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Is more always better: incorporating the concepts of incremental and marginal trade-offs in vaccine program design

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I have no actual or potential conflict of interest in relation to this program.

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Outline

- **Science vs decision**
- **Marginal protection vs marginal cost**
- **Examples**
  - Measles
  - Meningococcus
  - Hepatitis B
  - Mumps
  - Pneumococcus
- **Discussion**
- **Conclusion**

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Science vs decision making

- **Science refers to any systematic knowledge or prescriptive practice that is capable of resulting in a correct prediction (Wikipedia)**
  - Eg. Frequency of disease/complications/death, vaccine efficacy, resources required, etc…,
- **Decision making can be regarded as the mental processes (cognitive process) resulting in an outcome leading to the selection of a course of action among several alternatives.**
  - From a psychological perspective, it is necessary to examine individual decisions **in the context of a set of needs, preferences an individual has and values** they seek.

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Acceptability

- **Depends upon public health objectives**
  - Eradication
  - Control
    - Reduction of morbidity or of any disease (varicella?)
- **Social/professional/personal values**
- **Not science**

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Cost-effectiveness

- **Cost-effectiveness analyses standardize comparisons of health care investment on the basis of cost per outcome averted.**
- **Many preventive interventions include more than a single component (doses)**
- **Cost-effectiveness of an intervention is often calculated for all its components**
  - For vaccines, this generally applies to the full series of doses.
  - Although the price of each dose may be the same, the gain in protection induced by each dose is not.

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Cost-effectiveness of a vaccine program

- **Mean cost-effectiveness**
  - Cost for the total number of doses/components
  - Effectiveness of the entire program
- **Marginal cost-effectiveness**
  - Marginal effectiveness: Additional outcome prevented by the (last) dose/component of the intervention
  - Marginal cost: cost of the last dose/component
- **Decreasing % protected by each additional dose means an increasing marginal cost-effectiveness ratio (multiplying factor)**

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Number needed to treat (NNT)

- **NNT is the inverse of the absolute risk reduction**
- **NNT=1/(incidence$_{\text{no interv}}$ – incidence$_{\text{interv}}$)**
- **NNT= 1/incidence x Vaccine effectiveness**
- **Incidence is the cumulative incidence for the period of vaccine-induced protection**
- **NNT is directly related to cost-effectiveness**

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Measles

- **1st dose: 90% of vaccinees protected**
- **$NNT_{1st\ dose}$= 10/9= 1.1**
- **2nd dose: protection of 90% of the 10% left unprotected by the first dose**
- **$NNT_{2nd\ dose}$= 10/0.9= 11**
  - The additional protection provided by the second dose is much smaller
- **While the mean NNT would be ~2 (20/9.9, the NNT (and cost-effectiveness) ratio of the second vs the first dose is 10**
  - This corresponds to the **multiplying factor** of the number of vaccine doses required per outcome prevented for the additional dose compared to the first
- **Decision: Is it acceptable to give a 2nd dose?**
  - Objective of eliminating this disease

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Mean vs marginal cost-effectiveness ratio

- **Quebec catch-up campain in 2001**
  - 1 dose given children ≥1 year
  - 3 doses to infants at 2, 4, 6 months
- **Regular schedule for infants?**
  - Marginal cost-benefit of the 2nd and 3rd dose in infants?

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Conjugated meningo C vaccine

- **In Quebec between 1990 and 2000, 6% of all cases of invasive meningo C occurred in infants < 1 year of age (some before 4 months of age)**

- **Children ≥1 year of age**
  - One dose induces a protection in ≥ 90%
- **For infants:**
  - 3 doses at 2,4,6 months
  - Similar protection but 6-8 months earlier

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Meningococcal vaccine Marginal cost-benefit ratio

- **1 dose program at 12 months**
  - 94% of the incidence after that age
- **3 dose program at 2, 4, 6 months**
  - Additional (marginal) benefit is the reduction of incidence between 2 and 12 months (6%)
  - Additional (marginal) cost = 2 more doses
    - 1 dose→ 94% whereas 2 doses → 6%
    - 94%/ 6% = 15.6 times for ½ of the price
    - **Multiplying factor= 31.2**
- **De Wals et al** (*Vaccine 2004; 22:1233-40*)
  - 1 dose =$370k/case averted
  - 2nd,3rd doses=$7.3M/case averted (Multiplying Factor 34.8)
  - Is this acceptable?

Quadrivalent conjugate meningo vaccine

- Marginal cost is the difference between the price of the meningo C vaccine and the quadrivalent vaccine multiplied by the number of doses required
- Marginal benefit is the number of serogroup Y and W135 cases prevented
  - IMPACT reported 35 cases of Y and 14 cases of W135 in children (<20 years of age) from 2002 to 2007

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Hepatitis B Vaccines

	Recombivax 2,5 µg, 2 doses	Twinrix 360/10 2 doses	Recombivax2 ,5µg 3 doses	Engerix 10 µg 3 doses
% seroconverted (95% CI)	97.2% (94.9- 98.5)	97.1% (94.8- 98.4)	99.7% (99.0- 99.9)	99.1% (98.4- 99.5)
% seroprotected (95% CI)	94.4% (91.5- 96.3)	96.5% (94.1- 98.0)	99.2% (98.3- 99.6)	98.9% (98.2- 99.4)
GMT among all children	742 (593-929)	3248 (2579-4091)	3304 (2979-3665)	6761 (6031-7579)

B Duval International Hepatitis meeting, Sydney 2003

Marginal cost-benefit ratio

- **2 dose schedule provides protection to 96%**
- **3 dose schedule provides a protection to 99% of vaccinees**
  - 2 doses → 96%
  - 1 additional dose → 3%

  96% / 3% = 32 for 2 times the price

  Multiplying factor= 16
- **Is it acceptable to protect « only » 96% of the vaccinated population?**

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Mumps

- **Canada**
  - Before the vaccination program, there was a mean of 34 000 cases of mumps reported annually in Canada.
  - In 2007, there were ~ 1300 cases reported in Canada (a 96% decrease compared to pre-vaccine era)
    - 2007 was unusual as only 79 cases were reported annually between 2000 and 2006 (99,8 % reduction compared to pre-vaccine era)
- **USA**
  - About 150 000 cases reported annually before the vaccine
  - In 2006,~ 6 000 cases in 45 states (96% reduction)
  - Mean number of 265 cases between 2001 and 2005 (99.8% reduction)

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One dose to all persons who have not received 2 doses or adding a 3rd dose?

- **Measles two-dose program since 1996**
  - Vaccination with monovalent measles vaccine of school age children (5-18 years of age) in 1996 (now 19-32 years of age)
  - Vaccination of newborns with two doses of MMR since 1996 (now aged 1-14 years old)
  - Children 1-4 in 1996 (catch-up)
- **Benefit of a second dose**
  - Already a reduction of 96% even during epidemic year
  - The additional dose can at best reduce the incidence by 2-3%
  - In the 19-32 year old cohort:
    - Multiplying factor of 33-48
    - Assumes that the 2nd dose will be 100% effective
- **What are the objectives of the program?**
  - Are a few cases acceptable or should we set the goal of eliminating this disease?

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Conjugated pneumococcal vaccine

- **7-valent, 10-valent, 13 valent vaccines**
- **For the same price, it is better to get the vaccine with more serotypes**
- **If the price is different?**
  - Look at the marginal cost effectiveness for the protection against the serotypes not included in more expensive vaccine
  - Price difference/incidence of additional serotypes included
  - Acceptability has then to be evaluated

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Discussion

- **The cost of vaccines has largely increased and is a major obstacle to be able to protect all those who may benefit from these vaccines**
  - Eg. HPV vaccine
- **The marginal cost-effectiveness analysis permits to understand the gain provided by an additional dose or a vaccine that covers against more disease**

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Conclusion

- **It is relatively easy to derive an approximation of the multiplying factor.**
- **Cost is just one component of the analysis**
- **The acceptability of the persistence of a disease given the cost per outcome prevented can change over time**
- **The decision to recommend a specific vaccine or an additional dose is not a «scientific» action**
  - The science provides the data
  - The decision is a political process that judges the acceptability of doing/not doing an intervention based on personal/societal/professional needs and values
- **Given the limited resources, is it always the best option to include more doses or have a product that covers against more disease?**
  - Opportunity cost

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