Overview of Workshop

- Introduce infectious disease modelling
- Provide case studies of where infectious disease models have influenced policy
  - Kamal Desai, PhD – Research Scientist at United BioSource – “HIV Prevention in Industrialized Countries”
  - Professor Maarten Postma, PhD - Professor in Pharmacoeconomics at University of Groningen, member of the Netherlands Health Council that advises on vaccines – “Dynamic models for cost-effectiveness in infectious diseases; examples for Pertussis and HPV”
  - Déirdre Hollingsworth PhD - Research Fellow in infectious Disease Epidemiology, Imperial College London – “Mathematical models in outbreak control and mitigation”
- Each example will demonstrate where the use of infectious disease models can give insight into policy decisions
Definitions and Naming

- ‘Infectious Disease’ models – Transmission/dynamic
  - Where transmission is dependent on the number of other individuals infected in the model

- ‘Standard’ models – Static
  - Where transmission is not linked to number of other individuals infected in the model

Justification and Aims for Workshop

- Justification
  - Economic modelling and infectious disease modelling exist in separate spheres
  - Little cross-over between the two worlds
  - Only 11% economic studies of vaccines used an approach that could account for both direct and indirect effects (Kim, Goldie et al., Pharmacoeconomics, 2008)
Justification and Aims for Workshop

- **Aims**
  - Illustrate how transmission dynamic models have informed policy
  - Unify thinking of standard economic modellers and infectious disease modellers
  - Reveal the potential of infectious disease models in economic analysis
  - Demonstrate how standard economic models may misrepresent the impact of an intervention for infectious disease
  - Encourage using infectious disease modelling in policy decisions

Comparison of Modelling Worlds

**Infectious disease models**
- **Agencies**
  - JCVI, HPA in UK; CBER, ACIP in US
- **Developers**
  - Academics
- **Purpose**
  - Investigative
- **Perspective**
  - Societal – for the greater good
- **Underlying equations used**
  - ODEs
- **Software**
  - C/C++ or specialist/bespoke software

**Standard models**
- **Agencies**
  - NICE, EMA, other HTA authorities
- **Developers**
  - Private companies
- **Purpose**
  - Economics
- **Perspective**
  - Payer
- **Underlying equations used**
  - State equations
- **Software**
  - Excel often used but also specialist software
Key Differences in Interpretation

- **Herd immunity**
  - Removing infection in one individual can benefit the population by reducing the pool of infected individuals
- **Changes in age profile of infection/disease**
  - Lowering transmission can increase the age of infection where the impact of infection may differ — e.g., Rubella vaccination
- **Benefits are long term**
  - Particularly for cancer prevention through vaccination
- **Intervention does not necessarily benefit the individual**
  - Vaccinating males for HPV to protect females from cervical cancer
- **Targeting subgroups can have greater impact for same level of treatment**
- **Non-linear benefits of treatment/threshold properties**
- **Elimination possible**

ISPOR Modelling Taskforce Recommendations

- **V-1** A dynamic model is needed when evaluating an intervention against an infectious disease that
  1. Has an impact on disease transmission in the target population or
  2. Alters the frequency distribution of strains (e.g., genotypes or serotypes)
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HIV/AIDS Prevention in United States

- "High Impact Prevention"
  - CDC HIV Prevention strategy
  - Prioritize and implement optimal combinations of cost-effective, scalable interventions based on current science
- In the USA, populations at risk who are candidates for targeted interventions for HIV/AIDS prevention
  - Men who have sex with men (MSM)
  - Hispanics/Latinos
  - African Americans
  - Injection drug users
  - Bridging groups (e.g., IDUs, commercial sex workers)
  - Discordant couples (one partner is HIV+)

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HIV/AIDS Prevention in United States

1. **Oral PrEP or "pre-exposure prophylaxis"**
   - 44% reduction in the incidence of HIV in MSM taking once-daily oral tablet of TDF 300mg + FTC 200mg – 92% reduction in highly-adherent patients ([iPrEx trial, NEJM 2010](https://doi.org/10.1056/NEJMoa0908363))
   - Confirmed in heterosexual men and women in Botswana – 63% reduction in HIV infection ([TDF2 trial; Thigpen IAS Conf 2011](https://doi.org/10.1056/NEJMoa1004297))
   - Serodiscordant heterosexual couples from Kenya and Uganda – 75% reduction in HIV infection ([Partners PrEP trial; NEJM 2012](https://doi.org/10.1056/NEJMoa1208176))

2. **Voluntary adult circumcision**

3. **Early therapy to prevent transmission**
   - 96% reduction in HIV transmission in discordant couples ([HPTN052 trial; NEJM 2011](https://doi.org/10.1056/NEJMoa0909052))

4. **HSV-2 suppressive therapy to control HIV**
   - Suppressive valacyclovir reduced seminal HIV viral load by 44% in HIV-1/HSV-2 co-infected MSM ([Zuckerman; AIDS 2009](https://doi.org/10.1097/01.aids.0000273103.59636.88))
HIV/AIDS Prevention in United States

- **Some key discoveries in HIV prevention**

  1. **Oral PrEP or “pre-exposure prophylaxis”**
     - 44% reduction in the incidence of HIV in MSM taking once-daily oral tablet of TDF 300mg + FTC 200mg – 92% reduction in highly-adherent patients (iPrEx trial, NEJM 2010)
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**Question: Which prevention approaches are suited to the United-States?**

---

HIV/AIDS Prevention in United States

- **Some key discoveries in HIV prevention**

  1. **Oral PrEP or “pre-exposure prophylaxis”**
     - 44% reduction in the incidence of HIV in MSM taking once-daily oral tablet of TDF 300mg + FTC 200mg – 92% reduction in highly-adherent patients (iPrEx trial, NEJM 2010)
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**Question: Which prevention approaches is receiving the most attention today?**
Modelling the potential impact of PrEP strategies among MSM in the United States: HIV infections prevented and cost-effectiveness

Desai, Sansom, Ackers et al., AIDS 2008

Question: Which prevention approaches is receiving the most attention today?

- US FDA has approved the drug TDF+FTC for daily use by uninfected adults to help prevent the sexual acquisition of HIV
- First time any drugs have been approved for the prevention of sexually acquired HIV infection

PrEP Intervention Assumptions

- Nested within Prevention Case Management (PCM)
  - Client-centred HIV prevention strategy
  - Intensive, ongoing risk-reduction counselling
- Targeted to very high risk MSM (i.e., any of the following in last six months)
  - Unprotected sex with HIV-infected person
  - Unprotected sex in exchange for money/drugs
  - Anonymous or >5 sex/needle sharing partners
  - Diagnosed with STD
- Coverage:
  - 1,500 or 15,000 MSM annually corresponding to 2.5% or 25% of susceptible very high risk MSM in New York City
PrEP Intervention Assumptions

- **Efficacy:**
  - 50% or 70% reduction in susceptibility to HIV infection upon exposure
  - Assumes near-perfect patient adherence

- **Program adherence:**
  - 33%, 50% or 95%
  - Refers to % of TDF recipients taking pill *every day*

- **Unit price for HIV chemoprophylaxis:** $31 per daily dose (TDF+FTC)

- **Support services via prevention case management:** $5,370 per person, five yrs (initial screening, monitoring, exams, 40% dropout rate)

- **HIV/AIDS lifetime treatment costs** $343K (+/- 30%)
Model Parameters

- **Biological parameters**
  - Transmission probabilities by stage of infection
  - Natural history of HIV, survival under ARV Rx

- **Demographic parameters specific to population**
  - Population size 330,000 MSM in 2002; growth rate 0.77% /yr
  - Age distribution (13–24: 14%; 25–34: 28%; 35–44: 29%; 45+: 29%)
  - Non-AIDS death rate (0.08% – 0.3%, depending on age)

- **Behavioural parameters**
  - Annual number of partners (1–30, depending on age, activity class)
  - 30% high risk
  - Contact patterns: proportional to assortative mixing

Persons LWHA and Annual Number of New Infections in 200 Simulations (No PrEP)

47,720 LWHA (14.3% prevalence)

3,860 new infections annually (1.36% incidence per yr)
18,720 infections over 5 years
## Cases Averted Between 2008–2013 in NYC MSM

### Assumptions

**Program Adherence** | **Cases Averted** | **ICER ($ / QALY)**
--- | --- | ---
**Coverage 15,000, 50% efficacy if perfect patient adherence**
95% | 2620 | 300
50% | 1670 | 31,970
33% | 1040 | 81,700

**Coverage 1,500, 50% efficacy if perfect patient adherence**
95% | 240 | 680 direct
50% | 190 | 990 indirect
33% | 110 |
### Cases Averted Between 2008–2013 in NYC MSM

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>Program Adherence</th>
<th>Cases Averted</th>
<th>ICER ($ / QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage 15,000, 50% efficacy if perfect patient adherence</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Range 0-1500

High probability of no benefit

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### Are results conclusive?

- Desai et al. (AIDS 2008) report ICER of $32,000 / QALY

- Palteil et al. (CID 2009) report ICER of $298,000 / QALY
Are results conclusive?

- Desai et al. (AIDS 2008) report ICER of $32,000 / QALY
  - Targeted for highest impact
  - Dynamic

- Palteil et al. (CID 2009) report ICER of $298,000 / QALY
  - Not targeted, general MSM population
  - Static

- Juusola et al. (Ann Int Med 2012)
  - Consistent with above
    - $50,000 / QALY when targeted
    - $172,000 / QALY in general MSM

Some Agency Decisions Regarding PrEP

- US
  - FDA has approved the drug TDF+FTC for daily use by uninfected adults to help prevent the sexual acquisition of HIV
  - First time any drugs have been approved for the prevention of sexually acquired HIV infection
  - CDC released interim guidance; Leading development of detailed U.S. Public Health Service guidelines on the use of PrEP as part of comprehensive HIV prevention programs

- US, France
  - PrEP should be targeted to high-risk MSM
  - Exclude patients at risk of renal disease or bone demineralization (known toxicities of TDF+FTC)
  - Screening for breakthrough infection every 2-3 months
  - Monitoring for changes in risk practices and adherence disinhibition
Other strategies

- Male circumcision in MSM

  **Question:** Why is this not likely to be effective in the United-States?

- HSV-2 Suppressive therapy

  **Question:** Why is this not likely to be effective in the United-States?

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Dynamic Models for Cost-effectiveness in Infectious Diseases; Examples for Pertussis and HPV

Prof Maarten J Postma

Health Economics.... A New Toxicity?

“The drug itself has no side effects - but the number of health economists needed to prove its value may cause dizziness and nausea”
Contents

- Decision tree for modelling
  - Static
  - Dynamic

- Pertussis
  - Adolescent vaccine to protect infants
  - Illustrating age shift

- HPV-vaccine
  - Relatively low coverage
  - Illustrating herd immunity

Figure 1: Guide on choosing the appropriate modeling approach (*pathogens: bacteria, viruses & fungi)
Figure 1: Guide on choosing the appropriate modeling approach (*pathogens: bacteria, viruses & fungi)
Static Model

- Constant force of infection/chronic disease
- No herd immunity
- Modellers:
  - Keep it as simple as possible
  - However, grasp all essentials
- Used in:
  - Cocooning in pertussis
  - Rotavirus
  - Initially in pneumococcal
Dynamic Modelling

- Describing/simulating the spread of disease in populations
- Herd immunity
- Other effects:
  - Negative effects
  - Age shift
    - VZV
    - Pertussis
Dynamic Model

Susceptible → Infected → Susceptible (SIS)

\[ \frac{dS}{dt} = -\beta \cdot k \cdot S(t) \frac{I(t)}{N} + \nu I(t) \]
\[ \frac{dI}{dt} = \beta \cdot k \cdot S(t) \frac{I(t)}{N} - \nu I(t) \]

S(t) = number susceptible \hspace{1cm} I(t) = number infected
\beta = transmission parameter \hspace{1cm} \nu = recovery rate
k = number of partners \hspace{1cm} N = total population

Dynamic Model (Cont’d)

\[ \frac{dS}{dt} = -\beta \cdot k \cdot S(t) \frac{I(t)}{N} + \nu I(t) \]
\[ \frac{dI}{dt} = \beta \cdot k \cdot S(t) \frac{I(t)}{N} - \nu I(t) \]
Pertussis

- Dynamic model
  - Comartmental
  - Individual-based
  - Similar results

- Adolescent vaccination to protect (partly) unprotected infants against primary infections

- Duration of protection
  - Two years for infection
  - 10 years for symptomatic disease
Impact of a every 10 year booster compared with other booster strategies

- No booster
- Booster at 12 years (base case)
- Booster at 10 and 20 years
- Booster every 10 years

M Rozenbaum, Epidemiology & Infection 2011
Table 6. Mean age-specific outcomes* in terms of costs and QALYs. Situation with adolescent pertussis booster vaccination over the 25 years.

<table>
<thead>
<tr>
<th>Age</th>
<th>( R_n = 8 ) years</th>
<th>Direct medical costs (€)</th>
<th>Indirect costs (€)</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 yr</td>
<td>10,786</td>
<td>1612</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>1–3 yrs</td>
<td>601</td>
<td>4613</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td>4–9 yrs</td>
<td>669</td>
<td>77,474</td>
<td>8.86</td>
<td></td>
</tr>
<tr>
<td>10–19 yrs</td>
<td>737</td>
<td>275,300</td>
<td>137.76</td>
<td></td>
</tr>
<tr>
<td>20–49 yrs</td>
<td>-127</td>
<td>-281,796</td>
<td>-25.23</td>
<td></td>
</tr>
<tr>
<td>50–74 yrs</td>
<td>-42</td>
<td>-56,864</td>
<td>-8.00</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12,624</td>
<td>20,339</td>
<td>114.65</td>
<td></td>
</tr>
</tbody>
</table>

Negative numbers indicate an increase in costs or a decrease in QALYs as a result of adolescent pertussis booster vaccination.

*Due to the extensive running time of the model related to the high complexity, only 20 years were simulated. \( R_n \) = loss of immunity after natural infection.

doi:10.1371/journal.pone.0013392.t006
Adult pertussis vaccination strategies and their impact on pertussis in the United States: evaluation of routine and targeted (cocoon) strategies

L. COUDEVILLE, A. VAN RIE AND P. ANDRE

Fig. 1. Diagram of the immunological and infectious states and transitions between states in the age-specific pertussis model. WV1-3, Waning of natural immunity 1-3; VI-4, vaccination status 1-4; WV1-3, waning vaccine 1-3; vc, vaccine coverage.

We used in the base case a WAIFW matrix structure similar to the one considered in Van Rie & Hethcote [8].

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Incidence of pertussis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 months</td>
<td>600</td>
</tr>
<tr>
<td>6-12 months</td>
<td>200</td>
</tr>
<tr>
<td>1-3 years</td>
<td>400</td>
</tr>
<tr>
<td>10-19 years</td>
<td>600</td>
</tr>
<tr>
<td>&gt;20 years</td>
<td>100</td>
</tr>
</tbody>
</table>

Fig. 4. Annual, age-specific incidence of symptomatic (typical+ mild) pertussis cases once steady state situation has been reached. vc, Vaccination coverage.
Adult pertussis vaccination strategies and their impact on pertussis in the United States: evaluation of routine and targeted (cocoon) strategies

L. COUDEVILLE*, A. VAUE

We used in the Hethcote [8].

<table>
<thead>
<tr>
<th>Age of Contact</th>
<th>Age of Participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 mo.</td>
<td>0-5 yr.</td>
</tr>
<tr>
<td>6-11 mo.</td>
<td>1-4 yr.</td>
</tr>
<tr>
<td>1-4 yr.</td>
<td>5-9 yr.</td>
</tr>
<tr>
<td>5-9 yr.</td>
<td></td>
</tr>
</tbody>
</table>

Nieuwe uitdagingen voor de farmaco-economie

Introductie HPV-vaccin

Met de recente introductie van Gardasil en de verwachte registratie van Cervarix tegen humaan papillomavirus, rijst de vraag naar de kosteneffectiviteit van vaccinatie tegen baarmoederhalskanker, en naar de beste vaccinatiestrategie.

Tekst: Maarten Postma, Hans Nijman, Toos Duijnen, Ate van de Zee, Jan Willichut
HPV Vaccine

- HPV-vaccination in NL
  - 12-year-old girls
  - Bivalent vaccine was selected after tendering
  - Catch-up up-to-and-including 16 years
  - On top of successful screening program

- Unexpected low coverage of HPV vaccination

- Model calibration on
  - HPV-incidence for a sentinel study
  - National cancer registries
Comparing bivalent and quadrivalent human papillomavirus vaccines: economic evaluation based on transmission model

Mark Jit mathematical modeller¹, Ruth Chapman mathematical modeller¹, Owain Hughes clinical research fellow², Yoon Hong Choi mathematical modeller¹

¹Health Protection Agency, London NW9 6BT, UK; ²Institute of Child Health, London WC1N 1EH
Summary

- **Dynamic models**
  - Often required given complexity
  - Transparency is an issue for authorities

- **Pertussis**
  - Additional strategies needed to protect infants
  - Cocooning or maternal immunisation?
  - Age shift impacts on cost-effectiveness

- **HPV-vaccine**
  - Herd immunity effect helps improving cost-effectiveness
  - Notable other examples: MenC and pneumococcal
  - Economic results in preparation

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Mathematical Models and Outbreaks

- Public health agencies increasing depend on epidemiological transmission models
  - Estimate likely impact of an epidemic
  - Plan for effective design of control measures
- Recent examples
  - BSE, vCJD (1990s)
  - Foot and Mouth Disease in cattle in the UK (2001)
  - SARS (2003)
  - ‘Swine flu’ H1N1v 2009
Overview
- Travel restrictions
  - How transmission modelling helped us understand their effect
  - Impact on policy
- How should you intervene for a new outbreak
  - Interactive discussion, based on small number of choices

Aim of Travel Restrictions

PREVENT OR DELAY ARRIVAL

Rate of new infections

Time
What Can We Learn from the Past? SARS 2003

"The World Health Organization (WHO) today began recommending that persons travelling to Hong Kong Special Administrative Region of China and Guangdong Province, China consider postponing all but essential travel. This updated travel advice comes as a result of new developments in the multi-country outbreak of severe acute respiratory syndrome (SARS)."
International Travel SARS 2003 – Impact on Global Spread

- Global alert 13 March
- Up to 80% reduction in passenger numbers
- Coincident with peak in epidemic
- Continued beyond end of outbreak


Travel Restrictions

Travel Restrictions

Nature Medicine

No change
Large reductions in travel
Travel Restrictions

- Control outbreak, no change in travel
- Control outbreak, Large reductions in travel

Influenza: No change in travel or control

Nature Medicine
Impact on Policy

- Many papers with different model structures got similar results
  - Cooper et al., PLoS Med 2006
- Impact on policy, ECDC guidance (2009)

Guide to public health measures to reduce the impact of influenza pandemics in Europe: ‘The ECDC Menu’

Summary Table: Characteristics of potential interventions to reduce transmission during phase 6 of a pandemic/severe epidemic of seasonal influenza (see pages 18 to 34 for detail and evidence)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Quality of evidence</th>
<th>Effectiveness (benefits)</th>
<th>Direct costs</th>
<th>Indirect costs</th>
<th>Acceptability to Europe</th>
<th>Practicalities and other aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Travel advice</td>
<td>E</td>
<td>Minimal</td>
<td>Small</td>
<td>Moderate</td>
<td>Good</td>
<td>International travel will probably decline moderately</td>
</tr>
<tr>
<td>2. Entry screening</td>
<td>E</td>
<td>Minimal</td>
<td>Large</td>
<td>Large</td>
<td>May be expected by resident populations</td>
<td>International travel will probably decline severely</td>
</tr>
<tr>
<td>3. Border closure or severest restrictions</td>
<td>E</td>
<td>Minimal</td>
<td>Large</td>
<td>Large</td>
<td>Not feasible to screen</td>
<td>International travel will probably decline severely</td>
</tr>
</tbody>
</table>

Global Spread and the Epidemic in Mexico
What Policy Would you Choose?

- Information:
  - Moderately severe epidemic
  - Can’t prevent entry into Europe
  - Vaccine available in six months (26 weeks)
  - Social distancing can be used to reduce transmission, but costly
    - Close schools
    - Postpone mass gatherings – sport events, festivals

- How would you use your budget?
  - Stockpile drugs for 25% of the country so all severe cases treated, no additional interventions
  - Add strict social distancing interventions for the first six weeks of the epidemic to slow the initial impact of the epidemic
  - Add mild social distancing interventions in the middle of the epidemic to reduce peak so health services are not overwhelmed

Aim of Interventions

- SLOW GROWTH?
- REDUCE PEAK DEMAND?
- REDUCE TOTAL NUMBER OF CASES?
- REDUCE TOTAL NUMBER OF DEATHS?
What Policy Would you Choose?

- What’s your primary aim?
  1. Minimise total cases
  2. Reduce total deaths by reducing peak
  3. Minimise economic impact of the epidemic

- How would you use your budget?
  1. Stockpile drugs for 25% of the country so all severe cases treated
  2. Add strict social distancing interventions for the first 12 weeks of the epidemic to slow the initial impact of the epidemic
  3. Add mild social distancing interventions to reduce peak so health services are not overwhelmed

---

1. Stockpile Drugs to Treat all Cases

Hollingsworth et al., PLoS Computational Biology 2010

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2. Social Distancing First 12 Weeks

Hollingsworth et al., *PLoS Computational Biology* 2010

3. Late Social Distancing

Hollingsworth et al., *PLoS Computational Biology* 2010
Summary

- Non-linear dynamics of outbreak dynamics mean that the best intervention may be non-intuitive:
  - Impact of travel restrictions depends on control of source outbreaks
  - ‘Hit hard, hit early’ may not always be the best approach
- Multiple aims may not necessarily be achieved by the same intervention
- Transmission modelling is the only way to investigate the impact of these interventions:
  - Influential in pandemic and outbreak planning nationally and internationally
- Opportunities for bringing together economic modelling with outbreak modelling:
  - Balancing costs and benefits of interventions
  - Dynamic adjustment of policy based on new information