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EDITORIAL COMMENT

We commend the authors on their recent publication on trends in BCG utilization during periods of temporary supply shortages. Notably, the study compares the periods 2004-2012 versus 2013-2015, which does not include the most recent announcement in 2016 by Sanofi to exit the market completely. This begs the question: if temporary shortages decrease utilization growth by half, then what will be the impact of a complete market exit?

BCG is uniquely vulnerable to manufacturing shortages.[1] First, since it is a vaccine derived from a living organism, it is regulated as a biologic. To account for inherent variability in batches, special measures must be taken to ensure homogeneous identity, strength, quality, purity, and potency. Second, unlike traditional vaccines, BCG is delivered intravesically and manufactured quantities must be relatively large. When combined with high frequency of treatments in induction/maintenance regimens and expanding indications in nonmuscle-invasive bladder cancer, the market is predisposed to shortages. Lastly, the fact that BCG was discovered over 100 years ago makes it difficult to escape generic pricing. Thus, it is easy to see why manufacturers have struggled to cover higher cost structures involved in producing it. Although the SWOG trial, S1602, was developed in response to the recent shortage and is performing necessary work in comparing BCG strain efficacy, it is unclear how introducing the Tokyo strain in North America would circumvent the issues outlined here and prevent a future exit.

Regulatory reform must necessarily be part of the solution. The Biologics Price Competition and Innovation Act of 2009 was intended to enable quick approval for generic biologics (so-called "biosimilars"), but the first drug was not approved until 2015. Recently, the FDA expanded this program with an emphasis on time-to-market. Additionally, a FDA Drug Shortages Task Force was established to explore manufacturing issues like this one; however, BCG is not on the official drug shortages list. It is a mystery why – the authors of this study have clearly

demonstrated the impact of shortages on clinical practice, and it would behoove regulators to pay attention.

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AUTHOR REPLY

We appreciate the authors' insightful commentary on our recent study examining trends in BCG utilization during national supply shortages. We agree that the impact of even just temporary supply interruptions on BCG utilization is impressive. Certainly, exploring the impact of Sanofi's recent complete market exit is a worthwhile endeavor. However, due to a requisite time lag to allow maturation of data in the NCDB and other large administrative and population-based datasets, a more contemporary analysis is not yet feasible. Thus, while we anticipate that the recent cessation of BCG production by Sanofi may have profound effects on BCG treatment patterns, the necessary data to empirically study this question is not yet available. For this reason, we elected instead to explore the impacts of prior BCG supply interruptions, in hopes that prior trends might inform the current discourse about ongoing BCG supply shortages.

The authors also share valuable insight into the challenges faced by BCG manufacturers and the market forces that lead to supply shortages. We agree that even if scientifically validated, an additional strain of BCG (Tokyo) entering the marketplace may ultimately suffer from the same issues facing current BCG manufacturers, and would likely not be a panacea for this challenging drug shortage issue. Thus, in our manuscript we highlight the importance of exploring potential alternatives to BCG. However, none of these appears ripe for immediate widespread clinical use, and BCG is likely to continue as a mainstay of NMIBC treatment for the foreseeable future. Thus, addressing BCG supply remains a high priority for our bladder cancer patients.

We agree wholeheartedly that regulatory reform is a requisite and central component in addressing BCG shortages. We applaud the authors for their role in bringing BCG supply issues into the national spotlight.[1] Hopefully our current work can help frame these drug shortages into a real-world context that can ultimately be used to advocate for durable change.

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