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Dengvaxia controversy in the Philippines and Gardasil Trial in India

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Dengvaxia

- In April 2016 the Department of Health in the Philippines initiated a vaccine program against dengue among 830.000 schoolchildren
- In December 2017, the Philippine FDA withdrew approval for the vaccine after
  - Sanofi announced November 29 that vaccinated people who had not been exposed to Dengue before vaccination had a small, but increased risk of getting more severe dengue if they were exposed later, because protection of vaccine wanes over time
  - Therefore vaccine only recommended in high prevalence areas (Philippines 90% exposed)

Dengvaxia

- Initial claim that three deaths were related to the vaccine
  - Causal claim unlikely
- Government wants full refund of vaccines from Sanofi
- Later scores of additional deaths claimed to be the result of the vaccine
- Reducation in other vaccinations, including measles

Confusion, blame game fuel Dengvaxia vaccine scandal

Cecil Morella, Agence France-Presse

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PAO chief Persida Acosta along with families of Dengvaxia vaccine recipients file a criminal case against former Health Secretary Janette Garin, Sanofi and other DOH officials, April 5, 2018. ABS-CBN News

World Health Organization

- Revises its guidelines so that the vaccine should not be given to seronegative children or those without prior dengue infection

Lessons

- Difficult trade-off when deciding policy
  - Overall all evidence points to benefits of a vaccination program in high prevalence areas, even with the additional risk
- Public perceptions of risk important
- Should researchers and IRBs take these types of possible reactions and consequences into account when planning and approving research?

Gardasil, Background

- Gardasil approved as safe and effective based on clinical trials in around 25.000 women
- Prevent HPV related disease and cervical cancer
- Continued questions about appropriateness
  - Vaccination of young girls before sexual activity
  - Long term safety and efficacy
    - Editorial August 21, 2008 in NEJM, has not shown that it prevents cancer (only precancerous lesions)

India

- Approved for sale in 2008 after trial in 110 girls aged 10-14 (requirement of bridging trials)
- Cervical cancer most frequent cancer among women in India

Clinical trial

- Started in 2009 among 32.000 young girls as a collaboration between ICMR, two state governments (Gujarat, Andhra Pradesh), and PATH, and Merck
- Stopped in April 2010 because of reports of 4-6 deaths and several reports of adverse events
- Purpose of trial to demonstrate utility of vaccine in a public health programme and acceptability of Gardasil

Criticism

- Necessary approvals have not been obtained prior to start of trial
  - Ethics approval
  - Trials in adults
  - Bridging trials in India
- Pap smears more appropriate than vaccine in Indian context
- Vaccine has not yet been proven safe and effective

State investigations

- Deaths
  - One drowned, one snake bite, two suicide after pesticides, one malaria, one high fever, one cerebral hemorrhage (but no relation to vaccine determined)

Ministry of health panel, 2011

- Proper informed consent not obtained (paperwork missing)
- No mechanism for reporting of adverse events
- Lack of control group
- Inclusion of tribal groups without proper authorization

Parliamentery panel, 2013

- Failure to have conducted postmorten investigations on girls who died
- Trial was a means of getting the Indian government to introduce HPV as a mandatory vaccination program paid for by public funds. Other government agencies have the role of approving publicly funded vaccines
- ICMR has “completely failed to perform [its] mandated role and responsibility as the apex body for medical research in the country. … Rather, in [its] over-enthusiasm to act as a willing facilitator of the machinations of PATH, [it has] even transgressed into the domain of other agencies which deserves the strongest condemnation and strictest action against [it].”

Lessons

- Importance of ensuring regulatory compliance
- What role should evaluations of public health need play in approval of research?
- What is research?
  - Clinical trial vs.
  - «Demonstration project»