \left(\frac{p}{2}\right) \beta SI - f_L E_L - R_1 E_L \\
\frac{dL}{dt} &= \lambda_L + (1-p) \beta SI - R_1 L \\
\frac{dI}{dt} &= f_s E_S + f_L E_L - R_1 I - R_2 I \\
\frac{dH}{dt} &= R_2 I - \gamma I
\end{align*}
\]
Scenario simulations

- Base-case scenario
  - No TB pre-screening

- Intervention scenario
  - TB pre-screening
Incremental Cost-Effectiveness Ratio

\[ ICER = \frac{\text{Cost}_{\text{new intervention}} - \text{Cost}_{\text{control}}}{\text{Effectiveness}_{\text{new intervention}} - \text{Effectiveness}_{\text{control}}} \]

\[ ICER = - \frac{15,461}{\text{DALY averted}} \] (cost saving)
Fungal Meningitis

2012 outbreak
Fungal meningitis

- Fungus
- Symptoms
  - headache
  - stiff neck
  - fatigue
- Transmission
  - non-contagious
- New England compounding center
  - contaminated lots of methylprednisolone acetate
  - used in epidural spinal injections
Fungal meningitis outbreak

- Health facilities
  - 23 states
    - received contaminated lots
  - 20 states
    - 751 cases
    - 64 deaths

- Virginia
  - 54 cases
  - 5 deaths
Fungal meningitis outbreak (2012)
New River Valley
94 exposed residents

= location of facility that received potentially contaminated product

Kate Corvese, 2012
Surveillance process

- Get informed about the issue
- Visit NRHD Facility
- Visit Roanoke Facility
- NRHD Patients' Information
- Roanoke Patients' Information

Volunteers

Gather Case Definition and Work Instruction

Initial contact with patients

3 months after last injection passed?

Approved Symptoms?

- No
- Yes

Refer to medical care and lab test

Contact Patient's physician

Contact ER

Case Definition meet?

- No
- Yes

Follow up with patient after 10 days

Send patient to hospital for further medical care

Done
Time & costs

Hours

- Volunteer: 21%
- Director: 10%
- Planner: 5%
- Epidemiologist: 57%

Cost

- Nurse Epi: 55%
- EH Management: 12%
- Clerical: 5%
- Admin: 22%
Incremental Cost-Effectiveness Ratio (ICER) is a measure used in cost-utility analyses that compares the cost of new interventions to a control group. It is calculated as:

\[ ICER = \frac{Cost_{\text{new intervention}} - Cost_{\text{control}}}{Effectiveness_{\text{new intervention}} - Effectiveness_{\text{control}}} \]

In this case:

- **DALY**: 73.5 DALYs averted
- **Cost of Intervention**: $30,492

The ICER is calculated as:

\[ ICER = \frac{\$30,492}{73.5} \approx \$415 / \text{DALY averted} \]
Pertussis
Tuberculosis
Fungal Meningitis

Comparative analysis of different interventions

Uniform metric: ICER = $/DALY averted
# Prioritization of limited public health resources

<table>
<thead>
<tr>
<th>Intervention</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>-$15,461/DALY averted (Cost saving)</td>
</tr>
<tr>
<td>Fungal meningitis</td>
<td>$415 / DALY averted</td>
</tr>
<tr>
<td>Pertussis</td>
<td>$7,468 / DALY averted</td>
</tr>
</tbody>
</table>
## Cost-effectiveness thresholds

<table>
<thead>
<tr>
<th>Organization/group</th>
<th>Cost-effectiveness thresholds</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia*</td>
<td>Costs per LYG &lt; AU $ 42,000 – 76,000 (costs per LYG &lt; AU $ 42,000: reimbursement likely, costs per LYG &gt; AU $ 76,000 reimbursement unlikely)</td>
<td>George et al. (2001)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Costs &lt; € 20,000 per QALY or LYG: cost-effective* Costs &lt; € 80,000 per QALY: cost-effective**</td>
<td>Welte et al. (2004c); Raad voor de Volksgezondheid &amp; Zorg (2007)</td>
</tr>
<tr>
<td>UK National Institute of Clinical Evidence (NICE)*</td>
<td>Costs per QALY &lt; £ 20,000–30,000: cost-effective Costs per QALY &lt; £ 45,000: cost-effective</td>
<td>Devlin and Parkin (2004); Appleby and Devlin, Parkin (2007)</td>
</tr>
<tr>
<td>US Institute of Medicine (IOM)**</td>
<td>Saves money and QALYs: most favorable Costs per QALY &lt; US $ 10,000: more favorable Costs per QALY &gt; US $ 10,000 and &lt; 100,000: favorable Costs per QALY &gt; US $ 100,000: less favorable</td>
<td>Institute of Medicine (2000)</td>
</tr>
<tr>
<td>World Health Organization (WHO)**</td>
<td>Costs per DALY &lt; GDP per capita: highly cost-effective Costs per DALY = 1x – 3x GDP per capita: cost-effective Costs per DALY &gt; 3x GDP per capita: not cost-effective</td>
<td>WHO (2008)</td>
</tr>
<tr>
<td>International and especially US decision analysts**</td>
<td>Costs per QALY or LYG &lt; US $ 50,000: cost-effective</td>
<td>Grosse (2008)</td>
</tr>
<tr>
<td>US and British health economists**</td>
<td>Costs per LYG &lt; US $ 60,000: cost-effective</td>
<td>Newhouse (1998)</td>
</tr>
</tbody>
</table>

* Thresholds derived from past decisions
** Officially stated thresholds
LYG = Life year gained
QALY = Quality-adjusted life year
GDP = Gross domestic product
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