How to design an optimal vaccine launch

- Designing the optimal vaccine launch remains a challenge.
- So far, no significant study has attempted to unravel the critical steps towards an optimal vaccine launch.
- Dr Baudouin Standaert from the University Hasselt in Belgium and colleagues have studied the country's rotavirus vaccine programme for 15 years.
- Their study, the RotaBIS, has led to the design of a four-step approach that could change the future of vaccine launches for the better.

Identifying an appropriate vaccine launch for an existing infectious disease is crucial for its success. Typically, there are two approaches to launch a vaccine in the market when it is ready. The first approach involves ensuring that the vaccine enters the market on the same day it is approved. The second approach, however, involves a detailed strategy planned before releasing the vaccine to the market, considering the maximum number of people affected and the long-term socio-economic success of the intervention.

Dr Baudouin Standaert of University Hasselt, Belgium and colleagues strongly believe that when introducing a new vaccine, the second option could lead to better herd immunity in the short time frame that leads to fewer economic losses long term.
Spanning over 15 years, the researchers have conducted a detailed study around the launch of the rotavirus vaccine in a high-income country – Belgium, in this case – defining its flaws and proposing a better launch strategy that future vaccines may also use.

RotaBIS is the first-ever study aiming to uncover the ideal scenario for launching a new vaccine.

The rotavirus vaccine case in Belgium

Defining an ideal vaccine launch strategy is not an easy task to conceive. When a new vaccine enters the market, exploring different launching strategies would be highly unethical towards the people enrolled in such a vaccination study since this could lead to some people intentionally receiving a poor vaccination programme. Ultimately, the best way to describe an ideal vaccine launch would be to examine an ongoing vaccination project – which is exactly what Standaert and colleagues did in a span of 15 years.

Rotavirus is a very contagious virus targeting young children (0- to 5-year-olds). It causes diarrhoea, and the vaccination must happen at a very young age to be safe and effective (6–8 months). One of the first countries that has launched a vaccination programme against the rotavirus was Belgium; the country introduced rotavirus vaccination in 2006. In 2007, Standaert and colleagues designed the RotaBIS (Rotavirus Vaccine Belgium Impact Study), the first-ever study aiming to uncover the ideal scenario for launching a new vaccine in a country, which ran for 15 years. The only vaccination evaluations done at that time were models calculating the cost-effectiveness of the vaccine, led on a company level in 2006.

During the initial phase of their investigation, the researchers collected data on an annual basis from 11 hospitals across Belgium to measure the impact of the vaccination on hospitalisations. Overall, the results from the RotaBIS revealed that there was not such a strong response in the vaccine effect in the first years, while the impact curve on hospitalisations (showing the overall impact on the target population) reached a 'plateau', ie, maximised after three years. But surprisingly, new small biennial disease peaks appeared in the target group (2- to 5-year-olds) around 9 years after the vaccination had been initiated.

The RotaBIS concluded that the vaccine programme achieved only a 70% drop in the positive rotavirus tests for hospitalisation after five years due to the wrong start date of the vaccination programme. In fact, the annual peak season of the infection in Belgium is known to be from February to the end of March, indicating that the vaccinations should have been introduced 8–10 months before then. If the timely introduction of the vaccine had taken place, there would have been an estimated 90% drop in the positive tests, and the herd effect would have been noticeable in protecting the unvaccinated older children from infections and disease over a long period of time. The analysis also depicted that the target for infections shifted to older children within the target group, due to the failure to achieve a high herd immunity at start which causes the appearance of the small peaks later on, causing the hospitalisation rate to rise (figure 1).

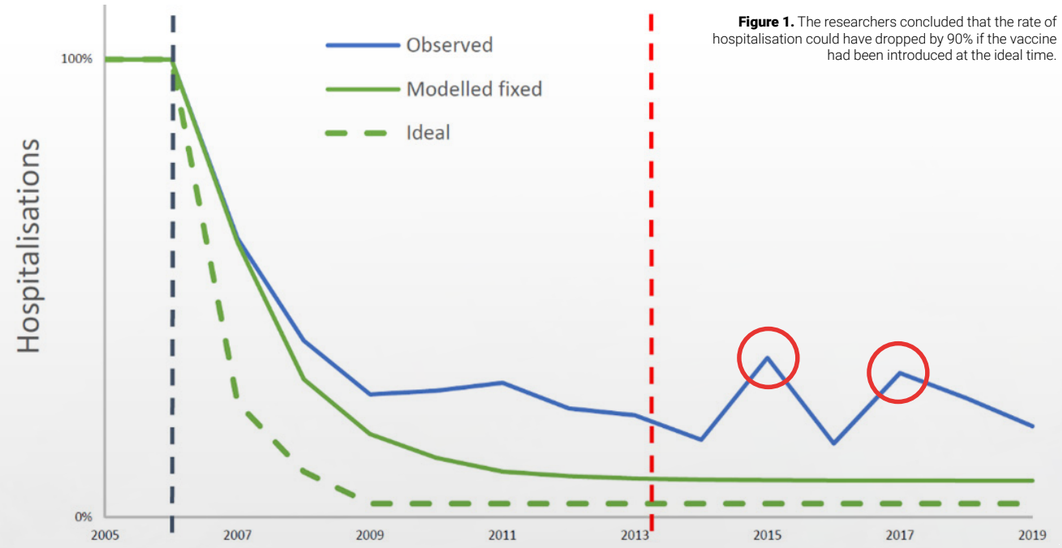


Figure 1. The researchers concluded that the rate of hospitalisation could have dropped by 90% if the vaccine had been introduced at the ideal time.

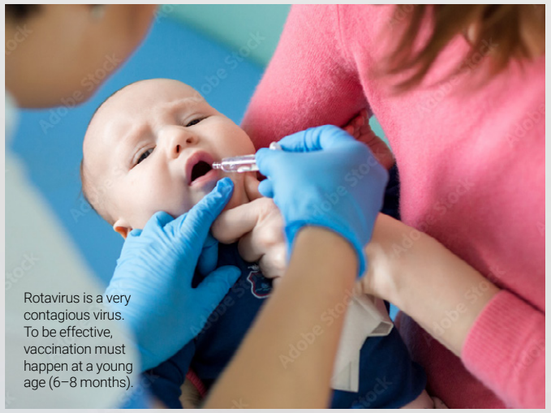
Modified from Standaert & Benninghoff (2022), doi.org/10.3390/v14020425

The steps towards a good vaccine launch

Is it possible to achieve an ideal scenario? Notably, countries such as the UK and Finland obtained much better results than Belgium with launches similar to the model predicted by Standaert and colleagues. The effect of an ideal scenario is direct as it could dramatically decrease the hospitalisations of children and act as a catalyst for the economic assessment of the vaccine campaign in the long term. The researchers emphasise that for an ideal vaccine launch, the cost–impact result needs to be the same as the cost-effectiveness, indicating that the results depend on the overall performance of the vaccination strategy, having no consequences anymore on the infection spread in unvaccinated people over time.

After carefully studying the RotaBIS case in Belgium, the researchers concluded that the ideal vaccine launch consists of four distinguished action points, of which the first two should already be done before the launch. The first action point involves an in-depth understanding of the infection and the disease epidemiology, including the infection speed and the factors it influences (seasonality, genders or ages targeted, primary and secondary sources of infection, and the cost data).

The second action point is modelling the epidemiology, taking into account the findings from the previous step. The modelling construct will include the vaccine launch and encompasses a period called the vaccine uptake period. The duration of that period is until the infection spread reaches its new infection equilibrium in the target group, with the vaccination routinely implemented. This typically happens when the target group to be vaccinated has been fully covered. In the model, one needs to investigate any other factors that could influence the vaccination, such as the effectiveness or the waning of the vaccine (direct forces) and other factors, such as the herd effect and the appearance of secondary sources of infection (indirect forces).



Rotavirus is a very contagious virus. To be effective, vaccination must happen at a young age (6–8 months).

The third action point is also a modelling process in which the long-term effect of the vaccination in the post-uptake period is processed given the dynamicity of the infection spread under control or not of the vaccine. That period comes late in the process after initiating the vaccination programme. In the case of RotaBIS it was starting 8 years after the beginning of the vaccination when the new smaller peaks of disease were happening every two years (biennial peaks). The fourth and last action point is keeping track of the monitoring of the vaccine effect continuously. This is achieved by collecting the same data as at initiation of the study by which the comparison is permanently made between the models initiated and the real-life data, trying

to understand and finding explanations for potential deviations observed. The fourth action point is most critical to identify what could be an ideal vaccine launch as a lesson learned for others who will initiate this vaccination.

Designing wiser vaccine launches

Standaert highlights that in the future, before entering the market, the disease and the vaccines need to be studied thoroughly, and the decision-makers should consider the four-action-point approach for initiating an optimal vaccine launch. Vaccines designed for known infections in a known population could vastly benefit from this approach, including the newer vaccines to come, such as vaccines against the Retroviral Syncytium Virus (RSV). Vaccines against many other known/studied diseases, such as those against pneumococcal infection and human papillomavirus infection, could follow this multi-step approach as described above. Ultimately, with this knowledge, we could walk towards carefully planned vaccine launches with great benefits for both the health condition of a country's population and its socio-economic development.

> **Vaccines designed for known infections in a known population could vastly benefit from this approach, with major clinical and socio-economic benefits to obtain the best return on investment.**

		A	B	C	D	E	F	G	H	I
	Age Groups	Pre	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
1	0–2 m	113	1					2		
2	3–12 m	678								
3	13–24 m	413		5				7		
4	25–36 m	102	3							
5	37–48 m	27				6		8		
6	49–60 m	12			4					
	Total observations	1345								
	Relative	100%								

Subgroup	Area #	Cell numbers	Definition
Direct vaccine effect	5	B2, C3, D4	First vaccinated birth cohort no waning
	6	E5, F6	First vaccinated birth cohort with waning
	7	C2-I2, D3-I3, E4-I4	Subsequent vaccinated birth cohorts no waning
	8	F5-I5, G6-I6	Subsequent vaccinated birth cohorts with waning
Indirect vaccine effect	1	B1	Pre-vaccinated period first birth cohort (0 to 2 m) no secondary source of infection
	2	C1-I1	Pre-vaccinated period subsequent birth cohorts (0 to 2 m) with secondary source of infection
	3	B2-B6	First year herd effect no secondary source of infection (13 to 60 m)
	4	C4-C6, D5-D6, E6	Subsequent years herd effect with secondary source of infection (25 to 60 m)

Figure 2. Defining the areas in the model grid with their regression equations. (m – months, Pre – pre-vaccination.)

Standaert, B, Benninghoff, B, (2022) doi.org/10.3390/v14020425

Decision-makers should consider the four-action-point approach for initiating an optimal vaccine launch.

Personal response

Do you expect differences in the infection profile between the rotavirus vaccine and vaccines for other known infections?

Absolutely. Every infection is different. It can't be completely the same, each having its own characteristics of contagion, preferred target group, dominance patterns, sources of infection, and temporal spread. We need to study this in depth, well in advance before any new vaccine is launched against a particular infection. It helps define the best vaccine launch scenarios with short-term (uptake period) and long-term (post-uptake period) effects.

Would you expect practical difficulties when implementing the four-action-point approach for a vaccine strategy against Retroviral Syncytium Virus (RSV)?

Many different interventional approaches have been developed that will soon come on the market for this disease. This complicates finding the right combination of interventions to control the infection in the shortest period of time (objective for the authorities). The problem of RSV infection control is more complex than for rotavirus, exacerbated by the fact that the disease is also very much present in different age groups (the very young ones and the ageing population). But the four-action-point approach, with the first two steps well developed, is a must for a clear prevention strategy for short-term gain to long-term benefit. It is an interesting but challenging problem in which constrained optimisation models could be very helpful.

What would be the benefits of governments adopting the proposed ideal vaccine launch?

Nowadays, new vaccines don't have the unique focus of reducing mortality as in the past. Today, the benefits of vaccination must be seen much broader: it's not only a gain for the individual being vaccinated, but also for the healthcare system and society as a whole, with a reduction in hospitalisations, improvement in quality of care, reduced seasonal burden of infection for primary healthcare, gain for employers and employees due to a reduction in work absenteeism, fiscal gain for the authorities to spend less on costly healthcare and paying compensations for sick leave, and working parents who don't have to stay home and care for a sick child as often. All these different elements have been demonstrated and reported in separate publications. They are quite substantial for the socio-economic gains of society as proven by the COVID-19 vaccine.

How do you envision the four-action points approach being implemented in low-income countries?

The four-action-points approach is a scenario developed in high-income countries. Why? Because the launch of rotavirus vaccination in high-income countries was not easy, even today. The main driver for vaccination, normally the high disease mortality, was not so prominently present in high-income countries for rotavirus disease. Introducing a new vaccine at the population level is always a big investment in prevention, and the authorities need to understand the full gain of their return on investment. We therefore had to be very precise in the working and the benefit generated by the vaccine – because with good prevention nothing should happen, and that is a very difficult story to sell unless you can clearly demonstrate and illustrate what was before and what comes after the vaccination. The focus was to find the best vaccine launch by which you can demonstrate when and where the greatest benefit of the vaccine will appear under ideal circumstances.

In low-income countries, the priority setting for vaccination differs greatly from high-income countries. Here, the primary focus on reducing mortality drives the vaccination strategy. However, the four-action-point approach, based on the experience in high-income countries, could also help to obtain a better-focused approach in low-income countries if there is, for instance, seasonality in the infection spread which would recommend a clear starting date of the vaccination programme. It's therefore always critical to understand the disease in all its aspects in any specific environment before the vaccine is newly introduced. However, facilities to collect information about the disease and its spread in the community do not always exist or may be cumbersome to develop and assemble, in part because the priority setting is so different (mortality reduction). Therefore, the focus in low-income countries will often be to maximise vaccine coverage of the target group.

What reasons do you attribute to the past lack of a similar study investigating the right path towards a suitable vaccine strategy?

Pressure among the producers of new vaccines to be the first on the shelf determines the price of the vaccine. Also, those rapid processes don't consider that introducing a vaccine in a population may cause heavy disturbances regarding health benefits and consequences. The Belgian case of rotavirus introduction is a good illustration of a too-rapid introduction of the vaccine without knowing the long-term consequences. People considered the 70% reduction in hospitalisations a great success; however, they could have obtained better results if they thought about an ideal launch scenario. Now, Belgium is exposed to biennial infection peaks that are difficult to attenuate because the vaccine has no direct impact on those secondary sources of infections causing those peaks. In that respect, the RotaBIS was a great initiative as it helped us discover those findings. If we had done the same study in the UK or Finland, we wouldn't have seen the short- and long-term consequences of a non-ideal vaccine launch.

Details

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Bio

Dr Baudouin Standaert completed his MD with specialities in Tropical Medicine, Epidemiology, and Health Economics in Belgium. He got his PhD at the University of Groningen, the Netherlands. His subjects of interest include infection and vaccination, cancer, and the elderly. After working in academia in Suriname, at U Antwerp, Burundi, WHO, and U Catholic Louvain, Standaert served as Head of the Provincial Institute of Hygiene, Antwerp. He also worked for the pharma companies of AMGEN and GSK Vaccines. Currently, he is a consultant and guest professor at U Hasselt, Belgium.

Collaborators

- Professor Dr Mark Raes
- Danielle Strens

Further reading

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