

Seasonal Influenza Vaccine Use in Low and Middle Income Countries in the Tropics and Subtropics

A systematic review

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EXECUTIVE SUMMARY

Background

Over the last decade an increasing number of Low and Middle Income Countries in the tropics have actively considered initiating or expanding their national policy and guidelines for seasonal influenza vaccination. This is critical following the WHO recommendation for giving the highest priority for maternal immunization against seasonal influenza. The biannual WHO recommendations for influenza vaccine composition are suitable for countries located in the temperate regions with distinct seasonality in influenza activity. Tropical and subtropical countries with variable seasonality patterns need to make evidence-based decisions regarding which population subgroups to vaccinate, which vaccine composition to use, when to vaccinate and what public health benefits to expect.

Objectives

The overall aim of this review is to assess the scientific evidence on seasonal influenza vaccine use and effectiveness in Low and Middle Income Countries in particular those situated in the tropical regions. Specifically it aims to review the –

1. Status of national policies on seasonal influenza vaccination in Low and Middle Income Countries in the tropics and subtropics
2. Seasonal influenza vaccine supply, availability and coverage in the tropics and subtropics
3. Seasonal influenza vaccine use in the tropic and subtropics with reference to timing of vaccination and the vaccine composition recommended biannually by the WHO, and
4. Effectiveness of the seasonal influenza vaccine in the tropics and subtropics in the context of seasonality and virological characteristics of the circulating influenza viruses

Methods

We searched multiple global and regional health databases using different combinations of pre-identified search terms (with synonyms and closely related words) such as 'seasonal influenza vaccine', 'tropics', 'effectiveness', 'timing', 'policy', 'campaign', 'Africa', 'Pacific', 'Latin America' and 'Africa'. Duplicates were removed and the title and abstract was screened for eligibility by two reviewers independently. Articles were included based on consensus discussions between the two reviewers. The full text of all included articles was further assessed for eligibility. We included articles that were newly identified through cross-references from articles that were already included. We contacted institutions and individuals involved in influenza research for currently ongoing influenza vaccine related studies with a request to share preliminary summaries of unpublished studies to assess their eligibility for inclusion in the review. An effort was made to identify unpublished studies by searching conference proceedings and agency reports. We restricted our inclusions to articles in the English language or any other language provided an abstract was available in English, articles related to policies and guidelines for seasonal human influenza vaccine use in tropical and subtropical countries, articles that referred to seasonal influenza vaccine composition, timing of vaccination, vaccination supply, availability and coverage and vaccine effectiveness. We supplemented our literature search by analysing four global databases. In addition, we administered an online survey to all the WHO Member States situated in the tropics and subtropics to update information on influenza seasonality, vaccination policy, timing, composition and coverage. We excluded studies that focused on the avian or pandemic influenza vaccine or pandemic preparedness. Studies on safety and immunogenicity of influenza vaccines, determinants of influenza vaccine uptake, licensing and regulatory aspects of influenza vaccine were also excluded. Studies that focused solely on influenza seasonality, disease burden and genetic or antigenic characteristics of the influenza virus without any linkage to seasonal influenza vaccine were beyond the scope of this review. We captured the heterogeneity amongst studies based on study population, ascertainment of seasonal influenza vaccination

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and endpoint variables such as influenza-like illness, hospitalization, and laboratory confirmed influenza, potential confounding and risk of bias. For all other articles, data extraction and synthesis was descriptive. Wherever possible, we triangulated different data sources to validate the information extracted from literature.

Results

Of the 3637 articles and 34 unpublished papers identified, 3247 were deemed ineligible based on the screening of the title and abstract. A further 178 articles were excluded after a full-text appraisal. A total of 215 published and 31 unpublished articles and four global databases were included in the final review.

Most developed countries had national policies on immunization against seasonal influenza. In contrast, 64 of the 138 (46%) Low and Middle Income Countries from the tropics and subtropics had a national vaccination policy against seasonal influenza. Notably, populous countries such as Bangladesh, China, India, Pakistan and Sri Lanka in Asia representing about 45% of the world's population did not have a national vaccination policy against influenza. Thirty-eight countries used the NH formulation, 21 used the SH formulation whereas four countries (Brunei Darussalam, Marshall Islands, Peru and Singapore) used both formulations. Five countries situated in the southern hemisphere tropics used the NH formulation whereas eight situated in the northern hemisphere tropics used the SH formulation. Moreover, three countries (El Salvador, Guatemala and the Philippines) situated in the northern hemisphere tropics switched from a NH to a SH formulation in recent years.

National policies of most tropical countries recommended targeted seasonal influenza vaccination of the elderly, children, and individuals with chronic illness and healthcare professionals. However the age groups recommended for vaccination varied. Thirty-five (55%) of the 64 tropical countries recommend seasonal influenza vaccination of pregnant women. A few countries in Asia required seasonal influenza vaccination for Hajj pilgrims. Seasonal influenza vaccine was available through the private sector in most countries.

Vaccination campaigns in most tropical countries were timed prior to the onset of the typical influenza season. Vaccination campaigns in Latin America and the Caribbean occurred in April – May prior to the influenza season except in Cuba and Costa Rica which are reconsidering the timing of their vaccination campaign and using the SH formulation. The vaccination campaign timing in Brazil was appropriate for its southern region but may have been late for its northern region where the influenza season frequently occurs earlier. In most countries in the Asia Pacific, vaccination was timed prior to the onset of their influenza season. However, several countries reported vaccination timings that were inconsistent with their influenza peaks. Philippines recently switched to the most recent SH vaccine formulation to time it prior to its influenza peak activity.

The vaccine and circulating virus antigen match has averaged 55 – 60% in both hemispheres since the introduction of the biannual vaccine composition recommendation by the WHO in 1998. Since the introduction of the first TIV in 1978 till the end of 2014, a total of 50 changes were recommended by the WHO (A/H3N2 – 23; A/H1N1 – 9; influenza B – 18). The genetic / antigenic match between the vaccine and the circulating virus varied in different seasons with a better match seen for influenza B viruses except in 2002 when the B/Victoria lineage re-emerged. Typically, there was a one-season delay before the circulating virus was covered by the influenza vaccine. Sometimes virus strains persisted locally or seemed re-seeded by international travellers and hence matched poorly with the vaccine strain that had subsequently changed in line with antigenic shifts in the influenza viruses globally.

Though the global seasonal influenza vaccination coverage increased two-fold in recent years, it remained low in all targeted groups in most Low and Middle Income Countries (<5 per 1000 pop.). Higher coverage was not correlated with higher level of economic development. Furthermore, higher coverage was seen when the vaccine was offered free through the public sector.

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Vaccine efficacy (VE) against seasonal influenza varied widely in different high risk groups in Low and Middle Income Countries. VE against laboratory-confirmed influenza in the elderly was lower (0 – 42%) in Low and Middle Income Countries than in High Income Countries. In children in Low and Middle Income Countries, VE against laboratory-confirmed influenza ranged widely from 20 – 77% depending on antigenic match but was largely comparable with High Income Countries. Similarly, VE against laboratory-confirmed influenza in healthy adults in Low and Middle Income Countries ranged from 50 – 59% and was comparable with that in High Income Countries. Vaccinating pregnant women against seasonal influenza prevented laboratory-confirmed influenza in both mothers (VE: 50%) and their new born (VE: 49 – 63%). VE against laboratory-confirmed influenza was 71% amongst COPD patients in Low and Middle Income Countries comparable to that in High Income Countries.

Discussion

The tropics where an estimated 41% of the world's population resides, is an important region that faces a similar if not higher burden of influenza.

Latin America and the Caribbean have led the introduction of seasonal influenza vaccine into their immunization campaigns since the 1990s. Large parts of sub Saharan Africa and the Indian subcontinent have yet to formulate national policies against seasonal influenza though the vaccine is available through the private sector in many countries in the region. Even as some High Income Countries expand their policies to vaccinate all persons above 6mo age unless medically contraindicated, targeted vaccination of high risk population subgroups remains the main strategy to reduce influenza disease burden. National policies recommended vaccination of pregnant women against seasonal influenza in countries in Latin America and the Caribbean but this has yet to happen in the South and Southeast Asia.

Historically countries in the tropics selected the WHO recommended NH or SH vaccine formulation largely based on whether they were situated north or south of the equator. Countries also timed their vaccination campaigns according to when the respective vaccine formulation became available irrespective of the influenza seasonality pattern in the country. Recent evidence suggested that vaccination campaigns in tropical countries (in both hemispheres), where peak influenza activity frequently coincides with the rainy season, should be timed with the availability of the SH vaccine formulation. For countries such as Brazil, China and India with a large latitudinal spread, a staggered approach that allows vaccination at different times in the year to cover multiple influenza activity periods using the most recent vaccine formulation may be more appropriate.

Antigenic and genetic studies from the tropics indicate a good antigenic match between the influenza virus strains that circulated during peak activity and the appropriate vaccine strain that was recommended during that period.

Overall seasonal influenza vaccination coverage was less than 1% in most parts of Africa and Asia. In contrast, reported coverage in Latin America and the Caribbean countries was higher at times than that of High Income Countries. Higher coverage was not correlated with the level of economic development but uptake improved when the vaccine was offered free through the public sector.

Evidence on the cost-effectiveness of seasonal influenza vaccine in Low and Middle Income Countries interested in improving coverage or expanding vaccination to pregnant women is scarce. Although the benefit of influenza vaccines has been questioned recently by several studies, vaccine effectiveness in Low and Middle Income Countries was comparable to that seen in High Income Countries. However comparison of VE estimates between studies is subject to inherent challenges.

The Global Action Plan for influenza vaccines provides for expanding influenza vaccine production in Low and Middle Income Countries in the tropics and subtropics to ensure greater equity, sustainability and public

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health benefits. The wide-scale manufacturing, supply and use of seasonal influenza vaccine globally is inextricably linked with pandemic preparedness. To be able to respond quickly to a pandemic, there must exist a high capacity to produce seasonal influenza vaccine. Only then can the production capacity be adapted and up-scaled quickly to meet the urgent demand of a pandemic situation. However, global demand for seasonal influenza vaccination is low and from an economic perspective, investment in further expanding production capacity may be difficult to justify without a concomitant demand and market expansion to use the supply.

Understanding the temporal and geographic circulation of influenza is important to develop and apply vaccination control strategies. As Low and Middle Income Countries consider introducing seasonal influenza vaccination, surveillance systems need to be strengthened to better understand the epidemiology and seasonality of influenza, to enable evidence-based decision on when to vaccinate, which groups to target, what vaccine benefits to expect and so on.

Conclusion

The bulk of scientific evidence on vaccine use and effectiveness in the tropics comes from Latin America and the Caribbean and Asia with large parts of Africa underrepresented. As more and more countries in the tropics and subtropics consider vaccinating their populations at risk for influenza, their capacity to make critical decisions on which vaccine to use, when to vaccinate, how much health benefit to expect etc., is greatly restricted by the limited evidence that is available about the epidemiology and virology of the viruses that circulate in their regions. Newly emerged evidence suggests that the timing of vaccination and the choice of formulation should be solely guided by laboratory-confirmed influenza data facilitated by strengthening capacity throughout the Global Influenza Surveillance and Response System. Countries in the tropics, especially those nearer to the equator, countries with large latitudinal spread, countries with varying seasonality, countries with influenza identifiable year-round, may need to consider a staggered approach that allows vaccination at different times in the year to cover multiple or year-round influenza activity periods based on their local seasonality pattern and the availability of the most recent WHO recommended formulation. There is probably no 'one size that fits all' strategy to influenza vaccination. Influenza disease and virological surveillance need to be strengthened to enable a better prediction and selection of the biannual updates for the influenza vaccine composition. Research is needed to evaluate alternate strategies for vaccination timing with the WHO recommended vaccine formulations that have the most recent vaccine virus strains for countries in the tropics and subtropics.

Key Messages

- 1) The bulk of scientific evidence on vaccine use and effectiveness in the tropics comes from Latin America and the Caribbean and Asia; Africa remains underrepresented.
- 2) Latin America and the Caribbean countries have led the seasonal influenza vaccination amongst Low

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