Healthy Ageing and Vaccines: Application of the P4 Medicine Concept to Immunizations

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Abstract

In today's tormented world, it appears useful to take advantage of communication channels to promote life-course immunization and affirm its major role in healthy ageing. Instead of developing the argument of chronological age, we demonstrate the life-course principle here based on the P4 medicine concept. Are vaccines "preventive, personalized, predictive, and participatory?" Based on detailed analysis of research findings, we successively demonstrate the seminal role of vaccines on preventable infectious diseases, post-sepsis functional decline, non-communicable diseases (cardio-neuro-vascular, respiratory, and renal diseases), community protection, antimicrobial resistance, and perhaps even old-age dementia. Healthy ageing and the promotion of immunization are closely dependent on health literacy and provision of information by skilled health-care professionals. However, personal autonomy and individual freedom are influenced by psycho-cognitive hurdles (cultural approaches, beliefs, emotions, and behaviours), the opinions of the pub-

lic/family/friends, and the increasing role of social media, which challenges scientific evidence. A similar phenomenon exists when dealing with the issue of healthy ageing, whose success depends greatly on life-course immunization.

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Introduction

The SARS-CoV-2 pandemic has revealed with acuity the far-reaching mutation of the scientific world, with biological systems totally integrated into the medical system. Both systems have benefitted from the digital revolution, putting customer-driven health care and social networks centre-stage [1]. Over the span of a few decades, the relationship between health-care professionals and patients has moved from a paternalistic paradigm to a patient-centred approach, in which patients appear to be the experts. In this rapidly changing context, it is appropriate to insist on the importance of the life-course vaccination approach [2, 3] to healthy ageing, whose definition has shifted substantially, moving from "free of disease" to "functioning well" [4]. This paradigm shift is perfectly captured by a short sentence from Margaret

Chan (former WHO director), who wrote in 2015, in the preface of the 1st WHO report on “Aging and Health,” that “healthy ageing is more than the absence of disease” [5, 6]. In the report itself, “healthy ageing” was defined as the “process of developing and maintaining functional ability that enables well-being until the end of life” [5]. Regardless of the definition of healthy ageing used, it appears that heretofore, not enough attention has been given to the importance of immunization. For this reason, the goal of this review is to demonstrate, using P4 medicine as a conceptual model, the usefulness of vaccines all along the life course.

P4 medicine (the 4 Ps being preventive, personalized, predictive, and participatory) was first proposed by Leroy Hood and corresponds to a proactive approach to medicine, quantifying wellness and demystifying disease [2, 7]. The P4 health-care system includes providing information that can be used by consumers to better manage their health. The emergence of this approach coincided with developments in the digital health industry, providing personalized data about activity levels, sleep, and nutrition, albeit with limited data analysis. During the SARS-CoV-2 pandemic, not only the pioneers of P4 medicine but the whole world has been inundated with a profusion of scientific information, including conflicting results, junk science, misinformation, and fake news [8]. These have been spread without restriction, transforming consumers into active and responsible citizens, and health-care professionals into science brokers [9]. In this new context, although COVID-19 vaccines seem to be the only means to control the pandemic, it is nonetheless important to attempt to elucidate whether the P4 medicine model can be applied to immunization to promote a healthy lifespan. If the scientific knowledge is not robust enough to convince people of the crucial role of vaccines, then it is logical to investigate the disturbing considerations that alter vaccine uptake and interfere with healthy ageing.

Diseases Targeted by Vaccines: Too Often Forgotten!

Too frequently, citizens today tend to forget that worldwide, vaccines prevent >2.5 million deaths per year from communicable diseases [10]. Attention tends to focus instead on the side effects, however minor or rare they may be. An even more disturbing observation is that today, the non-infectious beneficial effects of vaccines are also largely overlooked and not recognized as an additional advantage, even though they have been scientifi-

cally established [11]. It is now well-proven that beyond mortality and recovery, adverse postinfection outcomes, especially in old patients, include neurocognitive decline, acute sarcopenia, functional decline, and gut dysbiosis [12], which can be prevented by vaccination. In a study of 925 patients suffering from acute respiratory infection (mean age 79 years, 56.1% women, and 37% with laboratory-confirmed influenza), at 1 month after hospital discharge, 18.2% had increased functional decline, while 9.9% presented catastrophic disability [13]. Moreover, it has been shown that rotavirus vaccination decreases the incidence of childhood diabetes type 1 by 17–35% [14, 15], while influenza and pneumococcal vaccinations, respectively, reduce cardiovascular mortality and myocardial infarction by 56% and 17% [16]. The positive impact of seasonal influenza (flu) vaccination on cardiovascular health was first suspected in the 1990s by Siscovick et al. [17] who observed in a population-based case-control study of 342 cases of primary cardiac arrest (registered from 1988 to 1994 in the Washington area) and 549 demographically similar controls that flu vaccination appeared to be associated with a reduced risk of primary cardiac arrest (odds ratio [OR] = 0.51 [95% confidence interval [CI] 0.33–0.79]). The hypothesis was subsequently confirmed by a randomized controlled trial including 301 patients hospitalized for myocardial infarction or planned angiography/stenting, showing that mortality at 1 year was significantly lower in patients who were vaccinated than those who were non-vaccinated (relative risk of cardiovascular death at 1 year with vaccination = 0.34 [95% CI 0.17–0.71]) [18, 19]. Another randomized, double-blind, placebo-controlled study of vaccinated versus non-vaccinated groups with 12 months of follow-up in 658 optimally treated coronary artery disease patients (72% men, mean age 59.9 ± 10.3 years) also demonstrated differences in cardiovascular death and coronary revascularization in vaccinated patients (hazard ratio [HR] for ischemic coronary events at 1 year 0.54; 95% CI 0.29–0.99) [20]. These results prompted the American Heart Association and American College of Cardiology to recommend influenza vaccine (inactivated vaccine administered intra-muscularly) for secondary prevention in persons with coronary and other atherosclerotic diseases [21].

It has also been shown that there is an increased risk of stroke after clinically proven onset of herpes zoster in adults between the age of 50 and 60 years [22]. Here again, the positive preventive efficacy of herpes zoster vaccination was recently demonstrated by a nationwide cross-sectional telephone survey of 265,568 non-institutional-

ized US adults aged 50–79 years [23]. After stratification of participants into six 5-year age groups, Cox proportional hazards analysis indicated that those without herpes zoster vaccination were at significantly higher risk of stroke than those who received vaccination with the live attenuated vaccine (HR = 1.73 and 95% CI: 1.71, 1.76) [23].

These complementary preventive activities of vaccines on infectious and non-infectious conditions deserve to be highlighted. In particular, the positive outcomes of immunization on cardiovascular events in the aged population are far from receiving the attention they deserve.

Vaccinations Must Be Personalized

Vaccinations must be personalized to fit the needs of each individual patient. A leading example concerns patients suffering from diabetes mellitus. It is well-known this clinical condition favours not only the risk of developing severe infections but also alarming postinfection complications, including functional decline. Several observational and serological studies, though unfortunately, no randomized controlled studies, have demonstrated the positive effects of flu vaccination on hospitalization and mortality rates [24], justifying the inclusion of recommendations for DTaP, flu, pneumococcal, herpes zoster, and hepatitis B vaccines [25] and more recently COVID-19 vaccines [26] in guidelines for the management of diabetes.

We mentioned earlier the demonstrated preventive role of flu and pneumococcal vaccines on atherosclerosis, coronary artery disease, and mortality. The personalized effect of flu vaccination on cardiovascular events was showed in a nationwide Danish cohort study including all patients older than 18 years diagnosed with heart failure from January 2003 to June 2015 ($n = 134,048$). After the diagnosis of heart failure, 1 flu vaccine alone was sufficient to significantly reduce cardiovascular mortality (HR = 0.82 [0.81–0.84]), while 4 vaccinations were even more protective (HR = 0.72 [0.69–0.74]) ($p < 0.001$) [27].

Much recent evidence has emerged from 2 successive data analyses from the Taiwan Longitudinal Health Insurance Database (1996–2008). Both investigated the prevention of cardiovascular events by flu vaccine in patients with specific health conditions. The first study involved 7,722 patients older than 55 years with chronic obstructive pulmonary disease (and without known cardiovascular disease) and showed a significant decrease in the cumulative event rates for acute coronary syndrome

in vaccinated versus non-vaccinated individuals ($p < 0.001$). Moreover, individuals who received 4 flu vaccines during the course of the study were better protected against hospitalization for acute coronary syndrome than those who received only 1 vaccine ($p < 0.001$) [28]. The second analysis from the same database included 4,406 patients older than 55 years, with chronic kidney disease (CKD) (without known cardiovascular disease) [29]. Again, patients who received repeated flu vaccines ($N = 4$) had significantly lower cumulative event rates for acute coronary syndrome than those who received only 1 flu vaccine during the study period ($p < 0.001$) [29]. Furthermore, CKD patients receiving influenza vaccination had a lower risk of hospitalization for heart failure (adjusted HR, 0.31 [95% CI 0.26–0.39], and $p < 0.001$) [29]. These different examples of the personalized effect of vaccines in diabetes, cardiovascular diseases, respiratory disease, and CKD perfectly underline that targeting people of all ages suffering from chronic diseases for vaccination is essential, but in practice, it is not implemented widely enough.

Vaccinations Are Predictive

Predictive medicine is generally based on biological and genetic information, while in the field of vaccination, the predictive perspective is more closely linked to the collection of epidemiological data. Three examples, respectively, concerning herd immunity, antimicrobial resistance, and a possible infectious aetiology of dementia, underline the positive impact of vaccinating children and adolescents on the health of the whole population.

Herd immunity occurs when a sizeable enough proportion of the population becomes immune to an infectious disease (either through vaccination or natural infection) [30]. Herd immunity, also termed “community protection” [31], prevents the spread of the infection within the community from person to person. Examples of community immunity between younger and older generations are outlined later.

An observational epidemiological study from Japan investigating the impact of an influenza immunization programme in children was among the first explorations into the role of community protection [32]. In Japan in the 1950s, the rate of excess deaths from influenza and pneumococcal disease ranged between 10 and 14 per 100,000 inhabitants. In response, a mandatory national trivalent influenza vaccination programme in schoolchildren was initiated in 1962. Over the following years, the

rate of death linked to all-cause pneumonia decreased dramatically, reaching a rate of 3 to 4 deaths per 100,000 inhabitants. Unfortunately, under pressure from parents, the program was rendered voluntary and subsequently discontinued in 1986. The almost immediate repercussion of the cancellation was a rapid increase in the number of excess deaths [32]. The salient point to note from this experience is that the vaccination programme among schoolchildren conferred an adjusted reduction in mortality of 36% (95% confidence interval [CI] 17–51%) on Japanese seniors [33].

A more focused study performed in the Hutterite community in Canada also clearly illustrated the impact of vaccinating children in interrupting the spread of the virus within the global population. In this randomized trial, 947 Canadian children (aged 3–15 years) received either the flu vaccine ($n = 502$) or the hepatitis A vaccine ($n = 445$). During the 2008–2009 influenza season, in the community where children received the influenza vaccine, only 80 persons had laboratory-confirmed influenza. Conversely, in the communities where children got the hepatitis A vaccine, 159 cases of laboratory-confirmed influenza were recorded. Based on these findings, the overall protective effectiveness was estimated at 59%, when only children got the influenza vaccine [34].

Another powerful example of herd immunity was observed following the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) for all children younger than 5 years in the USA in 1998. A five-year follow-up clearly showed that the 7-valent pneumococcal conjugate vaccine not only drastically decreased the incidence of invasive pneumococcal disease in children but significantly reduced the incidence in older unvaccinated adults as well [35]. Conversely, an unexpected issue arising from the introduction of pneumococcal vaccination is its impact on antimicrobial resistance. In the USA, between 2000 and 2014, the level of antibiotic resistance associated with *Pneumococcal pneumonia*, *Staphylococcus aureus*, *Escherichia coli*, and *Enterobacter* spp. reached 34, 45, 55, and 88%, respectively, even without taking into account the proportion of strains that are resistant to >1 antibiotic class [36].

These examples highlight the usefulness of vaccines in halting intergenerational transmission of pathogens, thereby contributing to improved health among millions of people, through community protection. Moreover, herd immunity protects not only vaccinated people but also those who cannot be immunized, such as the immunocompromised [37], who also yield benefits from the indirect effect of vaccines on antimicrobial resistance

[38]. The well-known measures that can control antimicrobial resistance (sanitation and hygiene, development of rapid diagnostic tests, education to avoid inappropriate antibiotic use, promotion of antibiotic stewardship, and elimination of routine antibiotic use in livestock production) must be complemented by the development of new vaccines [39]. This makes them an attractive solution in the fight against antimicrobial resistance, by protecting people against major infectious diseases such as influenza or pneumococcal pneumonia, thereby reducing the spread of disease and the use of antibiotics.

A more hypothetical example of the impact of life-course vaccination on chronic diseases in adulthood comes from an analysis from the prospective Canadian Study of Health and Aging focused on a community sample of 3,865 cognitively impaired participants (Alzheimer's disease) aged 65 years and older [40]. The study investigated whether any links exist between the cognitive status of participants and previous vaccination, at baseline (1991–2) and during follow-up (1996–7). After adjusting for age, the authors found a significant association between a lower risk of Alzheimer's disease and exposure to diphtheria/tetanus, polio, and flu vaccines [40]. These astonishing results were the start of the infectious hypothesis of late-onset dementia, which has been the subject of ongoing debate in recent decades [41]. Indeed, in a life-course perspective, the role of infant vaccinations and boosters is fundamentally important. Therefore, not only are currently available vaccines excellent tools to fight against antimicrobial resistance but it is also necessary to facilitate access to vaccines, increase coverage rates, and accelerate the development and licensing procedures of new vaccines [39].

The Uptake of Vaccines Is Participatory

Health literacy encompasses people's knowledge, motivation, and competence to access, understand, appraise, and apply health information in order to make judgements and take decisions in everyday life concerning health care, disease prevention, and health promotion, to maintain or improve quality of life [42, 43]. This chain of tasks (information, comprehensibility, meaningfulness, and manageability) depends greatly on personal and contextual determinants, as well as on societal and environmental circumstances [42]. In this context, vaccine literacy requires the individual to seek out relevant information among the ever-increasing data glut in the media (particularly on the Internet) and make an appropriate decision about vaccina-

tion. An exploratory quantitative study from Hong Kong illustrates the complex relationships that exist between health literacy and vaccine practices. Among 486 community-dwelling older adults older than 65 years (60% of whom had low basic education), health literacy was evaluated by the Chinese version of the European Health Literacy Survey (HLS-Asia-Q) [44]. The HLS-Asia-Q findings revealed a high rate of problematic or inadequate health literacy, in particular in the domains relating to finding information (83.5%), understanding information (77.4%), evaluating information (84.1%), and applying information (63.9%). The consequences of deficient health literacy perfectly explain the participants' inability to find vaccine information, interpret it, and appraise it, resulting in increased difficulty in making vaccination decisions [44]. Generally, people with low education have low self-reported global health, and their main questions regarding vaccines relate to the duration of the vaccine protection and the cost to themselves [45]. Conversely, people with a high educational level, who do not always have high self-reported global health, are more concerned about the vaccine efficacy and possible vaccine side effects, as well as costs [45]. Health and vaccine literacy play a major role in the shaping the consumer's perception of a vaccine, namely, a confident, hesitant, or negative perception of vaccination, and they also challenge consumer-provider communication. Indeed, the role of providers as knowledge brokers is essential, but health-care professionals must adapt their communication to the educational or health/vaccine literacy level of the intended audience. The message must be clear, simple, and perfectly understood and not misinterpreted in any way, as stressed in the recent "WHO Decade of Healthy Ageing 2021–2030" [46].

Another key feature of the participatory aspect of vaccine uptake is related to ethics. Does the consumer consider the positive benefits of vaccine only at a personal level, or do they consider the potential benefit in terms of protecting the family or working community? This aspect raises innumerable questions and testifies to the need to add 2 additional dimensions to the P4 approach to vaccines, namely, psycho-cognitive and public [47, 48].

Vaccines Should Neglect neither Psycho-Cognition nor Transcultural Differences

As outlined earlier, the multiple advantages of vaccines clearly outweigh the disadvantages of adverse side effects. However, vaccine hesitancy and low vaccine uptake prove that scientific arguments are jeopardized by

cultural hurdles, beliefs, and emotions such as fear, which alter reasoning and behaviours. Personal autonomy and individual freedom take precedence, while collective safety and wellness are relegated to a position of lesser importance. This attitude is unfortunately often observed among health-care professionals in their choices regarding influenza vaccination, where individual considerations may override their professional duty to beneficence and non-maleficence [49].

Moreover, the increasing mistrust in governmental and local institutions, access to a glut of information via social media, and celebrity opinion can often dramatically increase the ambiguity of vaccination messages. The strength of rumour can be alternatively minimized or amplified by the family context, friends, and workplace colleagues. One seminal issue is that the basic level of health/vaccine literacy of most citizens precludes differentiation between true scientific news and pseudoscience, unscientific claims, or science that is not relevant in the clinical context [8]. This is partially the responsibility of clinicians since all too often their communication abilities are sub-optimal and their interpretation of data or the opinions they voice are discordant, leading to "truth decay" [50].

Conclusion

There is a vast body of solid scientific evidence in favour of the efficacy of vaccines, which have contributed greatly to increasing survival among millions of people and promoting healthy ageing. However, there is almost as much conflicting information and innumerable sources of false or pseudo-information, not to mention endemic misinformation, all of which significantly alter immunization rates. A P4 vaccine program, promoted by artificial intelligence, could become instrumental in the near future and help us to set the record straight so that current and future generations may continue to reap the benefits of vaccination and enjoy "healthy ageing."

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Conflict of Interest Statement

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Author Contributions

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