PROTECTION FOR NEWBORN

Prasen Adya

BCG VACCINE
**Mycobacterium tuberculosis**: leading cause of human disease and death in developing countries.

First used to immunise humans in **1921**.

WHO introduced BCG vaccination as part of EPI since **1974**.

Global coverage rates > **80 %** in countries endemic for TB.
Different Strains

At present about 100 mio children receive BCG vaccine every year.

Global demand pegged at 260 mio doses per annum.

Current vaccine strains are all descendants of the original M. bovis isolate that Calmette & Guerin passaged through numerous cycles during the 13 year period 1909-1921.  
(Ref.: Weekly Epidemiological Record, No.4, 23 January 2004 P34)

Subsequent passages under different laboratory conditions resulted in phenotypic and genotypic differences.  
(Ref.: Weekly Epidemiological Record, No.4, 23 January 2004 P34)

Different manufacturers supply product with different strains
The genealogy of BCG vaccine strains, displays the original virulent ancestor strain M. bovis and the subsequent series of genomic alteration including deletions of regions of difference (RD), and some strain-specific insertion.
As a routine, BCG vaccine and BCG for Bladder Cancer – manufactured from the same bulk.

The formulation is different.

Theoretically, **One dose of BCG** for Bladder cancer equals **240 vials of BCG vaccine** i.e. 4800 doses of BCG vaccine!
# BCG: Immunisation, Bladder Cancer

<table>
<thead>
<tr>
<th>BCG for Bladder Cancer</th>
<th>BCG Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Dose</td>
<td>4800 Doses</td>
</tr>
<tr>
<td>1 Vial</td>
<td>240 Vials</td>
</tr>
</tbody>
</table>

One Patient may require 27 doses of ONCO-BCG for Bladder Cancer.*

*: Lamm’s protocol
<table>
<thead>
<tr>
<th>Suppliers</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Institute of India</td>
<td>10/20 dose vial</td>
</tr>
<tr>
<td>Poonawalla Group</td>
<td></td>
</tr>
<tr>
<td>Japan BCG Laboratory</td>
<td>20 dose amp</td>
</tr>
<tr>
<td>Intervax Ltd</td>
<td>10 / 20 dose amp</td>
</tr>
<tr>
<td>GreenSignal Bio Pharma</td>
<td>20 dose vial</td>
</tr>
<tr>
<td>Limited</td>
<td></td>
</tr>
<tr>
<td>AJ Vaccines</td>
<td>10 dose vial</td>
</tr>
</tbody>
</table>

5 WHO PreQualified Suppliers!
DCVMN members currently supply more than 50% of the Global Demand.
2013-15: Global Availability of BCG vaccine

- Shortages reported by UN agencies, EU, US, ANZ, S Africa, several other countries.
- UN agencies & countries undertook strategies to mitigate the effects caused due to shortage.
- Studies reported impact of shortages on Global Paed. Mortality.


Period identified as a BCG shortage period
2013-15: Global Availability of BCG vaccine

- **SIIPL** facility under refurbishment
- **Japan BCG** facility under refurbishment
- **SSI**: upgradation
- **Sanofi Canada** plant under renovation

With so many plants being refurbishment, capacity gets blocked
unicef reported shortages as follows:

<table>
<thead>
<tr>
<th>Year</th>
<th>Shortages</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>8 mio doses</td>
</tr>
<tr>
<td>2014</td>
<td>23 mio doses</td>
</tr>
<tr>
<td>2015</td>
<td>17 mio doses</td>
</tr>
</tbody>
</table>

Facility Refurbishment – Only Reason for Shortage

- Cannot be !!!
- Clarity on stocks required.
- Non availability of BCG for Ca Bladder aggravated the situation – Capacities were diverted to manufacture BCG for Bladder cancer.
BCG for Bladder Cancer

- Incidence more in the developed countries.
- Few suppliers globally.

Supply Situation Aggravated!
BCG for Bladder Cancer

- Major supplier had mfg. issues.
- Resulted in Global shortage of that brand.
- Increased pressure on other brands.
- Existing capacities got diverted.

**Shortage Situation!**
Before shutdown, Manufacturers did manufacture stocks for **Orders in Hand**!

- Provision was also made for anticipated orders.
- Stocks not available for unplanned orders.
- To add to pressure, there was a shortage of BCG for Bladder cancer.
- In some cases, capacities got diverted.

**Shutdowns took place!**
The Issue

- BCG manufacturing takes a long time.
- Bulk manufacturing requires almost 60 days.
- Followed by fill finish and QC release – another 90 – 120 days.
- NRA release - another 45 days!

Due to long manufacturing timelines and capacity issues, manufacturers cannot supply BCG at short notice.
Regulatory Challenges!

- Registration in Individual countries – a long process!
- Documentation desired in CTD format!
- Audit as part of registration requirement by several countries – Despite having WHO PQ.
- Some countries insist on local clinical studies.
- Lot release for each batch – Mfg country NRA as well as exported country NRA for e.g. India, Thailand, Indonesia, Malaysia.
Current Situation

  (Ref. BCG vaccine supply & demand outlook December 2015)

- SII has resumed production.

- Japan BCG resumes production.*

- Merck increases capacity for their Bladder cancer BCG.

- WHO PQ granted to new manufacturer: Green Signal.

* : No conformal information available in public domain
Is all well?

- Not really !!!
- Sanofi announces plans to shut down their Canada plant.
- Demand for BCG for Bladder cancer is likely to surge.
- Capacities are likely to be diverted to meet this increased demand for Onco BCG.
- Again theoretically : 1 dose of Onco BCG consumes capacity of 4800 doses of BCG vaccine!

The pressure situation is building up, AGAIN !!!
Solution

Accurate Forecasting !!!

Converting forecasts into Confirmed Orders within an appropriate time.

Suppliers adhere to the prescribed supply schedule.

Help the manufacturers SERVE YOU BETTER!