

## Gender differences and workplace vaccinations

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**Summary.** Vaccination is the most effective strategy for the prevention of infectious diseases in the public and occupational health settings. Legislative decree 81/2008 introduced a sex/gender perspective in the risk assessment and management in all workplaces. Moreover, this perspective is also reinforced by law 3/2018 on gender medicine, and by the National plan for the diffusion of gender medicine in healthcare, research and education. Evidence-based studies and the results of a project funded by INAIL highlighted gender-related differences in response to vaccines, laying the foundation for future plans of sex/gender-tailored health surveillance programs.

**Keywords.** Vaccines, occupational risk, gender medicine.

### *Differenze di genere e vaccinazioni nei luoghi di lavoro.*

**Riassunto.** La vaccinazione rappresenta la strategia più efficace per la prevenzione di patologie infettive in sanità pubblica e occupazionale. Il decreto legislativo 81/2008 ha introdotto il concetto di valutazione e gestione dei rischi in ottica di genere in tutti gli ambiti lavorativi. Tale approccio è riportato anche nella legge 3/2018 sulla medicina di genere e nel Piano nazionale per la diffusione della medicina di genere. Studi scientifici e i risultati di un progetto finanziato dall'INAIL hanno documentato differenze tra uomini e donne in risposta ai vaccini, ponendo le basi per la pianificazione di programmi di sorveglianza sanitaria che tengano conto delle differenze di genere.

**Parole chiave.** Vaccinazioni, rischi occupazionali, medicina di genere.

Vaccination is the most effective strategy for the prevention of infectious diseases and for a prompt response to pandemic emergencies. Thanks to the introduction of vaccines, the epidemiological scenario of infectious diseases for which vaccination is available has radically changed over a few decades, leading to a drastic reduction in infection-associated morbidity and mortality in Italy and, to a different extent, at global level. Vaccination can be regarded as a “collective protection measure”, since – by controlling transmission – it reduces the number of individuals susceptible to infection and their likelihood to develop a disease. The extraordinary power of the vaccination strategy is due to the fact that it entails such significant benefits in terms of individual and collective (‘herd’) immunity.

### The legislative decree 81/2008 and the 2020-2025 National prevention plan

With regard to Italian workplaces, legislative decree 81/2008 (article 279) establishes that the employer – in accordance with the occupational physician or the authority responsible for the health surveillance of workers – adopts specific protective measures for workers exposed to biological agents, including vaccination for those without immunity to a transmissible pathogen which could be acquired during their work activities. Workers should be provided with appropriate information/training on the specific risks, as well as informed of the benefits and drawbacks of both vaccination and non-vaccination.

In the health sector, in spite of the poor compliance with vaccination on the part of healthcare professionals, there is a strong implementation of the use of vaccination through awareness programs.<sup>1</sup> In Italy, the recent ‘2020-2025 National prevention plan’ also reiterates the need for vaccination of healthcare professionals, in particular against measles and flu.

The recent dramatic experience of the SARS-CoV-2 pandemic – with the entire world’s population completely susceptible and the absence of specific treatments – has underlined the importance of vaccination as the main public health intervention to alleviate the complex consequences of the epidemic (e.g., the health, economic, social and psychological impact of the crisis).

Legislative decree 81/2008 guarantees “the uniformity of protection of female and male workers on the national territory, through the compliance with the essential levels of services concerning civil and social rights, also with regard to gender, age and condition of female and immigrant workers” (article 1). This introduces a gender perspective, overcoming the previous legislative decree 626/1994, whose recipient was a generic and neutral worker.

The current decree specifies that risk assessment and management must both take into account ‘gender differences’ (articles 28, 40), thus binding the employer to assess the risks according to gender differences, and consequently to adopt specific prevention and protection measures. The implementation of a gender approach in occupational medicine supports the following: the rela-

relationship between gender and risk assessment and the different effects of hazard exposure on workers of the two sexes; the evaluation of the sex-gender system as a multidisciplinary approach to health, aimed not only at a gender-specific prevention, but also focused on the personal history of the individual; the study and research on work-related diseases that express sex/gender differences in health outcomes; the investigation of gender risk assessment and management, to implement different prevention, diagnostic, therapeutic, rehabilitation and health promotion strategies; the drugs/vaccines testing, to highlight gender-dependent pharmacokinetic, pharmacodynamic, efficacy and toxicity differences; and the possible effects of hormonal fluctuations and reproductive cycle phases.

The implementation plan is also consistent with – and reinforced by – gender medicine law 3/2018 (article 3), and by the National plan for the diffusion of gender medicine in health, research and education.

### Sex and gender differences in the immune response to vaccinations

Sex and gender affect the susceptibility to infectious diseases and the intensity of the immune response, as well as the response to vaccines.<sup>2,3</sup>

A paradigmatic and topical example is that of the SARS-CoV-2 infection, whose severity and lethality are significantly greater for males than females, with the lethality in men over 30 about twice that in women.<sup>4</sup>

Vaccinated women produce higher protective antibody titers than men in response to most antiviral vaccines.<sup>2,5</sup> Such differences have not so far been considered in the design or dosing of drugs and vaccines. However, it is not yet known whether a greater female immune reactivity is associated with a longer-lasting protection in vaccinated women versus men. Few years ago, a US study conducted in men and women vaccinated for seasonal influenza showed that women receiving a half dose of the vaccine reached the same antibody titers as men vaccinated with the whole dose,<sup>6</sup> suggesting that sex-tailored vaccination strategies and dosages could be important to improve vaccination campaigns, also considering the financial commitment of the healthcare systems.

At the base of this different immunological response, hormonal milieu plays an important role: it is well known that estrogens are immuno-stimulants, while androgens (testosterone) and progesterone have immunosuppressive properties; in addition, progesterone has a positive immunomodulatory effect in response to viral infections.<sup>5</sup>

The immune response to infections and vaccinations is also affected by the genetic background, and in particular by the fact that the female cell genotype (XX) determines a redundant gene expression of immune

system molecules, such as Toll-like receptors (e.g., TLR7) and cytokines, which makes women more immunoreactive than men. Some gene expression regulators, such as microRNAs (miRNAs) are also encoded mostly on the X chromosome, giving XX cells a preponderant role in regulating the immune response.<sup>2,3</sup>

### Vaccinations among the healthcare workers

The knowledge of the response to vaccinations is particularly important in the general population, and even more in workers professionally exposed to infectious risk, mainly healthcare workers, because they can spread infection to patients, who are particularly vulnerable. With regard to the infectious risk, it is also known that the epidemiological trend of healthcare-related infections is clearly growing, due to the increase in the proportion of immune-compromised, frail and/or elderly patients, the increased frequency of invasive diagnostic-therapeutic procedures, and the spread of antibiotic resistance among nosocomial and community bacterial pathogens. Therefore, the personnel employed in health facilities should be aware of the need to be vaccinated, through education and/or work experience; in this regard, the occupational physicians play an important role, both as educators and health promoter.

### Preliminary data of a project on vaccination coverage in healthcare personnel promoted by INAIL

On the basis of the evidence of a sex-different immunological response to vaccines, INAIL (the Italian National Institute for Insurance against Accidents at Work) promoted and funded a project on vaccination coverage (antibody titers in response to anti-hepatitis B-HBV, -measles-mumps-rubella-MPR and -varicella-V) in healthcare personnel of both sexes, belonging to three Italian health facilities distributed throughout the Country (North, Center and South). The purpose of the study was to highlight any differences in the response to the vaccinations recommended for healthcare workers, and to correlate the differences detected with sex, age, time from vaccination and type of job (Table 1).

The preliminary data on 15,566 vaccinated health workers and students of medical faculties (32,8% males and 67,2% females), with known antibody titers for anti-HBV and VMMR vaccines, was acquired. The statistical analysis of the correlations between dependent variables (protective antibody titer at different vaccinations) and independent variables (sex, age, time from vaccination and professional skills) highlighted that women employed in the health sector, regardless of their age group, had higher antibody titers for almost all the vac-

**Table 1.** Major achievements of the project

- Female healthcare professionals had higher antibody titers for all the vaccinations considered (anti-hepatitis B-HBV, -measles-mumps-rubella-MPR and -varicella-V).
- In male and female healthcare professionals the HBV vaccination received after one year of age (late vaccination regime) produced greater and longer-lasting protective immune responses, versus a vaccination received before one year of age.
- Female healthcare professionals vaccinated after one year of age reached higher HBs Ab titers than males.
- A higher percentage of males vaccinated after one year of age had HBs Ab titers below the protection threshold (10IU/ml), with respect to females, even following a booster dose.

inations considered, except for rubella but limited to healthcare professionals working in pediatric hospitals. With regard to the anti-hepatitis B response, age upon the first administration of the vaccine was found to have the greatest impact on the antibody titer; in particular, in the student population and in the female subjects vaccinated after one year of age, antibody titers were 5 times higher than in women vaccinated before one year of age<sup>7</sup>. In general, the subjects with vaccine antibody titers below the protection threshold – both for the hepatitis B vaccine and for the other vaccinations considered – showed a higher percentage of males than females.

Therefore, starting from the awareness that males and females have a different immunological response to vaccination, also documented by the project outcomes, it would be desirable to apply a “gender-personalized vaccinology” that can achieve a more rational administration of some vaccines, to enhance their efficacy, expand the immune response in males and reduce the adverse reactions in females. Besides the 1977 FDA advice to include female subjects in clinical trials, so far in trials impacting both men and women the latter are not always being enrolled in adequate numbers, that is, proportionally to the levels at which they experience that disease state. The historical exclusion of women from vaccine and drug trials led to an unrepresentative assessment of the vaccines’ efficacy and side effects, potentially leaving them at risk of serious harm. Furthermore, data from the outcomes of the trials including both males and females is often provided not disaggregated by sex, which masks any potential sex-specific efficacy or adverse effects.

Based on the current evidence about the differences between men and women in their response to vaccines, it will be primarily important to collect and examine data relating to the response to vaccination among healthcare professionals in a sex-disaggregated way. This analysis may bring out particular situations, such as inadequacy or contraindications to vaccination or cases

of vaccine-reduced efficacy, based on sex differences. In addition, it can provide useful hints for designing sex/gender-tailored risk assessment in the workplace and for planning health surveillance programs.

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