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Evolution of public perception of vaccination: a growing need for non-market strategies within the pharmaceutical industry

Lara Salvi

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Lara Salvi. Evolution of public perception of vaccination: a growing need for non-market strategies within the pharmaceutical industry. Pharmaceutical sciences. 2018. dumas-01876103

HAL Id: dumas-01876103

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UNIVERSITÉ GRENOBLE ALPES
UFR DE PHARMACIE DE GRENOBLE

Année : 2018

EVOLUTION DE LA PERCEPTION PUBLIQUE DE LA VACCINATION : UN BESOIN
CROISSANT DE STRATEGIES NON MARCHANDES DANS L'INDUSTRIE
PHARMACEUTIQUE

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN PHARMACIE
DIPLOME D'ÉTAT

Lara SALVI

[Données à caractère personnel]

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE PHARMACIE DE
GRENOBLE

Le : 14/09/2018

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 UMR: Unité Mixte de Recherche
 UVHCI: Unit of Virus Host Cell Interactions

Mise à jour le 09/01/2018

Remerciements

En ce jour symbolique qui vient clôturer mon cursus, je tiens à remercier sincèrement l'ensemble des membres du jury ainsi que toutes les personnes présentes aujourd'hui à ma soutenance de Thèse d'Exercice en Pharmacie.

En premier lieu, je tiens à remercier **Madame Raphaële Germi**, ma Directrice de Thèse, pour avoir le pris le temps et l'intérêt d'encadrer ma thèse de Pharmacie d'industrie. Vos conseils ont été les bienvenus, et je vous remercie pour votre curiosité et votre engagement. Merci également pour votre implication tout au long de mon cursus de Pharmacie, et pour m'avoir donné goût à l'infectiologie.

Je remercie **Monsieur Jean Breton**, Président du Jury, pour sa disponibilité et sa présence aujourd'hui, mais également tout au long de ces cinq années d'études. Je me souviendrai de votre bienveillance et de votre envie de transmettre vos connaissances et votre passion.

Je remercie également **Monsieur Walid Rachidi**, membre du Jury, pour avoir accepté d'être membre de mon Jury de Thèse et pour son regard complémentaire sur ce travail.

Je souhaite remercier sincèrement **Madame Christine Lefournier**, Pharmacien officinal et membre actif du Rotary, pour m'avoir fait l'honneur d'être membre de mon Jury de Thèse. Merci pour tout ce que vous avez pu me transmettre et m'apporter, de votre énergie débordante à votre engagement profond envers autrui. Merci de m'avoir soutenu et de m'avoir guidé au cours de mon expérience au Rotaract.

Je remercie **Madame Charlotte Riquier**, Pharmacien officinal, pour m'avoir encadrée au cours de mon premier stage officinal et pour m'avoir fait partager sa passion débordante pour son métier et son engagement incroyable envers les patients.

Je remercie **Madame Véronique Morris**, Médecin et Directeur au sein de la Division Communication Scientifique Internationale chez les Laboratoires Servier, pour m'avoir encadrée

au cours de mon premier stage industriel. Merci pour ta simplicité, ta gentillesse, ta disponibilité et ton honnêteté. Merci de m'avoir transmis des valeurs simples mais essentielles dans le milieu industriel. Ce stage a confirmé mon envie de travailler au sein de l'industrie pharmaceutique et je t'en serai toujours reconnaissante.

A l'issue de ce cursus et en ce moment particulier, je tiens à remercier tout particulièrement **Monsieur Aziz Mellal**, mon maître de stage de fin d'étude et actuel manager au sein de la Division Régionale Vaccins chez Pfizer. Un grand merci pour ton accueil, ton accompagnement et tes conseils précieux.

Finalement, je tiens également à remercier **l'ensemble des Professeurs** qui m'en ont enseigné l'art de la Pharmacie au sein de la faculté de Grenoble, pour leur engagement et leur passion à transmettre leurs connaissances.

Parce que mon cursus n'aurait en rien été celui qu'il a été, je tiens enfin à remercier du fond du cœur **mes amis**, qui m'ont accompagnée au cours de ces années inoubliables. Merci pour votre présence, votre soutien indéfectible et votre bonne humeur, chaque jour. Merci pour votre simplicité, votre sincérité et votre énergie. Merci pour tout.

Enfin, je tiens à remercier du fond du cœur **ma famille**, qui a toujours été présente et qui continue de l'être malgré la distance. Merci infiniment à mes parents, pour m'avoir donné l'envie de faire et d'être ce que je suis aujourd'hui. Merci pour votre confiance et votre soutien dès le premier jour, et surtout, merci de m'avoir permis de voyager et m'ouvrir à un monde infini d'opportunités. Merci à ma sœur, Claire, pour ta présence et ton soutien à chaque fois que j'en avais besoin. Merci à mes grands-parents, pour tout leur amour, ainsi que le reste de ma famille, chère à mon cœur.

“Carelessness in the matter of vaccination is sure to tell against the health of a community, sooner or later.” *New York Daily Tribune, 1902.*

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Liste des Acronymes

ACIP: Advisory Committee on Immunization Practices

BCG: Bacille Calmette Guerin (tuberculosis vaccine)

CAGR: Compound Annual Growth Rate

CDC: Center for Disease Control

CEO: Chief Executive Officer

CSR: Corporate Social Responsibility

DALY: Disability Adjusted Life Years

DNA: Deoxyribonucleic Acid

DTP: Diphtheria-Tetanus-Poliomyelitis

DTP3: Third dose of Diphtheria-Tetanus-Poliomyelitis vaccine

EPI: Expanded Program of Immunization

E3M: Entraide aux Malades de Myofasciite à Macrophages

FDA: Food and Drug Administration

GAVI: Global Alliance for Vaccines and Immunization

GNP: Gross National Product

GSK: Glaxo Smith Kline

GVAP: Global Vaccine Action Plan

HCP: Health Care Professional

HepB BD: Hepatitis B birth dose

HepB3: Third dose of Hepatitis B vaccine

Hib: *Haemophilus influenzae* type B

Hib3: Third dose of *Haemophilus influenzae* type B vaccine

HIT: Herd Immunity Threshold

HIV: Human Immunodeficiency Virus

HPV: Human Papilloma Virus

ICCR: Interfaith Center on Corporate Responsibility

LYS: Life Years Saved

MCV1: First dose of Measles vaccine

MCV2: Second dose of Measles vaccine

MMR: Measles-Mumps-Rubella

MMRV: Measles-Mumps-Rubella-Varicella

MSF: Médecins Sans Frontières

NGO: Non-Governmental Organization

PAHO: Pan American Health Organization

PCV: Pneumococcal Conjugate Vaccine

PCV3: Third dose of pneumococcal pneumonia vaccine

Polio3: Third dose of Polio vaccine

R&D: Research & Development

SAGE: Strategic Advisory Group of Experts

SPMSD: Sanofi Pasteur Merck Sharp & Dohme

UK: United Kingdom

UNICEF: United Nations International Children's Emergency Fund

USA: United States of America

WHO: World Health Organization

WIG: Women In Government

Introduction

De nos jours, la vaccination est considérée comme l'une des plus grandes réussites de santé publique. Au cours du 20^{ème} siècle et tout particulièrement durant sa seconde moitié, les programmes de vaccination de masse ont contribué au déclin majeur de l'incidence et de l'impact de nombreuses maladies infectieuses, permettant à terme l'éradication de la variole ainsi que l'élimination de la diphtérie, du tétanos et de la poliomyélite dans de nombreuses régions du monde. Durant ce siècle, un développement sans précédent a résulté en un nombre important de nouveaux vaccins protégeant contre un large éventail de maladies. Par ailleurs, le perfectionnement des techniques a permis de réduire le nombre d'injections nécessaires et de fabriquer des vaccins jouissant d'un profil amélioré de pureté et de sécurité. A l'échelle mondiale, les vaccins sont désormais cités comme l'une des mesures sanitaires les plus rentables, apportant un bénéfice à l'ensemble de la population et à travers tous les âges.

Afin de contribuer à la réduction de l'impact des maladies infectieuses évitables, les programmes d'immunisation s'appuient sur une large couverture vaccinale au sein de la population. Cette dernière apporte non seulement une protection individuelle directe à l'individu qui se vaccine, mais aussi une protection indirecte connue sous le terme d'immunité de groupe au sein de la communauté qui l'entoure. Le taux élevé de couverture vaccinale infantile dans la plupart des pays indique que la vaccination demeure une mesure sanitaire largement acceptée à travers le monde. Toutefois, malgré le progrès évident et les nombreux programmes mis en place, il apparaît aujourd'hui clairement que le mouvement d'hésitation vaccinale est en croissance. Cette situation a mené à la réapparition de maladies évitables autrefois éliminées, résultant en de nombreuses épidémies et cas de maladie.

Aujourd'hui, plusieurs aspects suscitent les questions ainsi que l'inquiétude du grand public. Des préoccupations concernant la sécurité et l'efficacité des vaccins, le manque d'information à propos de la législation autour des vaccins et un malentendu des motivations et des gains de l'industrie pharmaceutique sont souvent cités comme les raisons majeures de cette hésitation

vaccinale. Pourtant, d'autres facteurs semblent influencer le phénomène. Ainsi, l'érosion globale de la confiance du public envers les preuves scientifiques et les gouvernements ainsi qu'un désir croissant de défendre sa liberté de penser et d'agir apparaissent comme des stimuli potentiels à considérer. En outre, la réticence de certains professionnels de santé à promouvoir les vaccins chez leurs patients ainsi que la multiplication sans précédents des canaux de communication ont finalement conjointement contribué à l'essor de ce phénomène.

Tous ces éléments appartiennent à l'environnement dit non marchand des entreprises pharmaceutiques. Ils ne sont donc pas directement liés à leurs activités commerciales alors qu'ils ont pourtant le potentiel d'impacter leur performance sur le long terme de façon significative. Les entreprises reconnaissent aujourd'hui que cet environnement externe se doit d'être considéré dans leurs affaires courantes et qu'un management efficace de cette sphère non marchande peut s'avérer bénéfique afin de guider leur activité dans un environnement complexe et changeant.

Après avoir présenté les vaccins et les activités commerciales qui y sont associées, cette thèse vise à exposer l'émergence de l'hésitation vaccinale et à discuter de ses sources et des potentiels leviers d'action. Enfin, la dernière partie évoquera les stratégies non marchandes au sein de l'industrie actuelle du vaccin, en exposant à la fois leur nécessité et l'option prometteuse qu'elles apportent.

Résumé synthétique de la thèse en langue française

Dans un contexte croissant de critiques et d'hésitations accrues envers les vaccins, ce travail vise à explorer ce phénomène actuel en présentant tout d'abord les vaccins eux-mêmes, depuis leur histoire et leur incroyable développement jusqu'à leur impact significatif et irréfutable à travers des siècles, avant d'analyser les possibles causes ayant menées graduellement à la situation que nous connaissons aujourd'hui. L'économie comportementale récente apporte tout particulièrement des éléments clés dans cette recherche étiologique, permettant de mettre ce phénomène de santé en regard de l'environnement et des grandes tendances mondiales actuelles. Ce cheminement scientifique et économique mène à la troisième et dernière partie – centrale – de ce travail, qui vise à démontrer que l'ancien modèle de l'industrie pharmaceutique semble aujourd'hui dépassé et que les entreprises modernes du vaccin doivent désormais s'ouvrir et placer leur environnement extérieur au centre de leurs stratégies au long terme.

Le développement et l'impact sans précédent de la vaccination.

Un vaccin est défini par l'Organisation Mondiale de la Santé comme une préparation administrée pour provoquer l'immunité contre une maladie, en stimulant la production d'anticorps. Les vaccins se présentent sous différentes formes, telles que des suspensions de micro-organismes inactivées ou vivantes et atténuées, ou des produits ou dérivés de micro-organismes, et visent à protéger un individu contre une maladie infectieuse spécifique. Ces derniers sont le plus souvent injectés, mais certains vaccins sont donnés par voie orale ou en pulvérisations nasales. L'un des concepts clés de la vaccination est l'immunité dite de groupe qu'elle confère au sein des populations, qui repose sur le fait que les vaccins protègent non seulement les individus propres qui se font vacciner, mais également leur environnement de part un effet de cohorte. Cette caractéristique clé, associée à des efforts menés sur le long terme et à l'échelle mondiale, a entre autres permis l'éradication de la variole ainsi que l'élimination d'autres maladies comme la diphtérie, le tétanos ou la poliomyélite dans bon nombre de régions du globe.

A l'origine, la vaccination a été mise en lumière et expérimentée par le jeune scientifique anglais Edward Jenner qui au 18^{ème} siècle déjà avait remarqué que les individus au contact d'une maladie bovine semblaient protégés de la variole. La technique de variolisation mise au point par ses soins sera plus tard reprise et approfondie par Louis Pasteur, qui mettra en évidence la relation de cause à effet reliant chaque maladie à un microbe spécifique. S'ensuit alors un développement des vaccins sans précédent, des vaccins à microorganismes vivants puis inactivés, aux vaccins atténués et 'ingénieurisés'. Chaque vaccin présente des caractéristiques propres à prendre en compte lors de la production, du transport ou encore de l'administration.

Au cours des décennies, aucune mesure sanitaire ne peut prétendre avoir préservée plus de vies des maladies infectieuses transmissibles que les vaccins. En quatre siècles de développement, l'apparition de nouveaux vaccins associés au lancement effectif de grands programmes de vaccination ont été de grands succès, et ont permis de faire chuter de façon dramatique l'incidence et la mortalité des maladies ciblées, telles que la diphtérie, le tétanos, la poliomyélite ou encore la rougeole et la tuberculose. Au sein des pays développés, les programmes de vaccination nationaux se sont rapidement développés et la couverture vaccinale des vaccins dits de base a augmenté de façon exponentielle. Au cours de la seconde partie du 20^{ème} siècle, des organisations supranationales telles que le Programme d'Expansion de l'Immunisation (EPI), l'UNICEF ou encore l'Organisation Mondiale de la Santé ont joint leurs efforts à ceux des gouvernements afin d'augmenter les taux de couvertures dans les pays en voie de développement. Malgré des efforts incontestables, ces pays jouissent encore aujourd'hui d'une pénétration moindre des vaccins de façon générale, pour des raisons majoritairement économiques. A travers le globe, les couvertures vaccinales varient donc en fonction des régions et des vaccins, de quelques pour cents de la population couverte à des couvertures frôlant les cent pour cents. Toutefois, un effort continu est absolument nécessaire dans le but de maintenir un seuil de couverture suffisant afin d'assurer l'immunité de groupe, défini en fonction du microbe et de l'infection qu'il provoque.

En dehors de son impact médico-sanitaire, il est important de souligner l'impact économique favorable de la vaccination, de par les millions de vies sauvées chaque années et les économies associées réalisées, qu'elles soient directes ou indirectes. La balance coût-utilité des vaccins apparaît toujours aujourd'hui comme extrêmement favorable.

Un marché du vaccin florissant.

A la différence du reste de l'industrie pharmaceutique qui fait actuellement face à une diminution de ses profits due à de nombreux facteurs, tels que la décroissance de la productivité du secteur de la recherche et du développement, la compétition croissante des génériques ainsi que la pression accrue des organismes payeurs envers les prix des médicaments et du remboursement de ces derniers, le secteur du vaccin apparaît quant à lui largement attractif et attire les grandes entreprises du médicaments.

Alors qu'il est longtemps apparu comme un secteur d'affaires non rentable et délaissé de l'industrie, ce dernier possède aujourd'hui ses propres caractéristiques qui en font un marché bien à part. En premier lieu, il s'agit d'un marché relativement petit et extrêmement concentré, qui repose fortement sur les appels d'offres et régulations publiques, malgré le fait que le secteur privé gagne lentement de l'importance. Par ailleurs, le marché du vaccin peut être considéré comme un ensemble de marchés uniques, tous régulés et fonctionnant différemment, rendant les barrières à l'entrée très importante pour les nouveaux acteurs, notamment en ce qui concerne la recherche et développement ainsi que la capacité de production et d'exploitation. Enfin, les avancées en microbiologie et en immunologie couplées aux efforts publics de financement des vaccins ont rendus le secteur beaucoup plus rentable aux yeux des acteurs déjà engagés en ce sens, d'autant plus que les entreprises du vaccin ne sont que rarement victimes de l'apparition de génériques sur le marché, du fait de la complexité de production et de la présence de brevets sur les procédés de production eux-mêmes.

Ainsi, alors que les vaccins ont longtemps été l'apanage des pays développés, les pays en développement sont désormais de plus en plus présents et demandants, notamment via le

support d'organismes mondiaux. De la sorte est maintenue une demande constante de nouveaux vaccins à haut prix parallèlement à des vaccins plus matures et aux coûts moins élevés, dans un environnement dynamique et attractif.

La valeur marchande du secteur du vaccin était estimée à 27 milliards de dollars en 2016, comparée à 6 milliards de dollars seulement en 2000. Ce montant devrait continuer à croître pour atteindre 34 milliards de dollars en 2022, jouissant d'un taux de croissance annuel composé de 12,4% sur cette période. Alors que les montants investis en recherche et développement sont capitaux et atteignent environ 15% des revenus des entreprises, il est prévu que les nouveaux vaccins mis sur le marché soient aussi ceux qui généreront en majorité la croissance prévue sur les prochaines années.

Seul un nombre limité de producteurs se partage actuellement la manufacture des vaccins existants, générant un équilibre fragile entre l'offre et la demande et occasionnant de façon régulière des ruptures de stock. Alors que la situation tend à changer avec de nouveaux acteurs arrivant sur le marché, quatre grosses entreprises se partagent actuellement presque l'entièreté du marché – Sanofi Pasteur, Merck & Co., GlaxoSmithKline et Pfizer. Ces quatre géants possèdent aujourd'hui tous un fort savoir-faire ainsi qu'une capacité de production importants, leur permettant d'investir à nouveau tout en commercialisant leurs vaccins déjà sur le marché avec succès.

L'hésitation vaccinale.

Alors que la vaccination a marqué un tournant dans la médecine et la santé publique moderne, nul ne peut ignorer aujourd'hui qu'un sentiment de scepticisme croissant envers les vaccins se développe mondialement. Dans un monde changeant et de plus en plus connecté, l'acceptation des vaccins semble aujourd'hui de plus en plus dépendante de facteurs émotionnels, psychologiques, socio-culturels et politiques. Cette 'crise de l'hésitation vaccinale' n'est plus un phénomène isolé mais comporte au contraire un nombre croissant d'individus ne rejetant pas complètement les vaccins mais les questionnant de façon croissante, dans une sorte de

continuum de l'incertitude. La crise du vaccin ROR au Royaume-Uni, du vaccin anti-hépatite B en France ou anti-HPV dans plusieurs pays sont un exemple de ce phénomène gagnant de l'ampleur.

La compréhension des raisons menant à ce sentiment d'hésitation est capitale afin de répondre à ce phénomène, alors que le lien entre hésitation vaccinale et demande est complexe et non congruente. Le comité de travail d'experts SAGE a proposé le concept des « 3Cs », en estimant que l'hésitation vaccinale reposait à la fois sur des facteurs de confiance, de complaisance et de commodité. Par ailleurs, ce même groupe a travaillé sur une matrice des déterminants de cette hésitation vaccinale, et il apparaît que les causes du phénomène sont nombreuses et variées, reposant soit sur l'individu et son environnement, soit sur le vaccin et le procédé de vaccination lui-même. Par ailleurs, la matrice met en évidence l'importance capitale de la perception et des croyances des individus, en relation avec les découvertes récentes de l'économie comportementale dans le domaine de la santé.

Evolution de la perception publique de la vaccination et économie comportementale.

De façon croissante, les théories comportementales néoclassiques soutenant que l'individu émet des choix rationnels et réfléchis guidés par des préférences stables sont mises à l'épreuve, ceci notamment dans le secteur de la santé. Il est aujourd'hui évident que l'individu est guidé à la fois par des facteurs rationnels et irrationnels, que ce soit la peur, l'impulsivité, le manque de volonté ou son environnement immédiat.

Dans le contexte de l'hésitation vaccinale, de nombreuses tentatives d'explications du phénomène ont ainsi progressivement émergé. L'une des raisons avancées met en évidence le cycle de vie des programmes d'immunisation, et le fait que les individus ont tendance à ne graduellement plus voir l'impact positif d'un vaccin *via* la maladie contre laquelle il protège, à mesure que celui-ci est adopté au sein d'une population – cet effet de dilution étant d'autant plus fort que le vaccin est efficace.

L'effet pyramide modélise quant à lui à la fois l'impact des vaccins sur la société (base de la pyramide) via les bénéfices à grande échelle non forcément perçus par le grand public jusqu'aux risques potentiels de danger (sommet de la pyramide), rares mais extrêmement percutants et relayés. La pyramide n'est donc pas équilibrée, et alors que la majorité des individus recevant des vaccins resteront de passifs receveurs, la minorité qui en expérimentera les effets indésirables exprimera féroce son désarroi.

A l'échelle individuelle, l'heuristique de disponibilité est avancée pour prédire la probabilité d'un évènement en fonction de la facilité avec laquelle il provient. Ceci explique par exemple pourquoi les taux de couvertures vaccinales chutent à la suite d'un scandale sanitaire puis ré-augmentent lentement, ou pourquoi les individus qui tombent malades à la suite d'une vaccination attribuent la maladie au vaccin lui-même. Les expériences négatives sont généralement plus marquantes que les positives, et tendent à une surévaluation du risque et du taux d'échec des vaccins, créant ainsi une boucle d'amplification.

D'autres recherches en psychologie ont montré que les individus tendent à créer des flux logiques d'information dans leurs esprits afin d'expliquer l'environnement complexe qui les entoure. Toutefois, cette prédisposition à la cohérence peut parfois mener à de fausses idées comme le fait que le vaccin contre une maladie soit responsable de cette maladie.

En outre, d'autres biais cognitifs avancent le fait que certains individus se sentent invulnérables et au-dessus de la moyenne, pouvant expliquer des situations de non-vaccination comme pour la vaccination contre la grippe (« je ne tomberai pas malade»), ou le fait que certains individus ne participeront à des mesures de prévention que s'ils se sentent personnellement à risque (« cette maladie ne me concerne pas donc je ne vois pas la nécessité de me faire vacciner »). Enfin, les biais d'omission, l'aversion personnelle au risque ainsi que la perception et le ressenti de l'environnement peuvent également contribuer et jouer un rôle clé dans la genèse de l'hésitation vaccinale.

Par ailleurs, alors que le phénomène semble se développer à travers le globe entier, il apparaît que ce dernier est concomitant à une tendance plus globale de remise en question de la confiance des individus envers les entités publiques, qu'elles soient gouvernementales, scientifiques ou politiques. Les choix individuels changent graduellement et semblent se transformer d'un modèle vertical vers un modèle horizontal, où le choix propre de l'individu et sa possibilité d'exercer ses droits est fondamental et se doit d'être respecté.

Aussi, la multiplication des sources d'information et le développement de fausses informations semblent contribuer à cette tendance mondiale de responsabilisation personnelle et donc au développement de l'hésitation vaccinale. Les individus sont aujourd'hui mieux connectés que jamais, et une part des voix équivalente semble de surcroît être attribuée par les médias entre une démonstration scientifique robuste et un article rédigé d'après des convictions erronées.

Finalement, le manque d'engagement et de convictions des professionnels de santé eux-mêmes semble affecter la tendance. Ainsi, alors que ces derniers apparaissent encore comme un facteur décisif influençant les choix en santé et en prévention des individus, il apparaît que ceux-ci ne sont pas toujours à l'aise et suffisamment équipés afin de faire face à un individu hésitant. Un manque de connaissances couplé à un manque de temps et de moyens, ou simplement de convictions personnelles semblent être au cœur de ce problème et se doivent d'être pris en compte.

Ainsi, ce phénomène d'hésitation vaccinale est alimenté par des facteurs nombreux et divers. Le problème est complexe et non nouveau, mais il est critique du fait de l'accélération de son ampleur, et son impact potentiel sur la santé publique est immense. Au-delà de son impact sociétal, l'hésitation vaccinale apparaît aussi comme une forte menace pour l'industrie du vaccin, pour laquelle de nouveaux modèles de communication et de fonctionnement semblent aujourd'hui s'imposer. En ce sens, les stratégies non marchandes semblent l'une des options les plus prometteuses.

Une nécessité de changement.

Il est clair que l'industrie du vaccin fait face à une crise importante d'image. Alors que les grandes entreprises du vaccin se sont longtemps reposées sur l'appui des gouvernements, des systèmes de santé et du public, la situation est aujourd'hui radicalement différente et il n'est plus possible de maintenir leurs activités comme à l'accoutumée.

Historiquement, les entreprises du vaccin ont commencé à promouvoir leurs produits dès lors que le secteur s'est montré rentable et attractif, ceci notamment auprès des professionnels de santé. Cette relation particulière s'est creusée au fil des décennies, au point de laisser les patients et le grand public de côté, avec finalement peu de connaissances en la matière. Ceci a contribué en une méfiance croissante de ces derniers envers ces entreprises, engendrant critiques et dégradation de la réputation des entreprises malgré leur contribution indéniable envers la société.

Cette relation chaotique entre la société et l'industrie pousse aujourd'hui cette dernière à repenser sa position et ses interactions avec ses parties prenantes indirectes. En effet, ces dernières semblent s'être multipliées durant ces dernières décennies et avoir gagné en puissance et en rayonnement sur la scène publique. Ceci concerne les associations de patients, les groupes de défense, les pharmaciens et autres professionnels de santé non prescripteurs, les autorités nationales de santé et conseils consultatifs mais encore les partenaires institutionnels, les payeurs et les médias pour n'en citer qu'un certain nombre. Tous ces acteurs poursuivent des intérêts bien différents, et pourtant, tous sont d'une certaine façon liés à l'industrie du vaccin et devraient de ce fait être considérés *per se*.

Par ailleurs, alors que l'industrie du vaccin a fortement attiré les investisseurs et grandes entreprises pharmaceutiques durant les vingt dernières années, et ceci à la suite d'une longue période de stagnation voire de déclin et de désinvestissement, il apparaît aujourd'hui que le modèle de croissance centré uniquement sur les activités commerciales et la promotion pure des vaccins n'est plus viable et se doit d'être repensée. Les individus et potentiels patients vivent au sein d'un environnement influencé par de nombreux facteurs sociaux, politiques et environnementaux qui

façonnent quotidiennement leurs besoins ainsi que leurs perceptions et leurs comportements. De la sorte, il est désormais capital pour une entreprise de considérer ces facteurs afin de rester en phase avec ses cibles et d'ainsi rester compétitive.

Il est aujourd'hui évident que chaque entreprise contribue d'une certaine façon à la société. Le problème réside en le fait que toutes ne le promeuvent pas. Communiquer de façon très ponctuelle sur la responsabilité sociale d'entreprise n'est pas suffisant, et apparaît souvent comme une manœuvre cynique et intéressée de la part des parties prenantes extérieures au commerce. A l'inverse, les entreprises qui réussissent à placer ces acteurs externes au cœur de leurs activités de tous les jours semblent construire et jouir d'une situation profitable avec leur environnement extérieur. Il ne s'agit pas là de mettre les affaires de côté, mais plus simplement de repenser ces dernières et de reconnaître la valeur au long terme qu'est capable de générer l'entreprise pour la société.

Les stratégies non marchandes.

L'environnement non marchand peut être défini comme toutes les relations qui ne sont pas intimement liées aux activités commerciales et qui pourtant présentent le potentiel d'affecter la capacité d'une entreprise à atteindre ses objectifs. En ce sens, le développement de stratégies non marchandes semble complémentaire et synergique aux activités commerciales classiques. Par ailleurs, elles semblent répondre à quatre facteurs clés actuels, qui sont la multiplication des acteurs interagissant avec l'industrie du vaccin, la mondialisation et l'importance croissante d'entités non gouvernementales, une hausse des régulations dans ce secteur et une compétition accrue entre les acteurs sur le marché.

A la différence des stratégies commerciales classiques, les stratégies non marchandes semblent être caractérisées par un profil bien particulier. Elles s'appuient majoritairement sur les coalitions et non sur le monopole, favorisent la cohérence à la flexibilité, sont sujettes à l'incertitude plus qu'à la prédictibilité et reposent sur *des* valeurs plus que sur *la* valeur. Enfin, la monnaie d'échange au cœur de ces stratégies est souvent l'information, et non les revenus.

Il est intéressant de se demander comment de telles stratégies lorsqu'elles sont mises en regard de l'hésitation vaccinale, peuvent aider à appréhender le problème et à y répondre. Le modèle (IA)³ développé par Bach en 2010 (Bach *et al.* 2010.) offre plusieurs directions afin de traiter un problème par le management non marchand. Ainsi, en partant du problème lui-même et en définissant clairement les acteurs en jeu, le modèle s'appuie également sur les intérêts propres des acteurs ainsi que l'arène au sein de laquelle ils évoluent et où pourrait intervenir l'entreprise en question. Finalement, il est important de se questionner sur le type d'information qui prévaudra dans l'échange ainsi que de capitaliser sur de potentiels atouts qui pourraient faire pencher la balance favorablement et générer de la valeur à long terme.

Dans l'optique de considérer dans un premier temps et contrer dans un second temps le phénomène croissant de l'hésitation vaccinale, une multitude de stratégies peuvent être envisagées, qu'elles concernent tel ou tel acteur ou tel ou tel canal de communication. Plus que l'impact, il semble que ce soit la cohérence et la durabilité de la démarche qui soit capitale pour le public. Il n'existe pas de solution unique, mais c'est à l'inverse un ensemble d'initiatives qui pourra faire pencher la balance vers une meilleure compréhension et acceptation de l'univers des vaccins et des entreprises qui le composent. L'heure est à la genèse de la démarche, mais il semble que cet axe stratégique soit définitivement porteur d'un réel avantage compétitif et d'un net bénéfice au long terme pour les acteurs industriels.

I. The Art of Vaccination: from an Outstanding Scientific Discovery to an Attractive Business

A. Birth and Rise of Vaccination

i. Definitions and Principle

According to the World Health Organization, immunization is the process whereby a person is made immune or resistant to an infectious disease¹. Immunization against infectious pathogens is typically obtained by the administration of vaccines, although some diseases such as chickenpox can lead to partial or complete natural immunity after recovery from a primary infection. Also, while the term immunization is often used interchangeably with the more popular term vaccination, the latter specifically refers to the act of introducing a vaccine into the body to produce immunity to a specific disease.

Vaccines are biological preparations designed to stimulate artificially a person's immune system in order to provide an acquired immunity to a specific disease, hence protecting one from that disease. A vaccine typically contains an agent –or active component- that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the pathogen, its toxins or one or several of its surface proteins. When introduced into the body, the agent allows stimulation of the immune system to recognize this particular agent as foreign, destroy it and keep a memory of it. This enables the immune system to better recognize and destroy any of these microorganisms that it later encounters, hence protecting the person against subsequent infection or disease. Vaccines are usually administered through intramuscular or intra-dermal needle injections, but can sometimes also be administered by mouth, or sprayed into the nose.

¹ WHO Website. *Immunization*. 2017.

ii. Concept of Herd Immunity

Coined in 1923, the term “herd immunity” is also known as “herd effect”, “community immunity”, “population immunity” or “social immunity”. It is described as an indirect form of protection from an infectious disease for which an efficient vaccine exists, which occurs when a large enough percentage of a population has become immune to that infection. In other terms, herd immunity provides a measure of protection for individuals who are not immune among a population predominantly immune. In such population, chains of infection are likely to be disrupted, which enables a slowdown or a cessation in the spread of disease, as illustrated by Figure 1.

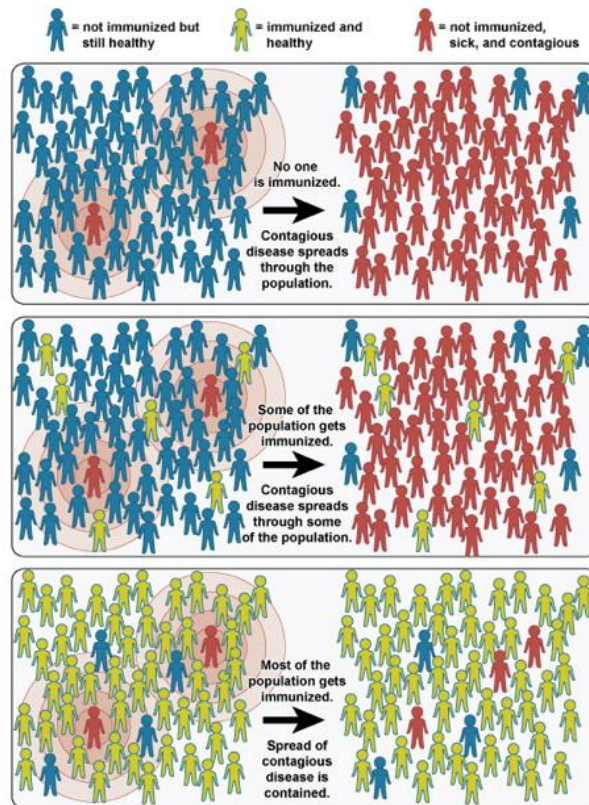


Figure 1 - Illustration of the concept of herd immunity.²

² US National Institutes of Health. *National Institute of Allergy and Infectious Diseases*. 2015

Herd effect induced by a large immunization coverage is particularly important for some individuals who cannot become immune, such as newborns with passive immunity or individuals who possess an immunodeficiency due to medical conditions.

Besides, herd immunity allows for gradual disease elimination in a population on the long-term. Once a certain threshold has been reached and can be maintained in the immunization coverage, a contagious disease cannot be transmitted anymore, leading to the disappearance of the pathogen deprived of its human host. Depending on the disease and therefore on the pathogen, the herd immunity threshold (HIT) can vary from 50 to over 90%³ as shown in table 1.

Infection	Herd Immunity Threshold
Diphtheria	85%
Influenza	50-75%
Measles	83-94%
Mumps	75-86%
Pertussis	92-94%
Rubella	83-85%
Smallpox	80-85%

Table 1 – Herd Immunity Thresholds – Ranges from Worldwide Data.³

If achieved on a global scale, disease elimination may result in a permanent reduction in the number of infections to none, leading to disease eradication. As an example, eradication of smallpox was achieved in 1977 in a global effort to decrease the number of disease cases. To date, other diseases such as poliomyelitis and diphtheria have also been regionally eliminated.

Importantly, herd immunity does not apply to all diseases, but only the ones that are contagious, meaning that they can be transmitted from one individual to another. As an example, tetanus is an infectious disease but is not contagious, so herd immunity does not apply.

³ Vynnycky E, et al. *An Introduction to Infectious Disease Modelling*. 2010.

iii. Birth of Vaccination

The formal vaccination process takes its roots in England from Edward Jenner's research and remarkable work in the 18th century. At that time, smallpox, known as "the speckled monster", devastated mankind. Symptoms appeared suddenly while the sequelae were disastrous, with an approximate 400,000 people dying annually of smallpox in Europe and a third of the survivors going blind. Smallpox was raging across all levels of society and the case-fatality rate varied between 20-60% with an even higher rate among children, approaching 80% in London and 98% in Berlin during the late 1800s⁴.

The word "*variola*" was then commonly used for mentioning smallpox. Introduced in Switzerland in the 6th century, it derives from the Latin words "*varius*" and "*varus*", meaning "stained" and "mark on the skin". The term smallpox itself derives from the expression "*small pockes*" that emerged in England in the 15th, to differentiate the disease from syphilis, then known as the great pockes.

At that time, it was commonly known that people who had recovered from smallpox infection became immune to the disease. And while many treatment attempts deriving from folk wisdom were widely used by physicians to cure the patients, the most successful way of combatting smallpox was inoculation. This technique consisted in instilling subcutaneously some fresh matter of smallpox virus taken from a ripe pustule of some infected patient to a nonimmune person. The material was administered through a lancet on the arms or legs. Also known as variolation, this method aimed at developing a benign form of the disease that would then protect the person for life. The practice seemed to have arisen independently in several European countries in the 18th century in an attempt to reduce the disastrous burden of disease.

Although the technique was generally a success, it was not without any risk, and 2 to 3% of inoculated people died from the procedure, either from the disease itself or by other diseases

⁴ Riedel S. *Edward Jenner and the history of smallpox and vaccination*. 2005.

transmitted through it such as tuberculosis or syphilis. Yet, variolation rapidly gained popularity among populations as the case-fatality rate of the procedure was approximately ten times lower than the one associated with natural smallpox, and the technique was hence widely practiced in Europe until Jenner's discovery.

In 1796, Edward Jenner, then an already renowned naturalist in Europe, made his first step in smallpox vaccination that would eventually lead to eradication of the disease. Based on the common observation that dairymaids who have had cowpox –a similar disease to smallpox but much milder- were protected against smallpox, he made the hypothesis that cowpox could confer cross-immunity to smallpox. Also, he decided to inoculate a young boy with fresh matter of cowpox. A few days later, he inoculated the boy once again, but this time with matter from smallpox lesions. He observed that no disease developed, and concluded that cross-protection was complete. The experiment was further confirmed with other cases, and Jenner decided to name the procedure “vaccination” after the Latin word “*vaccinia*”, meaning cowpox.

Although he was surely not the first to suggest and attempt cowpox inoculation to confer specific immunity to smallpox, Jenner however succeeded in sharing his work widely among the scientific community of that time, and his discovery is nowadays largely regarded as the foundation of vaccination.

It was almost a century later that French scientist Louis Pasteur demonstrated the principles of isolation, purification and injection of causative microorganisms in order to induce protective immunity in individuals⁵. In 1885, he was the first to successfully attempt post-exposure vaccination against rabies on a young boy. Subsequently, diverse vaccines were discovered such as those aimed at protecting against typhoid fever, cholera or plague in the late nineteenth century as well as vaccines against tuberculosis, diphtheria or tetanus in the early twentieth century⁶.

⁵ **Rappuoli R.** *Bridging the knowledge gaps in vaccine design.* 2007

⁶ **Plotkin S.** *History of vaccination.* 2014

iv. Classification of Vaccines

Early vaccines were developed through isolation followed by attenuation or inactivation of the causative agent, along with the use of complex and often not well characterized products. Although crude and often associated with safety concerns, this approach turned to be effective for eradication of smallpox as well as virtual elimination of diseases such as poliomyelitis, tetanus or diphtheria in many parts of the world. Over the decades, new approaches supported by the use of improved technologies have enabled to develop a large variety of vaccines protecting against an increasing range of vaccine-preventable diseases. Gradually, the quest towards enhanced vaccine safety has shifted development away from whole-cell inactivated and live attenuated vaccines towards subunit and non-replicating recombinant vaccines, essentially deprived of endogenous danger but also less immunogenic than naturally adjuvanted vaccines. Today, recent vaccines are characterized by their high level of safety compared with older vaccines as well as a large diversity of vaccine design technologies and an increased production-associated cost^{7,8}.

Killed microorganisms

Inactivated vaccines are produced by isolating, cultivating and killing the disease-causing agent with chemical or physical treatments. These vaccines are usually stable and safer than live vaccines as the dead microbe can't mutate back to its disease-causing state. They can be easily stored and transported, thus enabling their use in the developing countries.

However, despite the fact that these vaccines are usually efficacious and convenient, some pathogens appear difficult or almost impossible to be cultivated in a scalable setting. Also, inactivated vaccines induce a weaker immune system response than live vaccines, obliging several additional booster doses to maintain a person's immunity.

⁷ **U.S. Department of Health & Human Services.** *Types of Vaccines*. 2012.

⁸ **Rappuoli R, et al.** *Vaccine discovery and translation of new vaccine technology*. 2011.

Examples of such vaccines include the Salk polio vaccine, the rabies vaccine, the oral cholera vaccine, the whole pertussis vaccine and most influenza vaccines.

Live attenuated microorganisms

Live, attenuated vaccines are made up of the living causative agent that has been weakened in vitro so that it has lost the ability to cause the disease, usually after removal of several key genes. Due to their similarities with the natural agent, these vaccines are good inducers of the immune system. They elicit a strong body response and often confer lifelong protective immunity with a reduced dose regimen.

Despite their advantages, these vaccines also present some drawbacks. Thus, due to their live nature, the microorganisms used in such vaccines can, in some rare cases, mutate and revert to their virulent form to cause disease. Besides, live attenuated vaccines cannot be administered safely to people with a damaged or weakened immune system, such as patients under chemotherapy or HIV patients. Finally, these vaccines need to be refrigerated and are therefore more difficult to ship overseas and to store in the developing countries.

Examples of such vaccines include the Sabin polio vaccine, the intranasal influenza vaccine and the measles-mumps-rubella-varicella (MMRV) vaccine.

Subunit vaccines

Unlike early vaccines, subunit vaccines are constituted of a limited amount of antigens that best induce an immune response. Because they only contain the essential antigens and not all the other molecules that normally make up the microbe, the risk of adverse reactions to the vaccine are lower.

The choice of antigens that will best stimulate the immune system is a complicated and time-consuming process. Once they have been identified, antigens of interest can be obtained by either growing the microbe in the laboratory and then break it apart through chemical

treatments, or by directly manufacturing the molecule using recombinant DNA technology. Vaccines produced this way are called “recombinant subunit vaccines.”

Examples of such vaccines include the hepatitis B vaccine and the acellular pertussis vaccine.

Toxoid vaccines

These vaccines can be developed when a bacterial toxin is the main cause of illness. After inactivation by treatment with formalin, a solution of formaldehyde and sterilized water, the obtained detoxified toxins, also called toxoids, are safe for use in vaccines.

Toxoid vaccines work by enabling the immune system to recognize the toxoid and subsequently teach it how to fight off the natural toxin. The immune response leads to antibody production that will lock onto and block the toxin.

Examples of such vaccines include the diphtheria and tetanus vaccines.

Conjugate vaccines

Many harmful bacteria possess an outer coating of sugar molecules also called polysaccharides. As these molecules are generally not well recognized by immature immune systems of infants and young children, classical vaccines are not effective in such cases as polysaccharides antigens do not induce a sufficient immune response in these populations.

In conjugate vaccines, a special type of subunit vaccines, a polysaccharide component of the causative agent is chemically linked to a highly immunogenic protein carrier. The linkage elicits a better recognition of polysaccharide coatings from immature immune systems and therefore enable a sustained protection.

Example of such vaccines include the Haemophilus influenzae type B (Hib) vaccine and the conjugate pneumococcal vaccine.

v. Efficacy and Impact of Immunization Over the Decades

Since its discovery, surely no public health intervention has prevented more lives from infectious diseases than vaccines, with the exception perhaps of sanitary improvement and access to clean water⁹. From its origin with Jenner's observations in the late 18th, vaccine development has now entered its fourth century. From scientific discoveries to continuous improvement and multiplicity of vaccination strategies, vaccines have profoundly shaken medical care in the modern world. The public interest devoted to vaccination as well as the will of modern societies to improve their health and that of their children sustained that quest of progress and enabled great accomplishments in the past century, such as the key smallpox eradication worldwide in 1980.

Since the early nineteenth century, many vaccines have been developed against a large spectrum of previously dreadful infectious diseases. This multiplication of new vaccines rapidly led to development of combined vaccines, such as one protecting against diphtheria, tetanus and pertussis -also called DTP vaccine- first developed in 1931¹⁰. Even today, the DTP vaccine remains a key component of children immunization programs across the world. In many countries, its composition has been enhanced to confer a stronger and longer protection as well as ensure a more favorable safety profile. Besides, additional antigens have been gradually introduced in this historical combination vaccine in order to protect against a larger spectrum of diseases such as poliomyelitis, hepatitis B and Hib all at once.

The early discovery of adjuvants further enhanced vaccines potential and efficacy. Adjuvants are defined as additional components integrated in vaccines formulation which enable a better immune response from the body and hence a better protection against diseases, especially in the case of highly purified antigens inducing low immunostimulatory capabilities¹¹. Over the decades, many vaccines have been developed thanks to the use of adjuvants, and increased

⁹ Plotkin S. *Vaccines: the fourth century*. 2009.

¹⁰ Greenwood B. *The contribution of vaccination to global health: past, present and future*. 2014.

¹¹ CDC. *Vaccine Adjuvants*. 2016.

understanding of their role in the formulation of modern vaccines helped scientists to better tailor vaccine formulation towards desired clinical benefits, and ultimately towards a greater efficacy.

As a result, the nineteenth century has been an active and fruitful time for vaccine research and development, as shown in Figure 2.

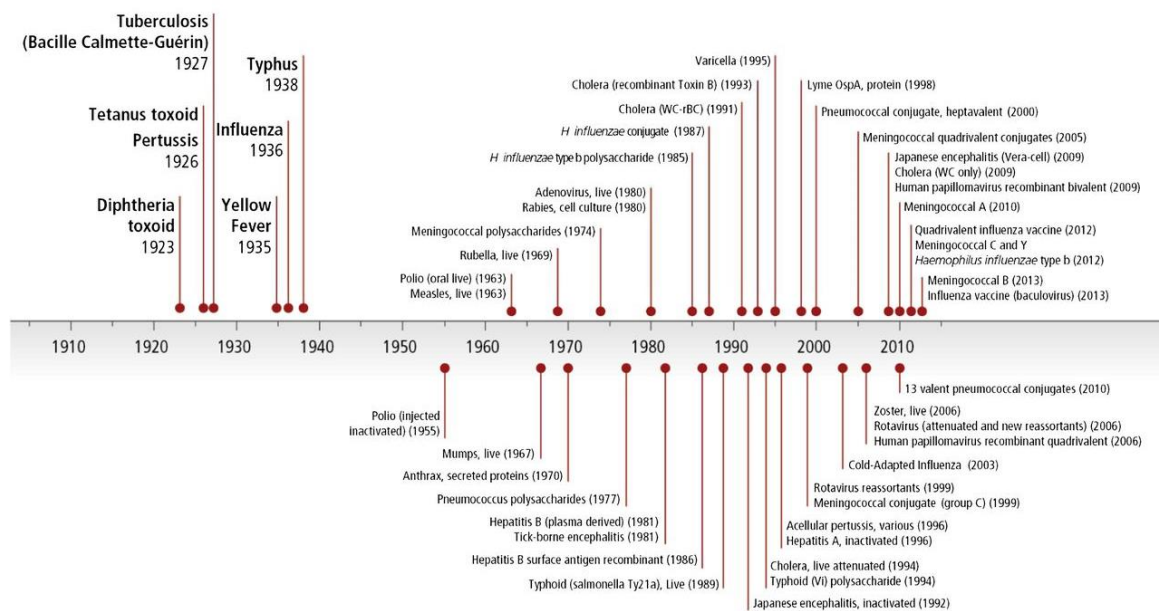


Figure 2 - Vaccine development from 1910–2013.¹²

Both the increased availability and the proven efficacy of vaccines rapidly led most of the children in the developed countries to receive routine immunizations with DTP, poliomyelitis and tuberculosis vaccines, driving a rising immunization coverage in these countries. As a consequence, case and mortality rates among infants and children for these common infectious diseases significantly decreased worldwide. This is illustrated hereafter by figure 3, showing the diphtheria mortality rate in the USA over the last century. Similarly, figure 4 highlights measles incidence and deaths in the USA from 1950 onwards, after the first vaccine protecting against

¹² Pickering L, et al. *The Red Book through the Ages*. 2013.

measles was introduced in 1965. In both examples, the introduction of an effective vaccine rapidly led to a sharp decrease in the number of cases and deaths attributed to the disease.

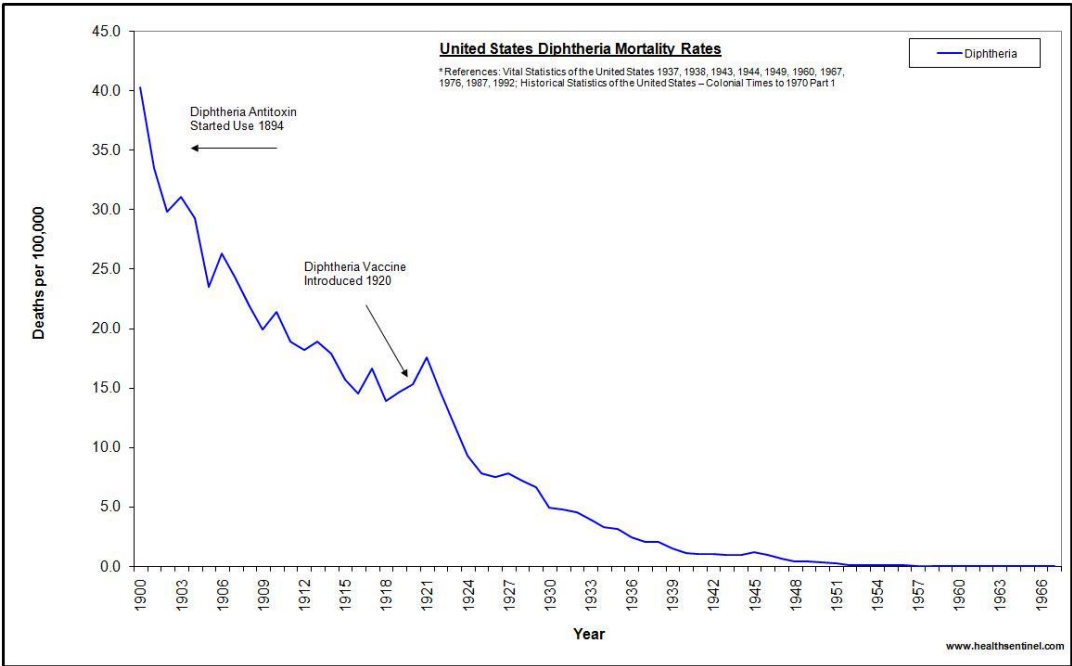


Figure 3 - Diphtheria mortality rates in the USA 1900-1966.¹³

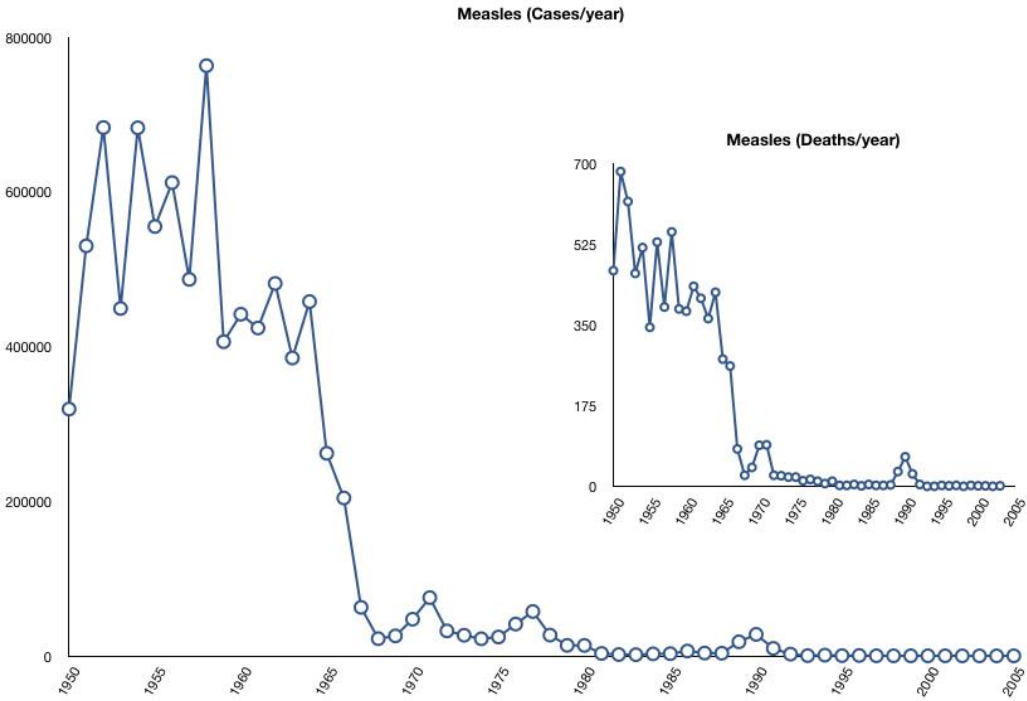


Figure 4 - Measles incidence and deaths in the USA, after 1950.¹³

¹³ U.S. Census Bureau. *Statistical Abstract of the United States. 20th Century Statistics.* 1999.

Along similar lines, an extensive perspective of the impact of the introduction of vaccines in France is presented in Appendix I.

As a matter of fact, global vaccination coverage against numerous childhood infectious diseases has increased drastically in the last few decades. However, these achievements would have not been possible without the creation and active implication of international organizations.

The origin of the modern global immunization system lays in diverse World Health Assembly resolutions that emerged in the 1970s. Based on the success of the global smallpox eradication program, the recognition of the great potential of vaccination in controlling communicable diseases as well as the fact that many children did not have access to vaccines in the developing world, the World Health Assembly decided to establish the Expanded Program of Immunization (EPI) in 1974, with the objective of developing global policies for vaccination and establishing the goal of providing universal immunization for children worldwide by 1990¹⁴.

By 1982, the slow progress attained in increasing access to vaccination led the United Nations Children's Fund (UNICEF), WHO member states and other international organizations to partake in organized efforts to reach the set objective. Hence, in 1984, additional actions were initiated to accelerate worldwide immunization coverage, with a reviewed objective of achieving 80% coverage of combined DTP, tuberculosis, oral polio and measles vaccines by 1990. Subsequently, the initiative allowed low-income and middle-income countries to be reached on a wider scale by immunization services and therefore by other healthcare interventions, leading to a substantial increase in immunization coverage (Figure 5). By 2005, the gap in vaccination uptake between low- and middle-income countries was erased, although coverage remained lower than in high-income countries.

¹⁴ **Levine O, et al.** *The future of immunization policy, implementation, and financing*. 2011.

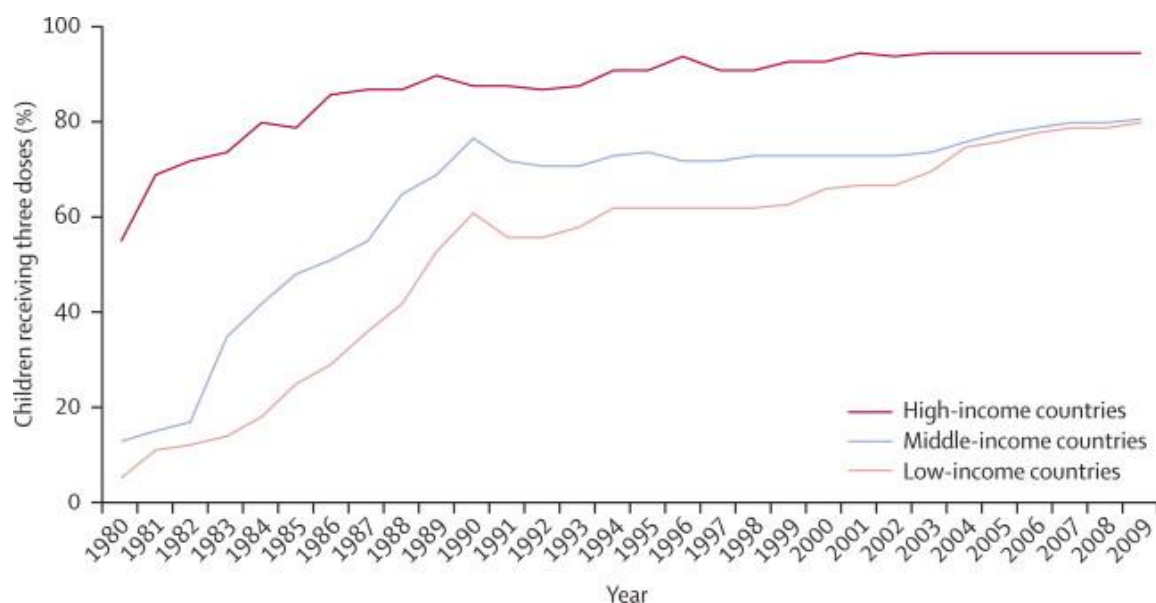


Figure 5 - Proportion of children younger than 1 receiving 3 doses of DPT vaccine, 1980-2009.¹⁴

For several decades, EPI has received sustained support and funding from national governments, donor organizations as well as international agencies such as the World’s Health Organizations or UNICEF, enabling large scale immunization programs and subsequently preventing millions of deaths and illnesses.

However as of the nineties, experience revealed weaknesses of the system, fragility of the gains and emerging challenges. Indeed, In spite of the promising progress made by the EPI in the previous two decades, approximately 30 million children living in poor countries remained not fully if not all immunized. Coverage was plateauing and even declining in some regions. Moreover, although new promising life-saving vaccines were becoming available on top of the original six EPI vaccines, virtually none were reaching infants in the developing world, those who needed them most, as they were too expensive to be affordable in those places.

It is within this context that the Global Alliance for Vaccines and Immunization (GAVI) was founded in 2000, with the objective of enhancing access to new and underused vaccines for children living in the world’s poorest countries¹⁵. With additional resources allocated to

¹⁵ The GAVI Alliance. *Gavi's mission*. 2017.

worldwide immunization, further progress has been achieved and global immunization coverage, defined by the percentage of infants receiving three doses of DTP vaccine before the age of one, was evaluated at about 82% in 2009¹⁶.

Since then, immunization services have strived to provide a continuous unique societal health impact. Polio has almost been eradicated and success in controlling measles made this infection another potential target for eradication. Besides, many other infectious diseases have incessantly been positively impacted by global access to vaccination, as presented in Figure 6.

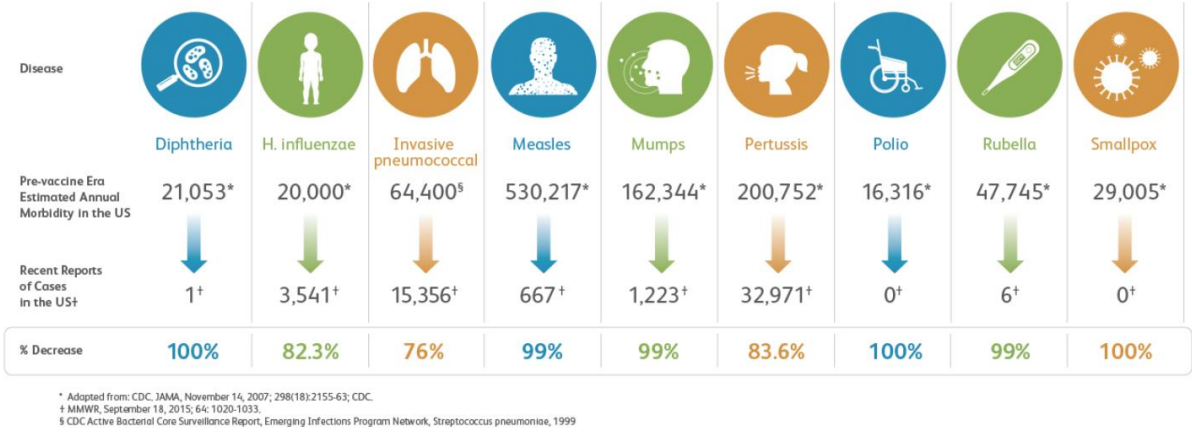


Figure 6 - Impact of vaccines on infectious disease morbidity in the US, Pre-vaccine era-2014.¹⁷

Van Panhuis et al. recently estimated that since 1924, immunization has prevented 103 million cases of childhood infection, corresponding approximately to 95 percent of infections that would have occurred in the meantime, including 26 million in the last decade alone¹⁸. Another possibility of evaluating the benefits achieved through vaccination is through Life Years Saved (LYS) and Disability Adjusted Life Years (DALYs). In her paper, J. Ehreth evaluates the impact of immunization based on these two indicators, and demonstrates the proven massive impact of vaccination on public health and ultimately on the countries’ economies (Table 2).

¹⁶ **The GAVI Alliance.** *GAVI helps DTP3 coverage rise after stagnation.* 2017.
¹⁷ **Pfizer.** *The Value of Vaccines in Disease Prevention.* 2014.
¹⁸ **Van Panhuis WG, et al.** *Contagious Disease in the United States from 1888 to the Present.* 2013.

Disease	US		Africa		Global	
	LYS	DALY	LYS	DALY	LYS	DALY
Smallpox ^a	1,685,740	NA	933,065	NA	5,000,000	NA
Polio ^b	212,690	NA	484,230	279,000	35,750,000	1,725,000
Measles ^c	5,811,852	26	2,125,500	17,463,000	71,500,000	29,838,000
Tetanus ^d	42,705	9	2,801,500	3,039,000	56,030,000	12,020,000

NA: not available.

^a Children's Vaccine Initiative, World Health Organization, 1995 MMWR, 2 April 1999. Note that the estimate of life years saved in the US is based upon 48,164 average deaths between 1900–1904 multiplied by 35-year life expectancy. JW Hopkins, *The Eradication of Smallpox*. Westview Press: San Francisco, CA, 1989. Estimate of life years saved in Africa based upon 26,659 deaths reported in 1971 multiplied by 35-year life expectancy.

^b Dr. Matthew McKenna at CDC; Murray and Lopez, *Global Burden of Disease, 1999*; Children's Vaccine Initiative, World Health Organization, 1995. Note: estimate of US life years saved is based on 21,269—average number of paralytic polio cases times an assumed 50% mortality rate between 1951–1954 times an assumed 20-year life expectancy (source: MMWR, 2 April 1999). Estimate of African life years saved is based on difference between 1999 polio cases (http://www.polioeradication.org/pdfs/polio_news_no7.pdf, Page 3) and 1988 cases (<http://www.ifrc.org/what/health/archi/fact/fpolerad.htm>) of 35,000–2718 times assumed 15-year life expectancy.

^c World Health Organization, 2000. Estimate of US life years saved based on 894,131 times a mortality rate at peak incidence of 10% times 65-year life expectancy. Estimate of African life years saved based upon estimate of 32,700 deaths prevented between 1998 and 2000 (<http://www.whoaf.org/ddc/vpd/2000tfi/measlescontrol/acceleratedmeaslescontrol.pdf>) times assumed 65-year life expectancy.

^d MMWR, International Notes Progress Toward the Global Elimination of Neonatal Tetanus, 1989–1993, vol. 43(48), 1994: 885–94 estimate of tetanus life years saved in the US is based on assumed 657 deaths prevented from peak incidence of 1314 and 50% mortality rate times 65-year life expectancy. Estimate of tetanus life years saved in Africa in 1993 based on estimate that 5% of world-wide tetanus deaths and deaths prevented occurred in Africa times 65-year life expectancy.

Table 2 - Benefits disease eradication and control by vaccination, in terms of annual life years saved (LYS) and disability-adjusted life years (DALYs) saved.¹⁹

Today, WHO estimates that immunizations save each year approximately 2.5 million lives from tuberculosis, diphtheria, pertussis, tetanus, polio, measles, hepatitis B, and Hib infections²⁰. Still according to WHO, an estimated 109 million infants under one were fully vaccinated with three doses of DPT vaccine in 2013 worldwide²¹.

In terms of economic impact, the implementation of recommended vaccination schedules as well as immunization programs in many countries have demonstrated to effectively prevent morbidity and mortality, and subsequently save millions of dollars each year in direct and indirect costs to healthcare systems²². As an example, the US Center for Disease Control (CDC) currently estimates that for each dollar spent in the US on childhood vaccination, healthcare systems save \$10.20 in disease treatment costs²³.

Immunization-related gains are diverse, both direct or indirect, as highlighted by table 3. In 2014, Zhou et al. published an analysis revealing that routine childhood immunization in the US

¹⁹ Ehreth J. *The global value of vaccination*. 2003.

²⁰ WHO, UNICEF, World Bank. *State of the world's vaccines and immunization*. 2009.

²¹ WHO. *World Immunization Week 2013*. 2013.

²² CDC. *Ten Great Public Health Achievements – United States, 2001-2010*. 2011.

²³ CDC. *Immunizations and Respiratory Factsheet*. 2017.

among the cohort of children born in 2009 was estimated to have prevented 20 million cases of disease as well as 42,000 early deaths, with subsequent net savings of \$13.5 billion in direct costs and \$68.8 billion in overall societal costs. According to Zhou’s findings, that makes direct and societal benefit-cost ratios for routine childhood immunization of 3 and 10, respectively²⁴.

Definition	
Narrow perspective	
Health gains	Reduction in mortality and morbidity through vaccination
Health-care cost savings	Savings of medical expenditure because vaccination prevents episodes of illness
Care-related productivity gains	Savings of parents’ productive time because vaccination avoids the need to take care of a sick child
Broad perspective	
Outcome-related productivity gains	Increased productivity because vaccination improves cognition and physical strength, as well as school enrolment, attendance, and attainment
Behaviour-related productivity gains	Benefits accrued because vaccination improves child health and survival and thereby changes household behaviour
Community external factors	Benefits accrued because vaccination improves outcomes in unvaccinated community members

Table 3 - Benefits in economic evaluations of childhood vaccinations.¹⁴

On a wider scale, immunization helps save tremendous amount of dollars by avoiding infectious disease-related expenses. Researchers at Johns Hopkins University calculated that savings from short-term costs of treatment could reach \$1.4 billion over the next ten years while savings from lost wages of caretakers’ would represent about \$313 million. Finally, they estimate that averting the long-term economic burden of lost productivity due to both disability and death may add up savings of \$61 billion to these economies in the long term²⁵. Today, a healthcare intervention is considered as cost-effective if it offers a year of healthy life for less than the country per-capita Gross National Product (GNP). As an illustration, immunizations currently usually cost less than US\$50 per healthy life saved¹⁹.

²⁴ **Zhou F, et al.** *Economic Evaluation of the Routine Childhood Immunization Program in the United States.* 2009.

²⁵ **International Vaccine Access Center at Johns Hopkins Bloomberg School of Public Health.** *Vaccines Work: Key Facts and Figures.* 2010.

Despite these elements of success, many challenges remain and numerous children still die each year from vaccine-preventable infectious diseases, including pneumonia, diarrhea and measles (Figure 7). As the world’s most powerful immunization-associated organization, the Bill & Melinda Gates foundation estimates today that an additional 7.6 million children lives could be saved in the current decade if vaccination uptake could be scaled up to 90%²⁶.

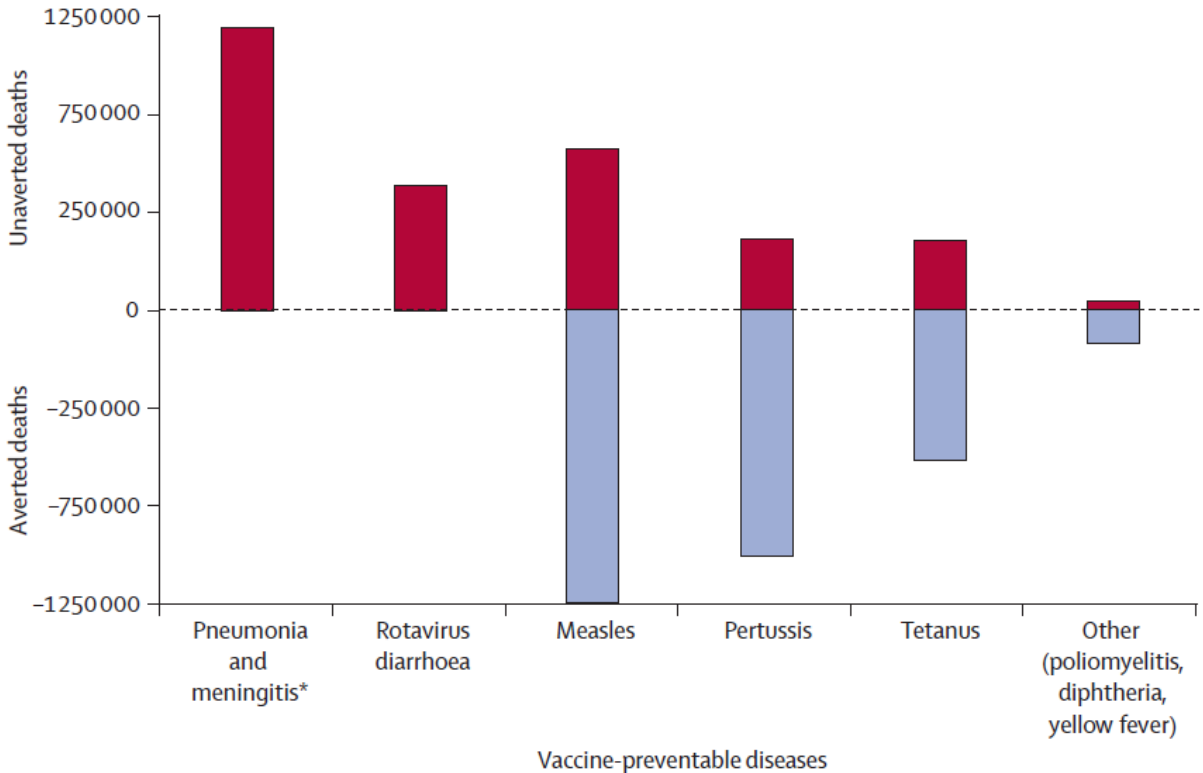


Figure 7 - Global annual estimates of deaths averted and still happening from vaccine-preventable diseases in children younger than 5; 2000-2004.¹⁴

Development of recent vaccines and current research against more complex infections such as HIV, malaria or Ebola infection have been challenging and achievements so far are modest in spite of continuous stringed efforts. Key lessons from recent history include the recognition that ambitious goals must be accompanied with sustained efforts to establish and maintain strong systems for vaccine delivery, surveillance and monitoring.

²⁶ Horton 2011, et al. *The vaccine paradox*. 2011.

vi. Present Vaccination Coverage of Common Vaccines

In order to monitor and assess the improvement being made worldwide in terms of vaccines development and global access to immunization, coverage with the third dose of DTP vaccine (DTP3) is an indicator of vaccination program performance²⁷. More broadly, coverages of additional vaccines such as the ones protecting against tuberculosis (BCG), polio, measles (first dose MCV1 and second dose MCV2), hepatitis B (birth dose HepB BD and three doses HepB3), Hib (three doses Hib3), rotavirus and pneumococcal pneumonia (three doses PCV3) are constantly monitored worldwide to assess the effectiveness of immunization programs and services.

WHO and UNICEF monitor and estimate annual coverage through an annual review of all available immunization-related data coming from the countries, including administrative material and survey-based information²⁸. The administrative coverage for a given antigen is defined as the number of vaccine doses administered to individuals in a specific target group divided by the number of individuals in the target population. Survey-based estimation is mostly used in less advanced countries. A significant sample of households are visited and inhabitants in care of children of a specified age group are interviewed. Vaccination dates are obtained from the child's home-based record, from healthcare facility records as well as directly from the caregiver recall. Survey-based vaccination coverage is defined as the proportion of individuals in a target age group who received a vaccine dose.

To ensure equity of vaccination coverage despite the difference in country profiles, countries were categorized by World Bank income classification which is based on the 2015 per capita gross national income²⁹ as well as eligibility for financial support from the GAVI Alliance for new vaccine introduction since 2005.

²⁷ **Burton A, et al.** *WHO and UNICEF estimates of national infant immunization coverage: methods and processes.* 2009.

²⁸ **WHO.** *Immunization, Vaccines and Biologicals – data, statistics and graphs.* 2016.

²⁹ **The GAVI Alliance.** *Countries eligible for support.* 2016.

In 2012, as part of a so-called Decades of Vaccines, the World Health Assembly endorsed the Global Vaccine Action Plan (GVAP) 2011–2020. Through this plan, countries were being called on to reach over 90% national coverage and over 80% coverage in every district for every vaccine present in the country's national immunization schedule³⁰.

According to the 2015 WHO and UNICEF estimates, worldwide vaccination coverage for DTP3, BCG, MCV1 and Pol3 increased from less than 5% at the time when the EPI was established in 1974 to over 85% in 2015 (Table 4).

Vaccination coverage (%) by WHO Region ^b – Couverture vaccinale (%) par Région OMS ^b								
Antigène – Antigen	No. of countries – Nbre de pays	Global – Ensemble du monde	AFR – AFRO	AMR – AMRO	EMR – EMRO	EUR – EURO	SEAR – SEARO	WPR – WPRO
BCG	158	88	80	95	87	89	87	96
HepB BD – DN de HepB	97	39	10	72	23	39	34	83
HepB3	185	84	76	89	80	81	87	90
DTP3 – DPC3	194	86	76	91	80	93	87	94
Hib3	191	64	76	90	80	77	56	25
Pol3	194	86	76	91	80	94	86	96
Rota last – Rota der.	84	23	41	76	21	18	0	1
PCV3 – VPC3	129	37	59	85	48	48	5	11
MCV1	194	85	74	94	76	94	85	96
RCV1	147	46	12	94	45	94	14	89
MCV2	160	61	18	53	68	89	71	93

AFR = African Region; AMR = Americas Region; EMR = Eastern Mediterranean Region; EUR = European Region; SEAR = Southeast Asian Region; WPR = Western Pacific Region. – AFR = Région africaine; AMR = Région des Amériques; EMR = Région de la Méditerranée orientale; EUR = Région Européenne; SEAR = Région de l'Asie du Sud-Est; WPR = Région du Pacifique occidental.

BCG = Bacille Calmette-Guérin; HepB BD = birth dose of hepatitis B vaccine; HepB3 = 3 doses of hepatitis B vaccine; DTP3 = 3 doses of diphtheria-tetanus-pertussis vaccine; Hib3 = 3 doses of *Haemophilus influenzae* type b vaccine; Pol3 = 3 doses of poliovirus vaccine; Rota last = last dose of rotavirus series; PCV3 = 3 doses of pneumococcal conjugate vaccine; MCV1 = first dose of measles-containing vaccine; MCV2 = second dose of measles-containing vaccine; RCV1 = first dose of rubella-containing vaccine. – BCG = Bacille Calmette-Guérin; DN de HepB = dose de naissance de vaccin contre l'hépatite B; HepB3 = 3 doses de vaccin anti-hépatite B; DTC3 = 3 doses de vaccin antidiphthérique-antitétanique-anticoquelucheux; Hib3 = 3 doses de vaccin contre *Haemophilus influenzae* type b; Pol3 = 3 doses de vaccin contre les poliovirus; Rota der. = dernière dose de la série de vaccinations contre les rotavirus; VPC3 = 3 doses de vaccin antipneumococcique conjugué; MCV1 = première dose de vaccin contenant une valence rougeole; MCV2 = deuxième dose de vaccin contenant une valence rougeole; RCV1 = première dose de vaccin contenant une valence rubéole.

^a Number of countries including specified vaccine in routine immunization schedule. – Nombre de pays incluant les vaccins spécifiés dans leur calendrier de vaccination systématique.

^b Weighted regional average. Coverage based on all countries listed in region or globally, including those that have not yet introduced a given vaccine. – Moyenne régionale pondérée. Couverture basée sur tous les pays de la Région ou dans le monde, y compris ceux dans lesquels un vaccin déterminé n'a pas encore été introduit.

Table 4 - Vaccination coverage by vaccine and WHO Region, worldwide, 2015.³¹

Beyond the traditional four EPI vaccines, WHO demonstrated that global coverage significantly increased from 2010 to 2015 for a completed series of vaccines, such as rotavirus vaccine (8%–23%), pneumococcal conjugate vaccine (PCV) (11%–37%), rubella vaccine (35%–46%), *Haemophilus influenzae* type b vaccine (42%–64%) and hepatitis B vaccine (74%–84%).

³⁰ WHO. *Global Vaccine Action Plan 2011–2020*. 2017.

³¹ WHO. *Global routine vaccination coverage*. 2015.

However, despite the undertaken efforts to ease the access to vaccination, coverage estimates in low-income countries remain lower than in other country income groups in 2015 (Table 5).

Countries by World Bank income classification^a – Pays classés par la Banque mondiale en fonction de leur revenu^a	MCV1	MCV2	DTP3	Polio3	HepB3	Hib3
High (56) – Revenu élevé (56)	51 (91)	33 (59)	55 (98)	53 (95)	41 (73)	53 (95)
Upper-middle (57) – Revenu moyen supérieur (57)	41 (72)	29 (51)	40 (70)	37 (65)	41 (72)	32 (56)
Lower-middle (50) – Revenu moyen inférieur (50)	22 (44)	14 (28)	23 (46)	24 (48)	22 (44)	22 (44)
Low (31) – Revenu faible (31)	5 (16)	1 (3)	8 (26)	8 (26)	8 (26)	8 (26)

DTP3 = 3 doses of diphtheria-tetanus-pertussis vaccine; HepB3 = 3 doses of hepatitis B vaccine; Hib3 = 3 doses of Haemophilus influenzae type b vaccine; MCV1 = first dose of measles-containing vaccine; MCV2 = second dose of measles-containing vaccine; Pol3 = 3 doses of poliovirus vaccine. – DTP3 = 3 doses de vaccin antidiphtérique-antitétanique-anticoquelucheux; HepB3 = 3 doses de vaccin anti-hépatite B; Hib3 = 3 doses de vaccin contre Haemophilus influenzae type b; MCV1 = première dose de vaccin contenant une valence rougeole; MCV2 = deuxième dose de vaccin contenant une valence rougeole; Pol3 = 3 doses de vaccin contre les poliovirus.

^a The World Bank income classification based on countries' per capital gross national income in 2015. – Le classement des pays par la Banque mondiale selon leur revenu se base sur le revenu national brut par habitant en 2015.

Table 5 - Number of countries reaching a 90% national coverage of MCV1, MCV2, DTP3, Pol3, HepB3 and Hib3 vaccines, by country income classification, 2015.³¹

Thus, strong and mutual commitment from governments along with the collaboration of multiple key global organizations have distinctly led to an increase in the number of children receiving fundamental vaccines, and this trend is intended to be maintained. Since 2000, more than 70 low- and middle-income countries have benefitted from GAVI support with the objective to increase equitable use of vaccines, both by enhancing health system capacity and accelerating the use and uptake of recent and underused vaccines³².

Vaccination has revolutionized disease prevention and quickly established itself as one of the greatest milestone of modern medicine. Concomitantly, it brought together a large number of diverse stakeholders with various interest, and also opened vast opportunities for business.

³² WHO. *Weekly epidemiological record*. 2016.

B. The Vaccine Business

i. The Vaccine Specific Market

After enjoying a so-called “golden age of the pharmaceutical industry”³³ in the past decades, companies in the pharmaceutical sector are currently facing diminishing growth prospects due to a declining research and development productivity strengthened by generics competition for off-patent products, as well as an increased regulatory scrutiny and an ever growing pressure on pricing from payers. Conversely, the vaccine sector that was earlier considered as a low-margin, low-growth industry, appears today as an increasingly attractive market characterized by strong growth prospects, an increased and promising R&D activity as well as higher valuations from the capital markets³⁴. Over the last decade, market expansion, realistic pricing, enhanced advocacy as well as wise health priorities have contributed to attract substantial new investment into the industry, driving a so-called “vaccine renaissance”³⁵.

In contrast with the biopharmaceutical market, the specific vaccine market stands as a relatively small and concentrated market, particularly on the supply side. One of its key characteristic relies on the fact that it is highly regulated and mostly dependent on public tenders and donor policies, although the private market is gaining importance within the developed countries. The vaccine market presents distinct features that lead to an increased complexity in assessing and understanding procurement and pricing for vaccines. In particular, the overall vaccine market is made up of many diverse individual markets for different vaccines or vaccine types, each presenting their own specificities, both on the supply and demand sides, but all being much consolidated grounds with giants vying for market share.

Today, we observe a continuous movement within the individual vaccine markets. As science enables the development of new vaccines, countries decide to introduce the latter alongside

³³ **Thepharmaletter**. *Golden Age of pharmaceutical industry*. 1999.

³⁴ **Cucurella J**. *The worldwide vaccine market: what are the main challenges with a full conversion toward pre-filled syringes?* 2009.

³⁵ **Smith J, et al**. *Vaccine production, distribution, access, and uptake*. 2011.

changing preferences for so called traditional vaccines. Up until recently, high-income countries were the only purchasers of complex and higher-priced vaccines while low- and most of the middle-income countries were mostly purchasing more mature vaccines and presentations. Today however, the trend is towards an increased convergence in the demand for newer vaccine types, simultaneously with a divergence in the demand for more mature and combination vaccine types, thus sustaining a dynamic and complex business environment.

From a demand perspective, the main buyers in the vaccine market are mostly governments of industrialized and developing countries, pooled procurement agencies such as UNICEF, the GAVI Alliance and the Pan American Health Organization (PAHO) revolving fund, the private sector as well as the various national regulatory authorities in countries, overseeing vaccine quality and safety.

From a supply perspective, only a limited number of vaccine manufacturers worldwide meet the international rigorous standards of quality for vaccine supply due to the stringent regulations established by WHO and other local authorities. Hence, an estimated 80% of global vaccine sales are currently manufactured by four large multi-national corporations that have arisen from various mergers and acquisitions of previous vaccine companies in the past decades³⁶. Today, most of these individual vaccine markets are monopolies or oligopolies, and barriers to entry are very high for potential new competitors.

Also, the limited number of vaccine producers and actual production capacities sustains a fragile balance between demand and supply in the diverse individual vaccine markets. Ensuring a sufficient supply of vaccines for all purchasers worldwide requires a continuous management as well as an efficient communication among all market players.

Nevertheless, the situation is changing with a growing number of vaccine manufacturers based in developing countries and the new investment by multinational companies in vaccine R&D. As an illustration, only three of the present top ten pharmaceutical companies had substantial

³⁶ WHO. *Immunization, Vaccines and Biologicals*. 2017.

activities in vaccines in 2005. Conversely today, this number is now eight of the top ten. Vaccines are increasingly considered as an attractive and sustainable business for a number of reasons.

First, the demand for vaccines has grown particularly over the last decade and looks certain to grow further. Second, numerous medical needs remain unmet and vaccines still do not exist for a number of critical disease targets. Third, innovative financing methods and programs have significantly contributed to expand markets, especially in the developing countries. Fourth, notable advances in microbiology and immunology along with an increased understanding of pathogenesis enable effective research and development on previously intractable targets. Last but not least, the vaccine business has not suffered from the sharp decline in revenues from expiry of patents that are plaguing much of the rest of the pharmaceutical industry. Part of the explanation driving this last point lays in the fact that vaccines are less easy to manufacture and not as much licensed generically as compared to small drug molecules. This is because it is the production processes in addition to the vaccines themselves that are approved and licensed by regulatory authorities. Hence, required R&D investment, industrial know-how as well as the remaining associated costs provide high barriers to entry for potential new comers. In addition, established vaccine companies benefiting from a range of already licensed antigens are better able to produce and commercialize combination vaccines. Yet, the will of countries along with support from governments to be self-sufficient in the production of fundamental vaccines has led to the development and expansion of diverse local producers.

Besides, one of the major trends being observed within the vaccines market is the notable increase in strategic partnerships and alliances. As a matter of fact, the increased threat coming from regional manufacturers in developing markets will increasingly contribute to price erosion and therefore compel major companies to operate under low-margin models. In this context, mergers and acquisition are usually completed in order to either increase the market penetration of the acquirer or to expand its product portfolio.

ii. Common Market Segmentation

The vaccine market, besides being divided into distinct individual vaccine markets, is furthermore commonly segmented in distinct branches –or segments- according to the perspectives at stake. Thus, common segmentations of this business includes a segmentation based on the vaccine recipient's age group and another one based on the payer types.

From a recipient's perspective, human vaccines are usually divided into four segments, which correspond to pediatric, adolescent, adult and traveler vaccines. While pediatric vaccines currently represent a large majority of the market due to their inclusion in designed standard immunization programs within countries, adolescent and adult segments are currently of strong interest for vaccine companies with the development of new vaccines such as the ones protecting against meningitis or zoster. The traveler segment stands aside, targeting in priority the developed countries with a high consumer purchasing power.

From a payer perspective, the vaccine market is generally divided between three distinct segments, which are the public market segment, the private market segment and the funded market segment. Each of these presents its own characteristics and function on its own model.

The public market segment is characterized by the implication of worldwide Governments. In this model, the payer for a given vaccine is a national Government who buys considerable amounts of doses in order to provide the citizens with the vaccine of interest for free or partially funded. Pediatric vaccines in numerous developed countries usually fall into this market of funding.

Within the private segment market, the payer is the recipient of the vaccine itself. Typically in less advanced countries, many vaccines fall into the scope of this market, also called "out-of-pocket" market. However, even vaccines in most developed countries can be part of this private segment, especially when the vaccine is not included in a national immunization schedule or when a patient does not meet the defined criteria required to receive a vaccine for free, funded

by the public sector. In particular, aged-based or risk-based criteria are often critical with regard to this segment.

Finally, the funded market segment is a key segment where the payers are generally non-governmental organizations such as UNICEF, but also global health partnerships such as the GAVI Alliance, receiving financial as well as organizational support from donor governments, private sector philanthropists, vaccines manufacturers, research institutes and multilateral organizations such as WHO and the World Bank. All these stakeholders are pursuing the goal of improving healthcare access for individuals worldwide. Hence, this segment is particularly important for the low- and middle-income countries often lacking efficient national healthcare and immunization systems.

iii. Market Size and Forecasts

According to market research firm Xerfi, worldwide pharmaceutical sales accounted for a value of €1.1 trillion in 2016 and are expected to grow at an average annual rate of 4-5%, exceeding €1.3 trillion by 2020³⁷. Within an increasingly challenging environment for the industry, the vaccine business does well compared with other therapeutic areas and investment within this business appears today as an attractive strategy for many big pharmas. The recurring incidence of epidemic diseases along with increased pandemic threats as well as favorable government initiatives appear as sustainable factors driving the growth of the global vaccines market. Besides, notable advancements in biotechnologies have significantly lowered the cost of vaccines and opened the field of possibilities.

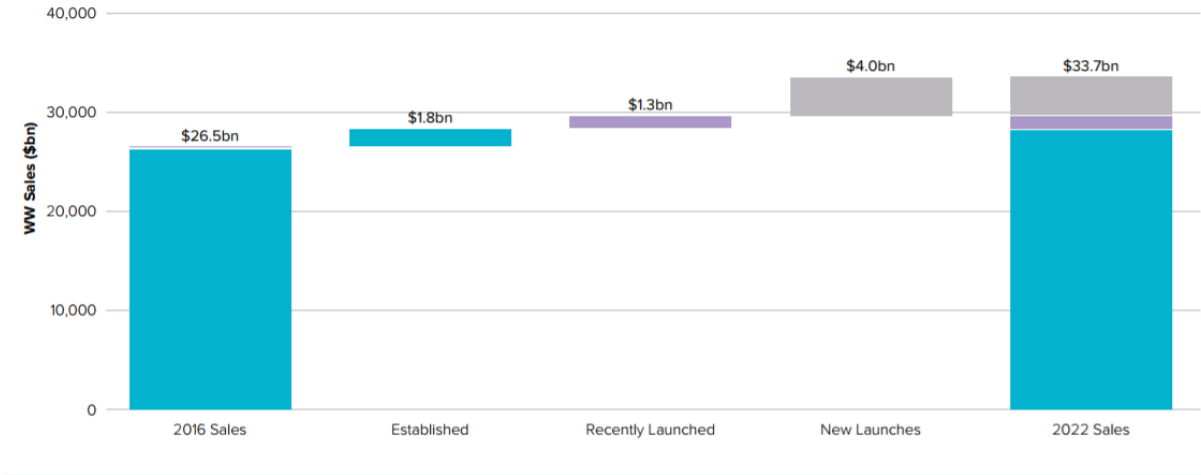
In 2016, the global preventive vaccines market amounted to US\$ 27 billion compared with \$6 billion in 2000 and is expected to reach US\$ 34 billion by 2022, growing at a compound annual growth rate (CAGR) of 12.4% during this forecast period^{38,39}. Furthermore, this growth is expected to be supported by a strong R&D investment, estimated to account for 15% of the

³⁷ **Xerfi Global.** *Pharmaceutical Groups – World.* 2016.

³⁸ **Mordor Intelligence.** *Preventive Vaccines Market - Trends and Forecasts (2017 - 2022).* 2017.

³⁹ **EvaluatePharma.** *World Preview 2017, Outlook to 2022.* 2017.

figures above-mentioned for the vaccine business⁴⁰. In its last report published in June 2017, research firm EvaluatePharma forecasted that new launches contribution will account for over 50% of the sales growth in 2022 (figure 8), making the vaccine business a lucrative ground in which to invest for pharmaceutical firms.



Note: Totals in chart above reflect sum of reported or forecasted product level company sales. These may not tally with company segment sales in previous tables. Established: launched prior to 2014 | Recently launched: 2014 to 2016 inclusive | New launches: launch expected after 2016 | 2016 and 2022 sales reflect the sum of these categories.

Figure 8 – Global Forecasted Product Segment Contribution to Sales in 2022.³⁹

Amongst the key regions serving the vaccine business worldwide, North America and Europe are expected to be lucrative markets throughout the forecast horizon. Growth in these regions will mainly be attributed to the increasing initiatives from governments to promote and support immunization programs against diseases such as influenza, pneumococcal pneumonia and HPV, along with a growing number of public and private organizations pouring funds into the research and development of novel vaccines and presentations.

For its part, the Asia Pacific region is anticipated to grow at a noteworthy CAGR over the same period, primarily owing to an expanding base of patients coupled with still high unmet medical needs. Emerging markets such as India and China are expected to be the major revenue contributors to the growth of the region. The rising disposable income as well as growing

⁴⁰ Moxon E, et al. *The next decade of vaccines: societal and scientific challenges*. 2011.

awareness with regard to the availability and benefits of vaccines will keep fueling the growth of the region⁴¹.

iv. Main Players

Within the global human vaccines business, four companies are widely recognized as the key players: Sanofi Pasteur, GlaxoSmithKline, Merck & Co. and Pfizer. Their vaccine business has been continuously strengthened through acquisitions, mergers and other strategic partnerships such as joint-ventures. Today, despite their similarities in the level of investment and performance in the vaccines space, the four competitors strive to differentiate from one another and use different implementation strategies as described hereinafter.

Sanofi Pasteur⁴²

Sanofi Pasteur corresponds to Sanofi's operating unit for vaccines. It is considered to be the world's largest vaccines provider by volume with over 1 billion doses of vaccines sold in 2016, generating net global sales of US\$ 5,065M. Until 2017, Sanofi Pasteur MSD (SPMSD) was a 50/50 joint venture partnership between Sanofi Pasteur and MSD (Merck). The purpose of this joint venture was for the development and commercialization of Sanofi Pasteur and Merck's vaccines exclusively for 19 countries within Europe. The partnership, which generated net sales of \$1 billion in 2016, was terminated on 31 December 2016.

Sanofi Pasteur has a broad portfolio of vaccines sold mainly in the US but also strongly addressing emerging markets. Key vaccines in the portfolio are influenza and polio vaccines both with close to €1.5 billion of revenue. Further public strategies include the will to maintain the leader position in the influenza market in Europe and the US by focusing on innovative approaches, to produce more and to increase R&D focused on tropical diseases and vaccines to address therapeutic areas with high unmet needs.

⁴¹ **Transparency Market Research.** *Vaccine Market - Global Industry Analysis, Size, Share, Growth, Trends and Forecast 2014 - 2020.* 2014.

⁴² **Sanofi.** *Company Annual Report.* 2016.

Worldwide, Sanofi Pasteur is particularly benefiting from favourable government funding for vaccines development and immunization programmes, a rise in global travel traffic as well as an increase in awareness on vaccine preventable diseases and in spending power of emerging economies. Thus, Sanofi Pasteur has been heavily investing in external growth over the past few years

From a constraint perspective, increasing competition from local manufacturers in densely populated and economically emerging regions are leveraging their cost/volume advantage as well as raising their level of technical capabilities and quality standards. Besides, cost containment measures from payers and governments also appear as a current barrier to market growth.

GlaxoSmithKline⁴³

Strengthened by it's the recent acquisition of Novartis' vaccines business in 2015, GSK currently offers the largest and most competitive vaccine portfolio with 41 vaccines that offer protection against 22 diseases. Key vaccines in the portfolio include paediatric combination vaccines as well as flu and hepatitis vaccines. Building on its expertise, GSK shows its ambition to progressively shift towards yet partially unmet markets by exploring new segments and expanding marketed vaccines indications. Other opportunities GSK has identified include growing target populations (elderly) and underserved populations.

For the longer term, areas of interest are likely to remain with novel infectious disease vaccines. Besides, GSK is expected to continue augmenting this key franchise with further in-licensing activity and strategic acquisitions. Its vaccines business is aligned with GSK's volume-based strategy, with over 70% of its vaccines being distributed in emerging markets at much lower cost than elsewhere, while 31% of revenue generated by vaccines comes from Europe.

⁴³ **GlaxoSmithKline.** *Company Annual Report.* 2016.

As part of its current strategy to simplify its operating model, strengthen its manufacturing network and reduce supply costs, GSK remarkably enjoyed a high operating profit margin of 31.6% in 2016, 5.3 points higher than in 2015.

Potential barriers to GSK business include the fact that the company's focus on emerging markets means that revenues and margins will be considerably lower than competitors. Furthermore, the unpredictability of the specific flu market results in large swings in revenues that strongly impact GSK's top-line.

Merck & Co (MSD)⁴⁴

Merck is the leading player in the vaccines market with a market share of approximately 20% in 2016. Merck's vaccines portfolio consists of preventive pediatric, adolescent and adult vaccines. To date, it has not invested significantly in the travel vaccines segment and most of its currently available vaccines are mature products. Therefore, the company has built a pipeline of late-stage programs to drive near-term growth and help make it the second-largest therapeutic franchise by 2023. Besides, the company supplements its R&D activities with a strong licensing and external alliance strategy, which focuses on making collaborations from early research to late-stage compounds.

The company's flagship vaccine, Gardasil, is a strong performer – the second biggest selling vaccine globally. Due to greater HPV strain coverage (thus broader indication), it far outsells its competition, Cervarix (\$2,2 billion vs \$81 million of revenue in 2016). Committed to strengthening its position in vaccines, Merck has been intensively investing in the development of both novel vaccines and “next generation products”: developing Gardasil 9, anticipated to realize sales of \$2.8 billion in 2023 (36% of total vaccines sales). Merck's pediatric vaccines franchise is the next-largest revenue generator, although negatively impacted by supply issues on a recurring basis.

⁴⁴ Merck & Co. *Company Annual Report*. 2016.

With only four vaccines in development, Merck's pipeline is limited in comparison to its key competitors. Current marketed vaccines and those in development suggest Merck's strategy to operate in high volume yet competitive markets. Hence, sales performance are expected to grow primarily by higher volumes and/or pricing in the US as well as higher demand in some emerging markets. However, although the company has been working to increase presence in emerging markets and actively sought government tenders in areas such as Brazil, Latin America and Asia Pacific, it may not be able to realize the expected benefits of its investments in those markets.

Pfizer⁴⁵

Pfizer's presence in the vaccine market changed dramatically with its acquisition of Wyeth in October 2009. Through the acquisition, Pfizer gained several vaccines and vaccine candidates, including the blockbuster Prevenar, the follow-on Prevenar 13, and a meningitis B vaccine development program that led to the launch of Trumenba. Pfizer's Prevenar franchise generated close to \$6b in sales in 2016, making it by far the best-selling vaccine brand.

Upon the integration of the Wyeth business in 2009, Pfizer quickly found a blockbuster franchise capable of offsetting some of the expected declines from the generic erosion to many of its small-molecule blockbusters. As a result, it is expected that the vaccines franchise become Pfizer's second-largest therapeutic franchise by 2023.

As the more recent player in the vaccine business, Pfizer currently commercialize six vaccines for three diseases in scope. Despite its reduced portfolio, Pfizer benefits from one of the largest vaccine revenues amongst an average geographical scope. It is notably the largest pneumococcal conjugated vaccine producer, supplying 70% of the global market with previously acquired Prevenar 13.

⁴⁵ **Pfizer Inc.** *Company Annual Report*. 2016.

With a reduced number of three vaccines in its pipeline, Pfizer focus is given in priority to novel bacterial targets. Relative to competitors, Pfizer invested a lower proportion of its global vaccines revenue into R&D in 2016 (6%), and with the limited company's late-stage pipeline, the success of Prevenar 13 will be critical to the future growth of Pfizer's vaccine portfolio. Central to Prevenar 13's success is notably its inclusion in national immunization programs outside of the United States.

Following its successful acquisition of Wyeth -propelling Pfizer into a key vaccine player- the company is pursuing further M&A, licensing, partnerships and product acquisitions with the objective to expand its presence and portfolio, particularly in emerging markets. Company management has stated that biologics and vaccines will be a key focus area for Pfizer in the future. As a result, Pfizer is expected to continue building upon Wyeth's legacy in vaccines through the formation of research collaborations with smaller specialty companies such as Phylogica (2010).

v. Challenges for Future Evolution

The remarkable past achievements and the thrilling forecasts for development and commercialization of improved and new vaccines however does not come without a price. Also, a realistic appraisal of the current situation is now tempered with the many challenges faced by the vaccine industry now and in the long term.

From a science perspective, vaccines are a never ending challenge as microbes are constantly evolving and mutating, therefore obliging scientists and industrials to develop further formulas and presentations. Furthermore, vaccine safety issues now massively heighten the scope of criteria governing vaccine public acceptability. As vaccines are pharmaceuticals mostly given to healthy individuals in order to confer future protection, safety is absolutely paramount and cannot be jeopardized. Increasingly, safety concerns are affecting an already complex and costly R&D process. Final achievement of a tolerable balance or benefit and risk remains a major

challenge and no vaccines can be exempted from the risk of adverse events. Besides, gathering the relevant data in the case of safety issues takes time and resources, and anxieties are often largely disseminated in society during that time. Finally, as immunization stands as a key element driving global efforts to improve public health in the most cost-effective manner, building sustainable policies and financing of global programs will be an increasing challenge in the next decades.

As one looks to the future of vaccination, it appears clear that global landscape of the vaccine business is undergoing substantial changes. The world is far more closely tied together than ever before. The spread of pathogens, but also of information as well as misinformation is faster than ever. As advocates of immunization continue to strongly engage with society, a fair appraisal to the contemporary and evolving environment is key. Freedom of speech is more and more considered as a fundamental right, irrespectively of content accuracy. Misinformation is a threat that needs to be addressed urgently to allow vaccine recipients build opinions on reliable facts and trust healthcare professional. Beyond the demonstrated and unequivocal benefits of immunization, how should one communicate with people who are skeptical or even opposed to vaccination?

Lessons from behavioral economics and other contemporary challenges such as the ones raised with genetically modified organisms or climate change could help apprehend these problems. Just like in every debate, balance is key, and the benefits of immunization should be acknowledged simultaneously with the possible adverse outcomes. However, although policy development and public discussion must rely on evidence, immunization perception falls to a greater extent into the hands and beliefs of consumers and media. Blindly champion the proven benefits of immunization to a world bringing together individuals differing by their sex, age, culture, education, religion, socio-economic status as well as aspirations is not a side issue. Providing society with clear and authoritative information is not sufficient anymore. Horizons must be expanded and an enhanced understanding of the variety of behavioral responses should

be increasingly considered. Divergence in risk perception along with theories underpinning cooperation and altruism are some examples of components that justify the diversity in vaccine acceptance, concomitantly to the rise of vaccine hesitancy, which appears today as one of the biggest threat for a whole business.

II. Vaccination Perception and Behavioral Economics

A. Vaccine Hesitancy

i. Definition and Examples

As a matter of fact, vaccination, which was once complimented as one the greatest public health breakthrough, is losing public confidence. Increasingly, vaccination decision process and vaccine acceptance are not driven exclusively by scientific or economic evidence alone. Instead, they are the result of an associated mix of emotional, psychological, sociocultural and political factors, which need to be further explored and taken into account by vaccine-related institutions and policy makers when promoting immunization within populations. Today, experts refer to this decline in vaccine confidence as “the crisis of vaccine hesitancy”. In a changing global environment with numerous characteristics contributing to an increased public inquiring of vaccines, there is a significant gap between current level of public trust in vaccines and level of confidence needed to ensure a sufficient and sustained vaccination coverage.

In today’s society, vaccine hesitancy is not a rare phenomenon or limited only to a small group of “anti-vaccinationists”. On the contrary, it includes many individuals who have not yet rejected vaccines. Therefore, focusing only on vaccination uptake and neglecting underlying perceptions and attitudes would likely be a mistake as it would strongly underestimate the current challenge of maintaining vaccination coverage in the future.

An example of vaccine hesitancy described above is illustrated by UK doctor Wakefield’s claims in the late nineties that the MMR vaccine would cause autism⁴⁶. The parents’ eagerness to find answers and reasons to their child’s illness led Wakefield’s statements to be embraced by a small community, establishing a wave of distrust towards this specific vaccine. Although numerous studies proved Wakefield’s findings to be unfounded and his research paper was formally retracted, the distrust engendered around the MMR vaccine remained in the population’s mind

⁴⁶ **Larson HJ, et al.** *Addressing the vaccine confidence gap*. 2011.

and even crossed borders, contributing to substantial declines in vaccine coverage and subsequent MMR outbreaks.

Another example lies in the numerous associations that have been raised as of the nineties between vaccines and incidence of auto-immune disorders⁴⁷. In the absence of valuable data supporting their hypothesis, anti-vaccine activists in France started in 1994 to spread the idea that hepatitis B immunization was causing multiple sclerosis among adolescents and young adults, and severely advocated a country shutdown of the vaccine among this age group. In response to the increasing pressure from these groups and the public in this affair, the French Government decided to suspend the immunization program in 1998, despite the recommendations of WHO and the lack of evidence supporting the activists' claims. A few years later, after it became clear that such link was unfounded and that the hepatitis B vaccine was safe, the program was reinstated by the Government. Yet, the strong impact of the case on public's perception concomitantly to a poor communication led levels of hepatitis B vaccine acceptance in France to fall dramatically.

More recently, a similar public matter was raised worldwide, sustaining that HPV vaccination was causing demyelination syndromes, again in the absence of plausible evidence supporting causation. All these examples illustrate the vulnerability of public confidence in vaccine, and highlight the importance of intangible elements in trust-building process and rise in vaccine hesitancy.

To address this concern, the Strategic Advisory Group of Experts (SAGE) on immunization -an entity established in 1999 by the General Director of WHO with the objective of providing guidance with regard to vaccines and immunization- decided in 2012 to create a working group specifically dedicated to vaccine hesitancy. The first tasks of the working group consisted in defining clearly the phenomenon of vaccine hesitancy and its scope as well as developing a model of its determinants in order to establish a framework for further research.

⁴⁷ **Poland G, et al.** *Understanding those who do not understand: a brief review of the anti-vaccine movement.* 2001.

In its paper released in 2015, the SAGE working group agreed upon the definition that “vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence.”⁴⁸

ii. Scope

For many decades, acceptance of vaccination was the norm globally and therefore rarely discussed within the populations. Today however, a small but increasing number of individuals appears to agree to some vaccines but refuse others, while some delay vaccination or accept it but feel unsure in doing so. The concept of hesitancy is thus a continuum between individuals who accept vaccines completely and without doubts and others who refuse vaccines completely and without doubts. In between these two extremes are a set of heterogeneous individuals who are to some extent hesitant towards vaccines (Figure 9).

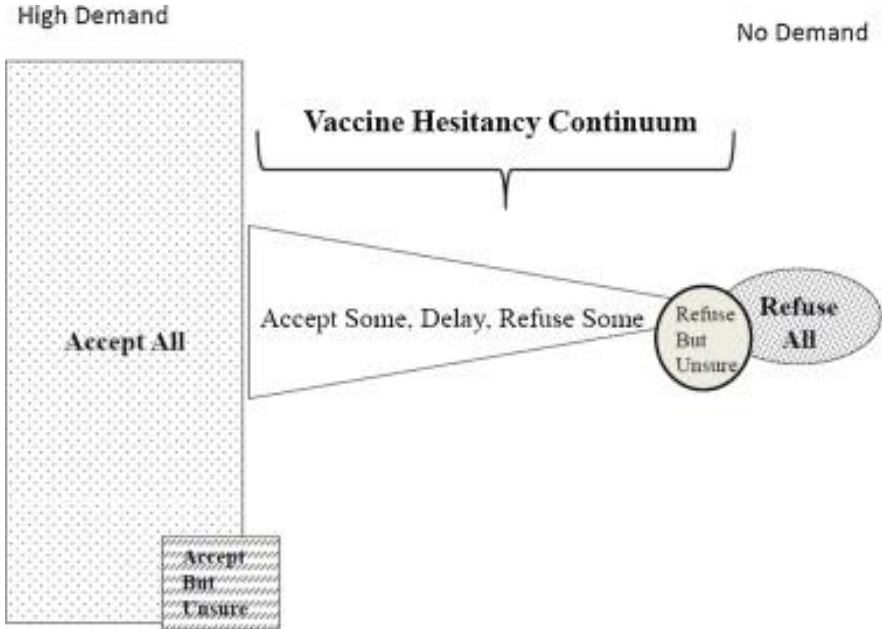


Figure 9 - The continuum of vaccine hesitancy between full acceptance and outright refusal of all vaccines.⁴⁸

⁴⁸ MacDonald ME, et al. *Vaccine hesitancy: Definition, scope and determinants*. 2015.

As a result, the scope of hesitancy has been further explored and it was emphasized that it is a behavioral phenomenon that is often vaccine and context specific, and which is measured against an expectation of a set vaccination coverage goal based on the immunization support and services available.

From a public health and economic perspective, differentiating hesitancy to from other reasons possibly leading to unvaccinated or under-vaccinated populations is key for being able to tackle this phenomenon.

Besides, the relationship between vaccine hesitancy and demand is complex and not completely congruent. Indeed, while high level of vaccine hesitancy leads to low demand of vaccines, low level of vaccine hesitancy does not necessarily lead to high vaccine demand. However, as hesitancy undermines demand, it is crucial for vaccine stakeholders to target vaccine hesitancy and take action in order to counteract actual trends.

iii. Determinants

Personal acceptance of vaccination appears to be an outcome behavior relying on a complex decision-making process that is influenced by a variety of internal and external factors. The SAGE working group proposed the “3 Cs” model to conceptualize the complexity of vaccine hesitancy, where the latter relies on both confidence, complacency and convenience factors.

Vaccine confidence is defined as the trust granted by individuals towards efficacy and safety of vaccines, but also towards health care services and health professionals dedicated to immunization, as well as the intentions of policy-makers who are in charge of the public decisions and vaccine manufacturers.

Vaccination complacency was defined as a behavior emerging when perceived risks of disease are low and vaccination is therefore not seen as a necessary and urgent preventive action. In this setting, complacency can be influenced by diverse factors, such as personal life and health responsibilities that may diverge between individuals and may be seen as more or less

important at a given point in time, as well as difference in risk perception and in the self-ability of individuals to take action and be vaccinated.

Vaccination convenience relies on practical vaccine characteristics such as physical availability, geographical accessibility, ability of individuals to communicate and understand as well as affordability. It is significant when it affects vaccines uptake and is particularly crucial in the developing countries where health care provision is often scarce. The quality of immunization services –real or perceived- and a specific cultural context may also affect the self-definition of convenience and ultimately affect the decision of being vaccinated.

Based on this model was developed a “Vaccine Hesitancy Determinants Matrix”, gathering potential influential factors grouped in the following three categories: contextual factors, group/individual factors and vaccine/vaccination factors (Table 6).

Contextual influences Influences arising due to historic, socio-cultural, environmental, health system/institutional, economic or political factors	a. Communication and media environment b. Influential leaders, immunization programme gatekeepers and anti- or pro-vaccination lobbies c. Historical influences d. Religion/culture/gender/socio-economic e. Politics/policies f. Geographic barriers g. Perception of the pharmaceutical industry
Individual and group influences Influences arising from personal perception of the vaccine or influences of the social/peer environment	a. Personal, family and/or community members’ experience with vaccination, including pain b. Beliefs, attitudes about health and prevention c. Knowledge/awareness d. Health system and providers – trust and personal experience e. Risk/benefit (perceived, heuristic) f. Immunization as a social norm vs. not needed/harmful
Vaccine/vaccination – specific issues Directly related to vaccine or vaccination	a. Risk/benefit (epidemiological and scientific evidence) b. Introduction of a new vaccine or new formulation or a new recommendation for an existing vaccine c. Mode of administration d. Design of vaccination programme/Mode of delivery (e.g., routine programme or mass vaccination campaign) e. Reliability and/or source of supply of vaccine and/or vaccination equipment f. Vaccination schedule g. Costs h. The strength of the recommendation and/or knowledge base and/or attitude of healthcare professionals

Table 6 - Vaccine Hesitancy Determinants Matrix.⁴⁸

These determinants were issues from research studies, field experience and discussions with vaccination experts, and the matrix is not perceived as a static information but rather as a dynamic basis for future research. Interestingly, the matrix shows that unlike for the social determinants of health, the vaccine hesitancy determinants like socio-economic status and

education do not influence decision outcome in only one decision, but may be associated with either higher or lower levels of vaccine acceptance.

Overall, the matrix particularly highlights the strong impact of individuals' perceptions and beliefs on their vaccination-related behaviors, in line with the recent findings from research in the field of behavioral economics, investigating the effects of psychological, cognitive, emotional and social factors on the economic decisions of individuals as well as the consequences for markets.

B. Evolution of Public's Perception of Vaccination and Contribution of Behavioral Economics

i. Introduction

The assumption supported in neoclassical and mainstream economics holding that individuals pursue their long-term self-interest and act accordingly, show stable preferences over time and make rational decisions has long served as a reference benchmark when trying to predict consumer behavior. In particular, this model of human behavior has been used to help design many public health policies including providing individuals with risk-related information, taxing harmful substances in the case of alcohol and tobacco as well as promoting and subsidizing prevention such as immunization⁴⁹.

Yet, practice has shown that these traditional economic decisions recurrently prove ineffective. Unlike neoclassical economics, the field of behavioral economics focuses on deviation from rationality, exploring how individuals' choices may be influenced by non-rational factors such as fear, impulsiveness, lack of willpower, social norms as well as the general context in which choices are made. To this end, the behavioral economics approach is strongly interconnected with other fields like neuroscience and psychology.

⁴⁹ **Matjasko J, et al.** *Applying Behavioral Economics to Public Health Policy*. 2011.

The following provides an overview of the key findings with regard to the causes of the rise in vaccine hesitancy and how these can be explained and potentially addressed by behavioral economics, to meaningfully inform public health and future prevention policies.

ii. Vaccination Perception Cycle and Rise of Vaccine Hesitancy

In the actual context of vaccines being increasingly questioned by the public, many proposed explanations have emerged, attempting to answer the 'why' and 'what' questions. A common perception sustains that in the quest of massively protecting populations, vaccines have somehow become victims of their own success, in the sense that their strong efficacy in disease prevention has shifted attention of individuals away from the risks of the now less prevalent infectious diseases to the potential risks of vaccines protecting against those. In high income countries, much of the actual health care community is not familiar with the vaccine-preventable diseases, as many are too young to have seen the consequences of those diseases. Today, on the contrary, as the incidence of infectious diseases decreases due to effective vaccines, the vaccine-related rare adverse events become more perceptible and highly mediatised. This leads to a loss of confidence in vaccines among the general population, with the result that vaccination coverage decreases and outbreaks once again occur. In practice, this usually then leads to natural resumption in vaccine confidence.

Based on this observation, the probability of harm or risk perception within the population arises from the dilution of the actual benefits. Indeed, as the risk of contracting a disease diminishes or disappears due to the widespread use of a vaccine, the public perception of the vaccines' value on its side decreases. This is due to the fact that the public no longer comes across the disease and its consequences, and therefore perceives little or no benefit. In other words, the success itself of a vaccine ultimately leads to a decrease in the value of its benefits once the disease is no longer a direct threat. Paradoxically, the more effective a vaccine appears to be, the stronger the dilution of benefit effect.

Chen et al. have proposed a model that illustrates the different stages of a full life-cycle immunization program⁵⁰, from the introduction of a new vaccine until the cessation of its use, going through the increase in vaccine uptake, the loss of confidence in the vaccine, the emergence of outbreaks, the resumption in lost confidence and finally the eradication of the disease (Figure 10). While complete eradication of a disease has been achieved once only with the case of smallpox, temporary elimination of disease appears to be in a delicate balance as a sudden loss in vaccine confidence rapidly leads to a decrease in vaccine uptake and ultimately in the reemergence of the disease.

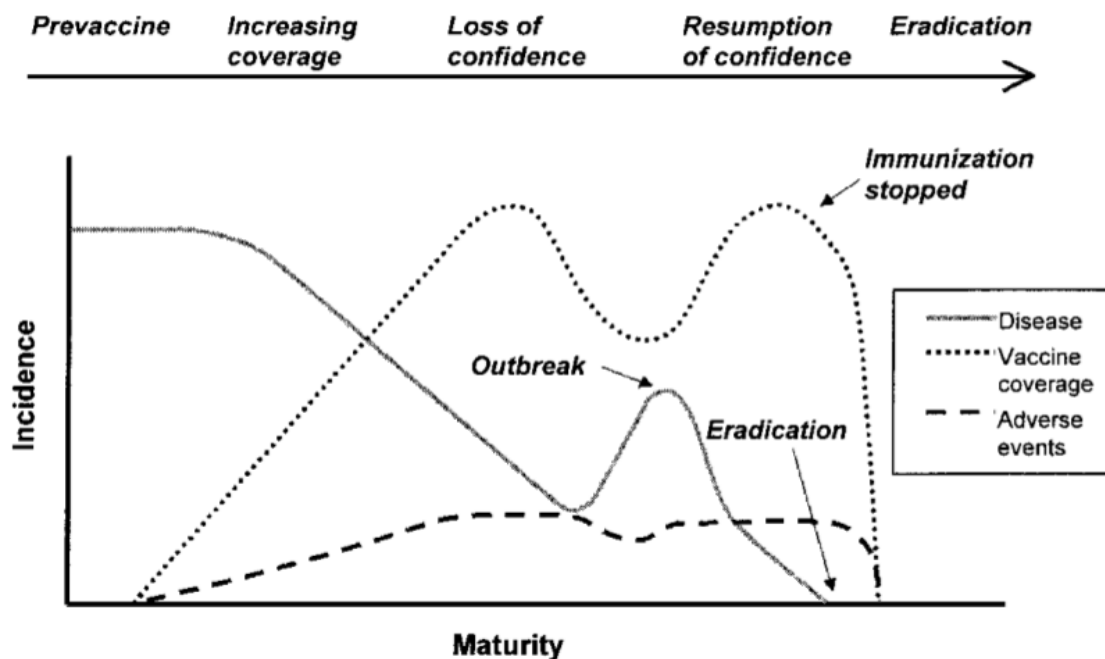


Figure 10 - Natural history of a vaccination program.⁵⁰

Similarly, Poland et al. have proposed the concept of a “pyramid effect”⁴⁷, modeling the way societal decisions are influenced with regard to vaccine safety and acceptance in society. The base of the pyramid represent the large-scale benefits of a widespread public health policy such as the implementation of vaccination programs. Most of the population actually benefits from

⁵⁰ Chen RT. *Vaccine risks: real, perceived and unknown*. 1999

the vaccine, but few are aware of the benefit. The peak of the pyramid, on the contrary, can be seen as potential harm or risk. Only a few will be harmed or at least perceive harm, but this state will be intense, acute and substantial. Therefore, the pyramid is imbalanced, and while the majority of recipients from an immunization program are passive voices, the minority who perceive or experience harm may become fiery and vociferous vaccine opponents.

Hence, there seems to have been a noticeable shift from an “active demand” towards a “passive acceptance” of vaccines in the last century, leading to gradual change in public perception and acceptance of vaccines. On an individual level, research on how individuals make their own decisions with regard to vaccines and immunization has also been enlightening on how to best apprehend the challenge of vaccine hesitancy. Findings related to risk aversion and divergence in risk perception along with irrationality in beliefs and decision making are particularly of interest in the case of vaccination.

iii. Heuristics, Irrationality and Biases in Decision

It has been demonstrated that the systematic errors individuals make often stem from their use of decision heuristics –or rules of thumb- in making decisions⁵¹. Despite their utility in providing instinctive guidance to judgement, heuristics may often lead decision-makers astray in complex situations. As an example, the availability heuristic occurs when people assume that the easiness with which they can recall a specific event, such as a dramatic media affair conveying the occurrence of an adverse event linked to a theoretical vaccine, is directly linked to the probability of this adverse event occurrence. This explains, for instance, why vaccination coverage tends to rapidly decrease for a specific vaccine right after a media-related scandal, but then steadily re-increase thereafter. Often, the correlation between immediate and salient available information on the one hand and actual facts in the external world on the other hand is so weak that this process can mislead individuals and drive a risk perception that is significantly different from the true likelihood of events occurring.

⁵¹ **Kahneman D.** *Thinking, Fast and Slow*. 2011.

In the case of vaccine hesitancy, the misconception that vaccines are not effective can easily arise from the availability heuristic⁵². When recognizing that no vaccine is fully effective, one can identify two potential outcomes when an individual gets vaccinated; the person can either be protected –as in the majority of cases- or ending up getting sick in some rare cases. However, these two possible outcomes are not equally salient. Indeed, in the case of the individual getting sick, there is an occurrence of an adverse event. On the contrary, when an individual is vaccinated and subsequently does not get sick, the actual positive achievement is the absence of a negative outcome. In other words, it is easy to see when a vaccine fails to protect while it is impossible to perceive when it does work well as people do not see anything different from their normal state of being. Thus, negative experiences are generally more salient than positive ones and may lead, by the availability heuristic, to overestimating the failure rate of vaccines. Besides, as examples of vaccines not working are generally more salient to people, they are often more conveyed and exposed to the public, creating a positive feedback loop, also called the availability cascade⁵³, that causes individuals to further exaggerate the actual failure rate of vaccines.

Further research in psychology has shown that people tend to construct coherent flows and stories in their minds, so as to be able to identify a sense of their often complex world and surroundings, although these stories do not always paint the reality as it is. As an example, individuals have a tendency to look for patterns in their life, even in random situations where orderly patterns do not exist. This predisposition towards coherency can also lead to misconception with regard to vaccines, and especially that immunization causes the disease. Thus, along with the availability heuristic and to some extent the availability cascade that make people exaggerate the probability as well as the negative outcome of getting sick after being vaccinated, the tendency to seek causality could attempt to explain the observed outcome. In the case of an individual getting sick, the first possible explanation would be that vaccine does not

⁵² **Chen F, et al.** *Applying lessons from behavioral economics to increase flu vaccination rates*. 2016.

⁵³ **Kuran T.** *Availability Cascades and Risk Regulation*. 2007.

work, while another explanation would be that vaccines must cause the disease. In both cases, mental shortcuts lead to misconception and vaccine hesitancy.

Human cognitive biases also convey the false belief that people are invulnerable to the disease and do not need to get vaccinated. Kahneman has shown that individuals tend to display unrealistic optimism about themselves, often believing that they are above average in many domains⁴⁵. This can be typically well illustrated with the flu vaccination. An individual who has never contracted the flu without being vaccinated may underestimate its susceptibility to the disease driven by the mental narrative that its influenza-free experiences thus far are wholly due to superior health and genetics.

Another behavioral theory, called the extended parallel process model, claims that individuals are unlikely to participate in a risk-control measure unless they personally feel at risk and assess the measure as relevant and serious for themselves, while feeling that the measure will effectively fully control the risk.

Finally, several other factors have been found to contribute to individuals' decision making as to whether to receive a vaccine. The omission bias for instance, occurs when an individual believes that a bad outcome is worse if it is the consequence of an active choice of doing something rather than doing nothing. This theory explains in part while individuals tend to prefer inertia rather than action. The free-loading theory, for its part, consists in thinking that so long as everybody else receives the vaccine, there is no need for a specific individual to get it. On the contrary, altruism tends to make people get the vaccine so as to be able to protect others. On a different note, risk perception and adverse event avoidance somewhat influence an individual's decision making process, and may lead him to get the vaccine ("I'd rather receive the vaccine than taking the risk of something worse happening to me" or "I prefer not to receive the vaccine as I could be subject to some adverse event"). Finally, bandwagoning refers to a situation where people act similarly to their peers ("I will get this vaccine because it seems like everybody else does").

Interestingly, it has been shown in social research that the highest rates of vaccination coverage are typically obtained in such environment of bandwagoning⁴³.

iv. Erosion of Public Trust

Along with cognitive processing, trust and legitimacy appear to be central components for cultivating active demand of vaccines. Trust refers to the ability for an individual to rely on someone else's claim with regard to a specific situation, while legitimacy represents the environment in which policy makers make decisions. When one or the other component is missing, many individuals tend to feel the need to re-interpret the information conveyed around them concerning vaccination⁵⁴. Such processed information can be elaborate although often relatively crude. Also, it appears that such re-interpretations are often country- and context-specific. For instance, the claim that the hepatitis B vaccine causes multiple sclerosis was mostly a French phenomenon while the claim that the MMR vaccine causes autism was mostly a UK phenomenon.

In their paper released in 2014, Yaqub et al. showed that among the wide diversity of reasons reported for vaccination attitudes, many were directly related to lack of trust towards key stakeholders in vaccination. Indeed, literature review of general population's reasons for vaccine hesitancy reported reasons such as "distrust of doctors", "distrust of government sources" as well as "distrust of pharmaceutical companies" at a significant level as underlying causes for vaccine hesitancy (Figure 11).

⁵⁴ **Yaqub O, et al.** *Attitude to vaccination: a critical review*. 2014.

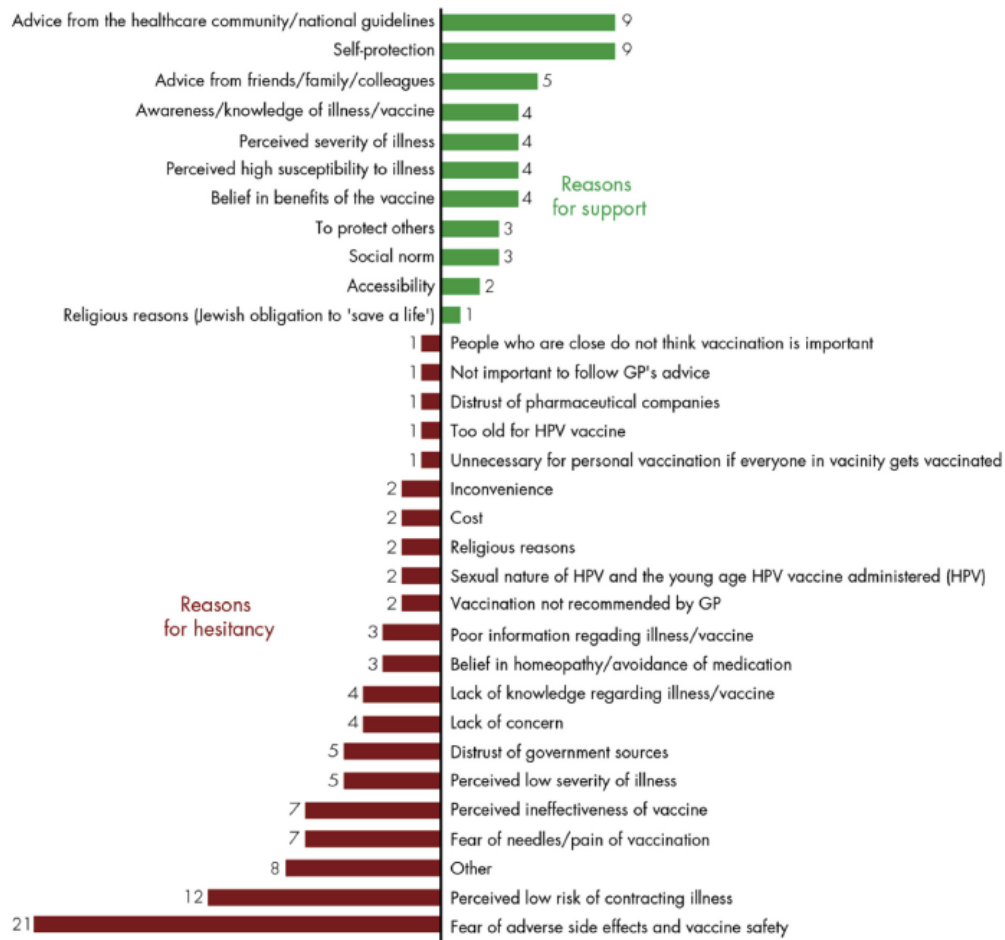


Figure 11 – General public’s reasons for vaccine hesitancy and number of times such kinds of reasons were cited in the literature.⁵⁴

Today, both trust and legitimacy are key concepts for assessing and trying to understand how sources of information are being categorized as trustful according to individuals, how information is being trusted or distorted or even how individuals non necessarily under-educated can build beliefs that are contrary to scientific evidence. To some extent, they attempt to explain current incongruous situations with regard to coverage, such as why the better-educated might mistrust vaccines while the under-educated might accept them more passively⁵⁵. Recent research revealed that many hesitant attitudes are being endorsed by the well-educated, therefore suggesting that access to relevant information seems not to be the decisive factor for

⁵⁵ **Hak E, et al.** *Negative attitude of highly educated parents and health care workers towards future vaccinations in the Dutch childhood vaccination program.* 2005.

better acceptance of vaccines within such populations. To some extent, it appears that in today's society, the credibility of institutions is more important in terms of influence than the content itself that is delivered to populations. A Dutch paper revealed that 83% of parents of unvaccinated children believed the fact that "the Government is strongly influenced by the vaccine industry⁵⁶". Furthermore, more than half of the parents believed that the national public health authorities would not cease vaccination programs if there was evidence of serious adverse events. Thus, while better information might help improve vaccination attitudes in some cases, it is very unlikely to be sufficient for the growing number of cases where the institutions are mistrusted.

For scholars such as Peters, the extent to which an individual or an institution is being trusted by the public relies on three central factors: the perception of expertise and knowledge, the honesty and openness of the source as well as its level of concern and care with regard to the situation. Hence, the credibility of vaccine-related information is influenced by the perceived reliability of the sender, but also by the perceived honesty and transparency being conveyed through the information⁵⁷. The H1N1 influenza pandemic in 2009 reflects well how lack of public trust can lead to both unexpected and puzzling situations. At that time, claims that governments and industrials had paired up in order to serve commercial interests coincided with evidence of increasing vaccine hesitancy worldwide, leading to very low influenza vaccination coverage. Ultimately, this provoked one of the biggest pandemic of the past few decades. About that situation, the WHO Director-General later declared "we did not anticipate that people would decide not to be vaccinated..."⁴⁸. Today, people are facing an incredible vast range of information sources. They make their own choices with regard to what sources should be trusted, and often act accordingly. More and more, policy makers can only observe that their organization do not enjoy the level of trust they were expecting when the recommended vaccination.

⁵⁶ **Gefenaite G, et al.** *Comparatively low attendance during Human Papillomavirus catch-up vaccination among teenage girls in the Netherlands: Insights from a behavioral survey among parents.* 2012.

⁵⁷ **Peters RG, et al.** *The Determinants of Trust and Credibility in Environmental Risk Communication: An Empirical Study.* 1997.

Recent scholars have suggested that the erosion of public trust in vaccination-related institutions was somewhat part of broader social trends⁵⁸. In fact, it appears that public health authorities and institutions issuing vaccination recommendations encounter difficulties in resonating with a general population increasingly enamored with concepts such as individual empowerment and exercising patient-choice. Public health decisions have gradually shifted towards the primacy of an individual's right, meeting patients' increasing expectations to make an informed and personal choice. This gradual transition appeared particularly visible when during the MMR vaccine affair in the UK, the public's response to lowered vaccination uptake took over the social benefit and duty of vaccination.

Finally, individual and group experiences also strongly affect public willingness to trust public institutions and vaccines in general. As an example, public trust of the nationally driven HPV vaccination in France was strongly undermined after parents began to claim without tangible foundation that the vaccine had caused their child to develop multiple sclerosis. Today, the trustworthiness once granted by individuals to public health authorities and scientific communities may easily and abusively shift towards individuals or groups that attempt to bring an answer to unexplained concerns. In their quest for answers to questions such as "why did my child develop multiple sclerosis?", individuals might be willing to trust crude information that is not scientifically proven, as long as it addresses somehow their immediate concerns.

v. New Media and Horizontal Communication

Democratization of the society along with the advent of the internet have deeply reshaped the legitimate environment around vaccines from a top-down, vertical expert-to-consumer communication towards a non-hierarchical, horizontal dialogue-based communication between individuals. Today, the public increasingly challenge the statements and recommendations of public institutions and scientific experts regarding vaccination, often on the basis of their own unfounded perceptions or web-based research. As discussed earlier in this work, such public

⁵⁸ **Blume S.** *Anti-vaccination movements and their interpretations.* 2006.

questioning appears to be more and more non-specific to vaccination, but rather part of a broader trend. This global increasing public questioning follows decades of authoritarian public policy implementation and comes along with the emergence of dissent groups. In particular, this trend is particularly visible in sectors that include risks, such as climate change or vaccination.

In today's society, individuals are better connected than ever before. The era of digital has substantially changed the way in which consumers seek information. The internet, social media and mobile phones have shifted to another level the methods and speed of communication worldwide, enabling information about immunization and vaccines to be shared, retrieved and analyzed quickly. Social media and blogs in particular have substantially shaken the way in which vaccine-related data is being used, compared with even a decade ago. The interactive and immediate exchanges between individuals has led to a completely different way of gathering information and granting confidence. Besides, the amount of information itself has skyrocketed, including peer-reviewed scientific data and evidence-based recommendations alongside any kind of personal opinions based on poor quality data including misinformation and distorted facts.

Furthermore, media attempts to give voice to all stakeholders and balance coverage by providing an equal opportunity to all viewpoints intensify the challenge to increase public confidence in vaccines. Hence, outlier views and minority extremist opinions are given the same media space than rational views resulting from a rigorous peer-review process within the scientific community. Besides, this disproportionate balance is sometimes further amplified when outlier views are being promoted by celebrities or particularly vociferous opponents, encouraging individuals and parents to question vaccines, often engaging them at an emotional level.

Today, the internet is frequently used as the primary source of information among individuals. Although it appears that some websites are generally more trusted than others, with public institution and government websites preferred over websites such as Wikipedia and personal

blogs, the latter are being increasingly trusted relative to scientific sources. Despite not being experts in vaccination, these sources may provide the public with welcome contrast to usual information intended for the general population and may serve as local, “just-like-me” reference points quite meaningful for numerous individuals.

Besides, the emergence of social media platforms such as Facebook and Twitters gathering hundreds of millions of users globally, has helped shape methods for self-creation and empowerment of new virtual communities, both at a local and global level, spreading ideas and arguing for as well as against vaccination. Although the majority of these vaccines-dedicated networks operate at a confined or national level, experience has shown that they can also be very quick to pick up and amplify facts and events occurring across geographic boundaries in other countries that support their cause.

Thus, it is clear that the newly emerging mix of varied and often antagonistic information highly contributes to the skepticism of the general public with regard to vaccination. These views need to be further explored as they are developing and better understood in order for public institutions and pharmaceutical companies to address individuals’ concerns and regain public confidence.

vi. Influence and Role of Health Care Professionals (HCPs)

Along with the erosion of public’s trust and the multiplicity of information, the level of involvement of HCPs in defending and promoting vaccines appears as a crucial determinant of the rise in vaccine hesitancy.

At present, HCPs still appear to be the most trusted advisor and influencer for individuals with regard to their vaccination decisions⁵⁹. Their recognized competence and legitimacy to issue recommendations about vaccination has long placed them as stakeholders of choice for patients seeking information or advice. However today, the capacity and confidence of HCPs are being

⁵⁹ **Paterson P, et al.** *Vaccine hesitancy and healthcare providers*. 2016.

challenged as they are faced with increasing time constraints due to heavy workload and limited resources, and suffer from a lack of adequate and up-to-date information and trainings with regard to vaccination and vaccines in order to be able to address properly individuals' inquiries.

As a matter of fact, insufficient time with patients hinder proper recommendation of vaccination to individuals. In their study, McCarthy et al. showed that although 90% of respondents agreed that the responsibility for vaccination primarily lay with HCPs, a lack of time with patients was often cited as a major barrier to recommendation for vaccination⁶⁰. Risks for HCPs is to become frustrated and simply dismiss non-compliant patients with regard to vaccination. However, this is very unlikely to persuade hesitant individuals and instill confidence. Ideally, HCPs would need to keep abreast of the latest vaccine information so as to be able to address patients' concerns with trustable data while remaining empathic and engaged with unusual concerns that could arise from some outliers.

However, the second biggest challenge in building trustful relationships with patients and promoting vaccination precisely lies in the fact that HCPs suffer from a lack of knowledge about new but also well-established vaccines, as well as awareness and knowledge regarding national guidelines. In the mind of most individuals, HCPs are expected to be knowledgeable about the risks of vaccine-preventable diseases as well as the risks and benefits of vaccination, and should be able to communicate and explain this information well to their patients. However today, even when they do receive information, HCPs may feel uncertain about their knowledge and not feel confident about discussing this information with patients in order to be convincing. While changes in national vaccination policies and scientific evidences are sometimes poorly communicated, HCPs tend to question their own competence to deliver relevant advice and address patients' concerns effectively in their daily practice. Along with a lack of time, this loss of confidence among HCPs in dispensing advice and encouraging vaccination is contributing to vaccine hesitancy.

⁶⁰ **McCarthy EM, et al.** *Knowledge, attitudes, and clinical practice of rheumatologists in vaccination of the at-risk rheumatology patient population.* 2012.

Thus, in the fast-changing current environment, HCPs struggle to manage demanding patients, often misinformed or reluctant, and need more support. To this end, current strategies typically include enhancing the relationships of trust between HCPs, policy makers and health authorities through increased collaboration and shared involvement in the decision for vaccination policies and recommendations.

However, evidence more and more suggests that a number of HCPs are themselves vaccine-hesitant, and therefore express their own reservations with regard to recommendations of some specific vaccinations⁶¹. A French study led by Verger et al. in 2015 revealed that 43% of the surveyed HCPs were not routinely recommending vaccination to their patients, challenging to some extent the safety and the efficacy of the vaccines⁶². Besides, the study highlighted a strong correlation between physicians' reported recommendations and their own vaccination behavior. Further research on this issue confirmed that HCPs' uncertainties regarding vaccines mostly include safety, efficacy and alternatives.

Overall, these findings suggest that many HCPs are therefore unlikely to dispel individuals' doubts and concerns about vaccines, ultimately hindering their role in public's acceptance of vaccines. Given their potential influence and impact on hesitant populations, further studies are needed to better assess and apprehend the causes of HCPs' hesitancy as well as the prevalence of this phenomenon. Also, the implementation of tailored interventions should be considered by national authorities, policy makers and vaccines companies in order to address this issue and restore sustained HCPs' confidence in vaccines.

⁶¹ **Karafillakis E, et al.** *Vaccine hesitancy among healthcare workers in Europe: A qualitative study.* 2016.

⁶² **Verger P, et al.** *Vaccine Hesitancy Among General Practitioners and Its Determinants During Controversies: A National Cross-sectional Survey in France.* 2015.

C. Impact and Perspectives

In recent years, concerns about efficacy and safety of vaccines along with a global trend towards erosion of trust in institutions and scientific bodies and an ambiguous attitude from HCPs paved the way for vaccine hesitancy to slowly grow among populations. Increasing global interconnections and the rapidity of the spread of information amplified the phenomenon, ultimately hampering the efforts undertaken at increasing immunization rates among individuals. As discussed in the previous sections, it is clear that the controversy and subsequent anxiety initiated by anti-vaccine groups has an attestable detrimental impact on population-level immunization coverage rates. This, in turn, affects the human burden of disease by increasing the incidence of vaccine-preventable diseases, leading to an increase in related healthcare costs and resources allocated that could have otherwise be useful for a more productive economy.

Beyond the public health impact of vaccine hesitancy, the phenomenon ultimately also appears to be of great interest from an economic perspective, as it presents the potential to substantially weaken current performance and future growth of the whole vaccine industry. After remaining quite silent towards patients in the previous decades, the pharmaceutical industry and in particular the vaccine firms are being pointed out and more distrusted than ever before. In today's context bringing individuals' empowerment and freedom of choice to the forefront, business as usual is not enough, and concerns raised by patients should be increasingly considered in order to define new business strategies responding to evolving and emerging needs and expectations.

It appears clear that a substantial change in the way vaccines are used and recommended within the population is about to take place. Although the benefits of vaccination have been clearly demonstrated both at an individual and at the society level, hard work and disruptive approaches will be necessary from governments, HCPs and the vaccine industry in order to address the concern of vaccine hesitancy in the modern society. Vaccine companies, in particular, will need to substantially reshape the way they are currently communicating about

their products, as well as review their consumer strategy. While market-focused initiatives have been the standard until recently, the multiplicity of stakeholders involved in the vaccine sphere along with an evolving public's perception now compel the industry to rethink its strategic model and its implementation mechanisms. For this purpose, the emergence of non-market strategies focused on the vaccine companies' specific external environment drives reflection and increasingly appears as part of the solution to deal effectively with the issues currently faced by the business. However, this change must be achieved together with the many and diverse vaccine stakeholders, in a way that respects and protects individual rights of freedom of choice and autonomy, including what could be considered as the misguided choice of refusing vaccination.

III. Non-market Strategies as a Growing Need for a Sustainable Vaccine Business

A. Multiplicity of Stakeholders and Complexity of Strategy Setting

As discussed previously, it is clear that the vaccine industry is currently undergoing an image crisis of unprecedented proportions. Until now, vaccine firms have heavily relied on the endorsement of immunization from governments, healthcare systems as well as the general public. Unfortunately, as described through this paper, it is clear today that stakeholders in the vaccination sphere tend to multiply and become more complex to manage and satisfied, thus making it difficult for vaccine firms to continue with “business as usual”.

If we look back to their history, and similarly to the pharmaceutical companies, vaccine firms started communicating on their specific products as early as the business started to become attractive. This prerogative was traditionally associated with health care professionals and especially general practitioners, contributing to and progressively enlarging the gap formed between firms and their various 'audiences'. As a result, the whole vaccine industry is today ailing from this structural flaw, as shown by the recent crises.

As an instance, it appears clear that both patients and the media are not familiar if not aware at all of the business activities and social contributions of the vaccine industry. This lack of knowledge is typically detrimental to the reputation of vaccine firms, which, as a result, are increasingly subject to fierce and peremptory criticisms despite their scientific contribution and undeniable societal commitments. This social pressure, whether expressed directly or covertly, adds up to an already strained business environment that must deal with economic constraints resulting from risks associated with product safety, research processes and legal obligations.

The chaotic relationship linking the industry and the society along with the subsequent challenges arising from this unbalanced communication have led vaccine companies to progressively rethink their position and interactions in order to increasingly account for key

indirect customers. Such external stakeholders include patients associations, advocacy groups, pharmacists, advisory committees, national health authorities, institutional partners, payers and media to name but a few. Although all these stakeholders follow very distinct objectives and vision, they all appear to interact with the vaccine industry to one extent or another, and should therefore increasingly be considered for a sustained success of new and established vaccination campaigns.

The commitment of policymakers (or each structure involved in the regulatory processes) and medical and scientific experts is, of course, essential, but in the later years (with delay compared to other areas like diabetes, cancer, or HIV), a cluster of new actors has increasingly emerged, including people from the civil society. They have structured themselves into organizations (mostly associations or patients' groups), independent from the government, and are engaged in favor of people's health and rights. All aspects of health can be covered by their activities, especially health policies.

Patients associations are a good example of such stakeholders whose importance is growing. Indeed, they were able to position themselves originally in the midst of a fast-changing health- and more specifically vaccine-industry. Today, they appear to be at the junction point between the interests of their members, laboratories, health practitioners and authorities. In many cases, they have become quite influential entities, whose opinion and input can be key for the implementation of certain law or, inversely, for the withdrawal of some vaccine-related policies. Interestingly, these associations often rely on pharmaceutical companies for promoting their activities and providing them with financial support. Although most pharmaceutical companies recognize the importance of these associations in the modern healthcare system and agree to provide such funds, the situation is sometimes more complicated and patients associations can strongly interfere against the industry. In France, for example, the association E3M ("Entraide aux Malades de Myofasciite à Macrophages") argues the case of patients claiming that vaccines

had directly caused them to develop macrophagic myofasciitis⁶³, a neuromuscular disease identified by some as induced by alum-containing vaccines despite the lack of supporting scientific evidence. In the current context of growing vaccine hesitancy along with the lack of communication and collaboration of vaccine companies towards such association, E3M was able to grow significantly in a short period of time and become an actual powerful lobby for diverse national policies, while being a strong influencer of public's perception regarding vaccination.

Similarly, activists have become important stakeholders that cannot be ignored anymore by the industry as their impact has proved to be potentially harmful to the diverse efforts being made towards a better access to vaccination worldwide. Often, they are the result of the political and societal conflicts that raged during the 1970s. Today, they claim to make up a new form of resistance, if not opposition, claiming their right to freedom of choice and fighting to express alternative opinions. In their quest for dismissing vaccine benefits, activists appear to maintain an ambiguous relationship with the media, often using them to echo their demands beyond their immediate activity circle. Besides, the recent advent of communication and information technology has enabled them to have significant more weight and influence towards institutions and governments. As a result, many militant groups worldwide now officially take a stand on the question of the obligation to vaccinate and demand governments to act by waiving such obligation.

Another example of a player increasingly involved in the vaccination sphere are religious and non-religious foundations. In the USA particularly, religious communities appear to be highly influential with regard to health-related matters and have a strong impact on corporate social responsibility. A good example of such foundation is the ICCR (Interfaith Center on Corporate Responsibility), founded in 1971 by protestant communities which decided to join their efforts into a single and united organization⁶⁴. Today, ICCR claims to harness their built collective influence to improve corporate decision-making on environmental and social issues. In the

⁶³ **Association E3M.** *For aluminium-free vaccines.* 2017.

⁶⁴ **ICCR Website.** 2017.

health sector, it appears to be a large faith-based network that brings together thousands of investors of more than 275 religious denominations such as hospitals, pension funds or insurance companies, with assets totaling over \$110 billion. In particular, they have been highly involved in immunization promotion and access.

Finally, the vaccine industry also has to deal and cooperate with many actors on the institutional side, may they be advisers, policy makers or payers. Increasingly, these types of actors are becoming a key source of focus for a vaccine industry heavily relying on national immunization programs intended primarily for infants but also more and more for adults. In a strengthened policy network increasingly considering vaccine efficiency and cost saving, vaccine companies have seen the widespread reimbursement of their products shifting from a given to something that must be managed effectively to ensure its sustainability. These stakeholders have required much more attention recently than they used to in the past and this trend is likely to continue and to further increase in the years to come.

Thus, in the last few decades, the witnessed transition from international to global health has reflected the rapid growth in the numbers and nature of stakeholders in health, as well as the constant change embodied in the process of globalization itself. Global health management today shares the characteristics of complex adaptive systems, with its diverse but multiple players, their polyvalent and constantly evolving relationships along with their rich and dynamic interactions. The multiplicity of initiatives, networks and influences along with the wide range of contexts in which development for health is played out all compound the complexity of this system.

As a result of this fast-changing environment embedded within a complex and widening group of diverse actors, business as usual has become more and more challenging for vaccines companies. In the recent years, key vaccine manufacturers have shown growing interest in understanding and assessing the dynamics between their various stakeholders with the objective to ultimately integrate this insight into their strategic decisions. Economic

considerations aside, the emergence of this complex new ecosystem has brought along new challenges, as illustrated by vaccine hesitancy, bringing together stakeholders with divergent rationalities and interests.

B. Establishment and Limitations of the Actual Business Model

i. From an Unattractive to a Profitable Business

As a matter of fact, today, vaccines are profitable. Because of this, however, they are often accused of fueling a conspiracy theory by enabling both healthcare professionals and pharmaceutical companies to profit financially from vaccination, thus supposedly leading to corrupt incentives in advocating for immunization. Despite being historically unfounded, this claim is far from the reality since one should underline that it wasn't too long ago that the vaccine industry was struggling with low profit margins and massive shortages. In 2010, *The Economist* stated in a paper that "for decades vaccines were a neglected corner of the drugs business, with old technology, little investment and abysmal profit margins. Many firms sold their vaccine divisions to concentrate on more profitable drugs"⁶⁵.

In fact, vaccines were so unprofitable at that time that several companies even stopped making them altogether. In 1967, there were 26 vaccine manufacturers. Due to the lack of profitability and visibility, that number dropped to only 17 by 1980⁶⁶. In the 1990s, the financial incentives to manufacture vaccines were so low that there was an expanding concern that vaccine producers would abandon the vaccine business for selling and concentrating their efforts on more-profitable drugs such as blockbuster drugs. As an example, the well-established vaccine company Wyeth, which has since been acquired by Pfizer in 2009, decided in the late 1990s to stop producing the flu vaccine due to insufficient margins.

⁶⁵ **The Economist.** *Vaccines, A smarter jab.* 2010.

⁶⁶ **The Atlantic.** *Vaccines Are Profitable, So What?* 2015.

However, increasing global demand -particularly in developing countries- along with the impact of flu pandemics starting in the late 1990s have changed things. The growing support from global organizations such as the GAVI Alliance and other diverse philanthropic donors largely contributed to this increase in demand. Besides, vaccines with the potential to turn a profit in high-income countries -constituting 82 percent of global vaccine sales according to the WHO- emerged as of the early 2000s. In particular, two blockbuster vaccines hit the market with Prevenar®, a pneumococcal conjugate vaccine protecting against pneumococcal pneumonia and Gardasil®, a vaccine protecting against human papillomavirus (HPV). In response to these factors, governments and payers in the developed world have started to accept paying higher prices for vaccines and the latter have therefore been rising dramatically in the recent decades. As an immediate consequence, the industry has substantially grown, rising from a few billion dollars in sales in 2000 to more than 20 billion today. However, although key companies today report several billion dollars of revenue for their vaccine franchises, it is hard to know the profit margins for this business, and analysts estimate the latter to range anywhere between 10 to over 40 percent for giant pharmaceutical companies.

Cost however is an issue. Where there were once worries that low vaccine prices would prevent manufacturers from entering the market or even drive them out of it, there are now worries that prices are becoming too high for both the developed and developing world. Besides, this period of relatively wide and enthusiastic acceptance of infant and childhood vaccines did not last and new challenges such as vaccine hesitancy have progressively emerged within both the civil society and healthcare professionals, as discussed earlier in this paper.

ii. Limitations of Current Strategies and Need for a Business Model Renewal

More and more, it appears that focusing only on their market environment is not enough for vaccine companies to drive a sustainable business in a modern society. Market environment traditionally deals with relationships between a company and its customers. It involves applying

diverse marketing strategies focused on the product, price, place and promotion (also known as the 4 Ps). An effective marketing strategy built on a well-designed mix of the 4 Ps and appropriate to the target market is necessary for a marketer to be successful within a given market⁶⁷. However, customers do not exist in a vacuum and are surrounded by an external environment, as shown in figure 12. They live amidst social, political and environmental forces that shape their need, perception and behaviors. While non-market elements are generally viewed as external to the core business, they however strongly frame the environment in which a company operates and influence its success. Hence, to effectively manage customers in the modern world, companies must increasingly take this non-market environment into account.

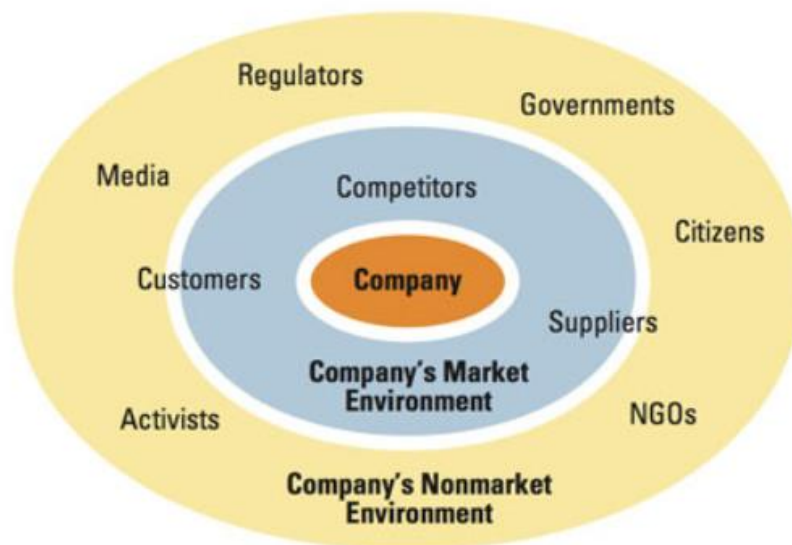


Figure 12 - The Non-market Environment of Business.⁶⁸

As a matter of fact, every company somehow makes a given contribution to society. From the most basic level, businesses offer goods and services that people need. Later on, they provide jobs, skills, ideas, capital and taxes. The problem faced today by many companies, including the vaccine manufacturers, is that they do not emphasize well their contribution to society. On one

⁶⁷ **Nowak GJ, et al.** *Addressing vaccine hesitancy: The potential value of commercial and social marketing principles and practices.* 2015.

⁶⁸ **Bach D, et al.** *What every CEO needs to know about nonmarket strategy.* 2010.

side, businesses internally focus on what they can get from society and market such as cheaper inputs, higher margins and more favorable regulation. On the other side, externally, they barely promote their humble corporate social responsibility (CSR) related contributions –vaccines they have donated for example, or dispensaries they have equipped- however ignoring the remaining vast contribution made by their day-to-day business.

This situation leads to two different problems. First, it undermines external credibility of vaccine suppliers. A company existing only to extract value from society and relying on rare CSR initiatives to attract sympathy will not drive any customer’s trust and engagement. External stakeholders including patients, NGOs and regulators will often view these efforts as largely insincere and cynical maneuvers, leading to difficult cooperation in such climate. Internally, a similar mindset can hinder the integration of valuable external engagement into daily activities. Former BHP Billiton’s CEO Marius Kopplers stated that “every single employee, contractor, and supplier should take responsibility for social issues”⁶⁹. However, this statement appears very difficult to achieve when the various stakeholders behave as if their relationship with the external environment was substantially extractive.

Inversely, companies that demonstrate their ability to build a profitable relationship with their external environment tend to think in a very different manner, defining themselves through what they contribute. This approach does not imply a change in the company’s purpose, but rather to be explicit about how fulfilling that purpose actually benefits society. Similarly, it does not mean discarding focus on shareholder value, but recognizing that the company is able to generate long-term value for shareholders only by delivering collateral value to society.

In fact the logic seems simple. The success of a business is dependent on its relationships with the external world, including patients, associations, activists, legislators and regulators in the sphere of vaccines. Decisions made at any level of the business -from the will to develop a specific new vaccine to the negotiations undermining its future price, from the promotion

⁶⁹ **McKinsey & Company**. *Beyond corporate social responsibility: Integrated external engagement*. 2013.

strategy of a given vaccine to the handling of a public crisis- ultimately affect those relationships. In this context, a new kind of business strategies, called non-market strategies, has appeared and is becoming crucial to develop for vaccine companies willing to be successful and sustainable in this time of change.

C. Non-market Strategies

i. Definition and Concept of Non-market Management

As a matter of fact, what happens within the non-market environment of businesses subsequently shape further dynamics between markets. In 2003, Bedewing referred non-market as “internal and external organizing and correcting factors that provide order to market and other types of societal institutions and organizations – economic, political, social and cultural – so that they may function efficiently and effectively as well as repair their failures”⁷⁰.

In other words, the non-market environment of business consists in all relationships that do not unfurl within markets yet nevertheless present the potential to affect the company’s ability to reach its business objectives. Surely there are differences between seeking regulatory approval for a merger, lobbying a key policy maker for reimbursement or teaming up with a charitable organization to provide free vaccines. However, it appears that compartmentalizing non-market management into branches such as public relations, government affairs or CSR has several drawbacks. First, it omits the significant synergies between the different strategies. Second, such compartmentalization of non-market management truly complicates the task to integrate non-market considerations within the global corporate strategy process. In many companies, non-market management remains an afterthought, often lying in a series of clumsily coordinated initiatives aimed at nonbusiness actors. However, a much more comprehensive approach is required to gain a competitive advantage. Carefully thinking and designing non-market strategies is key in order to complement, reinforce and enable market strategies.

⁷⁰ **Boddewyn J.** *Understanding and Advancing the Concept of ‘Nonmarket’*. 2003.

Today, investment in non-market management gradually appears as a growing imperative driven by four factors strongly linked to globalization. The multiple audiences now facing and interacting with vaccine companies along with the increased globalization of non-governmental organizations including NGOs and activists progressively force companies to adapt to a new type of audience. Besides, the numerous recent regulatory hurdles applying to this particular business and the quest towards an enhanced competitive edge ultimately push firms to seize the importance of the non-market environment and act urgently in that way.

In order to effectively handle non-market management, it is crucial to first understand how it differs from market management. Table 7 highlights the differences in “currency” between traditional markets and non-markets, highlighting the evidence that it is imperative for companies to become familiar with these settings.

MARKET	NONMARKET
Money	Information
Leadership	Coalitions
Flexibility	Consistency
Predictability	Uncertainty
Value	Values

Table 7 – Key differences between market and non-market environment.⁶⁸

In business, markets are simple models however operating with powerful mechanisms. They are characterized by being near-uniform and generally offer predictable cause and effect relationships. Non-markets, on the opposite, are far less homogeneous and predictable. Morals, regulatory processes and best practices vary widely across regions and issues. Moreover, the way the media will respond to a fact in a given culture often will be significantly different from the response in another culture. The rise in vaccine hesitancy worldwide perfectly illustrates this statement, as one can easily notice that this phenomenon is usually vaccine-dependent and

country-dependent. In such case, it appears that prior experiences, rather than cross-cultural extrapolation, are often the best pilot.

Besides, the non-market environment lacks the tangibility of money as an exchange medium. Investing money in a given initiative (eg. funding a vaccination campaign in some developing countries) will not necessarily help a company reach its immediate key business objectives (eg. obtain a market authorization for a different new vaccine). Non-market exchanges and trades are not about money, but rather information which is deeply context specific. As an illustration, the primary currency of lobbying lies in information such as the functioning of a particular policy, its alternatives, its costs and benefits or even the key players involved.

Leadership is fundamental in markets. One main goal for innovative and growth-oriented companies is often to secure a first-mover advantage and become the leader in a given industry. In contrast, excelling in the nonmarket environment often requires coalition and working with others. That does not imply forgetting competition, but rather emphasizes the fact that in politics, allies are key to be successful. Yet, working with other stakeholders such as public bodies, non-governmental groups, or even formal competitors on non-market issues can be quite difficult to apprehend for companies. A paper released by consulting firm McKinsey found that although one third of large corporations believe that engaging non-market actors to handle and tackle sociopolitical issues would be effective, only 13% of them actually do so. Besides, while 27% use advertising to manage such issues, only 20% believe such initiative as being effective⁷¹.

Another key difference between the market and non-market environment lies in their behaviors and intentions over time. While flexibility and ability to respond quickly to the market are key in the market sphere, managing non-market issues require a different approach. Indeed, even though society often demands that firms contribute to social ends, people are often skeptical of underlying intentions of companies doing so. Since only behaviors can be seen, and not

⁷¹ **McKinsey & Company.** *Tackling sociopolitical issues in hard times: McKinsey Global Survey results.* 2009.

intentions, consistency is key to manage the non-market environment. Hence it appears clear that a company cannot take alternative positions on political or social issues, by monitoring initiative outcomes and dropping those that fail to strengthen its business.

Finally, while market management aims primarily at creating value for its different direct stakeholders such as customers, shareholders or employees, non-market management is above all about values. In order to succeed, a non-market initiative must be in line with the firm's values and echoes its overall strategy, especially when the goal is long-term performance.

Thus, in a global economy, it increasingly appears that just pursuing business as usual is not enough and that gaining a sustained competitive advantage stems from the ability for companies to tackle political, social and environmental issues as part as their corporate market strategy. In the healthcare and vaccine business, diverse such attempts are noteworthy and can be seen as examples and source of inspiration.

ii. Business Cases

Novartis's fight for patent in India

Novartis Pharma, one of the world's largest and most influential pharmaceutical company, was engaged in the early 2000s in a crucial public battle with the Indian government with regard to its new drug Glivec, used in cancer therapy. In fact, India had denied Novartis a patent for its drug, pleading that the latter was not offering improved efficacy over its predecessor.

Novartis, which had already obtained patents for the drug in many countries including China, maintained its position that India's inflexible conditions for novelty breached international intellectual property rules and decided to stand against the government's decision. The company took the case in courtrooms and ministries but also to the public, through website videos highlighting the need for the drug in India and the consequences for patients deprived of its use at that time.

Somehow, Novartis was not only fighting for its intellectual property rights. Indeed, the giant was able, through a subtle and well managed strategy, to offer its drug to needy Indian patients at significantly lowered prices. The program was run as part of the company's "corporate citizenship" initiative, which also targeted other diseases such as leprosy, tuberculosis and malaria by offering drugs to millions of patients free of charge or at cost. As a result, Novartis later proudly declared that its "billion-dollar" support program had enable to reach over 80 million patients across the world, many of them in India. Key lessons from this case include the fact that in showing its concern and commitment towards the needy in developing countries, Novartis has won key allies in its fight against patent protection. In its quest, the company was able to both reach its ultimate business objective of securing its sales and to refute criticism from opponents concerned about drug access to the most needy. In being able to balance its assertive property rights along with some pharmaceutical philanthropy, Novartis has strongly shaped the environment in which it was competing, providing a great example of non-market strategy.

More recently, several similar examples have shown to be noteworthy with regard to non-market management in the specific vaccine business, as presented hereinafter.

Merck's role in HPV vaccination policymaking

In 2006, the first vaccine against HPV was approved by the FDA in the USA. Gardasil®, produced by major actor Merck, was licensed for vaccination of females of a certain age for the prevention of cervical cancer and genital warts. Rapidly, the company was able to obtain routine recommendation from the Advisory Committee on Immunization Practices (ACIP) from the Centers for Disease Control (CDC) in the USA. Within a few months, a remarkable amount of legislative milestones followed. In fact, Merck was able to serve as a key informational resource to health department officials and legislators, ultimately supporting its strategy to see its vaccine

recommended and funded among the largest pool of possible individuals⁷². The following will discuss some of the initiatives engaged by the company in order to best integrate the surrounding non-market considerations into its overall business objective.

First, Merck was able to provide the right information, at the right time and in a neutral manner. The firm responded to every specific requests for scientific information about the vaccine or potential policy strategies, and was able to do so without jeopardizing independent decision-making by policymakers. Furthermore, Merck engaged in direct lobbying through various actors. By doing so, the company was able to play an important role in the legislative process, by proposing specific legislation, drafting bills or even presenting policy alternatives. Most importantly, Merck's representatives succeeded in adapting their speeches to the different stakeholders and the lobbying was hence perceived as appropriate and reasonable.

Besides, Merck was able to mobilize the public and key legislators in its quest towards promoting Gardasil. By providing unrestricted educational grants to Women in Government (WIG), a key national, non-profit group of female state legislators, the firm enabled among other thing members to attend conferences on cervical cancer and gain awareness of the disease and the potential value of the vaccine. As a direct consequence, WIG members introduced many of the mandate bills later considered across the country. Furthermore, Merck ran various marketing campaigns directed to consumers and physicians and was even able to outreach to political interest groups, subsequently effectively preparing the political environment for the introduction of mandates. Through these campaigns, Merck created a public demand for the new vaccine while training physicians and engaging them in effective peer-to-peer education.

In addition to this, the company also mobilized medical professional and public health organizations as well as diverse interest groups, and offered important financial support to these groups. Efforts from the firm have paid as these key entities were largely surrounded and positively influenced by information concerning the new vaccines.

⁷² **Mello M, et al.** *Pharmaceutical Companies' Role in State Vaccination Policymaking: The Case of Human Papillomavirus Vaccination*. 2012.

Finally, one last key role Merck played was helping the poor populations to have access to the vaccine by filling the gaps and providing it for free through various vaccine patient assistance programs. In shipping vaccines to numerous clinics and licensed professionals for administration to low-income, uninsured adults, Merck has demonstrated its understanding of the remaining financial problems as well as its will to address them somehow.

GSK's and Pfizer's response to MSF's call for lower pneumococcal vaccine prices

In a report on vaccine pricing released in 2015 and following many years of negotiations, NGO Médecins Sans Frontières (MSF) called British actor GSK and US giant Pfizer to lower prices of their pneumococcal pneumonia vaccines to not more than \$5 per child in developing countries. Over the years, MSF had identified this specific vaccine as one of the biggest contributor to the soaring cost of vaccinating a child in the poorest regions, accounting for 45% of the total amount. The MSF's call to action urged the two major vaccine players - sole manufacturers of such pneumococcal vaccines- to act upon the urgency.

In September 2016, firm GSK announced that it would lower the price of its pneumonia vaccine intended for some of the world's most vulnerable children⁷³. In the wake, and after seeing its attempt to donate one million doses of vaccines for free refused by MSF, competitor Pfizer followed the decision to lower the price of its pneumococcal conjugate vaccine (PCV) for children caught in humanitarian emergencies⁷⁴.

In both cases, price reduction appeared as a significant and necessary step forward in protecting vulnerable children leaving in the poorest regions of the world and reached by humanitarian organizations like MSF. In taking such decisions, both GSK and Pfizer showed that they were able to receive signals coming from their external environment and demonstrated their concern as well as their will to work on a longer-term solution to enhance access and improve

⁷³ **MSF**. *MSF Welcomes GSK's Decision to Lower Price of Pneumonia Vaccine for Some of the World's Most Vulnerable Children*. 2016.

⁷⁴ **MSF**. *MSF welcomes Pfizer's pneumonia vaccine price reduction for children in humanitarian emergencies*. 2016.

affordability of their vaccines. Although many steps will follow in order to reach this goal, responding to this call was crucial for both vaccine companies as the media had started to get to grips with the case and spread it around society.

iii. Application to Vaccine Hesitancy

As highlighted in the previous section, vaccine companies are starting to act upon the need to define clear and sustainable non-market strategies, in order to be sustainable and pursue business. In the actual context of rising vaccine hesitancy, taking a step forward and trying to address the issue seems necessary and inevitable. While only few and timid initiatives are emerging from the business, the (IA)³ model presented by Bach in its 2010 paper could help lead and influence such ambition.



Figure 13 – The (IA)³ framework.⁶⁸

This (IA)³ framework is built around the analysis of six factors: the issue, the actors involved, their interests, the arena in which actors meet, the information dragging the issue in this given

area and the assets actors can prevail in this environment. The following will attempt to apply this model to the case of vaccine hesitancy.

What is the issue?

The first step in considering the non-market environment is to define issues. It is crucial for a business to take a position on a given issue not only for neutralizing a threat, but also for being able to leverage potential new opportunities that would emerge from the resolution of the issue. As described previously, vaccine hesitancy is a growing phenomenon hitting all kinds of vaccines, companies, countries and population types, and is embedded within a more global trend where individuals are increasingly pursuing individual empowerment and requesting patient-choice. Addressing vaccine hesitancy is becoming more and more urgent for vaccine companies as this issue has the ability to profoundly impact their business on the immediate but also on the long-term, besides its evident consequences with regard to public health.

Who are the actors?

Identifying the issue generally leads to defining the interested parties. Key actors are often those with an economic or ideological stake in the issue. In the case of vaccine hesitancy, stakeholders are multiple and various, as discussed in this paper. Key players interacting in a way or another with vaccine companies include vaccine recipients, patients' relatives and immediate social circle, patient associations, activist groups, healthcare professionals, lobbyists, legislators, payers and the media, to mention only the most important. From there, stakeholders can be organized and grouped, according to the strategy trying to be developed. For instance, a strategy intended to provide payers with some more transparency regarding vaccine revenues could potentially be shared with the media in order to reach the general public and demonstrate a bigger impact.

What are the actors' interests?

Understanding what drives the actors and motivate them to be engage in a given issue is key. Also, it is critical to assess how homogeneous a particular set of actor is. As an example, all vaccine hesitant people are not due to the same drivers and barriers. Probing the different stakeholders in this respect may help a given company draw up a strategic map highlighting potential allies and key opponents in its journey to manage vaccine hesitancy. For instance, a patient organization seeking accurate and reliable information about adjuvants in vaccine will need to be managed in a total different manner that a group of activists fundamentally opposed to vaccination and spreading misinformation on social media. However, subgroups of a given patient organization or group of activists may also need to be differentiated and apprehended in a specific manner as their ultimate motivation might differ. Indeed, a hesitant mother whose baby was sick after receiving a vaccine might not need to be approached in the same way as a young adult being fiercely against medicines. In view of efficiently addressing vaccine hesitancy, segmentation and personalization will without doubt play a very important role.

In what arena do the actors meet?

Non-market issues can be brought in many settings, from parliamentary committee hearings and courtrooms all the way to industry seminars or the media sphere. Knowing where stakeholders will meet matters greatly as the rules will vary importantly across setting. For instance, trying to engage with a community of bloggers will not require the same investment, resources and actions than trying to approach a group of lobbyists in a given parliament. Similarly, a patient association may prefer to be approached in person, whereas blogger communities may feel more comfortable and be more receptive by exchanging openly online. In particular, building on the potential offered by social media might offer interesting opportunities in the future. Indeed, social media platforms not only offer opportunities to the anti-vaccine movement, but also to public health in general. Hence knowing the targeted audience as well as its environment is key

and is likely to influence strongly a company's influence and implemented strategies towards its stakeholders.

What information moves this issue in this arena?

As discussed previously, information is the currency of non-market management. Yet, the type of valuable information that will trigger action and influence the resolution of an issue varies greatly across arenas. For instance, it might be helpful to possess public opinion data in order to lobby critical members of a decisional committee, while this won't be of any help in courtrooms. Similarly, mastering the blogosphere and social media will help address the concerns of the different communities multiplying online around vaccine hesitancy. In any case, owners of critical information will often benefit from a decisive advantage in their attempt to tackle such issue. Having the appropriate and relevant kind of information for a given issue and arena is key to success. As an example, vaccine companies may have to communicate better with the physicians, especially by providing them with additional scientific data supporting safety and efficacy of vaccines in order to restore the lost confidence.

What assets do the actors need to prevail in this arena?

Besides possessing the right information in the right context and arena, other criteria have the potential to significantly affect the management of an issue such as vaccine hesitancy. Hence, assets such as company's reputation and its perceived trustworthiness can appear to be of great importance in order to influence the public's perception. Similarly, detailed knowledge about a given tender or recommendation procedure can help convince the actors at stake and reach the intended goal. In any case, and particularly that of vaccine hesitancy, building a strong network of contacts and being able to assemble and mobilize coalitions rapidly can be a major asset to deploy. Also, and to conclude, vaccine companies should never forget to emphasize the great impact they are making every day worldwide by developing, manufacturing and commercializing vaccines.

Thus, together with a rigorous industry analysis, the (IA)³ framework can help addressing non-market issues and delivering a non-market edge. In the case of vaccine hesitancy, it helps imagine and picture some of the possible strategies that could help tackle this growing phenomenon among the various stakeholders involved. Such approach and framework won't guarantee immediate success, but will ensure proactive non-market management as opposed to reactive non-market management. Consistency is key to tackle a global and complex issue such as vaccine hesitancy. Possible initiatives are countless, but being able for a vaccine company to draw up a strategic roadmap by precisely identifying who cares, why and where will enable the company to define the information and assets most needed to anticipate and shape the issue's evolution in a manner that serves its ultimate business interests.

THÈSE SOUTENUE PAR : Lara SALVI

TITRE :

EVOLUTION DE LA PERCEPTION PUBLIQUE DE LA VACCINATION : UN BESOIN CROISSANT DE STRATEGIES NON MARCHANDES DANS L'INDUSTRIE PHARMACEUTIQUE

CONCLUSION :

« Le sentiment anti-vaccin est aussi vieux que la vaccination elle-même » citait Dubé en 2015. Alors qu'une faible fraction de la population exprime un tel sentiment, la situation alarmante tient du fait que la proportion de ces individus au sein de la société croît. Cette situation devient une préoccupation dans un contexte où une couverture vaccinale élevée est requise afin de pérenniser le succès de la vaccination. Ainsi, bien que la vaccination soit une mesure initiée au niveau de l'individu, elle s'avère être capitale pour la communauté environnante de par l'immunité de groupe qu'elle procure. De fait, l'hésitation vaccinale se doit d'être abordée non seulement au niveau individuel mais également sociétal. Aussi, malgré des efforts significatifs, il s'avère que les stratégies de santé publique basées sur des preuves scientifiques n'ont à ce jour pas suffi à contrer ce mouvement.

Dans la quête vers une meilleure compréhension des causes et du contexte menant à ce sentiment d'hésitation et de refus vaccinal, le domaine de l'économie comportementale a permis d'apporter de nouveaux éléments en démontrant notamment que les perceptions et actions des individus sont souvent irrationnelles et entraînées par des facteurs non-contrôlables. De plus en plus, il semble nécessaire de considérer le contexte social, culturel et politique au sein duquel évoluent les individus, tout en capitalisant sur le rôle essentiel des professionnels de santé.

En ce sens, les multinationales aujourd'hui également de plus en plus affectées par des facteurs externes, tels que l'évolution des réglementations, les politiques des gouvernements ou l'attention des médias, se doivent de fait d'opérer avec ces éléments environnants dits non-marchands. Au moyen de leviers sociaux et politiques, le management non-marchand encourage les entreprises à prendre soin de leur image, de leurs valeurs ainsi que de leur empreinte sociale, et tend ainsi à être envisagé de façon internationale et à long terme, en impliquant souvent des clients indirects. Aussi, la définition d'une stratégie non marchande claire est susceptible d'aider les entreprises du vaccin à capitaliser sur leur pouvoir souple de persuasion, leur crédibilité et influence, pour *in fine* transformer de tels atouts en avantages compétitifs.

En conclusion, il est clair que l'hésitation vaccinale est un problème complexe auquel aucune stratégie unique ne saurait répondre. Cependant, les entreprises se souciant de ce phénomène et l'appréhendant dans son ensemble semblent plus à même de remodeler favorablement leur environnement, et donc d'engendrer une meilleure acceptation des vaccins à long terme. Les parties prenantes autour de la vaccination se multiplient dans un environnement évoluant rapidement et il est aujourd'hui capital de se soucier et d'aborder l'hésitation vaccinale à l'échelle de la communauté. Il est certain que ce phénomène continuera d'évoluer et que de nouvelles questions apparaîtront à mesure que de nouvelles informations deviendront disponibles. Toutefois, il semble important dès à présent pour les entreprises du vaccin de reconnaître qu'une stratégie commerciale efficace est nécessaire mais non suffisante dans l'optique d'une performance économique pérenne. A l'inverse, une stratégie non marchande claire est rarement suffisante mais bien souvent nécessaire pour une performance durable.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 27/8/18 .

LE DOYEN



LE PRÉSIDENT DE LA THÈSE

Dr. Jean BRETON

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Liste des Annexes

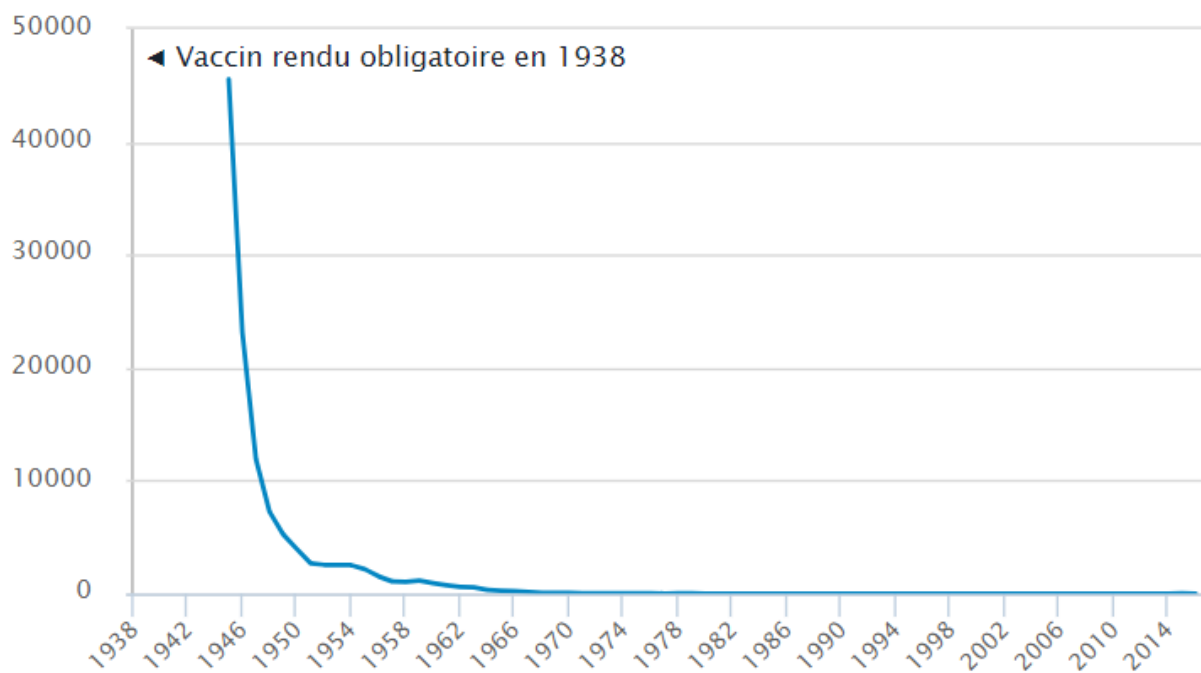
Annexe 1 – Impact of the introduction of vaccines in France.

Appendix I

Impact of the introduction of vaccines in France

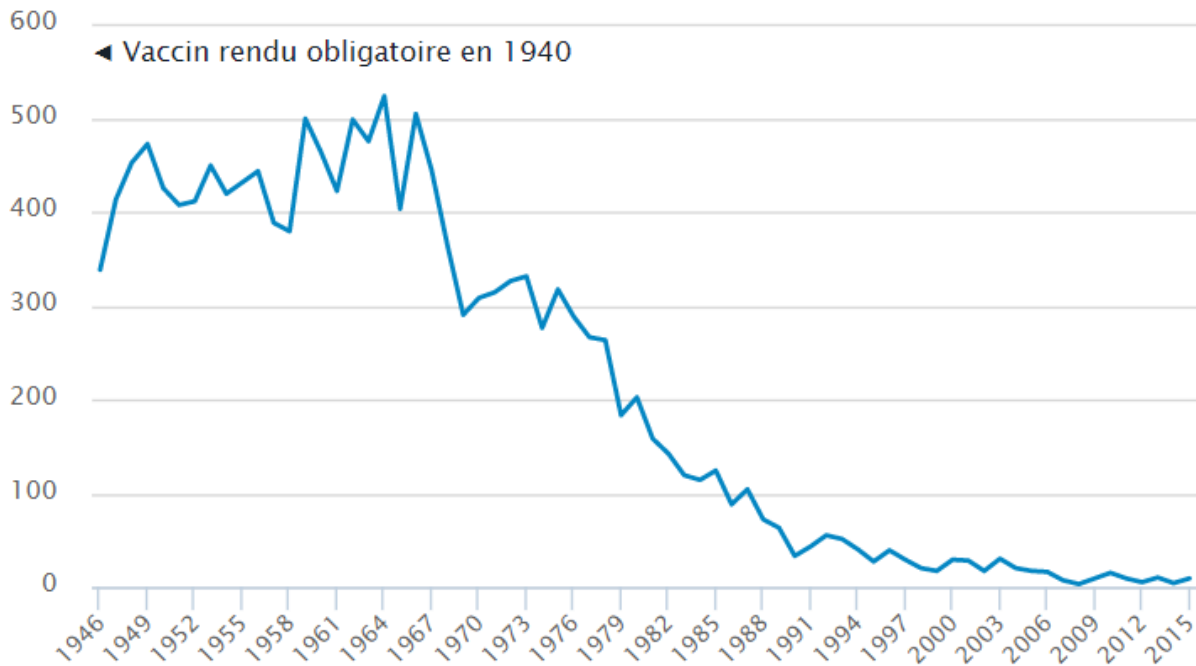
- Number of diphtheria cases in France between 1945 & 2016 (*Corynebacterium diphtheriae* + *Corynebacterium ulcerans*).

Source: Santé Publique France (compulsory declarations).



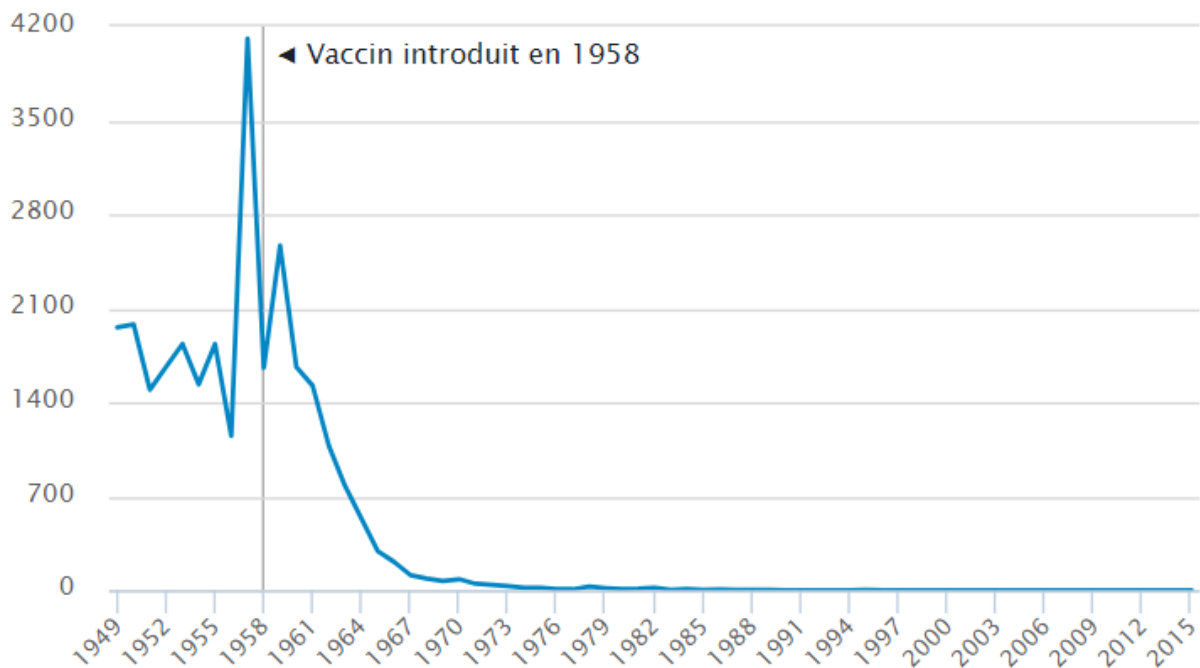
- **Number of tetanus cases in France between 1945 & 2015.**

Source: Santé Publique France (compulsory declarations).



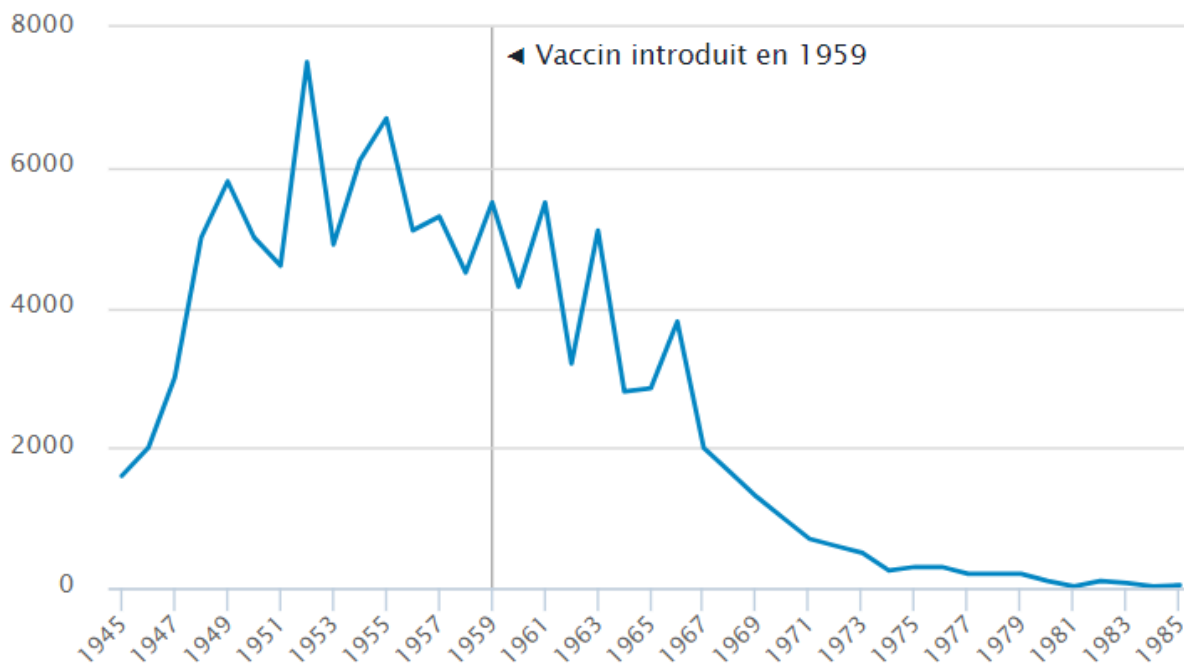
- **Number of poliomyelitis cases in France between 1949 & 2015.**

Source : Santé Publique France (compulsory declarations).



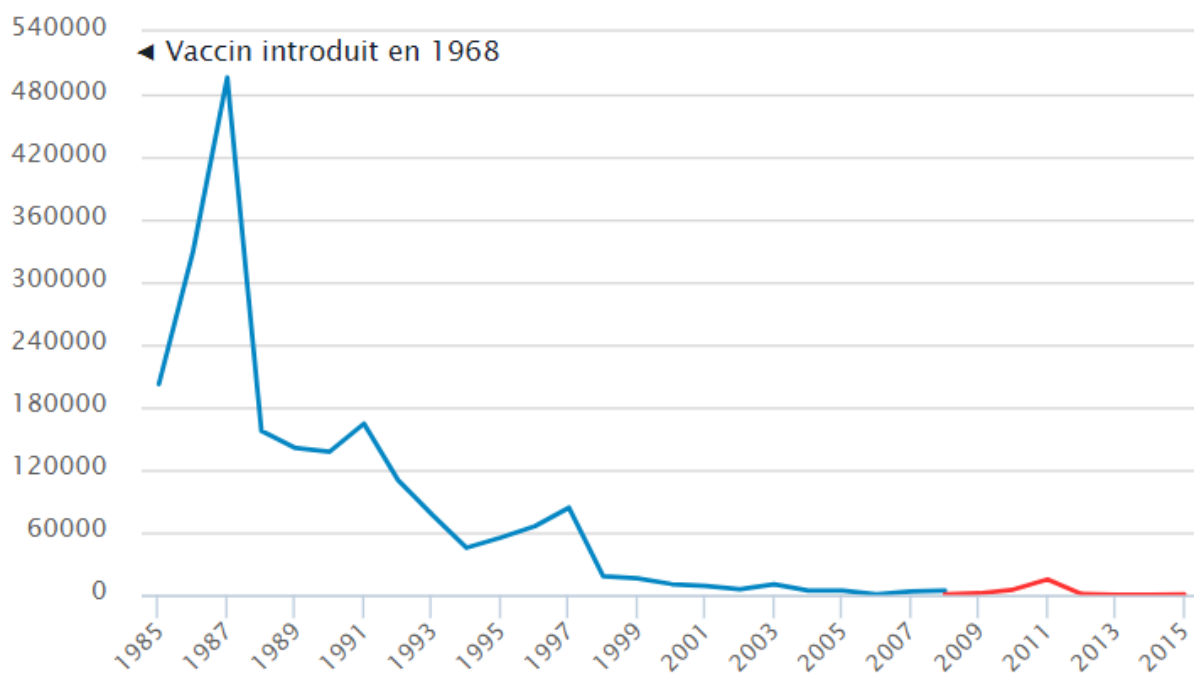
- **Number of pertussis cases in France between 1945 & 1985.**

Source : Santé Publique France (compulsory declarations).



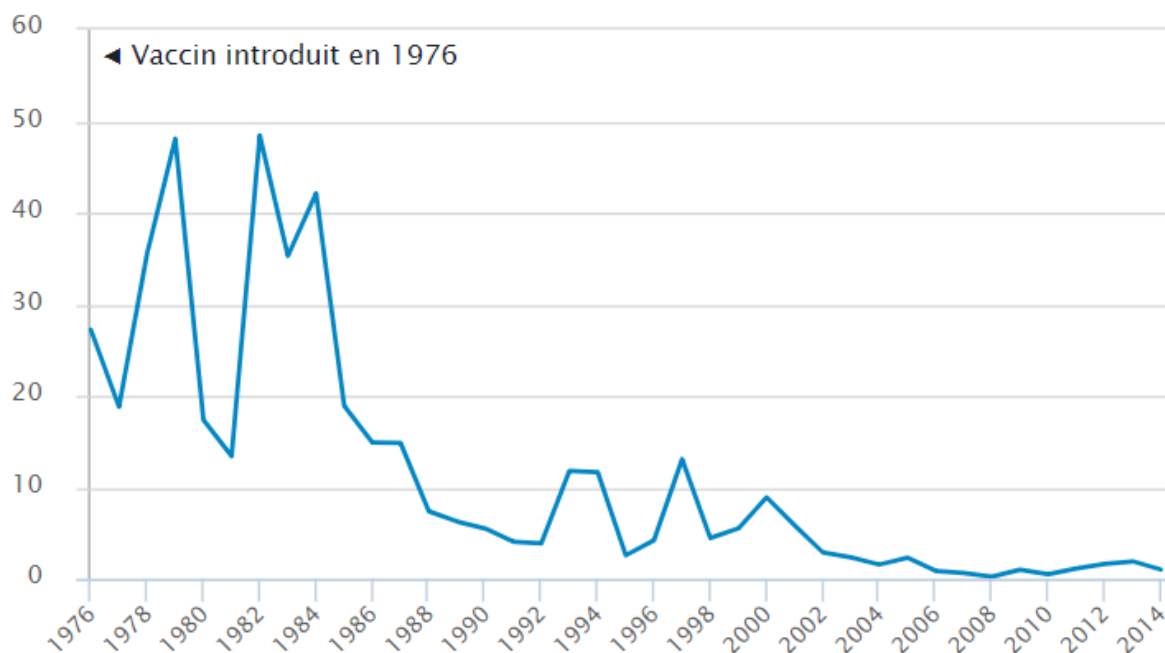
- **Number of measles cases in France between 1985 & 2015.**

Source : Santé Publique France (compulsory declarations) & Sentinel Network.



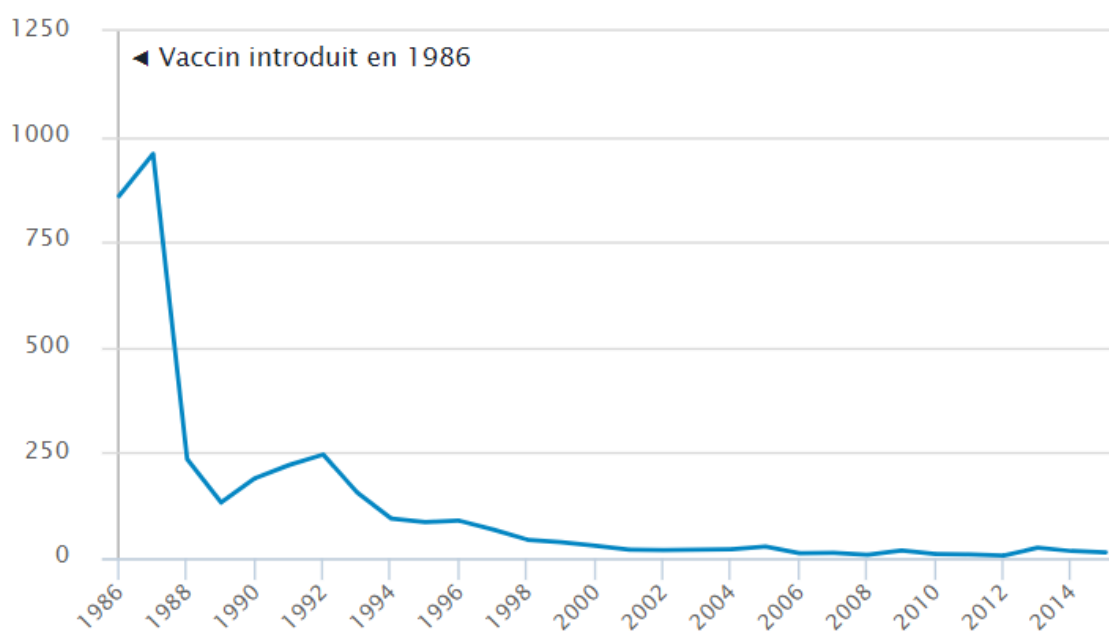
- **Incidence rate of rubella infections during pregnancy and congenital malformative rubella in France between 1976 & 2014.**

Source : Rénarub Network.



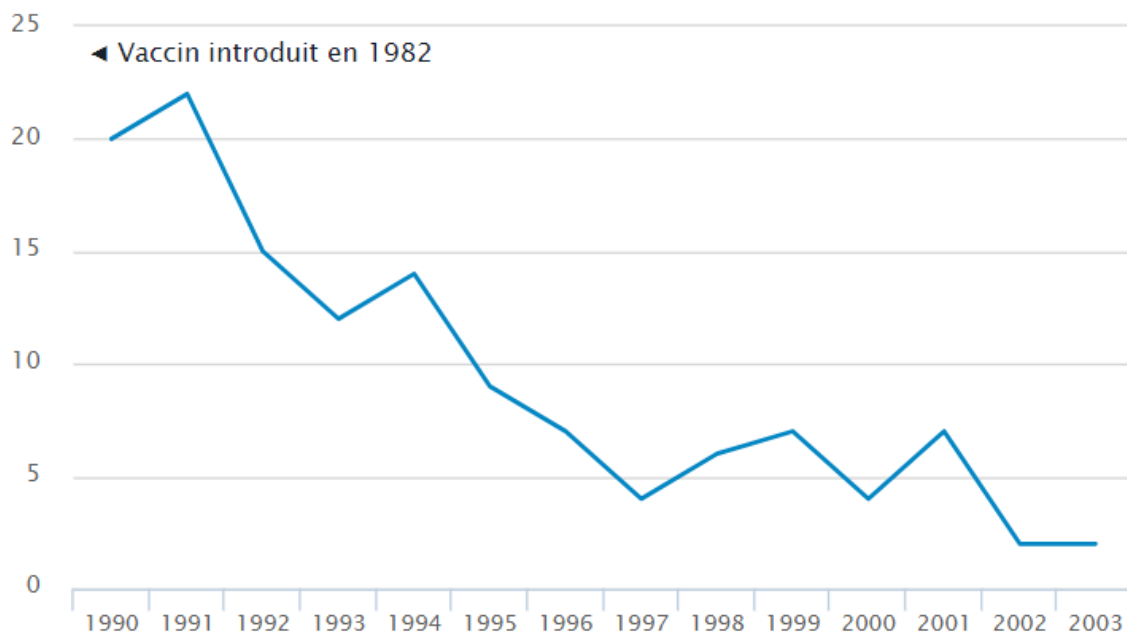
- **Mumps incidence rate in France between 1986 & 2015.**

Source : Sentinel Network.



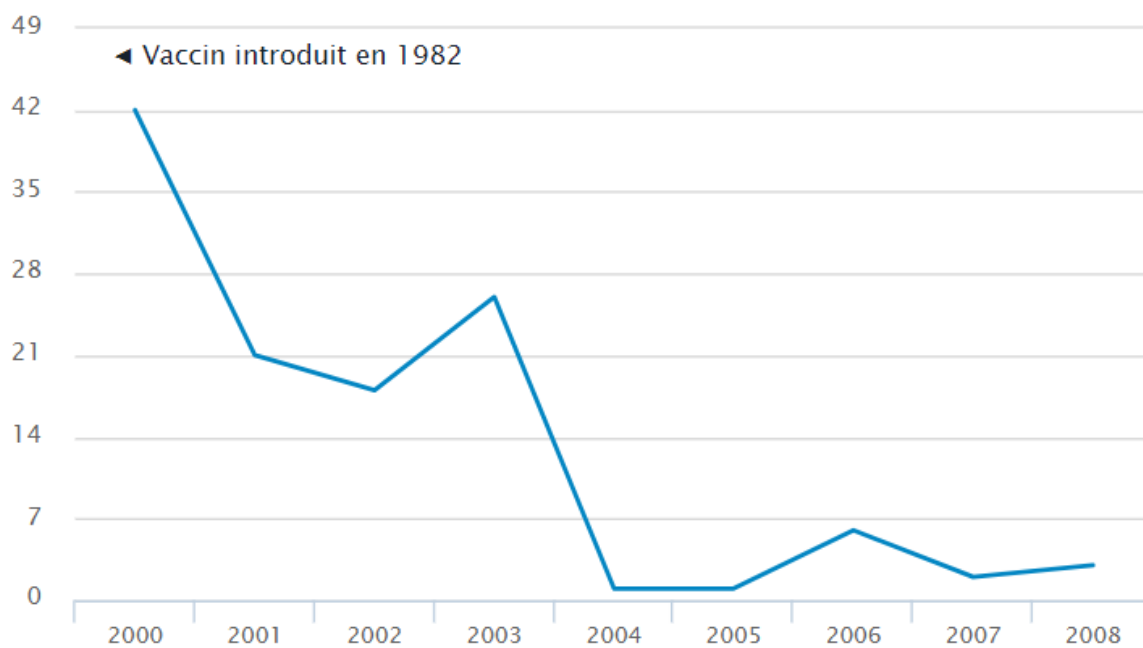
- **Number of transplants due to fulminant hepatitis B in France between 1990 & 2003.**

Source : European register of hepatitis transplants (ELTR), Pr D. Samuel.



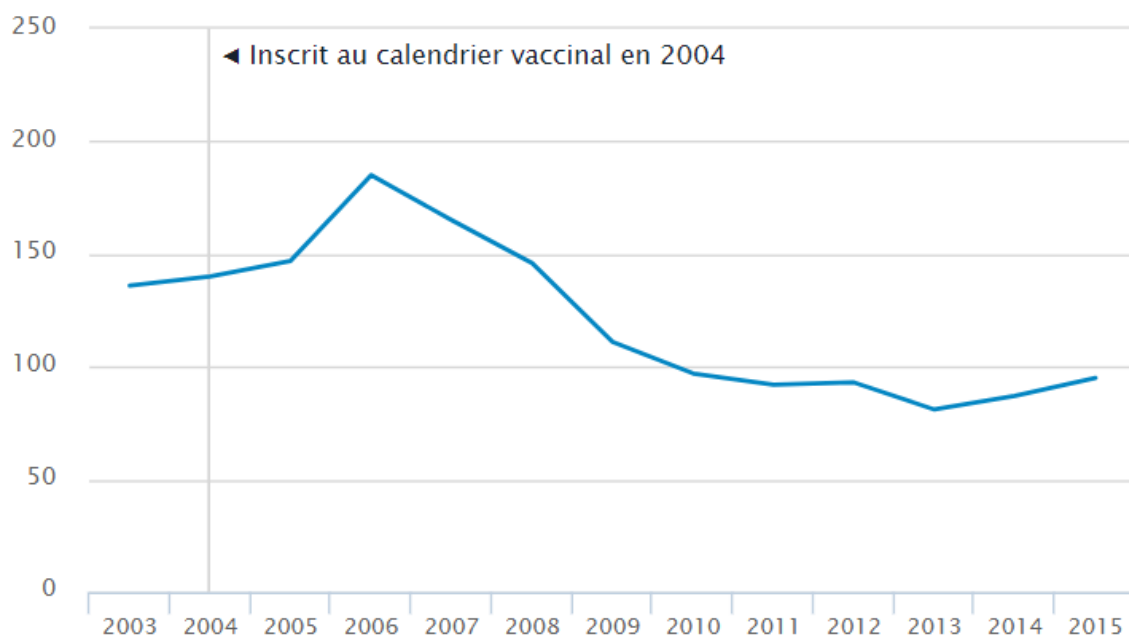
- **Incidence rate of acute hepatitis B in France between 2000 & 2008.**

Source : Sentinel Network.



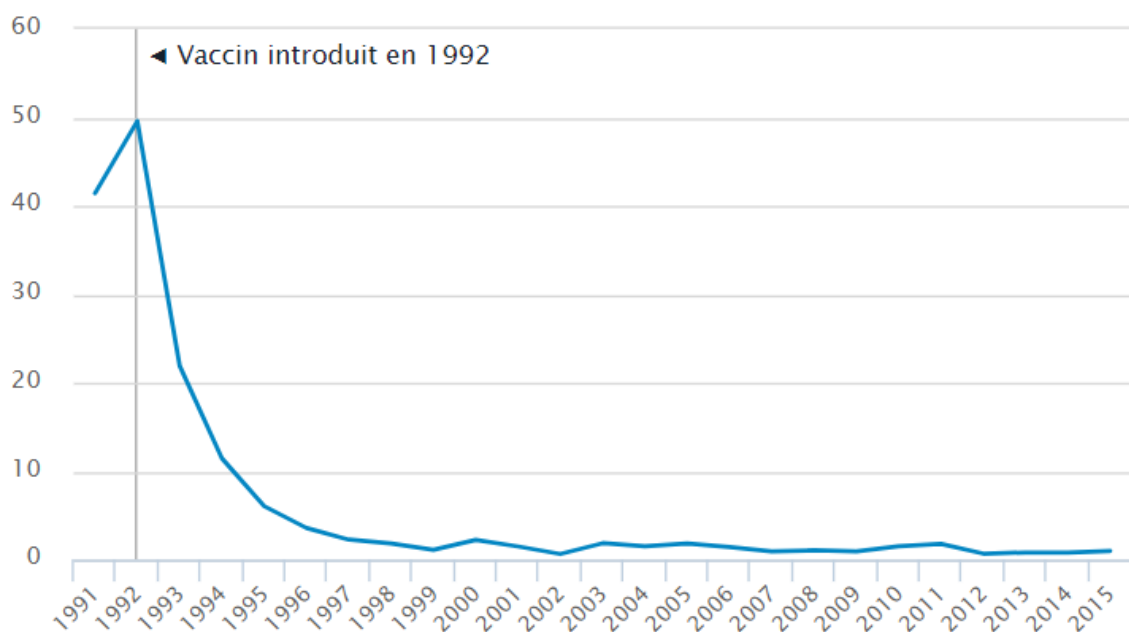
- **Estimated number of symptomatic hepatitis B cases in France between 2003 & 2015.**

Source : Santé Publique France (compulsory declarations).



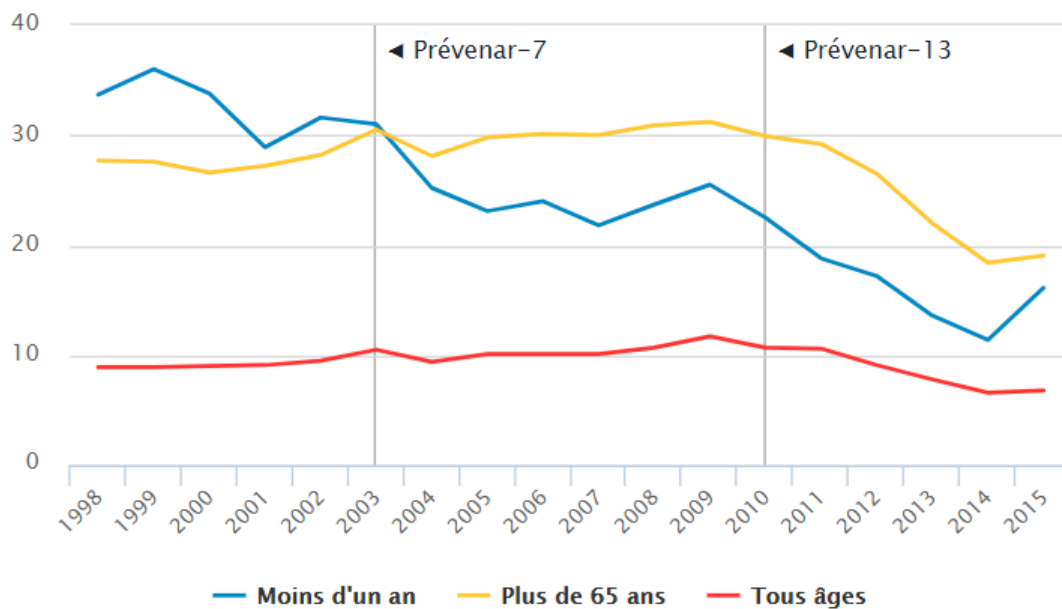
- **Incidence rate of *Haemophilus influenzae* meningitis amongst children under 5 in France between 1991 & 2015.**

Source : Epibac Network.



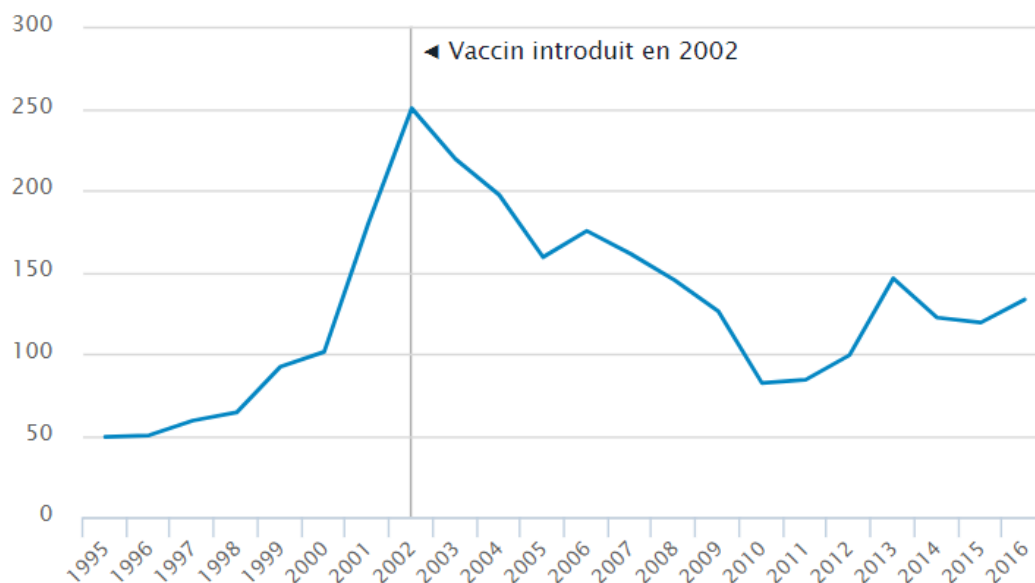
- **Number of cases of invasive pneumococcal disease per 100,000 people in France between 1998 & 2015.**

Source : Epibac Network, Santé Publique France & National Pneumococcal Reference Center.



- **Number of cases of invasive meningitis C infections in France between 1995 & 2016.**

Source : Santé Publique France (compulsory declarations).





Serment de Galien



« Je jure en présence des Maîtres de la Faculté, des Conseillers de l'Ordre des Pharmaciens et de mes condisciples :

D'honorer ceux qui m'ont instruit(e) dans les préceptes de mon art et de leur témoigner ma reconnaissance en restant fidèle à leur enseignement.

D'exercer, dans l'intérêt de la santé publique, ma profession avec conscience et de respecter non seulement la législation en vigueur, mais aussi les règles de l'honneur, de la probité et du désintéressement.

De ne jamais oublier ma responsabilité et mes devoirs envers le malade et sa dignité humaine ; en aucun cas, je ne consentirai à utiliser mes connaissances et mon état pour corrompre les mœurs et favoriser des actes criminels.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert(e) d'opprobre et méprisé(e) de mes confrères si j'y manque ».

Lara SALVI

EVOLUTION DE LA PERCEPTION PUBLIQUE DE LA VACCINATION: UN BESOIN CROISSANT DE STRATEGIES NON MARCHANDES DANS L'INDUSTRIE PHARMACEUTIQUE

RÉSUMÉ:

La vaccination représente l'une des plus grandes avancées de notre ère en termes de santé publique. Pourtant, l'acceptation des vaccins par la population n'a jamais été évidente. Malgré les évidences scientifiques et une technologie toujours plus performante, la vaccination systématique est perçue comme dangereuse et inutile aux yeux d'une fraction croissante de la population. L'érosion de la confiance envers les vaccins est désormais considérée comme une menace envers la viabilité des programmes de vaccination, et l'hésitation vaccinale est tenue pour responsable du déclin des couvertures vaccinales et du risque inhérent de maladies et d'épidémies qui pourraient être évitées. Le monde moderne est complexe et constitué d'une multitude de facteurs sociétaux, politiques et environnementaux qui contribuent à l'essor de ce phénomène. De ce fait, il est aujourd'hui capital pour les entreprises du vaccin d'en comprendre les causes et d'en analyser les effets. Alors que les acteurs liés aux vaccins tendent à se multiplier sur un marché toujours plus complexe et compétitif, les stratégies dites non marchandes sortent tout particulièrement du lot en termes d'initiatives modernes de management et s'imposent progressivement comme un besoin croissant et un élément clé de la solution à la crise de l'hésitation vaccinale.

ABSTRACT:

Vaccination is one of the greatest advances in public health of our times. Yet, public acceptance of vaccines has never been a given. Despite scientific proof and enhanced technology, routine immunization is perceived as unsafe and unnecessary by an increasing fraction of the population. Erosion of trust in vaccines is now considered a threat to the sustainability of immunization programs, and vaccine hesitancy is hence held liable for decreasing vaccine coverage rates and a subsequent increased risk of vaccine-preventable disease outbreaks and epidemics. In the actual context drawing together a set of societal, political and environment circumstances that may contribute to the rise in vaccine hesitancy among modern society, understanding and assessing the causes and effects of this phenomenon appears capital for vaccine companies to drive sustainable growth. As vaccine stakeholders tend to multiply in an increasingly complex and competitive market, non-market strategies particularly stand out from the noteworthy modern management initiatives and progressively appear as a growing need and a promising part of the solution to the vaccine hesitancy crisis.

MOTS CLÉS : vaccins, perception publique, industrie, stratégies non marchandes

FILIÈRE : Industrie