Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

U.S. FOOD & DRUG ADMINISTRATION

Challenges and Opportunities for Vaccine Strain Composition with the Reduced Public Health Threat from Influenza B/Yamagata Lineage Viruses

Vaccines and Related Biological Products Advisory Committee (10/5/2023)

Jerry P Weir, PhD, Director
Division of Viral Products/OVRR/CBER/FDA

The Need for a Quadrivalent Influenza Vaccine Containing Two B Strains

- Beginning in 1978, trivalent influenza vaccines incorporated 1 influenza B and 2 influenza A (H1 and H3) components
- Influenza B diverged into 2 antigenically distinct lineages in the early 80's (Rota PA et al 1990 Virology 175:59-68)

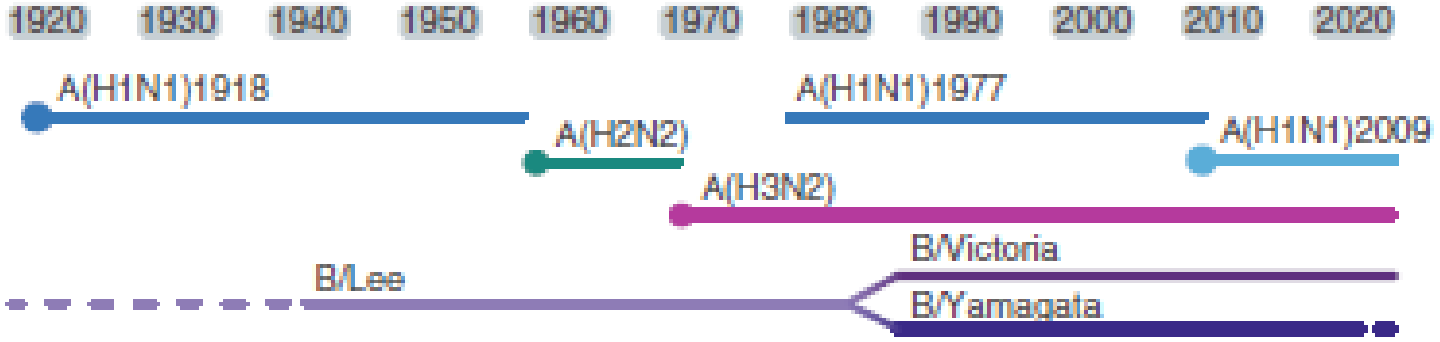


Diagram from Dhanasekaran V et al., 2022 Nat Commun 13:1721

- Influenza B was estimated to be responsible for ~26% of influenza infections in the years 1999-2012 (Heikkinen T et al., Clin Infect Dis. 2014 59:1519-1524)
- Mismatch frequency between recommended strain and the most commonly circulating B strain estimated to be ~50% in the years 2001-2011 (Ambrose CS and MJ Levine 2012 Hum Vaccin Immunother 8:81-88)
- Discussions at the WHO and at VRBPAC began in the early 2000's to discuss the feasibility and benefit of adding a 2nd B strain to seasonal vaccine

Development of Quadrivalent Influenza Vaccines Containing Two B Strains – 1

- Major issues that needed to be addressed for quadrivalent vaccine development
  - Understanding the public health need and the value added by modifying the vaccine composition to cover both influenza B lineages
  - Developing the required manufacturing capability
- The VRBPAC convened several times to discuss the issue of two circulating, antigenically distinct, influenza B lineages
  - Parallel discussions were taking place at WHO and other public health agencies
- At the Feb 27, 2007, VRBPAC, the committee discussed the major public health issues:
  - B viruses were a major cause of epidemics every 2 to 4 years
  - B infections were prominent among children and young adults; the impact was less than H3N2 but probably greater than H1N1
  - There were manufacturing concerns related to different formulations (e.g., capacity, technical challenges, etc.)
  - The various regulatory options would need further discussion

Development of Quadrivalent Influenza Vaccines Containing Two B Strains – 2

- At the Feb 18, 2009, VRBPAC, the committee had further discussions about the utility of adding a 2nd B strain to seasonal vaccine
  - CDC presented an analysis that predicted a moderate public health benefit of including both B lineages in the seasonal vaccine in terms of reduction in cases of influenza and hospitalizations
  - The committee had further discussions about the public health impact of two circulating lineages of influenza B and felt that recommending influenza vaccines containing two B strains might be considered in the future, particularly for the pediatric population; the committee encouraged all parties to collect more information to better understand the issue and to support regulatory decisions regarding inclusion of two B lineages in seasonal influenza vaccines
- Manufacturers worked with the FDA as they developed candidate quadrivalent vaccines and conducted clinical trials to generate supportive data for future vaccines containing 2 influenza B strains

Licensure of Quadrivalent Influenza Vaccines Containing Two B Strains

- VRBPAC Feb 28, 2012
  - First U.S. northern hemisphere recommendation for a 2nd B strain
  - Manufacturers reported to the committee on the status of their quadrivalent vaccine development (1 had already submitted a BLA to FDA), but none were licensed at the time
  - The committee expressed enthusiasm for a quadrivalent vaccine and hoped that one or more would be available soon
  - Quadrivalent vaccines began to be licensed later in 2012
- Approval of a quadrivalent formulation was based on manufacturing and clinical data generated by each manufacturer demonstrating safety, immunogenicity of the 2nd B strain component, and that inclusion did not adversely affect immune response to other vaccine components
- All currently distributed seasonal influenza vaccines licensed in the U.S. are quadrivalent (H1, H3, B/Vic, and B/Yam)

Recent Developments – 1

- There have been no confirmed detections of circulating B/Yamagata lineage viruses after March 2020, suggesting a greatly reduced public health threat and the possibility that B/Yamagata lineage viruses are no longer circulating in the population
  - No animal reservoir for influenza B
- In previous VRBPAC meetings, committee members discussed the recommendation for a B Yamagata component for a quadrivalent influenza vaccine considering the absence of detectable B Yamagata viruses worldwide
  - On March 7, 2023, the VRBPAC made recommendations on the selection of strains for the 2023 – 2024 northern hemisphere influenza season; the committee was asked to vote on each vaccine component using the WHO recommendation as a guide:
    - For questions #1 (H1N1), #2 (H3N2), and #3 (influenza B Victoria), the votes were 13 Yes, 0 No, 0 Abstain
    - For question #4 (influenza B/Yamagata), the vote was 7 Yes, 2 No, 4 Abstain
  - While the majority of the committee agreed with the WHO recommendation to continue to include a B/Yamagata component in quadrivalent vaccines for the North Hemisphere 2023 – 2024 influenza season, primarily because of uncertainty as to whether the B Yamagata virus lineage was truly extinct, the consensus was that this issue would require further discussion at future VRBPAC influenza strain composition meetings

Recent Developments – 2

- The WHO organized a meeting on 13 July 2023 to discuss the issue of the influenza vaccine B/Yamagata component
  - The meeting was held in conjunction with the 36th biannual meeting between WHO Essential Regulatory Laboratories, WHO Collaborating Centers, and influenza vaccine manufacturers
  - General agreement that in the absence of circulating B/Yamagata lineage viruses, that component of the vaccine should be removed
  - No agreement about the timing of such an action
  - Concern expressed by manufacturers about manufacturing and regulatory issues that would need to be addressed
  - Concern expressed by several participants about the possibility of a B/Yamagata return
- WHO convened a technical discussion on 25-29 September 2023 to recommend the composition of influenza vaccines for the southern hemisphere
  - "The absence of confirmed detection of naturally occurring B/Yamagata lineage viruses is indicative of very low risk of infection by B/Yamagata lineage viruses. Therefore, it is the opinion of the WHO influenza vaccine composition advisory committee that inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted, and every effort should be made to exclude this component as soon as possible."

Challenges in Changing the Composition of Influenza Vaccines – 1

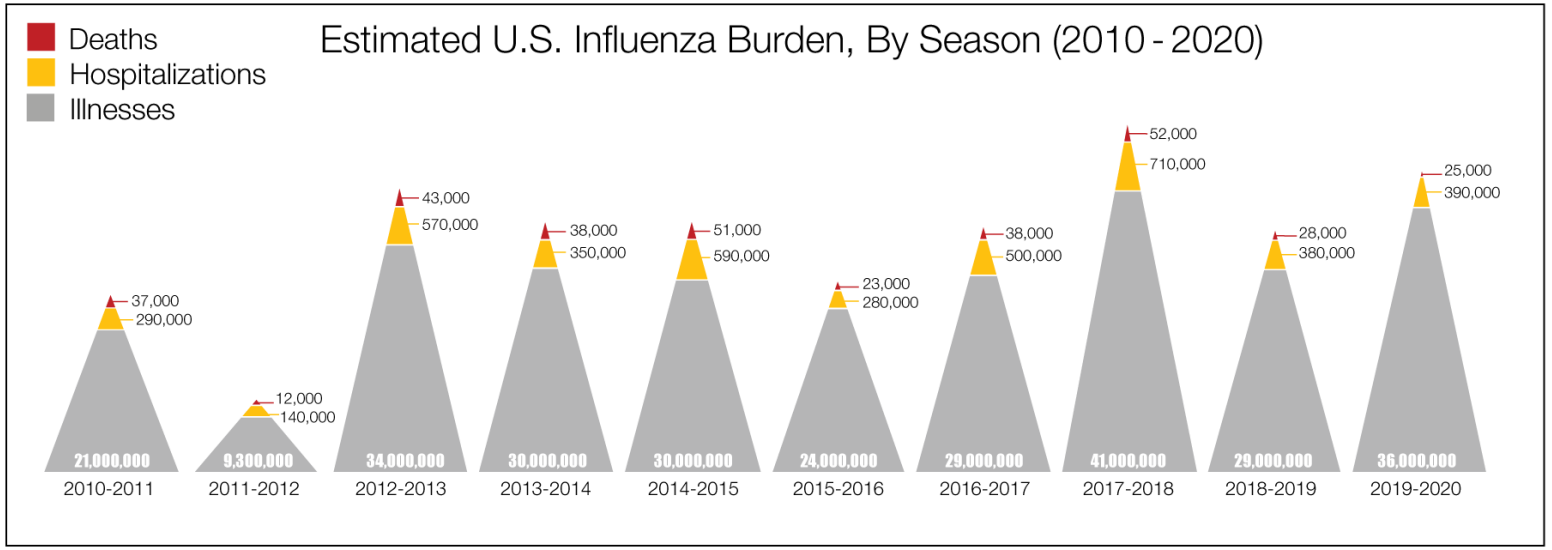
- Reverting from a quadrivalent vaccine (H1, H3, B/Vic and B/Yam) to a trivalent with H1, H3 and B/Vic
  - Regulatory challenges
    - Regulatory processes for reverting to a trivalent formulation differ in different parts of the world
    - In the U.S., all manufacturers of quadrivalent vaccines were originally licensed to produce trivalent vaccines
    - Trivalent vaccine are still licensed but currently "Discontinued"; procedures exist for removal from the Discontinued Product list
  - Manufacturing challenges
    - Some manufacturing changes have been implemented for quadrivalent vaccines since the prior licensure of trivalent vaccines
    - Changes implemented for quadrivalent vaccines are specific for each manufacturer
    - In the U.S., most manufacturing changes relevant to a trivalent formulation have already been reviewed as part of the quadrivalent license
  - Risk of re-emergence of B/Yamagata virus lineage
    - Current surveillance system is adequate to monitor re-emergence
    - Retaining quadrivalent licenses would facilitate an appropriate vaccine response
  - Timing
    - A global coordinated change in vaccine composition to a trivalent formulation may be difficult to effect

Challenges in Changing the Composition of Influenza Vaccines – 2

- For changing the current quadrivalent composition to an alternative vaccine composition
  - Developing a consensus regarding an alternative composition
    - Several alternative composition possibilities have been proposed
    - The process for making an alternative composition recommendation is not defined
  - Generating the clinical data needed to support a particular alternative composition
    - Data would be needed from each manufacturer
    - Data would be needed for each alternative composition
  - Addressing the technical challenges to formulation
    - Potency
    - Identity
    - Clinical evaluation (e.g., immunogenicity)
  - Determining the effect of an alternative composition recommendation on vaccine timelines
    - With current H1, H3, B/Vic and B/Yam vaccines, manufacturers prepare at least one antigen at risk before strain selection decisions

Opportunities in Changing the Composition of Influenza Vaccines – 1

- The disease burden of influenza remains high
  - Influenza B is the cause of ~25% of influenza cases in a season
    - 23.4% from 2000-2018, in Caini S et al 2019 PLoS One e0222381
    - 27.5% from 2010-2020, in Zanobini P et al 2022 Influenza Other Respi Viruses 16:696-706



From https://www.cdc.gov/flu/about/burden/index.html

- Current vaccine effectiveness suggests room for improvement
  - In recent years (2010-2023), adjusted VE (%) ranged from 19% (2014-2015) to 60% (2010-2011)
    - https://www.cdc.gov/flu/vaccines-work/past-seasons-estimates.html

Opportunities in Changing the Composition of Influenza Vaccines – 2

- Several alternative compositions have been proposed
  - Koutsakos M et al, 2021 Nature Reviews 19:741-742
  - Presentations at the WHO 13 July 2023 meeting on the influenza vaccine B/Yamagata component
- Examples of proposed alternative compositions
  - Two H3 antigens (or two H1 antigens) to better cover circulating virus diversity
  - Higher dose of H3 antigen to improve effectiveness against the virus with the greatest public health impact
  - Higher doses of all vaccine antigens to improve overall vaccine effectiveness
    - Experience with high-dose Fluzone (60 µg antigen) in the elderly indicates improved antibody titers and improved effectiveness against influenza-associated clinical outcomes compared to standard dose vaccine (15 µg antigen) - Lee J et al., 2021 Vaccine 39:A24-A35.
- Flexibility in composition recommendations would allow timely response to virus diversity
  - Recommendations would have to be driven by public health need and by consensus
  - Technical considerations would have to be addressed, preferably by collaboration between manufacturers and WHO ERLs
  - Every composition under consideration would need supporting data for each manufacturer to update their license
    - Data needed for development of quadrivalent vaccines provides a general guide, e.g., immunogenicity of new component, lack of interference with other vaccine components, safety

Summary – 1

- Development of quadrivalent influenza vaccines containing two influenza B lineage antigens succeeded in eliminating mismatches between the vaccine component and the predominant circulating lineage of influenza B
- Accumulating evidence indicates a greatly reduced, and possibly non-existent, public health threat from the B/Yamagata lineage virus
- Absence of circulating B/Yamagata lineage viruses suggests that inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted
- Reverting to a trivalent influenza vaccine with H1, H3 and B/Vic components presents some hurdles, which differ around the world, but are manageable by coordinated efforts between industry stakeholders and regulatory agencies

Summary – 2

- A change to an alternative influenza vaccine composition is an opportunity to provide flexibility and improvement for current vaccines, but will require additional work, investment, and coordination among stakeholders
- It is unlikely that removal of the B/Yamagata component from current quadrivalent vaccines can be coordinated with a change to an alternative composition
- Global harmonization and standardization of any alternative influenza vaccine composition will require:
  - Prioritization and consensus on alternative compositions
  - Generation of supportive data from each manufacturer to ensure the safety and effectiveness of new alternative compositions
  - Updating of licenses


FDA
U.S. FOOD & DRUG
ADMINISTRATION