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Bacillus Calmette-Guérin (BCG) vaccine: A global assessment of demand and supply balance

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ABSTRACT

Over the past decade, several countries across all regions, income groups and procurement methods have been unable to secure sufficient BCG vaccine supply. While the frequency of stock-outs has remained rather stable, duration increased in 2014–2015 due to manufacturing issues and attracted the attention of national, regional and global immunization stakeholders. This prompted an in-depth analysis of supply and demand dynamics aiming to characterize supply risks. This analysis is unique as it provides a global picture, where previous analyses have focused on a portion of the market procuring through UN entities. Through literature review, supplier interviews, appraisal of shortages, stock-outs and historical procurement data, and through demand forecasting, this analysis shows an important increase in global capacity in 2017: supply is sufficient to meet forecasted BCG vaccine demand and possibly buffer market shocks. Nevertheless, risks remain mainly due to supply concentration and limited investment in production process improvements, as well as inflexibility in demand. Identification of these market risks will allow implementation of risk-mitigating interventions in three areas: (1) enhancing information sharing between major global health actors, countries and suppliers, (2) identifying interests and incentives to expand product registration and investment in the BCG manufacturing process, and (3) working with countries for tighter vaccine management.

1. Introduction

Tuberculosis (TB) is one of the major causes of death worldwide, claiming 1.8 million lives in 2015, particularly among communities which already face socioeconomic challenges [1]. Mycobacterium tuberculosis (MTB), the etiological agent of TB, is transmitted via respiratory droplets by patients who are already infected. In 90 percent of infected persons, the bacterium is contained by the host immune response as a latent TB infection (LTBI). Bacillus Calmette-Guérin (BCG) is the only available vaccine to fight the disease, with a duration of protection of at least ten years with some residual vaccine effectiveness up to 20–25 years [2,3]; however, the vaccine only prevents acute forms of childhood TB, and not reactivation of LTBI (the main source for adult pulmonary disease and transmission of MTB) [1]. WHO recommends universal vaccination with a single birth dose of BCG in settings where TB is highly endemic or where there is high risk of exposure to TB [4].[1]

There is evidence that BCG also prevents leprosy [5], a skin-neurological disease caused by Mycobacterium leprae (200,000 cases in 2016, mainly in Southeast Asia) [6]. BCG vaccine is also effective against other mycobacterial infections, such as Buruli ulcer disease [7].

Over the ninety years since its development, the BCG vaccine has been administered to more than three billion children in the Expanded Programme on Immunization (EPI) across all regions [8]. Although reviews show little evidence that revaccination with BCG affords additional protection, several countries do report implementation of a two-dose schedule [9].[2]

All the BCG vaccines currently in use derive from the original strain of BCG produced by Albert Calmette and Camille Guérin in 1924 at the Pasteur Institute. The original strain was distributed to several countries, leading to generation of the many substrains used today [10]. Currently, the main substrains used for vaccine production are Brazilian (Moreau/Rio de Janeiro), Danish (Copenhagen – 1331), Japanese (Tokyo – 172-1), Russian (Moscow – 368) and Bulgarian (Sofia – SL222). Different strains tend to be

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[1] WHO is currently reviewing its position on BCG and will publish an updated position paper in early 2018.

[2] Reporting countries: Bulgaria, Kazakhstan, Russia, Seychelles, Tajikistan, Turkmenistan, Ukraine.

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used interchangeably, with no conclusive evidence existing to discriminate for efficacy and safety [11]. The choice of the strains used in the different countries is therefore the result of historical use, production, logistics or other factors [12].

Beyond the open questions on efficacy and interchangeability, continued supply availability has been a main challenge with BCG vaccine. The problem has become more acute in recent years: in 2015, UNICEF reported a supply shortfall of 16.5 million doses due to decreased supply capacity. Large middle-income countries (MICs), typically self-procuring, have also experienced issues in accessing supply [13], as have several high-income countries (HICs); in particular, this was a result of the production problems faced by one historical and large supplier (Statens Serum Institut of Denmark – SSI) [14].[3]

Manufacturing problems, in particular GMP issues, and decisions of suppliers to halt their production are not something new to the BCG vaccine market (as illustrated in Fig. 1) [13–20]. Manufacturing has remained mostly unchanged since the 1920s, with poor characterization and difficulties in maintaining control of the process. The low vaccine price, while affordable for countries, reduced incentives for manufacturers for starting complex and expensive activities for redesign and enhancement of the production process.[4]

This analysis aims to assess the level of risk of BCG vaccine supply in the short- and mid-term and to identify potential areas for intervention. Special attention has been dedicated to maintaining a global perspective: traditional analyses on vaccine availability tend to focus only on segments of the vaccine supply, generally the portion supplied via United Nations (UN) procurement. A global perspective is necessary when assessing vaccine markets, as supply is ultimately allocated on a global basis. In the specific case of BCG vaccine, self-procuring countries account for about 60 percent of total demand.

The analysis investigates BCG vaccine demand and supply dynamics for recent past, present (2017) and near future, with the goal of informing country choices and global policy decisions.

2. Methods

The work has been structured in five areas, as described below.

2.1. Vaccine shortages

A review of the extent and frequency of vaccine shortages over the past decade was conducted. For this work, vaccine shortages are defined as the inability of countries to meet national needs (population needs plus a required buffer). Nevertheless, in the absence of a precise measure of shortages, the analysis reviews country-reported data on national-level stock-outs[5] from the WHO/UNICEF Joint Reporting Form (JRF) for the period 2005–2015 [9]. For more recent years (2016 through early 2017), information on shortages has been obtained through consultations with the WHO regional offices.

2.2. Global demand

Modelling of global BCG vaccine demand was completed. Annual demand is calculated using the formula below:

$$[\text{Target Population} \times \text{Number of Doses} \times \text{Coverage} \times \text{Wastage}] + \text{Buffer}$$

All 194 WHO Member States report EPI schedules through the WHO/UNICEF JRF on an annual basis [9].[6] The currently reported schedules for countries reporting universal vaccination (see Fig. 2) were used to identify country-specific target ages as well as number of doses. The UN Population Division (UNPD) population forecast by year of life was used as the country target population for BCG vaccination [21].[7] The target population was multiplied by the WHO/UNICEF estimated national immunization coverage (WUENIC) [9] and the standard WHO wastage by vial size (in cases of BCG vaccine where the predominant presentations are 10 and 20 dose vials, a factor of 50 percent has been used). The standard buffer stock level (25 percent of the difference in demand between years (positive values only)) was added. The result was a forecast of BCG vaccine demand, per country, per year, for the period 2017–2030 [22].

In addition, data on historical BCG vaccine procurement was available for 146 countries (JRF and UNICEF [23]). This data was compared to the demand forecast for the same 146 countries to inform estimates.

Given the evidence that BCG vaccine can prevent leprosy [24],[8] we analyzed the EPI schedules for the 22 highest burden countries [9]. In addition, the 17 countries with the next highest case detection rates were also included in our assessment, for a total of 39 countries.[9] For these countries, we reviewed recommendations for BCG vaccination to estimate potential additional demand.

Finally, to assess the potential impact of migration flows on global demand of BCG vaccine, we looked at the estimates of the number of refugees/migrants arriving in countries/regions with BCG vaccination for high-risk groups; e.g., Canada (in 2015 and 2016, ~250,000 annually [25]). Vaccination of the entire migrant population with one dose of BCG vaccine was then assumed, given lack of comprehensive data on BCG vaccination practices for these populations. In connection with the recent migrant crisis in the European Union, we estimated the influx of migrants (in 2016, estimates range from 362,000 to 1.2 million [26,27]) and assumed one dose for each, independent of country policy.

2.3. Global supply

A list of manufacturers with available supply of BCG vaccine (and product characteristics) has been compiled with the help of PAHO Revolving Fund, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and Developing Countries Vaccine Manufacturers Network (DCVMN), as well as through a review of published literature [12,28–33], UNICEF Supply Division market updates [13],[10] and internal reports from Bill & Melinda Gates Foundation (BMGF) and Clinton Health Access Initiative (CHAI).

All manufacturers were contacted to obtain information on available products and their characteristics (presentation, shelf-life, route of administration, strain, disease and age indication), as well as information on countries of registration and manufactur-

[3] SSI completed divestment of its BCG vaccine business to AJ Biologics in 2016 after having experienced repeated production and GMP issues.

[4] Analysis of BCG vaccine price by income, region, manufacturer, volume and procurement method can be generated from the V3P website at http://apps.who.int/immunization/vaccineprice (last accessed 07 April 2017).

[5] Stock-out of a vaccine for at least one month indicates that "safety stocks have been depleted and vaccine availability for the national immunization programme could be compromised" [42].

[6] WHO/UNICEF JRF data includes country-reported EPI schedules and estimated coverage (WUENIC) and can be viewed or downloaded here: http://www.who.int/immunization/monitoring_surveillance/data/en/.

[7] The total birth cohort for 153 countries with BCG in EPI is 131 million [21].

[8] Of note: as of October 2017, WHO recommends universal birth dose vaccination with BCG in high burden leprosy settings regardless of the TB incidence (SAGE report: http://apps.who.int/iris/bitstream/10665/259533/1/WER9248.pdf?ua=1).

[9] Data on leprosy case detection rates provided by the WHO Global Leprosy Programme (GLP).

[10] All UNICEF Supply Division market updates are available here: https://www.unicef.org/supply/index_54214.html.

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