ETHICAL ISSUES: TROVAN (TROVAFLOXACIN) DRUG TRIALS ON CHILDREN WITH MENINGITIS IN KANO STATE, NIGERIA.

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Background

Meningococcal meningitis is a bacterial infection that attacks the protective membranes covering the brain and spinal cord and can cause serious neurologic damage or even death. Survivors can suffer long term complications, including, but not limited to, hearing loss, mental retardation, paralysis and seizures (WHO, 2008). Meningitis epidemics strike impoverished countries in sub-Saharan Africa, where crowded living conditions and dry climates contribute to the spread of disease. They occur in seasonal cycles (between November and June) during the dry season. The cyclical impact of the disease has earned this area of Africa the name the 'Meningitis Belt'.

The Genesis

A deadly meningitis epidemic had ravaged Nigeria in 1996. Described as the worst in the history of the country, the epidemic had claimed about 12,000 lives over a six-month period. The northern part of the country was mostly affected and health services were strained. *Pfizer*, under the guise of rendering humanitarian assistance in view of the epidemic, had joined other international relief agencies such as the Red Cross and Doctors Without Borders. It however used the opportunity to conduct a clinical test of its newly-developed anti-meningitis drug, *Trovan*, on children in Kano, and this proved fatal, resulting in the death of 11 of them and causing varying degrees of injuries and deformities in 100 others. The most worrisome aspect was that Pfizer even got an import duty waiver for the drug, just as the approval letter for the test was allegedly forged by an official of the Kano State Ministry of Health. Before conducting the *Trovan* study in Kano, *Pfizer* alleged to have sought and obtained all necessary approvals from relevant federal and state government agencies in Nigeria. In that regard, Pfizer has at least 12 letters between the company and Nigeria's NAFDAC, Ministry of Health and Ministry of Finance as well as the U.S. Food and Drug Administration, discussing and approving the study.

The Nemesis

The drug (Trovan) was tested on children without parents' informed consent, patients were unaware of the experiment, and the trial was not approved in advance by an ethical review committee. Out of 190 children that were enrolled in the trial, five receiving Trovan (trovafloxacin) and six receiving the existing treatment ceftriaxone (the injectable Rocephin) died. Others suffered brain damage and paralysis.

According to Hajara's father one of the Trovan victims, "The American doctors took advantage of our illiteracy and cheated us and our children. We thought they were helping us. "We did not suspect that our children were being used for an experiment. They have cheated us and our children. All I can say is that God will judge them according to their evil deeds".

Though Pfizer denied that the deaths were as a result of the clinical test of its new drug, 30 Nigerian families under the aegis of The Kano Trovan Victims' Forum (TVF) in 2001 dragged the pharmaceutical firm to court in the United States of America with legal suits initiated in New York and Connecticut. . The suit alleged: "Pfizer chose to select children to participate in a medical experiment of a new, untested and unproven drug without first obtaining their informed consent." Despite the initial challenges of the legal battle, the New York Division of the US Court of Appeal, in what had become a landmark judgment in January 2009, ruled that Pfizer could be sued in the US.

Ethical issues

According to ethical principles guiding the use of human subjects in research, its paramount that participant is duly informed. The Three most prominent statements on bioethics: the Nuremberg code, the declaration of Helsinki, and the Belmont report all agreed that testing on human subjects can only be done if test participants give *voluntary* and *informed* consent. In other words, human subjects cannot be coerced into participating in experiments or be kept ignorant of the risks to which they will be exposed.

Pfizer breached this ethical rule by carrying out research on the disadvantaged, exploiting their ignorance and infringing the right of the participants to know the risk involved or even be aware that it was an experimental drug.

The company has previously said that "verbal consent" had been obtained from the parents of the children concerned and that the exercise was "sound

from medical, scientific, regulatory and ethical standpoint and claimed that the protocol was approved by Nigerian authorities with anticipated risks and detailed procedures to manage those risks.

In a Trovan statement defense summary which reads: *An approval letter from NAFDAC obtained in March 20, 1996, states that (1) "We have been supplied with adequate information about the drug and its proposed investigational use by the sponsor" and (2) "The drug may be legally used by investigators in Nigeria." Approval was also obtained from Kano State's Ministry of Health. Dr. A. Dogunro met with Ms. Lawan Gadanya at the Kano State Ministry of Health, discussed the study's protocol and explained that Trovan was an investigational new drug. Ms. Gadanya gave her approval for the study. In a letter from Kano's Ministry of Health and Social Services to Pfizer, Ms. Gadanya stated that: "Approval is also hereby given for your staff to participate in treating patients at our hospitals."*

Meanwhile, the report of a medical panel set up by the Nigerian Government contradicted Pfizer's claims saying Pfizer staff conducted the trial and left while "the epidemic was still raging". Following pressure from rights groups and families affected by the trial, the Nigerian government set up an expert medical panel to review the drug trial.

However, the report conducted by the panel of Nigerian medical experts and obtained by the Washington Post in 2006 found that Pfizer never obtained authorisation from the government to give Trovan to children and infants. The panel said it was "an illegal trial of an unregistered drug," and a "clear case of exploitation of the ignorant". The report also contradicted Pfizer's claims that its aims in going to Nigeria were philanthropic: Pfizer staff conducted the trial and left while "the epidemic was still raging" (Dearn, 2011)

The panel also said there were no records showing Pfizer had informed either the children or their parents that they were participating in the trial of an experimental drug. It said that a letter from a Nigerian ethics committee used by Pfizer as evidence of its permission to carry out trials was fabricated and backdated, concluding that the trial broke Nigerian law, the Declaration of Helsinki, which governs medical research, and the UN Convention of the Rights of the Child.

On May 7, 2006, *The Washington Post* reported that it had been privileged to see a secret report of the panel's investigation, which alleged that Pfizer undertook an "illegal trial of an unregistered drug" when the company enrolled children into the Trovan trial (Lenzer, 2006). In response to the leaked report, Pfizer issued a press statement saying: "Pfizer is confident that no one associated with the Trovan clinical study conducted in Kano, Nigeria during a meningitis epidemic in 1996 ever put a patient's health at risk and that the company acted in the best interests of the children involved in the study, using the best medical knowledge available"

If innocent as they claimed, why did they conduct the trial and left while the epidemic was still raging? Why did the American doctor working with Pfizer, Dr. Juan Walterspiel, who was aware of the unethical conduct of the pharmaceutical firm and exposed its antics fired? The answers to these questions already prove the unethical process.

As Chippaux has noted, the justifications for the study protocols were weak, because they "overlooked the fact that the cost of the product and the limited chances of its commercialization without state subsidy made its use in Africa highly unlikely" (Chippaux, 2005). According to Shah, there were also warnings from within Pfizer, about the effectiveness of an oral drug on these particular children who were already sick, not only with meningitis but other illnesses, because the pre-existing injectable drug Rocephin worked more rapidly (Shah, 2006). Despite the results indicating that study drug Trovan was no better than the preexisting drug Rocephin, the problem was that the researchers did not respect the rights of the participants, and as such, South African bioethicist Solomon Benetar has argued that this lack of respect is 'colonial' (Benetar, 2005), because despite the questionable ethical conduct of this trial in Nigeria, and an unresolved class action put by 30 Nigerian families against Pfizer, the US Food and Drug Administration accepted the data from this trial.

Pfizer contends that there was no regulation or law in Nigeria requiring ethical committee approval before conducting a clinical trial or investigative study. Therefore, there was no need to obtain what the law did not require. In addition, there was no formal ethics committee sitting at either Kano's Infectious Disease Hospital or at the nearby Bayero Teaching Hospital. This claim will make one agree to Jean-Phillipe Chippaux article:

"*do African states support the intervention and investments by pharmaceutical companies trialing new drugs in their health systems? Does it make the state weak for approving clinical drug trials that would not be approved of in the western world,*

because they provided access to something (some drugs), which was better than nothing (no drugs)? Is this 'better than nothing' approach to health development enabling the Millennium Development Goals of Global Health for All? Or does it signify a patronizing and colonizing outcome for weak and developing states in the age of globalization? We can then ask if these big companies are exploiting the citizens of weak and/or developing states due to a failure or lack of ethical policies and rules designed to protect against unethical clinical drug trials."

Compensation

Although Pfizer had argued that meningitis and not its antibiotic had led to the deaths of 11 children and harm to dozens of others, in 2009 it reached a tentative out-of-court settlement with the Kano state government worth $75m. The pharmaceutical giant also agreed to sponsor health projects in Kano with the commencement of construction of an ultra-modern medical centre with an in-patient facility and about 200 beds space categorised into different infectious conditions, as a result of the out-of-court settlement between Pfizer Inc USA and the Kano State government as well as creating a fund of $35m to compensate those affected with each victim's family receiving $175000 (£108,000). But as Oct. 2011, there were claim that families of the 200 victims in Kano still have no respite. With only eight of the victims' families compensated so far, controversy is currently trailing the disbursement of the fund set up for that purpose. Olaolu Olusina of Thisday Live investigates how the Trovan Trust Fund was usurped by those who have no bearing with the saga, thus leaving the real victims in the dark as third parties smile to the banks, in what observers describe as a national disgrace.

The implication of the saga

Public trust is essential in promoting public health. Such trust plays an important role in the public's compliance with public health interventions, especially compliance with vaccination programs, which target mainly healthy people. Where public trust is eroded, rumours can spread and this can lead to rejection of health interventions.

The Pfizer experiment has since led to mistrust, lack of confidence and resistance in delivery of health care services. One implication was the rejection of polio vaccinations in many parts of northern Nigeria in recent years with some local Islamic preachers saying there are plots by westerners to sterilise Muslim women.

Outside the health implication, the irreparable loss of life and shattered dreams caused by the drug trial will forever remain in the hearts of the bereaved

REFERENCES

1996 Trovan trial: Pfizer's begins construction of medical Centre. Retrieved 20 November 2010 from http://www.gbooza.com/forum/topics/1996-trovan-trial-pfizers?groupUrl=crime

Anger at deadly Nigerian drug trials. Retrieved 20 June 2007 from http://bbc.co.uk/2/low/africa/6768799.stm

Chippaux, Jean-Phillipe, "Pharmaceutical Colonialism in Africa" *Le Monde Diplomatique*, August 2005, translated by Donald Hounam, accessed from http://mondediplo.com/2005/08/11pharma, accessed March 25, 2008Sonia Shah, *The Body Hunters: Testing New Drugs on the World's Poorest Patients*, (New Press, New York: London, 2006), pp.144-145

Lenzer J (2006) Secret report surfaces showing that Pfizer was at fault in Nigerian drug tests. BMJ 332: 1233

Mark Dearn on Pfizer Pays Families of Nigerian Drug Trial Children. www.thinkafricapress.com/author/mark-dearn 16 August 2011

Pfizer pays out to Nigerian families of meningitis drug trial victims. Retrieved 12 August 2011 from http://www.theguardian.com/world/2011/aug/11/pfizer-nigeria-meningitis-drug-compensation

Pfizer statement. 2006: 1996 Trovan clinical study in Nigeria. Pfizer News. Available: http://mediaroom.pfizer.com/index.php?s=press_releases&item=55. Accessed 15 February 2007

Shuaibu, Ibrahim Still No Compensation for Trovan Victims as Pfizer Cuts Corners. Thisday live, 23 Oct. 2011

Solomon Benetar quoted by Shah, 2006, p.153. Also see Jeremy Laurance, "The True Story of how multinational drug companies took liberties with

African lives", in The Independent/UK, September 26th, 2005.

Somo, "Briefing paper on ethics in clinical trials, #1 Examples of Unethical Trials", February 2008, http://www.somo.nl/html/paginas/pdf/Examples_of_unethical_trials_dec_2006_NL.pdf, (accessed May 14th 2008).

World Health Organization. 2008: Meningococcal Meningitis, http://www.who.int/mediacentre/factsheets/fsl41/en/ (Feb. 12, 2008).