SURE Rapid Response

What are the Effects and Guidelines of Mass immunization of Health workers against Hepatitis B?

October 2010

This rapid response was prepared by the Uganda country node of the Regional East African Community Health (REACH) Policy Initiative.

Key messages

- The hepatitis B vaccine available as plasma derived vaccine (PDV) and recombinant vaccine (RV) significantly reduces the number of hepatitis B events
- The number of HCWs without protective anti-HBs level is significantly higher when the vaccine is given by gluteal injection than when given by deltoid injection.
- There are significantly more HCWs without protective anti-HBs level following intradermal route as compared with intramuscular route.
- There is no significant difference in comparisons between different doses of the vaccine given by the same route and vaccines made in different countries.
- There are significantly more healthcare workers without protective anti-HBs level when given Recombivax than when given Engerix vaccine

Who requested this rapid response?

This document was prepared in response to a specific question from a policy maker in Uganda.

! This rapid response includes:

- Key findings from research
- Considerations about the relevance of this research for health system decisions in Uganda

X Not included:

- Recommendations
- Detailed descriptions

What is SURE Rapid Response Service?

SURE Rapid Responses address the needs of policymakers and managers for research evidence that has been appraised and contextualised in a matter of hours or days, if it is going to be of value to them. The Responses address questions about arrangements for organising, financing and governing health systems, and strategies for implementing changes.

What is SURE?

SURE – Supporting the Use of Research Evidence (SURE) for policy in African health systems - is a collaborative project that builds on and supports the Evidence-Informed Policy Network (EVIPNet) in Africa and the Regional East African Community Health (REACH) Policy Initiative (see back page). SURE is funded by the European Commission's 7th Framework Programme.
www.evipnet.org/sure

Glossary

of terms used in this report:
www.evipnet.org/sure/rr/glossary

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SURE Supporting the Use of Research Evidence

REACH Regional East African Community Health Policy Initiative

EVIPNet EVIDENCE-INFORMED POLICY NETWORK

Background

Hepatitis B is one of the major global occupational health hazards. It is estimated that more than one third of the world population has been infected with the hepatitis B virus (HBV); about 5% are chronic carriers and nearly 25% of the carriers go on to develop serious liver disease; in addition there are more than one million deaths from HBV-related disease every year (1).
Although it occurs worldwide with an estimated 300 million HBV carriers, the highest rates of HBsAg carrier rates are found in developing countries(1). Up to 95% of infected adults are able to clear the HBV from their body and become immune to further infections with hepatitis B (2). However, some people are not able to clear the HBV and it progresses to chronic (persistent) infection and inflammation of the liver.

Serologic studies conducted in low HBV prevalence countries from up to four decades ago show that healthcare workers have a prevalence of HBV infection up to 10 times higher than that in the general population (3). With a high prevalence of carriers of the disease, and poor working conditions in many of the health facilities in low and middle income countries, many of the accidental contact that leads to health workers getting infected is unavoidable. In Uganda it is estimated that it affects about 8-11% of health workers who contract it through contact with infected individuals' body fluids (4).
Uganda currently lacks a national policy on health worker protection including the immunisation against vaccine-preventable diseases; however it is recommended by the U.S Centres for Disease Control (CDC) that people with jobs that expose them to human blood be vaccinated against hepatitis B (2); that is, that all eligible health workers be vaccinated with the HBV vaccine against hepatitis B for their safety (CDC 1987); the vaccine is supposed to substantially reduce the incidence of clinical and subclinical hepatitis B infection in the immunized individual, and furthermore reduce the need for post-exposure prophylaxis with hepatitis B immune globulin (2). Vaccination has reduced the number of new cases of hepatitis B by more than 75% in the United States (2).

The first HBV vaccine, derived from the plasma of HBsAg carriers by a sequence of physical and chemical procedures was approved by the U.S. Food and Drug Administration in November 1981 (6). The chemicals used during the production of this plasma-derived vaccine (PDV) destroy all known life forms including the human immunodeficiency virus (7). HBV PDV containing S antigen segment of HBsAg has been shown to be effective in eliciting host immune response to HBV and is used widely in preventing HBV infection among health-care workers (2). However shortly after the launch of HBV PDV, recombinant HBV vaccine (RV) was developed by recombinant expression vectors (yeast or mammalian cells) because of the difficulty in obtaining plasma from HBsAg

carriers, the high cost of producing PDV, the public fear of infectious diseases transmitted by plasma, and the practicable DNA recombinant technology (6). The two types of vaccines (PDV and RV) have been proven safe and effective in eliciting protective anti-HBs[1] level in randomized trials conducted in populations with high risk of HBV infection, such as homosexual men (8, 9), patients who receive dialysis treatment (10), and health-care workers (10).

The vaccine is commonly given as an injection into the deltoid muscle of the arm. Severe problems from this vaccine are extremely rare with severe allergic reactions believed to occur about once in 1.1 million doses (5); soreness at the site where the shot is given occurring in up to about 1 person in 4 and temperatures of 99.9°F or higher in up to about 1 person in 15.
A blood test for hepatitis B antibodies is recommended after vaccination to ensure that antibodies have been produced. For the few who do not form antibodies, revaccination may improve the response (5).

This paper will highlight the documented effects or outcomes of mass vaccination of health workers and the documented guidelines or options for implementation of this intervention.

[1] *Anti-HBs: antibody to the surface antigen of the hepatitis B virus; indicative of active immunity to the hepatitis B virus in this case an immune response triggered as the result of having received vaccination against the hepatitis B virus.

Summary of findings

A recent systematic review done to assess the beneficial and harmful effects of all types of preventive hepatitis B vaccines in health-care workers based on randomised trials (11), found the following effects (summarised below). It further documented information that is supportive for the current CDC and WHO guidelines for the administration of the hepatitis B vaccine.

Effects are assessed on the following factors:

- Does the vaccine have any effect at all on health-workers?
- Is there a difference between the effects caused by the plasma derived vaccine (PDV) and the recombinant vaccine (RV)?

Evidence supporting Guidelines in current use is presented here looking at:

- The vaccine is commonly given as a deltoid intramuscular (IM) injection; what are the effects of the alternative gluteal intramuscular injection?
- The vaccine is commonly given through the intramuscular route; what are the effects of the alternative intra-dermal route?
- What is the effect of different alternative doses of the vaccine?
- There are vaccines manufactured in different countries on the market; what is the effect of similar alternative vaccines produced in different countries?
- What is the effect of different brands of RV?
- The standard schedule is (0, 1, 6 months), what is the effect of the alternative rapid schedule (0, 1, 2 months)?
- What is the effect of a booster vaccination with recombinant vaccine in non-responders?

How this Response was prepared

After clarifying the question being asked, we searched for systematic reviews, local or national evidence from Uganda, and other relevant research. The methods used by the SURE Rapid Response Service to find, select and assess research evidence are described here:

www.evipnet.org/sure/rr/methods

What the quality of evidence (GRADE) means

The quality of the evidence is a judgement about the extent to which we can be confident that the findings of the research are correct. These judgements are made using the GRADE framework, and are provided for each outcome. The judgements are based on the type of study design (randomised trials versus observational studies), the risk of bias, the consistency of the results across studies, and the precision of the overall findings across studies. For each outcome, the quality of the evidence is rated as high, moderate, low or very low using the definitions below.

⊕⊕⊕⊕
High: We are confident that the true effect lies close to what was found in the research.

⊕⊕⊕◯
Moderate: The true effect is likely to be close to what was found, but there is a possibility that it is substantially different.

⊕⊕◯◯
Low: The true effect may be substantially different from what was found.

⊕◯◯◯
Very low: We are very uncertain about the effect.

For more information about GRADE:

www.evipnet.org/sure

Effects

a) PDV versus placebo: To check whether the vaccine in form of PDV has any effect at all on the health care workers, a comparison of effects was made between PDV and a placebo. PDV significantly decreased the number of hepatitis B events at the maximum follow up period (see Table 1).

Table 1: Plasma-derived vaccine (PDV) vs placebo

Vaccines for preventing hepatitis B in health care workers

Patients or population: Healthy health care workers (HCWs) who are in contact with blood or blood products, blood contaminated instruments, stained body fluids, or tissues.
Settings: Low, Middle and High income country health facilities
Intervention: Hepatitis B vaccine (PDV) by IM route
Comparison: Placebo

Outcomes	Impact (Odds Ratios with confidence intervals)	Number of studies	Quality of the evidence (GRADE)
Hepatitis B events at maximum follow-up - Risk of infection	**PDV significantly reduced the number of hepatitis B events by half** 0.51 [0.35, 0.73] **PDV significantly reduced the number of hepatitis B events in HCWs with high risk of infection but not significantly in those with low risk.**	4	⨁⨁◯◯
High risk of infection	0.53 [0.36, 0.77]		
Low risk of infection	0.20 [0.02, 1.70]		
Hepatitis B events at maximum follow-up – Dose	**PDV at the different doses significantly reduced the number of hepatitis B events** 0.51 [0.35, 0.73]	4	⨁⨁◯◯
High dose (20 µg)	0.32 [0.16, 0.65]		
Low dose (3 or 5 µg)	0.64 [0.41, 0.99]		
Adverse events after each injection of vaccine	**There were no significant differences in adverse events between PDV and placebo**	4	⨁⨁◯◯ Low
After the first injection of vaccine (0 month)	1.11 [0.98, 1.24]		
After the second injection of vaccine (1 month)	1.07 [0.94, 1.22]		
After the third injection of vaccine (6 months)	1.15 [0.99, 1.33]		
Local adverse events after each injection of vaccine	**No significant difference in local adverse events between PDV and placebo**	3	⨁⨁◯◯ Low
After the first injection of vaccine (0 month)	1.03 [0.89, 1.20]		
After the second injection of vaccine (1 month)	1.09 [0.93, 1.28]		
After the third injection of vaccine (6 months)	1.10 [0.94, 1.29]		

Systemic adverse events after each injection of vaccine After the first injection of vaccine (0 month) After the second injection of vaccine (1 month) After the third injection of vaccine (6 months)	**No significant difference in systemic adverse events between PDV and placebo** 1.44 [0.65, 3.20] 1.26 [0.52, 3.06] 2.73 [0.75, 9.89]	1	⊕⊕◯◯ Low
Low quality of evidence: None of the four trials reported adequate generation of allocation sequence, only two reported adequate allocation concealment, only two trials reported sample size calculation, none of the four trials performed intention to treat analysis.			
GRADE: GRADE Working Group grades of evidence (see bar on the right, page 4)			

b) Is there a difference between the effects caused by the plasma derived vaccine (PDV) and the recombinant vaccine (RV).

Table 2: Recombinant vaccine (RV) versus Plasma-derived vaccine (PDV)

Vaccines for preventing hepatitis B in health workers

Patients or population: Healthy health care workers who are in contact with blood or blood products, blood contaminated instruments, stained body fluids, or tissues.
Settings: Low, Middle and High income country health facilities
Intervention: PDV
Comparison: RV

Outcomes	Impact	Number of studies	Quality of the evidence (GRADE)
Number of health care workers without protective anti-HBs level (< 10 IU/litre) at maximum follow up 20µg by IM route 2µg by ID route	No significant difference 1.26 [0.78, 2.04] 1.45 [0.88, 2.40] 0.13 [0.01, 2.22]	2	⊕⊕⊕◯
Adverse events after the first injection Pain Redness Myalgia	There was significantly more pain, redness and myalgia in the PDV group than the RV group. 0.60 [0.44, 0.80] 0.47 [0.29, 0.76] 0.48 [0.33, 0.71]	1	⊕⊕⊕◯ [Text]
Adverse events after the second injection	No significant difference	1	⊕⊕⊕◯ [Text]
Adverse events after the third injection Redness	There was more redness in the PDV group than RV group 0.51 [0.30, 0.85]	1	⊕⊕⊕◯ [Text]

GRADE: GRADE Working Group grades of evidence (see bar on the right, page 4)

Adverse events assessed include: fever, pain, redness, swelling, nausea, vomiting, myalgia, rash, fatigue, headache. Only those with significant findings are reported above.

Post-marketing surveillance literature looking at about 4.5 million doses of the vaccine found that the incidence of adverse events was one out of 15,500 doses and the incidence of local adverse events was one out of 85,000 doses. No serious or severe adverse events attributable to RV were reported (12).

Another post-marketing surveillance reported 19,931 adverse events out of 500 million doses of RV (yeast-derived) (13). The main adverse events included nausea (1:296,000), rash (1: 250,000), headache (1:326,000), fever (1:254,000), and injection site reaction (1:203,000) it also reported no serious adverse events attributable to RV.

Guidelines

a) The vaccine is commonly given as a deltoid intramuscular (IM) injection; what are the effects of alternatives?

Gluteal intramuscular injection vs deltoid intramuscular injection (20µg PDV)

Vaccines for preventing hepatitis B in health care workers

Patients or population: Healthy health care workers who are in contact with blood or blood products, blood contaminated instruments, stained body fluids, or tissues.
Settings: Low, Middle and High income country health facilities
Intervention: Deltoid intramuscular injection (PDV)
Comparison: Gluteal intramuscular injection (PDV)

Outcomes	Impact (effect size)	Number of studies	Quality of the evidence (GRADE)
Number of health care workers without protective anti-HBs level (< 10 IU/litre) at one year follow up.	The number of HCWs without protective anti-HBs level was significantly higher in the gluteal injection group than in the deltoid group 21.13 [2.91,153.32]	1	⊕⊕◯◯ Low

Geometric mean titre (IU/litre) of anti-HBs level at one year follow-up	The mean titre of anti-HBs in the gluteal group was also significantly lower than that in the deltoid group -241.0 [-242.30, -239.70]	1	⊕⊕◯◯ Low
Low quality of evidence: the trial did not report adequate generation of the allocation sequence, allocation concealment and double blinding. They also did not perform sample size calculation and intention to treat.			
GRADE: GRADE Working Group grades of evidence (see bar on the right, page 4)			

b) The vaccine is commonly given through the intramuscular route; what are the effects of the alternative intra-dermal route?

Intra-dermal versus intramuscular route

Vaccines for preventing hepatitis B in health care workers

Patients or population: Healthy health care workers who are in contact with blood or blood products, blood contaminated instruments, stained body fluids, or tissues.
Settings: Low, Middle and High income country health facilities
Intervention: Intramuscular route
Comparison: Intra-dermal route

Outcomes	Impact (effect size)	Number of studies	Quality of the evidence (GRADE)
Number of health-care workers without protective anti-HBs level (< 10 IU/litre) at maximum follow-up		8	⊕⊕◯◯ Low
PDV (2µg by intradermal route vs 2 µg by intramuscular route)	There was no significant difference between the two routes regarding numbers without protective anti-HBs level at similar dose 0.63 [0.22, 1.85]		
PDV (2 µg vaccine by intradermal route vs 20 µg vaccine by intramuscular route)	There were significantly more participants without protective anti-HBs level following 2µg PDV by intradermal route as compared with 20µg IM route. 2.33 [1.47, 3.68]		
RV (1 or 2 µg by intradermal route versus 10 or 20 µg by intramuscular route)	There were more participants without protective anti-HBs level following 2µg RV by intradermal route as compared with 10 or 20µg IM route. 1.41 [1.13, 1.76]		

Sensitivity analysis: number of health-care workers without protective anti-HBs level - follow-up Seven or eight months after the first injection of vaccine One year after the first injection of vaccine Two years after the first injection of vaccine	The higher dose IM vaccination was significantly superior to the lower dose intradermal vaccination irrespective of follow-up period. 1.49 [1.17, 1.89] 1.46 [1.07, 2.00] 1.33 [1.10, 1.62]	3	⊕⊕◯◯ Low
Geometric mean titre (IU/litre) of anti-HBs level at follow-up	The titres of anti-HBs are higher in high-dose IM PDV than in low-dose intradermal PDV. -346.0 [-347.28, -344.72]	1	⊕⊕◯◯ Low
Adverse events	No significant difference in general 0.93 [0.53, 1.53]	2	⊕⊕◯◯ Low
Local adverse events	More local adverse events by the intradermal route as compared to IM route 6.86 [4.63, 10.17]	2	⊕⊕◯◯ Low
Systemic adverse events Fever	Significantly less systemic adverse events in intradermal route than by IM route 0.31 [0.12, 0.82] 0.31 [0.12, 0.82]	2	⊕⊕◯◯ Low
Low quality of evidence: none of the trials reported adequate generation of allocation sequence and allocation concealment. Only one trial reported single blinding for the anti-HBs assessment, the other trials did not perform blinding. Only one trial reported sample size calculation and only three trials performed intention to treat analysis.			
GRADE: GRADE Working Group grades of evidence (see bar on the right, page 4)			

c) What is the effect of different alternative doses of the vaccine?

Different doses of plasma derived vaccine (PDV) by intramuscular route

Vaccines for preventing hepatitis B in health care workers

Patients or population: Healthy health care workers who are in contact with blood or blood products, blood contaminated instruments, stained body fluids, or tissues.

Settings: Low, Middle and High income country health facilities

Intervention vs Comparison: 2µg vs 1µg; 5µg vs 1µg; 5µg vs 2µg

Outcomes	Impact	Number of studies	Quality of the evidence (GRADE)

Number of health care workers without protective anti-HBs level (< 10 IU/litre) at one year follow up (12 months) 2µg vs 1µg 5µg vs 1µg 5µg vs 2µg	No significant difference in comparisons between 2µg and 1µg and 5µg and 1µg 1.47 [0.88, 2.46] 0.84 [0.46, 1.54] However significant difference between 5µg and 2µg-individuals with 5µg were two times less likely not to have protective anti HB s levels than those with 2µg 0.57 [0.33, 0.99]	1	⊕⊕◯◯ Low
Low quality of evidence: the trial did not report adequate generation of the allocation sequence, allocation concealment, double blinding and follow-up. They also did not perform sample size calculation and intention to treat analysis.			
GRADE: GRADE Working Group grades of evidence (see bar on the right, page 4)			

d) There are vaccines manufactured in different countries on the market, what is the effect of similar alternative vaccines produced in different countries?

Plasma derived vaccines produced in different countries: 20µg by intramuscular route

Vaccines for preventing hepatitis B in health care workers

Patients or population: Healthy health care workers who are in contact with blood or blood products, blood contaminated instruments, stained body fluids, or tissues.
Settings: Low, Middle and High income country health facilities
Intervention vs Comparison: PDV produced in Korea vs USA

Outcomes	Impact	Number of studies	Quality of the evidence (GRADE)
Number of health care workers without protective anti-HBs level (< 10 IU/litre) at one year follow up (7 months)	No significant difference 1.27 [0.89, 1.82]	1	⊕⊕◯◯ Low
Low quality of evidence: the trial did not report adequate generation of the allocation sequence and allocation concealment, but reported adequate double blinding and follow-up. The trial did not report sample size calculation and intention to treat analysis was not performed.			
GRADE: GRADE Working Group grades of evidence (see bar on the right, page 4)			

e) What is the effect of different brands of RV?

Different brands of RV (10µg Recombinavax-HB versus 20µg Engerix-B by intramuscular route)

Vaccines for preventing hepatitis B in health care workers

Patients or population: Healthy health care workers who are in contact with blood or blood products, blood contaminated instruments, stained body fluids, or tissues.
Settings: Low, Middle and High income country health facilities
Intervention: 10µg Recombinavax-HB
Comparison: 20µg Engerix-B

Outcomes	Impact	Number of studies	Quality of the evidence (GRADE)
Number of health care workers without protective anti-HBs level (< 10 IU/litre) at one year follow up (7 months)	Significantly more healthcare workers without protective anti-HBs level in the low dose Recombivax than the high dose Engerix group 1.31 [1.02, 1.68]	1	⊕⊕◯◯ Low

Low quality of evidence: the trial did not report adequate generation of the allocation sequence, allocation concealment and double blinding but adequate follow-up. The trial did not report sample size calculation and intention to treat analysis was not performed.

GRADE: GRADE Working Group grades of evidence (see bar on the right, page 4)

f) The standard schedule is (0, 1, 6 months), what is the effect of the alternative rapid schedule (0, 1, 2 months)?

Rapid schedule (0, 1, 2 months) vs standard schedule (0, 1, 6 months)

Vaccines for preventing

Patients or population: Healthy health care workers who are in contact with blood or blood products, blood contaminated instruments, stained body fluids, or tissues.
Settings: Low, Middle and High income country health facilities
Intervention: standard schedule (0, 1, 6 months)
Comparison: Rapid schedule (0, 1, 2 months)

Outcomes	Impact	Number of studies	Quality of the evidence (GRADE)

Number of health care workers without protective anti-HBs level (< 10 IU/litre) by recombinant vaccine	The rapid schedule elicited significantly more without protective anti-HBs level 3.45 [1.47, 8.07]	2	⊕⊕◯◯ Low
Non-smoker (20µg by intramuscular route) Smoker (20µg by intramuscular route) Common participants (20µg by intramuscular route)	7.0 [0.90, 54.25] 1.42 [0.40, 5.08] 5.2 [1.15, 23.42]		

Low quality of evidence: none of the trials reported adequate generation of the allocation sequence, allocation concealment and adequate. Both reported adequate follow-up. The trials did not report sample size calculation and only one performed intention to treat analysis.

GRADE: GRADE Working Group grades of evidence (see bar on the right, page 4)

g) What is the effective dose for a booster vaccination with recombinant vaccine in non-responders?

Booster vaccination with recombinant vaccine in non-responders

Vaccines for preventing

Patients or population: Healthy health care workers who are in contact with blood or blood products, blood contaminated instruments, stained body fluids, or tissues.

Settings: Low, Middle and High income country health facilities

Intervention vs Comparison: different doses of booster vaccination with RV in non-responders

Outcomes	Impact	Number of studies	Quality of the evidence (GRADE)
Number of health care workers without protective anti-HBs level (< 10 IU/litre) after booster vaccination	There were no differences in the number without protective anti-HBs level (< 10 IU/litre) after booster vaccination between different doses	2	⊕⊕⊕◯ Moderate
2.5µg or 5µg vs 10µg 5µg vs 20µg 5µg vs 40µg 10µg vs 20µg 20µg vs 40µg	1.38 [0.89, 2.16] 0.93 [0.56, 1.55] 1.44 [0.76, 2.75] 0.57 [0.29, 1.12] 1.56 [0.83, 2.91]		

Moderate quality of evidence: one of the trials reported adequate generation of the allocation sequence. No trial reported adequate allocation concealment. One trial reported adequate double blinding while the other reported adequate single blinding for anti-HBs assessment. Only one of the trials reported sample size calculation but both stated and performed intention to treat analysis.

GRADE: GRADE Working Group grades of evidence (see bar on the right, page 4)

Cost-effectiveness: Consideration of epidemiological and economic data shows that universal vaccination strategies are cost-effective even in countries with a low prevalence of hepatitis B. In this systematic review, only one trial looked at cost-effectiveness but in terms of difference in brands. They found that there was no significant difference in vaccination effect between PDV produced in Korea and America despite the price of the former being nine times less than the latter.

Contra-indications: there are people who should not get this vaccine and these have been identified as the following (5):

- Anyone with a life-threatening allergy to baker's yeast, or to any other component of the vaccine, should not get hepatitis B vaccine.
- Anyone who has had a life-threatening allergic reaction to a previous dose of hepatitis B vaccine should not get another dose.
- Anyone who is moderately or severely ill when a dose of vaccine is scheduled should probably wait until they recover before getting the vaccine.

Conclusion

Hepatitis B is a major occupational hazard for health workers with a prevalence higher than that in the general population. Vaccination of health workers against Hepatitis B has been shown to significantly reduce the infections or even a need for post exposure prophylaxis. This paper has shown the effects of vaccinating health workers against Hepatitis B. In addition, it has also presented evidence from the literature to support the current guidelines used when vaccinating health workers.

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Conflicts of interest
None known.

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The Regional East African Community Health-Policy Initiative (REACH) links health researchers with policy-makers and other vital research-users. It supports, stimulates and harmonizes evidence-informed policymaking processes in East Africa. There are designated Country Nodes within each of the five EAC Partner States.
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