Billijkheid, Efficiëntie en Volksgezondheid

Studies in de Ethiek en Economie van een Vaccinatiebeleid

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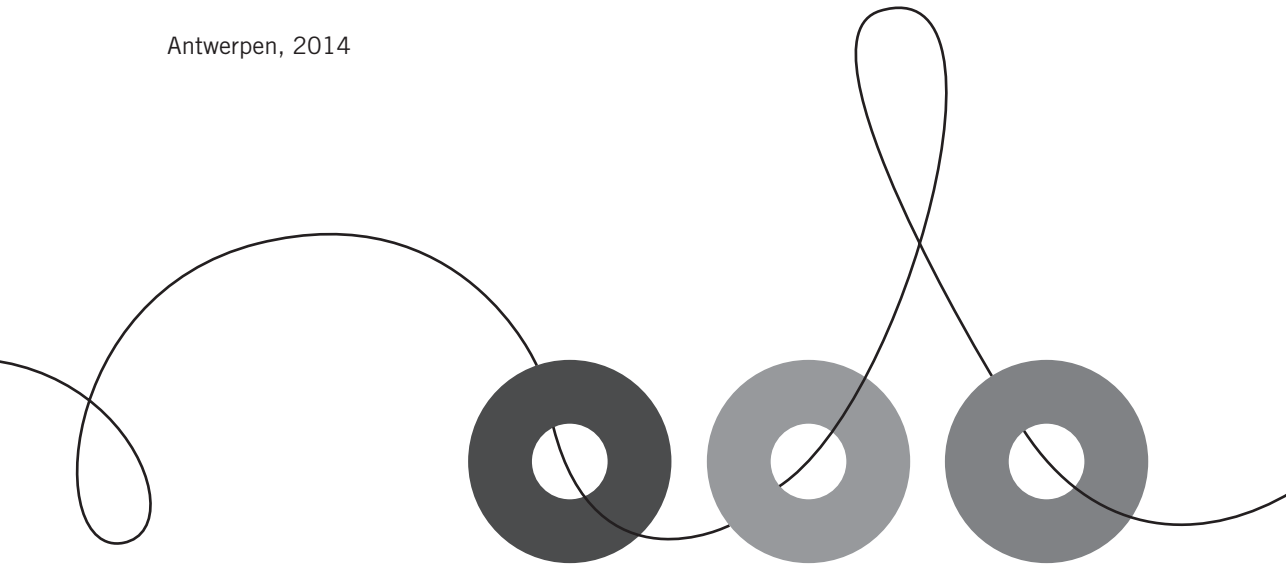

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Table of contents

Introduction

1. Infectious diseases: past, present and future 9
2. Vaccines: development, effectiveness and safety 12
3. Ethical challenges in vaccination policy 18
4. Outline of the thesis 20

PART I: Individual rights and social obligations

Chapter 1: Moral obligations to prevent infectious diseases

1.1 Introduction 30
1.2 The moral duty to become vaccinated 31
1.2.1 Duties to oneself: protect our own health 31
1.2.2 Duties to other individuals: not to harm others 33
1.2.3 Duties to the collective: contribute to public goods 36
1.3 The moral relevance of the transmission mode 38
1.4 The scope of obligatory precautions 41
1.5 Conclusion 44

Chapter 2: Kicking against the pricks: vaccine skeptics and their social orientation

2.1 Introduction 48
2.2 Vaccine refusers: motivations and correlates 48
2.3 Cognitive differences between skeptics and non-skeptics 50
2.3.1 Social orientation 50
2.3.2 Methods 52
2.3.2.1 Sample selection 52
2.3.2.2 Survey 52
2.3.2.3 Analysis 54
2.3.3 Results 55
2.4 Discussion 57

Chapter 3: Vaccination policy and ethical challenges posed by suboptimal uptake and subgroup targeting

3.1 Introduction 64
3.2 Targeting subgroups 64
3.2.1 Health equity 65
3.2.2 Non-discrimination 66
3.2.3 Protection of privacy 67
3.2.4 Non-stigmatization 68
3.3 Increasing vaccination coverage 68
3.3.1 Education 70
3.3.2 Nudges 70
3.3.3 Incentives 72
3.3.4 Legal compulsion 74
3.4 Conclusion 75

Chapter 4: Public preferences for efficiency, equity and autonomy in vaccination policy: an empirical study

4.1 Introduction 82
4.2 Survey 83
4.2.1 Sample 83
4.2.2 Background variables 85
4.2.3 Vaccination policy scenarios 85
4.2.4 Choice assignment 88
4.2.5 Statistical methods 91
4.3. Results 91
4.3.1 Preferences over vaccination policy options 91
4.3.2 Factors associated with preferred incentives 95
4.4 Discussion 97

Chapter 5: On the equity of vaccination programs that redistribute disease

5.1 Introduction 102
5.2 Vaccination with redistributive effects 102
5.3 Equity and health risk redistribution 104
5.3.1 Equivalence of equal health effects 105
5.3.2 Moral reasons to differentiate the value of health effects 105
5.4 Discussion 108

PART II: Allocation of health care resources

Chapter 6: Valuing health states: a comparison of methods in hepatitis A patients

6.1 Introduction 116
6.2 Methods 118
6.2.1 Data 118
6.2.2 QALY calculation 119
6.2.3 Analyses 120
6.2.4 Sample 120
6.3 Results 121
6.3.1 Comparison of QALY loss as predicted by EQ-5D and SF-6D 121
6.3.2 Significant predictors of QALY loss 126
6.3.3 Comparison of QALY loss as predicted by the SF-6D with parametric and non-parametric scoring algorithm 128
6.4 Discussion 129
6.5 Conclusion 132

Chapter 7: Costing infectious disease outbreaks for economic evaluation: a review for hepatitis A

7.1 Introduction 136
7.2 Methods 136
7.2.1 Literature search 136
7.2.2 Costing outbreaks 137
7.3 Results 141
7.3.1 Foodborne outbreaks 141
7.3.2 Outbreaks in schools 143
7.3.3 Outbreaks among adults 144
7.3.4 Other estimates for the cost of an outbreak 145
7.4 Discussion 146

Chapter 8: Cost-effectiveness of hepatitis A vaccination for adults in Belgium

8.1 Introduction 154
8.2 Data and methods 155
8.2.1 Study design 155
8.2.2 Data sources 155

8.2.3 Model 157
8.2.4 Input parameters 158
8.3 Results 168
8.3.1 Base case analysis 168
8.3.2 Sensitivity analysis 169
8.4. Discussion 173
8.5 Conclusion 175

Chapter 9: Public preferences for prioritizing preventive and curative health care interventions: a discrete choice experiment

9.1 Introduction 182
9.2 Methods 183
9.2.1 Identification of the attributes and attribute levels 183
9.2.2 Experimental design 186
9.2.3 Presentation of the surveys 189
9.2.4 Sample selection 189
9.2.5 Data analysis 192
9.3 Results 192
9.3.1 Main and interaction effects 192
9.3.2 Preference heterogeneity 196
9.4 Discussion 198
Appendix A 208
Appendix B 212

Conclusion

1. Summary 215
2. Strenghts, limitations and avenues for further research 218

Nederlandstalige samenvatting 221
List of publications related to the thesis 226
Curriculum vitae 228

Introduction

1. Infectious diseases: past, present and future

In his classic story "War of the Worlds" H.G. Wells describes an invasion of our planet by technically superior aliens. In order to survive, these "Martians" are in search of a new planet to colonize. They possess the purest intellect, have more advanced technology and, at first sight, they dominate humans in all imaginable ways. It seems as if they represent a further developed phase of life in the universe. The Martians however misjudge the fact that, on earth, life on the macro level - in which the aliens appear to be unstoppable - is only possible by grace of microscopic processes. Behind our everyday view of the world there lies an invisible microbiological dimension, in which there is a never-ending struggle for life. The aliens are ultimately stopped "…by the putrefactive and disease bacteria against which their systems were unprepared; slain as the red weed was being slain; slain, after all man's devices had failed, by the humblest things that God, in his wisdom, has put upon this earth…." [1].

This surrealistic fiction illustrates some inevitable truths. Our lives and cultures are built upon a microbiological level that has shaped our world for ages. Our body is the evolutionary result of thousands of years of exposure to pathogens. And, just as the Martians, we tend to forget microbes, their millennial record of disease and the extent to which today still we live by their grace. The skeletons of dinosaurs, left behind 140 million years ago, indicate that these giants were floored by minuscule organisms [2]. Since homo sapiens started living in increasingly larger and interconnected groups about 10 000 years ago, infectious diseases have decimated populations, swept out entire armies and disrupted societies in a way that reduces the impact of war to only a footnote in history. The 'black death' or 'the plague', raged for centuries in Asia before it finally came to Europe in the 14th century, presumably imported from there by a Genovian ship, where it killed - in two years time - about one third of the European population, with in some cities up to 90% of the inhabitants deceasing [3]. After burning down city after city, religious processions were organized all over the continent to break the spell but were likely instrumental into the further spread of the virus [2]. The smallpox, caused by the *variola* virus, is probably the most dreadful human disease. It killed an estimated 400,000 Europeans each

year by the late 18th century [4] and approximately 300 to 540 million people worldwide in the 20th century alone [5]. No one knows when or where it first emerged on earth but the scars on ancient Egyptian mummies from as long ago as 1580 B.C. reveal that at that point it was an endemic disease in the middle east [6]. Some argue that the virus has been imported from Mesopotamia into Europe by the Roman troupes of Marcus Antonius in the 1st century BC [2]. However, its real journey over the world had started with the crusades in the 11th and 12th century and the later colonial politics [7]. The discovery of the 'New World' in 1492 and the consequent annexation by the Spaniards introduced the smallpox into the susceptible Inca and Aztec empires and allowed Hernan Cortés to obliterate their - by then decimated - armies. Later, the heavily reduced population necessitated the Spanish conquistadores to import the first slaves from Africa [8]. Perhaps of specific interest for a philosopher is that Athens in the fifth-century BC, where in two generations' time democracy, philosophy, art, tragedy and science embarked on an unprecedented mission, was shortly after completely destroyed by an infectious disease (probably typhoid fever [9]). About a quarter of the Athenian population died from the epidemic, and this allowed the Spartans to demolish the walls of the Acropolis and to declare the end of a true philosophical era. In 1998 road works uncovered a mass grave dating from the period of the outbreak, which showed the anarchy and moral decay to which the, then, highly-developed city fell prey [10]. The last big historic pandemic occurred when in 1918 a mutation in the influenza virus strain, resulted in the unusually deadly Spanish flu. This virus infected more than 500 million individuals and caused a number of deaths – predominantly among young, healthy adults – between 20 and 100 million [11], about 1 to 5 percent of the world's population at that time [12]. By the end of the First World War more lives were lost due to the disease than to the actual war [13].

About half a century ago, the hazards of viruses, bacteria and infectious fungi were thought by some in the medical community to be on the verge of being vanquished through progress in sanitation, antibiotics and the development of safe and effective vaccines (see next section). In 1972 the Nobel Laureate Macfarlane Burnet concluded that "the most likely forecast about the future of infectious disease is that it will be very dull" [14]. That appeared to be an overly optimistic, perhaps hubristic prediction. Today infectious diseases are still worldwide the number one cause of death in children [15], the biggest cause of overall mortality in low-income countries

and the second biggest cause of mortality worldwide [16]. In 2009, 33.3 million individuals were HIV seropositive while 1.8 million died from their infection [17]. Tuberculosis killed an estimated 1.7 million people in 2009 [18]. Epidemics of seasonal influenza result every year in about three to five million cases of severe illness, and about 250 000 to 500 000 deaths worldwide [19].

Infectious diseases are likely to remain an important concern to our health. Global warming will affect the introduction and dissemination of many serious infectious diseases to places where they were inexistent before [20]. From 1940 to 2004 several hundred new pathogens have emerged as we have witnessed the more famous 'birth' of Severe Acute Respiratory Syndrome Virus (SARS), Human Immunodeficiency Virus (HIV) and Ebola [21]. Experts consider it a fact that sooner or later a novel influenza strain will appear that will pose a serious public health threat [22]. Some estimate that 175 to 350 million individuals risk dying when the common influenza virus undergoes a dangerous mutation [23]. The tremendous success of public health programs and the increased hygienic standards in the developed world have enormously reduced the incidence of most common infectious diseases [24]. But this also has a perverse effect in that it leaves us with a growing number of susceptible individuals. A re-emergence of a virus could lead to large-scale outbreaks in a population that has lost its naturally acquired immunity, or that simply never became immune. A deliberate release of a virus by terrorists remains a viable security threat. Concerns exist that the stocks of the (officially eradicated) smallpox virus that were artificially manufactured for military purposes in the former Soviet Union, may have fallen in dangerous hands after the fall of the communist regime in the early 1990's [25]. An organized release of this virus by terrorist organizations could according to experts trigger a global epidemic with the potential impact of a series of nuclear attacks [26]. But also non-deliberate introductions of microbes should be of concern. Changed travel patterns and the free movement of goods and persons in a globalized economy have enabled the spread of viruses across continents in a matter of hours. This could easily facilitate outbreaks and epidemics. There is also another - and perhaps even the most important - reason to believe that infectious diseases are likely to remain a serious risk to our health. The antibiotics used to treat infected patients are becoming less effective since infectious pathogens increasingly appear to develop resistance to their effects [27]. This means that the miracle drugs of the 20th century (such as e.g. penicillin) will lose their curative

potential for many common acute infections, without the prospect of having worthwhile alternatives in development. Arias and Murray conclude in the New England Journal of Medicine in 2009 that "it is more difficult than ever to eradicate infections caused by antibiotic-resistant "superbugs", and the problem is exacerbated by a dry pipeline for new antimicrobials with bactericidal activity against gram-negative bacteria and enterococci. A concerted effort on the part of academic researchers and their institutions, industry, and government is crucial if humans are to maintain the upper hand in this battle against bacteria – a fight with global consequences" [28]. The continuing threat of infectious diseases plus the diminished possibilities to cure infections increases the importance of prevention.

2. Vaccines: development, effectiveness and safety

The horrors caused by infectious diseases have inspired massive creative efforts to turn the tide, emerging from each era's prevailing medical paradigm. The Old Testament tells about golden representations of bubonic plague bumps and of the mice that spread it as an attempt to impel divine interventions [2]. Because of the evocative red color of smallpox rashes several cultures adhered to so-called "red treatment" by encircling a patient with red linens and curtains and allowing only red food and drink [29]. Indian Buddhists from the 7th century drank snake poison in an effort to gain immunity against disease, often with fatal consequences [30]. None of these efforts offered meaningful relief. The only remedy that appeared effective in controlling pathogens was to preventively isolate infected cases: quarantine, a term originating from the Venetian harbor in the 14th century where ships had to anchor on an island for 40 ("quaranta") days before they were allowed on the continent [31, 32]. However, from the 18th century onwards three developments have changed human destiny forever: variolation, vaccination and the Pasteurian method [30].

(1) It was already an established fact that those who have had a disease often developed some kind of immunity against it. Therefore, deliberately incurring a relatively minor case of the smallpox, and hoping that it would lead to a non-fatal disease episode, could provide lifelong immunity. In ancient China this practice was performed by inhaling a powder made from dried crusts scraped from the skin of an infected person. In the Ottoman Empire a small amount of puss from active smallpox lesions on one person

was injected into a fresh scratch on the arm of another. This practice, called 'variolation', usually caused milder symptoms. It was Lady Mary Wortley Montague, the wife of the British ambassador to the Ottoman Empire, who had observed the practice in Constantinople and successfully employed it on her own children. Despite opposition against variolation from the medical establishment, the British Royal Court became interested in her story and offered on 9 august 1721 6 prisoners with a death sentence the choice to become variolated. In case of survival they would receive the royal grace and be free. After that, the experiment was repeated on 5 orphans and when also they survived the experiment, the princess of Wales considered it safe to variolate her own children. At the same time, Boston's reverend Cotton Mather who had independently learned the technique from his African slave Onesimus, propagated variolation in America.

Of course variolation offered only limited improvements as compared to natural infection. About 1 in 50 variolations ended in a casualty [30]. Moreover, the more this practice trickled down to broader parts of the population, the risk on epidemics became bigger as a variolated person could still communicate full-strength smallpox and could trigger an outbreak of the very disease that was to be avoided in the first place.

(2) A second milestone in the human struggle with infectious disease was the discovery that someone who was infected with cowpox ("vaccinia" from the Latin word for cow "vacca") developed a similar but more benign form of smallpox and remained immune for the disease. Benjamin Jesty, a British farmer from Yetminster, noticed in 1774 that he and his milkmaids, because of their prior exposure to cowpox, were immune to the smallpox that was sweeping through the entire region. He deliberately brought his wife and children to his cattle to have them infected with vaccinia. This was the first deliberate attempt of vaccination, i.e. using an innocent and less virulent pathogen to protect against a more dangerous one. Edward Jenner, a rural doctor with the connections that Jesty lacked, started studying and documenting this folk wisdom with empirical studies and published his results in a way that was more orthodox to the medical community. This way Jenner popularized an effective method to prevent one of the most dreaded diseases.

(3) A third revolution came with the discoveries of Louis Pasteur. By then, vaccination was considered only possible for smallpox. However, in 1870,

about a century after Jesty's contested experiment, Pasteur made a major public health breakthrough. Backed by the steep technological progress of the era, Pasteur was the first to discover that the infectious power of a pathogen, its 'virulence', could be altered artificially. He discovered that cholera bacteria lost permanent virulence after exposure to sunlight or after being passed on between different host species. This was the first scientific explanation for Jenner's vaccination. The cowpox was actually related to smallpox but having made the adaptation from humans to cows weakened it. Nonetheless an infection with it still induces immunity against smallpox. Once the principle was known, the way was open for industrial applications. Through use of cell cultures, many infectious diseases could become manufactured in weakened forms. The first of such applications was the development of a vaccine against rabies in 1885. By the end of the 19th century there were 5 human vaccines: two containing life tissue (Jenner's vaccinia and Pasteur's rabies vaccine) and 3 without life tissue (against the Bubonic Plague, typhoid fever and cholera). In the 20th century more scientific discoveries (e.g. genetic engineering) allowed further developments of vaccines.

The mechanism was now well understood. By introducing a similar but mostly harmless version of a pathogen in our bodies, our immune system gets the opportunity to develop a response to this intruder. When it later becomes confronted with the real virus it has a blueprint of what an effective antibody should look like and this saves crucial time to clear the infection timely.

Table 1: Outline of the development of human vaccines

Live, Attenuated	Killed Whole Organism	Protein or Polysaccharide	Genetically Engineered
18th Century			
Smallpox			
19th Century			
Rabies	Typhoid, Cholera, Plague		
First Half 20th Century			
Tuberculosis (Bacille Calmette–Guérin), Yellow fever	Pertussis, Influenza, Typhus	Diphtheria toxoid, Tetanus toxoid	
Second Half 20th Century			
Polio (oral), Measles, Mumps, Rubella, Adenovirus, Typhoid (salmonella Ty21a), Varicella, Rotavirus reassortants, Cholera	Polio (injected), Rabies (cell culture), Japanese encephalitis, Tick-borne encephalitis, Hepatitis A, Cholera (WC-rBS)	Pneumococcus polysaccharide, Meningococcus polysaccharide, Haemophilus influenzae type b polysaccharide, Meningococcal conjugate, H. influenzae conjugate, Hepatitis B (plasma derived), Typhoid (Vi) polysaccharide, Acellular pertussis, Anthrax secreted proteins	Hepatitis B recombinant surface antigen, Lyme OspA, Cholera (recombinant Toxin B)
21th Century			
Cold-Adapted Influenza (CAIV), Rotavirus (attenuated and new reassortants), Zoster	Japanese encephalitis (Vero cell), Cholera (WC only)	Pneumococcal conjugates, Meningococcal quadrivalent conjugates	Human papillomavirus recombinant

Source: Plotkin, S.L. and S.A. Plotkin, *A short history of vaccination,* in *Vaccines,* S.A. Plotkin, W.A. Orenstein, and P.A. Offit [Ed.], 2008, New York: Elsevier, p. 1748. and CDC, *Impact of vaccines universally recommended for children--United States, 1990-1999.* Can Commun Dis Rep, 1999. 25(14): p. 122-7.

Since the discoveries of the vaccination pioneers mankind has developed a large number of vaccines with lab-confirmed efficacy (see **Table 1**). We succeeded in heavily reducing or controlling diphtheria, tetanus, yellow fever, pertussis, haemophilus Influenza B, polio, measles, mumps and rubella; and two diseases have even been completely eradicated: smallpox in 1980 and rinderpest, a livestock disease responsible for many famines, in 2011 [33]. A recent study estimates that in the United States only, since 1924, one-hundredth-and-three million cases of severe childhood diseases have been prevented, about 95% of those that would otherwise have occurred [34]. **Table 2** shows historical comparisons of disease burdens before and after the introduction of a vaccine. Although it remains difficult to empirically disentangle the exact contribution of vaccines from other factors such as sanitation, hygiene and demography, the striking and persistent reductions in disease incidence after the introduction of a vaccine strongly support the thesis that vaccination was a leading cause.

Table 2: Average number of deaths per year in the US related to an infectious disease before and after the introduction of a vaccine

Disease	Pre-vaccine era	Post-vaccine era	% reduction deaths
Diphteria	1822	0	100%
Measles	440	0	100%
Mumps	39	0	100%
Pertussis	4034	27	99.3%
Polio (acute)	1393	0	100%
Rubella	17	0	100%
Smallpox	337	0	100%
Tetanus	472	4	99.2%
Hepatitis A	137	18	86.9%
Hepatitis B	237	47	80.2%
Hib	1000	<5	>99.4
Pneumococcus	6500	4850	25.4%
Varicella	105	19	81.9%

Source: Roush, S.W. and T.V. Murphy, Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States, *Journal of the American Medical Association*, 2007. 298(18): p. 2155-63.

Because vaccines are given to healthy children and adults, a higher standard of safety is generally expected compared with other medical interventions. This lower tolerance for risks from vaccines translates into an increased need to investigate the possible causes of adverse events after vaccinations. Although the first generation of vaccines was effective in preventing disease, it also suffered from several safety issues. For instance, the first rabies vaccine developed by Pasteur had serious adverse effects such as seizures, paralysis and coma in about 1 in 230 people who used it [35]. Also production errors have occurred. For instance, in 1942 the American military injected hundreds of thousands of servicemen with a yellow fever vaccine. To stabilize the vaccine virus, scientists added human serum. Unfortunately some of the serum came from people unknowingly infected with hepatitis B virus. As a consequence, 330 000 soldiers were infected, 50 000 developed severe hepatitis and 62 died [35]. In 1955 five companies made formaldehyde-inactivated polio vaccine. However, one company failed to completely inactivate poliovirus: 120 000 children were accidently injected with life and dangerous poliovirus, 40 000 developed mild polio, 200 were permanently paralyzed and 10 were killed [35].

Through these unfortunate developments, today, vaccines are safe conform to the most extensive safety standards. Production processes are closely monitored and regulated and vaccines undergo extensive evaluation in laboratories, in animals, and in phased human clinical trials before licensure. For instance, both second-generation rotavirus vaccines were, after having widely shown their safety and efficacy in the lab, subjected to phase III trials that each included at least 60 000 infants [36]. Adverse effects from contemporary vaccines are mostly limited to muscular pain, headache and light fever. More serious adverse effects are related to anaphylactic shocks, a potentially fatal hypersensitivity reaction. However, such reactions occur very rarely. A study that investigated about 8 million vaccinated children and adolescents that are routinely vaccinated in the US estimates the risk on anaphylaxis at 0.65 cases per million doses of vaccines administered [37].

Important challenges to increase vaccines' safety even further are to continue training vaccinators on giving appropriate medical treatment should an adverse reaction occur and to improve selection methods to exclude individuals with a higher probability of developing adverse reactions. Because rare reactions, reactions with delayed onset, or reactions in subpopulations may not be detected before vaccines are licensed, post-licensure evaluation of vaccine safety is critical. Large systems and databases

are therefore put in place to improve the methodological capability to study rare risks of specific profiles. Many countries have also created a system of financial compensation for victims of vaccine injury [38]. The reasons of existence of these programs are (1) that this avoids litigation risks for vaccine manufacturers, which could jeopardize an adequate vaccine-supply, (2) solidarity with victims and (3) to maintain public trust and goodwill. The latter is extremely important to the success of vaccination. As a result of the substantial progress in reducing vaccine-preventable diseases, the memory of several infectious diseases has faded from the public consciousness while at the same time public concern about real or perceived adverse effects associated to vaccines has increased [39]. Moreover, vaccine safety issues have increasingly taken on a life of their own outside of the scientific communication channels. Examples are the (later refuted) links between vaccination and autism, Multiple Sclerosis (MS), mad cow disease, cancer, permanent brain damage, allergies and asthma, etc.

3. Ethical challenges in vaccination policy

In earlier days the lion's share of challenges in infectious disease prevention was to be found in the field of biomedical science (e.g. research and development of vaccines). Nowadays, a substantial part of the challenges are socio-political in nature. The burden of vaccine-preventable diseases (VPD) remains significant and substantial health gains are still within reach. For instance, worldwide (in both developed and developing countries) about 2 billion people have been infected with hepatitis B virus (HBV); about 350 million live with a chronic infection and an estimated 600 000 persons die each year due to the acute or chronic consequences of HBV infection, a disease for which a safe and effective vaccine is available since 1982 [40]. According to the World Health Organization (WHO) the main challenges for vaccination include: the need to develop and implement strategies for reaching the difficult to reach, support evidence-based decisions to prioritize new vaccines for introduction, expand vaccination to include older age groups, scale up VPD-surveillance and explore financing options for reaching the 'Global Immunization Vision and Strategy' from the WHO and UNICEF [41].

In facing such socio-political challenges governments are confronted with ethical difficulties. Given medical, scientific and economic constraints, vaccine policy makers aim to maximally promote and achieve population health (efficiency). If not, important potential health gains are left unutilized,

and perfectly avoidable morbidity and mortality will occur. On the other hand, vaccination policy is embedded in a wider social context, one where considerations of equity become important. Often, as will become clear in the next chapters, efficiency (i.e. making maximal use of available resources and opportunities) and equity (i.e. justice or fairness, giving everyone his/her fair share of burdens and benefits) will point into different directions.[3] If so, gains in terms of one value require sacrifices in terms of the other. In this thesis two prominent ethical problems, which require reconciliation of efficiency and equity, will be studied.

The first ethical subject is one of weighing public health interests with individual freedom in the context of participation with preventive programs. Who should become vaccinated? Who has the right to refuse? Fundamental rights such as individual autonomy and bodily integrity highlight that vaccination is in the first place a personal matter. On the other hand, it also affects others. A vaccinated person not only protects herself but also the people in her environment. On a large scale (population scale) the latter effect is called "herd immunity" (or community immunity or herd protection) and it implies that we can protect an entire population without having to vaccinate literally everyone. Do we owe it to fellow citizens to become vaccinated? And if so, why? And how should public health policy (i.e. the state) respond to those who do not comply? Governments can choose between a variety of policy measures to increase the uptake of a vaccine, ranging from on the one extreme the use of explicit coercion to on the other end offering rewards. However, any of such policies evidently raises its proper ethical concerns.

The second ethical subject is one of balancing efficiency and equity in the allocation of health care resources. Medical interventions increasingly have to compete for resources, and a fair procedure is needed to decide which health care should be financed with public funds, and which forms of health care can be referred to private resources (or the private tier of health insurance). This evidently has implications for vaccination policy. The increasing number of vaccine-candidates forces governments to prioritize between different vaccines, vaccine policy options, other methods of prevention and "wait and cure" options. In a context of limited resources, which vaccines should be offered by the state, and why?

Both issues are not completely unrelated. If there is an argument that vaccination is not just a right but also a social obligation, this gives

additional force to the claim that the vaccine should be financed from public funds. Second, as "ought' implies "can", it makes more sense to speak of an obligation when people are enabled to live up to their obligation, e.g. by society providing vaccines for free.

However, before going more deeply into the two problems I must acknowledge that, as compared to efficiency, equity is a much more difficult concept to define. The philosophical framework that will be implicit in the following discussions (and from which equity will be interpreted) is liberalism. The liberalist view of a just society is a broad umbrella under which different socio-political theories and philosophies subside. However, the high value attributed to the values of freedom and equality is common to its different lines of thought. The main stance are the ideas that in our society each individual should matter, that he or she possesses inalienable rights, that there are limits to the use of state-coercion, and that minorities deserve being protected. In the political cultures of the 'industrialized west' it is the dominant paradigm in contemporary thinking about the relation between the individual and the collective [42], and in public health ethics it is the standard framework [43]. Within liberalism discussion arises on the content and scope of individual rights. E.g. do we have just a right to be free from coercion (libertarianism, stressing negative freedom)? Or do we also have a right to certain means and resources (egalitarianism, highlighting positive freedom)? Opposing liberalism we find less-individualistic views of society like communitarianism, which take the community or the collective as the primary source of ethical value (and not the individual); utilitarianism (which takes the sum of individual utilities as the source of value), or the views held in traditional or non-secularized cultures. Important writers in liberalism, who will often explicitly return in the next chapters (or be implicitly present in the background), are John Stuart Mill, John Rawls, Thomas Scanlon, Gerald Dworkin and Norman Daniels.

4. Outline of the thesis

This thesis attempts to provide a discussion of (parts of) these two ethical issues in vaccination policy through combining theoretical argumentation and empirical research.

In the first part of the thesis (chapter 1 to 5) I will focus on the question whether vaccination is an individual right or a social obligation, and what

this implies for public policy. **Chapter 1** is a theoretical chapter in which I will discuss the normative grounds on which it could be argued that we either or not have a duty to prevent infectious disease transmission by becoming vaccinated, but also by implementing other precautions against infection (e.g. washing hands, wearing mouth masks, etc.). **Chapter 2** is a descriptive chapter about vaccine refusers: who are they and why do they refuse? After summarizing existing knowledge I will present an empirical study in which we investigated a previously neglected aspect of vaccine skeptics: their social orientation. **Chapter 3** discusses how vaccination policy should deal with the problems raised in chapter 1 and 2, and which ethical challenges are involved. When is the targeting of subgroups justified? And which policy measures are to be used to increase coverage in the population? **Chapter 4** continues on the raised policy dilemmas and explores through empirical study how the general population thinks about them. **Chapter 5** nuances the view that vaccination always has positive effects on others, an implicit assumption in the preceding chapters. It discusses the rare but realistic situations when the introduction of a vaccination program can leave unvaccinated others worse off than before.

In the second part of the thesis (chapter 6-9) I will focus on the resource allocation question. There are many grounds on which fairness in health care allocation could be defended. Four important ones are: efficiency (maximizing the impact of health policy on the existing burden of disease), necessity (giving priority to those individuals most in need of health care), age (differentiating the claims on health care resources according to the age of the recipient) or individual responsibility (taking into account whether ill health is self-inflicted or not). These criteria often point in different directions. In the first three chapters of part 2, I will focus on efficiency, and the methods used to quantify it. Cost-effectiveness (as indicator of efficiency) becomes increasingly influential as a tool to guide rationing decisions [44]. However, in the context of infectious diseases (where a patient is not only a victim but also a vector of disease) such analyses are complex. By insufficiently accounting for this complexity, cost-effectiveness analysis risks giving a wrong indication of the efficiency of subsidizing a vaccination program relative to making investments in other health care programs. The first 2 chapters (chapters 6 and 7) deal with this by focusing on hepatitis A, a contagious disease that occasionally has acute and severe consequences. **Chapter 6** will highlight the difficulties in quantifying the health impact of acute infections. Five different methods to value health states will be compared and discussed, and it will be shown that the choice which method

is used can have large implications for the resulting cost-effectiveness. **Chapter 7** will highlight the difference for economic evaluation between a non-communicable disease and an infectious one, by focusing on the costs of controlling outbreaks, an aspect unique to the latter that is - as shown in the chapter - often neglected in costing studies. In **chapter 8** I will present a cost-effectiveness analysis of hepatitis A vaccination for adults in Belgium that includes the concerns raised in **chapter 6** and **7.** In **chapter 9** the focus will go beyond efficiency and cost-effectiveness analysis. I will present an empirical study in which we investigated the relative support in the general population of efficiency considerations relative to other considerations such as age, responsibility and need as bases for allocating health care resources. The thesis ends with a summary of the main findings from parts 1 and 2 and a general discussion to point out areas for further research.

The entire thesis is written as much as possible to be accessible to readers of all kinds of backgrounds who are interested in this topic. Most chapters have been published in peer-reviewed articles and book chapters, integrally or parts of it that were later rewritten for clarity and consistence with the rest of the thesis, and they can all be read as stand-alone text. Occasionally, small parts between the chapters can overlap. A full list of publications related to this dissertation can be found at the back of the thesis.

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[1] Efficiency must be distinguished from efficacy and effectiveness. Efficacy designates the degree to which an objective is reached in experimental settings (e.g. to which degree a vaccine renders disease protection in lab-tests). Effectiveness describes the success in real life settings. Efficiency considers the effectiveness of an intervention, relative to the sacrifice it requires (price, cost, …).

[2] Equity is not the same thing as equality. The former is a normative concept, indicating in which respect individuals should be treated equally. Sometimes an unequal distribution is more equitable than an equal one (e.g. progressive income taxation).

[3] As argued by Legrand, theoretically, the efficiency-equity tradeoff remains an elusive one. Equity is an objective, whereas efficiency is the way that leads towards it. As such, strictly speaking, there is no conflict and no tradeoff between efficiency and equity but only between different interpretations of equity. However, in applied contexts of public policy, efficiency itself often serves as an objective and then it can nonetheless conlict with objectives of equity. Legrand, J., Efficiency versus equity: the elusive trade-off, *Ethics*, 1990, 100(3): p.554-568

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PART I

Individual rights and social obligations

Chapter 1: Moral Obligations to Prevent Infectious Diseases

Abstract: This chapter discusses whether we have moral obligations to prevent infections in others and ourselves. First, the main ethical arguments will be summarized why individuals should become vaccinated. Afterwards it will be argued that the mode by which pathogens are transmitted (e.g. via air droplets, contaminated food, insects, sexual contact, etc.) can be of moral relevance. Our duties to prevent are stronger when diseases are transmitted sexually. The final section will question whether the variety of precautionary measures other than vaccination that are at our disposal, like e.g. hand washing or wearing mouth masks, have an optional or an obligatory character.

Parts of this chapter have been published as:

Luyten J., "Mutual moral obligations to prevent infectious diseases" in Denier Y, Gastmans C & Vandevelde A (Ed.), 2012, *"Justice, Luck and Responsibility in Health Care. Philosophical Background and Ethical Implications for End-of-Life Care"*, Dordrecht: Springer

Luyten J, Engelen B, Beutels P, 'The sexual ethics of HPV vaccination for boys", *HEC Forum,* (2014), 26:1, p. 27-42

1.1 Introduction

Vaccination works in two ways. First, by mimicking an infectious agent, vaccines induce our immune system to create an immune response so that, in case we are confronted with the real pathogen, we have a blueprint of how to defend ourselves effectively. Second, vaccination also protects other individuals. Because an immunized individual can no longer transmit infection, vaccination reduces the chance that others come into contact with a contagious person. When a large part of a population is immune, the latter indirect protective effect is called 'herd immunity' (or 'community immunity' or 'herd protection') and, at least in theory, it allows to protect an entire population without having to vaccinate everyone.

Securing sufficiently high vaccination coverage in key groups (such as children, health care workers, food-handlers or travelers) is a cornerstone of public health policy. However, it has proven to be a never-ending mission. The fading memory of the severity of many vaccine-preventable diseases, with which individuals today have little or no experience, plus the increased awareness of adverse effects associated to vaccines, affect the public perception of the necessity to become vaccinated. In many regions of the world growing numbers of people have become reluctant to accept vaccination, and resistance to it has become more organized [1]. As such, vaccines have become the victim of their own success.

This raises the question whether immunization is an option or a social obligation.[4] In this chapter I will present and discuss the three main arguments why vaccination can be a moral duty. Afterwards I will investigate whether such obligations are different in the case of a sexually transmitted infection (STI). In the final section I will extend the focus of prevention beyond vaccination to other precautionary measures (such as washing hands, undergoing screening-tests and wearing mouth masks), and discuss how far the scope of obligatory precautions against infection may go.

[4] I will use the terms 'obligation' and 'duty' interchangeably, although there may be subtle semantic differences between both. For an elaborate discussion of this see [2] Brandt, R.B., The concepts of obligation and duty, *Mind,* 1964. 73(291): p. 374-393.

1.2 The moral duty to become vaccinated

A moral duty is a difficult concept to grasp. First, it must be distinguished from a legal obligation. There certainly is a close connection between ethics and the law. Moreover, there is a case to be made that it is our ethical duty to obey the law. Nonetheless both are not the same. Many legal obligations are amoral (e.g. spatial ordering requirements for houses). Some laws may even be immoral (e.g. former South-African apartheid laws). Moreover, moral duties need not be translated into the legal codex (e.g. the duty to tell the truth to one's partner). Second, moral duties are also different from commitments. The latter are obligatory, but only if we want to reach a certain objective. Ethical obligations do not have this conditional character. Because they appeal to (intuitions about) values they have a special authority that cannot easily be silenced, regardless of whether they are legally required or not, regardless also of whether we want to respect them or not.

In the next section I will explain why vaccination can be seen as a moral duty. There are three arguments; of which the first is a commonsensical one but the second and the third ones have most political relevance. Depending on the specific context (effectiveness and safety of the vaccine, severity of the disease, reimbursement by the health care system, background of the recipient, etc.) they help distinguishing obligatory vaccinations from more optional ones.

1.2.1 Duties to oneself: protect our own health

A straightforward first argument in favor of vaccination is that it is in our best interest to do so. Provided that vaccination is good for us, its refusal would put our health needlessly at risk, and this should be avoided. However, to make this claim not merely a matter of good advice but one of ethical duty is more difficult. For this to be true, it must be argued (1) that we have a moral obligation to protect our own health, not because this could be beneficial to others (e.g. to avoid costs to the health care system or to avoid that our talents are lost to society), but for our own sake, because we owe it to ourselves, and (2) that in the context of vaccination such a duty is not overridden by other, more stringent duties we have towards ourselves.

Concerning the first point most cultures and religions indeed adopt a critical view towards unhealthy behavior, self-mutilation, suicide, etc. Old Christian

texts refer to our bodies as 'temples'. The ancient Greek adagio 'mens sana in corpore sano' is still a widely shared ideal today and many people experience some feeling of guilt after giving in to unhealthy habits. Intuitively we tend to think that we owe it to ourselves to take good care of our health. Some notable philosophers have argued that this is not only because of prudential reasons but because it is indeed a matter of moral duty.[5] W. D. Ross for instance says that we have a *prima facie* duty to self-improvement, i.e. to act so as to promote one's own good [3]. This duty stands next to duties of justice, beneficence or harm-prevention. Also Kant argues that every human being has "a duty to himself to cultivate his natural powers", and this not because this would be good for our happiness or because in that way we avoid letting others down, but because by not doing so one would fail to respect one's own humanity [4]. Our rational capacities as a human being *a priori* oblige us to see ourselves as an end in itself. Aristotle's 'Ethica' is one long essay about how we should take good care for ourselves [5]. In his view, an ethical life is in the first place one of *eudaimonia*, a life where our talents and capabilities are brought to a maximal flourishing. Only with the right character and the right habits will we be capable of showing ethical behavior in particular circumstances. It is hard to think of any conception of 'the good life' that is widely supported and that does not make some reference to physical wellbeing. These views support the case that there is an ethical obligation to protect oneself against ill health, and in a way this can be read as a case to become vaccinated (provided again that this enhances our health).

Now, while there may be an obligation not to disregard our physical interests, this is clearly one duty amongst many. No one will equate a moral life with a healthy life. Indeed, neglecting one's health can be praiseworthy in certain circumstances. In the turmoil after a natural disaster we praise people who put their own life and health in danger in order to help others. The Belgian Father Damian, elected in 2005 as 'The Greatest Belgian Ever', was recognized as a saint because he made his life-purpose to help infected lepers on the isle of Molokai, a disease that eventually caused his own death.

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[5] Notable philosophers have also argued *against* the existence of duties to the self. For a more elaborate discussion on whether a person can genuinely owe something to him/herself see e.g. [25] Schofield, P., 'On the Existence of Duties to the Self (and Their Significance for Moral Philosophy)', *Philosophy and Phenomenological Research,* doi: 10.1111/phpr.12034

In sum, there is a fairly strong presumption in favor of accepting a moral duty to care for our own health, and consequently in favor of the duty to follow vaccination recommendations. However, health is only a means to a meaningful life and not an end in itself. Therefore a duty to become vaccinated will at best be a *prima facie* duty: it prevails as long as it is not overridden by other, more stringent duties. Some individuals indeed have conscientious objections against vaccination [6]. Vaccine refusers in the 'Bible Belt' in the United States and in The Netherlands see illnesses as an essential part of a meaningful life. They want to live in accordance with 'divine providence'. They therefore believe that vaccination reveals a lack of trust in God's purposes. This means that they perceive a more stringent moral duty, one that is incompatible with and superior to protecting themselves against infectious disease.

The question is then, and this brings us to the next section, whether this respect for divine providence survives in cases where non-vaccination threatens not only one's own health, but also that of others.

1.2.2 Duties to other individuals: not to harm others

In a multicultural, pluralistic society, where individual autonomy is a quintessential value, duties to oneself remain controversial. Any substantial conception of how we ought to live our lives risks being discredited as being moralistic or lacks a universal basis. A more powerful argument to show that we should become vaccinated can be found in the duties we have towards other people [26].

It does not require many words to argue that we have a moral obligation not to bring harm to others. Infectious diseases can definitely cause severe harm [7]. Measles can cause pneumonia, encephalitis, and death. Healthy infants die of pertussis every year. Mumps can cause meningitis and infertility (in males). Hepatitis can cause severe liver damage, may necessitate liver transplantation and can be lethal. A pregnant woman who contracts rubella is at significant risk of delivering a baby with severe birth defects. And influenza still causes thousands of deaths each year. Vaccines have a well-demonstrated potential to prevent such risks by reducing transmission in the population [8]. The logical inference is then that, as we have a duty not to harm others, we have a duty to become vaccinated because that way we manage to avoid infection of others. For most infectious diseases it is

indeed a mathematical certainty that the refusal of vaccination increases the risks for others[6]. However the following four points are crucial to determine whether the inference is correct, and whether the harm principle effectively mandates to become vaccinated.

First, when there is reason to doubt the safety of a vaccine, or when its safety is insufficiently demonstrated it would be unreasonable to ask from each other to become vaccinated for the sake of other people's protection. The same is true when vaccination implies unreasonable big sacrifices, e.g. when it is very costly. 'Ought' implies 'can'. The obligation not to infect each other depends on society reciprocating the obligation in the form of providing protection and compensation [9].

Second, which consequences are serious enough and which probability is statistically certain enough to speak of 'harming others'? Being part of a community inevitably implies being part of a transmission chain of microorganisms. So, in order to avoid having to label all our behaviours as suspect, we have to be able to distinguish between actions that impose acceptable risks, and actions that can be labelled as harmful. An analogy could be made with traffic. Driving a car implies many risks to others, however only excessive risks like drunk driving are considered unacceptable and therefore prohibited. For many infectious diseases, it will be difficult to settle whether not being immunized imposes a normal or an excessive risk on others. There is large uncertainty attached to the probability that someone who refuses vaccination will effectively catch a disease and transmit it to others. And even if this is the case, what counts as harm? Some diseases are benign for most people, but may cause severe illness in specific groups (e.g. a hepatitis A infection is usually not severe but can be lethal for hepatitis C patients [10]). With new pathogens, the effects are not always predictable (e.g. SARS or the 2009 influenza strain). Other viruses usually cause minor health problems but can have a large economic impact (e.g. hepatitis A [11]).

Third, the harm caused by an infection is often perfectly avoidable by the harmed party itself. This raises the question: who is responsible for whose health? Should person A prevent illness in person B by becoming

[6] An exception is tetanus, a disease that is not transmittable from person to person. Here refusal does not affect others. In chapter 5 I will discuss some scenarios where refusal would in fact be beneficial to others, i.e. where vaccination causes negative externalities.

vaccinated, or should B in the first place protect herself? It could be argued that every vaccinated individual remains unprotected to some statistical degree since a vaccine is never 100% effective and moreover protective efficacy may wane with the passing of time since vaccination. But this brings us back to the previous point. Is this statistical risk to be seen as 'harm to others' or as a 'normal risk'? The case is different however for people with a compromised immune system for whom some vaccines are contra-indicated (e.g., leukemic persons, pregnant women, HIV positive persons, elderly persons, young infants). They are at risk of severe disease against which they cannot defend themselves. Sometimes these groups can easily be identified (e.g. in hospitals or in nursery homes) and then the potential harm of not being vaccinated is more obvious [12, 13]. But, when this group of vulnerable individuals cannot easily be identified (as will often be the case in everyday life, e.g. in public transport) the answer becomes less clear. Is the chance that I, by refusing vaccination, infect a vulnerable person (e.g. a fellow traveller on the train) to be considered as an instance of doing harm or is it -averaged out over the entire population- rather to be seen as exposing others to an acceptable level of risk? How much protection is a society owed to those unfortunate individuals who cannot protect themselves?

A fourth nuance is that the harm principle requires us to refrain from *doing* harm (infecting others), and not necessarily from *allowing harm to occur* (not being vaccinated and as such allowing infections to occur). Whether there is a moral difference between an act and an omission is a longstanding debate in ethics [14]. Often an omission does not invoke a similar moral blame as an act. For instance, withholding truth is not the same thing as lying and letting a person commit suicide is not the same thing as killing that person. Also most laws usually prohibit harming others but few are `bad Samaritan' laws by which a person may be prosecuted for failing to help someone else in need [15]. The act-omission distinction largely depends upon our intentions. Omissions may result from ignorance. Acts usually involve more malicious motives than the corresponding omissions; and involve more effort, itself a sign of stronger intentions. In the context of infectious diseases it will however be difficult to draw a clear line between what counts as an act and what counts as an omission because prevention can fall in both categories [16]. For instance, is going to work when ill, having unprotected sexual intercourse or not being vaccinated an act or an omission? Much depends on what counts as the 'default' situation. If the standard practice is to implement prevention, forgoing it seems to be more of an act than an

omission, whereas the opposite is true when prevention is rather exceptional. In a context where individuals are unaware of how vaccines protect others (e.g. in a developing country), not being vaccinated would be an omission. But the more vaccination is the standard and refusal the exception, the better people for whom vaccination is recommended are informed, and the more we can expect them to make a conscious decision, refusal can qualify as an act rather than as an omission.

So in sum, the harm principle offers a strong argument why we should become vaccinated: to avoid jeopardizing the health of other individuals. However, its plausibility depends on the context in which vaccination occurs. Which sacrifice does becoming vaccinated require from an individual? How serious is the potential harm of forgoing it? How unavoidable is this harm for others? And to which extent can we expect that individuals know that they risk bringing about harm? If these questions are sufficiently answered, there will be a strong moral imperative to accept vaccination.

1.2.3 Duties to the collective: contribute to public goods

A third line of argument why vaccination can be a moral duty is that we have an obligation to contribute to 'public goods' [27, 28]. Public goods are goods of (1) common interest that are (2) non-excludable (we cannot exclude individuals from their benefits) and (3) non-rivalrous (consumption does not reduce the amount available to others). Typical examples of pure public goods are national defense and clean air. Many other collective goods are semi-public goods because they are not purely excludable or rivalrous (e.g. sanitation, roads, knowledge, etc.). Altogether these goods serve as a basic 'infrastructure' on which we all build our lives. However, their provision requires collective action. Because we all benefit from their existence, everyone has a duty to contribute his/her fair share. Not doing so would be to 'free ride' on others, or worse, to undercut the efforts of those who do comply.

Public health is such a public good that can only thrive if we all contribute our share. E.g. we have to dispose of our garbage properly, clear the ice from our footpath, implement hand hygiene in food handling, don't misuse antibiotics and illicit drugs, and become vaccinated. Vaccination is a pillar of public health, and high coverage in key groups is one of its cornerstones.

Those for whom vaccination is recommended have a duty to do so, even when refusal would not directly harm others, because widespread compliance is necessary to sustain the public good, *in casu* the absence of substantial infectious disease risks in the public domain. Refusing vaccination would be (1) unfair because it implies free riding on the efforts of those who do become vaccinated for the common good, and (2) it can even undercut these people's efforts (directly by introducing disease but also indirectly by inspiring others to forgo vaccination as well).

We need to nuance this argument. First, in a world of decreasing importance of geographical borders, where viruses can move from continent to continent in a matter of hours, herd immunity or disease eradication (both potential public goods resulting from wide-spread vaccination) are more difficult to establish than expected in theory. If the objective to which we ought to contribute is highly unlikely ever to be reached, then we cannot expect from everyone to make a contribution. Participation with a vaccination program to eradicate polio would only be necessary when the disease is considered 'eradicable'. Experts consider polio eradicable but for other diseases (e.g. measles or mumps) the feasibility of such an ambition is more controversial. Second, absence of disease is not always a beneficial thing. As will be explained in chapter 5, sometimes the circulation and transmission of pathogens in the community has beneficial consequences. Indeed, in these cases the indirect protection of others through vaccination has negative rather than positive effects, which would make it a public bad rather than a public good. Third, we have a duty to contribute our fair share to the goods we benefit from, but we are not obliged to make an *excessive* sacrifice. When vaccines are considered safe and effective, becoming vaccinated can hardly be called an excessive sacrifice for such an important collective benefit as public health. However, if they are not safe, or insufficiently effective, or when individuals hold religious objections it makes more sense to speak of an excessive sacrifice.

In sum, despite the preceding critical points, the public good argument can be convincing. If a substantial number of people were to opt out of vaccination programs, this may not immediately harm others but it would be unfair towards those who did contribute their share to public health and in the end the results of widespread refusal would be devastating at both the collective and individual level. Consequently it may be a civic duty to follow vaccination recommendations, because small efforts like this contribute to the safety and wellbeing of the community. These altogether small sacrifices

in freedom for the common good make that we can maintain our freedom in so many other instances.[7]

1.3 The moral relevance of the transmission mode

Infectious pathogens can be transmitted through various routes: inhalation of air droplets, contact with saliva, blood or mucosa, sexual contact, ingestion of contaminated food or drink, etc. Can this mode of transmission be of moral relevance? Do we have different duties to prevent infection depending solely on how a disease is transmitted? John Harris and Sören Holm took up this question in a seminal paper in which they argue that the mode of transmission of a disease is irrelevant [9]. In this section I will argue that it *does* matter whether a disease is a venereal one or not. Our duties to prevent are bigger in the case of a sexually transmitted infection (STI).

In Harris' and Holm's view, people's moral obligations not to infect others are no different in the case of an STI as compared to air-, food- or vector-borne infections. While they acknowledge that most people have different intuitions and attitudes towards infecting others with, for example, herpes lesions on the lips (*herpes labialis*) versus on the genitals (*herpes genitalis*), they argue that this does not raise different moral concerns. In their view, there are no valid explanations why the physical location of the same symptoms would be morally relevant, or why sexual contact would constitute additional moral duties over other forms of human contact. In answering the question – "is there a morally relevant difference at play, or is it just prejudice" – they clearly opt for the latter option and they suspect that we are dealing here "with the last remains of the puritan belief that pleasure is sin".[8]

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[7] Depending on the strength of the three arguments in a particular context, it can be determined whether vaccination is a matter of duty. One important and topical issue is the vaccination of health care workers (HCW). Although also here the discussion depends upon case-specific, empirical variables (effectiveness of vaccination in preventing harm, safety, severity of the disease, etc.) both the no-harm and the public good argument are convincing. As in patients the potential harm of an infection is substantial, and as people in ill-health are often unable to protect themselves, the duty of HCW to avoid spreading infections gains force. Moreover, also the public good argument is a powerful one. HCWs may owe it not just to patients to become vaccinated but perhaps also to society, as a matter of public service. Public trust is quintessential to the success of vaccination and HCWs play a central role in sustaining this trust. Their refusal adversely affects the general perception of the usefulness of vaccination, since HCWs are perceived to possess exceptional medical knowledge. Also, for many diseases various key groups are targeted by vaccination (e.g. travelers, sex-workers, immigrants, children, food handlers, etc.). The evidence-base for these policies is not fundamentally different from the HCW case. By accepting that HCWs refuse vaccination, we jeopardize a general sense of solidarity in preventing infections. It gives these other target groups a fairness argument to opt out of their participation as well.

First, Harris and Holm try to explain the difference in intuition by appealing to the consensual nature of sexual contact. *Herpes genitalis* is typically the result of consensual sex, whereas transmission of *herpes labialis* can occur without consent, as in the case in which two people share toothbrushes or cutlery [17]. Whereas consent is clearly relevant in attributing moral responsibility, a consistent view on individual responsibility would praise people who are careful not to become infected. Contrary to current practice, this would imply that we hold health care workers responsible if they get infected when treating ill patients (they knew the risks at stake) and that we praise rather than reproach someone who refuses to give mouth-to-mouth resuscitation in order to avoid infection. This (1) reveals the ambiguity involved in people's spontaneous attitudes (which disqualifies them as morally relevant justifications) or (2) shows that consent to risky activities is insufficient to explain the intuitive inclination to treat STIs different from infections acquired through other routes of transmission.

Second, Harris and Holm analyze the relevance of a distinction between morally correct and morally blameworthy acts, not on the basis of consent but on the basis of the kind of act it is and the context in which it occurs. The moral difference, they argue, lies in the fact that some acts are sexual and other acts are medical in nature. Here, however, the authors rightly argue that no criterion is sufficient to distinguish between both. The criterion of necessity does not hold because many forms of care – like a physician trying to appease a patient – are unnecessary from a purely medical perspective. The criterion of social usefulness does not work either, since many sexual acts are in fact extremely useful, as without them our societies would cease to exist.[9] In addition, it is far from clear whether physicians have a professional duty to expose themselves (at the risk of exposing other patients too) to communicable diseases. In sum, Harris and Holm conclude that – against most people's intuition – there are no good reasons why the sexual nature of an infection would yield special moral obligations.

If harm caused through sexual intercourse is indeed not morally different from harm caused through casual contact, then there is no reason to consider our

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[8] [9] Harris, J. and S. Holm, 'Is there a moral obligation not to infect others?', British Medical Journal, 1995. 311(7014): p. 1216

[9] Whereas the usefulness of sex for the continuation of humanity is obvious, this is in itself no judgment regarding the desirability of humanity and societies continuing to exist. A case against the latter can be found in [18] Benatar, D., *Better Never To Have Been: The Harm of Coming into Existence,* 2006, Oxford: Oxford University Press.

duty to prevent disease transmission different in the case of a STI. However, there is an important truth in the intuition that *herpes genitalis* differs from *herpes labialis*. In what follows, two reasons are given why the mode of transmission is a relevant factor – next to purely physical health risks – in deciding which duties people have towards each other.[10] Both of them are based on the hardly controversial claim that there is something special about sexual contact, that it has a specific symbolic value that is not reducible to its observable characteristics. If we account for this symbolic value, even in a contemporary society like ours which no longer regards pleasure as sin, then the harms caused by STI's like herpes, chlamydia, syphilis, gonorrhea or human papillomavirus are different in nature from those originating from different transmission modes.

First, STI's have a potential to cause *bigger* harm. A venereal infection can cause additional harms that are neglected in purely physical accounts of diseases and their symptoms. People who have a STI may suffer from psychological distress from having contracted a disease in what still counts as one of the most intimate forms of human contact. Moreover, if others know about the infection, there could be stigmatization. Such psychological and emotional harms are absent in more casual forms of contact and depend on the social norms and expectations that our environment has towards sexual contact. Harris and Holm are right in stressing that the mere fact that society treats sexual contact as special does not in itself constitute a good reason why it is a special moral case. But as long as society *thinks* it is special, the harm caused by STIs may be bigger, and this in itself is of moral relevance. It forms a legitimate argument why the mutual obligations between sexpartners are more demanding than those between people engaging in less symbolically laden activities.

Second, the same physical symptoms may be *weightier* in the case of an STI. This argument concerns the special nature of the relationship between sexual partners. A majority reserves the intimacy involved in sex to a limited number of people. Most of the time, our sexual partners are part of that group of people we consider 'near and dear'. Here, virtue and care ethicists rightly argue that the special relationship that we have to people close to us gives rise to special, more demanding moral obligations which we do not

[10] Perhaps a similar argument can be made for the vaccination of health care workers. Although in this case the transmission mode is not special, the resulting harm may be so. It may be weightier because HCW may have an comparable duty (a professional one) to protect other people's health.

have towards people with whom we interact on a less intimate basis [19]. If our duties are proportionate to our distance towards others, intimate acts like sex invoke more stringent duties and responsibilities as compared to interactions with complete strangers or fellow citizens with whom we only have an impersonal relation, e.g. strangers on the bus. Harming the health of those close to us may therefore be of special relevance.

If these arguments against Harris and Holm make sense, they imply that the mode of transmission is not morally irrelevant. The more general argument of not harming others is reinforced and strengthened in the case of a venereal disease. This also implies that the moral case pro vaccination is stronger in the case of an STI.

1.4 The scope of obligatory precautions

Vaccination is only one way to prevent infectious disease transmission. We have a plethora of other procedures and tools at our disposal to protect others and ourselves. More and more screening possibilities exist to test whether we carry infectious diseases. We can take behavioral precautions like safe sex practices, increased personal hygiene or social distancing. There is evidence that wearing mouth masks, gloves, gowns, head covers or regular hand washing (more than 10 times a day) are effective in reducing the transmission of respiratory viruses [20, 21]. Such preventive measures are not only relevant for those who *know* they are infected, or those who *suspect* having contracted a disease. It is relevant for *everyone, at any time*, because for some diseases the infectious period begins before a person is even aware of being infected [16]. The infectious period of an influenza episode starts at least a day before the onset of illness [22]. In the case of measles, infectiousness starts about four days before rashes appear [23]. How can we draw a line between obligatory precautions and more optional forms of prevention? If strict prevention would be morally required this would require nothing less than a behavioral revolution because it would impose limits to all our behaviors. How do we justify the fact that we do not do everything we can to avoid transmitting diseases, knowing that even mild diseases can occasionally have severe consequences?

This question is a question about how much solidarity we owe to each other. Contractualism is a philosophical framework that is often used in this context [16, 24]. What matters in this framework is whether our choice

to implement or to forgo precautions is justifiable in terms of universally acceptable principles, which follow from a hypothetical 'social contract'. This social contract is made between all individuals and in this they decide the most fundamental rules that should be respected in the community these individuals will later cohabitate. Whereas many influential contractualist variants exist, elements central to this approach are: (1) once individuals are devoid from their particular circumstances and interests (in the post-Rawlsian literature often referred to as an 'original position' with a 'veil of ignorance', i.e. on beforehand contractants do not know whether in their future society they will be poor or rich, sick or healthy, etc.) they can come to a consensus about which arrangements are fair and unfair; and (2) all community members' vital interests deserve consideration, if not, some contractants would have good reason not to undersign the contract. Morally wrong actions and unfair arrangements are then those acts or arrangements that cannot be justified in terms of these unanimously agreed-upon principles.[11] Underneath this framework lies the assumption that, once we are thinking counterfactual (i.e. when we are devoid from our particular interests and circumstances), human beings are *grosso modo* capable of forming a consensus about what is fair and unfair.

What would contractualism say about the scope of obligatory precautions against infection? At first sight: very strict preventive duties. As long as prevention is effective, there seems to be an obligation to implement it. One of the basic principles that reasonable individuals would agree upon is that we should try to avoid harming others. On this basis some argue that our duties are demanding, possibly overly demanding because we would not be able to justify the choice not to prevent contagion towards those that will be most at risk [16]. As Thomas Scanlon, who worked out an influential contractualist theory, notes: "if you are presented with a situation in which you can prevent something very bad from happening, or alleviate someone's dire plight, by making only a slight (or even moderate) sacrifice, then it would be wrong not to do so".[12] As the consequences of infections can be severe, and as prevention such as extensive hand washing is usually inconvenient but not excessively costly, this would imply that we have a duty to implement the full scope of prevention.

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[11] Or, a small nuance, they are based upon principles against which some individuals hold reasonable objections.

[12] [24] Scanlon, T., '*What we owe to each other*', 1998, Cambridge: Harvard University Press, p.224

However there are two principles (also discussed in section 2 of this chapter) on which grounds limited prevention could be justified in a social contract, even when it can imply harm to others. First, it seems reasonable to make everyone (at least to some extent) responsible for his/her proper health. That means that you can justify forgoing precautions if I in fact can protect myself in the first place. This nuance heavily relaxes duties to prevent. Many precautions (e.g. wearing mouth masks and gloves, washing hands, social distancing, etc.) become optional when we can equally well expect others to implement them for their own sake. Second, unlimited solidarity would not necessarily be implied by the foundational principles from the social contract. Reasonable contractants would agree that the limits of solidarity are reached when they require excessive sacrifices, for ourselves or for society in general. For instance, it would be unreasonable to expect prevention (e.g. a screening-test) when the screening itself implies substantial risks. The same is true when precautions are very costly. For instance, completely isolating ourselves when we are ill may be beneficial to other people but it can also be a heavy burden. Think of a storeowner who has to close his shop every time he suspects having contracted an infection. In many cases this would imply substantial income-loss. This could be facilitated by the state by subsidizing prevention (or by providing compensation for income loss). But also this state-support will have limits. The economic impact of extensive absenteeism to prevent the transmission of the common cold or the flu may be massive. Reasonable contractants would reject societal support for prevention when it requires an excessive cost in general welfare.

In sum, a reasonable scope of obligatory precautions against infection would imply that individuals protect themselves in the first place, and this would make many precautionary measures optional. However, towards those unable to protect themselves, many precautions become obligatory. However, overly demanding prevention would not be prescribed. It would be morally permitted to forgo excessive sacrifices.

1.5 Conclusion

The objective of this chapter was to discuss whether we have a moral duty to prevent infections in others and ourselves. I have summarized and discussed three arguments that there is a moral duty to accept vaccination: (1) protect our own health, (2) avoid harming others and (3) contribute to public goods. Depending on the vaccine, the disease and the specific context these arguments will become more or less convincing. Arguing that the sexual or non-sexual mode by which a disease is transmitted makes a moral difference, I have claimed that we have stricter duties to prevent sexual harm. Finally, also other precautions can be morally obliged, even though their implementation will be limited by people's duty to protect their own health and by reasonable limits to solidarity.

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Chapter 2: Kicking against the pricks: vaccine skeptics and their social orientation.

Abstract: In any country, part of the population is skeptical about the utility of vaccination. In order to develop successful vaccination programs, i.e. programs that manage to reach sufficient coverage in the population, it is important to understand the determinants of such negative attitudes. The aim of this chapter is to provide insight into the defining characteristics of vaccine skeptics. I will first summarize previous research on the reasons why people refuse and on the socio-demographic differences between vaccine skeptics and non-skeptics. Afterwards the results of a study will be presented in which was explored whether both groups also differ in terms of basic psychological dispositions. We held a population survey in a representative sample of the population in Flanders, Belgium (N=1050) in which was investigated whether respondents' attitude to vaccination was associated with their basic disposition towards other community members or society in general, as measured by the Triandis and Gelfand social orientation scale. It was found that skeptics and non-skeptics have a different social orientation, even when several variables are controlled for. More specifically, vaccine skeptics scored significantly lower on both horizontal individualism and horizontal collectivism, indicating a lower disposition to see others as equals. These findings need confirmation in the context of different countries. Such insights can be valuable to optimize the design of effective communication strategies on vaccination programs.

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2.1 Introduction

A central mission of public health policy is to ensure sufficiently high vaccination coverage in the population [1, 2]. Two goals motivate this objective [3]. First, to maximally prevent infections from occurring: either directly in those being vaccinated or indirectly in unprotected individuals through herd immunity (which is a consequence of reduced circulation of pathogens in a largely vaccinated population [4]). Second, to eradicate pathogens, as was the case for smallpox, and is the intention for polio through continued high coverage polio vaccination around the world [5].

Several countries, however, experience difficulties in reaching optimal participation in vaccination programs because increasing numbers of individuals hesitate or refuse to become vaccinated [6-9], in part precipitated by misinformation spread by anti-vaccination lobbies. Therefore an essential policy challenge consists of establishing an effective dialogue between scientists, policy makers and the public at large, with the aim to sustain public trust in public health policy and to convey the need for continued vaccination efforts [10-15]. Such a strategy requires a thoroughgoing understanding of who refuses vaccination, and for which reasons [6, 13]. In the next section I will summarize what is known about the reasons why individuals stand skeptically towards vaccination and which socio-demographic variables are found to be different in skeptical versus non-skeptical groups. Then I will present a study in which we investigated whether both groups also differ in terms of a basic psychological disposition: social orientation.

2.2 Vaccine refusers: motivations and correlates

Vaccine sceptics and refusers cannot be considered as a homogenous group. Based upon the following studies that investigate why individuals refuse vaccination [8, 10, 16-26], sceptics can be classified in the following four, generically different motivational categories.

(I) General distrust of vaccination. A first (and largest [25]) subgroup is not convinced of the scientific estimates of risks and benefits of vaccination. If the 'true' estimates would be attractive, this group would give up their refusal. But these people believe that the government, the scientific world or the pharmaceutical industry presents unreliable estimates about adverse effects from vaccination, the risks of certain diseases or vaccine efficacy. This

is the group that benefits most from educational campaigns that aim to increase the public's understanding of vaccination and that highlights the importance of trust and integrity for key persons in the field of vaccinology. In this group of disbelievers, there are on the one hand people who doubt the completeness of conventional medical science. This group consists of 'non-believers' (e.g. adherents of homeopathy), but also of individuals who claim to have a better insight into their personal immune system than statistical predictions on an aggregate level could provide (e.g. someone who had a bad experience with vaccines). On the other hand there are people who doubt the objectivity of the scientific estimates and mistrust governments in general, or particularly when they are perceived to be liaised with pharmaceutical industry.

(II) Free rider motives. A second subgroup can be labelled as 'free riders'. Freeriding is a typical problem in the creation of public goods through collective action. Individuals who are pro vaccination in general but who prefer to remain unvaccinated as long as enough others are vaccinated hold a free rider motive. This motivation differs from the previous one because here, individuals take a perspective that is different when they apply it to themselves, as individuals, rather than others in relation to public policy.

(III) Different risk-profiles. A third subgroup does believe the scientific arguments why someone should become vaccinated, but has a risk-profile that differs from the one assumed in the public health perspective. On the one hand this group consists of individuals with a differing time-preference. These people undervalue the benefits of future disease protection as compared to a present in which adverse effects may occur. They might value short-term wellbeing far more than risk protection in the future (hyperbolic discounting), which would strongly deflate the subjective value of vaccination (i.e. a high discount factor). For instance, in areas of low endemicity (as in most affluent countries) the risks of hepatitis B virus mainly occur in age groups above 20 years of age, while routine vaccination (and the associated risks on adverse effects) occurs in infants [27]. A second group suffers from what is known as omission bias (the tendency to consider a similar risk worse when it results from action rather than from omission). For them, the risks on adverse effects from vaccination and the risks of becoming infected with a disease are not measured on the same scale. The harmful effects of certain actions (i.e. an adverse effect following the choice to become vaccinated) are considered differently to the harmful effects of certain omissions (i.e. a natural infection following the choice not to become vaccinated). There is thus a (perceived) heterogeneity in the risks actively incurred by vaccination or passively incurred by infection [28].

(IV) Fundamental objections. Then a fourth subgroup refuses out of philosophical or religious disagreement with the very objective of vaccination. These groups trust in a spontaneous harmony that exists in nature, like a divine providence, and they consider infectious diseases to be part of this balance. For them, sickness is an essential element of life. Avoiding illnesses by vaccination will make life easier, but not necessarily more worthwhile. Because this motive relates to fundamental conceptions of 'the good life', it is sometimes considered to be the one most worthy of respect in line with a respect for autonomy [16, 29].[13]

Socio-demographic factors have also been shown to differ between vaccine refusers and non-refusers, including household income [26, 30, 31], level of education [23, 30-32], marital status [6], race [16], and family size [31] with refusal often being more prevalent in relatively higher educated, wealthier groups [6, 32].

2.3 Cognitive differences between skeptics and non-skeptics

2.3.1 Social orientation

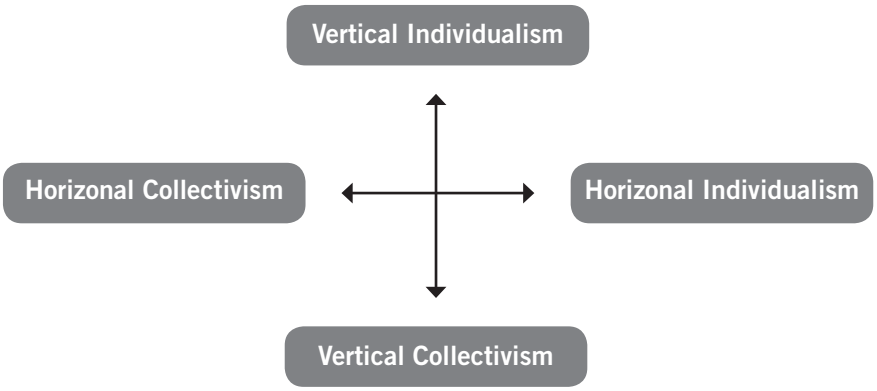
Little is known about the more general cognitive profile of vaccine skeptics. Nonetheless, such information could be essential for the design of social marketing strategies for vaccines [13]. As vaccination is - at least partly - a matter of being solidaristic with others or not, we hypothesized that differences in social orientation, i.e. in one's basic attitude towards other community members and society in general, may translate into a different valuation of vaccines.

Singelis et al. [33] and Triandis et al. [34] developed an influential framework to study social orientation. This framework distinguishes 2 basic relational dimensions: a collectivism/individualism axis that reflects someone's sense

[13] The religious motive may sound rather naive at first sight, but it is nonetheless -to some extent- present in most people's relation towards nature. Only few people would argue that environmental limitations to human behaviour have no moral value. The resistance against genetically modified foods or the wide-spread remorseful feeling that humans may be causing global warming, indicates that for most people environmental limitations are not ethically neutral. The religious motive against vaccination actually reveals the lack of a consistent attitude towards nature in the mainstream opinion. Which natural limits should be respected and which not? And why should they be respected, for our own wellbeing or out of respect for nature itself? These questions cannot be answered without relying on metaphysical convictions about the meaning of life and the place of man in the universe.

of social cohesion and his/her willingness to prioritize common goals over personal ones, and a horizontal/vertical axis that indicates to what degree an individual expects equality or accepts inequality in social relationships [34, 35]. This generates the 4-way typology horizontal and vertical individualism and collectivism (HI, VI, HC, VC) represented in **Figure 1.**

Figure 1: **The 4-way typology of social orientation**



Typically, a HI orientation promotes individuality and autonomy on a basis of equality in interpersonal interaction. A VI orientation encourages personal achievement through competitions, in which others are predominantly seen as competitors in a hierarchy. A HC orientation emphasizes interdependency, cooperation with others and communal sharing, on a basis of equality. Finally, VC is an orientation that also promotes subordination of personal under group goals while differences in social status and hierarchy are acknowledged. The next section reports on a survey in which we explored whether vaccine skeptics are different from non-skeptics in terms of these 4 dimensions of social orientation.

2.3.2 Methods

2.3.2.1 Sample selection

Between March and July 2011 3740 people were contacted by professional telephone operators using random digit dialing of fixed and mobile telephone numbers (during weekdays from 10 am to 9 pm, on Saturdays from 11 am to 7 pm). Every number was called once, except when respondents asked to call back at a more convenient time. Contacted persons were greeted and asked if they were willing to participate in a scientific survey concerning health policy (without knowing that the subject was vaccination). The 1540 respondents willing to cooperate (41% of those contacted) were consequently asked for their age, gender, educational attainment and location over the 5 Flemish provinces and were selected when they fulfilled the predetermined quota for these criteria. Consequently participants were asked whether they wanted to receive the survey either on paper or through an internet-link, and whether they wanted to return their responses by post (using a prepaid envelope) or online. The sample size of this survey was determined in function of the initial purpose of the survey (the study summarized in chapter 4).

2.3.2.2 Survey

In our survey we presented the Triandis and Gelfand scale to determine an individual's position on the four dimensions of social orientation [34]. It consists of sixteen value judgments on which every respondent is asked to express his/her agreement on a five-point likert scale ranging from "strongly disagree" to "strongly agree" (see **Figure 2**). All 4 types of social orientation are characterized by 4 statements *a priori* designated to reflect one specific type. E.g. "Winning is everything" is held to be a typical VI statement, whereas "I feel good when I cooperate with others" is held to be typically HC. For every respondent a score is obtained for all 4 dimensions (HI, VI, HC, VC) through calculating the average score attributed to the statements belonging to that dimension. The scale has proven to be a valid instrument to indicate how individuals see themselves in relation to other individuals and society as a whole and has been used and validated in numerous studies (for reviews see [36, 37]). Since the original scale was in English and the respondents are native Dutch speakers, translation and back-translation was conducted to ensure that all items contained equivalent meaning to the original.

Figure 2: Triandis' and Gelfand's 16-item scale for horizontal and vertical individualism/collectivism

Horizontal Individualism

1. I'd rather depend on myself than others.
2. I rely on myself most of the time; I rarely rely on others.
3. I often do "my own thing."
4. My personal identity, independent of others, is very important to me.

Vertical Individualism

5. It is important that I do my job better than others.
6. Winning is everything.
7. Competition is the law of nature.
8. When another person does better than I do, I get tense and aroused.

Horizontal Collectivism

9. If a coworker gets a prize, I would feel proud.
10. The well-being of my coworkers is important to me.
11. To me, pleasure is spending time with others.
12. I feel good when I cooperate with others.

Vertical Collectivism

13. Parents and children must stay together as much as possible.*
14. It is my duty to take care of my family, even when I have to sacrifice what I want.
15. Family members should stick together, no matter what sacrifices are required.
16. It is important to me that I respect the decisions made by my group*

* Because of unsatisfactory factor loadings these two items were excluded from the main analysis and were only used in the sensitivity analysis.

To determine the respondents' general attitude towards vaccination we asked them to indicate their agreement with the following statement on a five-point likert scale ranging from "strongly disagree" to "strongly agree" (see **Table II**):

"If a vaccine exists for a certain disease, then vaccination is usually a good way to protect someone against this disease."

In addition we asked for respondents' age, gender, level of education, profession, ethnic origin of mother and father, family size, age of family members, experience as health care worker, height, weight, smoking status (smoker/non-smoker), experience with travel vaccination, experience with severe illness (personal or within the family), province, and we subjected them to the EQ-5D-3L health survey, including the Visual Analogue Scale (VAS). The EQ-5D-3L is a standardized health measurement questionnaire consisting of 5 health dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Respondents can indicate their position on each dimension according to three levels. It allows valuing a patient's present health state in a single score. The VAS is a rating scale on which respondents can indicate their current health state, ranging from 0, the worst imaginable health state, to 100, the best imaginable health state [38].

2.3.2.3 Analysis

For the statistical analysis we used SAS and SPSS. We conducted a confirmatory factor analysis of the 16 items of the scale and found the original four-factor structure replicated. In our sample all items except two (VC13 and VC16) highly loaded on the intended dimension. Therefore, in line with the methodology followed in other studies [39, 40] we excluded these two items from the main analysis. The response measuring respondents' attitude towards vaccination was dichotomized giving zero to those who indicated "Agree" and "strongly Agree" (a positive attitude towards vaccination) and one otherwise (a non-positive attitude). First a univariate regression was performed between every variable in the dataset and attitude to vaccination. Then a logistic regression model was built through forward and backward stepwise selection of all covariates in order to determine for the 1050 respondents which variables were significantly associated with attitude to vaccination. The sensitivity of the results was explored by repeating the analyses using different categorizations of the dependent variable, and inclusion of the two previously excluded statements from the scale. Additionally, a mean response model was used to evaluate the impact on the results when the response is treated as continuous (i.e. without dichotomizing the dependent variable).

2.3.3 Results

We reached a sample of 1050 respondents, considered representative for the population in Flanders (6,208,877 inhabitants, about 60% of Belgium [41]). Forty-one percent of the 3740 contacted persons (1540 individuals) consented to participate. Sixty-eight percent of these 1540 candidates were effectively recruited, i.e. 28% of those who were initially contacted. Fifty-one percent of the sample was female, 50% received higher education (university or non-university degree) and the mean age was 43.

Table 1: Characteristics of the surveyed population (N=1050)

Variable	Classes	Count (%)
Age	18-25	202 (19)
	26-35	222 (21)
	36-50	241 (23)
	51-60	194 (18)
	61-76	191 (18)
Sex	Male	517 (49)
	Female	533 (51)
Education	None or primary education	28 (3)
	Professional secondary education	76 (7)
	Technical or general secondary	426 (40)
	Higher non-university education	374 (36)
	University	146 (14)
Profession*	Self-employed	125 (12)
	Office worker	540 (53)
	Manual worker	111 (11)
	Houseman/housewife	82 (8)
	Disabled	47 (5)
	unemployed	28 (3)
	student	53 (5)
	Other	37 (4)

* For 26 respondents profession was missing.

Five percent of the respondents stated explicitly to be against vaccination, 15% stated to be neutral while 80% considered vaccination a good way to prevent disease (see **Table 2**). The multiple regression results indicated that individuals who indicated a skeptical (i.e. a non-positive) attitude scored significantly lower on the dimensions HC and HI and were less likely to smoke. Per unit increase in their score on HI and HC, respondents had a 28% and 25% lower odds of being vaccine skeptic, respectively. The odds of non-smokers being vaccine skeptic were 40% bigger than those of smokers. None of the other variables, including educational attainment, age, current health state, profession or experience with severe illness had a significant predictive value in the model. On a univariate level 'vertical collectivism' was the only additional variable with a significant (negative) association. This was no longer significant in the multiple regression model, in which we adjust for the influence of other variables. The results using the mean response model confirmed a positive association between a more equally oriented profile and a more positive attitude towards vaccination. Furthermore, a second logistic regression model was fitted after reclassifying the neutral responses. However, moving neutral responders from the negative to the positive attitude category resulted in a very small number being classified as having a negative attitude (n=51, or 5%), such that this approach could not produce interpretable estimates. Inclusion of the hitherto omitted Triandis and Gelfand statements (items 13 and 16 in **Figure 2**) did not alter these results.

Table II: Overview of the sample's attitude to vaccination and logistic regression results of the significant covariates of a skeptical attitude towards vaccines

ATTITUDE TO VACCINATION						
"Vaccination is a good way to prevent disease..."	**Strongly disagree**	**Disagree**	**Neutral**	**Agree**	**Strongly agree**	
Count (%)	16 (2)	35 (3)	159 (15)	514 (49)	326 (31)	
LOGISTIC REGRESSION						
	Crude odds ratio			**Adjusted odds ratio***		
Effect	**Point estimate**	**95% CI**	**P-value**	**Point estimate**	**95% CI**	**P-value**
Smoking status (yes vs. no)	0,640	0,467 - 0,882	0,0059	0.597	0.424 – 0.841	0.0031
Horizontal collectivism	0,711	0,611 - 0,825	<0,0001	0.759	0.642 – 0,897	0.0012
Horizontal individualism	0,791	0,681 - 0,917	0,0018	0.724	0.617 – 0.849	<.0001

* List of non-significant parameters: age, gender, educational attainment, professional group, EQ-5D score, VAS-score, personal experience with severe illness, experience with severe illness in the family, origin mother, origin father, experience with travel vaccination, experience as health care worker, family size, age family members, province, height, weight, vertical individualism and vertical collectivism.

2.4 Discussion

The aim of this chapter was to discuss and explore what differentiates vaccine skeptics from non-skeptics. There are four different reasons why someone can be against vaccination, and the likelihood of holding any such views is correlated to several socio-demographic characteristics. Our study identified social orientation as an important additional criterion to differentiate.[14] Our results show that the values of horizontal individualism and horizontal collectivism are associated with whether or not people take a positive stand towards vaccines. These findings are notable for two reasons. First, given that social orientation was identified as a more important determinant than other more commonly reported socio-demographic variables (such as e.g. education or professional group); our findings underscore the value of investigating the psychological determinants of vaccine skepticism. Second, vaccination is a solidaristic intervention that benefits both the vaccinated individual and the wider community whereas the risks associated with vaccination remain strictly private. Therefore, one might intuitively expect that people's attitude towards vaccination will be determined by the individualistic versus collectivistic social orientation of individuals. However, our findings demonstrate that it is not so much individualism or collectivism that is of importance but particularly the degree to which people value equality in their social relations. The more people see others as equals, the more positive they stand towards vaccination.

Findings like ours may help to improve the design of effective communication strategies for vaccines. In several countries marketing research has shown that advertisements are more persuasive when their appeal is matched to the social orientation of their targeted audience [42, 43]. Individuals who scored high on HI, VI, HC or VC were found to be more susceptible for messages, which emphasized self-direction, power, universalism and tradition, respectively [37]. For instance, the higher the HC orientation of participants, the more they were in favor of a brand selling a shopping bag with which "you're doing your part to save the environment". The higher the

[14] The focus of our analysis was on social orientation. However, also the fact whether a respondent smoked or not was a significant factor in predicting attitude to vaccination. People who smoke were less likely sceptical about vaccines. We have no real explanation for this finding. However, several empirical studies suggest that smokers are less risk-averse than non-smokers (e.g. [48]). One could speculate that smokers are perhaps less afraid of taking (short-term) health risks than non-smokers, and that they therefore are less affected by the (short-term) risk of adverse effects associated to vaccination. Perhaps future studies can confirm (or refute) our finding and provide more insight into the relationship smoking - attitude to vaccination.

HI orientation, the more participants liked a brand selling T-shirts for which you could "pick your color, pick your message, and pick your style" [37]. Vaccination could be promoted by appealing to HC values like solidarity and interdependence (e.g. "vaccination is a matter of taking care of each other") or HI values such as individual freedom and self-expression (e.g. "vaccines enable you to safely explore the world by traveling" or "vaccines enable your children to play safely with other children"). Our findings suggest that such marketing strategies are less likely to be persuasive in vaccine-skeptical groups because these groups have a significantly lower HC and HI orientation. However, since we also found a positive association between valuing equality and having a more pro-vaccination attitude, our findings also project that vaccine skepticism may diminish through more structural strategies aimed at stimulating HI and HC orientations. One could speculate that large events that speak to HI or HC values such as music festivals or election days present an opportunity to embed pro-vaccine messages.

Some limitations of our study should be mentioned. First, our study may be influenced by the Flemish context (culture, education, experience with vaccination, etc.). It is noteworthy that most (but not all) childhood vaccines are given free of charge in Belgium. Although only polio vaccination is compulsory [44], uptake is high for most vaccines [45], and has remained largely unscathed by general and specific anti-vaccine lobby campaigns (e.g. false claims of causal links between measles-mumps-rubella vaccine and autism [46] and hepatitis B vaccine and multiple sclerosis [47]). Second, non-response bias is always a potential concern in survey-based research. We believe that the overall response (41% of contacted persons consented to participate) was acceptable, given the design and nature of the study. Third, this was an exploratory study. Further research in this area could expand the methodology we used with alternative and/or more specific instruments to capture attitude to vaccination and social orientation. Certainly it would be interesting to validate our study in other countries and to investigate the influence of other psychological attributes, perhaps also on other forms of health care refusal. As the success of infectious disease prevention largely depends on collective cooperation, all knowledge about what differentiates skeptics from non-skeptics allows more successful anticipation, communication and education. The identification of social orientation as an explanatory factor for vaccine skepticism presents an opportunity to rethink communication strategies, and conduct further research in this direction.

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Chapter 3: Vaccination policy and ethical challenges posed by suboptimal uptake and subgroup targeting

Abstract: Vaccination is a matter of collective importance that reaches into the most private sphere of citizens. Therefore, policy makers need to walk a tight rope in order to complement utilitarian public health values with individual rights and freedoms. This chapter discusses two pertinent ethical challenges in vaccination policy. First, targeting vaccination only at particular profiles or population subgroups can be both an effective and efficient use of health care resources. However, singling out individuals for public policy can also be ethically controversial. Under which circumstances are such selective measures justifiable? It is argued that a vaccination program must not only be evaluated on its effectiveness and cost-effectiveness but that also equity, non-discrimination, protection of privacy and non-stigmatization must be given proper consideration. Second, in any country a substantial number of individuals remain reluctant to become vaccinated. Which policy measures should be addressed when vaccination coverage is insufficient in a population? Information campaigns, legal compulsion, or the use of nudges and incentives can all be effective, but also controversial policy options. We will discuss the ethical trade-offs that are at stake and the circumstances in which such policy measures are defensible.

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3.1 Introduction

As acknowledged in the International Covenant on Economic, Social and Cultural Rights of the United Nations, governments ought "to provide immunization against the major infectious diseases of the community" [1]. In reality however, ethical vaccination policy is much more complex than a mere provision of vaccines. In this chapter I will discuss two ethical policy challenges.

First, the rise in health care costs and the increasing number of vaccine-candidates forces governments to rationalize vaccination programs and to prioritize between various public health strategies. The latter are increasingly judged upon their cost-effectiveness, indicating whether sufficient disease is being prevented per euro invested. In this respect, medical and economic research clearly indicates the potential benefits of implementing vaccination programs, targeted only at certain profiles or population subgroups. The latter can be defined by characteristics such as age, gender or profession; but also more controversial criteria such as ethnicity, sexual activity, religion or drug use can be relevant to select individuals. However, the broader ethical implications of such targeting remain unclear. I will discuss against which other ethical values the efficiency gains of such programs should be balanced.

Second, merely making vaccines available is insufficient when individuals are reluctant to become vaccinated. Experts become increasingly concerned about a diminishing trust in vaccination by growing numbers of citizens [2]. Chapters one and two discussed who these people are, why they refuse and whether they have the moral right to do so. This chapter explores how public policy can respond to this challenge. Different policy measures can be effective in increasing vaccine uptake but remain controversial from an ethical perspective.

3.2 Targeting subgroups

Often vaccination programs (in model-based explorations or in practice) are targeted only at a part of the population. This targeting of subgroups can be attractive since sometimes certain profiles are - from an epidemiological perspective - special. First, some individuals run higher risks of becoming infected than others. Second, when a specific profile is more likely to transmit a pathogen to many others ('superspreaders'), a selective vaccination program

for that group can be an efficient way to protect the entire population. Third, the consequences of an infection are not the same in every individual, i.e. some people are more vulnerable to develop serious symptoms.

In many cases such targeting will be uncontroversial and self-evident (e.g. vaccination targeted only at newborns or at certain professional profiles like health care workers). However, research has indicated both the economic and public health benefits of targeting vaccination programs at groups defined by sexual activity (e.g. men-who-have-sex-with-men [3]), ethnicity (e.g. immigrants [4]), religion (e.g. Muslim pilgrims [5]) or illicit drug use [6]. From an ethical perspective, such selective policies are more controversial. In the early twentieth century an ordinance from San Francisco, that required vaccination of the Chinese against bubonic plague before leaving the city, was struck down because it did not apply to the full population [7]. Today, vaccination is targeted at ethnic minorities in countries such as the Netherlands [4], France and Australia [8], and also in Belgium such policy recommendations were made (e.g. hepatitis A vaccination for children with Moroccan or Turkish origin [9]).

The moral justifiability of targeting depends on more than a comparison of costs and benefits. As explained in the next sections, the value of efficiency has to be balanced against wider considerations of equity, non-discrimination, privacy and non-stigmatization [10, 11].

3.2.1 Health equity

The distribution of different burdens and benefits of a vaccination program is in itself neglected in cost-effectiveness or cost-benefit analyses. It can nonetheless be a relevant issue for targeted vaccination, both (1) within the program as (2) on a wider scale.

(1) In most cases a vaccination program benefits those being vaccinated, with potentially indirect protective effects on the rest of society. But sometimes the persons who benefit most are not the ones who carry both the inconveniences of receiving vaccination (muscular pain, light fever, absence from work, et cetera) and the small risks of more serious adverse effects. One example could be a program of influenza vaccination for children set up in order to protect (mainly) the elderly [12]. Another one could be hepatitis A vaccination of children of ethnic minorities, a disease that usually has a

benign course in children but a more serious course at older age. Such skewed distributions of burdens and benefits may generate an equity concern.

(2) A powerful intuition of justice, which finds support in many theories of justice as well, is that public resources should be invested so as to equalize opportunities [13, 14] and to improve the prospects of those groups in society which are worst-off [15]. Implementing targeted policies does not necessarily reduce already existing health disparities. Targeted vaccination will make it harder for non-targeted groups to receive vaccination, i.e. they will experience a reduced access to the vaccine (e.g. because it is only subsidized for the target group). Moreover, opting for one program implies per definition that fewer health care resources are available for other policy options (opportunity costs).

3.2.2 Non-discrimination

Discrimination means that individuals are treated differently on the basis of a non-relevant criterion.[12] As such, it is objectionable from an ethical point of view. The principle of non-discrimination is enshrined in constitutions of liberal democracies around the world. It expresses a political dedication to promoting equality of opportunity among citizens. By treating individuals differently, targeted vaccination risks to be discriminatory. What is required for a characteristic to be an acceptable basis for public policy?

In the first place, its relevance has to be evident, backed by sufficient evidence and argumentation. Epidemiologically, it has to be convincing that a particular population group requires a differential treatment, as indicated by scientific estimates on incidences, transmission rates, etc. For instance, as long as human papillomavirus (HPV) is mainly a problem for girls the relevance of targeting girls only (and not boys) is evident. Or the characteristic needs to be evident because of ethical reasons. For some groups it can be less acceptable to become ill (e.g. soldiers, police officers or other professions of national security) or to spread a virus (e.g. HCW [16]).

However, there is a difference between relevance on the individual and on the group level. Statistics can indicate that on average one group is more at

[12] Although the term 'discrimination' is sometimes used to denote any form of differentiation between individuals, this chapter focuses only on illegitimate, unjust or prejudiced forms of discrimination.

risk than another group. For instance, individuals with dark skin are on average more at risk for HIV than others; Moroccan immigrants in Western Europe run a higher risk of hepatitis A virus [17] and the prevalence of STIs is often higher in homosexual men [18]. But, statistical facts do not necessarily inform us about the individual members of each group. On an individual level the risk incurred has nothing to do with having a dark skin, being Moroccan or being homosexual but with having a higher likelihood to adopt certain risk-behaviours. On an individual level targeting vaccination according to ethnicity or sexual orientation may still be discriminatory. Individuals with dark skin can equally well be celibate; immigrants do not necessarily visit endemic areas, and men-who-have-sex-with-men can avoid unsafe sex-practices.

Therefore, in order for a program not to be (perceived as) discriminatory the characteristic should be - as much as possible - relevant at the individual instead of the group level. For instance, instead of targeting Moroccan minorities, policy makers could also target the travellers that go to Morocco, with perhaps increased efforts in Moroccan neighbourhoods. Instead of targeting homosexual men, vaccination policy could focus on individuals with unsafe sex practices, with perhaps increased efforts in the gay community.

3.2.3 Protection of privacy

The non-discrimination restriction favours gathering reliable estimates of individual behaviours and building public policies upon this knowledge about individuals. However, characteristics like sexual activity, sociability or other behaviours relevant to disease transmission typically belong to an individual's private sphere. There is thus a tension between non-discrimination and protection of privacy. The latter will restrict policy options. If we want to uphold both values, then only individually relevant characteristics that clearly belong to the public domain (like age, gender, profession, location, et cetera) are legitimate bases for selective vaccination programs. For more private information, policy makers would have to count on the voluntary disclosure of behaviour by individuals, which in most cases would make it ineffective (e.g. only those people that disclose high sexual activity would get a free HBV-vaccine).

3.2.4 Non-stigmatization

Groups that play a key role in the transmission of viruses are often groups that already have a negative public image: homosexuals, sex-workers, immigrants, drug users, homeless people, et cetera. The social dynamics that are created by singling out these groups for vaccination programs can result in an increasingly negative reputation or stigma, which can play an important role in the lives of these population subgroups [19]. It risks conveying the, in many cases, false message that the targeted group is more prone to unhygienic or promiscuous behaviours, that the health risks of a disease are limited to this group or, even worse, that the target group is responsible for spreading a disease.

In summary, targeted vaccination is a promising public health strategy. The more we get to know about virus transmission the more will we be able to fine-tune preventive strategies on particular profiles and individuals. However equity, non-discrimination, protection of privacy and non-stigmatization are four ethical restrictions to targeting subgroups. In case of a value conflict policy makers will have to decide which value is more important to uphold. For instance, to prevent hepatitis A outbreaks one could opt (1) for an (in the Belgian context) inefficient universal vaccination program, (2) for a more efficient targeted program focussing on ethnic groups with close ties to endemic countries (which may be discriminatory and cause stigma) or (3) for an equally efficient targeted program that focuses on travellers to endemic countries (which may infringe privacy as individuals would have to disclose their travel destination to some public health authority). Arguably, when the efficiency gains are substantial, targeting travellers would be the most balanced strategy as discrimination against ethnic groups and inefficient use of resources have bigger ethical weight than infringing privacy in the context of tourism. Efficient hepatitis B (a STI) prevention could require targeting of homosexual men (which may be discriminatory) or unsafe-sex-practitioners (which would evidently violate privacy as it requires some categorization of individuals according to sexual habits). Arguably here, privacy infringements are weightier than discrimination.

3.3 Increasing vaccination coverage

Reaching and maintaining high vaccination coverage in the population is crucial to provide comprehensive disease protection and, in the long run,

to eradicate pathogens. However, many people remain unaware of (newly) available vaccinations, they forget to become vaccinated (or to complete the full schedule) and part of the population is just plainly reluctant to become vaccinated. In other words, vaccines are not used to full potential and a substantial gain in population health is left untapped. This raises questions about which role the government has to play in stimulating vaccination. Almost any political philosophy will judge the protection of public health as a key responsibility of the state. However, in a society that also values individual freedom, the objective of public health requires being balanced against individual's right to bodily integrity, physical security and more generally, individual autonomy. Indeed, such rights are very relevant in the case of vaccination as rarely a public policy measure (literally) intrudes the individual sphere in such a real and physical way.

How should individual freedom and public health be reconciled in vaccination policy? The importance, yet also the difficulty of balancing both the objectives of health and freedom is indicated in the following section, in which a senior WHO physician-epidemiologist who was assigned for the last phase of the smallpox eradication campaign in India from 1973-1975 describes his experience with a compulsory vaccination program:

"The initial stage in the evolution of a coherent containment policy was marked by an almost military style attack on infected villages. […] In the hit-and-run excitement of such a campaign, women and children were often pulled out from under their beds, from behind doors, from within latrines, etc. People were chased and, when caught, vaccinated. […] Almost invariably a chase or a forcible vaccination ensued in such circumstances […] We considered the villagers to have an understandable but irrational fear of vaccination […] We just couldn't let people get smallpox and die needlessly. We went from door to door and when they ran, we chased. When they locked their doors, we broke down their doors and vaccinated" [20].

Evidently, such forms of paternalism are highly controversial, even in the context of a developing country where the level of understanding medical science may be low. In the next section I discuss four possible answers to the problem of insufficient vaccine uptake in high-income countries. They are presented in an increasing order of coercion and a decreasing order of respecting individual choice.

3.3.1 Education

The least problematic way to induce compliance with vaccination recommendations is to create an effective dialogue between policy makers, scientists and the lay public, one that manages to rationally convince people of the necessity to become vaccinated. Increasing the public's understanding of prevention through educational campaigns about how vaccines work, how diseases are transmitted and which consequences they bring about is an essential part of this. It will be especially relevant to persuade those people who question the attractiveness of the risk-benefit ratio of vaccines (see chapter 2), but it will also help to make clear that in some cases vaccination can be a matter of ethical duty towards others (see chapter 1). As such, education does not violate individuals' freedom of choice. To the contrary, it enhances their capacity to make informed, competent decisions.

Occasionally however there may be an ethical concern with diffusing information. Public health is an important but not an absolute social objective, i.e. it stands next to other goals such as e.g. social cohesion or the social integration of minority groups. Diffusing reliable information about risks and benefits of vaccination, the transmission modes of viruses and about groups that play a key role in transmitting viruses could create a social dynamic and further decrease the already stigmatized public image of groups that are often associated with infectious disease transmission: sex-workers, homeless people, immigrants, homosexuals, etc. This can play an important role in the lives of these minority groups [19].

3.3.2 nudges

In recent decades a substantial body of research has emerged on 'libertarian paternalism' [21]. This behavioural approach to public policy aims to combine the best of both worlds: letting individuals free to make their own decisions (libertarian) while at the same time allowing policy makers to try to influence people's behaviour so that they make the right choice (paternalism). Many studies show that making small and apparently insignificant changes to the context in which individuals make choices (the 'choice architecture') can have a large impact on which decisions are effectively being made [21]. For instance, placing apples before donuts in school restaurants (or vice versa) will make a difference to healthy eating

habits. Setting the printer's default at double-sided printing strongly reduces paper consumption. Etching the image of a black fly into urinals for men heavily reduces spillage. The supply of donated organs dramatically increases when organ donation is done on an opt-in basis (no enrolment in case of a decease, unless explicitly stated) or an opt-out basis (automatic enrolment).

These so-called 'nudges', which gently stimulate a decision or behaviour to go in a desired direction without reducing actual freedom of choice, are also promising in the context of vaccination. Many unconscious biases and heuristics influence vaccine decision-making. By anticipating them, i.e. by making the choice architecture more favourable for vaccines, a higher compliance with vaccination recommendations could be reached. For instance, people typically overestimate the value of the present versus the future ('the immediacy effect'), give a higher weight to losses over gains ('framing effects') and they are very bad in understanding small probabilities [22]. These psychological mechanisms disadvantage vaccination because of the nature of its benefits and risks. On the other hand behavioural research also shows that people are highly sensitive to social norms, to the choices other people make (herd behaviour) and to the trustworthiness of the different parties who are involved in the entire decision-making process. All these insights can be used to frame vaccination choices and to 'nudge' individuals into making better decisions. For instance, knowledge of framing effects recommends that vaccination is presented as much as possible as the default, standard option. Instead of requiring individuals to make an active effort to become vaccinated (e.g. by necessitating individuals to buy vaccines in pharmacies and to go to the doctor themselves), the choice architecture could also be made such that becoming vaccinated is the 'passive outcome' whereas forgoing it requires an active effort (e.g. by increasing the administrative burden of refusing). The immediacy effect recommends offering (small) material benefits (e.g. candy or small toys for children, a voucher for adults, etc.) in order to compensate for the inconvenience of vaccination. The importance of social norms recommends clearly communicating that a large majority opts for vaccination, and that only a small minority (with diverging beliefs and/or free-rider motives) refuses it. And, perhaps most importantly, nudge-research highlights the importance of investing in building and supporting trust and trustworthiness of those who play a key role in vaccination policy: physicians, pharmaceutical industry, public health officials, academics, etc.

There are also moral objections against nudging decisions. An in-depth discussion would go beyond the scope of this chapter (for more elaborate discussion see e.g. [23]) but the following points could be of relevance to vaccination. First, nudges can easily be perceived as being manipulative. As there are many organized anti-vaccination movements who actively engage in discussions about vaccination, there is a real risk that the use of nudges, once discovered, instigates further suspicion, complot theories and - as trust is paramount to vaccination - creates backlash in the general public. It is therefore important that nudges are transparent and cannot be perceived as being dishonest. Second, paternalism implies that individuals are pushed into the direction that is good to themselves. However, in some contexts of vaccination policy this is not always very clear. Vaccinating new-borns against polio is mainly in the interest of the community (because the disease could become eradicated) but perhaps less in the direct interest of the child (who has little to fear of the disease). In such cases using nudges becomes more objectionable than when they are used to steer people's choices in a direction that indisputably improves their lives.

3.3.3 Incentives

When education and nudges prove to be insufficient, a more stringent option could be to use incentives: changing the consequences of choice outcomes in a more drastic way. Incentives are stronger than nudges because they imply a more intrusive and more burdened type of paternalism. Individuals are still free to choose but they will face non-negligible consequences. In countries such as the US or New Zealand some schools do not allow children to access without meeting vaccination requirements [24]. Such measures avoid the problems of explicit coercion as parents still have the option to send their children to a different school. Parents are still free to choose, but their options are more limited. In older age groups vaccination decisions could be influenced by implementing economic incentives such as the threat of a substantial loss (accountability), the attraction of a significant reward, or both. Such measures 'incentivize' vaccination in a way that goes beyond 'nudging'.

Rewarding vaccinated individuals is implemented in Austria [25]. It is a pragmatic solution, and perhaps in certain contexts it can also be an equitable one since vaccinated individuals deliver a service to society. For

vaccines with a large difference in private and social value of vaccination (against currently low-incidence diseases), immunized individuals might deserve some form of compensation. If the benefits are mostly located in distant futures, like in disease eradication programs, this could be a reason for financing vaccination programs through loans in which (a part of) the financial burden would fall on future generations (making abstraction from the general debt that is already being imposed on the future).

Another option to incentivize becoming vaccinated, albeit a more hypothetical and exploratory one, could be to change the reimbursement rate of health care costs in case an infection occurs in someone who has refused vaccination. Such a financial accountability system implies assigning responsibility for health states. In a very strict interpretation individuals can be held responsible when the following two conditions are met. (1) The person in question made a free and conscious choice to behave in a certain way [(s)he was fully informed of the consequences and was fully able to behave differently], and (2) there has to be 100% correlation between a specific behaviour and a specific outcome (choosing for A will automatically lead to outcome B) [26, 27]. In most domains of health care these necessary conditions to assign responsibility are indeed rarely met [28, 29]. For instance, responsibilizing smokers is controversial because tobacco is addictive and thus smoking is not a fully free and conscious choice. Moreover on an individual level there is no 100% certain relationship between smoking behaviour and e.g. developing cancer [30]. However, for vaccination these strict requirements could be met in a more satisfying way. When there are no limitations in access to safe vaccines, and large information campaigns available, travellers to endemic regions or health care workers who refuse vaccination might make a free and conscious choice not to become vaccinated. Moreover the correlation between catching an infectious disease and not being vaccinated against it, is extremely high. From a luck-egalitarian perspective such vaccine refusers may have a lower claim to the reimbursement of treatment or the allocation of other scarce resources (e.g. liver transplants for hepatitis A infections, hospital beds in an epidemic, etc.) in case an infection does occur.

Incentivizing vaccination is controversial. With regard to rewarding individuals a remaining ethical question is whether it is ethical to pay someone for doing his or her duty. Especially for health care workers (HCWs), people may see vaccination as a duty that is inherent to their profession [31], and for which they should not be rewarded. The same may apply to tourists [32].

If they choose to visit endemic areas (and by doing that, creating the risk of importing viruses in their home country), one could wonder whether it is fair that they get rewarded for taking precautionary measures. The issue of 'crowding out' is also an important point of critique. Rewards (but also sanctions) may 'crowd out' the intrinsic, altruistic motivation of individuals to perform one's civic duty, and as such it could backfire the initial objective to increase participation [33]. In the case of accountability it is clear that much will depend upon which 'choices' are to be considered sufficiently autonomous in order to hold someone responsible for their consequences. And even if this would be the case, it will be a rather harsh policy that conflicts with the rule of rescue.

3.3.4 Legal compulsion

In case more voluntary measures such as education, nudges and use of incentives have generally failed, governments can also mandate vaccination [34]. This could be an effective option to increase coverage and to reduce the number of VPD infections [35]. However, of all policy options, vaccine mandates are the most drastic (and ethically controversial) as they imply the strongest violation of individual autonomy. Also for pragmatic reasons coercion is to be treated with caution as it may induce hostile reactions against vaccination (or public health policy in general), negatively affect public trust and moreover be costly to enforce in practice. Nonetheless it is successfully used and supported as a public health measure in several European countries [36]. In Belgium for instance, recently two parents were sentenced to prison for refusing to have their child vaccinated against polio [37].[13] In Italy, 74% of Italian HCWs favours mandatory vaccination [38].

Vaccine mandates are theoretically justifiable on liberal grounds, often inspired by John Stuart Mill's influential essay 'On Liberty' [39-41]. Mill was strongly opposed against paternalistic measures and saw respect for self-determination as one of the most important social values. As a society we should cherish the ideal of raising each other to competent, autonomous individuals. However, he also stresses that strong paternalism (i.e. the use of explicit coercion that overrides an individual's autonomous choice) can

[13] In Belgium it is compulsory for parents to have their child immunised against poliomyelitis before the child reaches 18 months of age [35] Moran, N., et al., Are compulsory immunisation and incentives to immunise effective ways to achieve herd immunity in Europe?, in: *Ethics and Infectious disease,* M. Selgelid, M. Battin, and C. Smith, [Ed.] 2008, Oxford: Blackwell

be justified (1) when an individual is not considered capable of making autonomous decisions or (2) when his/her autonomous choice becomes a threat to the autonomy of others.

(1) A non-autonomous choice (e.g. an uniformed, influenced or incompetent choice) need not necessarily be accommodated based on the societal recognition of the importance of self-determination. The question is thus which motivations to refuse vaccination lead to an autonomous choice, and which not? It is both a practical and a theoretical challenge to filter out only those individuals that make a truly autonomous choice, out of the entire group of vaccine refusers (summarized in the four categories in chapter 2). Some argue that it does not seem to be possible to distinguish between legitimate and illegitimate reasons to refuse vaccination [16, 42]. Others argue that only religious perspectives that are credible and that fit a shared sense of reality in a community are autonomous [43].

(2) Those choices that are considered as autonomous, are owed respect, but – following Mill - the limits of this respect are reached when this self-determination becomes a threat to the autonomy of others. This can be in the form of explicit harm (the harm principle), or (as is often neglected [44]) when refusal implies that someone forgoes making his fair contribution to a common interest (the public good argument). If so, then there is a liberal ground to justify the use of coercion [39, 45]. But, as discussed in chapter 1, both arguments meet objections and require a nuanced discussion.

3.4 Conclusion

In this chapter the following two ethical issues in vaccination policy were discussed. First, medical and economic studies indicate the benefits of targeting vaccination at certain risk-groups that are defined by characteristics such as ethnicity, sexual activity, religion or (illicit) drug use. It is argued that such policies must not only be based upon considerations of efficiency and effectiveness, but that also values like equity, non-discrimination, protection of privacy and non-stigmatization should be considered. However, these values will often conflict and then policy makers need to decide which value is more important to uphold. Second, reaching sufficient vaccination coverage in the population appears to be a never-ending mission for public health policy. Vaccine uptake can be stimulated in several ways, but an important challenge in this is to find ways that reconcile as much

as possible the cherished ideals of individual freedom and public health. Nudges, incentives and legal compulsion can all be effective and, depending on the context, morally justifiable policy options. But it is evident that they require striking of a difficult balance, a challenge that can only be met by extensive and careful discussion of all dimensions relevant to the case at hand.

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Chapter 4: Ethical trade-offs in vaccination policy: a study of public preferences

Abstract: Vaccination programs increasingly have to comply with standards of evidence-based decision making. However, such a framework tends to ignore social and ethical sensitivities, risking policy choices that lack crucial public support. Research is needed under which circumstances and to which extent ethical values such as equity, autonomy, non-discrimination and non-stigmatization should prevail over effectiveness and cost-effectiveness in matters of infectious disease prevention. This chapter presents an empirical study investigating public preferences over various vaccination policy options that involve trade-offs between these values, based on a population survey in Flanders, Belgium (N=1049). It was found (1) that public support varied considerably between policies that were equally efficient in preventing disease but differed according to target group or incentives to improve uptake and (2) that preferences over the use of legal compulsion, financial accountability or the offering of rewards appear to be driven by individuals' social orientation. These results lend support to the view that, to evaluate vaccination programs, a broad framework is needed, one that also takes into account ethical norms and social sensitivities next to better quantifiable standards of evidence-based decision-making.

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4.1 Introduction

Evidence-based decision making (EBDM) has been developed as a discipline to support governments in making justifiable decisions on health care interventions, based on the best available scientific evidence regarding their quality, safety, efficacy or cost-effectiveness [1]. However, in its focus on aggregate, quantifiable outcomes it tends to neglect the complex social and ethical context in which many policy measures occur [2]. If this is left 'uncorrected' in the decision-making process, the resulting decision may lack public support, be less effective than a priori expected or could even be unethical [3, 4].

One of the domains where context has to be given full consideration is vaccination policy [5, 6]. EBDM may favor immunization programs targeted at epidemiologically important population subgroups [e.g. vaccination of children with the (shared) objective of protecting older generations], using hard or soft measures to increase vaccine uptake (e.g. a sanction for those who refuse to become vaccinated), or both. However, although these programs can be effective and efficient ways to protect public health, as indicated in chapter 3, they could be controversial in terms of other ethical values. Several recent papers have stressed the need for new, more adequate decision-making models for vaccines that take into account a broader range of ethical norms and social sensitivities [7-9].

In determining the right vaccination policy an influential parameter will be how the general public thinks about policy options. This chapter summarizes the results of a survey that explored for three types of common infectious disease scenarios (a public health threat, a risk-group disease and an 'economic' costly disease) whether the use of various uptake incentives (legal compulsion, accountability or offering rewards) and targeting certain population subgroups [children, health care workers (HCW), travelers or immigrants] was considered acceptable when it implied substantial efficiency gains. It was also investigated whether these preferences can be predicted on the basis of socio-demographic, health and psychological variables of respondents.

4.2 Survey

4.2.1 The sample

The sample consisted of 1049 respondents, representative for the population in Flanders (6,208,877 inhabitants, about 60% of Belgium [10]). Between March and July 2011 3740 people were contacted using random digit dialing of fixed and mobile telephone numbers, fulfilling quota in relation to age, gender, level of education and location over the 5 Flemish provinces. Of those who were initially contacted, 1540 (41%) were willing to participate in the study. Since these people did not necessarily fit the quota requirements at the time of contacting, 1049 (68%) of those who consented to participate were effectively recruited. Thus, overall 28% of those who were contacted took part. Participants received the survey either on paper or through an internet-link, and they returned their responses by post (using a prepaid envelope) or online. Seeking ethical approval was deemed unnecessary for this study because of its survey-based nature.

Table 1: **Socio-demographic characteristics of the surveyed population (N=1049)**

Variable	Classes	Sample (%)	Count
Age	18-25	19%	201
	26-35	21%	222
	36-50	23%	241
	51-60	18%	194
	61-76	18%	191
Sex	Male	49%	517
	Female	51%	532
Highest level of educational attainment*	None (none, primary or professional)	10%	104
	Low (technical or general, lower degree)	11%	111
	Medium (technical or general, higher degree)	30%	315
	High (higher education)	50%	519
Profession	Self-employed	12%	125
	White collar worker	53%	540
	Blue collar worker	11%	111
	Houseman/housewife	8%	82
	Handicapped	5%	47
	Unemployed	3%	28
	Student	5%	53
	Other	4%	37
Origin mother	Belgium	88%	920
	Europe	8%	83
	Outside Europe	4%	37
Origin father	Belgium	88%	920
	Europe	9%	92
	Outside Europe	3%	27
Experience as HCW	Yes	20%	207
	No	80%	839

* categorized according to the Belgian education system

4.2.2 Background variables

Every version consisted of an identical first part about the respondent's background: age, level of education, profession, gender, ethnic origin of mother and father, family size, age of family members, experience as HCW, the body-mass-index, a standardized health survey [the EQ-5D, including the Visual Analogue Scale (VAS)], smoking status, experience with severe illness (personal or within the family), and attitude towards vaccination as a means to prevent disease. The survey also included a psychological scale, which reflects the respondent's social orientation (SO) on the dimensions horizontal and vertical individualism and collectivism (HI, VI, HC and VC). The collectivist-individualist dimension of this construct relates to the respondent's sense of social cohesion and his/her willingness to prioritize common goals over personal ones. The horizontal-vertical axis aims to indicate an individual's emphasis on equality or hierarchy in social relationships [11, 12]. This instrument is well-established in the psychological literature and consists of 16 value judgments on which the respondent was asked to express his/her agreement on a likert-scale [12]. The 16 statements allow calculating for each individual a score for the dimensions HI, VI, HC and VC. The full scale can be found in **Figure 2** in Chapter 2.

4.2.3 Vaccination policy scenarios

We developed 15 fictitious infectious disease challenges (summarized in **Table 2**) which differ according to the type of disease and the population (sub)group that mainly transmits the pathogen.

We considered the following three generic types of disease:

(1) a Public Health Threat (PHT) presenting an imminent danger to the entire population. Infected persons experience severe and long-lasting morbidity and about 10% of infected persons die from their infection.
(2) a Risk-Group Disease (RGD) presenting no direct danger to most infected persons, apart from a few weeks of illness. However, for certain groups with vulnerable immune systems (pregnant women, young children, chronically ill people and elderly) the disease was lethal.
(3) an Economic Disease (ED) which causes - apart from a short period of illness - no lasting morbidity effects in anyone, but which imposes a significant economic cost on society because of treatment costs and productivity losses.

For each of these three disease types we singled out one of the following 5 target groups, which we described as mainly transmitting the pathogen: (1) children, (2) HCW, (3) travelers, (4) immigrants or (5) the entire population (i.e. no target subgroup).

We considered the following four ways to stimulate vaccine uptake.

(1) Subsidized voluntary vaccination: The vaccine is available free of charge for the target group.
(2) Subsidized compulsory vaccination: The vaccine is available free of charge for the target group and vaccination is compulsory by law.
(3) Accountability: The vaccine is available free of charge for the target group, the members of which are free to use or refuse it. However, target group members are held accountable for their vaccination choice. If vaccine refusers later acquire infection, the treatment costs of their infection would be at their own expense.
(4) Rewarding: Members of the target group, who choose to be vaccinated, receive a financial reward.

The 1049 respondents each completed one of the 15 versions of our survey (i.e. 70 respondents per version, equally distributed over the age groups 18-25, 26-35, 36-50, 51-60 and 61-75 years).

Table 2: **Overview of the division of the 15 survey versions between respondents**

Survey Number	N		Infectious Disease Challenge		Explored Vaccination policy options for target group (N=57)
			(Sub)group	Severity of disease	
I	839	70	Children	PHT	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
II		70	Children	RGD	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
III		70	Children	ED	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
IV		70	HCW	PHT	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
V		70	HCW	RGD	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
VI		70	HCW	ED	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
VII		70	Travelers	PHT	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
VIII		70	Travelers	RGD	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
IX		70	Travelers	ED	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
X		70	immigrants	PHT	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
XI		70	Immigrants	RGD	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
XII		69	Immigrants	ED	(1)Voluntary, (2)compulsion, (3)accountability, (4)rewarding
XIII	210	70	Entire population	PHT	(1)Compulsion, (2)accountability, (3)rewarding
XIV		70	Entire population	RGD	(1)Compulsion, (2)accountability, (3)rewarding
XV		70	Entire population	ED	(1)Compulsion, (2)accountability, (3)rewarding

PHT = Public Health Threat, RGD = Risk-Group Disease, ED = Economic Disease

4.2.4 The choice assignment

We first explained respondents the specific infectious disease challenge they had to consider: the type of disease (PHT, RGD or ED) and the important role of certain groups in transmitting the pathogen (i.e. children, HCW, travelers, immigrants or everyone). We also informed them about the safety of vaccination, specifying that 2% of vaccine recipients experienced a low fever and muscular pain at the injection site and 1 per million vaccinated individuals may experience dangerous side-effects (from serious allergic reactions to potentially death). These adverse event risks are realistic for most vaccines [13]. In **Figure 1** an example is given of a choice set that was presented to our respondents. Analogue choice sets were developed for the target groups of children, travelers and immigrants, but slightly different versions were used when the general population was targeted. Respondents had three response options for every question, two of which were the same across all questions (the less efficient options: no and universal vaccination). For the third response option, targeted vaccination (the more efficient option), the incentives to vaccinate rotated per respondent between vaccination (1) on a voluntary basis, (2) by legal compulsion, (3) with accountability in case of non-vaccination and (4) with rewarding in case of vaccination. Before the latter three policy options were introduced, respondents were explained that vaccination on a voluntary basis had failed because compliance with the program was too low.

In the scenarios without special target group (i.e. where the entire population is targeted for vaccination, surveys XIII, XIV and XV) respondents had to indicate their preference over slightly different options: option 1 (the efficient option: legal compulsion, accountability or offering rewards for everyone) as compared to option 2 (the inefficient option: voluntary vaccination for everyone with however insufficient uptake) and option 3 (no subsidized vaccination program).

Figure 1: **Example of 1 choice-set for 1 infectious disease challenge, i.e. targeted vaccination of HCW. Respondents had to indicate their preference over (1) the more efficient targeted option, (2) the less efficient universal option or (3) no subsidized vaccination.**

The government wants to introduce a vaccination program but has to choose between several options. We want to know which of these options you consider to be the best option.

Option 1

The government reimburses vaccination for **all health care workers** who choose to become vaccinated on a voluntary basis. Others have to pay for the vaccine, without being reimbursed.
Result: The total number of infections in Belgium is expected to decrease by 95%
Cost to society: Low

Option 2

The government reimburses vaccination for **everyone** who wants to be vaccinated on a **voluntary** basis.
Result: The total number of infections in Belgium is expected to decrease by 95%
Cost to society: Expensive

Option 3

The government reimburses vaccination for no one.
Result: the number of infections remains the same.
Cost to society: Expensive (because all infected persons need treatment)

Respondents also had to indicate which incentive (legal compulsion, accountability or rewards) they considered to represent the best policy option for the target group in question when vaccination on a voluntary basis had failed. Figure 2 shows how this information was presented to respondents, using the example of HCWs.

Figure 2: **Example of a choice-set in which respondents have to indicate their preference over using legal compulsion, accountability or rewarding to increase vaccine-uptake for the target group HCW.**

The government wants to introduce a vaccination program but has to choose between several options. We want to know which of these options you consider to be the best option.

Extra information: Previously, the government has funded vaccination for health care workers on a voluntary basis, but despite large information campaigns, an insufficient number of health care workers chose to become vaccinated.

Option 1

The government introduces a new regulation: **Health care workers** who choose to be vaccinated, receive a **financial reward** from the government. Because of this new regulation most health care workers opt for vaccination.
Result: the number of infections in Belgium is expected to decrease by 95%
Cost to society: low

Option 2

The government introduces a new regulation: **Health care workers** who refuse to be vaccinated free of charge will be held **accountable for the costs they give rise to** if they acquire infection with the virus, and need treatment. Because of this new regulation most health care workers opt for vaccination
Result: The number of infections in Belgium is expected to decrease by 95%
Cost to society: low

Option 3

The government makes vaccination (free of charge) **compulsory by law** for all **health care workers.** Refusers will be prosecuted. Because of this new regulation health care workers opt for vaccination.
Result: The number of infections in Belgium is expected to decrease by 95%
Cost to society: low

4.2.5 Statistical methods

The preferences for different vaccination policy options (as illustrated in **Figure 1**) were analyzed considering each of the 15 surveys separately. Ninety-five percent confidence intervals were calculated for the proportion of subjects in favor of the more efficient policy option, which included subgroup targeting and/or use of incentives. This proportion's complement (i.e. those in favor of no or universal vaccination) consists predominantly of proponents of universal vaccination as the number of respondents choosing the no-vaccination option was very small (in 57 choice sets with each 70 responses: median 2, mean 2.7). The 95% confidence intervals were estimated assuming a binomial distribution of responses and considering the standard normal random variable as a pivotal statistic.

We also looked for factors associated with the answers to the final question where respondents had to indicate which of these three incentives was best for that specific infectious disease challenge (see **Figure 2**). Logistic regression models and multinomial models were used in order to identify which covariates were significantly associated to a preference for using either legal compulsion, accountability or rewards [14]. The model parameters were tested using likelihood ratio tests but because those tests were repeated three times, it increased the number of false positive results. To correct this problem of multiplicity an adjusted p-value was calculated (The False Discovery Rate [FDR]) that takes into account the number of tests that have been carried out [15].

4.3. Results

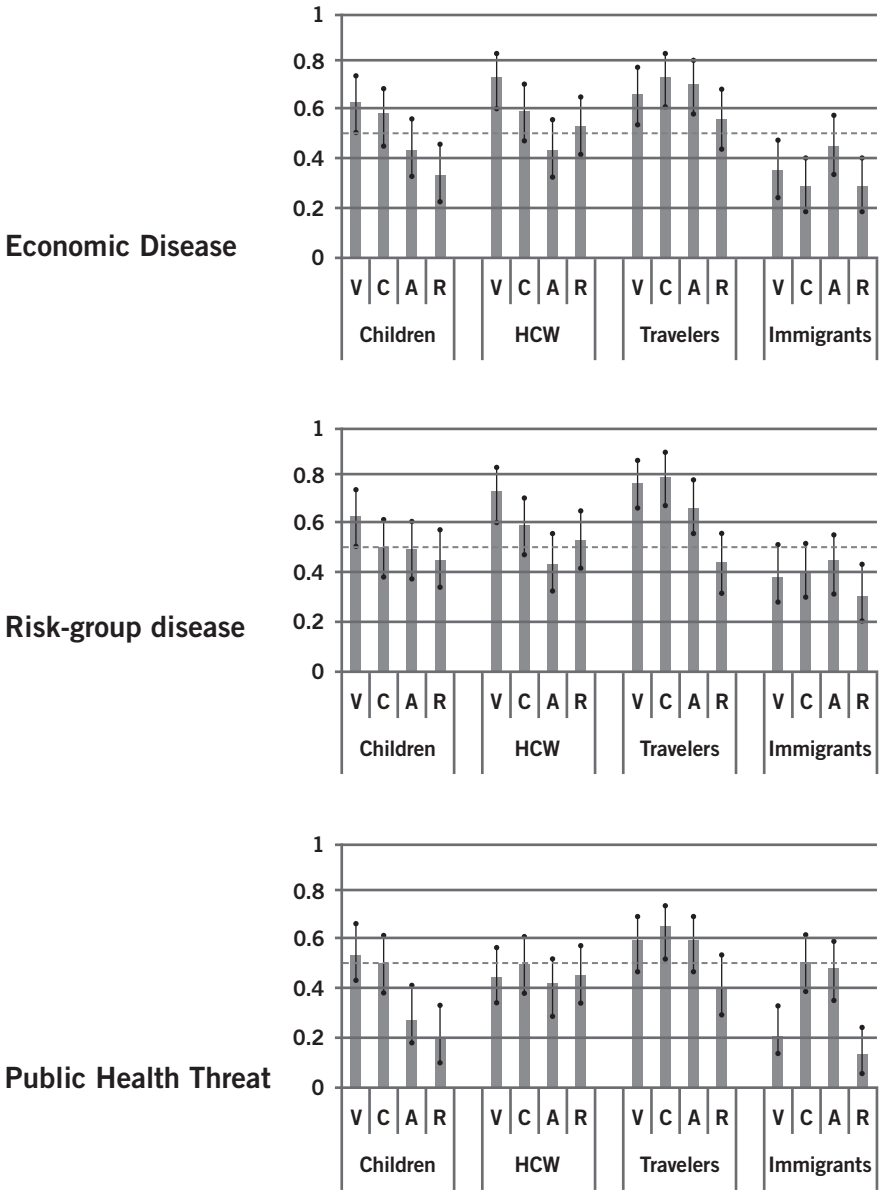
4.3.1 Preferences over vaccination policy options

Ninety-five % of respondents expressed a positive attitude towards vaccination as a means to prevent disease. The results of the vaccination policy scenarios (illustrated in **Figure 1** and **2**) are summarized in **Figures 3, 4** and **5.**

Figure 3 shows the proportion of respondents who prefer the more efficient, targeted vaccination program to the less efficient alternatives. It shows that there is rarely a significant majority or minority. Also, the difference in support was often small between the targeted options based on voluntary participation, and the options for which a stronger uptake-incentive was in-

troduced. Moreover, the more efficient options were generally less attractive for a PHT. Respondents tended to favor targeted policy options for travelers, while disfavoring such options for immigrants. When applied to specific target groups, legal compulsion was not considered worse than the use of financial incentives. In fact, repressive options (compulsion and accountability) seemed to be equally –if not more– attractive than those that aim to promote healthy behavior (rewards). An exclusion of relevant subgroups from the analysis [those that indicated a negative attitude to vaccination (N=51) or those that indicated difficulties in completing the survey (N=51)] yielded consistent results.

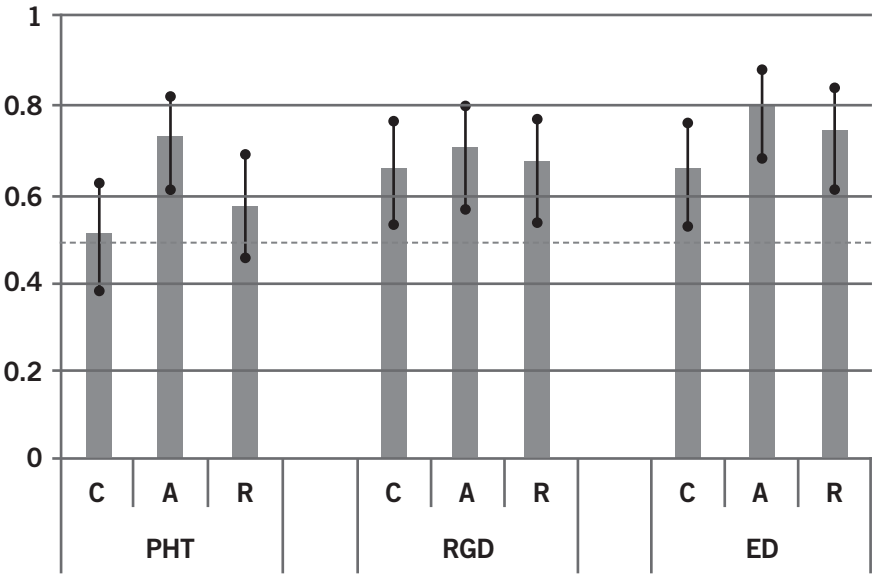
Figure 3: **Proportion of respondents (N=839, with N≈70 per scenario) preferring the more efficient, vaccination option over the less efficient universal vaccination or no subsidized program at all (with 95% confidence intervals).**



V= voluntary vaccination, C= compulsory, A= accountability and R= rewarding, Striped line indicates 50% of the sample.

The results of the scenarios for the entire population (surveys XIII, XIV and XV in **Table 2**) are summarized in **Figure 4.** Only a minority had problems with the use of incentives for the entire population, provided that these measures are effective. The use of legal compulsion was generally less supported than the softer alternatives, but still half the sample favored it over an ineffective policy based on voluntary cooperation.

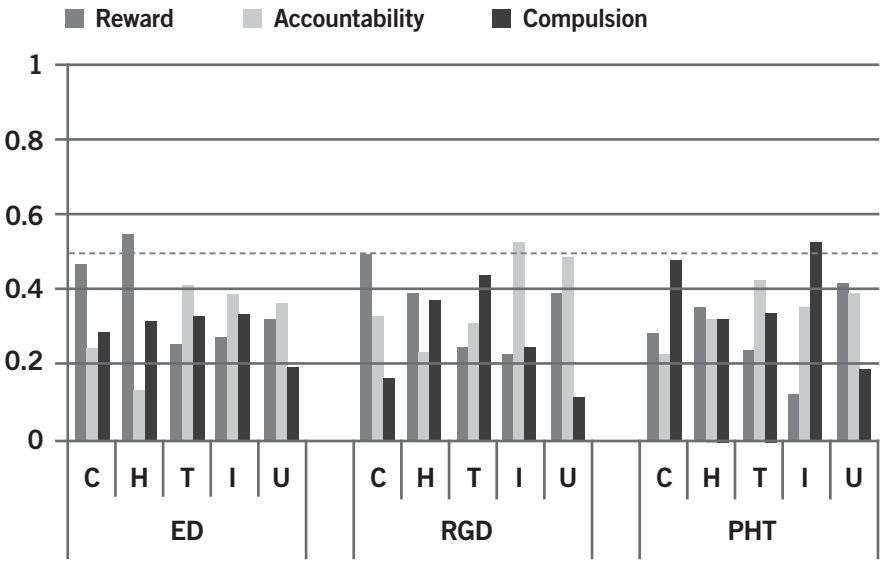
Figure 4: **Proportion of respondents (N=210, with N=70 per scenario) preferring the more efficient universal vaccination option with incentives over the less efficient universal vaccination option on a voluntary basis or no subsidized program at all (with 95% confidence intervals).**



C = compulsory vaccination, A = accountability and R = rewarding, PHT = public health threat, RGD = risk-group disease, ED = economic disease, striped line indicates 50% of the sample.

The preferred incentive varied according to target group and disease scenario (see **Figure 5**). Although compulsion was usually considered to be the worst of the three, it was the preferred incentive for vaccinating children or immigrants under a public health threat, and vaccinating travelers for a risk group disease.

Figure 5: **Proportion of respondents preferring the use of legal compulsion, accountability or rewarding as incentive to improve vaccine-uptake, given 15 different infectious disease challenges (N=1049, with N≈70 per scenario).**



C = children, H = HCW, T = travelers, I = immigrants, U = universal, PHT = public health threat, RGD = risk-group disease, ED = economic disease, striped line indicates 50% of the sample.

4.3.2 Factors associated with preferred incentives

Legal compulsion. In the logistic regression model (see **Table 3**) proponents of compulsion had a higher probability of being of a 'vertical individualist' profile than those that preferred accountability or rewarding.

Accountability. No significant associations were found for those in favor of accountability. However, when this group was compared only to those in favor of rewarding (i.e. in the multinomial model), the former group was less likely to have experience as HCW, more likely to be of older age, more likely to have a large family size and more likely to score high on the dimensions horizontal collectivism and vertical individualism.

Offering rewards. Respondents in favor of offering rewards were more likely to have experience as a HCW, to be of younger age and to score low on vertical individualism.

Table 3: Factors associated with an individual's preference for the use of legal compulsion, accountability or rewarding to increase vaccine-uptake (*: ∂ < 0.05)

Parameter	Estimate	Standard Error	P-value (FDR)
LOGISTIC REGRESSION			
Legal compulsion			
Intercept	-0.8037	0.0678	<.0001 (0.0020)*
Vertical Individualism	0.1914	0.0681	0.0049 (0.0049)*
Rewarding			
Intercept	-0.0186	0.2522	0.9411 (0.9411)
Age	-0.00991	0.00426	0.0199 (0.0333)*
Size Family	-0.1079	0.0530	0.0419 (0.0523)
Health_care_worker (Yes vs. No)	0.4470	0.1620	0.0058 (0.0145)*
Vertical Individualism	-0.2075	0.0664	0.0018 (0.0090)*
Accountability			
Intercept	-0.8028	0.1702	<.0001 (0.0005)*
Education (High vs.medium)	-0.2087	0.1523	0.1706 (0.1706)
Education (Low vs. medium)	-0.3654	0.2326	0.1162 (0.1452)
Education(None vs. medium)	-1.2295	0.5499	0.0254 (0.0635)
Family Size	0.1057	0.0533	0.0475 (0.0791)

MULTINOMIAL MODEL (Reference = rewarding)				
	Category	**Estimate**	**Standard Error**	**P-value**
Intercept	Compulsion	-0.8100	0.3384	0.0167*
Intercept	Accountability	-1.2980	0.3484	0.0002*
Education (High vs medium)	Compulsion	-0.1844	0.1641	0.2612
Education (High vs medium)	Accountability	0.1444	0.1921	0.4521
Education (Low vs medium)	Compulsion	0.3492	0.2142	0.1031
Education (Low vs medium)	Accountability	0.2875	0.2462	0.2428
Education (None vs medium)	Compulsion	-0.0519	0.3276	0.8742
Education (None vs medium)	Accountability	-0.8346	0.4442	0.0603
Experience as HCW (Yes vs. No)	Compulsion	-0.1979	0.1027	0.0540
Experience as HCW (Yes vs. No)	Accountability	-0.2285	0.1002	0.0226*
Horizontal Collectivism	Compulsion	0.0901	0.0817	0.2697
Horizontal Collectivism	Accountability	0.1676	0.0807	0.0379*
Vertical Individualism	Compulsion	0.2698	0.0820	0.0010*
Vertical Individualism	Accountability	0.1669	0.0797	0.0362*
Age	Compulsion	0.0098	0.0052	0.0597
Age	Accountability	0.0106	0.0051	0.0375*
Family Size	Compulsion	0.0895	0.0661	0.1757
Family Size	Accountability	0.1603	0.0634	0.0115*

4.4 Discussion

This study yields two major findings. First, public support appears to vary considerably between equally efficient vaccination programs that differ according to the subgroup targeted (i.e. related to equity) and the uptake-incentive (i.e. related to autonomy) used. A vaccination policy purely based on economic and public health considerations would neglect the weight of ethical norms and social sensitivities in what the general public considers as "just policy". Vaccines require a multi-dimension EBDM framework that is also sensitive to these aspects, in addition to better quantifiable standards of safety, efficacy and cost-effectiveness. A second finding of this study was that preferences over incentives to increase vaccine uptake are correlated to a respondent's SO. An individual's willingness to sacrifice personal goals for the common good (collectivism/individualism) and his/her emphasis on equality vs. hierarchy in social relations (horizontal/vertical) appeared to predict vaccination policy preferences. Those who scored high on vertical individualism were more likely to support legal compulsion and less likely to be in favor of offering rewards.

Some of our findings can be of practical relevance for vaccination policy. For instance, during recent decades the risk of hepatitis A outbreaks in low-endemic countries has increased because adults have lower immunity while the potential to import this virus from endemic regions has increased [16]. While a universal vaccination program may be too expensive, targeted options towards travelers and immigrants can be more cost-effective [17]. Our survey indicated that vaccination of immigrants was not supported, while vaccination of travelers was, including incentives to comply. This is relevant as cross-sectional surveys conducted at various airports have demonstrated that less than 50% of travelers to developing countries are protected against HAV, despite WHO recommendations [18]. Another active debate in vaccination policy is whether HCW should become vaccinated in order to protect risk-groups and whether either the use of coercion or rewards is most appropriate if vaccine uptake on a voluntary basis is insufficient [19]. The sample from this study supported the use of compulsory vaccination for HCWs in order to tackle risk-group diseases, one of the few scenarios for which a significant preference was found. HCW themselves however are likely to favor positive incentives for vaccination. This was also visible in the survey as a correlation was found between having experience as HCW and preferring financial rewards as incentive to increase vaccine-uptake.

Some limitations of the study should be mentioned. First, it was carried out in a single European region and responses may be influenced by the Flemish context (culture, education, experience with vaccination, etc.). It is noteworthy that most (but not all) childhood vaccines are given free of charge in Belgium. Although only polio vaccination is compulsory [20], uptake is relatively high for most vaccines [21]. Accountability and rewarding have not yet been implemented as policy measures for vaccines in Belgium. Second, non-response bias is always a potential concern in survey-based research. We believe that the overall response (41%) was acceptable, given the design and nature of the study. Third, the general public was surveyed on a complex ethical topic. The purpose was to explore public support for or against certain measures, as this can be an important input for decision makers. Such public preferences are however not necessarily just and are not meant to be a substitute for the deliberative judgment of policy experts [22].

It is our hope that this study can inspire further empirical research and stimulates discussions to determine to which extent and how these social and ethical considerations must be integrated into existing EBDM methodology.

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Chapter 5: On the equity of vaccination programs that redistribute disease

Abstract: In most circumstances vaccination programs have positive externalities for non-vaccinated groups. However, exceptionally they may reduce the health risks for one population group, but increase the health risks for others. One example is varicella-zoster virus (VZV) vaccination, where a program for children may induce illness in older generations. The need for more discussion on the fairness of such interventions has been signalled, but remains lacking from the literature. Meanwhile, to evaluate the social desirability of interventions, policy makers increasingly rely on cost-effectiveness analyses (CEA) whereas it is widely acknowledged that these analyses are insufficiently distribution-sensitive. In this paper a more in-depth framework is provided to discuss inequitable risk redistribution under the influence of vaccination.

5.1 Introduction

Individuals who become vaccinated protect their own health but also affect their environment because they reduce the possibility for a pathogen to transmit itself in a population. In most circumstances this indirect protective effect is to be considered beneficial for others. Moreover, it is often a direct objective of public health policy as, at least in theory and for a number of infectious diseases, high vaccine uptake enables protection of an entire population without having to vaccinate everyone [1]. Therefore many people consider it to be a social obligation to accept certain vaccinations [2].

However, the link between on the one hand reducing pathogen circulation and exposure and on the other hand preventing illness and improving public health is not always straightforward. In exceptional circumstances, vaccination, which alters the natural epidemiology of a disease, can leave third parties worse-off than before, at an increased risk of serious morbidity and mortality. If so, implementation of a program will at the same time generate health gains in those who are vaccinated, and redistribute health risks towards others in the population who are not vaccinated.

From an equity perspective this requires discussion. Several papers in the literature have pointed out that the justifiability of introducing such programs is not self-evident [3-6]. The objective of this chapter is to provide a more extensive framework to discuss and assess this dimension of vaccination policy. We begin by explaining when and how vaccination can induce negative externalities.

5.2 Vaccination with redistributive effects

Vaccination programs, in general, redistribute health risks: vaccination protects against disease but also – very exceptionally – causes severe adverse reactions. Therefore, unless 100% safe, a vaccination program always 'trades in' a number of adverse effects in exchange for protection against some dangerous natural infections. Of course, for a licensed vaccine, the relative size of both burdens is so different that this is rarely framed as an equity issue, but occasionally it is: when the persons who benefit from the disease protection are not primarily the same as those who undergo the risks of adverse effects; for instance, vaccination of young children with a secondary major objective to protect older generations (e.g.

childhood influenza vaccination). However, sometimes the health risks emerging from introducing a vaccination program, can be more extensive than merely adverse effects associated to the vaccine. The following three examples illustrate that a vaccination program can redistribute disease burdens.

A first example is prevention of 'chickenpox' (CP), which is caused by varicella-zoster virus (VZV) and predominantly occurs in children. At present, several countries have introduced, or are considering introduction of widespread childhood vaccination against chickenpox (e.g. USA, Germany, Australia). Universal childhood CP vaccination in the USA has been shown to be a success in regard to morbidity (hospitalisation reduction up to 88%) and mortality (deaths reduction >74%) related to CP [7]. Importantly, VZV remains latently present in neural ganglia after CP and VZV reactivation can cause herpes zoster (i.e. shingles) at an older age [8]. It is hypothesised that older generations benefit from re-exposure to children with chickenpox as it helps their immune system prevent reactivation of VZV, thus reducing their risk of shingles (Hope-Simpson, 1965). Consequently, the introduction of a childhood vaccination program against chickenpox may lead to an increase in herpes zoster cases, predominantly in older generations [6, 9-12]. Indeed, recent simulation studies have predicted that a net population increase in HZ incidence after introduction of widespread childhood CP vaccination, due to the loss of protection from exposure to CP, would occur for about 30 years depending on CP vaccination scenario and exogenous boosting assumptions [6], with the latter assumptions being highly uncertain [13]. Furthermore, HZ leads to higher morbidity, higher mortality and higher costs than CP [14].

A second example is prevention of diseases of which the severity of symptoms increases with age (such as e.g. measles, rubella, hepatitis A or VZV). Prevention will reduce the likelihood for a pathogen to spread, which - mathematically speaking - implies an upward shift in the age at which the average susceptible individual becomes exposed to the pathogen [15-17]. Consequently, if participation with the preventive program is suboptimal, it risks substituting a large number of mild infections in younger-aged susceptibles, with a smaller number of more severe infections in older-aged ones. The following infamous example illustrates that the latter concerns are not purely theoretical. In 1975 Greece introduced universal rubella vaccination for 1-year olds [18, 19], however uptake levels remained intermediate. Gradually the proportion of teenagers and

young adults, who were susceptible to rubella increased because - compared to the pre-vaccination era - they were less likely to be immunised (either through vaccination, or through natural exposure during childhood). This phenomenon is well known to be a consequence of herd immunity (i.e. reduced circulation of a pathogen under the influence of widespread vaccination). Then, in 1993, a major rubella epidemic took place in Athens. Whereas previous epidemics mainly affected children (leading on average to mild illness), this time it affected mainly teenagers and young adults. The suboptimal implementation of the vaccination program had shifted the age distribution of rubella cases upwards. Since severity of rubella disease increases with age, severe disease occurred more frequently. Most gravely, since women at childbearing age were more likely to acquire rubella during pregnancy after the vaccine was introduced, the incidence of congenital rubella syndrome rose to the highest ever-recorded levels. This is a medical condition that affects cognition and can lead to sensory deprivation, severe birth defects and premature death. Note that other countries were able to avoid this problem by vaccinating girls at age 11 years (thus not affecting the transmission dynamics) and/or by achieving consistently high vaccine uptake and/or by combining childhood rubella vaccination with a catch-up programme.

A third example consists of vaccination programmes with 'replacement' effects. Certain vaccines, (e.g. against pneumococcus, meningococcus or rotavirus) reduce the circulation of serotypes or serogroups covered by the vaccine, but because they modify ecological pressure, they may at the same time increase circulation of similar non-vaccine serotypes. Different serotypes and serogroups may result in a different age-specific pathogenicity [20-22]. It is therefore possible that under the influence of vaccination, non-vaccine serotypes replace the vaccine serotypes not only in terms of circulation and carriage, but also in terms of disease by age. As such, the introduction of a large-scale vaccination program could affect the distribution of health risks, including for those not participating in the program.

5.3 Equity and health risk redistribution

The question arising from the previous examples is whether it is wrong to introduce prevention when it improves the health of many, knowing that it will adversely affect the health of others. This is a problem of distributive justice (i.e. equity).

A first equity concern with health risk-redistribution is that externalities should at least be acknowledged. The vital interests of everyone involved in a program or a policy change, either directly or indirectly, must be understood and considered before implementation. It is noteworthy that in health-economic evaluation, on which basis the social value of prevention is increasingly being assessed, indirect effects of vaccination are often not or insufficiently accounted for [4, 23, 24]. Because of the increasing complexity, third-party effects are often not included in the mathematical models used to predict the consequences of policy options.

A second point, which will be discussed in the following section, is: how should competing interests be balanced against each other?

5.3.1 The equivalence of equal health effects

One approach would be to equalize the value of similar health effects. For instance all quality-adjusted life years (QALY) gained or lost as a result from implementing a vaccination program can be given the same value, regardless who they accrue to. Such a philosophy is implicitly endorsed in cost-effectiveness analysis, and is often summarized with the equity-principle 'a QALY is a QALY is a QALY'. Risk re-distribution would – following this view - not be inequitable, as long as the generated accumulated health gain outweighs the shifted disease burden.
This view rightly highlights efficiency and opportunity costs. Forgoing the health-maximising outcome implies that avoidable morbidity and mortality would occur, which would at the least demand for a sound justification. However, besides the concern that health metrics like QALYs are imperfect representations of real health effects, there are reasons – explained in the next section - why this perspective is morally deficient and why some health effects, despite their similarity in severity of illness, are 'more equal than others'.

5.3.2 Moral reasons to differentiate the value of health effects

Roughly speaking, utilitarianism is the underlying ethical framework on which basis equivalence of health effects is defended [25]. It starts from the premises that (1) what ultimately matters is our common ability to experience wellbeing and suffering, and (2) that, in this, everyone's interests

deserve exactly equal consideration. In an imperfect world, one where tough choices are unavoidable, a policy is justified when it – compared to the available choice alternatives – generates a more attractive ratio of good over bad consequences. Utilitarianism has been highly influential in several domains of public policy. However, as a normative theory it is contested [26], mainly because of its blindness towards more complex considerations of distributive justice. First, as it relies on a form of cost-benefit analysis, it would justify excessive sacrifices concentrated in a few individuals for the benefit of a majority. Second, the expected gains and losses of a policy measure are dependent upon the circumstances in which those involved are already situated. This starting position will often be unfair and utilitarianism does not necessarily rectify such unjust beginnings. It may even widen instead of flatten existing inequities. For instance, preventive resources are often found to be more effective when targeted at rich and well off groups in society, and these groups might even have more wellbeing to lose by not receiving prevention than others at the bottom of the socio-economic ladder (who were already in a lower state of health and wellbeing). As exactly such, more complex distributive concerns are relevant in the context of this chapter, the main theoretical rival of utilitarianism, contractualism, offers a valuable alternative framework [27].

In a contractualist framework the particular effects and consequences of policy measures are in themselves insufficient foundation to either justify or reject policies. What matters is whether a distribution of burdens and benefits is justifiable in terms of universally acceptable principles, which follow from a hypothetical 'social contract'. This social contract is made between all individuals from a position where everyone is knowledgeable about how the world works but no one knows which position he or she will occupy in it. From this 'original position' people will come to a social contract that lays down the most fundamental rules, which should be respected in the community they will later cohabitate. Many influential social contract theories exist, ranging from 17-18th century theories by philosophers such as Hobbes, Locke and Rousseau to late 20th century authors such as Rawls or Scanlon. Whereas they differ in many ways, elements central to this approach are: (1) all community members' vital interests deserve consideration; if not, some contractants would have good reason not to undersign the contract and (2) once individuals are forced to think counterfactual, devoid of their particular circumstances and interests (wealth, age, etc.; often referred to as a 'veil of ignorance') they can come to a consensus about which actions and policies are impermissible.

In the present context of public health programs with redistributive effects, the relevant issue is thus not whether the aggregate benefits of the program quantitatively outweigh the burdens, but whether their introduction can be justified in terms of universal principles, to which also those who stand to lose cannot reasonably object. In such a framework it is unlikely that similar health effects will automatically receive equal weight because this weight is, next to the clinical severity of the health effect, also determined by the wider societal circumstances in which it occurs. The following 5 considerations are relevant in the present context. They may give equal health effects nonetheless a different weight.

Avoidability. A first consideration is related to freedom and responsibility. If those who risk to undergo the negative externalities of a vaccination program can be expected to be capable of protecting themselves, (e.g. by becoming vaccinated themselves), but refuse or neglect to do so, their claim to solidarity will lose appeal. Consequently, the health effects that result from such a choice are not equivalent to health effects that are beyond individual choice. It would be inequitable to ask from others to refrain from the freedom to protect themselves for my benefit, when I can in fact protect myself.

Personal characteristics. Personal characteristics determine the burden of the same infection in different individuals. Policy measures should be designed so as to equalize opportunities and improve the prospects of those groups in society which are worst-off [28, 29]. Furthermore, it is often argued that health care should provide individuals with an equal opportunity to live a lifespan that can somehow be considered as 'normal' [30]. In this respect, the ones who have had their "fair innings" may have a reduced entitlement to having their interests protected as compared to those who have not yet received their share [31-33]. If such considerations would have a universal basis, health risks and benefits would receive lower value when they accrue to older individuals, or at least those who are beyond a certain age threshold. Thus, there is a case for avoiding policies that further increase already existing inequities, implying that priority should be given to preventing disease that occurs in groups that are disadvantaged in other respects, or in younger age groups.

The per-person size of health effects. It remains largely unclear how severe illness relates to non-severe illness especially when both arise on a vastly different population scale. Comparing aggregate disease burdens allows big,

possibly excessive sacrifices concentrated in a small group who faces very serious health risks, in exchange for small gains (e.g. a transient episode of illness without lasting effects) in a large group. From an ethical perspective, the 'per-person health impact' is something that definitely matters. Such concerns on the level of individuals should complement a consideration of aggregate health gains on a population level. One could argue that there exists a deontological minimum of health, a threshold below which no trade-offs are accepted.

Uncertainty. Whereas there may be no rational difference between the occurrence of 200 cases with 50% certainty or 100 cases without uncertainty, people are unlikely to remain indifferent between both options [34]. If a preventive program will produce protection with certainty, but has uncertain externalities, then equity would likely demand a more favourable weighing of those outcomes of which we can be sure.

The origins of the health loss. Another consideration relevant to equity may be the difference between natural risks (e.g. letting VZV infections run their natural course) versus 'man-made' or 'policy-induced' risks (e.g. changing the natural epidemiology by introducing VZV-vaccination). This brings us to the ancient health care principle primum non-nocere, 'first do no harm' [35]. There is a well-known difference in the way we psychologically judge the harms following from actions and omissions [36]. Although the moral difference between both remains controversial, in matters of vaccination it may be relevant as harms following the introduction of a program (an action) may have repercussions for public trust in vaccination, whereas harms resulting from not implementing the vaccination program (an omission) may simply confirm a general fact of life as people know it (i.e. that infectious diseases can be dangerous).

5.4 Discussion

The objective of this chapter was to highlight a specific equity dimension of infectious disease prevention. A framework was proposed to stimulate discussion and to guide moral reasoning about the introduction of vaccination programs that are beneficial to those who become vaccinated but that also have negative externalities for those outside of the program. Whereas attributing an equal value to equal health effects could be a good starting point to evaluate the merits of a program, a more elaborated view

must take into account the avoidability of the harm, morally-relevant personal characteristics of those involved, the per-person size of health effects, the origins of health effects and uncertainty.

Contractualism could offer a coherent ethical framework to balance these different and often conflicting claims. For instance, when prevention would spare a large number of individuals from suffering severe illness, whereas it would imply an uncertain risk on inducing equally severe illness in a small group, there would be no reasonable grounds to claim that such a policy should not be introduced. Moreover, when those negatively affected have easy access to vaccination this only adds to the case pro vaccination. When prevention would drastically increase health risks in a small but non-negligible group whereas it would prevent transient disease in many others, the former group would rightly contest. There would be no universally acceptable principle that could justify the introduction of a program that brings about such an unequal distribution of burdens and benefits. Often uncertain empirical issues will determine the strength of the different arguments. Perhaps empirical data may facilitate decision making here. As such, social value research could be useful to estimate support for the particular judgements involved in the issue at stake, such as intergenerational priority-setting in matters of prevention, estimating what the public considers to be an acceptable sacrifice for preventing relatively mild illness or the level of solidarity with vulnerable groups that is considered reasonable.

In case the current (non) use of a vaccine is considered inequitable, then there is a strong reason for governments to intervene. This can be done by either stimulating or dissuading vaccine uptake, or by arranging compensation to those who would be negatively affected by the program. In the introductory example of Greece's rubella epidemic, the vaccination program could have been optimised (e.g. through a catch-up component, combined with stimulating demand, either or not by using compulsion). In the case of VZV this would be different. If the chickenpox vaccine were made available to all children (preferable those at risk for serious complications of chickenpox), only keeping the uptake low enough such that the population transmission dynamics remain largely unaffected, this would seem to offer a potential solution to the problem (e.g. through a restriction of vaccine supply or by inhibiting or dissuading individuals to become vaccinated once a certain level of vaccination is reached). Clearly such a policy would be difficult to justify vis-à-vis concerned parents and vaccine manufacturers.

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PART II

Allocation of health care resources

Chapter 6: Valuing health states: a comparison of methods in hepatitis A patients

Abstract: This chapter explores the impact of applying different non-standardised analytical choices for Quality of Life measurement to obtain Quality Adjusted Life Years (QALYs). In addition to more widely discussed issues such as the choice of instrument (e.g. EQ-5D or SF-6D?) researchers must also choose between different recall periods, scoring algorithms and interpolations between points of measurement. A prospective survey was made among 114 Belgian patients with acute hepatitis A illness. Using non-parametric tests and generalized linear models (GLM's), four different methods to estimate QALY losses were compared, two based on the EQ-5D (administered during the period of illness without recall period) and two based on the SF-6D (administered after illness with 4 weeks recall period). Statistically significant differences were found between all methods, with the non-parametric SF-6D based method yielding the highest median QALY impact (0.032 QALYs). This is more than five times as high as the EQ-5D based method with linear health improvement, which yields the lowest median QALY impact (0.006 QALYs). Economic evaluations of health care technologies predominantly use QALYs to quantify health benefits. Non-standardised analytical choices like the ones we explored can have a decision-changing impact on cost-effectiveness results, particularly if morbidity takes up a substantial part of the total QALY loss. Yet these choices are rarely subjected to sensitivity analysis. Researchers and decision makers should be aware of the influence these somewhat arbitrary choices may have on their results.

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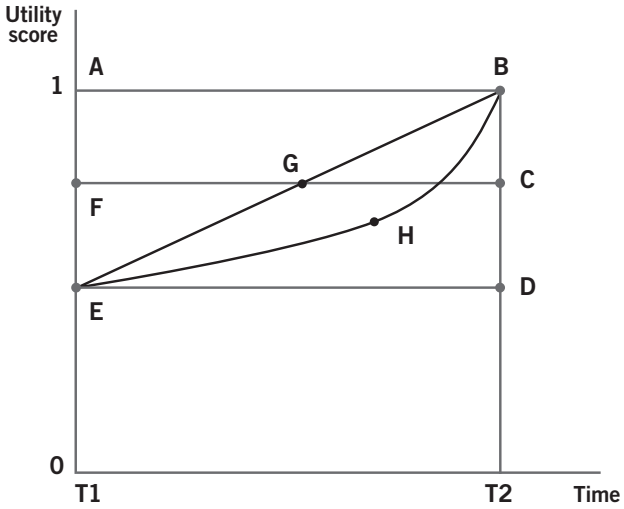
6.1 Introduction

In order to compare health benefits across different medical treatments the Quality Adjusted Life Year (QALY) has become a widely used summary health outcome comprising both morbidity and mortality effects. Nevertheless QALYs and cost-utility analyses continue to be seen by some as a controversial instrument for policy analysis [1-4]. One reason for criticisms is that there is no single objective standardised tool to obtain the morbidity impact of disease and different methods appear to generate different results [5-7]. Amongst the many instruments available to estimate the quality of life (QoL) associated with living in different health states, the EQ-5D [8] and the SF-6D [9-11] are both popular multi-attribute classification systems. These surveys typically generate a single time point utility value for each relevant health state, which is then used to value an average patient's health path. There are several important steps in this process, all with their specific pitfalls and problems. The health state of interest should be defined, described and it should be valued. This is done by asking questions across several dimensions that are assumed to contribute to enjoying a healthy life. Respondents summarise their position on the ordinal scale of each dimension. In order to be a valid measure of health, these dimensions should exhaustively cover all relevant dimensions of health-related QoL. The EQ-5D covers the dimensions of mobility, self care, usual activities, pain/discomfort and anxiety/depression. The SF-6D distinguishes between physical functioning, role limitations, social functioning, pain, mental health and vitality. The choice of respondents (most often patients, health practitioners or the general population) can be of substantial influence on such valuations [12]. In this chapter the patient is considered to be the most appropriate judge of his/her health experience. Ideally a survey, which asks for the patient's current state, should be taken frequently during the period of illness, in order to estimate the health-related QoL due to morbidity over the patient's health path. However, a day-to-day evaluation of a sufficiently large patient group is usually impractical. A common approach is therefore to have a survey filled in once (or multiple times) and consequently assuming a linear change between the QoL at the measurement point(s) and perfect health [13]. An alternative method consists of measuring patients' health status during a specified recall period. Both methods aim to estimate the same health path and it is therefore important to establish to which extent this is the case, and whether the choice for one of these methods introduces an additional source of uncertainty in economic evaluation.

The objective of this study is to explore the effects of different methods for estimating the impact of an acute illness on the QoL valued by patients. Figure 1 illustrates five different methods to calculate the QoL impact for a patient experiencing 4 weeks of illness. Three of these methods are based on a current state health survey like the EQ-5D and two are based on a survey with a specified recall period like the SF-6D. At T1 patients were surveyed regarding their health state. Their health path is consequently estimated using either of the following assumptions: the patient has a constant QoL for the duration of the illness, a linear improvement in QoL, or the marginal improvement in QoL increases every day (an exponential health improvement). The alternative for these interpolations is to ask the patient after recovering, at T2, to recall his/her health state over the entire disease episode. On **Figure 1** these different methods yield the following health burden: the rectangle ABDE for a constant health state, the triangle ABE for a linear health improvement and the area between the points ABEH for an exponential change. Assuming that respondents value their health state between time T1 and T2, at "F", their retrospective health loss is illustrated as the rectangle ABCF in **Figure 1**. This rectangle can be obtained with two different scoring algorithms.

Figure 1: Graphical representation of the different health measurement methods for a patient experiencing 4 weeks of illness



Note: The X-axis represents the duration of illness and the Y-axis the health utility score. The health burden for the EQ-5D is taken at T1 and estimated by the area between ABDE for a constant health state, the triangle ABE for a linear health improvement and ABEH for an exponential change. The SF-6D is taken at T2 and the estimated health burden is the rectangle ABCF (for both scoring algorithms).

This study empirically investigates whether these conceptually different methods lead to significantly different QALY loss estimates. To test this we focused on hepatitis A, which – in contrast to hepatitis B or hepatitis C - can only give rise to acute disease. Hepatitis A affects the liver, and may cause mild to severe illness (exceptionally leading to fulminant hepatitis and death) for on average two to four weeks [14-16]. We compared the QALY loss estimates of patients resulting from four different but conceptually defensible measurement methods. Two methods are based on the EQ-5D (taken during their illness, without a recall period): one with a linear health improvement and one with a constant health state during the period of illness. We will not discuss the exponential method since the results would always fall between the other two methods. The other two methods are based on the SF-6D (taken after illness, with a recall period of four weeks): one using the commonly used parametric scoring algorithm [9] and one using the more recent non-parametric scoring algorithm [17].

6.2 Methods

6.2.1 Data

Hepatitis A is a notifiable disease in Belgium, implying that physicians and laboratories should communicate new hepatitis A patients to the health inspection services.

Three interlinked surveys were administered prospectively to all hepatitis A patients who were notified to the Flemish public health services from February 1, 2008 to January 31, 2009. First, the EQ-5D, including a Visual Analogue Scale (VAS), was sent to the patient immediately after notification of illness (approximately a week after the first symptoms appeared) and requested the patient to value his/her health state at that time. The SF-12 was sent to the same patients approximately three weeks later, and asked patients to describe their health state during the preceding four weeks. A third survey was administered immediately after the SF-12, in order to collect information on the number of days of symptomatic illness the patient had experienced from their hepatitis A episode as well as the nature of the symptoms experienced, and health care consumption associated with their period of illness [18]. All three surveys were linked to an individual patient by a unique anonymous code.

6.2.2 QALY calculation

The SF-12 cannot be directly translated into an utility score but Brazier et al. [9] reduced the number of questions which resulted in a shorter survey (the SF-6D), which can be used for calculating QALYs. Utility scores from the EQ-5D and the SF-6D were calculated using respectively the UK York time trade-off (TTO) algorithm [19] and the UK Sheffield standard gamble (SG) algorithm (we use both the parametric [9] and the non-parametric [17] versions of the latter).

To transform these incomparable utilities into comparable QALY loss estimates, a time dimension needs to be introduced. Assuming that the utility weight associated with non-affected health states in these patients corresponds to a value of 1, the parametric SF-6D utility score, representing the patient's health during the entire month of illness, can be transformed into QALY loss estimates as follows:

$$\text{QALYlossSF6D} = 1 - \frac{(\text{SF6Dscore} + 11)}{12}$$

The QALY loss from the same SF-6D-survey but with use of the more recent non-parametric method is calculated in a similar manner but uses the algorithm described by Kharroubi et al. [20].

$$\text{QALYlossSF6DNP} = 1 - \frac{(\text{SF6DNPscore} + 11)}{12}$$

The terms SF-6D and SF-6DNP will be used to refer to the QALY loss resulting from using the parametric and the non-parametric scoring algorithm for the SF-6D-survey, respectively.

To calculate QALYs from the EQ-5D we need to make an assumption about the evolution of the patient's health experience. In this study we only consider a constant and a linear progression (referred to as EQ5DConstant and EQ5DLinear respectively hereafter), and potential alternative improvements in adverse health experience (e.g., exponential) are not explored.

$$\text{EQ5DConstant} = \frac{\text{days of illness x (1-EQ5DScore)}}{365}$$

$$\text{EQ5DLinair} = \frac{1}{2}\,\frac{\text{days of illness x (1-EQ5DScore)}}{365}$$

Figure 1 shows a graphical representation of the intuitive meaning of these equations, with 1 – EQ5DScore being represented by the line AE and $\frac{\text{Days of illness}}{365}$ being represented by $T2 - T1$.

6.2.3 Analyses

The responses from the survey were analysed using SPSS 15.0 (Chicago, Illinois), R 2.8.1, @Risk (Ithaca, New York), and MS Excel 2003 (Redmond, Washington) software. Missing data were excluded list wise. We tested the potential bias for excluding data by calculating the correlation between the VAS-score and the number of questions answered and found this to be insignificant (p-value = 0.362). Summary statistics of the variables obtained in the survey were produced. The QALY loss predicted by the EQ-5D and the SF-6D was compared using a paired Wilcoxon Signed Rank test. The QALY loss estimated by the SF-6D was regressed onto that of the EQ-5D to enable analysis of the relationship between these two measures. The natural logarithm of the ratio of the QALY loss predicted by the SF-6D and the EQ-5D was taken to further investigate the difference in these measures. A linear regression model was used to determine and compare the significant explanatory variables that affect the QALY loss predicted by the EQ-5D and the SF-6D. The sensitivity of the QALY loss measures with respect to the explanatory variables was compared using a generalized linear model (GLM) with interaction term [21]. This approach is similar to that followed by Kontodimopoulos et al [5]. Relationships between the five dimensions of the EQ-5D and the six dimensions of the SF-6D were analysed with Kendall's Tau rank correlation coefficient. A 95% level of confidence was used.

6.2.4 Sample

The total sample size was 161. Of the entire sample 111 patients completed the number of days of illness and all questions on the EQ-5D, both necessary to obtain a valid QALY loss estimate from the EQ-5D. One hundred and fourteen respondents filled in the SF-6D survey. For 96 patients we were able to obtain a valid QALY-estimate for both surveys. **Table 1** shows the sample characteristics of the discrete variables.

Table 1: **Sample characteristics**

Gender	% (N)
Male	52.2% (72)
Female	47.8% (66)
Education	
Primary education	18.6% (24)
Secondary education	41.1% (53)
Tertiary education	27.9% (36)
Other education	12.4% (16)
Working status	
Student or child	38.5% (50)
Fulltime & part time employed	50.8% (66)
Unemployed	6.2% (8)
Other employment	4.6% (6)

6.3.1 Comparison of QALY loss as predicted by EQ-5D and SF-6D

Table 2 provides summary statistics of the continuous variables in the sample, which includes the QALY loss estimates from the four measurement methods. Due to the asymmetric nature of the EQ-5D and SF-6D measures, the median QALY loss values offer the best basis for comparison between these two instruments. The SF-6D based method resulted in median QALY loss values that were more than twice that of the EQ-5DConstant and nearly five times that of the EQ-5DLinear. The SF-6DNP yielded median values more than five times that of the EQ-5Dlinear and more than 2.5 times that of the EQ-5DConstant. The standard deviations indicate that the range of health outcomes is smaller for the SF-6D based method than for the EQ-5D based methods. The difference in spread and location can be seen from the descriptive statistics in **Table 2.** As suggested by Kharoubi et al. [17], the differences between outcomes from the SF-6D and SF-6DNP were small. The comparisons between the EQ-5D and the SF-6D survey are consequently similar for both algorithms. Therefore we focus mainly on the parametric SF-6D score and expand our results with the non-parametric method where necessary.

Table 2: **Sample characteristics**

	Nr of valid responses	Mean	Median	Min	Max	Standard deviation
Age	52.2% (72)	27.71	25.50	0	74	17.192
VAS score	47.8% (66)	66.31	67.00	20	100	19.765
Nr. of symptoms	18.6% (24)	5.60	6.00	0	11	3.12
Days of illness	41.1% (53)	17.82	14.00	0	65	12.32
EQ-5DConstant QALY loss	27.9% (36)	2.55×10^{-2}	1.22×10^{-2}	0	1.73×10^{-1}	3.33×10^{-2}
EQ-5DLinear QALY loss	12.4% (16)	1.28×10^{-2}	6.10×10^{-3}	0	8.65×10^{-2}	1.67×10^{-2}
SF-6D QALY loss	38.5% (50)	2.80×10^{-2}	2.98×10^{-2}	0	4.68×10^{-2}	1.08×10^{-2}
SF-6DNP QALY loss	50.8% (66)	3.00×10^{-2}	3.27×10^{-2}	0	4.66×10^{-2}	1.02×10^{-2}

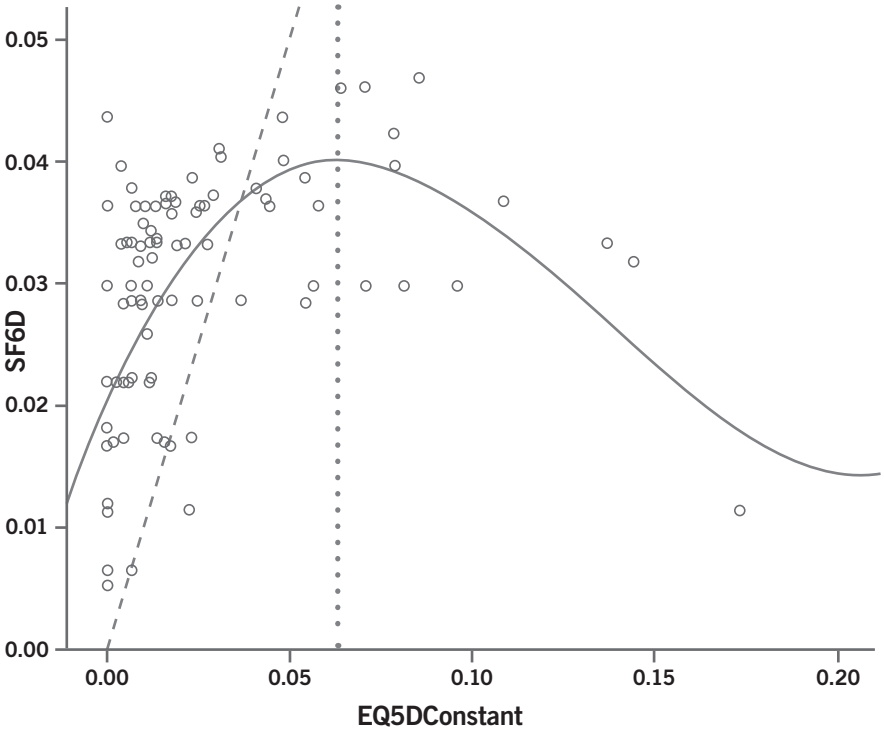
Note: These statistics were obtained for all respondents that indicated a response to the specific question. The minimum number of days of illness and symptoms can be attributed to an asymptomatic patient. In our sample there were 3 asymptomatic patients. They are also notified to the health inspection services through laboratory tests of family members of an infected patient. This is also part of the clinical image of HAV and should therefore be included.

Non-parametric tests indicate a statistical difference between the median QALY loss predicted by the EQ-5DLinear and the SF-6D (p-value < 0.0001). Similarly, there is a significant difference between the median QALY loss predicted by the EQ-5DConstant and the SF-6D (p-value = 0.001). Also, the EQ5DConstant, the EQ5DLinear and the SF-6D outcomes are all significantly different from the SF-6DNP (p-value < 0.0001 for all comparisons).[14] A scatter plot of the coupled health surveys, shown in **Figure 2,** compares the outcomes of the QALY loss measures for the EQ-5DConstant and the SF-6D. Theoretically, all observations on the scatter plot should be on the 45° reference line if the two QALY measures produce the same QALY loss estimates. This is rarely the case. In line with other studies, the EQ-5D is more responsive for patients with apparently more severe illness, but relatively insensitive for patients in milder disease states, whereas the SF-6D is also sensitive for apparently milder illness [10]. Patients, who indicated greater disease severity on the EQ-5D, tend to have a lower score on the SF-6D. Patients with lower QALY loss on the EQ-5D tend to generate higher health burdens on the SF-6D. A number of patients, indicating no health impact on the EQ-5D during the first week of illness,

[14] Also expressed as means instead of medians there were statistically significant differences between these 4 methods.

indicated an adverse health impact on the SF-6D. The EQ5DLinear by definition results in half the QALY loss compared to the EQ5DConstant and consequently only results in a higher QALY loss than the SF-6D in patients who indicate severe levels of adverse health impact on the EQ-5D. The QALY loss estimated by the SF-6DNP is not shown on **Figure 2** since its relationship is similar to that of the EQ-5D and the SF-6D. We found a linear relationship between SF-6D and SF-6DNP with greater values of QALY loss for the SF-6DNP as shown in **Table II.**

Figure 2: Fitted 3rd order polynomial estimating the QALY loss resulting from the SF-6D as a function of the EQ 5D



Dots are observations, solid line is 3rd order polynomial fitted to the data, dashed line is the 45° reference line, and dotted line is reference line at the turning point of the polynomial)

We fitted the QALY loss resulting from the SF-6D as a function of the EQ-5D. The best fit was a 3rd order polynomial (adjusted $R^2 = 0.343$) and is also shown in **Figure 2.** The estimated regression equation is as follows:

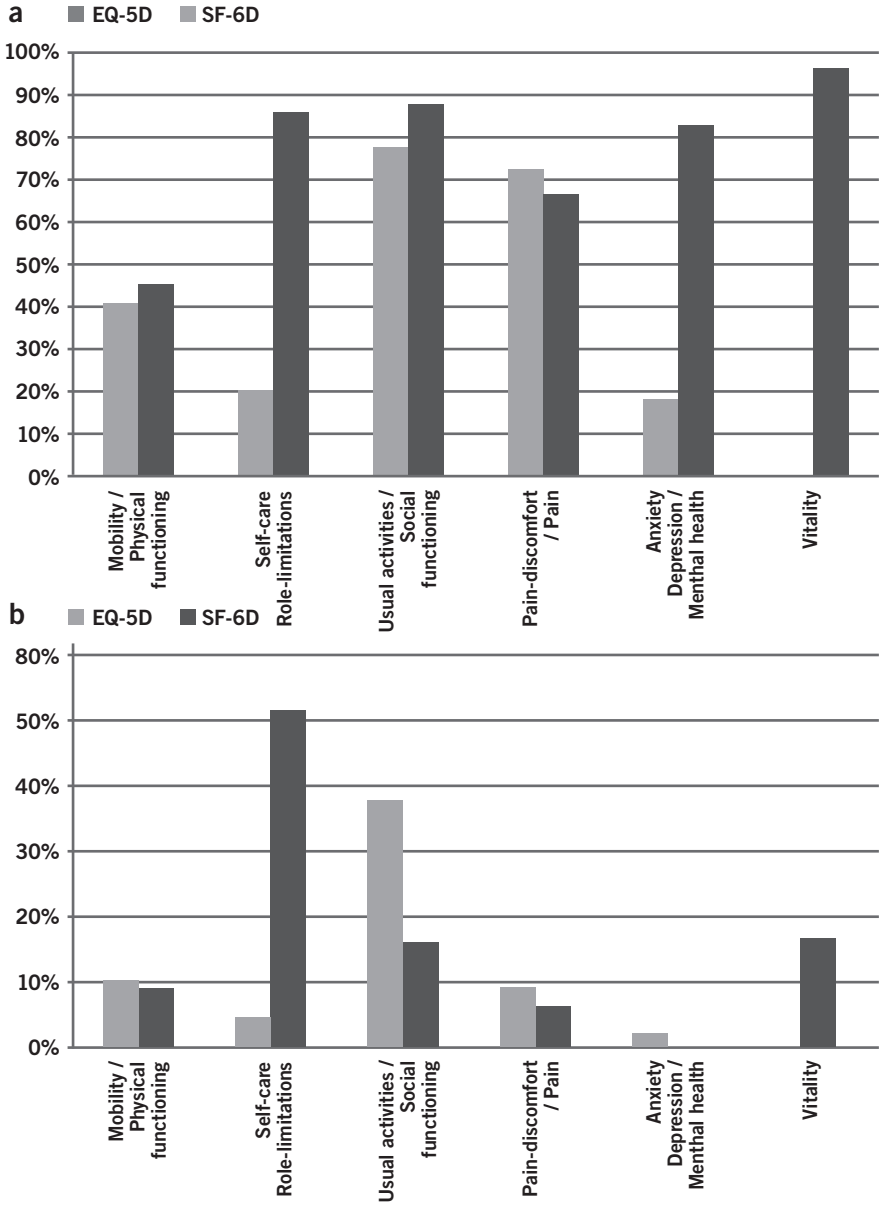
$$\widehat{\text{SF-6D}} = 0.02 + 0.685\ \text{EQ5DConstant} - 7.057(\text{EQ5DConstant})^2 + 17.413(\text{EQ5DConstant})^3 \quad (1)$$

The regression line between the EQ5Dlinear and the SF-6D has a similar shape as that of the EQ5DConstant and the SF-6D. The turning point for the EQ5DConstant is 0.063 and for the EQ5DLinear it is 0.032. Therefore it is estimated that the SF-6D based method is an increasing function of the EQ5DConstant if EQ5DConstant < 0.063 and decreasing otherwise (we ignore the second turning point since it is outside the range of the EQ5DConstant). We found similar results for the SF-6DNP estimate. The quadratic equation was the best fit with an adjusted R-square of 0.369 and the estimated curve had the same turning point.

The differences between the EQ-5D and SF-6D QALY loss estimates were further investigated by calculating the ratio of the natural logarithm of the EQ-5D and SF-6D QALY loss estimates. A cluster emerged for respondents that indicated perfect health on the EQ-5D and imperfect health on the SF-6D. This clustering was confirmed by a two-step cluster analysis. The same cluster emerged for the SF-6DNP.

Figure 3 summarizes the distribution of the responses on the different pairs of similar health-dimensions on both instruments [22]. The EQ-5D dimensions reflect the health experience as it is measured during the illness (usually at the start). The SF-6D dimensions reflect how the illness was experienced in retrospect, 4 weeks after onset of illness. Patients indicate more intermediate levels of health problems on the SF-6D survey, especially on the dimensions 'role limitations' and 'anxiety/depression' (>80% vs. ≤ 20%). The 'vitality' dimension is lacking on the EQ-5D but is shown to be an important aspect of hepatitis A illness on the SF-6D survey. The percentage of respondents indicating the most severe levels of problems also differs between the surveys. Fifty-one percent indicated most severe problems with 'role limitations' on the SF-6D vs. 5 % in the EQ-5D. 'Usual activities' was a stronger contributor to the patients health state on the EQ-5D than 'social functioning' on the SF-6D.

Figure 3: **a) Comparison of dimensions for patients indicating any problem. b) Comparison of dimensions for patients indicating severest level of problems**



Note: The health dimensions of the EQ-5D and the SF-6D are relating to different moments in time. The former is administered from a current state description at the start of the illness, the latter is administered after the illness, whereby the health state description is related to a period of 4 weeks after the onset of illness.

The relationship between the dimensions of the EQ-5D and the SF-6D survey were analysed using Kendall's Tau rank correlation coefficient. This indicated that all of the dimensions are correlated to each other with the exception of 'pain/discomfort' and 'self-care' (p-value = 0.197), 'vitality' and 'anxiety/depression' (p-value = 0.074); and 'social functioning' and 'self-care' (p-value = 0.057) being uncorrelated.

6.3.2 Significant predictors of QALY loss

A multiple regression model indicated that the VAS-score and number of symptoms were significant predictors of the QALY loss estimated by the EQ-5D and the SF-6D. Multicollinearity in these linear models was not significant despite a degree of correlation (Pearson correlation coefficient = -0.2) between VAS and the number of symptoms. The cost of treatment, number of days of illness (only tested for the SF-6D), gender, smoking status, previous experience with serious illness and age of the patient, were found non-significant.

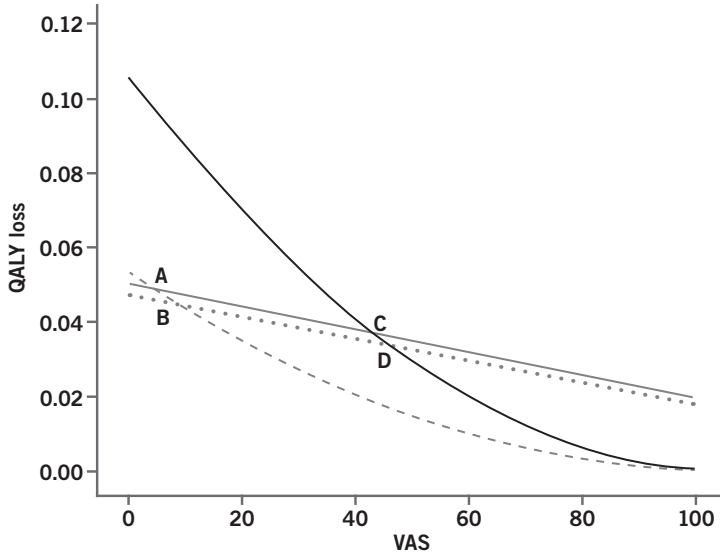
As can be expected, there is a negative relationship between the VAS score and the QALY loss for both the EQ-5D and the SF-6D. Both QALY loss measures indicated a positive relationship with the number of symptoms. The same results were obtained for the SF-6DNP as for the SF-6D.

The sensitivity of the QALY loss measures to the VAS score and the number of symptoms was analysed by fitting two GLMs. The GLMs had the QALY loss estimates as dependent variable and an intercept and three dummy variables for the four possible QALY loss estimators. Furthermore, the first model had three interaction terms for the QALY measures and the VAS score, and the second model had three interaction terms for the QALY measures and the number of symptoms. A significant coefficient for an interaction term indicates a threshold for the VAS/number symptoms such that below this threshold, the QALY loss estimated by one of the methods will be greater than that of the other methods and an opposite relationship above the threshold.

The interaction between the VAS score and the QALY loss measure was significant (p-value < 0.001 for EQ5DLinear*VAS; p-value < 0.001 for SF-6D*VAS; p-value < 0.001 for SF-6DNP*VAS), but not between the VAS score and the number of symptoms (p-value = 0.123 for EQ5DLinear*Number of symptoms ; p-value = 0.140 for SF-6D*Number of symptoms; p-value =

0.098 for SF-6DNP*Number of symptoms). This suggests the existence of a threshold for VAS. Below this threshold the QALY loss estimated by the EQ-5D is greater compared to the one based on the SF-6D, and vice versa above the threshold. Four linear regression equations were fitted to explore the relationship between the QALY loss estimates as predicted by the three measures and the VAS score. These regression lines are shown in **Figure 4**, which indicates that for some VAS scores the QALY loss estimates as predicted by the EQ5DConstant is larger than that of the SF-6D and SF-6DNP, and similarly for the EQ5DLinear. The threshold between EQ5DLinear and SF-6D is estimated at 7.17 and at 46.11 between EQ5DConstant and SF-6D. It is therefore estimated that for patients with a VAS score less than 7.17, a greater QALY loss will be predicted by the EQ5DLinear than by the SF-6D, but for VAS scores greater than 7.17 the QALY loss estimates from the SF-6D will be greater than that of the EQ5DLinear. A similar conclusion can be made for the threshold between the EQ5DConstant and the SF-6DNP. The thresholds between the EQ5DLinear and the SF-6DNP and between the EQ5DConstant and the SF-6DNP are 4.95 and 43.35, respectively. It is estimated that such thresholds do not exist for the number of symptoms due to the insignificant interaction between the QALY loss measure and the number of symptoms.

Figure 4: Regression lines of the EQ5DConstant, EQ5DLinear and SF-6D onto VAS

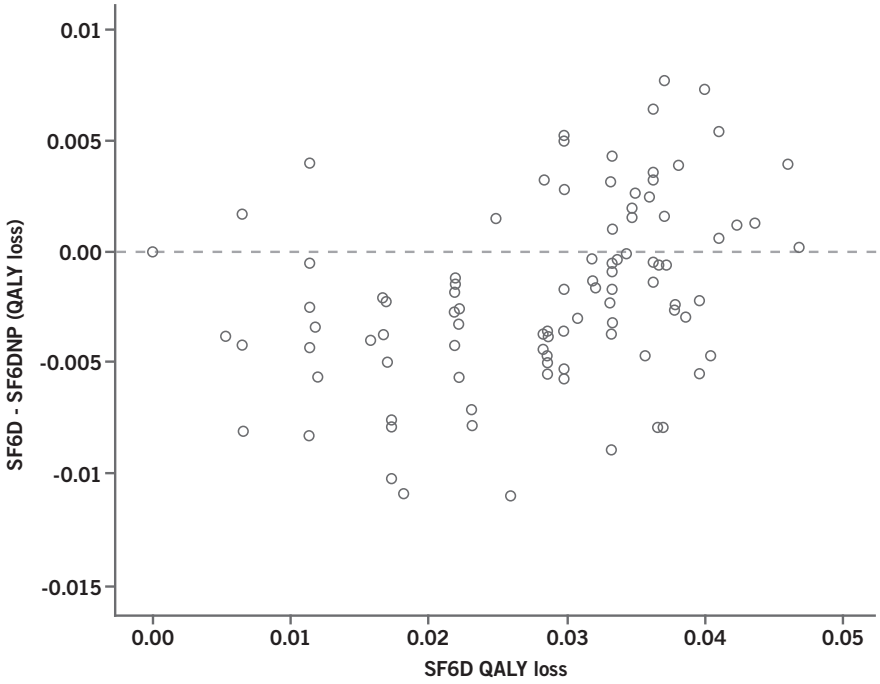


Solid black line: EQ5DConstant, dashed line: EQ5DLinear, dotted line: SF-6D, solid grey: SF-6DNP. Intersection points: A: EQ5DLinear and SF6DNP (VAS score = 4.95), B: ED5DLinear and SF6D (VAS score = 7.17), C: EQ5DConstant and SF6DNP (VAS score 43.35), D: EQ5DConstant and SF6D (VAS score = 46.11)

6.3.3 Comparison of QALY loss as predicted by the SF-6D with parametric and non-parametric scoring algorithm

Figure 5 shows the difference in QALY loss obtained with the two scoring algorithms for the SF-6D in hepatitis A patients. In our sample the utility values ranged [0.439; 1] in the SF-6D and [0.4406; 1] in the SF-6DNP. This does not allow us to compare the poorest health states in the entire spectrum of possible health states on the SF-6D survey since the lowest possible utility is 0.257 and 0.203, respectively. On the opposite side of the scale, the best health states, we found higher QALY loss in the non-parametric method. For average health states the results seem to be more equally distributed.

Figure 5: **Difference of the resulting QALY loss with the parametric (SF-6D) and the nonparametric (SF-6DNP) scoring algorithm for the responses to the SF-6D survey**



6.4 Discussion

We compared the QALY loss estimates produced by measurement methods based on the EQ-5D and the SF-6D by means of an interlinked survey from hepatitis A patients in Belgium. The four different health valuation methods produced significantly (p-value < 0.05) different results. Expressed as a median from the population sample, the SF-6D generated QALY losses that were about two to five times those obtained with the EQ-5D, assuming a constant QALY loss or a linear improvement in QALY loss over the illness period, respectively. All methods were able to identify groups of patients with a different health state according to criteria with a known relationship to health-related QoL such as the VAS and the number of symptoms. Both surveys yielded higher values of QALY loss for patients with an apparently more severe form of illness, thus supporting their validity. However, the magnitude of the difference between severely ill and mildly ill patients differed between the instruments. The EQ-5D resulted in higher values of QALY loss than the SF-6D for patients with more severe illness (as indicated by a low VAS score and a relatively high QALY loss on both surveys). The SF-6D generated greater QALY losses for the majority of patients with only minor or moderately severe illness. Most (93.33%) patients who indicated no health burden on the EQ-5D indicated a positive adverse impact on the SF-6D. On average the SF-6DNP had a similar relation to the EQ-5D as the SF-6D but yielded higher QALY loss. The differences in our sample between the SF-6D with parametric and with non-parametric scoring algorithm are consistent with the finding of Kharroubi et al.[17] who state that the parametric method overestimates the utility of patients in superior health states, thereby resulting in lower QALY loss estimates than the non-parametric method.

Our study highlights the variety of analytical choices that underlie QALY-calculations in practice, and indicates the magnitude of differences in outcome they may generate. Because of multiple contributory factors, which are associated with the choice and use of a particular standard instrument (i.e. the recall period, the algorithm, and the requirement to infer many time points from a single or a small number of time points), our study design could not quantify the effect of a single of these associated factors. Future research may estimate the effect of a single factor by creating more subgroups in which more combinations of these associated factors can be kept constant.

Nonetheless several explanations can be proposed for the observed differences between the EQ-5D and the SF-6D survey. First, there is a difference in recall period. For the SF-6D survey, patients recall their health state over a four-week period, while the EQ-5D survey captures a patient's current state. For hepatitis A, with an expected duration of clinical symptoms during 3 to 4 weeks (and in our sample up to 65 days, median 14, mean 17.8, proportion ill for more than 1 week: 79%), the so-called "acute" version of the SF (with only 1 week recall period) would not enable us to capture the full disease-episode for the majority of patients. However, when considering the course of illness in retrospect, the memory may average out the experienced extremes to a more constant level [23]. Since the patients we surveyed were not ill for exactly four weeks they had to reconcile in their valuation their period of ill-health with their period of good health over the total recall period.

The SF-6D and the EQ-5D surveys also differ in the coverage of health dimensions and in the number of levels of severity in each dimension. The SF-6D survey can generate 18,000 health states while the EQ-5D survey distinguishes between 243 states. Some studies found the SF-6D survey to be suffering from a 'floor effect'. Responses on the dimensions of physical functioning and role limitations have a disproportionate number of responses at the lowest level for patient groups with more severe illness [10, 22, 24]. In our study, the difference was only pronounced for 'role limitations'. The EQ-5D survey however is said to be suffering from a 'ceiling effect'. Other studies reported that patients indicated perfect health (state 11111) on the EQ-5D survey and imperfect health on the SF-6D survey [22, 24]. In our sample 15% of the coupled responses indicated perfect health on the EQ-5D and lower levels on the SF-6D. This refers to the cluster analysis mentioned above.

The SF-6D survey has a dimension that is not present in the EQ-5D, vitality, which can be of special significance for an illness like hepatitis A. In our sample 95% indicated to have at least some problems with vitality on the SF-6D. Patients with a milder form of illness may not suffer from pain, mobility or anxiety but still score low on the vitality level. More than 50% of the respondents indicated severe role limitations, while 5% had problems with self-care on the EQ-5D. Role limitations are however more severe than self-care and perhaps more appropriate to capture the limiting effects of having an infectious disease on the patient's behaviour. Infected people may be capable of performing several duties but be limited in the

fulfilment thereof out of precaution for infection to others. This effect, if it is considered to be part of health-related QoL, is possibly better measured by the SF-6D than in the EQ 5D and may explain the higher QALY loss for patients with only mild symptoms. Apart from the differing dimensions, the descriptive system of the SF-6D allows for more levels on each dimension to respond (four to six vs. three). Patients with only slight problems may be more capable to indicate it on the SF-6D scale than on the EQ-5D.

A third possible explanation is the scoring algorithm used to value the described health states. A multidimensional health description needs to be reduced to one dimension in order to be useable for economic evaluation. The EQ-5D and the SF-6D both use different methods to do this: respectively the time trade-off (TTO) and the standard gamble method (SG). A number of publications indicated that SG generates higher utility scores for more severe health states than TTO because of the inclusion of risk aversion and positive time preference. For milder states the TTO seems to generate higher values [10, 25, 26]. These differences in scoring algorithm lead to an EQ-5D scale with twice the range of the SF-6D scale: [-0.59 to 1.00] vs. [0.25 to 1.00] for the parametric one and [0.20 to 1.00] for the non-parametric one. This is reflected in the range of the different QALY loss measures as shown in **Table 2**. The differences between both SF-6D based scoring algorithms remains small compared to the difference with the EQ-5D.

There may be several reasons why cost-utility analysis remains to be considered a controversial instrument for policy advice. One of them is the lack of an unambiguous method for valuing morbidity. Different methods for valuing the health burden of an acute illness for which only a single time point measurement is available, can lead to different results. The inclusion of a recall period or the assumption of a linearly improving or a constant health state, are analytical choices with a great impact if the health burden of the illness is substantially attributable to morbidity. The most appropriate method for health description is a matter of discussion since there is no 'gold-standard' to determine which measure approximates best the 'true health state'. Much depends on the concept of health that policy makers want to use to prioritise. For example, is it the better-digested memory of a specific health state (captured in a survey with recall period) that counts or is it the immediate experience (as captured in a current state survey)? Clearly, relying on memory suffers from all kinds of biases [27, 28]. The fact that the SF-6D produces more consistent outcomes across the sample than the EQ-5D may explain more on the functioning of the memory than on the

actual disease experience. Conversely, a current state description requires the analyst to make assumptions on the further evolution of the illness between the different points of measurement, which can have a significant impact on the estimated QALY, if there is no opportunity to administer surveys regularly. Opting for a linear health improvement instead of a constant health state between two points in time yields per definition half the QALY loss. This leads to an ICER of twice the magnitude (if only morbidity QALYs are considered).

Considering these differences and the advantages and disadvantages of each method, researchers should therefore consider performing economic evaluations using different estimates of health benefits, and incorporate the range of the measures by means of sensitivity analysis rather than assuming a single utility score. We have provided a conversion equation between the QALY loss estimated by the EQ-5D and SF-6D measures in the case of hepatitis A, which may simplify this process if one of the measures is available.

6.5 Conclusion

This study made clear that four conceptually defensible methods for measuring the health burden of an acute illness, based on the EQ-5D and the SF-6D survey, produce statistically different results. The hypotheses that the methods based on the EQ-5D lead to better health scores in healthy patients and worse scores in severely ill patients than methods based on the SF-6D, were confirmed. However, the most appropriate method remains a matter for further debate. Researchers should not only choose between surveys but also consider the effect of the time at which the survey is taken, the length of the recall period, the assumed disease progression and the scoring algorithm underlying the resulting outcome. Cost-utility analyses should make explicit the underlying techniques and assumptions behind a summary health utility score and if possible expand the results with other measurement methods in a sensitivity analysis.

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Chapter 7: Costing infectious disease outbreaks for economic evaluation: a review for hepatitis A

Abstract: With the aim to understand and estimate the economic impact of outbreaks of endemic community-acquired infections, we performed a review focusing on hepatitis A virus (HAV) outbreaks. Thirteen papers were retained, which had collected relevant cost information during such outbreaks. The costs of HAV outbreaks ranged from $140,000 to $36 million, and the costs per case in an outbreak situation from $3,824 to $200,480. These costs were typically found to be substantially higher than estimates from cost-of-illness studies and estimates used in cost-effectiveness analyses, mostly due to costly outbreak control measures. Post exposure prophylaxis is a major cost factor, especially for food borne outbreaks. Due to the increasing proportion of susceptibles for HAV in countries of (very) low endemicity, future outbreaks could, on average, increase in size. The increasing occurrence of HAV cases in outbreak situations and the associated control costs should appropriately be accounted for in economic evaluations of HAV vaccination programs in (very) low endemic countries. In order to do this, more studies documenting such outbreak control strategies in terms of costs and resource use are needed.

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7.1 Introduction

Hepatitis A virus (HAV) is transmitted from person to person through the faecal-oral route and through ingestion of contaminated food or drink. After an average incubation period of 28 days, symptoms such as fatigue, jaundice, nausea, abdominal pain, and discoloured urine and stool may occur [1]. The probability of symptomatic infections is low for children but rises with age at infection until adulthood. More than 75% of adults, who incur an HAV infection, show symptoms but 70% of infections in children younger than six years of age remain asymptomatic [1]. Armstrong and Bell estimated that 85% of infected adults show symptoms of jaundice [2]. Although most patients recover fully, the disease can be severe and hospitalization may be required. Exceptionally HAV can give rise to fulminant hepatitis, hepatic coma and death.

The incidence of HAV infections has been declining in most parts of the world during recent decades. This decline has generally been attributed to improvements in hygienic, sanitary and socio-economic circumstances and the use of effective vaccines. This has led to a situation in which, in (very) low endemic areas, domestic transmission of infection is usually linked to outbreaks. Since the incidence of HAV declined, by adulthood a decreasing proportion of the population acquires immunity through HAV infection, leaving an increasing proportion susceptible to infection. Therefore, outbreaks could potentially become larger, if they are not controlled in some way. In view of this, the estimation of the economic cost of an HAV outbreak is gaining importance in order to estimate the cost-effectiveness of HAV vaccination, particularly in (very) low endemic areas. In order to establish the various components that contribute to the costs of such outbreaks, we review here the literature on the costs of HAV outbreaks.

7.2 Methods

7.2.1 Literature search

On April 28, 2008 we performed the following search in Pubmed, NHSEED, EconLit and DARE: (cost* OR economic) AND outbreak* AND “hepatitis A”. The search in Pubmed resulted in 76 publications. In Web of Science, NHSEED and DARE we respectively found 102, 11 and 0 articles. After elimination of duplicates and inspection of all abstracts, 22 full-text articles

were retrieved. The other articles were excluded because of their purely epidemiological content. Of the 22 articles considered, 7 included fairly comparable data on the costs of an outbreak, which are summarized in **table 1**. The relevant information related to outbreaks was extracted from 6 other articles in the text below. Note that one short Danish publication, on an outbreak in men who have sex with men, was not assessed in full [3] (only Dutch, English, French, German and Spanish articles fell within the authors' language skills). The nine other articles did not contain relevant information on costs.

7.2.2 Costing outbreaks

In order to estimate the societal cost associated with an outbreak, one needs to describe all economic resources used to mitigate the outbreak and treat the cases arising from it, and consequently one should value these resources. Amongst resources consumed when an outbreak occurs, we mainly distinguish medical from non-medical resources. Medical resources are further divided in direct treatment costs (e.g., hospital beds, doctor visits, medication) and direct control costs or costs from mitigation strategies to control the outbreak (health department investigations and announcements, purchase and administration of prophylaxis such as immunoglobulin injections and vaccine).

Listing economic resources is one thing, valuing them another. Valuation should be based on opportunity costs and therefore not necessarily on actual expenditures. For an outbreak, medical resources can be valued according to the price paid for them because their purpose was already determined prior to the outbreak and there was no alternative use. However if there is scarcity in medical resources like, for instance, hospital beds, strictly speaking opportunity costs should also be implied. Nonmedical resources represent mainly indirect costs. These arise as a consequence of the outbreak interrupting people's normal activities and include the economic value of lost time at work, lost business opportunities, as well as household and leisure time. Mostly the average local (or national) income is used to value time losses, meaning that only lost work time is assumed to be of economic relevance. Other nonmedical costs (like costs due to litigation, bad publicity or bankruptcy) are virtually always ignored. Pain and suffering have an important impact on wellbeing and should in theory be included in a societal cost valuation. These so called intangible cost valuations however,

are controversial because of measuring problems and are therefore excluded from most analyses.

Most estimates discussed here need to be interpreted conservatively because of difficulties in describing all costs generated by the outbreak. Both total costs and average costs per case are presented in **table 1**. The use of average costs per case facilitates comparisons between different outbreaks. However, note that fixed costs are allocated over a smaller number of cases in smaller outbreaks, and thus cause greater total costs per case compared to a larger outbreak in the same setting (all else being equal). This implies that for the smaller-type outbreaks the marginal costs - i.e. the costs of one extra case - are lower than the average cost per case.

Table 1: Total costs of an outbreak, specified according to different cost categories (in parentheses: costs per case, % of total costs) (in US$ 2007)

Location	Denver, US [4]	Spokane, US [5]	Franklin County, US [6]	Narzole, Italy [7]	Puglia, Italy [8]	Liverpool, UK [9]	Toronto, CND [10]
Main source of outbreak	Food handler	Injecting drug use	Men who have sex with men	Primary School or day care centre children	Infected food and person to person	Primary school children	Food handler
Nr of cases	43	590	136	11	5889	9	3
Direct costs	$1,281,800 ($29,809 ; 92%)	$2,538,004 ($4,301 ; 78%)	$270,720 ($1,991 ; 52%)	$118,499 ($10,773 ; 84%)	$28,398,494 ($4,822 ; 78%)	NS	NS
Direct treatment costs	$80,292 ($1,867 ; 6%)	$1,148,025 ($1,946 ; 35%)	$220,615 ($1,622 ; 42%)	$116,876 ($10,652 ; 83%)	$28,398,494 ($4,822 ; 78%)	NS	NS
Non-hospital costs	$54,195 ($1,260 ; 4%)	$445,760 ($756 ; 14%	$78,410 ($577 ; 15%)	$11,853 ($1,078 ; 8%)	$4,411,325 ($749 ; 12%)	NS	NS
Hospital costs	$26,097 ($607; 2%)	$702,265 ($1,190 ; 21%)	$140,527 ($1,033 ; 27%)	$105,024 ($9,548 ; 75%)	$23,987,169 ($4,073 ; 66%)	NS	NS
Direct control costs	$1,201,508 ($27,942 ; 87%)	$1,389,978 ($2,356 ; 42%)	$50,105 ($368 ; 10%)	$1,622 ($147 ; 1%)	NA	$7,818 ($869)	$601,440 ($200,480)
Prophylaxis used	IG	IG	IG	IG	NO	Vaccine	Vaccine & IG
Tests	$232,205 ($5,400 ; 17%)	NS	$381 ($3 ; 0%)	NS	NA	NS	NS
Prophylaxis costs	$785,064 ($18,257 ; 57%)	$1,389,978 ($2,356 ; 42%)	$22,290 ($164 ; 4%)	$318 ($29 ; 0%)	NA	$5,478 ($609)	$342,019 ($114,006)
Health personnel costs	$184,239 ($4,285 ; 13%)	NS	$27,434 ($202 ; 5%)	$1,304 ($119 ; 1%)	NA	$1,302 ($145)	$259,421 ($86,474)
other	NS	NS	NS	NS	NA	$1,036 ($115)	NS
Indirect costs	$106,653 ($2,480 ; 8%)	$733,533 ($1,243 ; 22%)	$249,318 ($1,833 ; 48%)	$21,923 ($1,993 ; 16%)	$7,892,334 ($1,340 ; 22%)	NS	NS
Productive time lost	$42,083 ($979 ; 3%)	$733,533 ($1,243 ; 22%)	$249,318 ($1,833 ; 48%)	$21,923 ($1,993 ; 16%)	$7,180,231 ($1,219 ; 20%)	NS	NS
Other time lost	$64,570 ($1,502 ; 5%)	NS	NS	NS	$712,102 ($121 ; 2%)	NS	NS
Mean Number of workdays lost	12.5*	9.1	12	7.5	12.8	NS	NS
Total cost	$1,388,452 ($32,290; 100%)	$3,271,537 ($5,545 ; 100%)	$520,039 ($3,824 ; 100%)	$140,422 ($12,766 ; 100%)	$36,290,828 ($6,162 ; 100%)	NS	NS

* Median instead of mean, IG: Immunoglobulin, NS: Not stated, NA: Not applicable, NS: Not stated

Table 2: cost-estimates for hepatitis A patients in cost of illness studies (in US$ 2007)

Author	Tolsma et al [11]	Chossegros et al [12]	Berge et al [13]	Hadler [28]	De Juanes et al [14]	Todd [15]	Diel et al [16]
Main source of outbreak	Food handler	Injecting drug use	Men who have sex with men	Primary School or day care centre children	Infected food and person to person	Primary school children	Food handler
Country	US	France	US	US	Spain	US	Germany
Direct costs per case	$583	$655	$2,586	$1,295	NS	NS	$1,020
Indirect costs per case	$967	$1,988	$7,361	$3,397	NS	NS	$4,315 (adult) $449 (child)
Total costs per case	$1,550	$2,782	$9,948	$4,692	$764	$9,691	$1,469 (child) $5,335 (adult)

Table 3: cost-estimates for hepatitis A patients from economic evaluations in the US, Canada and France (in $US 2007)

Author	Bauch et al. [17]	Jacobs et al. [18]	Myers et al. [19]	Péchevis et al. [20]	Jacobs et al. [21]	O'connor et al [22]	Smith et al [23]
Target population	Children Canada	Adolescents US	Chronic HCV US	Secondary infections France	Children US	Adults US	Students US
Outbreak control costs	$355	NS	None	NS	NS	NS	NS
Direct costs per case	From $1,000 to $1,686	$985	$3,783 (moderate cases)	$356 (mild) $3,355 (hospital)	$668 (nonhospital) $9,506 (hospital)	$183 (non hospital) $9,219 (hospital)	NS
Total costs per case	From $1,607 to $3,189	$2,658	NS	NS	NS	NS	$10,491

All outbreaks were documented in very different ways. We attempted to report the cost calculations in a general format in order to improve direct comparability.

All costs described in this article are expressed as $US 2007. We used Purchasing Power Parities (PPP) to convert to $US [24]. To capture price effects we used for direct costs the Consumer Price Index (CPI) for medical care, for indirect costs the CPI for all items, both from the US Bureau of Labour Statistics. We opted for this approach, i.e. first converting and then inflating, because some non-US articles only reported costs in $US and for some countries medical care specific CPIs were not available.

7.3 Results

In this section we summarize the 13 articles considered relevant following our search described above.

7.3.1 Foodborne outbreaks

A food-borne outbreak of hepatitis A in Denver, Colorado, US [4]

In 1992 an outbreak of hepatitis A associated with a catering facility, resulted in 43 cases and the potential exposure of 5,000 persons who attended parties catered by the food handler [4]. Initially only 50 food handlers were given immune globulin prophylaxis. Later when the potential breadth of the outbreak became clear, more than 16,000 people received immune globulin prophylaxis. The total cost of this outbreak was estimated at $1.38 million, or $32,290 per case. Eight percent were indirect costs, 92 % direct costs. Total direct costs were $29,809 per case of which $27,942 (94 %) were disease control costs and $1,867 (6 %) direct medical expenses for treatment. Most of the disease control costs were for immune globulin injections (65 %). Still these costs were underestimated since immune globulin given by the approximately 1,400 private physicians was not included. Direct medical expenses were both for hospitalized and for non-hospitalized cases. Note that only 2 of the 43 cases were hospitalized but made up 33% of the costs of illness for all cases. Total indirect costs were estimated at $2,480 per case, i.e. including both business and productivity losses. Business losses ($1,502 per case) were due to lost profits as well as the food discarded by the catering company. Productivity losses due to these 43

cases, based on median duration of absence, average national earnings and the imputed value of household work, were estimated at $979 per case. This outbreak demonstrates that the cost of an outbreak can be substantially higher than just the direct medical costs for cases. Indeed, for every dollar spent on medical treatment for the illness of cases, nearly $15 were spent on controlling the outbreak.

An outbreak of hepatitis A in Puglia, Italy [8]

In 1996 a total of 5889 cases of hepatitis A were identified during an outbreak in Puglia, Italy [8]. The primary cause of the outbreak was consumption of contaminated food, with a contributory factor of person-to-person transmission. Information of resources used was obtained by taking a random sample of 250 patients. Eighty-six percent of the sample patients were aged between 11 and 30 years. Ninety percent of the cases were treated in hospital for 9.3 days as outpatients and for 15.3 days as inpatients (i.e. with nights spent at the hospital). Preventive procedures included recommendations to the public on handling and consuming raw seafood. No attempt was made to control the outbreak by immunization, which may have been a factor in the outbreak being sustained over several months. The total cost of this outbreak was $36,290,828. Direct costs were $28,398,494 or 78 % of total costs. Indirect costs were $7,892,334 or 21 % of total costs. Note that the region had a high unemployment rate, and that losses to tourism were ignored, implying that the indirect cost estimates can be considered conservative. The majority of all the identified costs were due to hospitalizations, i.e. $23,987,169 or 66 % of total costs. This can be explained by the high caseload, mainly in adults, resulting in a relatively high hospitalization rate. The total costs per patient were $6,162. The total costs of the outbreak corresponded to 0.04 % of the regional GDP in 1996.

An outbreak in Toronto related to a food-handler [10]

Trico et al [10] stated that foodborne outbreaks appear regularly in Canada and intervention programs are implemented timely. Approximately 3 incidents with infected food handlers occurred per year from 2001 to 2004. Outbreak control measures in Canada were described as typically including communicable disease investigation, food-inspection and control, risk communication and immunization and surveillance of secondary cases. The median number of immunized individuals was 5,750 in incidents with

large interventions. In August 2002 an HAV outbreak occurred in Toronto, related to a food handler in a high-volume grocery store, located in a high-density urban area. The eventual number of cases was only 3, but the number of people receiving immunization as a form of post exposure prophylaxis was remarkably high: 19,208. The total public health cost corresponded to $601,440 or $200,480 per reported case. The cost-of-illness (COI) for the 3 cases arising from this outbreak was not discussed but would seem negligible compared to the outbreak control costs.

7.3.2 Outbreaks in schools

A small outbreak of hepatitis A in Narzole, Italy [7]

During the period December 1993 – March 1994 11 cases of Hepatitis A were reported, mainly children [7]. The source of the outbreak was unknown but either related to a state school or a day care centre for children from broken homes. The day care centre also sported a catering facility, and some of the children ate their lunch there. Outbreak control measures consisted of interviewing cases, tracing all family and school contacts and offering gammaglobulin prophylaxis to contacts. All cases were hospitalized. The total cost of this outbreak was estimated at $140,422, or $12,766 per case. Direct costs represented 84 % of total costs, whereas the remaining 16 % were indirect costs. The direct costs totaled $118,499 of which only $1,622 (i.e. 1% of total costs) were outbreak control costs. The direct medical expenses for the 11 cases represented 83 % of all costs. Hospitalizations took up 75% of the total cost of the outbreak. Note that a large part of hospitalization costs were fixed, and that these would decrease proportionate to an increase in caseload. Indirect costs included only productivity losses and amounted to $21,923. This share in total costs is rather small since the epidemic involved mainly children. Most productivity losses were incurred through parental time spent caring for their children, instead of at their work place. The cost structure of this outbreak might be atypical because of some special characteristics. The outbreak remained small with considerable fixed costs and a relatively greater proportion of direct costs, compared to larger outbreaks. Moreover most of these cases were children, which would likely be associated with relatively lower indirect costs compared to adult cases. If the outbreak had expanded then the indirect costs would likely have gained in relative importance.

A school outbreak in Liverpool [9]

In January 2006, nine symptomatic hepatitis A cases occurred in a socio-economically deprived area of Liverpool with high levels of drug abuse [9]. The main route of transmission was from person to person, and five cases were linked within a primary school. Since previous outbreaks in the area around Liverpool caused up to 300 cases, a range of outbreak control measures were taken. Post exposure vaccination was considered a viable strategy and was offered to all of the school children and staff, with a total of 100 saliva tests taken and 188 vaccines administered. This study had its focus on the cost-effectiveness of the intervention. Total costs including direct medical expenses and indirect costs of the outbreak were not discussed. The outbreak control measures gave rise to a total expense of $7,818, or $869 per infected case.

7.3.3 Outbreaks among adults

An outbreak in a mid-sized urban community, Spokane, Washington, US [5]

An outbreak of hepatitis A occurred in Spokane in 1997 and 1998, resulting in 590 cases of acute hepatitis A [5]. The outbreak was thought to be associated with increased injecting methamphetamine use. Approximately 6 % was hospitalized for an average period of seven days. A total of 7,134 individuals received immune globulin in public health departments. The other costs were derived from a sample of 145 respondents. The outbreak was associated with increased drug use and people who were not included in the sample may have had a lower socio-economic status. The authors state that direct medical expenditures were probably underestimated, due to poor health access despite the relatively severe nature of these cases. The total cost of this outbreak was estimated at $3,271,537 with 35 % direct medical costs, 42 % outbreak control costs and 22 % indirect costs. The outbreak control costs substantially exceeded all other cost categories, indicating again that the majority of societal costs are not necessarily related to the actual cases arising. A total of no less than $1,389,978 was spent on prophylactic IG. Inpatient hospital care for 6 % of the cases represented the largest fraction of total direct medical costs. Indirect costs included lost salaries, but also childcare costs. Total costs per case averaged $5,545 with $1,946 for medical care, $2,356 for administering IG to contacts

and $1,243 costs for time losses. Clearly at $3 million, an outbreak of this nature in a rural area can have a significant local impact.

An outbreak in men who have sex with men in Franklin County, Ohio, US [25]

Between November 1998 and May 1999 136 HAV cases were reported in the city of Colombus (Ohio), which represented more than a threefold increase compared to the previous years [25]. Of these cases, 118 (87%) were male adults and 47 (64%) described themselves as 'men who have sex with men'. About 1 in 6 (18 %) of reported cases was hospitalized and 1 person died. Outbreak control measures consisted of community outreach, public notification and administration of immunoglobulin to 485 individuals who may have been exposed to HAV. The estimated total cost of the outbreak was $520,039 including approximately $220,615 (43 %) medical costs, $50,105 (10 %) outbreak control costs and $249,318 (47 %) indirect costs of lost productivity. The largest direct cost item was the cost of hospitalization, which constituted for 52 % of the total direct costs and 27 % of the total costs, despite the fact that it affected only a minority of patients. The costs per case were on average $3,824, with $1,991 direct and $1,833 indirect costs. Outbreak control costs were probably underestimated since no private IG provision was included. Additionally, 1 patient died and no attempt was made to estimate the associated costs of death and life-years lost.

7.3.4 Other estimates for the cost of an outbreak

Several other studies also documented the costs of outbreaks [Bauch et al [17], Postma et al [26], Chodick et al [27], Egoz [28], Patnaik et al [29], Howitz et al [3], most of these as part of a larger study (eg, a cost-effectiveness analysis)]. The partial or implicit way in which the outbreaks were described in these studies does not make it possible to summarize these in the same manner as the outbreaks listed in the previous sections (3.1-3.3). In this section we briefly highlight the outbreak information these studies contain. Bauch et al. [17] made a cost-utility analysis in which they incorporated public health interventions by attributing $355 per symptomatic case. Postma et al [26] calculated the average cost of an outbreak at $9,545 per case, based on registered outbreaks in Amsterdam. Intervention costs contributed the most to direct costs (23% of total costs), with 100 doses of immunoglobulin administered per outbreak. Additional cost items were

indirect costs (61%), hospital care (14%), GP-visits and serology (2%). Chodick et al [27] estimated the cost of prophylaxis in an outbreak at $130 per case. Egoz [28] described the cost of avoiding an outbreak of HAV through contaminated drinking water in 1985. In total 12,644 doses of IG were administered to children and pregnant women, corresponding to a cost of $58,121. Patnaik et al [29] reported on the outbreak control measures of an infected food worker in Colorado. Immunoglobulin was administered to 693 individuals, corresponding to a cost of $54,678. Finally, Howitz et al [3] reported on an outbreak causing 220 symptomatic cases in homosexuals, which costed $823,081 or 3,798$ per case.

7.4. Discussion

Despite the self limited non-malignant course hepatitis A usually takes, the economic impact of an HAV outbreak can be substantial. Nonetheless up till now, a fairly limited number of studies describing the economic impact of HAV outbreaks have been published. Intuitively, the bulk of the economic burden of hepatitis A is often attributed to the indirect costs because people with symptomatic infection may be unable to work for several weeks, while the cost of treating them is considered only minor [15,13,11]. However, the descriptions of the outbreaks we retrieved from the literature (table 1) show the opposite. The indirect costs represented 8% to 48% (average 26.8%, median 20%), whereas the direct costs made up 52% to 92% (average 76.8%, median 78%) of the total costs of the outbreaks. Note that, in view of the valuation method used, indirect cost estimates are sensitive to the employment status of the persons affected by the outbreak.

In COI studies and economic evaluations of HAV vaccination the direct costs may typically be underestimated. The COI studies summarized in **Table 2** estimated the direct cost per patient between $583 and $2,586. The economic evaluations in **table 3** we retrieved for the same geographic areas, also use estimates for direct costs per case that are, on average, smaller: ranging from $183 (for a non-hospitalized case) to $9,506. For instance for the US, two widely cited COI studies, estimate the direct costs of an adult hepatitis A case at $1,295 [30] and $2,586 [13]. To come to this estimate these studies applied a hospitalization rate of 15% and 14%, respectively. Cost-effectiveness analyses for adults and adolescents from the same country estimated the average direct cost per case at $985 [18] (with 10 % to 43 % of cases hospitalized) and $1,628 [22] (with 16% of cases

hospitalized). However direct costs per case in the reviewed outbreaks in the US, which included the public health costs of outbreak control, were $29,809 [4]; $4,302 [5] and $1,991 [25]. The respective hospitalization rates were 5%, 6% and 18%. These cost estimates from outbreaks are on average higher than the ones obtained in COI studies or used in economic evaluations. This may imply that he average costs per case (especially for non-hospitalized cases) might be underestimated in economic analyses. In one outbreak massive post-exposure prophylaxis costed $250,881 per reported case. Disease control costs can be a substantial component of total costs, especially if the outbreak was related to a food handler.

Based on the published costing studies of outbreaks, it remains difficult to estimate a value that can serve as a general approximation for outbreak control costs for inclusion in economic analyses. Only a small proportion of outbreak control measures can be considered as fixed cost, e.g. the costs of school cleaning interventions or public notification campaigns. On this fixed part, little is documented in the articles we reviewed. The bulk of the control costs are variable (i.e. related to the size of the outbreak), dependent on the main source of the outbreak (foodhandler or not) and the control strategy that was chosen. Bauch et al [17] were the only economic evaluation to include the costs for outbreak control and estimated these at $355 per case. This could represent a good estimate of disease control costs in school outbreaks, but if there is a food handler involved, these costs could be significantly higher. Control strategies with massive public notification can provoke panic and this can lead to an overconsumption of prophylaxis, as was the case in Denver. Implementing no outbreak control measures, as was the case in Puglia, can still turn out to be very costly.

Many authors of the studies under review emphasized the difficulties in gathering the required information. Outbreaks are often documented from an epidemiological point of view, but the collection of cost data remains very rare. For instance, on only one of 16 outbreaks that occurred in Canada between November 1998 and September 2004, information on the public cost of the incident was available [10]. Information on private medical consumption is even harder to retrieve.

The outbreaks described in the literature could be subject to publication bias since outbreaks with an exceptional impact may stimulate interest in economic analysis more than the “average outbreak”. However these give in any case an indication of the upper boundaries of such events, and the

information they provide are likely to become more important in choosing cost-effective programs for the prevention of hepatitis A. In most high-income countries, typically situated in areas of (very) low HAV endemicity, uptake rates of HAV vaccination remained low, except in a number of risk groups (such as health care personnel and travellers to high endemic areas). However, the proportion of susceptible persons in the population increases as people experience an overall lower force of infection, especially during childhood. In view of this, in these populations, importations of HAV infection giving rise to outbreaks may become the only indication of local HAV transmission in the future. At present, it remains difficult to predict whether these outbreaks will occur more frequently or infect more people compared to outbreaks in the past. Nonetheless, model-based economic evaluations of options for HAV vaccination would need to assume the frequency and size of future outbreaks, as well as estimate their costs, especially in countries where HAV is no longer endemic.

In the outbreaks described here, local economies had to face a cost ranging from $140,000 to $36 million over a short time span. The COI estimates in the outbreak studies seem to be higher than estimates produced for sporadic cases. Post exposure prophylaxis is a major cost factor, especially for food borne outbreaks. Economic evaluations (eg, cost-effectiveness analyses) often ignore these costs. If the epidemiological situation, for which such an evaluation is designed, makes it unlikely for an outbreak to occur, or if it is likely that outbreaks remain very small (and non-food borne), then the exclusion of outbreak-specific costs may remain an acceptable analytical choice. Otherwise, analysts aiming to determine the most cost-effective option for HAV prevention, should attempt to estimate such specific costs as accurately as they can. Clearly, in view of the general paucity of HAV outbreak costing studies, more such studies are needed, especially in countries of low endemicity where outbreak costs would matter the most for the cost-effectiveness of universal vaccination strategies.

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Chapter 8: Cost-effectiveness of hepatitis A vaccination for adults in Belgium

Abstract: Hepatitis A vaccination targeting adults (or adult risk-groups like e.g. travellers, health care workers, soldiers or teachers) could be considered an alternative to a universal infant or adolescent vaccination program in low endemic countries. We estimated the current disease burden of hepatitis A in Belgium, and evaluated whether adult vaccination is cost-effective. A Markov cohort model was used to simulate the costs and effects of (1) vaccination of adults and (2) serological screening of adults and vaccination of susceptibles and we compared these with the current situation. The results indicated that these expanded vaccination strategies are not cost-effective in the epidemiological circumstances of a typical low-endemic western country. In order to gain 1 quality-adjusted life year, the health care payer would have to pay 185,000€ for vaccination and 223,000€ for screening and vaccination of seronegatives. For adult vaccination to be cost-effective, risk-groups would need to be exposed to a force of infection that is 3.5–4 times higher than currently estimated in the general population; or the total costs of vaccination would have to drop with approximately 75%.

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8.1 Introduction

With about 1.5 million reported cases annually, hepatitis A is one of the more common vaccine-preventable infectious diseases in the world [1]. The virus is transmitted from person to person via the faecal-oral route and through ingestion of contaminated food or drink. After an average incubation period of a month, symptoms like fever, fatigue, dark urine, jaundice, nausea and abdominal pain may occur [2]. Whereas an infection with Hepatitis A Virus (HAV) is often asymptomatic in children, older people more often experience severe morbidity [3]. Although most patients recover fully, the disease can be severe and hospitalisation may be required. Exceptionally an HAV infection can give rise to fulminant hepatitis (which requires liver transplantation), hepatic coma and death. Although there exists no effective treatment, and the associated medical treatment costs per patient tend to be small, the economic burden can be significant. Indirect costs are substantial and outbreak control costs can have a large impact on health care budgets [4].

The incidence of infections with HAV has been declining in most parts of the world during recent decades [5, 6]. This decline has generally been attributed to improvements in hygienic, sanitary, and socio-economic circumstances. The introduction of a safe, well-tolerated and effective vaccine might have an auxiliary effect [7]. Paradoxically, this decline also implies that more children grow up without prior exposure to hepatitis A, leading in the future to a larger group of susceptible adolescents and adults that may experience more severe clinical symptoms when infected with HAV [8]. Societal evolutions such as increased globalisation, migration and modified travel patterns increase the risk of importing HAV from high into low-endemic areas. This may cause outbreaks with potentially serious medical and economic consequences.

On the other hand, a universal immunization program may be considered undesirable in low incidence countries because of the substantial programme costs. Furthermore, since Belgian parents have expressed opposition to overcrowding of the schedule [9], there is a concern that an additional childhood vaccine injection may negatively influence the uptake of other possibly more needed vaccines. Therefore it is relevant to evaluate the cost-effectiveness of an immunization program for a cohort of adults in general, or for specific risk groups in particular such as health care workers, teachers, soldiers or frequent travellers.

Through the Health Care Knowledge Centre, the Belgian Minister of Health requested an analysis to establish whether the evolution of the epidemiology, of prices, and of treatment practice could warrant government-funded vaccination of adults. In this paper we report the findings of the cost-effectiveness analysis that was commissioned to address this policy question, using representative current day HAV-data (on epidemiology, health-related quality of life, outbreak control costs and health care consumption) and a generic approach distinguishing levels for the risk of infection in adults. Belgium has evolved since the 1980s to a typical country of low-endemicity for hepatitis A, with very low prevalence of hepatitis A virus immunity in children and teenagers (with the exception of Maghreb country immigrant clusters) [10].

8.2 Data and methods

8.2.1 Study design

We evaluate three strategies for Belgium: (1) vaccination of an entire cohort of 100 000 adults at age 20 (the presumed average age of entering of the labour market), (2) serologic testing of the cohort at age 20 and vaccination of those who are seronegative or (3) no preventive program. We assumed a two-dose vaccine schedule with 6 months between administrations [11]. The costs and effects of each strategy were simulated using a Markov-cohort model (see below).

8.2.2 Data sources

To estimate the parameters for the model we made use of the following data sources.

Prospective survey. We retrieved input data for costs, health-related quality of life and clinical symptoms, by setting up a two-stage survey that was sent to all HAV infected cases, notified to the department of control of infectious diseases from 1st February 2008 until the 1st February 2009. Since in Belgium physicians have a legal obligation to notify any hepatitis A infection, we believe that with our prospective survey design we were able to reach a representative sample of infected persons. A first survey included the Euroqol [EQ-5D [12]], to estimate the quality of life impact at the

time of administration. The EQ-5D is a standardized health measurement questionnaire consisting of 5 health dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), which allows valuing a patient's present health state in a single score. It is explicitly endorsed in the Belgian guidelines for economic evaluation [13]. This survey was sent to the patient immediately after notification, and thus reached patients within the first week after notification. A second survey was sent three weeks after the first survey and gathered information on the symptoms, the total consumption of medical care over the entire episode, characteristics of the patient and the description of their health state during the last month [measured with the SF-12v2 health survey [14]. The SF-12v2 is an alternative standardized health measurement questionnaire which also allows calculating a patient's health score, but on six dimensions (physical functioning, pain, role limitations, mental health, social functioning and vitality) and in a retrospective design (e.g. with a recall period of 4 weeks). Both waves of the survey carried a unique code, so that they could be coupled on a per-patient basis. In total we received 161 responses (response rate: 39%). For 111 patients we were able to calculate a valid EQ-5D estimate of Quality-Adjusted Life Years (QALYs), i.e. no missing items on the EQ-5D plus a response on the number of days of illness (valid 111/invalid 29). For 114 respondents we were able to calculate a valid SF-6D score, i.e. all necessary items on the SF-12v2 were filled in (valid 114/invalid 20). For 96 patients we were able to obtain a valid estimate of Quality-Adjusted Life Years (QALYs) for both the EQ-5D and the SF-12v2 survey. For more elaborate info on these data and methods we refer the reader to Luyten et al [15].

Hospital Billing Data (HBD). The HBD is a mandatory database for all Belgian hospitals which contains clinical data from the hospitals linked on a yearly base to the hospital reimbursement claims data from the Belgian national health insurers. We used information on diagnoses associated with hospitalisations [International Classification of Diseases - ninth revision (ICD9) codes 070.0 'Viral hepatitis A with hepatic coma', 070.1 'Viral hepatitis A without mention of hepatic coma' and combinations of 070.1 with 5722 'hepatic coma'], as well as the associated costs to the health care system [16].

Death-certificates. We also obtained access to data from death-certificates in Flanders. The information we obtained related to deceased individuals whose death certificate contained ICD9 codes in relation to hepatitis A (070.0, 070.1, 5722) during the period 1999-2005.

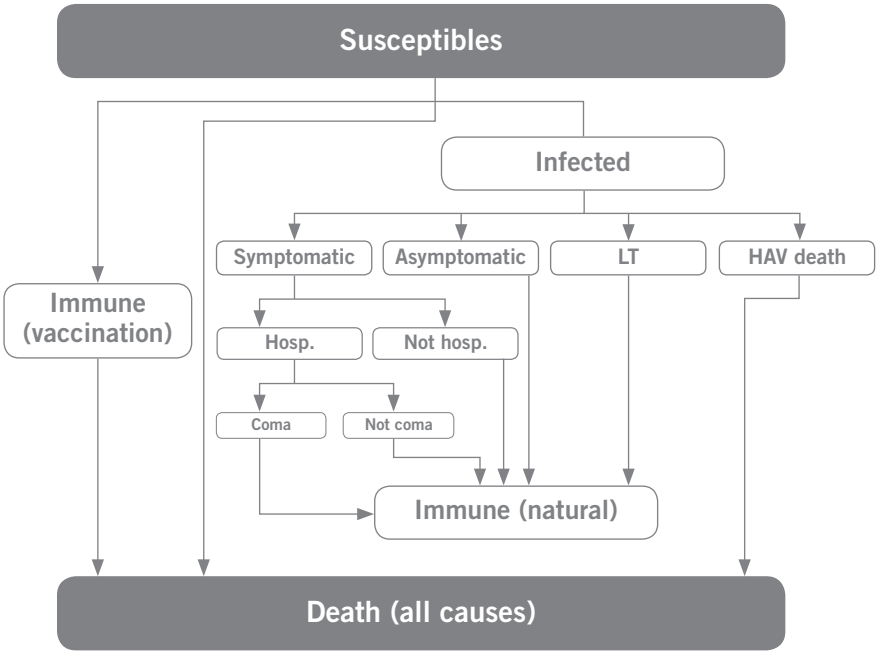
Belgian transplant centres and European Liver Transplant Registry. Information on liver transplantations for hepatitis A was obtained from the European Liver Transplant Registry (ELTR), which keeps track of liver transplantations carried out in Europe. Since liver transplantations for hepatitis A are always urgent, the ELTR has a specific code A1: "acute hepatic failure: fulminant or subfulminant hepatitis A". Basic information on the liver transplantations reported to the ELTR under the above code A1 were provided to us for the period 1987-2007. In addition we obtained directly from all Belgian transplant centres information on the liver transplantations they performed for hepatitis A since 2000 in order to verify the ELTR data for Belgium.

Expert opinion. Four independent specialists internal medicine (3 of which were hepatologists) were asked to validate our interpretation and use of the data we obtained from the general databases (i.e. on hospitalisations, transplantations and deaths).

8.2.3 Model

We developed a static Markov model in MS Excel 2007 to calculate the expected costs and effects associated with hepatitis A infections in a single cohort that is followed from age 20 until age 100 years. The choice for a static Markov model can be justified because herd-immunity effects are negligible by vaccinating a relatively small and disperse group of susceptibles [17, 18]. The cohort is modelled to progress and/or regress between different relevant disease stages according to age, from the average age at entry in the target group in question, until death (distinguishing deaths from hepatitis A from other causes). The transition between the depicted states (**Figure 1**) was determined by annual age-specific rates. The fraction of the cohort in the state "Infected" is used to calculate, at each age in years, quality of life weights in specific health states and unit costs (according to age-specific probabilities), as explained in the next sections.

Figure 1: **Structure of the Markov-model**



8.2.4 Input parameters

The parameters that were used are summarized in **Table 1.**

The *force of infection*, i.e. the per-susceptible rate of infection, was estimated in a separate dynamic transmission model based on seroprevalence data and data on outbreak-related notifications in Belgium. More details on this model are to be found elsewhere [10].

Transition between disease states. For the purpose of our model, we distinguished disease states as shown in Figure 1. Infections are either symptomatic or asymptomatic. Armstrong et al. [19] estimated the age-specific probability that an infected case becomes jaundiced. We combined this estimate with our specific survey results. Based on the symptoms described by respondents, we derived the fraction of those with a symptomatic hepatitis A infection, who experienced jaundice. We combined our with Armstrong et al's estimates, to obtain the probability

of a symptomatic infection. Symptomatic patients are either hospitalised or non-hospitalised. The incidence of hospitalisation was based upon the number of hospitalisations with a diagnostic code of hepatitis A in the HBD database (codes 070.0, 0.70.1 and 5722). For hospitalised cases, we distinguish those with hepatic coma (ICD9 070.0 and ICD9 070.1 in combination with 5722) or without hepatic coma (ICD9 070.1). This fraction was based on a selection of 300 hospitalisations in the HBD that can be exclusively attributed to hepatitis A infection [10]. The outcomes of death and liver transplantation were directly related to the entire infected population according to age, and are thus modelled independently from other disease states.

Health-related quality of life. The health related impact of hepatitis A on quality of life was derived using four conceptually different methods. We undertook a Euroqol (EQ-5D) survey among notified cases in their first week of illness and obtained the number of days of illness three weeks after the first survey. To estimate the quality of life, we assumed a linear health improvement (method I: EQ-5Dlin) and a constant health state (method II: EQ-5Dcon). Four weeks after notification we also obtained the SF-12v2 (which can be reduced to the SF-6D for use in economic evaluation) with a four-week recall period. We had the choice between a parametric (method III: SF-6DP) [14] and a non-parametric (method IV: SF-6DNP) scoring algorithm [20] to estimate QALY losses through the SF-6D. We use the EQ-5D with constant health state for the base case, and show the influence of applying the other methods in the sensitivity analysis. Non-hospitalised patients on average had an EQ-5D utility score of 0.56 and were sick for 17 days. Hospitalised patients scored 0.364 on the EQ-5D utility scale and were sick for 21 days. To hospitalised patients with hepatic coma we assigned a EQ-5D utility score of -0.01 conform the Belgian baseline EQ-5D estimates for comatic patients. We assumed these patients were also ill for 21 days.

Deaths. The number of deaths attributable to HAV is not directly traceable in existing Belgian databases. We had access to 2 separate datasets, which allow inferences to be made. First, we extracted data from the HBD database, of all Belgian "in-hospital-deaths", which through their diagnostic code could be linked to an infection with HAV for the period 2000-2004. Second, we used death certificate data of residents in the Flemish region for whom infection with Hepatitis A or unspecified viral hepatitis was registered as a cause of death during the period 1999-2005. The HBD cover all Belgian

hospitalised patients with a diagnosis of hepatitis A, including those who died in the hospital. In order to estimate the number of these in-hospital-deaths that are actually attributable to HAV, we asked four clinical experts (3 hepatologists, 1 internal medicine) to give their opinion on which patients most probably died because of their hepatitis A infection. This yielded a mean number of HAV deaths per year between 1 (based on the HBD data) and 3 to 4 (based on the death certificates) in a population of 10.6 million people [21].

Liver transplantation. Summarising the Belgian data for the period 2000-2008, we conclude there were at least 3 liver transplantations necessitated by hepatitis A (based on individual centres' reporting), and possibly 9 (based on the Minimal Clinical Data), or between 0.33 and 1 per year, on average. In the simulation model we assume therefore that in Belgium the occurrence of HAV liver transplantations currently varies between 0.33 and 1 per year.

Vaccine and screening test. To date, several million doses of hepatitis A vaccines have been administered to children and adults worldwide, with no serious adverse event statistically linked to their use [22]. The protective efficacy of inactivated hepatitis A vaccines against disease has been documented in several controlled clinical trials [22, 23]. Hepatitis A vaccine has a recommended 2-dose schedule, with a 6-18 month interval between both doses. With regards to duration of immunity, long-term follow-up studies have shown persistence of protective anti-HAV antibodies for at least 15 years in adults, post-vaccination [3]. Mathematical models using data from vaccinated adults have estimated protective antibodies to persist for at least 25 years in more than 95% of vaccines [23-25]. In this analysis we assumed that there was no waning of the vaccine-induced protection (cfr. infra). Relevant parameters on serologic screening were based on Desbois et al. [26]. Based on current practice, we estimated two GP visits would be charged to administer a full two-dose vaccination schedule. We assumed that for a screening test an additional third GP consultation would be required.

Direct costs. All costs are expressed in Euros for 2008. We obtained the outpatient cost from our prospective survey. Consumption of these resources was valued using unit cost data provided by the Belgian Centre for Pharmacotherapeutic Information [27]. In our sample of 300 patients that were hospitalized for HAV infection, the mean cost incurred for hospitalization is €1,401, the median €1,262, and the range € 316 – €4,182

for all age groups. The subgroup of patients >14 years (N=160) incurred a mean inpatient cost of €1,527 per patient (median 1,447€) [10]. The costs of liver transplantations were based on Ratcliffe et al [28]. The immunization costs consisted of the price paid for the vaccine and the administration costs. In contrast with previous analyses [with exception of Bauch et al [29]], we included the disease control costs of vaccinating close contacts of infected cases [30]. For every infected person in our sample, on average 3 other persons in their vicinity were vaccinated out of precaution. This public health cost constitutes 58 % of the total direct costs per HAV case.

Indirect costs. The indirect costs were estimated by multiplying the number of workdays lost per case, with the average productive value per day in the part of the population that is potentially employed, i.e. the age group 18-65. In our survey patients were asked for the number of workdays lost due to their hepatitis A episode. Not only was the number of lost workdays by symptomatic cases considered, also the number of lost workdays for people, who were assisting the infected patient, was included. Retired people were assumed to be assisted by someone who is also retired, meaning that there was no indirect cost involved for patients above 65.

All costs and health gains of the intervention that would occur in the future were annually discounted conform the Belgian pharmacoeconomic guidelines [13] at 3% for the costs and 1.5% for the health gains, respectively. Other discount rates were used in the sensitivity analysis.

Table 1: Age-specific estimates of epidemiological, disease progression, quality of life and resource use parameters, distributions and sources*

Parameter	Age	Estimate	90% interval	Distribution	Source
ANNUAL FORCE OF INFECTION					
	20-30	0.00015	NA	NA	Dynamic model estimates [10]
	above 30	0.00011	NA	NA	Dynamic model estimates [10]
DEATHS					
1. basecase scenario					
number of HAV deaths 1999-2005 (Flanders)	20-30	0.5	[0.05-0.95]	Uniform	Death certificates for Flanders 1999-2004
	above 30	14	[9.5-18.5]	Uniform	Death certificates for Flanders 1999-2004
probability to die from HAV 1999-2005	20-30	0.0000000648	0.0000000003 - 0.0000002491	Beta	Death certificates for Flanders 1999-2004 + expert opinion (N=4) + demographic data
	above 30	0.000000506	0.00000031 - 0.00000075	Beta	Death certificates for Flanders 1999-2004 + expert opinion (N=4) + demographic data
Mean annual number of HAV deaths Belgium	20-30	0.13	/	/	Death certificates for Flanders 1999-2004 + 4 experts + demographic data
	Above 30	3.40	/	/	Death certificates for Flanders 1999-2004 + 4 experts + demographic data
2. Alternative scenario					
Number of HAV deaths 2000-2004	20-30	0.33	(0.025 - 0.776)	Triangular	MCD data 2000-2004 + 4 experts
	above 30	6.33	(2.33 - 12.09)	Triangular	MCD data 2000-2004 + 4 experts
Probability to die from HAV 2000-2004	20-30	0.000000034189	(0 - 0.0000001511)	Beta	MCD data 2000-2004 + 4 experts
	above 30	0.000000188705	(0.0000000844 - 0.0000003265)	Beta	MCD data 2000-2004 + 4 experts
Mean anual number of HAV deaths Belgium	20-30	0.07	/	/	MCD data 2000-2004 + 4 experts
	Above 30	1.27	/	/	MCD data 2000-2004 + 4 experts

LIVERTRANSPLANTATIONS					
Number of livertransplants 2000-2004 in Belgium	20-30	1	[1-1]	Triangular	Belgian transplant centres + ELTR
	above 30	1.67	(1.051-2.553)	Triangular	Belgian transplant centres + ELTR
Probability of livertransplant from HAV 2000-2008	20-30	0.000000057	(0.0000000029 - 0.0000001707)	Beta	Belgian transplant centres + ELTR + demographic data
	above 30	0.000000028	(0.0000000038 – 0.0000000694)	Beta	Belgian transplant centres + ELTR + demographic data
Mean annual number of livertransplants in Belgium	20-30	0.11	/	/	Belgian transplant centres + ELTR + demographic data
	Above 30	0.19	/	/	Belgian transplant centres + ELTR + demographic data
DISEASE STATES					
Symptomatic rate	20-100	[0.91-0.94]	NA	NA	Prospective survey (N=67) [19]
Proportion jaundiced/symptomatic	20-100	0.91	(0.85-0.96)	Beta	prospective survey (N=67)
Proportion hospitalised/infected	20-30	0.0687	NA		MCD, subgroup selection (n=300), dynamic model calibration
	above 30	0.0475	NA		MCD, subgroup selection (n=300), dynamic model calibration
Proportion coma/hospitalised	20-100	0.01	(0.00812 – 0.02332)	Beta	MCD, subgroup selection (n=300)
QUALITY OF LIFE SCORE					
Patients without coma					
A. EQ-5D					
Not hospitalised	20-100	0.556	[-0.166 - 1]	Discrete	EQ-5D, prospective survey (n=64)
Hospitalised without coma	20-100	0.364	[-0.166-1]	Discrete	EQ-5D, prospective survey (n=21)
B. SF-6D					
Parametric scoring algorithm					
Not hospitalised	20-100	0.642	[0.448-0.922]	Discrete	SF-6D, retrospective survey (n=58)
Hospitalised without coma	20-100	0.734	[0.4930-0.9370]	Discrete	SF-6D, retrospective survey (n=19)
Non-parametric scoring algorithm					
Not hospitalised	20-100	0.608	[0.463-0.857]	Discrete	SF-6D, retrospective survey (n=58)

Hospitalised without coma	20-100	0.695	[0.499-0.911]	Discrete	SF-6D, retrospective survey (n=19)
Comatic patients	20-100	-0.016	NA	NA	EQ-5D, [31]
Patients with livertransplantation					
In the hospital (days after LT)	20-100	0.368	NA	NA	[28]
3 months after LT	20-100	0.576	NA	NA	[28]
6 months after LT	20-100	0.601	NA	NA	[28]
12 months after LT	20-100	0.626	NA	NA	[28]
24 months after LT	20-100	0.629	NA	NA	[28]
COST ESTIMATES					
Direct costs non-hospitalised patient	20-100	€690	[€0.1 - €1584]	Log Normal	Resource consumption: Prospective survey (N=64) Unit costs: [27]
Indirect costs non-hospitalised patient	20-100	€2994	[€210 - €6962]	Triangular	Resource Consumption: Prospective survey (N=64) unit costs: [48]
Direct costs hospitalised patient	20-100	€1527	[€581 - €2852]	Weibull	MCD-MFD, specific selection (n=300)
Indirect costs hospitalised patient	20-100	€3272	[€250- €7620]	Triangular	Resource consumption: Prospective survey (N=21) Unit costs: [48]
Direct cost per liver transplantation	20-100	€80680	NA	NA	[49]
Indirect costs livertransplant	20-100	€21389	NA	NA	[48, 49]
VACCINE AND SCREENTEST					
Coverage vaccine		0.95	NA	NA	[50]
vaccine protective efficacy		0.95	(0.90-0.99)	Beta	[51]
Vaccine price (Havrix)		€45.66	NA	NA	[27]
sensitivity screening test		0.98	(0.980-0.995)	Uniform	[26]
specificity screening test		0.99	(0.994-0.999)	Uniform	[26]
compliance test (min-max)		0.5-0.8	(0.51-0.78)	Uniform	Our assumption
Price screening test		€22.4	NA	NA	Personal communication medical lab
Health personnel costs		€21.5	NA	NA	[52]

* The estimates and intervals used in this table are a result of distributions that were fitted to the observations in accordance to the guidelines for health-economic evaluations given in Briggs, Claxton & Sculpher [53]

Table 2: **Cost-effectiveness ratio's for three strategies using different effect measures: results from 10,000 simulations (in €)**

	Vaccinate vs. Do nothing				Screen and Vaccinate vs. Do nothing				Vaccinate vs. Screen and Vaccinate			
	Mean	Median	5th perc.	95th perc.	Mean	Median	5th perc.	95th perc.	Mean	Median	5th perc.	95th perc.
HEALTH CARE PERSPECTIVE												
Cost/QALY gained	203,454	185,378	112,394	352,860	248,623	223,815	136,090	428,947	103,649	108,086	32,174	258,131
Cost/infection saved	35,961	35,263	31,001	42,337	44,025	42,632	37,793	50,801	18,526	21,608	6,825,443	36,517
Cost/hospitalisation saved	1,151,381	1,118,059	859,207	1,536,074	1,413,693	1,351,129	1,043,066	1,851,552	593,958	667,304	211,753	1,228,060
Cost/life year saved	231,227	208,707	125,770	410,068	282,041	251,466	152,403	497437	117,651	122,376	36,129	295,605
Cost/death averted	5,396,215	4,863,489	2,919,680	9,629,622	6.581.409	5,855,648	3,536,977	11,681,330	2,743,383	2,848,812	842,288	6,922,633
SOCIETAL PERSPECTIVE												
Cost/QALY gained	192,338	175,091	104,994	334,158	237,507	213,119	128,802	409,804	92,533	97,849	22,476	240,949
Cost/infection saved	33,993	33,431	28,241	40,827	42,058	40,771	35185	49,088	16,558	19,512	4,594,295	34,753
Cost/hosp saved	1,088,490	1,055,766	795,552	1,477,941	1,350,803	1,287,210	984,175	1,787,069	531,068	605,262	144,907	1,170,996
Cost/life year saved	218,580	196,771	117,731	388,644	269,394	239,568	145,024	476,355	105,004	110,462	25,746	278,414
Cost/death averted	5,100,978	4,577,651	2,735,103	9,122,254	6,286,172	5,581,488	3,366,165	11,160,740	2,448,145	2.576.041	607,327	6,476,877

Table 3: **Sensitivity analyses: Direct costs per QALY gained from the health care payer perspective (in €)**

	"Vaccinate" vs. "Current strategy"				"Screen + vacc" vs. "Current strategy"				"Vaccinate" vs. "Screen + Vacc"			
	Mean	Median	5th percentile	95th percentile	Mean	Median	5th percentile	95th percentile	Mean	Median	5th percentile	95th percentile
Basecase	203,454	185,378	112,394	352,860	248,623	223,815	136,090	428,947	103,649	108,086	32,174	258,131
Discount rates												
0% costs 0% effects	102,790	95,643	58,263	170,984	124,565	115,980	71,650	204,428	58,782	53,907	18,701	112,565
3% costs 0% effects	106,316	97,802	59,357	186,150	128,102	117,580	71,619	223,280	62,297	58,250	20,763	113,691
3% costs 3% effects	349323	321,389	195,695	595,748	422,189	388,547	236,491	717,247	202,652	188,150	64,862	393,235
5% costs 5% effects	689,920	639,863	365,876	1,182,291	832,414	778,252	447,482	1,438,997	403,838	364,551	133,935	789,074
Deaths												
MCD-data	582,178	441,767	191,628	1,342,063	703,345	528,659	229,807	1,624,204	337,456	243,427	71,952	824,860
Force of Infection scaling factor												
*2	99,459	91,474	55,070	174,858	118,855	109,369	66,263	209,388	60,580	55,892	21,470	113,615
*4	49,715	45,737	27,919	85,443	58,840	53,972	33,299	99,471	31,480	28,584	11,332	59,376
*6	32,956	30,127	17,646	55,616	38,642	35,509	20,952	65,393	21,518	19,437	9,129,169	1,170,996
Total vaccine and test costs												
50% reduced vaccine and test price	129,492	118,165	71,332	220,764	162,495	148,976	91,806	278,870	62,250	59,876	8,589,464	128,045
50% reduced total costs	98,158	89,239	55,843	173,309	118,073	107,150	66,989	208,275	57,994	52,811	19,230	117,454
75% reduced total costs	47,592	43,477	27,274	78,632	57,547	52,797	32,835	95,909	27,527	25,263	8,491,911	53,901
Other QoL valuations												
EQ-5D linear	215,772	198,136	121,267	369,106	260,836	238,437	147,391	447,531	124,806	115,961	40,314	237,326

SF-6D (par.)	188,667	176,608	112,372	306,417	226,104	211,553	136,278	364,410	112,217	105,053	40,482	205,571
SF-6D (non-par)	185,643	174,487	112,000	297,017	222,870	209,468	134,658	357,971	110,462	104,138	39,745	201,044
Combinations												
50% total cost and FOI * 2	48,311	44,628	26,763	82,716	57,994	53,436	32,193	98,590	28,689	26,531	9,245,791	55,727
SF-6D (par) and FOI * 2	94,114	88,001	55,314	150,006	112,383	105,189	66,822	180,506	57,212	52,971	19,083	10,5478
SF-6D (par) and FOI * 3	62,669	58,258	37,522	99,336	74,543	69,666	45,182	120,642	38,761	35,641	14,984	70,677
SF-6D (par) and 50% total costs	92,871	87,581	55,717	147,244	111,734	105,442	67,966	176,692	54,649	51,761	19,228	98,726

8.3 Results

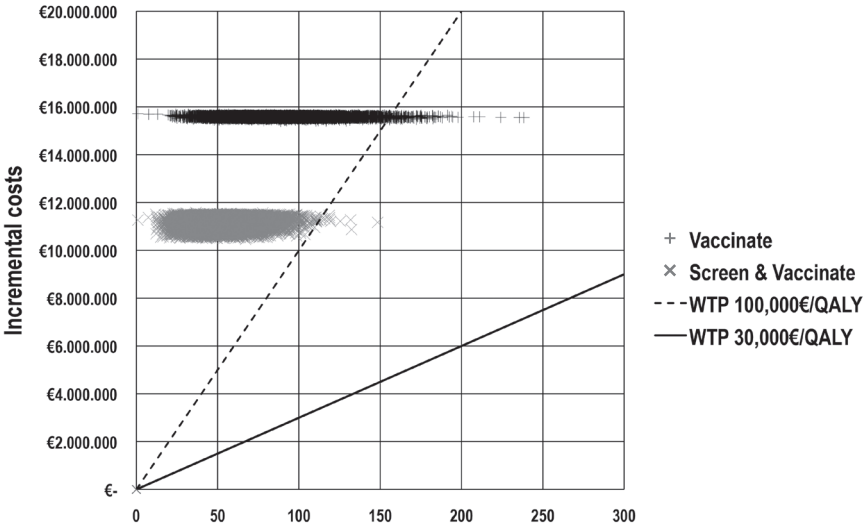
8.3.1 Base case analysis

The following analysis is the result of 10.000 Monte-Carlo simulations. Due to the existence of occasional distribution-driven outliers, we focus in the results on the median of the Incremental Cost-Effectiveness Ratios (ICER's). An ICER indicates how the extra health benefits generated by an intervention relate to the extra costs they incur.

In comparison to current practice (i.e. no subsidized HAV vaccine), it would cost the health care payer €185,000 (CI: €112,000 – €352,000) in order to gain one QALY by subsidizing adult immunization against HAV. The total cost of the program would be 15 600 000€ and it would generate 85 QALYs. Screening first and vaccinating the seronegatives would cost €223,000 (CI: €136,000 - €428,000) in order to gain one QALY. The total cost of this program would be 11 190 000 and it would generate 50 QALYs. There is extended dominance (weak dominance) of the strategy "vaccinate" over the strategy "screen & vaccinate" because vaccination has a more favorable ICER and it yields a higher number of QALYs gained.* Compared to a screening and vaccinate strategy, vaccination of everyone in the target cohort would cost the health care budget €108,000 (CI: $32,000 – €258,000) per QALY gained. The societal perspective, which includes the indirect savings in time costs due to lost work days, yielded results that were about €10,000 per QALY less expensive than the health care payer results. Table 2 also shows ICERs in other health outcomes than QALYs.

* There is strong dominance of one strategy over another when an intervention has lower costs and better effects. Extended dominance occurs when one strategy yields more incremental QALYs (better effects) at a more attractive cost-effectiveness ratio. The interpretation of extended dominance is that a policy maker with a willingness to pay per QALY that is big enough to include the weakly dominated strategy would be irrational not to choose the dominating strategy which has a more favorable ICER and better effects (making abstraction from budget impact).

Figure 2: **Cost-effectiveness plane showing incremental costs and incremental QALYs for the strategies "vaccinate" and "screen & vaccinate" from the health care payer perspective (results from 10 000 Monte Carlo Simulations). The reference lines represent a societal willingness to pay of 30,000€ and 100,000€ per QALY.**

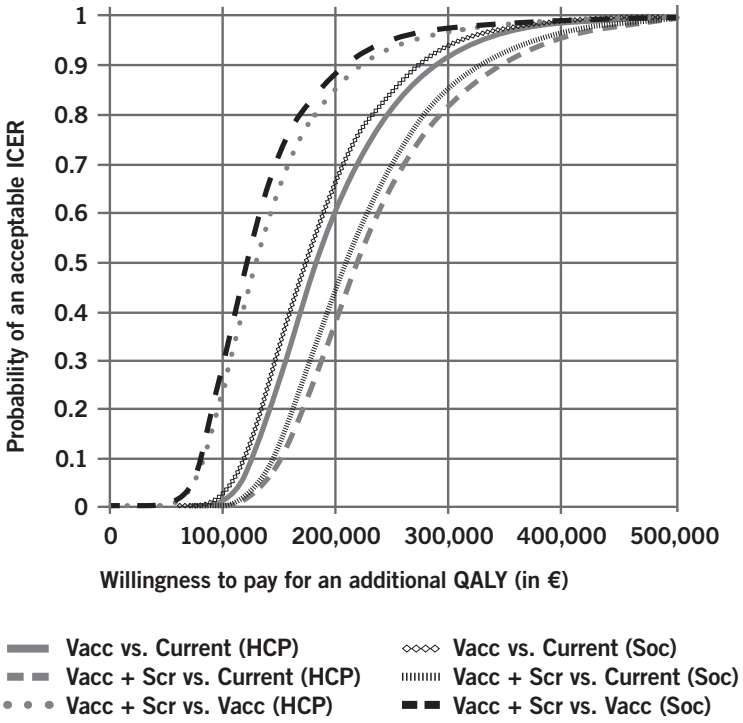


8.3.2 Sensitivity analysis

In order to determine the effect of uncertainties in parameter values we conducted a probabilistic sensitivity analysis by using @RISK, a simulation add-in for MS EXCEL. 10,000 simulations were run from the distributions of each input variable in order to calculate 10,000 ICER's that fall within the range of reasonable possibilities.

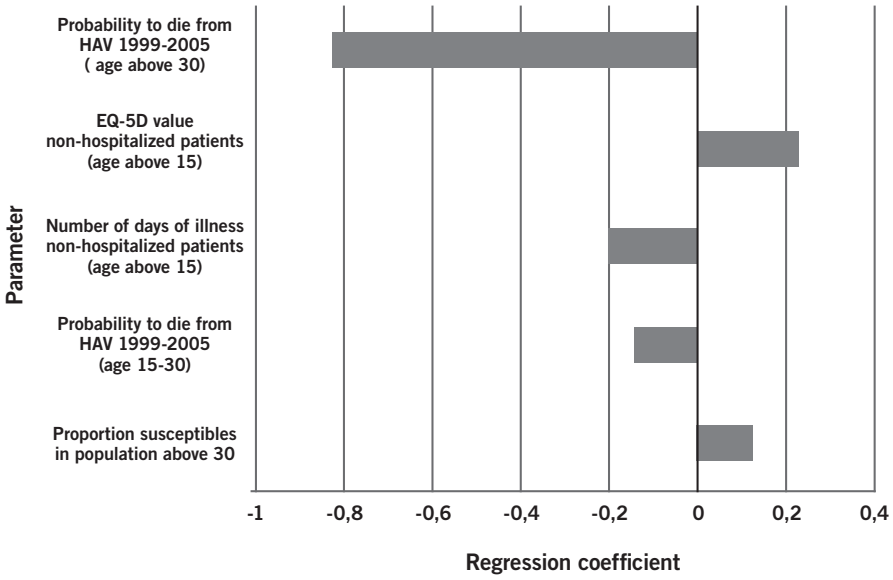
Figure 3 presents the cost-effectiveness acceptability curves for the different strategies. In order for policy makers to justify a decision pro vaccination on efficiency grounds, they have to judge that the societal willingness to pay for an additional QALY is approximately €170,000 to €180,000 per QALY gained (i.e. the point at which 50% of the simulations show the ICER to be lower, depending on the perspective). For screening and vaccination, the required willingness to pay would amount to €210,000 up to €220,000 per QALY gained.

Figure 3: **Cost-effectiveness acceptability curves (CEACs) for three strategies for the health care payer and the societal perspective (results from 10,000 Monte Carlo simulations)**



Sensitivity analyses were performed on all influential parameters in order to investigate the effect of conceptual and data source choices [32]. The model was most sensitive to the 'probability to die from HAV in the age group above 30'. In the base case analysis we used the highest estimate for the number of deaths. If the alternative scenario was used, i.e. the Minimal Clinical Data (with lower mortality), then all ICER's would exceed €400,000 per QALY. Parameters that were to a lesser extent influential were the EQ-5D score and the days of illness in non-hospitalised patients, the probability to die from HAV in the group below age 30 and the proportion of susceptibles in the group above 30 years. The results of a sensitivity analysis can be displayed as a "tornado" chart, with longer bars at the top representing the most significant input variables. Figure 3 shows for one strategy such a tornado chart with the parameters that had the biggest impact on the final cost-effectiveness ratio. In the represented strategy the input variable 'probability to die from HAV' in the age-group above 30 had the largest effect. For the other strategies the variables exerted similar influences.

Figure 4: Tornado chart representing the most influential input variables for the cost-effectiveness results of the strategy Vaccinate vs. Do nothing from the payer perspective.



The coefficients are normalized regression coefficients associated with each input parameter, of which we list the most important in the figure (coefficients > 0.1). A coefficient of 0 indicates that there is no significant association between the input and the output, while a coefficient of 1 or -1 indicates a 1 or -1 standard deviation change in the output for a 1 standard deviation change in the input [33].

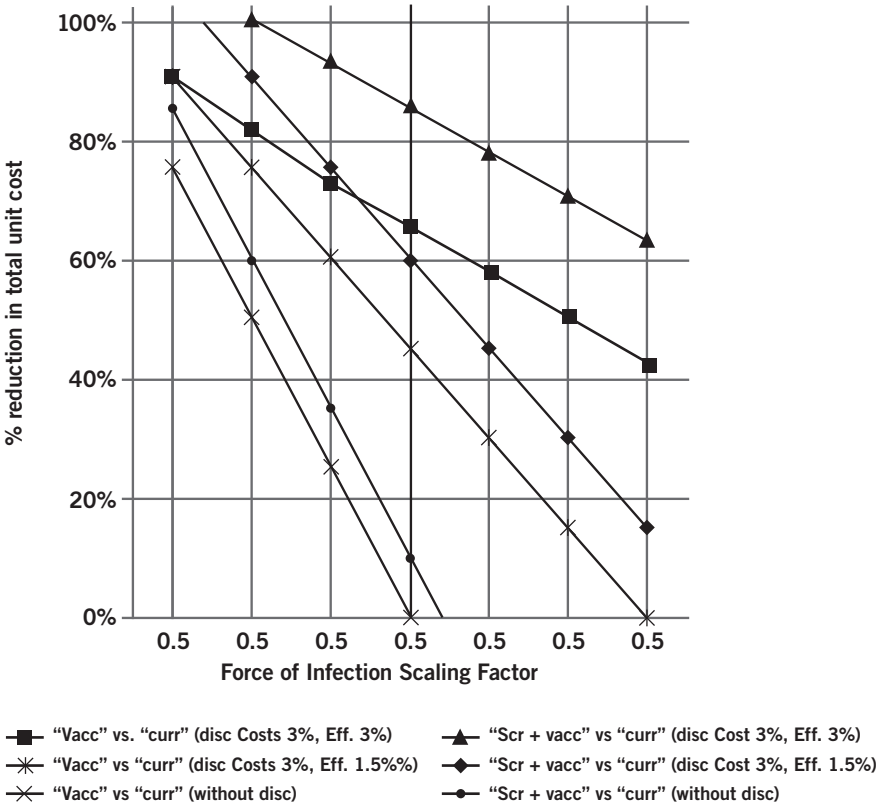
We also investigated the evolution of the cost-effectiveness over time in order to investigate the impact of our assumption that the vaccine offers lifelong protection, but this did not alter the overall picture. The cumulative cost-effectiveness improves with time until it becomes relatively stable approximately 40 years after the intervention.

Use of another method to calculate the QALYs resulting from hepatitis A related morbidity, yielded different ICER's but would not make the results economically attractive. In this study we opted as base case for the EQ-5D score taken in the first week of illness multiplied by the number of days of illness. When we assume that a patient linearly improves his/her health over the period of illness (i.e. gradually recovers instead of assuming a constant health state) the ICERs become slightly less attractive, while using the SF-12 with 4-week recall period (i.e. administered after the disease experience), would make the ICERs more attractive. The results that were obtained by

using these other methods can be found in **Table 3.** For a more in-depth analysis of the impact of using different health measurement methods in cost-effectiveness analyses we refer the reader to the following reference [15].

Threshold analysis (summarized in **Table 3** and **Figure 4**) revealed that, for a willingness to pay of €50,000 per QALY, an adult in a target group needs to be confronted with a risk that is 3.5 times as high as in the general population, in order to make the immunization strategy cost-effective. In order to reach an ICER of about €50,000 per QALY, the total costs of immunization, the screening test and the administration of both, in total had to drop by 75%. Large quantities of vaccines can be bought at a lower price than the current over-the-counter price, but even with 50% reduction in vaccine price, the ICERs would still exceed €118,000 per QALY. At this reduced price, the force of infection needs to be three times as high as currently in the general population in order to generate ICERs below €50,000. A combination of changes in influential variables occasionally showed the median cost per QALY gained to decrease below €50,000, but not below €30,000 (even when the force of infection increased 6-fold). A force of infection twice as high as the current one, would make immunization cost-effective if either no discounting is used or if the total cost of immunization (vaccine plus administration) could be reduced with 50%. The results that we obtained when we compare the strategy "screening + vaccination" to the current practice (no vaccination and no screening) are similar over the entire line but slightly more expensive. **Figure 5** summarizes the combinations of total cost reduction and increased force of infection that generate median ICERs around €50,000 for the strategies "vaccinate" and "screen plus vaccinate". All results were insensitive to changes in any other variables within plausible ranges.

Figure 5: **Combinations of reductions in cost per person of the intervention (price vaccine, price screentest and cost administration) and force of infection scaling factors that generate a median ICER of €50,000 per QALY from the payer perspective (results are medians from 10,000 simulations)**



8.4. Discussion

Anonychuk et al. [30] reviewed economic evaluations on hepatitis A immunization. There were large differences in study design and in crucial epidemiological or economic parameters, which sometimes makes a comparison difficult, but in general similar results were found. Immunization for travellers was found to be cost-effective if they travelled to high-endemic regions [34, 35]. Immunization for health care workers resulted in ICERs over $US 100,000 per QALY or per LY (36-39), except in one study that evaluated the combined hepatitis A/hepatitis B vaccine and with a lower vaccine price [40]. Targeting military personnel was only

interesting when the soldiers were assumed to be regularly or over long periods employed in high-endemic areas [41, 42]. HAV immunization was found to be cost-effective for food handlers in the US [43] or for patients with chronic hepatitis C at young age [44].

Our study indicated the following results. Considering a cost-effectiveness threshold that based on previous funding decisions for most countries would vary between €20 000 and €100 000 per QALY, investing in adult vaccination against HAV (with or without prior screening test) is unlikely to be a cost-effective way of allocating scarce health care resources. In the current epidemiologic and economic circumstances in a western low-endemic country, we found ICERs that ranged from €174,000 to €198,000 per QALY for vaccination and €209,000 to €238,000 for screening plus vaccination of seronegatives, depending on how health benefits were measured. However, variation of certain input variables revealed scenario's for which our conclusions change and prevention becomes cost-effective. Target groups should face a force of infection that is at least 3.5 times greater than in the current situation. This may for instance be the case for frequent travellers to endemic regions or military personnel on a foreign mission in a high incidence area. Schoolteachers or health care workers may also face a higher risk than other adults because of their increased likelihood to be in contact with an infected person. These groups are targeted because they are at increased risk of infection, while they do not play a pivotal role for the transmission dynamics. In sum, if the force of infection is considerably higher than in the general population, immunization of these groups may be considered cost-effective.

For food-handlers, there is an additional consideration. This professional group is faced with a similar force of infection as the rest of the population (and thus vaccinating them to protect themselves is cost-ineffective) but they nevertheless may infect a large number of people through contaminated food [45]. These potential additional benefits were not considered in our analysis. However, it is programmatically difficult to vaccinate all food handlers in Belgium, and the rotation of food handlers in and out of the profession is high, while foodborne outbreaks have been rare and limited in size [10]. Therefore other measures (e.g. strict code of conduct)) are likely to be more cost-effective in a country with overall good hygienic standards than trying to vaccinate all food handlers. However, this requires a continuous education and re-enforcement program with regular inspections, allowing these measures to partially replace and complement protection provided by an immunization program.

Our results were highly dependent on the discount rates used (especially for health benefits). Without discounting, the cost per QALY was halved and target groups need to have a force of infection that is only twice as high in order to become cost-effective. The exact choice of discount rates is an influential factor for economic evaluations of vaccines where the costs are concentrated early in the time period considered and the health benefits can accrue over longer periods [47, 46].

8.5 Conclusion

The incidence of hepatitis A has decreased considerably during the last decades. This has led to a higher number of susceptible adults in western low-endemic countries, in which a hepatitis A infection can lead to more severe morbidity and mortality. With increased possibilities to import the virus from endemic areas, the possibility of extended outbreaks also increases. While a universal immunization program may be considered unnecessary, it could be considered worthwhile to invest in immunization targeted at adults or certain adult-risk groups. This study indicated that such a strategy is not cost-effective in the current epidemiological and economic setting (whether candidates are screened before immunization or not). For adult immunization to be cost-effective, risk-groups would require a force of infection that is 3.5 to 4 times higher than currently estimated in the general population.

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Chapter 9: Public preferences for prioritizing preventive and curative health care interventions: a discrete choice experiment

Abstract: Through a discrete choice experiment we elicited the Belgian adult population's (18-75y; N = 750) preferences for prioritizing health care. We used a Bayesian D-efficient design with partial profiles, which enables considering a large number of attributes and interaction effects. We included the attributes (i) type of intervention (cure versus prevention), (ii) effectiveness, (iii) risk of adverse effects, (iv) severity of illness, (v) link between the illness and patient's health-related lifestyle, (vi) timespan between intervention and effect and (vii) patient's age group. All attributes were significant, with patient's lifestyle and age being the most influential. Interaction effects were found, showing that prevention was preferred to cure for disease in young adults, as well as for severe and lethal disease in people of any age. Substantial preference heterogeneity exists between respondents from different age groups, with different lifestyles and different health states.

9.1 Introduction

Finding a fair match between ever-increasing medical needs on the one hand and finite health care budgets on the other counts among the greatest challenges our societies are facing. Consensus exists that such priority setting should reflect a concern for both efficiency (making maximal use of valuable resources) and equity (avoiding that some people become deprived of their deserved share) [1, 2]. Over the past decades, the concern for efficiency has been operationalized in cost-utility analysis (CUA), informing decision makers on the ratio between incremental costs and incremental Quality-Adjusted Life Years (QALYs) attributable to interventions [3]. Equity, however, remains a much more elusive concept as a large number of contextual considerations of patients, illnesses or interventions could justify a more or less favorable weighing in rationing decisions [4]. Therefore, an important research objective remains to clarify distributive principles that carry social support in order to better align priority setting with societal preferences. With this paper, we contribute to the empirical literature describing the general public's distributive preferences regarding health care. We do so by means of a discrete choice experiment (DCE) held in a representative sample of the Belgian adult population.

Our study is innovative in three ways. First, published studies about preferences for health care resource allocation largely ignored the difference in nature between prevention and cure. However, unlike cure, prevention (i) avoids the intangible costs of experiencing ill-health, (ii) can give rise to substantial externalities, with consequences for efficiency and equity (e.g. herd immunity through vaccination [5]), (iii) is closely related to social justice (e.g. by adjusting social determinants of health) [6] and (iv) is only attributed a small fraction (< 5%) of the health care budget in most countries [7], and may be first to be cut in times of scarcity. In this study, we pay specific attention to the relative value of either type of health care and investigate whether their nature affects rationing principles.
Second, preference elicitation studies predominantly use DCEs. We use a Bayesian D-efficient experimental design with partial profiles, which has the following advantages: (i) it takes into account prior knowledge concerning the respondents' preferences, (ii) it allows estimation of interaction effects, (iii) it results in estimates of the attributes' main effects and interaction effects with maximum precision, (iv) it avoids the use of uninformative choice sets in the DCE and (v) it allows investigating a larger number of attributes without increasing the cognitive burden on respondents.

Third, an important criticism against studies eliciting social preferences is that aggregation covers up important heterogeneity in the ethical views of different respondents [8]. We therefore pay much attention to differences in the preferences of relevant subgroups, via the inclusion of several respondent characteristics as covariates in our analysis.

9.2 Methods

Discrete choice experiments (DCEs) are a widely used technique to quantify individuals' preferences by observing their stated choices in a number of hypothetical scenarios [9, 10]. Respondents are confronted with a sequence of choice sets consisting of two competing options. For each choice set they have to indicate the option they like best. The options are described in terms of a fixed set of attributes or dimensions that differ in their levels. The data from a DCE allow the assessment of the relative importance of each attribute in the total value attributed to the options under valuation. DCEs are predominantly used to elicit personal preferences (for a general review of applications, see [11]), but, in a number of studies, they have also been used to explore a population's social and ethical views regarding priority setting in health care (e.g. [12, 13]; for specific reviews, see [14-16]).
Conducting a DCE involves the following steps: (i) identification of the attributes and attribute levels, (ii) statistical design of the choice sets, (iii) survey development, (iv) sample selection and (v) quantification of and statistical inference about the relative importance of the attributes and attribute levels.

9.2.1 Identification of the attributes and attribute levels

For our research objective, it was important to identify a number of decontextualized, generic characteristics that provide a workable description of both preventive and curative interventions. These characteristics should enable respondents to make a meaningful judgment regarding the moral necessity to reimburse a given intervention. We considered literature review and expert opinion the preferable sources of information. Reviews have classified considerations, potentially relevant for rationing health care programmes, in three groups: characteristics belonging to (i) the patient, (ii) the intervention and (iii) the health condition [14, 17]. We updated a review of DCEs about priority setting [16] and identified 12 DCEs exploring

the social value of health care [12, 13, 16, 18-26]. We reviewed these studies focusing on the attributes used. We observed that all studies used combinations of attributes to indicate (i) what would happen when a patient would not receive care (severity of illness (SOI), expressed in morbidity and/or mortality), and (ii) what would happen in case a patient received care (effectiveness of the intervention/health improvement). Additionally, the studies involved (iii) a cost or budget impact attribute, (iv) the number of patients affected, (v) alternative treatment options and (vi) characteristics of the recipient (mainly age or health-related lifestyle).

The reviewed studies, however, mainly focused on cure, either explicitly or implicitly by shaping a context that is intuitively associated with curing patients, rather than with preventing illness. Therefore, we carried out a separate review of studies aiming to elicit preferences for prevention in order to find additional attributes. In a review of 114 DCEs [11], we found nine specifically applied to preventive interventions such as screening tests or vaccines [27-35]. These nine studies suggested the inclusion of two additional attributes in our DCE, namely (i) the intervention's risk on adverse effects and (ii) the timespan between the intervention and its clinical effect.

A few studies in the literature did compare stated preferences for prevention and treatment (see Section 4) [36-39], but these studies did not provide us with additional attributes. They were all exploratory studies describing interventions in terms of merely one or two dimensions on top of the type of intervention (i.e. health gain [36, 37] and number of patients [40]), or comparisons of preventive and curative interventions in specific circumstances (e.g. food safety or cancer prevention) [38, 39].

In sum, our literature review suggests the following list of nine attributes as most useful to include in our DCE: type of intervention (curative or preventive), effectiveness of the intervention, adverse effects associated with the intervention, SOI, cost of the intervention, number of patients, relation to health-related lifestyle, timespan between the intervention and the expected effect and age group of the patient.

Subsequently, we organized group discussions with convenience samples consisting of researchers (N = 10) and lay persons (N = 14) in which we presented interventions in terms of these nine characteristics to investigate whether (i) we overlooked potentially important attributes and (ii) the

descriptions we used for the attributes and their levels allowed a realistic mental image of a health care program. No additional attributes were considered essential. However, when we presented exploratory choice sets to our test subjects, it appeared that inclusion of all nine attributes made the cognitive burden too large for respondents. Therefore, after re-testing, we decided to exclude the attributes intervention costs and number of patients by mentioning in every choice set that the interventions had the same cost and were beneficial for the same number of patients.

The next challenge was to refine the wording used to describe the attributes and their levels, and to consider other than verbal presentations of the attribute levels. First, we presented all attributes to our convenience sample in various formulations to determine which one was easiest to understand. Since the use of attributes representing risks or chances is cognitively demanding, we considered using visualizations for the levels of the attributes effectiveness, risk on adverse effects and lifestyle instead of verbal descriptions [41]. However, we learnt from our convenience sample that a verbal description was most reliable, because it minimized the cognitive burden imposed on the respondents while still bringing across the intended meaning. Also for the other attributes, we experimented by describing levels using absolute numbers and percentages, and found that the choice task was most intuitive when we described levels verbally.

We utilized three levels for each attribute, except for the attributes type of intervention, which has two levels, and age group of the patient, which has five levels. For the age attribute, we decided against covering all ages and to opt for equally wide age intervals at different stages of life. **Table 1** shows the descriptions of the attributes and their levels used. We presented the attributes one by one to the members of our convenience sample and asked them how they interpreted each attribute. We encountered no difficulties in understanding.

Table 1: **Attributes and levels**

Attribute	Level
What type of intervention is it?	1. preventive (aiming to prevent healthy persons from becoming ill) 2. curative (aiming to cure people who are ill)
How big is the probability of success of the intervention?	1. 1 in 3 is successful (33%) 2. 2 in 3 is successful (66%) 3. always successful (100%)
How often do adverse effects occur?	1. often 2. rarely 3. never
How severe is the illness for which the intervention is developed?	1. not lethal, but everyone who gets the disease will experience a short period of illness without lasting effects (not severe) 2. not lethal, but everyone who gets the disease will experience a severe and lasting reduction in quality of life (severe) 3. lethal, everyone who gets the disease will die from it (lethal)
Does the patient cause the disease through his or her own lifestyle?	1. fully 2. partly 3. not at all
How long does it take before the patient becomes ill/ shows signs/ symptoms of illness?	1. after 20 years 2. after 5 years 3. within a year
At what age does the patient become ill?	1. 80 – 90 years 2. 60 – 70 years 3. 40 – 50 years 4. 20 – 30 years 5. 0 – 10 years

9.2.2 Experimental design

The DCE presented respondents with 14 choice sets of two competing medical interventions, termed 'profiles' henceforth. For each choice set, respondents had to indicate the profile they preferred. The profiles are

combinations of levels of the seven attributes in Table 1. To limit the cognitive burden imposed on the respondents, we varied the levels of only four of the seven attributes in the choice sets. We kept the levels of the other attributes constant, but also showed them to the respondents. Showing the levels of the constant attributes improves the validity of the parameter estimates on the one hand [42], and allows for the estimation of interaction effects on the other hand. The resulting profiles are called 'partial profiles' [43-45]. To facilitate the choice tasks, we highlighted the varying attributes in each choice set. **Figure 1** shows an example choice set where respondents had to choose between two interventions A and B.

Figure 1: Example of a choice set

Medical interventions A and B are exactly equally expensive and they apply to a similar number of patients. If you were forced to make a choice, which of both interventions should be reimbursed by the government? To make it easier for you, we have highlighted in yellow the characteristics that differ between both interventions. There are no right or wrong answers; we are interested in your opinion.

	A	B
What type of intervention is it?	Curative (meant to cure patients who are ill)	Preventive (meant to prevent healthy persons becoming ill)
How big is the probability of success of the intervention?	2 in 3 is successful	Always successful
How often do adverse effects occur?	Often	Often
How severe is the illness for which the intervention is developed?	Not lethal, but everyone who gets the disease will experience a severe and lasting reduction in quality of life	Lethal, everyone who gets the disease will die from it
Does the patient cause the disease through his or her own lifestyle?	Not at all	Not at all
How long does it take before the patient becomes ill/ shows signs/ symptoms of illness?	Within a year	Within a year
At what age does the patient become ill?	0 to 10 years	40 to 50 years
YOUR PREFERENCE:	◘	◘

To maximize the information content of the DCE, we created three different surveys by constructing a partial profile design involving 42 choice sets and dividing it into three groups of 14 choice sets such that each group or survey has a similar partial profile design structure (see below). In constructing the design profiles, we excluded four unrealistic combinations of levels of two attributes, shown in Appendix A, which also includes the three surveys. We ensured that each survey was filled out an equal number of times. As pointed out by [46], using 42 instead of 14 different choice sets results in a larger amount of information on the respondents' preferences and therefore in more precise estimates of the relative importance of the attributes and attribute levels.

Besides the estimation of the main effects of the attributes, we were also interested in estimating the interactions between "Type of Intervention" and any other attribute. However, because of the disallowed level combinations associated with the attribute "Timespan" (shown in Appendix A), the interaction between "Type of Intervention" and "Timespan" cannot be estimated. As a discrete choice model, we used a multinomial logit (MNL) model, which is common practice in discrete choice design and analysis [10]. The partial profile design in Appendix A is D-efficient or D-optimal for the MNL model, meaning that it guarantees precise estimates of the main effects and the interactions between "Type of Intervention" and five other attributes [47].

Each choice set of the D-efficient partial profile design varies the levels of four of the seven attributes. These varying attributes differ from choice set to choice set. We determined them using the attribute balance approach that attempts to vary each attribute in an equal number of choice sets and to pair varying attributes an equal number of times [44, 45]. That is why each attribute is varied in eight choice sets of each survey of the partial profile design.

The D-efficient partial profile design takes into account prior knowledge concerning the respondents' preferences. For our DCE, for example, it generally holds that the expected priority ranking for reimbursement of interventions is, from low to high, related to a mild disease, followed by a severe, but not lethal disease, and finally, a lethal disease. Similarly, for all other attributes, we took into account expert prior information about the most logical ordering of the levels of the attributes, from low priority to high priority, the result of which is shown in **Table 1.** We also ranked the attributes in order of expected importance and expressed our uncertainty regarding the

a priori orderings of the attributes and attribute levels in a prior multivariate normal distribution. In Appendix B, we discuss in detail how we obtained that multivariate normal prior distribution to optimize the design. The design that maximizes the information content (as measured by the log-determinant of the information matrix; see (Kessels et al., 2011c)) of the DCE, when averaged over that prior distribution, is called a Bayesian D-efficient design. The Bayesian D-efficient design approach is increasingly considered a state of the art approach for DCEs (see, e.g., [47-50]). Major benefits of Bayesian D-efficient designs are that, using a proper prior distribution, they avoid choice sets in which one profile is completely dominating the other profile(s) on every attribute [51], and such designs can be constructed to efficiently estimate interaction effects (as demonstrated below).

9.2.3 Presentation of the surveys

We provided respondents with a web link that allowed them to carry out the choice tasks at their earliest convenience. To help respondents, we presented a thorough explanation of the choice tasks at the beginning of the DCE to familiarize them with (i) the context of increasing scarcity in health care and the problem of setting priorities, and (ii) all seven attributes and their levels and how they are used in the description of a treatment or a preventive intervention. We asked respondents to choose, based upon their opinion about social justice, between two interventions of which only one could be reimbursed by the government.

After the DCE, we asked respondents a number of background questions concerning their age, gender, height, weight, educational attainment, family size, experience as health care worker (HCW), smoking status and experience with severe illness (personal or within the family). In order to have an estimate of the respondent's current health state, the respondents also had to complete the EuroQol health survey (i.e. the Visual Analogue Scale (VAS) and the generic EQ-5D-5L) [52, 53].

9.2.4 Sample selection

In June 2012 a sample was drawn, representative for the Belgian population in terms of age, gender, region and educational attainment, from an actively managed, continuously updated panel of 10,753 Belgians. Participation was incentivized with (i) credits by means of which, after a number of

positively evaluated survey participations, gifts could be bought and (ii) a lottery organized on a per survey basis. Only one respondent per household was allowed. The market research company guarantees high-quality data through checks and ensures that only 'serious' respondents are included. To this end, fraudulent, inattentive, hyperactive or conditioned respondents were removed from the sample, e.g. respondents who complete the survey unreasonably fast ('speedsters'), consistently give the same answer ('straightliners'), etc.

A total of 30% (N = 3,160) of the 10,753 contacted individuals agreed to participate, of which 937 were selected based upon the quota requirements. Of the selected individuals, 187 either did not finish the survey or did not meet the quality criteria. This left us with a sample of 750 respondents (250 respondents for each of the three versions of the survey), and 10,500 observed choices in total, i.e. 14 per respondent. Table 2 compares basic characteristics of the sample to those of the population, showing overall good agreement. Given the societal context of this study, and a lack of clarity about which additional criteria can identify irrational response data in a DCE [54, 55], all 750 respondents were included in our analysis.

Table 2: Sample characteristics relative to those of the Belgian population.

	Sample	Belgian population
Language		
Dutch	56%	56%
French	44%	44%
Gender		
Male (M)	50%	50%
Female (F)	50%	50%
Gender per age group °		
18 – 25 M	6%	6%
18 – 25 F	6%	6%
25 – 34 M	9%	9%
25 – 34 F	10%	9%
35 – 44 M	10%	11%
35 – 44 F	10%	10%
45 – 54 M	10%	10%
45 – 54 F	11%	10%

	Sample	Belgian population
55 – 64 M	9%	8%
55 – 64 F	10%	8%
65 – 74 M	6%	6%
65 – 74 F	4%	6%
Level of education *		
None or lower education	8%	19%
Lower secondary education	10%	20%
Higher secondary education	31%	33%
Higher non-university education	35%	18%
University	15%	10%
Province		
Antwerp	15%	16%
West Flanders	10%	11%
East Flanders	13%	13%
Limburg	8%	8%
Hainault	13%	12%
Liege	10%	10%
Luxemburg	3%	2%
Namur	5%	4%
Brussels	10%	10%
Flemish Brabant	11%	10%
Walloon Brabant	3%	3%
Smoking status §		
Never smoked	45%	54%
Ex-smoker	30%	22%
Smoker	25%	25%

Source Belgian Data: Federale Overheidsdienst Economie (FOD-economie, 2012)
° Age: The percentages reported are proportions in the selected population (18-75), representing 71% of the total Belgian population.
* Education: The percentages reported for the Belgian population are for the age group 15 years or older. The percentages for our sample are only for the age group 18-75 years. The overrepresentation of higher educated respondents in our sample as compared to the total population can be explained by our exclusion of the group 15-18 years that is too young for higher education, and the age group 75 years or older for which higher education was less democratically accessible.
§ Smoking percentages from the population are based upon the following study (SIPH, 2008) and are representative for the population aged 15 years or older.

9.2.5 Data analysis

The data collected using a DCE allow estimating the respondents' utility function as part of the multinomial logit (MNL) model. We started by estimating the a priori MNL model, i.e. the model that seemed most useful when planning the entire study and which was used as a basis for constructing the D-efficient design for the DCE. That model includes the main effects of all attributes and the interactions between type of intervention and five other attributes. Next, we dropped the insignificant model terms until we obtained a final model in which all remaining effects had significant explanatory value. We carried out the entire data analysis using the Choice Modeling platform in the statistical software package JMP 10, which is a user-friendly product of SAS.

9.3 Results

9.3.1 Main and interaction effects

Figure 2 and **Table 3** summarize the results of our analysis. All attributes except for type of intervention had a significant main effect, indicating their relevance for priority setting to the Belgian public. Two significant interaction effects were found: the interaction between type of intervention and age of the patient and the interaction between type of intervention and SOI. Hence, our data provide statistical support for the hypothesis that the relative value of cure versus prevention differs as a function of the age group of the patient and the severity of the health problem. The main-effect estimates in **Table 3** represent the utilities attached to the different levels of the attributes. The directions and the incremental changes of these coefficients across the levels of each attribute are in line with the a priori expectations. As shown in **Figure 2,** the most influential attributes were the patient's age and health-related lifestyle, followed by the intervention's effectiveness. Type of intervention is also an important attribute for the model because it appears in two significant interaction effects. Its importance is shown by the likelihood ratio (LR) test for the joint significance of the three effects involving this attribute (LR Chi-square = 26.19; DF = 7; p-value = 0.0005).

Figure 2: **Contribution of the 7 attributes (main and interaction effects) to the social value attributed to a health care program (relative to the weight of the lifestyle attribute, arbitrarily set to 100)**

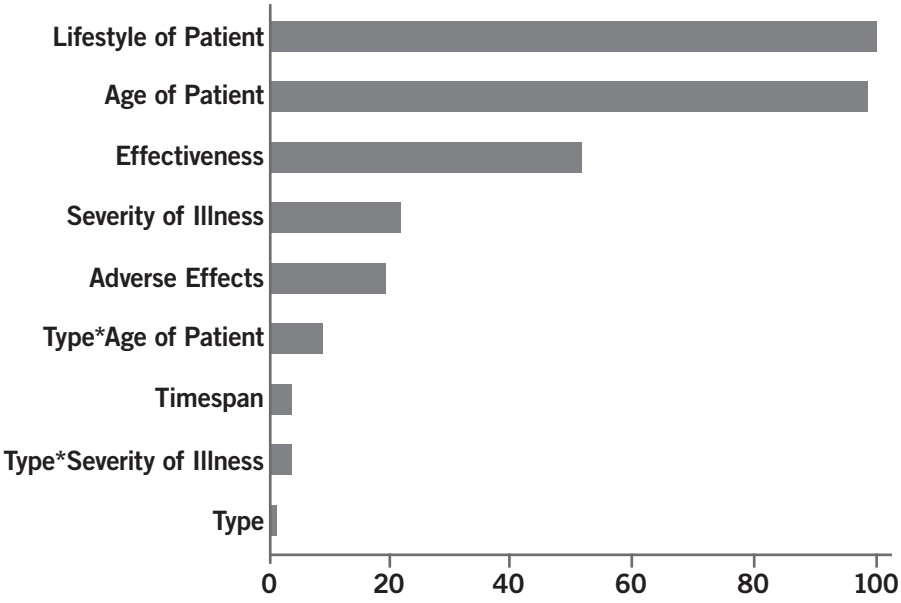


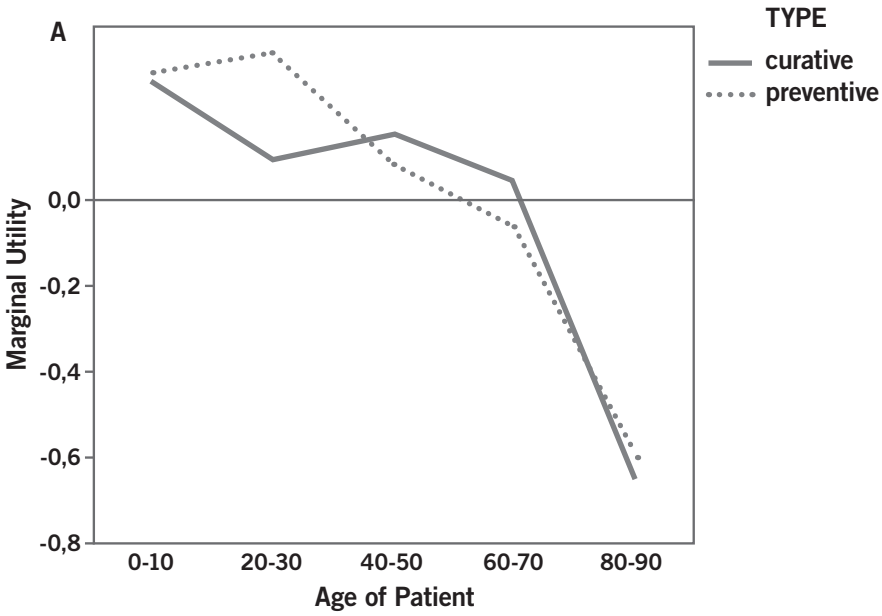
Table 3: Estimates of coefficients in the MNL model and significances of the attribute effects obtained from likelihood ratio (LR) tests.

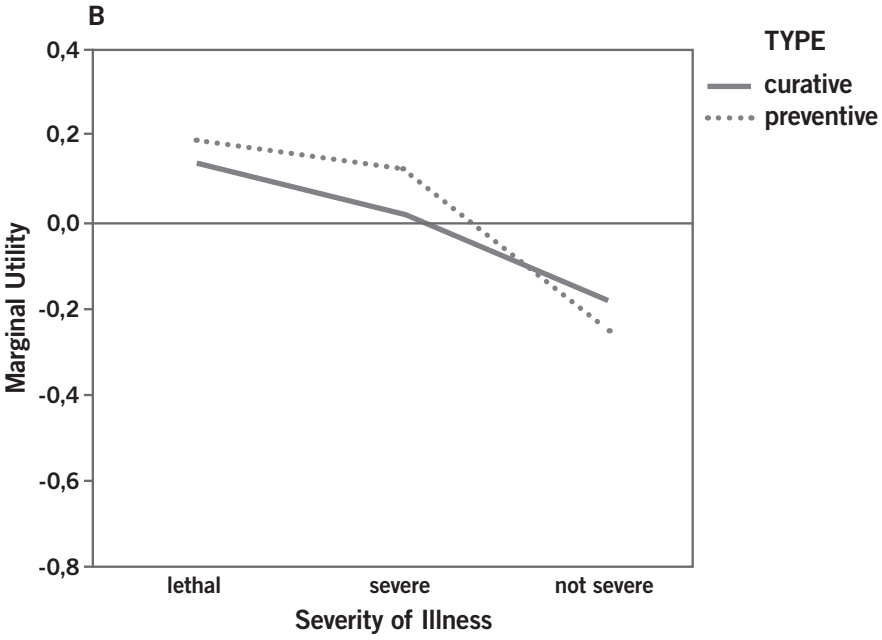
Term	Estimate		DF	P-value
Lifestyle of Patient				
fully	-0.3742			
partly	0.0483	**174.784**	2	<0.0001
not at all	*0.3259**			
Age of Patient				
80 – 90 years	-0.6160			
60 – 70 years	-0.0067			
40 – 50 years	0.1168	**181.700**	4	<0.0001
20 – 30 years	0.2206			
0 – 10 years	*0.2853**			
Effectiveness				
33%	-0.2584			
66%	0.0282	**89.185**	2	<0.0001
100%	*0.2302**			
SOI				
not severe	-0.2210			
severe	0.0653	**37.928**	2	<0.0001
lethal	*0.1557**			
Adverse Effects				
often	-0.1582			
rarely	0.0856	**33.601**	2	<0.0001
never	*0.0726**			
Type*Age of Patient				
preventive*80 – 90 years	0.0120			
preventive*60 – 70 years	-0.0676			
preventive*40 – 50 years	-0.0480			
preventive*20 – 30 years	0.1103			
preventive*0 – 10 years	*-0.0067**			
curative*80 – 90 years	*-0.0120**	**20.218**	4	0.0005
curative*60 – 70 years	*0.0676**			
curative*40 – 50 years	*0.0480**			
curative*20 – 30 years	*-0.1103**			
curative*0 – 10 years	*0.0067**			
Timespan				
after 20 years	-0.0843			
after 5 years	0.0234	6.42	2	0.0404
within a year	*0.0609**			
Type*SOI				
preventive*not severe	-0.0431	6.043	2	0.0487

* Coefficient estimates corresponding to the last level of an attribute, either as main effect or involved in an interaction, are indicated in italic to stress that they are calculated as minus the sum of the estimates for the other levels of that attribute.

Figure 3 shows two interaction plots. The plot in Panel A shows that prevention has a substantially greater value than cure for patients in the age group of 20-30 years. For patients older than 30, the utility of prevention steeply declines, whereas the value of cure remains relatively stable over the age interval from 20 to 70. For the youngest patients, prevention and cure are considered equally important, while for the oldest patients, prevention and cure are considered equally unimportant. **Figure 3**'s Panel B shows that SOI has a bigger impact on the utility of a preventive intervention than on that of a curative one. Prevention was valued lower than cure in case of a non-severe, transient illness. However, it was valued higher for severe long-lasting and life-threatening diseases. As no other interaction with type of intervention was significant, our respondents did not consider effectiveness, risk of adverse effects or lifestyle to be of differential importance for choosing between prevention and cure.

Figure 3: **Marginal utility values for different combinations of "Age of Patient" and "Type of Intervention" (Panel A) and for different combinations of "Severity of Illness" and "Type of Intervention" (Panel B).**





9.3.2 Preference heterogeneity

In this section, we discuss the statistically significant heterogeneity between various subgroups of respondents.

Age. When respondent's age was included as a covariate in the discrete choice model, we found that younger respondents attribute significantly more importance to patient's age and lifestyle, and to SOI. Older respondents attribute more importance to the effectiveness of the intervention. To visualize the impact of the respondent's age, we partitioned the respondents of our dataset in three age groups: 18-35y, 36-60y and 61-75y (see **Figure 4**). For the youngest respondents, the social value of an intervention depends more strongly on the patient's age (Panel A, dotted line) and the link between the disease and the patient's lifestyle (Panel B, dotted line) than for the older respondents.

Gender. The covariate gender appeared in two significant interactions, one involving the attribute patient's age and one involving the attribute effectiveness. Female respondents attach less value to interventions for older patients than male respondents. Male respondents attribute a higher value to effectiveness.

Level of education and experience in health care. Respondents with a degree of higher education (university or non-university) attribute more value to prevention. In addition, they discount future health gains to a lesser extent, and therefore value interventions with long-term benefits more highly. Also, higher educated respondents are more willing to ration based on age, and attribute more importance to SOI. No differences in opinion were found between higher and lower educated respondents for the attributes lifestyle, effectiveness and adverse effects. Present or past experience as health care worker (14% of the sample) did not result in significant interactions.

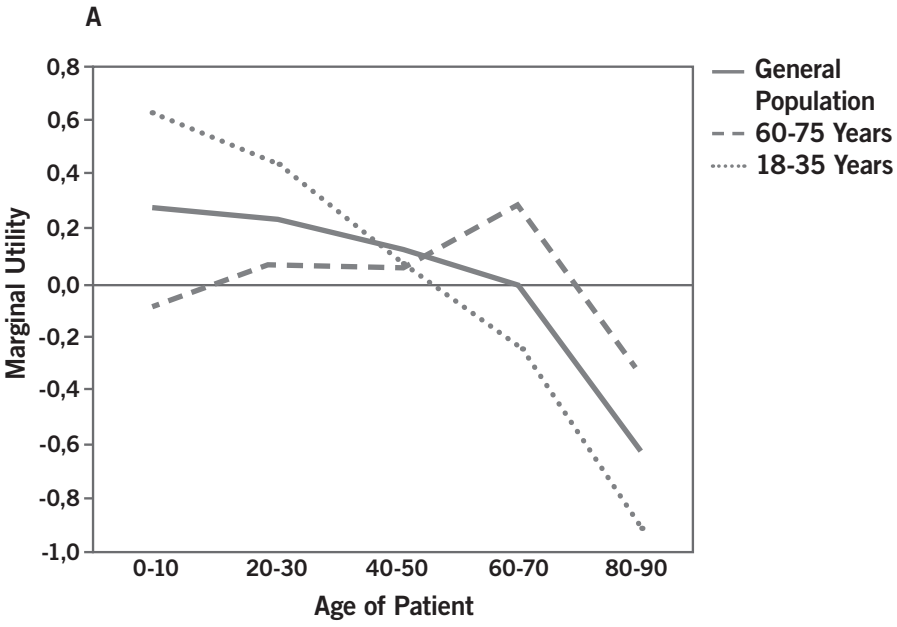
Household. The larger the household of the respondent, the larger the extent to which prevention was preferred to cure and the more the value of health care decreased as a function of patient's age. Respondents living with children gave more importance to patient's age. No significant interactions were found with other attributes.

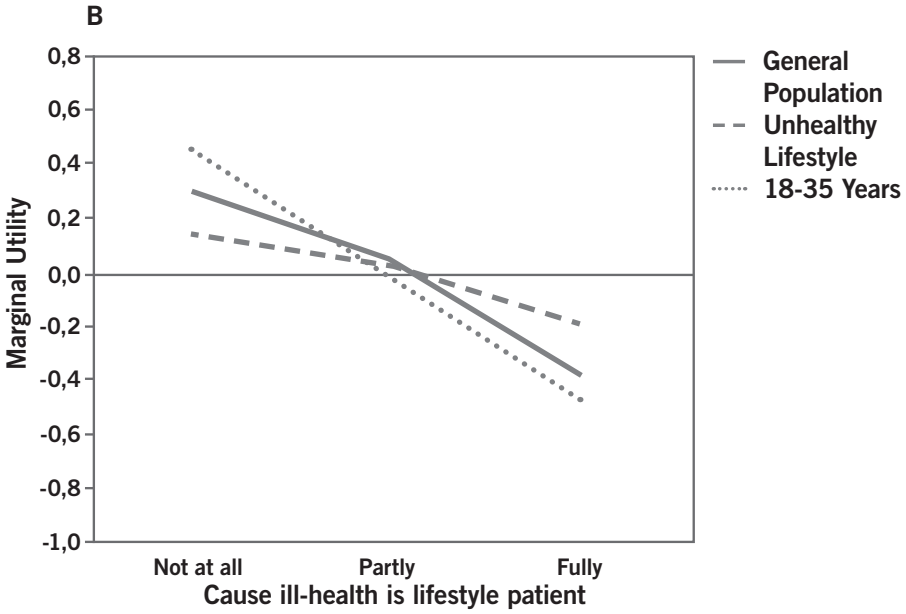
Health state. Respondents who reported having had personal experience with severe illness attach greater value to cure than to prevention, and to current rather than to future health gains. They attribute less importance to adverse effects and are less inclined to take the age of patients into account. Also, we found some significant interactions with respondents' EQ-5D-5L and VAS scores. The lower their EQ-5D-5L score, the more likely respondents were to prefer cure over prevention and to prefer current health gains over future ones. Similarly, the lower the VAS score, the stronger the preference for cure over prevention and the lower the importance of the patient's age group. We also partitioned our sample in a 'good health' group (74% of the sample) and a group with 'present or past health problems' (26%), depending on whether or not they had personal experience with severe illness, or have an EQ-5D-5L score below 0.6 or a VAS score below 60. Both groups differ in that the 'good health' group prefers prevention, discounts future health gains to a lesser extent and is more willing to ration based on age. Respondents' choices did not differ significantly based on experience with severe illness in their family.

Lifestyle. Whether or not the respondent is a smoker is a highly influential covariate and, hence, an important factor explaining preference heterogeneity among the respondents. Smokers clearly prefer cure to prevention, discount future health gains to a greater extent and attribute a lower importance to the attributes lifestyle and patient's age. Also, Body Mass Index (BMI) turns out to be an important covariate. The higher the BMI score, the more

a respondent prefers cure to prevention and discounts future health gains. Also, respondents with a large BMI do not value the SOI, the disease's link with lifestyle and the patient's age as highly as respondents with a low BMI. To visualize the differential valuation by respondents with a 'healthy' lifestyle and patients with an 'unhealthy' lifestyle, we partitioned the respondents in two groups, one group containing respondents with a BMI exceeding 30 (i.e. the obesity threshold [58]) as well as smokers (in total 38% of the sample) and one group containing non-smokers that have a BMI lower than 30. The 'unhealthy' lifestyle group preferred cure to prevention, attributed a lower value to lifestyle and patient's age (as illustrated in Panel B of Figure 4), and, remarkably, attached more importance to the risk of adverse effects.

Figure 4: Marginal utility values for the attributes "Age of Patient" (Panel A) and "Lifestyle of Patient" (Panel B) for different population subgroups.





9.4 Discussion

We elicited preferences of Belgians for the allocation of the health care budget. We paid particular attention to the distinction between preventive and curative health care. Although characteristics of the intervention (effectiveness and risk on adverse effects) and of the illness (SOI and timespan) were found to matter, mainly characteristics of the patient (age and health-related lifestyle) drive respondents' distributive preferences. SOI and patient's age group played a different role in prevention and cure: for young patients and for more severe diseases, to prevent was considered better than to cure. We also detected substantial heterogeneity in the preferences: young, healthy, highly educated or more health-conscious adults responded in a markedly different way than older, unhealthy, less well educated and health-unconscious ones.

Our results confirm studies in other countries indicating that the context (partly) shapes the social value of QALYs, and that the general public's distributive preferences diverge from a simple health maximization approach, as would be prescribed by CUA (i.e. minimizing cost/QALY) (e.g. [12, 13, 15, 16, 21-23, 25, 59]). While several of these studies also showed that the attributes age and lifestyle are relevant factors, our results suggest a much stronger impact of the lifestyle attribute.

Studies that explored preferences for prevention and cure (see Section 2.1) found no preference [37, 39], a preference for prevention [25, 38, 60] or a preference for cure [36, 39]. Our sample valued prevention higher than cure only when it is targeted at relatively young age groups and when it protects against more severe illness. However, as the self-inflicted nature of a health condition was a factor of major moral relevance in our study, indirectly, our results can also be interpreted as providing further support for prevention in general. An allocation scheme that accounts for individual responsibility would mainly ration on curative treatments as accountability for lifestyle is less relevant for (not) providing prevention, especially when it comes to primary prevention. Preventive programs can incentivize, or even enable citizens to adopt healthy and responsible lifestyles before their lifestyle associated risk exposure requires cure.

Priority setting in health care requires societal support [61]. However, as the majority is not necessarily right [62, 63], the results of our study should always be complemented by ethical considerations regarding the priorities defined by the respondents of our study. These considerations are concerned with accountability and age-based rationing.

First, the respondents in our study held the opinion that people who knowingly take health risks should somehow be held accountable. This idea is supported by several arguments [64, 65]. (i) A powerful intuition of justice is that our lives should predominantly depend upon the choices we make ourselves, and not upon social determinants and accidental developments (luck-egalitarianism, e.g. [66]). Analogously, in the name of justice, society has a bigger moral obligation to help those who were struck by bad luck than those who can be held personally responsible. (ii) In a health insurance pool those who voluntarily engage in risky behaviors behave in an antisocial fashion and free ride on the efforts of others, as they knowingly increase their need for future medical services, impose costs on others and pressurize the system. However, strong ethical arguments can also be brought forward against accountability for lifestyle [67]: (i) While we can identify conduct that increases the risk of illness or injury, it remains very difficult to conclude that a particular health consequence was actually caused by a particular lifestyle choice and not by other factors. (ii) We can only hold individuals accountable for informed, voluntary choices. Lifestyle choices are, however, often related to addiction, absence of willpower or lack of education, in which case we should wonder just how voluntary such behavior is. (iii) Some argue that in the long run healthy lifestyles are not

less but more expensive to society [68]. (iv) The practical implementation of lifestyle accountability might be costly and detrimental to personal privacy, since it would require investigation and documentation of citizens' lifestyles. And (v) whereas it can be fair to account for lifestyle, there is a strong moral case for a health care system that is also compassionate [65]. For these reasons, introducing lifestyle considerations in health care rationing remains hitherto controversial. Currently, preventive policies aimed at dissuading unhealthy lifestyles such as, for instance, alcohol, fat, sugar or smoking taxes are gaining more interest [69, 70]. Such measures, if effective, would increase short-term government income and reduce lifestyle-related morbidity.

Second, although support differed in magnitude between subgroups of respondents, our sample – including the older generations – supported some form of age-based rationing. The view that a lower weight must be given to health care once a certain age threshold has been reached, is in essence egalitarian [71, 72]. It relies on the view that society should aim to correct unjust inequality of opportunity, in this case promoting a more equal distribution of healthy life years among its members [73]. In this respect, the ones who have had their 'fair innings' have a reduced entitlement to the available resources as compared to those who have not yet received their share [74]. However, biomedical progress in extending human longevity obscures the idea of fair innings, i.e. what constitutes a normal or a natural lifespan and which functionings are to be considered essential for which stage of life [75] and in which era in time.

Some limitations in the methodology of our study must also be mentioned. First, although our sample was broadly representative for the Belgian population, respondents were recruited from an online panel. This excluded respondents older than 75 years. Moreover, membership of the panel may be associated with unobservable characteristics. Second, we surveyed our sample on a complex topic, in a single recording. We encouraged respondents to think thoroughly about their answer and evidence suggests that respondents' answers to DCEs like ours are reliable [24]. Nonetheless, it would be interesting to repeat this study in a non-panel sample (e.g. generated through random digit dialing of telephone numbers), and to organize a follow-up study in the same sample to compare the results. Third, an inherent limitation of DCEs is that only a limited number of attributes can be used. Although we included a relatively large number of relevant attributes, the choice alternatives we presented remain simplified versions

of health care programs. Fourth, because this simplified the choice tasks, we excluded the cost attribute. A disadvantage of this was that it became impossible to quantify willingness to pay for changes in the attributes levels. However, such inferences were not our primary objective, and, moreover, they have also been shown to be less informative than expected on various occasions [76, 77].

The objective of our study was to provide empirical input into the unavoidable debate about health care rationing. We found that the average Belgian does not want priorities to be set purely on an efficiency basis, i.e. maximizing health gains within the budget, but that (s)he takes into account personal characteristics of the recipient such as age and health-related lifestyle. However, the heterogeneity we encountered in respondents' preferences reveals important disagreements on how priorities must be set. These findings provide an empirical basis for an explicit public debate, in which these diverging opinions should be recognized, scrutinized and reconciled as much as possible. In the end, it seems preferable that society defines which distributive principles it considers to be fair, rather than having to rely on a trustworthy decision-making process that holds decision-makers accountable for setting reasonable limits on health care [78, 79], without specifying which criteria are important to do this.

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Appendix A: Bayesian D-efficient partial profile design consisting of three surveys for the discrete choice experiment.

The design of the discrete choice experiment involved three surveys of 14 choice sets with two alternative medical interventions. The surveys appear in Tables A.1, A.2 and A.3. The choice sets in each survey were presented in a randomized order to the respondents. Each survey was filled out by 250 respondents. The choice sets are described by four attributes of which the levels are varied and three attributes of which the levels are kept constant. The levels of the varying attributes are indicated in yellow (as in Figure 1). The constant attributes are shown to the respondents to present actual alternative interventions as well as to be able to estimate interactions. In each survey, each attribute is held constant in six choice sets and is varied in eight choice sets.

When constructing the Bayesian D-efficient partial profile design, we excluded the following four combinations of attribute levels, because we believe they are unrealistic:

i. Type of Intervention [curative] & Timespan [after 20 years],
ii. Type of Intervention [curative] & Timespan [after 5 years],
iii. Lifestyle of Patient [fully] & Age of Patient [0 – 10 years],
iv. Lifestyle of Patient [partly] & Age of Patient [0 – 10 years].

Table A.1: **Survey 1 of the Bayesian D-efficient partial profile design.**

Choice Set	Type of Intervention	Effectiveness	Adverse Effects	Severity of Illness	Lifestyle of Patient	Timespan	Age of Patient
1	preventive	always successful	never	lethal	fully	after 5 years	40 – 50 years
1	preventive	always successful	never	severe	not at all	within a year	60 – 70 years
2	preventive	2 in 3 is successful	often	not severe	fully	after 5 years	20 – 30 years
2	preventive	2 in 3 is successful	rarely	severe	fully	after 20 years	60 – 70 years
3	preventive	2 in 3 is successful	rarely	severe	partly	within a year	40 – 50 years
3	preventive	1 in 3 is successful	rarely	severe	not at all	after 20 years	0 – 10 years
4	curative	1 in 3 is successful	rarely	not severe	not at all	within a year	0 – 10 years
4	curative	2 in 3 is successful	often	not severe	partly	within a year	40 – 50 years
5	preventive	always successful	never	not severe	not at all	after 20 years	40 – 50 years
5	preventive	1 in 3 is successful	often	severe	not at all	after 5 years	40 – 50 years
6	curative	always successful	rarely	not severe	partly	within a year	80 – 90 years
6	curative	1 in 3 is successful	often	lethal	not at all	within a year	80 – 90 years
7	curative	1 in 3 is successful	never	not severe	partly	within a year	60 – 70 years
7	preventive	1 in 3 is successful	never	severe	not at all	within a year	40 – 50 years
8	curative	1 in 3 is successful	rarely	lethal	partly	within a year	20 – 30 years
8	preventive	1 in 3 is successful	never	lethal	not at all	after 5 years	20 – 30 years
9	preventive	2 in 3 is successful	never	lethal	partly	after 5 years	60 – 70 years
9	curative	2 in 3 is successful	often	lethal	not at all	within a year	60 – 70 years
10	preventive	always successful	rarely	severe	fully	within a year	20 – 30 years
10	curative	always successful	often	lethal	fully	within a year	60 – 70 years
11	curative	1 in 3 is successful	rarely	severe	not at all	within a year	80 – 90 years
11	preventive	2 in 3 is successful	rarely	severe	not at all	after 5 years	20 – 30 years
12	preventive	2 in 3 is successful	often	lethal	not at all	after 5 years	0 – 10 years
12	curative	always successful	often	not severe	not at all	within a year	0 – 10 years
13	curative	1 in 3 is successful	often	severe	partly	within a year	60 – 70 years
13	preventive	always successful	often	lethal	fully	within a year	60 – 70 years
14	curative	2 in 3 is successful	rarely	not severe	not at all	within a year	80 – 90 years
14	preventive	always successful	often	not severe	not at all	within a year	0 – 10 years

Table A.2: **Survey 2 of the Bayesian D-efficient partial profile design.**

Choice Set	Type of Intervention	Effectiveness	Adverse Effects	Severity of Illness	Lifestyle of Patient	Timespan	Age of Patient
1	preventive	2 in 3 is successful	often	lethal	not at all	within a year	80 – 90 years
1	preventive	2 in 3 is successful	rarely	lethal	fully	after 5 years	60 – 70 years
2	curative	2 in 3 is successful	rarely	lethal	partly	within a year	40 – 50 years
2	curative	2 in 3 is successful	never	severe	fully	within a year	20 – 30 years
3	preventive	2 in 3 is successful	often	not severe	not at all	after 5 years	0 – 10 years
3	preventive	1 in 3 is successful	often	lethal	not at all	after 20 years	20 – 30 years
4	preventive	2 in 3 is successful	rarely	lethal	partly	after 20 years	80 – 90 years
4	preventive	always successful	rarely	severe	fully	after 5 years	80 – 90 years
5	preventive	2 in 3 is successful	often	not severe	partly	after 20 years	20 – 30 years
5	preventive	always successful	rarely	not severe	partly	after 5 years	80 – 90 years
6	curative	always successful	rarely	severe	not at all	within a year	80 – 90 years
6	curative	2 in 3 is successful	never	lethal	fully	within a year	80 – 90 years
7	preventive	2 in 3 is successful	rarely	not severe	not at all	after 5 years	80 – 90 years
7	curative	2 in 3 is successful	rarely	not severe	fully	within a year	60 – 70 years
8	preventive	always successful	never	not severe	not at all	after 5 years	40 – 50 years
8	curative	always successful	never	severe	fully	within a year	40 – 50 years
9	preventive	1 in 3 is successful	rarely	lethal	not at all	within a year	0 – 10 years
9	curative	1 in 3 is successful	never	severe	not at all	within a year	40 – 50 years
10	preventive	always successful	rarely	lethal	partly	after 20 years	20 – 30 years
10	curative	always successful	never	not severe	partly	within a year	20 – 30 years
11	curative	always successful	rarely	lethal	fully	within a year	80 – 90 years
11	preventive	2 in 3 is successful	rarely	lethal	not at all	within a year	40 – 50 years
12	curative	2 in 3 is successful	often	severe	not at all	within a year	0 – 10 years
12	preventive	always successful	often	lethal	not at all	within a year	40 – 50 years
13	preventive	always successful	often	lethal	partly	after 5 years	80 – 90 years
13	curative	1 in 3 is successful	never	lethal	partly	within a year	80 – 90 years
14	preventive	1 in 3 is successful	never	severe	partly	within a year	80 – 90 years
14	curative	always successful	often	severe	fully	within a year	80 – 90 years

Table A.3: **Survey 3 of the Bayesian D-efficient partial profile design.**

Choice Set	Type of Intervention	Effectiveness	Adverse Effects	Severity of Illness	Lifestyle of Patient	Timespan	Age of Patient
1	preventive	1 in 3 is successful	often	severe	partly	after 20 years	80 – 90 years
1	preventive	1 in 3 is successful	often	not severe	fully	within a year	60 – 70 years
2	curative	2 in 3 is successful	often	not severe	not at all	within a year	20 – 30 years
2	curative	2 in 3 is successful	never	severe	partly	within a year	60 – 70 years
3	preventive	2 in 3 is successful	never	not severe	fully	within a year	80 – 90 years
3	preventive	1 in 3 is successful	never	not severe	partly	after 5 years	40 – 50 years
4	preventive	always successful	often	lethal	not at all	after 5 years	60 – 70 years
4	preventive	1 in 3 is successful	never	lethal	not at all	within a year	0 – 10 years
5	preventive	always successful	never	severe	fully	after 20 years	20 – 30 years
5	preventive	1 in 3 is successful	rarely	not severe	fully	within a year	20 – 30 years
6	curative	always successful	never	not severe	not at all	within a year	60 – 70 years
6	curative	2 in 3 is successful	rarely	severe	partly	within a year	60 – 70 years
7	curative	2 in 3 is successful	never	not severe	not at all	within a year	0 – 10 years
7	preventive	2 in 3 is successful	never	severe	not at all	after 5 years	20 – 30 years
8	preventive	1 in 3 is successful	never	not severe	partly	after 5 years	60 – 70 years
8	curative	1 in 3 is successful	rarely	not severe	fully	within a year	60 – 70 years
9	curative	1 in 3 is successful	often	not severe	partly	within a year	80 – 90 years
9	preventive	1 in 3 is successful	rarely	not severe	not at all	after 20 years	80 – 90 years
10	preventive	2 in 3 is successful	rarely	severe	partly	within a year	40 – 50 years
10	curative	2 in 3 is successful	never	not severe	partly	within a year	20 – 30 years
11	curative	1 in 3 is successful	rarely	not severe	fully	within a year	40 – 50 years
11	preventive	always successful	rarely	not severe	partly	within a year	20 – 30 years
12	curative	2 in 3 is successful	never	not severe	not at all	within a year	80 – 90 years
12	preventive	1 in 3 is successful	never	lethal	fully	within a year	80 – 90 years
13	preventive	2 in 3 is successful	often	severe	fully	after 20 years	40 – 50 years
13	curative	1 in 3 is successful	often	not severe	fully	within a year	40 – 50 years
14	preventive	always successful	often	severe	not at all	within a year	0 – 10 years
14	curative	2 in 3 is successful	rarely	severe	not at all	within a year	20 – 30 years

Appendix B: Multivariate normal prior parameter distribution used to construct the Bayesian D-efficient partial profile design for the discrete choice experiment.

To construct the Bayesian D-efficient partial profile design for the discrete choice experiment shown in Appendix A, we used a multivariate normal prior distribution that reflects the prior beliefs about the unknown parameter values associated with the levels of the seven attributes. Based on expert interviews and literature review, we ranked the seven attributes in order of importance and specified mean parameter values and variances for the multivariate normal prior distribution accordingly.

Table B.1 shows the seven attributes in order of importance, as suggested by a literature review and a panel of experts prior to our study. Based on these orders of importance, we specified prior mean utility values for the main effects of the seven attributes. The more important an attribute, the larger in magnitude the a priori mean utility values specified for the main effects of that attribute. We adopted the same ordering of the levels of the attributes as shown in **Table 1,** where they are ranked from least preferred to most preferred. Note that the utility values associated with the levels of each attribute sum to zero. This is because we used effects-type coding for the attribute levels, which means that the levels of the 2-level attribute, "Type of Intervention", are coded as 1 and -1, the levels of every 3-level attribute as [1 0], [0 1] and [-1 -1], and the levels of the 5-level attribute, "Age of Patient" as [1 0 0 0], [0 1 0 0], [0 0 1 0], [0 0 0 1] and [-1 -1 -1 -1]. The a priori mean utility values for each attribute are symmetric around zero, except for the attributes "Timespan" and "Adverse Effects". For these two attributes, the literature and the experts suggested that the prior utility values for the last two levels lie closer to each other than to the utility value for the first level.

Table B.1: **A priori order of importance of the main effects of the seven attributes and conversion into mean utility values used in the multivariate normal prior distribution.**

Rank	Attribute	Prior mean				
		Level 1	Level 2	Level 3	Level 4	Level 5
1	Severity of Illness	-0.8	0	0.8		
2	Age of Patient	-0.5	-0.25	0	0.25	0.5
	Lifestyle of Patient	-0.5	0	0.5		
	Effectiveness	-0.5	0	0.5		
	Timespan	-0.5	0.2	0.3		
3	Adverse Effects	-0.4	0.1	0.3		
	Type of Intervention	-0.4	0.4			

For the prior variances around the mean utility values for the main effects of the attributes, we used a value of 0.09 for all levels of all attributes. This way, we ensured that the multivariate normal prior distribution preserved the preference ordering for the levels of any given attribute as much as possible. Following a suggestion of (Kessels et al. (2008)), we specified negative covariances of -0.045 for the 3-level attributes and of -0.0225 for the 5-level attribute.

Regarding the interaction effects between "Type of Intervention" and any other attribute except for "Timespan", we had no prior information about people's preferences. Therefore, we specified zero mean utility values for these effects. For ease of computation, we also assumed zero prior variances around the utility values for the interaction effects, allowing for no uncertainty around these values. This implies that the prior parameter specification of the interaction effects corresponds to a local instead of a Bayesian approach.

Conclusion

1. Summary

There are many fundamental, moral issues involved in vaccination. The objective of this thesis was to contribute to discussions about two ethical challenges. The first part (chapters 1-5) deals with aspects of the problem of balancing individual rights with social obligations in preventing disease. The second part (chapters 6-9) focused on the resource allocation question: which vaccines should be offered by the state, and why?

PART I

Chapter 1 investigated whether infectious disease prevention is a matter of ethical duty. Three grounds were presented on which one could argue that vaccination can - depending on the circumstances - be considered morally obligatory. The same applies to other forms of prevention such as wearing mouth masks, undergoing screening-tests or extensive hand washing. The scope of our preventive duties is however limited by other individuals' responsibility for their own health, and by what can generally be considered to be an acceptable risk or sacrifice. It was argued that such preventive duties are stronger in the case of a sexually transmitted infection.

Chapter 2 summarized the different reasons why some individuals refuse vaccination, the socio-demographic differences between skeptics and non-skeptics and a cognitive dimension was presented in which terms both groups appear to be different: social orientation. Vaccine skeptics show a lower agreement with the orientations horizontal individualism (HI) and horizontal collectivism (HC) than individuals with a positive attitude towards vaccination. HI is typically associated with valuing individual autonomy and equality in interpersonal interaction whereas typical HC values are interdependency and cooperation on a basis of equality. Such cognitive differences are important to understand vaccine skepticism and to design communication strategies to increase vaccine uptake.

Chapter 3 turned to vaccination policy. It was argued that targeted vaccination (selective reimbursement and/or active approach of particular subgroups) should not only be done on the basis of efficiency (cost-effectiveness) but that

policy makers should weigh such benefits against wider social consequences related to the values (health) equity, non-discrimination, protection of privacy and non-stigmatization. Increasing uptake can be achieved through education, use of nudges, incentives or coercion. All of these measures can be justified means but they have ethically controversial dimensions. The justifiability of using (more coercive) measures depends upon the specifics of the vaccine challenge (mainly whether vaccination can be considered a moral duty) and the extent to which more voluntary measures have failed.

Chapter 4 explored how the general population thinks about the issues raised in chapter 3. For which disease and in which target group is selective vaccination justified? Large differences were found between targeting health care workers, children or travelers on the one hand and immigrants on the other. In the former groups targeted vaccination was considered acceptable. In the case of immigrants this was not. Here, wider social concerns outweighed the gains in efficiency. With regards to the introduction of uptake increasing measures, in general, the use of compulsion, accountability and offering of rewards were all supported measures if they were necessary to guarantee the success of prevention, and there were only limited differences in support between these measures. Preferences between the three measures were correlated to the respondent's social orientation (see also chapter 2). A high score on VI lead to a higher (lower) likelihood of preferring legal compulsion (rewards).

In the preceding chapters, but also in most of the published literature, externalities from vaccination (herd immunity) are considered to be desirable. However, occasionally they are not. In **chapter 5** the moral relevance of negative externalities from vaccination was discussed. It was argued that such programs may redistribute disease and that, as such, they can present a problem of distributive justice. From a contractualist perspective their introduction must be justifiable in terms of universal principles to which also those who stand to lose cannot reasonably object.

PART II

Chapter 6 focused on the resource allocation question. Like chapters 7 and 8 it deals with efficiency, whereas chapter 9 takes up a wider perspective. The concern for efficiency is based upon the idea that it is wrong not to make maximal use of valuable health care resources (we should not

waste opportunities to prevent/cure illness). Cost-effectiveness analysis (CEA) is an important tool to guide policy makers on the efficiency level. However, there are still some methodological problems in their application to vaccines. As such, these analyses risk giving a wrong indication of the efficiency of a vaccination program. This chapter addressed difficulties with quantifying the health impact of acute infections into QALYs. Five different but defensible methods to value health states were compared in hepatitis A patients and it was shown that the choice which method is used can lead to greatly differing estimates of morbidity losses. This can have large implications for the resulting cost-effectiveness of an intervention. Therefore it was argued that the choice of health valuation method constitutes an additional source of uncertainty in CEA.

Chapter 7 highlighted the difference for economic evaluation between a non-infectious disease and an infectious one. The latter can imply large outbreak control costs. In the case of HAV this is even the bulk of its economic burden. Such costs must be included in the economic evaluation of prevention. Otherwise, their efficiency will systematically be underestimated. It was shown that in the case of HAV cost-of-illness studies and CEA in the literature typically do so.

Chapter 8 presented a cost-effectiveness analysis of hepatitis A vaccination for adults in Belgium, one that takes into account the methodological concerns raised in chapters 6 and 7. Based upon a large number of data sources, and accounting for many uncertainties it was shown that state-funded HAV vaccination for adults is an expensive investment. In order to gain 1 QALY the health care payer would have to pay 185 000€ for vaccination and 223 000€ for screening and vaccination of seronegatives. For adult vaccination to be cost-effective (below 50 000€ per QALY) risk-groups would need to be exposed to a force of infection that is 3.5-4 times higher than currently estimated in the general population, or the total costs of vaccination would have to drop with approximately 75%.

In **chapter 9** the focus of the rationing debate was extended beyond efficiency and cost-effectiveness towards wider concerns for fairness. A discrete choice experiment was summarized that was executed in a representative sample of the Belgian population and in which the relative importance of considerations of, among others, individual responsibility for health outcomes, severity of illness and patient's age was investigated. Specific attention was paid to the difference prevention/cure, and the differential

impact rationing principles have depending on the type of intervention. It was found that personal responsibility and patient's age are of major relevance to the Belgian public for setting health care priorities. Prevention is extra valuable (more than cure) for severe illnesses and in young adults. Substantial heterogeneity was found between respondents differing in age, health state, lifestyle, education and other variables.

2. Strengths, limitations and avenues for further research

Next to the more specific points that were already raised in the separate chapters, the following strengths and limitations of the thesis have a more general reach.

Much of the thesis has an interdisciplinary nature. The subjects covered have roots in the disciplines of economics, philosophy and preventive medicine and the discussions and methods used cross the traditional boundaries between these separate academic domains. This interdisciplinary field appeared to be a fruitful wasteland to cultivate new research questions, to start up exciting and original studies and to frame long-standing issues or polarized debates from new perspectives. I believe that in the thesis some seeds of promising, new avenues of interdisciplinary research can be found such as e.g. using discrete choice experiments to elicit moral preferences, including ethical concerns into economic evaluation of health care, finding better ways to evaluate public goods, further explore the cognitive profile of public health skeptics (and its consequences for communication strategies) or investigation of public attitudes towards prevention policy. An interdisciplinary approach (combining economics and ethics) to public health is a promising endeavor, not only for interdisciplinary purposes but also because many of the new issues raised are interesting to the contributing disciplines themselves.

Second, instead of focusing on one problem this thesis touches upon a wide range of topics. The case of vaccination was a perfect vehicle to engage in many separate, interesting areas of research, ranging from areas as diverse as valuing health outcomes, theories of justice (in health), cost-effectiveness analysis, public health ethics, behavioral economics, health policy, epidemiology and theoretical ethics. In several of these discussions this thesis has made a contribution.

Third, in this thesis a substantial role is dedicated to public preferences. On the one hand, such research is important. Matters such as allocation of health care resources, demarcation of public health mandates or prioritization of diseases have important implications for everyone. Empirical research allows anticipating opposition to and public support for policy changes and often (especially in vaccination policy where trust and participation are so important) the latter is a key variable to success. Moreover one could doubt that experts have a better epistemological access to solve ethical dilemmas (i.e. in their most naked form ethical problems are difficult for everyone). On the other hand it is also clear that the majority is often wrong and that just policy is not always in line with the gut feeling of the public. Therefore the normative value of public preference research remains also limited and it can at best serve as a complement to the judgment of experts.

Fourth, the ethical background of the thesis was philosophical liberalism. This is a fruitful and consistent ethical approach to societal problems. Also in the context of vaccination this framework provides good answers to complex questions. However, it is also increasingly acknowledged that this framework has limitations for the future problems with which public health policy will be confronted. An important challenge is therefore to develop new theoretical frameworks for public health ethics. Further research on vaccination ethics should explore answers provided by other ethical frameworks (e.g. civic republicanism).

Another limitation of the thesis consists in the ethical topics of vaccination policy that were not discussed. (1) Test-subjects for clinical trials are vital to the development of vaccines. Nonetheless developing a fair procedure to select candidates remains difficult. Within a population it should be monitored that the burden of developing such products of general interest is not concentrated in less-advantaged societal groups. The fact that clinical trial participation often occurs on a remunerated basis (albeit a limited one) gives reason to follow up how participation is distributed over socio-economic groups in the population. On a global scale the same concern relates to organizing clinical trials in low-income countries (LIC). One could argue that the development of vaccines is a global public good to which all parts of the world have to contribute their fair share. (2) More and more vaccines are being developed for purposes other than infectious diseases. Besides therapeutic vaccines, also vaccines against lifestyle problems such as cocaine or nicotine addiction and obesity are under development. Such

vaccines will further sharpen the ethical question to which extent we should rely on a technical fix (a vaccine) to overcome a lifestyle problem. To some individuals this question is already relevant now, as there exist vaccines against sexually transmitted infections, i.e. diseases that can be prevented by limiting one's sexual partners and not by vaccination. Whereas the latter view may be extreme, vaccines against e.g. cocaine addiction do raise the issue about which natural limits to our behavior we consider as moral limits, and which of them can be overcome by use of technology. (3) I focused only on vaccination in a developed, high-income country, but it is evident that the topics discussed in this thesis impose many more ethical challenges in a LIC. Issues of paternalism and resource allocation are not only more pressing in LICs, they also become more complex as they raise questions of global justice.

Nederlandstalige samenvatting:

Historisch gezien heeft de meest minuscule levensvorm op aarde het grootste aantal menselijke slachtoffers opgeëist. Virussen, bacteriën en andere microben hebben een dergelijk hoge impact op ons welzijn gehad dat ze de gevolgen van oorlog bijna doen verbleken tot een voetnoot in de geschiedenis. Vanaf de 19e eeuw echter is de menselijke conditie fundamenteel gewijzigd. Door toedoen van pioniers zoals Benjamin Jesty, Edward Jenner en Louis Pasteur werden vaccins ontdekt en ontwikkeld. Sindsdien is vaccinatie een hoeksteen geworden van onze volksgezondheid. Ziekten zoals polio en difterie, die tot voor kort in onze streken nog jaarlijks slachtoffers maakten, zijn ofwel gereduceerd tot overzichtelijke proporties, ofwel nagenoeg volledig uit de wereld verdwenen. In 1982 verklaarde de Wereldgezondheidsorganisatie dat de pokken uitgeroeid zijn en in 2011 bevestigde de Voedsel- en Landbouworganisatie van de VN dat de runderpest, een veeziekte die hongersnood veroorzaakt, niet langer meer bestaat. Momenteel leeft bij beleidsmakers de ambitie om o.a. ook polio en mazelen uit te roeien.

Het fenomenale succes van vaccinatie heeft de volksgezondheid dus grondig hertekend. Maar dit veranderde landschap heeft eveneens gewijzigde beleidsuitdagingen met zich meegebracht. Waar de relevante vragen vroeger in de eerste plaats van technische aard waren (‘wat kunnen we doen?’), zijn de uitdagingen nu in belangrijke mate ethisch geworden (‘wat moeten we doen?’). In een hedendaags vaccinatiebeleid moeten verschillende, vaak tegenstrijdige belangen met elkaar verzoend worden, en vaak gaan meningsverschillen terug op fundamentele overtuigingen over de rechten en plichten van het individu in de samenleving.

Het doel van dit proefschrift is bij te dragen aan discussies over twee prominente ethische kwesties. Het eerste deel (hoofdstukken 1-5) behandelt aspecten van het probleem hoe individuele rechten en maatschappelijke verplichtingen moeten afgewogen worden inzake ziektepreventie. Wie moet er gevaccineerd worden en om welke reden? Wie zijn de vaccinatieweigeraars en waarom staan ze kritisch t.o.v. vaccinatie? Welke maatregelen kan de overheid nemen om de participatiegraad op te krikken? Het tweede deel (hoofdstukken 6-9) richt zich op de allocatie van het budget voor gezondheidszorg. Mensen hebben recht op basisgezondheidszorg, en - zoals erkend in het Charter van Economische en Culturele Rechten van de Verenigde Naties - kunnen veel vaccinaties tot dit basispakket gerekend

worden. Bovendien beschermen we d.m.v. inenting ook anderen in onze omgeving en leveren we op die manier een dienst aan de samenleving. Dit zijn twee sterke argumenten om vaccins gratis (of aan een sterk verminderde prijs) ter beschikking te stellen van diegenen die gevaccineerd willen worden. Tegelijk weten we dat de gezondheidszorg financieel onder druk staat en dat niet alle medische zorg automatisch kan worden terugbetaald. Doordat er steeds meer vaccins op de markt komen, die wel degelijk effectief zijn in het vermijden van ziekte maar tegelijk erg duur zijn, dringt de ethische vraag zich op of wel alle vaccinatieprogramma's gesubsidieerd moeten worden. Maar indien niet, welke ziekte wensen we dan als samenleving te bestrijden en van dewelke aanvaarden we het bestaan?

Hoofdstuk 1 onderzoekt of deelname aan de preventie van infectieziekten al dan niet beschouwd kan worden als een morele plicht. Drie argumenten worden besproken op basis waarvan men kan stellen dat vaccinatie - afhankelijk van de omstandigheden - als verplicht kan worden beschouwd. Hetzelfde geldt voor andere vormen van preventie zoals het dragen van mondmaskers, het ondergaan van screening-tests of het veelvuldig wassen van onze handen. De reikwijdte van verplichte preventieve maatregelen wordt echter beperkt door de verantwoordelijkheid die andere mensen dragen voor hun eigen gezondheid, en door wat in het algemeen kan worden beschouwd als een (on)redelijke opoffering of een (on)aanvaardbaar risico. Er wordt beargumenteerd dat onze plicht tot preventie sterker is in het geval van een seksueel overdraagbare aandoening.

Hoofdstuk 2 vat de verschillende redenen samen waarom sommige mensen vaccinatie weigeren, alsook de socio-demografische verschillen die bestaan tussen voorstanders en sceptici. Ook wordt een cognitieve dimensie besproken waarin beide groepen blijken te verschillen: maatschappelijke oriëntatie. Vergeleken met individuen die een positieve houding hebben t.o.v. vaccinatie scoren sceptici lager op de oriëntaties horizontaal individualisme (HI) en horizontaal collectivisme (HC). HI wordt doorgaans geassocieerd met een hoge waardering van enerzijds individuele autonomie en anderzijds gelijkheid in interpersoonlijke interactie. Typische HC waarden zijn enerzijds wederzijdse afhankelijkheid en anderzijds samenwerking op basis van gelijkheid. Dergelijke verschillen kunnen belangrijk zijn voor het ontwerp van communicatiestrategieën voor vaccins.

Hoofdstuk 3 richt zich tot het vaccinatiebeleid. Er wordt aangevoerd dat doelgerichte vaccinatie (selectieve terugbetaling en/of actieve benadering van

specifieke subgroepen) niet alleen mag gebeuren o.w.v. efficiëntie (kosten-effectiviteit), maar dat beleidsmakers deze voordelen moeten afwegen tegen hun bredere maatschappelijke gevolgen (in termen van rechtvaardigheid, non-discriminatie, bescherming van de privacy en non-stigmatisering). Het verhogen van de participatiegraad kan bereikt worden d.m.v. onderwijs, gebruik van zogenaamde 'nudges' (kleine stimuli), incentieven of wettelijke dwang. Al deze maatregelen zijn in de juiste context ethisch verdedigbaar. Dit laatste hangt af van de specifieke kenmerken van de vaccinatie-uitdaging (vooral dan het feit of vaccinatie beschouwd kan worden als een morele plicht) en de mate waarin vrijwillige medewerking tekortschiet.

Hoofdstuk 4 onderzoekt hoe de bevolking denkt over de kwesties die besproken worden in hoofdstuk 3. Voor welke ziekte en in welke doelgroep wordt selectieve vaccinatie ondersteund door de bevolking? We vinden grote verschillen tussen het benaderen van gezondheidswerkers, kinderen of reizigers enerzijds en immigranten anderzijds. In de eerste groepen wordt doelgerichte vaccinatie als een aanvaardbare beleidsoptie beschouwd. Bij immigranten is dit niet het geval. Hier vinden mensen dat de efficiëntiewinst van een dergelijke benadering niet opweegt tegen de bredere maatschappelijke kost. De introductie van maatregelen met als doel het opkrikken van de participatiegraad wordt in het algemeen niet als problematisch beschouwd (zolang dit noodzakelijk is om het succes van preventie te waarborgen). Er zijn slechts beperkte verschillen in de steun die toegekend wordt tussen het toekennen van financiële consequenties (beloning of straf) en het gebruik van wettelijke dwang. Voorkeuren tussen deze drie maatregelen blijken tevens geassocieerd te zijn met de maatschappelijke oriëntatie van de respondent (zie ook hoofdstuk 2). Een hoge score op verticaal individualisme leidt tot een hogere (lagere) kans om juridische dwang (beloningen) te verkiezen als beleidsmaatregel.

In de voorgaande hoofdstukken, maar eveneens in een groot deel van de gepubliceerde literatuur, worden externaliteiten van vaccinatie (groepsimmuniteit) beschouwd als een wenselijk fenomeen. Echter, soms is dit niet het geval. In **hoofdstuk 5** wordt de morele relevantie van negatieve externaliteiten besproken. Er wordt aangevoerd dat dergelijke programma's de ziektelast herverdelen en dat ze als zodanig beschouwd kunnen worden als een probleem van verdelende rechtvaardigheid. Vanuit een contractualistisch perspectief moet hun introductie gerechtvaardigd kunnen worden in universele principes, waartegen ook diegenen die zullen verliezen zich niet redelijkerwijs kunnen verzetten.

In het tweede deel van het proefschrift wordt de verdeling van het budget voor gezondheidszorg besproken. Hoofdstukken 6,7 en 8 gaan over efficiëntie. Het streven naar efficiëntie is gebaseerd op het idee dat we maximaal gebruik moeten maken van de beperkte middelen die beschikbaar zijn voor gezondheidszorg (i.e. we mogen geen kansen laten liggen om mensen te helpen in hun medische noden). Kosten-effectiviteitsanalyses zijn hierin een belangrijk instrument om beleidsmakers te informeren. Echter, bij de toepassing van deze analyses op vaccinatieprogramma's treden er een aantal methodologische problemen op.

Hoofdstuk 6 behandelt problemen met het kwantificeren van de gezondheidseffecten van acute infecties in 'Quality-Adjusted Life Years' (QALY). Vier verschillende maar verdedigbare methoden om een gezondheidstoestand te kwantificeren worden vergeleken bij hepatitis A patiënten. Er wordt aangetoond dat de keuze van methode kan leiden tot substantieel hogere schattingen van morbiditeitsimpact. Dit kan grote gevolgen hebben voor de daaruit voortvloeiende kosten-effectiviteit van een interventie. Daarom wordt aangevoerd dat dergelijke keuzes een extra bron van onzekerheid vormen bij kosten-effectiviteitsanalyses, waarvoor indien mogelijk gecorrigeerd moet worden.

Hoofdstuk 7 wijst op een belangrijk verschil tussen de economische evaluatie van een niet-besmettelijke en een besmettelijke ziekte. Bij deze laatsten kunnen grote extra kosten optreden die voortvloeien uit de indamming van een besmettingshaard. Bij hepatitis A is dit zelfs het grootste deel van de economische last. Dergelijke kosten moeten worden opgenomen in de economische evaluatie van preventie, zoniet zal de doelmatigheid van vaccinatie systematisch onderschat worden. Er wordt aangetoond dat dit inderdaad het geval is bij de beschikbare economische studies over hepatitis A in de literatuur.

Hoofdstuk 8 presenteert een kosten-effectiviteitsanalyse van hepatitis A vaccinatie voor volwassenen in België, waarin rekening gehouden werd met de methodologische bevindingen uit de hoofdstukken 6 en 7. Op basis van een groot aantal gegevensbronnen, en rekening houdend met veel onzekerheden, wordt aangetoond dat publiek gefinancierde hepatitis A vaccinatie voor volwassenen een dure investering is. Om 1 QALY te winnen zou de gezondheidszorg 185 000 € moeten betalen voor vaccinatie en 223 000 € moeten betalen voor screening en vaccinatie van seronegatieven. Om kosteneffectief te worden (minder dan 50 000 € per QALY) moeten risico-

groepen blootgesteld worden aan een infectiekracht die 3,5 tot 4 maal hoger is dan momenteel geschat wordt in de algemene bevolking, of de totale kosten van vaccinatie zouden moeten dalen met ongeveer 75 %.

In **hoofdstuk 9** wordt de focus van het rantsoeneringsdebat verbreed. Er wordt een keuze-experiment samengevat dat uitgevoerd werd in een representatieve steekproef van de Belgische bevolking. Hierin wordt het relatieve belang van bredere overwegingen (zoals o.m. individuele verantwoordelijkheid voor gezondheid, noodzaak van interventie en de leeftijd van de patiënt) onderzocht. Specifieke aandacht wordt besteed aan het verschil tussen preventie en behandeling; eveneens wordt onderzocht of rantsoeneringsprincipes een verschillende invloed hebben naar gelang van het type van interventie. Het blijkt dat individuele verantwoordelijkheid en patiëntenleeftijd van groot belang zijn voor de Belgische bevolking. Preventie is extra waardevol wanneer het bedoeld is voor ernstige ziekten en jonge volwassenen. Er zijn substantiële verschillen in de voorkeuren van respondenten die onderling verschillen in o.a. leeftijd, geslacht, gezondheidstoestand, gezondheidsgerelateerde levenstijl, en opleidingsniveau.

Tot slot, vaccinatie blijft een hoeksteen van volksgezondheid. In een tijd waarin de gevolgen van bepaalde ziekten meer en meer uit het collectieve geheugen verdwijnen, en waarin nevenwerkingen breed uitgesmeerd worden in de media, is het blijvende succes van vaccinatie onlosmakelijk verbonden met het vertrouwen van de bevolking. Dit wordt voor een groot deel bepaald door de manier waarop beleidsmakers omspringen met ethiek. In deze thesis heb ik twee ethische moeilijkheden behandeld: (1) Waar ligt de balans tussen individuele vrijheid en maatschappelijke plicht inzake vaccinatie? En (2), welke vaccinatieprogramma's moeten gesubsidieerd worden? In beide gevallen blijkt dat vaccinatiebeleid een complexe materie is waarbij verschillende ethische waarden, principes en gevolgen zorgvuldig afgewogen moeten worden, waarin er geen eenduidige antwoorden zijn en waarin steeds een specifieke aandacht noodzakelijk is voor de bredere maatschappelijke context.

List of publications related to the thesis

Peer-reviewed, international scientific journal articles:

- Luyten J, Engelen B, Beutels P, "The sexual ethics of HPV vaccination for boys", *HEC Forum,* (2014), 26 (1), p. 27-42
- Luyten J., Desmet P., Dorgali V., Hens N. & Beutels P., "Kicking against the pricks: vaccine skeptics have a different social orientation", *European Journal of Public Health,* (2013), 2014, 24(2): p. 310-314
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Submitted manuscripts:

- Luyten J, Ogunjimi B. & Beutels P, "On the equity of vaccination programs that redistribute disease"
- Luyten J, Kessels R., Goos P. & Beutels P, "Public preferences for prioritizing preventive and curative health care interventions: a discrete choice experiment"

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Curriculum vitae

I studied Applied Economics at the University of Antwerp and Philosophy at the University of Leuven. Since 2007 I have been working as a researcher at the Centre for Health Economics Research & Modelling Infectious Diseases. My main research interest lies in health economics, public health ethics and social philosophy. I was a visiting scholar at the Centre for Economics and Ethics of the University of Leuven, The School of Public Health and Community Medicine of the University of New South Wales in Sydney, Australia and the Rotterdam Institute of Law and Economics (EUR) in The Netherlands. In 2009 I received Pfizer's European HTAcademy scholarship, a competitive grant for a young health economist.

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