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Abstract

Vaccine development is a lengthy, expensive and risky venture, with the research and development (R&D) process costing billions of dollars. The pre-clinical stage of vaccine R&D is largely performed by academic research institutions, then continued by the pharmaceutical industry through licensing agreements, taking the most promising candidates to the clinical testing stage. Governments play a major role in de-risking the early stages of vaccine R&D for the pharmaceutical industry through the funding of research in public institutes and academic research laboratories, and providing loans and tax credit to pharmaceutical companies involved in vaccine R&D. Through these initiatives, governments fuel the industry, shape markets and aid the development of novel products and technologies. Many of the blockbuster vaccines currently on the market benefited greatly from government funding, however, pharmaceutical companies are reaping most of the rewards of the billions of dollars these vaccines generate every year. The present review will discuss the role that government funding and academic research has played in vaccines R&D. Furthermore, it will discuss some of the elaborate schemes pharmaceutical companies use to reduce their tax payments, and how strategies such as patenting government-funded innovations can help ensure that governments receive a share of the generated revenues.

Keywords: Vaccine; Patent; R&D; Financing; Government

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1. Introduction

The increase in antimicrobial resistance (AMR) and the threat of global epidemics have made the development of new vaccines an indispensable weapon to fight infectious diseases. One of the main causes of AMR is the widespread use of antibiotics. Vaccines generally target various strains of a pathogen, thus narrowing the spectrum of antibiotics required to treat diseases, and this effect can be enhanced through herd immunity (Lipsitch and Siber, 2016). However, the extensive use of antibiotics disturbs the gut flora, which increases the risk of opportunistic infections such as *Clostridium difficile*. Hence, by reducing the use of antibiotics, vaccines have the potential to prevent diseases caused by pathogens they would otherwise not cover (Kwok *et al.*, 2012; Theriot *et al.*, 2014; Lipsitch and Siber, 2016).

Vaccine development is a complex and expensive endeavour surrounded by many uncertainties. It is estimated that it costs around US\$500 million to develop simpler vaccines, and more than a US\$1 billion to develop more complex products such as the pneumococcal vaccine Prevnar (Plotkin, Mahmoud and Farrar, 2015). Despite the heavy investment and involvement of highly qualified personnel, only 7% of vaccine candidates that enter the preclinical testing stage actually reach the market (Pronker *et al.*, 2013). This high rate of failure is due to a multitude of factors, including the increasing difficulty in identifying vaccine targets for more complex diseases, tighter laws and regulations on animal and human testing, the complex patent landscape and competition (Kola and Landis, 2004; DiMasi and Grabowski, 2007). All of these challenges mean that it now takes a minimum of 10 years for a vaccine candidate to go from conception to the market (Oyston and Robinson, 2012).

This high degree of uncertainty over the success of the vaccine research and development (R&D) process means financing institutions have to be willing to take on a high level of risk, endure the long R&D process and delayed profits. Vaccine R&D is financed by a wide range of NGOs, and private and public institutions. Due to the high degree of uncertainty, there has been a steady decrease in the amount of venture capital invested in the early stages of R&D (Fleming, 2015). Nowadays, venture capital usually focuses on investment exit strategies of 3 years, which is quite short considering that drug and vaccine development takes at least 10 years (Mazzucato, 2015a).

Pharmaceutical companies themselves finance vaccine R&D, but in many cases they invest in promising candidates that are close to clinical stage testing, and which were developed by academic research laboratories and other institutions funded by governments, charities and funding bodies (e.g. the Gates Foundation, the Wellcome Trust and the European Union). In

addition to funding R&D in public institutes and academic research laboratories, the government also contributes to R&D finance through loans and tax credits, thus supplying the early-stage high-risk finance to the pharmaceutical industry (Mazzucato and Semieniuk, 2017). To further help the pharmaceutical industry, the United States of America (USA) passed the Orphan Drug Act in 1983, which offered companies conducting research into rare diseases generous tax credits and market exclusivity for 7 years following their products' approval by the Food and Drug Administration (FDA), even if it is not patented (Lazonick and Tulum, 2011).

One of the major achievements in biomedical research was the sequencing of the human genome, achieved under the Human Genome Project. The project was founded in 1990 by the National Human Genome Research Institute (NHGRI, formerly known as US National Center for Human Genome Research), which later partnered with institutions in the US and around the world (Green, Watson and Collins, 2015). The sequencing of the human genome has helped scientists understand better the role of genetic factors in the pathogenesis of diseases such as cancer, Alzheimer's and schizophrenia. In addition to gaining a better understanding of diseases' pathogenesis, the knowledge gained from the human genome can be used in the development of drugs and vaccines, public health, clinical genetics and personalised medicine (Wilson and Nicholls, 2015).

The sequencing of the human genome was a major breakthrough and cost over US\$3 billion, which mainly came from governments and various funding bodies (e.g., the Wellcome Trust) (Hayden, 2014). Since the sequence of the first human genome, the cost of sequencing the human genome has fallen from US\$10 million to a couple of thousand dollars. The NHGRI has been the main funder of the R&D of sequencing technologies, awarding grants to 97 groups of academic and industrial scientists between 2004-2014 (Hayden, 2014). In addition, the NHGRI also aided the launch of companies and laboratories, thus helping to create an entire new genome sequencing industry. Illumina (San Diego, USA), the market leader in sequencing technology, has benefited greatly from NHGRI efforts and today employs many professionals, and has acquired companies that were once funded by the NHGRI (Hayden, 2014).

In 1980 the Bayh-Dole Act gave universities and hospitals property rights over knowledge, technology and products developed through federal funds. However, this act allows privately-owned companies, through patent purchases or paid licenses (including exclusive licenses), to gain ownership of government-funded research (Mowery *et al.*, 2001). The aim of the Bayh-Dole Act was to promote the growth of firms and the development of new products, since it

was feared that research would remain unexplored if intellectual property could not be transferred to private companies (Mowery *et al.*, 2004).

Most of the funds that governments invest on vaccine R&D come from the tax payers, and very little comes from the sales of the products that reach the market through the pharmaceutical industry, even though their early stage was government funded. In the current article, I propose a scheme involving the patenting and copyrighting of government-funded innovations as a strategy to raise capital to further fund vaccine R&D. Section 2 of this article will describe the crucial role governments play in funding vaccine R&D, section 3 will present evidence that government-funded academic research was vital for the development of some of the most lucrative vaccines in the market today, and sections 4 and 5 will discuss strategies governments could implement to gain a share of the revenues generated by the sales of vaccines whose preliminary development was government funded.

2. Vaccine R&D and public funding

Governments finance vaccine R&D through various forms of tax credit or grants to universities, institutes and the pharmaceutical industry.

2.1. R&D tax credits

R&D tax credits allow companies to reduce their tax bill or claim payable cash credits as a proportion of their R&D expenditure. This type of credit is designed to incentivise private companies to invest more on R&D, particularly in areas with high public importance such as vaccine development. By reducing the tax bill on expenditures on R&D, companies can make a higher return on investment on products that reach the market. Thus, tax credits contribute to de-risking R&D investments, and through these savings it has been estimated that the net costs of R&D are reduced by 50% (Tax Policy Center, 2002; Rao, 2011).

In 2005, US pharmaceutical companies claimed over US\$6 billion in tax credits, and one fifth of the companies in the country applied for R&D tax credits (Rao, 2011). In the USA, companies are entitled to up to 20% credit on research and experimentation (R&E) expenditures (Table 1). In the United Kingdom (UK), under the Vaccine Research Relief Programme, companies developing vaccines can claim up to 40% tax credit (Rao, 2011). According to Young and Surrusco (2001), the effective tax rate for the pharmaceutical industry is approximately 40% less than the average tax rate charged to other industries (Young and Surrusco, 2001). There are four types of tax credit: foreign, possessions, R&E and orphan drug

(Table 1) (Young and Surrusco, 2001). Through these tax credits, it is estimated that pharmaceutical companies save between US\$4-10 billion per year in taxes (Young and Surrusco, 2001).

	Country	Purpose	Year introduced
Orphan Drug Tax Credit	USA	Provides 50% tax credit for clinical testing for rare and neglected diseases.	1983
Qualifying Therapeutic Discovery Research Project Tax Credit	USA	Aims to provide up to 50% tax credit to support research for unmet medical needs, the reduction of long-term healthcare costs and the development of new cancer treatments. It is targeted at companies with a maximum of 250 employees.	2010
R&E Credit	USA	It is divided into two types: Regular credit: a company may claim as a credit 20% of any qualified research expenses. Alternative Simplified Credit: Firms can claim a credit equal to 14% of the amount of their qualified research expenses, including contracting projects to biotechnology companies	1981
Vaccine Research Relief Programme	UK	Aims to promote vaccine R&D by allowing up to 40% credit on R&D expenses, including work subcontracted to other firms in the country and internationally.	2003

Source: (Rao, 2011)

Table 1. Tax credit strategies in the USA and the UK.

2.2.Direct investment in vaccine R&D

Government funding of academic research plays a crucial role in the early stages of vaccine development, thus fuelling the industry, shaping the market, and encouraging the development of new technologies. This section will discuss the role of the two of the biggest sources of government funding for vaccine R&D: the US National Institute of Health (NIH) and the European Union (EU).

2.2.1. NIH

The NIH is the biggest funder of biomedical research in the world and is one of the main organizations responsible for the biotechnology and pharmaceutical revolution. The NIH has invested over US\$900 billion (in 2015 dollars) between 1936-2015, and since 2004 has spent on average over US\$30 billion per year (Mazzucato, 2015b). Between 2000 and 2013, the NIH invested over US\$400 billion (in 2013 dollars) in biotechnology and pharmaceutical knowledge base (Mazzucato, 2017). In comparison, venture capital in the USA only spent US\$27.6 billion in the biotechnology and pharmaceutical industries between 2001-2006 (Lazonick and Tulum, 2011). As a result of all of this investment, approximately 75% of “new molecular entities” (the

most innovative medicine candidates) were funded in total or partially by the NIH (Mazzucato, 2015b).

Approximately 10% of the NIH budget is spent on personnel working in its 26 research centres and institutes, and 80% is for research grants awarded to over 325,000 researchers spread across 3000 academic research institutes and medical schools in the USA and around the world (Lazonick and Tulum, 2011). Between 2008 and 2019, the NIH invested US\$28.5 billion in vaccine R&D projects (Table 2) (NIH, 2019) thus helping to expand the industry.

	Funding for research (in millions of US\$)											
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
HPV and/or Cervical Cancer Vaccines	19	25	25	24	26	25	38	31	38	59	82	84
Malaria Vaccine	32	34	41	39	40	34	36	44	47	61	64	58
Tuberculosis Vaccine	18	15	13	17	21	26	31	23	27	29	31	28
Vaccine Related	1632	1593	1737	1717	1691	1608	1573	1585	1773	1823	2016	1845
Vaccine Related (AIDS)	556	561	535	550	557	518	533	541	605	562	565	545
Total/year	2,257	2,228	2,351	2,347	2,335	2,211	2,211	2,224	2,490	2,534	2,758	2,560
Total from 2008-2019	28,506											

Following a Congress request, the NIH began to make its expenditure publicly accessible from 2008.

Source: (NIH, 2019)

Table 2. Annual estimates of NIH funding of vaccine R&D projects between 2008-2019.

2.2.2. European union vaccine funding

The EU is one of the main funders of basic vaccine research and under its flagship initiative, Horizon 2020, has been at the forefront of the field. Horizon 2020 is the largest funder of research and innovation in Europe, with a total budget of €97.6 billion (European Commission, 2018a). Horizon 2020 aims to drive European economic growth and well-being by actively investing in all stages of the R&D process, from basic research to the market. The Horizon 2020 vision is divided into three pillars (European Commission, 2018a):

- The open science pillar – provision of competitive fellowships and funding research projects through the European Research Council and the Marie-Skłodowska-Curie actions.
- The global challenges pillar – the support of research into various societal challenges, including the development of new therapies for cancer, clean energy, and plastic-free oceans.

- The open innovation pillar – this aims to place Europe as the leading market-creating region for innovation.

Horizon 2020, through agreements between the European Commission and NIH, also funds research projects in the USA (Zerhouni and Potocnik, 2008). The initiative provides a wide range of funding schemes for vaccine research around the world, for both the academic and private sectors (Gancberg *et al.*, 2015). For instance, following the 2014/15 Ebola outbreak, Horizon 2020 disbursed €24.4 million to fund a trial for an Ebola vaccine developed by pharmaceutical giant GlaxoSmithKline plc (GSK) and 2 projects to assess the passive administration of antibodies (Gancberg *et al.*, 2015).

Furthermore, under the Framework Program 6 and 7 (FP6 and FP7), the EU spent over €500 million on vaccine projects between 2007-2016 covering the various aspects of vaccine development (adjuvants, vectors, antigens, delivery systems, animal models, and clinical trials) (Draghia-Akli, 2017). One of the most prominent projects under FP7 is the Advanced Immunization Technologies (ADITEC) program, a multinational collaborative project involving 43 partners (28 academic, 13 small and medium enterprises (SMEs) and 2 pharmaceutical companies) from 13 different nations. Under ADITEC, 9 clinical trials were undertaken and over 110 peer-reviewed articles were published (Gancberg *et al.*, 2015).

Another initiative funded by the EU is the European and Developing Countries Clinical Trials Partnership (EDCTP). In the EDCTP1 (2003-2013), the EU disbursed €64 million to fund 26 vaccine research projects and has committed to contributing a further €683 million for EDCTP2 (2014-2023). European Member States have committed to cover the remaining funds to reach the required €1.4 billion budget (Gancberg *et al.*, 2015).

The EU is also part of the Innovative Medicines Initiative (IMI), created in 2009 in partnership with the European Federation of Pharmaceutical Industries and Associations (EFPIA) (Gancberg *et al.*, 2015; Draghia-Akli, 2017). The aim of this initiative is to support research and innovation (novel vaccines, medicines and treatments) to achieve both public health benefits and commercial success (Draghia-Akli, 2017). The total budget for 2014-2024 is €3.27 billion (€1.64 billion from the EU) and €215 million have already been committed in the form of grants for projects researching the Ebola vaccine (Gancberg *et al.*, 2015; Draghia-Akli, 2017). The IMI funding is destined to small and medium-sized pharmaceutical companies, academic research institutions, patient organisations and regulatory agencies (Draghia-Akli, 2017).

In addition to the programmes mentioned above, the EU is also involved in funding vaccine research through a range of partnerships and initiatives:

- Coalition for Epidemic Preparedness Innovations (CEPI)

The CEPI was launched following the 2013-16 Ebola outbreak with the objective of supporting the development of vaccine candidates for a range of neglected infectious diseases (Wellcome Trust, 2019). The CEPI has received approximately US\$740 million (target is US\$1 billion) from the EU, the Gates Foundation, the Wellcome Trust and several governments (Japan, Germany, Norway and Canada). The EU contributed in kind with €250 million (Wellcome Trust, 2019).

- InnovFin Infectious Diseases (InnovFin ID)

The InnovFin ID, an EU initiative, funds research into drugs and vaccines at their early stages of clinical development, medical devices, and infrastructure (European Commission, 2018b). The initiative mainly provides loans and grants valued between €7.5-75 million to pharmaceutical companies, research institutions and legal bodies. Through this initiative, the EU aims to share the risks involved in developing novel products with the pharmaceutical and biotechnology industries, thus promoting growth, de-risking R&D investment into infectious diseases, and reducing the risk of global epidemics (European Commission, 2018b).

- Fast Track to Innovation (FTI)

With this initiative, the EU aims to accelerate the development, market entry and take-up of novel innovations. FTI is committed to disbursing €100 million per year between 2015-2020 (Schmaltz, 2015). The initiative sets out to help private and public partners to collaborate to create and test novel revolutionary products and services (Schmaltz, 2015; European Commission, 2019).

3. The role of government-funded academic research in the R&D of vaccines currently on the market

3.1. Human papilloma virus (HPV) vaccines: Gardasil and Cervarix

HPV is a group that encompasses over 100 virus, where 15 of them have been shown to be responsible for almost all cases of cervical cancer (Clifford *et al.*, 2005). Globally, around 630 million people are infected with HPV and half of women in the world will have an infection caused by this virus in their lifetime (Merck, 2008). On average, there are 530,000 new cases

of cervical cancer and approximately 266,000 deaths per year, with the highest incidence in developing nations where HPV vaccine coverage is low (UNICEF, 2018).

Fifteen HPV types have been shown to have oncogenic potential: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. One of the challenges to create a vaccine and treatment for HPV is the fact that an individual can be infected by more than one HPV type (Choi *et al.*, 2012). Globally, HPV 16 and 18 are responsible for approximately 70% of all cases of cervical cancer. HPV type 16 causes mainly squamous cell carcinoma, whereas HPV 18 causes the less aggressive adenocarcinoma (Bosch *et al.*, 2008).

The two most widely used prophylactic vaccines on the market are Gardasil-4 (Merck, USA) and Cervarix (GSK, UK), entering the market in 2006 and 2007, respectively (McKee, Bergot and Leggatt, 2015). Both vaccines contain virus-like particles (VLPs) for HPV 16 and 18, which cause cervical cancer, but Gardasil-4 also has VLPs for HPV 6 and 11, which cause benign genital warts (Ma, Roden and Wu, 2010).

Academic institutes in the USA (The National Cancer Institute (NCI) and Georgetown University) and Australia (University of Queensland) first developed the L1-VLP technology employed in the VLP-based vaccines in the early 1990s (Padmanabhan *et al.*, 2010).

John T. Schiller and Douglas R. Lowy from NCI (part of the NIH) produced non-infectious HPV VLPs capable of inducing the production of protective antibodies that could neutralize a HPV infection (Roden *et al.*, 1996; Pastrana *et al.*, 2001; NIH, 2017). Jian Zhou and Ian H. Frazer from the Papillomavirus Research Unit (University of Queensland) developed a method to express HPV L1 and L2 capsid proteins that self-assembled into VLPs. Furthermore, they also found that the minor HPV capsid protein L2 is essential for virus life cycle (Zhou *et al.*, 1991, 1994, 1999). The research by Schiller and Lowy was funded by the NCI (hence the NIH), while the research conducted by Zhou and Frazer was funded by the NIH, National Health and Medical Research Council, the Queensland Cancer Fund, the Mayne Bequest, and the Princess Alexandra Hospital Research and Development Foundation.

The NCI licensed the technology to Merck and MedImmune (which also paid for an exclusive license of the intellectual property (IP) belonging to Georgetown University). Merck later also paid for an exclusive license for the VLP related IP belonging to the University of Queensland (Padmanabhan *et al.*, 2010). GSK then bought the entire MedImmune IP portfolio in 1998, meaning that Merck and GSK held all the VLP IP available at the time. Due to a significant uncertainty over patent infringement because of the large scope of some of the patents, GSK

and Merck signed a cross-license agreement that allowed the companies to use each other's technologies related to HPV vaccine development (Padmanabhan *et al.*, 2010).

Merck and GSK then improved on the original government-funded research that was carried out in academic institutions and performed the subsequent steps required to bring the vaccine to the market (Padmanabhan *et al.*, 2010). Merck's Gardasil-4, the first VLP-based vaccine, was patented in the USA in 1998 and introduced to the market in 2006 (Castro *et al.*, 2017). Between the first patent approval and 2010, 81 HPV vaccine-related patents were granted in the USA, with Merck leading the way with 24 patents (Padmanabhan *et al.*, 2010). GSK released their VLP-based vaccine in 2007.

Both vaccines target HPV L1 major capsid protein which assembles to form VLPs with a morphology similar to the HPV native virions, and generates robust antibody responses against the targeted HPV types (Ma, Roden and Wu, 2010). Merck introduced a new HPV vaccine, Gardasil-9, in the USA and Europe in 2014 and 2015 respectively. In addition to the four HPV types covered in Gardasil-4, the new vaccine also provides protection against HPV types 31, 33, 45, 52 and 58 (Merck, 2018). Table 3 shows the global revenues of Gardasil and Cervarix between 2006 and 2017.

	Revenue in (in millions of US\$)													
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015*	2016*	2017*	2018*	Total
Gardasil *	242,30	1,956.6	2,268.1	1,667.6	1,338.0	1,462.0	1,895.0	2,122.0	1,986.0	2,092.0	2,389.0	2,308.0	3,151	24,877.6
Cervarix **	-	20.1	248.75	306.68	367.84	814.66	423.9	261.44	202.96	137.28	106.92	172.86	180.78	3,244.17

* Includes sales of Gardasil-4 and Gardasil-9. *Sources* (Merck, 2008, 2009, 2012, 2015, 2017, 2018, 2019). ** *Sources* (GSK, 2008, 2011, 2014a, 2017a, 2018, 2019). Original revenues are in Great Britain Pound (£). Used the exchange rate of the respective year on July 2 (MacroTrends, 2019) to calculate the revenue in US\$.

Table 3. Revenue of Gardasil and Cervarix from 2006-2018.

3.2. Pneumococcal conjugate vaccines

Pneumococcal disease is a bacterial infection by *Streptococcus pneumonia* that causes inflammation in the lungs, bacteremia (bacteria in the blood stream), meningitis (infection of the tissue surrounding the brain and spinal cord), pneumonia and infection of the middle ear (Bencker, 2013). The disease can affect all age groups, but young children, the elderly and individuals with particular chronic medical conditions are significantly more susceptible. Pneumococcal disease is by far the biggest cause of child death globally, the vast majority in the developing world, and it is estimated that it causes around 800,000 deaths in children

younger than 5 years of age annually (Bencker, 2013). According to the World Health Organization (WHO), pneumonia alone is responsible for 23% of deaths of children under 5 years of age globally (WHO, 2016).

The major challenge for developing a polysaccharide vaccine was the fact that children under 2 years of age respond poorly and do not develop an immunologic memory (Brueggemann *et al.*, 2007). This challenge was overcome by Oswald T. Avery and Walther F. Goebel of the Rockefeller Institute for Medical Research hospital, who covalently linked polysaccharides with immunogenic proteins, thus enabling the vaccine candidate to induce the recruitment of CD4⁺ T cells while establishing immunologic memory and high IgG titer (Avery and Goebel, 1931). The two scientists thus gave rise to the conjugation technology that was further developed by other academic research groups (Paul, Katz and Benacerraf, 1971; Lindberg *et al.*, 1974; Boquet and Pappenheimer, 1976; Talwar *et al.*, 1976) and later employed in various conjugated vaccines, including the *Haemophilus influenzae* type b (Hib) diphtheria CRM197 conjugate vaccine (Bixler *et al.*, 1989).

Prevnar 7, the first pneumococcal conjugate vaccine (approved in 2000), is composed of 7 saccharides derived from the capsular antigens of the *Streptococcus pneumoniae* serotypes covered in the vaccine individually conjugated to the immunologic carrier protein (the diphtheria CRM197 protein) (Gruber, Scott and Emini, 2012). Prevnar 7 was developed by Wyeth, which was later acquired by Pfizer (Pfizer 2011), following the principles employed to develop the *Haemophilus influenzae* type b (Hib) CRM197 conjugate vaccine (Poolman, Peeters and van den Dobbelsteen, 2013).

For the Prevnar 7 vaccine, Pfizer used an aluminium-based adjuvant to allow the serotypes to act together and was granted a patent on the grounds of the vaccine's novelty, capability for industrial application and the research methodology that enabled the increased therapeutic efficacy (Garçon, Leroux-Roels and Cheng, 2011; Rajam and Poddar, 2018).

Adjuvants are used in vaccines to induce an early high and long-term immune response. Adjuvants have been employed in vaccine development since Ramon first described in 1925 their benefiting effects on immune response following the injection of tetanus and diphtheria toxoids with compounds such as agar, tapioca, lecithin and saponin (Ramon, 1925, 1926). The technology for using aluminium-based adjuvants in vaccines has been extensively studied and developed by various academic research groups since the mid-20th century (Aprile and Wardlaw, 1966; Jensen and Koch, 1988; Bomford, 1989; Gupta and Siber, 1994; Gupta *et al.*,

1995). Thus, the technology employed to create the pneumococcal conjugate vaccines was largely developed by academic research institutions with government funding.

Prevnar 7 was the first vaccine in the world to generate over US\$1000 million in net revenue (Wyeth, 2006). In 2010, Pfizer and GSK released two new pneumococcal conjugate vaccines, the Prevnar 13 (Pfizer) and PCV10 or Synflorix (GSK) (GSK, 2011; Pfizer, 2012). Globally, the Prevnar vaccines have brought in revenue of US\$56,950.70 million, whereas Synflorix sales have brought in £ 3,577.00 million (Table 4).

Prevnar 7 (revenue in millions of US\$)													
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Revenue per year	461	798.2	647.5	945.6	1,053.6	1,508.3	1,961.3	2,439.1	2,715.5	287	1253	488	399
Total revenue	14,956.7												

Sources: (Wyeth, 2003, 2006, 2009; Pfizer, 2012, 2015)

Prevnar 13 (revenue in millions of US\$)									
	2010	2011	2012	2013	2014	2015	2016	2017	2018
Total per year	2,416.00	3,657.00	4,117.00	3,974.00	4,464.00	6,245.00	5,718.00	5,601.00	5,802.00
Total generated	41,994								

Sources: (Pfizer, 2012, 2015, 2018, 2019)

PCV 10 or Synflorix (revenue in millions of US\$)*									
	2010	2011	2012	2013	2014	2015	2016	2017	2018
Total/year*	335.92	563.5	604.45	615.6	684.56	594.36	665.28	656.61	555.44
Total revenue	5,275.72								

* Original revenues are in £. Used the exchange rate of the respective year on July 2 (MacroTrends, 2019) to calculate the revenue in US\$. Sources: (GSK, 2011, 2014b, 2018, 2019)

Table 4. Revenue gained from the sales of pneumococcal conjugate vaccines from 2000-2017.

3.3. Rotavirus vaccine: Rotateq and Rotarix

The rotavirus is the main cause of severe diarrhoea among children under 5 years of age, killing between 200,000-300,000 annually. It is responsible for 111 million cases of gastroenteritis, 25 million hospital consultations and 2 million hospitalizations per year (de Oliveira *et al.*, 2008; Tate *et al.*, 2016). The vast majority of rotavirus cases occur in low and middle-income countries. The introduction of two rotavirus vaccines, RotaTeq (Merck) and Rotarix (GSK), as part of routine immunization programmes in over 70 countries has helped reduce the number of deaths from 528,000 in 2000 to 215,000 in 2013 (Tate *et al.*, 2016).

RotaTeq provides protection against 5 strains of rotavirus (pentavalent), and was developed by H. Fred Clark and Stanley Plotkin of the Wistar Institute (University of Pennsylvania), and Paul Offit of the Children's Hospital of Philadelphia (CHOP).

The scientists identified rotavirus surface proteins capable of inducing the production of protective antibodies, determined the strain specificity of the antibody response, and discovered that the vaccine had to act in the intestinal mucosa to induce the immune protection (Offit and Blavat, 1986; Offit, Shaw and Greenberg, 1986; Shaw *et al.*, 1986; Offit and Dudzik, 1989; Offit *et al.*, 1991, 1994; Offit, 1994; Treanor *et al.*, 1995). The scientists also performed efficacy and safety clinical trials in infants in a couple of cities in the USA and Central African Republic (Clark *et al.*, 1986, 1988; Treanor *et al.*, 1995). The work was mainly funded by the NIH, but other institutions such as the Merieux Institute (France), WHO and the Hassel Foundation (USA) also contributed.

Merck acquired the license from CHOP (fee plus royalties) and took the then vaccine candidate to efficacy clinical trials in 1992. Following a series of clinical trials, the vaccine was licensed in 2006 (Clark, 2008; Light, Andrus and Warburton, 2009).

Rotarix, a monovalent vaccine, was developed by Richard Ward and David Bernstein at the Cincinnati Children's Hospital Medical Center in the beginning of the 1990s, and was granted a patent in 1995 (Ward, Bernstein and Plotkin, 2009). The two scientists isolated the human rotavirus strain, created an orally-deliverable vaccine candidate, and performed the early efficacy and safety clinical trials (Ward, Bernstein and Plotkin, 2009). The research was largely funded by the NIH (Ward, Bernstein and Plotkin, 2009).

	Revenue (in millions of US\$)													
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
RotaTeq (Merck) *	163	525	665	522	519	651	601	636	659	610	652	686	728	7,617
Rotarix (GSK) **	81.40	182.91	332.33	462.48	357.20	483.00	565.20	570.00	646.72	650.52	619.08	675.96	682.51	6,309.31

Sources: *(Merck, 2008, 2009, 2012, 2015, 2018, 2019) **(GSK, 2008, 2011, 2014a, 2017b, 2018, 2019). Original revenues are in £. Used the exchange rate of the respective year on July 2 (MacroTrends, 2019) to calculate the revenue in US\$.

Table 5. Rotavirus vaccines revenue between 2006-2017

The patent was then licensed to the Virus Research Institute which later merged with T Cell Sciences to give rise to a new company named Avant Immunotherapeutics (Drugs R&D, 2004). Avant Immunotherapeutics then undertook further phase II clinical trials, which showed that the vaccine provided 89% protection and resulted in few adverse events. In 1997, GSK acquired the global marketing rights of the vaccine candidate, assumed all development costs and paid Avant US\$5.5 million in milestone payments plus a royalty of 10% on net sales (Drugs R&D,

2004; Light, Andrus and Warburton, 2009). GSK then took the vaccine candidate to phase III clinical trials and the vaccine was licensed in 2006 (Light, Andrus and Warburton, 2009).

From 2006 to 2017, RotaTeq resulted in sales of US\$6,889 million, whereas Rotarix saw sales of £3,640 million (Table 5).

4. How governments can take a share of the vaccine sales revenue

The vaccines described above have generated over US\$100 billion in sales revenue. Based on the information presented in this article, it is clear that the governments that funded the early stage of the R&D of these vaccines should receive a percentage of the revenues generated. The current belief is that governments get some of the money back through taxes paid by the companies themselves and their employees. However, in addition to tax breaks, companies have elaborate strategies to reduce the amount of tax that they pay.

One of the most common strategies pharmaceutical companies use is tax inversion, which consists of relocating a corporation's legal domicile to countries or states with low-tax or no-tax jurisdictions (i.e., Republic of Ireland) while maintaining its revenue generating operations in the country of origin which has high taxes (i.e., USA) (Sikka and Willmott, 2010; Houlder, Boland and Politi, 2014).

In the mid-20th century, the Republic of Ireland began to adopt low-tax policies to attract major corporations to the country and now has a 12.5% corporate tax, much lower than the 35% corporate tax in the USA (Houlder, Boland and Politi, 2014). Nine of the ten biggest pharmaceutical companies in the world have corporate headquarters in the Republic of Ireland (Houlder, Boland and Politi, 2014). In the Republic of Ireland, the pre-tax profits to wages ratio is between 30-40% for Irish companies, but for foreign companies this ratio can be as high as 800% (Tørsløv, Wier and Zucman, 2018). On the other hand, in the USA the pre-tax profits to wages ratio is between 30-40% for both local and foreign companies (Tørsløv, Wier and Zucman, 2018). These figures clearly show that big global corporations are shifting their revenues to countries such as the Republic of Ireland in order to pay less corporate tax.

One of the most recent cases of tax inversion was Endo International, a generics and specialty branded pharmaceutical company, which moved its corporate headquarters to the Republic of Ireland in 2013. The company generates almost all of its revenue in the USA, with only US\$230 million of the US\$3.47 billion generated in 2017 coming from outside the USA, but the vast majority of its corporate tax is paid in the Republic of Ireland (Houlder, Boland and Politi,

2014; Endo, 2018). In addition, Endo International will save around US\$75 million per year through “operational and tax synergies” (Houlder, Boland and Politi, 2014). Furthermore, tax inversion also allows companies to offshore IP, thus avoiding tax on it (Houlder, Boland and Politi, 2014).

The USA pharmaceutical industry only paid 6% on more than US\$100 billion in profits registered in the Republic of Ireland between 2004-2014 (Houlder, Boland and Politi, 2014). A recent report by OXFAM estimated that Pfizer, Johnson & Johnson, Abbott and Merck avoided US\$4.8 billion in taxes between 2013 and 2015 in nine developed economies (Germany, New Zealand, Spain, France, Australia, Italy, Denmark, the United Kingdom and the USA) (OXFAM, 2018). Approximately US\$2.3 billion in taxes was avoided in the USA alone during that period (OXFAM, 2018). While such elaborate strategies to reduce tax payments are not illegal, they nonetheless hurt both the economies of those countries (OXFAM, 2018).

The overall corporate tax in the USA is 35%, but for the pharmaceutical industry the average effective corporate tax between 2008-2015 was 27.7% (ITEP, 2017). If profits generated abroad were to be repatriated to the USA, the company would have to pay the 35% tax rate minus the tax rate paid in the country in which the profit was generated (ITEP, 2017). This is one of the reasons companies keep their profits in tax heavens such as the Republic of Ireland, Bermuda, the Cayman Islands and the Bahamas (ITEP, 2017). Illustrative of the creative profit shifting strategy is the fact that USA companies based in Bermuda and the Cayman Islands reported collective profits that were over 15 times higher than the GDP of these two countries (ITEP, 2017).

	Amount of unrepatriated foreign income in millions of US\$			
Company	2016	2015	2014	Total
Pfizer	197,096	193,589	175,798	566,483
Merck	63,100	59,200	60,000	182,300
Total				748,783

Source: (ITEP, 2017)

Table 6. Amount of unrepatriated foreign income held by Pfizer and Merck between 2014-2016.

According to the Institute on Taxation and Economic Policy (ITEP), collectively the Fortune 500 corporations avoided paying around US\$767 billion in USA federal income taxes through the keeping of over \$2.6 trillion of “permanently reinvested” profits offshore (ITEP, 2017). For

instance, between 2014–2016, Merck and Pfizer collectively held almost US\$750 billion in unrepatriated foreign income (Table 6).

In addition, corporations often use their own stocks to pay their executives and other employees as compensation or bonuses. Through this strategy, corporations can claim “excess stock-option tax benefits” and between 2008-2015 it was estimated that USA corporations collectively saved \$51.6 billion in taxes (Gardner, McIntyre and Phillips, 2017)

Other strategies to lower a company’s tax bill include complex pricing schemes. GSK was accused of avoiding approximately US\$ 5.2 billion worth of taxes in the USA by undercharging marketing services supplied by its subsidiary in the country from 1989 to 1996, and agreed to settle the case in 2006 for US\$3.4 billion (Sikka and Willmott, 2010). Furthermore, companies often shift manufacturing to other countries where the labour costs are lower, meaning that a significant number of jobs and taxes are lost (Mazzucato, 2015a).

Governments invest a significant amount of money and resources into the development of vaccines and other medical products, thus playing a crucial role in de-risking the R&D process for the pharmaceutical industry. Below, we present four possible ways through which a government can recoup its investment in R&D:

- A government should sign agreements with companies to ensure that the loans it provides have to be repaid once the product/company start generating profits above a certain threshold (Mazzucato, 2015a).
- Retain equity in the companies that receive tax credits and loans. For instance, Sitra, the Finnish National Fund for R&D that reports to the parliament, provided capital for Nokia during the company’s early stages and retained equity in return (Hira and Hira, 2012). Through such a scheme, the government of Finland ensured that it would recoup its investment and make a profit in case the company became successful.
- Patent and copyright – another strategy would be for the government to hold intellectual property and rent the license in order to guarantee a share of the revenue generated from the products that benefited from government-funded R&D. Through such a strategy, the government would guarantee a constant inflow of capital that could be used to fund new R&D projects and cover the losses of failed projects (Mazzucato, 2015a). The government could also prevent the adverse effects of market monopolies by issuing a general public license.

5. Patents as a strategy to generate revenue for governments

The most common strategy to generate revenue from patents is through licenses, a contract between the patent holder and a third party who wishes to use the protected technology for further innovation. The third party pays the patent holder a fee upfront and/or royalties overtime (Palomeras, 2007).

Patents give the holder market exclusivity. This exclusivity may encompass the product, regulatory exclusivity (e.g., data exclusivity), developmental technologies and product composition. Typically, patents are granted for 20 years, but often holders successfully apply for extensions of up to five years (Lakdawalla, 2018).

The majority of the research undertaken at universities is funded by governments. It is common practice for universities, through invention disclosures, to retain part or full IP of the innovation that takes place on their premises (Sine, Shane and Gregorio, 2003). Patents, due to their ability to influence the market through monopolies, are the most common strategy universities use to retain IP, and previous studies have found that the probability of patenting by universities is much higher for biomedical innovations (Mowery *et al.*, 2001). According to some estimates, universities hold approximately 8% of the total number of patents issued in the USA (Sine, Shane and Gregorio, 2003).

In terms of biomedical research, universities perform the early stages of R&D and the later stages are undertaken by private companies, who pay for the license or buy the patent. Most universities have technology licensing personnel who, along with the innovators, identify and target entities in both the private and public sector who could be interested in the development (Sine, Shane and Gregorio, 2003).

One of the main features that influences the profitability of a patent is its scope. The patent scope determines the technological space that the innovation covers. A broad patent scope therefore would generate more revenue due to the higher probability that a product will infringe the patent (Merges and Nelson, 1990).

As mentioned earlier, patents generate revenue through up-front cash payment and/or royalties as a percentage of sales (Feldman *et al.*, 2002). Sen and Taumann (2007) found that a combination of royalties and fees generates more revenue than royalties or license fees alone (Sen and Tauman, 2007). However, Rickard *et al.* found that higher revenues are generated when royalties are used alone with a nonexclusive contract (Rickard, Richards and Yan, 2016). If governments retain the IP of the inventions/innovations they have funded, it would allow

revenue to be obtained and then used to fund additional research, as well as prevent the negative effects of monopolies (Palomeras, 2007).

However, to take full advantage of licensing, governments need to set up structures to market IP. One strategy could be to employ interdisciplinary scientists who are able to identify a variety of applications of a technology, publish detailed description of patents in online repositories which are easily accessible to interested stakeholders, and adopt a portfolio management approach to manage patents. Such a government-run market place would overcome transaction costs, without introducing the rigidities of traditional technology markets (Palomeras, 2007).

6. Conclusion

The prevailing view is that governments and academia play a small role in the development of new vaccines. However, this article showed that they have indeed played a crucial role in the R&D process of some of the most lucrative vaccines currently on the market. However, the pharmaceutical companies are reaping the majority of the benefits of the resulting revenue, with relatively little in the form of taxes going back to governments.

A new strategy is urgently needed because governments are increasingly working on tighter budgets, leading to circumstances such as the US government attempting to reduce the budget available for biomedical research (Pear, 2017; Salzberg, 2017). Such budget cuts would have negative consequences for biomedical research and by extension, public health.

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7. References

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Abstract

Vaccine development is a lengthy, expensive and risky venture, with the research and development (R&D) process costing billions of dollars. The pre-clinical stage of vaccine R&D is largely performed by academic research institutions, then continued by the pharmaceutical industry through licensing agreements, taking the most promising candidates to the clinical testing stage. Governments play a major role in de-risking the early stages of vaccine R&D for the pharmaceutical industry through the funding of research in public institutes and academic research laboratories, and providing loans and tax credit to pharmaceutical companies involved in vaccine R&D. Through these initiatives, governments fuel the industry, shape markets and aid the development of novel products and technologies. Many of the blockbuster vaccines currently on the market benefited greatly from government funding, however, pharmaceutical companies are reaping most of the rewards of the billions of dollars these vaccines generate every year. The present review will discuss the role that government funding and academic research has played in vaccines R&D. Furthermore, it will discuss some of the elaborate schemes pharmaceutical companies use to reduce their tax payments, and how strategies such as patenting government-funded innovations can help ensure that governments receive a share of the generated revenues.

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