INTRODUCTION
Tuberculosis infection and disease among children are much more prevalent in developing countries, where resources for control are scarce. It is estimated that in developing countries the annual risk of tuberculosis infection in children is 2-5 per cent. Widespread coverage with BCG vaccine has possibly led to modification in the pattern of clinical manifestations. It has been suggested that BCG vaccination is responsible for decrease in the occurrence of disseminated and severe disease. Localized forms of illness, e.g., intrathoracic lymphadenopathy, and localized CNS disease have been reported to occur with greater frequency [1] but these need confirmation from large epidemiological studies. Complications of BCG vaccine are collectively known as BCG disease [2]. Local and regional complications (0.4-1/1000 vaccinees) develop irrespective of immune competency status while distant disseminated BCG disease is generally associated with well-defined immune deficiencies [2,3]. An increase in the number of BCG-associated suppurative lymphadenitis has been reported in many countries in recent years [3-6]. Inherited disorders of INFγ/Interleukin-12 (INFγ/IL-12) axis have been increasingly reported in association with disseminated BCG disease [7,8], now known as Mendelian Susceptibility to Mycobacterial Diseases (MSMD). There is limited published data on clinical profile, outcome and immunological status of BCG disease in Indian literature. We undertook this study to describe the clinical profile, immunological status and outcome of BCG disease.

METHODS: This observational study was conducted at a tertiary care hospital from February 2015 to September 2016. All infants with clinically suspected BCG disease were included in the study and classified as local, regional, distant or disseminated disease [2]. Children who were already on anti-tubercular treatment (ATT) were excluded. Strain, dose and timing of BCG vaccine were documented. Fine needle aspiration cytology of the node (FNAC) and HIV antibody testing were performed on infants with confirmed distant/disseminated disease. Four of these infants were products of second degree consanguinity. All infants had normal immunoglobulin assays, flow cytometry and neutrophil functions. Genetic analysis of the infant with confirmed disseminated disease revealed a novel homozygous mutation in IFNγ-R1 gene at P130H location. All these Ten infants received initially 2HRZEO/7HREO; six among 10 responded over 2-3 months. The mean duration of follow-up after treatment completion was 7 months with no recurrences. Though infants with confirmed distant/disseminated disease showed adequate response initially, they developed skeletal tuberculosis and increasing organomegaly over after 4-6 months. Currently, they are stable on amikacin, azithromycin and linezolid.

DISCUSSION:
In the present study, three-fourth of infants having BCG disease had local or regional involvement. All six children with suspected distant/disseminated BCG disease had normal immunological work-up; IFNγ-R1 gene mutation was documented in one infant. Hesseling, et al. [2] reported dissemination in 32% of their infants with BCG disease [2]. They demonstrated HIV infection in 68% infants [2]. None of our infants were HIV-positive. Primary immune-deficiencies like severe combined immune-deficiency and chronic granulo-matous disease were diagnosed in 25-50% of children in these studies [2,9], but none in our study population. Treatment of BCG disease is challenging as it is complicated by inherent resistance to Pyrazinamide and partial resistance to INH [2]. Resistance to INH was documented in two of our isolates compared to 75% in the Saudi Arabian study [3]. We followed protocol of 2HRZEO, 7HREO and found good results [2]. Various second-line drugs like aminoglycosides, linezolid, and ethionamide have been used for resistant disease [10].

TABLE 1- Profile of Infants with distant/disseminated disease

<table>
<thead>
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<th>Features</th>
<th>No.</th>
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<tr>
<td><em>Age at presentation of lymphadenopathy</em></td>
<td>4.2 month(-1.72)</td>
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<tr>
<td><em>Age at presentation of disseminated</em></td>
<td>7.1 month(-2.2)</td>
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RESULTS:
Fifty children were diagnosed with BCG disease during the study period. Thirty Eight children (76%) presented with local/regional disease alone and 12 (24%) with both local/regional disease and suspected or confirmed distant/disseminated disease. All infants were vaccinated in neonatal period. Eighteen out of 50 had received BCG vaccination in the study hospital with 0.1 mL of Danish 1331 strain. The mean (range) age of presentation was 3.6 (1.5-9) months. Four of 10 infants with disseminated disease required second-line anti-tubercular treatment. One infant with confirmed disseminated disease had INFγ-R1 receptor deficiency. There was no mortality. Conclusion: Most infants with BCG-related disease have local or regional disease.
Two of our infants were prescribed amikacin, azithromycin, and linezolid with good response. Mortality rate among distant/disseminated disease can be as high as 60-80% [2, 10]. Our study has potential limitations. Though we described 50 infants with BCG disease, we could not comment on true incidence and trend as it was a hospital based study, and we have no previous data to compare with. Notification of adverse effects to BCG vaccine is also not strictly followed. Duration of follow-up is also short to comment on complex response, recurrence and mortality.

In our study we found that most of the infants with BCG disease have regional or localized disease but should be followed up for development of any disseminated disease.

REFERENCES