Since 1972, the UN cosponsored special programme, HRP, has pursued a vision of sexual and reproductive health and rights (SRHR) for all. This is the third in a series of stories to share key moments from HRP’s history and the impact of its work on advancing the attainment of SRHR. Find out more about the Human Reproduction Programme here.
Since the 2014 Ebola outbreak in West Africa, HRP has established a Sexual and Reproductive Health (SRH) Outbreak Working Group (OWG) to conduct rigorous research on sexual and reproductive health in epidemic and pandemic situations and ensure the findings translate to benefits in countries.

**Ebola outbreak in West Africa**

Ebola virus disease (EVD) is a rare but serious disease with sudden onset of symptoms and a case fatality rate of around 50%. The virus was first discovered in 1976 in near-simultaneous outbreaks in the Democratic Republic of the Congo and what is now South Sudan. In March 2014, the Ministry of Health of Guinea notified WHO of a rapidly evolving EVD outbreak in the south-east of the country. Quickly spreading to neighbouring Liberia and Sierra Leone, this was to become the largest outbreak since the virus was first discovered. In August 2014, WHO declared the outbreak a public health emergency of international concern (PHEIC). By the time the outbreak ended in June 2016, 28 600 people had been infected and 11 325 people had died.

During the outbreak, reports of suspected transmission of the virus through survivors’ body fluids began to emerge, and sexual transmission was posited to be the most likely mode of infection in several clusters of cases.

HRP quickly established an SRH Outbreak Working Group (OWG) in 2014, made up of a cross-cutting group of experts from several units in the department, who engaged in the work of sexual transmission of EVD with the WHO Health Emergencies Programme (WHE) – a collaboration that would lead the team to look at other research questions, including the impact of EVD on pregnant women and babies.

“The West Africa Ebola virus disease epidemic was unprecedented in terms of numbers of cases and survivors. Before this epidemic, we had little data on the presence and persistence of Ebola virus in survivors’ body fluids and the potential risk of transmission. It was the question of possible sexual transmission that was paramount.

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transmission that first triggered HRP’s involvement in the outbreak response,” said Nathalie Broutet who led HRP’s OWG from 2014-2022.

On reviewing the available evidence on EVD persistence in body fluids from people who had survived EVD infection, HRP scientists could not rule out sexual transmission from EVD survivors and identified an urgent need for cohort studies of survivors for longer term analysis of viral persistence in body fluids. Close collaboration with survivors’ associations was advised to mitigate any negative effects on an already vulnerable group.

Responding to the urgency to determine whether the Ebola virus persisted in survivors’ body fluids, the Sierra Leone Ministry of Health and Sanitation (MoHS) began an observational cohort study in collaboration with the Ministry of Social Welfare, Gender and Children’s Affairs, WHO and HRP, and the US, African and Chinese Centers for Disease Control to support the national outbreak response. HRP was responsible for overall coordination of the Sierra Leone Ebola Virus Persistence Study with the MoHS.

The first phase of the study investigated the persistence of Ebola virus in the semen of 100 adult men using qRT-PCR testing. “The study was conducted under extremely difficult circumstances during a public health emergency in the context of an overwhelmed and weak health system. There were many challenges, especially when factoring in the fear, stigma and suspicion rife in communities. Engaging with survivor groups proved critical to the study’s success.” said Nathalie Broutet.

Study enrolment began in May 2015, within five months of initial protocol discussions, and preliminary results were published in October 2015. The initial evidence showed that 49% of study participants had positive results on quantitative qRT-PCR. Ebola virus RNA was detected in the semen of all men with specimens obtained two to three months after onset of EVD symptoms, 65% of those with
specimens obtained four to six months after onset and 26% of those with specimens obtained seven to nine months after onset.

The findings were key to informing the overall epidemic response. Previously, EVD survivors were advised to practise sexual abstinence or to use a condom for three months after recovery. These interim data led WHO to issue guideline updates in January 2016, recommending that abstinence or correct and consistent condom use should be adopted for at least 12 months after the onset of symptoms in survivors without access to semen testing.

The results also supported implementation of semen testing services as part of overall EVD survivor-care programmes. The Sierra Leone government established and accelerated the implementation of semen testing as part of a comprehensive programme of services for EVD survivors and engaged with the Ministries of Health in Liberia and Guinea to establish and implement national semen testing programmes with preventive behavioural counselling to ensure safer sexual practices.

“This study was instrumental in convincing governments affected by the Ebola outbreak to develop and rapidly implement national semen testing programmes for Ebola disease survivors. Research is a vital component of the public health response to an epidemic and can lead to real time change in programming on the ground,” said Nathalie Broutet.

The methods, mechanisms and tools developed for this study would also inform studies examining viral persistence in body fluids in subsequent outbreaks.

Zika in Latin America

The Zika virus (ZIKV) was first isolated from a rhesus monkey in Uganda in 1947, with evidence of infection in humans in the 1950s. Although the virus is primarily transmitted through the bite of an infected Aedes aegypti mosquito, non-vector borne transmission, including perinatal, transfusion-related and sexual had also been described.

In mid-2015, an outbreak of ZIKV in Brazil drew international attention. An unexpected increase in the number of babies born with microcephaly, a condition where a baby's head is much smaller than other babies of the same age and sex, sparked fears of an association between ZIKV infection in pregnant women and congenital abnormalities in newborns. Brazil announced a national public health emergency in November 2015. By June 2016, 60 countries and territories reported continuing mosquito-borne transmission.

“This was the first time we faced an outbreak causing congenital anomalies in babies of mothers infected with a mosquito-borne virus during pregnancy, with the possibility of sexual transmission. The experience the OWG had gained in research protocol development to understand sexual transmission of Ebola, the impact on pregnant women, and implementing studies was invaluable in allowing us to explore these questions in the context of ZIKV.” said Edna Kara, Medical Officer in HRP and WHO Department of Sexual and Reproductive Health and Research and part of the OWG.

In February 2016, WHO declared the clusters of microcephaly cases and other neurological disorders in endemic areas a PHEIC. Responding to the need for research to better characterize the infection, the OWG, together with the Special Programme for Research and Training in Tropical Diseases (TDR) and the WHO Immunization, Vaccines and Biologicals Department, developed the WHO Zika Virus Research Agenda. HRP proposed the implementation framework for the research agenda that was adopted by all partners to coordinate research activities and played an important role in leading several key highlighted research activities.
In February 2016, HRP and the University of Bern established the WHO Zika Causality Working Group and led the development of a framework establishing causal links between ZIKV and congenital brain abnormalities and Guillain-Barré syndrome (GBS) – a rare condition in which a person’s immune system attacks the peripheral nerves. The group conducted a systematic review of published and unpublished evidence, including 72 studies of congenital brain abnormalities and 36 studies of GBS, and convened a multidisciplinary panel of experts to assess the findings and develop consensus on causality.

The panel found the evidence sufficient to conclude that ZIKV infection was the most likely cause of adverse pregnancy and congenital brain outcomes, including microcephaly, and a trigger of GBS. Based on this work, WHO recommended increased public health measures that were adopted by all countries affected by the outbreak.

Developing research protocols to better understand disease

Protocols are a key component of evidence generation, providing the rationale, design, methods and analytical approaches for research. HRP developed a total of seven standardized clinical and epidemiological research protocols to better understand the effects of ZIKV on women, newborns and infants, viral persistence in body fluids, risk factors, seroprevalence in the general population and the natural history of infection in partnership with PAHO, Institut Pasteur and the networks of Fiocruz, CONSISE and ISARIC.

Coordinating with Brazil’s Ministry of Health, HRP developed the largest and longest cohort study assessing ZIKV persistence in body fluids – ZIKABRA – bringing together a multi-disciplinary groups of scientists to design the protocol and implement the study in different sites. The final results are expected to be published in July 2023.
HRP also developed research protocols in Brazil, Honduras and Panama to review, assess and strengthen health systems’ responses to challenges, areas for improvement in policy and practice and to explore community perceptions related to contraceptive services and post-abortion care in the context of ZIKV infection.

“This health systems research highlighted key service gaps. The findings were shared with local health authorities who took immediate steps to improve the quality of existing services in contraception and access to safe abortion services.” said Moazzam Ali, Medical Officer in HRP and WHO Department of Sexual and Reproductive Health and Research.

The protocols were designed to support countries to develop their own research and maximize opportunities for data and biological samples to be systematically collected and rapidly shared in a format that can be easily aggregated, tabulated and analyzed across different settings.

The use of standardized protocols also contributes to meta-analysis of individual participant data. In February 2017, HRP convened key partners and researchers from leading cohort studies to establish the Zika Virus Individual Participant Data Consortium, a global initiative to estimate the effects of exposure to Zika virus during pregnancy on fetal, infant, and child health outcomes. The consortium includes individual data on 33,061 pregnant women and 18,281 babies from 64 sites in 22 countries and territories. Meta-analysis of pooled data will provide more precise estimates of the absolute and relative risks of adverse outcomes. The preliminary results are expected to be published in the near future.

“While the threat of ZIKV was dwarfed by the urgent need to understand and address the COVID-19 pandemic, more than two billion Zika-naïve individuals still live in Aedes aegypti endemic areas. As research on ZIKV continues, the evidence that HRP is generating through these activities in the recovery phase will blend into the preparedness phase and inform the response for the next outbreak,” said Caron Kim, Medical Officer in HRP and WHO Department of Sexual and Reproductive Health and Research and member of the OWG.

The COVID-19 pandemic

The arrival of SARS-CoV-2 in December 2019 and declaration of a PHEIC by WHO in January 2020 saw the OWG re-convene to support the global response to the COVID-19 pandemic. For years, HRP’s OWG had been preparing for an outbreak of the magnitude of COVID-19. When it happened, we were able to immediately gather and develop an HRP research agenda based on our experience and the generic protocols we had developed that could be adapted to any outbreak,” said Nathalie Broutet.

The OWG identified key topics to which HRP could contribute in line with WHO research and normative priorities. Crucial among these were research, coordination and implementation pertaining to the effects of COVID-19 on pregnancy, appropriate treatment and prevention interventions for pregnant women, and maintenance of essential SRH services and access during the pandemic.
Members of the OWG supported WHE to develop a web-based Global Clinical Platform to collect patient-level anonymized data to better understand the clinical characteristics of COVID-19. Given the limited evidence on the characteristics of COVID-19 in pregnant women at the time, the team led the development of a case report form specifically characterizing the clinical management of pregnant women who were hospitalized with COVID-19.

In April 2020, HRP scientists, in collaboration with the University of Birmingham and other partners, began coordinating a living systematic review and meta-analysis of published studies to investigate the clinical manifestations, risk factors and outcomes of COVID-19 in pregnant and recently pregnant women and perinatal transmission. First published in September 2020, the analysis showed that pregnant women with COVID-19 infection were more likely to need intensive care and invasive ventilation than non-pregnant women of reproductive age. Compared with pregnant women without COVID-19, those with COVID-19 had an increased risk of maternal death and were more likely to have babies born prematurely and requiring neonatal intensive care.

Further, the OWG developed a generic protocol for a prospective cohort study to better understand how SARS-CoV-2 infection affects pregnant women and their neonates, following them for a range of outcomes. The protocol was adapted when COVID-19 vaccines became available to collect critical data on the safety and impact of COVID-19 vaccination during pregnancy. The WHO COVID-19 and pregnancy cohort protocol has been implemented in nine low- and middle-income countries.
countries under the coordination of HRP, and more than 15,000 women have been recruited. Preliminary data analyses are expected in December 2023. As evidence for the high-risk of adverse outcomes for pregnant women infected with COVID-19 has grown, reassurance about vaccine safety during pregnancy has become increasingly important. HRP has been advising, steering and participating in a living systematic review and meta-analysis on the safety, immunogenicity and effectiveness of COVID-19 vaccines during pregnancy in collaboration with Tulane University, the Institute for Clinical Effectiveness and Health Policy in Argentina, the London School of Hygiene & Tropical Medicine and the University of Washington.

The findings have provided key data for the WHO Strategic Advisory Group of Experts (SAGE) on Immunization. Members of the OWG have been giving in-depth insights on COVID-19 vaccination in pregnancy, contributing to the update process of WHO SAGE recommendations on COVID-19 vaccines and vaccine prioritization strategies.

“Pregnant women were not included in the initial clinical trials of COVID-19 vaccine safety and efficacy, leaving millions of pregnant women and their providers uncertain about COVID-19 vaccination during pregnancy. Now, a growing body of evidence demonstrates that COVID-19 vaccines are safe and effective during pregnancy. Given the consequences of acquiring COVID-19 during pregnancy, all pregnant women should have access to potentially lifesaving COVID-19 vaccines, to protect themselves and their babies,” said Sami Gottlieb, Medical Officer in HRP and WHO Department of Sexual and Reproductive Health and Research and member of the OWG.

The revised SAGE roadmap for prioritising use of COVID-19 vaccines, published on 30 March 2023, places pregnant women and adolescents in the high priority-use groups, recommending the primary series and booster vaccination as soon as possible, and an additional booster dose once during pregnancy if the previous dose was more than six months prior. This recommendation aims to protect the pregnant woman, the fetus and the infant up to the age of six months.
COVID-19 disruption to health services

The Ebola and Zika virus outbreaks highlighted the severe disruptions to SRH services that expose women and girls, in particular, to preventable health risks. The OWG adapted the ZIKV social science research and community perceptions protocols to the context of COVID-19. Additionally, the OWG developed a generic health systems strengthening protocol and a protocol to capture the effect of quarantine on SRH services at the community level. This enabled HRP to implement research and generate evidence on SRH service gaps in nine countries to inform health authorities to take corrective measures.

By leading the development of an evidence base to support countries to overcome the extensive disruptions to health systems during the COVID-19 pandemic, including where appropriate with home-based care, telemedicine and use of self-care interventions for SRHR, HRP played a key role in enabling maintenance of essential SRH services.

Furthermore, HRP scientists contributed to the WHO guidance on maintaining essential services in the context of COVID-19, specifically the section on maternal health and SRH services. As the guidance states, the pandemic highlighted the importance of prioritising self-care interventions for individuals to protect their own health when facility-based provision of SRH services is disrupted, including ensuring access to contraception and abortion to the full extent allowed by the law.

In May 2020, the Partnership for Maternal, Newborn and Child Health (PMNCH) invited HRP scientists to be part of the technical review group for a series of four short animated films promoting self-care practices around key SRH issues during the COVID-19 pandemic. The films helped to translate the latest WHO guidance on self-care.
interventions and practices in the context of COVID-19, including on breastfeeding, responsive care-giving, COVID-19 vaccination and pregnancy. They aimed to dispel some of the main myths and misinformation around COVID-19 vaccines and give practical guidance to women and children experiencing violence during lockdowns.

The collaboration and coordination of outbreak SRH activities through the OWG has grown and expanded over time, finding form and shape through standardized approaches and development of robust methods to answer critical research questions.

At the time of writing, the OWG is collaborating with WHE to support the research and normative response to the fourth emergency outbreak of global concern – monkeypox virus (Mpox). Members of the working group have been involved since the start of the 2022 outbreak to inform the SRHR and STI research agenda. The interim guidance on clinical management and infection prevention and control for monkeypox, published in June 2022, includes considerations for sexually active persons, pregnant or breastfeeding women, and neonates. A full guideline is being developed and the OWG is on the WHO steering committee for its development.

HRP is continuing to build on its rigorous response to the Ebola virus, ZIKV, and COVID-19 outbreaks to meet the sexual and reproductive health needs and rights of people by determining key research questions and reviewing and generating new evidence in a timely manner to support operational guidance and tools.

For more information about HRP’s SRH Outbreak Working Group, please see www.who.int/teams/sexual-and-reproductive-health-and-research-(srh)/areas-of-work/sexual-reproductive-health-and-rights-in-health-emergencies. 