

RESEARCH PAPER



Epidemiology, diagnosis, vaccines, and bibliometric analysis of the 100 top-cited studies on Hepatitis E virus

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ABSTRACT

Introduction: In low-income countries, Hepatitis E infection is a common cause of acute hepatitis. So far, only two recombinant vaccines (rHEV and HEV 239) have been developed against Hepatitis E virus (HEV). Of which HEV 239 is licensed in China, but is not yet available in any other country.

Objective: This study aims to discuss epidemiology, diagnosis, available vaccines for HEV, and provides an overview of 100 top-cited studies on HEV.

Methods: A bibliometric analysis was conducted on the topic “HEV” through a systematic search of the Web of Science. The keywords used were “Hepatitis E” and retrieved articles were assessed for number of attributes.

Results: The search returned a total of 3,235 publications, cited 95,858 times with h-index 129. The main finding for the 100 top-cited articles on HEV showed: number of authors ranging from 1 to 23, cited references range from 4 to 304, global citations score per year range from 6.61 to 175, and global citations score range from 148 to 791. Of the 100 top-cited studies, the authors who published most articles are Purcell (n = 18), Meng (n = 17), and Emerson (n = 15). Most The largest share of articles on HEV was contributed by United States of America (n = 49) with 12,795 citations. The National Institute of Allergy and Infectious Diseases was leading institute with greatest number of publications (n = 16), cited 3,950 times.

Conclusions: The studies conducted on HEV have increased over time. The information presented would be very useful in decision making for policy makers providing health care, and for academicians in providing a reference point for future research.

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Introduction

Many pathogenic microorganisms such as bacteria, fungi, parasites, and viruses can cause different infections and diseases in humans and animals. Every year due to contagious and non-contagious diseases millions of people die around the globe.¹ Hepatitis E virus (HEV) has become a global public health problem causing acute hepatitis. In the past HEV has not been studied as per its risk,^{2–4} however, in recent years the number of studies on HEV have been conducted to understand the natural history, transmission, and animal reservoirs of HEV infection.^{4–6} The burden of infection is high in low-income countries. In recent years, increasing number of HEV cases have been reported in industrialized countries as well. In large-scale outbreaks of HEV, high morbidity and mortality have been reported, particularly in pregnant women.⁷

Hepatitis is disease of liver which is caused by several different viruses including Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Hepatitis D virus (HDV), and HEV. Hepatitis A, B, C, and E are responsible for majority of infections and health-related complication, if not treated on time, they can lead to death.⁸

HEV incubation period varies from 2 to 10 weeks (average 5 to 6 weeks). HEV symptomatic infection is most common among people of age 15 to 40 years.⁹

Common symptoms of HEV include fever (mild), nausea, vomiting, anorexia, abdominal and joint pain, skin rash, jaundice, dark urine, pale stools, and hepatomegaly. Acute HEV infection can get severe in rare cases and results in fulminant hepatitis (acute liver failure). The fulminant hepatitis is more frequently reported during pregnancy.⁹ These diseases can spread from one person to another by direct or indirect contact. Zoonotic diseases have also been reported in humans, which transmit from animals to humans.¹⁰

In general, the HEV infection transfers through fecal-oral route (usually through drinking contaminated water and by ingestion of poorly cooked food). HEV infection can be transmitted through other sources such as blood transfusion, zoonotic transmission, and from mother to child. However, person to person transmission of HEV infection is not that common.^{11–13}

Up until now, seven closely related genotypes of HEV (HEV-1-7) have been documented.¹⁴ Large scale waterborne epidemics in developing countries are linked to HEV-1 and HEV-2. On the other hand, genotypes HEV-3 and HEV-4 are

associated with sporadic cases occurring in developed countries.⁷ The possible courses of HEV infections are presented in Figure 1.

The zoonotic isolates (HEV-3 and HEV-4) as it transfers from animals to humans via the consumption of uncooked and contaminated meat.⁴ Recent studies documented that genotype HEV-3 is associated with liver cirrhosis and chronic hepatitis.¹⁶ Furthermore, the number of HEV cases among immune-compromised patients is of serious concern worldwide.⁷

Transmission

In general, the HEV infection transmits by fecal-oral route, usually through drinking contaminated water and ingesting food such as undercooked meat). HEV infection can transmit through other sources such as blood transfusion, zoonotic transmission, and from mother to child. However, person to person transmission of HEV infection is rare.^{11–13,17} Zoonotic transmission of HEV, genotype 3 and 4 results from sporadic and cluster cases in humans. Many outbreaks of HEV infection due to fecal contamination of drinking water are reported in some countries in Africa and Asia.¹⁸

In China, the pork industry is the largest contributor; therefore, the human population engaged in pig-farming risks exposure, as well as those who consume the animals as food. Personal hygiene combined with pork consumption influences health. Waste water contaminated with HEV can be a possible route of environmental contamination through pig slurry.

Replication

HEV is an important human pathogen that historically has been difficult to study. Our understanding of the viral life

cycle is limited.¹⁹ Previously published literature reported that the life cycle of HEV is largely unknown due to the lack of a robust cell-culture for Hepatitis virus.^{20–22} Recently, the replicon and in vitro infection system became available, a lot of work has been generated on HEV positive-strand RNA viruses and sub-genomic expression of viral open reading frames.²²

For translation and cleavage process the virus uses common cellular mechanism. The successful propagation of the HEV in cell culture has been limited. In other viruses, the ORF 1 contains particular motifs with unknown functions. The virus uses viral RNA polymerase for the synthesis of genomic and messenger RNA through a negative-strand RNA intermediate. The sub-genomic RNA transcripts (2.0 and 3.7 kb) have been reported but the significance is not known.²³

Lack of standardized detection methods, sporadic and low-level virus shedding, and subclinical infections made the development of animal models difficult for HEV infection. Continued animal models development of HEV will be instrumental in understanding the many complex questions associated with HEV infection.¹⁹

Vulnerable groups

HEV can cause infection at any stage of life. But during the HEV outbreaks, adolescents and adults between ages of 15 and 40 years are at a particularly high risk for infection. However, in young children the HEV infection is less likely to cause disease. HEV infection appears to be more common in men than women.²⁴ Beside this, among pregnant women the HEV infection is associated with an increased likelihood of symptomatic disease, fulminant hepatic failure and death, as compared to non-pregnant women and men. In pregnant women, the mortality rate is as high as 15 to 20%.²⁵ People with pre-existing chronic liver disease are also at high risk of serious

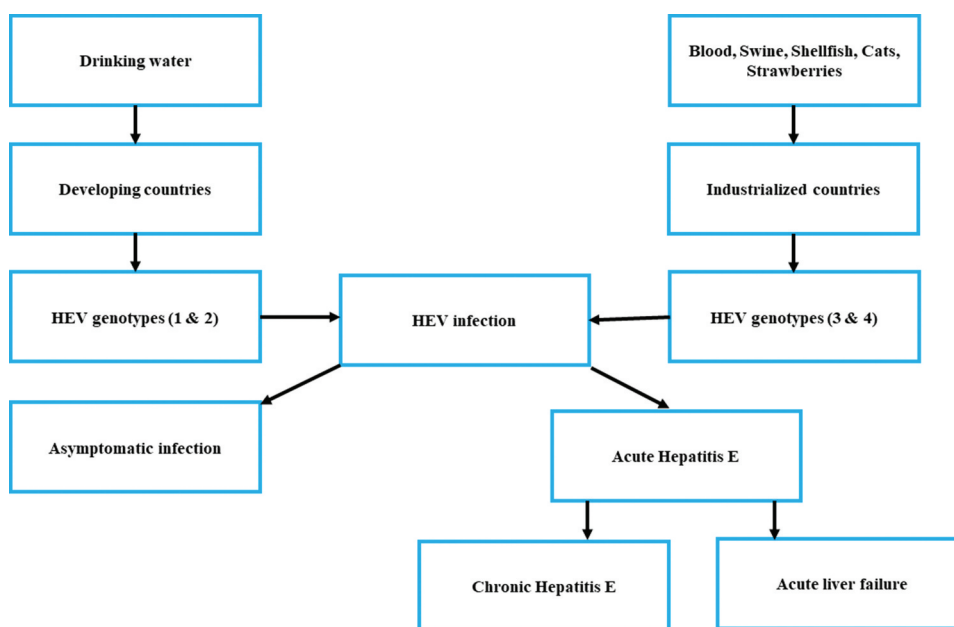


Figure 1. Possible courses of HEV infection.¹⁵

illness, which may lead to life threatening conditions.^{26,27} The marginalized communities living in, internally displaced people (IDP) refugees' camps, migrants, urban slums, cross-border populations and ethnic minorities are hard to reach and therefore at increased risk of HEV and other infectious diseases.²⁸ A total of 1,117 HEV suspected cases were reported during April 2014 to January 2015 among the refugees residing in the Gambella region. Of the total cases the mortality rate was 21 (1.9%).²⁹

HEV history

In 1980, HEV was first time isolated during a waterborne outbreak in India. Through the application and uses of antibody's assays for the detection of Hepatitis A virus (HAV) and Hepatitis B virus (HBV) subsequent outbreaks across Asia, the Middle East and North Africa were recognized.^{30,31} Initially HEV was designated as enterically transmitted non-A, non-B hepatitis (ET-NANBH) due to similar clinical presentations to hepatitis A and B.³²

Few years later, in 1983, from HEV affected patients a scientist had experimentally ingested a fecal suspension showed the symptoms of disease after 30–35 days. Study of his fecal inoculations during his infection period reported HEV through immune electron microscopy. This discovery and identification of virus brought a new revolution in the field of virology.³²

Early studies implied that RNA virus was the potential agent to cause ET-NANBH. Analysis of a cDNA library was performed for infectious bile sample, which resulted in a highly conserved RNA-dependent RNA-polymerase (RdRp) motif usually found in RNA viruses.³³

As a result in 1991, the scientists cloned and sequenced the HEV successfully, and found that the HEV genome contains three opening reading frames (ORF1, ORF2, and ORF3) with a size of 7.2kb. The ORF1 codes for transcription of non-structural proteins, ORF2 codes for capsid protein, and ORF3 responsible for protein of unknown origin.^{23,34} The exact function of ORF3 still remains unclear. However, numerous functions and roles have been proposed.^{22,34}

In the year 2009, the HEV structure was studied through X-ray crystallography.³⁵ Later on a number of studies have been conducted on the molecular biology and genetics of HEV. It was found the virus shares some genetic similarities with rubella virus, and some physical similarities with caliciviruses. Based on those similarities, the virus was assigned to its own genus "Hepevirus" and family "Hepeviridae".¹⁴

Global statistics of HEV

HEV cases are reported from both developed and developing countries, but the HEV is more common in East and South Asia. Global statistics of HEV infection shows that, every year an estimated 20 million cases are reported. Of the reported cases approximately 3.3 million lead to symptomatic cases of hepatitis E. In 2015, HEV caused approximately 44,000 deaths, accounting for 3.3% deaths due to viral hepatitis. Of the total reported cases great majority were from developing countries.⁹ In contrast to large scale outbreaks in the developing countries, the cases in developed countries are associated

with zoonotic transmission.¹⁸ In Africa and Asia, the estimated prevalence of HEV ranges from 15 to 25%.³⁶

Prevalence of HEV in developed countries

In past, among developed regions there was a perception that HEV is a rare disease and is caused by visiting epidemic centers.³⁷ In Europe and other developed countries, the autochthonous hepatitis E was caused by genotype 3.³⁸ Recently, increases in HEV cases have been observed in developed/industrialized countries. The seroprevalence of HEV in developed countries ranges from <5 to >50%. The variation in seroprevalence may be attributed to the different ethnic groups, geographical location, and the type of serological assays used.³⁹

Another study reported the estimated seroprevalence of HEV in Europe ranges from 0.6 to 52.5%, which increases with age. Depending on assays method the seroprevalence varied among the general population; Wantai (WT): 17%, Mikrogen (MG): 10%, MP-diagnostics (MP): 7%, DiaPro: 4%, Abbott 2%. Communities living in close contact with wild animals and swine had significantly higher seroprevalence than the general population ($p < .0001$).³⁸ The prevalence of anti-HEV antibodies among blood donors in European countries range from 1.3% in Italy (Scotto et al., 2014) to 52% in France (Mansuy et al., 2011).^{40,41}

HEV infection in kidney transplant patients

HEV infection for organ recipients can lead to chronic hepatitis and complications. Some previous studies showed an unexpectedly high prevalence of anti-HEV antibodies in hemodialysis patients.^{42–45} In hemodialysis patients, the high prevalence of HEV could be related to their impaired immunity.^{46–48} A study conducted in Italy showed, the HEV prevalence was 6% in dialysis patients, 3.3% in transplant recipient, while in general population the prevalence was 2.7%.⁴⁹

HEV infection in pregnancy

HEV infection is more lethal in pregnant women compared to general population. The HEV may result in severe consequences during pregnancy for both mother and fetus such as fulminant hepatic failure, vertical transmission, and maternal mortality.^{50,51} A systematic review was conducted on 23 observational studies with a sample size of 1338. The median maternal rate was 26% (IQR 17–41%), fetal 33% (IQR 19–37%) and neonatal case-fatality rate was 8% (IQR 3–20%). The overall median prevalence of fulminant hepatic failure was found to be 45.3%. The findings suggested high case-fatality rate among pregnant women and adverse outcomes on their children.⁵⁰

A recent study conducted on a rabbit model to study the adverse pregnancy outcomes and their prevention by Hepatitis E vaccine. The results demonstrated that different HEV genotypes infected pregnant rabbits and resulted in adverse pregnancy outcomes and as well as vertical transmission. The HEV vaccine 239, is very effective to protect the pregnant women from HEV infection and their adverse pregnancy outcomes.⁵¹

A research was conducted by Li et al.⁵² among 946 pregnant women in China. The overall positivity rate for anti-HEV IgG antibody was (74/365, 20.27%), anti-HEV IgM antibody was (15/365, 4.11%), and both anti-HEV IgM and IgG antibodies were (12/365, 3.29%). The infections were significantly higher ($p < .05$) in third trimester than in the first and second. The average level of alanine transaminase (ALT) was (34.49 ± 10.15), and both anti-HEV IgM and IgG positive group had the incidence of adverse pregnancy outcomes (13/18, 72.22%) that were significantly higher than other groups ($p < .05$). Only one sample had the HEV RNA which belonged to sub-genotype 4a.

A recent study shows that, of the total 7160 pregnant women, 1182 were positive to anti-HEV IgG antibody and only 66 were positive to anti-HEV IgM antibody. The overall pooled prevalence among pregnant women was 16.51% (95% CI: 0.10–0.23).⁵³

Number of studies reported HEV outbreaks in pregnant women in different countries as shown in Table 1. Highest number of outbreaks occurred in India in 1987, 1988, and in 1991. The recent outbreaks of HEV in pregnant women were reported in Sudan during 2010–2011.

HEV and HAV co-infection

The⁵⁴ co-infection of both Hepatitis A virus (HAV) and HEV lead to serious complications resulting in acute viral hepatitis.⁶⁸ The epidemics of HAV are not very common and affect infants and young children in developing countries.⁶⁹ While the HEV affects the older children and young adults in the tropical regions. However, the epidemics of HEV are common.^{68,70}

A cross-sectional study was conducted among 1230 individuals. The serum samples were processed for the presence of HAV and HEV antibodies. The result shows that the prevalence of HAV and HEV were 15.5, and 27.2%, respectively. The co-infection of HAV-HEV was 5.1%. Furthermore, the prevalence of HEV is higher than that of HAV. The screening of HEV especially in pregnant women and improved levels of personal hygiene among lower socio-economic communities is of great importance.⁶⁸

Table 1. HEV outbreaks (serologically confirmed) in pregnant women in different countries.

No.	Country	Year	Total cases	Deaths	References
1	Nepal	1987	73	18	54
2	India	1987	19	3	55
3	India	1988	30	2	56
4	Somalia	1988–1989	346	48	57
5	Indonesia	1991	19	5	58
6	Kenya	1991	28	4	59
7	India	1991	48	12	24
8	Djibouti	1991–1993	3	1	60
9	Pakistan	1993–1994	35	4	61
10	Central African Republic	2002	7	1	62
11	Sudan	2004	61	19	63
12	Uganda	2007–2009	189	13	64
13	Bangladesh	2008–2009	21	4	65
14	Bangladesh	2010	12	3	66
15	Sudan	2010–2011	39	11	67

Laboratory diagnosis of HEV

Recently, number of HEV cases linked to blood transfusion have increased and are considered as transfusion-transmitted virus. To confirm a diagnosis of HEV infection, clinical manifestations and biochemical tests not only diagnose HEV infections, but are helpful in identifying the onset and stage of infections. Therefore, to diagnose HEV infection properly, it requires optimally a combination of both molecular and serological techniques, and to monitor the treatment response in chronically HEV-infected individuals. There are several serological and molecular detection methods for HEV infection. However, the detection of HEV laboratory diagnostic techniques varies in their specificity and sensitivity. The antigen, viral nucleic acid, and viral protein can be detected by direct techniques, while the HEV specific antibodies (IgM and IgG) can help establish a diagnosis in acute and chronic infections.⁷¹ Diagnostic methods of HEV are presented in Figure 2.

Treatment of HEV

The acute HEV infection in immunocompetent individuals does not usually require antiviral therapy. However, some patients might require symptomatic treatment, but almost all patients are able to clear the disease spontaneously.⁷² A 61-year-old patient infected with HEV genotypes 3, who developed impaired liver function and severe acute hepatitis E, with no sign of liver encephalopathy was treated with ribavirin therapy. The result showed that after therapy alanine aminotransferase level (ALT) had normalized, and the level of bilirubinemia was 138 $\mu\text{mol/L}$. Furthermore, the HEV RNA was almost undetectable in the serum from same patient.⁷³ Treatment recommendation of HEV is presented in Figure 3.

Vaccines

The mortality rate of HEV (3.3%) demands a globally available vaccine. Usually, pregnant women with HEV-1 infection have shown worse effect and have been considered to be the main target group to receive vaccination.^{75,76} Public health surveillance of overall population is also extremely important to overcome on outbreaks with improving sanitation and hygiene in endemic and non-endemic countries.^{77,78}

It has been found that to develop live attenuated or inactivated vaccine by in vitro cell culture replication is not feasible.⁷⁹ Symptomatic relief by passive immunoprophylaxis has been achieved but not succeeded to prevent the infection. So, the focus was shifted on development of recombinant vaccine.⁸⁰

So far, two recombinant vaccines against HEV infection have been developed by Glaxo SmithKline, Belgium,⁸¹ and Xiamen Innovax Biotech, China.⁸²

The only licensed HEV vaccine is HEV 239 vaccine (Hecolin, Xiamen Innovax Biotech, China), which was approved and registered in China in 2011 but has not yet been approved in any other country. Further clinical trials of this vaccines are ongoing in Bangladesh.^{83,84} HEV is antigenically conserved in that it presents only one known serotype that is protective for all four HEV genotypes. Thus, a group-common vaccine approach is possible.^{85,86}

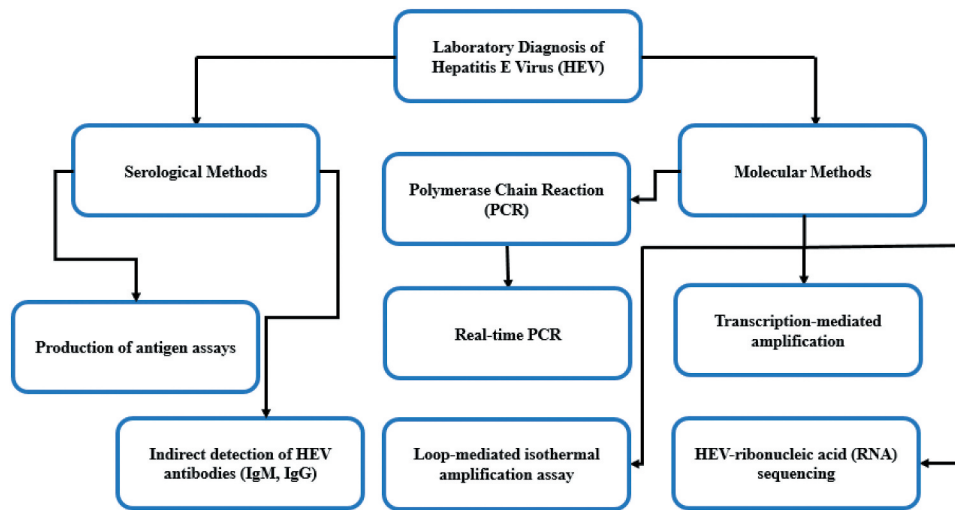


Figure 2. HEV diagnosis methods.⁷¹

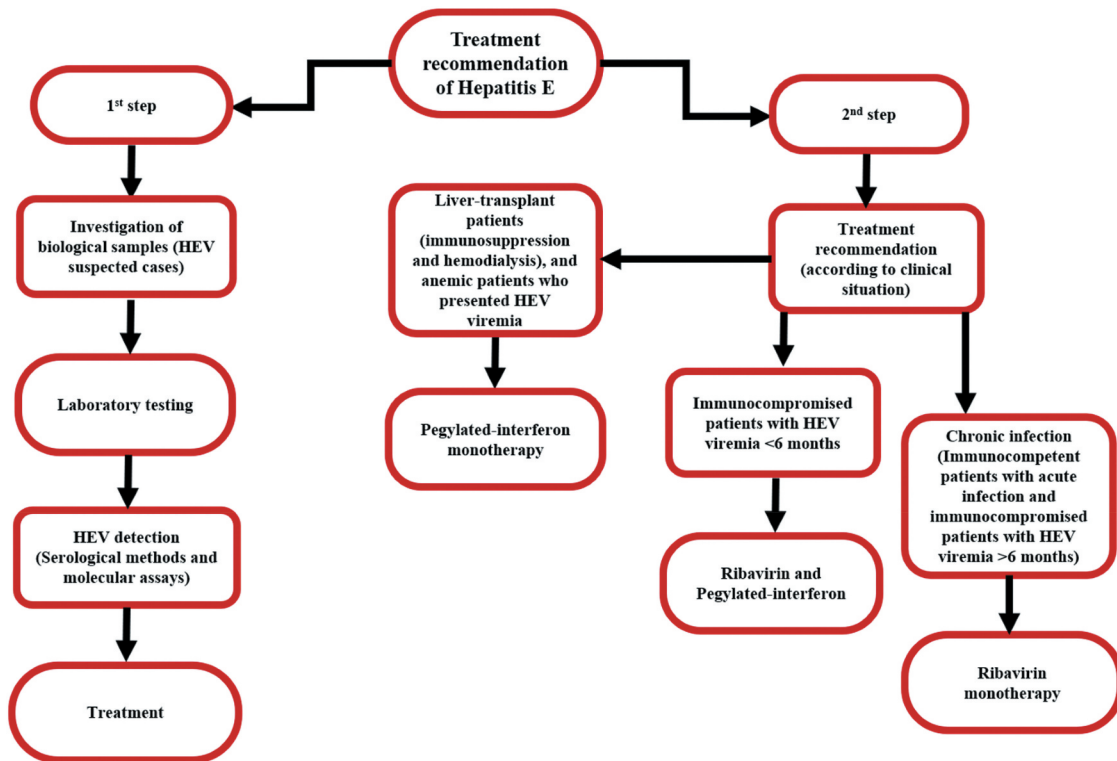


Figure 3. Treatment recommendations of HEV infection.⁷⁴

Prevention

There is a dire need of “One Health” initiative to forge co-equal, all inclusive research collaboration and disease prevention measurements between physicians, veterinarians, environmentally related disciplines, and other scientific-health domains. For HEV, there is no globally approved and commercially available vaccine. Good hygiene practices, improved sanitation measures, clean drinking water, and avoidance of high-risk situations is the best ways to prevent the HEV infection. While traveling to endemic areas, special care and prevention must be observed, including boiling water or drinking bottled water, and avoiding

raw or steamed shellfish such as, oysters that live in contaminated waters. Pregnant women are at high risk of infection especially those living or traveling to the endemic areas must take special care according to the standard traveling guideline to the endemic regions. The prevention strategies of HEV are presented in Figure 4.

Objective

This study aimed to discuss the epidemiology, diagnosis, available vaccines, and provides an overview of the 100 most cited studies on HEV. This study may help and provide the base line

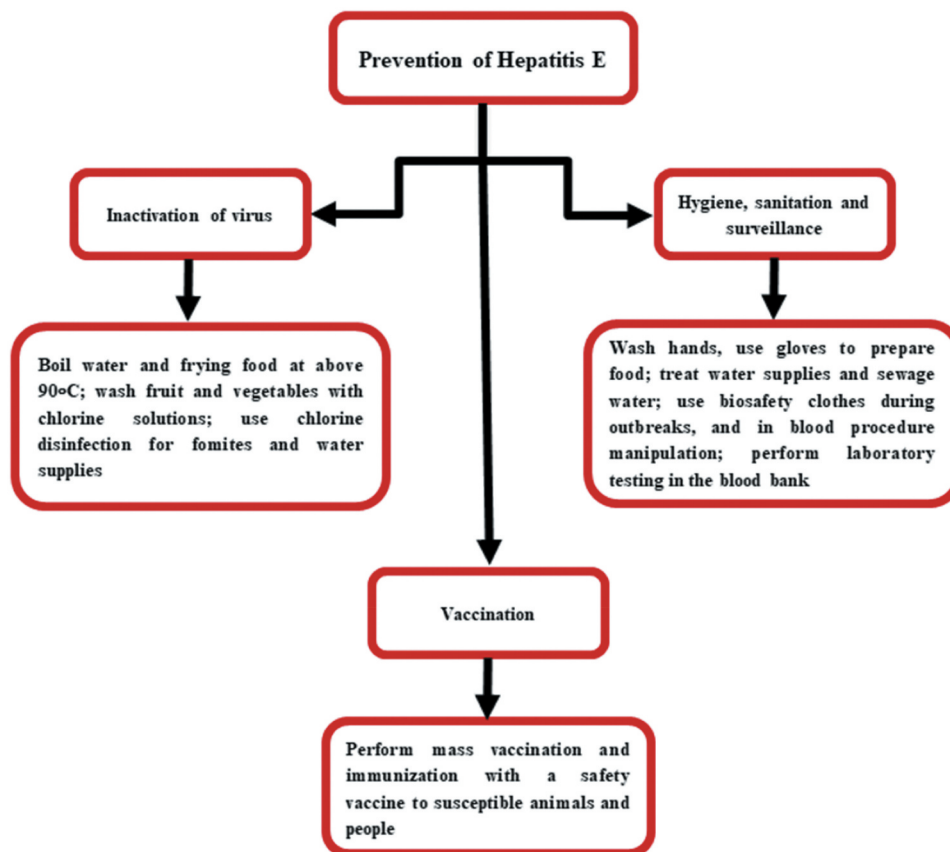


Figure 4. Prevention and control strategies of HEV.⁷⁴

information on the distribution of studies on HEV, and to help the researchers and policy makers to understand the characteristics of research output and provide reference for future studies.

Methodology

Study design

A bibliometric method analysis was conducted.

Data sources

An electronic search was conducted on Web of Science, Clarivate Analytics for time span from inception of Web of Science till December, 2016 on the topic “HEV”, and articles were retrieved on January 01, 2020. For articles searching, following keywords were used such as “Hepatitis E” “Title” field. The records obtained were refined by document types (articles, reviews, editorials, meeting abstracts and others) from Web of Science Core Collection (ISI-Thomson Reuters Web of Knowledge, hosted by Clarivate Analytics). To identify the 100 most cited papers on HEV, all the articles were ranked by the number of citations.

Eligibility criteria

Studies conducted mainly on HEV and articles, reviews, editorials or research letters were included in the analysis. Studies identified the word “Hepatitis E” but did not deal

with Hepatitis E were excluded. Furthermore, abstracts, correspondence, and errata/corrigenda were excluded.

Data extraction

On the same day of search, data were obtained by two independent investigators (Tauseef Ahmad and Taha H. Musa) to avoid any bias in data collection. The discrepancies were discussed and resolved after discussion with a third investigator. The retrieved data information was assessed for a number of attributes including title of article, author names, times cited, cites per document, most frequently cited articles, year of publication, type of paper, countries/region, institutes/organizations, and name of journal.

Data analysis

The descriptive statistical analysis was carried out in Microsoft Excel 2016 such as year of publication, authors, type of publication, number of citations, countries/regions, institutes/organizations, and journal names.

Ethics

No ethical approval was required for this study as this was an analysis of already published studies. None of the author of the included studies was contacted for further information regarding their publications.

Results

Characteristics of the total studies

A total of 3,235 publications were extracted from Web of Science (from inception to December, 2016) with a total of 95,858 citations. The average citations per publication were 29.63 times. The overall, h-index was 129.

Characteristics of 100 top-cited studies

Based on cited frequency the articles are listed in descending order. The top 100 highest cited articles were further processed for citations analysis. The major findings were; total number of authors were 470, range from 1 to 23, countries (n = 27), institutions (n = 220), journals (n = 33), local references (n = 92), global references (n = 1610), all cited references (n = 1702), cited reference range from 4 to 304, global citation score per year range from 6.61 to 175, and global citation score range from 148 to 791.

Citations analysis

The 100 top-cited studies on HEV are presented in Table 2. Overall, the included 100 top-cited studies have been cited 24,901 times (range from 148 to 791 times). Of the included studies, only 6 studies were cited more than 500 times, 45 studies were cited between 200 and 500 times, and a great number of studies (n = 49) were cited below 200 times. The first top-cited study was “A novel virus in swine is closely related to the human hepatitis E virus” authored by Meng et al. (1997), published in the “*Proceedings of The National Academy of Sciences of The United States of America*”. The study was cited 791 times with 32.96 average citations per year. This study opened a new avenue of research focusing xenozoonosis and xenotransplantation. This study formed the basis of further highly cited articles not only by Meng and his study group but also for others working on various aspects of pig organs transplantations in humans. It also provided a reference point for further studies on alternative animal model for HEV studies. The second top-cited was “Hepatitis-E Virus (HEV) – Molecular-Cloning and Sequencing of The Full-Length Viral Genome” published in the journal “*Virology*” by Tam et al. (1991), with 753 citations and 25.1 average citations per year. The findings on the genetic organization and expression strategy of HEV suggested in the article form the basis of a new era of studies on molecular cloning and protein assays. The third top-cited study published by Kamar et al. (2008), in the “*New England Journal of Medicine*” entitled “Hepatitis E virus and chronic hepatitis in organ-transplant recipients. The study was cited 718 times with an average per year citations 55.23. After the discovery of HEV in early 80 s most of the research for the next two decades was focused on phylogenetic analyzes and molecular diagnostics of HEV. The focus of research was shifted more toward treatment and vaccine development mostly in the last decade. The 10 top-cited studies on HEV vaccine is presented in Table 3. The most cited study was “Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial” cited 372 times.

Distribution of authors

Among the 100 top-cited studies, the authors who published most studies were Purcell (n = 18) with 4923 times, Meng (n = 17) with 4714 citations, and Emerson (n = 15) with 4286 citations as shown in Table 4.

Distribution of institutions

Of the total included studies majority of the studies were published from The National Institute of Allergy and Infectious Diseases [NIAID, (n = 16)], cited 3950 times, followed by Virginia Polytechnic Institute and State University (n = 13) with 3124 citations as presented in Table 5.

Distribution of countries

Most of studies were published from United States of America [USA, (n = 49)] with 12795 citations, followed by United Kingdom [UK, (n = 18)] with 4344 citations, and France (n = 15) received 4247 citations as described in Table 6. In spite of the fact that the global burden of HEV is more in East and South Asia, and in Africa, the research output from these countries is not much. This may raise concerns for the health organizations to support and fund HEV research in disease burdened countries for developing effective control and prevention strategies.

Distribution of journals

Table 7 shows the journal with 5 or more than 5 published studies among 100 top-cited articles. The “*Journal of General Virology*” was the leading journal with 12 publications with 2,573 citations.

Distribution of keywords

Table 8 showed the hotspots keywords; the hotspots keywords included Hepatitis (n = 100), and Virus (n = 75).

Distribution of document types

Number of articles were found to be 73 (with 18254 citations), and review were 16 (4271 citations) as shown in Table 9.

Distribution of published years

The highest number of studies published in 2007 (n = 10) with 1949 citations, and in 2008 (n = 09) cited 2761 times as shown in Table 10.

Discussion

In the last two decades, greater number of studies has been published on the HEV antibodies prevalence in different human populations. However, in recent years, the HEV cases have increased up to 70% in some industrialized countries. The heterogeneity of HEV prevalence may be attributed to different factors such as assays methods, and geographical regions.³⁹

Table 2. The 100 top-cited studies on Hepatitis E virus.

Ranking	Title	Journal	Publication Year	Total Citations	Average per Year
1	A novel virus in swine is closely related to the human hepatitis E virus	Proceedings of The National Academy of Sciences of The United States of America	1997	791	32.96
2	Hepatitis-E Virus (HEV) – Molecular-Cloning and Sequencing of The Full-Length Viral Genome	Virology	1991	753	25.1
3	Hepatitis E virus and chronic hepatitis in organ-transplant recipients	New England Journal of Medicine	2008	718	55.23
4	Zoonotic transmission of hepatitis E virus from deer to human beings	Lancet	2003	639	35.5
5	Hepatitis E	Lancet	2012	553	61.44
6	Phylogenetic analysis of global hepatitis E virus sequences: genetic diversity, subtypes and zoonosis	Reviews in Medical Virology	2006	552	36.8
7	Hepatitis E: An emerging awareness of an old disease	Journal of Hepatology	2008	436	33.54
8	Genetic and experimental evidence for cross-species infection by swine hepatitis E virus	Journal of Virology	1998	427	18.57
9	Hepatitis E: an emerging infection in developed countries	Lancet Infectious Diseases	2008	424	32.62
10	Sporadic acute or fulminant hepatitis E in Hokkaido, Japan, may be food-borne, as suggested by the presence of hepatitis E virus in pig liver as food	Journal of General Virology	2003	412	22.89
11	Pig Liver Sausage as a Source of Hepatitis E Virus Transmission to Humans	Journal of Infectious Diseases	2010	404	36.73
12	A broadly reactive one-step real-time RT-PCR assay for rapid and sensitive detection of hepatitis E virus	Journal of Virological Methods	2006	398	26.53
13	Hepatitis E virus	Reviews in Medical Virology	2003	373	20.72
14	Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomized, double-blind placebo-controlled, phase 3 trial	Lancet	2010	364	33.09
15	Prevalence of antibodies to hepatitis E virus in veterinarians working with swine and in normal blood donors in the United States and other countries	Journal of Clinical Microbiology	2002	350	18.42
16	Factors Associated with Chronic Hepatitis in Patients with Hepatitis E Virus Infection Who Have Received Solid Organ Transplants	Gastroenterology	2011	325	32.5
17	Persistent Carriage of Hepatitis E Virus in Patients with HIV Infection.	New England Journal of Medicine	2009	323	26.92
18	Computer-Assisted Assignment of Functional Domains in The Nonstructural Polyprotein of Hepatitis-E Virus – Delineation of an Additional Group of Positive-Strand RNA Plant and Animal Viruses	Proceedings of The National Academy of Sciences of The United States of America	1992	323	11.14
19	Hepatitis E virus transmission from wild boar meat	Emerging Infectious Diseases	2005	316	19.75
20	Safety and efficacy of a recombinant hepatitis E vaccine	New England Journal of Medicine	2007	314	22.43
21	Hepatitis E virus: Animal reservoirs and zoonotic risk	Veterinary Microbiology	2010	296	26.91
22	The global burden of hepatitis E virus genotypes 1 and 2 in 2005	Hepatology	2012	286	31.78
23	Hepatitis E Virus Infection	Clinical Microbiology Reviews	2014	281	40.14
24	Current Concepts Hepatitis E	New England Journal of Medicine	2012	270	30
25	The sequence and phylogenetic analysis of a novel hepatitis E virus isolated from a patient with acute hepatitis reported in the United States	Journal of General Virology	1998	266	11.57
26	Molecular-Cloning and Sequencing of the Mexico Isolate of Hepatitis-E Virus (HEV)	Virology	1992	265	9.14
27	Hepatitis E virus in blood components: a prevalence and transmission study in southeast England	Lancet	2014	258	36.86
28	Detection by reverse transcription-PCR and genetic characterization of field isolates of swine hepatitis E virus from pigs in different geographic regions of the united states	Journal of Clinical Microbiology	2002	252	13.26
29	Genetic identification and characterization of a novel virus related to human hepatitis E virus from chickens with hepatitis-splenomegaly syndrome in the United States	Journal of General Virology	2001	251	12.55
30	Hepatitis E Virus Antibodies in Blood Donors, France	Emerging Infectious Diseases	2011	249	24.9
31	Detection and characterization of infectious Hepatitis E Virus from commercial pig livers sold in local grocery stores in the USA	Journal of General Virology	2007	244	17.43
32	Genetic heterogeneity of hepatitis E virus	Journal of Medical Virology	2001	239	11.95
33	Genetic variability and evolution of hepatitis E virus	Virus Research	2007	234	16.71
34	Comparative pathogenesis of infection of pigs with hepatitis E viruses recovered from a pig and a human	Journal of Clinical Microbiology	2001	232	11.6
35	Characterization of a Prototype Strain of Hepatitis-E Virus	Proceedings of The National Academy of Sciences of The United States of America	1992	230	7.93
36	Complete or near-complete nucleotide sequences of hepatitis E Virus genome recovered from a wild boar, a deer, and four patients who ate the deer	Virology	2004	228	13.41
37	Severe hepatitis E virus infection after ingestion of uncooked liver from a wild boar	Journal of Infectious Diseases	2003	227	12.61
38	Ribavirin for Chronic Hepatitis E Virus Infection in Transplant Recipients	New England Journal of Medicine	2014	224	32
39	Chronic hepatitis E with cirrhosis in a kidney-transplant recipient	New England Journal of Medicine	2008	222	17.08
40	A Novel Genotype of Hepatitis E Virus Prevalent Among Farmed Rabbits in China	Journal of Medical Virology	2009	221	18.42

(Continued)

Table 2. (Continued).

Ranking	Title	Journal	Publication Year	Total Citations	Average per Year
41	Age-Specific Prevalence of Antibodies to Hepatitis-A and Hepatitis-E Viruses in Pune, India, 1982 and 1992	Journal of Infectious Diseases	1995	219	8.42
42	Zoonotic hepatitis E: animal reservoirs and emerging risks	Veterinary Research	2010	218	19.82
43	Chronic hepatitis E virus infection in liver transplant recipients	Liver Transplantation	2008	214	16.46
44	Expression and self-assembly of empty virus-like particles of hepatitis E virus	Journal of Virology	1997	214	8.92
45	Solid-Phase Enzyme-Linked-Immunosorbent-Assay for Hepatitis-E Virus IgG And IgM Antibodies Utilizing Recombinant Antigens and Synthetic Peptides	Journal of Virological Methods	1992	214	7.38
46	Detection of a novel hepatitis E-like virus in feces of wild rats using a nested broad-spectrum RT-PCR	Journal of General Virology	2010	210	19.09
47	Hepatitis E virus epidemiology in industrialized countries	Emerging Infectious Diseases	2003	208	11.56
48	Hepatitis E and pregnancy: understanding the pathogenesis	Liver International	2008	206	15.85
49	Acute Hepatitis E Infection Accounts for Some Cases of Suspected Drug-Induced Liver Injury	Gastroenterology	2011	205	20.5
50	Transfusion-transmitted hepatitis E in a 'nonhyperendemic' country	Transfusion Medicine	2006	201	13.4
51	Identity of a novel swine hepatitis E virus in Taiwan forming a monophyletic group with human hepatitis E virus	Journal of Clinical Microbiology	1999	200	9.09
52	Vertical Transmission of Hepatitis-E Virus	Lancet	1995	199	7.65
53	A case of transfusion-transmitted hepatitis E caused by blood from a donor infected with hepatitis E virus via zoonotic food-borne route	Transfusion	2008	195	15
54	Maternal and fetal outcomes in pregnant women with acute hepatitis e virus infection	Annals of Internal Medicine	2007	194	13.86
55	Enzyme-Linked-Immunosorbent-Assay for Diagnosis of Acute Sporadic Hepatitis-E in Egyptian Children	Lancet	1992	192	6.62
56	Hepatitis e in the south west of France in individuals who have never visited an endemic area	Journal of Medical Virology	2004	190	11.18
57	Novel hepatitis E virus (HEV) isolates from Europe: Evidence for additional genotypes of HEV	Journal of Medical Virology	1999	190	8.64
58	Elisa for Antibody to Hepatitis-E Virus (HEV) Based on Complete Open-Reading Frame-2 Protein Expressed in Insect Cells – Identification of HEV Infection in Primates	Journal of Infectious Diseases	1993	185	6.61
59	Epidemiology of Hepatitis E Virus in the United States: Results from the Third National Health and Nutrition Examination Survey, 1988–1994	Journal of Infectious Diseases	2009	184	15.33
60	Seroactivity to hepatitis E virus in areas where the disease is not endemic	Journal of Clinical Microbiology	1997	183	7.63
61	Hepatitis E Virus and Neurologic Disorders	Emerging Infectious Diseases	2011	182	18.2
62	Hepatitis-E Virus – Identification of Type-Common Epitopes	Journal of Virology	1991	182	6.07
63	From barnyard to food table: The omnipresence of hepatitis E virus and risk for zoonotic infection and food safety	Virus Research	2011	181	18.1
64	Autochthonous hepatitis E in Southwest England: natural history, complications and seasonal variation, and hepatitis E virus IgG seroprevalence in blood donors, the elderly and patients with chronic liver disease	European Journal of Gastroenterology & Hepatology	2008	181	13.92
65	Evidence of extrahepatic sites of replication of the hepatitis E virus in a swine model	Journal of Clinical Microbiology	2001	180	9
66	Transfusion-transmitted hepatitis E caused by apparently indigenous hepatitis E virus strain in Hokkaido, Japan	Transfusion	2004	178	10.47
67	Hepatitis-E in pregnancy	Hepatology	1993	177	6.32
68	Swine hepatitis E virus strains in Japan form four phylogenetic clusters comparable with those of Japanese isolates of human hepatitis E virus	International Journal of Gynecology & Obstetrics	2004	176	10.35
69	A divergent genotype of hepatitis E virus in Chinese patients with acute hepatitis	Journal of General Virology	2003	176	9.78
70	Proposed reference sequences for hepatitis E virus subtypes	Journal of General Virology	1999	176	8
71	Determination and analysis of the complete genomic sequence of avian hepatitis E virus (avian HEV) and attempts to infect rhesus monkeys with avian HEV	Journal of General Virology	2016	175	35
72	Hepatitis E virus sequences in swine related to sequences in humans, the Netherlands	Journal of General Virology	2004	175	10.29
73	The ORF3 protein of hepatitis E virus is a phosphoprotein that associates with the cytoskeleton	Emerging Infectious Diseases	2001	175	8.75
74	Ribavirin Therapy Inhibits Viral Replication on Patients with Chronic Hepatitis E Virus Infection	Journal of Virology	1997	175	7.29
75	Polyphyletic strains of hepatitis E virus are responsible for sporadic cases of acute hepatitis in Japan	Gastroenterology	2010	174	15.82
76	Transfusion-associated hepatitis E, France	Journal of Clinical Microbiology	2002	173	9.11
77	Evidence for widespread infection of wild rats with hepatitis E virus in the United States	Emerging Infectious Diseases	2007	172	12.29
78	Experimental infection of pigs with the newly identified swine hepatitis E virus (swine HEV), but not with human strains of HEV	American Journal of Tropical Medicine and Hygiene	1999	172	7.82
79	Chronic infection with Camelid Hepatitis E Virus in a Liver Transplant Recipient Who Regularly Consumes Camel Meat and Milk	Archives of Virology	1998	172	7.48
80	A hepatitis E virus variant from the United States: molecular characterization and transmission in cynomolgus macaques	Gastroenterology	2016	171	34.2
81	A Large Waterborne Viral Hepatitis-E Epidemic in Kanpur, India	Journal of General Virology	1999	168	7.64
82		Bulletin of The World Health Organization	1992	168	5.79

(Continued)

Table 2. (Continued).

Ranking	Title	Journal	Publication Year	Total Citations	Average per Year
83	Cross-species infections of cultured cells by hepatitis E virus and discovery of an infectious virus-host recombinant	Proceedings of The National Academy of Sciences of The United States of America	2011	167	16.7
84	Epidemiology of hepatitis E: Current status	Journal of Gastroenterology and Hepatology	2009	167	13.92
85	Hepatitis-E Virus Transmission to a Volunteer	Lancet	1993	167	5.96
86	Hepatitis E virus: Molecular virology, clinical features, diagnosis, transmission, epidemiology, and prevention	Journal of Medical Virology	2008	165	12.69
87	Evaluation of assays for antibody to hepatitis E virus by a serum panel	Hepatology	1998	164	7.13
88	Development and evaluation of an efficient cell-culture system for Hepatitis E virus	Journal of General Virology	2007	163	11.64
89	Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death	Journal of Hepatology	2007	162	11.57
90	Fulminant liver failure from acute autochthonous hepatitis E in France: description of seven patients with acute hepatitis E and encephalopathy	Journal of Viral Hepatitis	2007	160	11.43
91	Hepatitis E virus antibody prevalence among persons who work with swine	Journal of Infectious Diseases	2001	158	7.9
92	Pathogenesis and Treatment of Hepatitis E Virus Infection	Gastroenterology	2012	157	17.44
93	The complete sequence of hepatitis E virus genotype 4 reveals an alternative strategy for translation of open reading frames 2 and 3	Journal of General Virology	2000	157	7.48
94	Hepatitis E virus	Reviews in Medical Virology	2007	156	11.14
95	Hepatitis E: An overview and recent advances in clinical and laboratory research	Journal of Gastroenterology and Hepatology	2000	156	7.43
96	Bats Worldwide Carry Hepatitis E Virus-Related Viruses That Form a Putative Novel Genus within the Family Hepeviridae	Journal of Virology	2012	152	16.89
97	Successful Passive and Active Immunization of Cynomolgus Monkeys Against Hepatitis-E	Proceedings of The National Academy of Sciences of The United States of America	1994	152	5.63
98	Hepatitis E Outbreak on Cruise Ship	Emerging Infectious Diseases	2009	150	12.5
99	The role of hepatitis E virus testing in drug-induced liver injury	Alimentary Pharmacology & Therapeutics	2007	150	10.71
100	Hepatitis E	Hepatology	2011	148	14.8

Table 3. The 10 top-cited studies on HEV vaccine.

Ranking	Title	Journal	Publication Year	Total Citations	Average per Year
1	Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomized, double-blind placebo-controlled, phase 3 trial	Lancet	2010	372	33.82
2	Safety and efficacy of a recombinant hepatitis E vaccine	New England Journal of Medicine	2007	317	22.64
3	A bacterially expressed particulate hepatitis E vaccine: antigenicity, immunogenicity and protectivity on primates	Vaccine	2005	139	8.69
4	Long-Term Efficacy of a Hepatitis E Vaccine	New England Journal of Medicine	2015	138	23
5	Pre-clinical immunogenicity and efficacy trial of a recombinant hepatitis E vaccine	Vaccine	2003	98	5.44
6	Recombinant vaccine against hepatitis E: dose response and protection against heterologous challenge	Vaccine	1997	98	4.08
7	Randomized-controlled phase II clinical trial of a bacterially expressed recombinant hepatitis E vaccine	Vaccine	2009	75	6.25
8	Hepatitis E, a Vaccine-Preventable Cause of Maternal Deaths	Emerging Infectious Diseases	2012	71	7.89
9	Hepatitis E vaccine development A 14-year odyssey	Human Vaccines & Immunotherapeutics	2012	60	6.67
10	Chimeric recombinant hepatitis E virus-like particles as an oral vaccine vehicle presenting foreign epitopes	Virology	2002	56	2.95

Table 4. Authors with at least five studies as first author or coauthor.

No.	Author	Records	Total Local Citations	Total Global Citations
1	Purcell RH	18	271	4923
2	Meng XJ	17	228	4714
3	Emerson SU	15	243	4286
4	Izopet J	11	68	3231
5	Dalton HR	10	65	2835
6	Ijaz S	9	71	2422
7	Kamar N	8	43	2706
8	Mushahwar IK	8	155	1845
9	Halbur PG	7	141	2298
10	REYES GR	7	151	2159
11	Okamoto H	6	59	1333
12	Abравanel F	5	43	1587
13	Jameel S	5	32	864
14	Mansuy JM	5	52	1499
15	Mishiro S	5	78	1467
16	Peron JM	5	58	1424
17	Rostaing L	5	38	1623
18	Takahashi K	5	78	1467
19	Toth TE	5	69	1189
20	Tsarev SA	5	83	969
21	Tsareva TS	5	109	1530

Table 5. Institutes with at least five studies.

Ranking	Institution	Records	Total Local Citations	Total Global Citations
1	NIAID	16	215	3950
2	Virginia Polytech Inst & State Univ	13	113	3124
3	CHU Purpan	7	41	2457
4	Ctr Dis Control & Prevent	7	38	1425
5	Royal Cornwall Hosp Trust	7	46	1906
6	Univ Toulouse 3	7	24	1988
7	Abbott Labs	6	137	1466
8	CHU Ranguel	6	41	2233
9	GENELABS INC	6	126	1894
10	Hlth Protect Agcy	6	56	1864
11	Iowa State Univ	6	95	1507
12	Toshiba Gen Hosp	6	93	1643
13	UCL	5	40	987

Table 6. Countries with at least five studies.

Ranking	Country	Records	Total Local Citations	Total Global Citations
1	USA	49	669	12795
2	UK	18	123	4344
3	France	15	93	4247
4	Japan	13	158	3330
5	India	12	68	2063
6	Peoples R China	6	67	2023
7	Germany	5	13	1019

Recently, various fields tried to identify the “citation classics” in that field, where the top 100 cited articles in that field identified.⁸⁷ The present study represents the analysis of citation classics in the field of hepatitis E, a disease widely prevalent in both, developed and developing countries. A large number of studies (research articles, systematic review/meta-analysis) on diagnosis, treatment, control and prevention of HEV have been conducted by researchers across the globe. However, despite the importance of bibliometric studies as a way of exploring research quantum, directions and collaborations between researchers and medical practitioners, very few

Table 7. Leading journals in the field in Hepatitis E research.

Ranking	Journal	Records	Total Local Citations	Total Global Citations
1	Journal of General Virology	12	171	2573
2	Emerging Infectious Diseases	7	32	1452
3	Journal of Clinical Microbiology	7	111	1570
4	Lancet	7	70	2372
5	Journal of Infectious Diseases	6	74	1377
6	New England Journal of Medicine	6	62	2071
7	Gastroenterology	5	18	1032
8	Journal of Medical Virology	5	60	1005
9	Journal of Virology	5	69	1150
10	Proceedings of The National Academy of Sciences of The United States of America	5	104	1663

Table 8. Top ten hotspots keywords.

Ranking	Word	Records	Total Local Citations	Total Global Citations
1	Hepatitis	100	1078	24901
2	Virus	75	880	19029
3	Infection	19	160	4450
4	Swine	10	183	2881
5	Liver	9	84	2124
6	Acute	8	103	1778
7	Chronic	8	58	2229
8	Novel	8	153	2281
9	Patients	8	82	1729
10	Transmission	8	92	2316

Table 9. Distribution of document types.

Ranking	Document Type	Records	Total Local Citations	Total Global Citations
1	Article	73	848	18254
2	Review	16	88	4271
3	Article; Proceedings Paper	4	59	847
4	Letter	4	47	944
5	Note	3	36	585

Table 10. Publication frequency per year.

Ranking	Publication Year	Records	Total Local Citation	Total Global Citations
1	1991	2	56	935
2	1992	6	103	1392
3	1993	3	29	529
4	1994	1	6	152
5	1995	2	28	418
6	1997	4	90	1363
7	1998	4	96	1029
8	1999	5	80	906
9	2000	2	18	313
10	2001	6	67	1235
11	2002	3	47	775
12	2003	6	97	2035
13	2004	5	55	947
14	2005	1	11	316
15	2006	3	33	1151
16	2007	10	75	1949
17	2008	9	83	2761
18	2009	5	32	1045
19	2010	6	38	1666
20	2011	7	25	1457
21	2012	5	7	1418
22	2014	3	1	763
23	2016	2	1	346

studies have been performed focused on bibliometric analysis on HEV; to the best of our knowledge no bibliometric analysis was performed on the 100 top cited studies on HEV research. Therefore, this study was conducted to determine the citation analysis and their principal characteristics in details. A steady increase in HEV publications was observed over the last few years, owing to increase in the global burden of this disease. An estimated 20 million HEV infections are reported worldwide by WHO, resulting in a large number of deaths.⁹ Therefore, understanding the characteristics of published studies on HEV may be worthwhile for several reasons. Our findings showed that 100 top-cited studies were cited 24901 times, reflecting their impact and importance. There were 6 studies that were cited more than 500 times in the literature.

Previous studies done to analyze hepatitis literature found a steady increase in publications on hepatitis in general, and on hepatitis E specifically in the last few decades.^{88,89} Wani et al.⁸⁸ performed a bibliometric analysis on all articles on hepatitis E using Web of Science, and the authors advised for further projects on hepatitis E. USA, UK, and Germany are the top countries publishing on Hepatitis in general.⁸⁹ Wani et al.⁸⁸ found that USA, India, and China are the top three countries publishing on HEV in general. Our study found that USA, UK, and France are the countries publishing most from HEV top-cited articles. This trend of publishing is not in consonance with the global geographical distribution of disease as it is more common in low- and middle-income countries where the disease occurs both as outbreaks and as sporadic cases. This study accentuates the need to establish research collaborations between researchers of developed countries and researchers in resource limited countries. The researchers, especially from resource limited countries need to be encouraged by providing technical and financial assistance to focus more on HEV research to prevent and control the disease outbreaks.

Quality and coverage of journals play an important role in dissemination of research to all stakeholders. The top journal publishing top articles on hepatitis E was “*Journal of General Virology*” as found in our study, “*Journal of Medical Virology*” was the journal with the highest number of publications on Hepatitis E.⁶ Both of these journals do not levy any publication charges although most of the journals charge quite heavy fee for publication/article processing. This highlights the need that the other quality journals may make waiver policies to attract quality publications from developing countries. Quality research may be carried out in low/middle income countries on local levels but it never gets published in international journals for lack of funds and is not disseminated to a wider audience. This study will not only provide a referral point for potential researches but will also help in planning and policy-making regarding prevention and control of HEV.

Study limitations

This study has several limitations. In our study we only extracted data from the articles indexed in Web of Science Core Collection database, and on the other hand articles in other databases such as Scopus and PubMed have missed

which may affect final findings. Furthermore, quality of the top-cited articles was not assessed which may influence the interpretation of the findings. In addition, the data generated in this article was through electronic search rather than selecting and collecting manually, therefore the findings of our study may be subject to bias. The manual selection of studies and extraction of data is required for systematic reviews/meta-analysis.

Translational value

The results presented in this article may be very useful for researchers and scientists to focus their research objectives in more appropriate domain in the field of HEV, and most importantly it can provide direction to guide health care decision making policies. Furthermore, it will help the academicians and teachers to provide the quality bibliographic references for learning and teaching purpose.

Highlights

- This study provides an overview on the epidemiology, diagnosis, available vaccines, and 100 top-cited studies on HEV.
- HEV is considered as the leading cause of enterically transmitted viral hepatitis infection in both developing and developed countries.
- So far, only two recombinant vaccines (rHEV, Belgium and HEV 239, China) have been developed against HEV but they are not available for commercial use yet.
- Most of the studies on HEV are published from developed countries.
- This study emphasizes the need of establishing research collaborations between researchers of developed countries and low-income countries.
- The researchers, especially from resource limited countries, need to be encouraged by providing technical and financial assistance to focus more on HEV research to prevent and control the disease outbreaks.

Authors contributions

Conceptualization: TA; Methodology: TA. Data collection: TA and THM. Formal analysis: TA and THM. Writing—original draft: TA. Review and editing: TA, SN, SASA, MK, and HJ. Funding acquisition: HJ. All the authors read and approved the final manuscript for publication.

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Disclosure of potential conflicts of interest

All the authors agreed and declare no conflict of interests.

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