The Permissibility of Using Rotavirus Vaccines – Lessons from Oral Poliovirus Vaccines
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Introduction

Pneumonia and diarrheal disease are the two top killers of children. United Nations International Cultural and Educational Foundation (UNICEF) and World Health Organization (WHO) reports that these two diseases kill more than 2 million children each year. They make up 29% of childhood deaths under the age of 5 worldwide (1).

Poor sanitation, insufficient water treatment systems, lack of access to appropriate medical care and lack of life-saving vaccines lead to an estimated 800,000 diarrheal deaths in children under five and millions more hospitalizations every year. While many pathogens can cause diarrhea, rotavirus is the leading cause of severe and fatal diarrhea in infants and young children. Virtually every child in the world would have been infected with the rotavirus (RV) by the age of three. Globally, rotavirus gastroenteritis kills 527,000 (475,000-580,000) children under five and is responsible for millions of hospitalizations and clinic visits each year (Figure I). Ninety-five percent of rotavirus deaths occur in developing countries in Africa and Asia (2).

In the management of diarrhea, basic interventions include; encouraging infant breastfeeding, improving access to clean drinking water, zinc supplementation and oral rehydration solutions (ORS). However, the rotavirus is so contagious and resilient that these simple measures, so effective in curbing other diarrheal diseases, do not effectively eliminate it (3).

Rotavirus Vaccines

Children infected with the rotavirus develop strong immunity against a repeat severe rotavirus infection. Vaccination induces a primary infection without causing illness and is thus the optimal strategy to decrease the burden associated with severe and fatal rotavirus gastroenteritis (RVGE). The rotavirus vaccine mimics the protective first infection without causing illness thus inducing strong and broad heterotypic immunity, after repeated doses, against future severe rotavirus infections.

Two orally administered RV vaccines are available today. Both have been extensively studied in trials in Africa, Asia, Europe, Latin America and the United States.

First introduced in the US in July 2006, it reduced hospitalizations for severe rotavirus by a significant 58-86% over three years (4). Two years after the introduction of the vaccine in Queensland, Australia in July 2007, there was an 89-94% reduction in rotavirus-related hospitalizations in children under five years of age (5). Nicaragua was the first developing country to introduce the vaccine. The rotavirus vaccine was 60% effective in preventing severe RVGE (6).

In June 2009, the Strategic Advisory Group of Experts (SAGE), supported by the evidence from these and other pivotal studies, recommended the global inclusion of RV vaccination into all national programs for all infants (7).

The special supplement, “Rotavirus Vaccines for Children in Developing Countries,” to the journal Vaccine in April 2012, reaffirmed that RV vaccines are proven to be effective, safe, cost-effective and are life saving. Although the RV vaccine was relatively less efficacious in clinical trials in developing countries compared to US or Europe, the much higher burden of severe RVGE in developing countries would confer a much higher public health benefit with the inclusion of the vaccine(8).
In Africa and Asia, where 95 percent of deaths due to rotavirus occur, more than 2.4 million child deaths can be prevented by 2030 by increasing access to lifesaving rotavirus vaccines. Universal use of RV vaccines can avert 6 million clinical and hospital visits, thereby saving US$68 million annually in treatment costs (8).

**Islamic Jurisprudence**

In the hierarchy of the goals of Islamic Jurisprudence (Maqasid al-Shariah); the preservation of life comes only second after the preservation of the Deen (religion). Life is a gift from Allah (SWT) and its protection and continuation is of utmost importance and urgency.

The sanctity of human life is emphasized in the Quran “…and if anyone saved a life, it would be as if he saved the life of all mankind.” (9)

The Prophet (may peace be upon Him) related, "We are a people who do not eat until we are hungry. And if we eat, we do not eat to our fill.” This narration, among others, is the backdrop to a powerful medical maxim “Prevention is better than cure”.

This medical aphorism is further reinforced by the jurisprudence principle; “sadd-ul-dhara’i” – closing the doors to destruction or blocking the means of corruption.

These back to basics rulings alone are sufficient justification for the permissibility of immunizations to save the lives of innocent children, notwithstanding the issues related to the “halalness” of the vaccines. The question of "halalness" (permissibility) was raised because of the inclusion of the porcine enzyme trypsin in the manufacturing process of the two available RV vaccines namely Rotateq (MSD) and Rotarix (GSK). This has triggered some concern in the Muslim medical fraternity, the Fatwa Councils and by extension the lay public.

The 81st Conference of the Fatwa Committee National Council of Islamic Religious Affairs, Malaysia was held on March 31, 2006 and discussed the ruling of using a rotavirus vaccine that utilized porcine sources in its production process (10). The Committee decided that the usage of the rotavirus vaccine is not permitted based on the following three reasons:

1. There is no urgent need at the moment
2. There are alternative substances or medicines besides using pig sources in the production of the said vaccines
3. There is no concrete proof that people in the country are in dire need of such vaccine.

Trypsin is an enzyme that cleaves protein into smaller fractions. In the manufacture of the RV vaccine, trace amounts of trypsin is used to activate the virus and later to separate the virus from the cultured cells. Trypsin of porcine origin was preferred primarily based on a safety reason, being free of Transmissible Spongiform Encephalopathies. Through various steps of micro-filtration, the trypsin was completely removed from the end-product. (Figure II)

This however is not a new issue because it has been previously addressed by Muslim physicians, scientists, public health experts who are at the cutting edge of vaccinology and child survival strategies as well as jurists (fuqaha) in relation to the use of the oral poliovirus vaccine (OPV).

The Oral Poliovirus Vaccine (OPV) which has led to the virtual global eradication of polio, utilizes a similar technology in its manufacturing process. It utilizes small, virtually negligible amounts of trypsin derived from porcine origin, to disconnect the contiguous
cells in the tissue culture. At that time there was a significant fatwa from the European Council of Fatwa and Research (ECFR) which in 2003 opined that “Out of piety, some brother Muslims in various parts of the world, particularly in East Asia, have issued a fatwa that it is not permissible to administer this vaccine (OPV) to children, due to the fact that porcine trypsin is used in preparing it.” (10)

The Council argued as follows:

a) what God forbids is the partaking of pork, and trypsin has nothing to do with pork
b) even if we admit that trypsin is forbidden, the amount used in preparing the vaccine is negligible, if one applies the rule that “when the amount of water exceed 2 qillas (343 litres)”, impurities no longer affect it”
c) supposing that trypsin is unclean, it is thoroughly filtered, that it leaves no traces whatsoever in the final vaccine
d) in case the three arguments forwarded are still insufficient, the haram (forbidden) is made permissible in cases of necessity.

In their concluding remarks they emphasized, “The Council urges Muslim leaders and officials at Islamic Centers not to be too strict in such matters that are open to considered opinion and that bring considerable benefits to Muslim children, as long as these matters involve no conflict with any definite text.”

Such is the latitude of rationale and magnanimity of our scholars (fuqaha) in addressing the bigger picture of child survival strategies and the advocacy of life saving vaccines.

Global Advocacy for Polio Eradication

WHO Regional Office for the Eastern Mediterranean (EMRO) recently hosted a high-level consultation of Islamic scholars, from 6-7 March 2013, in the WHO Regional Office in Cairo (12). In its global efforts to eradicate polio, the consultation noted with much concern that this paralyzing and fatal disease remains endemic in three Muslim countries, namely Nigeria, Pakistan and Afghanistan. Up until 1 May 2013, there were 16, 6 and 2 cases of polio in the three countries respectively. There were no other reported cases elsewhere in the world (13).

The consultation unanimously reaffirmed that the polio vaccine is safe and does not contain any haram substance and emphasized the urgent need to rectify mis-conceptions about the polio vaccine and the global polio eradication program.

With the universal use of OPV this killer and paralyzing disease has been reduced by more than 99% to only 24 cases in 2013. The Federation of Islamic Medical Associations (FIMA) recently issued the Cairo Declaration for Polio Eradication on 28 February 2013 (14). FIMA was also a signatory of the Scientific Declaration on Polio Eradication launched on 11 April 2013, joining hundreds of scientists and technical experts from 80 countries (15).

Since the manufacturing process of the two oral vaccines (OPV and RV) are similar, involving the use of minute amounts of trypsin which is later removed by ultra-filtration, the pivotal judicial edict of the permissibility of OPV can be similarly applied to the RV vaccine.

Towards Universal Mass Vaccination with Rotavirus Vaccines

RVGE continues to scourge our youngest and most vulnerable, killing more than 1,200 children under five each day. The human tragedy is that RVGE is a vaccine preventable disease and many of these deaths can be averted by universal mass vaccination with the RV vaccine. RV vaccination offers the best protection against severe rotavirus diarrhea,
and have been shown to save lives in countries which have incorporated RV vaccines in their National Immunization Program (NIP).

About 50 countries in the world have introduced RV vaccination in their national and/or regional immunization program (Figure III). Muslim countries which have included RV vaccination in their NIP include Morocco, Iraq, Bahrain, Qatar, Yemen, Saudi Arabia and Sudan. Muslim Pakistan and Nigeria are 2 of 5 countries which together contribute up to half of the global RV diarrheal deaths in 2008 (16). Through funding from the GAVI Alliance, formerly the “Global Alliance for Vaccines and Immunization” Pakistan has recently introduced the RV vaccine as part of their NIP.

**Rotavirus Gastroenteritis and Vaccination in Malaysia**

The RV vaccine has been in use in Malaysia since 2006. Since it is not part of the Malaysian National Immunization Program (NIP), it is mainly utilized in the private health sector. The uptake of the RV vaccine is still very low. Less than 20% of the birth cohort in the private medical facilities are immunized against RV.

A study of under-5 mortality in Malaysia in 2006 showed that there were 1,699 deaths (17). Deaths due to diarrhea was the number 3 cause of deaths, contributing 83 deaths (4.9%), after congenital anomalies (25.1%) and pneumonia deaths (9.2%). This is unacceptably high for a country moving towards a developed nation status. Many of the developed nations in Europe, US, Canada and Australia have included the RV vaccine in their NIP.

Discharge records from government hospitals showed that the cumulative risk of RV related disease by 5 years of age was 1 in 61 for hospitalizations and 1 in 37 for outpatient clinic visits (18). The out of pocket cost associated with RVGE admission was estimated at USD 226 (106-799) which was 26% of the studied household income. The mean parental day work loss associated with RVGE admission was 4.8 days (19). All of these data suggest that the burden of RV disease is considerable and would be a substantial drain on the nation’s health expenditure.

At present there are no other medicines or substances which can act as an alternative to the present two oral RV vaccines. These have been studied in virtually all regions of the world and proved to be effective, safe, cost-effective and are life saving.

It behoves Muslim healthcare providers as well as religious leaders to propagate this information especially its similarity with the polio vaccination program and work to increase the utilization of the RV vaccine generally and specifically its inclusion in the NIP of Malaysia.

**Conclusions**

Rotavirus is the leading cause of severe childhood diarrhea and fatalities from gastroenteritis. Ninety five percent of these deaths occur in developing countries in Africa and Asia. Integrated with a package of interventions that includes ORS, zinc, breastfeeding, nutrition, good sanitation and hygiene, rotavirus vaccination offers the best hope for preventing severe diarrheal disease, and could save nearly 2.4 million lives by 2030.

However, the use of minute amounts of porcine trypsin in the manufacturing process of both RV vaccines has raised concerns amongst some in the Muslim community about the permissibility of the vaccine.

Lessons can be learnt from a precedent, an earlier fatwa issued on the use of OPV which is similarly manufactured using trace amounts of porcine trypsin. The European Council
of Fatwa and Research (ECFR) chaired by Dr Yusuf al-Qaradawi and consisting of numerous renowned scholars in the Muslim world, when allowing the use of OPV added that “the hesitation of some parents to have their children immunized with this vaccine (OPV) poses a risk to Muslim children alone. At the same time, it gives an unfavorable image which portrays Muslims as hindering a process that aims to eradicate, with God’s permission, the existence of this disease on earth once and for all. After all, this eradication cannot be complete while there is even one child on earth carrying the virus.”

References

1. Integrated Global Action Plan for Prevention and Control of Pneumonia and Diarrhea (GAPPD). UNICEF and WHO, April 2013


4. Reduction in Rotavirus After Vaccine Introduction - United States, 2000-2009. MMWR. October 23, 2009 / 58(41);1146-1149


9. Surah Al-Ma’idah, Verse 32


15. http://vaccines.emory.edu/poliodeclaration/signatories.html


17. A study on under five deaths in Malaysia in the year 2006. Ministry of Health, Malaysia


Figure I

Rotavirus deaths among children under 5

Source: Tate, et al. JID. 12(2).
Figure II

Add virus stock seed

Virus grow and replicate in cultured cells (growth medium)

Incubation

Cultured cells contain trace amount of trypsin to activate virus through cleavage of VP4 protein

Harvest and diluted with solution

Trypsin is required to dissociate virus from cultured cells

Micro-filtration

Removal of trypsin and other medium components

Sterile filtration through 0.2 µm membrane

Ultra-filtration

HVF: Harvested virus fluids
FVF: Filtered virus fluids
National RV introductions by WHO region: 46 countries*

*National introductions by WHO region as of 1 July 2013
**Not a WHO member state
RV: rotavirus vaccine