1 ABSTRACT

Title

Post Authorisation Safety Study: Effectiveness evaluation of the local additional risk minimisation measures for STAMARIL® in the United Kingdom: a survey for healthcare professionals and vaccinees

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Keywords

additional Risk Minimisation Measures (aRMMs), survey, STAMARIL, yellow fever vaccine, effectiveness evaluation

Rationale and background

STAMARIL is a live attenuated yellow fever (YF) 17D-204 strain vaccine indicated in individuals over 9 months of age for active immunisation against YF caused by YF virus. Following the implementation of local additional Risk Minimisation Measures (aRMMs) in the STAMARIL Risk Management Plan in November 2021, requested by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK), the marketing authorisation holder (MAH) committed to evaluate the effectiveness of the aRMMs. This post authorisation safety study (PASS) survey was designed to assess the effectiveness of a standardised UK checklist, developed by MHRA [hereby referred to as 'UK (STAMARIL) YF pre-vaccination checklist' in this report] among the qualified healthcare professionals (HCPs) of designated authorised YF vaccination centres (YFVCs) and the effectiveness of the STAMARIL patient information leaflet (PIL) among YF vaccinees in the UK. Note that National Travel Health Network and Centre (NaTHNaC) and Public Health Scotland (PHS) also produced a similar YF pre-vaccination checklist which is a screening tool and is intended for vaccinees (travellers) to read and complete in advance of, or duing, the travel health consultation. Therefore, both checklists are referred as standardised YF pre-vaccination checklists in this study.

Research question and objectives

The purpose of this study was to evaluate the effectiveness of the local aRMMs in the STAMARIL Risk Management Plan. The study objectives were: to measure awareness of the UK (STAMARIL) YF pre-vaccination checklist and utilisation of any standardised YF pre-vaccination checklist(s), to evaluate knowledge and understanding of the key safety messages of any standardised checklist(s), and to measure distribution of the STAMARIL PIL, among the qualified HCPs of designated authorised YFVCs. The study objectives also included verification of the receipt of the STAMARIL PIL by YF vaccinees in the UK.

Study design

This was a national, multicentre, prospective, cross-sectional, and multi-channel survey through web questionnaires conducted separately among qualified HCPs and STAMARIL vaccinees in the UK.

Setting

- **Site and participant selection***:* The online survey was conducted among the qualified HCPs from designated authorised YFVCs and YF vaccinees (or their parents/guardians when vaccinees were younger than 18 years old) in the UK.

- **Overall participation status**: HCPs and vaccinees were recruited from England, Northern Ireland, Wales and Scotland.

- **Data collection**: During the 24 weeks (March through August 2023) of fieldwork, data was collected from an HCP questionnaire and a vaccinee questionnaire.

Participants and study size, including drop-outs

Initially, it was planned to have a minimum sample size of 200 HCPs and 150 vaccinees, who met all the inclusion criteria and none of the exclusion criteria, answering the questionnaires. After extension of the data collection period from 12 weeks to 24 weeks, 153 HCPs and 125 vaccinees submitted completed questionnaires and were included in the final analysis.

- **Inclusion criteria***:* Qualified HCPs from designated authorised YFVCs with experience of consultation and/or administration of YF vaccine and vaccinees who received YF vaccine in the UK.
- **Exclusion criteria***:* HCP's who were not qualified to provide consultation and/or administration of YF vaccine and those HCPs or vaccinees who declared having conflict of interest with the survey.

Variables and data sources

- **Data management, review, validation:** This was a primary data collection survey conducted through an HCP questionnaire and a vaccinee questionnaire.

- **Statistical considerations:** All the analyses were descriptive. The analysis was conducted using the SAS® software V9.4 (SAS Institute North Carolina, USA) on Windows™.

- **Variables:**

    - From the HCP questionnaire, variables related to HCPs practice, HCPs awareness, utilisation, and distribution of the aRMM materials and related to the knowledge and understanding of the key safety messages in any standardised YF pre-vaccination checklist(s) were collected.
    - From the vaccinee questionnaire, variables related to vaccinees demographic information and vaccinees receipt of the STAMARIL PIL were collected.

- Study endpoints: There were four effectiveness indicators for the aRMMs among HCPs and one effectivness indicator among vaccinees. Each indicator was considered successful when at least 80.0% of the participants succeeded at each study endpoint.
    - Awareness was assessed through the percentage of qualified HCPs who were aware of the UK (STAMARIL) YF pre-vaccination checklist.
    - Utilisation was assessed through the percentage of qualified HCPs who frequently or always used any standardised YF pre-vaccination checklist(s).
    - Distribution was assessed through the percentage of qualified HCPs who frequently or always distributed the STAMARIL PIL among YF vaccinees.
    - Knowledge and understanding were assessed through the percentage of qualified HCPs who provided at least 80% of desirable responses to the related 27 sub-questions on key safety messages associated with YF vaccination in any standardised YF pre-vaccination checklist(s).
    - Receipt of the STAMARIL PIL was assessed through the percentage of vaccinees who received the PIL.

- **Data analyses:** Categorical variables were described as the total number and relative percentage per category. The proportions of respondents who provided correct answers to each question were calculated for the study endpoints defined above. Open questions or questions with free-text options were categorised by identified keywords. Wilson confidence intervals of 95% was evaluated on the endpoints. All the analyses were described by overall and per region (if greater than five respondents) for HCPs and vaccinees separately.

Results

- **Overall participation status:** A total of 34,444 UK HCPs were identified from the OneKey database, regardless of working in YFVCs or not, and invited to participate in the study. Among the HCPs contacted, 296 (0.9%) originally agreed to participate and 153 (0.4%) completed the questionnaire. Approximately 95.0% of the HCPs (n=145) who completed the questionnaire participated from YFVCs located in England. With regards to vaccinees, 125 (39.4%) out of 317 vaccinees who clicked the survey link completed the web questionnaires with majority from England (n=84).

- **Descriptive data:** The key characteristics of the 153 HCPs who completed the study survey included an almost equivalent proportion of male and female participation (51.6% vs. 48.4%) across the UK. Professionally, most of the HCPs were either pharmacists (34.6%) or nurses (34.0%), aged between 40 to 59 years (75.8%) having more than 10 years of professional practice in a general practice setting (60.8%).

  The key characteristics of vaccinees who completed the study questionnaire comprised of 76.0% of adult vaccinees mostly between 30 to 49 years of age and least in the age group of 60 years or older; approximately 41.0% of vaccinees were males and approximately 85.0% were at least secondary school educated or higher.

- **Main findings on endpoints:**

Two out of the four indicators for the effectiveness of the aRMMs among the HCPs were successful as the pre-defined success criteria were met. The key observations on each indicator are presented below:

  - *Awareness:* Around 74.0% of HCPs (n=113) reported awareness of the UK (STAMARIL) YF pre-vaccination checklist and therefore the 'awareness' indicator was not successful.
  - *Utilisation:* Approximately 90.0% of HCPs (n=137) utilised at least one of the standardised YF pre-vaccination checklists and therefore, the indicator of 'utilisation' was successful, meaning the YF checklist(s) were widely utilised in the UK. For both standardised checklists, most HCPs had no comments or positive comments such as a useful or good resource, comprehensive or adequate, and easy to use, etc.
  - *Distribution:* Approximately 92.0% of HCPs (n=141) reported that they distributed the STAMARIL PIL to vaccinees and therefore, the indicator of 'distribution' was successful.
  - *Knowledge and understanding:* Approximately 46.0% of HCPs (n=71) were successful in the knowledge and understanding of the key safety messages and therefore the 'knowledge and understanding' indicator did not achieve success. Most HCPs selected incorrect information as correct statements for the sub-questions, resulting in decreased success.

With regards to vaccinees, a total of 87.2% of them received the PIL, which was the only effectiveness indicator among vaccinees. Thus, the aRMM effectiveness was successful among vaccinees.

Discussion

This study provided insights into the effectiveness of local aRMMs in the STAMARIL Risk Management Plan amongst target populations that included qualified HCPs of designated authorised YFVCs and YF vaccinees in the UK. Two out of four effectiveness indicators for HCPs were successful, *namely* utilisation of any standardised YF pre-vaccination checklist(s) and distribution of the STAMARIL PIL, considering an *a priori* threshold of 80.0%. Another two indicators were not successful, *namely* awareness of the UK (STAMARIL) YF pre-vaccination checklist and knowledge and understanding of the key safety messages in any standardised YF pre-vaccination checklist(s), given that the pre-defined success criteria were not met. It should be acknowledged that the effectiveness definition was stringent among HCPs, relying on the combination of four successful endpoints achieved by ≥80% of HCPs. With regards to vaccinees, a total of 87.2% vaccinees received the STAMARIL PIL. Thus, the aRMM effectiveness was successful among vaccinees but not for HCPs.

Some limitations of this online survey study should be considered in interpreting the study findings. First, the results were restricted to the HCPs and vaccinees who were willing to participate in this study. The demographic details of the invited persons who did not participate were lacking and therefore could not quantify potential differences with the included participants. Second, non-

response bias might have been introduced into the study if targeted HCPs had activated filters in their mailbox that blocked spam and unsolicited emails. Third, the pre-specified minimum sample sizes (200 HCPs and 150 vaccinees) were not reached. Despite this, there was no or minimal impact on the precision of the study findings based on the actual sample sizes. Fourth, coronavirus disease-2019 (COVID-19) pandemic had a negative impact on the numbers of YFVCs and YF vaccinations, which could have affected the results. Fifth, although the HCP questionnaire was estimated to take 10 to 15 minutes to complete, it might be still long for HCPs given their potential busy schedules. Therefore, some HCPs might not read each question carefully before answering it for lack of time, particularly for 27 sub-questions related to knowledge and understanding of the key safey messages associated with YF vaccination. Finally, the distribution of the UK (STAMARIL) YF pre-vaccination checklist was implemented around 18 months prior to the survey, therefore, recall bias in awareness of this checklist cannot be ruled out.

Despite these limitations, there are three major strengths in this study. First, HCPs were recruited using a high-coverage database (OneKey). Weighting per region increased the fitment of the results to the target populations. Unweighted and weighted results, where relevant, are reported. Therefore, the results are generalizable to the UK population. Second, the checklist issued by NaTHNaC and PHS is not part of aRMMs for STAMARIL, but this checklist includes similar contents as the UK (STAMARIL) YF pre-vaccination checklist and is commonly used in YFVCs. Therefore, we considered any standardised YF pre-vaccination checklists for 'utilisation' and 'knowledge and understanding of the key safety messages' indicators to increase the possibility of achieving successful endpoints. Finally, there were open questions in both HCP and vaccinee questionnaires to help detect and describe any issues that HCPs or vaccinees might have with the YF pre-vaccination checklists or STAMARIL PIL.

To assess the effectiveness of aRMMs, an *a priori* threshold of ≥80.0% of successful participants for each endpoint was considered appropriate. The threshold was also set to define overall success. It should be noted that a threshold of ≥80.0% was relatively high. In the absence of a defined success threshold in good pharmacovigilance practices guidelines, literature or regulatory requirements, the threshold selection was arbitrary.

Although the success indicator of awareness of UK (STAMARIL) YF pre-vaccination checklist (73.9%) was not achieved by ≥80.0% of HCPs, most of HCPs (95.0%) were aware of a standardised checklist. For HCPs, knowledge and understanding of the key safety messages associated with YF vaccination showed most room for improvement. However, no actual vaccine errors were found in NaTHNaC Annual Return reports for 2021 and 2022 after the standardised YF pre-vaccination checklists were widely used in YFVCs.

The objective of a standardised checklist is to ensure compliance of HCPs with indications, contraindications, warnings, and precautions of YF vaccine; notably 90% of the HCPs utilised at least one standardised checklist indicating that they possess sound practical knowledge of the safety concerns associated with YF vaccination. More importantly, the findings of no actual vaccine errors being reported in NaTHNaC Annual Return reports for 2021 and 2022 provide evidence to support that a standardised YF pre-vaccination checklist is a useful and effective tool to help an HCP appropriately evaluate individual risk-benefit balance during the travel consultation. This also echoes with the positive comments given by most of the HCPs on the standardised YF pre-

vaccination checklists in our survey. Therefore, we conclude that the local aRMMs are sufficient to ensure safe administration of STAMARIL in the UK.