Executive summary

The first WHO meeting on seasonal influenza vaccine composition for the tropics and subtropics was held in Geneva from 23 to 24 April 2015 to review evidence of influenza seasonality and evolution of the influenza viruses in the tropics and subtropics and develop practical guidance on vaccination timing and choice of vaccine composition for countries that planned to introduce or revise influenza immunization practice.

Main challenges

The continuing antigenic drift of influenza virus necessitates a biannual review of the influenza vaccine composition by WHO to ensure vaccine effectiveness against the circulating viruses. In the tropics and subtropics, influenza activity is variable and very complex with multiple peaks and identifiable year-round activity. Therefore countries in the tropics and subtropics have been advised to decide on the vaccine formulation and vaccination timing based on local influenza epidemiology and virology surveillance, which is not fully established in many countries. Furthermore, in recent years, a new challenge is to make influenza vaccine available all year-round in countries planning to introduce maternal influenza immunization. Current vaccines have a shelf life of one year from release date and typically expire by June of those with northern hemisphere formulation and January of those with southern hemisphere formulation. This leads to a gap of 2 to 3 months from the expiration of the current vaccine and the distribution of vaccine with the next updated formulation during which no usable vaccine is available.

Current evidence on influenza seasonality, virus evolution, vaccine policy, use and effectiveness for the tropics and subtropics

A systematic review of evidence suggests that countries in the tropics and subtropics show varied patterns of influenza activity. Most tropical and subtropical countries have a distinct seasonality pattern though countries near the equator often have time-varying multiple peaks and/or year-round activity. Furthermore, countries with large latitudinal spread exhibit subnational variability. Current evidence also suggests that the genetic and antigenic evolution pattern of influenza viruses in the tropics and subtropics is similar to that in the temperate regions. There is no unusual evolution of viruses in tropics and subtropics that require a separate WHO review on the composition of influenza vaccines aside from the February and September ones for the northern and southern hemisphere influenza season respectively.

Most of Asia and Africa is yet to introduce an influenza immunization policy. Influenza vaccination coverage is low (less than 5 per 1000 population) in most countries in the tropics and subtropics. Moreover, vaccine effectiveness varies widely in different risk groups and there are inherent challenges in assessing and comparing vaccine effectiveness across populations and seasons.
Practical guidance for the tropics and subtropics

Geographically contiguous “Influenza Vaccination Zones” based on similarity in seasonality and virus evolution patterns are proposed to provide practical guidance for choice of vaccination timing and vaccine formulation. Overall vaccination timing should be guided by the local seasonality pattern and countries should use the most recent vaccine formulation. Current scientific evidence does not indicate the need for a third formulation for the tropics and subtropics aside from the northern and southern hemisphere recommendations, neither is it feasible operationally due to the inherent challenges of influenza vaccine production cycle.

Next steps

An operational framework for implementation of the recommendations of seasonal influenza vaccine compositions and vaccination timings for the tropics and subtropics needs to be developed. The next step would be to develop a roadmap for countries with laid-out actions. A meeting is planned in July 2015 to review the recently developed recommendations of influenza vaccination timing and choice of vaccine formulation, share experiences and lessons learnt from countries in the tropics and subtropics that have recently introduced or revised guidelines, and better understand the needs, priorities and challenges faced by countries that plan to introduce or revise influenza immunization guidelines and explore how WHO can support countries to make informed decisions of vaccination timing and choice of vaccine formulation.
The following is a report from a WHO expert working group meeting on seasonal influenza vaccine composition for the tropics and subtropics, held 23-24 April 2015. The aim of the meeting was to review evidence on influenza seasonality and evolution of the influenza viruses in the tropics and subtropics and develop practical guidance on vaccination timing and choice of vaccine for countries that planned to introduce or revise influenza immunization guidelines.

**Setting the Context**

Because of the antigenic shift and drift of the virus, the influenza vaccine composition needs regular updates, and as of 1989, WHO presents biannual vaccine composition recommendations to capture the most recent circulating viruses. The recommendations take several aspects into account e.g. virological surveillance data from the WHO Global Influenza Surveillance & Response System (GISRS); epidemiological data from WHO FluNet; genetic analysis; vaccine effectiveness; and serology studies. The recommendation for the northern hemisphere (NH) formulation is presented in February, and for the southern hemisphere (SH) formulation in September. The ensuing vaccine production, including tests, licensing, filling, packaging, release and shipping, takes six to eight months; followed by approximately three months of immunization. Based on current technologies, the vaccine strain selection to production cycle cannot be shortened. The biannual recommendations for the vaccine composition by the WHO is suitable for the temperate regions with distinct influenza seasonality patterns. Influenza activity is more variable and complex in the tropics and subtropics with multiple peaks and identifiable year-round activity. Countries in the tropics and subtropics are therefore advised to decide on vaccine formulation and vaccination timing based on local influenza epidemiology and virology surveillance. Most virus isolates analysed for antigenic and genetic characteristics by GISRS are from temperate regions. Virus sharing by countries in Central and South America countries and Southeast Asia has increased over the years, however there is still inadequate data from Africa. Moreover, the terms NH and SH vaccine could be misleading in terms of choice of vaccine in the geographical context of the tropics and subtropics. However, the term appears on the vaccine label and hence changing it would require regulatory approvals.

Furthermore, the WHO Strategic Advisory Committee of Experts on Immunization (2012) recommends countries with seasonal influenza vaccine programs to prioritize persons at high risk of severe influenza virus infection, including pregnant women at any stage of their pregnancy. For countries in the tropics and subtropics planning to introduce maternal influenza immunization, the challenge is to make influenza vaccine available all year-round. Depending on the regulatory and distribution processes, the Northern Hemisphere vaccine typically becomes available between August and September of a given year, while Southern Hemisphere vaccine usually becomes available in March of the subsequent year. Current vaccines have a shelf life of one year from release date following production and filling and typically expire by June (northern hemisphere formulation) and
January (southern hemisphere formulation). This leads to a gap of 2 to 3 months from the expiration of the current vaccine and availability of the next formulation during which no usable vaccine is available. To bridge this gap, influenza vaccine can be made available year-round by either (a) alternating between northern and southern hemisphere formulation within the same year, (b) by extending the shelf life by either delaying the filling and release date or by extending the expiration date, to cover the gap period and enable the use of a single formulation throughout the year, or (c) by aligning the production timelines with local seasonality in the tropics. Each approach poses challenges and opportunities and countries may opt for any of these strategies based on their priorities, and regulatory and logistic capacities. A final aspect on vaccine supply is that manufacturing and establishment of vaccination programmes need a coordinated approach.

**Summarizing the Evidence**

This session focused on summarizing the evidence on influenza seasonality, virus evolution, vaccine policy, use and effectiveness in the tropics and subtropics.

**Influenza Seasonality in the tropics and subtropics**

Seasonality in the tropics and subtropics has been independently assessed by CDC, NIVEL, PATH, and WHO using different data sources and analytic approach. The results (number of peaks, period of increased influenza activity, year-round activity etc.) were compared with published literature. Country experts were consulted when there was discordance in seasonality findings, and consensus was reached. A common limitation was scarce data for some regions. Overall, countries show a varied pattern of influenza seasons, either one or multiple peaks with or without year-round activity or year-round activity without a clear peak. Nonetheless, most countries have a distinct seasonality pattern, even though countries near the equator often have time-varying multiple peaks and/or year-round activity. As a result, the seasonality pattern suggests a clear timing for vaccination for many countries. Nevertheless, analysing local and sub-national data before deciding on influenza vaccine guidelines is suggested. Impact modelling to explore optimal timing and impact of increasing vaccination coverage before introducing or revising policy guidelines can be useful.

**Key points from discussion:**

Vaccination timing could be a challenge in tropical countries with year-round activity as vaccine effectiveness may decrease over time. Where seasonality pattern differs within a country, multiple vaccination campaigns may be considered at different times using the same or the most recent formulation within the same year to target different populations. However, multiple vaccination campaigns within the same year may pose logistic and regulatory challenges as also affect vaccination coverage. It was also noted that seasonality can change, and countries need to strengthen surveillance systems for influenza. Countries should use simple methods such as proportion of influenza positives and number of positives, to assess and compare seasonality patterns within the region. So far the
results from complex methods have converged well with results from simpler methodology approaches. Data quality was considered more important than the complexity of the analytic approach. It was also noted that influenza-like illness (ILI) may not be a good substitute for determining seasonality and laboratory confirmation of influenza is the preferred measure. Guidance to regional offices on how to evaluate quality of national data and inter-country coordination may be useful for countries to make informed decisions on timing of vaccination.

Illustration 1: Timing of primary influenza seasons as found in the seasonality analysis by CDC, NIVEL, PATH, WHO and published literature, and the resulting Influenza Vaccination Zones.

**Influenza Virus Evolution in the Tropics and Subtropics**

The WHO Global Influenza Surveillance and Response System (GISRS) has been conducting laboratory-based surveillance since 1952. Virus specimens are tested in countries and a representative subset are sent to WHO Collaborating Centres of GISRS for further analysis. Using antigenic cartography, the pathway of antigenic evolution of A(H3N2) viruses globally since 2002 was shown. Although the number of viruses from tropics and subtropics is small in comparison with that from temperate countries, available genetic and antigenic data of influenza A(H3N2) and influenza B viruses circulating in Southeast Asia since 2002 and in tropical South America between 2009 and 2014 suggest that there is no unusual evolution of seasonal influenza viruses in tropics and subtropics away from those circulating elsewhere in the world.
Furthermore, analyses of immune response before and after infection indicate that an infection leads to protection against the current variant of the virus, meanwhile boosts a protection against previous variants. Overall, the current evidence suggests that the influenza virus evolution in the tropics and subtropics is similar to that in the temperate regions. A third influenza vaccine composition selection, aside from the one for the northern and southern hemisphere formulation, is not necessary.

**Seasonal Influenza Vaccine Policy, Use and Effectiveness in the Tropics and Subtropics**

To assess seasonal influenza vaccine policy and guidelines, use and effectiveness in the tropics and subtropics WHO conducted a systematic literature review. The results show that most of Asia and Africa has yet to introduce an influenza vaccine in their vaccine policy. Countries with a policy most often follow the WHO guidelines. In general, there is a lack of data on vaccination coverage. It is low (less than 5 per 1000 population) in most low and middle income countries in the tropics. The vaccine is generally administered prior to onset of the primary season, with some exceptions. The NH formulation is used by 38 countries, SH formulation by 21, and 4 countries use both. Vaccine effectiveness varies widely in different risk groups, and is lower in the tropics, as for the elderly; or largely comparable to high income countries as for children, and healthy adults. However, the vaccine effectiveness studies are often observational, prone to bias, or on non-comparable cohorts. Overall most of the evidence comes from studies in Latin America and Asia.

**Country Perspectives and Experiences**

Country perspectives from Brazil, India, Kenya and Lao People's Democratic Republic were presented and the following key points emerged: 1) Large countries e.g. Brazil, may need a phased roll-out of the vaccine due to subnational variability in onset of influenza activity, 2) Two distinct influenza circulation patterns within a country (e.g. India) was seen that may require a staggered approach to vaccination, 3) Although a tropical country has year-round influenza activity, there often is a distinct primary peak that could be targeted by prior influenza vaccination, and 4) Demand for seasonal influenza vaccination may exceed supply, and sustainable vaccine delivery should be prioritized.

**Developing Practical Guidance**

The third session focused on development of practical guidance for seasonal influenza vaccine formulation and timing of vaccination for Central and South America, Africa and Asia Pacific.

**Seasonal Influenza Vaccination Zones**

Based on the similarity in seasonality and virus evolution patterns, grouping of countries into geographically contiguous Influenza Vaccination Zones was proposed (Illustration 1). When no data was available for a country, neighbouring country data informed the grouping decision. The Influenza Vaccination Zones were intended to provide guidance for vaccination timing and choice of vaccine.
formulation taking into consideration the availability of the most recent formulation. A separate exercise would reconcile the proposed Influenza Vaccination Zones with the existing Influenza Transmission Zones. However, the grouping has limitations; large countries may exhibit more than one seasonality pattern, the grouping is at times based on sparse data, and the choice of neighbouring country seasonality to be guided by may at times be suboptimal.

Practical Guidance
In subsequent group discussions on the practical guidance the following key points emerged:

In countries with multiple peaks with or without year-round activity, vaccination should be timed to occur before onset of the primary influenza season. In specific situations, different timing would be required in sub-regions of countries. In transition zones, without an identifiable primary season, there are two options: either biannual vaccination campaigns or, if only one campaign is possible, before the major peak. However, this poses several logistic and regulatory challenges. Furthermore, the vaccine should be the most recent formulation. There is at present no scientific evidence to indicate the need for a third separate vaccine formulation. Moreover, it is currently unfeasible because of the manufacturing time.

The establishment of Influenza Vaccination Zones has the advantage of simplicity. Moreover, it was deemed acceptable that countries with inadequate data infer from neighbouring countries, but recognized to be problematic when different neighbouring countries exhibit different seasonality. One suggestion was to group countries solely on similarity in seasonal and virus evolution patterns without considering the geographic contiguity of countries within the group.

Several other related issues were also highlighted - (a) Competing public health priorities, (b) The choice between campaign approach prior to the primary period of influenza activity or year-round immunization, (c) Need for WHO regional offices to support countries build capacities for vaccine access and delivery, (d) Low vaccination coverage, including difficulties in identifying risk groups and/or reaching populations due to social disruption, (e) Once a decision on vaccine formulation has been made, changes may be problematic due to limited production of the formulations, and (f) It was suggested that WHO review the guidance every five years.

Next steps
The final session consisted of a preliminary discussion on the piloting of the practical guidance for seasonal influenza vaccine formulation and timing in the tropics and subtropics. The scope of the pilot could have a narrow scope of piloting the guidance on vaccination timing and formulation; or a more broad scope of introduction of the seasonal influenza vaccine in a country on a pilot basis. The following key issues emerged:

The overall scope of the pilot could be to assess how WHO can facilitate introduction of influenza vaccination. The objectives could be to: (I) review evidence, and develop tools and advocacy measures
needed to develop and influence influenza vaccination policy, and (II) demonstrate the feasibility and impact of implementing the guidance. Furthermore, these two objectives could be achieved in countries in different situations, e.g.: 1) a country with no influenza vaccination policy; 2) a country where a change in an existing policy guideline is desirable, or 3) a country with year-round influenza circulation. Table 1 shows the different dimensions and country scenarios in which the guidance can be tested.

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<thead>
<tr>
<th>Type of influenza seasonality</th>
<th>Influenza vaccine policy alteration</th>
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<tbody>
<tr>
<td>One peak</td>
<td>Change in vaccination timing</td>
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<tr>
<td>Two peaks</td>
<td>Change in vaccination formulation</td>
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<tr>
<td>Year-round circulation</td>
<td>Change in vaccination timing and formulation</td>
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<td></td>
<td>Introduction of vaccination programme</td>
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Table 1. Variables by which the practical guidance for seasonal influenza vaccine composition in the tropics and subtropics can be tested.

Meeting participants opined that the term pilot-testing may be a misleading and instead suggested the terms demonstration, evaluation, feasibility, or assessment as alternate terms.

The eligibility criteria for countries where the guidance can be tested was also discussed. Pre-requisites for inclusion would be a functioning surveillance system, and an expression of intent by a country to pilot the guidance. It was also suggested that dissimilar countries be opted for. Some suggestions of countries that could be included were Mali, countries in Central and South America such as Peru, Costa Rica, Cuba that were considering a change in their guidelines, Singapore, Kenya, and sub-regions of India. However, it was agreed that WHO would be guided by its regional offices in identifying potential countries and the piloting of the guidance.

The discussion also touched upon the guidance that would be piloted. It was felt necessary and useful for WHO to document experiences of countries that had introduced or revised influenza vaccination guidelines in recent years or planned to do so in the near future. The decision making process regarding vaccine choice, timing and introduction in Costa Rica was presented as an example – regional discussions, leveraging the use of existing data (however incomplete) to inform policy, strengthening of surveillance systems, cost analysis, involving the private sector, laboratories, advocacy for obtaining the political commitment – a process that took 10 years in Costa Rica. It was also felt that evaluation of vaccine effectiveness in the tropics and subtropics should be integral to piloting the guidance, as was done in Singapore.

It was felt that piloting the guidance would take more than one year. It was suggested that WHO should compile experiences and lessons-learnt by countries that had already introduced or revised influenza vaccination guidelines. In addition, experiences from the WHO work on maternal immunization guidelines could be incorporated in the guidance.
Finally, with regard to financing of the pilot it was noted that some of the work related to disease burden may fall within the scope of the pandemic influenza preparedness (PIP) framework.

**Conclusion and Continued Work**

Most of Asia and Africa has yet to introduce an influenza immunization policy. The evidence suggests that despite increasingly variable patterns of influenza activity and year round transmission seen with increasing proximity to the equator, most countries in the tropics and subtropics were found to exhibit a distinct influenza seasonality pattern. Evidence did not suggest unusual patterns of evolution or emergence of variant viruses in tropical and subtropical regions compared to the temperate regions. There was no evidence to suggest the need of a 3rd consultation (aside from the February and September consultations for the northern and southern hemisphere formulations respectively) for seasonal influenza vaccine composition for the tropics and subtropics. Current evidence suggests that the timing of vaccination should be determined solely by country seasonality and the most recent WHO recommended vaccine composition be used prior to the primary peak of influenza activity. To facilitate the implementation of the recommendations of seasonal influenza vaccine composition and vaccination timing for the tropics and subtropics, WHO should develop a guidance framework for that purpose, in particular for countries that plan to introduce or revise their influenza vaccination guidelines. The continued work will include: 1) A continued review of the operational guidance document, 2) a meeting in July 2015 to develop an operations plan to pilot the guidance in countries planning to introduce or revise guidelines for seasonal influenza vaccine formulation and timing of vaccination.
Annex 1.
Meeting participants

Eduardo Azziz-Baumgartner, USA
Ian Barr, Australia
Joseph Bresee, USA
Mandep Sukhdev Singh Chadha, India
Daouda Coulibaly, Côte d'Ivoire
Nancy Cox, USA
James F. Cummings, USA
Gideon Emukule, Kenya
John McCauley, UK
Wyller Alencar de Mello, Brasil
Hanna Merk, Sweden
Mark Miller, USA
Talat Mokhtari-Azad, Iran
Anna Morice, Costa Rica
Kathy Neuzil, USA
Laura Newman, USA
Kankawinpong Opart, Thailand
John Paget, Netherlands
Michael Pfleiderer, Germany
Mahmudur Rahman, Bangladesh
Derek Smith, UK
Samba Sow, Mali
John Tam, Hong Kong SAR
Niteen Wairagkar, USA
Anonh Xeuavongsa, Cambodia
Weigong Zhou, USA
Theodor Ziegler, Finland

WHO Secretariat

Terry Besselaar
Sylvie Briand
Julia Fitzner
Jan Hendriks
Joachim Hombach
Philippe Lambach
Réka Lüthi
Jeffrey McFarland
Justin Ortiz
Hirve Siddhivinayak
Raphael Slattery
Katelijn Vandemaele
David Wood
Wenqing Zhang

Joseph Bresee was selected as chair of the meeting. Michael Pfleiderer, Derek Smith, John McCauley, Nancy Cox were appointed as co-chairs for sessions A-D, respectively. Hanna Merk was appointed as rapporteur.
Annex 2.

Declarations of interest

DOI: none, except for Ian Barr, John Paget, John Tam and Theodor Ziegler

No further updates made at the meeting. After review, WHO concluded that the declared interests by IB, JP, JT and TZ did not conflict with the objectives of the meeting and the above participants could participate in the meeting.