HBV Vaccination program for regular blood donors

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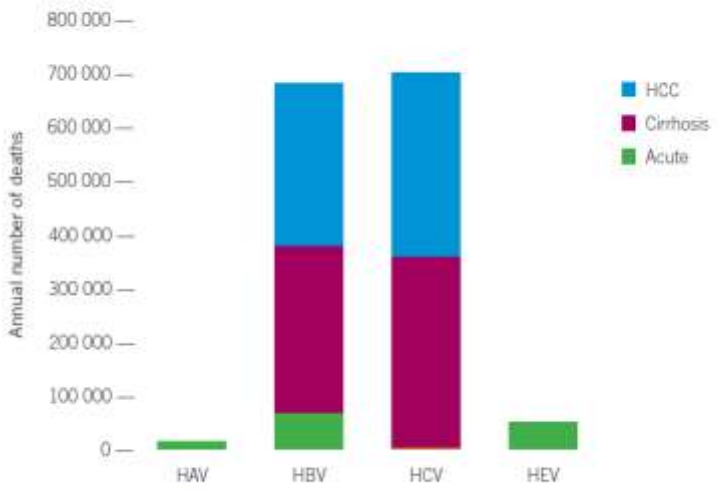
Introduction

- In 2013, viral hepatitis was a leading cause of death worldwide ***(1.46 million deaths)***
- More than 90% of this burden is due to the sequelae of infections with the hepatitis B virus (HBV) and hepatitis C virus (HCV)
- Prevention can reduce the rate of new infections, but the number of those already infected would remain high for a generation.
- In the absence of additional efforts, 19 million hepatitis-related deaths are anticipated from 2015 to 2030
- Treatment now can prevent deaths in the short- and medium term.

FIGURE 1 Deaths from viral hepatitis, by virus and type of sequelae, 2013 *(1)*



HAV: hepatitis A virus; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HEV: hepatitis E virus.

WHO: COMBATING HEPATITIS B AND C TO REACH ELIMINATION BY 2030

- **Mortality from viral hepatitis is on the increase because of poor access to treatment**
- **Combining treatment with prevention could eliminate viral hepatitis as a public health problem by 2030**
- **Prevention is effective and cost–effective, but needs to reach the unreached**
- **There is now a solid case to scale up testing and treatment: treatment works and can save lives within a short time horizon**

- **Combining prevention and treatment to combat hepatitis makes elimination feasible**
- **Prevention needs to reach the unreached**

Reaching five prevention and treatment service coverage targets would eliminate hepatitis B and C as public health threats

WHO has identified five key service coverage targets:

- 90% coverage of hepatitis B childhood vaccination,
- 90% coverage of birth-dose vaccination or other means to prevent mother-to-child transmission,
- 100% of blood donations screened in a quality-assured manner,
- 90% of injections given with safety-engineered devices,
- distribution of at least 300 sterile needles, syringes/PWID/year

Target areas				Baseline 2015	2020 target	2030 target
Service coverage	Prevention	1 Three-dose hepatitis B vaccine for infants (coverage %)		82%	90%	90%
		2 Prevention of mother-to-child transmission of HBV: hepatitis B birth-dose vaccination or other approaches (coverage %)		38%	50%	90%
		3 Blood and injection safety (coverage %)	Blood safety: donations screened with quality assurance	89%	95%	100%
			Injection safety: use of engineered devices	5%	50%	90%
		4 Harm reduction (sterile syringe/needle set distributed per person per year for people who inject drugs [PWID])		20	200	300
	5 Treatment	5a. Diagnosis of HBV and HCV (coverage %)		<5%	30%	90%
		5b. Treatment of HBV and HCV (coverage %)		<1%	5 million (HBV) 3 million (HCV)	80% eligible treated

Reaching these five service coverage targets by 2030 would reduce the incidence of chronic infections by 90% and mortality by 65% (as compared to 2015 levels), which would eliminate hepatitis B and C as public health threats

HBV as a TTI

- HBsAg carrier rate varies from 0.1 – 20% in general population globally. It is more prevalent in endemic areas like Africa and some parts of Asia (South East and Eastern Mediterranean).
- In the Middle East the endemicity of HBV is intermediate with prevalence rate 2-7%. Among countries in this region, Iran, Kuwait and Bahrain are low endemic.
- The prevalence rate of HBsAg in Iranian blood donors in 2007 was reported as 0.41% by Amini and her colleagues, (ranged from 0.34% in Fars province to 1.15% in Sistan).

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- With respect to blood safety, in 2011, among 97 countries that reported data, 89% were screening all blood donations in a quality-assured manner *(6)*.
- As per the principle of "first, do no harm", health-care services should not lead to infections

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- Over the past decades, universal vaccination has led to a 70–90 % decrease in chronic HBV carrier rates worldwide

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Ringwald J, *et al*. Hepatitis B virus vaccination of blood donors–what costs may be expected? *Transfusion Medicine*. 2005;15(2): 83-92.

- German experiment has also depicted that vaccination can cause near-elimination of HBV transfusion transmission and also reduces the cost of screening in comparison to molecular testing, in addition to decreasing the cost of treatments, repeated testing and tracing the recipients.

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- Totally about 4000 young regular blood donors were immunized by recombinant HBV vaccine and enrolled in the study based on the inclusion criteria.
- Among these, 357 blood donors were randomly studied for vaccination efficacy and adherence rate. 286 subjects completed the whole study evaluation; the adherence rate of vaccination among donors was 80%.

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Population Study

- Mean age of vaccinated donors was 26 ± 3.5 year, the age group distribution was found as: 191 (53.5%) 20-24 years old,

  111 (31%) 25-29

  55 (15.5%) 30-35 years old.

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Post vaccination antibody titer among three dose recipients :

- 13 (4.5%) under 10 IU/ml,
- 103 (36%) 10-100 IU/ml
- 171 (59.5%) more than 100 IU/ml

So it could be resulted that 4.5% was non-responders

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- All non-responders were recommended to receive additional booster 1-2 months after the last dose.
- Antibody titer was more than 10 in all of them which lead to 100% response rate after one booster dose.

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- Effect of vaccination on blood safety was assessed by comparing the HBsAg seropositivity among age matched donors one year before vaccination and four years later.
- HBsAg seropositivity in 20-35 years old donors at 2007 was 0.96 % and dramatically decreased to % 0.54 by the end of 2012 in 24-39 years old (p value<0.05)

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Trend of HBsAg positivity rate among Sistan & Baluchistan blood donors during 6 years

Year	2007	2008	2009	2010	2011	2012
%HBsAg positive donor	0.96%	1.08%	0.78%	0.66%	0.65%	0.54%

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Zhen Wang,. Prevalence of hepatitis B surface antigen (HBsAg) in a blood donor population born prior to and after implementation of universal HBV vaccination in Shenzhen, China, BMC Infectious Diseases (2016) 16:498

- Young blood donors born after implementation of universal HBV vaccination in China presented higher prevalence of HBsAg but lower incidence of HBsAg seroconversion than older, presumed unvaccinated donors.
- HBV vaccine boosting for adolescents at 15–17 years old prior to reaching blood donor age might help improve blood safety

Wang et al. BMC Infectious Diseases (2016) 16:498

Table 3 Prevalence of HBsAg in first-time donors born before and after 1992 tested at the same ages

Age year	Born <1992		Born ≥1992		Overall		*P* value
	HBsAg+/total	%	HBsAg+/total	%	HBsAg+/total	%	inter-group
18	152/4600	3.30	162/5151	3.15	314/9751	3.22	0.656
19	373/10,158	3.67	280/8212	3.41	653/18,370	3.55	0.340
20	545/14,797	3.68	253/6029	4.20	798/20,826	3.83	0.080
21	612/17,982	3.40	191/3833	4.98	803/21,815	3.68	0.000
22	682/20,146	3.43	99/2097	4.72	791/22,243	3.56	0.002
All ages	2374/67,683	3.51	985/25,322	3.89	3359/93,005	3.61	0.005

Intra-population of first-time donors, *P* = 0.228–0.74 from 18 v.s. 20, 21 or 22 years born <1992; *P* = 0.003–0.0001, 18 v.s. 21, or 22 years born ≥1992

JVH, April 2018, Xi Tan, etal , Incidence of HBV infection in young Chinese blood donors born after mandatory implementation of neonatal hepatitis B vaccination nationwide

- Repeat blood donors born between 1992 and 1997 were enrolled, who gave blood at least twice during the past three years. Donors were tested for HBV infection markers of HBsAg, anti-HBc, anti-HBs and viral DNA by immunoassays (EIAs) and nucleic acid tests (NAT).
- A total of 14937 pre-donation screening qualified young repeat donors aged 18-23 were tested with 9 (0.06%) being HBsAg by EIA and 10 (1:1494) HBV DNA positive by NAT (10.4 IU/L), respectively.

- HBV DNA was further detected in 1:192 (9/1732) anti-HBc+ repeat donors with NAT (3.4 IU/L). Mostly was OBI cases.
- Of 14,937 repeat donors, 20.9% were anti-HBc+ positive, while approximately 50% of 12,024 repeat donors were anti-HBs negative or had levels <100 IU/L.
- infection in repeat donors was approximately 1:18.5 person-years (1.1%/yr) but significantly less frequent in donors with confirmed HBV vaccination (2.4%-3.3%) than those unsure of vaccination status (10.5%; P=0.0023).

Marta Spreafico, etal POOR EFFICACY OF NUCLEIC ACID TESTING IN IDENTIFYING OCCULT HBV INFECTION AND CONSEQUENCES FOR SAFETY OF BLOOD SUPPLY IN ITALY; Journal of Hepatology 2015

- Between 2008 and 2011 6-MP NAT identified 18 carriers of occult HBV infection among 12,695 donors;
- 28 sample from previous donations were available from 13 of these carriers.
- Highly sensitive HBV DNA detection methods showed that 6-MP HBV DNA screening failed to identify 14/28 (50%) viremic donations, that were released for transfusion.
- HBV marker testing of such blood product recipients

revealed two cases of transfusion-transmitted HBV infection, documented by donor-recipient sequence identity

brackets. RCC: red cell concentrate; PC: platelet pools from buffy coats.

Donor	Donation date	HBsAg (S/Co) [0.0-0.03]	Anti-HBs (mIU/mL) [>10]	Anti-HBc (S/Co) [0-0.9]	Transfused blood component
Donor 1	8/1/2009	NEG	POS (559.9)	POS (2.81)	RCC
Donor 2	13/1/2009	NEG	NEG (8.6)	POS (8.51)	PC
Donor 3	13/1/2009	NEG	POS (29.9)	POS (9.96)	PC
Donor 4	27/1/2009	NEG	POS (212.9)	POS (10.12)	PC
Donor 5	19/2/2009	NEG	NEG	POS (1.30)	PC
Donor 6	13/3/2009	NEG	POS (32.2)	POS (10.55)	RCC

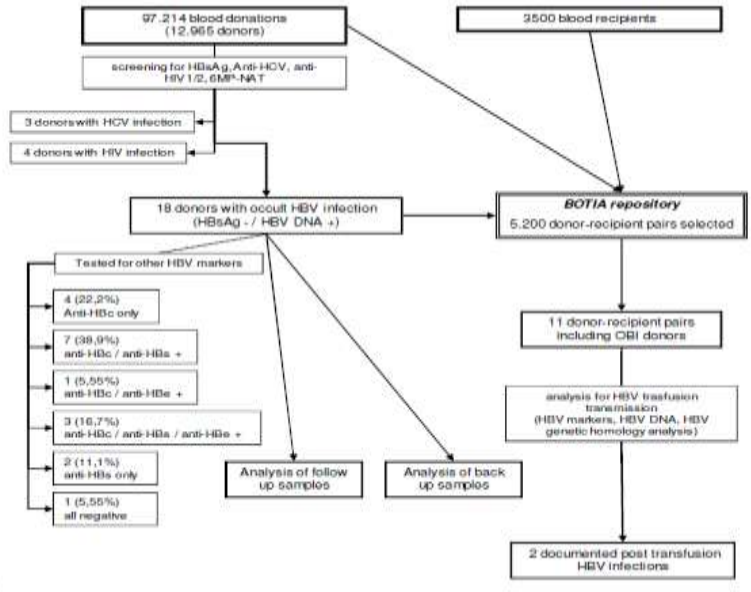

Table 2. Confirmation of HBV DNA in neat or enriched index plasma samples from OBI carriers identified with 6-MP screening.

OBI code	Roche MP-NAT	Roche ID-NAT	Roche qPCR on neat samples	Roche qPCR on enriched samples	In-house qPCR on enriched samples
OBI 1	Pos	Pos	Neg	Pos	Pos
OBI 2	Pos	Pos	<20 IU/mL	Pos	Pos
OBI 3	Pos	Pos	<20 IU/mL	Pos	Pos
OBI 4	Pos	Pos	<20 IU/mL	Pos	Pos
OBI 5	Pos	Pos	52 IU/mL	Pos	Pos
OBI 6	Pos	Pos	<20 IU/mL	Pos	Pos
OBI 7	Pos	Pos	<20 IU/mL	Pos	Neg
OBI 8	Pos	Pos	Neg	Pos	Pos
OBI 9	Pos	Pos	Neg	Pos	Pos
OBI 10	Pos	Pos	22	Pos	Pos
OBI 11	Pos	Pos	Neg	Pos	Pos
OBI 12	Pos	Pos	Neg	Neg	Pos
OBI 13	Pos	Pos	Neg	Neg	Pos
OBI 14	Pos	Pos	<20 IU/mL	Pos	Pos
OBI 15	Pos	Pos	<20 IU/mL	Pos	Pos
OBI 16	Pos	Pos	Neg	Neg	Pos
OBI 17	Pos	Pos	<20 IU/mL	Pos	Pos
OBI 18	Pos	Neg	Neg	Pos	Pos
Positive samples	**18/18 – 100%**	**17/18 – 94%**	**10/18 – 56%**	**15/18 – 83%**	**17/18 – 94%**

- The clinical impact of post-transfusion hepatitis transmitted by OBI donors is substantial, not least
- because blood recipients have comorbidities that can worsen or accelerate the clinical course of liver disease

- One patients developed acute hepatitis and had to be hospitalized after receiving an RBC unit from an OBI donor with a low HBV viral load (<12 IU/mL in a 10 mL enriched sample), and it can be estimated that the final infectious dose transfused was

  ~140 copies of HBV.

- The other patient who acquired HBV infection after being transfused with an RCC unit initially developed a protective anti-HBs titer, but experienced the reactivation of HBV infection after bone marrow transplantation for hematological disease, and actually died of acute liver failure.

Multiple HBV transfusion transmissions from undetected occult infections: revising the minimal infectious dose. Gut. BMJ. 2018

- Candotti *et al.* identified three multiple donors who had occult HBV infection (OBI) with particularly low and variably detectable numbers of HBV particles in their blood

- Transfusion transmission was confirmed by >99% identity of donor/recipient sequences in five cases
- probable in three and possible in one.
- HBV active infection remained unsuspected for 24–57 months in three recipients.
- Five non-infected recipients carried anti-HBs when transfused.
- Six patients transfused with platelet concentrates treated with a pathogen reduction method were not infected.

Wolfram H, Hepatitis B viral safety of blood donations: new gaps identified, Annals of Blood; Sep 2018

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Chronic low symptomatic HBV infections

(high replicative, low inflammatory state (previously called "immunotolerant")

infected liver cells produce huge amounts of HBV antigens and virus particles but remain largely functional without being attacked by the immune system.

Early phase HBV infections

- Donors in the early phase of the infection (the so-called window phase) have still low viremia and a not-yet activated immune response to HBV

Patients in the late acute or chronic phase

- In the transition from the high replicative, low inflammatory phase to the immune clearance phase with decreasing viremia and HBsantigenemia
- Absence of HBeAg indicates the breakdown of the “immune tolerance” to HBV and an enhanced immune clearance combined with intensified pathogenicity
- levels of viremia usually decrease faster than the levels of HBs-antigenemia

Inactive HBsAg carriers

- low or undetectable HBV numbers <104 per mL while HBsAg is usually readily detectable.
- It appears that immune clearance often targets hepatocytes expressing all HBV antigens while cells expressing only HBsAg due to integrated HBV DNA fragments encoding HBsAg are saved.

Occult HBV infection (OBI)

- Most if not all HBV infections virtually never become completely cured in the sense that all viable HBV genomes got eliminated.

- OBI is defined as the presence of the virus in the liver, with detectable or undetectable HBV DNA in the serum of individuals testing hepatitis B surface antigen (HBsAg) undetectable in blood, using the most sensitive commercial assays."

- True OBI is characterized by low viremia <200 IU/mL (or ca. <1,000 HBV genome equivalents, ge/mL) and low HBsAg
- Masking by anti-HBs is a plausible explanation, even if anti-HBs is not detectable.
- In a longitudinal analysis of the HBV quasi-species present in an anti-HBs negative OBI positive donor, the S gene was highly variable in the HBs-antigenic loop with 10–14% altered amino acids suggesting presence of unrecognized selection-relevant anti-HBs

- Transmission of HBV by NAT negative donations was repeatedly reported as summarized by Candotti and Laperche
- Infection experiments with chimpanzees or humanized mice suggest that one single HBV particle from early phase sera may induce a full HBV infection whereas particles from later still HBsAg positive phases are usually less infectious
- The recent paper from Candotti *et al.* (1) provides deeper insight because it shows that in certain OBI cases HBV particles may be as infectious as particles from the early phase.

- NAT screening should be applied to all donations at a limit of 95% detection of 0.8 ge/mL (or 0.15 IU/mL) which would require testing of several mL of single donations and virtually exclude minipool testing.

Locarnini and Raimondo:

- universal hepatitis B immunization will more often protect recipients against HBV in blood donations.
- *Even passively administered anti-HBs by concomitant donations from immunized donors protects against donations from OBI donors*.

Pilot study Donor Vaccination

- با حمایت مرکز مدیریت بیماری های واگیر وزارت بهداشت، درمان و آموزش پزشکی برنامه ایمن سازی اهداکنندگان مستمر بر علیه بیماری هپاتیت B در دستور کار سازمان انتقال خون قرار گرفت. بدین منظور در مرداد ماه سال 1395، 5 استان تهران، البرز، اصفهان، گیلان وکرمان برای اجرای برنامه در فاز پایلوت انتخاب و تعداد اهداکنندگان مستمر تحت پوشش آن استان ها به مرکز مدیریت بیماری ها اعلام و تعداد واکسن مورد نیاز تأمین شد

با اطلاع رسانی عمومی و فراخوان اهداکنندگان مستمر، ادارات کل انتقال خون حدود 10.500 نفر از اهداکننده های مستمر خون نوبت اول، و حدود 9.400 نفر نوبت دوم این واکسن را دریافت نموده اند.(89.5%)

	1th	2nd	%
گیلان	4092	4085	99%
اصفهان	1642	1538	93%
کرمان	3162	2610	82%
تهران	877	641	73%
البرز	731	522	71%

در این برنامه تعداد اهداکنندگان مستمر حدود 600.000 نفر تخمین زده شده و تأمین واکسن مورد نیاز برای سه نوبت واکسیناسیون ایشان توسط مرکز مدیریت بیماری ها مورد تعهد قرار گرفته است.

فاز اول برنامه که به صورت بسیج همگانی 5 ماهه از 1/7/97 آغاز گشته و تا 1/12/97 ادامه خواهد داشت

اهداکنندگان مستمر گروه سنی 29 سال به بالا (متولدین 1/1/68 به قبل) که قبلاً طبق برنامه ایمن سازی علیه هپاتیت B واکسینه نشده اند از طریق اداره کل انتقال خون استان به مراکز بهداشتی درمانی مجری برنامه واکسیناسیون معرفی شده و واکسن هپاتیت B و کارت واکسیناسیون ویژه اهداکنندگان خون دریافت خواهند کرد.