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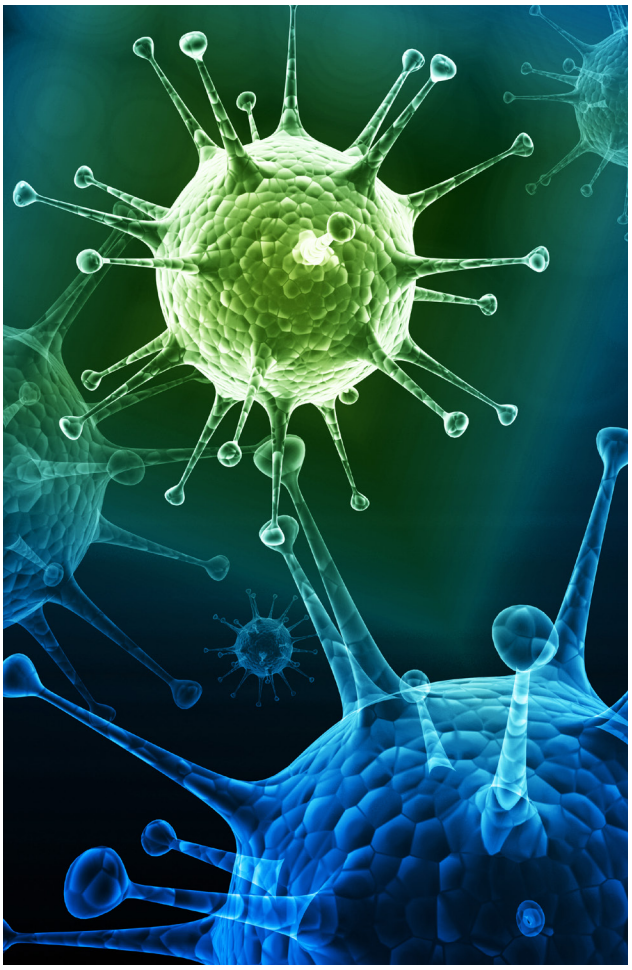
VACCINE UPDATE



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The *Canada Communicable Disease Report* (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public health professionals, and policy-makers to inform policy, program development and practice.

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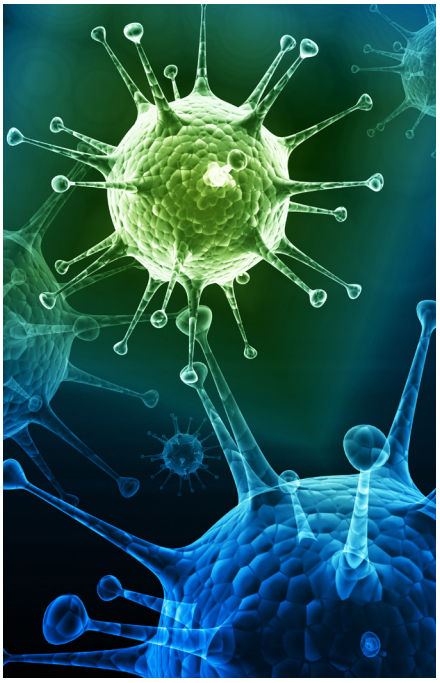

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Summary of the NACI Seasonal Influenza Vaccine Statement for 2018–2019

W Vaudry[1,2], L Zhao[3], R Stirling[3] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: There are many different influenza vaccines authorized for use in Canada and new evidence on influenza and vaccines is emerging all the time. The National Advisory Committee on Immunization (NACI) provides recommendations annually regarding seasonal influenza vaccines to the Public Health Agency of Canada (PHAC).

Objective: To summarize the NACI recommendations regarding the use of seasonal influenza vaccines for the 2018–2019 influenza season in light of two NACI reviews conducted on 1) the risk of serious influenza-related complications in children and adults with neurologic and neurodevelopment conditions and 2) the efficacy/effectiveness of high-dose and adjuvanted inactivated influenza vaccines in persons 65 years of age and older.

Methods: For both topics, NACI's Influenza Working Group developed a predefined search strategy to identify all eligible studies, assessed their quality, summarized and analyzed the findings, proposed recommendations and identified the Grade of evidence that supported them. In light of the evidence, the recommendations were then considered and approved by NACI.

Results: NACI concludes there is fair evidence to recommend that children and adults with neurologic and neurodevelopment conditions are groups for whom influenza immunization is particularly recommended (Evidence Grade B recommendation). On choosing influenza vaccines for persons 65 years of age and older, at a programmatic level, NACI recommends that any of the four influenza vaccines available for use should be used. There is insufficient evidence to make a comparative recommendation on the use of these vaccines at a programmatic level (Grade I). At an individual level, NACI recommends that high-dose trivalent inactivated influenza vaccine (TIV) should be offered over standard-dose TIV to persons 65 years of age and older (Grade A). There is insufficient evidence to make comparative recommendations on the use of MF59-adjuvanted TIV and quadrivalent inactivated influenza vaccine over standard-dose TIV (Grade I).

Conclusion: NACI continues to recommend annual influenza vaccination for all individuals aged six months and older, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk, people who provide essential community services and people in direct contact during culling operations with poultry infected with avian influenza.

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Keywords: National Advisory Committee on Immunization, influenza, vaccine

Introduction

Together, influenza and pneumonia are ranked among the top 10 leading causes of death in Canada (1). Although the burden of influenza can vary from year to year, it is estimated that, in a given year, there are an average of 12,200 hospitalizations related to influenza (2) and approximately 3,500 deaths (3). The National Advisory Committee on Immunization (NACI) provides annual recommendations regarding seasonal influenza vaccines to the Public Health Agency of Canada (PHAC).

For the 2018–2019 influenza season, NACI developed recommendations regarding the use of seasonal influenza vaccines in light of two reviews. The reviews examined 1) the risk of serious influenza-related complications in children and adults with neurologic and neurodevelopment conditions (NNCs) and 2) the efficacy/effectiveness of high-dose and adjuvanted inactivated influenza vaccines in persons 65 years of age and older. Complete details can be found in the *Statement*

on Seasonal Influenza Vaccine for 2018–2019 (4) and related publications. The objective of this article is to summarize this annual seasonal influenza statement.

Methods

In the preparation of the *Statement on Seasonal Influenza Vaccine for 2018–2019*, NACI's Influenza Working Group (IWG) followed NACI's evidence-based process for developing recommendations. The IWG identified and reviewed evidence relating to the two literature reviews and, following the review and analysis of this information, the IWG proposed recommendations (5). The NACI critically appraised the available evidence and approved the specific recommendations brought forward.

Neurologic or neurodevelopment conditions

The review of evidence utilized a rapid review approach, whereby elements of a full systematic review process were modified due to time and resource limitations, but the modified process remained rigorous and transparent. The NNCs were defined as neuromuscular, neurovascular, neurodegenerative, neurodevelopment conditions and seizure disorders (and, for children, included febrile seizures and isolated developmental delay), but excluded migraines and psychiatric conditions without neurological conditions.

A predefined search strategy was used to search two electronic databases (MEDLINE and EMBASE) from inception to October 25, 2016 for studies relating to the risk of serious influenza-related complications in children and adults with NNCs. After removal of duplicates, a single reviewer screened (title, abstract and full-text) studies retrieved from the database searches for potential eligibility. Hand-searching of the reference lists of a random subset of included studies was also conducted to identify additional relevant publications. One reviewer extracted data from eligible studies into an evidence table using a piloted data abstraction template and a second reviewer independently validated the abstracted data, with any disagreements or discrepancies resolved by discussion and consensus. The methodological quality of included studies was assessed independently by two reviewers using the design-specific criteria by Harris et al., which was adopted by NACI for rating the internal validity of individual studies (6).

A narrative synthesis of the extracted information was used to explore overall patterns in the data, including similarities and differences by age group (children and adults), influenza type (pandemic and seasonal) and outcome (emergency department presentation, hospitalization, intensive care unit [ICU] admission, respiratory failure, need for mechanical ventilation and death).

Efficacy and effectiveness of high-dose and adjuvanted inactivated influenza vaccines in persons 65 years of age and older

Five electronic databases (MEDLINE, EMBASE, Global Health, ProQuest Public Health Database and Scopus) were searched using separate search strategies for Fluzone® High-Dose (June 1, 2014 to March 22, 2017) and Fluad® (January 1, 2012 to March 22, 2017) adapted from the previously conducted NACI review, *A Review of the Literature of High Dose Seasonal Influenza Vaccine for Adults 65 Years and Older* (7). These literature search updates were performed with at least one year of overlap with the last searches for literature related to the efficacy and effectiveness of these vaccines. After removal of duplicates, two reviewers independently screened (title, abstract and full-text) studies retrieved from the database searches for potential eligibility. Hand-searching of the reference lists of included studies and any secondary research articles identified in the database search was performed to identify additional relevant publications. One reviewer extracted data from eligible studies into an evidence table using a piloted data abstraction template. A second reviewer independently validated the abstracted data, with any disagreements or discrepancies resolved by discussion and consensus. The methodological quality of included studies was assessed independently by two reviewers using the design-specific criteria by Harris et al., which was adopted by NACI for rating the internal validity of individual studies (6).

A narrative synthesis of the extracted information was used to explore overall patterns in the data, including summaries of the direction, size and statistical significance of reported effect estimates for various study-defined outcomes.

Results

Neurologic or neurodevelopment conditions

The evidence related to the risk of serious influenza-related complications in adults and children with NNCs came mostly from descriptive studies (i.e., case series), which are generally considered of lower quality (level III evidence); therefore, the findings should be interpreted with consideration of the increased potential for confounding factors and bias from these types of studies. In addition, some studies lacked clarity in the conditions that constituted NNCs and there was also a lack of consistency across studies with the specific NNCs investigated. However, the body of evidence is suggestive of a relatively high burden of pre-existing NNCs in adults and children who had experienced serious pandemic influenza A(H1N1) pdm09- and seasonal influenza-related complications, such as hospitalization, ICU admission and death. Of the individuals with at least one study-defined risk factor for influenza-related complications, 12%–17% of adults and 24%–26% of children hospitalized for pandemic or seasonal influenza had NNCs as a risk factor. Similarly, of individuals with at least one study-defined risk factor for influenza-related complications, approximately 18% of adults admitted to the ICU with pandemic influenza and 40% of children admitted to the ICU with pandemic or seasonal influenza had NNCs as a risk factor. Of individuals with at least one study-defined risk factor for influenza-related complications, almost 25% of adults who died from pandemic influenza infection and 58%–62% of children who died from pandemic or seasonal influenza infection had NNCs as a risk factor.

There is also consistent evidence from this mostly descriptive body of evidence to suggest that pre-existing NNCs increase the risk for serious influenza-related complications; for example, neurologic conditions and seizure disorder in children and neuromuscular conditions in adults were identified as statistically significant risk factors for influenza-related hospitalization. Among those hospitalized for influenza infection, neurologic, neurodevelopment and neuromuscular conditions in children

and neurologic and neurocognitive conditions in adults were identified as statistically significant risk factors for ICU admission. Similarly, among children hospitalized for influenza infection, neurologic conditions were identified as a statistically significant risk factor for death. There was limited evidence identified for other serious influenza-related complications in this population, such as emergency department presentation, respiratory failure and the need for mechanical ventilation.

The findings of this rapid review of the literature are consistent with previous preliminary evidence reviewed by NACI indicating that children and adults with NNCs are at risk for influenza-related complications and hospitalization.

Therefore, based upon current evidence and expert opinion, NACI concludes there is fair evidence to recommend that children and adults with neurologic and neurodevelopmental conditions are groups for whom influenza immunization is particularly recommended (NACI Evidence Grade B Recommendation).

The NACI recommendation remains consistent with international bodies, including the United States Centers for Disease Control and Prevention, the United Kingdom's Joint Committee on Vaccination and Immunisation and the Australian Technical Advisory Group on Immunization, all of which have listed both children and adults with neurologic conditions as a high-risk group for influenza complications.

Complete details of the literature review, rationale and relevant considerations for the updated recommendations can be found in the *Literature Review on Individuals with Neurologic or Neurodevelopment Conditions and Risk of Serious Influenza-Related Complications* (8).

Efficacy and effectiveness of high-dose and adjuvanted inactivated influenza vaccines in persons 65 years of age and older

The updated literature search identified five studies that assessed the effectiveness of Fluzone High-Dose in adults 65 years of age and older: two studies providing supplementary analysis to a previously published randomized controlled trial (RCT); two retrospective cohort studies; and a multicentre, cluster RCT. Four observational studies were identified in the updated literature review that assessed the effectiveness of Fluad in this population. Observational studies, which comprise the majority of the studies identified in the updated review, may be susceptible to residual confounding, selection bias and other biases that may complicate the interpretation of effectiveness estimates. Therefore, these methodological limitations should be considered when interpreting the current body of efficacy and effectiveness evidence for Fluzone High-Dose and Fluad.

Findings from the newly identified studies suggest that Fluzone High-Dose is significantly more effective than standard-dose vaccine in preventing influenza-like illness, all-cause hospitalization, serious cardiorespiratory events possibly related to influenza and non-laboratory confirmed influenza-related death. Studies to date have not shown high-dose vaccine to be more effective than standard-dose vaccine in preventing hospitalization for influenza or pneumonia, all-cause mortality or functional decline; however, there is some evidence to suggest that current season vaccination with Fluzone High-Dose is likely to provide clinical benefit over standard-dose vaccine, irrespective of vaccination received in the previous season (high-dose or standard-dose vaccine). The updated review also found some further evidence that Fluzone High-Dose may provide additional benefit over standard dose vaccine in the very elderly, but further studies are needed to validate this purported age effect.

The observational studies identified provide some additional evidence that Fluad vaccination of adults 65 years of age and older provides clinical benefit against hospitalization for influenza or pneumonia and for laboratory-confirmed influenza infection compared with no vaccination. The potential added benefit of using the MF59-adjuvanted vaccine over unadjuvanted vaccines could not be assessed in these studies due to either a lack of a comparison against an unadjuvanted vaccine or to methodological or sample size limitations.

Previously noted evidence gaps have not been addressed by the newly identified studies; there remain no studies that directly compare high-dose vaccine with MF59-adjuvanted vaccine or compare either of these trivalent inactivated influenza vaccines (TIVs) with quadrivalent inactivated influenza vaccines (QIVs).

Based on updated reviews of the literature on the efficacy and effectiveness of high-dose and adjuvanted inactivated influenza vaccines in persons 65 years of age and older, NACI has concluded that there is no substantial change in the conclusions to be drawn from the scientific literature; however, NACI has updated its recommendation on the choice of vaccine product for this age group by creating programmatic-level (i.e., provinces and territories making decisions for publicly funded immunization programs) and individual-level (i.e., individuals wishing to prevent vaccine-preventable disease or a clinician wishing to advise individual patients) recommendations.

At a programmatic level, NACI recommends that any of the four influenza vaccines available for use in adults 65 years of age and older should be used: standard-dose TIV, high-dose TIV, MF59-adjuvanted TIV, and QIV. High-dose TIV is expected to provide superior protection compared to standard-dose TIV; however, with cost-effectiveness assessments having been outside the scope of the evidence review and without data on the relative efficacy and effectiveness between high-dose TIV, MF59-adjuvanted TIV, and QIV, there is insufficient evidence to make a comparative recommendation on the use of these vaccines at the programmatic level (Grade I).

At an individual level, NACI recommends that high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older. NACI concludes that, given the burden of disease associated with influenza A(H3N2) and the good evidence of better efficacy compared to standard-dose TIV in this age group, high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older (Grade A). There is insufficient evidence to make comparative recommendations on the use of MF59-adjuvanted TIV and QIV over standard-dose TIV (Grade I).

Complete details of the literature review, rationale and relevant considerations for the updated recommendations can be found in the *Literature Review Update on the Efficacy and Effectiveness of High-Dose (Fluzone® High-Dose) and MF59-Adjuvanted (Fluad®) Trivalent Inactivated Influenza Vaccines in Adults 65 Years of Age and Older* (9).

Summary of NACI recommendations for the use of influenza vaccines for the 2018–2019 influenza season

NACI continues to recommend influenza vaccination for all individuals aged six months and older who do not have contraindications to the vaccine, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk of complications and others as indicated in **Table 1**.

Table 1: Groups for whom influenza vaccination is particularly recommended

People at high risk of influenza-related complications or hospitalization

- All pregnant women[a]
- Adults and children with the following chronic health conditions:
  - cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma)
  - diabetes mellitus and other metabolic diseases
  - cancer, immune compromising conditions (due to underlying disease, therapy or both)
  - renal disease
  - anemia or hemoglobinopathy
  - neurologic or neurodevelopment conditions[b]
  - morbid obesity (body mass index [BMI] of 40 and over)
  - children and adolescents (age six months to 18 years) undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye syndrome associated with influenza
- People of any age who are residents of nursing homes and other chronic care facilities
- People 65 years of age and older
- All children 6– 59 months of age
- Indigenous peoples

People capable of transmitting influenza to those at high risk

- Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications
- Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized):
  - household contacts of individuals at high risk, as listed in the section above
  - household contacts of infants under 6 months of age as these infants are at high risk of complications from influenza but cannot receive influenza vaccine
  - members of a household expecting a newborn during the influenza season
- Those providing regular child care to children 59 months of age and under, whether in or out of the home
- Those who provide services within closed or relatively closed settings to persons at high risk (e.g., crew on a ship)

Others

- People who provide essential community services
- People in direct contact during culling operations with poultry infected with avian influenza

[a] The risk of influenza-related hospitalization increases with length of gestation (i.e., it is higher in the third than in the second trimester)
[b] These neurologic or neurodevelopmental conditions include neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions and seizure disorders (and for children, include febrile seizures and isolated developmental delay), but exclude migraines and psychiatric conditions without neurological conditions

Recommended influenza vaccine options by specific age and risk groups and by dosage and route of administration by age are summarized in **Tables 2** and **3**, respectively.

Table 2: Choice of influenza vaccine for selected age and risk groups (for persons without a contraindication to the vaccine)[a]

Recipient by age group	Vaccine types available for use	Comments
Children 6–23 months of age	• TIV • QIV • Adjuvanted TIV	As TIV, QIV and adjuvanted TIV are authorized for this age group NACI recommends that, given the burden of influenza B disease, QIV should be used. If QIV is not available, either unadjuvanted or adjuvanted TIV should be used.
Children 2–17 years of age	• TIV • QIV • Quadrivalent LAIV	In children without contraindications to the vaccine, any of the following vaccines can be used: LAIV; QIV; or TIV. The current evidence does not support a recommendation for the *preferential* use of LAIV in children and adolescents 2–17 years of age. Given the burden of influenza B disease in children and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, NACI continues to recommend that a quadrivalent formulation of influenza vaccine be used in children and adolescents 2–17 years of age. If a quadrivalent vaccine is not available, TIV should be used. LAIV is contraindicated for children with immune compromising conditions. LAIV, TIV or QIV can be used in children with chronic health conditions and without contraindications (see the *Contraindications and Precautions* (Section II) and *Choice of vaccine product for children 2 to 17 years of age* (Section V) sections of the Statement for more details) (4).
Adults 18–59 years of age	• TIV • QIV • Quadrivalent LAIV	TIV and QIV are the recommended products for adults with chronic health conditions. TIV and QIV, instead of LAIV, are recommended for health care workers. LAIV is contraindicated for adults with immune compromising conditions.
Adults 60–64 years of age	• TIV • QIV	TIV and QIV are authorized for use in this age group.
Adults 65 years of age and older	• TIV • QIV • Adjuvanted TIV • High-dose TIV	**At the programmatic level, NACI recommends that any of the four influenza vaccines available for use in adults 65 years of age and older should be used: standard-dose TIV, high-dose TIV, MF59-adjuvanted TIV, and QIV. High-dose TIV is expected to provide superior protection compared to standard-dose TIV; however, with cost-effectiveness assessments having been outside the scope of the evidence review and without data on the relative efficacy/effectiveness between high-dose TIV, MF59-adjuvanted TIV, and QIV, there is insufficient evidence to make a comparative recommendation on the use of these vaccines at the programmatic level (Grade I).** **At the individual level, NACI recommends that high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older. NACI concludes that, given the burden of disease associated with influenza A(H3N2) and the good evidence of better efficacy compared to standard-dose TIV in this age group, high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older (Grade A). There is insufficient evidence to make comparative recommendations on the use of MF59-adjuvanted TIV and QIV over standard-dose TIV (Grade I).**
Pregnant women	• TIV • QIV	LAIV is not recommended because of the theoretical risk to the fetus from administering a live virus vaccine.

Abbreviations: LAIV, live attenuated influenza vaccine (quadrivalent formulation); QIV, quadrivalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine
[a] Updated recommendations noted in **bold**

Table 3: Recommended influenza vaccine dosage and route, by age, for the 2018–2019 influenza season

Age group	TIV without adjuvant[a] (Intramuscular)	QIV without adjuvant[b] (Intramuscular)	TIV without adjuvant, high dose (Fluzone® High-Dose) (Intramuscular)	MF59-adjuvanted TIV (Fluad Pediatric® or Fluad®) (Intramuscular)	LAIV (FluMist® Quadrivalent) (Intranasal)	Number of doses required
6–23 months	0.5 mL[c]	0.5 mL[c]	N/A	0.25 mL	N/A	1 or 2[d]
2–8 years	0.5 mL	0.5 mL	N/A	N/A	0.2 mL (0.1 mL per nostril)	1 or 2[d]
9–17 years	0.5 mL	0.5 mL	N/A	N/A	0.2 mL (0.1 mL per nostril)	1
18–59 years	0.5 mL	0.5 mL	N/A	N/A	0.2 mL (0.1 mL per nostril)	1
60–64 years	0.5 mL	0.5 mL	N/A	N/A	N/A	1
65 years and older	0.5 mL	0.5 mL	0.5 mL	0.5 mL	N/A	1

Abbreviations: LAIV, live attenuated influenza vaccine (quadrivalent formulation); N/A, not applicable; QIV, quadrivalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine
[a] Influvac® three years and older, Fluviral® six months and older, Agriflu® six months and older
[b] Flulaval® Tetra six months and older, Fluzone Quadrivalent six months and older
[c] This information may differ from the product monograph. Published and unpublished evidence suggest moderate improvement in antibody response in infants, without an increase in reactogenicity, with the use of full vaccine doses (0.5 mL) for unadjuvanted inactivated influenza vaccines (10,11). This moderate improvement in antibody response without an increase in reactogenicity is the basis for the full dose recommendation for unadjuvanted inactivated vaccine for all ages. For more information, refer to *Statement on Seasonal Influenza Vaccine for 2011–2012* (12)
[d] Children six months to less than nine years of age who have never received the seasonal influenza vaccine require two doses of influenza vaccine, with a minimum interval of four weeks between doses. Eligible children under nine years of age who have properly received one or more doses of seasonal influenza vaccine in the past should receive one dose per influenza vaccination season thereafter

Conclusion

The NACI continues to recommend annual influenza vaccination for all individuals aged six months and older (noting product-specific age indications and contraindications), with particular focus on people at high risk of influenza-related complications or hospitalization, including the following: all pregnant women; people capable of transmitting influenza to those at high risk; people who provide essential community services; and people in direct contact during culling operations with poultry infected with avian influenza. For the 2018–2019 influenza season, NACI has reaffirmed its recommendation regarding the inclusion of children and adults with neurologic and neurodevelopmental conditions as being at increased risk for influenza-related complications and hospitalization. The Statement also provides updated recommendations on the use of a high-dose inactivated split virion vaccine (Fluzone High-Dose, Sanofi Pasteur) and an MF59-adjuvanted inactivated subunit vaccine (Fluad, Seqirus) in persons 65 years of age and older.

Authors' statement

WV – Writing – original draft, writing – review and editing
LZ – Writing – original draft, writing – review and editing
RS – Writing – original draft, writing – review and editing

The NACI Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2018–2019 was prepared by R Stirling, L Zhao and W Vaudry and approved by NACI.

Conflict of interest

None.

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REVIEW

Summary of the NACI literature review on the comparative effectiveness of subunit and split virus inactivated influenza vaccines in older adults

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Abstract

Background: Subunit and split virus inactivated influenza vaccines (IIV) are two commonly used types of seasonal influenza vaccines in Canada. The comparative effectiveness of these two formulations is particularly relevant for older adults, as older adults have reduced influenza vaccine effectiveness and experience more severe influenza than younger adults.

Objective: To compare the vaccine effectiveness and immunogenicity of unadjuvanted, standard-dose subunit IIVs versus unadjuvanted, standard-dose split virus IIVs in adults 65 years of age and older.

Methods: An a *priori* written protocol based on rapid review methods was developed that included studies published in 2007 or later in the EMBASE, MEDLINE and ClinicalTrials.gov databases with terms used in the objective. Due to the small number of records returned, hand searches of reference lists were completed, the publication date limit was removed, three additional databases (the Cochrane Central Register of Controlled Trials, Scopus and Web of Science) were searched, and studies including adults 60 years of age and older were included. Data from included studies were extracted into evidence tables and quality assessments were completed. The results were synthesized narratively.

Results: Eight eligible studies were identified. In the three studies that assessed vaccine effectiveness of subunit and split virus IIVs, there were no statistically significant differences in vaccine effectiveness in adults 65 years of age and older against laboratory-confirmed infection with any influenza virus strain, or against laboratory-confirmed infection with influenza A(H1N1), A(H3N2) or B virus, specifically. In the five studies that assessed immunogenicity, the findings were not consistent and the overall quality of immunogenicity evidence was weak.

Conclusion: The National Advisory Committee on Immunization (NACI) concludes that there is insufficient evidence to determine significant differences in the vaccine effectiveness or immunogenicity of unadjuvanted, standard-dose subunit and split virus IIVs in adults 65 years of age and older (Grade I evidence).

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Keywords: The National Advisory Committee on Immunization, influenza vaccine, subunit vaccine, split virus vaccine

Introduction

Many different technologies are currently used in the formulation of influenza vaccines. Split virus and subunit inactivated influenza vaccines, both consisting of disrupted virus particles, were some of the first technologies developed following early inactivated whole virus vaccines, which were developed in the 1940s (1). Split virus vaccines contain whole inactivated viruses that have been split with detergent, ether, or both, while subunit vaccines are made of purified hemagglutinin (HA) and neuraminidase.

Newer technologies and formulations for influenza vaccines have since been introduced, such as higher doses of antigen or combining the antigen with adjuvants; however, standard-dose subunit and split virus inactivated influenza vaccines (IIVs) are still the most commonly used seasonal influenza vaccines, as these vaccines have well-established safety profiles and are less expensive than newer formulations. A large number of the seasonal influenza vaccines available for use in Canada are standard-dose subunit or split virus IIVs (2).

The National Advisory Committee on Immunization (NACI) has not previously critically appraised the evidence on the comparative vaccine effectiveness and immunogenicity of subunit versus split virus IIV in any age group. If one of the vaccine types was more effective, it would be important to know, particularly for older Canadian adults (65 years of age and older), who are at highest risk of influenza-related hospitalizations (3) and deaths (4). Older adults may also experience reduced vaccine effectiveness against influenza infection compared with younger age groups (5).

The primary objective of this literature review was to compare the vaccine effectiveness and immunogenicity of unadjuvanted, standard-dose subunit IIV versus unadjuvanted, standard-dose split virus IIV in adults 65 years of age and older. A full report is available online (6).

Methods

A rapid review methodology was used that was based on methods developed by Tricco et al. (7). The research question addressed in this review is as follows: Does the vaccine effectiveness, immunogenicity, or both of unadjuvanted, standard-dose subunit IIV differ from unadjuvanted, standard-dose split virus IIV among adults 65 years of age and older?

A priori search strategy

A search strategy was developed in consultation with a federal Reference Librarian, and included search terms for subunit influenza vaccine, split virus influenza vaccine, vaccine effectiveness and immunogenicity. The search was restricted to studies published in English or French, in EMBASE, MEDLINE and ClinicalTrials.gov databases published in 2007 or later.

Inclusion and exclusion criteria

Studies were included if they met the following criteria:

- the study directly or indirectly compares the vaccine effectiveness or immunogenicity of an unadjuvanted, standard-dose subunit IIV to an unadjuvanted, standard-dose split virus IIV;
- the study population is within the age range of interest (65 years of age and older).

Studies were excluded if they met one or more of the following criteria:

- the study does not present vaccine effectiveness or immunogenicity for both vaccine types of interest;
- the study is in a language other than English or French;
- the study is a non-human, in vivo or in vitro study;
- the article is an editorial, opinion or news report;
- the study presents only secondary research.

Screening and eligibility assessments were completed by a single reviewer.

Data extraction, synthesis and quality assessment

Data from included studies were extracted into evidence tables, defined a *priori*. The quality (internal validity) of included studies was assessed using criteria outlined by Harris et al. (8). Data extraction and quality assessment were completed by one reviewer and verified by a second reviewer. Results from included studies were synthesized narratively.

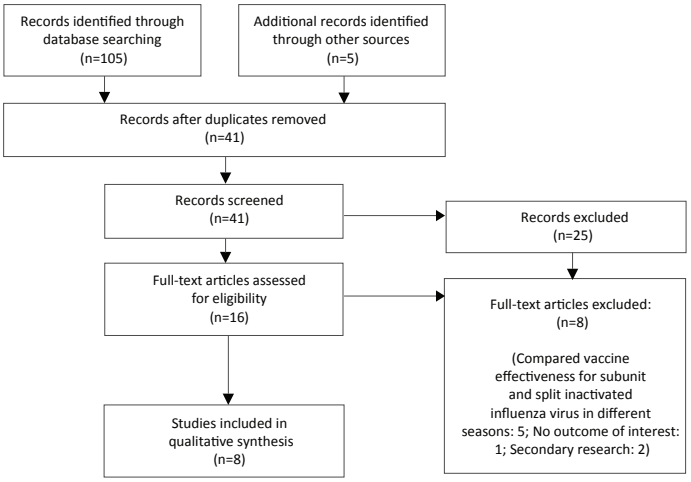
Post-hoc modifications

Due to the small number of records retrieved from the initial database search, search criteria were modified. The publication date restriction was removed, three additional databases were added (the Cochrane Central Register of Controlled Trials, Scopus and Web of Science) and, since a number of studies defined older adults as individuals 60 years of age and older but were otherwise eligible, the eligibility criteria were modified to include adults 60 years of age and older.

Results

The initial database search retrieved 30 records; only three of these studies met inclusion criteria. After *post-hoc* modifications, 41 unique studies were identified through the search and eight met the revised inclusion criteria (**Figure 1**). Three of the included studies reported on vaccine effectiveness, and five of the studies reported on immunogenicity. None of the identified studies compared quadrivalent with trivalent vaccine formulations of subunit or split virus IIVs. The study characteristics of the included studies are shown in **Table 1** below.

Figure 1: Flow diagram for comparative effectiveness and immunogenicity of subunit and split virus IIVs in older adults: October 2017[a]



[a] Initial search October 13, 2017 and re-run with modifications on October 16, 2017

Vaccine effectiveness

Three of the included studies reported on the vaccine effectiveness of unadjuvanted, standard-dose subunit and split virus IIVs (11,13,15), with only one study reporting a direct estimate for the difference in vaccine effectiveness between the two types of influenza vaccines (15). All three studies used test-negative case-control designs and all three were rated as "fair" according to criteria outlined by Harris et al. (8). None of the studies reported a significant difference in vaccine effectiveness between subunit IIV and split virus IIV against

Table 1: Study characteristics of included studies

Study	Location	Season	Design	Population	Outcome
Camilloni, 2016 (9)	Italy	1988–1989 to 2014–2015	Cohort	60 years of age and older	Immunogenicity
Del Giudice, 2006 (10)	Not stated	2003–2004	Not stated	60 years of age and older	Immunogenicity
Kissling, 2014 (11)	Seven European countries	2012–2013	Test-negative case-control	60 years of age and older	Vaccine effectiveness
Morales, 2003 (12)	Colombia	1999–2000	RCT	60 years of age and older	Immunogenicity
Rondy, 2017 (13)	11 European countries	2015–2016	Test-negative case-control	65 years of age and older	Vaccine effectiveness
Skowronski, 2012 (14)	Canada	2011–2012	RCT	65 years of age and older	Immunogenicity
Talbot, 2015 (15)	United States	2008–2009, 2010–2011, and 2011–2012	Test-negative case-control	50 years of age and older (subpopulation: 65 years of age and older)	Vaccine effectiveness
Zei, 1991 (16)	Italy	1989–1990	CCT	60 years of age and older	Immunogenicity

Abbreviations: CCT, clinical controlled trial; RCT, randomized controlled trial

any laboratory-confirmed influenza virus strain (11,15), against influenza A(H1N1), A(H3N2) or B virus specifically (11,15), or against hospitalization due to influenza (13).

Immunogenicity

Five studies were identified that reported on the immunogenicity of subunit and split virus trivalent influenza vaccines (TIVs) (9,10,12,14,16). Of these studies, only two reported a direct comparison between the two types of vaccines (9,16). Three of the five studies were evaluable by Harris et al. criteria (9,12,16), of which one received a "fair" rating (12) and two received "poor" ratings (9,16). The two other studies did not report study methodology in sufficient detail to assess study quality (10,14). The immunogenicity outcomes assessed by the identified studies included geometric mean fold rise in HA titres (i.e., ratio of post- to pre-vaccination geometric mean titre), seroprotection rate (i.e., proportion of participants with HA titres of at least 40 post-vaccination) and seroconversion rate (i.e., proportion of participants with at least a four-fold increase in HA titres post-vaccination, HA titre increase from less than 10 pre-vaccination to at least 40 post-vaccination, or both). Four studies assessed protection against the influenza virus strains contained within the vaccines. Two studies reported direct comparisons of immunogenicity measures (9,16) and two reported indirect comparisons (10,12). Overall, the studies showed no consistent significant differences in geometric mean fold rise, seroprotection rate or seroconversion rate between split virus IIVs and subunit IIVs against influenza A(H1N1), A(H3N2) or B. In addition, two studies indirectly assessed cross-protection against variant influenza strains (10,14). Neither of these studies found a significant difference in geometric mean fold rise, seroprotection rate or seroconversion rate between split virus IIVs and subunit IIVs.

Discussion

The overall quality of vaccine effectiveness evidence was fair, with one study reporting a direct vaccine effectiveness estimate and two studies reporting an indirect vaccine effectiveness estimate. The reported vaccine effectiveness estimates for split virus IIVs and subunit IIVs all had widely overlapping confidence intervals; however, without a direct comparison, it is difficult to draw firm conclusions on the comparative vaccine effectiveness of the two vaccines types. The authors of one of these studies also noted that there were likely important differences between study sites that were not controlled for, and that any comparisons between vaccine effectiveness of subunit IIV and split virus IIV should be interpreted with caution (13).

Findings from the studies that reported on immunogenicity were not consistent, and the overall quality of immunogenicity evidence was weak. All studies had at least one serious concern, the most common being the comparability between intervention groups. Two studies did not provide enough information to evaluate their quality (10,14). Also, all included studies assessed immunogenicity by hemagglutination inhibition assay. These assays assess antibody as opposed to cell-mediated response, but the latter has been shown to be a more robust correlation of protection in older adults (17). In addition, the amount of HA antigen in unadjuvanted, standard-dose subunit IIVs and split virus IIVs is standardized; therefore, HA antibody titres may not be an appropriate measure of immunogenicity to answer this research question.

Limitations

Due to the small number of records returned by the initial database search, *post-hoc* protocol modifications were made that were more consistent with a traditional systematic review than the initial rapid review protocol; however, screening was still conducted by a single reviewer. A study by Edwards et al. found that study selection involving only one reviewer missed an average of 8% of eligible studies compared with study selection involving two reviewers (18); therefore, some studies may have been erroneously excluded. The impact that this factor would have on the conclusions drawn from a rapid review are still unclear. In addition, it is possible that the database search strategy missed some studies that examined vaccine effectiveness or immunogenicity by vaccine type in sub-analyses or as a secondary outcome; however, hand searching reference lists would help mitigate the number of eligible articles of this type that may have been excluded by the search criteria.

Another important limitation of this review is that many of the included studies defined older adults as participants who were 60 years of age and older. The inclusion of adults 60 to 64 years of age may lead to greater healthy vaccinee bias, as adults in this age range on average may be healthier than adults 65 years of age and older; therefore, estimates from these studies should be interpreted with caution in the Canadian context, where older individuals are commonly defined as adults 65 years of age and older.

Conclusion

The NACI concludes that there is insufficient evidence to determine significant differences in the vaccine effectiveness or immunogenicity of unadjuvanted, standard-dose subunit and split virus IIVs in adults 65 years of age and older (Grade I evidence). The evidence is inconsistent and is not of sufficient quantity or quality to make specific recommendations on the differential use of unadjuvanted, standard-dose subunit and split virus IIVs in older adults.

Authors' statement

IG – Writing – original draft, writing – review and editing
KY – Writing – original draft, writing – review and editing

The NACI Literature Review on the Comparative Effectiveness and Immunogenicity of Subunit and Split Virus Inactivated Influenza Vaccines in Adults 65 Years of Age and Older was prepared by K Young, L Zhao, R Stirling and MK Doll and approved by NACI.

Conflict of interest

None.

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Do health care providers trust product monograph information regarding use of vaccines in pregnancy? A qualitative study

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Abstract

Background: Influenza immunization is recommended in pregnancy to prevent severe infections in pregnant women and newborns, yet vaccine uptake remains low. Studies suggest that cautionary language in vaccine product monographs regarding safety and use in pregnancy affects health care providers' perceptions of vaccine safety and how they counsel pregnant women.

Objective: To conduct a qualitative analysis of health care provider perceptions of the safety of inactivated influenza vaccines and their recommendations for use in pregnancy based on product monograph language statements.

Methods: Health care providers were recruited at two international health conferences and from teaching programs in Ethiopia, Ghana, Uganda, and Laos during September and October 2015. After reading the product monograph excerpts for three licensed inactivated influenza vaccines, participants completed a ten-item online survey with quantitative and qualitative components that captured perceptions of vaccine safety.

Results: Health care providers identified a lack of trust in manufacturers' and product monograph information. They perceived product monograph language as ambiguous and not "up-to-date" with current evidence. Health care providers wanted product monograph language that clearly conveyed evidence for the risks and benefits of the vaccine in an understandable manner.

Conclusion: This study suggests that adopting best practices in the wording of product monographs would help to support evidence-based use of vaccines in pregnant women.

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Keywords: product monographs, vaccines, pregnancy, qualitative study

Introduction

Seasonal influenza is associated with an increased risk of hospitalization during pregnancy and in infants younger than six months of age (1,2). The Canadian National Advisory Committee on Immunization (NACI) and World Health Organization (WHO) recommend influenza immunization during pregnancy to reduce the risk of severe infection in pregnancy and early infancy (1,3). The safety of influenza immunization in pregnancy has been demonstrated in numerous studies and summarized in several systematic reviews (3-6). Based on systematic reviews, including a review by the WHO Global Advisory Committee on Vaccine Safety (3), inactivated influenza vaccines (IIVs) demonstrated no increased risk of adverse outcomes, such as spontaneous abortion, stillbirth or congenital anomalies. Yet vaccine uptake among pregnant women remains low (7,8). Unresolved safety concerns among health care providers and patients pose a potential barrier to vaccine acceptance.

The NACI, Canada's National Immunization Technical Advisory Group (NITAG), reviews evidence from clinical trials and observational studies of the safety and effectiveness of vaccines licensed for use in Canada, as well as the epidemiology of the disease, and develops recommendations for vaccine use (1). Influenza vaccination recommendations updated after annual review of the most recent data are freely accessible online in full and as a pocket guide (1).

Vaccine product monographs are another source of vaccine information for health care providers, presenting information about approved indications, contraindications, warnings and precautions. Publicly available online, product monographs are meant to be "used by health care professionals in making prescribing decisions and in counselling patients about a product's risks and benefits" (9). The product monograph text

is developed by the vaccine manufacturers with input and authorization from Health Canada, the National Regulatory Authority (NRA). Health Canada reviews safety and effectiveness data presented by the manufacturer that is generally limited to product-specific data from randomized clinical trials; however, few clinical trials on IIVs have been conducted in pregnant women (6). Consequently, product monograph language may appear more cautionary than NACI recommendations (e.g., "use only following the advice of a health care professional, based on consideration of the benefits and risks to the mother and the foetus", FluLaval®, GlaxoSmithKline, Sainte-Foy, Québec) (10). The above statement also highlights the circularity of the language, which directs the reader (a health care professional) to follow the advice of a health care professional. Moreover, product monograph language may differ markedly among vaccines with similar composition and safety profiles (11). These factors may contribute to confusion among health care providers.

We conducted a survey with quantitative and qualitative components to determine the effects of product monograph language statements on health care providers' perceptions of the safety of IIVs and their recommendations for use in pregnancy (12). The 141 survey respondents included obstetricians, family physicians, nurses, midwives, and other health professionals from 49 low-, middle- and high-income countries, including Canada, and representing the six WHO regions.

The quantitative results, published elsewhere, demonstrated that health care providers in low-, middle- and high-income countries perceived the safety of the vaccine differently, depending on which of three product monograph statements they read, with fewer than half rating the vaccine as safe (12). Many respondents provided additional comments regarding product monograph language. We conducted a qualitative analysis of those comments to identify themes and suggestions for improving product monograph language.

Methods

Study design and subjects

Health professionals who provided prenatal care were eligible to complete a survey regarding their perceptions of product monograph statements describing influenza vaccine safety and use in pregnancy. Between September and October 2015, participants were recruited at two health conferences: International Federation of Gynaecology and Obstetrics, Vancouver; and Global Maternal Newborn Health Conference, Mexico City. To include representation from all six WHO regions, participants were recruited from teaching programs for local health care providers in Ethiopia, Ghana, Uganda and Laos (12). To ensure a diverse sample of respondents, a maximum of six participants could be enrolled from the same country. In order to gather data specific to the Canadian context, we did not limit the number of Canadian respondents who could participate.

Survey instrument

The development of the 10-item survey instrument has been described previously (12). Briefly, respondents were asked to read three different statements from product monographs for similar vaccines (IIVs) with similar safety profiles that were licensed in the United States (US), Canada and France. All three vaccines were prequalified by the WHO for procurement by United Nations agencies. The first statement emphasized uncertainty: "safety and effectiveness in pregnancy is not established [and it should be used] only if clearly needed" (Fluvirin®, Novartis Vaccines and Diagnostics, Ltd, Liverpool, United Kingdom; Fluzone®, Sanofi Pasteur Inc, Swiftwater, Pennsylvania, US). The second statement described conditions for vaccine use: "use only following the advice of a health care professional, based on consideration of the benefits and risks to the mother and the foetus" (FluLaval®, GlaxoSmithKline, Sainte-Foy, Québec, Canada). The third statement most closely aligned with public health recommendations: "use only from the 2nd pregnancy trimester onwards [limiting use throughout pregnancy to women] at risk of complications of infection" (Vaxigrip®, Sanofi Pasteur Ltd, Lyon, France).

Respondents were then asked to indicate their perception of the safety of the vaccine described in the statement and provide additional comments about product monograph information regarding vaccine use in pregnancy. The final question was open-ended, seeking further comments regarding vaccine product monographs. The survey was professionally translated into French and Spanish, and back-translated.

Opinion survey software version 6.9.1 (ObjectPlanet, Oslo, Norway) was used on a server hosted in Halifax, Nova Scotia, Canada.

Analysis and synthesis

Four co-authors (CA, KAT, NEM and JEG) analysed free text responses qualitatively via inductive content analysis using established methodology to identify themes (13). One co-author (CA) then refined the themes over several subsequent iterations. The co-authors KAT, NEM and JEG reviewed and approved the final themes. Data were hand-coded.

Ethics

This study received ethics approval from the IWK Health Centre Research Ethics Board (Approval #1020057) and WHO Research Ethics Review Committee.

Results

Sixty-one respondents provided comments about product monograph information, of which eight (14%) comments were from Canadians and 44 (72%) comments were from respondents in low- and middle-income countries. Comments came from all WHO regions and broadly represented professions and languages.

The principal theme was lack of trust in product monograph content and vaccine manufacturers (**Table 1**). Respondents described product monograph statements as "ambiguous", non-specific and lacking essential information. Several respondents stated that product monographs are not "up-to-date" with current evidence. Some respondents expressed a view that product monograph content is restricted by

vaccine manufacturers who are "protecting themselves against litigation". Respondents indicated that they were more inclined to trust organizations such as the WHO for vaccine information and guidance, rather than the product monograph.

Table 1: Major themes identified from the open-ended question, "Do you have any specific comments to add about product monograph safety statements on vaccines that might be used in pregnancy?"

Themes	Examples
Lack of trust in product monograph content	"Statements are ambiguous and not helpful" – Obstetrician, Canada "Some product monographs confuse. Make me anxious about using in pregnant women even when recommended by the immunization program. Why does monograph says is risk when program recommends? Who is correct?" – Midwife, Ethiopia "Sometimes the monographs are not up to date with the current literature and therefore can be very misleading regarding effectiveness and safety" – Obstetrician, Canada "Instead of having a blanket statement, like 'it's not safe', it should be specific about trimesters/ side-effects so that you can properly weigh the benefits and the risks." – Midwife, Botswana "Monographs should be authenticated by professional expert[s] and meta-analysis" – Obstetrician, India "Should be user-friendly to read" – Obstetrician, Indonesia
Lack of trust in manufacturers	"Manufacturers are usually very reluctant in their advices [sic] for pregnant women, which can lead to more harm than good. Therefore I usually follow the authority guidelines in these." – Obstetrician, Netherlands "Since product monographs are written by pharmaceutical companies, that have an extra agenda of protecting themselves against litigation, it is my routine to consult other sources of information" – Obstetrician, Sweden
Lack of evidence regarding vaccine safety in pregnancy	"Vaccines need to be tested in pregnancy so [we] know [they are] safe" – Midwife, Ethiopia "It should be clear that the data comes from research studies…" – Obstetrician, Democratic Republic of Congo "Vaccines should be used in pregnancy only if they are not harmful to both mother and her baby." – Obstetrician, Nigeria

Respondents opined the lack of evidence of vaccine safety in pregnancy. They expressed low tolerance for risk and the need for certainty when caring for pregnant women. Some respondents stated that they would only feel comfortable administering a vaccine if safety could be assured. They called for more research into vaccine safety in pregnancy while acknowledging the difficulties associated with such investigation.

To improve the product monographs, some respondents called for more specific information regarding vaccine efficacy and the risks associated with use in pregnancy. Others indicated that product monographs ought to be "easy to read" and written in "laymen [sic] language".

Discussion

The results suggest that health care providers were distrustful of vaccine product monographs and manufacturers. This is concerning because our quantitative results showed that the majority of health care providers read product monographs at least occasionally or for new products (12).

The qualitative findings add to the quantitative findings which showed that health care providers' perceptions of the safety of the vaccine were affected by the language in the product monograph statements and that language affected their recommendations to patients about vaccination; for example, after reading the statement, "safety and effectiveness in pregnancy is not established [use] only if clearly needed", 38% of respondents perceived the vaccine described in the statement as moderately or very unsafe and 18% of respondents indicated that they would not recommend the vaccine if it was recommended by national public health authorities. In contrast, after reading the statement, "use only from the second pregnancy trimester onwards", 28% of respondents perceived the vaccine as unsafe and 12% would not recommend the vaccine. Approximately 75% of respondents indicated that the language would affect how they counselled patients about immunization during pregnancy (12).

We hypothesized that perceptions among health care providers that manufacturers restrict product monograph content and product monographs disagree with NACI recommendations contribute to distrust of product monograph information.

Respondents expressed a desire for more informative, clearly worded product monographs that provide guidance for vaccine use, suggesting that health care providers want product monographs to include detailed information about the safety and effectiveness of the vaccine in pregnancy. Comments by respondents that product monographs should be understandable to a layperson highlight the challenges of revising the product monographs.

Regulators and public health organizations, as well as the WHO Strategic Advisory Group of Experts on Immunization, are beginning to recognize that differences between product monographs and NITAG (e.g., NACI) recommendations may influence vaccine uptake, and have called on NRAs and NITAGs to resolve these differences (14,15). The WHO and several NRAs have developed guidance for interpreting the pregnancy subsections of the monograph and have begun to revise product monograph language (14,16). These efforts, however, have not involved end users (i.e., frontline health care providers).

With support from the Public Health Agency of Canada, in collaboration with the Society of Obstetricians and Gynaecologists of Canada, we have adopted an interdisciplinary approach to develop product monograph language that will help to convey the quality and specificity of the evidence regarding vaccine safety and effectiveness in pregnancy to health care providers, and thus promote evidence-based use of vaccines. This research directly involves health care providers, public health experts, epidemiologists, legal scholars, social scientists, Health Canada regulators and other key stakeholders. We expect that this work will inform efforts to standardize product monograph language for vaccines with similar safety profiles and levels of

evidence in Canada and abroad. This will be an important first step to improve the product monographs and increase trust among Canadian health care providers in vaccines recommended in pregnancy.

In addition, the findings suggest a need for Health Canada to work with manufacturers and independent evaluators to update and reconcile product monograph content with the most recent evidence. They may consider including a hyperlink to the NACI recommendation in the product monograph so readers can access the most up-to-date guidance for vaccine use. We also encourage Health Canada and NACI to participate in international efforts to resolve perceived conflicts between product monographs and public health recommendations. Health Canada may consider, along with other NRAs, the need to impose regular manufacturer updates. Finally, further research into vaccine safety and effectiveness in pregnancy and enhanced active surveillance for adverse events during pregnancy and the newborn period are needed to ensure that product monographs and NACI recommendations are supported by high quality evidence throughout the vaccine lifecycle.

This study had limitations. Convenience sampling may have resulted in selection and response bias. Participants recruited at the two conferences may not have been representative of frontline health care workers in Canada or other countries. Most comments were from respondents in low- and middle-income countries who may have different perspectives than Canadian health care providers; however, responses to the multiple-choice questions did not differ by country income level or WHO region (12).

Conclusions

Rather than enabling the evidence-based use of vaccines, ambiguously worded and outdated product monograph statements may be a barrier to vaccine uptake during pregnancy in Canada. Health Canada, NACI and vaccine manufacturers should consider adopting best practices for developing product monograph content that clearly conveys the risks and benefits of vaccination during pregnancy in language that health care providers can understand.

Authors' statement

KAT – Conceptualization, investigation, analysis, writing – original draft
CA – Investigation, analysis, writing – review and editing
JG – Analysis and interpretation, writing – review and editing
HS, JM, SAM – Investigation, writing – review and editing
NEM – Conceptualization, investigation, analysis, writing – review and editing

Conflict of interest

KAT has received research support and consultancy fees from Pfizer and research grants from GlaxoSmithKline outside the submitted work. SAM has received research grants from GlaxoSmithKline and Pfizer outside the submitted work. All other authors report no conflicts of interest.

Contributors

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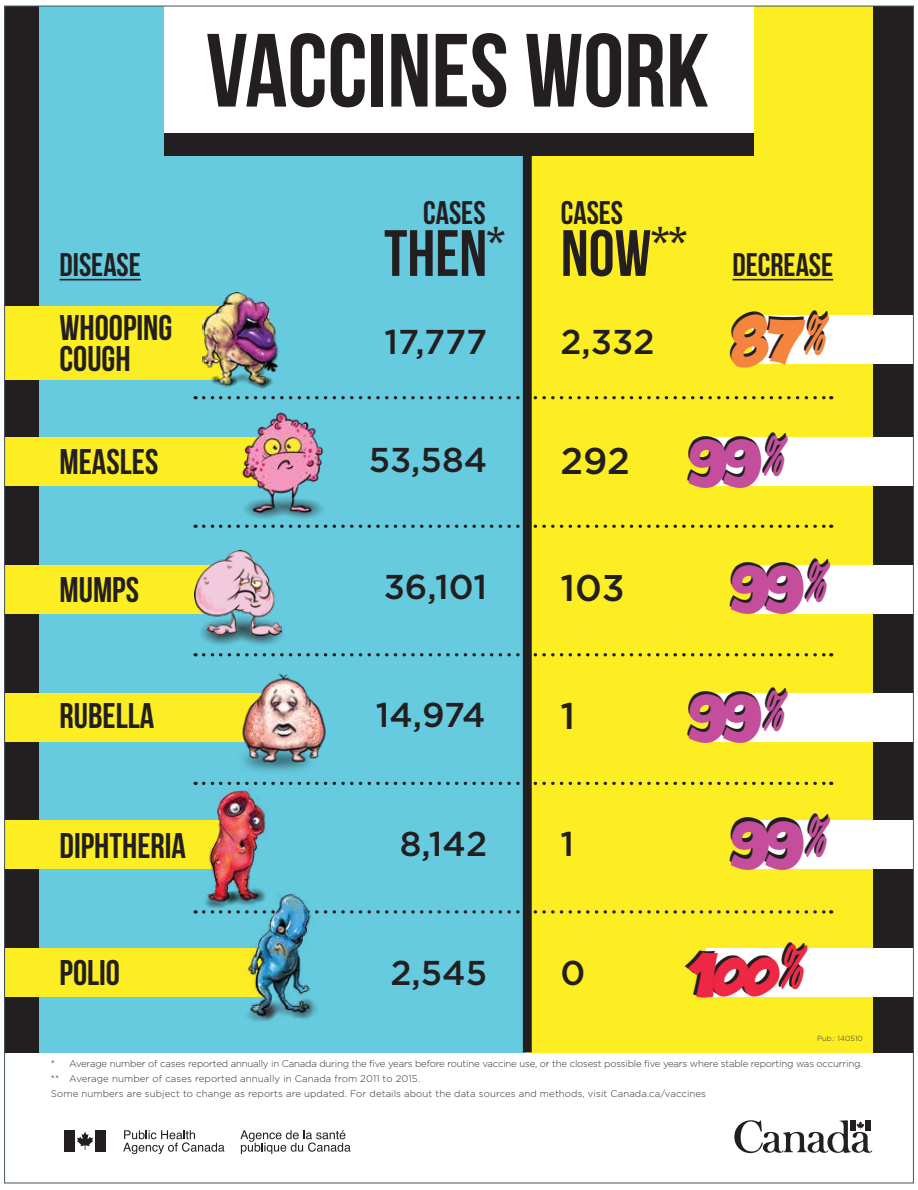

COMMENTARY

Pre-clinical development of a vaccine against Lassa fever

L Banadyga[1], DR Stein[1,2], X Qiu[1,2], D Safronetz[1,2,*]

Abstract

Lassa virus (LASV) is a persistent global health threat that causes about half a million cases of Lassa fever each year in Western Africa. Although most cases are mild, the disease can cause significant morbidity and results in as many as 5,000 deaths per year. Since 2015, Nigeria has been experiencing a severe and extended outbreak of Lassa fever, raising concerns that it could spill over into other countries and reach a magnitude similar to the West African Ebola outbreak of 2013–2016. Despite the burden that Lassa fever places on public health, both in Africa and around the world, there are still no clinically-approved therapeutics or vaccines to treat or prevent it. Nevertheless, a number of promising candidate vaccines have been developed over the last several years, and there is a growing political and social determination to drive at least one of these candidates towards licensure.

This paper describes a LASV vaccine candidate that is being developed at Canada's National Microbiology Laboratory. Based on the same live attenuated vesicular stomatitis virus (VSV) vaccine platform that was used to produce the successful Ebola virus vaccine, the VSV-based LASV vaccine has been shown to elicit a potent and protective immune response against LASV. The vaccine shows 100% protection in the "gold-standard" nonhuman primate model of Lassa fever, inducing both humoral and cellular immune responses. Moreover, studies have shown that a single vaccination may offer universal protection against numerous different strains of the virus, and additional studies have shown that immunization with the VSV platform appears to be unaffected by pre-existing immunity to VSV. The next step in the development of the VSV-based LASV vaccine is phase I human clinical trials to assess vaccine safety and dosage.

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Keywords: Lassa virus; Lassa fever; vesicular stomatitis virus; vaccine; pre-clinical development

Introduction

The 2013–2016 Ebola virus (EBOV) outbreak in Western Africa demonstrated that an outbreak anywhere could pose a threat everywhere (1). With nearly 29,000 cases and over 11,000 deaths, EBOV ravaged the countries of Sierra Leone, Liberia and Guinea, and the disease was ultimately exported to numerous neighbouring countries and some Western nations, including the United States (US) (2). Moreover, the outbreak not only devastated the public health infrastructure of Western Africa, but it also strained the global health response. Thousands of health care workers from around the world were deployed to Western Africa where they suffered a disproportionate burden, and over 50% of those infected with EBOV succumbed to the disease (3). At least part of the reason for the magnitude and severity of this outbreak was the lack of a clinically-approved treatment or a vaccine to prevent it.

In the wake of the EBOV outbreak, as well as the Zika virus outbreak that followed in 2015, the Bill and Melinda Gates Foundation recognized a global need for advanced epidemic preparedness. In collaboration with the Wellcome Trust, the World Economic Forum, and the governments of Norway and India, the Bill and Melinda Gates Foundation co-founded the Coalition for Epidemic Preparedness and Innovations in 2016. The main objective of this coalition was to fund the development of promising vaccines for emerging pathogens that may cause significant outbreaks in the near future, with the goal of rapid scale-up into phase III clinical trials in the event of an outbreak. One of the pathogens selected for accelerated funding and development by this Coalition was Lassa virus (LASV).

Lassa virus, an enveloped, single-stranded, ribonucleic acid (RNA) virus from the family *Arenaviridae*, is the causative agent of the viral hemorrhagic fever known as Lassa fever. Typically, the virus is transmitted from exposure to the urine or feces of infected Mastomys rats, although it may also be spread from human to human through direct contact with infected blood, urine, feces or other bodily secretions. Following an incubation period of one to three weeks, the disease is marked by the gradual onset of fever, malaise, and muscle and joint pain. As the disease progresses, fever and myalgia worsen, and patients may become prostrate. Diarrhea, vomiting and other gastrointestinal disturbances are common, as are retrosternal pain and cough. Hemorrhagic manifestations are uncommon but an indication of a poor prognosis, as is facial edema and pleural effusions.

Fatal cases culminate in shock and death, whereas nonfatal cases resolve over the course of two to three weeks, during which deafness is common and often permanent (4).

Approximately 300,000 to 500,000 cases of Lassa fever occur in West Africa each year, making it one of the most prevalent viral hemorrhagic fevers in humans (5,6). Although typically only 1–2% of these cases are fatal, the scale of infections pushes the overall number of fatalities up to several thousand per year. Cases of Lassa fever are mainly restricted to the West African countries of Sierra Leone, Liberia, Guinea, and Nigeria; however, imported cases of LASV have been extensively documented, along with human-to-human transmission (7-10). Since 2015, Nigeria has been suffering a prolonged outbreak of Lassa fever, sparking fears of another epidemic that may rival the scope of the recent West African EBOV outbreak. Since the beginning of 2018, LASV has resulted in thousands of suspected cases, 413 confirmed cases, nine probable cases and 114 deaths. Based on confirmed and probable cases, the Nigerian outbreak has had a remarkably high case fatality rate of 25% (11).

Despite the significant burden that LASV places on global public health, the virus remains understudied, with no approved treatment or vaccine. Nevertheless, several candidate LASV vaccines have been identified and await further clinical development, including the LASV vaccine that is under development at Canada's National Microbiology Laboratory (NML). This vaccine is a replication-competent vesicular stomatitis virus (VSV)-based vaccine that has shown remarkable efficacy in LASV disease animal models. In this overview, we discuss the pre-clinical development of the VSV-based LASV vaccine, placing it in the context of the EBOV vaccine that was developed from the same VSV vaccine platform, and we describe some other promising LASV vaccine candidates.

Background

Vesicular stomatitis virus as a vaccine platform

The most effective vaccines against viruses usually use a live attenuated virus. Live attenuated vaccines, such as the measles vaccine, are often more effective at inducing protective immune responses and durable immunity than killed virus vaccines or subunit vaccines. One approach to generating live attenuated vaccines has relied on using a relatively harmless "backbone" virus as a vaccine platform to carry antigens from another, more pathogenic virus. At the NML, we have been working with VSV as a vaccine platform for a variety of different viruses, including EBOV, Marburg virus (MARV) and LASV.

Vesiculoviruses comprise their own genus within the family *Rhabdoviridae* and cause disease primarily in mammals and fish (12). In the Western hemisphere, two vesiculoviruses predominate: vesicular stomatitis Indiana virus; and vesicular stomatitis New Jersey virus (13). Both VSVs are insect-vectored viruses that cause vesicular stomatitis in horses, cattle and swine and cause erosive lesions on the tongue, gums, lips, hooves and teats of infected animals (14). In humans, VSV infection is also possible, although infrequent, and can lead to a self-limiting, influenza-like illness with or without the presentation of vesicular lesions (15-17). Because of the similarity in presentation to foot-and-mouth disease in livestock and agricultural animals, VSV is considered a reportable disease by the Government of Canada.

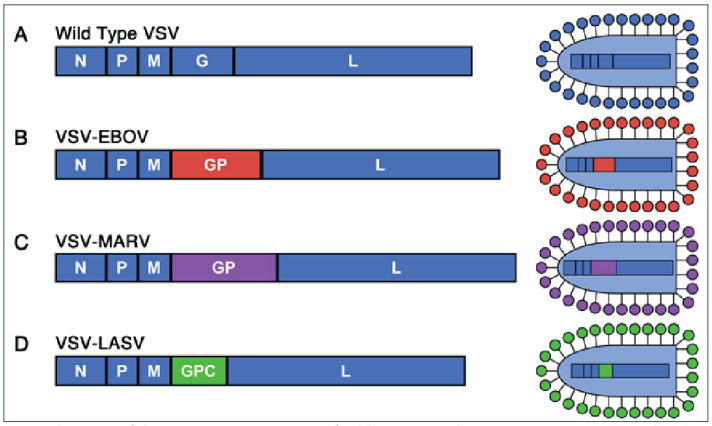
The development of a system to engineer *de novo* recombinant VSV from DNA plasmids (18,19) greatly increased the utility of VSV as a vaccine delivery platform (20). Wild type VSV already possessed several qualities that made it a suitable vaccine vector and the ability to engineer recombinant VSV only increased its usefulness. The VSV genome has the capacity to tolerate the addition of large and multiple transgenes, which serve as vaccine antigens (21,22), and the virus itself is capable of replicating to high titers in a variety of cell types (23-25), thus ensuring the ease of vaccine production. Moreover, infection with VSV induces a strong humoral and cellular response (26-28), thereby promoting a robust immune response against the incorporated transgene, and pre-existing immunity in humans is rare (15-17), thereby maximizing the vaccine's effectiveness. Additionally, VSV replicates in the cytoplasm without a DNA intermediate, which precludes the possibility of genetic recombination with the host cell, and the VSV genome is non-segmented, which precludes the possibility of genetic shift. Thus, given the potential for VSV to serve as a safe and effective vaccine vector, it is not surprising that this system has been widely exploited to develop vaccines against numerous viruses, including HIV, for which "first-in-human" evaluations have already been completed (29).

A notable variation of the VSV vaccine platform employed by the NML is known as VSVΔG because it lacks the viral glycoprotein (G), which enables virus entry and serves as the virus's major pathogenicity factor. The removal of VSV G not only attenuates the virus by eliminating its potential to infect the nervous system, but it also provides the opportunity to substitute in an analogous viral glycoprotein, thus directing a potent immune response towards an important antigenic target. This strategy was used to develop the highly successful VSV-based EBOV vaccine, which recently demonstrated 100% efficacy against EBOV disease in a small phase III clinical trial (30). Our work at the NML on the LASV vaccine is built on the same VSVΔG backbone (**Figure 1**).

Development of vesicular stomatitis virus-based Ebola and Lassa fever vaccines

The development of the VSV-based vaccine against LASV has been closely associated with the development of the VSV-EBOV vaccine. The origins of both vaccines can be traced to a single publication. In 2004, Garbutt and colleagues published the first report of replication-competent VSVs (serotype Indiana; VSIV) expressing the glycoproteins of EBOV, MARV or LASV, referred to as VSV-EBOV, VSV-MARV and VSV-LASV, respectively (31). All three viruses exhibited slightly attenuated growth kinetics compared with wild type VSV, and all three viruses exhibited robust expression of their glycoprotein, as well as the expected proteolytic processing patterns. Moreover, none of these VSVs caused disease in mice, suggesting that they were apathogenic. Garbutt and colleagues then inoculated all three groups of mice with a lethal dose of mouse-adapted EBOV twenty-eight days after their initial inoculation with VSV. All mice developed disease and succumbed—except those that had been originally inoculated with VSV-EBOV. This was the first indication that the VSV-based vaccine platform could be used to elicit an immune response against a heterologous glycoprotein that, in turn, could protect animals from disease.

Figure 1: Vesicular stomatitis virus vaccine platform



(A) A schematic of the genome organization of wild type vesicular stomatitis virus (VSV) is shown on the left, with the open reading frames for the nucleoprotein (N), the phosphoprotein (P), the matrix protein (M), the glycoprotein (G) and the RNA-dependent RNA polymerase large protein (L) indicated. A schematic of the VSV virion is shown on the right, with the genome encased within the bullet-shaped virion studded with G. (B) A schematic of the genome organization of VSV-EBOV is shown on the left, with VSV G replaced with the Ebola virus (EBOV) glycoprotein (GP) open reading frame. A schematic of the VSV virion is shown on the right, with the genome encased within the bullet-shaped virion studded with GP. (C) A schematic of the genome organization of VSV-Marburg virus (MARV) is shown on the left, with VSV G replaced with the MARV glycoprotein (GP) open reading frame. A schematic of the VSV virion is shown on the right, with the genome encased within the bullet-shaped virion studded with GP. (D) A schematic of the genome organization of VSV-LASV is shown on the left, with VSV G replaced with the Lassa virus (LASV) glycoprotein precursor (GPC) open reading frame. A schematic of the VSV virion is shown on the right, with the genome encased within the bullet-shaped virion studded with GPC

Shortly after the efficacy of the VSV-EBOV vaccine was demonstrated in mice (31), the same group published the first characterization of the VSV-LASV vaccine in nonhuman primates (32). Cynomolgus macaques were vaccinated intramuscularly with a single dose of VSV-LASV. The animals neither developed signs of disease nor shed vaccine virus, underscoring the safety of this vector. Twenty-eight days later, the animals were challenged with LASV. All the vaccinated animals survived, and none developed signs of Lassa fever. The vaccine appeared to induce both humoral and cellular immune responses, and there were no marked differences in the blood chemistry or hematology of the animals before and after LASV challenge. In contrast, two control animals vaccinated with VSV-EBOV developed clinical manifestations consistent with Lassa fever and succumbed to disease, with no detectable LASV-specific immune response. This study offered a preliminary—but extremely promising—demonstration of the efficacy of the VSV-LASV vaccine; however, it would be nearly a decade before follow-up experiments were performed.

In 2013, EBOV emerged for the first time in Western Africa and sparked an unprecedented outbreak. The EBOV was now present, and possibly endemic, in the same geographical location as LASV, and concerns were raised that a single vaccine platform may be ineffective if used to vaccinate separately against multiple pathogens. To address this concern, Marzi et al. (33) vaccinated a group of three cynomolgus macaques with a single dose of VSV-LASV and challenged the animals twenty-eight days later with LASV. None of the animals exhibited any signs of disease and the absence of a strong antibody response suggested that vaccination induced sterile or near-sterile immunity. Sixty days later, the same three animals were vaccinated with a single dose of VSV-EBOV and were subsequently challenged with EBOV. Despite high titers of anti-VSV antibodies at the time of the second vaccination, all three animals were completely protected from EBOV infection and exhibited a robust immune response. Thus, pre-existing immunity to the VSV backbone did not compromise the efficacy of the vaccine, indicating that multiple VSV-based vaccines can likely be used in a single population.

There remained the critical question of whether a single VSV-LASV vaccination could prevent disease caused by multiple LASV isolates, since LASV exhibits a high degree of genetic diversity among geographically separated viruses (34). Safronetz et al. (35) addressed this question first in a guinea pig model of LASV infection, demonstrating that VSV-LASV completely protected animals from three heterologous LASV isolates: Z-132 (from Liberia), Soromba-R (from Mali) and Pinneo (from Nigeria). Likewise, vaccination with VSV-LASV protected cynomolgus macaques from lethal challenge with LASV strain Z-132. These results indicate that a single vaccination may offer universal protection against all strains of LASV and may be deployable over the entire LASV endemic range, which comprises at least nine countries and hundreds of millions of people.

Pre-clinical development of vesicular stomatitis virus-based vaccines

Pre-clinical testing of VSV-LASV in various animal models, including nonhuman primates, has demonstrated that this vaccine is safe and effective at eliciting a broadly protective immune response against LASV, in spite of pre-existing immunity to VSV. Despite the promise of this vaccine, clinical development of VSV-LASV is still pending. Nevertheless, the VSV platform has been extensively tested via the VSV-EBOV vaccine, which has undergone rigorous pre-clinical and clinical development (36,37), including phase III human clinical trials where it demonstrated 100% efficacy (30). Similarly, VSV-MARV has undergone extensive pre-clinical development (38), and VSV-based vaccines have also been developed for other filoviruses, including Sudan and Bundibugyo virus (39,40), all of which show remarkable prophylactic efficacy (36-38). Indeed, work with VSV-based filovirus vaccines over the last several years has contributed significantly to our understanding of filovirus disease and the VSV vaccine platform.

Research on the VSV-EBOV vaccine has identified that the formation of antibodies is a critical correlate of protection (41). Studies with VSV-MARV have indicated that vaccine-induced immunity is durable, remaining effective for at least 14 months in the nonhuman primate model (42). Moreover, the VSV-EBOV vaccine—and, by extension, the VSVΔG backbone—has been demonstrated to be safe in immunocompromised animals (i.e., nonhuman primates infected with simian-human immunodeficiency virus) and livestock animals (43,44). Owing to the poor cross-species protection offered by the monovalent VSV-based vaccines, trivalent and blended monovalent single-dose vaccines have also been developed and demonstrate 100% efficacy, suggesting that the VSV platform can be manipulated and optimized to protect against multiple viruses at once (22,39). Finally, phase I, II and III clinical trials have affirmed the overall safety, tolerability, and immunogenicity of the VSV-EBOV vaccine, even at high doses (25,30,45-49). Of note, rare adverse effects have been observed (30), with one phase I clinical trial recording a relatively high incidence of vaccine-induced arthritis, dermatitis, and vasculitis (45,46).

Assessing the risk to livestock

The use of a live, VSV-based vaccine impacts not only the humans who receive it, but also potentially the animals that come into contact with vaccinated humans. Because VSV is a reportable livestock illness, the use of a VSV-based vaccine carries with it the risk that the VSV vector may impact livestock animals, potentially precipitating an agricultural and regulatory crisis. To address this concern, de Wit et al. (44) inoculated pigs with high doses of VSV-EBOV or wild type VSV and monitored the animals for signs of infection and disease. Remarkably, regardless of the virus used for infection, virus replication was detected in a minority of animals, viremia was absent, virus shedding was minimal, and no animal displayed any overt signs of infection. Given the absence of disease in the pigs following direct inoculation of virus, it is unlikely that a vaccinated human could transmit virus to a pig in a way that would trigger a productive infection with overt signs of disease. Moreover, even in the event of such a transmission, the vaccine virus is unlikely to be maintained in the animal population. This study confirms the safety of VSV-based vaccines and suggests that the potential impact of these vaccines on livestock health is minimal.

Alternatives to vesicular stomatitis virus-based Lassa fever vaccine

In an effort to identify a safe and effective vaccine against LASV, a number of different platforms have been developed over the last several decades (50,51) (**Table 1**). Replication-competent vaccinia virus-vectored vaccines encoding the LASV nucleoprotein and/or glycoprotein were among the first platforms to be devised and have demonstrated reasonable efficacy in guinea pigs and nonhuman primates (52-56). Due to the immunosuppressive nature of vaccinia virus, further development of this vaccine platform was abandoned out of safety concerns, particularly in immunocompromised individuals (51). The yellow fever virus 17D (YF17D) backbone, which encodes the LASV glycoprotein or glycoprotein subunits, has also been developed as a LASV vaccine, although its immunogenicity is poor and it lacks efficacy in nonhuman primates (50,57,58). Likewise, inactivated LASV failed to protect nonhuman primates from fatal Lassa fever (59). Alphavirus replicons, which are self-replicating RNA molecules expressing foreign antigens instead of alphavirus structural proteins and packaged in virus-like particles, have shown promising results as LASV vaccines, including the ability to promote CD8+ T-cell responses and confer complete protection in guinea pigs, but they await additional characterization (60-62). Notably, a DNA-based LASV vaccine offered complete protection from LASV in guinea pigs and nonhuman primates but required multiple administrations, which may not be practical in LASV-endemic regions (63-65).

In addition to VSV-LASV, the most advanced LASV vaccine candidate is based on a reassortant between LASV and the reportedly non-pathogenic Mopeia virus (MOPV) (50,51). Clone ML29 possesses genetic material from both MOPV and LASV—including the nucleoprotein and glycoprotein genes from the latter—and includes several additional point mutations that are thought to further attenuate the virus (66,70,71). Vaccination with ML29 has been shown to be safe and to elicit a potent and protective immune response against LASV. Indeed, it offers complete protection in guinea pigs and nonhuman primates, remains efficacious when administered up to two

Table 1: Lassa virus vaccine candidates and their evaluation in animal models

Platform	LASV antigen	Guinea pig efficacy	Nonhuman primate efficacy	Reference
Replication-competent vaccines				
Vaccinia virus (Lister)	N	100% survival	-	55
Vaccinia virus (NYBH)	GPC	100% survival	-	54
		-	100% survival (rhesus)	53
		79% survival	-	52
		-	67% survival (cynos) 100% survival (rhesus)	51
	GP1	-	0% survival (cynos)	51
	GP2	-	0% survival (cynos)	51
	GP1 & GP2 (separate vector)	-	100% survival (rhesus)	51
	N	94% survival	0% survival (cynos) 43% survival (rhesus)	51,52
	N & GPC (separate vectors)	58% survival	75% survival (cynos) 100% survival (rhesus)	51,52
	N & GPC (same vector)	-	100% survival (rhesus)	51
VSV	GPC	100% survival	100% survival (cynos)	31,32,34
	N	67% survival	-	34
ML29	N & GPC (same vector)	100% survival	100% survival (marmosets)	66,67,68
YFV17D	GPC	80% survival	0% survival (marmosets)	57,69
	GP1 & GP2 (same vector)	83% survival	-	56
Other vaccines				
Inactivated LASV	Inactivated LASV	-	0% survival (rhesus)	58
Alphavirus replicon	N	100% survival	-	60
	GPC	100% survival	-	60
	N & GPC (separate vector)	100% survival	-	60
	GPC & EBOV GP (same vector)	100% survival	-	60
DNA/ electroporation	GPC	83–100% survival	100% survival	62–64

Abbreviations: EBOV, Ebola virus; GP, glycoprotein; GP1, glycoprotein 1; GP2, glycoprotein 2; GPC, glycoprotein precursor; LASV, Lassa virus; N, nucleoprotein; NYBH, New York Board of Health; VSV, vesicular stomatitis virus; YF17D, Yellow fever 17D; "-", not done

days post-infection, is safe in immunocompromised animals and appears to be genetically stable with no propensity to undergo reassortment with pathogenic LASV (67,68,70,72,73); however, until recently, ML29 was classified by the US Centers for Disease Control as a Risk Group 3 pathogen, indicating that further safety validation may be warranted.

Discussion

Lassa virus causes hundreds of thousands of infections each year and results in thousands of deaths (5). Despite the clear threat that LASV poses to public health, the virus, as well as the disease that it causes, remain under studied. Largely for this reason, the World Health Organization has listed LASV as a priority disease in their Research and Development Blueprint that is designed to improve global research coordination, accelerate development of countermeasures and provide a framework for outbreak response (74). This Blueprint aims to develop a five-year accelerated research plan to advance LASV vaccines into phase III clinical trials. Moreover, the Coalition for Epidemic Preparedness and Innovations has committed to funding the advanced development of select candidate LASV vaccines, although exactly which vaccine platforms will be pursued has yet to be announced.

Although significant progress has been made towards the goal of developing a safe and effective LASV vaccine, further research is required. Many important questions concerning the use and efficacy of the VSV-LASV vaccine remain, particularly the question of the mechanism(s) of action. Activated CD8+ T-cells were noted in a majority of nonhuman primates vaccinated with VSV-LASV (32), suggesting that the cellular immune response plays an important role in protection. Indeed, control of Lassa fever in nonhuman primates has been correlated with the circulation of activated CD4+ and CD8+ T-cells (75), and nonfatal Lassa fever in humans has been shown to be associated with high levels of T-cell-attracting chemokines (76-78). Conversely, the humoral response to LASV infection does not appear to play a significant role in recovery from infection (75,79-81), and neutralizing antibodies seem to be poorly elicited (32,69,75,78). In contrast to the VSV-EBOV vaccine, in which antibodies play a critical role in protection (41), the humoral response appears to play little role in the protection elicited by VSV-LASV vaccine, although more work is required in this area. Time-to-immunity, immune durability and post-exposure therapeutic efficacy of the vaccine also remain to be investigated. Finally, whether the VSV-LASV vaccine, like the EBOV vaccine, is safe and efficacious in immunocompromised individuals is of particular concern should the vaccine ever be deployed in LASV endemic regions, where HIV-1 seropositivity is high. Despite the work that remains to be done, VSV-LASV is still among the most promising of the LASV vaccines currently in development.

Conclusion

The VSV-LASV vaccine is ready for further clinical development. A panel of experts surveyed by *Science* magazine has already identified it as one of two LASV vaccine candidates with the most potential (82). Not only does the VSV-LASV vaccine offer complete protection against a number of different LASV strains, but the platform upon which it is built, VSVΔG, has also been extensively characterized. Although safety concerns have been raised regarding the VSV platform, particularly in the context of the EBOV vaccine, the majority of available clinical trial data suggests that VSV-EBOV is both safe and effective. Likewise, the vector appears unlikely to pose a threat to livestock animals.

The next step in the development of the VSV-LASV vaccine is phase I human clinical trials to assess vaccine safety and dosage. As LASV continues to exact its perennial toll upon Western Africa, including the outbreak currently affecting Nigeria, the political and social will to develop a safe and effective vaccine against this disease has never been stronger. The VSV-LASV seems well positioned to be part of the solution to reduce the threat that LASV poses to the world.

Authors' statement

LB – Writing – original draft; writing – reviewing and editing
DRS – Writing – original draft; writing – reviewing and editing
XQ – Writing – reviewing and editing; supervision
DS – Initial conception; writing – reviewing and editing; supervision
LB and DRS contributed equally to this article.

Conflict of interest

The authors declare no conflict of interest.

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Strategies for increasing uptake of vaccination in pregnancy in high-income countries: A systematic review

Source: Bisset KA, Paterson P. **Strategies for increasing uptake of vaccination in pregnancy in high-income countries: A systematic review**. Vaccine 2018;36:2751-2759. https://www.ncbi.nlm.nih.gov/pubmed/29661584

Introduction: Vaccination in pregnancy is an effective method to protect against disease for the pregnant woman, foetus and new born infant… Improvement in the uptake of both pertussis and influenza vaccination among pregnant women is needed to prevent morbidity and mortality for both the pregnant women and unborn child.

Aim: To identify effective strategies in increasing the uptake of vaccination in pregnancy in high-income countries…

Methods: A systematic review of peer-reviewed literature was conducted using a keyword search strategy applied across six databases (Medline, Embase, PsychInfo, PubMed, CINAHL and Web of Science). Articles were screened against an inclusion and exclusion criteria and papers included within the review were quality assessed.

Results and conclusion: Twenty-two articles were included in the review. The majority of (studies) were conducted in the USA and looked at strategies to increase influenza vaccination in pregnancy. There is limited high quality evidence for strategies in high-income countries to increase coverage of pertussis and influenza vaccination in pregnancy. A number of strategies have been found to be effective; reminders about vaccination on antenatal healthcare records, midwives providing vaccination, and education and information provision for healthcare staff and patients.

Biological feasibility and importance of a gonorrhea vaccine for global public health

Source: Vincent LR, Jerse AE. **Biological feasibility and importance of a gonorrhea vaccine for global public health**. Vaccine. 2018 Apr 18. pii: S0264-410X(18)30278-0. doi: 10.1016/j.vaccine.2018.02.081. [Epub ahead of print]. https://www.ncbi.nlm.nih.gov/pubmed/?term=Biological+feasibility+and+importance+of+a+gonorrhea+vaccine+for+global+public+health

There is a growing public health interest in controlling sexually transmitted infections (STIs) through vaccination due to increasing recognition of the global disease burden of STIs and the role of STIs in women's reproductive health, adverse pregnancy outcomes, and the health and well-being of neonates. *Neisseria gonorrhoeae* has historically challenged vaccine development through the expression of phase and antigenically variable surface molecules and its capacity to cause repeated infections without inducing protective immunity. An estimated 78 million new *N. gonorrhoeae* infections occur annually and the greatest disease burden is carried by low- and middle-income countries (LMIC). Current control measures are clearly inadequate and threatened by the rapid emergence of antibiotic resistance. The gonococcus now holds the status of "super-bug" as there is currently no single reliable monotherapy for empirical treatment of gonorrhea. The problem of antibiotic resistance has elevated treatment costs and necessitated the establishment of large surveillance programs to track the spread of resistant strains. Here we review the need for a gonorrhea vaccine with respect to global disease burden and related socioeconomic and treatment costs, with an emphasis on the impact of gonorrhea on women and newborns…(and) we review recent research that suggests a gonorrhea vaccine is feasible and discuss challenges and research gaps in gonorrhea vaccine development.

First imported case of Mayaro virus disease detected in Canada

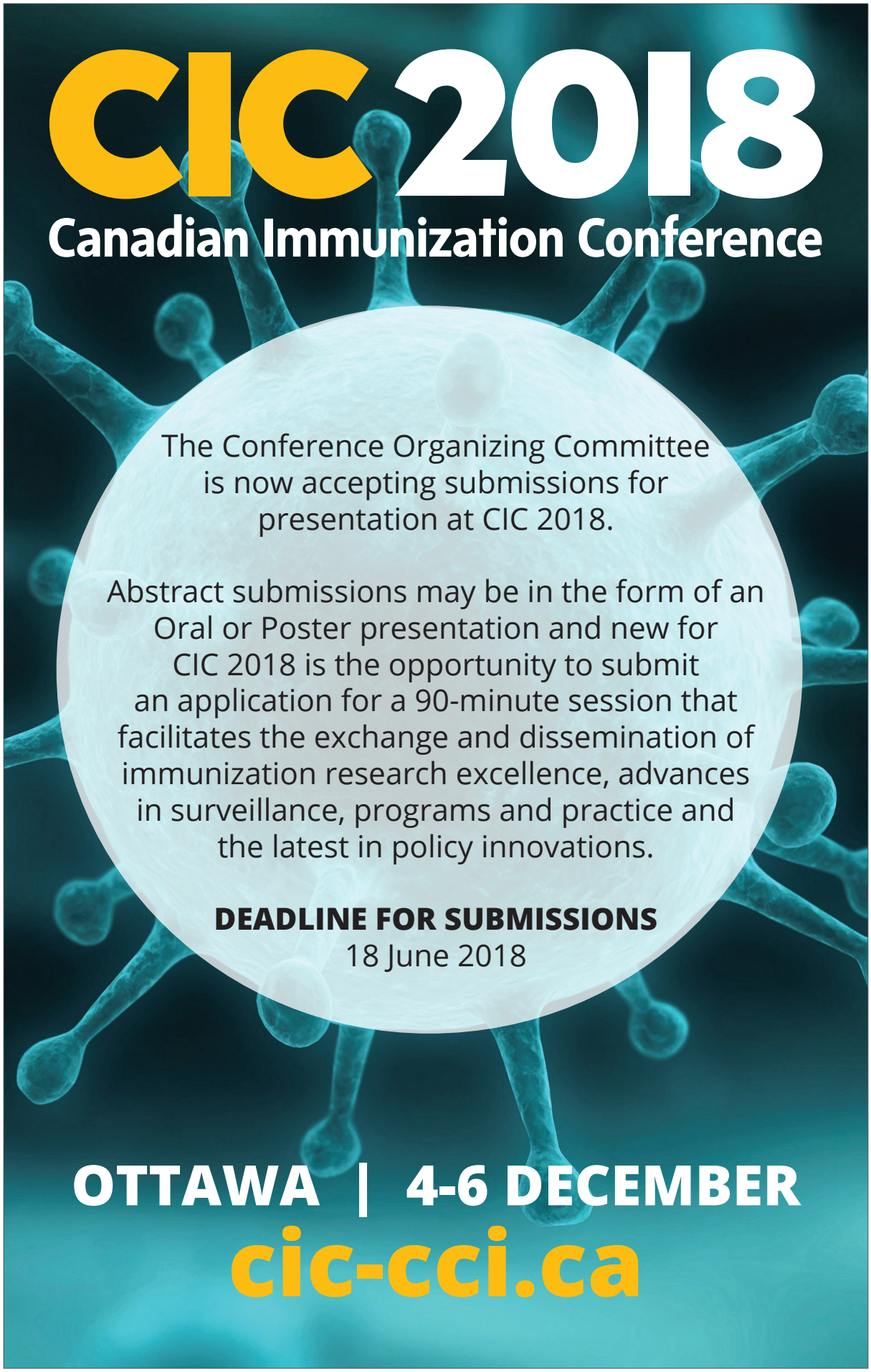
Source: MAYARO VIRUS DISEASE - CANADA: (ALBERTA) ex PERU A ProMED-mail post <http://www.promedmail.org/direct.php?id=20180518.5804085>
Date: Thu 17 May 2018 From: Kevin Fonseca <kevin.fonseca@albertahealthservices.ca>
Published Date: 2018-05-18 14:26:36 Archive Number: 20180518.5804085 [edited summary]

Mayaro virus (MAYV) has been detected in a 60-year-old male who recently returned from a vacation in South America that included a jungle tour in the Amazon basin. This is the first confirmed Canadian case.

His jungle tour began at Puerto Maldonado, Peru, on March 12, 2018, and lasted for four days. He flew back to Alberta, Canada, on Mar 18, 2018. The following day he experienced rigors and chills, although he felt afebrile during these episodes. Over the next few days the symptoms progressed to arthralgias in the large joints of his knees, elbows, and ankles as well as the small joints of his hands, together with myalgias and severe fatigue. He sought medical attention on two occasions, the first at his family physician's clinic the day after his onset of symptoms. Four days after symptom onset, he was seen by an infectious diseases specialist (Dr. Shannon Turvey), who noted a bilateral non purulent conjunctivitis, with a confluent, macular, erythematous rash on his chest, arms, and back, pharyngitis with no tonsillar involvement, no lymphadenopathy or organomegaly, and no signs of meningismus. His complete blood count (CBC) performed two days after symptom onset was mildly abnormal, with a low white blood cell count 3.7 x10^9/L, but normal hemoglobin and no thrombocytopaenia. Tests were negative for malaria on three consecutive collections. His C-reactive protein was high at 39.2 mg/L. His urine showed mild haematuria and 1+ protein; the liver enzymes and liver function tests were within normal limits. Whole blood and serum were collected to test for arboviruses, leptospirosis, and other probable infectious causes of rashes and viral syndromes. Additionally, nasopharyngeal, eye, and throat swabs were collected to test for the respiratory viruses, viral causes of conjunctivitis and *Streptococcus pyogenes*. None of these yielded a positive result.

Laboratory investigations commenced for an arboviral etiology specific for dengue (DENV), chikungunya (CHIKV), and Zika (ZIKV) viruses, but the results were negative. At day 19 after symptom onset, a convalescent serum tested positive for CHIKV IgM and indeterminate for IgG. This result prompted the infectious disease physician to query whether a related alphavirus, such as MAYV, could cross-react in the CHIKV serologic assays, given the patient's recent travel and the earlier negative CHIKV polymerase chain reaction (PCR) finding. As a result, the acute serum collected two days after symptom onset was retested and PCR amplification was carried out (and the results compared) to the National Center for Biotechnology Information (NCBI) nucleotide database. The closest match showed 98 percent identity with a human MAYV genotype D isolate from Peru in 2000.

Mayaro virus and CHIKV are closely related alphaviruses. The MAYV is localized to South America and the Caribbean; CHIKV, in contrast, is now widely prevalent in South and Central America and the Caribbean. Broader tourist expansion into eco-conservation areas bring tourists into much closer contact with mosquitoes carrying these agents. This case raises the distinct possibility that an unknown proportion of cases may have been or are misclassified as acute CHIKV infections instead of MAYV infections, especially if these persons have been to travel destinations where this agent circulates.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