SCIENCE AND TECHNOLOGY BRIEFINGS
PARLIAMENTARY OFFICE FOR SCIENTIFIC AND TECHNOLOGICAL ASSESSMENT

Briefing 17 — July 2019

Vaccination Policy in France

Summary:

- *The contribution made by vaccines to public health is undeniable: they have enabled smallpox to be eradicated, and poliomyelitis is close to being eliminated. Vaccine research must be encouraged as it is currently being frustrated by HIV, tropical diseases and tuberculosis.*
- *To combat the misinformation which encourages vaccine hesitancy, transparency and rigorous education by the health authorities are more necessary than ever before. Vaccine safety must be guaranteed by enhanced pharmacovigilance.*
- *In France, the dramatic resurgence of measles has been caused by vaccine hesitancy and other factors, such as the decline in immunity and, potentially, the nature of the viral strains in circulation. Mandatory vaccinations were expanded in 2018 to improve vaccine coverage against this virus and seven other pathogenic agents.*
- *Vaccine strategy research suggests that targeted mandatory vaccination could reduce the incidence of influenza, which claimed almost ten thousand victims during the winter of 2018-2019.*

Mr. Jean-François Eliaou, MP (National Assembly),
Mr. Cédric Villani, MP (National Assembly), First Vice-Chairman,
Mrs Florence Lassarade, Senator

Among those diseases that have continued to occur in recent years despite the availability of preventive vaccines, measles is an emblematic case as 90% of people who contract it are not immunized, or are poorly immunized. Whilst there is a high level of coverage of mandatory vaccines, that of others, like the vaccine against measles, is not sufficient to halt the propagation of the virus. It was for this reason that the list of mandatory vaccines was expanded from 3 to 11 in late 2017[1]. There is a significant level of vaccine hesitancy in France[2], reflecting the anxiety of its citizens regarding vaccine safety.

The development of vaccination

From variolation to vaccination

"Variolation" was already practised in Asia back in the 10th century to combat smallpox and consisted in inoculating pus from a patient into healthy individuals. This was thought to prepare their immune system (IS)[3] for a possible subsequent infection and to protect them from the disease. The technique was dangerous, as the risk of contracting smallpox from the inoculation and of dying from it was high, although less than when the disease was contracted naturally.[4] Edward Jenner made inoculation safer in 1796 when he demonstrated that inoculating cowpox vaccine,[5] which is benign in humans, also protected against human smallpox.

Advances made by Pasteur and the Pasteurians

Louis Pasteur and his pupils extended the principle of vaccination to other diseases (rabies, etc.).[6] Their work aimed in particular to attenuate the virulence of viruses and bacteria[7] to allow their inoculation in patients without an infection being triggered. Today, attenuated pathogenic agents are used more rarely[8] in favour of an inert version, an inactivated toxin or indeed a single component, such as a surface protein. In this last case, we are speaking of natural or synthetic antigens.

The advent of biotechnologies

Biotechnologies allow to synthesise these antigens in culture using genetically modified yeasts or bacteria, rather than extracting them directly from the infectious agents. Inoculation of these compounds as vaccines eliminates the risks caused by injection of an entire microorganism. Another innovation has allowed infants to be vaccinated against bacteria such as pneumococci, meningococci and *Haemophilus influenzae* type b. Naturally covered with sugars (polysaccharides) that make them invisible to the IS of in-

fants[9], which partly explains their major role in infant mortality, the coupling of their saccharide antigens to immunogenic proteins (conjugate vaccines)[10] makes it possible for them to be detected and eliminated by the IS.[11]

- **The contribution of adjuvants**

Inoculation of the antigen alone is not always enough to induce an immune response, without which no immune memory forms. Adjuvants are used to strengthen the immune response and therefore vaccine efficacy. Discovered in the 1920s, they were developed empirically; thus, the mechanism of action of aluminium salts, the most commonly used adjuvants, is not completely understood.[12]

Vaccination and public health

At the beginning of the 19th century, when smallpox, cholera, tuberculosis and diphtheria were rife, life expectancy was only 30 years.[13] In the next century, improvements in hygiene conditions[14] made a reduction in the incidence of these diseases possible. The development of antibiotics, in the 1940s, and of vaccines, from the 1880s to the present day, has considerably reduced the occurrence of epidemics. Smallpox has been eradicated[15] and poliomyelitis could disappear by 2023.[16]

Protection against infectious diseases by vaccination may be strictly individual - this is particularly the case with tetanus - or individual and collective.[17] Collective protection (herd immunity) is based on the fact that above a certain threshold of vaccine coverage of the population,[18] too few individuals contract the disease for it to circulate and trigger an epidemic. This threshold is variable: 95% for measles, which is highly contagious, but only 87% for mumps, which is less so.[19] Herd immunity also protects individuals with a defective IS[20] or those who cannot be vaccinated ("cocooning" strategy[21] for neonates to combat whooping cough for example).

Risks associated with vaccination

As with all medicines, vaccine safety must be demonstrated in clinical trials to obtain marketing authorisation.

Vaccines are liable to cause adverse effects caused by local inflammation at the injection site or an inflammatory reaction, leading to local or systemic symptoms such as muscle pain or fever. The risk of developing a severe allergic reaction (anaphylaxis) following vaccination is between 1 in 100,000 and 1 in 1,000,000.[22]

- **Vaccination and autoimmune diseases**

The principle of vaccination is based on the activation of the IS, yet an overly strong immune response can itself cause an allergic reaction, even an autoimmune disease.[23] A link between the anti-HPV (papillomavirus) vaccine or the anti-HBV (hepatitis B virus) vaccine and the development of multiple sclerosis has been dismissed.[24] The suspicions regarding multiple sclerosis that appeared during vaccination campaigns against HBV and HPV concerned young adults, the age group in which symptoms of the disease occur naturally. However, concomitance and causality must be clearly distinguished.[25] If HPV vaccination was practised in young children, as is now the case with the HBV vaccine, suspicions of causality would be avoided.[26]

Rare cases of narcolepsy arising after vaccination against the influenza H1N1 virus have been reported,[27] but infectious diseases, such as influenza, which also recruit the IS, also increase the risk of developing autoimmune diseases,[28] and in a more marked manner. A study has shown that in the United States, fewer cases of Guillain-Barré syndrome developed in individuals vaccinated against the influenza H1N1 virus in 2009[29] than in unvaccinated individuals.[30]

- **Controversies associated with adjuvants**

Some scientists have suggested that the autoimmune syndromes associated with vaccines could be caused by adjuvants and have grouped them together under the term ASIA for *autoimmune syndromes induced by adjuvants*.[31] They suggest that aluminium adjuvants, because of their persistence in the organisms of some individuals, are potentially toxic to the nervous system.[32] However their work is criticised by the scientific community, especially on account of methodological aspects.[33]

The Cochrane Collaboration,[34] which promotes a medicine based on scientific evidence, is currently carrying out a study on the safety of adjuvants based on aluminium salts used in vaccines, analysing all the clinical studies that compare subjects receiving a vaccine with and without an adjuvant.[35]

The origins of vaccine hesitancy

There is currently a high level of scepticism towards vaccines in France.[36] There are multiple reasons for this distrust, some of which lie in the controversies associated with the risks posed by vaccines, whether proven or not, and their wide dissemination.[37] In 2016, an international study showed that France was the European country with the highest level of suspicion with regard to vaccine safety.[38]

- **The perception of risks**

Some risks associated with vaccination are real but very rare and must be assessed in the light of its benefits. During the period of variolation (18th century), mathematician Daniel Bernoulli put forward a theory of the benefit-risk ratio, justifying the procedure.[39]

Currently, vaccination is the "victim of its own success": diseases that can be avoided by vaccination have become very uncommon, which contributes to the poor benefit-risk ratio evaluation. The perception of the importance of vaccines for health is therefore distorted, which can lead some people to defend the preference for natural immunity, a belief in the importance of certain diseases in building and strength-

ening the IS, or the idea that good hygiene is sufficiently preventive.[40]

In addition, the risks to be compared – of contracting avoidable diseases and of being the victim of adverse effects – are not symmetrical, as active risk-taking (vaccination) is psychologically more difficult than passive exposure to risks (non-vaccination).[ibid] Moreover, there is still a persisting "fear of needles".[41]

The management of controversies by the public authorities has also played a role in vaccine hesitancy: the sudden termination of the vaccination campaign against hepatitis B in 1998, following unproven suspicions, may have been perceived as "an admission that the vaccine was dangerous".[42] More generally, the pro-vaccine message of governments does not convince individuals who are hesitating, if it does not answer their questions adequately.[43]

- **Information**

Generally, citizens consider themselves poorly informed on the subject of vaccines.[44] According to some studies, individuals who refuse to be vaccinated look elsewhere for information.[45] The question of information and misinformation appears paramount as the "anti-vaccine" arguments circulated via social media can influence the decision of whether or not to get vaccinated.[46] Several social networks, after becoming aware that they represented platforms for misinformation, made a commitment to delete "anti-vaccine" content.[47]

- **The medical profession and the pharmaceutical industry**

The reluctance of a fraction of the medical profession[48] contributes to vaccine hesitancy as the opinion of a health professional is a determining factor.[49] There is also mistrust of the pharmaceutical industry. The recurrent supply problems that translate into vaccine shortages[50] and the high price of new vaccines[51] are pointed out as problems. Laboratories chose to offer some vaccines only in combined form before the expansion of mandatory vaccination, meaning that inoculation of just the mandatory vaccines was not possible.[52]

- **The imposed nature of vaccination**

Citizens have long distrusted medical procedures which are imposed upon them, a distrust which appeared when the proposed Liouville law suggested making vaccination against smallpox mandatory in France at the end of the 19th century.[53]

Expansion of mandatory vaccination

At the end of 2017, scientists, doctors and sociologists were divided on the expansion of mandatory vaccination: some were critical, fearing radicalisation of the anti-vaccine position,[54] whilst others, the vast majority, lauded the decision.[55]

The legislative decision[56] to temporarily expand[57] mandatory vaccination to eight additional vaccines[1] clarified the doubts surrounding the "recommended" status of the other vaccines, regarding which the French Court of Auditors had issued a warning.[58] This difference in status appeared all the less legitimate as the eight infectious agents against which the new mandatory vaccines provide protection are responsible for more cases than diphtheria, poliomyelitis and tetanus, the only diseases for which vaccination was mandatory until 2018.

Taking up the question that mandatory vaccination represents an impediment to individual liberty, the Conseil Constitutionnel stated in 2015 that collective protection took precedence.[59] In this respect, the law stipulates that an unvaccinated child cannot join a community infrastructure (crèche, school).[60]

One year after the expansion of mandatory vaccination, the results appeared positive: coverage of some vaccines has improved (even in children not affected by the obligation), as has the opinion of parents with regard to vaccination.[61] The frequency of adverse effects has not increased in comparison with the 2012-2017 period.[62]

New issues around vaccines

- **Scientific advances in support of the choice of vaccine strategy**

Depending on the danger level, the contagiousness and the probability of disease resurgence, vaccination strategy specifies which vaccines must be produced, the vaccine schedule, and the public targeted.

In the case of influenza, France prioritises both individual protection by vaccinating the elderly and those with a chronic disease, and collective protection *via* the vaccination of healthcare staff. Other countries recommend vaccination of children[63] as they represent the main focus of influenza transmission; the efficacy of this strategy has been demonstrated.[64]

To halt propagation of the HPV virus, the logic of herd immunity supposes that not only girls but also boys should be vaccinated. This would confer individual protection on men who can also develop cancers caused by this type of virus.[65]

In the 2000s, the problem of the heterogeneity of the immune response within the population following vaccination was raised. The vaccine against influenza, for example is thought to be less effective in obese individuals.[66] There could also be a sex-related heterogeneity[67] and it was shown that latent infections could also modulate the immune response to other microorganisms.[68] The intensity of the post-vaccine immune response could depend on genetic factors.[69] Moreover, some studies suggest that autoimmune diseases could also depend on genetic susceptibilities specific to each individual.[70] If they were corroborated, these differences would highlight the limits of a system designed for the largest number of people and in the long term, would raise the question of the personalisation of vaccine strategy.[71]

- **Resistance to antibiotics**

Resistance to antibiotics is tending to increase all over the world, with the risk that we may find ourselves with no therapeutic solution for some bacterial infections. In this context, vaccination is a tool to prevent infections and to limit the prescription of antibiotics and the appearance of resistance.[72]

The challenges of vaccinology research

New types of adjuvants are in development and some are already used, such as molecules similar to bacterial antigens, capable of triggering an immune response.[73] However, these new adjuvants do not display as good a benefit-risk ratio as aluminium adjuvants.[74] They could however represent a solution to the poor response to vaccines by the senescent immune system in elderly individuals.[75]

Some infectious agents, such as the dengue virus and the influenza virus, cause a complex response to the vaccine, particularly because of the existence of significant genetic variability between the circulating strains, which represents a research challenge for the development of a universal vaccine[76] and in public health. There is thus no totally satisfactory vaccine solution for dengue fever[77], tuberculosis or influenza, as the vaccine is only effective for one season and only against four strains.[78] Research is in progress to develop a vaccine against HIV and malaria,[79] for which there is a manifest need.

Finally, all the factors contributing to the propagation of diseases, such as the participation of children in communities at a very young age, must be taken into consideration in establishing the vaccine strategy[80].

Conclusions and recommendations

Certain measures could help to improve public health strategy and reduce the reluctance of citizens with regard to vaccines.

Instituting an annual evaluation of vaccine policy

The continuous monitoring of threats posed by infectious diseases and scientific advances should result in the optimisation and adjustment of vaccination strategy.[81] In the absence of a schedule established by the authorities to re-examine obligations relative to vaccination, vaccine strategy could be re-evaluated annually by an independent health authority.[82] This would be the opportunity for collaboration with pharmaceutical laboratories and the WHO to develop/improve certain vaccines,[83] when appropriate.**Studying the relevance of new obligations and expanding reimbursement**

The efficacy of the vaccination of children against influenza that has been observed in other countries would justify the examination of its benefits. The mandatory vaccination of medical and paramedical staff against influenza could be reinstated,[84] and this could be extended to measles and whooping cough, according to a recent opinion of the Académie Nationale de Pharmacie.[85] Anti-HPV vaccination should be reimbursed by social security for boys also.[86]

- **Strengthening pharmacovigilance**

As there is only low-level reporting of the adverse effects that follow injection of vaccines, the monitoring system, which is based on declarations by doctors and patients, should be strengthened to detect all adverse effects,[87] for example with active monitoring by the health authorities of large cohorts of vaccinated patients.[88]

- **Increasing transparency**

As a known risk is better accepted than a doubt associated with a supposed danger,[89] the health authorities should adopt a clear, transparent, and educational discourse. The Académie Nationale de Médecine has demanded a higher level of transparency and communication from the health

Authorities.[90] Learned European societies have proposed that the non-optimal nature of some vaccines, in terms of efficacy and safety, should be recognised.[91] An educational initiative on the benefits of vaccination is still necessary for a more accurate estimation of the benefit-risk ratio.

- **Improving monitoring**

For better monitoring of vaccinations, a digital vaccination record could be instituted, as recommended by the Citizen Consultation on Vaccination.[92] In view of the removal of the criminal sanction stipulated for refusing vaccination, it is important that the vaccine status of a child can be verified when they join a crèche or a school, so as to not endanger children who cannot be vaccinated for medical reasons.

The OPECST websites:

http://www.assemblee-nationale.fr/commissions/opecst-index.asp

http://www.senat.fr/opecst/

Experts consulted

– Mme Sophie Ugolini, Inserm Research Director, Centre d'Immunologie de Marseille-Luminy (CIML), member of the Office Scientific Council

– Mme Eve Dubé, Researcher in Anthropology at the Research Centre of Quebec University Hospital - Laval University, and in the Scientific Immunisation Group of the National Public Health Institute of Quebec

– M. Alain Fischer, Professor of Paediatric Immunology and Researcher, Inserm and Pasteur Institute, Member of the Académie Nationale de Médecine, Chairman of the Steering Committee of the Citizen Consultation on Vaccination

– M. Romain Gherardi, University Professor and Specialist in the Neuromuscular System, Researcher at the Mondor Institute of Biomedical Research (IMRB), Inserm, Henri Mondor University Hospital (Créteil)

– M. Eric Jeziorski, Paediatrician at Montpellier University Hospital, Head of the General Paediatrics, Infectiology and Clinical Immunology team

– Mme Odile Launay, Professor of Infectious and Tropical Diseases, Coordinator of the Centre d'Investigation Clinique en Vaccinologie Cochin-Pasteur (Inserm), Coordinator of the I-REIVAC network and former Vice President of the Technical Committee on Vaccinations of the Haut Conseil de Santé Publique

– M. Jean-Daniel Lelièvre, Professor, Specialist in Immunology, Head of Department at Henri Mondor University Hospital (Créteil), Researcher at the Mondor Institute of Biomedical Research (IMRB), Inserm, Member of the Technical Committee on Vaccinations of the HAS and of the WHO Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC)

– M. Daniel Lévy-Bruhl, Medical Epidemiologist, Head of Unit, Infectious Diseases Department, Santé Publique France agency

– M. Didier Raoult, University Professor and Director of the Mediterranean University Hospital Infection Institute (Marseille)

– M. Jocelyn Raude, Social Psychologist, Lecturer at the École des Hautes Etudes en Santé Publique (EHESP), Researcher in the Emerging Viral Diseases Unit (Aix-Marseille University – IRD 190 – Inserm 1207 – Mediterranean University Hospital Infection Institute)

– M. Jean Sarlangue, Referring Paediatrician in Infectiology at Bordeaux Children's Hospital

– M. Yehuda Shoenfeld, Professor at Tel-Aviv University (Israel), Zabludowicz Center for Autoimmune Diseases

– M. Pierre Verger, Director of the Observatoire Régional de la Santé PACA, Researcher in the mixed research unit VITROME "Vectors – Tropical and Mediterranean Infections", IRD, Aix-Marseille University (Marseille), member of the I-REIVAC network (network of excellence for clinical research in vaccinology)

** NB: The individuals consulted, in some cases, expressed opinions that diverged from one or more aspects of the briefing.*

Scientific coordination by Mme Mathilde Lecompte, Scientific Advisor

Reference works consulted:

– "Immunisés? Un nouveau regard sur les vaccins", L. Barnéoud, Premier Parallèle

– "Le guide des vaccins", Science & Vie, special article No. 77, December 2016

– "Les vaccinations" Actualité et dossier en santé publique No. 71, June 2010

References

(1) In addition to vaccines against diphtheria, tetanus and poliomyelitis which were already mandatory, children born from 1st January 2018 must be vaccinated against measles, mumps, rubella, whooping cough, hepatitis B, meningococcal, pneumococcal and *Haemophilus influenzae* type b infections.

(2) See the Citizen Consultation on Vaccination of 2016, chaired by Prof Alain Fischer and Mme Claude Rambaud, commissioned by the Minister of Social Affairs and Health.

(3) The immune system (IS) acts particularly via antibodies, whose role is to recognise pathogenic agents capable of triggering an infection – viruses, bacteria or parasites – and to neutralise them. An infection activates a memory: the antibodies which specifically recognise the pathogen will be available in sufficient quantity to neutralise it if it reappears; vaccination is based on this principle.

(4) The risk of dying from smallpox after variolation was between 1/50 and 1/250; nevertheless it remained lower than that of contracting smallpox naturally and dying of it (1/5). Statement by Dr Françoise Salvadori, on France Culture (programme The Scientific Method, on 28 March 2019).

(5) *Variolæ vaccinæ*, from which the term vaccine is derived.

(6) Pasteur also developed vaccines against animal diseases such as chicken cholera, anthrax and swine erysipelas.

(7) The attenuation is produced by heating (denaturing), culture under non-optimal conditions (exposure to oxygen in the air) or dilution.

(8) Excluding vaccines against measles, mumps and rubella, which are the only mandatory vaccines that are attenuated.

(9) Polysaccharides are complex sugars. They are recognised by the immune system via B lymphocytes, which are immature in infants.

(10) The polysaccharides are conjugated to immunogenic proteins, that are exogenous and capable of being recognised by the immune system as they are detected by other cells, the T lymphocytes; inactivated versions (anatoxin) of the tetanus toxin or the diphtheria toxin are classically used. Pichichero (2013). "Protein carriers of conjugate vaccines." *Hum. Vaccin. Immunother.* 9, 2505–2523.

(11) De Gregorio *et al.* (2014). "From empiricism to rational design: a personal perspective of the evolution of vaccine development". *Nature Reviews Immunology* 14, 505–514.

(12) The adsorption of antigens onto aluminium salts, that is the binding of antigens on the surface of particles of aluminium salts, is thought to increase the efficacy of immunisation by improving the handling of antigens by immune system cells. De Gregorio *et al.* (2014). "From empiricism to rational design: a personal perspective of the evolution of vaccine development". *Nature Reviews Immunology* 14, 505–514.

(13) INED website consulted on 3 April 2019: https://www.ined.fr/fr/tout-savoir-population/graphiques-cartes/graphiques-interpretes/esperance-vie-france/.

(14) The improvements in hygiene conditions consisted in the disposal of waste water (the "faecal peril" being a major source of infection) and in access to healthy food, water and housing.

(15) Greenwood (2014). "The contribution of vaccination to global health: past, present and future." *Philosophical Transactions of the Royal Society B: Biological Sciences* 369, 20130433. And statement by Prof Arnaud Fontanet, on France Culture (programme The Scientific Method on 8 February 2019). Life expectancy almost doubled during the 20th century[13].

(16) The WHO counted only around thirty cases of poliomyelitis in 2018. Joint declaration of the Committees of the WHO Global Polio Eradication Initiative, in January 2019: http://polioeradication.org/news-post/to-succeed-by-2023-extraordinary-joint-statement-to-polio-eradicators/ consulted 19 February 2019.

(17) Of the mandatory vaccines, only the anti-tetanus vaccine offers just individual protection as the disease is not transmitted from one individual to another. Tetanus is in fact caused by a microorganism present in the soil which is impossible to eradicate. Vaccines against yellow fever and tick-borne encephalitis and to a lesser extent, dengue fever, do not provide "herd immunity" protection as wild animals also harbour the infectious agent.

(18) Vaccine coverage is the percentage of individuals vaccinated in a population.

(19) On average, an individual who has contracted measles infects 16 others, while someone with mumps infects 8. Santé Publique France. (2017). *Vaccination: la protection collective - Dossier pédagogique.*

(20) Immunodeficiency affects frail individuals (infants, the elderly) and may be the consequence of a disease (leukaemia, HIV infection, etc.).

(21) The "cocooning" strategy consists in vaccinating the parents of a neonate against whooping cough or against measles, to protect the infant who cannot yet be vaccinated and for whom the disease is dangerous. The "cocooning" strategy also applies to immunosuppressed individuals. Vaccination against rubella has an almost solely collective, not individual objective: the virus is benign in adults but can cause severe damage to the developing foetus.

(22) Radice *et al.* (2019). "Allergic reactions after vaccination: translating guidelines into clinical practice." *Eur. Ann. Allergy. Clin. Immunol.* 51, 51–61.

(23) An autoimmune disease is a disorder of the immune system, characterised by the erroneous recognition of cells of the organism as elements to be attacked.

(24) Report of the ANSM. "*Vaccins anti-HPV et risque de maladies auto-immunes: étude pharmacoépidémiologique*" 2 September 2015 and Mailand *et al.* (2017). "Vaccines and multiple sclerosis: a systematic review." *J. Neurol.* 264, 1035–1050.

(25) Genovese *et al.* (2018). "HPV vaccine and autoimmune diseases: systematic review and meta-analysis of the literature" *J. Prev. Med. Hyg.* 59, E194–E199.

(26) However, currently, the vaccines Cervarix® and Gardasil9® only have an indication for subjects over nine years of age. Further, there is little long-term data on the efficacy of the vaccine. A meta-analysis by the Cochrane Institute showed a reduction in the incidence of precancerous lesions of the uterine cervix in young women: Arbyn *et al.* (2018). Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database of Systematic Reviews.*

(27) Among the proven risks of autoimmune disease, it was shown that the vaccine against type A influenza Pandemrix® could cause narcolepsy via an autoimmune mechanism. In some people, the antibodies produced following vaccination also recognise the receptors for orexin (the waking hormone), preventing its detection by the system that maintains the awake state, in the brain. Information review from the ANSM: "*Vaccins pandémiques grippe A (H1N1) et narcolepsie: Résultats de l'étude européenne et de l'étude cas-témoins française*" and Ahmed *et al.* (2015). "Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2." *Science Translational Medicine 7*, 294.

A French pharmacoepidemiological study in 2015 showed that the anti-HPV vaccine quadrupled the possibility of developing Guillain-Barré syndrome, which however was not shown in the studies which followed. Report by the ANSM. "*Vaccins anti-HPV et risque de maladies auto-immunes: étude pharmacoépidémiologique*." 2 September 2015. Mouchet *et al.* (2018). Human papillomavirus vaccine and demyelinating diseases - A systematic review and meta-analysis. *Pharmacological Research* 132, 108–118; Andrews *et al.* (2017). No increased risk of Guillain-Barré syndrome after human papilloma virus vaccine: A self-controlled case-series study in England. *Vaccine* 35, 1729–1732; Angelo *et al.* (2014). Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. *Pharmacoepidemiology and Drug Safety* 23, 466–479; Grimaldi-Bensouda *et al. (2017*). Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance. *Journal of Autoimmunity* 79, 84–90.

(28) This is particularly the case with autoimmune thrombocytopenia (a decrease in the quantity of platelets in the blood): the risk of developing the condition following measles is six times higher than that of developing it after a vaccination against measles. Wraith *et al.* (2003). "Vaccination and autoimmune disease: what is the evidence?" *The Lancet* 362, 1659–1666.

Several infections, such as *Campylobacter jejuni*, *Haemophilus influenzae* infections, or those caused by the influenza, dengue fever or Zika viruses can also increase the probability of developing Guillain-Barré syndrome. Willison *et al.* (2016). "Guillain-Barré syndrome." *The Lancet* 388, 717–727; Cao-Lormeau *et al.* (2016). "Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study." *The Lancet* 387, 1531–1539; Carod-Artal *et al.* (2013). "Neurological complications of dengue virus infection." *The Lancet Neurology* 12, 906–919; Mori *et al.* (2000). Haemophilus influenzae infection and Guillain–Barré syndrome. *Brain* 123, 2171–2178.

(29) Guillain-Barré syndrome is characterized by peripheral nerve damage of autoimmune origin: the myelin sheath that covers the nerves is attacked by the immune system, causing symptoms of variable intensity, ranging from simple pins and needles to paralysis of a limb. This syndrome is frequently preceded by an infection. In the vast majority of cases the outcome is favourable without neurological sequelae (90 to 100% of cases in children and adolescents).

(30) Vellozzi *et al.* (2014). Cumulative Risk of Guillain–Barré Syndrome Among Vaccinated and Unvaccinated Populations During the 2009 H1N1 Influenza Pandemic. *Am J Public Health* 104, 696–701.

(31) The term ASIA encompasses symptoms such as chronic fatigue, muscle and joint pain, as well as neurological symptoms such as fever and demyelinating diseases, such as multiple sclerosis, which consists of an attack by the immune system on the myelin sheath that protects neurones. Watad *et al.* (2018). "The autoimmune/inflammatory syndrome induced by adjuvants (ASIA)/Shoenfeld's syndrome: descriptive analysis of 300 patients from the international ASIA syndrome registry." *Clin. Rheumatol.* 37, 483–493. These theories are defended at international level, notably by Prof Shoenfeld in Israel, Prof Exley in the United Kingdom and Prof Shaw in Canada.

(32) The persistence of aluminium particles may be observed several years after vaccination, depending on the profiles. Prof Romain Gherardi, of Henri Mondor Hospital in Créteil, was heard by the Office at a public hearing "*Les adjuvants vaccinaux: une question controversée*" on 29 January 2015. Several studies by the "Neuromuscular system biology" team at Henri Mondor Hospital, state this point of view: Khan *et al.* (2013). "Slow CCL2-dependent translocation of biopersistent particles from muscle to brain." *BMC Medicine* 11, 99; Gherardi *et al.* (2015). "Biopersistence and brain translocation of aluminum adjuvants of vaccines." *Front. Neurol.* 6, 4; Crépeaux *et al.* (2017). "Non-linear dose-response of aluminium hydroxide adjuvant particles: selective low dose neurotoxicity." *Toxicology* 375:48-57; Crépeaux *et al.* (2018). "ASIA, chronic fatigue syndrome, and selective low dose neurotoxicity of aluminum adjuvants." *J. Allergy Clin. Immunol. Pract.* 6, 707 Masson et al. (2018) "Critical analysis of reference studies on the toxicokinetics of aluminum-based adjuvants." *J Inorg Biochem* 181:87–95 and Gherardi *et al.* (2019). Myalgia and chronic fatigue syndrome following immunization: macrophagic myofasciitis and animal studies support linkage to aluminum adjuvant persistency and diffusion in the immune system. *Autoimmun Rev.* Note: it is known that aluminium is a neurotoxin, but at doses much higher than those received via vaccines.

(33) The studies carried out were case studies, that is a description of the symptoms of individuals suffering from a pathology, compared to a control group. This type of study does not allow an estimation of the incidence of the disease in the general population, unlike a cohort study. In 2013, a report by the Haut Conseil de la Santé Publique "*Aluminium et vaccins*" examined the studies published on the potential toxicity of aluminium adjuvants as well as the knowledge available on the macrophagic myofasciitis syndrome. The HCSP judged that there was not sufficient evidence to reach a decision on the toxicity of aluminium adjuvants, pointing out in particular the epidemiological inconsistency of macrophagic myofasciitis syndrome: "Why is a disease for which more than 1,000 patients were identified in a few years in France so rare in other countries? But all the same it called for more research to assess this possible toxicity. "The most recent step aims to demonstrate the mode of migration and penetration of aluminium into the brain by the "Trojan horse" mechanism, involving monocytes which are thought to phagocytose the aluminium nanoparticles and to transport them into various organs including the brain, by taking them across the blood brain barrier. These hypotheses are based on an experimental study in mice which requires confirmation". The "Neuromuscular system biology" team of Henri Mondor Hospital subsequently developed a new technique for detecting aluminium particles (Eidi *et al.* (2015). Fluorescent nanodiamonds as a relevant tag for the assessment of alum adjuvant particle biodisposition. *BMC Med* 13, 144) and observed behavioural effects in mice associated with the injection of low doses of aluminium (Crépeaux *et al.* (2017). Non-linear dose-response of aluminium hydroxide adjuvant particles: Selective low dose neurotoxicity. *Toxicology* 375, 48–57).

No consensus has been reached to date regarding the recognition or refutation of the existence of the ASIA syndrome and the causal link between macrophagic myofasciitis and neurological symptoms as in chronic fatigue syndrome has not been demonstrated in humans. The question of the safety of aluminium adjuvants in vaccines is debated vigorously in the scientific community (read, on one side: Hawkes *et al*, 2015; Ameratunga *et al*, 2017; Hawkes *et al*, 2017; on the other: Blasco, 2018; Crépeaux *et al*, 2018 a et b; Gherardi *et al*, 2019), and is the subject of regular accusations of conflicts of interest. On this subject, Prof Yehuda Shoenfeld was also heard by the Office on 20 January 2015 and bemoaned being the subject of non-scientific criticisms (Bragazzi *et al.* (2017). Debate on vaccines and autoimmunity: Do not attack the author, yet discuss it methodologically. *Vaccine* 35, 5522–5526).

Hawkes *et al.* (2017). "Response to: HPV vaccine and autoimmunity incidence of new-onset autoimmune disease in girls and women with pre-existing autoimmune disease after quadrivalent human papillomavirus vaccination: a cohort study." *J. Intern. Med.* 281, 530–

531Ameratunga *et al.* (2017). "Evidence Refuting the Existence of Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants (ASIA)." *J Allergy Clin Immunol Pract.* 5, 1551-1555.e1
Hawkes *et al.* (2015). "Revisiting adverse reactions to vaccines: A critical appraisal of Autoimmune Syndrome Induced by Adjuvants (ASIA)." *Journal of Autoimmunity* 59, 77–84
Blasco. (2018). Refutation is a strong word for partial evidence in ASIA. *J Allergy Clin Immunol Pract.b* 6:707-708
Crépeaux *et al.* (2018). ASIA, chronic fatigue syndrome, and selective low dose neurotoxicity of aluminum adjuvants. *J Allergy Clin Immunol Pract.* 6:70 and Crépeaux *et al.* (2018). Letter To Editor. *Toxicology.* 1;410:166-167
Gherardi *et al.* (2019). Animal studies are mandatory to investigate the poorly understood fate and effects of aluminum adjuvants administered to billions of humans and animals worldwide. *Autoimmun Rev.*17:735

(34) The Cochrane Collaboration is an international institution composed of scientists and doctors, brought together by the desire to promote a science based on scientific evidence. Accordingly, it produces critical meta-analyses of the literature.

(35) The protocol of this study was revealed out of concern for transparency: Djurisic *et al.* (2017). "Aluminium adjuvants used in vaccines versus placebo or no intervention." *Cochrane Database of Systematic Reviews.*

(36) Refusing vaccination originated in the attempt to make vaccination against smallpox mandatory, in France and in other European countries, at the end of the 19th century. Today, France stands out from other European countries in having a greater prevalence of individuals refusing vaccination, as illustrated in the Eurobaromètre of March 19. The points on which there is a great divergence of opinion between the French and Europeans (study conducted in 27,524 Europeans, including 1,013 French people) are:

- To the question "At what level do you think vaccination programmes should be coordinated?": 15% of French people responded "there should not be vaccination programmes, it is a personal choice" – only 9% of Europeans chose this response;

- 23% of French people disagreed with the statement "Not being vaccinated can cause serious health problems", compared with 15% of Europeans;

- 30% of French people disagreed with the statement "It is important that everyone is vaccinated as a matter of routine", compared with 15% of Europeans;

- To the question "Why have you not been vaccinated during the last 5 years?", 22% of French people responded that "vaccines are not safe and that they can have side effects", compared with 9% of Europeans.

(37) The suspicions concerning autism cases associated with the MMR vaccine (Wakefield affair), those regarding multiple sclerosis (anti-HPV and anti-HBV vaccines), and those regarding sudden infant death, etc. can be mentioned.

Wakefield Affair: in 1998 Andrew Wakefield and his colleagues published a study in 12 children with autism, 2/3 of whom had been vaccinated (MMR measles – mumps – rubella), suspecting a cause and effect relationship (Wakefield *et al.* (1998). "Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children." *The Lancet* 351, 637–641). This study was reported widely in the press. In the years that followed, other laboratories studied this hypothesis but concluded there was no link (particularly the study Hviid *et al.* (2019). "Measles, Mumps, Rubella Vaccination and Autism: A Nationwide Cohort Study." *Ann. Intern. Med.*) Wakefield's study was retracted by the journal The Lancet in 2010, as evidence was brought that it represented scientific fraud. The affair caused a 10% drop in coverage of the MMR vaccine, and more generally led to increased distrust among the general public.

(38) In France, 45% of people questioned did not agree with the statement "vaccines are safe" (highest in Europe), but less than 15% disagreed with the statement "It is important that children are vaccinated" (6th highest in Europe). Larson *et al.* (2016). "The State of Vaccine Confidence 2016: Global Insights Through a 67-Country Survey." *EBioMedicine* 12, 295–301.

(39) Daniel Bernoulli showed that the number of lives saved was higher than that of lives lost, justifying variolation. Bernoullii (1766). "*Essai d'une nouvelle analyse de la mortalité causée par la petite vérole.*" *Mémoires de mathématique et de physique*, presented to the Académie Royale des Sciences.

(40) Dubé *et al.* (2013). "Vaccine hesitancy." *Human Vaccines & Immunotherapeutics* 9, 1763–1773.

(41) The "fear of needles" remains one of the reasons for vaccine hesitancy; however recent developments might allow this problem to be solved. Transcutaneous needle-free vaccines are now being developed, which although effective, are not really thought to be less painful. Edible vaccines and vaccines in the form of aerosols also exist, although they are designed especially with the aim of marketing them in developing countries where maintenance of the cold chain cannot always be envisaged. Ferrari *et al.* (2011). "Evaluation of the immune response induced by intradermal vaccination by using a needle-less system in comparison with the intramuscular route in conventional pigs." *Research in Veterinary Science* 90, 64–71; Shapiro *et al.* (2019). "Needle-free delivery of influenza vaccine using the Med-Jet® H4 is efficient and elicits the same humoral and cellular responses as standard IM injection: A randomized trial." *Vaccine* 37, 1332–1339 and Lal *et al.* (2007). "Edible vaccines: current status and future." *Indian J. Med. Microbiol.* 25, 93–102.

(42) Report "*La résistance aux vaccinations: d'un défi de santé publique à un enjeu de société*" by Miviludes (Interministerial Mission for Vigilance and Combating Sectarian Aberrations).

(43) Goldenberg (2016). "Public Misunderstanding of Science? Reframing the Problem of Vaccine Hesitancy." *Perspectives on Science* 24, 552–581.

(44) In the French context preceding the expansion of mandatory vaccination, 47% of parents questioned indicated they were not precisely aware of the scope of the measure, and almost one third considered themselves badly informed on the subject of mandatory vaccination. Public health bulletin of April 2019 by Santé publique France.

(45) Goldenberg (2016). "Public Misunderstanding of Science? Reframing the Problem of Vaccine Hesitancy." *Perspectives on Science* 24, 552–581. Moreover, in 2017, a study by Santé publique France (Gautier, Chemlal, Jestin, and the group Baromètre santé 2016 –

Santé publique France (2017). "*Adhésion à la vaccination en France: résultats du Baromètre santé 2016.*" *Bull. Epidémiol. Hebd.* 21, 7) revealed that distrust of vaccines differed according to socio-professional category:

- The level of compliance with the global principle of vaccination is significantly higher in individuals with a high educational level and a high income (according to the highest qualification obtained: 73% of individuals without a qualification or with a qualification lower than a Baccalaureate had a favourable opinion compared with 81% of individuals with a qualification at a level of bac+4 (1st year of Masters degree) and above; according to income: 73% of individuals in the 1st tertile group had a favourable opinion compared with 78% in the 3rd tertile group);

- An unfavourable opinion of the anti-HPV and anti-HBV vaccines is associated with a higher educational and income level (according to the highest qualification obtained: 7 to 8% (HPV) and 15 to 17% (HBV) of individuals with an educational level of 2 to 3 years of higher education or more had an unfavourable opinion compared with 3 to 4% (HPV) and 7 to 12% (HBV) for individuals without a qualification or with a qualification lower than a Baccalaureate; according to income, for the anti-HBV vaccine: 10% of individuals in the 1st tertile group had an unfavourable opinion compared with 5% in the 3rd tertile group).

(46) Studies show that "anti-vaccine" messages have a real effect on the decision taken (Jolley *et al*, 2014); others suggest that consulting these messages instils doubt without necessarily guiding the decision on vaccination (Ward *et al*, 2017). Jolley *et al.* (2014). "The Effects of Anti-Vaccine Conspiracy Theories on Vaccination Intentions." *PLOS ONE* 9, e89177; Ward *et al.* (2017). 'I don't know if I'm making the right decision': French mothers and HPV vaccination in a context of controversy. *Health, Risk & Society* 19, 38–57.

(47) Combatting Vaccine Misinformation | Facebook Newsroom https://newsroom.fb.com/news/2019/03/combatting-vaccine-misinformation/ consulted on 8 April 2019.

(48) 8% of doctors questioned in this study by the DREES are not confident about vaccination. Collange *et al.* (2015) "*Vaccinations: attitudes et pratiques des médecins généralistes", Études et Résultats*, No. 910, Drees.

(49) A German study showed that low vaccine coverage, at local level, was associated with a more negative attitude of general practitioners with regard to vaccines. Weigel *et al.* (2014). "Impact of physicians' attitude to vaccination on local vaccination coverage for pertussis and measles in Germany." *Eur. J. Public Health* 24, 1009–1016.

(50) Shortage in BCG and DTaP-IPV/Hib vaccines https://ansm.sante.fr/S-informer/Informations-de-securite-Ruptures-de-stock-des-medicaments#vac consulted on 8 April 2019.

(51) This is the case with the anti-HPV vaccine Gardasil® for example, which is sold at a little more than €120 (65% reimbursed) while the DTP – diphtheria, tetanus and inactivated poliovirus – vaccine Revaxis® is sold for less than €10; http://base-donnees-publique.medicaments.gouv.fr consulted on11 April 2019.

(52) The combination of mandatory vaccines with recommended vaccines (such the combination of DTP – diphtheria, tetanus and inactivated poliovirus – and whooping cough, hepatitis B and Hib vaccines) met the public health objective set by the WHO and enabled increased coverage of these non-mandatory vaccines. However, as the DTP vaccine was no longer available as a single vaccine, a feeling developed that the pharmaceutical industry was taking liberties with regard to the objectives set by the government.

(53) Creation of the Ligue Universelle des Anti-Vaccinateurs by Hubert Boëns in 1880.

(54) Ward *et al.* (2017). "France's risky vaccine mandates." *Science* 358, 458–459.

(55) Plotkin *et al.* (2018). "Vaccine mandates in France will save lives." *Science* 359, 283–284.

(56) Article 49 of the law No 2017-1836 of 30 December 2017 on social security funding for 2018, modifying article L3111-2 of the Public Health Code. All entry by children into community infrastructures (crèche, school) is subject to the performance of mandatory vaccinations, unless medically contraindicated.

(57) No deadline was announced for the re-examination of mandatory vaccinations. Article 49 of the law No. 2017-1836 of 30 December 2017 on social security funding for 2018 specifies only that "an evaluation of the impact of the expansion of mandatory vaccinations is carried out by the Government every year as of the last quarter of 2019. It is made public."

(58) "*La politique vaccinale: un enjeu de santé publique, une confiance à conforter*" Annual report of the Court of Auditors of 2018, 205–235.

(59) Decision No. 2015-458 QPC of 20 March 2015 of the Conseil Constitutionnel.

(60) Article L3111-2 of the Public Health Code.

(61) For children affected by the expansion, an increase in vaccine coverage for the vaccines against hepatitis B (+8 points), meningococcus C (+36 points) and the MMR vaccine (+3 points) was observed. It was also observed that mothers had a more favourable opinion (+3.7 points) and were better informed (+4.8 points). Public health bulletin of April 2019 from Santé publique France, Cohen *et al.* (2019). "Impact of mandatory vaccination extension on infant vaccine coverages: Promising preliminary results." *Med. Mal. Infect.* 49, 34–37.

(62) ANSM. First safety report on mandatory vaccines for children aged between 0 and 23 months -*Etat des lieux sur la période 2012-2017 précédant l'extension de l'obligation vaccinale et sur les premiers 6 mois de sa mise en oeuvre*. 26 June 2019.

(63) In Europe, vaccination of children in good health against influenza is recommended in Austria, in Poland and in Estonia regardless of age. It is recommended for some age groups in Latvia, in Finland, in Slovakia, in Slovenia, and in the United Kingdom; Principi *et al.* (2018). "Influenza immunization policies: Which could be the main reasons for differences among countries?" *Human Vaccines & Immunotherapeutics* 14, 684–692.

(64) The efficacy of vaccination against seasonal influenza is greater and propagation of the disease in the general population is better contained when it is the children who are vaccinated, even if the vaccine coverage is low (30 to 63%), than when caregivers are vaccinated with higher coverage (51 to 77%), and when the elderly are vaccinated with higher vaccine coverage (66 to 70%). The WHO

however recommends systematic vaccination of caregivers to prevent absenteeism during epidemics and to limit the risk of nosocomial epidemics affecting the most frail individuals. Bambery *et al.* (2018). "Influenza Vaccination Strategies Should Target Children." *Public Health Ethics* 11, 221–234 and report of the working group SAGE (Strategic Advisory Group of Experts) of the WHO "Background Paper on Influenza Vaccines and Immunization." 2002.

(65) Oropharyngeal cancers, particularly of the throat, and anal cancer. Young *et al.* (2015). "Increase in head and neck cancer in younger patients due to human papillomavirus (HPV)." *Oral Oncology* 51, 727–730. In Australia, boys and girls are vaccinated, which has had the result of lowering the prevalence of strains of the virus responsible for cancer lesions by 77%. (http://www.hpvvaccine.org.au/the-hpv-vaccine/has-the-program-been-successful.aspx). In France, at the request of the Ministry of Health and Solidarity, the health authority HAS must deliver an opinion on the benefit of recommending vaccination of boys during 2019.

(66) Young *et al.* (2013). Is obesity a risk factor for vaccine non-responsiveness? *PLoS ONE 8*, e82779 and Sheridan *et al.* (2012). Obesity is associated with impaired immune response to influenza vaccination in humans. *Int J Obes* (Lond) 36, 1072–1077.

(67) Some studies have been able to observe a stronger immune response in women, and it has been suggested that this could be the cause of the sometimes more frequent observation of adverse effects in women. Klein *et al.* (2013). Personalized vaccinology: One size and dose might not fit both sexes. *Vaccine* 31, 2599–2600 and Engler *et al.* (2008). Half- vs Full-Dose Trivalent Inactivated Influenza Vaccine (2004-2005): Age, Dose, and Sex Effects on Immune Responses. *Arch. Intern. Med.* 168, 2405–2414.

(68) The infection of young people by the cytomegalovirus, a latent virus which passes unnoticed in individuals who are not immunosuppressed, leads to better immunisation against influenza, while this same infection, leads to a lower level of immunisation in the elderly. Furman *et al.* (2015). Cytomegalovirus infection enhances the immune response to influenza. *Science Translational Medicine 7*, 281ra43-281ra43.

(69) It has been observed that some HLA alleles – very variable from one person to another, involving genes essential to the immune response – are associated with a weak immune response, while others are associated with a strong response. These observations were made in the context of vaccination against measles, rubella, and HBV. Poland *et al.* (2007). Heterogeneity in Vaccine Immune Response: The Role of Immunogenetics and the Emerging Field of Vaccinomics. *Clinical Pharmacology & Therapeutics* 82, 653–664.

(70) An explanation of the appearance of rare cases of autoimmune diseases following vaccination, without this being significant at a population level, could theoretically lie in the existence of a susceptibility to develop an autoimmune syndrome when the immune system is stimulated by an infection or vaccination. Some genes of the HLA (human leukocyte antigen) system, are thought to confer susceptibility to develop an autoimmune disease or to confer protection. *Wraith et al. (2003*). "Vaccination and autoimmune disease: what is the evidence?" *The Lancet* 362, 1659–1666; Matzaraki *et al.* (2017). "The MHC locus and genetic susceptibility to autoimmune and infectious diseases." *Genome Biology* 18, 76; Arango *et al.* (2017). "HLA-DRB1 the notorious gene in the mosaic of autoimmunity." *Immunol Res* 65, 82–98 and Guis *et al. (2002)*. "HLA–DRB1*01 and macrophagic myofasciitis." *Arthritis & Rheumatism* 46, 2535–2537.

(71) A predictive vaccinology could consist in adjusting vaccination (dose, boosters, etc.) according to the sex or weight of the individual, or their genetic profile (presence of susceptibility to present a weak – or strong – immune response to vaccination). However, as this last possibility requires a genetic analysis, the prospect of it being implemented is remote.

(72) Antibiotics are drugs which kill bacteria directly, instead of or in addition to the immune system. However, bacteria have a high capacity to adapt to their environment, allowing them to become resistant to antibiotics. So, countries like India and China are facing real epidemics of bacteria resistant to antibiotics. The overconsumption of antibiotics is one of the factors which leads to the appearance of resistance. Vaccination then appears as a solution by allowing less use of antibiotics and reducing the appearance of resistance: a direct solution as it directly limits the use of antibiotics by preventing bacterial infections, but also indirect as vaccination prevents viral diseases which favour the appearance of secondary bacterial infections. For example, cases of bacterial superinfection following influenza, are common. Statement by Prof Yves Buisson, of the Académie Nationale de Médecine and O'Brien *et al.* (2000). "Severe Pneumococcal Pneumonia in Previously Healthy Children: The Role of Preceding Influenza Infection." *Clin. Infect. Dis.* 30, 784–789. The arrival of the vaccine against invasive pneumococcal infections was effectively accompanied by a reduction in the prevalence of bacterial strains resistant to penicillin (Temime *et al.* (2004). Short- and Long-Term Effects of Pneumococcal Conjugate Vaccination of Children on Penicillin Resistance. *Antimicrobial Agents and Chemotherapy* 48, 2206–2213; Dagan and Klugman. (2008). Impact of conjugate pneumococcal vaccines on antibiotic resistance. *The Lancet Infectious Diseases* 8, 785–795).

(73) For example, components of the bacterial wall or the capsid (external envelope) of viruses, like the adjuvant MPL, which stimulates the innate immune system, responsible for triggering the immune response. Other adjuvants are surfactants, molecules which allow the formation of emulsions. For example, the adjuvant MF59 with a squalene base allows the formation of emulsions (drops of oil in an aqueous medium). McKee *et al.* (2007). "How Do Adjuvants Work? Important Considerations for New Generation Adjuvants." *Immunity* 27, 687–690.

(74) Villa *et al.* (2013). "Safety of MF59-Adjuvanted Influenza Vaccination in the Elderly: Results of a Comparative Study of MF59-Adjuvanted Vaccine Versus Nonadjuvanted Influenza Vaccine in Northern Italy." *Am. J. Epidemiol.* 178, 1139–1145.

(75) The senescent immune system requires a higher level of stimulation. Vaccines against influenza containing adjuvants have been developed to stimulate the immune response of elderly individuals, they are offered particularly in the United States, in Germany, in Italy and in Spain, but no longer in France. Ciabattini *et al.* (2018). "Vaccination in the elderly: The challenge of immune changes with aging." *Seminars in Immunology* 40, 83–94.

(76) The obstacle to the development of a universal vaccine against influenza lies in the difficulty in developing a vaccine which would target the antigenic element conserved in all strains (more stable), as this is practically inaccessible to antibodies. The complex immune response encountered in dengue fever and influenza is based on the concept of original antigenic sin (Hoskins effect): following infection by a virus, an immune memory is formed; during a second infection, by a slightly different virus, the immune system tends to activate the acquired immunity to combat this virus, although it is less effective against this new virus, while other immune mechanisms would have fought this new strain better. In the case of the dengue virus, this results in a greater impact of the disease on the organism, when the second strain encountered is different from the first.

(77) Dengue fever is thought to cause between 50 and 100 million symptomatic cases per year and several thousand deaths. The disease is advancing very rapidly: before 1970, only 9 countries experienced epidemics, today the disease is endemic in more than 100 countries and the WHO considers that there is a risk of a dengue fever outbreak in Europe. There is a dengue fever epidemic in La Réunion: between January and May 2019, 12,000 confirmed cases were identified and the Indian Ocean Regional Health Agency estimates that there have been more than 30,000 cases in 2019, while the Agency counted only a little more than 6,000 cases in 2018.

(78) Paules *et al.* (2018). "Chasing Seasonal Influenza — The Need for a Universal Influenza Vaccine." *New England Journal of Medicine* 378, 7–9.

(79) In 2017, malaria affected more than 200 million people and causes more than 400,000 deaths per year, according to the WHO.

(80) There are other factors, independent of vaccination, which can foster epidemics, like community life – such as caring for infants in a crèche before they have received all their vaccinations – and hygiene remains a health strategy not to be neglected. In this respect, studies suggest that crèche staff should be vaccinated against whooping cough and measles, as a "cocooning" strategy to protect children. Parker *et al.* (2017). "Advocating for Childcare Employee Single-Dose Tdap Vaccination to Combat Infant Pertussis." *Journal of Pediatric Health Care* 31, 241–245. Barker *et al. (2001)*. "Spread and prevention of some common viral infections in community facilities and domestic homes." *Journal of Applied Microbiology* 91, 7–21.

(81) The surveillance of infectious disease threats could result in a re-examination of recommendations, inasmuch as vaccines against diseases which affect a large number of people, such as chickenpox, rotavirus gastroenteritis and hepatitis a, do not have a recommendation in France.

(82)The Haute Autorité de Santé or the Haut Conseil de Santé Publique could be in charge of this annual examination.

(83) Vaccines against pneumococcus are so effective that we are witnessing the replacement of strains targeted by the vaccine by other, non-targeted strains. It appears appropriate to regularly re-evaluate the utility of the vaccine in protecting against different strains. Weinberger *et al.* (2011). "Serotype replacement in disease after pneumococcal vaccination." *The Lancet* 378, 1962–1973. Concerning measles, we have witnessed changes in the strains circulating in France since the 2000s, especially with the B3 and D8 strains: the efficacy of the vaccine against these strains is disputed. Santibanez *et al.* (2002). Rapid replacement of endemic measles virus genotypes. *Journal of General Virology* 83, 2699–2708; Melenotte *et al.* (2018). Measles: is a new vaccine approach needed? *The Lancet Infectious Diseases* 18, 1060–1061 and Fatemi Nasab *et al. (2016)*. Comparison of neutralizing antibody titers against outbreak-associated measles genotypes (D4, H1 and B3) in Iran. *Pathog Dis* 74. However some studies testify to the capacity of the vaccine to protect against these strains. Holzmann *et al.* (2016). Eradication of measles: remaining challenges. *Med Microbiol Immunol* 205, 201–208.

(84) Mandatory vaccination had been stipulated in the law for caregivers in the same way as for vaccination against hepatitis B (law No. 2005-1579 of 19 December 2005 on social security funding for 2006). This obligation was removed by Order No. 2006-1260 of 14 October 2006 (on the basis of article L. 3111-1 of the Public Health Code relative to the mandatory vaccination against influenza of the professionals mentioned in article L. 3111-4 of the same code).

(85) Recommendations adopted by the Académie Nationale de Pharmacie on 21 March 2019 "*Vaccination des professionnels de santé*".

(86) The anti-HPV vaccine is reimbursed by social security for girls between 11 and 14 years old, with catch-up vaccination possible between 15 and 19 years.

(87) Statement by Virginie Belle, during the public hearing on aluminium adjuvants, organised by the Office In 2014. Non-declaration of adverse effects following the taking of a healthcare product is thought to be in the region of 80 to 95% (Hazell and Shakir. (2006). Under-Reporting of Adverse Drug Reactions. *Drug-Safety* 29, 385–396).

(88) Pharmacoepidemiological surveys such as the study "*Vaccins anti-HPV et risque de maladies auto-immunes: étude pharmacoépidémiologique*." (2015) conducted by the ANSM and the CNAM could be undertaken. A communication from members of the Académie Nationale de Médecine, in 2016, pleaded for enhanced pharmacovigilance. Montastruc *et al.* (2016). "Which pharmacovigilance for vaccines?" *Bull. Acad. Natl. Med.* 200, 241–250.

(89) Blaisdell *et al.* (2016). "Unknown Risks: Parental Hesitation about Vaccination." *Med Decis Making* 36, 479–489 and Morris (1997). "Risk, uncertainty and hidden information." *Theory and Decision* 42, 235–269.

(90) Montastruc *et al.* (2016). "Which pharmacovigilance for vaccines?" Bull. Acad. Natl. Med. 200, 241–250. The opening of the website vaccination-info-service.fr by Santé Publique France, which has already received more than 6 million visitors reflects this view.

(91) Vaccination in Europe – an EASAC/FEAM Commentary on the EC Roadmap "Strengthened cooperation against vaccine preventable diseases", https://www.feam.eu/wp-content/uploads/EASAC-FEAM-Statement-on-vaccines-April-2018-FINAL.pdf.

(92) The dematerialised nature of the vaccination record would allow better preservation of the health record and its consultation by the school or crèche in order to check that the child is up to date with their vaccinations. The Steering Committee of the Citizen Consultation on Vaccination also recommended vaccination at school, by the school doctor, as is performed in the United Kingdom and Northern Europe. Report on vaccination of the Steering Committee of the Citizen Consultation on Vaccination, 30 November 2016 http://concertation-vaccination.fr/wp-content/uploads/2016/11/Rapport-de-la-concertation-citoyenne-sur-la-vaccination.pdf