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Forcing Vaccine Progress

Financial interests and health policies in the Philippines

by Oumy Thiongane

A recent dengue vaccine has provoked serious reservations among the scientific community. In 2016, its implementation in the Philippines seems to respond to public health issues while serving diplomatic and commercial interests. More fuel to the fire of distrust in vaccines?

In October 2015, the annual seminar on tropical medicine organised by the French Army Tropical Medicine Institute in Marseille, on the occasion of the 19th Actualités du Pharo, focused on vaccination in the global South. On the third day of the conference at the Timone hospital, several researchers were surprised by the presentation made by the Director of Sanofi Pasteur's dengue vaccine programme about the six types of targeted vaccines in development against the viral pathology. Did he notice the astonishment in the audience when he revealed the limitations of Dengvaxia[®], Sanofi's most developed candidate vaccine that was to obtain its South East Asian licence two months later? A retired immunologist, who had worked at one of the largest French pharmaceutical firms exclaimed to my colleague: 'I would never authorise a vaccine like that!' The strategy for introducing Dengvaxia[®] in Asia and Latin America, targeting children aged 9 and above, was incomprehensible given the vaccine's apparent drawbacks.

Dengue is on the list of neglected tropical diseases drawn up by the World Health Organisation and its partners. WHO estimates that between 50 and 100 million cases of infection occur annually.¹ In Asia and South America, dengue is a public health issue, leading to 3 to 4 million infections and 9000 deaths a year (WHO 2016). Dengue monitoring systems in Africa are relatively new, and in certain countries like Niger, still developing. The

¹ 3.2 million cases were reported to the WHO in 2015. There are two types of figures available for dengue, those from the WHO region reports and those provided by mathematical models, which are three times higher.

pathology of Dengue is also complex and difficult to understand. Most dengue cases are asymptomatic; for a long time the pathology was under-diagnosed due to a lack of knowledge of the disease and confusion with symptoms of other diseases like malaria during the first signs of fever (Amarasinghe et al. 2011). The virus is transmitted by two types of mosquitos belonging to the *Aedes* family. Human infection due to a bite from a female mosquito is caused by one of the four strains of dengue (DEN-1, DEN-2, DEN-3, DEN-4).

Since April 2016, 830 000 Filipino schoolchildren have received between one and three doses of Dengvaxia® as part of a vaccination campaign. The pharmacovigilance follow-up reports several dozen severe dengue cases, and approximately twenty deaths among the schoolchildren vaccinated. Fifteen autopsies have been carried out and three deaths are probably linked to the vaccination administered by the Filipino authorities according to the Philippines General Hospital's dengue investigative task force whose results were disputed by the Public Attorney Service who defends the complainants. The Filipino Food and Drug Administration (FDA) authority has suspended the commercial license for the vaccine. The country is now asking Sanofi to reimburse the entire cost (about 60 million euros) of the vaccination programme.

Vaccines like Dengvaxia® are called '*leaky vaccines*' or '*partially effective vaccines*'. They are first or second generation vaccines (Greenwood and Targett 2011). They require several booster doses (3 to 4) after the primary vaccination due to the low protection level they provide. Their promoters are careful to state that other preventive measures are required in addition to the vaccine (RTS, S Clinical Trials Partnership et al. 2012; RTS, S Clinical Trials Partnership 2014). Nonetheless, Dengvaxia® obtained a commercial license from national regulatory agencies in Asia and South America, for example in Brazil, the Philippines and Mexico. The Dengvaxia® affair is representative of the limits of '*propped up*' vaccines, that various interest groups may well try to exploit to bring vaccinology in general into disrepute.

A '*partially effective*' vaccine

It is well established that following a primary dengue infection the patient is immunised against the infecting strain, but runs a higher risk of developing a severe case of dengue if re-infected. Higher levels of viral replication, signifying higher risk of infection, have been observed both in patients who have had previous contact with the dengue virus, and in new-borns whose mother is positive. In medical terminology, this is known as '*antibody-dependent enhancement*' (ADE), which is the facilitation of infection by antibodies. The dengue virus renders the antibodies antagonistic in order to increase its

virulence, a phenomenon that goes against the dogma in immunology that the immune system protects us against pathogens.

This raises the question of whether Dengvaxia® which targets four strains of dengue, may induce this phenomenon in subjects who have not previously suffered from the pathology. Does the vaccine act initially as a silent infection allowing receptors to recognize the virus and facilitate its replication in the targeted immune cells (Katzelnick et al. 2017)? In other words, are the seronegatives, those who received the vaccination without having had a previous dengue infection, more likely to develop a more severe form of dengue? This question triggered a controversy in several scientific reviews, including *The Lancet Infectious Diseases*.

Between 2016 and 2017, several articles by two university-based modelling groups in Lisbon and Brazil on the one hand, and at Imperial College of London, John Hopkins School of Public Health and the University of Florida, on the other, warned of the risks that a dengue vaccine posed to naïve populations. Their analyses contesting Sanofi's results (Aguilar, Stollenwerk, and Halstead 2016b) established that Dengvaxia® is likely to increase the hospitalisation rate for severe dengue among seronegatives, regardless of age. The authors recommend that the vaccine's promoters conduct diagnostic tests to establish an individual's medical story, before administering the product. They also emphasise that the WHO should not recommend the vaccine solely on the basis of results provided by the pharmaceutical company. The company researchers had interpreted the negative results of the vaccine for children as an immune response related to the immaturity of the patients' immune system. They recommended that Dengvaxia® be administered only to individuals above the age of 9 (Aguilar, Stollenwerk and Halstead 2016a). The WHO Position Paper, that expresses the WHO's position on and opinion of an immunization product, recognised the possibility that the dengue vaccine could increase ADE and discouraged travellers from being vaccinated. They nonetheless recommended it in endemic countries and for seropositive individuals (WHO 2016)².

In February 2018, while the Dengvaxia® scandal was raging in the Philippines, *The Lancet Infectious Diseases* published an editorial titled 'The Dengue Vaccine Dilemma'. In line with the Lisbon epidemiologists and modellers mentioned above, the editorial reminds readers that vaccination should be bound by certain ethics. The editorial concludes: 'Age was clearly used as a proxy for seropositive status in the original recommendations: a position that is no longer tenable'. (*Lancet Infectious Diseases* 2018).

This raises several questions: when and based on what data sets should the precautionary principle be applicable? How many unknown parameters are required to prevent licensing a vaccine when the scientific community has expressed serious doubts? How many alerts are required to redirect a vaccine's introduction, and for example only target

² Seronegatives had infectious antecedents due to the dengue virus.

seropositive individuals? Can the WHO limit itself to making recommendations and does it under-estimate the normative power of its opinions and the authority its voice carries in national decisions involving public health?

Although the WHO did review its recommendation in the light of Sanofi's latest studies revealing the limitations of the dengue vaccine, it is untenable to defend the added value this vaccine provides. So why would anyone vaccinate themselves with a product that has limited preventive effectiveness that produces the same symptoms as the natural infection and may even increase the probability of it occurring in populations that were unaffected?

The risk of a pandemic?

In 2009, Sanofi Pasteur invested 300 million euros to construct a factory entirely dedicated to its candidate vaccine in the municipality of Neuville-sur-Saône, in the metropolis of Lyon. One hundred and seventy-five professionals were involved in the conversion of this industrial site with the production target of 100 million doses of dengue vaccine announced for 2016. The company was hoping for a return on investment and displayed extremely ambitious growth projections. A year earlier, in 2008, it had acquired an Anglo-American biotechnology company Acambis, at a cost of 332 million euros. The latter had developed a promising dengue vaccine, based on the yellow fever virus, genetically modified to express certain proteins found in dengue. Once the factory was up and running, they had to hurry as dengue was 'beginning to take on pandemic proportions' explained Vincent Hingot, production director at Sanofi Pasteur, in the newspaper *Le Monde*.

In order to act quickly, without waiting for the results of the second phase of the study that had been launched in 2009 in Thailand, Sanofi began the third phase in ten countries in 2011. The Research and Development department at the Lyon site coordinated a total of 33 clinical trials, and shared the study results as early as 2014, almost immediately after the minimum period of 4 years required by the WHO to monitor the security and efficiency of an experimental vaccine.

The Philippines, the first country to licence the vaccine, began a large scale vaccination programme three months before the WHO publicly announced its opinion of Dengvaxia®, and despite concerns expressed by Filipino doctors regarding the government's hasty implementation of the vaccination campaign. The pressure exerted by the Filipino government at the time in favour of the vaccination revived the debate on the connection between politics and public health.

Geopolitics in Health

President Holland's visit to the Philippines in February 2015 was officially dedicated to climate agreements. He was however accompanied by a Sanofi representative based in the country. This was reciprocated by a courtesy visit from President Benigno Aquino III, who travelled to France accompanied by his State Secretary for Health. The result was a declaration by the Filipino government of its intention to buy 3 million doses of the dengue vaccine, for a sum of 3.5 billion Filipino pesos, equivalent to 56.5 million euros. In November 2014, a similar visit to Guinea by President Holland, a memorable one for the country's public health authorities, aimed to promote a diagnostic test developed by a French company during the Ebola epidemic. The urgency of such an initiative was far from obvious to the local actors. The business-orientation aspect of French health diplomacy has already been questioned by some Guinean actors in the health sector, as well as by geopolitical health analysts. The latter recalled that health, particularly that of the poor, is a parameter of the power and security of rich nations (Kerouedan 2013). But should we treat negotiations for the sale of an Airbus and the validation of diagnostic equipment for Ebola, in the context of an epidemic, in the same manner?

The budget allocated to the dengue vaccination campaign in the Philippines was one million pesos higher than that of the routine vaccination against nine antigens. Allegations claim that the former State Secretary for Health Jeannette Garin, the wife of an elected member of the House of Representatives, embezzled part of this sum for electoral purposes. Corruption is a national issue in the Philippines. It ranks third on the list of concerns mentioned by voters during the 2016 presidential campaign (Holmes 2017). The current President, Rodrigo Duterte, based his campaign on this theme, proclaiming that change was coming. The dengue vaccine was introduced during this campaign, and the outgoing president, Benigno Aquino III, used it as his warhorse. The Filipino plaintiffs who claim to be victims of the vaccine's side effects, are supported today by VACC, Volunteers Against Crime and Corruption, a non-governmental organisation born out of the Filipino Catholic Church. In October 2017, Duterte appointed one of its founders, Dante Jimenez, to the position of president of the PACC, the Presidential Anti-Corruption Commission that is the President's armed wing in his war against drugs and, incidentally, against his own detractors.

The social sciences have underscored countless times how vaccination serves as an instrument of governance (Moulin, Anne-Marie 2007; Thiongane, Graham and Broutin 2017). The blurring of public health policies by the games politicians play is the backdrop against which the Dengvaxia® case occurred. These various phenomena may serve to further discredit vaccines and vaccination.

The conditions that create trust in vaccines

The media overexposure of purported adverse safety events following vaccination exacerbate the debate on the danger of vaccines. New ineffective vaccines weaken the general trust in vaccines and discredit those that do good work. In this context, it is not unreasonable to believe that the Dengvaxia® scandal aggravates this crisis of confidence and reinforces the arguments put forward by the detractors of vaccines and their components, in Europe and elsewhere (H. Larson, Brocard Paterson and Erondy 2012; H. J. Larson et al. 2014). About fifty Filipino doctors have already contributed to an opinion piece calling for a renewal of trust in vaccines and the weighting of the debates around on Dengvaxia®.

The French government's 2016 citizen consultation on vaccination, coordinated by the French Ministry for Solidarity and Health, reinforced the obligation to vaccinate children and increased the number of compulsory vaccinations from 3 to 11. This has probably served to heighten the distrust of vaccines and reinforce the lack of understanding between politicians, experts and citizens (Ward, Colgrove and Verger 2017). Legally enforcing vaccination while it is the subject of passionate and sometimes violent debates is unlikely to work in its favour. Although they remain a minority, vaccine critics claim that the infectious diseases targeted by the recommended vaccinations (which became compulsory in January 2018) no longer carry the same fatality burden, nor do they have the same devastating effects as in the past. Vaccination has become the victim of its success: its effectiveness against polio or tetanus has erased the stigmas and deformations provoked by these diseases from collective European memory (Orobon 2016). In places where the vaccination rate has dropped dramatically or where populations cannot easily access preventive measures, such as Guinea, one still sees cases of paralysis caused by diseases that could have been prevented by a vaccine.

If vaccination is to remain one of the pillars of public health and one of the most valuable weapons in the first phase of French public health policy in terms of prevention, politicians, public health experts and medical researchers have a duty to seriously consider and address the arguments put forward by sceptics, critics, the undecided and naturalists. These groups' knowledge and experience should not be disqualified on the basis of positivist and scientific arguments that are closed to debate, and serve to reinforce categorical positions. Let us recall that vaccination is not an insignificant or neutral act. It is a socio-political medico-technical action carried out on a healthy body that inflames conceptions of nature, politics, ethics, economics, culture and religion. The undesirable effects, that indeed occur very rarely, are legitimately considered unacceptable to a population that respects the demands of public health and biosecurity.

With its epistemological perspective, medical anthropology also has a role to play. It can help explain the interactions between perceptions of risk and social representations of disease and vaccine technology in a complex world. It provides pathways to allow immunisation decisions to be explained and debated in a democratic and neutral manner. These efforts necessarily involve an analysis of the connections between the new forms of contestation and the reconfiguration of vaccinology.

For the pharmaceutical industries, whose efforts in this field are supported by philanthropic companies like the Bill and Melinda Gates Foundation and the Rockefeller Foundation, the Ebola epidemic in West Africa was an opportunity to forcefully demand the fast-tracking of vaccine development. This includes a reduction in development timeframes to give the most needy populations faster access to these vaccines. Sanofi Pasteur used the fear of a pandemic to accelerate the production of their vaccine. The American FDA states that this accelerated procedure may be implemented when there is an anticipated public health need—the resulting pharmaceutical product must correspond to an unsatisfied health concern. The European Drug Agency demands that the product correspond to a major health requirement. A “requirement” is several levels above a “concern”. Two key health regulatory authorities thus have two very different interpretations of this important question. It is necessary to resist the tyranny of the production of scientific facts that emerge from hastily developed clinical trials (Adams, Burke and Whitmarsh 2014). Regulatory authorities must reconsider fast-tracking and instead develop a process that produces high added value health products like vaccines. This would prevent a precipitous handling of bioethical and security issues and ensure that vaccine development and licencing remain rigorously controlled procedures.

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