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EDITORIAL

# The well-known and less well-known benefits of vaccines

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## Introduction

With the outbreak of a new coronavirus (COVID-2019) that has been rearing its ugly head for several weeks in China and worldwide [1–3], the international press and the Coalition for Epidemic Preparedness Innovations have already advocated the urgent need to develop an appropriate vaccine [4]. This request illustrates without a doubt that although current uptake of adult vaccines is still too low in Italy, and in Europe in general [5], vaccines have a powerful (if not magic) perceived efficacy for the general public. Indeed, everyone seems to have understood that vaccines train the immune system to recognize and respond to a pathogen by mounting a rapid and effective immune defence, preventing the establishment of infection or disease, or decreasing the disease severity [6].

As stressed in the paper by Antonelli Incalzi and colleagues in this issue [5], vaccine hesitancy is linked to "the constant flow of contradictory, distorted or plainly false news about vaccines in the media, and much of this information stems from sources that are not scientifically robust". Disinformation of the public about vaccination is not compensated for by medical and paramedical personnel, in whom there is a notable lack of training, and who are often not updated about the burden of vaccine preventable diseases (VPDs) [7]. Yet, the fight against VPDs is a major public health priority. The tremendous positive clinical, social and economic impacts of vaccines on preventable infectious diseases are part of a multidimensional and integrated approach to healthy ageing. In their paper, Antonelli Incalzi et al. propose homogeneous and efficacious strategies to scale up vaccination rates from children to seniors in Italy [5], recipes that will be very useful in other European countries. Among the most important recommendations, the following stand out in particular:

- Set-up of a centralized registry of immunization, enabling continuous monitoring at regional and national levels, which will enable epidemiological evaluation of the impact of vaccinations as well as their socio-economic benefits.
- Implementation of specific teaching about vaccines and vaccination, not only in paediatrics or public health but also in internal and geriatric medicine in all medical and health care faculties.
- Development of a wide-reaching, attractive and repeated media campaign about vaccinations, explaining how they positively impact survival and life expectancy.

Moreover, it is now scientifically proven that vaccines have a significant efficacy on the prevention of cardio- and neuro-vascular events. These benefits are only known to a few professionals [8], who are also aware of the expected benefits of vaccines in the fight against another major health threat, namely antimicrobial resistance.

## The well-known and too often forgotten anti infectious efficacy of current vaccines

As stressed by Antonelli Incalzi et al., vaccination (for adults as well as for children) is recognized as a right and a social value for all. In 2017, thirty-six different vaccines were developed, and over the last thirty years, a number of vaccines have appeared, using firstly live-attenuated strains, then killed whole organisms and more recently, protein or polysaccharide subunits technology [9]. These developments have enabled comparison of morbidity and mortality data on VPDs between the pre-vaccine era and the modern era, across various regions of the world (including Australia, Canada, the UK and the

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USA). These comparisons show an estimated 68 to 100% reduction in preventable infectious diseases such as congenital rubella, diphtheria, hemophilus influenza A, measles, mumps, pertussis, rubella, tetanus and indeed smallpox [9]. These findings explain the observation that communicable diseases worldwide decreased from 33% of total deaths in 1990 to 25% in 2010 [10], thus preventing more than 2.5 million deaths annually from communicable diseases [11]. A related question is whether vaccines have other beneficial impacts on health, in addition to preventing infectious diseases.

## Positive vaccine outcomes on the global health burden

The positive impact of seasonal influenza (flu) vaccination on cardiovascular health was first suspected in the 1990s by Siscovick et al., 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)] [12]. This hypothesis was subsequently confirmed by a randomized, controlled trial including 301 patients hospitalized for myocardial infarction or planned angiography/stenting, showing that mortality at one year was significantly lower in patients who were vaccinated compared to non-vaccinated patients [relative risk of cardiovascular death at 1 year with vaccination = 0.34 (95% CI 0.17–0.71)] [13, 14]. Another randomized, double blind, placebo-controlled study of two population groups (vaccinated vs non-vaccinated) that had 12-month follow-up of 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)[15]. 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 [16].

More recent evidence has been provided by two successive data analyses from the Taiwan Longitudinal Health Insurance Database (1996–2008). Both concern the prevention of cardiovascular events by flu vaccine. The first study involved 7722 patients aged over 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 individual ($p < 0.001$). Moreover, persons who got four flu vaccines during the course of the study period were better protected against hospitalization for acute coronary syndrome than those who received only one vaccine ($p < 0.001$) [17]. The second analysis from the same database included 4,406 patients aged over 55 years, with chronic kidney disease (without known cardiovascular disease) [18]. Again, patients who received repeated flu vaccines ($N = 4$) had significantly lower cumulative event rates for acute coronary syndrome compared to those who received only one flu vaccine during the study period ($p < 0.001$) [18]. 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), $p < 0.001$] [18]. Finally, the protective effect of flu vaccination on cardiovascular events was also demonstrated in a Danish nationwide cohort study including all patients over 18 years of age and diagnosed with heart failure (from January 2003 to June 2015) ($n = 134{,}048$). After the diagnosis of heart failure, one flu vaccination alone was sufficient to significantly reduce cardiovascular mortality [HR = 0.82 (0.81–0.84)], while four vaccinations were even more protective [HR = 0.72 (0.69–0.74)] ($p < 0.001$) [19].

Another frequent disease among older adults is herpes zoster, and it has 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[20]. Here again, the positive preventive efficacy of herpes zoster vaccination was recently demonstrated by a cross-sectional nationwide telephone survey of 265,568 non-institutionalized US adults aged 50 to 79 years old [21]. After stratification of participants into six 5-year age groups, Cox proportional hazards analysis indicated that those without zoster vaccination were at significantly higher risk of stroke compared to those receiving vaccination with the live attenuated vaccine (HR = 1.73, 95% CI 1.71–1.76) [21].

This cumulating body of evidence now clearly testifies to the incontestable beneficial effect of flu vaccination on the onset of cardiovascular events (coronary artery disease, heart failure and cardiovascular death). Moreover, live attenuated herpes zoster vaccine reduces the incidence of post-herpes zoster stroke. It is evident that up to now, the positive outcomes of immunization on all cardiovascular events in the older population are most definitely not receiving enough attention [22].

## Positive vaccine outcomes on antimicrobial resistance

In the European Union, approximately 25,000 people die each year from resistant infections, which are estimated to engender an annual financial burden in the order of 1.5 billion Euro [23]. Among the many well-known measures that can control antimicrobial resistance, which include

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, an additional avenue towards eradicating resistance is the development of new antimicrobial agents and vaccines [24]. However, the time to first detection of human pathogens resistant to antimicrobial drugs is critically shorter and shorter, while new antibiotics are becoming scarce [25]. 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 [26], even without taking into account the proportion of strains that are resistant to more than one antibiotic class.

On the contrary, vaccines do not acquire significant resistance. 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. Moreover, herd immunity protects not only vaccinated people, but also those who cannot be immunized, such as the immunocompromized. Antipneumococcal vaccines that protect against multiple strains also decrease the density of oral carriage of the microbes and thereby diminish genetic exchanges of resistance, even though a few serotypes that are not contained in the vaccine (A19) have emerged. Two years after the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010, the resistance of macrolides, cephalosporins, tetracyclines and penicillin decreased, respectively, by 63%, 81%, 81% and 83% [24], which is very impressive. Therefore, while currently available vaccines are considered as excellent tools to fight against antimicrobial resistance, it is nonetheless necessary to facilitate access to vaccines, increase coverage rates and accelerate the development and licensing procedures of new vaccines [24]. The WHO has already identified possible targets for new vaccines, and clinical trials will investigate extended epidemiological outcomes, including the impact on clinical prescription of antibiotics and reduction in antimicrobial resistance [22].

The useful public health paper from Antonelli Incalziet al. in this issue [5] underlines with strong arguments and acknowledgeable scientific honesty, the need for increased vaccine awareness among the general public, health care professionals and health care deciders. To succeed in the current era marked by successive new infectious pandemics, vaccine policies must be better harmonized, widely disseminated and constantly updated. The less well-known effects of vaccines on the prevention of cardiovascular events and reduction of antimicrobial resistance are good examples of the constant and growing interest of lifelong immunization.

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## Compliance with ethical standards

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