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EDITORIAL

The long and winding road leading to evidence-based medicine

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The SARS-Cov-2 pandemic has generated an unprecedented reaction from the scientific community. An impressive deployment of financial and intellectual resources has resulted in the availability of effective vaccines for clinical use within a year—a period which is eight times shorter than any similar previous attempt (Patel *et al.*, 2022). To a great extent, this was made possible by an active attempt to reduce the bureaucracy around the many regulatory steps normally required for the development of an interventional medical product. Pre-clinical research, pharmacological quality assessment, Phase I, Phase II, Phase III clinical trials, scientific evaluation, authorization and large-scale production were initiated without necessarily waiting for the previous step to be fully completed i.e. in parallel, rather than in series. This represents a milestone in the history of medicine and demonstrates what can be achieved through collective will and determination.

In contrast, equitable distribution of vaccines against SARS-Cov-2 has been less successful, even amongst healthcare providers. The use of mRNA-based vaccines and rapid process of development has inevitably led to concerns about long-term effectiveness and safety (Manby *et al.*, 2022). A clearer view of the attributes of the vaccines has emerged in recent months. The variable protection against infection, the satisfactory prevention of severe forms of disease, the impact of antigenic variations, the waning immunity and the need for repeated doses are all aspects that have surfaced several months after the initiation of the large-scale vaccination campaigns (Monto, 2021). We are just beginning to understand the true therapeutic profile of the vaccines, and the final scenario will probably reveal itself a few years.

In fact, the rapid development of vaccines against SARS-Cov-2 represents an exception in medical research. The severity of COVID-19 and the urgent need to stem the pandemic have emboldened the scientific community to shed its natural conservatism. This contrasts with the conventional extended time horizon generally required to implement effective medical interventions. The existing framework of evidence-based medicine generally requires years, if not decades, for a treatment to be evaluated and recommended for clinical use. There are some examples of this in reproductive medicine. Ovarian cortex freezing for fertility preservation was first hypothesized in the 1960s (Parrott, 1960). While the first birth using this technique occurred in 2004 (Donnez *et al.*, 2004), the experimental label has only recently been removed in 2019 (Practice Committee of the American Society for Reproductive Medicine, 2019). Reluctance to discontinue ineffective treatments is more common. Preimplantation genetic testing for aneuploidy was proposed in the 1990s (Verlinsky and Kuliev, 1996), shown to be detrimental with a pivotal randomized controlled trial (RCT) in 2007 (Mastenbroek et al., 2007), re-proposed with blastocyst stage biopsy and next-generation sequencing (NGS) technologies and shown to be ineffective again by a number of outstanding randomized trials (Munné *et al.*, 2019; Yan *et al.*, 2021). Endometrial scratching has undergone a similar journey and several contributions over a time span of more than two decades were needed to arrive at the current conclusion that the intervention is of uncertain benefit (Lensen *et al.*, 2021). Despite a number of pivotal studies, many clinicians are unwilling to conclude that these treatments are of no benefit at all. In the era of precision medicine, one cannot exclude the possibility that, despite overall negative findings, a specific treatment might be of value in a subgroup of subjects not yet identified. As lack of proof of effectiveness does not necessarily imply proof of ineffectiveness, treatments of unproven clinical benefit may be justified on the grounds of affordability, psychological benefit and lack of harm. In fact, scientific learning is incremental, and uncertainty is an essential attribute which should be considered a strength rather than a weakness (Bhattacharya *et al.*, 2022).

Most clinical questions do not generally lend themselves to quick definitive answers and the value of cumulative evidence cannot be overstated. An iterative process of investigation usually follows a standard sequence involving laboratory studies, case reports, case series, comparative studies and RCTs. Confirmatory studies followed by systematic reviews and meta-analyses add to the robustness of any conclusion.

This traditional approach requires time for the scientific and clinical community to get closer to the truth. There are no short cuts as greater precision around scientific results is contingent on increasing amounts of data. Development and distribution of vaccines against SARS-Cov-2 were an exceptional journey, requiring an unprecedented investment in terms of resources, expertise and energy. However, we are still some distance from capturing the genuine effectiveness of these vaccines, the most appropriate regimens for their administration and their long-term safety. Ultimately, it is time which is critical in

facilitating the cumulative accumulation of evidence. Rome was not built in a day.

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