

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Emerging Diseases

**Epidemiology of
Hepatitis E**

**Shahid Beheshti University of
medical sciences, 2018**

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https://sites.google.com/site/emergingreemergingdisappearing/emerging_ebook/emerging_index-htm

Definition

History

Etiology

Definition of hepatitis

- **Inflammation of the liver**
- *Classic hepatitis ?*
- **Can be caused by a variety of different viruses such as hepatitis A, B, C, D and E**
- *Correct diagnosis* **can only be made by testing patients' sera for the presence of specific viral antigens and/or anti-viral antibodies & molecular assays**

History of Hepatitis E

- **Hepatitis E was not recognized as a distinct human disease until 1980,** بیماری مستقل
- **Specific tests for antibody against hepatitis A were first applied to the study of epidemic waterborne hepatitis in India**
- **They examined collected serums from 1958 Indian large epidemic of hepatitis**
- **The first experimental evidence for the existence of an additional waterborne hepatitis agent was reported in 1983** اولین مطالعه تجربی

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History

- **Non-A, non-B hepatitis**
- **Enterically transmitted non-A non-B hepatitis (ET-NANB),**
- **Epidemic non-A non-B hepatitis (ENANB),**
- **Faecal-oral non-A non-B hepatitis,**
- **The major cause of sporadic hepatitis cases in regions where the epidemic form was known to exist**

کدامیک از هیات‌های کلاسیک به عنوان شایعترین هیاتیت تک
گیر (اسپورادیک) در مناطق آندمیک هیاتیت E مطرح شده
است؟

Health Importance

- **Every year there are 20 million hepatitis E infections**
- **Over 3.3 million acute cases of hepatitis E,**
- **44000 hepatitis E-related deaths in 2015.** (accounting for 3.3% of the mortality due to viral hepatitis)
- **High mortality rate in pregnant women**

WHO, Fact 2018

https://sites.google.com/site/emergingreemergingdisappearing/emerging_ebook/emerging_index-htm

Viral Hepatitis - Overview

Type of hepatitis

	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	Type 1&2 no Type 3&4 Yes
Prevention	pre/post- exposure immunization	pre/post- exposure immunization	blood donor screening; risk behavior modification	pre/post- exposure immunization; risk behavior modification	ensure safe drinking water immunization

Etiology

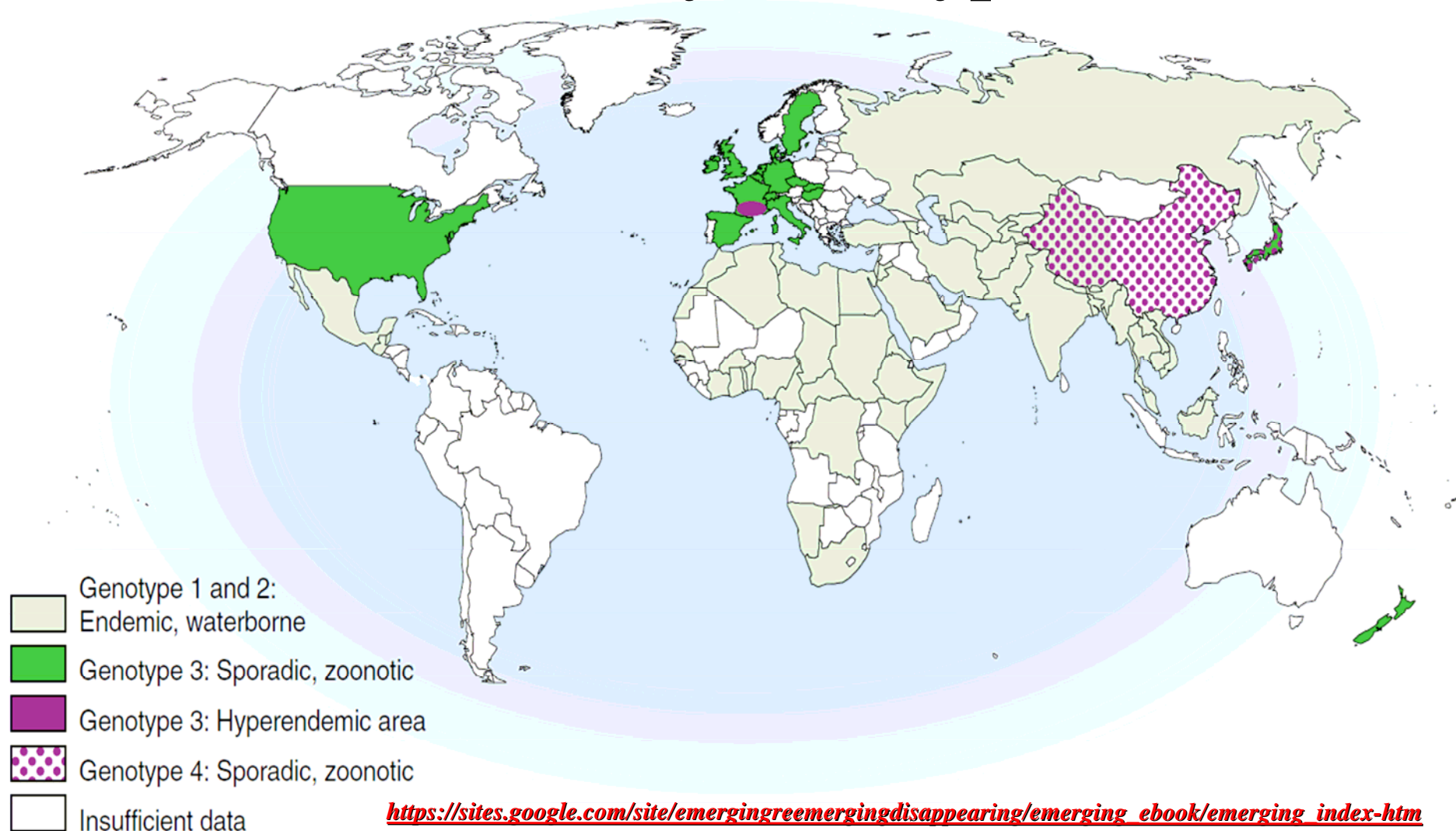
- **Hepatitis E virus (HEV),**
- **A nonenveloped, single stranded RNA virus**
- **Originally classified within the family of caliciviruses,**
- **Genus Hepevirus**
- **Family Hepeviridae**
- **Spherical**
- **Several different strains**

Etiology

- **Genotypes 1 and 2 have been found only in humans.**
- **Genotype 3 and 4 viruses circulate in several animals.**
- **Genotype 1 is usually seen in developing countries & causes community level outbreaks**
- **Genotype 3 is usually seen in the developed countries & does not cause outbreaks.**

Fact 2017

Etiology / Geographical Distribution of Virus, by Genotypes



Spherica

Spherical

Stability

- **HEV is extremely sensitive to high salt concentrations**
- **HEV should be stored as cold as possible,**
- **It is rapidly degraded when freeze-thawed.**
- **The virus is sensitive to degradation by proteolytic enzymes**

Stability

- Relative stability to acid and mild alkaline conditions
- Remain unaltered after exposure to trifluorotrchloroethane
- Outbreaks of HEV have been successfully controlled by chlorination of water supplies

Stability

- **Iodinated disinfectants or autoclaving destroys the virus**
- **For transportation, should be kept frozen in dry ice (solid CO₂, -70°C), or preferably in liquid N₂ (-120°C)**

مقاومت در مقابل اسید؟ باز؟ حرارت؟ کلر؟ یُد؟ اتوکلاو؟

Pathogenesis

- **In monkeys, viral replication apparently causes liver damage**
- **The immune response successfully eliminates viremia**
- **Seroconversion marks the clearing of virus from faeces and blood**
- **Severe or fulminant cases may show submassive and massive hepatic necrosis**

تاثیر پاسخ ایمنی در سیر بیماری حاد؟

ویژگی‌های مهم عامل عفونت‌زا

- * **Infectivity**
- * **Pathogenicity**
- * **Virolence**
- * **Antigenicity**
- * **Immunogenicity**

تعريف مورد (Case definition)

Clinical case definition:

- Discrete onset of an acute illness with signs/symptoms of (i) acute viral illness (e.g. fever, malaise, fatigue)
- and (ii) liver damage, which can be clinical
- (e.g. anorexia, nausea, jaundice, dark urine, right upper quadrant tenderness), and/or biochemical (alanine aminotransferase [ALT] levels more than 10 times the upper limit of normal)

تعريف مورد (Case definition)

Probable case:

- **Clinical criteria:** person meeting the case definition for acute hepatitis (*Previous slide*)
- **Biomarker criterion:** positive for IgM anti-HEV
- **Epidemiological criterion:** occurrence in the context of a biomarker-confirmed outbreak

مورد محتمل؟ مورد قطعي؟

تعريف مورد (Case definition)

Confirmed case:

- A case of acute hepatitis that tests positive for the biomarker criterion mentioned at previous slide

OR

- A case of acute hepatitis with an epidemiological link to a confirmed case

*Descriptive
epidemiology
and
occurrence*

https://sites.google.com/site/emergingreemergingdisappearing/emerging_ebook/emerging_index-htm

Clinical epidemiology of Hepatitis E

- **Definition and public health importance**
- **Etiologic agents**

- 1) **Incubation period**
- 2) **Natural course**
- 3) **Geographical distribution**
- 4) **Timeline trend**
- 5) **Age, Gender, Occupation, Social situation**
- 6) **Predisposing factors**
- 7) **Susceptibility & Resistance**
- 8) **Secondary attack rate**
- 9) **Modes of transmission, period of communicability**

OCCURRENCE

- **Prevention : primary, secondary, tertiary**

1 -Incubation Period

Average 6 weeks
Range 2-9 weeks

به نظر شما چه عواملی بر طول دوره نهفتگی
ویروس اثر می گذارد؟

سیر طبیعی هیپاتیت E

- میزان موارد بدون علامت (ساب کلینیکال)
- میزان موارد حاد
- میزان موارد مزمن
- میزان موارد بهبودی خودبخودی
- سیر بعدی بیماری با درمان و بدون درمان
- میزان مرتالیتی و مریدیتی
- میزان مصونیت بعد از بهبودی

2 - Natural course

- **Usually a self limited illness**
- **Liver failure can occur, particularly during pregnancy**
- **Case-fatality rate:** Overall, 1%-3%
Pregnant women, 15%-25%
- **Illness severity:** Increased with age
- **Chronic sequelae:** Genotype 1 & 2 -
Genotype 3 & 4 +

2 - Natural course

Chronic Hepatitis E

- HEV causes protracted and chronic hepatitis only in immunosuppressed patients, include:
 - Solid-organ recipients,
 - HIV-infected patients,
 - Patients receiving chemotherapy for hematologic malignancies.

2 - Natural course

۲- سیر طبیعی / عوارض خارج کبدی

Extrahepatic complications

- **Neurologic manifestations, such as:**
 - Guillain-Barré syndrome,
 - Bell's palsy,
 - Peripheral neuropathy,
 - Muscle wasting,
 - Acute transverse myelitis,
 - Acute meningoencephalitis.
- **Chronic glomerulonephritis & cryoglobulinemia**
- **Neurologic and kidney manifestations may completely or partially resolve if HEV is cleared.**

Natural course

- **Hepatitis E virus causes acute sporadic and epidemic viral hepatitis**
- **Symptomatic HEV infection is most common in young adults aged 15-40 years**
- **Asymptomatic and anicteric infection is frequent in children**
- **Comparable to hepatitis A**

Natural course

- A fulminant form of hepatitis develops, with mortality rates ranging between 0.5% - 4.0% of the overall population of patients
- Fulminant hepatitis cases in pregnancy may reach a mortality rate of 20% in the 3rd trimester
- Premature deliveries with high infant mortality of up to 33% are also observed
- The reason of high mortality is not clear

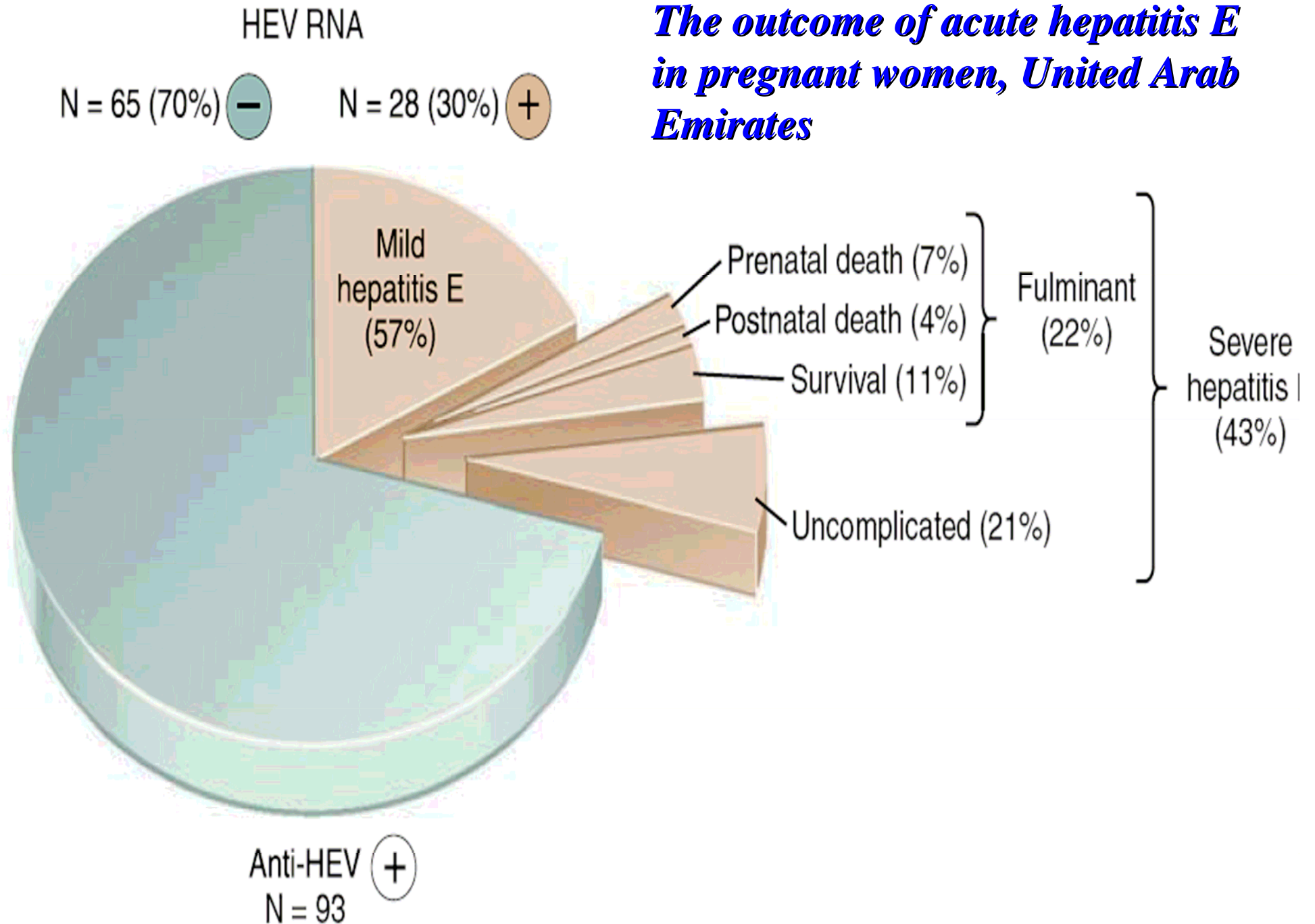
Natural course

- **Some of the complications of pregnancy are toxemia with hypertension, proteinuria, edema, and kidney lesions**
 - **HEV might precipitate eclampsia**
-
- *Common cholestatic jaundice can persist for several weeks*

Natural course Coinfection

- Coinfection of young children with **HEV** and **HAV** may lead to severe forms of disease, including acute liver failure.
- Coinfection of HIV-positive patients with HEV genotype 1, 2, or 4 has not been reported to date.

The outcome of acute hepatitis E in pregnant women, United Arab Emirates

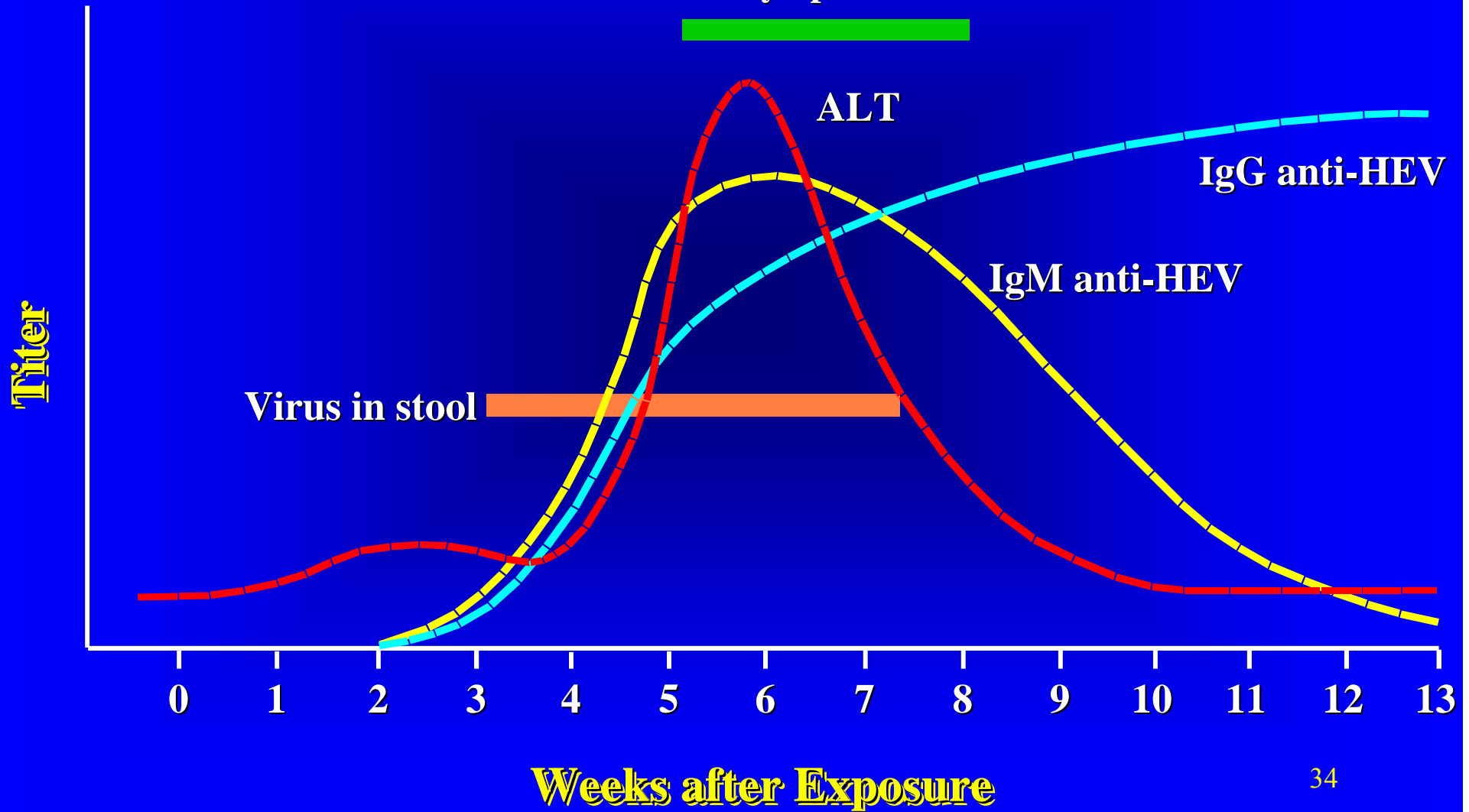


Host immune response

- **Virus excretion in stools continues for up to 14 days after onset of illness,**
- **Antibodies to HEV (IgM and IgG) develop at the time symptoms occur,**

Hepatitis E Virus Infection Typical Serologic Course

Symptoms



Host immune response

- **Viremia may persist after appearance of serum antibodies**
- **IgM anti-HEV titres decline rapidly during early convalescence**
- **IgG anti-HEV have been shown to persist for long periods of time (>16 yrs) and provide protection against subsequent infections**

Host immune response

- **Monkeys** infected with human **HEV** are protected against new challenge with homologous or heterologous strains
- The **immunity** is **incomplete** since only the clinical disease seems to be prevented

سیر طبیعی هیاتیت E ناشی از زئو تاپ های مختلف

Table 1. Clinical and Epidemiologic Characteristics of HEV Infections According to Genotype.

Characteristic	Genotypes 1 and 2 (Epidemic)	Genotypes 3 and 4 (Autochthonous)
Geographic distribution	Developing countries only	Both developing and developed countries
Pattern of spread	Epidemic and sporadic	Sporadic
Occurrence in United States	Travel-related, imported	Autochthonous
Species specificity	Human	Swine, human (humans are accidental host)
Major mode of spread	Fecal–oral, waterborne	Foodborne
Secondary spread	Uncommon	Extremely rare
Rate of icteric illness	High	Low
Age distribution	Disease rates highest among adolescents and young adults	Disease rates highest among older adults
Sex distribution	Similar disease rates among men and women	Higher disease rates among men
Mortality	High among pregnant women	High among older adults
Extrahepatic features	Few	Neurologic complications
Chronic infection	None	Common in immunosuppressed persons
Therapy	None known	Ribavirin, peginterferon (experimental)
Prevention	Vaccine*	Vaccine*

* An HEV vaccine has been approved in China but not elsewhere.

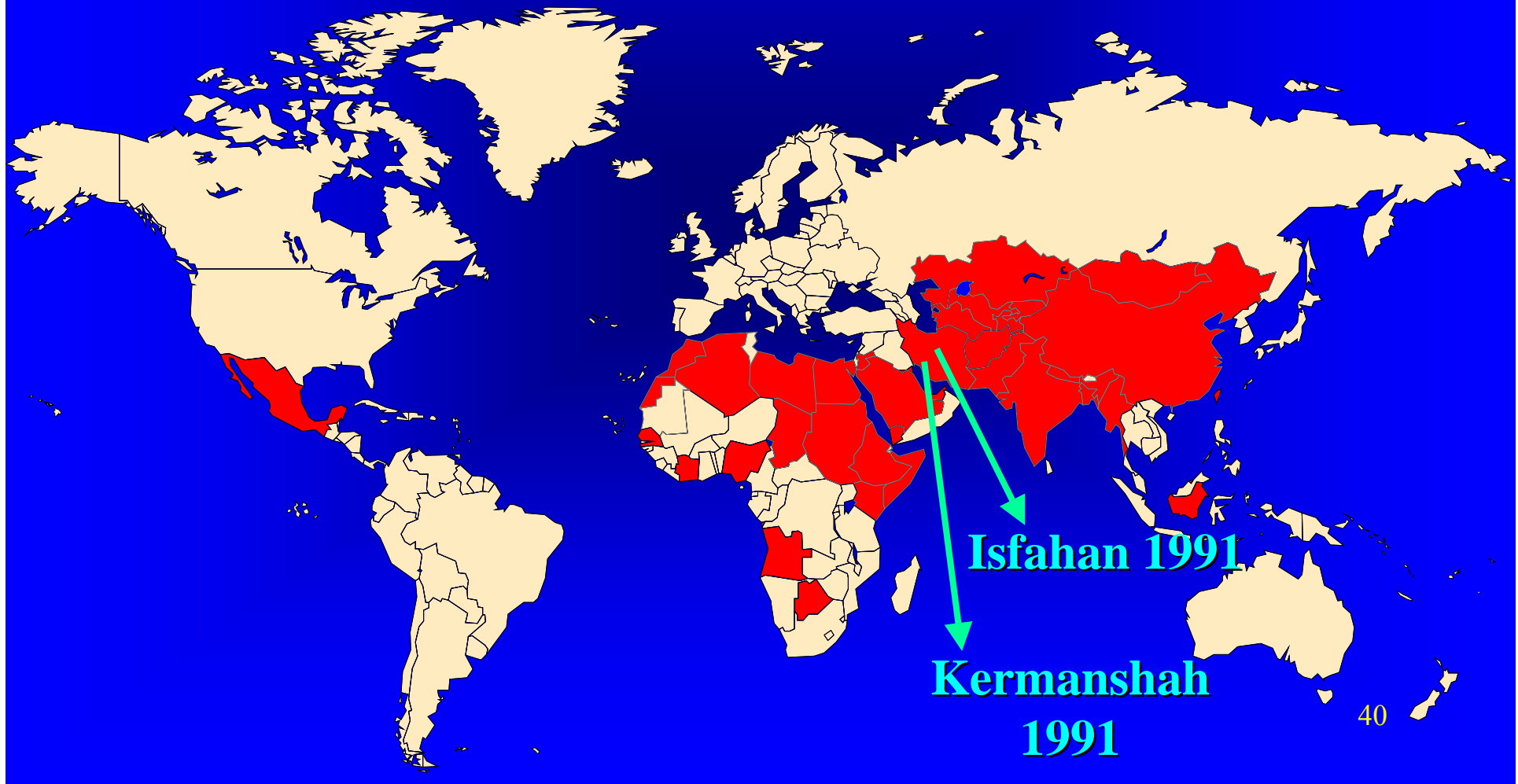
سیر طبیعی هیپاتیت E

- میزان موارد بدون علامت (ساب کلینیکال)
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- میزان مرتالیتی و مریدیتی
- میزان مصونیت بعد از بهبودی

مصادر

3 – Geographical distribution

Outbreaks or Confirmed Infection in >25% of Sporadic Non-ABC Hepatitis



Geographical distribution

- **Hepatitis E is found worldwide, but the prevalence is highest in East and South Asia.**
- **The highest prevalence of infection occurs in regions where low standards of sanitation**
- **The prevalence of antibody to HEV in suspected or documented endemic regions has been much lower than expected (3 - 26%)**

Geographical distribution

- **Screening of blood donors in central Europe and North America has shown a prevalence of anti-HEV antibodies of 1.4 - 2.5%,**
- **In South Africa of 1.4%,**
- **In Thailand of 2.8%,**
- **In Saudi Arabia of 9.5%, and**
- **In Egypt of 24.0%.**

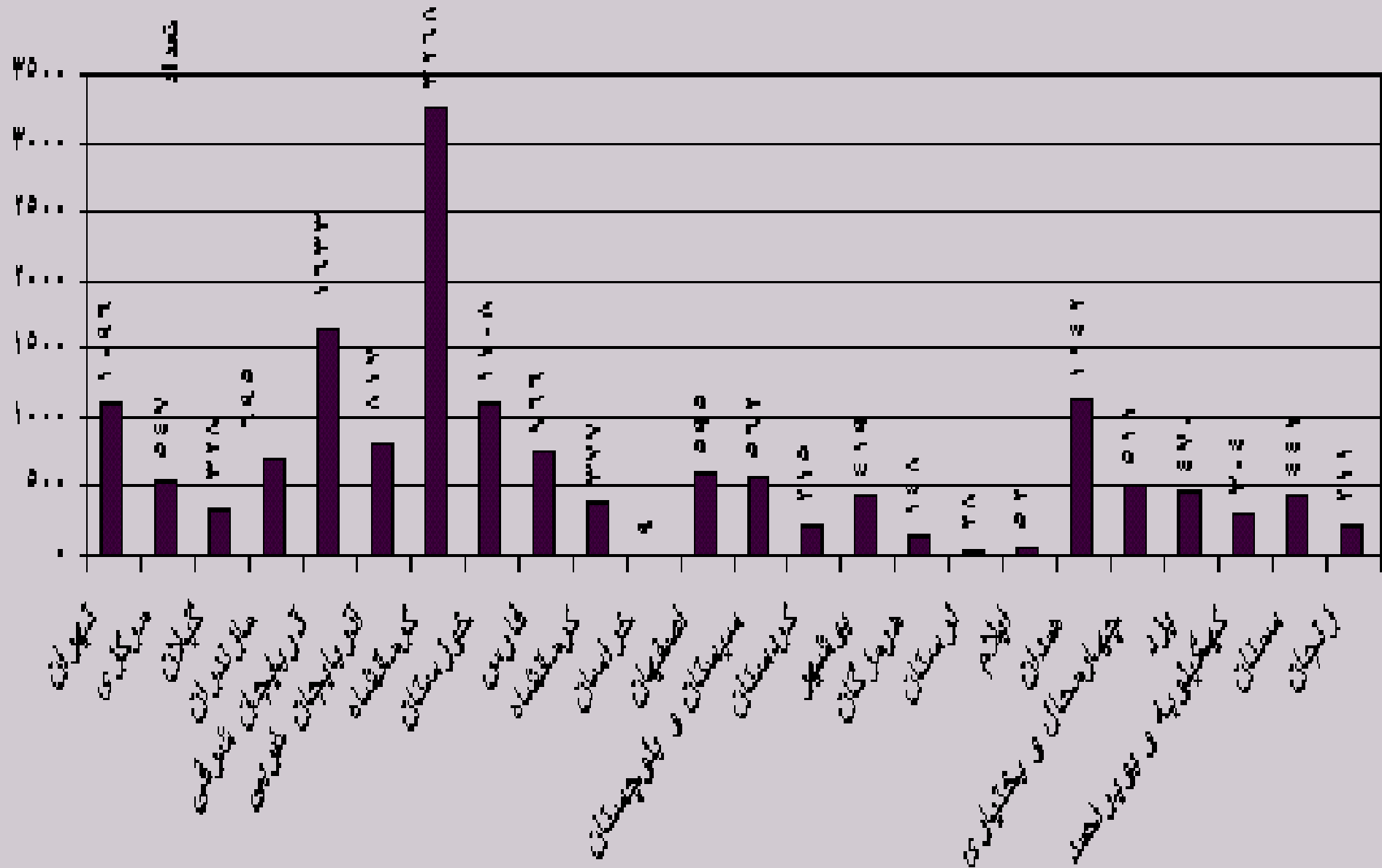
Hepatitis E in Iran

- We faced to an epidemic of hepatitis E in Kermanshah at winter and spring 1991
- It was the first one and so an emerging infectious disease in Iran
- Hundreds of young men and women were visited as outpatients

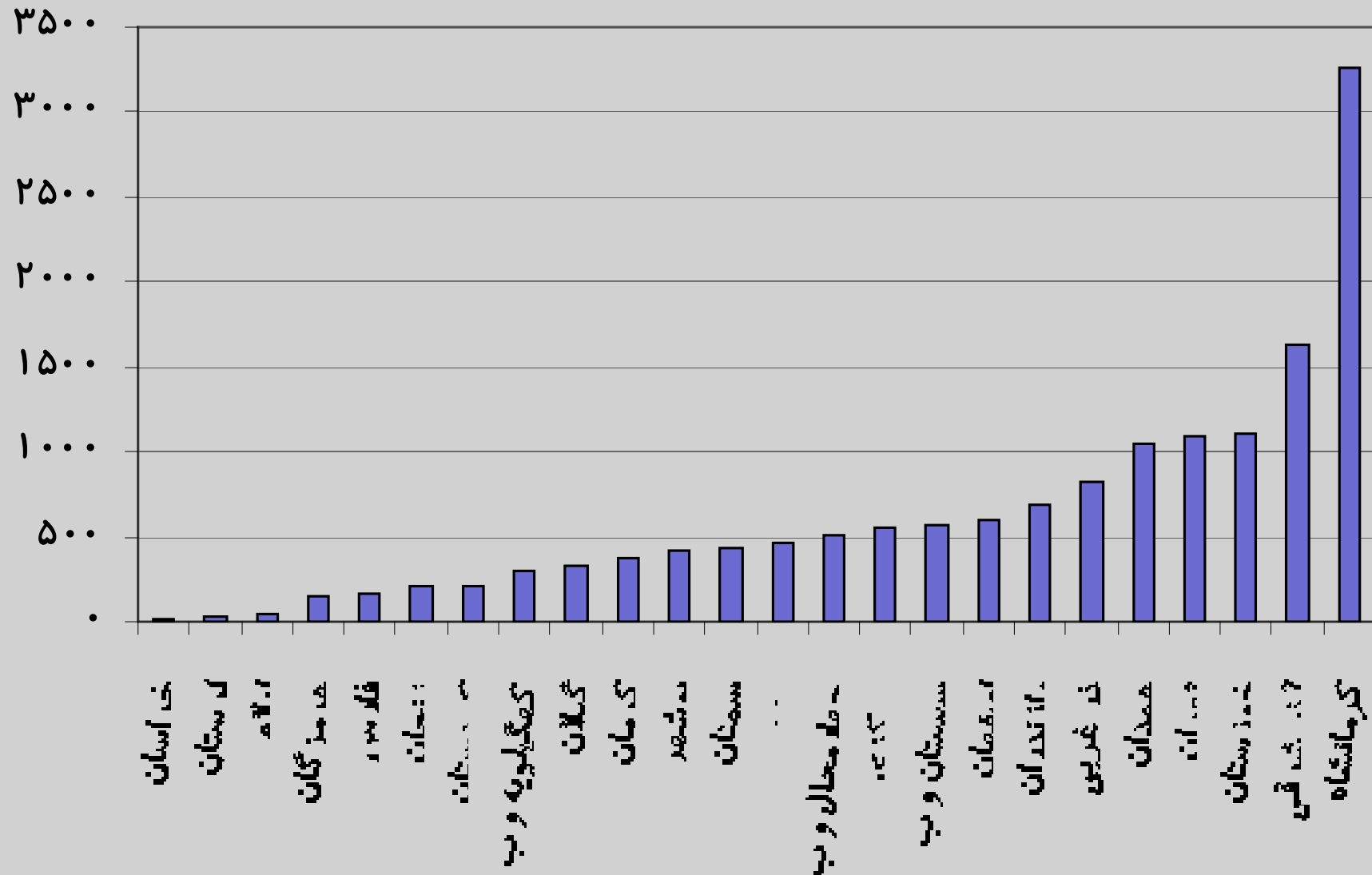
Hepatitis E in Iran

- **Hundreds of them admitted in Sina hospital**
- **It was due to water contamination by sewage of a part of the city**
- **The sewage had entered the river (Gharahsoo) in an area before the water purification system**

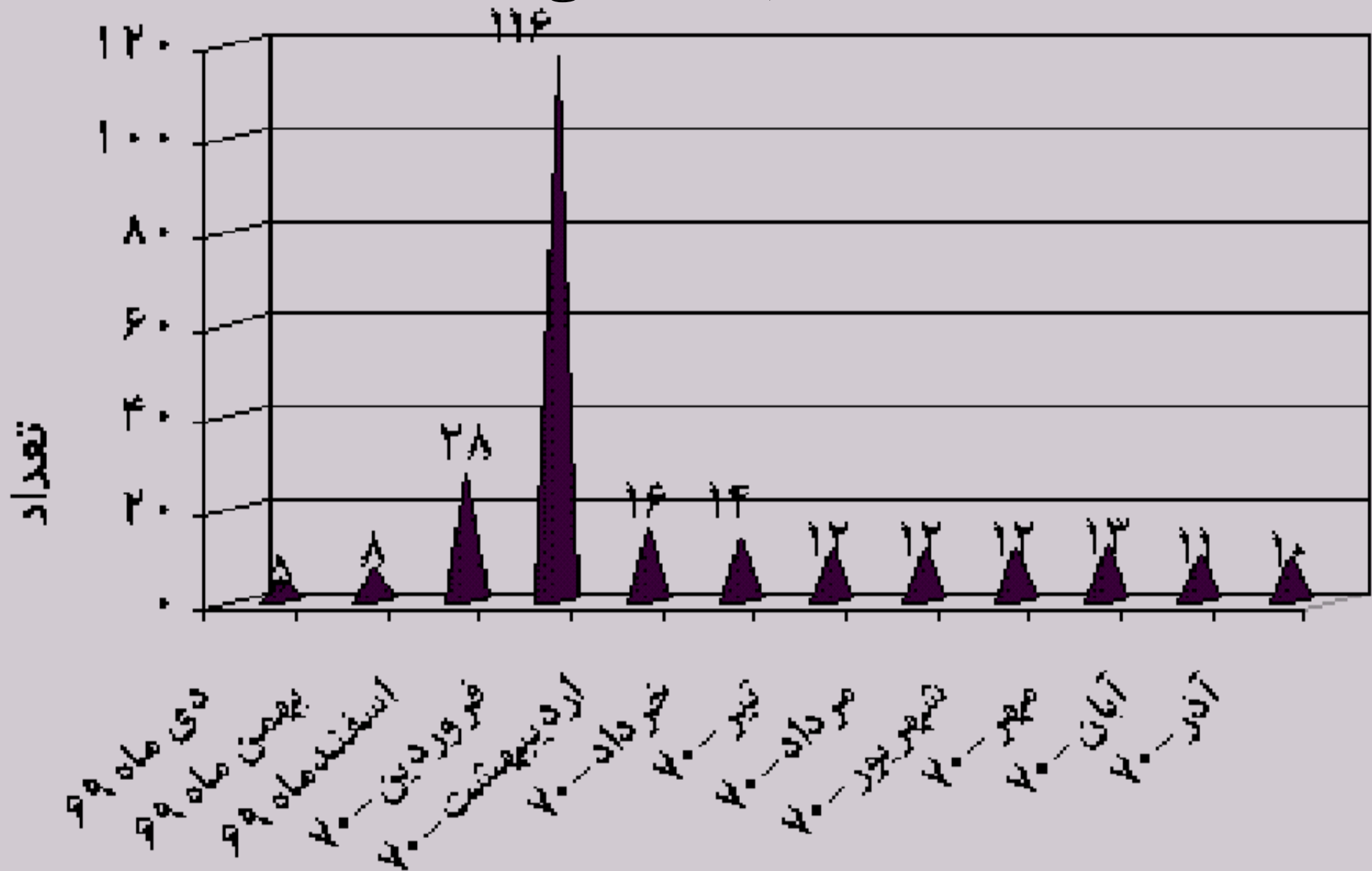
Hepatitis cases reported to Center for Diseases Management, IR.**IRAN** 1991



Hepatitis cases reported to Center for Diseases Management, IR.IRAN 1991



Hepatitis cases reported to Center for Diseases Management, IR.**IRAN** 1991



Hepatitis E in Iran

- **It was forgotten because of the Iraq and Iran war**
- **Many pregnant women that were in 3rd trimester died because of fulminant hepatitis**
- **There were many abortion, stillbirth, and preterm labor**

Hepatitis E in Iran

- **We told the general populations about what happened, by T.V., radio newspapers, schools, prayer places**
- **We added the chloride to water supply,**
- **Asked the peoples to boil the water,**
- **Changed the direction of the sewage**
- **Drilled 10 well for safe water supply**

4 - Timeline trend

- **Pandemics**
- **Epidemics**
- **Outbreaks**
- **Seasonality**

Seasonality

- **Outbreaks of hepatitis E are more common in parts of the world with hot climates**
- **Rare in temperate climates**
- **Usually in rainy seasons**

شرایط وقوع همه گیری هیئت E

Outbreaks and epidemics

Most outbreaks have occurred following:

- **Monsoon rains,**
- **Heavy flooding,**
- **Contamination of well water,**
- **Massive uptake of untreated sewage into city water treatment plants**

Outbreaks and epidemics

- *Outbreaks have been reported from :*
- **Algeria, Bangladesh, China, Egypt, Ethiopia, Greece, India, Indonesia, Iran, Côte d'Ivoire, Jordan, Libya, Mexico, Myanmar, Nepal, Nigeria, Pakistan, southern Russia, Somalia, eastern Sudan, and the Gambia**

Some of the epidemics

Place	Year	Number of cases
India	1955	30000
Myanmar	1976	20000
Kashmir	1978	52000
China	1986	100000
Somalia	1988	11000
Mexico	1989	4000
Iran (Kermanshah)	1991	Hundreds
Sudan	2004	4000
Chad	2004	1000
Iraq	2004	hundreds

Recent epidemics / Ethiopia & Sudan

- **More than 2000 cases occurred in 1985 and 1986 in Ethiopian refugee camps in Somalia and Sudan**
- **Between May and August of 2004, almost 4000 suspected cases of hepatitis E were reported in Greater Darfur region of Sudan.**

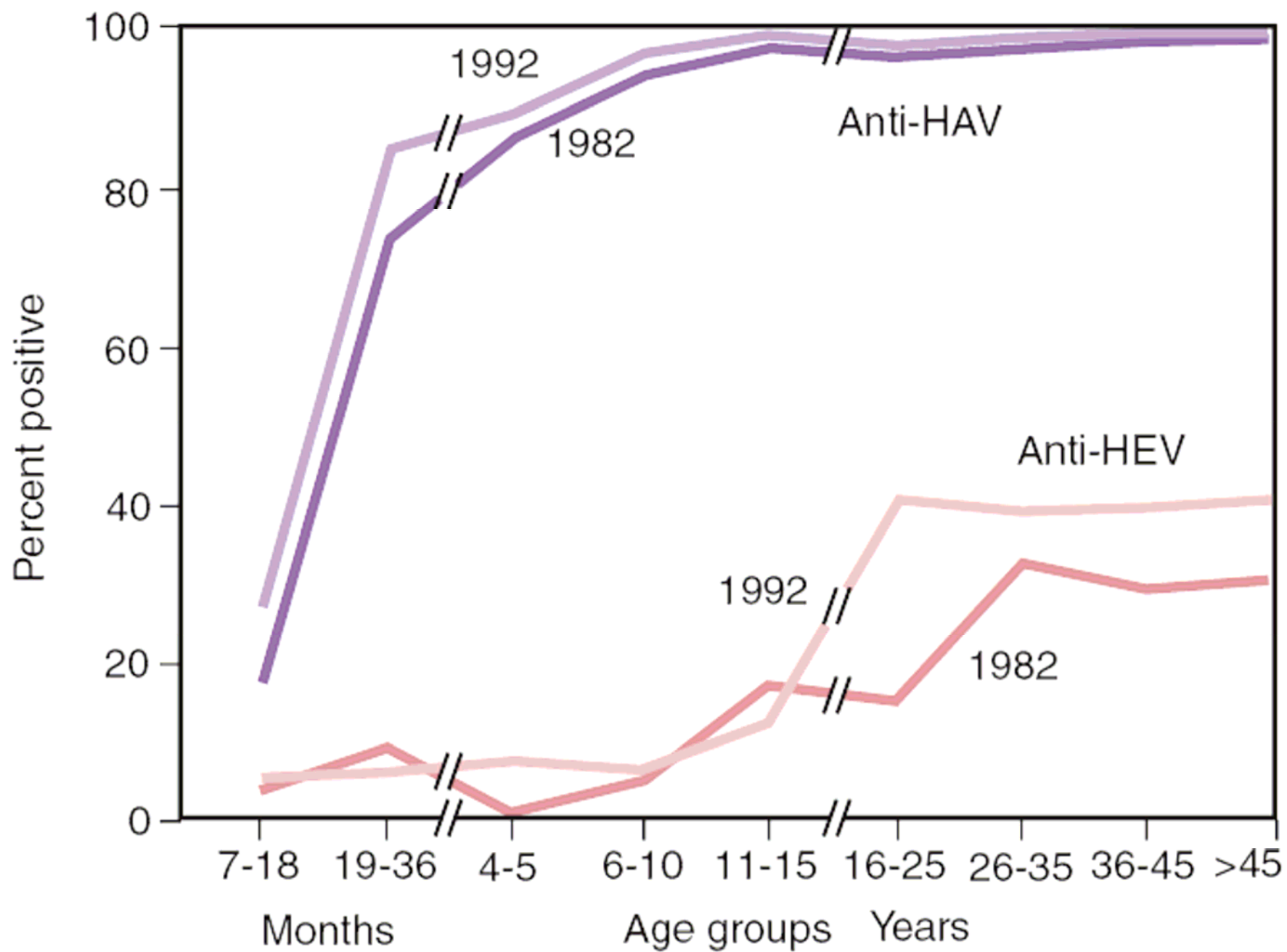
Recent epidemics (2004) / Chad

- **Sudanese refugees who fled to camps in neighboring Chad have fared no better, and more than 1000 suspected cases of hepatitis E were identified between June and September.**

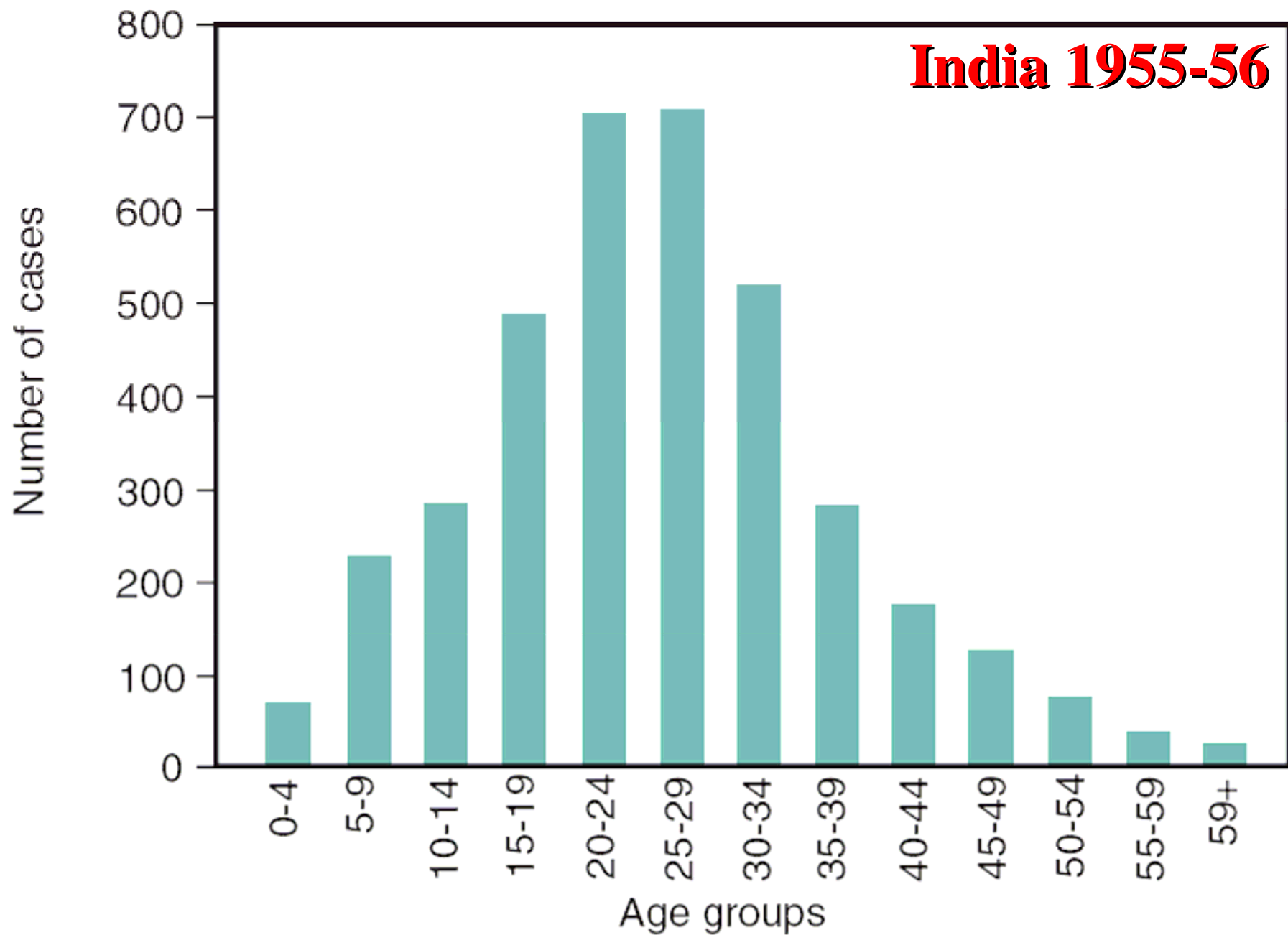
Recent epidemics / Iraq

- **In Iraq, where conflict also rages, probable cases of hepatitis E were identified in Sadr City Mahmudiya,**
- **Number of reported cases in Iraq is in the hundreds rather than the thousands,**
- **Lower numbers could reflect underreporting and the lack of a routine diagnostic test**

5 – Age, Gender, Occupation, Social conditions



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Age distribution

- **Asymptomatic and anicteric infection is frequent in children**
Comparable to hepatitis A

عوامل مساعد کننده همه‌گیری هیپاتیت E

تماس نزدیک با بعضی از حیوانات
مسافرت به مناطق آندمیک
حوادث طبیعی (سیل، زلزله)
بیماریهای مزمن کبدی
پناهندگی و آوارگی
جنگ

6 – Predisposing factors

- **International travelers** to regions of the world where HEV is endemic
- **Refugees** residing in overcrowded temporary camps following catastrophies, especially in Sudan, Somalia, Kenya and Ethiopia
- **Persons who have chronic liver disease**
- **Possibly persons working with non-human primates, pigs, cows, sheep and goats**

7 – Susceptibility and Resistance

- **People who never have contracted HEV are at risk of infection**
- **Poor sanitation**

The risk factors for hepatitis E are related to poor sanitation in large areas of the world and shedding of the hepatitis E virus in faeces.

8 – Secondary attack rate

- **Minimal person-to-person transmission**
- **The low amount of intact HEV particles present in patient stools accounts for the generally lower rate of person-to-person transmission**

راه‌های انتقال ویروس هیپاتیت E

9 - Modes of Transmission

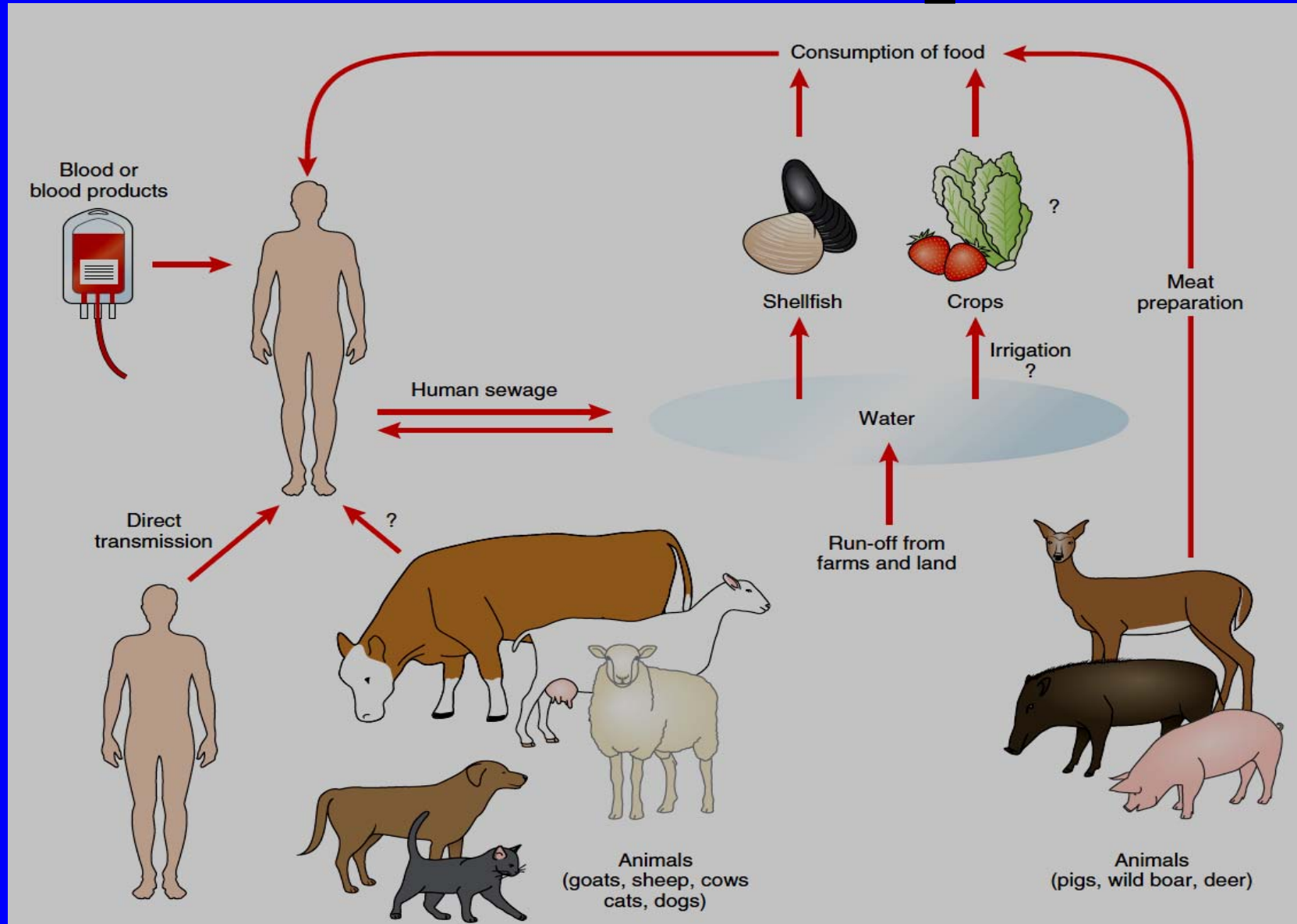
- **HEV is most commonly transmitted via the fecal-oral route:**
 - Waterborne
 - Foodborne
 - Zoonotic HEV (associated with consumption of HEV-infected pig or deer meat)
 - Person to person
 - Nosocomial
 - Transfusion-associated HEV
 - Vertical transmission
 - Sexually

9 - Transmission

- **HEV is spread by the oral-faecal route**
- **Consumption of faecally contaminated drinking water has given rise to epidemic cases,**
- **Ingestion of raw or uncooked shellfish has been the source of sporadic cases in endemic areas**

- *Most outbreaks associated with faecally contaminated drinking water*

Transmission of Hepatitis E



Zoonotic transmission

- **Naturally acquired HEV antibodies have been detected in primates, rodents and swine**
- **Swine HEV cross-reacts with antibodies to the human HEV**
- **Human hepatitis E has been transmitted under laboratory conditions to various species of primates, pigs, lambs, rats**

Zoonotic transmission

- **Species specific HEV has been demonstrated in pigs with the identification of swine HEV**
- **Swine HEV is distinct, but closely related to human HEV strains**
- **Swine HEV raises a potential public health concern for zoonosis and xenozoonosis following xenotransplantation with pig organs**

Zoonotic transmission

- **A zoonotic spread of HEV is not excluded**
- **Monkeys, pigs, cows, rodents, sheep and goats are susceptible**
- **Anti-HEV has been found in a significant proportion, up to 28% in some areas, of healthy individuals in industrialized countries**

Zoonotic transmission

- **Subclinical infection of humans may be due to exposure to animals**
- **Some HEV is imported into industrialized countries and some is probably endemic, possibly as a zoonosis**

Period of communicability

- HEV has been detected in the stools of infected patients after the onset of illness (jaundice) for up to 14 days.
- Maximal HEV shedding occurs during the incubation period and during early acute stage of the disease.

peak fecal shedding occur during the incubation period and early acute phase. M2015

*Prevention
and
Control*

Prevention and Control

- **Primary Prevention:**
 - Prevention of disease in “well” individuals
- **Secondary Prevention:**
 - Identification and intervention in early stages of disease
- **Tertiary Prevention:**
 - Prevention of further deterioration, reduction in complications

1 - Primary Prevention:

- Avoid **drinking water** (and beverages with **ice**) of unknown purity, uncooked **shellfish**, and uncooked **fruit/vegetables** not peeled or prepared by traveler
- **IG** prepared from donors in Western countries **does not prevent** infection
- Unknown efficacy of IG prepared from donors in endemic areas
- **Vaccine?**



موقعیت فعلی واکسن هیپاتیت E طبق
نظر کمیته راهبردی مشورتی WHO
آذرماه ۱۳۹۳

Weekly epidemiological record, No. 50, 12 DECEMBER 2014

Vaccines

The Strategic Advisory Group of Experts (SAGE)

- The vaccine is approved for use in China in those aged **16–65 years**.
- **Hecolin®** is well tolerated and has been demonstrated to have a good safety profile in this age range.
- This vaccine is **highly immunogenic**, with nearly **all the recipients seroconverting** after 3 doses administered in a **0, 1 and 6 month** schedule.

Vaccines

The Strategic Advisory Group of Experts (SAGE)

- The vaccine protects against symptomatic HEV infection, with **over 90% efficacy** based on clinical trials involving 109 959 individuals.
- Data on protection are primarily applicable to **genotype 4** associated disease;
- Data on disease caused by other genotypes:
 - Are too limited (genotype 1) or
 - Not available (genotype 2 and 3).

Vaccines

The Strategic Advisory Group of Experts (SAGE)

- Data on safety and efficacy in children aged <16 years or persons aged >65 years, and in areas with **genotype 1, 2 and 3** HEV infections, are lacking.
- Data on the safety and efficacy of the vaccine in **pregnant** women are limited.

محدودیتها

2 - Secondary Prevention:

Identification

And

intervention

**in early stages of
disease**

Diagnosis of hepatitis E

- Cases of hepatitis E are not **clinically** distinguishable from other types of acute viral hepatitis.
- Diagnosis is usually based on the detection of **specific IgM** antibodies to the virus in the blood.
- Additional tests include **RT-PCR** to detect the hepatitis E virus RNA in blood and/or stool, but this assay may require specialized laboratory facilities.

Diagnosis of hepatitis E

- *Hepatitis E should be suspected in outbreaks of waterborne hepatitis occurring in:*
 - **Developing countries,**
 - **Especially if the disease is more severe in pregnant women,**
 - **Or if hepatitis A has been excluded**
 - **If laboratory tests are not available, epidemiologic evidence can help in establishing a diagnosis.**

Hepatitis E should be suspected in outbreaks of waterborne hepatitis, especially if the disease is more severe in pregnant women, or if hepatitis A has been excluded.

Secondary prevention

Diagnosis

- Diagnosis of HEV had previously been made **serologically**,
- Molecular diagnosis via **PCR** has better sensitivity and specificity
- **Molecular** diagnosis is the diagnostic technique of choice, if available.
- **Culture** and detection of viral antigen are not appropriate for diagnostic tests because of their **poor sensitivity**.

Secondary prevention

Diagnosis

- Detection of HEV-specific IgM can be used for serologic diagnosis of acute HEV infection in areas of low prevalence, but
- Comparative studies have shown a wide range of assay performance.
- Diagnostic assays for the detection of HEV-specific IgG could be useful for the diagnosis of acute hepatitis in returning travelers
- For differential diagnosis, more-specific tests are necessary.

Secondary prevention

Diagnosis

- Diagnostic assays for the detection of HEV-specific IgG could be useful for the diagnosis of acute hepatitis in returning travelers
- For differential diagnosis, more-specific tests are necessary.
- Although the titer of HEV-specific **IgG** tends to decline markedly in the first year after infection, this relationship is not reliable enough to aid in **differential diagnosis**.

Secondary prevention

Diagnosis

- **IgG** is of little use for diagnosis of acute infection in developing countries where HEV is endemic.
- Because HEV may account for as much as 70% of the cases of acute viral hepatitis in endemic countries, specificity of assays is less critical than assay sensitivity in these settings.
- A **rapid point-of-care IgM test** may have promise for diagnostic use in HEV-endemic areas, with sensitivity and specificity comparable to IgM ELISA assays.

Secondary prevention

Diagnosis

- **RT-PCR RNA** in serum is the gold standard in specificity for diagnosis of acute HEV
- It is **impractical for field use**, especially in rural areas where the virus is endemic or in refugee settings.
- **RT-PCR** has also been particularly useful in **research situations** for the detection of divergent HEV strains where the serologic responses may not be detected with some assays.

Secondary prevention

Diagnosis

- RT-PCR is an important **confirmatory** assay for positive HEV IgM tests in nonendemic countries
- Can be used to **monitor infection**
- Inter-laboratory variability is a concern.
- Furthermore, during acute infection, sensitivity is constrained by the relatively brief duration and level of viremia as well as the stability of HEV RNA in clinical samples collected in the field.

Secondary prevention

Diagnosis

- Genomic-based methods are essential for diagnosis of chronic HEV infection, especially because **many patients never seroconvert.**
- Following HEV viremia using a molecular method is also important in **monitoring response to antiviral treatment in chronic HEV.**

Secondary prevention

Diagnosis

- **The primers for RT-PCR** must be chosen carefully because HEV is genetically heterogeneous, with four genotypes recognized to date.
- Primers located in highly conserved regions of the genome or degenerate primers must be used to ensure detection of all recognized variants of HEV.

Secondary prevention Treatment

- Acute HEV infection is generally self-limited and requires only supportive care.
- **Severe acute** cases have been treated successfully with **ribavirin**.
- Ribavirin monotherapy appears to be highly effective in treatment of **chronic hepatitis E** in solid-organ transplant recipients

3 - Tertiary Prevention:

- **Liver transplantation**

Surveillance

- **Provision of safe drinking water and proper disposal of sanitary waste**
- **Monitoring disease incidence**
- **Determination of source of infection and mode of transmission by epidemiologic investigation**
- **Detection of outbreaks**
- **Spread containment**

Future considerations

- **The development of more sensitive and specific serologic tests**
- **Insight into the epidemiology of the disease**
- **The manufacture of hyperimmune E globulin**
- **Production of a vaccine against all 4 genotypes**
- **There is a need for determining the durability of anti-HEV neutralizing antibody after natural infection or vaccination**

Future considerations

- **The development of differential diagnostic tests to distinguish between infections with swine HEV and human HEV is necessary**
- **The pathogenesis of the disease, especially in infected pregnant women, needs to be elucidated**
- **International measures should be established**

Sources:

- **WHO, Hepatitis E, Fact sheet, September 2018**
- **Kevin Forward, Departments of Pathology, Microbiology and Immunology and Medicine, Hepatitis A through E.**
- **CDC, Internet site, 2016**
- **Control of communicable diseases, 2008**
- **Harrison 2015**
- **Mandell 2015**
- **Canada site, 2014**
- **New England journal of medicine, 2014.**

اپیدمیولوژی بالینی و کنترل بیماری‌های عفونی

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