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The evolving landscape of cancer-causing viruses and clinical trials for vaccine development

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Abstract. Viral infections cause some of the world's most deadly cancers, including cervical, liver and nasopharyngeal cancers. In this review, we spotlight the major oncogenic viruses (HPV, HBV/HCV, EBV and others) describing their mechanisms of carcinogenesis and pathogenetic impact. With a primary focus on the landscape of vaccine development, we review preventative vaccines that have had broad success in reducing cancer (for HPV and HBV). The study also includes an overview of current Phase I and II clinical trials for both prophylactic and immunotherapeutic vaccines against viral infections like EBV, HCV, and HTLV-1. Although substantial hurdles remain, especially for viruses with high genetic diversity, the research underscores encouraging progress in mRNA-, DNA- and T-cell-based immunotherapies and the pivotal need for further research to ultimately conquer global cancer.

Keywords: Oncogenic Viruses; Cancer Vaccines; Clinical Trials; HPV; Immunotherapy.

1. Introduction

Cancer is one of the leading causes of death worldwide and is responsible for 3 in 10 global premature deaths from noncommunicable diseases (NCDs) [1]. According to the World Cancer Report 2020, in 2018, there were 9.6 million deaths due to cancer [2]. In addition to its effects on human health, cancer also creates huge economic costs for patients and countries, as the estimated global cost of cancer from 2020 to 2050 is $25.2 trillion [3]. Given the difficulty of treating and managing most cancers, scientists worldwide are exploring innovative approaches to overcome current challenges and ultimately improve cancer prevention and early diagnosis.

Various pathogens, such as bacteria and viruses, can cause cancer. It is known that pathogens can cause stomach, liver, and cervical cancer. In 2022, around 2.5 million new cases were related to these organs. However, the oncogenic pathogens that cause these cancers are either preventable or treatable (see Table 1).

Table 1. List of major pathogen-related cancer types. The information has been retrieved from GLOBECAN.

Cancer Type	Pathogen	Percentage of cancer caused by pathogens	Preventative or Treatment method
Non-cardia gastric adenocarcinoma	Helicobacter pylori	9/10 for noncardia gastric cancer (105,106)	Can be treated with antibiotics
Liver - Hepatocellular carcinoma (HCC) 75%-85% of cases - Intrahepatic cholangiocarcinoma 10%-15% of cases	HBV or HCV	21%-55% of cases of HCC were attributable to HBV or HCV infection (105,119)	HBV infection is preventable through vaccination.
Cervical carcinoma	HPV	12.1 to 19.3 cases per 100,000 for incidence	HPV infection is preventable through vaccination.
Nasopharyngeal cancer	EBV	60% of the 200,000 new tumor cases	EBV infection can be treated with immunotherapy.
Kaposi sarcoma	Human herpes virus 8 (HHV-8)	95%-98%	HHV-8 infection can be treated with immunotherapy.
adult T-cell leukemia/lymphoma (ATL)	Human T-lymphotrophic virus-1 (HTLV-1)	2%-5%	HTLV-1 infection can be treated with immunotherapy.
Merkel cell carcinoma	Merkel cell polyomavirus (MCV)	80%	There is no preventative vaccines; treatment depends on the stages of the cancer.

It is important to understand, though, that only prolonged infection by several known viruses will lead to cancer. To establish a relationship between cancer and a certain type of virus, one has to prove that there is a direct correlation between viral infection and carcinogenesis. In the following paragraphs, we will be reviewing some of the prevailing cancer-causing viruses and their research development.

2. Cervical Cancer

Among various cancer types, cervical cancer has caused 661,021 cases and 348,189 deaths in 2022, based on the research by Bray et al. [1] Cervical cancer was ranked 4th in cancer incidence rates and mortality in women, as shown in Figure 1. In addition to posing a threat to human lives and macroeconomic development, cancer also causes many kids to become maternal orphans, according to research conducted by Guida et al. The economic burden extends to families, healthcare systems,

and national productivity, with billions spent annually on cancer treatment and lost labor. This issue is particularly significant in low- and middle-income countries, where access to early detection and treatment remains limited.

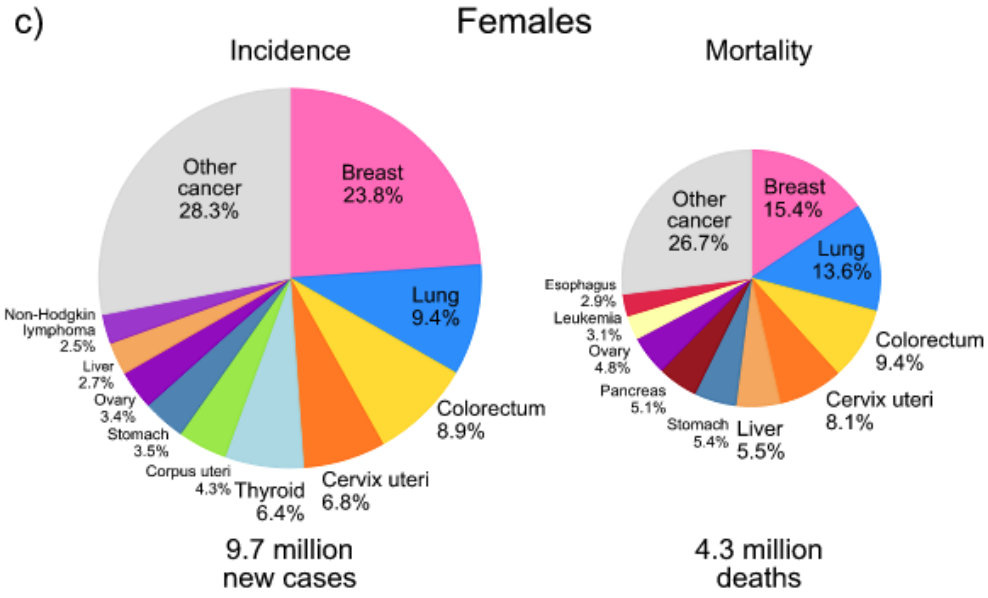

Figure 1. Incidence rate and mortality rate for women suffering from cancer worldwide as of 2022 [1].

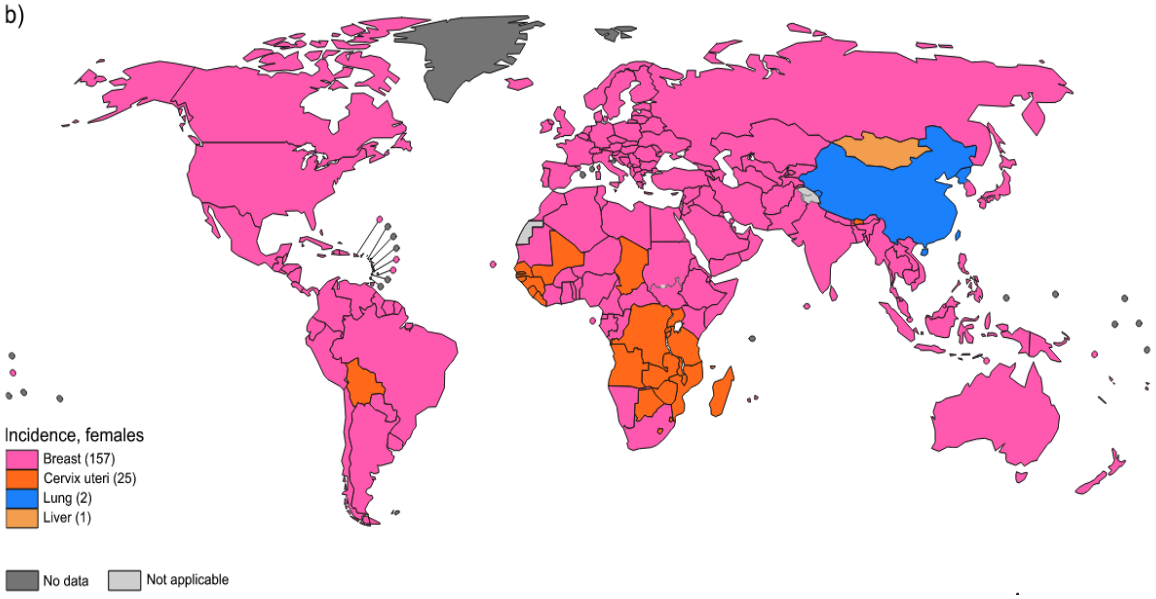

Figure 2. Global maps present the most common type of cancer incidence in females in 2022 in each country.

It is fair to notice that even though cervical cancer ranked as the 4th in incidence and mortality rates, it ranked as the 2nd most common type globally (Figure 1). The discrepancy is probably due to the global population density distribution.

Cervical cancer incidence and mortality rates are inversely related to income levels from different countries, indicating a health disparity (Figure 2).

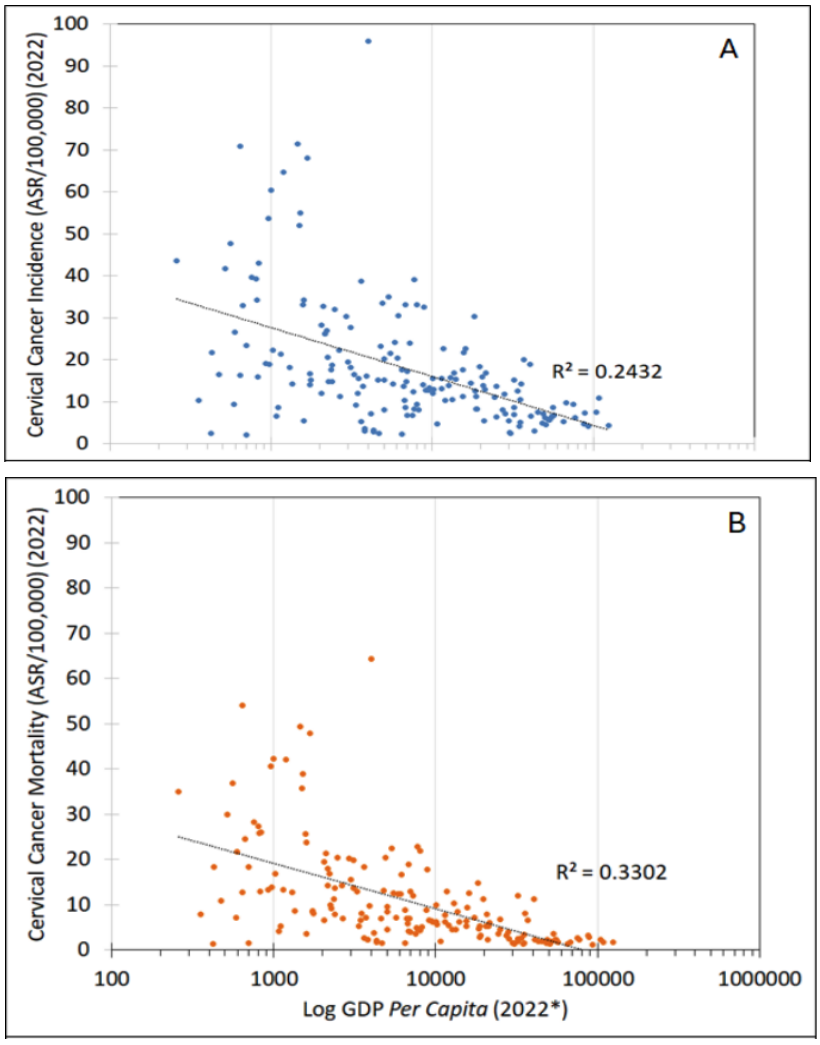

Figure 3. (A) Relationship between cervical cancer incidence rate and GDP per capita from different countries. (B) The relationship between cervical cancer mortality rate and GDP per capita from different countries. The images were taken from Castle's review [4].

Compared with other types of cancer, the incidence of cervical cancer is decreasing, especially in developed countries. It has been found that cervical cancer can be caused by human papillomavirus (HPV). Papillomaviridae is a non-enveloped icosahedral double-stranded DNA virus. There are 53 genera of this virus based on the L1 capsule protein nucleotide sequence. Among the 53 genera, there are 5 genera (α, β, γ, μ, and ν) that infect humans; therefore, they are named human papillomavirus or HPV [5]. Research has shown that 12 α HPV are highly carcinogenic and are called high-risk HPV or HR-HPV; while 8 β HPV can cause cancer. The 12 HR-HPVs are HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Among the 12 HR-HPVs, HPV16 and HPV18 are the two HR-HPVs targeted by most vaccines on the market because they account for approximately 70% of cervical cancer. Specifically, HPV16, being the most carcinogenic HPV type, causes 55-60% of cervical cancer, with the remaining 10-15% caused by HPV18 [4]. About 5% of cancers globally are attributable to HPV infection [6]. Two possible factors contribute to the decreasing trend of cervical cancer: more advanced screening technology and HPV vaccination. The vaccination is highly effective for previously unexposed pre-adolescent girls and women. It can successfully defend against HPV16, 18, 31, 33, 45, 52, and 58. With increasing coverage of the HPV vaccine around the globe, the rate of getting HPV-caused cervical cancer has decreased significantly.

A Cervical Cancer Elimination Initiative was launched in 2020 by the World Health Assembly. Specifically, by 2030, the targets should be reached: 90% of girls fully HPV vaccinated by age 15, 70% of women screened twice using a high-performance test by the ages of 35 and 45, 90% of women diagnosed with pre-cancer, and 90% of women with invasive cancer treated [7].

2.1. The history of HPV vaccine

In 1983, Harald Zur Hausen first discovered the existence of Human Papillomavirus (HPV) by cloning the genomes of HPV-16 and HPV-18 [8]. He found out HPV virus has influenced the development of the majority of cases of cervical cancer. In the 1990s, scientists started to use epidemiology to support a causal link for HPV based on the detection of HPV DNA in small clinical samples of cervical dysplasia. Within the same year, scientists also investigated the HPV16 and HPV18 E6 and E7 proteins that are consistently expressed in cervical cancer cell lines. Chronic infections with HPV16 and HPV18 are known to cause cancers such as vulvar, vaginal, anal, penile, and oropharyngeal cancers. Research has shown that the E6 and E7 proteins bind to and inhibit the function of several tumor suppressor proteins, such as P53 (targeted by E6) and PRB (targeted by E7). This understanding led to the development of HPV vaccines that can prevent HPV-related cancers.

3. Liver Cancer

Primary liver cancer includes 75%-85% of cases of hepatocellular carcinoma (HCC) and 10%-15% of cases of intrahepatic cholangiocarcinoma. HBV and HCV chronic infection are found to be responsible for 21%-55% of HCC. The incidence of HBV in the U.S. is estimated to be 21,900 new cases in 2015. However, it is also estimated that about 850,000 individuals living with HBV infection live in the U.S. [9].

HBV can cause HCC through various mechanisms. The chronic inflammation caused by HBV can lead to the cell death of hepatocytes and liver regeneration, contributing to liver fibrosis and cirrhosis, eventually causing hepatocellular carcinoma. In addition, the HBV virus can also insert its genome into host cells and disrupt the host's immune response.

HCV, on the other hand, due to the lack of a tissue culture system and related studies, has not been fully studied. Similar to HBV, chronic infection by HCV can lead to liver cirrhosis and fibrosis, eventually leading to hepatocellular carcinoma.

HBV vaccine has been introduced to the majority of the world countries with a global coverage of 84% for 3-dose administration. The HBV vaccination has greatly reduced the chances of chronic HBV infection, therefore decreasing the HCC cases caused by it.

On the other hand, because of the difficulty in isolating and culturing HCV in a tissue culture system, relevant studies have been hampered and no available vaccine has been developed.

4. Other virus-induced cancers

4.1. Nasopharyngeal carcinoma caused by Epstein-Barr virus

(EBV) Nasopharyngeal carcinoma (NPC) is a type of epithelial tumor. It is more common in South China and Southeast Asia, with incidence rates up to 25 per million. The prognosis of advanced-stage NPC is poor, and treatment oftentimes causes lifelong morbidity. Epstein-Barr virus (EBV), also known as human herpesvirus 4 (HHV-4), is from the gammaherpesvirus family. It contains a genus called Lymphocryptovirus and was the first virus discovered to cause tumors in humans. The transmission of the virus is primarily through saliva. EBV has a global impact and commonly establishes lifelong, asymptomatic infection in B cells, particularly within memory B cells. There are two main types of EBV (types 1 and 2), and under normal conditions, the virus does not cause disease in healthy individuals. Nearly 90% of the people are silent carriers of this virus. However, intrinsic factors such as genetic mutations and extrinsic factors like HIV co-infection can augment EBV-induced tumorigenesis.

In addition to nasopharyngeal carcinoma, EBV also causes Burkitt's lymphoma, Hodgkin lymphoma, and gastric carcinoma [10].

4.2. T cell leukemia and lymphoma

Human T-lymphotropic virus type 1 (HTLV-1) is the first retrovirus with oncogenic properties to be discovered. It has impacted 5-10 million people globally, with particular prevalence in endemic regions, including parts of Japan, sub-Saharan Africa, South America, the Caribbean area, and regions in the Middle East and Australo-Melanesia. The virus is primarily spread through direct contact with bodily fluids, with risk factors including unprotected sexual contact, sharing needles, and organ transplants. People who are infected by this virus have a risk of risk of developing a rare and aggressive peripheral T-cell neoplasm called adult T-cell leukemia/lymphoma (ATLL), accompanied with a severe and progressive neurological disorder named myelopathy/tropical spastic paraparesis (HAM/TSP). Today, one of the challenges in controlling HTLV-1 transmission is its long incubation period, which often results in delayed diagnosis and awareness of the infection. Once detected, individuals should be informed that HTLV-1 infection is lifelong, and they should avoid donating blood or tissues to prevent further spread.

4.3. Kaposi Sarcoma

HHV8, also known as Kaposi sarcoma herpesvirus (KSHV) is the causal pathogen of Kaposi sarcoma [11]. HHV8 is also related to several lymphoproliferative diseases [12]. HHV8 is a double-stranded DNA virus and is primarily transmitted through saliva [13]. Although the incidence rate and mortality rate for HHV8-related lymphoproliferative diseases are hard to estimate, research has shown that in 2022, there were 35,359 new cases and 15,911 deaths for Kaposi sarcoma [1].

4.4. Merkel cell carcinoma

JC polyomavirus (JCPyV) is another cancer-causing double-stranded DNA virus that belongs to the human non-enveloped polyomavirus family. It is transmitted through the intake of raw sewage, air droplet inhalation, or parent-to-child transmission. JCPyV can cause cancer through the interaction between its T antigen and host p53, Rb, PI3K/Akt, and AMPK signal pathways in some cells [14]. The incidence rates and mortality rates of JCPyV-associated cancer are unknown.

5. Materials and Methods

Clinical trials data were retrieved from https://clinicaltrials.gov/. While various virus names were used as the search criteria, we filtered for Phase I and II clinical trials that focus on prevention. Various virus names were also used to perform search for therapeutic vaccines for related cancers, we also filtered for Phase I and II clinical trials.

6. Results

6.1. Preventative Vaccines

6.1.1. HPV

As of mid-2025, several clinical trials are underway to advance human papillomavirus (HPV) vaccine research, focusing on both preventive and therapeutic approaches. Here's an overview of key ongoing studies:

Preventive Vaccine Trials

Several clinical trials have been going on to study whether we can offer comparable long-term protection to the standard three-dose regimen. There is one ongoing trial- Merck’s Single-Dose Gardasil 9 Trials (NCT00635830).

Some other clinical trials have been targeted to offer broader protection by targeting additional HPV types, particularly those prevalent in African and Asian populations. Merck has also been developing this trial: Merck’s Multivalent HPV Vaccine [15].

6.1.2. EBV

The development of EBV preventative vaccines has been aided by the mRNA vaccine research. Several clinical trials are going on:

1. Moderna's mRNA-1189 (Eclipse Trial) is undergoing Phase I and II (Clinical trial No.: NCT05164094)

2. Moderna's mRNA-1195 (Clinical trial No.: NCT05831111), which aims to prevent long-term complications of EBV infection.

6.1.3. HHV8

As of now, there are no active clinical trials for vaccines targeting human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV). However, significant research efforts are underway to develop both prophylactic and therapeutic vaccines.

6.1.4. HTLV-1

As of now, there are no human T-cell lymphotropic virus type 1 (HTLV-1) vaccines in clinical trials. However, significant preclinical research is ongoing to develop both prophylactic and therapeutic vaccines.

6.1.5. Hep B

As of mid-2025, several innovative clinical trials are underway to develop new vaccines and therapeutic strategies against HBV, aiming to achieve functional cures for chronic infections.

6.1.6. Hep C

As of mid-2025, the development of a hepatitis C virus (HCV) vaccine remains a significant global health priority. Despite the availability of effective antiviral treatments, the high cost and limited accessibility underscore the need for a preventive vaccine. Several promising initiatives are currently underway. However, there are significant challenges in HCV Vaccine Development due to the fact of HCV's high genetic variability, the virus's ability to evade the immune system, and the lack of reliable animal models.

6.1.7. Polyomavirus JC

As of June 2025, there are no ongoing clinical trials specifically targeting vaccines for JC polyomavirus (JCPyV). However, several preclinical studies and experimental therapies are exploring vaccine development and immunotherapeutic strategies to prevent or treat JCPyV-related diseases. Just like Hep C, research and development of polyomavirus JC vaccine is also facing a lot of difficulties.

6.2. Cancer vaccines or therapeutic vaccines

6.2.1. HPV cancer vaccines

Development of HPV therapeutic vaccines is focused on targeting crucial proteins such as E6/E7 of HPV16, such as Vvax001 for Cervical Intraepithelial Neoplasia (CIN3) with Phase II clinical trials ongoing, HB-201 and HB-202 Arenavirus-Based Vaccines with Phase I/II trials underway. Some vaccines aim to boost T-cell immune responses, such as Lenti-HPV-07 by TheraVectys (Clinical trial No.: NCT06319963).

6.2.2. EBV Cancer vaccines

Two independent studies using dendritic cell-based vaccines have shown limited efficacy results in Phase II clinical trials. These two vaccines used key proteins in nasopharyngeal carcinoma, like LMP1 and LMP2, in recombinant adenovirus constructs. While one study showed partial tumor reduction in 2 out of 16 patients [16], the other showed no obvious results [17]. However, a modified

vaccinia Ankara (MVA) virus expressing LMP2 was shown to be promising as it boosted T-cell responses, with a follow-up study coming up (NCT01800071) [18].

6.2.3. HBV

HBV therapeutic vaccines focus on enhancing immune responses. Gilead Sciences is developing GS-2829 and GS-6779 (Clinical trial No.: NCT05770895). There are some novel studies such as the epigenetic therapy developed by Tune Therapeutics, aiming to modulate gene expression with one injection and eliminate HBV replication in the liver.

6.2.4. HCV

The development of HCV therapeutic vaccines that target T-cell immune response has been in its early phase. Inovio Pharmaceuticals is performing Phase I clinical trials of INO-8000, a synthetic multi-antigen DNA vaccine targeting HCV genotypes 1a and 1b.

7. Summary

Table 2. Cancer-causing viruses and vaccine research and development status.

Virus	cancer	vaccine	notes
HPV	Cervical cancer	YES	
EBV	Lymphoma	Clinical trials	The current clinical trials are focused on Phase I and II. At least one of the EBV vaccines, which finished phase II trials, has shown efficacy, and further trials are needed [19].
HHV8 (Kaposi Sarcoma Herpes Virus)	Kaposi sarcoma	Not for vaccines, yes for treatments (antibody-based, HHART, chemotherapy)	in immunocompromised, fatal in 2 years after diagnosis
HTLV-1	T cell leukemia and lymphoma	No	There were animal experiments to study the toxicity and efficacy of HTLV-1 based on different platforms, however, they are still in the early phase, and the results are a mixture of failures and successes. There is one therapeutic application of the vaccine that could be promising, but with the limited trial size, it is not convincing [20].
Hep B	Hepatocellular carcinoma	YES	
Hep C	Hepatocellular carcinoma and non-Hodgkin lymphoma	Several early-stage Clinical trials but were not successful	
Polyomavirus JC	Merkel cell carcinoma	No preventative vaccines	Ongoing studies investigating T-cell based treatments [21]

The table 2 summarizes the development of vaccines for various cancer-causing viruses. Overall, the studies have shown that therapeutic cancer vaccines, if designed properly, can induce remission in patients with low virus antigen burden. Progress has been made in prevention of HPV and HBV. As mentioned in the introduction, preventative measures are particularly important for developing countries. Ongoing efforts are aimed at addressing the issues of vaccine manufacturing and distribution. Continued research is crucial to prevent spread globally. Research is essential to the treatment of cancers caused by viruses like EBV, HCV, HTLV-1, HHV8, etc.

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