REPORT N°1

ADVERSE EVENTS FOLLOWING IMMUNIZATION WITH ORAL CHOLERA VACCINES IN LEBANON

Phase I: November 12, 2022 – December 7, 2022

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Abbreviations

AAH: Action Against Hunger

AEFI: Adverse Evet Following Immunization

DPNA: Development for People and Nature Association

ER: Emergency Room

ICRC: International Committee of the Red Cross

IMC: International Medical Corps

IOCC: International Orthodox Christian Charities

IOM: International Organization for Migration

LMIC: Low- and Middle-Income Countries

LNPVP: Lebanese National Pharmacovigilance Program

LRC: Lebanese Red Cross

MoPH: Ministry of Public Health

MSF: Médecins Sans Frontières

NGO: Non-Governmental Organizations

NRC: Norwegian Refugee Council

OCV: Oral Cholera Vaccine

ORS: Oral Rehydration Salts

ORT: Oral Rehydration Therapy

PT: Preferred Term

SC: Save the Children

SI: Solidarités International

SOC: System Organ Class

SOP: Standard Operating Procedure

UN: United Nations

UNHCR: United Nations High Commissioner for Refugees

WHO: World Health Organization

WVI: World Vision International

Executive Summary

Cholera is an acute diarrheal infection caused by the ingestion of food or drinks contaminated by the bacterium *Vibrio cholerae*. It is associated with acute watery diarrhea which can lead to dehydration and death if left untreated[1].

On October 6th 2022, Lebanon recorded its first confirmed case of cholera since 1993. The outbreak spread across eight governorates and 19 out of the 26 districts in Lebanon[2]. The number of the suspected cases gradually increased across all affected areas, to reach 4,966 cases and 23 deaths by the end of the period covered by this report (December 7th, 2022). In response, a multi-sectorial work plan was developed in collaboration with all relevant partners to contain the outbreak[2]. A collaboration between the World Health Organization, the United Nations High Commissioner for Refugees, the Ministry of Public Health, and their partners was initiated to manage and coordinate the cholera response[3].

As a result, the foundations for Phase I deployment were set with 13,440 doses of Shanchol® Oral Cholera Vaccine (OCV), entirely administered to their target population (prisoners and healthcare workers), and 600,000 doses of OCV Euvichol-Plus® out of which 479,679 doses have been administered[4]. The Lebanese National Pharmacovigilance Program (LNPVP) with its aim to ensure patient and medication safety was the main entity concerned with monitoring and evaluating Adverse Events Following Immunization (AEFIs) with OCVs during Phase I of the campaign.

This report provides an overview of the AEFIs that were temporally associated (i.e., occurred after administration of the vaccine) to the OCV Euvichol-Plus® available in Lebanon during Phase I of the national immunization campaign and deployed between November 12th, 2022, and December 7th, 2022.

The objective of this report is to document serious and non-serious AEFIs caused by the OCV Euvichol-Plus®. It aims to:

- Estimate the rate of AEFIs among people receiving OCV
- Rapidly respond to vaccine safety concerns
- Identify risk factors for specific AEFIs in people having received the OCV
- Monitor trends in known AEFIs

Highlights

A total of 22 case reports and 50 AEFIs were received by the LNPVP following the administration of 479,679 doses of OCV Euvichol-Plus® in Lebanon during Phase I of the OCV vaccination campaign between the 12th of November 2022 and the 7th of December 2022: (Table 1)

- This is equivalent to a reporting rate of 0.046 case reports and 0.104 AEFIs per 1,000 doses administered
- The age group of vaccine recipients who mostly reported AEFIs was between 2 and 11 years old (40.9%), with females reporting more than males (54.5% vs.45.5%) (Tables 3 and 4)
- Most of the reports were received through the OCV hotline 1787 (50.0 %) (Table 2)
- Only 5 case reports (22.7%) were classified as serious as per the WHO seriousness classification criteria (Table 7)
- Most of the reported AEFIs, 17 AEFIs (77.3% of the total AEFIs), belonged to the "Gastrointestinal Disorders" System Organ Class (Table 5) with abdominal pain (10 AEFIs, 45.5%) being the most reported AEFI (Table 6).

1. Background

1.1. Cholera Overview

Cholera is an acute intestinal infection caused by the ingestion of food or water contaminated with toxigenic serogroups of the bacterium *Vibrio cholerae*. The hallmark of the disease is profuse secretory diarrhea, which can lead to dehydration and even death if untreated [5].

Historically, devastating outbreaks of cholera resulted in millions of cases and hundreds of thousands of deaths. Currently, despite all the major advances in research, the condition is still a global threat to public health occurring as an endemic disease in some regions and is causing major epidemics in some Low- and Middle-Income Countries (LMICs)[6] lead by Nigeria, Niger, India and Bangladesh[7].

1.1.1. Transmission

Cholera is transmitted by the fecal-oral route. It has two main reservoirs, humans and water.

V cholerae is a saltwater organism, and its primary habitat is the marine ecosystem. Primary infection in humans is incidentally acquired. Risk of primary infection is facilitated by seasonal increases in the number of organisms. Secondary transmission occurs through fecal-oral spread of the organism through person-to-person contact or through contaminated water and food. Infection rates predictably are highest in communities in which water is not potable and personal and community hygiene standards are low[8].

1.1.2. Pathophysiology

Although more than 200 serogroups of *V cholerae* have been identified, *V cholerae* O1 and *V cholerae* O139 are the principal ones associated with epidemic cholera. Both serogroups cause clinical disease by producing an enterotoxin that promotes the secretion of fluid and electrolytes into the lumen of the small intestine, through the feces and vomitus[9].

1.1.3. Symptoms

Most *Vibrio cholerae* infections are asymptomatic; mild to moderate diarrhea due to *V cholerae* infection may not be clinically distinguishable from other causes of gastroenteritis.

Symptoms of cholera can begin as soon as a few hours or as long as five days after infection. Most infected people do not develop any symptoms, although the bacteria are present in their feces for 1-10 days after infection, which could increase risk of infectiosity[1].

Among people who develop symptoms, the majority have mild or moderate symptoms. Approximately 1 in 20 people infected have severe watery diarrhea accompanied by vomiting, which can quickly lead to dehydration. Patients with severe disease may present with a stool of an opaque white color that is not malodorous and often is described as having a "rice water" appearance.

If not promptly treated, the severe dehydration and associated complications such as renal failure, shock, hypokalemia, and pulmonary oedema can lead to death within hours. Signs and symptoms of dehydration include: rapid heart rate, loss of skin elasticity (the ability to return to original position quickly if pinched), dry mucous membranes(including the inside lining of the mouth, throat, nose, and eyelids), low blood pressure, and muscle cramps[9].

1.1.4. Diagnosis

According to World Health Organization (WHO) standard case definition, a case of cholera is suspected when the following conditions are met[10]:

- Suspected case: in areas where a cholera outbreak has not been declared: any person aged two years and older presenting with acute watery diarrhea (AWD) and severe dehydration or dying from AWD; once a cholera outbreak has been declared: any person presenting with or dying from AWD.
- Confirmed case: A suspected case with *Vibrio cholerae* O1 or O139 confirmed by culture or Polymerase Chain Reaction (PCR) and, in countries where cholera is not present or has been eliminated, the *Vibrio cholerae* O1 or O139 strain is demonstrated to be toxigenic

Isolation of *V. cholerae* from fecal samples remains the gold standard for confirmation of cholera diagnosis. A positive culture test from several patients is required for outbreak confirmation. More

accurate techniques such as PCR methods are becoming available for cholera confirmation, but require enhanced laboratory capacity. Additionally, detection can be facilitated using Rapid Diagnostic Tests (RDTs), where one or more positive samples triggers a cholera alert. This means of diagnosis offers point-of-care diagnostic options, especially in the absence of skilled personnel[5].
In Lebanon, Ministerial Decision Number 41 describing the cholera management process decrees that diagnosis is done through RDTs, or referral to the nearest reference hospital in case of absence of the tests[11].

1.1.5. Treatment

Cholera is an easily treatable disease. If patients have access to appropriate care, the case fatality rate is greatly reduced. Rapid rehydration constitutes the primary treatment for cholera, either through Oral Rehydration Therapy (ORT), or the administration of Intravenous (IV) fluids preferably Ringer's Lactate Solution to replace fluids and electrolytes in severe cases. Patients with mild or moderate dehydration are usually treated with Oral Rehydration Salts (ORS). Rehydration can be lifesaving but it has no effect on the duration of the disease or excretion of bacteria in feces.
For children under the age of 5, Zinc is an important adjunctive therapy to reduce the duration of diarrhea, and potentially prevent future episodes of other causes of acute watery diarrhea.
Mass administration of antibiotics is not recommended, as it has no proven effect on the spread of cholera and may contribute to antimicrobial resistance[1,6].
In Lebanon, treatment guidelines abide by the international standards where the specified appropriate course of action is based on the symptoms: the volume of administered ORS is increased with signs of dehydration. More severe cases are given Ringer Lactate IV drips and antibiotics regimens[12].

1.1.6. Prevention and Control

A multifaceted approach is key to control cholera. A combination of hygienic and treatment measures remains the mainstay of prevention of both endemic cholera and cholera outbreaks.
Improving access to clean potable water, adequate sanitation, and promotion of good WAter, Sanitation and Hygiene (WaSH) practices are indicated. Also important for cholera prevention is

the enforcement of standard sanitation laws for food industries. Proper case management is additionally vital in reducing mortality from the disease and limiting its spread.

Details about the prevention and control plans in Lebanon can be found in Ministerial Decision number 41[11].

On the other hand, cholera vaccination is a complementary cholera prevention measure, which can be implemented in the short-to-medium term.

1.1.7. Epidemiology

Cholera first emerged from its original reservoir in India during the 19th century. Six subsequent pandemics spread across the world to kill millions of people across all continents[1].

Cholera is now endemic in many countries. After a long hiatus, a seventh cholera pandemic spread in 1961, then subsided in the 1970s but continues today on a smaller scale. Outbreaks occur across the developing world to the current day[9].

Cholera continues to be a significant problem globally, with large epidemics, such as those experienced in Haiti and Yemen, and surges in endemic disease in areas of sub-Saharan Africa and Asia. While epidemic cholera attracts attention and accounts for most of the cases reported to WHO each year, endemic cholera continues to be present in large parts of sub-Saharan Africa, south and south-east Asia, as well as Haiti[1].

An estimated 2.86 million cholera cases (uncertainty range 1.3 m – 4.0 m) occur annually in endemic countries. The spatial distribution of cholera cases is highly heterogeneous. Systematic reviews have shown the wide variation of cholera epidemiology across the world[13].

Almost every developing country in the world faces cholera outbreaks or the threat of a cholera epidemic. Specifically, the Eastern Mediterranean Region (EMR) continued to experience recurring cholera outbreaks in the last two decades and it is becoming a major public health threat to the region with increased social and economic consequences[9].

After decades without a single case of cholera, outbreaks declared in Syria and Lebanon marked an unwelcome comeback. On 10 September 2022, the Syrian Ministry of Health (MoH) declared an outbreak of cholera in Aleppo Governorate following 15 confirmed laboratory cases, including one death[14]. This is part of a worsening pattern across the region, and the globe, as 8 of the 22

countries in the EMR are facing outbreaks of cholera and acute watery diarrhea; these include Lebanon, Syria, Pakistan, Somalia, Iraq, Yemen, Afghanistan, and the Islamic Republic of Iran[15].

Nationally, cholera has returned to Lebanon after almost a 3-decade hiatus. An outbreak was declared on the 6th of October 2022, the first since 1993, after a person residing in an informal settlement in Akkar was admitted to Halba Governmental Hospital and presented with dehydration and clinically reported rice-water diarrhea. Further investigations revealed more positive cases in the same settlement, and water samples returned positive for *V cholerae*[16].

Amid a worldwide spike in cholera infections, the outbreak in Lebanon was evolving at an alarming rate. From the date of declaration of the epidemic in October, the suspected and confirmed cases count increased exponentially from 239 to 4,966 reported cases along with a total of 23 associated deaths, resulting in a case fatality ratio of 0.46%[2]. Overall, 21% of the confirmed cases have required hospitalization, to occupy an average of 50 hospital beds for cholera treatment[17].

So far, 53% of the suspected and confirmed cases were reported among females, and 47% among males. Around 45% of the confirmed patients are less than 15 years of age, 15% are between 15 and 24 years of age, 22% are between 25 to 44 years of age, 11% are between 45-64 and 7% are aged 65 years and older. The Caza of Akkar, Minieh-Dennieh, Tripoli, Baalbeck, Keserwan, Zahle, Zgharta, Baabda, Saida and Metn were affected so far (Figure 1).

1.1.8. Multi-Sectorial Response to the Cholera Outbreak

A timely and well-coordinated response among all stakeholders[3] was promptly implemented to control the outbreak and curb the further spread of cases and deaths within the affected area[15].

- Surveillance of suspected cholera cases at the community level and the primary health care centers was carried out by the United Nations High Commissioner for Refugees (UNHCR), International Organization for Migration (IOM), AMEL, International Medical Corps (IMC), and the International Orthodox Christian Charities (IOCC).
- The OCV campaign was supported by UNHCR for operational cost and coordination and carried out by MEDAIR, AMEL, Lebanese Red Cross (LRC), and Médecins Sans Frontières (MSF) Swiss and Belgium. In addition, UNICEF provided technical support to MoPH on planning and implementation of the OCV campaign.

- Community support through a full-scale cholera WaSH response was conducted by UNICEF with its partners Action Against Hunger (AAH), Development for People and Nature Association (DPNA), LebRelief, LOST, SAWA, Save the Children (SC), Solidarités International (SI), and World Vision International (WVI), as well as Oxfam and Norwegian Refugee Council (NRC).

The WHO worked closely with the MoPH, providing technical guidance to ensure proper clinical management practices, infection prevention, control, and cholera testing protocols are in place. WHO's response has been also extended to include supplying life-saving treatment kits and medicines and raising awareness among healthcare workers and populations on prevention protocols. Clinical care guidelines and SOPs have been disseminated to referral hospitals, Primary HealthCare Centers (PHCs) and other frontline health workers. Training sessions on surveillance and reporting were also undertaken for staff in hospitals, health facilities, medical centers, and NGOs at all levels[16].

Additionally, Sanofi donated to the Ministry of Public Health 13,440 doses of Shanchol® targeting prisoners and healthcare workers, and WHO supported the Ministry with 600,000 doses of cholera vaccine for the most vulnerable populations, including frontline workers, prisoners, refugees and their host communities[4]. Also, two reference laboratories, three prisons and 12 hospitals designated for cholera treatment with laboratory reagents, treatment kits and rapid diagnostic tests, and deployed nurses and doctors to surge capacity in hospitals in the most affected areas[3].

The MoPH has developed the Lebanon Cholera Preparedness and Response Strategic Plan and Operational Plan under the overall coordinating and advising role of the WHO as lead in the Health Emergency response. On behalf of the Government of Lebanon, the MoPH is leading the overall response to the outbreak. The Minister of Public Health issued and chaired a national Task Force that convenes twice a week and gathers representatives from the different stakeholders involved. These include departments within the MoPH, other involved Ministries, the Lebanese Red Cross (LRC), the International Committee of the Red Cross (ICRC), and representatives from the United Nations (UN) agencies and Non-Governmental Organizations (NGO) partners[16].

The MoPH continues to lead the overall guidance of the response with cross-sectional coordination with the involved stakeholders[3].

1.1.9. Lebanese National Pharmacovigilance Program Response to the Cholera Outbreak

To ensure safety, any vaccine-related adverse event should be detected, assessed, and actions should be taken to prevent their occurrence and reduce their harm on the vaccine recipients. This is the role of pharmacovigilance. As part of the MoPH response to the outbreak, the LNPVP undertook the responsibility of AEFIs surveillance following the deployment of the OCV.

The LNPVP was appointed to detect and document AEFIs caused by the OCV. The responsibilities charged to the LNPVP are as follows:

- Ensure that monitoring of AEFI with OCV is part of the immunization campaign
- Define the methods of reporting of AEFIs associated with the OCV vaccination campaign
- Prepare a case management plan
- Conduct an AEFI causality review when required
- Investigate reports of serious AEFIs to decide on the causality of the reaction to the OCV
- Prepare a final report on the reported AEFIs with OCV.

A reporting form adapted to the OCV in Arabic and English (ANNEX 1) was disseminated to all relevant channels. New and existing reporting tools specific to the OCV were promoted by the LNPVP since the initiation of the vaccination campaign. These tools includes 1787 Hotline call center and the LNPVP landline (01-830254), and the KoboToolbox AEFIs reporting Software for healthcare professionals and hospitals[18].

Received reports are managed by the LNPVP through the regular AEFI handling protocol that was put in place. Patient follow-up, data cleaning and validation, and data entry to VigiFlow (a web-based PV management system), are performed for each reported case. When the received case report falls under the WHO seriousness classification criteria, an additional investigation step and causality assessment are performed to confirm or reject the causal relationship of the reported event with the OCV. As a final communication effort, the received cases are aggregated in a report set to be a regular release, the first issue of which is the present document.

1.2. Vaccine Overview

Three OCVs are currently pre-qualified by WHO[19]:

- Dukoral® is a vaccine used mainly by travelers. It includes inactivated whole cells and a component of the cholera toxin
- Shanchol® and Euvichol-Plus®, which contain only inactivated whole cells.

All three vaccines have usually a two-dose regimen with a two weeks' interval between the two doses (three doses for Dukoral® in children aged 2–5 years). However, the WHO set out to temporarily suspend of the standard two-dose vaccination regimen and replace it with a single dose due to vaccine shortages and rising outbreaks worldwide[20].

All three listed OCVs have a good safety profile. Shanchol® and Euvichol-Plus® have the same formulation with comparable safety and immunogenicity profiles and are considered as reformulated versions of Dukoral®. Unlike Dukoral®, Shanchol® and Euvichol-Plus® does not require a buffer to be administered[21].

Shanchol® and Euvichol-Plus® are the vaccines currently available for the mass vaccination campaigns through the Global OCV Stockpile. More than 20 million doses of OCVs have been used in mass vaccination campaigns. The campaigns have been implemented in areas experiencing an outbreak, in areas at heightened vulnerability during humanitarian crises, and among populations living in highly endemic areas, known as "hotspots"[19].

In Lebanon, the OCV vaccination campaign was initiated on November 12th, 2022 as part of the outbreak mitigation efforts. The aim of the campaign was to restrain the spread of cholera in Lebanon particularly among prisoners and vulnerable populations (refugees and hosting community) living in areas identified as hotspot areas with confirmed cases. The first campaign was considered as Phase I which was between the period of November 12th till December 7th. It targeted 600,000 doses of the Euvichol-Plus® OCV supplied by the WHO. The aim of Phase I was to reduce morbidity and mortality, break the chain of transmission to limit the outbreak, and to reduce the strain on the health system by reducing the need for hospitalization. UNHCR is

providing ongoing support for operational cost and coordination for the OCV campaign in partnership with MEDAIR, AMEL, LRC, and MSF Swiss and Belgium.

Until the 7th of December, i.e. throughout the totality of Phase I of the national cholera vaccination campaign, a total of 479,679 OCV doses have been administered in Lebanon. As part of phase II planning of this campaign, WHO is supporting the MoPH to complete a second application for an additional two million doses of OCV to cover 19 districts at the national level[3,17]. (Figure 1)

Since the LNPVP only received reports of adverse reactions resulting from Euvichol-Plus® which was the main vaccine administered during Phase I, the following section will be concerned with this specific OCV, knowing that Shanchol® was also deployed in a pre-Phase I stage targeting specific populations (prisoners and healthcare workers).

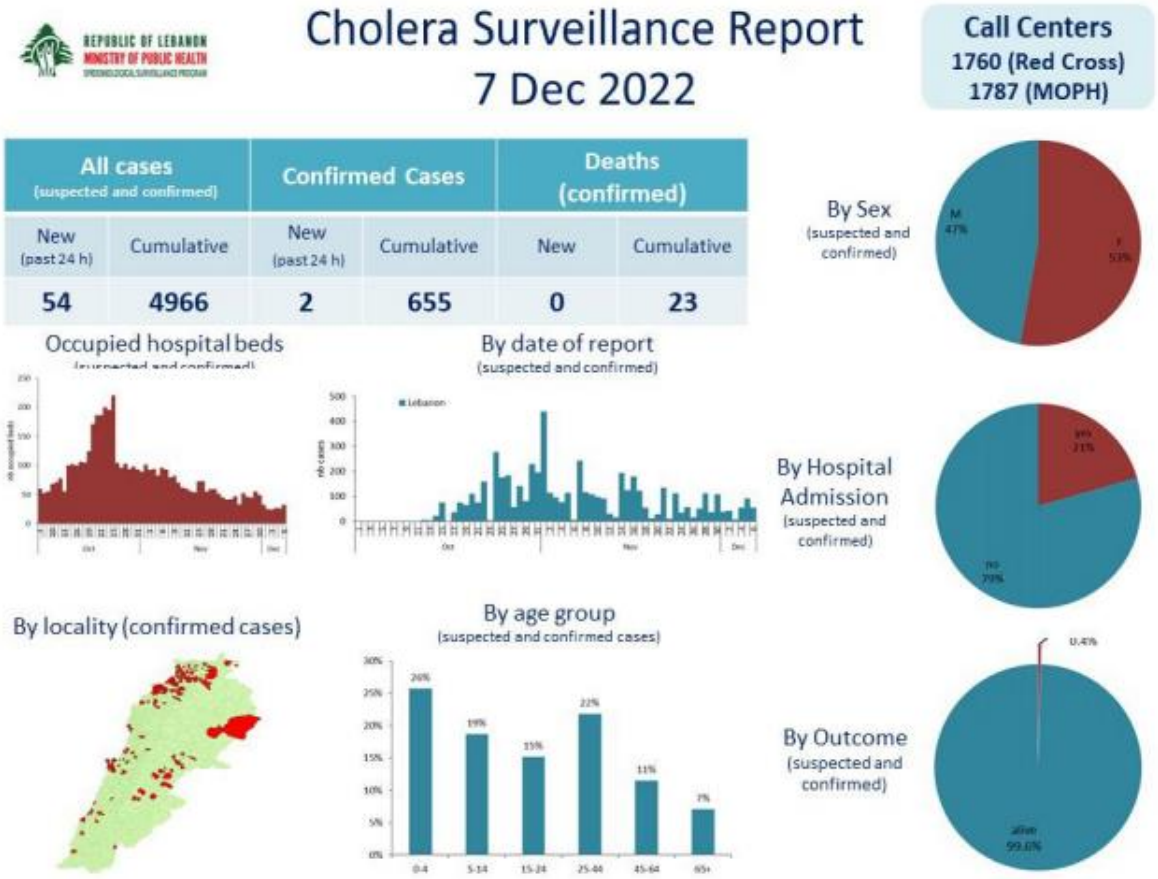

Figure 1: MoPH Cholera Surveillance Report, 7 December 2022

1.2.1. Euvichol-Plus® Overview

Euvichol-Plus® is indicated for active immunization against *Vibrio cholerae*. It is a liquid formulation (1.5 mL mono-dose) of Oral Cholera Vaccine containing O1 and O139 of *Vibrio cholerae* inactivated by heat or formalin. The vaccine should be administered orally to anyone above the age of 1 year. However, it should not be administered to persons with either known hypersensitivity to any component of the vaccine, or having shown signs of severe reaction due to the previously taken dose. No specific clinical studies have been conducted to evaluate the efficacy and safety of Euvichol-Plus® in pregnant and lactating women, nor in infants (less than 1 year of age). Therefore, the vaccine is not recommended for use in these populations[22].

1.2.2. Euvichol-Plus® Safety Profile

Overall, Euvichol-Plus® has a good safety profile. In a clinical study conducted to evaluate the safety of the vaccine, only 102 (3.40 %) out of 2,999 enrolled subjects reported AEFIs during the first 7 days. The most frequent reported AEFIs included headache, fever, diarrhea, nausea/vomiting, and myalgia. While after 28 days, 69 subjects (2.30 %) reported adverse events where gastrointestinal disorders including diarrhea, abdominal pain, and vomiting were the most frequently reported AEFIs. No serious adverse events were reported during the clinical trial period[22].

Figure 2: Euvichol-Plus®

2. Cholera Surveillance in Lebanon

2.1. Reporting Overview

Within the scope of the AEFIs surveillance related to the deployed OCVs in Lebanon, the LNPVP established a multi-step protocol for the management of the reported AEFIs. Vaccine recipients experiencing any AEFIs can report through one of the following means: 1787 Hotline Call Center, "KoboToolbox: AEFIs Software for reporting", or by direct contact with the PV program through the available landline (01-830254). All received case reports are screened and validated for data completion and accuracy. Direct follow-up with the reporters is initiated in the aim of retrieving all relevant information to properly complete the case narrative. The case reports are then classified as serious or non-serious cases, as per the WHO seriousness criteria. Each category will be handled following a specific protocol developed by the LNPVP, as detailed in the following sections.

The non-serious case reports are entered directly into VigiFlow after being validated and cleaned, while serious cases go through investigation and causality assessment before they are entered into VigiFlow. The surveillance aims to establish a rigorous safety profile regarding the cholera vaccine administered in Lebanon.

Between November 12th and December 7th 2022, the LNPVP has managed 22 cases associated with 50 AEFIs following the immunization with the OCV: Euvichol-Plus®.

An Adverse Event Following Immunization (AEFI) is defined as any untoward medical event that follows immunization and that does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease[23]. It is important to note that a given case report can include more than one AEFI.

Table 1 details the 22 case reports that have been received and completed since the initiation of Phase I of the cholera national immunization campaign on the 12th of November 2022, till its end on December 7th 2022.

Table 1: *Overview of the 22 case reports following immunization with Euvichol-Plus®, from November 12th, 2022, till December 7th, 2022*

	Patient Details					Vaccine Details			AEFI Details							
Code	Initials	Gender	Age (years)	Nationality	Case Sent By	Vaccine Name	Vaccination date	Dose	AEFI	Date of onset of AEFI	Time interval between vaccine and AEFI (days)	Seriousness	Date of outcome	Updated outcome	Date of updated outcome	Narrative text/ Special consideration
OCV01	MKB	Male	3	Lebanese	Hotline (1787)	Euvichol-Plus	12/11/2022	1st and 2nd	Overdose	-	-	Non-Serious	-	Recovered	16/11/2022	MKB is a 3 year old boy who received the dose of Euvichol-Plus on 12/11/2022. No symptoms were reported. The following day, 13/11/2022, the child was at his grandparents house, a second dose of OCV (Euvichol-Plus) was given to him, the grandparents were not aware that the child already received a dose and the team gave the dose before registering the patient on the system. The uncle AMK reached out to the Pharmacovigilance Team. Follow up was conducted on 14/11/2022. No symptoms were reported. Another follow up was conducted on 16/11/2022, no symptoms were reported. The child is doing good.
OCV02	AAA	Female	4	Syrian	Hotline (1787)	Euvichol-Plus	14/11/2022	1st	Nausea, vomiting abdominal pain tiredness fever	14/11/2022	0	Non-Serious	14/11/2022	Recovered	17/11/2022	AASA is a 4 year old girl who received the dose of OCV Euvichol-Plus on14/11/2022. Father of the patient reported that his daughter started having symptoms of fever, shortness of breath and tiredness (the onset of symptoms was not specified). Patient was treated with cold compresses and anti-inflammatory medications. Note: The father of the patient was not cooperative. He affiremed that he cannot afford to take his daughter to the primary healthcare center.
OCV03	NS	Male	26	Lebanese	Landline	Euvichol-Plus	21/11/2022	1st	Tachycardia Paresthesia of limbs Dizziness	21/11/2022	5 mins	Non-Serious	21/11/2022	Recovered	23/11/2022	NS is a 26 year old male who experienced tachycardia, paresthesia of the limbs, and dizziness 5 mins after receiving his 1st dose of OCV on the 21st of November 2022. On the same day, the patient went to his doctor and he told him it is an anxiety related reaction. The patient was recovered on the same day.
OCV04	IMA	Female	7	Syrian	KoboToolbox	Euvichol-Plus	17/11/2022	1st	Diarrhea abdominal Cramps	19/11/2022	2	Non-Serious	19/11/2022	Recovered	23/11/2022	IMA is a 7 year old female who received her 1st dose of OCV on 17/11/2022. Noting that, the patient was having a diarrhea and abdominal pain for 2 days pre-vaccination. On 19/11/2022, 2 days after vaccination, the patient had exagerrated diarrhea and abdominal pain that got recovered on the next day (20/11/2022).
OCV05	MMA	Female	11	Syrian	Landline	Euvichol-Plus	17/11/2023	1st	Abdominal Pain	19/11/2022	2	Non-Serious	19/11/2022	Recovered	23/11/2022	MMA is an 11 year old female who received her 1st dose of OCV on 17/11/2022. On 19/11/2022, 2 days after vaccination, the patient had abdominal pain that got recovered on the next day (20/11/2022).

	Patient Details					Vaccine Details			AEFI Details							
Code	Initials	Gender	Age (years)	Nationality	Case Sent By	Vaccine Name	Vaccination date	Dose	AEFI	Date of onset of AEFI	Time interval between vaccine and AEFI (days)	Seriousness	Date of outcome	Updated outcome	Date of updated outcome	Narrative text/ Special consideration
OCV06	MA	Male	49	Syrian	Landline	Euvichol-Plus	17/11/2022	1st	Abdominal Pain	19/11/2022	2	Non-Serious	19/11/2022	Recovered	23/11/2022	MAA is a 49 year old male who received his 1st dose of OCV on 17/11/2022. On 19/11/2022, 2 days after vaccination, the patient had abdominal pain that got recovered on the next day (20/11/2022).
OCV07	NH	Female	49	Syrian	Landline	Euvichol-Plus	17/11/2022	1st	Abdominal Pain	19/11/2022	2	Non-Serious	19/11/2022	Recovered	23/11/2022	NH is a 49 year old female who received her 1st dose of OCV on 17/11/2022. On 19/11/2022, 2 days after vaccination, the patient had abdominal pain that got recovered on the next day (20/11/2022).
OCV08	KMA	Male	23	Syrian	Landline	Euvichol-Plus	17/11/2022	1st	Flu Like Symptoms Abdominal Pain	19/11/2022	2	Non-Serious	19/11/2022	Recovered	23/11/2022	KMA is a 23 year old male who received his 1st dose of OCV on 17/11/2022. On 19/11/2022, 2 days after vaccination, the patient had flue like symptoms and abdominal pain that got recovered on the next day (20/11/2022).
OCV09	AMA	Male	21	Syrian	Landline	Euvichol-Plus	17/11/2022	1st	Abdominal Pain	19/11/2022	2	Non-Serious	19/11/2022	Recovered	23/11/2022	AMA is an 21 year old male who received his 1st dose of OCV on 17/11/2022. On 19/11/2022, 2 days after vaccination, the patient had abdominal pain that got recovered on the next day (20/11/2022).
OCV10	MAA	Female	31	Syrian	Hotline (1787)	Euvichol-Plus	17/11/2022	1st	Ongoing Diarrhea Abdominal Cramps	18/11/2022	1	Non-Serious	19/11/2022	Recovered	13/12/2022	MAA is a 31 year old female who received her 1st dose of OCV on 17/11/2022. On the next day, on 18/11/2022, the patient experienced diarrhea and abdominal cramps. On 23/11/2022, a follow up with the patient was done and the reactions were ongoing. She was adviced to seek medical care. On the next day, the patient went to a PMC and they gave her ORS and other drugs (she doesn't know their names). She got recocvered on that day.

	Patient Details					Vaccine Details			AEFI Details							
Code	Initials	Gender	Age (years)	Nationality	Case Sent By	Vaccine Name	Vaccination date	Dose	AEFI	Date of onset of AEFI	Time interval between vaccine and AEFI (days)	Seriousness	Date of outcome	Updated outcome	Date of updated outcome	Narrative text/ Special consideration
OCV11	MGS	Female	43	Lebanese	Hotline (1787)	Euvichol-Plus	16/11/2022	1st	Headache Bitter Taste Epigastric Pain	18/11/2022	1	Non-Serious	18/11/2022	Recovered	24/11/2022	MGS is a 43 year old female who received her 1st dose of OCV on 16/11/2022. On 18/11/2022, 2 days after receiving the vaccine, the patient started to have headache, epigastric pain, and bitter taste. The patient took Gastrimut and she is recovering.
OCV12	RAM	Male	4	Syrian	Hotline (1787)	Euvichol-Plus	24/11/2022	1st	Fatigue Vomiting Abdominal Pain	26/11/2022	1	Non-Serious	29/11/2022	Recovered	28/11/2022	RAM is a 4 year old male who received his 1st dose of OCV on 24/11/2022. After 2 days, he started to have fatigue, vomiting and abdominal pain. He recovered on the next day.
OCV13	AAA	Male	7	Syrian	Landline	Euvichol-Plus	24/11/2022	1st	Fever Vomiting	25/11/2022	1	Non-Serious	29/11/2022	Recovered	28/11/2022	AAA is a 7 year old male who received his 1st dose of OCV on 24/11/2022. After 1 day, he started to have fatigue, vomiting, and abdominal pain. he recovered the next day.
OCV14	EAE	Female	51	Syrian	Landline	Euvichol-Plus	26/11/2022	1st	Fatigue Vomiting	25/11/2022	1	Non-Serious	29/11/2022	Recovered	28/11/2022	EAE is a 51 year old female who was vaccinated with her 1st of OCV vaccine on 25/11/2022. On the next day, she had fatigue and vomiting. Patient recovered.
OCV15	AHR	Female	2	Syrian	Hotline (1787)	Euvichol-Plus	27/11/2022	1st	Fever Vomiting Diarrhea (x3/day)	28/11/2022	1	Non-Serious	30/11/2022	Recovered	30/11/2022	One day after receiving the vaccine, the patient started to have fever, vomiting, and diarrhea. These symptoms lasted for few days and she recovered completely.
OCV16	ZHR	Female	9	Lebanese	Landline	Euvichol-Plus	27/11/2022	1st and 2nd	Overdose	28/11/2022	1	Non-Serious	28/11/2022	Recovered	12/12/2022	ZHR is a 9 year old female who received his 1st dose of Euvichol-Plus vaccine through a mobile clinic on 27/11/2022. On the next day after receiving the vaccine, while she was at school, a mobile clinic vaccinated her with the 2nd dose. So the patient took 2 doses in 2 consecutive days. Patient did not encounter any ADR.
OCV17	YAC	Male	8	Lebanese	Hotline (1787)	Euvichol-Plus	7/12/2022	1st	Fever Abdominal Pain Fatigue Nausea	Unknown	1	Unknown	Unknown	Unknown	Unknown	Unable to reach the patient due to wrong phone number

	Patient Details					Vaccine Details			AEFI Details							Assessment at LNPVC Level
Code	Initials	Gender	Age (years)	Nationality	Case Sent By	Vaccine Name	Vaccination date	Dose	AEFI	Date of onset of AEFI	Time interval between vaccine and AEFI (days)	Seriousness	Date of outcome	Updated outcome	Date of updated outcome	Narrative text/ Special consideration
OCVSC01	MK	Female	39	Lebanese	Hotline (1787)	Euvichol-Plus	Unknown	1st	Allergic reaction		0	Serious		Recovered	20/11/2022	MK is a 39 year old female that received her 1st dose of Euvichol-Plus Oral Cholera Vaccine on 13/11/2022 at 11:00 am. The same day at 4:00 p.m., she experienced ear pain, chills, fever (39C), and constipation. At night, patient expressed symptoms of angioedema. The next day on 14/11/2022, she reported her first symptoms to the nearest infirmary (Ausrati Governmental Clinic), and the treating physician prescribed Dexamethasone IM immediately. Patient was then discharged on Loratine (loratadine) tablets 2x/d. On the same day after taking the second tablet of Loratadine, the patient experienced flushing and a systemic rash with burning sensation namely in the genital area. MK reported her symptoms to the MoPH by calling 1787 hotline. The physician advised her to continue her treatment and to follow-up after 3 days (Nov 16 th 2022). On 16/11/2022, patient's symptoms started resolving, but the patient reported experiencing new symptoms of shortness of breath. On 17/11/2022, as per the physician's initial recommendation, the patient discontinued the Loratadine treatment but refrained from following up with her physician due to financial reasons.
OCVSC02	AEC	Male	14	Lebanese	Hotline (1787)	Euvichol-Plus	17/11/2022	1st	Vomiting Epigastric Pain Chills	18/11/2022	1	Serious - ER Visit	21/11/2022	Recovered	23/11/2022	AHE is a 14 year old male who was vaccinated with the 1st dose of OCV on 17/11/2022. On 18/11/2022, patient started experiencing severe vomiting. The vomiting persisted for several days, so on 21/11/2022, he was admitted to the ER. At the ER, CBC and Electrolytes tests were done and they revealed normal results. IV hydration was given and the patient got recovered and discharged with a prescription of ORS.
OCVSC03	TAF	Male	74		KOBO TOOL BOX	Euvichol-Plus	18/11/2022	1st	Severe Diarrhea	18/11/2022	0	Serious - ER Visit	18/11/2022	Recovered	19/11/2022	TSF is a 74 year old male who was vaccinated with his 1st dose of OCV on the 18th of November 2022. On the same day after few hours, the patient had severe diarrhea. His son transferred him the ER at Al Batoul and he was received the appropriate treatment. The patient started to feel better on the next day.

	Patient Details					Vaccine Details			AEFI Details							Assessment at LNPVC Level
Code	Initials	Gender	Age (years)	Nationality	Case Sent By	Vaccine Name	Vaccination date	Dose	AEFI	Date of onset of AEFI	Time interval between vaccine and AEFI (days)	Seriousness	Date of outcome	Updated outcome	Date of updated outcome	Narrative text/ Special consideration
OCVSC04	NZ	Female	78	Lebanese	Hotline (1787)	Euvichol-Plus	23/11/2022	1st	Cardiac Arrest	24/11/2022	1	Fatal	24/11/2022	Died	24/11/2022	NZ is a 78 year old female (weight: 60 kg, height: 155 cm) with a history of heart failure and arrhythmias maintained on Lasix 40mg, Concor 5mg, Lanoxin 0.25mg, and Aspirin 81mg. She was vaccinated with a 1st dose of Euvichol-Plus Oral Cholera Vaccine on 23/11/2022. On the same day at 4:00 p.m, she experienced diarrhea. The diarrhea was severe at the beginning, but later throughout the day, the severity decreased with a frequency of three times per day. The next day on 14/11/2022, the diarrhea persisted so her children decided to give her a hydration treatment. They contacted a nurse and she administered IV hydration with NaCl 0.9% and Vitamin B Complex Ampoule. The patient received 100 mL (over around 15 minutes) only of IV hydration before passing away. A cardiologist was contacted and he confirmed her death secondary to cardiac arrest on 24/11/2022.
OCVSC05	AHR	Male	14	Lebanese	Hotline (1787)	Euvichol-Plus	27/11/12022	st and 2n	Overdose Watery Diarrhea Vomiting Dehydration	28/11/2022	1	Serious - ER Visit	29/11/2022	Recovered	8/12/2022	AHR is a 14 year old male who received his 1st dose of Euvichol-Plus vaccine through a mobile clinic on the 27/11/2022. On the next day after receiving the vaccine, while he was at school, a mobile clinic vaccinated him with a 2nd dose. So the patient took two doses in two consecutive days. He immediatly started to have diarrhea and vomiting on the same day. The diarrhea was severe as he started to have dehydration, so he was given IV hydration treatment 5 times during the week. Patient was admitted to the ER and multiple primary healthcare centers. He did not recover, and a follow-up will be performed in the upcomming days. The patient was referred to Al Batoul PMC by the MoPH. 13/12/2022: Follow-up was performed by phone, the patient recovered.

2.1.1. Case Reports per Means of Reporting

Table 2 summarizes the received case reports by reporting means, which include: 1787 Hotline Call Center, "KoboToolbox: AEFIs Software for reporting", and the LNPVP landline.

Table 2: *Summary of case reports by means of reporting related to the OCV Euvichol-Plus®, for the period between November 12th, 2022, till December 7th, 2022*

Means of Reporting	Count N=22	Percentage
1787 Hotline Call Center	11	50%
Landline	9	40.9%
KoboToolbox AEFIs: AEFIs Software for Reporting	2	9.1%

The majority (50%) of case reports were reported through the hotline accounting for half of the received cases (11 cases), followed by the landline which received 9 cases (40.9%).
The 2 remaining cases were reported through the KoboToolbox: AEFIs Software for Reporting, which is specified for healthcare professionals present on field or any healthcare professional.

2.2. Demographics

All cases were reported by consumers i.e. non health professionals.

2.2.1. Case Reports per Gender

Table 3 summarizes the case reports by gender.

Table 3: Summary of case reports by gender related to the OCV Euvichol-Plus®, for the period between November 12th, 2022, till December 7th, 2022

Patient sex	Count N=22	Percentage
Female	12	54.5%
Male	10	45.5%

Out of the 18 received cases, 12 (54.5%) were female, while 10 (45.5%) were males.

2.2.2. Case Reports per Age Group

Table 4 summarizes the case reports by age group.

Table 4: Summary of case reports by age group related to the OCV Euvichol-Plus®, for the period between November 12th, 2022, till December 7th, 2022

Patient age	Count N=22	Percentage
2 - 11 years	9	40.9%
12 - 17 years	2	9.1%
18 - 44 years	6	27.3%
45 - 64 years	3	13.6%
65 - 78 years	2	9.1%

The majority (40.9%) of the cases were reported by patients between the ages of 2 and 11 years old with 9 patients, followed by the category between 18 and 44 years old with 6 patients (27.3%). Three cases (13.6%) were reported by patients between 45 and 64 years old, two (9.1%) by patients between 12 and 17 years old, and two (9.1%) between 65 and 78 years old.

2.3. Adverse Events Following Immunization Classification

Knowing that a case report may include multiple AEFIs, the following section is concerned with the 50 AEFIs that have resulted from the 22 reported case reports, which explains why the total count of AEFIs exceeds the total number of cases received.

When a report is entered into VigiFlow, the relevant Medical Dictionary for Regulatory Activities (MedDRA) terms are assigned to describe the adverse event and other medical terms as necessary. MedDRA is a medical terminology used to categorize information related to adverse events associated with the use of medical products including vaccines. MedDRA terms are classified into a hierarchy from System Organ Class (SOC) which includes the most general terms, to the Low-Level Terms (LLT) which consists of more specific terminologies[24].

2.3.1. Case Reports Related to the OCV: Euvichol-Plus® by System Organ Class

Table 5 summarizes the received case reports per SOC, which is the highest level of the MedDRA terminology, distinguished by anatomical or physiological system, etiology or purpose.

Table 5: Case reports by System Organ Class (SOC) related to the OCV Euvichol-Plus®, from November 12th, 2022, till December 7th, 2022

Reaction (MedDRA) (SOC)	Count* N= 22	Percentage
Gastrointestinal disorders	17	77.3%
General disorders and administration site conditions**	7	31.8%
Injury, poisoning and procedural complications	3	13.6%
Nervous system disorders	3	13.6%
Cardiac disorders	2	9.1%
Immune system disorders	1	4.5%
Metabolism and nutrition disorders	1	4.5%
Respiratory, thoracic and mediastinal disorders	1	4.5%
Skin and subcutaneous tissue disorders	1	4.5%

**One case report can contain more than one AEFI*
One case report can include AEFIs belonging to different SOCs
***A class of disorders that encompasses conditions of a general kind that result from a disease, the treatment of disease or administration of treatment at a particular site and are manifested by a characteristic set of symptoms and signs*[25]

The reported reactions spanned a total of nine SOCs. Gastrointestinal disorder was the SOC associated with most reactions, accounting for 17 out of the 22 case reports (77.3% of the received cases). These findings are consistent with Euvichol-Plus® safety profile[22].

The second most reported SOC was the General disorders and administration site conditions, which accounted for 7 case reports (31.8%). This was followed by both the Injury, poisoning and procedural complications SOC and the Nervous system disorders SOCs, each of which accounted for three (13.6%) of the total received case reports.

2.3.2. Reported AEFIs Related to the OCV: Euvichol-Plus® by Preferred Term

Table 6 summarizes the AEFIs by their Preferred Term (PT), which is the second most specific level in the MedDRA hierarchy, and that is a distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, indication, investigation, surgical or medical procedure, and medical social or family history characteristic[24].

To note, a given case report can contain multiple AEFIs i.e. multiple PTs.

Table 6: AEFIs by reported Preferred Terms (PTs) related to the OCV Euvichol-Plus®, from November 12th, 2022, till December 7th, 2022

Reported preferred terms (MedDRA) (PT)	Count* N= 50	Percentage
Abdominal pain	10	45.5%
Vomiting	7	31.8%
Diarrhea	5	22.7%
Fatigue	4	18.2%
Pyrexia	4	18.2%
Overdose	3	13.6%
Abdominal pain upper	2	9.1%
Nausea	2	9.1%
Angioedema	1	4.5%
Burning sensation	1	4.5%
Cardiac arrest	1	4.5%
Dehydration	1	4.5%
Dizziness	1	4.5%
Dysgeusia	1	4.5%
Dyspnea	1	4.5%
Headache	1	4.5%
Hypersensitivity	1	4.5%
Influenza like illness	1	4.5%
Paraesthesia	1	4.5%
Rash	1	4.5%
Tachycardia	1	4.5%

**One case report can contain more than one AEFI*

The most reported reaction following immunization with Euvichol-Plus® was abdominal pain, accounting for 10 AEFIs (45.5% of the received case reports), followed by vomiting which accounted for 7 AEFIs (31.8%), and thirdly diarrhea which accounted for 5 AEFIs (22.7%). These findings are consistent with the

safety profile of Euvichol-Plus® , stating that gastrointestinal disorders are the most commonly encountered reactions following OCVs[22].

To note that three out of the 22 received case reports resulted from immunization errors, where the recipients accidentally received two doses of the OCV in two consecutive days. One case was associated to severe dehydration and recovered (case OCVSC05, Table 1), while the other two cases had no associated adverse events (cases OCV01 and OCV16, Table 1).

2.4. Serious Adverse Events Following Immunization

According to the WHO, a serious AEFI is an event that results in death, hospitalization, or prolongation of an existing hospitalization, persistent or significant disability or incapacity, congenital anomaly/birth, defect or is life-threatening[23].

Table 7 summarizes the received cases by seriousness criteria.

Table 7: Summary of case reports by seriousness

Seriousness	Count	Percentage
Yes	5	22.7%
No	17	77.3%
Total	22	100.0%

Out of the 22 received cases, 5 (22.7%) cases were classified as serious since they all required ER visit to manage their AEFI, while the remaining 17 cases (77.3%) were non-serious.

2.4.1. Handling of Serious AEFIs

Figure 3: Handling of serious case reports in the context of Oral Cholera Vaccines

The serious case reports undergo a longer process before they are entered into the central database (Figure 3).

AEFIs are classified as serious according to the seriousness criteria of WHO. These cases either require a phone call only or an investigation followed by a causality assessment to evaluate the potential relationship between the AEFI and the vaccine and to implement the appropriate follow-up actions. The investigation is carried out by the PV team members. It includes an extensive and rigorous scientific evaluation based on available information about the vaccination process, the patient's medical records, laboratory results, and information retrieved from the recipient or his/her relatives. After collecting all the available information, the investigation report is filled, and a causality assessment is performed to review the potential causal association between the AEFI and the vaccine. WHO forms and tools are used to carry out both the investigation and the causality assessment[26]. In the period of time covered by this report, there were 5 case reports classified as serious per the WHO-UMC definition that resulted in either hospitalization or death, representing 22.2% of all case reports.

The case is classified as coincidental, indeterminate, or consistent (Table 8).

*Table 8: Causality assessment classification**

A. Consistent causal association to immunization	B. Indeterminate	C. Coincidental causal association to immunization
1. Vaccine product-related reaction 2. Vaccine quality defect-related reaction 3. Immunization error-related reaction 4. Immunization anxiety-related reaction	1. Consistent temporal relationship but insufficient evidence for causality 2. Conflicting trends of consistency and inconsistency with causality	1. Underlying or emerging condition(s), or condition(s) caused by exposure to something other than the vaccine

**Retrieved from the Global manual on surveillance of adverse events following immunization by the WHO*[23]

The annexed (ANNEX I) serious case provides an example on the process.

2.4.2. Overview of Serious AEFIs

In the period covered by this report, the LNPVP has received a total of 5 serious cases (Table 7). Table 9 summarizes those five cases by patient details, medical history, AEFI details, and performed assessments. To note that while the LNPVP followed-up, assessed and validated all five cases, investigation was only initiated to two out of the five conditions (case 1 and case 4). This decision was made after the full recovery that patients 2, 3 and 5 made promptly after their release from the ER.

Table 9: Summary of the reported serious cases

Serious case		Case 1	Case 2	Case 3	Case 4	Case 5
Patient details	Gender	Female	Male	Male	Female	Male
	Age (years)	39	14	74	78	14
	Means of reporting	Hotline	Hotline	KoboToolbox by the mobile clinic	Hotline	Hotline
Medical history	Previous intervention	-	-	Myocardial Infarction	Hospitalization due to Pneumonia 6 months pre-vaccination	-
	Underlying condition	-	-	Dyslipidemia Hypertension Myocardial Infarction	Heart Failure Arrythmias	-
	Concomitant medication	-	-	Concor Simvastatin Ribavan	Lasix 40 mg 1 tab per day Aspirin mg 81 1 tab per day Concor 5 mg 1 tab per day	-

					Lanoxin 0.25 mg 1 tab per day	
AEFI details	**AEFI**	Allergic reaction	Vomiting Epigastric Pain Chills	Severe Diarrhea	Cardiac Arrest	Overdose Watery diarrhea Vomiting Dehydration
	Date of onset	13/11/2022	18/11/2022	18/11/2022	24/11/2022	04/12/2022
	Time interval between vaccine and AEFI	5 hours	1 day	3 hours	1 day	1 day
	Seriousness	Serious - ER Visit	Serious - ER Visit	Serious – ER Visit	Serious-Fatal	Serious – ER visit
	Outcome	Recovered	Recovered	Recovered	Fatal	Recovered
Assess-ment	**Investigation**	Yes	No	No	Yes	No
	Causality assessment	Consistent	-	-	Coincidental	-

After completing the full investigation protocol, case 1, which is an allergic reaction following the OCV, was concluded to have a consistent causal association with the vaccine. Details of the investigation initiated for case 1 can be found in Annex I. Case 4 which was a fatal cardiac arrest, had a coincidental causal association to the vaccine since the patient 4 was an elderly patient with predisposing comorbid diseases. These findings were aligned with the final decision of the Serious AEFI Special Committee.
To note that case 5 resulted from an immunization error as signaled in section 2.3.2.

2.4.3. Serious AEFIs by Seriousness Criteria

Out of the 5 reported serious cases, 1 was resulted in death, while 4 were classified as other medically important conditions.

3. Conclusion

In Lebanon, from November 12th, 2022, till December 7th, 2022, 4,966 confirmed cholera cases have been reported, with 23 deaths declared to the MoPH.

Phase I of the national immunization campaign was first deployed on November 12th, 2022, with 600,000 doses of OCVs, and concluded on December 7th, 2022, the end date of this report. Euvichol-Plus® is the only cholera vaccine currently available in Lebanon. Until the date of this report, 479,679 doses have been administered to the initial target population.

In the period of time covered by this report, 77.3% of the cases reported were classified as non-serious, and 22.7% were classified as serious.

The Lebanese National Pharmacovigilance Program at the Ministry of Public Health is the reference entity of reporting concerned with AEFIs associated with OCVs. In collaboration with its partners, the PV team continues to conduct constant monitoring for the safety of the vaccines. Reporting of any encountered AEFI is highly encouraged to contain the outbreak and to reduce the strain on the health system.

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5. Annex I: AEFI Reporting Form for OCV

Reporter, patient & institution identities will remain confidential Questions with an asterisk (*) sign are mandatory				
1) Patient Details *				
Name (or initials)				
Address				
Phone				
Gender		□ Male	□ Female	□ Pregnant □ Lactating
Date of Birth		**Weight (kg):**		**Height (cm):**

2) History of chronic diseases*	□ No	□ Yes, specify:

3) Product(s) Details *

Health Facility / Vaccination Center Name & Address :

Brand Name of Vaccine	Manufacturer	Expiry Date	Batch Number	Dose Number	Date of Vaccination	Time of Vaccination

4) Adverse Event *

Suspected Adverse Event Following Immunization		Onset Date				Recovery Date (if applicable)			
		Time (Hr, Min)	Day	Month	Year	Time (Hr, Min)	Day	Month	Year
Abdominal Pain	□								
Diarrhea	□								
Nausea	□								
Vomiting	□								
Headache	□								
Loss of Appetite	□								
Tiredness	□								
Fever≥ 38°C	□								
Other/ Specify:									

Adverse Event Description / Case Narrative (Development, Symptoms, Management, etc.)

Relevant Laboratory and Diagnostic Tests Performed	Result	Date

Did the patient have a similar reaction to the same or other vaccines in any previous exposure? *

□ Yes/ Specify:	□ No	□Unknown

5) Seriousness of the Adverse Event *:	□ Yes			□ No	
If yes, specify if the Adverse Event led to:	□ Death	Date of death		□ Life Threatening Situation	
		Cause of death			
	□ Hospitalization			□ Prolongation of Hospitalization	Specify additional duration:
	□ Surgical Intervention			□ Congenital Anomaly	
	□ Persistent or Significant Disability or Incapacity			□ Other Serious Consequences	

6) Outcome of Adverse Event *				
Actual Status of Patient	□ **Recovered**			□ **No Improvement**
	□ **Recovered with Sequalae**	**Specify Sequalae**		□ **Fatal**
	□ **Is Recovering**			□ **Unknown**

7) Reporter *	
Name (or initials)	
Profession or Specialty	
Facility Name	
Email Address	
Phone Number	
Signature	
Date	

الأسئلة مع إشارة النجمة (*) هي إلزامية / المعلومات المتعلقة بالمرسل والمريض والمؤسسة سوف تظل سرية			
١- بيانات المريض *			
الاسم (أو الأحرف الأولى)			
العنوان			
الهاتف			
الجنس	□ ذكر	□ أنثى	□ حامل □ مُرضعة
تاريخ الولادة		**الوزن (كغ):**	**الطول (سم):**

٢- هل تعاني من أمراض مزمنة؟*	□ لا	□ نعم ، حدّد:

٣ - بيانات المستحضر*						
مركز التطعيم: إسم وعنوان المرفق الصحي/						
اسم اللقاح	**الشركة المصنعة**	**تاريخ انتهاء الصلاحية**	**رقم التشغيلة**	**الجرعة (الأولى، الثانية...)**	**تاريخ التطعيم**	**وقت التطعيم**

٤ - الحادث الجانبي *									
التابع للتطعيم المشتبه به الحادث الجانبي		**تاريخ ظهوره**				**تاريخ توقفه (إذا وجد)**			
		الوقت (الساعة و الدقيقة)	**اليوم**	**الشهر**	**السنة**	**الوقت (الساعة و الدقيقة)**	**اليوم**	**الشهر**	**السنة**
مغص	□								
إسهال	□								
غثيان	□								
تقيؤات	□								
صداع	□								
فقدان و/أو انعدام الشهية	□								
ارهاق	□								
حرارة ≤٣٨ °C	□								
عوارض أخرى، حدد:									
(تطوره، أعراضه، طريقة المعالجة ، وصف للحادث الجانبي ...)									

الفحوص المخبرية و التشخيصية المتعلقة بالحادث	**تاريخ إجراء الفحص**	**نتائج الفحص**

هل كان للمريض تفاعل مماثل مع نفس الدواء أو الأدوية /اللقاح أو اللقاحات المشابهة في أي تعرض سابق؟*		
نعم □	لا □	□ غير معروف

٥ - خطورة الحادث الجانبي *	نعم □		لا □
اذا كان الحادث الجانبي خطيرا، أدى إلى:			
□ الوفاة	تاريخ الوفاة:	□ دخول المستشفى	□ إطالة مدة الإقامة في المستشفى	تحديد مدة الإقامة:
	سبب الوفاة:			
□ تهديد حياة المريض		□ الحاجة لعملية جراحية	
□ ظهور عيب خلقي	□ ظهور إعاقة أو عجز		□ تبعات أخرى

٦- نتيجة الحادث الجانبي*: الوضع الحالي للمريض:			
□ تعافى	□ تعافي مع مضاعفات	تحديد المضاعفات:	
□ ما زال يتعافى	□ لا تحسن	□ الحالة مميتة	□ غير معروف

٧ - مُقدم الإبلاغ *	
الإسم أو الأحرف الأولى	
المهنة	
عنوان العمل	
البريد الإلكتروني	
الهاتف	
التوقيع	
التاريخ	

ANNEX II: Template on the Handling of a Serious Case Report: Serious Case 1

5.1. Case Narrative Form

Date of patient report: November 14, 2022

Date of report documentation: November 15, 2022

Patient initials: MK **DOB:** 39 Y.O.

Causality Assessment #: INVAEFI2022OCV01 **Case#:** OCV01

Vaccine: Euvichol-Plus®

Route: oral **Lot Number**:

Dose 1:☒ Dose 2:☐ Dose 3:☐

- Vaccine Site: Mobile Clinic - Akkar

- Vaccination date: November 13, 2022 – 11: 00am

- First key symptom date: Nov 13, 2022-4:00pm

- Duration between vaccine and AEFI: 5 hrs

- Hospital: Ausrati Governmental Clinic **- Date of admission: T**reated at ER

- Date of discharge: N/A

Contact: ☒ Patient ☐ Family: ☒ Immunization site ☐ Hospital

AVAILABLE INFORMATION

☐ Hospital Report **☐ ER Report** **☐ Post-mortem report**

☐ Radiology Report **☐ Laboratory Report**

☒ Other Report (Specify): - Phone call with the patient: retrieved photos of the symptoms from the patient sent by WhatsApp
- Phone call with the treating physician**:** retrieved case narrative and diagnosis with prescribed medications

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<u>Case Presentation</u>:

MK, a 39 Y.O. female, was vaccinated with her 1st dose of Euvichol-Plus® Oral Cholera Vaccine. The patient took her first OCV dose on Nov 13th, 2022 at 11:00 am. The same day at 4:00 p.m., she experienced ear pain, chills, fever

(39°C), and constipation. At night, patient expressed symptoms of angioedema. The next day on November 14th 2022, she reported her first symptoms to the nearest infirmary (Ausrati Governmental Clinic), and the treating physician prescribed Dexamethasone IM immediately. Patient was then discharged on LORATINE (loratadine) tablets 2x/d. On the same day after taking the 2nd tablet of loratadine, the patient experienced flushing and a systemic rash with burning sensation namely in the genital area. MK reported her symptoms to the MoPH by calling 1787 hotline. The physician advised her to continue her treatment and follow-up after 3 days (Nov 16th 2022). On November 16th 2022, the old symptoms started resolving, but the patient experienced shortness of breath. On November 17th 2022, as per the physician's initial recommendation, the patient discontinued the loratadine treatment but refrained from following up with her physician due to financial reasons.

History of Present Illness:

MK has no history of illness nor medication intake.

On the same day after receiving her 1st dose of the OCV Euvichol-Plus® , the patient started experiencing angioedema, a headache, and a fever (39°C), which her treating physician treated with dexamethasone and loratadine. After initiating treatment with loratadine the patient started experiencing flushing and a systemic rash. Her treatment is in progress and will follow-up with her physician.

- **On the 13th of November,** the patient received her 1st dose of the Euvichol-Plus® Oral Cholera Vaccine.
- **On the 13th of November 2022,** 5 hours post-vaccination, the patient started experiencing headache, fever (39°C), chills, constipation and ear pain.
- **On the 13th of November 2022,** at night, she experienced angioedema.
- **On the 14th of November 2022,** one day post-vaccination, the patient reported her symptoms to the nearest infirmary (Ausrati Governmental Clinic), where the treating physician prescribed an immediate treatment of dexamethasone IM, and discharged her with loratadine (2 tablets/day for 3 days).
- **On the 14th of November 2022, after taking the 2nd tablet of loratadine,** one day post-vaccination, she experienced flushing and systemic (namely in her genital area) rash with burning sensation.
- **On the 14th of November 2022,** one day post-vaccination, after following up with her physician, she is progressing with her prescribed treatment and will report back 3 days after treatment initiation (16th of November 2022 = 3 days post-vaccination).
- **On the 16th of November 2022,** three days post-vaccination, the patient's old symptoms: angioedema, rash, fever started resolving; and constipation resolved completely. However, she started experiencing shortness of breath.
- **On the 17th of November 2022,** four days post-vaccination, the symptoms kept resolving. The patient discontinued the loratadine treatment three days after initiation, but refrained from following-up with her physician due to financial reasons.

Medical Treatment - During Hospitalization: N/A

Medications Upon Discharge: N/A

Laboratory Tests: N/A

Urine Analysis result

Radiology: N/A

Past Medical History: No medical history

Past Medication History: No medication history

Family History: N/A

Past Surgical History: N/A

Social History: N/A

Allergy: N/A

Diagnosis: N/A

Information Complete:

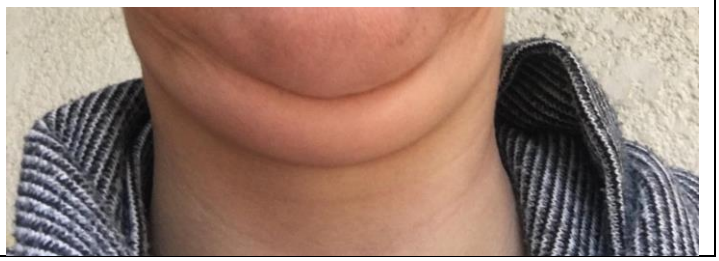
☐ **Yes** ☒ **No (Specify):** Contacted physician: Dr. XX

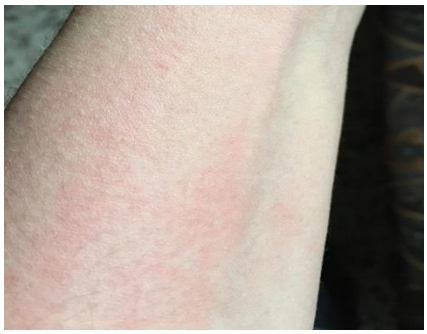
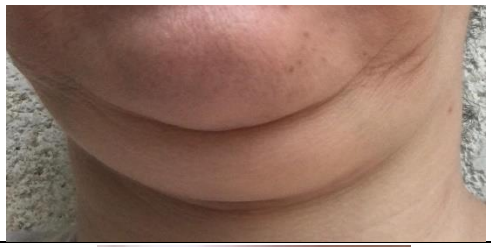
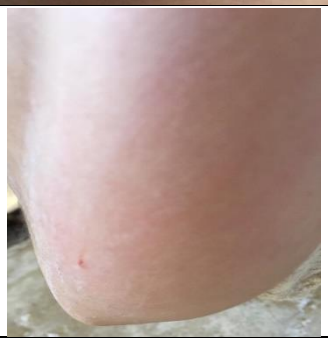
As per the physician's recommendation, the patient still needs follow-up 3 days after initiation of treatment, i.e. one day after drafting this report

Sources of Information and Contact Number: patient, treating physician

Attending Physician in charge of the patient: Dr. XX

Symptoms Progression:

Date	Symptom	Photo
November 14, 2022	Angioedema	

November 14, 2022	Rash	
November 16, 2022	Angioedema	
November 16, 2022	Rash	

Literature review:

- **Case Definition: "Allergic Reaction" within "Anaphylaxis" case definition: (according to the Brighton Collaboration Case Definition):**

(case definition: 10.1016/j.vaccine.2007.02.064, glossary of terms: Anaphylaxis glossary of terms)

- **Anaphylaxis**: an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources including food, aeroallergens, insect venom, drugs, and immunizations.
- **Angioedema:** Areas of deeper swelling of the skin and/or mucosal tissues in either single or multiple sites which may not be well circumscribed and usually not itchy. (Reported symptoms of "swelling of the tongue" or "throat swelling" should not be documented as angioedema unless there is visible skin or mucosal swelling).
- **Risk Factors: (according to the Brighton Collaboration Case Definition):**

https://docs.google.com/spreadsheets/d/1QgF35nYcsaFN3DZTOtV_lP0TYqQzsDMUQBAd5M9brrM/edit#gid=0&range=K69

Anaphylaxis Risk Factors

1.1. Anaphylaxis Risk Factors

TABLE 1. ANAPHYLAXIS RISK FACTORS [1-10]

Age	• Children[3]: large majority of anaphylaxis triggered by foods; less than 5% by insect venom. • Adults[3]: relative to children, medication triggered anaphylaxis more common (about 1/3), food triggered anaphylaxis less common (about 1/3), insect venom more common (close to 20%) • Increased severity of anaphylaxis: infants[2,3] (where recognition can be more difficult) and elderly[2,4]
Gender	• Males – more common in those aged <15 years[2] • Females – more common in those aged >15 years[2] • Increased severity of anaphylaxis: pregnancy [3], menses[3]

- **Case Reports:**

1 out 100 patients in a clinical study in India experienced "Swelling At Neck Region": https://pubmed.ncbi.nlm.nih.gov/31211792/

- **Background Rates:** Unknown
- **Euvichol-Plus® Package Insert Adverse Drug Reactions:**

According to the vaccine's package insert issued by the World Health Organization (WHO): https://extranet.who.int/pqweb/content/Euvichol-Plus®

2,999 healthy children and adults (1-40 years) were participated in the clinical study for evaluating the safety:

1. After taking the vaccines, during first 7 days, the most frequently reported adverse drug reactions in the clinical trial were headache, fever, diarrhea, Nausea/Vomiting and Myalgia. The incidence rate for children and adults is described on the table below:

	Total (N=2,999)	1 ~ 17 years (N=1,118)	18~40 years (N=1,881)
Total	3.40%	3.04%	3.62%
Headache	1.83%	0.81%	2.45%
Fever	1.00%	1.97%	0.43%
Diarrhea	0.67%	0.54%	0.74%
Nausea/Vomiting	0.37%	0.63%	0.21%
Myalgia	0.10%	0.00%	0.16%

2. After taking the vaccines, adverse drug reactions were examined for a period of 28 days. 69 subjects (2.30%) among 2,999 subjects were reported with the adverse effects. Similar symptoms to those experienced by the patient were reported as Uncommon (0.1~5%) and Rare (less than 0.1%): skin and subcutaneous tissue disorders (rash) and vascular disorders (flushing) were reported. The adverse drug reactions during the study (28 days) were described on the table below.

	Incidence rate	
	Uncommon	Rare
Gastrointestinal disorders	Abdominal pain, Toothache Diarrhea	Vomiting, Abdominal pain upper
General disorders and administration site condition	Pyrexia	Thirst
Infection and infestations	Nasopharyngitis	Gastroenteritis
Nervous system disorders	Headache	Dizziness
Respiratory, thoracic and meditational disorders	Cough	Oropharyngeal pain
Skin and subcutaneous tissue disorders	Pruritus	Rash macular
Musculoskeletal and connective tissue disorders	-	Arthralgia, Neck pain, Pain in extremity
Vascular disorders	-	Flushing

LNPVP activity log:

Nb	Date	Activity	Description	PV Team Member
0	November 14, 2022	Receipt of patient report	- Patient reported to 1787 - Report communicated to the LNPVP through WhatsApp	RK
1	November 15, 2022	Documentation of case	Initiated an OCV case narrative form	SS
2	November 15, 2022	Follow-up 1 with patient	- Retrieved primary case narrative from patient - Retrieved photos of symptoms (rash, angioedema) by WhatsApp	- AZ - CA
3	November 15, 2022	Follow-up 1 with physician	- Confirmed case narrative - Retrieved diagnosis and prescribed treatment	AZ
4	November 16, 2022	Follow-up 2 with patient	- Followed-up on the symptoms	CA
5	November 24, 2022	Follow-up 3 with the patient	- Followed-up on the symptoms	CA

5.2. AEFI Investigation Form

(Only for Serious Adverse Events Following Immunization – Death / Disability / Hospitalization / Cluster)

Section A	**Basic details**	
Province/State: Akkar	**District**	**Case ID INVAEFI2022OCV01**
Place of vaccination *(✓)*: ☐ Govt. health facility ☐ Private health facility ☐ Other (specify) Mobile Clinic	Vaccination in *(✓)*:	Campaign ☐ ..... Routine ☐ Other (specify)
Address of vaccination site: **Akkar**		
Name of Reporting Officer: Dr. AZ / Dr. SS	Date of investigation: 15/11/ 2022	
Designation / Position: **Clinical and Technical manager/PV officer**	Date of filling this form: 16/11/ 2022	
Telephone # landline (with code):	This report is: *First* *Interim* *Final*	
	Mobile:	e-mail:
Patient Name (MK)		Sex: M F

(use a separate form for each case in a cluster)
Date of birth (DD/MM/YYYY): __ __ / __ __ / __ __ __ __
OR *Age at onset:* __39 __ *years* __ __ *months* __ __ __ *days* ***OR*** *Age group:< 1 year 1–5 years> 5 years*
Patient's full address with landmarks *(Street name, house number, locality, phone number etc.)*:

Name of vaccines/diluent received by patient	Date of vaccination	Time of vaccination	Dose (e.g. 1st, 2nd, etc.)	Batch/Lot number	Expiry date
Euvichol-Plus®	November 13, 2022	11: 00am	1st	Vaccine Diluent	Vaccine Diluent
				Vaccine Diluent	Vaccine Diluent
				Vaccine Diluent	Vaccine Diluent
				Vaccine Diluent	Vaccine Diluent
				Vaccine Diluent	Vaccine Diluent

Type of site *(✓)* Fixed Mobile Outreach Other _____

Date of first/key symptom *(DD/MM/YYYY)*: __13 __ / __ 11__ / __ _2022_ __ __ Time of first symptom (*hh/mm): 4:00 p m* __ __ / __ __
Date of hospitalization *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __
Date first reported to the health authority *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __

Status on the date of investigation (✓): Died Disabled Recovering Recovered completelyUnknownIf died, date

and time of death *(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __ (*hh/mm): __ __ / __ __*
Autopsy done? (✓) Yes (date)_____ No Planned on (date)_____Time Attach report (if available)

Section B	**Relevant patient information prior to immunization**	
Criteria	**Finding**	**Remarks (If yes provide details)**
Past history of similar event	Yes / No / Unkn	
Adverse event after previous vaccination(s)	Yes / No / Unkn	
History of allergy to vaccine, drug or food	Yes / No / Unkn	
Pre-existing illness (30 days) / congenital disorder	Yes / No / Unkn	
History of hospitalization in last 30 days, with cause	Yes / No / Unkn	
Patient currently on concomitant medication? (If yes, name the drug, indication, doses & treatment dates)	Yes / No / Unkn	
Family history of any disease (relevant to AEFI) or allergy	Yes / No / Unkn	

For adult women
- Currently pregnant? Yes (weeks)_____/ No / Unknown
- Currently breastfeeding? Yes / No

For infants
The birth was full-term pre-term post-term. Birth weight:

Delivery procedure was Normal Caesarean Assisted (forceps, vacuum etc.) with complication (specify)

Section C **Details of first examination** of serious AEFI case**

Source of information (✓ *all that apply*): **Examination by the investigator** **Documents** **Verbal autopsy** **Other**
Patient and treating Physician_____*If from verbal autopsy, please mention source* __ .....

Name of the person who first examined/treated the patient: Dr. XX_____
Name of other persons treating the patient: _____
Other sources who provided information (specify): _____

Signs and symptoms in chronological order from the time of vaccination:

MK, a 39 Y.O. female, was vaccinated with her 1st dose of Euvichol-Plus® Oral Cholera Vaccine. The patient took her first OCV dose on Nov 13th, 2022 at 11:00 am. The same day at 4:00 p.m., she experienced ear pain, chills, fever (39ºC), and constipation. At night, the patient expressed symptoms of angioedema. On the next day, (Nov. 14th, 2022), she reported her first symptoms to the nearest infirmary (Ausrati Governmental Clinic), and the treating physician prescribed her Dexamethasone IM immediately. The patient was then discharged on prescription of LORATINE (Loratadine) tablets BID. On the same day after taking the 2nd tablet of Loratadine, the patient experienced flushing and a systemic rash with burning sensation including the genital area. MK reported her

symptoms to the MoPH by calling the 1787 hotline. The physician advised her to continue her treatment and to follow-up with him after 3 days (expected on Nov 16th 2022).

For more information refer to the case narrative

Name and contact information of person completing these clinical details: Dr AZ/SS	Designation: **Clinical and Technical manager/PV officer**	Date/time 16/11/2022

****Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents, i.e.**

- ***If patient has received medical care*** – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below
- ***If patient has not received medical care*** – obtain history, examine the patient and write down your findings below (add additional sheets if necessary)

Provisional / Final diagnosis:

Section D	**Details of vaccines provided at the site linked to AEFI on the corresponding day**									
Number immunizedfor each antigen at session site. Attachrecord if available.	Vaccine name	**Euvichol-Plus®**								
	Number of doses	1								

a) When was the patient immunized? (✓ the below and respond to ALL questions)	
Within the first vaccinations of the session Within the last vaccinations of the session Unknown	
In case of multidose vials, was the vaccine given within the first few doses of the vial administered? within thelast doses of the vial administered? unknown?	
b) Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes* / No / Unable to assess
c) Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes* / No / Unable to assess
d) Based on your investigation, do you feel that the vaccine's physical condition (e.g. colour, turbidity, foreign substances etc.) was abnormal at the time of administration?	Yes* / No / Unable to assess
e) Based on your investigation, do you feel that there was an error in vaccine reconstitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	Yes* / No / Unable to assess
f) Based on your investigation, do you feel that there was an error in vaccine handling (e.g. break in cold chain during transport, storage and/or immunization session etc.)?	Yes* / No / Unable to assess
g) Based on your investigation, do you feel that the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes* / No / Unable to assess
h) Number immunized from the concerned vaccine vial/ampoule	unknown
i) Number immunized with the concerned vaccine in the same session	unknown
j) Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations:	unknown
k) Could the vaccine given to this patient have a quality defect or is substandard or falsified?	Yes* / No / Unable to assess
l) Could this event be a stress response related to immunization (e.g. acute stress response, vasovagal reaction, hyperventilation, dissociative neurological symptom reaction etc.)?	Yes* / No / Unable to assess
m) Is this case a part of a cluster?	Yes* / No / Unkn
i. If yes, how many other cases have been detected in the cluster?	
a.Did all the cases in the cluster receive vaccine from the same vial?	Yes* / No / Unkn
b.If no, number of vials used in the cluster (enter details separately)	

*It is compulsory for you to provide explanations for these answers separately

Section E	Immunization practices at the place(s) where concerned vaccine was used (Complete this section by asking and/or observing practice)			
Syringes and needles used:				
• Are AD syringes used for immunization? ☐ ☐ ☐ ☐				Yes / No / Unkn/ NA
If no, specify the type of syringes used: Glass Disposable Recycled disposable Other				
Specific key findings/additional observations and comments:				
Reconstitution: (complete only if applicable, ✓ NA if not applicable)				
• Reconstitution procedure (✓)	Status			
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA	
Same reconstitution syringe used for reconstituting different vaccines?Separate reconstitution syringe for each vaccine vial?	Yes	No	NA	
Separate reconstitution syringe for each vaccination?	Yes	No	NA	
	Yes	No	NA	
• Are the vaccines and diluents used the same as those recommended by the manufacturer?	Yes	No	NA	
Specific key findings/additional observations and comments:				
Injection technique in vaccinator(s): (Observe another session in the same locality – same or different place)				
• Correct dose and route?				Yes / No

• Time of reconstitution mentioned on the vial? (in case of freeze dried vaccines)	Yes / No / NA
• Non-touch technique followed?	Yes / No / NA
• Contraindications screened prior to vaccination?	Yes / No / NA
• How many AEFI were reported from the centre that distributed the vaccine in the last 30 days?	
• Training received by the vaccinator? (If Yes, specify the date of last training_____)	Yes / No / NA
Specific key findings/ additional observations and comments?	

Section F	Cold chain and transport (Complete this section by asking and/or observing practice)
Last vaccine storage point: / NA	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes / No
○ If "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?	Yes / No
○ If "yes", provide details of monitoring separately.	
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes / No/ Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes / No/ Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes / No/ Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes / No/ Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No/ Unkn
Specific key findings/additional observations and comments:	
Vaccine transportation: / NA	
• Type of vaccine carrier used	
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes / No/ Unkn
• Was the vaccine carrier returned from the site on the same day as vaccination?	Yes / No/ Unkn
• Was a conditioned ice-pack used?	Yes / No/ Unkn

Specific key findings/additional observations and comments:

Section G Community investigation (Please visit locality and interview parents/others)
Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality?Yes / No / Unknown If yes, describe:
If yes, how many events/episodes?
Of those effected, how many are • Vaccinated:_____ • Not vaccinated:_____ • Unknown:_____
Other comments:

Section H Other findings/observations/comments

ADVERSE EVENT FOLLOWING IMMUNIZATION

This report is prepared using inputs and decisions made by the PV team
Report on AEFI causality Assessment using the tool developed by WHO for the revised AEFI causality assessment methodology

5.3. Causality Assessment Form

Step 1 *(Eligibility)*

Name of the Patient	MMK
Patient Id	INVAEFI2022OCV01
Name of one or more vaccines administered before this event	Cholera: inactivated oral
Brand Name	Euvichol-Plus®
What is the Valid Diagnosis?	Allergic Reaction
Does the diagnosis meet a case definition?	Yes
Case definition is	Case Definition: "Allergic Reaction" within "Anaphylaxis" case definition: (according to the Brighton Collaboration): (case definition: 10.1016/j.vaccine.2007.02.064, glossary of terms: Anaphylaxis glossary of terms) • Anaphylaxis: an acute hypersensitivity reaction with multi-organ- system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources including food, aeroallergens, insect venom, drugs, and immunizations. • Angioedema: Areas of deeper swelling of the skin and/or mucosal tissues in either single or multiple sites which may not be well circumscribed and usually not itchy. (Reported symptoms of "swelling of the tongue" or "throat swelling" should not be documented as angioedema unless there is visible skin or mucosal swelling).
Sex	Female
Date of Birth	39 years

Create your question on causality here

Step 2 *(Event Checklist)*

	Y ..... N	Remark

ADVERSE EVENT FOLLOWING IMMUNIZATION

This report is prepared using inputs and decisions made by the PV team

	..... UK..... NA	
I. Is there strong evidence for other causes?		
1) In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the Allergic Reaction?	☐ ☐ ☑ ☐	Females are more prone to developing allergic reactions1 0.1016/j.vaccine.2007.02.064, glossary of terms: Anaphylaxis glossary of terms
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product(s)		
1) Is there evidence in published peer reviewed literature that this Cholera: inactivated oral may cause such an Allergic Reaction even if administered correctly?	☐ ☐ ☑ ☐	1 out 100 patients in a clinical study in India experienced “Swelling At Neck Region”: https://pubmed.ncbi.nlm.nih.gov/31211792/

ADVERSE EVENT FOLLOWING IMMUNIZATION

This report is prepared using inputs and decisions made by the PV team

Report on AEFI causality Assessment using the tool developed by WHO for the revised AEFI causality assessment methodology

2) Is there a biological plausibility that this Cholera: inactivated oral vaccine could cause such an Allergic Reaction?	☐ ☑ ☐ ☐	
3) In this patient, did a specific test demonstrate the causal role of the Cholera: inactivated oral vaccine ?	☐ ☑ ☐ ☐	
Vaccine quality		
4)Could the Cholera: inactivated oral vaccine given to this patient have a quality defect or is substandard or falsified?	☐ ☐ ☑ ☐	
Immunization error		
5) In this patient, was there an error in prescribing or non-adherence to recommendations for use of the Cholera: inactivated oral vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐ ☐ ☑ ☐	
6) In this patient, was the Cholera: inactivated oral vaccine (or diluent) administered in an unsterile manner?	☐ ☐ ☑ ☐	
7) In this patient, was the vaccines physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	☐ ☐ ☑ ☐	
8) When this patient was vaccinated, was there an error in Cholera: inactivated oral vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐ ☐ ☑ ☐	
9) In this patient, was there an error in Cholera: inactivated oral vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐ ☐ ☑ ☐	
10) In this patient, was the Cholera: inactivated oral vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐ ☐ ☑ ☐	
Immunization anxiety		
11) In this patient, could this Allergic Reaction be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	☐ ☑ ☐ ☐	The AEFI is not related to a stress response
II (time): Was the event in section II above within the time window of increased risk?		
12) In this patient, did the Allergic Reaction occur within a plausible time window after vaccine administration?	☐ ☐ ☐ ☐	
III. Is there strong evidence against a causal association?		
1) Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) against a causal association between the Cholera: inactivated oral vaccine and the Allergic Reaction?	☐ ☑ ☐ ☐	
IV. Other qualifying factors for classification		
1) In this patient, did such an Allergic Reaction occur in the past after administration of a similar Cholera: inactivated oral vaccine?	☐ ☑ ☐ ☐	
2) In this patient did such an Allergic Reaction occur in the past independent of vaccination?	☐ ☑ ☐ ☐	
3) Could the current Allergic Reaction have occurred in this patient without vaccination (background rate)?	☐ ☐ ☑ ☐	
4) Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the Allergic Reaction?	☐ ☑ ☐ ☐	

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5) Was this patient taking any medication prior to the vaccination?	☐ ☑ ☐ ☐	
6) Was this patient exposed to a potential factor (other than vaccine) prior to the Allergic Reaction (e.g. allergen, drug, herbal product etc.)?	☐ ☑ ☐ ☐	

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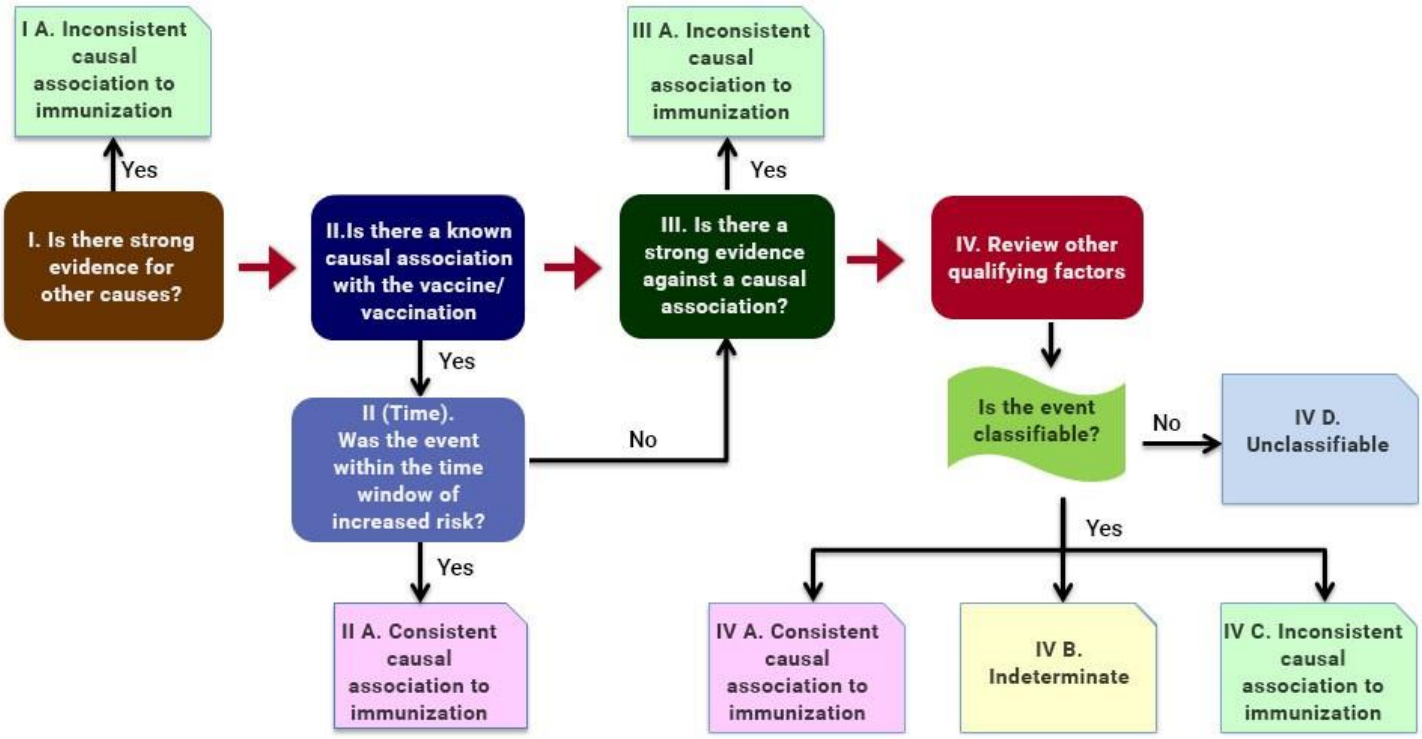
Step 3 *(Algorithm)*



ADVERSE EVENT FOLLOWING IMMUNIZATION

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Step 4 *(Classification)*

A. Consistent causal association to immunization

- [x] A1. Vaccine product-related reaction(As per published literature)
- [ ] A2. Vaccine quality defect-relatedreaction
- [ ] A3. Immunization error-related reaction
- [ ] A4. Immunization anxiety- relatedreaction

B. Indeterminate

- [x] *B1. Temporal relationship is consistentbut there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event)
- [x] B2. Qualifying factors result in conflicting trends of consistency and inconstistency with causal associationto immunization.

C. Inconsistent causal associationto immunization

- [x] C. Coincidental Under lying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine

Summarize the classification logic:

With available evidence, we could conclude that the classification is - A1. Vaccine product-related reaction (As per published literature) because: 1) • 1 out 100 patients in a clinical study in India experienced “Swelling At Neck Region”:https://pubmed.ncbi.nlm.nih.gov/31211792/

Other considerations include:

C. Coincidental Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine this is because 1) Females are more prone to developing allergic reactions10.1016/j.vaccine.2007.02.064, glossary of terms: Anaphylaxis glossary of terms, 2) The AEFI is not related to a stress response

This report is prepared using inputs and decisions made by: AZ/SS