Minutes of the Meeting of the National Technical Advisory Group on Immunization (NTAGI)

4:00 PM-5:00 PM, Tuesday, December 19, 2017
Nirman Bhawan, New Delhi

Agenda

Chair: Ms. Preeti Sudan, Secretary, Ministry of Health and Family Welfare (MoHFW). ***Co-chair: Dr. VijayRaghavan, Secretary , Department of Biotechnology (DBT) & Department of Health Research (DHR).***				
16:00-16:15	Agenda 1	Welcome & action arising from previous meeting	JS (RCH), MoHFW	
16:15-16:40	Agenda 2	Human Papilloma Virus (HPV)	Dr. N.K. Arora, INCLEN Trust	
16:40-16:45	Agenda 3	Standing working group on Vaccine Preventable Disease (VPD) surveillance	For information to NTAGI as these groups are under STSC	Dr. M D. Gupte, NIV Pune
16:45-16:50	Agenda 4	Standing working group on Research and Capacity building		Dr. Nivedita, ICMR
16:50-17:00	Agenda 5	NTAGI Annual Work Plan 2018-19	Dr. G. Sridharan, CMC Vellore	
17:00-17:15	Recommendations		Chair, Co-chairs and NTAGI members	

List of attendees

	Name	Designation
Chair		
1	Smt. Preeti Sudan	Secretary, Dept. of Health & Family Welfare
Co-Chair		
2	Prof. K. VijayRaghavan	Secretary, Dept. of Biotechnology
		Secretary, Dept. of Health Research
Core Members, Ex-officio		
3	Dr. Jagdish Prasad	Director General of Health Services
4	Shri Manoj Jhalani	Additional Secretary & Mission Director, NHM
5	Dr. A C Dhariwal	Director, National Centre for Disease Control
Core Members, Independent Experts		
6	Dr. Parvaiz Koul	Professor, Sher-i-Kashmir Institute of Medical Sciences, Srinagar
7	Dr. Dileep Mavalankar	Director, IIPH Gandhinagar
8	Dr. Arun Kumar Agarwal	Professor, PGI, Chandigarh
9	Dr. M D Gupte	National Institute of Virology, Pune
10	Prof. Indrani Gupta	Professor, Institute for Economic Growth, Delhi
11	Dr. N K Arora	Executive Director, INCLEN, New Delhi
12	Dr. G Sridharan	Consultant Virologist, Vellore
Liaison Members, MoHFW Representatives		
13	Ms. Vandana Gurnani	Joint Secretary, RCH
14	Dr. M.K. Agarwal	DC (UIP)
15	Dr. Pradeep Haldar	DC (Immunization)
16	Dr. G.N Singh	DCGI
Representatives from International Partners		
17	Dr. Henk Bekedam	Country Representative, WHO
Others		
18	Dr. Nivedita Gupta	Scientist E, ICMR
19	Dr. Pankaj Bhatnagar	WHO
20	Dr. S Eswara Reddy	JDCI, CDSCO
21	Dr. Sheenu Chaudhary	MoHFW, New Delhi
22	Dr. Pankaj Agrawal	MoHFW, New Delhi
Members represented by others		
23	Dr. Ajay Gambhir	Indian Academy of Pediatrics (for Dr. Anupam Sachdeva)
24	Dr. K K Kalra	Indian Medical Association (for Dr. K K Agrawal)
25	Henriette Ahreus	UNICEF India
26	Dr. Yaron Wolman	UNICEF India
27	Dr. Bhrigu Kapuriya	UNICEF India
NTAGI Secretariat		
28	Dr. Saurabh Gupta	NTAGI Secretariat
29	Dr. Jitesh Kuwatada	NTAGI Secretariat
30	Dr. Awnish Kumar Singh	NTAGI Secretariat

Members Apologized		
31	Dr. A K Panda	Director, National Institute of Immunology
32	Dr. D T Mourya	National Institute of Virology, Pune
33	Dr. Gagandeep Kang	Executive Director, THSTI
34	Dr. J Muliyil	Professor, CMC Vellore
35	Dr. Dileep Kumar Das	Professor, Burdwan Medical College, West Bengal
36	Dr. Jacob Puliyel	Consultant Pediatrician, St Stephen's Hospital, Delhi
37	Lt. General Raghunath	Bangalore
38	Dr. Vinod Paul	Professor, AIIMS, New Delhi
39	Prof. K. Srinath Reddy	Public Health Foundation of India
Members not present		
40	Dr. M K Bhan	Former Secretary DBT
41	Dr. Y K Gupta	Professor, AIIMS, New Delhi

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The National Technical Advisory Group on Immunization (NTAGI) met as per calendar on Tuesday, December 19, 2017, at Nirman Bhawan, New Delhi under the chairpersonship of Ms. Preeti Sudan, Secretary, Ministry of Health and Family Welfare (MoHFW). The meeting was co-chaired by Dr. VijayRaghavan, Secretary, Department of Biotechnology (DBT) and Department of Health Research (DHR).

The Co-Chair welcomed the members and participants to the meeting.

Conflict of Interest and Confidentiality: The co-chair ensured that the confidentiality agreement was duly filled and signed by all members, invited participants and NTAGI Secretariat team. Declaration of conflicts of interest were reviewed by the co-chair and no conflict of interest was noted.

All members/participants introduced themselves. Following self-introduction, the meeting was called to order. As per the agenda, the following items were discussed:

1) Agenda Item 1: Action arising from previous NTAGI meeting held on 9th December, 2016

The Joint Secretary- RCH presented an update on key agenda items from the minutes of the previous NTAGI meeting, held on December 9th, 2016 as follows:

a) HPV vaccine: The members and participants were apprised that as per the recommendations to undertake a thorough evaluation of HPV control strategies including a cost effectiveness analysis, NTAGI secretariat has conducted an in-house study on cost effectiveness of HPV using WHO PRIME tool. The Non-Communicable Disease (NCD) division, MoHFW has initiated screening of cervical cancer.
b) Typhoid: During the last NTAGI meeting, STSC recommendations were to enhance typhoid surveillance mechanisms to inform a future NTAGI discussion and recommendations on typhoid vaccine use in India. In this regard, initiation of typhoid disease surveillance by THSTI and CMC Vellore under the guidance of ICMR has been initiated. Also, ICMR and WHO will carry out a study on typhoid conjugate vaccine in Navi Mumbai, to understand vaccine effectiveness, disease burden and antimicrobial resistance. One participant asked about the brand of vaccine used in typhoid vaccine efficacy study. It was informed that since SAGE has evaluated three vaccines out of which only one vaccine will be used for the said demonstration study.

It was also apprised that the vaccine proposed for the demonstration study is approved by DCGI, CDSCO as well.

c) Tetanus and adult diphtheria vaccine: The members were informed that NTAGI's recommendations of replacing existing TT vaccine doses under country's UIP with Td vaccine has been accepted by the MoHFW. It was informed that technical specifications of Td vaccine have been finalized and procurement is under process. Td vaccine is likely to be a part of the UIP from the last quarter of 2018. It was also stated that supply of Td vaccine may be available only after that last quarter of 2018. One participant asked the reason for the replacement of TT with Td vaccine. It was stated that decision on replacement has been taken due to the epidemiological shift of diphtheria cases to higher age groups.
d) Hepatitis A vaccine: It was informed that the vaccine was recommended for epidemic control and individual use, and not for inclusion in the UIP. There was no action required on this vaccine, as recommendations were advisory in nature.

2) Agenda item 2: HPV Vaccine

The Chair HPV of the Working Group presented the updates on HPV vaccine as follows:

- HPV is the most common viral infection of the reproductive tract and is the cause of precancerous lesions that may progress to cancer. Although the majority of HPV resolve spontaneously, persistent infection with HPV may result in cancers. In women, persistent infection with specific HPV types (most frequently HPV-16 and HPV-18) may progress to cervical cancer. HPV infection is also associated with oropharyngeal and anogenital cancers and other conditions in men and women.
- As per the population based cancer registries reports, globally, cervical cancer is the 4th most common cancer in women. In India, cervical cancer is the 2nd most common cancer in women and country contributes to largest proportion of global cervical cancer burden. Nearly 99,099 estimated cervical cancer cases and 66,552 deaths due to cervical cancer occur annually in country. At any given point of time, nearly 4,18,175 cervical cancer cases are present in country. These facts imply that there is significant burden of HPV disease in the country.
- Amongst all cancer cases in females, cervical cancer is responsible for nearly 10.8 % cases. Cervical cancer occurs predominantly in age group of 35-64 years (74% of total cervical cancer cases).
- Between different parts of the country, there is a six-fold variation in the incidence in cervical cancer (age adjusted rate of 4.9 per 100,000 in Dibrugarh, Assam to 30.2 per 100,000 in Papumpare District, Arunachal Pradesh). The causes for this variation are not understood at present.
- Regarding relative contribution of different viral types to cervical cancer in India, HPV-16 is incriminated in more than 60% cases and HPV-18 in >15% cases.

- Three HPV vaccines, directed against high-risk HPV types, are currently available for the prevention of HPV-related disease: the bivalent vaccine, the quadrivalent vaccine and the nonavalent vaccine. All of these vaccines are intended to be administered if possible before the onset of sexual activity, i.e. before first exposure to HPV infection. None of the vaccines contains live biological products or viral DNA, and are therefore noninfectious; they do not contain antibiotics or preservative agents.
- HPV types: 16, 18, 31, 33, 45, 52, 58 are considered as high risk types as they can cause cancer. Type 6 and 11 are considered low risk types as they cause anogenital warts and not directly implicated in cancer causation. All three available vaccines against HPV: Bivalent (against type 16, 18), Quadrivalent (against type 6,11,16,18), nonavalent (against type 6,11,16,18, 31,33,45,52,58) contain HPV 16 and 18 which are the most commonly types involved in cervical cancer.
- It was informed that bivalent HPV vaccine use is associated with a significant reduction in prevalence of HPV 16 and 18 from 29.8% (95% confidence interval 28.3, 31.3%) to 13.6% (95% confidence interval 11.7, 15.8%). The data also suggest cross-protection against HPV 31, 33 and 45.
- Clinical efficacy against infection and cervical lesions of any grade has been demonstrated with all HPV vaccines. Current evidence suggests that the three vaccines have nearly similar effectiveness for the prevention of cervical cancer associated to HPV types 16/18. It was also informed that all available HPV vaccines afford long term protection against HPV infection (bivalent and quadrivalent more than 10 years and 9-valent vaccine- more than 6 years, depending upon the available minimum follow-up period).
- The safety of these vaccines has been reviewed by multiple medical authorities and regulatory agencies globally including World Health Organisation, Global Advisory Committee on Vaccine Safety (GACVS), Food and Drug Administration (FDA), European Medicines Agency (EMA) and International Federation of Gynaecology & Obstetrics (FIGO). Available HPV vaccines have an excellent safety profile and nearly 270 million doses have been given globally. The risk of anaphylaxis has been characterized as approximately 1.7 cases per million doses, and syncope was established as a common anxiety or stress-related reaction to the injection and not because of vaccine per se. No other adverse reactions have been identified and GACVS considers HPV vaccines to be extremely safe.
- Using India specific data, the NTAGI secretariat has adapted the WHO PRIME tool to assess the cost-effectiveness of HPV vaccination in girls. The incremental cost averted is $137/DALY which makes the HPV vaccination of girls very cost-effective (as per WHO definition) intervention for inclusion in the UIP.
- HPV vaccination is a primary prevention measure. In several countries including the US, both boys and girls are given HPV vaccines. In modeling data reviewed by WHO, giving HPV vaccine to both boys and girls drives down disease faster, but in terms of cost-effectiveness, giving vaccines to female alone is more cost-effective. Cervical

screening is a secondary prevention targeted at women aged 30-65 years. Therefore, these are 2 different and independent strategies to prevent cervical cancer, aimed at different age groups. It is to be noted that the transmission can be reduced by only vaccination and not screening.

- Besides the cost of the HPV vaccine, costs for the inclusion of HPV vaccine under UIP includes (but is not limited to): Immunization-specific personnel; Injection supplies; transportation for fixed sites and outreach activities; trainings; additional cold chain equipment; social mobilization; advocacy and communication activities; incentives given to Accredited Social Health Activists (ASHAs). These were included in the cost effectiveness model.
- Uninterrupted vaccine supply is a crucial issue for sustainability of HPV immunization.
- Programmatic Issues to be considered before introduction are: Program preparedness for introduction of a new vaccine, selection of target population (age group and gender), delivery strategy (schools'/health facility/outreach), selection of vaccine, state-wise roll out plan, advocacy and communication activities, AEFI surveillance, impact assessment & developing a concurrent program relevant research agenda (surveillance, additional benefits) and delivery through common adolescent platform.
- It was informed that country has experience of HPV vaccination in Punjab. Apart from this there are research publications to guide policy decisions on immunogenicity and safety of HPV vaccines.

In view of above facts, STSC made following recommendations:

- The HPV vaccine is recommended for inclusion in India's Universal Immunization Programme (UIP) by the STSC. The vaccine with the highest valency which has an assured vaccine supply is recommended by STSC.
- Price of the vaccine will be an important criterion for vaccine selection.
- While immunizing both boys and girls may be a strategy for the future, because of cost constraints the current priority of HPV immunization will be the immunization of girls, prior to becoming sexually active to prevent cervical cancer.
- The age range should be harmonized to that of the extended 2-dose immunization schedule (0, 6/12 Months) recommended by WHO, i.e. 9 – 14 years – which gives the best immune response.
- Achieving high coverage is a priority.
- The goal should be to introduce the HPV vaccine country-wide. Phased introductions toward that eventual goal can be done because of vaccine supply, affordability and implementation challenges of a country-wide vaccination programme in India.
- HPV vaccination for adolescent girls should be integrated with the other adolescent interventions of the RMNCH-A, delivered though a common adolescent platform, in order to bring greatest impact

- A modelling unit for vaccine preventable disease is established at the NTAGI secretariat to build in-house capacity for undertaking vaccine cost-effectiveness estimates

Concerns were expressed regarding the recommendation of vaccine to girls 9-14 years of age as the average age of marriage among Indian girls is increasing over time and therefore the age of initiation of sexual activity is delayed. It was clarified that the priming effect of vaccine given at early age will prevent infection in later life as it will boost the antibody response on subsequent exposures. It was added that the changing life styles may have substantial effects on initiation of sexual activity and therefore a significant proportion of HPV infection amongst Indian females may be acquired at younger age. It was further informed that if HPV vaccination is started after 15 years of age, 3 doses are required (as compared to 2-dose schedule before 15 years) which raises the cost of programme by 50%.

One of the members raised concerns about the role of cervical cancer screening, post marketing surveillance and genotype shift after HPV vaccine introduction. It was informed that according to Operational Framework for Management of Common Cancers 2016 developed by MoHFW, the screening for cervical, breast and oral cancer will be rolled out in a phased manner. Cervical screening programme will be rolled out for all women aged 30-65 using Visual Inspection with Acetic acid (VIA) technique, with the screening happening every 5 years. However, the practical challenges of a mass screening programme implementation have been revealed in Tamil Nadu, which has shown that there is significantly less compliance for colposcopy in real field settings as compared to research settings. Regarding genotype replacement, it was mentioned that there is no evidence that after controlling transmission of existing strains, other strains emerges as more oncogenic. It was informed that DCGI has been collecting data on HPV vaccine for the past 4 years from the private market and the Pharmacovigilance Programme of India (PvPI) and Adverse Event Following Immunization (AEFI) surveillance are working hand in hand to strengthen post marketing surveillance.

The need to strengthen the post marketing surveillance and the involvement of the private sector in the programme was emphasized. A member highlighted that as valency of vaccine varies from two, four or nine valent, it will lead to change in cost and in turn cost-effectiveness of the HPV vaccine. Another member mentioned that there is only marginal difference in the cost of these vaccines. It was also informed that once the recommendation of introduction is given, the vaccine production may increase and vaccine cost may come down to as low as $2 per dose. It was also discussed that a HPV vaccine from an indigenous manufacturer is in an advanced stage of clinical trials and may be licensed soon, which will help to reduce the cost of HPV vaccine further.

Concerns were raised by an NTAGI member that the matter regarding licensure of HPV vaccines (Gardasil & Cervarix) use in India is subjudice in Supreme Court of India and HPV vaccine introduction in country to be taken up with caution. Another member added that the

comparative cost effectiveness need to be looked for HPV and other vaccines planned for further expansion like PCV, RVV, in view of the National Nutrition Mission Programme.

The need to carry out further research on comparative effectiveness of single Vs. two doses of vaccines and the effectiveness of vaccines in malnourished population was iterated during discussions. It was discussed that the NTAGI is an advisory body and can give recommendation of HPV vaccine introduction in UIP. However, the MoHFW, being the programme implementation agency, needs to prioritize the resources.

Other concerns were raised regarding recommendations of HPV vaccine inclusion under UIP as follows:

a) Both the available bi-valent and quadrivalent vaccine in country have been licensed in India without sufficient clinical trials. The validity of licenses/clearances are sub judice before the Supreme Court and no conclusion has been reached so far.
b) a report from one of the manufacturers of HPV vaccine have shown that the vaccine may actually increase the risk of disease it is supposed to prevent.
c) Adolescent girls in India are anemic and malnourished which puts them at risk of adverse effects of administering HPV.

STSC working group stated that the study where increased risk of disease was demonstrated was actually because vaccine efficacy was studied in females who were already exposed to HPV infection. HPV vaccine is supposed to be taken before exposure of infection to prevent the risk of cervical cancer. Another member informed that effects of malnutrition on immunogenicity of vaccines are minimal and also it does not increase the risk of side effects.

Recommendations: The NTAGI endorsed the STSC recommendation for introduction of HPV with certain points in mind as follows:

i. An effective communication strategy has to be in place with all the important information. It was stressed that communication should bring out
    a) That cervical cancer is the disease caused by HPV infection which is transmitted sexually,
    b) The vaccination is recommended for both boys and girls. However, as girls bear direct burden of the disease and given current costs, introduction of vaccine will be done for girls in the initial period.
    c) Vaccine does not eliminate the need for screening and screening should be done regularly in the susceptible population after the age of 30 years.
    d) The public must be informed of the goals, delivery and potential impact of the vaccination programme.

ii. There is need to have ongoing research and studies specially in Punjab, which has included HPV in its immunization programme. Studies need to be done to understand the protective efficacy of vaccine among married vs unmarried population. This is important because uninformed rollout is unfair for the recipients.

iii. The inclusion of specific HPV vaccines in the programme is subject to the outcome of the pending Supreme Court judgment.

3) Agenda item 3: Standing Working Group on VPD Surveillance

A member from NTAGI informed the participants that the STSC had a detailed discussion regarding the need of collating the data from existing multiple surveillance systems. The STSC has created a standing working group on VPD surveillance. This was for information only.

4) Agenda item 4: Standing Work Group on Research and Capacity Building

It was informed to NTAGI that the STSC has created a standing working group on Research and Capacity Building.

5) Agenda item 5: NTAGI Annual Work Plan for 2018-2019

A brief of draft annual work plan of NTAGI for 2018-2019 was presented. It was discussed that NTAGI to carry on Secretariat and Committee functions as follows;

a. Logistical and administrative organization of 2 NTAGI and 4 STSC meetings
b. Organization of working group meetings under STSC
c. Circulation of Agenda note and coordination for meetings

The Chair and Co-chair thanked all the participants for their invaluable contribution and concluded the meeting.

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