leem
LES ENTREPRISES DU MÉDICAMENT

FRANCE TO SET THE BENCHMARK IN EUROPE FOR VACCINATION POLICY

OUR SET OF 15 PRIORITY PROPOSALS

Serge Montero
Chairman of Leem's Vaccines Committee

France aims to become the European benchmark for vaccination policy by 2022

The enormous value that vaccination brings to our health, well-being and the economy is very widely documented these days. According to the WHO, vaccination prevents 2 to 3 million deaths each year from diphtheria, tetanus, whooping cough and measles. Vaccination is even considered to be one of the most cost-effective investments in the field of health[1].

However, there is no denying that trust in vaccines has been undermined.

Although France has satisfactory coverage rates for diphtheria, tetanus and polio, there are many other vaccinations providing insufficient immunisation cover for children, adolescents and adults, some of which included in the mandatory vaccination programme. Between 2008 and 2017, over 24,500 cases of measles were reported in France, resulting in nearly 1,500 cases of lung disease, 38 neurological complications and 20 deaths[2]. The number of deaths attributable to hepatitis B in France[2] is estimated to be about 1,500 per year. Moreover, some diseases that were thought to have disappeared are now resurfacing.

The time has come for pragmatism and it seems that the public authorities have grasped the scale of the problem. The Government's health strategy is based on 4 core principles, 2 of which are directly related to vaccination policy, namely the introduction of a health promotion policy, including disease prevention, and overcoming social and territorial inequalities in access to healthcare.

Given the complexity of the challenges and the current distrust towards vaccines, the vaccination policy should undergo a complete overhaul to incorporate long-term vision, dialogue and trust between citizens and all stakeholders in the healthcare system so that vaccination as a civic duty is reinstated as central to this national disease prevention policy.

Vaccine companies recognise their responsibility and involvement throughout the vaccine life cycle, from R&D and manufacture to supply and monitoring, and as such have joined Leem's Vaccines Committee in their desire to be part of the discussion and joint effort. Our vaccines are safe, effective and efficient health products. Their incorporation into a bold and ambitious health policy will bring about significant health benefits in France and boost the performance of our healthcare system. Leem's Vaccines Committee is presenting its proposals through this platform which represents the outcome of an ongoing dialogue with the authorities and practitioners in the field.

Improving the immunisation coverage of our population is a public health imperative[3]. My hope is that in 5 years' time, thanks to the efforts of everybody, we will have succeeded in making France the European benchmark for vaccination policy in order to reduce disease and protect life.

March 2018

[1] *WHO Immunization FACT SHEET*
[2] *Public Health Data France*
[3] *Speech by Agnès Buzyn, Minister of Solidarity and Health, on mandatory vaccination, 5 July 2017*

CONTENTS

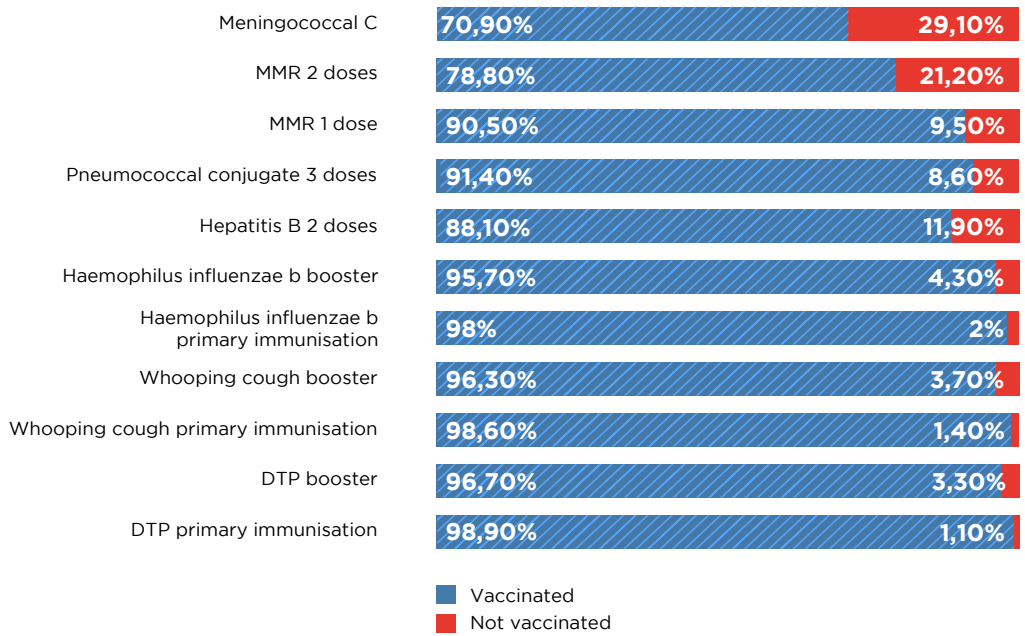
Our set of 15 priority proposals

Health overview

A worrying situation

- **Meningococcal C:** insufficient immunisation coverage for 2 year olds (71%), low among 10-14 year olds (36%) and very low among 20-24 year olds (7%)[1].
- **Hepatitis B and MMR** (measles, mumps, rubella) «2 doses»: insufficient coverage of children (88% and 79% respectively)[1].
- **Papillomavirus (HPV):** lower vaccine coverage in 2016 for the 3 doses at 16 years of age (20% vs 28% in 2010), while average immunisation coverage across Europe was approximately 70%[1].
- **Seasonal influenza:** disturbing drop in immunisation coverage in 2016-2017 (46% vs 60% in 2009-2010)[1].

Immunisation coverage in France of children under 2 years of age[2]



Slightly insufficient immunisation coverage

THE FACTS

In France, the epidemiological data show good immunisation coverage for diphtheria, tetanus and polio, especially in children (> 90%), but show a significant delay in vaccinations that have become mandatory or are recommended during adolescence (84%) or in adulthood (44% after 65 years of age).

These rates are not sufficient enough to provide good collective protection against these diseases. This explains the resurgence of serious and highly contagious infectious diseases, in the form of epidemics, as in the case of the measles outbreaks in 2008 and 2012[3].

At present, some 41% of the French public express doubts about the safety of vaccines, and healthcare professionals[3], who are broadly convinced of the individual and collective value of vaccination, appear to be undermined by the current climate of distrust.

THE PROSPECTS

The World Health Organization recommends at least 95% coverage nationally to prevent outbreaks from occurring.

In the words of the experts

Solidarity and responsibility must be highlighted. The slogan «I'm vaccinated and I protect others» reminds us that the more people are vaccinated (over 90%) the fewer bacteria are circulating.

Routine vaccination against childhood diseases with severe complications would prevent teenagers from dying at the age of 16 as happened in 2018 in France, the homeland of Louis Pasteur.

[1] *Immunisation coverage data - Public Health France*
[2] *Public Health France 2016*
[3] *Vaccine Confidence Project Study - London School of Hygiene and Tropical Medicine (2016)*

Political overview

11

The number of mandatory vaccinations in France for children under 2 years of age born after 1 January 2018.
(Polio - Diphtheria - Tetanus - Pertussis - Haemophilus influenza b - Measles - Rubella - Mumps - Hepatitis B - Pneumococcal meningococcus C).

Impact of vaccination on preventable diseases in France

Disease or infection	Number of cases before vaccination	Number of cases after vaccination	Estimated reduction (%)
Diphtheria	45 000	0	> 99 %
Tetanus	1 000	17	> 99 %
Whooping cough	500 000 à 600 000	1000	> 99 %
Paralytic polio	4 000	0	> 99 %
Measles	500 000 à 600 000	< 50 000	> 87 %
Hepatitis B, chronic infection	300 000	28 000	> 87 %
Rubella, during pregnancy	200	40	> 55 %
Mumps	500 000 à 600 000	< 30 000	> 90 %
Haemophilus influenzae type B	1000	< 50	> 90 %

Source: Leem

THE FACTS

Public authorities in France and throughout Europe are working on the expansion of the policy of immunisation against infectious diseases.

Across France, several projects have helped make the improvement in immunisation coverage a priority public health objective. Vaccination has been clearly recognised as an important tool for the prevention of infectious diseases.

More specifically, it transpired from the big public consultation held in 2016 and coordinated by Professor Alain Fisher that the public health policy on immunisation was in urgent need of revival through the long-term mobilisation of public authorities and healthcare stakeholders - general practitioners, paediatricians, citizens and patient representatives.

The minister wanted 11 mandatory vaccinations to cover 11 diseases of early childhood, justifying the measure as a safeguard of the collective good. She also pledged to ensure that the extension of mandatory vaccination will not incur any additional cost to the patients. All mandatory vaccines will continue to be covered by the health insurance and supplementary schemes.

Planned and expected breakthroughs

THE PROSPECTS

The French authorities have proposed that an annual meeting be arranged to review the status of immunisation in France. In light of the National Health Strategy and the target immunisation coverage rates, it is essential that this goal remain unchanged so that an annual assessment can be made of the progress in immunisation coverage and vaccination adherence along with a discussion of forthcoming developments in the vaccination schedule.

Several factors need to converge to restore confidence and increase immunisation coverage: a demand for greater transparency from industry towards citizens, a commitment from the public authorities to an information and communications drive and a streamlining of the vaccination policy tools (pathways and immunisation schedule in particular).

Moreover, as pointed out in conclusion of its work by the Steering Committee for Citizen Consultation on Immunisation, the future of the vaccination policy also lies in increased support for healthcare professionals, greater value placed on vaccination in medical practice and more time teaching practitioners about vaccination.

Beyond this finding, the vaccination of adolescents and young adults calls for appropriate tools (specific communication, outreach, streamlining of pathways, etc.).

The Joint Action on Vaccination

Work is also well advanced at European level. Launched in 2017 by the European Commission's Directorate-General for Health, the French-led[2] «Joint Action on Vaccination» aims to identify mechanisms of cooperation at EU level for vaccine policy development.

The programme of work features several priorities that include improving vaccine coverage, implementing solutions to prevent vaccine shortages, promoting access to vaccines and making vaccine research more effective in the European Union[3].

[1] *Report on Vaccination - Steering Committee for Citizen Consultation on Vaccination*
[2] *European Commission - Report Workshop on Vaccination «Seeking new partnerships for EU action on vaccination» - 31 May 2017*
[3] *European Commission - CHAFEA Call 2017 Joint Actions*

Stimulating research to address medical needs

€2 bn

The annual budget allocated to vaccine R&D in Europe.

Source: : Vaccine Europe 2016

13

The number of key R&D sites in Europe.

Source: : Vaccine Europe 2016

A vaccine is a biologically derived medicinal product whose active substances cannot be synthesised chemically. Scientific advances have made great strides while making the research phases more complex.

The vaccine development cycle is divided into three successive phases, on completion of which companies can apply for a Marketing Authorisation (MA).

2 to 4 years

Exploratory phase

Identifying antigens for the selection of vaccine candidates.

1 to 2 years

Preclinical phase

Evaluating these antigens to select the best vaccine candidate.

6 to 8 years

Clinical development phase and evaluation of the vaccine candidate in healthy subjects

Testing the safety of the vaccine (10 to 100 subjects), the immune response of the vaccinees (100 to 3000 subjects) and finally efficacy and tolerance on a very large scale (3000 to 70000 subjects). In this last phase, the number of subjects is considerably higher than for the development of a conventional pharmaceutical product (a few thousand patients).

French and European excellence in research

THE FACTS

France and Europe, regions of excellence for vaccine research

Development is complex, lengthy and expensive

As a result of these different sequences, the research process for developing a vaccine is complex, lengthy (8 to 18 years) and expensive (approximately 800 million euros[1]) but is also subject to intense monitoring. No other health product involves as many subjects in its clinical trials to help detect rare adverse reactions long before it is marketed.

Improving the ease and safety of vaccines is a constant concern for manufacturers. Research does not stop at the end of the clinical development phase but continues long after the MA is issued with real-life studies.

Heavy investment

Vaccine companies invest around EUR 2 billion each year in R&D, i.e. 71% of global investments[2].

To meet the need for lasting protection, research is being geared towards new targets (Clostridium Difficile, Respiratory Syncytial Virus, Staphylococcus Aureus, Ebola, Zika, etc.), new combinations, the development of new adjuvants tailored to new vaccines (to reduce the antigen dose, prolong the immunity protection period, protect specific populations and broaden the immune response) and new routes of administration.

Renowned expertise in the field of vaccination

France has developed world-renowned expertise in the field of vaccination and has spearheaded public research in infectious diseases and the challenges they pose in terms of public health and safety.

At European level, the European Vaccine Initiative has also been established as an EU coordination action to pool research efforts into vaccines for diseases of poverty in particular.

[1] *IFPMA - Vaccine research and development – Avril 2013*
[2] *Vaccine Europe – The European vaccines industry in figures*

To find out more

Vaccine adjuvants

Our immune system, which is composed of the body's defence cells, must respond to eliminate a germ when it enters our body.

When a vaccine is injected, it acts in such a way that the body develops its own protection against bacteria or viruses that are the cause of the disease targeted by the vaccine.

Source: vaccinationinfoservice.fr

For the majority of inactivated vaccines (not containing live microorganisms), the presence of adjuvants is essential to stimulate an immune response which then provides protection. Moreover, the addition of an adjuvant to the vaccines makes it possible to reduce the amount of antigens per vaccine dose and lower the number of injections.

Aluminium salts have been among the most widely used adjuvants worldwide for more than 90 years, with hundreds of millions of doses injected.

258

The number of vaccines or combination vaccines in development in 2016.

Source: PhRMA – Medicines in development for vaccines – 2016 update

124

The number of vaccines in development that are specifically designed to treat infectious diseases.

Source: PhRMA – Medicines in development for vaccines – 2016

MEETING THE NEEDS

Being more open to private research projects so as to remain competitive and join forces to discover vaccines for the future

In this era of global competition to attract investment in research, the synergies between public research and private research should be stepped up. In addition, private investment in research should be given greater prominence. In recent years, the public authorities have established interfaces to bring public and private research operators closer together, in both France and Europe (example: Aviesan set up in France in April 2009).

These partnership mechanisms should be built upon and collaborative platforms should be promoted to complement public funding.

The development of new research programmes is also achieved through attractive mechanisms that take account of the investments made by the pharmaceutical companies (CSIS Credits, CEPS-Leem Framework Agreement).

The implementation of clause 18 of the latest Framework Agreement, in which investments are considered for price setting, should allow account to be taken of the research programmes developed in France and in Europe.

OUR COMMITMENTS

Industry's research efforts to combat infectious diseases

Guaranteeing high-quality research

Vaccine research encompasses the discovery of new antigens, new combination vaccines, new manufacturing platforms, new adjuvants, as well as new vaccine delivery methods and the optimisation of existing devices. 70% of investments are earmarked for the development of highly innovative new vaccines[1].

In 2016, 258 vaccines or combination vaccines were in development, including 124 specifically designed to treat infectious diseases (Clostridium Difficile, Respiratory Syncytial Virus, Staphylococcus Aureus, Ebola, Zika, Dengue, Shingles, etc.)[2].

CEPS: Economic Committee for Health Products
CSIS: Strategic Council for the Healthcare Industries
ANSM: National Agency for Medicines and Health Products Safety

Our proposals

PRIORITY 1: Foster the development of public/private partnerships

1. Greater international recognition of the strengths of French public research on vaccines (dedicated communication tools, increasing participation in international research conferences, etc.).

2. The spread of a private/public partnership culture, primarily by encouraging the creation of professional gateways and exchanges between the two sectors.

3. The introduction of standard contracts which lay down rules for sharing the value derived from joint research.

PRIORITY 2: Support research development by facilitating the set-up of clinical trials

No clinical trial may commence without the approval of the CPP (Ethics Committee) and the authorisation of ANSM (French National Agency for Medicines and Health Products Safety).

1. Given that the clinical trial application procedures have become lengthier, it is essential for ANSM and the CPPs to be given all the human, technical and financial resources necessary to carry out their task.

PRIORITY 3: Provide better public policy guidance through social sciences research

Identifying and understanding the different underlying mechanisms that promote or impede support for immunisation from the public and healthcare professionals is essential to achieving better public policy guidance.

1. Research in the social and behavioural sciences should be encouraged and further developed through allocated funding. Research must not only advance immunisation coverage but also make it possible to ascertain perceptions and support among the public and healthcare professionals.

2. Calls for projects by Public Health France could be launched nationally to identify obstacles to vaccination and put effective interventions in place, thereby convincing them of the merits of vaccination.

3. The vaccine companies can contribute to the debate by leveraging the experiences of other countries.

In the words of the experts

«Vaccines afford significant research potential for France, especially when it comes to the optimisation of existing vaccines. This is where research can make its most visible contribution: helping to better identify the benefits of vaccines and combat vaccine hesitancy by improvements in the effectiveness of the vaccines currently in use.
Ongoing research seeks to identify adjuvant molecules that would further optimise the specific immune response to vaccine antigens. In order for this research to be successful, the creation of public/private partnerships must be encouraged.»

Brigitte AUTRAN, Immunology Expert
University Professor - Hospital Practitioner (PU-PH)
at Pitié-Salpêtrière Hospital

[1] *Vaccine Europe - Vaccines' contriubution to Europe's future - Mars 2010*
[2] *PhRMA - Medicines in development for vaccines - 2016 update*

Producing and ensuring the supply of vaccines

70 %

The share of production time dedicated to quality control.

Source: Leem

Between 100 and 500

The number of in-process controls during the manufacturing of the vaccine

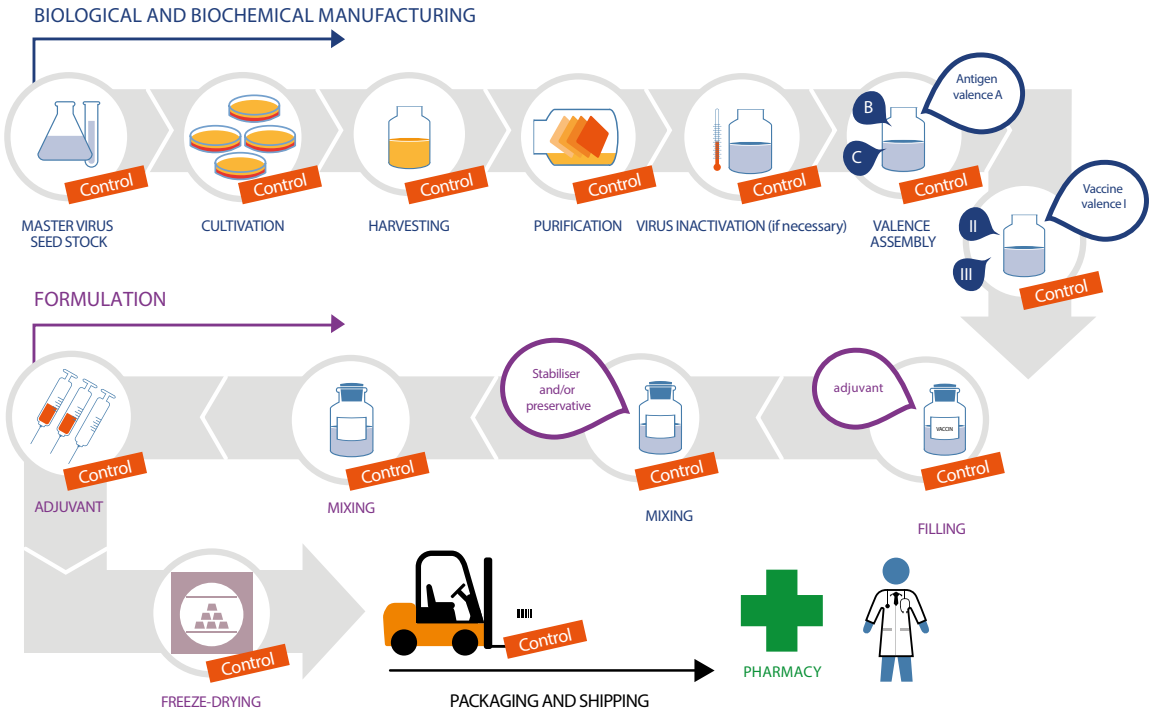
Source: Leem

7 to 10 ans

The time it takes to build a manufacturing site and for it to be accredited by the health authorities.

Source: Leem

The steps in the vaccine manufacturing process



Vaccine production, a European area of excellence

The production of a vaccine is a highly technical operation that relies on specialist expertise.
It requires 6 to 22 months to make whereas a conventional pharmaceutical product takes from a few weeks to a maximum of 4 to 6 months.

Depending on the vaccine and the number of antigens, between 100 and 500 quality controls are needed to produce one batch.

Thus, 1 in 4 people on average on a production site work in quality control or assurance and receive specific training. Europe enjoys a competitive advantage thanks to the quality of its infrastructure, as evidenced by the dynamism of the sector, worth EUR 28 billion in 2014 compared to EUR 5 billion in the early 2000s1.

Europe produces 80% of the 4 billion vaccine doses produced annually around the globe2.

Producing and supplying the world population: a challenge for the vaccine industry

THE FACTS

Vaccine production as a strategic activity for France

The vaccine industry is global: 85% of French output is exported[2]. It is also a high value-added high-tech industry, characterised by extremely rigorous manufacturing techniques and numerous sophisticated and highly technological quality control processes.

Manufacturers contribute locally to the vitality of the areas in which they are sited: in 2015, 6,000 people3 were employed at the 8 human and animal vaccine production sites in France. The jobs generated by this industry are highly skilled because of the complex technical nature of the vaccine product. France has gained great expertise in vaccine production and its firm footing in the local regions makes it a leading player in Europe.

The challenge of production forecasting

Vaccine supply pressures are a constant concern for vaccine companies as they contribute to the public's feeling of distrust.
Production is further complicated by the surge in global demand (in the space of 4 years, the number of countries recommending, for example, the whooping cough vaccination during pregnancy has increased from 1 to 34), the small number of manufacturers (5 laboratories account for 80% of supply4), the tight deadlines and the steady introduction of increasingly stringent standards. These disruptions in supply pose a threat to both public health and public confidence.

Control and release by the health authorities

Vaccine control has become ever more complex over the past decade with a threefold increase in the number of countries that conduct their own batch control and release procedures.

Some vaccine batches can now undergo more than 3 sets of successive tests and releases, which means that testing accounts for some 70% of the vaccine's production cycle time. Any delay will directly affect the availability of the vaccines by significantly impacting their shelf-life.

Complexity through diversity

The diversity of regulations enacted by the various international and national authorities is a complicating factor in vaccine production and makes dose reallocation difficult.

Companies have to respond to the different and changing vaccine schedules in addition to the specific requirements of each country. These arrangements call for adjustments that are unachievable through increased production (due to tight production deadlines). These different schedules and regulations make it difficult for businesses to manage production schedules and reduce flexibility of supply for countries, thereby potentially increasing pressure or even shortages.

What is more, the approval procedures are not standardised: neither their content requirements nor their assessment periods are uniform or always predictable. It can take up to 5 years for a change to be approved. These delays are not compatible with people's immunisation needs and are a curb on scientific progress.

Parallel exports as an aggravating factor when pressure builds in the event of an epidemic

Each break in supply has a specific origin.
At a time when supplies are under strain, parallel exports are an aggravating factor by encouraging the shunting of vaccine batches to countries where the sale prices are higher.

In the words of the experts

«Controlled vaccine production is one of the keys to public trust. The task lies with manufacturers to continue investing to boost their manufacturing capacity and optimise the robustness of their manufacturing processes. Despite the fact that France and Europe excel to a certain extent in this area, some production times are irreducible.

In order for us to anticipate changes in the vaccination schedule and give better direction to the industrial choices we make, we have to step up cooperation with the authorities. Besides that, the challenges of vaccine production reach far beyond Europe's borders: the issues of international harmonisation of batch release controls and the management of regulatory variations are high-priority challenges that the authorities need to address in order to help ensure that vaccines are made available. «

Philippe JUVIN, Head Pharmacist
Product Quality Manager at Sanofi Pasteur

[1] *WHO - Global Vaccine Market - March 2010*
[2] *Vaccine Europe - Facts and Figures - 2013*
[3] *Leem Vaccines Committee Factsheet - Available from leem.org*
[4] *Vaccine Europe - Vaccines' contribution to Europe's future - March 2010*

80 %

Europe's share of the 4 billion doses produced annually around the globe.

Source: Leem

€ 2 bn

The investment budget over the last 10 years across 4 major sites in France.

Source: Leem

MEETING THE NEEDS

Create conditions conducive to ensuring that production continues to be outstanding and responsive throughout the country

A joint effort must be made by industrialists and public authorities to avert supply disruptions. Building a more regular dialogue between governments and manufacturers would enable companies to predict and anticipate any changes that may have an impact on production.

To ensure that the French vaccine industry remains strong, French and European actors in the public and private sectors are working together to maintain a sector of excellence on the Continent of Europe by taking measures to support the location of production sites throughout the land along with the development of manufacturing capacity.

OUR COMMITMENTS

What French and European manufacturers are doing to maintain their leadership position in vaccine production

Guaranteeing product safety

We use the best technologies to detect unwanted substances (successive safety and quality controls). These systems are introduced into each laboratory to supplement the stringent regulatory framework imposed by the public authorities.

Moreover, most vaccines are subject to a specific monitoring procedure within a national or European framework. Once the vaccine is placed on the market, as is the case with all medicinal products, we analyse the adverse reaction reports to further improve the safety of our products.

Close cooperation with the public authorities

On 28 January 2017, we made four commitments to improve the management of vaccine stocks1:

1. Notify the authorities on a regular basis of stock levels;
2. Produce shortage management plans for each vaccine;
3. Work to reduce production times and increase manufacturing capacity;
4. Prevent wastage and increase the amount of conformity-certified vaccines.

A proactive attitude to minimise the risks of stock-outs

We are closely monitoring the market and its changes and have been preparing shortage management plans accessible to the health authorities since January 2017.

All companies have programmes to minimise the risks of stock-outs by reducing the various components of the manufacturing process (especially the control aspect), by reducing production times or by investments to expand manufacturing capacity.

Our proposals

PRIORITY 4: Create an attractive framework for private investment in the means of production

1. Implement the framework agreement provision to capitalise on industrial investments and the complexity of the manufacturing base by establishing specific price setting criteria when assessing a medicinal product.

2. Guarantee price stability after 24 months in cases where highly sophisticated industrial investments are made in Europe. Although provided for in the LEEM-CEPS framework agreement 2016-2018, this measure has barely been implemented.

PRIORITY 5: Establish close cooperation at European level between vaccine companies and institutional partners

through the creation of a joint decision-making platform. By bringing together European authorities and agencies, scientists and vaccine manufacturers, this platform will:

1. Assess the benefit of the dual release of batches in an effort to optimise existing manufacturing capacity.

2. Promote upstream information sharing on any changes in national vaccine recommendations in order to minimise the risk of shortages. Harmonisation of vaccination schedules between countries would facilitate the production of vaccines in several countries and their sharing should health problems arise in a given country.

3. Share the need to streamline regulatory procedures for the simultaneous update of the quality module of marketing authorisation dossiers where several changes affect more than one vaccine.

4. Apply to the European Commission to initiate the harmonisation of packaging and leaflets, in line with changing regulations, in an attempt to reduce the number of national specificities and thus improve flexibility of supply or indeed avoid having to destroy products on account of obsolete packaging that does not affect the intrinsic quality of the vaccine.

5. Help to foster a better understanding of the issues facing the entire sector so that joint operational solutions can be found, especially in respect of supply disruptions.

PRIORITY 6: Improve the management of parallel exports to minimise the risks of supply pressures

1. Produce and publish the ministerial order provided for in articles L.245-6 CSS (Social Security Code) defining the list of the medicinal products of major therapeutic significance in respect of which retailers must inform the MA holder of the quantities intended for sale abroad[2].

2. Implement the tripartite agreement provided for in the same articles between the State, the association(s) of wholesale distributors and the association(s) representing companies manufacturing or marketing a medicinal product. The purpose of this agreement is to define the conditions under which retailers notify manufacturers/pharmaceutical traders (exploitants) of the quantities exported[3].

In the words of the experts

«Vaccine production is a highly technical field in which France is renowned. A vaccine is a product with a very long life cycle (36 months required to produce an active ingredient and 9 to 10 months for the resulting product to be converted into a vaccine syringe, a process involving numerous controls). We only work on orders that materialise a good two years later.

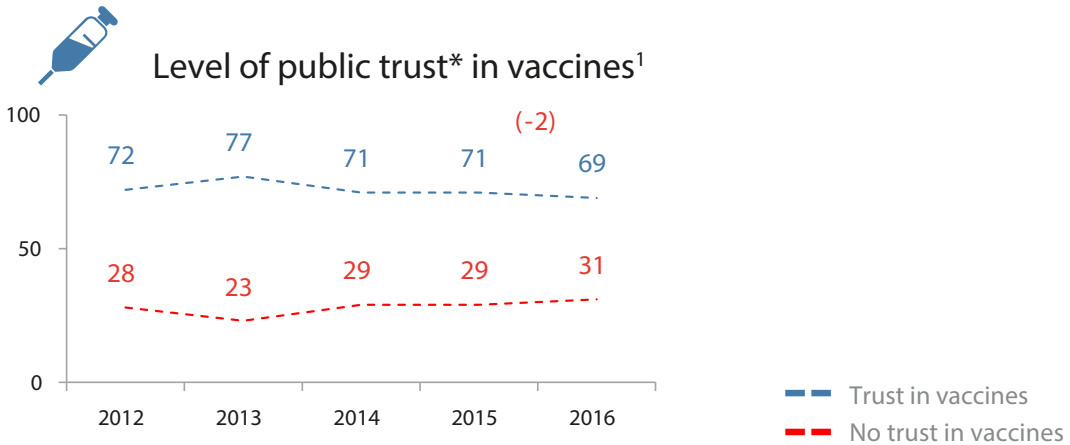
Predicting demand is essential but complex and our ability to react is therefore limited. In a climate of rising demand for vaccines and ever growing country-specific regulations, solving the logistics equation is no easy feat.»

Gaël RUCHE - *Director of a GSK vaccine production site*

[1]Commitments from companies to Marisol Touraine on 28 January 2017
[2]Healthcare Industries and Technologies Sector Agreement - Measure 26: Export price: implementation of article 45 of the Law of 29 December 2011 (page 94)
[3]Healthcare Industries and Technologies Sector Agreement - Measure 26: Export price: implementation of article 45 of the Law of 29 December 2011 (page 94)

Restoring trust in vaccines

LEEM - IPSOS OBSERVATOIRE SOCIÉTAL 2016



SOME KEY DATES

1902

First mandatory vaccination (against smallpox).

1970

The new vaccines in the vaccination schedule are recommended from now on and no longer mandatory.

1984

Cessation of mandatory vaccination against smallpox.

2007

Cessation of mandatory vaccination against TB

2018

Extension of mandatory vaccination

What should be done to counter rising distrust?

THE FACTS

A feeling of distrust towards vaccination is prevalent in France

A growing feeling of distrust

A survey conducted in 2015 by researchers from the «Vaccine Confidence Project»[2] shows that 41% of respondents in France express doubts about the safety of vaccines. This shared feeling has many roots:

1. The positive effects of vaccines are less visible following the disappearance of major pandemics.

2. Media controversy and scientifically unfounded claims have played their part in shaking public confidence in vaccination and in the health authorities.

3. Nearly 1/4[3] of general practitioners, who had spearheaded vaccine policy, express doubts over the usefulness of some vaccines.

The re-emergence and resurgence of diseases such as measles and meningitis, as well as the huge burden of certain diseases (e.g. pre-cancerous lesions and cervical cancer caused by papillomavirus), are illustrative of this disenchantment towards vaccines on the part of patients and doctors alike.

The insufficient number of hours devoted to teaching vaccinology to healthcare professionals and the limited number of resources made available to them to answer patients' questions prevent them from making an informed choice about vaccination and from carrying out their work to ensure that vaccination is used as a preventive measure.

MEETING THE NEEDS

To restore public confidence in vaccination and its benefits

The extension of mandatory childhood immunisation to 11 vaccinations to cover 11 diseases creates a corresponding need for long-term follow-up of the recommended vaccines in order to focus the efforts of healthcare professionals on the vaccination schedule and on the other vaccinations, which are still indispensable.

Essentially, it is a question of «protection through persuasion»[4]. Trust in vaccines needs to be restored. A number of proposals emerged from the 2016 citizen consultation to help restore trust in vaccination:

1. Arrange for the publication of verifiable resources on a comprehensive single website in closer touch with the public.

2. Restore schools to their rightful place by reinstating student health monitoring and health education.

3. Develop an ambitious public communications system, coupled with vaccination information tools designed for professionals. The Internet appears to be a good channel in that it offers great scope for communication with a broad section of the French public who have questions about their vaccinations and the role of vaccine companies in France.

The great public consultation

The big public consultation held in 2016 and coordinated by Professor Alain Fisher highlighted the urgent need to revive the public health policy on immunisation1 through the long-term mobilisation of public authorities and healthcare stakeholders - general practitioners, paediatricians, members of the public and patient representatives.

In keeping with the «prevention revolution» sought by the Head of State, the Minister of Solidarity and Health Agnès Buzyn has affirmed her willingness to take concrete steps and introduce an ambitious vaccination policy in France.

1The Leem 2016 Observatoire sociétal
[2] Vaccine Confidence Project - www.vaccineconfidence.org
[3] DREES Report - «Vaccinations: attitudes and practices of general practitioners» - March 2015
[4] Report by Senator Paul BLANC - Vaccines: Persuasion and Innovation for Better Protection - September 2007

75 %

The number of 15-75 year olds who express support for vaccination.

Source: 2016 Baromètre Santé (Health Survey) by Public Health France

OUR COMMITMENTS

What manufacturers are doing to boost public confidence

Guaranteeing the safety, efficacy and quality of our products

Throughout the vaccine life cycle (from research and development to manufacture, and including marketing), our products undergo stringent controls.
70% of production time is devoted to quality control. On average, one in four people at a vaccine production site is employed in quality assurance. Over 100 quality controls are needed to produce one batch of vaccines[1].
Controls are then continued to the batch release stage, until the vaccines are made available for use.
The pharmacovigilance system then takes over.

Bringing together the different vaccination stakeholders

Around the action taken by the health authorities, so that everyone is moving in the same direction and everyone can play their part in broadcasting the value of vaccination. Giving a platform to committed and responsible vaccine manufacturers will help lay to rest some misconceptions that may fuel distrust. We pledge to explain:

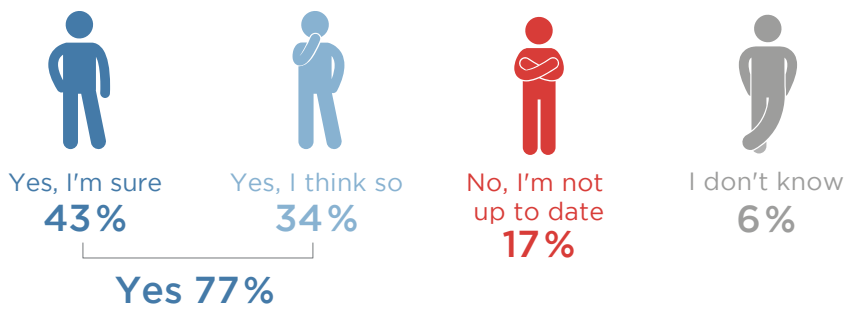
1. The vaccine manufacturing process, quality controls and the need to forecast demand in order to avoid supply pressures.

2. The role of adjuvants, vaccine safety monitoring.

3. The determinants of vaccine pricing.

ARE YOUR VACCINATIONS UP TO DATE ?

Fewer than 1 in 2 French people are sure that they are up to date with their vaccinations and nearly 1 in 4 people are either not up to date or are unable to say[2].



Our proposals

PRIORITY 7: Create a genuine culture of prevention through vaccination

to make immunisation a cornerstone of our health system. This can be achieved through various means.

1. Sustained messages tailored for the public and more specifically healthcare professionals thanks to the increased resources allocated to the various health authorities involved in immunisation (Public Health France and the Health Insurance Fund in particular) so they can be active on networks and spread information more widely.

2. Better initial and continuing training on immunisation to healthcare professionals.

3. Given the importance of extending immunisation coverage beyond the paediatric populations, there needs to be a return to the basics of immunisation so that the public is made aware of its crucial importance at all ages of life. A strong political gesture is needed to send an urgent reminder that immunisation is a civic duty which everyone should uphold, making no distinction between the mandatory vaccination of children and the other equally useful vaccines in the vaccination schedule.

Through an accreditation mark awarded by health authorities, such civic duty would come to be appreciated by the general public and healthcare professionals as an act of solidarity and altruism at any age. This accreditation mark should be complemented by a public information campaign on the value of immunisation in general and of each vaccine in particular, backed up by validated and reliable scientific information and the implementation of targeted actions.

PRIORITY 8: Involve schools in the «health learning experience» by teaching awareness of the importance of vaccination from an early age

The wider involvement of schools is pivotal to the promotion of a prevention through vaccination policy.

1. It is essential that immunisation be built into the learning experience. It must be possible to enlist external contributors to conduct outreach, information and training activities.

2. It would also be desirable to use schools once again as vaccination locations, in tandem with an increase in the resources allocated to national education or the involvement of healthcare professionals from outside the institutions.

PRIORITY 9: Promote clear and transparent information about vaccines

Searches for health information ranks third among online activities in France3. It is a powerful tool through which the authorities should be able to communicate effectively to keep the public better informed and restore its trust. Distrust impacts on vaccines and science overall. Fake news needs to be countered.

1. The design of an accreditation mark on vaccine information sites would help the public identify verified information and the mark could be endorsed by an Monitoring Agency set up to fact-check data on vaccines.

2. Set up a social media monitoring tool using community managers trained and hired by the public authorities. Their role would be to detect controversial issues and act online to offer sourced information.

3. Companies can also play a role in spreading the public health messages of the authorities.

In the words of the experts

«It is essential to reconcile the French public to immunisation by answering their doubts in plain language. To make absolutely sure that diseases once thought to have disappeared do not resurface, emphasis on vaccination as a civic duty is key to getting the message across.

When we get vaccinated, we're protecting ourselves and others too. To meet this challenge, schools seem to me to provide fertile ground for a vaccination culture to be entrenched from a very young age.»

Dominique GODARD *- - Representative from the AVNIR Group - President of the French Scleroderma Association*

[1] *Source Sanofi Pasteur*
[2] *Source Leem - IPSOS Observatoire sociétal 2016*
[3] *V. Gombault - «L'internet de plus en plus prisé, l'internaute de plus en plus mobile» (The greater the popularity of the internet the more mobile the web user) - Insee Première 2013*

Facilitating access to vaccination

3 000 000

The number of deaths averted each year worldwide through vaccination according to WHO estimates.

Source: WHO Report 2017

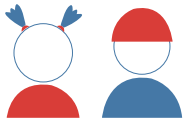
0

The number of cases of polio in France since 1997 and smallpox worldwide since 1977. Results achieved through vaccination.

Source: WHO Report 2017

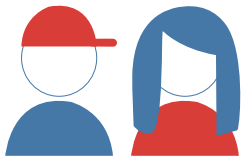
A vaccine for every age

NEONATES, INFANTS AND YOUNG CHILDREN



Diphtheria, Tetanus, Poliomyelitis, Whooping Cough, Haemophilus influenzae b, Measles, Mumps, Rubella, Pneumococcus, Meningococcus C, Hepatitis B. Children at risk: Hepatitis A, Meningococcus B, Meningococcus ACYW, Tuberculosis, Chickenpox, Influenza.

ADOLESCENTS

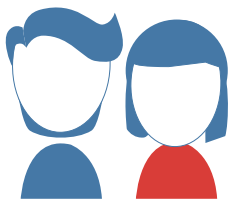


Boosters for Diphtheria, Tetanus, Poliomyelitis, Whooping Cough plus Papillomavirus (HPV) Infections and catch-up for Meningococcus C, Hepatitis B, Measles, Mumps, Rubella (for those not previously vaccinated). Adolescents at risk: Tuberculosis, Hepatitis A, Meningococcus B, Meningococcus ACYW, Pneumococcus, Chickenpox, Influenza.

PREGNANT WOMEN

Before or after pregnancy: Whooping Cough, Measles, Mumps, Rubella, Chicken Pox. During pregnancy: Influenza.

ADULTS

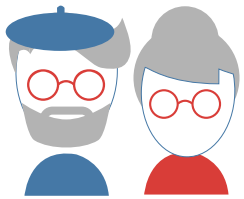


Boosters for Diphtheria, Tetanus, Poliomyelitis (whooping cough by cocooning) and catch-up (for those not previously vaccinated). Adults at risk: Influenza, Chickenpox, Pneumococcus, HPV. Occupations at risk: Hepatitis A, Hepatitis B, Typhoid, Leptospirosis, Yellow Fever, Meningococcus B, Meningococcus ACYW, Rabies, Chicken Pox, Influenza.

TRAVELLERS

Be up to date with the vaccines recommended in France + Yellow Fever, Rabies, Typhoid, Leptospirosis, Tick-borne Encephalitis, Japanese Encephalitis, Hepatitis A, Meningococcus, Pneumococcus.

THE ELDERLY



Boosters for Tetanus, Diphtheria, Poliomyelitis plus Influenza, Shingles. People at risk: Pneumococcus, Hepatitis A, Whooping Cough (by cocooning).

Overcoming the obstacles

THE FACTS

Initiatives to be put into practice to counter the fall in vaccination rates

A decline in confidence, especially in France

In previous decades, the high rates of immunisation coverage led to the eradication of previously fatal diseases. Despite these benefits, the level of immunisation coverage is now declining sharply for some vaccinations and France is lagging behind its European neighbours in terms of immunisation coverage. Vaccination rates are particularly low in adults (influenza, pneumococcus, whooping cough, etc.) and in adolescents (meningococcus C, HPV, hepatitis B, etc.).

An overly complex and insufficiently coordinated prevention pathway

Insufficient immunisation coverage can be explained in part by the lack of fluidity in the health pathway, which involves multiple steps: initial prescription by the doctor, delivery by the pharmacist and return to the doctor or nurse for administration.
In addition, some healthcare professionals (occupational doctors, school nurses) are able monitor their patients' vaccinations but are not allowed to vaccinate them during their consultations and must instead refer them to their general practitioner. These many time-consuming steps can deter some people from having the vaccination.

Actions that lack impetus

Despite numerous initiatives and the publication of several reports and plans that point out the limits of immunisation coverage and make recommendations, France is struggling to implement the proposals and roll out local initiatives nationally.

1. An electronic vaccination record (CVA) aims to keep citizens informed about their immunisation status and generates automatic alerts when the booster date arrives. Due to a lack of awareness of when immunity wears off, few adults are up to date with their boosters. Despite several initiatives, the national roll-out of a CVA has yet to happen.

2. In countries where in-pharmacy vaccination is permitted, a tangible improvement in immunisation coverage has been reported1. Although the opening-up of vaccination delivery to other healthcare professions is still in its infancy, the in-pharmacy vaccination trials that began in the autumn of 2017 should lead to an improvement in the care pathway and in immunisation coverage against influenza.

3. General practitioners and paediatricians are key to the success of the vaccination policy and are enlisted through the medical agreement signed between the Health Insurance Fund and the medical practitioners' unions on 25 August 2016. The new agreement has added vaccination indicators to the prevention component of the ROSP (Payment for Public Health Objectives).

THE NEEDS

Equipping France with an ambitious vaccination policy

The stated ambition of the President of the Republic and the Minister of Solidarity and Health to enhance prevention is clear: it involves the revival in France through the National Health Strategy of a «culture of prevention» supported by dedicated funding. One of the programme's flagship measures is to provide health students with a 3-month internship in schools and businesses to carry out screening, prevention and outreach activities. It is a channel worth exploiting as a reminder of the importance of vaccinations.

The shift to 11 mandatory vaccines against 11 diseases for infants, in keeping with the recommendations of Fisher's big public consultation report is a courageous step which, if accompanied by clear and objective public information, will allow confidence in vaccines to be restored. This momentum must continue by involving all stakeholders so they can work together for better protection of public health. France is also a driving force in the European Union's Joint Action on Vaccination. France is in need of such impetus so that the WHO recommendations on immunisation coverage can be met.

OUR COMMITMENTS

What manufacturers are doing to improve immunisation coverage in France

Making vaccination accessible to everyone

We are and remain firmly committed to the fight against infectious diseases. We intend to respond to the public health needs identified by the health authorities and to participate actively in improving the health of the population by supporting the initiatives launched by the government. We are making commitments at the national level with local contacts to support our initiatives.

Societal benefits

Good immunisation coverage provides better protection for everyone: herd immunity Herd immunity can indirectly protect people

who have no ready access to healthcare or vaccination programmes or who cannot be immunised (such as neonates or immunosuppressed persons).

Protecting yourself means also protecting others

Our proposals

PRIORITY 10: Help improve access to vaccination

1. Streamline the vaccination pathway for the public by extending vaccination practice to all prevention and care facilities (community health and social welfare centres, schools, pharmacies, etc.), provided that the premises are fit for this purpose. Vaccine companies can contribute by sharing the experiences of other countries.

2. Expand the skills of healthcare professionals to diversify vaccination access points: their presence throughout the country makes occupational doctors, midwives, nurses and pharmacists vital linchpins, especially for patients not included in the care pathway. Vaccination by pharmacists, under certain conditions for certain vaccines and after skills training in vaccination, would be an appropriate response to the drop in immunisation coverage. Other transfers of skills and organisational methods should be considered following an appraisal of their financial value (especially the storage of vaccines in doctors' surgeries).

PRIORITY 11: Make it easier for citizens to track their immunisation status

A large proportion of the adult population is unaware of their vaccination status. This can be remedied through various means:

1. Roll out an electronic vaccination record nationally and incorporate it as soon as possible into everyone's health data monitoring tools (shared medical records).

2. Introduce automatic prevention visits (including vaccination) at key stages in life: school years, adolescence, entry into the labour market, retirement. These visits could be arranged with general practitioners, healthcare professionals such as school nurses and occupational doctors, with the support of health and prevention centres, supplementary health cover, etc. This measure could be tied in with the dispatch by CNAM (French National Health Insurance Fund) of information and prescription tickets for all vaccines included in the vaccination schedule and their boosters.

3. Establish vaccination programmes by precise mapping of the area, to include an analysis of cantons or urban districts, in order to locate under-vaccinated - and hence inadequately protected - populations, launch suitable campaigns and prioritise targeted actions. This approach would help to overcome some of the social and territorial inequalities in access to healthcare.

PRIORITY 12: Reward vaccination practices by financial means

Develop policy incentives for the individual achievement of immunisation coverage targets (payment for public health objectives - ROSP) and interprofessional cooperation (new compensation methods - NMR) directed at all healthcare professionals, especially GPs and paediatricians.

In the words of the experts

«Through the efforts of all healthcare professionals, immunisation coverage will increase in France: it's a challenge that needs to be tackled collectively! Getting vaccinated means protecting the most vulnerable too.»

Carine WOLF-THAL - President of the National order of Pharmacists

Valuing the specificity of vaccines in the healthcare system

50

The number of vaccines or combination vaccines available to the French public.

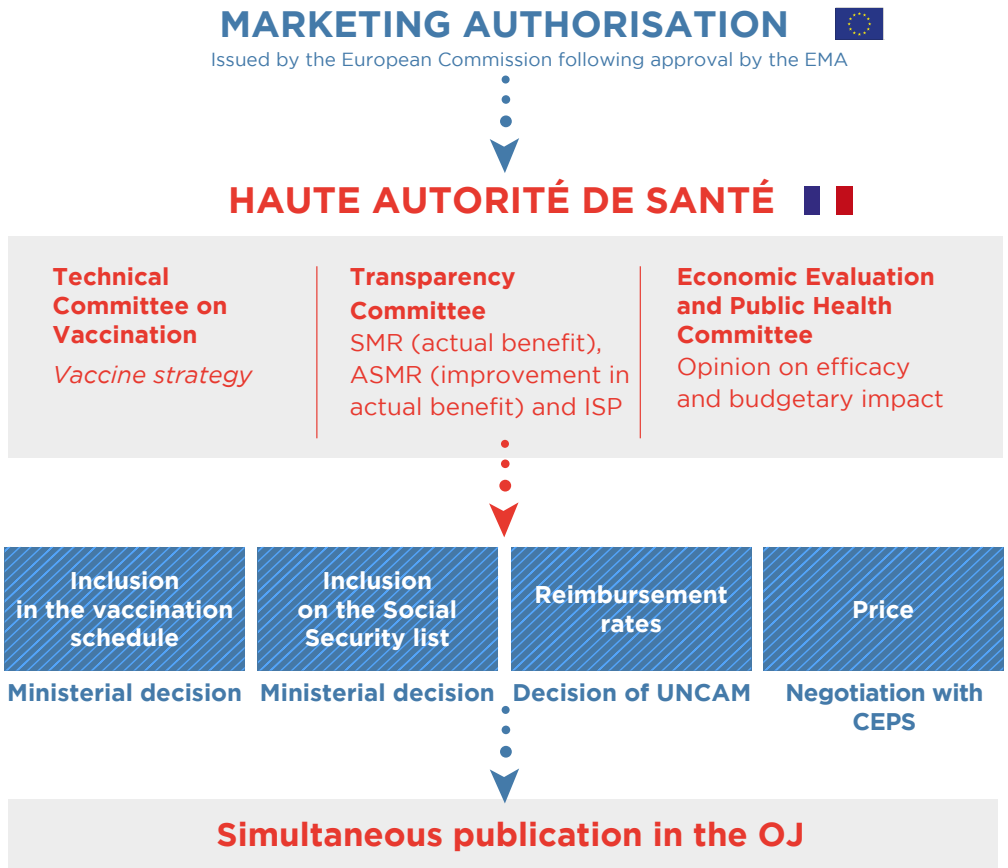
Source: Vaccines Today

23 times cheaper

The cost of a measles vaccination for a child compared to treating this disease.

Source: Source: SP/MSD - Report on the Economic Value of Vaccination - 2014

How are vaccines made available to the population?



Source: Leem

CEPS: Economic Committee for Health Products
EMA: European Medicines Agency
ISP: Public Health Impact
UNCAM: National Union of Health Insurance Funds

The uniqueness of vaccines

THE FACTS

Vaccines are products with high value added which obey the very strict rules governing market access

Vaccines contribute to population health and to the sustainability of our health system.

Vaccination has immunological benefits that extend beyond the vaccinated individual to protect the entire population1 when coverage is sufficient, including those unable to receive the vaccine. Finally, vaccination saves money by avoiding the costs incurred in treating the associated diseases. For example, the cost of vaccinating a child against measles is 23 times cheaper than treating measles[2].

Investing in vaccines is investing in the future

Economically speaking, vaccines are particularly efficient health products. By protecting against disease, vaccines help reduce the societal costs of disease: a reduction in hospital admissions, sick leave, prescriptions for antibiotics, etc. By protecting the population from serious diseases, vaccines maximise their chances of staying active longer and thus contributing to the economic growth of the country[3].

Specific market access conditions for a particular health product

Vaccines require specific procedures for market access. Besides the Marketing Authorisation (MA) and the assessments of the Transparency Committee (CT), the Economic Evaluation and Public Health Committee (CEESP) and the Economic Committee for Health Products (CEPS), which determine the eligible population, the reimbursement rate and the price of the vaccine, they are also scrutinised by the Technical Commission on Vaccinations (CTV), now a division of the French National Authority for Health (HAS).

The opinion of the CTV is based on pharmacoepidemiological and health economic studies. As a division of the HAS, it able to undertake scientific monitoring, strive for greater transparency of its work throughout the decision-making process, ensure consistency with the subsequent decisions of the CT and the CEESP and maintain the independence of its expertise, particularly in the area of health economics. Studies of this kind are extremely expensive and difficult to produce, due primarily to the lack of a usable national database and network of expertise in health economics, and to the diversity of the study populations.

As a result, the time to market for vaccines is considerably lengthy, harms their availability and may represent a loss of chance for French patients. However, the incorporation of the CTV into the HAS should help towards reducing these timeframes.

In the words of the experts

« The current system of marketing authorisation for a pharmaceutical product, which is based on prior clinical trials, could be improved, especially when it comes to bringing the medicines to market faster. The current decision-making process (placing and keeping on the market, pricing), which involves evidence upstream on the one hand and post-market monitoring on the other, is unbalanced for all medicines.

It seems to me that one option could be to restore balance in the real-life studies, once the product is on the market, which should be strictly monitored to detect any adverse events. Of course, in no way does this mean dispensing with studies altogether, especially given the mandatory nature of vaccines.

Pierre-Yves GEOFFARD *- Professor at the Paris School of Economics, CNRS Research Director*

[1] *Conseil de l'Union Européenne – Conclusions du Conseil sur la vaccination, un outil de santé publique performant – Décembre 2014*
[2] *SP/MSD – Rapport sur la valeur économique de la vaccination – 2014*
[3] *Dagaonkar et al. Zhou et al Pediatrics 2014*

THE NEEDS

ADAPTING THE CURRENT MARKET ACCESS PROCESS TO THE SPECIFICITIES OF VACCINES

If a vaccine meets a specific eligibility procedure for reimbursement, the criteria taken into account to set its SMR and ASMR level are identical to other medicines. The health, economic and social benefits of a vaccine are therefore not fully valued in such an assessment nor is the specificity of its clinical assessment.

Leem advocates further development of vaccine assessments to take into account their inherent specificities. New vaccine assessment criteria should be adopted to more fully assess the direct and indirect benefits of vaccination and to value its economic implications.

Moreover, although Leem recognises the value of each stage of the lengthy process in bringing a vaccine to market as a way of guaranteeing an objective appraisal process, it believes that certain adjustments are required. As the authorities place great and growing demands on epidemiological and health economic data, the specificity of vaccines means that there is a significant issue surrounding the production and forecasting of such data. Therefore, there is seemingly a need to adapt the expectations of the authorities to the specificity of vaccines or devote the necessary resources to producing such studies.

OUR COMMITMENTS

TO DEMONSTRATE THE BENEFITS OF OUR VACCINES

We are working ceaselessly to quantify the direct and indirect effects of vaccination:

DID YOU KNOW?

3 %

The share of total health expenditure spent on prevention by European Union countries[1]

0,5 %

The share of spending on vaccines (and even less) in the national health budgets of European Union countries[1]

AND YET

Vaccination affords numerous benefits and delivers significant returns on investment

NICE: National Institute of clinical Excellence (Royaume-Uni)

Our proposals

PRIORITY 13: Argue a special case for vaccines in their assessment process.

Leem calls on the health authorities to promote a modern health technology and health economy vision of vaccines in their assessment process so that their positive externalities can be valued over the long term.

1. Specific criteria that take into account the health and economic benefits of vaccines should be incorporated as soon as possible into the vaccine assessment procedure for pricing purposes.

2. A two-tier assessment must be made: one of the vaccine in itself and one of the vaccination programme best suited to disseminate the vaccine and thus provide guidance to the different vaccination stakeholders on the implementation of prevention policies.

3. A breakdown of the impact of a vaccination into its constituent parts (intrinsic value of the vaccine, population strategy, dissemination method, externalities) would better harness the innovation made and identify the mechanisms at play to maximise their benefit for the French population.

4. Increased sharing of experience to improve vaccine dissemination would raise greater awareness among the population. Alongside the public health recommendations, HAS has identified the obstacles to implementing a new health initiative. This experience should be beneficial to the formulation of vaccine recommendations.

In addition, the introduction of tools to promote their dissemination would help to improve the impact of vaccination in France. By way of illustration, NICE has recently established the Health Technologies Adoption Programme, which makes available to healthcare providers web resources providing real-life examples of their implementation, describing the experiences of and methods used by other centres and the tools helping to support change management. Manufacturers can provide valuable information to help develop the programme but are not involved in the drafting of documents.

PRIORITY 14: Reduce waiting times for access to vaccines by the French population.

1. The authorities have a deadline of 180 days between submission of the transparency dossier and publication of the negotiated price in the Official Journal1. Reimbursement requests are only possible, however, if a national vaccination recommendation is in place, a decision-making procedure that could take up to 17 months, especially where a new vaccine is concerned. And ensuring a satisfactory timeframe for access to reimbursements is only possible if the departments within HAS are able to bring forward the vaccine assessment work of the CTV and if the quality of interaction with industry is high.

2. A deadline should be set for assessment by the CTV, starting from the date of the recommendation request, so that reimbursement requests can be completed within a reasonable period of time and vaccines made available sooner, thereby minimising the loss of chance for the population; the early access schemes for certain innovative products through temporary authorisations for use are ill-suited to vaccines.

3. Thought should be given to reconciling the annual update of the childhood vaccination schedule with that of the list of mandatory vaccines.

4. The timetabling of the work to be undertaken by HAS for the CTV deserves further support by introducing a genuine Horizon Scanning process involving annual consultative meetings with companies. This Horizon Scanning process would also lead to the creation of a network of expertise in health economics and social economics, to be organised around the priority needs of data generation and modelling.

5. Though the accuracy of the data demanded by the health authorities serves to guarantee maximum product safety, such data are not always easy to apply to all the specificities of vaccines. In an effort to respond more effectively to the requirements of the authorities and to make available to the population, within a reasonable timeframe, safe vaccines whose indirect and societal value can be assessed in current practice, the formulation of recommendations for health economic modelling and a national pharmacoepidemiological database in the country would result in repositories and resources that can be readily and swiftly mobilised to conduct such studies.

PRIORITY 15: Produce data on immunisation coverage and on the monitoring of vaccination programmes.

1. By generating immunisation coverage data by vaccine at national and local levels, a real assessment could be made of the performance of the vaccine programmes, which could be adapted according to the results obtained.

1Vaccines Europe
1Article R-163-9 of the French Social Security Code

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