The vaccines' contribution to unmet medical need in the context of the revision of the EU General Pharmaceutical legislation

Joint position paper

September 2023

On 26 April 2023, the European Commission published a proposal for the revision of EU General Pharmaceutical Legislation, with the objectives to ensure access to affordable medicines, address unmet medical needs, support competitiveness, innovation, and sustainability of the EU's pharmaceutical industry, enhance crisis preparedness and response and address medicines shortages[1]. Vaccines play an important role in achieving these objectives.

The European Commission aims, as part of its revision of the Pharmaceutical Package, to formalise the definition of Unmet Medical Needs and to enhance incentives for innovation in areas of UMN. Currently, there is no established, unified definition for UMN, although the concept of UMN is used, throughout medicines' lifecycles and the value chain for i.e. directing public funds for R&D, determining eligibility to PRIME, accelerated assessment, conditional regulatory approval and orphan designation.

There are 100 vaccine candidates in the industry pipeline aiming at tackling challenges of today and tomorrow[2]. We call for a broad, inclusive, and mission oriented UMN concept which takes the evolution of science and society needs as a starting point, encompasses innovation needs from prevention to care, and can truly benefit individuals, public health, healthcare systems, economy and society at large.

In this position paper, we propose additional considerations relevant to the UMN concept based on the unique aspects of vaccines as a critical preventive tool, the challenges related to the implementation of vaccination programmes, the public health dimension, the unknown nature of infectious diseases and global threats, as well as the complexity of research, development, manufacturing and supply processes of vaccines.

Recognising Primary Prevention in addressing UMN: The unique aspects of vaccines and vaccination programmes

Vaccination is considered one of the greatest healthcare interventions of our time, having saved millions of lives and greatly reduced disease, disability and inequity worldwide. Over the last century, vaccination has supported the development and maintenance of healthy and productive societies and continues to do so. As one of the leading cost-effective preventive interventions, vaccination significantly reduces the burden of infectious diseases and has a wider positive impact at macroeconomic level[3].

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[1] European Commission – A pharmaceutical strategy for Europe

[2] https://www.vaccineseurope.eu/vaccines-pipeline/

[3] Bloom et al (2021). The Societal Value of Vaccination in the Age of COVID-19.

Savings thanks to vaccines result from preventing the disease in the first place. In addition to protecting individuals, vaccines are an important means to strengthen healthcare systems, resulting in fewer individuals requiring healthcare services, occupying emergency departments and hospital beds (in particular during periods of high utilisation, e.g., winter stress). Vaccines also help preventing serious short-term complications (e.g., stroke[4] or heart attack following influenza infection, sepsis), long-term sequelae (e.g., meningococcal infections) and secondary infections (e.g., pneumonia). Avoiding primary and secondary infections also contributes to the fight against Antimicrobial Resistance (AMR) by preventing spread of resistant pathogens and reducing antibiotic usage[5].

Many of the benefits of vaccines can only be realised through population-wide vaccination programmes, a feature that is unlike to any other medical intervention. Population-wide access to vaccines is generally secured via government-funded national immunisation programmes (NIPs). Inclusion and uptake of existing and new vaccines is highly dependent upon National Immunisation Technical Advisory Groups (NITAGs) and competent authorities. Unfortunately, national vaccination calendars vary considerably between and within countries, and across age categories. Moreover, there is high variability in population time to access new vaccines, as well as trust in vaccination and vaccination coverage rates across the EU.

The importance to consider population level vaccine impact for investment and introduction decision making is further described in the WHO Full Value of Vaccine Assessments (FVVA) framework, a framework and methodology to broaden the evaluation of 'vaccine value' beyond solely the demonstration of individual health benefits, to include broader socioeconomic and indirect impact(s) that the vaccine could have.[6]

The UMN concept should recognise the unique features of vaccines and vaccination programmes, and especially the value of preventing diseases, in addition to treating them.

Shaping policy and research priorities: Complexity and Iterative Nature of Vaccine Development

Vaccines are complex biological products with lengthy development, licensing, manufacturing, and distribution processes. Depending on the technology platform, developing a vaccine can take up to 10-15 years or beyond, and hundreds of millions of Euros investments. Manufacturing capacity is often built at risk with very limited sight on future demand and uptake across the world and maintaining high quality standards over time is capital intensive. This requires a high degree of certainty for the industry, which can be undermined by, among others, changes to incentive mechanisms, funding streams, and government priorities over time. Only a limited number of innovative vaccine companies are willing and able to develop and manufacture vaccines.

COVID-19 vaccine development and approval were the most rapid in the history of vaccinology, but this would not have been possible without prior investment in the underlying technologies. Especially, the mRNA technology proved to be a disruptive innovation that

[4] Elkind et al. (2020) Infection as a Stroke Risk Factor and Determinant of Outcome After Stroke.
[5] WHO – Vaccines for Antimicrobial Resistance (AMR)
[6] WHO - The Full Value of Vaccine Assessments (FVVA)

addressed a clear UMN for COVID-19, and it saved millions of lives worldwide, with benefits to individuals, economy and society at large. The COVID-19 crisis saw the establishment of a proof of concept for the mRNA platform, but also for other new technology platforms thanks to a well-defined public health need and demand, as well as extraordinary financial incentives and regulatory flexibilities. Yet, we shouldn't only rely on pandemics to foster the right conditions to enable new platform development.

New technology development and optimisation may start by working on a known pathogen where they might not yield superior response but may be a necessary breakthrough to address other elusive pathogens, or for rapid response in case of a pandemic. Innovation is often iterative, each step providing incremental benefits and setting the stage for further development and improving the benefit/risk ratio. If various aspects of vaccine development are not incentivised, it would stifle innovation to address unmet medical needs. Examples include combination vaccines, next generation vaccines with improved thermostability, better tolerability, higher efficacy (in specific target populations), and/or longer duration of protection, that may have important public health benefits. Overall, those developments may lead to improved vaccine acceptability, confidence and coverage rates, and address population access needs across the world, especially in the low-and middle-income countries.

The UMN concept should consider the complexity and iterative nature of vaccine development and incentivise innovation in vaccine R&D and diverse technology platforms in a sustainable way.

Future-proofing UMN concept: Preparedness for known and unknown global threats

The global challenges that we are currently facing, such as new or emerging infectious diseases, AMR, climate change and an ageing population, remind us of the need for resilient health systems and a strong support to innovation coming from academia, SME's and biopharmaceutical companies.

- **AMR** is a rising threat worldwide and insufficient incentives and value assessments hamper our ability to direct innovation towards this area.
- The epidemiologic trends of some pathogens are rapidly evolving as a result of **climate change** (e.g., dengue, yellow fever) and population shifts (e.g., invasive meningococcal disease, invasive *Escherichia coli*).
- **Europe is ageing** and we need adults contributing to socio-economic prosperity for longer whilst being at risk/complications of vaccine preventable diseases (such as Flu, Herpes Zoster, Pneumococcal infection and RSV).
- The rise of new types of **geopolitical threats** such as cyberterrorism reminds us of the need to be prepared against biothreats of diverse nature including bioterrorism weapons.

Unfortunately, adequate and interconnected surveillance systems, diagnosis, registries and population education on communicable disease are insufficiently developed throughout the EU. As such these diseases are under-assessed or un-recognised and could possibly fail to apply for a UMN concept, especially if the disease burden is low or non-existent in the EU (e.g., pertussis in adults when primary care providers are not aware of the disease or SARS-CoV-2 in geographic regions before testing was available).

The UMN concept should consider the impact of infectious diseases on European and global populations, and support improvements in public health and surveillance infrastructures.

Embracing a broader perspective in UMN concept: Ensuring Inclusivity of Populations

When discussing the UMN in the context of vaccines, it is worthwhile to note the difference between **the perspective of** individual patient (the level of disease burden and direct vaccine protection), and the perspective of the target population (the **population level of disease burden** and both direct but also indirect vaccine protection). As a critical tool to prevent infectious diseases, vaccines are designed to benefit everyone for whom the vaccine is indicated, as well as the general population through community immunity.

Moreover, most prophylactic vaccines are meant to prevent communicable diseases among persons who are at increased risk of acquiring the infection or, once infected, are at high risk for serious consequences or death. Vulnerable individuals may be identified by age group, gender, race, ethnicity, socioeconomic status, access to healthcare, residence (e.g., geographic region, metropolitan vs. rural, living in crowded conditions), health status, frailty, lifestyle (e.g., travel, smoking, alcohol consumption) and occupation. The UMN may be substantial even in situations where the severity of the disease is moderate, but it brings (or might bring) significant value to a part of population previously neglected.

The UMN concept should embrace the perspective of target population, both healthy individuals and vulnerable populations, ensuring the inclusivity across many different populations and recognizing the concept of community immunity.

Calls for action

We strongly call for a broad, inclusive, and mission oriented UMN concept which encompasses innovation needs from prevention to care, emphasises the benefits of safe and effective immunisation, reconciles the different stakeholders' perspectives on the value of vaccination and can truly benefit future public health needs.

We need a paradigm shift in health policies prioritisation from prevention to care and the UMN concept can be part of the solution. It is a unique opportunity for the EU to ensure that innovative vaccine development will flourish in the EU, providing broad benefits to the EU and global community, healthcare systems, economy and society at large.

The UMN concept should:

- **Recognise the unique features of vaccines and vaccination programmes, and especially the value of preventing diseases, in addition to treating them.**
- **Consider the complexity and iterative nature of vaccine development and incentivise innovation in vaccine R&D and diverse technology platforms in a sustainable way.**
- **Consider the impact of infectious diseases on European and global populations, and support improvements in public health and surveillance infrastructures.**
- **Embrace the perspective of target population, both healthy individuals and vulnerable populations, ensuring the inclusivity across many different populations and recognizing the concept of community immunity.**