LIMITS TO OUR KNOWLEDGE

In this last chapter I summarise what we have learned from studying rotavirus vaccination during the past years and from analysing the approach we took in health economics for this vaccine worldwide. I will present in addition what I consider remaining challenges and I will indicate ways I would like to further explore these domains as there is still much to examine and to value.

6.1 WHAT DID WE LEARN?
When selecting the subject of health economic analysis of rotavirus vaccination for this thesis I thought at start -and many with me as well- this will be an easy task to accomplish. The analysis is straightforward because the disease happens in a well-defined target group -the very young ones- and the results of the vaccine from the European trial were quite impressive, especially when the disease was severe with a 100% reduction in hospitalisation rate during 1st year [31].

Well, that statement about easiness in the analysis is not completely true. Rotavirus disease creates a more complex environment than seen at first sight and the impact the vaccine has is quite sophisticated. But 3 elements came out from the studies we undertook in Belgium that now better clarify how the rotavirus puzzle and its immunisation process fits together that was unclear before the vaccine was introduced in the market.

One is that we observed from the trial results that the vaccine efficacy measured with the formula we all know $\left\{ \frac{\text{rate of events in the vaccine arm}}{\text{rate of events in the control arm}} \right\}$- significantly decreases in the 2nd year compared with the 1st year measurement. An explanation for that phenomenon easily given was that the vaccine’s efficacy is waning after one year and that this waning process will continue during the subsequent years. It took much effort to convince other parties that the vaccine efficacy was not waning over time rather the increase in natural immunity in the child population is the reason for a decreased denominator in the formula of measuring the vaccine efficacy. On top of that an important herd effect was present in the control arm of the European trial during the 2nd year of evaluation as the children were randomised 2 to 1. The finding that there is no waning in vaccine efficacy to be suspected after one year –this is based on the comparison between model predicted and observed data-, had major consequences [24]. Many specialists thought that we should go now for a booster dose if the vaccine waning is prominently present in the vaccinated population after 2 years. This booster dose is currently heavily promoted in developing and emerging markets like India for instance. But the opposite is the truth. Earlier vaccination of the child population in the developing world is a more sensitive way to create more health gain than planning a 3rd dose later on when an already high spread of the natural immunity in the child population will compete with the vaccine immunisation process stimulated by the 3rd dose. Also from an economic point of view is a 3rd dose program not such a good option to select when the vaccine prevention budget is limited as we have shown with the optimisation modelling technique.
We could have been stronger in our assessment about the post-vaccine findings of ‘no vaccine efficacy waning’ over time at the moment of the product launch in Europe. But what we missed were reliable and detailed epidemiology data on the natural history of the infection and the disease. These data should have shown the progressive immune protection generated by the natural, subsequent infections with the virus. We had data from Mexico of Dr Raul Velazquez who did a remarkable study on infection rates in a cohort of children in 1996 a few years before the RotaShield vaccine was on the market [32;33]. However, that was all we had. We had no information about the detailed spread of the infection and the disease by specific age-groups under 5 years old in Europe. We did not know how the children were normally behaving in their contact patterns when they were very young. Much at the time we started modelling the disease was ‘best guessing’. Still today we have no good explanation why the spread of the virus preferentially occurs during the winter period each year in our world of the northern hemisphere.

Second is that the disease spread has an intimate connection with the vaccine impact through the way children are nurtured during their first year of life: are the children going to a hub site such as day-care centres where the spread of the infection is heavily multiplied or not [33]? Vaccination with a high uptake will stop the spread of the infection in day-care centres not only amongst those vaccinated but especially amongst the unvaccinated children. They could be younger or older than the first target group. As a consequence the drop in hospitalisation when one starts introducing the vaccine at the right moment —no later than the end of the 2nd quarter of the year prior the next epidemic period—, will be huge during the epidemic period as we have observed now in the UK. In addition we are suspecting that there is another source of rotavirus infection that hits the children besides themselves. These are the professional and non-professional care-givers. As the vaccine doesn’t impact that specific source directly, it is likely that the rotavirus will continue being endemic and infecting the child population at a much slower pace than if the infection comes from within the group. At the end it will be difficult to reach a ‘disease elimination’ status soon if we keep the vaccination strategy as it is now.

A last interesting finding is related to the previous one with the massive hit the vaccine causes on the reduction of hospitalisation. We should have had a better focus on that point from the beginning when we were thinking about rotavirus vaccination: understanding under which circumstances the disease appears and what could be the impact of a huge drop in hospitalisation on the management of this sector in health care after the vaccine introduction. We were maybe a little naïve or blind about the results of the clinical trial with a 100% reduction in hospitalisation. This finding was too much considered as if it was another interesting finding of the trial but we were not thinking behind the numbers reported. Meanwhile 1/3 of the hospitalisations during the winter period are caused by rotavirus diarrhea, the virus is a major cause of nosocomial infection in hospital care amongst children, the disease happens in a period when other prominent infections occur. Under such circumstances the introduction of the vaccine with a high uptake must create an imbalance into the health care system during the epidemic period. We should have better observed, measured
Exploring new ways of measuring the economic value of vaccination

and reported those findings. The imbalance could be a cause of unrest amongst the professional health care workers or it could be considered a major breakthrough benefit by the same personnel desperately seeking for a solution against overcrowded wards during each winter period. This is what we analysed with our quality of care study that reports for one hospital in Belgium the in-house benefit of moving into a vaccination program against rotavirus disease. That change engendered positive consequences on bed-day patient management and on personnel management during the epidemic periods in hospital care.

I could have listed other interesting data observed from all the other research undertaken in many different countries across the world. We measured for the first time the real benefit of absenteeism reduction amongst working mothers after the introduction of the vaccine. We discovered a high cost at home of a sick child in many middle-income countries where the whole village passes by to nurture the family members. This is a perfect spread of the disease we now can easily stop with the introduction of the vaccine and make important savings at the level of the family unit. We also measured the impact the disease has on the quality of life of parents and particularly on working mothers. All these different studies indicate that a simple disease as rotavirus diarrhea has a much broader societal impact than we ever first thought. The benefit of vaccination can be more intense than we estimated in our models of economic evaluation as we don’t always capture all the -sometimes small, but critical- values to be expressed into monetary terms or in QALYs in the equation.

6.2 REMAINING CHALLENGES
While our research has put new light on what was first seen as a simple infection and disease with an easy to value vaccine, I also discovered remaining challenges regarding understanding well what could be the full economic benefit of the vaccine in different parts of the world. I summarise them hereunder in a few points.

A first challenge is that we transferred without analysing in depth the economic assessment tool of Incremental Cost Utility Analysis (ICUA) performed with therapeutic drugs in a well-established health care market to preventative vaccines in the world of public health that is currently suffering in having no much of an attractive image. We then also easily transposed the same technique from developed to the developing world. So, we moved around with a health economic evaluation tool that was not well tested whether it was appropriate for the evaluation of new features in new environments.

The question is now why do we think that ICUA is maybe not appropriate for the evaluation of prevention and particularly for the prevention against infectious diseases with vaccines and why will this tool also have difficulties to be applied in developing countries? Let me first answer the first question about treatment versus prevention.

6.2.1 Treatment versus prevention
As explained in my introduction ICUA has been initiated a while ago within a health care program that at that time was already well focussed on treatment
and cure. Within that programme the action of health care only starts if there are patients who have complaints, then step into the system for getting their symptoms diagnosed and measured by a physician who is waiting for them to come. The doctor will subsequently apply a treatment that shows signs of improvement for the patient. In that patient-physician relationship the physician will chose a treatment amongst many options. He will select the one that guarantees best chances of success for him and his patient. That approach is workable and sustainable if there is a social security system in place behind the scene to finance the process of diagnosis and treatment. In all aspects of that program everything is directed to the individual, from care-giver to care-taker. In addition the health gain for the individual patient, achieved through the treatment applied, has been financially estimated to a maximum price set in the range between 20,000 and 50,000€/effect gained or 54€ to 137€ for a perfect healthy day. All new treatment options that enter the health care market today from which a physician can chose, have been evaluated within that scheme of extra-payment for extra health gain achieved to a certain maximum level. If the physician choses another treatment option, the system doesn't collapse. Rather it is expected that he makes the change because there is more chance of treatment success for the individual patient.

Now, looking at prevention, the starting points are quite different from treatment and cure and the way to measure success. First, with prevention performed through vaccination one doesn't need to be sick before entering the program rather the opposite. When a person is sick, adding vaccine prevention at that time is too late. In addition, with prevention one likes to reach the largest group of the at risk population as possible. So, the action of the medical personnel is in the opposing direction to treatment. Not waiting until the patient comes, but being active until all subjects are covered by the vaccine. The organisational consequences and logistics of vaccine prevention are therefore completely different from therapeutic care. Many countries have developed a special health care structure for implementing successfully a vaccine preventative program for infants and children separate from normal care. If one achieves a high vaccine coverage rate, there is then more benefit to be measured at the population level than summing the individual gain per subject because of the potential herd effect caused by the vaccine. So, measuring vaccine success should preferentially occur at the population than at the individual, patient level. Meanwhile, calculating the specific, preventative successes is a challenge because with good prevention nothing should happen and measuring nothing over a long period of time is not very exciting. It can often lead to errors as surprising this may be (cfr. pap smear results in cervical cancer screening after the introduction of HPV-vaccination [34]). In addition because nothing is happening a tendency will appear to weaken the continuation of the vaccine program as initially developed leading to a lower coverage rate and to a higher susceptible group of individuals at risk.

Next is that, if one shifts from one health care intervention type such as treatment and cure to another one such as prevention, there is a major change that must occur within the delivery of care that is not obvious to organise quickly and well. It is certainly not as easy as switching treatment options as mentioned in the previous paragraph. For instance when the rotavirus vaccine was brought into the European
Exploring new ways of measuring the economic value of vaccination

market in 2006, we all thought that authorities will choose for it immediately. In reality nothing like that happened. It rather took time (= years) to get it implemented because of lack of budget availability, organisational changes to get a new vaccine prevention train rolling, convincing many stakeholders about the additional hidden benefit of the vaccine. We should have better prepared ourselves to get the vaccine prevention train right on the rails with the health administration of a country, but we did not. We went too quick and were too self-reassured.

Finally comes the issue of economic comparison between treatment and prevention. Treatment always comes late in the process of disease development and the evaluation often stops when there is any more medical attention whereas the person still may recover from his disease and my not function under optimal conditions so that his Quality of Life (QoL) is still impaired. Prevention always comes before treatment when symptoms appear that don’t always need medical attention and avoids as well the quality impact period post-medical treatment. As a consequence the accumulated QALY-benefit in a cohort will always be higher with prevention than with treatment because prevention will avoid more harm as it operates earlier in the disease process and it can avoid subsequent disease impact that isn’t captured by the normal medical attention during the period of medical treatment and post-medical recovery. Avoiding more QALY loss with prevention than with treatment may lead to a higher cost for vaccine prevention if the price setting happens the same way we are doing it as for treatment. The next Table 6-1 and Figure 6-1 gives a better sense about what amount of QALY-loss difference between treatment and vaccine prevention we are talking about. It is a simple hypothetical disease case comparable to rotavirus but other infectious diseases in childhood could be compared as well such as pertussis, for instance. The accumulated benefit gain expressed in reduced QALY-loss is measured for a

<table>
<thead>
<tr>
<th>Impact</th>
<th>Sp treatment</th>
<th>No Sp treatment</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days</td>
<td>Dysutility</td>
<td>QALYs</td>
</tr>
<tr>
<td>Pre-medical Disease</td>
<td>-0.1</td>
<td>4</td>
<td>-0.00110</td>
</tr>
<tr>
<td>Medical Disease 1st day</td>
<td>-0.2</td>
<td>1</td>
<td>-0.00055</td>
</tr>
<tr>
<td>Disease subsequent days</td>
<td>-0.3</td>
<td>7</td>
<td>-0.00575</td>
</tr>
<tr>
<td>Post-medical Recovery</td>
<td>-0.1</td>
<td>3</td>
<td>-0.00822</td>
</tr>
<tr>
<td>Sum</td>
<td>-0.00822</td>
<td>-0.0025</td>
<td>-0.0007</td>
</tr>
</tbody>
</table>

Table 6-1 Measuring and comparing the amount of QALY loss by special treatment or prevention

<table>
<thead>
<tr>
<th>Impact</th>
<th>Sp treatment</th>
<th>No Sp treatment</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days</td>
<td>Dysutility</td>
<td>QALYs</td>
</tr>
<tr>
<td>Pre-medical Disease (proportion)</td>
<td>0.3</td>
<td>-32.87671</td>
<td>-32.8767</td>
</tr>
<tr>
<td>Medical Disease 1st day</td>
<td>0.15</td>
<td>-8.21918</td>
<td>-8.2192</td>
</tr>
<tr>
<td>Disease subsequent days</td>
<td>0.15</td>
<td>-86.30137</td>
<td>-8.6301</td>
</tr>
<tr>
<td>Post-medical Recovery</td>
<td>0.1</td>
<td>-8.21918</td>
<td>-2.7397</td>
</tr>
<tr>
<td>Sum</td>
<td>Total cohort</td>
<td>100 000</td>
<td>-135.61644</td>
</tr>
</tbody>
</table>

Gain 1 83.1507 122.0548
Gain 2 38.9041
cohort of 100,000 subjects over a period of one year. With vaccine prevention one may avoid close to 4 times more disutilities than with a new special treatment option. The disease utility loss that is never expected to be impacted by the medical care program is now prevented by the vaccine.

I like to raise here two questions that are part of the challenge to position vaccines in an attractive way compared with treatment. One is: should the monetary threshold per QALY gained be the same as the one used in treatment for disease events that don’t need medical attention? In other words should we maintain a threshold of € 20,000/QALY for the whole prevention period or do we need to adjust in function of what is prevented when, where? The other question is: should the sick periods avoided through prevention be financed by the health care system or by other means that see benefit in obtaining those particular additional gains?

The two questions are critical as they are related to the financial sustainability of the health care program especially in light of the new trend of evaluating new interventions in terms of value based pricing. To put the issue at the extreme with a very simple health problem we are all exposed to every year: common cold. It is a very frequent illness with a seasonal peak during wet and cold periods each year. It doesn’t always need medical attention. But let’s suppose we develop a nasal vaccine –easy to administer with no side effects. The vaccine is very effective and especially efficacious if we achieve a high coverage rate during pre-seasons. Who should pay and how much? This is a domain of investigation I would like to explore during the coming periods so that price setting of vaccines better reflects the true economic value.
Each vaccine in the market has an important part of its benefit that has no return on investment to the health care program (see Figure 6-1, the non-measured or intangible benefit). We often don’t consider these features as critical to be separated from the total medical benefit because they are underreported or not always transparent in the way they are measured and quantified. Meanwhile this extra gain is part of the individual benefit as well as part of the societal benefit. More coverage with a vaccine of the susceptible group will lead to more societal than individual gain. So, if everything within vaccine prevention is preferentially driven towards a level of assessment that is the population instead of the individual, shouldn’t we then look for economic evaluation tools that preferentially assess the benefit and the cost at that level? Could therefore CBA, a technique that has more a societal ambition in economic evaluation than CUA, be a better option to work with for our economic assessment of vaccine prevention? Again, this is a domain I would like to explore in the coming years.

Finally, one should accept that vaccine positioning in society has evolved over time: from reducing and avoiding deaths, to limiting costly medical interventions and outbreaks, to also gaining in preventing non-medical disease events as we see it today. This can only be well accepted if the economic evaluation is recommended to be initiated at the level of a population. Prevention has of course benefit or value for the individual but the full value can only be demonstrated at the higher level. The evaluation must have that ambition to look preferentially at the level of a population [35]. Three arguments push me therefore to think and to act in the economic evaluations of vaccines into that direction: the herd effect caused by the vaccine; the maximum benefit that can only be attained with a high vaccine coverage in the population; and more benefit is obtained than with treatment through the avoidance of disease events that don’t impact directly the health care program but society.

6.2.2 Developed versus developing countries
The other challenge or question I identified about the appropriateness of ICUA for vaccines is when transposing this analysis tool from the developed to the developing world. More striking for a developing country is that it is still in its infancy of developing a full health care program. Under such circumstances priority setting between different health care development options (public health versus care) is critical with a confrontation between two worlds of applying medicine (prevention versus therapy; societal versus individual). In that type of environment could prevention been cheaper than treatment? Low-income countries may therefore go in the opposing direction of high income countries (see further) and start with public health development before investing in treatment and therapies.

As mentioned in chapter 5 the technique of cost-effectiveness analysis is for low-income countries an instrument of economic evaluation that is not so helpful because the right threshold is difficult to be identified and the CE-price-range is much too large for making a sensible selection for new interventions. Identifying and communicating that there is a problem is one objective of the paper submitted. Bringing a solution to that problem is the next step to take and to present.
One way to give direction in solving the problem regarding which priority to take in health care development (treatment versus prevention) is an analysis we recently undertook to be further explored with real data. Our starting point is that every major infectious disease condition can be tackled from two different angles: treatment and prevention. With treatment we have to build extra hospital beds to achieve our goal to maintain a certain controlled level of mortality rate caused by the disease. With prevention we need to establish a vaccination program with a certain level of coverage to maintain the same level of mortality rate. Suppose that our ambition is to work with both options (treatment and prevention), we should be able to demonstrate what combination of treatment and prevention will give a same result in output (same mortality reduction). In a next step we can calculate the budget needed to get this combination of cure and prevention in place. It shouldn’t be difficult to demonstrate that the more prevention is pushed forward the budget will be lower whereas the more one pushes for extra hospital beds, the higher the budget. The next graphs illustrate what could be an analysis and presentation of the results.

The first graph (left) indicates the construction of a mortality rate isoquant for a specific infectious disease by combining hospital beds with vaccination that leads to a same output along the blue line plotted. In the next graph (right) we construct in addition a budget line that indicates a combination of money to be spent on hospital beds versus vaccination coverage. The Y-axis in the right graph is split into two (one left and one right). The right one and going up in value, is about the availability of extra hospital beds to manage a certain level of mortality rate for a specific disease (same Y-axis as in the first graph). The left one and going down to increase value, is the budget needed to manage and maintain the specific mortality rate for that disease split into a budget for hospital beds versus vaccination. The X-axis indicates the coverage rate needed for vaccination to reduce to the same level of mortality rate (same X-axis in both graphs). It is not so difficult to see that under such circumstances there is an ideal point of low budget that fits the 3 points: mortality, vaccination coverage rate and extra hospital beds. The objective in the coming months is to collect now field data from registries and literature on mortality, budget, hospital care and vaccination for a specific infectious disease to
feed the model design for a country that still needs to build up its total health care program. This graph should help designing priority setting for a given budget and a given health goal to be achieved.

6.2.3 Optimisation modelling

That brings us to the next analysis performed to identify solutions for the economic assessment of vaccines in low income countries and emerging markets using optimisation modelling. The technique helps solve different issues I have highlighted in the previous paragraphs such as the difficulty of defining a maximum threshold for valuing the QALY/DALY gain, having a too large price range for being cost-effective, being unable to combine different intervention options, identifying what is really a relevant combination of options, and at what price level for the new intervention can we work under specific constraints. But let's make it clear from start. Optimisation modelling isn't the unique solution we were all waiting for that suddenly solves all our problems in the economic assessment of new medical interventions to be introduced in the health care market. Using this technique it will lead to new problems and new challenges to tackle. But the approach helps indicate directions where solutions seem to be better accepted than with ICUA and it helps thinking in a frame of working under specific constraints.

Because the big challenge of today for any health care program to be developed whether it is in the developed or in the developing world, is Money, Finance. How to make the health care program progressing and sustainable for the future? One cannot deliver good health care if there is no right price defined by which everyone can get access who needs medical support of good quality and that motivate the workers in the system to stay tuned and focussed on their tasks. In addition it must have the incentive for good research by which continuously additional health gain can be achieved. Sometimes the health gain should preferentially to be measured, sustained, and developed at the population level as we are trying to argue here for prevention of infectious diseases through vaccination. But sometimes the health gain can only be achieved and measured at the individual, patient level.

A good health care development program has the right balance between both types of medical interventions. It is not always easy to find that perfect equilibrium because in some environments the approach of the population level through public health with vaccination has been neglected and been overwhelmed by treatment and cure. Sometimes the opposite has been seen that too much public health is promoted where the treatment approach could have done a more efficient job. This is for me a next big challenge to explore: identifying the world of ideal combination between prevention and treatment for different groups (age, sex, social, and environment) within an attractive budget equilibrium sustained by a good financial support and depending of the health care development status.
6.3 **FINAL CHALLENGES**

Finally, there is one other area of interest, I would like to further explore. To disentangle the cost-effectiveness analysis we are doing now into more valuable pieces of better information. I like to express the following reflection regarding CEA that needs further exploration in depth. A big weakness of ICEA is the way we are using it now. We are blind in trying to achieve incremental health gain with any new intervention we want to bring on the market. If we achieve that goal, we expect to get a price premium for the new intervention that as an end-result will increase the total cost side of the health care budget as long as the ratio of the cost-difference divided by the effect difference is below a certain threshold. What we assume in our way of applying the cost-effectiveness threshold is that the QALY-gain occurs independently from the cost-difference, which is not always the case. As a matter of fact we often do at double counting. We reduce the cost-side for hospitalisation reduction and improve the QALY side by not going to the hospital. We can skip one of both if we know that the cost we pay in the medical sector for any intervention we have avoided, perfectly reflects the QALY improvement the new intervention generates. But we know that the prices we are paying are not real market prices and the QALY changes we obtain are an approximation of the value we gain. As an end-result both sides are biased. However working in a cost contained environment we should try to focus the analysis on cost-reduction and cost-offset and less on QALY-gain if that gain is anymore marginal or result in a sensitive improvement.

What could be an interesting domain to explore in CEA is to include the level of cost-offset as a barrier to allow an increase in price-setting independent of the QALY-gained. That seems counter-intuitive but we shouldn’t try to deliver a health care program that focus on cost increase how acceptable it is, rather than on a cost-containment strategy. The cost-increase should be allowed for those situations that cause a QALY-gain but with limited cost-offset in order to stimulate a reasonable price setting for any new intervention and research initiative that generates better quality health.

Related to that we should further investigate the statement about why vaccines are considered to be cheap. That question has been raised to me many times. By looking at the problem more in depth it helped to explore two additional features about the use of vaccines today. One is the current investment in vaccination as part of the total health care budget in a high income country. That amount is surprisingly very low: around 0.03% in the UK and the same can be found for France and other European countries using the OECD data-base analysis. The other is that we observe that in the latter type of countries an expansion of preventative activities against diseases other than the infectious ones occurs these days such as the use of statins against cardio-vascular diseases. What we should try to analyse and to compare are data per prevention technique (vaccine versus drugs) and per broad disease area (infectious diseases versus cardio-vascular diseases) in a country like the UK for which there is a sufficient number of relevant data available. We should explore the investment rate, the benefit, the cost-effectiveness, and the budget impact analysis per disease area and per intervention type. We may discover two
forces that explain why statins compared to vaccines can achieve a much higher investment budget while the health gain could be lower and still be cost-effective (see Figure 6-3).

One force (F1) is related to what is happening under the budget horizon of cardiovascular diseases versus infectious diseases. Cost-offssets in cardio-vascular diseases are much higher while infectious disease management is much cheaper. So, the cost-neutral price to start with is much higher in statins than in vaccines. Therefore the cost-neutral point (the point where the curve per product crosses the X-axis) shifts from left (vaccines) to right (statins). The second force that benefits the statins in a better price setting than vaccines is a better ability to define the at-risk population. The at risk population for rotavirus infection is the whole birth cohort although we know that only 40% of them will get the disease up to the age of 5 years. With statins we are able to delimit a group where the risk for getting the disease is much higher than 40%. As a consequence the slope factor of the curve for vaccines is much higher than for statins (a1> a2) because the benefit is diluted over a higher number of individuals in the cohort than for statins. Statins can therefore go for a higher maximum price than vaccines (M2 > M1). So, it shouldn’t be so much of a surprise that the investment in statins is so much higher than in vaccines because the disease conditions are so different regarding management cost and focus. However the question remains, should the price of prevention be equivalent or being higher than treatment + the additional health gain in order to go for it?