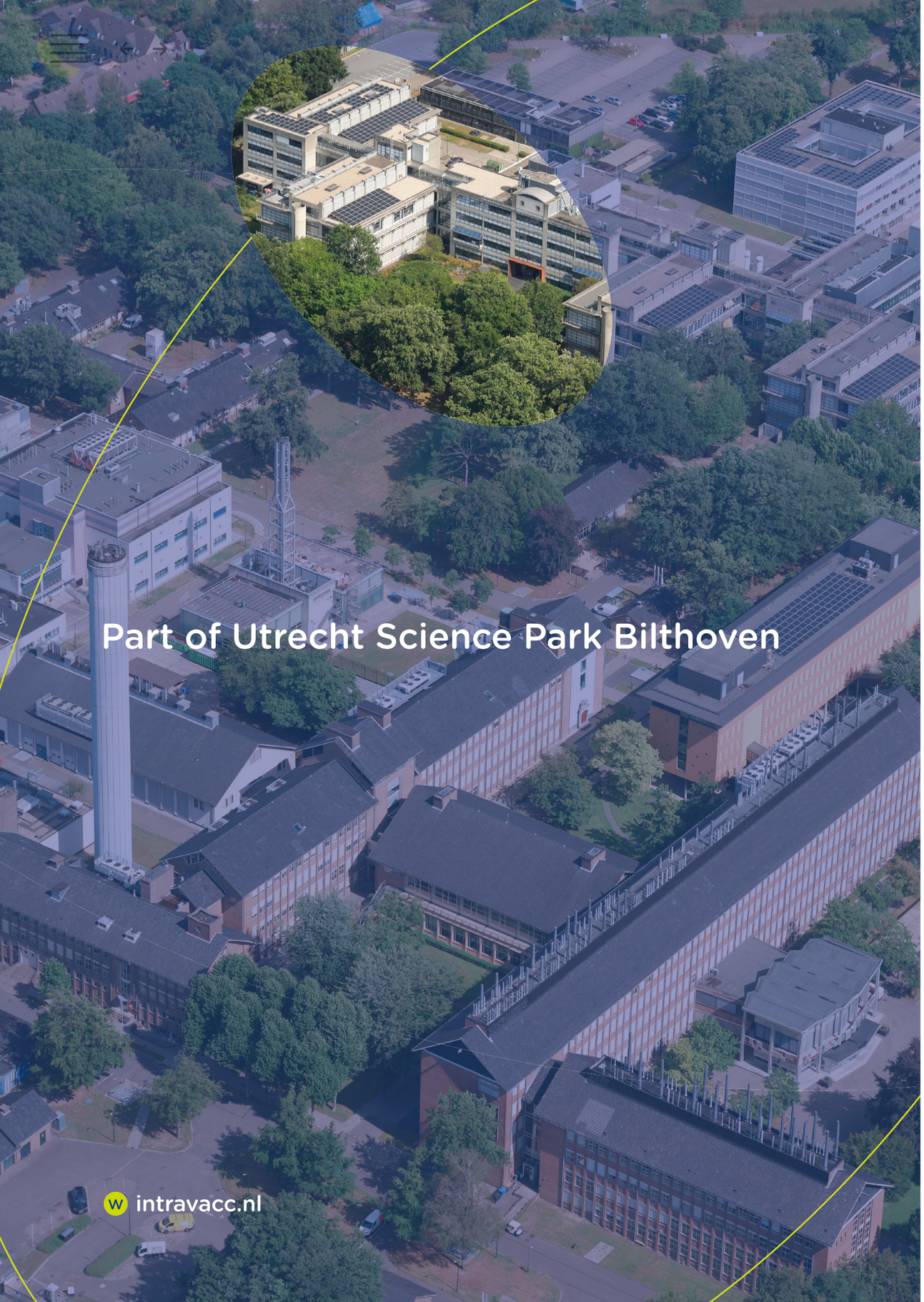
ANNUAL REPORT 2020

Intravacc.
Innovating vaccines



Content

Dear stakeholders,

The year 2020 was a remarkable and challenging year for all of us around the globe. In one way or the other, we were all affected by the Covid-19 pandemic. However, for most companies in the vaccine business, this pandemic triggered the start of an exciting period. During this dynamic year, we successfully continued our efforts to leverage Intravacc's track record to become a stand-alone private contract development and manufacturing organization (CDMO). With our state-of-the-art infrastructure, equipment, experienced staff and unique market position we are able to bridge the gap between vaccine concepts and late-stage clinical trials. Together, we set to work to build Intravacc 2.0. This included a restructure of the organization, implementation of a business matrix, a design controlled product development processes and the establishment of a business development department which will engage with our existing and future customers to expand our services and product pipeline. We also rebranded the company and launched a new website to match our ambition to become a leading CDMO within the vaccine industry.

Many vaccine campaigns are integrated in governmental vaccination programs, in particular those for newborns and young children. These so-called childhood vaccine programs are well established markets. Currently, many of these vaccines are produced in Asia and the average price for these vaccines is already less than $10 per dose. Next to this, the market for traveler- and emerging disease vaccines as well as vaccines for elderly is quite limited. In general one can see that, with the exception of the current Covid-19 pandemic and other strategies for pandemic preparedness, the future market for the prevention of infectious diseases by using vaccines is decreasing. After infectious diseases, cancer is the second largest disease related healthcare problem. Therapeutic vaccines can have a major positive impact on the treatment of cancer patients, but nowadays, this field still heavily relies on surgery, radiotherapy and chemotherapy. Presently, only a handful of cancer vaccines are on the market, so compared to the market for vaccines against infectious diseases, this is an underdeveloped market. Besides, the treatment of cancer patients is quite costly. Using therapeutic cancer vaccines may contribute to a more effective and cheaper alternative treatment of cancer patients. For these reasons, the traditional vaccine CDMO's are quickly moving towards the development of cancer vaccines and gene therapies. The current technology and infrastructure within Intravacc can also be applied for the development of these therapeutic cancer vaccines.

Our Objectives

The year 2020 was a year full of changes. Apart from all our efforts to prepare Intravacc for the future as a commercial CDMO, we accelerated our portfolio review and significantly progressed with the carve-out of more targeted vaccine development projects. We strengthened our commercial effort resulting in over €10 million of new projects to be completed in the coming years. We also published 15 scientific papers addressing the value of our platforms and technology, initiated 4 Covid-19 vaccine development projects and started with the implementation of a vaccine development pathway to streamline our vaccine development projects and gain efficiency. Our leadership changes did not have any impact on our employees and our commitment to deliver to our customers and stakeholders. Concurrently, we worked to strengthen a culture of shared values, collective accountability, commitment and transparency. We will also continue to work on the visibility of Intravacc in The Netherlands and worldwide by sharing our accomplishments in press releases and interviews. In 2020 we appeared in all the major newspapers in the Netherlands as well as on the radio and television with our expertise in vaccine research.

Our Pipeline

In 2020 we continued to expand our services and to fill our pipeline with novel vaccine concepts as part of our mission and vision. Our most advanced novel platform is based on OMV technology for various vaccine concepts. Although produced by bacteria, OMV's can also be used to target viruses and are thus not only limited for the development of bacterial vaccines. Currently we are developing three viral vaccine- and two bacterial concepts on this platform, including Covid-19 vaccines. In 2020 we also licensed a new vaccine technology named iBoost from CimCure, a spin-off from the University of Amsterdam (VUMC). The iBoost technology was initially developed for therapeutic oncology vaccines. In a joint program Intravacc and CimCure are conducting studies to leverage this technology for infectious disease and cancer vaccines. Whereas the growth of the vaccine market against infectious diseases is very low the market needs for therapeutic vaccines is significantly increasing.

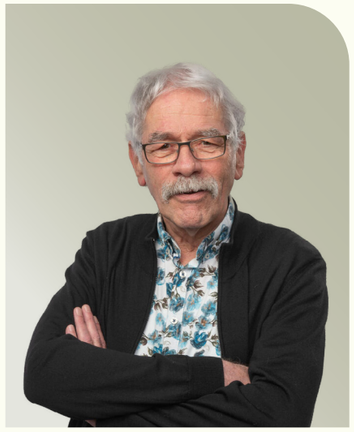
Our People

Due to the length of the privatization process starting in 2016, Intravacc lost some talented people. In the course of 2020 the status of Intravacc as a stand-alone entity became more clear and on January 1st 2021 Intravacc became a private entity with the Dutch government (Ministry of Health) as the only shareholder. Today Intravacc has approximately 130 employees. In the coming years we will significantly invest in people to build Intravacc as one of the leading CDMO's in the world. The fact that the US National Institute of Health (NIH) rewarded Intravacc with a $10 million project to develop an enterovirus vaccine known as the "new polio virus" (EVD 68) is the result of hard work, the dedication of our highly educated workforce and their decision to stay with Intravacc. Due to their strong commitment to Intravacc throughout the years we are well prepared to continue building Intravacc as a stand-alone business. On behalf of the management and the Supervisory Board of Directors, we sincerely thank all of our employees, consultants and advisors for their daily contribution to our progress.

The Future

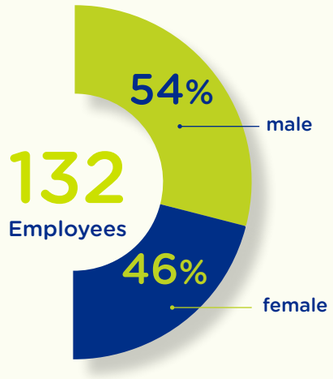
We are very pleased with our progress and expect 2021 to be another very exciting year of growth and accomplishment as we advance our strategic plan to become a leading CDMO providing high quality vaccine development services and bringing innovative vaccine concepts to the market. The investment we have made and will continue to make in our vaccine platforms, the focus on quality, vaccine development and clinical validation, as well as the early success of our Covid-19 vaccine concepts, progress with our oncology strategy and increasing number of commercial service projects is clearly recognized by our industry players. We believe that we are in the very early stages of a sustained growth cycle, with the ultimate goal of offering healthcare providers and governments a wide range of affordable preventive and therapeutic vaccines.

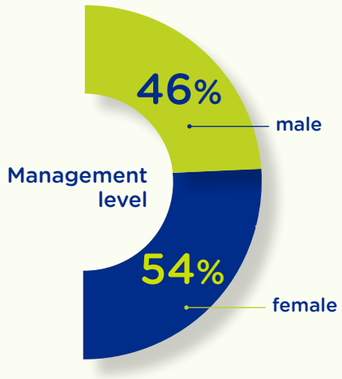
The Supervisory Board and the Board of Directors of Intravacc sincerely appreciates the support and contributions of our stakeholders, scientific collaborators, the medical community, Ministry of Public Health and other stakeholders who have entrusted us to deliver on our mission of developing innovative vaccines to contribute to the reduction of human disease burden.



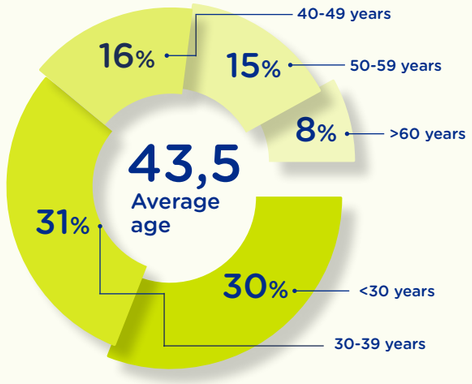
Chapter 1 Strategy and business review

1.1 Key figures

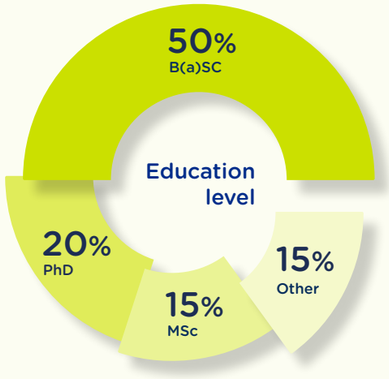




Number of employees and male female ratio employees

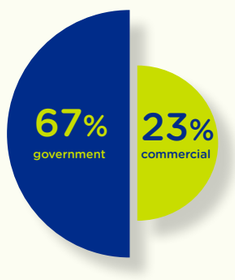


Employee distribution by age 2020

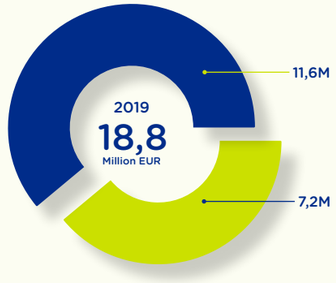


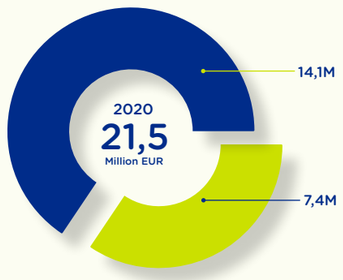
Education level;
% with PhD, Msc and BSc

Number of
GMP batches



Revenue split

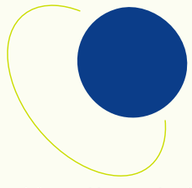




Annual revenue

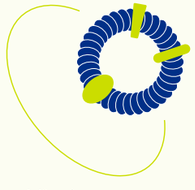
Intravacc's vaccine platforms

Vero cell platform



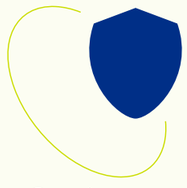
- Live attenuated
- Inactivated
- Vector

OMV platform



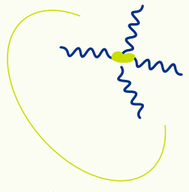
- Viral
- Bacterial
- Adjuvant

iBoost

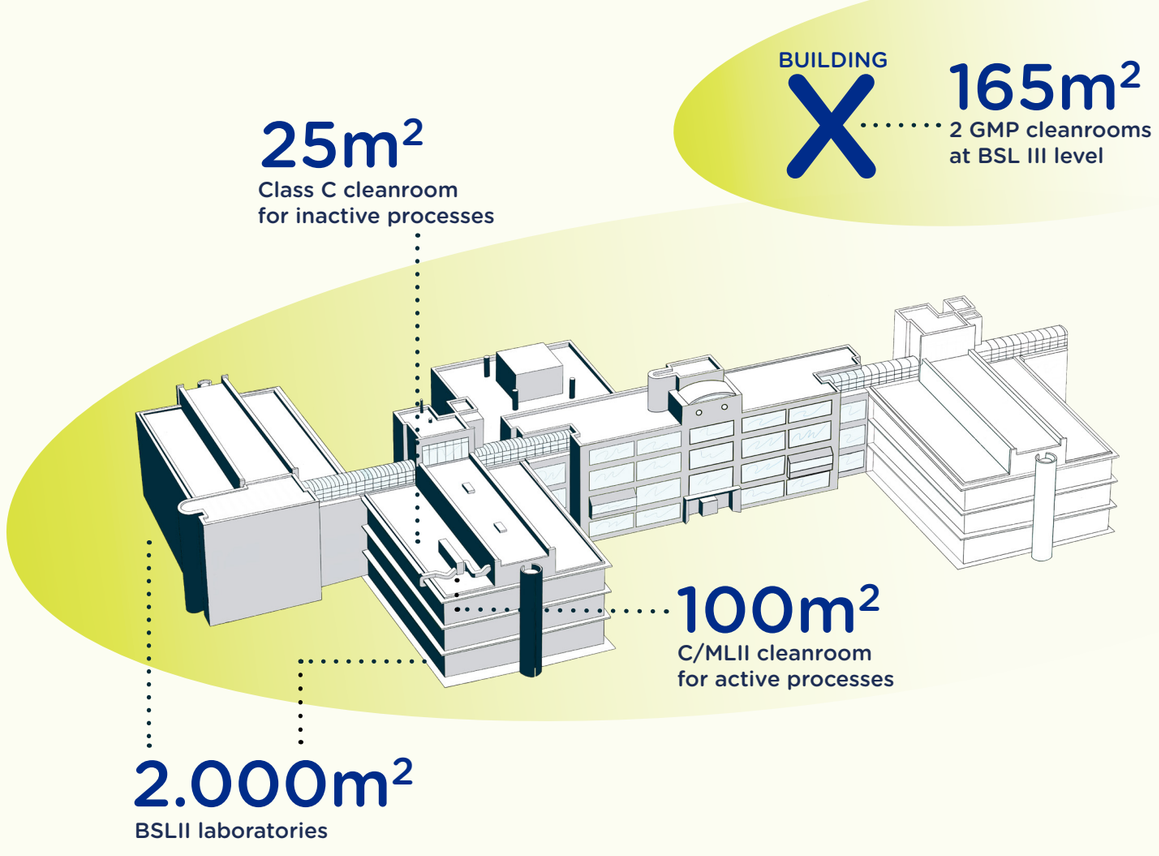


- Oncology
- Infectious disease

Conjugation



- Infectious disease
- Combination with OMV

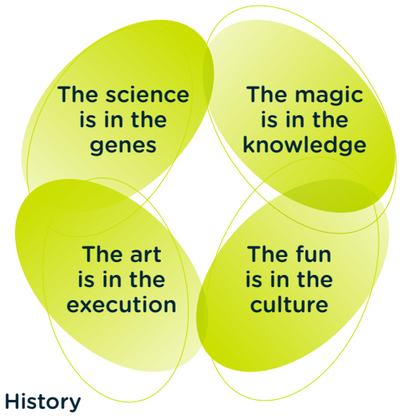


1.2 Introduction

Intravacc B.V. is located on the Utrecht Science Park Bilthoven in the Netherlands and is a leading global contract development and manufacturing organization (CDMO) of innovative vaccines against infectious diseases.

As an established independent CDMO with over 100 years of experience in the development and optimization of vaccines and vaccine technologies, Intravacc developed and transferred its technology and knowhow worldwide, including those related to polio, *Haemophilus influenzae* type B (Hib), Meningococcal and influenza vaccines. Intravacc offers a wide range of expertise for independent vaccine development, from concept to Phase I/II clinical studies for partners around the world. Our core values are excellence, customer oriented and results oriented and our philosophy (figure 1) shapes the Intravacc way of innovating vaccines.

Figure 1: Intravacc philosophy



History

The history of Intravacc started in 1909 with the establishment of the Central Laboratory (CL). This later fused in 1934 with the Bacterio Therapeutic institute (BTI) that was founded in 1894 and became the national institute of health (RIV, NIPH, figure 2). This later became the RIVM when also the environmental monitoring was added as a core task. The RIV conducted research studies with polio antisera, tuberculosis and diphtheria amongst others. Over the years the RIVM worked on vaccine development alongside its other public health activities and in 2003 the Dutch government decided to concentrate all vaccine-related research in the Netherlands Vaccine Institute (NVI). This institute developed and produced vaccines for the Dutch market. In 2012 the NVI was discontinued and the production side of the operation was sold to Serum Institute of India; the research and development group remained part of the Dutch Ministry of Health under the name Intravacc. In 2019 Intravacc's Animal Research Center was acquired by Poonawalla Science park (PSP).
After a 7-year process Intravacc was privatized per January 1st, 2021. This long history of Intravacc and its predecessors in Bilthoven made it that around 40% of all childhood vaccines are based on its technology.

Success of vaccines

After the availability of clean water and soap, vaccination is the second most effective method to prevent and reduce infectious diseases. Vaccines made it possible to eradicate smallpox and to significantly reduce the disease burden of, for example, polio, rubella, and measles worldwide. Intravacc wants to reduce human diseases by using its advanced platform technologies in the development of vaccines.

2020

In 2020, Intravacc invested in the development of vaccines to prevent diseases like Covid-19, gonorrhea and hand, foot, and mouth disease (HFMD). Intravacc also continued to improve its proprietary (platform) technologies so that they can be used for new products to fast-track vaccine development in case of an epidemic or a pandemic.

Partners

Intravacc offers a wide range of expertise bridging the gap between discovery and pilot scale Good Manufacturing Practices (GMP) production. Our clients can be divided into four categories: (Dutch) government(s), global health parties, universities and private partners. Intravacc is a reputable and highly valued partner of several global health parties, such as the World Health Organization (WHO), the Bill & Melinda Gates Foundation (BMGF), the European Union, Centers for Disease Control and prevention (CDC), National Institute of Health (NIH) and Health Holland. Intravacc has frequently provided services for these parties to advance their objectives in promoting global health. Intravacc has played a significant role in collaboration with the WHO and BMGF in the eradication of polio worldwide and remains a trusted partner in the development of vaccines for existing and new (pandemic) diseases.

Figure 2: History of Intravacc.

1.3 Strategy and mission

Intravacc's vision:

"Reduction of human diseases through innovative vaccine technology"

Intravacc's mission:

"To partner with (non) governmental agencies and private entities to help to reduce disease burden"

Intravacc is one of few players in the vaccine field that has in-house knowledge on and experience in all the aspects of the vaccine value chain to bridge the gap between basic research and advanced clinical studies in human volunteers. In 2020 the company made the transition from a publicly funded institution to a commercially focused organization.

Our value proposition is: *"One-stop-shop for high quality vaccine development from lead to early-stage clinical trials."*

One-stop-shop: Intravacc has all expertise in-house to bring any vaccine project through the pipeline from lead to the end of phase II clinical trials.

High quality: Intravacc has high quality standards, to assure this, regulatory affair (RA) and quality affairs (QA) are involved early in the project to monitor the quality and to assure a smooth transition into in clinicals testing.

Vaccine development: Intravacc has an extensive track record in developing vaccines for its customers. Highlights include Sabin inactivated polio vaccine (sIPV) and *Haemophilus influenzae* type B (Hib) vaccine that are on the market and are WHO prequalified.

Lead to early-stage clinical trials: While Intravacc has the knowledge and expertise to advance projects through the complete vaccine development chain up to phase II clinical trials, Intravacc can also customize based on the partner's needs and just perform some activities to further develop their product, for instance, formulation, process development, certain assays, Good Manufacturing Practices (GMP), etc. The business strategy of Intravacc is to leverage our knowledge and technology base into financially rewarding projects. Intravacc's ultimate objective is to generate sustainable revenue streams from R&D Services and, when possible, from licensing/royalty agreements.

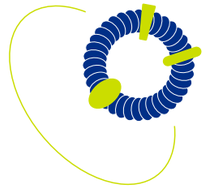
Intravacc serves as a CDMO for various companies in developing their vaccines. These are start-up companies, spin-offs from universities and also larger pharmaceutical companies. Currently, Intravacc has out-licensed some of its own vaccines to pharmaceutical companies, like BCHT and CDBIO (both China), collaborates on gonorrhea vaccine development with Therapyx, acts as a CDMO for Provention-Bio and Versatope. In 2020, Intravacc was active in 3 markets: the US, China/Asia, and Europe. Specifically, for its in-house developed vaccine concepts, China is a very attractive market, as there are many vaccine companies with manufacturing capacity and due to the large population it has a very large market potential.

1.4 Platforms

Platform	Vaccine Targets			
	Viral infectious diseases	**Bacterial infectious diseases**	**Oncology**	**Others**
OMV	Yes	Yes	TBD	Experimental (Alzheimer)
Cell Vero	Yes	No	Yes, only tested for oncolytic viruses (HPV)	TBD
iBoost	Experimental (Covid-19)	Not yet tested	Yes	
Conjugation	Yes	Yes	Possible	Possible

Tabel 1: Versatility of the platforms.

Intravacc has developed several platforms to reduce time and costs for the development of new vaccines. These are the Vero cell platform, the OMV platform and conjugation platform. In 2020 Intravacc in-licensed the iBoost platform.



These platforms are built on the extensive knowledge that Intravacc has obtained in the long history of the company. This knowledge is captured in general procedures that form the blueprints to quickly design and develop new vaccines. The goal is to use the already developed techniques and assays "as is" for new vaccines with some small optimization studies.

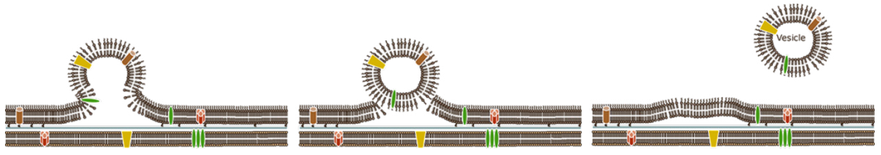
The versatility of the platforms is evidenced by the fact that they are used for vaccines for different disease indications (see table 1).

Outer membrane vesicle (OMV) platform

Intravacc has a long track record in outer membrane vesicle technology (OMV, figure 3), as is evidenced by 84 scientific publications in peer reviewed publications and 8 patent families since 2013.

In the early 2010s the knowledge of OMV research on MenB and Pertussis was captured in a platform that consists of blueprints on how to quickly generate homologous OMVs from new

Figure 3:
Generation of outer membrane vesicles.



	Live attenuated	Inactivated	Subunit	DNA	Viral vector
PROS	Good efficacy	Good safety	Good safety	Good stability	Good efficacy
CONS	Safety issue	Poor efficacy	Poor efficacy	Poor efficacy	One time use

OMV platform

Good safety
Good efficacy
Good yield
Good stability

Figure 4:
Pros and cons of different vaccine types.

bacteria. This was later expanded to expressing heterologous proteins in MenB vesicles and by external loading of peptides and proteins by using either chemistry or biological techniques through a self inserting linker.

The benefits of OMVs are that they do not replicate, are generally safe, give a good immune response, are very stable and give a good yield (figure 4). In addition, OMVs can be administered intramuscularly, but also intranasally when mucosal immunity is preferred.

Intravacc uses three approaches to develop OMV vaccines: homologous and heterologous expression and heterologous click. Homologous OMV vaccines are in general the best choice if multiple antigens of the pathogen are needed to induce protective immunity. However, not all bacteria are suited for OMV generation. This may be due to the inability to cultivate these bacteria under laboratory conditions or may be impractical if a bacterium is classified as a BSL-3 or BSL-4 organism. In these cases, heterologous OMV vaccines are generated. The foreign antigens can be inserted in the model MenB bacterium by molecular techniques. So far at least 3 large antigens have been placed and more could be possible.
One drawback of this approach is that not all proteins can be expressed by the host bacterium, for instance when post translational modification is needed. To overcome this, Intravacc developed the OMV-click approach. A heterologous expressed protein, for instance from mammalian or insect cells, is coupled with the already produced OMV. This can be achieved through a biological linker that inserts in the membrane or through conjugation to the outer membrane proteins present in the OMV.

Currently, most bacterial vaccine projects at Intravacc are based on the OMV platform (see figure 5 for the current project pipeline).

Figure 5:
Product pipeline of the OMV based vaccines.

Type	Target	Development	Pre-clinical	Phase I	Phase II
Homologous	*N. meningitidis* group B*				
	*B. pertussis**				
	*N. gonorrhoeae**				
Heterologous	*N. men.* group B – lyme*				
	E. coli – influenza*				
	N. men. group B - gonorrhoeae				
Click/Mix	Covid-19 peptide*				
	Enterovirus 71*				
	RSV*				

*** Open for licensing**

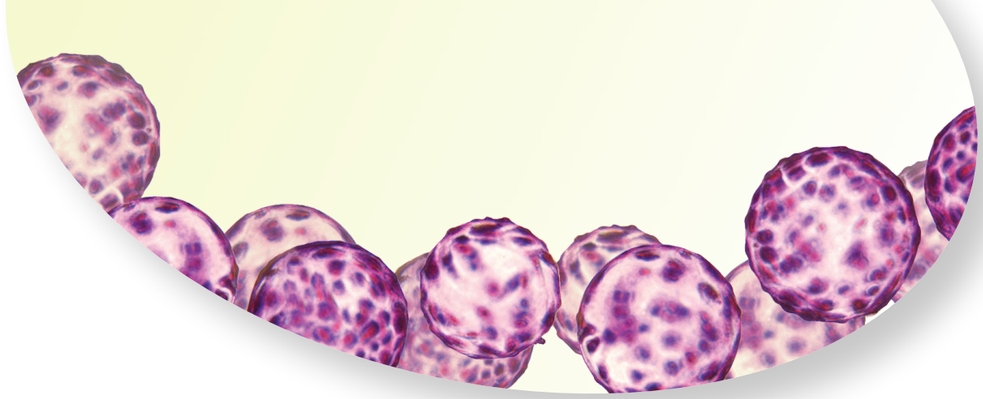


Figure 6: Vero cells grown on microcarriers.

Vero Cell platform

In 1962 the Vero cell line was isolated and immortalized from African Green Monkey kidney cells. Currently, the Vero cell line is the most widely used and reliable cell line in viral vaccine production in terms of quality, yield and safety. At Intravacc, we have been developing viral vaccines using the Vero cell line since 1987. Intravacc has its own cGMP-grade, regulatory approved, Vero cell line. The viral vaccine program is based on this cell line and since 2013 there have been over 30 peer reviewed publications and 2 patent families to back up the expertise Intravacc has with this platform. Intravacc's Vero cells are being used for routine large-scale commercial vaccine manufacturing by clients worldwide. In addition, virus seed lots and clinical batches have regularly been produced on our Vero cells, for example Poliovirus, Enterovirus (EV71), Coxsackie virus and Respiratory Syncytial Virus (RSV).

Intravacc has established this platform for viral vaccine production processes at both lab and pilot scale to enable a fast-track proof-of-concept; in addition, the process is fully scalable. The Vero cells can grow on microcarriers (figure 6) in a controlled manner in bioreactors and can be used for virus production. Besides this, several downstream processes (DSP) to purify the vaccine are in place as well as assays, for instance for host cell proteins. Intravacc has "ready to use" cGMP grade cell banks enabling partners to immediately start the project. A full technology transfer package is in place.

Currently, most viral projects at Intravacc are based on this platform (see figure 7 for the current project pipeline).

Figure 7:
Product pipeline of the VERO based products.

Type	Target	Development	Pre-clinical	Phase I	Phase II
Inactivated	Polio (Sabin IPV)	Market approval			
	HFMD (EV71, CVA10, CVA16)*				
	HFMD (CVA6)*				
	Pentavalent Coxsackievirus B	Provention Bio			
	EVD68	NIH/NIAD			
Live attenuated	RSV*				
	Covid-19 NDV vector*				

*** Open for licensing**

Interview with

Tom van der Aalst

Since 2018 Tom has been part of the process development viral vaccines (PDVV) team at Intravacc. He started as a student and after successfully completing his master Biotechnology at the Wageningen University and Research, he continued working at Intravacc. *“I like the innovative character of the work. The work is a combination of costumer driven innovation to develop vaccines and organization driven innovation to improve and extend the possibilities of the platform. I enjoy looking for solutions to overcome complex challenges and to find ways to optimize processes and technologies”.*

The power of Intravacc’s Vero cell platform is that it is versatile for vaccine development. The Vero technology has a strong proven track record as several vaccines (e.g. polio and influenza vaccines) based on this platform technology are on the market and part of immunization programs. In combination with the expertise and up- and down-scaling models within Intravacc the platform technology can also be used to quicky develop a vaccine in the context of pandemic preparedness. Especially, in the combination with the BSL-3 laboratories that are under construction.

Many viruses are and can be propagated on Vero cells, even if the Vero cells are not susceptible for the virus. In a recent project, Tom managed to design a production process that enables propagation of the Newcastle Disease Virus (NDV) in Vero cells. Based on research and experience, the team identified several factors that could make the Vero cells susceptible for NDV. They selected the twelve most promising solutions and ended up with one successful process. *“Biotechnological process are complex and innovating them is also a gamble. We were lucky that we were successful in our first attempt.”*

Innovation never stops for Tom and for Intravacc. *“I would like to work on adding a new cell based platform to Intravaccs’ toolbox, preferably a cell line that can grow in suspension.”* Suspension cells are easier to cultivate and can reach higher concentrations, making a production process more efficient. Furthermore, a second cell line will be susceptible to other viruses than the Vero cells. With two cell lines we would be able to give the customer an even better choice.

iBoost platform

In October 2020, Intravacc in-licensed CimCure's iBoost technology, which can be employed to induce polyclonal antibody responses against cancer-specific antigens (figure 8). This is a strong addition to Intravacc's pipeline, which can generate many potential future opportunities.

The agreement entails both an exclusive license for the use of iBoost for Covid-19 vaccines and a non-exclusive license for oncology applications. The iBoost technology is currently applied to elicit antibody responses against the tumor vasculature, a strategy that conquers the problem of drug resistance. This treatment strategy has a long-term efficacy and is extremely cost-effective.

The platform consists of a truncated thioredoxin protein fused to a specific "self" antigen. The knowhow has been captured in 4 publications by CimCure and a patent. The fusion proteins have shown good preclinical results, and are ready to enter the clinical stages of development. This will require a translation from research to GMP, as the plasmid, strain and process have to be modified to allow CTM production. In general, this new technology fits our vision to create innovative vaccines. For Intravacc this is a great opportunity to step into the field of oncology to expand our business but do not have a track record yet. See figure 9 for the current project pipeline for iBoost.

Figure 9:
Pipeline of the iBoost based products.

Type	Target	Development	Pre-clinical	Phase I
Oncology*	*Colon Cancer*			
	Prostate			
	Melanoma			
	Bladder			
Infectious disease*	Covid-19 spike			

*** In collaboration with VUMC/CimCure**

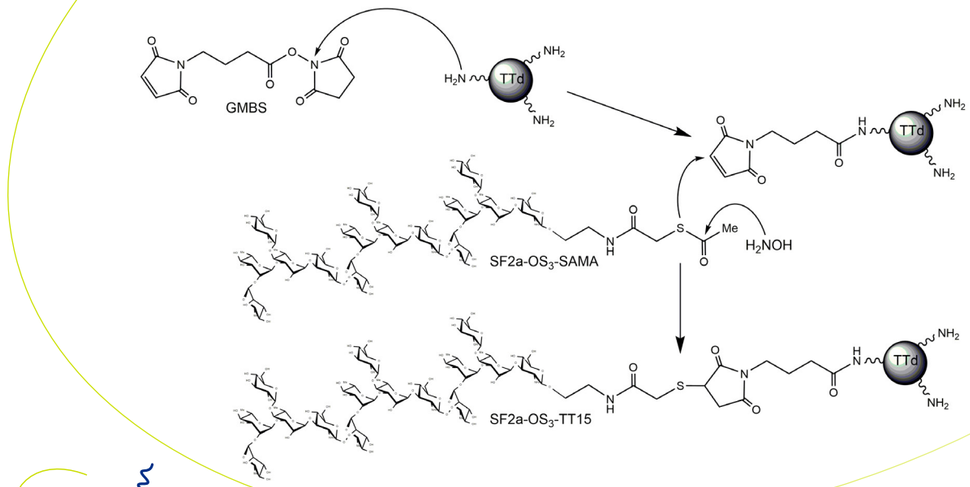


Figure 10:
Conjugation process of the Shigella conjugate vaccine.

Conjugation platform

Conjugation is the fastest growing vaccine segment in terms of financial value, mostly due to pneumococcal vaccines. The technology is fast, cheap, and highly effective.

A conjugate vaccine is created by covalently attaching a bacterial polysaccharide or peptide, which by itself is not able to induce immunological memory, to a protein carrier antigen, thereby eliciting a stronger and sustained immunological response. Intravacc has a 20-year track record in designing, developing, and characterizing conjugate vaccines. Intravacc's Hib vaccine, which has been based on the conjugation platform, has been on the market in India for many years and has saved numerous lives. Intravacc published 6 manuscripts on its Hib vaccine and holds 1 patent family.

More recently, Intravacc was a partner to produce a semi-synthetic conjugate vaccine against *Shigella flexnerii* 2a (figure 10). Here, Intravacc was responsible for the development and up-scaling of the process and the production of the vaccine for phase I and II clinical studies. This vaccine is currently being tested in phase II clinical trials. Intravacc has one paper published and one in preparation on *Shigella* conjugate vaccine.

Besides the methods to purify polysaccharides and the conjugation methodology, a full array of HPLC, mass spectrometry, NMR and colorimetric assays are at our disposal to evaluate all production process steps and assess the quality of the vaccine. In addition, besides these classical conjugation processes, Intravacc is investigating conjugation of polysaccharides and peptides to outer membrane vesicles and to synthetic polymers. The innovative nature of combining the effective classical conjugation with our OMV technology fits the vision and mission of Intravacc. See figure 11 for the current project pipeline.

Figure 11:
Pipeline of the conjugation platform products.

Type	Target	Development	Pre-clinical	Phase I	Phase II
Biological	*Haemophilus influenzae**	Marketed			
Semi-synthetic	*Shigella flexnerii 2a*				
Synthetic	*Polymer chemistry***				
OMV	*various*				

*** Open for licencing** ****Open for partnering**

1.5 Products

Using the platforms described above, Intravacc has developed several vaccine products in different fields. Some of these products are out-licensed to vaccine manufacturers in different countries.
In addition, Intravacc is developing new potential vaccine products to be out-licensed in the future.

sIPV

Worldwide efforts to eradicate polio (figure 12) caused a strategic change in polio vaccination recommendations. A switch from oral polio vaccine, which can cause circulating and virulent vaccine derived polioviruses, to inactivated polio vaccines (IPV) is in sight. However, current IPV supply is limited, and the cost is relatively high when compared with oral polio vaccine. To enhance worldwide production of affordable IPV, Intravacc developed a cost-effective manufacturing process using attenuated (Sabin) poliovirus strains, instead of wildtype polioviruses, in collaboration with the World Health Organization (WHO). The resulting Sabin-IPV (sIPV) was developed for technology transfer to manufacturers world-wide to locally produce the vaccine. The advantage of using the attenuated Sabin strains is that they are safer to work with.

To accommodate sIPV production process improvement and optimization, a scale-down version of the legacy production process was set-up. This scaled down process for sIPV was transferred to manufacturers in low- and middle-income countries. Intravacc has licensed the sIPV technology to a number of selected industrial partners and provided training and support. In 2020, one partner obtained market authorization and WHO pre-qualification, and two partners concluded phase III clinical trials and requested market approval. In parallel, continued process optimization contributed to an increase in the sIPV quantities available to an enable eradication and for the post-eradication era.

Figure 12: Logo of the polio eradication program.

Hib

The current available *Haemophilus influenza* type b (Hib) vaccines rely on the production, purification, and conjugation of the capsular polysaccharide polyribosyl-ribitol-phosphate (PRP, figure 13) to Tetanus toxoid. Intravacc developed a patented manufacturing process that is simple, scalable, affordable, and robust, and results in stable intermediate and final products. The vaccine production has a high yield, which is a good indicator for cost effectiveness. Both the active ingredient PRP and the final conjugated PRP-T vaccine comply with legislation and guidelines. The Hib conjugate technology can be used for both lyophilized and liquid formulations for either standalone or combination vaccines.

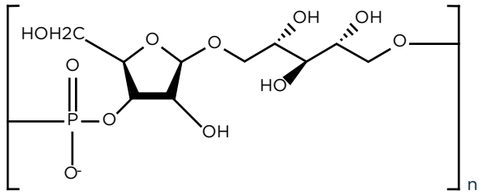


Figure 13:
Drawing of the PRP sugar of the Hib vaccine.

The comprehensive technology transfer package of the process includes the seed lots, process, documentation, and the related quality control tests (both in-process controls and release tests). The technology transfer has led to the licensing and production of several Hib vaccines (liquid - standalone and in combination with other vaccines - and freeze-dried) in India. These vaccines are available for the national and international market. This technology was transferred successfully to multiple partners and resulted in marketed products. The Hib vaccine technology developed at Intravacc has reduced the price of Hib vaccines significantly. In 2018, Intravacc started to transfer the Hib vaccine to another partner, BCHT in China. BCHT is currently implementing the process in their plants. In 2020 Intravacc assisted with documentation and troubleshooting.

MenB

Intravacc developed Nonamen®, an outer membrane vesicle (OMV, figure 14) vaccine based on 9 serotypes of the major protective antigen PorA to achieve broad protection. The patented detergent-free production process results in highly stable OMVs with low reactogenicity. The vaccine contains 9 different serotypes of the variable antigen PorA which protect against a wide range of *Neisseria meningitidis* strains. In all theoretical studies on broadness of protection of the licensed vaccines and Nonamen®, Nonamen® is always superior. The manufacturing process is scalable and gives a high yield (approximately one dose per ml broth), ensuring a low cost of goods. The vaccine complies with all requirements laid down in the European Pharmacopoeia and GMP.

Three vaccine strains have been genetically engineered, each harboring 3 *porA* genes at carefully selected loci representing different *Neisseria* serotypes. Further genetic modifications result in enhancement of vesicle formation and reduction of the LPS related toxicity while maintaining the intrinsic adjuvant properties. Together the 3 vaccine strains comprise antigens of 9 different *Neisseria* serotypes strains. The vaccine strains have been adapted to a specifically developed chemically defined, animal-component-free production medium. GMP master and working seed lots have been prepared and tested. The nonavalent OMV vaccine is stable for at least 24 months based on physiochemical testing and efficacy. Based on physiochemical testing alone it is stable for at least 48 months. Based on our Nonamen® vaccine and with input of the Chinese CDC about the strains circulating in China, a comparable, but new vaccine was designed and constructed to optimally cover Chinese strains. This new vaccine as well as the production technology is transferred to a Chinese partner and Intravacc is assisting the further development for the Chinese market. The flexibility of our strain generation can tailor the MenB vaccin for any market and can be optimized when the circulating strain change. *N. meningitidis* work is ongoing at Intravacc.

Pertussis

The incidence of Pertussis has substantially increased since the mid-1990's, especially in the population of the Western world vaccinated with the acellular pertussis vaccine (aPV). It is generally suggested that an improved vaccine should have a safety profile comparable to acPV, but with respect to the longevity of protection as well as reduction of airway colonization to reduce or even block transmission, a next generation vaccine should fill the shortcomings of the current aPV.

The OMV-based pertussis vaccine developed at Intravacc has three mutations to improve safety (of which one is patented) and two mutations that improve the yield (both patented). The OMV vaccine is highly stable, has been proven safe in mice and shows the type of immune response that is associated with long term protection. In addition, this vaccine could reduce airway colonization, especially after intranasal administration.

Since this is one of the few new concepts for pertussis vaccines worldwide, we have received interest from both the scientific community, which resulted in two grants, one of which will be used to study the effect on transmission, and industry. In 2020, the pertussis project successfully past stage A (discovery) of our vaccine development pathway.

LPS

Lipopolysaccharides or LPS (figure 15) can be exploited for use as an adjuvant in vaccines. LPS is known for its endotoxic activity, however, at Intravacc we genetically modified LPS to decrease the toxicity while maintaining its immune activating properties. Intravacc used systematic molecular bioengineering of the meningococcal as well as pertussis LPS to yield a variety of novel LPS mutant strains with changes in both lipid A acylation and phosphorylation (figure 15) that exhibit a varying degree of immune activation.

Intravacc has a large panel (see table 2) of modified LPS species that are patented. These can be used as part of the OMV vaccine or LPS can be isolated and used directly as adjuvant. To isolate the LPS, Intravacc has a phenol-free production process that gives >95 % purity. Furthermore, we have a mass spectrometry method in place to determine the detailed composition of the LPS. HEK cells expressing TLR4 and MD-2 (of different species) are available to analyze the activation properties of LPS or LPS containing vaccines. Currently there is one LPS adjuvant on the market, which is MPL from GSK. They do not license the technology to other manufacturers to use in their vaccines. This makes it still an open market for us to enter. We do receive many questions and inquiries about adjuvants, highlighting the large demand.

Figure 15:
Schematic representation of the lipid A moiety of LPS. In color are the enzymes that would remove (or not attach) one acyl chain or phosphate group.

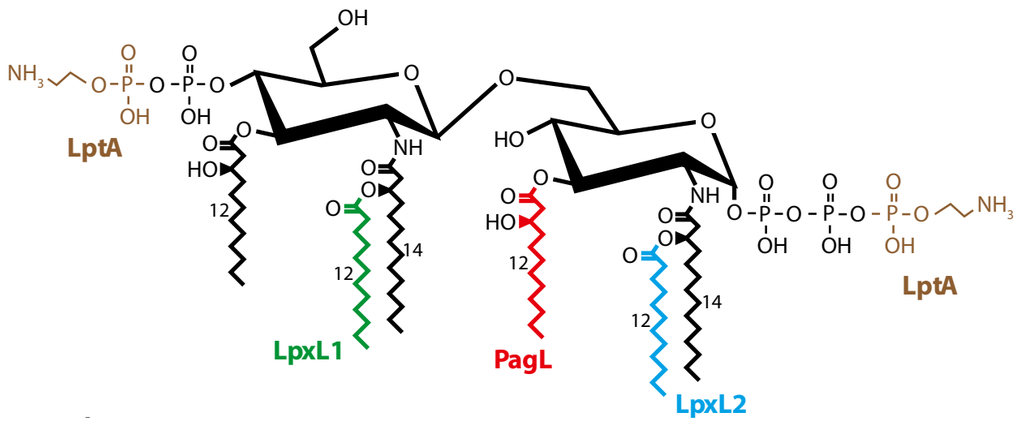


Table 2:
Different LPSs available.

Neisseria		
Mutation	**Effect**	**Application**
lgtB	Targeting to DC-SIGN	OMV and adjuvant
lpxL1	Reduced TLR4 activation	OMV and adjuvant
lpxL2	Complete loss of TLR4 activation	OMV and adjuvant
pagL	Slightly reduced TLR4 activation	OMV and adjuvant
pagL+lpxL1	Reduced TLR4 activation	OMV and adjuvant
pagL+lptA	Reduced TLR4 activation	OMV and adjuvant
lptA	Slightly reduced TLR4 activation	
lpxP	Secondary acylation regulated by growth temperature	OMV and adjuvant
kdtA	Only lipid A made	OMV
lpxA	Complete loss of LPS	OMV
Bordetella		
Mutation	**Effect**	**Application**
pagL	Increased TLR4 activation and release of LPS	OMV
lpxA (Pa)	Reduced TLR4 activation	OMV
lpxD (Pa)	Reduced TLR4 activation	OMV
arnT	Reduced TLR4 activation	OMV
kdtA (Cb)	Inner core epitope from *Coxiella* expressed	OMV

Covid-19

In response to the Covid-19 pandemic, Intravacc started to develop four vaccines against the Sars-CoV-2 virus in 2020. Years ago, Intravacc started the development of a platform for rapid emergency preparedness, by clicking peptides and proteins to stockpiled outer membrane vesicles. As the blueprints and some preliminary data were ready, it was decided to use the OMV-click method for the development of two Covid-19 vaccine concepts. As literature shows that a T-cell response is needed, Intravacc, together with Epivax, designed a peptide that would induce a T-cell response against a broad range of beta corona viruses. The other method is to elicit an antibody response by using the whole spike protein clicked to the OMVs. However, the expression of the protein is more difficult and takes longer.

A third Covid-19 vaccine concept is being developed together with our partners Wageningen BioVetrinary Research (WBVR) and Utrecht University (UU) and is vector based. The NDV vector with the spike protein is propagated in Vero cells and harvested. This project will get us familiar with vector vaccines and is partially funded by Health Holland.

The fourth and final concept is based on the iBoost system. Here parts of the RBD of Spike protein are fused to the thioredoxin and this fusion protein is then the vaccine. The license agreement was signed in October 2020, the work is also partially funded by Health Holland and is started at Cimcure.

Intravacc is behind the front runners in the development of Covid-19 vaccines. However, with 4 approved vaccines in the EU, at the time of writing, there are still many uncertainties like, how long will they protect, whether they protect against variants, etc. Therefore it is detrimental that other companies like Intravacc continue the innovative work on Covid-19 vaccines. Boosted by the pandemic, Intravacc has leaped forward its OMV technology, started with vector-based vaccines and has shaped the iBoost system in 2020. This provides a large growth opportunity for Intravacc.

Anti-tumor vaccines

Cancer is one of the fast-growing diseases in developed countries. The treatment of cancer is expensive and current drugs often have a big impact on the quality of life. Today most of the new drugs for cancer treatment take advantage of the human immune system. Activating the immune system with new drugs activates the immune system to target the tumor. It has been shown that tumors can be prevented or cured using active immunization by cancer vaccines. The technology behind cancer vaccines is in principle not so different from those against infectious diseases and has an enormous impact on public health.

Perhaps the best example in oncology is the prophylactic HPV vaccine that significantly reduces the chance of cervical cancer. Besides prophylactic anti-viral immunization against virus-induced cancer active therapeutic immunization based on specific tumor antigens are intensely investigated.

Intravacc has the knowhow to develop vaccines, including therapeutic vaccines and has decided to enter this market firstly by providing our services and platforms for vaccines to treat tumors. In addition, Intravacc has licensed the iBoost technology in 2020, that has the potential to tackle the tumor vasculature. Intravacc will further develop this technology for a broader range of oncological applications. Other Intravacc's platforms may also serve as a backbone to develop vaccines for oncologic targets. For instance, Intravacc's Vero cell platform, as well as its OMVs and molecular virology knowledge can be utilized to target tumor specific or tumor associated antigens. Intravacc's knowledge and experience would fast track development towards clinical studies. Oncology is a greenfield opportunity for Intravacc that started in 2020 and will continue in 2021.

1.6 Services

Besides licensing its products to manufacturers, Intravacc also provides services. These services can include all phases of the vaccine development pathway, from lead to phase I-II clinical trials (one-stop-shop), or just one or more parts of it. These services link our product development (R&D) services, analytical support, and manufacturing into one integrated process.

Vaccine development

Intravacc designs and develops vaccines, improves the production processes of vaccines, and produces drug substances and products at cGMP-level to enable pre-clinical and clinical studies. Our leading principle in this is the Vaccine Development Pathway (VDP), which was fully implemented in 2020.

For the development of new vaccines, Intravacc uses established blueprints and scalable platform production processes. These are designed according to the regulatory requirements, using mathematical models, and are scalable from lab to high-volume production-scale bioreactors. Rationally designed processes and their products are tested in our state-of-the-art laboratory facilities using the latest ICH-guidelines and insights.

Assays

Quality, potency and safety are key features in the specification of biopharmaceutical drug substances and products. Therefore, choosing the right assays for determining the consistency of production and the quality of the produced vaccines is crucial. Intravacc provides all aspects of vaccine-related assay development, assay validation, vaccine quality control and method transfer. Intravacc has a proven track record in establishing validated methods according to ICH guidelines for quality control of vaccines. Intravacc offers a wide range of analytical method development, characterization, validation, and analysis services (table 3).

Formulation

Intravacc focusses on the development of a proper formulation suitable for the intended administration route of a new vaccine, and that is also stable upon storage. Intravacc designs, develops, and improves formulations and adjuvants for new vaccine candidates. The stability of new formulations is tested in accelerated, real-time and in-use stability studies using the appropriate set of assays. However, some vaccines are difficult to stabilize in a liquid formulation, especially if these vaccines contain live-attenuated viruses. To solve this, Intravacc has the facilities and expertise to develop water-free vaccine products (e.g. by lyophilization or spray-drying). Drying techniques are also applied for the preparation of stable seed lots and reference materials. Furthermore, Intravacc is working on developing products for alternative routes of administration of vaccines other than intramuscular administration (e.g. mucosal routes, such as intranasal administration).

Cell and seed lot

For the out-licensed experimental vaccines and for the active development projects, Intravacc produces the cell and seed lots in-house. This can also be provided as a standalone service for other companies. Intravacc has the experience, knowledge, and equipment to do this.

GMP

Intravacc has experience in the production of GMP clinical material for both viral and bacterial vaccines. Intravacc has two GMP facilities, one in the main building and a new facility in a separate building on the campus, which will be operational in Q2 2021. A variety of production technologies are available in both single-use or stainless steel bioreactors for production of vaccines on pilot scale. The GMP facility of Intravacc consists of a 100 m^2 class C/MLII cleanroom for active processes and 25 m^2 class C cleanroom for inactive processes. In addition, the new building X harbors 2 GMP cleanrooms at BSLIII level (total 165 m^2). These cleanrooms are fully adaptable and can be equipped to comply to the required processes.

Quality Control (QC) is responsible for release testing of GMP batches, sampling and testing of raw materials and the management and execution of stability programs. Furthermore, the QC department performs Intravacc's environmental monitoring program. Release and stability testing is performed by QC under GMP regime by qualified technicians. In addition, Quality Control is involved in the validation of product specific analytical techniques that is performed in close collaboration with the department Product Characterization according to ICH Q2 (R1) guideline.

Identity of bacteria, viruses, drug substances and drug products	Mass spectrometry (Orbitrap Fusion Lumos) PCR/qPCR ELISA
Content of drug substances and drug products	Mass spectrometry qPCR ELISA Calibration free concentration analysis (biosensor analysis) HPLC GC Protein assays (BCA, Lowry, Peterson, and Bradford)
Primary sequences of antigens, antibodies, proteins, and viruses	Mass spectrometry (de novo sequencing)
Higher Order Structure of proteins and viruses	Circular dichroism (secondary structure of proteins) Fluorescence spectroscopy (tertiary structure of proteins) Dynamic Light Scattering (particle size and protein aggregation) Electrophoretic Light Scattering (surface charge of particles) Asymmetric Flow Field-Flow Fractionation - Multi Angle Light Scattering (FFF-MALS) Nanoparticle Tracking Analysis (NTA)
Antigenicity	Biosensor analysis (Biacore T200) Affinity measurements of antibodies Epitope mapping (biosensor analysis or mass spectrometry) 2D Western blotting (Immunoproteomic profiles)
Impurities	Host cell proteins content (ELISA or mass spectrometry) DNAse activity (gel electrophoresis) LPS identification and quantification (mass spectrometry or GC) Residual DNA concentration (qPCR) Average chain length of residual DNA from mammalian cells (qPCR) Protease activity
Excipient testing	NMR GC HPLC
Compendial Testing to USP, EP, JP	Appearance pH Osmolality
Cell-based bioassays	TCID50 Virus-neutralization tests Specific toxicity tests on Vero cell
Stability testing	Accelerated stability studies. Real time stability studies

Table 3: Overview of product characterization assays currently developed at Intravacc.

Interview with

Hugo Meiring

Hugo has worked the vast majority of his career at Intravacc and its pre decessors. “Since the start of my professional career in 1984 I have worked with Mass Spectrometry. And it still fascinates me, it never gets boring. The technique has been around for over one hundred years but it keeps evolving”.

In essence, a mass spectrometer identifies a compound by breaking it up into smaller pieces; it subsequently maps these fragments based on their masses using dedicated software tools. Mass spectrometry (MS) is now common practice in a wide range of applications, ranging from the analysis of small molecules to large proteins. Even intact viruses can now be analyzed and characterized (e.g. their capsid assemblies) by this technology.

In the last three decades, technological improvements in MS have boosted biomolecular research: “we can now not only identify and quantify peptides and proteins , but we can even study transient interactions between proteins: for example, antigen-antibody interactions, but also complex protein-protein interaction networks in whole cells”.

With so many applications, it is important to tailor the design of each mass spectrometric analysis (i.e. sample preparation, chromatographic separation, mass spectrometric analysis and data interpretation) to the research question. In Hugo’s words: “Intravacc is well equipped to answer any research question on vaccine research and development. Our mass spectrometer is the cream of the crop. We also have dedicated software tools and an IT environment for comprehensive immunoproteomics research and fast data analysis”.

Last but not least, Intravacc has decades of experience in designing custom-made sample preparation and chromatographic solutions for the most challenging questions. Hugo himself co-developed the miniaturization of liquid chromatography columns: a technology to improve sensitivity in biomolecular mass spectrometric research, that is now common practice worldwide. “Miniaturized (nanoLC) columns are commercially available, but I make them myself. You need a custom-made approach to obtain the best results of an MS analysis”.

MS plays an essential role in the development stages for every biotechnology-based drug that reaches the market. But MS is also becoming increasingly important for monitoring process consistency, identification and quantification of content and impurities, and for pharmaceutical product releases. “At Intravacc, we mainly use the MS technology to answer fundamental vaccine-related research questions and for monitoring process consistency in the development stage. To be able to use the MS technology for quality control analysis, as well, Intravacc should develop towards high throughput analyses of our MS-based targeted proteomics assays under GMP performance and validation guidelines.”

Medium design and testing

Intravacc developed a specific growth medium for the whole cell *Bordetella pertussis* vaccine (Thijs medium) that is still used worldwide. Subsequently, Intravacc also developed a specific chemically defined animal component free medium for *Neisseria meningitidis*. This medium, called TriCx, also allows growth to high optical densities of many other bacteria. Intravacc has the knowledge to design media for specific organisms and in the past Intravacc generated a blueprint for quick media design for bacterial cultivation.

A few years ago, together with Biological industries, Intravacc developed a medium called NutriVeroTM flex10 (figure 16) for the cultivation of Vero cells in monolayers as well as on microcarriers. This medium is serum free and chemically defined. The benefit of chemically defined media is that it allows better monitoring of what is happening with the cells and it improves the batch-to-batch consistency. With our NMR, GC and HPLC methods we can monitor the media during cultivation and fine-tune when needed.
In 2020 Intravacc did not invest in designing and testing of new media.

Figure 16: Bottle of NutriVero Flex10 medium.

3R research

Intravacc is one of the leading players in global 3R research (Reduce, Replace and Refine) for animal experiments. We have developed several new methods for tetanus, diphtheria and pertussis vaccines, some of which were accepted by the European Pharmacopoeia. In addition, Intravacc is a front runner in the development and distribution of a new paradigm in vaccine lot release testing, known as the consistency approach. To promote the implementation of this strategy, Intravacc participates in an IMI2 (EU)-funded project on consistency testing, named VAC2VAC. The VAC2VAC consortium consist of 21 participants, representing industry (e.g. GSK, Sanofi-Pasteur, MSD-Animal Health), regulatory agencies (CBG/MEB), national reference laboratories (OMCL network members e.g. NIBSC, ISS, PEI), academia (e.g. Utrecht University, UMCG), translational Research institutions (e.g. Intravacc, RIVM, BPRC) and other international organizations, such as EURL-ECVAM and IABS.

The 3R research focuses on:

- Development of cell-based *in-vitro* models, physio-chemical techniques and immunochemical assays that can be used in the consistency approach.
- Development of mass spectrometry-based methods for the quality control of vaccines
- Development of assays for future release of Covid-19 vaccines which are currently under development at Intravacc

In 2020 Intravacc developed several assays which can be used as part of the consistency approach to reduce or replace animal studies in for example the release of pertussis vaccine batches and formaldehyde inactivated vaccines.

1.7 Business model

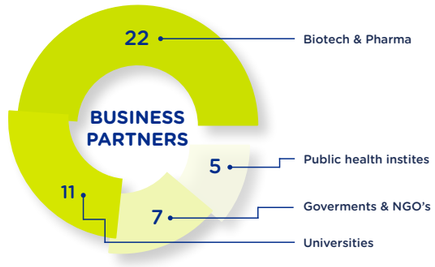
The gap between early-stage vaccine research and clinical proof of concept in human, and thereafter obtaining market authorizations to bring the vaccine to market is often a risky and expensive process, which requires research and development expenses ranging from EUR 200 million to EUR 700 million towards the final stages of approval.

As a partner with extensive experience, Intravacc is ideally positioned as a valuable collaborator for private parties to bridge this gap and significantly reduce the associated risks and required investment in the early phases of vaccine development.

The business strategy of Intravacc is to leverage knowhow and proprietary vaccine technologies established in the projects into financially rewarding collaborations mainly with our partners. Current (and foreseen future) projects are centered on private partners, like vaccines manufacturers and the Dutch Government.

Intravacc's ultimate objective is to generate sustainable revenue streams primarily from CDMO services and secondarily from licensing agreements, including royalties. In addition, Intravacc has been the recipient of subsidies and grants issued by the Dutch government and global health partners, highlighted by the recent awarded multi-million-dollar grant from the NIH. These grants will push innovation and revenues but will not contribute to the profit in the near future, however, they might increase income after potential licensing of the generated innovations.

Intravacc's client base can be divided in four categories: governments, global health, universities and private partners (figure 17). Projects performed for governments and global health partners are primarily research and development projects with the aim to provide solutions for the unmet vaccine demands in the global market. Intravacc is focused on the early stages of vaccine development and aims to find private partners to co-develop and/or transfer the concept at a certain phase in the clinical research process.



Intravacc benefits from a strong and diversified project portfolio and corresponding customer base, which include:

- the improvement of existing and the development of new vaccines in collaboration with public and private partners.
- projects improving global health in collaboration with, among others, the World Health Organization (WHO), which facilitate the vaccine-related technology transfer of, for example production processes, to low- and middle-income countries.
- research programs commissioned by the Ministry of Health (MoH), focused on specific vaccine needs. Intravacc performs strategic research, also commissioned by the MoH, for future vaccines, technology platforms and formulations.

Intravacc has formulated the strategic ambition to become more commercially focused, which it plans to achieve by increasing the number of partnerships with and projects from private partners. In its current form, a relatively large portion of Intravacc's revenue originates from projects commissioned by MoH/the Dutch state. Intravacc's business strategy provides the company with a solid foundation to transition to its new commercial focus. The main growth in revenue will come from CDMO services where Intravacc further develops vaccines for our partners. These activities can be full-scale vaccine development projects but also components thereof such as, process development, formulation development, clinical trial material (CTM) production, production of reference material and assay services.

Figure 17: Overview of some of the different business partners of Intravacc.

Revenue model

Intravacc's revenue and profit scheme is based on services and licensing deals. Part of this income will be reinvested into research and development to maintain a competitive advantage and expand out in-house platforms, research programs, and/or acquire new equipment. By licensing technologies, it is anticipated that Intravacc will get a return on investment for the efforts conducted at the early stages of vaccine development, and ultimately funding its research programs through the attained milestone and royalty payments. This business model gives Intravacc the possibility to decrease the margin on certain projects with a large unmet medical need (global health). Moreover, a larger profit can be realized on commercial projects which can generate milestones and royalties that can be reinvested in platforms and products. Those will in turn be licensed out to generate further profit (figure 18).

Royalties

Intravacc has out licensed its sIPV production technologies to multiple manufacturers. Some of these partners have finished their clinical studies and in December 2020 the first partner received market approval and WHO pre-qualification for the licensed asset. Intravacc will obtain a royalty percentage from these partners. Next to this we have out-licensed our Hib vaccine and our meningococcal B vaccine. These will bring royalties as well in the near to mid term future.

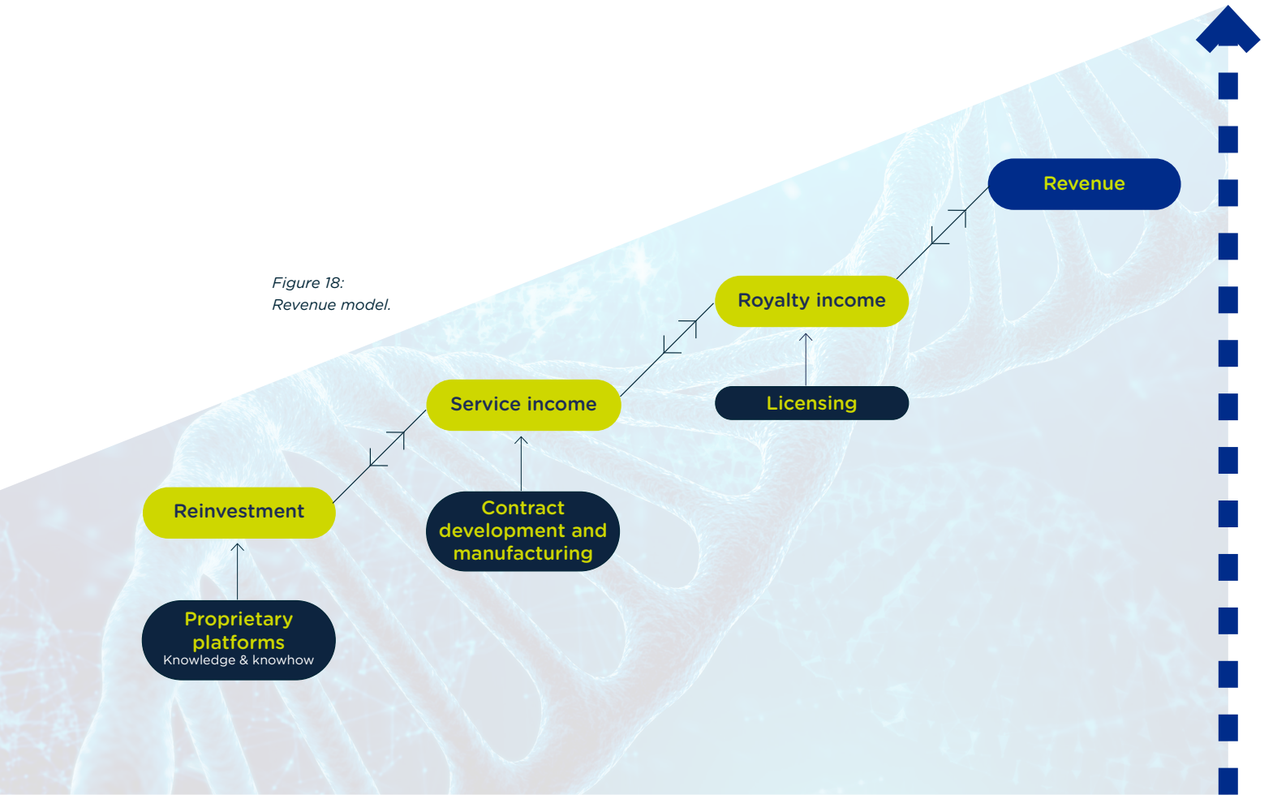


Figure 18: Revenue model.

1.8 Stakeholders

Category	Stakeholder	Interaction
Shareholder	VWS (MoH)	Shareholder meetings
Customers	Governments NGO Universities Pharma	Collaborations, fee for service projects and license agreements Assignments in the field of vaccine research from VWS Assignments in the field of reduction, refinement, and replacement of animal experimentation from LNV
Personnel	Employees	Meetings, coaching, education
Suppliers	Materials Equipment	Audits in case of GMP Service mechanics.
Site	Stichting ALT Surrounding companies PSP • Real estate • Services • ARC	Permit holder (mainly environment) Sharing of facilities (security) Landlord On building/site related items Animal research in projects

Table 4. Stakeholders of Intravacc.

Shareholder (January 1st 2021)

The Dutch Ministry of Health (MoH/VWS) is a stakeholder with a dual role. They are the sole shareholder of Intravacc and gave us an assignment in the field of vaccine research. These different roles of the Ministry of Health are represented by different groups, with different discussion partners. We have therefore different meetings with this stakeholder. The Shareholder meeting is once a year and twice yearly a meeting on the research progress is held. The research activities are captured in a 5-year program with a more detailed year plan.

Customers

The customers of Intravacc are all entities that pay for our services. They consist of universities, governments, nongovernmental entities, and pharma. Pharma can be subdivided in start-up and spin-off companies, small, middle, and large pharmaceutical companies, and biotech companies. These entities ask Intravacc for services in the field of vaccine development. This can be a complete project from lead to clinical trials or just the execution of an assay or the production of material. The business development team will engage with the company or (N)GO/university to come to a service agreement. The project manager has extensive contact with its counterpart at the company on the progress of the project.

Site

Stichting ALT holds and maintains all the environmental permits for the complete Utrecht Science Park Bilthoven (USPB). A yearly inspection reviews all laboratories and storage places with potentially dangerous substances if they are up to date with the current regulations. In case of a safety breach the Stichting ALT is immediately notified.

Poonawalla Science Park (PSP) is the owner of the site (Utrecht Science Park Bilthoven) and buildings that we rent. They maintain the building and building specific installations.

1.9 Outlook 2021

Privatization
On January 1st, 2021 Intravacc became a privately held company with limited liability (B.V.). The Ministry of Healthy is currently the sole shareholder. Intravacc can therefore operate as a private company with a more commercial focus and expand its services to private companies worldwide.

Facilities
In 2021 Intravacc's new state-of-the-art pilot production facility will become operational. This facility will house multiple cleanrooms for the production of clinical trial material for phase I and II. This facility is also located on the Utrecht Science Park Bilthoven, just 50 meters from the main laboratories of Intravacc. In addition, a class D cleanroom will become operational in the main building of Intravacc for the assembly and sterilization of material for our GMP projects.

Investments
Intravacc routinely invests in equipment for our laboratories. With the expansion of our cleanrooms additional equipment is needed. In the event an in-licensing opportunity arises that complements Intravacc's platforms and strategy, this might require investment as well.

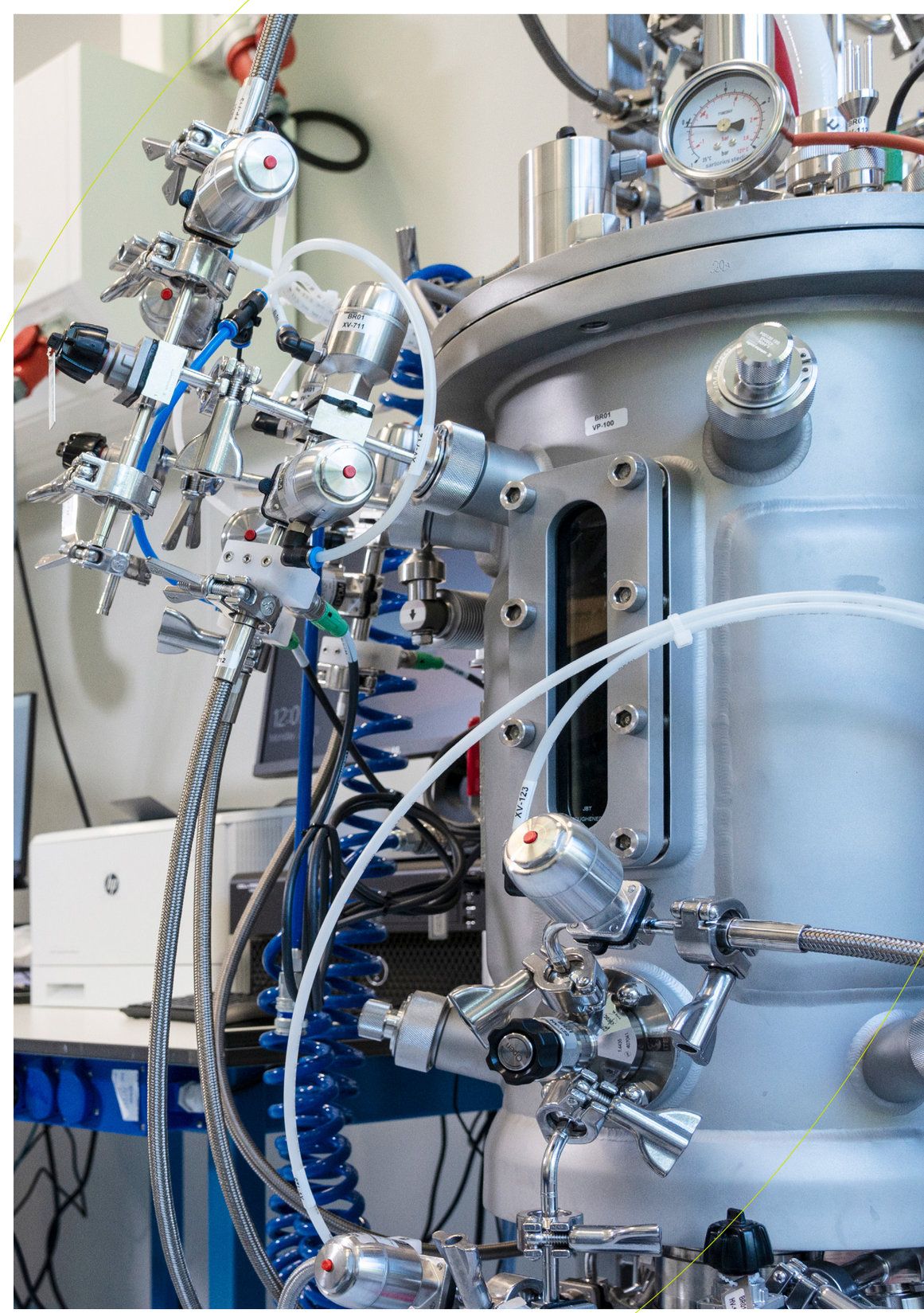
Employees
With new projects and the expansion of our cleanrooms we envision to increase the number of employees over the next year(s).
Also, career paths and development opportunities will be laid out and the terms of employment like review, renumeration and job structure will be further elaborated.

Business development
In 2020, the business development group was established at Intravacc with the task to engage with existing and new customers to obtain and expand the project pipeline. The vaccine market is a rapidly growing market, and the Covid-19 pandemic is boosting funds available for vaccine development. In addition, it will help the acceptance for vaccination as approach to prevent disease among the general population. This in turn will generate a good environment with many opportunities for Intravacc to expand its businesses.

Project pipeline 2021
The project pipeline for 2021 contains some projects that already started in previous years and new projects that will start in 2021. Table 5 below shows a subset of the ongoing projects at Intravacc.

Table 5:
Subset of the ongoing projects in 2021.

Platform	Project
VERO	Vector vaccine based on NDV
	Hand Foot and Mouth disease (HFMD)
	EVD68
OMV	*Neisseria gonorrhoeae*
	Neisseria meningitidis
	Bordetella pertussis
	Influenza
	Covid-19
Conjugation	*Shigella flexnerii* 2a
	Hib
	CliCr
3R	Several projects in the field of reduction, replacement, and refinement for the use of animals in vaccine research.
iBoost	Oncology
	Covid-19



Chapter 2 Corporate governance

2.1 General

Intravacc B.V. is a limited liability company incorporated under Dutch law. Intravacc B.V. was established on February 1st 2019. Per January 1st 2021 the privatization process of Intravacc was finalized; all assets of Intravacc (until December 2020 owned by the Dutch government) were transferred to Intravacc B.V..

As of January 1st, 2021, supervision and management of Intravacc are structured in accordance with the two-tier model, meaning a Board of Directors supervised by a Supervisory Board.

The Dutch State is the sole shareholder of Intravacc B.V. Intravacc is positioned as a policy participation under the Ministry of Health, Welfare and Sports (hereafter VWS). The Deputy Secretary General of VWS is appointed in the role of shareholder.

The main powers of the General Meeting of Shareholders consist of appointing, suspending and dismissing and discharging members of the Board of Directors and Supervisory Board, determining the remuneration (policy) of the Board of Directors and the Supervisory Board, adopting the financial statements and discharging the Board of Directors and the Supervisory Board from liability. A General Meeting of shareholders is held at least once a year.

Besides the role as sole shareholder, VWS provides funding for projects of Intravacc with a specific public interest. The Director Public Health of VWS is appointed as principal. Intravacc and the principal have regular meetings to discuss the progress of these projects.

This annual report and Intravacc's corporate governance are based on the applicable statutory requirements and on the company's articles of association. Furthermore, Intravacc closely follows developments in legislation on corporate governance in order to further improve its governance.

2.2 Supervisory Board

The Supervisory Board is entrusted with supervising and advising the Board of Directors and overseeing Intravacc's strategy and the general course of its businesses.
The Supervisory Board performs its tasks in accordance with the Dutch law and Intravacc's articles of association. Each individual Supervisory Board member acts in the best interests of Intravacc, its businesses and all of its internal and external stakeholders.

Composition

The Supervisory Board consists of three members who have been appointed for a period of four years. A member can be reappointed under the understanding that a member cannot serve on the Supervisory Board for more than twelve years. The composition of the Supervisory Board is well balanced in terms of expertise and competences.
Appointed as secretary of the supervisory board is the General Counsel of Intravacc, Erik Popping LL.M.

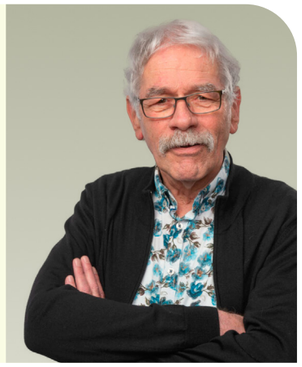
Commissions

The Supervisory Board started the formation of an audit commission in the beginning of 2021.

All members of the Supervisory Board have the Dutch nationality and were appointed on January 1st 2021. Their first date of re-election will be January 1st 2025. The members are:

Nico Oudendijk (Chair)

For 20 years, Nico Oudendijk worked at the interface of Youth Care, Psychiatry and Crisis Care, 12 years of which as General Director of the Amsterdam psycho-social and psychiatric institute 'Triangel'. Since 1991, Oudendijk has held various positions within the Dutch Ministry of Health. These include director Mental Health Care and Professions, director of Curative Somatic Care, Director General Public Health, acting inspector-general at the Health Care Inspectorate (IGZ) and Envoy for the BES islands (The Caribbean Netherlands). From 2010 to 2012, he was director of the Netherlands Vaccine Institute (NVI), where he oversaw the sale of its production facilities. From 2013 to 2020, he coordinated the preparations for the privatization of Intravacc.



Bruno Bruins

From October 2017 to March 2020, Bruno Bruins was Minister for Medical Care and Sport at the Dutch Ministry of Health. Between 2012 and October 2017, Bruins was chairman of the board of Dutch National Employee Insurance Agency (UWV) and from 2008 to 2011 he was a member of the board of directors of public transportation company Connexxion Holding N.V. Bruins was State Secretary for Education, Culture and Science from July 2006 to February 2007 and from 2000 to 2006 he served as alderman of The Hague and, between 2004 and 2006, as deputy mayor. His side activities included the chairmanship of the Supervisory Board of the Dutch public broadcasting organization NPO (2016-2017).

Dr. Karin Dorrepaal

Dr. Karin Dorrepaal is an experienced senior manager in the life science and pharmaceutical industry. In 1990 Dorrepaal joined Booz Allen Hamilton, Management Consultants. In 2004, the Supervisory Board of Schering AG appointed Dr. Dorrepaal as member of the Board of Management. After the takeover of Schering by Bayer, Dorrepaal left the company in 2006. Since then, she has held various board positions with private and listed companies in Germany, Ireland, Spain, and the Netherlands.

2.3 Board of Directors

Intravacc B.V. has a Board of Directors that may consist of one or more Board members. The Board is entrusted with the overall management of the company and as such responsible for the company strategy and the realization of all the company targets.

The Board member is appointed for a period of four years and can be reappointed for periods of at most four years each time.

Until December 31st 2020 the Board of Directors consisted of Nico Oudendijk and Dr. Jan Groen (appointed on May 1st 2020). Mr. Oudendijk resigned from the Board on December 31st 2020.

The Board of Directors currently consists of one Board member: Dr. Jan Groen. Dr. Groen was appointed as Chief Executive Officer on May 1st 2020. His first date of re-election as director will be May 1st 2024.

2.4 Executive management

Intravacc is led by an ambitious and experienced management team (figure 19) under leadership of its CEO dr. Jan Groen.

Together the management team has a strong track record in vaccine development. The management team of Intravacc consists of:

Figure 19: Management team of Intravacc in 2020.

Dr. Jan Groen,
Chief Executive Officer

Jan Groen joined Intravacc in May 2020 as Chief Executive Officer. Previously Jan Groen was the CEO of Novigenix in Switzerland, a privately held immunotranscriptomic diagnostic company and MDxHealth, a Euronext listed genomic diagnostics company.
Jan's career spans over many years in the global biotech industry. Jan was President and COO of Agendia, co-founder of ViroClinics and DxOrange and he has held management and scientific positions at Focus Diagnostics, the Erasmus Medical Center, National Institute of Public Health and Akzo-Nobel. Dr. Jan Groen has published over 125 papers in inter national scientific journals. He holds a Ph.D. degree in Medical Microbiology from the Erasmus University Rotterdam.

Additional positions Board of Directors:

- Chairman of the board of Cergentis (since July 2019)
- Board member at Angle Plc., Guilford (UK) (since November 2018)

Nathalie Laarakker, RA
Chief Financial Officer

Nathalie Laarakker is an experienced CFO and finance director in multinational companies with a proven track record of financial and senior-level management primarily in high tech and healthcare industry. Nathalie joins Intravacc from cancer immunotherapies R&D company Gadeta, after having served as Chief Financial Officer and Managing Director since 2019. Nathalie started her professional career at PricewaterhouseCoopers and worked for both the Amsterdam and the Boston (US) office. She qualified as a certified public accountant in 2001, after which she held various senior positions in several companies. Her previous positions include Head of Finance at Nasdaq listed biotech company Merus. She holds a bachelor's degree from the Amsterdam Business School and a post-doc degree from the University of Amsterdam, the Netherlands. Nathalie starts April 1st 2021 as the CFO of Intravacc.

Prof. dr. Virgil Schijns
Chief Scientific Officer

Virgil Schijns joined Intravacc in November 2020. He was appointed special Professor in Immunology and Virology at North Carolina State University (NCSU) USA, in 2002, and Guest Professor of Immune Intervention at Wageningen University, The Netherlands, Department Cell Biology & Immunology in 2008. Since 2013, he has been Guest Professor at Strathclyde University, Glasgow, United Kingdom.
Virgil also has extensive experience in the life science and biotech sector. He is the CSO of Epitopoietic Research Corporation S.A. in Namur, Belgium. Before that, he was Chief Technology Officer of Crossbeta Biosciences, and before that, Virgil was principal Immunologist of Nobilon and Head of Vaccine Technology and Immunology at Intervet-AKZONOBEL.

Daniëlle Lankveld, DVM, PhD
Chief Operating Officer

Daniëlle Lankveld is Chief Operational Officer of Intravacc since 2017. As a doctor in veterinary medicine, she started her career in 1995 as a resident in equine surgery at the former Department of General and Large Animal Surgery of the Utrecht University. After completing this she continued her career as a veterinary anesthetist for the same department and obtained her PhD in 2007. In this year she moved to the National Institute of Public Health to work as both a researcher in nanotoxicology and an assessor of human medical dossiers for cardiovascular medicine. In 2011 Daniëlle became Manager of the Animal Research Center of the former Netherlands Vaccine Institute and member of the management team. In 2013, when the Animal Research Center became part of Intravacc, Daniëlle moved to the position of Chief Development Officer until 2017 when she became the COO.

Figure 19:
Management team of Intravacc in 2020.

Michiel Stork, PhD.
Vice President Business Development

Michiel Stork started his current position as VP business development in July 2020 and works at Intravacc for over 9 years. Trained in molecular microbiology he first came in contact with vaccines in 2005. He worked in this field ever since. He started with antigen discovery and animal models followed by vaccine design and process development. This allowed him to work on the complete chain from lead finding up to clinical trials. Prior to his current position he was head of the Process Development Bacterial Vaccine department at Intravacc, where he focused on the design and upscaling of processes for conjugate and vesicle vaccines. During this time, he studied the biogenesis of outer membrane vesicle vaccines to unravel the mechanism of formation and subsequent yield increases.

Elly van Riet, PhD.
Vice President Research & Development

Elly van Riet has been working at Intravacc since 2013 and has been Vice-President of R&D since November 2020. She earned her MSc as an engineer in biotechnology at Wageningen University and Research Centre, followed by a PhD in immunology at the Department of Parasitology at Leiden University Medical Centre. During her PhD she got involved in vaccine research when she studied the effect of helminth infections on the immune responses to vaccination in Gabonese children. She continued vaccine related research as a postdoc at the Leiden Academic Centre for Drug Research where she was involved in designing nanoparticle vaccines for transcutaneous and intranasal delivery. She was granted a postdoctoral fellowship to investigate human immune responses to intranasal administration of influenza vaccines at the Influenza Virus Research Center of the National Institute of Infectious Diseases in Tokyo. In 2013 she joined Intravacc as Head of the department of Clinical Development.

Minke Wessels, MA
HR Manager

Minke Wessels joined Intravacc in September 2019. She brings more than 15 years of HR experience to Intravacc. After her master's degree in international law at Leiden University, she started out as Team manager at the ING Bank. Five years into the job she chose a new career path within HR, to pursue her interests in individual & group development and change management. Before joining Intravacc, she was senior HR Business Partner at Nationale-Nederlanden. Minke is an experienced coach and trainer and she has a track record in creating a culture of collaboration and managing change.

Erik Popping, LL.M
General Counsel

Erik Popping joined Intravacc in January 2016. He has more than 14 years of experience within the pharmaceutical / healthcare industry as corporate and legal counsel. Before Erik joined Intravacc, he was Corporate & Legal counsel at the Hal Allergy Group. Prior to that he was the Legal Counsel of the Netherlands Vaccine Institute, a predecessor of Intravacc. He holds a master's degree in law (LL.M.) (Radboud University) and a bachelor's degree in business administration (HAN University of applied sciences).

2.5 Scientific Advisory Board

The Scientific Advisory Board (SAB) of Intravacc consists of six scientific leaders in the fields of vaccinology, infectious diseases and oncology; dr. Marien de Jonge, dr. Harry Flore, prof. dr. Anke Huckriede, dr. Paul Wichgers Schreur, dr. Paul Oostvogel, prof. dr. Evelien Smits and is chaired by the CSO of Intravacc prof. dr. Vrigil Schijns.

The SAB will be consulted to help define the proper vaccine strategies and solutions to establish an impact on public health supported by convincing scientific clinical data. The SAB will also advise on the company's research strategy and approaches to optimize therapy effectiveness and added value.

Dr. Marien de Jonge is Associate Professor at Radboud University Medical Center, acting as Head of the Pediatric Infectious Diseases Section. He has more than 15 years of experience in both academic research and industrial R&D, mainly in the field of vaccine development and infectious diseases.

Dr. Harry Flore is Chairman of the Supervisory Board of HAL Allergy Holding of Leiden, the Netherlands - one of Europe's top players in the field of allergen immunotherapy, and a world leader in the production of modified allergen extracts for both therapeutic and diagnostic purposes. He is also active in HALIX, a CDMO, specializing in cell culture-based pharmaceutical production.

Prof. dr. Anke Huckriede is Professor of Vaccinology at the University of Groningen, the Netherlands, and is affiliated with the University Medical Center Groningen. Huckriede's research activities are aimed at vaccine development, with a focus on rational vaccine design. Her work on (influenza) vaccines focuses, among other things, on developing *in vitro* techniques for vaccine evaluation and understanding the effects of pre-existing immunity on responses to vaccination.

Dr. Paul Wichgers Schreur is a senior scientist in the field of arbovirology at Wageningen Bioveterinary Research (WBVR). Using techniques like reverse-genetics, single-molecule microscopy, and bacterial superglue he studies the infection cycle of bunyaviruses and uses this knowledge to (co)develop therapeutic antibodies and vaccines.

Dr. Paul Oostvogel M.D. is medical microbiologist. He has been involved in the Polio Eradication Initiative from the start in 1989. He retired in 2019 as head of the Public Health Laboratory of the Public Health Service (GGD) Amsterdam.

Prof. dr. Evelien Smits is research professor in tumor immunology and cancer immunotherapy at the University of Antwerp, Belgium. She is researching how the immune system of cancer patients can be provided with the necessary weapons to win the battle against cancer cells.

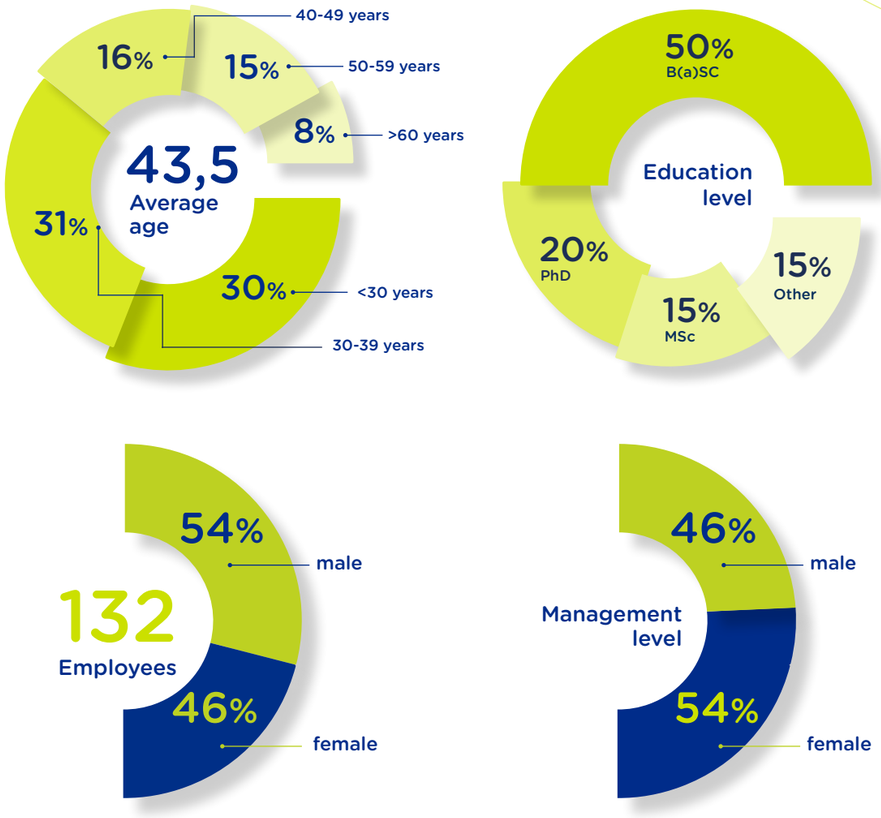
2.6 People and organization

A characteristic of Intravacc is its highly educated and qualified employees. A relatively large group holds as highest education a PhD degree (~20%), a significant amount of employees has a Master's (~15%) degree and most of the other employees have a Bachelor's degree.

Intravacc depicts a balanced age structure and male-female ratio, in both the organization as well as in management positions. The average age in 2020 was 43,5 years of the 132 employees 46% were female and 54% male (figure 20).

Intravacc emphasizes the importance of education and development of its employees. In addition, Intravacc regularly offers student internships. Even though Covid-19 meant postponing a few internships in the spring and early summer of 2020, an average of 7 interns was maintained.

Figure 20: Education level and male-female ratio.

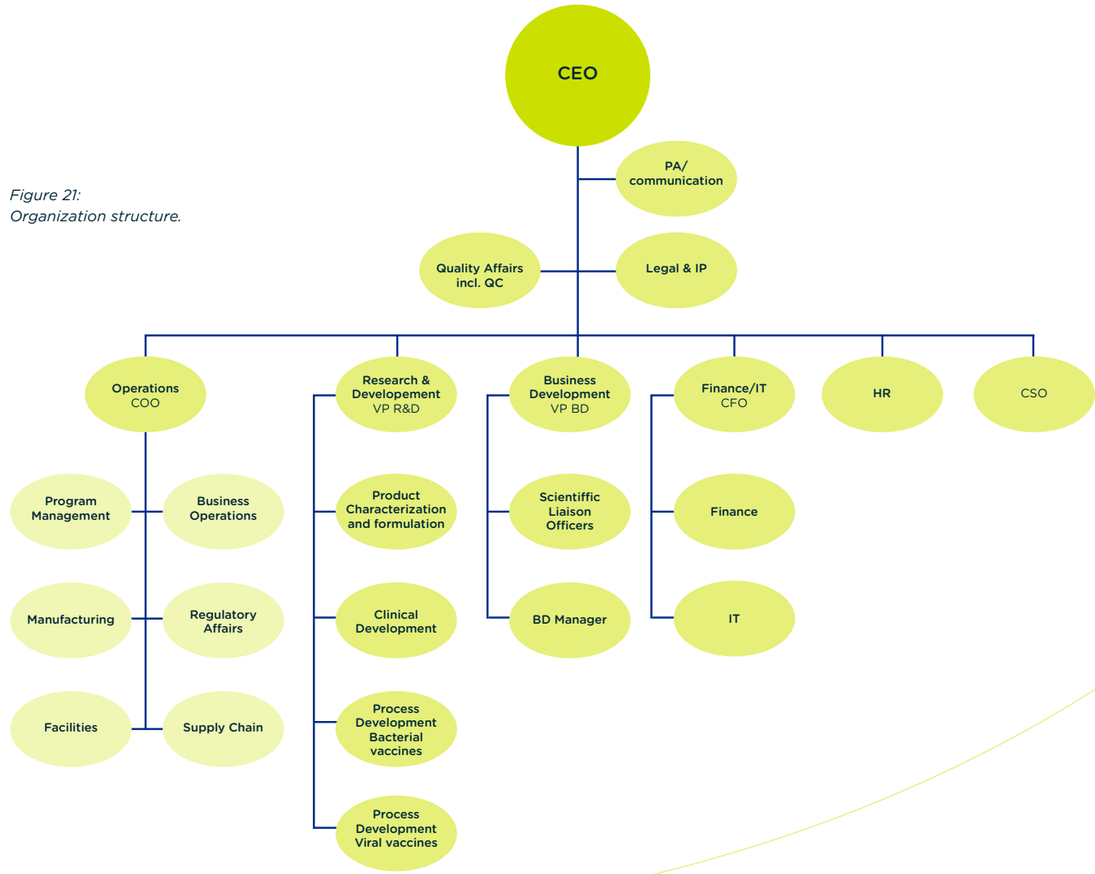


Organization structure

In 2020 the organization structure was revised in order to prepare the organization for a more commercially focused approach (figure 21). The further establishment and expansion of the business development department and changes in the alignment of the different departments in general, according to business standards in the sector, were also part of this organizational change.

The Research & Development department is organized into four major subdepartments, namely Product Characterization, Clinical Development, Process Development Bacterial and Process Development Viral. The majority of the personnel is placed in this department.

Figure 21: Organization structure.



Privatization and transition

With the pending privatization many processes were prepared and started to assure a smooth transition from a government institute into a private company. These included the new financial systems for the administration and many aspects concerning personnel, like compensation and benefits, to have a agreement and personnel manual in place before the actual privatization, and an updated Social Plan. From the end of October when the final decision to privatization was made, all efforts were focused on the transition date, January 1st 2021. Only a very small number of the personnel took advantage of the social plan and did not move to the company. This did not cause any problems in the continuation of projects.

The actual privatization, further professionalization, and a more business focused mindset within our highly qualified and dedicated employees, will help Intravacc to make this transition to a market and client-oriented company. To support and help facilitate this transition, company goals and the connected department goals were introduced to give management and the teams the means to focus and set priorities.

This transition of Intravacc to a more business minded approach (client and goal oriented) while at the same time retaining the dedication, high standards and involvement of employees is a long term goal. The current and future employees and managers will influence the success of Intravacc. Especially the managers are the role models for the desired attitude and behavior within Intravacc.

Works council

The works council of Intravacc consists of seven employees and is supported by a secretary without voting rights. They promote and protect the interests of the employees according to the Dutch Works Councils Act and advise the CEO on certain topics. The term of office of the works council is three years. The new works council starts February 2021 and will be in office till February 2024.

Chapter 3 Risk and opportunities

Risks and oppurtunities are regularly monitored and are embedded in the management systems of Intravacc. They connect well to the ISO 14001 (environment) and ISO 9001 (management) standards for which Intravacc is accredited.

3.1 SWOT

A SWOT analysis is a tool to understand where the company stands in terms of strengths and opportunities but also highlights the weaknesses and threats.

Intravacc possesses unique strengths in the field of vaccine development. The one-stop-shop is often appreciated by our customers to de-risk the project. The shipment of samples is significantly reduced, which is often seen as a positive aspect, especially as now movement across borders of biological substances is more and more difficult and requires more and more paperwork and time. There are many opportunities for Intravacc to expand its business.

Threats and weaknesses will be worked on. We will strengthen our weaknesses where we can. And for issues and risks beyond our control, we will endeavor to mitigate these. The risks associated with Intravacc are discussed below.

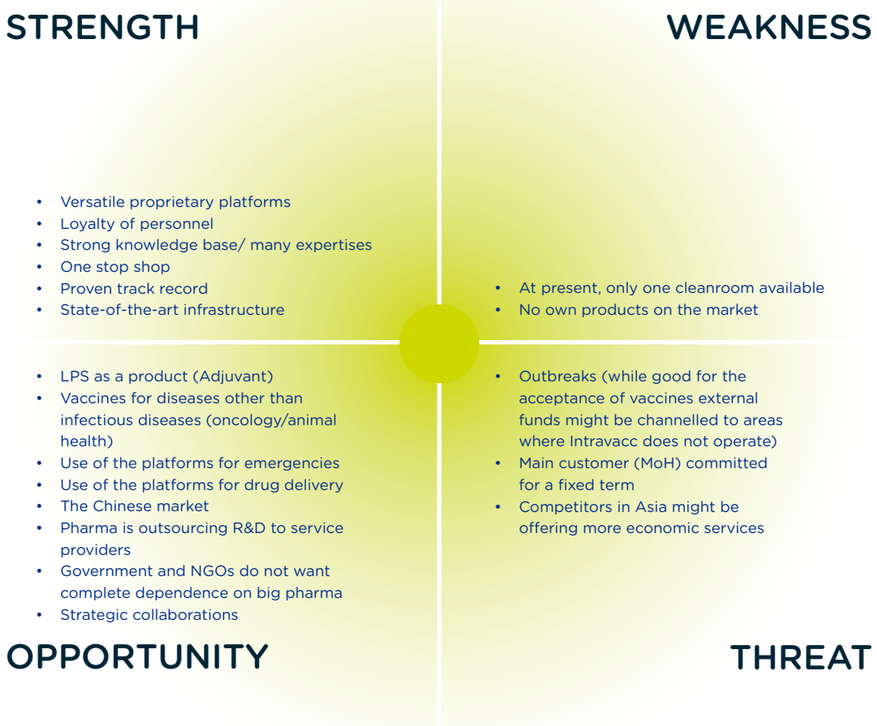


Figure 22: SWOT analysis.

3.2 Opportunities

As the “easy” vaccines have been developed, the design of new vaccines is more challenging. This is a great opportunity for Intravacc as most companies will need help at some point in their vaccine development projects. While the most devastating children’s diseases have been tackled there are many niches that still have a large unmet medical need. A lot of focus worldwide (and thereby funding opportunities) are in the field of antimicrobial resistance (AMR) and emerging infectious diseases (EID). For these infectious diseases Intravacc’s platforms are suitable and can be very successful. In addition to this, Intravacc seeks to enter the oncology field. This is a large market with a lot of capital. Moreover, leads in oncology can be licensed out earlier and can generate higher revenues. Intravacc has no track record yet and the network is not as vast as for infectious diseases. The in-licensing of the iBoost technology and the potential collaboration with Cristal Therapeutics can give Intravacc the quick start it needs to initiate the research in this field.

Other opportunities are in- and out-licensing of products and technologies. Intravacc can still transfer Hib two more times to specific regions in the world. In addition, once Nonamen® shows good results in China, Intravacc can out-license this to EU and the USA. Also, Intravacc should be able to out-license its proprietary Vero cells and OMVs (or technology) worldwide.

The current SARS-CoV2 crisis brings many problems but also provides opportunities. For instance, when a Covid-19 vaccine can reduce the disease burden it is a great (additional) showcase that vaccination works and could boost worldwide funding of vaccine projects. Intravacc can use this as an advantage.

3.3 Risk management

In order to provide a comprehensive view of Intravacc's risks, a structured risk assessment takes place yearly, applying a top-down and bottom-up approach. The process is supported by organizing workshops in which the Intravacc management team identifies, assesses and prioritizes risks on the basis of impact, likelihood and effectiveness of controls and appropriate risk responses are implemented. The management team monitors developments in the risk profile and risk response effectiveness, which are discussed in the management review cycle. The risk assessment takes into account various inputs on operational, strategic, financial, commercial and legal topics.

Developments in the risk profile and management's initiatives to improve risk responses are also discussed and monitored during the quarterly meeting of the Supervisory Board.

3.4 Risk table

As any other company, our business is subject to numerous risks and uncertainties. In the table below, we focus on the key risks and uncertainties Intravacc currently faces. Some of these risks and uncertainties are outside the control of Intravacc, others may be influenced or mitigated.

Category	Area	Specific	Risk	Expected impact	Mitigation
Operational	**Supply chain**	**Materials**	**Delay and unavailability due to Brexit, US first, Covid-19 pandemic, different execution due to Covid-19 restrictions and measures**	Delay and postponement in projects	Ordering early, ordering more and redundant systems
		Equipment		Longer lead time of new equipment followed by project delays	Anticipate investments
		Services		Lack of repair and maintenance resulting in downtime	Find local suppliers
	Certification	IGJ; manufacturing license	No license Problems during audit that affect project deliverables.	No possibility to produce and store CTM. Recalls	Quality system in place that is subject to annual internal audits
		ISO 9001:2015 and ISO14001:2015		Loss of reputation, remediation costs	
	Vaccine development	Development stages	Linger in specific stage	Exceeding time and budget	The vaccine development pathway that is now in place should avoid this
	Regulatory	Clinical trial authorization	It is a complex dynamic process that could result is a delay	Delay in clinical study, delay in revenue	Regulatory affairs contributes actively in projects to avoid problems later on
	Personnel	Key personnel and skills	Pursuing career elsewhere	Inability to perform certain tasks	Generating back-ups for all key persons/skills
	IT	**Down time**	**Not able to reach systems, no email and phone possibilities.**	Unproductivity	Find reliable IT supplier
		Cyber-crime	Loss of sensitive information	Bad appearance of company Loss of trade secrets	Good IT security and education of employees

Table 6: Possible risks Intravacc can face.

Category	Area	Specific	Risk	Expected impact	Mitigation
Strategic	**Privatization**	**Uncertainty**	**Employees leave**		This depends largely on external factors beyond the control of Intravacc
			Customers hesitate	Some customers are hesitant to place the project at Intravacc which reduced the project portfolio and revenues	
	IP	Patents	Field protected by others	Forced to obtain license or stop the project	IP landscaping and opposition
			Insufficient protection of field/product	Lower value of the product/project	Broad patents and or trade secrets
Financial	Revenue	Cashflow	Negative balance	The impact in 2020 is minimal as we are directly under the MOH. After privatization there is an impact i.e., debit interest/loans	Monitor budget and expenditure
Commercial	Projects	Fee for service	Insufficient projects	Intravacc depends largely on projects financed by third parties. When we obtain less projects it directly affects the financial situation and output of the company.	Dedicated BD team to obtain new project. Out licensing of our products and technology to assure fixed revenues/
	Competition	Product pipeline	Faster development timelines so that they are earlier in the position to engage third parties.	Smaller market to license our products.	Monitoring competition and IP management
			Better product	Smaller market to license our products.	Early Go/NoGo decision in the VDP
			More economic services	Less projects	Lower price or outperform competition

Category	Area	Specific	Risk	Expected impact	Mitigation
Legal	Customer Contracts	Non / limited performance	Claims	Financially (liability claims), reputational (loss of clients).	Concluding contracts that can be well managed and performed by the company. Appropriate insurance (for 2021), limiting contractual liability.
	Noncompliance with laws and regulations	Privacy laws / compliance with EU tender/ competition regulations	Data breach / third party claims / penalty	(reputational) damage / penalty	Good IT security and education of employees. Privacy policy and processing register available. Legal advice and dossier filing.

Not all of the above risks have occurred in 2020, some due timely mitigation. The ones in bold did occur. The backorder of materials was managed and while it did result in a prioritization of projects and experiments it did not cause any critical delays. The downtime for IT systems was limited to short interruptions that did not cause loss of data or delays. The privatization delay did cause some people to leave, however this did not cause problems in 2020. We did miss out on some projects due to the uncertainties around the privatization. This is unfortunate and we will try to discuss these again with our customers now that we are privatized.

Chapter 4 Additional information

4.1 Glossary

Abbreviation	Details	Explanation
AMR	Antimicrobial Resistance	
aPV	Acellular Pertussis Vaccine	Product from Intravacc
ARC	Animal Research Center	Animal research in projects
B.V.	Besloten Vennootschap	
BCA	Bicinchoninic Acid	Refers to an assay to determine total protein in a sample based on the chemical compound BCA
BCHT	Bring Health Care Tomorrow	Chinees vaccine manufacturer
BD	Business Development	
BMGF	Bill & Melinda Gates Foundation	
BPRC	Biomedical Primate Research Center	
BSc	Bachelor of Science	
BSL	Biological Safety Levels	These are classification ranging from 1 (generally safe) to 4 (not safe and no cure available)
BTI	Bacterial Typing Institute	
CBG	College ter Beoordeling van Geneesmiddelen	
CDBIO	Liaoning Cheng Da Biotechnology	Chinese Vaccine manufacturer
CDC	Center for Diseases Control	
CDMO	Contract Development and Manufacturing Organization	
CEO	Chief Executive Officer	
CFO	Chief Financial Officer	
cGMP	Current Good Manufacturing Practices	Good manufacturing practices are the practices required in order to conform to the guidelines recommended by agencies that control the authorization and licensing of the manufacture and sale of food and beverages, cosmetics, pharmaceutical products, dietary supplements, and medical devices.
COO	Chief Operation Officer	
Covid-19	Corona virus disease	Covid-19 is the name given by the World Health Organization (WHO) for the disease caused by the novel coronavirus SARS-CoV2

Abbreviation	Details	Explanation
CSO	Chief Scientific Officer	
CTM	Clinical Trial material	
CTO	Chief Technical Officer	
DNA	Deoxyribonucleic Acid	
DP	Drug Product	The drug product is the finished dosage form of the product. The drug product contains the drug substance(s) formulated with other ingredients in the finished dosage form ready for marketing. Other ingredients, active or inactive, may include adjuvants, preservatives, stabilizers, and/or excipients. For vaccine formulation, the drug substance(s) may be diluted, adsorbed, mixed with adjuvants or additives, and/or lyophilized to become the drug product (USFDA)
DS	Drug Substance	The drug product is the finished dosage form of the product. The drug product contains the drug substance(s) formulated with other ingredients in the finished dosage form ready for marketing. Other ingredients, active or inactive, may include adjuvants, preservatives, stabilizers, and/or excipients. For vaccine formulation, the drug substance(s) may be diluted, adsorbed, mixed with adjuvants or additives, and/or lyophilized to become the drug product (USFDA).
DSP	Downstream process development	In general DSP in the case of vaccines is the process of purifying the vaccine from the cultivated cells
EID	Emerging infectious diseases	
ELISA	Enzyme-linked Immunosorbent Assay	
EP	European Pharmacopoeia	
EU	European Union	
EV71	Enterovirus	
EVD68	Non-polio Enterovirus	
GC	Gas Chromatography	
HFMD	Hand Foot and Mouth Disease	
Hib	*Haemophilus influenzae* type B	Conjugate vaccine product from Intravacc
HPLC	High-Performance Liquid chromatography	

Abbreviation	Details	Explanation
HPV	Human Papillomavirus	
HR	Human Resources	
iBoost		Platform for oncology vaccines in-licensed by Intravacc
ICH	International Conference on Harmonization	International Council of Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IP	Intellectual Property	
ISS	Istituto Superiore di Sanità	
IT	Information Technology	
LNV	Ministerie van Landbouw, Natuur en Voedselkwaliteit	
LPS	Lipopolysaccharides	Intravacc produces LPS to be used as adjuvants.
MCB	Master Cell Bank	Cell bank is used for cells used for the production of viral vaccines
MenB	*Neisseria meningitidis* type B	
MoH	Ministry of Health	
MSc	Master of Science	
MSL	Master Seed Lot	Seed lot is used for viral or bacterial seeds
NCSU	North Carolina State University	
NGO	Non-Governmental Organization	
NIBSC	National Institute for Biological Standards and Control	
NIH	National Institute of Health	
NIPH	National Institute for Public Health	
NMR	Nuclear Magnetic Resonance	
Nonamen		*Neisseria meningitidis* type B vaccine developed by Intravacc. OMV vaccine based on 9 serotypes of the major protective antigen PorA to achieve broad protection.
NRA / RA	(National) Regulatory Authorities	Government agencies tasked with regulating and supervising pharmaceuticals and biological products such as vaccines released for public distribution. All countries need some sort of NRA, but “producing” countries need to exercise six critical control functions in a competent and independent manner backed up with enforcement power.

Abbreviation	Details	Explanation
NTA	Nanoparticle Tracking Analysis	
NVI	Netherlands Vaccine Institute	
OMV	Outer Membrane Vesicle	Platform of Intravacc
PCR	Polymerase Chain Reaction	
PEI	Paul Ehrlich Institute	
pH	Power of Hydrogen	
Ph1	Phase 1 clinical trial	
Ph2	Phase 2 clinical trial	
PhD	Doctor of Philosophy	
PoC	Proof of Concept	
Preclinical studies		All studies in animals that are performed during product development
PRP	Polyribosyl-Ribitol- Phosphate	
PSP	Poonawalla Science park	
QA	Quality Assurance	
QC	Quality Control	
R&D	Research and Development	
RIVM	Rijksinstituut voor Volksgezondheid en Milieu	
RSV	Respiratory Syncytial Virus	
SAB	Scientific Advisory Board	
sIPV	Sabin Inactivated Polio Vaccine	Vaccine product developed by Intravacc
SME	Small Medium Enterprise	
Stichting ALT	Stichting Antonie van Leeuwenhoek Terrein	
Supply Chain		A supply chain is the network of all the individuals, organizations, resources, activities, and technology involved in the creation and sale of a product, from the delivery of source materials from the supplier to the manufacturer, through to its eventual delivery to the end user.
SWOT	Strengths, Weaknesses, Opportunities, Threats	
UMCG	Universitair Medisch Centrum Groningen	
USA	United States of America	

Abbreviation	Details	Explanation
USP	Upstream Process development	In general, USP in the case of vaccines is the process of cultivating the cells or bacteria.
USPB	Utrecht Science Park Bilthoven	The terrain where the buildings of Intravacc are situated is call Utrecht science park Bilthoven and is affiliated with the Utrecht Science park.
UU	Utrecht University	
Validation		The action proving and documenting that any asset, process, procedure, or method actually and consistently leads to expected results. Can be used interchangeable with qualification in case of assets.
VDP	Vaccine Development Pathway	
Vero Cell		The Vero cell is a cell line derived from the kidney from the African green monkey. It is used by Intravacc for virus propagation.
VP	Vice President	
VWS	Volksgezondheid, Welzijn en Sport	
WBVR	Wageningen Bioveterinary Research	
WCB	Working Cell Bank	
WHO	World Health Organization	
WSL	Working Seed Lot	

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