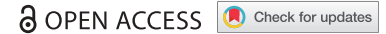


REVIEW



## Unique product quality considerations in vaccine development, registration and new program implementation in Malaysia

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### ABSTRACT

This review aims to present the unique considerations for manufacturing and the regulation of new vaccines in Muslim-populated countries such as Malaysia. Our specific objectives are to highlight vaccine production and the ingredients of concern, summarize the current mechanism for ruling and recommendations on new vaccines, outline the different steps in decision-making on incorporating a new vaccine into the National Immunization Program, describe its issues and challenges, and explore the commercial viability and challenges of producing local permissible (*halal*) vaccines. Through this review, we hope readers understand that alternatives are present to replace ingredients of concern in vaccines. *Halal* certification and introduction of a new vaccine into a program are strictly conducted and health-care providers must be prepared to educate the public on this. At the same time, it is hoped that the production of *halal* vaccine in Malaysia will promote self-reliance in Muslim-populated countries.

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### Introduction

Vaccination refusal among parents in Malaysia has increased tremendously.<sup>1–3</sup> In 2016, Ministry of Health, Malaysia identified 1,600 unvaccinated children in Malaysia with the highest numbers of unvaccinated children recorded in the states of Selangor, Kedah, Terengganu, Perak, Pahang, Kelantan, and Penang.<sup>4</sup>

This situation has led to the resurgence of vaccine-preventable diseases such as hepatitis B, measles, and whooping cough.<sup>4</sup> Such re-emergence of vaccine-preventable diseases due to vaccine refusal has been troubling medical practitioners and alarms the authorities.<sup>2,5</sup>

Parents are reluctant to provide childhood vaccination for their children as scheduled in the Malaysian National Immunization Program (NIP).<sup>2,3</sup> Religious beliefs may be one of the core influences on the refusals. There is an increase in public awareness among Muslims with regard to vaccine antigen and excipients of animal origin. Parents are hesitant to vaccinate their children as they are wary of the presence of ritually unclean materials (*najs*) in vaccines.<sup>2,6</sup> Islamic community made up 61.3% of Malaysian population.<sup>7</sup> Thus, it is important for health professionals to educate the community on the religious concerns regarding vaccination.

To clarify this issue, our review aims to explain the mechanism of vaccine production and distribution in a Muslim-majority country, namely Malaysia. Specifically, the objectives are to: (1) highlight vaccine production and the ingredients of concern, affected vaccines and implication on user acceptability; (2) summarize the current mechanism for ruling and current recommendations on new vaccines by

religious authorities in Muslim-populated countries including Malaysia; (3) outline the different steps in decision-making on incorporating a new vaccine in the NIP; (4) describe issues and challenges in promoting vaccination and immunization programs; and (5) explore the commercial viability of permissible (*halal*) vaccines.

### Current situation in vaccination refusals

The number of press-reported vaccine refusal has been increasing by the year. In 2013, 470 Malaysian parents refused to get their children vaccinated and the number of cases has tripled to 1,054 cases in May 2015.<sup>2,3</sup> In the state of Selangor, 637 vaccine refusal cases were reported in 2013 and it has increased to 1,541 cases in 2016.<sup>2</sup> The same pattern has been seen in the state of Pahang, where 84 cases of parents rejecting immunization have been reported in 2014 and the number has increased to 126 and 178 cases in 2015 and 2016, respectively.<sup>2,4</sup>

Local studies reporting vaccination refusal and defaulter rates are still lacking. Currently, two published studies reporting the refusal rates were successfully traced. One study conducted in the state of Perak in 2013 demonstrated that the vaccination refusal and defaulter rates were 8 and 30 per 10,000 children per year, respectively.<sup>8</sup> Another study conducted in the state of Kedah on the refusal rate throughout 2013–2016 reported that there was an overall vaccination refusal rate of 6.84 per 1,000 newborns.<sup>9</sup>

Although vaccination might appear beneficial only to the vaccinated individual, collectively it forms herd immunity in

the community and protects those who are not yet eligible for vaccination and immunocompromised.<sup>10,11</sup> Through herd immunity, the number of susceptible host and transmission rate will be reduced to a level low enough to eradicate the microorganism. Despite having the disease eradicated, continuous vaccination will keep the organism level below the threshold and prevent the re-emergence of the disease.<sup>10</sup> Thus, the act of rejecting vaccination will increase the number of unvaccinated individuals, creating a gap in the herd immunity and allowing the disease to be transmitted again.

The number of reported cases of vaccine-preventable diseases is increasing following the vaccine refusal. The number of reported pertussis cases, including death cases, has increased tremendously by 154-fold from 0.2 cases per 100,000 population in 2006 to 3.08 cases per 100,000 population in 2016. Measles incidence has also increased by 18-fold from 2.3 cases per 1,000,000 population to 43.2 cases per 1,000,000 population over the same period.<sup>12</sup> The incidence rates for diphtheria and hepatitis B in 2013 were 0.01 and 11.51 per 100,000 population, while the mortality rates were 0.01 and 0.04, respectively.<sup>13,14</sup> There was a sudden increase in diphtheria cases in 2016 where 31 cases were reported in that year alone, which includes death of an unvaccinated patient.<sup>14</sup>

The increase in vaccine-preventable disease outbreaks has also occurred during the past decade in other parts of the world. Pakistan has faced an increase in polio cases whereby the Khyber Pakhtunkhwa province was considered as the world's largest reservoir of the endemic poliovirus in 2014.<sup>15</sup> Nigeria has also encountered the same outbreak after being free from polio cases for 2 years in 2016.<sup>16</sup> The occurrence is not limited to developing countries as it has also affected developed countries and regions such as the United States of America (US)<sup>17,18</sup> and Europe.<sup>19</sup> In these reports, the US has experienced an increase in mumps,<sup>18</sup> measles, and pertussis cases,<sup>17</sup> while Europe has observed an increase in reported cases of mumps, pertussis, and rubella.<sup>19</sup> Although under-vaccination<sup>15,16</sup> and vaccine-acquired immunity waning<sup>18</sup> might be the main reasons for the reported outbreaks, vaccine refusal still plays a role in the increase in a number of vaccine-preventable disease re-emergence.<sup>17,19</sup>

## Concerns leading to refusals

Studies in other countries have documented various factors affecting parents' decision to vaccinate their children.<sup>20-22</sup> These factors include influence from past public health crises; religious factors such as the perspective that vaccination is against God's will and the involvement of prohibited (*haram*) substances; influence from rumors and negative information on vaccines shared on social media and internet; unpleasant experience with previous vaccination and health services; concerns on effectiveness and safety such as side effects; incorrect perceptions on children's health and underestimating the complications of vaccine-preventable diseases; and availability of vaccines.

In Malaysia, parents are concerned about the *halal* status of the ingredients in vaccines as they believe that vaccines are contaminated with porcine deoxyribonucleic acid (DNA), thus making

the vaccines *haram* as the consumption of porcine-sourced products including medicines is generally not permissible for Muslims.<sup>2,6,10,23</sup> This issue is a major concern since Muslims comprise the majority of the Malaysian population.<sup>10</sup>

While *halal* vaccine is the biggest issue among Malay-Muslim parents (46.1%), vaccine safety is the main concern among Chinese (37.5%) and Indian (36.9%) parents.<sup>23</sup> These parents are troubled by safety issues related to the active components in the vaccine and how these components affect their children's innate immune system.<sup>10</sup> Other factors that may contribute to vaccine refusal are the tendency to choose alternative treatments e.g. homeopathy for their children<sup>4</sup> as well as misinformation from social media or influence from family members, friends, religious groups, or individuals with no expertise in science and medicine.<sup>3,4,10</sup> Such observation has also been reported by Kusnin,<sup>1</sup> which shows that *halal* and *haram* issues are the main reason for refusal since 2013. In 2016, 468 out of 1,815 reported vaccine refusal cases are due to *halal* and *haram* concerns. It surpasses the concern on vaccine contents (410 cases), internet influence (217 cases) and choosing homeopathy as a disease prevention method (215 cases).

The NIP was introduced in 1960 with the first vaccine listed being DTP (anti diphtheria, tetanus and pertussis vaccine). The program was expanded in the following year by the introduction of BCG (bacillus Calmete-Guérin) vaccine against tuberculosis. The next few decades saw the sequential addition of new vaccines in the list. Currently, the NIP provides free vaccination services to protect Malaysian children from infectious diseases including hepatitis B, poliomyelitis, *Haemophilus influenzae* type b, measles, mumps, rubella, human papillomavirus (HPV), and Japanese encephalitis (JE).<sup>10,24</sup> The reported immunization coverage of this country by 2015 was above 90% for BCG (98.53%), DTP (third dose, 99.04%), oral polio vaccine (third dose, 99.04%), measles (third dose, 93.07%), and hepatitis B (third dose, 99.27%).<sup>10</sup> However, the increasing number of vaccine refusal may reduce the coverage rate and threaten the existing herd immunity, exposing those who have not or cannot be vaccinated to dangerous diseases. Thus, communities must be educated and directed to accurate information on vaccination and these include addressing current religious ruling and controversies on the subject matter.

## Definition of "halal pharmaceuticals"

In the pharmaceutical industry, "*halal* pharmaceuticals" are products that contain ingredients permitted by the *Shariah* law.<sup>25,26</sup> A *halal* pharmaceutical product: (1) must be free of parts or derivatives of animals that are declared non-*halal* by *Shariah* law or not slaughtered according to *Shariah* law; (2) must not contain *najs*; and (3) must not be poisonous, intoxicating, or pose a health hazard to the users when taken according to prescription.<sup>25,26</sup>

Pigs are one of the animals declared as non-*halal* in *Shariah* law. Thus, the use of their parts and derivatives in pharmaceutical products will cause the products to be non-permissible for consumption by Muslims.

## Review on vaccine ingredients of concern and affected vaccines

### Composition of vaccines and vaccine manufacturing process

The content of a vaccine can be either the entire disease-causing microorganism that has been weakened or inactivated/killed, or some of the microorganism's component such as inactivated toxins and fragments of bacteria cellular structure.<sup>27</sup> From these compositions, vaccines can be divided into five categories:

- (1) Live-attenuated vaccine. This vaccine contains the living microorganisms that have been weakened or genetically modified to reduce their disease-causing ability yet still able to induce immune response when administered (e.g. MMR (measles, mumps, and rubella));
- (2) Inactivated vaccine containing microorganisms that have been inactivated/killed using chemical, thermal, or other methods yet still able to create immune response (e.g. hepatitis A and influenza);
- (3) Recombinant vaccine, which contains the component of the disease-causing microorganism such as protein molecules from bacteria cell wall and nucleic acid (e.g. hepatitis B);
- (4) Toxoid vaccine, which is made of inactivated toxins produced by the disease-causing microorganisms (e.g. diphtheria and tetanus); and
- (5) Conjugate polysaccharide-protein vaccine, which contains linked polysaccharide and protein to improve humoral response and immune memory in infants (e.g. pneumococcal and *Haemophilus influenzae* type b).

Vaccine production process is conducted in a highly controlled environment, regulated by the national and international regulatory control, and must comply with specifications for Good Manufacturing Practices (GMP).<sup>24,27</sup> There are four basic steps of vaccine production:<sup>27</sup>

- (1) Propagation, which is the cell culturing process involving multiplication (or amplification) of the living organisms or pathogens used in the vaccine.<sup>24,28</sup> The pathogen's proteins or DNA are grown and harvested in growth media, primary cells or cell lines.<sup>24,28,29</sup>
- (2) Isolation, which is the process of separating the living organisms from the cells (in the case of viral vaccines) or culture media (in the case of bacterial vaccine) used in the propagation step.<sup>24,28</sup>
- (3) Purification, the process of removing all materials that may be adhering to the isolated organisms to produce a high purity/quality vaccine product. Microorganism inactivation and polysaccharide conjugation happen during this step.<sup>27</sup>
- (4) Formulation, a process that involves mixing the purified product in solutions to obtain a desired concentration by adding components such as diluents, preservatives,

adjuvants, and stabilizers prior to packaging and shipping.<sup>24,28,29</sup> Combination with other antigens to create vaccines such as MMR and DTaP (diphtheria, tetanus, and pertussis) also happens at this stage.<sup>27</sup>

Some ingredients added during a vaccine manufacturing process can potentially raise concern among end-users. They are described in the following paragraphs.

### Porcine trypsin

Porcine trypsin extracted from the pancreas of pigs is a reagent used in the propagation stage in the production of certain vaccines,<sup>30,31</sup> e.g. inactivated polio and JE vaccines. It is used to remove or detach cells from the culture tank or vessels before harvesting.<sup>30</sup> It is also used during the final culture stage of virus production for activation of a vaccine, such as influenza virus and rotavirus.<sup>30</sup>

Semi-synthetic (recombinant) trypsin is commercially available. However, porcine trypsin is still commonly used as it is cheaper in cost compared to recombinant trypsin. The porcine trypsin is washed and thoroughly removed from the harvested cells before further processing and is normally tested for its presence in the final vaccine product.<sup>31</sup> Validation studies on the removal process have demonstrated mostly undetectable amounts of porcine trypsin in the final vaccine product. Furthermore, a vaccine is generally administered only a few times in life to confer protection against diseases. This is different from other medicinal products, some used as lifelong treatment with repeated exposure to product ingredients of concern.

### Hydrolyzed porcine gelatine

Hydrolyzed porcine gelatine is a mixture of peptides and proteins produced by partial hydrolysis of collagen, typically extracted from pig skin, bones, or other components. It is used as a stabilizer, to help stabilize and preserve active ingredients during freeze-drying and storage in the final vaccine formulation and may also act as a solvent.<sup>31</sup>

Although it is present in small amounts (e.g. Varivax Refrigerated Varicella Virus Vaccine, MSD ~9mg/dose),<sup>32,33</sup> the declaration on the product label stating "Contains trace quantities of porcine content" is required by local product registration policy. Similarly, MMR vaccines also contain gelatine<sup>32,34</sup> and should have the statement of its origin on the vaccine product labels. Although recent listing shows the presence of MMR vaccine containing porcine gelatine, the Ministry of Health, Malaysia has opted for an alternative manufacturer producing porcine gelatine-free MMR vaccine.

### Other ingredients from animal sources

Culture medium for the propagation of host cells sometimes contains ingredients of animal origin, e.g. L-cysteine from poultry feather, fetal bovine serum (FBS), bovine lactose, bovine casamino acids, and porcine/bovine casein peptone.<sup>32,35</sup> As culture medium is normally not present in the final vaccine product, there is no declaration on the vaccine label on ingredients of animal origin.

Research and development in Malaysia have produced *halal* bovine gelatine that acts as the vaccine's stabilizer in place of porcine gelatine.<sup>10</sup> Similarly, the manufacturing of current injectable polio vaccines used in the NIP involves the virus being grown in special growth medium, which supports viral growth, i.e. a vero cell line, which is derived from monkeys' kidneys. This growth medium is removed during the isolation process, leaving the live virus ready for inactivation in the subsequent purification step. At the same time, there are no oral polio vaccines containing materials of porcine origin.<sup>36</sup>

## Review on religious ruling (*fatwa*) on vaccination

### *Fatwas* by JAKIM regarding vaccination

Both the Director Generals of Health Malaysia and the Department of Islamic Development Malaysia (JAKIM) have agreed that vaccination is encouraged to prevent the occurrence of vaccine-preventable diseases. At the same time, vaccination is also in line with Islamic teaching, which supports the act of preventing harm while protecting lives and public interests.<sup>31</sup>

Three factors will be considered before declaring a vaccine is permissible for use. First, the priority is given to vaccines produced via recombinant methods and do not contain *najs*.<sup>24</sup> In this method of vaccine production, the vaccine contains antigen purified from bacteria or yeast.<sup>37-39</sup> These microorganism vectors are declared *halal* in the Halal Pharmaceutical guideline unless the strain is prohibited by competent authority, thus they can be used without compromising the *halal* status.<sup>26</sup>

The second factor is to make certain that the vaccine's benefit is greater than its harm.<sup>31</sup> In this context, the vaccine used should not produce side effects worse than the effect obtained from the disease it was supposed to prevent.

The third factor applies during a dire situation when there is an urgent need to use the vaccine in the respective country.<sup>2</sup> Among the examples applicable to these factors is the use of Biothrax vaccine in Malaysia, which is declared as *haram*. The declaration was made as it is produced using sources of porcine origin, there is no reported outbreak in Malaysia and a permissible alternative vaccine is currently present, thus removing the urgent need to supply the vaccine nationwide.<sup>24</sup>

Several vaccines that have already been declared as permissible are hepatitis B, HPV, and rubella vaccines.<sup>24</sup> In addition, the declaration of prohibition may be revised. A case in point is the currently discontinued Sanofi Pasteur meningococcal vaccine, Menomune,<sup>40</sup> which was originally declared prohibited upon registration but was subsequently declared permissible upon review in 2014.<sup>24</sup>

### Overview on *halal* certification of medicinal products in Malaysia

JAKIM is the sole agency with the authority to provide *halal* certification in Malaysia.<sup>41</sup> In general, a medicinal product intended for *halal* certification must first obtain an approval to market from the Drug Control Authority (DCA).<sup>42</sup> Registration with DCA will mark that the product has been reviewed for quality, safety, and efficacy according to the Drug Registration

Guidance Document (DRGD), 2nd Edition, September 2016 as issued by the Director of Pharmaceutical Services under Regulation 29, Control of Drugs and Cosmetics Regulations 1984. The product will then be audited by JAKIM through a Halal Pharmaceutical Audit, which is based on MS 2424:2012 standard. The product assessment will incorporate input provided by the National Pharmaceutical Regulatory Agency (NPR) on its manufacturing process and formulation. A product that has been successfully audited and fully complies with set standards can then proceed with the *halal* certification process.<sup>25</sup>

### The process of *halal* certification for consumer products in Malaysia

All *halal* certification applications in Malaysia are performed online through the MYeHALAL system. Following the acceptance of the application, the applicants are required to submit the related supporting documents online along with a certification fee for the process to continue.

During the certification process, the applicant's premise is audited by external officers, who are well versed with Islamic regulation and technical matters related to the manufacturing process. The audit covers inspections on the condition of the applicant's premise, documentation, materials, and equipment involved in the manufacturing. Sampling for laboratory analysis or corrective action could be needed to resolve any doubt and ambiguity. The audit report is then discussed during a Malaysia Halal Certification Panel Meeting to determine whether the applicant passed or failed the inspection.<sup>25</sup>

A comparative analysis between global *halal* certification bodies reported in 2014 has indicated that JAKIM requires the highest number of criteria to be met before granting the certificate to the applicant. JAKIM has the largest number of criteria investigated during certification process, scoring 80% in overall criteria.<sup>43</sup> Strict certification by JAKIM also focuses on the company's premise condition, workers' qualification and condition, equipment used, logistics and the supplier's *halal* certification.

As a point to note, despite allowing registered pharmaceutical products to obtain *halal* certification, the current DCA policy does not allow the use of *halal* logo on packaging of poison category products including vaccine.<sup>42</sup> Most poison category products are intended for treatment. Therefore, the policy is concerned that the presence of the *halal* logo on poison category products could cause confusion and anxiety in the market, which could later lead to a situation where patients refuse the medications prescribed to them. Obtaining *halal* certification is perceived as a value-added element to improve vaccine acceptance, from the perspective of a vaccine manufacturer. Nonetheless, in the course of balancing vaccine efficacy and vaccine safety, *halal* certification should not be an integral part of the risks versus benefits evaluation because there are more elements involved to strengthen the confidence in immunization programs. Having a *halal* logo on poison category products may also lead to medication refusals, compromising patient's treatment and aggravating patient compliance issues. Thus, the best option to circulate the information on the *halal* certification of a vaccine is through JAKIM's Halal Malaysia Official Portal ([www.halal.gov.my](http://www.halal.gov.my)) instead.

### Practices in other Muslim-populated countries

Neighboring countries such as Thailand, Singapore, and Indonesia have their own *halal* certification administrators, namely Central Islamic Committee of Thailand, Islamic Religious Council of Singapore and Ulama Council of Indonesia, respectively.<sup>43,44</sup> These certification bodies have their own protocol in granting the *halal* certificate to the applicants. However, they do share major similarities with JAKIM in considering the *halal* certification applications, such as the cleanliness of the applicant's premise and equipment, the selection of ingredients, and cross-contamination between *halal* and non-*halal* products.<sup>43</sup>

In general, the certifications granted by these bodies are also recognized by JAKIM and the certified products such as food and cosmetics can be directly used without the need of repeated evaluation.<sup>45</sup> However, the MS 2424:2012 has clearly stated that the *halal* status for pharmaceutical products is issued by the competent authority in Malaysia.<sup>26</sup> Thus, this recognition is not applicable for vaccines and related pharmaceutical products as we have not seen a precedent in the case of marketed vaccines in this country.

Some other smaller certification agencies are also present. However, most of these smaller organizations are not recognized by JAKIM, thus any products certified *halal* by these bodies may need to be re-evaluated before certification for Malaysian consumption.<sup>43</sup>

### The role and relevance of IFANCA and HFCE certification

Although Muslim-dominant countries have their own *halal* certification agency, the huge demand for *halal* products opens up opportunities for other major exporting countries to globally provide *halal* products.<sup>43</sup> Thus, major exporting countries such as United States of America, Europe, and Australia have established their own *halal* certification bodies to support global demands. The Islamic Food and Nutrition Council of America (IFANCA) and Halal Food Council of Europe (HFCE) are among the agencies established to provide third-party *halal* certification of products. Other than supporting the growing Muslim population, this effort also benefits other health-conscious non-Muslim communities.<sup>46,47</sup>

With regard to certification, *halal* certificates issued by these agencies are recognized by JAKIM and are applicable for Malaysian consumption. Thus, products certified *halal* by these agencies do not require any reassessment prior to distribution.<sup>45</sup> Yet, due to the ruling in MS 2424:2012 on *halal* pharmaceutical products, this recognition is also not applicable for vaccines.<sup>26</sup>

### Porcine derivatives and their net effects on the final halal certification

In terms of vaccine acceptance, many scholars and authorities of Middle Eastern countries have accepted vaccines that involve impure substance such as gelatine of porcine origin in their production process. The vaccines can be consumed provided that the impure substance is completely transformed and changed into a new substance, different from its origin.

This view is based on the principle of "transformation" in *Shariah* law, which is mainly applied in the case of vinegar production from wine.<sup>31,48</sup> Majority of these authorities also accept *halal* certificates from IFANCA and HFCE for their *halal* certification (personal communication).

In comparison with other countries, there is a lack of supporting data showing that the current *fatwa* in Malaysia accepts vaccines that involve impure substances. The current *fatwa* in Malaysia seems to hold the view that vaccines produced from sources of porcine origin are not permissible. Alternative, porcine derivative-free vaccines are prioritized for use unless there is an urgent need to use such products.<sup>24</sup>

*Halal* certification will not be given to applicants producing and distributing both *halal* and non-*halal* products. Thus, pharmaceutical products with porcine derivatives detected will not be considered for *halal* certification. In addition, detection of porcine derivatives after the products has been certified will lead to serious consequences to the manufacturer, where the certification can be revoked immediately.<sup>25</sup>

In the case regarding vaccines that have gone through the additional process of removing porcine-derived ingredients, a thorough discussion between scholars from both religious and scientific institutions might be required to determine its permissible status.<sup>24</sup> The three considerations before a vaccine are assigned as permissible (the use of recombinant method, benefit versus harm, and urgent needs) may be referred before the official declaration is made.

### Steps in decision-making on incorporating a vaccine in the NIP

In Malaysia, the formulation of policies related to vaccination program was previously handled by the National Advisory Committee on Immunization Practices. This committee, which was set up in 1980s, was chaired by the then Deputy Director-General of Health (Public Health). It had both permanent and *ad hoc* members. The participation of non-MOH personnel was limited to selected experts for their technical input. The decision on vaccination policies, including for both pediatric and adult vaccination, was made based on technical input by an Expert Group of members.<sup>49</sup>

The committee was disbanded in 2006 and has since been replaced in early 2007 by the National Immunization Technical Committee. It is a government body with 18 appointed members and chaired by the Director-General of Health Malaysia. It has co-opted members, invited based on related issues. Along with heads of respective programs, other members were appointed based on their expertise, namely clinical and laboratory management of infectious diseases. In 2012, its name was changed to National Advisory Committee on Immunization Policies and Practices (personal communication).

New policies and recommendations on immunization are proposed based on:

- (1) World Health Assembly (WHA) resolutions;
- (2) Proposals from Regional Technical Advisory Group (TAG) on Immunization;
- (3) WHO position papers;
- (4) Proposals from national professional bodies;

- (5) Outcome of national health research assessment; and
- (6) Other related sources.

The burden of a disease i.e. the morbidity, mortality, hospitalization, and outcome of the disease is widely used to aid decision-making. The potential for the disease to cause frequent outbreaks is also taken into consideration. Besides that, the cost-benefit and cost-effectiveness of the new vaccination programs, either using local data or those from neighboring countries, are deliberated. Approval of new recommendations is determined by consensus after considering all evidence in totality.

Funds are required for sustenance when introducing new vaccines into NIP. For this reason, the proposal will be tabled to the Ministry of Health's Policy Development Committee, which is chaired by the Secretary-General of Health for consideration and approval. The Director-General of Health is a permanent member of this committee. Once it is approved, the proposal will be submitted to the Ministry of Finance for fund allocation. In some instances, the proposal is submitted to the Cabinet for approval and support before being submitted to the Ministry of Finance.

Updates on new policies on immunization are disseminated to all health state departments, hospitals, and private bodies who provide health services in an official circular. This is to ensure that private health service providers are in tune with latest policies.

In the event a new policy results in a total change of the existing program, the national vaccination schedule is reviewed. Training of staff in clinics, especially those implementing the program is carried out to ensure that they fully comprehend the implementation of the new program. They must be trained to communicate the rationale of policy changes to the public.

In implementing new vaccination policies which involve introduction of vaccines, the selection of vaccines is made based on the safety, quality, and efficacy of the vaccines as well as objective of the vaccination program. As a given, the vaccines must be registered at the NPRA, Ministry of Health Malaysia, which serves as secretariat to the DCA, based on set requirements.<sup>42</sup>

### Issues and challenges in promoting vaccination and immunization program

Introducing new vaccines into NIP poses some unique challenges. The price of new vaccines and combination vaccines is more expensive than the previous "old" vaccines or monovalent vaccines.<sup>50</sup> Furthermore, funding for the new programs is not determined by the Expanded Program Immunization (EPI) Managers within a country. Such a constraint delays the implementation of new vaccination programs.

The number of parents hesitant in taking their children for vaccination has increased.<sup>2,3</sup> Their arguments and reasoning are often irrelevant but can appear very convincing to some parties.<sup>2,6</sup> This has contributed to the increase in vaccine hesitancy.

Parents from the younger age groups were found to be more prone to vaccination refusal.<sup>51</sup> These parents rely more on the internet particularly social media networks (for example Facebook

and Twitter) as their main source of information. With debates on vaccination already available online for more than a decade,<sup>52,53</sup> these young parents are readily exposed to the wrong information on vaccination.<sup>51</sup>

Clearly, promotional activities need to be heightened using innovative and different approaches. Health-care providers have to be equipped with information to give convincing answers to all queries related to vaccines and immunization. Accurate health information needs to be pro-actively disseminated to the communities, especially the young generation and parents-to-be.

### Commercial viability of *halal* vaccines

Islam is an expanding religion. In 2014, the global Muslim population had reached approximately 1.8 billion, which makes up 25% of the global population. It has been estimated that the world's Muslims would reach up to 2.2 billion people in 2030.<sup>54</sup> Malaysia is among the countries with a high Muslim population; with Muslims comprising 61.3% of its total population.<sup>7</sup> With the growing number of Muslims globally, it is estimated that demands for *halal* products will continue to increase, with *halal* vaccines as one of the possible highly requested products.

The estimated worldwide vaccine market was USD26.4 billion back in 2014 and it has been expected to increase to USD34.7 billion by 2020.<sup>55</sup> With the Saudi Arabia government issuing a rule to have all pilgrims vaccinated against meningococcal disease prior to entering the country for Hajj,<sup>55</sup> the demand for *halal* vaccines in the future will definitely escalate.

To support vaccine demand of its member countries, the Organisation of Islamic Cooperation (OIC) launched a program named as Self Reliance in Vaccine Production (SRVP).<sup>56</sup> This SRVP program was initiated due to the increased demands on vaccines, which might cause a price increase and negatively affect the immunization program in its member countries. Thus, the program aims to promote self-reliance by encouraging vaccine production among OIC countries.

Malaysia is in collaboration with Saudi Arabia in achieving its aspiration to be a vaccine producing country.<sup>2,57</sup> A USD35 million project has been initiated by two entities in Malaysia: the Bioeconomy Corporation and AJ Pharma Holdings Sdn Bhd. The production facility will be built at the Enstek *Halal* Park, targeting the inadequately supplied *Halal* Pharmaceutical market. Initial production activity focuses on vaccines for meningitis, hepatitis, and flu. This effort serves to develop Malaysia's bio-economy sector while at the same time, reducing the nation's reliance on imported vaccines. It also supports the demand for immunization of pilgrims to Saudi Arabia.<sup>58-60</sup>

However, the public needs to know that the development and introduction of a new vaccine are a lengthy process. Upon successful laboratory testing and development of a new vaccine, it will need to undergo a benefits and risks assessment to evaluate the balance between its efficacy and safety to ensure the production of a well-characterized and safe vaccine. The new vaccine formulation including new vaccine antigens needs to be tested to prove its effectiveness and safety to users. Alternative excipients such as semi-synthetic trypsin that have

been discussed earlier in this review could cost more than the conventional ingredient. Therefore, this could affect the vaccine's cost and availability as well.

Besides the technical and development hurdles, the new vaccine will also be subjected to various phases of complicated trials and long-term observations to prove its effectiveness against existing vaccines. This is among the prerequisite to getting approval from a drug regulatory agency.<sup>61,62</sup> An alternative is to have the vaccine prequalified by WHO before it is released to the public.<sup>63</sup>

### Limitations and recommendations

The current review covers a wide topic on production and *halal* certification of vaccines, process of introducing a new vaccine into a vaccination program, issues on vaccination education, and the future of *halal* vaccines. The review provides information on the major religious concerns related to vaccination refusal and how Malaysia has been trying to overcome the issue and cater to vaccine needs. However, as these aspects can only be elaborated in general, certain details might be unintentionally left out. Future studies involving thorough systematic reviews or reports on each aspect in the Malaysian context and in relation to other Muslim-majority countries are recommended to provide a deeper insight into the issue.

In addition, this review is trying to tackle the vaccine hesitancy one at a time by first elaborating the challenges related to the *halal* vaccine issues. The authors expect that by clarifying this concern, vaccine acceptance in some parts of the population could be improved and health professionals could move to educate the public on other factors contributing to the vaccination refusal. Future focus on other elements such as ingredient safety is also needed as issues in vaccination hesitancy among non-Muslim parents are also important to address.<sup>51</sup>

### Conclusion

Vaccine refusal could pose a threat to herd immunity and expose vulnerable individuals to dangerous diseases. Through this review, we hope that readers understand the steps involved in vaccine production. Certain ingredients of concern may be included along the line; however, alternatives are present for use. JAKIM has been stringent in *halal* certification of vaccines for use in NIP, in addition to the laborious decision-making phases involved in introducing a new vaccine into a program. Health-care providers need to be prepared for the challenges in educating the public on vaccination at the same time. There will be a huge demand for *halal* vaccine, and it is hoped that its production in Malaysia will promote self-reliance in other Muslim-populated countries as well.

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Dr AG is an employee of Pfizer Inc. and may be eligible for stock and stock options. Dr AAN is a previous employee of Pfizer Inc.

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