Evaluation of goat based ‘Indigenous vaccine’ against Bovine Johne’s Disease in endemically infected native cattle herds

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‘Indigenous vaccine’ prepared from ‘Indian Bison Type’ a native bio-type of Mycobacterium avium subspecies paratuberculosis strain ‘S5’ of goat origin (goat based) was evaluated in indigenous cattle herds located in gaushalas (cow shelters), endemic for Bovine Johne’s disease. Cows (893) were randomly divided into vaccinated (702 = 626 adults + 76 calves) and control (191 = 173 adults + 18 calves) groups. Response to vaccination was evaluated on the basis of health (mortality, morbidity), productivity (growth rate, reproductive performance, total milk yield), immunological parameters (LTT, ELISA titer), survivability of animals naturally infected with MAP, bacterimia (by specific blood PCR), sero-conversion (by indigenous ELISA) and status of shedding of MAP in feces (by microscopy) in the two groups before and after vaccination. Reduction in MAP shedding [to the extent of 100% in Herd A; and from 82.1% (0 DPV) to 10.7% (270 DPV) in Herd C] was the major finding in vaccinated cows. Whereas, the control group cows have shown no improvement. As the first indicator of vaccine efficacy, MAP bacilli disappeared from the blood circulation as early as 15 days post vaccination, however, peak titers were achieved around 90 DPV. Peak titers initially declined slightly but were maintained later throughout the study period. Control animals did not show any pattern in antibody titers. Mortality was low in vaccinated as compared to the control groups. Vaccination of endemically infected native cattle herds with inactivated whole-cell bacterin of novel ‘Indian Bison Type’ bio-type of goat origin strain ‘S5’ effectively restored health and productivity and reduced clinical BJD. Application of goat based ‘indigenous vaccine’ for therapeutic management of BJD in native cattle herds (gaushalas) is the first of its kind.

Keywords: BJD, Cows, Gaushala, JD, Mycobacterium avium subsp. paratuberculosis (MAP), Tuberculosis

Mycobacterium avium subspecies paratuberculosis (MAP), the etiological agent of Bovine Johne’s disease (BJD) is mainly responsible for causing heavy losses to the Indian dairy farms primarily by way of reduction in the milk production1. Though India is the highest milk producer in the world, the low ‘per animal productivity’ of the majority of 214.3 million cattle heads2 is the major concern of Indian dairy farmers. The BJD could be attributed to the loss of best germplasm of native cattle breeds that endemically suffer from MAP infection3. Clinically infected cattle exhibit gradual loss in body weights, progressive wasting and death, besides other production losses such as low fertility, high morbidity and mortality and increased culling. Diarrhoea, though not a primary symptom for BJD, it is continuous and un-treatable when sets in.

Live MAP bacilli are cultured from pasteurized milk and milk products4 and from soil and water resources5. MAP has also been associated with Crohn’s disease in human beings6,7. In the absence of National control policy, prevalence of MAP is not only high but also increasing in the domestic livestock population both in farm and farmer’s herds3. Due to low productivity and zero salvage value of cows (in view of ban on cow slaughter), there is major shift in animal husbandry practices, whereby, goats or buffaloes or sheep husbandary is preferred over dairy cows.

Vaccination against Bovine Johne’s disease has been shown to control the MAP infection8. ‘Indigenous vaccine’ developed9 using native ‘Indian
Bison type’ strain (S5) of goat origin (a new biotype)\textsuperscript{10} was both ‘therapeutic’\textsuperscript{11} and preventive\textsuperscript{9} in goats and sheep. In the present study, we evaluated ‘therapeutic potential’ of ‘indigenous goat based vaccine’ against infection of MAP in native cattle herds living in gaushalas and suffering from symptoms of clinical to advanced clinical Johne’s disease.

Materials and methods

Animals—Gaushalas are charitable community shelters for unproductive and abandoned cows. Condition of cows in gaushalas is generally poor and majority of them suffer from various health disorders, clinical JD being the most common ailment. Following four gaushalas had volunteered for the present ‘vaccine trial’. A total of 893 cows (19, 680, 36 and 158 cows from Golo gaushala, Farah, Mathura - Herd A; Govind gaushala, Vrindavan, Mathura - Herd B; Vaishnav gaushala, Vrindavan, Mathura - Herd C; and Swadeshi gaushala, Agra - Herd D, respectively) were included in this study (Table 1). Physical condition of the cows (in variable age and of both sexes) was poor (weak, debilitated, emaciated) and 50-75% of these cows were suffering from clinical to advance clinical Bovine Johne’s disease. All the cows in vaccine trial were ear-tagged for identification. Of the total 893 animals in four herds, 94 were calves (6 months to 1 year) and 799 adult cows (1 to 7 years). Of these, 702 (76 calves and 626 adults) were vaccinated and 191 (18 calves and 173 adults) were observed as control.

Vaccine—‘Indigenous vaccine’ was first developed in 2005 using native ‘S5’strain of ‘Indian Bison type’ (a new biotype of MAP not reported outside India)\textsuperscript{10,12}, isolated from Jamunapari breed of goat with advance clinical disease, which later died of JD. ‘Indigenous vaccine’ has been evaluated both for therapeutic potential in naturally infected spontaneous cases of JD in goats and sheep\textsuperscript{11,13,14}, and as preventive vaccine (vaccination and challenge)\textsuperscript{9}. One mL of vaccine contained 2.5 mg (dry wt) inactivated (at 72 °C for 2 h in water bath) culture containing $5 \times 10^9$ bacilli/mL of adjuvant (Gerbu Biotechnik, Germany). Vaccine dose was 1 mL subcutaneous in goats and sheep and 2 mL in cattle and buffaloes for life. Cows above 6 months of age were vaccinated with 2 mL (5.0 mg/cow) of ‘indigenous goat based vaccine’ subcutaneously in the middle of neck region behind ear.

Monitoring parameters—Health status of cows before and after vaccination was compared. Cows were monitored on physical condition, health (mortality, morbidity, reproductive performance), production parameters (growth rate, total milk yield), immunological parameters (LTT, ELISA titer) and survivability of animals naturally exposed to MAP in vaccinated and controls, bacterimia of MAP (by blood PCR), sero-conversion (by ELISA) and status of MAP shedding in fecal samples (by microscopy). Improvement in physical traits like appearance, weakness, alertness and changes in body coat (colour, roughness, shining) and status of diarrhea, if any, at monthly intervals were also monitored. Sick animals were treated symptomatically. Owner’s views with respect to general body

<table>
<thead>
<tr>
<th>Herd code</th>
<th>Cattle herds &amp; locations</th>
<th>No. of Cattle</th>
<th>Vaccinated</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Calves</td>
<td>Adults</td>
</tr>
<tr>
<td>A</td>
<td>Golo Gaushala, Mathura</td>
<td>19</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>B</td>
<td>Govind Gaushala, Mathura</td>
<td>680</td>
<td>31</td>
<td>501</td>
</tr>
<tr>
<td>C</td>
<td>Vaishnav Gaushala, Mathura</td>
<td>36</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>D</td>
<td>Swadeshi Gaushala, Agra</td>
<td>158</td>
<td>35</td>
<td>93</td>
</tr>
<tr>
<td>Total cows</td>
<td></td>
<td>893</td>
<td>76</td>
<td>626</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Mortality
conditions (feeding, health, physical condition and appearance, milk yield) were also recorded during visits to the gaushalas.

Collection of samples and tests—Fecal, blood and serum samples of representative cows (25% from vaccinated and controls) were collected at monthly intervals post-vaccination (DPV) up to a maximum of 360 days in herd B.

Fecal microscopy—Shedding of MAP in fecal samples was monitored by microscopy. Shedding of MAP was measured quantitatively (0 to +4 scale) and animals that measured +1 to +4 were taken as positive for MAP infection.

IS900 PCR—DNA was isolated from the blood samples and subjected to specific IS900 PCR as described by Singh et al.

Cellular Immune Response (Stimulative Index)—Peripheral blood mononuclear cells (PBMCs) were harvested from blood using Histopaque (Sigma-Aldrich) up to 4 months post vaccination and Lymphocyte Transformation Test (LTT) was done as per the method of Uma et al. Proliferation of lymphocytes was indicated by optical densities of test wells with un-pulsed (control) wells. The Stimulative Index (SI) was calculated for each cow using average OD at 570 nm in stimulated wells and in the non-stimulated control wells. SI values were only considered as positive for MAP infection.

Indigenous ELISA—Indigenous ELISA kit employed for screening of BJD and monitoring of vaccine response used semi-purified protoplasmic antigen (PPA) from the highly virulent native isolate (‘SS’) of MAP ‘Indian Bison type’ biotype of goat origin. The test originally developed and standardized for goats and sheep has since been standardized for use in bovines and also employed for screening of cattle and buffaloes. OD values were converted to S/P ratio and animals in positive and strong positive categories in S/P ratio were only considered as positive for MAP infection or sero-reactor(s).

Sero-conversion—Indigenous ELISA kit was used to monitor sero-conversion. Pre and post vaccination serum samples were collected from 93 of total 893 vaccinated and control animals (~13%) from all age groups. Antibody titers were monitored in the cows at 30-day interval as per Singh et al and the results were presented as percent sero-reactors at respective sampling intervals.

Autopsy examination and Histopathology—Tissues (mesenteric lymph nodes and large intestines) from animals died during the study were sectioned and stained by Hematoxyline-Eosine and Ziehl-Neelsen methods to know the status of disease and the effect of vaccine. Histopathological changes were recorded on the basis of localization and extension of the lesions. The lesions were categorized as ‘no lesion’, ‘focal’ or ‘diffused’ in the target tissues as per Perez et al.

Statistical analysis—‘t’-test was applied on the data obtained from the vaccinated and control animals. SI values of P <0.05 were considered statistically significant.

Results

Animal health and growth (morbidity and mortality)—No significant illness was noticed in vaccinated cows during the study period barring mild anorexia for 3 days in 3 vaccinated cows following vaccination. In ‘control’ group, diarrhea was the frequent cause of illness. In Herd A, most of the cows suffered repeated parasitic and tick infestation due to poor hygiene up to 210 DPV and were treated with Ivomec (USA).

General body condition of the vaccinated cows showed marked improvement during the study period (Fig. 1A and B). Body coat regained luster, shining and pliability. Regeneration of hair and brightness in eyes were also observed. Vaccinated cows could be easily differentiated from the control groups by their improved body condition at 180 DPV. Most of the vaccinated animals developed notable ‘swelling or granuloma’ at the vaccination site. Stunted calves started growing after vaccination.

Overall, six cows (2 adults and 1 calf in vaccinated; and 1 adult and 2 calves in control group) died during the study. Johne’s Disease was the main cause of mortality in controls. Mortality rate was low in vaccinated group (0.4%) compared to control (1.6%) (Table 1).

Shedding of MAP—Generally, vaccinated cows showed decreased MAP shedding during post vaccination days. Few vaccinated cows reverted back to shedding of MAP after 300 DPV, and were re-vaccinated and the shedding of MAP was again reduced. At ‘0’ DPV, 83.3, 44.1, 82.1 and 63% cows in vaccinated groups of herds A, B, C and D, respectively were shedding MAP in feces (positive for MAP infection). Whereas 50, 31.6, 87.5 and 57.1% cows in control groups of herds A, B, C and D, respectively were shedding MAP in feces at ‘0’ DPV (Tables 2 and 3). Vaccinated cows in herds A and C
showed significant reduction of 100 and 89.3%, respectively in MAP shedding at 270 DPV. Whereas, herds B and D showed only 10.8 and 33.3% reduction at 360 and 120 DPV, respectively. The control groups in all the herds showed either no change or increased MAP shedding (Tables 2 and 3).

**Monitoring of MAP in blood using IS900 PCR**—At zero DPV, 66.7, 30, 57.1 and 22.2% cows tested positive for MAP (blood PCR) in herds A, B, C and D respectively of vaccinated groups, whereas 50, 21.7, 40 and 42.9%, respectively were positive in control groups. Presence of MAP in blood circulation was reduced in vaccinated cows over the period, while there was either no variation or increased incidence of MAP in the control groups.

**Cellular immune response (Stimulative Index)**—PBMCs of vaccinated group had higher ‘Stimulative Index’ (SI) when pulsed with protoplasmic antigen of ‘S5’ strain than the control groups. SI value of vaccinated cows was significantly higher at 30 DPV onwards ($P <0.05$) at 95% confidence interval (Fig. 2). On the basis of LTT, it was clear that the vaccine induced effective CMI response.

**Humoral immune response (sero-conversion)** using ‘indigenous ELISA kit’—In vaccinated groups, peak titer was achieved around 90 DPV followed by mild decline.
Table 2—Status of MAP infection (shedders) at 0, 60, 90, 120, 180, 210, 270 and 360 days post vaccination

<table>
<thead>
<tr>
<th>Day(s) post vaccination (DPV)</th>
<th>Tests</th>
<th>0</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>180</th>
<th>210</th>
<th>270</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>V C V C V C V C V C V C V C V C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Herd A, Golo gaušala

<table>
<thead>
<tr>
<th>Tests</th>
<th>Samples (n)</th>
<th>Positive (n)</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopy</td>
<td>6 2 6 2 6 2 - - 6 2 - -</td>
<td>5 1 4 2 0 2 - - 0 1 - -</td>
<td>83.3 50 66.7 100 0 100 - - 0 50 - -</td>
</tr>
<tr>
<td>Blood PCR</td>
<td>6 2 6 2 6 2 - - 6 2 - -</td>
<td>4 1 2 1 2 0 - - 1 0 - -</td>
<td>66.7 50 33.3 50 33.3 0 - - 16.7 0 - -</td>
</tr>
</tbody>
</table>

Herd B, Govind gaušala

<table>
<thead>
<tr>
<th>Tests</th>
<th>Samples (n)</th>
<th>Positive (n)</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopy</td>
<td>102 19 - - - - - - -</td>
<td>45 6 - - - - - - -</td>
<td>44.1 31.6 - - - - - - -</td>
</tr>
<tr>
<td>Blood PCR</td>
<td>80 23 - - 63 17 - - -</td>
<td>24 5 - - 14 4 - - -</td>
<td>30 21.7 - - 22.2 23.5 - - -</td>
</tr>
</tbody>
</table>

Herd C, Vaishnav gaušala

<table>
<thead>
<tr>
<th>Tests</th>
<th>Samples (n)</th>
<th>Positive (n)</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopy</td>
<td>28 8 28 8 - - 28 8 25 7 13 1 28 8 - -</td>
<td>23 7 11 4 - - 2 6 11 5 4 1 3 7 - -</td>
<td>82.1 87.5 39.3 50 - 7.1 75 44 71.4 30.8 100 10.7 87.5 - -</td>
</tr>
<tr>
<td>Blood PCR</td>
<td>7 5 7 5 - - 7 5 7 5 7 5 7 5 7 5 - -</td>
<td>4 2 4 3 - - 0 2 0 2 0 2 0 2 - -</td>
<td>57.1 40 57.1 60 - 0 40 0 40 0 40 0 40 - -</td>
</tr>
</tbody>
</table>

V, vaccinated; C, control; -, Data not available

Table 3—Status of MAP Infection (shedders) at zero day (Herd D, Swadeshi gaušala)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age</th>
<th>Animals (Cattle)</th>
<th>Positive cattle, number (percent)</th>
<th>MAP genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Microscopy</td>
<td>Blood PCR</td>
<td>I-ELISA</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>Calf</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Adult</td>
<td>22</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>17 (63%)</td>
<td>6 (22.2%)</td>
<td>25 (92.6%)</td>
</tr>
<tr>
<td>Control</td>
<td>Calf</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Adult</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>4 (57.1%)</td>
<td>3 (42.9%)</td>
<td>5 (71.4%)</td>
</tr>
<tr>
<td>Grand Total</td>
<td>34</td>
<td>21 (61.76%)</td>
<td>9 (26.4%)</td>
<td>30 (88.2%)</td>
</tr>
</tbody>
</table>

I-ELISA, Indigenous ELISA
Fig. 3—Humoral Immune response (as per the sero-conversion ratio) in vaccinated and control groups of herds A-D

and was maintained afterwards. In control groups, slight increase in the antibodies titer was also seen (Fig. 3).

Autopsy examination—In herd D, 5 cows (3 calves and 2 adults) both from vaccinated and control groups died within a week after vaccination due to cold weather and sudden rains. Autopsy showed advanced lesions (corrugation of intestines, complete gelatinization of visceral fat and fat layer around visceral organs, excessive peritoneal fluid and emaciation) of JD (Fig. 4). Histology showed that there was desquamation, sloughing, marked fusion and degeneration of the intestinal villi with proliferation of mucosal gland and infiltration of lymphocytes (Fig. 5).

Discussion

Majority of cows have shown increasing weight loss and loose feces before vaccination. Histological sections of the tissues (large intestine and mesenteric lymph nodes) of young calves and adult cows showed typical lesions (infiltration of epitheloid cells and macrophages in the form of multiple granulomas in the lamina propria of large intestine and in mesenteric lymph nodes) of Johne’s disease, showing that both young calves and adult cows in the herds were suffering from clinical symptoms of weakness, emaciation and cachexia, were due to MAP infection leading to clinical and advance clinical and advance BJD and not due to other health or nutritional problems, such as parasitism and malnutrition. (Figs. 4 and 5).

The ‘Indigenous vaccine’ developed against JD using the most prevalent and highly pathogenic ‘S5’ strain of Mycobacterium avium subspecies paratuberculosis...
(MAP) biotype ‘Indian Bison Type’\textsuperscript{10} has been already shown to protect vaccinated goats from twice-challenge with vaccine strain\textsuperscript{9}. The ‘goat-based vaccine’ when administered in cattle, did not cause any untoward reaction or abscess formation. The vaccine proved to be safe for the cows as well. Perez \textit{et al.}, have reported large and fistulated nodules in sheep\textsuperscript{8}. Screening of herd A at 300 DPV revealed increased MAP shedding after reduction in shedding until then. Therefore, the cows were revaccinated and thereby the shedding was again reduced. This reversion revealed that the initial dose of vaccine was insufficient for cows in advance clinical JD. Moreover, stress factors like low plane of nutrition, poor management and health, unhygienic conditions in the shed complex, extreme environment temperatures, pregnancy, lactation and concurrent parasitic infestations also played critical role in pathogenesis limiting the response to vaccination. The Herd B suffered from most of the above stress factors and ranked lowest on nutritional scale. Environmental stress (excessive winter and summer) could have made cows vulnerable to re-infection. Poor animal hygienic conditions could have contributed to reversion of symptoms due to repeated infection with MAP, along with other endo and ecto-parasites. Hygienic farm conditions (Herd A and C) have shown to play important role in decreasing shedding of the bacilli in feces that limits opportunities for reinfection and transmission of MAP\textsuperscript{24}. Considerable ‘swelling or granuloma’ that developed at the vaccination site in the neck region was also a proof of MAP infection. This ‘granuloma or swelling’ regressed in most of the cows and was retained by some cows up to 120-360 DPV.

The present study also indicated that in cases of MAP infection, vaccination could be practiced in sub-clinical to advance clinical stages of BJD in cows aged \(>6\) months, and in any physiological state (dry, lactating, pregnant). Other studies on vaccination of adult animals also have shown considerable results in controlling JD\textsuperscript{25,26}. Corpa \textit{et al.}\textsuperscript{27} also showed that immune response was higher in adult animals as compared to weeks old lambs and kids. Similar results were reported by Singh \textit{et al.}\textsuperscript{13} in Bharat Merino and Patanwadi sheep vaccinated with goat based ‘Indigenous vaccine’. We have also observed earlier significant reduction in morbidity, mortality and shedding of MAP in feces after vaccination of the goats endemically infected with MAP, which lead to the reduction in the contamination of the animal environment, and thereby reduced the daily dose of MAP infection. Sigurdsson and Gunnarson\textsuperscript{28} eradicated JD by vaccinating lambs with single dose. Using goat based ‘Indigenous vaccine’ against MAP infection showed reduction in the prevalence of clinical JD in goat herds by 50-90\%\textsuperscript{29}.

The reduced MAP shedding in feces along with visible improvement in physical condition of vaccinated cows as compared to controls confirmed the ‘therapeutic effect’ of the goat based ‘Indigenous vaccine’. Other significant improvements such as body coat regaining its luster, shining, pliability, regeneration of hairs and increased growth rate in growing calves were apparent after 180 DPV (Figs 1A and B). Multi-bacillary MAP shedders turned into pauci-bacillary shedders. Similar reduction was observed in number of shedders by microscopy of serially sampled cohort by Hines \textit{et al.}\textsuperscript{30} on vaccination of spheroplast and cell wall component based MAP vaccine in experimentally challenged goat kids.

The low mortality rate in vaccinated groups observed in the present study is in alignment with Gwozdz \textit{et al.}\textsuperscript{31}. Earlier, Uzonna \textit{et al.}\textsuperscript{32} too observed that the ‘native field strain’ based vaccine for JD was more effective and efficacious than the commercial vaccines. ‘Indigenous JD’ vaccine demonstrated therapeutic response with low morbidity and mortality rate, low MAP shedding and high immune response. As most of these monitored parameters exhibited improvement up to 360 DPV, it is concluded that the
therapeutic effect’ is sustainable in vaccinated herds. However, the optimal age of animals for vaccination, stage of infection and management conditions for this ‘Indigenous vaccine’ remains to be investigated.

In humoral immune response study, seroconversion rates were significantly higher in the vaccinated groups as compared to controls. The peak titers around 90 DPV declined afterwards in vaccinated cows whereas control animals did not show any pattern. Spangler et al reported similar rise in the antibody titer at 60 to 360 DPV in vaccinated calves; and Copra et al, in goats at 60 and 180 DPV. The second rise with comparatively low peak observed by the latter may not provide the protection against MAP infection but would indicate the degree of activation of immune system against mycobacteria.

The ability of PBMCs to recognize and respond to MAP infection/antigen was investigated up to 120 DPV. Proliferative response and stimulatory index was higher in PBMCs of vaccinated groups on stimulation with MAP antigen than that of the controls. Low responsiveness may be attributed to the suppressive factors secreted by monocytes and lymphocytes.

**Conclusion**

Goat based ‘Indigenous vaccine’ developed by Microbiology laboratory of Goat Health Division (CIRG, Makhdoom) using MAP strain ‘S5’ (‘Indian Bison Type’) was effective for therapeutic management of BJD in Indian gaushalas. It has significantly reduced morbidity, mortality and shedding of MAP, reduced bio-load of MAP, improved physical condition, birth of healthy calves and enhanced humoral and cellular immunity, and productivity in cattle herds endemic for JD. Also, it underlined nutrition as the primary stress for variable response to JD vaccination and the need for revaccination in the herds under deficient nutritional status annually. It concludes that the ‘goat based’ ‘indigenous vaccine’ can be safely used to treat and salvage cows suffering from sub-clinical, clinical and advance clinical JD in the country.

**Conflict of Interest**

No conflict of interest to declare.

**Acknowledgement**

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