Economic Evaluation of Outbreak Responses of Pertussis, Tuberculosis and Fungal Meningitis in New River Valley, Virginia

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Economic Evaluation of Outbreak Responses of Pertussis, Tuberculosis and Fungal Meningitis in New River Valley, Virginia

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Conflict of interest: None

- We declare that we have no conflict of interest, and we comply with the American Public Health Association Conflict of Interest and Commercial Support Guidelines.
Learning objectives

- Identify the costs and epidemiological benefits of outbreak responses of pertussis, tuberculosis and fungal meningitis in New River Valley, Virginia.

- Evaluate the incremental cost-effectiveness ratio for each of the disease outbreak responses.

- Compare the incremental cost-effectiveness ratios to prioritize the limited resources of the local health department among different interventions.
Study 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 Cases</th>
<th>Decrease</th>
<th>Most Recent Reports in the U.S.</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>530,217</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>47,745</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
## 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>Clinic</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

<table>
<thead>
<tr>
<th>Category</th>
<th>Cost</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 = YLL + YLD

**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.

\[ \text{DALY} = \text{YLD} + \text{YLL} \]

- **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>Duration of illness (years)[L]</th>
<th>YLD= I<em>DW</em>L</th>
<th>YLD&lt;sub&gt;Averted&lt;/sub&gt;= YLD&lt;sub&gt;Possible&lt;/sub&gt;-YLD&lt;sub&gt;Actual&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>YLD&lt;sub&gt;Actual&lt;/sub&gt;</td>
<td>.125</td>
<td>1.23</td>
</tr>
<tr>
<td>YLD&lt;sub&gt;Possible&lt;/sub&gt;</td>
<td>.29</td>
<td>2.86</td>
</tr>
</tbody>
</table>

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

\[
\text{Cost of Intervention} = \$44,133.24
\]
\[
\text{Cost of no Intervention} = \$0
\]

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

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

\[
\text{ICER} = \$7,468 / \text{DALY averted}
\]
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)
- **4-6 weeks**
  - Elimination of bacteria
- **Years-decades**
  - Initial immune control of bacteria
  - Granuloma
  - Elimination of bacteria
- **Latent TB**
  - Lifelong containment
  - Reactivation
- **Active TB**
  - Onward transmission
  - Inability to control bacteria
  - Macrophage
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

![Diagram]

- \( S \) (Susceptibles)
- \( E \) (Exposed)
- \( I \) (Infectious)

Transitions:
- \( \beta \cdot I \cdot S \)
- \( \gamma \cdot I \)
- \( \delta \cdot E \)

\( \lambda = \) Force of infection

\( \lambda \cdot S \)
The SEIS model for tuberculosis can be described by the following differential equations:

\[
\frac{dS}{dt} = -\beta SI + \gamma I
\]

\[
\frac{dE}{dt} = +\beta SI - \delta E
\]

\[
\frac{dI}{dt} = +\delta E - \gamma I
\]
TB transmission dynamics

- Susceptible
  - Exit S

-Short latent (ES)
  - Exit ES
  - Ent ES

-Long Latent (EL)
  - Exit EL
  - Ent EL

-Lifetime latent (L)
  - Exit L
  - Ent L

-Infectious (I)
  - Exit I
  - Ent I

-Treatment (H)
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>$\tau$</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>$1/($diagnosis delay$)$</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

- Susceptibles
  $$dS/dt = \lambda - \beta SI - R_1 S + \tau H$$
- Short Latent
  $$dE_s/dt = \lambda_{E_s} + (p/2) \beta SI - f_s E_s - R_1 E_s$$
- Long Latent
  $$dE_l/dt = \lambda_{E_l} + (p/2) \beta SI - f_l E_l - R_1 E_l$$
- Lifetime Latent
  $$dL/dt = \lambda_L + (1-p) \beta SI - R_1 L$$
- Infectious
  $$dI/dt = f_s E_s + f_l E_l - R_1 I - R_2 I$$
- Hospitalized
  $$dH/dt = R_2 I - \tau H$$
Scenario simulations

● Base-case scenario
  ○ No TB pre-screening

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

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

$ICER = -\$15,461 / DALY averted$

(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
Surveillance process

1. Outbreak Started
2. Epidemiologist visited NR health facility
3. Update case definition and surveillance instruction
4. Initial contact with exposed patients
5. Volunteers
6. 3 months passed from the last injection?
   - Yes: Done
   - No: Approved symptoms?
     - Yes: Refer to medical care for lab tests
     - No: Contact local emergency department
6. Met case definition?
   - Yes: Send to hospital for further medical care
   - No: Follow up with patient after 10 days
Time & costs

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

Cost
- Epidemiologist: 55%
- Director: 22%
- Planner: 12%
- EH Management: 5%
- Clerical: 5%
- Admin: 5%
- Nurse Epi: 5%
- Volunteer: 5%
**ICER**

Incremental Cost-Effectiveness Ratio

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

**DALY**  =  100.52 DALYs averted

Cost of Intervention  =  $30,492

\[ \text{ICER} = \frac{\$30,492}{100.52} \]

**ICER**  =  $303 / DALY averted

- **High cost and low effectiveness**
  - Reject new intervention
  - (Dominated)

- **High cost and high effectiveness**
  - CEA

- **Low cost and low effectiveness**
  - CEA

- **Low cost and high effectiveness**
  - Adopt new intervention
  - (Dominant)
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>Pertussis</td>
<td>$7,468 / DALY averted</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>-$15,461/DALY averted (Cost saving)</td>
</tr>
<tr>
<td>Fungal meningitis</td>
<td>$303 / DALY averted</td>
</tr>
</tbody>
</table>
# Cost-effectiveness thresholds

Table 15.4 International thresholds for cost-effectiveness

<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 $42,000 – 76,000 (costs per LYG $42,000: reimbursement likely, costs per LYG &gt; $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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Thank you