**Delivery of Cytosine Phosphodiester Guanine Oligonucleotides (CpG-ODN) by the intrapulmonary route protects neonatal broiler chicks against *Escherichia coli* septicemia**

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Bacterial infections occurring in neonatal broiler chickens especially during the first week of the life cause major economic losses. Synthetic oligodeoxynucleotides (ODN) containing unmethylated CpG motifs (CpG-ODN) are effective immunostimulatory agents against a variety of viral, bacterial, and protozoan diseases in different animal species including poultry. We have previously demonstrated that *in ovo* delivery of CpG-ODN confers protection in neonatal chickens against bacterial septicemia. The objective of this study was to investigate the effectiveness of intrapulmonary (IPL) delivery of CpG-ODN micro-droplets against *Escherichia coli* infection in neonatal chicks. Chicks were IPL delivered CpG-ODN or saline at the day-1 of age at hatch. Three-days following CpG-ODN treatment chicks were challenged with a lethal dose of *E. coli*. Chicks treated with CpG-ODN by the IPL route had significantly lower clinical signs and bacterial load compared to the group treated with saline (P<0.05). CpG-ODN treated groups were significantly protected against *E. coli* septicemia (P< 0.01). We observed a dose- and exposure time-dependent immunoprotective effects of IPL CpG-ODN delivery in chicks. We found that IPL delivery of CpG-ODN can induce protective immunity as early as 6 h that remain effective during the first of the life of broiler chickens. Moreover, there were no any adverse effects of IPL delivery of CpG-ODN on growth of broilers chickens during the grow-out period of broiler chickens. Based on these findings, CpG-ODN delivery by IPL route is a promising alternative to antibiotics for inducing protective immunity in chicks during the critical first week of neonatal life.