Priority setting in resource allocation for health research: Orphan drug R&D

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How much should be spent on R&D for new drugs against African trypanosomiasis?

A 19-year-old recent mother lies dying from late-stage disease and adverse reactions to melarsoprol

Source: WHO/TDR/Crump Uganda 1996
Priority setting in resource allocation: Orphan drug R&D

• Introduction

• Conflicting ethical principles
  – Justice
    • Utilitarian
    • Rights-based
  – Beneficence
    • Non-abandonment
    • Scientific advancement

• Conclusions
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Orphan drugs: the research funding dilemma

A: Global diseases (e.g. cancer, cardiovascular disease)

B: Neglected diseases (e.g. malaria, TB)

C: Most neglected diseases (e.g. Chagas, leishmaniasis, sleeping sickness)

Z: Non-medical pharmaceutical market (baldness, wrinkles etc)

Source: MSF Access to Essential Drug Campaign 2001
The 10/90 gap in global health research

< 10% of funding for health research is directed to 90% of the world’s health problems

Source: IMS Health/Population Reference Bureau (see note 3, below)

Source: MSF Access to Essential Drug Campaign 2001
EU Orphan Drug Legislation (2000)

Orphan drug status: Drug is intended for diagnosis, prevention, or treatment of life-threatening or chronically debilitating condition which affects < 5/10,000 in the Community (EC regulation No 141/2000)

Definition can be extended to conditions with higher prevalence, if “the return on the marketing of a medicinal product would not be expected to justify the investment in its development”.

Incentives for industry:
- Tax breaks
- Market exclusivity
How much should a society spend on research for orphan diseases?

The *economic* perspective: Setting priorities for research should be conducted in order to make the most efficient use of scarce resources.

The *bioethical* perspective:

Four principles approach*:

- Autonomy
- Beneficence
- Non-maleficence
- Justice

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Moral dilemma of resource allocation for orphan drug R&D:

- Justice
- Beneficence

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*Beauchamp & Childress 2001*
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Utilitarian approach – Basis for economic analysis

“The greatest good for the greatest number”

But which values to maximise?
• Health benefits – index measures combining LE & QoL

Orphan diseases are *infrequent* by definition:
no or very little resources would be allocated on their behalf,
although affected individuals have a high need for treatment
(“capacity to benefit”)

6000 orphan diseases together affect 25-30 mio people in EU
• How much funding for orphan drug research overall?
• How much for each individual disease?
Utilitarian approach

Extreme uncertainty of benefits from research:
• Only 1 in 10 pharmaceutical compounds is successfully marketed: predictions of future success were misguided in 90%!
• Cost estimates for R&D vary widely: consensus that minimum size of a potentially interesting market is $100 million

Some tropical diseases are high prevalence conditions: but not in EU countries!

• Does a moral obligation of beneficence extend to individuals outside the economic and political remit of the society providing the funds?
• Traditional economic approaches to priority-setting fail to answer this question
• International funding agencies (e.g. Global Fund) might be a solution
Rights-based approach

Positive right: requires others to do something beneficial or enabling for right-bearers, e.g. right to a decent minimum of health care

EU Charter (2003) & EU Constitution (2007?): “Everyone has the right of access to preventive health care and the right to benefit from medical treatment under conditions established by national laws and practices”

• Scope of right is open to interpretation
• Legal rights can only apply to existing treatment options,
• Difficult to enforce an individual right to research funding for non-existent treatments
Rights-based approach

• Only social right or general moral obligation possible

• But why are decisions then left to industry? Public bodies now only approve decisions *a posteriori*

• Are public-private partnerships a solution?

e.g. African onchocerciasis programme very successful to channel research funds in hitherto under-researched tropical parasitosis

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Non-abandonment

• Basic moral and public policy commitment to not abandon persons with needs for highly specialised care when making resource allocation decisions (Landman & Henley 1999)

• Are Orphan Drug Acts attempts of democratic society to pursue principle of non-abandonment to counteract distributive injustice caused by market incentives?

• Public subsidies and fiscal benefits as incentives for industry have opportunity costs and may not maximise society’s utility according to standard economic and utilitarian theory

• But take account of “caring externalities”
Scientific advancement

• Medicine as a profession has a moral duty to advance scientific knowledge in pursuing new therapies. This justifies some overriding of short-term utility considerations (Rhodes 1998)

• Reflected in professional codes, e.g. Royal College of Physicians of London

• Ad hoc Committee on Health Research recommendations or Value of Information framework follow standard utilitarian reasoning – and neglect rare diseases!

• Are there other reasons for scientific study of rare diseases?
Scientific advancement

“Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rarer forms of disease.”

William Harvey (1578-1657)
Scientific advancement

• Study of rare diseases often repays research efforts manifold with medical insights and useful drugs for common conditions!

• Rare diseases often result from single gene defects – clear causal link to consequences, e.g. study of homozygous familial hypercholesterolemia led to development of statins

• However, future benefits of funding orphan drug R&D are particularly hard to predict, because of increased potential for scientific breakthroughs but otherwise limited markets and low profitability

• Argument does not apply to tropical orphan diseases
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Health research priority-setting: Trade-off between expected cost-effectiveness and beneficence

Burden of disease?

Expected cost-effectiveness

Beneficence

<table>
<thead>
<tr>
<th>Expected cost-effectiveness (Utilitarian justice)</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>New cost-saving surgical technique</td>
<td>Low</td>
<td>HIV/AIDS vaccine</td>
</tr>
<tr>
<td>New neuro-imaging technique</td>
<td>High</td>
<td>New drug against MS</td>
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</tbody>
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Moral obligation of beneficence

Socially most desirable health research
Conclusions

• Conflicting moral obligations of beneficence and distributive justice demand very different levels of funding for orphan drug research

• Development of research priority setting tools which consider ethical issues would foster transparency of decision-making process and increase public accountability of decision-makers

• This could lead to improved social performance of funding agencies

• Improvement of existing priority setting tools should be the objective of further research and academic debate
Need to act now...

• Absence of appropriate technical tools should not lead to complacency on the side of decision-makers

• Even in the absence of adequate technical tools, the public should expect the following minimum requirements for decision-making on funding health research:

  • Clear rationale underlying decisions
  • Transparent, explicit and participative decision-making process