Advisory Board Technical Consultation for COVAX Maternal Immunization Work Group: Maternal Immunization Post-Licensure Safety Needs for Pregnant Women and their Infants

Technical Consultation Report

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1. Introduction

The COVAX Maternal Immunization Work Group (WG) was established with the goal of developing a report that identifies and provides recommendations on COVID-19 candidate vaccine(s) for potential use in pregnant women. The larger Maternal Immunization Work Group consists of approximately 25 experts, with three subgroups covering: 1) Product Mapping, 2) Pre-Clinical/Clinical, and 3) Vaccine Safety. This online technical consultation was developed to support the goal of the COVAX WG Safety Subcommittee, whose goal is "to outline post-licensure safety surveillance needs for pregnant women and their infants, particularly in LMICs."

2. Research questions

The COVAX Maternal Immunization WG provided six areas of interest to center this technical consultation:

1. What adverse outcomes, specific pregnancy outcomes, neonate outcomes following immunization (**AEFIs**) should be monitored?
2. What adverse outcomes, specific pregnancy outcomes, or neonate outcomes of special interest (**AESIs**) should be monitored?
3. What is the appropriate duration of follow-up for the mother? The newborn?
4. What active safety surveillance approaches could be used to identify AESIs in LMICs?
    a. Are Hospital-based systems or Sentinel sites approaches feasible?
    b. What study design approaches should be considered?
    c. Is it feasible to do a retrospective study of COVID-19 vaccinated pregnant women?
    d. Is it feasible to do a prospective study of vaccinated pregnant women?
5. How should passive safety surveillance systems be strengthened for signal detection?
6. What should be done to manage vaccine hesitancy due to misinformation?

3. Methodology

This brief report consisted of an online technical consultation with closed- and open-ended questions that were disseminated using the web-based questionnaire platform Survey Monkey™. Fourteen eligible participants on the Advisory Board for the Bill & Melinda Gates Foundation funded study titled, "Landscape analysis: Sentinel site readiness for Maternal Immunization Active Safety Surveillance in LMIC" were sent an invitation to fill out this online questionnaire. This group was chosen due to their expertise in the content area of maternal immunization and post-licensure surveillance in LMICs.

Questionnaire development was informed by a bibliographic search on PubMed and relevant information from a previous study to search for information on the research questions of interest. Experts from the COVAX WG Safety Subcommittee validated the content of this questionnaire prior to disseminating to the Advisory Board. Those invited to participate had one week to respond to this questionnaire from Monday, October 5th, 2020 to Monday, October 12th, 2020. This questionnaire can be found in **Appendix A**.

Given the small sample size, all quantitative questions were analyzed to calculate and graphically represent the distribution of the absolute frequency of responses using the software Stata/SE 16.1. Qualitative questions were coded thematically and either quantitatively represented using absolute frequency or narratively summarized. The qualitative analysis thematic coding can be found in **Appendix B**.

3.1 Statement of Confidentiality

All questionnaire responses were anonymous. This online questionnaire did not collect email addresses nor personal identification data, for reference.

4. Results

Of 14 invited Advisory Board members, 8 responded to this consultation, with 1 partial response and 7 complete responses. This reflects a response rate of 57.1% and a completion rate of 87.5%.

4.1 Pregnancy and neonatal outcome-specific AEFIs

> *Item included in the online questionnaire: Which adverse events specific to pregnancy and neonatal outcomes following immunization (AEFIs) are most important for post-licensure safety surveillance? (Choose all that apply)*

Figure 1. Absolute frequency (N=8)

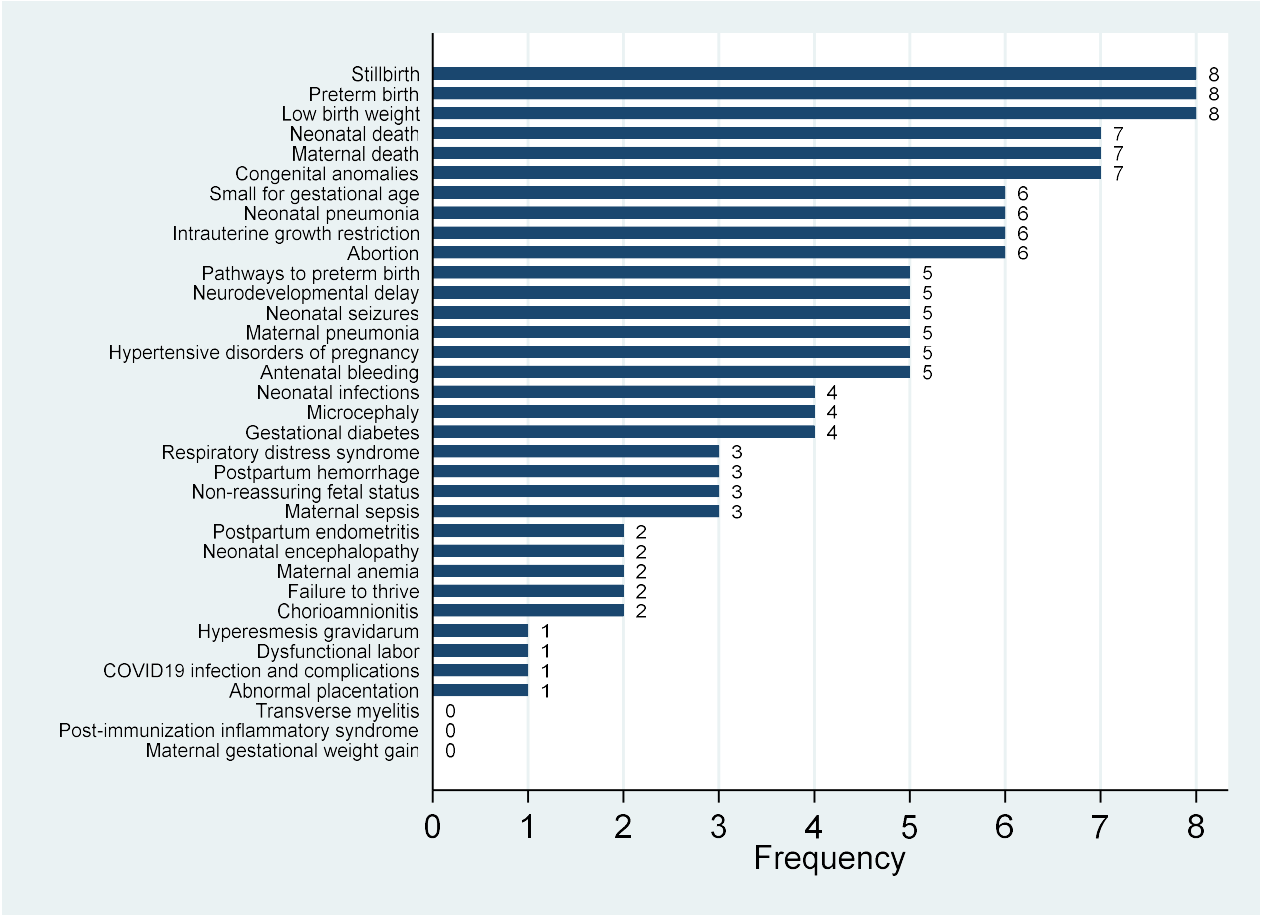

Figure 1 shows the absolute frequencies of experts' ratings on each AEFI specific to pregnancy and neonatal outcomes that were proposed. AEFIs were chosen based on the outcome pregnancy and neonatal case definitions created by the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project[1] and a previous study conducted by this team.

4.2 Pregnancy and neonatal AESIs for COVID-19

> *Item included in the online questionnaire: What adverse events specific to pregnancy outcomes, or neonatal outcomes of **special interest** (AESIs) should be monitored for COVID-19 post-licensure safety surveillance? (open-ended response)*

Various adverse events specific to maternal and neonatal outcomes of special interest (AESIs) for COVID-19 we mentioned by 7 respondents. These answers were analyzed and coded from the qualitative responses that participants provided (**Appendix B**). AESI outcomes mentioned by respondents were as follows (number of respondents that mentioned an outcome are represented in parentheses):

- Maternal death (5)
- Preterm birth (4)
- Pregnancy loss (4). This outcome refers to responses that suggested spontaneous abortion and/or stillbirth
- Infant death (3). This outcome includes responses "early neonatal death", "neonatal death", and "infant death"
- Congenital anomalies (3)
- Hypertensive disorders of pregnancy (2). This outcome includes responses that suggested monitoring pre-eclampsia and hypertension in pregnancy
- Small for gestational age (1)
- Respiratory distress syndrome (1)
- Neurologic outcomes (1)
- Low birth weight (1)
- Other (1)

The participant whose response was coded as "Other" suggested adapting VSD influenza vaccine surveillance outcomes for pregnant women.

4.3 Follow-up time of pregnant women

> *Item included in the online questionnaire: What is the appropriate time to end follow-up of pregnant women vaccinated for COVID-19?*

Most respondents replied that the appropriate time to end follow-up of pregnant women vaccinated for COVID-19 was from the time of vaccination to 42 days postpartum. All seven respondents who rated this question provided their rationale. Participants commented that this period is appropriate logistically and allows for sufficient time for development of an AEFI. One participant commented that studies longer than 42 days postpartum do not generate as conclusive

of evidence given limitations in data availability and the subsequent consequences for adjustment of time-varying confounders. Only one participant considered that follow up should end 12 months for ensuring sufficient time to be able to identify delayed AEFIs and that this time frame aligns with the current requirements of COVID-19 vaccine follow-up. Although no participants selected the appropriate time of follow-up to end to be at birth, one participant commented this may be acceptable in the case of LMICs if longer follow-up is not feasible. No participants selected the option of time of vaccination to 28 days postpartum.

4.4 Follow-up duration of offspring

> *Item included in the online questionnaire: What is the appropriate time to end follow-up of the offspring of women who were vaccinated for COVID-19 during pregnancy?*

The absolute frequency of the participant responses on the appropriate amount of follow-up time of the offspring of pregnant women vaccinated for COVID-19 for post-licensure immunization safety surveillance was approximately evenly divided between two options: follow-up from birth to 6 months postpartum (n=3) and follow-up from birth to 1 year postpartum (n=4).

Five out of seven survey respondents provided their rationale for this item. Participants who commented on their rationale for their answer primarily were those who cited birth through 1 year postpartum. Those who voted birth through 1 year postpartum all commented that their rationale for this answer was to allow for time of development of a delayed AEFI in the infant, such as neurodevelopmental delays or congenital anomalies not obvious or clear at birth. One participant who voted "birth through 6 months postpartum" commented that this allows for the waning of maternal antibodies in the infant, facilitating infection assessment and effects of breastfeeding after this period. However, this participant also commented that follow-up through 1 year postpartum might be necessary in the event of ongoing exposure to COVID-19.

4.5 Feasibility of active safety surveillance approaches for identification of AESIs in LMICs

Participants were asked to rate the feasibility of three approaches for identification of AESIs in LMICs, as well as rate the feasibility of pursuing approaches not explicitly outlined. The option to provide recommendations for other approaches was also provided to participants in this survey.

4.5.1 Facility-based systems/sentinel site approaches

> *Item included in the online questionnaire: How feasible is it to use facility-based systems/sentinel site approaches for active safety surveillance for identification of AESIs of pregnant women vaccinated for COVID-19 in LMICs? (1 = not feasible; 9 = highly feasible)*

Figure 2. Absolute frequency (N=7)

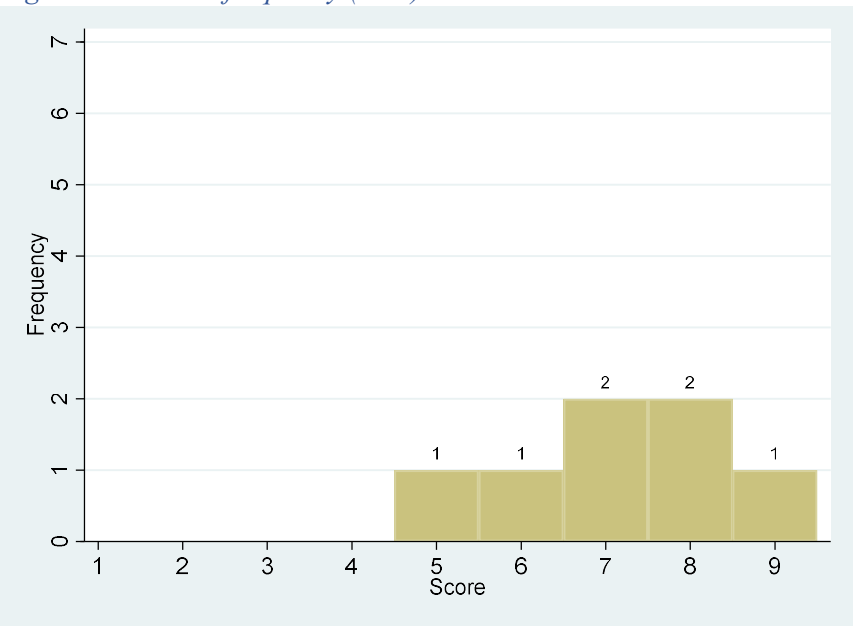

Figure 5 represents the distribution of scores for the feasibility of this active safety surveillance approach. The majority of participants voted that facility-based/sentinel site approaches for safety surveillance is feasible, as indicated by the scores primarily in the upper third of the scale.

4.5.2 Retrospective study approach

Item included in the online questionnaire: How feasible is it to conduct a retrospective study of pregnant women vaccinated for COVID-19? (1 = not feasible; 9 = highly feasible)

Figure 3. Absolute frequency (N=7)

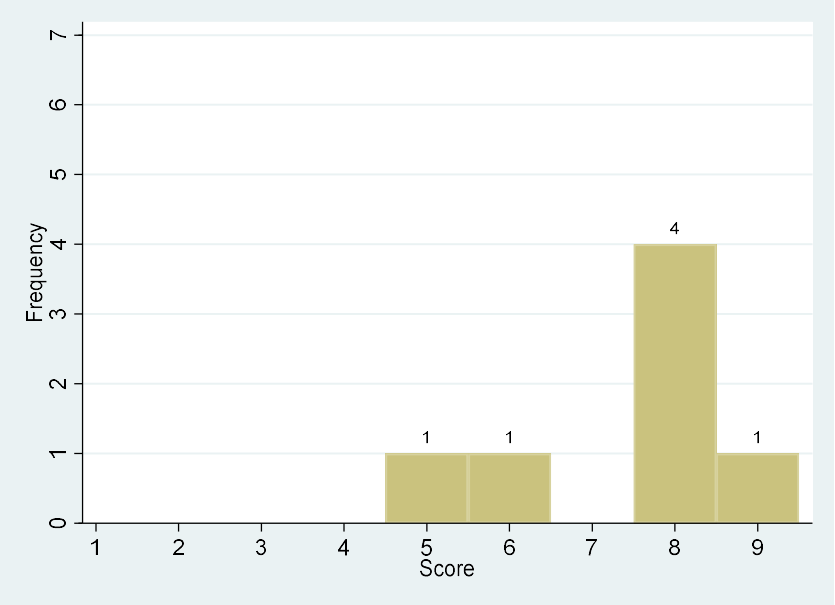

Figure 6 represents the distribution of votes for feasibility of retrospective studies for active safety surveillance of pregnant women vaccinated for COVID-19. The majority (n=5) of

participants rated this as highly feasible, but two participants were less certain on the feasibility of this approach, as indicated by scores in the middle range (score 4-7) of the scale.

4.5.3 Prospective study approach

Item included in the online questionnaire: How feasible is it to conduct a prospective study of pregnant women vaccinated for COVID-19? (1 = not feasible; 9 = highly feasible)

Figure 4. Absolute frequency (N=7)

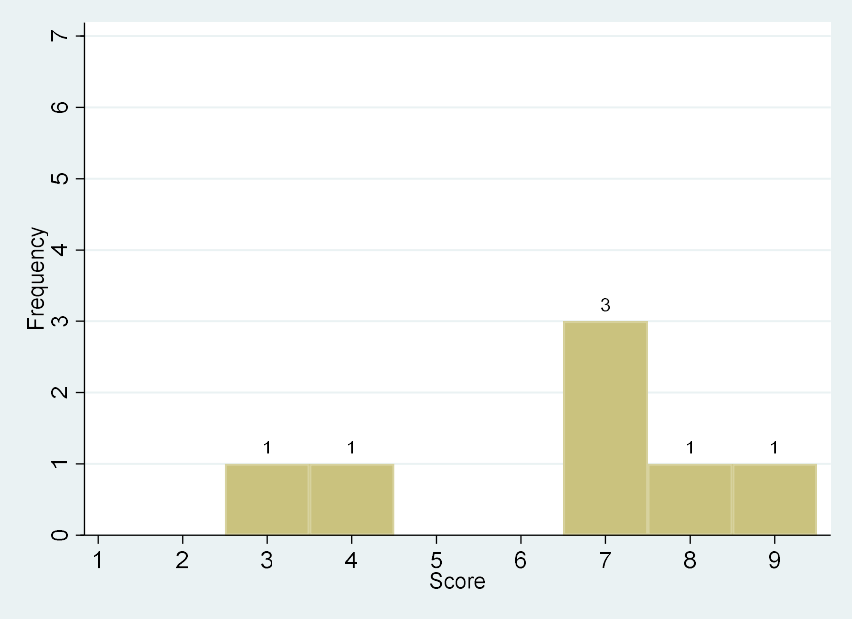

Figure 7 represents the distribution of ratings on the feasibility of conducting a prospective study of pregnant women vaccine for COVID-19. Most participants (n=5) responded that this was feasible, as indicated by the scores in the upper third of the scale. However, two participants felt that this approach is less feasible, indicated by the lower scores.

4.5.4 Other study design approaches

Item included in the online questionnaire: Based on your experience, how feasible is to use other study design approaches for active safety surveillance to identify AESIs in LMICs? (1 = not feasible; 9 = highly feasible)

Figure 4. Absolute frequency (N=7)

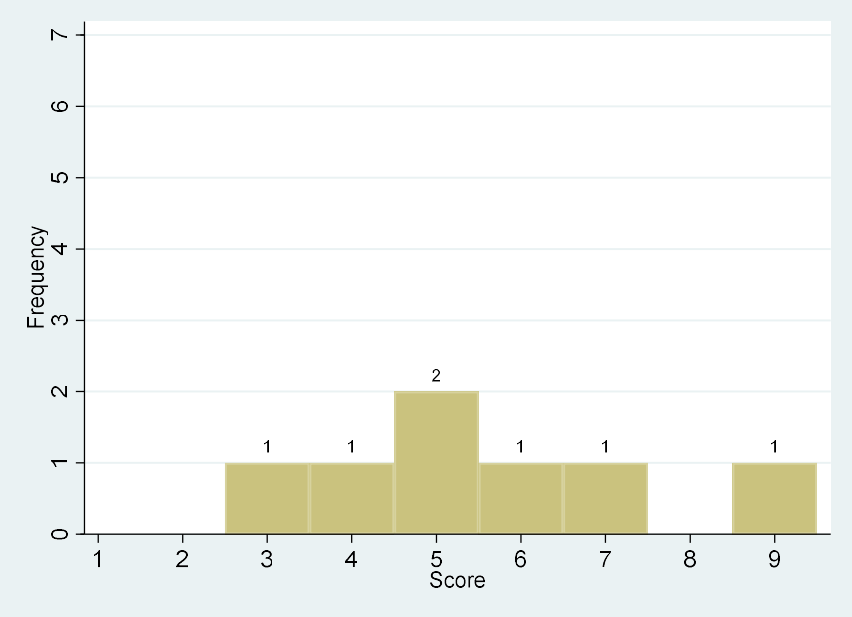

Figure 8 represents the distribution of ratings for the feasibility of other study design approaches. Three participants responded to the optional open-ended response question that asked for recommendations on other study design approaches. Participants cited two other study designs that a case-control study or cohort event monitoring study, and one participant suggested a resource to use in studies for active safety surveillance. One participant who rated feasibility of other approaches highly suggested cohort event monitoring and one participant who gave a mid-range rating for feasibility suggested case-control study design. The participant who suggested database review (e.g. electronic health records) to identify AESIs in LMICs gave a mid-range rating and cited lack of clarity on the question. This participant also noted that this is highly dependent on the study setting due to logistic capability and availability of these databases. It is important to note that other study design approaches were suggested by those participants who gave a score above 5 for feasibility.

4.6 Strengthening passive safety surveillance systems

> *Item included in the online questionnaire: How should passive safety surveillance systems be strengthened for signal detection? (Open-ended response, optional)*

The majority of participants (n=6) provided a response suggesting mechanisms for strengthening passive surveillance systems for signal detection. One mechanism suggested was to increase engagement of health care providers in signal reporting in the available systems. Another suggested mechanism was to increase engagement among the public. For example, one respondent commented that "a lot more information should be provided to mothers during their health education sessions" to increase awareness around relevant information for signal detection. Many participants suggested adaptation and strengthening of existing mechanisms (i.e. systems, reporting forms and tools) to ensure that instructions are clear, exposure and outcome data are correctly captured, and that sufficient amount of data are collected (i.e. confounder data). A few participants suggested adaptation of surveillance systems to use digital methods of reporting (e.g. mobile devices). One participant commented that data from immunization and

maternal and child health programs need to be linked to facilitate communication of events and ensure linkage of exposure to outcome.

4.7 Timing of communication of vaccine safety findings to decision-makers

> *Item included in the online questionnaire: What is the appropriate timing to begin to communicate vaccine safety findings to vaccine decision-makers (e.g. funding agencies, national ministries of health, public health programs, etc.)? (Choose all that apply)*

Figure 5. Absolute frequency (N=7)

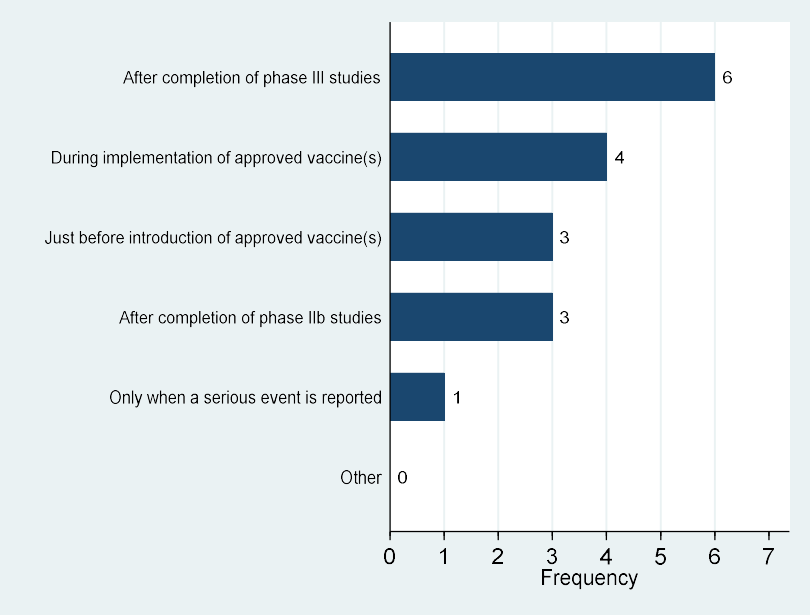

Figure 6. Frequency of number of options selected (N=7)

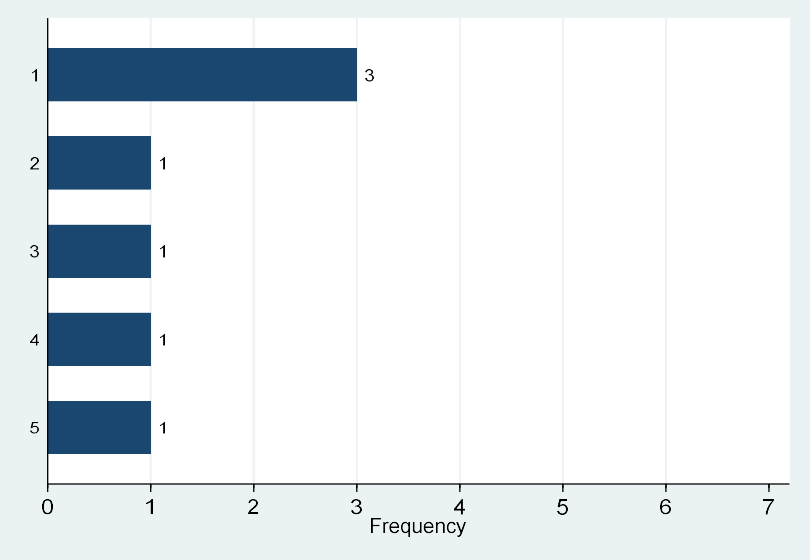

Figure 9 represents the absolute frequency for number of responses for each answer option. The options that received the most responses from participants were after completion of phase III

studies (n=6) and during implementation of approved vaccine(s). However, it is important to note that participants had the option to select one or more options to indicate their opinion on when vaccine safety findings should be communicated with decision-makers. Respondents were split in their responses, with three respondents indicating only one time for communication and four respondents indicating more than one option. Those respondents who indicated only one option for when communication should occur selected options for earlier stages, with two respondents indicating after completion of phase III studies and one respondent indicating after completion of phase IIb studies. Those respondents who selected more than one option were those who also responded for communication to occur later in the vaccine development and implementation process. One respondent selected all options and commented that his/her belief is that vaccine communication should occur only when a serious event is reported.

Four out of seven participants provided their rationale for their answer. Participants who answered Phase IIb cited reasons such as that it may help the approval process and that vaccine data should be made available as early as possible and be communicated throughout the entire development continuum, and that early communication and engagement can facilitate post-approval processes and implementation. One participant who responded after phase III commented that data is more robust after this phase. One participant highlighted that their rationale for during implementation was due to the potential of new events during scale-up of the vaccine.

4.8 Management of vaccine hesitancy due to misinformation

> *Item included in the online questionnaire: Based on your experience, what should be recommended to manage vaccine hesitancy due to misinformation? (optional)*

Most participants (n=6) provided recommendations for managing vaccine hesitancy. The most common recommendations participants cited were strong communication to the community and target population, and transparency around vaccine safety information, especially during vaccine development and early implementation. One participant highlighted the importance to allow the community and target population to voice their concerns prior to vaccine introduction. Participants suggested that this communication should be clear, ongoing, and begin early in the process. Participants also noted the importance of continuous stakeholder engagement, including those who will receive the vaccine, as well as other important community members. Lastly, participants recommended the identification of a "champion" or advocate of the vaccine in the community.

5. Acknowledgements

This survey was supported by the Bill & Melinda Gates Foundation INV008443.

The authors would like to thank all members of the "Landscape analysis: Sentinel Site Readiness for Maternal Immunization Active Safety Surveillance in LMICs" for their support and advice during the conceptualization, conduct, and analysis of this survey. The authors would also like to thank those from the COVAX WG for their advice on the design of this survey.

6. Appendices

Appendix A. Online questionnaire

Advisory Board Survey for COVAX Maternal Immunization Safety Work Group Survey: Maternal Immunization Post-Licensure Safety Needs for Pregnant Women and their Infants

Introduction

The COVAX Maternal Immunization Work Group was established with the goal of developing a report that identifies and provides recommendations on COVID-19 candidate vaccine(s) for potential use in pregnant women. The larger Maternal Immunization Work Group consists of approximately 25 experts (including some of you) and there are three subgroups covering: 1) Product Mapping, 2) Pre-Clinical/Clinical, and 3) Vaccine Safety.

The goal of the COVAX WG Safety Subcommittee (co-chaired by Steven Anderson and Andy Stergachis) is "To outline post-licensure safety surveillance needs for pregnant women and their infants, particularly in LMICs". This subcommittee is seeking this Advisory Board's broad expertise in the vaccine safety area to assist in answering some of the key questions in their review.

Instructions

We ask that you review and answer the following questions to provide insight and support to this COVAX review. The survey should take you approximately 10-15 minutes to complete. If you are unable to complete the survey in one session, your responses will be saved, and you can return later to complete it. You will have until Monday, October 12th to please complete and submit this survey.

If you have any questions, please send an email to Sarah Matthews at smatthe2@tulane.edu.

* Which adverse events specific to pregnancy and neonatal outcomes following immunization (AEFIs) are most important for post-licensure safety surveillance? (Choose all that apply)

- [ ] Hypertensive disorders of pregnancy
- [ ] Non-reassuring fetal status
- [ ] Postpartum hemorrhage
- [ ] Pathways to premature birth
- [ ] Maternal death
- [ ] Abortion
- [ ] Antenatal bleeding
- [ ] Gestational diabetes
- [ ] Dysfunctional labor
- [ ] Intrauterine growth restriction
- [ ] Chorioamnionitis
- [ ] Postpartum endometritis
- [ ] Stillbirth
- [ ] Preterm birth
- [ ] Congenital anomalies
- [ ] Neonatal infections
- [ ] Neonatal death
- [ ] Low birth weight
- [ ] Small for gestational age
- [ ] Neonatal encephalopathy
- [ ] Respiratory distress in the newborn
- [ ] Failure to thrive
- [ ] Microcephaly
- [ ] Neonatal seizures
- [ ] Neurodevelopmental delay
- [ ] Maternal pneumonia
- [ ] Maternal sepsis

- [ ] Neonatal pneumonia
- [ ] Maternal gestational weight gain
- [ ] Hyperemesis gravidarum
- [ ] Abnormal placentation
- [ ] Maternal anemia
- [ ] Other (please specify)

* What adverse events specific to pregnancy outcomes or neonatal outcomes of special interest (AESIs) should be monitored for COVID-19 post-licensure safety surveillance?

* What is the appropriate time to end follow-up of pregnant women vaccinated for COVID-19?

- ◯ From time of vaccination through birth/abortion
- ◯ From time of vaccination through 28 days postpartum
- ◯ From time of vaccination through 42 days postpartum
- ◯ From time of vaccination through 1 year postpartum
- ◯ Other (please specify)

Please provide your reasoning for your answer. (optional)

* What is the appropriate time to end follow-up of the offspring of women who were vaccinated for COVID-19 during pregnancy?

- ◯ From birth through 7 days postpartum (perinatal period)
- ◯ From birth through 28 days postpartum (neonatal period)
- ◯ From birth through 6 months postpartum
- ◯ From birth through 1 year postpartum (infant period)
- ◯ Other (please specify)

Please provide your reasoning for your answer. (optional)

The following questions will be focused on approaches to conduct **active safety surveillance for identification of AESIs of pregnant women vaccinated for COVID-19 in LMICs**. Please answer all questions with this context in mind.

* How feasible is it to use facility-based systems/sentinel site approaches for active safety surveillance for identification of AESIs of pregnant women vaccinated for COVID-19 in LMICs?
(1 = not feasible; 9 = highly feasible)

1	2	3	4	5	6	7	8	9
○	○	○	○	○	○	○	○	○

* How feasible is it to conduct a retrospective study of pregnant women vaccinated for COVID-19?
(1 = not feasible; 9 = highly feasible)

1	2	3	4	5	6	7	8	9
○	○	○	○	○	○	○	○	○

* How feasible is it to conduct a prospective study of pregnant women vaccinated for COVID-19?
(1 = not feasible; 9 = highly feasible)

1	2	3	4	5	6	7	8	9
○	○	○	○	○	○	○	○	○

* Based on your experience, how feasible is it to use other study design approaches for active safety surveillance to identify AESIs in LMICs?
(1 = not feasible; 9 = highly feasible)

1	2	3	4	5	6	7	8	9
○	○	○	○	○	○	○	○	○

What other study design approaches, if any, would you recommend for active safety surveillance to identify AESIs in LMICs?

* How should passive safety surveillance systems be strengthened for signal detection?

* What is the appropriate timing to begin to communicate vaccine safety findings to vaccine decision-makers (e.g. funding agencies, national ministries of health, public health programs, etc.)? (Choose all that apply)

- [ ] After completion of phase IIb studies
- [ ] After completion of phase III studies
- [ ] Just before introduction of approved vaccine(s)
- [ ] During implementation of approved vaccine(s)
- [ ] Only when a serious event is reported
- [ ] Other (please specify)

Please provide your reasoning for your answer. (optional)

Based on your experience, what should be recommended to manage vaccine hesitancy due to misinformation? (optional)

Thank you for actively participating in this survey.

Your contribution is highly appreciated.

7. References

1. Chen RT, Moro PL, Bauwens J, Bonhoeffer J. Obstetrical and neonatal case definitions for immunization safety data. *Vaccine.* 2016;34(49):5991-5992.